# Applications of DABSO for the delivery of sulfur dioxide in organic synthesis

Alex Deeming

St Edmund Hall, University of Oxford

Trinity Term 2015

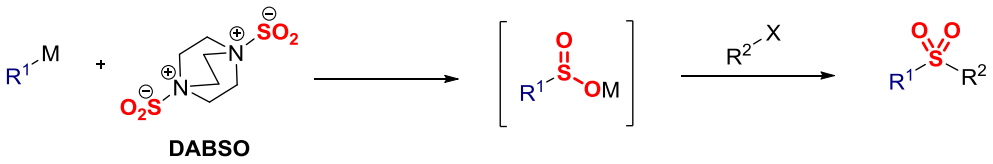
A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Organic Chemistry

# Abstract

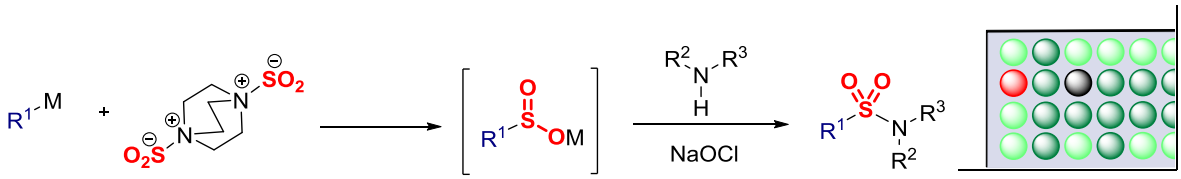
This thesis documents the development of novel synthetic methodologies for the incorporation of sulfur dioxide into organic molecules employing the amine-sulfur dioxide complex DABSO (*vide infra*). These developed processes serve to access a range of sulfonyl-containing (-$SO_2$-) compounds including sulfones and sulfonamides, *via* sulfinic acid precursors.

**Chapter 1** provides an overview of the synthesis and applications of sulfonyl-containing compounds and the organic chemistry of sulfur dioxide. A comprehensive introduction to the developed uses of sulfur dioxide surrogates in organic chemistry is given. The synthetic utility of metal sulfinates towards accessing sulfonyl-containing compounds is also discussed.

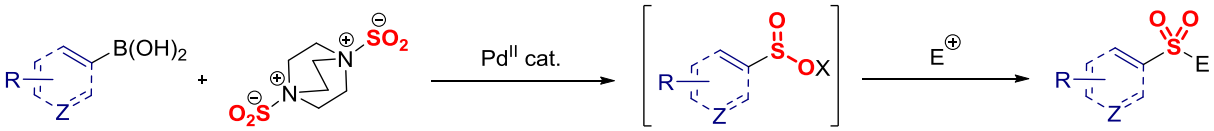
**Chapter 2** details the development of a one-pot sulfone synthesis *via* metal sulfinates generated from organometallic reagents and DABSO.[1] Alkyl, alkenyl and (hetero)aryl sulfinates prepared from organolithium and Grignard reagents can be efficiently coupled with a range of electrophiles to access a range of products including diaryl, aryl-heteroaryl and *β*-hydroxy sulfones.




**Chapter 3** describes an array-compatible, one-pot sulfonamide synthesis employing metal sulfinates and *N*-chloroamines as *in situ*-generated intermediates.[2] This employs DABSO and sodium hypochlorite (bleach) as simple reagents and organolithium, organozinc and Grignard reagents along with amines as readily-accessible building blocks. The robust nature of this methodology and its potential application in discovery chemistry is demonstrated with a 65-compound array synthesis.



**Chapter 4** documents the development of a palladium-catalysed sulfination reaction of boronic acids to access a range of sulfonyl-containing compounds. This involved the establishment of a one-pot/one step synthesis of sulfones leading to the discovery of a redox-neutral, ligand-free sulfination procedure using DABSO and palladium(II) catalysis. Sulfinic acid derivatives can be generated and subsequently trapped *in situ* with a variety of electrophiles to furnish sulfones and sulfonamides.



**Chapter 5** summarises the research and the potential future work.

**Chapter 6** provides experimental details and data.

# Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated. This thesis has not been previously submitted for a degree, diploma or any other qualification at the Univeristy of Oxford or elsewhere.

Alex Deeming
June 2015

# Acknowledgements

Firstly, I would like to thank Prof. Michael Willis, not only for giving me the opportunity to work in his group, but for being a brilliant supervisor to work for. Throughout my DPhil he has been very supportive and provided great enthusiasm for the project. I am also grateful for his trust in me to carry out the project, and I feel this has allowed me to develop significantly. For this, I am indebted to him. Thank you.

I would like to thank Syngenta and the EPSRC for funding and my industrial supervisor Claire Russell. I have to pay particular thanks to Dave Langton and Russell Ellis from Syngenta for their help during my placement at Jealott's Hill. Thanks also go to the Oxford University CRL and St Edmund Hall for the continued support throughout my studies.

I thank all the past and present members of the Willis group. It has been a pleasure to work with so many great people over the years. Thanks go to Ed, Anais, James and Maitane for proof-reading and Milan and Matt for the good times from the start. I would like to pay particular tribute to two people who have been there from day one. Firstly, Ryan for his friendship during our time in the lab and onwards. The office banter, Vince McMahon walk and famous hand-shake are all great memories I will hold forever. Your presence made a tough first year a lot more enjoyable. Secondly, to Ed, who has been an unbelievable friend and colleague. I am particularly thankful for the support in the early days and thoroughout – I owe you a lot. From the lab to Colorado it has been an absolute pleasure. I look forward to working together on our next project…on the golf course.

I would like to thank my family for their constant support throughout this process. I will forever be grateful to my parents, Anne and Steve, who have been there for me from the start. Thank you both. I owe great thanks to my brother Leon for the wisdom and chemical ideas. To Abi, for being there throughout, your love, enthusiasm and patience, I am eternally grateful. Thank you for putting up with me during this time and helping me through, I couldn't have done this without you.

I would like to dedicate this thesis to my late Grandad, Jim. This is for him.

# Table of contents

# Abbreviations and acronyms

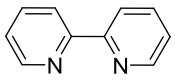
| | |
|---|---|
| Å | Angström |
| *a* | array |
| acac | acetylacetonate |
| app. | apparent |
| aq. | aqueous |
| Ar | aryl |
| br. | Broad |
| Bt | benzotriazole |
| BTEABr | benzyltriethylammonium bromide |
| BTEAC | benzyltriethylammonium chloride |
| Bu | butyl |
| c | cyclo |
| cat. | catalyst or catalytic |
| COSY | correlation spectroscopy |
| CRL | Chemistry Research Laboratory |
| d | doublet or deuterated |
| Da | Dalton |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DABSO | 1,4-diazabicyclo[2.2.2]octane-bis(sulfur dioxide) adduct |
| DBE | dibutyl ether |
| DCM | dichloromethane |
| Dioxane | 1,4-dioxane |
| DIBAL | diisobutylaluminium |
| DIPEA | *N*,*N*-diisopropylethylamine |
| DMA | dimethylamine |
| DMAc | *N*,*N*-dimethylacetamide |
| DMAP | 4-dimethylaminopyridine |
| DME | 1,2-dimethoxyethane |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| DPhil | Doctor of Philosophy |

| | |
|---|---|
| DSC | differential scanning calorimetry |
| E | electrophile |
| EI | electron impact |
| EPSRC | Engineering and Physical Sciences Research Council |
| eq. | equation or equivalents |
| equiv. | equivalents |
| ESI | electrospray ionisation |
| Et | ethyl |
| FI | field ionisation |
| FT | Fourier transform |
| g | gram or gas |
| *h*DA | hetero-Diels Alder |
| hept. | heptet |
| Het. | heteroaryl |
| HIV | human immunodeficiency virus |
| HOMO | highest occupied molecular orbital |
| HPLC | high performance liquid chromatography |
| hr | hour(s) |
| HRMS | high resolution mass spectrometry |
| HSQC | heteronuclear single quantum coherence |
| Hz | Hertz |
| *i* | iso |
| IPA | 2-propanol |
| IR | infrared |
| *J* | coupling constant |
| l | liquid |
| L | ligand or litre |
| LA | Lewis acid |
| LC-MS | liquid chromatography - mass spectrometry |
| LDA | lithium diisopropylamide |
| logP | logarithmic partition coefficient |
| LRMS | low resolution mass spectrometry |
| LUMO | lowest unoccupied molecular orbital |
| M | metal or molar |

| | |
|---|---|
| m | meter or milli ($10^{-3}$) or multiplet |
| *m* | *meta* |
| *m*CPBA | 3-chloroperoxybenzoic acid |
| Me | methyl |
| min | minutes(s) |
| mol | mole |
| mp | melting point |
| MS | mass spectrometry |
| *m/z* | mass to charge ratio |
| *n* | normal |
| NCS | *N*-chlorosuccinimide |
| NHC | *N*-heterocyclic carbene |
| NMR | nuclear magnetic resonance |
| Nuc | nucleophile |
| *o* | *ortho* |
| [O] | oxidant |
| *p* | *para* |
| Ph | phenyl |
| ppm | parts per million |
| Pr | propyl |
| py | pyridine |
| q | quartet |
| quant. | quantitative |
| quin. | quintet |
| R | generic group/substituent |
| red | reductant |
| ret | retention |
| RM | organometallic |
| RT | room temperature |
| s | singlet or solid |
| sat. | saturated |
| sec | second(s) |
| sext. | sextet |
| $S_N2$ | nucleophilic substitution (bimolecular) |

| | |
|---|---|
| $S_NAr$ | nucleophilic aromatic substitution |
| t | triplet |
| *t* | tertiary |
| TBAB | tetrabutylammonium bromide |
| TBAC | tetrabutylammonium chloride |
| TBAF | tetrabutylammonium fluoride |
| TBAI | tetrabutylammonium iodide |
| TBAOH | tetrabutylammonium hydroxide |
| TBS | *tert*-butyldimethylsilyl |
| TBHP | *tert*-butyl hydroperoxide |
| temp. | temperature |
| Tf | triflyl |
| TFA | trifluoroacetic acid |
| THF | tetrahydrofuran |
| TIPS | triisopropylsilyl |
| TLC | thin layer chromatography |
| TMA | trimethylamine |
| TMS | trimethylsilyl |
| TOF | time-of-flight |
| Tol | tolyl |
| TPSA | topological polar surface area |
| UV | ultraviolet |
| wt | weight |
| X | (pseudo)halide or generic counterion |
| Z | heteroatom |
| δ | chemical shift |
| μ | micro ($10^{-6}$) |
| υ | frequency |
| Δ | heat |

# Ligand and chemical structures

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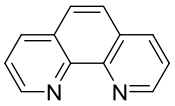
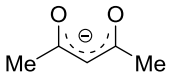



phenanthroline

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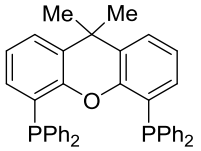


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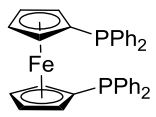
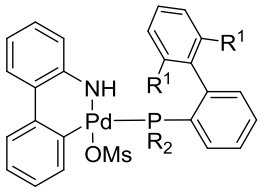
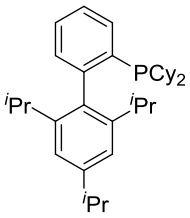



dppf




R = Ph
$R^1 = NMe_2$
PhCPhos (**P5**)

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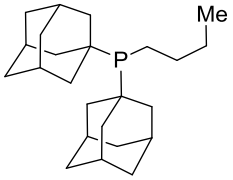


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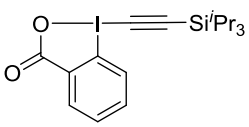


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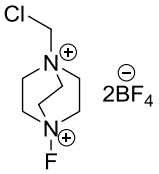


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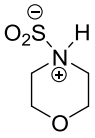
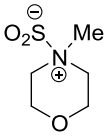
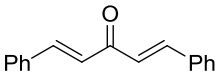



Morph-$SO_2$




*N*-Me-Morph-$SO_2$




dba

# 1. Introduction

## 1.1 Sulfonyl-containing compounds

### 1.1.1 Biological and synthetic applications of sulfonyl-containing compounds

The importance of the sulfonyl moiety (-$SO_2$-) as a structural motif in molecular targets is demonstrated by its ubiquity in pharmaceutical[3] and agrochemical products,[4] as well as polymeric materials.[5] The most common sulfonyl functional groups found in biologically active molecules and synthetic intermediates are sulfonamides and sulfones; less common moieties include sulfonyl ureas and sulfonic acid esters (Figure 1.1).

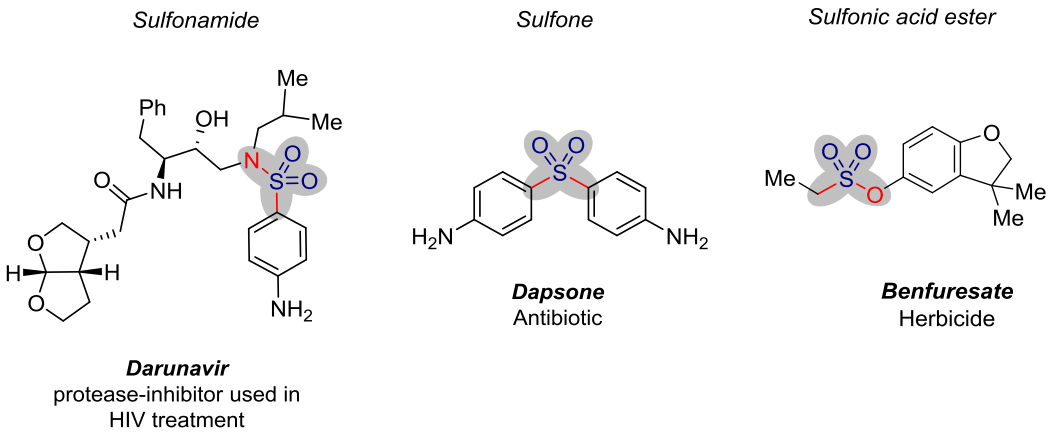
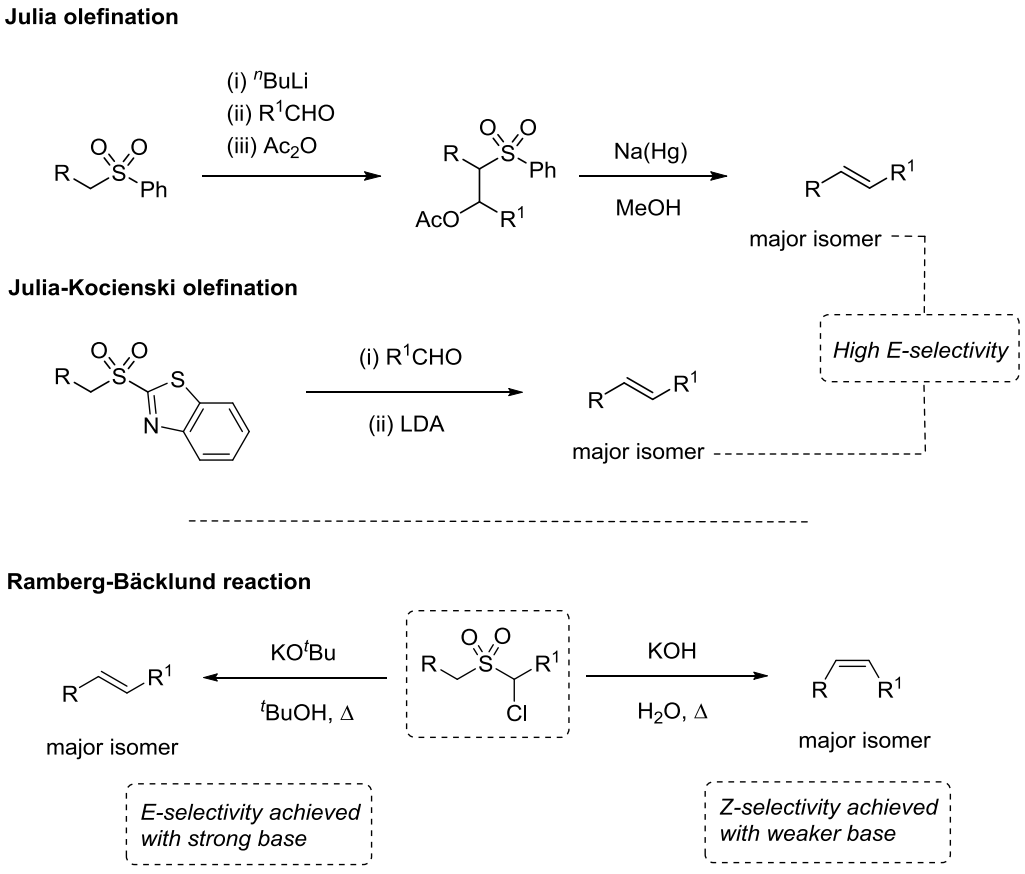



Figure 1.1 Examples of sulfonyl-containing pharmaceutical and agrochemical agents.

Sulfone and sulfonamide containing compounds are best known to possess key antibacterial properties and as a result have found many applications in antibiotic drugs; so much so that the term “sulfa drugs” has evolved to represent this class of medicinal agents.[6] Sulfonamide antimicrobial agents are particularly prevalent due to their activity as competitive inhibitors of dihydropteroate synthetase (DHPS),[7] an enzyme involved in folate synthesis in microorganisms. In addition, (hetero)aromatic sulfonamide compounds are known to act as inhibitors of carbonic anhydrase and this activity has been exploited in diuretic and glaucoma treatment.[8]

More recently, the potential tumour inhibition properties of targets bearing the sulfonamide moiety have been discovered,[9] leading to potential anti-cancer agents, while compounds containing the sulfonamide and sulfone motif have also been developed as anti-HIV drug candidates.[10]

As well as possessing latent biological activity, compounds containing the sulfonyl moiety have found use as synthetic intermediates in organic chemistry.[11] While sulfonamides are chiefly employed as protecting groups for amines, sulfones have been exploited in transformations whereby the -$SO_2$- unit serves as a leaving group, yielding desulfonylated products. Examples of such processes include the Julia-Kocienski[12] and Ramberg-Bäcklund[13] reactions with both generating alkene products through the extrusion of the -$SO_2$- unit (Scheme 1.1).

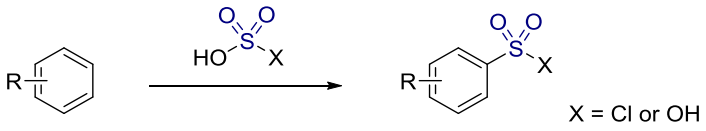



Scheme 1.1 Julia-type olefination and Ramberg-Bäcklund reaction employing sulfone substrates.

In addition, both the sulfone and sulfonamide moieties have been employed as directing groups for *ortho*-lithiation reactions allowing for the construction of aromatic sulfonyl compounds with challenging substitution patterns.[14]

### 1.1.2 Synthesis of sulfonyl-containing compounds

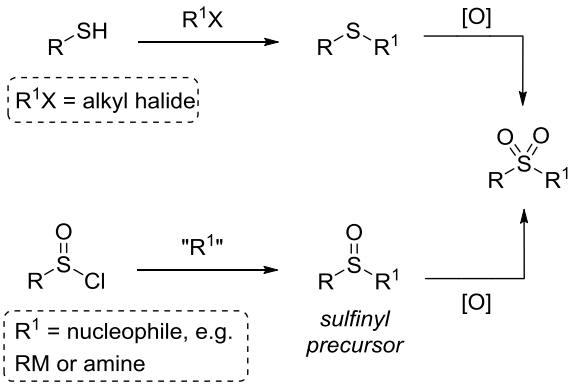
As a result of the prevalence of the sulfonyl moiety in synthetic targets, ways in which this group can be incorporated into organic molecules are highly sought. Many methods for accessing such compounds exist but three general strategies are typically employed. Firstly, and arguably the most common approach, is the preparation of arylsulfonic acid derivatives *via* electrophilic aromatic sulfonation (Scheme 1.2).[15]




Scheme 1.2 Friedel-Crafts-type synthesis of sulfonic acid derivatives.

The use of chlorosulfonic acid in such a reaction delivers arylsulfonyl chlorides; species that are commonly employed as precursors to more useful functional groups such as sulfones,[16] sulfonamides[17] and sulfonic acid esters.[18] With the use of such harsh acidic conditions however, these sulfonation procedures suffer from poor functional group tolerance. An additional constraint of these Friedel-Crafts-type processes is the limited application to arenes with higher levels of substitution due to the regioselectivity issues invoked by electronic and steric factors.

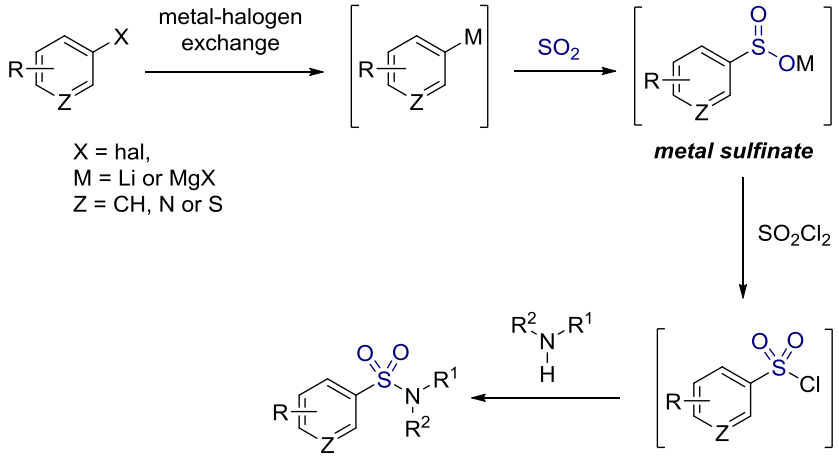
The second general method is based on the oxidation of the corresponding sulfenyl or sulfinyl equivalents (Scheme 1.3). This, the most common route to sulfones, is achieved in a two-step protocol involving initial sulfide synthesis from the corresponding thiol and subsequent oxidation with reagents such as hydrogen peroxide[19] or *m*CPBA.[20]




Scheme 1.3 Oxidation strategies to access sulfonyl functional groups.

In addition, both sulfones and sulfonamides can be accessed through trapping sulfinyl chloride derivatives with a nucleophile such as an organometallic reagent or amine to deliver the corresponding sulfoxide or sulfinamide, respectively (Scheme 1.3).[21] These intermediates can subsequently be oxidised to the sulfonyl oxidation level.[22] These strategies suffer from the additional step required to prepare the sulfide and sulfinyl precursors and the use of strong oxidative conditions which can lead to reduced functional group compatibility.

Sulfonyl chlorides can also be accessed *via* the addition of sulfur dioxide to organometallic reagents. This *in situ* preparation of metal sulfinate intermediates serves as a second general strategy for "$SO_2$" incorporation. Hamada and Yonemitsu demonstrated that arenesulfonyl chlorides could be prepared by combining aryllithium reagents with sulfur dioxide followed by treatment of the corresponding lithium sulfinates with sulfuryl chloride (Scheme 1.4).[23] This methodology was further developed by Barrett where aromatic and heteroaromatic Grignard reagents were employed to deliver the corresponding sulfonamides following trapping of the sulfonyl chloride intermediate *in situ* (Scheme 1.4).[24]

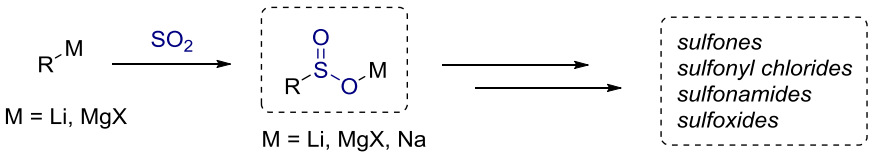



Scheme 1.4 Yamamoto's and Barrett's routes to sulfonyl chlorides and sulfonamides.

Although sulfonyl chlorides are frequently employed as precursors to sulfonyl-containing targets,[25] their application is somewhat limited by the conditions required for their synthesis; highly acidic and/or reactive reagents lead to restricted functional group tolerance and hinder access to such products.

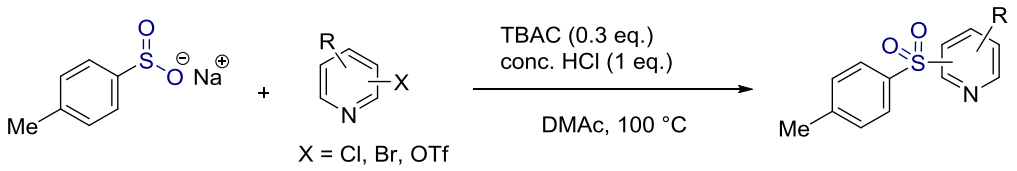
### 1.1.3 Metal sulfinates as versatile intermediates

Sulfinic acid salts have found widespread applications in the synthesis of sulfonyl-containing compounds. Sulfones can be obtained by reacting these nucleophilic precursors with carbon-based electrophiles. The sulfinates are generally obtained as a commercial salt (although very few are readily available) or generated *in situ* by combining organolithium or Grignard reagents with sulfur dioxide (Scheme 1.5).[23,24]



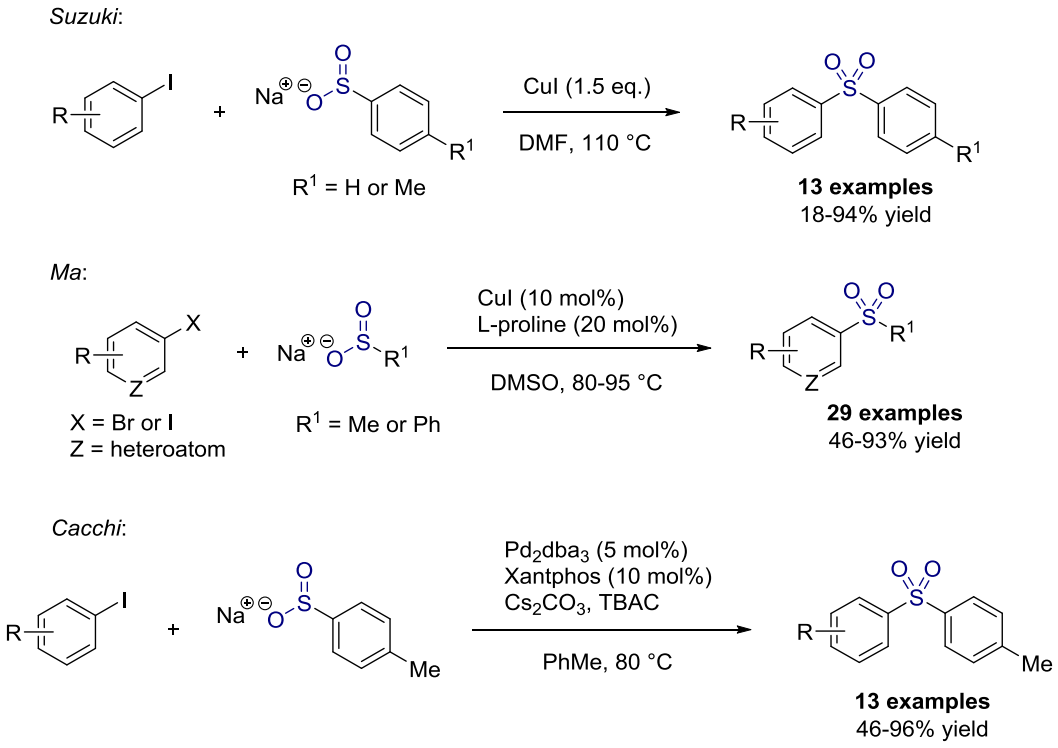

Scheme 1.5 General strategy for preparing and derivatising metal sulfinates.

Sodium sulfinates have been employed in $S_NAr$ reactions with activated (electron poor) aryl halides to afford diaryl sulfone products (Scheme 1.6).[26]




Scheme 1.6 $S_NAr$ reaction of sodium sulfinates with electron deficient aromatic substrates.

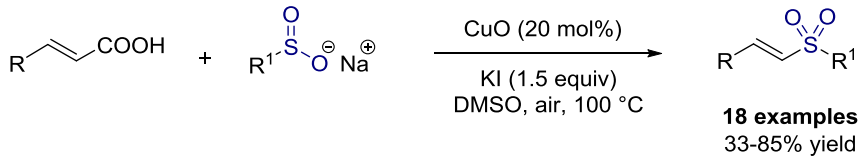
In addition, diaryl sulfones can be accessed by employing aryl sulfinates as nucleophilic coupling partners in transition-metal catalysed processes. Suzuki established that aryl sodium sulfinates could be coupled with aryl iodides using stoichiometric copper iodide (Scheme 1.7).[27] Ma advanced this chemistry with a catalytic copper-mediated system compatible with aryl and heteroaryl iodides and bromides as well as aryl and alkyl sodium sulfinates (Scheme 1.7).[28]Cacchi also introduced a palladium-catalysed variant of the diaryl sulfone synthesis (Scheme 1.7).[29]




Scheme 1.7. Examples of sodium sulfinates used in metal catalysis to access diaryl sulfones.

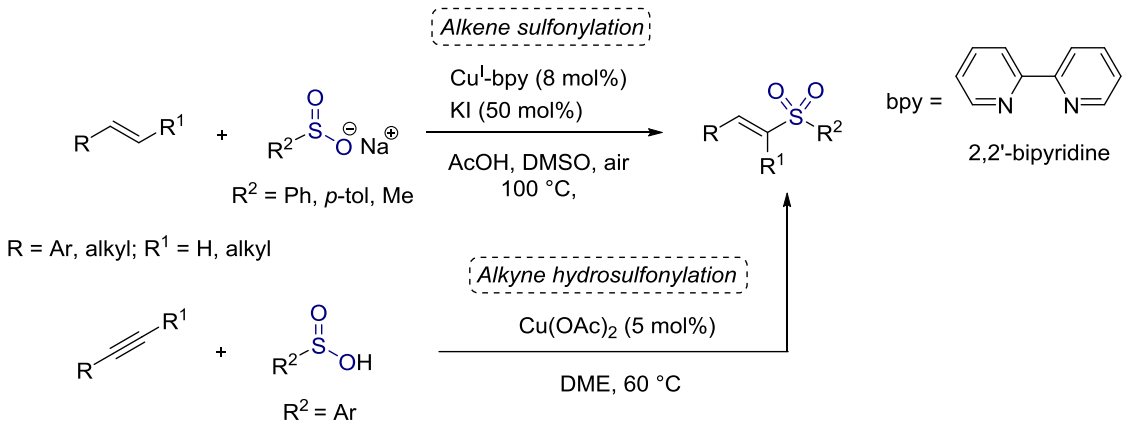
Further to this, copper-catalysed diaryl sulfone syntheses have been developed with boronic acid substrates. Beller *et al.* established such a system coupling (hetero)aromatic and alkenyl boronic acids with methyl- and *p*-tolyl-sodium sulfinates under oxidative conditions.[30]

More recently, Guo *et al.* demonstrated the use of sodium sulfinates with alkenyl carboxylic acids in a copper-catalysed decarboxylative cross-coupling process to access *α,β*-unsaturated sulfones (Scheme 1.8).[31]




Scheme 1.8 Cu-catalysed decarboxylative coupling of carboxylic acids with sodium sulfinates.

Sodium sulfinates have also been shown to act as precursors to sulfonyl radicals.[32] Copper-mediated oxidation of the sulfinate results in a $RSO_2^{\bullet}$ radical which can then react with alkenes in a propagation step and ultimately form alkenyl sulfones (Scheme 1.9).[33] This chemistry was further developed by Wang *et al*. with the addition of sulfinic acids to alkynes in a copper-catalysed, radical-based hydrosulfonylation reaction (Scheme 1.9).[34]




Scheme 1.9 Cu-catalysed oxidation of sodium sulfinates and additions across alkenes and alkynes.

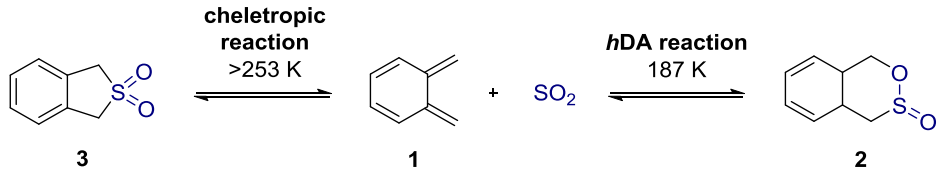
## 1.2 Sulfur dioxide in organic chemistry

### 1.2.1 Background

The primary uses of sulfur dioxide are as a source of sulfuric acid and a food preservative.[35] Despite its highly toxic nature, several classical reactions employ $SO_2$ as a reagent in organic synthesis.[36] With a high HOMO and low LUMO, sulfur dioxide is amphoteric, acting as a Lewis acid or base. As a result, $SO_2$ has been found to be a versatile reagent in organic synthesis, serving as an electrophile, dienophile and radical acceptor.

### 1.2.2 Pericyclic reactions

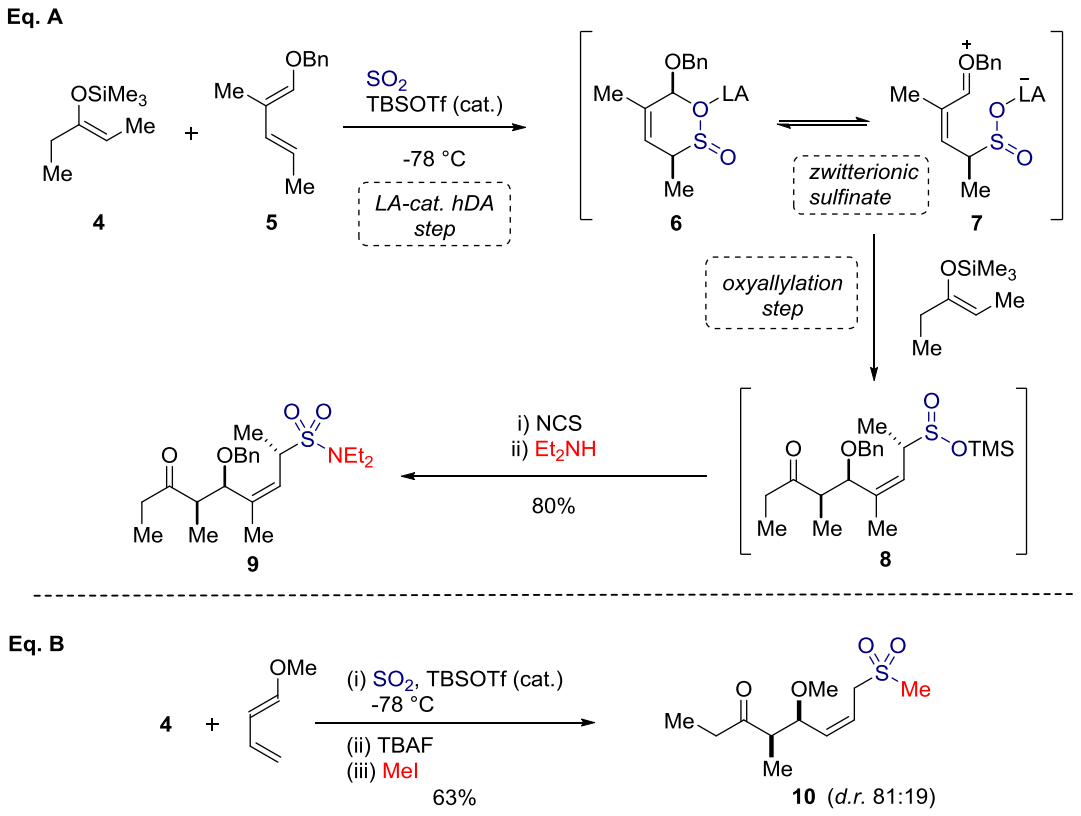
Pericyclic reactions are amongst the most investigated class of organic transformations employing sulfur dioxide. [4+1] Cheletropic additions and hetero-Diels-Alder (*h*DA) reactions of $SO_2$ with dienes are well-precedented routes to sulfolenes and cyclic sulfinic acid esters (Scheme 1.10).[37] For example, the addition of sulfur dioxide to the simple diene **1** at low temperature (187 K) generates the corresponding sulfinic acid ester **2** which on warming (253 K) undergoes cycloreversion to the diene and $SO_2$ with the cheletropic addition subsequently affording the sulfolene product **3**.[38]




Scheme 1.10. Pericyclic reactions of $SO_2$ with dienes.

More recent advances in the area of sulfur dioxide pericyclic chemistry have been made by Vogel with the development of a number of efficient transformations.[37] In particular, Vogel has pioneered the application of Lewis acid mediated sulfur dioxide *h*DA processes that incorporate C-C bond formation along with $SO_2$ insertion.[39]

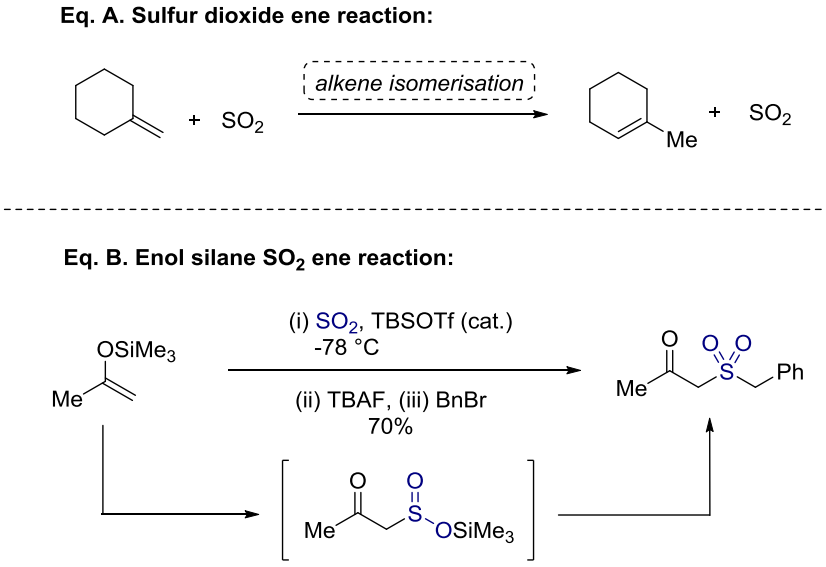
The application of silyl-based acid catalysts with electron-rich dienes such as **5** in the presence of sulfur dioxide was found to deliver the sultine Lewis acid adduct **6** which can undergo a ring opening to the zwitterionic sulfinate intermediate **7** (Scheme 1.11).[40] This key intermediate can then react with the silyl-enol ether nucleophile **4** (C-C bond forming oxyallylation step) to generate the corresponding silyl sulfinate **8** which can be converted to sulfonamide product **9** (Eq A, Scheme 1.11).[41]




Scheme 1.11 Lewis acid catalysed *h*DA/oxyallylation sequence leading to sulfones and sulfonamides.

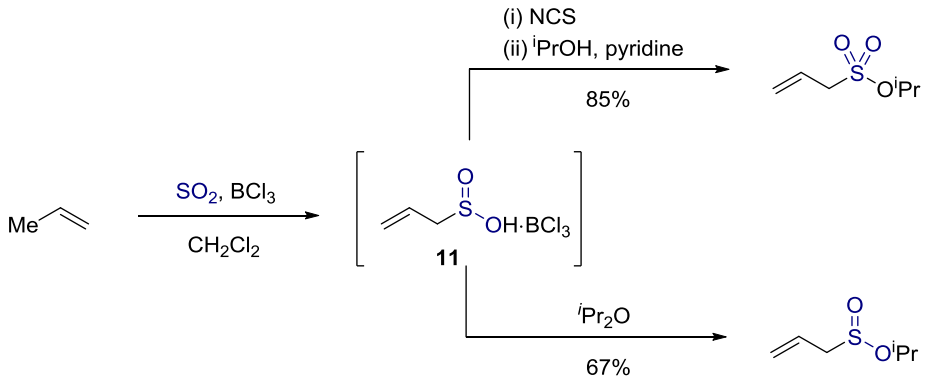
Alternatively, this process can be used to access sulfones (such as **10**) with deprotection of the silyl sulfinate followed by trapping with methyl iodide (Eq B, Scheme 1.11).[42] This one-pot *h*DA/oxyallylation sequence can be employed to construct highly functionalised sulfones and sulfonamides with good to high levels of diastereoselectivity.[43]

In addition, Vogel was able to demonstrate the applicability of silyl enol ethers and allylsilanes as substrates in Alder-ene reactions with sulfur dioxide (Eq. B, Scheme 1.12).[44] The sulfur dioxide-ene reaction is one of the earliest developed organic transformations involving $SO_2$ gas[45] and was initially demonstrated with the sulfur dioxide-mediated isomerisation of alkenes (Eq. A, Scheme 1.12).[46] The mechanistic rationale for this process was generally accepted as an ene/[1,3]-sigmatropic shift/retro-ene sequence. However, more extensive work by Vogel provides evidence for a radical-based mechanism with a polysulfone generated *in situ* acting as an organocatalyst.[47]




Scheme 1.12 $SO_2$-ene reaction and Vogel's silyl enol ether-ene reaction.

More recently, in 2010, Vogel provided an extension to this work with the development of a bora-ene reaction with sulfur dioxide, employing simple alkenes together with boron trichloride as a Lewis acid promoter.[48] The stabilised sulfinic acid·$BCl_3$ complex **11** generated *in situ* was demonstrated as a particularly versatile precursor to sulfonic and sulfinic products (Scheme 1.13). This chemistry was extended to access sulfoxide products with the addition of $SO_2$ to prop-2-ene boronic acid esters generating sulfinic boronate anhydrides and subsequent trapping with Grignard reagents.[49]




Scheme 1.13 Bora-ene reaction of $SO_2$ and alkenes.

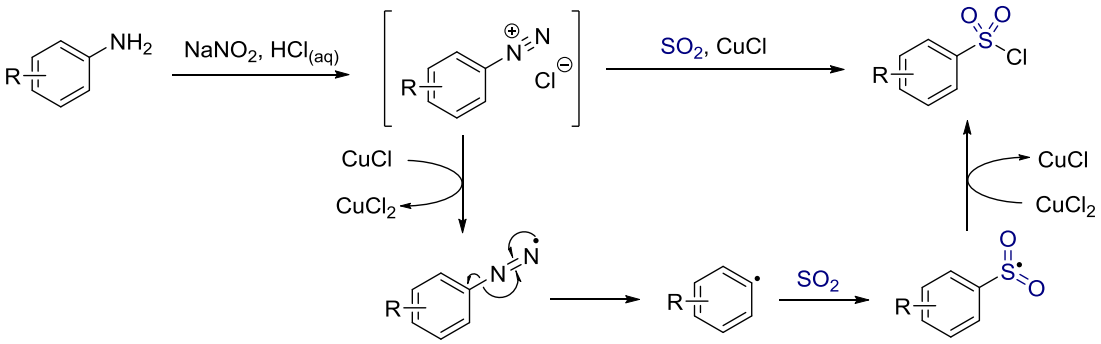
### 1.2.3 Sulfur dioxide and transition metals

The coordinating properties of sulfur dioxide as a ligand have been well studied for almost half a century with accompanying advances in the field of inorganic $SO_2$ reactions.[50] However, by contrast, far less progress has been made during this period with regard to metal-catalysed processes incorporating "$SO_2$", directed towards organic synthesis.

#### Radical chemistry

One of the earliest and most prominent examples of metal-catalysed $SO_2$ insertions is the Meerwein reaction.[51] This transformation is based on classical Sandmeyer radical chemistry[52] employing aryl diazonium substrates and a copper catalyst with the incorporation of sulfur dioxide to yield aryl sulfonyl chlorides (Scheme 1.14).[53] Once more, these products can be trapped *in situ* with amines.[54]

The diazonium salt generated *in situ* from the corresponding aniline undergoes $N_2$ extrusion mediated by the copper catalyst to give the aryl radical. In the presence of an excess of sulfur dioxide the aryl radical is intercepted by the $SO_2$ with chlorination of the sulfonyl radical delivering the sulfonyl chloride product.

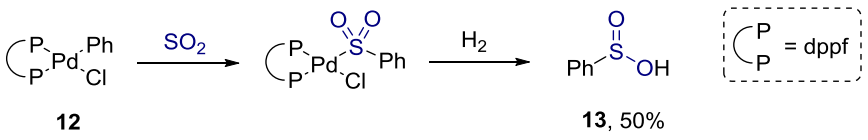



Scheme 1.14 Meerwein's sulfonylative Sandmeyer chemistry

## Sulfur dioxide M-C bond insertion

Due to its amphoteric nature, sulfur dioxide serves as an effective σ-donor and π-acceptor ligand when coordinating to transition metal centres. These characteristics bear close resemblance to carbon monoxide as a ligand. A wide range of coordination modes are possible in metal-$SO_2$ bonding and as such, a diverse history of stoichiometric transition metal-sulfur dioxide chemistry exists.[55] The earliest studies into transition metal-$SO_2$ reactions involved insertions into metal-carbon σ-bonds to generate metal-sulfonyl intermediates. Wojkicki was the first to demonstrate this with insertion into an iron-alkyl complex using liquid sulfur dioxide.[56]

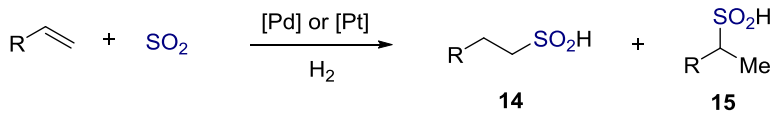
The first example of a synthetic organic chemistry application of sulfur dioxide M-C σ-bond insertion was presented by Pelzer *et al*. Employing a stoichiometric aryl palladium complex **12**, treatment with sulfur dioxide and subsequently hydrogen led to the formation of the corresponding sulfinic acid **13** in moderate yield (Scheme 1.15).[57]




**12** **13**, 50%

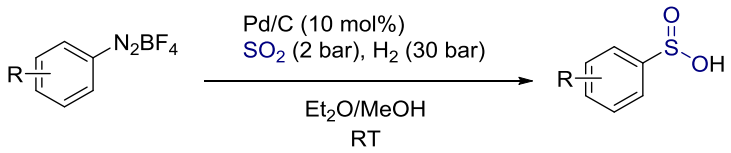
Scheme 1.15 $SO_2$ insertion into a Pd-C bond leading to sulfinic acids.

Very few examples of sulfonylative processes using catalytic transition metals followed this work. The most notable development came in the form of the hydrosulfination reaction;[58] the sulfonylative variant of hydroformylation. Both palladium(II) and platinum(II) catalysts were found to affect the reaction of alkenes with sulfur dioxide in the presence of hydrogen to form regiosomeric sulfinic acids **14** and **15** (Scheme 1.16).[57, 59]




Scheme 1.16 Pd and Pt catalysed hydrosulfination of alkenes.

Related to Meerwein's chlorosulfonylation reaction, Pelzer *et al*. developed a palladium-catalysed sulfination of diazonium salts.[57] Aryl sulfinic acids could be obtained by employing Pd/C as the catalyst, sulfur dioxide gas and a high pressure of hydrogen gas (Scheme 1.17).[60]




Scheme 1.17 Hydrosulfination of aryl diazonium salts

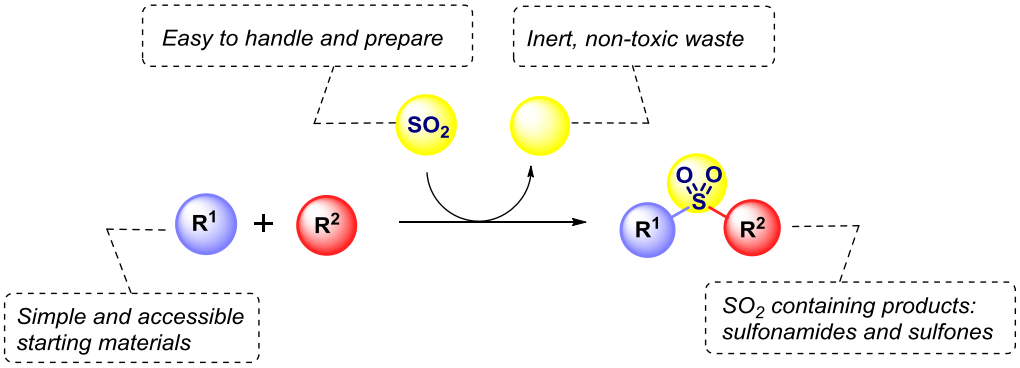
Despite these studies and the analogy between carbon monoxide and sulfur dioxide as ligands, sulfonylative transition-metal catalysed processes remained relatively unexplored. This is particularly surprising considering the rich history of metal-catalysed carbonylation processes and the potential for similar reactivity of $SO_2$.

While carbonylative cross-coupling has become one of the most prevalent classes of transformations in transition metal catalysis, sulfonylation chemistry has only recently gained significant attention (see Section 1.4). This could be qualified by the fact that sulfur dioxide is a highly toxic and gaseous reagent; although, carbon monoxide possesses similar properties. With the limited use of sulfur dioxide in transition metal-catalysed processes, the Willis group became interested in advancing this area.

## 1.3 Sulfur dioxide surrogates

Despite its versatility as a reagent and the established methods for its incorporation, sulfur dioxide is rarely employed in organic transformations to access sulfonyl-containing compounds. This is arguably due to the gaseous and highly toxic nature of sulfur dioxide which requires the use of specialist pressurised equipment and significant safety precautions. Controlling the amount of $SO_2$ added to reactions is also particularly difficult due to the gaseous nature and the reagent is usually used in excess. This has the potential to increase unwanted side reactions or specifically in transition-metal catalysed sulfur dioxide chemistry, sequester the catalyst. Hence new, safe, efficient and controlled methods of delivering sulfur dioxide to reaction systems to achieve $SO_2$ molecular incorporation are highly sought.

Sulfur dioxide surrogates are compounds that carry the $SO_2$ unit or under certain conditions undergo "decomposition" to form sulfur dioxide *in situ*. The application of these compounds as surrogates for sulfur dioxide in synthesis provides several potential advantages over use of the gas. Eradicating the requirement to use specialised equipment for delivering $SO_2$ gas and the hazards associated with using such a toxic and corrosive reagent on a regular basis is particularly attractive. The use of easily handled and prepared surrogates as replacements for the gas, whereby the residual carrier or by-products are inert in reactions serves as an appealing strategy (Scheme 1.18). With the aforementioned prevalence of sulfonyl-containing compounds in pharmaceutical and agrochemical products, the development of such safe and efficient means of preparing these compounds is particularly advantageous for industrial applications.




Scheme 1.18 General outline for the use of sulfur dioxide surrogates in organic chemistry.

### 1.3.1 Amine-sulfur dioxide complexes

Complexes between amines and sulfur dioxide have been known for over a century and can be prepared by directly combining the two precursors.[61] Studies involving amine-sulfur dioxide complexes, until recently, focused mainly on spectroscopic investigations into the structure and bonding of various alkylamine-$SO_2$ adducts.[62] The formation of these charge-transfer complexes centres on the donation of the nitrogen lone pair to the empty sulfur dioxide LUMO resulting in a dative covalent N-S bond (Figure 1.2).

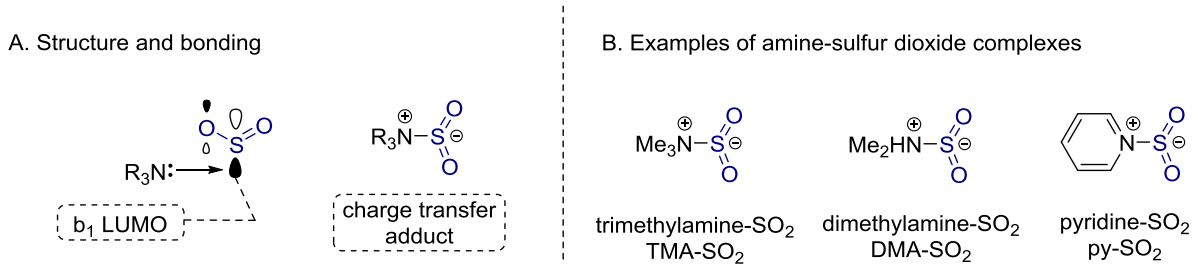
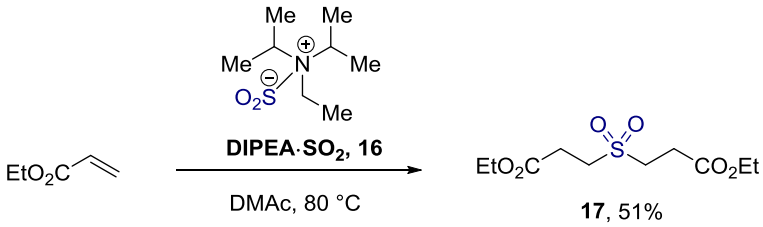



Figure 1.2 Amine-sulfur dioxide complexes.

The strength of the N-S bond and hence the stability of the complex is dependent on the donor ability of the nitrogen of the amine. In accordance with frontier molecular orbital (FMO) theory, an amine with a higher-lying HOMO closer in energy to the LUMO of the $SO_2$ will serve as a better donor due to the increased stabilisation energy on forming the complex. This larger enthalpy gain results in a stronger N-S bonding interaction and as a result a more thermodynamically stable donor-acceptor adduct. For example, studies have shown that the bonding in alkyl complexes such as TMA-$SO_2$ is stronger than in the py-$SO_2$ complex, with the former proving more stable.[63]

Although amine-$SO_2$ complexes and their preparation have been well established since the early twentieth century, few synthetic applications materialised during this period. Eugene *et al.* initially demonstrated the potential of these complexes for $SO_2$ incorporation with the observation that the diisopropylethylamine-$SO_2$ complex **16** in combination with a Michael acceptor affords the corresponding symmetrical sulfone **17** in a moderate yield (Scheme 1.19).[64]




Scheme 1.19. An early example of an amine-$SO_2$ complex affecting $SO_2$ incorporation.

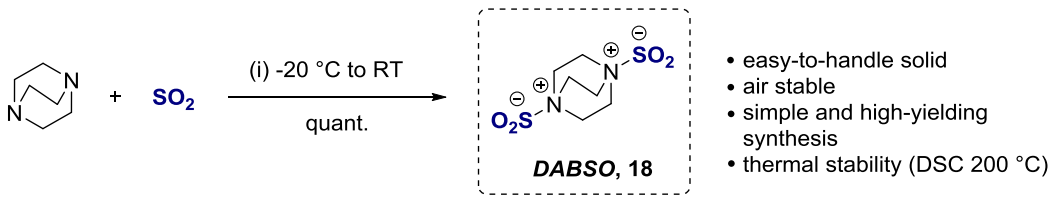
A more established example of an amine-sulfur dioxide complex being employed in organic synthesis was introduced by Olah and co-workers in the late 1970s, with the use of the trimethylamine-sulfur dioxide complex to affect a range of reduction and dehydration reactions.[65] Such transformations include the dehalogenation of α-halo-ketones[66] and the reduction of sulfoxides[67] and pyridine *N*-oxides.[68] Further to this, the same authors also developed a polymeric amine-sulfur dioxide complex, PVP(poly-4-vinylpyridine)·$SO_2$, and demonstrated its application as a mild acid catalyst in Strecker reactions.[69]

## 1.4 Amine-sulfur dioxide complexes as $SO_2$ surrogates in organic synthesis

Recently, research within the Willis group has focused on the development of novel methodologies employing amine-sulfur dioxide complexes to achieve molecular incorporation of $SO_2$. These species satisfy the criteria for an effective sulfur dioxide surrogate, serving as a safe and convenient source of $SO_2$. Many of the complexes are stable solids and can therefore be delivered to reactions with much greater ease and importantly, in a measured fashion. Studies initially focused on the use of the *bis*-complex formed between DABCO and sulfur dioxide, 1,4-diazabicyclo[2.2.2]octane *bis*(sulfur dioxide) (DABCO.$SO_2$, 'DABSO'). This charge transfer adduct has served as the basis of most studies in this thesis.

### 1.4.1 1,4-Diazabicyclo[2.2.2]octane *bis*(sulfur dioxide), DABSO

The *bis*-$SO_2$ charge transfer adduct of DABCO **18**, named DABSO, was first prepared by Mello *et al*. in 1988 and as with many amine-sulfur dioxide complexes it was only the focus of spectroscopic studies.[70] DABSO is easily prepared by condensing sulfur dioxide directly onto solid DABCO (Scheme 1.20). Warming the reaction to room temperature to evaporate the remaining $SO_2$ gas allows DABSO to be isolated as a pure solid without the need for further purification. Alternatively, DABSO is also accessible from DABCO and Karl Fischer reagent.[71] The white crystalline solid is air-stable and easily handled so it can be added to reactions in a much more practical and measured fashion in comparison to the gas.

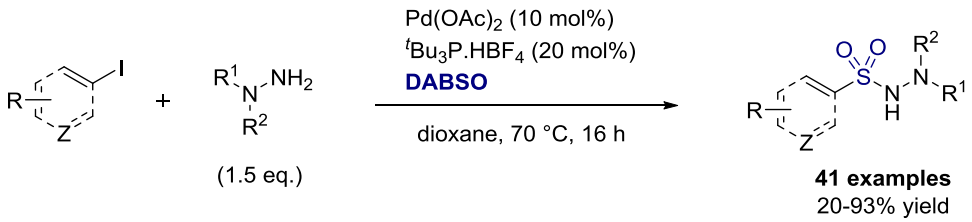



Scheme 1.20 Formation of the complex DABSO.

As a *bis*-complex DABSO is >50 wt% $SO_2$, offering the advantage of delivering two moles of $SO_2$ per mole of complex and minimising the inherent amine carrier waste. Furthermore, the residual tertiary amine is relatively inert, particularly in comparison to primary or secondary amines. DABSO also possesses thermal (DSC 200 ºC) and vacuum stability.

### 1.4.2 Applications of DABSO in transition metal catalysis

The application of DABSO as a sulfur dioxide surrogate by the Willis group initially focused on $SO_2$ insertions in metal catalysis. Such sulfonylative processes bear analogy with the well-established carbonylation chemistry of carbon monoxide in transition metal catalysis. The group pioneered the use of DABSO in a palladium-catalysed aminosulfonylation reaction. The sulfonylative coupling of aryl iodides and hydrazines could be affected with a palladium(0) catalytic system in the presence of DABSO (Scheme 1.21).[72] The mechanistic rationale for this process took inspiration from the palladium catalysed aminocarbonylation coupling of aryl halides with amines and CO.

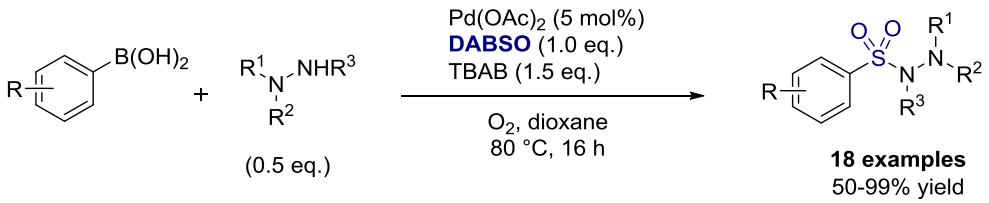



Scheme 1.21 Palladium catalysed aminosulfonylation reaction using DABSO

*Reaction conditions*: DABSO (0.6 equiv.) and DABCO (0.5 equiv.), or DABSO (1.1 equiv.).

In addition to aryl iodides bearing electron-withdrawing and -donating groups the reaction was found to work well with heteroaryl and alkenyl iodide substrates.[73] Interestingly, only hydrazines were capable of serving as the nucleophilic coupling partner in this system with amines proving unreactive under these conditions.

During the course of this PhD further studies into the applications of DABSO in metal catalysis were reported. Initially, Wu *et al*. performed analogous aminosulfonylation chemistry with the use of arylboronic acid substrates under oxidative conditions (Scheme 1.22).[74]

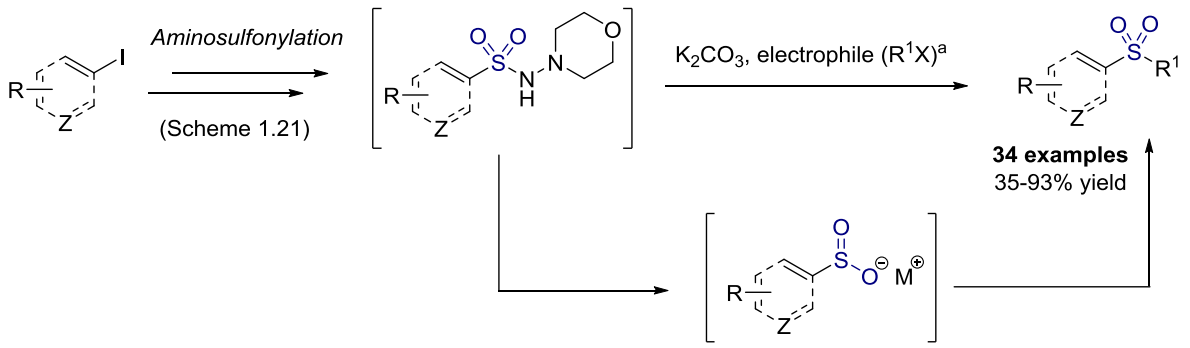



Scheme 1.22 Boronic acids as substrates in the oxidative aminosulfonylation process.

Further to this, the same authors developed a C-H activation/aminosulfonylation sequence employing a gold(II)/palladium(II) co-catalytic system.[75] The same *N*-aminosulfonamide products can be obtained *via* gold-catalysed arene C-H iodination with the aryl iodide intermediate undergoing *in situ* aminosulfonylation.

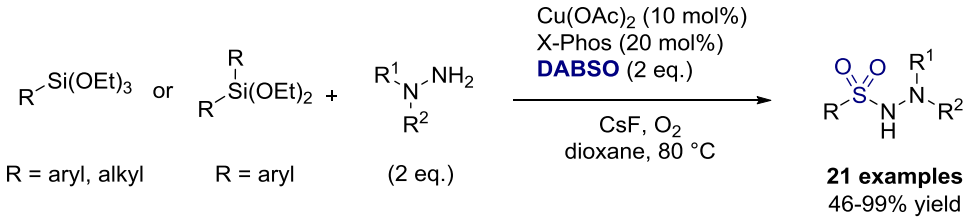
Following on from these initial studies into DABSO as a sulfur dioxide surrogate, similar applications of the inorganic compound potassium metabisulfite ($K_2S_2O_5$) were established and are discussed later (Section 1.4.4).

As a progression on the aminosulfonylation reaction, our group was able to exploit the *N*-aminosulfonamide products as precursors to sulfinates.[76] A one-pot format with an initial aminosulfonylation step, followed by the *in situ* basic deprotection of the aminosulfonamide to give the sulfinate and subsequent electrophilic trapping, delivered sulfone products (Scheme 1.22).




Scheme 1.22 One-pot sulfone synthesis based on the palladium catalysed aminosulfonylation of aryl iodides. [a] *Reaction Conditions*: $K_2CO_3$ (2.5 equiv.), electrophile (2.5 equiv.), $H_2O$, 90 ºC or $K_2CO_3$ (2.5 equiv.), BnBr (0.95 equiv.), 90 ºC, 1 h, then electrophile (2 equiv.), 19 h.

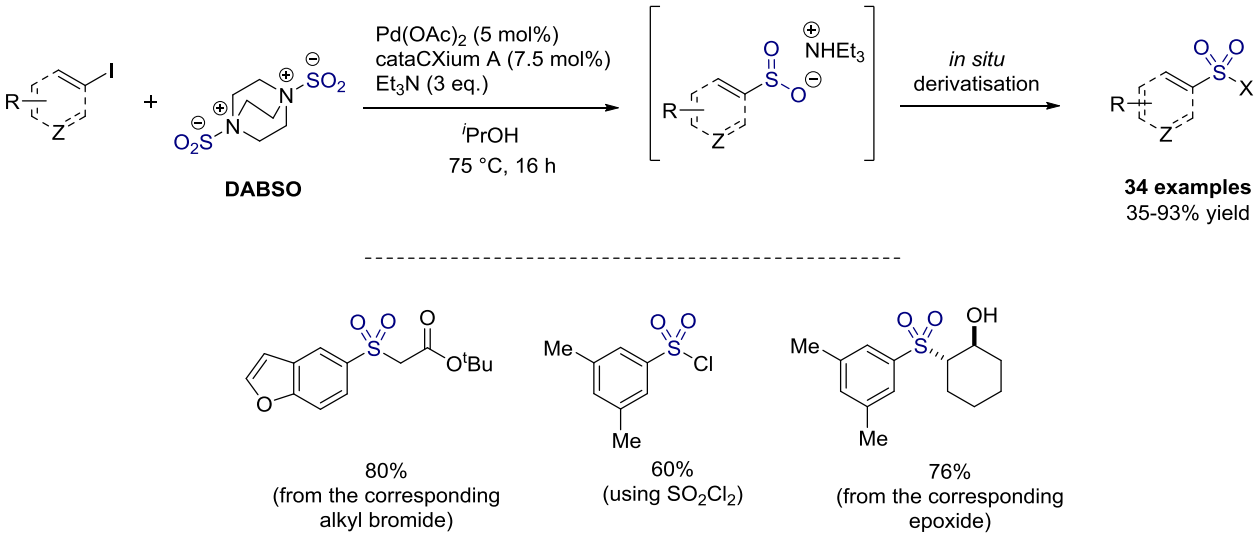
Wang *et al*. provided another version of the aminosulfonylation reaction with the development of a copper(II)-catalysed sulfonylative coupling of aryl(alkoxy)silanes and hydrazines in the presence of DABSO, under oxidative conditions (Scheme 1.23).[77]




Scheme 1.23 Cu-catalysed aminosulfonylation reaction employing aryl silanes.

Both aryl and alkyl triethoxysilanes were compatible with this system, as well as diethoxydiarylsilanes. Interestingly, as with other studies involving palladium catalysis, only hydrazines served as effective coupling partners, with no reaction observed with amines.

More recently, the Willis group demonstrated the effectiveness of DABSO as a sulfur dioxide source in the formation of sulfinic acid salts using palladium catalysis. This work was based on the established reaction of $SO_2$ gas with aryldiazonium salts and a palladium catalyst to generate sulfinic acids under reductive hydrogenation conditions (see section 1.2.3). Aryl and heteroaryl iodides could be converted into the corresponding ammonium sulfinates by employing a palladium(0) catalyst and *iso*propanol as the solvent and co-reductant, together with DABSO (Scheme 1.24).[78] These species could be subsequently derivatised *in situ* allowing access to a wide range of sulfonyl-containing compounds.



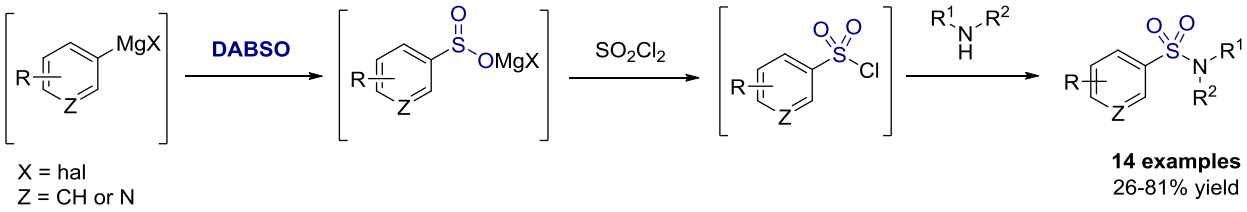

Scheme 1.24 Pd-catalysed ammonium sulfinate synthesis using DABSO.

Not only does this system avoid the need for high pressure sulfur dioxide gas, but also exploits *iso*propanol as a more attractive and convenient reductant. Other variants of this reaction have also been developed using alternative $SO_2$ sources and catalytic systems (see section 1.4.4).

### 1.4.3 Applications of DABSO in non-transition metal catalysis

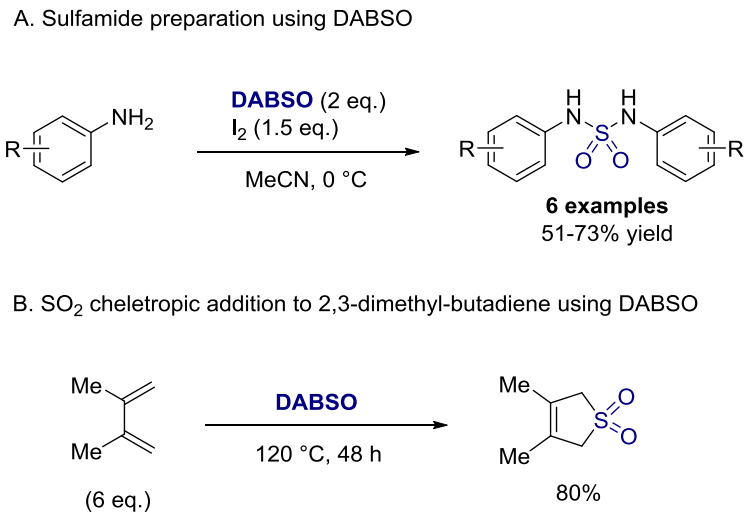
As well as leading the way in sulfonylative transition-metal catalysis, DABSO has been employed as an efficient replacement for sulfur dioxide gas in general organic chemistry.

The Willis group demonstrated this initially with the development of a streamlined version of Barrett's sulfonamide synthesis (see section 1.1.1).[24] Combining Grignard reagents with DABSO *in lieu* of $SO_2$ gas was found to generate the corresponding magnesium sulfinate which was successfully converted to the sulfonamide product *in situ*, employing Barrett's oxidative chlorination and amine trapping sequence (Scheme 1.25).[79]



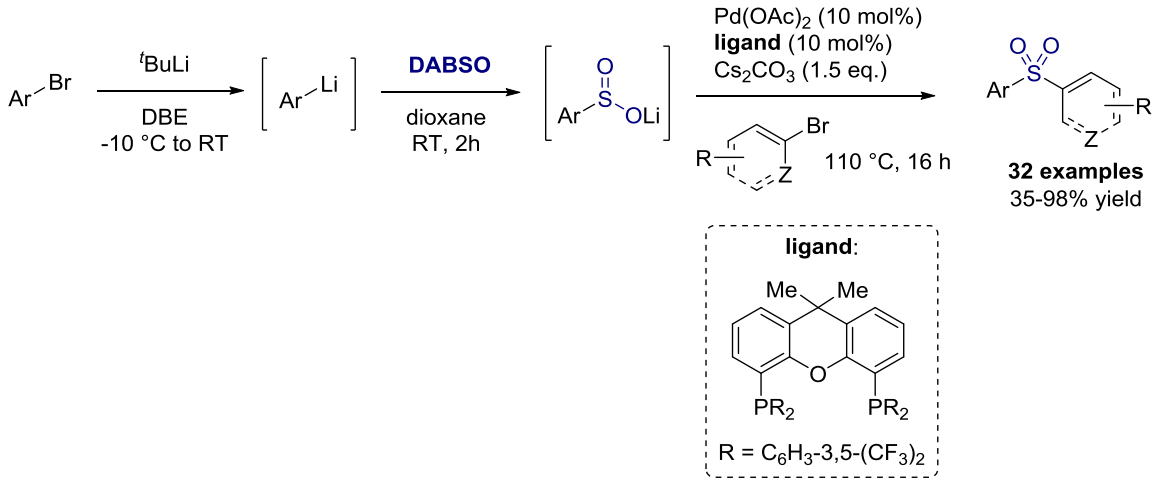

Scheme 1.25 Stepwise sulfonamide synthesis employing DABSO and Grignard reagents.

This report also exemplified the proficiency of DABSO to serve as a sulfur dioxide substitute in cheletropic additions and for the synthesis of sulfamides (Scheme 1.26).[80]



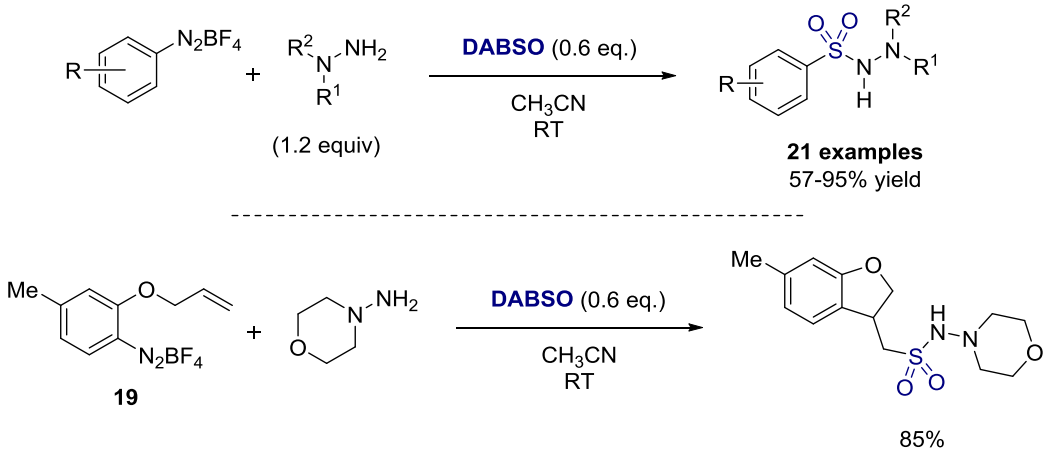

Scheme 1.26 Further applications of DABSO in a cheletropic addition and sulfamide synthesis.

The DABSO-based sulfination of organometallic reagents was extended to aryllithium reagents by the Willis group. Lithium sulfinates prepared *in situ* were subjected to palladium(0)-catalysed coupling with aryl bromides to afford diaryl sulfones (Scheme 1.27).[81]




Scheme 1.27 Pd-catalysed diaryl sulfone synthesis employing lithium sulfinates generated from DABSO and organolithiums.

An interesting progression of the palladium-catalysed aminosulfonylation reaction (section 1.4.2) was established by Wu *et al*. with metal-free conditions, employing diazonium salts and DABSO (Scheme 1.28).[82] It is proposed that this process takes place *via* a radical-based mechanism with the use of 2-allyloxy-derived aryldiazonium salt **19** delivering the 5-exo-trig cyclised product.

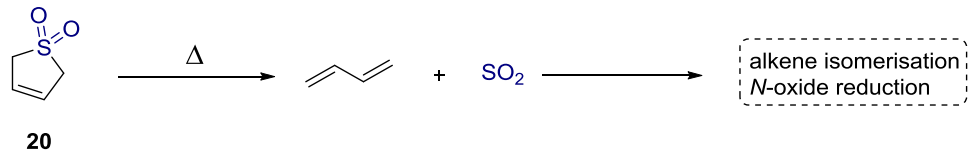



Scheme 1.28 Metal-free aminosulfonylation reaction employing diazonium salts.

Their radical-based intramolecular cyclisation/sulfonylation process was expanded to a one-pot process involving *in situ* diazotisation of aniline substrates to deliver 3-sulfonamide derived dihydrobenzofuran products.[83]

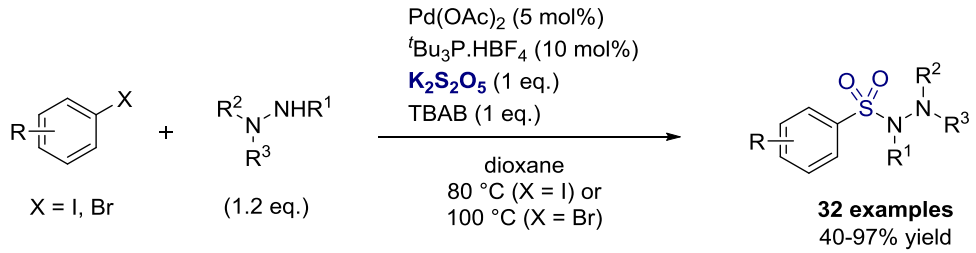
### 1.4.4 Applications of alternative sulfur dioxide surrogates

Although the use of sulfur dioxide surrogates in synthesis has only recently gained significant attention, as early as the 1970s sulfolene **20** was demonstrated as a source of $SO_2$ for organic reactions.[84] Subjecting **20** to high temperature, results in equilibration to butadiene and sulfur dioxide, with the latter being consumed *in situ* to effect alkene isomerisation or a reduction process (Scheme 1.29).



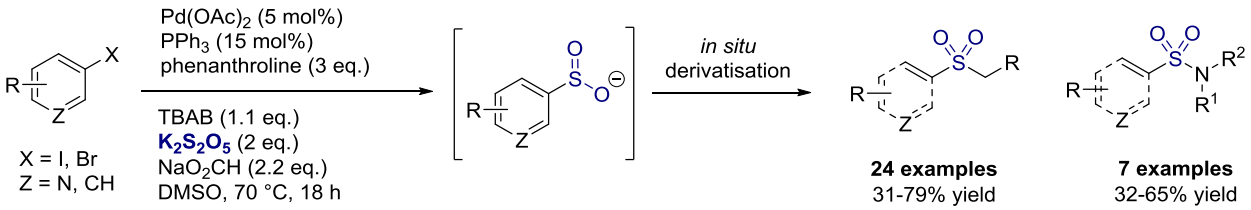

Scheme 1.29 Sulfolene as an $SO_2$ source in organic chemistry.

More recently, inorganic sulfite salts have emerged alongside DABSO as sources of $SO_2$.[85] Potassium metabisulfite, in particular, has been demonstrated as a sulfur dioxide surrogate in a number of metal-catalysed transformations. The first example was provided by Wu *et al.* with the use of $K_2S_2O_5$ in place of DABSO in the palladium-catalysed aminosulfonylation reaction (Scheme 1.30).[86]



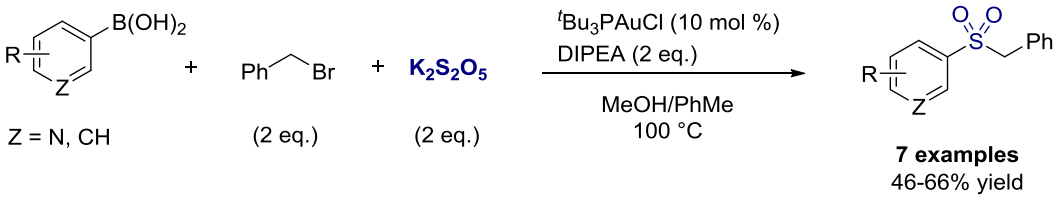

Scheme 1.30 Pd-catalysed aminosulfonylation reaction with potassium metabisulfite.

A group from Pfizer reported a palladium-catalysed synthesis of (hetero)aryl sulfinates from the corresponding halides employing $K_2S_2O_5$; a process bearing analogy to the DABSO-based system developed by the Willis group (Section 1.4.3). In this work, sodium formate was used as a formal reductant along with both triphenylphosphine and phenanthroline as ligands to deliver sulfones and sulfonamides in one pot (Scheme 1.31). [87]




Scheme 1.31 Potassium metabisulfite based, Pd-catalysed sulfinate synthesis.

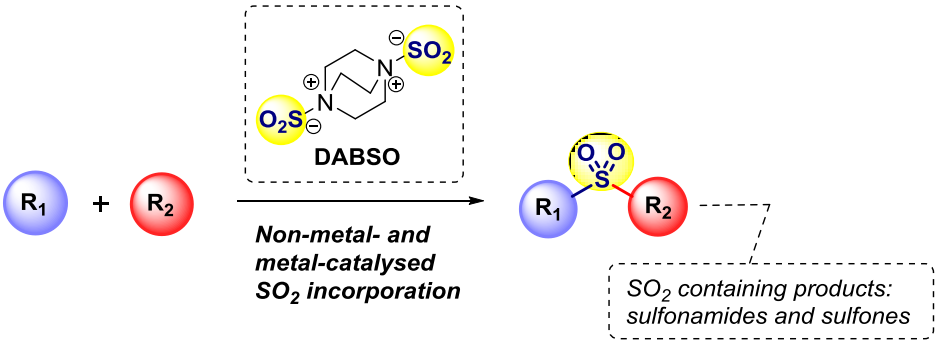
Employing $K_2S_2O_5$, the same authors in collaboration with the Toste group, reported the first example of sulfur dioxide insertion using gold catalysis.[88] Aryl sulfinate salts could be generated from the corresponding boronic acids and functionalised in a similar fashion to previous work.[78,87] With this catalytic system sulfones were also prepared in a one-step manner with benzyl bromide present from the start of the reaction (Scheme 1.32).




Scheme 1.32 Au-catalysed sulfinate formation and trapping from boronic acid substrates.

## 1.5 Project aims

With the discovery of DABSO as an effective sulfur dioxide surrogate in the palladium-catalysed aminosulfonylation reaction and in combination with Grignard reagents, this DPhil project set out to further explore the potential applications of amine-sulfur dioxide complexes in organic synthesis. As with initial studies conducted in the Willis group, this research centred on the use of DABSO as an $SO_2$ source to develop novel methodologies towards the synthesis of salient sulfonyl-containing compounds, such as sulfones and sulfonamides (Scheme 1.33).




Scheme 1.33 General outline of project aims employing DABSO.

# 2. A one-pot sulfone synthesis using DABSO and organometallic reagents

## 2.1 Applications and preparation of sulfones

Sulfones are one of the most important classes of sulfonyl-containing compounds, possessing key physiochemical properties. The most prominent properties exemplified by sulfones bearing aryl, alkyl, or vinyl groups are antibacterial,[89] anti-tumour[90] and anti-fungicidal activity.[91] As such, the R-$SO_2$-R moiety is found in many biologically active entities and is often central to medicinal chemistry and agrochemical targets (Figure 2.1). In an analogous fashion to sulfonamides, sulfone based antibiotics serve to inhibit bacterial folic acid synthesis. Hence many pharmaceutical agents bearing the sulfone motif have been employed for treatments of conditions such as pneumonia, tuberculosis and acne. Diaryl sulfones, in particular, have gained attention as potent inhibitors of the HIV-1 reverse transcriptase enzyme resulting in the emergence of this subclass in anti-HIV targets.[92,93] In addition, anti-tumour agents bearing the sulfone functional group have been developed in the treatment of certain types of cancer.[94]

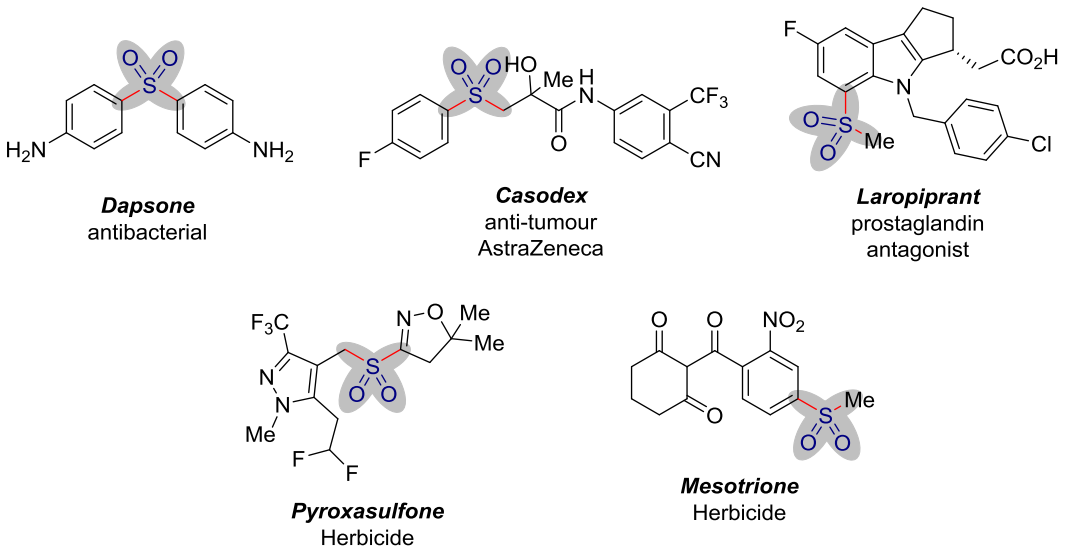
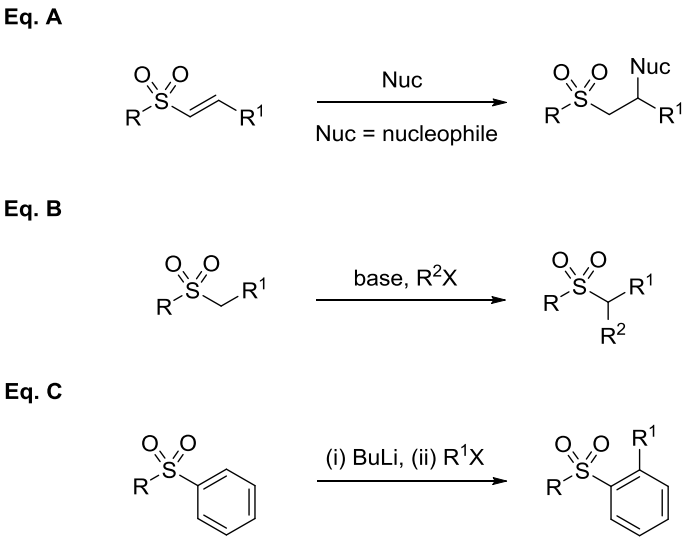



Figure 2.1 Examples of commercial sulfone-containing products.

In addition to synthetic applications in the Julia olefination[12] and Ramberg Bäcklund[13] reactions (Section 1.1.1), sulfones have found utility as functional groups in other transformations whereby the sulfonyl unit has remained intact, as opposed to serving as a leaving group. Examples include Michael additions to *α,β*-unsaturated sulfones (Eq. A, Scheme 2.1)[95] and α-deprotonation/alkylation sequences of saturated substrates (Eq. B).[96]

As well as this, the sulfone moiety has been demonstrated as an effective directing group for installing *ortho*-functionality. In particular, *ortho*-lithiations of aryl sulfones have been shown to be an effective strategy with subsequent electrophilic trapping (Eq. C).[14] Hence, not only is the sulfone functionality important for biological activity in medicinal targets but it can also serve as an effective group for constructing such building blocks.




Scheme 2.1. Methods for derivatising sulfone building blocks.

As a result of the prevalence of sulfones in biologically active agents and medicinal, agrochemical and synthetic building blocks, efficient and versatile methods for their synthesis are highly sought. The most common strategy for accessing the various classes of sulfones (aryl, alkyl and alkenyl combinations) is oxidation of the corresponding sulfide.[19,20,97] This method necessitates a two-step protocol with initial formation of the sulfide from the corresponding thiol. Significantly, not only does this synthesis suffer from the use of

malodorous thiol reagents but also from the restricted availability of alkenyl and heterocyclic variants of these substrates. In addition, the use of oxidative conditions (e.g. $H_2O_2$, *m*CPBA, $NaIO_4$) can have negative implications for the functional group tolerance of such syntheses.

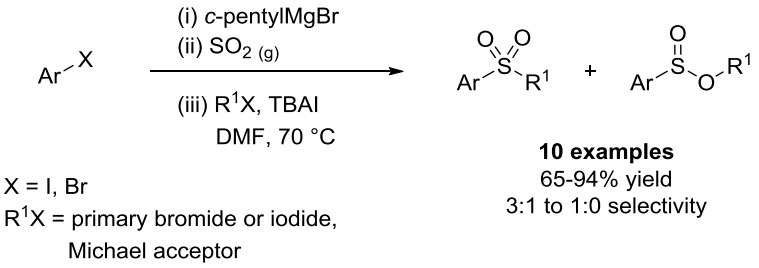
## 2.2 Sulfinate salts as precursors to sulfones

As described in Section 1.1.3, sodium sulfinates have been employed as substrates for the preparation of sulfones. In particular, systems designed for the synthesis of diaryl sulfones have received significant attention. Palladium- and copper-catalysed couplings[27-30] and $S_NAr$ reactions[26] are the most common routes to unsymmetrical diaryl sulfones *via* the commercially available sodium sulfinates (Section 1.1.3). These methods suffer from the limited commercial availability of sodium sulfinic acid salts, with only methyl-, benzene- and *p*-tolyl-derivatives readily accessible. The sodium salts can also be prepared from the corresponding sulfonyl chloride using sodium sulfite.[98] However, extension of the scope of sulfones accessible *via* this route necessitates a further step and is limited by the commercial availability of sulfonyl chlorides and the harsh conditions required for their synthesis (Section 1.1.1).

The Willis group's work on the DABSO-based, palladium-catalysed coupling of aryl lithium sulfinates and aryl bromides offers an alternative to these approaches (Section 1.4.3).[81] Despite providing further scope for the synthesis of diaryl sulfones, this system was limited to aryl lithium precursors; with alkyl and heteroaryl variants and Grignard reagents proving incompatible with the reaction.

The application of sodium sulfinates to access sulfones *via* electrophilic trapping has also been explored, but once more these protocols are only demonstrated with the commercially available salts.[99] Such examples include $S_N2$ reactions with alkylating agents as well as $S_NAr$ processes with activated aryl halides (Section 1.1.3). Alkylation of magnesium sulfinates generated from Grignard reagents and sulfur dioxide gas has also been reported, but in this case sulfones were obtained along with the sulfinic acid esters (*O*-alkylation) in generally moderate selectivity (Scheme 2.2).[100] In addition, this protocol remains unattractive due to the use of an excess of gaseous $SO_2$. Further transformations involving sulfinates as

nucleophilic precursors to sulfones include Michael additions,[101] epoxide ring openings[102] and reactions with iodonium salts.[103]

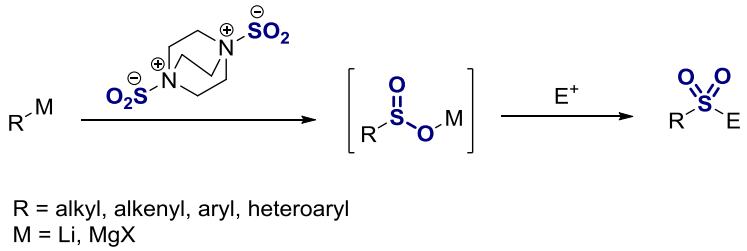



Scheme 2.2 Alkylation of magnesium sulfinates resulting in mixtures of sulfones and sulfinic acid esters.

## 2.3 Project outline

With the limited substrate scope offered by conventional sodium sulfinate-based sulfone syntheses and the requirement for sulfur dioxide gas to access the salts derived from organometallic reagents, a more robust and versatile means of accessing sulfones is highly sought. It was the aim of this project to develop such a system by employing the $SO_2$ surrogate DABSO and satisfying the following criteria; a one-pot protocol employing easily accessible and readily handled reagents and providing access to a variety of sulfone products covering different combinations of aryl, heteroaryl, alkenyl and alkyl groups.

The generation of metal sulfinates from organometallic reagents and DABSO was identified as a potentially general and efficient route towards sulfones. Employing DABSO as an easily-handled and convenient source of sulfur dioxide would allow for simple access to the sulfinate precursors avoiding the use of high excesses of $SO_2$ gas. With such an attractive route to sulfinates, it was hoped that (hetero)aryl, alkyl and alkenyl derivatives could be prepared and serve as effective nucleophilic precursors in combination with a range of carbon-based electrophiles *in situ*. Overall, with the use of readily accessed and prepared organometallic reagents and DABSO as a convenient source of $SO_2$, an effective one-pot coupling process would serve as an attractive method for accessing sulfones (Scheme 2.3).



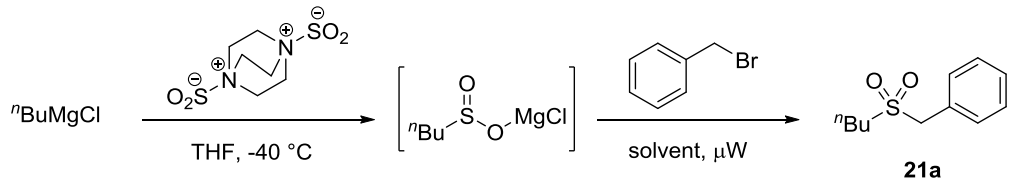

Scheme 2.3 General outline for DABSO-based sulfone synthesis.

With the combination of DABSO and Grignard reagents proving effective in the Willis group's sulfonamide synthesis (Section 1.4.3),[79] we aimed to establish whether, under these conditions, both lithium and magnesium sulfinates could undergo a variety of coupling reactions with carbon-based electrophiles to deliver the desired diverse range of sulfones.

## 2.4 Reaction conditions and optimisation

Studies into the sulfone synthesis were initiated by examining the *in situ* electrophilic trapping of alkyl magnesium sulfinates. Using *n*-butylmagnesium chloride and DABSO to generate the sulfinate and with benzyl bromide as the electrophile, conditions to affect *S*-alkylation were explored (Table 2.1). Initially, THF was maintained as the solvent for the second step and with conventional and microwave heating the desired alkyl-benzyl sulfone **21a** could be obtained in low to moderate yields (Entries 1 to 3, Table 2.1). Based on the higher yield and shorter reaction time from microwave heating, this method was maintained for the majority of the screening experiments. On moving to a water/THF co-solvent system only a slight improvement in yield was observed, with competing hydrolysis of the benzyl bromide observed (Entry 4). Employing the polar, aprotic solvent DMF with THF resulted in a 10% increase in yield (Entry 5) and this was further improved by using DMF solely (Entry 6). The optimum set of conditions was realised with DMF as the solvent at 120 °C and a reaction time of 3 hours with microwave heating (Entry 7). Subjecting the sulfinate intermediate to a higher microwave temperature of 150 °C (Entry 8) or conventional heating of 120 °C (Entry 11) offered little or no improvement in yield.

Table 2.1 Initial screening and optimisation of conditions for *S*-alkylation of DABSO-generated magnesium sulfinates.




| Entry | Solvent | Temp | Time | Yield |
|---|---|---|---|---|
| **1** | THF | 120 °C | 1 h | 49% |
| **2** | THF | 70 °C[a] | 16 h | 30% |
| **3** | THF | 120 °C | 2 h | 55% |
| **4** | THF/$H_2O$ | 120 °C | 2 h | 58% |
| **5** | THF/DMF | 120 °C | 2 h | 68% |
| **6** | DMF | 120 °C | 2 h | 80% |
| **7** | DMF | 120 °C | 3 h | 85% |
| **8** | DMF | 150 °C | 3 h | 86% |
| **9** | DMF | 120 °C[b] | 3 h | 85% |
| **10** | DMF | 70 °C[a] | 16 h | 78% |
| **11** | DMF | 120 °C[a] | 16 h | 81% |
| **12** | EtOH | 120 °C | 3 h | 68% |
| **13** | DMAc | 120 °C | 3 h | 72% |

*Reaction conditions*: $^n$BuMgCl (0.25 mmol, 1 equiv.), DABSO (1 equiv.), THF, -40 °C *then* benzyl bromide (3 equiv), solvent and microwave. [a] overnight conventional heating. [b] 5 equiv. benzyl bromide.

Examining alternative protic (Entry 12) and aprotic (Entry 13) solvents also offered no improvement, with reduced yields observed in both cases. Under all of these conditions we were pleased to note that only *S*-alkylation was accomplished with the sulfinic acid ester (*O*-alkylation) product not detected.

## 2.5 Initial reaction scope

With an optimised set of conditions in hand the scope of organometallic reagents – and hence sulfinates generated *in situ* – was examined. Pleasingly, it was found that both lithium and magnesium sulfinates, in combination with benzyl bromide, delivered the corresponding sulfones in good yields; little difference in reactivity was observed between the different counterions. Sulfinate intermediates derived from a range of alkyl, alkenyl, aryl and heteroaryl organometallic reagents were successfully generated and alkylated (Figure 2.2).

As anticipated, alkyl sulfinates and aromatic variants bearing electron donating groups served as the most effective nucleophiles with the corresponding sulfones obtained in high yields. Alkenyl and electron-poor aromatic organometallic reagents were found to be less reactive but the desired products could be accessed in moderate to good yields with the use of a higher excess of the electrophile or an extended reaction time. Aryl Grignard and organolithium reagents that are not commercially available could be simply generated and employed *in situ via* magnesium-halogen (e.g. **21k**) or lithium-halogen exchange (e.g. **22b**).

A particularly pleasing aspect of this system was the use of *N*-methylindole (**22f**) and benzothiazole (**22e**) as substrates to generate challenging heteroaromatic sulfone products. Selective lithiation was achieved through deprotonation by butyllithium allowing these heterocycles to be converted into functionalised sulfones in one-pot.

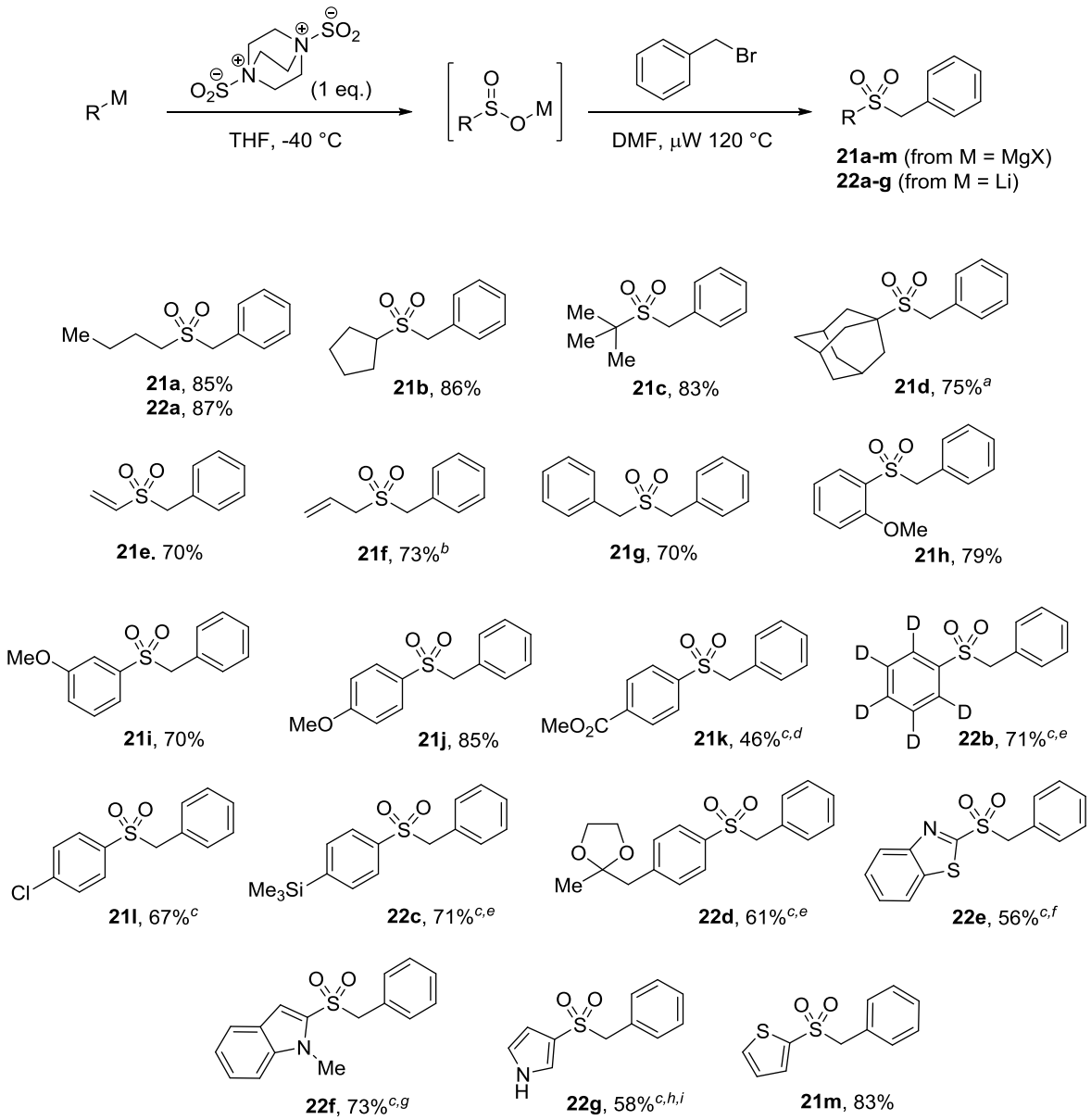



Figure 2.2 Organometallic scope for benzyl sulfone synthesis.

*Reaction conditions*: Organometallic (0.25 mmol, 1 equiv., commercial reagent unless stated), DABSO (1 equiv.), THF, -40 °C *then* benzyl bromide (3 equiv.), DMF, 120 °C using microwave heating, 3 h. [a] RMgBr generated from the corresponding bromide and Mg turnings. [b] Using 5 equiv. BnBr and microwave heating for 5 h. [c] Using 5 equiv. BnBr. [d] RMgCl generated from the corresponding iodide and $^{i}$PrMgCl. [e] RLi generated from the corresponding bromide and $^{n}$BuLi. [f] RLi generated *via* deprotonation with $^{n}$BuLi. [g] RLi generated *via* deprotonation with $^{t}$BuLi. [h] RLi generated from the corresponding bromide and $^{t}$BuLi. [i] Product obtained from TIPS-protected starting material.

The product **22e** belongs to a class of benzothiazol-2-yl derived sulfones employed as substrates in the modified Julia olefination.[12] The use of such heteroaromatic alkyl sulfones allows for a simpler preparation of alkenes, removing the need for a sodium/mercury amalgam reduction.

At the time of carrying out this study, a group from Pfizer was at a similar stage with related research into the combination of DABSO and organozinc reagents to access sulfones. The *in situ* generated alkyl and aryl zinc sulfinates could be efficiently trapped with alkyl halides.[104]

Following on from the organometallic substrate scope, the range of electrophiles compatible with this system was explored. Initially the use of alternative alkyl halides was examined (Figure 2.3).

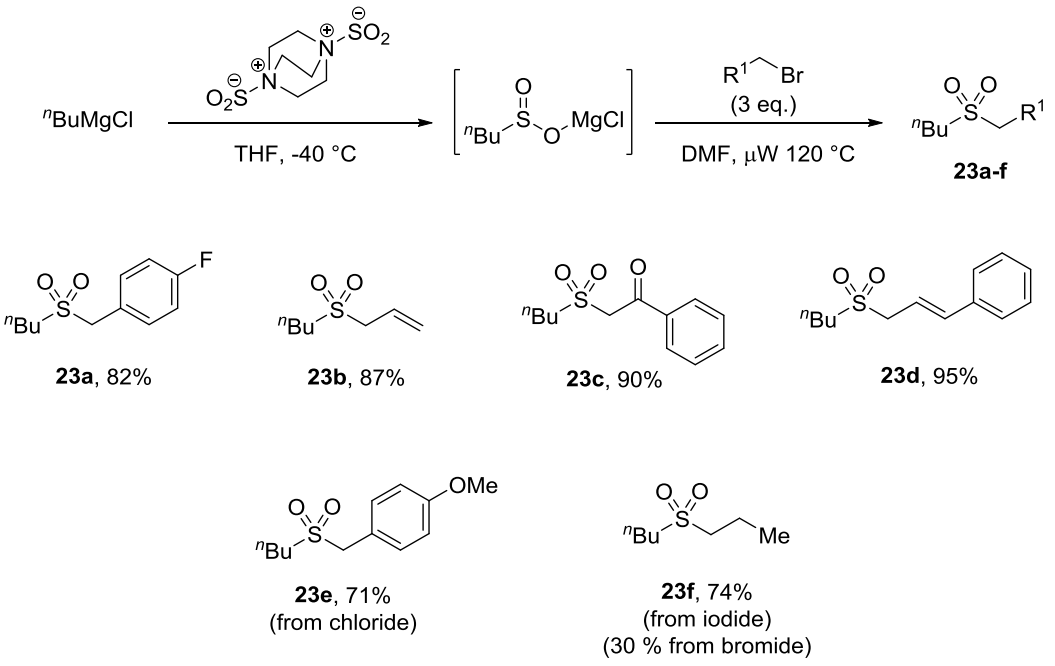



Figure 2.3 Alkyl halide scope in sulfinate trapping.

A range of alkyl bromides served as effective coupling agents with allyl (**23b**), *β*-keto (**23c**), styryl (**23d**) and functionalised benzyl sulfones (**23a**) accessible in good to high yields. Benzyl chlorides were also found to be effective electrophiles in combination with the alkyl magnesium sulfinate (**23e**). The sulfinate reactivity limit was identified when employing

*n*-propyl bromide as the electrophile. Dialkyl sulfone **23f** was obtained in a reduced yield with this less activated alkyl bromide. However, this reactivity constraint could be simply overcome with the use of the corresponding iodide providing a much improved yield of **23f**.

## 2.6 Further electrophile reaction scope – access to an extended range of sulfone products

Having examined the electrophilic trapping of magnesium and lithium sulfinates with alkyl halides, subsequent experiments focused on expanding the classes of sulfones accessible using this system. Up to this point, sulfinate alkylations had allowed for the synthesis of alkyl sulfones incorporating alkyl, vinyl, aryl and heteroaryl functionality from the sulfinate precursor. By exploiting their simple preparation using DABSO, it was hoped that both magnesium and lithium sulfinates could be derivatised with other carbon-based electrophiles in one-pot to deliver a diverse collection of sulfones.

### 2.6.1 Diaryliodonium salts as electrophiles

As mentioned previously, diaryl sulfones are a particularly prominent class of medicinally active compounds. More recently, the sulfone functional group has emerged as a core component of drug targets for the treatment of HIV.[92,93] Therefore, the ability to construct diaryl sulfones was identified as a key requirement for this chemistry.

Diaryliodonium salts have recently been employed as effective electrophilic aromatic coupling partners in both metal-[105] and non-metal catalysed reactions.[106] These hypervalent iodine reagents act as $[Ar]^+$ synthons generating an aryl iodide leaving group in the process. We envisaged that metal sulfinates generated from DABSO could undergo coupling with symmetrical diaryl iodonium salts. At a similar time, Manolikakes *et al.* reported the reaction of iodonium salts with sodium sulfinates[103] and later lithium sulfinates[107] generated from the corresponding aryl lithium reagents and sulfur dioxide gas. Considering the potential benefits of a DABSO-based preparation of diaryl sulfones – avoiding the need to prepare sodium

sulfinates or employ $SO_2$ gas – symmetrical diaryliodonium salts were assessed as electrophilic aromatic counterparts.

By initially employing diphenyliodonium triflate and the previously established conditions for the alkylation of metal sulfinates, the desired phenyl group transfer was achieved with both alkyl and aromatic substrates. Alkyl-aryl (**24b**) and diaryl sulfones (**24a, c and d**) were obtained in good yields under microwave heating (Figure 2.4).

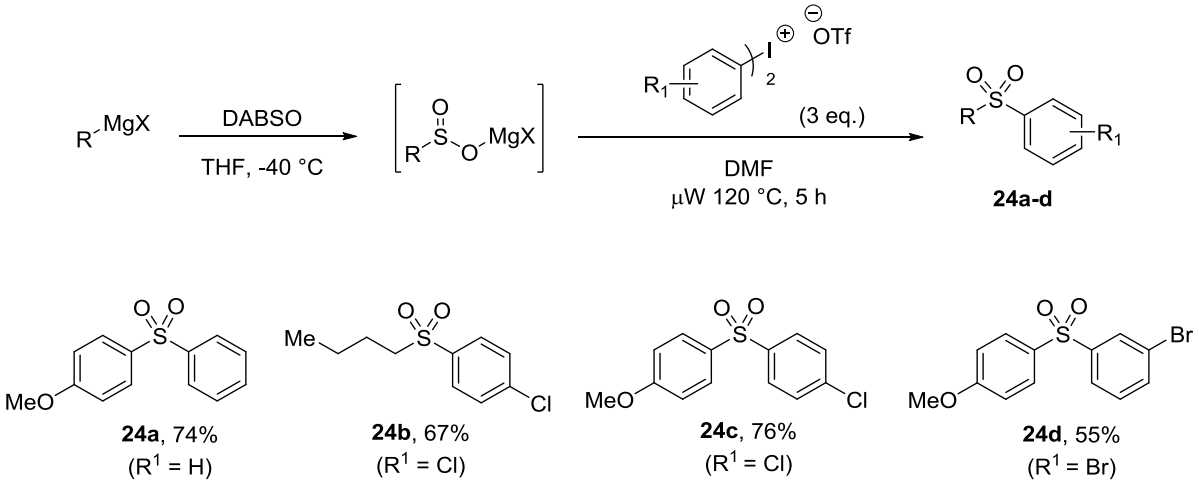
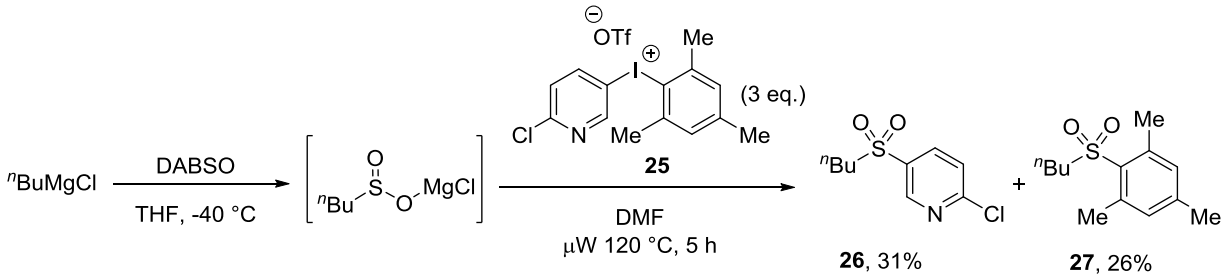



Figure 2.4 Symmetrical diaryliodonium salts as electrophiles.

Having demonstrated the application of symmetrical diaryliodonium salts in this system, it was conceived that unsymmetrical salts could be used to selectively deliver more highly functionalised aromatic groups. Despite significant advances in the field,[108] the synthesis of symmetrical, functionalised aryliodonium salts, particularly di-heteroaromatic variants, remains a challenge. Importantly, the generation of an equivalent of a highly functionalised aryl iodide as a by-product is particularly wasteful. More attractive is the use of easily prepared unsymmetrical substrates with a less complex, cheaply available aryl iodide selectively serving as the leaving group; potentially providing a more cost-effective and atom economical method of achieving aryl group transfer.

Selective transfer of an aromatic ring from unsymmetrical iodonium salts can be achieved by tuning the electronics[109] or sterics[110] of the ligands. A common strategy, particularly in metal-catalysed

processes, involves the use of (hetero)aryl-mesityl iodonium reagents. The sterically encumbering mesityl group generally favours the formation of the (hetero)aryl-metal complex with mesityl iodide as the leaving group.[111] On attempting a similar tactic in our system to achieve heteroaryl group transfer, the pyridyl-mesityl iodonium salt **25** resulted in a mixture of sulfones **26** and **27**, demonstrating poor selectivity (Scheme 2.4).




Scheme 2.4 Attempted selective heteroaryl sulfone synthesis using heteroaryl-mesityl iodonium **25**.

Following this disappointing result, our attention turned to electronically distinguished aryl iodoniums. Maintaining the 6-chloro-pyridyl group (as an electron-withdrawing group) iodonium **28** was prepared, incorporating the electron-donating *p*-methoxyphenyl group. Pleasingly, using the previously established sulfinate trapping conditions, alkyl-heteroaryl sulfone **29a** was prepared in a good yield and selectivity (Figure 2.5). Use of lower reaction temperatures (80 and 100 ºC) under conventional heating offered no improvements, with selectivity remaining unchanged but yield deteriorating.

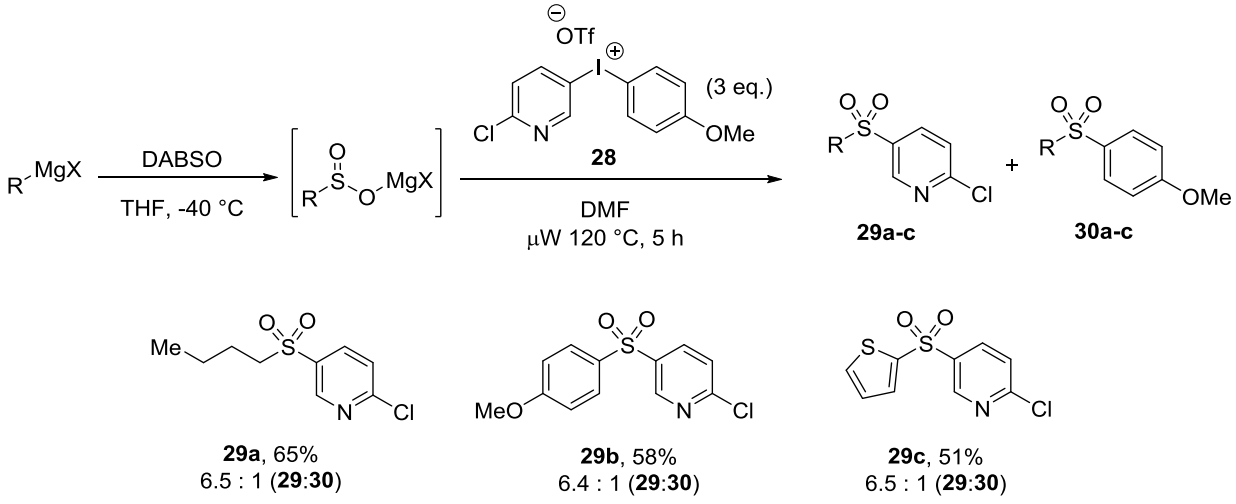
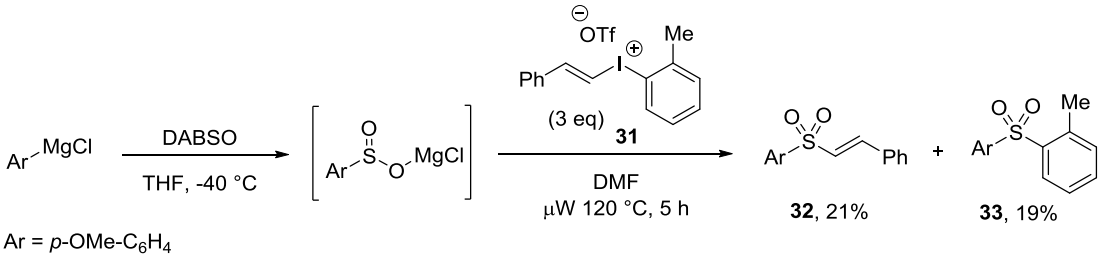



Figure 2.5 Heteroaryl group incorporation employing electronically-differentiated unsymmetrical iodonium salts.

The ability to incorporate heteroaryl groups into sulfone products significantly enhanced the scope of this system. Of particular note is the potential of this chemistry to access functionalised di-heteroaryl sulfone products, such as **29c**.

In a final attempt to further increase the yield/selectivity, the *p*-methoxy group in iodonium **28** was replaced with a dimethyluracil substituent. This was based on the 1,3-dimethyluracil-5-iodonium derivative having recently been employed by Gaunt *et al*. to achieve selective pyridyl group transfer in an NHC-catalysed C-H arylation of aldehydes.[112] In our system, despite exclusive pyridyl incorporation, use of this reagent resulted in a significantly lower yield (25%) of the sulfone **29a**. The use of higher reaction temperatures provided no improvement on productivity.

Finally, a brief study into whether selective formation of alkenyl sulfones could be achieved was undertaken. Due to limitations in the synthesis of alkenyl iodonium salts, alkenyl-aryl iodonium **31** was employed in this study. This was based on the application of this iodonium salt by Gaunt *et al.* for selective styryl group incorporation in the copper-catalysed carbofunctionalisation of alkynes.[113] Unfortunately, in our system a 1:1 mixture of the alkenyl and diaryl sulfone products **32** and **33** was obtained in a low yield (Scheme 2.5).




Scheme 2.5 Attempt to access alkenyl sulfones *via* unsymmetrical alkenyl iodonium salt **31**.

A development in this field was recently made by Waser *et al*. with the coupling of sulfinates and the cyclic alkynyl hypervalent iodine reagent TIPS-EBX.[114] Employing the same method for generating sulfinates as presented here, silyl-protected alkynylaryl sulfone products could be obtained.

### 2.6.2 Epoxide ring opening – *β*-hydroxy sulfone synthesis

Having achieved the unification of alkyl, aryl and heteroaryl groups, originating from both the sulfinate and electrophile, our attention turned towards accessing a different class of products, *β*-hydroxy sulfones. Such species can be accessed by ring opening epoxides with sodium sulfinate nucleophiles and serve as precursors to alkenyl sulfones; a medicinally important subset of the sulfone family receiving particular attention as potent inhibitors of cysteine protease.[115] The scope of *β*-hydroxy sulfones delivered using sodium sulfinates has remained restricted to benzene and *p*-tolyl derivatives. It was therefore proposed that a general one-pot process providing access to a range of *β*-hydroxy sulfones would be attractive.

Initial attempts at the reaction of *n*-butylmagnesium sulfinate with cyclohexene oxide in THF or DMF were unsuccessful. On switching to an aqueous reaction medium, however, the ring opening could be effected with the sulfone **34a** obtained in 78% yield (Figure 2.6). It has been previously reported with sodium sulfinates that the use of a polar protic solvent is key for such a transformation to occur;[102b] most likely due to hydrogen bonding between water and the epoxide oxygen activating the ring towards nucleophilic attack. Having adapted the system to allow for effective epoxide ring opening, the scope of *β*-hydroxy sulfones was examined (Figure 2.6).

A diverse range of *β*-hydroxy sulfones was prepared, demonstrating the potential of this system to access a relatively underexplored compound class. Employing cyclohexene oxide as the electrophile, alkyl, aryl and heteroaryl sulfinates delivered products in moderate to good yields. As such, the scope of *β*-hydroxy sulfones accessible from DABSO-generated metal sulfinates has been expanded beyond those originating from the commercially available sulfinates.

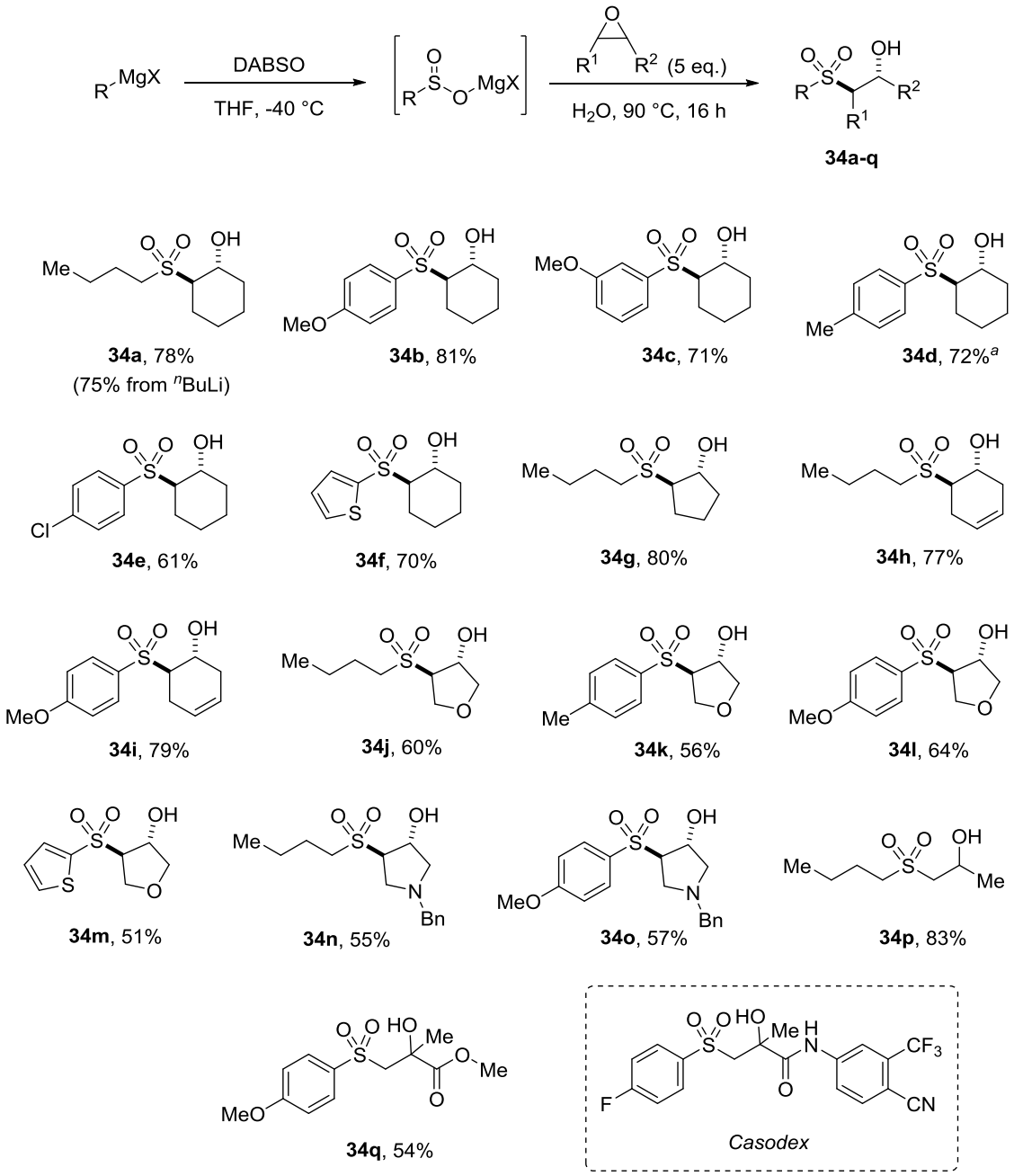



Figure 2.6 Scope of *β*-hydroxy sulfones in sulfinate-epoxide ring opening.

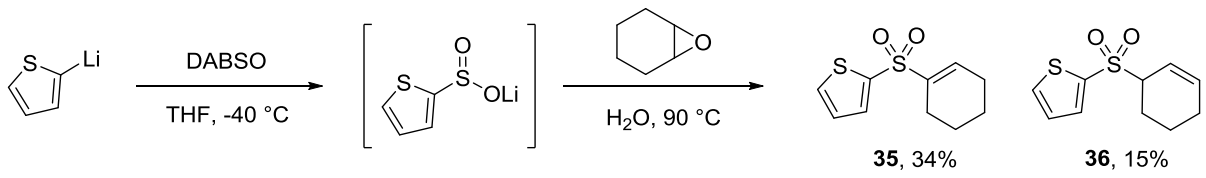
[a] Example used as a reference to confirm stereochemistry by comparison with literature data.

Once more, aryl sulfinates bearing electron-donating groups and alkyl sulfinates were found to be the most effective nucleophiles. Electron-withdrawing groups bound to aryl sulfinates were less effective but still compatible with this system, with the sulfone **34e** obtained in a reasonable yield. Of particular note is the use of thienyl-2-magnesium bromide to prepare the

heterocyclic *β*-hydroxy sulfone **34f** in good yield.

On exploration of the scope of the epoxide fragment, it was found that *N*- and *O*-heterocyclic substrates were compatible with this system, providing access to interesting *β*-hydroxy sulfone structures (**34j**-**34o**). Sulfone **34m** serves to demonstrate the potential of this system to construct compounds with latent biological properties, with the polar, heterocyclic product displaying herbicidal activity.[116] Acyclic propylene oxide performed well in this reaction with sulfinate attack occurring predominantly at the less hindered site to afford the sulfone **34p** in a high yield; only a trace amount of the regioisomer was detected. As a final note, by employing ester-derived epoxide methyl 2-methylglycidate, sulfone **34q** could be prepared in a moderate yield, serving as a carbon backbone analogue of the anti-androgen Casodex used in the treatment of prostate cancer.

Interestingly, when 2-thienyllithium was used in place of the corresponding Grignard reagent a mixture of sulfones **35** and **36** was obtained (Scheme 2.6, c.f. **34f**). As a result, it was postulated whether this reactivity was an inherent feature of lithium sulfinates in this system. However, using *n*-butyllitihum in combination with cyclohexene oxide or propylene oxide failed to give any elimination products with the *β*-hydroxy sulfones proving unreactive in these cases (**34a**, Figure 2.6).




Scheme 2.6 *In situ* elimination of 2-thienyl-derived β-hydroxy sulfone.

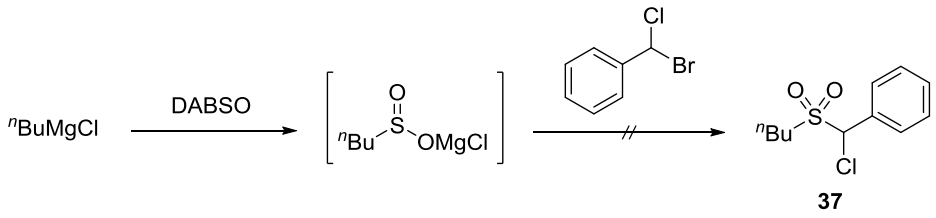
Considering the emergence of vinyl sulfones as potent inhibitors of cysteine proteases and consequently lead targets in drug discovery,[90] further attempts to affect the dehydration of the *β*-hydroxy sulfone products *in situ* were made. Employing lithium and magnesium *n*-butyl sulfinates and propylene oxide, the use of lithium bromide and chloride as Lewis acids to mediate the desired dehydration reaction of **34p** was unsuccessful.[117] Further efforts to affect this transformation were made by converting the *β*-hydroxy sulfone to the corresponding

tosylate *in situ*. Once more, the sulfone product was found to be unreactive under these conditions. Finally, subjecting sulfone **34p** to heating in the presence of strong acid or base, surprisingly, also resulted in no reaction.

### 2.6.3 Failed attempts at alternative sulfinate derivatisation

Magnesium and lithium sulfinates prepared using this method were found to be ineffective nucleophiles in certain cases. Attempts to couple these intermediates with Michael acceptors and $S_NAr$ substrates (such as 2-chlorobenzothiazole) were unsuccessful, despite the proven reactivity of sodium sulfinates in these more challenging transformations. This difference in reactivity could be explained by the bonding between the sulfinate oxygen and the three metal cations. It is possible that the tighter ion pair formed in the lithium sulfinate and the more covalent character of the O-MgX bond in the magnesium salt influence the reactivity in these cases. Alternatively, the presence of DABCO remaining from the sulfinate-forming step could account for the incompatibility of Michael acceptors with amine nucleophilic attack possible.

In addition, efforts to access the $\alpha$-chlorosulfone **37**, with the view to incorporating a Ramberg-Bäcklund step into the one-pot methodology, proved fruitless (Scheme 2.7). Despite the electronic activation (inductive effects) of this alkyl bromide, it is likely that the $\alpha$-chloro functionality sterically hinders the desired nucleophilic attack.




Scheme 2.7 Attempted $\alpha$-chlorosulfone synthesis.

## 2.7 Project summary

In summary, a versatile synthesis of sulfones has been developed based on the simple generation and coupling of magnesium and lithium sulfinates using DABSO. The transformation serves as an attractive alternative to current methods by converting readily accessible organometallic reagents into diverse sulfone products under the action of the bench-stable and easily-handled $SO_2$ surrogate DABSO in a one-pot process; avoiding the use of gaseous sulfur dioxide and more linear approaches that require thiol substrates.

This one-pot process provides access to a range of sulfones, incorporating alkyl, alkenyl, aryl and heteroaryl groups from both the nucleophilic (sulfinate) and electrophilic components of the reaction. Successfully employing symmetrical and unsymmetrical iodonium salts was key to expanding the scope to diaryl, aryl-heteroaryl and di-heteroaryl sulfones. The ring opening of epoxides with alkyl and (hetero)aryl sulfinates in a slightly modified protocol allows for much greater access to novel $\beta$-hydroxy sulfones and serves as another distinguishing feature of this chemistry.

# 3. Array-compatible sulfonamide synthesis

## 3.1 Applications and syntheses of sulfonamides

### 3.1.1 Biological and medicinal applications

Sulfonamides form a fundamental class of organic compound with widespread applications as biologically active agents. A large class of pharmaceutical and agrochemical products exists whereby the R-$SO_2$-N moiety is the key to activity (Figure 3.1). This is rationalised by the unique combination of properties this functional group invokes; hydrogen bond donor and acceptor capability,[118] suitable lipophilicty and chemical and metabolic stability.[119]

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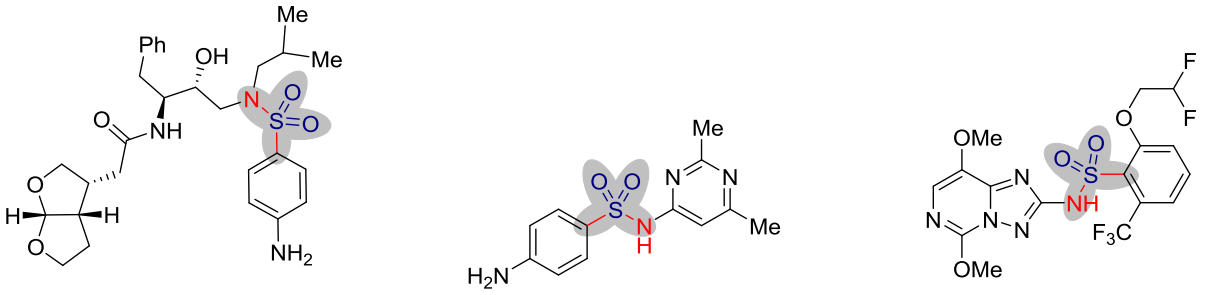



***Darunavir***
protease-inhibitor used in HIV treatment

***Sulfadimidine***
antibacterial agent

***Penoxsulam***
herbicide

Figure 3.1 Examples of biologically active sulfonamide products.

In particular, some sulfonamide-containing compounds possess potent antibacterial properties and as such this sulfonyl motif has been incorporated into many antibiotic products. It was the emergence of sulfonamide antibiotics in the 1930s that initially inspired the development of the "sulfa drugs". Such antibacterial agents show activity against many common bacteria by inhibition of folic acid synthesis and have found applications in the treatment of urinary tract, respiratory tract, enteric and soft tissue infections.[8]

The diverse biological activity of sulfonamides is demonstrated by their wider application in other medicinal agents such as anti-convulsants and anti-diuretics.[8] In addition, sulfonamides have gained recent attention as medicinal chemistry targets directed towards HIV[10] and cancer treatments.[9] Further to this, sulfonamide products have also been exploited in agrochemical crop protection, displaying herbicidal, fungicidal and pesticidal activity.[4]

### 3.1.2 Traditional sulfonamide syntheses

Due to the prominence of sulfonamide targets in medicinal and herbicidal chemistry, synthetically efficient and versatile methods for preparing sulfonamides are highly sought. The most common route to sulfonamides is *via* amine coupling with the corresponding sulfonyl chloride (Section 1.1.2). Whilst this N-S bond formation is generally very effective – being amenable to a wide variety of amines – it is access to the sulfonyl chloride precursors that tends to limit this synthetic route.

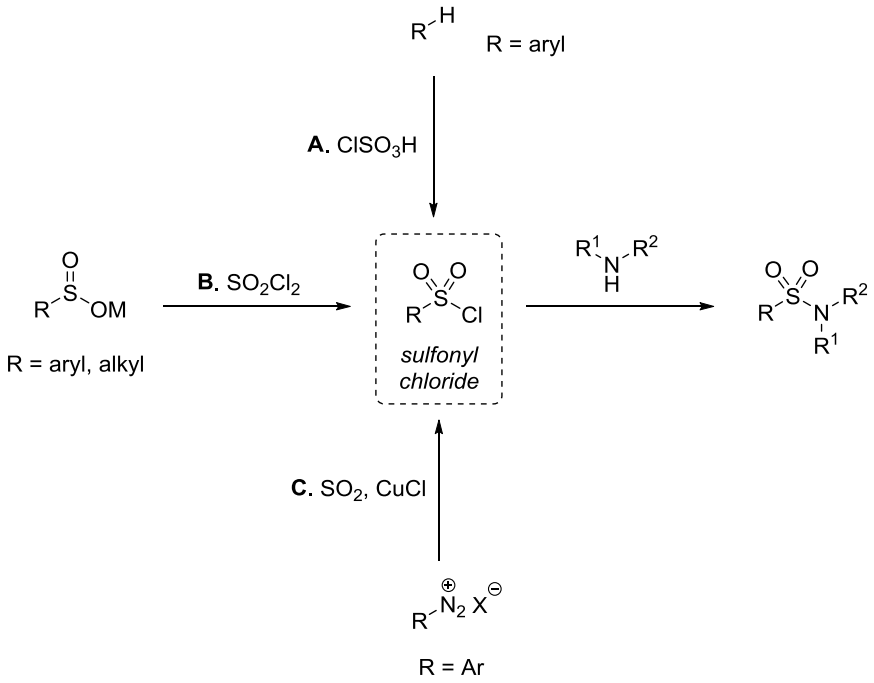



Figure 3.2 General synthetic strategies towards sulfonamides *via* sulfonyl chlorides.

The most general methods for accessing sulfonyl chlorides are Friedel-Crafts-type arene sulfonylations (Figure 3.2, route A) and oxidative chlorination of metal sulfinates (route B). However, the use of harsh acidic and/or functional group intolerant reagents has negative implications for the functional group compatibility of such synthetic routes. In addition, access to the desired substitution patterns in the electrophilic aromatic sulfonation process is limited as the inherent electronic or steric properties of the arene can favour substitution at alternative positions resulting in the wrong regioisomer or mixtures. The Meerwein reaction (Section 1.2.3) serves as another means of preparing sulfonyl chlorides (route C).[51] Although it has been implemented in a flow process,[120] the practicality of this chemistry suffers from the use of difficult-to-handle sulfur dioxide gas (in high excesses) and unstable aryl diazonium salts as substrates.

As a result of these limitations and the moisture sensitivity and poor shelf-life of sulfonyl chlorides, alternative electrophilic sulfonic acid derivatives have been explored as precursors to sulfonamides. Examples include sulfonylbenzotriazoles[121] and phosphine- and pentafluorophenol- activated sulfonates (Figure 3.3).[122] Although these species serve as more stable sulfonyl chloride variants, their synthesis relies on the use of sulfonic and sulfinic acid derivatives as precursors and their application represents poor atom economy.

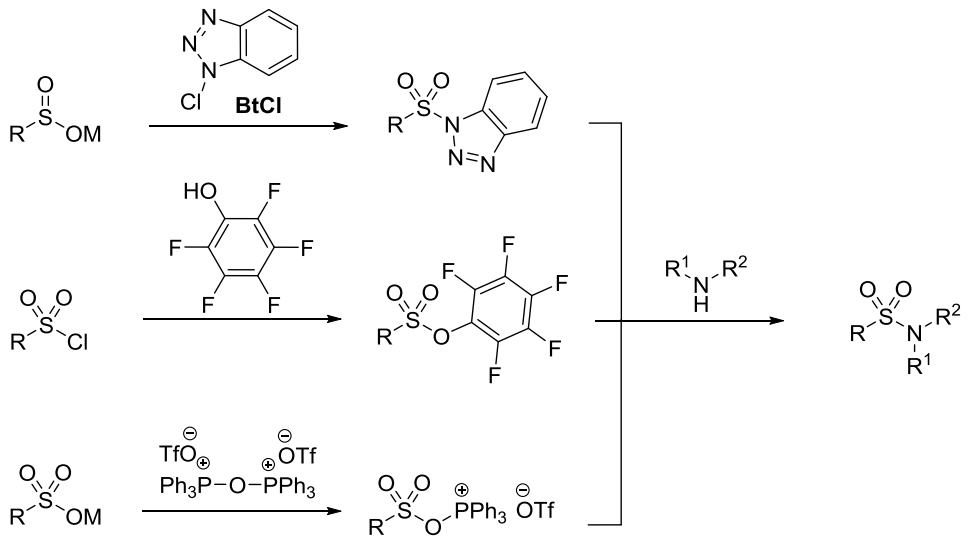


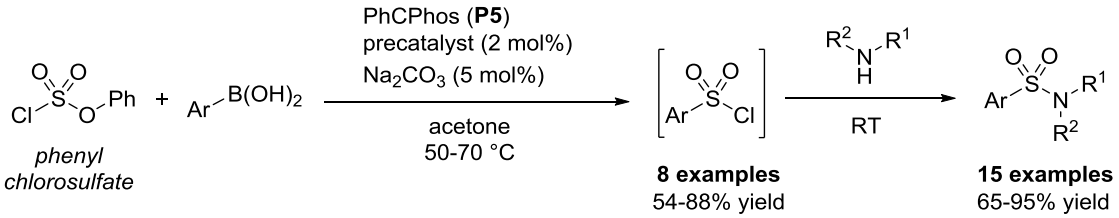

Figure 3.3 Alternative sulfonic acid derivatives as precursors to sulfonamides.

### 3.1.3 Recent advances in the synthesis of sulfonamides

As discussed in Chapter 1, the exploration of DABSO as a sulfur dioxide surrogate has allowed novel methods for the synthesis of sulfonamides to be developed. In particular, the palladium-catalysed aminosulfonylation and its variants serve as efficient means of preparing *N*-aminosulfonamides (Section 1.4.2). The primary limitation of these syntheses is the restricted variation in the nucleophilic coupling partner with non-hydrazino amines proving incompatible.

Combining DABSO with organometallic reagents to access sulfonyl chlorides *via* oxidative chlorination of the resulting metal sulfinates offers a gas-free route to sulfonamides (Section 1.4.3).[79,123] The Willis group has demonstrated this with Grignard reagents as substrates, however, the use of sulfuryl chloride, a reagent with limited functional group compatibility and prone to decomposition, only allowed simple sulfonamide products to be accessed.

Building on the aminosulfonylation reaction, Buchwald *et al*. reported the use of phenyl chlorosulfate as an $[SO_2Cl]^+$ synthon in a palladium-catalysed cross-coupling reaction with aryl boronic acids.[124] The corresponding aryl sulfonyl chlorides could be isolated or trapped *in situ* with amines to afford sulfonamide products (Scheme 3.1).




Scheme 3.1 Buchwald's sulfonamide synthesis *via* palladium-catalysed chlorosulfonylation.

Despite serving as an important progression on the aminosulfonylation reaction to access aryl sulfonamides, this system is still somewhat restricted in terms of scope (only aromatic variants are accessible), in addition to the fact that phenyl chlorosulfate is not commercially available (requiring sulfuryl chloride for its synthesis) and a complex palladium catalyst is needed.

## 3.2 Project outline

On account of the prevalence of the sulfonamide moiety in medicinal and agrochemical agents, improved methods for constructing this functional group are highly sought. A desirable system would address the inherent limitations of current methods (as described above), using simple conditions and readily accessible reagents, as well as removing the need to prepare a sulfonyl chloride precursor in a formal step. In addition, due to the interest in new sulfonamide-based drug and agrochemical entities, novel syntheses that can be applied to target-based discovery and generate sulfonamide arrays efficiently would be particularly attractive. All of these factors served as the motivation for studies into a novel DABSO-based sulfonamide synthesis, as outlined in this chapter.

### 3.2.1 Array synthesis towards drug discovery

Array synthesis is a discovery chemistry strategy commonly exploited in medicinal chemistry to build libraries of new organic entities.[125] Such processes involve initial array design (identifying desirable functionality and substitution patterns), the combination of many variants of the coupling partners in a particular given reaction and the relevant biological evaluation of the obtained compounds (Figure 3.4). This is particularly pertinent in drug discovery whereby large ensembles of molecules possessing latent biological properties can be generated efficiently and screened for the desired activity.[126] This provides the opportunity to explore new chemical space and assess lead targets in a short time-frame.[127]

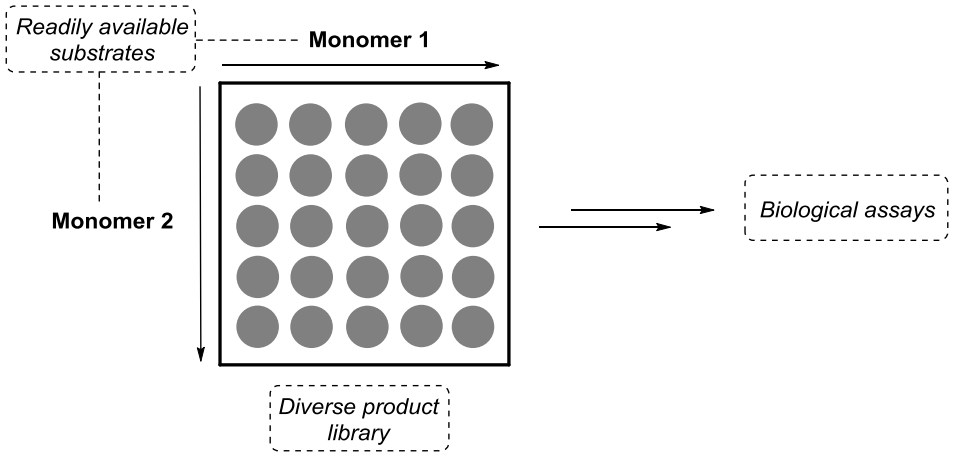



Figure 3.4 General outline for array synthesis.

Applying a synthetic methodology in an array format serves as an effective means of "stress-testing" the reaction. To challenge methodologies in this way is an important measure of their efficacy and potential for application in discovery chemistry i.e. for the preparation of arrays of compounds with "drug-like" properties in a practical and efficient manner.[128] In order to be array-compatible, there are several defining features the reaction must possess. Employing simple conditions in a practically straightforward fashion is a necessity. Furthermore, the use of readily accessible and diverse building blocks is vital for achieving high levels of product diversity.

With the emergence of sulfonamide-containing anti-HIV and anti-tumour agents, sulfonamide syntheses that are amenable to target-based discovery and an array format are highly sought. Library syntheses of sulfonamides have been previously reported based on amine-sulfonyl chloride coupling.[129] Such examples generally involve building a library from a specific amine or sulfonyl chloride substrate, with little differentiation in product functionality. This diversity can also be confined further by the accessibility of the sulfonyl chloride coupling partners; the classical means of preparation, shelf-life and limited commercial availability of alkyl and heteroaryl derivatives all contributing.

Considering the above factors, we aimed to develop a DABSO-based synthesis of sulfonamides that satisfied several criteria; a one-pot protocol employing simple conditions and readily accessible substrates that avoids the need to formally prepare a sulfonyl chloride precursor. Consequently, this system would be amenable to an array synthesis format to access diverse collections of novel sulfonamides with latent biological activity (Figure 3.5).

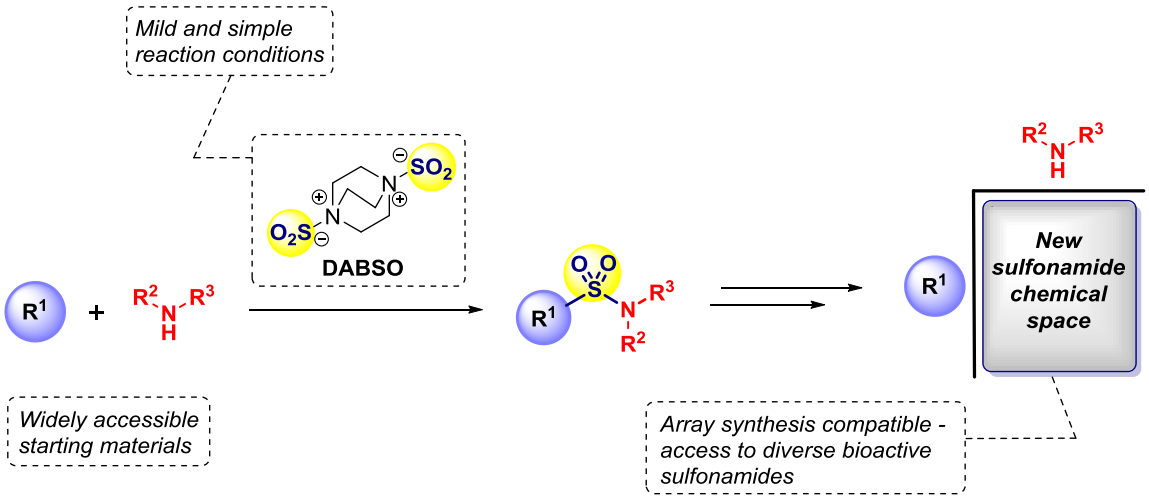
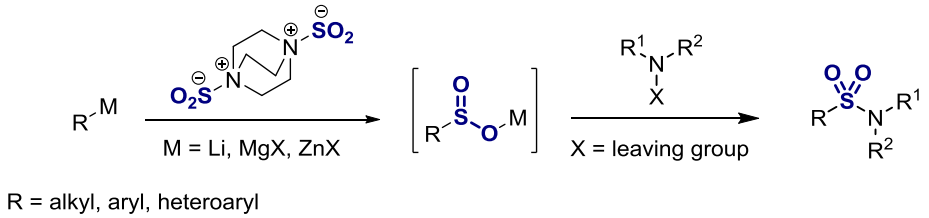



Figure 3.5 General outline for a DABSO-based sulfonamide synthesis.

### 3.2.2 Origin of project

Following on from the studies into the derivatisation of metal sulfinates, generated from DABSO and organometallic reagents using carbon-based electrophiles (Chapter 2), and with the considerations discussed above, our attention turned towards applying nitrogen-based electrophiles to access sulfonamides (Scheme 3.2). This proposed system would avoid the need for a formal sulfonyl chloride substrate or intermediate and we aimed to identify an effective amine electrophile and suitable conditions for subsequent applications in array syntheses.

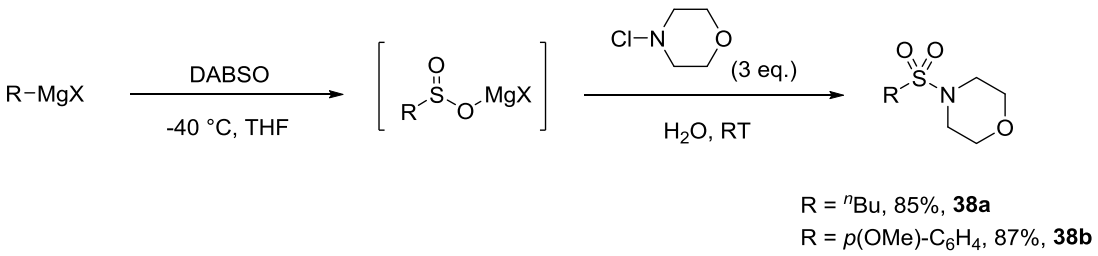



Scheme 3.2 Proposed DABSO-based sulfonamide synthesis employing electrophilic amines.

## 3.3 Reaction conditions and optimisation

*N*-Chloroamines were identified as potential coupling partners, based on their prevalence as electrophilic amine reagents in both metal- and non-metal-catalysed coupling reactions.[130] In addition, we were encouraged by the precedent set by literature examples for combining selected isolated sodium sulfinates (benzene and *p*-tolyl) and *N*-chloroamines.[131] Consequently, preliminary studies focused on determining whether such coupling was possible with *in situ* generated magnesium sulfinates.

Pleasingly, by treating both alkyl and aryl magnesium sulfinates with an excess of *N*-chloromorpholine, using water as the solvent, the corresponding sulfonamides **38a** and **38b** could be obtained in high yields (Scheme 3.3).




Scheme 3.3 Coupling of magnesium sulfinates with isolated *N*-chloromorpholine.

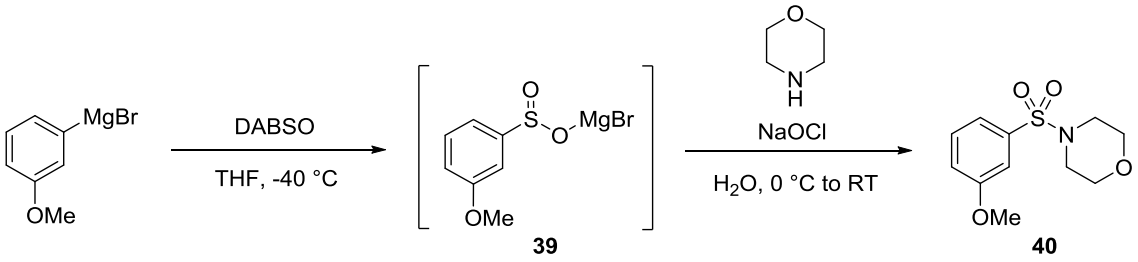
Despite having established the desired intrinsic reactivity, the need to prepare the isoalted *N*-chloroamine substrates did not meet the criterion of employing readily available starting materials. In addition, the instability of these isolated species would limit the compatibility with an array synthesis format. With this in mind, the focus turned to the development of a one-pot system involving *in situ* generation of the *N*-chloroamine precursor. As such, amines and organometallic reagents, along with DABSO, would serve as readily available core building blocks to sulfonamides.

While a number of ways to generate *N*-chloroamines exist, the use of aqueous sodium hypochlorite (bleach) to affect this was identified as a particularly attractive method. Not only does this facilitate rapid N-Cl bond formation, but employing bleach as a reagent, along with DABSO, constitutes an attractive system employing mild and simple conditions.

Accordingly, studies into this mode of transformation were initiated with the combination of sulfinate **39** (generated from 3-methoxyphenylmagnesium bromide and DABSO), morpholine and aqueous sodium hypochlorite (Table 3.1). Promisingly, with a THF/water co-solvent system, sulfonamide **40** was observed, albeit in a low yield (Entry 1, Table 3.1). On moving to a water only solvent system, **40** could be obtained in a higher yield (Entry 2). Further improvements were achieved by increasing the loadings of the amine and hypochlorite (Entries 3 and 4) and subsequently an optimised ratio of 5:3 equivalents (respectively) was established (Entry 5). Increasing the amounts of the amine and bleach further provided no significant advance in yield (Entries 6 and 7). Other polar solvents were also examined (Entries 8-11), but water was found to be the optimal (and arguably most convenient) reaction medium.

Due to the possibility of the sulfinate attacking the chlorine of the *N*-chloromorpholine and generating the corresponding sulfonyl chloride *in situ*, the reaction was carried out in the presence of the nucleophilic catalysts DMAP and pyridine (Entries 12 and 13); however, both offered no further improvement in the yield of **40**. A similar outcome was noted with the use of acetic acid as a pH buffer to limit hydrolysis of a potential sulfonyl chloride intermediate (Entry 14).

Table 3.1 Initial screening and optimisation of conditions for sulfonamide synthesis.




| Entry | Solvent | Amine (eq.) | NaOCl (eq.) | Yield (40) |
|---|---|---|---|---|
| **1** | THF/$H_2O$ | 2.0 | 1.2 | 38% |
| **2** | $H_2O$ | 2.0 | 1.2 | 51% |
| **3** | $H_2O$ | 3.0 | 2.0 | 60% |
| **4** | $H_2O$ | 4.0 | 2.0 | 66% |
| **5** | $H_2O$ | 5.0 | 3.0 | 78% |
| **6** | $H_2O$ | 5.0 | 4.0 | 78% |
| **7** | $H_2O$ | 7.5 | 5.0 | 79% |
| **8** | THF/$H_2O$ | 5.0 | 3.0 | 67% |
| **9** | $CH_3CN$ | 5.0 | 3.0 | 70% |
| **10** | MeOH | 5.0 | 3.0 | 75% |
| **11** | DMSO | 5.0 | 3.0 | 72% |
| **12**[a] | $H_2O$ | 5.0 | 3.0 | 79% |
| **13**[b] | $H_2O$ | 5.0 | 3.0 | 73% |
| **14**[c] | $H_2O$ | 5.0 | 3.0 | 75% |

*Reaction conditions*: 3-OMe-$C_6H_4MgBr$ (0.25 mmol, 1 equiv.), DABSO (0.6 equiv.), THF -40 °C *then* amine, solvent and aq. NaOCl (15.8% aq. solution) at 0 °C followed by overnight stirring at room temp. [a] 2.0 equiv. DMAP. [b] 4 equiv. pyiridine. [c] 5 equiv. AcOH.

## 3.4 Initial reaction scope

Having established an optimised set of conditions, the next step was to examine the scope of organometallic reagents that could be employed in this system (Figure 3.6). We were pleased to discover that lithium, magnesium and zinc sulfinates all served as effective nucleophiles in combination with the *in situ* generated *N*-chloromorpholine. The ability to employ aliphatic and aromatic organolithium, organozinc and Grignard reagents, both commercially available and generated using a variety of methods, is a particularly important feature of this reaction. This allows for a versatile process with extended levels of functional group diversity; particularly as functional group tolerant methods for preparing Grignard and organozinc reagents exist. Interestingly, the identity of the metal counter-cation of the sulfinate was found to have an effect on the inherent reactivity of the intermediate. This was particularly noteworthy in the case of alkyl sulfinates, where the magnesium sulfinates proved to be the most effective with *n*-butylmagnesium chloride delivering the corresponding sulfonamide in a high yield (**41a**, Figure 3.6); this product was obtained in a much reduced yield with the analogous organolithium reagent (**42a**). The difference in the reactivity of aromatic substrates was less pronounced, with the three metal sulfinates affording sulfonamide products in good to high yields.

As with the previous studies into sulfinate trapping with carbon-based electrophiles, it was noted that aromatic sulfinates bearing electron-donating groups were the most effective as nucleophiles in this system. Use of aromatic substrates with electron-withdrawing substituents did result in reduced yields, but products could still be obtained in moderate to good yields (**41d**, **41f**, **43b**).

Heteroaromatic substrates affording products **41g** and **42e** performed well in this reaction although the 3-pyridyl sulfonamide **41i** could only be isolated in a low yield. Alkenyl sulfonamide **41h** was prepared in a moderate yield from the corresponding magnesium sulfinate.

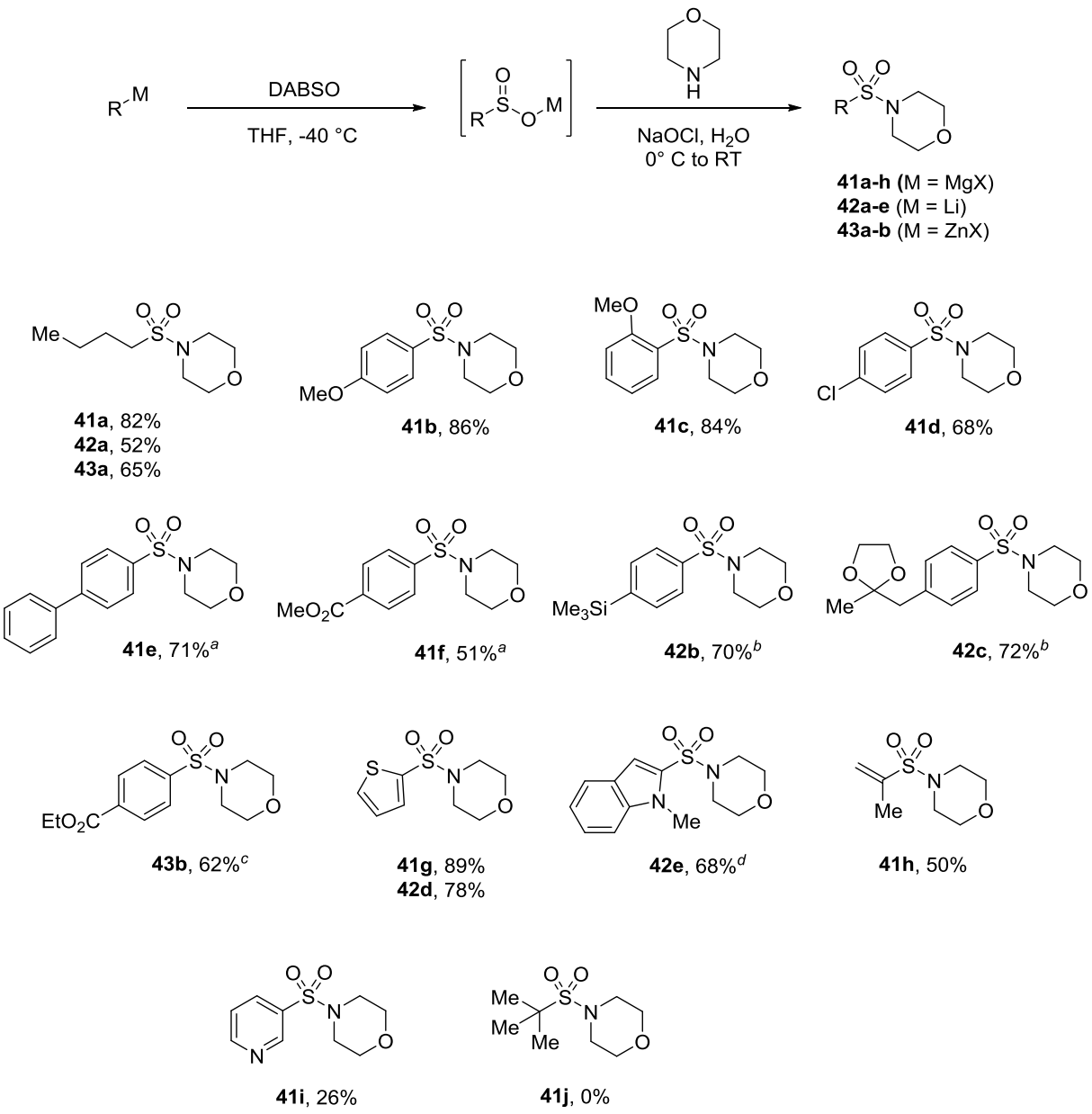



Figure 3.6 Organometallic scope for sulfonamide synthesis.

*Reaction conditions*: Organometallic reagent (0.25 mmol, 1 equiv.), DABSO (0.6 equiv.), THF -40 °C *then* amine (5 equiv.), $H_2O$ and NaOCl (15.8% aq. solution, 3 equiv.) at 0 °C followed by overnight stirring at room temp.[a] RMgX generated from the corresponding iodide and $^{i}$PrMgCl. [b] RLi generated from the corresponding bromide and $^{n}$BuLi. [c] RZnX generated from the corresponding iodide with zinc metal. [d] RLi generated *via* deprotonation with $^{t}$BuLi.

Finally, *tert*-butylmagnesium sulfinate failed to deliver the corresponding sulfonamide **41j**. With the generation of this intermediate demonstrated in the previous sulfone synthesis (Chapter 2), it is likely that the steric bulk of the sulfinate prevents the desired coupling in this process.

Having assessed the reactivity of a range of metal sulfinates, attention turned towards the scope of the amine component, in combination with 3-methoxyphenylmagnesium bromide (Figure 3.7). It was found that a range of primary and secondary amines were compatible with this system. Pleasingly, aniline derivatives delivered products in moderate to high yields despite competing decomposition (aromatic chlorination) of the amine on addition of the aqueous NaOCl to the reaction mixture.[132]

Another interesting feature was the performance of amino acids in this system. The free acids served as effective coupling partners with sulfonamides **44k** and **44l** (Figure 3.7) isolated in high yields (with no erosion of enantiopurity) after simple acidification of the reaction medium. Although formation of *N*-chloro derivatives of amides is known,[133] unfortunately these nucleophiles were not amenable to this system (**44m**). It is possible that this observation is the result of the instability of such *N*-chloro derivatives towards Hofmann type rearrangements[134] or it could be indicative of a mechanism based on the sulfinate attacking the chloride rather than the nitrogen of the *N*-chloroamine. Consequently, the free amide may not be nucleophilic enough to couple with the resulting sulfonyl chloride intermediate. This reactivity difference was exploited with the application of an amide-bearing aniline substrate to deliver the corresponding sulfonamide **44j** exclusively.

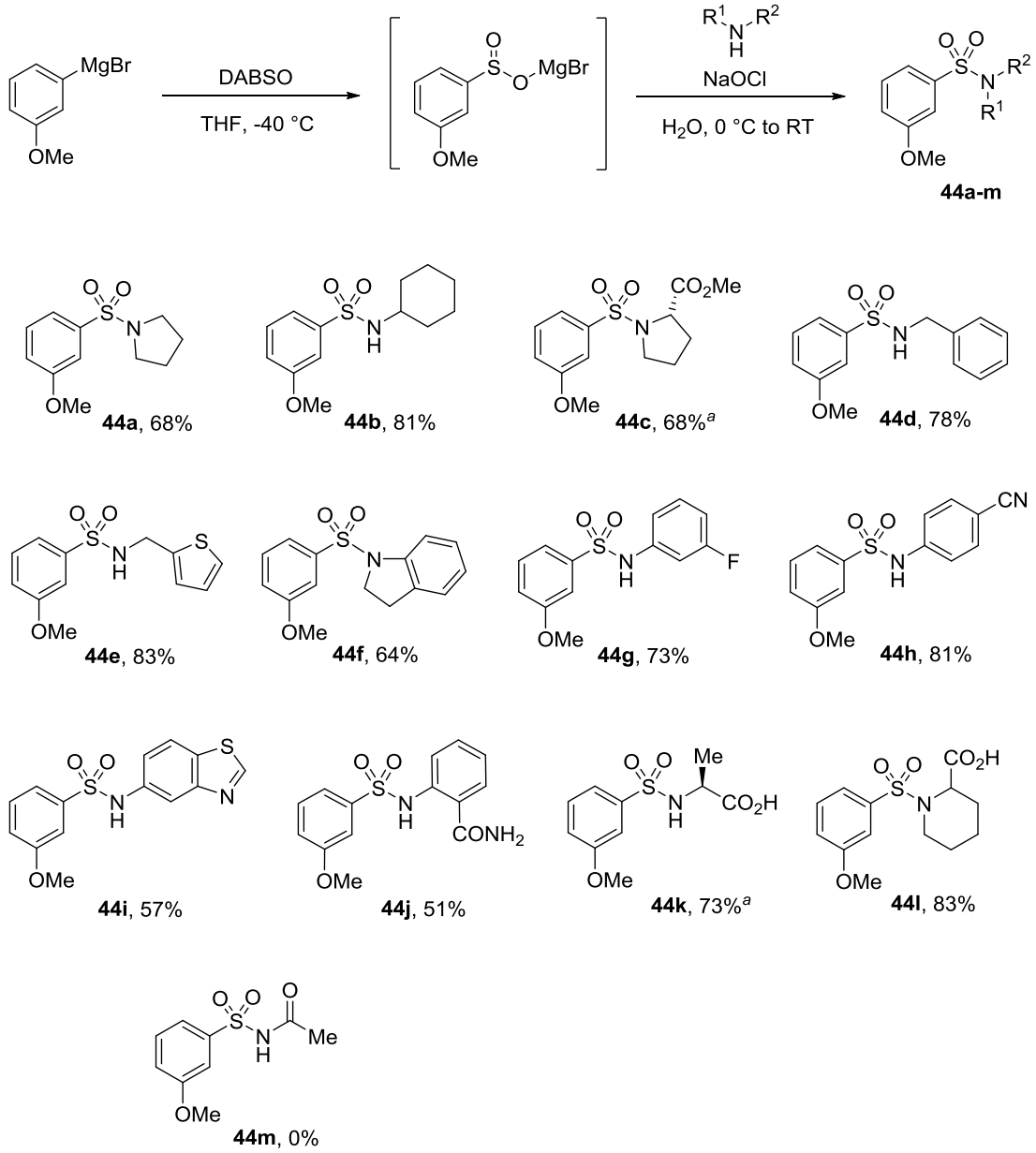



Figure 3.7 Scope of amines for the one-pot sulfonamide synthesis.

*Reaction conditions*: see above (Figure 3.5). [a] ee > 99%.

## 3.5 Mechanistic considerations

The original hypothesis of the project centred on employing *N*-chloroamines as direct electrophilic coupling partners with sulfinates i.e. S-N bond formation *via* the sulfur lone pair attacking the nitrogen directly with chloride displacement (Figure 3.8). However, an alternative mechanism is possible whereby the sulfinate attacks the electrophilic chlorine to form a sulfonyl chloride intermediate (Figure 3.8). Subsequent rapid amination of this sulfonyl chloride in the presence of an excess of the amine affords the corresponding sulfonamide product. This pathway has been proposed previously based on mechanistic studies into the reaction between a sodium sulfinate and an *N*-chloroamine.[131] In this report the corresponding sulfonyl chloride was isolated by reacting the two precursors in water at low concentration ($1 \times 10^{-4}$ M).

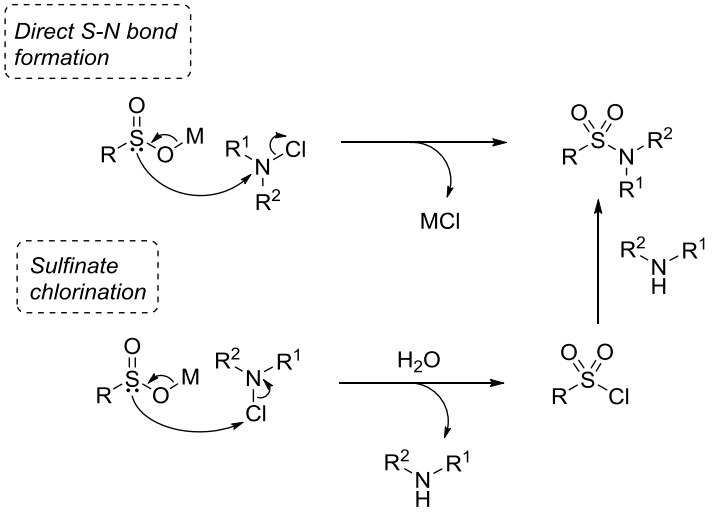



Figure 3.8 Sulfonamide formation *via* two possible mechanisms.

With this in mind, a similar experiment was designed to investigate this in our system by mixing dilute solutions ($1 \times 10^{-3}$ M) of the *p*-tolylmagnesium sulfinate, generated from DABSO and the corresponding Grignard reagent, and *N*-chloromorpholine. A similar observation was made to the previous report with the formation of tosyl chloride observed without any sulfonamide by HPLC. This protocol was replicated with a solution ($1 \times 10^{-3}$ M) of the *in situ* generated *N*-chloromorpholine (using sodium hypochlorite) in combination with the sulfinate solution ($1 \times 10^{-3}$ M). However, in this case tosyl chloride formation was not

observed. It is possible that sulfinate chlorination does occur but due to the low amine concentration, relative to the original optimised reaction (excess of amine), and basic conditions, hydrolysis of the sulfonyl chloride intermediate takes place instead.

Based on the electronegativites of chlorine and nitrogen, sulfinate attack at the nitrogen is most likely, but on steric grounds it may be argued that a sulfinate chlorination pathway is more favourable. Indeed, it is possible that the reaction proceeds *via* both mechanisms with sulfonyl chloride formation favoured with amines where the nitrogen atom is more sterically hindered.

## 3.6 Array synthesis of sulfonamides

With a practically simple method and an encouraging general reaction scope encompassing alkyl, alkenyl, aryl and heteroaryl groups from magnesium, lithium and zinc sulfinates, as well as a variety of amines, the next task was to assess the potential of this sulfonamide synthesis for applications in target-based discovery with an array synthesis. It was the aim of this experiment to design and prepare a diverse collection of sulfonamides incorporating varying functionality from both organometallic and amine coupling partners.[135]

It was particularly important to be able to access compounds possessing desirable physiochemical properties for medicinal and agrochemical agents (e.g. logP, topological polar surface area and molecular weight).[136] As such, the substrate criteria was based on functional group density, heteroatom composition and polarity; relatively low molecular weight, heteroatom-rich, polar monomers were selected. An additional defining feature of the organometallic reagents employed was that the corresponding sulfonyl chloride was not readily (commercially) available, demonstrating further the ability of this system to generate novel entities that are inaccessible *via* conventional strategies. Hence, a group of seven organometallic reagents was chosen for this study covering polar, aliphatic and (hetero)aromatic, magnesium, lithium and zinc derivatives (Figure 3.9).

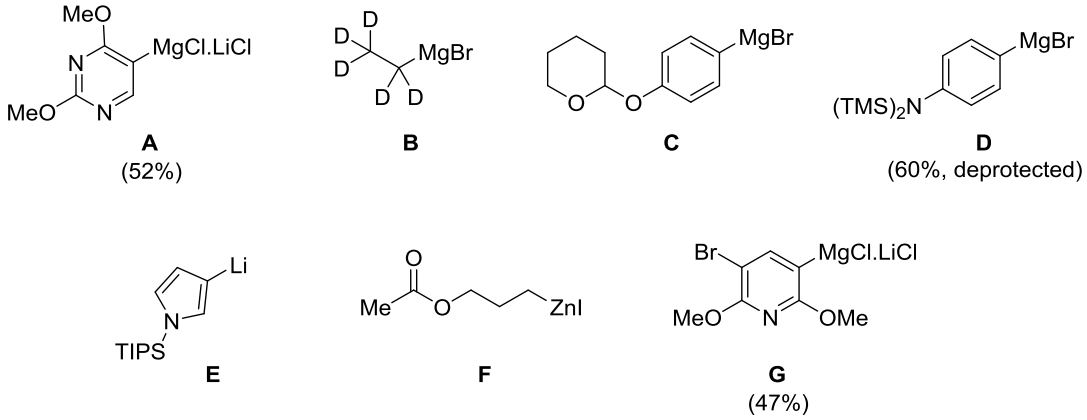



Figure 3.9 Organometallic reagents selected for array synthesis.

Prior to conducting the array experiment, reagents **A**, **D** and **G** were tested using the standard reaction protocol. Employing morpholine, the corresponding heteroaromatic sulfonamides could be obtained in reasonable yields (Figure 3.9, yields in brackets). Interestingly, use of the *bis*-silyl-protected aniline Grignard reagent **D** resulted in the isolation of the deprotected sulfonamide product. This deprotection occurs during the second step of the reaction and allows for direct access to the *para*-aminophenyl sulfonamides; a class of compounds renowned for their antibacterial properties.[137] Based on the yields obtained here and considering the criteria set above, these substrates were confirmed as suitable monomers for the array synthesis.

The amine series was chosen primarily to include linear and cyclic alkyl amines and aniline derivatives, as well as an amino acid derivative (Figure 3.10). The use of monomers *a***1** and *a***5** would allow for further heterocycle incorporation.

