One-pot, Three-Component Sulfonimidamide Synthesis exploiting the Sulfinylamine Reagent *N*-Sulfinyltritylamine, TrNSO

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Abstract: Sulfonimidamides are increasingly important molecules in medicinal chemistry and agrochemistry, but their preparation requires lengthy synthetic sequences, which has likely limited their use. We describe a one-pot *de novo* synthesis of sulfonimidamides from widely available organometallic reagents and amines. This convenient and efficient process uses a stable sulfinylamine reagent, *N*-sulfinyltritylamine (TrNSO), available in one step on 10 gram scale, as a linchpin. In contrast to classical approaches starting from thiols or their derivatives, our TrNSO-based approach facilitates the rapid assembly of the three reaction components into a variety of differentially substituted sulfonimidamides containing medicinally relevant moieties, including pyridines and indoles. Analogues of the sulfonamide-containing COX-2 inhibitor Celecoxib were prepared and evaluated.

Sulfonamides have a rich history in medicinal chemistry, and their stability, hydrogen bonding capabilities, and three-dimensional shape make them prized functional groups in the design of bioactive molecules. In contrast, their mono-aza analogues, sulfonimidamides **1**, have only recently started to attract significant attention.[1] Like their congeners, they are chemically and metabolically stable,[2] but in addition, the substitution of an oxygen atom for a nitrogen leads to a stereogenic sulfur center, presents further opportunities for directed hydrogen bonding, and provides an additional site for functionalization. These properties present unique opportunities for medicinal chemists and agrochemists, and they have been reported as carboxylic acid[3] and sulfonamide bioisosteres,[4] and their use as BACE inhibitors[5] and kinase inhibitors[6] has been disclosed in recent patents. Their use in medicinal- and agrochemistry has recently been the subject of a review by Arvidsson and co-authors, where it is noted that "since 2012, there have been more patents and publications on compounds with a sulfonimidamide moiety than collectively over history, demonstrating that this functional group is gaining momentum".[1] In order to capitalize on this momentum and the increasing awareness of sulfonimidamides, more convenient and efficient methods for their preparation are required; unlike sulfonamides, there has been little progress in this regard.

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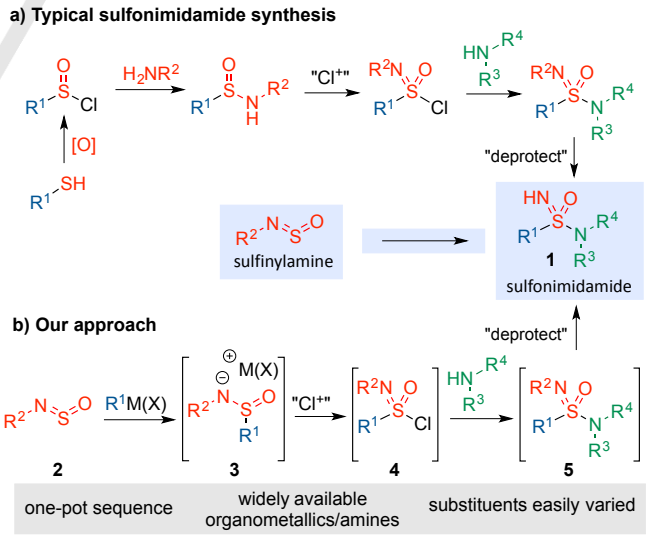
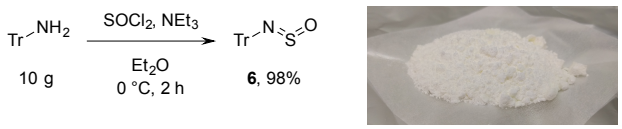
Sulfonimidamides are typically prepared from the reaction of amines with sulfonimidoyl chlorides, themselves obtained *via* electrophilic chlorination of sulfinamides (Scheme 1a).[7],[8],[9] Direct N-H transfer to a sulfinamide has also been reported.[10] However, sulfinamides are not easily accessible and have limited commercial availability, and are typically prepared from sulfinyl chlorides, accessible *via* oxidation of thiols or disulfides, or reduction of moisture-sensitive sulfonyl chlorides.[11] In addition, sulfinyl chlorides are unstable and generally demand immediate combination with an amine. An additional disadvantage for discovery chemists is that these lengthy sequences are not conducive to analogue synthesis, as the R^1 group on sulfur is determined by the initial choice of thiol or sulfonyl chloride at the first step of the sequence. We envisioned that many of these deficiencies could be addressed by a synthetic strategy based on the use of a sulfinylamine[12] as a key N=S=O linchpin (Scheme 1b). The resulting one-pot, three-component reaction sequence would involve combination of the sulfinylamine with an organometallic reagent (**2** → **3**), chlorination of the resultant anionic sulfinamide species[13] to generate a sulfonimidoyl chloride (**3** → **4**),[7c] and then combination with an amine to afford an *N*-substituted sulfonimidamide (**4** → **5**).[14] The N-R^2 substituent would be cleavable under mild conditions to give medicinally and synthetically valuable *N*-H sulfonimidamides (**5** → **1**).



