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This work may now be cited as: *Chin. J. Chem.* **2020**, *38,* 10.1002/cjoc.202000175.

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ISSN 1001-604X • CN 31-1547/O6
mc.manuscriptcentral.com/cjoc
www.cjc.wiley-vch.de

Report

Keyword 1, Keyword 2, Keyword 3, Keyword 4, Keyword 5, Keyword 6

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Arenesulfonyl fluoride synthesis via copper-free Sandmeyer-type fluorosulfonylation of arenediazonium salts

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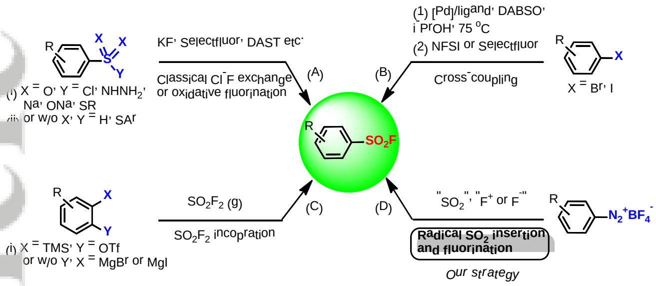
Cite this paper: *Chin. J. Chem.* **2019**, *37*, XXX—XXX. **DOI: 10.1002/cjoc.201900XXX**

Summary of main observation and conclusion The limited availability of highly valuable arenesulfonyl fluorides seriously hinders their further application in many research fields including medicinal chemisty and chemical biological, organic synthesis, polymer preparation, etc.. We report herein a mild and efficient copper-free Sandmeyer-type fluorosulfonylation reaction of various arenediazonium salts to prepare valuable arenesulfonyl fluorides using $K_2S_2O_5$ as both a reductant and a practical sulfonyl source in combination with N-fluorobenzenesulfonimide as an effective fluorine source. This methodology provides an attractive route to diverse important arenesulfonyl fluorides given the overall practicality and scope.

Background and Originality Content

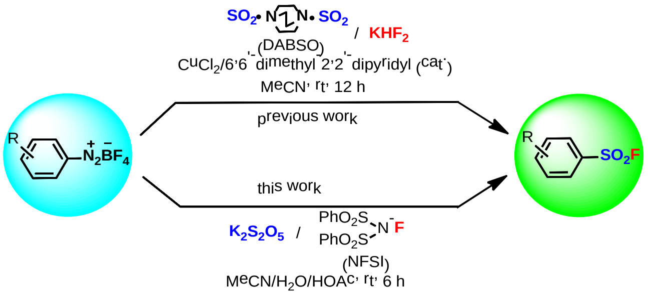
Since sulfonyl fluoride groups (SO_2F) have unique properties including special stability-reactivity pattern and proton-mediated reactivity that is sensitive to the micro-environment,[1] arenesulfonyl fluorides are highly valuable synthetic motifs that have been adopted in a variety of applications including the prominent sulfur fluoride exchange (SuFEx) reaction for "click chemistry" pioneered by Sharpless and co-workers,[1] attracting fast-growing attention in the community of both chemical biologists and synthetic organic chemists.[2] However, there are only limited synthetic methods to efficiently access them, which seriously hinders their further applications. The classical chloride-fluoride exchange of arenesulfonyl chlorides for the synthesis of corresponding arenesulfonyl fluorides requires preparation of arenesulfonyl chlorides that are relatively unstable and moisture-sensitive (Scheme 1A).[1,3] Alternative starting materials including $ArSO_2NHNH_2$[4], $ArSO_2Na$[5], $ArSO_3Na$[6], ArSSAr[7], ArSH[8], etc., have been successfully converted into the desired corresponding arenesulfonyl fluorides using an appropriate oxidant and fluorinating reagents (Scheme 1A). An efficient synthesis of various arenesulfonyl fluorides by palladium-catalyzed cross-coupling of aryl halides with 1,4-diazabicyclo[2.2.2]octane-bis(sulfur dioxide) adduct (DABSO) in combination with electrophilic fluorinating reagents has been developed recently (Scheme 1B).[9] Two recent reports have demonstrated the synthesis of arenesulfonyl fluorides via sulfuryl fluoride incorporation from arynes or various Grignard reagents (Scheme 1C).[10] Despite these advances, access to various arenesulfonyl fluoride from inexpensive and wildly available starting material by a practical and mild method is still highly desired.