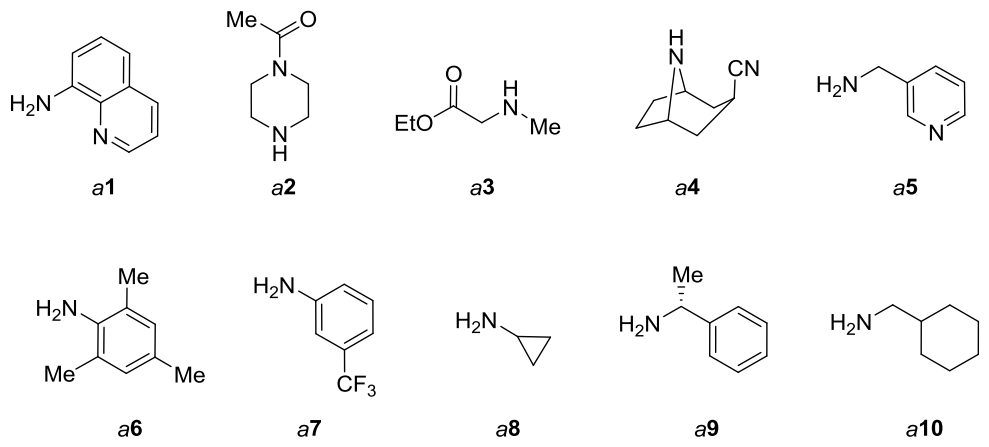



Figure 3.10 Amine series selected for sulfonamide array synthesis.

The combination of these two sets of substrates under the established reaction conditions would potentially generate an array of 70 diverse sulfonamide products.

The array was conducted as a plate experiment with the use of an XT-block reactor and a slightly modified protocol from the original general reaction. The initial sulfinate formation was conducted at room temperature and THF was retained in the second step by simply adding water to give a 1:1 co-solvent system. Target compounds were detected by LC-MS and subsequently purified by mass directed preparatory HPLC allowing for isolated yields to be determined. The purity of the products was determined by LC-MS and in some cases $^{1}$H NMR spectroscopy was used as a further confirmation of purity and structure.

Pleasingly, we found that out of a possible 70 combinations, 65 delivered sulfonamides of high purity, in yields of 20 to 60% (Figure 3.11). Although these isolated yields are low to moderate, with respect to the constraints of an array format these are considered acceptable. 56 Novel structures were generated in sufficient quantities for bioactivity screening and an overall "array yield" of 93% (65 hits out of a possible 70) was achieved. Of the 70 reactions, there was only one case (**B3**) where product was not observed and the remaining four "failed" examples were the result of ineffective purification with the products contaminated with significant impurities.

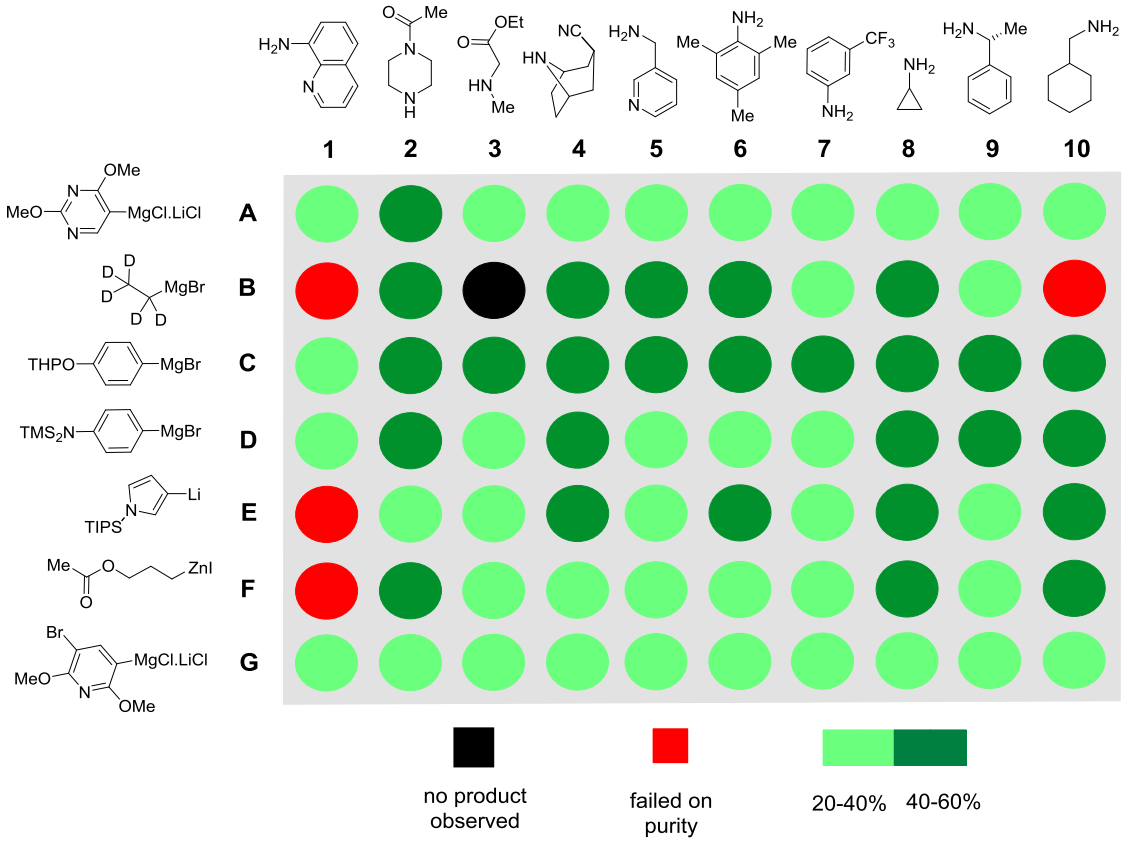
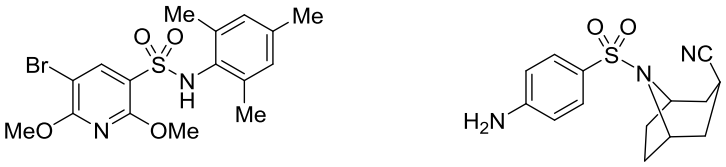



Figure 3.11 Synthesis of a 65-sulfonamide array.

The effect of carrying out the reaction in a modified array format was assessed by taking two substrate combinations and performing these as individual reactions using the standard protocol. Sulfonamides **G6** and **D4** were prepared in yields of 39% and 54% respectively, showing deviations of 6% and 10% respectively from the results obtained from the array synthesis (Figure 3.12). These reductions in isolated yield can be rationalised by the use of a THF/water co-solvent system (instead of 100% aqueous) and the inherent loss of material incurred on employing automated work-up and purification procedures.



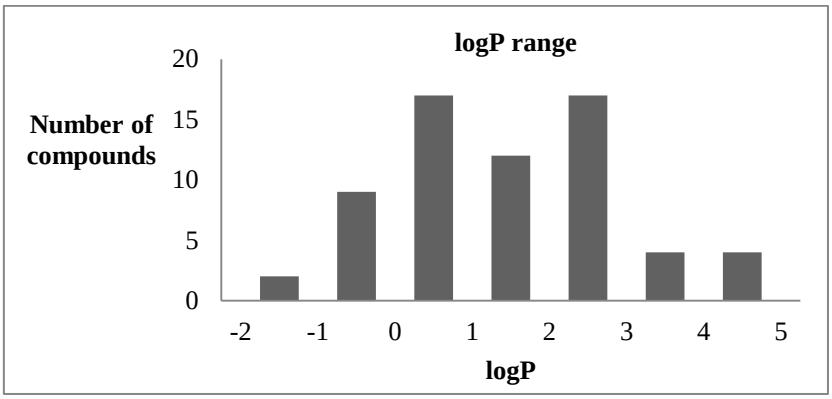
**G6**
39% (individual)
33% (array)

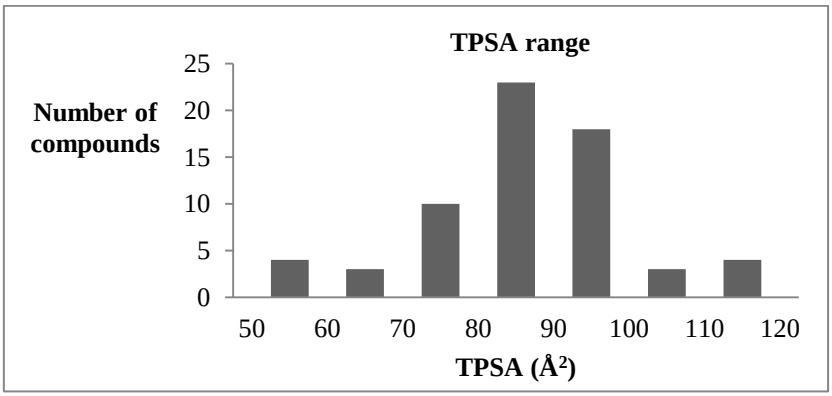


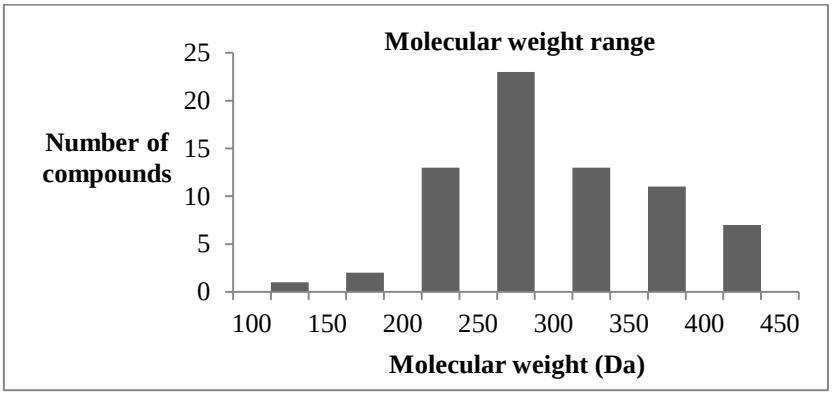
**D4**
54% (individual)
44% (array)

Figure 3.12 A comparison of array and individual reaction yields.

With a diverse collection of sulfonamides constructed in a simple and rapid fashion, attention turned towards evaluating the physiochemical properties of the 65 compounds. An important aspect of this work was not just to be able to prepare compounds successfully but ones that possessed desirable attributes in accordance with medicinal and agrochemical criteria.[138] Hence logP and topological polar surface area (TPSA) values were calculated along with the molecular weights of the products (Figure 3.13).[139]



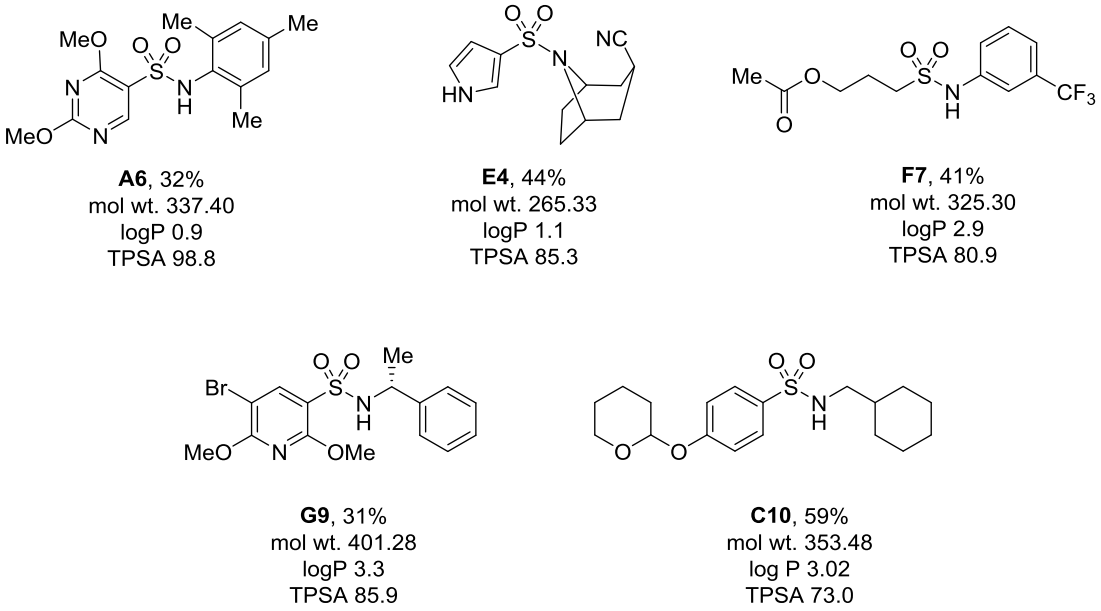



Figure 3.13 Distributions of calculated logP, TPSA and molecular weight values for the 65 array sulfonamides along with selected examples and their profiles.

It is apparent from this data that with the combination of readily available drug-like fragments in the array format, the majority of compounds generated possess properties that are desirable for drug and agrochemical candidates (Figure 3.13 for examples). The logP of a molecule is the logarithm of the partition coefficient between an aqueous (water) and hydrophobic phase (*n*-octanol) i.e. its lipophilicity. In biology this translates to the transfer between aqueous media and lipophilic cell membranes. Hence, this is a particularly important property with regard to drug potency and toxicity, as well as herbicidal and fungicidal activity.[138] Of the 65 compounds obtained here 59 were calculated as having logP values between 0 and 5, satisfying the criterion for lipophilicity of drug-like compounds proposed by Lipinski's "Rule of Five"[138c,140] as well as that suggested for pesticide-likeness ($\leq 6$).[138b,141] Additionally, the majority of these values were in the range of 0 to 3 which has been identified as a requisite for "lead-like" targets in drug discovery.[142]

Topological polar surface area is a parameter relating to the pharmacokinetic behaviour of compounds and more specifically their oral bioavailability.[138] The proposed lower and upper limits of TPSA for desirable bioavailability of drug-like molecules are 75 and 140 $Å^2$; the majority of the sulfonamides prepared in this study were found to have TPSA values in this

range. Finally, all the molecular weights of the products were below the 500 Da threshold set by the "Rule of Five" for oral bioavailability, while the vast majority were also lower than the suggested upper limit for pesticide candidates, 435 Da.[138,141]

With this promising physiochemical profile in hand, we were pleased to see these results translated into in vivo activity in a series of agrochemical assays; 67% of the sulfonamides displayed fungicidal, herbicidal or insecticidal activity.

## 3.7 Project summary

In summary, a robust one-pot synthesis of sulfonamides has been developed based on the coupling of *in situ* generated metal sulfinates and *N*-chloroamines. This is achieved with the use of DABSO and sodium hypochlorite as simple and convenient reagents. Not only does this system employ attractive conditions but organometallic reagents and amines as readily accessible building blocks. In addition, unlike most traditional sulfonamide syntheses, this process does not rely on the formal preparation of a sulfonyl chloride substrate or intermediate. It is possible however, that a sulfonyl chloride intermediate is formed and rapidly consumed *in situ* as a result of sulfinate attack at the chlorine site of the *N*-chloroamine. Alkyl, alkenyl, aromatic and heteroaromatic sulfonamides are readily accessed from organolithium, organozinc and Grignard reagents using this methodology. In addition, a broad range of amines were compatible with this system including anilines and amino acids.

Further to this, the potential for this methodology to be applied in discovery chemistry was demonstrated with the successful preparation of a 65 sulfonamide array. Applying methodologies in this format serves as an effective means of "stress testing" reactions. Hence we were encouraged to find that a 93% "array yield" could be achieved with 56 novel entities generated and the majority of products possessing promising physiochemical profiles. Being able to efficiently prepare such collections of sulfonamides with lipophilicity, topological surface area and molecular weight values desirable for medicinal and agrochemical applications, is a particularly attractive feature of this system.

# 4. A palladium-catalysed preparation of sulfinic acid derivatives

## 4.1 Applications of sulfinates to access sulfonyl- and sulfinyl-containing compounds

As discussed and demonstrated in the previous chapters, metal sulfinates serve as versatile precursors to a variety of sulfonyl-containing compounds.[26-34] Whether they are employed as the commercial sodium salts or generated *in situ*, sulfinic acid derivatives can be exploited as nucleophiles for direct access to products such as sulfones and sulfonamides (Section 1.1.3 and Chapters 2 and 3). Alternatively, sulfinic acids and sulfinates can be converted to electrophilic sulfonic and sulfinic intermediates and subsequently trapped with nucleophiles (Figure 4.1).[23,24,79,143]

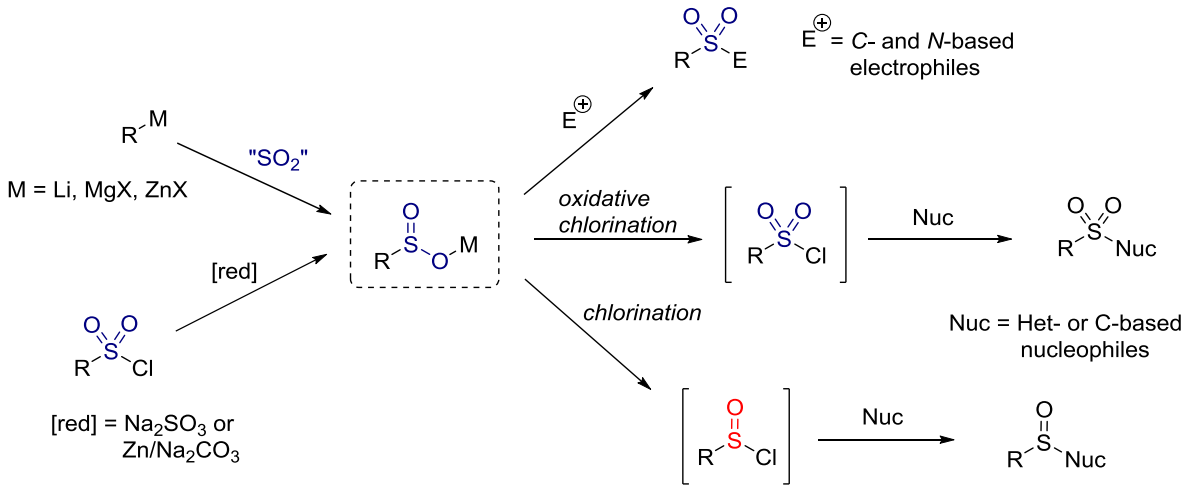



Figure 4.1 General routes to metal sulfinates and subsequent derivatisations.

For such applications of sulfinates in preparing sulfonyl- and sulfinyl-containing products, the sodium salts are accessed as the commercially available compound or, for a wider scope,

*via* reduction of the corresponding sulfonyl chloride.[98,144] As discussed previously, this scope can be extended by preparing the sulfinates from organometallic reagents and DABSO (Chapters 2 and 3).

## 4.2 Extended uses of sulfinates in organic synthesis

Aside from their utility in synthesising sulfonyl and sulfinyl targets, the sulfinate moiety has been exploited as an activating group in a number of processes. In particular, aliphatic metal sulfinates have been demonstrated to act as alkyl radical precursors.[32,145] The C-S bond can undergo homolytic cleavage in the presence of a mild oxidant with the entropically favourable loss of sulfur dioxide. This desulfonylative application of metal sulfinates offers significant advantages over the traditional use of carboxylic acids as radical precursors in Minisci chemistry; such decarboxylative processes generally require strong oxidants, heat or specialised precious metal catalysts.[146] Baran has pioneered the use of zinc and sodium alkyl sulfinates as general reagents for the formation of radical species in a range of C-H alkylation processes.[147] Through employing such sulfinates, significant advances have been made in the field of radical-mediated heterocycle C-H alkylation (Figure 4.2).[148]

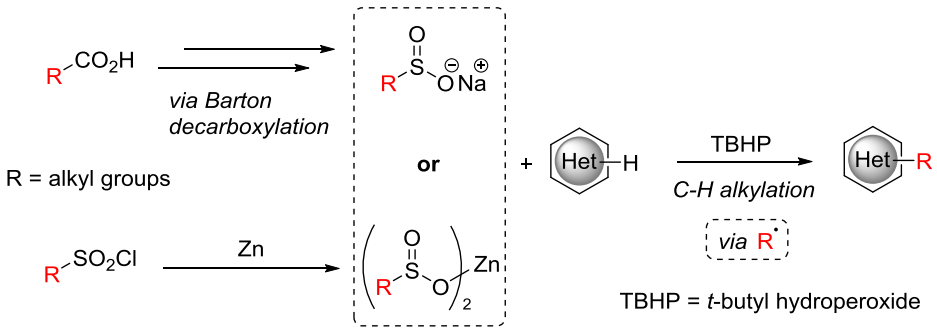



Figure 4.2 Alkyl sulfinates as radical precursors in heterocycle C-H alkylation.

The sodium sulfinates employed in these cases were prepared from the corresponding carboxylic acids in a linear fashion involving Barton's decarboxylation protocol.[147a,149] Sulfonyl chloride reduction with elemental zinc was employed to access the corresponding zinc sulfinates.[147b]

In addition to this radical-based transformation, aryl sulfinic acids and sulfinates have been employed in transition metal catalysis as activated coupling partners whereby the [$SO_2$] unit serves as a leaving group.[150] Such desulfitative processes resemble the well-established metal-catalysed decarboxylative couplings of carboxylic acids[151] and examples include Sonogashira- and Heck-type reactions (Eq. A, Figure 4.3)[152,153] as well as cross couplings with activated halides (Eq. B)[154] and C-H activation.[151b,c]

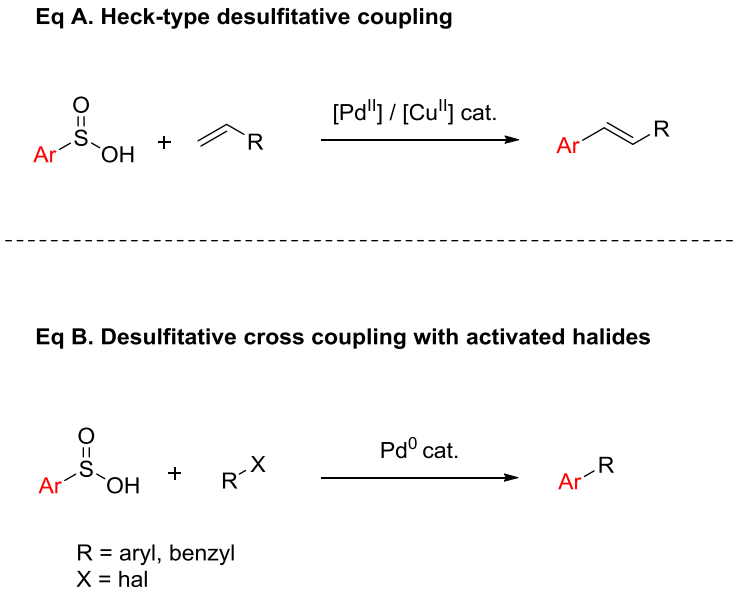


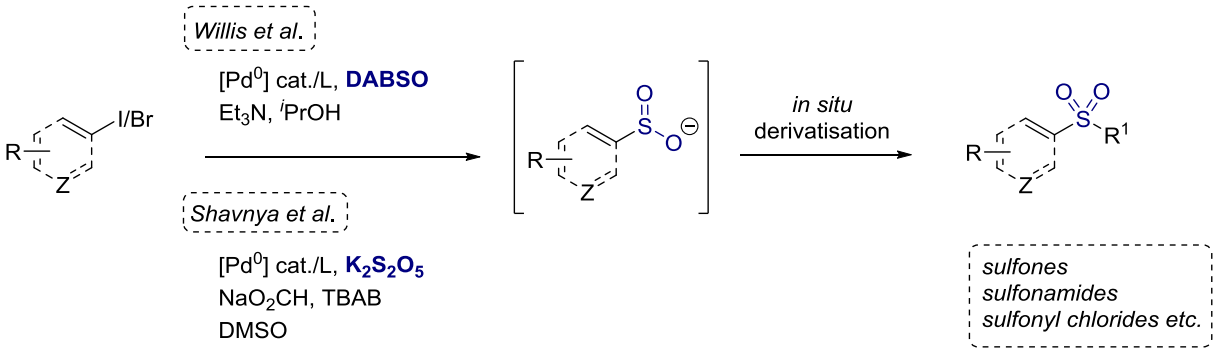

Figure 4.3 Transition metal-catalysed desulfitative cross couplings of aryl sulfinic acids and sulfinates.

## 4.3 Project outline

### 4.3.1 Advances in sulfinate synthesis

Further to the generation of metal sulfinates from organometallic reagents and DABSO, recent developments have been made employing sulfur dioxide surrogates in palladium catalysis to access these versatile precursors. A preparation of aryl sulfinic acids from the corresponding diazonium salt using sulfur dioxide was reported by Pelzer *et al*. at the end of the nineties. However, this system suffers from the use of unstable diazonium substrates and

both sulfur dioxide and hydrogen gases at high pressures.[57,60] This precedent served as the inspiration for the Willis group to explore metal-catalysed sulfination reactions employing DABSO and more attractive coupling partners. As such, a palladium(0)-catalysed preparation of ammonium sulfinates from aryl iodides was developed with the use of DABSO under mild reductive conditions (Section 1.4.2 and Scheme 4.1).[78] At a similar time, Shavnya *et al.* reported a comparable transformation of aryl iodides and bromides in the presence of $K_2S_2O_5$ (Section 1.4.4 and Scheme 4.1).[87] In comparison to the DABSO-based process this sulfinate synthesis suffers from poorer yields and uses a dual ligand catalytic system (phenanthroline and triphenylphosphine) with a high combined loading (30 mol%).




Scheme 4.1 General outline of palladium-catalysed aryl halide sulfinations using DABSO or $K_2S_2O_5$.

### 4.3.2 Origin of project

Having demonstrated the synthetic applications of metal sulfinates generated from organometallic reagents and DABSO in Chapters 2 and 3, the focus of this research shifted towards developing alternative methods for their synthesis. The formation of lithium, magnesium and zinc sulfinates *via* addition of the corresponding organometallic reagent to DABSO has expanded the utility of metal sulfinates in organic chemistry; avoiding the use of $SO_2$ gas and taking advantage of the advanced methods available for preparing more challenging organometallic substrates.[1,2,104,123] Despite the convenience and further scope of metal sulfinates accessible with this method, the use of organometallic reagents can still impose certain functional group constraints. With this in mind we became interested in

further exploring the area of metal-catalysed synthesis of sulfinic acid derivatives.

In particular, the use of boronic acids as alternative "organometallic" substrates to access sulfinates was identified as an attractive strategy. It was proposed that a palladium- or copper-catalysed, DABSO-based process would be redox-neutral and may allow for a simple system that avoids the requirement for specialised ligands (Figure 4.4). As such, this transformation would serve as an attractive addition to the Willis group's previous work in this area.

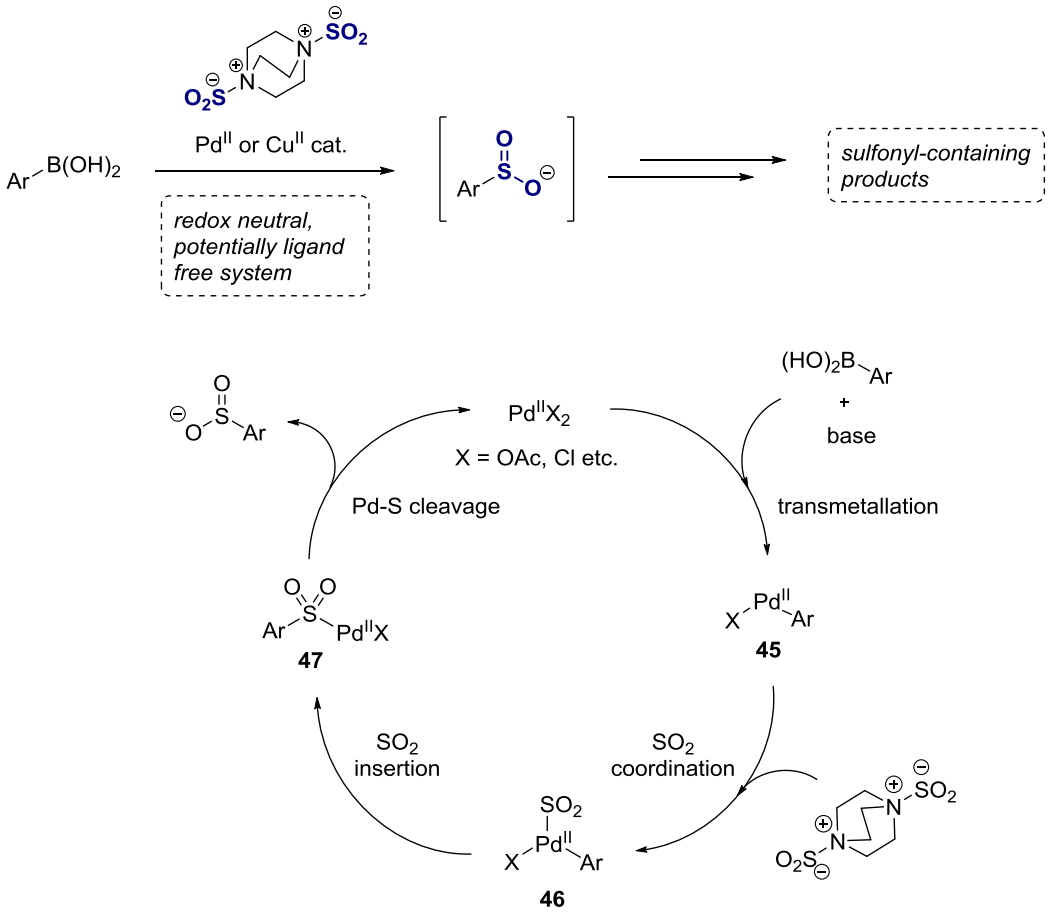
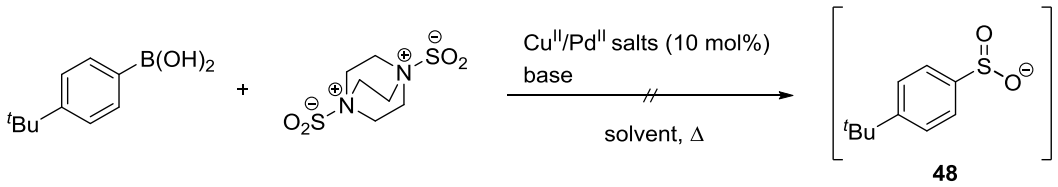



Figure 4.4 General outline and proposed mechanism for a redox-neutral, metal-catalysed synthesis of sulfinates from boronic acids.

Additionally, at the time of conducting the initial investigations into this chemistry, Toste and co-workers reported the conversion of aryl boronic acids to sulfinates *via* gold catalysis in the presence of $K_2S_2O_5$ (Section 1.4.4).[88] Despite serving as a novel progression in metal-catalysed sulfonylative chemistry (being applied to gold catalysis), this reaction suffers from the use of high gold loadings and restricted onwards sulfinate reactivity with products obtained in low to moderate yields. This served as further inspiration to explore the proposed copper- or palladium-catalysed DABSO-mediated system.

## 4.4 Initial investigations

Studies into the desired transformation were initiated with the use of copper(II) and palladium(II) catalysts in the presence of base and DABSO (Scheme 4.2). Unfortunately, experimenting with a range of catalysts, bases and solvents, sulfinate **48** was not observed by HPLC.




Scheme 4.2 Attempted generation of *p*-tolyl sulfinate using copper(II) and palladium (II) catalysis.

In these cases the reaction outcome was generally negligible conversion of the boronic acid substrate, or biphenyl and Pd(0) formation from homocoupling. The biphenyl formation can be explained by standard homocoupling from **45** or after $SO_2$ extrusion from **47**. Once this C-C bond formation occurs, Pd(0) is generated and the catalytic cycle terminates. With this disappointing outcome, we reconsidered the mechanistic cycle for the transformation (Figure 4.4). In doing so, it was reasoned that the process leading to the $Pd^{II}$-sulfinate **47** was possible under these conditions but that the subsequent Pd-S heterolytic bond cleavage may require an alternative driving force to ligand exchange with base. Based on this rationale and the use of an electrophile in the reaction mixture from the beginning in Toste's report, we were intrigued

to assess this reaction with an alkylating agent present. It was proposed that the Pd-sulfinate **47** could serve as the nucleophile to generate the desired sulfone and simultaneously turnover the Pd(II) catalyst (Pathway A, Figure 4.5). Alternatively, it is possible for the free sulfinate to re-coordinate to the $Pd^{II}X_2$ resulting in equilibration with **47** (Pathway B). Hence, in the presence of an electrophile the free sulfinate can be consumed, pulling it out of equilibrium and allowing the catalytic cycle to continue.

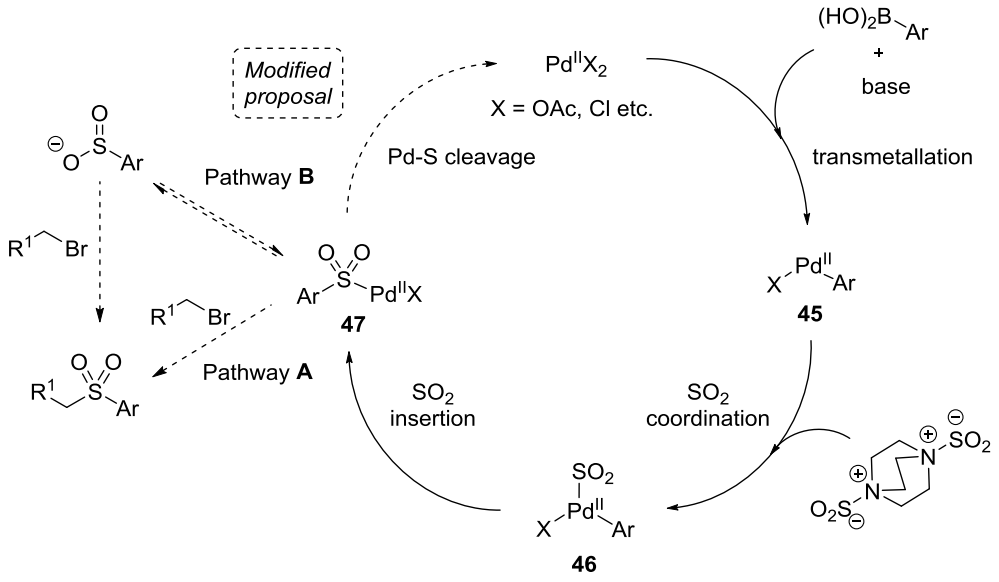
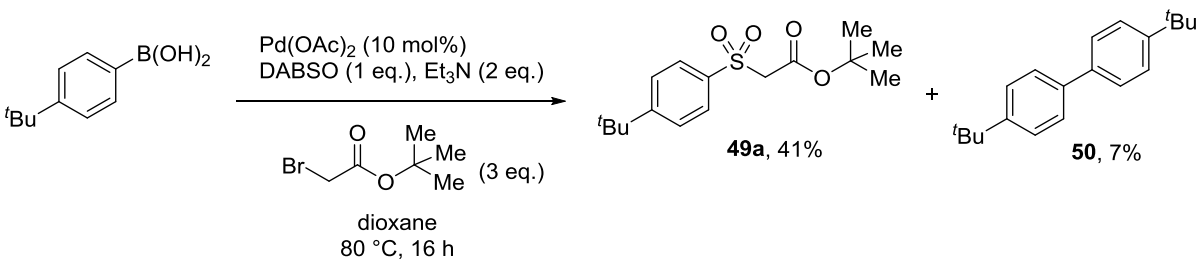



Figure 4.5 Proposed mechanistic catalytic cycle for the sulfination of aryl boronic acids.

Pleasingly, using *tert*-butylphenylboronic acid with $Pd(OAc)_2$ (10 mol%) and *tert*-butyl bromoacetate as the electrophile, the corresponding sulfone **49a** could be obtained in a 41% yield together with a small amount of the homocoupled product **50** and unreacted boronic acid starting material (Scheme 4.3).




Scheme 4.3 Initial formation of sulfone **49a** in a one-step format.

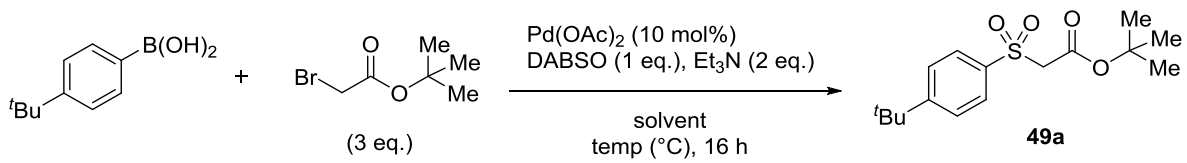
However, use of copper(II) catalysts to affect this transformation were unsuccessful with no reaction observed. Consequently, an assessment of the reaction conditions was conducted in order to optimise the palladium-catalysed, one-step process.

## 4.5 Optimisation of the one-step/one-pot sulfone synthesis

The screening study initially focused on the variation of solvents, while maintaining the same temperature, reagents and catalyst/reagent loadings. The reaction was monitored by HPLC and yields were obtained relative to 4,4'-dimethylbiphenyl as an internal standard.

From an extensive examination of solvents, dioxane was initially identified as the optimum reaction medium. Despite its poor performance as the solvent by itself (Entry 4, Table 4.1) inspiration was taken from Toste's report and MeOH in combination with dioxane was assessed (Entry 9). Pleasingly, the use of this co-solvent system resulted in a significant improvement in the yield of **49a**. Replacing MeOH with other alcoholic or aprotic polar solvents resulted in degradation of the yield (Entries 11 to 14). Analysis of the ratio of MeOH/dioxane and a brief study into the reaction temperature revealed no further improvements (Entries 15 to 18).

Table 4.1 Initial screen of conditions to optimise the synthesis of sulfone **49a**.




| Entry | Solvent [a] | Temp | Yield (49a) [b,c] |
|---|---|---|---|
| **1** | Dioxane | 80 °C | 49% |
| **2** | $CH_3CN$ | 80 °C | 31% |
| **3** | Toluene | 80 °C | 19% |
| **4** | MeOH | 80 °C | 11% |
| **5** | $^t$BuOH | 80 °C | 27% |
| **6** | EtOH | 80 °C | trace |
| **7** | DMF | 80 °C | 36% |
| **8** | Toluene/ MeOH | 80 °C | 36% |
| **9** | Dioxane/ MeOH | 80 °C | 77% |
| **10** | DMF/ MeOH | 80 °C | 49% |
| **11** | Dioxane/ EtOH | 80 °C | 13% |
| **12** | Dioxane/ $^t$BuOH | 80 °C | 70% |
| **13** | Dioxane/ $CH_3CN$ | 80 °C | 37% |
| **14** | Dioxane/ IPA | 80 °C | 13% |
| **15** | Dioxane/ MeOH (2:1) | 80 °C | 49% |
| **16** | Dioxane/ MeOH (1:2) | 80 °C | 56% |
| **17** | Dioxane/ MeOH | 70 °C | 44% |
| **18** | Dioxane/ MeOH | 90 °C | 61% |

*Reaction conditions*: 4-$^t$Bu-phenylboronic acid (0.25 mmol, 1 equiv.), $Pd(OAc)_2$ (l0 mol%), DABSO (1 equiv.), $Et_3N$ (2 equiv.), solvent [0.16 M]. [a] 1:1 ratio. [b] HPLC yield relative to 4,4'-dimethybiphenyl as the internal standard. [c] Obtained with 3-6% of homocoupled product **50**.

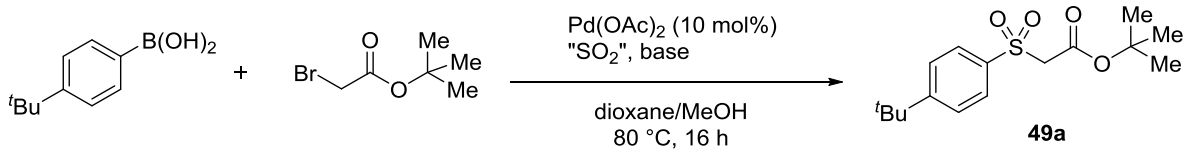
Having identified a dioxane/MeOH (1:1) co-solvent system as the optimum reaction medium, further studies were conducted looking at the identity and loadings of the base and sulfur-dioxide surrogate, along with the loading of the electrophile and use of additives (Table 4.2).

The base loading was found to influence the reaction outcome with higher and lower equivalents of triethylamine both resulting in reduced yields of **49a** (Entries 1 to 3, Table 4.2). A similar effect on the yield was observed when altering the loading of DABSO present in this system (Entries 4 to 6). These results suggest that an excess of "$SO_2$" is required to promote $SO_2$ insertion and therefore reduce the homocoupling side reaction as the catalytic cycle progresses and achieve higher yields of **49a**. However, a high excess (3 equivalents of "$SO_2$") was found to be detrimental to the yield of **49a** (Entry 6). This can be explained by $SO_2$ poisoning of the palladium catalyst or the additional amount of DABCO present which is supported by the observed reduction in yield when it was used as the base in place of triethylamine (Entries 8 and 9). Additionally, on replacing triethylamine with the more sterically hindered nitrogenous base DIPEA, a much reduced yield of **49a** was observed (Entry 7).

An examination of alternative sulfur dioxide surrogates in this system revealed DABSO as the superior reagent. While other amine-$SO_2$ complexes in this system served to deliver sulfone **49a** in reduced yields (Entries 18 and 19), interestingly $K_2S_2O_5$ proved ineffective in this Pd-catalysed process with only biphenyl **50** observed (Entry 20; cf. Toste's Au-catalysed sulfination chemistry). Similarly, the use of inorganic bases *in lieu* of triethylamine resulted in no reaction of the boronic acid (Entries 10 and 11).

Based on its use in Wu's aminosulfonylation of boronic acids (Section 1.4.2), tetrabutylammonium bromide (TBAB) was assessed as an additive in this system (Entries 14 to 17). It was found that the yield of sulfone **49a** could be improved by introducing a sub-stoichiometric amount of TBAB into the reaction (Entry 16). Employing a higher excess of the electrophile in an attempt to further increase the yield, surprisingly, led to a significant reduction (Entry 13). A possible explanation for this observation is that with such an excess of the alkyl bromide, alkylation of the triethylamine and DABCO is more prominent, resulting in smaller quantities of free base and consequently a lower yield; this can be compared with the reduction in yield observed with lower triethylamine loadings (Entries 1 and 2).

Table 4.2 Initial screen of conditions to optimise the synthesis of sulfone **49a**.

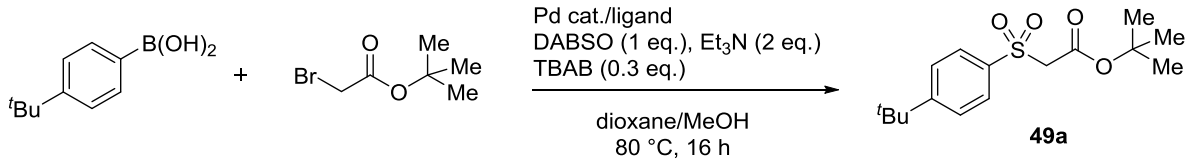



| Entry | "$SO_2$" (equiv.) | Base (equiv.) | $E^+$ equiv. | Additive (equiv.) | Yield (49a) [a, b] |
|---|---|---|---|---|---|
| **1** | DABSO (1.0) | $Et_3N$ (1.0) | 3.0 | - | 37% |
| **2** | DABSO (1.0) | $Et_3N$ (1.5) | 3.0 | - | 54% |
| **3** | DABSO (1.0) | $Et_3N$ (3.0) | 3.0 | - | 55% |
| **4** | DABSO (0.6) | $Et_3N$ (2.0) | 3.0 | - | 48% |
| **5** | DABSO (0.75) | $Et_3N$ (2.0) | 3.0 | - | 61% |
| **6** | DABSO (1.5) | $Et_3N$ (2.0) | 3.0 | - | 54% |
| **7** | DABSO (1.0) | DIPEA (2.0) | 3.0 | - | 34% |
| **8** | DABSO (1.0) | DABCO (1.0) | 3.0 | - | 57% |
| **9** | DABSO (0.6) | DABCO (0.5) | 3.0 | - | 66% |
| **10** | DABSO (1.0) | $K_2CO_3$ (2.0) | 3.0 | - | 0% |
| **11** | DABSO (1.0) | $Cs_2CO_3$ (2.0) | 3.0 | - | 0% |
| **12** | DABSO (1.0) | $Et_3N$ (2.0) | 2.0 | - | 40% |
| **13** | DABSO (1.0) | $Et_3N$ (2.0) | 5.0 | - | 49% |
| **14** | DABSO (1.0) | $Et_3N$ (2.0) | 3.0 | TBAB (1.0) | 64% |
| **15** | DABSO (1.0) | $Et_3N$ (2.0) | 3.0 | TBAB (0.5) | 75% |
| **16** | DABSO (1.0) | $Et_3N$ (2.0) | 3.0 | TBAB (0.3) | 84% |
| **17** | DABSO (1.0) | $Et_3N$ (2.0) | 3.0 | TBAB (0.1) | 64% |
| **18** | *N*-Me-Morph-$SO_2$ (2.0) [c] | $Et_3N$ (2.0) | 3.0 | - | 32% |
| **19** | Morph-$SO_2$ (2.0) [d] | $Et_3N$ (2.0) | 3.0 | - | 50% |
| **20** | $K_2S_2O_5$ (2.0) | $Et_3N$ (2.0) | 3.0 | - | 0% |

*Reaction conditions*: as previous (Entry 9, Table 4.1). [a] HPLC yield relative to 4,4'-dimethybiphenyl as the internal standard. [b] Obtained with 3-6% of biphenyl **50**. [c] *N*-methylmorpholine·$SO_2$. [d] Morpholine·$SO_2$.

As a final aspect of this optimisation study, an assessment of different palladium(II) sources and the effect of ligands in this system was conducted (Table 4.3). A variety of alternative Pd(II) salts were all found to deliver sulfone **49a** in moderate to high yields, but the original conditions employing $Pd(OAc)_2$ in a catalytic loading of 10 mol% remained optimal (Entries 1 to 4, Table 4.3).

Table 4.3 Screen of palladium(II) sources and ligands.

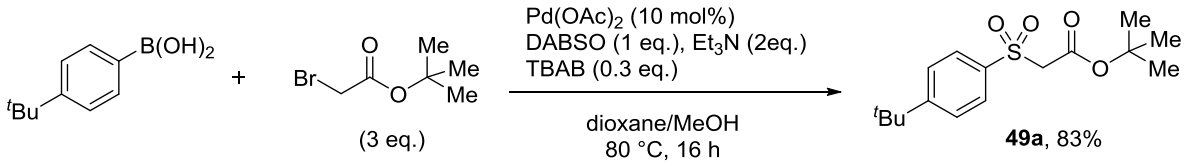



| Entry | Pd cat.[a] | Ligand | Yield (49a)[b, c] |
|---|---|---|---|
| **1** | $Pd(OAc)_2$ | - | 84% |
| **2** | $PdCl_2$ | - | 67% |
| **3** | $Pd(TFA)_2$ | - | 80% |
| **4** | $Pd(acac)_2$ | - | 81% |
| **5** | $Pd(OAc)_2$/ $Cu(OAc)_2$ | - | 23% |
| **6** | $Pd(OAc)_2$ [d] | - | 52% |
| **7** | $PdCl_2(PPh_3)_2$ | - | 65% |
| **8** | $Pd(OAc)_2$ | $^tBu_3P.HBF_4$ [e] | 67% |
| **9** | $Pd(OAc)_2$ | CataCXium A [e] | 23% |
| **10** | $Pd(OAc)_2$ | $PPh_3$ [e] | 20% |
| **11** | $Pd(OAc)_2$ | Xantphos [a] | 33% |
| **12** | $Pd(OAc)_2$ | bpy [a] | 30% |

*Reaction conditions*: as previous (Entry 16, Table 4.2). [a] 10 mol%. [b] HPLC yield relative to 4,4'-dimethybiphenyl as the internal standard. [c] Obtained with 3-6% of homocoupled product **50**. [d] 5 mol%. [e] 20 mol%.

Introducing ligands into this system proved to be detrimental to the yield of **49a** (Entries 7 to 12). The majority of the phosphine ligands tested, along with 2,2'-bipyridine resulted in low yields of 20 to 40%. The poor results obtained with the phosphine ligands may be attributed to their ability to stabilise Pd(0) with formation of $Pd^0(PR_3)_2$ complexes.

After this comprehensive screening study, the optimum set of conditions for the one-step sulfone synthesis was identified as heating the boronic acid substrate in dioxane/MeOH (1:1) at 80 ºC in the presence of $Pd(OAc)_2$ (10 mol%), DABSO (1 equiv.), $Et_3N$ (2 equiv.) and TBAB (0.3 equiv.) (Scheme 4.4).




Scheme 4.4 Optimised reaction conditions for the one-step sulfone synthesis.

## 4.6 Reaction scope of the one-step/one-pot process

With this optimised set of conditions in hand, a brief examination of the scope of boronic acids and electrophiles compatible with this one-pot, one-step system was conducted. We observed that aryl boronic acids bearing electron-rich functional groups served as effective substrates in this system while electron-withdrawing groups were found to impair reactivity somewhat; however sulfones could still be obtained in reasonable yields (Figure 4.6).

Heteroaromatic boronic acids were also found to deliver the corresponding sulfones in moderate yields (**49f** and **49g**, Figure 4.6) and the alkenyl sulfone **49h** was obtained in a low yield. This could be improved, to a small extent, with the analogous potassium trifluoroborate salt delivering the same product in a higher, albeit relatively low yield; aromatic $BF_3K$ salts were also found to be compatible with this system in good yield (**49e**), but pinacol boronic esters were found to be unreactive.

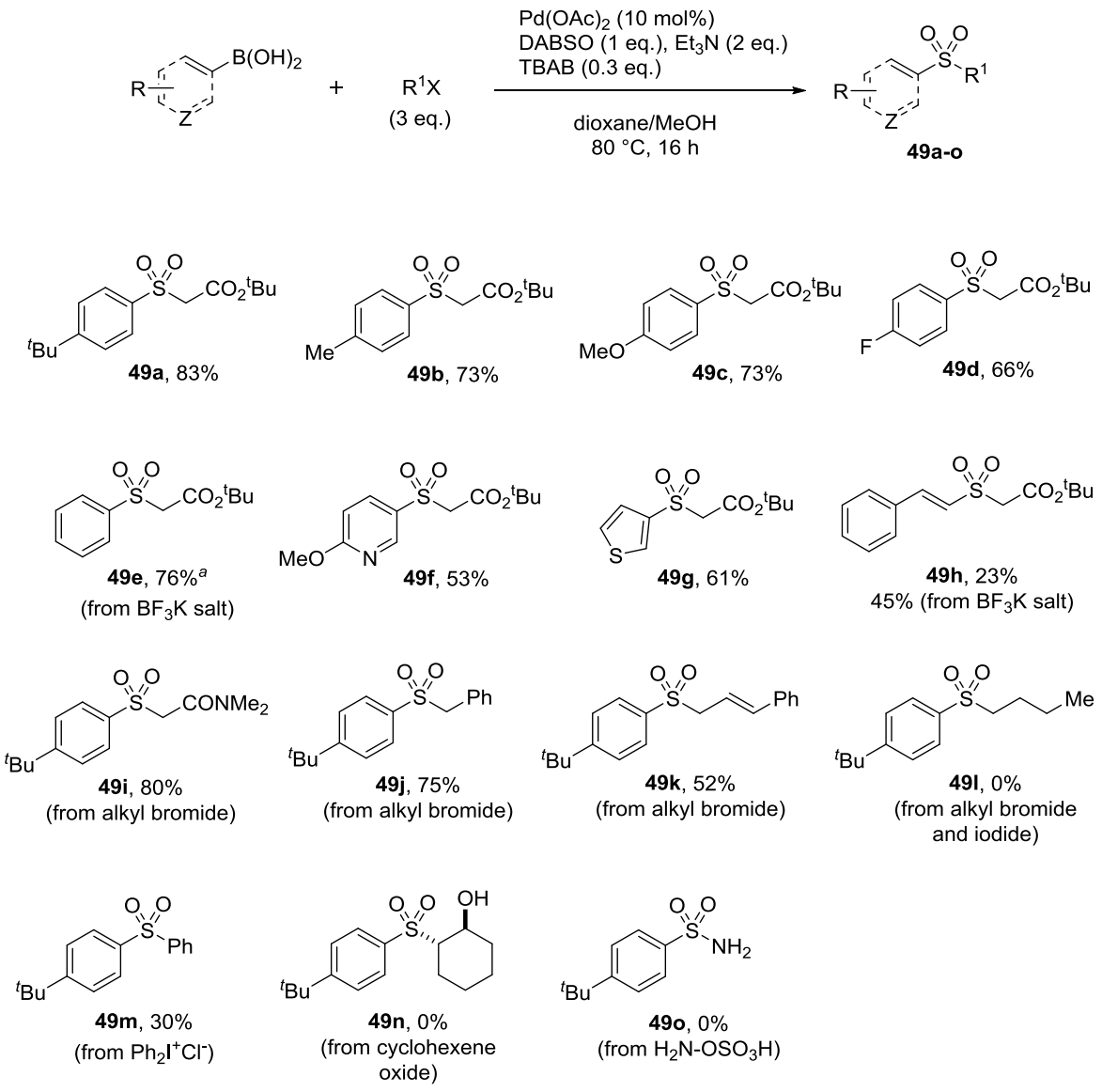



Figure 4.6 Boronic acid and electrophile scope for palladium-catalysed sulfone synthesis.

*Reaction conditions*: Boronic acid (0.25 mmol, 1 equiv.), $Pd(OAc)_2$ (10 mol%), DABSO (1 equiv.), $Et_3N$ (2 equiv.), MeOH/dioxane (1:1) [0.16 M], RX (0.75 mmol). [a] 100 °C.

On introducing different carbon-based electrophiles into this reaction, it was found that only the more activated alkylating agents could deliver sulfones in reasonable yields (**49i**, **49j** and **49k**). By moving to simple primary alkyl halides (bromides and iodides) the reaction failed, with immediate biphenyl and Pd black (Pd(0)) formation (**49l**). Additionally, use of diphenyliodonium chloride in this system afforded the corresponding diaryl sulfone **49m** in a low yield. These results, with alkyl halides in particular, could be indicative of a sulfinate

intermediate with reduced nucleophilicity e.g. Pd-sulfinate **47** (Figure 4.5). Alternatively, the incompatibility of such electrophiles could be attributed to the presence of β-hydrogens available for β-hydride elimination.

A further limitation of this one-step protocol, with the electrophile present at the start of the reaction, is the constraint on the reaction medium for the sulfinate derivatisation step. The optimum conditions for the Pd-catalysed process are not necessarily suitable for the subsequent electrophilic trapping step, so more complex electrophiles may not be compatible with this system. This was exemplified with the failed application of cyclohexene oxide (**49n**) and *O*-hydroxylaminesulfonic acid (**49o**) which require water as a reaction medium for sulfinate coupling.

Despite serving as an efficient means of preparing sulfones from boronic acids and activated electrophiles in a one-pot protocol, we were motivated to build on this and pursue the original proposal for preparing sulfinates as formal intermediates in a Pd-catalysed step followed by subsequent *in situ* trapping. This would potentially serve to generate a more reactive sulfinate intermediate, allow for solvent tuning in the separate coupling step and hence, greater electrophile variation and product scope would hopefully be achievable in this format.

## 4.7 Further investigation into the two-step sulfination reaction

Working from the original hypothesis and the results obtained up to this point, we proposed two methods to accomplish the desired Pd-S heterolytic bond cleavage of **47** in order to generate the "free" sulfinate and turnover the Pd(II) catalyst. It was postulated that metal-exchange with the Pd-sulfinate **47** or ligand coordination to the $Pd^{II}$ could promote the dissociation of the sulfinate and complete the catalytic cycle (Figure 4.7).

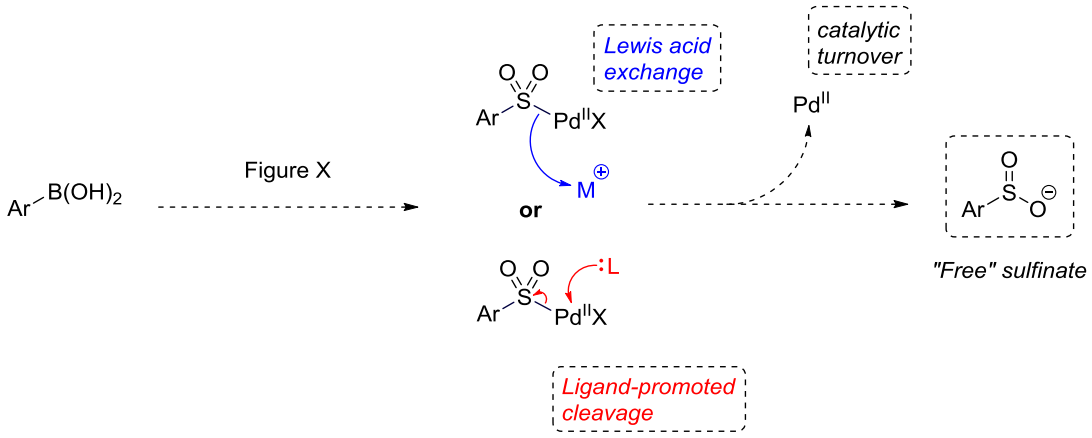
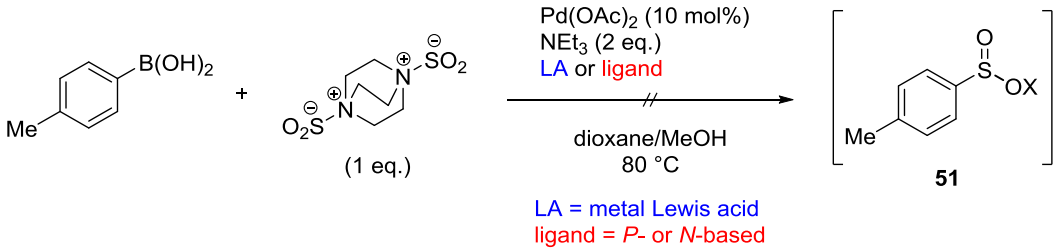



Figure 4.7 Proposed metal- and ligand-exchange of Pd-sulfinate **47**.

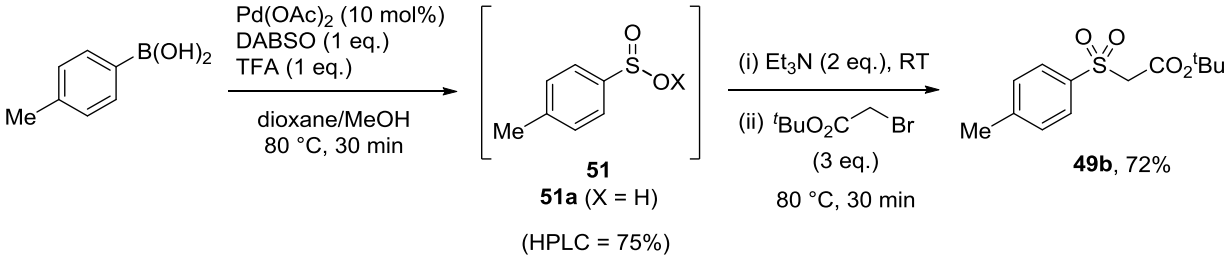
Unfortunately, using a range of metal salts (including, $Li^{+}$, $Na^{+}$, $Cs^{+}$, $Zn^{2+}$, $Ca^{2+}$, $Cu^{2+}$ and $Al^{3+}$) as Lewis acid additives or alkylammonium salts (TBAB, TBAI and TBAOH) to affect cation exchange, formation of *p*-tolyl sulfinate **51** was not observed by HPLC, with either no consumption of the starting material or biphenyl formation taking place (Scheme 4.5). A similar outcome was noted when introducing different phosphine or nitrogen-based ligands into the reaction.




Scheme 4.5 Attempted formation of sulfinate **51** *via* metal- and ligand-exchange.

In-keeping with the above hypothesis to displace the sulfinate from palladium, attention was turned towards identifying whether a Brønsted acid additive could deliver the sulfinic acid **51a** (Scheme 4.6). Use of such acidic conditions would require the absence of triethylamine and rely on the activation of the boronic acid substrate for transmetallation without a base. Promisingly, an initial reaction with trifluoroacetic acid led to the observation of the *p*-tolyl sulfinic acid **51** (or **51a**) in 75% HPLC yield, along with biphenyl formation after one hour (Scheme 4.6); this result was confirmed by treating the intermediate with base and subsequently

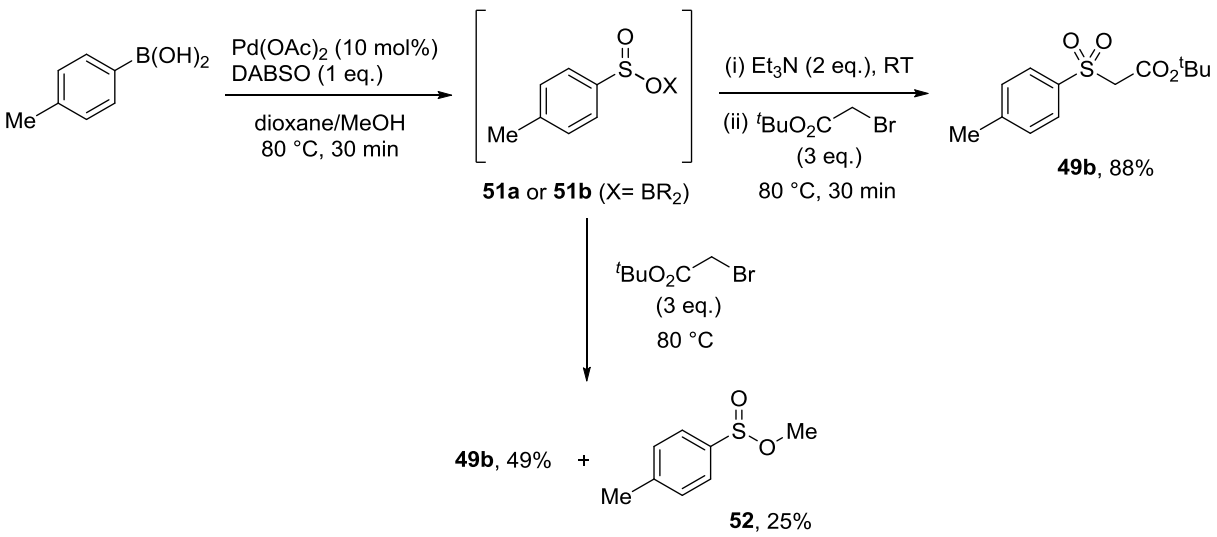
trapping with *tert*-butylbromoacetate to deliver the corresponding sulfone **49b** in 72% isolated yield. Further investigation of this sulfinate preparation was carried out with increasing loadings of the acid which was found to slow the rate of formation of **51** with no further improvements in the final yield.




Scheme 4.6 Synthesis of sulfone **49b** in two-steps *via* sulfinic acid **51a** as the proposed key intermediate.

With this encouraging result in hand, we were intrigued to test this reaction without any acid or base present. To our delight, by simply treating the aryl boronic acid with $Pd(OAc)_2$ and DABSO in dioxane/MeOH, the sulfinic acid derivative was observed in 92% HPLC yield after 30 minutes at 80 ºC. Subsequent base treatment and alkylation delivered sulfone **49b** in 88% isolated yield (Scheme 4.7). This result represented a significant breakthrough in that the desired sulfination of the boronic acid could be achieved in a short reaction time to generate the desired sulfinic acid derivative.

In addition, this result also served as an interesting observation from a mechanistic viewpoint. It is possible that small quantities of acid generated during the course of the reaction (methanol, boronic acid and "$SO_2$") accounts for the formation of sulfinic acid **51a** or even a boron sulfinate **51b** could be generated from the Lewis acidic boronic by-products (Scheme 4.7). Interestingly, when this two-step protocol was conducted without triethylamine, with the direct addition of the alkyl bromide to the sulfinic acid intermediate, the methyl sulfinic acid ester **52** was obtained in a low yield, together with sulfone **49b** in a reduced yield (Scheme 4.7). This observation supports the possible generation of an electrophilic sulfinic acid derivative that can undergo nucleophilic attack by methanol (see Section 4.9 for further mechanistic considerations).



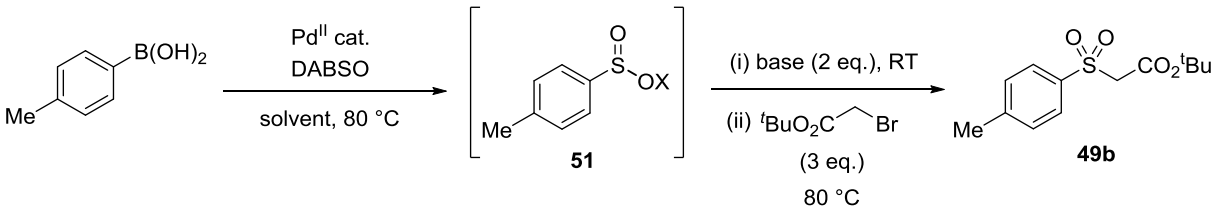

Scheme 4.7 Two-step sulfination and alkylation process with and without base treatment.

Prior to examining the substrate scope of this two-step system, a brief exploration of the reaction conditions was conducted (Table 4.4). Interestingly, replacing methanol with alternative alcoholic solvents, in combination with dioxane, failed to generate the sulfinic acid intermediate **51** (Entries 1 to 3, Table 4.4). The significance of methanol as the reaction medium was further demonstrated with its successful use as both the solvent and a co-solvent with dioxane (Entries 4 and 5).

Use of alternative $Pd^{II}$ salts was also found to afford **51** in high yields, but offered no advantage over $Pd(OAc)_2$ (Entries 6 and 7). Pleasingly, the catalyst loading could be reduced to 3 and 5 mol% with little or no reduction in yields, respectively (Entries 8 and 12). Employing *N*-methylmorpholine sulfur dioxide complex or $K_2S_2O_5$ in place of DABSO resulted in only biphenyl formation (Entries 10 and 11). Finally, employing alternative organic (Entry 13) and inorganic bases (Entries 14 and 15) in the second step of this sequence did deliver **49b** in good yields but lower than with triethylamine; a potential consequence of the different sulfinate counterions.

Therefore, the optimised set of conditions carried through to the reaction scope assessment was that outlined in Scheme 4.7 but with a lower catalyst loading of 5 mol% (Entry 8).

Table 4.4 Examination of reaction conditions for two-step synthesis of sulfone **49b**.



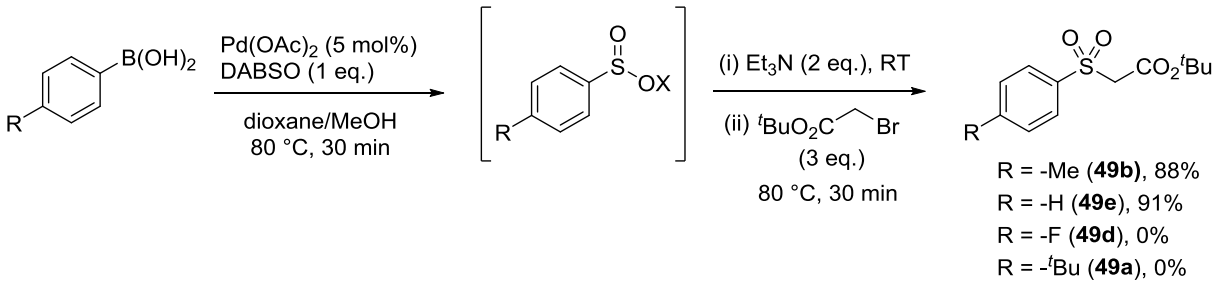

| Entry | Solvent | Pd source (mol %) | Base | Yield (51) [a] | Yield (49b) [a] |
|---|---|---|---|---|---|
| **1** | Dioxane/EtOH | $Pd(OAc)_2$ (10) | $Et_3N$ | 0% | - |
| **2** | Dioxane/$^t$BuOH | $Pd(OAc)_2$ (10) | $Et_3N$ | 0% | - |
| **3** | Dioxane/IPA | $Pd(OAc)_2$ (10) | $Et_3N$ | 0% | - |
| **4** | Dioxane | $Pd(OAc)_2$ (10) | $Et_3N$ | 0% | - |
| **5** | MeOH | $Pd(OAc)_2$ (10) | $Et_3N$ | 84% [b] | 82% |
| **6** | Dioxane/MeOH | $PdCl_2$ (10) | $Et_3N$ | 86% [b] | 83% |
| **7** | Dioxane/MeOH | $Pd(TFA)_2$ (10) | $Et_3N$ | 81% [b] | 81% |
| **8** | Dioxane/MeOH | $Pd(OAc)_2$ (5) | $Et_3N$ | 93% [b] | 89% [c] |
| **9** | Dioxane/MeOH | $Pd(OAc)_2$ (5) [d] | $Et_3N$ | 76% [b] | - |
| **10** | Dioxane/MeOH | $Pd(OAc)_2$ (5) [e] | $Et_3N$ | 0% [f] | - |
| **11** | Dioxane/MeOH | $Pd(OAc)_2$ (5) [g] | $Et_3N$ | 0% [f] | - |
| **12** | Dioxane/MeOH | $Pd(OAc)_2$ (3) | $Et_3N$ | 91% [b] | 86% [c] |
| **13** | Dioxane/MeOH | $Pd(OAc)_2$ (10) | DIPEA | - | 78% |
| **14** | Dioxane/MeOH | $Pd(OAc)_2$ (10) | $K_2CO_3$ | - | 70% |
| **15** | Dioxane/MeOH | $Pd(OAc)_2$ (10) | $Cs_2CO_3$ | - | 78% |

*Reaction Conditions*: Boronic acid (0.25 mmol, 1 equiv.), Pd cat. (3-10 mol%), DABSO (1 equiv.), base (2 equiv.), solvent [0.16 M].[a] HPLC yields relative to benzophenone as an internal standard. [b] Observed with 3-6% of homocoupled product [c] Isolated yields. [d] With DABSO (0.6 equiv.). [e] With *N*-methylmorphiline·$SO_2$. [f] Starting material and biphenyl formation observed. [g] With $K_2S_2O_5$ (2 equiv.).

# 4.8 Reaction scope for the two-step reaction

## 4.8.1 Boronic acid substrates

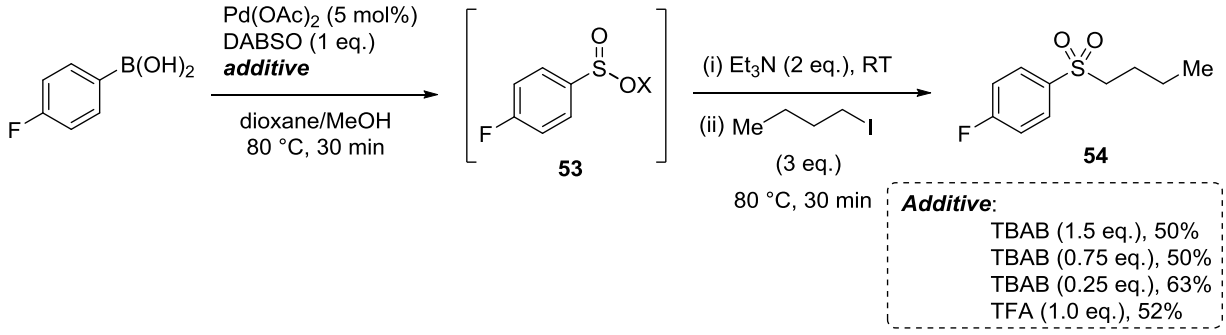
On initially assessing different aryl boronic acid substrates in the two-step protocol, it was quickly established that changing the electronics of the aromatic ring was detrimental to the sulfination reaction. While *p*-tolyl- and phenylboronic acid could undergo the sulfination and deliver the corresponding sulfones in high yields, employing the *p*-fluoro and *p-tert*-butyl substrates under the same conditions resulted in no desired reaction with biphenyl and Pd black formation (Scheme 4.8). This observation bears some resemblance to that made by Toste and co-workers in their gold-catalysed sulfination reaction, where aryl boronic acid substrates bearing electron-withdrawing groups were found to be incompatible.[88]




Scheme 4.8. Reactivity of electronically differentiated aryl boronic acids in the palladium-catalysed sulfination reaction.

Following this disappointing result, a brief investigation into the reaction with *p*-fluorophenylboronic acid was carried out. In particular, attention turned towards employing an additive in this system to limit the homocoupling side reaction. Taking inspiration from Wu's boronic acid aminosulfonylation chemistry (Section 1.4.2)[74] the use of TBAB was explored. Pleasingly, by introducing an excess of TBAB (1.5 equiv.) the *p*-fluorophenyl sulfinate **53** was obtained. Addition of triethylamine and *tert*-butylbromoacetate at this point would potentially allow any remaining boronic acid to react in the one-step manner (as outlined above in Section 4.5). Hence, this would lead to a combined yield of sulfone **49d** (Figure 4.6) from the sulfinate intermediate and the unreacted boronic acid. As a result, in order to gain differentiated insight into the sulfination of *p*-fluorophenylboronic acid with

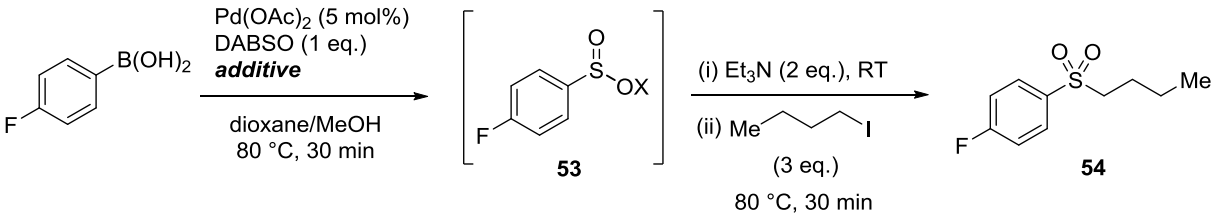
TBAB as an additive, *n*-butyliodide was used *in lieu* of *tert*-butylbromoacetate; this simple alkyl iodide was known to be unreactive in the one-step reaction (Section 4.6). Having confirmed the compatibility of *n*-butyliodide as an electrophile in the two-step procedure with *p*-tolylboronic acid (Section 4.8.2, **56**, Scheme 4.11), intermediate **53** was treated with triethylamine and the alkyl iodide to afford sulfone **54** in a moderate yield (Scheme 4.9).




Scheme 4.9 Use of TBAB to affect the sulfination of *p*-fluorophenylboronic acid.

With further investigation of this reaction, it was observed that sulfone **54** could be isolated in a higher yield of 63% using lower loadings of TBAB (Scheme 4.9). Trifluoroacetic acid was also tested as an additive, based on its successful use in the original studies into the sulfination of *p*-tolylboronic acid (Section 4.7). However, sulfone **54** was obtained in a reduced yield in comparison with TBAB. Prior to continuing with the boronic acid scope using these modified conditions, a brief screen of alternative bromide sources and ammonium halides was conducted (Table 4.5). Employing BTEABr in place of TBAB was found to affect the sulfination, but in reduced yield (Entry 6, Table 4.5), while the use of metal bromide salts resulted in no reaction (Entries 1 to 5). Interestingly, use of ammonium chloride salts as additives also resulted in sulfinate formation but once again in lower yields compared to TBAB (Entries 9 to 12).

Table 4.5 Examination of alternative additives for the sulfination of *p*-fluorophenylboronic acid.




| Entry | Additive | Equiv. | Isolated yield (54) |
|---|---|---|---|
| **1** | NaBr | 0.25 | 0% |
| **2** | NaBr | 1.0 | 0% |
| **3** | KBr | 0.25 | 0% |
| **4** | KBr | 1.0 | 0% |
| **5** | $ZnBr_2$ | 0.25 | 0% |
| **6** | BTEABr | 0.25 | 52% [a] |
| **7** | TBAF | 0.25 | 0% [a] |
| **8** | TBAI | 0.25 | 0% [a] |
| **9** | TBAC | 0.25 | 12% [a] |
| **10** | TBAC | 1.0 | 26% [a] |
| **11** | BTEAC | 0.25 | 18% [a] |
| **12** | BTEAC | 1.0 | 40% [a] |

*Reaction Conditions*: Boronic acid (0.25 mmol, 1 equiv.), Pd cat. (5 mol%), DABSO (1 equiv.), base (2 equiv.), additive (0.25 or 1 equiv.), dioxane/MeOH (1:1) [0.16 M].[a] Starting material and biphenyl formation also observed.

Having identified a modified optimal set of conditions, with the use of TBAB as an additive, the boronic acid scope was continued. Employing *tert*-butylbromoacetate as the electrophile, a range of sulfones could be obtained incorporating diverse functionality and substitution patterns (Figure 4.8).

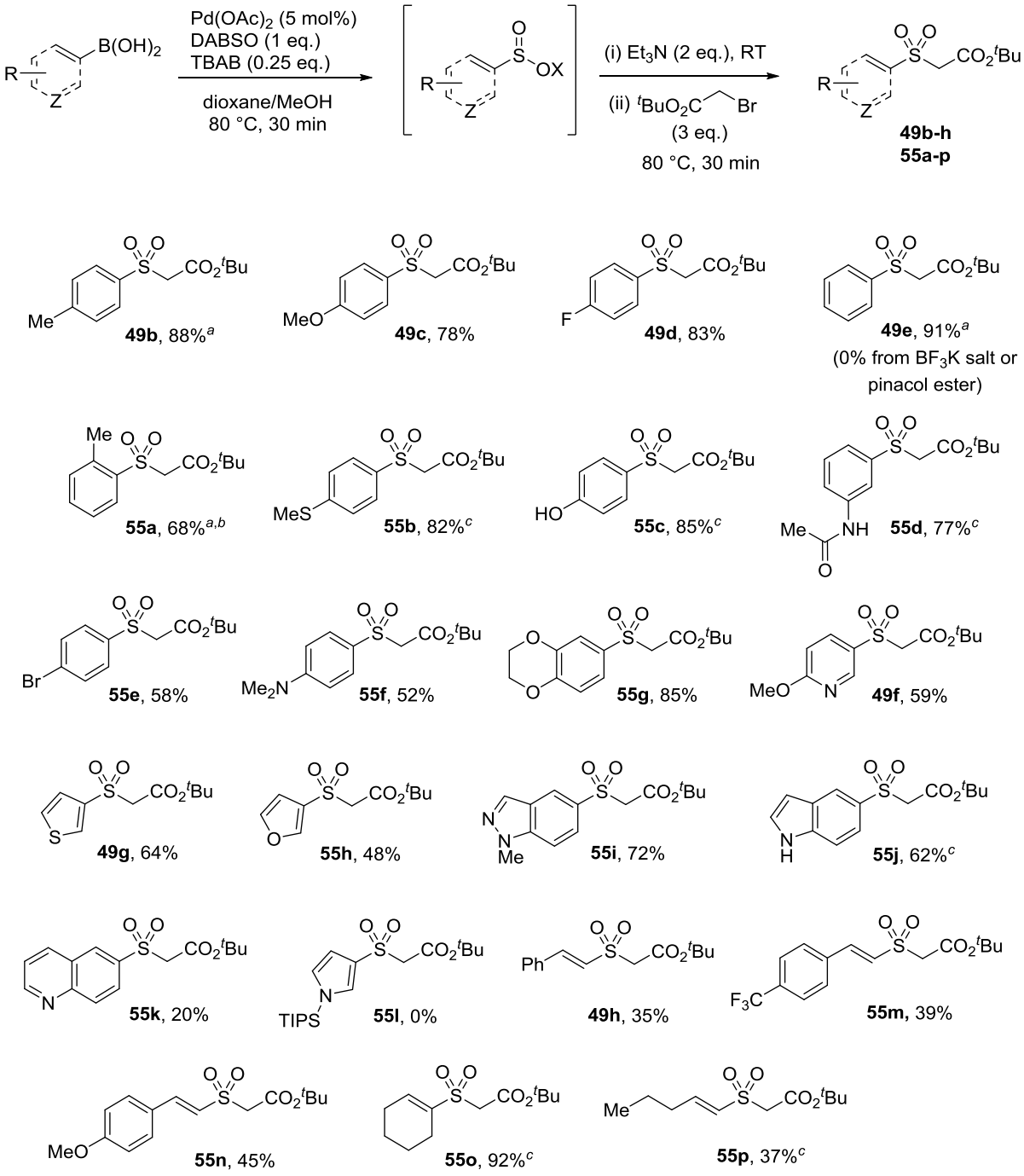



Figure 4.8 Boronic acid scope for the synthesis of sulfones in the two-step sulfination protocol.

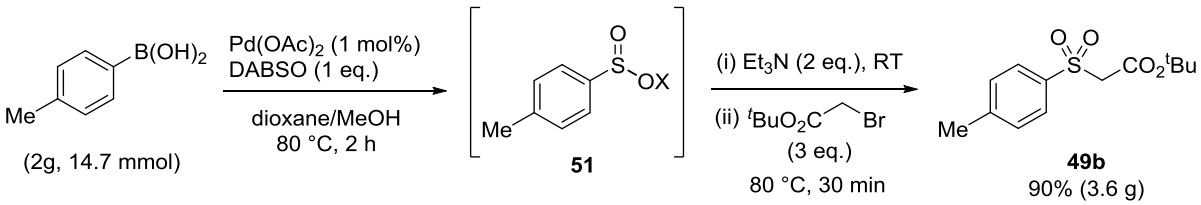
*Reaction conditions*: (i) Boronic acid (0.25 mmol, 1 equiv.), $Pd(OAc)_2$ (5 mol%), DABSO (1 equiv.), TBAB (0.25 equiv.) dioxane/MeOH (1:1) [0.16 M], 80 ºC. (ii) $Et_3N$ (2 equiv.) RT, 1 min. (iii) *tert*-butylbromoacetate (3 equiv.), 80 ºC, 30 min. [a] Without TBAB. [b] Sulfination step for 3 hr. [c] Sulfination step for 1 hr.

Substrates bearing electron-donating and -withdrawing groups, as well as *ortho*, *meta* and *para* substitution patterns were all well tolerated in this system. The sulfination of the *ortho*-substituted boronic acid required a longer reaction time, but the corresponding sulfone could be obtained in a good yield (**55a**, Figure 4.8). A particularly pleasing aspect of this scope was the compatibility of sensitive functional groups such as phenol (**55c**), amide (**55d**) and indole (**55j**) moieties. This serves as a progression on the previous organometallic/DABSO chemistry (Chapters 2 and 3) where such functionality would require protection. Additionally, the successful use of the methylthio-substituted boronic acid (**55b**) demonstrates the benefit of this chemistry over traditional sulfide oxidation strategies, where access to such products would not be possible. In contrast to the one-step system, aromatic $BF_3K$ salts did not serve as substrates in this procedure, with only remaining starting material observed; pinacol boronic esters were also found to be incompatible.

On further examination of the reaction scope with more challenging boronic acid substrates, we were pleased to find that a variety of heteroaromatic groups could be tolerated. Thiophene and furan substrates delivered the corresponding products in reasonable yields (**49g** and **55h**, respectively), while *ortho* substitution to the pyridine nitrogen was necessary for its introduction in sulfone product **49f**; use of pyridine-3-boronic acid unfortunately returned no product with only biphenyl formation detected. In addition, benzodioxane (**55g**) and indazole (**55i**) substrates were found to perform well.

An assessment of alkenyl boronic acids as substrates was also carried out. It was found that styryl boronic acids were compatible under the reaction conditions but sulfones could only be obtained in relatively low yields (**49h**, **55m** and **55n**); a consequence of the observed rapid homocoupling and Pd(0) formation. Interestingly, while the simple straight chain alkenyl boronic acid exemplified similar reactivity (**55p**), the cyclohexenyl substrate delivered the corresponding sulfone **55o** in a pleasingly high yield with no homocoupling observed.

Further to this, we were pleased to find that this sulfination/alkylation sequence could be carried out on a preparative scale. Employing 1% catalyst loading, the sulfination of *p*-tolylboronic acid (14 mmol) went to completion in 2 hours by simply refluxing open to air and subsequent trapping with *tert*-butylbromoacetate afforded sulfone **49b** in a 90% yield (Scheme 4.10).



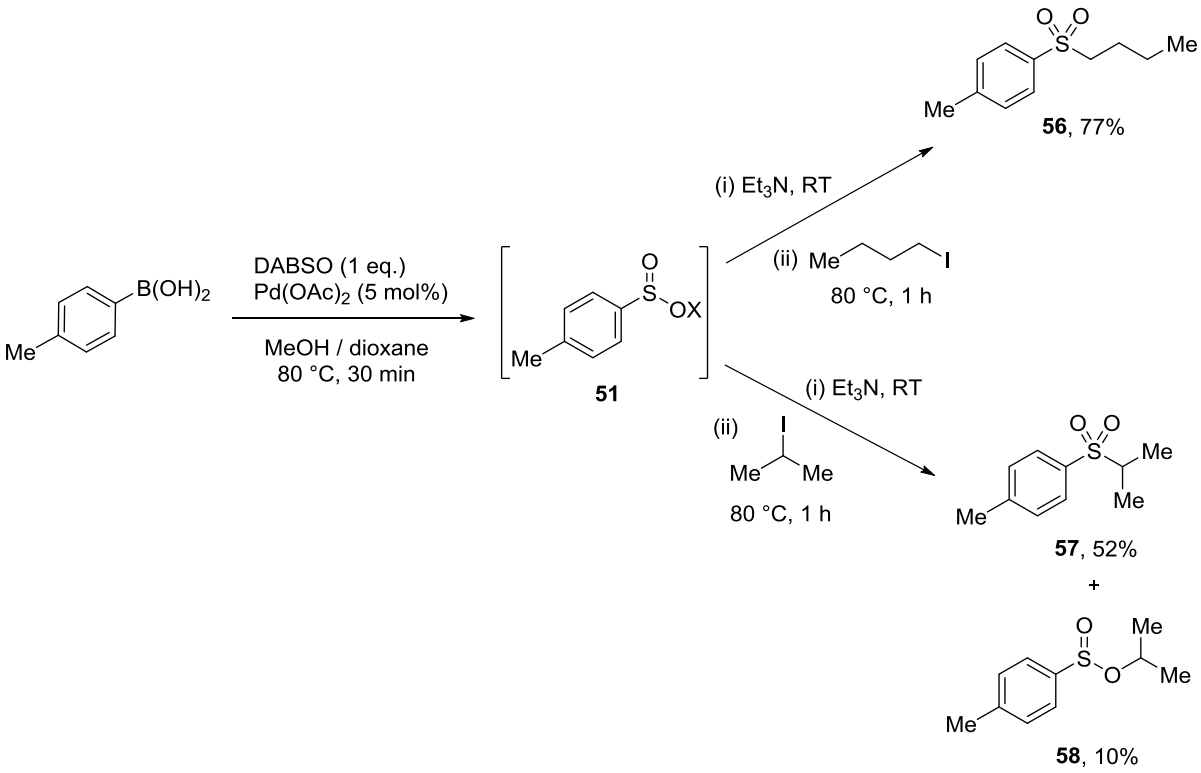

Scheme 4.10 Synthesis of sulfone **49b** on a preparative scale.

## 4.8.2 *In situ* sulfinate derivatisations

Satisfied with the scope of boronic acids amenable to this sulfination process, assessing the subsequent *in situ* derivatisation of sulfinates became the focus of the investigation. It was the aim of the study to expand the scope of sulfonyl-containing products beyond those accessible with the one-step procedure. With an effective (separate) sulfination step, we hoped to progress from employing activated electrophiles, to applying a range of coupling partners in this stepwise protocol. This would be accomplished by encompassing transformations demonstrated in the previous work involving magnesium, lithium and zinc sulfinates (Chapters 2 and 3). Additionally, we were eager to exploit the simple conditions used to affect the boronic acid sulfination to achieve sulfinate derivatisations that had previously failed or been low yielding in the aryl halide palladium-catalysed methodologies (Willis and Shavnya, Section 4.3.1).[78,87]

### Preparation of sulfones

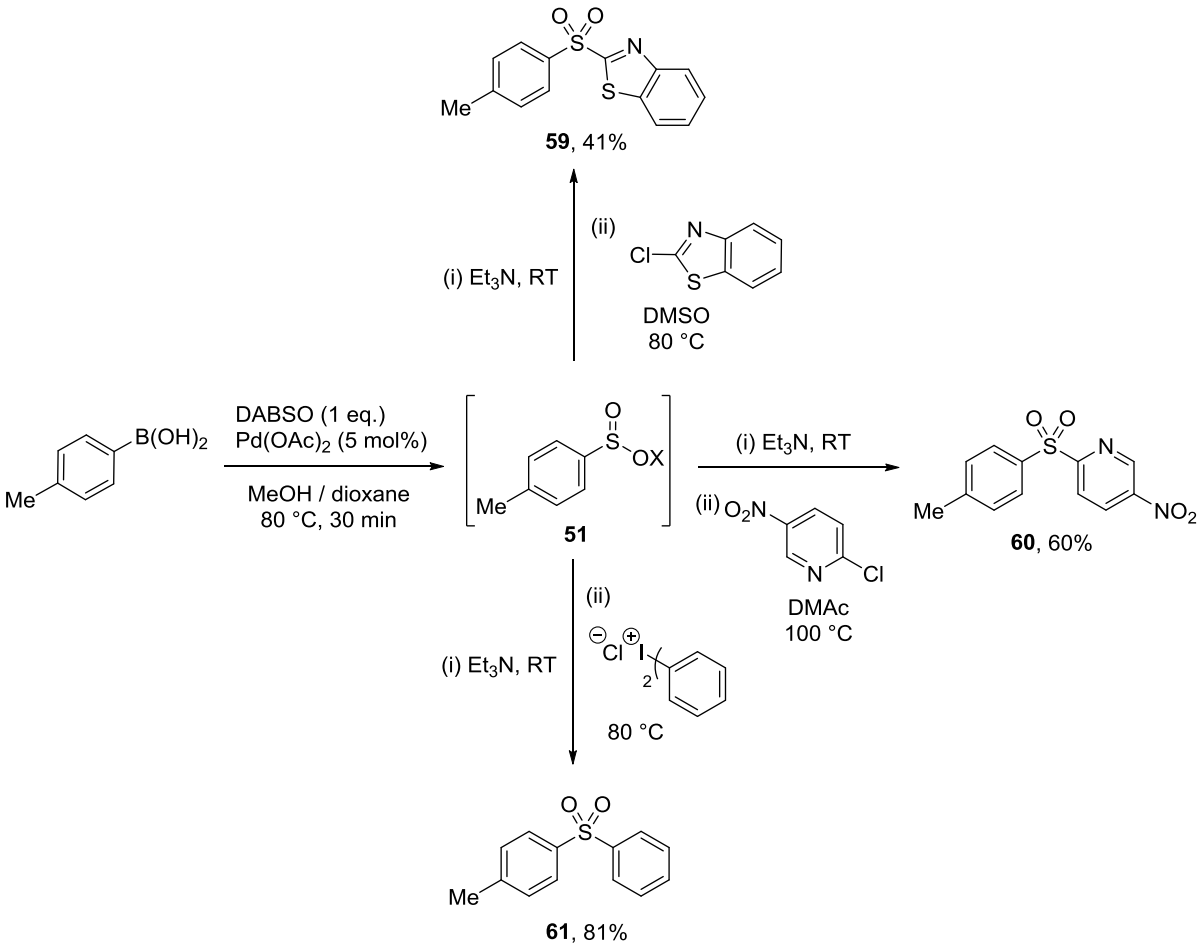
Initial experiments concentrated on the applications of electrophiles that had been tested and proved to be incompatible in the one-step process. Pleasingly, simple alkyl halides were demonstrated as effective coupling partners even maintaining the MeOH/dioxane co-solvent system. Where the use of *n*-butyliodide in the one-step process resulted in no sulfone formation, it served as an effective electrophile in the second step in this reaction with sulfone **56** obtained in a 77% yield (Scheme 4.11). This significant reactivity difference could be the consequence of two different sulfinate intermediates being generated in the one- and two-step reactions.




Scheme 4.11 Alkylations of sulfinic acid derivative **51**.

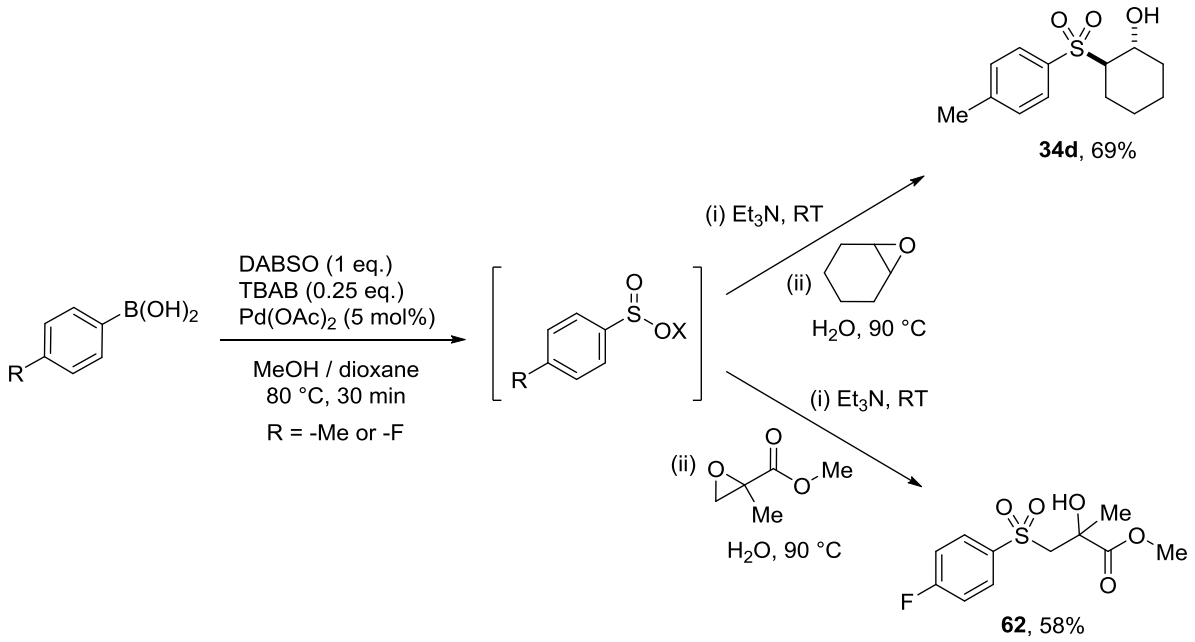
The compatibility of secondary alkyl iodides was also demonstrated with the use of *iso*propyl iodide to afford sulfone **57** in a moderate yield (Scheme 4.11). In this case, the sulfone was obtained together with a small amount of the corresponding sulfinic acid ester **58**, the result of sulfinate *O*-alkylation. Such ambident behaviour of sulfinate ions in alkylation reactions has been rationalised by Baidya *et al*. on kinetic and thermodynamic grounds.[155] It was proposed that *O*-attack is intrinsically highly favoured over *S*-attack and reactions under kinetic control promote *O*-alklyation, giving rise to mixtures of the sulfone and sulfinic acid ester products. Therefore, with the sterically hindered alkyl iodide in this reaction, the sulfinate nucleophilic approach is impaired resulting in a reduced rate of reaction and the potential for the less thermodynamically stable *O*-alkylated product to be formed.

Diaryl sulfones can also be accessed through this chemistry with both diaryliodonium salts and "$S_NAr$ coupling partners" delivering products in high and moderate yields, respectively (Scheme 4.12).




Scheme 4.12 Arylations of sulfinic acid derivative **51**.

With the ability to modify the reaction conditions in the second step by generating the sulfinate as a formal intermediate, epoxide ring opening could be achieved. *β*-Hydroxy sulfones could be accessed by removing the original solvents and treating the crude sulfinate with the epoxide in water (Scheme 4.13). Further to this, the efficacy of *p*-fluorophenylboronic acid as a substrate (**49d**, Figure 4.8) was exploited with the synthesis of the *β*-hydroxy sulfone **62** in a respectable yield (Scheme 4.13); this product is the ester derivative of the anti-androgen Casodex.




Scheme 4.13 *In situ* epoxide ring-opening providing access to *β*-hydroxy sulfones from boronic acids.

## Preparation of sulfonamides

With the successful coupling of carbon-based electrophiles to prepare a variety of sulfones, we turned our attention to exploiting this sulfination reaction to access sulfonamides. This was initially explored by applying the sulfinate amination strategy for preparing sulfonamides developed in previous work (Chapter 3). Taking these exact conditions, we were pleased to find that treatment of crude sulfinate **51** with morpholine and sodium hypochlorite in water, delivered the corresponding sulfonamide in a high yield (**63a**, Figure 4.9). The combination of boronic acids and *N*-chloroamines to access more challenging sulfonamides was demonstrated with the synthesis of products **63b** and **63c** in moderate and high yields respectively (Figure 4.9).

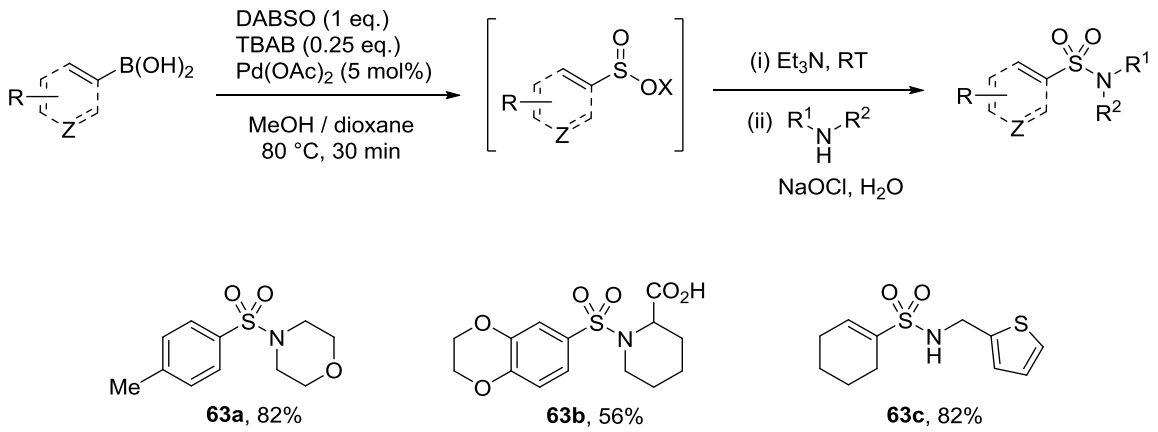



Figure 4.9 Combination of boronic acid sulfination and *N*-chloroamine-based sulfonamide preparation.

Further to this, we aimed to exploit this sulfinate preparation for the synthesis of unsubstituted sulfonamides. Electrophilic trapping of sodium sulfinates has been precedented with *O*-hydroxylaminesulfonic acid[156] but attempts at performing this in previous palladium-catalysed sulfinations (Willis group and Shavnya *et al.*)[78,87] were either low yielding or delivered no product. We were therefore pleased to find that with this boronic acid sulfination method, treatment of the crude sulfinate **51** with an excess of *O*-hydroxylaminesulfonic acid in water afforded the unsubstituted sulfonamide in a high yield (**64a**, Figure 4.10). Once more, products **64b** and **64c** were prepared as representative structures accessible with this reaction (Figure 4.10).

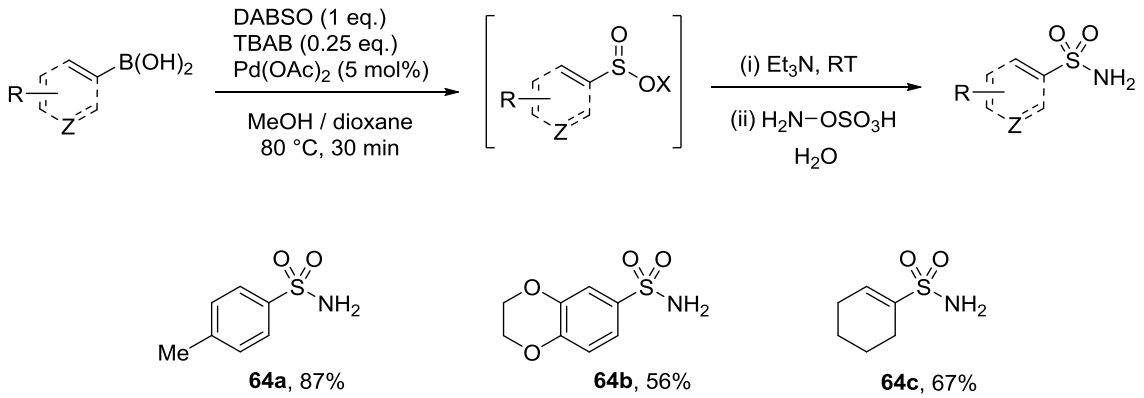
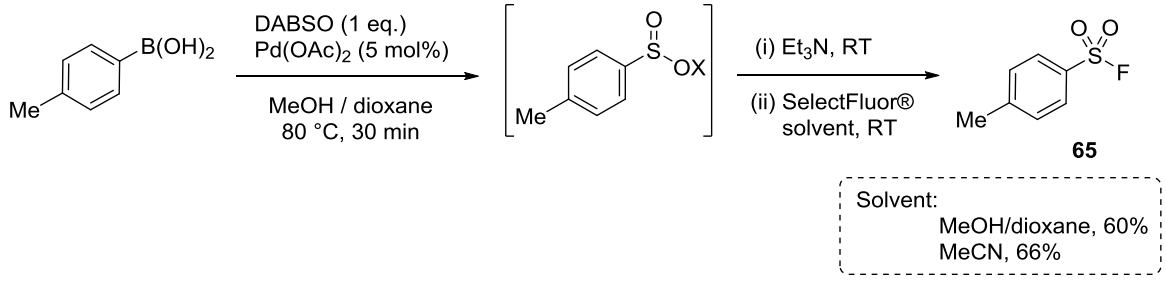



Figure 4.10 Synthesis of unsubstituted sulfonamides *via* palladium-catalysed sulfination of boronic acids.

**Preparation of sulfonyl fluorides**

Sulfonyl fluorides have gained recent attention as convenient alternatives to sulfonyl chlorides as electrophilic sulfonyl precursors.[157] Not only do sulfonyl fluorides possess enhanced thermodynamic and aqueous stability, but they are more suitable electrophiles for specific amino acid reactivity.[158] Hence, these fluorinated variants have been established as effective probes in medicinal chemistry for monitoring enzyme binding sites and protein residues.[159]

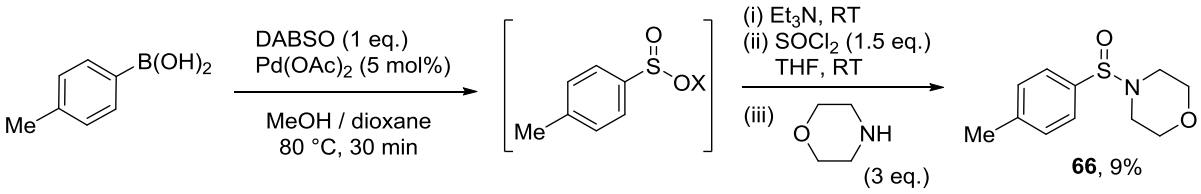
With this in mind, accessing sulfonyl fluorides *via* our sulfination reaction was identified as an attractive transformation. The fluorination of sodium sulfinates with SelectFluor® was established by Banks *et al*. and as such the use of this electrophilic fluourinating agent was exploited in our system.[160] It was found that with an excess of SelectFluor® (5 equiv.) and retaining the MeOH/dioxane co-solvent system, the corresponding sulfonyl fluoride **65** could be obtained in a reasonable 60% yield (Scheme 4.14). This yield could be enhanced slightly by performing a solvent swap to acetonitrile (Scheme 4.14). In all cases, complete consumption of the sulfinate intermediate was observed but frustratingly this did not translate into high isolated yields.




Scheme 4.14 Fluorination of sulfinic acid **51** using SelectFluor®.

**Preparation of sulfinyl chlorides**

It was postulated whether sulfinyl compounds could be accessed with this chemistry. A brief inspection of the *in situ* chlorination of sulfinate **51** to generate the corresponding sulfinyl chloride was carried out. Employing thionyl chloride to affect this chlorination and morpholine as the nucleophile, sulfinamide **66** was isolated in a poor yield (Scheme 4.15).




Scheme 4.15 Attempted sulfinamide synthesis from sulfinic acid derivative **51**.

Despite this low yield, this serves as a promising result for accessing the sulfinyl oxidation level *via* the boronic acid sulfination methodology. Further advances with this mode of transformation are possible by employing alternative sulfinate activation strategies to access electrophilic sulfinic acid derivatives such as carbodiimide-mediated couplings.[161]

## 4.9 Mechanistic considerations

As well as serving as a versatile means of preparing sulfonyl-containing compounds, this boronic acid sulfination chemistry is particularly interesting from a mechanistic viewpoint. By carrying out extensive screening studies and assessing the influence of many variables on the reactivity, in both the one- and two-step one-pot protocols, certain mechanistic scenarios can be postulated.

### 4.9.1 Formation of the sulfinic acid derivative

The observed reduction in yield of sulfone **49b** and the formation of methyl ester **52** in the absence of triethylamine supports the theory that a sulfinic acid of the type **51** is generated under the sulfination conditions (Scheme 4.7, Section 4.7). Firstly, by undergoing nucleophilic attack with methanol at high temperature it is suggestive of an electrophilic character to this intermediate and is akin to the behaviour of carboxylic acid derivatives towards alcohol nucleophiles. Furthermore, the requirement for a base to aid the nucleophilic reactivity could be due to the deprotonation of sulfinic acid **67** (Path A, Figure 4.11) or activation of the boron sulfinate **68** (Path B) to arrive at **70**. The latter of these pathways would proceed *via* boronate complex **69**.

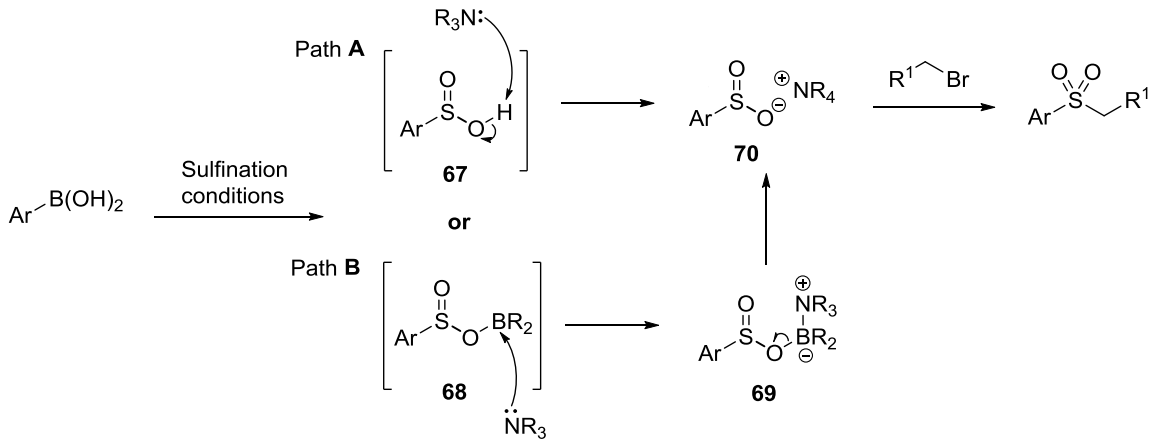
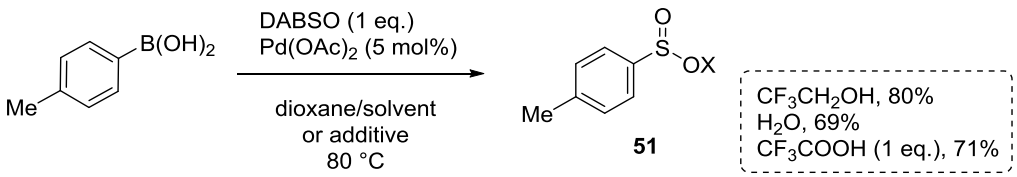



Figure 4.11 Two possible sulfinic acid intermediates and possible reaction pathways for the sulfination reaction.

With the potential generation of sulfinic acid **67**, the identity of the proton source was contemplated. Reflecting on previous screening results, the dependence on methanol as the reaction solvent led us to consider it as the "$H^+$" source in this process. Initially, it was noted that the pKa of methanol (15.5) is slightly lower than those of the other alcoholic solvents that failed in this reaction; ethanol (16.0), *iso*-propanol (16.5) and *tert*-butanol (17.0). As a result, 2,2,2-trifluoroethanol (pKa 12.5) and water (pKa 15.7) were assessed in this reaction as similar or more acidic alternative solvents to test this hypothesis. Interestingly, these two protic solvents were found to be suitable media with the acid derivative **51** prepared in good (HPLC) yields (Scheme 4.16). Furthermore, formation of **51** could be affected by carrying out the reaction in dioxane and in the presence of trifluoroacetic acid (Scheme 4.16); without this proton source no reaction was observed with dioxane as the solvent (Table 4.4, Section 4.7).

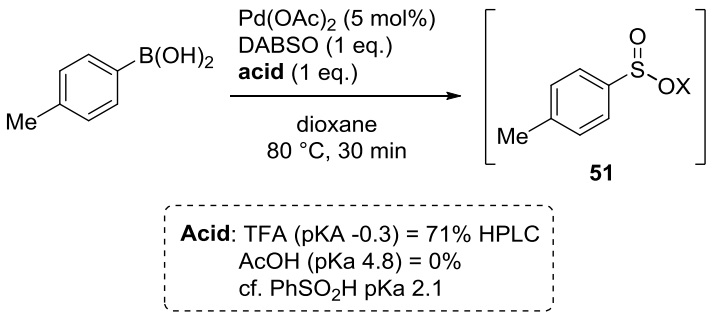



Scheme 4.16 Sulfinate formation with alternative solvents and additives.

Together these results indicate that a proton source is required for the sulfination to take place either in the form of a protic solvent - with a low enough pKa and aided by Lewis acid coordination ($BR_3$, $SO_2$ or Pd) - or an acid additive. This provides further support for the formation of the sulfinic acid type **67** in this sulfination process.

Bringing these findings together, along with the observed formation of methyl sulfinic acid ester **52** in a low yield (without base addition), it is proposed that as the reaction proceeds DABCO is generated *in situ* and can deprotonate the sulfinic acid. With the requirement for base addition to the sulfinate intermediate to ensure only sulfone formation, it is suggested that the *in situ* proton exchange does not go to completion resulting in a mixture of the sulfinic acid and the sulfinate; a potential consequence of limited DABCO present in the reaction as a result of consumption by Lewis acidic boron by-products. Therefore, in the absence of extra base (triethylamine) the DABCO-sulfinate is trapped by *tert*-butylbromoacetate as expected while the sulfinic acid **67** can react as an electrophile in the presence of an excess of methanol.

To test the theory of sulfinic acid formation further, acetic acid was employed (with dioxane as solvent) as an acid additive with a higher pKa (4.8) than phenyl sulfinic acid (pKa of 2.1). Interestingly, acetic acid proved ineffective with no reaction observed, while as aforementioned, in the presence of trifluoroacetic acid (pKa -0.3) sulfination of *p*-tolylboronic acid (in the absence of MeOH) was achieved in a high yield (Scheme 4.17). Hence, an acid with a pKa higher than that of the *p*-tolyl sulfinic acid (~2.1) is unable to affect its protonation and the catalytic cycle cannot proceed; acids with a lower pKa, in contrast, allow for the completion of the catalytic cycle.




Scheme 4.17 Comparison of TFA and AcOH as acid sources in the formation of sulfinic acid **51**.

Consequently, the preliminary mechanistic hypothesis for the formation of sulfinic acid derivative **67**, based on the initial findings from this study, is outlined below (Figure 4.12). It was proposed that an activated methanol proton source is generated during the course of the reaction and serves to protonate the Pd-sulfinate **47**. Two possibilities for the origin of the acid formation are alcohol coordination to the Lewis acidic sulfur dioxide (A, Figure 4.12) or boron by-products (B). Furthermore, it also feasible that all three components, sulfur dioxide, $BR_3$ derivatives and methanol, play a role in forming the acid required.

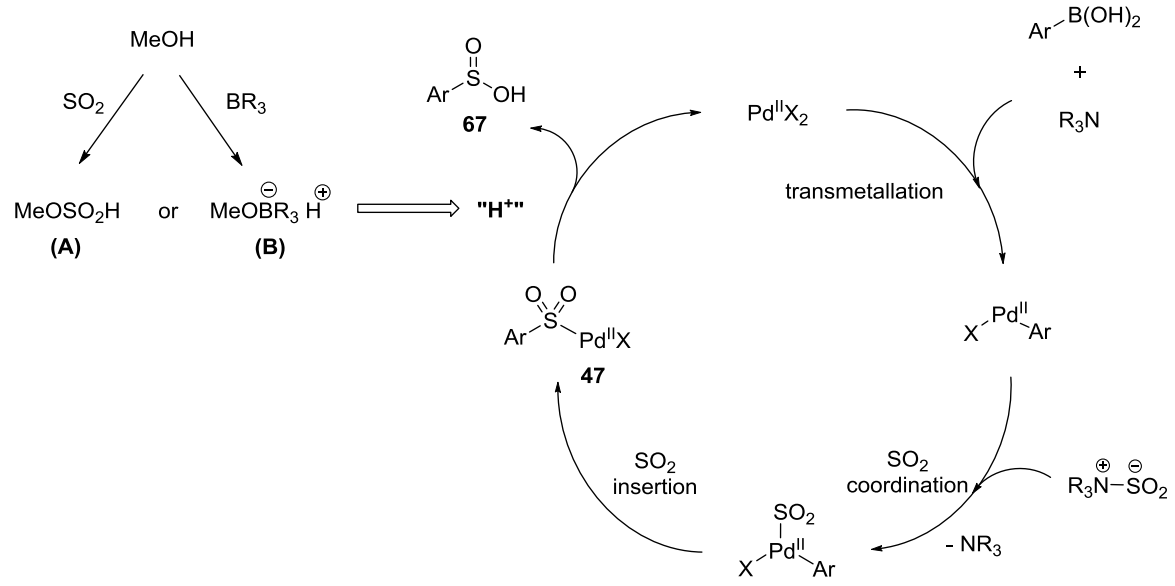


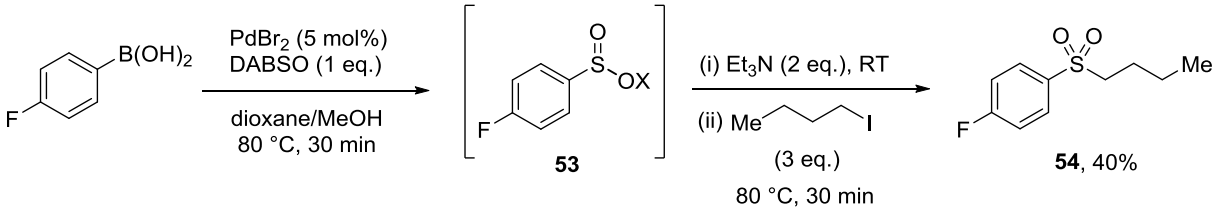

Figure 4.12 Working mechanistic hypothesis for the boronic acid sulfination reaction.

Considering the observed solvent dependency in this reaction, it is possible that like methanol, the corresponding sulfurous (A) or boron-based (B) acids generated when water and trifluoroethanol are used as solvents have pKa's low enough for the formation of sulfinic acid **67**. In contrast, the other, less acidic alcoholic solvents tested in this reaction, ethanol, *iso*-propanol and *tert*-butanol, serve to form weaker acids incapable of affecting the protonation of sulfinate intermediate **47** i.e. pKa's $\geq$ 2.1.

This is very much a working hypothesis based on early experimental findings and comprehensive studies are required to elucidate this mechanism further.

### 4.9.2 Role of TBAB

A final mechanistic aspect to consider is the role of TBAB as an additive to favour the desired sulfination pathway and limit the competing homocoupling of electron-rich and deficient boronic acids. Building on the original assessment of the sulfination of *p*-fluorophenyl boronic acid (Table 4.5, Section 4.8.1), $PdBr_2$ was tested in this reaction *in lieu* of $Pd(OAc)_2$/TBAB. Interestingly, the formation of sulfinic acid **53** was observed by HPLC and sulfone **54** was obtained in a 40% yield (Scheme 4.18).




Scheme 4.18 Formation of sulfinic acid derivative **53** using $PdBr_2$.

This result, relative to the 63% yield obtained with TBAB as an additive (Scheme 4.9, Section 4.8.1), suggests that the alkylammonium salt acts as a bromide source in the reaction and demonstrates the apparent influence of bromide ligands coordinating to the $Pd^{II}$ centre in promoting the sulfination pathway. It is possible that the bromide coordination serves to limit the homocoupling side reaction and hence the reduction of the Pd(II) to Pd(0), or it could promote $SO_2$ coordination/insertion.

Further to this, having observed the formation of **53** with BTEAC in place of TBAB (Entries 11 and 12, Table 4.5, Section 4.8.1), the reaction was attempted with $PdCl_2$ as the catalyst (without an additive). However, only boronic acid homocoupling was observed under these conditions. Therefore, based on these results and the incompatibility of metal bromide sources, it is suggested that TBAB plays a dual role in this process, with the bromide and ammonium components having a beneficial impact. While TBAB may simply serve to aid the solvation of charged species (such as $SO_2$ or boronate complexes), alkylammonium salts have been employed as additives in palladium-catalysed Suzuki-type cross-couplings to limit the competing hydrodeboronation side-reaction.[162] In these cases it is thought that the formation

of ammonium boronates, $[Ar(BOH)_3]^-[R_4N]^+$, is central to the observed reactivity. It is possible that the ammonium salt in our reaction plays a similar role in limiting the homocoupling of the boronic acid substrate.

## 4.10 Project summary

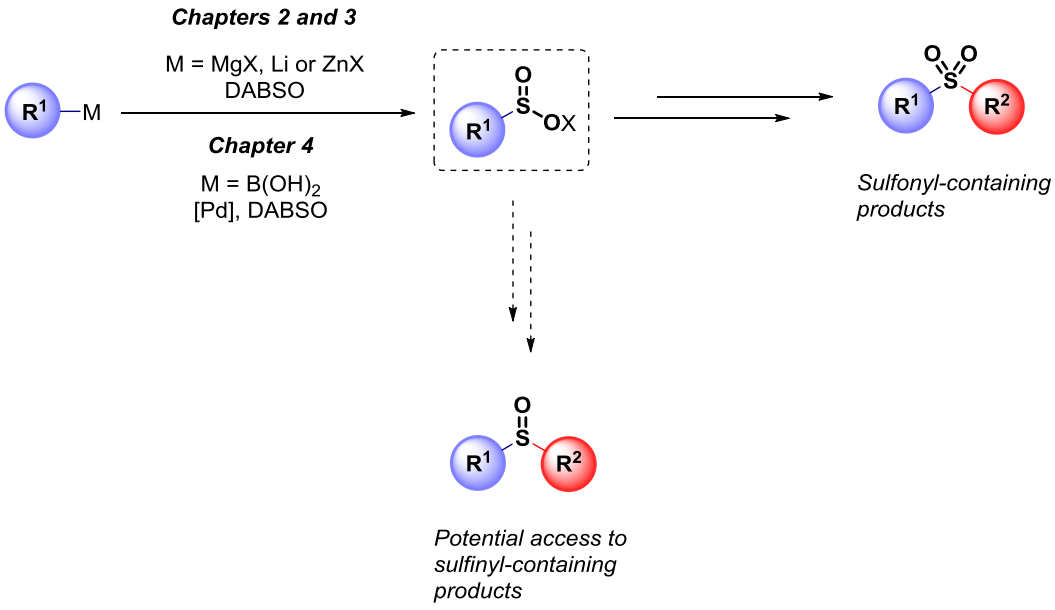
In summary, we have developed a novel transformation of boronic acids into both sulfinic acid and sulfonyl-containing products. This has been achieved with the initial one-step/one-pot palladium-catalysed preparation of sulfones *via* the sulfination of boronic acid substrates employing DABSO. This process involves the addition of the electrophile at the beginning of the reaction and relies on trapping with activated alkylating agents in order to access sulfone products.

Building on this initial work, the desired formation of sulfinic acid derivatives was accomplished with a base-free sulfination of boronic acids using a Pd(II) catalyst and DABSO along with methanol as a key (solvent) component. A range of aryl and heteroaryl boronic acids performed well in this system while alkenyl substrates were tolerated but generally afforded products in reduced yields. A pleasing aspect of this chemistry was the compatibility of various coupling partners in combination with the generated sulfinates allowing for the preparation of a diverse range of sulfonyl-containing compounds including sulfones, sulfonamides and sulfonyl fluorides. Where only activated carbon-based electrophiles could be employed in the original one-step process, the two-step reaction allows for greater versatility in the further derivatisations of the sulfinic acid precursors.

As well as serving as a useful methodology, this chemistry is intriguing from a mechanistic perspective. Initial exploration into the two-step sulfination reaction points towards the formation of a sulfinic acid derivative. The observed solvent dependency and results obtained with Brønsted acid additives has led to the proposal that a sulfinic acid is generated from the catalytic cycle. Further investigative studies are required to gain further insight into the mechanism of this process.

# 5. Conclusion and future work

Since the discovery of DABSO as an easy-to-handle sulfur dioxide surrogate in the palladium-catalysed aminosulfonylation reaction,[72,73] advances have been made in this field towards constructing sulfonyl-containing compounds. The Willis group has made significant contributions to this area; establishing DABSO as a sulfur dioxide source in catalytic sulfonylative processes as well as a safe and effective replacement for the gas. The work presented in this thesis has served to make advances in both capacities with a particular focus on the derivatisation and synthesis of metal sulfinic acid salts. Firstly, the effective functionalisation of metal sulfinates, derived from organometallic reagents and DABSO, allowed attractive and robust methodologies for the construction of sulfones and sulfonamides to be developed. Secondly, and of particular significance, was the discovery of a palladium-catalysed sulfination reaction of (hetero)aryl and alkenyl boronic acids.




Not only does this ligand-free, redox-neutral process serve as an effective route to sulfinic acids and subsequently sulfonyl-containing products, but it is also interesting from a mechanistic perspective. Hence, important future work specific to this chemistry is to conduct further investigations into the mechanism of this reaction. Gaining further insight into the identity of the key sulfinic acid species generated in the catalytic cycle and how it is formed

would be of particular interest. Being able to prepare this intermediate would potentially provide the opportunity to exploit the observed electrophilic reactivity to access sulfinyl-containing compounds. Also of great interest is the use of metal sulfinates obtained from DABSO and organometallic reagents to access the sulfinyl oxidation level. Studies into the generation of electrophilic sulfinic acid derivatives from magnesium sulfinates are currently underway in our group.

More generally, continuing investigations into the application of amine-sulfur dioxide complexes in transition metal catalysis is of particular interest. Extending this sulfonylative chemistry to different metals (e.g. copper) and substrates (e.g. aryl chlorides) would represent significant advances in the field. With this, gaining a mechanistic understanding of the role of DABSO in palladium-catalysed sulfonylative processes would be particularly valuable i.e. through isolation of intermediates, computational studies etc.

# 6 . Experimental data and procedures

## 6.1 General considerations

Chemicals were purchased from Sigma Aldrich, Alfa Aesar, Apollo Scientific or Acros Organics and used without further purification with the exception of the following: (i) DABCO – sublimed (50 °C, 1 mbar). (ii) Morpholine and *N*-methylmorpholine used for the preparation of amine-sulfur dioxide complexes were purified by distillation. (iii) Starting materials for organometallic reagent preparation were purified by distillation or re-crystallisation as appropriate.

Solvents were purchased from Sigma Aldrich, Fisher Scientific or Rathburn and unless otherwise mentioned, used directly without further purification. 'Petrol' refers to the fraction of light petroleum ether boiling in the range 40-60 °C. Anhydrous (KF titration < 10 ppm) THF, DCM, $CH_3CN$, $Et_2O$, MeOH and toluene were obtained from an in-house Grubbs solvent drying system (Innovative Technology Inc. PS-400-7) having passed through dried alumina columns. 1,4-Dioxane was purified prior to use by stirring over $CaH_2$ for 24 hr before distilling onto activated 4Å molecular sieves.

Grignard reagents were titrated with salicylaldehyde phenylhydrazone prior to use.[163] Organolithium reagents were titrated against a 1.0 M solution of 2-propanol in toluene with 0.2% 1,10-phenanthroline as the indicator prior to use. Organozinc reagents were titrated with iodine and lithium chloride.[164] The concentration of aqueous sodium hypochlorite was determined by standard sodium thiosulfate/iodine titration.

Reactions were performed with continuous magnetic stirring, under an atmosphere of nitrogen (passed through a Drierite®filled tube), unless otherwise stated, using standard Schlenk techniques and all glassware was dried in an oven (>200 °C, overnight) and allowed to cool under vacuum (10 mbar) prior to use. All manipulations involving organometallic reagents were carried out under a nitrogen atmosphere. DABSO was left under vacuum (10 mbar) for 10 min prior to use. "Reaction tube" refers to a 10 mL CEM microwave reaction vial. Microwave heating was carried out using a CEM Discover-S unit. Cooling between -20 °C and -78 °C was achieved using a dry ice-acetone bath. Flash column chromatography was

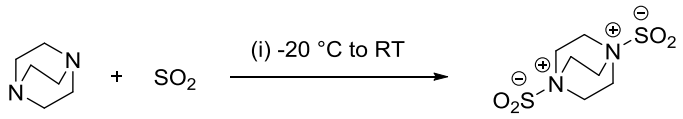
performed using Apollo scientific silica gel 60 (particle size 0.040-0.063 nm) with the indicated eluents. Thin Layer Chromatography (TLC) analysis was carried out on Merck Kieselgel 60 PF254 pre-coated aluminium backed sheets and visualised either by UV fluorescence (254 nm) and/or by staining with potassium permanganate ($KMnO_4$).

NMR spectra were recorded at ambient temperature on a Brüker AVIII400 (400 MHz) spectrometer or AVII500 (500 MHz). Chemical shifts (δ) are reported in parts per million (ppm) and referenced relative to the residual solvent peak(s) (as specified). Coupling constants (*J*) are given in Hertz (Hz) and rounded to the nearest 0.5 Hz. Assignments were made on the basis of chemical shifts, coupling constants, COSY, HSQC and comparison with spectra of related compounds. Signal multiplicities are denoted as: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; sext., sextet; hept., heptet; m, multiplet; br., broad. Multiplicities are reported as observed.

Melting points were measured using a Leica Gallen III hot-stage microscope. Low resolution mass spectra were recorded on a Fisons Platform spectrometer (ESI). High resolution mass spectra were measured by the internal service at the University of Oxford using a Bruker Daltronics microTOF spectrometer. *m/z* ratio values are reported in Daltons; high resolution values are calculated to four decimal places from the molecular formula, all found within a tolerance of 5 ppm. Infrared spectra were determined neat using a Bruker Tensor 27 FT spectrometer with an internal range of 600-4000 $cm^{-1}$.

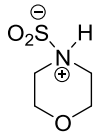
# 6.2 Synthesis of amine-sulfur dioxide complexes

## 6.2.1 General procedure A for the synthesis of amine-sulfur dioxide complexes as exemplified by the preparation of 1,4-diazabicyclo[2.2.2]octane *bis*(sulfur dioxide), DABCO-$(SO_2)_2$, DABSO (18)



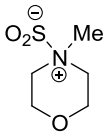

Modification on the procedure documented by Santos and Mello.[70] A 250 mL round-bottom flask fitted with a cold-finger condenser and connected to a Dreschel bottle oil bubbler system was cooled under a flow of nitrogen. Sublimed 1,4-diazabicyclo[2.2.2]octane (DABCO) (12.0 g, 107.0 mmol) was added to the flask followed by flushing with nitrogen for 2 min. The nitrogen atmosphere was replaced with sulfur dioxide gas (~2 bubbles/sec) and the system flushed for 3 mins. The flask was then cooled to -30 ºC by which point sulfur dioxide began to condense dropwise and this was aided further by cooling of the condenser to -78 ºC. This was continued until the DABCO was fully submerged in liquid $SO_2$ and a free flowing slurry was obtained. The gas flow was then stopped and the flask warmed to -10 ºC and left stirring at "reflux" for 1 hr. The flask was warmed to room temp. and the reaction left to stir under a flow of nitrogen for 16 hr. After this time, the excess of sulfur dioxide had evaporated through the bubbler system to afford DABSO as a white powder (25.6 g, 99%); $^1$H NMR (400 MHz, MeOD-$d_4$) 3.22 (12 H, s); $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 45.4; IR $\nu_{max}$ (neat)/cm$^{-1}$ 1476, 1459, 1354 ($SO_2$), 1100 ($SO_2$), 1088.

**Morpholine-sulfur dioxide**



Prepared according to general procedure A using morpholine (5 mL, 57.8 mmol) affording the titled complex as an off-white solid (8.59 g, 97%); mp 75-76 ºC (decomp.); $^{1}$H NMR (400 MHz, MeOD-$d_4$) 3.92-3.86 (4H, m, $NCH_2CH_2$), 3.25-3.20 (4H, m, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 64.5, 44.5; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2982, 2532, 1462, 1309 ($SO_2$), 1199, 1104 ($SO_2$).

***N*-Methylmorpholine-sulfur dioxide**

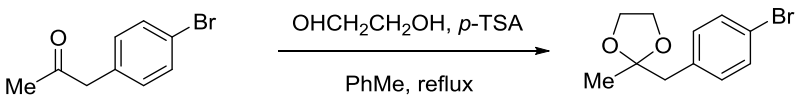


Prepared according to general procedure A using *N*-methylmorpholine (5.0 mL, 45.5 mmol) affording the titled complex as an off-white solid (6.92 g, 96%); mp 86-87 $^{o}$C (decomp.); $^{1}$H NMR (400 MHz, MeOD-$d_4$) δ 3.93 (4H, br. s, $N(CH_2CH_2)_2O$), 3.49 (4H, br. s, $N(CH_2CH_2)_2O$), 2.88 (3H, s, N*Me*); $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 65.1, 54.5, 44.0; IR $\upsilon_{max}$ (neat)/cm$^{-1}$ 2322, 1456, 1368 ($SO_2$), 1180, 1155 ($SO_2$), 1112, 1065.

# 6.3 Chapter 2 data

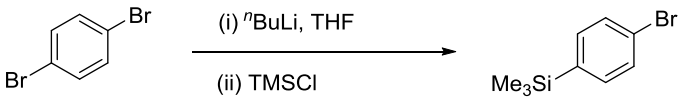
## 6.3.1 Starting materials

### 2-(4-Bromobenzyl)-2-methyl-1,3-dioxolane




To a stirred solution of 1-(4-bromophenyl)propan-2-one (3.20 g, 15.0 mmol) and ethylene glycol (7.5 mL, 135 mmol) in toluene (30 mL) was added *p*-toluenesulfonic acid (70 mg, 0.4 mmol). The resulting mixture was heated at reflux with a Dean Stark trap for 16 hr. After cooling to room temp. the two phases were separated and the toluene washed with sat. $NaHCO_{3(aq)}$ (20 mL). The ethylene glycol was diluted with water (30 mL) and washed with EtOAc (30 mL). The organic phases were combined, washed with $NaHCO_{3(aq)}$ (50 mL) and dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the titled ketal as a colourless oil (3.7 g, 96%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* 8.5, 2H, Ar-*H*), 7.17 (d, *J* 8.5, 2H, Ar-*H*), 3.93-3.89 (m, 2H, C$H_2$C$H_2$O), 3.69-3.64 (m, 2H, C$H_2$C$H_2$O), 2.90 (s, 2H, CC$H_2$Ar), 1.28 (s, 3H, C$H_3$) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 136.1, 132.2, 131.2, 120.8, 109.1, 65.3, 44.5, 24.2; HRMS (FI) found *m/z* 256.0101 ([M]$^+$, 100%), $C_{11}H_{13}{}^{79}BrO_2$ requires *m/z* 256.0104. Data in accordance with that previously reported.[165]

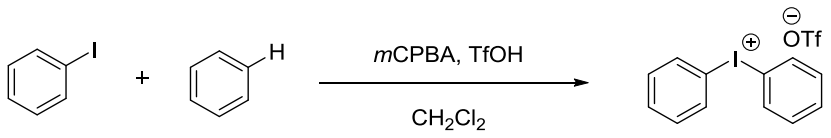
### (4-Bromophenyl)trimethylsilane




A solution of 1,4-dibromobenzene (3.50 g, 14.8 mmol) in anhydrous THF (30 mL) was cooled to -78 ºC and $^n$BuLi (1.66 M solution in hexane, 9.2 mL, 15.3 mmol) added dropwise

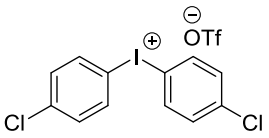
over 10 min. The reaction mixture was stirred at this temp. for 4 hr before dropwise addition of chlorotrimethylsilane (2.3 mL, 17.9 mmol). After stirring for 10 min at this temp., the mixture was allowed to warm to room temp. and stirred for a further 2 hr. The reaction was then quenched with water (50 mL), and the aqueous layer extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The crude oil obtained was purified by Kugelrohr distillation to afford the titled aryl silane as a colourless oil (3.04 g, 90%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* 8.0, Ar-*H*), 7.38 (2H, d, *J* 8.0, Ar-*H*), 0.28 (9H, s, Si*Me*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 139.0, 134.6, 130.9, 123.5, -1.1; HRMS (FI) found *m/z* 227.9976 ([M]$^+$, 100%), $C_9H_{13}{}^{79}BrSi$ requires *m/z* 227.9970. Data in accordance with that previously reported.[166]

**General Procedure B for the synthesis of diaryliodonium triflates as exemplified by the preparation of diphenyliodonium triflate**



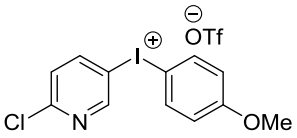

To a solution of iodobenzene (135 μL, 1.2 mmol), benzene (120 μL, 1.32 mmol) and *m*CPBA (77% active oxidant, 296 mg, 1.32 mmol) in $CH_2Cl_2$ (5 mL) was added triflic acid (320 μL, 3.6 mmol) dropwise at 0 ºC. The resulting mixture was allowed to warm to room temp., stirred for 10 min and then concentrated *in vacuo*. $Et_2O$ (5 mL) was added and the mixture stirred for a further 10 min to aid precipitation. The solid was filtered off, washed with $Et_2O$ (10 mL) and dried under vacuum to afford the titled iodonium salt as an off-white solid (307 mg, 91%); $^1$H NMR (400 MHz, MeOD-$d_4$) δ 8.25 (d, *J* 8.0, 4H, Ar-*H*), 7.68 (t, *J* 8.0, 2H, Ar-*H*), 7.52 (t, *J* 8.0, 4H, Ar-*H*); $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 136.0, 132.9, 132.6, 120.8 (q, $J_{CF}$ 316.5), 114.9; $^{19}$F NMR (377 MHz, MeOD-$d_4$) δ -80.3; LRMS (ESI) *m/z* 281 (100%, [M-OTf]$^+$); HRMS (ESI) found *m/z* 280.9822 [M-OTf]$^+$, $C_{12}H_{10}I^+$ requires *m/z* 280.9822. Data in accordance with that previously reported.[167]

**_Bis_(4-chlorophenyl)iodonium triflate**



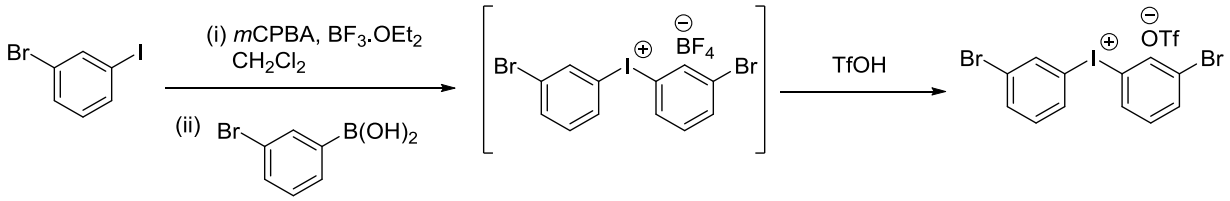

Prepared according to general procedure B using 4-chloroiodobenzene (286 mg, 1.2 mmol) and chlorobenzene (135, $\mu$L, 1.32 mmol). The reaction was stirred overnight at room temp. to afford the titled iodonium salt as a white solid (463 mg, 93%); $^{1}$H NMR (400 MHz, MeOD-$d_4$) δ 8.23 (d, *J* 8.0, 4H, Ar-*H*), 7.55 (d, *J* 8.0, 4H, Ar-*H*); $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 139.2, 136.7, 132.0, 122.0 (q, $J_{CF}$ 318.5), 112.3; $^{19}$F NMR (377 MHz, MeOD-$d_4$) δ -80.1; LRMS (ESI) *m/z* 349 (100%, [M-OTf]$^+$); HRMS (ESI) found *m/z* 348.9044 [M-OTf]$^+$, $C_{12}H_8Cl_2I^+$ requires *m/z* 348.9042. Data in accordance with that previously reported.[167]

**(6-Chloro-pyridin-3-yl)(4-methoxyphenyl)iodonium triflate (28)**



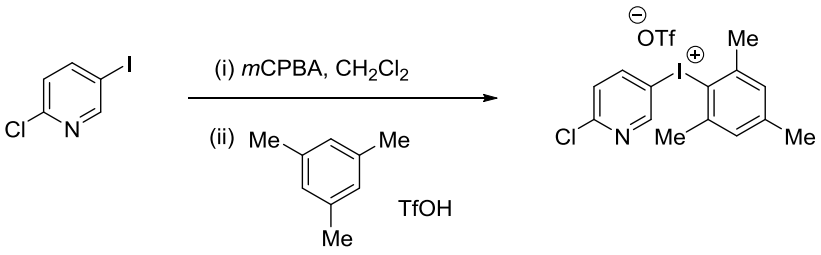

Prepared according to general procedure B using 2-chloro-5-iodopyridine (480 mg, 2.0 mmol), anisole (240, $\mu$L, 1.32 mmol), *m*CPBA (494 mg, 2.2 mmol) and triflic acid (530 $\mu$L, 6.0 mmol). The reaction was stirred at room temp. for 15 min to afford the titled iodonium salt as an off-white solid (1.25 g, 63%); $^{1}$H NMR (400 MHz, MeOD-$d_4$) δ 8.92 (d, *J* 2.0, 1H, Ar-*H*), 8.45 (dd, *J* 8.5, 2.0, 1H, Ar-*H*), 8.08 (d, *J* 9.0, 2H, Ar-*H*), 7.50 (d, *J* 8.5, 1H, Ar-*H*), 6.96 (d, *J* 9.0, 2H, Ar-*H*), 3.77 (s, 3H, O*Me*); $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 167.4, 158.6, 157.5, 148.6, 141.4, 131.4, 121.6 (q, $J_{CF}$ 320.5), 118.2, 116.3, 107.2, 59.0; $^{19}$F NMR (377 MHz, MeOD-$d_4$) δ -80.1; LRMS (ESI) *m/z* 346 (100%, [M-OTf]$^+$); HRMS (ESI) found *m/z* 345.9492 [M-OTf]$^+$, $C_{12}H_{10}ClINO^+$ requires *m/z* 345.9490. Data in accordance with that previously reported.[167]

### *Bis*(4-bromophenyl)iodonium triflate




Prepared according to the method of Olofsson.[168] To a solution of *m*CPBA (740 mg, 3.3 mmol) in $CH_2Cl_2$ (10 mL) was added 3-bromoiodobenzene (380 $\mu$L, 3.0 mmol) followed by $BF_3{\cdot}OEt_2$ (930 $\mu$L, 7.5 mmol) at room temp. The mixture was stirred for 30 min and cooled to 0 ºC followed by the addition of 3-bromophenylboronic acid (663 mg, 3.3 mmol). The mixture was stirred for 15 min at room temp. and triflic acid (290 $\mu$L, 3.3 mmol) was added. After stirring for a further 15 min the solvent was removed *in vacuo*, $Et_2O$ (5 mL) was added and the mixture stirred for a further 10 min to aid precipitation. The solid was filtered off, washed with $Et_2O$ (10 mL) and dried under vacuum to afford the titled iodonium salt as an off-white solid (1.60 g, 91%); $^1$H NMR (400 MHz, MeOD-$d_4$) δ 8.56 (s, 2H, Ar-*H*), 8.25 (d, *J* 8.5, 2H, Ar-*H*), 7.86 (d, *J* 8.5, 2H, Ar-*H*), 7.48 (t, *J* 8.5, 2H, Ar-*H*); $^{13}$C NMR (400 MHz, MeOD-$d_4$) δ 137.2, 135.7, 133.9, 133.2, 124.0, 122.0 (q, $J_{CF}$ 321.5), 115.7; $^{19}$F NMR (377 MHz, MeOD-$d_4$) δ -79.9; LRMS (ESI) *m/z* 437 (100%, [M($^{79}$Br)-OTf]$^+$) and 439 (100%, [M($^{81}$Br)-OTf]$^+$); HRMS (ESI) found *m/z* 436.8026 [M($^{79}$Br)$_2$-OTf]$^+$ and 438.8002 [M($^{79}$Br)$_2$-OTf]$^+$, $C_{12}H_8Br_2I^+$ requires *m/z* 436.8032 and 438.8012. Data in accordance with that previously reported.[169]

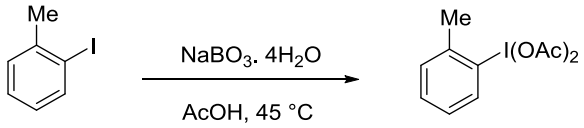
### (6-Chloropyridin-3-yl)(mesityl)iodonium triflate (25)




To a solution of 2-chloro-5-iodopyridine (478 mg, 2.0 mmol) in $CH_2Cl_2$ (10 mL) was added *m*CPBA (77% active oxidant, 494 mg, 2.2 mmol) and the resulting mixture heated at 80 ºC

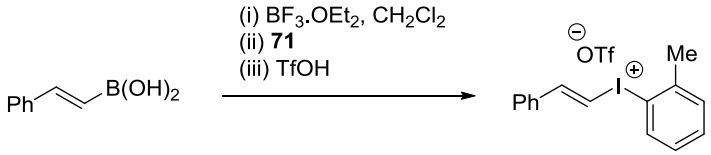
for 2 hr. The mixture was then cooled to 0 ºC and triflic acid (602 $\mu$L, 6.0 mmol) was added dropwise before warming to room temp. with further stirring for 6 hr. After this time, the solvent was removed *in vacuo*, $Et_2O$ (5 mL) was added and the mixture stirred for a further 10 min to aid precipitation. The solid was filtered off, washed with $Et_2O$ (10 mL) and dried under vacuum to afford the titled iodonium salt as an off-white solid (540 mg, 53%); $^1$H NMR (400 MHz, MeOD-$d_4$) δ 8.74 (dd, *J* 2.5, 0.5, 1H, Ar-*H*), 8.19 (dd, *J* 8.5, 2.5, 1H, Ar-*H*), 7.50 (dd, *J* 8.5, 0.5, 1H, Ar-*H*), 7.18 (s, 2H, Ar-*H*), 2.59 (s, 6H, Ar*Me*), 2.28 (s, 3H, Ar*Me*); $^{13}$C NMR (400 MHz, MeOD-$d_4$) δ 154.6, 152.9, 144.9, 144.1, 142.1, 130.2, 127.8, 121.0 (q, $J_{CF}$ 319.0), 110.0, 100.0, 25.7, 19.6; $^{19}$F NMR (377 MHz, MeOD-$d_4$) δ -79.5; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3033, 2823, 1568, 1453, 1208, 1107; LRMS (ESI) *m/z* 358 (100%, [M-OTf]$^+$); HRMS (ESI) found *m/z* 358.0514 [M-OTf]$^+$, $C_{14}H_{14}ClIN^+$ requires *m/z* 358.0516. Data in accordance with that previously reported.[112]

**_Bis_(acetyloxy)(2-methylphenyl)-λ$^3$–iodane (71)**



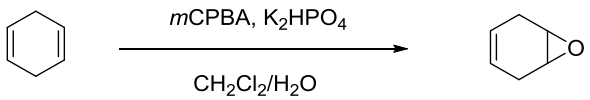

To a solution of 2-iodotoluene (1.09 g, 5.0 mmol) in acetic acid at 45 ºC was added sodium perborate tetrahydrate (7.69 g, 50.0 mmol) portionwise over 20 min. The mixture was stirred at room temp. for 16 hr and subsequently concentrated *in vacuo*. The resulting residue was washed with $CH_2Cl_2$ (200 mL) and the filtrate re-concentrated *in vacuo*. The resulting solid was dissolved in $CH_2Cl_2$ (100 mL) and washed with water (80 mL). The aqueous phase was extracted with $CH_2Cl_2$ (50 mL) and the combined organic extracts dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The resulting crude solid was recrystallized ($CH_2Cl_2$/petrol) to afford the titled iodoarene as a white solid (1.26 g, 75%); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* 8.0, 1H, Ar-*H*), 7.58-7.54 (m, 2H, Ar-*H*), 7.31-7.34 (m, 1H, Ar-*H*), 2.78 (s, 3H, Ar*Me*), 1.98 (s, 6H, CO*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.2, 140.2, 137.0, 131.8, 131.3, 127.6, 127.1, 25.6, 20.5. Data in accordance with that previously reported.[113]

**(*E*)-Styryl(*o*-tolyl)iodonium triflate (31)**




To a suspension of *trans*-vinylphenylboronic acid (734 mg, 4.96 mmol) in $CH_2Cl_2$ (40 mL) at 0 ºC was added $BF_3{\cdot}OEt_2$ (734 $\mu$L, 5.95 mmol). The mixture was stirred for 15 min before adding a solution of iodoarene diacetate **71** (2.0 g, 5.95 mmol) in $CH_2Cl_2$ (20 mL). After stirring the reaction for 1 hr, triflic acid (530 $\mu$L, 5.95 mmol) was added dropwise. The reaction was stirred for a further 1 hr before water (30 mL) was added and the resulting aqueous phase was extracted with $CH_2Cl_2$ (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the titled iodonium salt as an off-white solid (1.12g, 45%); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.01 (dd, *J* 8.0, 1.0, 1H, Ar-*H*), 7.48 (td, *J* 7.5, 1.0, 1H, Ar-*H*), 7.41 (dd, *J* 7.5, 2.0, 1H, Ar-*H*), 7.38-7.22 (m, 7H, Ar-*H* and C*H*), 7.22-7.15 (m, 1H, C*H*), 2.56 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 147.5, 141.8, 138.2, 134.3, 133.6, 132.0, 130.9, 129.7, 129.1, 127.8, 121.8 (q, $J_{CF}$ 319.5), 116.0, 97.6, 25.7; $^{19}$F NMR (377 MHz, $CDCl_3$) δ -79.7; LRMS (ESI) *m/z* 321 (100%, $[M\text{-}OTf]^+$); HRMS (ESI) found *m/z* 321.0139 $[M\text{-}OTf]^+$, $C_{15}H_{14}I^+$ requires *m/z* 321.0146. Data in accordance with that previously reported.[113]

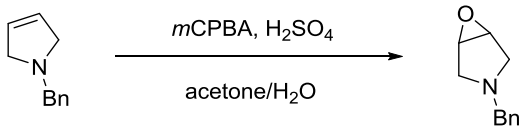
**7-Oxabicyclo[4.1.0]hept-3-ene**




To a biphasic solution of *m*CPBA (77% active oxidant, 9.68 g, 172.57 mmol) and $K_2HPO_4$ (7.52 g, 43.1 mmol) in $CH_2Cl_2/H_2O$ (150:1, 300 mL) was added 1,4-cyclohexadiene (4.0 mL, 42.3 mmol) at room temp. and the resulting mixture was allowed to stir at this temp. for 16 hr. The reaction was quenched with sat $NaHCO_{3(aq)}$ (100 mL) and the phases separated. The organic phase was washed with sat $NaHCO_{3(aq)}$ (150 mL) and the combined aqueous

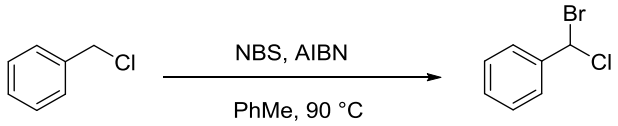
extracts were extracted with $CH_2Cl_2$ (100 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The resulting crude oil was distilled at reduced pressure to afford the titled epoxide as a colourless oil (2.88g, 71%); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.38-5.37 (m, 2H, C(O)$CH_2$C*H*), 3.18-3.19 (m, 2H, COC*H*), 2.55-2.45 (m, 2H, C$H_2$), 2.42-2.32 (m, 2H, C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 121.5, 51.0, 25.0; HRMS (EI) found *m/z* 96.0574 ([M]$^+$, 100%), $C_6H_8O$ requires *m/z* 96.0575. Data in accordance with that previously reported.[170]

**3-Benzyl-6-oxa-3-azabicyclo[3.1.0]hexane**



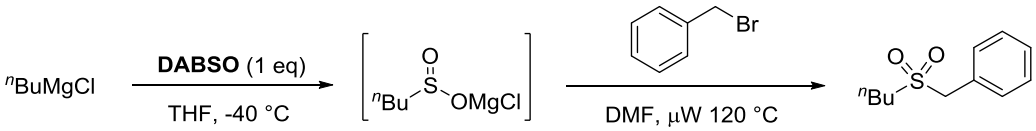

To a solution of 1-benzylpyrroline (1.90 mL, 10.0 mmol), conc. $H_2SO_4$ (639 μL, 12.0 mmol), water (1.5 mL) and acetone (20 mL) was added *m*CPBA (77% active oxidant, 2.91 g, 13.0 mmol). The resulting mixture was stirred at room temp. for 30 hr and subsequently concentrated *in vacuo*. The crude mixture was neutralised with NaOH (1M, 30 mL) and extracted with toluene (3 × 30 mL). The organic extract was then washed with water (2 × 10 mL) dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the titled epoxide as a light yellow oil (964 mg, 55%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33-7.10 (m, 5H, Ar-*H*), 3.65 (s, 2H, NC$H_2$Ph), 3.56 (s, 2H, COC*H*), 3.13 (d, *J* 12.0, 2H, NC$H_2$CH), 2.48 (d, *J* 12.0, 2H, NC$H_2$CH); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 138.6, 128.8, 128.3, 127.1, 60.1, 56.0, 53.4; IR $\nu_{max}$ (neat)/cm$^{-1}$ 1663, 1402, 1229, 1142, 1089, 1017; LRMS (ESI) *m/z* 176 (100%, [M+H]$^+$); HRMS (ESI) found *m/z* 176.1070 [M+H]$^+$, $C_{11}H_{14}NO$ requires *m/z* 176.1070.[171]

**(Bromochloromethyl)benzene**




To a solution of NBS (23.2 g, 130 mmol) and benzyl chloride (15 mL, 130 mmol) in toluene (200 mL) was added 2,2'-azobisisobutyronitrile (32 mg, 0.20 mmol). The reaction was heated at reflux for 4 hrs and after cooling to room temp., the mixture was filtered. The resulting solution was distilled under reduced pressure to afford the titled benzyl bromide as a colourless oil (15.7 g, 59%); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.31-7.49 (m, 3H, Ar-*H*), 7.56-7.72 (m, 2H, Ar-*H*), 6.74 (s, 1H, PhC*H*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 137.5, 128.9, 128.4(2C), 56.1. Data in accordance with that previously reported.[172]

## 6.3.2 General Procedure C for the synthesis of sulfones from organometallic reagent, DABSO, and alkyl halide/ iodonium salt electrophiles as exemplified by the preparation of *n*-butylbenzylsulfone (21a)



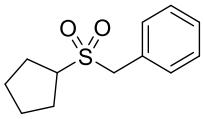

To a reaction tube was added DABSO (60 mg, 0.25 mmol) and THF (1 mL) and the resulting suspension flushed with nitrogen gas for 2 min. After cooling to -40 °C, *n*-butylmagnesium chloride (2.0 M in THF, 125 $\mu$L, 0.25 mmol) was added dropwise and the mixture stirred at this temp. for 1 hr. On warming to room temp. a strong flow of nitrogen gas was applied to remove the solvent before addition of DMF (2 mL) and benzyl bromide (90 $\mu$L, 0.75 mmol). The mixture was subjected to microwave heating at 120 °C for 3 hr. After cooling, $Et_2O$ (20 mL) was added and the solids filtered off before removing the solvent *in vacuo*. Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (45 mg, 85%); mp 95-96 °C ($CH_2Cl_2$) [lit.[173] mp 95-97 °C]; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.36-7.33 (m, 5H, Ar-*H*), 4.15 (s, 2H, SC$H_2$Ph), 2.77-2.73 (m, 2H, SC$H_2$CH$_2$), 1.76-1.68 (m, 2H, SCH$_2$C$H_2$), 1.34 (app. sext., *J* 7.5, 2H, C$H_2$CH$_3$), 0.85 (t, *J* 7.5, 3H, CH$_2$C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 130.5, 129.1, 129.0, 128.1, 59.4, 50.8, 23.8, 21.7,

13.5; LRMS (ESI) *m/z* 235 (70%, $[M+Na]^+$), 447 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 235.0759 $[M+Na]^+$, $C_{11}H_{16}O_2SNa$ requires *m/z* 235.0763. Data in accordance with that previously reported.[173]

### *n*-Butylbenzylsulfone, using *n*-butyllithium (22a)

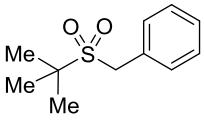
Prepared according to general procedure C using *n*-butyllithium (1.8 M in hexane, 139 $\mu$L, 0.25 mmol) and benzyl bromide (90 $\mu$L, 0.75 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfone as a white solid (46 mg, 87%). Data as above.

### [(Cyclopentylsulfonyl)methyl]benzene (21b)



Prepared according to general procedure C using cyclopentylmagnesium bromide (2.0 M in THF, 125 $\mu$L, 0.25 mmol) and benzyl bromide (90 $\mu$L, 0.75 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfone as an off-white solid (49 mg, 88%); mp 84-85 °C ($CH_2Cl_2$) [lit.[174] mp 84-85 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39-7.30 (m, 5H, Ar-*H*), 4.15 (s, 2H, S$CH_2$) 3.21-3.10 (m, 1H, C*H*), 2.09-1.97 (m, 2H, $CH_2$), 1.89-1.80 (m, 2H, $CH_2$), 1.79-1.68 (m, 2H, $CH_2$), 1.59-1.48 (m, 2H, $CH_2$) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 130.5, 129.0, 128.9, 128.3, 59.1, 58.3, 26.8, 26.1; LRMS (ESI) *m/z* 247 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 247.0767 $[M+Na]^+$, $C_{12}H_{16}O_2SNa$ requires *m/z* 247.0763. Data in accordance with that previously reported.[174]

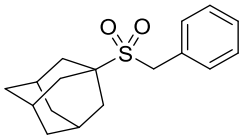
### [(*tert*-Butylsulfonyl)methyl]benzene (21c)



Prepared according to general procedure C using *tert*-butylmagnesium chloride (1.0 M in THF, 250 $\mu$L, 0.25 mmol) and benzyl bromide (90 $\mu$L, 0.75 mmol). Flash column

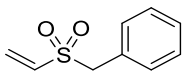
chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (44 mg, 82%); mp 122-123 °C ($CH_2Cl_2$) [lit.[175] mp 122 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.51-7.35 (m, 5H, Ar-*H*), 4.22 (s, 2H, SC$H_2$), 1.45 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 131.2, 128.8, 127.2, 60.0, 52.8, 23.8; LRMS (ESI) *m/z* 235 (20%, $[M+Na]^+$), 447 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 235.0768 $[M+Na]^+$, $C_{11}H_{16}O_2SNa$ requires *m/z* 235.0763. Data in accordance with that previously reported.[175]

**1-(Benzylsulfonyl)adamantine (21d)**



Prepared according to general procedure C using 1-adamantylmagnesium bromide (0.31 M in $Et_2O$, 810 μL, 0.25 mmol) and benzyl bromide (90 μL, 0.75 mmol). The alkyl Grignard was prepared as a stock solution from 1-bromoadamantane: To a mixture of 1-bromoadamantane (2.15 g, 10.0 mmol) and magnesium turnings (3.65 g, 150 mmol) in $Et_2O$ (15 mL) was added 1,2-dibromoethane (40 μL, 0.46 mmol). The mixture was heated at 35 °C without stirring for 18 hr. Flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (54 mg, 75%); mp 178-179 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37-7.28 (m, 5H, Ar-*H*), 4.06 (s, 2H, SC$H_2$), 2.12 (br. s, 3H, SCCH$_2$C*H*), 2.01 (d, *J* 2.5, 6H, SCC$H_2$), 1.67 (dd, *J* 22.5, 12.5, 6H, SCCH$_2$CHC$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 131.3, 128.7, 128.6, 127.1, 61.5, 51.7, 35.8, 35.1, 28.3; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2901, 2846, 2160, 1493, 1301 ($SO_2$), 1133 ($SO_2$); LRMS (ESI) *m/z* 313 (100%, $[M+Na]^+$), 603 (40%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 313.1241 $[M+Na]^+$, $C_{17}H_{22}O_2SNa$ requires *m/z* 313.1236.

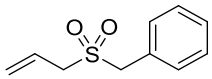
**[(Vinylsulfonyl)methyl]benzene (21e)**



Prepared according to general procedure C using vinylmagnesium chloride (1.0 M in THF, 250 μL, 0.25 mmol) and benzyl bromide (150 μL, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (32 mg, 70%);

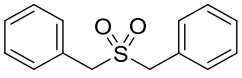
mp 96-97 °C ($CH_2Cl_2$) [lit.[176] mp 95-96 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34-7.27 (m, 5H, Ar-*H*), 6.43 (dd, *J* 16.5, 10.0, 1H, $CH_2CHS$), 6.23 (d, *J* 16.5, 1H, $CH_{cis}HCHS$), 6.02 (d, *J* 10.0, 1H, $CH_{trans}HCHS$), 4.18 (s, 2H, $SCH_2Ph$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 135.1, 131.2, 130.9, 129.0, 128.9, 127.7, 61.1; LRMS (ESI) *m/z* 205 (100%, $[M+Na]^+$), 387 (30%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 205.0297 $[M+Na]^+$, $C_9H_{10}O_2SNa$ requires *m/z* 205.0299. Data in accordance with that previously reported.[176]

**[(Allylsulfonyl)methyl]benzene (21f)**



Prepared according to general procedure C using allylmagnesium bromide (2.0 M in THF, 125 μL, 0.25 mmol) and benzyl bromide (150 μL, 1.25 mmol) with microwave heating for 5 hr. Flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (36 mg, 73%); mp 65-66 °C ($CH_2Cl_2$) [lit.[177] mp 64-65 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34-7.31 (m, 5H, Ar-*H*), 5.85 (ddt, *J* 17.0, 10.0, 7.5, 1H, $CH_2CHCH_2$), 5.45 (dd, *J* 10.0, 1.0, 1H, $CH_{trans}HCHCH_2$), 5.34 (dd, *J* 17.0, 1.0, 1H, $CH_{cis}HCHCH_2$), 4.15 (s, 2H, $SCH_2Ph$), 3.52 (d, *J* 7.5, 2H, $SCH_2CHCH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 130.8 (2C), 129.1, 127.7, 124.9 (2C), 58.0, 56.0; LRMS (ESI) *m/z* 219 (100%, $[M+Na]^+$), 415 (30%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 219.0443 $[M+Na]^+$, $C_{10}H_{12}O_2SNa$ requires *m/z* 219.0450. Data in accordance with that previously reported.[177]

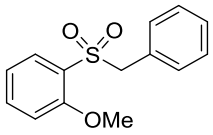
**[Sulfonylbis(methylene)]dibenzene (21g)**



Prepared according to general procedure C using benzylmagnesium bromide (1.85 M in THF, 135 μL, 0.25 mmol) and benzyl bromide (150 μL, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfone as a white solid (41 mg, 72%); mp 152-153 °C ($CH_2Cl_2$) [lit.[178] mp 152 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35-7.29 (m, 10H, Ar-*H*), 4.06 (s, 4H, $SCH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 130.9, 129.1, 129.0, 127.5,

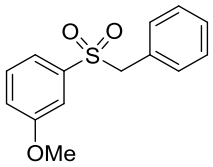
58.0; LRMS (ESI) *m/z* 269 (40%, $[M+Na]^+$), 515 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 269.0604 $[M+Na]^+$, $C_{14}H_{14}O_2SNa$ requires *m/z* 269.0607. Data in accordance with that previously reported. [178]

**1-(Benzylsulfonyl)-2-methoxybenzene (21h)**




Prepared according to general procedure C using 2-methoxyphenylmagnesium chloride (1.0 M in THF, 250 $\mu$L, 0.25 mmol) and benzyl bromide (90 $\mu$L, 0.75 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfone as a white solid (52 mg, 79%); mp 123-124 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, *J* 8.0, 1.5, 1H, Ar-*H*), 7.49-7.44 (m, 1H, Ar-*H*), 7.20-7.08 (m, 5H, Ar-*H*), 6.97 (d, *J* 8.0, 1H, Ar-*H*), 6.90-6.86 (m, 1H, Ar-*H*), 4.52 (s, 2H, SC*H*$_2$), 3.98 (s, 3H, O*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.3, 135.6, 131.1, 130.7, 128.6, 128.5, 128.3, 126.0, 120.7, 112.1, 60.6, 56.4; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2011, 1584, 1327 ($SO_2$), 1109 ($SO_2$), 1023; LRMS (ESI) *m/z* 285 (30%, $[M+Na]^+$), 547 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 285.0566 $[M+Na]^+$, $C_{14}H_{14}O_3SNa$ requires *m/z* 285.0556.

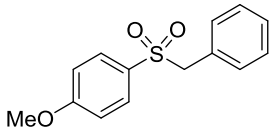
**1-(Benzylsulfonyl)-3-methoxybenzene (21i)**




Prepared according to general procedure C using 3-methoxyphenylmagnesium bromide (0.9 M in THF, 280 $\mu$L, 0.25 mmol) and benzyl bromide (150 $\mu$L, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (46 mg, 70%); mp 104-105 °C ($CH_2Cl_2$) [lit.[179] mp 105-107 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34-7.16 (m, 5H, Ar-*H*), 7.08-7.01 (m, 3H, Ar-*H*), 6.96-6.94 (m, 1H, Ar-*H*), 4.23 (s, 2H, SC*H*$_2$), 3.64 (s, 3H, O*Me*) ; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.6, 138.9, 130.9, 130.0, 128.8, 128.6, 128.2, 120.8, 120.7, 112.7, 62.9, 55.6; LRMS (ESI) *m/z* 285 (100%, $[M+Na]^+$); HRMS (ESI)

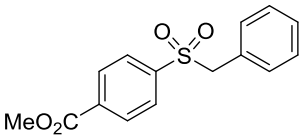
found *m/z* 285.0551 $[M+Na]^+$, $C_{14}H_{14}O_3SNa$ requires *m/z* 285.0556. Data in accordance with that previously reported.[179]

**1-(Benzylsulfonyl)-4-methoxybenzene (21j)**




Prepared according to general procedure C using 4-methoxyphenylmagnesium chloride (0.5 M in THF, 500 $\mu$L, 0.25 mmol) and benzyl bromide (90 $\mu$L, 0.75 mmol). Flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as an off-white solid (55 mg, 84%); mp 83-84 °C ($CH_2Cl_2$) [lit.[180] mp 83 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* 9.0, 2H, Ar-*H*), 7.28-7.17 (m, 3H, Ar-*H*), 7.03-6.99 (m, 2H, Ar-*H*), 6.82 (d, *J* 9.0, 2H, Ar-*H*), 4.22 (s, 2H, S*CH*$_2$), 3.79 (s, 3H, O*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.7, 130.8 (2C), 129.4, 128.7, 128.6, 128.5, 114.0, 63.1, 55.7; LRMS (ESI) *m/z* 285 (40%, $[M+Na]^+$), 547 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 285.0566 $[M+Na]^+$, $C_{14}H_{14}O_3SNa$ requires *m/z* 285.0556. Data in accordance with that previously reported.[180]

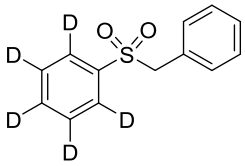
**Methyl 4-(benzylsulfonyl)benzoate (21k)**




Prepared according to general procedure C using (4-(methoxycarbonyl)phenyl)magnesium bromide (0.25 mmol) and benzyl bromide (150 $\mu$L, 1.25 mmol) and microwave heating for 5 hr. The aryl Grignard solution was prepared *in situ* by dropwise addition of *iso*propylmagnesium bromide (1.8M in THF, 139 $\mu$L, 0.28 mmol) to a solution of methyl-4-iodobenzoate (66 mg, 0.25 mmol) in THF (0.8 mL) at -40 °C. The solution was stirred at this temp. for 1 hr before being transferred *via* syringe to a DABSO-THF suspension. Flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfone as a white solid (34 mg, 48%); mp 176-177 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* 8.5, 2H, Ar-*H*), 7.62 (d, *J* 8.5, 2H, Ar-*H*), 7.28-7.23 (m, 1H, Ar-*H*), 7.22-7.16 (m, 2H, Ar-*H*), 7.00 (d, *J* 8.5,

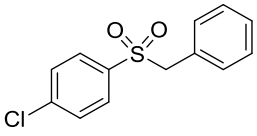
2H, Ar-*H*), 4.27 (s, 2H, SC*H*$_2$), 3.89 (s, 3H, CO$_2$*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.5, 141.6, 134.8, 130.8, 130.0, 129.0, 128.8, 128.7, 127.6, 62.8, 52.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2955, 2160, 1722 (CO), 1492, 1301 ($SO_2$), 1275, 1149 ($SO_2$); LRMS (ESI) *m/z* 313 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 313.0505 $[M+Na]^+$, $C_{15}H_{14}O_4SNa$ requires *m/z* 313.0505.

**1-(Benzylsulfonyl)benzene-*d*$_5$ (22b)**




Prepared according to general procedure C using *d*$_5$-phenyllithium (0.25 mmol) and benzyl bromide (150 μL, 1.25 mmol). The aryl lithium solution was generated *in situ* by dropwise addition of *n*-butyllithium (1.8 M in hexane, 153 μL, 0.28 mmol) to a solution of *d*$_5$-bromobenzene (26 μL, 0.25 mmol) in THF (0.8 mL) at -78 °C. The solution was stirred at this temp. for 1 hr before being transferred *via* syringe to a DABSO-THF suspension. Flash column chromatography (petrol/$Et_2O$ 3:2) afforded the product as a white solid (42 mg, 71%); mp 149-150 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.27-7.21 (m, 1H, Ar-*H*), 7.20-7.15 (m, 2H, Ar-*H*), 7.03-6.98 (m, 2H, Ar-*H*), 4.23 (s, 2H, SC*H*$_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 137.8, 133.7, 130.8, 128.9, 128.8, 128.7, 128.6, 128.1, 62.9; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2953, 2160, 1323 ($SO_2$), 1202, 1117 ($SO_2$), 1049; LRMS (ESI) *m/z* 260 (70%, $[M+Na]^+$), 497 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 260.0764 $[M+Na]^+$, $C_{13}H_7D_5O_2SNa$ requires *m/z* 260.0772.

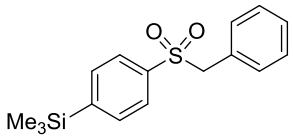
**1-(Benzylsulfonyl)-4-chlorobenzene (21l)**




Prepared according to general procedure C using 4-chlorophenylmagnesium chloride (1.0 M in THF, 250 μL, 0.25 mmol) and benzyl bromide (150 μL, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfone as a white solid (45 mg, 68%); mp 119-120 °C ($CH_2Cl_2$) [lit.[179] mp 118 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* 8.5,

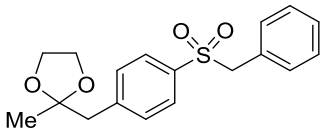
2H, Ar-*H*), 7.34 (d, *J* 8.5, 2H, Ar-*H*), 7.29-7.24 (m, 1H, Ar-*H*), 7.21 (t, *J* 7.5, 2H, Ar-*H*), 7.02 (d, *J* 7.5, 2H, Ar-*H*), 4.24 (s, 2H, SC$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 140.5, 136.3, 130.8, 130.2, 129.2, 129.0, 128.7, 127.9, 62.9; LRMS (ESI) *m/z* 289 (100%, [M($^{35}$Cl)+Na]$^+$), 291 (30%, [M($^{37}$Cl)+Na]$^+$); HRMS (ESI) found *m/z* 289.0053 [M($^{35}$Cl)+Na]$^+$ and 291.0027 [M($^{37}$Cl)+Na]$^+$, $C_{13}H_{11}ClO_2SNa$ requires *m/z* 289.0060 and 291.0031. Data in accordance with that previously reported.[179]

**[4-(Benzylsulfonyl)phenyl]trimethylsilane (22c)**



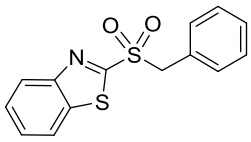

Prepared according to general procedure C using (4-(trimethylsilyl)phenyl)lithium (0.25 mmol) and benzyl bromide (150 μL, 1.25 mmol). The aryl lithium solution was generated *in situ* by dropwise addition of *n*-butyllithium (1.8 M in hexane, 153 μL, 0.28 mmol) to a solution of 4-trimethylsilylbromobenzene (57 mg, 0.25 mmol) in THF (0.8 mL) at -78 °C. The solution was stirred at this temp. for 1hr before being transferred *via* syringe to a DABSO-THF suspension. Flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (54 mg, 71%); mp 97-98 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.54-7.50 (m, 4H, Ar-*H*), 7.28-7.23 (m, 1H, Ar-*H*), 7.22-7.16 (m, 2H, Ar-*H*), 7.06-7.02 (m, 2H, Ar-*H*), 4.24 (s, 2H, SC$H_2$), 0.23 (s, 9H, Si$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 149.8, 139.5, 135.1, 132.3, 130.1, 129.9, 129.5, 128.8, 64.2, 0.0; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2963, 1406, 1317 ($SO_2$), 1251, 1131 ($SO_2$), 1029, 845; LRMS (ESI) *m/z* 327 (100%, [M+Na]$^+$), 631 (40%, [2M+Na]$^+$); HRMS (ESI) found *m/z* 327.0847 [M+Na]$^+$, $C_{16}H_{20}O_2SSiNa$ requires *m/z* 327.0845.