Scheme 1. a) A typical linear synthesis of sulfonimidamides *via* the intermediacy of unstable sulfinyl chlorides. b) This work: a one-pot sulfinylamine-based synthesis of sulfonimidamides.

Sulfinylamines have been known since the 19th century and are prepared by the reaction of primary amines with thionyl chloride.[15] Several known sulfinylamines, including those derived from *p*-toluenesulfonamide[16] and *tert*-butylcarbamate,[17] were prepared but exhibited low hydrolytic stability, which is a

general property of these highly electrophilic compounds.[12a] However, we were delighted to find that the reaction of commercially available tritylamine (100 g, £117, Fluorochem) with thionyl chloride in the presence of triethylamine gave a moisture-insensitive white solid, isolated in pure form after filtration through Celite (Scheme 2). *N*-Sulfinyltritylamine, TrNSO (**6**), showed undiminished reactivity after storage for four months in the freezer (–20 °C), and could be isolated on 10 gram scale in excellent yield. The observed stability is attributed to the considerable steric bulk of the trityl group.[18]

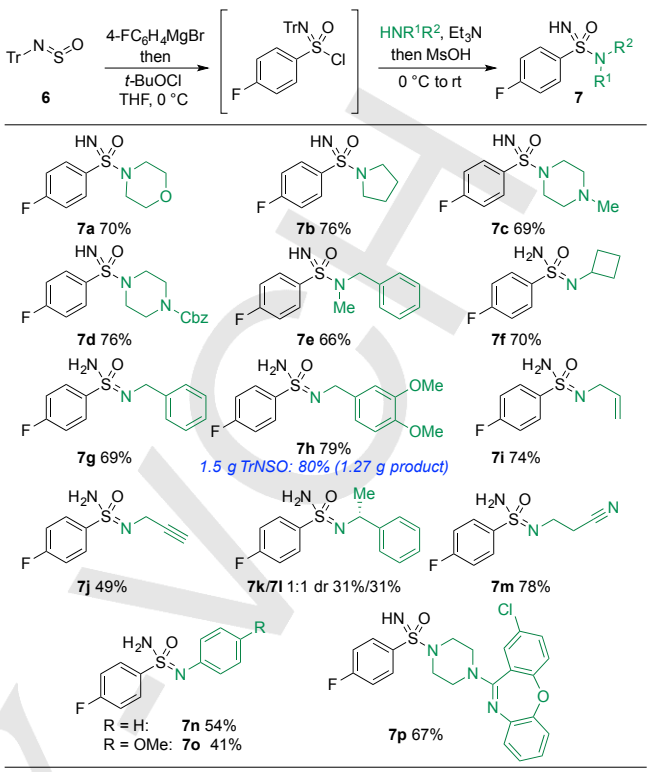


Scheme 2. Preparation of the sulfinylamine reagent *N*-sulfinyltritylamine, TrNSO. Tr = triphenylmethyl, trityl.

