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COMMUNICATION

Rapid Access to Sulfinyl Fluorides for the Preparation of Sulfonimidoyl Fluorides

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Herein, we report a new thionyl fluoride-based method that rapidly converts sulfinic acids into the corresponding sulfinyl fluorides in 62–97% yield. The unstable sulfinyl fluorides can be directly treated with chloramine-T to afford sulfonimidoyl fluorides, an important class of sulfur(VI)-fluoride exchange (SuFEx) hubs, in 56–92% isolated yields.

The past two decades have witnessed a surge in new methods for efficiently accessing sulfur(VI) fluoride motifs, driven by their valuable biological properties and distinctive balance of stability and reactivity.[1] Among these, sulfonyl fluorides (Figure 1a, **1**) have emerged as key motifs in pharmaceutical drug development[2] and chemical biology,[3] and are widely used as SuFEx reagents.[4] In contrast, studies of sulfur(IV) fluorides have largely focused on their use as reagents, such as DAST[5] and XtalFluor-E®,[6] with relatively few investigations exploring these motifs as synthetic intermediates.

An intriguing class of sulfur(IV) fluoride motifs are sulfinyl fluorides (Figure 1b, **2**) as they have the potential to be used as intermediates for the formation of important sulfur(IV) or (VI) motifs. Despite the synthetic potential of sulfinyl fluorides, reports of their successful isolation are rare, as they are typically unstable during purification.[7] The preparation and use of sulfinyl fluorides as reactive intermediates in one-pot processes would, therefore, be a versatile strategy. Unfortunately, existing methods for the preparation of sulfinyl fluorides are not readily adaptable to these protocols.[8,9] The only one-pot method reported thus far involves the deoxyfluorination of trifluoromethylsulfinate (**3**), where the resulting sulfinyl fluoride (**4**) is a gas at room temperature and can be readily separated from the reaction mixture.[10] Beyond this isolated example, there are currently no general, one-pot methods available for the preparation and use of these sulfur(IV) motifs.

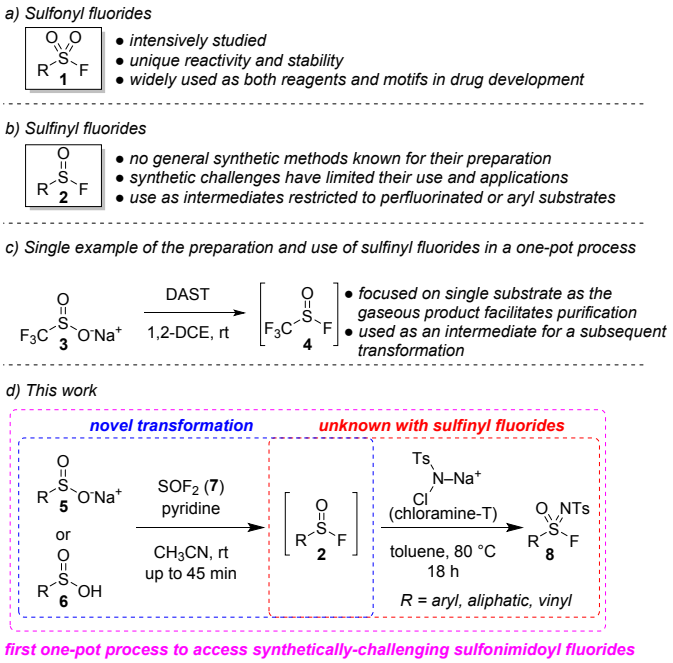

Figure 1. Sulfinyl fluorides: background, preparation, and novel synthesis and application.

We hypothesized that a general and expedited strategy (Figure 1d) could be achieved using ex situ-generated thionyl fluoride (SOF_2, **7**). This reagent has been shown to enable rapid deoxyfluorination of other motifs, and one-pot processes were readily be achieved[11] as the byproducts had minimal impact on downstream reactions. Unlike previous methods, this approach would not be limited to gaseous sulfinyl fluoride intermediates.