**2-[4-(Benzylsulfonyl)benzyl]-2-methyl-1,3-dioxolane (22d)**



Prepared according to general procedure C using {4-[(2-methyl-1,3-dioxolan-2-yl)methyl]phenyl}lithium (0.25 mmol) and benzyl bromide (150 $\mu$L, 1.25 mmol). The aryl lithium solution was generated *in situ* by dropwise addition of *n*-butyllithium (1.8 M in hexane, 153 $\mu$L, 0.28 mmol) to a solution of 2-(4-bromobenzyl)-2-methyl-1,3-dioxolane (64 mg, 0.25 mmol) in THF (0.8 mL) at -78 °C. The solution was stirred at this temp. for 1hr before being transferred *via* syringe to a DABSO-THF suspension. Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfone as a white solid (51 mg, 61%); mp 146-147 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* 8.5, 2H, Ar-*H*), 7.28 (d, *J* 8.5, 2H, Ar-*H*), 7.26-7.21 (m, 1H, Ar-*H*), 7.20-7.14 (m, 2H, Ar-*H*), 7.02-6.98 (d, *J* 7.5, 2H, Ar-H), 4.23 (s, 2H, S$CH_2$), 3.83-3.79 (m, 2H, $CH_2CH_2O$), 3.58-3.53 (m, 2H, $CH_2CH_2O$), 2.91 (s, 2H, $CCH_2$Ar), 1.24 (s, 3H, $CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.5, 135.8, 131.1, 130.8, 128.7, 128.5, 128.3, 128.2, 109.2, 64.9, 62.9, 45.3, 24.7; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2945, 1496, 1255, 1129 ($SO_2$), 1089, 1045; LRMS (ESI) *m/z* 355 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 355.0972 $[M+Na]^+$, $C_{18}H_{20}O_4SNa$ requires *m/z* 355.0975.

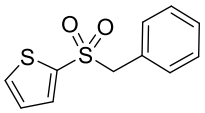
**2-(Benzylsulfonyl)benzothiazole (22e)**



Prepared according to general procedure C using 2-lithiobenzothiazole (0.25 mmol) and benzyl bromide (150 $\mu$L, 1.25 mmol). The aryl lithium solution was prepared *in situ* by dropwise addition of *n*-butyllithium (1.8 M in hexane, 153 $\mu$L, 0.28 mmol) to a solution of benzothiazole (29 $\mu$L, 0.25 mmol) in THF (0.8 mL) at -78 °C. The solution was stirred at this temp. for 30 min before being transferred *via* syringe to a DABSO-THF suspension. Flash column chromatography (petrol/EtOAc 4:1) afforded the titled sulfone as a yellow solid (39 mg, 54%); mp 110-111 °C ($CH_2Cl_2$) [lit.[181] mp 112-113 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.21-8.18 (m, 1H, Ar-*H*), 7.89-7.84 (m, 1H, Ar-*H*), 7.58 (ddd, *J* 8.5, 6.0, 1.0, 1H, Ar-*H*),

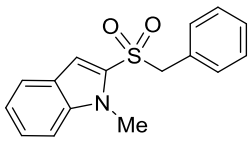
7.51 (ddd, *J* 8.5, 6.0, 1.0, 1H, Ar-*H*), 7.28-7.16 (m, 5H, Ar-*H*), 4.68 (s, 2H, SC$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.2, 152.6, 137.1, 131.1, 129.3, 128.9, 128.0, 127.7, 126.3, 125.5, 122.3, 61.0; LRMS (ESI) *m/z* 312 (100%, $[M+Na]^+$), 601 (70%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 312.0133 $[M+Na]^+$, $C_{14}H_{11}NO_2S_2Na$ requires *m/z* 312.0127. Data in accordance with that previously reported.[181]

**2-(Benzylsulfonyl)thiophene (21m)**



Prepared according to general procedure C using 2-thienylmagnesium bromide (0.95 M in THF, 263 μL, 0.25 mmol) and benzyl bromide (90 μL, 0.75 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfone as a yellow solid (48 mg, 83%); mp 139-140 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* 5.0, 1.5, 1H, Ar-*H*), 7.29-7.19 (m, 4H, Ar-*H*), 7.09-7.06 (m, 2H, Ar-*H*), 6.98 (dd, *J* 5.0, 4.0, 1H, Ar-*H*), 4.33 (s, 2H, SC$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 138.5, 134.9, 134.3, 130.7, 129.0, 128.7, 128.2, 127.7, 64.1; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3102, 1495, 1402, 1303 ($SO_2$), 1223, 1121 ($SO_2$); LRMS (ESI) *m/z* 261 (100%, $[M+Na]^+$), 499 (60%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 261.0008 $[M+Na]^+$, $C_{11}H_{10}O_2S_2Na$ requires *m/z* 261.0014.

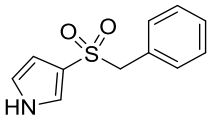
**2-(Benzylsulfonyl)-1-methyl-1*H*-indole (22f)**



Prepared according to general procedure C using 2-lithio-*N*-methylindole (0.33 M in THF, 760 μL, 0.25 mmol) and benzyl bromide (90 μL, 0.75 mmol). The aryl lithium was prepared as a stock solution by dropwise addition of *tert*-butyllithium (1.88 M in hexane, 2.34 mL, 4.40 mmol) to a solution of *N*-methylindole (500 μL, 4.0 mmol) in THF (10 mL) at -78 °C. The mixture was then warmed to room temp. and stirred for 1 hr before use. Flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfone as an off-white solid (53 mg,

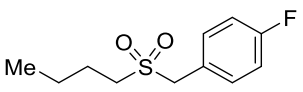
74%); mp 175-176 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* 8.0, 1H, Ar-*H*), 7.35-7.25 (m, 2H, Ar-*H*), 7.20-7.11 (m, 5H, Ar-*H*), 6.96 (d, *J* 8.0, 2H, Ar-*H*), 4.37 (s, 2H, SC*H*$_2$), 3.24 (s, 3H, N*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 139.2, 132.2, 131.0, 129.1, 128.8, 127.7, 125.9, 125.1, 122.9, 121.2, 112.0, 110.5, 64.7, 30.4; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2160, 1493, 1312 ($SO_2$), 1125 ($SO_2$), 1028; LRMS (ESI) *m/z* 286 (100%, $[M+H]^+$), 308 (90%, $[M+Na]^+$); HRMS (ESI) found *m/z* 308.0721 $[M+Na]^+$, $C_{16}H_{15}NO_2SNa$ requires *m/z* 308.0716.

**3-(Benzylsulfonyl)-1H-pyrrole (22g)**




Prepared according to general procedure C using 3-lithio-1(triisopropysilyl)pyrrole and benzyl bromide (150 μL, 1.25 mmol). The aryl lithium solution was prepared *in situ* by dropwise addition of *tert*-butyllithium (1.88 M in hexane, 146 μL, 0.28 mmol) to a solution of 3-bromo-1-(triisopropysilyl)pyrrole (66 μL, 0.25 mmol) in THF (0.8 mL) at -78 °C. The solution was stirred for 30 min at this temp. before being transferred *via* syringe to a DABSO-THF suspension. Flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled sulfone as an off-white solid (31 mg, 58%); mp 155-156 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.36-7.26 (m, 3H, Ar-*H*), 7.21-7.26 (m, 2H, Ar-*H*), 7.03 (app. t, *J* 2.0, 1H, Ar-*H*), 6.85 (dd, *J* 3.0, 2.0, 1H, Ar-*H*), 6.30 (dd, *J* 3.0, 2.0, 1H, Ar-*H*), 4.40 (s, 2H, SC*H*$_2$); $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 130.7, 129.5, 128.0, 127.9, 123.6, 119.9, 119.8, 108.1, 62.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3322 (NH), 2505, 2160, 1484, 1281, 1102 ($SO_2$); LRMS (ESI) m/z 244 (80%, $[M+Na]^+$), 465 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 244.0408 $[M+Na]^+$, $C_{11}H_{11}NO_2SNa$ requires *m/z* 244.0403.

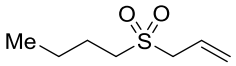
***n*-Butyl(4-fluorobenzene)sulfone (23a)**




Prepared according to general procedure C using *n*-butylmagnesium chloride (2.0 M in THF, 125 μL, 0.25 mmol) and 4-fluorobenzyl bromide (92 μL, 0.75 mmol). Flash column

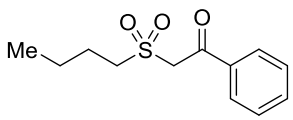
chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (47 mg, 82%); mp 91-92 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, *J* 8.5, 5.0, 2H, Ar-*H*) 7.03 (app. t, *J* 8.5, 2H, Ar-*H*), 4.12 (s, 2H, SC*H*$_2$Ar), 2.75 (t, *J* 8.0, 2H, SC*H*$_2$CH$_2$), 1.75-1.71 (m, 2H, SCH$_2$C*H*$_2$), 1.35 (app. sext., *J* 7.5, 2H, C*H*$_2$CH$_3$), 0.86 (t, *J* 7.5, 3H, CH$_2$C*H*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.2 (d, $J_{CF}$ 249.0), 132.4 (d, $J_{CF}$ 8.5) 123.9 (d, $J_{CF}$ 3.5), 116.2 (d, $J_{CF}$ 22.0), 58.4, 51.0, 23.8, 21.7, 13.5; $^{19}$F NMR (377 MHz, $CDCl_3$) δ -112.1; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2967, 1943, 1507, 1320 ($SO_2$), 1271, 1157 ($SO_2$); LRMS (ESI) *m/z* 253 (60%, [M+Na]$^+$), 583 (100%, [2M+Na]$^+$); HRMS (ESI) found *m/z* 253.0671 [M+Na]$^+$, $C_{11}H_{15}FO_2SNa$ requires *m/z* 253.0669.

**1-(Allylsulfonyl)butane (23b)**




Prepared according to general procedure C using *n*-butylmagnesium chloride (2.0 M in THF, 125 μL, 0.25 mmol) and allyl bromide (65 μL, 0.75 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfone as a colourless oil (37 mg, 87%); $^1$H NMR (400 MHz, $CDCl_3$) δ 5.94-5.83 (m, 1H, C*H*CH$_2$), 5.43 (dd, *J* 10.0, *J* 1.0, 1H, CHC*H*$_{trans}$), 5.38 (dd, *J* 17.0, *J* 1.0 Hz, 1H, CHC*H*$_{cis}$), 3.64 (d, *J* 7.5, 2H, SC*H*$_2$CH), 2.89 (m, 2H, SC*H*$_2$CH$_2$), 1.75 (m, 2H, SCH$_2$C*H*$_2$), 1.40 (app. sext., *J* 7.5, 2H, C*H*$_2$CH$_3$), 0.89 (t, *J* 7.5, 3H, CH$_2$C*H*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 125.3, 124.4, 57.6, 51.0, 23.7, 21.7, 13.5; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2963, 1653, 1314 ($SO_2$), 1129 ($SO_2$), 1100, 994; LRMS (ESI) *m/z* 185 (100%, [M+Na]$^+$), 347 (90%, [2M+Na]$^+$); HRMS (ESI) found *m/z* 185.0601 [M+Na]$^+$, $C_7H_{14}O_2SNa$ requires *m/z* 185.0607.

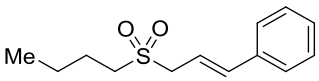
**2-(Butylsulfonyl)-1-phenylethan-1-one (23c)**




Prepared according to general procedure C using *n*-butylmagnesium chloride (2.0 M in THF, 125 μL, 0.25 mmol) and 2-bromoacetophenone (149 mg, 0.75 mmol). Flash column

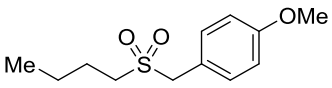
chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a yellow solid (54 mg, 90%); mp 68-69 °C ($CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* 8.0, 1.5, 2H, Ar-*H*), 7.59 (tt, *J* 7.0, 1.5, 1H, Ar-*H*), 7.46 (app. t, *J* 8.0, 2H, Ar-*H*), 4.50 (s, 2H, SC*H*$_2$CO), 3.19 (t, *J* 8.0, 2H, SC*H*$_2$CH$_2$), 1.84-1.78 (m, 2H, SCH$_2$C*H*$_2$), 1.44 (app. sext., *J* 7.5, 2H, C*H*$_2$CH$_3$), 0.90 (t, *J* 7.5, 3H, CH$_2$C*H*$_3$); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 189.3, 135.8, 134.7, 129.3, 129.0, 59.5, 53.5, 23.9, 21.6, 13.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2960, 2870, 2160, 1687 (CO), 1599, 1311 ($SO_2$), 1210, 1121 ($SO_2$); LRMS (ESI) *m/z* 263 (40%, [M+Na]$^+$), 503 (100%, [2M+Na]$^+$); HRMS (ESI) found *m/z* 263.0709 [M+Na]$^+$, $C_{12}H_{16}O_3SNa$ requires *m/z* 263.0712.

**(*E*)-[3-(Butylsulfonyl)prop-1-en-1-yl]benzene (23d)**




Prepared according to general procedure C using *n*-butylmagnesium chloride (2.0 M in THF, 125 μL, 0.25 mmol) and 3-bromo-1-phenyl-1-propene (110 μL, 0.75 mmol). Flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (56 mg, 94%); mp 87-88 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 2H, Ar-*H*), 7.31-7.21 (m, 3H, Ar-*H*), 6.63 (d, *J* 16.0, 1H, C*H*CHCH$_2$), 6.19 (dt, *J* 16.0, 7.5, 1H, CHC*H*CH$_2$), 3.79 (d, *J* 7.5, 2H, CHCHC*H*$_2$), 2.94-2.89 (m, 2H, SC*H*$_2$CH$_2$), 1.81-1.72 (m, 2H SCH$_2$C*H*$_2$), 1.39 (app. sext., *J* 7.5, 2H, C*H*$_2$CH$_3$), 0.88 (t, *J* 7.5, 3H, CH$_2$C*H*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 138.8, 135.6, 128.8 (2C), 126.7, 115.6, 57.3, 51.1, 23.8, 21.8, 13.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2961, 2874, 1646, 1451, 1319 ($SO_2$), 1292, 1146 ($SO_2$); LRMS (ESI) *m/z* 261 (100%, [M+Na]$^+$), 499 (60%, [2M+Na]$^+$); HRMS (ESI) found *m/z* 261.0924 [M+Na]$^+$, $C_{13}H_{18}O_2SNa$ requires *m/z* 261.0920.

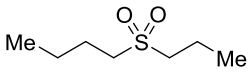
**1-[(Butylsulfonyl)methyl]-4-methoxybenzene (23e)**




Prepared according to general procedure C using *n*-butylmagnesium chloride (2.0 M in THF, 125 μL, 0.25 mmol) and *p*-methoxybenzyl chloride (102 μL, 0.75 mmol). Flash column

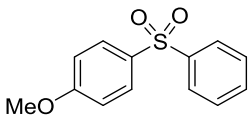
chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as an off-white solid (43 mg, 71%); mp 78-79 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* 8.5, 2H, Ar-*H*), 6.85 (d, *J* 8.5, 2H, Ar-*H*), 4.09 (s, 2H, SC*H*$_2$Ar), 3.75 (s, 3H, O*Me*), 2.76-2.70 (m, 2H, SC*H*$_2$CH$_2$), 1.76-1.66 (m, 2H, SCH$_2$C*H*$_2$), 1.34 (app. sext., *J* 7.5, 2H, C*H*$_2$CH$_3$), 0.85 (t, *J* 7.5, 3H, CH$_2$C*H*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.2, 131.7, 120.0, 114.5, 58.7, 55.3, 50.6, 23.8, 21.7, 13.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2933, 1549, 1462, 1320 ($SO_2$), 1155 ($SO_2$); LRMS (ESI) *m/z* 265 (100%, $[M+Na]^+$), 507 (40%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 265.0870 $[M+Na]^+$, $C_{12}H_{18}O_3SNa$ requires *m/z* 265.0874.

**1-(Propylsulfonyl)butane (23f)**




Prepared according to general procedure C using *n*-butylmagnesium chloride (2.0 M in THF, 125 μL, 0.25 mmol) and iodopropane (73 μL, 0.75 mmol). Flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (30 mg, 74%); mp 81-82 °C ($CH_2Cl_2$) [lit.[182] mp 81-82 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 2.90-2.84 (m, 4H, SC*H*$_2$), 1.87-1.71 (m, 4H, SCH$_2$C*H*$_2$), 1.41 (app. sext., *J* 7.5, 2H, SCH$_2$CH$_2$C*H*$_2$) 1.03 (t, *J* 7.5, 3H, SCH$_2$CH$_2$C*H*$_3$), 0.90 (t, *J* 7.5, 3H, SCH$_2$CH$_2$CH$_2$C*H*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 54.4, 52.5, 23.9, 21.8, 15.8, 13.6, 13.2; LRMS (ESI) *m/z* 187 (40%, $[M+Na]^+$), 351 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 187.0760 $[M+Na]^+$, $C_7H_{16}O_2SNa$ requires *m/z* 187.0763. Data in accordance with that previously reported.[182]

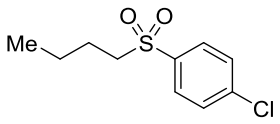
**1-Methoxy-4-(phenylsulfonyl)benzene (24a)**




Prepared according to general procedure C using 4-methoxyphenylmagnesium bromide (0.5 M in THF, 500 μL, 0.25 mmol) and diphenyliodonium triflate (323 mg, 0.75 mmol) with microwave heating for 5 hr. Flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as an off-white solid (46 mg, 74%); mp 92-93 °C ($CH_2Cl_2$) [lit.[183] mp 92-93 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86-7.82 (m, 2H, Ar-*H*), 7.81 (d, *J* 9.0, 2H, Ar-*H*),

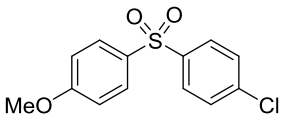
7.45-7.38 (m, 3H, Ar-*H*), 6.89 (d, *J* 9.0, 2H, Ar-*H*), 3.77 (s, 3H, O*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.4, 142.4, 133.1, 132.8, 129.9, 129.2, 127.3, 114.5, 55.7; LRMS (ESI) *m/z* 271 (100%, $[M+Na]^+$), 519 (80%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 271.0394 $[M+Na]^+$, $C_{13}H_{12}O_3SNa$ requires *m/z* 271.0399. Data in accordance with that previously reported.[183]

**1-(Butylsulfonyl)-4-chlorobenzene (24b)**




Prepared according to general procedure C using *n*-butylmagnesium chloride (2.0 M in THF, 125 μL, 0.25 mmol) and di(4-chlorophenyl)iodonium triflate (374 mg, 0.75 mmol) with microwave heating for 5 hr. Flash column chromatography (petrol/$Et_2O$ 4:1) afforded the titled sulfone as a colourless oil (38 mg, 67%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* 8.5, 2H, Ar-*H*), 7.48 (d, *J* 8.5, 2H, Ar-*H*), 3.11-2.90 (m, 2H, S$CH_2$), 1.68-1.51 (m, 2H, $SCH_2CH_2$), 1.43-1.25 (m, 2H, $CH_2CH_3$), 0.83 (t, *J* 7.5, 3H, $CH_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 140.4, 137.6, 129.6, 129.4, 56.1, 24.6, 21.5, 13.5; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2983, 1595, 1476, 1314 ($SO_2$), 1287, 1140 ($SO_2$), 1068; LRMS (ESI) *m/z* 255 (100%, $[M(^{35}Cl)+Na]^+$), 487 (50%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 255.0208 $[M(^{35}Cl)+Na]^+$ and 257.0183 $[M(^{37}Cl)+Na]^+$, $C_{10}H_{13}ClO_2SNa$ requires *m/z* 255.0217 and 257.0188.

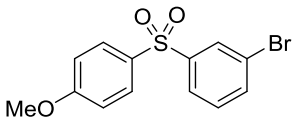
**1-Chloro-4-[(4-methoxyphenyl)sulfonyl]benzene (24c)**




Prepared according to general procedure C using 4-methoxyphenylmagnesium chloride (0.5 M in THF, 500 μL, 0.25 mmol) and di(4-chlorophenyl)iodonium triflate (374 mg, 0.75 mmol) with microwave heating for 5 hr. Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfone as an off-white solid (54 mg, 76%); mp 101-102 °C ($CH_2Cl_2$) [lit.[184] mp 103-104 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.80-7.75 (m, 4H, Ar-*H*), 7.38 (d, *J* 8.5, 2H, Ar-*H*), 6.90 (d, *J* 9.0, 2H, Ar-*H*), 3.77 (s, 3H, O*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.6, 140.9, 139.5, 132.6, 129.9, 129.5, 128.8, 114.7, 55.7; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2997, 1593,

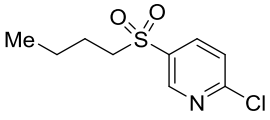
1497, 1321 ($SO_2$), 1258, 1150 ($SO_2$); LRMS (ESI) *m/z* 305 (100%, $[M(^{35}Cl)+Na]^+$), 587 (50%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 305.0012 $[M(^{35}Cl)+Na]^+$ and 306.9983 $[M(^{37}Cl)+Na]^+$, $C_{13}H_{11}ClO_3SNa$ requires *m/z* 305.0018 and 306.9997. Melting point data in accordance with that previously reported.[184]

**1-Bromo-3-[(4-methoxyphenyl)sulfonyl]benzene (24d)**




Prepared according to general procedure C using 4-methoxyphenylmagnesium chloride (0.5 M in THF, 500 $\mu$L, 0.25 mmol) and di(3-bromophenyl)iodonium triflate (440 mg, 0.75 mmol) with microwave heating for 5 hr. Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfone as a colourless oil (48 mg, 55%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.97 (app. t, *J* 2.0, 1H, Ar-*H*), 7.80 (d, *J* 9.0, 2H, Ar-*H*), 7.77 (ddd, *J* 8.0, 2.0, 1.0, 1H, Ar-*H*), 7.58 (ddd, *J* 8.0, 2.0, 1.0, 1H, Ar-*H*), 7.29 (app. t, *J* 8.0, 1H, Ar-*H*), 6.91 (d, *J* 9.0, 2H, Ar-*H*), 3.78 (s, 3H, O*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.7, 144.3, 135.9, 132.3, 130.8, 130.2, 130.1, 125.9, 123.2, 114.7, 55.7; IR $\nu_{max}$ (neat)/$cm^{-1}$ 1593, 1497, 1461, 1414, 1323 ($SO_2$), 1261, 1152 ($SO_2$); LRMS (ESI) *m/z* 349 (100%, $[M(^{79}Br)+Na]^+$), 351 (50%, $[M(^{81}Br)+Na]^+$); HRMS (ESI) found *m/z* 348.9506 $[M(^{79}Br)+Na]^+$ and 350.9487 $[M(^{81}Br)+Na]^+$, $C_{13}H_{11}BrO_3SNa$ requires *m/z* 348.9504 and 350.9484.

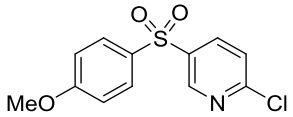
**5-(Butylsulfonyl)-2-chloropyridine (29a)**




Prepared according to general procedure C using *n*-butylmagnesium chloride (2.0 M in THF, 125 $\mu$L, 0.25 mmol) and (6-chloropyridin-3-yl)(4-methoxyphenyl)iodonium triflate (372 mg, 0.75 mmol) with microwave heating for 5 hr. Flash column chromatography (petrol/EtOAc 4:1) afforded the titled sulfone as an off-white solid (38 mg, 65%); mp 56-57 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* 2.5, 1H, Ar-*H*), 8.07 (dd, *J* 8.5, 2.5, 1H, Ar-*H*), 7.48 (d, *J* 8.5, 1H, Ar-*H*), 3.09-3.04 (m, 2H, S*CH*$_2$CH$_2$), 1.69-1.60 (m, 2H, SCH$_2$*CH*$_2$), 1.36 (app.

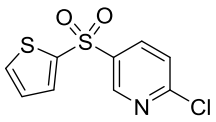
sext., *J* 7.5, 2H, C*H*$_2$CH$_3$), 0.85 (t, *J* 7.5, 3H, CH$_2$C*H*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 156.8, 149.6, 138.4, 134.6, 124.9, 56.5, 24.6, 21.5, 13.5; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2961, 2876, 2161, 1565, 1453, 1324 ($SO_2$), 1105 ($SO_2$); LRMS (ESI) *m/z* 256 (100%, [M($^{35}$Cl)+Na]$^+$), 258 (20%, [M($^{37}$Cl)+Na]$^+$); HRMS (ESI) found *m/z* 256.0169 [M($^{35}$Cl)+Na]$^+$ and 258.0137 [M($^{37}$Cl)+Na]$^+$, $C_9H_{12}ClNO_2SNa$ requires *m/z* 256.0169 and 258.0140.

**2-Chloro-5-[(4-methoxyphenyl)sulfonyl]pyridine (29b)**




Prepared according to general procedure C using 4-methoxyphenylmagnesium bromide (0.5 M in THF, 500 μL, 0.25 mmol) and (6-chloropyridin-3-yl)(4-methoxyphenyl)iodonium triflate (372 mg, 0.75 mmol) with microwave heating for 5 hr. Flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfone as a white solid (41 mg, 58%); mp 94-95 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.81 (dd, *J* 2.5, 0.5, 1H, Ar-*H*), 8.04 (dd, *J* 8.5, 2.5, 1H, Ar-*H*), 7.81 (d, *J* 9.0, 2H, Ar-*H*), 7.37 (dd, *J* 8.5, 0.5, 1H, Ar-*H*), 6.93 (d, *J* 9.0, 2H, Ar-*H*), 3.80 (s, 3H, O*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.1, 155.7, 148.8, 138.0, 137.5, 131.7, 130.1, 124.8, 115.0, 55.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2098, 1593, 1498, 1301 ($SO_2$), 1260, 1156 ($SO_2$); LRMS (ESI) *m/z* 306 (100%, [M($^{35}$Cl)+Na]$^+$), 308 (30%, [M($^{37}$Cl)+Na]$^+$); HRMS (ESI) found *m/z* 305.9960 [M($^{35}$Cl)+Na]$^+$ and 307.9925 [M($^{37}$Cl)+Na]$^+$, $C_{12}H_{10}ClNO_3SNa$ requires *m/z* 305.9962 and 307.9933.

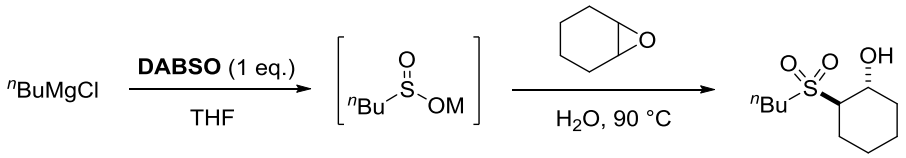
**2-Chloro-5-(thiophen-2-ylsulfonyl)pyridine (29c)**




Prepared according to general procedure C using 2-thienyllithium (0.95 M in THF, 263 μL, 0.25 mmol) and (6-chloropyridin-3-yl)(4-methoxyphenyl)iodonium triflate (372 mg, 0.75 mmol) with microwave heating for 5 hr. Flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfone as a white solid (33 mg, 51%); mp 167-168 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.89 (dd, *J* 2.5, 0.5, 1H, Ar-*H*), 8.11 (dd, *J* 8.5, 2.5, 1H, Ar-*H*), 7.71-

7.64 (m, 2H, Ar-*H*), 7.41 (dd, *J* 8.5, 0.5 Hz, 1H, Ar-*H*), 7.08 (dd, *J* 5.0, 4.0 Hz, 1H, Ar-*H*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 156.2, 148.8, 141.6, 137.7, 137.5, 135.2, 134.4, 128.4, 124.9; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2160, 1565, 1447, 1326 ($SO_2$), 1285, 1157 ($SO_2$), 1021; LRMS (ESI) *m/z* 260 (100%, [M($^{35}$Cl)+H]$^+$), 282 (80%, [M($^{35}$Cl)+Na]$^+$); HRMS (ESI) found *m/z* 281.9422 [M($^{35}$Cl)+Na]$^+$ and 283.9404 [M($^{37}$Cl)+Na]$^+$, $C_9H_6ClNO_2S_2Na$ requires *m/z* 281.9421 and 283.9391.

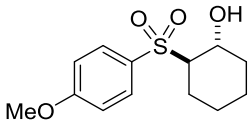
### 6.3.3 General procedure D for the synthesis of *β*-hydroxy sulfones from Grignard reagent, DABSO, and epoxides as exemplified by the preparation of 2-(butylsulfonyl)cyclohexan-1-ol (34a)




To a reaction tube was added DABSO (60 mg, 0.25 mmol) and THF (1 mL) and the resulting suspension flushed with nitrogen gas for 2 min. After cooling to -40 °C, *n*-butylmagnesium chloride (125 *μ*L, 0.25 mmol) was added dropwise to the suspension which was stirred at this temp. for 1 hr. On warming to room temp. a strong flow of nitrogen gas was applied to remove the solvent before addition of $H_2O$ (1.5 mL) and cyclohexene oxide (126 *μ*L, 1.25 mmol). The resulting mixture was heated to 90 °C and stirred at this temp. for 16 hr. After cooling, sat. $NH_4Cl$ (10 mL) and subsequently $CH_2Cl_2$ (10 mL) were added, the two phases separated and the aqueous layer extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled *β*-hydroxy sulfone as an off-white solid (43 mg, 78%); mp 68-69 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 3.97 (td, *J* 10.0, 4.5, 1H, C*H*OH), 3.29 (br. s, 1H, O*H*), 3.02 (t, *J* 8.0, 2H, SC*H*$_2$CH$_2$), 2.81 (ddd, *J* 13.0, 10.0, 4.0, 1H, SC*H*CH$_2$), 2.13-2.03 (m, 2H, SCHC*H*$_2$ and CH(OH)C*H*$_2$), 1.83-1.69 (m, 4H, SCH$_2$C*H*$_2$ and C*H*$_2$) 1.53-1.35 (m, 3H, C*H*$_2$CH$_3$ and 1 × SCHC*H*$_2$), 1.34-1.16 (m, 3H, 1 × CH(OH)C*H*$_2$ and C*H*$_2$), 0.90 (t, *J* 7.5, 3H, CH$_2$C*H*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 68.8, 66.2, 52.9, 34.8, 24.6, 24.4, 23.8, 23.3, 21.8, 13.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3490 (br. OH), 2928, 2869, 2159, 1311 ($SO_2$), 1130 ($SO_2$); LRMS (ESI) *m/z* 243 (40%, [M+Na]$^+$), 463 (100%,

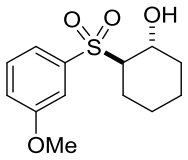
$[2M+Na]^+$); HRMS (ESI) found *m/z* 243.1031 $[M+Na]^+$, $C_{10}H_{20}O_3SNa$ requires *m/z* 243.1025.

**2-[(4-Methoxyphenyl)sulfonyl]cyclohexan-1-ol (34b)**




Prepared according to general procedure D using 4-methoxyphenylmagnesium bromide (0.5 M in THF, 500 $\mu$L, 0.25 mmol) and cyclohexene oxide (126 $\mu$L, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled $\beta$-hydroxy sulfone as a colourless oil (55 mg, 81%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* 9.0, 2H, Ar-*H*), 6.97 (d, *J* 9.0, 2H, Ar-*H*), 4.32 (br. s, 1H, O*H*), 3.83 (s, 3H, O*Me*), 3.79 (td, *J* 10.0, 5.0, 1H, C*H*OH), 2.87 (ddd, *J* 12.0, 10.0, 4.0, 1H, SC*H*$CH_2$), 2.09-2.01 (m, 1H, CH(OH)C$H_2$), 1.88-1.81 (m, 1H, SCHC$H_2$), 1.67-1.60 (m, 2H, C$H_2$), 1.33-1.06 (m, 4H, 1 × CH(OH)C$H_2$, 1 × SCHC$H_2$ and C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.1, 131.2, 128.0, 114.5, 69.0, 68.3, 55.8, 34.1, 25.8, 24.6, 23.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3448 (br. OH), 2963, 1623, 1433, 1316 ($SO_2$), 1128 ($SO_2$); LRMS (ESI) *m/z* 293 (20%, $[M+Na]^+$), 563 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 293.0819 $[M+Na]^+$, $C_{13}H_{18}O_4Na$ requires *m/z* 293.0818.

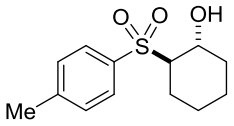
**2-[(3-Methoxyphenyl)sulfonyl]cyclohexan-1-ol (34c)**




Prepared according to general procedure D using 3-methoxyphenylmagnesium chloride (0.9 M in THF, 280 $\mu$L, 0.25 mmol) and cyclohexene oxide (126 $\mu$L, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled $\beta$-hydroxy sulfone as a colourless oil (49 mg, 73%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.45-7.40 (m, 2H, Ar-*H*), 7.32-7.30 (m, 1H, Ar-*H*), 7.14 (dt, *J* 7.5, 2.5, 1H, Ar-*H*), 4.22 (br. s, 1H, CHO*H*), 3.88 (td, *J* 10.0, 5.0, 1H, C*H*OH), 3.82 (s, 3H, O*Me*), 2.92 (ddd, *J* 12.5, 10.0, 4.0, 1H, SC*H*$CH_2$), 2.11-2.04 (m, 1H, CH(OH)C$H_2$), 1.86-1.79 (m, 1H, SCHC$H_2$), 1.68-1.62 (m, 2H, SCHC$H_2$ and C$H_2$), 1.33-1.06 (m, 4H, 3 × C$H_2$ and 1 × CH(OH)C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.0,

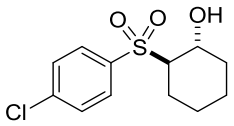
137.9, 130.3, 121.1, 120.5, 113.5, 69.0, 68.2, 55.8, 34.2, 25.8, 24.6, 23.6; IR $\nu_{max}$ (neat)/$cm^{-1}$ 3429 (br. OH), 2968, 1657, 1432, 1329 ($SO_2$), 1148 ($SO_2$); LRMS (ESI) *m/z* 293 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 293.0819 $[M+Na]^+$, $C_{13}H_{18}O_4SNa$ requires *m/z* 293.0818.

**2-Tosylcyclohexan-1-ol (34d)**




Prepared according to general procedure D using *p*-tolylmagnesium chloride (2.0 M in THF, 125 $\mu$L, 0.25 mmol) and cyclohexene oxide (126 $\mu$L, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled $\beta$-hydroxy sulfone as a yellow solid (46 mg, 72%); mp 125-126 °C ($CH_2Cl_2$) [lit.[185] mp 123 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* 8.5, 2H, Ar-*H*), 7.32 (d, *J* 8.5, 2H, Ar-*H*), 4.29 (s, 1H, O*H*), 3.82 (td, *J* 10.0, 5.0, 1H, C*H*OH), 2.89 (ddd, *J* 12.0, 10.0, 4.0, 1H, SC*H*$CH_2$), 2.40 (s, 3H, Ar*Me*), 2.09-2.02 (m, 1H, CH(OH)C$H_2$), 1.87-1.80 (m, 1H, SCHC$H_2$), 1.66-1.60 (m, 2H, C$H_2$), 1.32-1.05 (m, 4H, 1 × CH(OH)C$H_2$, 1 × SCHC$H_2$ and C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 145.3, 133.7, 129.9, 129.1, 68.9, 68.2, 34.1, 25.7, 24.6, 23.6, 21.7; LRMS (ESI) *m/z* 277 (20%, $[M+Na]^+$), 531 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 277.0876 $[M+Na]^+$, $C_{13}H_{18}O_3SNa$ requires *m/z* 277.0869. Data in accordance with that previously reported.[185]

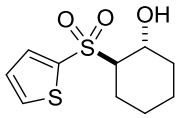
**2-[(4-Chlorophenyl)sulfonyl]cyclohexan-1-ol (34e)**




Prepared according to general procedure D using 4-chlorophenylmagnesium chloride (1.0 M in THF, 250 $\mu$L, 0.25 mmol) and cyclohexene oxide (126 $\mu$L, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled $\beta$-hydroxy sulfone as a white solid (42 mg, 61%); mp 118-119 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* 8.5, 2H, Ar-*H*), 7.50 (d, *J* 8.5, 2H, Ar-*H*), 4.05 (s, 1H, O*H*), 3.83 (td, *J* 10.0, 5.0, 1H, C*H*OH), 2.91 (ddd, *J* 12.0, 10.0, 4.0, 1H, SC*H*$CH_2$), 2.11-2.03 (m, 1H, CH(OH)C$H_2$), 1.89-1.81 (m, 1H,

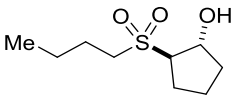
SCHC*H*$_2$), 1.71-1.61 (m, 2H, C*H*$_2$), 1.34-1.04 (m, 4H, 1 × CH(OH)C*H*$_2$, 1 × SCHC*H*$_2$ and C*H*$_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 141.0, 135.4, 130.5, 129.6, 69.1, 68.3, 34.2, 25.7, 24.5, 23.5; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3448 (br. OH), 2021, 1426, 1344 ($SO_2$), 1109 ($SO_2$), 1034; LRMS (ESI) *m/z* 297 (100%, [M($^{35}$Cl)+Na]$^+$), 299 (20%, [M($^{37}$Cl)+Na]$^+$); HRMS (ESI) found *m/z* 297.0325 [M($^{35}$Cl)+Na]$^+$ and 299.0306 [M($^{37}$Cl)+Na]$^+$, $C_{12}H_{15}ClO_3SNa$ requires *m/z* 297.0323 and 299.0294

**2-(Thiophen-2-ylsulfonyl)cyclohexan-1-ol (34f)**




Prepared according to general procedure D using 2-thienylmagnesium bromide (0.95 M in THF, 265 µL, 0.25 mmol) and cyclohexene oxide (126 µL, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled *β*-hydroxy sulfone as a yellow oil (43 mg, 70%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* 5.0, 1.5, 1H, Ar-*H*), 7.64 (dd, *J* 4.0, 1.5, 1H, Ar-*H*), 7.14 (dd, *J* 5.0, 4.0, 1H, Ar-*H*), 4.10 (s, 1H, O*H*), 3.84 (td, *J* 10.0, 5.0, 1H, C*H*OH), 3.00 (ddd, *J* 12.0, 10.0, 4.0, 1H, SC*H*CH$_2$), 2.12-2.04 (m, 1H, CH(OH)C*H*$_2$), 2.04-1.97 (m, 1H, SCHC*H*$_2$), 1.75-1.62 (m, 2H, C*H*$_2$), 1.35-1.22 (m, 2H, CH(OH)C*H*$_2$ and SCHC*H*$_2$), 1.21-1.07 (m, 2H, C*H*$_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 137.4, 135.4, 134.9, 128.1, 70.1, 68.3, 34.1, 26.0, 24.6, 23.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3514 (br. OH), 2937, 2862, 1451, 1402, 1304 ($SO_2$), 1133 ($SO_2$); LRMS (ESI) *m/z* 269 (40%, [M+Na]$^+$), 515 (100%, [2M+Na]$^+$); HRMS (ESI) found *m/z* 269.0281 [M+Na]$^+$, $C_{10}H_{14}O_3S_2Na$ requires *m/z* 269.0277.

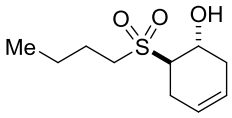
**2-(Butylsulfonyl)cyclopentan-1-ol (34g)**




Prepared according to general procedure D using *n*-butylmagnesium chloride (2.0 M in THF, 125 *µ*L, 0.25 mmol) and cyclopentene oxide (109 *µ*L, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled *β*-hydroxy sulfone as a light yellow oil

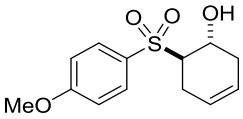
(41 mg, 80%); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 4.60 (app. q, *J* 6.5, 1H, C*H*OH), 3.20 (ddd, *J* 9.0, 8.5, 6.5, 1H, SC*H*$CH_2$), 2.93 (t, *J* 7.5, 2H, SC*H*$_2$$CH_2$), 2.46 (br. s, 1H, O*H*), 2.13-1.93 (m, 3H SCHC*H*$_2$ and 1 × CH(OH)C*H*$_2$), 1.83-1.60 (m, 5H, $SCH_2$C*H*$_2$, CH(OH)$CH_2$C*H*$_2$ and 1 × CH(OH)C*H*$_2$) 1.41 (app. sext., *J* 7.5, 2H, C*H*$_2$$CH_3$), 0.90 (t, *J* 7.5, 3H, $CH_2$C*H*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 73.2, 67.8, 52.2, 34.7, 25.3, 23.6, 22.1, 21.8, 13.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3459 (br. OH), 2928, 2861, 1499, 1337 ($SO_2$), 1228, 1121 ($SO_2$); LRMS (ESI) *m/z* 229 (30%, $[M+Na]^+$), 435 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 229.0869 $[M+Na]^+$, $C_9H_{18}O_3SNa$ requires *m/z* 229.0876.

**6-(Butylsulfonyl)cyclohex-3-en-1-ol (34h)**



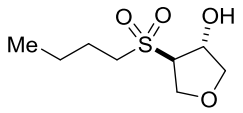

Prepared according to general procedure D using *n*-butylmagnesium chloride (2.0 M in THF, 125 μL, 0.25 mmol) and 7-oxabicyclo[4.1.0]hept-3-ene (120 mg, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled *β*-hydroxy sulfone as an off-white solid (42 mg, 77%); mp 57-58 °C ($CH_2Cl_2$); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 5.63-5.53 (m, 2H, C*H*C*H*), 4.23-4.14 (m, 1H, C*H*OH), 3.21 (br. s, 1H, O*H*), 3.17-3.08 (m, 3H, SC*H*$_2$$CH_2$ and SC*H*$CH_2$), 2.56-2.34 (m, 3H, SCHC*H*$_2$ and 1 × CH(OH)C*H*$_2$), 2.18-2.07 (m, 1H, CH(OH)C*H*$_2$), 1.84-1.74 (m, 2H, $SCH_2$C*H*$_2$), 1.41 (app. sext., *J* 7.5, 2H, C*H*$_2$$CH_3$), 0.90 (t, *J* 7.5, 3H, $CH_2$C*H*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 124.6, 123.5, 66.7, 62.3, 54.4, 34.5, 24.7, 23.5, 21.8, 13.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3461 (br. OH), 2966, 2923, 1687, 1449, 1313 ($SO_2$), 1260, 1126 ($SO_2$); LRMS (ESI) *m/z* 241 (40%, $[M+Na]^+$), 459 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 241.0873 $[M+Na]^+$, $C_{10}H_{18}O_3SNa$ requires *m/z* 241.0869.

**6-[(4-Methoxyphenyl)sulfonyl]cyclohex-3-en-1-ol (34i)**



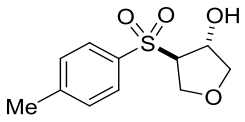

Prepared according to general procedure D using 4-methoxyphenylmagnesium bromide (0.5 M in THF, 500 $\mu$L, 0.25 mmol) and 7-oxabicyclo[4.1.0]hept-3-ene (120 mg, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled $\beta$-hydroxy sulfone as a white solid (53 mg, 79%); mp 74-75 °C ($CH_2Cl_2$): $^1$H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* 9.0, 2H, Ar-*H*), 6.98 (d, *J* 9.0, 2H, Ar-*H*), 5.53-5.39 (m, 2H, C*H*C*H*), 4.15 (br. s, 1H, O*H*), 4.11-4.04 (m, 1H, C*H*OH), 3.83 (s, 3H, O*Me*), 3.20 (td, *J* 10.5, 6.0, 1H, SC*H*$CH_2$), 2.56-2.46 (m, 1H, CH(OH)C$H_2$), 2.28-2.03 (m, 3H, SCHC$H_2$ and 1 × CH(OH)C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.2, 131.2, 128.2, 124.6, 122.8, 114.5, 65.7, 65.2, 55.8, 34.0, 26.1; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3432 (br. OH), 2961, 1542, 1407, 1338 ($SO_2$), 1143 ($SO_2$); LRMS (ESI) *m/z* 291 (30%, $[M+Na]^+$), 559 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 291.0665 $[M+Na]^+$, $C_{13}H_{16}O_4SNa$ requires *m/z* 291.0662.

**4-(Butylsulfonyl)tetrahydrofuran-3-ol (34j)**



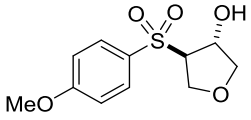

Prepared according to general procedure D using *n*-butylmagnesium chloride (2.0 M in THF, 125 $\mu$L, 0.25 mmol) and 3,4-epoxytetrahydrofuran (90 $\mu$L, 1.25 mmol). Flash column chromatography (100% $Et_2O$) afforded the titled $\beta$-hydroxy sulfone as a colourless oil (31 mg, 60%); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.81 (dt, *J* 5.5, 4.0, 1H, C*H*OH), 4.23 (dd, *J* 10.0, 8.5, 1H, SCHC$H_2$), 4.05 (dd, *J* 10.0, 6.5, 1H, SCHC$H_2$), 3.98 (dd, *J* 10.0, 5.5, 1H, CH(OH)C$H_2$), 3.69 (dd, *J* 10.0, 4.0, 1H, CH(OH)C$H_2$), 3.53 (ddd, *J* 8.5, 6.5, 4.0, 1H, SC*H*$CH_2$), 2.95-2.92 (m, 2H, SC$H_2$$CH_2$), 1.83-1.75 (m, 2H, $SCH_2$C$H_2$), 1.47-1.38 (m, 2H, C$H_2$$CH_3$), 0.91 (t, *J* 7.5, 3H, $CH_2$C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 74.9, 72.5, 69.0, 66.6, 52.5, 23.3, 21.8, 13.5; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3471 (br. OH), 2963, 2876, 1467, 1301 ($SO_2$), 1132 ($SO_2$); LRMS (ESI) *m/z* 231 (100%, $[M+Na]^+$), 439 (30%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 231.0669 $[M+Na]^+$, $C_8H_{16}O_4SNa$ requires *m/z* 231.0662.

**4-Tosyltetrahydrofuran-3-ol (34k)**



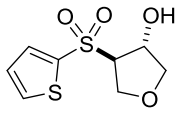

Prepared according to general procedure D using *p*-tolylmagnesium chloride (2.0 M in THF, 125 $\mu$L, 0.25 mmol) and 3,4-epoxytetrahydrofuran (90 $\mu$L, 1.25 mmol). Flash column chromatography (100% $Et_2O$) afforded the titled *β*-hydroxy sulfone as a white solid (34 mg, 56%); mp 75-76 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* 8.0, 2H, Ar-*H*), 7.32 (d, *J* 8.0, 2H, Ar-*H*), 4.80 (m, 1H, C*H*OH), 4.04 (dd, *J* 10.0, 8.5, 1H, SCHC$H_2$), 3.97 (dd, *J* 10.0, 6.0, 1H, SCHC$H_2$), 3.89 (dd, *J* 10.0, 4.5, 1H, CH(OH)C$H_2$), 3.68-3.62 (m, 2H, SC*H*$CH_2$ and CH(OH)C$H_2$), 2.93 (d, *J* 5.0, 1H, O*H*), 2.39 (s, 3H, Ar*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 145.5, 135.1, 130.3, 128.4, 74.9, 72.5, 72.0, 67.2, 21.7; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3512 (br. OH), 2961, 1553, 1427, 1358 ($SO_2$), 1136 ($SO_2$); LRMS (ESI) *m/z* 265 (100%, $[M+Na]^+$), 507 (70%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 265.0509 $[M+Na]^+$, $C_{11}H_{14}O_4SNa$ requires *m/z* 265.0505.

**4-[(4-Methoxyphenyl)sulfonyl]tetrahydrofuran-3-ol (34l)**



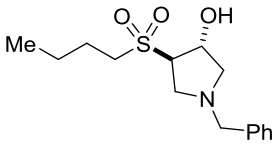

Prepared according to general procedure D using 4-methoxymagnesium bromide (0.5 M in THF, 500 $\mu$L, 0.25 mmol) and 3,4-epoxytetrahydrofuran (90 $\mu$L, 1.25 mmol). Flash column chromatography (100% $Et_2O$) afforded the titled *β*-hydroxy sulfone as a colourless oil (41 mg, 64%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* 9.0, 2H, Ar-*H*), 7.05 (d, *J* 9.0, 2H, Ar-*H*), 4.79 (br. s, 1H, C*H*OH), 4.06 (dd, *J* 10.0, 8.5, 1H, SCHC$H_2$), 3.96 (dd, *J* 10.0, 6.0, 1H, SCHC$H_2$), 3.90 (dd, *J* 9.5, 5.5, 1H, CH(OH)C$H_2$), 3.83 (s, 3H, O*Me*), 3.67-3.61 (m, 2H, SC*H*$CH_2$ and CH(OH)C$H_2$), 2.71 (br. s, 1H, O*H*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.2, 130.6, 129.4, 114.8, 74.9, 72.6, 72.3, 67.3, 55.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3465 (br. OH), 1595, 1499, 1303 ($SO_2$), 1264, 1141 ($SO_2$), 1085; LRMS (ESI) *m/z* 281 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 281.0465 $[M+Na]^+$, $C_{11}H_{14}O_5SNa$ requires *m/z* 281.0454.

**4-(Thiophen-2-ylsulfonyl)tetrahydrofuran-3-ol (34m)**



Prepared according to general procedure D using 2-thienylmagnesium bromide (0.95 M in THF, 265 $\mu$L, 0.25 mmol) and 3,4-epoxytetrahydrofuran (90 µL, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled $\beta$-hydroxy sulfone as a colourless oil (30 mg, 51%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* 5.0, 1.5, 1H, Ar-*H*), 7.67 (dd, *J* 4.0, 1.5, 1H, Ar-*H*), 7.14 (dd, *J* 5.0, 4.0, 1H, Ar-*H*), 4.84 (dt, *J* 5.5, 3.5, 1H, C*H*OH), 4.14 (dd, *J* 10.5, 8.0, 1H, SCHC$H_2$), 4.07 (dd, *J* 10.5, 6.0, 1H, SCHC$H_2$), 3.91 (dd, *J* 10.0, 5.5, 1H, CH(OH)C$H_2$), 3.74 (ddd, *J* 8.0, 6.0, 3.5, 1H, SC*H*$CH_2$), 3.67 (dd, *J* 10.0, 3.5, 1H, CH(OH)C$H_2$), 2.40 (br. s, 1H, O*H*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 138.6, 135.1, 135.0, 128.4, 74.9, 73.3, 72.9, 67.4; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3467 (br. OH), 1402, 1311 ($SO_2$), 1229, 1142 ($SO_2$), 1089, 1017; LRMS (ESI) *m/z* 257 (100%, $[M+Na]^+$), 491 (30%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 256.9910 $[M+Na]^+$, $C_8H_{10}O_4S_2Na$ requires *m/z* 256.9913.

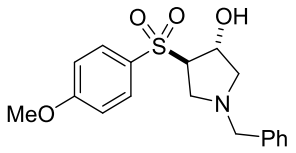
**1-Benzyl-4-(butylsulfonyl)pyrrolidin-3-ol (34n)**



Prepared according to general procedure D using *n*-butylmagnesium chloride (2.0 M in THF, 125 $\mu$L, 0.25 mmol) and 3-benzyl-6-oxa-3-azabicyclo[3.1.0]hexane (201 $\mu$L, 1.25 mmol). Flash column chromatography (petrol/EtOAc 2:3) afforded the titled $\beta$-hydroxy sulfone as a white solid (39 mg, 55%); mp 115-116 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29-7.18 (m, 5H, Ar-*H*), 4.60 (dt, *J* 6.0, 3.5, 1H, C*H*OH), 3.59 (d, *J* 13.0, 1H, NC$H_2$Ph), 3.54 (d, *J* 13.0, 1H, NC$H_2$Ph), 3.42 (ddd, *J* 8.5, 7.0, 3.5, 1H, SC*H*$CH_2$), 3.24 (br. s, 1H, O*H*), 3.05 (dd, *J* 10.0, 8.5, 1H, SCHC$H_2$), 2.92-2.87 (m, 2H, SC$H_2CH_2$), 2.78-2.72 (m, 2H, CH(OH)C$H_2$ and SCHC$H_2$), 2.67 (dd, *J* 10.0, 3.5, 1H, CH(OH)C$H_2$), 1.79-1.70 (m, 2H, $SCH_2CH_2$), 1.39 (app. sext., *J* 7.5, 2H, C$H_2CH_3$), 0.88 (t, *J* 7.5, 3H, $CH_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 137.5, 128.9, 128.5, 127.5, 71.5, 68.8, 61.6, 59.4, 52.1, 51.8, 23.3, 21.8, 13.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3418 (br. OH), 2876, 1577, 1339 ($SO_2$), 1124 ($SO_2$), 1047; LRMS

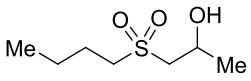
(ESI) *m/z* 298 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 298.1470 $[M+Na]^+$, $C_{15}H_{23}NO_3SNa$ requires *m/z* 298.1471**.**

**1-Benzyl-4-[(4-methoxyphenyl)sulfonyl]pyrrolidin-3-ol (34o)**




Prepared according to general procedure D using 4-methoxyphenylmagnesium chloride (0.5 M in THF, 500 $\mu$L, 0.25 mmol) and 3-benzyl-6-oxa-3-azabicyclo[3.1.0]hexane (200 $\mu$L, 1.25 mmol). Flash column chromatography (EtOAc/$Et_2O$ 1:4) afforded the titled $\beta$-hydroxy sulfone as a white solid (49 mg, 57%); mp 82-83 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* 9.0, 2H, Ar-*H*), 7.25-7.15 (m, 5H, Ar-*H*), 6.93 (d, *J* 9.0, 2H, Ar-*H*), 4.59 (dd, *J* 8.0, 4.5, 1H, C*H*OH), 3.80 (s, 3H, O*Me*), 3.58 (d, *J* 13.0, 1H, NC$H_2$Ph), 3.57-3.53 (m, 1H, SC*H*$CH_2$), 3.52 (d, *J* 13.0, 1H, NC$H_2$Ph), 3.12 (br. s, 1H, O*H*), 2.97 (dd, *J* 10.5, 8.5, 1H, SCHC$H_2$), 2.72-2.68 (m, 3H, CH(OH)C$H_2$ and 1 × SCHC$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.0, 137.3, 130.7, 129.6, 128.7, 128.5, 127.5, 114.7, 71.7, 71.6, 61.4, 59.3, 55.7, 52.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3478 (br. OH), 2993, 1671, 1489, 1318 ($SO_2$), 1278, 1156 ($SO_2$); LRMS (ESI) *m/z* 348 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 348.1266 $[M+Na]^+$, $C_{18}H_{21}NO_4SNa$ requires *m/z* 348.1264.

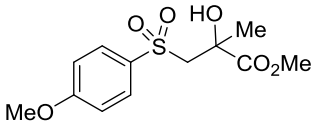
**1-(Butylsulfonyl)propan-2-ol (34p)**




Prepared according to general procedure D using *n*-butylmagnesium chloride (2.0 M in THF, 125 $\mu$L, 0.25 mmol) and propylene oxide (87 $\mu$L, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled $\beta$-hydroxy sulfone as a colourless oil (37 mg, 83%); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.45-4.36 (m, 1H, C*H*OH), 3.10-2.98 (m, 3H, SC$H_2CH_2$ and 1 × SC$H_2$CH(OH)), 2.94 (dd, *J* 14.5, 2.0, 1H, SC$H_2$CH(OH)), 1.80-1.72 (m, 2H, $SCH_2CH_2$), 1.41 (app. sext., *J* 7.5, 2H, C$H_2CH_3$), 1.26 (d, *J* 6.5, 3H, CH(OH)C$H_3$), 0.90 (t, *J* 7.5, 3H, $CH_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 62.6, 59.9, 54.2, 23.8, 23.1, 21.7, 13.5; LRMS

(ESI) *m/z* 203 (50%, $[M+Na]^+$), 383 (100%, $[2M+Na]^+$);HRMS (ESI) found *m/z* 203.0704 $[M+Na]^+$, $C_7H_{16}O_3SNa$ requires *m/z* 203.0712. Data in accordance with that previously reported.[186]

**Methyl 2-hydroxy-3-[(4-methoxyphenyl)sulfonyl]-2-methylpropanoate (34q)**

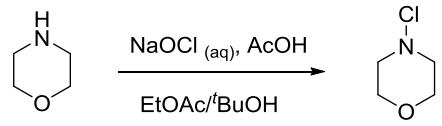



Prepared according to general procedure D using 4-methoxyphenylmagnesium chloride (0.5 M in THF, 500 $\mu$L, 0.25 mmol) and methyl 2-methylglycidate (132 $\mu$L, 1.25 mmol). Flash column chromatography (100% $Et_2O$) afforded the titled $\beta$-hydroxy sulfone as a white solid (39 mg, 54%); mp 103-104 °C ($CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* 9.0, 2H, Ar-*H*), 6.93 (d, *J* 9.0, 2H, Ar-*H*), 3.81 (s, 3H, ArO*Me*), 3.72 (s, 3H, $CO_2$*Me*), 3.67 (d, *J* 14.5, 1H, SC$H_2$), 3.44 (d, *J* 14.5, 1H, SC$H_2$), 1.39 (s, 3H, C(OH)*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.5, 163.8, 132.0, 130.4, 114.3, 72.4, 64.0, 55.7, 53.4, 27.2; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3239 (br. OH), 2894, 1732, 1389, 1352 ($SO_2$), 1117 ($SO_2$), 1011; LRMS (ESI) *m/z* 311 (40%, $[M+Na]^+$), 599 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 311.0566 $[M+Na]^+$, $C_{12}H_{16}O_6SNa$ requires *m/z* 311.0560.

# 6.4 Chapter 3 Data

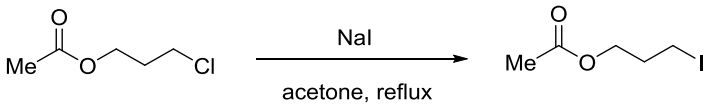
## 6.4.1 Starting materials

### *N*-Chloromorpholine




To a solution of morpholine (1.75 mL, 20 mmol) and $^{t}$BuOH (960 $\mu$L, 10 mmol) in EtOAc (60 mL) was added NaOCl (10.1% aqueous solution, 18.5 mL, 30 mmol) and acetic acid (1.75 mL, 30 mmol) simultaneously at 0 ºC dropwise. The reaction was allowed to stir open to air for 30 min, before diluting with EtOAc (50 mL) and washing with sat. $NaHCO_3$ (60 mL) and brine (60 mL). The organic phase was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to afford the titled *N*-chloroamine as a light yellow oil (1.76 g, 69%); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 3.77 (br. s, 4H, $NCH_2CH_2$), 3.20 (br. s, 4H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 67.6, 62.8. Data in accordance with that previously reported.[130d]

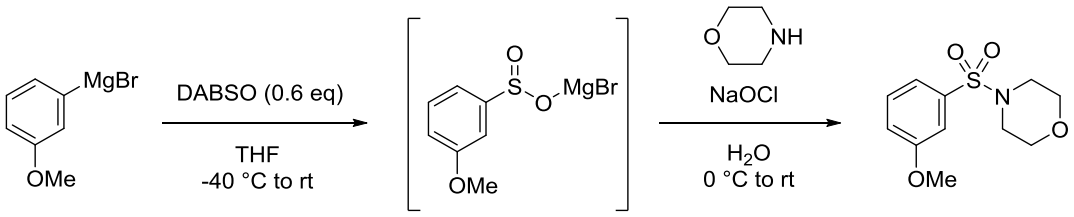
### 3-Acetoxypropyl iodide




To a solution of 3-acetoxypropyl chloride (2.46 mL, 20 mmol) in acetone (50 mL) was added NaI (7.2 g, 48 mmol) and the resulting mixture was heated at reflux for 24 hr. After cooling to room temp. the mixture was diluted with $Et_2O$ (50 mL) and subsequently washed with water (50 mL × 3). The organic phase was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. The resulting oil was purified by Kugelrohr distillation to afford the titled alkyl iodide as a light yellow oil (3.32 g, 72% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 4.14 (t, *J* 6.0,

2H, OC*H*$_2$), 3.23 (t, *J* 7.0, 2H, $CH_2CH_2I$), 2.19-2.12 (m, 2H, $CH_2CH_2I$), 2.06 (s, 3H, $CO_2Me$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 169.5, 62.7, 31.0, 19.5, 0.2; HRMS (EI) found *m/z* 228.0259 ($[M]^+$, 100%), $C_5H_9IO_2$ requires *m/z* 228.0263. Data in accordance with that previously reported.[187]

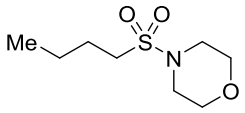
## 6.4.2 General procedure E for the synthesis of sulfonamides from organometallic reagent, DABSO, NaOCl and amines, as exemplified by the preparation of 4-[(3-methoxyphenyl)sulfonyl]morpholine (40)




To a reaction tube was added DABSO (36 mg, 0.15 mmol) and THF (1 mL) and the resulting suspension flushed with nitrogen gas for 2 min. After cooling to -40 °C, 3-methoxyphenylmagnesium bromide (0.97 M in THF, 258 μL, 0.25 mmol) was added dropwise and the mixture stirred at this temp. for 30 min. On warming to room temp. a strong flow of nitrogen gas was applied to remove the solvent before addition of water (1.5 mL) and morpholine (109 μL, 1.25 mmol). The resulting mixture was cooled to 0-5 °C (ice-water bath) and NaOCl (15.8% aqueous solution, 295 μL, 0.75 mmol) was added dropwise before allowing the reaction to warm to room temp. (Note: addition of NaOCl to mixtures containing anilines results in coloured oxidation products which can be flushed off with 100% $CH_2Cl_2$ on chromatography). After stirring for 16 hr, sat. $NaS_2O_{3(aq)}$ (10 mL) was added and the mixture stirred for a further 20 min. The aqueous mixture was then extracted with $CH_2Cl_2$ (3 × 15 mL) and the combined organic extracts subsequently washed with 1M $HCl_{(aq)}$ (1 × 30 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfonamide as a white solid (50 mg, 79%); mp 128-129 °C ($CH_2Cl_2$) [lit.[188] mp 132 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40 (app. t, *J* 8.0, 1H, Ar-*H*), 7.26 (d, *J* 8.0, 1H, Ar-*H*) 7.18 (app. t, *J* 2.0, 1H, Ar-*H*), 7.08 (ddd, *J* 8.0, 1.5, 1.0, 1H, Ar-*H*), 3.80 (s, 3H, O*Me*), 3.68 (t, *J* 4.5, 4H, $NCH_2CH_2$), 2.95 (t, *J* 4.5, 4H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.0,

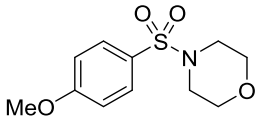
136.2, 130.2, 120.0, 119.1, 112.8, 66.1, 55.7, 46.0; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2986, 1582, 1426, 1336 ($SO_2$), 1240, 1151 ($SO_2$); LRMS (ESI) *m/z* 258 (50%, $[M+H]^+$), 280 (50%, $[M+Na]^+$), 537 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 280.0617 $[M+Na]^+$, $C_{11}H_{15}NO_4SNa$ requires *m/z* 280.0614. Data in accordance with that previously reported.[188]

**4-(Butylsulfonyl)morpholine (41a)**




Prepared according to general procedure E using *n*-butylmagnesium chloride (2.1 M, 120 $\mu$L, 0.25 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfonamide as a white solid (42 mg, 82%); mp 42-43 °C ($CH_2Cl_2$) [lit.[79] mp 40-45 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 3.69 (t, *J* 4.5, 4H, $NCH_2CH_2$), 3.20 (t, *J* 4.5, 4H, $NCH_2CH_2$), 2.84 (t, *J* 8.0, 2H, $SCH_2$), 1.78-1.70 (m, 2H, $SCH_2CH_2$), 1.40 (app. sext., *J* 7.5, 2H, $CH_2CH_3$), 0.89 (t, *J* 7.5, 3H, $CH_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 66.6, 48.6, 45.8, 24.9, 21.8, 13.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2965, 2863, 1454, 1322 ($SO_2$), 1259, 1110 ($SO_2$); LRMS (ESI) *m/z* 208 (70%, $[M+H]^+$), 230 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 230.0830 $[M+Na]^+$, $C_8H_{17}NO_3SNa$ requires *m/z* 230.0821. Data in accordance with that previously reported.[79]

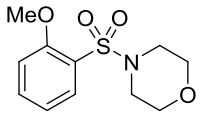
**4-[(4-Methoxyphenyl)sulfonyl]morpholine** (**41b**)




Prepared according to general procedure E using 4-methoxyphenylmagnesium bromide (0.51 M in THF, 490 $\mu$L, 0.25 mmol). Flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfonamide as an off-white solid (55 mg, 86%); mp 109-110 °C ($CH_2Cl_2$) [lit.[124] mp 110-111 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* 9.0, 2H, Ar-*H*), 6.95 (d, *J* 9.0, 2H, Ar-*H*), 3.82 (s, 3H, O*Me*), 3.68 (t, *J* 4.5, 4H, $NCH_2CH_2$), 2.91 (t, *J* 4.5, 4H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.3, 130.0, 126.7, 114.3, 66.1, 55.7, 46.0; LRMS (ESI) *m/z* 258 (90%, $[M+H]^+$), 280 (100%, $[M+Na]^+$); HRMS (ESI) found

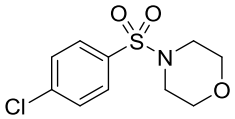
*m/z* 280.0606 $[M+Na]^+$, $C_{11}H_{15}NO_4SNa$ requires *m/z* 280.0614. Data in accordance with that previously reported.[124]

**4-[(2-Methoxyphenyl)sulfonyl]morpholine (41c)**



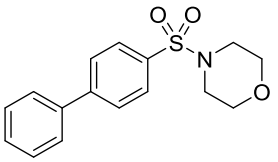

Prepared according to general procedure E using 2-methoxyphenylmagnesium bromide (1.0 M in THF, 250 $\mu$L, 0.25 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfonamide as an off-white solid (54 mg, 84%); mp 85-86 °C ($CH_2Cl_2$) [lit.[124] mp 86-87 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* 4.0, 1.5, 1H, Ar-*H*), 7.55-7.51 (m, 1H, Ar-*H*), 7.06-7.02 (m, 2H, Ar-*H*), 3.93 (s, 3H, O*Me*), 3.72 (t, *J* 4.5, 4H, $NCH_2CH_2$), 3.24 (t, *J* 4.5, 4H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.0, 134.8, 131.9, 125.8, 120.5, 112.4, 66.8, 56.0, 46.1; LRMS (ESI) *m/z* 258 (20%, $[M+H]^+$), 280 (20%, $[M+Na]^+$), 537 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 280.0621 $[M+Na]^+$, $C_{11}H_{15}NO_4SNa$ requires *m/z* 280.0614. Data in accordance with that previously reported.[124]

**4-[(4-Chlorophenyl)sulfonyl]morpholine (41d)**



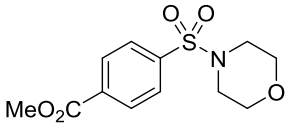

Prepared according to general procedure E using 4-chlorophenylmagnesium bromide (1.0 M in THF, 250 $\mu$L, 0.25 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfonamide as an off-white solid (43 mg, 68%); mp 143-144 °C ($CH_2Cl_2$) [lit.[189] mp 146-147 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* 8.5, 2H, Ar-*H*), 7.47 (d, *J* 8.5, 2H, Ar-*H*), 3.68 (t, *J* 4.5, 4H, $NCH_2CH_2$), 2.93 (t, *J* 4.5, 4H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 139.8, 133.7, 129.5, 129.2, 66.1, 45.9; LRMS (ESI) *m/z* 262 (20%, $[M(^{35}Cl)+H]^+$), 284 (100%, $[M(^{35}Cl)+Na]^+$); HRMS (ESI) found *m/z* 262.0296 $[M(^{35}Cl)+H]^+$, $C_{10}H_{13}ClNO_3S$ requires *m/z* 262.0299. Data in accordance with that previously reported.[189]

**4-[(1,1'-Biphenyl)-4-ylsulfonyl]morpholine (41e)**



Prepared according to general procedure E using (1,1'-biphenyl)-4-ylmagnesium bromide (0.25 mmol). The aryl Grignard reagent was generated *in situ* by dropwise addition of cyclopentylmagnesium chloride (2.0 M, 150 $\mu$L, 0.30 mmol) to a solution of 4-iodobiphenyl (70 mg, 0.25 mmol) in THF (1 mL) at -40 °C. The solution was allowed to warm to room temp. and was stirred for 1 hr before use. Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfonamide as an off-white solid (54 mg, 71%); mp 206-207 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* 8.5, 2H, Ar-*H*), 7.68 (d, *J* 8.5, 2H, Ar-*H*), 7.56-7.53 (m, 2H, Ar-*H*), 7.46-7.40 (m, 2H, Ar-*H*), 7.39-7.34 (m, 1H, Ar-*H*), 3.70 (t, *J* 4.5, 4H, $NCH_2CH_2$), 2.98 (t, *J* 4.5, 4H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 146.1, 139.2, 133.6, 129.1, 128.6, 128.4, 127.8, 127.4, 66.1, 46.0; IR $\nu_{max}$ (neat)/cm$^{-1}$ 1451, 1346, 1330 ($SO_2$), 1261, 1108 ($SO_2$); LRMS (ESI) *m/z* 304 (60%, $[M+H]^+$), 326 (100%, $[M+Na]^+$), 629 (60%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 326.0822 $[M+Na]^+$, $C_{16}H_{17}NO_3SNa$ requires *m/z* 326.0821.

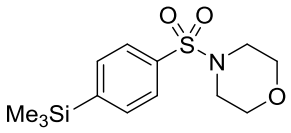
**Methyl 4-(morpholinosulfonyl)benzoate (41f)**



Prepared according to general procedure E using 4-[(methoxycarbonyl)phenyl]magnesium chloride (0.25 mmol). The aryl Grignard solution was prepared *in situ* by dropwise addition of *iso*propylmagnesium chloride (1.85M in THF, 151 $\mu$L, 0.28 mmol) to a solution of methyl-4-iodobenzoate (66 mg, 0.25 mmol) in THF (0.8 mL) at -40 °C. The solution was stirred at this temp. for 1 hr before being transferred *via* syringe to a DABSO-THF suspension. Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfonamide as an off-white solid (36 mg, 51%); mp 143 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* 8.5, 2H, Ar-*H*), 7.84 (d, *J* 8.5, 2H, Ar-*H*), 3.98 (s, 3H, $CO_2Me$), 3.76 (t, *J* 4.5, 4H,

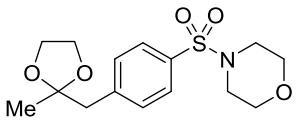
$NCH_2CH_2$), 3.03 (t, *J* 4.5, 4H, $NCH_2CH_2$); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 160.0, 130.2, 120.0, 119.1, 112.8, 66.1, 55.7, 46.0; IR $\nu_{max}$ (neat)/$cm^{-1}$ 2849, 1726 (CO), 1450, 1349 ($SO_2$), 1260, 1110 ($SO_2$); LRMS (ESI) *m/z* 286 (30%, $[M+H]^+$), 308 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 308.0559 $[M+Na]^+$, $C_{12}H_{15}NO_5SNa$ requires *m/z* 308.0563.

**4-[4-(Trimethylsilyl)phenylsulfonyl]morpholine (42b)**




Prepared according to general procedure E using 4-[(trimethylsilyl)phenyl]lithium (0.25 mmol). The aryl lithium solution was generated *in situ* by dropwise addition of *n*-butyllithium (1.78 M in hexane, 157 μL, 0.28 mmol) to a solution of 4-trimethylsilylbromobenzene (57 mg, 0.25 mmol) in THF (0.8 mL) at -78 °C. The solution was stirred at this temp. for 1 hr before being transferred *via* syringe to a DABSO-THF suspension. Flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfonamide as an off-white solid (54 mg, 72%); mp 144 °C ($CH_2Cl_2$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.65-7.60 (m, 4H, Ar-*H*), 3.68 (t, *J* 4.5, 4H, $NCH_2CH_2$), 2.94 (t, *J* 4.5, 4H, $NCH_2CH_2$) 0.23 (s, 9H, $SiMe_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 148.9, 136.5, 135.3, 128.1, 67.5, 47.3, 0.0; IR $\nu_{max}$ (neat)/$cm^{-1}$ 1449, 1348 ($SO_2$), 1259, 1111 ($SO_2$), 1085; LRMS (ESI) *m/z* 300 (100%, $[M+H]^+$), 322 (60%, $[M+Na]^+$), 621 (40%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 322.0906 $[M+Na]^+$, $C_{13}H_{21}NO_3SSiNa$ requires *m/z* 322.0904.

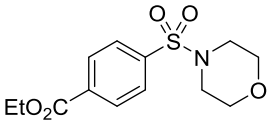
**4-{[4-((2-Methyl-1,3-dioxolan-2-yl)methyl)phenyl]sulfonyl}morpholine (42c)**




Prepared according to general procedure E using 4-{[(2-methyl-1,3-dioxolan-2-yl)methyl]phenyl}lithium (0.25 mmol). The aryl lithium solution was generated *in situ* by dropwise addition of *n*-butyllithium (1.8 M in hexane, 153 μL, 0.28 mmol) to a solution of 2-(4-bromobenzyl)-2-methyl-1,3-dioxolane (64 mg, 0.25 mmol) in THF (0.8 mL) at -78 °C. The solution was stirred at this temp. for 1 hr before being transferred *via* syringe to a

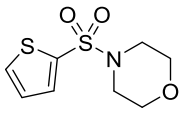
DABSO-THF suspension. Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfonamide as an off-white solid (59 mg, 62%); mp 115-116 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* 8.5, 2H, Ar-*H*), 7.40 (d, *J* 8.5, 2H, Ar-*H*), 3.85-3.82 (m, 2H, COC$H_2$), 3.68 (t, *J* 4.5, 4H, NCH$_2$C$H_2$), 3.62-3.59 (m, 2H, COC$H_2$), 2.94 (s, 2H, CC$H_2$), 2.92 (t, *J* 4.5, 4H, NC$H_2$CH$_2$), 1.26 (s, 3H, C*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 142.8, 133.0, 131.3, 127.5, 109.2, 66.1, 64.9, 46.0, 45.2, 24.7; IR $\nu_{max}$ (neat)/cm$^{-1}$ 1408, 1329 ($SO_2$), 1224, 1111 ($SO_2$), 1038; LRMS (ESI) *m/z* 328 (100%, $[M+H]^+$), 350 (20%, $[M+Na]^+$); HRMS (ESI) found *m/z* 350.1032 $[M+Na]^+$, $C_{15}H_{21}NO_5SNa$ requires *m/z* 350.1033.

**Ethyl 4-(morpholinosulfonyl)benzoate (43b)**



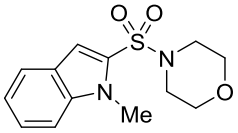

Prepared according to the general procedure E using 4-[(ethoxycarbonyl)phenyl)]zinc iodide (0.69M in THF, 360 μL, 0.25 mmol).[190] The aryl zinc reagent was prepared as a stock solution *via* zinc-halogen exchange: zinc dust (458 mg, 7.0 mmol) in THF (2 mL), and in the presence of anhydrous LiCl (212 mg, 5.0 mmol), was activated with 1,2-dibromoethane (22 μL, 0.25 mmol) and chlorotrimethylsilane (10 μL, 0.09 mmol). 4-(Ethoxycarbonyl)phenyl iodide in THF (2 mL) was added and the mixture stirred for 16 hr before use. Flash column chromatography ($CH_2Cl_2$/$Et_2O$ 0-5%) afforded the titled sulfonamide as an off-white solid (46 mg, 62%); mp 82-83 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* 8.5, 2H, Ar-*H*), 7.75 (d, *J* 8.5, 2H, Ar-*H*), 4.38 (q, *J* 7.0, 2H, OC$H_2$CH$_3$), 3.68 (t, *J* 4.5, 4H, NCH$_2$C$H_2$), 2.95 (t, *J* 4.5, 4H, NC$H_2$CH$_2$), 1.36 (t, *J* 7.0, 3H, OCH$_2$C$H_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.1, 139.1, 134.6, 130.3, 127.8, 66.1, 61.8, 46.0, 14.3; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2855, 1713 (CO), 1451, 1296 ($SO_2$), 1273, 1108 ($SO_2$); LRMS (ESI) *m/z* 300 (20%, $[M+H]^+$), 322 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 300.0897 $[M+H]^+$, $C_{13}H_{18}NO_5S$ requires *m/z* 300.0900.

**4-(Thiophen-2-ylsulfonyl)morpholine (41g)**



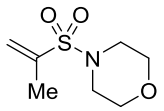
Prepared according to general procedure E using 2-thienylmagnesium bromide (0.85 M in THF, 294 $\mu$L, 0.25 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfonamide as an off-white solid (52 mg, 89%); mp 102-103 °C ($CH_2Cl_2$) [lit.[191] mp 104-105 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* 5.0, 1.5, 1H, Ar-*H*), 7.48 (dd, *J* 3.5, 1.5, 1H, Ar-*H*), 7.11 (dd, *J* 5.0, 3.5, 1H, Ar-*H*), 3.71 (t, *J* 4.5, 4H, $NCH_2CH_2$), 2.99 (t, *J* 4.5, 4H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 135.4, 132.8, 132.5, 127.8, 66.0, 46.0; IR $\nu_{max}$ (neat)/cm$^{-1}$ 1450, 1401, 1299 ($SO_2$), 1220, 1112 ($SO_2$); LRMS (ESI) *m/z* 234 (10%, $[M+H]^+$), 256 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 256.0078 $[M+Na]^+$, $C_8H_{11}NO_3S_2Na$ requires *m/z* 256.0073. Data in accordance with that previously reported.[191]

**4-[(1-Methyl-1H-indol-2-yl)sulfonyl]morpholine (42e)**



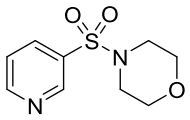
Prepared according to general procedure E using 2-lithio-*N*-methylindole (0.31 M in THF, 806 $\mu$L, 0.25 mmol – see above for preparation, Section 6.2). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfonamide as an off-white solid (46 mg, 65%); mp 123-124 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* 8.0, 1H, Ar-*H*), 7.37-7.30 (m, 2H, Ar-*H*), 7.14 (ddd, *J* 8.0, 6.0, 2.0, 1H, Ar-*H*), 7.09 (s, 1H, Ar-*H*), 3.91 (s, 3H, N*Me*) 3.67 (t, *J* 4.5, 4H, $NCH_2CH_2$), 3.11 (t, *J* 4.5, 4H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 139.4, 130.2, 125.6, 125.1, 122.6, 121.3, 111.0, 110.4, 66.3, 45.6, 31.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2855, 1502, 1451, 1349 ($SO_2$), 1260, 1112 ($SO_2$); LRMS (ESI) *m/z* 281 (40%, $[M+H]^+$), 303 (100%, $[M+Na]^+$), 583 (80%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 303.0774 $[M+Na]^+$, $C_{13}H_{16}N_2O_3SNa$ requires *m/z* 303.0774.

**4-(Prop-1-en-2-ylsulfonyl)morpholine (41h)**



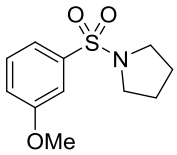
Prepared according to general procedure E using *iso*propenylmagnesium bromide (0.52 M, 480 $\mu$L, 0.25 mmol). The acid wash afforded the pure titled sulfonamide as a colourless oil (24 mg, 50%) without further purification; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 5.91 (m, 1H, C*H*CMe), 5.64 (app. q, *J* 1.5, 1H, C*H*CMe), 3.68 (t, *J* 4.5, 4H, $NCH_2CH_2$), 3.15 (t, *J* 4.5, 4H, $NCH_2CH_2$), 2.00 (dd, *J* 1.5, 1.0, $CH_2CMe$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 142.69, 124.7, 66.6, 45.7, 17.7; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2859, 1449, 1338 ($SO_2$), 1261, 1219, 1113 ($SO_2$); LRMS (ESI) *m/z* 214 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 192.0688 $[M+H]^+$, $C_7H_{14}NO_3S$ requires *m/z* 192.0689.

**4-(Pyridin-3-ylsulfonyl)morpholine (41i)**



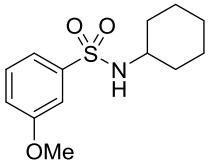
Prepared according to general procedure E using 3-pyridylmagnesium chloride (0.25 mmol). The aryl Grignard solution was prepared *in situ* by dropwise addition of *iso*propylmagnesium chloride (1.85M in THF, 151 $\mu$L, 0.28 mmol) to a solution of 3-bromopyridine (25 $\mu$L, 0.25 mmol) in THF (0.8 mL) at -40 °C. The solution was allowed to warm to room temp. and stirred for 1 h before being transferred *via* syringe to a DABSO-THF suspension. Flash column chromatography (100% EtOAc) afforded the titled sulfonamide as an off-white solid (15 mg, 26%); mp 121-122 °C ($CH_2Cl_2$) [lit.[192] mp 120 °C]; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, *J* 2.5, 1H), 8.80 (dd, *J* 5.0, 1.5, 1H), 7.98 (ddd, *J* 8.0, 2.5, 1.5 Hz, 1H), 7.45 (ddd, *J* 8.0, 5.0, 1.0, 1H), 3.70 (t, *J* 4.5, 4H, $NCH_2CH_2$), 2.99 (t, *J* 4.5, 4H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 152.7, 147.6, 134.4, 131.1, 122.8, 65.0, 44.8; LRMS (ESI) *m/z* 229 (100%, $[M+H]^+$); HRMS (ESI) found *m/z* 229.0643 $[M+H]^+$, $C_9H_{13}N_2O_3S$ requires *m/z* 299.0641. Data in accordance with that previously reported.[192]

**_N_-[(3-Methoxyphenyl)sulfonyl]pyrrolidine (44a)**



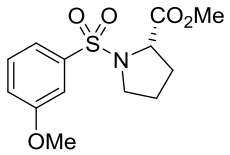
Prepared according to general procedure E using 3-methoxyphenylmagnesium bromide (0.97 M in THF, 258 $\mu$L, 0.25 mmol) and pyrrolidine (105 $\mu$L, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfonamide as an off-white solid (47 mg, 79%); mp 117-118 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39-7.32 (m, 2H, Ar-*H*), 7.28-7.26 (m, 1H, Ar-*H*), 7.04 (app. dt, *J* 7.5, 2.0, 1H, Ar-*H*), 3.80 (s, 3H, O*Me*), 3.21-3.17 (m, 4H, NC$H_2$), 1.72-1.68 (m, 4H, NCH$_2$C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.9, 138.1, 130.1, 119.6, 118.8, 112.4, 55.7, 48.0, 25.3; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2977, 1591, 1477, 1333 ($SO_2$), 1287, 1152 ($SO_2$); LRMS (ESI) *m/z* 242 (20%, $[M+H]^+$), 264 (10%, $[M+Na]^+$), 505 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 264.0667 $[M+Na]^+$, $C_{11}H_{15}NO_3SNa$ requires *m/z* 264.0665.

**_N_-Cyclohexyl-3-methoxybenzenesulfonamide (44b)**



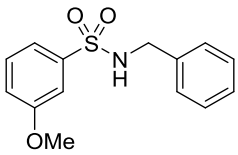
Prepared according to general procedure E using 3-methoxyphenylmagnesium bromide (0.97 M in THF, 260 $\mu$L, 0.25 mmol) and cyclohexylamine (143 $\mu$L, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfonamide as an off-white solid (51 mg, 76%); mp 40 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40 (app. dt, 1H, *J* 7.5, 1.5. Ar-*H*), 7.35-7.31 (m, 2H, Ar-*H*), 7.05 (ddd, *J* 8.5, 2.5, 1.5, 1H, Ar-*H*), 4.62 (d, *J* 7.5, 1H, N*H*), 3.79 (s, 3H, O*Me*), 3.12-3.04 (m, 1H, NHC*H*), 1.72-1.65 (m, 2H, C$H_2$), 1.59-1.53 (m, 2H, C$H_2$), 1.48-1.40 (m, 1H, C$H_2$), 1.22-0.99 (m, 5H, C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.9, 142.6, 130.1, 119.1, 118.8, 111.6, 55.7, 52.7, 33.9, 25.1, 24.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3288 (NH), 2930, 1597, 1476, 1326 ($SO_2$), 1156 ($SO_2$); LRMS (ESI) *m/z* 270 (20%, $[M+H]^+$), 292 (10%, $[M+Na]^+$), 561 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 292.0975 $[M+Na]^+$, $C_{13}H_{19}NO_3NaS$ requires *m/z* 292.0978.

**(*S*)-Methyl-*N*-[(3-methoxyphenyl)sulfonyl]-pyrrolidine-2-carboxylate (44c)**




Prepared according to general procedure E using 3-methoxyphenylmagnesium bromide (0.97 M in THF, 258 $\mu$L, 0.25 mmol) and (*L*)-proline methyl ester hydrochloride (207 mg, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 1:3) afforded the titled sulfonamide as a light yellow oil (51 mg, 68%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.40-7.36 (m, 2H, Ar-*H*), 7.34-7.32 (m, 1H, Ar-*H*), 7.05 (app. dt, *J* 7.5, 2.0, 1H, Ar-*H*), 4.26 (dd, *J* 8.0, 4.0, 1H, NC*H*$CO_2$Me), 3.80 (s, 3H, O*Me*), 3.65 (s, 3H, $CO_2$*Me*), 3.46-3.41 (m, 1H, NC$H_2$), 3.30-3.24 (m, 1H, NC$H_2$), 2.00-1.87 (overlapping m, 3H, NCHC$H_2$ × 2 and $NCH_2CH_2$), 1.75-1.67 (m, 1H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.5, 159.9, 139.3, 130.1, 119.6, 119.1, 112.2, 60.4, 55.7, 52.4, 48.6, 30.9, 24.7; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2954, 1750 (CO), 1596, 1480, 1343 ($SO_2$), 1153 ($SO_2$); LRMS (ESI) *m/z* 300 (50%, $[M+H]^+$), 621 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 322.0718 $[M+Na]^+$, $C_{13}H_{17}NO_5SNa$ requires *m/z* 322.0720; ee > 99% (Major = 18.31 mins : Minor = 16.43 mins, *n*-hexane/IPA 90:10, 1 ml/min); $[\alpha]_D$ = -97.13 (0.01 g/mL, $CHCl_3$).

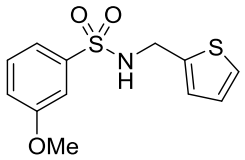
***N*-Benzyl-3-methoxybenzenesulfonamide (44d)**




Prepared according to general procedure E using 3-methoxyphenylmagnesium bromide (0.97 M in THF, 258 $\mu$L, 0.25 mmol) and benzylamine (137 $\mu$L, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfonamide as an off-white solid (57 mg, 78%); mp 77-78 °C ($CH_2Cl_2$) [lit.[193] mp 80 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.39 (app. dt, 1H, *J* 7.5, 1.5, Ar-*H*), 7.34 (t, *J* 8.0, 1H, Ar-*H*), 7.29 (t, *J* 2.0, 1H, Ar-*H*), 7.23-7.17 (m, 3H, Ar-*H*), 7.14-7.11 (m, 2H, Ar-*H*), 7.03 (ddd, *J* 8.0, 2.5, 1.5, 1H, Ar-*H*), 4.71 (t, *J* 6.0, 1H, N*H*), 4.08 (d, *J* 6.0, 1H, C$H_2$NH), 3.76 (s, 3H, O*Me*);$^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.0, 141.0, 136.2, 130.2, 128.7, 128.0, 127.9, 119.3, 119.2, 111.8, 55.7, 47.4; LRMS

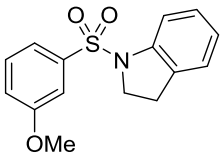
(ESI) *m/z* 278 (40%, $[M+H]^+$), 300 (100%, $[M+Na]^+$), 577 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 300.0665 $[M+Na]^+$, $C_{14}H_{15}NO_3SNa$ requires *m/z* 300.0665. Data in accordance with that previously reported.[193]

**3-Methoxy-*N*-(thiophen-2-ylmethyl)benzenesulfonamide (44e)**



Prepared according to general procedure E using 3-methoxyphenylmagnesium bromide (0.97 M in THF, 258 $\mu$L, 0.25 mmol) and 2-thiophenemethylamine (120 $\mu$L, 1.25 mmol). Flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfonamide as a white solid (59 mg, 83%); mp 70-71 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.49 (app. dt, *J* 8.0, 1.5, 1H, Ar-*H*), 7.45 (app. t, *J* 8.0, 1H, Ar-*H*), 7.39 (app. t, *J* 2.5, 1H, Ar-*H*), 7.23 (dd, *J* 5.0, 1.5, 1H, Ar-*H*), 7.14 (ddd, *J* 8.0, 2.5, 1.5, 1H, Ar-*H*), 6.92-6.88 (overlapping m, 2H, Ar-*H*), 4.80 (t, *J* 6.0, 1H, N*H*), 4.40 (d, *J* 6.0, 2H, C$H_2$NH), 3.88 (s, 3H, O*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.0, 140.9, 138.8, 130.2, 126.9, 126.6, 125.9, 119.4, 119.3, 111.7, 55.7, 42.2; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3288 (NH), 1597, 1485, 1417, 1314 ($SO_2$), 1150 ($SO_2$); LRMS (ESI) *m/z* 306 (100%, $[M+Na]^+$), 589 (90%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 306.0227 $[M+Na]^+$, $C_{12}H_{13}NO_3S_2Na$ requires *m/z* 306.0229.

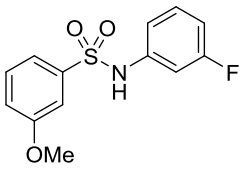
***N*-[(3-Methoxyphenyl)sulfonyl]indoline (44f)**



Prepared according to general procedure E using 3-methoxyphenylmagnesium bromide (0.97 M in THF, 258 $\mu$L, 0.25 mmol) and indoline (149 mg, 1.25 mmol). Flash column chromatography ($Et_2O$ /$CH_2Cl_2$ 0-5%) afforded the titled sulfonamide as an off-white solid (46 mg, 64%); mp 97 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* 8.0, 1H, Ar-*H*), 7.31 (app. dt, *J* 7.5, 1.5, 1H, Ar-*H*), 7.27 (app. t, *J* 8.0, 1H, Ar-*H*), 7.16 (app. t, *J* 2.0, 1H, Ar-

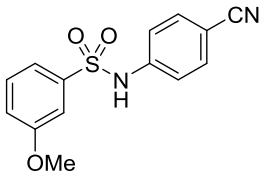
*H*), 7.13 (app. t, *J* 8.0, 1H, Ar-*H*), 7.03-6.98 (overlapping m, 2H, Ar-*H*), 6.92 (app. td, *J* 7.5, 1.0, 1H, Ar-*H*), 3.86 (t, *J* 8.5, 2H, NC$H_2$), 3.66 (s, 3H, O*Me*), 2.81 (t, *J* 8.5, 2H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 159.8, 142.0, 138.0, 132.0, 130.0, 127.7, 125.2, 124.0, 119.7, 119.4, 115.2, 111.8, 55.5, 50.0, 27.9; IR $\nu_{max}$ (neat)/cm$^{-1}$ 1578, 1480, 1435, 1349 ($SO_2$), 1292, 1150 ($SO_2$); LRMS (ESI) *m/z* 290 (40%, $[M+H]^+$), 312 (80%, $[M+Na]^+$), 601 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 312.0667 $[M+Na]^+$, $C_{15}H_{15}NO_3SNa$ requires *m/z* 312.0665.

**_N_-(3-Fluorophenyl)-3-methoxybenzenesulfonamide (44g)**



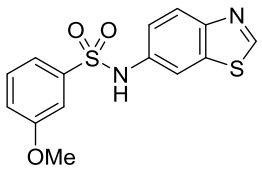

Prepared according to general procedure E using 3-methoxyphenylmagnesium bromide (0.97 M in THF, 258 μL, 0.25 mmol), acetic acid (70 μL, 1.25 mmol) and 3-fluoroaniline (120 μL, 1.25 mmol). Flash column chromatography ($Et_2O/CH_2Cl_2$ 0-5%) afforded the titled sulfonamide as an off-white solid (51 mg, 73%); mp 87 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.41-7.34 (m, 2H, Ar-*H*), 7.29 (br. s, 1H, N*H*), 7.20 (app. td, *J* 8.5, 6.5, 1H, Ar-*H*), 7.08 (app. dt, *J* 7.5, 2.0, 1H, Ar-*H*), 6.91 (app. dt, *J* 10.0, 2.0, 1H, Ar-*H*), 6.83-6.80 (m, 3H, Ar-*H*), 3.78 (s, 3H, O*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.1 (d, $J_{CF}$ 247.0), 159.9, 139.8, 138.0 (d, $J_{CF}$ 10.0), 130.6 (d, $J_{CF}$ 9.5), 130.2, 119.9, 119.3, 116.6 (d, $J_{CF}$ 3.0), 112.2 (d, $J_{CF}$ 21.0), 111.7, 108.5 (d, $J_{CF}$ 25.0), 55.6; $^{19}$F NMR (377 MHz, $CDCl_3$) δ -110.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3287 (NH), 1599, 1488, 1324 ($SO_2$), 1162 ($SO_2$); LRMS (ESI) *m/z* 282 (10%, $[M+H]^+$), 304 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 304.0416 $[M+Na]^+$, $C_{13}H_{12}FNO_3SNa$ requires *m/z* 304.0414.

**_N_-(4-Cyanophenyl)-3-methoxybenzenesulfonamide (44h)**



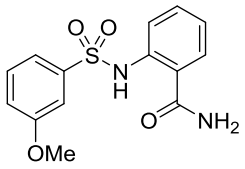

Prepared according to general procedure E using 3-methoxyphenylmagnesium bromide (0.97 M in THF, 258 $\mu$L, 0.25 mmol), acetic acid (70 $\mu$L, 1.25 mmol) and 4-aminobenzonitrile (148 mg, 1.25 mmol). Flash column chromatography ($Et_2O$ /$CH_2Cl_2$ 0-5%) afforded the titled sulfonamide as an off-white solid (59 mg, 81%); mp 156-157 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CD_3CN$) δ 8.44 (br. s, 1H, N*H*), 7.62 (d, *J* 9.0, 2H, Ar-*H*), 7.49-7.42 (m, 2H, Ar-*H*), 7.38-7.35 (m, 1H, Ar-*H*), 7.29 (d, *J* 9.0 , 2H, Ar-*H*), 7.19 (ddd, *J* 7.5, 2.5, 2.0, 1H, Ar-*H*), 3.83 (s, 3H, O*Me*);$^{13}$C NMR (100 MHz, $CD_3CN$) δ 165.3, 147.0, 145.4, 138.9, 135.9, 124.8, 124.6, 124.4, 123.7, 117.2, 112.4, 60.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3223 (NH), 2232 (CN), 1597, 1430, 1315 ($SO_2$), 1288, 1150 ($SO_2$); LRMS (ESI) *m/z* 289 (10%, $[M+H]^+$), 311 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 287.0497 $[M-H]^-$, $C_{14}H_{11}N_2O_3S$ requires *m/z* 287.0496.

**_N_-(Benzothiazol-6-yl)-3-methoxybenzenesulfonamide (44i)**



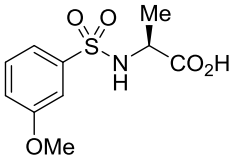

Prepared according to general procedure E using 3-methoxyphenylmagnesium bromide (0.97 M in THF, 258 $\mu$L, 0.25 mmol) and 6-aminobenzothiazole (188 mg, 1.25 mmol). Flash column chromatography ($Et_2O$ /$CH_2Cl_2$ 0-5%) afforded the titled sulfonamide as an off-white solid (46 mg, 57%); mp 130-131 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.93 (s, 1H, Ar-*H*), 8.09 (br. s, 1H, N*H*), 7.84 (d, *J* 9.0, 1H, Ar-*H*), 7.76 (d, *J* 2.0, 1H, Ar-*H*), 7.29 (app. t, *J* 8.0, 1H, Ar-*H*), 7.24 (app. dt, *J* 8.0, 1.5, 1H, Ar-*H*), 7.19-7.15 (m, 2H, Ar-*H*), 7.01 (ddd, *J* 8.0, 2.5, 1.5, 1H, Ar-*H*), 3.66 (s, 3H, O*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 160.4, 155.6, 151.3, 140.7, 135.6, 135.4, 130.9, 124.1, 121.2 (2C), 119.7, 114.9, 112.4, 55.9; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3198 (NH), 1595, 1466, 1323 ($SO_2$), 1245, 1151 ($SO_2$); LRMS (ESI) *m/z* 321 (100%, $[M+H]^+$), 343 (60%, $[M+Na]^+$), 663 (10%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 321.0360 $[M+H]^+$, $C_{14}H_{13}N_2O_3S_2$ requires *m/z* 321.0362.

**2-[(3-Methoxyphenyl)sulfonamido]benzamide (44j)**



Prepared according to general procedure E using 3-methoxyphenylmagnesium bromide (0.97 M in THF, 260 $\mu$L, 0.25 mmol), acetic acid (70 $\mu$L, 1.25 mmol) and anthranilamide (170 mg, 1.25 mmol). Flash column chromatography ($Et_2O$ /$CH_2Cl_2$ 0-5%) afforded the titled sulfonamide as an off-white solid (39 mg, 51%); mp 128-129 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 10.88 (s, 1H, $SO_2NH$), 7.65 (dd, *J* 8.5, 1.0, 1H, Ar-*H*), 7.39-7.32 (overlapping m, 3H, Ar-*H*), 7.26-7.22 (overlapping m, 2H, Ar-*H*), 7.00 (app. td, *J* 8.0, 1.0, 1H, Ar-*H*), 6.95 (ddd, *J* 8.5, 2.5, 1.0, 1H, Ar-*H*), 5.92-5.62 (overlapping br. s, 2H, $CONH_2$), 3.72 (s, 3H, O*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 170.5, 159.8, 140.6, 139.5, 133.4, 130.0, 127.5, 123.5, 121.3, 119.6 (2C), 119.5, 111.6, 55.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3419 (CON-H), 3201 (NH), 1671 (CO), 1484, 1380, 1333 ($SO_2$), 1113 ($SO_2$); LRMS (ESI) *m/z* 307 (80%, $[M+H]^+$), 329 (100%, $[M+Na]^+$), 635 (40%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 307.0741 $[M+H]^+$, $C_{14}H_{15}N_2O_4S$ requires *m/z* 307.0747.

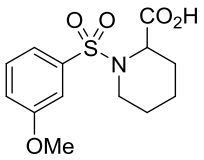
**(*S*)-[(3-Methoxyphenyl)sulfonyl)]alanine (44k)**



Prepared according to general procedure E using 3-methoxyphenylmagnesium bromide (0.97 M in THF, 258 $\mu$L, 0.25 mmol) and (*L*)-alanine (111 mg, 1.25 mmol). The aqueous acid wash gave the pure titled sulfonamide as a white solid (47 mg, 73%) without further purification; mp 126-127 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.36-7.30 (m, 2H, Ar-*H*), 7.29-7.27 (m, 1H, Ar-*H*) 7.04 (app. dt, *J* 7.0, 2.5, 1H, Ar-*H*), 3.80 (q, *J* 7.0, 1H, C*H*NH), 3.75 (s, 3H, O*Me*), 1.20 (d, *J* 7.0, 3H, CH*Me*); $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 173.9, 160.0, 142.0, 129.8, 118.7, 118.4, 111.5, 54.7, 51.4, 18.2; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3257 (NH), 2826 (br. OH), 1709 (CO), 1476, 1334 ($SO_2$), 1138 ($SO_2$); LRMS (ESI) *m/z* 260 (20%,

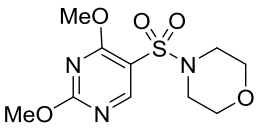
$[M+H]^+$), 282 (100%, $[M+Na]^+$), 541 (60%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 260.0581 $[M+H]^+$, $C_{10}H_{14}NO_5S$ requires *m/z* 260.0587; ee > 99% (Major = 17.97 mins, *n*-hexane/IPA 60:40, 1 ml/min); $[\alpha]_D$ = +29.5 (0.01 g/mL, $CHCl_3$).

**1-[(3-Methoxyphenyl)sulfonyl]piperidine-2-carboxylic acid (44l)**



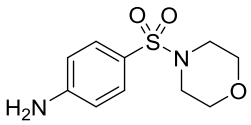

Prepared according to general procedure E using 3-methoxyphenylmagnesium bromide (0.97 M in THF, 258 $\mu$L, 0.25 mmol) and (*D*,*L*)-pipecolinic acid (161 mg, 1.25 mmol). The aqueous acid wash gave the pure titled sulfonamide as an off-white solid (62 mg, 83%) without further purification; mp 122-123 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.65 (br. s, 1H, $CO_2H$), 7.34-7.30 (m, 2H, Ar-*H*), 7.27-7.25 (m, 1H, Ar-*H*), 7.04-7.00 (m, 1H, Ar-*H*), 4.71 (app. d, *J* 5.0, 1H, C*H*$CO_2$H), 3.78 (s, 3H, O*Me*), 3.72-3.66 (app. d, *J* 12.5, 1H, NC$H_2$), 3.16 (td, *J* 12.5, 3.0, 1H, NC$H_2$), 2.14-2.07 (m, 1H, CHC$H_2$), 1.81-1.76 (m, 1H, CHC$H_2$), 1.71-1.59 (overlapping m, 2H, $NCH_2CH_2$ and $CHCH_2CH_2$), 1.44-1.23 (overlapping m, 2H, $NCH_2CH_2$ and $CHCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 176.7, 159.8, 141.0, 130.0, 119.3, 118.9, 111.9, 55.6, 54.9, 42.7, 27.5, 24.4, 20.0; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2726 (br. OH), 1706 (CO), 1599, 1488, 1318 ($SO_2$), 1112 ($SO_2$); LRMS (ESI) *m/z* 300 (100%, $[M+H]^+$), 621 (50%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 300.0894 $[M+H]^+$, $C_{13}H_{18}NO_5S$ requires *m/z* 300.0900.

**4-[(2,4-Dimethoxypyrimidin-5-yl)sulfonyl]morpholine (A)**



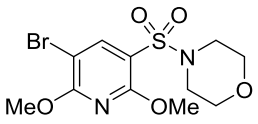
Prepared according to general procedure E using 2,4-dimethoxypyrimidin-5-ylmagnesium chloride.lithium chloride (0.25 mmol). The aryl Grignard solution was prepared *in situ* by dropwise addition of *iso*propylmagnesium chloride.LiCl solution (1.17 M in THF, 225 $\mu$L, 0.26 mmol) to a solution of 5-iodo-2,4-dimethoxypyrimidine (67 mg, 0.25 mmol) in THF (0.5 mL) at -20 °C. The solution was stirred at this temp. for 1 hr before being transferred *via* syringe to a DABSO-THF suspension. Flash column chromatography (petrol/EtOAc 2:3) afforded the titled sulfonamide as an off-white solid (37 mg, 52%); mp 113-114 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H, Ar-*H*), 4.11 (s, 3H, O*Me*), 4.08 (s, 3H, O*Me*), 3.74 (t, *J* 4.5, 4H, $NCH_2CH_2$), 3.25 (t, *J* 4.5, 4H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.5, 167.2, 162.1, 113.3, 66.6, 55.8, 54.9, 45.9; IR $\nu_{max}$ (neat)/cm$^{-1}$ 1598, 1487, 1420, 1324 ($SO_2$), 1162 ($SO_2$), 1040; LRMS (ESI) *m/z* 290 (100%, $[M+H]^+$), 312 (30%, $[M+Na]^+$); HRMS (ESI) found *m/z* 290.0798 $[M+H]^+$, $C_{10}H_{16}N_3O_5S$ requires *m/z* 290.0805.

**4-(Morpholinosulfonyl)aniline (D)**



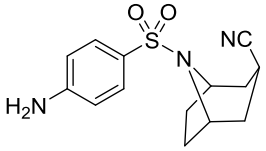
Prepared according to general procedure E using 4-[Bis(trimethylsilyl)amino]phenylmagnesium bromide (0.48 M in THF, 520 $\mu$L, 0.25 mmol). Flash column chromatography (petrol/EtOAc 3:2) afforded the titled sulfonamide as an off-white solid (36 mg, 60%); mp 218-219 °C ($CH_2Cl_2$) [lit.[194] mp 221-222 °C]; $^1$H NMR (400 MHz, $CD_3CN$) δ 7.47 (d, *J* 9.0, 2H, Ar-*H*), 6.76 (d, *J* 9.0, 2H, Ar-*H*), 4.91 (s, 2H, $NH_2$), 3.67 (t, *J* 4.5, 4H, $NCH_2CH_2$), 2.88 (t, *J* 4.5, 4H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CD_3CN$) δ 153.3, 130.5, 121.8, 113.8, 66.3, 46.7; LRMS (ESI) *m/z* 243 (30%, $[M+H]^+$), 265 (40%, $[M+Na]^+$), 507 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 265.0624 $[M+Na]^+$, $C_{10}H_{14}N_2O_3SNa$ requires *m/z* 265.0617. Data in accordance with that previously reported.[194]

**4-[(5-Bromo-2,6-dimethoxypyridin-3-yl)sulfonyl]morpholine (G)**




Prepared according to general procedure E using 3-bromo-2,6-dimethoxypyridinyl-5-magnesium chloride.litihum chloride (0.25 mmol). The aryl Grignard solution was prepared *in situ* by dropwise addition of *iso*propylmagnesium chloride.LiCl solution (1.17 M in THF, 235 $\mu$L, 0.28 mmol) to a solution of 3,5-dibromo-2,6-dimethoxypyridine (74 mg, 0.25 mmol) in THF (1 mL) at 0 °C. The solution was stirred at this temp. for 1 hr before being transferred *via* syringe to a DABSO-THF suspension. Flash column chromatography (petrol/EtOAc 2:3) afforded the titled sulfonamide as an off-white solid (43 mg, 49%); mp 145-146 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H, Ar-*H*), 4.07 (s, 3H, O*Me*), 4.05 (s, 3H, O*Me*), 3.73 (t, *J* 4.5, 4H, $NCH_2CH_2$), (t, *J* 4.5, 4H, $NCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.4, 158.7, 145.6, 113.0, 95.6, 66.6, 55.3, 54.6, 46.1; IR $\nu_{max}$ (neat)/cm$^{-1}$ 1612, 1403, 1390, 1312 ($SO_2$), 1147 ($SO_2$); LRMS (ESI) *m/z* 389 (50%, [M($^{79}$Br)+Na]$^+$), 391 (100%, [M($^{81}$Br)+Na]$^+$); HRMS (ESI) found *m/z* 388.9783 [M($^{79}$Br)+Na]$^+$ and 390.9762 [M($^{81}$Br)+Na]$^+$, $C_{11}H_{15}BrN_2O_5SNa$ requires *m/z* 388.9777 and 390.9757.

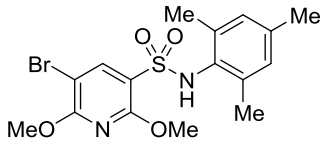
**8-[(4-Aminophenyl)sulfonyl]-8-azabicyclo[3.2.1]octane-3-carbonitrile** (**D4**)




Prepared according to general procedure E using 4-[Bis(trimethylsilyl)amino]phenylmagnesium bromide (0.48 M in THF, 520 $\mu$L, 0.25 mmol) and exo-8-azabicyclo[3.2.1]octane-3-carbonitrile (170 mg, 1.25 mmol). Flash column chromatography (petrol/EtOAc 1:1) afforded the titled sulfonamide as an off-white solid (40 mg, 54%); mp 181-182 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* 9.0, 2H, Ar-*H*), 6.69 (d, *J* 9.0, 2H, Ar-*H*), 4.87 (br s, 2H, $NH_2$), 4.19-4.15 (m, 2H, NC*H*), 2.96 (tt, *J* 11.5, 6.5, 1H, C*H*CN), 2.00-1.89 (m, 4H, $CNCHCH_2$), 1.55-1.44 (m, 4H, $NCHCH_2CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 153.2, 129.9, 126.6, 122.6, 113.9, 56.5, 36.2, 27.7, 20.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3542 (NH), 3362 (NH), 3251, 2968, 2241 (CN), 1636, 1348 ($SO_2$), 1148 ($SO_2$); LRMS (ESI) *m/z* 292 (100%,

$[M+H]^+$), 314 (50%, $[M+Na]^+$); HRMS (ESI) found *m/z* 292.1110 $[M+H]^+$, $C_{14}H_{18}N_3O_2S$ requires *m/z* 292.1114.

**5-Bromo-*N*-mesityl-2,6-dimethoxypyridine-3-sulfonamide** (**G6**)



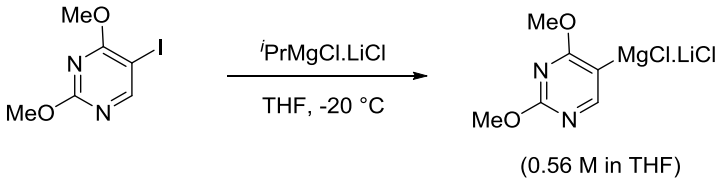

Prepared according to general procedure E using 3-bromo-2,6-dimethoxypyridinyl-5-magnesium chloride.lithium chloride (0.25 mmol) and 2,4,6-trimethylaniline (180 $\mu$L, 1.25 mmol). The aryl Grignard reagent was generated *in situ* as described above. The mixture was stirred at room temp. for 1 hr before being transferred to a DABSO-THF suspension. Flash column chromatography ($CH_2Cl_2$/$Et_2O$ 0-5%) afforded the titled sulfonamide as an off-white solid (40 mg, 39%); mp 213-214 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H, Ar-*H*), 6.78 (s, 2H, Ar-*H*), 6.25 (s, 1H, N*H*), 4.07 (s, 3H, O*Me*), 4.01 (s, 3H, O*Me*), 2.17 (s, 3H, Ar*Me*), 2.05 (s, 6H, Ar*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.2, 158.0, 143.2, 138.0, 137.5, 129.9, 129.5, 117.7, 95.5, 55.3, 54.9, 20.9, 18.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3273 (NH), 2995, 1567, 1311 ($SO_2$), 1160 ($SO_2$); LRMS (ESI) *m/z* 415 (90%, $[M(^{79}Br)+H]^+$), 417 (100%, $[M(^{81}Br)+H]^+$), 437 (90%, $[M(^{79}Br)+Na]^+$), 439 (100%, $[M(^{81}Br)+Na]^+$); HRMS (ESI) found *m/z* 415.0316 $[M(^{79}Br)+H]^+$ and 417.0294 $[M(^{81}Br)+H]^+$, $C_{16}H_{20}BrN_2O_4S$ requires *m/z* 415.0322 and 417.0301.

### 6.4.3 Array Synthesis

The array synthesis of sulfonamides was performed as a matrix using a Mettler-Toledo-Bohdan XT block equipped with an inert/purging manifold. The experiments were conducted in two runs using the same ten amines each time with 4 organometallic reagents in the first run and three in the second (1 × 40 combinations and 1 × 30 combinations). Non-commercially available organometallic reagents were prepared as stock solutions, as described below.

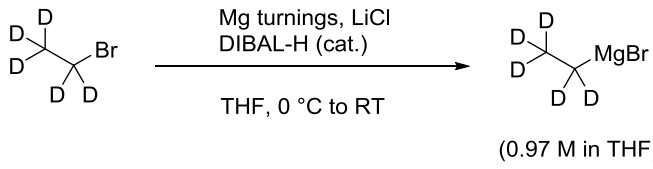
**Organometallic reagent stock solutions**

**2,4-Dimethoxypyrimindin-5-ylmagnesium chloride.LiCl, (A)**




To a solution of 5-iodo-2,4-dimethoxypyrimidine (2.0 g, 7.52 mmol) in THF (5 mL) was added $^{i}$PrMgCl.LiCl (1.17 M solution in THF, 6.8 mL, 7.90 mmol) dropwise at -20 ºC. The reaction was stirred at this temp. for 1 hr before warming to room temp. to give a light brown solution (0.56 M).[195]

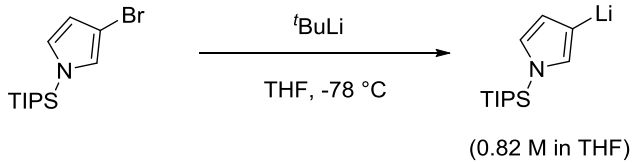
***d*$_5$-Ethylmagnesium bromide (B)**




To a mixture of magnesium turnings (490 mg, 20.1 mmol), anhydrous LiCl (682 mg, 16.1 mmol) and DIBAL-H (1M solution in THF, 134 $\mu$L, 0.13 mmol) in THF was added

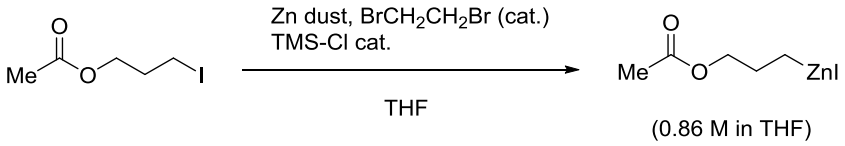
bromoethane-$d_5$ at 0 ºC. The reaction mixture was stirred at this temp. for 2 hr before warming to room temp. to give a pale yellow solution (0.97 M).[196]

**3-Lithio-1-(triisopropysilyl)pyrrole (E)**



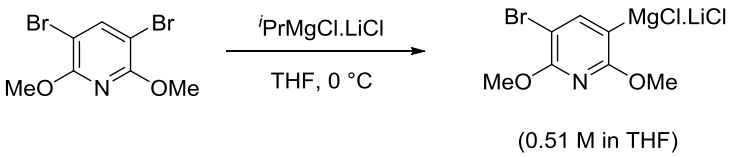

To a solution of *N*-TIPS-bromopyrrole (2.9 mL, 11.0 mmol) in THF (10 mL) at -78 ºC was added *tert*-butyllithium (1.32 M solution in hexane, 10 mL, 13.2 mmol) dropwise. The mixture was stirred at this temp. for 1 hr before warming to room temp. to give a pale solution (0.82 M).[123]

**3-Acetoxypropylzinc iodide (F)**




To a suspension of zinc dust (1.15 g, 17.54 mmol) in THF (2 mL) was added 1,2-dibromoethane (61 $\mu$L, 0.70 mmol). The resulting mixture was heated to 65 ºC until refluxing and cooled to room temp. (repeated twice). Chlorotrimethylsilane (71 $\mu$L, 0.56 mmol) was then added and the mixture was stirred for 10 min before addition of a solution of 3-acetoxypropyl iodide (1.2 mL, 8.77 mmol) in THF (6 mL) dropwise over 20 min. The reaction mixture was stirred at 40 ºC for 4 hr to give a clear solution (0.86 M). [197]

**3-Bromo-2,6-dimethoxypyridinyl-5-magnesium chloride.LiCl (G)**




To a solution of 3,5-dibromo-2,6-dimethoxypyridine (2.08 g, 7.0 mmol) in THF (5 mL) was added $^{i}$PrMgCl.LiCl (1.17 M solution in THF, 6.6 mL, 7.7 mmol) dropwise at 0 ºC. The reaction was stirred at this temp. for 1 hr before warming to room temp. to give a yellow solution (0.51 M).[198]

**General Procedure**

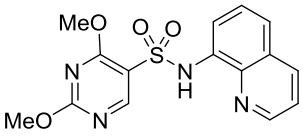
Oven-dried test tubes were placed in the block reactor which was connected to a manifold and the tubes were cooled by flushing with nitrogen gas. DABSO (36 mg, 0.15 mmol) was added to each of the tubes which were subsequently flushed with nitrogen for 2 min. THF (0.5 mL) was added to the tubes followed by the corresponding organometallic reagent (0.25 mmol). The resulting mixtures were stirred at this temp. for 30 min. To each of the tubes was added sequentially, $H_2O$ (1 mL), amine (1.25 mmol) and NaOCl (15.8% aqueous solution, 295 $\mu$L, 0.75 mmol). The resulting mixtures were stirred at room temp. for 16 hr before being transferred to glass vials containing sat. $NaS_2O_{3\ (aq)}$ (10 mL) and stirred for a further 30 min. EtOAc (10 mL) was added to each of the vials which were vigorously shaken (robotic assisted agitation) for 1 min before automated extraction of the organic layer *via* syringe. This process was repeated 3 times before removing the solvent by flushing with hot air (40 °C). The resulting crude reaction mixtures were purified using automated preparative liquid chromatography-mass spectrometry to deliver the desired sulfonamides as identified by LC-MS (retention times given in minutes). Representative $^{1}$H NMR spectra were obtained for certain examples where LC-MS data contained discrepancies and as confirmation of purity. The four examples that failed by purity were judged to have done so by LC-MS and $^{1}$H NMR Spectroscopy.

**Sample purification – Preparative HPLC**

Compounds were purified by mass directed preparative HPLC using a mixed trigger of UV with ES+ on a Waters Fraction Lynx system comprising a 2767 injector/collector with a 2525 gradient pump, pump control module two 515 isocratic pumps, CFO, 2996 photodiode array, 2420 ELSD and Micromass ZQ2000. A Waters XBridge dC18 5micron 19 × 10mm guard column was used with an XBridge dC18 5micron OBD 30 × 100mm prep column.

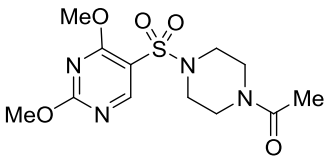
The preparative HPLC was conducted employing a generic 11.4 minute run time using $H_2O$ with 10mM ammonium acetate (solvent A) and $CH_3CN$ (solvent B). Isolated compounds were transferred to individual vials by dissolving in DMSO.

**Sulfonamide Data**



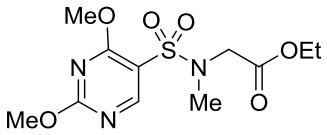

**A1**

Product obtained as a yellow solid (20 mg, 23%). LC-MS data – Ret. time 0.64: MS ES+ *m/z* 347 (100%, $[M+H]^+$); MS ES- *m/z* 345 (100%, $[M-H]^-$); $^1H$ NMR (400 MHz, $CDCl_3$) δ 9.58 (br s, 1H, $SO_2NH$), 8.81 (dd, *J* 4.0, 1.5, 1H, Ar-*H*), 8.77 (s, 1H, Ar-*H*), 8.13 (dd, *J* 8.5, 1.5, 1H, Ar-*H*), 7.81 (dd, *J* 7.0, 2.0, 1H, Ar-*H*), 7.53-7.40 (m, 3H, Ar-*H*), 3.99 (s, 3H, O*Me*), 3.95 (s, 3H, O*Me*).



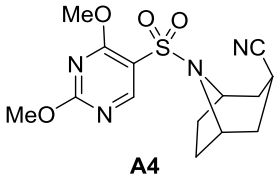

**A2**

Product obtained as an off-white solid (36 mg, 44%). LC-MS data – Ret. time 0.36: MS ES+ *m/z* 331 (100%, $[M+H]^+$), 353 (40%, $[M+Na]^+$).



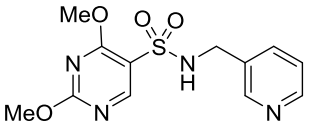
**A3**

Product obtained as an off-white solid (22 mg, 28%). LC-MS data – Ret. time 0.51: MS ES+ *m/z* 320 (100%, $[M+H]^+$), 342 (20%, $[M+Na]^+$).



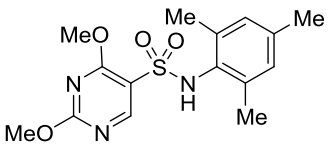
**A4**

Product obtained as an off-white solid (34 mg, 40%). LC-MS data – Ret. time 0.49: MS ES+ *m/z* 339 (100%, $[M+H]^+$), 361 (20%, $[M+Na]^+$).



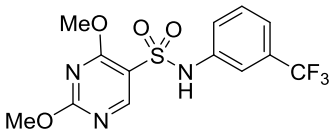
**A5**

Product obtained as a yellow solid (28 mg, 36%). LC-MS data – Ret. time 0.28: MS ES+ *m/z* 311 (100%, $[M+H]^+$); MS ES- *m/z* 309 (100%, $[M-H]^-$).



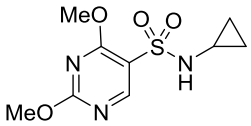
**A6**

Product obtained as an off-white solid (27 mg, 32%). LC-MS data – Ret. time 0.65: MS ES+ *m/z* 338 (100%, $[M+H]^+$); MS ES- *m/z* 336 (100%, $[M-H]^-$).



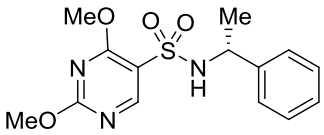
**A7**

Product obtained as an off-white solid (22 mg, 24%). LC-MS data – Ret. time 0.65: MS ES+ *m/z* 364 (100%, $[M+H]^+$); MS ES- *m/z* 362 (100%, $[M-H]^-$).



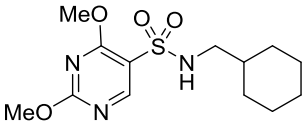
**A8**

Product obtained as an off-white solid (26 mg, 40%). LC-MS data – Ret. time 0.42: MS ES+ *m/z* 260 (100%, $[M+H]^+$); MS ES- *m/z* 258 (100%, $[M-H]^-$).



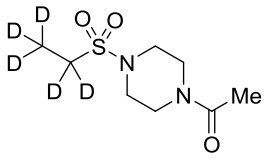
**A9**

Product obtained as a white solid (28 mg, 35%). LC-MS data – Ret. time 0.55: MS ES+ *m/z* 324 (100%, $[M+H]^+$), 346 (100%, $[M+Na]^+$); MS ES- *m/z* 322 (100%, $[M-H]^-$).



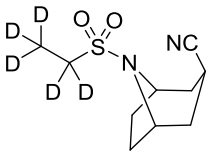
**A10**

Product obtained as an off-white solid (28 mg, 36%). LC-MS data – Ret. time 0.68: MS ES+ *m/z* 316 (100%, $[M+H]^+$); MS ES- *m/z* 314 (100%, $[M-H]^-$).



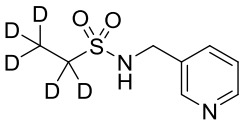
**B2**

Product obtained as an off-white solid (26 mg, 46%). LC-MS data – Ret. time 0.30: MS ES+ *m/z* 226 (100%, $[M+H]^+$), 248 (40%, $[M+Na]^+$); $^1$H NMR (400 MHz, $CDCl_3$) δ 3.71 (t, *J* 5.0, 2H, N(COMe)C*H*$_2$), 3.55 (t, *J* 5.0, 2H, N(COMe)C*H*$_2$), 3.32 (t, *J* 5.0, 2H, N(COMe)CH$_2$C*H*$_2$), 3.28 (t, *J* 5.0, 2H, N(COMe)CH$_2$C*H*$_2$), 2.12 (s, 3H, CO*Me*).



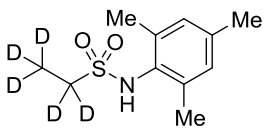
**B4**

Product obtained as an off-white solid (26 mg, 45%). LC-MS data – Ret. time 0.42: MS ES+ *m/z* 234 (100%, $[M+H]^+$), 256 (25%, $[M+Na]^+$).



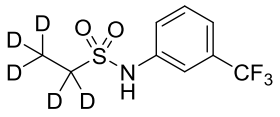
**B5**

Product obtained as an off-white solid (27 mg, 53%). LC-MS data – Ret. time 0.25: MS ES+ *m/z* 205 (100%, $[M+H]^+$); MS ES- *m/z* 203 (80%, $[M-H]^-$).



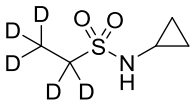
**B6**

Product obtained as an off-white solid (29 mg, 50%). LC-MS data – Ret. time 0.58: MS ES+ *m/z* 255 (20%, $[M+Na]^+$); MS ES- *m/z* 231 (20%, $[M-H]^-$); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 2H, Ar-*H*), 5.61 (br. s, 1H, N*H*), 2.31 (s, 6H, Ar*Me*), 2.20 (s, 3H, Ar*Me*).



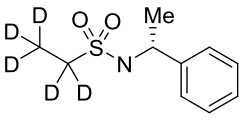
**B7**

Product obtained as a yellow oil (25 mg, 39%). LC-MS data – Ret. time 0.59: MS ES+ *m/z* 259 (50%, $[M+H]^+$); MS ES- *m/z* 257 (100%, $[M-H]^-$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.53-7.40 (m, 4H, Ar-*H*), 7.02 (br. s, 1H, N*H*).



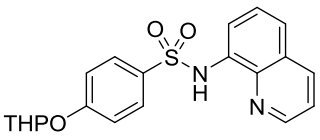
**B8**

Product obtained as a white solid (18 mg, 47%). LC-MS data – Ret. time 0.34: MS ES+ *m/z* 155 (100%, $[M+H]^+$); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.70 (br. s, 1H, N*H*), 2.65-2.51 (m, 1H, NHC*H*), 0.77-0.65 (m, 4H, CHC$H_2$).



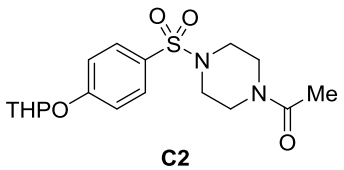
**B9**

Product obtained as an off-white solid (29 mg, 53%). LC-MS data – Ret. time 0.50: MS ES- *m/z* 217 (60%, $[M-H]^-$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.43-7.29 (m, 5H, Ar-*H*), 4.80-4.57 (overlapping br. s, 1H, N*H* and q, *J* 7.0, 1H, C*H*Me), 1.57 (d, *J* 7.0, 3H, CH*Me*).



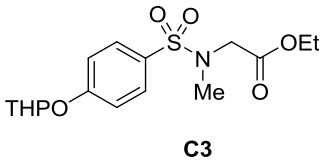
**C1**

Product obtained as a light brown oil (32 mg, 33%). LC-MS data – Ret. time 0.85: MS ES+ *m/z* 385 (100%, $[M+H]^+$), 407 (20%, $[M+Na]^+$); MS ES- *m/z* 383 (100%, $[M-H]^-$).



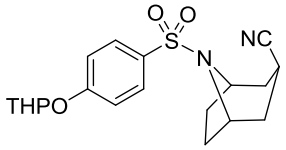

**C2**

Product obtained as a yellow solid (47 mg, 51%). LC-MS data – Ret. time 0.53: MS ES+ *m/z* 369 (100%, $[M+H]^+$), 391 (70%, $[M+Na]^+$).



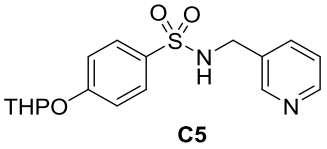

**C3**

Product obtained as a clear oil (46 mg, 51%). LC-MS data – Ret. time 0.74: MS ES+ *m/z* 358 (90%, $[M+H]^+$), 380 (100%, $[M+Na]^+$).



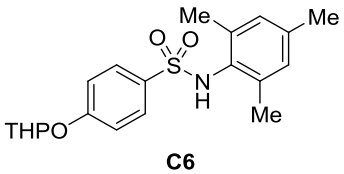

**C4**

Product obtained as a yellow solid (46 mg, 49%). LC-MS data – Ret. time 0.71: MS ES+ *m/z* 377 (90%, $[M+H]^+$), 399 (100%, $[M+Na]^+$).



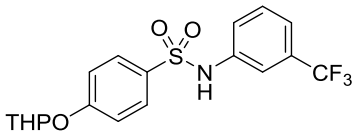

**C5**

Product obtained as an off-white solid (45 mg, 52%). LC-MS data – Ret. time 0.37: MS ES+ *m/z* 349 (100%, $[M+H]^+$), 371 (10%, $[M+Na]^+$); MS ES- *m/z* 347 (100%, $[M-H]^-$).



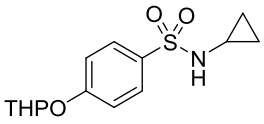

**C6**

Product obtained as an off-white solid (41 mg, 44%). LC-MS data – Ret. time 0.85: MS ES+ *m/z* 376 (25%, $[M+H]^+$), 398 (30%, $[M+Na]^+$); MS ES- *m/z* 374 (100%, $[M-H]^-$).



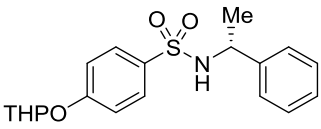
**C7**

Product obtained as an off-white solid (42 mg, 42%). LC-MS data – Ret. time 0.82: MS ES- *m/z* 400 (100%, $[M-H]^-$).



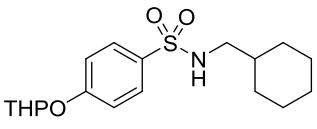
**C8**

Product obtained as an off-white solid (39 mg, 53%). LC-MS data – Ret. time 0.65: MS ES+ *m/z* 298 (60%, $[M+H]^+$), 320 (25%, $[M+Na]^+$); MS ES- *m/z* 296 (100%, $[M-H]^-$).



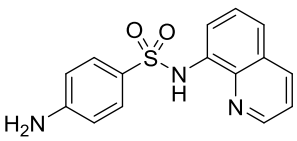
**C9**

Product obtained as an off-white solid (49 mg, 54%). LC-MS data – Ret. time 0.77: MS ES+ *m/z* 384 (100%, $[M+Na]^+$); MS ES- *m/z* 360 (100%, $[M-H]^-$).



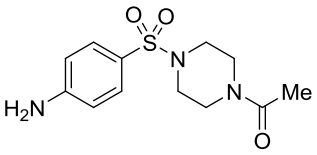
**C10**

Product obtained as a white solid (52 mg, 59%). LC-MS data – Ret. time 0.87: MS ES+ *m/z* 354 (90%, $[M+H]^+$), 376 (30%, $[M+Na]^+$); MS ES- *m/z* 352 (100%, $[M-H]^-$).



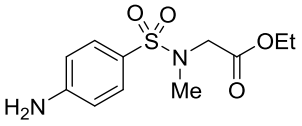
**D1**

Product obtained as an off-white solid (20 mg, 27%). LC-MS data – Ret. time 0.55: MS ES+ *m/z* 300 (100%, $[M+H]^+$); MS ES- *m/z* 298 (100%, $[M-H]^-$).



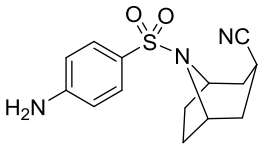
**D2**

Product obtained as a yellow oil (32 mg, 45%). LC-MS data – Ret. time 0.33: MS ES+ *m/z* 284 (100%, $[M+H]^+$), 306 (20%, $[M+Na]^+$); MS ES- *m/z* 282 (50%, $[M-H]^-$).



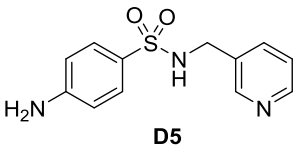
**D3**

Product obtained as an off-white solid (25 mg, 37%). LC-MS data – Ret. time 0.45: MS ES+ *m/z* 273 (100%, $[M+H]^+$), 295 (20%, $[M+Na]^+$).



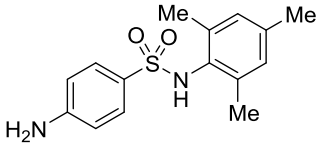
**D4**

Product obtained as an off-white solid (31 mg, 43%). LC-MS data – Ret. time 0.44: MS ES+ *m/z* 292 (100%, $[M+H]^+$), 314 (20%, $[M+Na]^+$); MS ES- *m/z* 290 (70%, $[M-H]^-$).



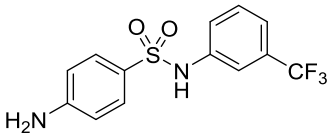
**D5**

Product obtained as a yellow oil (20 mg, 30%). LC-MS data – Ret. time 0.26: MS ES+ *m/z* 264 (100%, $[M+H]^+$); MS ES- *m/z* 262 (100%, $[M-H]^-$).



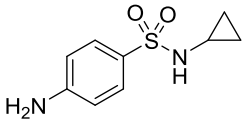
**D6**

Product obtained as an off-white solid (24 mg, 33%). LC-MS data – Ret. time 0.60: MS ES+ *m/z* 291 (80%, $[M+H]^+$), 313 (45%, $[M+Na]^+$); MS ES- *m/z* 289 (100%, $[M-H]^-$).



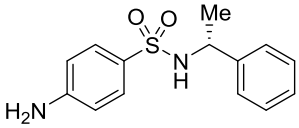
**D7**

Product obtained as an off-white solid (24 mg, 30%). LC-MS data – Ret. time 0.58: MS ES+ *m/z* 317 (100%, $[M+H]^+$); MS ES- *m/z* 315 (100%, $[M-H]^-$).



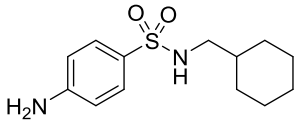
**D8**

Product obtained as a clear oil (22 mg, 42%). LC-MS data – Ret. time 0.38: MS ES+ *m/z* 213 (90%, $[M+H]^+$).



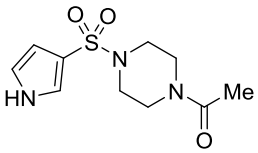
**D9**

Product obtained as an off-white solid (30 mg, 43%). LC-MS data – Ret. time 0.50: MS ES+ *m/z* 277 (100%, $[M+H]^+$); ES MS- *m/z* 275 (100%, $[M-H]^-$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, *J* 9.0, 2H, Ar-*H*), 7.12-7.08 (m, 5H, Ar-*H*), 6.47 (d, *J* 9.0, 2H, Ar-*H*), 4.20 (q, *J* 7.0, 1H, NHC*H*), 1.20 (d, *J* 7.0, 3H, CH*Me*).



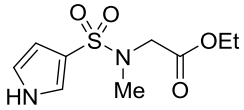
**D10**

Product obtained as an off-white solid (28 mg, 42%). LC-MS data – Ret. time 0.60: MS ES+ *m/z* 269 (100%, $[M+H]^+$), 291 (10%, $[M+Na]^+$); ES MS- *m/z* 267 (100%, $[M-H]^-$).



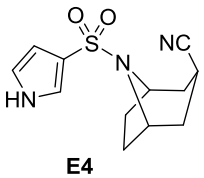
**E2**

Product obtained as an off-white solid (26 mg, 40%). LC-MS data – Ret. time 0.31: MS ES+ *m/z* 258 (100%, $[M+H]^+$), 280 (30%, $[M+Na]^+$); MS ES- *m/z* 256 (100%, $[M-H]^-$); $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.32 (app. t, *J* 2.0, 1H, Ar-*H*), 6.93 (dd, *J* 3.0, 2.0, 1H, Ar-*H*), 6.42 (dd, *J* 3.0, 2.0, 1H, Ar-*H*), 3.72-3.62 (m, 4H, N(COMe)C$H_2$), 3.03-2.91 (m, 4H, N(COMe)$CH_2$C$H_2$), 2.09 (s, 3H, CO*Me*).



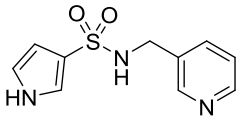
**E3**

Product obtained as an off-white solid (20 mg, 33%). LC-MS data – Ret. time 0.39: MS ES+ *m/z* 247 (100%, $[M+H]^+$), 269 (40%, $[M+Na]^+$); ES MS- *m/z* 245 (100%, $[M-H]^-$).



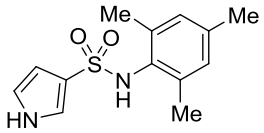
**E4**

Product obtained as an off-white solid (29 mg, 44%). LC-MS data – Ret. time 0.39: MS ES+ *m/z* 266 (100%, $[M+H]^+$), 288 (40%, $[M+Na]^+$); MS ES- *m/z* 264 (100%, $[M-H]^-$).



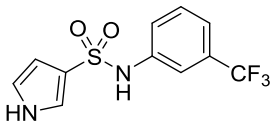
**E5**

Product obtained as a white solid (19 mg, 32%). LC-MS data – Ret. time 0.26: MS ES+ *m/z* 238 (100%, $[M+H]^+$); ES MS- *m/z* 236 (100%, $[M-H]^-$).



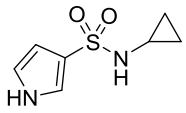
**E6**

Product obtained as an off-white solid (27 mg, 41%). LC-MS data – Ret. time 0.55: MS ES+ *m/z* 265 (10%, $[M+H]^+$), 287 (40%, $[M+Na]^+$); ES MS- *m/z* 263 (25%, $[M-H]^-$).



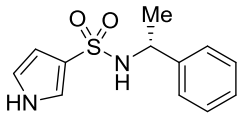
**E7**

Product obtained as an off-white solid (23 mg, 32%). LC-MS data – Ret. time 0.55: MS ES- *m/z* 289 (70%, $[M-H]^-$).



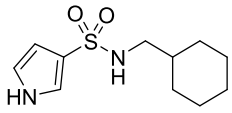
**E8**

Product obtained as an off-white solid (20 mg, 43%). LC-MS data – Ret. time 0.33: MS ES+ *m/z* 187 (30%, $[M+H]^+$), 209 (30%, $[M+Na]^+$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.72 (br. s, 1H, ArN*H*), 7.38-7.36 (m, 1H, Ar-*H*), 6.84 (dd, *J* 3.0, 2.5, 1H, Ar-*H*), 6.54-6.52 (m, 1H, Ar-*H*), 4.75 (br. s, 1H, N*H*), 2.34-2.29 (m, 1H, NHC*H*), 0.68-0.63 (m, 2H, CHC$H_2$), 0.62-0.56 (m, 2H, CHC$H_2$).



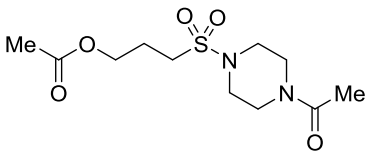
**E9**

Product obtained as a yellow oil (24 mg, 38%). LC-MS data – Ret. time 0.47: MS ES+ *m/z* 273 (90%, $[M+Na]^+$); MS ES- *m/z* 249 (100%, $[M-H]^-$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.46 (br. s, ArN*H*), 7.21-7.09 (overlapping m, 6H, Ar-*H*), 6.70 (dd, *J* 4.5, 2.0, 1H, Ar-*H*), 6.33-6.31 (m, 1H, Ar-*H*), 4.56 (br. s, 1H, N*H*), 4.43-4.35 (m, 1H, NHC*H*), 1.40 (d, *J* 7.0, 3H, CH*Me*).



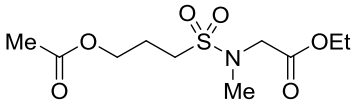
**E10**

Product obtained as an off-white solid (25 mg, 41%). LC-MS data – Ret. time 0.55: MS ES+ *m/z* 243 (100%, $[M+H]^+$), 265 (40%, $[M+Na]^+$); MS ES- *m/z* 241 (100%, $[M-H]^-$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.73 (br. s, 1H, ArN*H*), 7.24-7.22 (m, 1H, Ar-*H*), 6.76 (dd, *J* 5.0, 2.5, 1H, Ar-*H*), 6.43-6.41 (m, 1H, Ar-*H*), 4.27 (br s, 1H, N*H*), 2.71 (d, *J* 6.5, 2H, NHC$H_2$), 1.65-1.58 (m, 5H, C$H_2$), 1.42-1.32 (m, 1H, NHCH$_2$C*H*), 1.18-1.00 (m, 3H, C$H_2$), 0.86-0.75 (m, 2H, C$H_2$).



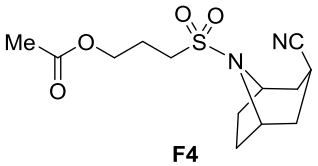
**F2**

Product obtained as an off-white solid (31 mg, 42%). LC-MS data – Ret. time 0.32: MS ES+ *m/z* 293 (100%, $[M+H]^+$), 315 (30%, $[M+Na]^+$); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.18 (t, *J* 6.0, 2H, OC$H_2$), 3.72 (t, *J* 5.0, 2H, N(COMe)C$H_2$), 3.57 (t, *J* 5.0, 2H, N(COMe)C$H_2$), 3.32 (t, *J* 5.0, 2H, N(COMe)CH$_2$C$H_2$), 3.28 (t, *J* 5.0, 2H, N(COMe)CH$_2$C$H_2$), 3.02-2.98 (m, 2H, SC$H_2$), 2.19-2.13 (m, 2H, OCH$_2$C$H_2$), 2.12 (s, 3H, NCO*Me*), 2.07 (s, 3H, OCO*Me*).



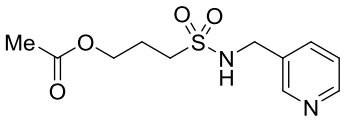
**F3**

Product obtained as a yellow oil (25 mg, 36%). LC-MS data – Ret. time 0.46: MS ES+ *m/z* 282 (50%, $[M+H]^+$), 304 (80%, $[M+Na]^+$).



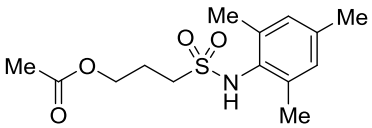
**F4**

Product obtained as a yellow oil (31 mg, 40%). LC-MS data – Ret. time 0.44: MS ES+ *m/z* 301 (75%, $[M+H]^+$), 323 (65%, $[M+Na]^+$).



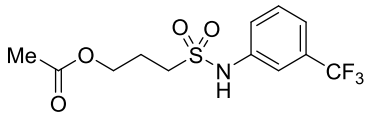
**F5**

Product obtained as a light brown oil (27 mg, 40%). LC-MS data – Ret. time 0.26: MS ES+ *m/z* 273 (100%, $[M+H]^+$), 295 (10%, $[M+Na]^+$).



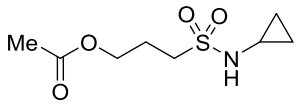
**F6**

Product obtained as an off-white solid (30 mg, 40%). LC-MS data – Ret. time 0.60: MS ES+ *m/z* 322 (75%, $[M+Na]^+$); MS ES- *m/z* 298 (60%, $[M-H]^-$); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 2H, Ar-*H*), 5.68 (br. s, 1H, N*H*), 4.14 (t, *J* 6.0, 2H, OC$H_2$), 3.19-3.14 (m, 2H, SC$H_2$), 2.30 (s, 6H, Ar*Me*), 2.23-2.15 (overlapping s, 3H, Ar*Me* and m, 2H, $OCH_2CH_2$), 2.00 (s, 3H, OCO*Me*).



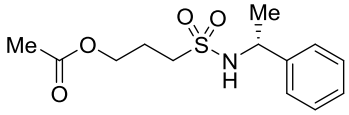
**F7**

Product obtained as a yellow oil (33 mg, 40%). LC-MS data – Ret. time 0.59: MS ES+ *m/z* 348 (80%, $[M+Na]^+$); MS ES- *m/z* 324 (70%, $[M-H]^-$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.44-7.35 (m, 4H, Ar-*H*), 7.14 (br. s, 1H, N*H*), 4.10 (t, *J* 6.0, 2H, OC$H_2$), 3.18-3.14 (m, 2H, SC$H_2$), 2.14-2.03 (m, 2H, $OCH_2CH_2$), 1.93 (s, 3H, OCO*Me*).



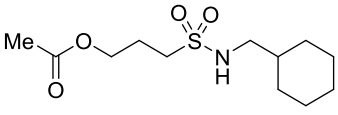
**F8**

Product obtained as a light yellow oil (28 mg, 51%). LC-MS data – Ret. time 0.37: MS ES+ *m/z* 222 (10%, $[M+H]^+$), 244 (80%, $[M+Na]^+$).



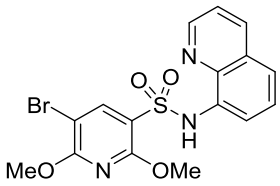
**F9**

Product obtained as an off-white solid (27 mg, 38%). LC-MS data – Ret. time 0.51: MS ES+ *m/z* 308 (100%, $[M+Na]^+$).



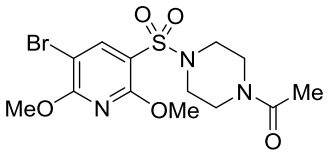
**F10**

Product obtained as an off-white solid (30 mg, 43%). LC-MS data – Ret. time 0.60: MS ES+ *m/z* 278 (75%, $[M+H]^+$), 300 (85%, $[M+Na]^+$).



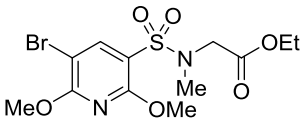
**G1**

Product obtained as an off-white solid (27 mg, 25%). LC-MS data – Ret. time 0.87: MS ES+ *m/z* 424 (75%, $[M(^{79}Br)+H]^+$), 426 (100%, $[M(^{81}Br)+H]^+$); MS ES- *m/z* 422 (85%, $[M(^{79}Br)-H]^-$), 424 (100%, $[M(^{81}Br)-H]^-$).



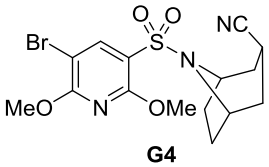
**G2**

Product obtained as an off-white solid (36 mg, 35%). LC-MS data – Ret. time 0.54: MS ES+ *m/z* 408 (75%, $[M(^{79}Br)+H]^+$), 410 (100%, $[M(^{81}Br)+H]^+$).



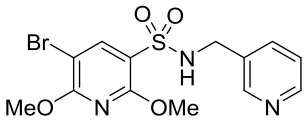
**G3**

Product obtained as a yellow oil (28 mg, 28%). LC-MS data – Ret. time 0.72: MS ES+ *m/z* 397 (75%, $[M(^{79}Br)+H]^+$), 399 (100%, $[M(^{81}Br)+H]^+$), 419 (50%, $[M(^{79}Br)+Na]^+$), 421 (60%, $[M(^{81}Br)+Na]^+$)



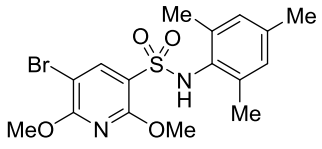
**G4**

Product obtained as a white solid (30 mg, 29%). LC-MS data – Ret. time 0.71: MS ES+ *m/z* 416 (75%, $[M(^{79}Br)+H]^+$), 418 (100%, $[M(^{81}Br)+H]^+$), 438 (40%, $[M(^{79}Br)+Na]^+$), 440 (50%, $[M(^{81}Br)+Na]^+$).



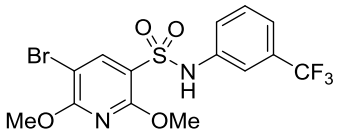
**G5**

Product obtained as an off-white solid (30 mg, 31%). LC-MS data – Ret. time 0.37: MS ES+ *m/z* 388 (75%, $[M(^{79}Br)+H]^+$), 390 (100%, $[M(^{81}Br)+H]^+$); MS ES- *m/z* 386 (80%, $[M(^{79}Br)-H]^-$), 388 (100%, $[M(^{81}Br)-H]^-$).



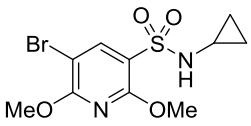
**G6**

Product obtained as an off-white solid (35 mg, 34%). LC-MS data – Ret. time 0.85: MS ES+ *m/z* 415 (10%, $[M(^{79}Br)+H]^+$), 417 (10%, $[M(^{81}Br)+H]^+$); MS ES- *m/z* 413 (80%, $[M(^{79}Br)-H]^-$), 415 (100%, $[M(^{81}Br)-H]^-$).



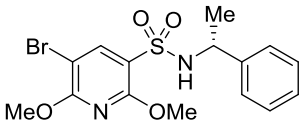
**G7**

Product obtained as an off-white solid (29 mg, 26%). LC-MS data – Ret. time 0.82: MS ES+ *m/z* 441 (25%, $[M(^{79}Br)+H]^+$), 443 (30%, $[M(^{81}Br)+H]^+$); MS ES- *m/z* 439 (80%, $[M(^{79}Br)-H]^-$), 441 (100%, $[M(^{81}Br)-H]^-$).



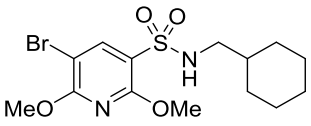
**G8**

Product obtained as an off-white solid (27 mg, 32%). LC-MS data – Ret. time 0.66: MS ES+ *m/z* 337 (65%, $[M(^{79}Br)+H]^+$), 339 (75%, $[M(^{81}Br)+H]^+$); MS ES- *m/z* 335 (95%, $[M(^{79}Br)-H]^-$), 337 (100%, $[M(^{81}Br)-H]^-$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H, Ar-*H*), 5.20 (br. s, 1H, N*H*), 4.04 (s, 3H, O*Me*), 4.00 (s, 3H, O*Me*), 2.07-2.00 (m, 1H, NHC*H*), 0.66-0.63 (m, 2H, CHC$H_2$), 0.55-0.51 (m, 2H, CHC$H_2$).



**G9**

Product obtained as an off-white solid (31 mg, 31%). LC-MS data – Ret. time 0.87: MS ES+ *m/z* 423 (25%, $[M(^{79}Br)+Na^{+}]$), 425 (30%, $[M(^{81}Br)+Na]^{+}$); MS ES- *m/z* 399 (80%, $[M(^{79}Br)-H]^{-}$), 401 (100%, $[M(^{81}Br)-H]^{-}$).

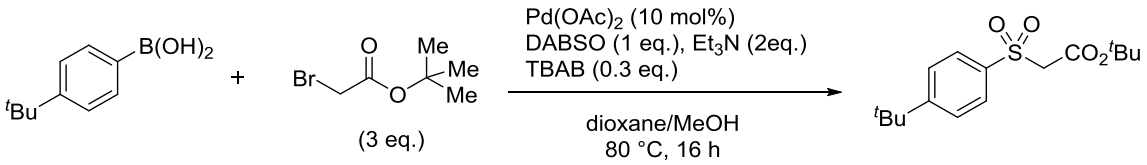


**G10**

Product obtained as an off-white solid (32 mg, 33%). LC-MS data – Ret. time 0.90: MS ES+ *m/z* 393 (75%, $[M(^{79}Br)+H]^{+}$), 395 (100%, $[M(^{81}Br)+H]^{+}$); MS ES- *m/z* 391 (85%, $[M(^{79}Br)-H]^{-}$), 393 (100%, $[M(^{81}Br)-H]^{-}$).

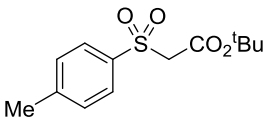
# 6.5 Chapter 4 data

## 6.5.1 General Procedure F for the synthesis of sulfones from boronic acids, DABSO, and alkyl halides as exemplified by the preparation of *tert*-butyl 2-{[4-(*tert*-butyl)phenyl]sulfonyl}acetate (49a)




To a reaction tube was added DABSO (60 mg, 0.25 mmol), *tert*-butylphenylboronic acid (45 mg, 0.25 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), TBAB (24 mg, 0.075 mmol), $Et_3N$ (70 $\mu$L, 0.50 mmol) and *tert*-butylbromoacetate (110 $\mu$L, 0.75 mmol). After addition of dioxane (0.8 mL) and MeOH (0.8 mL) the resulting mixture was heated at 80 ºC and stirred at this temp. for 16 hr. The reaction mixture was allowed to cool to room temp. and filtered through a plug of silica before removing the solvent *in vacuo*. Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (52 mg, 83%); mp 107-108 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* 8.5, 2H, Ar-*H*), 7.60 (d, *J* 8.5, 2H, Ar-*H*), 4.05 (s, 2H, C$H_2$), 1.37 (s, 18H, Ar-C$Me_3$ and C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.4, 158.1, 136.0, 128.4, 126.2, 83.5, 62.2, 35.3, 31.0, 27.7; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2982, 1730 (CO), 1591, 1495, 1328 ($SO_2$), 1143 ($SO_2$); LRMS (ESI) *m/z* 330 (100%, $[M+NH_4]^+$), 335 (80%, $[M+Na]^+$), 647 (30%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 335.1283 $[M+Na]^+$, $C_{16}H_{24}O_4SNa$ requires *m/z* 335.1288.

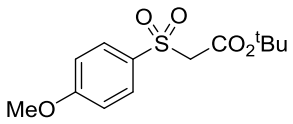
### *tert*-Butyl 2-tosylacetate (49b)




Prepared according to general procedure F using *p*-tolylphenylboronic acid (33 mg, 0.25 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the

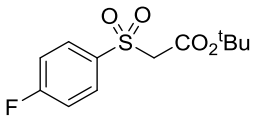
titled sulfone as a white solid (54 mg, 79%); mp 56-57 °C ($CH_2Cl_2$) [lit.[199] mp 57-58 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* 8.5, 2H, Ar-*H*), 7.30 (d, *J* 8.5, 2H, Ar-*H*), 3.94 (s, 2H, C$H_2$), 2.39 (s, 3H, Ar*Me*), 1.31 (s, 9H, C$Me_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.4, 145.2, 136.0, 129.7, 128.6, 83.6, 62.2, 27.7, 21.7; LRMS (ESI) *m/z* 293 (30%, $[M+Na]^+$), 563 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 293.0817 $[M+Na]^+$, $C_{13}H_{18}O_4SNa$ requires *m/z* 293.0818. Data in accordance with that previously reported.[199]

**_tert_-Butyl 2-[(4-methoxyphenyl)sulfonyl]acetate (49c)**




Prepared according to general procedure F using *p*-methoxyphenylboronic acid (38 mg, 0.25 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a colourless oil (52 mg, 73%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* 9.0, 2H, Ar-*H*), 6.96 (d, *J* 9.0, 2H, Ar-*H*), 3.94 (s, 2H, C$H_2$), 3.82 (s, 3H, OC$H_3$), 1.33 (s, 9H, C$Me_3$). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 164.1, 161.6, 130.8, 130.5, 114.3, 83.5, 62.4, 55.7, 27.8; LRMS (ESI) *m/z* 309 (30%, $[M+Na]^+$), 595 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 309.0767 $[M+Na]^+$, $C_{13}H_{18}O_5SNa$ requires *m/z* 309.0767. Data in accordance with that previously reported.[78]

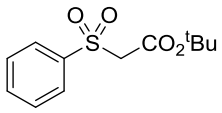
**_tert_-Butyl 2-[(4-fluorophenyl)sulfonyl]acetate (49d)**




Prepared according to general procedure F using *p*-fluorophenylboronic acid (35 mg, 0.25 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a colourless oil (45 mg, 66%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93-7.87 (m, 2H, Ar-*H*), 7.22-7.15 (m, 2H, Ar-*H*), 3.97 (s, 2H, C$H_2$), 1.32 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 166.1 (d, $J_{CF}$ 257.5), 161.3, 135.0 (d, $J_{CF}$ 3.5), 131.6 (d, $J_{CF}$ 9.5), 116.5 (d,

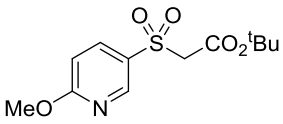
$J_{CF}$ 22.5), 83.8, 62.1, 27.7; $^{19}$F NMR (377 MHz, $CDCl_3$) δ -102.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2982, 1730 (CO), 1590, 1495, 1328 ($SO_2$), 1144 ($SO_2$), 1083; LRMS (ESI) *m/z* 297 (30%, $[M+Na]^+$), 571 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 297.0568 $[M+Na]^+$, $C_{12}H_{15}O_4FSNa$ requires *m/z* 297.0567.

**_tert_-Butyl 2-(phenylsulfonyl)acetate (49e)**



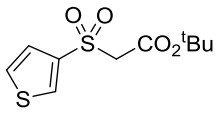

Prepared according to general procedure F using potassium phenyltrifluoroborate (46 mg, 0.25 mmol) and heating at 100 ºC. Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a colourless oil (44 mg, 76%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.90-7.86 (m, 2H, Ar-*H*), 7.65-7.59 (m, 1H, Ar-*H*), 7.52 (dd, *J* 8.5, 7.0, 2H, Ar-*H*), 3.97 (s, 2H, C$H_2$), 1.30 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.3, 139.0, 134.1, 129.2, 128.6, 83.7, 62.1, 27.7; LRMS (ESI) *m/z* 279 (30%, $[M+Na]^+$), 535 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 279.0660 $[M+Na]^+$, $C_{12}H_{16}O_4SNa$ requires *m/z* 279.0662. Data in accordance with that previously reported.[104]

**_tert_-Butyl 2-[(6-methoxypyridin-3-yl)sulfonyl]acetate (49f)**



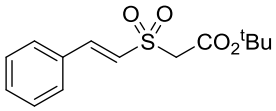

Prepared according to general procedure F using 2-methoxy-5-pyridylboronic acid (38 mg, 0.25 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a colourless oil (38 mg, 53%); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.74 (dd, *J* 2.5, 0.5, 1H, Ar-*H*), 8.05 (dd, *J* 9.0, 2.5, 1H, Ar-*H*), 6.90 (dd, *J* 9.0, 0.5, 1H, Ar-*H*), 4.06 (overlapping s, 5H, C$H_2$ and OC$H_3$), 1.45 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.4, 161.4, 149.5, 138.6, 128.1, 111.4, 84.0, 62.5, 54.5, 27.8; LRMS (ESI) *m/z* 288 (50%, $[M+Na]^+$), 597 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 288.0898 $[M+H]^+$, $C_{12}H_{18}NO_5S$ requires *m/z* 288.0900. Data in accordance with that previously reported.[78]

**_tert_-Butyl 2-(thiophen-3-ylsulfonyl)acetate (49g)**



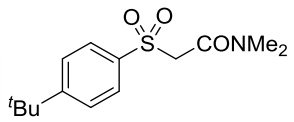
Prepared according to general procedure F using thienyl-3-boronic acid (32 mg, 0.25 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfone as a colourless oil (40 mg, 61%); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, *J* 3.0, 1.5, 1H, Ar-*H*), 7.41 (dd, *J* 5.0, 3.0, 1H, Ar-*H*), 7.38 (dd, *J* 5.0, 1.5, 1H, Ar-*H*), 3.99 (s, 2H, C*H*$_2$), 1.34 (s, 9H, C*Me*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.3, 139.3, 133.7, 128.0, 126.5, 83.7, 62.3, 27.8; LRMS (ESI) *m/z* 285 (40%, $[M+Na]^+$), 547 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 285.0225 $[M+Na]^+$, $C_{10}H_{14}O_4S_2Na$ requires *m/z* 285.0226. Data in accordance with that previously reported.[78]

**_tert_-Butyl (_E_)-2-(styrylsulfonyl)acetate (49h)**



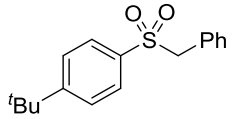
Prepared according to general procedure F using potassium *trans*-styryltrifluoroborate (37 mg, 0.25 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 7:3) afforded the titled sulfone as a colourless oil (30 mg, 45%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* 15.5, 1H, PhC*H*), 7.46 (dd, *J* 7.5, 2.0, 2H, Ar-*H*), 7.40-7.33 (m, 3H, Ar-*H*), 7.00 (d, *J* 15.5, 1H, $SO_2$C*H*), 3.93 (s, 2H, C*H*$_2$), 1.41 (s, 9H, C*Me*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.9, 145.2, 132.1, 131.6, 129.2, 128.7, 125.0, 83.9, 61.3, 27.9; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2937, 1726 (CO), 1623, 1493, 1301 ($SO_2$), 1149 ($SO_2$), 1091; LRMS (ESI) *m/z* 305 (70%, $[M+Na]^+$), 587 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 305.0816 $[M+Na]^+$, $C_{14}H_{18}O_4SNa$ requires *m/z* 305.0818.

**2-[(4-(*tert*-Butyl)phenyl)sulfonyl]-*N*,*N*-dimethylacetamide (49i)**



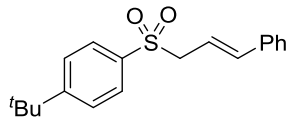

Prepared according to general procedure F using *tert*-butylphenylboronic acid (45 mg, 0.25 mmol) and 2-bromo-*N*,*N*-dimethylacetamide (90 $\mu$L, 0.75 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled sulfone as a colourless oil (57 mg, 80%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* 8.5, 2H, Ar-*H*), 7.50 (d, *J* 8.5, 2H, Ar-*H*), 4.17 (s, 2H, C$H_2$), 3.10 (s, 3H, N*Me*), 2.91 (s, 3H, N*Me*), 1.28 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.4, 158.1, 136.1, 128.3, 126.2, 59.9, 38.7, 36.1, 35.3, 31.1; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2962, 1649 (CO), 1593, 1494, 1398, 1317 ($SO_2$), 1154, ($SO_2$), 1081; LRMS (ESI) *m/z* 306 (20%, $[M+Na]^+$), 589 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 306.1133 $[M+Na]^+$, $C_{14}H_{21}NO_3SNa$ requires *m/z* 306.1134.

**1-(Benzylsulfonyl)-4-(*tert*-butyl)benzene (49j)**



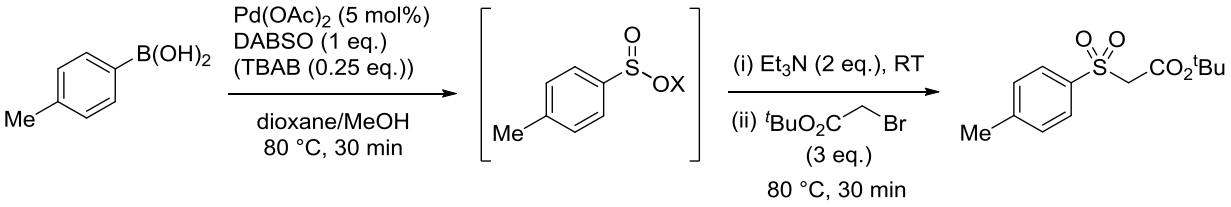

Prepared according to general procedure F using *tert*-butylphenylboronic acid (45 mg, 0.25 mmol) and benzyl bromide (90 $\mu$L, 0.75 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (54 mg, 75%); mp 102-103 °C ($CH_2Cl_2$) [lit.[76] mp 98-101 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* 8.5, 2H, Ar-*H*), 7.48 (d, *J* 8.5, 2H, Ar-*H*), 7.38-7.31 (m, 1H, Ar-*H*), 7.32-7.26 (m, 2H, Ar-*H*), 7.13 (d, *J* 7.0, 2H, Ar-*H*), 4.32 (s, 2H, C$H_2$), 1.36 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.7, 135.0, 130.9, 128.7, 128.5, 128.5, 128.3, 125.9, 63.0, 35.3, 31.1; LRMS (ESI) *m/z* 311 (70%, $[M+Na]^+$), 599 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 311.1076 $[M+Na]^+$, $C_{17}H_{20}O_2SNa$ requires *m/z* 311.1076. Data in accordance with that previously reported.[76]

**1-(*tert*-Butyl)-4-(cinnamylsulfonyl)benzene (49k)**



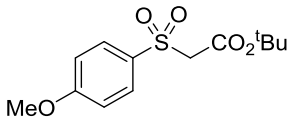

Prepared according to general procedure F using *tert*-butylphenylboronic acid (45 mg, 0.25 mmol) and 3-bromo-1-phenyl-1-propene (148 mg, 0.75 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a yellow solid (42 mg, 52%); mp 117-118 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* 8.5, 2H, Ar-*H*), 7.57 (d, *J* 8.5, 2H, Ar-*H*), 7.38-7.26 (m, 5H, Ar-*H*), 6.42 (dt, *J* 16.0, 1.0, 1H, PhC*H*), 6.15 (dt, *J* 16.0, 7.5, 1H, $CH_2$C*H*), 3.97 (dd, *J* 7.5, 1.0, 2H, C$H_2$), 1.37 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 157.7, 139.1, 135.9, 135.5, 128.7, 128.5, 128.4, 126.6, 126.1, 115.3, 60.6, 35.3, 31.1; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2928, 1588, 1490, 1306 ($SO_2$), 1155 ($SO_2$), 1038; LRMS (ESI) *m/z* 337 (100%, $[M+Na]^+$), 651 (80%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 337.1234 $[M+Na]^+$, $C_{19}H_{22}O_2SNa$ requires *m/z* 337.1233.

### 6.5.2 General Procedure G for the two-step synthesis of sulfones from boronic acids, DABSO, and alkyl halides as exemplified by the preparation of *tert*-butyl 2-tosylacetate (49b)



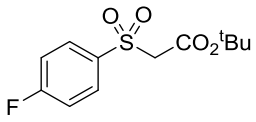

To a reaction tube was added DABSO (60 mg, 0.25 mmol), *p*-tolylboronic acid (33 mg, 0.25 mmol) and $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol). After addition of dioxane (0.8 mL) and MeOH (0.8 mL) the resulting mixture was heated at 80 ºC and stirred at this temp. for 30 min. The reaction was then allowed to cool to room temp., $Et_3N$ (70 $\mu$L, 0.50 mmol) added and the mixture stirred for 1 min. *tert*-Butylbromoacetate (110 $\mu$L, 0.75 mmol) was then added and the reaction was heated at 80 ºC and stirred at this temp. for 30 min. The reaction mixture was allowed to cool to room temp. and filtered through a plug of silica before removing the solvent *in vacuo*. Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (60 mg, 88%). Data as outlined above.

#### *tert*-Butyl 2-[(4-methoxyphenyl)sulfonyl]acetate (49c)



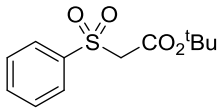

Prepared according to general procedure G using *p*-methoxyphenylboronic acid (38 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a colourless oil (54 mg, 78%). Data as outlined above.

**_tert_-Butyl 2-[(4-fluorophenyl)sulfonyl]acetate (49d)**



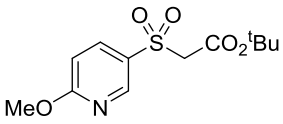

Prepared according to general procedure G using *p*-fluorophenylboronic acid (35 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a colourless oil (57 mg, 83%). Data as outlined above.

**_tert_-Butyl 2-(phenylsulfonyl)acetate (49e)**



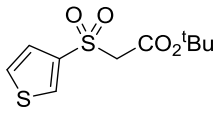

Prepared according to general procedure G using phenylboronic acid (30 mg, 0.25 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a colourless oil (59 mg, 91%). Data as outlined above.

**_tert_-Butyl 2-[(6-methoxypyridin-3-yl)sulfonyl]acetate (49f)**



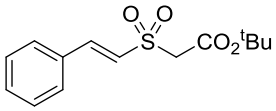

Prepared according to general procedure G using 2-methoxy-5-pyridylboronic acid (38 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a colourless oil (42 mg, 59%). Data as outlined above.

**_tert_-Butyl 2-(thiophen-3-ylsulfonyl)acetate (49g)**



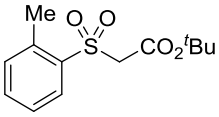
Prepared according to general procedure G using thienyl-3-boronic acid (32 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfone as a colourless oil (42 mg, 64%). Data as outlined above.

**_tert_-Butyl (_E_)-2-(styrylsulfonyl)acetate (49h)**



Prepared according to general procedure G using *trans*-2-phenylvinylboronic acid (37 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 7:3) afforded the titled sulfone as a colourless oil (24 mg, 35%). Data as outlined above.

