N-Heterocyclic carbene-catalyzed silicon-free sulfur fluoride exchange reactions of sulfonimidoyl fluorides

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Abstract:

As the monoaza analogous of sulfonates and sulfonamides, sulfonimidate ester and sulfonimidamide have attracted growing attention in recent years. In this paper. We report an organocatalytic silicon-free sulfur fluoride exchange (SuFEx) reaction of sulfonimidoyl fluorides for the synthesis of these valuable organosulfurs. Under the catalysis of 10 mol% N-heterocyclic carbene (NHC), and MS 4Å, sulfonimidoyl fluorides reacted with phenols to produce sulfonimidate esters in 55-99% yields. In addition, under the relay catalysis of 10 mol% NHC and HOBt, various amines coupled with sulfonimidoyl fluorides to give sulfonimidamides in 55-99% yields.

Introduction:

Sulfur (VI)-containing compounds such as sulfonamide and sulfonates have been well established as privileged structural motifs in numerous FDA-approved drugs, and the synthesis of these compounds had been explored thoroughly over the past decades.[1] In contrast, sulfonimidamide and sulfonimidate ester, the bioisosteres of sulfonamide and sulfonate, have been long been neglected in drug discovery due to the lack of commercial availability and synthetic accessibility.[2] Compared to their oxygenated analogous, these compounds possess unique structural and physiochemical properties, such as intrinsic stereogenic sulfur centers, multiple hydrogen-bond acceptor and donor functionalities, high stability and good aqueous solubility.[3] Fortunately, sulfonimidamides, sulfonimidate esters and other sulfonimindoyl compounds have recently gained significant attention of medicinal chemists.[4] Some of these sulfonimidoyl derivatives have been successfully used as new drugs and pesticides.[5]

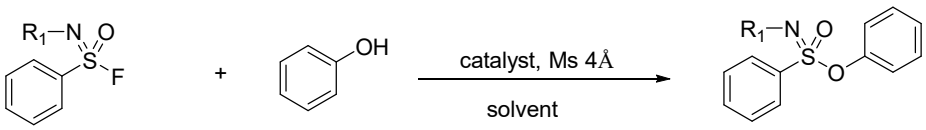
Giving the growing significance of sulfonimidamides and sulfonimidate esters in drug discovery, considerable efforts have been exerted to develope new method for the synthesis of these sulfur (VI)-containing compounds in recent years. In addition to the classical substitution reactions of sulfonimidoyl chlorides,[6] the transformation of sulfinyamine derivatives,[7] and other elegant reactions[8] provide different protocols for the synthesis of sulfonimidamides and sulfonimidate esters.

Sulfur fluoride exchange (SuFEx) click chemistry that developed by Sharpless and coworkers provides a powerful tool for modular assembly of molecular linkages.[9] This new embodiment of click chemistry has been used in the fields of synthetic chemistry,[10] chemical biology,[11] drug discovery[12] and polymer synthesis.[13] In particular, click reactions of sulfonimidoyl fluorides with O- and N- nucleophiles provide efficient synthesis of sulfonimidamides and sulfonimidate esters.[14] Sharpless and coworkers reported DBU can catalyze SuFEx of sulfonimidoyl fluorides and aryl silyl ethers to give sulfonimidate esters in high yields.[14a, b] In 2020, Zuilhof and coworkers documented[15] an interesting silicon-free SuFEx click reaction of sulfonimidoyl fluorides and free phenols. They found that 1.0 equivalent can efficient mediate the coupling of sulfonimidoyl fluorides and phenols to give sulfonimidate esters in high yields within several minutes. Recently, the same group further reported[16a] Lewis acid mediated enantiospecific synthesis of sulfonimidamides. They found that l.0 equivalent of Ca $(NTf_2)_2$ can promote the SuFEx click reaction of sultonimidoyl fluorides and aromatic amines to produce sulfonimidamides in high yields. Very recently, our group reported[17a] an organocatalytic SuFEx reaction of sulfonyl fluorides. As a continuous study, we further studied the SuFEx reations of sulfonimidoyl fluorides. Herein, we would like to report the result of this research.

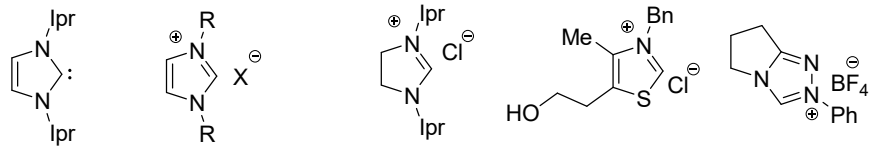
Results and Discussion:

In our initial study, N-propyl sulfonimidoyl **1a** and phenol **2a** were chosen as the model substrates to investigate the optimal reaction conditions. In the presence of MS 4Å and 10 mol% of a stable NHC **A**,[18] the desired sulfonimidate ester **3a** was obtained in 15% yield (Table1, entry1). Pleasingly, with the addition of HOBt (10 mol%) as cocatalyst, the yield

Table 1. Screening of reaction conditions



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



A **B1**: R = 2,4,6-$Me_3C_6H_2$, X = Cl; **B2**: R = t-Bu, X = BF_4; **B3**: R = Cy, X = BF_4 **C** **D** **E**

Entry	Catalyst and additives	Solvent	*t* (h)	Yield(%)[a]
1[b]	**A**, 200 mg MS 4Å	CH_3CN	24	15
2[c]	**A/HOBt**, 200 mg MS 4Å	CH_3CN	24	74
3	**B1/HOBt**, 200 mg MS 4Å	CH_3CN	24	75
4	**B2/HOBt**, 200 mg MS 4Å	CH_3CN	24	42
5	**B3/HOBt**, 200 mg 4Å	CH_3CN	24	54
6	**C/HOBt**, 200 mg MS 4Å	CH_3CN	24	65
7	**D/HOBt**, 200 mg MS 4Å	CH_3CN	24	28
8	**E/HOBt**, 200 mg MS 4Å	CH_3CN	24	56