Scheme 1 Established synthetic methods for arenesulfonyl fluorides



The Sandmeyer reaction has been widely used for the conversion of aromatic amino groups into a variety of functional groups, such as halogen, hydroxyl, cyano, boryl groups etc.[11] Recently Sandmeyer-type fluoroalkylation of arenediazonium salts has been developed, and various fluorine-containing functional groups including CF_3[12], SCF_3[13], SCF_2H[14], CF_2H[15], CF_2HSO_2/CH_2FSO_2[16], C_nF_{2n+1} (n>2)[17] and OCF_3[18] can be efficiently incorporated into arenes. Moreover, clorosulfonylation of arenediazonium salts has been achieved as well.[19] However, to our best knowledge, the corresponding Sandmeyer-type fluorosulfonylation reaction of arenediazonium salts has never been reported such far. We conceived that the combination of economical SO_2 and an appropriate fluoride source would achieve it via radical SO_2 insertion and fluorination strategy (Scheme 1D). Based on this new strategy, we have already developed an efficient method for the preparation of a number of alkyl sulfonyl fluorides.[20] Very recently, we have established the first synthesis of various arenesulfonyl fluorides from arenediazonium salts in combination of KHF_2 as a fluorine source and SO_2 surrogate 1,4-diazabicyclo[2.2.2]octane-bis(sulfur dioxide) adduct (DABSO) as a sulfonyl source via copper-catalyzed radical SO_2 insertion and fluorination strategy (Scheme 2).[21] As a good complement to this method and as a continuation of our research interest in fluorosulfonylation, we report herein copper-free Sandmeyer-type fluorosulfonylation of various arenediazonium salts with the use of *N*-fluorobenzenesulfonimide (NFSI) as an efficient fluorine source and $K_2S_2O_5$ as an inexpensive and practical sulfonyl source (Scheme 2)[22].

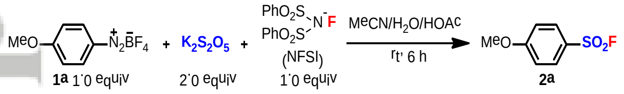
Scheme 2 Arenesulfonyl fluoride synthesis from arenediazonium salts via radical SO_2 insertion and fluorination strategy



Results and Discussion

Our initial studies on the Sandmeyer-type fluorosulfonylation of arenediazonium salts were carried out using *p*-methoxybenzenediazonium salt **1a** as the model substrate, DABSO as a popular and commercially available solid SO_2 source[23], and NFSI as a fluoride source. As shown in Table 1, initial experiments revealed that the combination of 2.0 equiv of DABSO, 1.0 equiv of NFSI in MeCN at room temperature for 6 hours did not efficiently generate the desired arenesulfonyl floride, and only trace amounts of the product **2a** were detected (entry 2). Careful analysis of the reaction mixture demonstrated that the majority of starting arenediazonium salt **1a** was not consumed. Then UV irradiation or copper powder was used to improve the reaction, and increased yields of the desired product were observed (entries 3 and 4). It is well-known that $K_2S_2O_5$ can be used as both good inorganic SO_2 surrogate[24] and effective reductant. It was found that the desired reaction was improved when DABSO was replaced with $K_2S_2O_5$ (entry 5). Notably, water had positive effect on the reaction and good yield of the desired product **2a** was obtained in its presence (entry 6). To our delight, when HOAc was used as co-solvent, the desired reaction was further improved and a good yield of 80% was achieved (entry 1), which might be ascribed to the suppression of formation of undesired products by HOAc including Sandmyer-type or azo byproducts. Interestingly, lower yield of the product was observed in the absence of water (entry 7), thus demonstrating the key role of water in the desired Sandmeyer-type fluorosulfonylation reactions probably by increasing the solubility of $K_2S_2O_5$ in the reaction mixture. The utilization of Selectfluor as electrophilic fluorine source was not effective for the transformation and obvious drop in the yield of the desired product was observed (entry 8). Furthermore, the increased concentration of $K_2S_2O_5$ or NFSI did not have a significant effect on the reaction (entries 9 and 10). These extensive screening of reaction conditions showed that the combination of 2.0 equiv of $K_2S_2O_5$ and 1.0 equiv of NFSI in $MeCN/H_2O/HOAc$ at room temperature for 6 hours provided optimal reaction conditions to generate the desired fluorosulfonylation product in good yield (entry 1).

