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Installation of sulfonyl fluorides onto primary amides

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Abstract

A protocol of SO_2F_2 mediated installation of sulfonyl fluoride onto primary amide was developed providing a new portal to sulfur(VI) fluoride exchange (SuFEx) click chemistry. The generated molecules contain pharmaceutically important amide and -SO_2F moieties for application in discovery of new therapeutics.

Keywords: N-fluorosulfonyl amides; Sulfuryl fluoride (SO_2F_2); primary amides

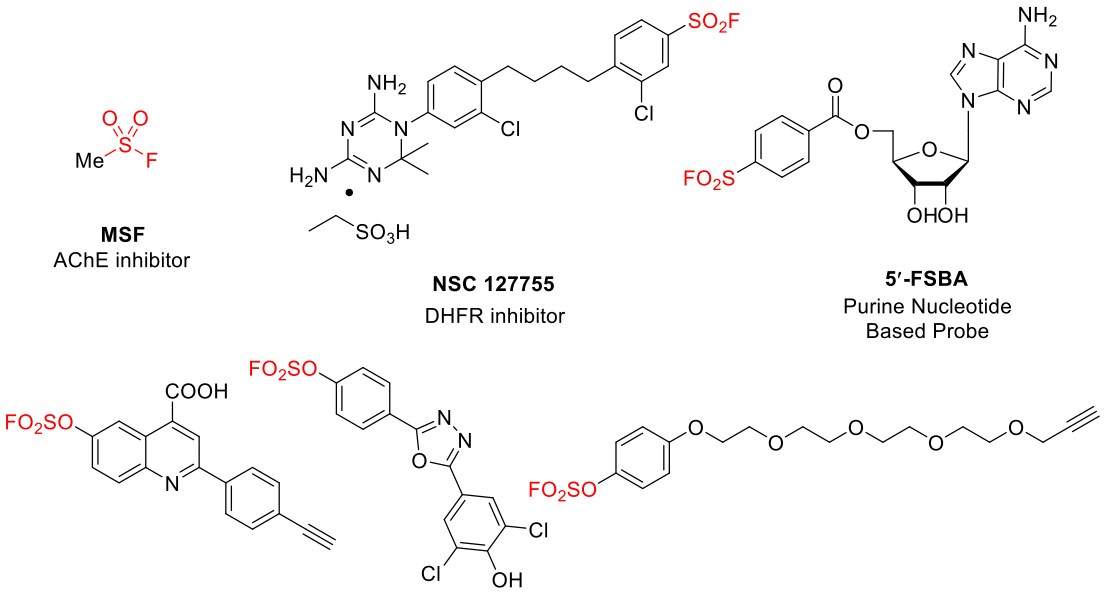
Introduction

Sulfur(VI) fluoride exchange (SuFEx), is a new class of click chemistry developed by Professor K. B. Sharpless and coworkers in 2014, for creating molecular connections based on the unique stability-reactivity pattern of S^{VI}-F bond with absolute reliability and unprecedented efficiency, which has been widely applied in organic synthesis, chemical biology and drug discovery [1-19]. Among all the developed S(VI)-F species, sulfonyl fluoride (RSO_2F) was specifically recognized as unique scaffold for covalent protein inhibitors and biological probes with the affinity-driven activation for forming covalent linkages with the amino acid residues of protein binding sites (**Figure 1**) [20]. The smallest member of this family, methyl sulfonyl fluoride (MSF), is known as a selective and irreversible inhibitor of acetylcholinesterase (AChE) [21-22]. The sulfonyl fluoride inhibitors NSC 127755 was found for specifically modifying tyrosine-31 of DHFR in chicken liver [23]. The nucleotide-derived probe 5'-p-fluorosulfonylbenzoyl adenosine (5'-FSBA) was used for labelling the second nucleotide binding site, the adenine nucleotide regulatory site [24]. In addition, aryl fluorosulfates have also been widely applied as sustainable alternative to aryl halides in coupling reactions and as potential covalent probes in protein profiling [14, 25-28].

Phenols (or alcohols) and amines as the most common nucleophiles have been found to undergo SuFEx with different S^{VI} connectors to provide diversified sulfonyl fluoride

derivatives. The reactions of phenols (or alcohols) with SO_2F_2 [29] or the fluorosulfuryl imidazolium salt were developed for mild and effective formation of the corresponding fluorosulfates to act as biology probes in chemical proteomics studies (**Scheme 1**, a) [1, 30].

