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Sulfur Hot Paper

2-Methylimidazole-1-(*N*-*tert*-octyl)sulfonimidoyl Fluoride: A Bench-Stable Alternative to SOF_4 as Precursor to N,O-Substituted S(VI) Compounds

Natassa Lional, Fedor M. Miloserdov, and Han Zuilhof**

Abstract: S(VI) compounds with multiple N or O substituents are often difficult to make and several crucial routes, such as multimodal SuFEx (Sulfur (VI) Fluoride Exchange) chemistry, rely on the highly useful but hazardous SOF_4 gas. Safety issues and inaccessibility of SOF_4 strongly hamper the developments of these organic compounds. Here we describe the synthesis and applications of 2-methyl**im**idazole-1-(*N*-*tert*-octyl)**s**ulfonimidoyl **f**luoride (ImSF), a novel bench-stable analogue of SOF_4. ImSF is synthesized on a gram scale via a double fluorination of *t*-OctNSO. We show ImSF can undergo substitution reactions with phenols and amines, which lead to sulfurimidates and sulfuramidimidates, respectively, the intrinsically chiral analogous of medicinally relevant sulfates and sulfamates in which an S=O moiety is replaced by S=NR unit. Finally we demonstrate that such substitutions can occur enantiospecifically, providing the first entry to chiral sulfurimidates and sulfuramidimidates.

Sulfur is a crucial heteroatom in medicinal chemistry.[1] The last decade witnessed the renaissance of organic sulfur (VI) chemistry, with significant focus to the development of synthetic pathways to analogues of the $-SO_2-$ unit with the substitution of one or two of the S=O moieties with an S=NR linker (Figure 1A,B).[2] Such substitutions open a wide chemical space, providing new handles for further modifications with the potential to improve pharmacological potency.[3] Main efforts in this field focus on the synthesis of compounds with S=NR units and a C–S bond, such as sulfoximines,[4] sulfonimidamides[5] and sulfonimidates[6]

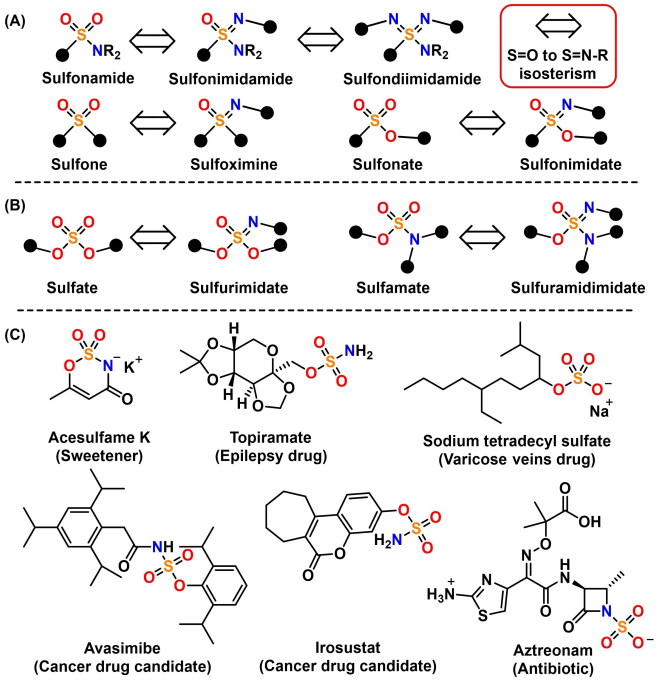

Figure 1. (A) S=NR isosters of sulfonamides, sulfones and sulfonates (S(VI) with S–C bond). (B) S=NR isosters of sulfates and sulfamates (S(VI) without S–C bond). (C) Examples of molecules with sulfate and sulfamate groups.

