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COMMUNICATION

Regioselective installation of fluorosulfate (-OSO_2F) functionality into aromatic C(sp^2)–H bonds for the construction of *para*-amino-arylfluorosulfates

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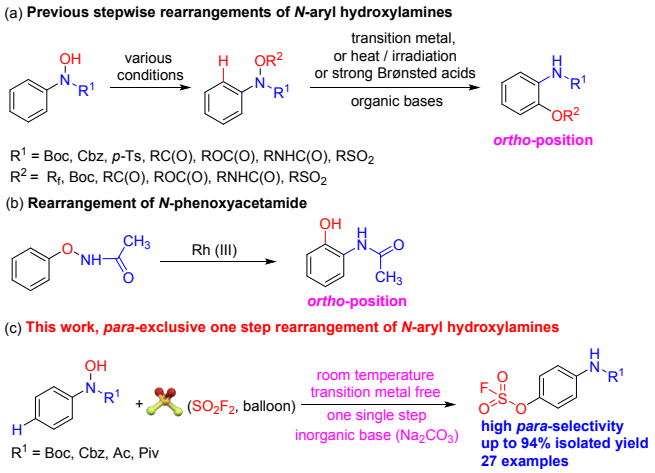
The construction of *para*-amino-arylfluorosulfates was achieved through installation of fluorosulfate (-OSO_2F) functionality into aromatic C(sp^2)–H bonds from the reaction of *N*-arylhydroxylamine with sulfuryl fluoride (SO_2F_2). This method provides a mild process for the preparation of the broadly applicable fluorosulfate moieties without requirement of phenols or transition metals.

Sulfur (VI) fluoride exchange (SuFEx), a class of new click reactions developed by Professor K. B. Sharpless and coworkers,[1] have emerged as one of the most powerful scaffolds and been successfully applied in the fields of covalent protein inhibitors and biological probes,[2] ^{19}F radiolabeling agents,[3] heterocycles synthesis,[4] and polymer synthesis and modifications.[5] Among all the SuFEx clickable moieties, arylfluorosulfates (ArOSO_2F) with their unique properties of relatively unreactive toward hydrolysis, reduction, nucleophilic substitution, thermolysis, whereas, exclusively reactive at the sulfur center under appropriate conditions, have been particularly recognized as a family of selectively addressable protocols applied in a wide variety of targets in chemical biology and drug discovery [6] and as building blocks similar to aryl triflates or aryl halides for various chemical transformations.[7] However, nowadays nearly all fluorosulfates are derived from their phenolic compounds, which has unfortunately limited the diversifying and accessing to new fluorosulfates. On the other hand, anilines are prevalent in pharmaceuticals and natural products and have been widely utilized as versatile building blocks in peptides chemistry, synthetic chemistry and fine chemicals.[8] Therefore, the development of efficient and novel methods for the preparation of arylfluorosulfates (ArOSO_2F) possessing aniline moieties without the usage of phenols is of great importance and highly desirable.



Scheme 1. Representative rearrangement strategies for synthesis of protected-anilines

The rearrangement of functionalized *N*-arylhydroxylamines for the syntheses of functionalized phenols feathering aniline derivatives has been extensively studied, which typically requires elevated temperature, and/or strong Brønsted/Lewis acids, transition metals or oxidants (Scheme 1a).[9] In addition, for this class of transformations, electron-deficient groups [CF_3, RSO_2, RC(O), et al] are generally required to be preinstalled onto both the hydroxyl (OH) groups and the amine (NH) groups to activate the N-O bond for facilitating the rearrangement process. The Rh(III)-catalyzed rearrangement of *N*-phenoxyacetamide derivatives has also been successfully conducted *via* migration of functionalized NH groups instead of OH groups, which provides another valuable method for the synthesis of functionalized phenols with aniline moieties (Scheme 1b).[10] However, most of the rearrangements of *N*-arylhydroxylamines or *N*-phenoxyacetamide derivatives proceeded through *ortho* C-H activation of aromatic rings with the formation of *ortho* C-O bond or C-N bond, while the *para* C-H activation type of rearrangement has gained limited exploration. And SO_2F_2 (an inexpensive (about 1$/kg), relatively inert gas (stable up to 400 ºC when dry) has been served as one of the key reagents for SuFEx click chemistry nowadays.[11] Herein, we reported a SO_2F_2-mediated and