For the second step in the one-pot process, we targeted the synthesis of sulfonimidoyl fluorides. This important class of fluorinated motifs serve as sulfur(VI) fluoride exchange (SuFEx) hubs and are particularly valuable because of their enhanced stability relative to sulfonyl fluorides.[12] Existing approaches to

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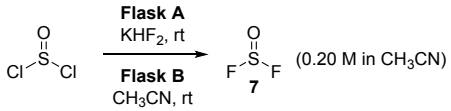
these compounds typically require at least two synthetic steps, and the intermediates require isolation.[13] A subsequent transformation of the sulfinyl fluoride intermediate (**2**), such as a novel oxidation to the corresponding sulfonimidoyl fluoride (**8**) would serve as a useful application toward an important class of molecules.

We began our investigation with the deoxyfluorination of *p*-fluorophenyl sodium sulfinate (Table 1, **5a**), which enabled analysis of the crude reaction mixture by ^{19}F NMR spectroscopy. For these experiments, an acetonitrile solution of thionyl fluoride was readily generated from thionyl chloride using our ex situ method (Scheme 1).[14] Acetonitrile was used for the optimization[15] as it was observed to efficiently solubilize the starting salts (entry 1). Even though some heterogeneity persisted, the desired sulfinyl fluoride **2a** was formed in 30% yield by ^{19}F NMR spectroscopy. Increasing the amount of thionyl fluoride to 3 equivalents resulted in a modest improvement in the yield (entry 2, 38%). The addition of pyridine led to a substantial increase in yield (entry 3, 69%), consistent with previous observations regarding the beneficial effect of amine bases in thionyl fluoride-promoted reactions.[16]

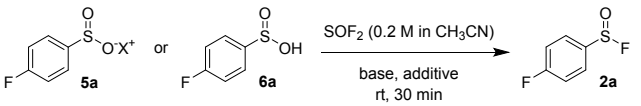


Scheme 1. Ex situ method of thionyl fluoride generation.[11a]

To further improve the solubility profile of the reaction mixture, we evaluated the use of 15-crown-5,[17] which provided sulfinyl fluoride **2a** in 83% yield (entry 4). Use of this crown ether in combination with other bases, including diisopropylethyl amine (DIPEA, entry 5), piperidine (entry 6), and *N,N*-dimethylaminopyridine (DMAP, entry 7), resulted in diminished yields. The corresponding pyridinium sulfinate salt was also evaluated as a starting material to improve solubility, affording **2a** in 73% yield (entry 8). Treatment of sulfinic acid **6a** with 3 equivalents of both pyridine and thionyl fluoride proved highly effective, delivering the sulfinyl fluoride (**2a**) in near quantitative yield (entry 9, 97%).[18] Other sulfur(IV)- and sulfur(VI)-fluoride reagents were also examined, but the yields were either poor or the byproducts narrowed the scope of subsequent transformations.[19]

With the optimized conditions established (Table 1, entry 9), we next explored the scope of this new method (Table 2) with a focus on substrates that lack viable preparative methods.[20] Consistent with prior reports,[21] significant degradation was observed upon attempted isolation of the sulfinyl fluorides (**2**). To evaluate the efficiency of the deoxyfluorination step, we therefore used ^{19}F NMR spectroscopic yields of the substrates.[22]

Table 1. Optimization experiments for the deoxyfluorination of sodium sulfinate **5a** and sulfinic acid **6a**.

