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Photocatalytic fluorosulfonylation of aliphatic carboxylic acid NHPI esters†

Honghai Zhang,^a Shaojie Li,^a Han-Liang Zheng,^b Gangguo Zhu,^b Saihu Liao^{a,c} and Xingliang Nie^{a,*}Received 27th May 2022,
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Sulfonyl fluorides have been increasingly favored by medicinal chemists and chemical biologists because of their unique reactivity and stability, but their synthetic methods still have certain limitations. Based on the SO₂ radical insertion/fluorination strategy, we have developed a novel method for photocatalytic induced synthesis of alkylsulfonyl fluorides (low to 1 mol% P.C. and up to 92% yield), which covers primary, secondary and tertiary aliphatic carboxylic acid NHPI esters, providing a facile method for the late-stage fluorosulfonylation of natural products and drugs. This method provides an efficient and reliable approach for the synthesis and application of alkylsulfonyl fluorides.

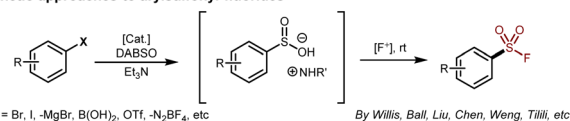
Introduction

The discovery of sulfonyl fluorides can be traced back to 1921, when Steinkopf treated toluene with fluorosulfonic acid.¹ However, sulfonyl fluorides did not get enough attention until 2014, when Sharpless and colleagues proposed the concept of sulfur(vi) fluoride exchange (SuFEx),² which became known as an excellent reaction for click chemistry and came to be widely used in organic synthesis,³ chemical biology,⁴ drug discovery,⁵ materials science,⁶ etc.⁷ Then, a new chapter opened up for the syntheses and applications of sulfonyl fluorides. The growing demand for sulfonyl fluorides has led to an increasing emphasis on the development of novel and efficient synthetic methods.

In recent years, the synthesis methods of sulfonyl fluorides have developed rapidly.⁸ Typical methods mainly include: (1) accessing the fluorosulfonyl group *via* the chloride–fluoride exchange⁹ and alternative methods;¹⁰ (2) introducing sulfonyl fluoride fragments into the target molecules *via* sulfonyl fluoride hubs;¹¹ and (3) direct fluorosulfonylation *via* FSO₂ reagents or FSO₂ synthons.¹² Due to decades of development, the classic approaches to access the fluorosulfonyl group have proven to be a straightforward and efficient way.

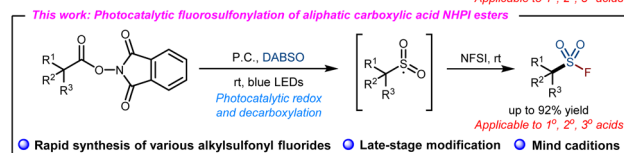
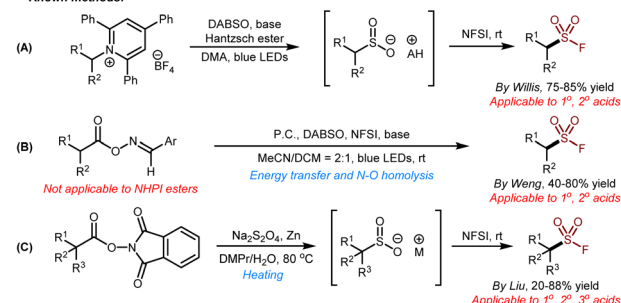
DABSO was developed by Santos *et al.* in 1988¹³ and was first applied as a novel SO₂ source by Willis and co-workers to deliver aryl aminosulfonamides in 2010.¹⁴ Since then, DABSO has frequently been used as a solid precursor of SO₂ gas in the synthesis of various sulfonyl products,¹⁵ especially arylsulfonyl fluorides in recent years (Scheme 1, I).¹⁶ Unsurprisingly, it can also be used to synthesize aliphatic sulfonyl fluorides.¹⁷ For example, the Willis group reported a radical approach toward

I. Synthetic approaches to arylsulfonyl fluorides



II. Synthetic approaches to alkylsulfonyl fluorides

Known methods:



Scheme 1 Approaches for fluorosulfonyl group installation *via* SO₂ radical insertion/fluorination.

^aKey Laboratory of Molecule Synthesis and Function Discovery (Fujian Province University), State Key Laboratory of Photocatalysis on Energy and Environment, College of Chemistry, Fuzhou University, Fuzhou 350108, China.

