Organocatalytic silicon-free SuFEx click reactions of SO_2F_2

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KEYWORDS: Sulfur (VI) fluoride exchange, click chemistry, organocatalysis, fluorosulfates, sulfamoyl fluorides

Abstract:

An organocatalytic method for silicon-free SuEEx click reaction of SO_2F_2 is described. Different organic bases such as DBU, TBD, triethylamine and Hünig's base can efficiently catalyze the SuFEx of SO_2F_2 with various phenols to produce aryl fluorosulfates in 61-97% yields. Under the same conditions, pyridone, pyrazolone and secondary amines can also react with SO_2F_2 to afford the corresponding heteroaryl fluorosulfates or sulfamoyl fluorides in good yields. In this process, molecular sieves absorb the acidic HF efficiently, which avoid the using of stoichiometric amount of silicon reagents and excess of bases.

Introduction:

Organosulfur compounds have been widely utilized in organic synthesis, material science, pharmaceutical and agrochemical industry.[1] Among different types of sulfur-containing compounds, aryl fluorosulfates can serve as triflate surrogates in transition-metal catalyzed coupling reactions[2] (e.g. Suzuki-Miyaura coupling, Buchwald-Hartwig coupling, Negishi coupling), Substitution reactions[3] and other reactions.[4] More importantly, aryl fluorosulfates have been successfully used in chemical biology and drug discovery, including late-stage drug functionalization,[5]

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late-stage radiosynthesis,[6] the synthesis of fluorogenic probes[7] and so on.[8] As a result, the development of new method for the synthesis of aryl fluorosulfates is highly significant. Unfortunately, there was no applicable method for the preparation of these important organosulfur compounds for a long time. Early developed synthetic methods, such as the pyrolysis of arenediazonium fluorosulfate salts,[9] the reaction of phenols with $ClSO_2F$ or fluorosulfonic acid anhydride[10] usually suffer from risky conditions, costly starting materials and low reaction yield. In 2014, Sharpless and coworkers launched Sulfur (VI) - Fluoride Exchange (SuFEx) click chemistry.[11] This new embodiment of click chemistry provides a powerful and robust tool for modular assembly of various sulfonylated compounds.[12] In particular, Sharpless and coworkers recognized the gaseous SO_2F_2 as an valuable SuFExable hub.[11a] In the presence of excess of base, SO_2F_2 can react with phenols to give aryl fluorosulfates in excellent yields.[13] Interestingly, using aryl silyl ethers instead of phenols, catalytic amounts of DBU can catalyze the reaction in quantitatively yields. Recently, Moses and coworkers reported an interesting accelerated SuFEx click chemistry for quick synthesis of various sulfonylated compounds.[14] They reported that in the presence of 1.0 equivalent of hexamethyldisilazane (HMDS), catalytic amount of Barton's base BTMG can catalyze the heterogeneous SuFEx click reaction of phenols and SO_2F_2 to give aryl fluorosulfates in high yields within 15 min. Despite progress made in this research, no general and catalytic silicon-free for SuFEx of SO_2F_2 has been disclosed. As part of our continuous research on the synthesis of organosulfur compounds,[15] herein, we wish to report an organocatalytic silicon-free[16] SuFEx reaction of SO_2F_2 and phenols for facile synthesis of aryl fluorosulfates.

Our initial studies were carried out with the commercially available 4-biphenylol **1a** and SO_2F_2 **2a**. Pleasingly, in the presence of 10 mol% triethylamine and 800 mg molecular sieves 4Å, the reaction proceeded smoothly in acetonitrile at room temperature to form aryl fluorosulfate **3a** in 94% yield (Table 1, entry 1). Encouraged by this result, other common bases were then examined. The Hünig's base catalyzed the reaction in 95% yield (Table 1, entry 2). DMAP, DABCO and cinchonine catalyzed the reaction in good yields (Table 1, entries3-5). Organic superbases DBU,

