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Synthetic Methods

# The Modular Synthesis of Sulfondiimidoyl Fluorides and their Application to Sulfondiimidamide and Sulfondiimine Synthesis

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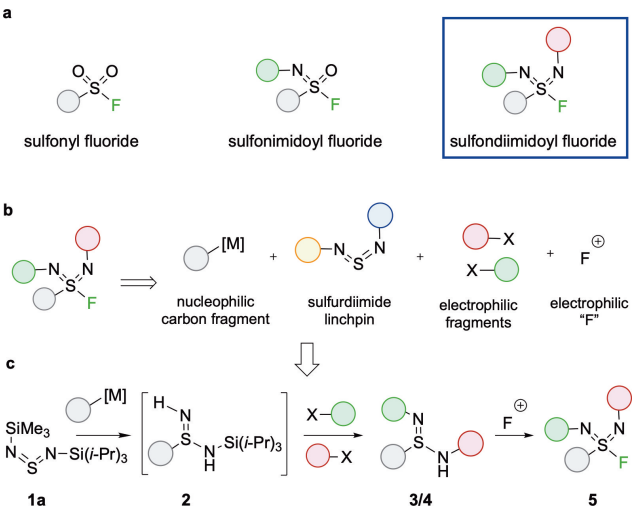
**Abstract:** A modular synthesis of sulfondiimidoyl fluorides—the double aza-analogues of sulfonyl fluorides—allowing variation of the carbon and both nitrogen-substituents is reported. The chemistry uses readily available organometallic reagents, commercial sulfinylamines, simple electrophiles, and N-fluorobenzenesulfonimide (NFSI), as the starting materials. The reactions are broad in scope, efficient, and scalable. We show that the sulfondiimidoyl fluoride products can be combined with amines to provide sulfondiimidamides, and with organolithium reagents to provide sulfondiimines, and that reactivity in these transformations can be modulated by variation of the N-substituents.

The displacement of fluorine from electrophilic sulfur centres is now established as one of the most reliable bond constructions for the conjugation of biologically relevant nucleophiles to electrophilic warheads.[1] Sulfur centres at different oxidation states, cloaked with varied heteroatom combinations, have all been used, but the dominant features that contribute to the utility of these groups are the high strength of the S–F bond, and the tunability of the fluoride leaving ability through modulation of its local environment. The burgeoning field of SuFEx chemistry is primarily based on these principles.[2] The dominant functional group that showcases these attributes are sulfonyl fluorides (Scheme 1a),[3] and they have been used extensively in multiple applications in chemical biology,[4] medicinal chemistry,[5] and synthetic chemistry.[6] Sulfonyl fluoride reactivity is controlled by the steric and electronic nature of the carbon substituent, and by the "activator" used to promote reactions. Activation methods include the use of H-bonding solvents, silylated nucleophiles,[7] fluorophilic Lewis acids such as calcium salts,[8] and Lewis bases such as DBU and guanidine,[8] or combinations thereof.[9] Sulfonimidoyl fluorides,[10] the mono-aza variants of sulfonyl fluorides, are a less-developed but emerging class of electrophilic sulfur functional group.[11] The introduction of an imidic S=N–R group in these molecules provides an additional opportunity to modulate reactivity through variation of the size and electronic properties of the N-substituent, and the chirality of the sulfur centre offers further prospects to achieve selectivity in reactions with nucleophiles.[12] The di-aza variants of sulfonyl fluorides, sulfondiimidoyl fluorides, are much less common, and although they can be traced to a report from 1976,[13] there is scant use of these intriguing functional groups with only minimal syntheses and reactivity studies known.[14] The additional imidic S=N–R group, together with their potential chiral S-atom, make sulfondiimidoyl fluorides alluring motifs for investigation.[15] A recent report from our laboratory on the synthesis of sulfondiimidamides exploited sulfondiimidoyl fluorides as key intermediates;[16] despite this success, several limitations remained, and in particular, extremely limited variation on the imidic N-substituents of the sulfondiimidoyl fluorides was possible, with all examples prepared featuring the N-*t*-Oct, N'-Ns combination. In this present work we describe a modular synthesis of sulfondiimidoyl fluorides that uses readily available building blocks (Scheme 1b) and allows independent variation at the carbon and both imidic nitrogen substituents. We also show that the nature of the nitrogen substituents can be used to control reactivity at the sulfur center, and use this feature in syntheses of sulfondiimidamides and sulfondiimines.