Our efforts then turned to applying this rare example of a stable sulfinylamine to our planned one-pot synthesis of sulfonimidamides. The reaction of TrNSO with commercially available 4-fluorophenylmagnesium bromide in THF was selected for initial investigation. Despite the steric demands of the trityl group, complete consumption of the starting material was observed within five minutes at 0 °C. Furthermore, subsequent chlorination of the anionic sulfinamide intermediate with *tert*-butyl hypochlorite[19] proceeded with full conversion within fifteen minutes at the same temperature. The use of *N*-chlorosuccinimide[7a] was also explored, but the reaction did not achieve completion even after five hours using 1.5 equivalents, while just 1.05 equivalents of *tert*-butyl hypochlorite proved sufficient. The *in-situ* generated sulfonimidoyl chloride was stirred at room temperature for 16 h with two equivalents of morpholine, before methanesulfonic acid was added to effect trityl deprotection. To our delight, the desired *N*-H sulfonimidamide was isolated following flash chromatography in 70% yield.

Encouraged by this success, we next explored the scope of amines that could be used in this transformation (Table 1). The stoichiometry of the amine nucleophile was reduced to 1.2 equivalents relative to TrNSO, and 1 equivalent of triethylamine was employed. Under these conditions, a range of secondary amines delivered sulfonimidamides in high yields (**7a**-**e**), including an example with an additional basic nitrogen (**7c**). Primary amines were also found to be competent nucleophiles, in these cases delivering products with a double bond to the more substituted nitrogen (**7f**-**m**).[20] Importantly, the reaction worked equally well on gram scale; the 80% yield obtained for compound **7h** corresponds to a 95% yield per transformation, demonstrating the efficiency of the one-pot process. Propargylamine could be incorporated, albeit in slightly reduced yield, potentially enabling the convenient application of sulfonimidamides to click chemistry (**7j**). When enantiopure (*R*)-α-methylbenzylamine was employed, a 1:1 mixture of separable diastereomers was generated, highlighting the potential for chemical resolution (**7k**,**l**). *N*'-Aryl sulfonimidamides were obtained by reaction with anilines, although in the case of **7n** and other more electron-poor anilines (e.g. 4-bromoaniline), acid sensitivity of the products was observed. The more electron-rich **7o**, in contrast, did not show any sign of decomposition on silica. A sulfonimidamide derived from the complex amine-containing antidepressant drug Amoxapine could also be obtained in good yield (**7p**).

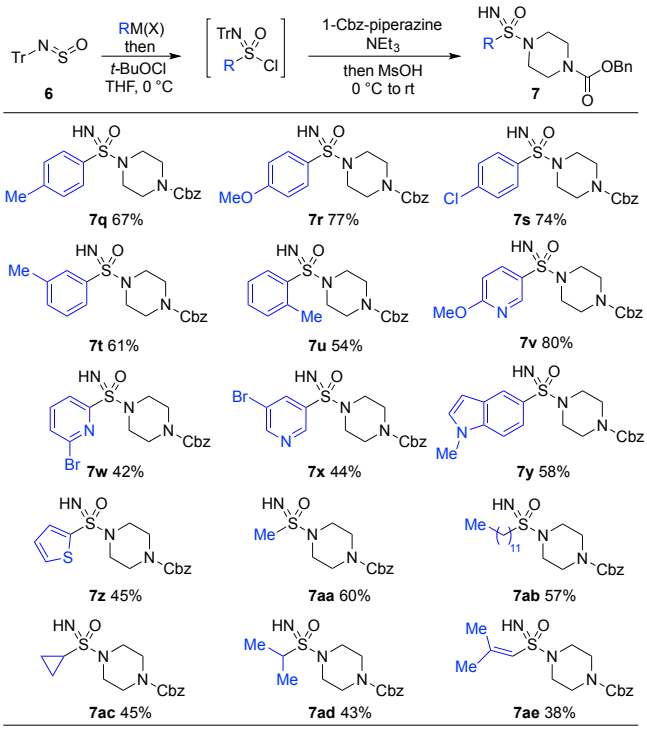
Table 1. Scope with respect to amines.[a]



[a] Reaction conditions: (i) TrNSO (0.16 mmol), 4-fluorophenylmagnesium bromide (1.0 equiv), THF [0.16 M], 0 °C, 5 min, (ii) *t*-BuOCl (1.05 equiv), 0 °C, 15 min, (iii) amine (1.20 equiv), triethylamine (1.0 equiv), 0 °C to rt, 16 h, (iv) MsOH (5.0 equiv), 15 min, rt. Isolated yields. Cbz = benzyloxycarbonyl.