On the other hand, the reactions of primary and secondary aliphatic amines as well as anilines with SO_2F_2 or the fluorosulfuryl imidazolium salt have been achieved for assembly of *N*-sulfonyl fluorides [1, 30], and the corresponding products have served as important active precursors for the development of noncovalent inhibitors (**Scheme 1**, a) [1, 30, 31]. Amides are the key connections in proteins, amides, and a vast number of synthetic structures, such as polymers, biologically active compounds and pharmaceutical products [32-35]. However, the installation of sulfonyl fluoride (SO_2F) onto nitrogen atoms of amides has not been achieved, which, if accomplished, would provide a very important class of sulfonyl fluorides, namely, *N*-fluorosulfonyl amides, for the development of potential covalent inhibitors [1-24]. The Roesky group described a pioneering protocol for the synthesis of *N*-fluorosulfonyl amides from fluorosulfonylisocyanate (**Scheme 1**, b) [36]. And the available procedures for the preparation of *N*-fluorosulfonyl amides are very limited which relied on using either the isocyanate approach, or theamidosulfofluoride (FSO_2NH_2) [37-39]. Therefore, the development of new method for the assembly of *N*-fluorosulfonyl amides from cheap and abundant reagent is highly desirable. Herein, we report the first, to the best of our knowledge, SO_2F_2 mediated *N*-fluorosulfonylation [40-42] of amides by using DBU as base for the constructions of a series *N*-acyl-substituted sulfamoyl fluorides (**Scheme 1**, c).

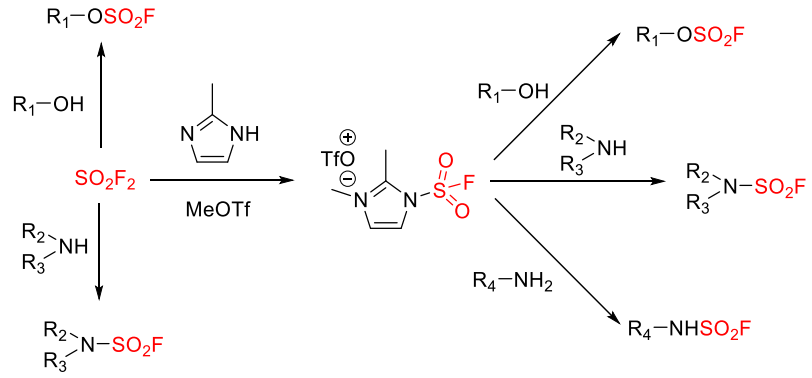


Application of arylfluorosulfate in fluorescent probe

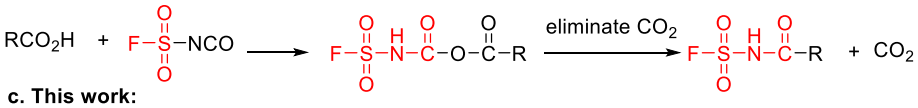
Figure 1. Representative sulfonyl fluorides compounds applied in medicinal chemistry and chemical biology.

Previous work:

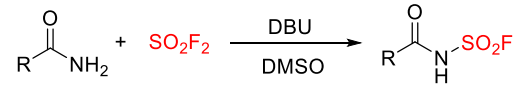
a. The the use of SO_2F_2 for reactions with amines and phenols



b. Current method for preparation of *N*-fluorosulfonyl amides.



c. This work:



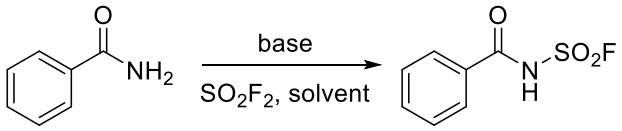
R = H, alkyl, aryl

Scheme 1. Background of synthesis of N-fluorosulfonyl amides and fluorosulfates.