(Figure 1A), and—more recently—chiral variants of such molecules.[2c,d,5a,b,6–7] At the same time, synthetic methods to access S(VI) compounds with S=NR units and no C–S bond, such as sulfuramidimidates (or imidosulfamates) and sulfurimidates (Figure 1B), are still scarce.[8] Such molecular units would represent S=NR analogues of conventional sulfates and sulfamates, which are e.g. present in the artificial sweetener acesulfame K,[9] epilepsy treatment medicine topiramate,[8a,10] beta-lactam antibiotic aztreonam,[11] varicose veins medication sodium tetradecyl sulfate,[12] and in molecules that participated in clinical trials, such as avasimibe[13] and irosustat (Figure 1C).[14]

Currently, the only modular approach to synthesize sulfuramidimidates and sulfurimidates with variation of all substituents around sulfur center is based on the use of thionyl tetrafluoride SOF_4 as the source of key SF_2-based intermediates (Figure 2).[7b,8b,e] Although this method is highly effective to produce various sulfur (VI) compounds,[7b,8e] it is not practical, because SOF_4 is a non-

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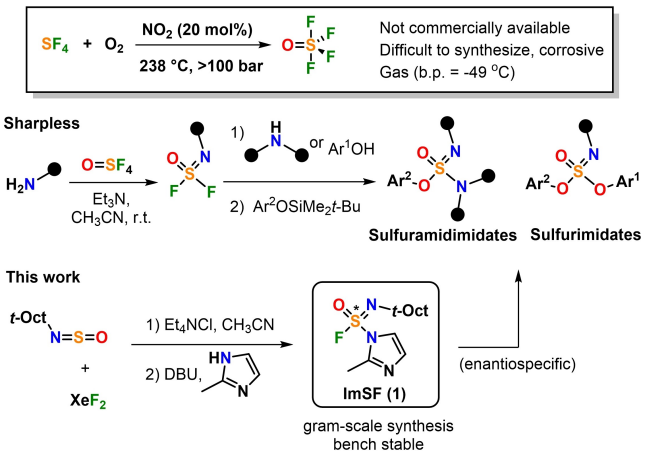
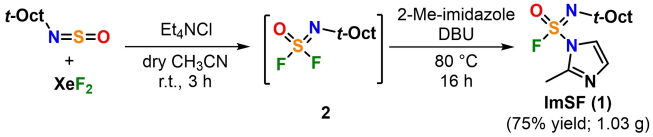


Figure 2. SOF_4-based synthesis of sulfuramidimidates and sulfurimidates, and the ImSF (**1**) reagent developed in this work.

commercially available, highly corrosive and hazardous gas, which is difficult to handle. Accessibility and handling issues of SOF_4 evidently hampered the development and use of the chemistry of sulfuramidimidates and sulfurimidates. We thus set out to derive an easy-to-handle species of the form R–N=S(VI)-XY, in which leaving groups X and Y could be easily replaced by O- or N-centered nucleophiles as in multimodal SuFEx (Sulfur (VI) Fluoride Exchange) reactions,[15] so as to stimulate the further development of multimodal S(VI) exchange chemistry and synthesis of sulfuramidimidates and sulfurimidates. In the chemistry outlined in this manuscript we overcome forementioned limitations via the efficient synthesis of ImSF (**1**, stands for 2-methyl**im**idazole-1-(*N-tert*-octyl)**s**ulfonimidoyl **f**luoride). The route towards **1** does not require the use of SOF_4, and provides ImSF as a bench-stable chemical on a gram scale. ImSF remains stable and shows no signs of degradation when stored on the bench for at least six months. The reactivity of **1** allows the synthesis of a wide range of sulfuramidimidates and sulfurimidates through controlled nucleophilic substitutions at the sulfur center. We also for the first time demonstrate that such substitutions occur enantiospecifically, allowing for the first time to prepare sulfuramidimidates and sulfurimidates in a chiral form.

We envisioned that the oxidative difluorination of readily available sulfinylamines R-NSO (commercial or can be synthesized in one step)[2b] could be a viable route to iminosulfur oxidifluorides $RNS(O)F_2$ (**2**), which are key intermediates in the synthesis of sulfuramidimidates and sulfurimidates (Scheme 1). The difluorination of CF_3NSO to $CF_3NS(O)F_2$ was previously reported with the use of



Scheme 1. Gram-scale synthesis of ImSF (**1**).

XeF_2.[16] We started our experiments with investigating whether a similar XeF_2-mediated difluorination could be applied to other sulfinylamines. For PhNSO, the reaction was not selective, resulting in the formation of only trace amounts of $PhNS(O)F_2$ under various reaction conditions (monitored by ^{19}F NMR, see Supporting Information for details). At the same time, reactions of XeF_2 with cyclohexyl- and *t*-octyl-substituted sulfinylamines showed a better performance—and corresponding products were obtained in 49 % and 69 % NMR yields, respectively. Since the *t*-octyl is also a well-established protecting group of a sulfonimidoyl unit, that can be easily cleaved under acidic conditions and replaced with other functionalities,[2a,b,17] we selected *t*-OctNSO as a substrate for further reaction optimization.

