Installation of -SO$_2$F groups onto primary amides

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Abstract
A protocol of SO$_2$F$_2$-mediated installation of sulfonyl fluoride onto primary amides has been developed providing a new portal to sulfur(VI) fluoride exchange (SuFEx) click chemistry. The generated molecules contain pharmaceutically important amide and -SO$_2$F moieties for application in the discovery of new therapeutics.

Introduction
Sulfur(VI) fluoride exchange (SuFEx) is a new class of click chemistry developed by Sharpless and co-workers in 2014, for creating molecular connections based on the unique stability–reactivity pattern of the S(VI)–F bond with reliability and 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$_2$F) 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’-(para-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 react with different S(VI) connectors (SO$_2$F$_2$, CH$_2$=CH-SO$_2$F, SOF$_4$ etc.) to provide diversified sulfonyl fluoride derivatives. The reactions of phenols (or alcohols) with SO$_2$F$_2$ [29] or the fluorosulfuryl imidazolium salt
were developed for mild and effective formation of the corresponding fluorosulfates to act as biological probes in chemical proteomics studies (Scheme 1, (1)) [1,30]. On the other hand, the reactions of aliphatic or aromatic amines with SO$_2$F$_2$ or the fluorosulfurylimidazolium salt have been achieved for assembly of N-sulfonyl fluorides [1,30], which have served as important active precursors for the development of noncovalent inhibitors (Scheme 1, (1)) [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$_2$F) 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 fluorosulfonyl isocyanate (Scheme 1, (2)) [36]. The available procedures for the preparation of N-fluorosulfonyl amides are very limited which relied on using either the isocyanate approach, or the amidosulfonfluoride (FSO$_2$NH$_2$) (Scheme 1, (2)) [37-39]. Therefore, the development of a 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$_2$F$_2$-mediated N-fluorosulfonylation [40-42] of amides by using DBU as base for the constructions of a series N-fluorosulfonyl amides (Scheme 1b).

Results and Discussions
Initially, benzamide (1a) was selected as model substrate to test the feasibility of this proposed N-fluorosulfonylation reaction in the presence of Cs$_2$CO$_3$ in DMSO under SO$_2$F$_2$ 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, different solvents were screened (Table 1, entries 5, 8–12) and DMSO was found to be the best option. Decreasing the temperature from 50 °C to 40 °C or even room temperature, or cutting down the amount of DBU to 4 equivalents resulted in decreased yields (Table 1, entries 13–15).

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 benzoysulfamoyl fluoride derivatives (Scheme 2) in moderate to excellent isolated yields. Both electron-withdrawing groups, such as halogen atoms (1b–d, 1j, 1m, and 1n), NO$_2$ (1e, 1k) and CF$_3$ (1f), and electron-donating groups, such as Me (1g, 1l, and 1o), tert-butyl (1h) and 2-naphthyl (1i) on the aromatic rings, were well tolerated under the optimized conditions. It was
Scheme 1: Synthesis background of N-fluorosulfonyl amides and fluorosulfates.

(a) previous work:
(1) the use of SO$_2$F$_2$ for reactions with amines and phenols

(b) this work:

Table 1: Optimization of the reaction conditions.$^a$

| Entry | Base   | Solvent | Temp. (°C) | Yield (2a, %)$^b$ |
|-------|--------|---------|------------|------------------|
| 1     | Cs$_2$CO$_3$ | DMSO    | 50         | 25               |
| 2     | K$_2$CO$_3$  | DMSO    | 50         | 13               |
| 3     | KOH     | DMSO    | 50         | 19               |
| 4     | NaOH    | DMSO    | 50         | 15               |
| 5     | DBU     | DMSO    | 50         | 99               |
| 6     | Et$_3$N  | 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 conditions: benzamide (1a, 1.0 mmol, 1.0 equiv), DBU (5.0 equiv), and DMSO (1.0 mL) stirred with a SO$_2$F$_2$ balloon for 12 h. $^b$Isolated yield. $^c$4 equiv of DBU was used.
Scheme 2: Screening of the substrate scope of amides. Reaction conditions: a mixture of amides 1 (1.0 mmol), DBU (5.0 mmol, 5.0 equiv), and DMSO (1.0 mL) was added to a reaction flask before SO$_2$F$_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 12 h. Isolated yields.

-worth noting that not only para- (1b–h) but also meta- (1j–l) and ortho- (1m–o) substituted benzamides afforded the desired products in generally good yields. Arylcarboxylic amides (1p and 1q) bearing bis-substitutions also behaved well under the standard conditions. Heterocyclic aromatic carboxylic amides (1r–u) were well-tolerated and afforded the target products in 56–90% yields. In addition, alkyl carboxylic amides were also smoothly transformed into the corresponding products (2v–z).

However, primary amides bearing an amino group or a phenolic hydroxy group were not successfully converted to the corresponding N-fluorosulfonyl amides and only a mixture of undesired products were observed.

Interestingly, during the work-up process of drying 2e with Na$_2$SO$_4$, a colourless crystal 4e was observed and its structure was confirmed by XRD analysis (Scheme 3). We speculate that the tautomerism of amides [43] may occur in the reaction process and the tautomer 3e could react with Na$_2$SO$_4$ to generate 4e, which indicated that N–H connected with two electron-withdrawing groups (carbonyl, and SO$_2$F) can behave as an acid to donate a proton for chemical transformations. This property of fluorosulfonyl amides 2 with nucleophilicity may attract significant attention for further applications.

As depicted in Scheme 4, a plausible reaction mechanism is proposed for SO$_2$F$_2$-mediated transformation of amides to N-fluorosulfonyl amides. The reaction was initiated by the deprotonation of amide 1 with the base (DBU) to generate an intermediate A, which subsequently went through a SuFEx process with SO$_2$F$_2$ to deliver the final product 2.
Conclusion
In conclusion, we have developed a novel method for N-fluoro-
sulfonylation of amides. This simple, convenient, and mild
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.

Supporting Information
Supporting Information File 1
Experimental part.
[https://www.beilstein-journals.org/bjoc/content/
supplementary/1860-5397-15-186-S1.pdf]

Supporting Information File 2
Crystallographic information file of 4e.
[https://www.beilstein-journals.org/bjoc/content/
supplementary/1860-5397-15-186-S2.cif]

Supporting Information File 3
Checkcif file of 4e.
[https://www.beilstein-journals.org/bjoc/content/
supplementary/1860-5397-15-186-S3.pdf]

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Conflicts of Interest
The authors declare no competing financial interest.

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