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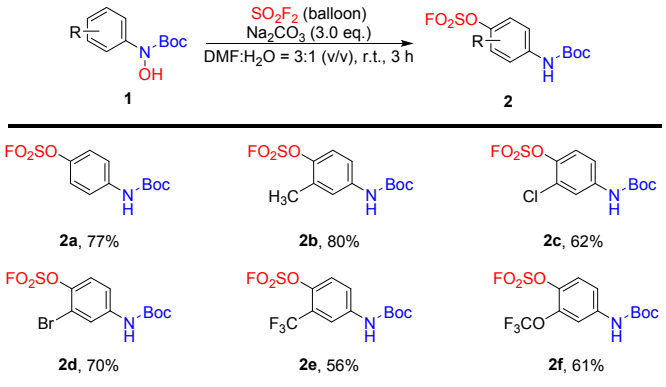
inorganic base promoted rearrangement of *N*-arylhydroxylamine, a *para* selective, mild and practical method for the synthesis of arylfluorosulfates ($ArOSO_2F$) possessing *para*-aniline moieties with broad functional group compatibility (Scheme 1c).

After screening a large variety of conditions (see Supporting Information for details), we were delighted to find that the SO_2F_2-mediated rearrangement of *N*-aryl hydroxylamines for highly *para*-selective installation of $-OSO_2F$ into aromatic $C(sp^2)$–H bonds was accomplished in good yield using Na_2CO_3 as promoter in a co-solvent of DMF-H_2O (v/v = 3:1) at room temperature.

Table 1. Scope of SO_2F_2-mediated Rearrangement of *tert*-Butoxycarbonyl(Boc)-Protected *N*-Aryl hydroxylamines[a, b]



[a]Reaction conditions: Boc-Protected *N*-aryl hydroxylamine (**1**, 1 mmol) and Na_2CO_3 (318 mg, 3 mmol, 3.0 eq.) were stirred in the co-solvent (10 mL, 0.1 M, DMF:H_2O =3:1 (v/v)) with a SO_2F_2 balloon at r.t. for 3 h. [b]Isolated yields.

To investigate the reaction scope, further extension of other substrates possessing representative functional groups was conducted subsequently and the results were collected in Table 1. Gratefully, *tert*-butoxycarbonyl(Boc)-protected *N*-aryl hydroxylamines reacted under the optimized conditions smoothly to afford their corresponding rearrangement-products in moderate to good yields (56-80%) on a standard 1.0 mmol scale (**2a**-**2f**). It's important to note that the efficiency of this transformation was significantly influenced by the electronic effect on the aryl rings, owing to the stability of carbocation intermediates during the rearrangement process. The starting materials functionalized with electron-donating groups usually afforded higher yields of their corresponding products comparing to those with electron-withdrawing groups, for example, the yield of **2b** (CH_3, 80%) *vs* the yield of **2e** (CF_3, 56%).

To further study the reaction scope of this transformation, we shifted the carbamate protecting group of the starting material arylhydroxylamines to Cbz group. As shown in the Table 2, a large variety of structurally and electronically diverse Cbz-protectd *N*-arylhydroxylamines were smoothly converted to their corresponding products in good to excellent yields under the aforementioned optimal condition (57-94%). Both the prevalent electron-donating and electron-withdrawing substituents on the aromatic rings were well tolerated. Interestingly, the substrates **3c** and **3d** possessing aliphatic ester groups provided higher yields of the corresponding fluorosulfates (**4c** and **4d**) comparing to their counterparty **3e** possessing aromatic ester. Furthermore, halide-containing starting materials (**4f-4i** and **4m-4o**) tolerated this SO_2F_2-mediated rearrangement system well. Besides, the position of substituents on the aryl rings also exhibited an obvious influence on the efficiency. The substituents on the *ortho*-position to $-OSO_2F$ group possessing steric hindrance accomplished less effectively than their *meta*-position counterparties, to generate their corresponding products in lower yields (e.g. **4g** compared to **4n** and **4h** compared to **4o**). The acetal moiety in **3j** remained intact during the rearrangement to provide the desired product **4j** in 94% isolated yield. Pleasingly, ketone, a versatile building block in synthesis, tolerated well without undergoing side reactions (**4k**). This method was also applied to Cbz-protected *N*-arylhydroxylamines functionalized with multi-substituents on the aromatic rings (**3p** and **3q**), to provide their corresponding products (**4p** and **4q**) in 73% and 71% yield, respectively. Notably, extending reaction time to 5 hours seemed to be crucial for complete consumption of **3q** due to the steric-hindrance effect of two methyl groups at the *ortho*-position. Notably, a detectable trace amount of the *ortho*-rearrangement products was also produced during this SO_2F_2-mediated rearrangement process. Pleasingly, the scalability of this transformation was achieved through a gram-scale experiment of **3a** (5 mmol, 1.22 g) resulting in 69% isolated yield of the corresponding product **4a** consuming about 2.25 equivalent of SO_2F_2. However, when the *para*-functionalized *N*-aryl hydroxylamines were used, the rearrangement provided a mess mixture of undesired products.