In this, the addition of Et_4NCl was found to be crucial for the successful difluorination of *t*-OctNSO, in line with results of Wilson,[18] for the conversion of SO_2 to SO_2F_2. Et_4NCl in the presence of XeF_2 produces fluoride ions,[19] which facilitate the oxidative fluorination of sulfur(IV) to sulfur(VI). We also noticed that the concentration of Et_4NCl is important, as e.g. 0.5 equiv. of Et_4NCl gave double the yield of difluoride **2** compared to using 2 equiv. of this halide salt. Variation of the solvent showed preference for acetonitrile over dichloromethane (DCM), with a 1:1 mixture of DCM/CH_3CN performing as well as acetonitrile. Since we aimed for a one-pot synthesis of ImSF, operational simplicity steered us to pure CH_3CN, as the second step requires overnight heating at 80 °C. In addition, a relatively high 1 M concentration of *t*-OctNSO was found to provide the highest NMR yield (full list in SI, Tables S4–S6). The synthesis of mg-scale amounts of **2** required only 60 min for the first step, while for its synthesis on a gram scale, a longer reaction time of 3 h was shown to be optimal (see ESI for details).

Next, we also aimed to introduce tunable dual reactivity, with both smaller or higher reactivity than S(VI)-bound F atoms, and preferably in a manner that is also chiral, to allow asymmetric syntheses. Therefore, we transformed **2** into ImSF (**1**) via the in situ addition of 2-methylimidazole and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) with 75 % yield on a gram-scale (Scheme 1). This step also solved issues related to the isolation of **2**, as it is volatile and non UV-active.

Having ImSF in hand, we explored the scope of SuFEx reactions with it using phenols as nucleophiles. The parent compound phenol yields sulfuramidimidate product **3a** in 87 % yield. To bring the reaction to completion overnight in CH_3CN, 3 equivalents of phenol were used, while excess base was used to prevent activation of imidazole to imidazole salt (as that converts imidazole into a good leaving group), and thus results in the formation of double substitution by-product (Figure 3). We found that **1** also reacted well with phenols bearing both electron-donating and mildly withdrawing groups. Phenols with a *para*-substituted electron-donating group (4-OMe, 4-*t*-Bu, 4-SMe; **3b–d**) gave corresponding products in 71–83 % yield, while *meta*-substituted methyl phenol (**3e**) gave the highest 92 % yield. The reaction was found to be somewhat sensitive to

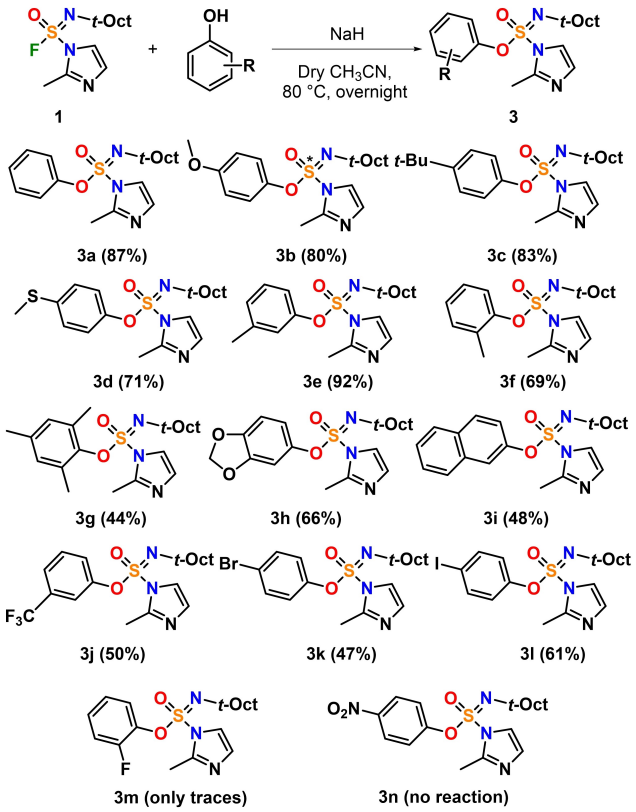


Figure 3. Scope of SuFEx reaction between ImSF (1) with phenolic derivatives. Reaction conditions: [a] **1** (0.15 mmol; 1 equiv), phenols (3.0 equiv), NaH (4.0 equiv) in dry CH_3CN (0.6 mL) at 80 °C, overnight.