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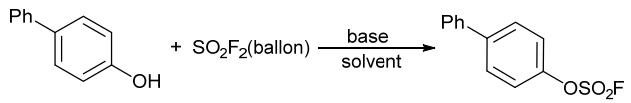
DBN, TBD and TMG catalyzed the reaction in high yields (Table 1, entries 6-9). *t*-BuOK catalyzed the reaction to give **3a** in 43% yield (Table 1, entry 10). Inorganic bases were also tested for the reaction. NaOH, K_2CO_3 and Cs_2CO_3 catalyzed the reaction in moderate yields (Table 1, entries 11-13). Using 10 mol% DBU as catalyst, we next studied the effect of different solvents. The product **3a** was formed in low yield when the SuFEx reaction was performed in dichloromethane (Table 1, entry 14). Moderate yield of **3a** was obtained when the reaction was conducted in dichloroethane (Table 1, entry 15). Other tested solvents, such as THF, MTBE, DME, toluene and DMF gave product **3a** in high yield (Table 1, entries 16-21). Decreasing the amount of DBU to 5 mol%, or reducing the loading of MS 4Å resulted in decreased reaction yield (Table 1, entries 22-23). Control experiments showed that in the absence of DBU, no desired product was formed (Table 1, entry 24). Without the addition of MS 4Å, only 27% yield of **3a** was obtained (Table 1, entry 25).

Table 1 Optimization of reaction conditions [a]



1a **2a** **3a**

Entry	Base	Solvent	Time (h)	Yield (%)[b]
1	Et_3N	CH_3CN	24	94
2	DIPEA	CH_3CN	24	95
3	DMAP	CH_3CN	24	85
4	DABCO	CH_3CN	24	70
5	cinchonine	CH_3CN	24	70
6	DBU	CH_3CN	24	97
7	DBN	CH_3CN	24	82
8	TBD	CH_3CN	24	97
9	TMG	CH_3CN	24	89
10	*t*-BuOK	CH_3CN	24	43
11	NaOH	CH_3CN	24	63
12	CS_2CO_3	CH_3CN	24	35
13	K_2CO_3	CH_3CN	24	47
14	DBU	CH_2Cl_2	48	16
15	DBU	DCE	24	53
16	DBU	THF	24	78
17	DBU	MTBE	24	81
18	DBU	DME	24	92
19	DBU	toluene	24	94

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20	DBU	DMF	24	93
21	DBU	DMAc	24	87
22[c]	DBU	CH_3CN	24	81
23[d]	DBU	CH_3CN	24	86
24	No base	CH_3CN	48	32
25[e]	DBU	CH_3CN	48	27

[%a] **1a** (0.80 mmol), base (10 mol%), MS 4Å (800 mg), solvent 2.0 mL, room temperature. [b] Isolated yield. [c] **1a** (0.80 mmol), DBU (10 mol%), MS 4Å (400 mg). [d] **1a** (0.80 mmol), DBU (5 mol%), MS 4Å (800 mg). [e] Without MS 4Å.

With the optimized reaction conditions in hand, we then examined the scope of phenols and the results are summarized in Table 2. Both electron-donating and electron-withdrawing substituents substituted phenols participated in the SuFEx reaction well, producing the corresponding aryl fluorosulfates in high yields. The electronic properties and different positions of the substituents have little influence on the rection yield (**3b-3t**). Many useful groups, such as halogenations (**3e-3g, 3m-3o**), nitrile (**3h**), aldehyde (**3l**), ketone and ester group (**3i** and **3j**) were tolerated well. Pinacol boronic ester substituted phenol underwent the SuEFx reaction to give **3wt** in 71% yield (**3u**). Sterically hindered substrates **1o** and **1t** reacted with SO_2F_2 to afford the corresponding fluorosulfates **3o** and **3t** in 81% and 64% yields, respectively. 6-hydroxyindole and pyridinol performed well yielding the corresponding heteroaryl fluorosulfates in good yields (**3y** and **3z**). Interestingly, when 1,3-benzenediol **1h** was used for the reaction, the corresponding fluorosulfate **3ah** was formed in 85% yield, which is a very useful substrate in the synthesis of polysulfates. It is noteworthy that many natural phenols, such as (+)-δ-tocopherol， D-tyrosine，deoxyarbutin，maltol and so on， were proven to be very good reactants, furnishing the corresponding fluorosulfates in high yields (**3ab-3ah**).