E-mail: shliao@fzu.edu.cn, nxl646036@163.com

^bKey Laboratory of the Ministry of Education for Advanced Catalysis Materials, Department of Chemistry, Zhejiang Normal University, 688 Yingbin Road, Jinhua 321104, P. R. China. E-mail: xingliangnie@zjnu.edu.cn

^cBeijing National Laboratory of Molecular Science (BNLMS), Beijing 100190, China

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primary and secondary alkylsulfonyl derivatives *via* donor-acceptor activation of pyridinium salts which were trapped by DABSO to generate sulfonyl radicals (Scheme 1, II, A).¹⁸ Hence, the SO₂ radical insertion/fluorination strategy became a popular method for the construction of the fluorosulfonyl group, with special synthetic advantages in the direct synthesis of sulfonyl fluorides *via* C–SO₂F bond formation.⁸ Very recently, the Weng group reported a photocatalytic decarboxylative fluorosulfonylation approach for converting aldoxime esters to the corresponding sulfonyl fluorides,^{17f} which was enabled by energy-transfer-mediated photocatalysis and N–O bond homolysis. However, this protocol delivers the corresponding sulfonyl fluorides usually in modest yields and is not applicable to tertiary carboxylic acids (Scheme 1, II, B). Moreover, SO₂ sources including SO₂ gas and its surrogates,^{15a–c} such as inorganic hypervalent sulfur sources like sodium/potassium metabisulfite, are the key factors for the introduction of sulfone groups.¹⁹

Aliphatic carboxylic acids, as a type of cheap and easily available organic compound, are widely used in the synthesis of various organic compounds. In particular, redox-active *N*-hydroxyphthalimide (NHPI) esters, readily prepared from abundant and widely available carboxylic acids, are considered to be reliable precursors of alkyl radicals, which are widely used in the synthesis of various C–X bonds.²⁰ This year, the Liu group developed an efficient method for obtaining alkylsulfonyl fluorides from aliphatic carboxylic acid NHPI esters using sodium dithionite as the SO₂ source.¹⁹ⁱ However, limited by the equivalent amount of zinc powder to be used and high temperature conditions, this method afforded the corresponding alkylsulfonyl fluoride products in moderate yields (Scheme 1, II, C). Our group is dedicated to the synthesis of various types of sulfonyl fluorides by the photocatalytic redox strategy. Based on the SO₂ radical insertion/fluorination strategy, we envisaged a facile method to synthesize alkylsulfonyl fluorides through photocatalytic redox active ester decarboxylation with carboxylic acids as the alkyl radical source, DABSO as the SO₂ source and NFSI as the fluorine source. Herein, we wish to report our efforts toward this goal and the establishment of a facile method to access aliphatic sulfonyl fluorides based on visible light-mediated decarboxylative radical fluorosulfonylation *via* SO₂ radical insertion/fluorination of alkyl NHPI esters (low to 1 mol% P.C. and up to 92% yield). This method is characterized by the rapid synthesis of a broad range of alkylsulfonyl fluorides from primary, secondary, and tertiary acids, late-stage modification of natural products and drugs, and mild conditions (Scheme 1, II).

Results and discussion

To achieve the photocatalytic decarboxylated fluorosulfonylation of aliphatic carboxylic acid NHPI esters, an initial study was conducted with 4-bromophenylpropionic acid-derived NHPI ester **1a** as the model substrate (Table 1). Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ was first tested as the photocatalyst in combi-

Table 1 Optimization of the reaction conditions^a

Entry	Variation from the standard conditions	Yield ^b (%)
1	None	91 (85) ^c
2	Addition of Hantzsch esters (2.0 eq.)	85
3	Eosin Y-Na ₂ instead of Ir[dF(CF ₃)ppy] ₂ (dtbbpy)PF ₆	6
4	<i>fac</i> -Ir(ppy) ₃ instead of Ir[dF(CF ₃)ppy] ₂ (dtbbpy)PF ₆	17
5	Ru(bpy) ₃ Cl ₂ instead of Ir[dF(CF ₃)ppy] ₂ (dtbbpy)PF ₆	5
6	MeCN instead of <i>i</i> -PrOH	13
7	DMF instead of <i>i</i> -PrOH	17
8	THF instead of <i>i</i> -PrOH	N.P.
9	DCM instead of <i>i</i> -PrOH	N.P.
10	Et ₃ N instead of DIPEA	13
11	DABSO (1.5 eq.)	84
12	DIPEA (3.0 eq.)	61
13	Selectfluor TM instead of NFSI	18
14	NFSI (3.0 eq.)	90
15	Without P.C.	N.P.
16	No light	Trace
17	In air	Trace