Results and discussion

Initially, benzamide **1a** was selected as model substrate to test the feasibility of this proposed *N*-fluorosulfonylation reaction in the presence of Cs_2CO_3 in DMSO under SO_2F_2 atmosphere (balloon) at 50 °C, and excitingly, the desired product benzoylsulfamoyl fluoride **2a** was obtained in 25% yield (**Table 1**, entry 1). Encouraged by this preliminary success, several common bases were evaluated, among which, 1,8-diazabicycloundec-7-ene (DBU) catalysed the proposed transformation most effectively to provide the desired product **2a** in nearly quantitative yield (**Table 1**, entries 2-7). Subsequently, possible solvent effects were investigated with different solvents, among which, DMSO was found to be the best solvent. Decreasing the temperature from 50 °C to 40 °C or even room temperature, or cutting down the amount of DBU to 4 equivalent resulted in decreased yields (**Table 1**, entries 13-15).

Table 1. Optimization of the reaction conditions.[a]



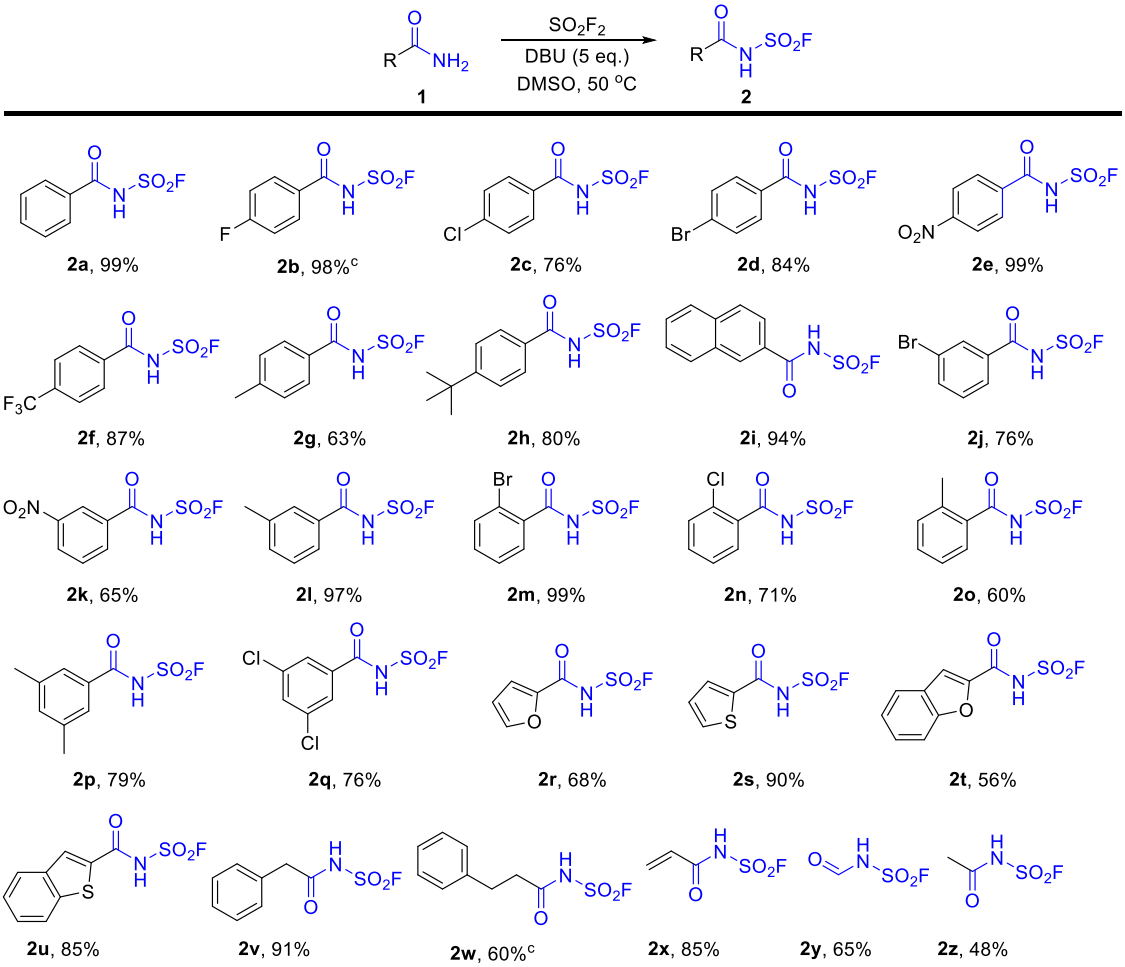
1a **2a**

Entry	Base	Solvent	Temp. (°C)	Yield (**2a**, %)[b]
1	Cs_2CO_3	DMSO	50	25
2	K_2CO_3	DMSO	50	13
3	KOH	DMSO	50	19
4	NaOH	DMSO	50	15
5	**DBU**	**DMSO**	**50**	**99**
6	Et_3N	DMSO	50	-
7	DIPEA	DMSO	50	-
8	DBU	NMP	50	81
9	DBU	MeCN	50	75
10	DBU	Toluene	50	87
11	DBU	Dioxane	50	60
12	DBU	THF	50	79
13	DBU	DMSO	40	82
14	DBU	DMSO	R.T.	51
15[c]	DBU	DMSO	50	69

[a] Reaction condition: benzoyl amide **1a** (1.0 mmol, 1.0 eq.), DBU (5.0 eq.), and DMSO (1.0 mL) stirred with a SO_2F_2 balloon for 12h. [b] Isolated yield. [c] 4 equiv of DBU was used.

With the optimized conditions in hand, we next turned our efforts to investigate the scope of substrates. Under the standard conditions, a variety of substituted amides were examined which were smoothly converted to their corresponding substituted benzoylsulfamoyl fluoride derivatives (**Scheme 2**) in moderate to excellent isolated yields. Both electron-withdrawing groups, such as halogen atoms (**1b**-**1d**, **1j**, **1m**-**1n**), NO_2 (**1e**, **1k**) and CF_3 (**1f**), and electron-donating groups, such as Me (**1g**, **1l**, **1o**), tert-butyl (**1h**) and 2-naphthyl (**1i**) on the aromatic rings, were