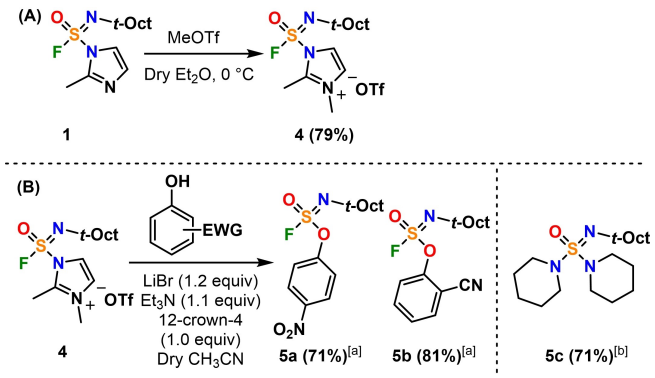


Figure 4. (A) Synthesis of imidazolium salt **4**. Reaction conditions: **1** (3.20 mmol; 1 equiv), methyl triflate (1.1 equiv) in dry Et_2O (6.4 mL), 0 °C to rt, 30 min. (B) Reactions between **4** and electron-poor phenols. Reaction conditions: [a] **4** (0.10 mmol; 1.0 equiv), LiBr (1.2 equiv), phenols (1.05 equiv), TEA (1.1 equiv), 12-crown-4 (1.0 equiv) in dry CH_3CN (0.5 mL) at 40 °C, overnight; [b] **4** (1.0 equiv), piperidine (6.0 equiv), LiBr (5.0 equiv), in CH_3CN (0.5 mL) at 80 °C, overnight.

sterics, as for *o*-cresol product **3f** was isolated in a bit lower, 69 % yield. However, the impact of steric hindrance is limited, as even for bulkier mesitol, the reaction worked, and product **3g** was isolated in 44 % yield. With 5-benzodioxolol (**3h**) and 2-naphthol (**3i**) the reaction resulted in products with 48–66 % yield. Phenols with mildly electron-withdrawing groups (3-CF_3; 4-Br; 4-I, **3j–l**) also worked, although the isolated yields of 47–61 % were slightly lower than for the more electron-rich phenols. For 2-F substituted phenol only traces of the product were observed, and phenols with a strong electron-withdrawing group at the *para*-position, such as 4-NO_2 (**3n**), showed no reaction with **1**.

To resolve the limitation and to generate a much better leaving group, we synthesized imidazolium salt **4** (Figure 4A), a sister compound of ImSF. Methyl triflate (MeOTf) activates the imidazole moiety of **1**, which then proved to be more reactive than fluorine, and thus acts as the first leaving group (Figure 4B).[20] We initially attempted to substitute **4** with 1.05 equiv. of phenol in the presence of 1.1 equiv. of triethylamine as a base. However, the formation of fluoride ion led to the generation of the SF_2 by-product (**2**) which was seen by ^{19}F NMR. Addition of 1.2 equiv. of a fluoride scavenger[5a,b] (here: LiBr/12-crown-4) was found to strongly improve the reaction performance. We observed that **4** reacted well with phenols bearing strong electron-withdrawing substituents: 4-NO_2-phenol gave product **5a** in 71 % yield, while *ortho*-CN phenol gave product **5b** with 81 % yield. We also looked at double substitution with N-nucleophiles, as synthesis of imidosulfurdiamides are rather underdeveloped.[8d] The reaction with 6 equiv. of piperidine along with 5 equiv. of LiBr were added, we observed double substitution reactions with both the activated imidazole and fluorine to provide **5c** in 71 % yield. While imidazolium salt **4** showed efficient reactivity towards strongly electron-poor phenols, it demonstrated poor selectivity in reactions involving phenol and electron-rich *p*-OMe phenol. Therefore, the—also shorter—route via **1** is preferable for such substrates.