^a Reaction conditions: **1a** (0.2 mmol), DABSO (0.4 mmol), DIPEA (1.0 mmol), Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (1 mol%), *i*-PrOH (4.0 mL), 24 W blue LEDs ($\lambda_{\max}$ = 460 nm), rt, argon, 3 h; then NFSI (0.4 mmol), 1 h; N.P. = no product was detected. ^b Yields were determined by ¹⁹F NMR analysis with 4-iodofluorobenzene as the internal standard. ^c Isolated yield is shown in parentheses.

nation with DIPEA as the reductant and DABSO as the SO₂ source. After 3 h of stirring, NFSI was added as the F source and the reactions proceeded for an additional 1 h. The desired product **2a** was obtained in 91% yield (85% isolated yield, Table 1, entry 1). The addition of Hantzsch ester (HE) as the additional reductant slightly reduced the yield (entry 2 *vs.* entry 1). This is probably due to the formation of a cloudy mixture upon the addition of HE, which negatively affects the light absorption of the photocatalyst. Next, changing the photocatalyst to eosin Y (disodium salt), *fac*-Ir(ppy)₃, or Ru(bpy)₃Cl₂ would dramatically reduce the yields (entries 3–5). Furthermore, varying the solvent proved that MeCN, DMF, THF or DCM are all not suitable for the reaction (entries 6–9). Replacing the sacrificial agent DIPEA with Et₃N also significantly reduced the yield to 13% (entry 10). When reducing the equivalents of DABSO or DIPEA, the yield of **2a** also decreased accordingly (entries 11 and 12). In contrast, SelectfluorTM gave a reduced reaction yield of 18% compared to NFSI (entry 13). Also, more equivalents of NFSI did not result in a better yield for this reaction (entry 14). Finally, control experiments showed that photocatalyst, light source and inert gas protection were necessary (entries 15–17).

Having established the optimized reaction conditions, we turned our attention to investigate the reaction scope. A variety of primary, secondary and tertiary carboxylic acid-derived NHPI esters were examined, and the results are shown in Table 2. In the case of primary carboxylic acids, we could observe good compatibility toward phenyl (**2b**, 86%), 4-methoxybenzene (**2c**, 79%), thienyl (**2d**, 78%), chloride (**2e**, 73%), C–C

Table 2 Substrate scope^a

(A) Primary aliphatic carboxylic acid NHPI ester	
(B) Secondary aliphatic carboxylic acid NHPI ester	
(C) Tertiary aliphatic carboxylic acid NHPI ester	
(D) Late-stage modification of natural products and drugs	

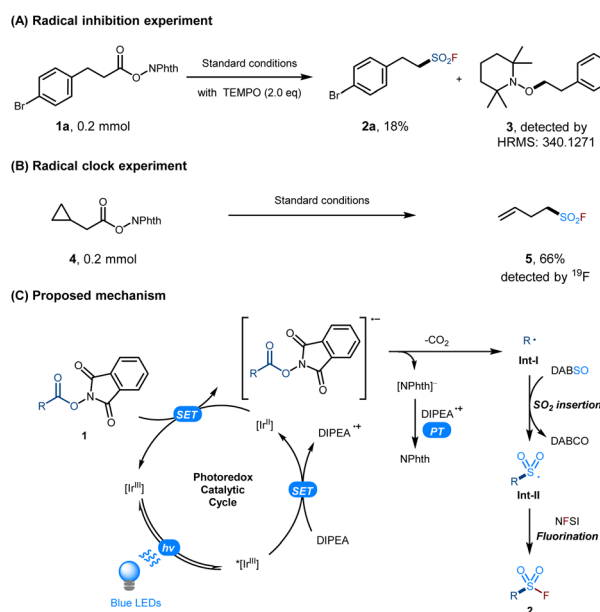
^a Standard conditions: at the 0.2 mmol scale, isolated yields.

triple bond (**2f**, 70%) and benzyl (**2g**, 71%). Secondary acids could also be efficiently converted into the corresponding alkylsulfonate fluorides in high yields (**2h–2l**, 78%–92%), including norbornylane (**2i**, 90%), cyclohexene (**2j**, 92%), cycloheptane (**2k**, 88%) and α -methylbenzyl (**2l**, 78%) substrates. Delightfully, compared with the existing synthetic methods of tertiary alkylsulfonate fluorides which suffer from synthetic difficulties or moderate yields,^{17f,19i} the most prominent feature of this novel method is that it allows for direct fluorosulfonation of tertiary aliphatic carboxylic acid NHPI ester to access tertiary alkylsulfonate fluorides in high yields, including adamantane (**2n**, 93%). Remarkably, due to mild conditions and excellent compatibility, this method can also be used in the late-stage modification of natural products or drugs to obtain the corresponding fluorosulfonation products in good to high yields, including **2q** (83%, from palmitic acid), **2t** (79%, from oxaprozin), **2u** (86%, from flubiprofen) and **2v** (84%, from abietic acid). As shown in Table 2, primary, secondary and tertiary alkyl carboxylic acid-derived NHPI esters can all be well accommodated under the reaction conditions, providing rapid access to alkyl boronic esters with considerable structural diversity.