Table 1 Optimization of reaction conditions[a]

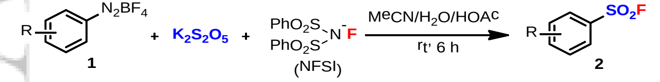


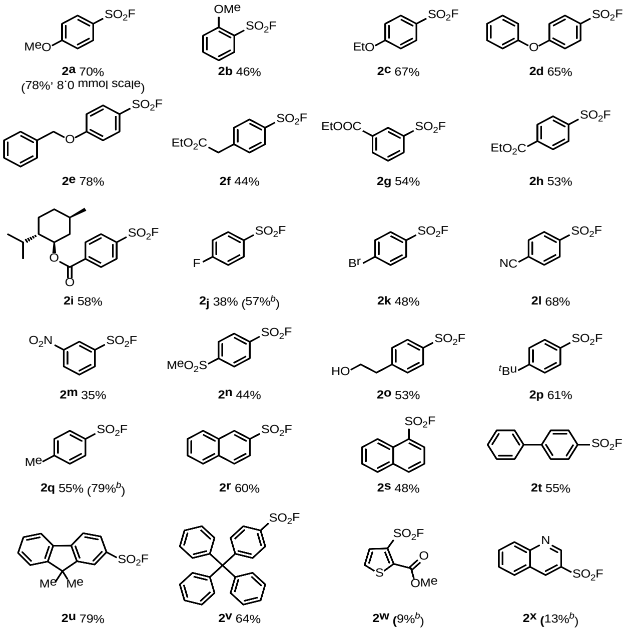
Entry	Variation from the standard conditions	Yield of **2a** (%)[b]
1	none	80
2	DABSO instead of $K_2S_2O_5$, MeCN	trace
3	DABSO instead of $K_2S_2O_5$, MeCN, 1.0 equiv of Cu	32
4	DABSO instead of $K_2S_2O_5$, MeCN, UV irradiation	8
5	without HOAc and H_2O	35
6	without HOAc	56
7	without H_2O	45
8	Selectfluor instead of NFSI	57
9	2.0 equiv of NFSI	80
10	4.0 equiv of $K_2S_2O_5$	78

[a] General reaction conditions: arenediazonium salt (**1a**, 0.2 mmol), $K_2S_2O_5$ (0.4 mmol), NFSI (0.2 mmol) in $MeCN/H_2O/HOAc$ (3/0.05/0.2 mL) under Ar atmosphere at room temperature for 6 hours. [b] Yields were determined by ^{19}F NMR spectroscopy using 1-methoxy-4-(trifluoromethoxy)benzene as an internal standard.