***Scheme 1.*** a) Sulfonyl fluorides, sulfonimidoyl fluorides, and sulfondiimidoyl fluorides. b) General retrosynthesis of sulfondiimidoyl fluorides, and c) proposed forward synthesis.

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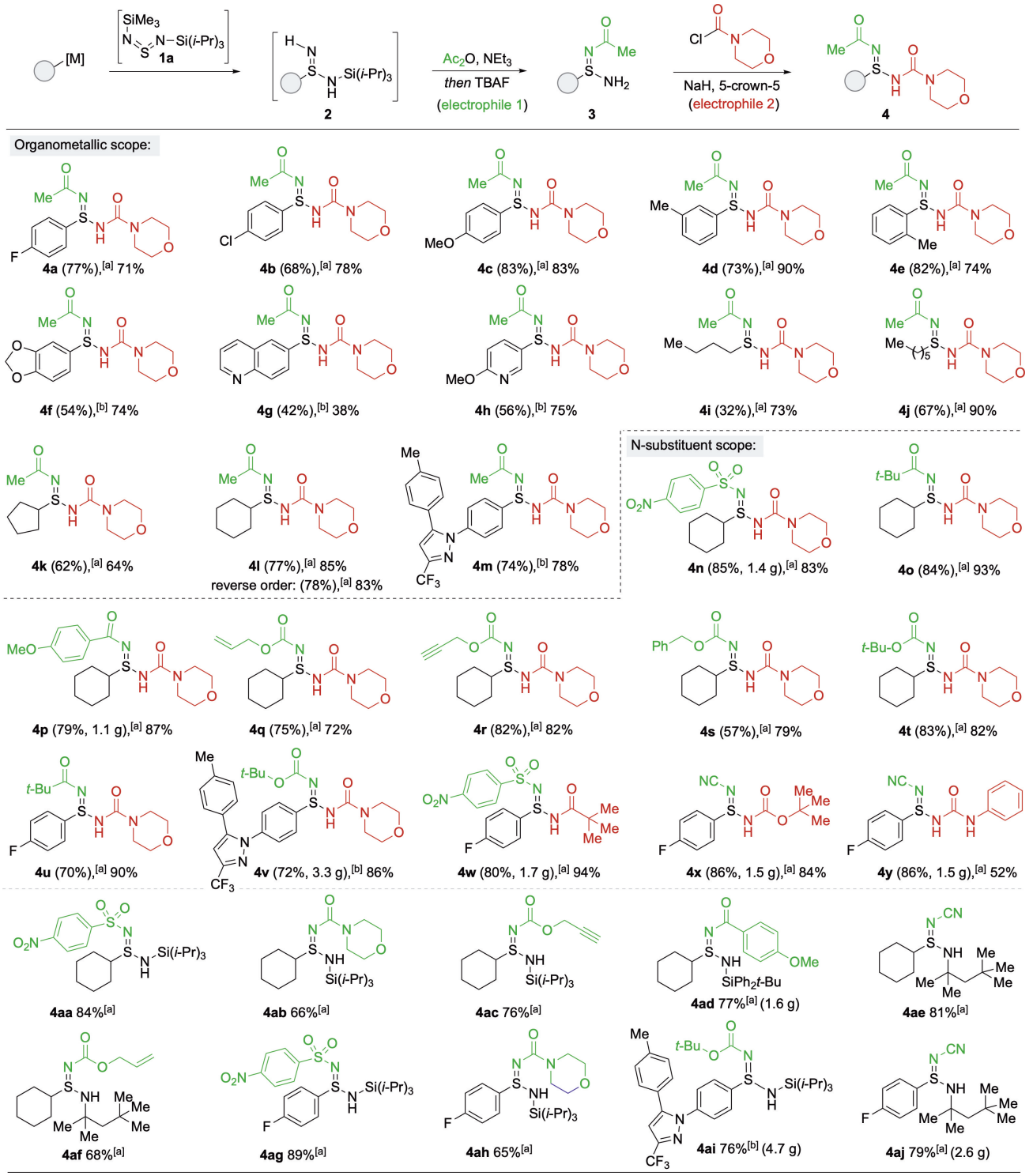
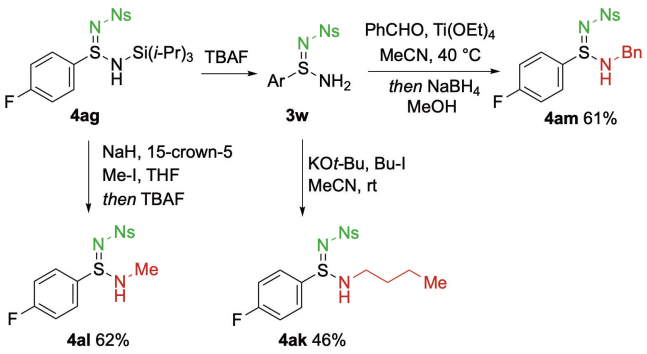