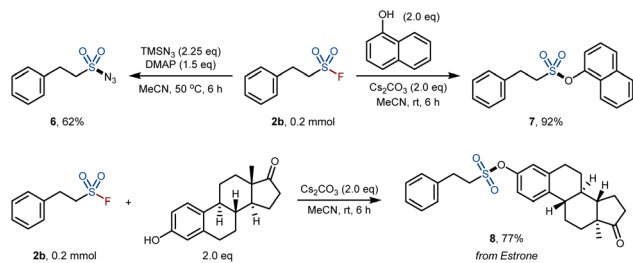
In order to gain a better understanding of the reaction mechanism, 2,2,6,6-tetramethylpiperidinoxy (TEMPO) was added to the reactions under the standard conditions. It was found that the yield of the expected product **2a** was dramatically reduced and the TEMPO-trapped product **3** was detected by HRMS analysis (Scheme 2A). In addition, we obtained the corresponding ring-opened fluorosulfonation product **5**¹⁹ⁱ in 66% ¹⁹F yield when cyclopropionate was used as the radical probe under the standard conditions (Scheme 2B). The above results showed that the reaction proceeds through an alkyl radical mechanism. According to the above studies and previous work,²¹ a plausible mechanism for this visible light-mediated decarboxylative radical fluorosulfonation *via* SO₂ insertion/fluorination is proposed, as shown in Scheme 2C.

Initially, the single electron transfer (SET) between the excited photocatalyst Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆ (P.C., [Ir]) and DIPEA produces DIPEA⁺ and the reductive [Ir^{II}] species. Subsequently, the reduction of NHPI esters **1** by the resulting [Ir^{II}] species leads to the formation of the alkyl radical **Int-I** and the regeneration of the photocatalyst [Ir^{III}]. The insertion of SO₂ into the alkyl radical **Int-I** then gives rise to the sulfonyl radical **Int-II**, which is captured by NFSI through fluorine atom transfer^{17ef} to afford the final fluorosulfonation product **2**.

To demonstrate the synthetic value of our products, we carried out the derivatization of the obtained product **2b** (Scheme 3). We investigated the multifunctional synthesis of various sulfonyl-containing derivatives based on the fluorosulfonate group. For example, sulfonyl azide **6** was obtained through SuFEx click reactions with trimethylsilyl azide (TMSN₃). On the other hand, sulfonate ester **7** was achieved through the reaction of **2b** with naphthol. Moreover, the sulfonate derivatives of estrone **8** can also be obtained in 77% yield by the SuFEx click reaction.



Scheme 2 Mechanistic study and proposed mechanism.



Scheme 3 Derivatization reactions of 2-phenylethane-1-sulfonyl fluoride (2b).

Conclusions

In conclusion, by combining photoredox catalysis and SO₂ radical insertion, a visible light-mediated decarboxylative radical fluorosulfonylation *via* SO₂ insertion/fluorination of aliphatic carboxylic acid NHPI esters has been successfully developed for the first time. This method is applicable to a variety of alkyl carboxylic acids, including primary, secondary, and tertiary ones, as well as several natural products and drugs, allowing for facile access to various alkylsulfonyl fluorides, which are important compounds in multiple fields of chemistry, biology and materials science. Moreover, the value of the products has been demonstrated once again with a direct transformation of sulfonyl fluorides to sulfonyl azides and sulfonate esters. We anticipate that this radical photocatalytic decarboxylative fluorosulfonylation will provide a useful and complementary new approach for the synthesis of sulfonyl fluorides.

Author contributions

X. Nie conceived this study, developed the reactions, performed the reaction optimization and completed this manuscript; H. Zhang and S. Li completed the scope investigation, mechanistic study and product diversification; and H. Zheng, G. Zhu and S. Liao helped complete this manuscript with feedback from X. Nie. In addition, S. Liao provided financial and experimental material support. We thank the members of the NMR and HRMS departments for their excellent service.

Conflicts of interest

There are no conflicts to declare.

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