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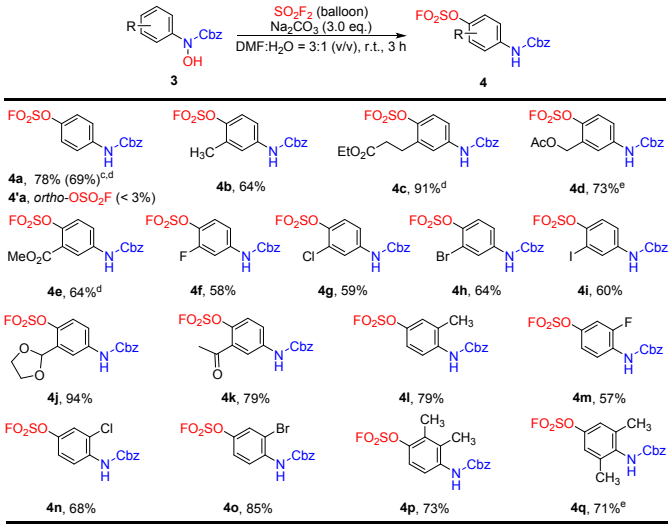
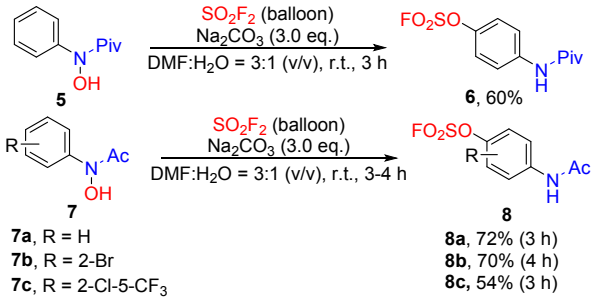
Table 2. Substrate Scope Study of Cbz-Protected *N*-Aryl hydroxylamines[a, b]

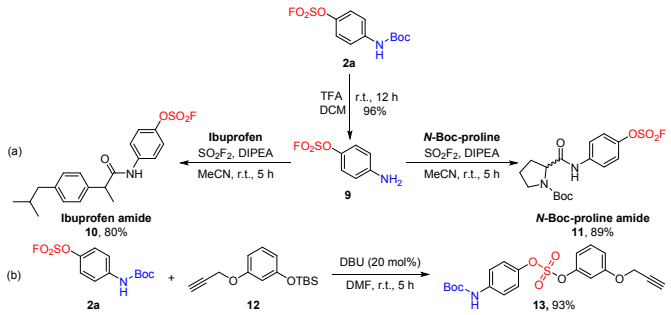


[a]Reaction conditions: Cbz-Protected *N*-aryl hydroxylamine (**3**, 1 mmol) and Na_2CO_3 (318 mg, 3 mmol, 3.0 eq.) were stirred in the co-solvent (10 mL, 0.1 M, DMF:H_2O =3:1 (v/v)) with SO_2F_2 balloon at r.t. for 3 h. [b]Isolated yields. [c]Gram-scale experiment (**3a**, 5 mmol, 1.22 g). [d]r.t., 4 h. [e]r.t., 5 h.



Scheme 2. Examination of Carbonyl-Protected *N*-Arylhydroxylamines

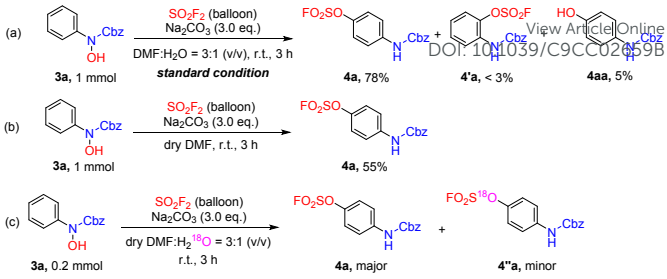
To further demonstrate the wide scope of our developed method in synthesis, carbonyl (Piv and Ac group) protected *N*-arylhydroxylamines (Scheme 2), were also subjected to the SO_2F_2 mediated rearrangement to afford their corresponding arylfluorosulfates in acceptable yields (54-72%). Not surprisingly, somewhat lower yield was also observed for the electron-deficient substrate **7c**.