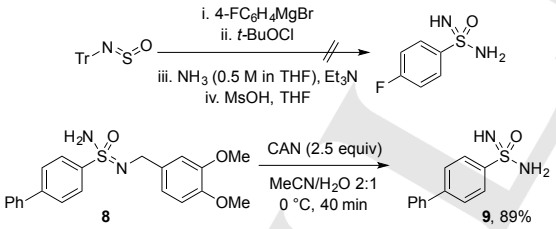
Having demonstrated a wide scope of amines, we focused on the tolerance of the reaction towards various (hetero)aromatic organometallic reagents; a Cbz-protected piperazine was chosen as the amine component to produce a scaffold which could be of interest in medicinal chemistry (Table 2). A range of electron-rich and electron-poor benzene derivatives provided high yielding reactions (**7q**-**t**), and substitution was tolerated even in the *ortho*- position with only a minor reduction in yield (**7u**); a remarkable result considering the steric crowding around sulfur atom in the intermediate *N*-trityl sulfonimidoyl chloride. Heterocyclic organometallics were also suitable substrates for the reaction (**7v**-**z**). The organolithium reagent derived from 5-bromo-2-methoxypyridine could be employed in an excellent 80% yield (**7v**), and a challenging 2-pyridyl organomagnesium reagent (**7w**), generated using Knochel's turbo Grignard,[21] proceeded in moderate yield. Indole- and 2-thienyl-substituted sulfonimidamides were also obtained (**7y**,**z**). Pleasingly, the reaction was not limited to aromatic nucleophiles; alkyl Grignard reagents, notably including cyclopropylmagnesium bromide (**7ac**), were also amenable. An *S*-alkenyl sulfonimidamide (**7ae**) was obtained in low yield, likely due to decomposition related to its strong Michael acceptor ability.

Table 2. Scope with respect to organometallic reagents.[a]



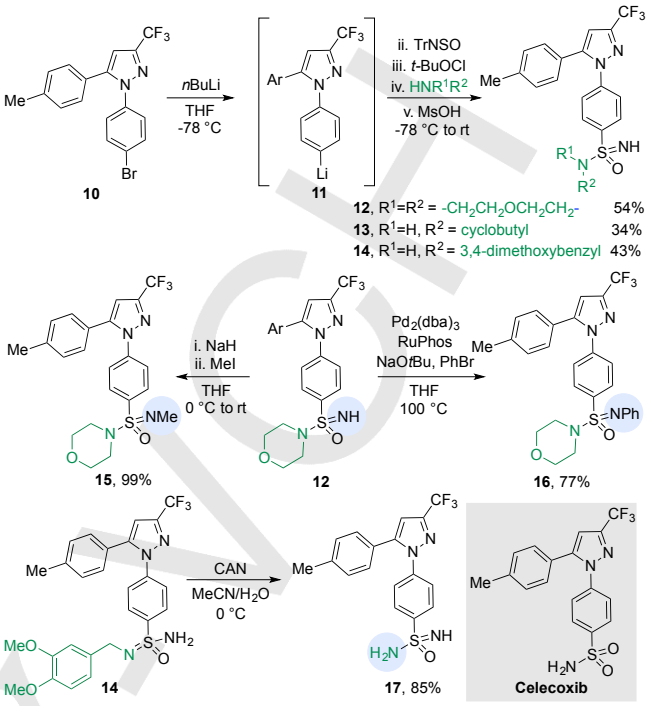
[a] Reaction conditions: (i) TrNSO (0.16 mmol), organometallic reagent (1.0 equiv), THF [0.16 M], 0 °C, 5 min, (ii) *t*-BuOCl (1.05 equiv), 0 °C, 15 min, (iii) 1-Cbz-piperazine (1.0 equiv), triethylamine (1.0 equiv), 0 °C to rt, 16 h, (iv) MsOH (5.0 equiv), 15 min, rt. Isolated yields. Cbz = benzyloxycarbonyl.