***Scheme 2.*** Sulfinamidine scope. Reaction conditions: TIPS-NSO (1.0 equiv), LiHMDS (1.0 equiv), THF (0.5 M), −30 °C, 5 min, then 0 °C, 5 min, then TMSCl (1.0 equiv), 0 °C, 10 min, then organometallic reagent (1.2 equiv), 0 °C, 10 min. Aqueous work up. Then $Et_3N$ (1.1 equiv), electrophile 1 (1.0 equiv), $CH_2Cl_2$ (0.2 M), 0 °C to rt, 20 min to 26 h, then TBAF (1.1 equiv), 0 °C, 10 min. Isolated yields in parenthesis. Then primary sulfinamidine **3** (1.0 equiv), NaH (2.0 equiv), 15-crown-5 (2.0 equiv), THF (0.1 M), 0 °C to rt, 20 min, then electrophile 2 (2.0 equiv), 0 °C to rt, 24 h. Isolated yields. [a] Grignard reagent used. [b] Organolithium reagent used.

Following the blueprint from our earlier report of sulfondiimidoyl fluoride synthesis,[16] we envisioned a synthetic route combining the addition of nucleophilic carbon fragments into N-functionalised sulfurdiimides to provide sulfinamidines **2** (Scheme 1c). Manipulation of both N-substituents should be possible at this stage (**3** and **4**), before