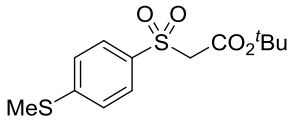
**_tert_-Butyl 2-(_o_-tolylsulfonyl)acetate (55a)**



Prepared according to general procedure G using 2-methylphenylboronic acid (33 mg, 0.25 mmol) and running the first step for 3hr. Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a yellow solid (46 mg, 68%); mp 65-66 °C ($CH_2Cl_2$) [lit.[78] mp 66-67 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* 8.0, 1.5, 1H, Ar-*H*), 7.47 (app. td, *J* 7.5, 1.5, 1H, Ar-*H*), 7.34-7.31 (m, 1H, Ar-*H*), 7.29 (ddd, *J* 7.5, 1.5, 0.5, 1H, Ar-*H*), 4.02 (s, 2H, C$H_2$), 2.65 (s, 3H, Ar*Me*), 1.22 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.1, 138.2, 137.1, 134.1, 132.7, 130.7, 126.5, 83.5, 61.6, 27.6, 20.3; LRMS (ESI) *m/z* 293 (40%, $[M+Na]^+$), 563 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 293.0817

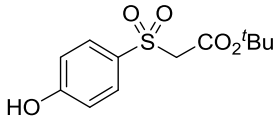
$[M+Na]^+$, $C_{13}H_{18}O_4SNa$ requires *m/z* 293.0818. Data in accordance with that previously reported.[78]

### *tert*-Butyl 2-{[4-(methylthio)phenyl]sulfonyl}acetate (55b)



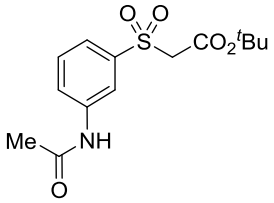

Prepared according to general procedure G using 4-(methylthio)phenylboronic acid (42 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol) and running the first step for 1 hr. Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as an off-white solid (62 mg, 82%); mp 44-45 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* 8.5, 2H, Ar-*H*), 7.37 (d, *J* 8.5, 2H, Ar-*H*), 4.04 (s, 2H, C*H*$_2$), 2.56 (s, 3H, S*Me*), 1.42 (s, 9H, C*Me*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.4, 147.9, 134.5, 128.8, 125.2, 83.7, 62.2, 27.7, 14.7; LRMS (ESI) *m/z* 325 (40%, $[M+Na]^+$), 627 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 325.0537 $[M+Na]^+$, $C_{13}H_{18}O_4S_2Na$ requires *m/z* 325.0539. Data in accordance with that previously reported.[78]

### *tert*-Butyl 2-[(4-hydroxyphenyl)sulfonyl]acetate (55c)



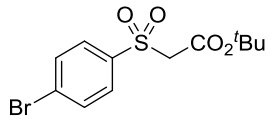

Prepared according to general procedure G using 4-hydroxyphenylboronic acid (34 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol) and running the first step for 1 hr. Purification by flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfone as a colourless oil (58 mg, 85%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* 9.0, 2H, Ar-*H*), 6.85 (d, *J* 9.0, 2H, Ar-*H*), 3.96 (s, 2H, C*H*$_2$), 1.34 (s, 9H, C*Me*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.1, 161.3, 131.0, 129.7, 116.0, 84.1, 62.5, 27.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3386 (br. OH), 1728 (CO), 1602, 1586, 1302 ($SO_2$), 1289, 1135 ($SO_2$); LRMS (ESI) *m/z* 295 (20%, $[M+Na]^+$), 567 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 295.0610 $[M+Na]^+$, $C_{12}H_{26}O_5SNa$ requires *m/z* 295.0611. Data in accordance with that previously reported.[78]

**_tert_-Butyl 2-[(3-acetamidophenyl)sulfonyl]acetate (55d)**



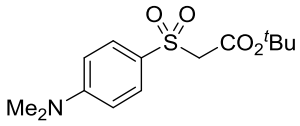
Prepared according to general procedure G using 3-acetamidophenylboronic acid (45 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol) and running the first step for 1 hr. Purification by flash column chromatography (petrol/EtOAc 3:7) afforded the titled sulfone as a colourless oil (60 mg, 77%); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.11 (ddd, *J* 8.0, 2.0, 1.0, 1H, Ar-*H*), 7.90 (s, 1H, CON*H*), 7.85 (app. t, *J* 2.0, 1H, Ar-*H*), 7.58 (ddd, *J* 8.0, 2.0, 1.0, 1H, Ar-*H*), 7.47 (app. t, *J* 8.0, 1H, Ar-*H*), 4.00 (s, 2H, C$H_2$), 2.15 (s, 3H, CO*Me*), 1.29 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.8, 161.1, 139.3, 139.2, 130.1, 125.2, 123.4, 118.9, 83.9, 61.9, 27.7, 24.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3356 (NH), 2982, 1730 ((OR)C=O), 1675 ((NH)C=O), 1538, 1480, 1302 ($SO_2$), 1256, 1139 ($SO_2$); LRMS (ESI) *m/z* 336 (100%, $[M+Na]^+$), 649 (20%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 336.0873 $[M+Na]^+$, $C_{14}H_{19}NO_5SNa$ requires *m/z* 336.0876.

**_tert_-Butyl 2-[(4-bromophenyl)sulfonyl]acetate (55e)**



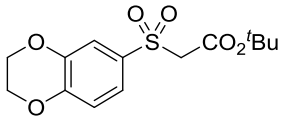
Prepared according to general procedure G using 4-bromophenylboronic acid (50 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as an off-white solid (49 mg, 58%); mp 74-75 °C ($CH_2Cl_2$) [lit.[78] mp 73-74 °C]; $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* 8.5, 2H, Ar-*H*), 7.66 (d, *J* 8.5, 2H, Ar-*H*), 3.96 (s, 2H, C$H_2$), 1.33 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.2, 137.9, 132.5, 130.2, 129.6, 84.0, 62.0, 27.7; LRMS (ESI) *m/z* 357 (90%, $[M(^{79}Br)+Na]^+$), 359 (100%, $[M(^{81}Br)+Na]^+$); HRMS (ESI) found *m/z* 358.9745 $[M(^{81}Br)+Na]^+$, $C_{12}H_{15}O_4{}^{81}BrSNa$ requires *m/z* 358.9746. Data in accordance with that previously reported.[78]

**_tert_-Butyl 2-[(4-(dimethylamino)phenyl)sulfonyl]acetate (55f)**



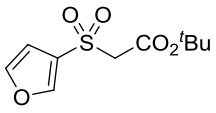
Prepared according to general procedure G using 4-dimethylaminophenylboronic acid (41 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfone as an off-white solid (39 mg, 52%); mp 98-99 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* 9.0, 2H, Ar-*H*), 6.62 (d, *J* 9.0, 2H, Ar-*H*), 3.90 (s, 2H, C$H_2$), 3.00 (s, 6H, N$Me_2$), 1.34 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.0, 153.7, 130.3, 123.9, 110.7, 83.1, 62.7, 40.1, 27.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2975, 1722 (CO), 1599, 1314 ($SO_2$), 1295, 1148 ($SO_2$), 1082; LRMS (ESI) *m/z* 322 (70%, $[M+Na]^+$), 621 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 322.1081 $[M+Na]^+$, $C_{14}H_{21}NO_4SNa$ requires *m/z* 322.1084.

**_tert_-Butyl 2-{(2,3-dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl}acetate (55g)**



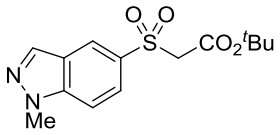
Prepared according to general procedure G using 1,4-benzodioxane-6-boronic acid (45 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as an off-white solid (67 mg, 85%); mp 78-79 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* 2.5, 1H, Ar-*H*), 7.44 (dd, *J* 8.5, 2.5, 1H, Ar-*H*), 7.03 (d, *J* 8.5, 1H, Ar-*H*), 4.50-4.18 (m, 4H, OC$H_2$), 4.01 (s, 2H, C$H_2$), 1.43 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.4, 148.6, 143.6, 131.3, 122.3, 118.3, 117.9, 83.5, 64.6, 64.1, 62.4, 27.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2986, 2934, 1736 (CO), 1495, 1311 ($SO_2$), 1157 ($SO_2$), 1074; LRMS (ESI) *m/z* 337 (50%, $[M+Na]^+$), 651 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 337.0714 $[M+Na]^+$, $C_{14}H_{18}O_6SNa$ requires *m/z* 337.0716.

**_tert_-Butyl 2-(furan-3-ylsulfonyl)acetate (55h)**



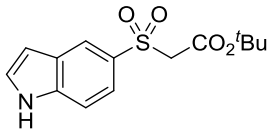
Prepared according to general procedure G using furan-3-boronic acid (28 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 2:3) afforded the titled sulfone as a yellow oil (29 mg, 48%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* 1.5, 1.0, 1H, Ar-*H*), 7.47 (app. t, *J* 2.0, 1H, Ar-*H*), 6.69 (dd, *J* 2.0, 1.0, 1H, Ar-*H*), 3.98 (s, 2H, C*H*$_2$), 1.38 (s, 9H, C*Me*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.4, 147.9, 144.7, 126.9, 109.3, 83.9, 62.3, 27.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2982, 1729 (CO), 1498, 1327 ($SO_2$), 1152 ($SO_2$), 1008; LRMS (ESI) *m/z* 269 (70%, $[M+Na]^+$), 515 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 269.0454 $[M+Na]^+$, $C_{10}H_{14}O_5SNa$ requires *m/z* 269.0454.

**_tert_-Butyl 2-[(1-methyl-1H-indazol-5-yl)sulfonyl]acetate (55i)**



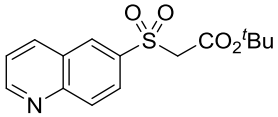
Prepared according to general procedure G using 1-methylindazole-5-boronic acid (44 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfone as an off-white solid (56 mg, 72%); mp 98-99 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, *J* 2.0, 1.0, 1H, Ar-*H*), 8.19 (d, *J* 1.0, 1H, Ar-*H*), 7.93 (dd, *J* 9.0, 2.0, 1H, Ar-*H*), 7.57 (app. dt, *J* 9.0, 1.0, 1H, Ar-*H*), 4.17 (s, 3H, N*Me*), 4.10 (s, 2H, C*H*$_2$), 1.39 (s, 9H, C*Me*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.5, 141.4, 134.8, 131.1, 125.2, 124.5, 123.2, 109.6, 83.6, 62.5, 36.0, 27.7; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3010, 2947, 1719 (CO), 1410, 1319 ($SO_2$), 1157 ($SO_2$); LRMS (ESI) *m/z* 333 (10%, $[M+Na]^+$), 643 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 333.0878 $[M+Na]^+$, $C_{14}H_{18}N_2O_4SNa$ requires *m/z* 333.0880.

**_tert_-Butyl 2-[(1H-indol-5-yl)sulfonyl]acetate (55j)**



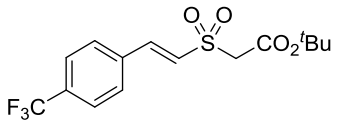
Prepared according to general procedure G using 5-indolylboronic acid (40 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol) and running the first step for 1 hr. Purification by flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled sulfone as an off-white solid (46 mg, 62%); mp 102-103 °C ($CH_2Cl_2$) [lit.[78] mp 104-105 °C];; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.72 (br. s, 1H, N*H*), 8.20 (app. dt, *J* 2.0, 1.0, 1H, Ar-*H*), 7.64 (dd, *J* 8.5, 2.0, 1H, Ar-*H*), 7.45 (app. dt, *J* 8.5, 1.0, 1H, Ar-*H*), 7.30 (dd, *J* 3.5, 2.0, 1H, Ar-*H*), 6.62 (ddd, *J* 3.5, 2.0, 1.0, 1H, Ar-*H*), 4.00 (s, 2H, C$H_2$), 1.26 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.8, 138.4, 129.9, 127.4, 127.0, 123.0, 121.3, 111.6, 104.2, 83.4, 62.8, 27.7; LRMS (ESI) *m/z* 318 (10%, $[M+Na]^+$), 613 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 318.0769 $[M+Na]^+$, $C_{14}H_{17}NO_4SNa$ requires *m/z* 318.0771. Data in accordance with that previously reported.[78]

**_tert_-Butyl 2-(quinolin-6-ylsulfonyl)acetate (55k)**



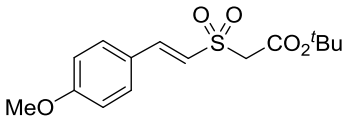
Prepared according to general procedure G using quinolone-6-boronic acid (43 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a colourless oil (15 mg, 20%); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.04 (dd, *J* 4.5, 2.0, 1H, Ar-*H*), 8.47 (d, *J* 2.0, 1H, Ar-*H*), 8.26 (ddd, *J* 8.5, 2.0, 1.0, 1H, Ar-*H*), 8.23 (app. dt, *J* 9.0, 1.0, 1H, Ar-*H*), 8.09 (dd, *J* 9.0, 2.0, 1H, Ar-*H*), 7.51 (dd, *J* 8.5, 4.5, 1H, Ar-*H*), 4.07 (s, 2H, C$H_2$), 1.27 (s, 9H, C$Me_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.2, 153.7, 149.9, 137.4, 136.6, 131.2, 130.7, 127.1, 126.8, 122.8, 83.9, 62.0, 27.7; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2980, 1728 (CO), 1493, 1315 ($SO_2$), 1139 ($SO_2$), 1071; LRMS (ESI) *m/z* 308 (100%, $[M+H]^+$); HRMS (ESI) found *m/z* 308.0950 $[M+H]^+$, $C_{15}H_{18}NO_4S$ requires *m/z* 308.0951.

**_tert_-Butyl (_E_)-2-[(4-(trifluoromethyl)styryl)sulfonyl]acetate (55m)**



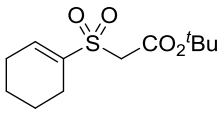
Prepared according to general procedure G using *trans*-2-(4-trifluoromethylphenyl)vinylboronic acid (54 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as an off-white solid (35 mg, 39%); mp 110-111 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* 8.0, 2H, Ar-*H*), 7.61-7.56 (m, 3H, Ar-*H* and $SO_2CHCH$), 7.12 (d, *J* 15.5, 1H, $SO_2CH$), 3.95 (s, 2H, $CH_2$), 1.42 (s, 9H, $CMe_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.8, 143.1, 135.4 (q, $J_{CF}$ 1.0), 133.0 (q, $J_{CF}$ 33.0), 128.9, 127.7, 126.2 (q, $J_{CF}$ 4.0), 123.6 (q, $J_{CF}$ 272.5), 84.2, 61.1, 27.9; $^{19}$F NMR (377 MHz, $CDCl_3$) δ -63.0; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2989, 1723 (CO), 1615, 1319 ($SO_2$), 1137 ($SO_2$), 1108, 1064; LRMS (ESI) *m/z* 373 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 373.0694 $[M+Na]^+$, $C_{15}H_{17}O_4F_3SNa$ requires *m/z* 373.0692.

**_tert_-Butyl (_E_)-2-[(4-methoxystyryl)sulfonyl]acetate (55n)**



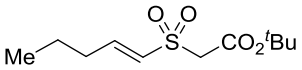
Prepared according to general procedure G using trans-2-(4-methoxyphenyl)vinylboronic, acid (45 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a colourless oil (35 mg, 45%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* 15.5, 1H, $SO_2CHCH$), 7.41 (d, *J* 9.0, 2H, Ar-*H*), 6.86 (d, *J* 9.0, 2H, Ar-*H*), 6.82 (d, *J* 15.5, 1H, $SO_2CH$), 3.91 (s, 2H, $CH_2$), 3.78 (s, 3H, O*Me*), 1.40 (s, 9H, $CMe_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 162.3, 162.0, 144.9, 130.6, 124.7, 122.0, 114.6, 83.8, 61.5, 55.48, 27.9; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2979, 1728 (CO), 1601, 1512, 1309 ($SO_2$), 1129 ($SO_2$), 1026; LRMS (ESI) *m/z* 335 (50%, $[M+Na]^+$), 647 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 335.0922 $[M+Na]^+$, $C_{15}H_{20}O_5SNa$ requires *m/z* 335.0924.

**_tert_-Butyl 2-(cyclohex-1-en-1-ylsulfonyl)acetate (55o)**



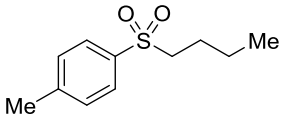
Prepared according to general procedure G using 1-cyclohexen-1-yl-boronic acid (32 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol) and running the first step for 1 hr. Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (60 mg, 92%); mp 52-53 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.99 (tt, *J* 4.0, 2.0, 1H, $CH_2CH$), 3.87 (s, 2H, $SO_2CH_2$), 2.43-2.39 (m, 2H, $CH_2$), 2.35-2.29 (m, 2H, $CH_2$), 1.85-1.77 (m, 2H, $CH_2$), 1.72-1.65 (m, 2H, $CH_2$), 1.49 (s, 9H, $CMe_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.7, 141.4, 138.0, 83.4, 58.4, 27.8, 25.6, 23.5, 21.9, 20.8; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2948, 1723 (CO), 1644, 1311 ($SO_2$), 1288, 1134 ($SO_2$); LRMS (ESI) *m/z* 283 (60%, $[M+Na]^+$), 543 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 283.0972 $[M+Na]^+$, $C_{12}H_{20}O_4SNa$ requires *m/z* 283.0975.

**_tert_-Butyl (_E_)-2-(pent-1-en-1-ylsulfonyl)acetate (55p)**



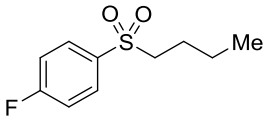
Prepared according to general procedure G using penten-1-yl-boronic acid (29 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol) and running the first step for 1 hr. Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a colourless oil (23 mg, 37%); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.90 (dt, *J* 15.0, 7.0, 1H, $SO_2CHCH$), 6.43 (dt, *J* 15.0, 1.5, 1H, $SO_2CH$), 3.82 (s, 2H, $SO_2CH_2$), 2.18-2.25 (m, 2H, $CHCH_2$), 1.50-1.44 (m, 2H, $CH_3CH_2$), 1.43 (s, 9H, $CMe_3$), 0.90 (t, *J* 7.5, 3H, $CH_2CH_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 161.9, 150.0, 128.2, 83.8, 60.9, 33.5, 27.9, 20.8, 13.6; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2965, 1730 (CO), 1635, 1323 ($SO_2$), 1294, 1132 ($SO_2$); LRMS (ESI) *m/z* 271 (70%, $[M+Na]^+$), 519 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 271.0971 $[M+Na]^+$, $C_{11}H_{20}O_4SNa$ requires *m/z* 271.0975.

**1-(Butylsulfonyl)-4-methylbenzene (56)**




Prepared according to general procedure G using *p*-tolylboronic acid (33 mg, 0.25 mmol) and *n*-butyl iodide (85 $\mu$L, 0.75 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a colourless oil (41 mg, 77%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* 8.0, 2H, Ar-*H*), 7.38 (d, *J* 8.0, 2H, Ar-*H*), 3.17-3.00 (m, 2H, $SO_2CH_2$), 2.48 (s, 3H, Ar*Me*), 1.70 (tt, *J* 8.0, 6.5, 2H, $SO_2CH_2CH_2$), 1.41 (app. sext., *J* 7.5, 2H, $CH_3CH_2$), 0.91 (t, *J* 7.5, 3H, $CH_3CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.5, 136.3, 129.9, 128.1, 56.2, 24.7, 21.6 (2C), 13.5; LRMS (ESI) *m/z* 235 (30%, $[M+Na]^+$), 447 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 235.0762 $[M+Na]^+$, $C_{11}H_{16}O_2SNa$ requires *m/z* 235.0763. Data in accordance with that previously reported.[200]

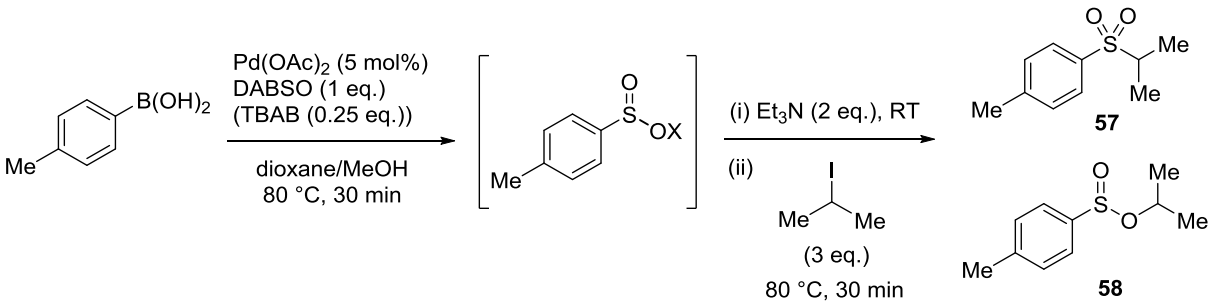
**1-(Butylsulfonyl)-4-fluorobenzene (54)**




Prepared according to general procedure G using *p*-fluorophenylboronic acid (35 mg, 0.25 mmol), TBAB (20 mg, 0.0625 mmol) and *n*-butyl iodide (85 $\mu$L, 0.75 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a colourless oil (34 mg, 63%); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.91-7.81 (m, 2H, Ar-*H*), 7.21-7.16 (m, 2H, Ar-*H*), 3.12-2.90 (m, 2H, $SO_2CH_2$), 1.70-1.53 (m, 2H, $SO_2CH_2CH_2$), 1.32 (app. sext., *J* 7.5, 2H, $CH_3CH_2$), 0.83 (t, *J* 7.5, 3H, $CH_3CH_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 165.8 (d, $J_{CF}$ 256.5), 135.3 (d, $J_{CF}$ 3.0), 130.9 (d, $J_{CF}$ 9.5), 116.6 (d, $J_{CF}$ 22.5), 56.2, 24.7, 21.5, 13.5; $^{19}$F NMR (377 MHz, $CDCl_3$) δ -103.7; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2963, 1591, 1493, 1317 ($SO_2$), 1288, 1141 ($SO_2$); LRMS (ESI) *m/z* 239 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 239.0513 $[M+Na]^+$, $C_{10}H_{13}O_2FSNa$ requires *m/z* 239.0513.

.

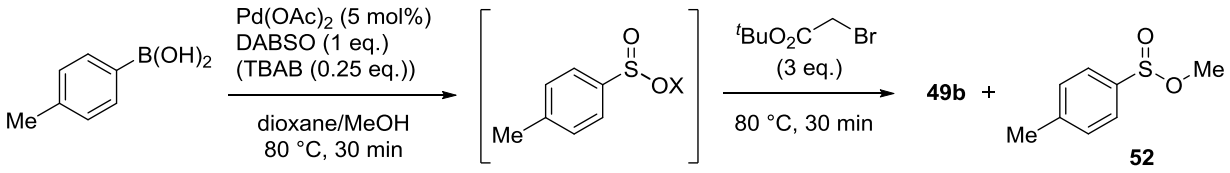
**1-(*Iso*propylsulfonyl)-4-methylbenzene (57)**




Prepared according to general procedure G using *p*-tolylboronic acid (33 mg, 0.25 mmol) and *iso*propyl iodide (75 $\mu$L, 0.75 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone **57** as a white solid (28 mg, 52%) and sulfinic acid ester **58** as a colourless oil (5 mg, 10%); **57**: mp 76-77 °C ($CH_2Cl_2$) [lit.[201] mp 76-77 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* 8.5, 2H, Ar-*H*), 7.29 (d, *J* 8.5, 2H, Ar-*H*), 3.10 (hept., *J* 7.0, 1H, C*H*($CH_3$)$_2$), 2.38 (s, 3H, Ar*Me*), 1.21 (d, *J* 7.0, 6H, CHC*H*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.5, 134.0, 129.7, 129.1, 55.6, 21.6, 15.8; LRMS (ESI) *m/z* 221 (20%, $[M+Na]^+$), 419 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 221.0607 $[M+Na]^+$, $C_{10}H_{14}O_2SNa$ requires *m/z* 221.0607. Data in accordance with that previously reported.[201]

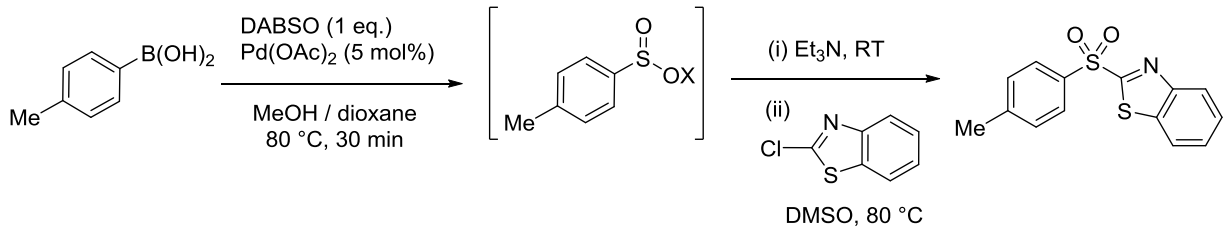
**58**: $^1$H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* 8.0 Hz, 2H, Ar-*H*), 7.26 (d, *J* 8.0 Hz, 2H, Ar-*H*), 4.53 (hept., *J* 6.0 Hz, 1H, C*H*$CH_3$), 2.35 (s, 3H, Ar*Me*), 1.31 (d, *J* 6.0 Hz, 3H, CHC*H*$_3$), 1.18 (d, *J* 6.0 Hz, 3H, CHC*H*$_3$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 142.7, 142.5, 129.6, 125.0, 72.7, 24.0, 23.8, 21.5; LRMS (ESI) *m/z* 199 (60%, $[M+H]^+$), 221 (100%, $[M+Na]^+$), 419 (50%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 221.0607 $[M+Na]^+$, $C_{10}H_{14}O_2SNa$ requires *m/z* 221.0607.Data in accordance with that previously reported.[202]

**Methyl 4-methylbenzenesulfinate (52)**




Prepared according to general procedure G using *p*-tolylboronic acid (33 mg, 0.25 mmol) and *tert*-butylbromoacetate (110 $\mu$L, 0.75 mmol) without triethylamine addition. Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded **49b** as a white solid (33 mg, 49%) and the titled sulfinic acid ester as a colourless oil; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* 8.0 Hz, 2H, Ar-*H*), 7.28 (d, *J* 8.0 Hz, 2H, Ar-*H*), 3.40 (s, 3H, SO*Me*), 2.36 (s, 3H, Ar*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 142.9, 140.9, 129.7, 125.4, 49.4, 21.5; LRMS (ESI) *m/z* 171 (80%, $[M+H]^+$), 193 (100%, $[M+Na]^+$), 363 (60%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 193.0295 $[M+Na]^+$, $C_8H_{10}O_2SNa$ requires *m/z* 193.0294. Data in accordance with that previously reported.[202]

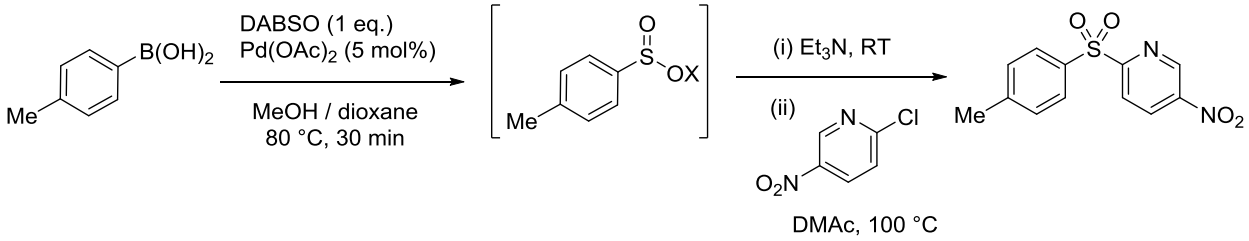
**Synthesis of 2-tosylbenzo[*d*]thiazole (59)**




To a reaction tube was added DABSO (60 mg, 0.25 mmol), *p*-tolylboronic acid (33 mg, 0.25 mmol) and $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol). After addition of dioxane (0.8 mL) and MeOH (0.8 mL) the resulting mixture was heated at 80 ºC and stirred at this temp. for 30 min. The reaction was then allowed to cool to room temp., $Et_3N$ (70 $\mu$L, 0.50 mmol) added and the mixture stirred for 1 min. Following this, the solvents were removed *in vacuo* and 2-chlorobenzothiazole (100 $\mu$L, 0.75 mmol) and DMSO (1.5 mL) were added. The resulting mixture was heated at 80 ºC and stirred at this temp. for 2 hr. After cooling, water (10 mL) and EtOAc (15 mL) were added, the two phases separated and the aqueous layer extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and

the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/$Et_2O$ 3:1) afforded the titled sulfone as a white solid (30 mg, 41%); mp 133-134 °C ($CH_2Cl_2$) [lit.[26b] mp 130-132 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.11-8.04 (m, 1H, Ar-*H*), 7.97 (d, *J* 8.5, 2H, Ar-*H*), 7.89-7.86 (m, 1H, Ar-*H*), 7.54-7.42 (m, 2H, Ar-*H*), 7.30 (d, *J* 8.5, 2H, Ar-*H*), 2.35 (s, 3H, Ar*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 167.7, 152.9, 145.9, 137.0, 135.5, 130.2, 129.0, 127.8, 127.5, 125.5, 122.2, 21.8; LRMS (ESI) *m/z* 312 (40%, $[M+Na]^+$), 601 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 312.0124 $[M+Na]^+$, $C_{14}H_{11}NO_2S_2Na$ requires *m/z* 312.0123. Data in accordance with that previously reported.[26b]

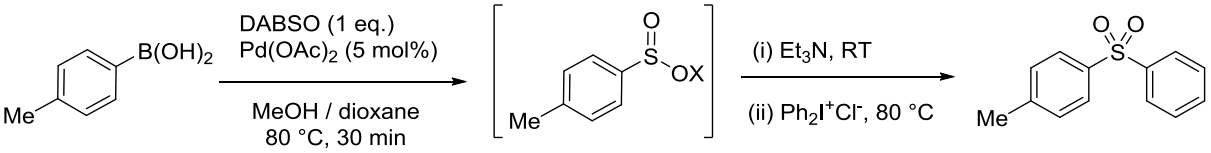
**Synthesis of 5-nitro-2-tosylpyridine (60)**




To a reaction tube was added DABSO (60 mg, 0.25 mmol), *p*-tolylboronic acid (33 mg, 0.25 mmol) and $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol). After addition of dioxane (0.8 mL) and MeOH (0.8 mL) the resulting mixture was heated at 80 ºC and stirred at this temp. for 30 min. The reaction was then allowed to cool to room temp., $Et_3N$ (70 $\mu$L, 0.50 mmol) added and the mixture stirred for 1 min. Following this, the solvents were removed *in vacuo* and 2-chloro-5-nitropyridine (80 mg, 0.50 mmol) and DMAc (1.5 mL) were added. The resulting mixture was heated at 100 ºC and stirred at this temp. for 1hr. After cooling, water (10 mL) and EtOAc (15 mL) were added, the two phases separated and the aqueous layer extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfone as an off-white solid (41 mg, 60%); mp 146-147 °C ($CH_2Cl_2$) [lit.[26a] mp 144-145 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.34 (dd, *J* 2.5, 0.5, 1H, Ar-*H*), 8.62 (dd, *J* 8.5, 2.5, 1H, Ar-*H*), 8.33 (dd, *J* 8.5, 0.5, 1H, Ar-*H*), 7.88 (d, *J* 8.5, 2H, Ar-*H*), 7.30 (d, *J* 8.5, 2H, Ar-*H*), 2.37 (s, 3H, Ar*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 163.6, 146.0, 145.7, 145.1, 134.3, 133.5, 130.1, 129.5, 122.4, 21.8; LRMS (ESI) *m/z* 301

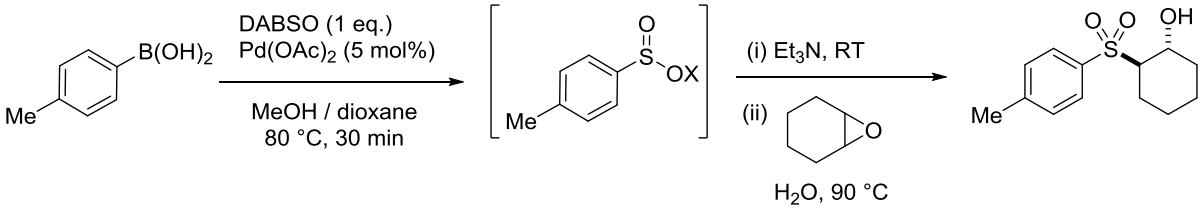
(100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 301.0254 $[M+Na]^+$, $C_{12}H_{10}N_2O_4SNa$ requires *m/z* 301.0254. Data in accordance with that previously reported.[26a]

**Synthesis of 1-methyl-4-(phenylsulfonyl)benzene (61)**



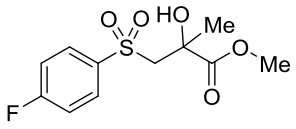

To a reaction tube was added DABSO (60 mg, 0.25 mmol), *p*-tolylboronic acid (33 mg, 0.25 mmol) and $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol). After addition of dioxane (0.8 mL) and MeOH (0.8 mL) the resulting mixture was heated at 80 ºC and stirred at this temp. for 30 min. The reaction was then allowed to cool to room temp., $Et_3N$ (70 $\mu$L, 0.50 mmol) added and the mixture stirred for 1 min. Following this, diphenyliodonium chloride (237 mg, 0.75 mmol) was added and the resulting mixture was heated at 80 ºC and stirred at this temp. for 6hr. The reaction mixture was allowed to cool to room temp. and filtered through a plug of silica before removing the solvent *in vacuo*. Purification by flash column chromatography (petrol/$Et_2O$ 3:2) afforded the titled sulfone as a white solid (47 mg, 81%); mp 124-125 °C ($CH_2Cl_2$) [lit.[81] mp 124-125 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* 8.5, 2H, Ar-*H*), 7.76 (d, *J* 8.5, 2H, Ar-*H*), 7.53-7.36 (m, 3H, Ar-*H*), 7.22 (d, *J* 8.5, 2H, Ar-*H*), 2.32 (s, 3H, Ar*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 144.2, 142.0, 138.7, 133.0, 129.9, 129.2, 127.7, 127.5, 21.6; LRMS (ESI) *m/z* 255 (100%, $[M+Na]^+$), 487 (90%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 255.0450 $[M+Na]^+$, $C_{13}H_{12}O_2SNa$ requires *m/z* 255.0450. Data in accordance with that previously reported.[81]

### 6.5.3 General procedure H for the synthesis of *β*-hydroxysulfones as exemplified by the preparation of 2-tosylcyclohexan-1-ol (34d)




To a reaction tube was added DABSO (60 mg, 0.25 mmol), *p*-tolylboronic acid (33 mg, 0.25 mmol) and $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol). After addition of dioxane (0.8 mL) and MeOH (0.8 mL) the resulting mixture was heated at 80 ºC and stirred at this temp. for 30 min. The reaction was then allowed to cool to room temp., $Et_3N$ (70 $\mu$L, 0.50 mmol) added and the mixture stirred for 1 min. Following this, the solvents were removed *in vacuo* and cyclohexene oxide (125 $\mu$L, 1.25 mmol) and $H_2O$ (1.5 mL) added. The resulting mixture was heated at 90 ºC and stirred at this temp. for 6hr. After cooling, sat. $NH_4Cl$ (10 mL) and subsequently $CH_2Cl_2$ (10 mL) were added, the two phases separated and the aqueous layer extracted with $CH_2Cl_2$ (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled sulfone as an off-white solid (44 mg, 69%). Data as outlined above (Section 6.3).

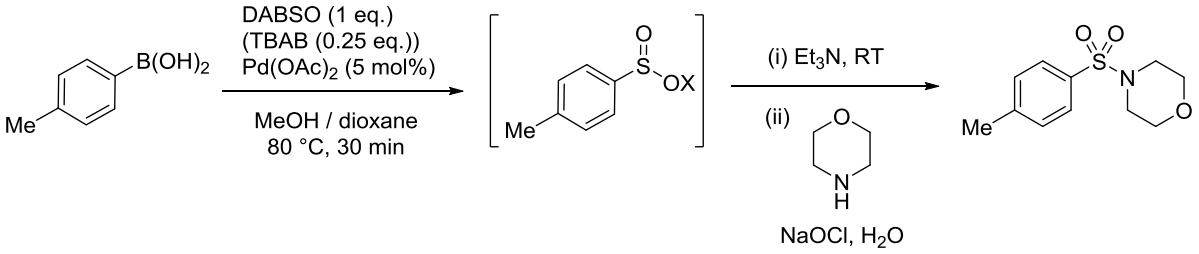
**Methyl 3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanoate (62)**




Prepared according to general procedure H using *p*-fluorophenylboronic acid (35 mg, 0.25 mmol), TBAB (20 mg, 0.0625 mmol) and methyl 2-methylglycidate (130 $\mu$L, 1.25 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled sulfone as an off-white solid (40 mg, 58%); mp 66-67 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.89-7.81 (m, 2H, Ar-*H*), 7.15 (dd, *J* 9.0, 8.0, 2H, Ar-*H*), 3.77 (s, 3H,

$CO_2$*Me*), 3.70 (d, *J* 15.0, 1H, $SO_2CH_2$), 3.59 (br. s, 1H, O*H*), 3.49 (d, *J* 15.0, 1H, $SO_2CH_2$), 1.38 (s, 3H, C(OH)*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 174.5, 165.8 (d, $J_{CF}$ 256.5), 136.7 (d, $J_{CF}$ 3.0), 131.1 (d, $J_{CF}$ 10.0), 116.4 (d, $J_{CF}$ 23.0), 72.3, 63.9, 53.6, 27.3; $^{19}$F NMR (377 MHz, $CDCl_3$) δ -103.3; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3468 (br. OH), 3080, 2952, 1750 (CO), 1590, 1316 ($SO_2$), 1145 ($SO_2$), 1083; LRMS (ESI) *m/z* 299 (100%, $[M+Na]^+$), 575 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 299.0362 $[M+Na]^+$, $C_{11}H_{13}O_5FSNa$ requires *m/z* 299.0360.

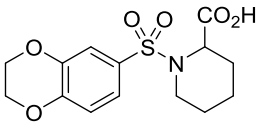
## 6.5.4 General Procedure I for the synthesis of substituted sulfonamides as exemplified by the preparation of 4-tosylmorpholine (63a)




To a reaction tube was added DABSO (60 mg, 0.25 mmol), *p*-tolylboronic acid (33 mg, 0.25 mmol) and $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol). After addition of dioxane (0.8 mL) and MeOH (0.8 mL) the resulting mixture was heated at 80 ºC and stirred at this temp. for 30 min. The reaction was then allowed to cool to room temp., $Et_3N$ (70 $\mu$L, 0.50 mmol) added and the mixture stirred for 1 min. Following this, the solvents were removed *in vacuo* and water (1.5 mL) and morpholine (110 $\mu$L, 1.25 mmol) were added. NaOCl (14.5 % aqueous solution, 320 $\mu$L, 0.75 mmol) was added to the mixture at 0 ºC and the reaction was allowed to warm to room temp. and stirred at this temp. for 16 hr. $NaS_2O_{3(aq)}$ (10 mL) was added and the mixture stirred for a further 20 mins. The aqueous mixture was then extracted with $CH_2Cl_2$ (3 × 15 mL) and the combined organic extracts were subsequently washed with 1M $HCl_{(aq)}$ (1 × 30 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfonamide as a white solid (49 mg, 82%); mp 148-149 °C ($CH_2Cl_2$) [lit.[203] mp 148-150 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* 8.5, 2H, Ar-*H*), 7.35 (d, *J* 8.5, 2H, Ar-*H*), 3.77-3.69 (m, 4H, $NCH_2CH_2$), 3.02-2.94 (m, 4H, $NCH_2CH_2$), 2.46 (s, 3H, Ar*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.9, 132.0, 129.7, 127.9, 66.1, 46.0, 21.5; LRMS (ESI) *m/z* 264 (100%, $[M+Na]^+$), 505 (80%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 264.0951

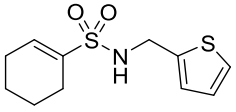
$[M+Na]^+$, $C_{11}H_{15}NO_3SNa$ requires *m/z* 264.0952. Data in accordance with that previously reported.[203]

**1-{(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)sulfonyl}piperidine-2-carboxylic acid (63b)**



Prepared according to general procedure I using 1,4-benzodioxane-6-boronic acid (45 mg, 0.25 mmol), TBAB (20 mg, 0.0625 mmol) and and (*D*,*L*)-pipecolinic acid (161 mg, 1.25 mmol). The aqueous acid wash (extracted with EtOAc) gave the pure titled sulfonamide as an off-white solid (46 mg, 56%) without further purification; mp 123-124 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* 2.0, 1H, Ar-*H*), 7.21 (dd, *J* 8.5, 2.0, 1H, Ar-*H*), 6.85 (d, *J* 8.5, 1H, Ar-*H*), 4.67 (app. d, *J* 6.0, 1H, C*H*$CO_2$H), 4.25 (s, 4H, OC$H_2$), 3.70-3.62 (m, 1H, NC$H_2$), 3.12 (td, *J* 12.5, 3.0, 1H, NC$H_2$), 2.10-2.03 (m, 1H, C$H_2$), 1.79-1.50 (m, 3H, C$H_2$), 1.47-1.16 (m, 2H, C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 176.7, 147.4, 143.5, 132.1, 120.9, 117.5, 116.8, 64.6, 64.2, 54.7, 42.5, 27.5, 24.5, 20.0; IR $\nu_{max}$ (neat)/cm$^{-1}$ 2940 (br. OH), 1715 (CO), 1493, 1315 ($SO_2$), 1285, 1150 ($SO_2$), 1055; LRMS (ESI) *m/z* 326 (100%, $[M-H]^-$); HRMS (ESI) found *m/z* 326.0698 $[M-H]^-$, $C_{14}H_{16}NO_6SNa$ requires *m/z* 326.0693.

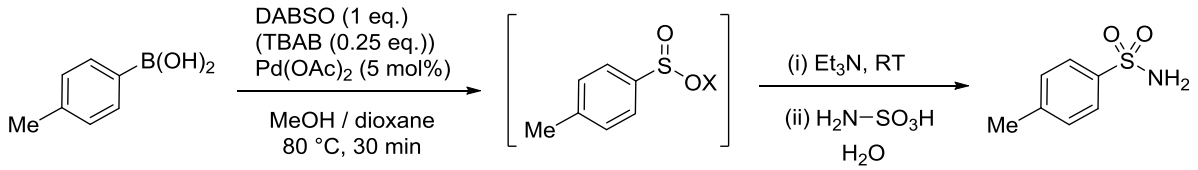
***N*-(Thiophen-2-ylmethyl)cyclohex-1-ene-1-sulfonamide (63c)**



Prepared according to general procedure I using 1-cyclohexen-1-yl-boronic acid (32 mg, 0.25 mmol), TBAB (20 mg, 0.0625 mmol) and 2-thiophenemethylamine (120 μL, 1.25 mmol) and running the first step for 1 hr. Purification by flash column chromatography (petrol/$Et_2O$ 1:1) afforded the titled sulfonamide as a white solid (53 mg, 82%); mp 120-121 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 1H, Ar-*H*), 6.98 (overlapping m, 2H, Ar-*H*), 6.85 (tt, *J* 3.5, 1.5, 1H, $CH_2$C*H*), 4.51 (t, *J* 6.0, 1H, N*H*), 4.39 (d, *J* 6.0, 2H, NHC$H_2$), 2.36-2.18 (m, 4H, C$H_2$), 1.74-1.67 (m, 2H, C$H_2$), 1.64-1.57 (m, 2H, C$H_2$);

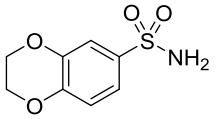
$^{13}$C NMR (100 MHz, $CDCl_3$) δ 139.5, 138.0, 137.6, 126.9, 126.7, 125.7, 41.7, 25.3, 23.0, 21.8, 20.9; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3265 (NH), 2947, 1724, 1434, 1311 ($SO_2$), 1292, 1140 ($SO_2$), 1050; LRMS (ESI) *m/z* 280 (70%, $[M+Na]^+$), 537 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 280.0437 $[M+Na]^+$, $C_{11}H_{15}NO_2S_2Na$ requires *m/z* 280.0436.

## 6.5.5 General procedure J for the synthesis of unsubstituted sulfonamides as exemplified by the preparation of 4-methylbenzenesulfonamide (64a)



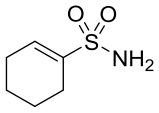

To a reaction tube was added DABSO (60 mg, 0.25 mmol), *p*-tolylboronic acid (33 mg, 0.25 mmol) and $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol). After addition of dioxane (0.8 mL) and MeOH (0.8 mL) the resulting mixture was heated at 80 ºC and stirred at this temp. for 30 min. The reaction was then allowed to cool to room temp., $Et_3N$ (70 $\mu$L, 0.50 mmol) added and the mixture stirred for 1 min. Following this, the solvents were removed *in vacuo* and water (1.5 mL) and hydroxylamine-*O*-sulfonic acid (141 mg, 1.25 mmol) added. The resulting mixture was stirred at room temp. for 2 hr before adding $NaHCO_{3(aq.)}$ (10 mL) and extracting with $CH_2Cl_2$ (3 × 15 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled sulfonamide as a white solid (37 mg, 87 %); mp 138-139 °C ($CH_2Cl_2$) [lit.[204] mp 136-138 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* 8.5, 2H, Ar-*H*), 7.24 (d, *J* 8.5, 2H, Ar-*H*), 4.84 (br s, 2H, N*H*$_2$), 2.36 (s, 3H, Ar*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 143.6, 139.0, 129.7, 126.5, 21.6; LRMS (ESI) *m/z* 194 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 194.0249 $[M+Na]^+$, $C_7H_9NO_2SNa$ requires *m/z* 194.0246. Data in accordance with that previously reported.[204]

**2,3-Dihydrobenzo[*b*][1,4]dioxine-6-sulfonamide (64b)**



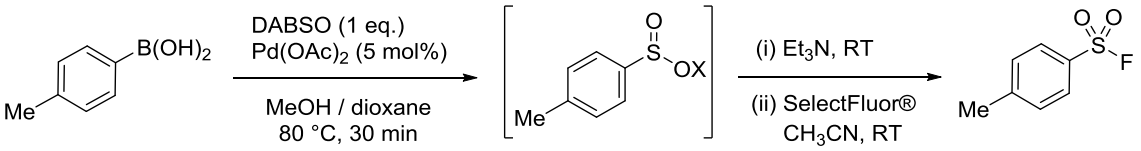
Prepared according to general procedure J using 1,4-benzodioxane-6-boronic acid (45 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol). Purification by flash column chromatography (petrol/$Et_2O$ 3:7) afforded the titled sulfonamide as a white solid (30 mg, 56 %); mp 194-195 °C ($CH_2Cl_2$); $^1$H NMR (400 MHz, MeOD-$d_4$) δ 7.28-7.23 (overlapping s, 1H, Ar-*H* and dd, *J* 8.5, 2.0, 1H, Ar-*H*), 6.85 (app. dt, *J* 8.5, 1.0, 1H, Ar-*H*), 4.23-4.16 (m, 4H, OC$H_2$); $^{13}$C NMR (100 MHz, MeOD-$d_4$) δ 147.0, 143.5, 136.1, 119.2, 117.1, 115.2, 64.5, 64.2; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3231 (NH), 2923, 1583, 1498, 1321 ($SO_2$), 1284, 1146 ($SO_2$), 1060; LRMS (ESI) *m/z* 238 (90%, $[M+Na]^+$), 453 (100%, $[2M+Na]^+$); HRMS (ESI) found *m/z* 238.0144 $[M+Na]^+$, $C_8H_9NO_4SNa$ requires *m/z* 238.0145.

**Cyclohex-1-ene-1-sulfonamide (64c)**



Prepared according to general procedure J using 1-cyclohexen-1-yl-boronic acid (32 mg, 0.25 mmol) and TBAB (20 mg, 0.0625 mmol) and running the first step for 1 hr. Purification by flash column chromatography (petrol/$Et_2O$ 1:4) afforded the titled sulfonamide as a colourless oil (27 mg, 67 %); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.76 (tt, *J* 4.0, 1.5, 1H, $CH_2CH$), 4.74 (br. s, 2H, N$H_2$), 2.31-2.38 (m, 2H, C$H_2$), 2.20-2.14 (m, 2H, C$H_2$), 1.74-1.65 (m, 2H, C$H_2$), 1.61-1.53 (m, 2H, C$H_2$); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 139.6, 135.7, 25.1, 23.0, 21.9, 20.9; IR $\nu_{max}$ (neat)/cm$^{-1}$ 3323 (NH), 3233 (NH), 2927, 1558, 1433, 1315 ($SO_2$), 1151 ($SO_2$); LRMS (ESI) *m/z* 184 (100%, $[M+Na]^+$); HRMS (ESI) found *m/z* 184.0405 $[M+Na]^+$, $C_6H_{11}NO_2SNa$ requires *m/z* 184.0403.

**Synthesis of 4-methylbenzenesulfonyl fluoride (65)**

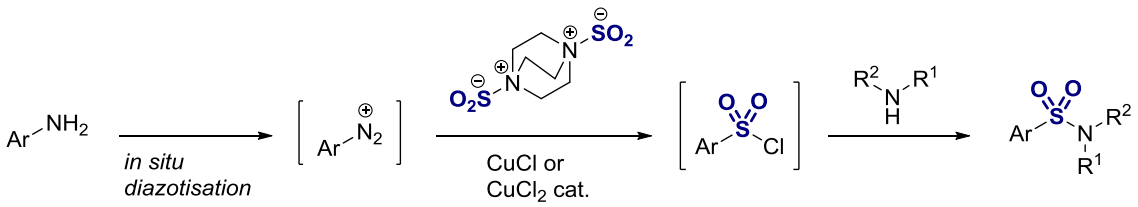



To a reaction tube was added DABSO (60 mg, 0.25 mmol), *p*-tolylboronic acid (33 mg, 0.25 mmol) and $Pd(OAc)_2$ (2.8 mg, 0.0125 mmol). After addition of dioxane (0.8 mL) and MeOH (0.8 mL) the resulting mixture was heated at 80 ºC and stirred at this temp. for 30 min. The reaction was then allowed to cool to room temp., $Et_3N$ (70 $\mu$L, 0.50 mmol) added and the mixture stirred for 1 min. Following this, the solvents were removed *in vacuo* and $CH_3CN$ (1.5 mL) and SelectFluor® (443 mg, 1.25 mmol) added. The resulting mixture was stirred at room temp. for 2 hr before adding water (10 mL) and extracting with $CH_2Cl_2$ (3 × 15 mL). The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Purification by flash column chromatography (petrol/$Et_2O$ 9:1) afforded the titled sulfonyl fluoride as a white solid (29 mg, 66 %); mp 39-40 °C ($CH_2Cl_2$) [lit.[205] mp 39 °C]; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* 8.5, 2H, Ar-*H*), 7.35 (d, *J* 8.5, 2H, Ar-*H*), 2.42 (s, 3H, Ar*Me*); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 147.1, 130.2, 130.0, 128.45, 21.8; $^{19}$F NMR (377 MHz, $CDCl_3$) δ 66.3; IR $\nu_{max}$ (neat)/cm$^{-1}$ 1594, 1403, 1309 ($SO_2$), 1203, 1185, 1124 ($SO_2$); HRMS (FI) found *m/z* 174.0151 ([M]$^+$, 100%), $C_7H_7FO_2S$ requires *m/z* 174.0156. Data in accordance with that previously reported.[205]

# Appendix. Copper-catalysed chlorosulfonylation of aryl diazonium salts with DABSO

Attempts to expand the applications of amine-sulfur dioxide complexes were made with their use in the Meerwein reaction.[51] With the well-established synthesis of *N*-aminosulfonamides *via* palladium-catalysed aminosulfonylation of aryl halides, the use of DABSO in copper catalysis to affect sulfonamide synthesis was appealing as a potentially cheaper, more versatile, and less toxic alternative.[77]

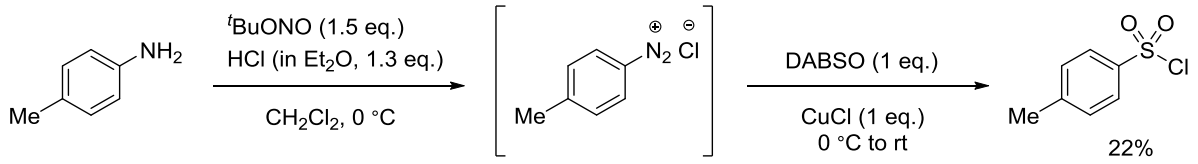
The copper (I)/(II) catalysed chlorosulfonylation of aryldiazonium salts is a relatively under-utilised yet advantageous method with respect to the ready availability of the aniline starting materials (Scheme 1).[53] As such, studies into a streamlined Meerwein reaction were conducted with the use of DABSO *in lieu* of $SO_2$ gas.




Scheme 1 Proposed DABSO-based Meerwein reaction.

## Reaction conditions and optimisation

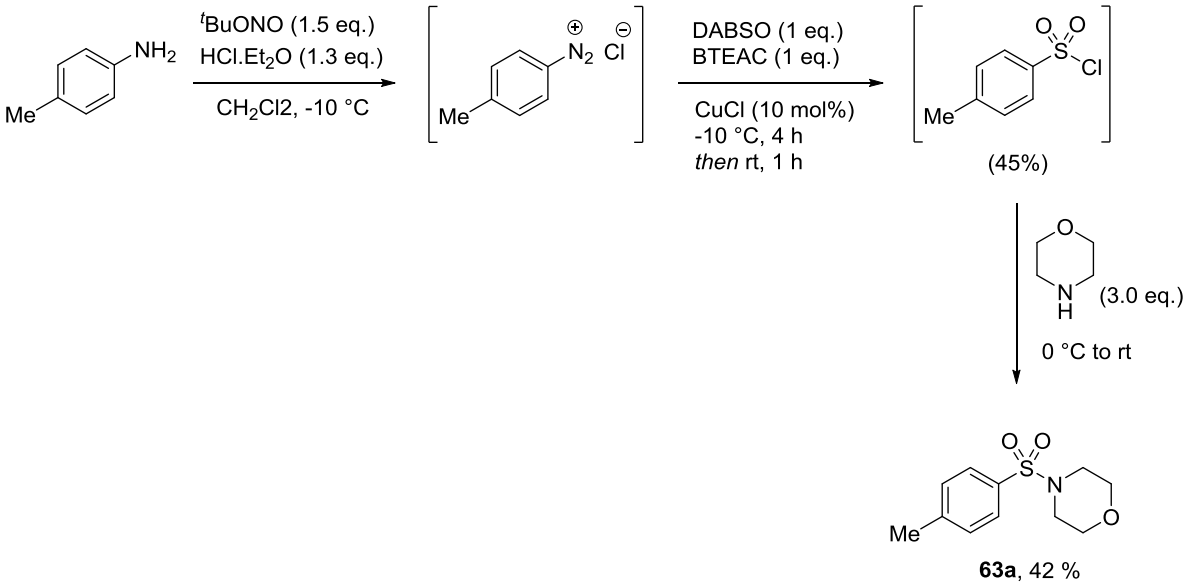
Investigations into the compatibility of DABSO with copper-catalysed radical mediated processes were conducted with initial diazotisation achieved *in situ* using *tert*-butyl nitrite in the presence of hydrochloric acid (Scheme 2).[120] Pleasingly, an initial reaction with *p*-toluidine employing dichloromethane as solvent together with DABSO and stoichiometric copper(I) chloride furnished tosyl chloride in 22% yield (Scheme 2).




Scheme 2 Initial conditions for the DABSO-based chlorosulfonylation reaction.

Attempts to optimise the reaction conditions focused on a screen of solvent, temperature, copper source, DABSO equivalents, and catalyst loading. On conducting the reaction with a range of solvents, it was established that moving away from DCM resulted in slight deterioration in yield, with THF (19%) and acetonitrile (20%) being the only solvents to provide comparable results. Hence, based on the initial findings, only THF, DCM, and acetonitrile were employed in subsequent experiments.

It was noted that addition of the copper(I) chloride to the reaction mixture (containing DABSO) resulted in immediate reaction of the diazonium salt with expulsion of nitrogen to give the desired tosyl chloride along with a complex mixture of decomposition products. As a result, it was hoped that on moving to lower (catalytic) copper loadings a more controlled reaction of the diazo intermediate could be achieved. Hence, maintaining DCM as the solvent, benzyltriethylammonium chloride (BTEAC) was introduced into the system as a chloride source.[120] Initially, reduced loadings of CuCl (50 to 10 mol%) led to an increased tosyl chloride yield of 30%. Subsequent modifications identified that, by conducting the reaction with 10 mol% CuCl at -5 to -10 ˚C and maintaining this temperature for several hours before warming, tosyl chloride could be obtained in 45% yield (Scheme 3). Interestingly, with these conditions a much cleaner reaction occurred whereby the desired sulfonyl chloride was formed in a 2:1 ratio with a persisting aromatic polar by-product which unfortunately, could not be isolated or identified throughout these investigations. Subsequent treatment of the generated sulfonyl chloride with an excess of morpholine furnished 4-tosylmorpholine **63a** in 42% yield over three steps (Scheme 3).




Scheme 3 Synthesis of 4-tosylmorpholine, employing DABSO, in three steps.

It is apparent from Meerwein's work that sulfur dioxide saturation is beneficial for sulfonylation of the aryl radical intermediate to occur. Unfortunately, upon increasing the DABSO loading, deterioration of the yield was observed, with 1 equivalent identified as optimal. It is possible that the presence of DABCO retards formation of the sulfonyl chloride, due to the considerable nucleophilicity of the tertiary amine, resulting in attack of the electrophilic diazonium[206] or poisoning the copper catalyst.[207] Based on this hypothesis, alternative complexes with less basic amines were investigated in an attempt to increase $SO_2$ liberation and simultaneously limit the potential diazonium degradation and catalyst binding. Therefore, TMA-$SO_2$, py-$SO_2$ and the *N*-methylmorpholine complex (Figure 1) were prepared from the corresponding amine[208] and subsequently employed in the established system.

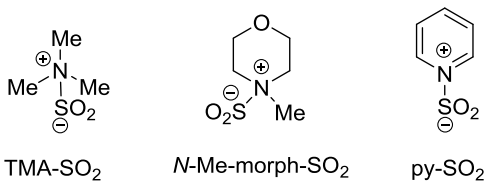
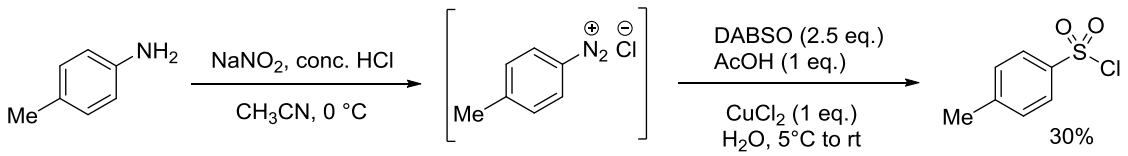



Figure 1 Amine-sulfur dioxide complexes prepared and tested in addition to DABSO.

Unfortunately, slightly lower yields (22-30%) were obtained with the reappearance of undesirable diazonium salt decomposition.

Based on the work of Hogan and Cox,[209] a modified aqueous system was examined with the use of sodium nitrite and concentrated hydrochloric acid to generate the diazonium salt and a $CuCl_2$/AcOH/DABSO mixture to affect the chlorosulfonylation reaction (Scheme 4).[210]




Scheme 4 Aqueous conditions based on the classical Meerwein reaction.

After a screen of DABSO and $CuCl_2$ loadings, a 30% yield of tosyl chloride could not be improved upon with the use of an excess of the amine-sulfur dioxide complex and stoichiometric copper. As previously witnessed, an increase in the amount of DABSO was found to have a detrimental impact.

Further attempts to optimise the reaction focused on ways to affect the formation of the aryl radical from the *in situ* generated diazonium salt. In addition to the commonly used copper(II) chloride, tetrakis(acetonitrile)copper(I) tetrafluoroborate[211] and copper(I) thiophene-2-carboxylate[212] catalysts were examined in the original system based on their superior solubility in organic solvents, but these gave similar yields of 38% and 40% of tosyl chloride, respectively. Iron salts have also been shown to induce radical decomposition of aryldiazonium salts,[213] however the use of iron(II) chloride and ferrocene in this system proved ineffective, affording the sulfonyl chloride in less than 20% yield.

Despite having failed to improve the yield of the reaction with *p*-toludine, alternative electron-rich and -deficient substrates were examined. The classical reaction with gaseous sulfur dioxide reaction is considered to be most effective with electron-deficient aryl amines as initial reduction of the diazonium salt to the corresponding diazenyl radical ($Ar\text{-}N_2^{\bullet}$) should be easier with these substrates.[214] However, both electron-withdrawing (*p*-CN or *p*-$CF_3$) and -donating (*p*-MeO) groups were not well tolerated. A possible explanation for the

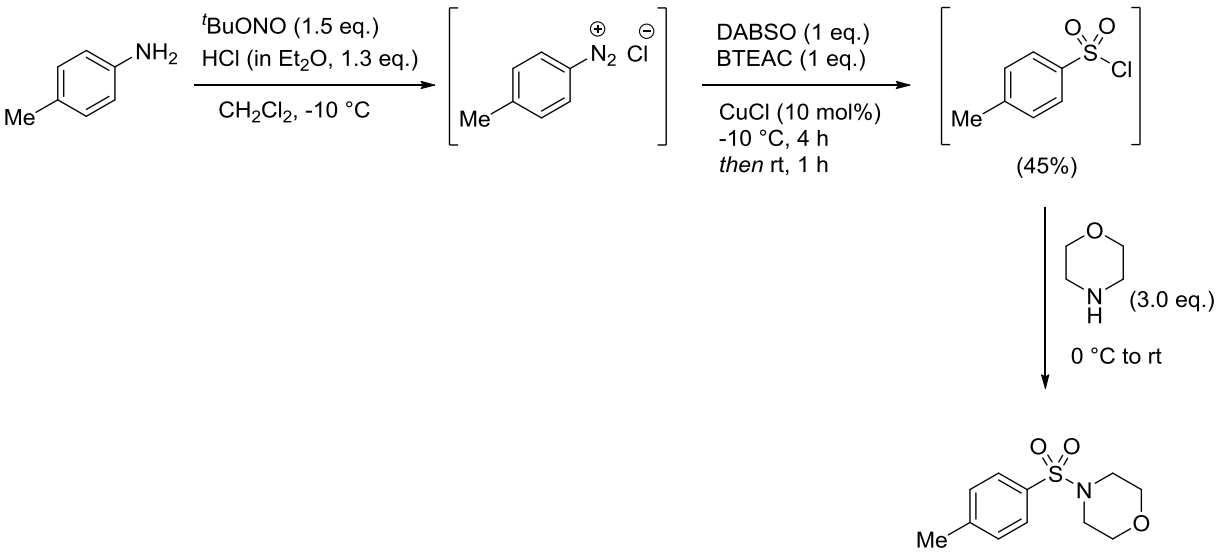
poor reactivity of the electron-deficient species is the increased electrophilicity of the diazonium salt and hence susceptibility to loss of nitrogen by alternative (heterolytic) pathways. As a result of these findings and the moderate yield obtained with *p*-toluidine, the original reaction was performed with $SO_2$ gas in place of DABSO. The sulfonyl chloride was obtained in 63% yield, comparing well with the literature for such electron neutral substrates. This result provides further support for the need for an excess of sulfur dioxide to access the sulfonyl chloride in a higher yield. Interestingly, the apparent by-product formed in the DABSO-based reaction was also observed in the reaction with the gas in a 1:4 ratio with tosyl chloride. This suggests that this alternative pathway is inherent of the gaseous process but is somewhat more prominent in our reaction, potentially as a result of the smaller quantity of sulfur dioxide present.

A final attempt to optimise this chemistry was made by omitting the *in situ* diazonium chloride forming step and instead preparing the more stable *p*-toluenediazonium tetrafluoroborate salt.[215] As a direct substrate or with its preparation *in situ*, the diazonium tetrafluoroborate proved to be inferior to the corresponding chloride as a substrate, with increased levels of diazonium decomposition observed.

## Summary

Unfortunately, despite extensive studies into this streamlined version of the Meerwein reaction, the system could not be fully optimised. It is postulated that the inefficiency of this transformation is the result of limited sulfur dioxide loading and/or residual DABCO promoting diazonium decomposition.

## General procedure for the chlorosulfonylation of aryldiazonium salts using DABSO as exemplified by the preparation of 4-tosyl morpholine (63a)




To a glass reaction tube was added *p*-toluidine (42 mg, 0.39 mmol), *tert*-butyl nitrite (70 $\mu$L, 0.59 mmol) and $CH_2Cl_2$ (1.6 mL). The mixture was cooled to -5 ˚C and HCl in $Et_2O$ (2.0 M, 250 $\mu$L, 0.51 mmol) was added dropwise. The resulting suspension was stirred at this temperature for a further 10 min before addition of benzyltriethylammonium chloride (89 mg, 0.39 mmol), DABSO (94 mg, 0.39 mmol) and CuCl (4.0 mg, 0.039 mmol). After stirring for 4 hrs at this temp., the mixture was allowed to warm to 5 ˚C and was brought to room temperature after 1 hr. This was followed by cooling to 0 ˚C and dropwise addition of morpholine (102 µL, 1.17 mmol) with subsequent warming to room temperature. The resulting mixture was stirred for 3 hrs before concentrating *in vacuo* and was purified by flash column chromatography (1:1 petrol/$Et_2O$) to afford the sulfonamide as a white solid (40 mg, 42%). Data as shown in Section 6.5.4.

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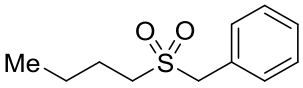
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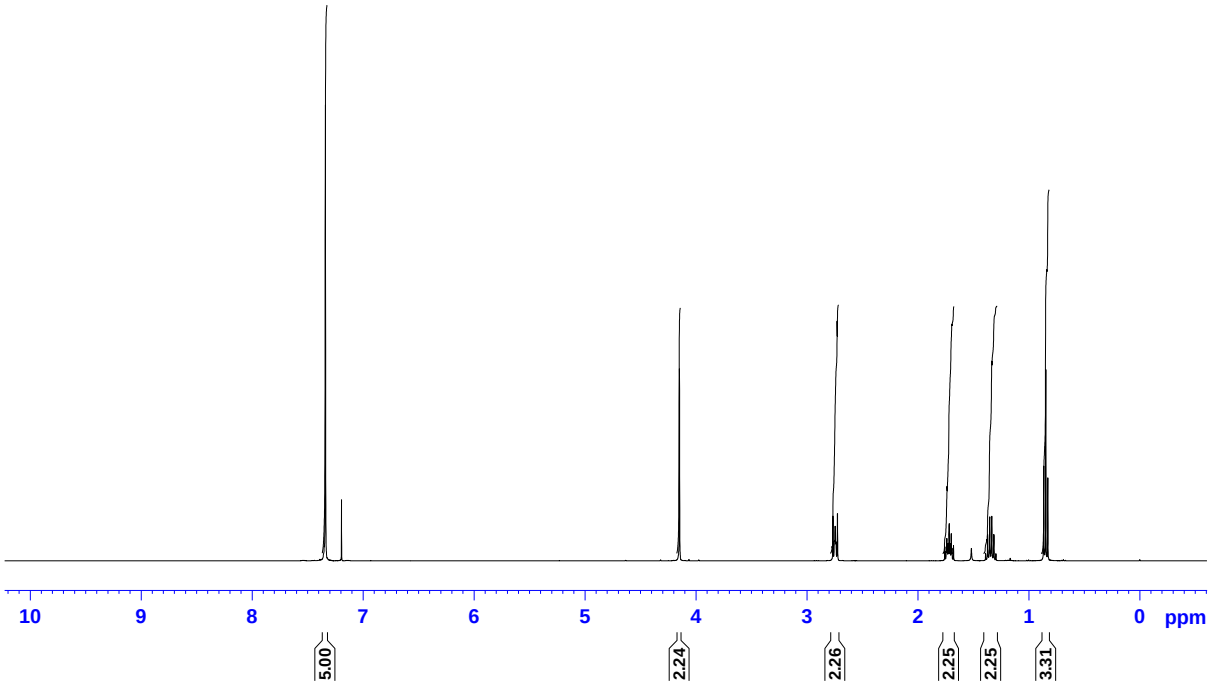
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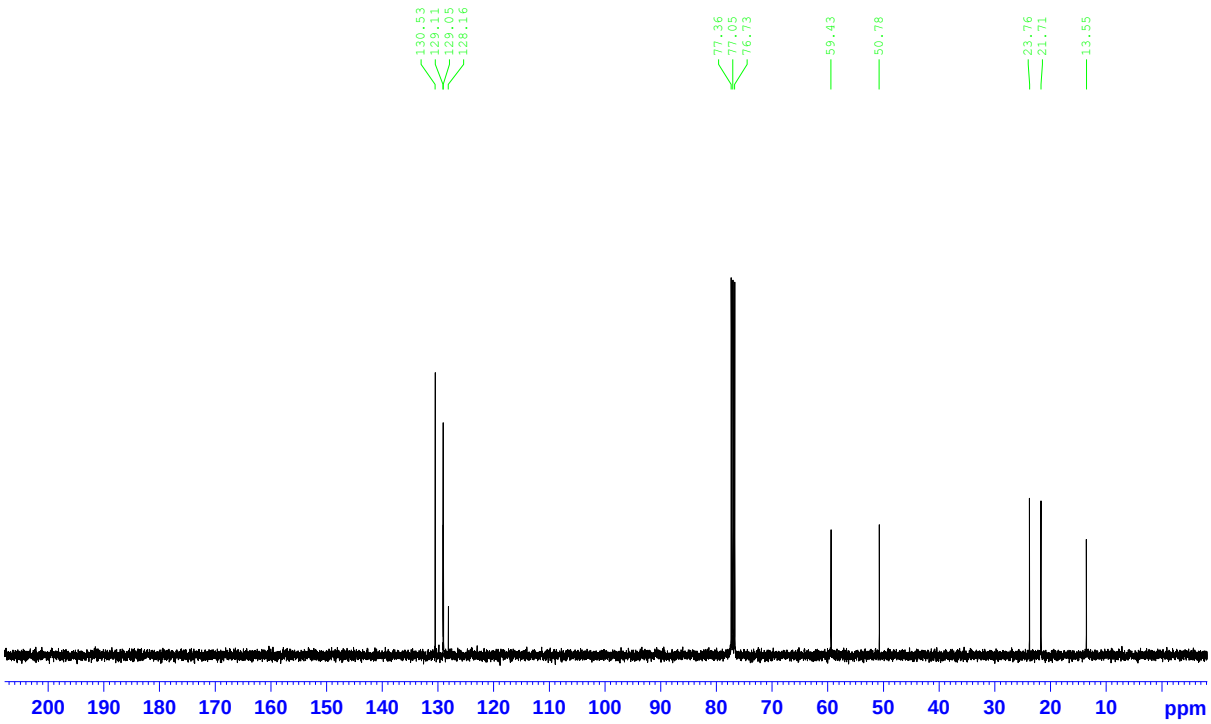
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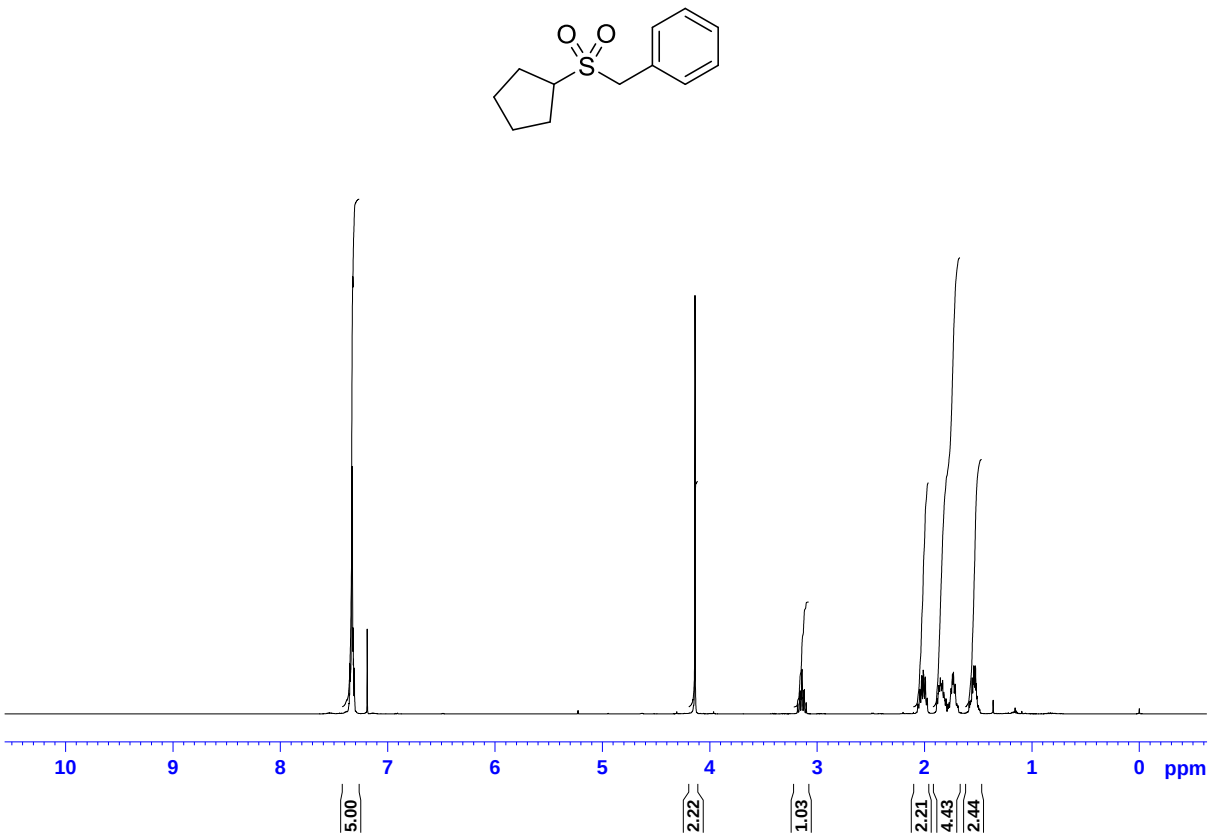
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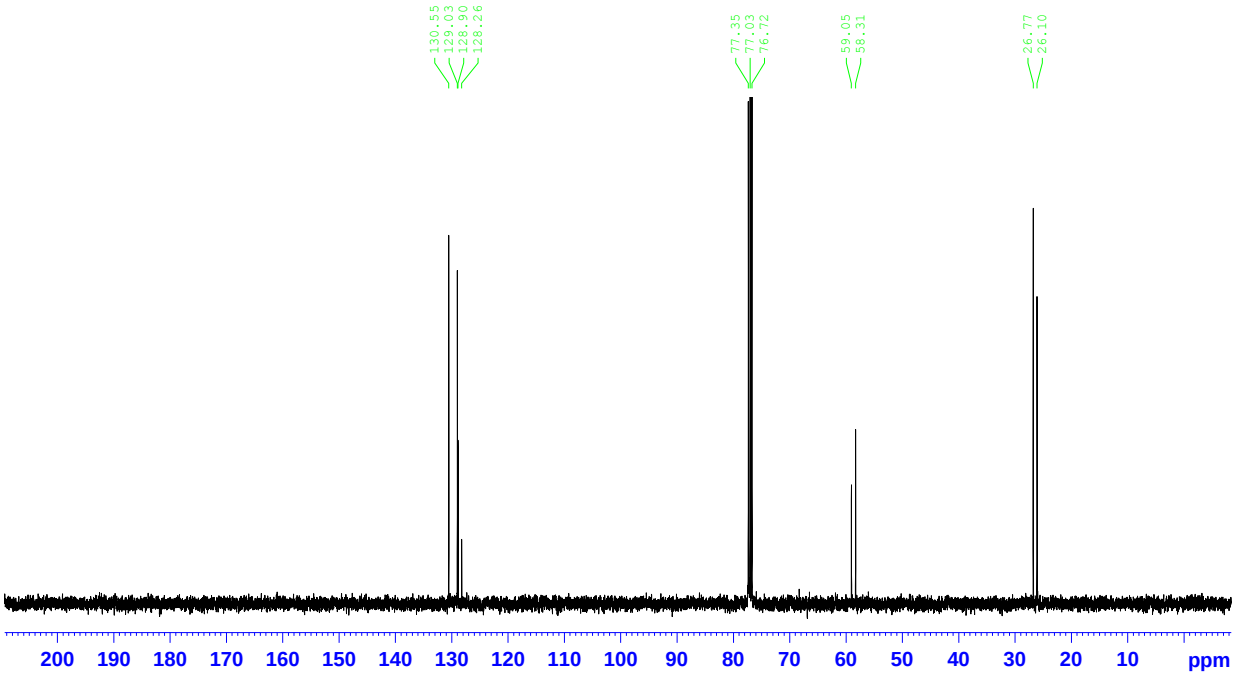
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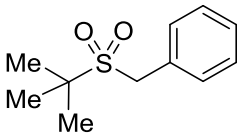
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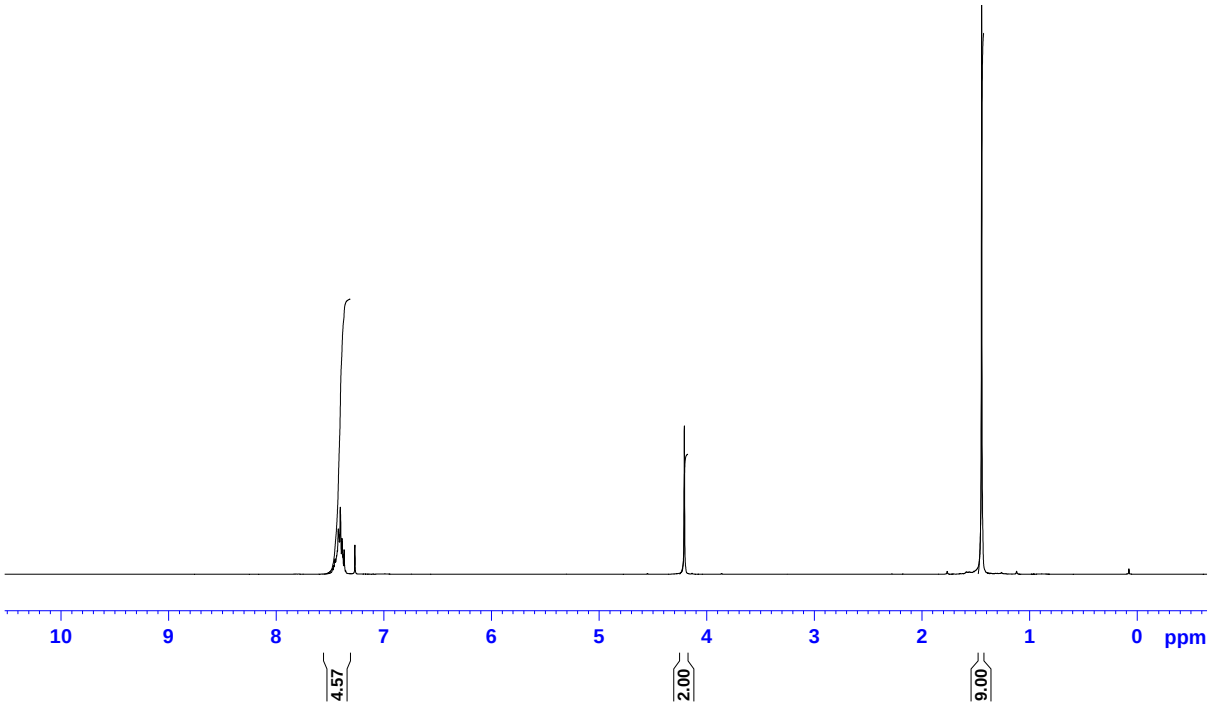
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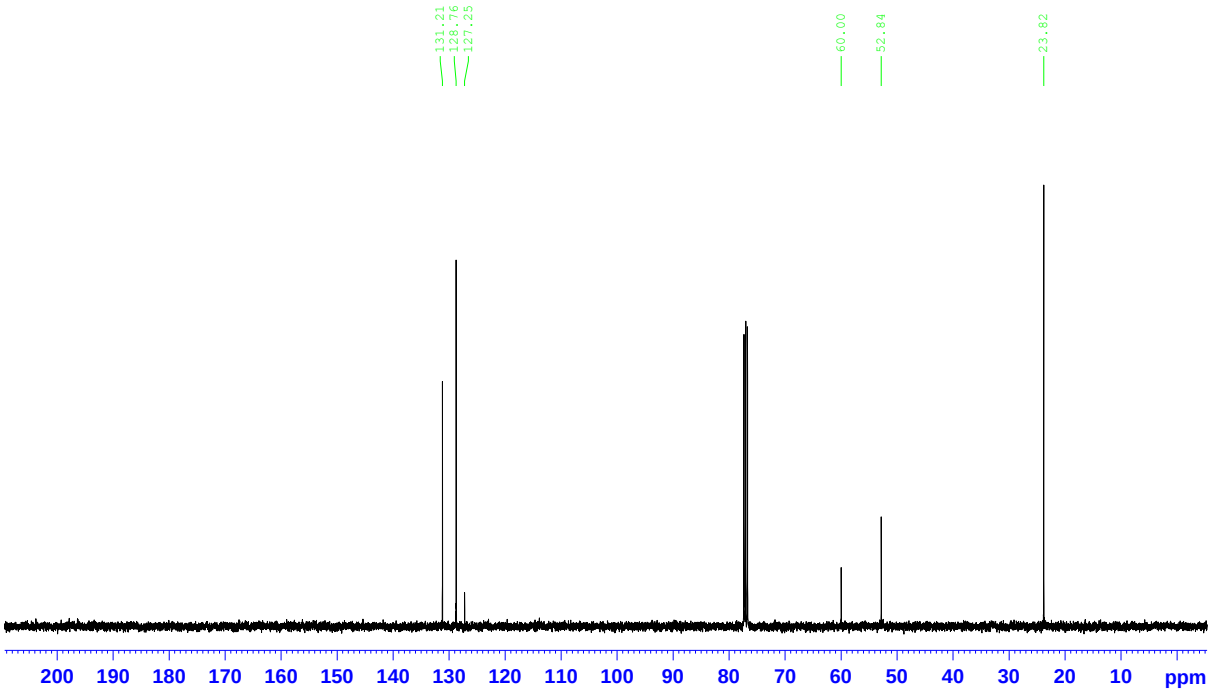
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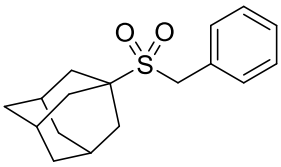
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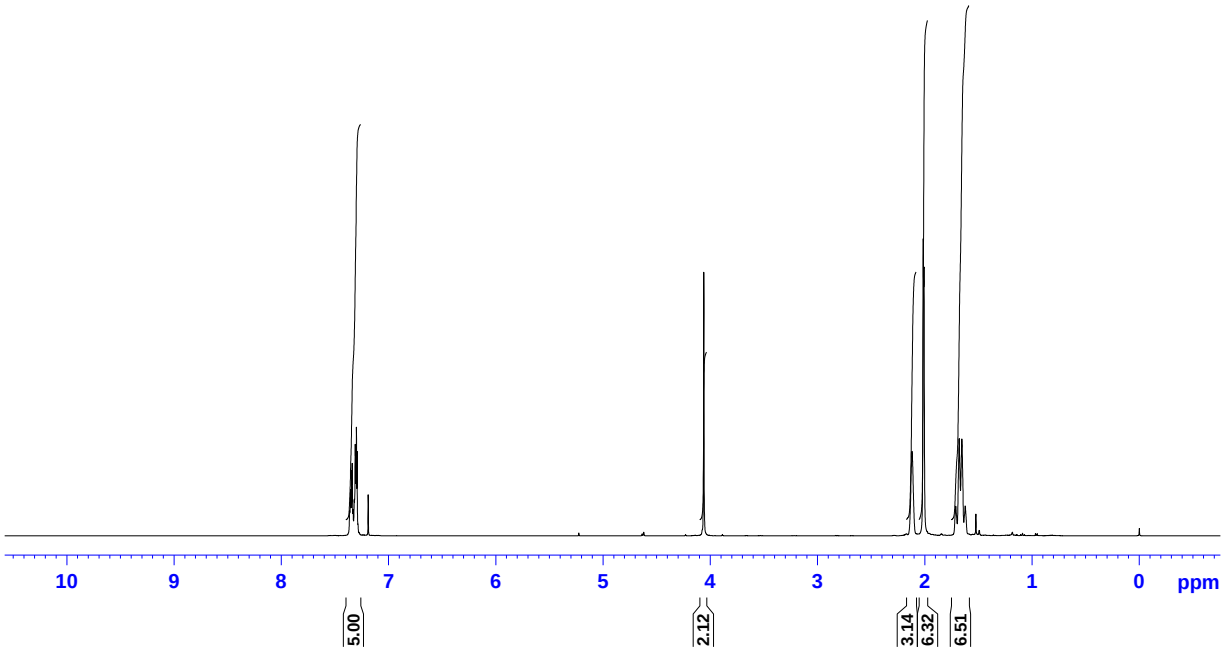
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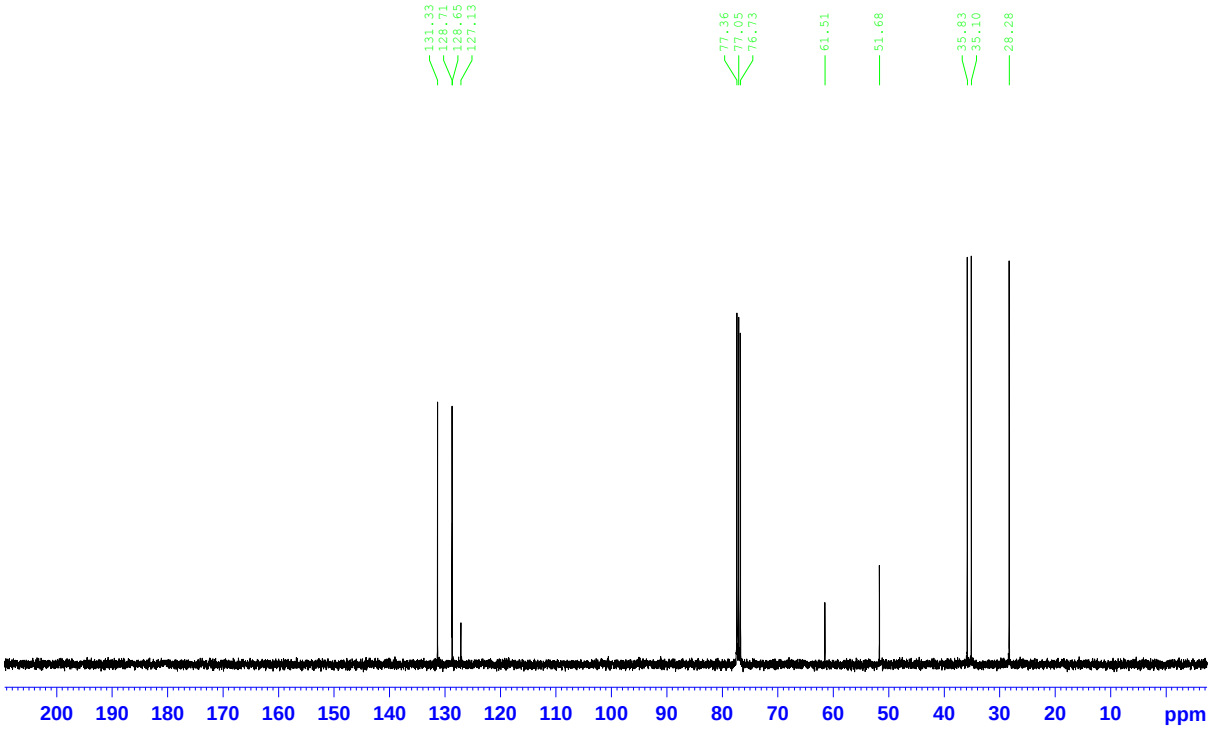
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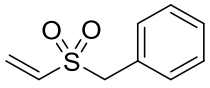

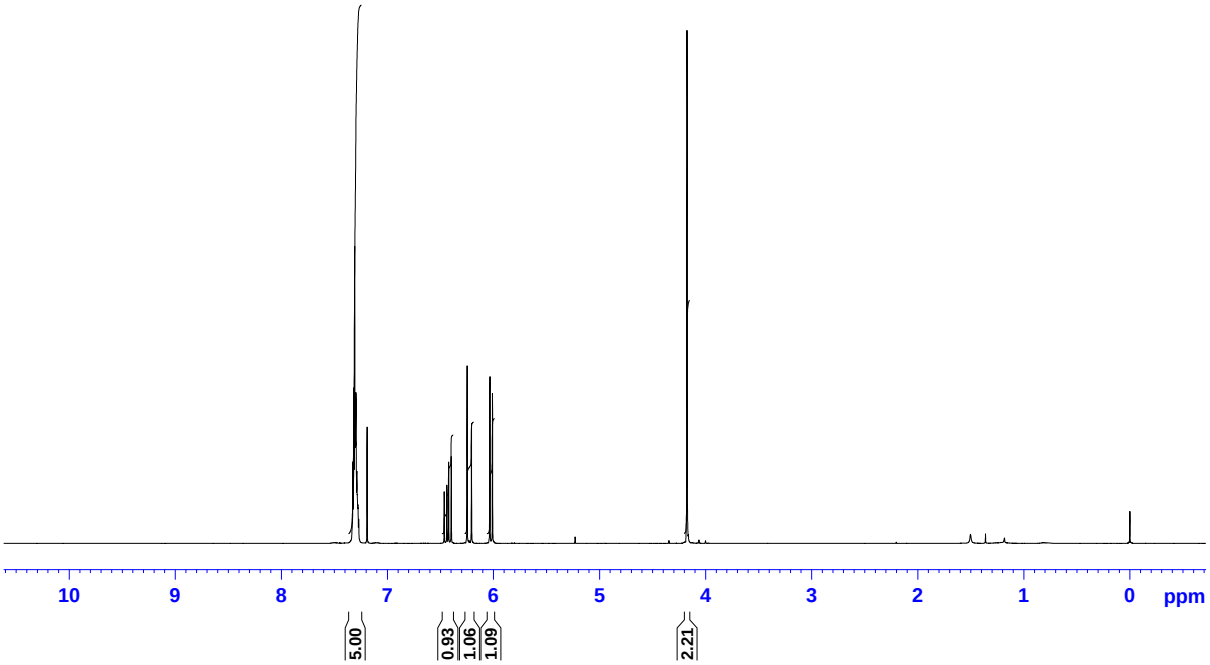
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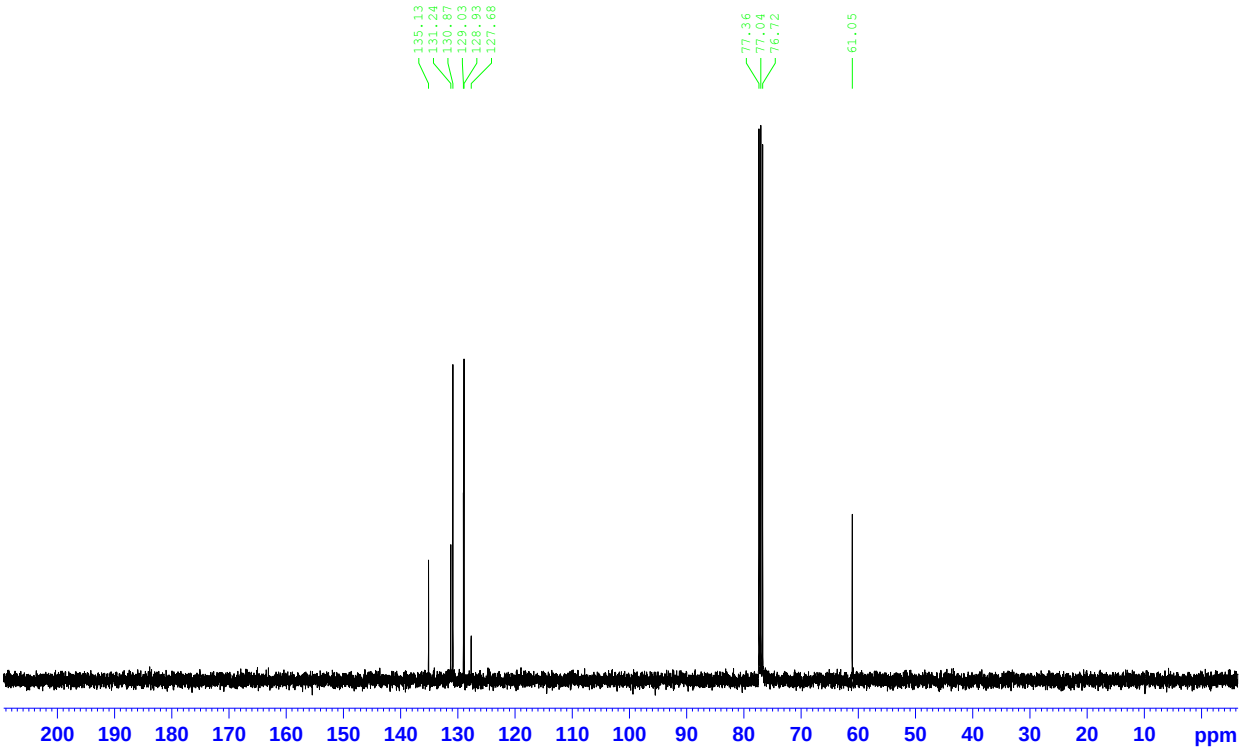
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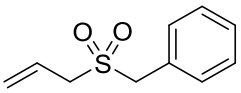
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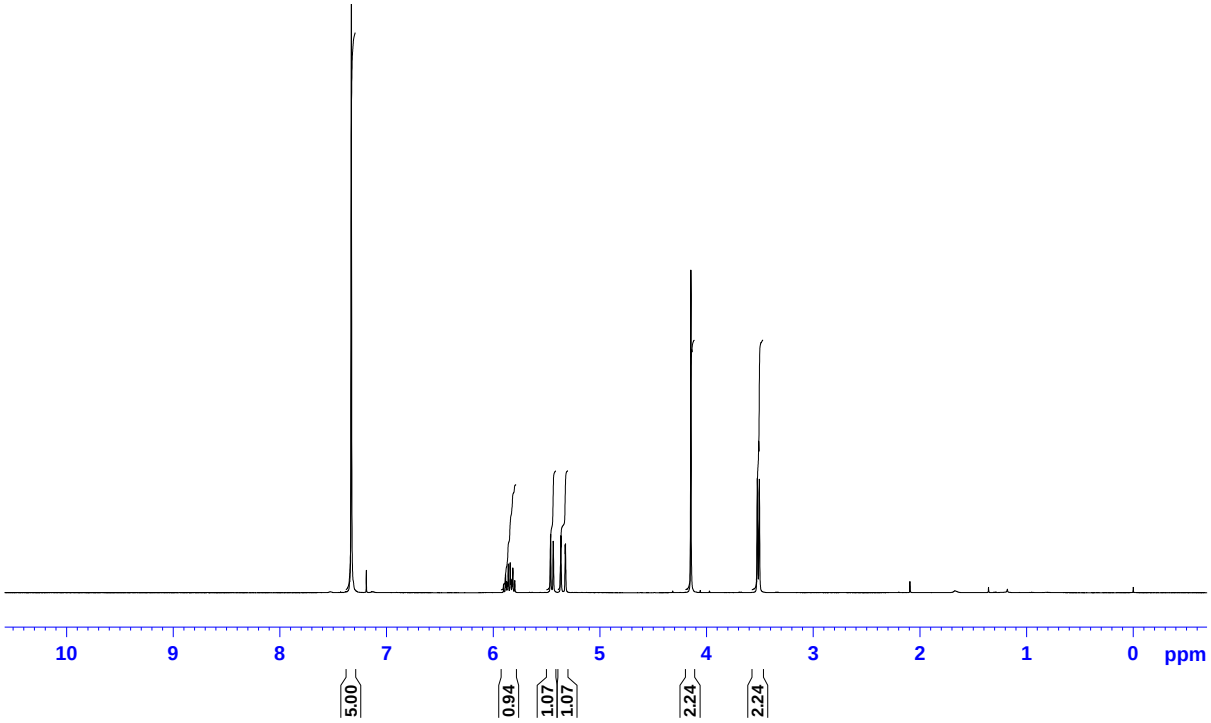
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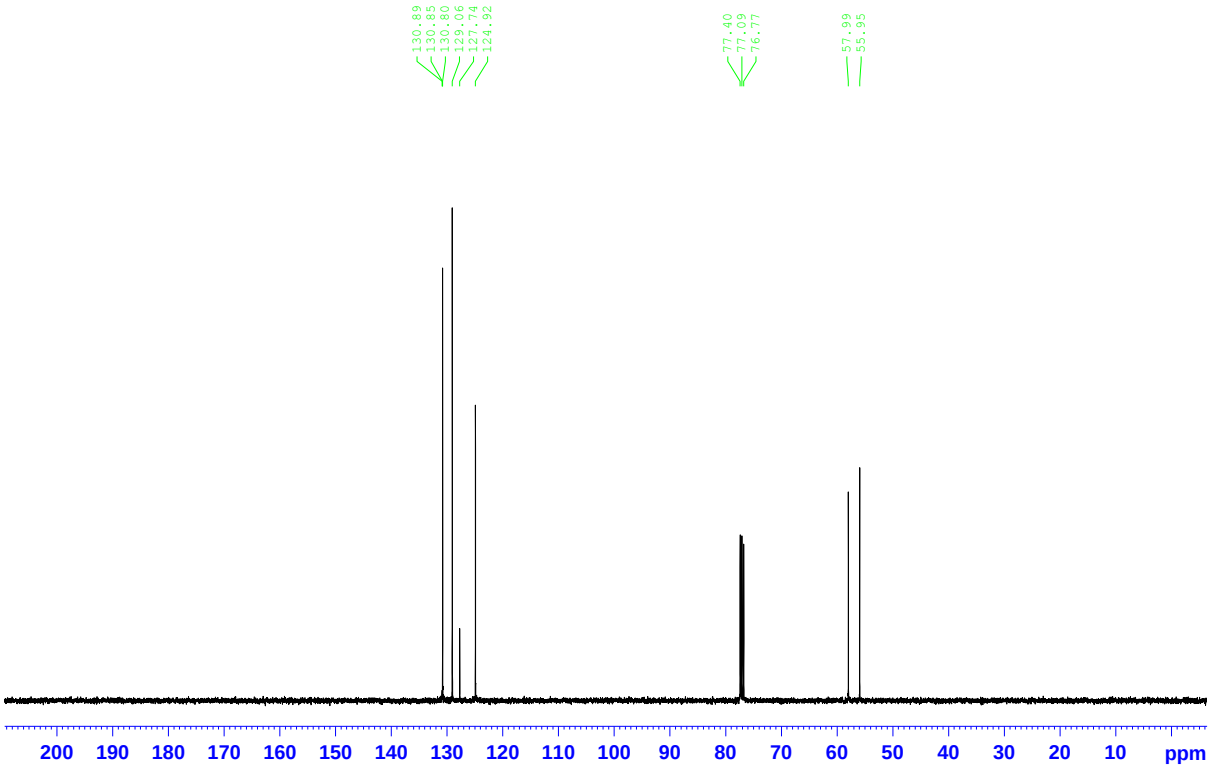
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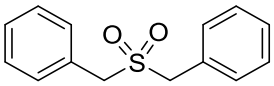
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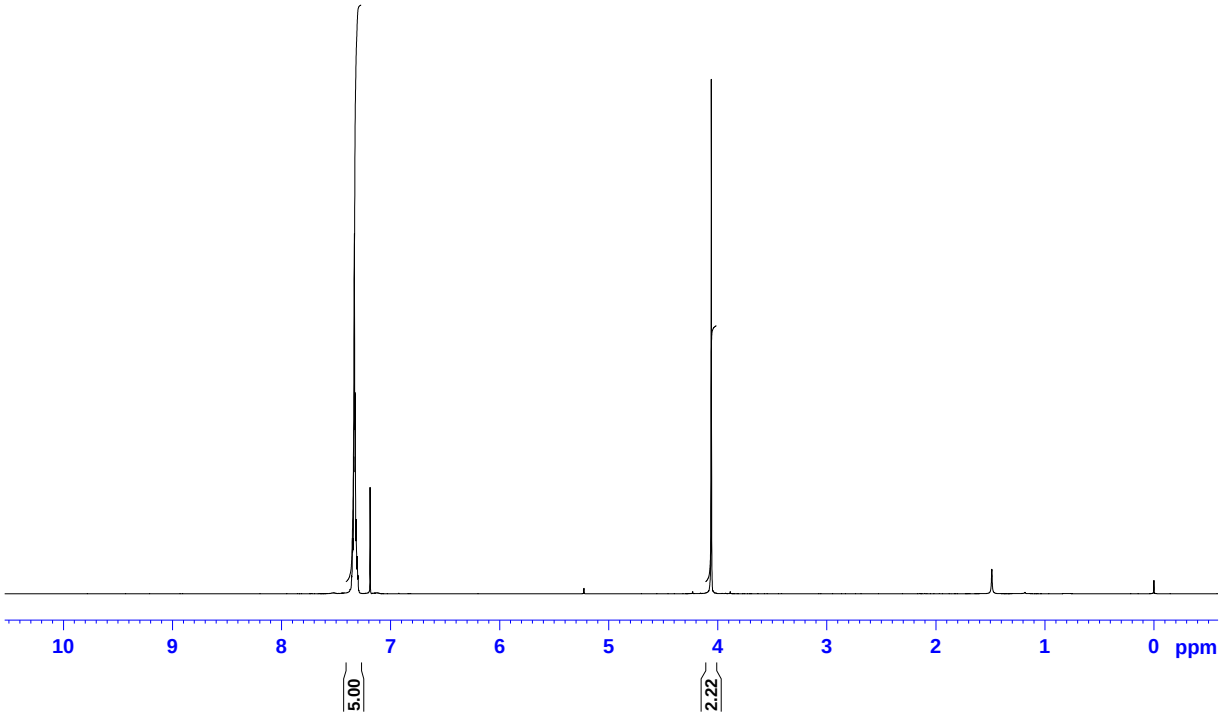
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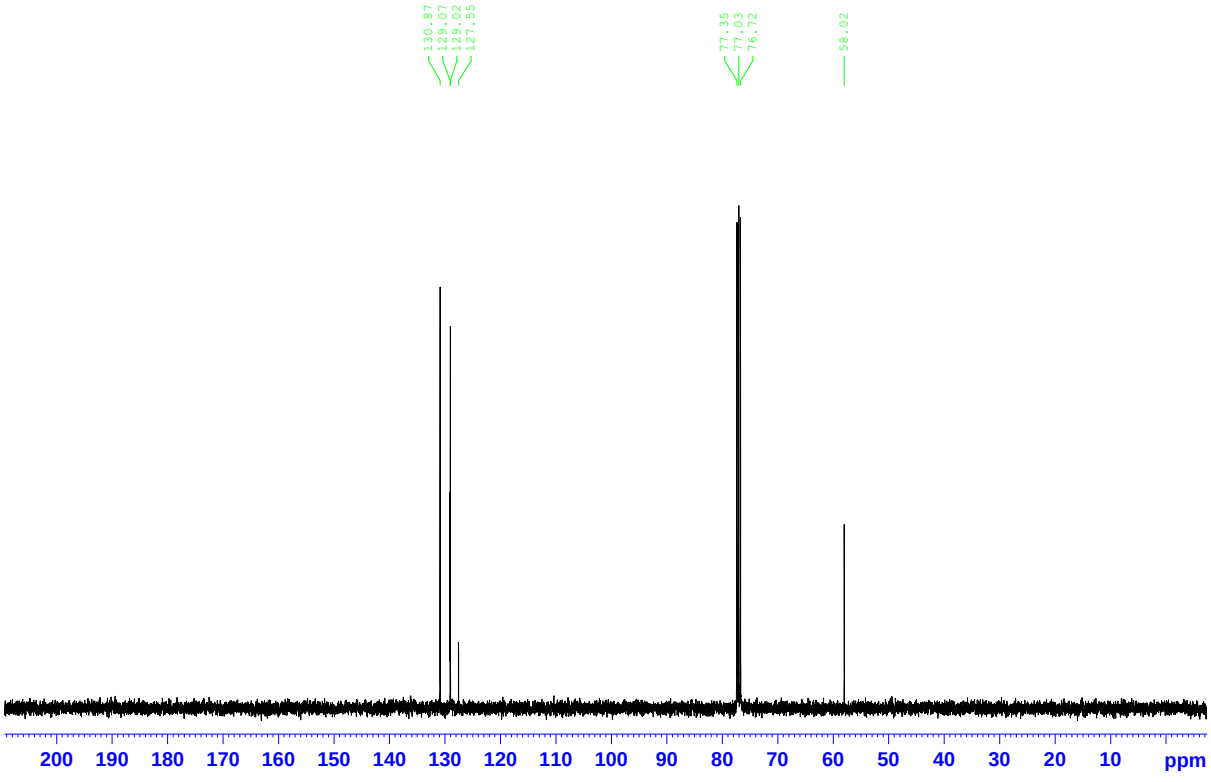
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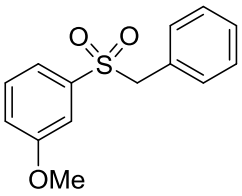
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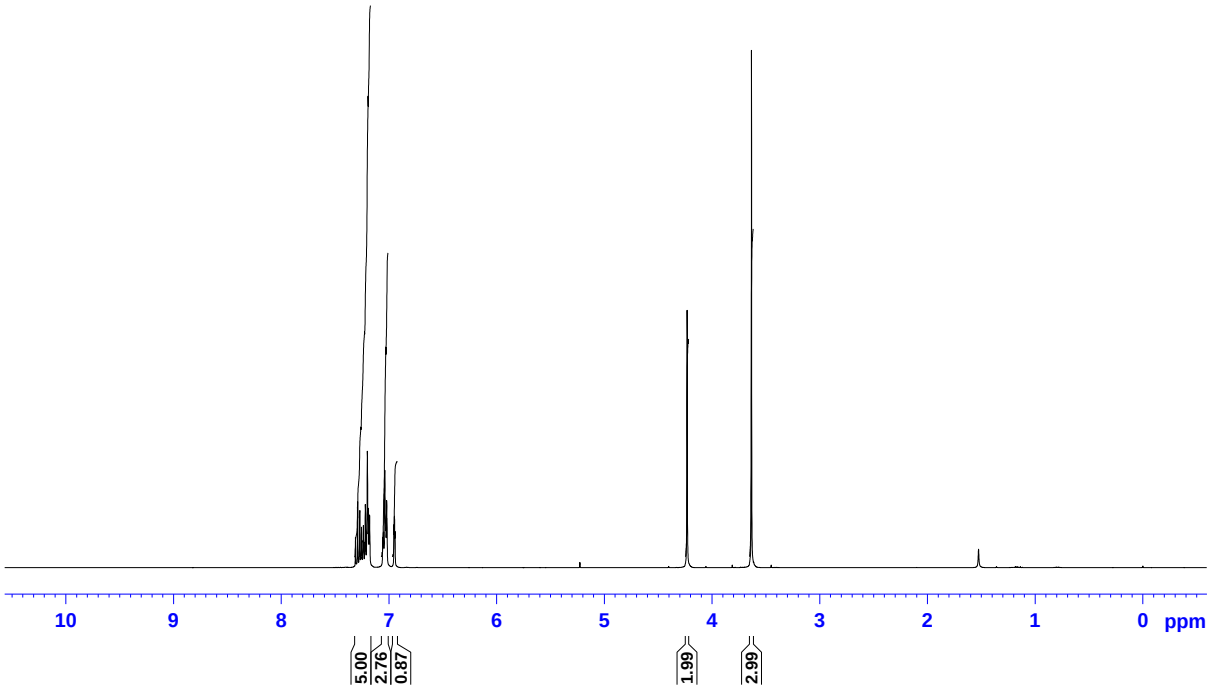
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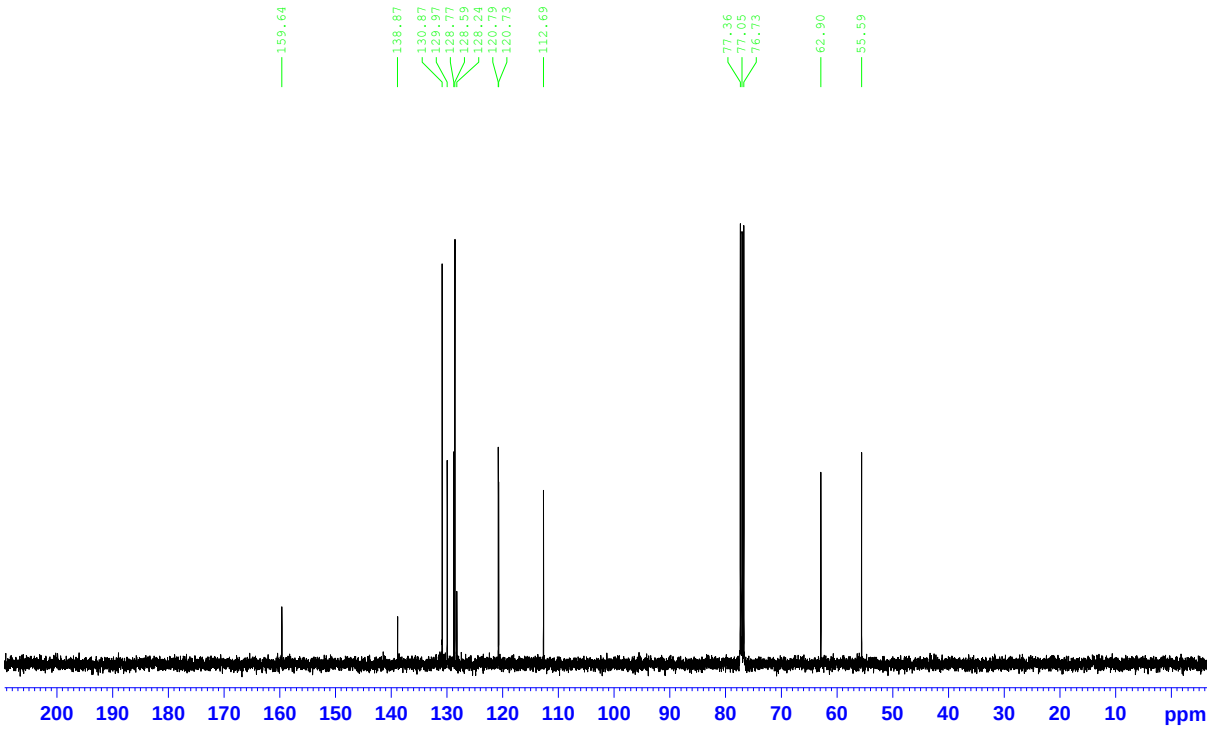
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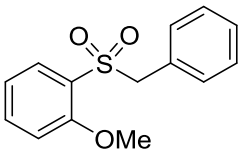
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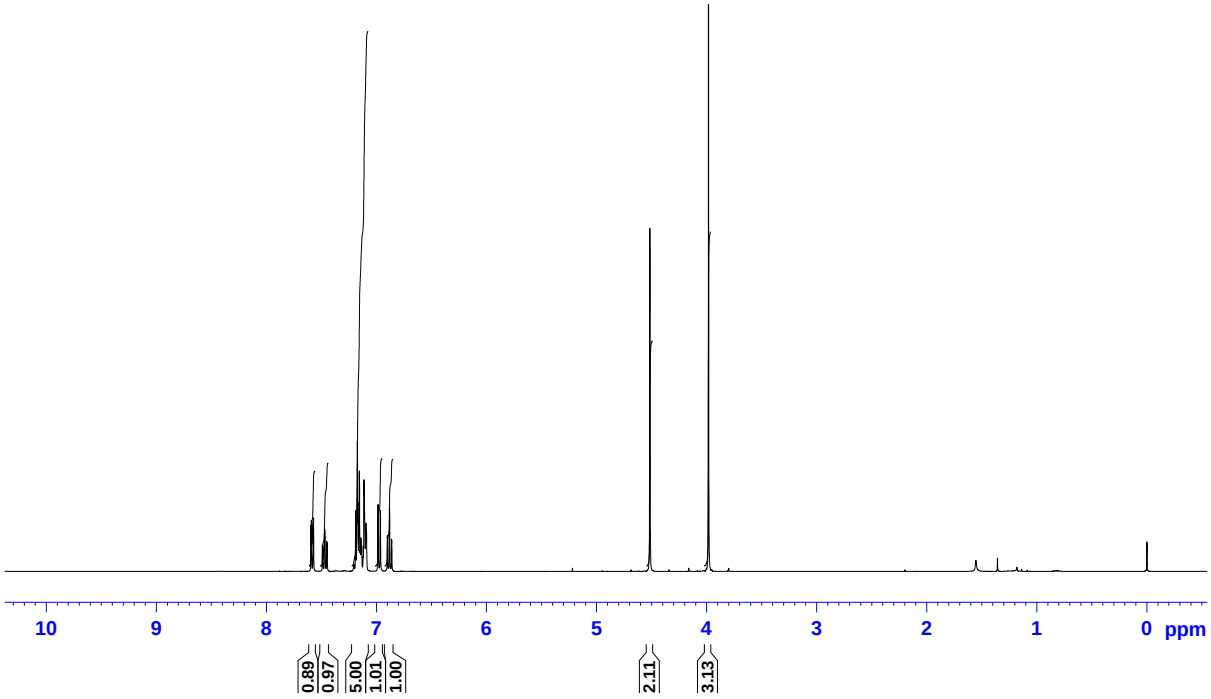
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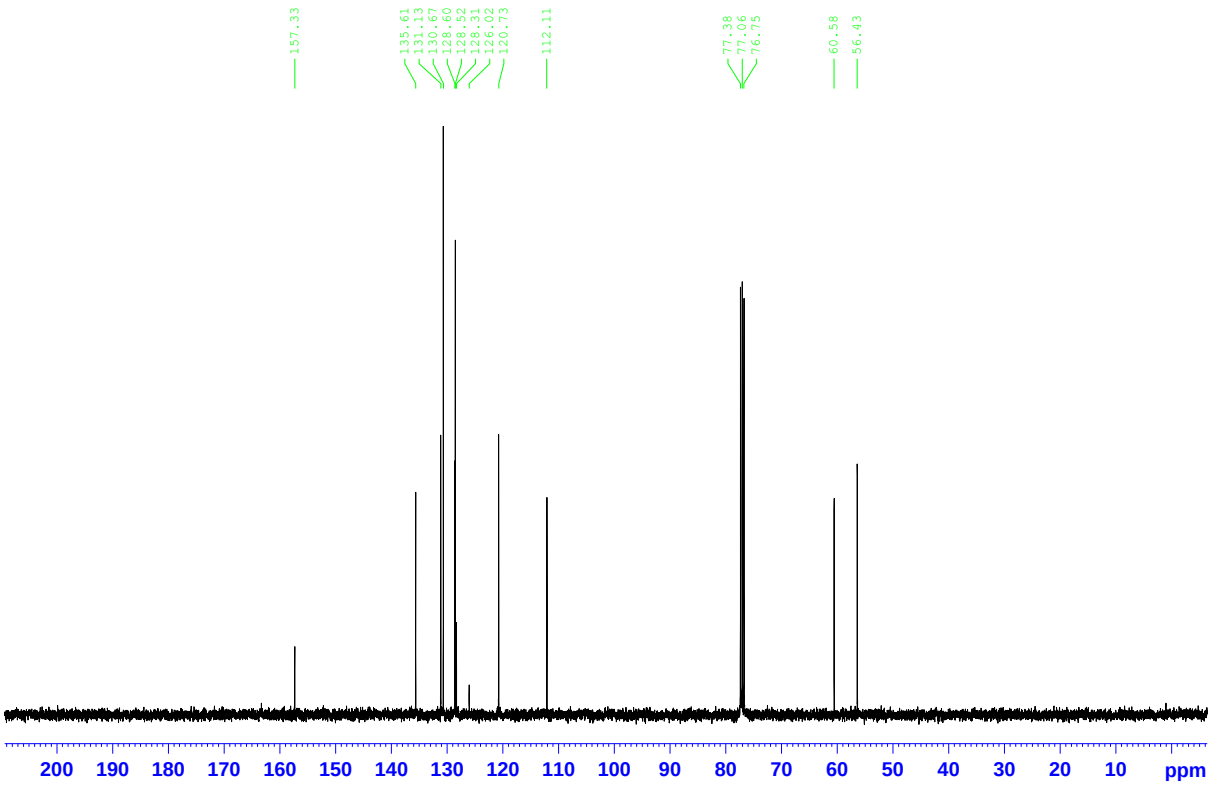
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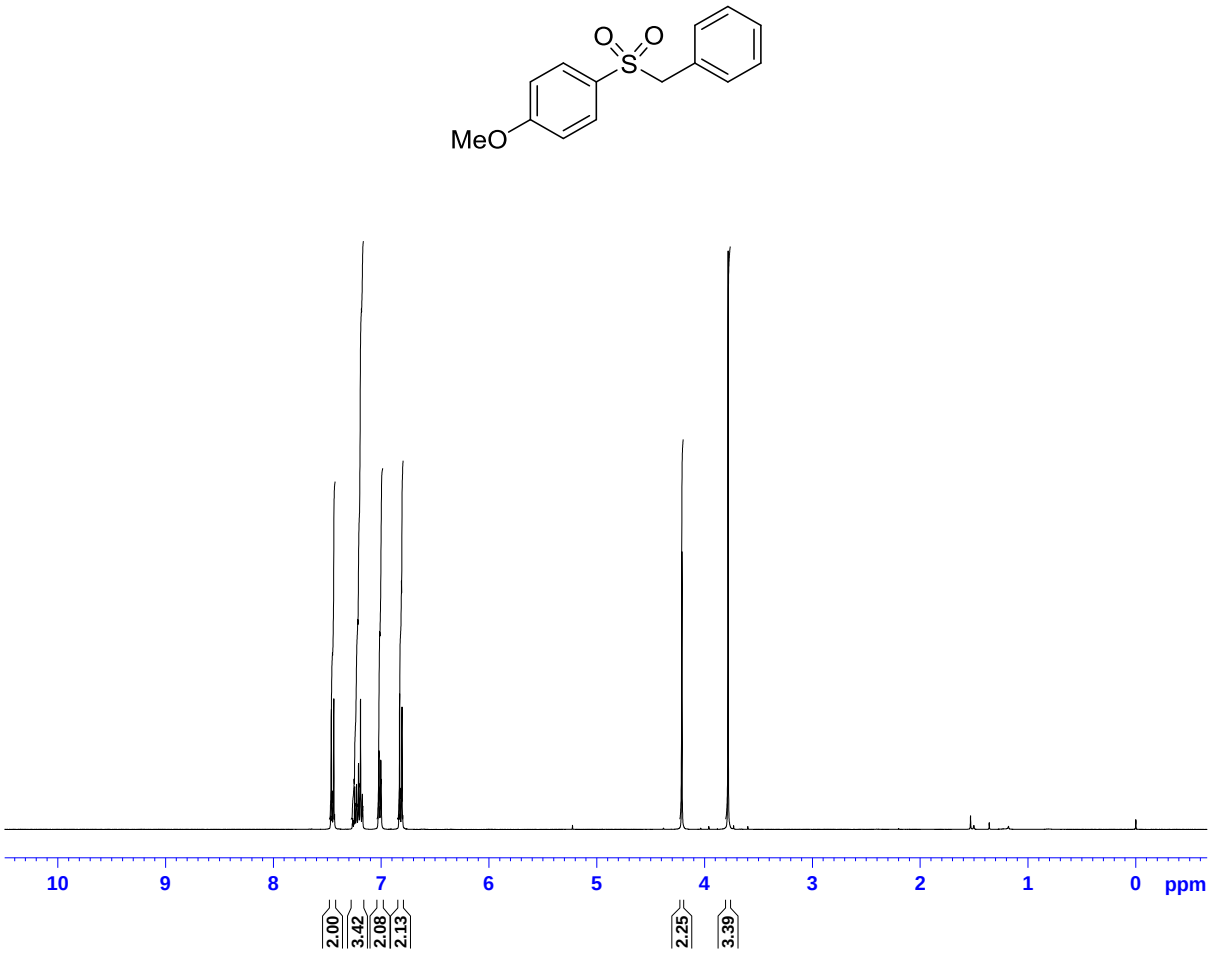
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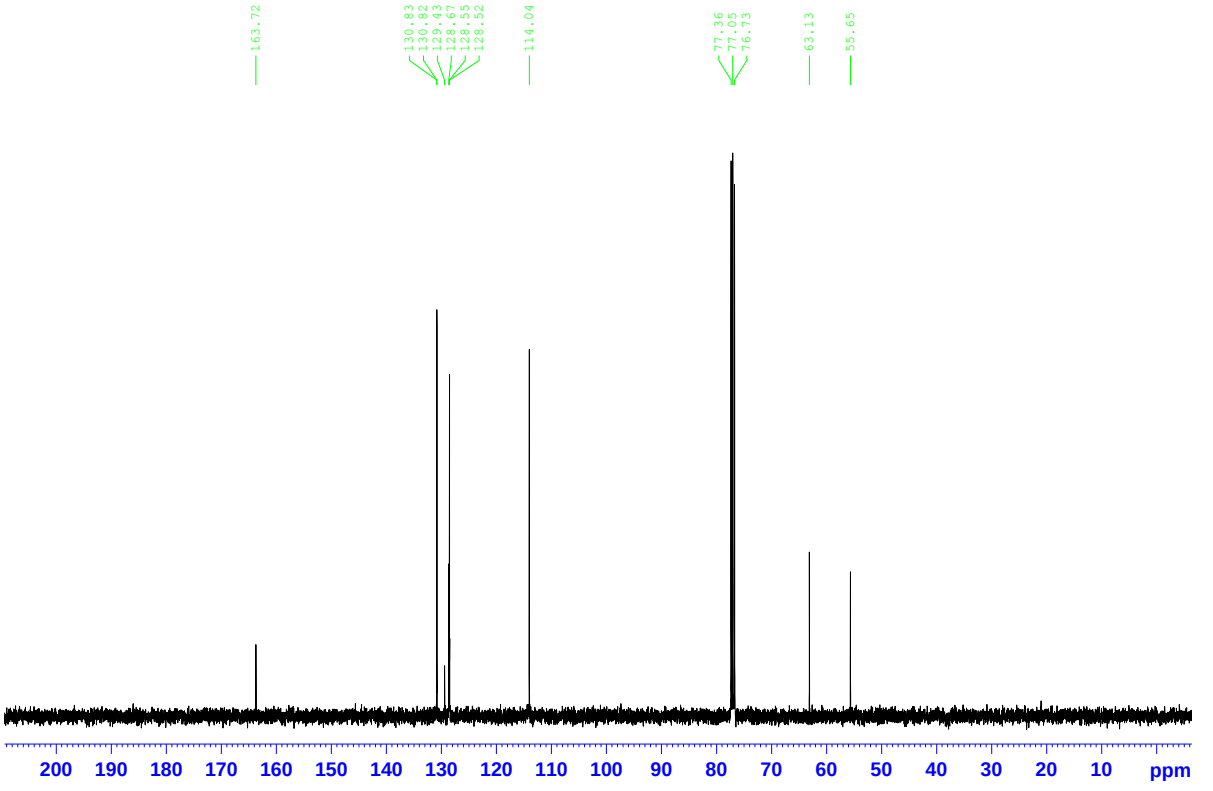
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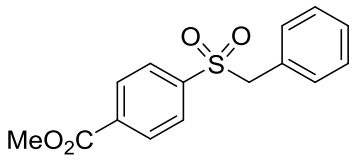
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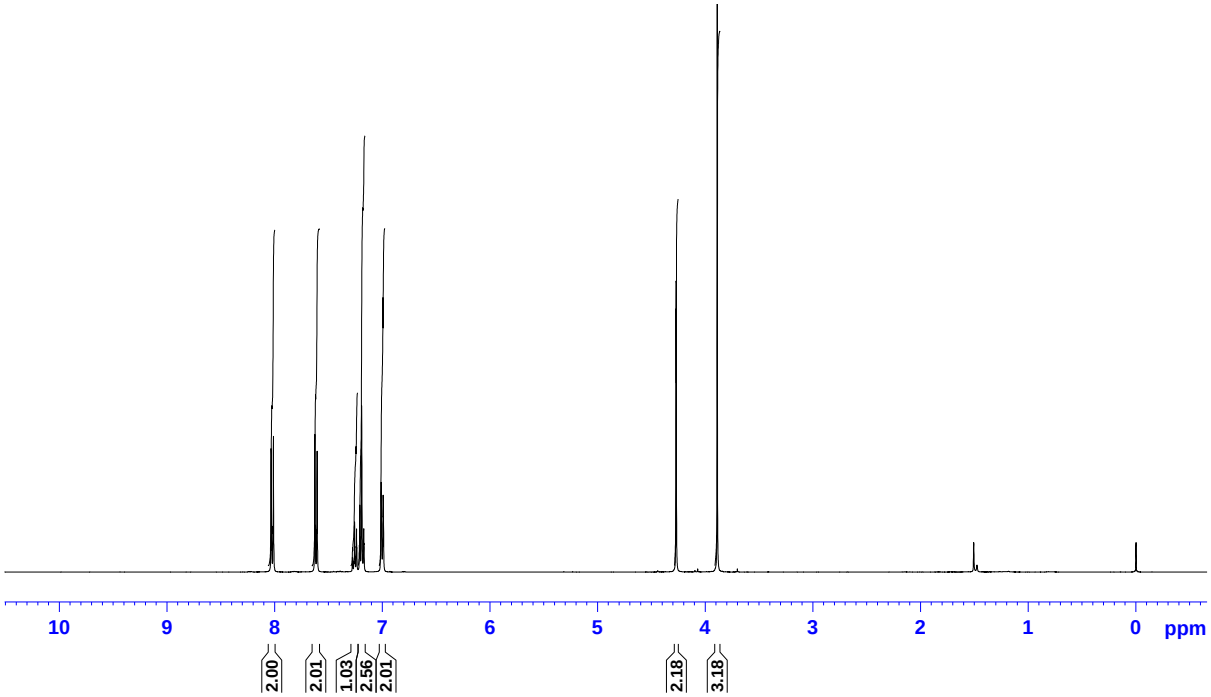
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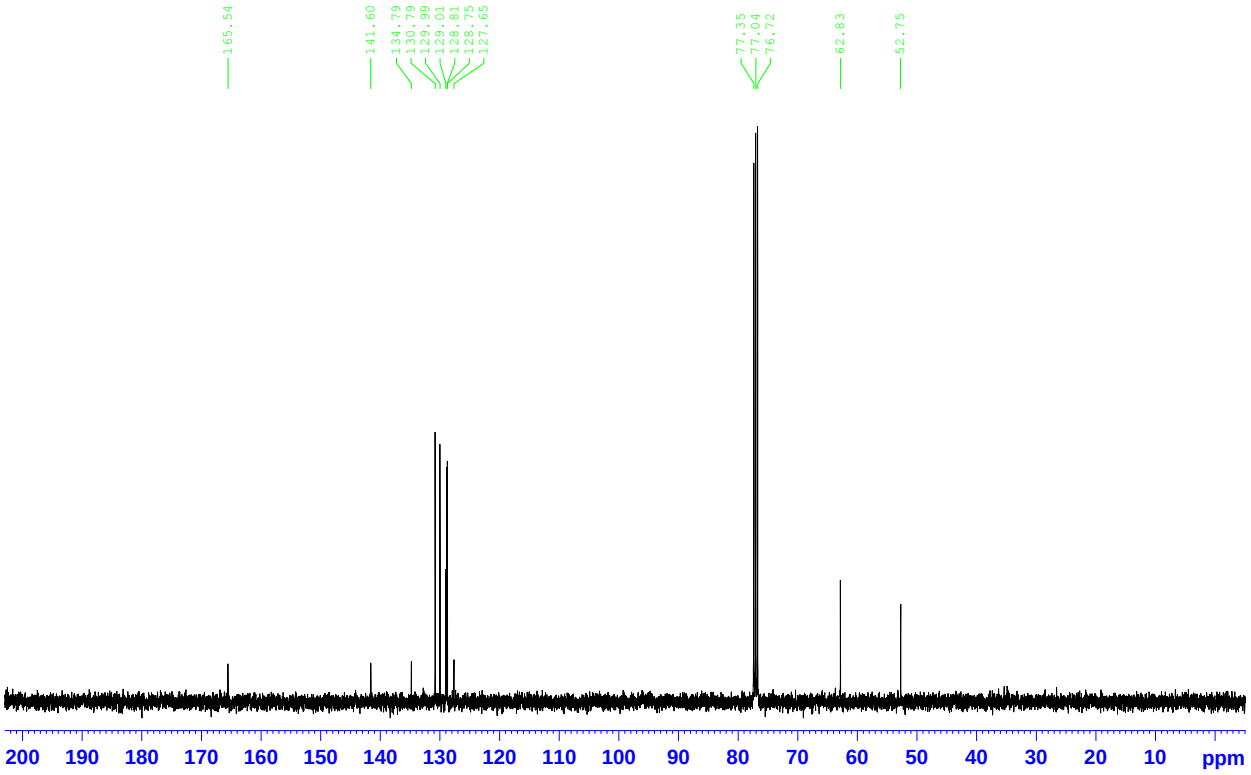
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129.01
128.81
128.75
127.65
77.35
77.04
76.72
62.83
52.75
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150
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110
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70
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30
20
10
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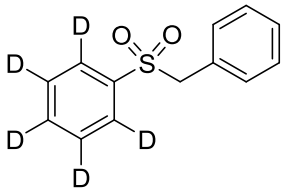
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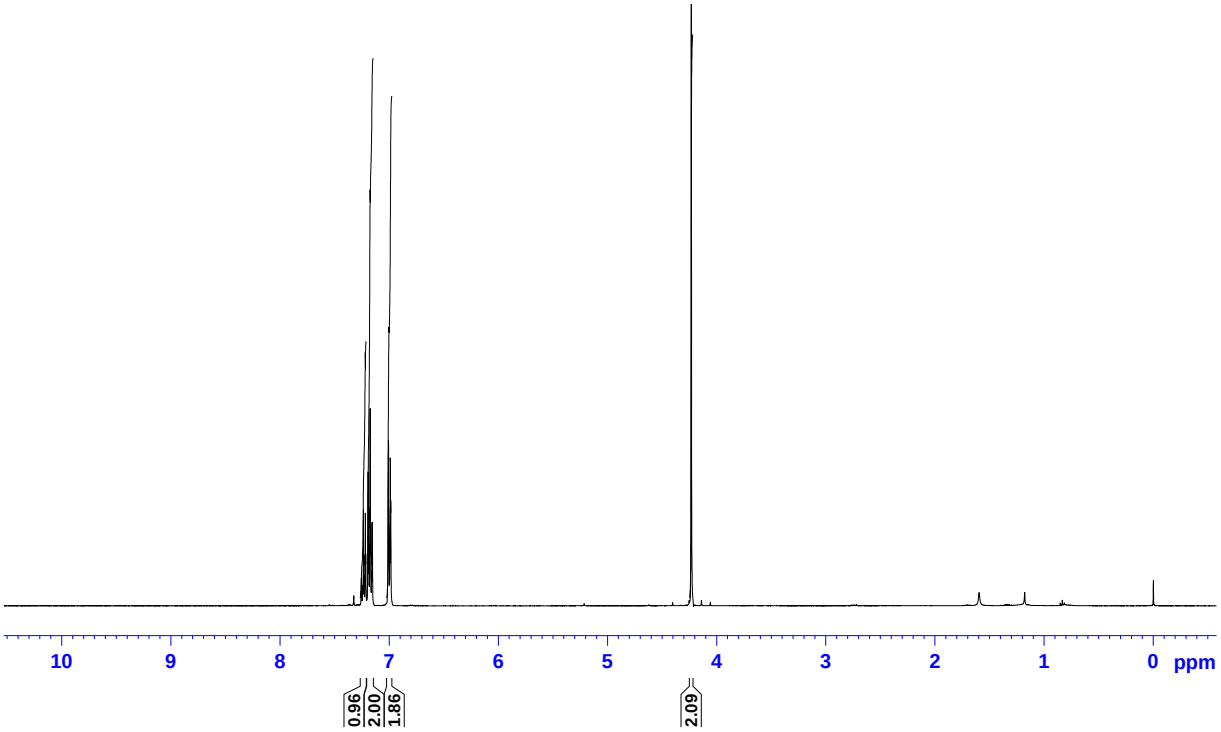
S
D
D
D
D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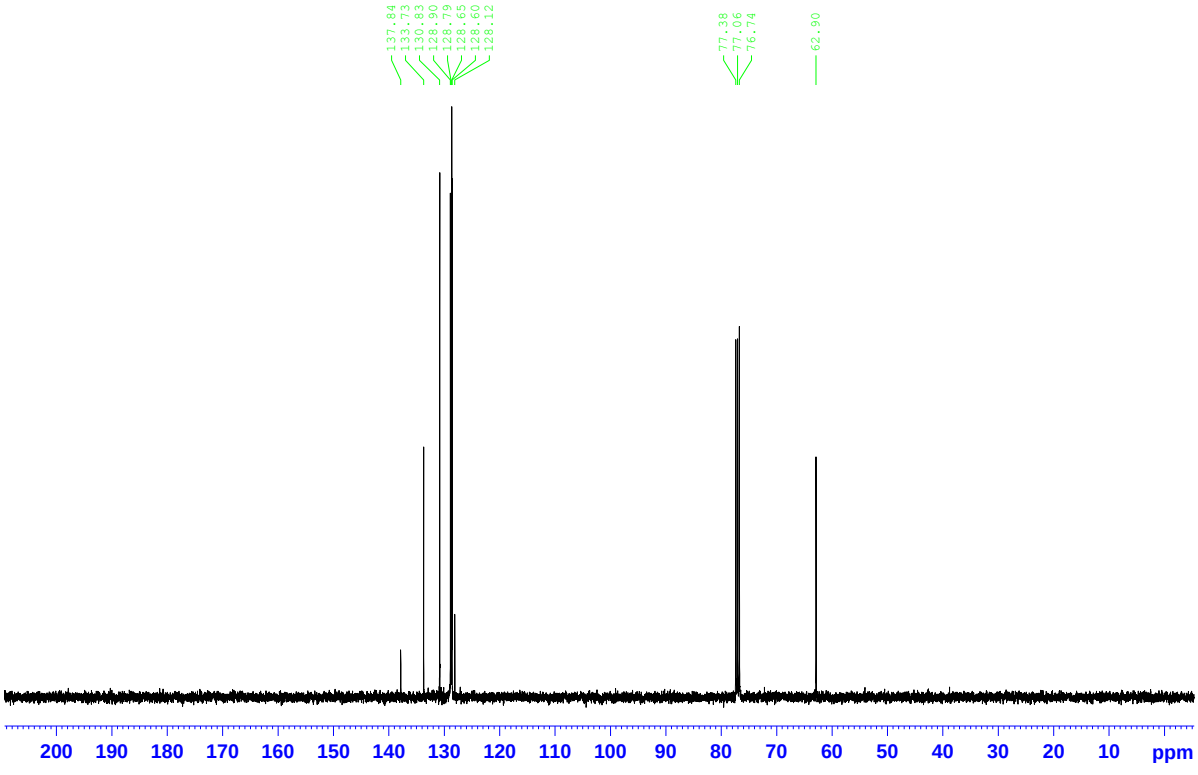
2.09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128.60
128.12
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77.06
76.74
62.90
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150
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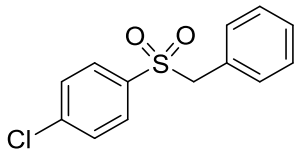
20
10
ppm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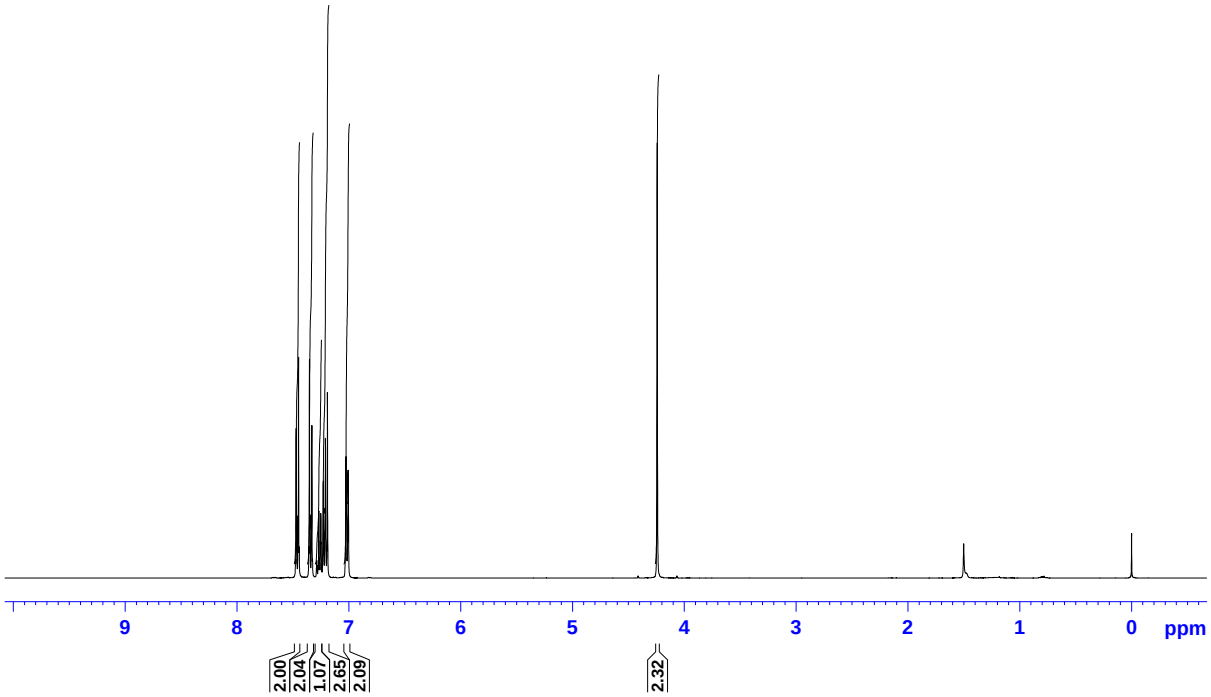
O
S
Cl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ppm
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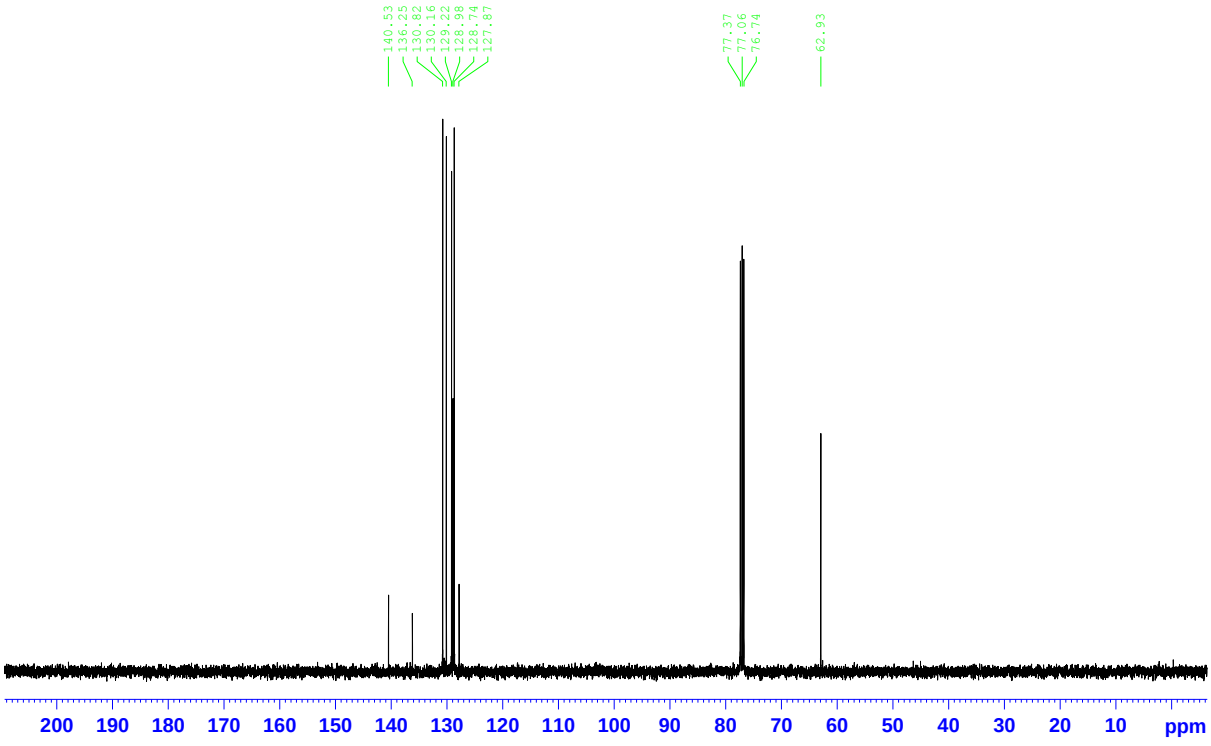
2.65
2.09
2.32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128.98
128.74
127.87
77.37
77.06
76.74
62.93
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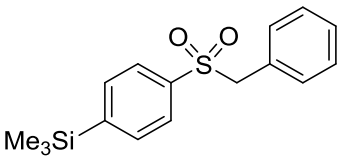
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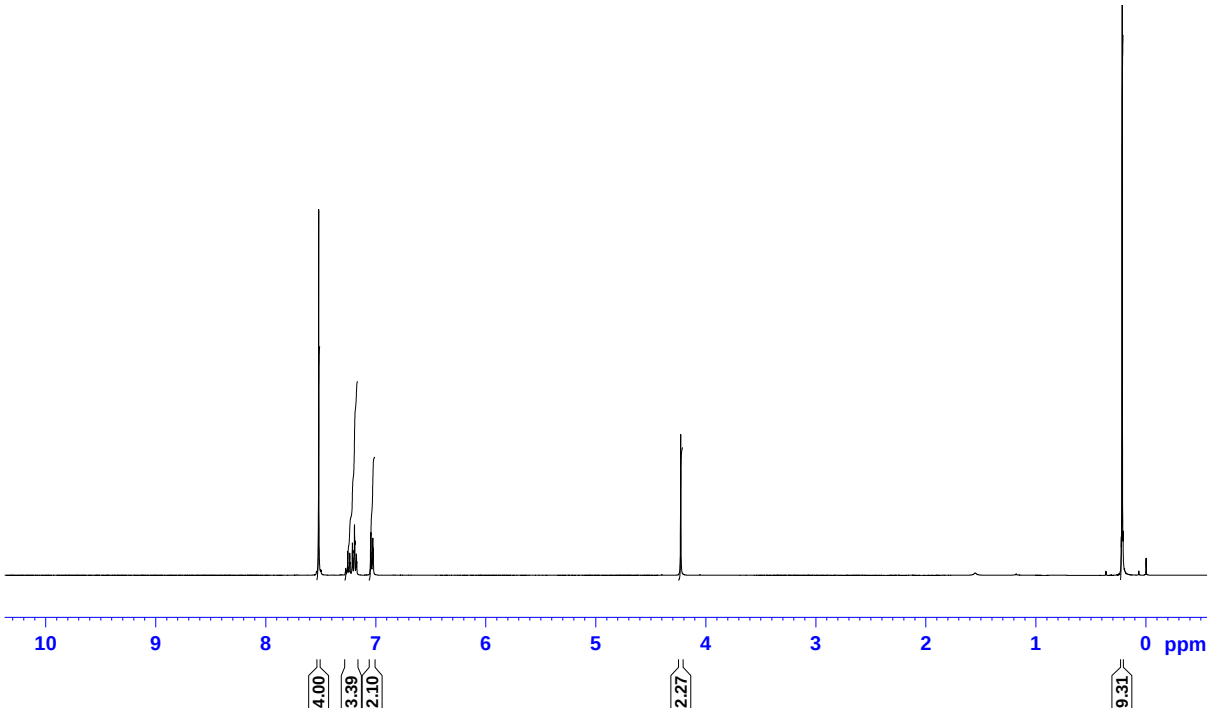
O
S
Me3Si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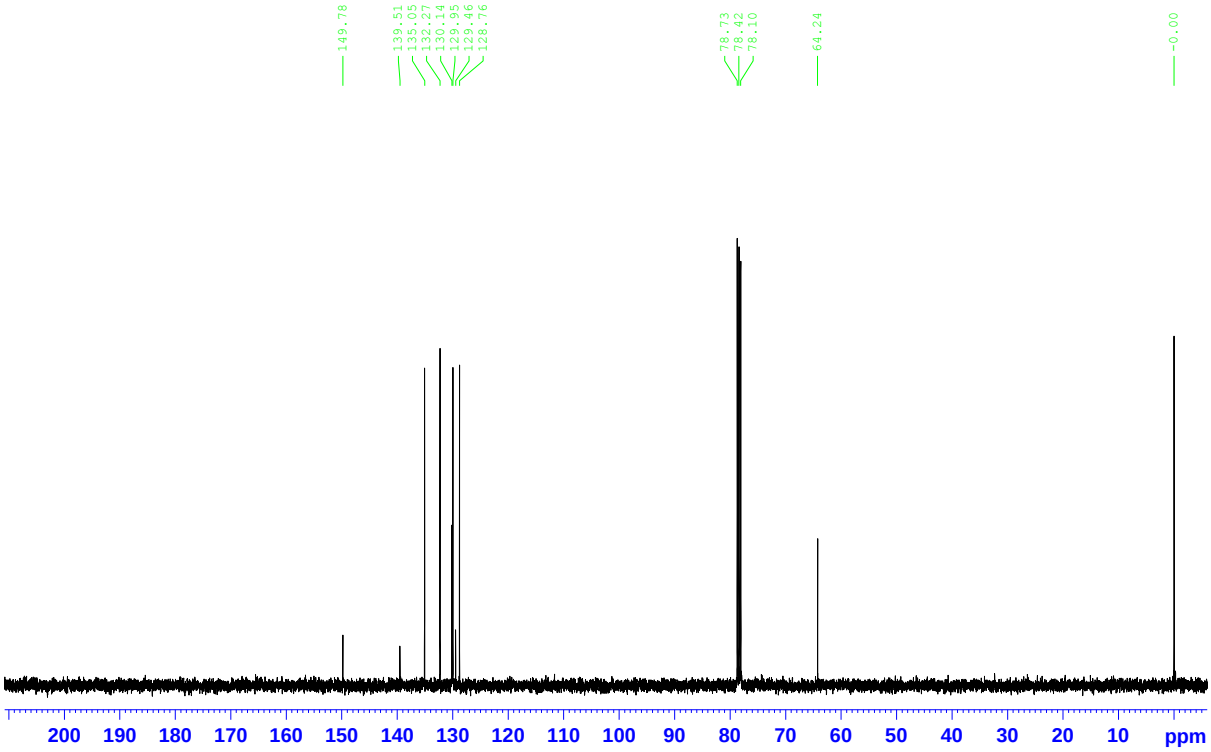
7
6
5
4
3
2
1
0
ppm
4.00
3.39
2.10
2.27
9.31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139.51
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132.27
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129.95
129.46
128.76
78.73
78.42
78.10
64.24
-0.00
200
190
180
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150
140
130
120
110
100
90
80
70
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30
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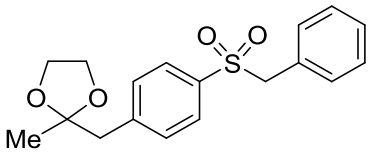
10
ppm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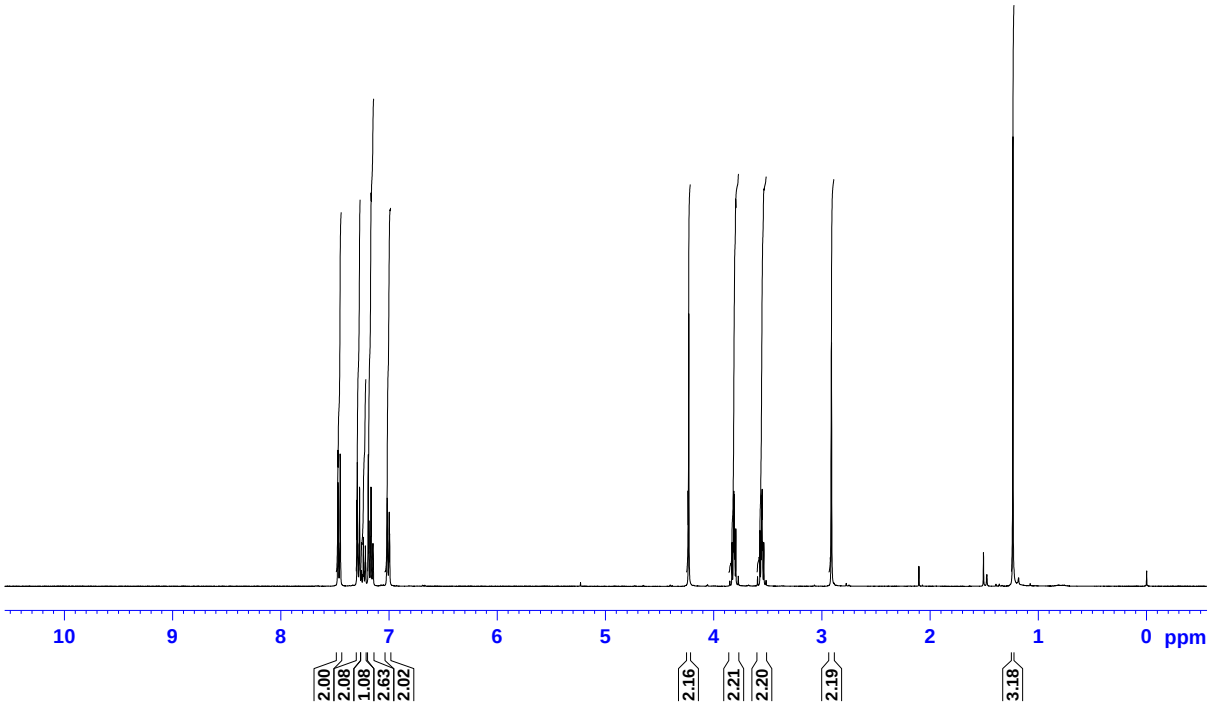
O
S
O
O
Me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9
8
7
6
5
4
3
2
1
0 ppm
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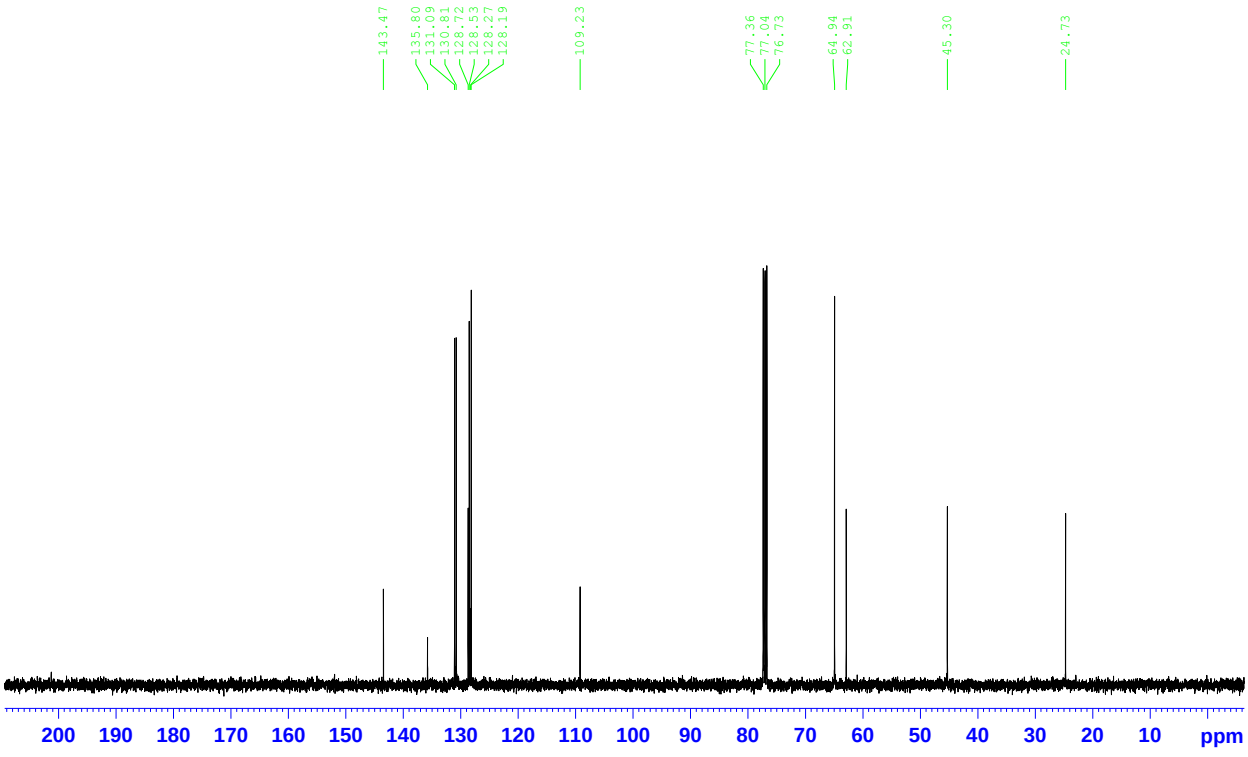
1.08
2.63
2.02
2.16
2.21
2.20
2.19
3.18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130.81
128.72
128.53
128.27
128.19
109.23
77.36
77.04
76.73
64.94
62.91
45.30
24.73
200
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150
140
130
120
110
100
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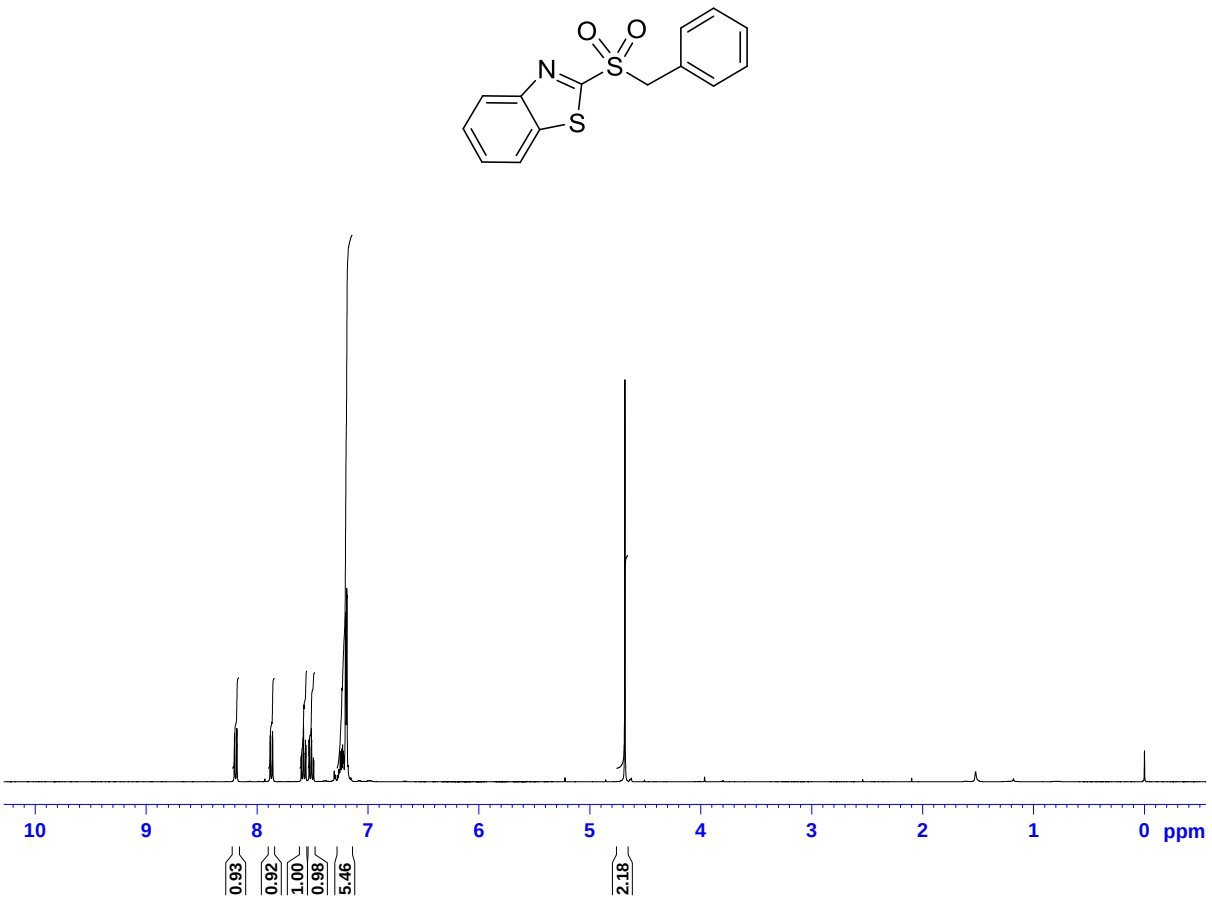
80
70
60
50
40
30
20
10
ppm


O
O
N
S
S
10
9
8
7
6
5
4
3
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0
ppm
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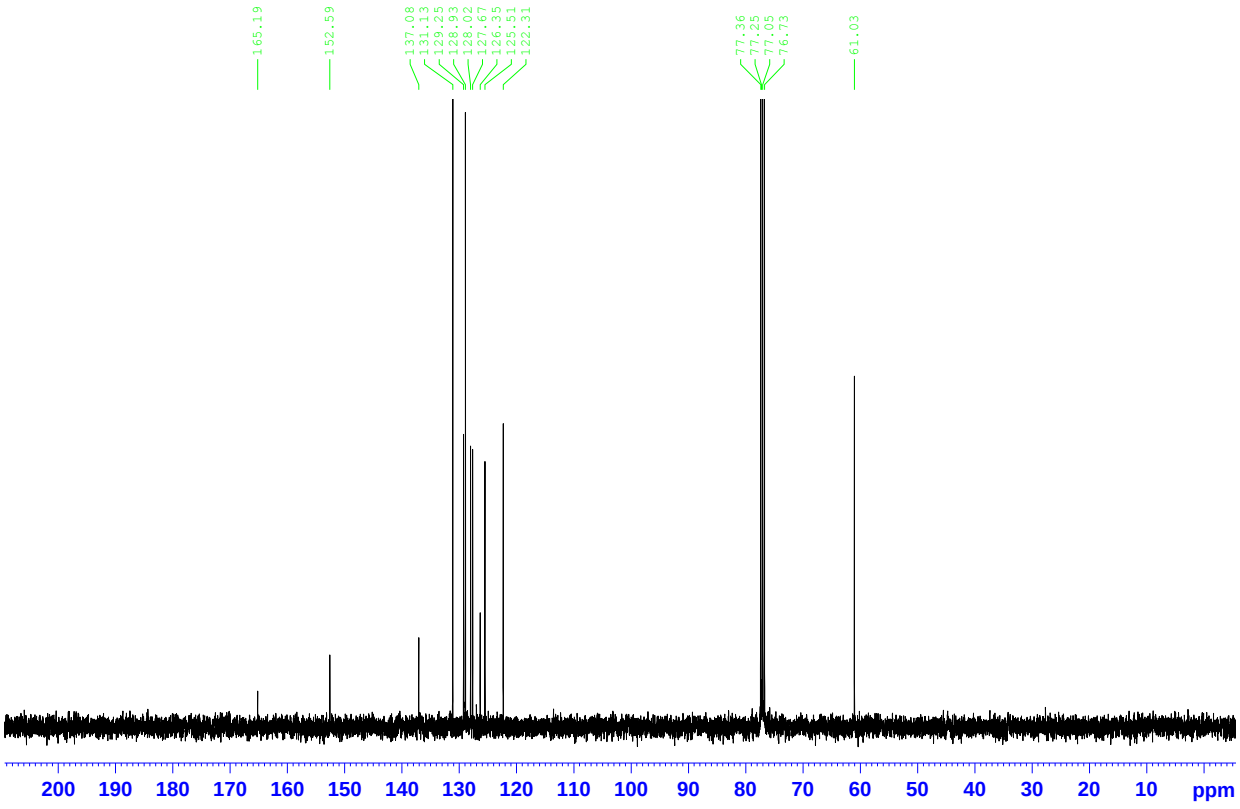
0.92
1.00
0.98
5.46
2.18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131.13
129.25
128.93
128.02
127.67
126.35
125.51
122.31
77.36
77.25
77.05
76.73
61.03
200
190
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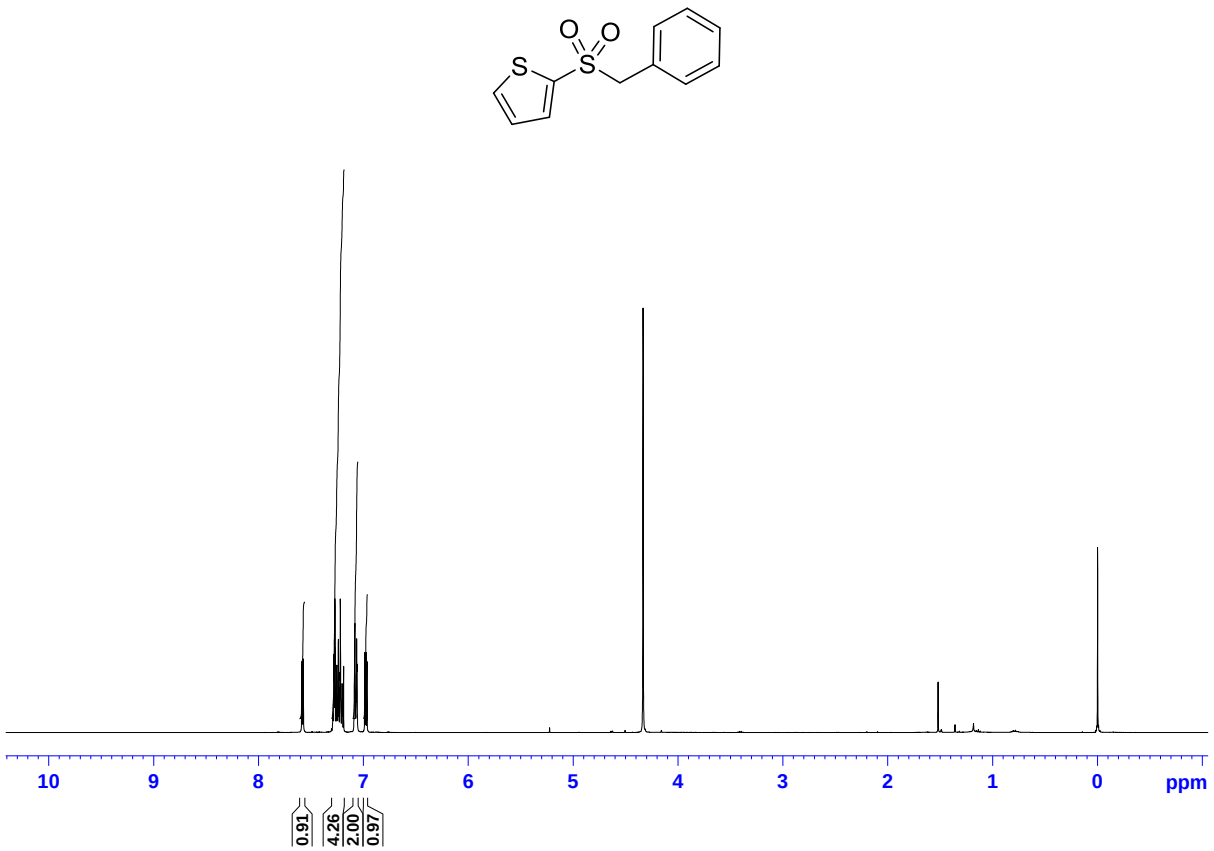
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
O
S
S
10
9
8
7
6
5
4
3
2
1
0
ppm
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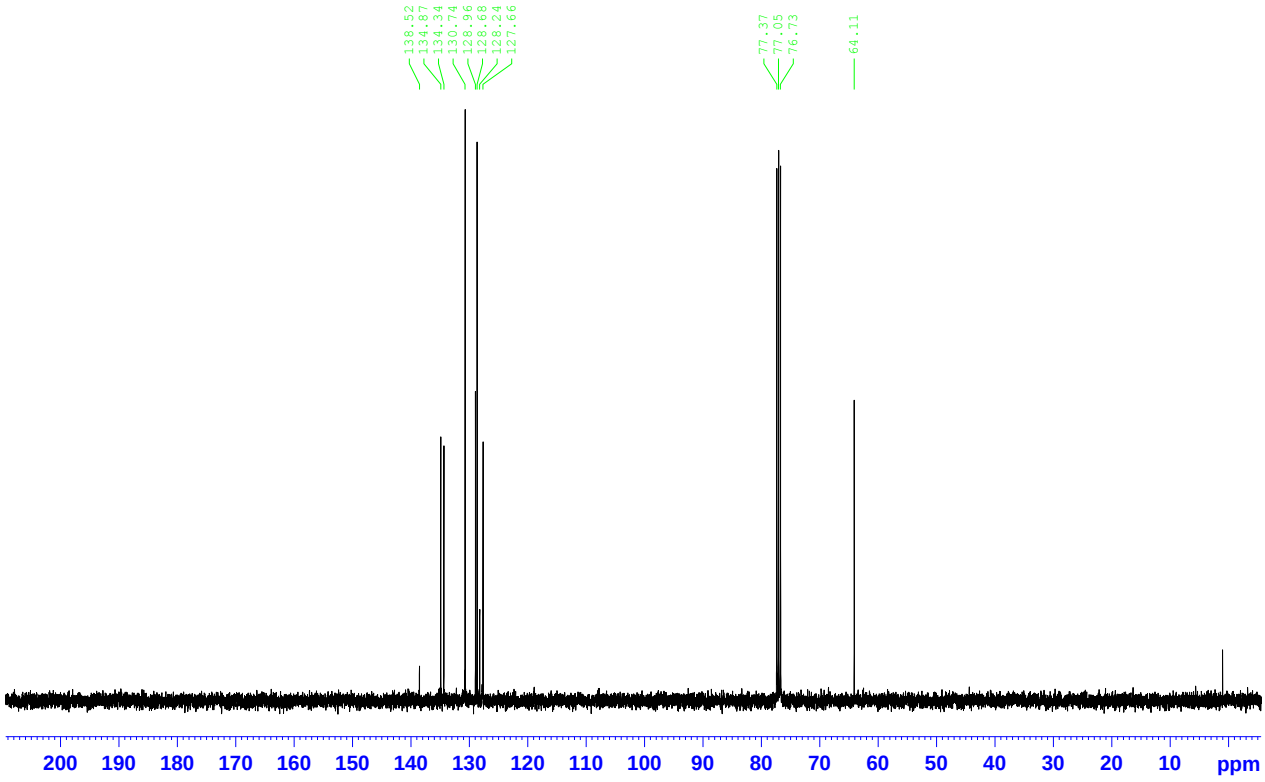
4.26
2.00
0.97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130.74
128.96
128.68
128.24
127.66
77.37
77.05
76.73
64.11
200
190
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150
140
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70
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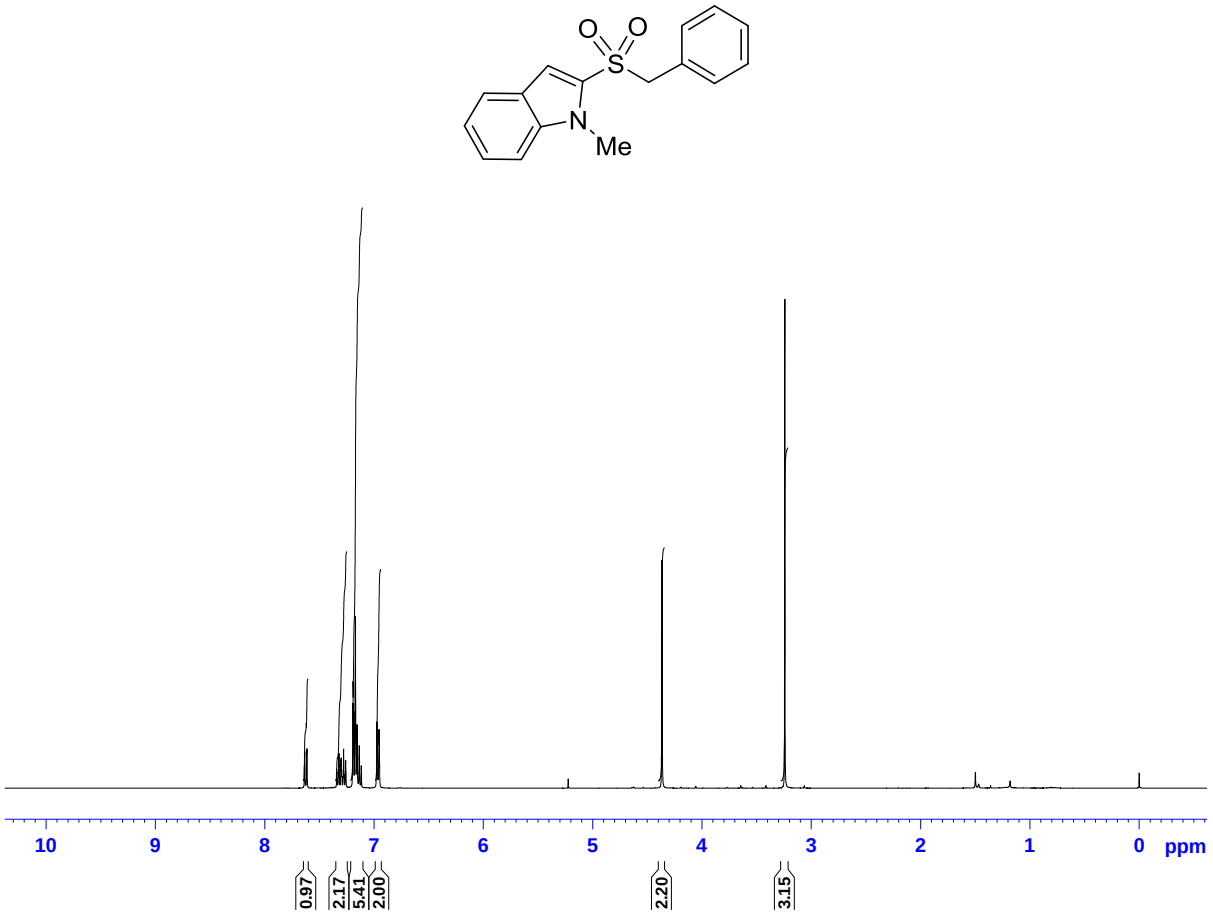
30
20
10
ppm