Having established an efficient method to synthesize products **3** and **5**, we next focused on the synthesis of sulfuramidimidates and sulfurimidates, using compound **3b** as a model substrate (Figure 5). To convert imidazole into a good leaving group, **3b** was first treated with methyl triflate, and the generated imidazolium salt **6** was *in- situ* reacted with amine or phenolate nucleophiles. Aliphatic secondary amines reacted with **6** to readily form sulfuramidimidates **7a–d** with yields ranging from 71 % to 79 %. Compound **6** did not exhibit any reactivity with 3-aminopyridine (yielding **7e**), whereas the reaction with primary *n*-butylamine did not result in the formation of product **7f**, and elimination of 4-methoxyphenol from the sulfur center was observed instead. This observation is in line with previous report of Sharpless and co-workers, which reported the synthesis of sulfuramidimidates derived only from secondary amines.[8e,21]

Our method also gave an entry point to sulfurimidates—reactions with sodium phenolates produced sulfurimidates **7g–j** with comparable yields of 71–76 %. The inductive effects of iodine and CF_3 groups (yielding **7h–i**) did not significantly impact the yield of sulfurimidates, unlike the *ortho*-substituted 2-Me group (**7k**), for which no reaction was observed.

Next we showcased that our approach using ImSF also potentially allows functionalization of the sulfimide S=NR unit, and thereby full control over all reaction site of the

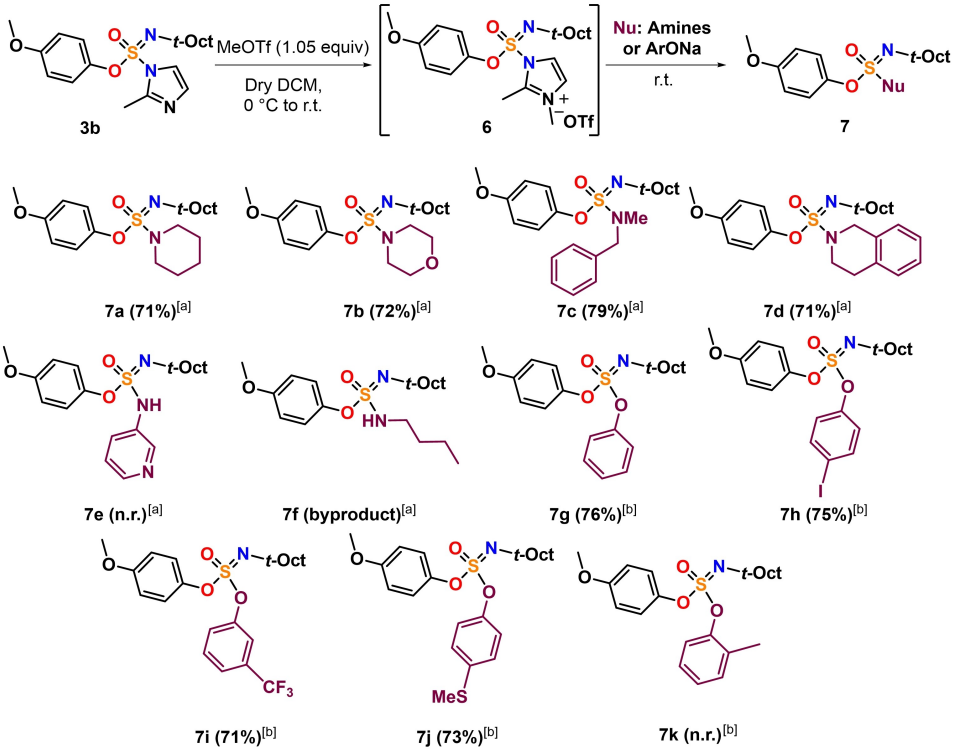
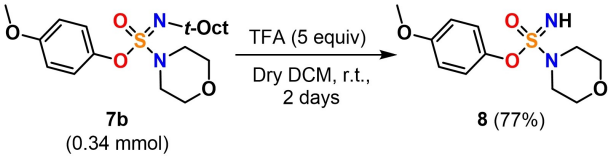