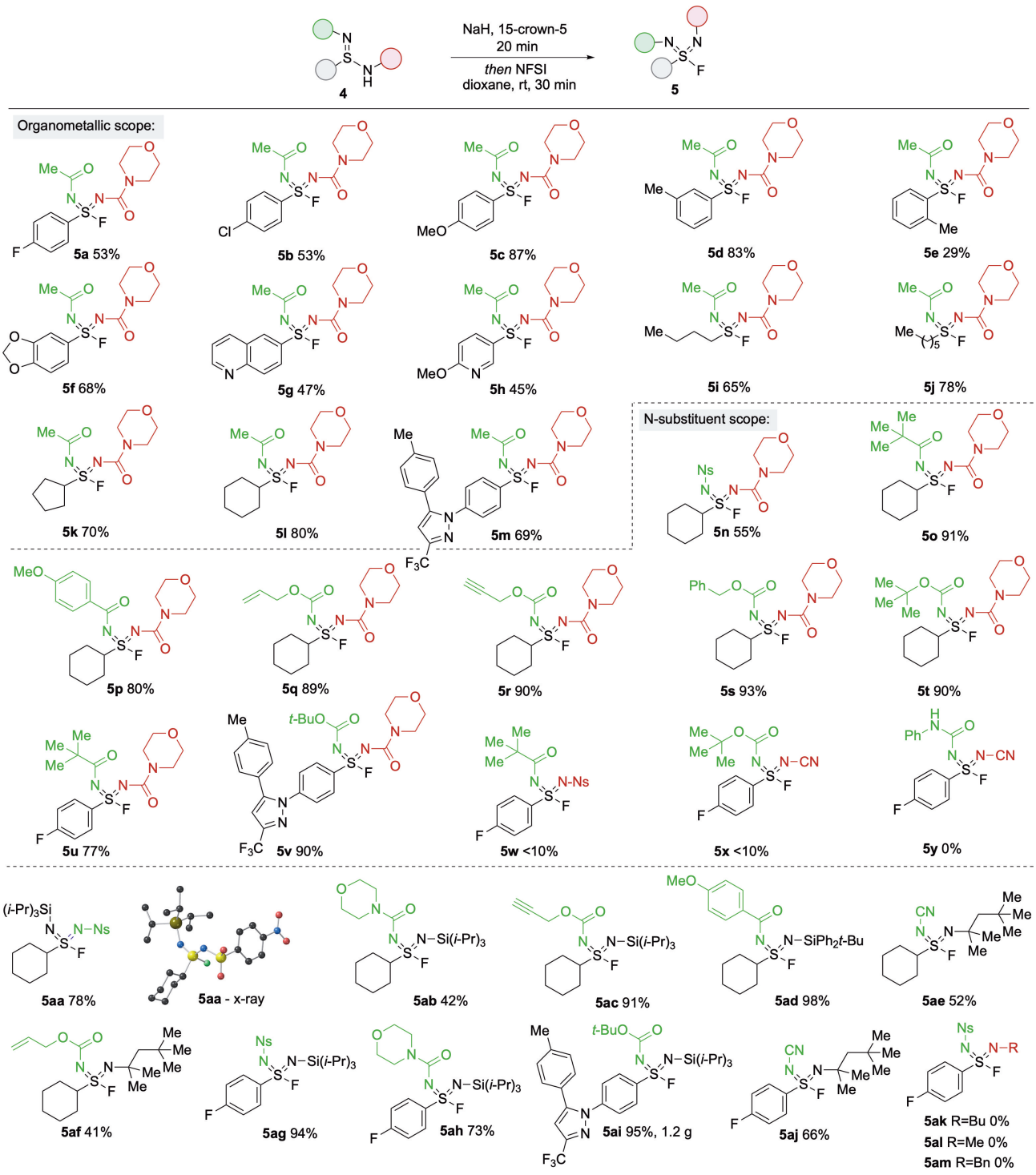

***Scheme 3.*** Synthesis of N–Bu, Me, and Bn sulfinamidines (**4ak–am**).

oxidative S-fluorination provides the target sulfondiimidoyl fluorides (**5**). An important consideration in our planning was that the sulfurdiimide reagent should be readily prepared, and used without recourse to a glovebox. Accordingly, we settled on reagents such as **1a** featuring two different N-silyl substituents; these reagents can be prepared on gram scale from the commercially available sulfinylamine TIPS-NSO,[17] display the necessary reactivity, but are sufficiently stable to be used outside of a glovebox. The in situ preparation and use of **1a** is also straightforward.[18] Combining sulfurdiimide **1a** with organometallic reagents would provide N–H, N'-TIPS substituted sulfinamidines **2**. Subsequently, a sequence of N-functionalisation and in situ N'-TIPS deprotection (with TBAF) would generate the first sulfinamidine intermediates **3**, on which the second N-substituent could be installed to give bis-substituted sulfinamidines **4**. Finally, oxidative fluorination would provide the corresponding sulfondiimidoyl fluorides **5**.