O
O
S
N
Me
10
9
8
7
6
5
4
3
2
1
0
ppm
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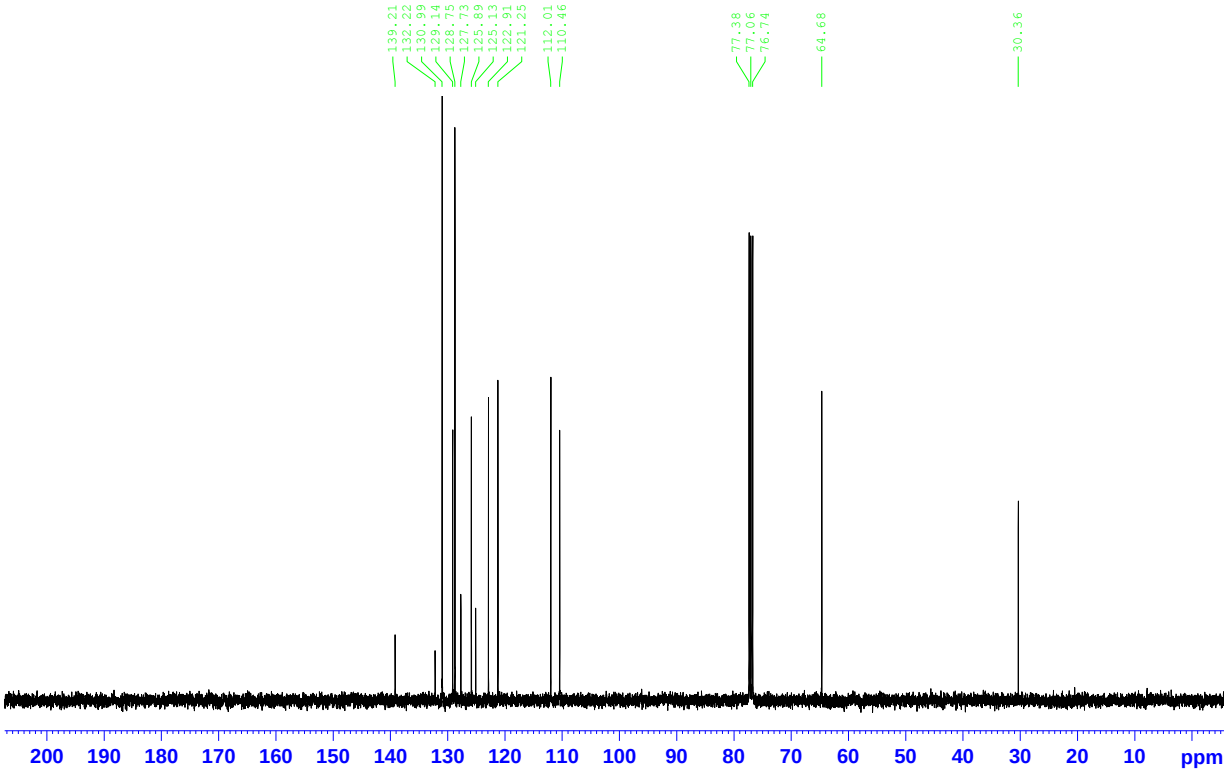
2.00
2.20
3.15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129.14
128.75
127.73
125.89
125.13
122.91
121.25
112.01
110.46
77.38
77.06
76.74
64.68
30.36
200
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100
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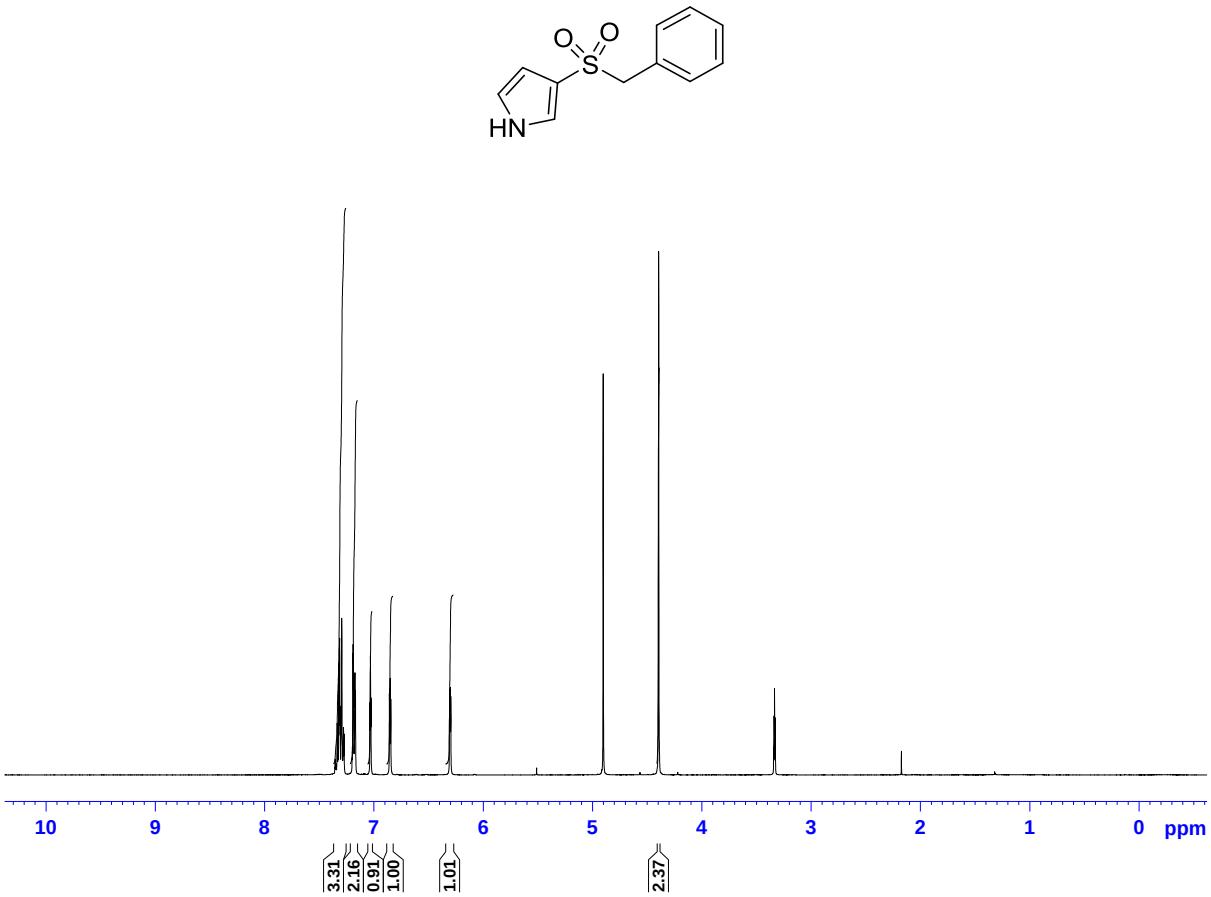
80
70
60
50
40
30
20
10
ppm


O
O
S
HN
10
9
8
7
6
5
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3
2
1
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ppm
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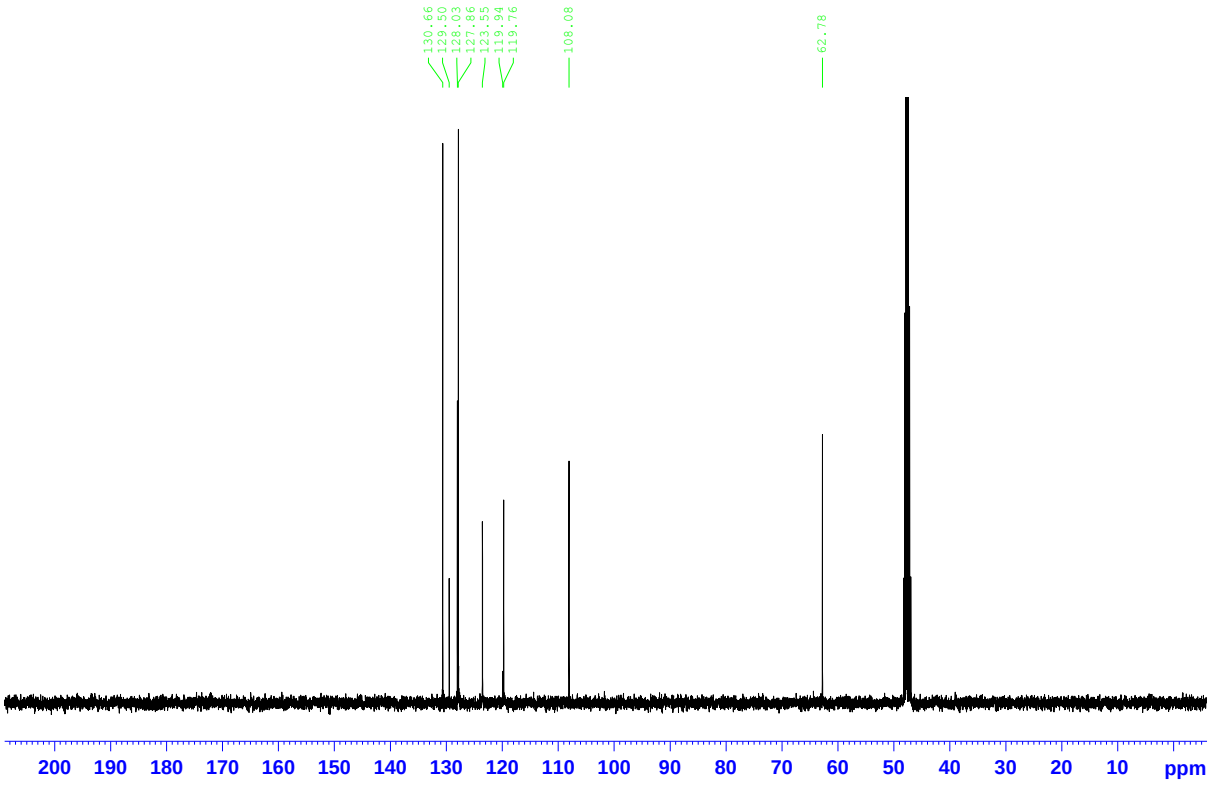
1.00
1.01
2.37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128.03
127.86
123.55
119.94
119.76
108.08
62.78
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150
140
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110
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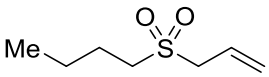
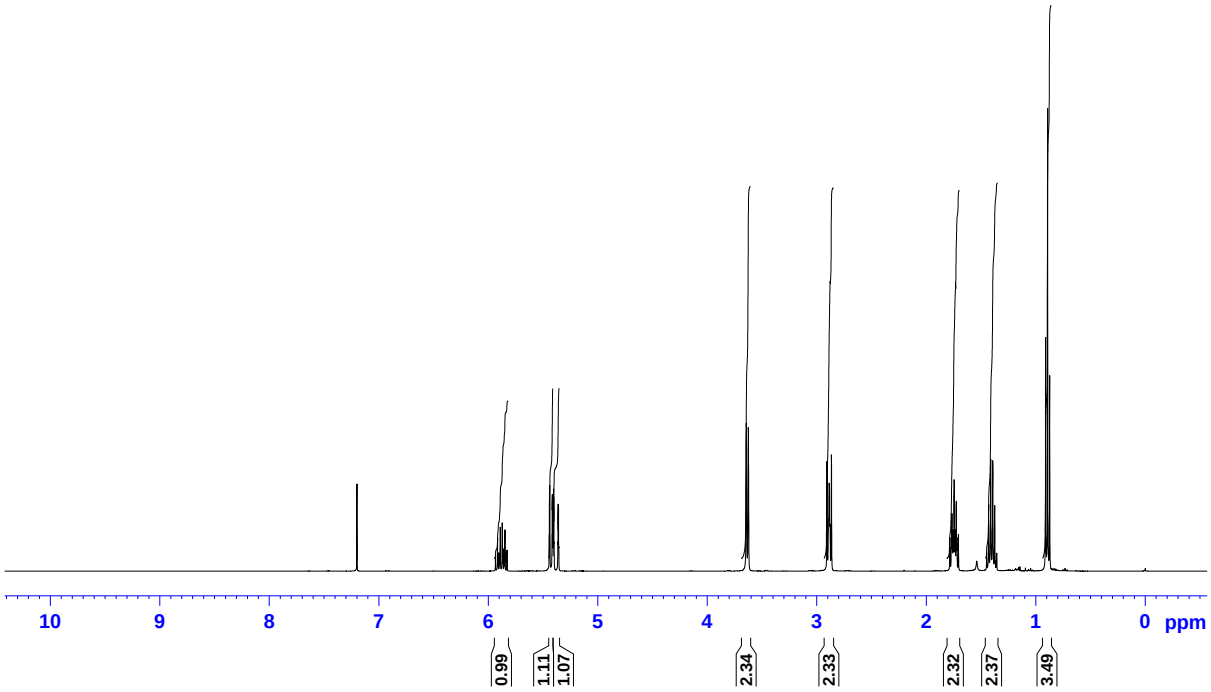
30
20
10
ppm


Me
O
O
S


10
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8
7
6
5
4
3
2
1
0
ppm
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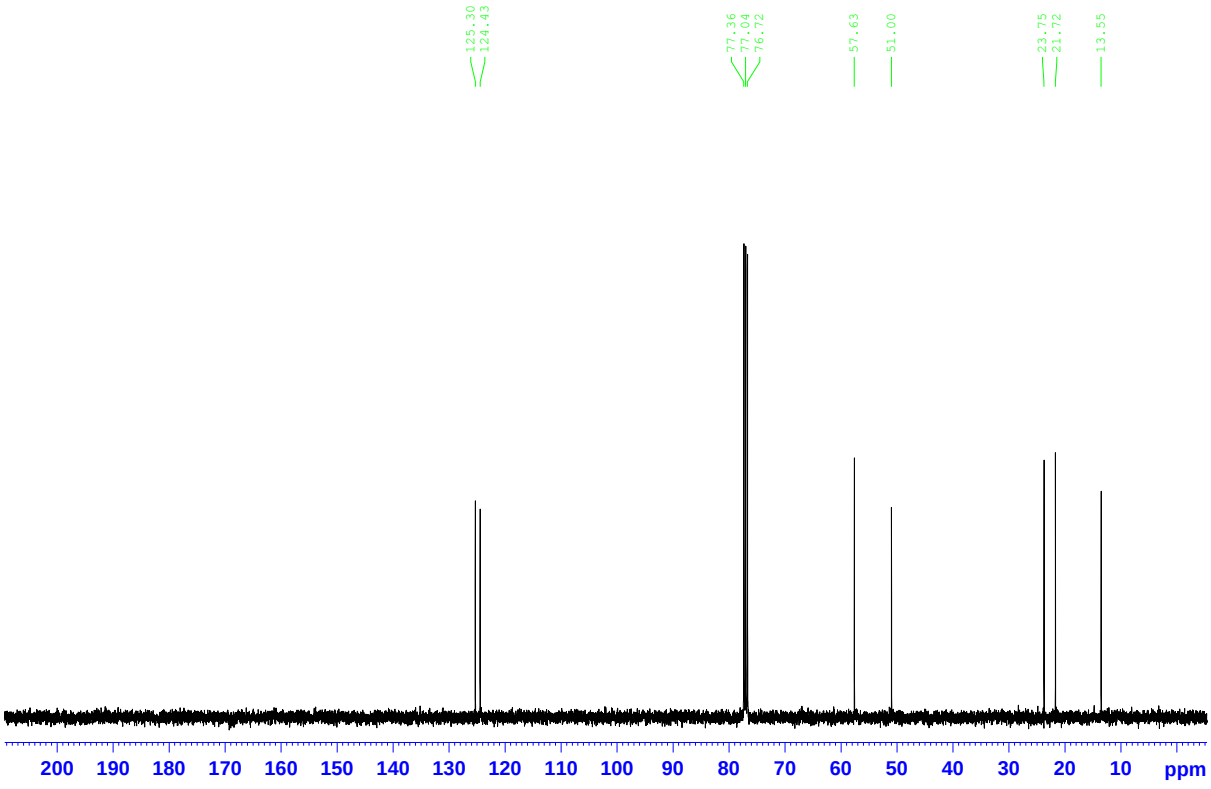
1.07
2.34
2.33
2.32
2.37
3.49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77.36
77.04
76.72
57.63
51.00
23.75
21.72
13.55
200
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180
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150
140
130
120
110
100
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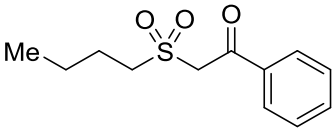
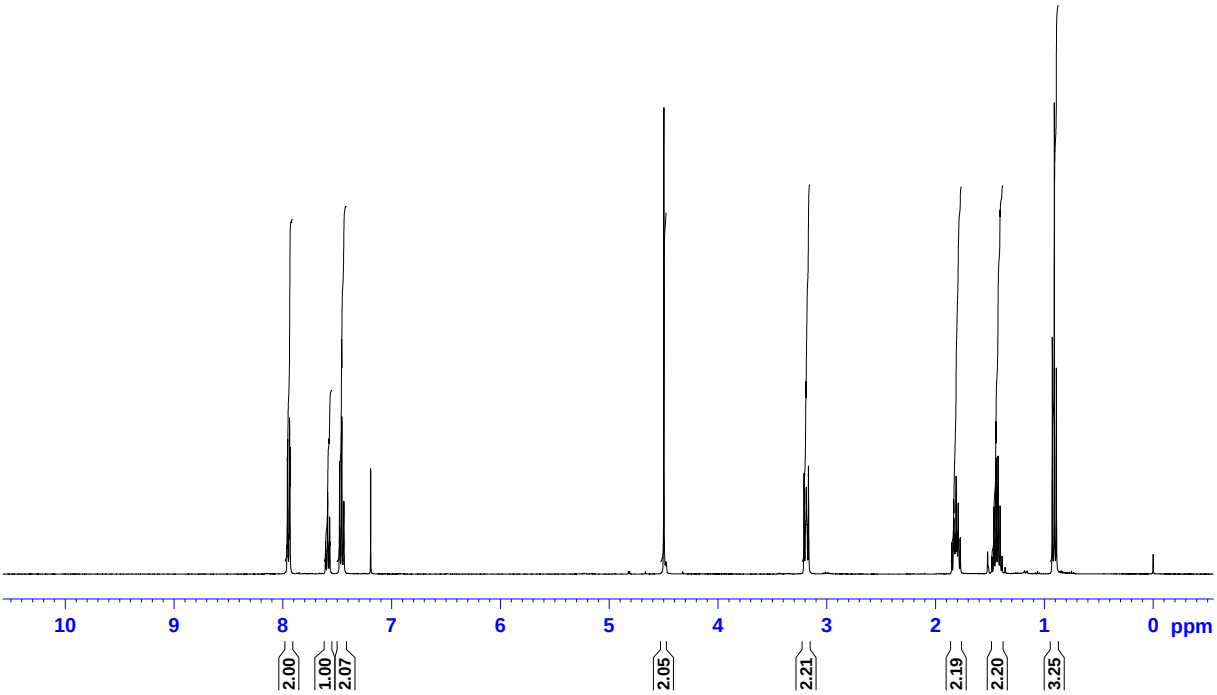
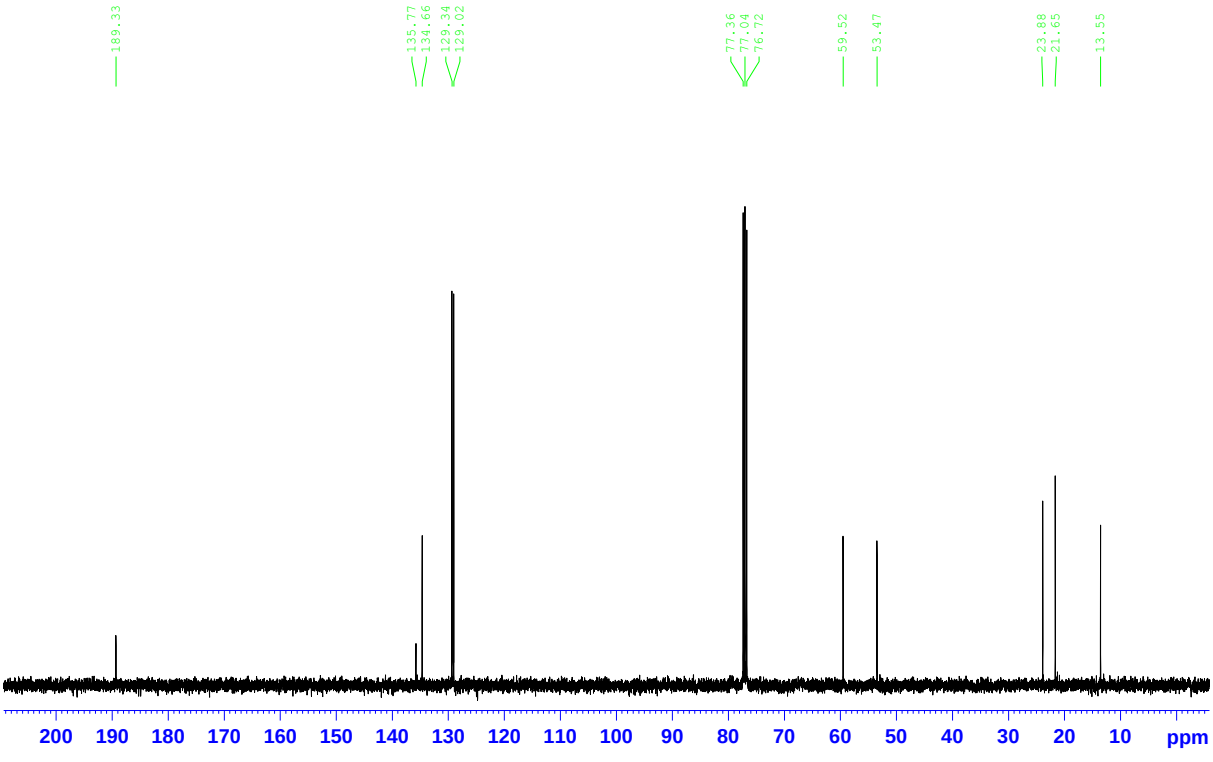
80
70
60
50
40
30
20
10
ppm


Me
S
O
O
O


10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.00
2.07
2.05
2.21
2.19
2.20
3.25

1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129.34
129.02
77.36
77.04
76.72
59.52
53.47
23.88
21.65
13.55
200
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180
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150
140
130
120
110
100
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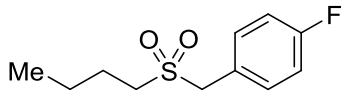
80
70
60
50
40
30
20
10
ppm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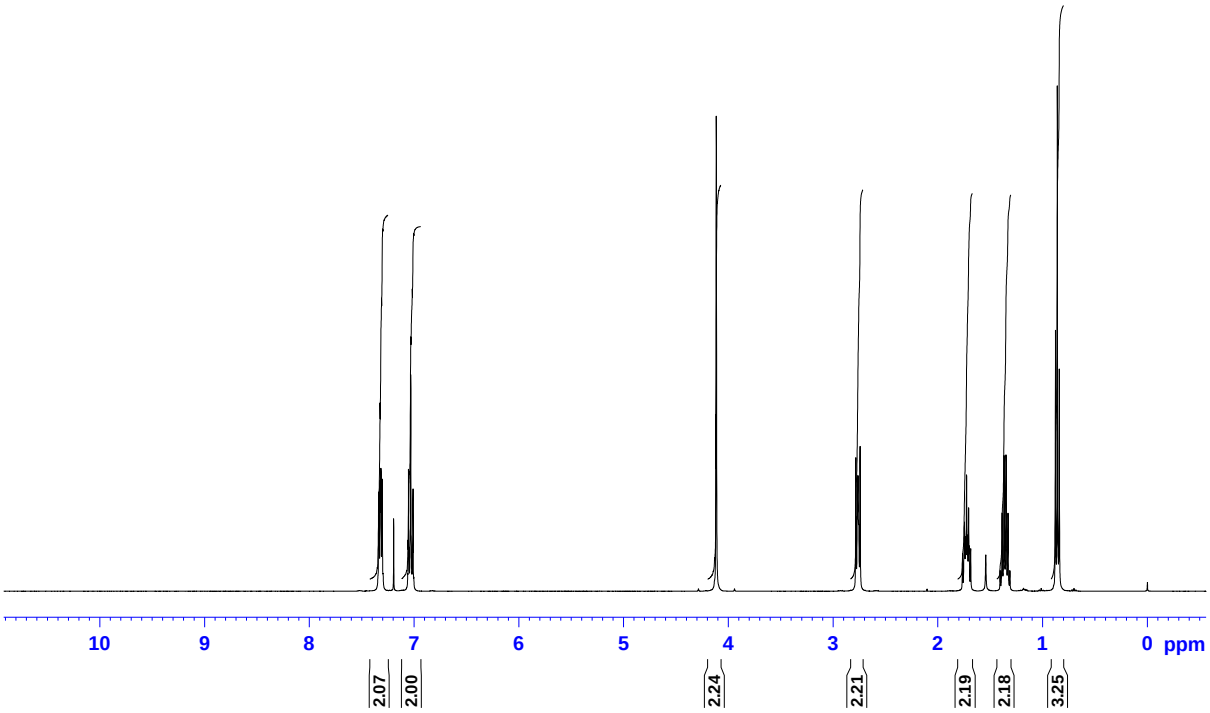
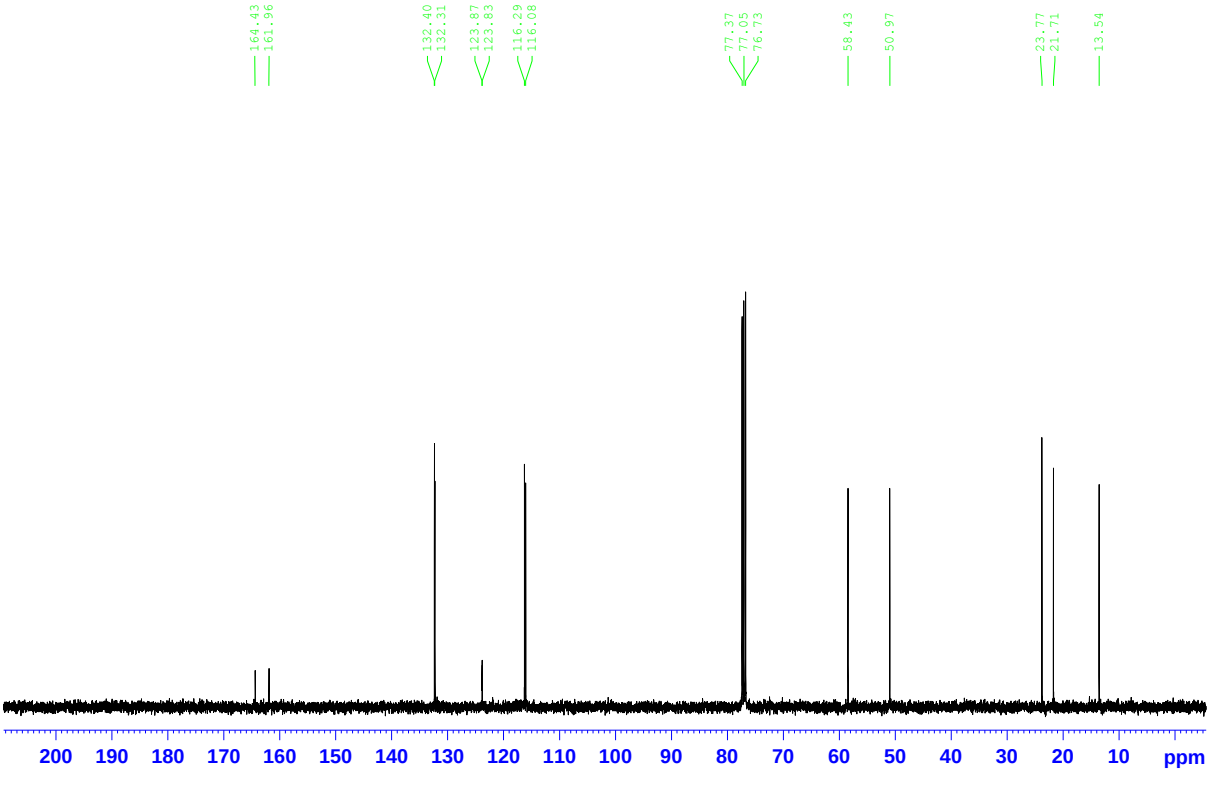
S
O
O
F


10
9
8
7
6
5
4
3
2
1
0
ppm
2.07
2.00
2.24
2.21
2.19
2.18
3.25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161.96
132.40
132.31
123.87
123.83
116.29
116.08
77.37
77.05
76.73
58.43
50.97
23.77
21.71
13.54
200
190
180
170
160
150
140
130
120
110
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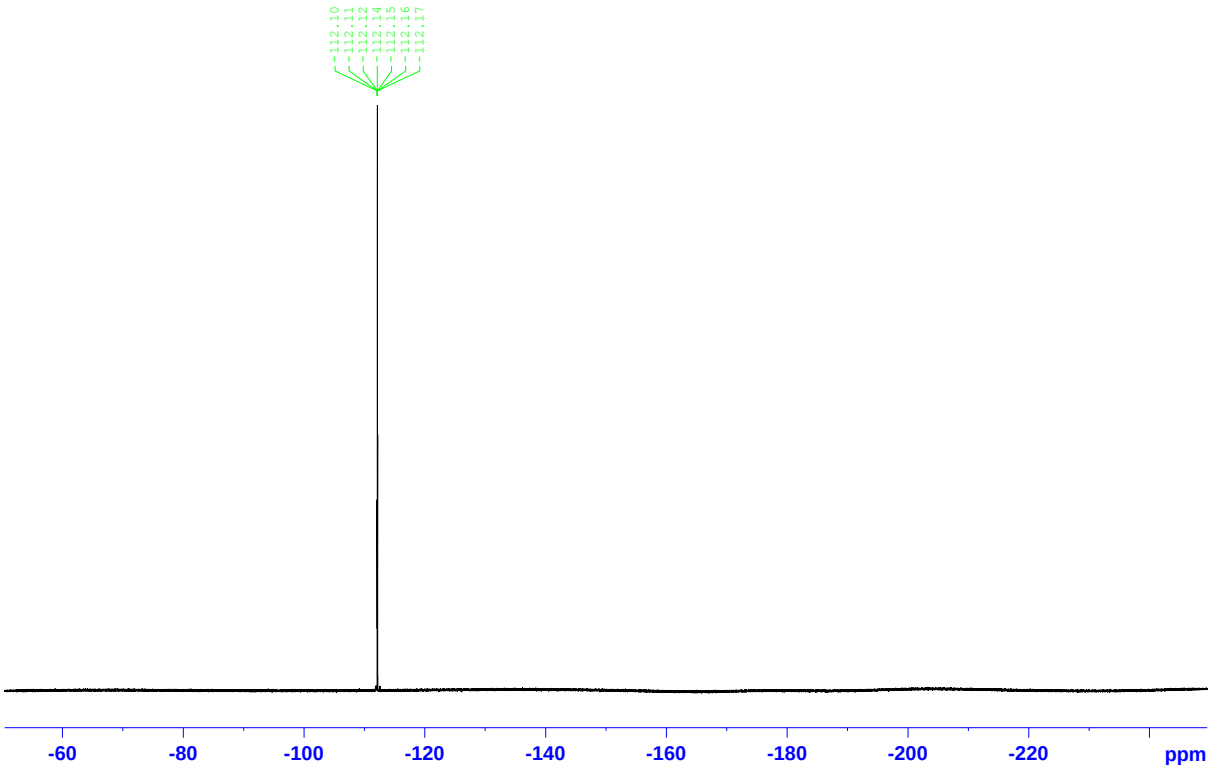
70
60
50
40
30
20
10
ppm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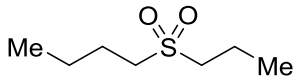
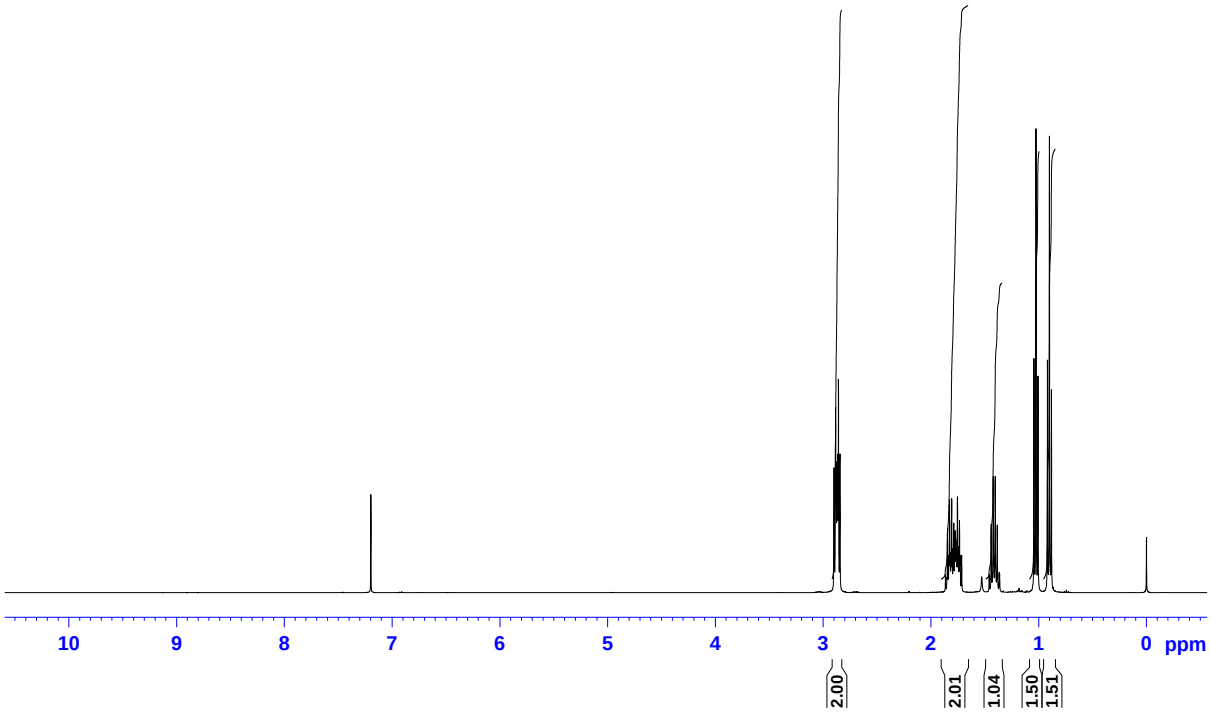
-112.11
-112.12
-112.14
-112.15
-112.16
-112.17
-60
-80
-100
-120
-140
-160
-180
-200
-220
ppm


Me
O
O
S
Me


10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.01
1.04
1.50
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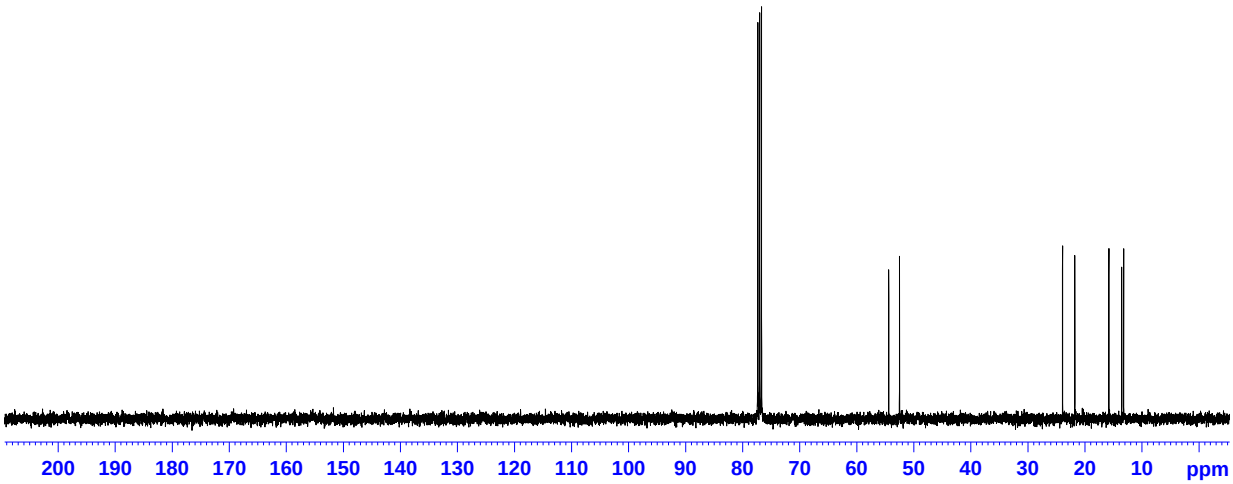
52.52
23.94
21.80
15.82
13.57
13.22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140
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100
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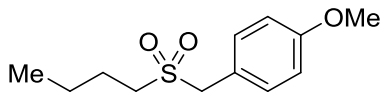
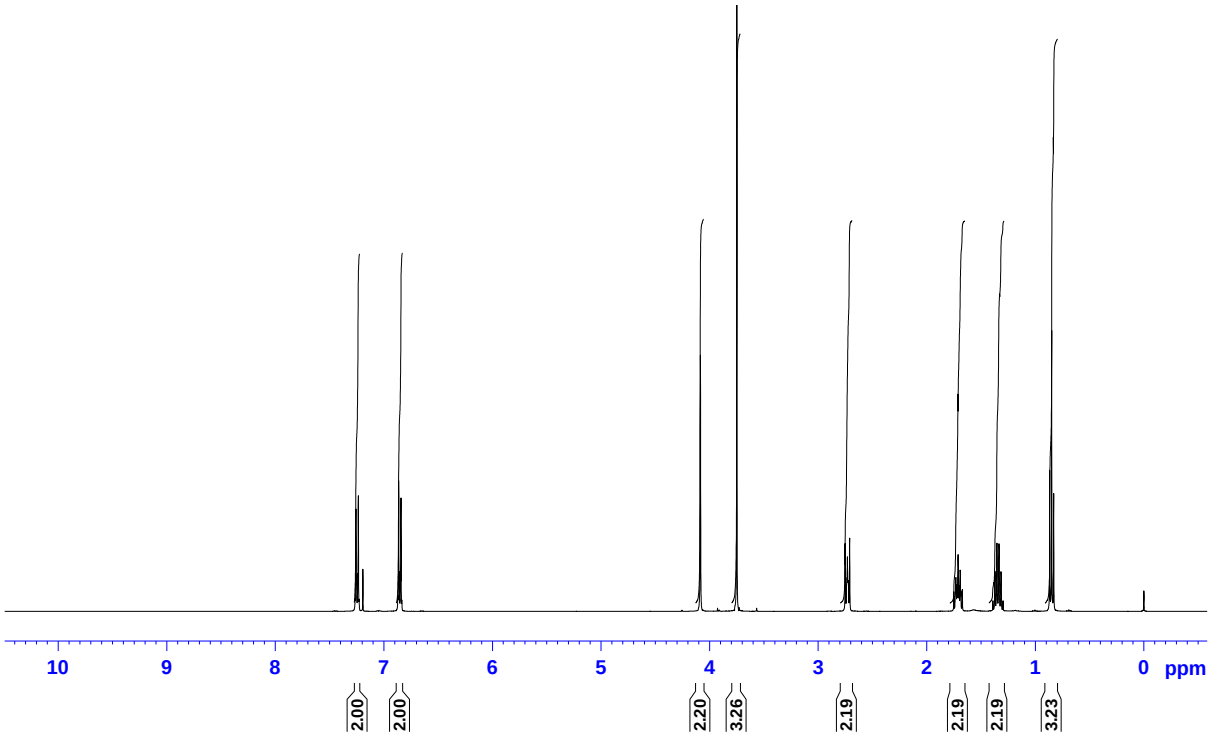
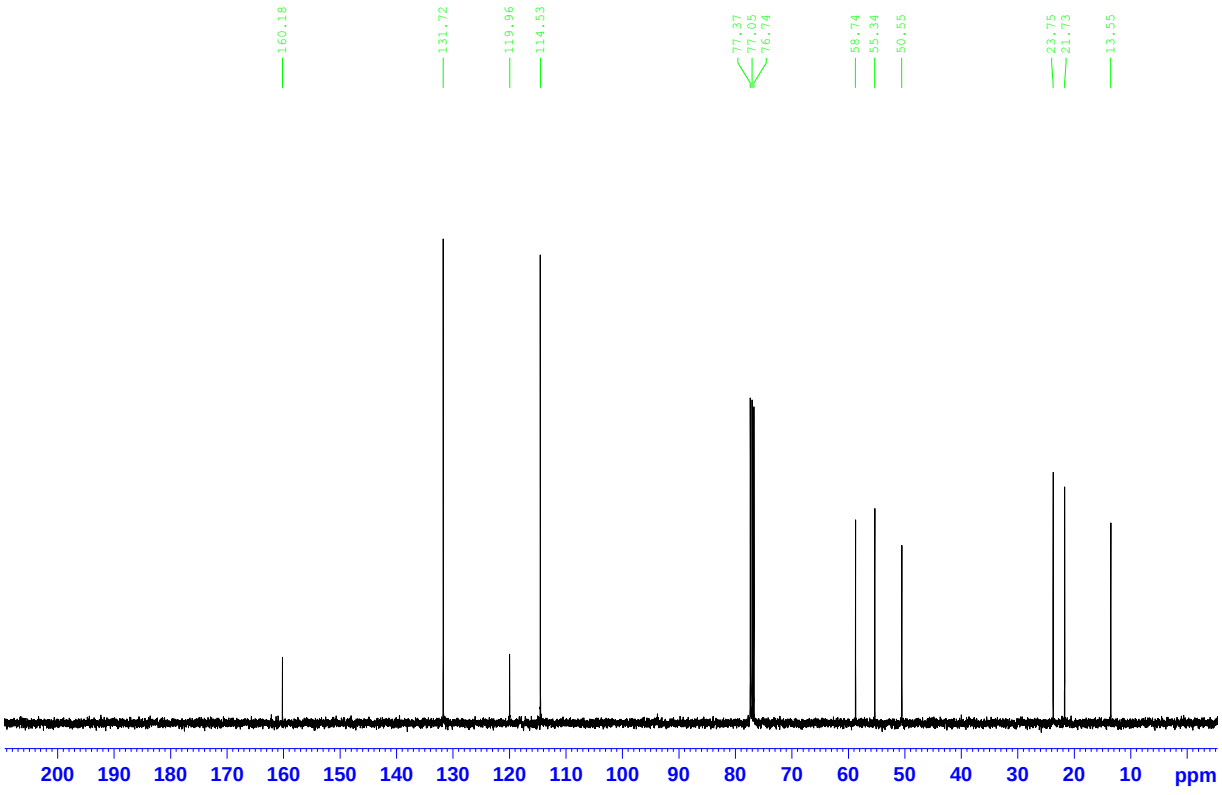
70
60
50
40
30
20
10
ppm


OMe
O
O
S
Me


10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.00
2.20
3.26
2.19
2.19
2.19
3.23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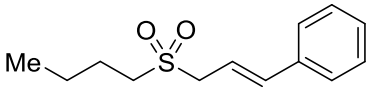
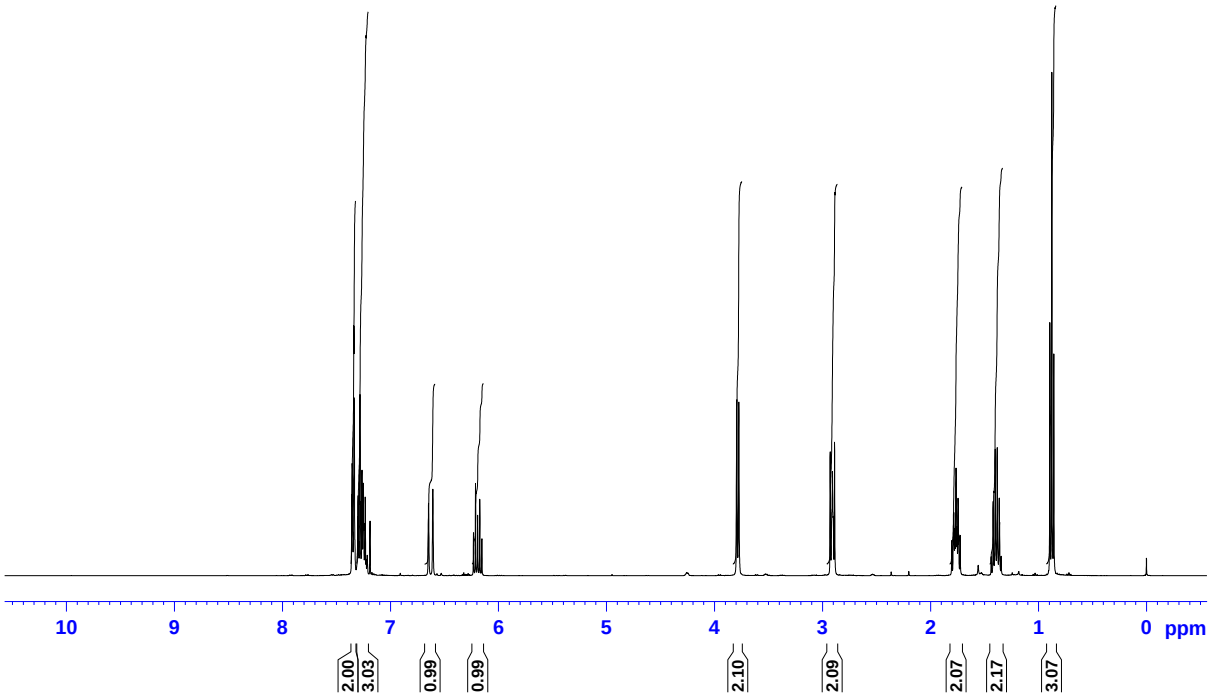
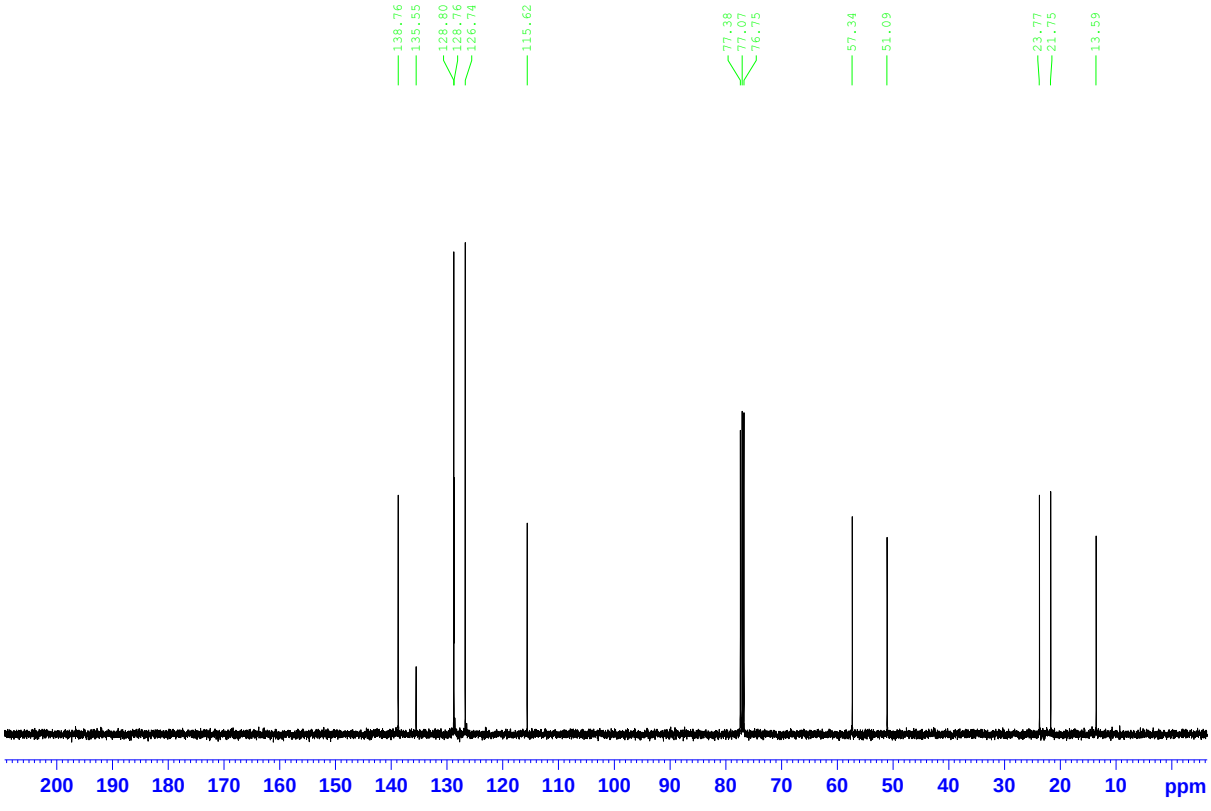
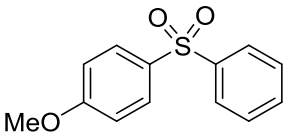
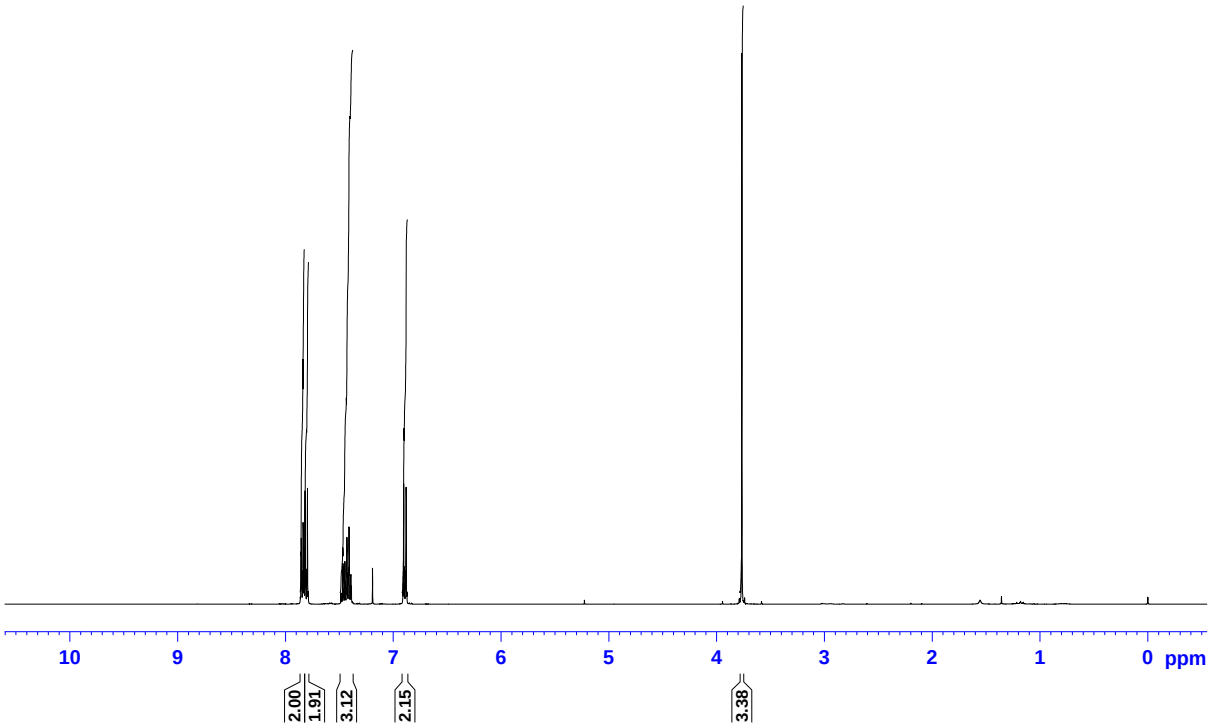
131.72
119.96
114.53
77.37
77.05
76.74
58.74
55.34
50.55
23.75
21.73
13.55
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Me
O
O
S


10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
3.03
0.99
0.99
2.10
2.09
2.07
2.17
3.07


138.76
135.55
128.80
128.76
126.74
115.62
77.38
77.07
76.75
57.34
51.09
23.77
21.75
13.59
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
O
S
MeO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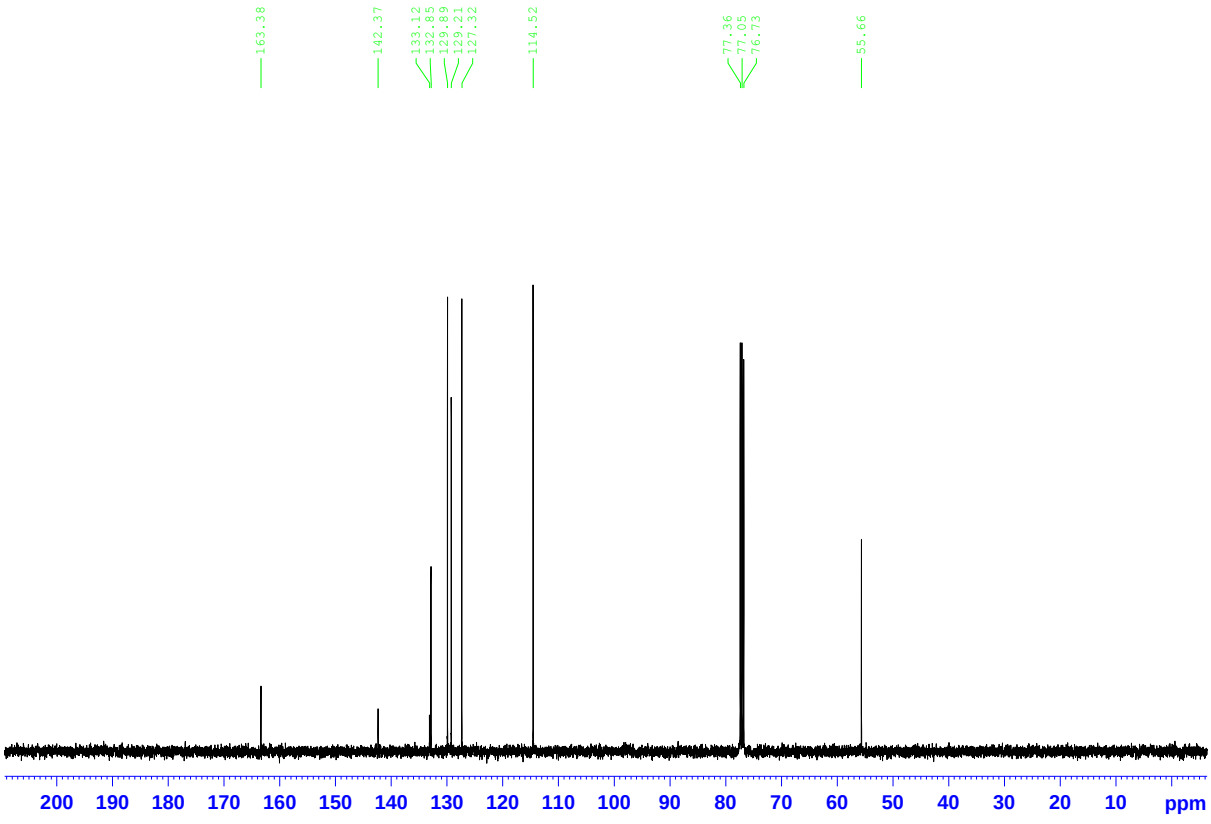
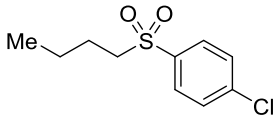
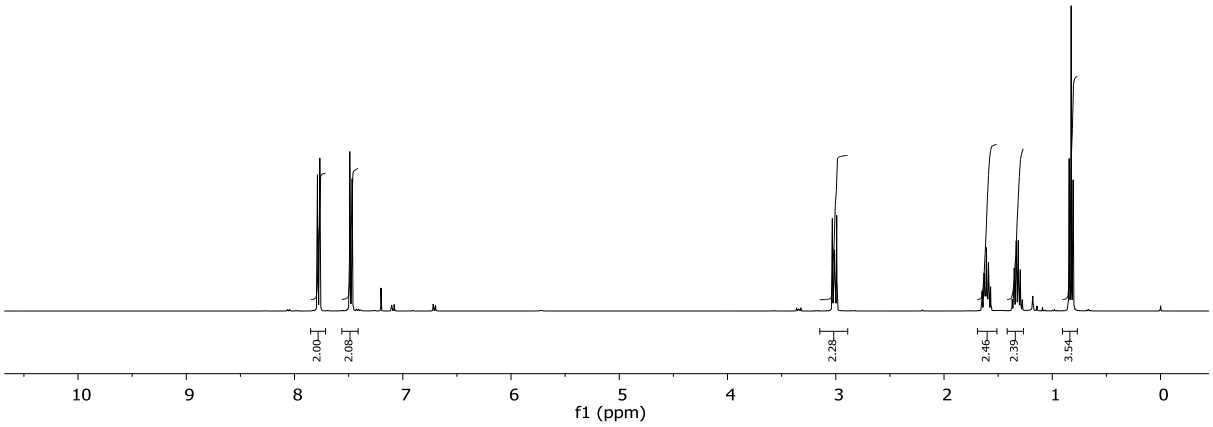
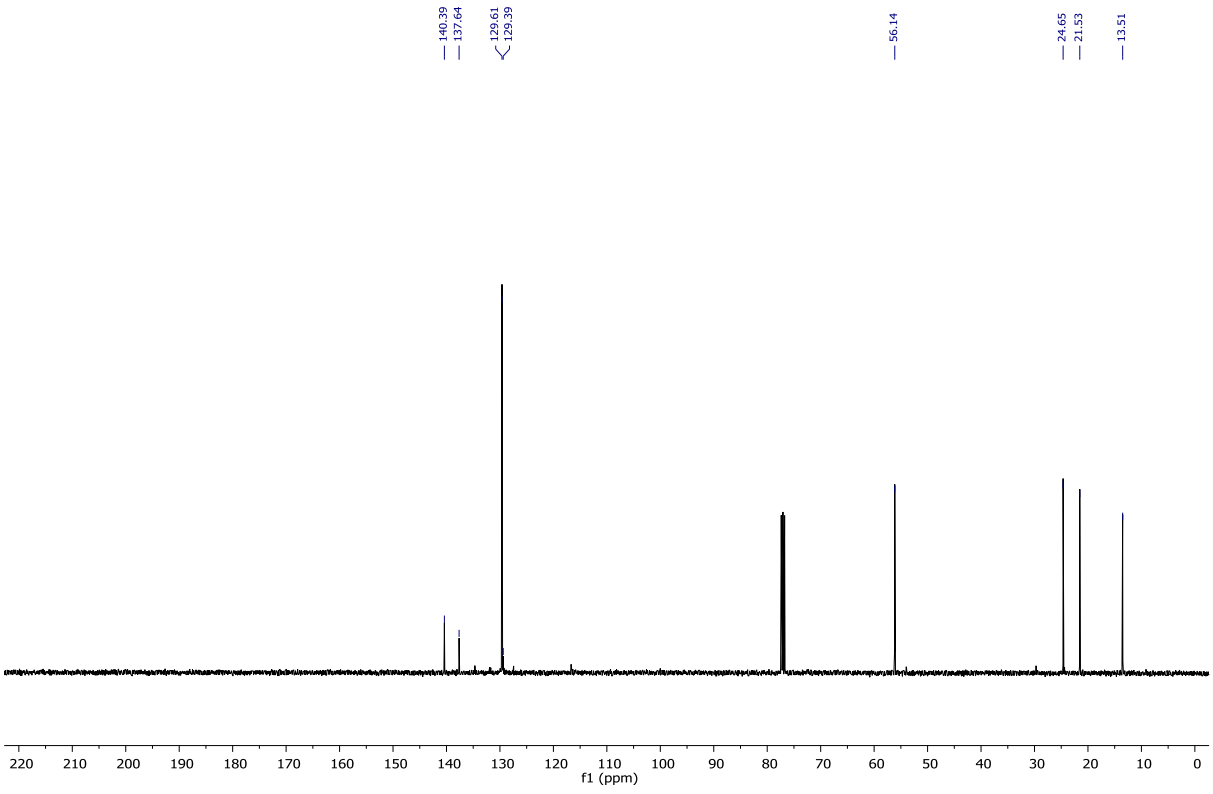
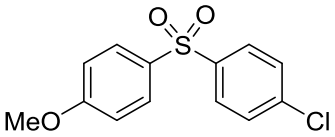
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.91
3.12
2.15
3.38

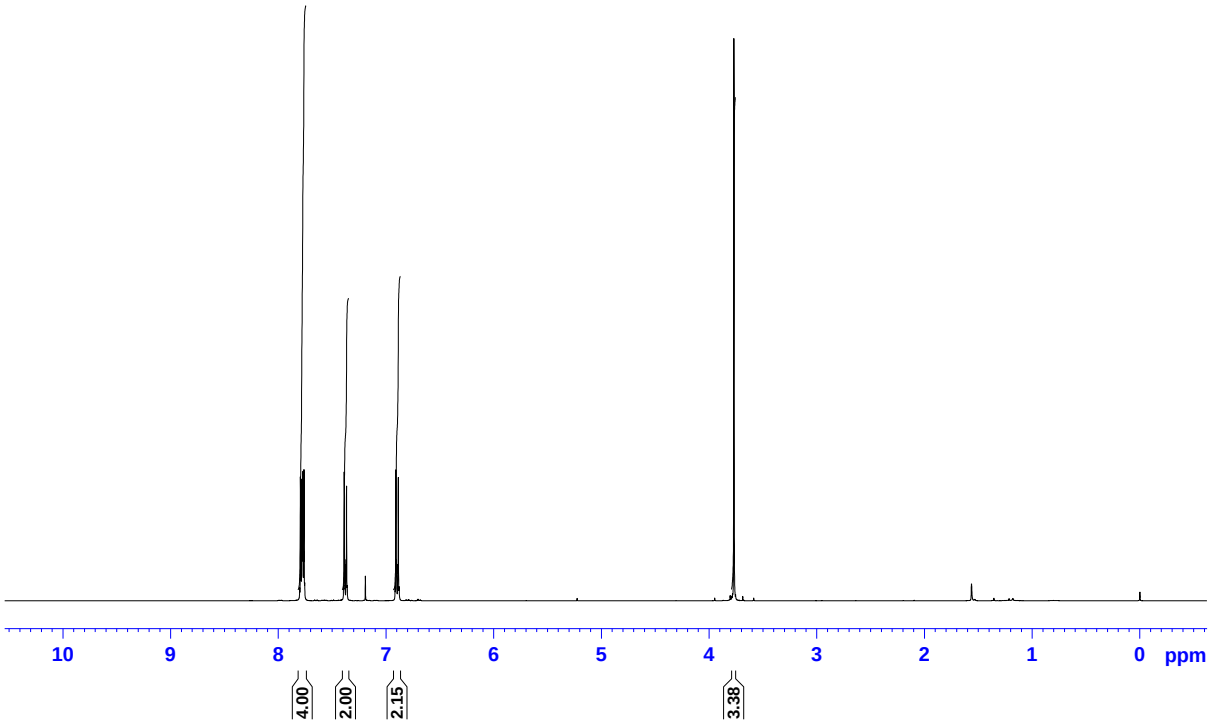

163.38
142.37
133.12
132.85
129.89
129.21
127.32
114.52
77.36
77.05
76.73
55.66
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

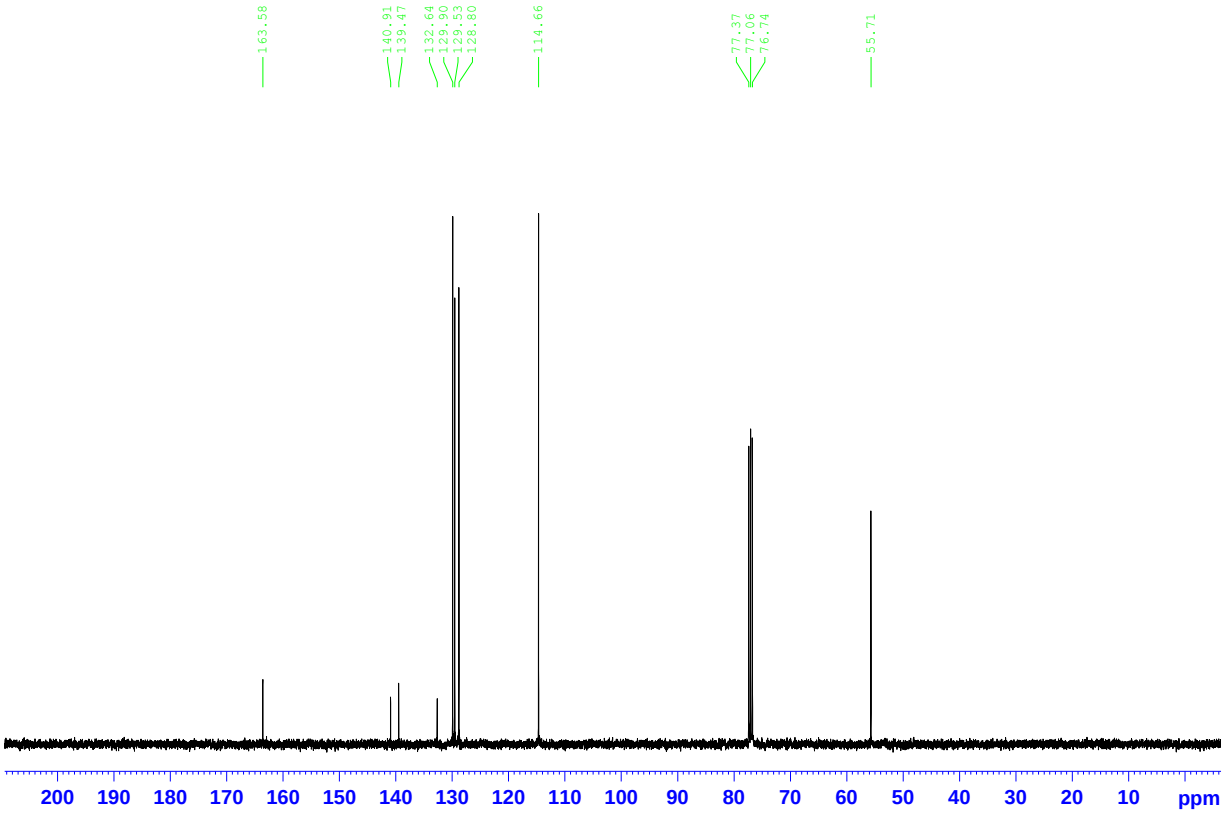

Me
O
O
S
Cl

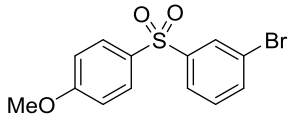

2.00
2.08
2.28
2.46
2.39
3.54
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

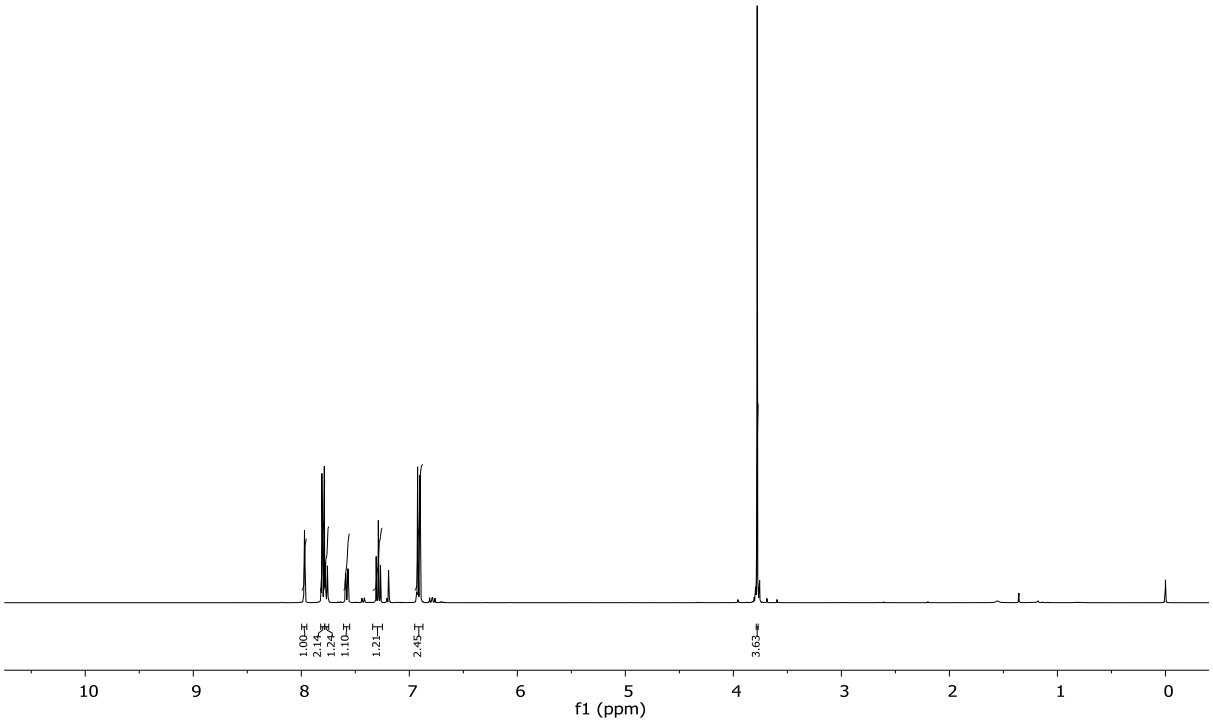

140.39
137.64
129.61
129.39
56.14
24.65
21.53
13.51
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
MeO
Cl

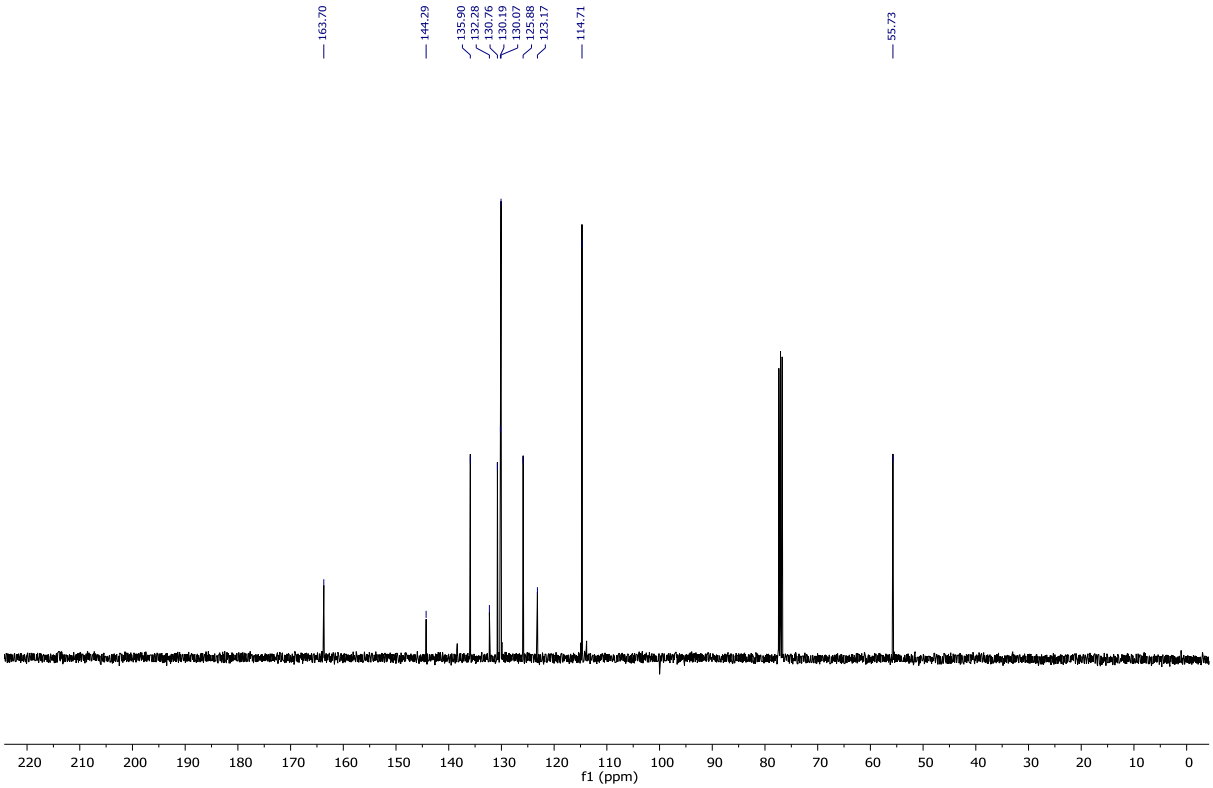

10
9
8
7
6
5
4
3
2
1
0
ppm
4.00
2.00
2.15
3.38

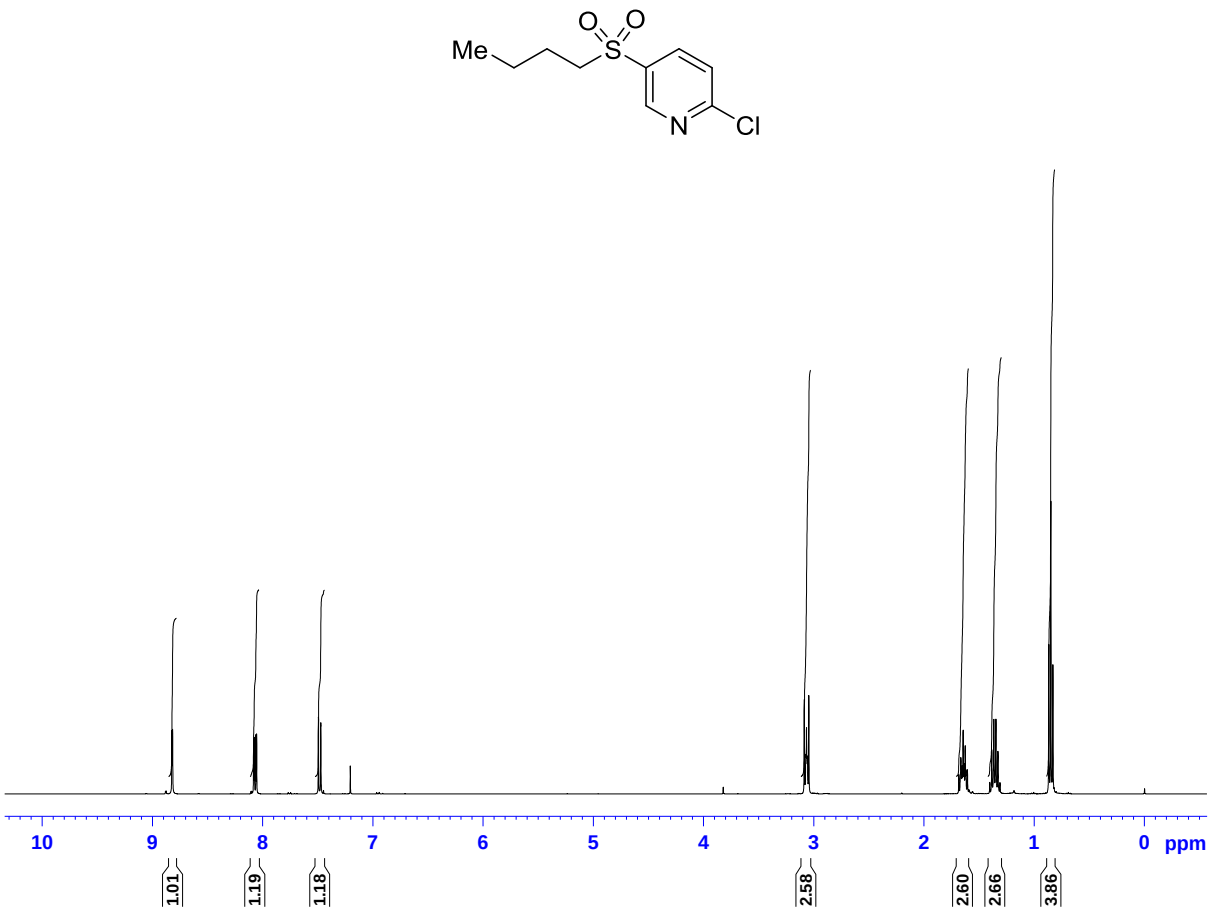

163.58
140.91
139.47
132.64
129.90
129.53
128.80
114.66
77.37
77.06
76.74
55.71
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

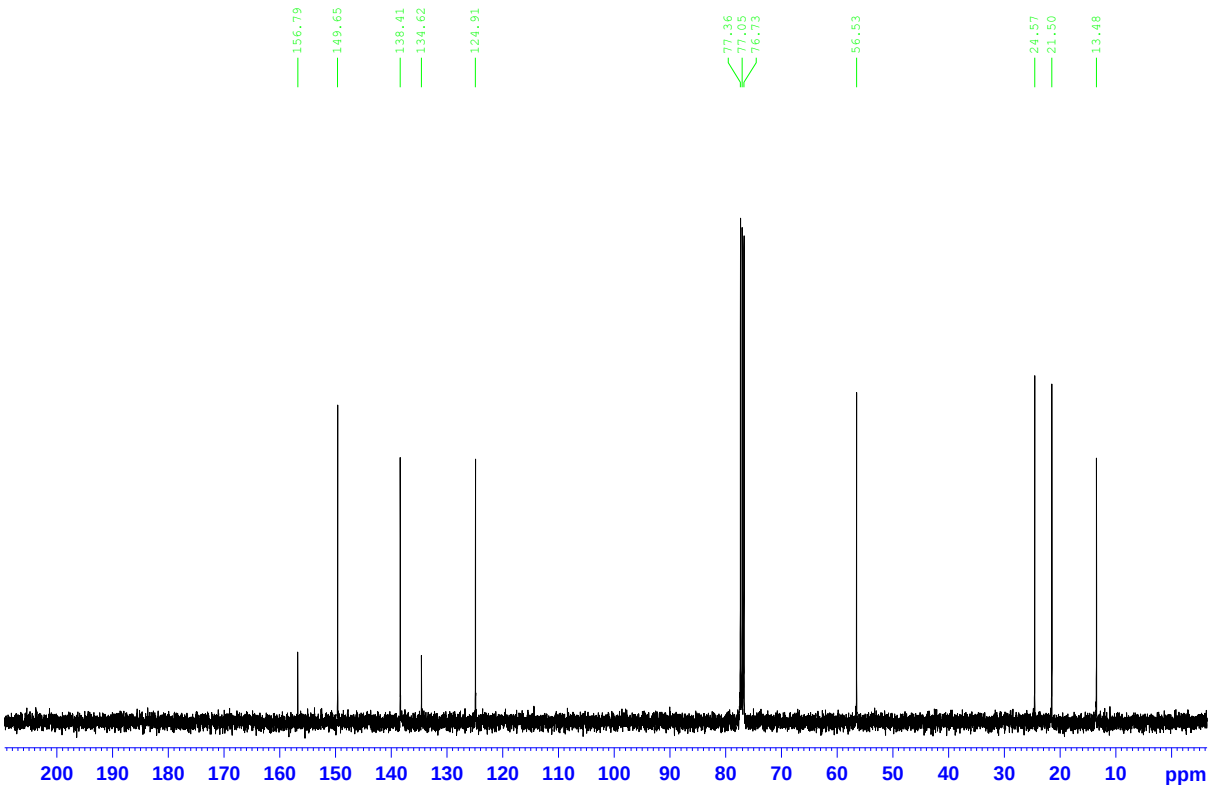

O
O
S
Br
MeO


1.00
2.14
1.24
1.10
1.21
2.45
3.63
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

1


163.70
144.29
135.90
132.28
130.76
130.19
130.07
125.88
123.17
114.71
55.73
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
O
O
S
N
Cl
10
9
8
7
6
5
4
3
2
1
0
ppm
1.01
1.19
1.18
2.58
2.60
2.66
3.86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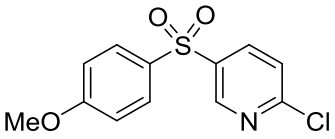
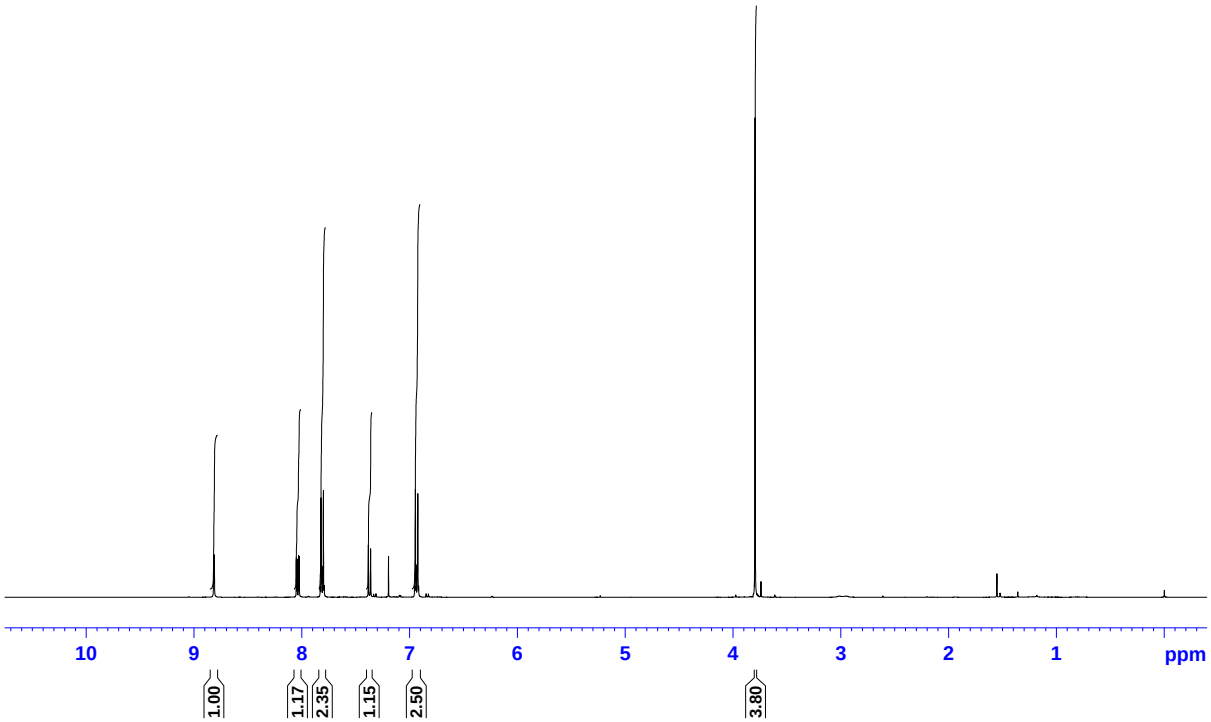
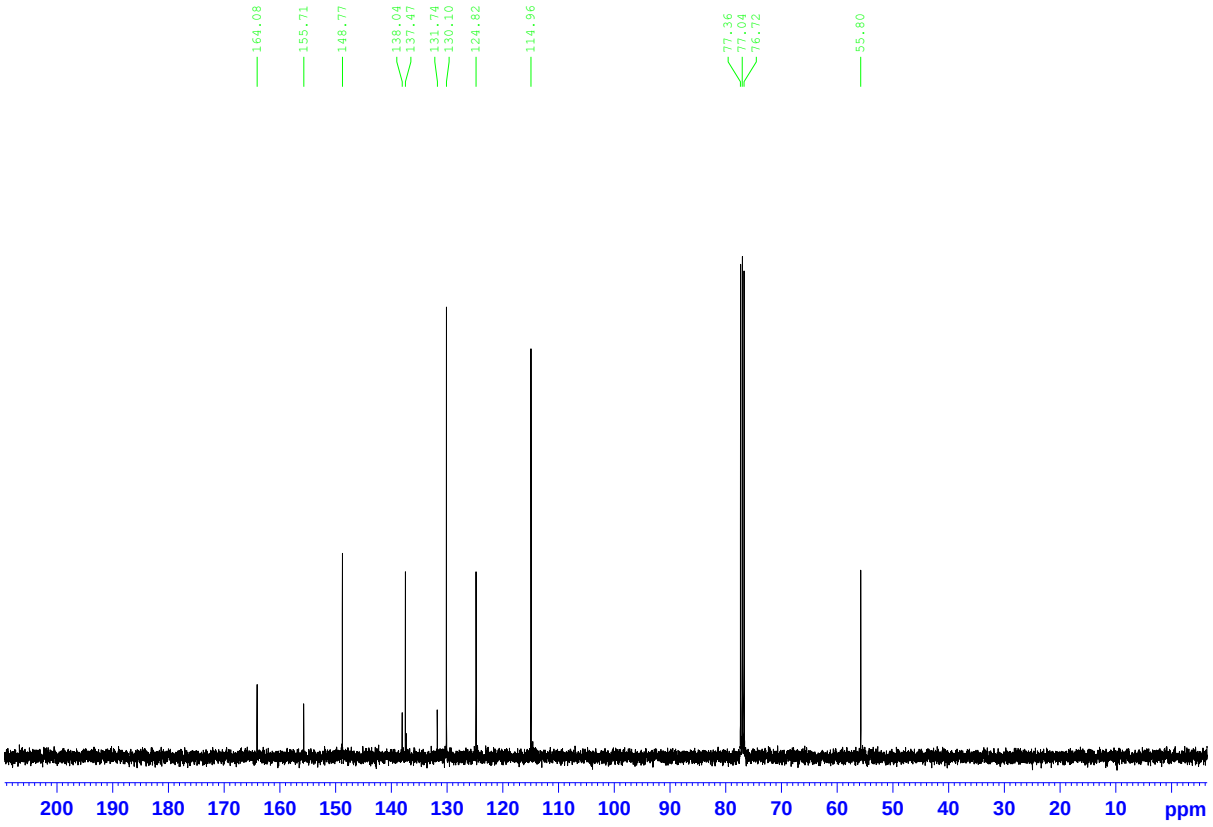
149.65
138.41
134.62
124.91
77.36
77.05
76.73
56.53
24.57
21.50
13.48
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
O
S
MeO
N
Cl


10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.17
2.35
1.15
2.50
3.80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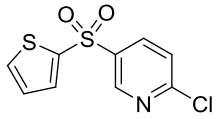
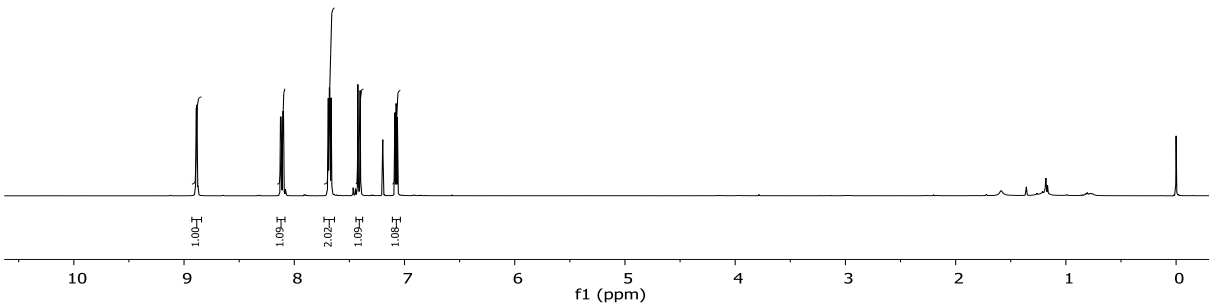
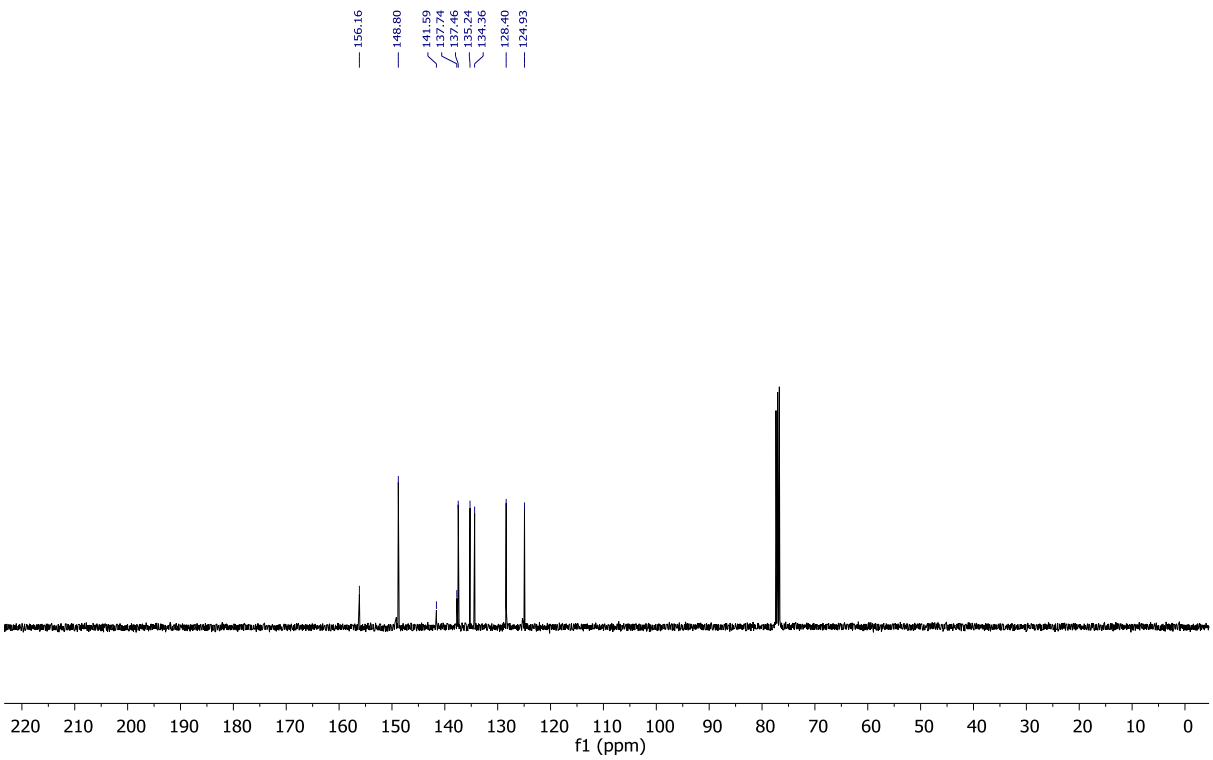
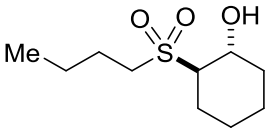
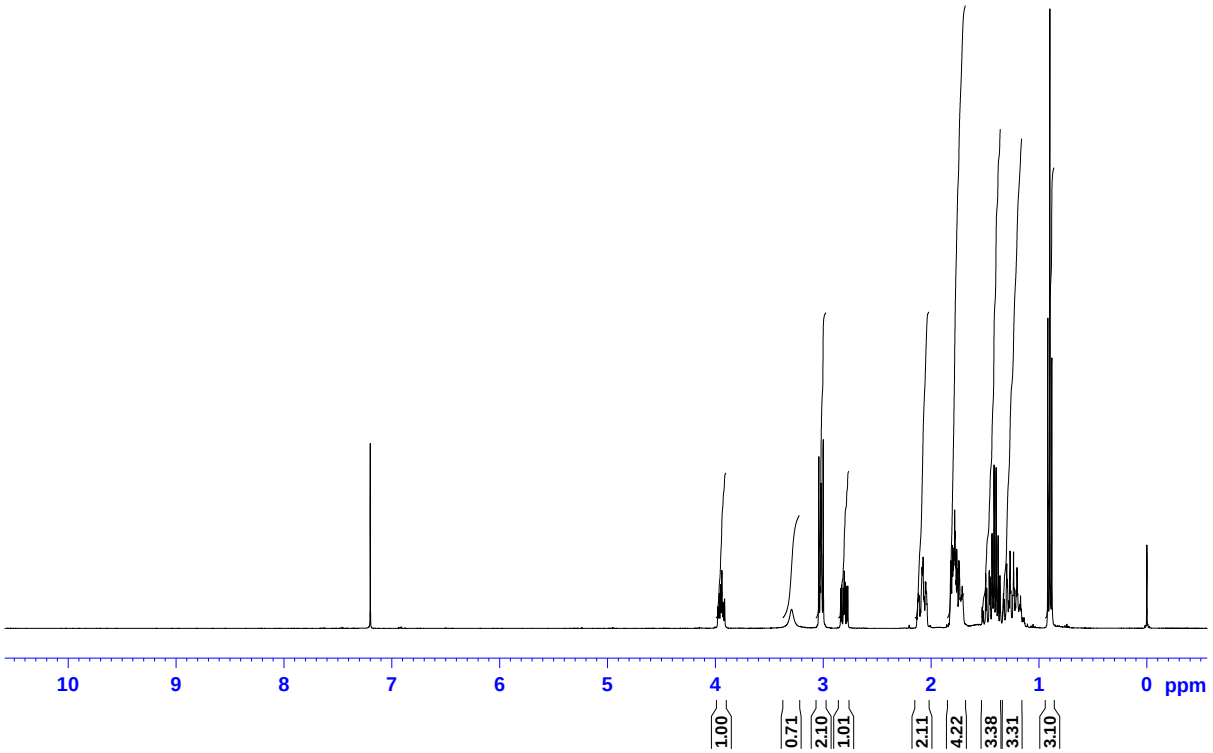
155.71
148.77
138.04
137.47
131.74
130.10
124.82
114.96
77.36
77.04
76.72
55.80
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

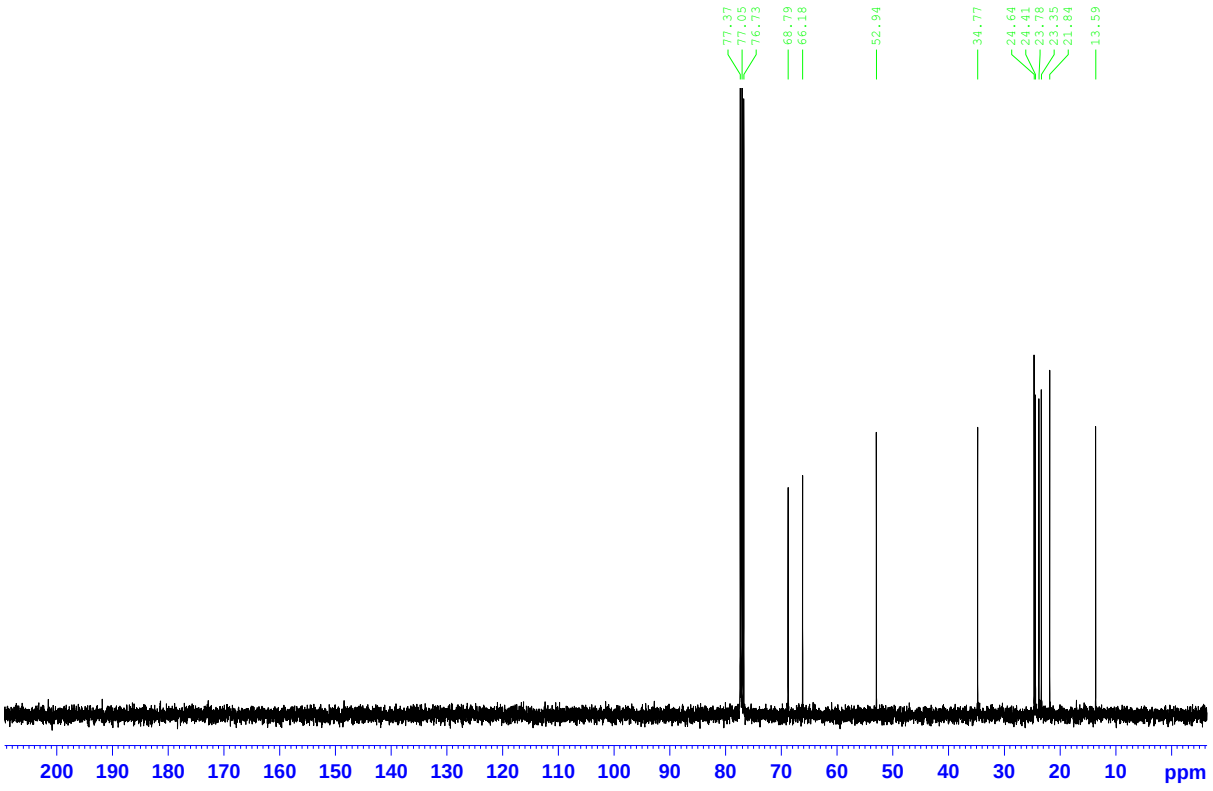

O
O
S
S
N
Cl

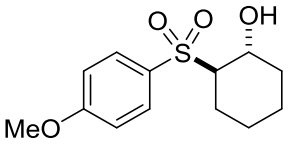

1.00
1.09
2.02
1.09
1.08
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

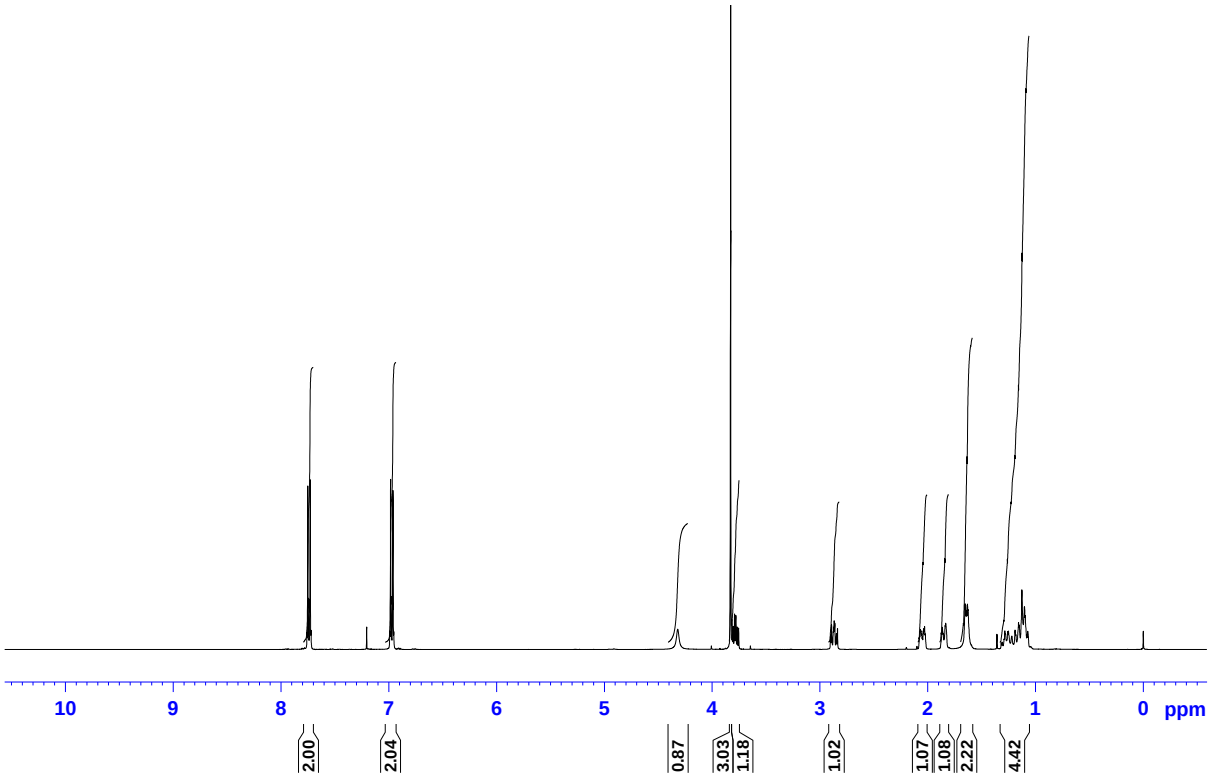

156.16
148.80
141.59
137.74
137.46
135.24
134.36
128.40
124.93
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

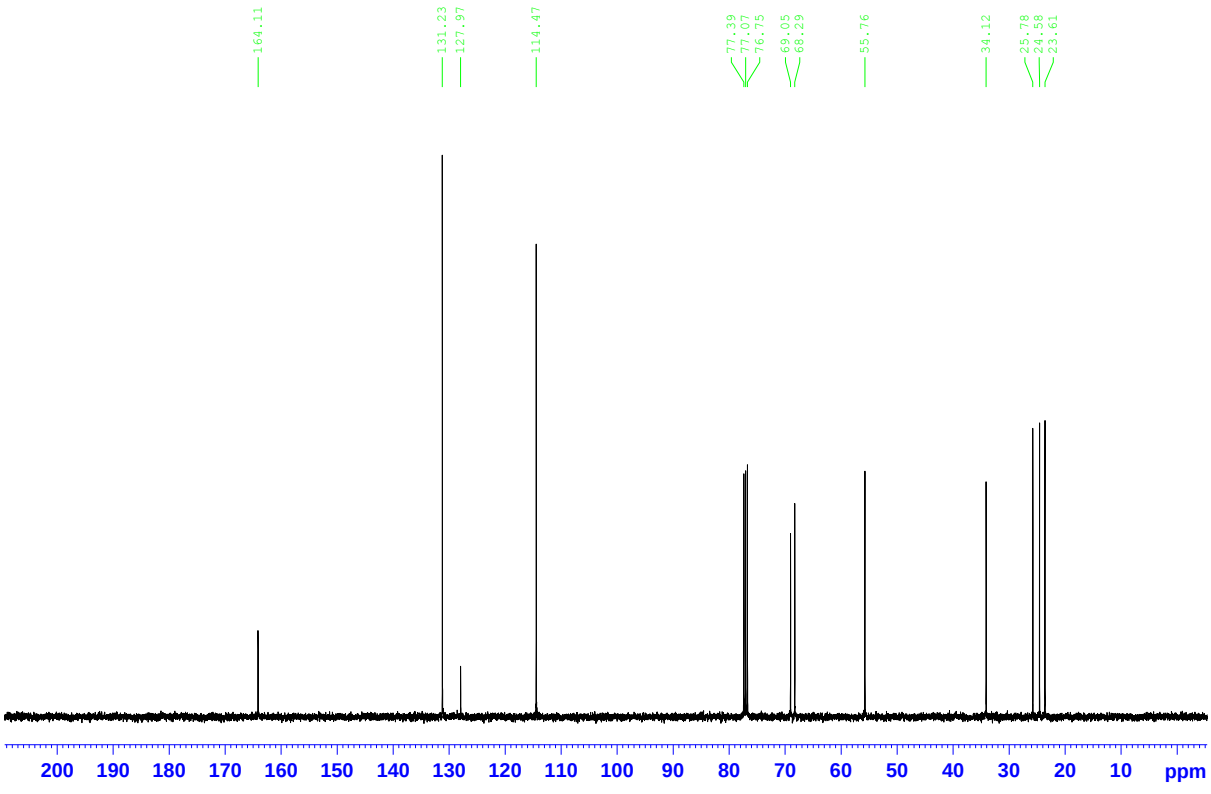

O
O
OH
Me
S


10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
0.71
2.10
1.01
2.11
4.22
3.38
3.31
3.10


77.37
77.05
76.73
68.79
66.18
52.94
34.77
24.64
24.41
23.78
23.35
21.84
13.59
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
O
S
OH
MeO


10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.04
0.87
3.03
1.18
1.02
1.07
1.08
2.22
4.42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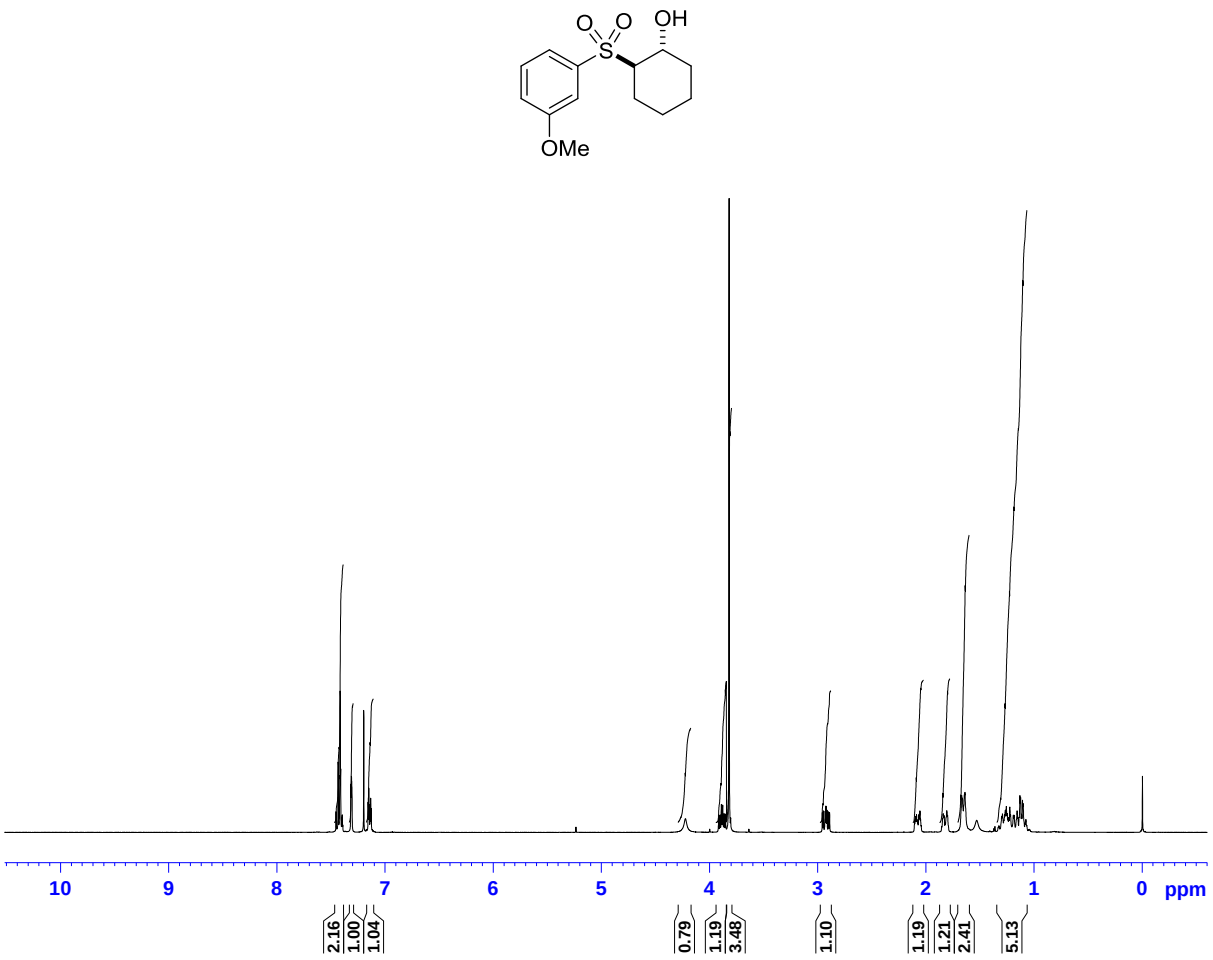
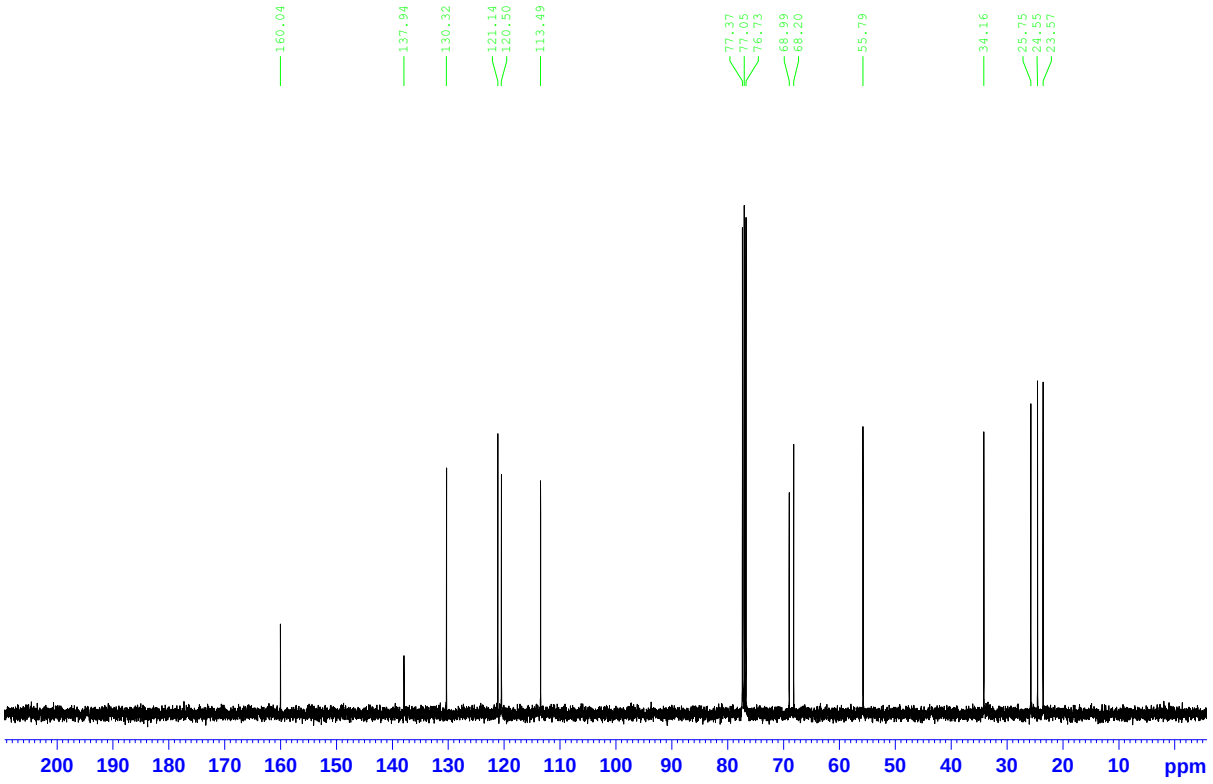
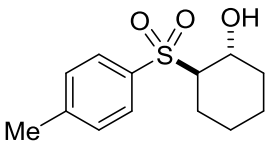
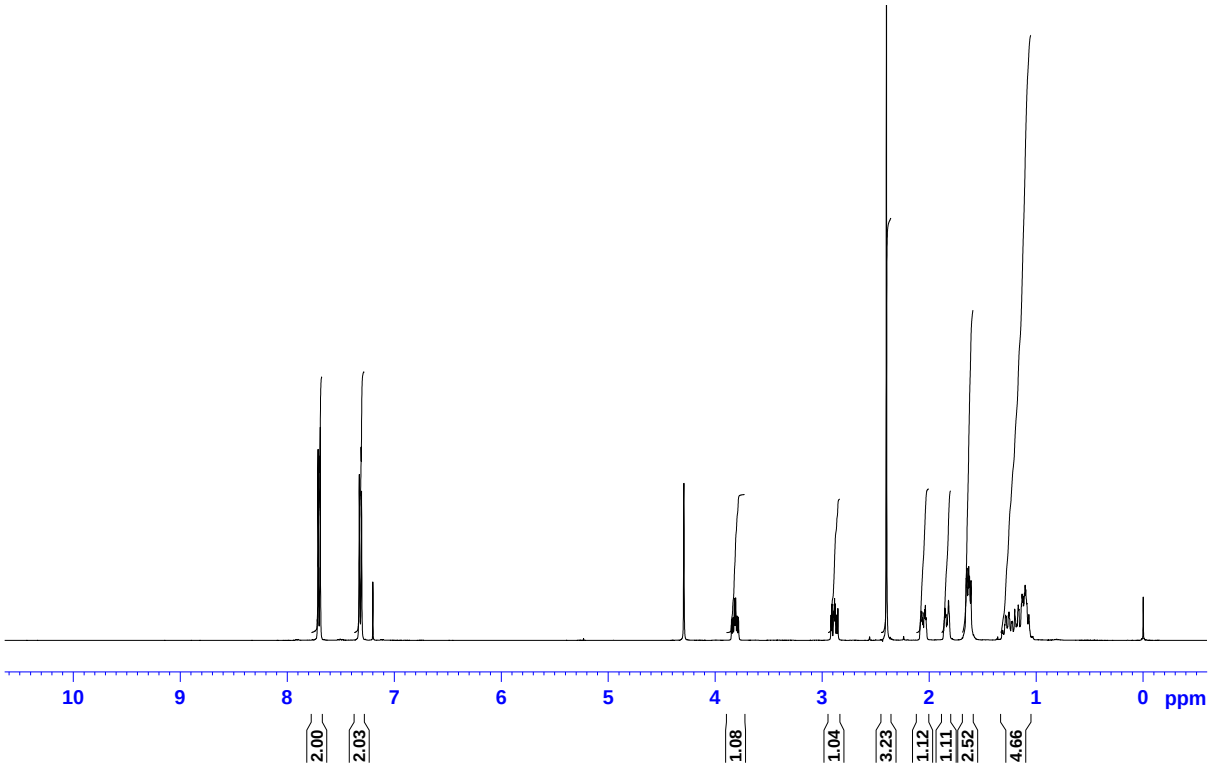
131.23
127.97
114.47
77.39
77.07
76.75
69.05
68.29
55.76
34.12
25.78
24.58
23.61
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
O
S
OH
OMe
10
9
8
7
6
5
4
3
2
1
0
ppm
2.16
1.00
1.04
0.79
1.19
3.48
1.10
1.19
1.21
2.41
5.13


160.04
137.94
130.32
121.14
120.50
113.49
77.37
77.05
76.73
68.99
68.20
55.79
34.16
25.75
24.55
23.57
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
O
OH
S
Me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9
8
7
6
5
4
3
2
1
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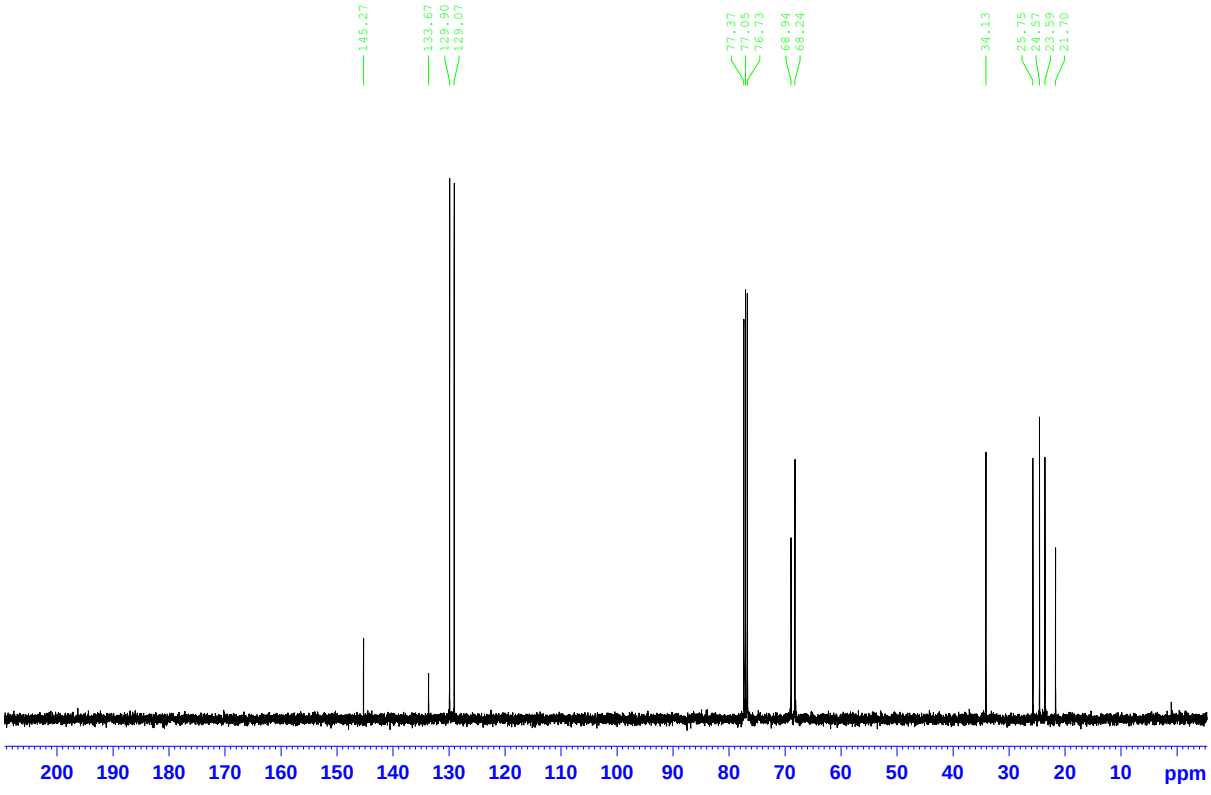
ppm
2.00
2.03
1.08
1.04
3.23
1.12
1.11
2.52
4.66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133.67
129.90
129.07
77.37
77.05
76.73
68.94
68.24
34.13
25.75
24.57
23.59
21.70
200
190
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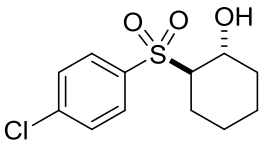
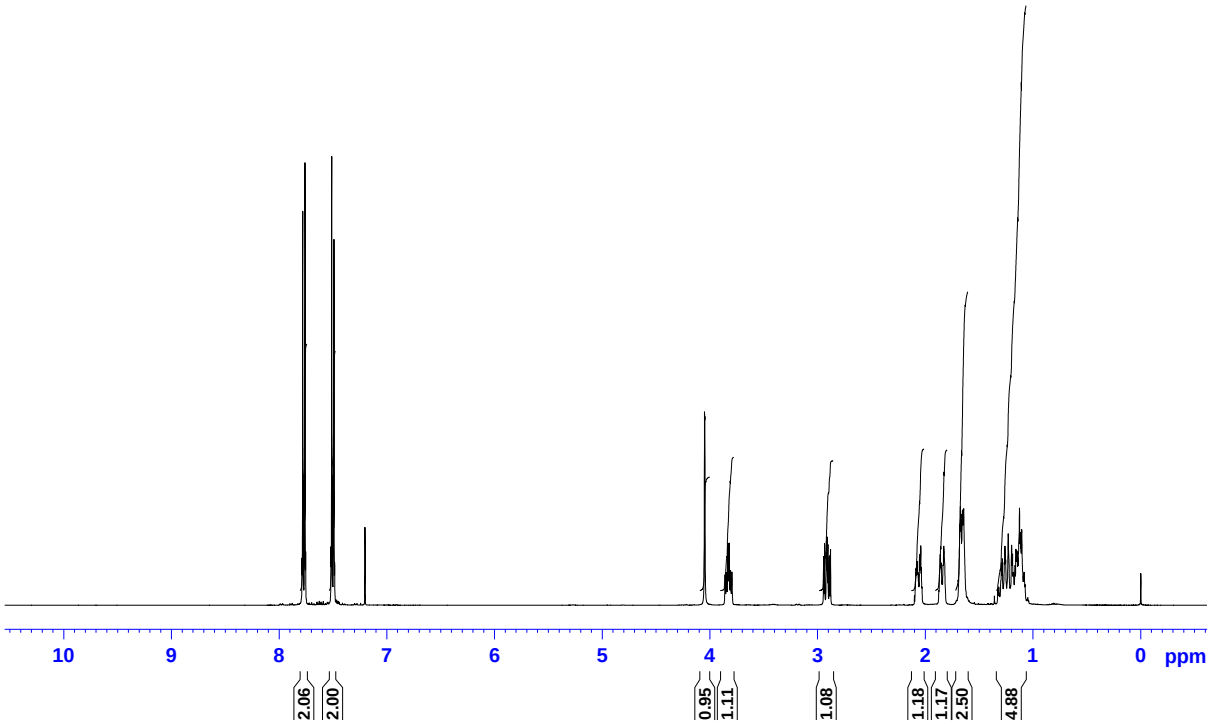
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
O
OH
S
Cl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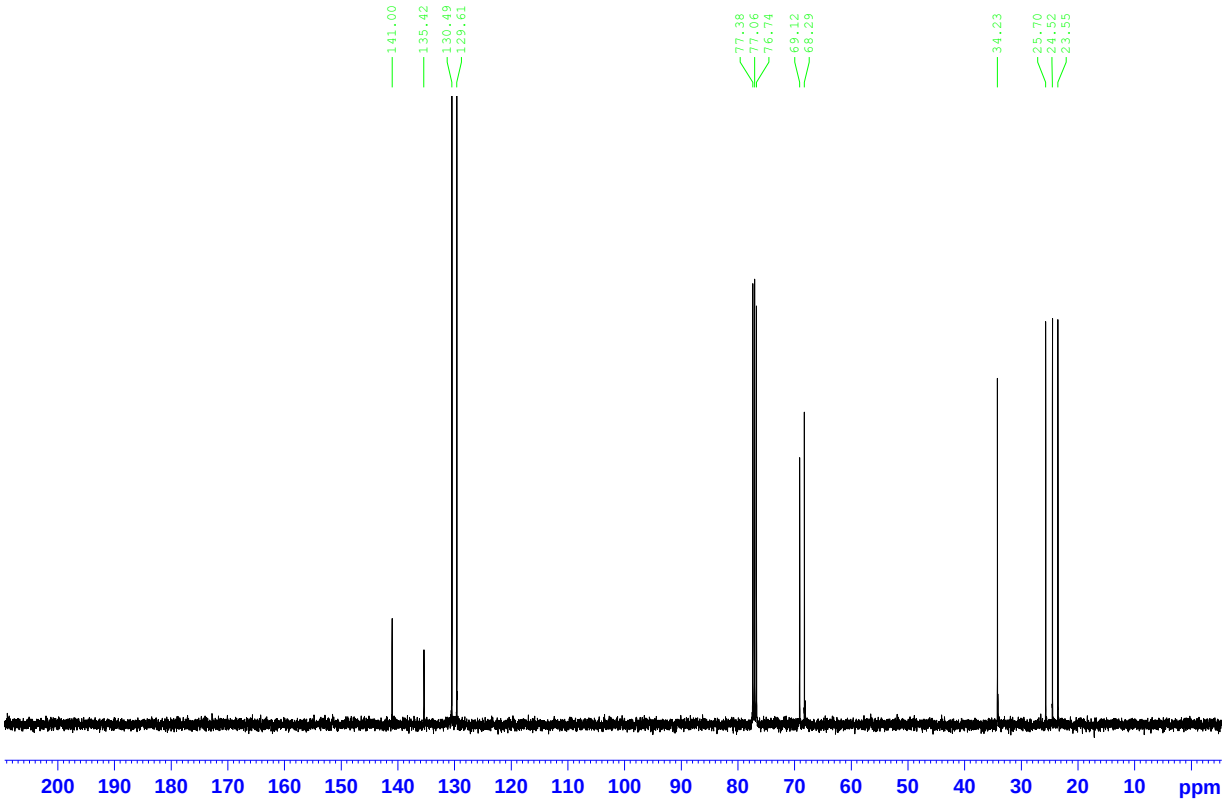
9
8
7
6
5
4
3
2
1
0
ppm
2.06
2.00
0.95
1.11
1.08
1.18
1.17
2.50
4.88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135.42
130.49
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77.06
76.74
69.12
68.29
34.23
25.70
24.52
23.55
200
190
180
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150
140
130
120
110
100
90
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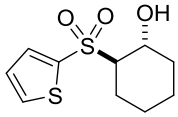
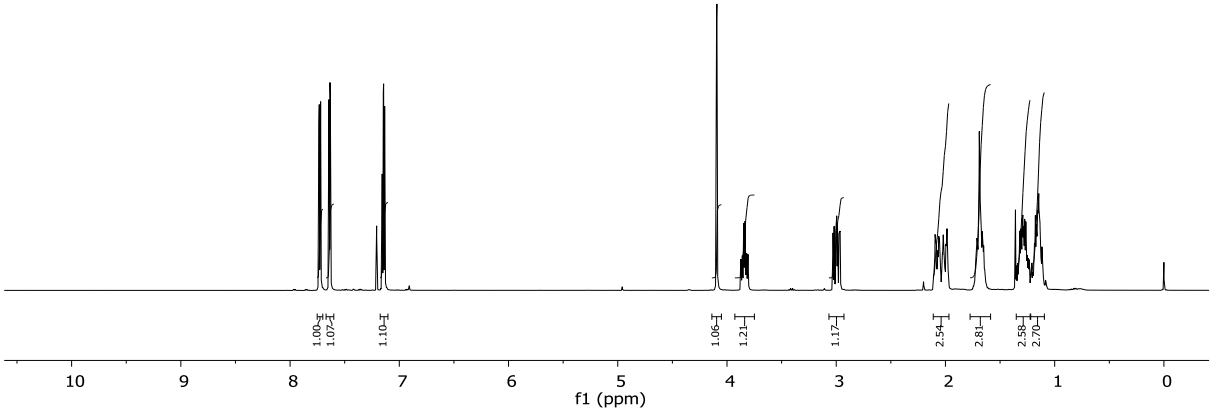
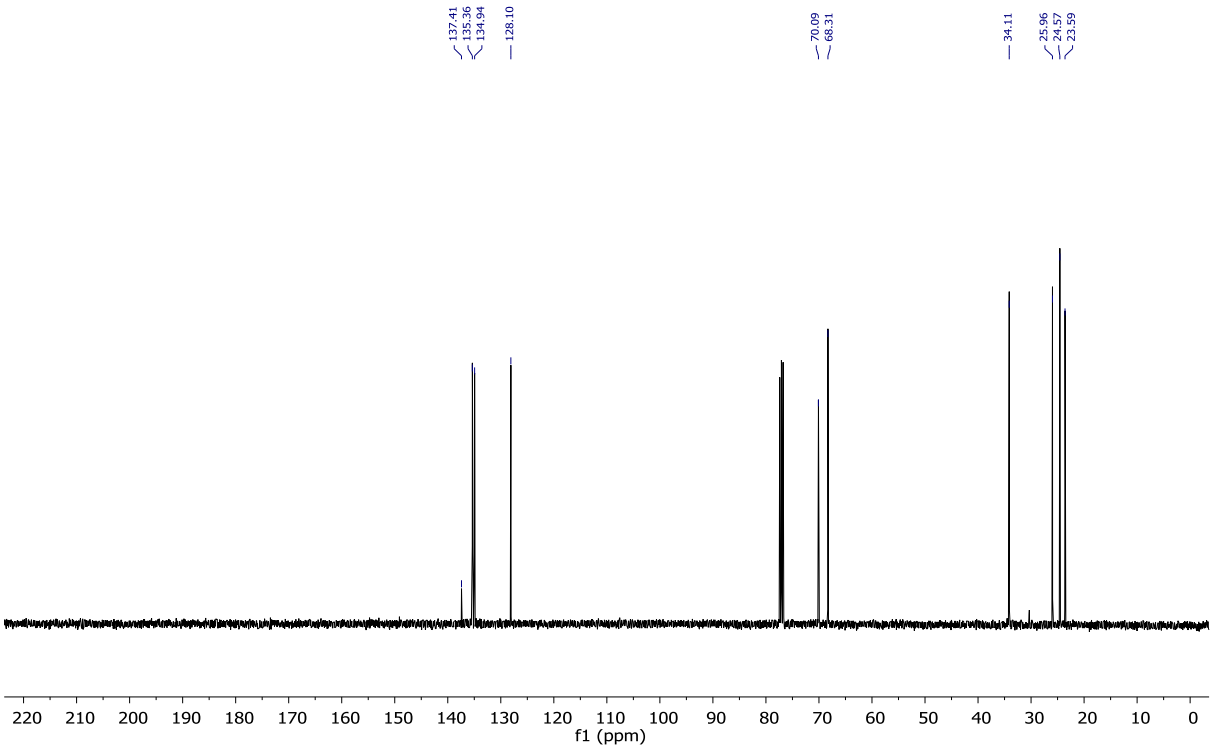
70
60
50
40
30
20
10
ppm


O
O
S
OH
S


1.00
1.07
1.10
1.06
1.21
1.17
2.54
2.81
2.58
2.70
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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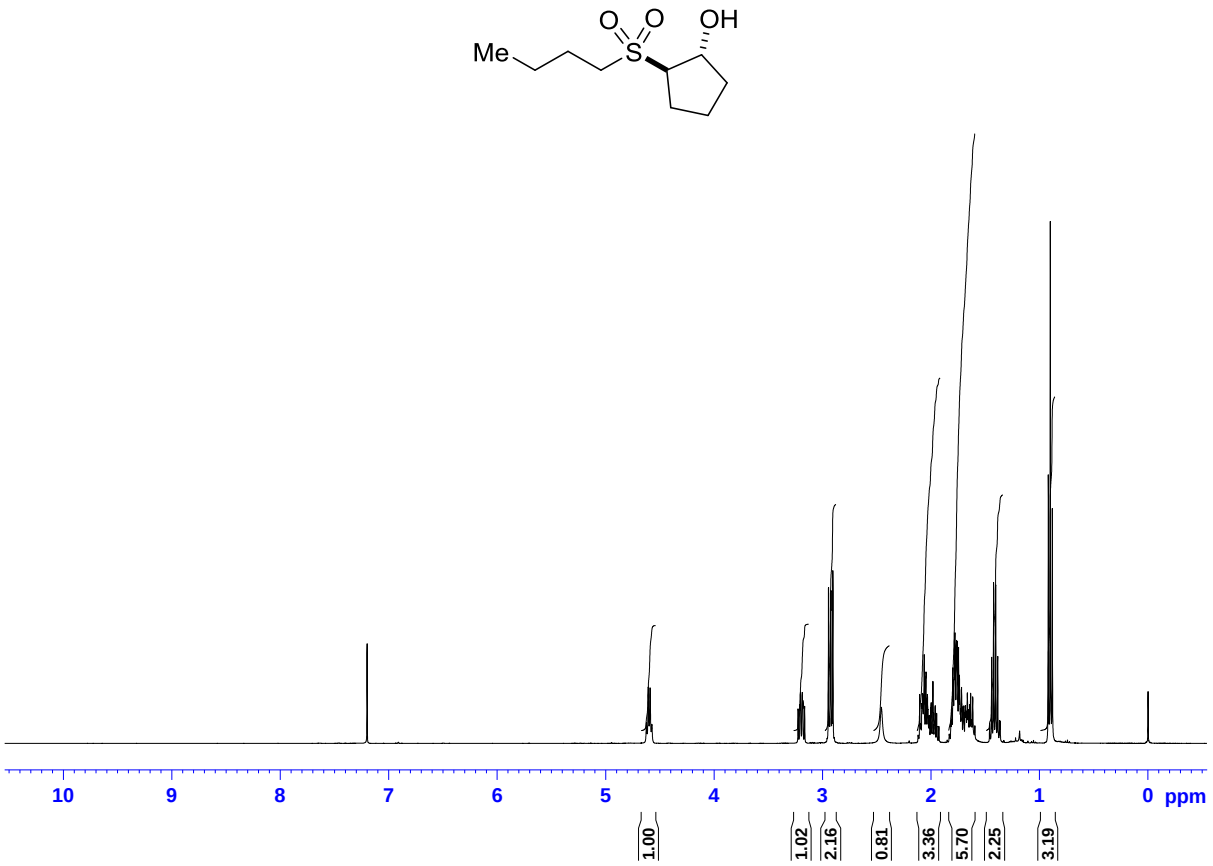
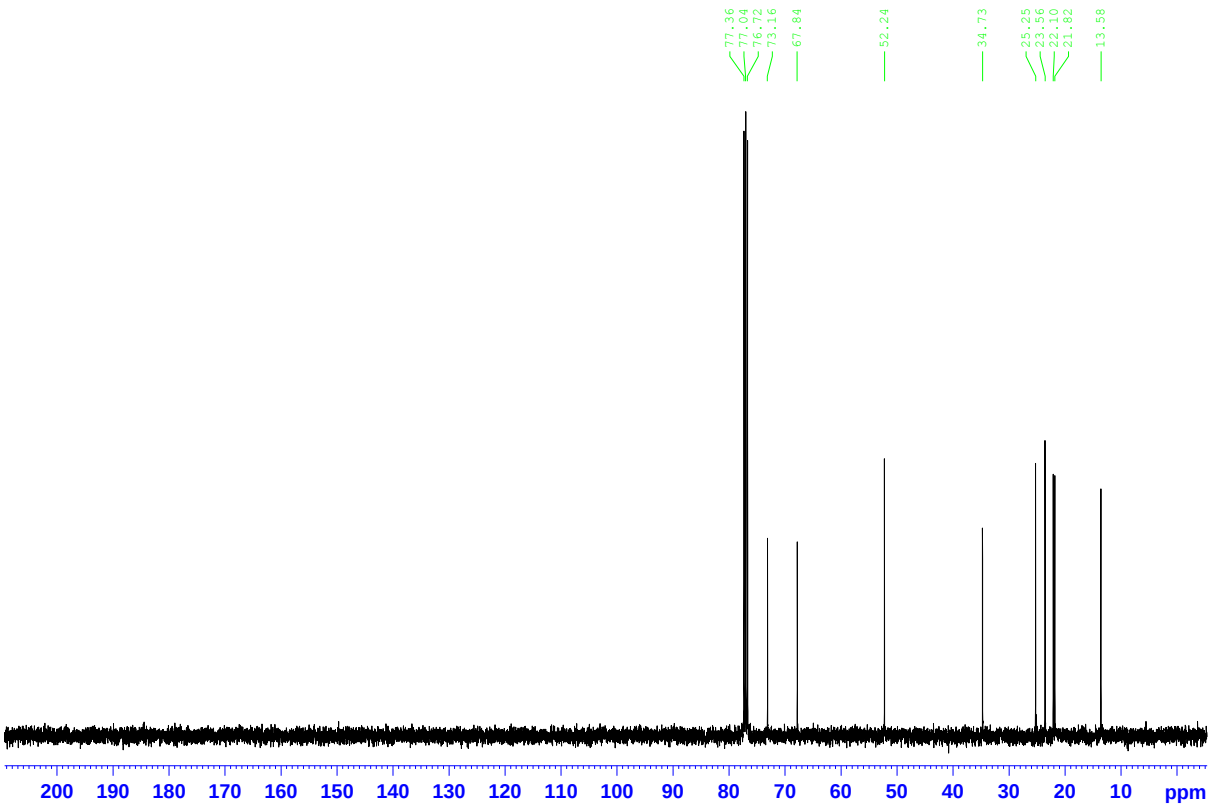
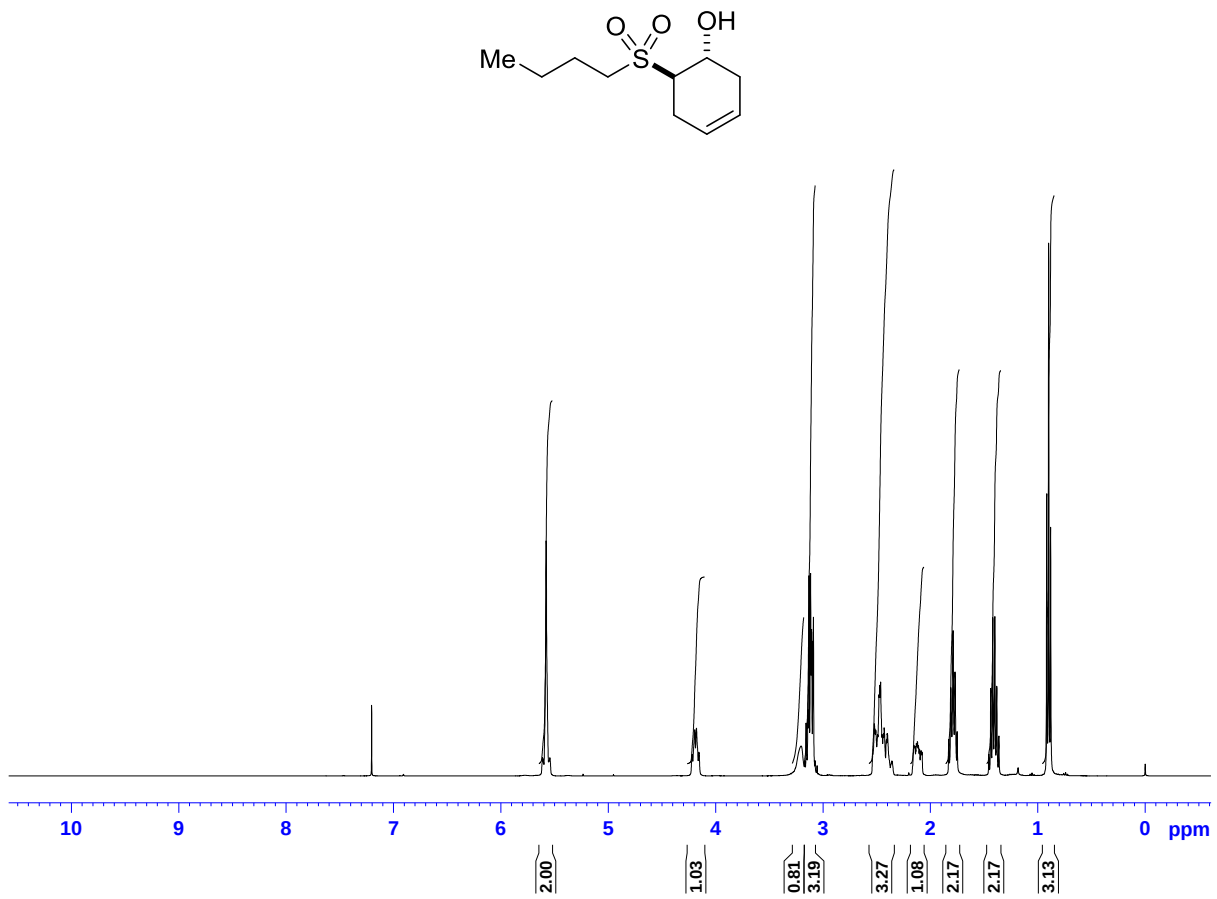
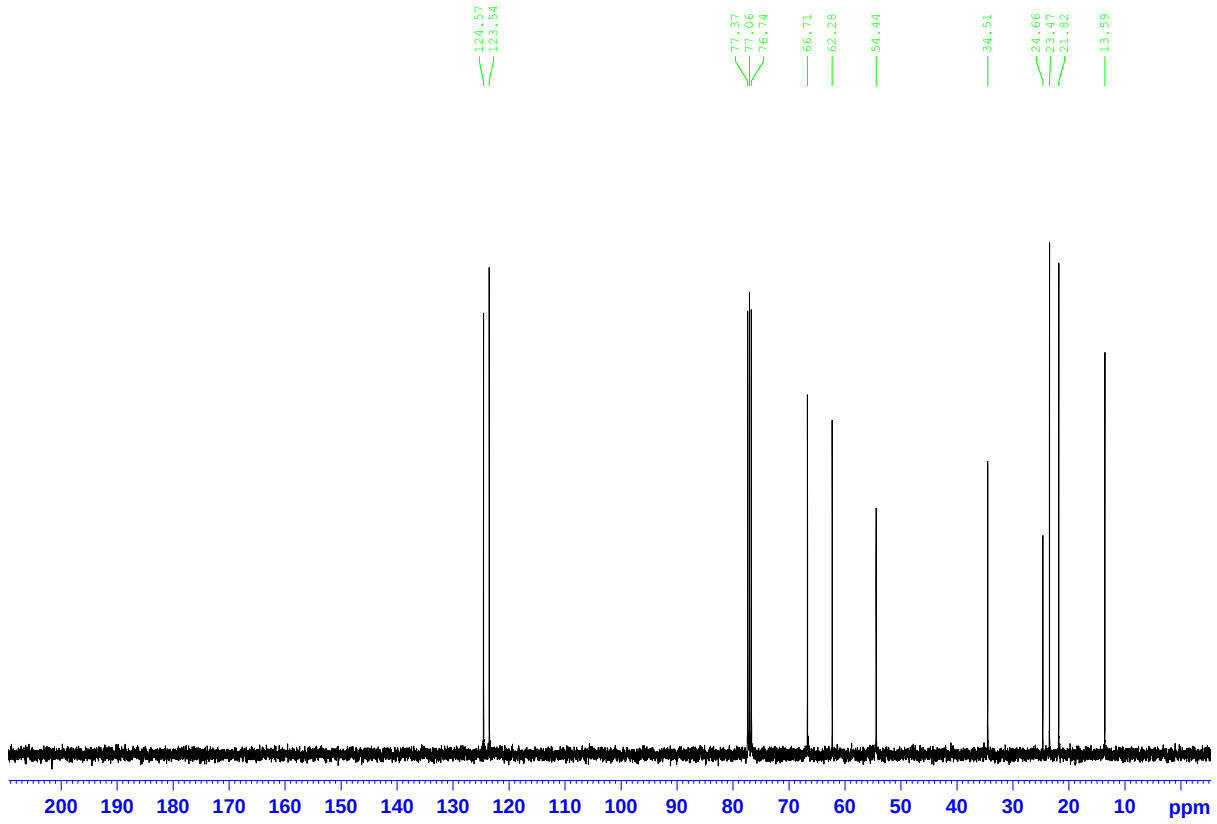
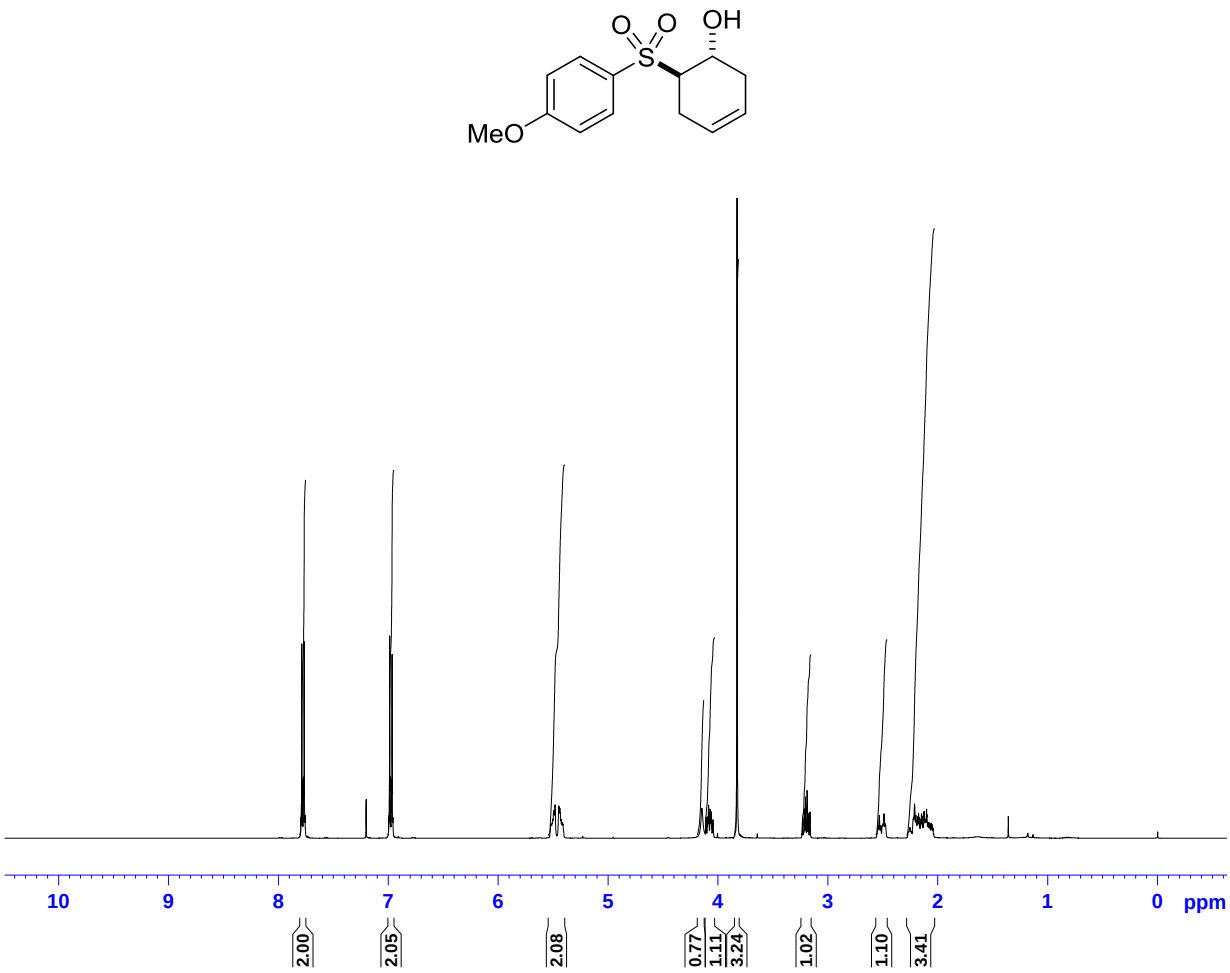
135.36
134.94
128.10
70.09
68.31
34.11
25.96
24.57
23.59
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

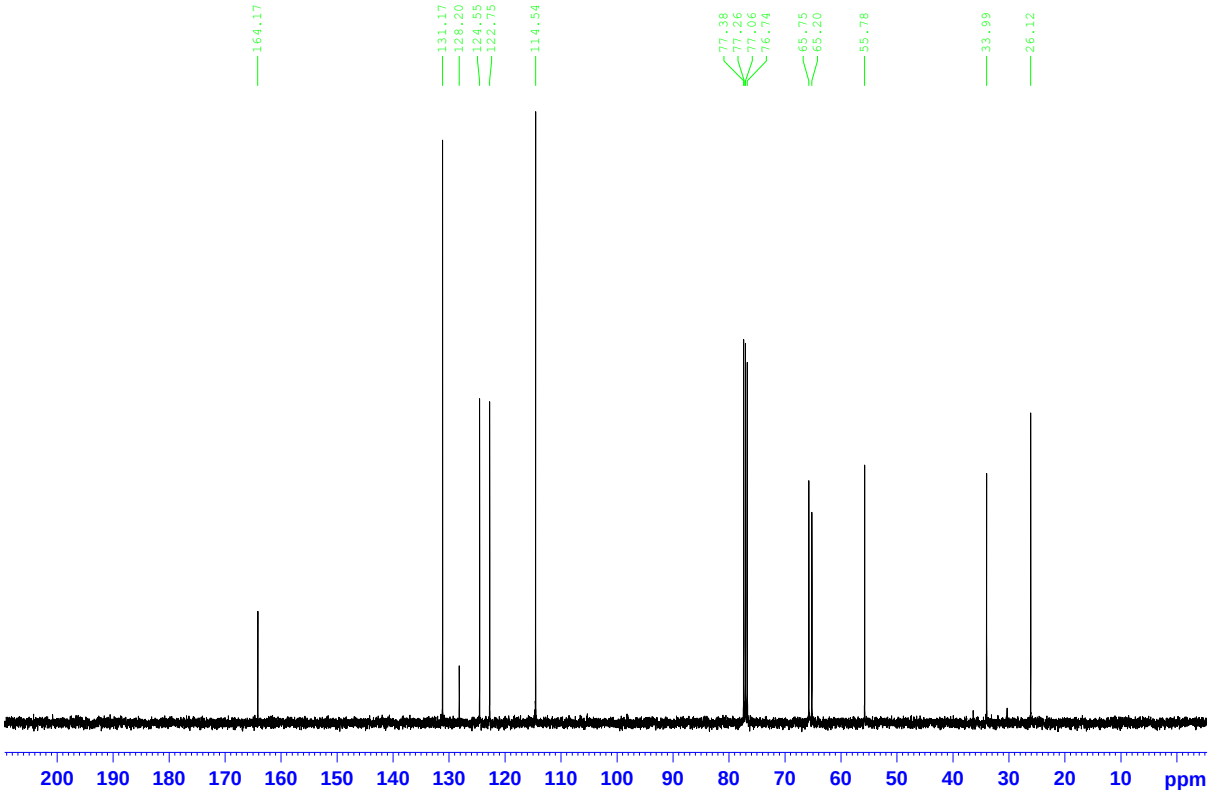

O
O
OH
Me
S
10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.02
2.16
0.81
3.36
5.70
2.25
3.19

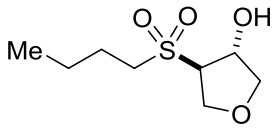

77.36
77.04
76.72
73.16
67.84
52.24
34.73
25.25
23.56
22.10
21.82
13.58
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

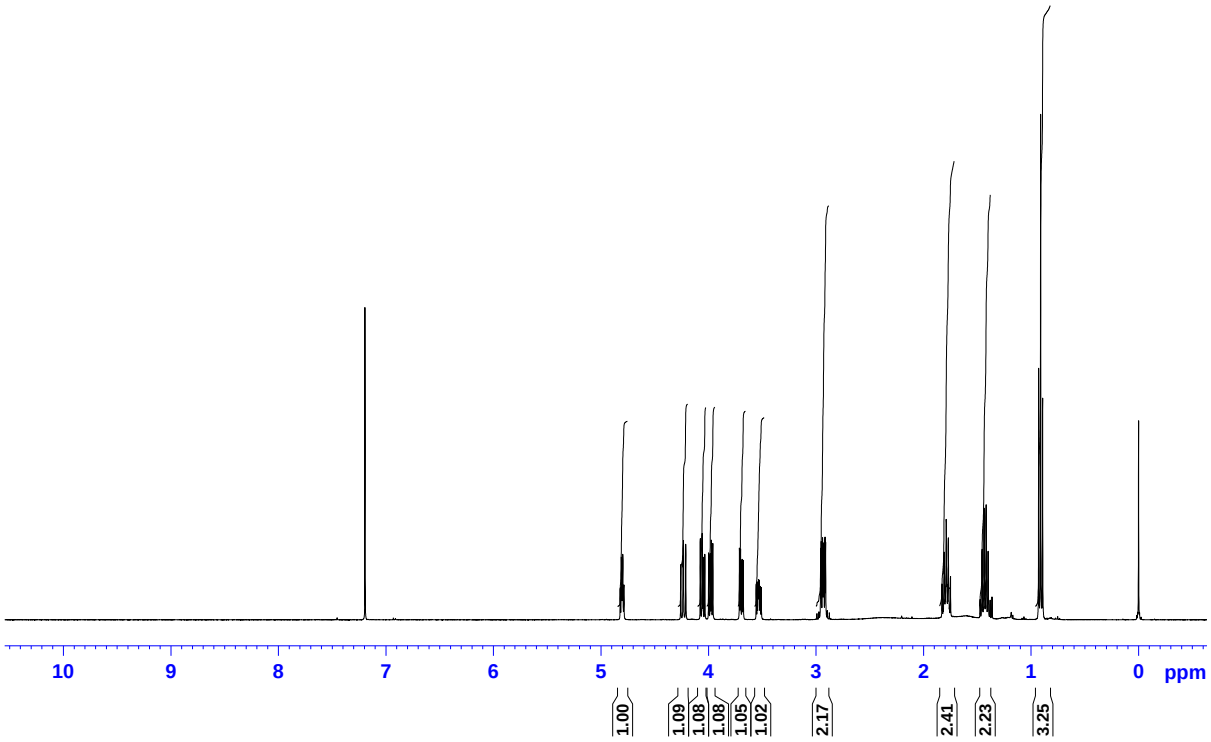

Me
O
O
S
OH
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
1.03
0.81
3.19
3.27
1.08
2.17
2.17
3.13


124.57
123.54
77.37
77.06
76.74
66.71
62.28
54.44
34.51
24.66
23.47
21.82
13.59
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
O
OH
S
MeO
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.05
2.08
0.77
1.11
3.24
1.02
1.10
3.41


164.17
131.17
128.20
124.55
122.75
114.54
77.38
77.26
77.06
76.74
65.75
65.20
55.78
33.99
26.12
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
O
OH
Me
S
O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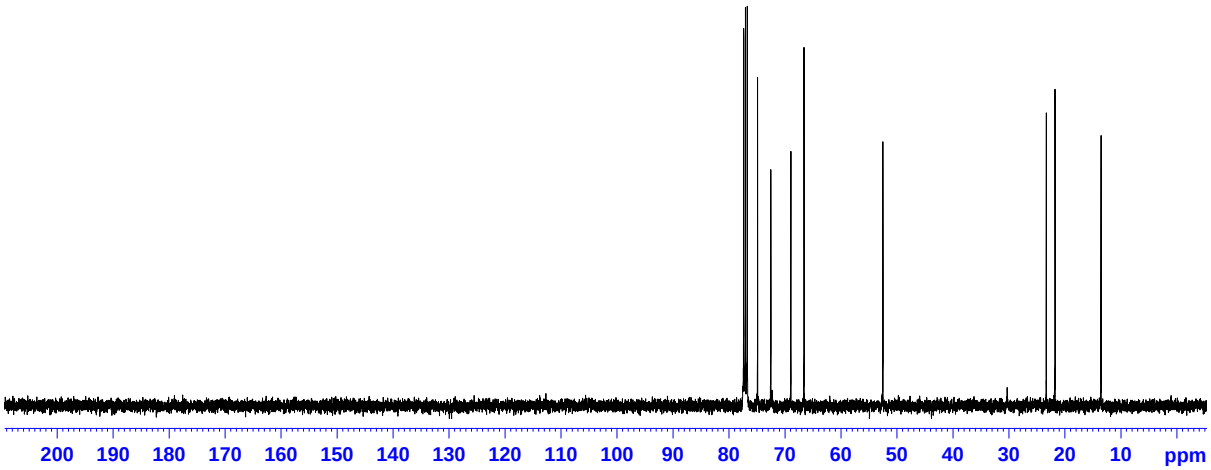
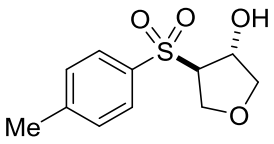
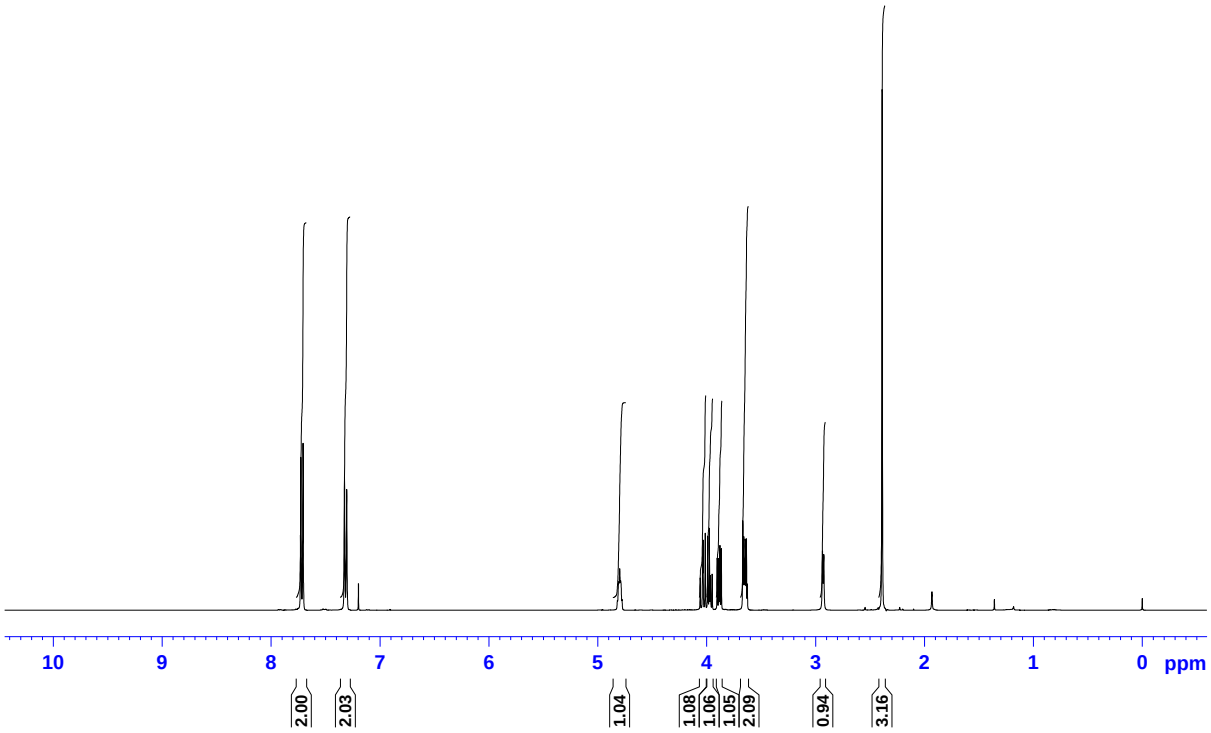
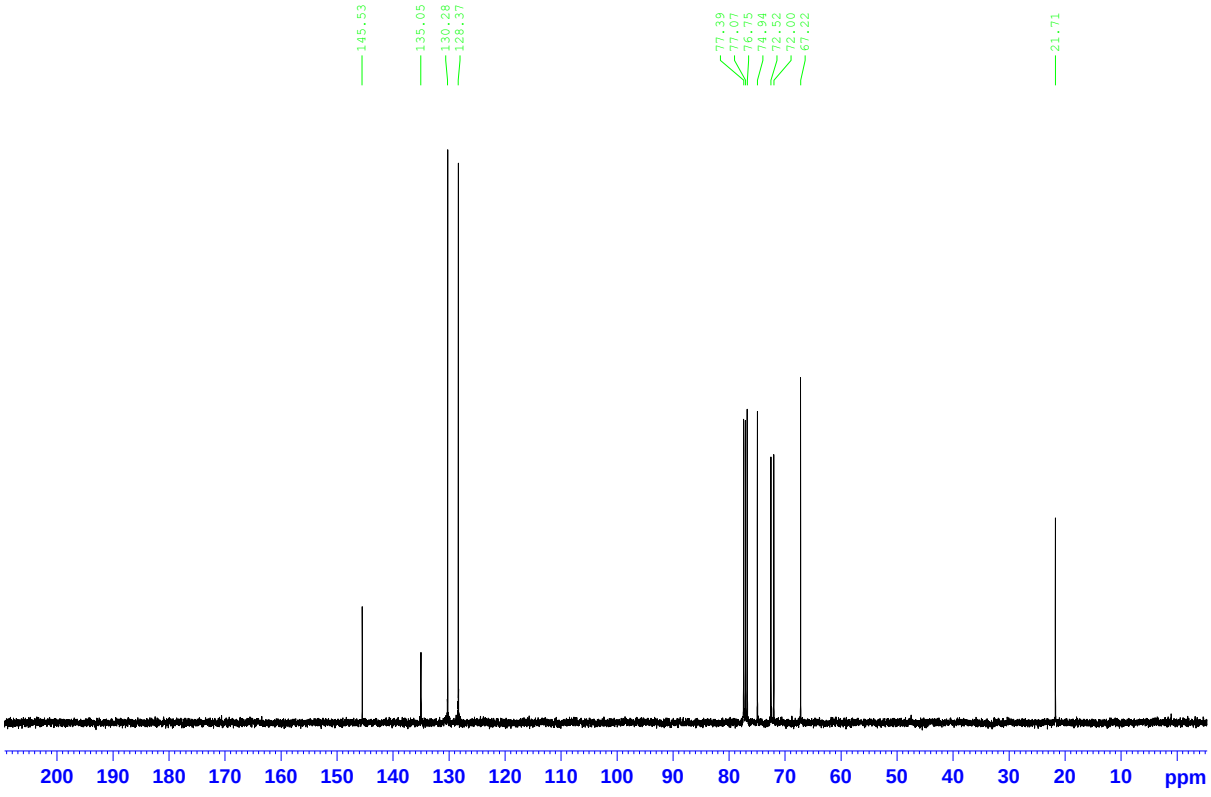
9
8
7
6
5
4
3
2
1
0
ppm
1.00
1.09
1.08
1.08
1.05
1.02
2.17
2.41
2.23
3.25

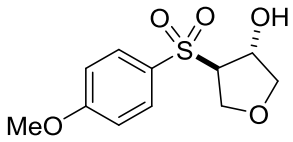

77.37
77.05
76.73
74.90
72.53
68.95
66.60
52.51
30.32
23.32
21.76
13.54

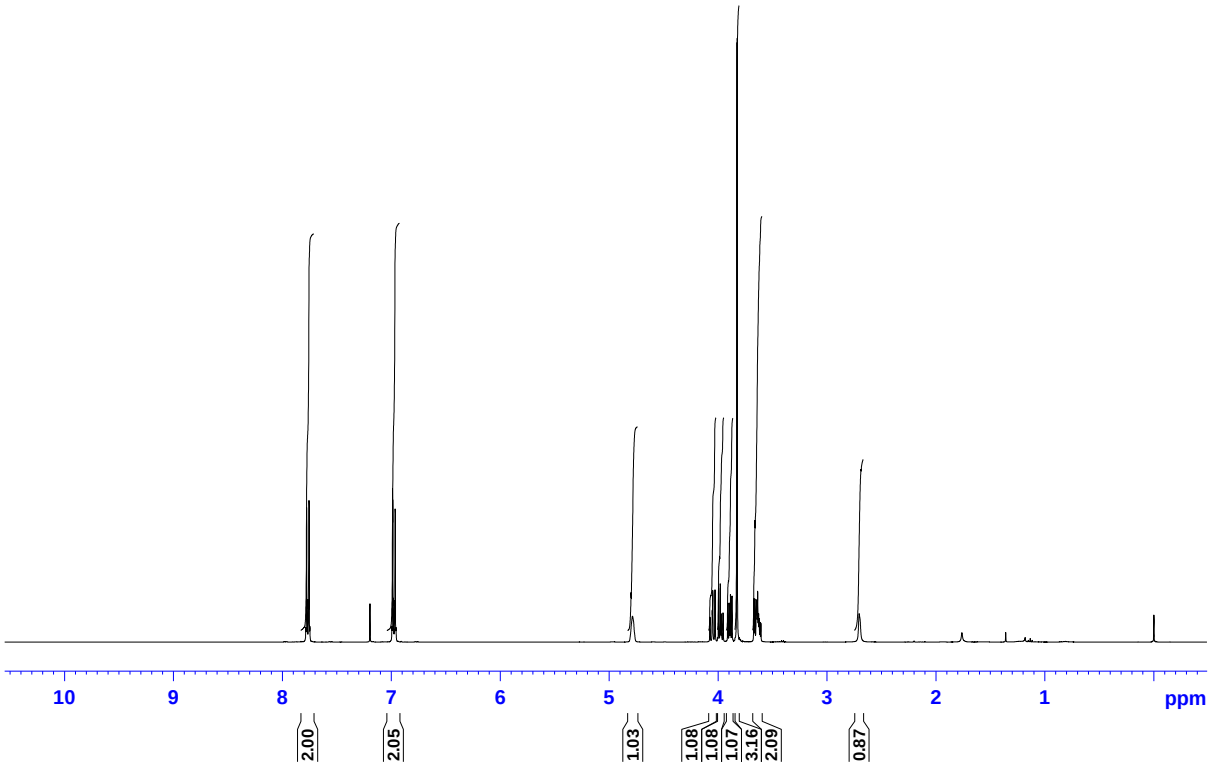

200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

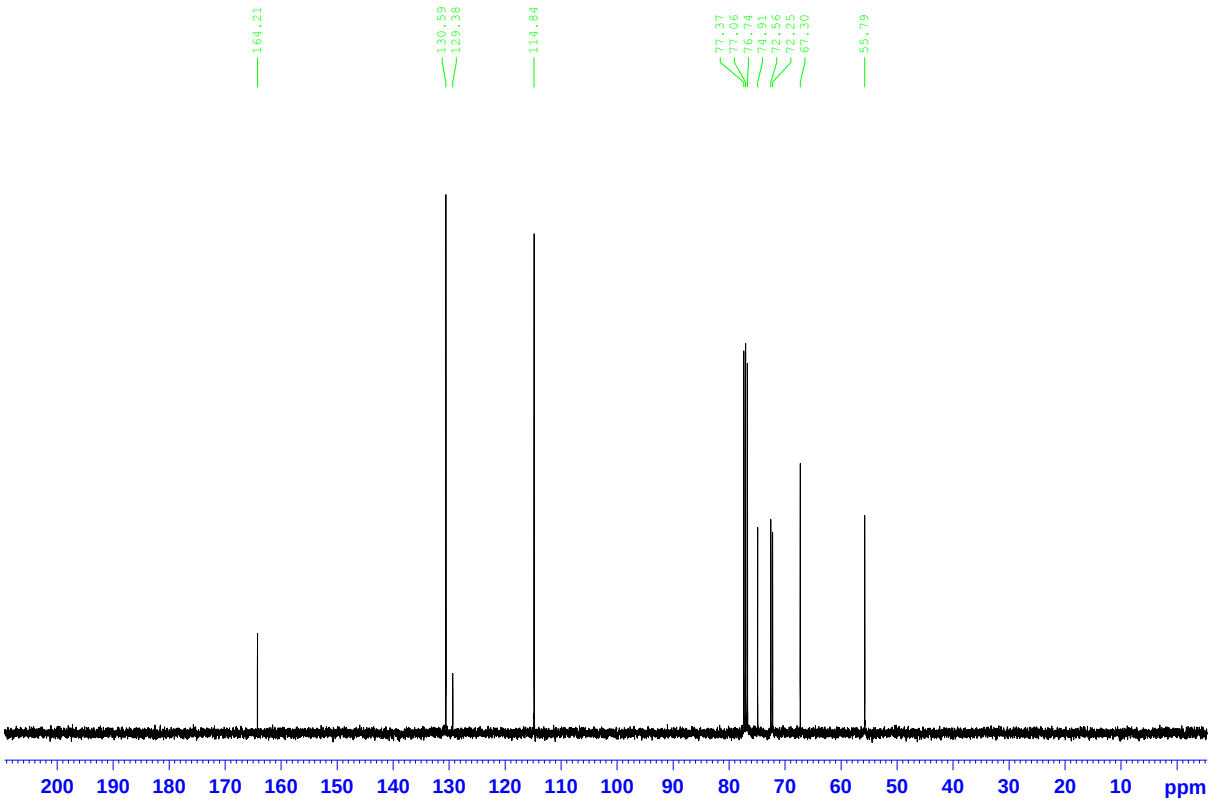

O
O
S
OH
Me
O

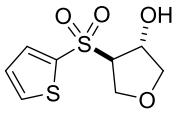

10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
2.03
1.04
1.08
1.06
1.05
2.09
0.94
3.16

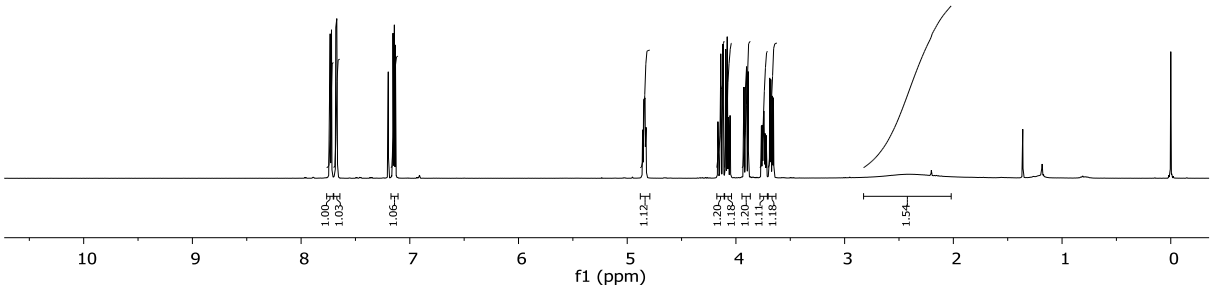

145.53
135.05
130.28
128.37
77.39
77.07
76.75
74.94
72.52
72.00
67.22
21.71
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