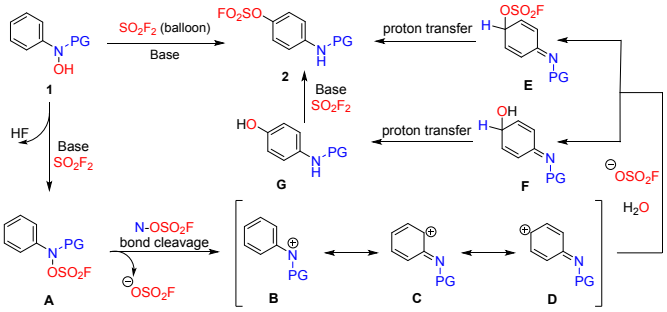
Scheme 3. Diversifications of Rearrangement Product **2a**.

Subsequently, some extended work focusing on the applications of this novel class of arylfluorosulfates ($ArOSO_2F$) in organic transformations was conducted using the rearrangement product **2a** as the starting material. Primary aniline **9** was isolated with nearly quantitatively yield and high purity after hydrolysis of **2a** with trifluoroacetic acid in DCM, and the subsequent coupling with Ibuprofen (a nonsteroidal anti-inflammatory drug) and *N*-Boc-proline (a prevalent amino acid) provided their corresponding amides **10** and **11** in 80% and 89% yields, respectively (Scheme 3a). Besides, as depicted in Scheme 3b, the SuFEx click reaction of **2a** with TBS-protected phenol derivate **12** generated sulfate **13** with excellent yield, leaving an intact terminal alkyne moiety for further transformations.

As described in the Scheme 4, some investigations were performed to figure out the mechanism of this SO_2F_2-mediated rearrangement process. The reaction of **3a** conducted under the standard reaction condition resulted in a mixture of desired product **4a**, by-product aminophenol **4aa** and the *ortho*-OSO_2F product **4'a** in 78%, 5% and <3% yields respectively (Scheme 4a). Interestingly, when the reaction was operated in dry DMF, 55% yield of **4a** was obtained (Scheme 4b). Furthermore, the resulted mixture of **4a** (majority) and **4''a** (minority) in the ^{18}O labeled experiment (Scheme 4c) revealed that both the OSO_2F anion and H_2O have served as nucleophiles during this transformation, while the later one (H_2O) provided the aminophenol intermediate **4aa** initially before the subsequent conversion to the corresponding fluorosulfate **4a**.



Scheme 4. Mechanism investigation



Scheme 5. Proposed mechanism of the SO_2F_2 mediated *para*-selective rearrangement.

As illustrated in Scheme 5, a plausible mechanism for the base-promoted, SO_2F_2 mediated *para*-selective rearrangement was proposed. The hydroxy group of *N*-arylhydroxylamine proceeded a SuFEx type of substitution with SO_2F_2 to afford the fluorosulfates **A**. Subsequent cleavage of N-OSO_2F bond generates nitrogen cationic intermediate **B**, which have two other resonance contributors **C** and **D**. The following nucleophilic addition of OSO_2F anion and H_2O to the most favorable and stable carbocation intermediate **D** occurred predominately to provide a mixture of corresponding precursor **E** and **F** respectively, which further went through a proton transfer process to generate their product fluorosulfate **2** and aminophenol **G**, respectively. After reacting with another equivalent of SO_2F_2, the aminophenol **G** was also converted to the corresponding fluorosulfate **2**.

In conclusion, we have developed an efficient method for the synthesis of arylfluorosulfates ($ArOSO_2F$) possessing *para*-aniline moieties through a SO_2F_2-mediated rearrangement of *N*-arylhydroxylamine process without any metal catalyst. The starting material substrates were readily prepared from the abundant nitroarenes. The transition-metal-free protocol proceeded with high regioselectivity, wide scope, and functional group compatibility without strict requirement of the exclusion of moisture and air to afford the extremely useful *para*-amino-arylfluorosulfates.

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Conflicts of interest

There are no conflicts to declare.

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