This approach was highly effective in practise, and as can be seen in Scheme 2, a broad range of organometallic reagents undergo efficient addition to bis-silyl sulfurdiimide **1a**. Aryl reagents featuring functional groups at all positions of the aromatic ring (**4a–f**), heteroaromatics (**4g**, **h**), and acyclic (**4i**, **j**) and cyclic (**4k**, **l**) alkyl groups, are all effective. The arene core of the medicinal agent celecoxib was also incorporated (**4m**), and both Grignard and organolithium reagents were used. For these examples, exploring variation of the carbon fragment, we selected an acetyl and a morpholine urea as the two N-substituents, with acetyl chloride and the corresponding carbamoyl chloride acting as 'electrophile 1' and 'electrophile 2', respectively.[19] The $SiMe_3$ group was simply removed on work-up towards non-isolated intermediate **2**, while removal of the $Si(i\text{-}Pr)_3$ group required the addition of TBAF before addition of 'electrophile 2'. Yields are given for both mono-functionalised sulfinamidines **3**, and double functionalized sulfinamidines **4**, which are the only isolated intermediates in the sequence. We next established that the electrophilic N-functionalization could tolerate a selection of reagents; nosyl (**4n**, **w**), pivaloyl (**4o**, **u**, **w**), aryl amide (**4p**), allyl and propargyl carbamates (**4q**, **r**), Cbz (**4s**), Boc (**4t**, **v**, **x**), and cyano (**4x**, **y**) groups could all be incorporated, and aryl and cycloalkyl carbon fragments were similarly effective in these reactions. Omitting the TBAF and 'electrophile 2' steps from this sequence allows the non-TMS N-substituent of the starting sulfurdiimides to be incorporated in the sulfinamidine products. Using this approach N–$Si(i\text{-}Pr)_3$ groups could be partnered with N-nosyl (**4aa**, **ag**), urea (**4ab**, **ah**), propargyl carbamate (**4ac**), and Boc (**4ai**) substituents. *tert*-Octyl, and N-$SiPh_2t$-Bu groups were also introduced (from the respective sulfinylamines), and combined with amide (**4ad**), carbamate (**4af**) and cyano (**4ae**, **aj**) substituents. Multiple sulfinamidines were prepared on >gram scale (**3n**, **p**, **v**, **w**, **x**, **y**, **4ad**, **ai** and **aj**), and sulfinamidine **4l** was prepared with the two electrophile steps being performed in either order, highlighting the versatility of the route.

The telescoped route shown in Scheme 2 was not amenable for the synthesis of sulfinamidines with simple N-alkyl substituents such as methyl or benzyl, with only trace amounts of the desired products being formed in these cases. However, direct alkylation of isolated N–Ns aryl sulfinamidine **3w** using 1-iodobutane and KO*t*-Bu proceeded smoothly in MeCN at ambient temperature, resulting in the isolation of N–Ns, N'-butyl sulfinamidine **4ak** in 46 % yield (Scheme 3). N-Methylation was more challenging, with double methylation being the dominant pathway. An alternative approach using N-TIPS sulfinamidine **4ag** as the substrate was developed; methylation using iodomethane, and then N-TIPS cleavage with TBAF successfully delivered the targeted N-mono-methyl sulfinamidine **4al** in 62 % yield. Reductive amination of sulfinamidine **3w**, achieved using benzaldehyde and the Lewis acid $Ti(OEt)_4$ in MeCN at 40 °C, followed by addition of $NaBH_4$, provided N-benzyl sulfinamidine **4am** in 61 % yield.