Table 2 Scope of phenols [a]

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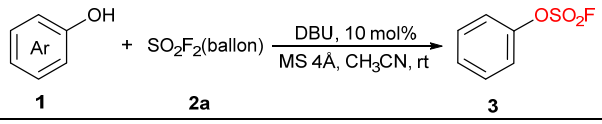
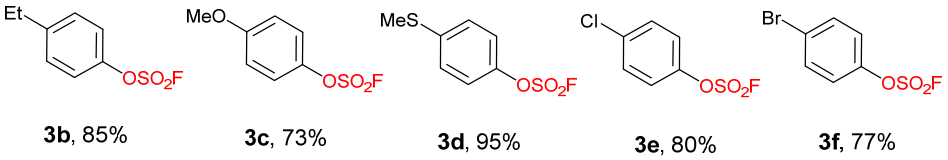


1 2a 3



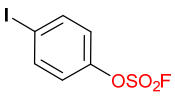
3b, 85%

3c, 73%

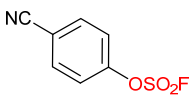
3d, 95%

3e, 80%

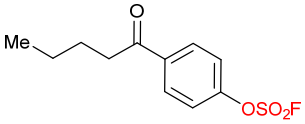
3f, 77%



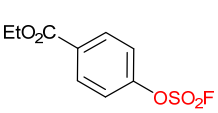
3g, 92%



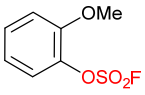
3h, 91%



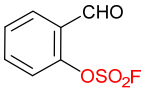
3i, 99%



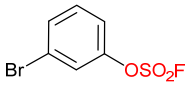
3j, 97%



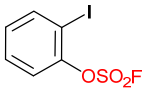
3k, 73%



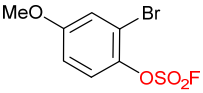
3l, 73%



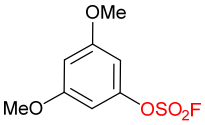
3m, 79%



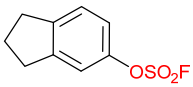
3n, 94%



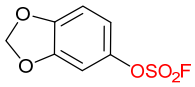
3o, 96%



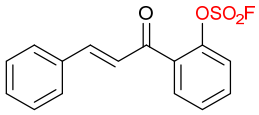
3p, 94%



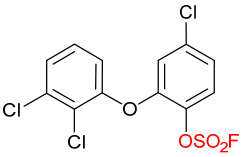
3q, 96%



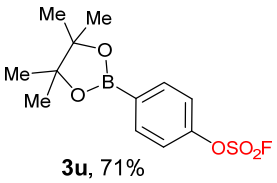
3r, 78%



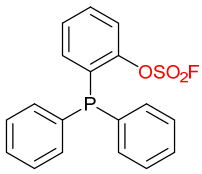
3s, 61%



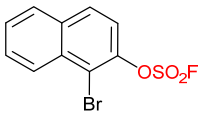
3t, 88%



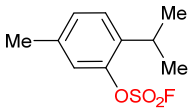
3u, 71%



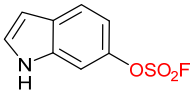
3v, 64%