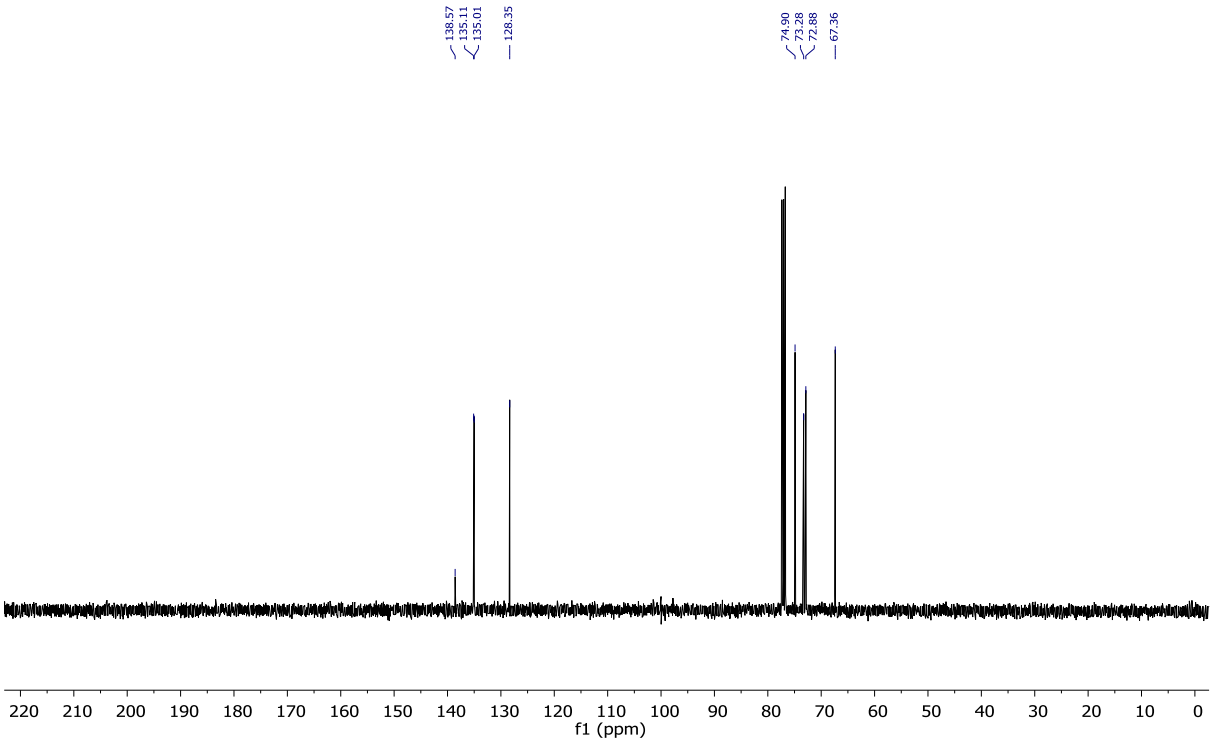

O
O
OH
S
MeO
O

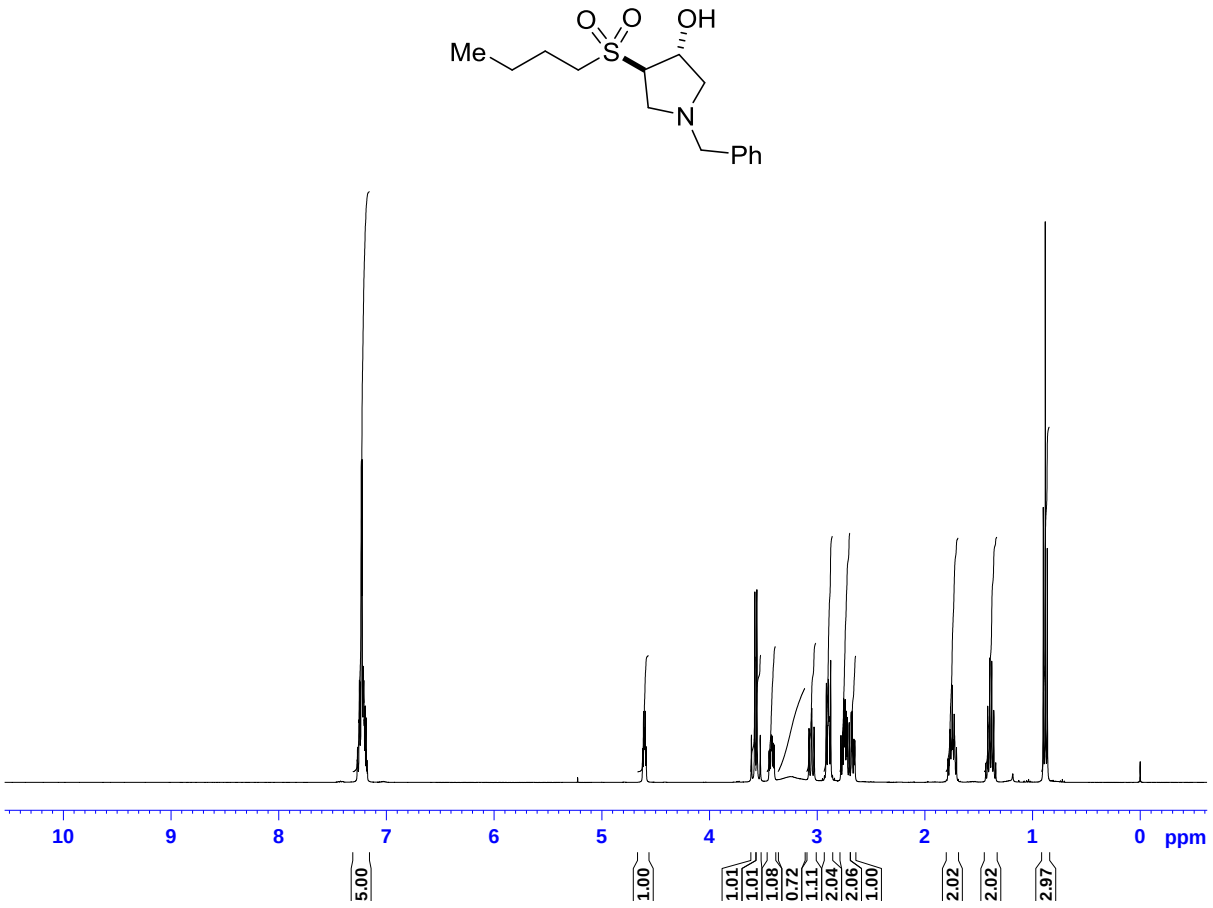

10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.05
1.03
1.08
1.08
1.07
3.16
2.09
0.87

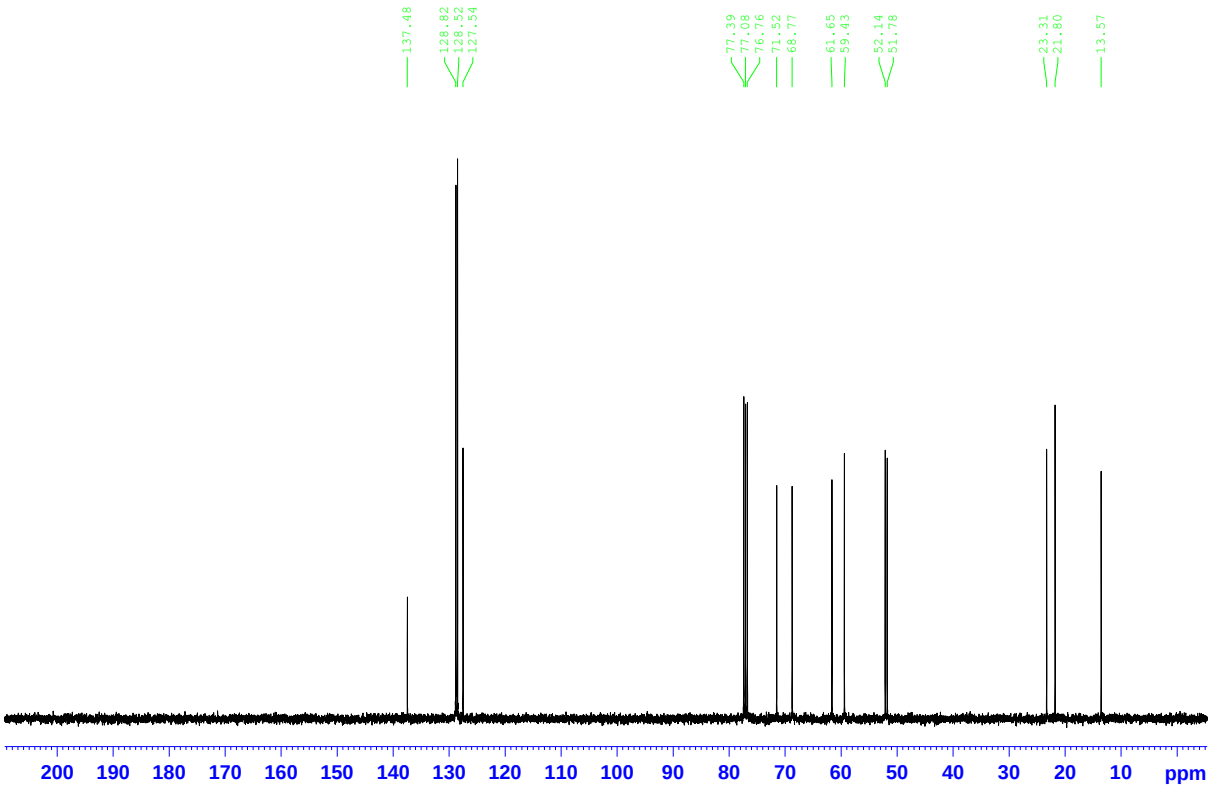

164.21
130.59
129.38
114.84
77.37
77.06
76.74
74.91
72.56
72.25
67.30
55.79
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
O
OH
S
S
O


1.00
1.03
1.06
1.12
1.20
1.18
1.20
1.11
1.18
1.54
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


138.57
135.11
135.01
128.35
74.90
73.28
72.88
67.36
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
O
O
S
OH
N
Ph
10
9
8
7
6
5
4
3
2
1
0
ppm
5.00
1.00
1.01
1.01
1.08
0.72
1.11
2.04
2.06
1.00
2.02
2.02
2.97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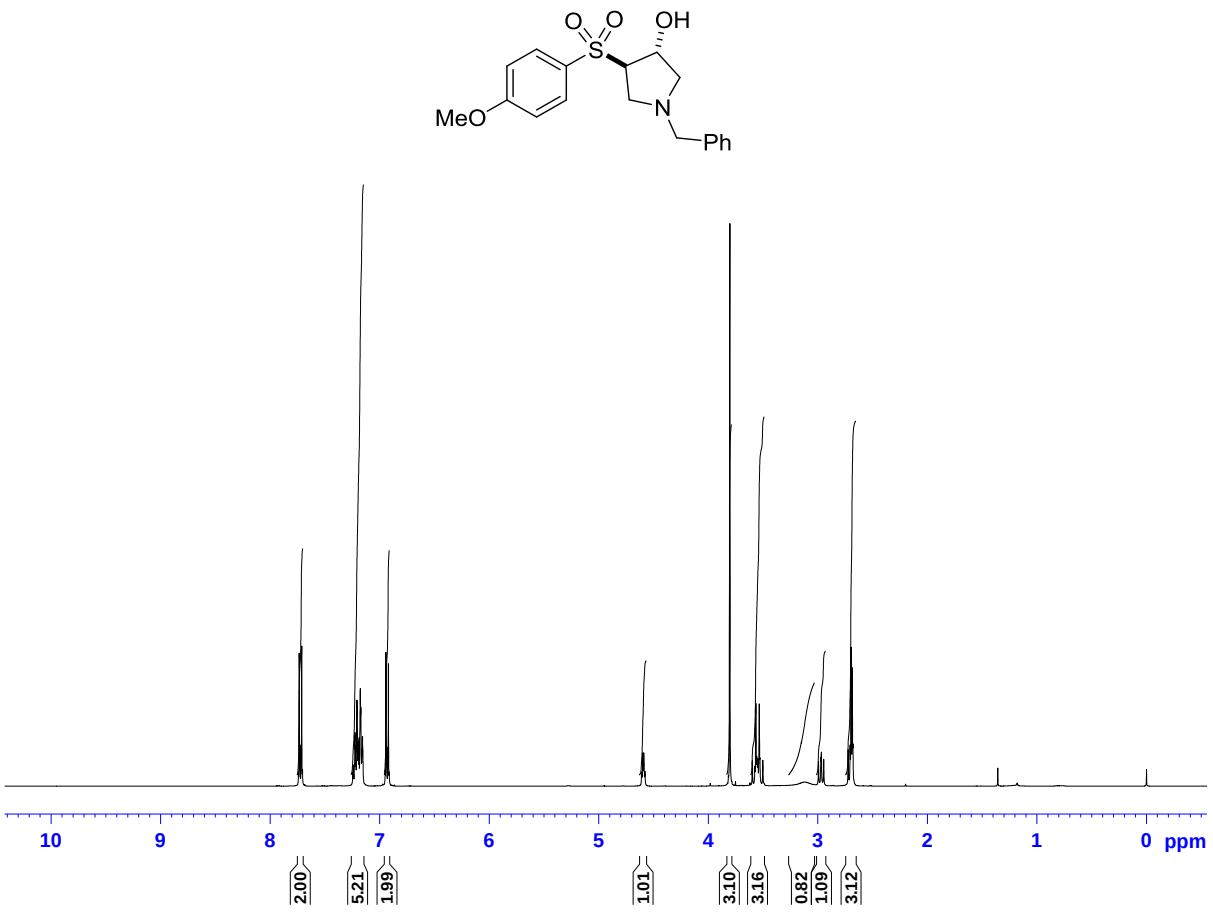
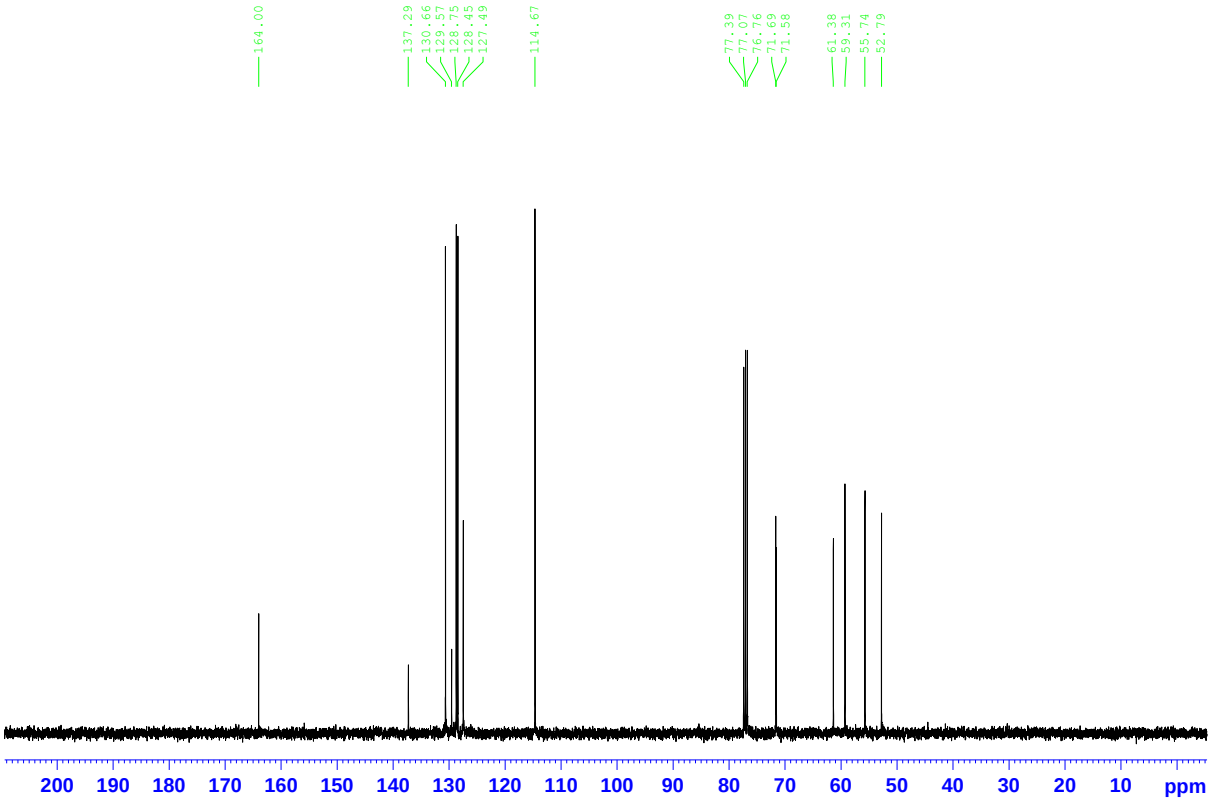
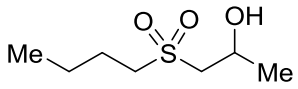
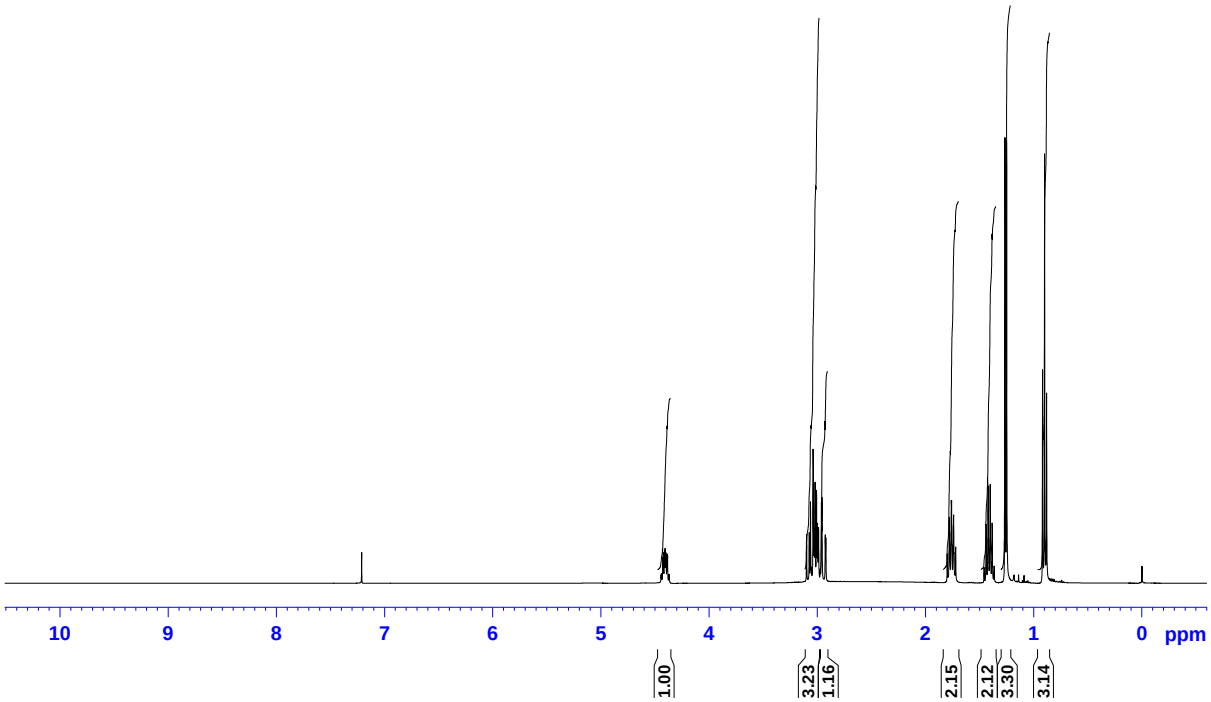
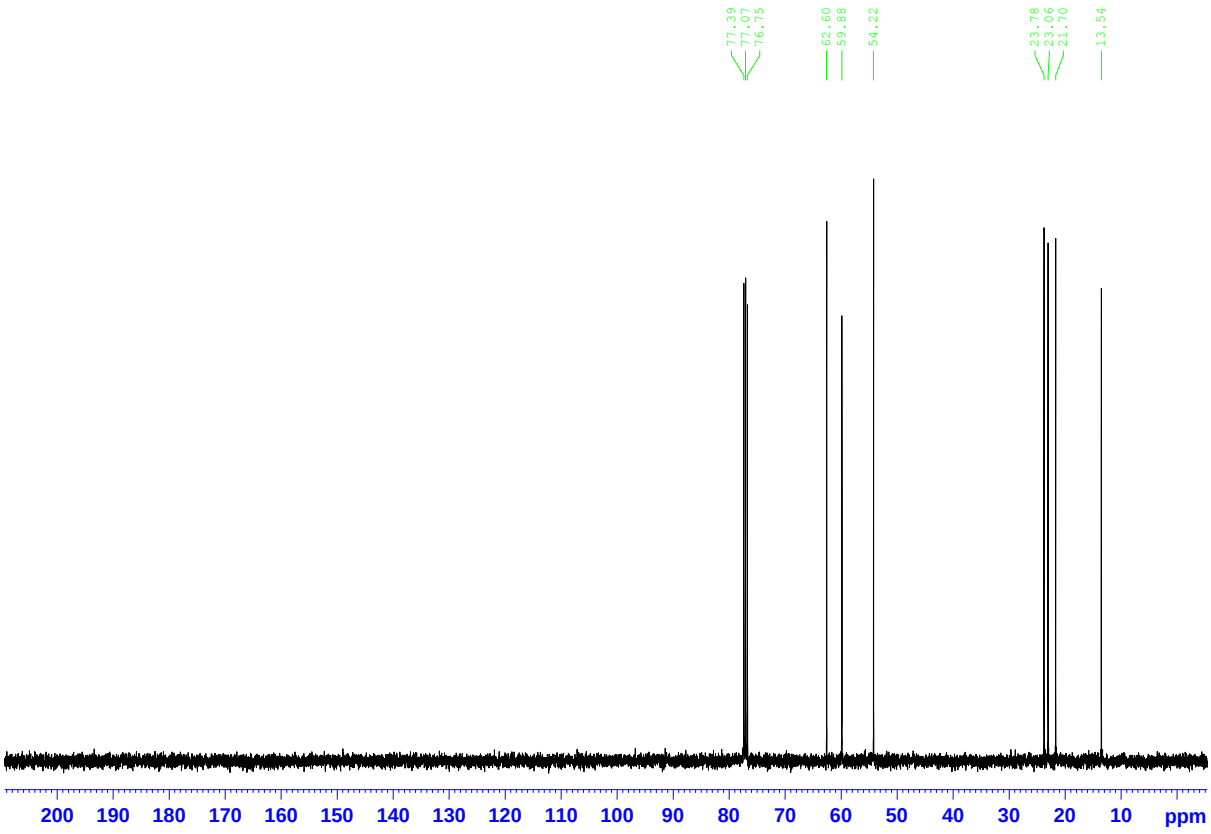
128.82
128.52
127.54
77.39
77.08
76.76
71.52
68.77
61.65
59.43
52.14
51.78
23.31
21.80
13.57
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

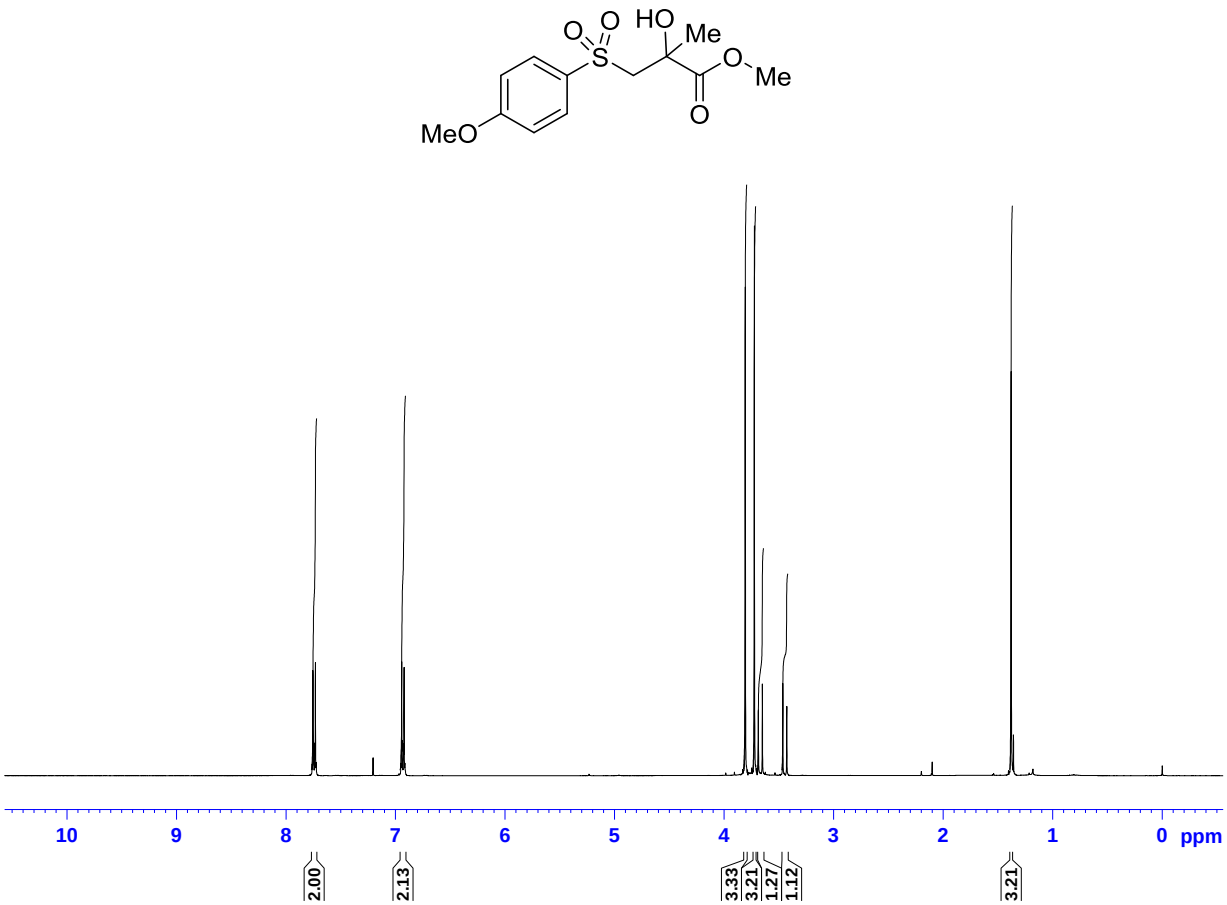

O
O
S
OH
MeO
N
Ph
10
9
8
7
6
5
4
3
2
1
0
ppm
2.00
5.21
1.99
1.01
3.10
3.16
0.82
1.09
3.12


164.00
137.29
130.66
129.57
128.75
128.45
127.49
114.67
77.39
77.07
76.76
71.69
71.58
61.38
59.31
55.74
52.79
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


O
O
OH
Me
S
Me


10
9
8
7
6
5
4
3
2
1
0
ppm
1.00
3.23
1.16
2.15
2.12
3.30
3.14


77.39
77.07
76.75
62.60
59.88
54.22
23.78
23.06
21.70
13.54
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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HO
Me
S
O
Me
O
MeO
10
9
8
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1
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ppm
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3.33
3.21
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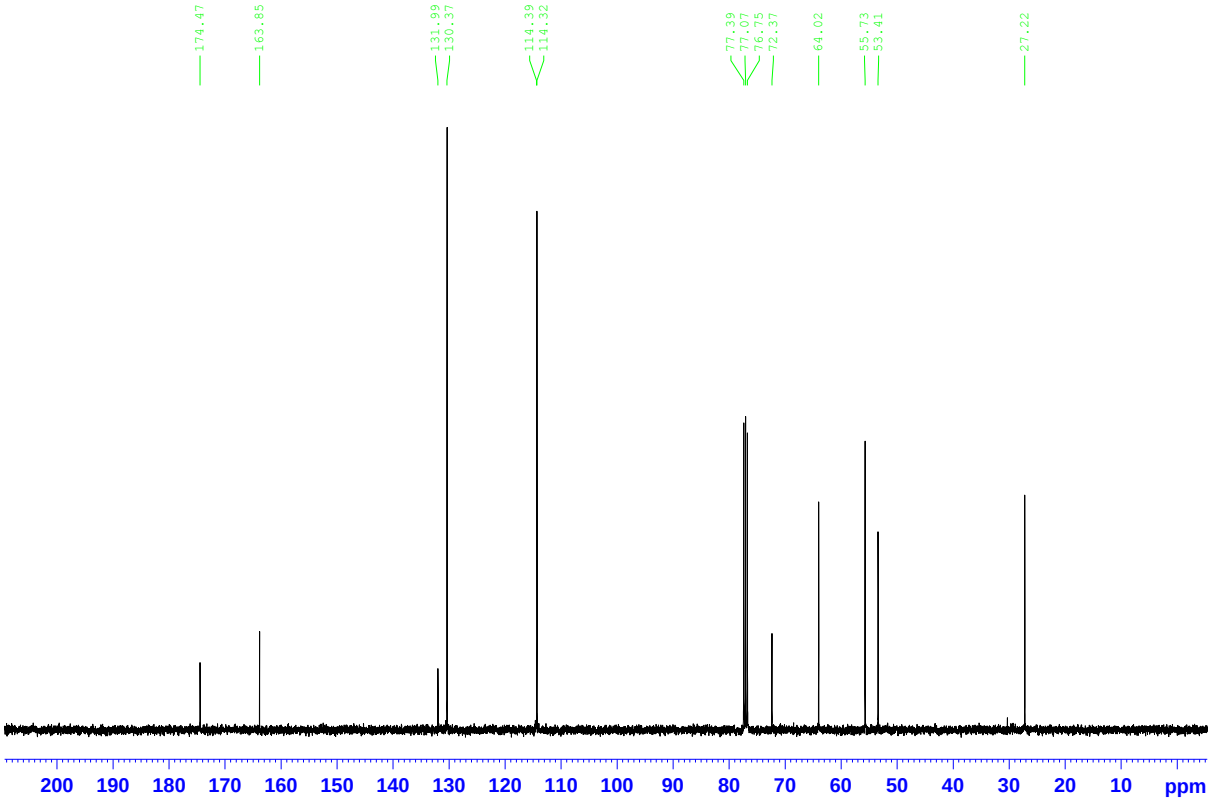
1.12
3.21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131.99
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114.39
114.32
77.39
77.07
76.75
72.37
64.02
55.73
53.41
27.22
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150
140
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110
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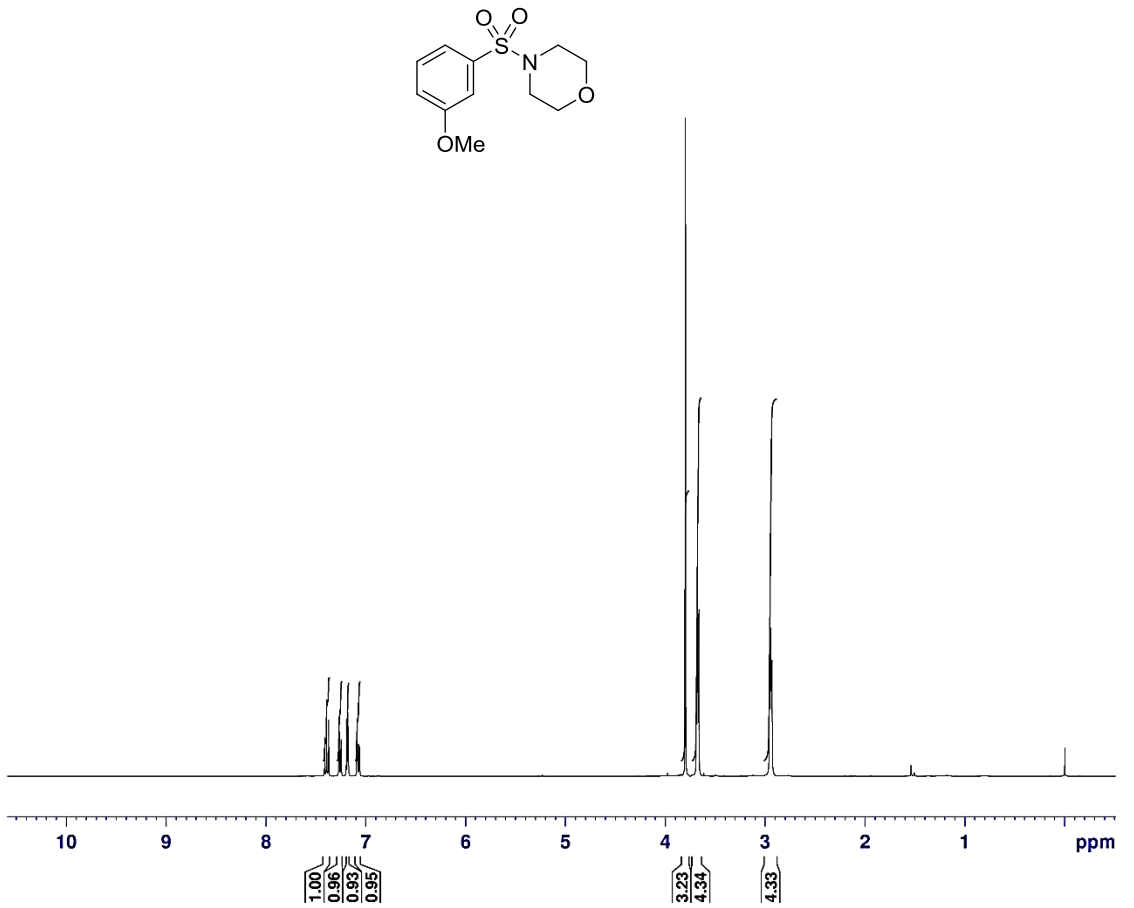
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O
S
N
O
OMe
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9
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6
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ppm
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0.93
0.95
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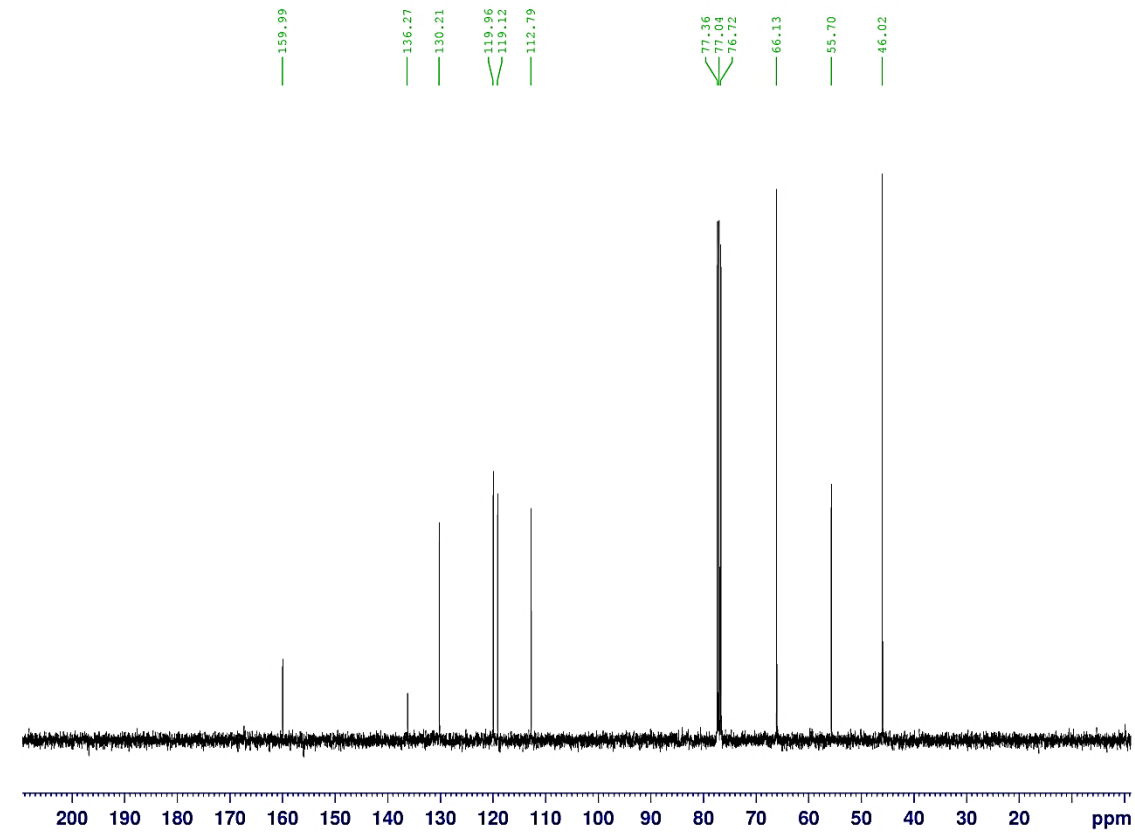
4.33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112.79
77.36
77.04
76.72
66.13
55.70
46.02
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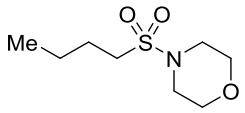
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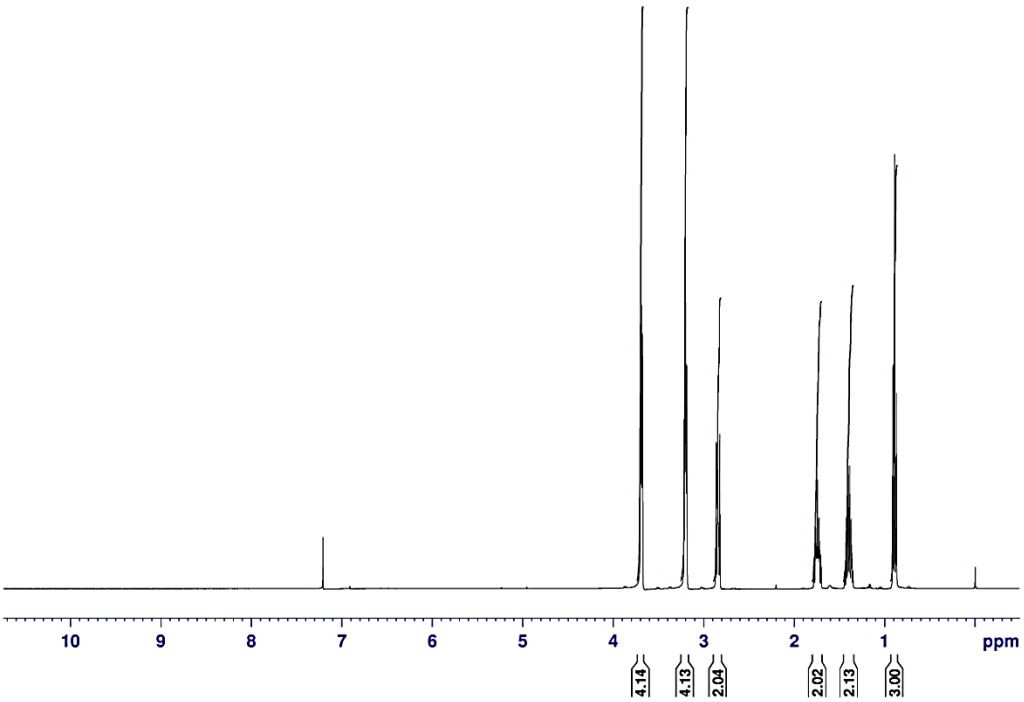
O
S
N
O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3
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ppm
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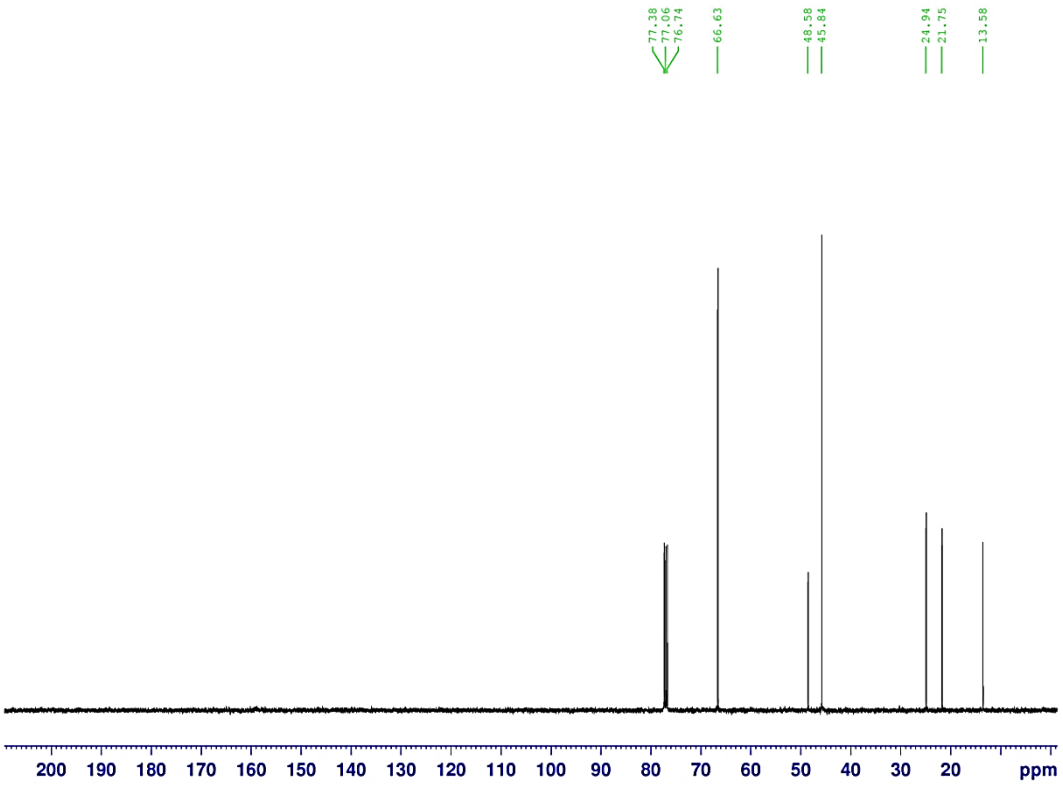
2.02
2.13
3.00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21.75
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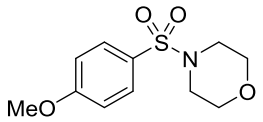
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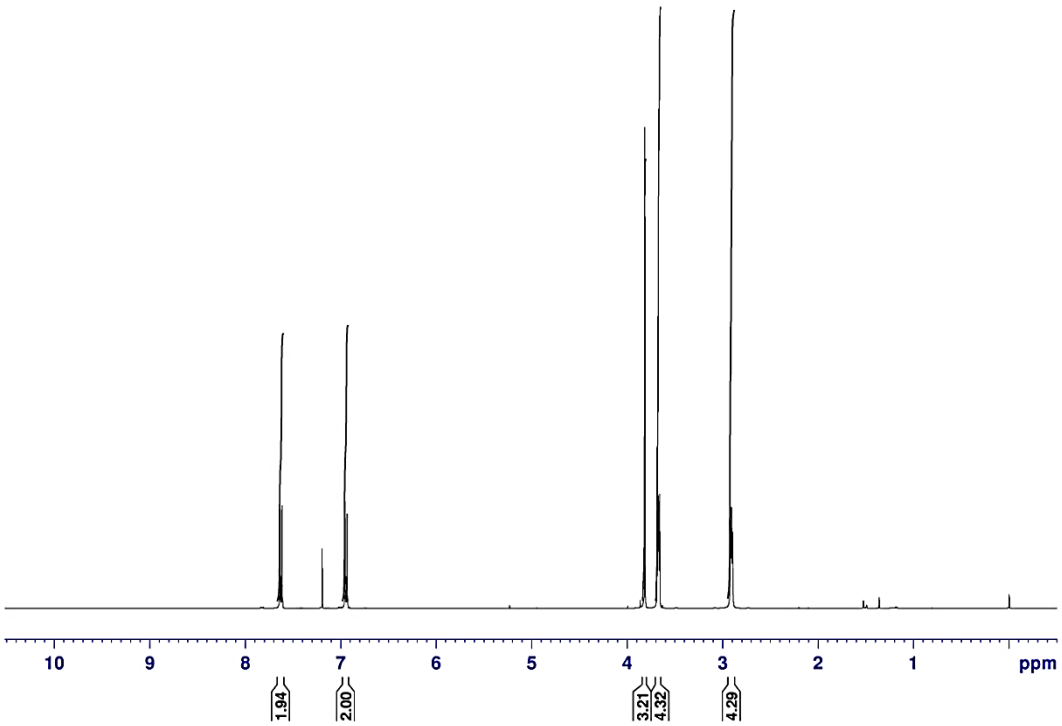
S
N
O
MeO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8
7
6
5
4
3
2
1
ppm
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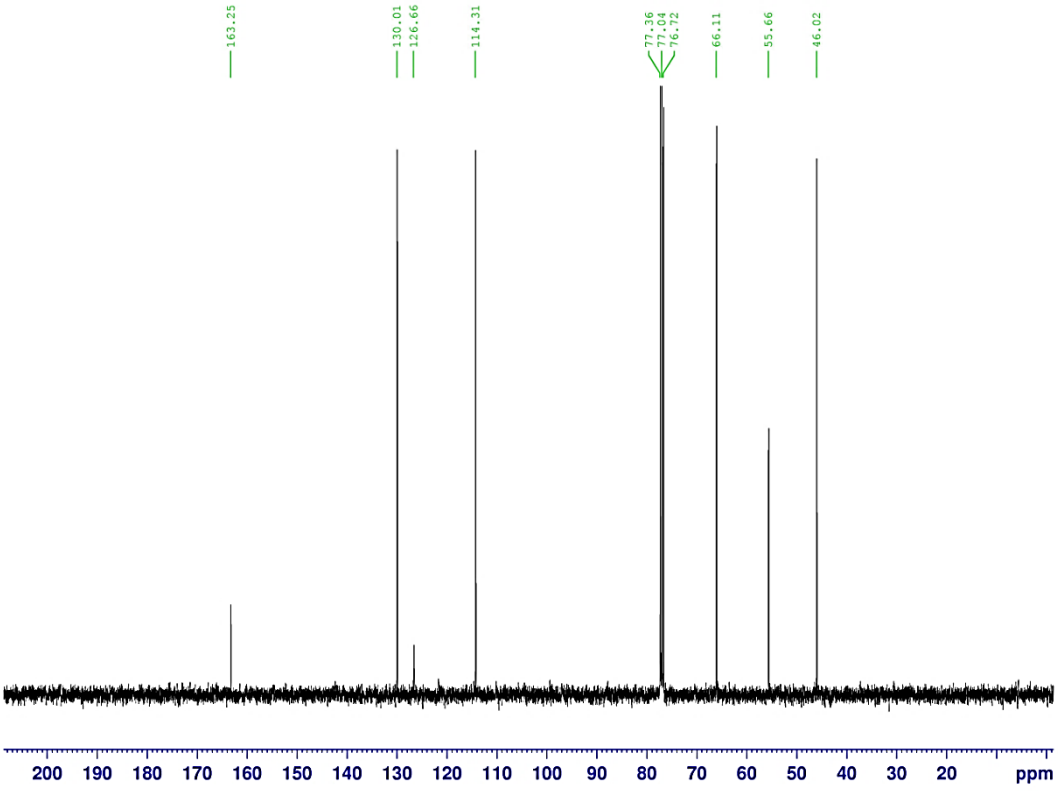
2.00
3.21
4.32
4.29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130.01
126.66
114.31
77.36
77.04
76.72
66.11
55.66
46.02
200
190
180
170
160
150
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130
120
110
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80
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40
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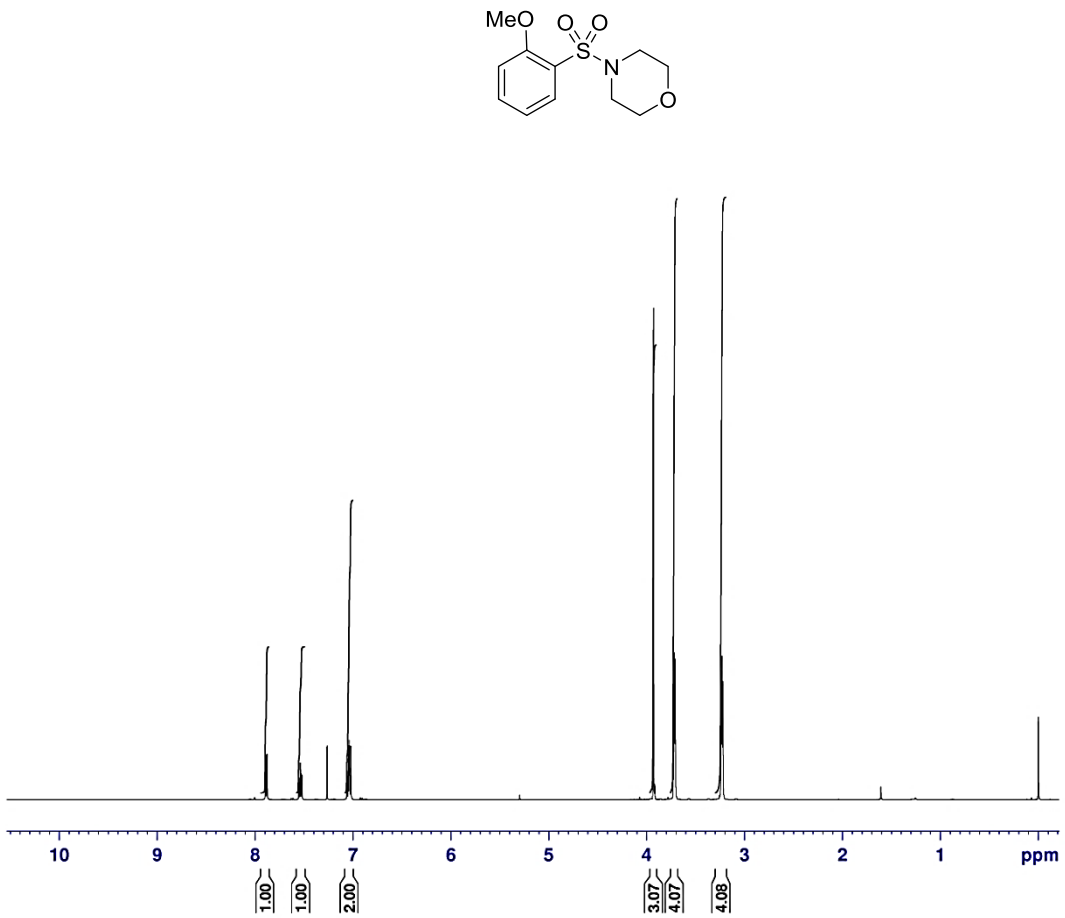
20
ppm


MeO
O
O
S
N
O
10
9
8
7
6
5
4
3
2
1
ppm
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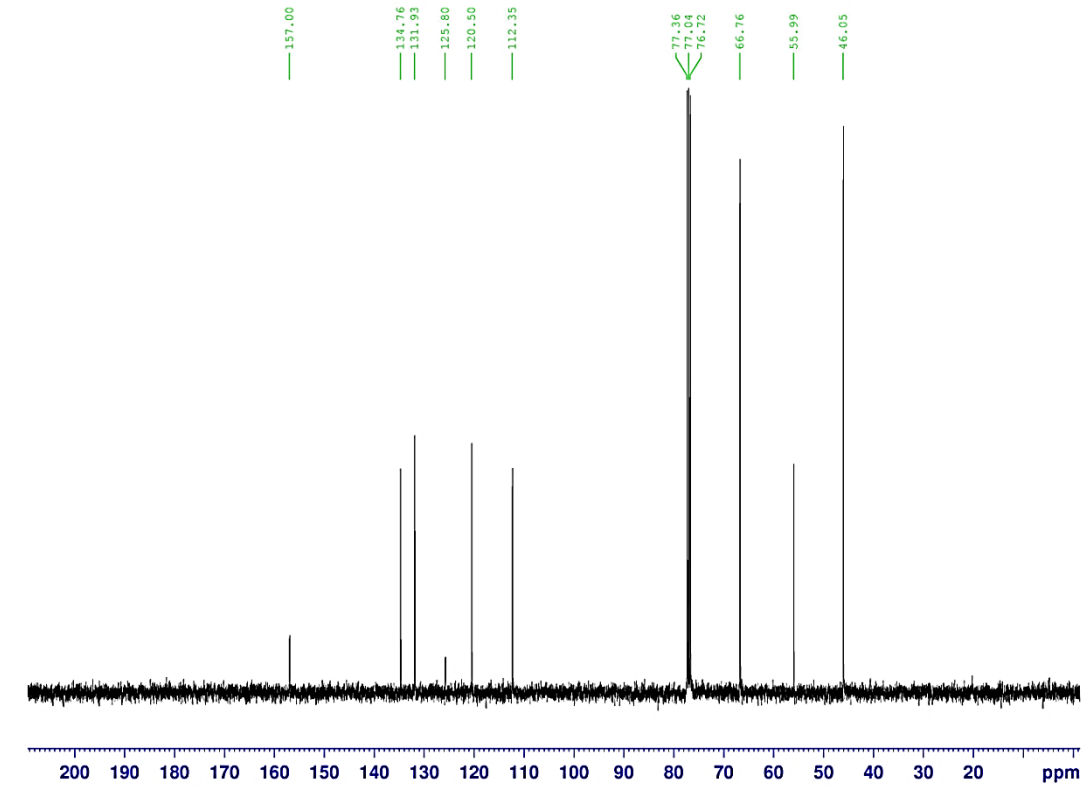
1.00
2.00
3.07
4.07
4.08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112.35
77.36
77.04
76.72
66.76
55.99
46.05
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160
150
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120
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80
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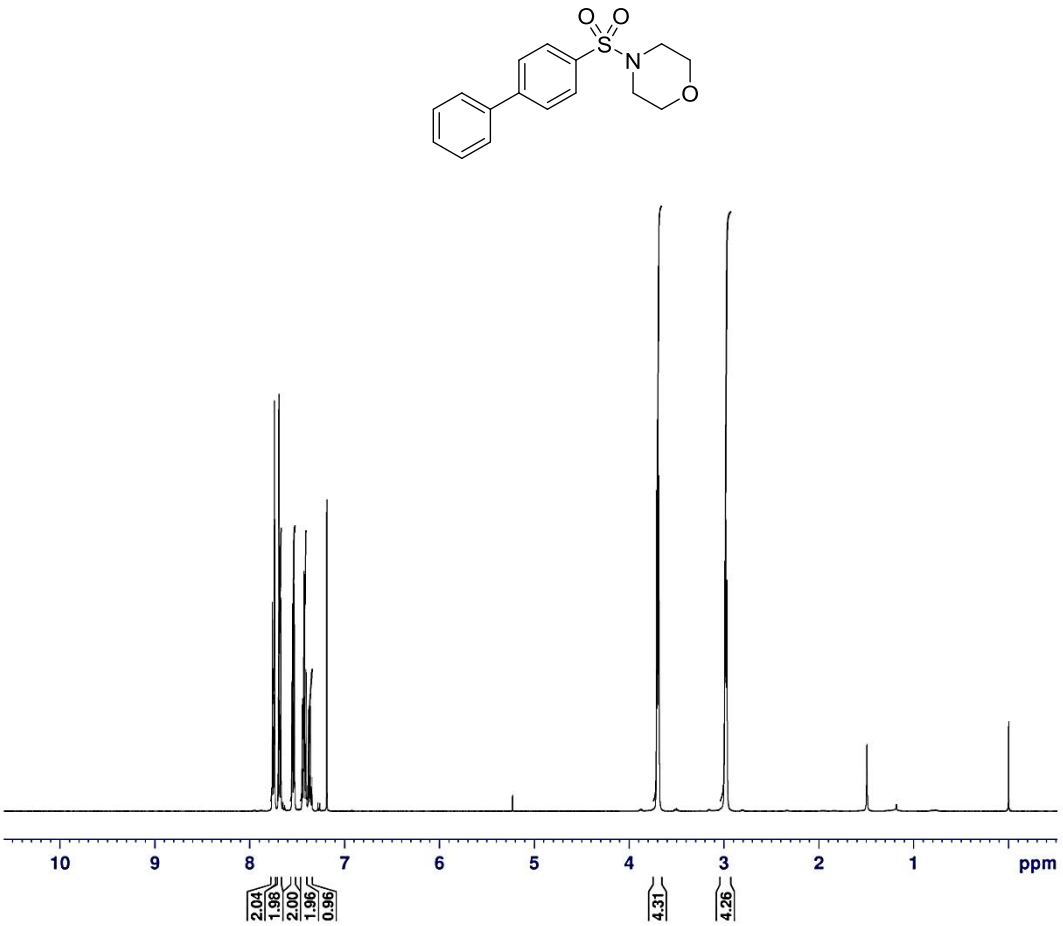
20
ppm


10
9
8
7
6
5
4
3
2
1
ppm
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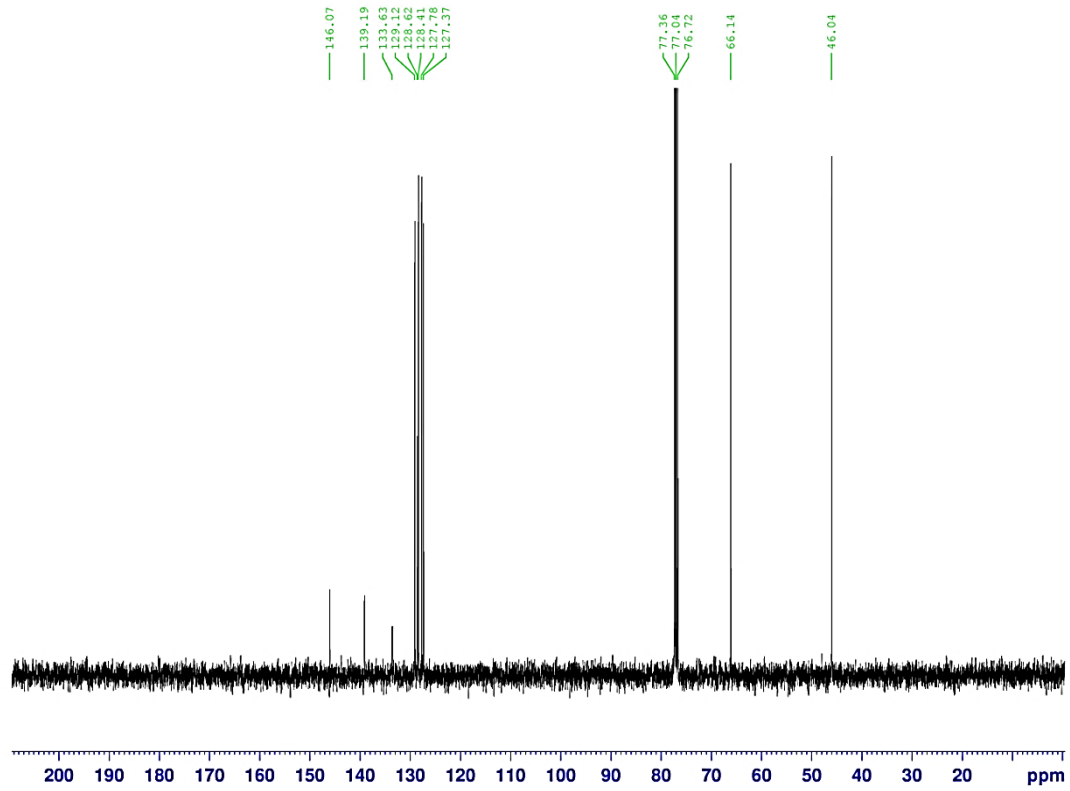
1.98
2.00
1.96
0.96
4.31
4.26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128.62
128.41
127.78
127.37
77.36
77.04
76.72
66.14
46.04
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160
150
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80
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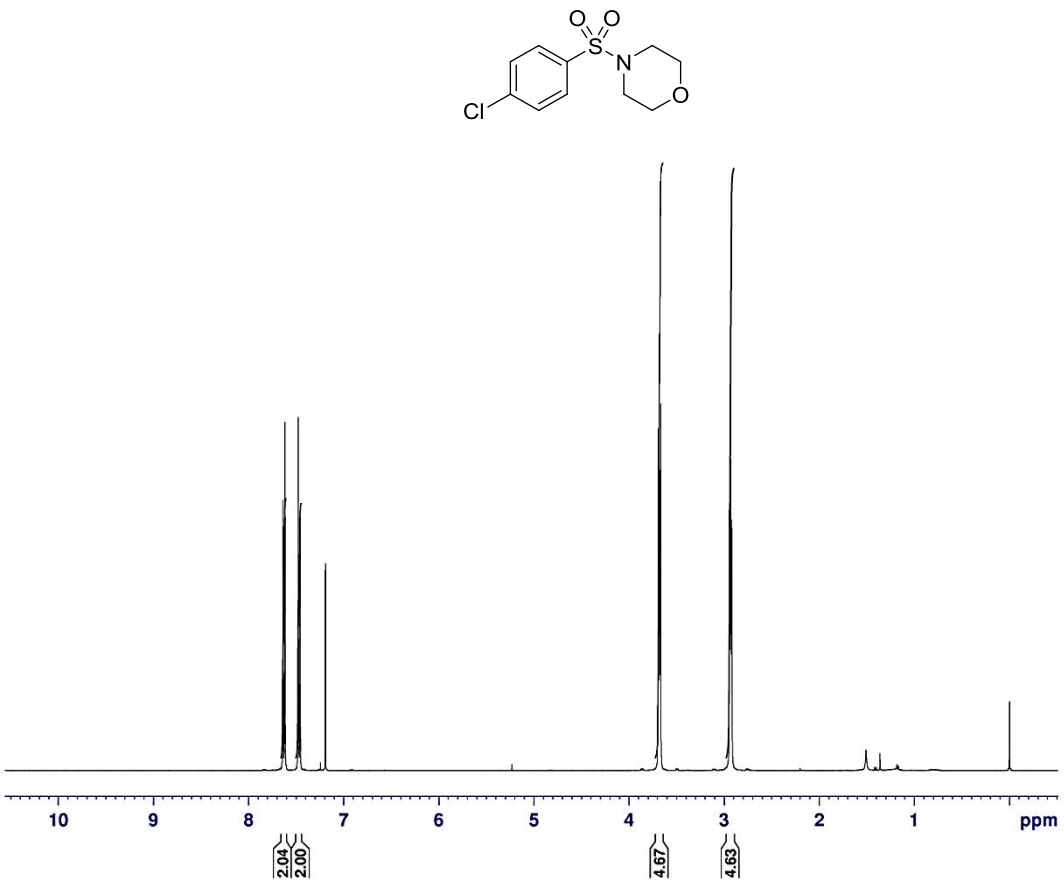
20
ppm


O
O
S
N
O
Cl
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9
8
7
6
5
4
3
2
1
ppm
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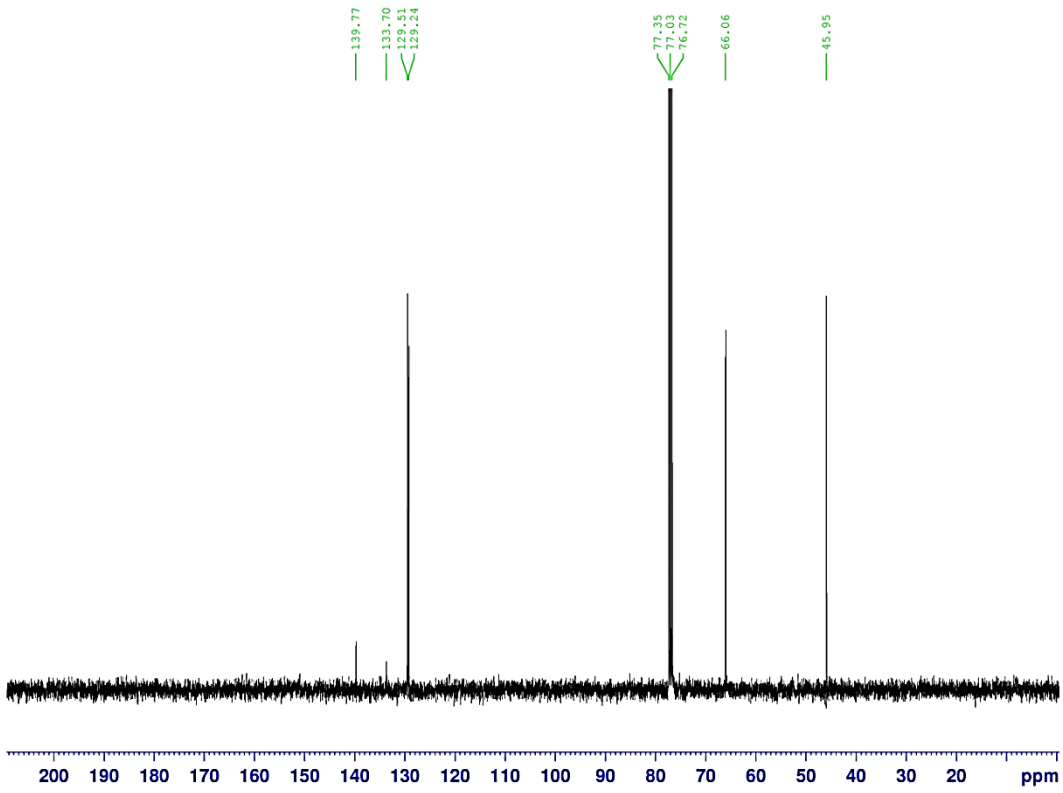
2.00
4.67
4.63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129.24
77.35
77.03
76.72
66.06
45.95
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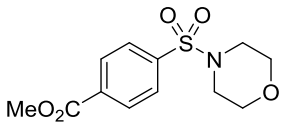
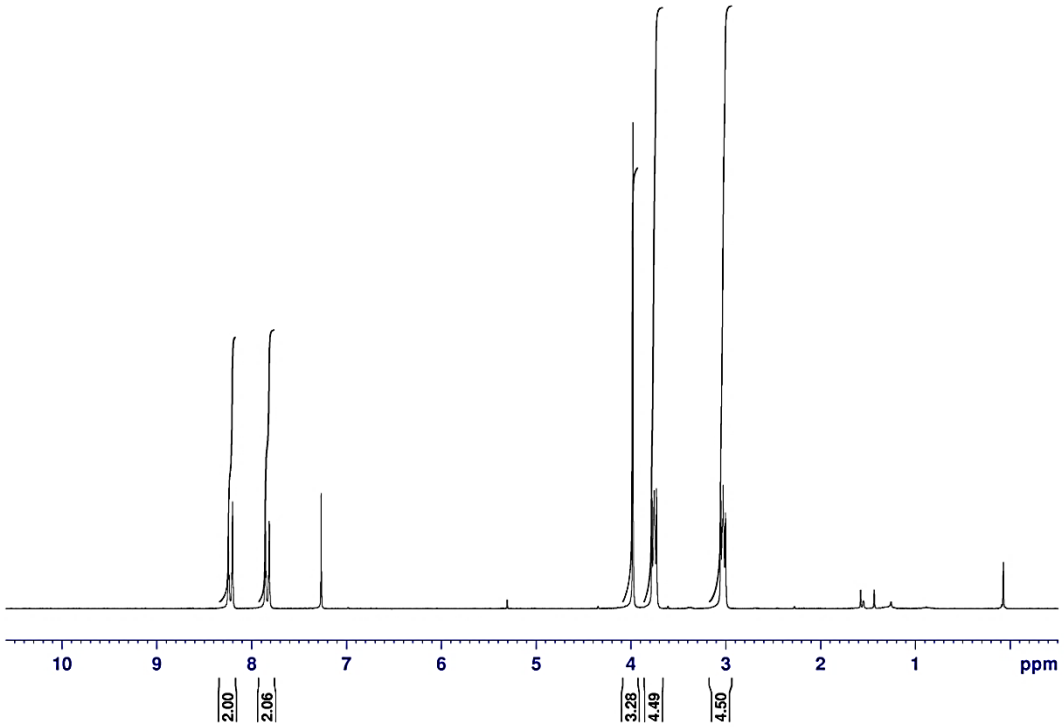
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


O
O
S
N
O
MeO2C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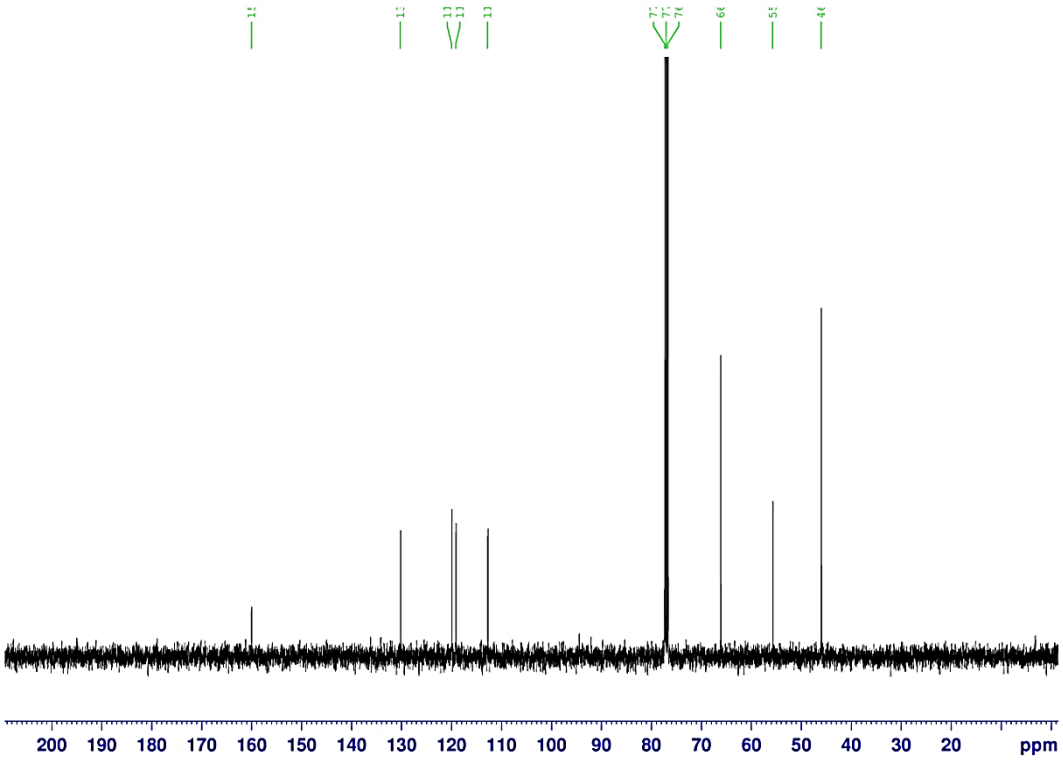
9
8
7
6
5
4
3
2
1
ppm
2.00
2.06
3.28
4.49
4.50


200
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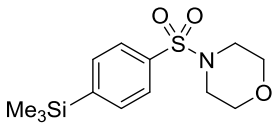
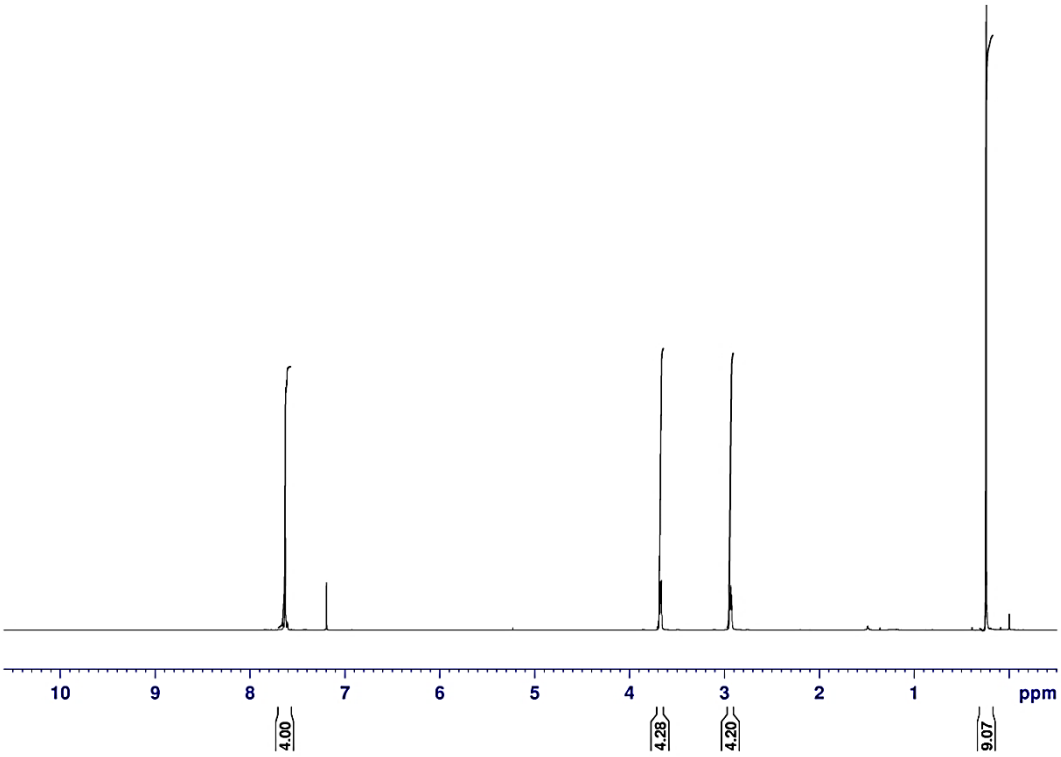
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


O
O
S
N
O
Me3Si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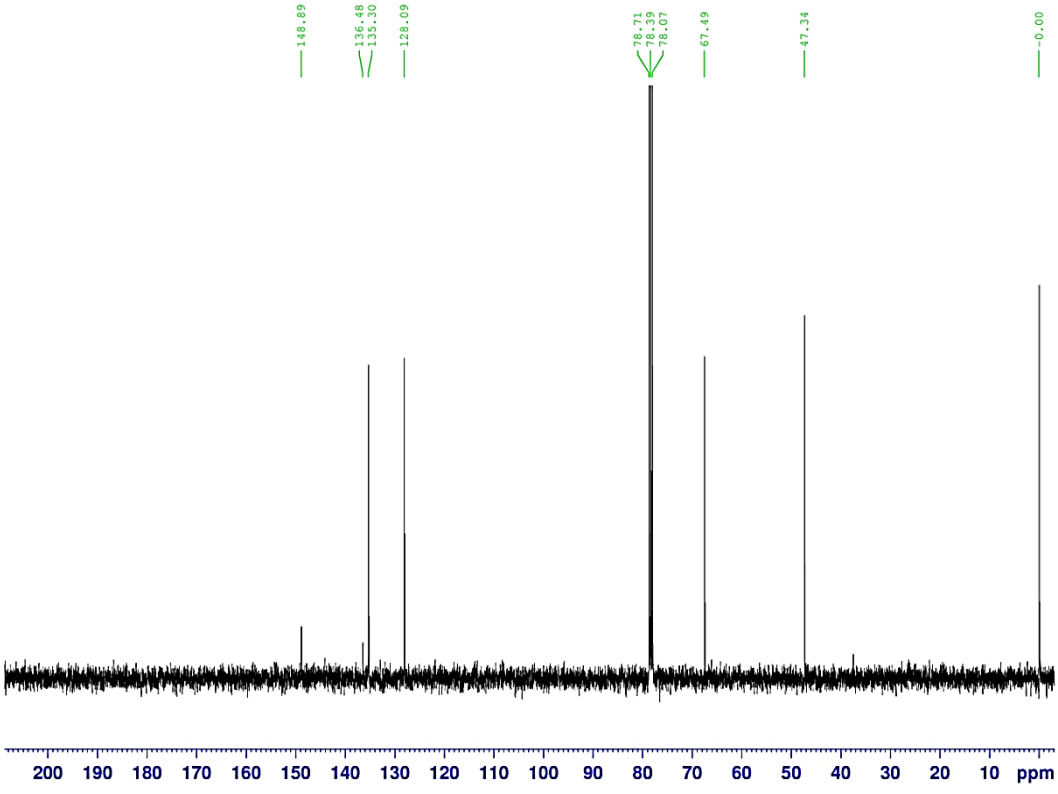
8
7
6
5
4
3
2
1
ppm
4.00
4.28
4.20
9.07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78.07
67.49
47.34
-0.00
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70
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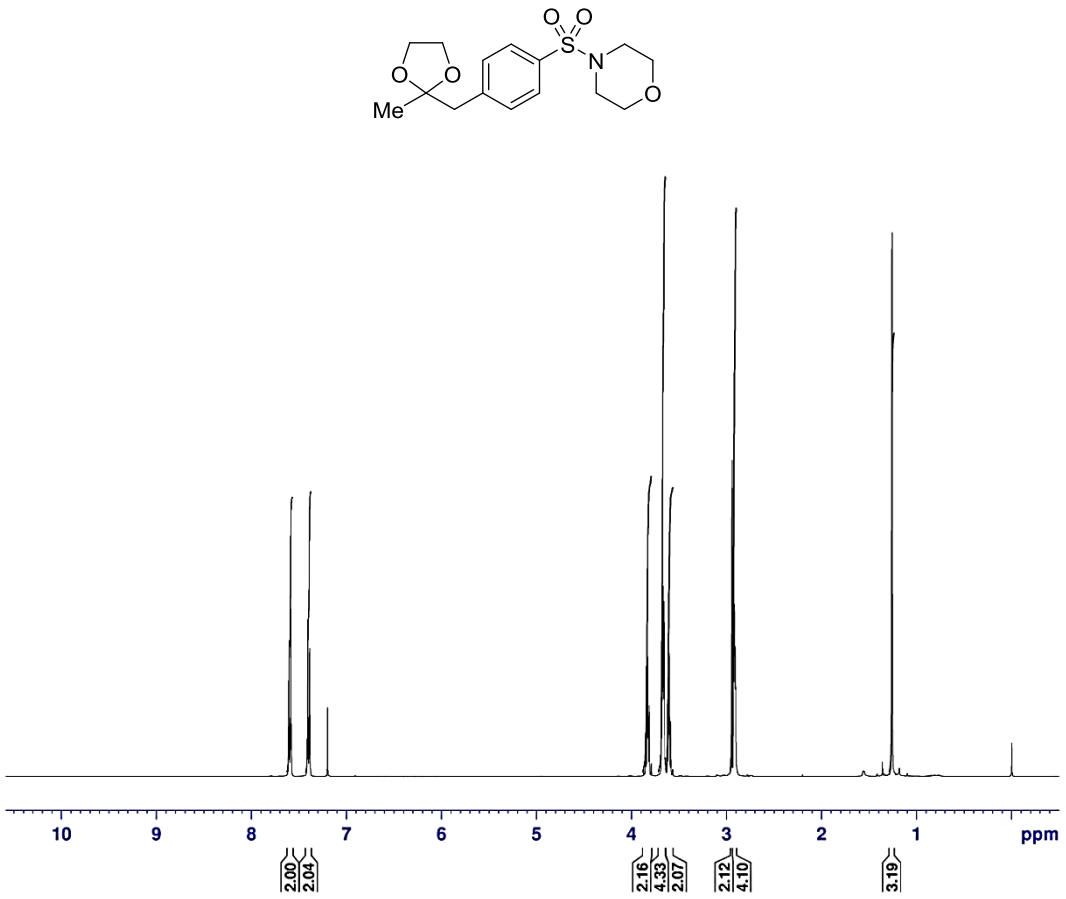
20
10
ppm


O
O
S
N
O
O
O
Me
10
9
8
7
6
5
4
3
2
1
ppm
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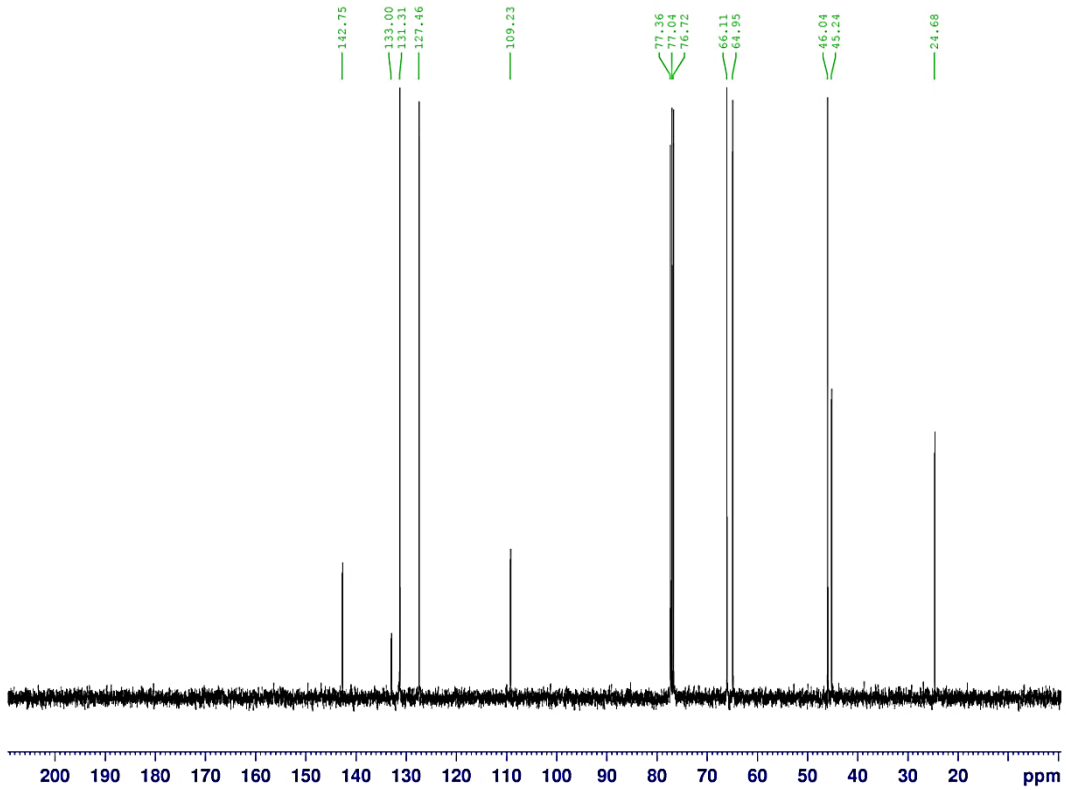
2.04
2.16
4.33
2.07
2.12
4.10
3.19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77.36
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76.72
66.11
64.95
46.04
45.24
24.68
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80
70
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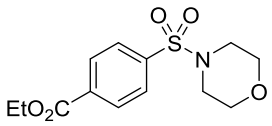
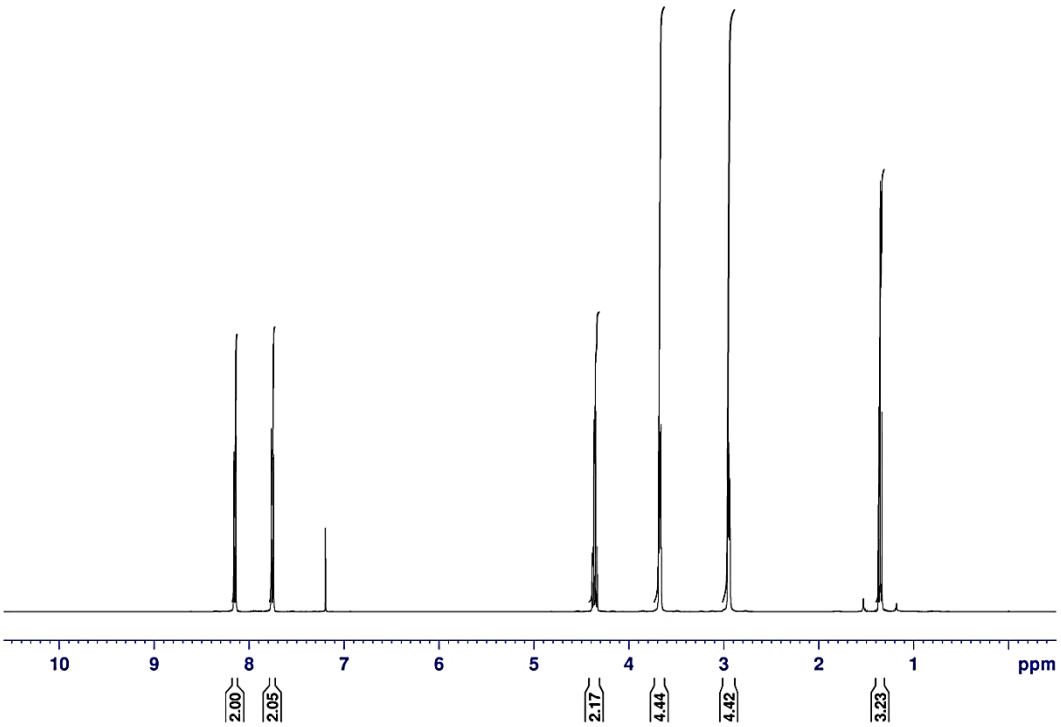
20
ppm


O
O
S
N
O
EtO2C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7
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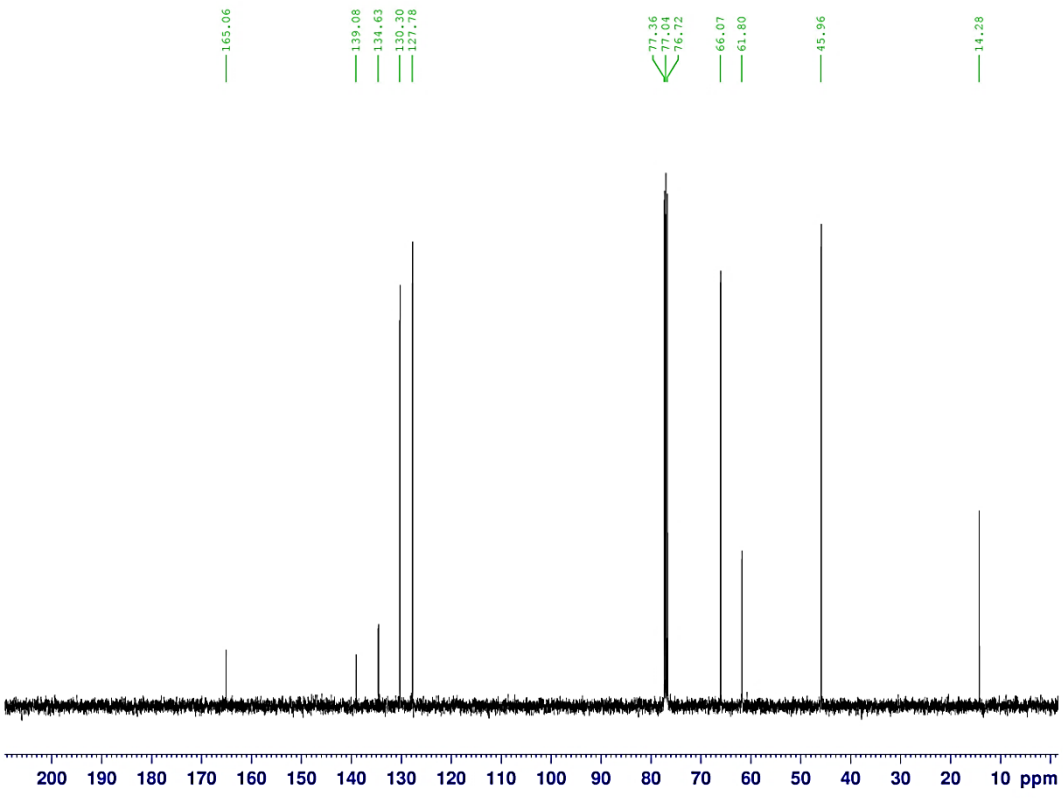
5
4
3
2
1
ppm
2.00
2.05
2.17
4.44
4.42
3.23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77.36
77.04
76.72
66.07
61.80
45.96
14.28
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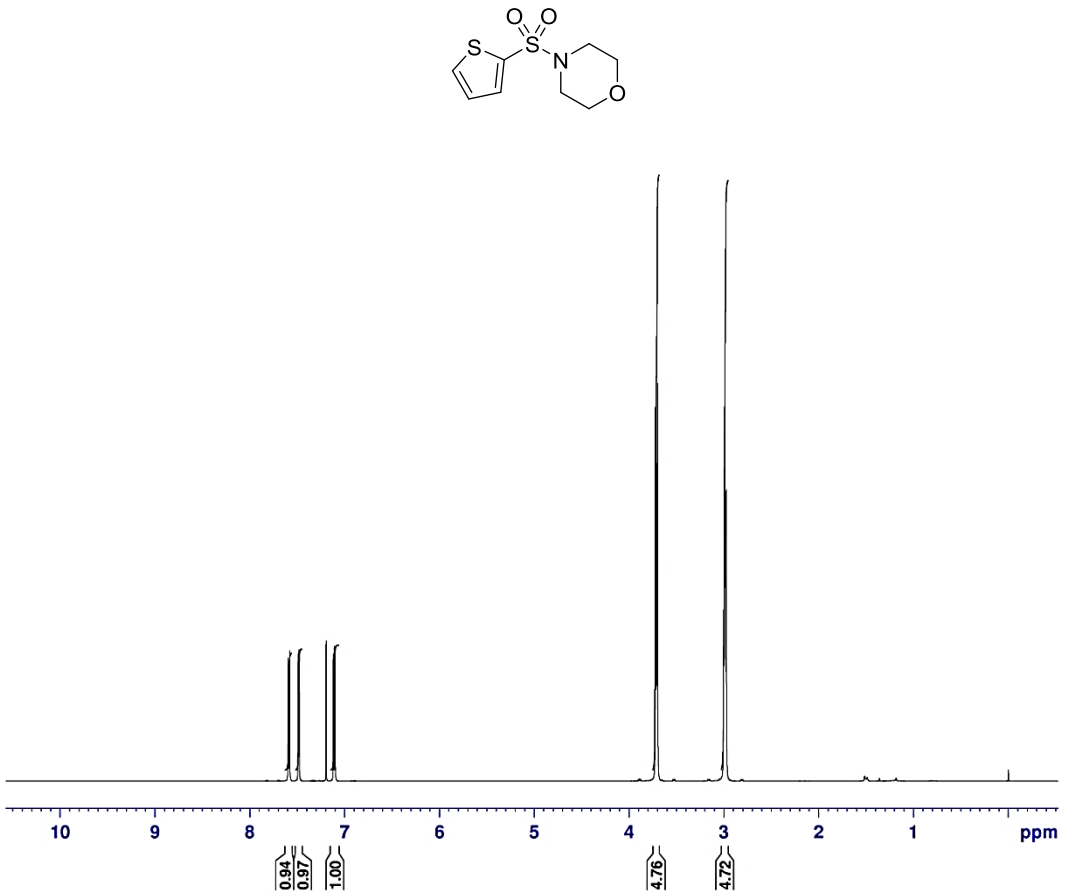
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10 ppm


O
O
S
S
N
O
10
9
8
7
6
5
4
3
2
1
ppm
0.94
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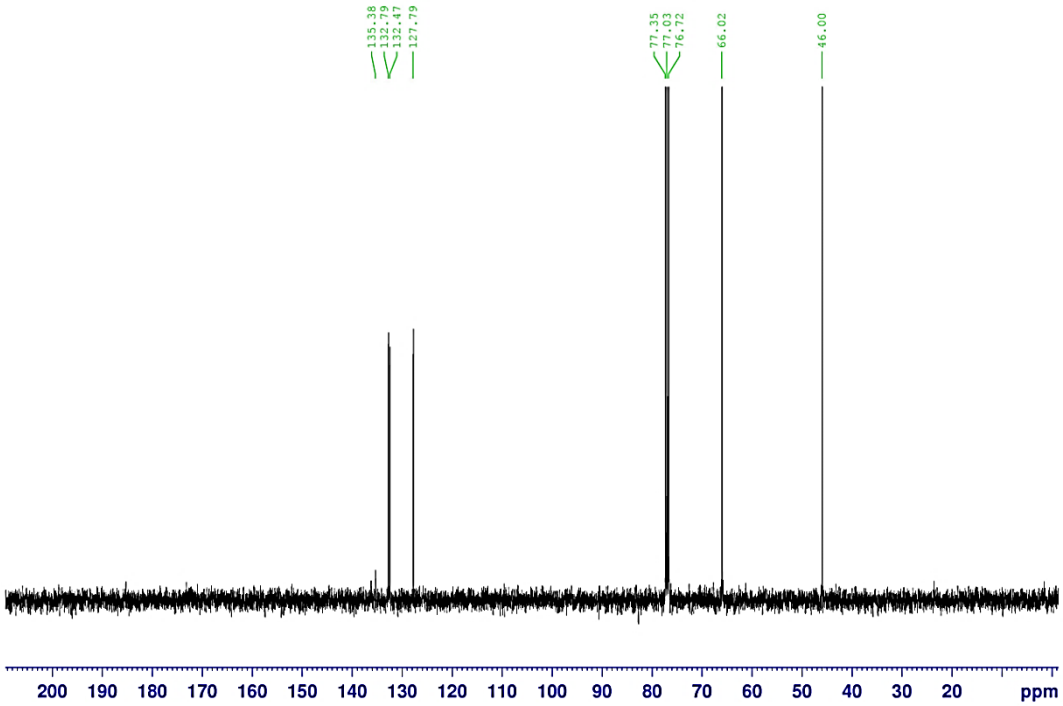
1.00
4.76
4.72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127.79
77.35
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76.72
66.02
46.00
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80
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40
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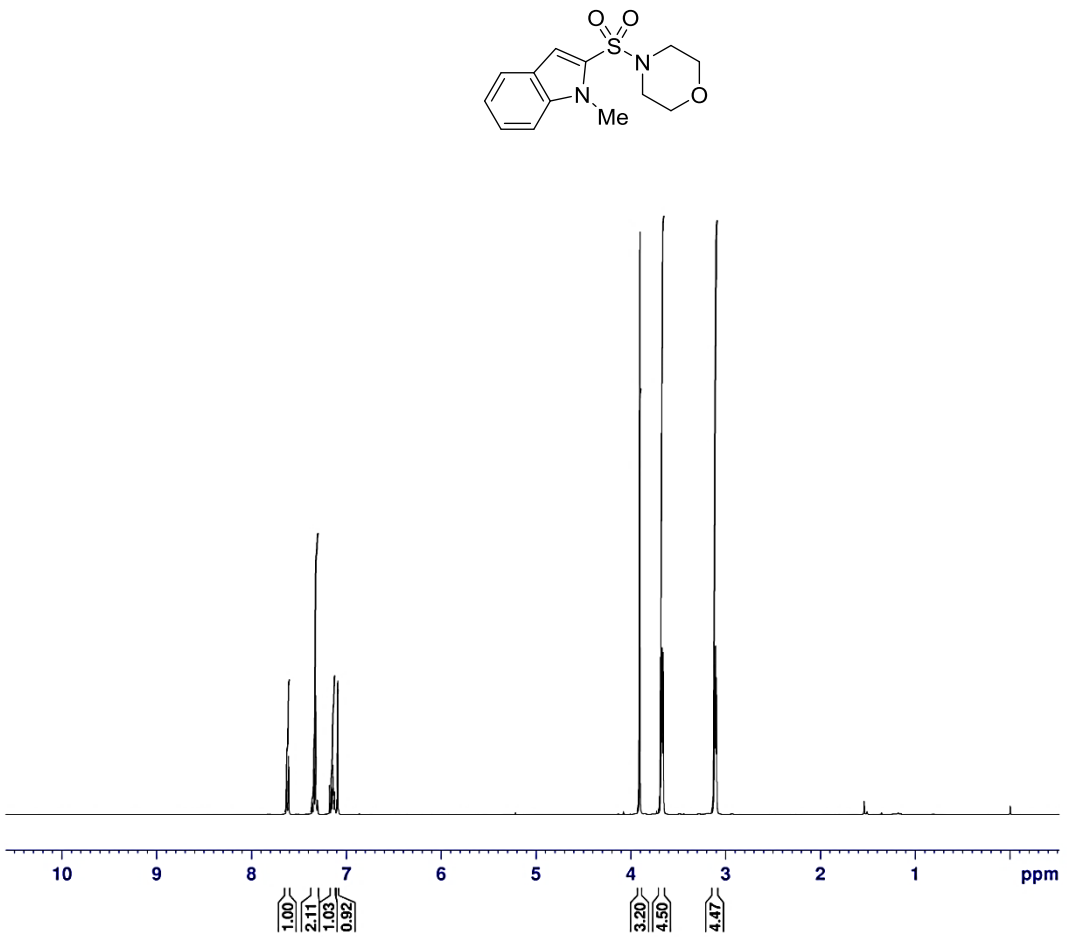
20
ppm


O
O
S
N
N
Me
O
10
9
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6
5
4
3
2
1
ppm
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2.11
1.03
0.92
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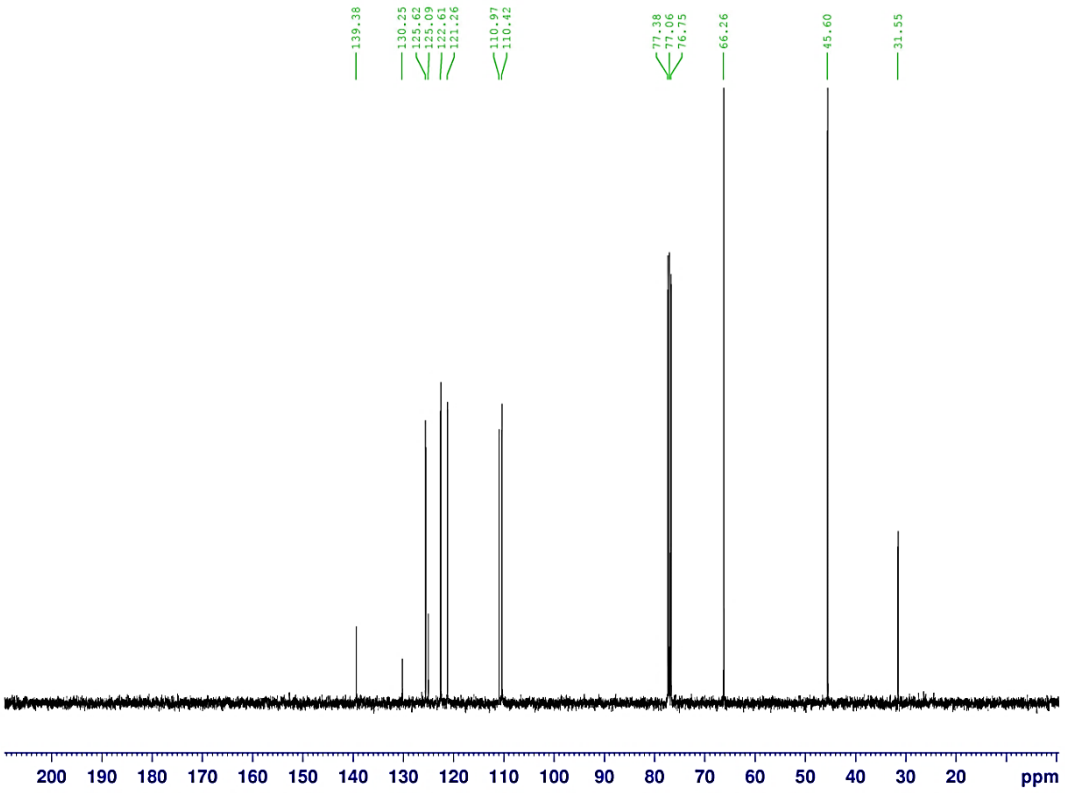
4.50
4.47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125.62
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121.26
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110.42
77.38
77.06
76.75
66.26
45.60
31.55
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150
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130
120
110
100
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80
70
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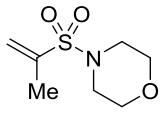
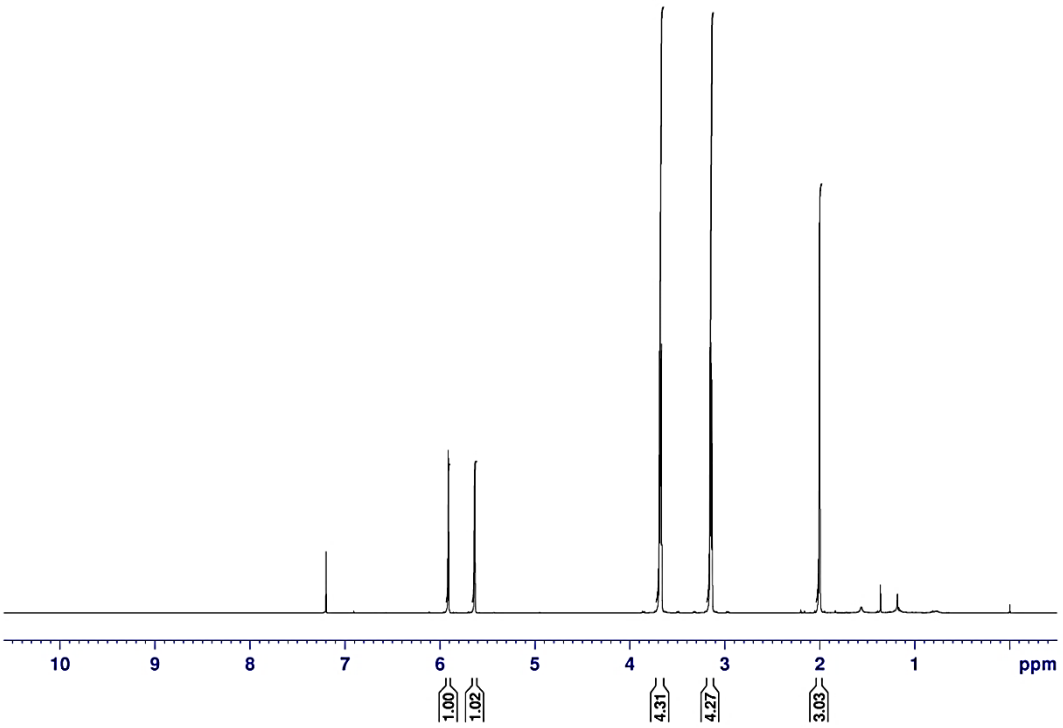
50
40
30
20
ppm


O
O
S
N
Me
O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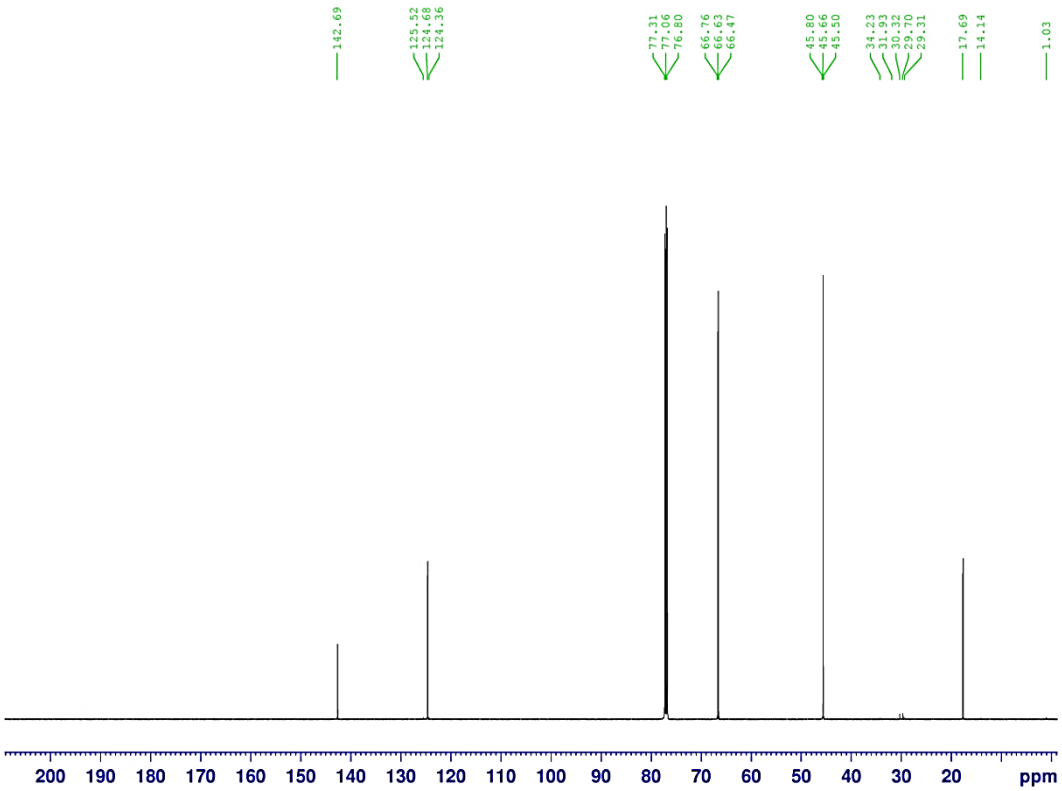
9
8
7
6
5
4
3
2
1
ppm
1.00
1.02
4.31
4.27
3.03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124.36
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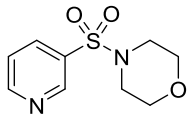
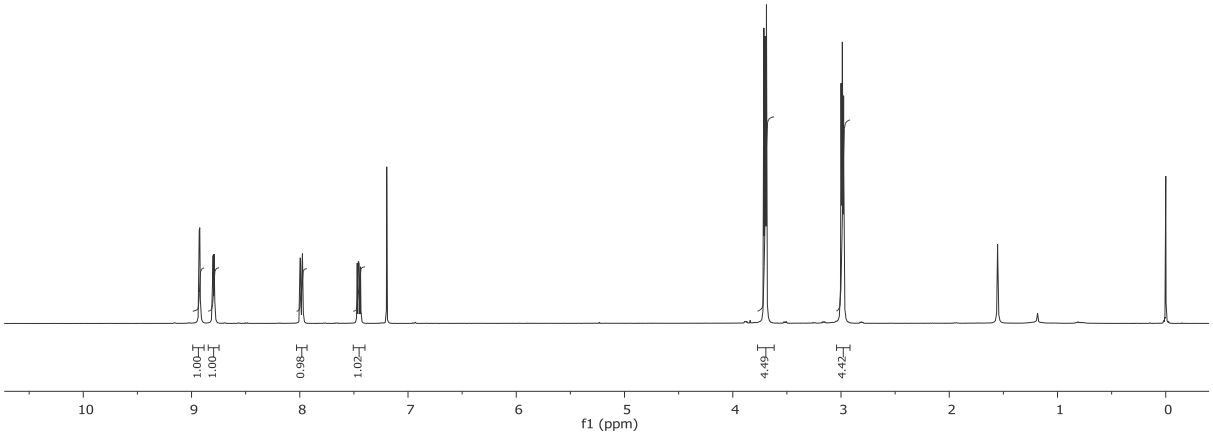
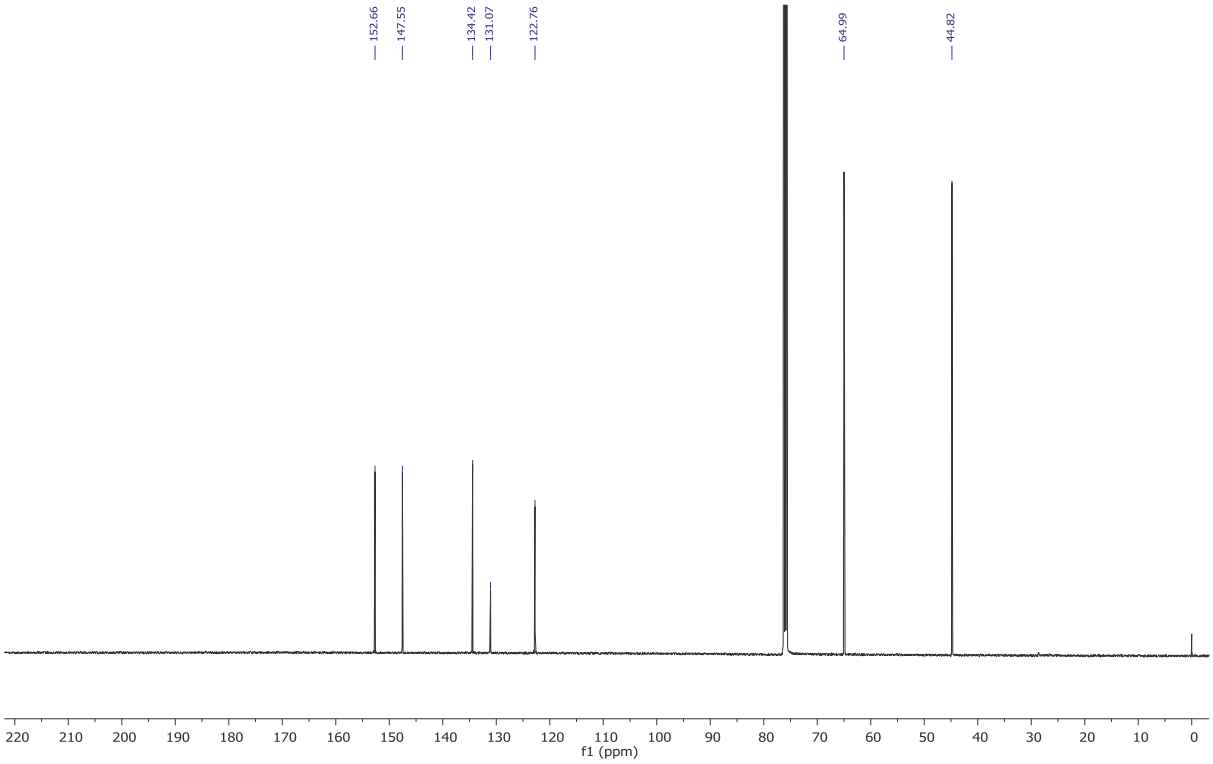
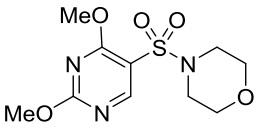
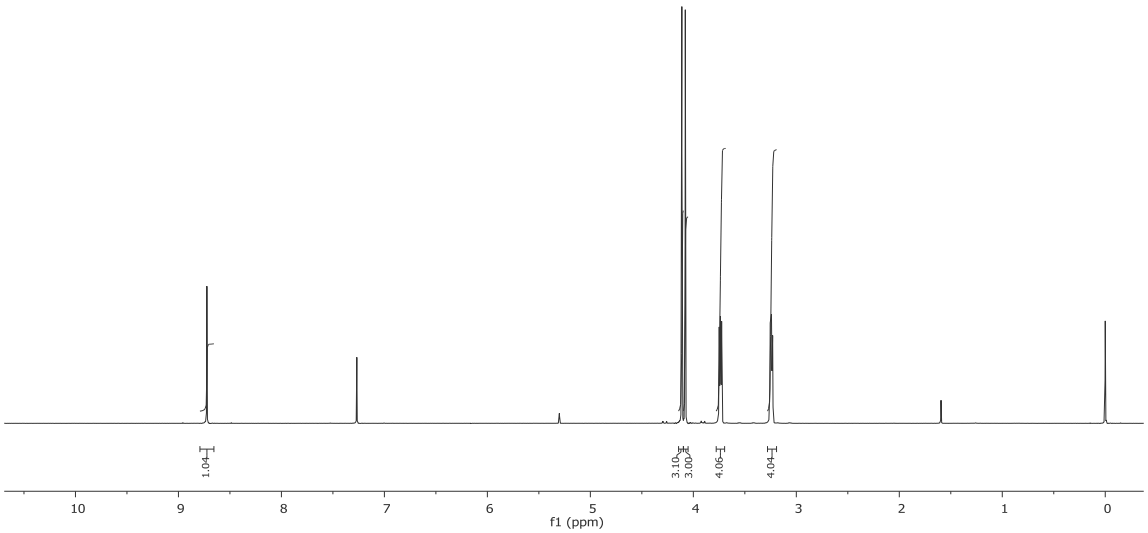
66.76
66.63
66.47
45.80
45.66
45.50
34.23
31.93
30.32
29.70
29.31
17.69
14.14
1.03
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


O
O
S
N
O
N


1.00
1.00
0.98
1.02
4.49
4.42
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


152.66
147.55
134.42
131.07
122.76
64.99
44.82
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


MeO
O
O
S
N
N
O
MeO
N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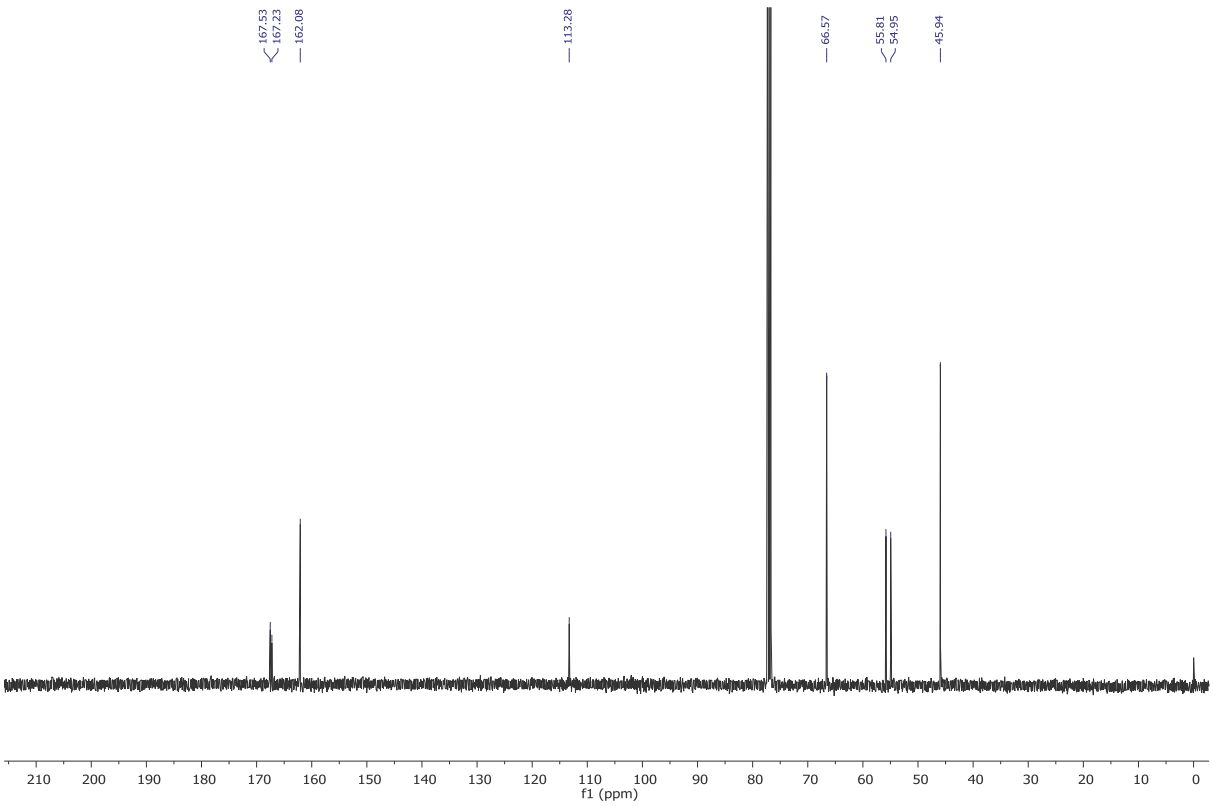
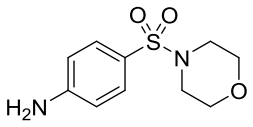
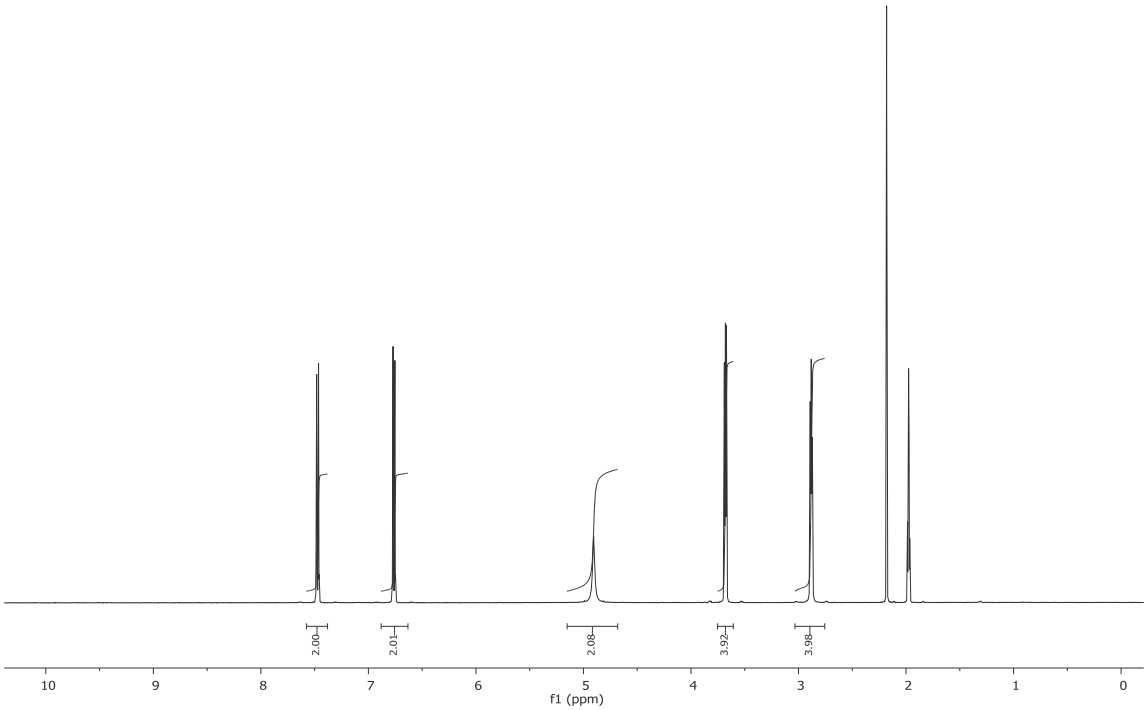
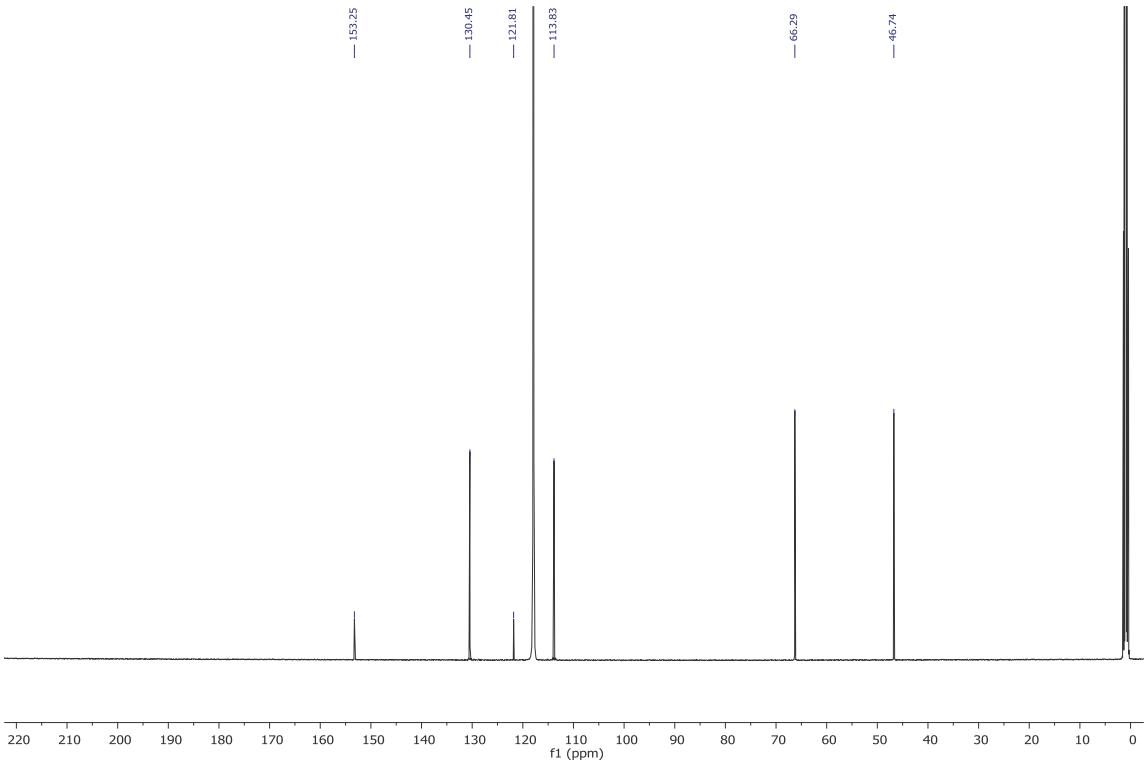
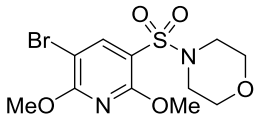
3.10
3.00
4.06
4.04
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

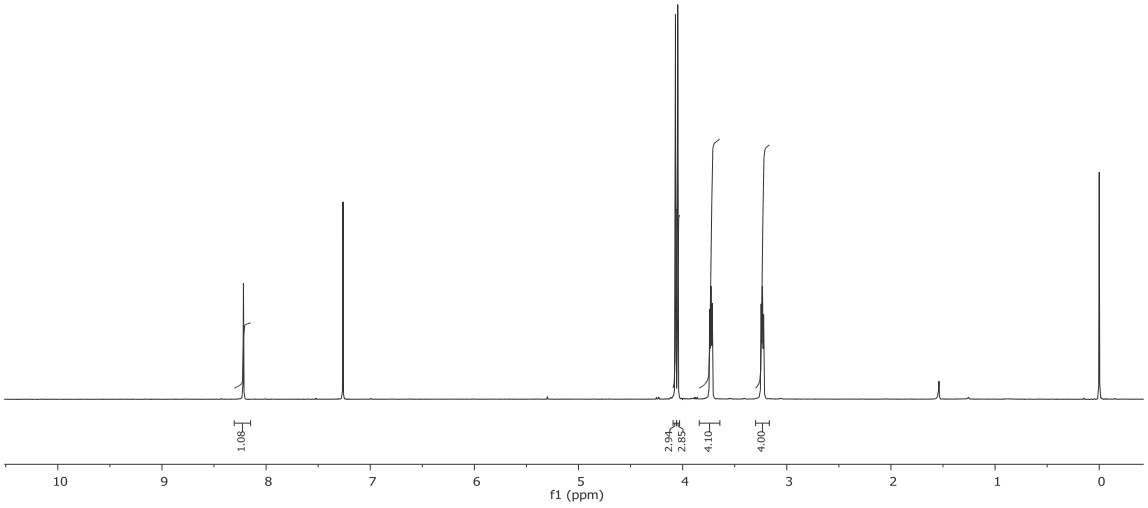

167.53
167.23
162.08
113.28
66.57
55.81
54.95
45.94
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

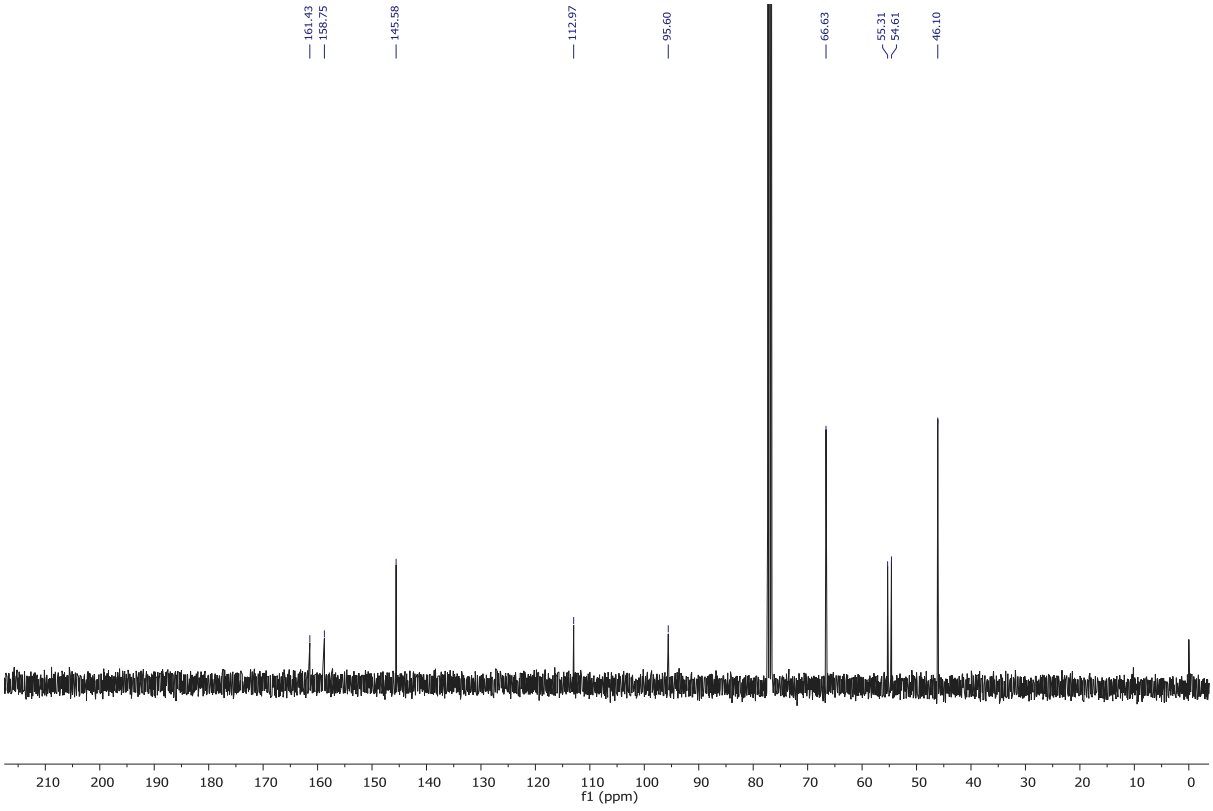

O
O
S
N
O
$H_2N$

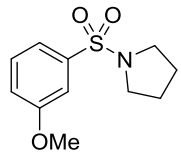

2.00
2.01
2.08
3.92
3.98
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

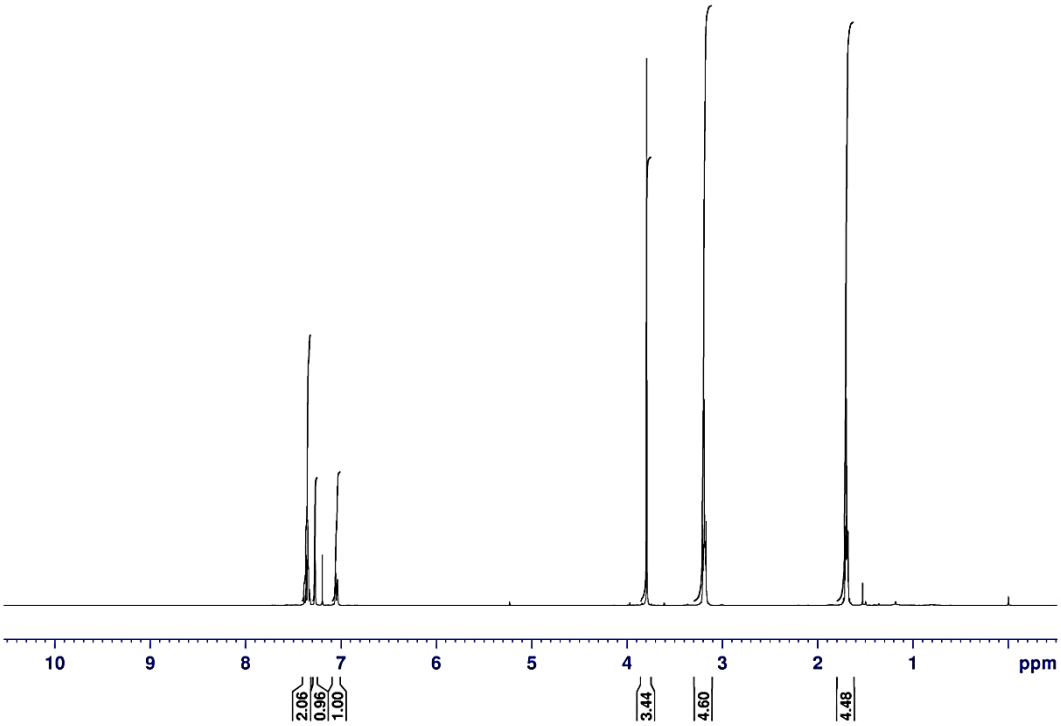

153.25
130.45
121.81
113.83
66.29
46.74
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

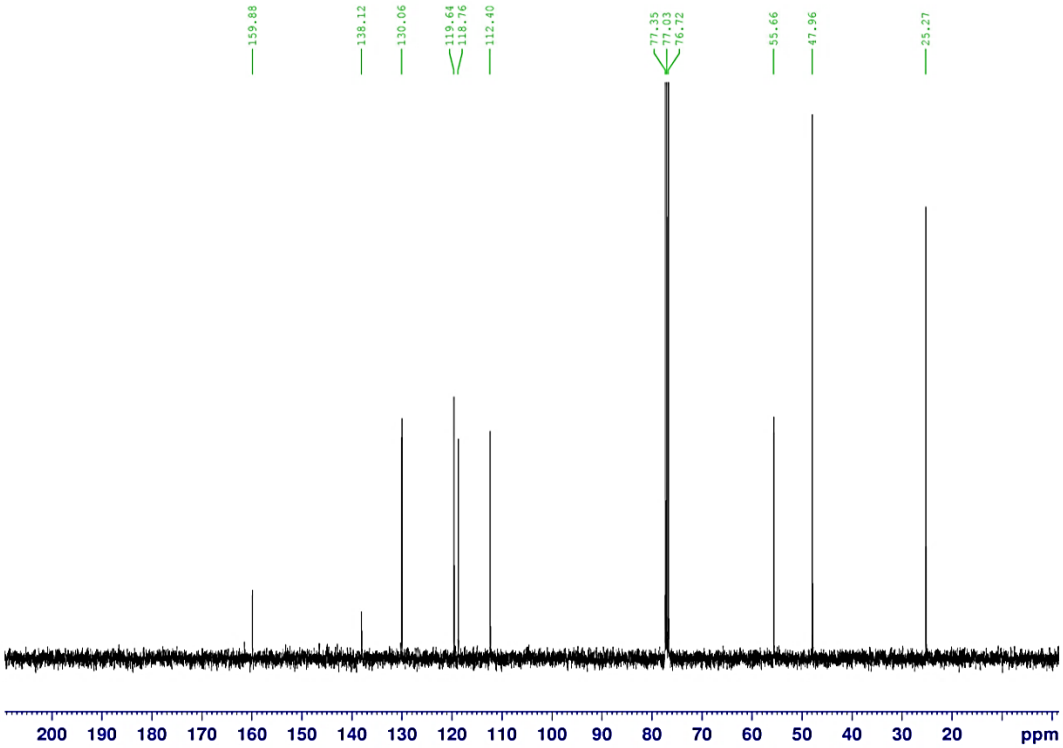

Br
O
O
S
N
O
MeO
N
OMe


1.08
2.94
2.85
4.10
4.00
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

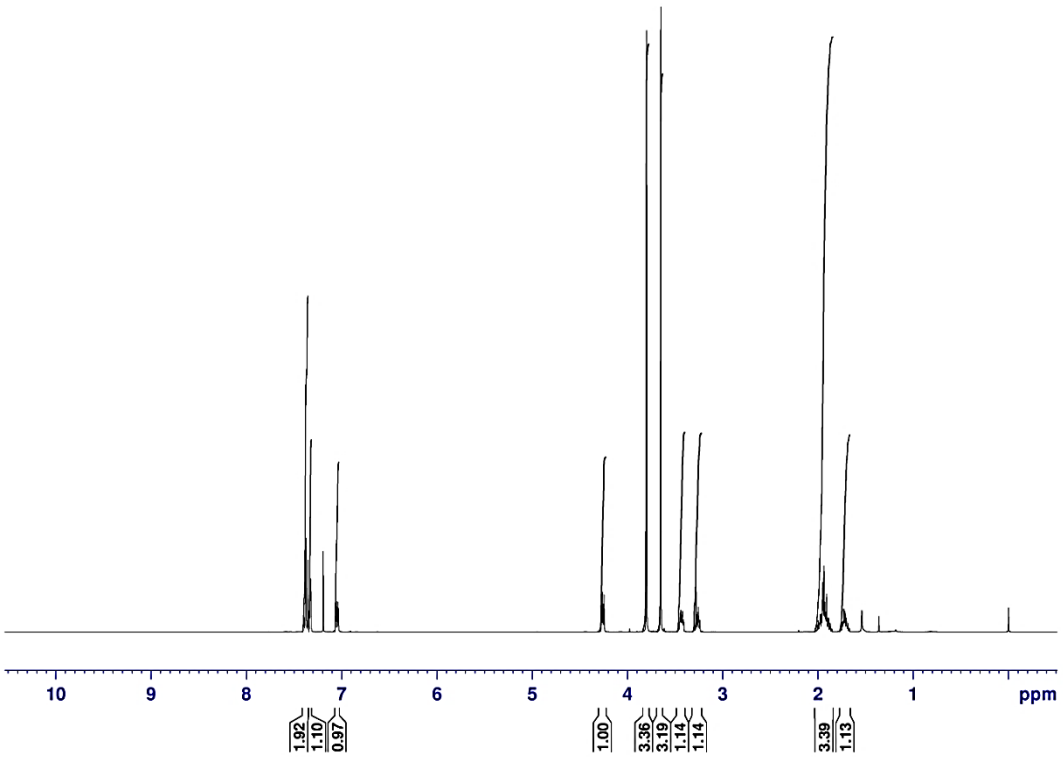

161.43
158.75
145.58
112.97
95.60
66.63
55.31
54.61
46.10
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

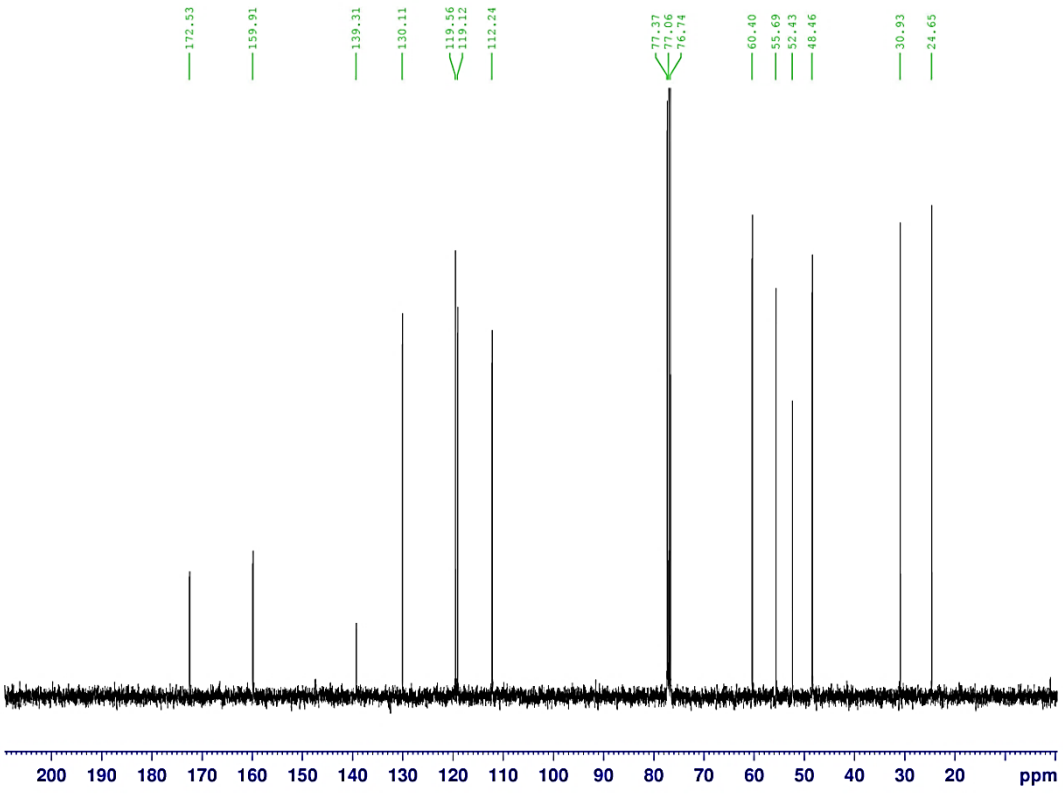

O
O
S
N
OMe


10
9
8
7
6
5
4
3
2
1
ppm
2.06
0.96
1.00
3.44
4.60
4.48

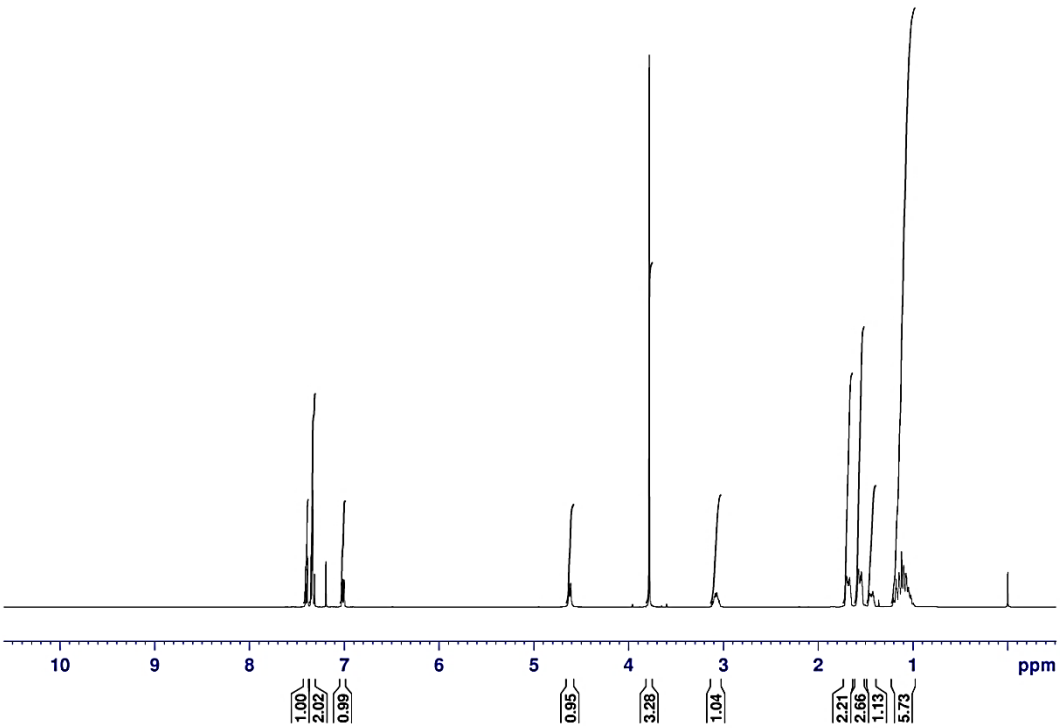

159.88
138.12
130.06
119.64
118.76
112.40
77.35
77.03
76.72
55.66
47.96
25.27
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

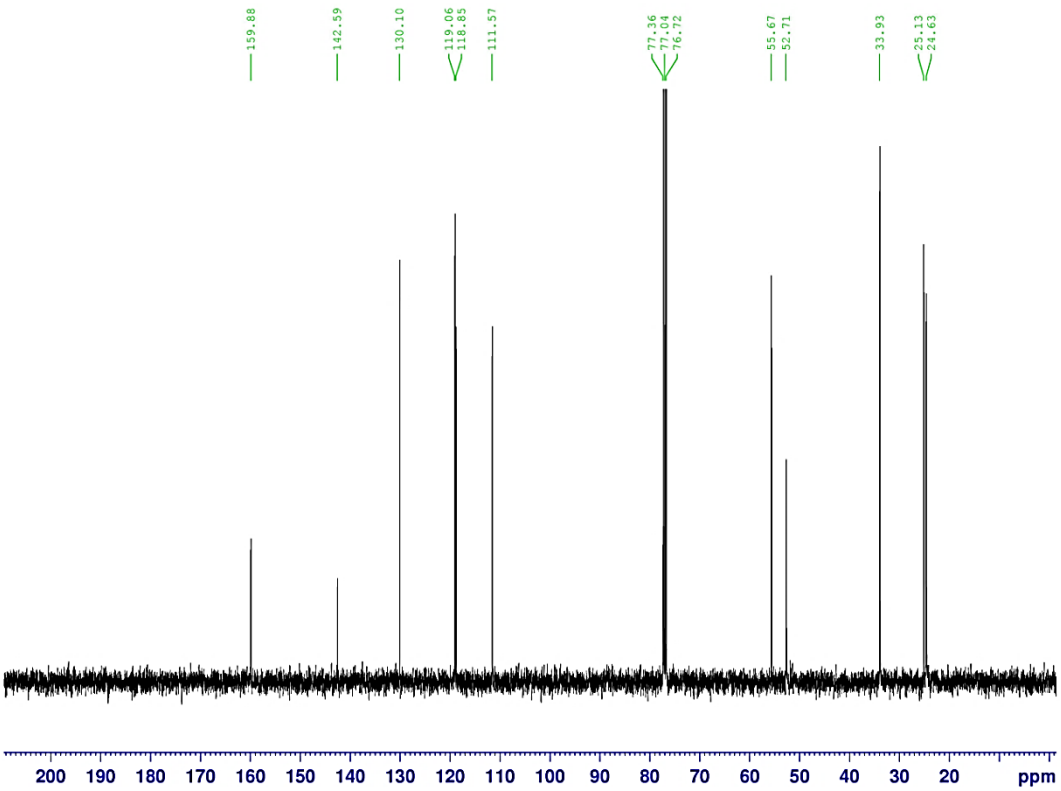

O
O
CO2Me
S
N
OMe


10
9
8
7
6
5
4
3
2
1
ppm
1.92
1.10
0.97
1.00
3.36
3.19
1.14
1.14
3.39
1.13

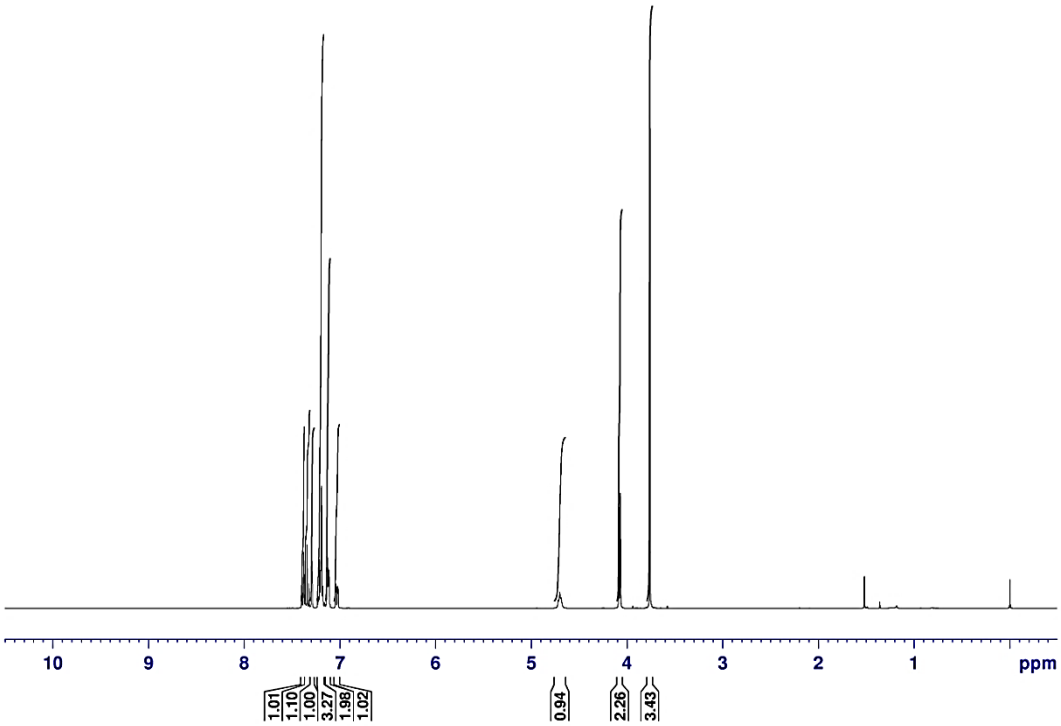

172.53
159.91
139.31
130.11
119.56
119.12
112.24
77.37
77.06
76.74
60.40
55.69
52.43
48.46
30.93
24.65
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

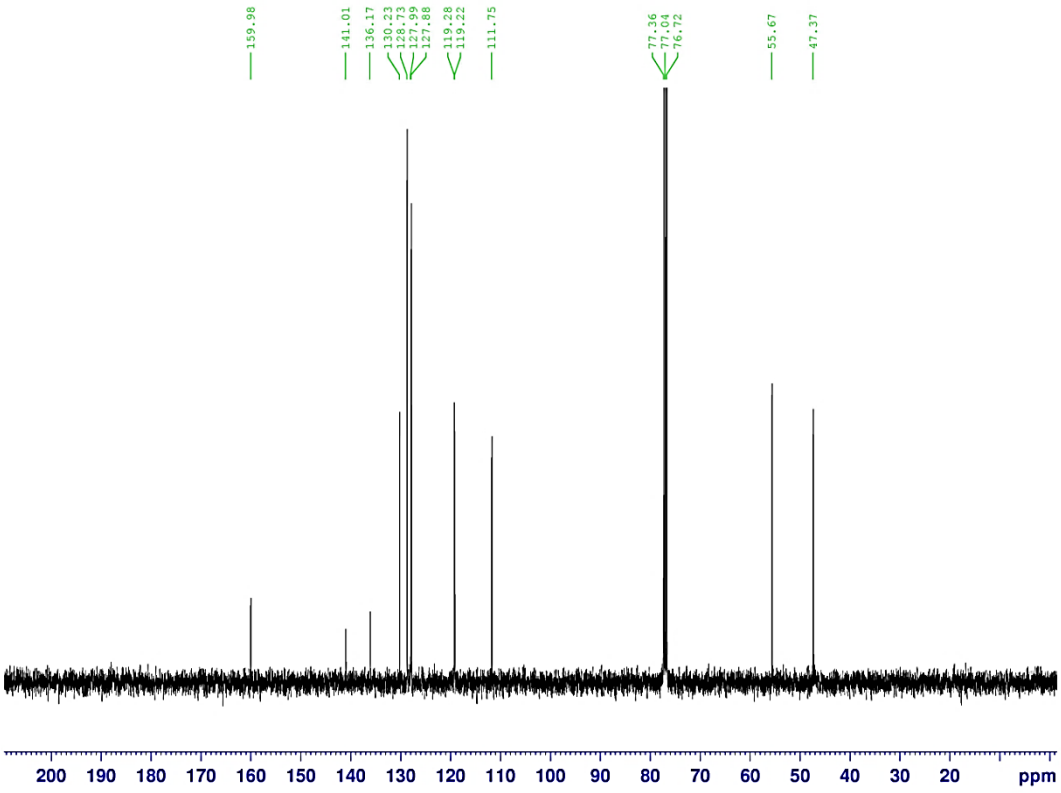

O
O
S
N
H
OMe


10
9
8
7
6
5
4
3
2
1
ppm
1.00
2.02
0.99
0.95
3.28
1.04
2.21
2.66
1.13
5.73


159.88
142.59
130.10
119.06
118.85
111.57
77.36
77.04
76.72
55.67
52.71
33.93
25.13
24.63
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


O
O
S
N
H
OMe


10
9
8
7
6
5
4
3
2
1
ppm
1.01
1.10
1.00
3.27
1.98
1.02
0.94
2.26
3.43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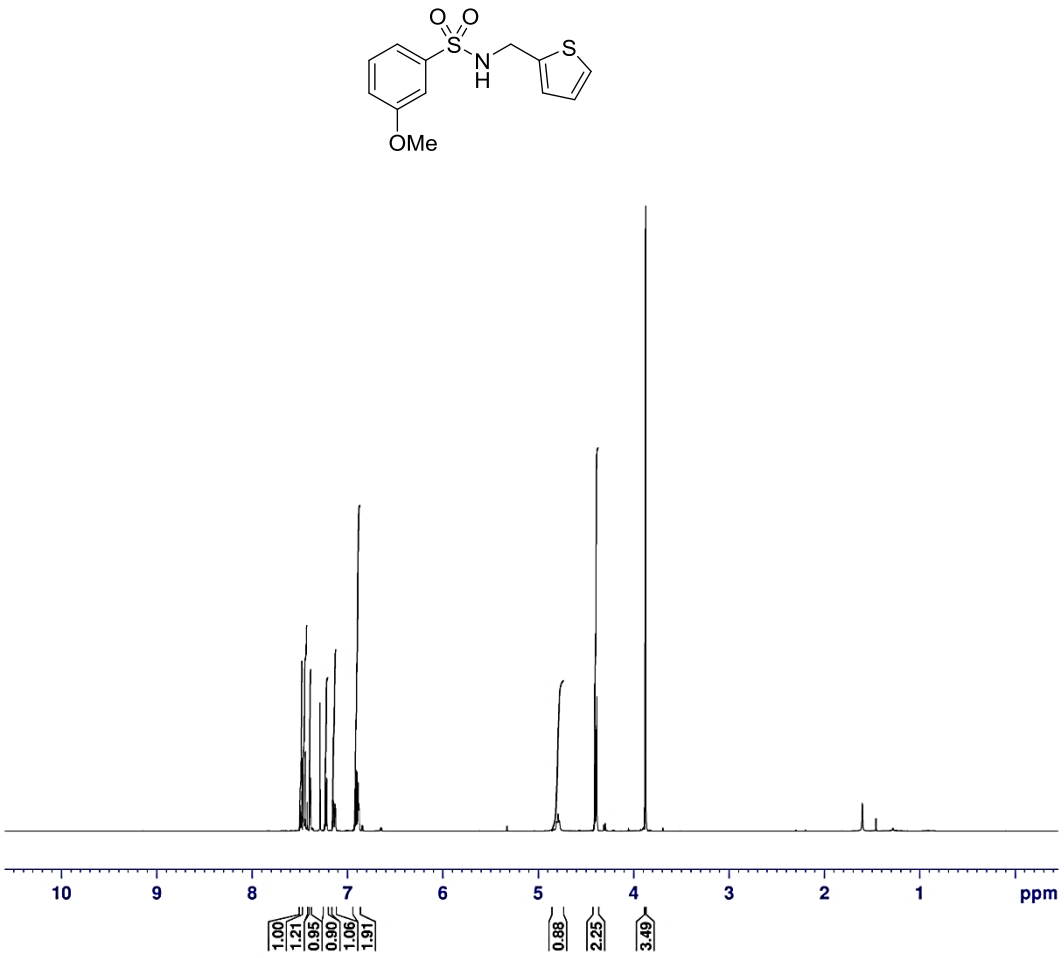
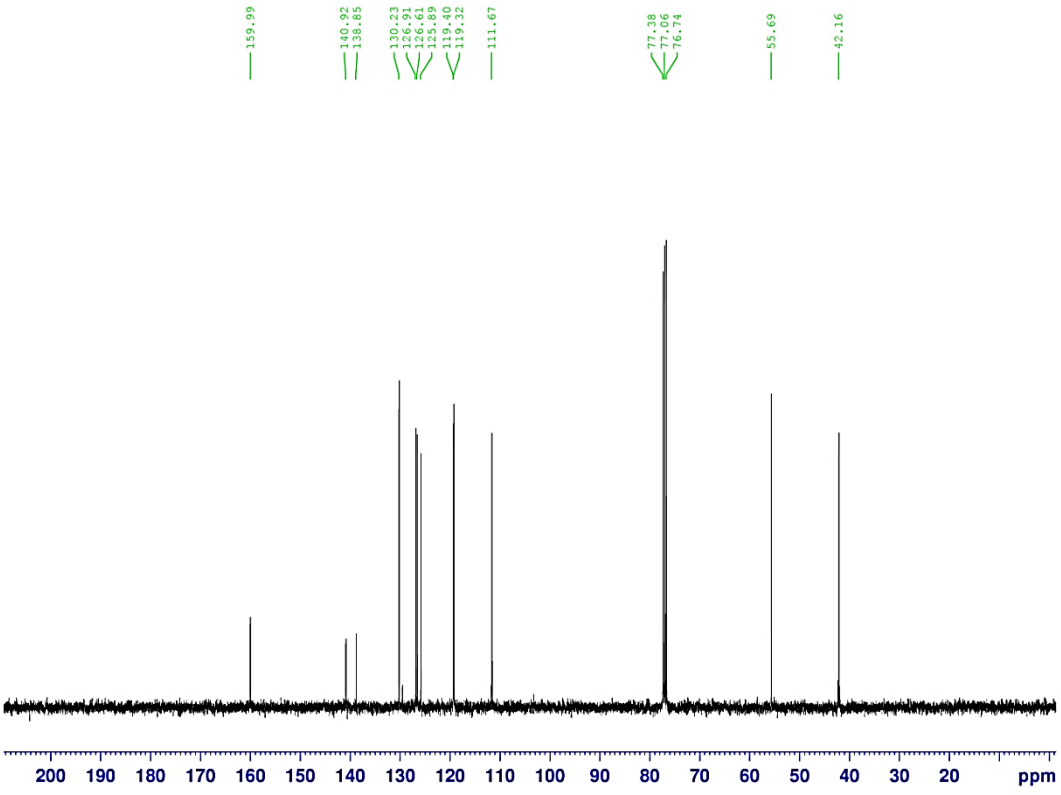
141.01
136.17
130.23
128.73
127.99
127.88
119.28
119.22
111.75
77.36
77.04
76.72
55.67
47.37
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


O
O
S
N
H
S
OMe
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.21
0.95
0.90
1.06
1.91
0.88
2.25
3.49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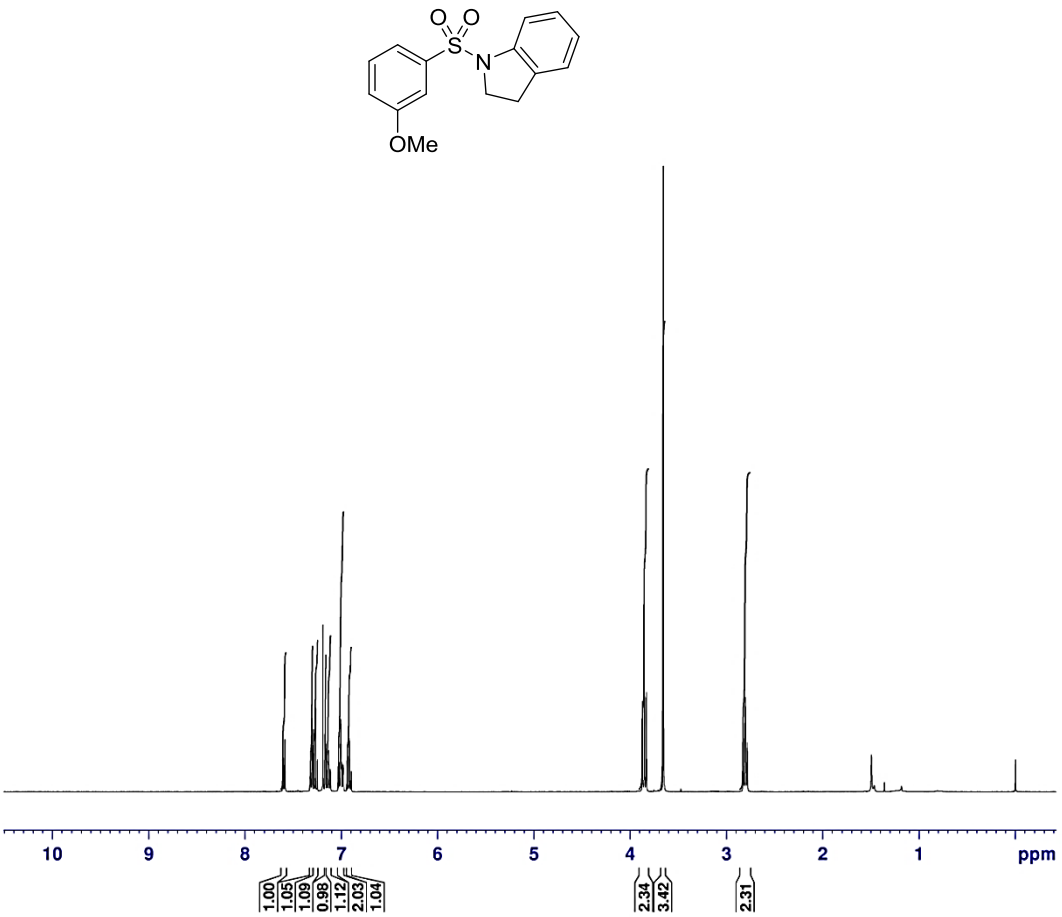
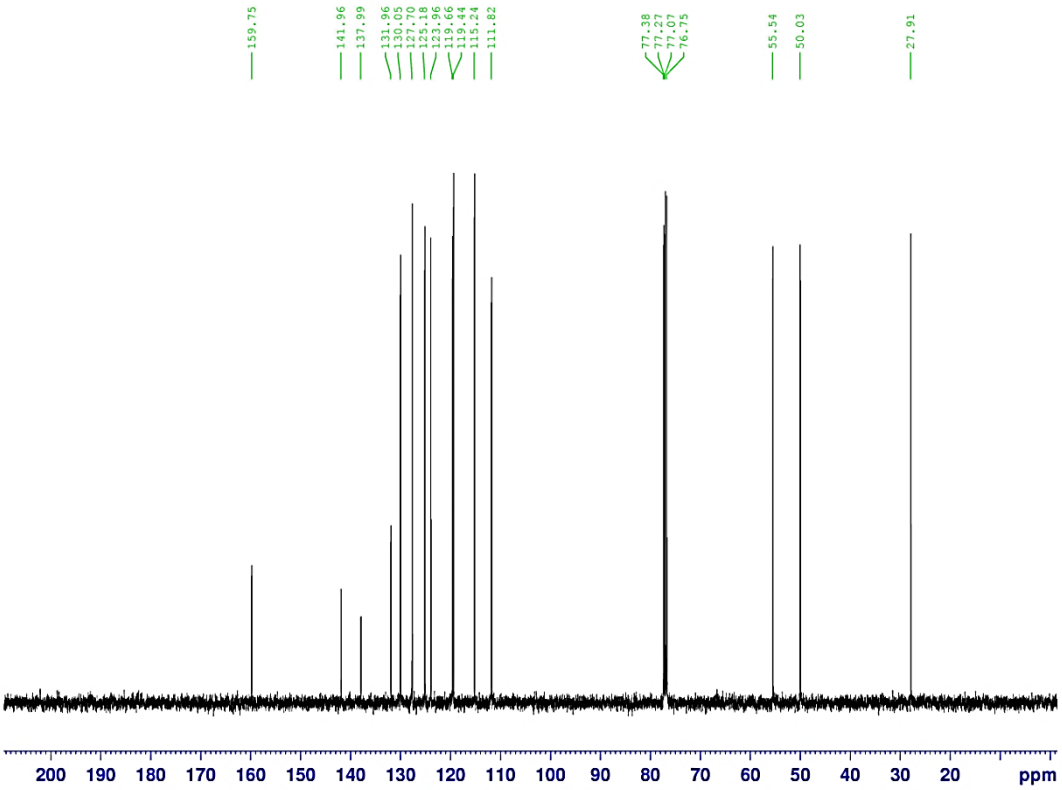
130.23
126.31
126.01
125.89
119.40
119.32
111.67
77.38
77.06
76.74
55.69
42.16
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


OMe
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.05
1.09
0.98
1.12
2.03
1.04
2.34
3.42
2.31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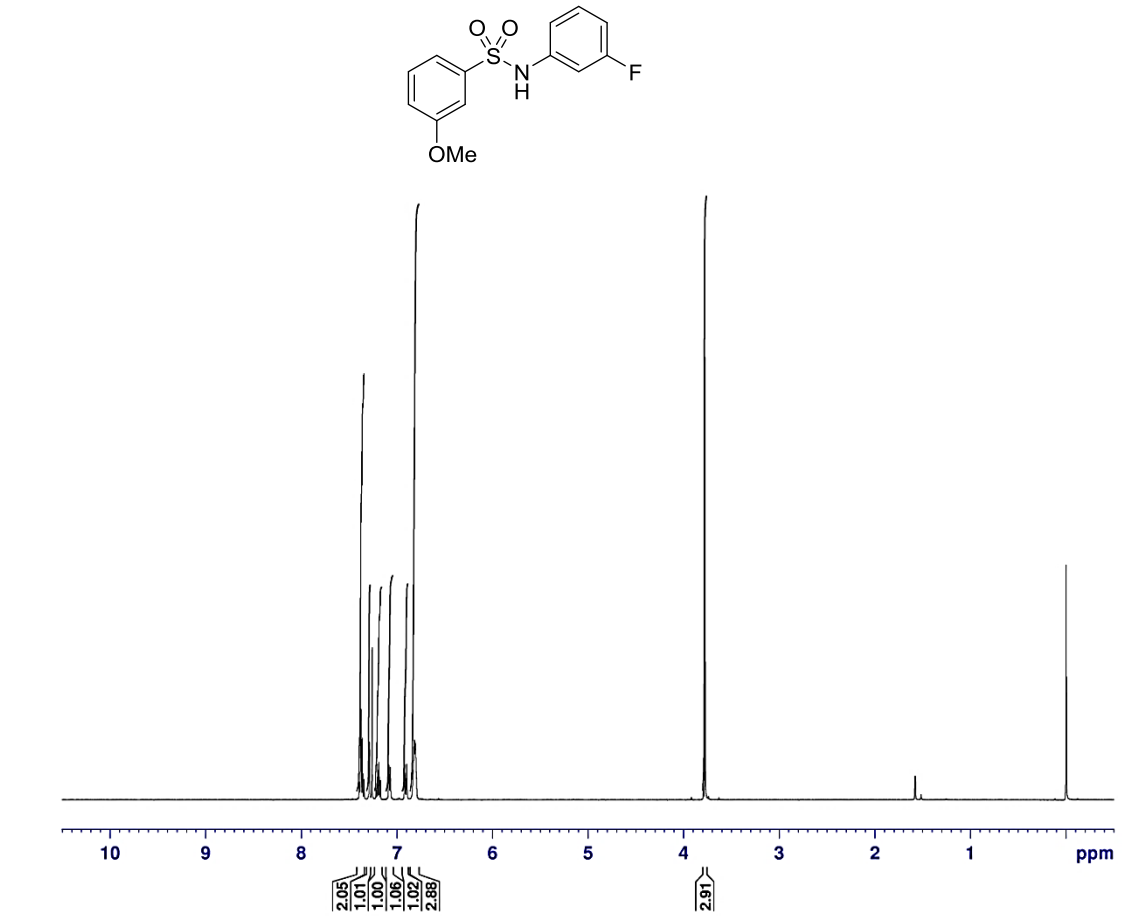
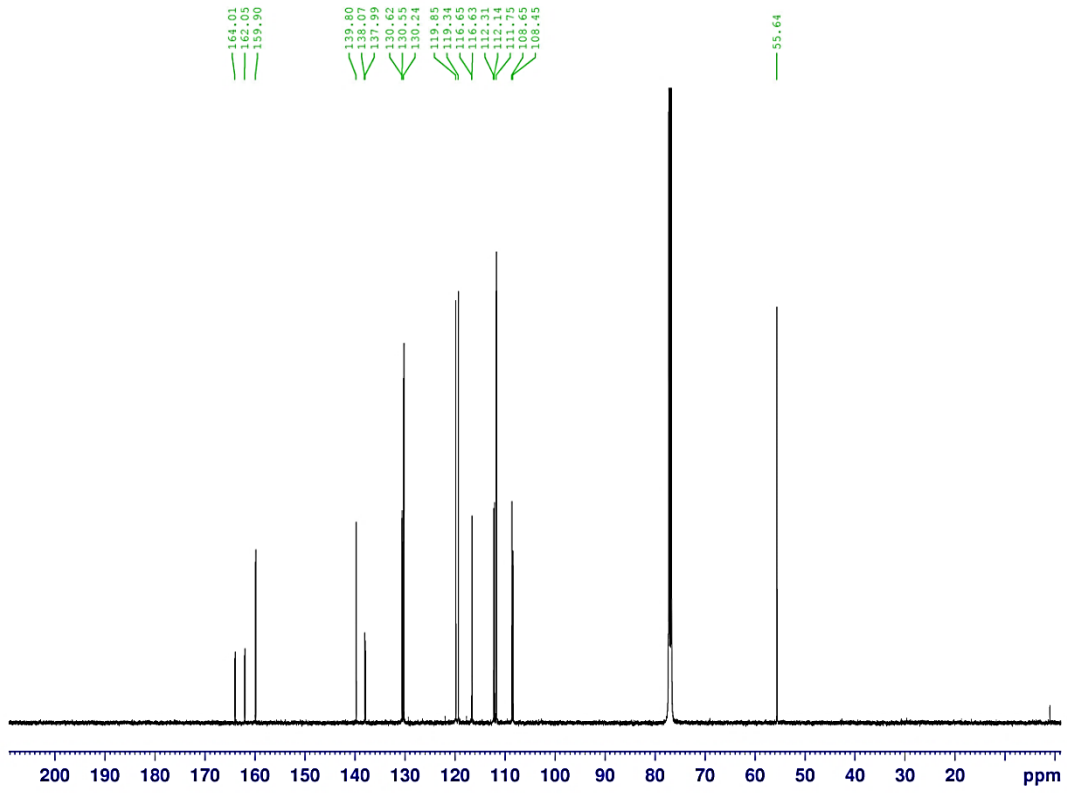
137.99
131.96
130.05
127.70
125.18
123.96
119.66
119.44
115.24
111.82
77.38
77.27
77.07
76.75
55.54
50.03
27.91
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


O
O
S
N
H
F
OMe
10
9
8
7
6
5
4
3
2
1
ppm
2.05
1.01
1.00
1.06
1.02
2.88
2.91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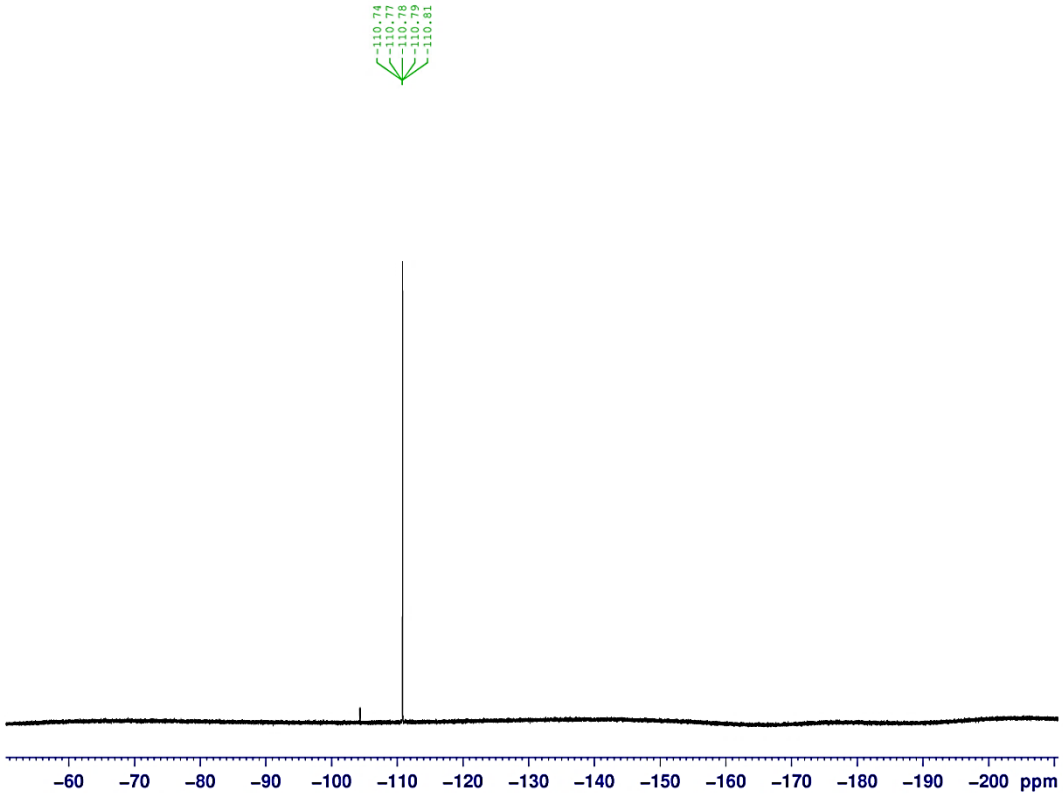
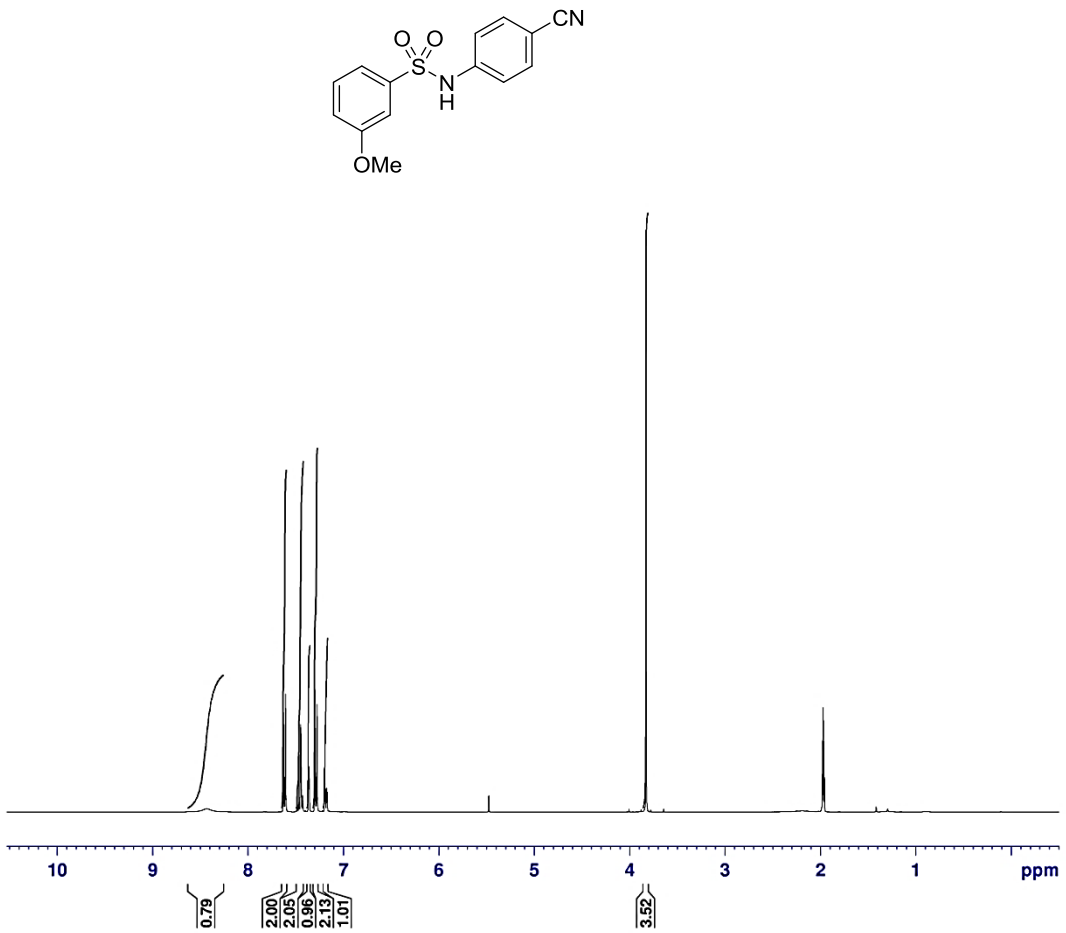
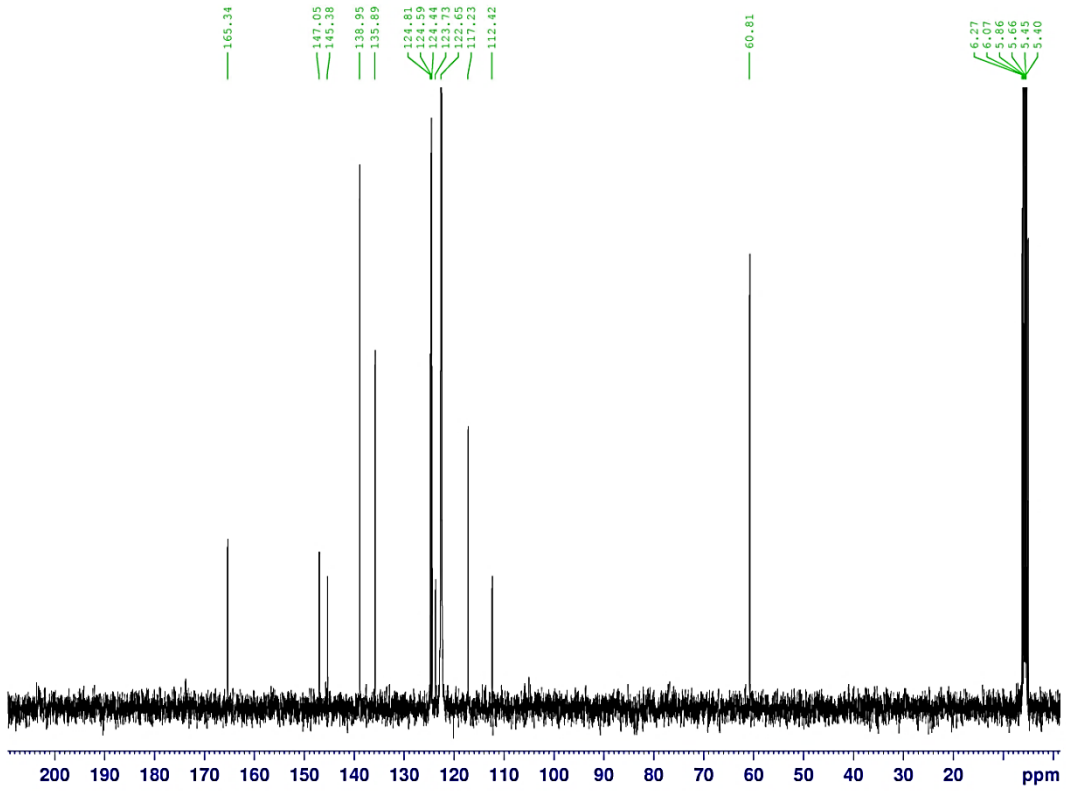
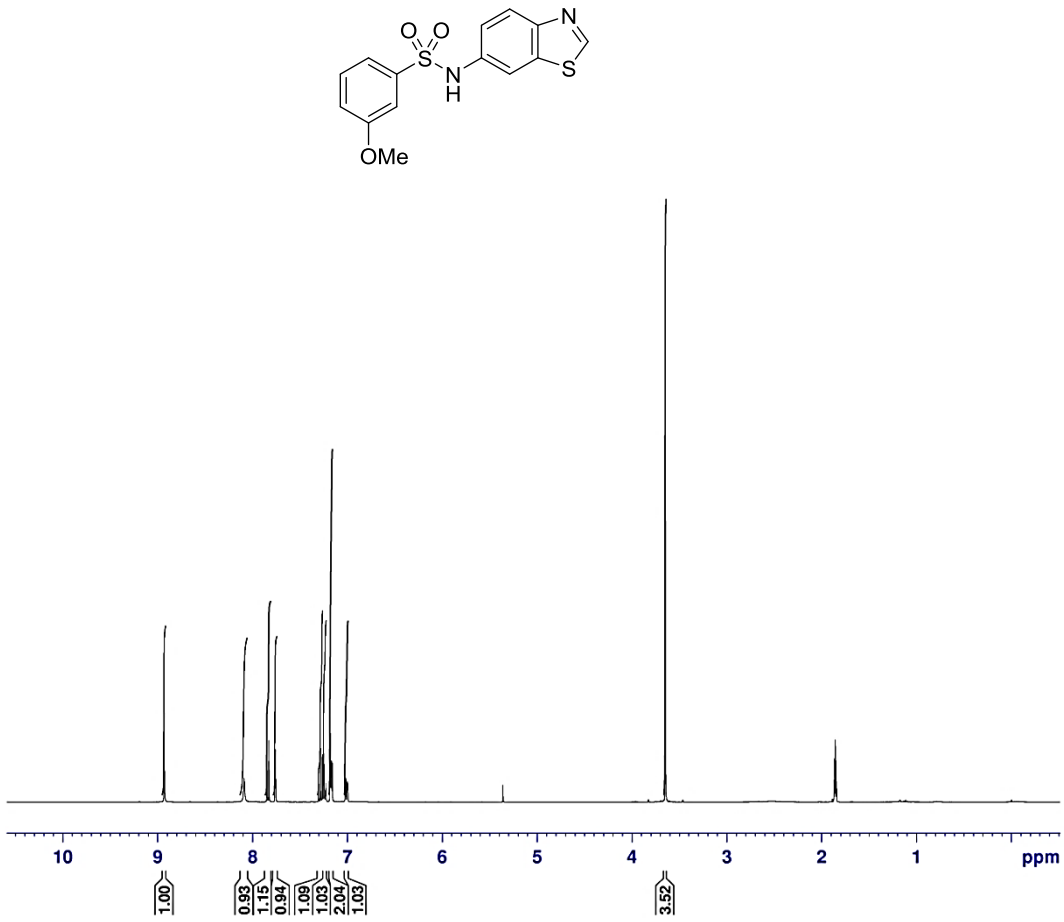
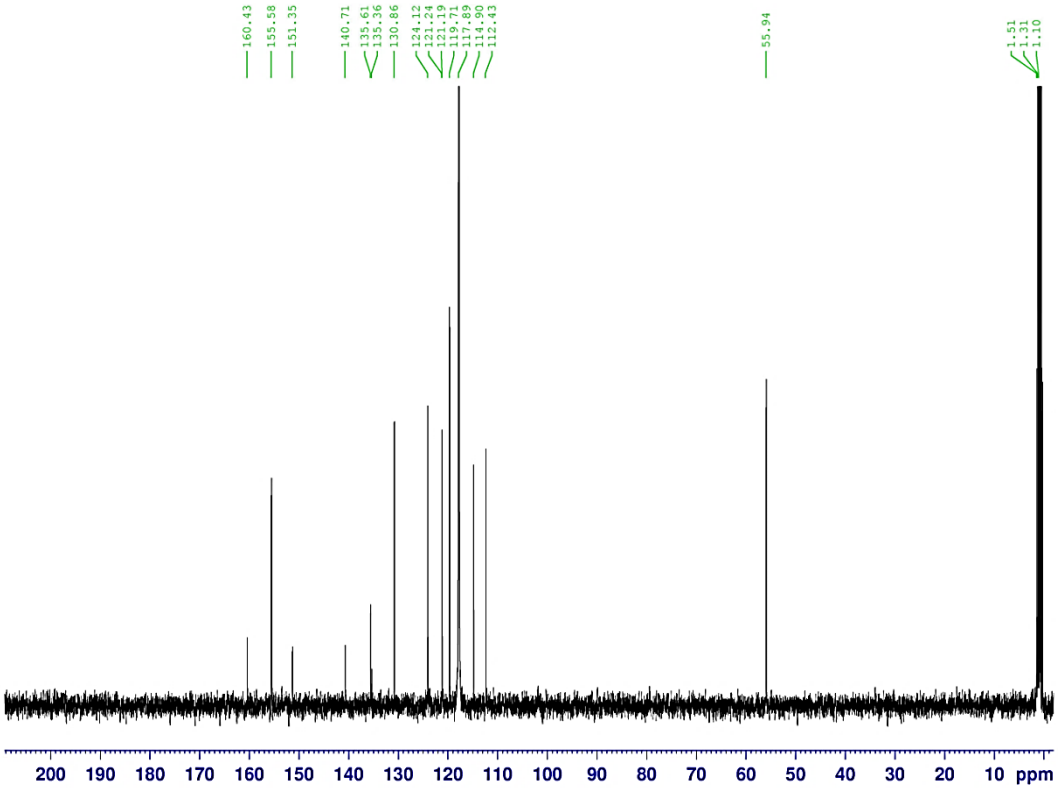
159.90
139.80
139.07
137.99
130.62
130.55
130.24
119.85
119.34
116.65
116.63
116.31
112.14
111.75
108.65
108.45
55.64
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