With the optimal reaction conditions in hand, we next engaged in examining the generality of this copper-free Sandmeyer-type fluorosulfonylation of various arenediazonium salts and the results are summarized in Table 2. A wide range of arenediazonium salts with electron-donating, neutral, and electron-withdrawing substituents were smoothly transformed into the corresponding Sandmeyer-type fluorosulfonylation products in good yields. As expected, no fluorinated byproducts were formed in these reactions, but some polar and complicated Sandmeyer-type or azo byproducts were observed. Thanks to the mild reaction conditions employed, a series of functional groups including ether (**2a**-**e**), ester (**2f**-**i**), halogen (**2j**, **2k**), cyano (**2l**), nitro (**2m**), sulfonyl (**2n**) and hydroxyl (**2o**) were well tolerated under the reaction conditions providing the corresponding target products in good yields. In particular, the substrate **1o** bearing an active OH group delivered the corresponding products in good yields. However, it was found that heteroarenediazonium salts **2w** and **2x** are not suitable reaction partners for the current transformation and lower yields of the corresponding fluorosulfonylation products were formed. Furthermore, gram-scale synthesis of **2a** was performed on 8.0 mmol scale to estimate practicality of this reaction and a good yield of the target product was obtained, thus demonstrating good viability of the transformation for scale-up.

Table 2 Substrate scope for the copper-free Sandmeyer-type fluorosulfonylation of various arenediazonium salts[a]

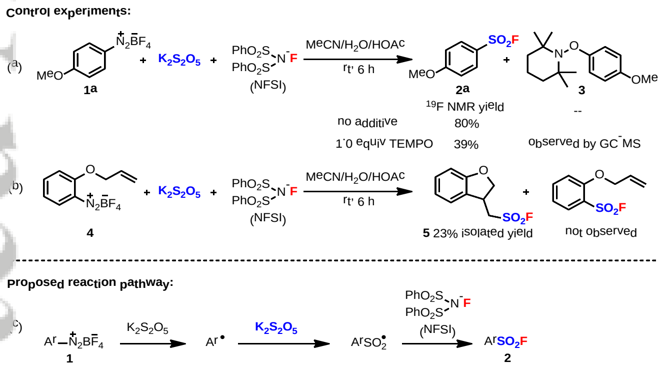



2a 70% (78%, 8.0 mmol scale)
2b 46%
2c 67%
2d 65%
2e 78%
2f 44%
2g 54%
2h 53%
2i 58%
2j 38% (57%[b])
2k 48%
2l 68%
2m 35%
2n 44%
2o 53%
2p 61%
2q 55% (79%[b])
2r 60%
2s 48%
2t 55%
2u 79%
2v 64%
2w (9%[b])
2x (13%[b])

[a] Standard reaction conditions: arenediazonium salt (0.3 mmol), $K_2S_2O_5$ (0.6 mmol), NFSI (0.3 mmol) in MeCN/H_2O/HOAc (4.5/0.075/0.3 mL) under Ar atmosphere at room temperature for 6 hours. Yields of isolated products are given. [b] Yields were determined by ^{19}F NMR spectroscopy using 1-methoxy-4-(trifluoromethoxy)benzene as an internal standard.

Some preliminary mechanistic studies on the Sandmeyer-type fluorosulfonylation of arenediazonium salts were carried out in order to gain some insights into the reaction pathway. First, 2,2,6,6-tetramethyl-1-piperidyloxy (TEMPO) as a radical scavenger was added to the reaction of **1a**, resulting in an obvious decrease in the yield and successful observation of the corresponding TEMPO-trapped complex **3** (Scheme 3a). Second, arenediazonium salt **4** was subjected to the standard reaction conditions to generate the ring-closed product **5** in 23% isolated yield (Scheme 3b). This might be ascribed to the fact that the alkyl radical generated in situ from addition of aryl radical to the alkenyl group in **4** undergoes irreversible intramolecular cyclization at a much fast rate than that of the consequent aryl radical SO_2 insertion. All these results strongly demonstrate the radical character of the reaction. Based on the above experimental results and literature,[25] we propose the following reaction pathway for the desired copper-free Sandmeyer-type fluorosulfonylation reaction of arenediazonium salts. Arenediazonium salt **1** readily generates the corresponding aryl radical by $K_2S_2O_5$ via a single electron transfer (SET) process under the reaction conditions. It is rapidly trapped by SO_2 originated from $K_2S_2O_5$ to form the corresponding [$ArSO_2\cdot$] intermediate, and their subsequent rapid fluorination by NFSI results in the desired arenesulfonyl fluoride **2** (Scheme 3c).