well tolerated under this condition. It was worth noting that not only *para*-(**1b**-**1h**) but also *meta*- (**1j**-**1l**) and *ortho*- (**1m**-1**o**) substituted benzamides afforded the desired products in generally good yields. Arylcarboxylic amides (**1p**-**1q**) bearing bis-substitutions also behaved well under the standard conditions.

Heterocyclic aromatic carboxylic amides (**1r-1u**), tolerated well and afforded the target products in 56-94% yields. In addition, alkyl carboxylic amides were also smoothly transformed into the corresponding products (**2v-2z**).

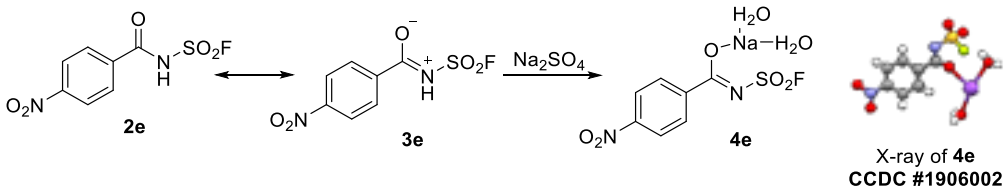


[a] Reaction conditions: a mixture of amides (**1**, 1.0 mmol), DBU (5.0 mmol, 5.0 eq.), DMSO (1.0 mL) was added to a reaction flask before SO_2F_2 was introduced into the stirred reaction mixture by slowly bubbling from a balloon, and the mixture was allowed to stir at 50 °C for 12h. [b] Isolated yields. [c] 50 °C, 18 h.

Scheme 2. Screening of substrate scope of amides [a, b]

Interestingly, during the work-up process of drying **2a** with Na_2SO_4, a colourless crystal **4e** was observed and its structure was confirmed by XRD analysis. We speculate that the tautomerism of amides [43] may occur in the reaction process and the tautomers **3e** could react with Na_2SO_4 to generate **4e**, which indicated that N-H connected with two electron-withdrawing groups (carbonyl, and SO_2F) can behave as an acid to donate a proton for

chemical transformations. This property of fluoro sulfonyl amides **2** may attract significant attention for further applications.



Scheme 3. Amide resonance model and X-ray single crystal structure of **4e** (CCDC 1906002).

Conclusions

In conclusion, we have developed a novel method for *N*-fluorosulfonylation of amides. This simple, convenient, mild and protocol provides a portal to a class of novel sulfonyl fluorides for SuFEx click chemistry with great potential to be applied in the development of covalent inhibitors. Further studies of this class of molecules in chemical biology and drug discovery are underway in our laboratory.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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