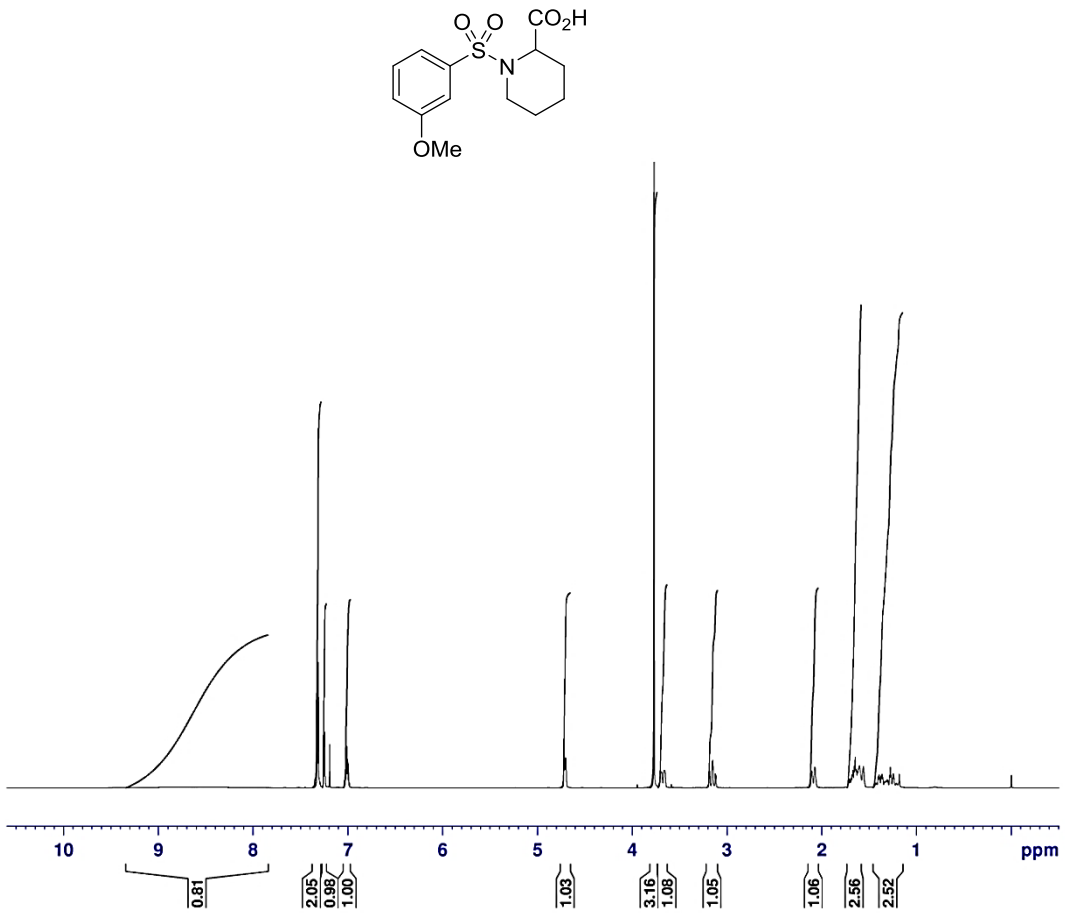

-110.74
-110.77
-110.78
-110.79
-110.81
−60
−70
−80
−90
−100
−110
−120
−130
−140
−150
−160
−170
−180
−190
−200
ppm

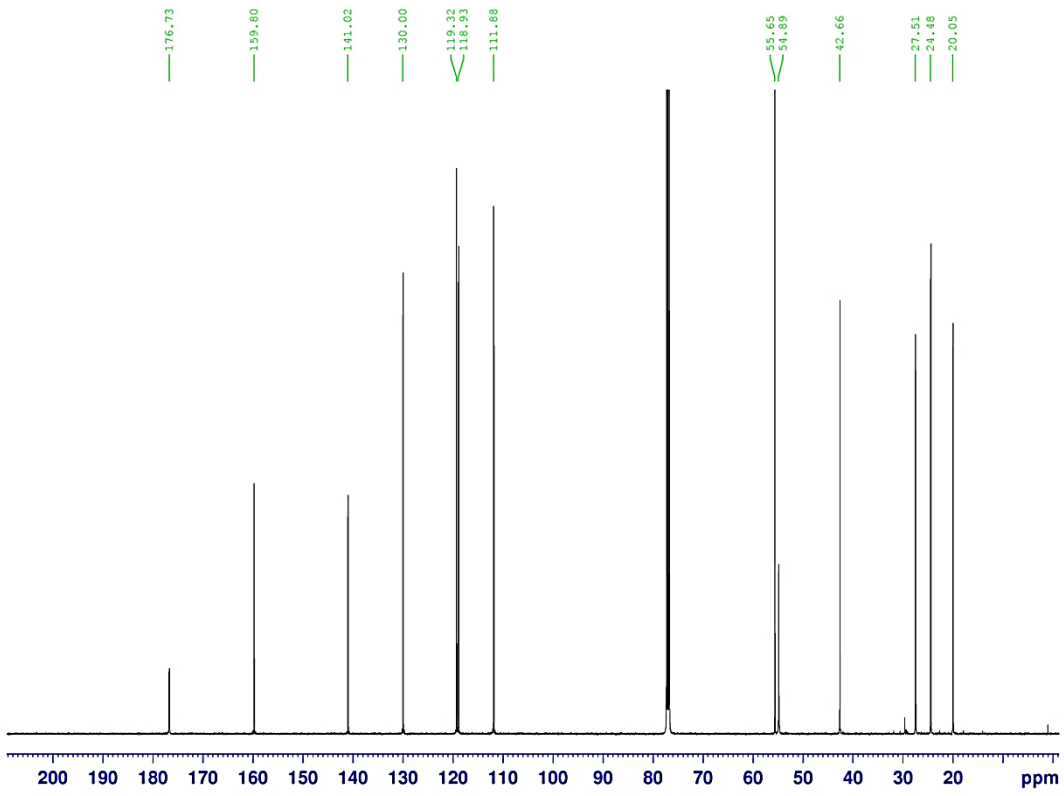

CN
O
O
S
N
H
OMe
10
9
8
7
6
5
4
3
2
1
ppm
0.79
2.00
2.05
0.96
2.13
1.01
3.52

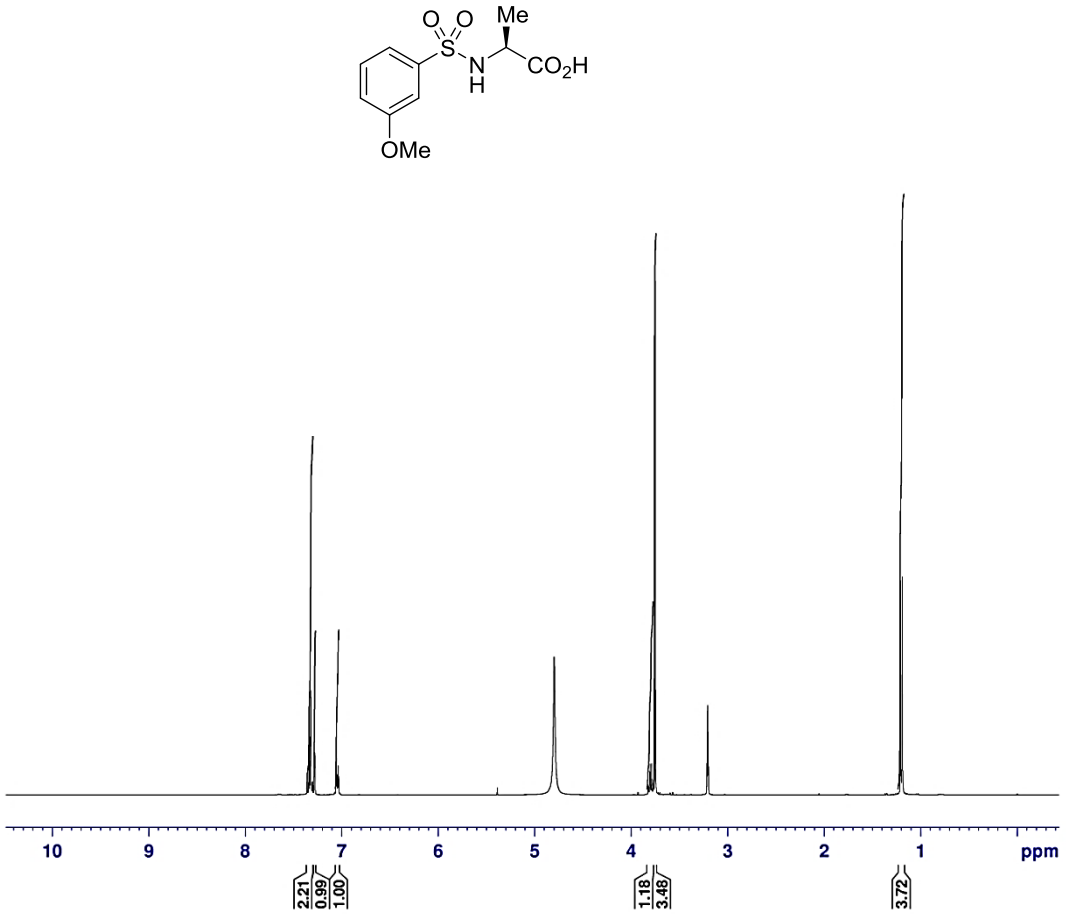

165.34
147.05
145.38
138.95
135.89
124.81
124.59
124.44
123.73
122.65
117.23
112.42
60.81
6.27
6.07
5.86
5.66
5.45
5.40
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

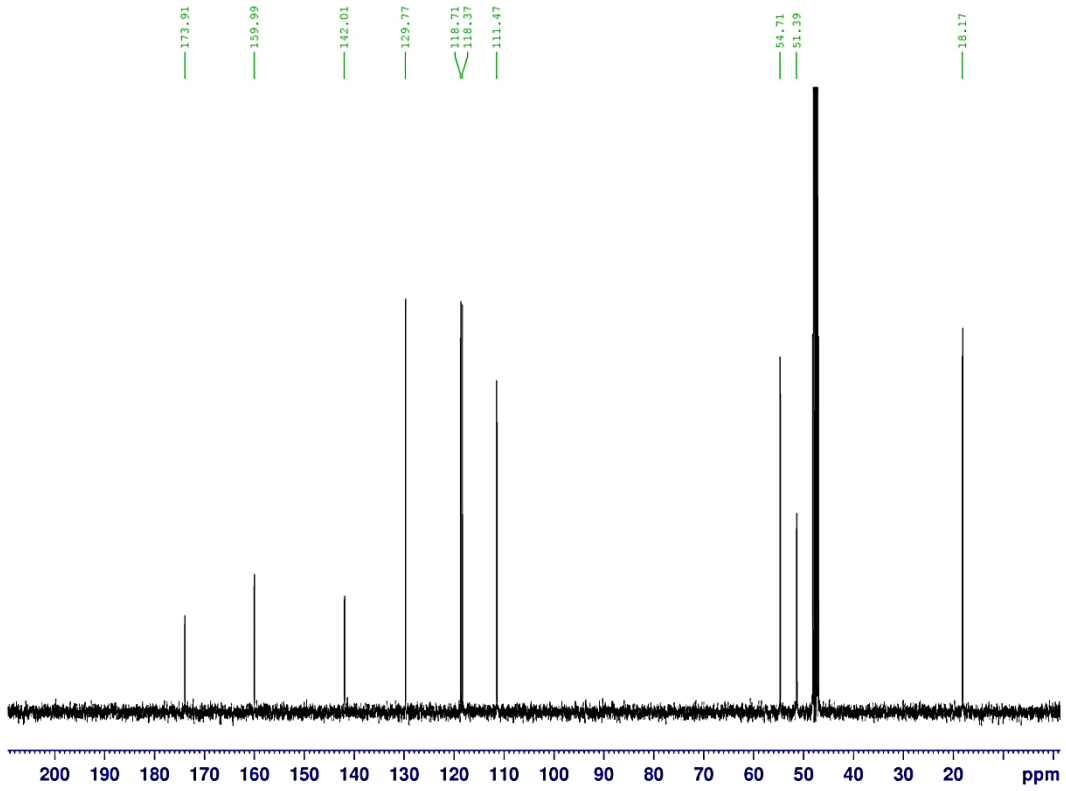

O
O
S
N
H
N
S
OMe
10
9
8
7
6
5
4
3
2
1
ppm
1.00
0.93
1.15
0.94
1.09
1.03
2.04
1.03
3.52

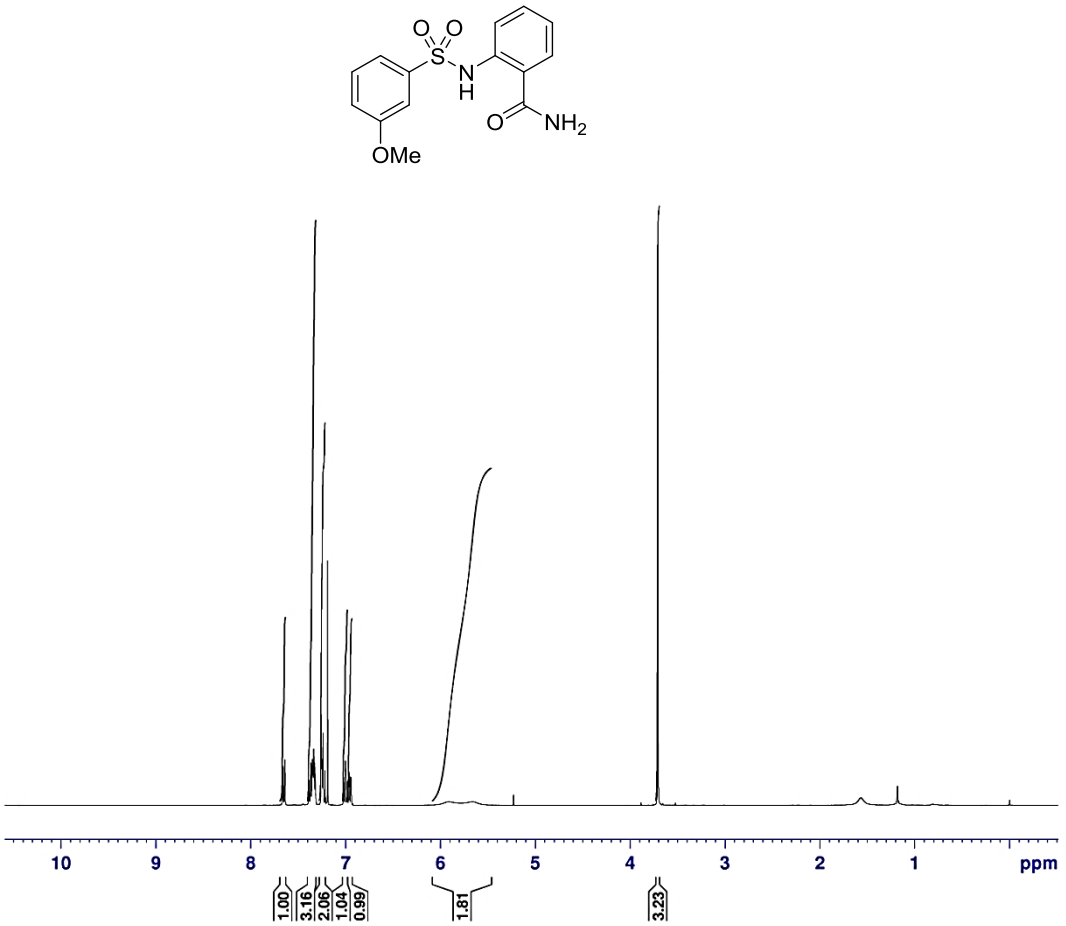

160.43
155.58
151.35
140.71
135.61
135.36
130.86
124.12
121.24
121.19
119.71
117.89
114.90
112.43
55.94
1.51
1.31
1.10
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

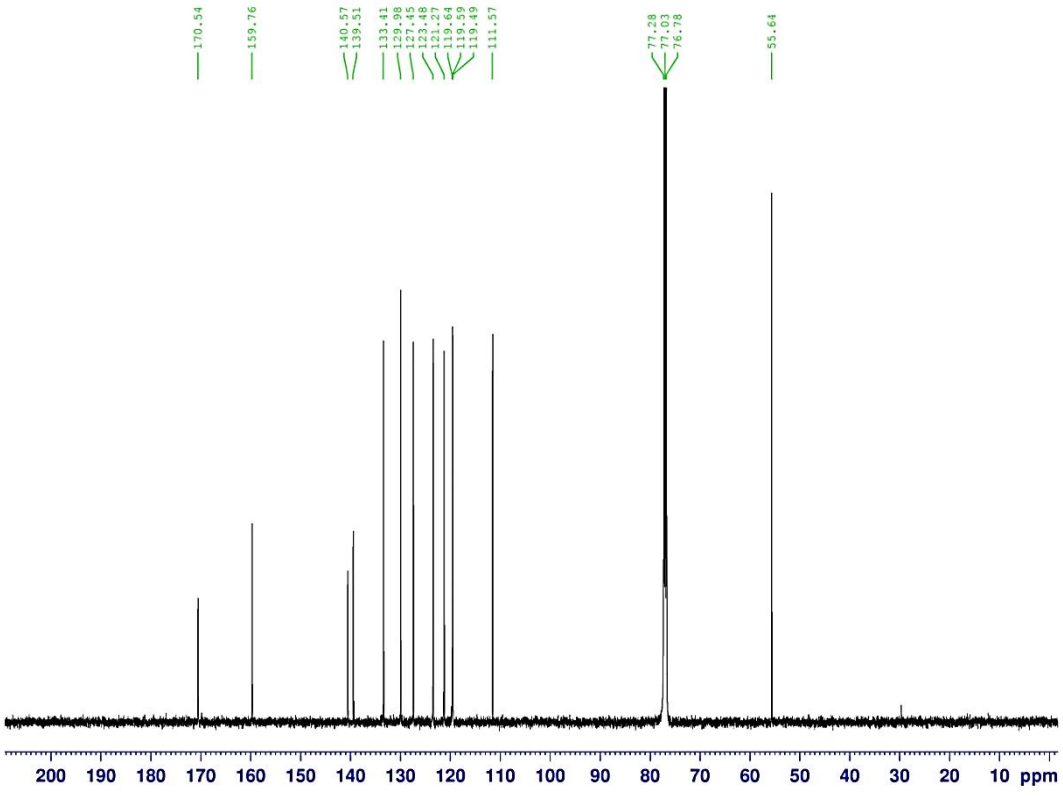

O
O
CO2H
S
N
OMe
10
9
8
7
6
5
4
3
2
1
ppm
0.81
2.05
0.98
1.00
1.03
3.16
1.08
1.05
1.06
2.56
2.52

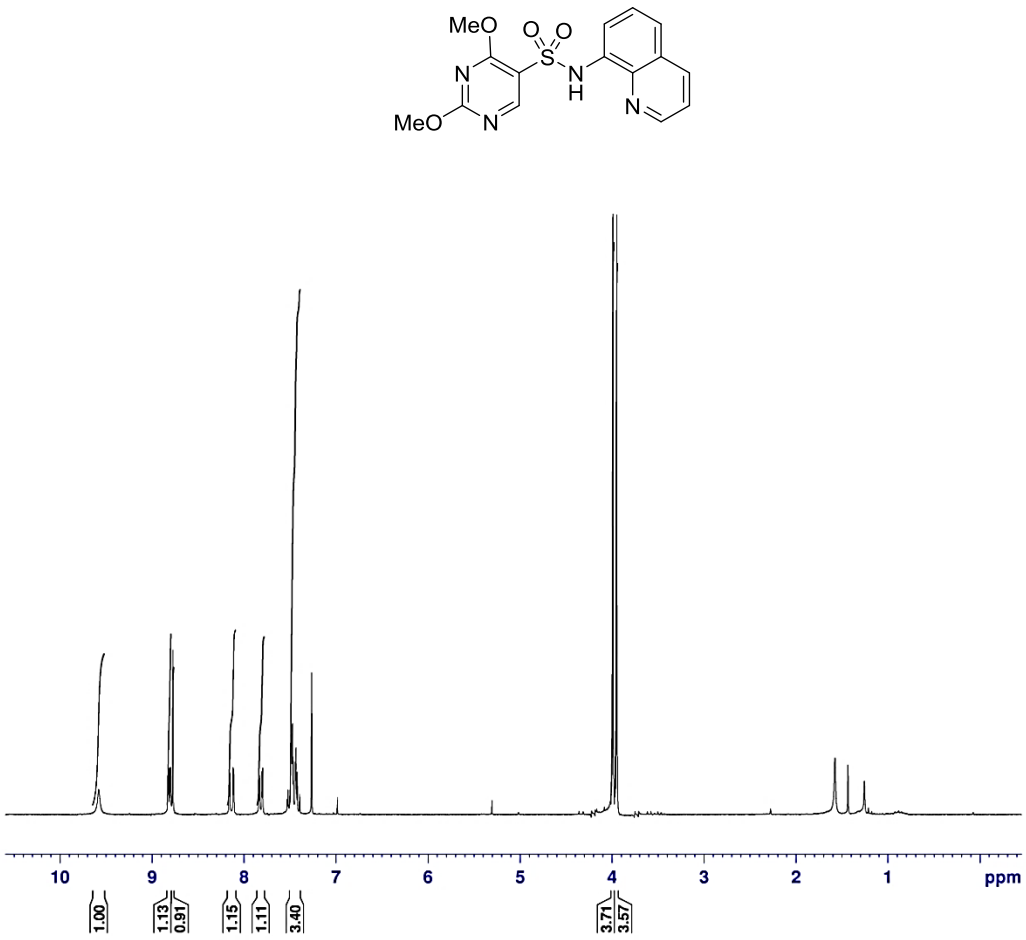

176.73
159.80
141.02
130.00
119.32
118.93
111.88
55.65
54.89
42.66
27.51
24.48
20.05
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

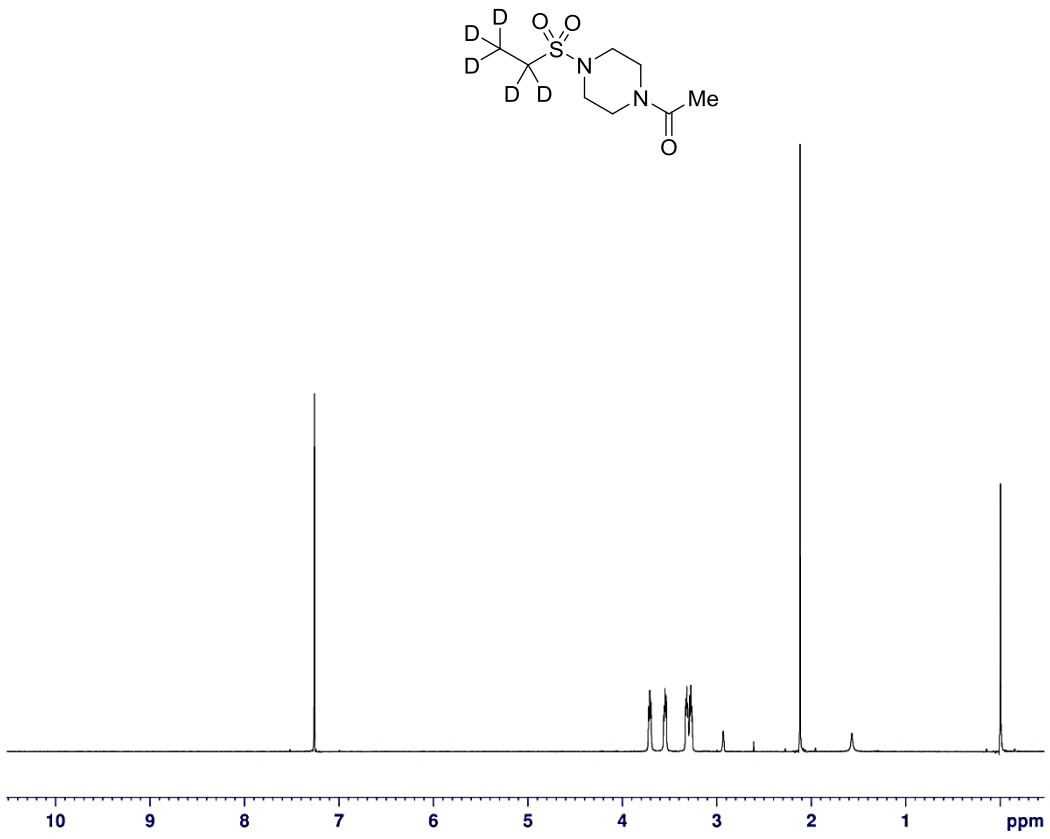

O
O
Me
S
N
H
CO2H
OMe
10
9
8
7
6
5
4
3
2
1
ppm
2.21
0.99
1.00
1.18
3.48
3.72

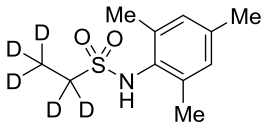

173.91
159.99
142.01
129.77
118.71
118.37
111.47
54.71
51.39
18.17
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

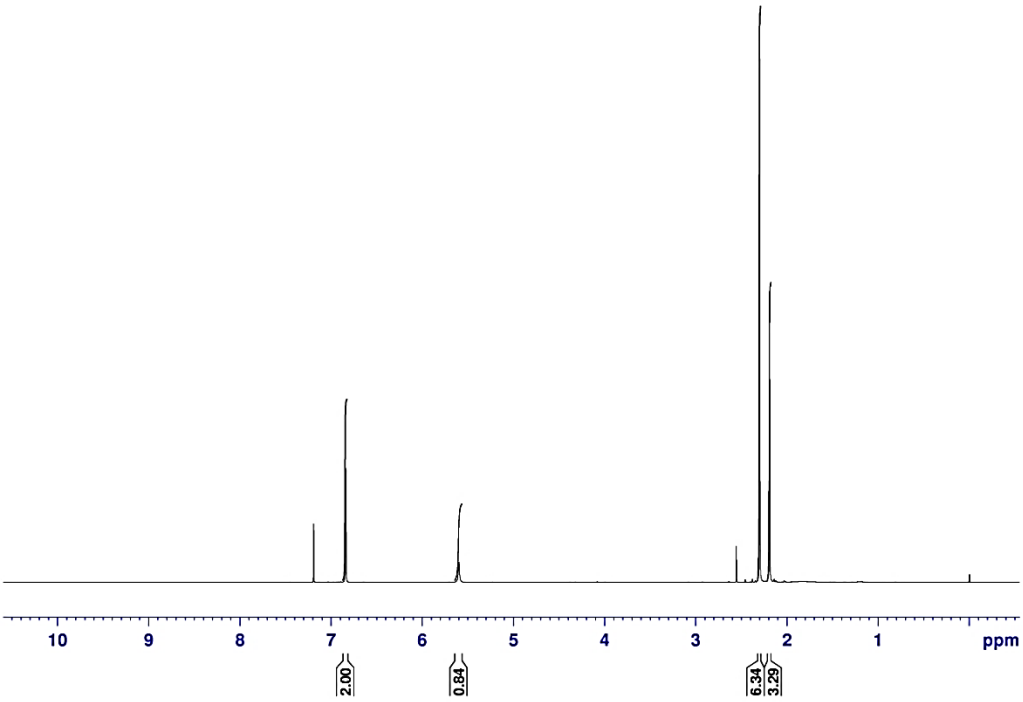

O
O
S
N
H
O
NH2
OMe
10
9
8
7
6
5
4
3
2
1
ppm
1.00
3.16
2.06
1.04
0.99
1.81
3.23

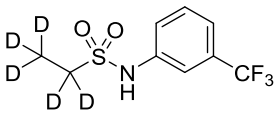

170.54
159.76
140.57
139.51
133.41
129.98
127.45
123.48
121.27
119.64
119.49
119.49
111.57
77.28
77.03
76.78
55.64
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

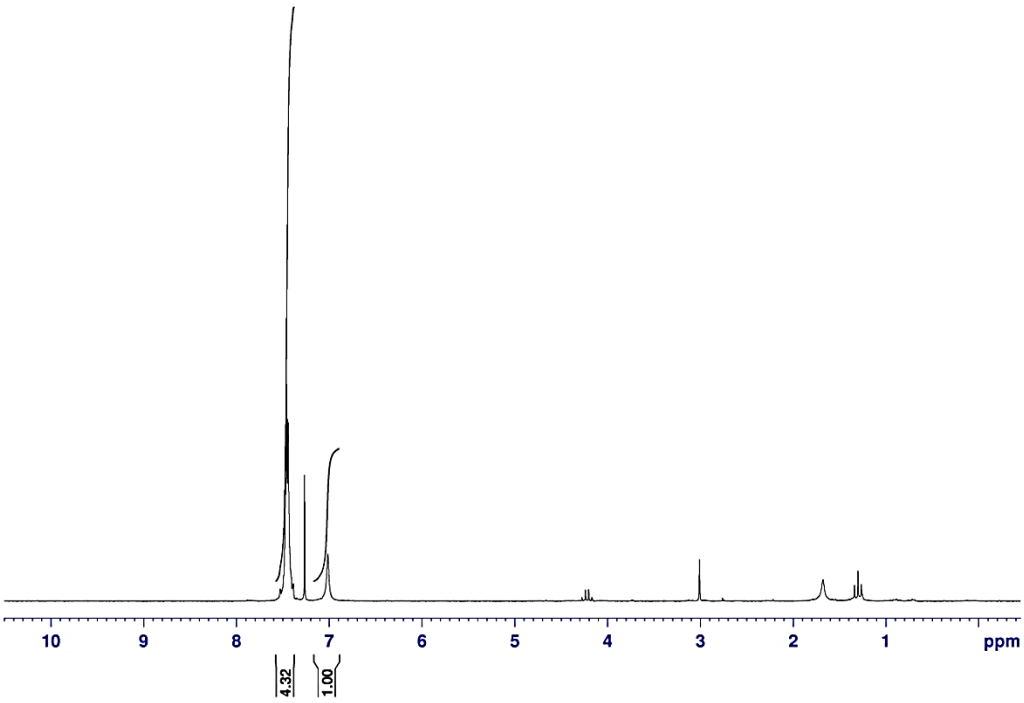

MeO
O
O
S
N
H
N
MeO
N
N
10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.13
0.91
1.15
1.11
3.40
3.71
3.57


D
D
D
O
O
S
N
D
D
N
Me
O
10
9
8
7
6
5
4
3
2
1
ppm

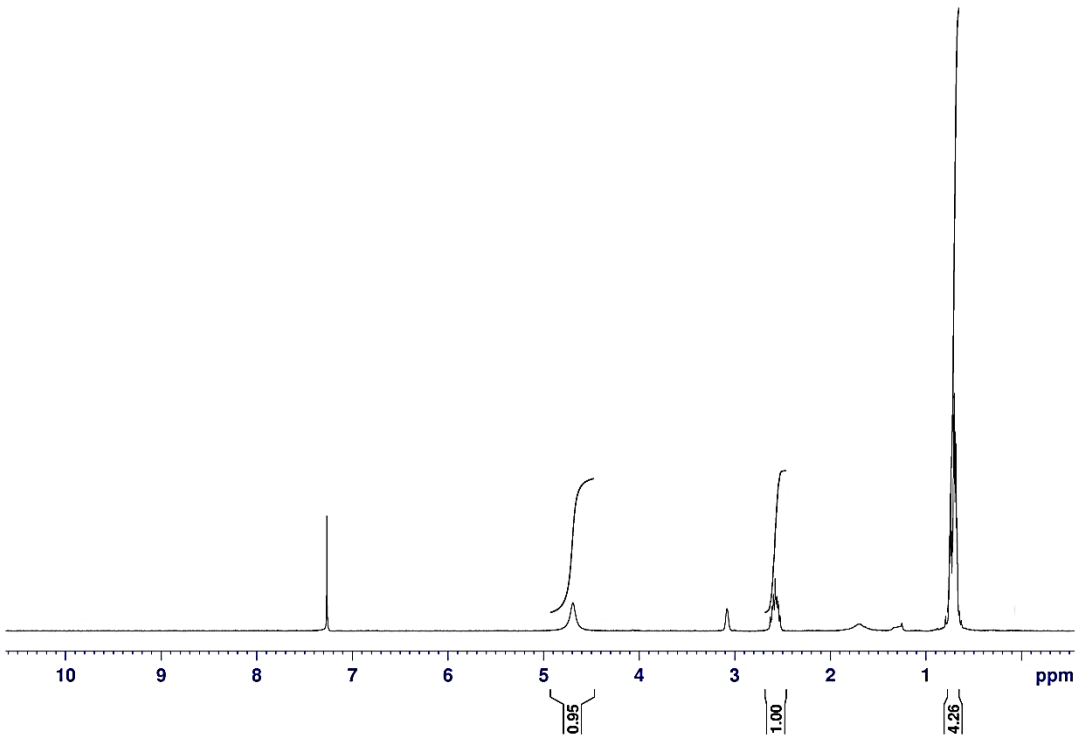

Me
Me
D
D
D
D
D
O
O
S
N
H
Me

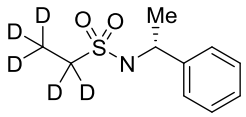

10
9
8
7
6
5
4
3
2
1
ppm
2.00
0.84
6.34
3.29

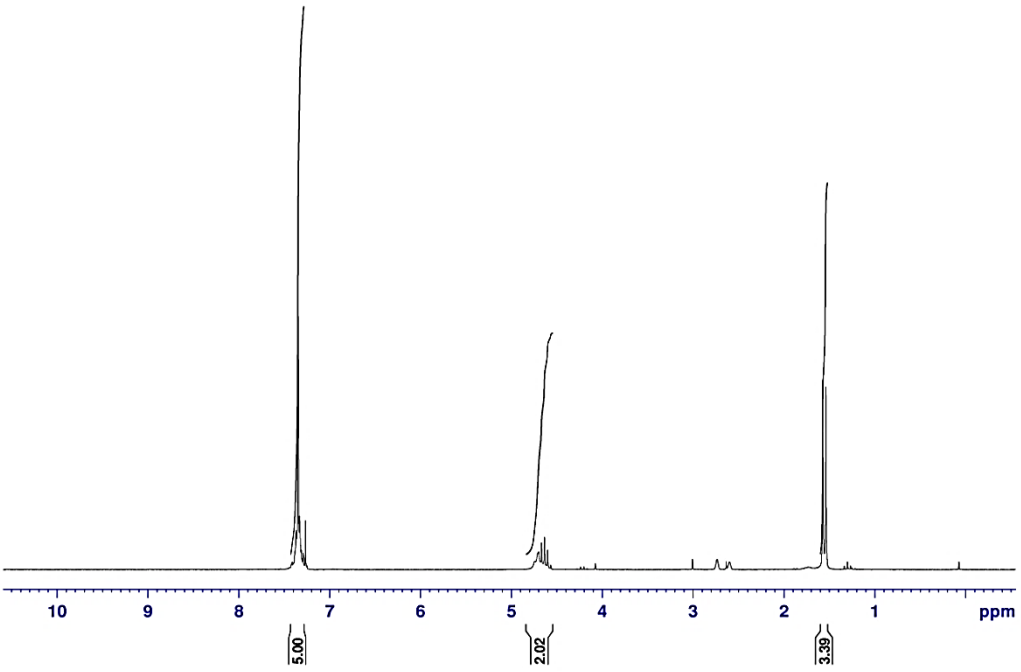

D
D
D
D
D
O
O
S
N
H
CF3

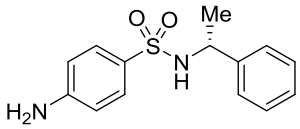

10
9
8
7
6
5
4
3
2
1
ppm
4.32
1.00

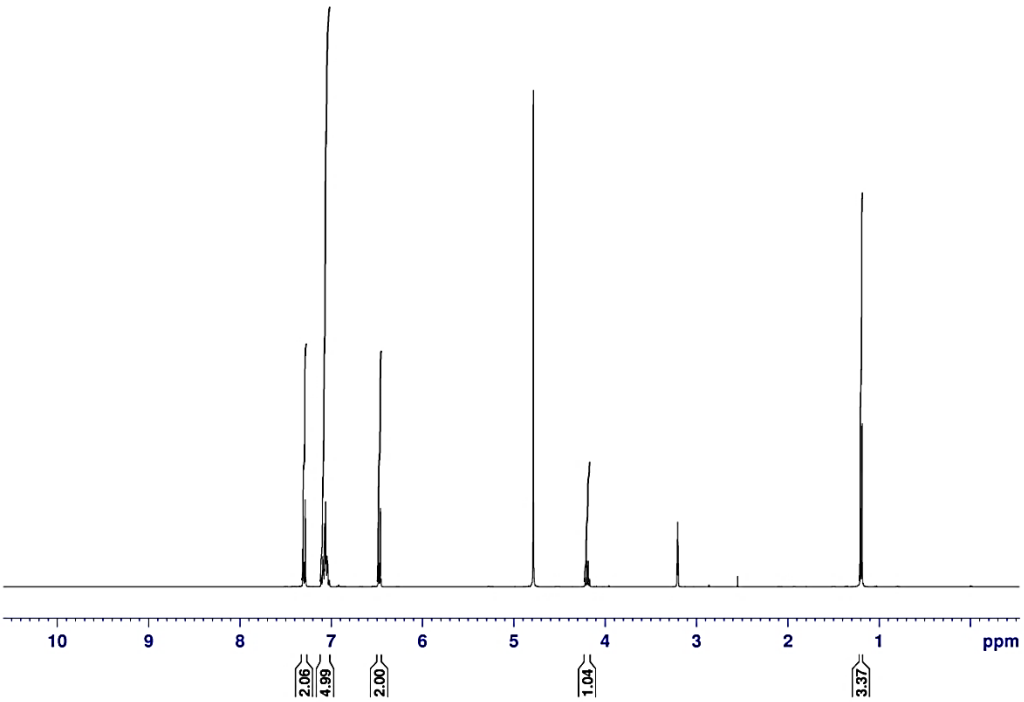

D
D
D
O
O
S
N
H
D
D

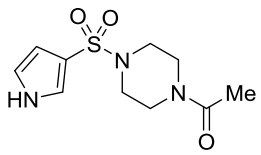

10
9
8
7
6
5
4
3
2
1
ppm
0.95
1.00
4.26

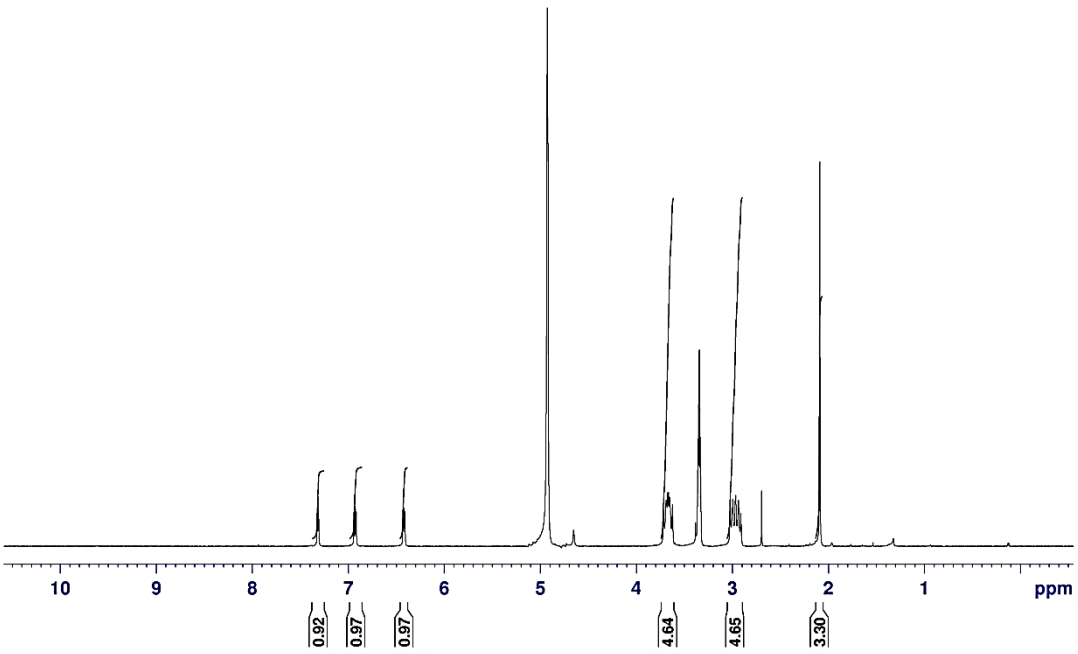

D
D
D
O
O
S
N
Me
D
D

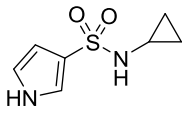

10
9
8
7
6
5
4
3
2
1
ppm
5.00
2.02
3.39

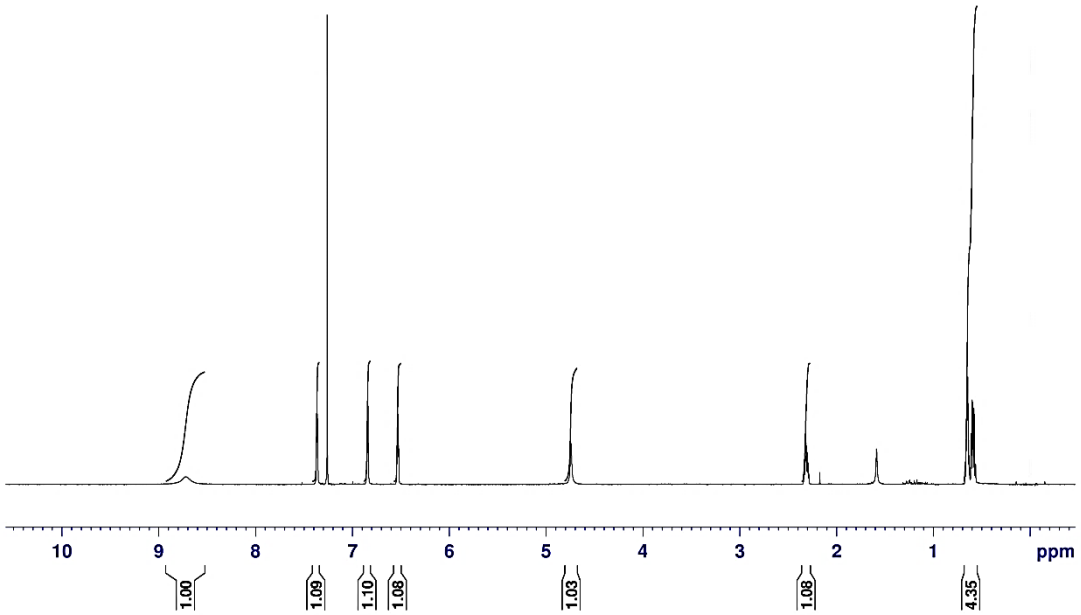

O
O
Me
S
N
H
$H_2N$

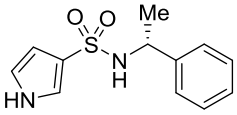

10
9
8
7
6
5
4
3
2
1
ppm
2.06
4.99
2.00
1.04
3.37

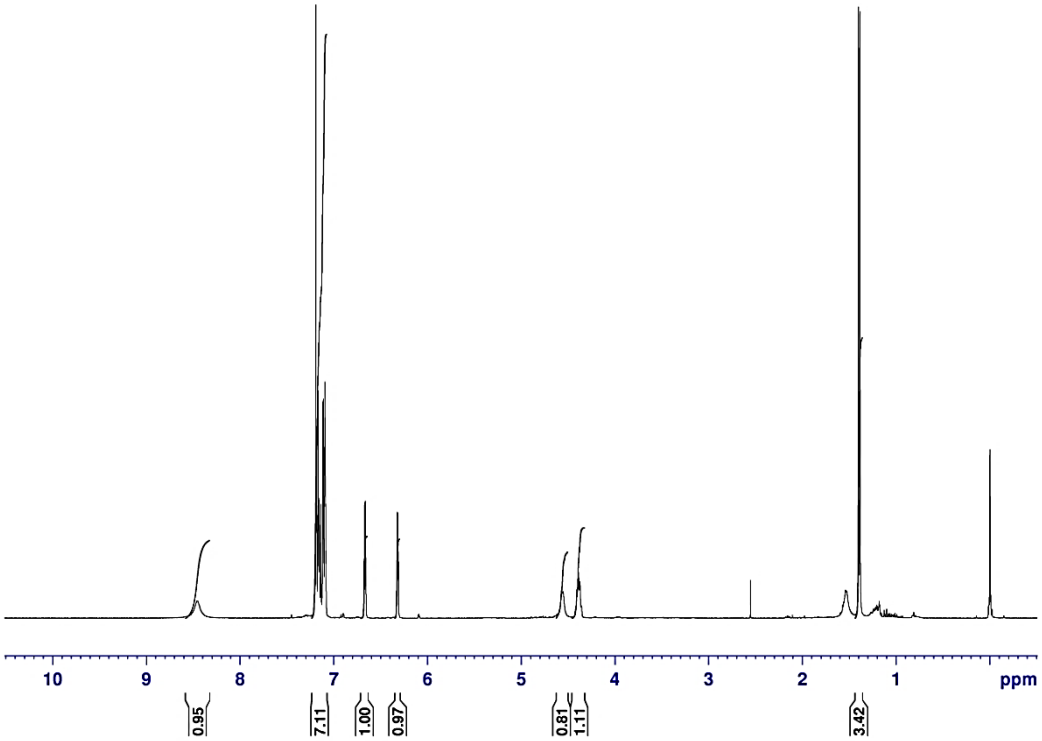

O
O
S
N
HN
N
Me
O

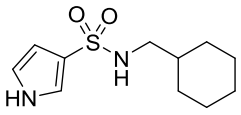

10
9
8
7
6
5
4
3
2
1
ppm
0.92
0.97
0.97
4.64
4.65
3.30

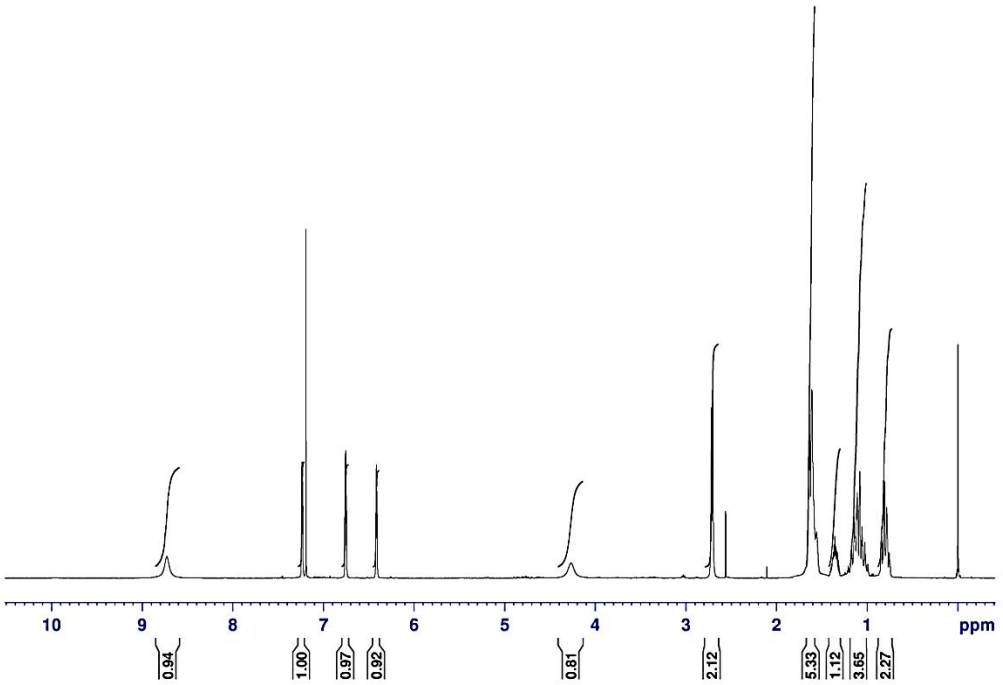

O
O
S
N
H
HN

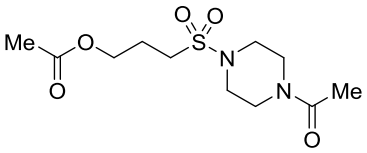

10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.09
1.10
1.08
1.03
1.08
4.35

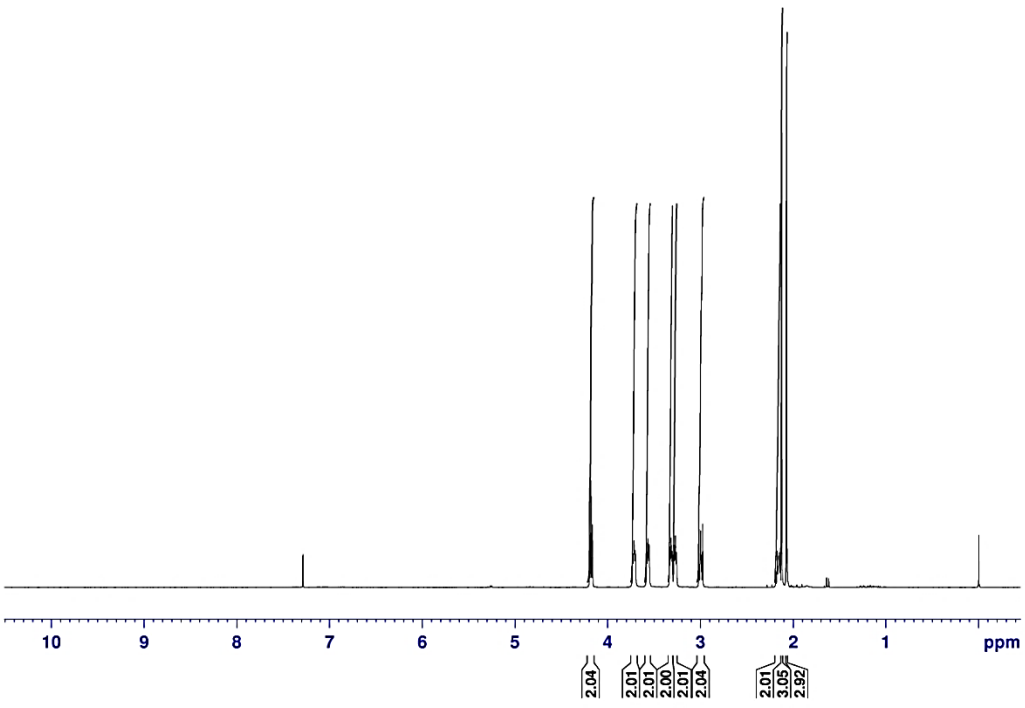

O
O
S
N
H
Me
HN

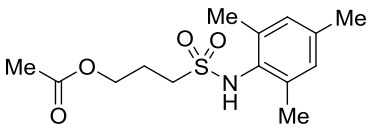

10
9
8
7
6
5
4
3
2
1
ppm
0.95
7.11
1.00
0.97
0.81
1.11
3.42

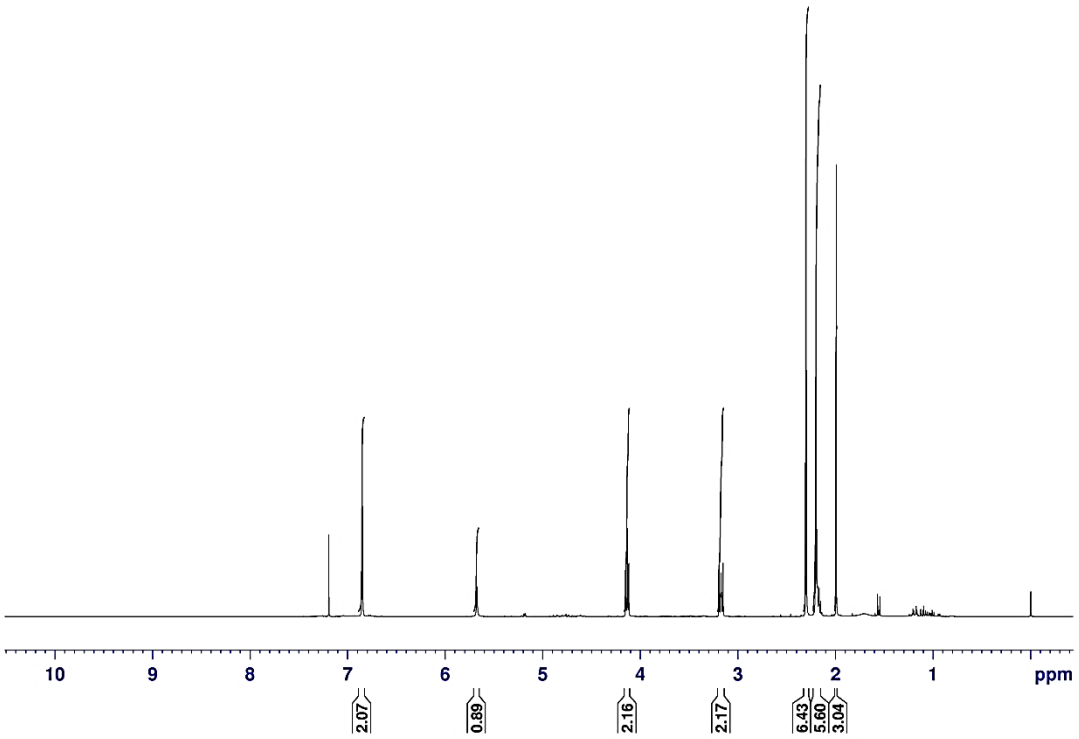

O
O
S
N
H
HN

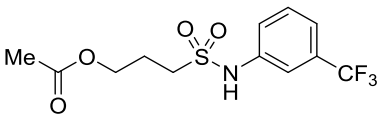

10
9
8
7
6
5
4
3
2
1
ppm
0.94
1.00
0.97
0.92
0.81
2.12
5.33
1.12
3.65
2.27

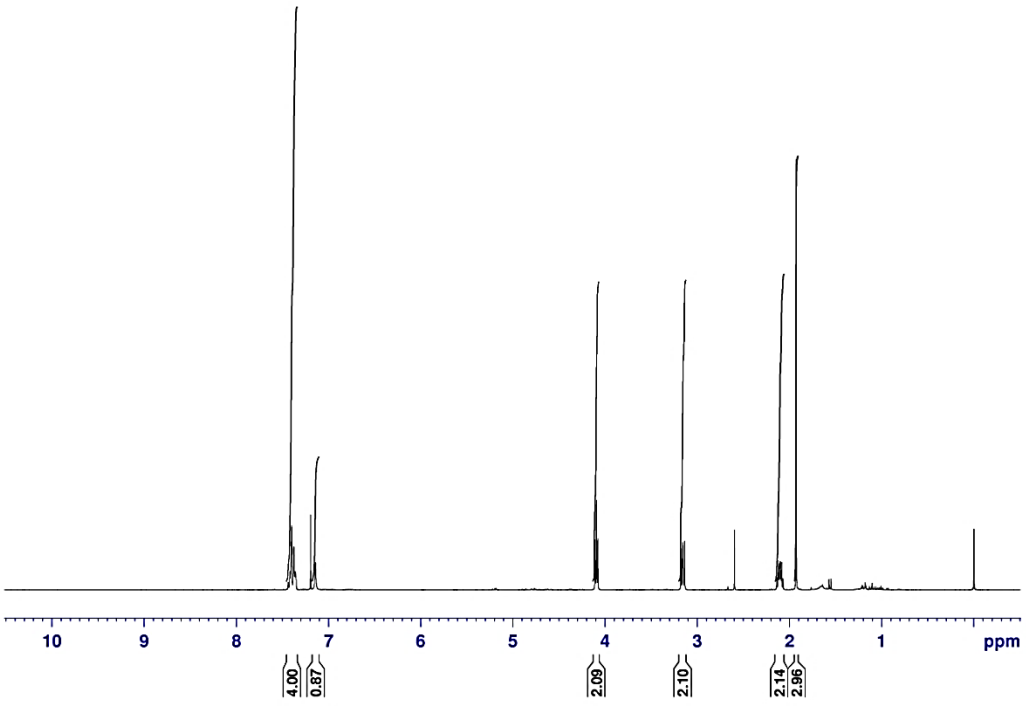

Me
O
O
O
S
N
N
Me
O

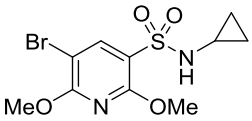

10
9
8
7
6
5
4
3
2
1
ppm
2.04
2.01
2.01
2.00
2.01
2.04
2.01
3.05
2.92

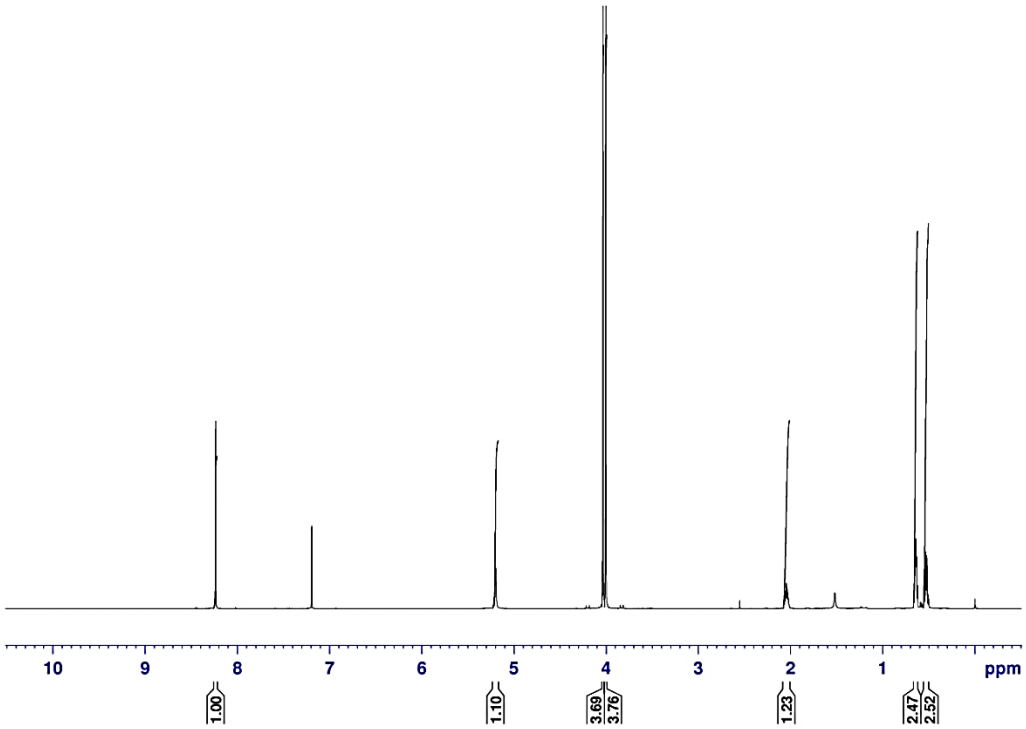

Me
Me
O
O
Me
O
S
N
H
O
Me

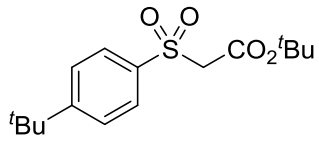

10
9
8
7
6
5
4
3
2
1
ppm
2.07
0.89
2.16
2.17
6.43
5.60
3.04

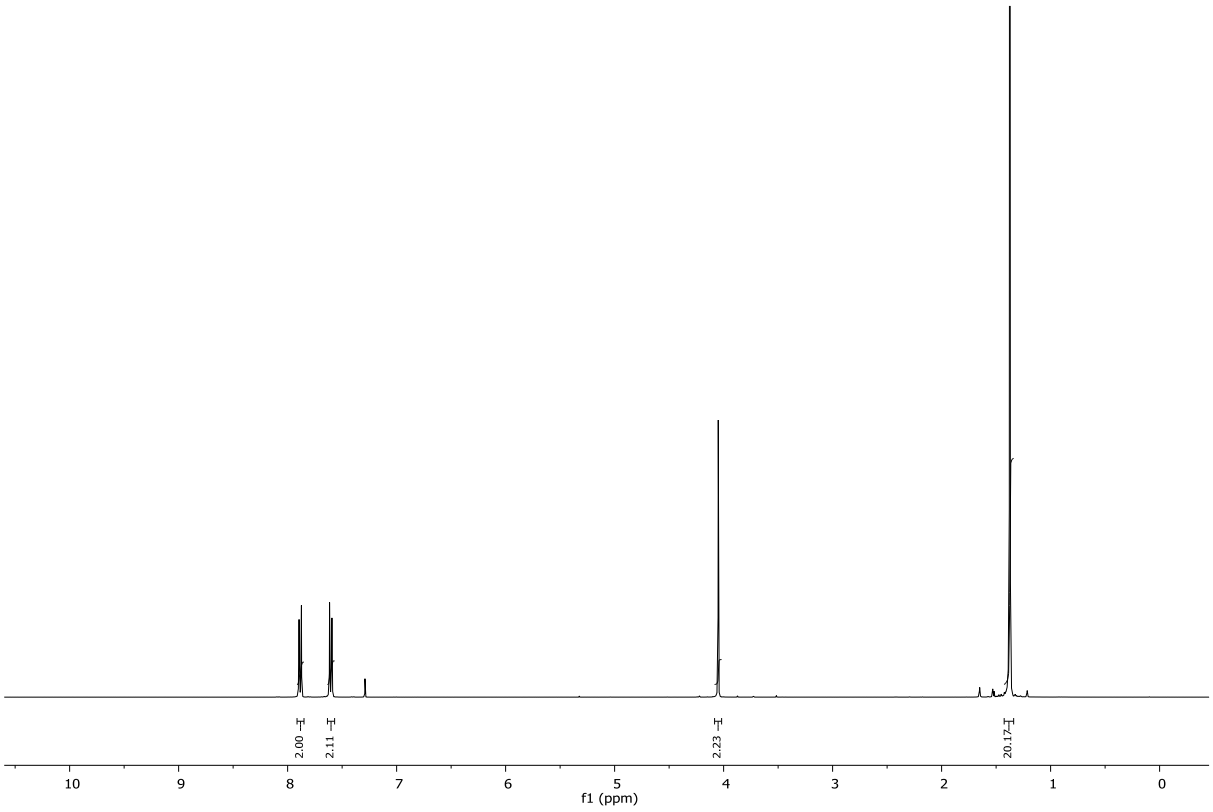

Me
O
O
O
S
N
H
CF3

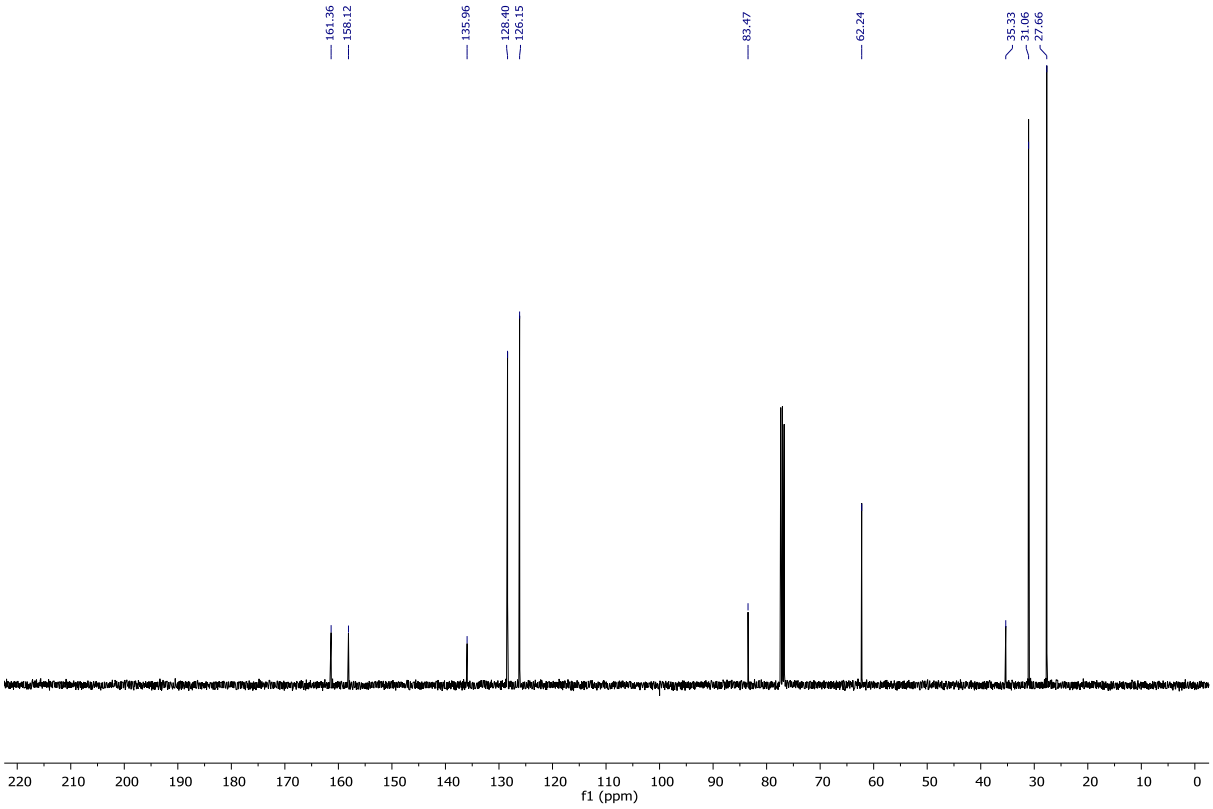

10
9
8
7
6
5
4
3
2
1
ppm
4.00
0.87
2.09
2.10
2.14
2.96

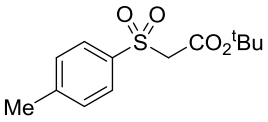

Br
O
O
S
N
H
MeO
N
OMe

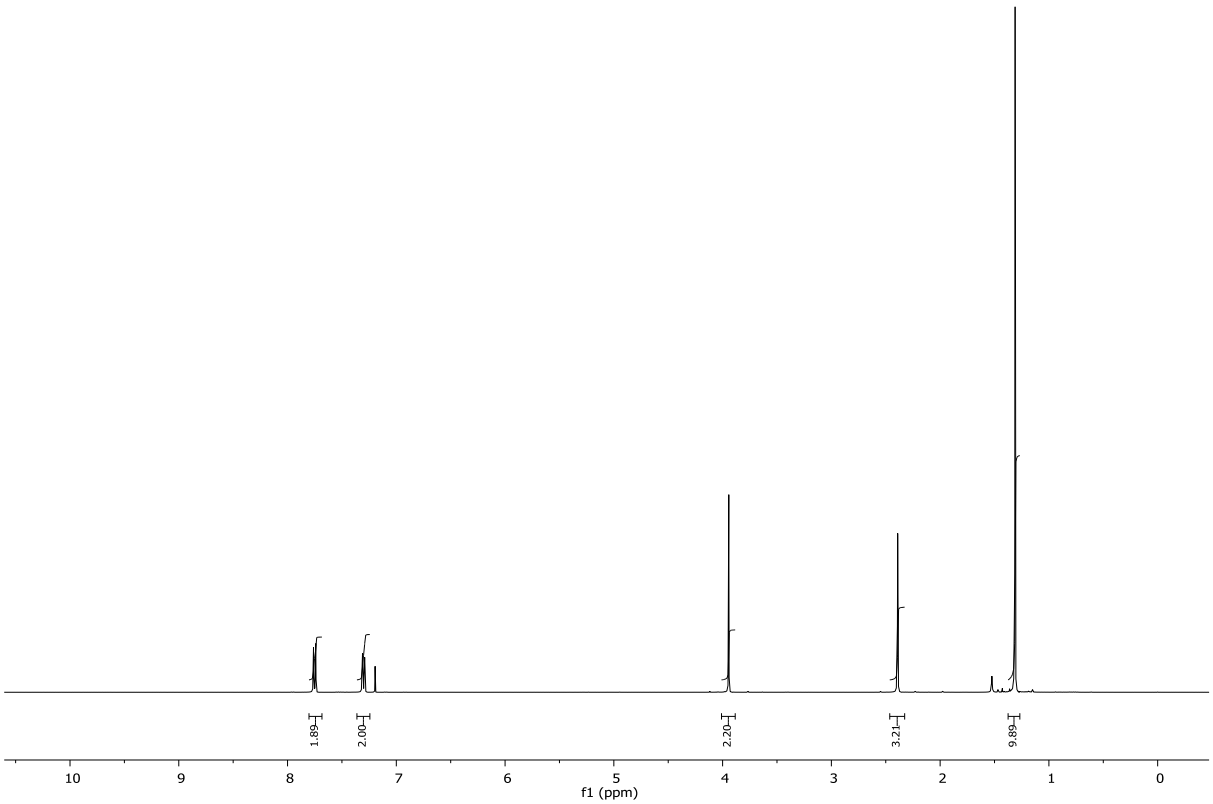

10
9
8
7
6
5
4
3
2
1
ppm
1.00
1.10
3.69
3.76
1.23
2.47
2.52


O
O
S
CO2tBu
tBu


2.00
2.11
2.23
20.17
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


161.36
158.12
135.96
128.40
126.15
83.47
62.24
35.33
31.06
27.66
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
CO2tBu
Me


1.89
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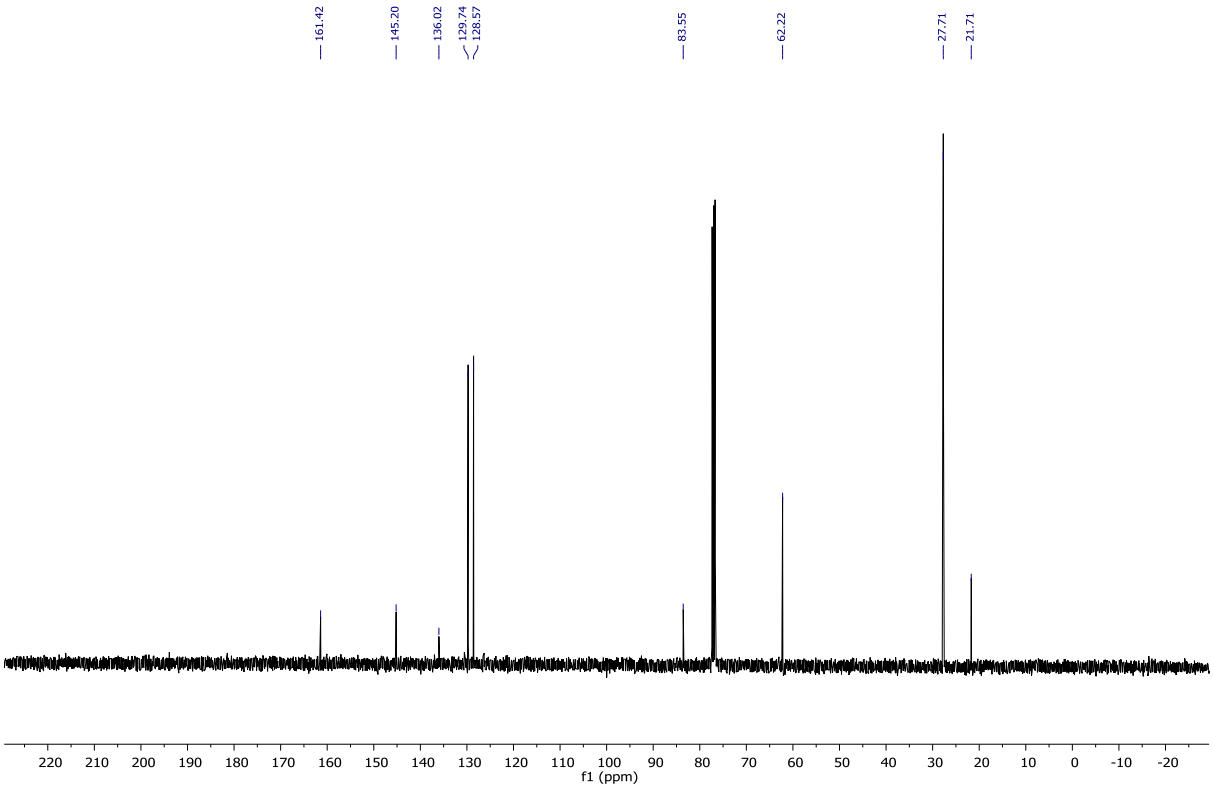
3.21
9.89
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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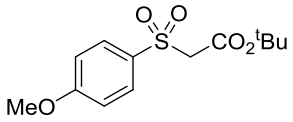
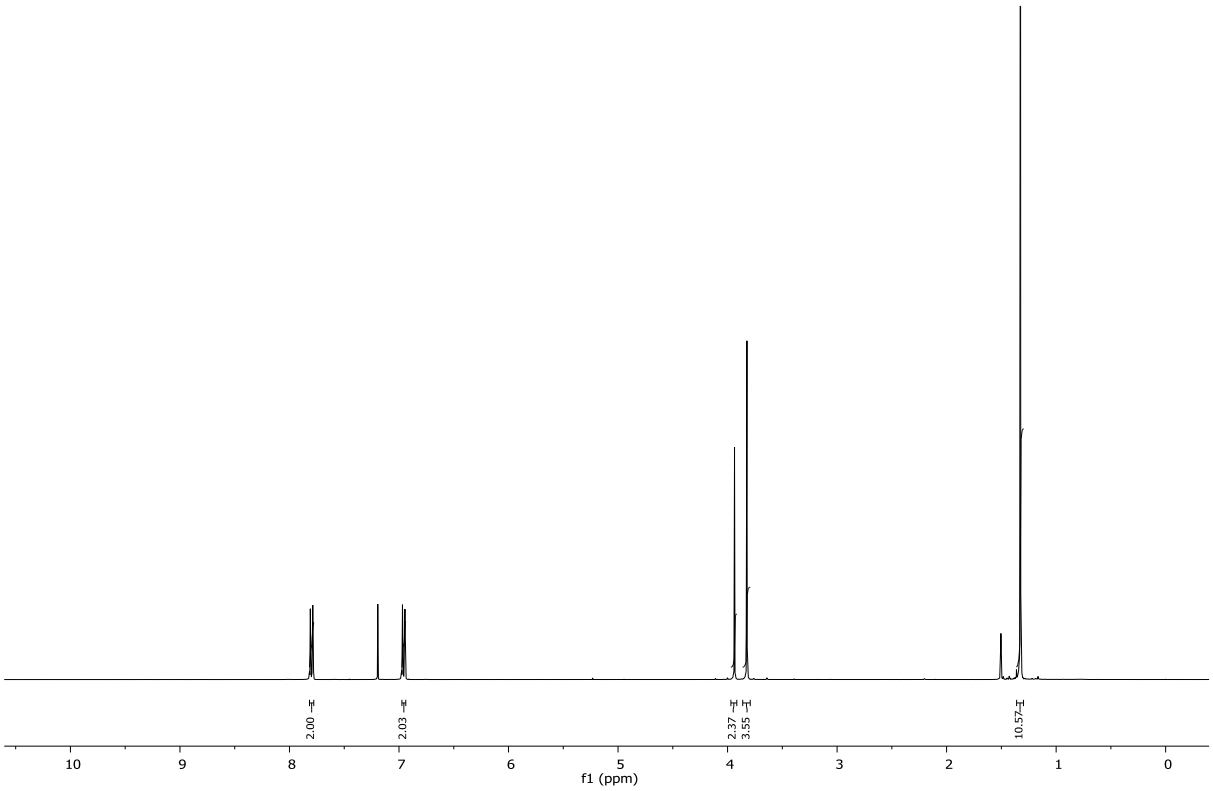
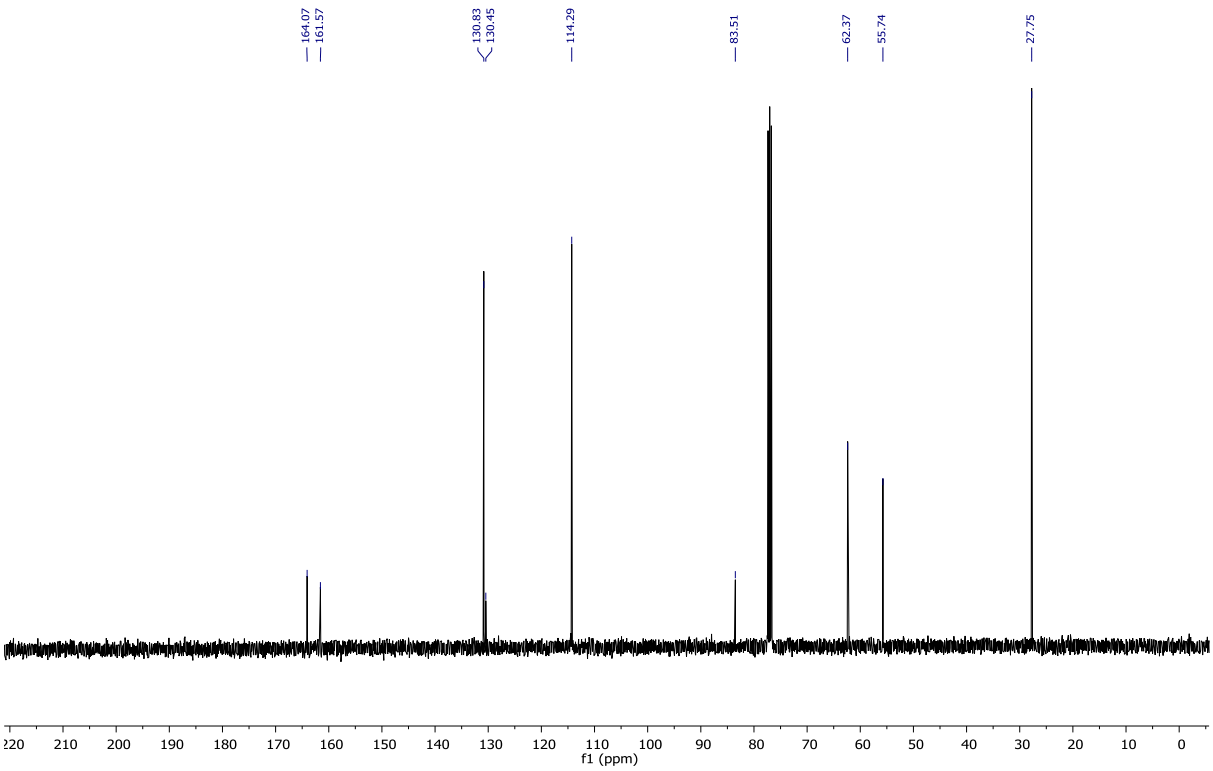
145.20
136.02
129.74
128.57
83.55
62.22
27.71
21.71
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


O
O
S
CO2tBu
MeO


2.00
2.03
2.37
3.55
10.57
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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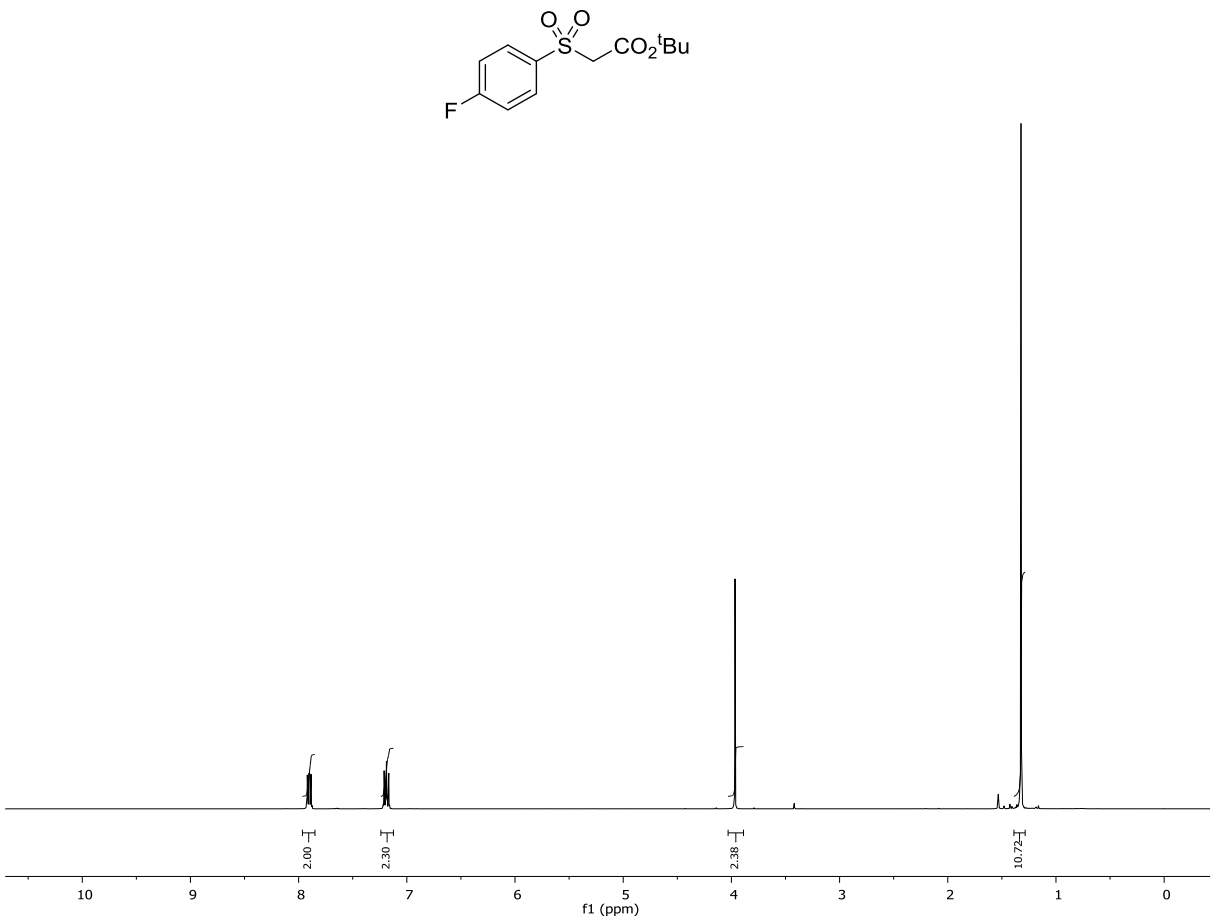
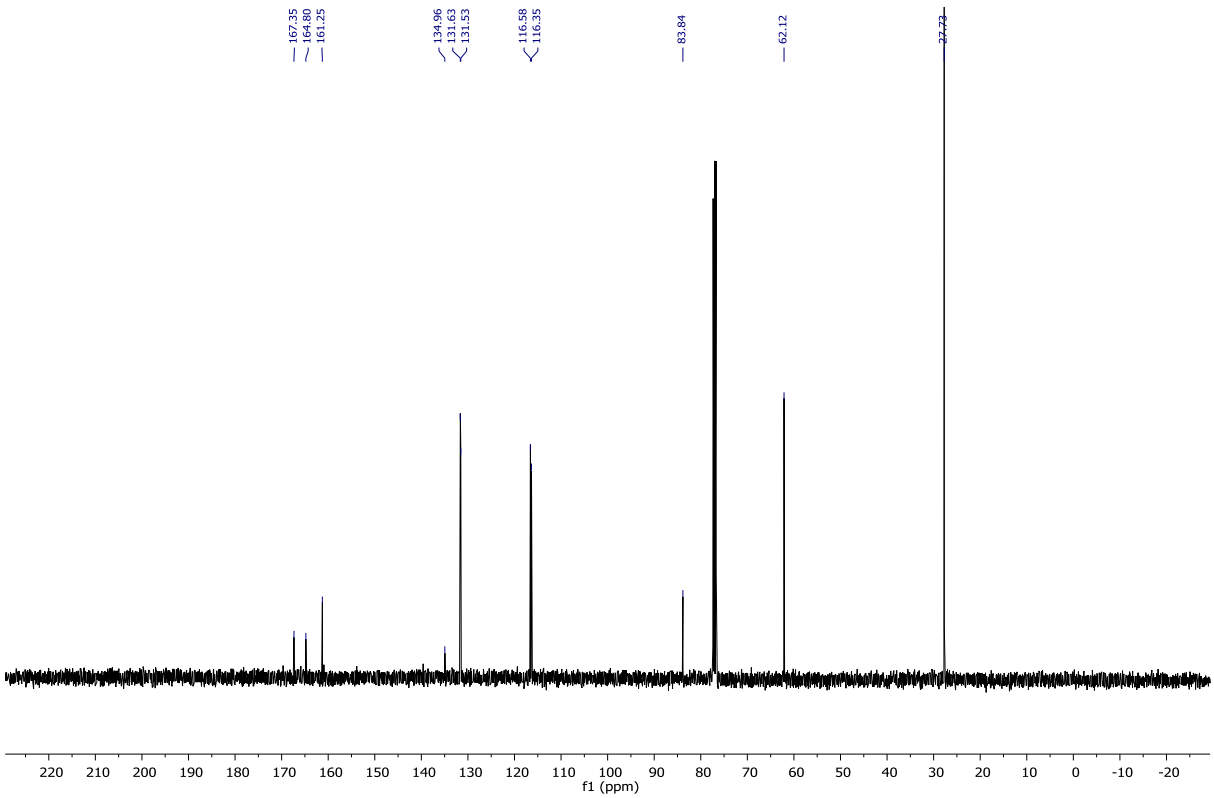
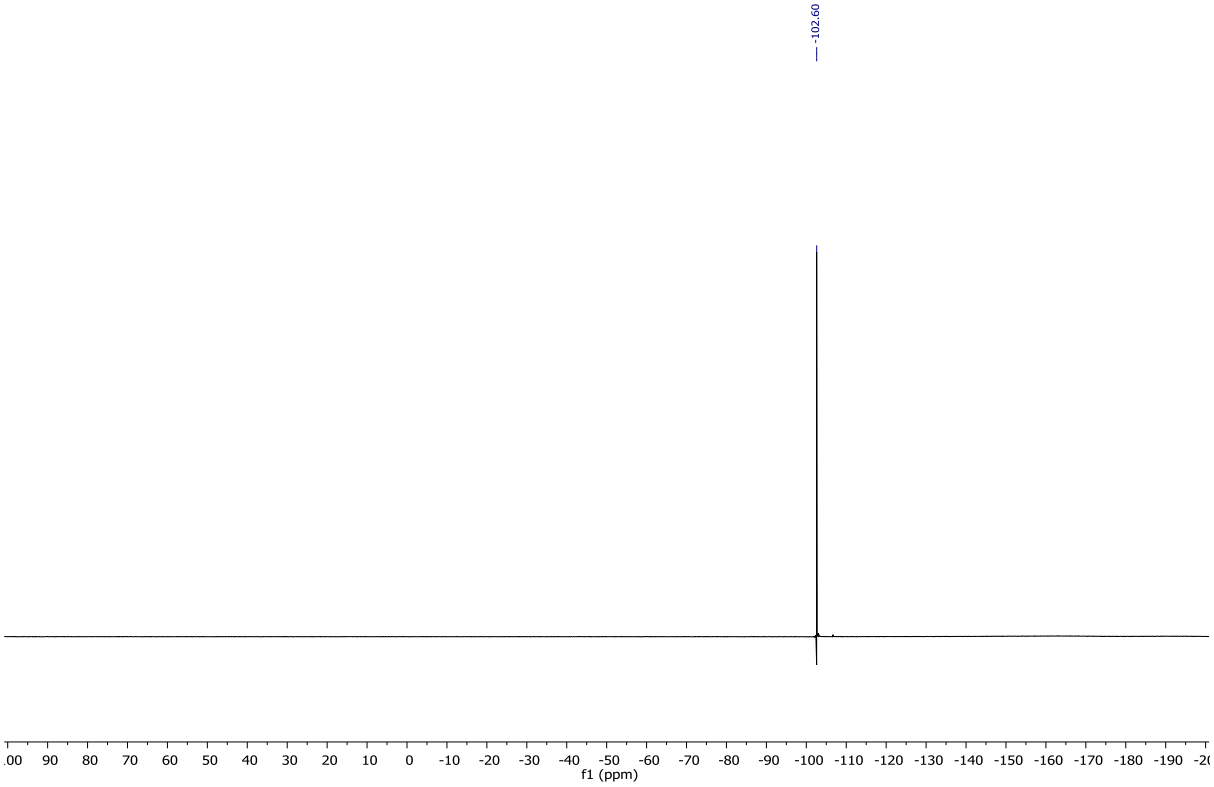
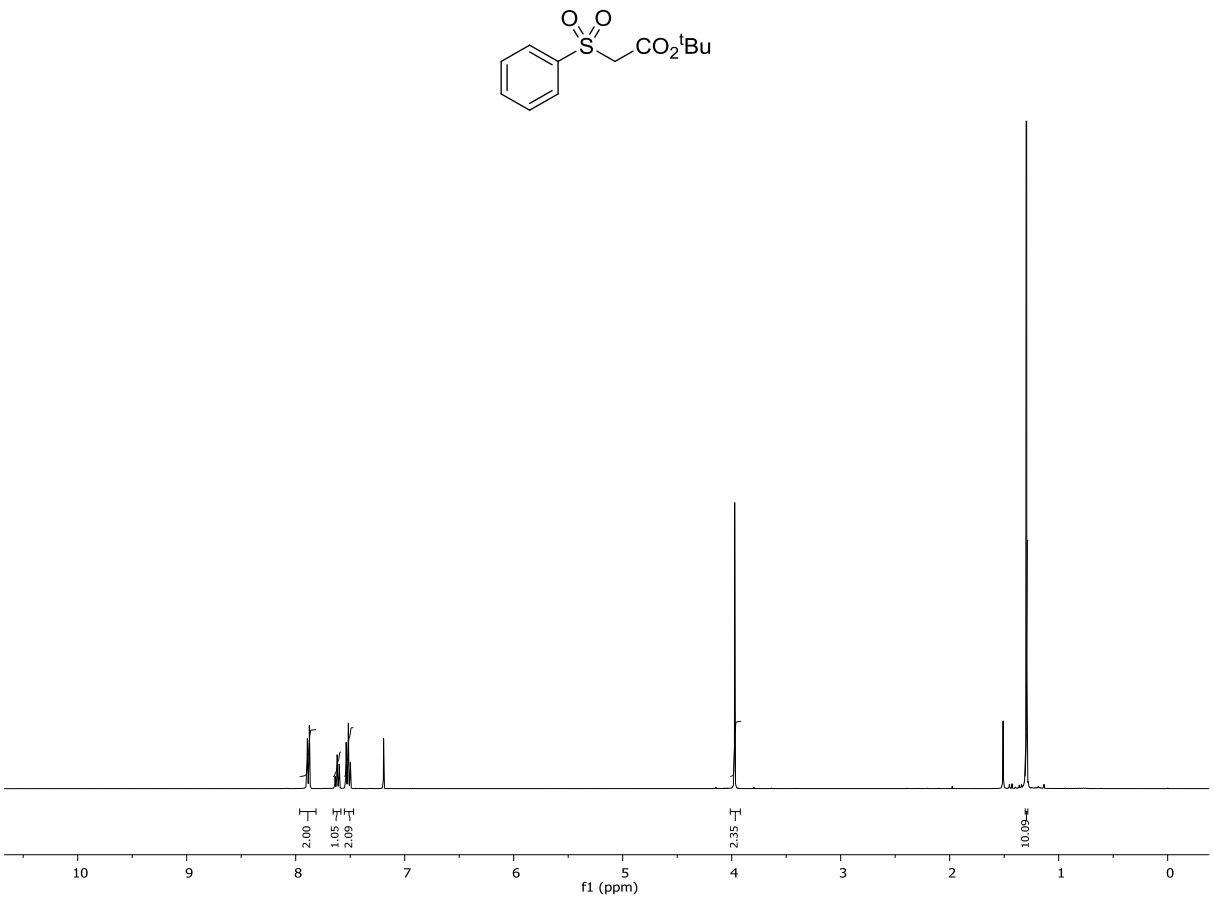
161.57
130.83
130.45
114.29
83.51
62.37
55.74
27.75
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
CO2tBu
F
2.00
2.30
2.38
10.72
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


167.35
164.80
161.25
134.96
131.63
131.53
116.58
116.35
83.84
62.12
27.72
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


-102.60
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190
f1 (ppm)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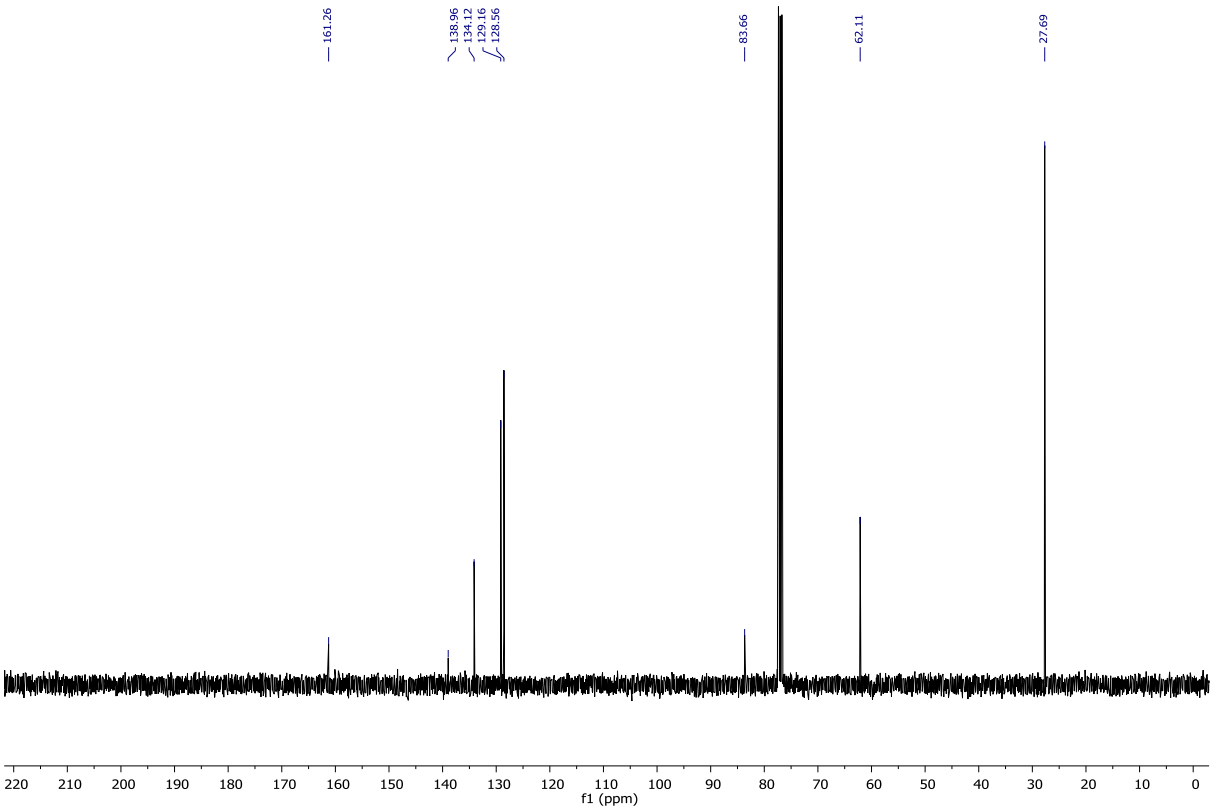
1.05
2.09
2.35
10.09
f1 (ppm)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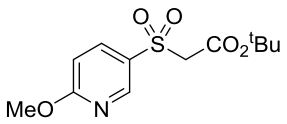
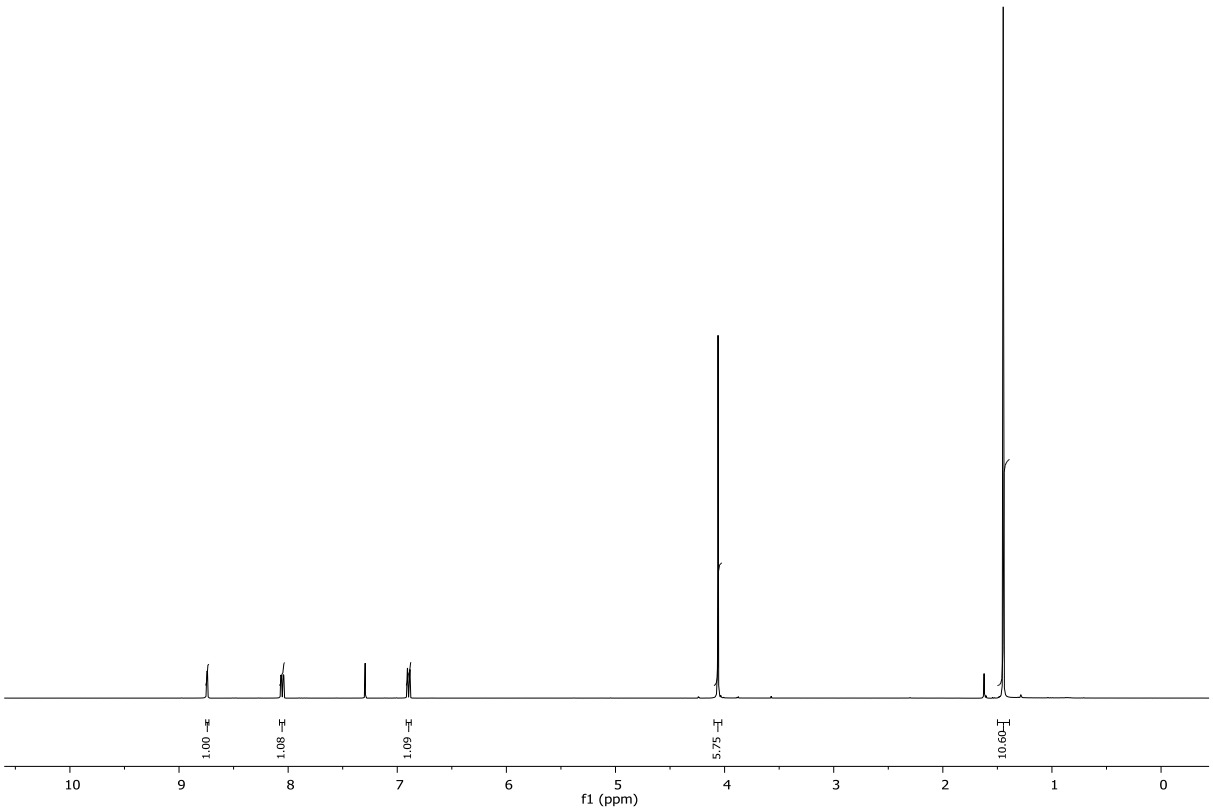
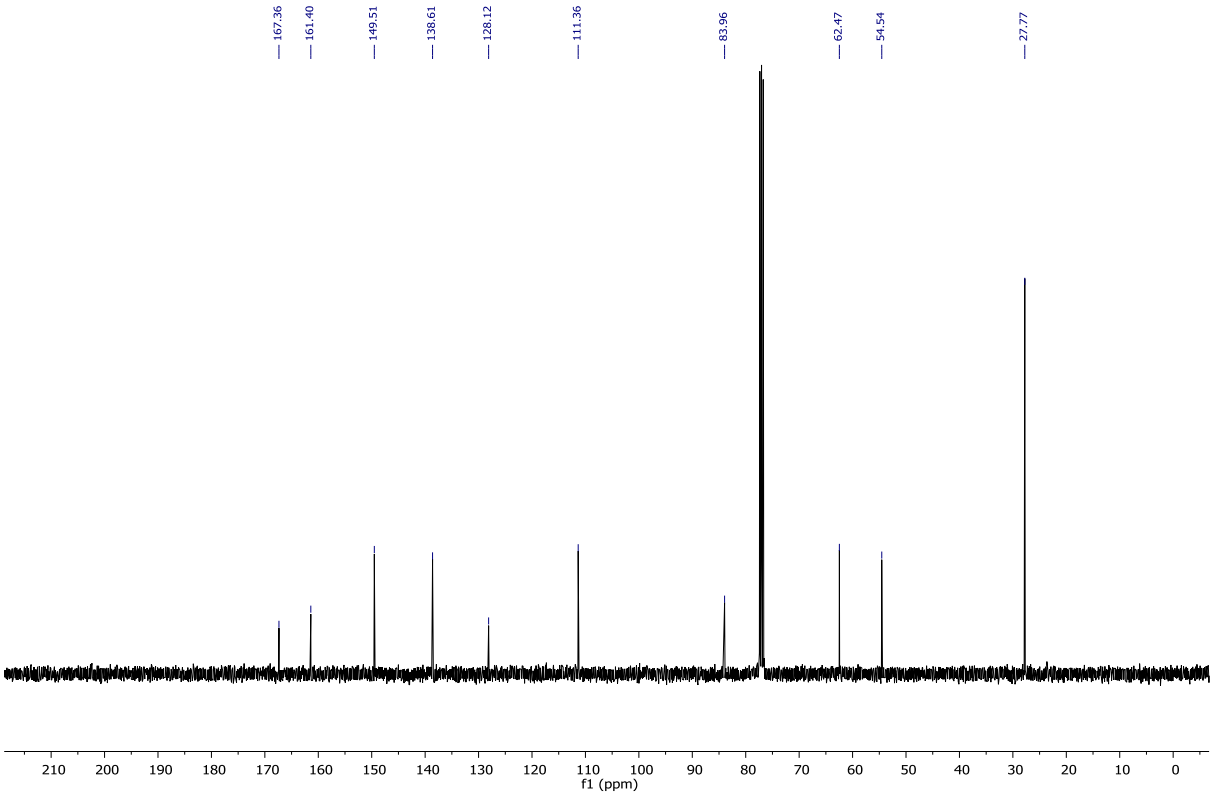
138.96
134.12
129.16
128.56
83.66
62.11
27.69
f1 (ppm)


O
O
S
CO2tBu
MeO
N


1.00
1.08
1.09
5.75
10.60
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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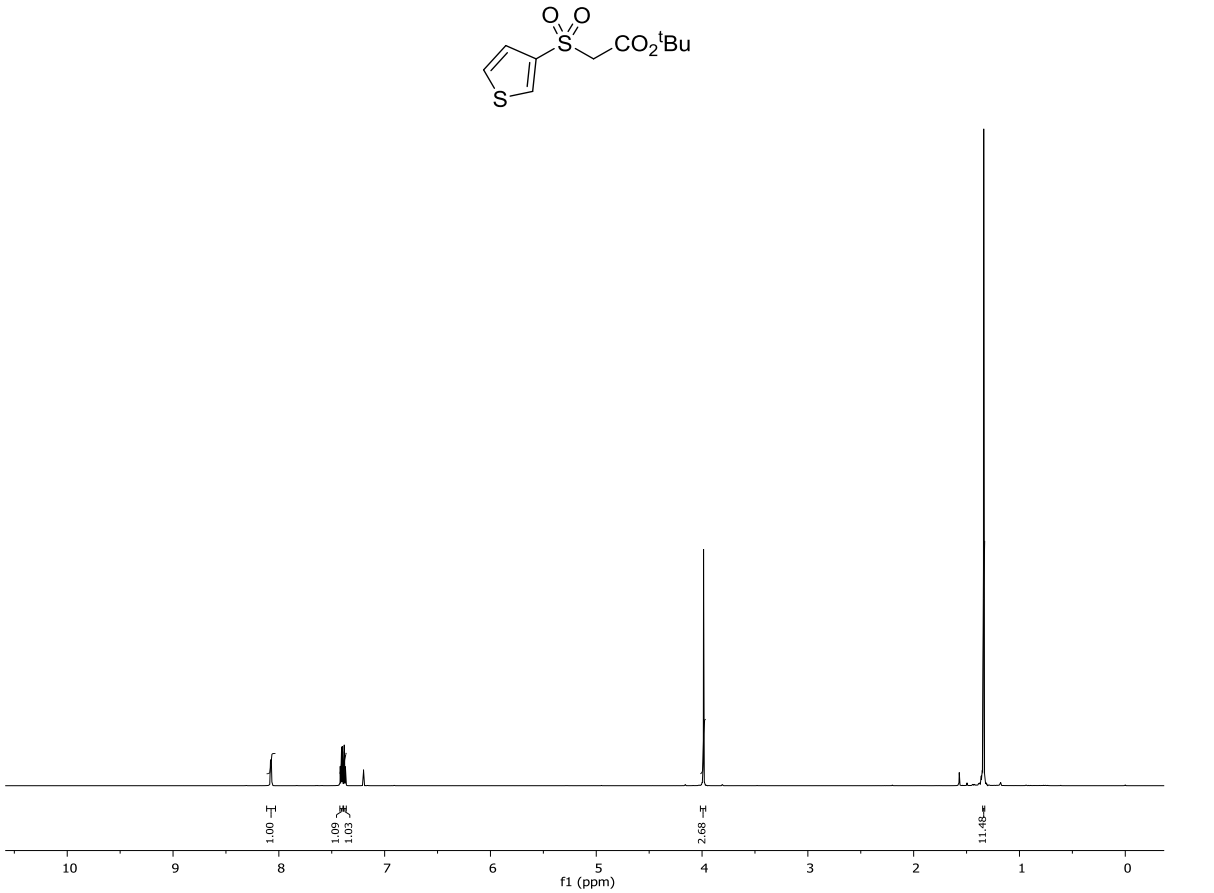
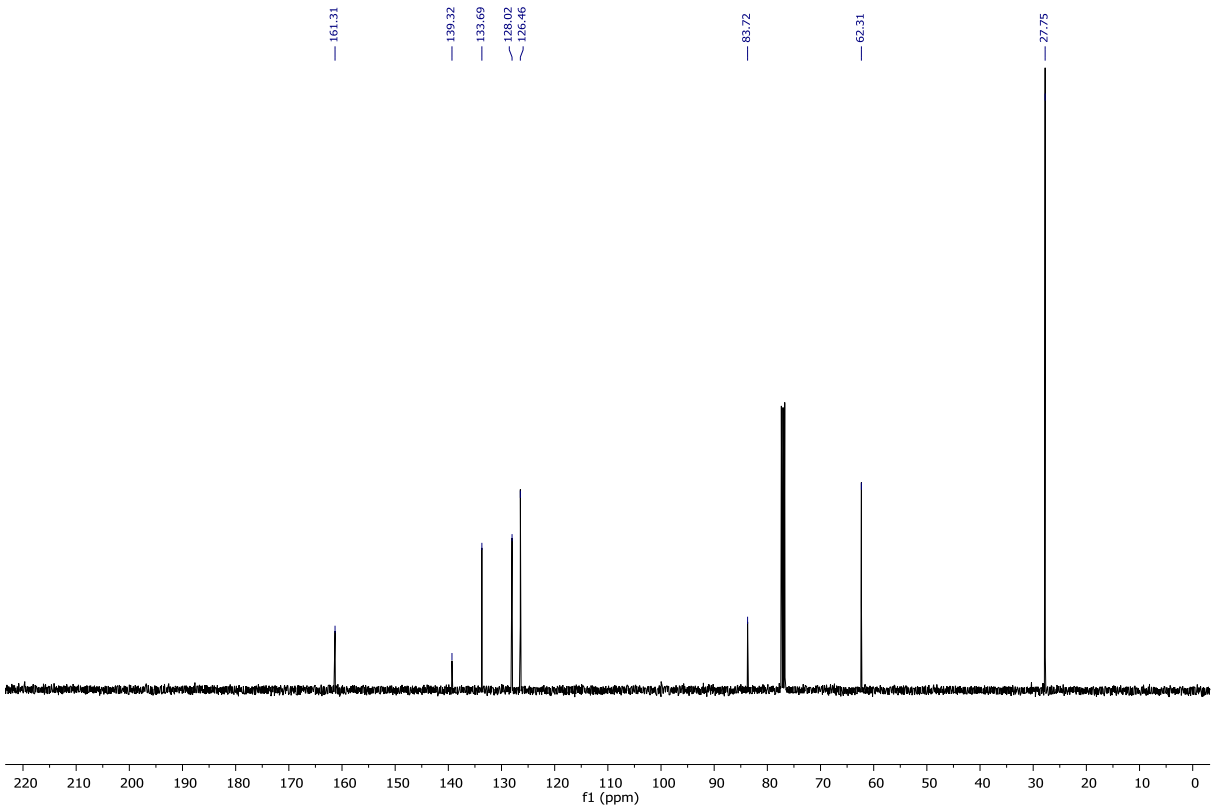
161.40
149.51
138.61
128.12
111.36
83.96
62.47
54.54
27.77
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
CO2tBu
S
1.00
1.09
1.03
2.68
11.48
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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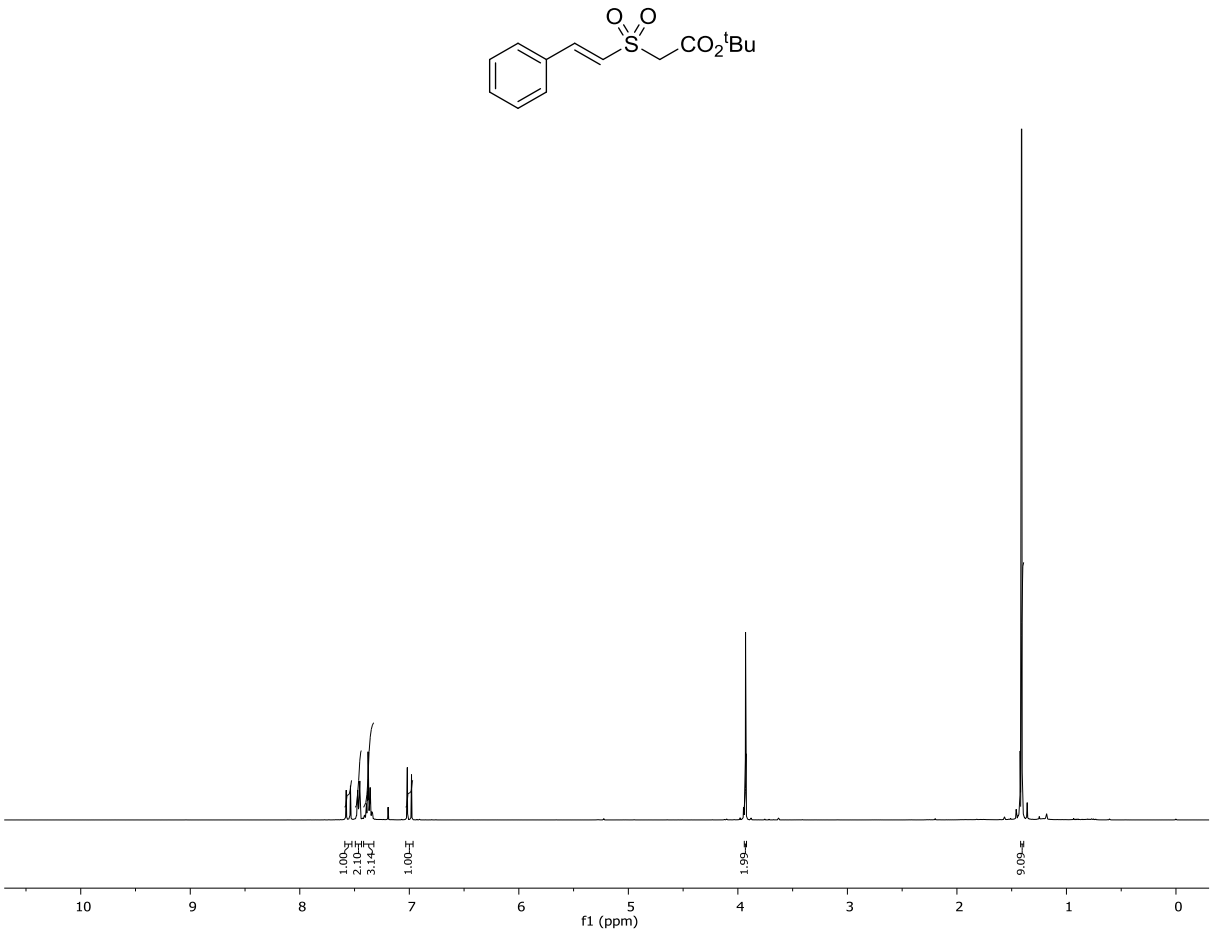
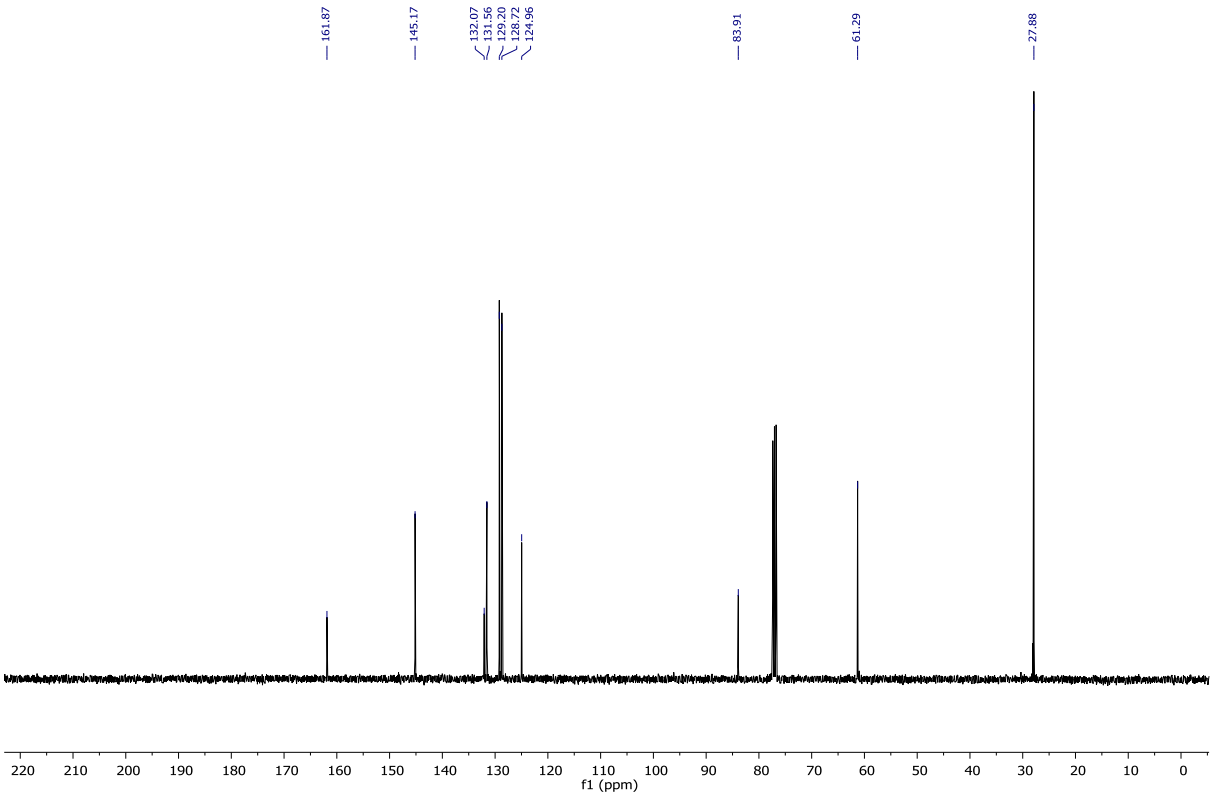
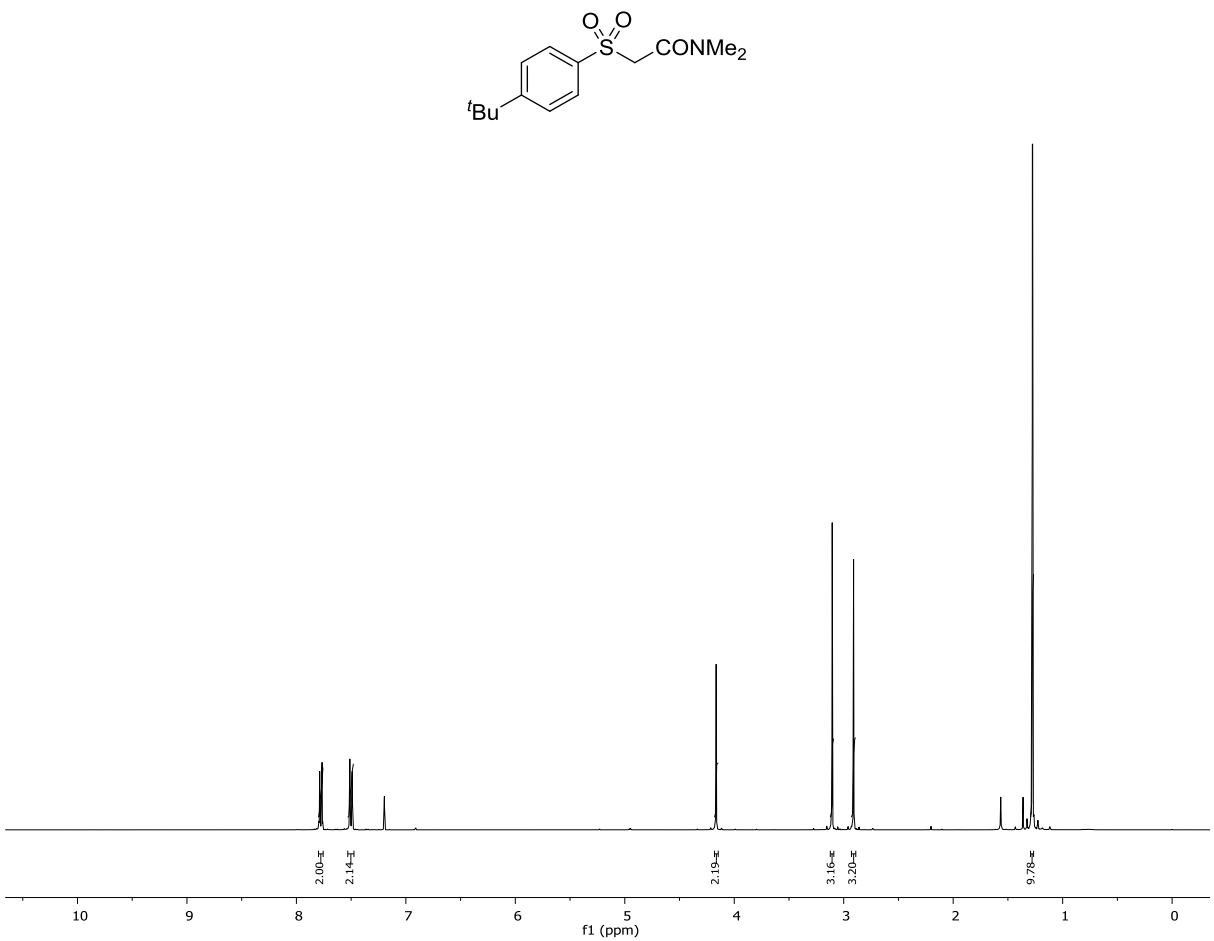
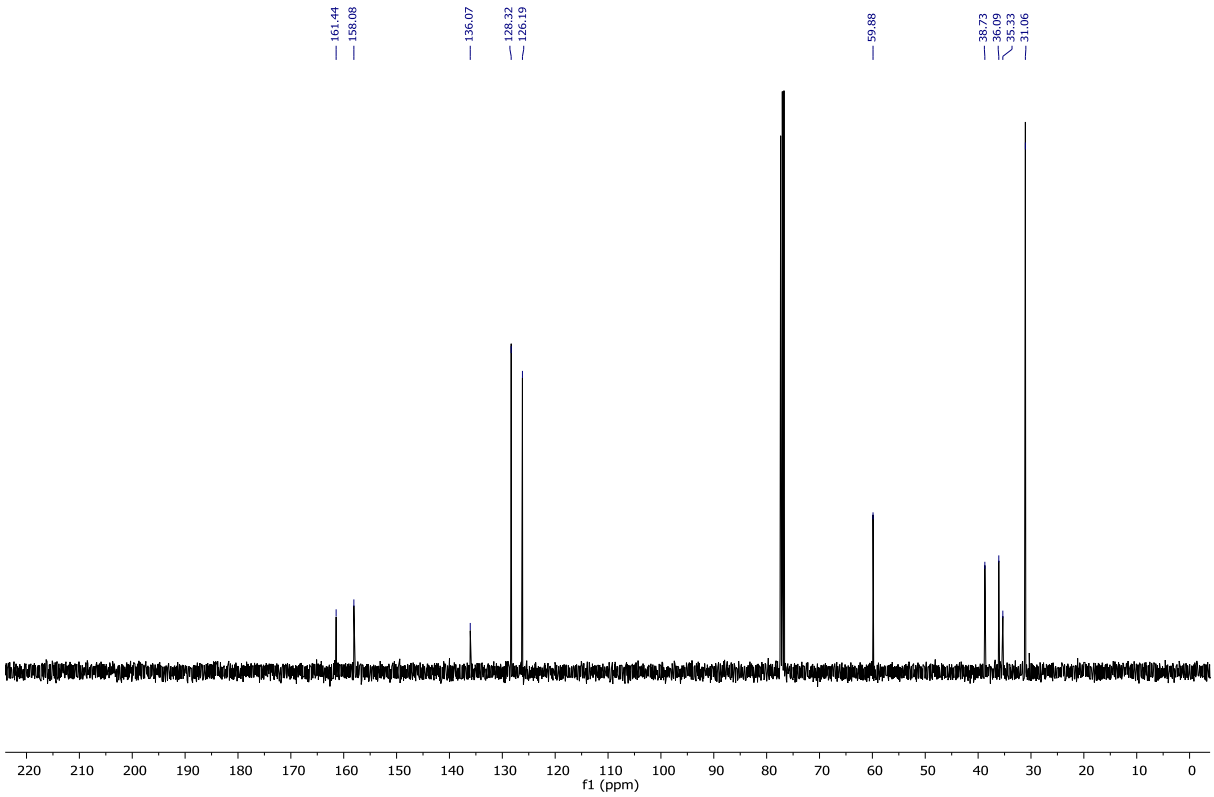
139.32
133.69
128.02
126.46
83.72
62.31
27.75
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
CO2tBu
1.00
2.10
3.14
1.00
1.99
9.09
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


161.87
145.17
132.07
131.56
129.20
128.72
124.96
83.91
61.29
27.88
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
CONMe2
tBu
2.00
2.14
2.19
3.16
3.20
9.78
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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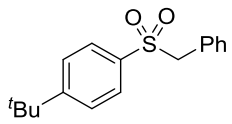
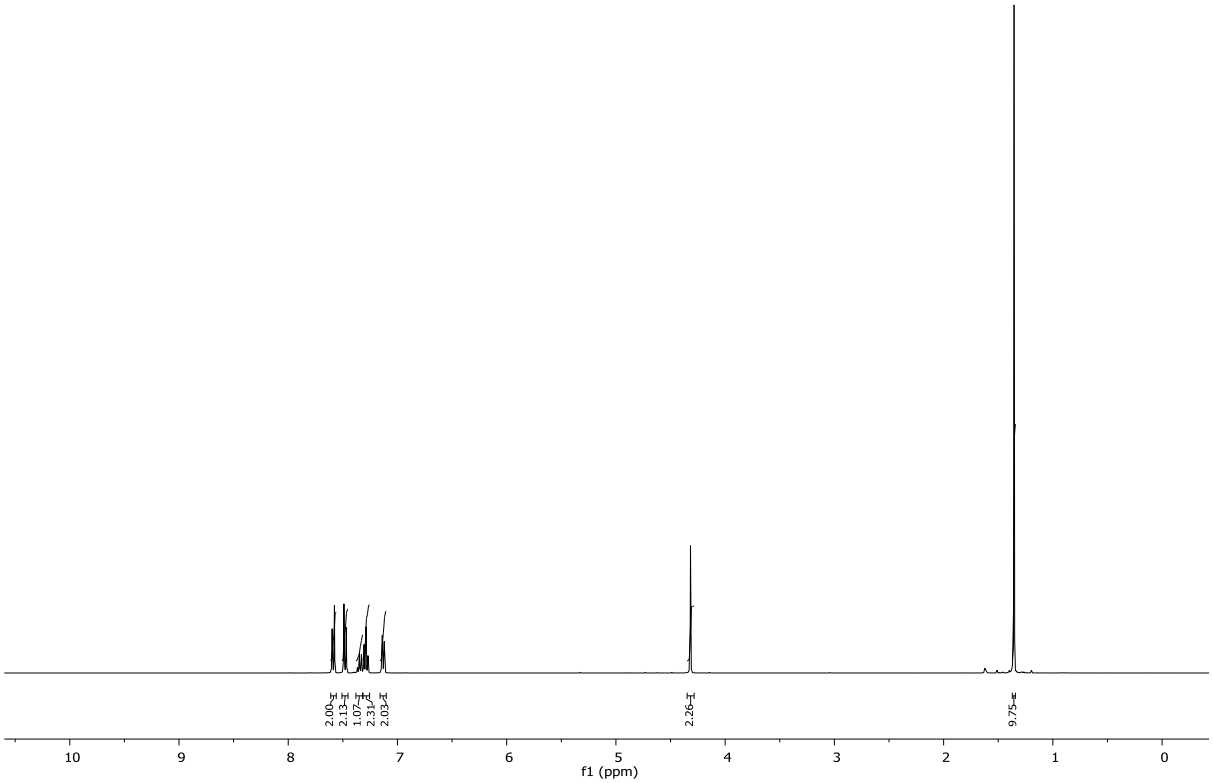
158.08
136.07
128.32
126.19
59.88
38.73
36.09
35.33
31.06
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
Ph
tBu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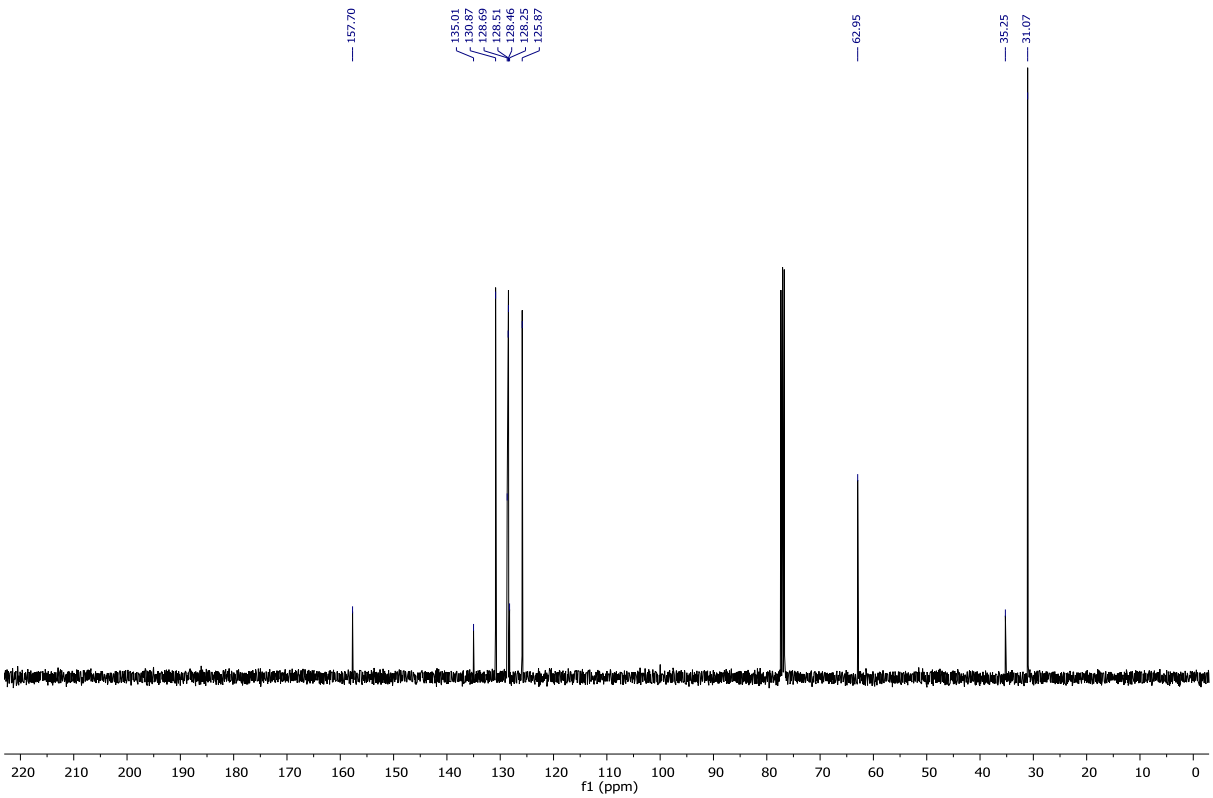
2.13
1.07
2.31
2.03
2.26
9.75
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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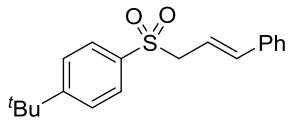
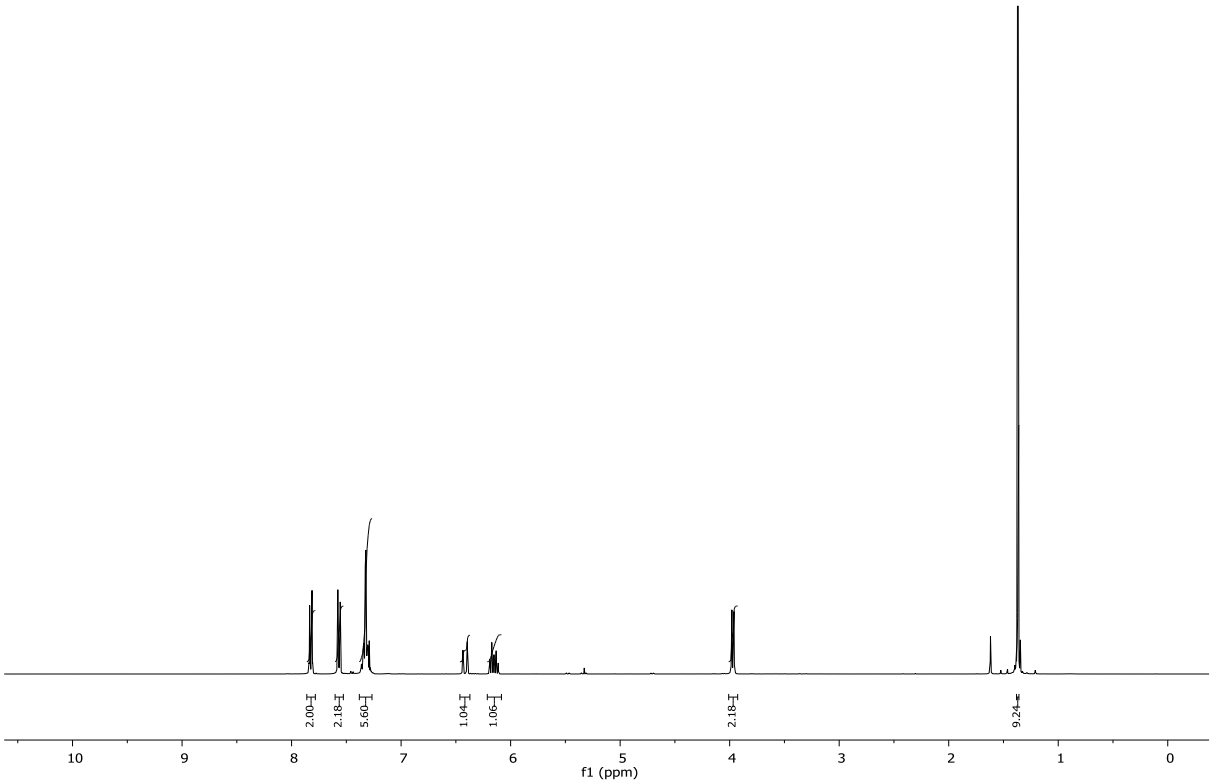
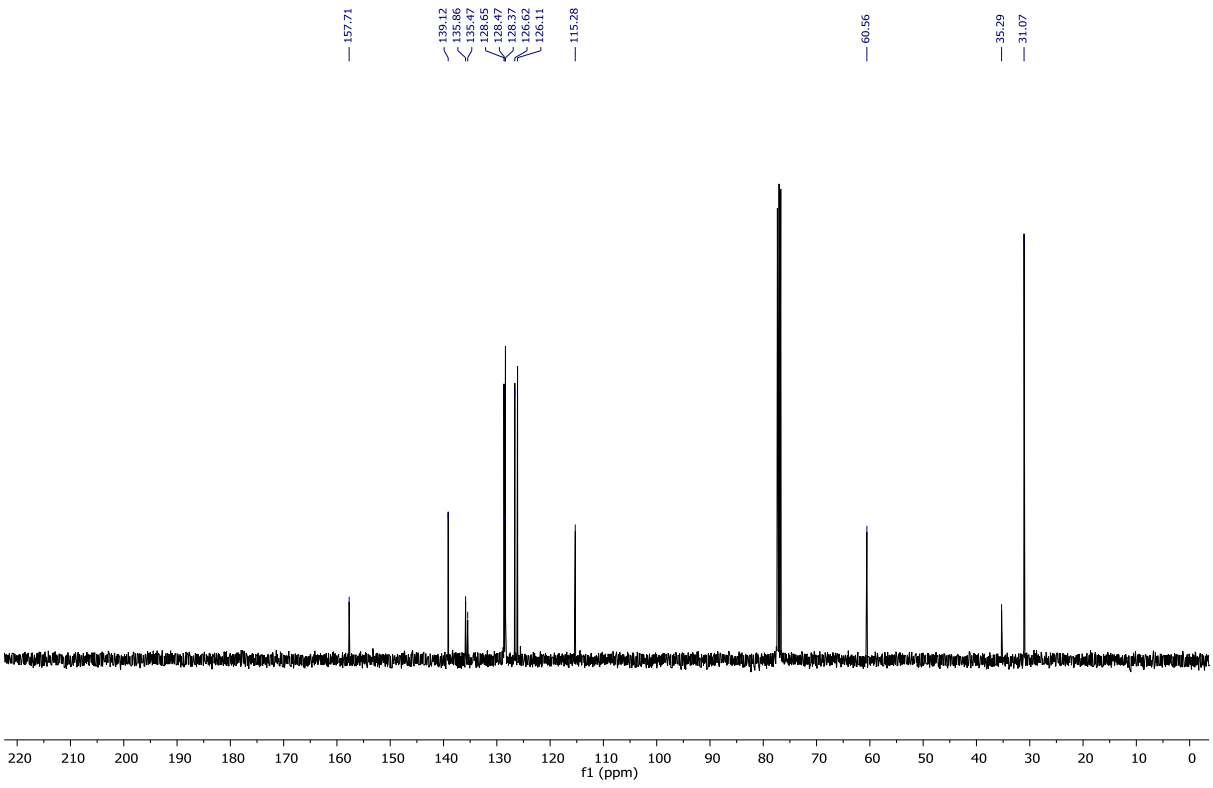
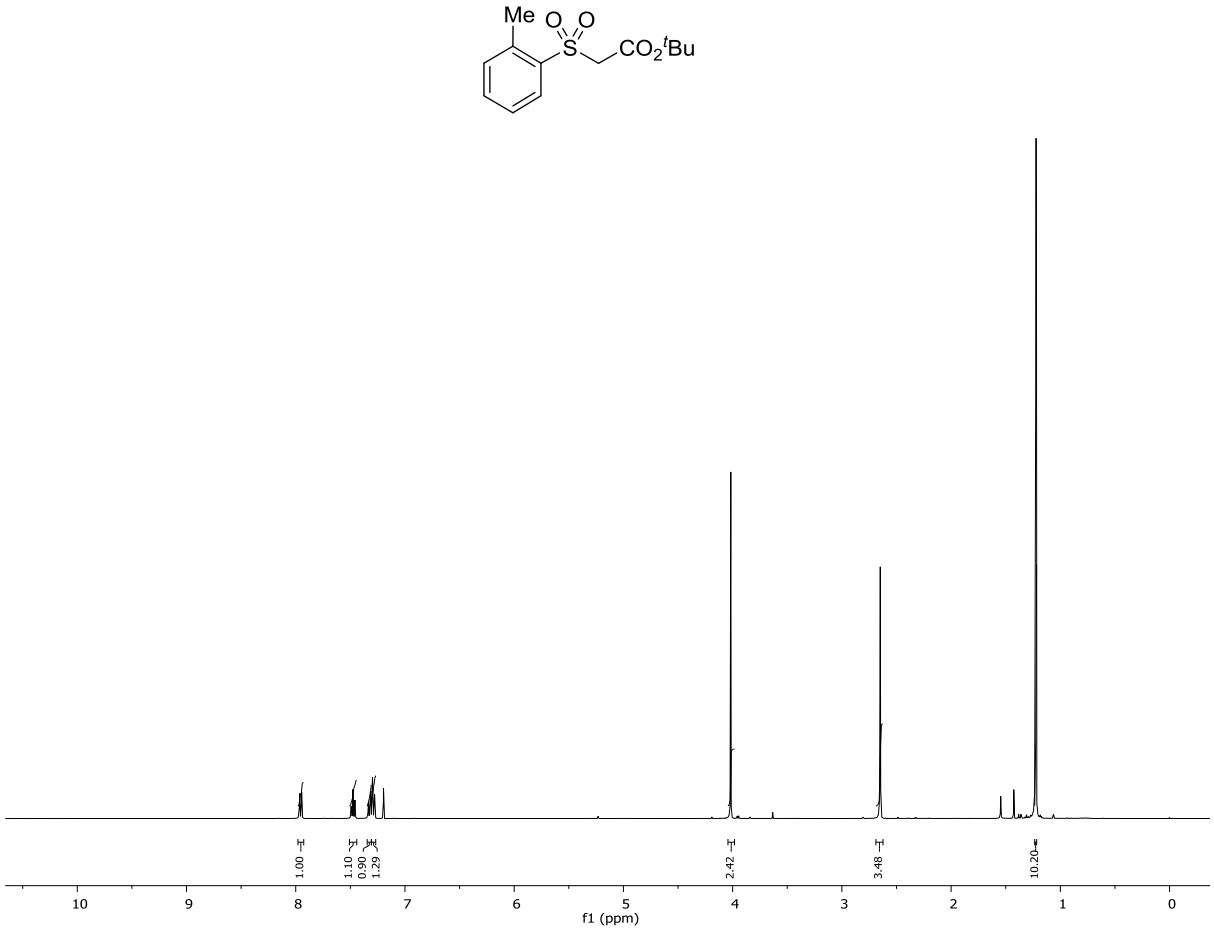
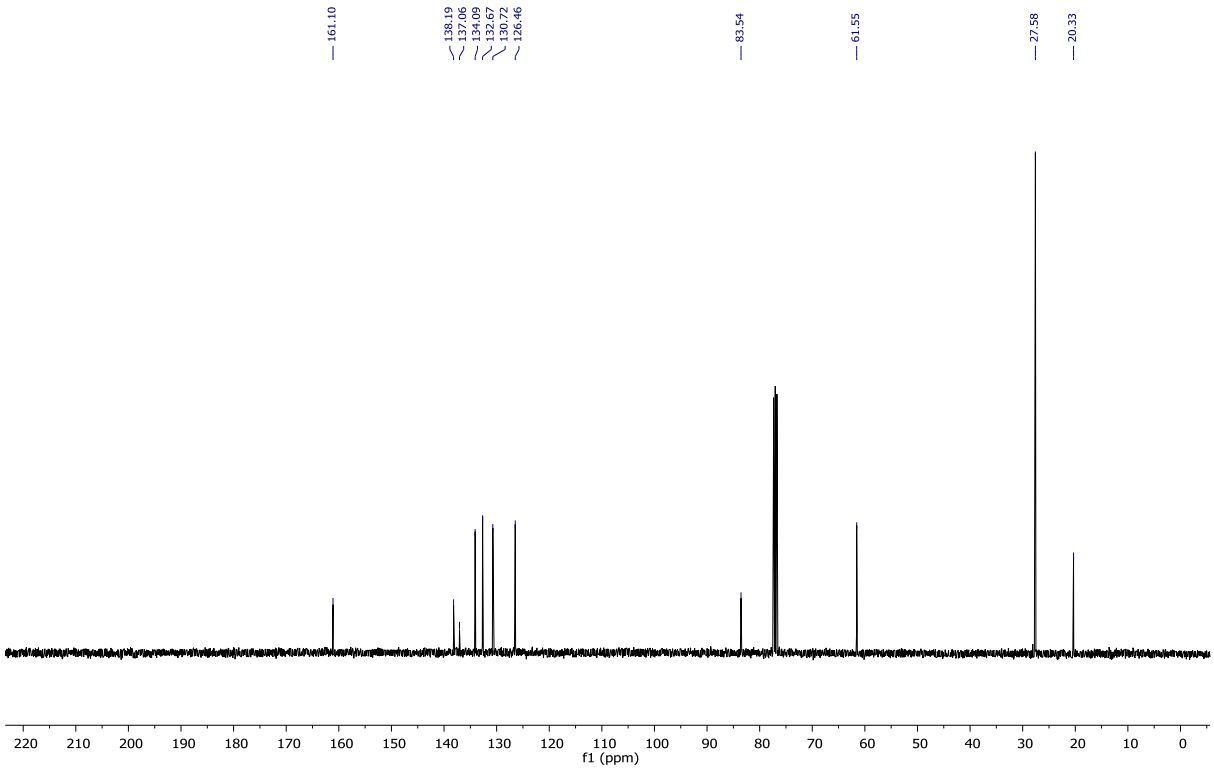
135.01
130.87
128.69
128.51
128.46
128.25
125.87
62.95
35.25
31.07
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
Ph
tBu


2.00
2.18
5.60
1.04
1.06
2.18
9.24
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


157.71
139.12
135.86
135.47
128.65
128.47
128.37
126.62
126.11
115.28
60.56
35.29
31.07
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


Me
O
O
S
CO2tBu
1.00
1.10
0.90
1.29
2.42
3.48
10.20
f1 (ppm)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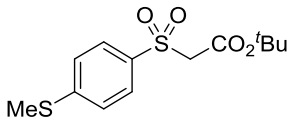
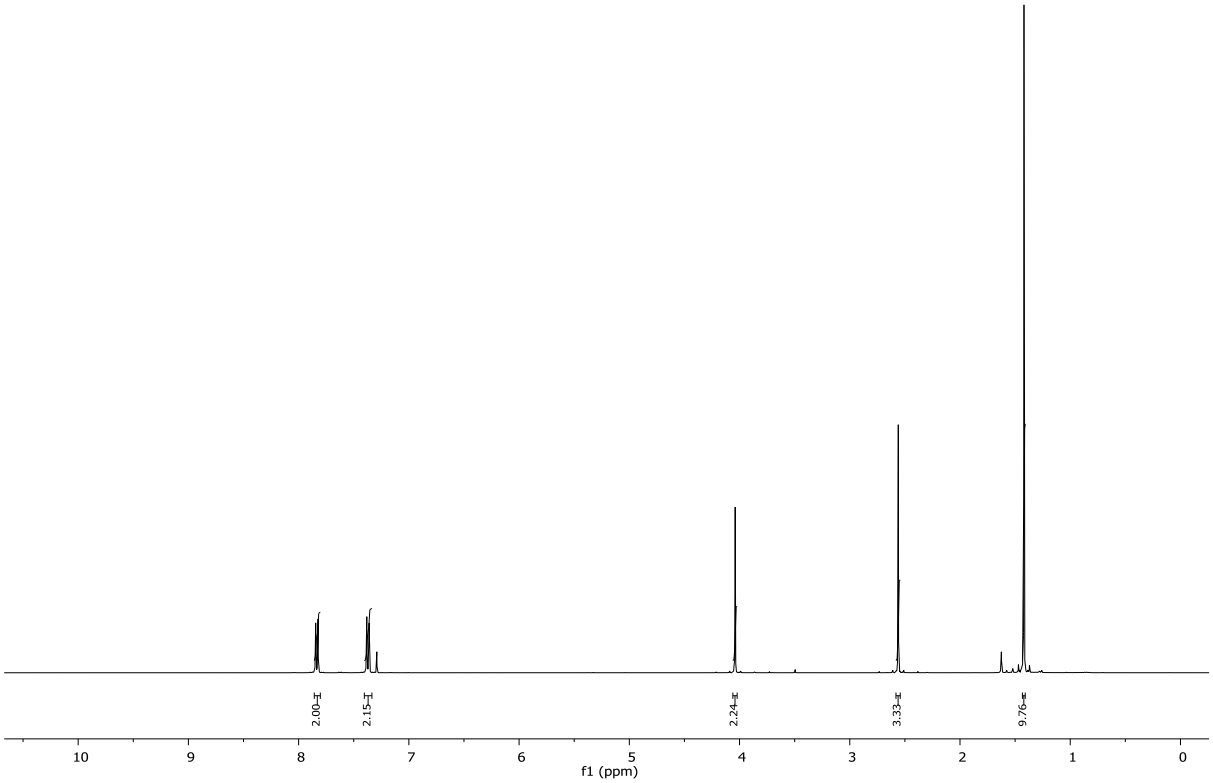
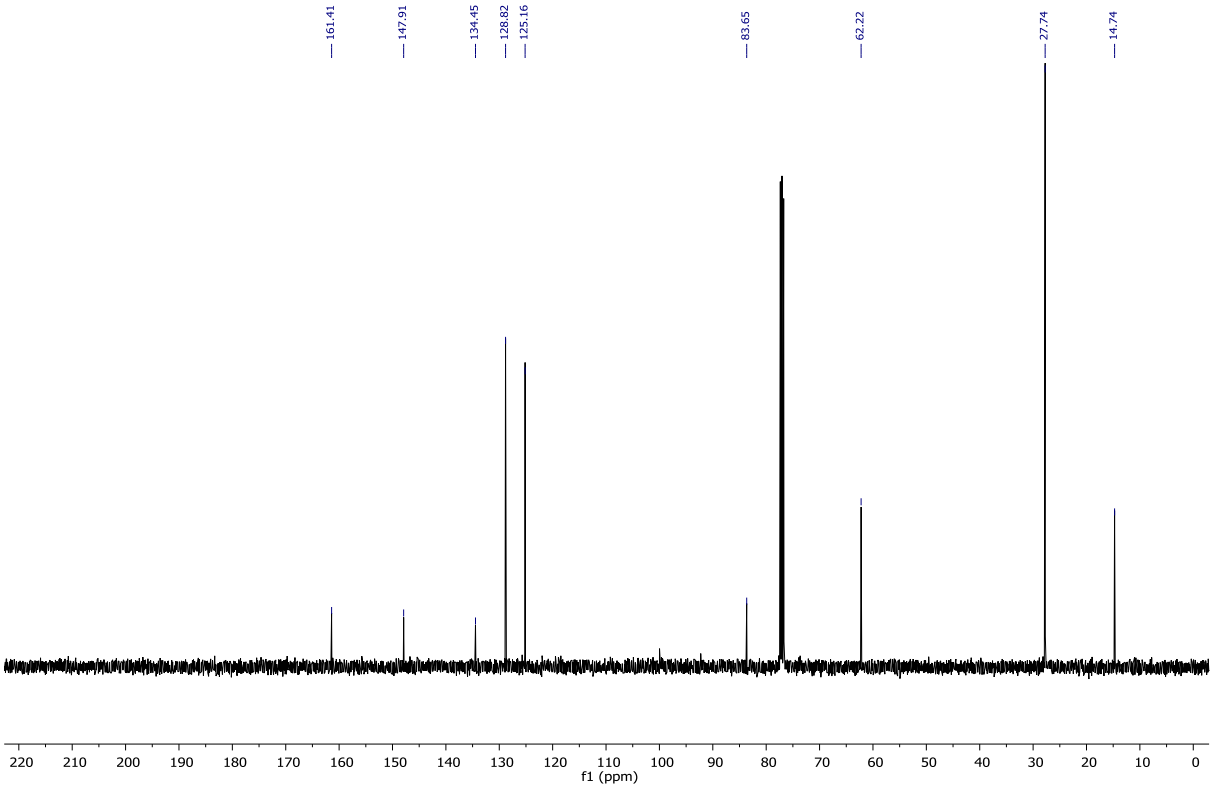
134.09
132.67
130.72
126.46
83.54
61.55
27.58
20.33
f1 (ppm)


O
O
S
CO2tBu
MeS


2.00
2.15
2.24
3.33
9.76
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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147.91
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128.82
125.16
83.65
62.22
27.74
14.74
220
210
200
190
180
170
160
150
140
130
120
110
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90
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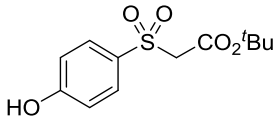
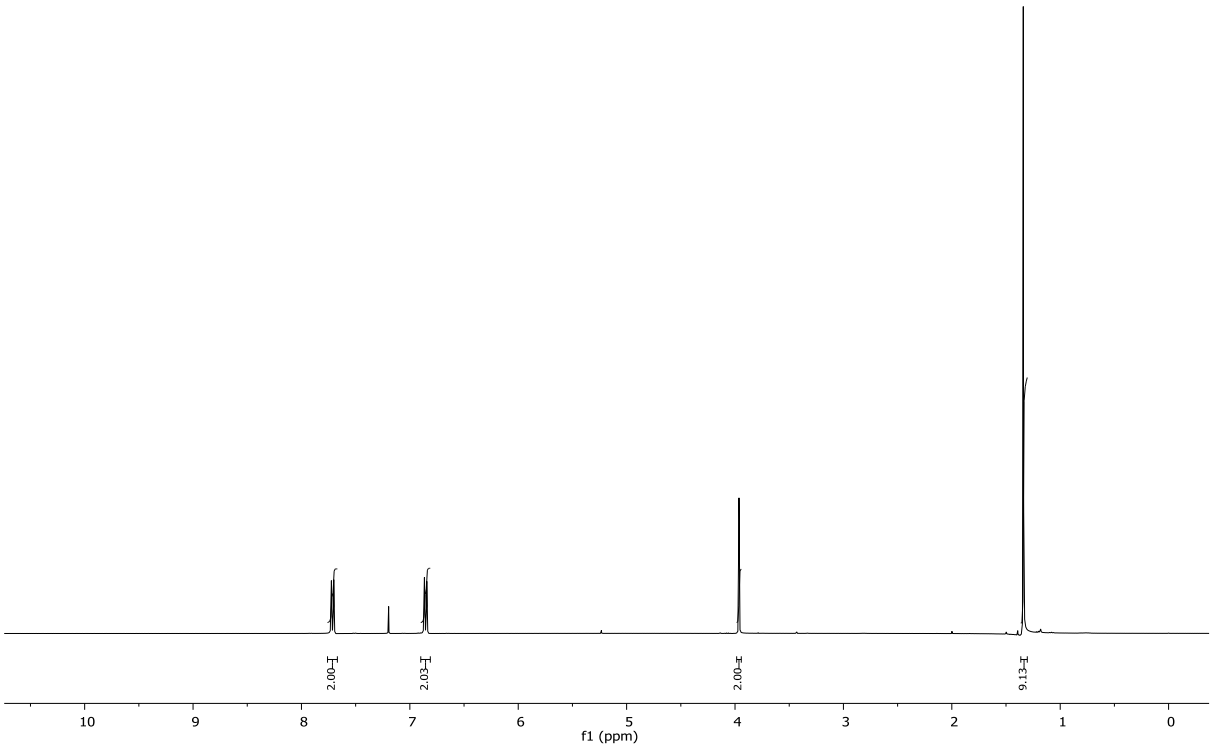
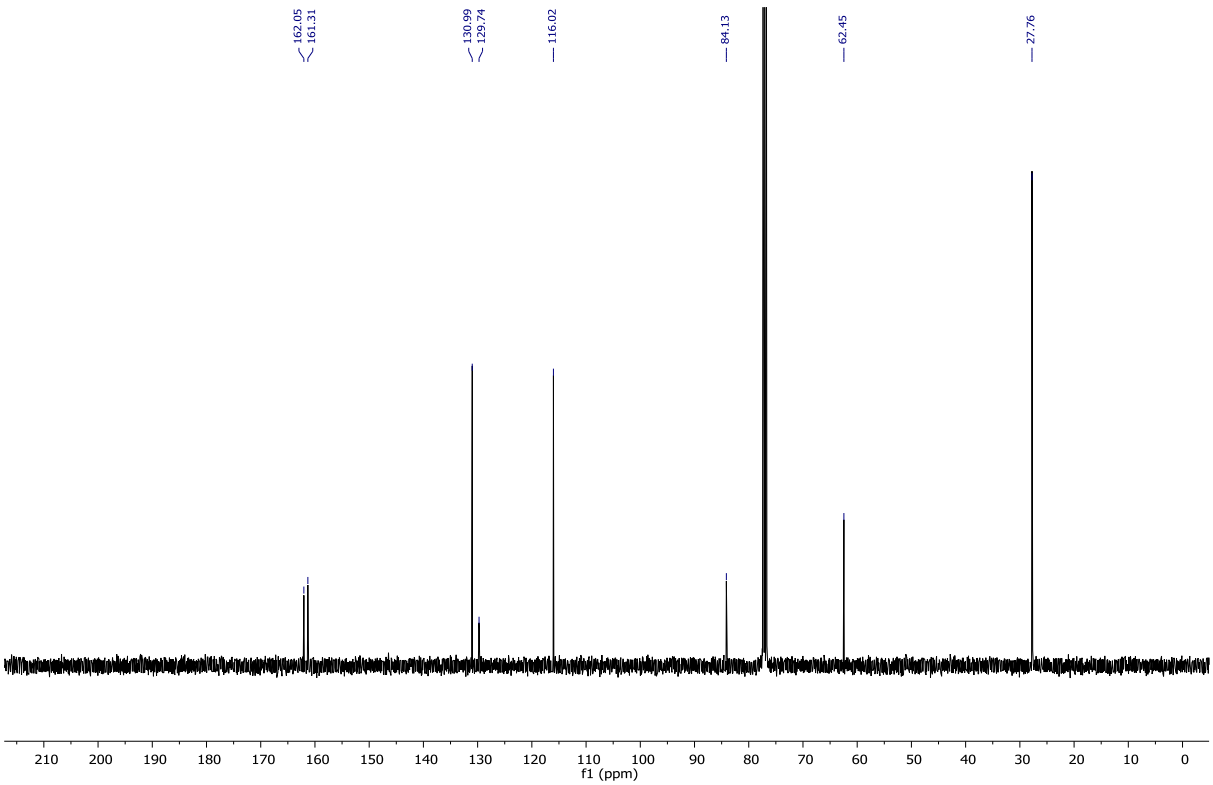
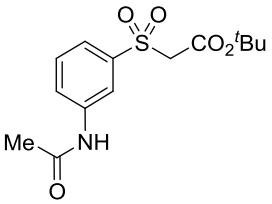
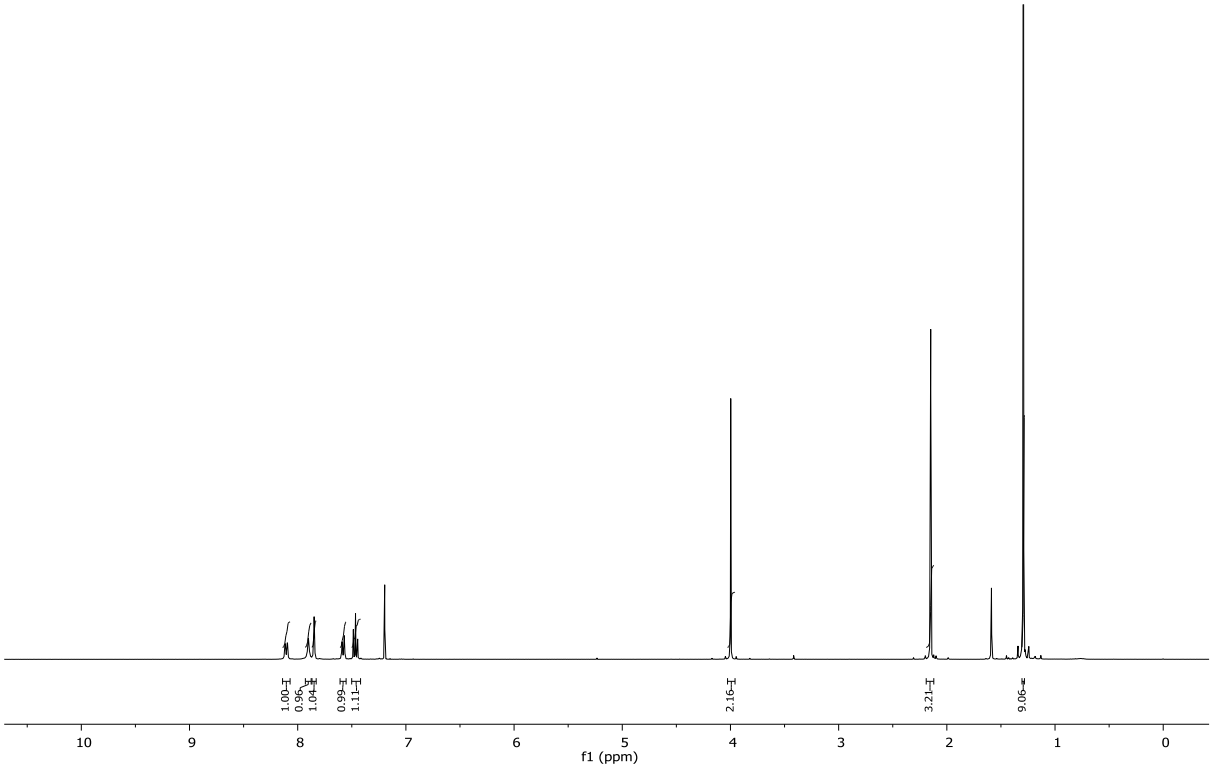
70
60
50
40
30
20
10
0
f1 (ppm)

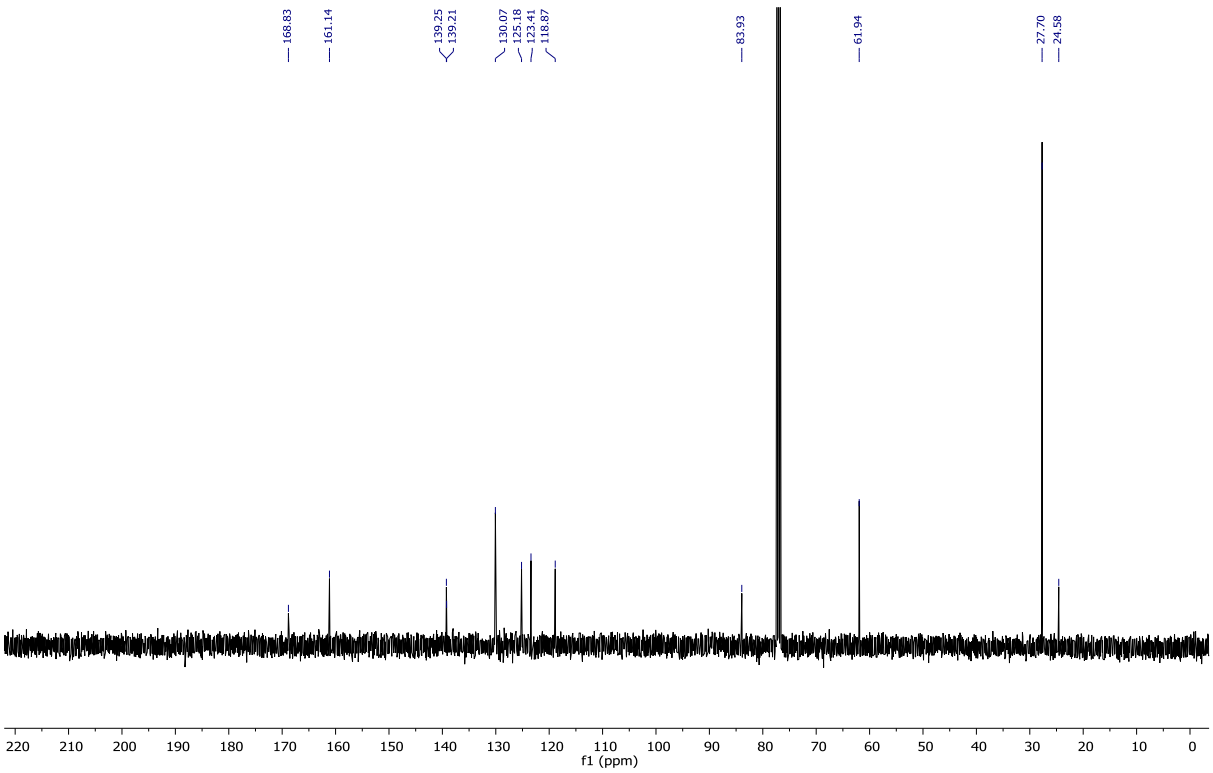

O
O
S
CO2tBu
HO


2.00
2.03
2.00
9.13
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


162.05
161.31
130.99
129.74
116.02
84.13
62.45
27.76
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
CO2tBu
Me
NH
O