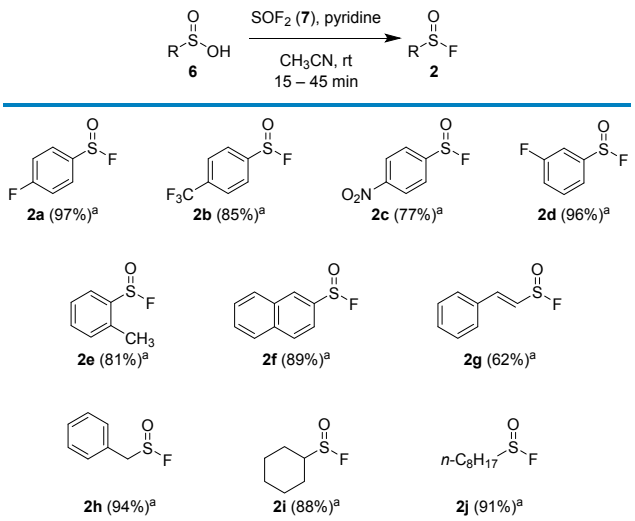


entry[a]	X	SOF_2 (equiv)	base[b]	additive	^{19}F NMR yield[c]
1	Na	1	-	none	30%
2	Na	3	-	-	38%
3	Na	3	pyridine	-	69%
4	Na	3	pyridine	15-crown-5	83%
5	Na	3	DIPEA	15-crown-5	75%
6	Na	3	piperidine	15-crown-5	51%
7	Na	3	DMAP	15-crown-5	60%
8	Pyr	3	-	-	73%
9	H (**6a**)	3	pyridine	-	97%

Reaction Conditions: [a]To a vial containing **5a** or **6a** and additive under argon was added a solution of base and SOF_2 in acetonitrile (0.20 M, see SI for SOF_2 generation). The mixture was stirred at rt for 30 min and then analyzed by ^{19}F NMR spectroscopy. Reactions were performed on 0.25 mmol scale. [b]1.0 equiv of base was used. [c]Conversion was determined by ^{19}F NMR spectroscopy using trifluorotoluene as the internal standard.

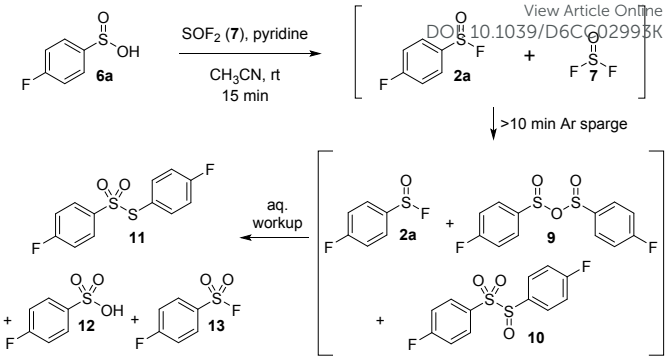
Electron-withdrawing groups in the *para*-position were tolerated, with the corresponding sulfinyl fluorides formed in 77 to 97% yield (**2a**–**2c**). Likewise, *meta*- and *ortho*-substituted substrates, as well as napthyl sulfinyl fluoride were obtained in good to excellent yields (**2d**–**2f**, 81–96%). While there are methods that can access aryl sulfinyl fluorides, there are only a few literature examples of non-fluorinated aliphatic products.[9a,c] Our new method also proved to be effective for these non-aromatic substrates (**2g**–**2j**). Vinyl- and benzyl-substituted sulfinic acids proved to be suitable substrates, affording **2g** and **2h** in 62% and 94% yield, respectively. Finally, the protocol was successfully extended to aliphatic sulfinyl fluorides, delivering **2i** and **2j** in 88% and 91% yield.

Table 2 Sulfinyl fluoride scope.



[a]Reaction Conditions: To a vial containing sulfinic acid **6** (0.25 mmol) under argon was added a solution of pyridine (1 equiv) and SOF_2 in acetonitrile (0.20 M, see SI for SOF_2 generation method). The mixture was stirred at rt for up to 45 min, and the conversion was determined by ^{19}F NMR spectroscopy using fluorobenzene or trifluorotoluene as the internal standard.