Scheme 3 Preliminary mechanistic investigation of the copper-free Sandmeyer-type fluorosulfonylation of arenediazonium salts



Conclusions

In conclusion, based on the radical SO_2 insertion and fluorination strategy, we have developed a copper-free Sandmeyer-type fluorosulfonylation reaction of readily available arenediazonium salts using cheap $K_2S_2O_5$ as both a reductant and a sulfonyl source and NFSI as an effective fluorine source. This transformation permits a fast and facile construction of various highly valuable arenesulfonyl fluorides from low-cost and widely available starting materials, and is expected to greatly expand the toolkit of arenesulfonyl fluorides and significantly promote their further application in different fields. Further studies on the synthesis of other sulfonyl fluorides via the radical SO_2 insertion and fluorination strategy are in progress.

Experimental

General Procedure for the Sandmeyer-type fluorosulfonylation of arenediazonium salts. Arenediazonium salt **1** (0.3 mmol), $K_2S_2O_5$ (133.2 mg, 0.6 mmol) and NFSI (94.5 mg, 0.3 mmol) were added to a sealed tube. The system was then evacuated and backfilled with Ar (3 times) and distilled CH_3CN (4.5 mL), H_2O (75 μL) and HOAc (0.3 mL) were added in turn via syringe under Ar atmosphere. The reaction mixture was sealed and stirred at room temperature for 6 hours. Yields of the desired product were measured by 19F NMR spectroscopy before working-up. Then the reaction mixture was filtered through a pad of celite, diluted with DCM (20 mL) and H_2O (50 mL). The resulting mixture was extracted with DCM (2 × 20 mL). The organic layers were combined, washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The crude product was purified by silica gel chromatography to give the desired product.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

Acknowledgement (optional)

The authors gratefully acknowledge the financial support from the National Natural Science Foundation of China (Nos. 21421002, 201871283, 21737004, 21672239), Science and Technology Commission of Shanghai Municipality (No. 17ZR1437000), and the Foundation of Science and Technology on Sanming Institute of Fluorochemical Industry (FCIT201701BR).

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(The following will be filled in by the editorial staff)

Manuscript received: XXXX, 2019

Manuscript revised: XXXX, 2019

Manuscript accepted: XXXX, 2019

Accepted manuscript online: XXXX, 2019

Version of record online: XXXX, 2019

Entry for the Table of Contents

Page No.

Arenesulfonyl fluoride synthesis via copper-free Sandmeyer-type fluorosulfonylation of arenediazonium salts

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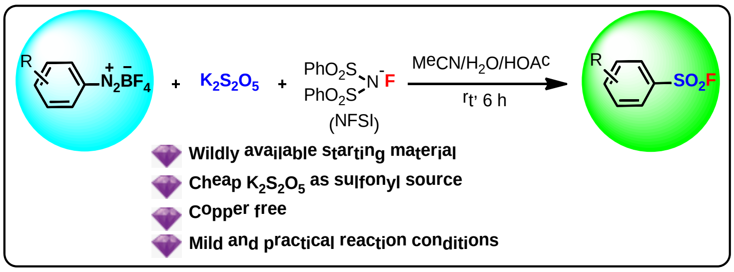

iongzhen Lin, Zhanhu Ma, Changge Zheng,* Xiao-Jun Hu,* Yong Guo, Qing-Yun Chen, Chao iu*

A mild and efficient copper-free Sandmeyer-type fluorosulfonylation reaction of various arenediazonium salts was developed to prepare valuable arenesulfonyl fluorides using $K_2S_2O_5$ as a practical sulfonyl source in combination with *N*-fluorobenzenesulfonimide as an effective fluorine source.