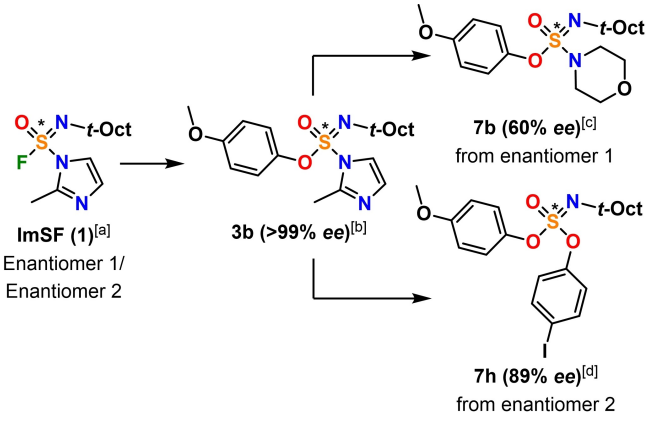
Figure 5. Synthesis of sulfuramidimidates and sulfurimidates. Reaction conditions: [a] **3b** (0.10 mmol), methyl triflate (1.05 equiv), amines (4.2 equiv) in dry DCM (0.33 mL), r.t., overnight; [b] **3b** (0.10 mmol), methyl triflate (1.05 equiv), phenols (2.1 equiv), NaH (2.1 equiv) in dry DCM/CH_3CN mixture (0.53 mL), r.t., 2 d.

central sulfur atom. The removal of the *t*-octyl protecting group in **7b** occurs readily upon treatment with trifluoroacetic acid (TFA), providing imidic NH derivative **8** in 77 % isolated yield (Scheme 2), which opens the way for potential N-functionalization. Subsequent S=NH functionalization with various functional groups is well-established in the literature for related sulfondiimidamides.[2a,b,17]

Finally, we investigated the synthesis of chiral sulfuramidimidates and sulfurimidates via the ImSF route. Since ImSF is an inherently chiral molecule and stable under ambient conditions, we could readily separate it into two enantiomers using chiral preparative high-performance liquid chromatography (HPLC). Having both single enantiomers of ImSF at hand allowed us for the first time to investigate the enantiospecificity of nucleophilic substitutions at a non-C bonded S(VI) center (Scheme 3), which further explores available enantioselective methods to functionalize non-C substituted S(VI).[7b] The reaction between both single enantiomers of ImSF and 4-methoxyphenol (in separate reactions) proceeds with complete enantiospecificity, leading to both enantiomers of chiral **3b** with 99 % *ee*. Preliminary subsequent reactions of one enantiomer of **3b** with 4-iodo phenol proceeded with 94 % enantioselectivity producing **7h** with 89 % *ee*, while the



Scheme 2. Removal of *t*-octyl group. Reaction conditions: **7b** (0.34 mmol; 1 equiv), TFA (5 equiv).



Scheme 3. Synthesis of chiral sulfuramidimidate and sulfurimidate. Reaction conditions: [a] The two enantiomers of **1** were separated by chiral prep HPLC, enantiomer 1 is >99 % *ee*, enantiomer 2 is 99 % *ee* [b] **1** (0.075 mmol), 4-methoxyphenol (3.0 equiv), NaH (4.0 equiv) in CH_3CN (0.3 mL) at 80 °C, overnight; [c] **3b** (0.053 mmol; 1 equiv), methyl triflate (1.05 equiv), morpholine (4.2 equiv) in dry DCM (0.18 mL), r.t., overnight; [d] **3b** (0.057 mmol; 1 equiv), methyl triflate (1.05 equiv), 4-iodophenol (2.1 equiv), NaH (2.1 equiv) in dry DCM/CH_3CN mixture (0.3 mL), r.t., 2 d.

reaction of the other enantiomer of **3b** with morpholine led to a partially racemized product **7b** with 60 % *ee*. Upon to our knowledge, products **7h** and **7b** are the first reported examples of chiral sulfurimidates and sulfuramidimidates.

In conclusion, we have developed a novel reagent, ImSF (**1**), which is a bench-stable SOF_4 analogue. ImSF can be efficiently synthesized on gram-scale from commercially available starting materials, and we showed that it is a viable precursor of sulfuramidimidates and sulfurimidates. The use of ImSF potentially allows independent functionalization of all three modification points at the sulfonimidoyl core, providing complete flexibility in their synthesis.

The intrinsic chirality of ImSF combined with its high stability allowed us to realize the synthesis of first chiral sulfurimidate (**7h**) and sulfuramidimidate (**7b**). We expect the ImSF reagent to pave the way toward chiral S=NR isosters of medicinally relevant sulfates and sulfamates, allowing to further fine-tune the chemical structure of these molecules for improved medicinal performance. Research focusing on the development of asymmetric methods for multigram-scale chiral separation of ImSF and protocols for its subsequent enantiospecific functionalization with various nucleophiles is currently ongoing in our group.

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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: SOF_4 · Sulfur (VI) · SuFEx · sulfuramidimidates · sulfurimidates

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