To ensure the method is compatible with one-pot processes, we next sought an effective strategy to remove excess thionyl fluoride. Initial attempts focused on sparging sulfinyl fluoride solutions with a dry inert gas, such as nitrogen or argon. However, extended sparging consistently resulted in lower yields of the corresponding sulfinyl fluorides (**2**). Moreover, sparged solutions exhibited significantly faster degradation compared with solutions that retained residual thionyl fluoride. To better understand this unexpected behavior, we first synthesized sulfinyl fluoride **2a** using our optimized protocol (Scheme 2), and then analyzed the reaction mixture every 2 minutes over a 10-minute degassing period using ^{19}F NMR spectroscopy.[23] Over the 10 minutes, sulfinyl fluoride **2a** was depleted and several new sulfur species increased in concentration. ^{19}F NMR spectroscopic analysis suggested that these species corresponded to sulfinic anhydride (**9**) and sulfinyl sulfone **10**. These structures are also consistent with previously reported decomposition pathways.[24] Aqueous workup of the reaction mixture afforded thiosulfonate **11** as the major byproduct, along with sulfonic acid **12** and sulfonyl fluoride **13**, which are known to form from **9** and **10**.[24] To minimize formation of these side products, we found it advantageous to leave trace thionyl fluoride present in the reaction mixture (the reaction was sparged for approximately 5 minutes).[25]



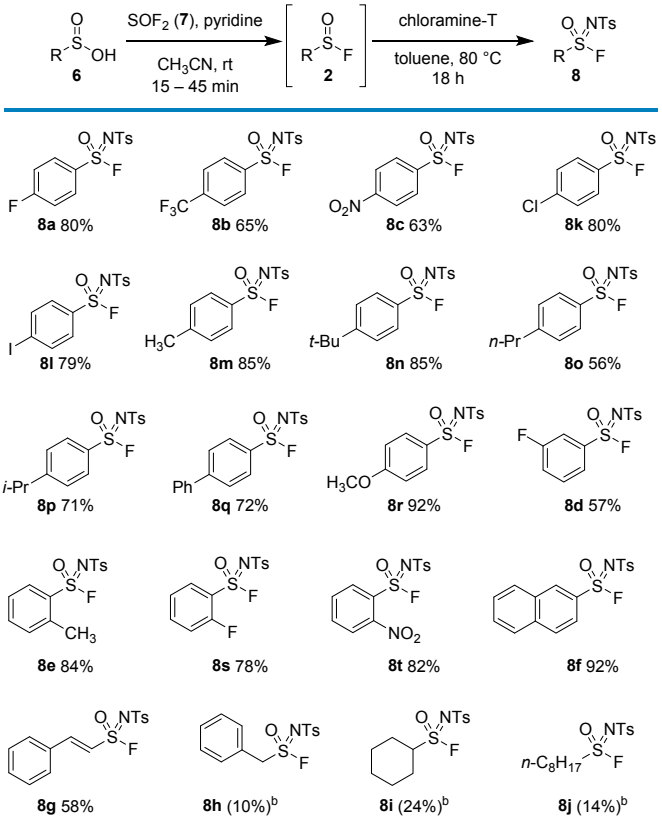
Scheme 2. Side reactions of sulfinyl fluorides after prolonged sparging with argon.

To evaluate whether the newly developed sulfinyl fluoride synthesis is compatible with one-pot protocols, we targeted the preparation of sulfonimidoyl fluorides (Figure 1, **8**). We hypothesized that we could access these important motifs in a sequence involving initial formation of the sulfinyl fluoride, followed by oxidation using chloramine-T. While nitrene additions to sulfinyl chlorides have been reported,[26] there are no examples of analogous transformations using sulfinyl fluorides.