1.00
0.96
1.04
0.99
1.11
2.16
3.21
9.06
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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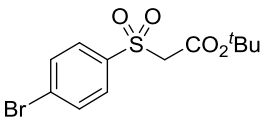
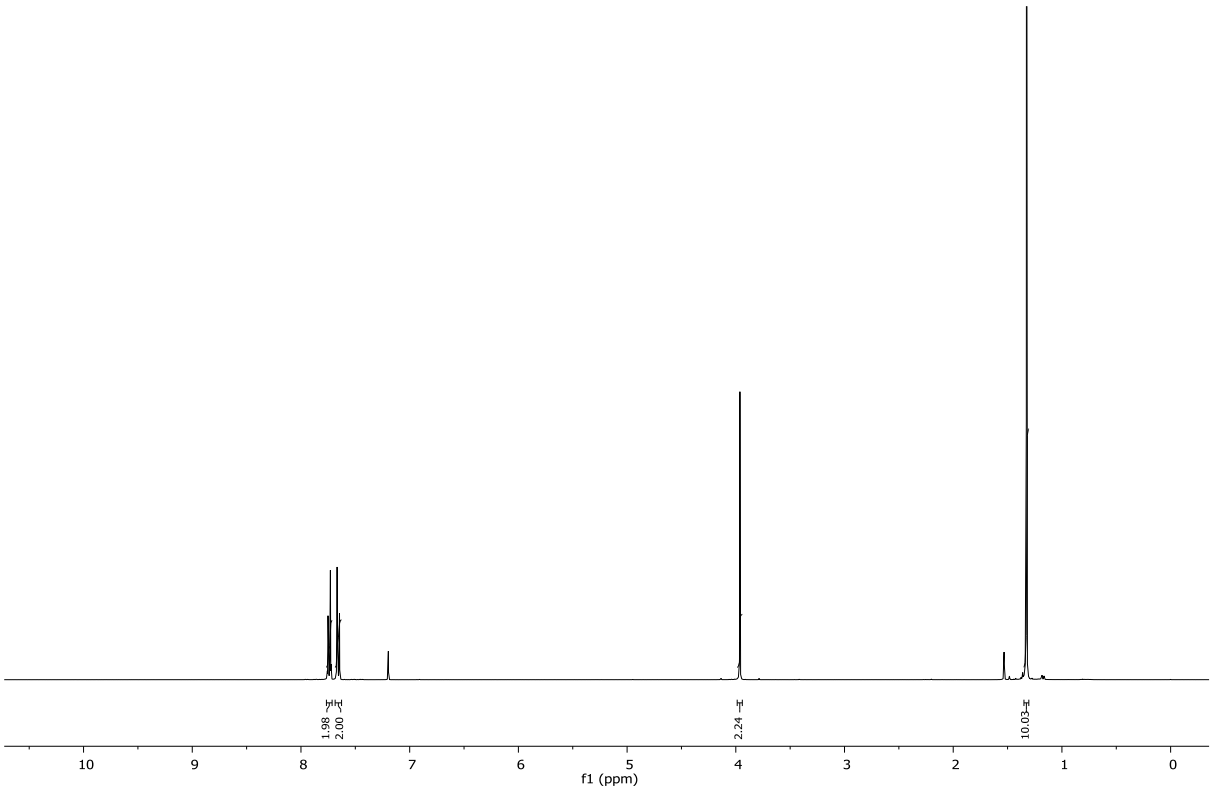
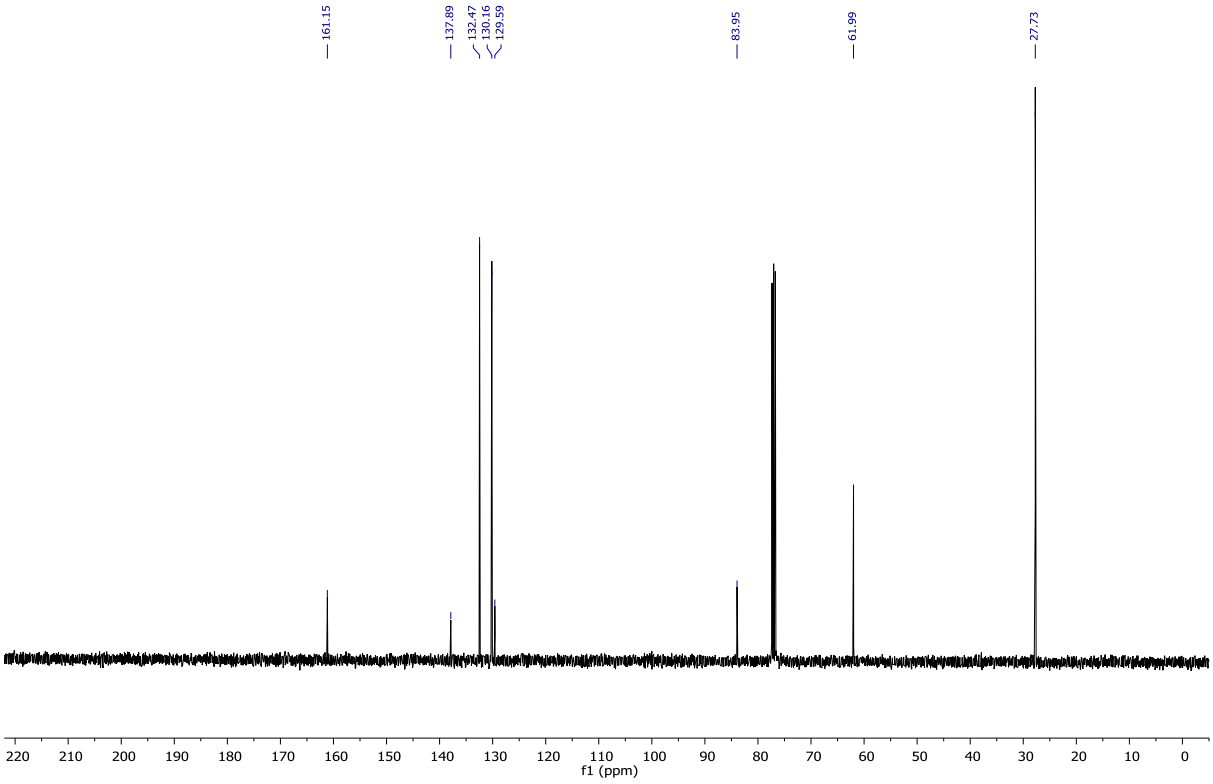
161.14
139.25
139.21
130.07
125.18
123.41
118.87
83.93
61.94
27.70
24.58
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
CO2tBu
Br


1.98
2.00
2.24
10.03
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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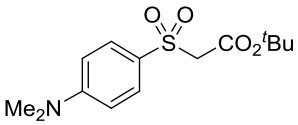
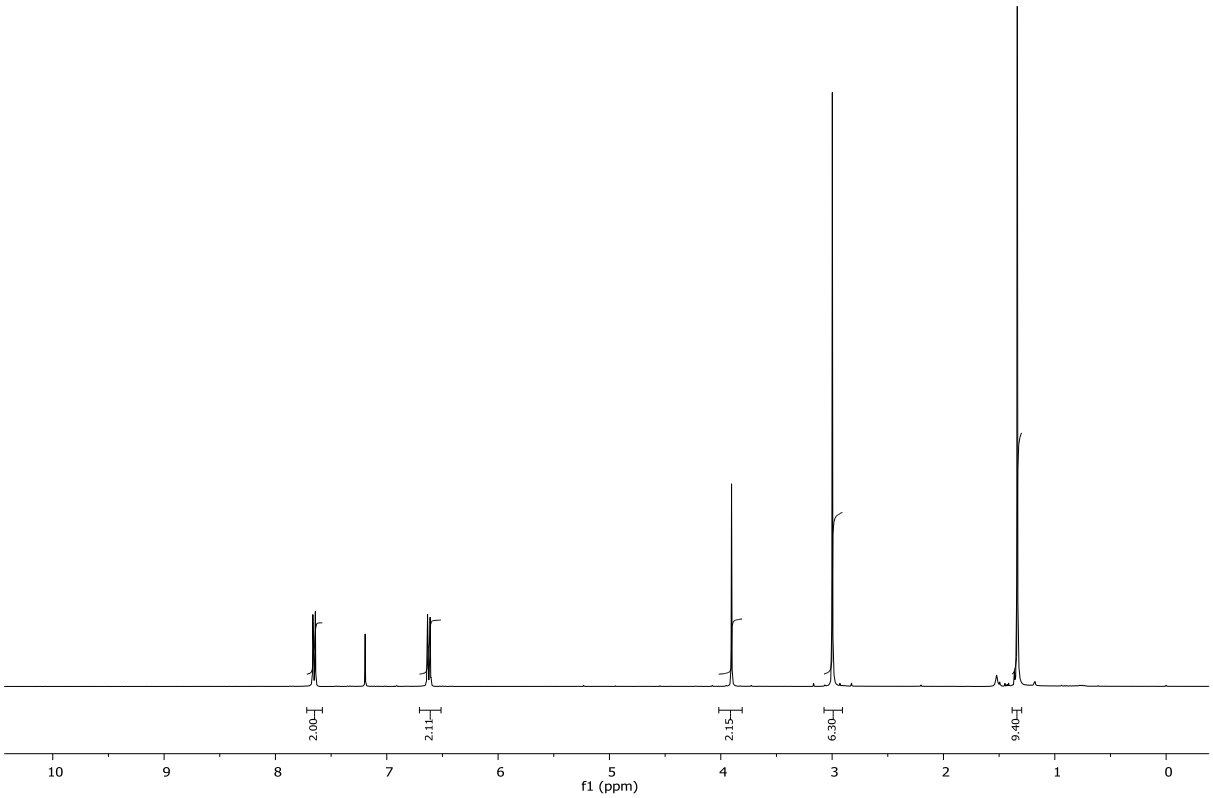
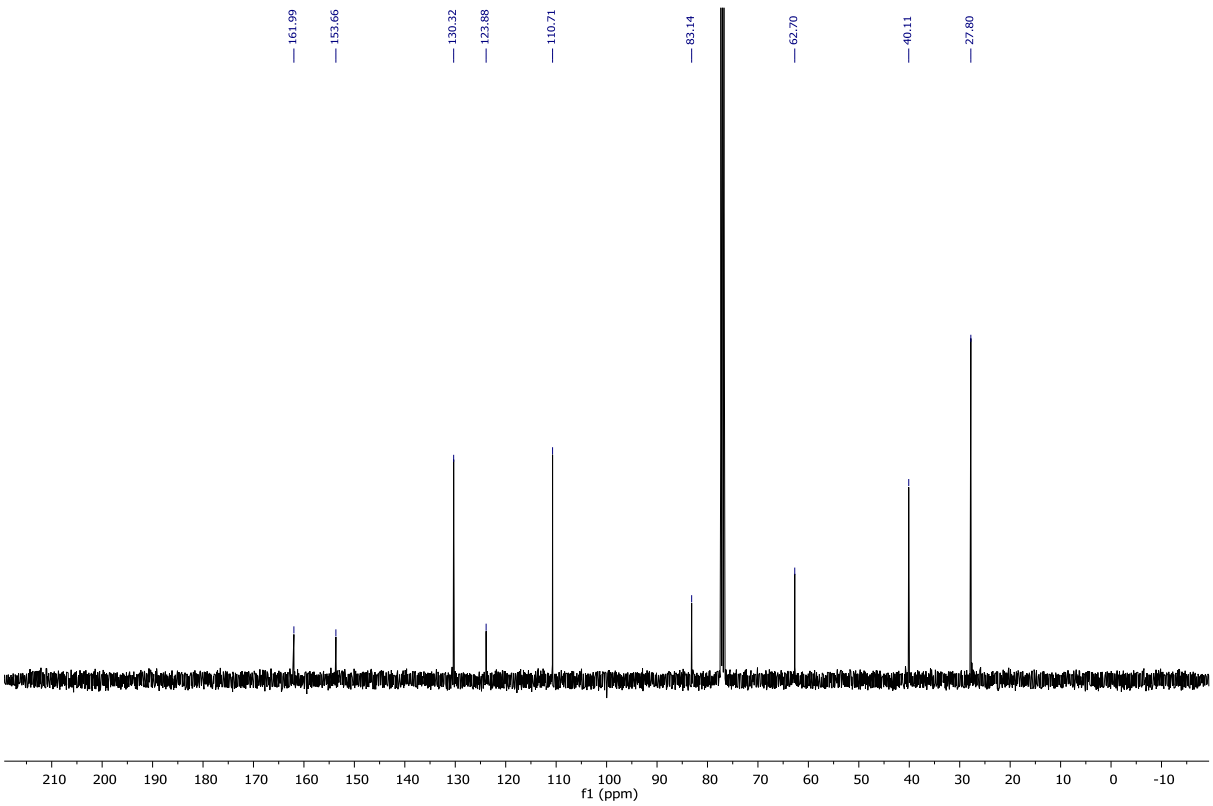
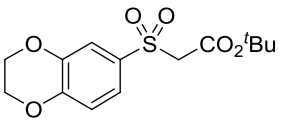
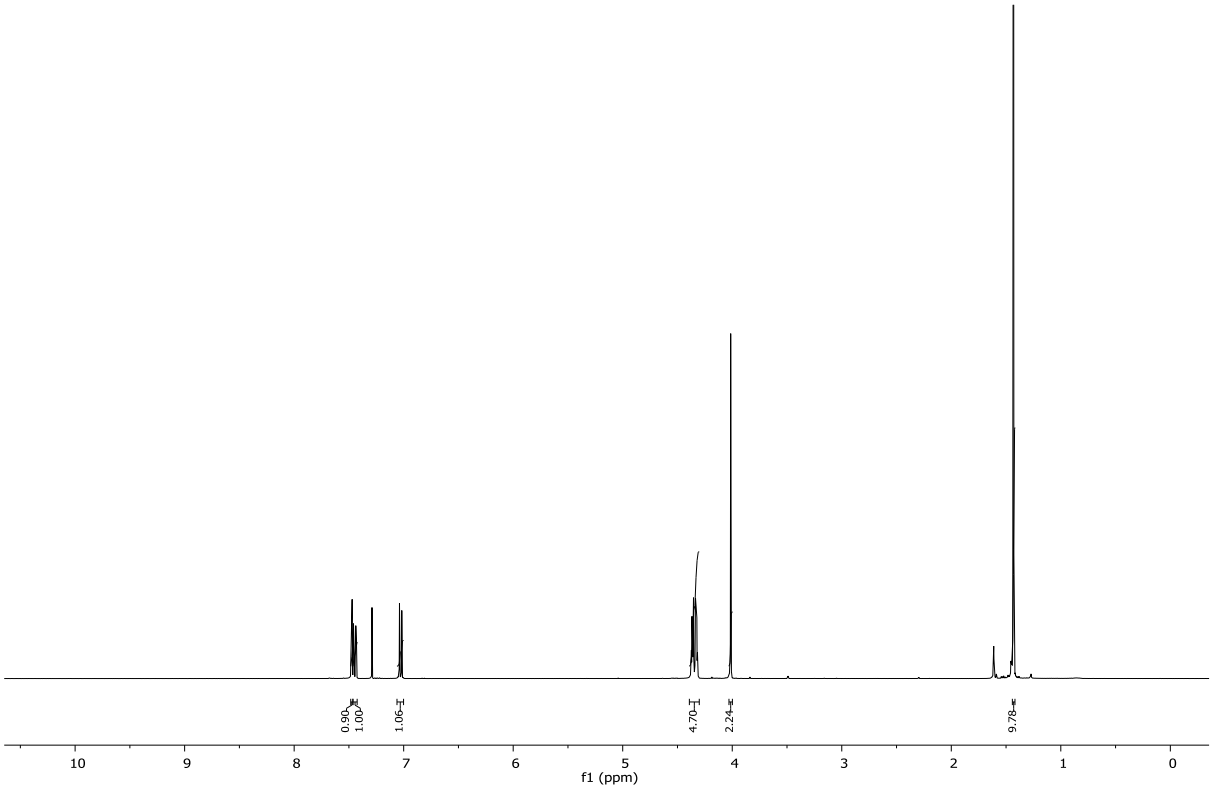
137.89
132.47
130.16
129.59
83.95
61.99
27.73
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

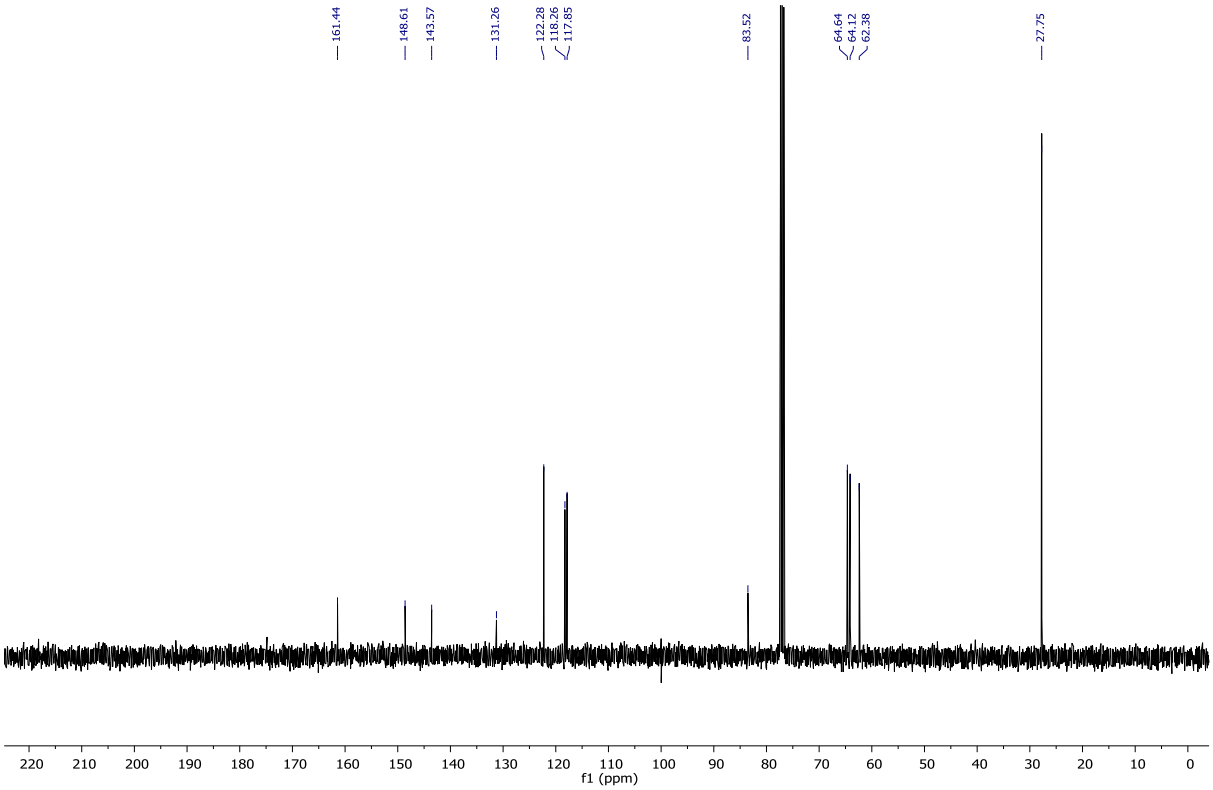

O
O
S
$CO_2{}^tBu$
$Me_2N$

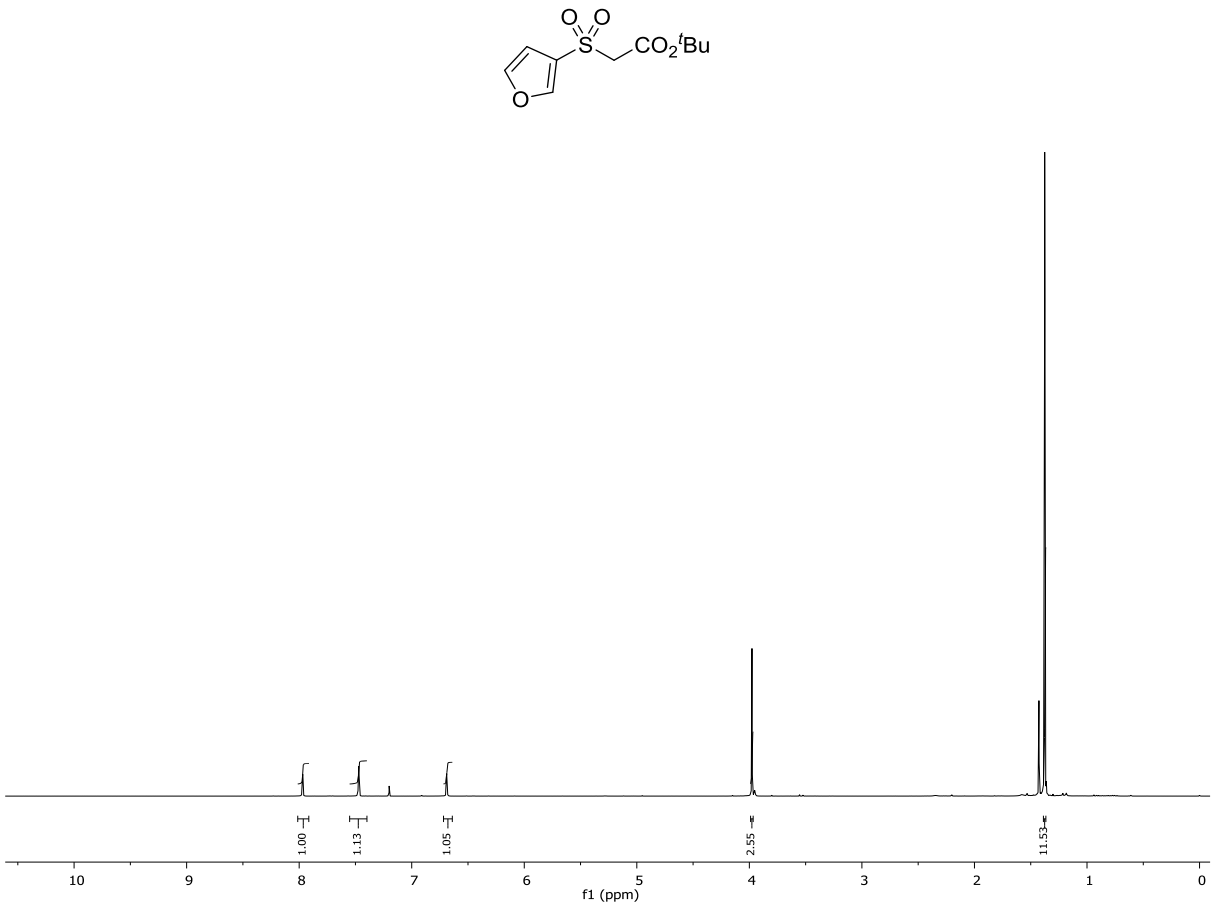

2.00
2.11
2.15
6.30
9.40
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

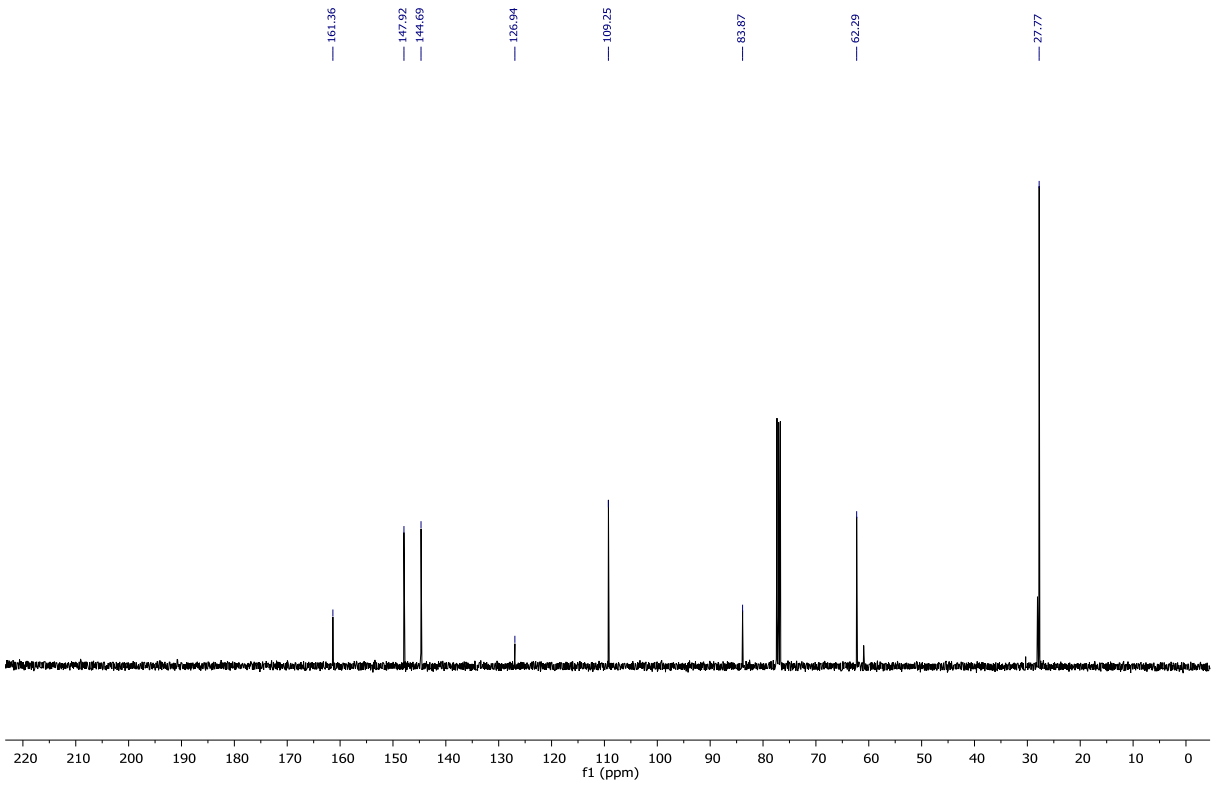

161.99
153.66
130.32
123.88
110.71
83.14
62.70
40.11
27.80
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


O
O
S
O
O
$CO_2{}^tBu$


0.90
1.00
1.06
4.70
2.24
9.78
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


161.44
148.61
143.57
131.26
122.28
118.26
117.85
83.52
64.64
64.12
62.38
27.75
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
CO2tBu
O
1.00
1.13
1.05
2.55
11.53
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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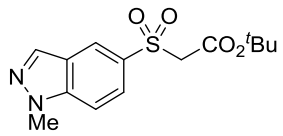
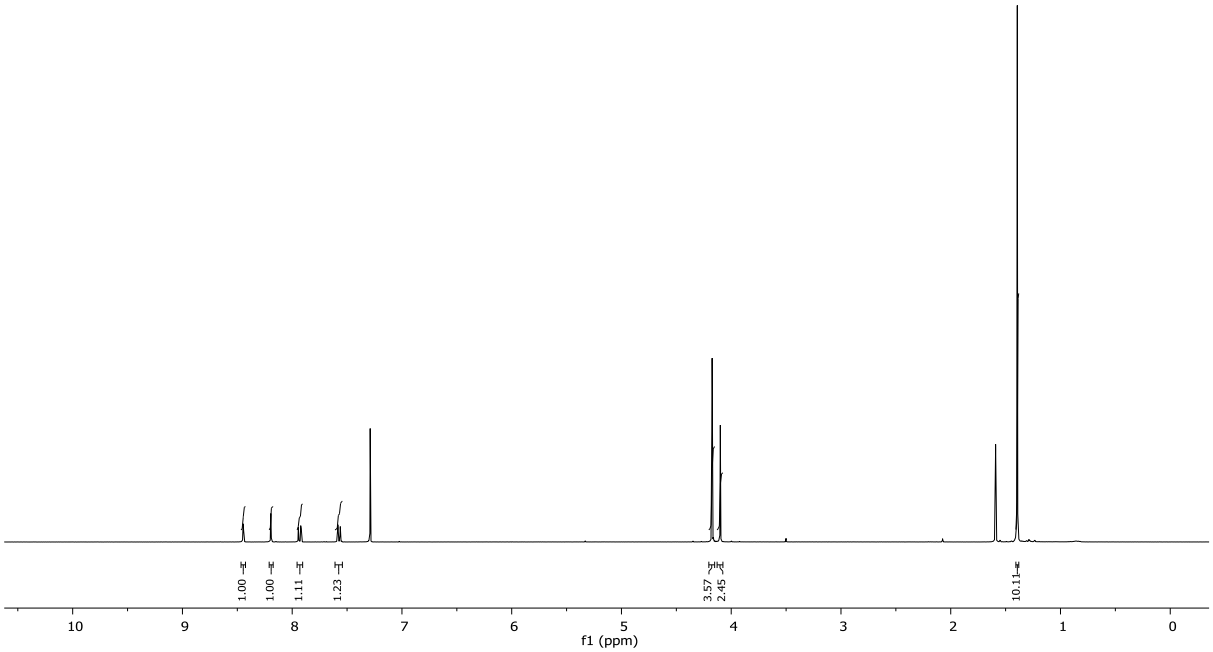
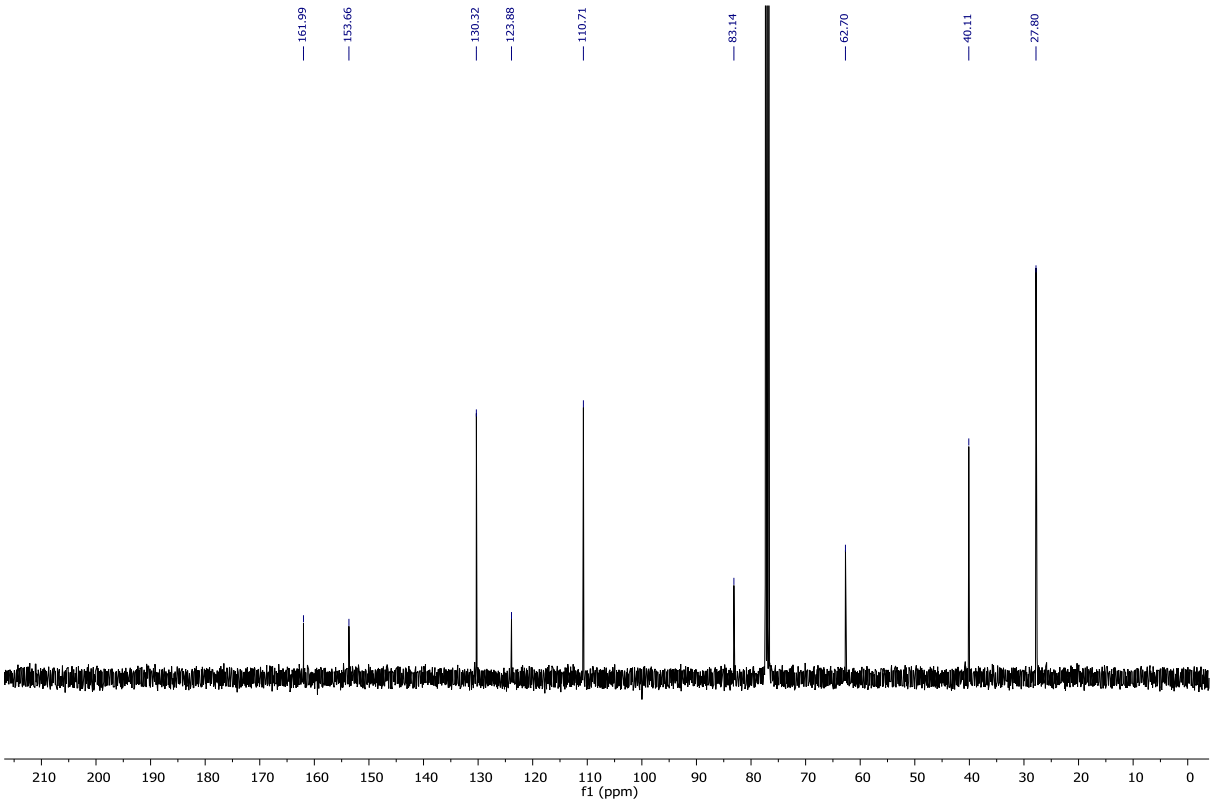
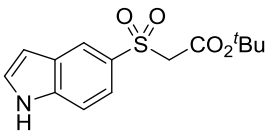
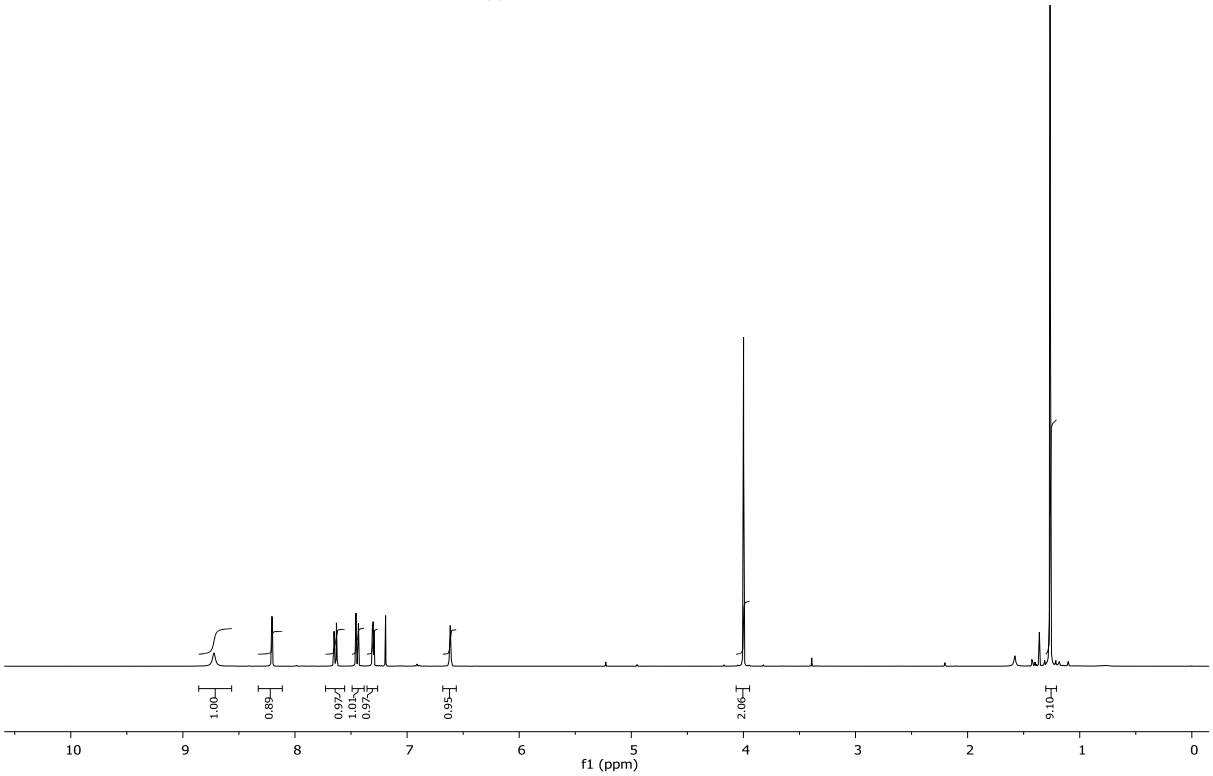
147.92
144.69
126.94
109.25
83.87
62.29
27.77
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

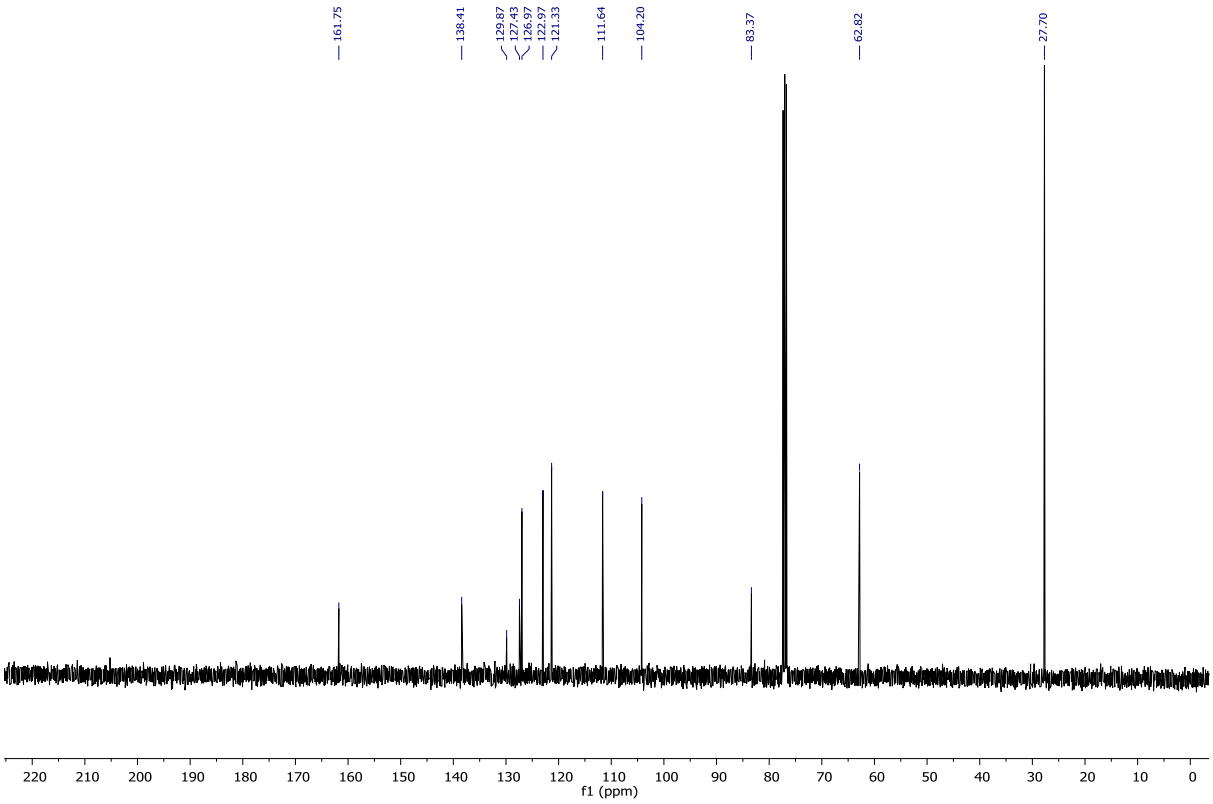

O
O
S
CO2tBu
N
N
Me

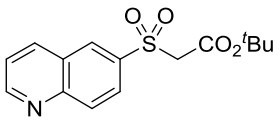

1.00
1.00
1.11
1.23
3.57
2.45
10.11
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

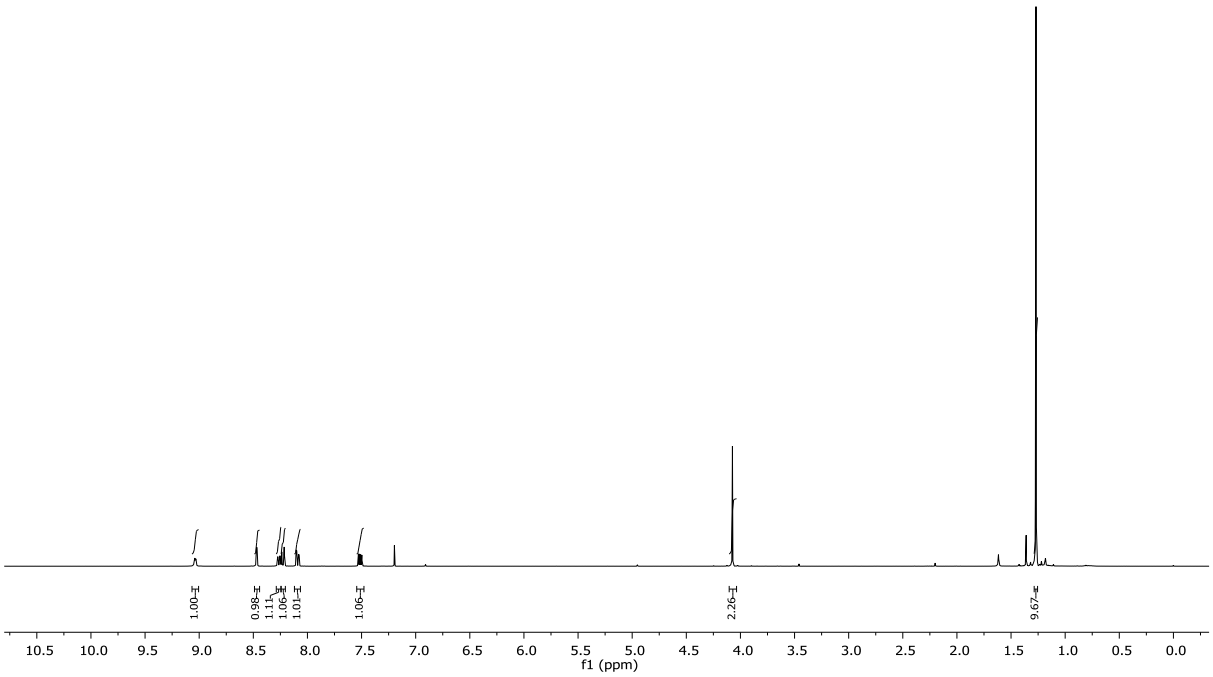

161.99
153.66
130.32
123.88
110.71
83.14
62.70
40.11
27.80
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

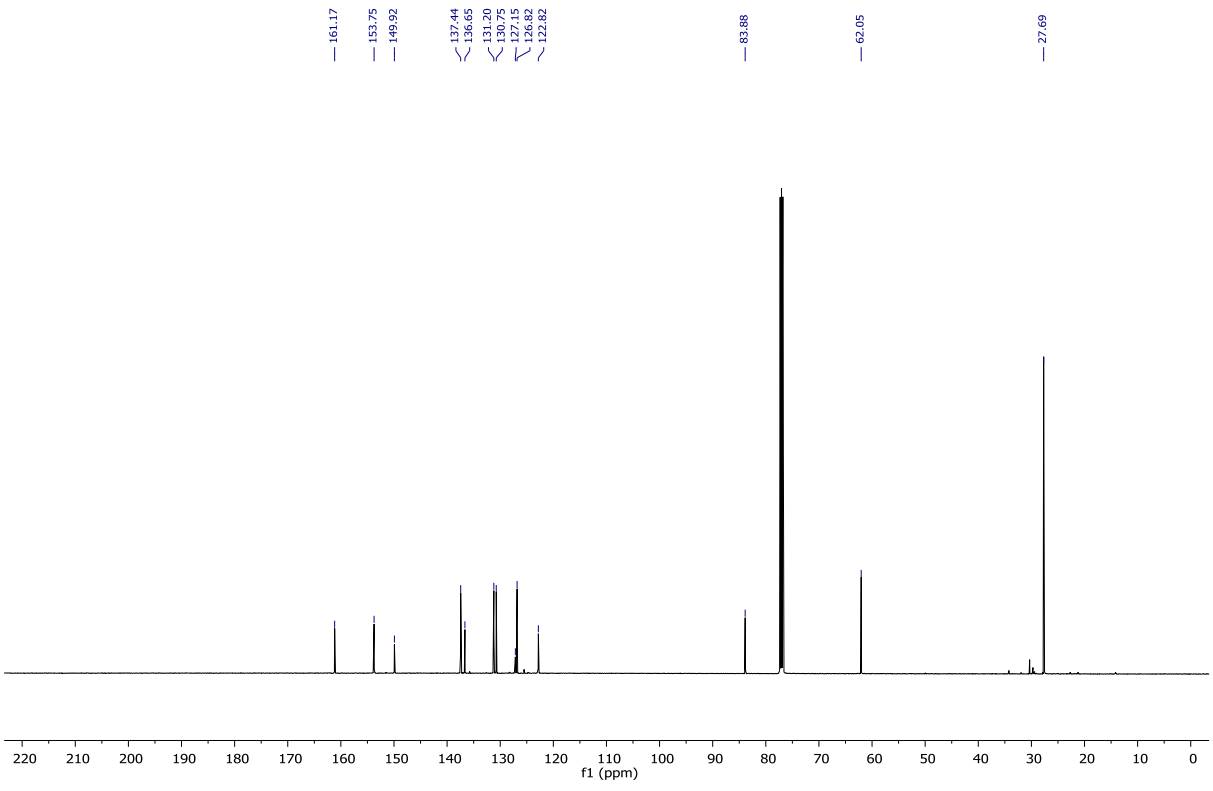

O
O
S
CO2tBu
N
H

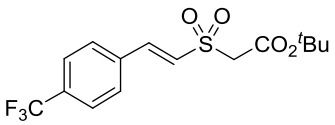

1.00
0.89
0.97
1.01
0.97
0.95
2.06
9.10
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

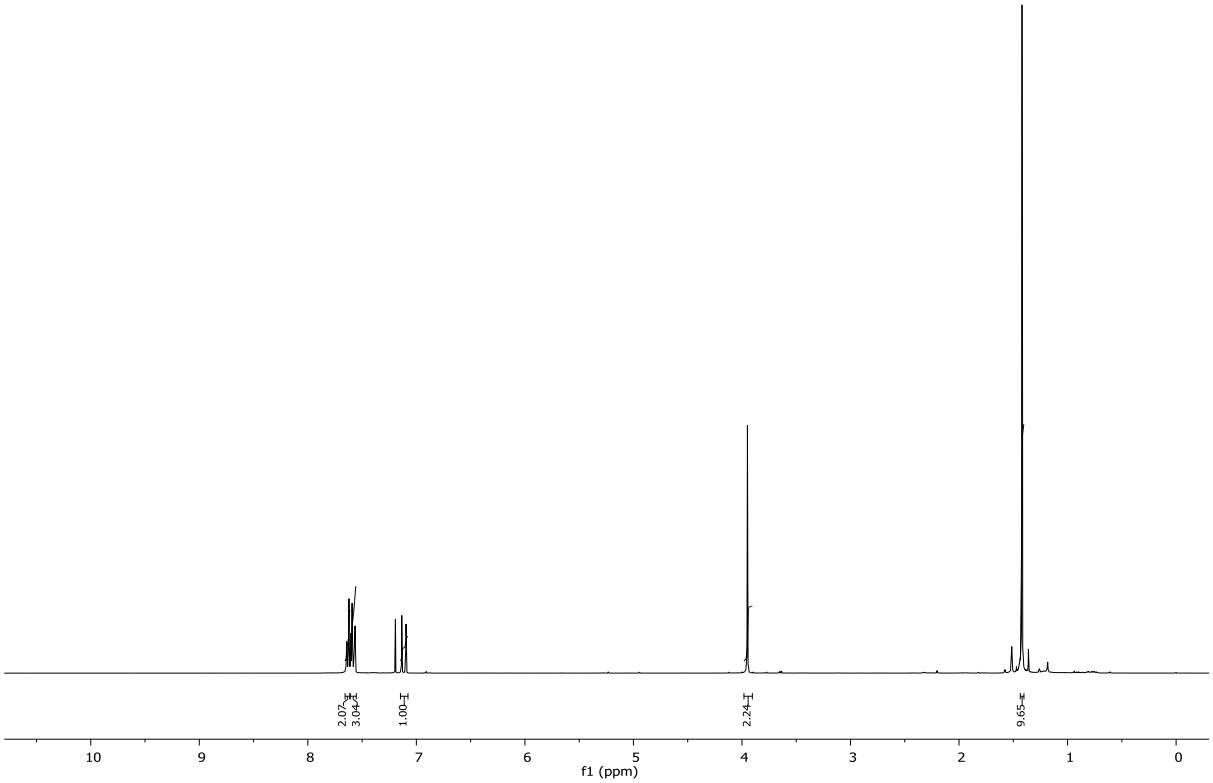

161.75
138.41
129.87
127.43
126.97
122.97
121.33
111.64
104.20
83.37
62.82
27.70
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

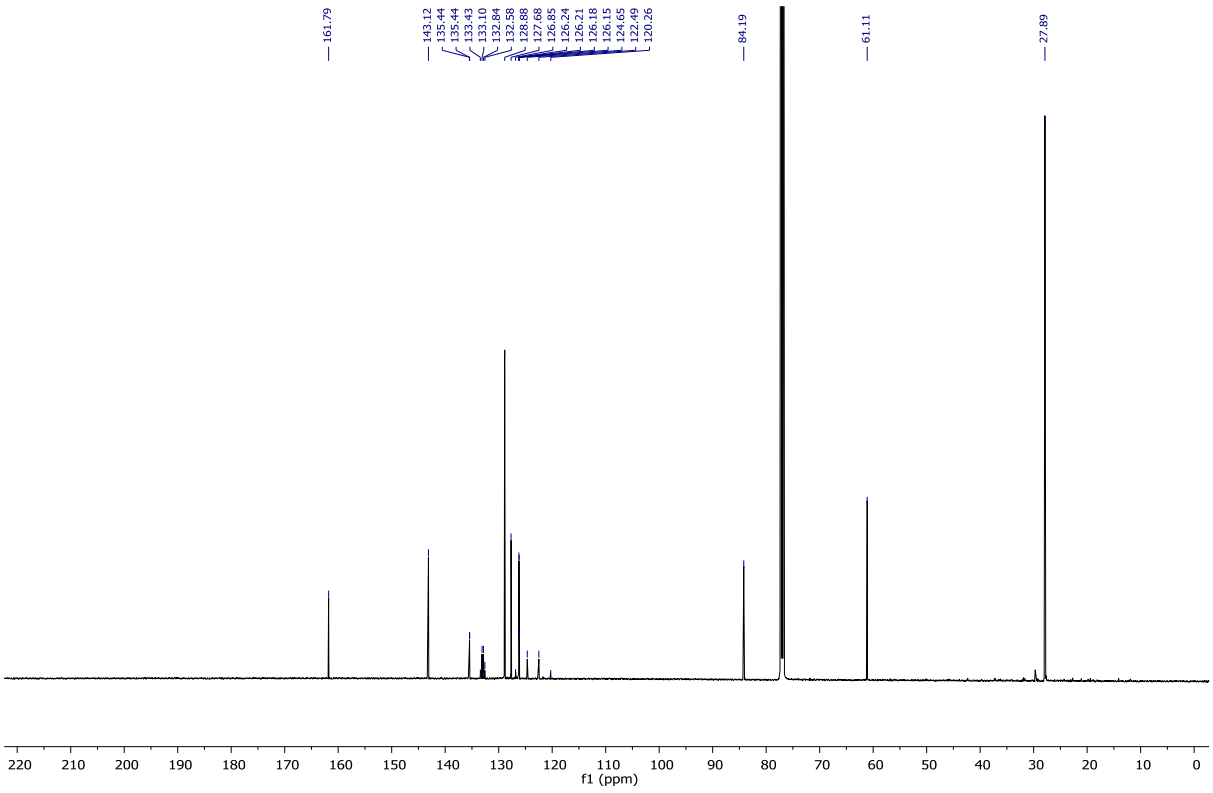

O
O
S
CO2tBu
N

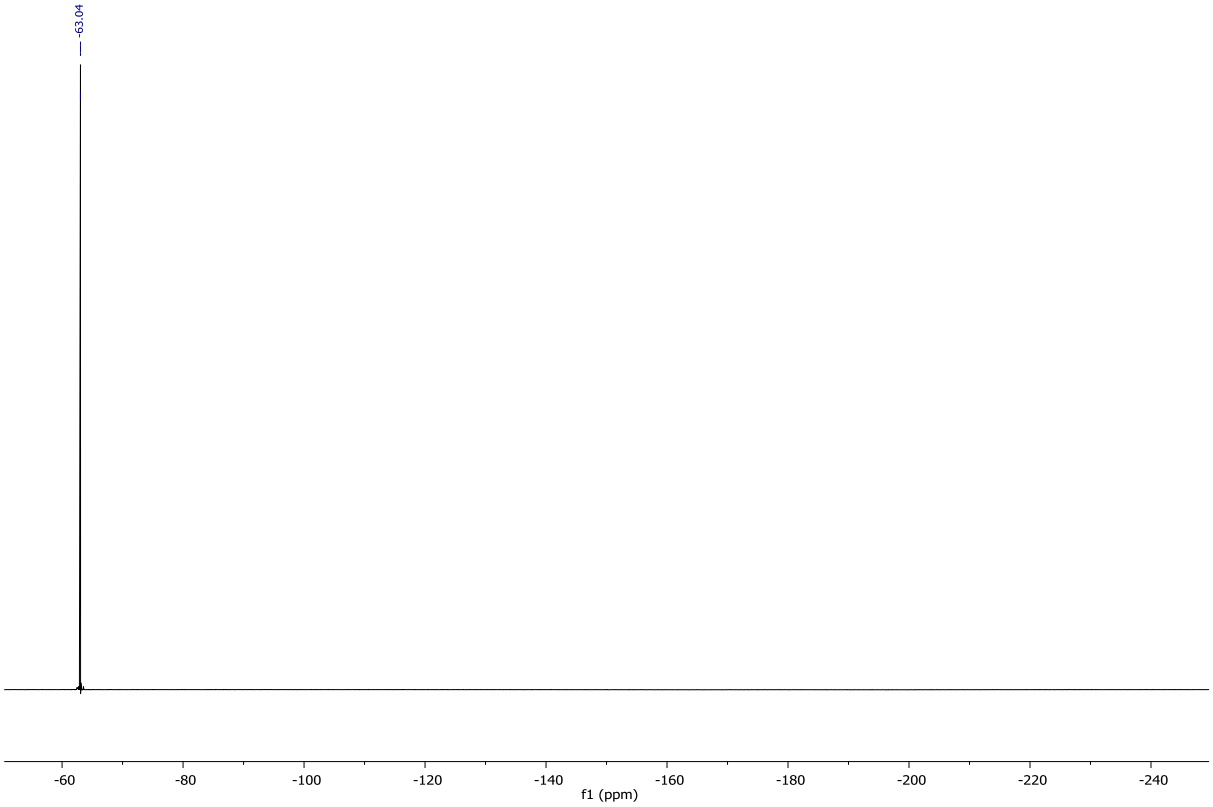

1.00
0.98
1.11
1.06
1.01
1.06
2.26
9.67
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

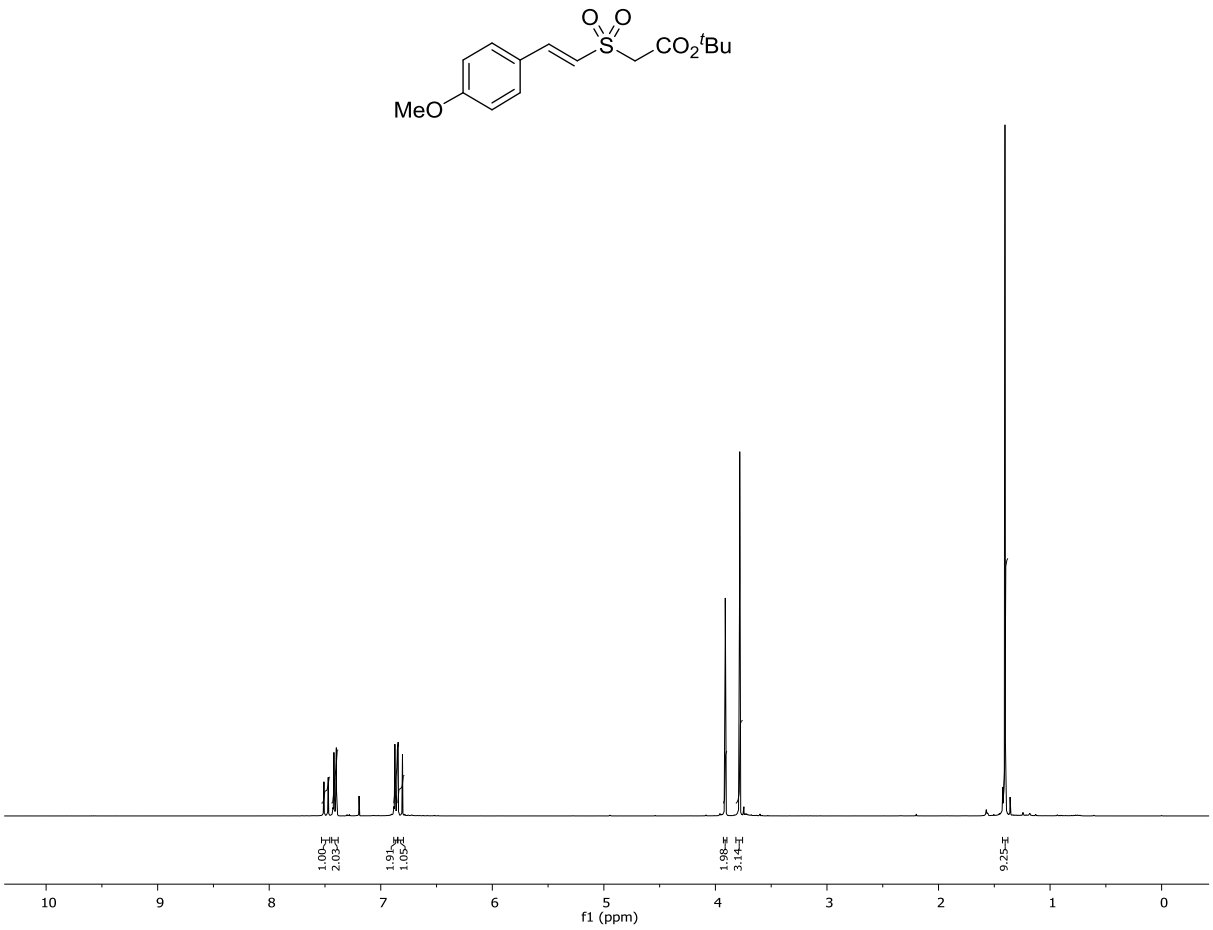

161.17
153.75
149.92
137.44
136.65
131.20
130.75
127.15
126.82
122.82
83.88
62.05
27.69
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

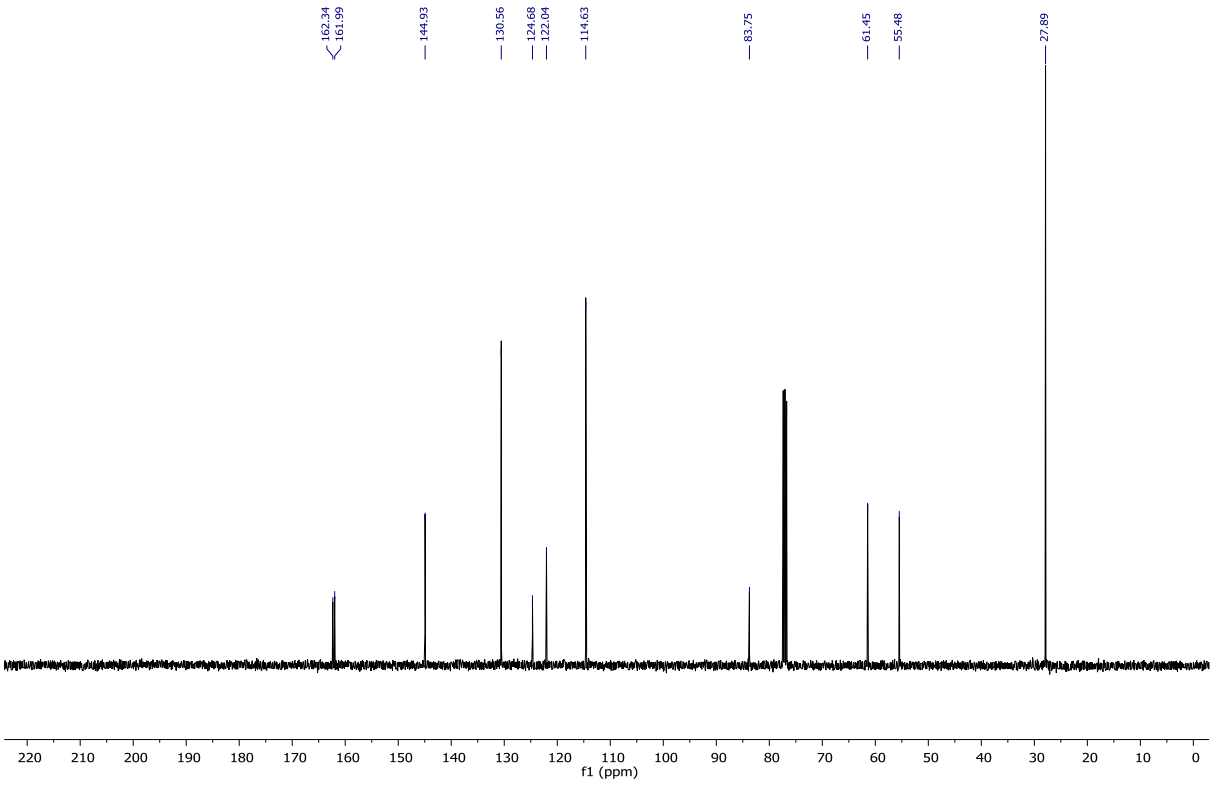

O
O
S
CO2tBu
F3C

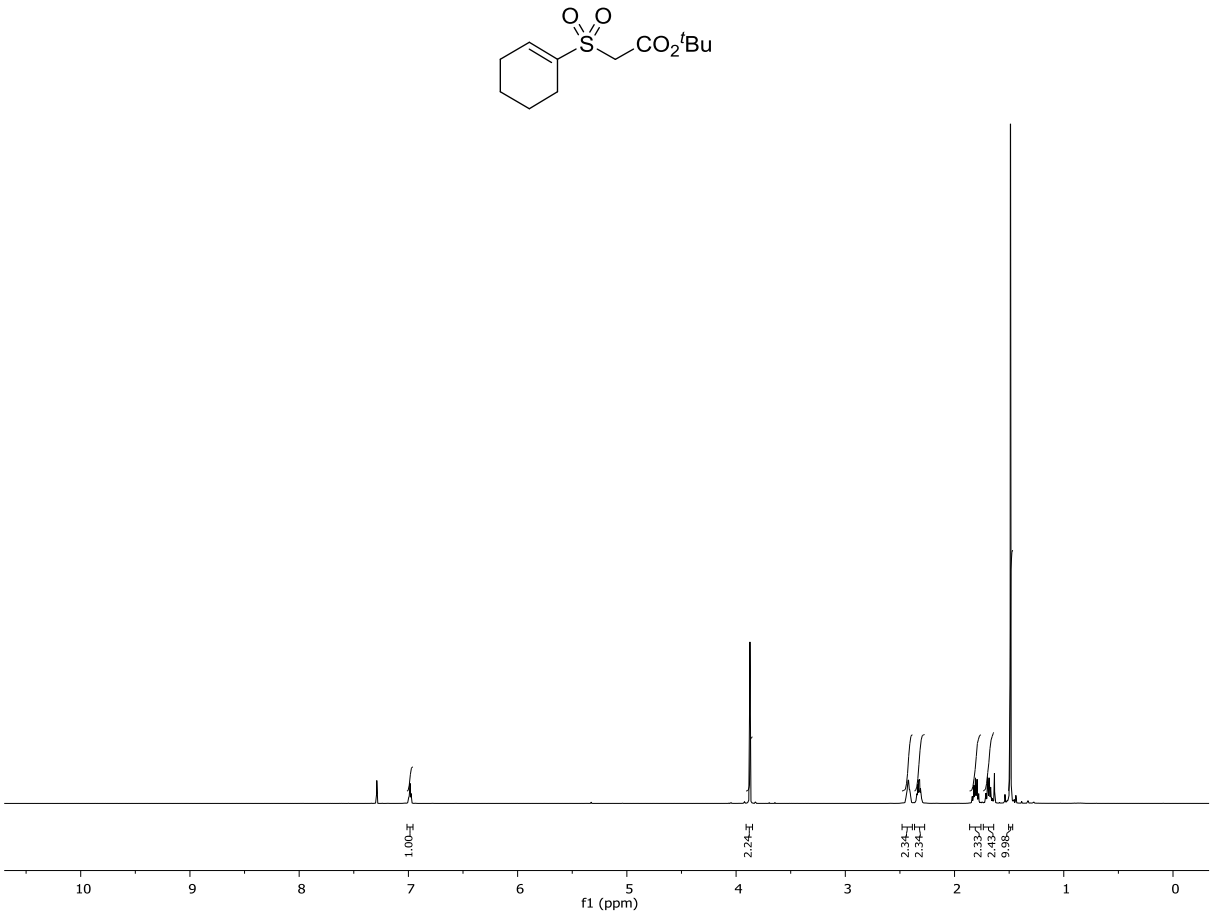

2.07
3.04
1.00
2.24
9.65
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

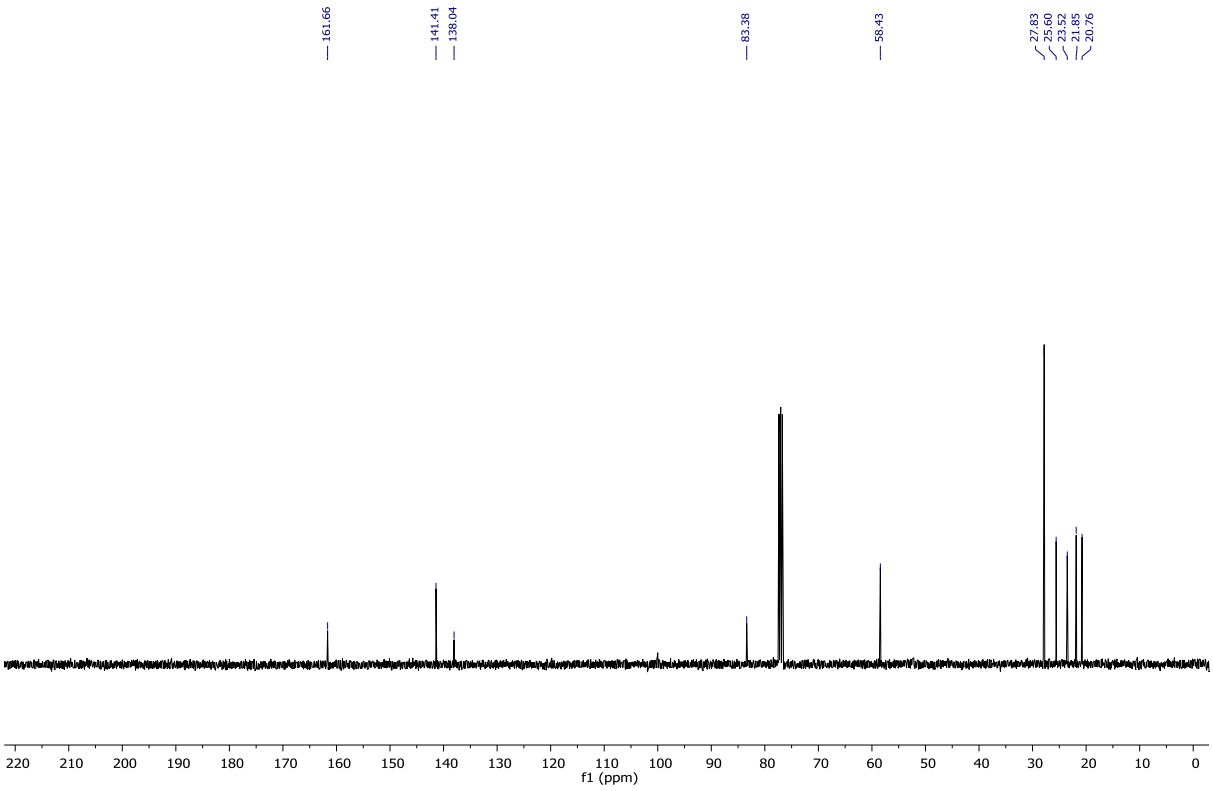

161.79
143.12
135.44
135.44
133.43
133.10
132.84
132.58
128.88
127.68
126.85
126.24
126.21
126.18
126.15
124.65
122.49
120.26
84.19
61.11
27.89
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

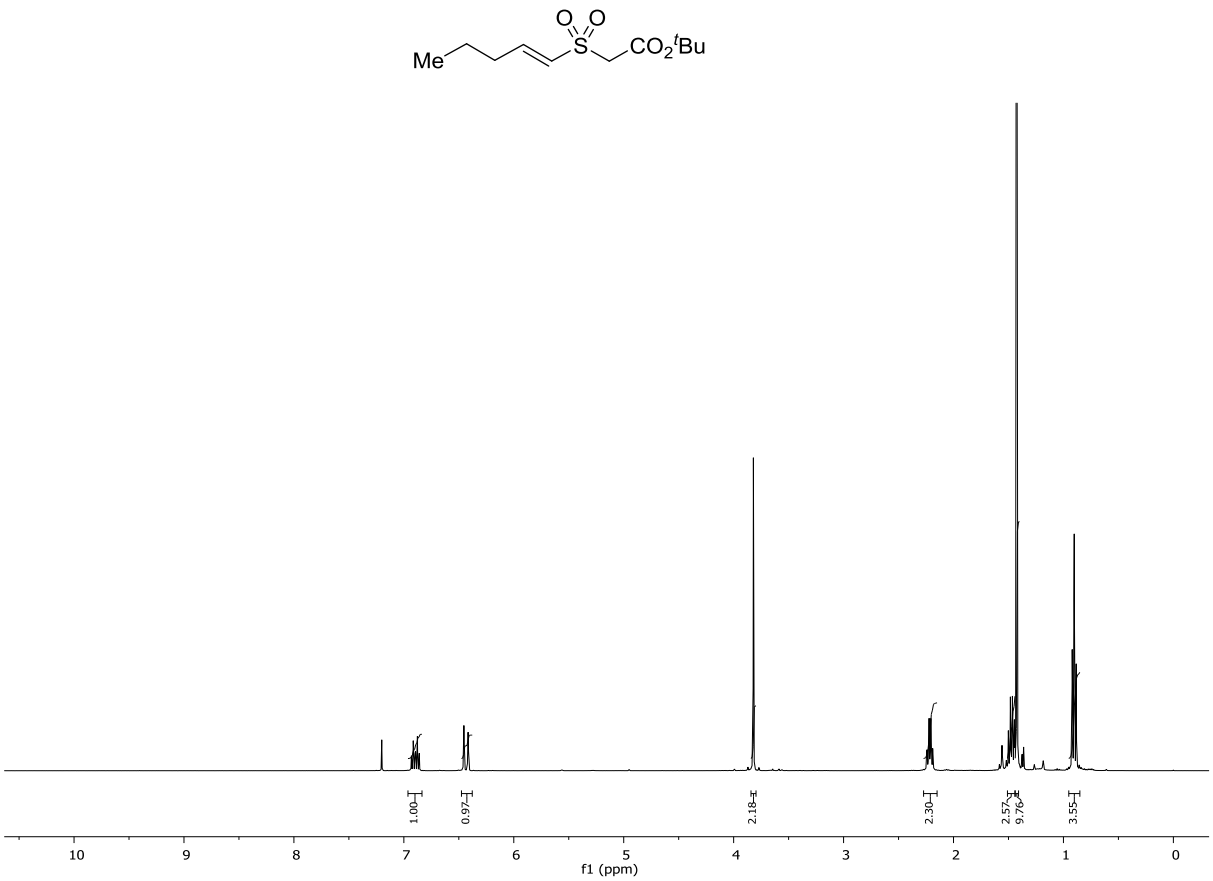

-63.04
-60
-80
-100
-120
-140
-160
-180
-200
-220
-240
f1 (ppm)

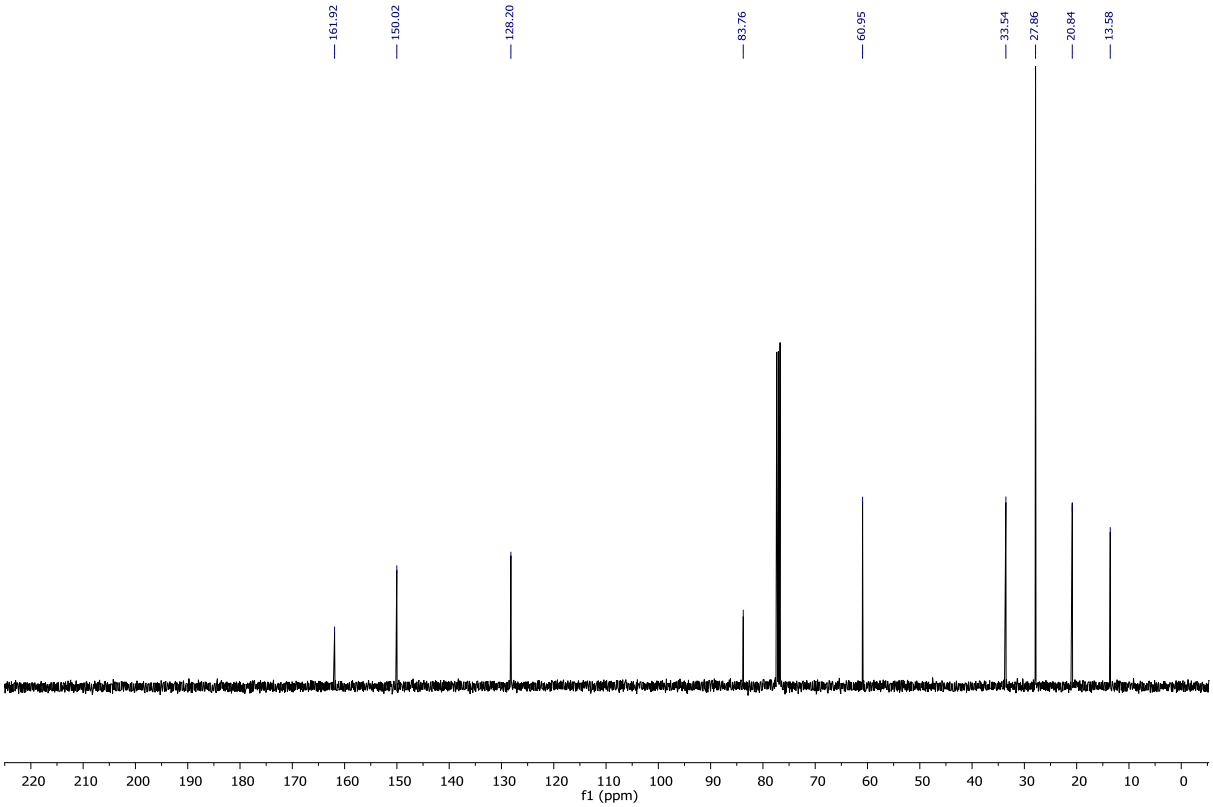

MeO
O
O
S
CO2tBu
1.00
2.03
1.91
1.05
1.98
3.14
9.25
f1 (ppm)

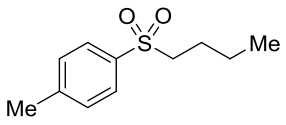

162.34
161.99
144.93
130.56
124.68
122.04
114.63
83.75
61.45
55.48
27.89
f1 (ppm)

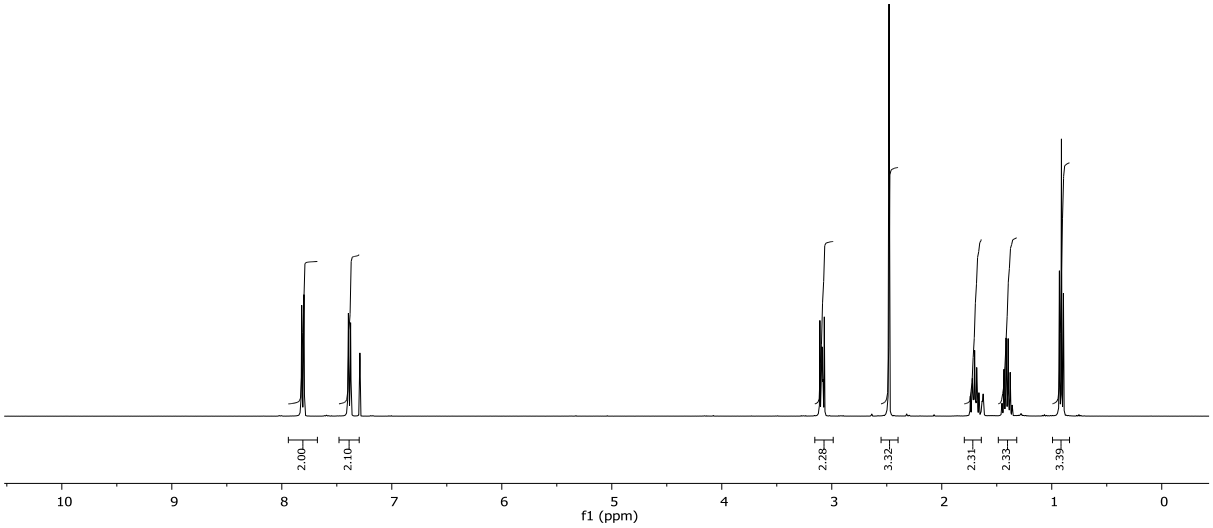

O
O
S
CO2tBu
1.00
2.24
2.34
2.34
2.33
2.43
9.98
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)

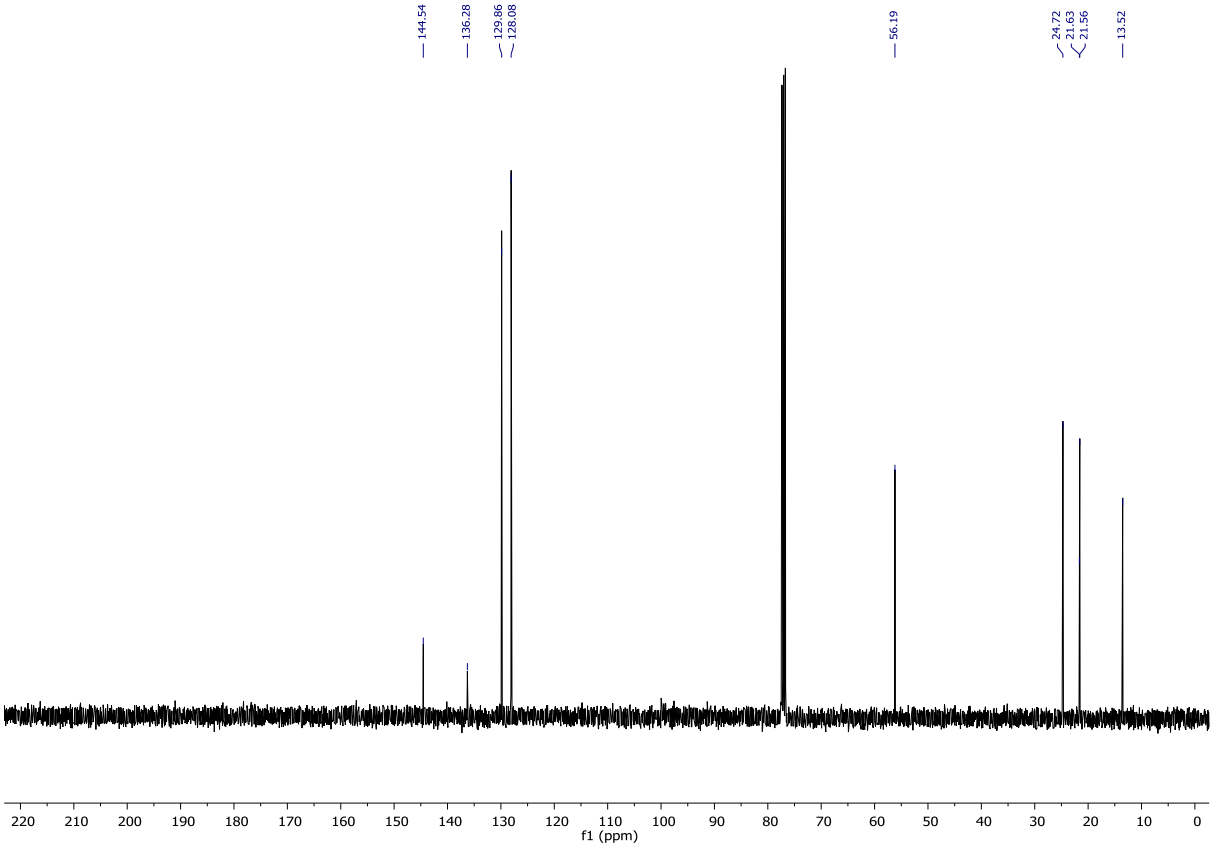

161.66
141.41
138.04
83.38
58.43
27.83
25.60
23.52
21.85
20.76
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

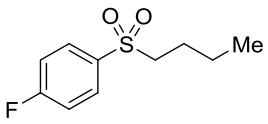

Me
O
O
S
CO2tBu
1.00
0.97
2.18
2.30
2.57
9.76
3.55
f1 (ppm)

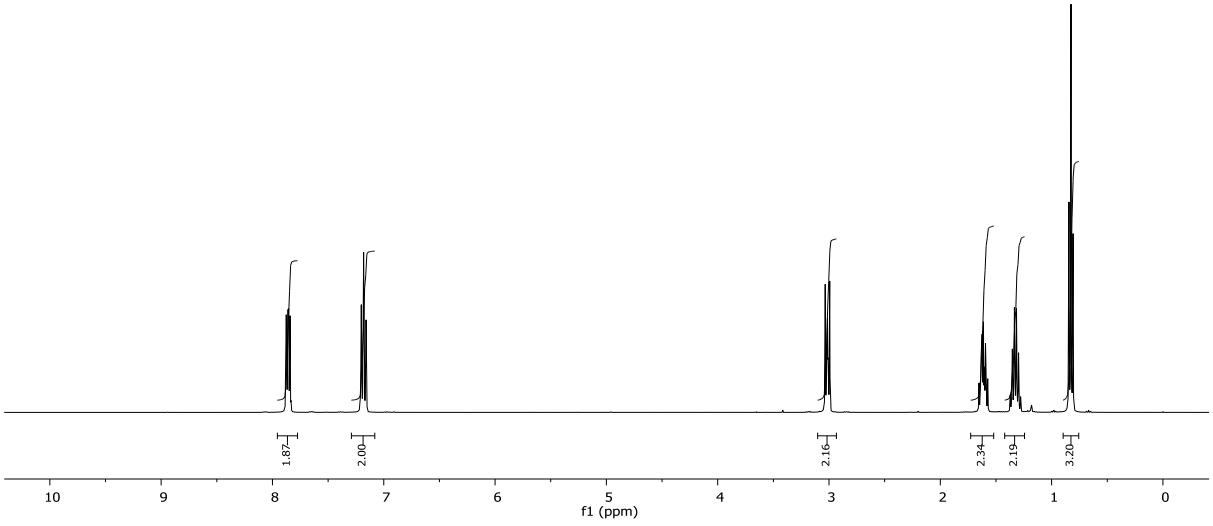

161.92
150.02
128.20
83.76
60.95
33.54
27.86
20.84
13.58
f1 (ppm)


O
O
S
Me
Me


2.00
2.10
2.28
3.32
2.31
2.33
3.39
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


144.54
136.28
129.86
128.08
56.19
24.72
21.63
21.56
13.52
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


O
O
S
Me
F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3.20
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4
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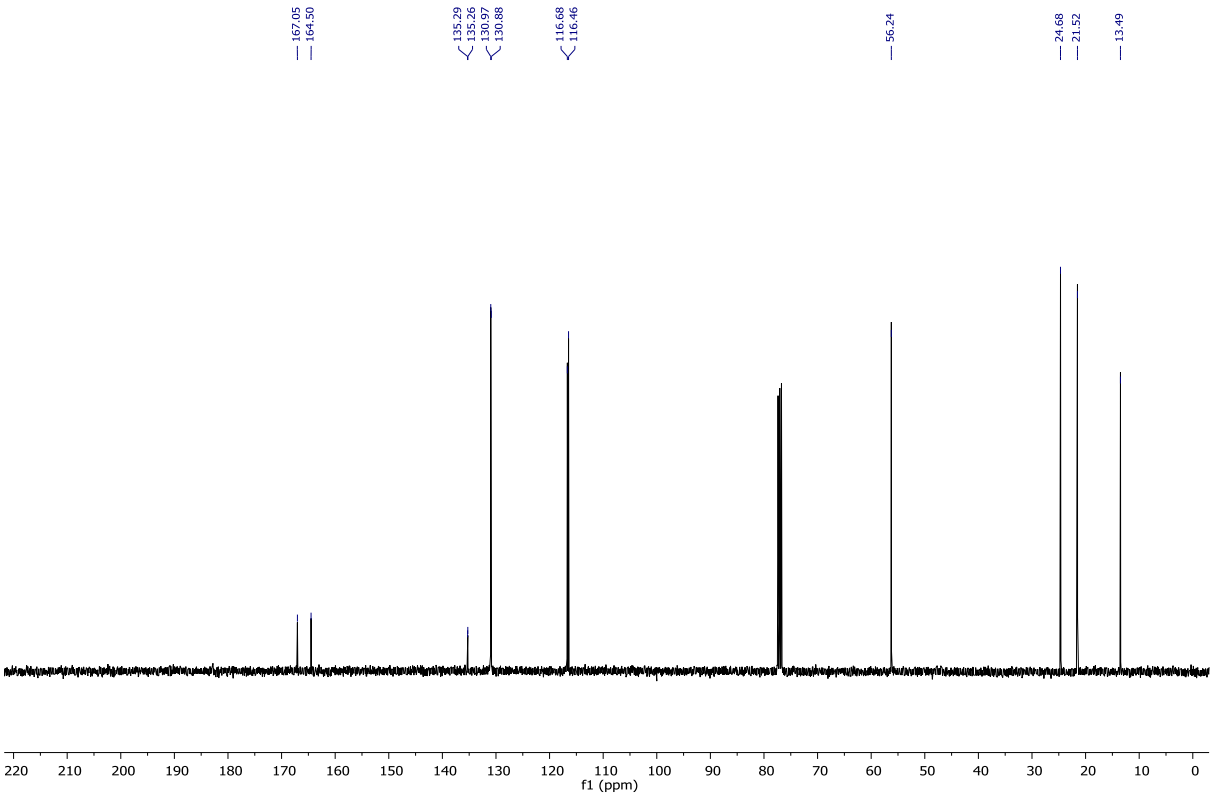
f1 (ppm)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164.50
135.29
135.26
130.97
130.88
116.68
116.46
56.24
24.68
21.52
13.49
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210
200
190
180
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90
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50
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10
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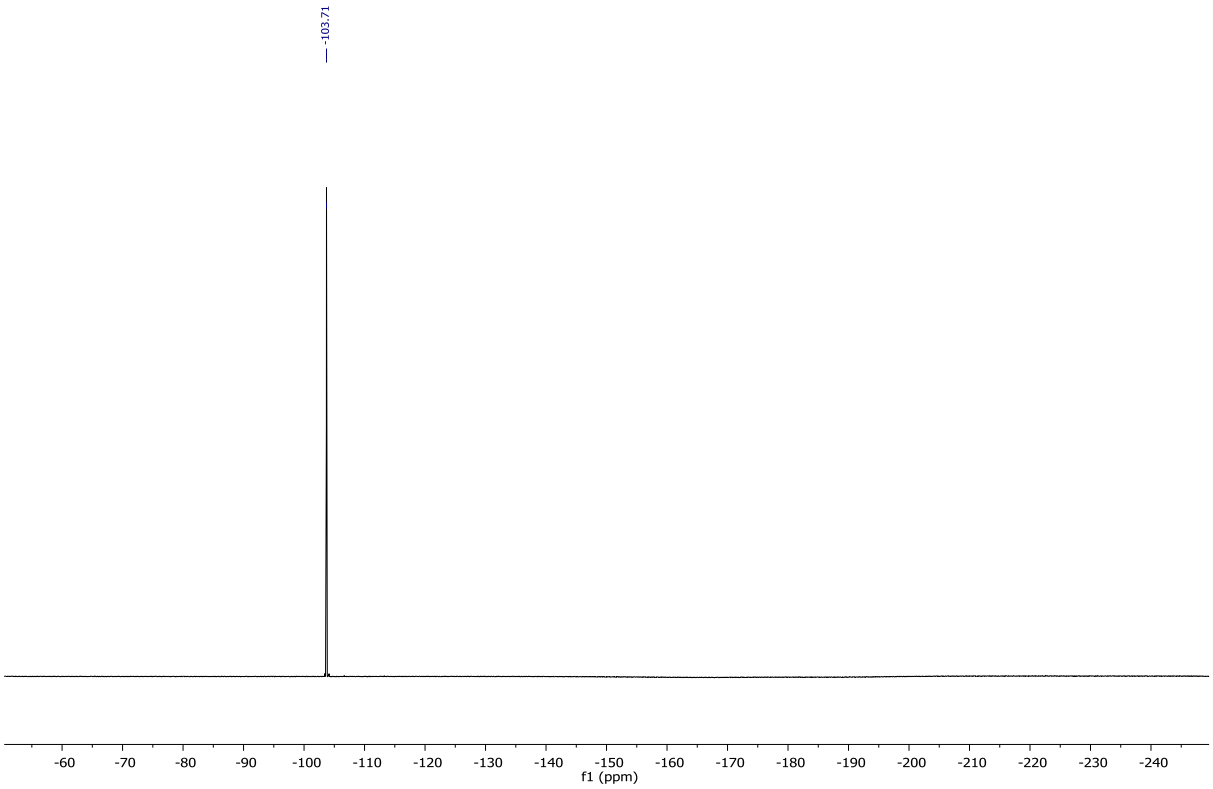
f1 (ppm)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-90
-100
-110
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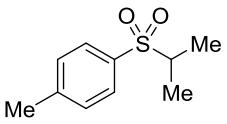
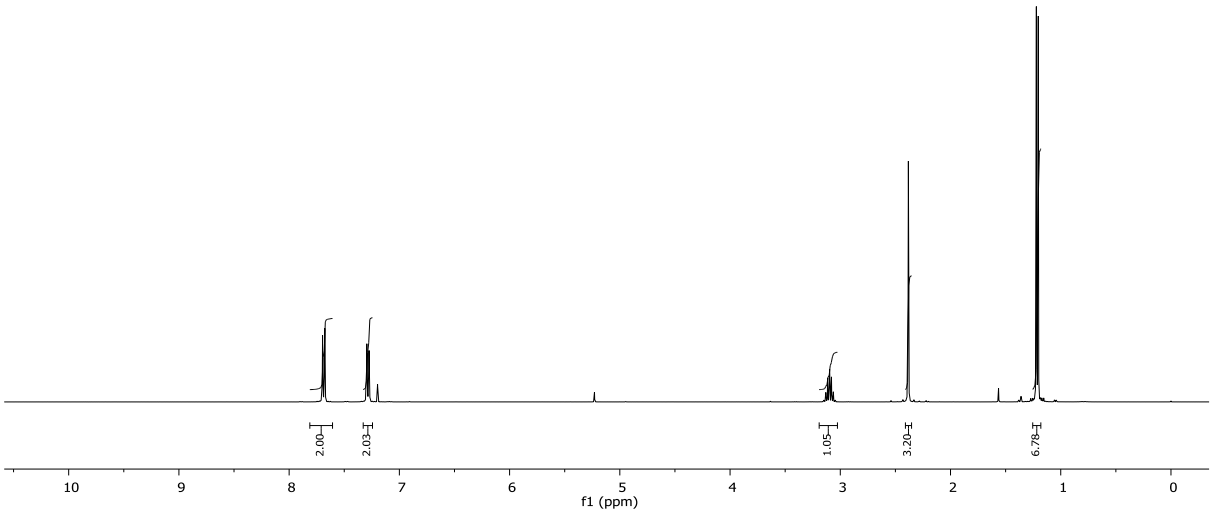
-160
-170
-180
-190
-200
-210
-220
-230
-240
f1 (ppm)


O
O
S
Me
Me
Me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8
7
6
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4
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1
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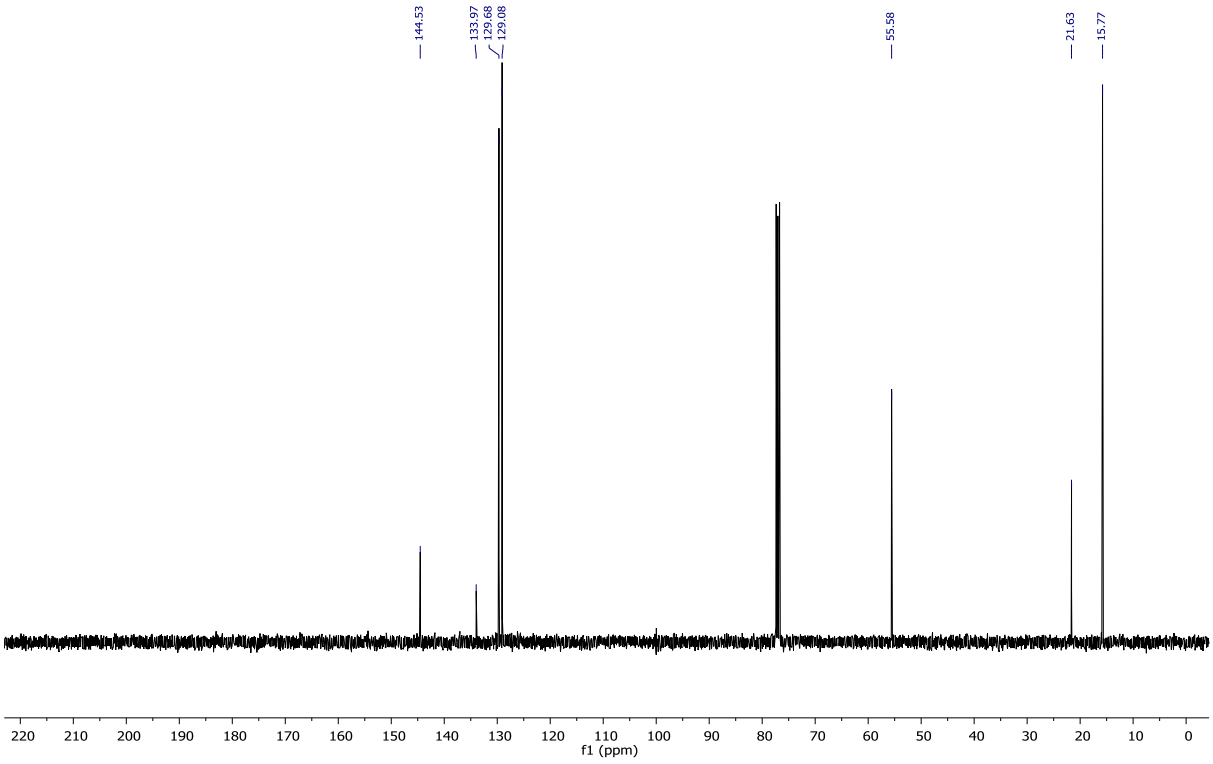
f1 (ppm)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129.68
129.08
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21.63
15.77
220
210
200
190
180
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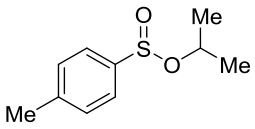
f1 (ppm)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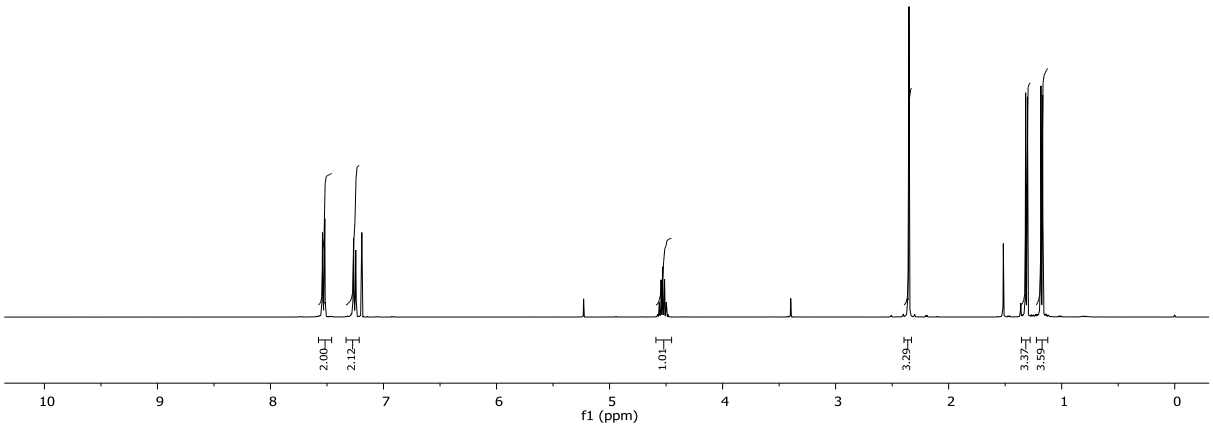
Me
S
O
Me
Me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9
8
7
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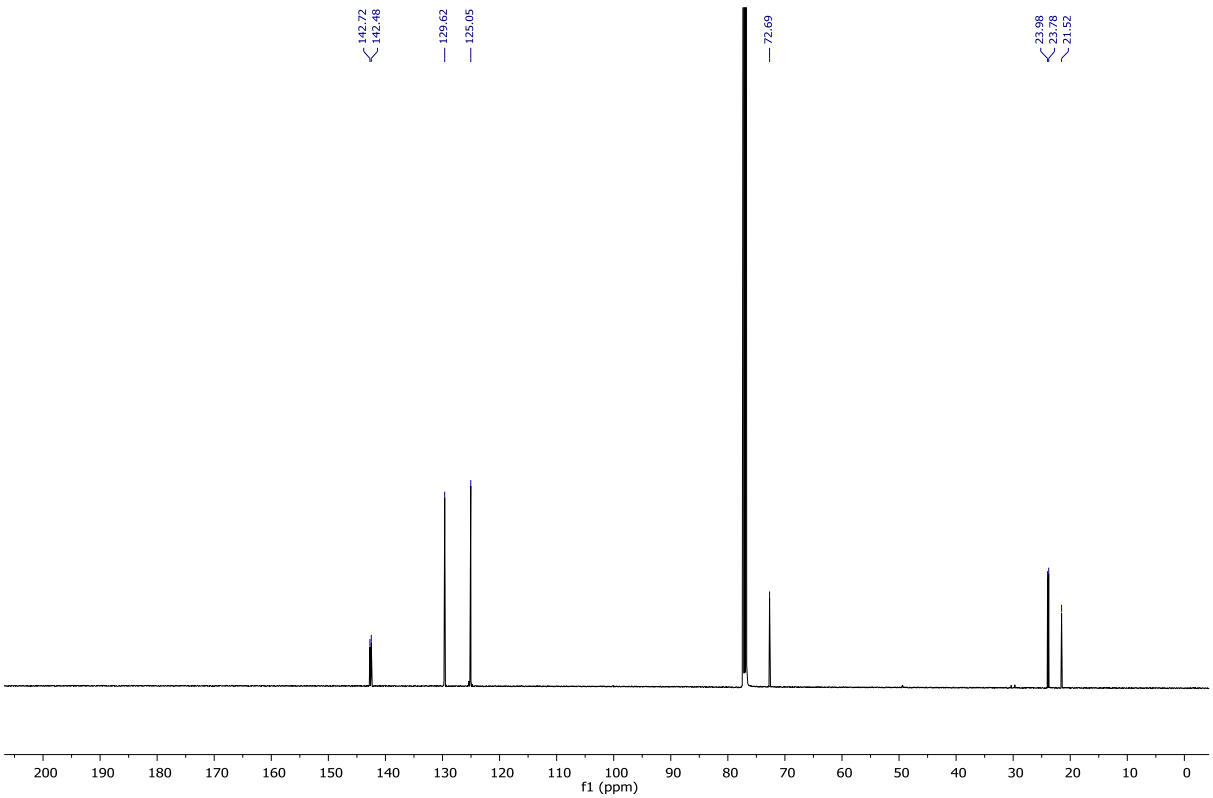
5
4
3
2
1
0
f1 (ppm)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129.62
125.05
72.69
23.98
23.78
21.52
200
190
180
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150
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130
120
110
100
90
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70
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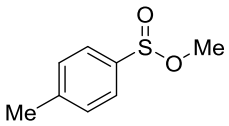
50
40
30
20
10
0
f1 (ppm)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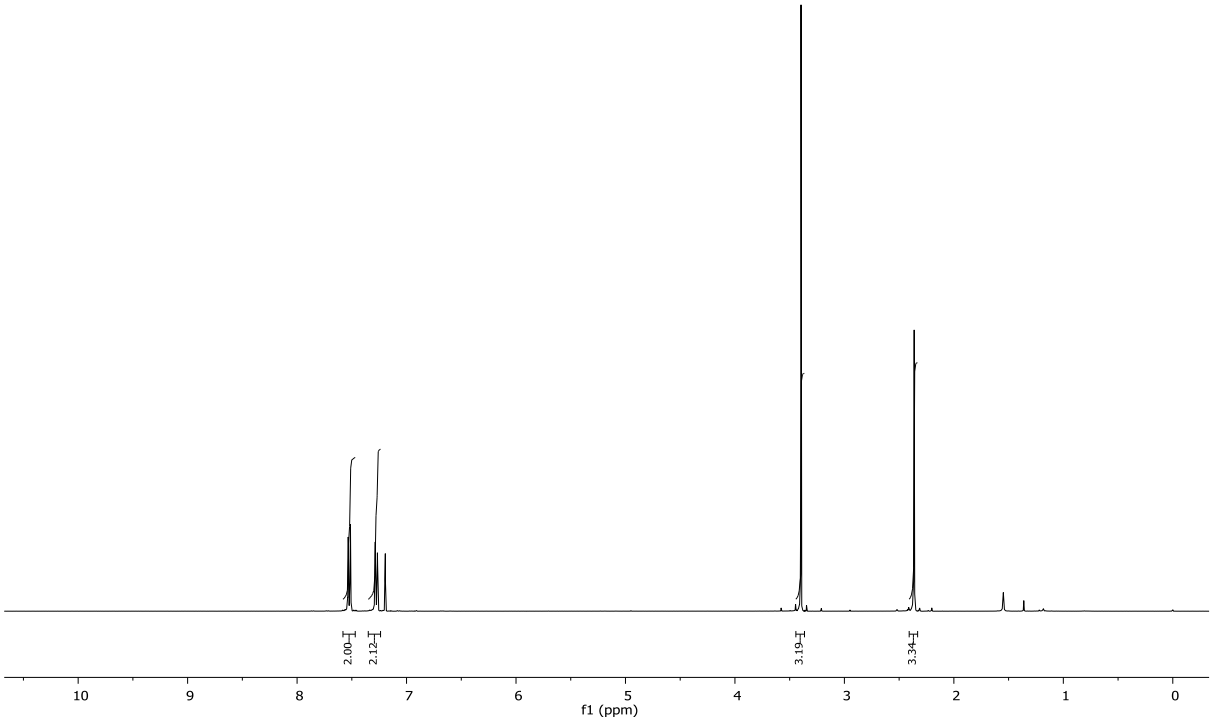
S
O
Me
Me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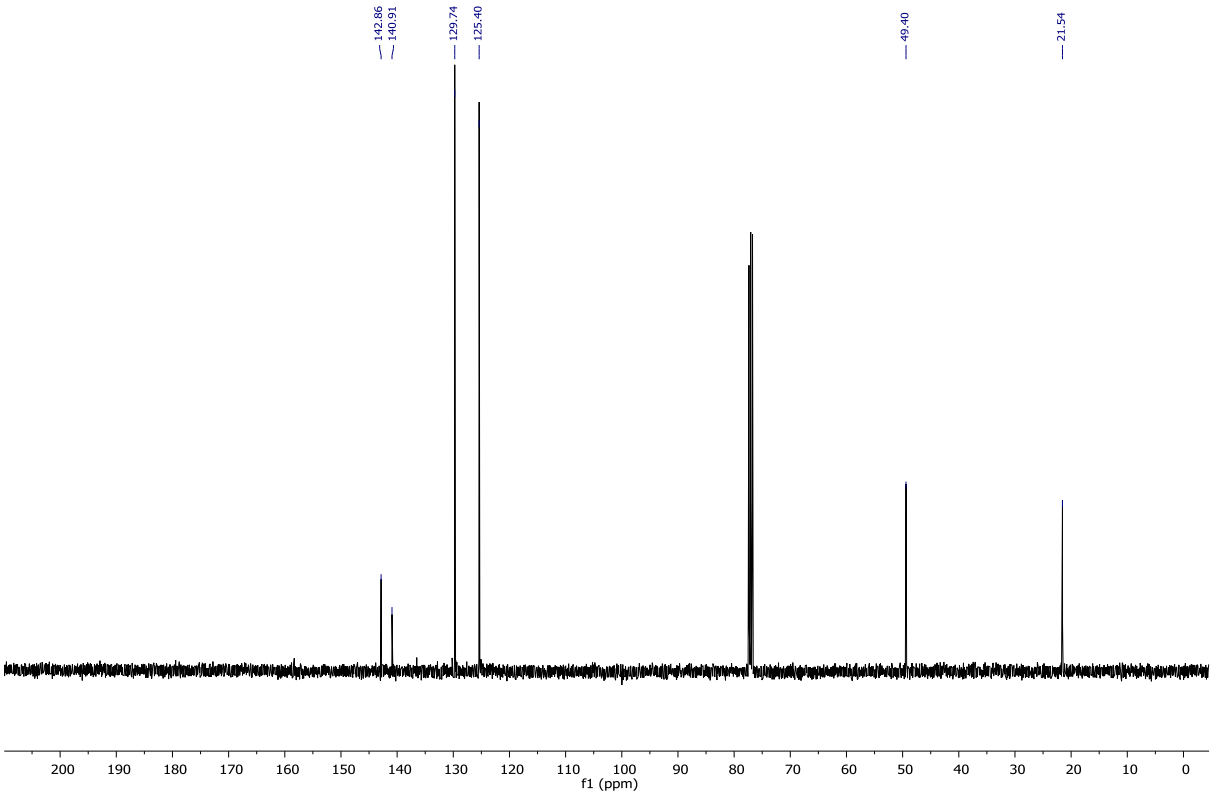
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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140.91
129.74
125.40
49.40
21.54
200
190
180
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160
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120
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90
80
70
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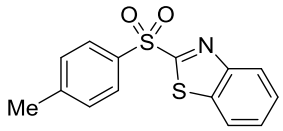
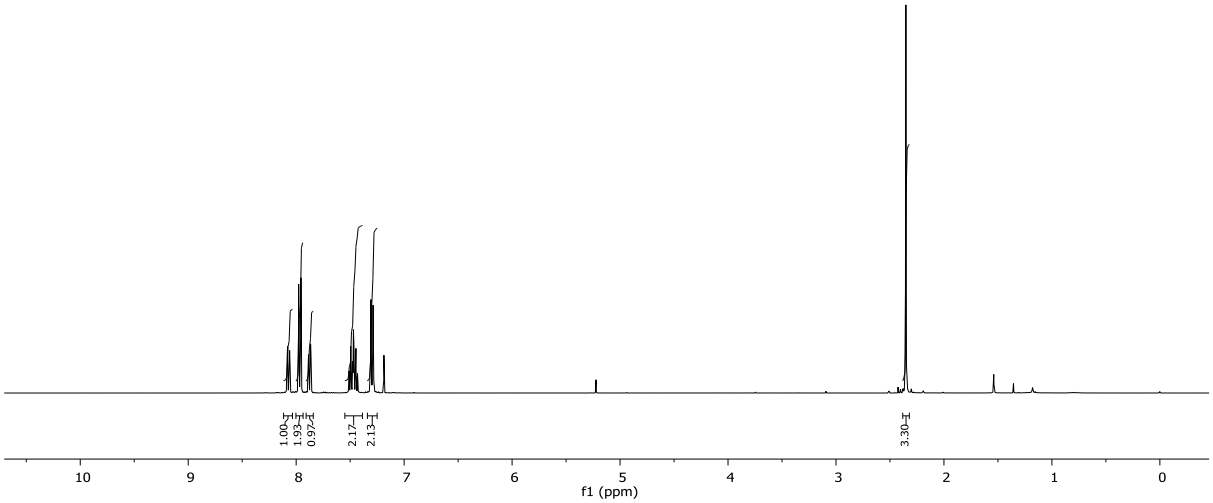
50
40
30
20
10
0
f1 (ppm)


O
O
S
N
S
Me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1.93
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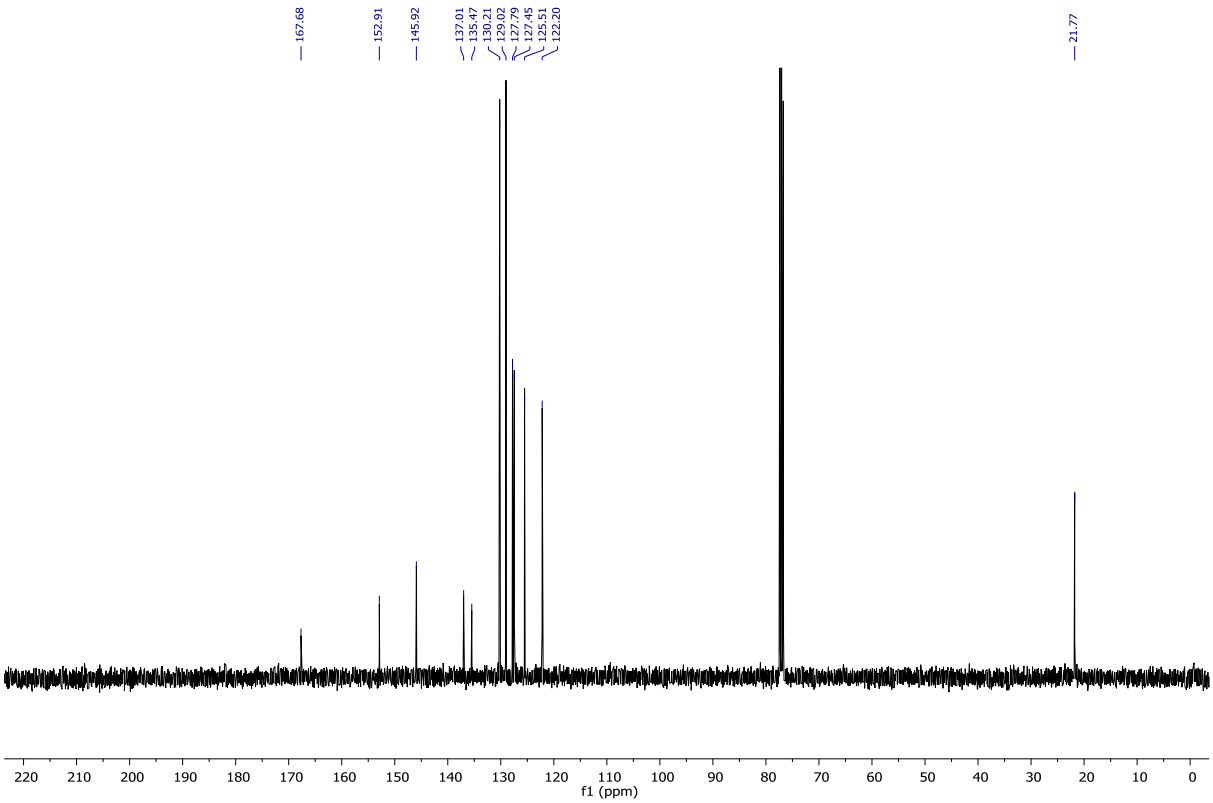
2.13
3.30
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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135.47
130.21
129.02
127.79
127.45
125.51
122.20
21.77
220
210
200
190
180
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160
150
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130
120
110
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90
80
70
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50
40
30
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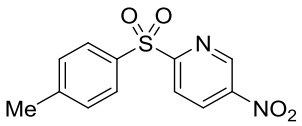
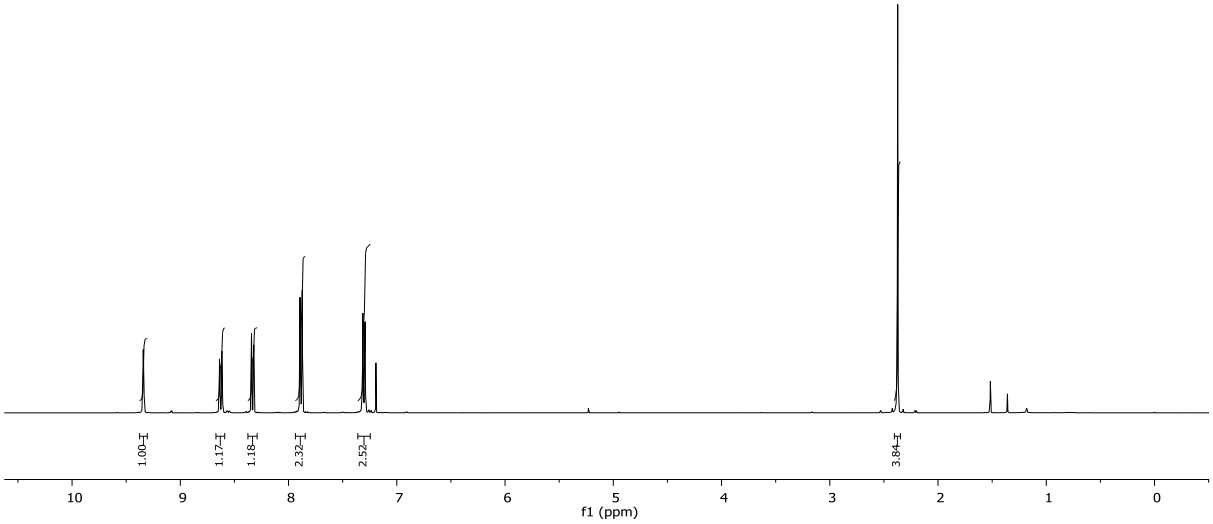
10
0
f1 (ppm)


O
O
S
N
Me
NO2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1.17
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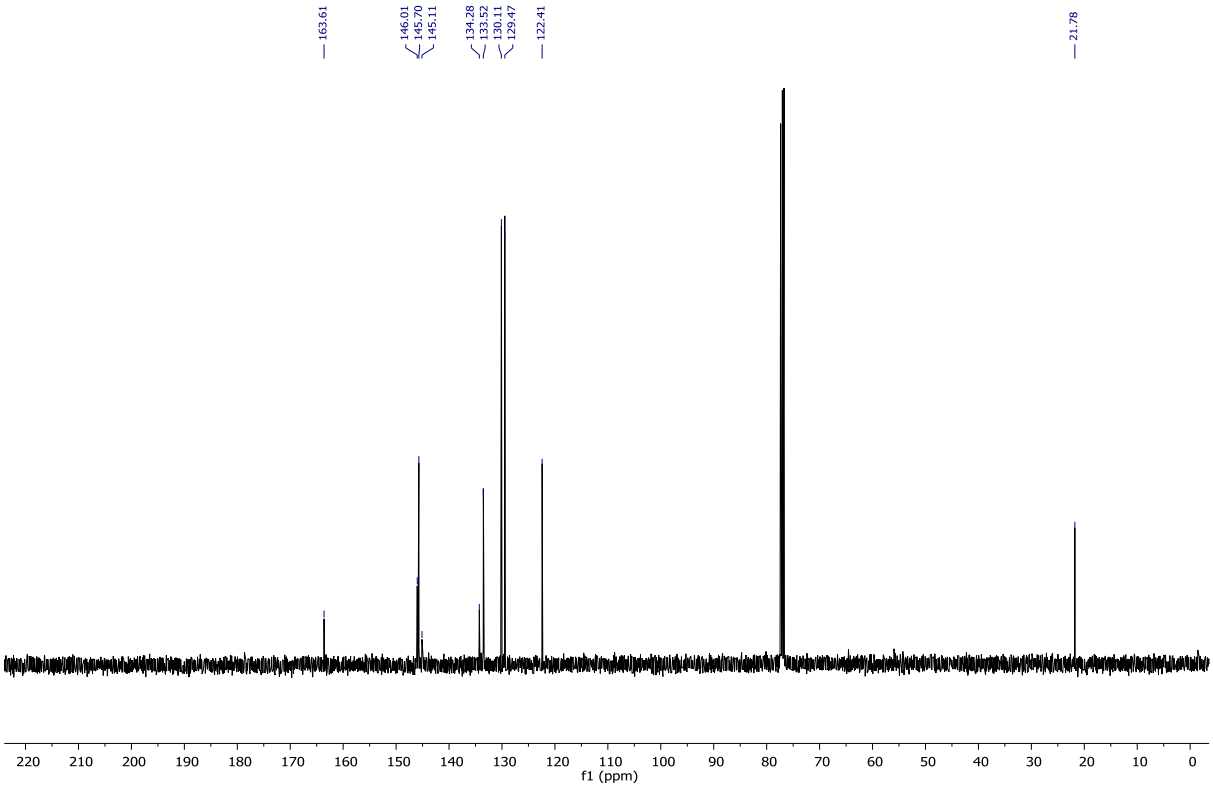
2.52
3.84
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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146.01
145.70
145.11
134.28
133.52
130.11
129.47
122.41
21.78
220
210
200
190
180
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160
150
140
130
120
110
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90
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70
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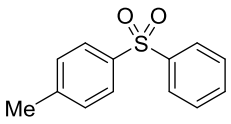
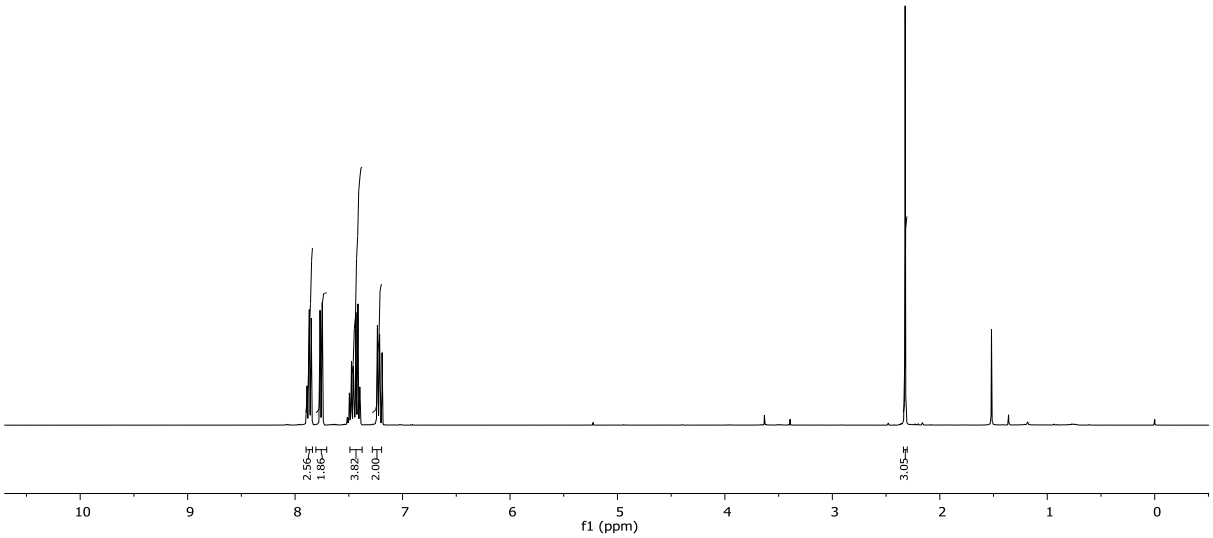
50
40
30
20
10
0
f1 (ppm)


O
O
S
Me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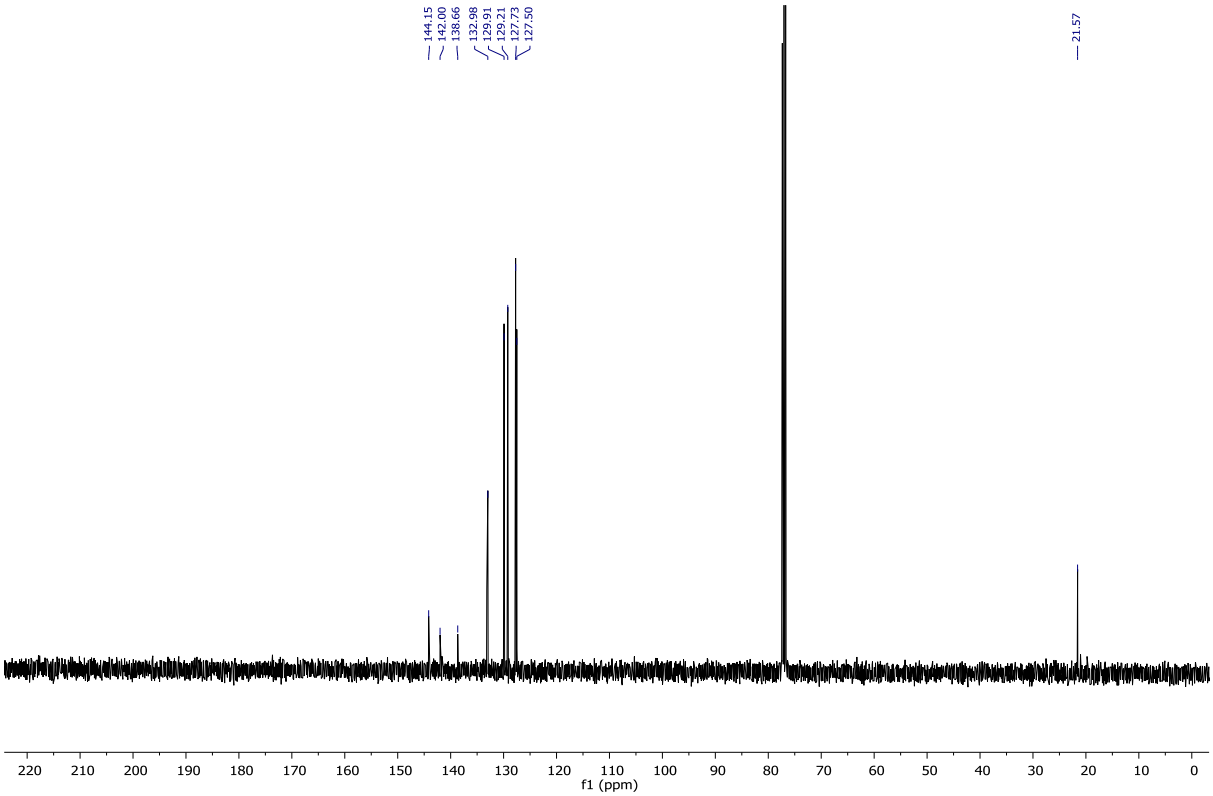
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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142.00
138.66
132.98
129.91
129.21
127.73
127.50
21.57
220
210
200
190
180
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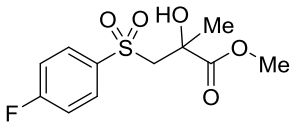
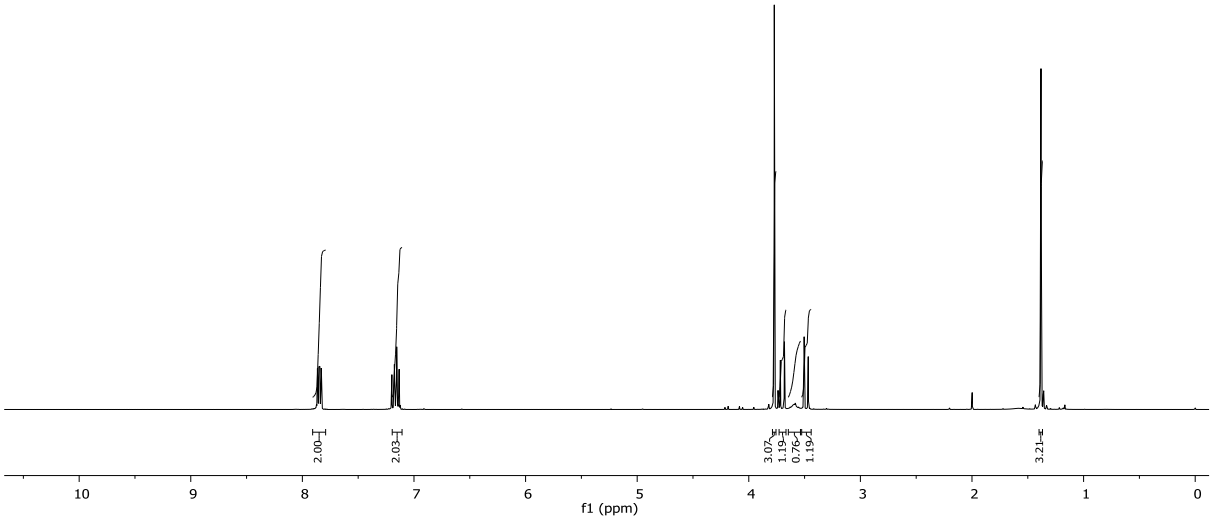
10
0
f1 (ppm)


O
O
HO
Me
S
O
Me
F
O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3.07
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1.19
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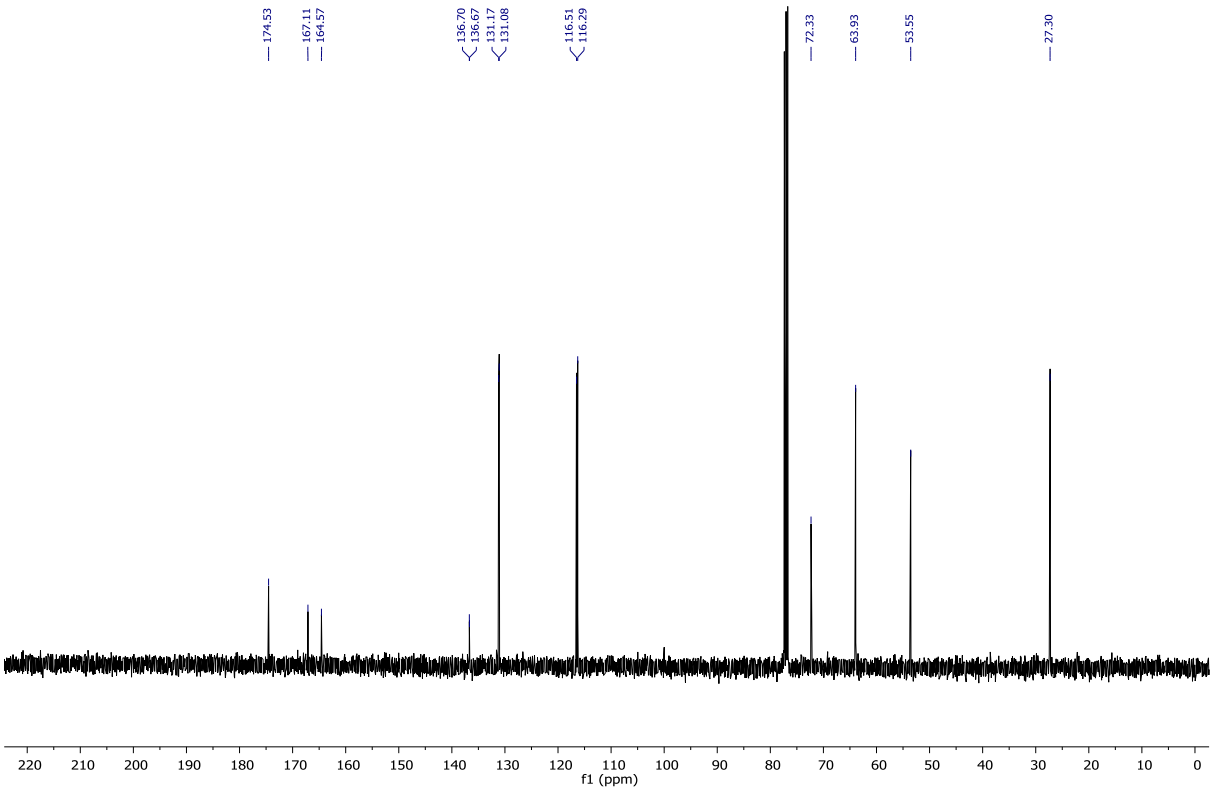
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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164.57
136.70
136.67
131.17
131.08
116.51
116.29
72.33
63.93
53.55
27.30
220
210
200
190
180
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160
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50
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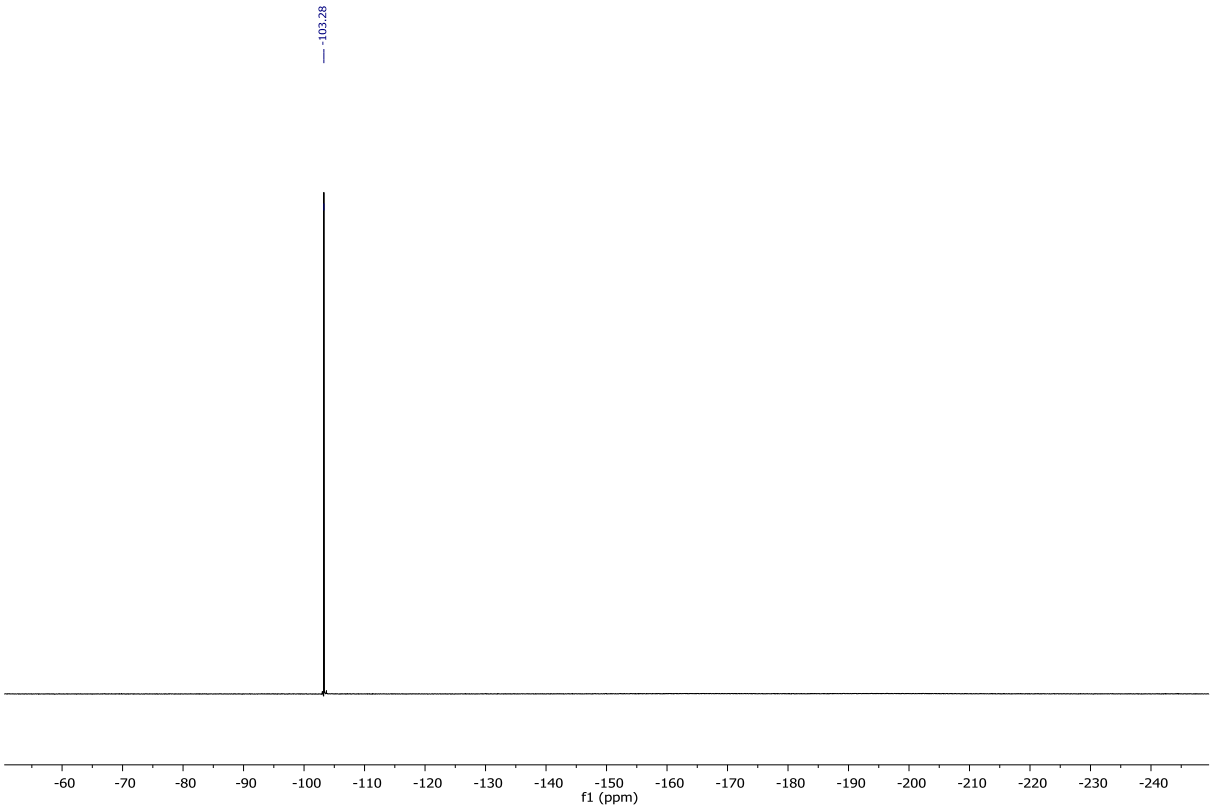
10
0
f1 (ppm)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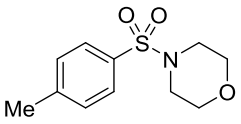
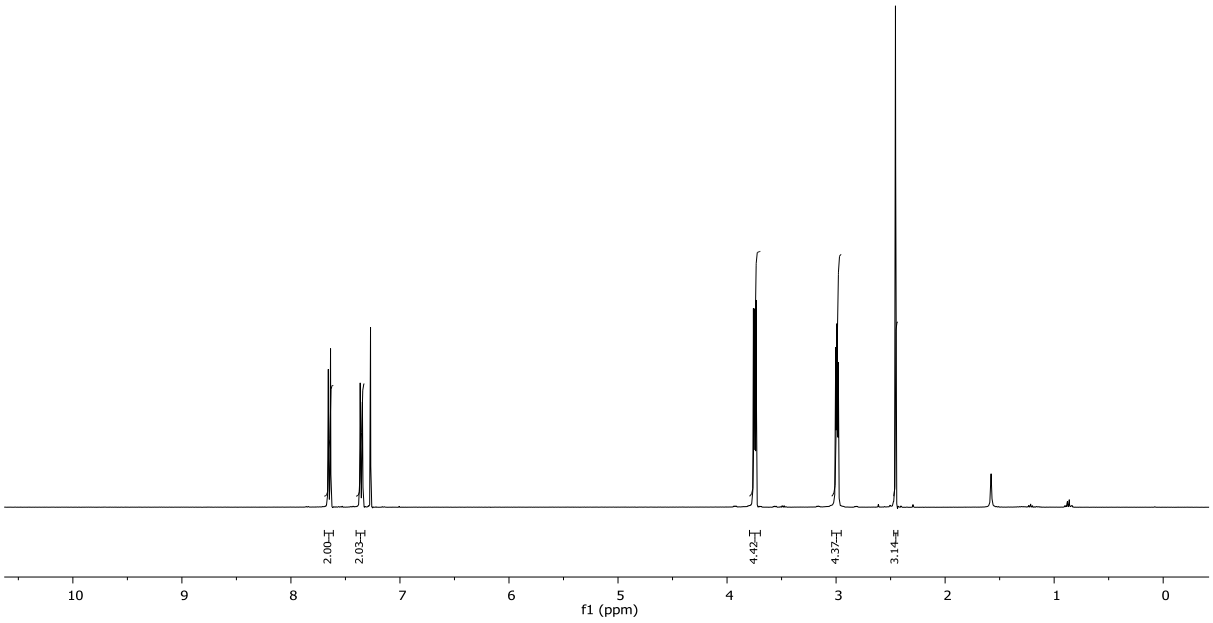
-150
-160
-170
-180
-190
-200
-210
-220
-230
-240
f1 (ppm)


O
O
S
N
O
Me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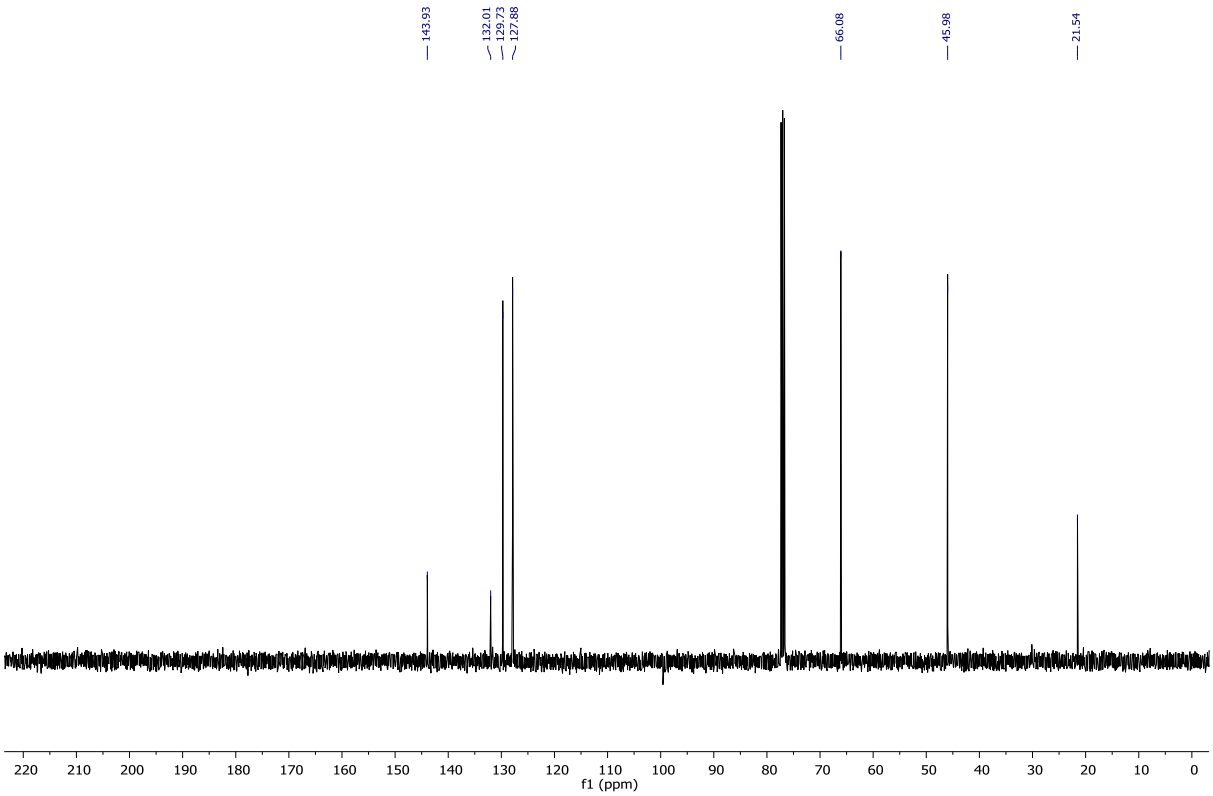
8
7
6
5
4
3
2
1
0
f1 (ppm)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132.01
129.73
127.88
66.08
45.98
21.54
220
210
200
190
180
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130
120
110
100
90
80
70
60
50
40
30
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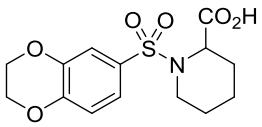
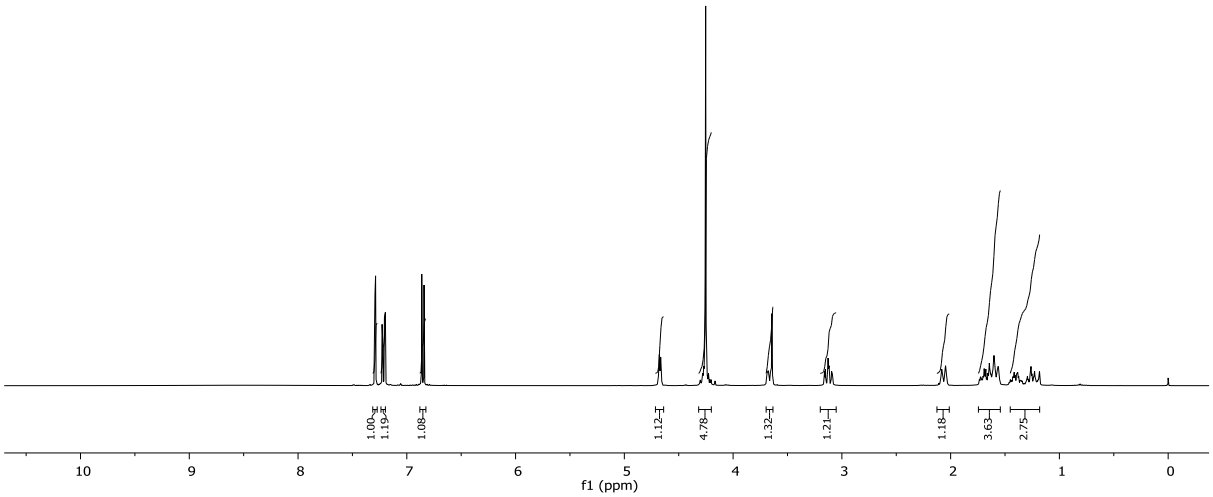
10
0
f1 (ppm)


O
O
S
N
CO2H
O
O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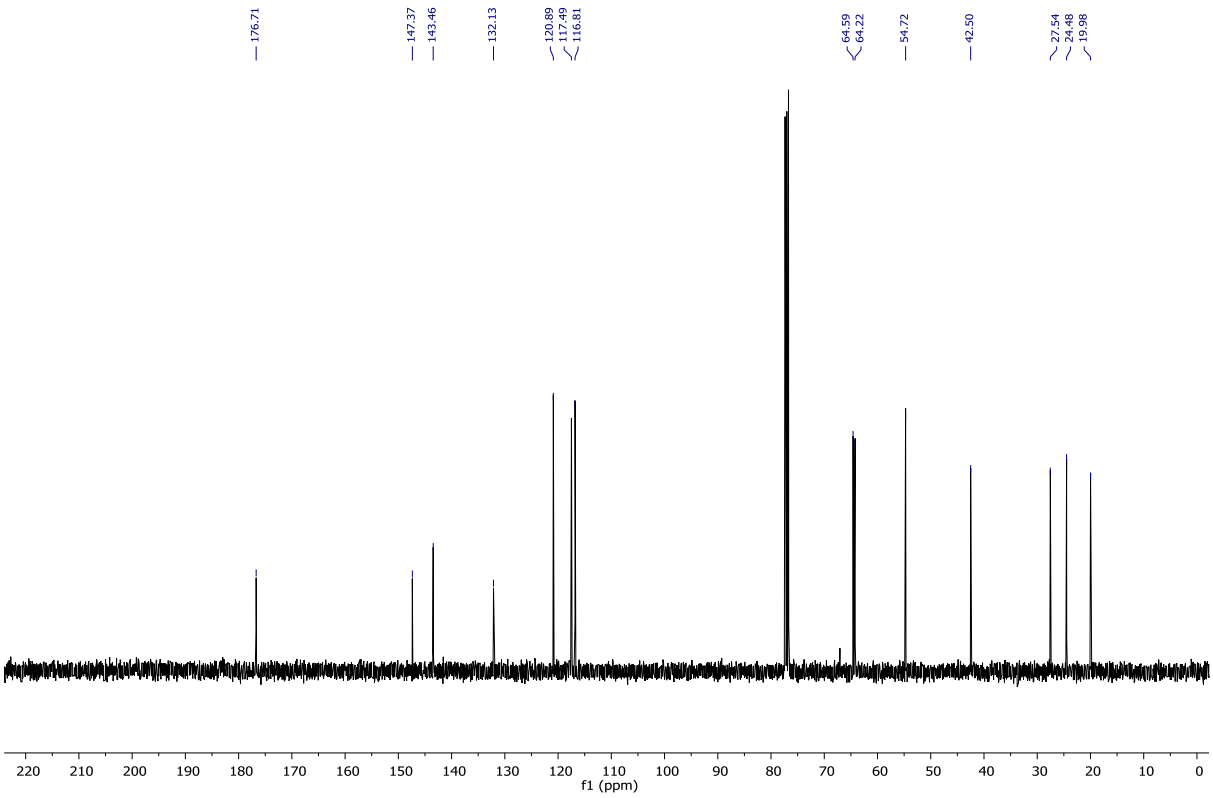
1.08
1.12
4.78
1.32
1.21
1.18
3.63
2.75
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)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143.46
132.13
120.89
117.49
116.81
64.59
64.22
54.72
42.50
27.54
24.48
19.98
220
210
200
190
180
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130
120
110
100
90
80
70
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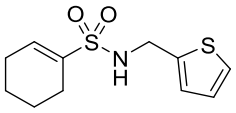
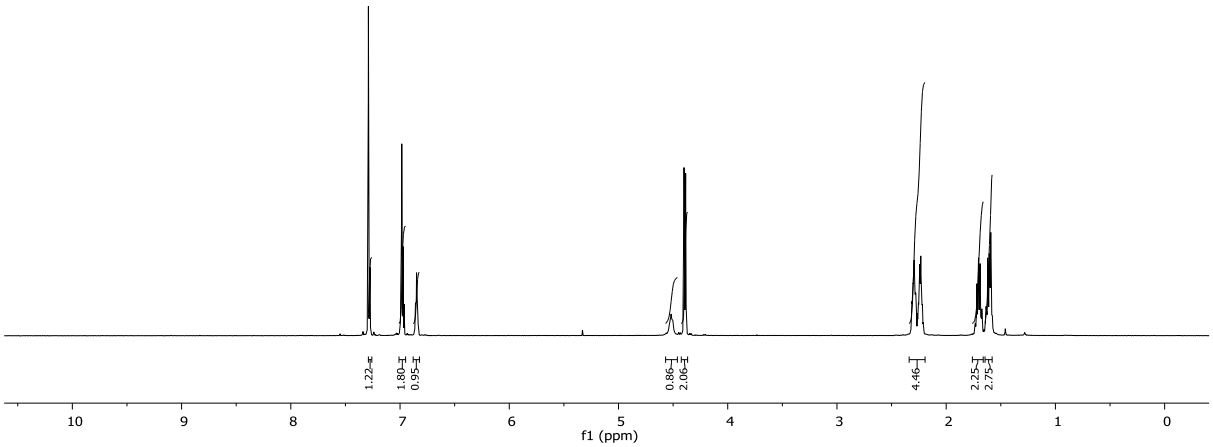
50
40
30
20
10
0
f1 (ppm)


O
O
S
N
H
S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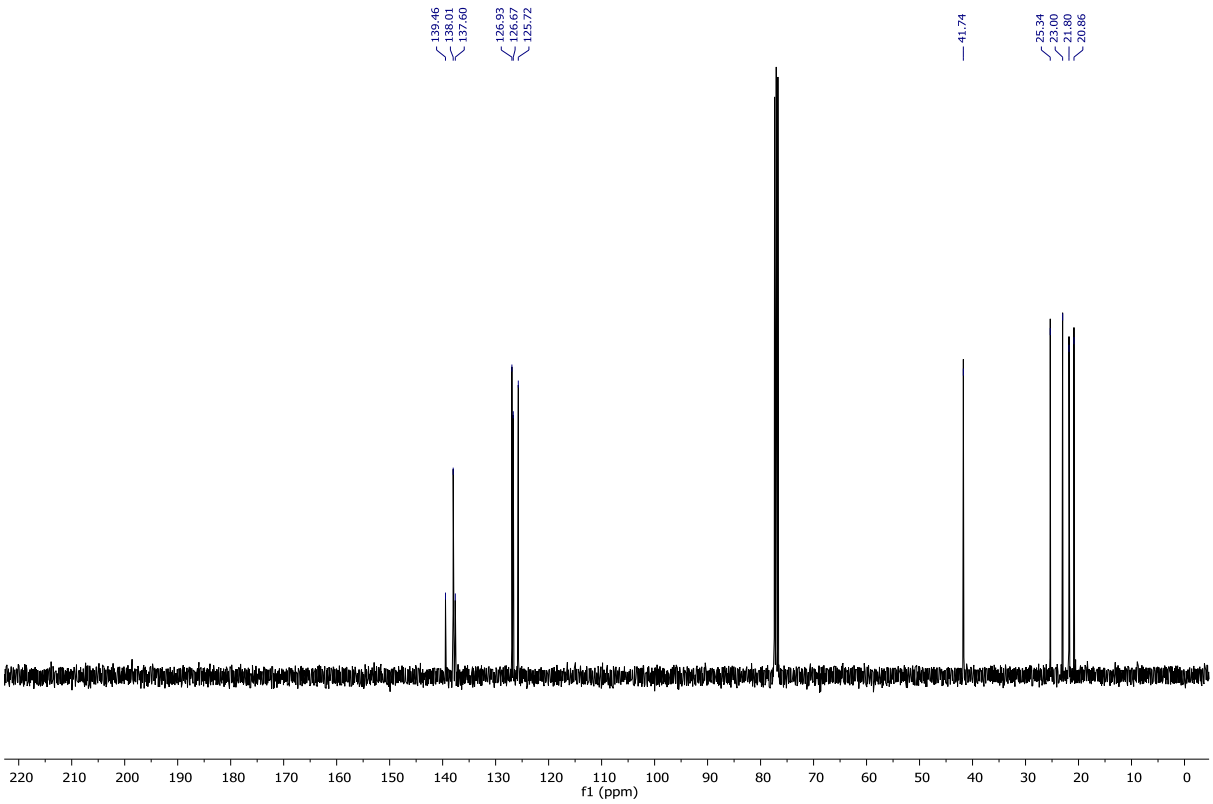
4.46
2.25
2.75
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


139.46
138.01
137.60
126.93
126.67
125.72
41.74
25.34
23.00
21.80
20.86
220
210
200
190
180
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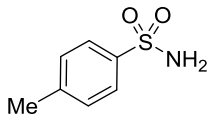
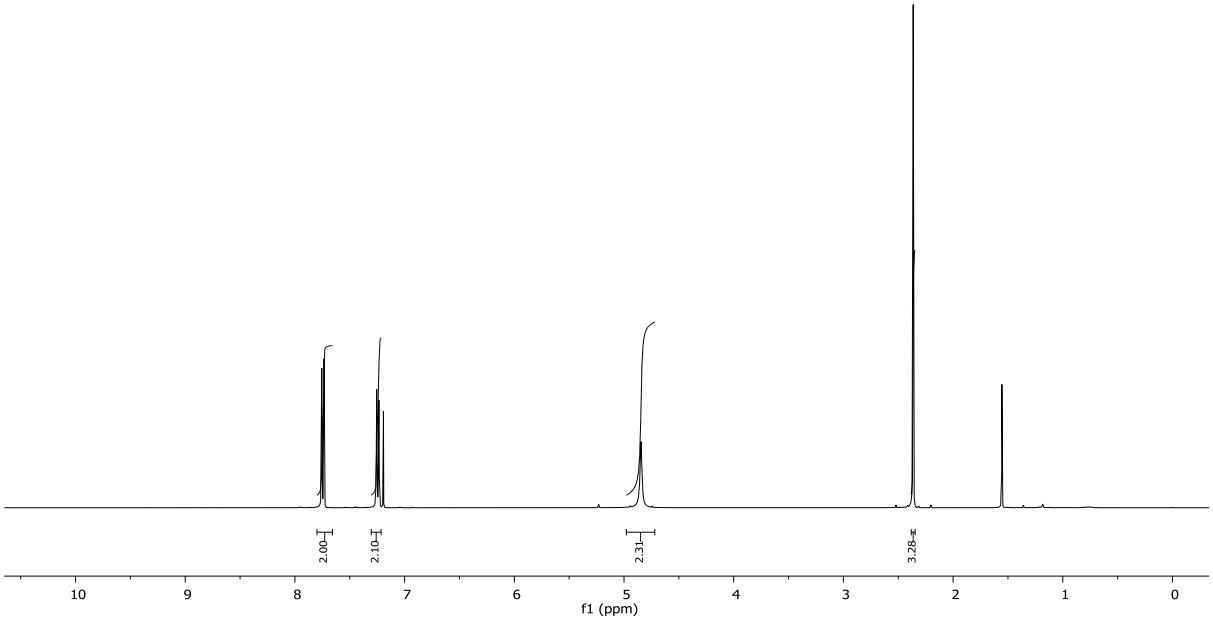
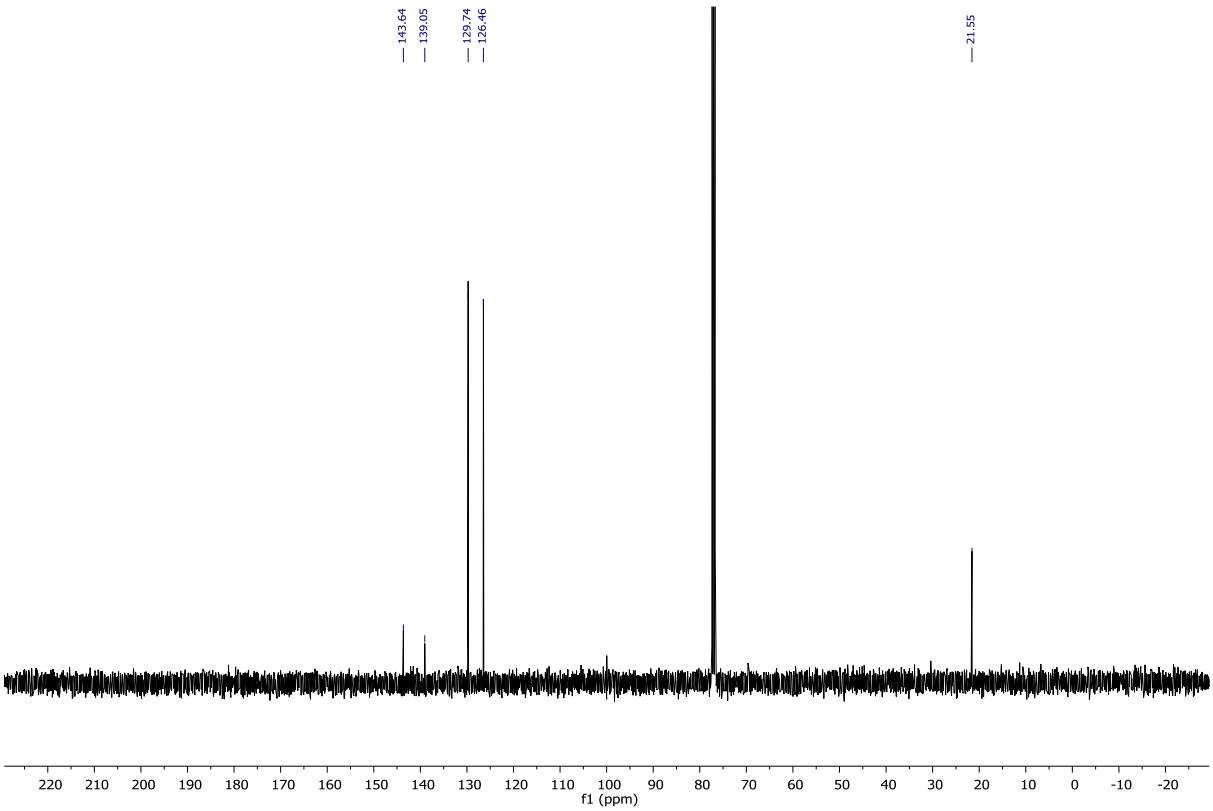
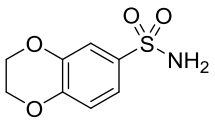
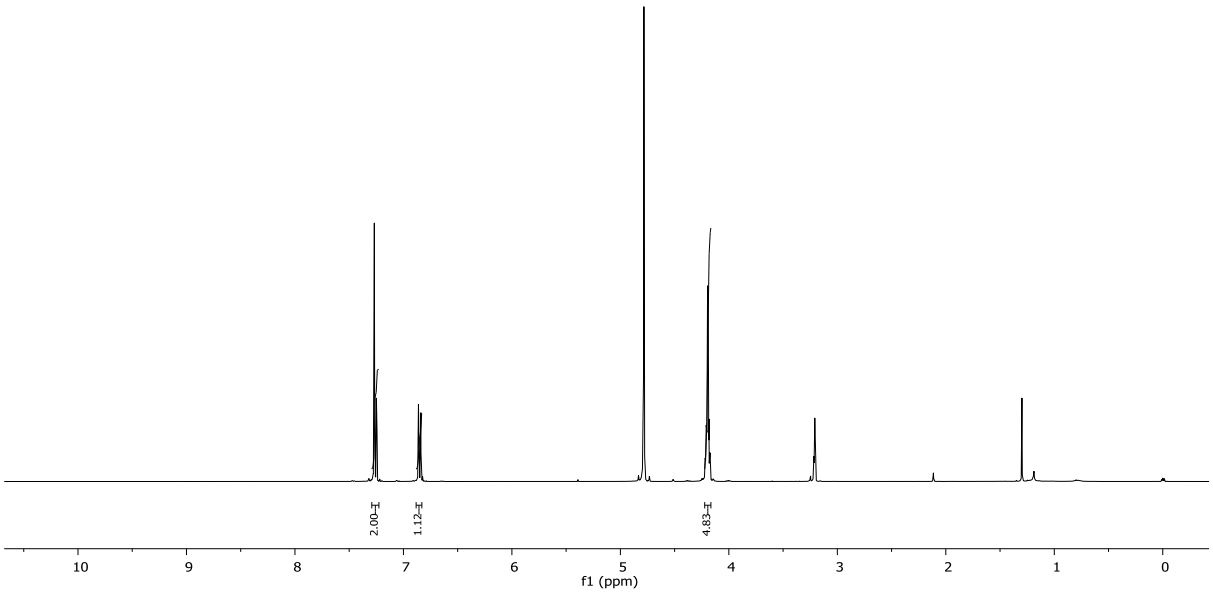
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

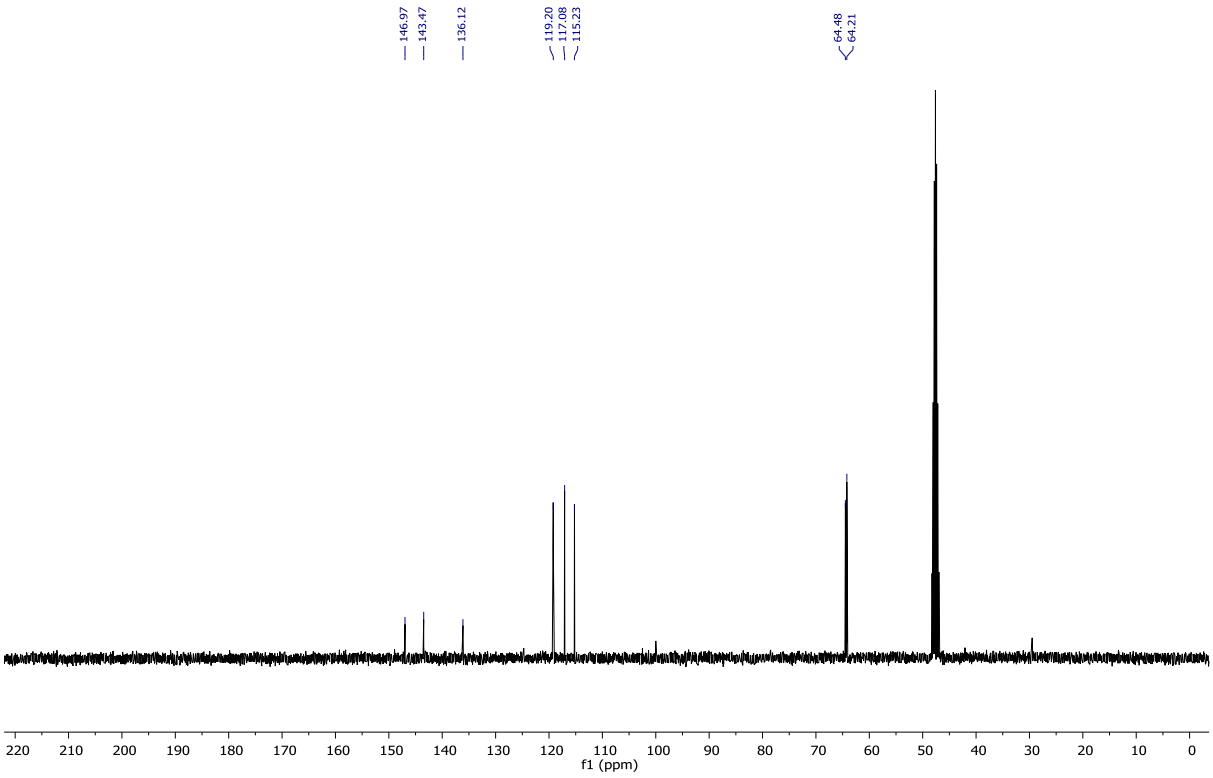

O
O
S
NH2
Me


2.00
2.10
2.31
3.28
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


143.64
139.05
129.74
126.46
21.55
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


O
O
S
NH2
O
O


2.00
1.12
4.83
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


146.97
143.47
136.12
119.20
117.08
115.23
64.48
64.21
220
210
200
190
180
170
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150
140
130
120
110
100
90
80
70
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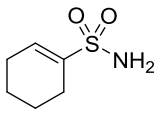
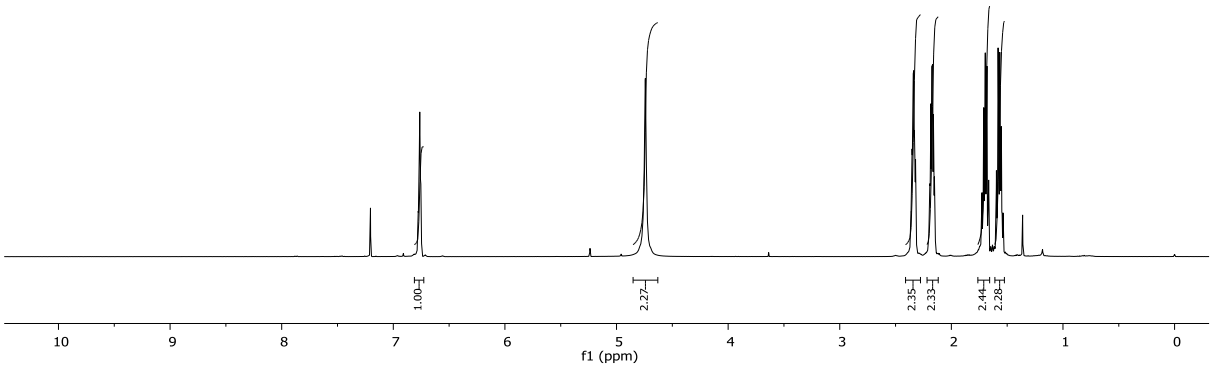
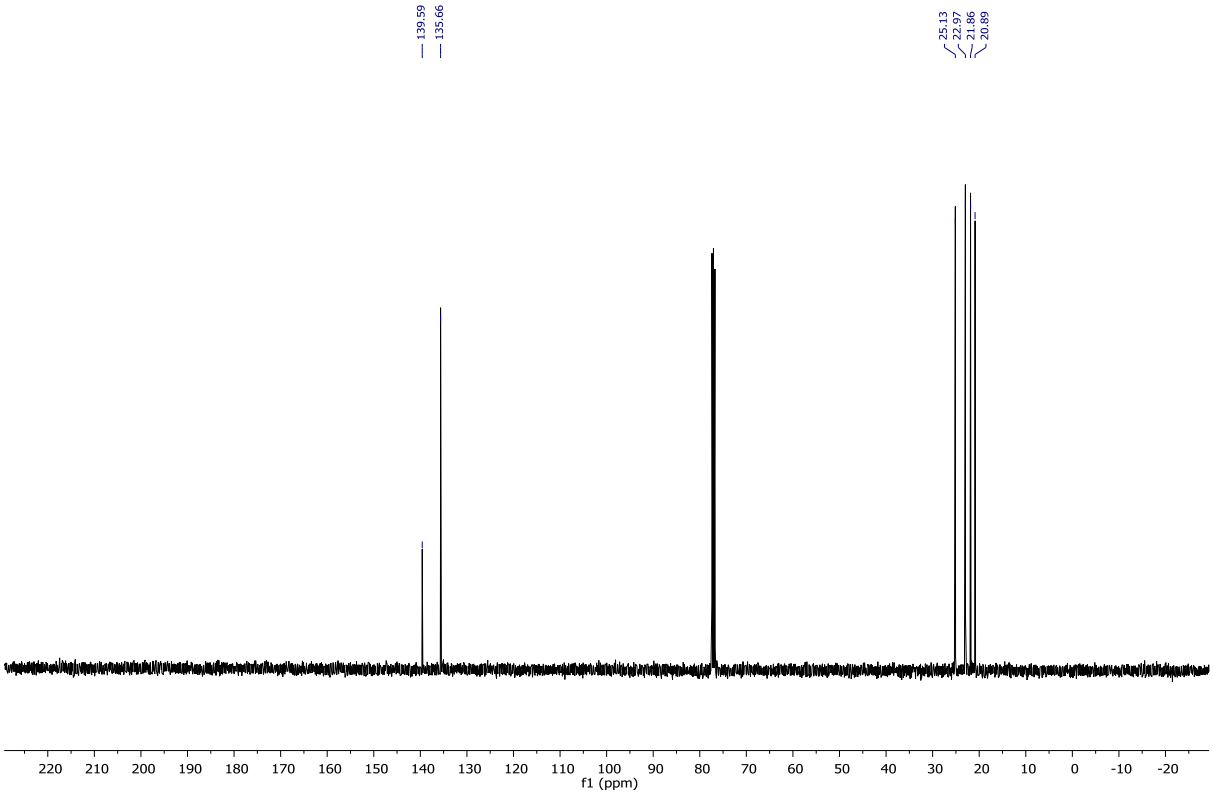
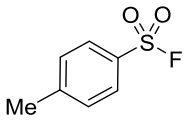
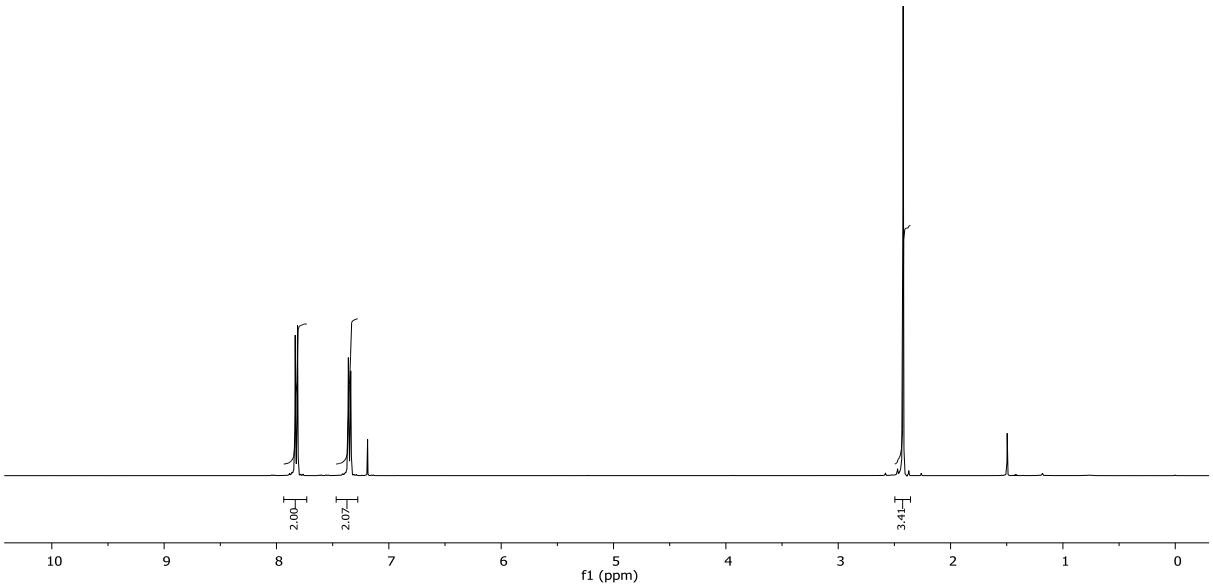
50
40
30
20
10
0
f1 (ppm)


O
O
S
NH2


1.00
2.27
2.35
2.33
2.44
2.28
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


139.59
135.66
25.13
22.97
21.86
20.89
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


O
O
S
F
Me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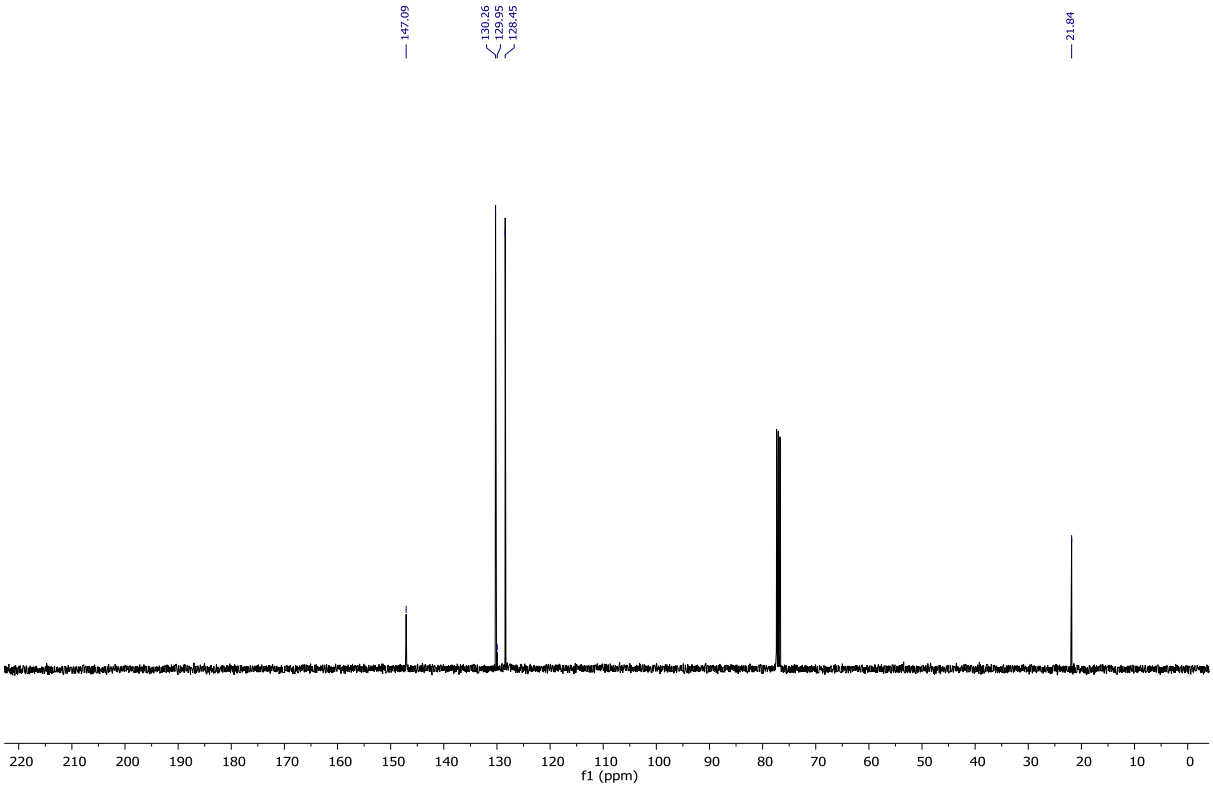
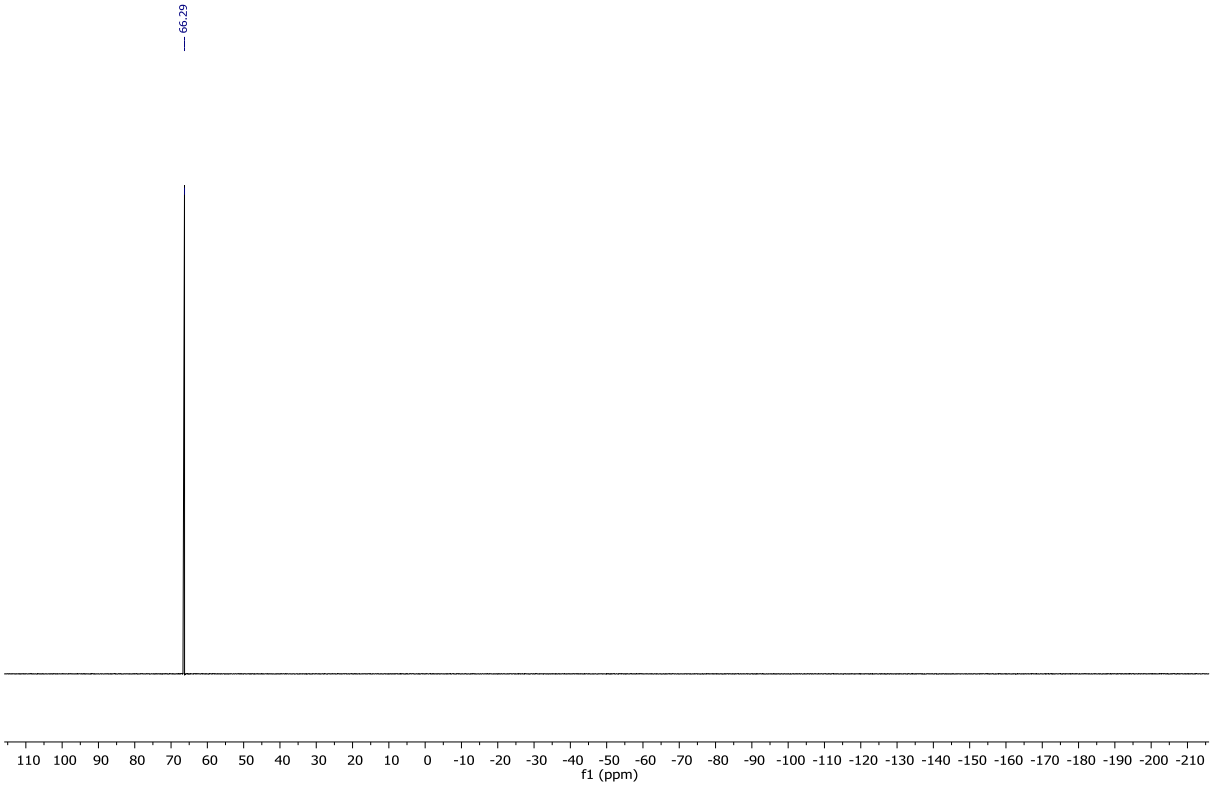
2.07
3.41
10
9
8
7
6
5
4
3
2
1
0
f1 (ppm)


147.09
130.26
129.95
128.45
21.84
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


66.29
110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)