Significant reduction of the intermediate sulfonimidoyl chloride was observed when ammonia was used as the amine component, complicating the preparation of the parent sulfonimidamide (Scheme 3). After extensive experimentation, it was found that 3,4-dimethoxybenzyl-protected sulfonimidamide **8** was a suitable precursor to the desired product. Oxidative cleavage with ceric ammonium nitrate proceeded quickly and cleanly at 0 °C, affording sulfonimidamide **9** in excellent yield.



Scheme 3. a) Ammonia fails to give desired unsubstituted sulfonimidamide. b) Ready oxidative cleavage of DMB-protected sulfonimidamide. CAN = ceric ammonium nitrate.

Having developed a convenient method to prepare sulfonimidamides, we wished to investigate its suitability for preparing complex, drug-like molecules. We therefore elected to investigate the preparation of sulfonimidamide analogues of the sulfonamide-containing non-steroidal anti-inflammatory drug (NSAID) Celecoxib (Scheme 4). Organolithium reagent **11** was obtained from the corresponding bromide and employed in the synthesis of three sulfonimidamides (**12**-**14**). Possibilities for further functionalization on these complex structures were explored; *N*-alkylation of **12** with methyl iodide proceeded quantitatively (**15**), while *N*-arylation *via* a palladium-catalyzed cross-coupling was also successful (**16**).[22] Pleasingly, the parent sulfonimidamide (**17**) could be prepared in high yield by oxidative cleavage of the DMB-protected sulfonimidamide **14**.



Scheme 4. Synthesis of sulfonimidamide drug analogues.

With several drug analogues in hand, we investigated their properties in comparison to Celecoxib. The biological inhibition of COX-2 was investigated for three analogues,[23] namely the parent sulfonimidamide (**17**), the closest analogue, and the morpholino (**12**) and cyclobutyl (**13**) derivatives. The data show that replacement of the sulfonamide by the sulfonimidamide decreases COX-2 inhibition by almost 100-fold, whereas additional substitution of the sulfonimidamide is not well tolerated and results in a further decrease in activity (Table 3). A head-to-head comparison between Celecoxib and the parent sulfonimidamide analogue (**17**) reveals some beneficial parameters, including lower lipophilicity and increased metabolic stability, particularly in human liver microsomes, which also results in a lower calculated hepatic extraction ratio. Although it is unclear whether the improvement in metabolic stability for the sulfonimidamide is simply due to the lower lipophilicity or as a result in weakened interactions with the metabolic enzyme, it supports the further investigation and use of the sulfonimidamide in medicinal chemistry.

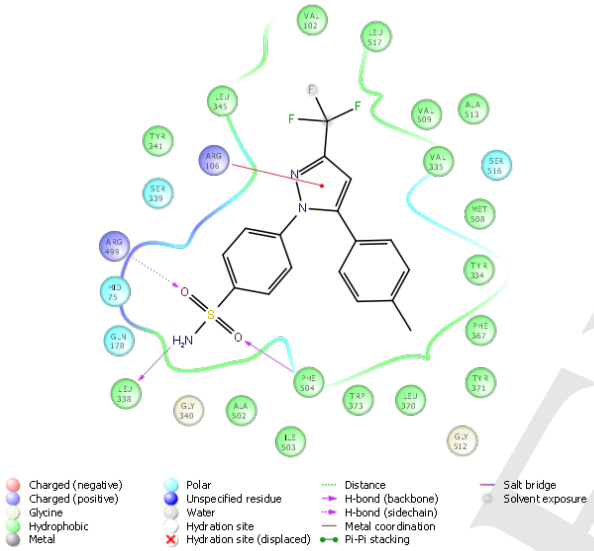
Table 3. Summary of data for Celecoxib *versus* compounds **17**, **12** and **13**.