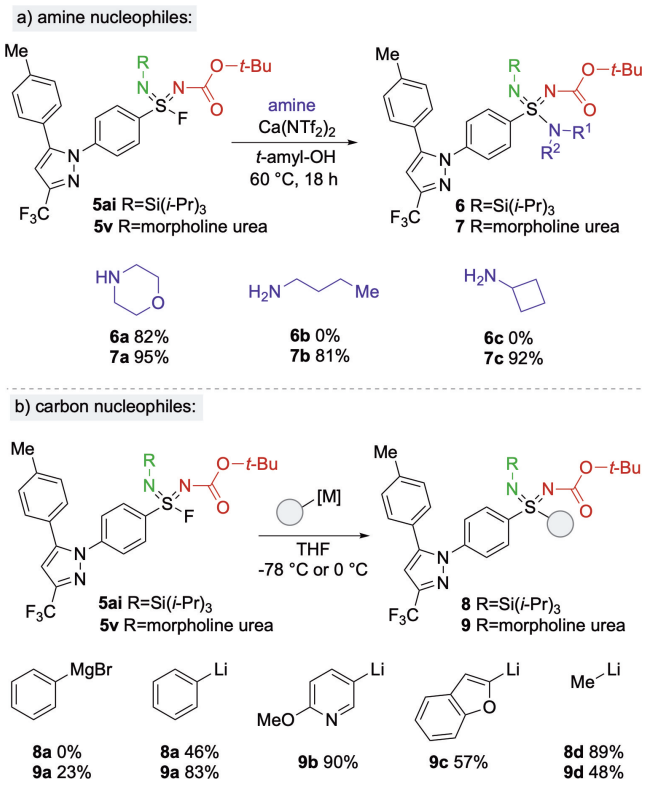
With a range of structurally diverse sulfinamidines available, we next explored their conversion into the final sulfondiimidoyl fluorides. The optimized conditions involved deprotonation using NaH in combination with 15-crown-5, before treatment with the $F^+$ reagent N-fluorobenzenesulfonimide (NFSI, Scheme 4, see Supporting Information for optimization studies). Using this method, all N-acetyl, N'-urea derived secondary sulfinamidines were converted to the corresponding sulfondiimidoyl fluorides (**5a–5m**, Scheme 4), and all were stable to isolation by column chromatography. In contrast to the slow fluorination step (1–8 days) observed in the preparation of N–Ns, N'-*t*-Oct sulfondiimidoyl fluorides in our previous report,[16] all reactions were complete within 30 minutes. The same conversion, but using sulfinamidine substrates bearing alternative electron-withdrawing N-substituents was then explored, and the majority of substrates again provided the corresponding sulfondiimidoyl fluorides in good to moderate yields (**5n–5v**). There were a small number of unsuccessful examples (**5w–y**); these substrates featured the most electron-deficient sulfur-centres, resulting in reduced nucleophilicity. The $^{19}F$ NMR shift of the 4-F-substituent in a series of representative 4-F-aryl sulfinamidines was used as a proxy for electron density at sulfur, and was found to correlate with the observed reactivity (see Supporting Information). A selection of sulfondiimidoyl fluorides featuring an N-electron-withdrawing group partnered with N'-*t*-Octyl, N'-$Si(i\text{-}Pr)_3$, or N'-$SiPh_2t$-Bu substituents were prepared in good yields (**5aa–5aj**). However, the related




***Scheme 4.*** Sulfondiimidoyl fluoride scope. Reaction conditions: sulfinamidine (1.0 equiv), NaH (1.5 equiv), 15-crown-5 (1.5 equiv), 1,4-dioxane (0.1 M), rt 20 min, then NFSI (2.0 equiv), rt 30 min. Isolated yields.

substrates featuring N'-Me, N'-Bu, or N'-Bn substituents (partnered with an N-electron-withdrawing group) were not accessible, with only decomposition observed (**5ak**–**am**). From these latter reactions we concluded that alkyl substituents on N-alkyl sulfinamidines can not feature α-protons for these transformations.

With efficient syntheses of myriad sulfondiimidoyl fluorides achieved, we set out to generate preliminary data on the influence of N-substituents on their SuFEx reactivity. Our earlier report on sulfondiimidamide syntheses had established that N–Ns, N'-*t*-Oct substituted sulfondiimidoyl fluorides could be combined with secondary amines using




***Scheme 5.*** SuFEx reactions of sulfondiimidoyl fluorides with a) nitrogen and b) carbon nucleophiles.

stoichiometric $Ca(NTf_2)_2$ as an activator,[16] however, primary amines were not reactive under these conditions. To investigate if the nature of the N-substituents could be used to modulate reactivity, for example to allow primary amines to be used, we selected sulfondiimidoyl fluorides **5ai** and **5v** as representative substrates. **5ai** features N-Boc, N'-TIPS imidic substituents, while **5v** has N-Boc, N'-urea substituents in place (Scheme 5a). Both sulfondiimidoyl fluorides **5ai** and **5v** reacted with morpholine using stoichiometric $Ca(NTf_2)_2$ in *t*-amyl alcohol at 60 °C,[8] to provide corresponding sulfondiimidamides **6a** and **7a** in 82 % and 95 % yields, respectively. The more electron-rich sulfondiimidoyl fluoride **5ai** was unreactive when primary amines were used; however, sulfondiimidoyl fluoride **5v**, featuring the two electron-withdrawing N-substituents, reacted smoothly with both butylamine and cyclobutylamine, providing sulfondiimidamides **7b** and **7c** in excellent yields.