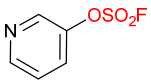
3w, 81%



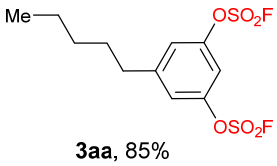
3x, 85%



3y, 70%

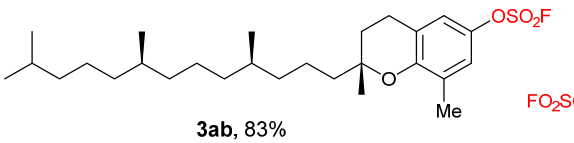


3z, 64%

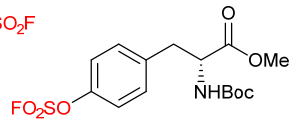


3aa, 85%

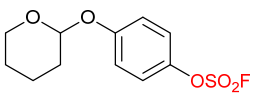
Natural products



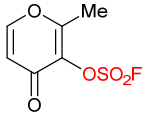
3ab, 83%
(*from (+)-d-tocopherol*)



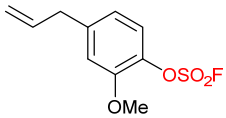
3ac, 91%
(*from D-tyrosine*)



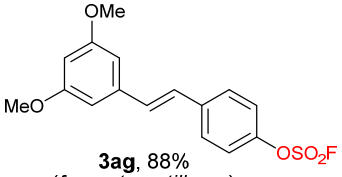
3ad, 93%
(*from deoxyarbutin*)



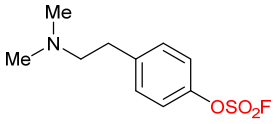
3ae, 85%
(*from maltol*)



3af, 81%
(*from eugenol*)



3ag, 88%
(*from pterostilbene*)



3ah, 53%
(*from hordenine*)

[a] 1 (0.8 mmol), DBU (10 mol%), MS 4Å (800 mg), CH_3CN (2.0 mL), room temperature, 24h, isolated yield.

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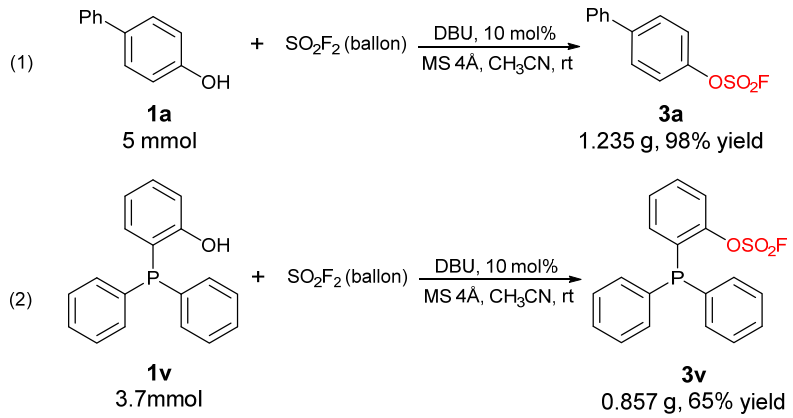
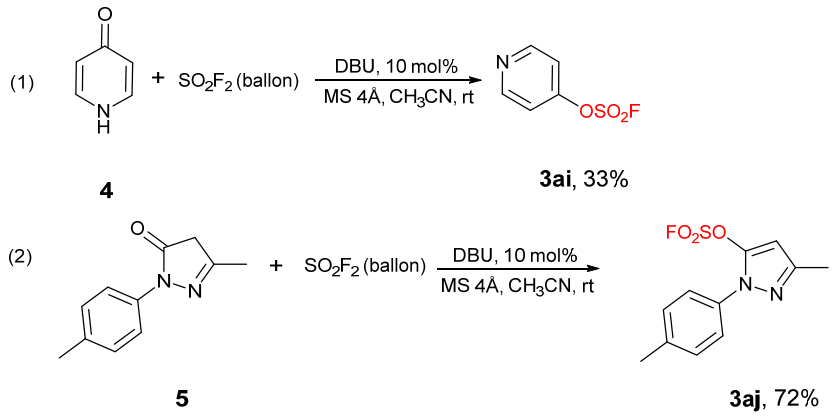
To explore the synthetic utility of this organocatalytic protocol, gram-scale experiments were conducted (Scheme 1). The desired aryl fluorosulfate **3a** was isolated in 1.245 g, 98% yield (eq. 1). The sterically hindered fluorosulfate **3x** can also be obtained in 0.857g a and 65% yield (eq. 2).