Compound	COX-2 pIC_{50}	HT logD[a]	HLM CL_{int}[b]	HLM E_h[c]	RLM CL_{int}[b]	RLM E_h
Celecoxib	7.33	3.6	16.1	0.439	11.2	0.223
17	5.46	3.0	4.84	0.19	8.21	0.174
12	< 5 (42%@10 uM)	3.7	404	0.951	114	0.745
13	<5 (39% @ 10 uM)	4.3	95	0.822	50	0.561

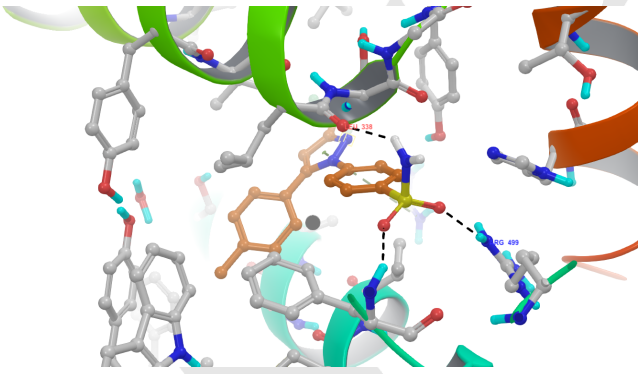
[a] High Throughput (HT) logD. [b] Intrinsic clearance (CL_{int}) measured in human or rat liver microsomes (HLM or RLM respectively), in µL/min/mg protein. [c] Calculated hepatic extraction ratio, based on the assumption F_u (fraction unbound) = 1 for all compounds. See Supplementary Information for assay details.

Analysis of the crystal structure of Celecoxib bound to

mouse COX-2 reveals a potential explanation for the reduced activity of the sulfonimidamide analogue (**17**). Celecoxib is a lipophilic compound which largely makes hydrophobic interactions with COX-2 (Scheme 5), apart from the sulfonamide moiety which makes polar interactions, namely the NH_2 group donates a hydrogen bond to the backbone carbonyl moiety of Leu338, whilst each of the O-atoms accept a hydrogen bond (Arg499 & Phe504, see Schemes 5 and 6). Thus, replacement of one of the O-atoms by NH would be predicted to be detrimental due to the loss of a HBD interaction (resulting in ~10-fold decrease in activity), in addition to a potential unfavourable interaction with Arg499 or Phe504. Furthermore, there may be an additional cost due to an increased desolvation penalty for the more polar sulfonimidamide-containing ligand. The weaker activity of the substituted sulfonimidamide analogues (**12** & **13**) can be rationalised by the increased steric requirements of the ligands.



Scheme 5. Depiction of the interactions formed between Celecoxib and mouse COX-2 (PDB: 3LN1). Generated using Maestro Elements 2.5 (Schrödinger), Release 2016-1.



Scheme 6. Depiction of Celecoxib bound to mouse COX-2 (PDB: 3LN1), hydrogen bonds denoted by dashed lines. Generated using Maestro Elements 2.5 (Schrödinger), Release 2016-1.

In conclusion, we have developed a convenient and high-yielding one-pot synthesis of sulfonimidamides, exploiting the sulfinylamine TrNSO as a linchpin reagent. (Hetero)aryl and alkyl organometallic reagents were found to be compatible with the process, while primary and secondary amines and anilines all proved competent nucleophiles, allowing access to a truly broad range of medicinally relevant sulfonimidamides and in so doing opening up previously difficult-to-access chemical space. Furthermore, several analogues of the COX-2 inhibitor Celecoxib were prepared using the methodology and their biological activity and physicochemical properties were evaluated. Although COX-2 inhibition decreased for the tested compounds, the metabolic stability of the parent sulfonimidamide (**17**) was improved relative to Celecoxib, demonstrating a potential benefit of sulfonimidamides in medicinal chemistry. We anticipate that this method will quickly find use in medicinal chemistry and agrochemistry programmes, and should encourage further investigation into this increasingly important class of molecules.

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Keywords: sulfur functional groups • medicinal chemistry • sulfonimidamides • sulfinylamines • one-pot synthesis

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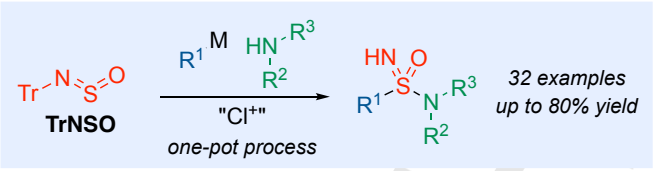

The stable, readily prepared sulfinylamine reagent TrNSO is exploited as a linchpin to join organometallic reagents and amines to provide sulfonimidamides in a high yielding one-pot process. Good variation of both reaction components is possible.