Using sulfondiimidoyl fluorides in SuFEx reactions with carbon nucleophiles would provide direct access to sulfondiimines,[11d,20] which are a class of sulfur(VI) products that are attracting considerable attention in medicinal chemistry.[21] Crucially, there are no examples of this type of reactivity with sulfondiimidoyl fluorides. We first combined sulfondiimidoyl fluorides **5ai** and **5v** with phenylmagnesium bromide; sulfondiimidoyl fluoride **5ai**, featuring the N-Boc, N'-TIPS substituents was unreactive, however, sulfondiimidoyl fluoride **5v** provided sulfondiimine **9a** in 23 % yield. Using organolithium nucleophiles was more successful, and reaction of both sulfondiimidoyl fluorides with 2 equiv. of organolithium reagent at low temperature (−78 °C or 0 °C) for 1 hour resulted in the expected sulfondiimines in good yields (Scheme 5b). Under these conditions, both *N*-TIPS derived substrate **5ai** and urea derived substrate **5v** could be combined with a variety of organolithiums, including commercially available reagents, and those generated by deprotonation or lithium-halogen exchange (see Supporting Information for details), providing sulfondiimines derived from alkyl, aryl, and heteroaryl reagents. Although both sulfondiimidoyl fluorides were effective substrates, the efficiency of the transformation was generally greater for the more-electron deficient substrate (**5v**), thus providing a further example of imidic N-substituents influencing reactivity at the sulfur centre. The superiority of organolithium reagents relative to Grignard reagents in these transformations mirrors the trend in reactivity reported by Johnson using sulfonimidoyl fluoride substrates.[22] The N-substituents of the sulfondiimidamides and sulfondiimines available from this preliminary study could be further manipulated. For example, the TIPS group was removed from sulfondiimidamide **6a** by treatment with TBAF, providing the corresponding N–H derivative in 97 % yield (see Scheme S2 in the Supporting Information). Similarly, removal of the TIPS group from sulfondiimine **8d** was achieved in 98 % yield; treatment of the resultant NH-derivative with TFA provided the double NH sulfondiimine in 93 % yield (Scheme S2).

In conclusion, a general and practical synthesis of sulfondiimidoyl fluorides has been developed that allows extensive variation of the carbon and both nitrogen substituents. Organometallic reagents, commercial sulfinylamines, simple electrophilic reagents such as acyl, sulfonyl & carbamoyl chlorides, and NFSI are the substrates, allowing a structurally diverse collection of sulfondiimidoyl fluorides to be prepared. The route is readily scalable, with multiple examples being delivered on >1 gram scale. Preliminary results in the SuFEx reactivity of sulfondiimidoyl fluorides show that both nitrogen and carbon nucleophiles can be used, and that the nature of the imidic N-substituents influences reactivity at sulfur. Given the current interest in covalent modification of biologically relevant nucleophiles, we anticipate these underutilized functional groups will attract the attention of discovery chemists and biologists.

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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** SuFEx · Sulfur · Electrophiles · Synthetic methods · Fluorine


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[19] Tautomerisation in sulfinamidines and sulfondiimidamides is possible, with the positions of the S–N single and S–N double bonds being dependent on the identity of the N-substituents, and also the solvent that NMR spectra are recorded in. For sulfinamidines featuring two electron-withdrawing substituents the major tautomer is challenging to identify. For sulfinamidines featuring one electron-withdrawing and one electron-donating substituent (such as 4ae) the major tautomer usually has alkyl-substituent on the S–N single bond.

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