Scheme 1. Gram-Scale Synthesis of aryl fluorosulfates

Interestingly, under the standard reaction conditions, pyridone and pyrazolone can react with SO_2F_2 to give the corresponding heteroaryl fluorosulfates in 33% and 72% yields, respectively (Scheme 2).



Scheme 2. SuFEx reactions of pyridone and pyrazolone

To further demonstrate the utility of this organocatalytic method, the analogous SuFEx reaction of amines and SO_2F_2 was investigated. Under similar reaction conditions, different secondary amines reacted with SO_2F_2 smoothly to furnish the desired sulfamoyl fluorides in good yields (Scheme 3).

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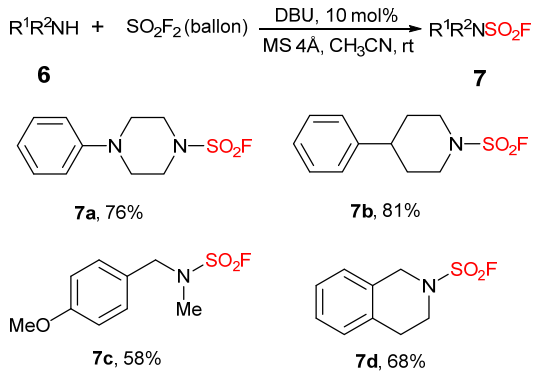
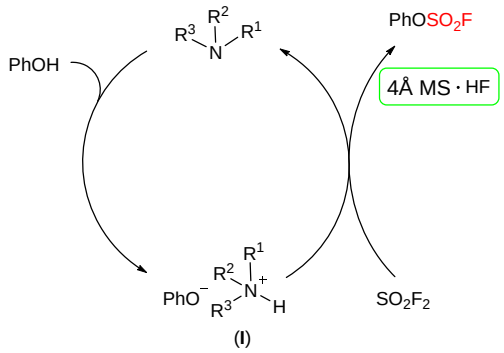


Scheme 3. SuFEx reactions of secondary amines and SO_2F_2

Based on pioneering studies of Sharpless, Zuilhof, Moses and our previous report, a plausible mechanism was proposed and depicted in Scheme 4, the basic tertiary amine first reacts with phenol to generate the nucleophilic phenolate (I), which subsequently undergoes SuFEx click reaction with SO_2F_2 to produce aryl fluorosulfate with releasing of catalyst. The acidic HF the generated in the reaction can be absorbed by the basic MS 4Å.



Scheme 4. Proposed Mechanism

In summary, have developed an organocatalytic silicon-free SuFEx click reaction of SO_2F_2 for modular synthesis of aryl fluorosulfates and sulfamoyl fluorides. This novel method features extreme mild conditions, generally high reaction yields and easy scalability. Further studies on a broader substrate scope and the applications of this organocatalytic approach are currently underway in our laboratory.

Notes

The authors declare no competing interests.

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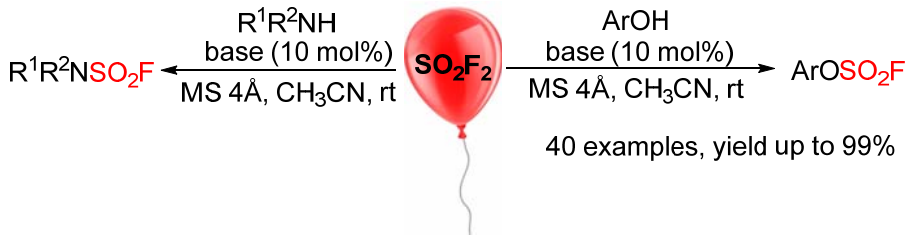

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