We investigated the scope of this one-pot procedure for accessing sulfonimidoyl fluorides (**8**) using a wide range of aryl, vinyl, and aliphatic sulfinic acids (Table 3).[27] Electron-deficient sulfinic acids were amenable to this process, affording fluoro- (**8a**), trifluoromethyl- (**8b**), and nitro-substituted sulfonimidoyl fluoride (**8c**) in 63–80% yield. Chloride and iodide substituents in the *para*-position (**8k** and **8l**) provided comparable yields (79-80%) to the fluoride derivative (**8a**). *para*-Alkyl substituted sulfinic acids were successfully converted to the corresponding sulfonimidoyl fluorides (**8m**–**8p**) in good to excellent yields (56–85%). *para*-Phenyl substrate **2q** was also a viable substrate, affording **8q** in 72% yield. The reaction also proved to be effective for strongly electron-donating arenes, such as *para*-methoxy sulfinic acid (**8r**, 92% yield). *meta*-Substitution was also tolerated (**8d**, 57% yield). The reaction was largely tolerant of both electron-donating and withdrawing group in the *ortho* position, with sulfonimidoyl fluorides **8e**, **8s**, and **8t** all furnished in comparable yields (78–84%). Naphthyl-substituted sulfonimidoyl fluoride **8f** was obtained in 92% yield.

This method could also be extended to access vinyl sulfonimidoyl fluoride **8g** in 58% yield. Benzyl-substituted sulfonimidoyl fluoride **8h** could be obtained, albeit in a low yield (10%). Likewise, aliphatic sulfonimidoyl fluorides **8i** and **8j** were generated under these conditions in 24% (**8i**) and 14% (**8j**) yield. Products **8h**–**8j** were formed in poor yields and decomposition was observed.[28] Thus, they were not isolated and the yields were determined by quantitative ^{19}F NMR spectroscopy.

Table 3 Scope of sulfonimidoyl fluorides via one-pot procedure from sulfinyl fluorides.[a]



[a]Reaction Conditions: To a vial containing sulfinic acid **6** (1.0 mmol) under argon was added a solution of pyridine (1 equiv) and SOF_2 in acetonitrile (0.20 M, see SI for SOF_2 generation method). The mixture was stirred at rt for up to 45 min, upon which it was sparged with argon for 5 min. Chloramine-T (3 equiv) and anhydrous toluene (0.38 M) were then added, and the mixture was stirred at 80 °C for 18 h. Purification by flash column chromatography yielded the corresponding sulfonimidoyl fluoride. [b]The yields of sulfonimidoyl fluorides **8h** - **8j** were low, and are reported using ^{19}F NMR spectroscopy with fluorobenzene as the internal standard.

Overall, we have developed a novel method for synthesizing sulfinyl fluorides using thionyl fluoride via the deoxyfluorination of sulfinic acids. This approach rapidly generates aromatic and aliphatic sulfinyl fluorides in situ (≤ 45 min, 62–97% yield), and represents the most general method for preparing sulfinyl fluorides reported to date. Importantly, the reaction produces relatively unreactive byproducts, which enables a second transformation in the same reaction pot. We have leveraged this feature to demonstrate that sulfinyl fluorides generated by our method can be converted to sulfonimidoyl fluorides through reaction with chloramine-T in a one-pot process. This transformation represents one of the most efficient routes to sulfonimidoyl fluorides and constitutes the first example of nitrene addition to sulfinyl fluorides. The extension of this methodology to access additional sulfur(IV) and sulfur(VI) motifs from sulfinyl fluorides is currently under investigation.

The project was conceptualized by B.J.T., T.G.B., N.D.B., and G.M.S. B.J.T., R.P., T.G.B., M.S., C.B., and W.Y. conducted the experiments. M.S., C.L.J., R.P., N.D.B., and G.M.S. wrote and edited the manuscript.

Conflicts of interest

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There are no conflicts to declare.

Data availability

The datasets supporting this article have been uploaded as part of the ESI material.

Acknowledgements

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28 See the ESI for details.

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The data supporting this article have been included as part of the SI.