9	**TMG/HOBt**, 200 mg MS 4Å	CH_3CN	24	18
10	**BTMG/HOBt**, 200 mg MS 4Å	CH_3CN	24	27
11	**DIPEA/HOBt**, 200 mg MS 4Å	CH_3CN	48	8
12	**DBU/HOBt**, 200 mg MS 4Å	CH_3CN	24	51
13	**CS_2CO_3/HOBt**, 200 mg MS 4Å	CH_3CN	24	33
14	**K_2CO_3/HOBt**, 200 mg MS 4Å	CH_3CN	24	18
15	**B1/HOBt**, 200 mg MS 4Å	Toluene	24	78
16	**B1/HOBt**, 200 mg MS 4Å	THF	24	74
17	**B1/HOBt**, 200 mg MS 4Å	DCM	24	42
18	**B1/HOBt**, 200 mg MS 4Å	DCE	24	54
19	**B1/HOBt**, 200 mg MS 4Å	DMSO	24	65
20	**B1/HOBt**, 200 mg MS 4Å	TBME	24	28
21	**B1/HOBt**, 200 mg MS 4Å	ACETONE	24	56
22	**B1/HOAt**, 200 mg MS 4Å	Toluene	24	47
23	**B1/HATu**, 200 mg MS 4Å	Toluene	24	30
24	**B1/HFIP**, 200 mg MS 4Å	Toluene	24	13
25[d]	**B1/HOBt**, 200 mg MS 4Å	Toluene	24	65
26[e]	**B1/HOBt**, 200 mg MS 4Å	Toluene	24	73
27[f]	**B1**, 200 mg MS 4Å	Toluene	1	99

[a] Isolated yield. [b] **1a** (R_1 = nPr, 0.30 mmol, 60.4 mg), **2a** (0.20 mmol, 18.8 mg), Catalyst (10 mol%), MS 4Å (200 mg), solvent (0.5 ml), room temperature. [c] Additives (10 mol%) [d] **1a** (R_1 = nPr, 0.20 mmol, 40.3 mg), **2a** (0.30 mmol, 28.2 mg). [e] 80°C. [f] **1b** (R_1 = Bz, 0.30 mmol, 79.0 mg), **2a** (0.20 mmol, 18.8 mg), NHC **B1** (11 mol%, 7.5 mg), DBU (10 mol%, 3 mg), MS 4Å (200 mg), toluene (0.5 ml), room temperature,1h.

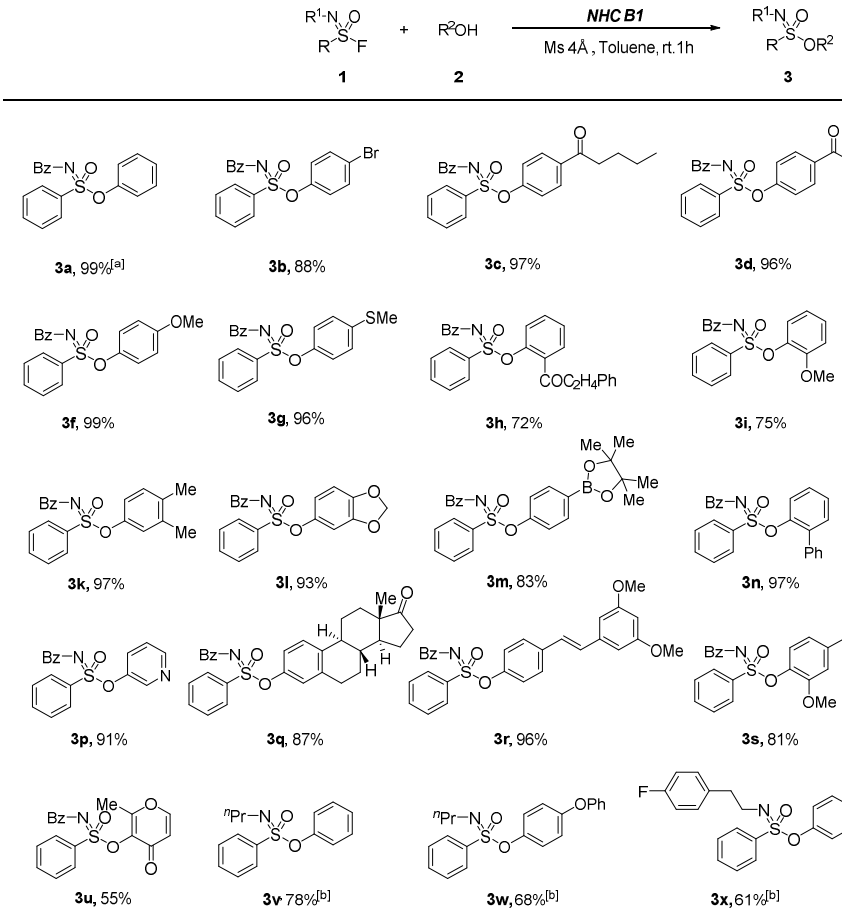
of **3a** was dramatically improved to 74% (Table 1, entry 2). Other NHCs generated from imidazolium and imidazolinium catalyzed the reaction in good yields, while NHC generated from thiazolium catalyzed the reaction in low yield (Table 1, entry 3-7). Triazolium derived NHC

catalyzed the SuFEx in 56% yield (Table 1, entry 8). Other Brønsted bases, were also tested for the reaction. TMG, BTMG and DIPEA catalyzed the reaction in low yield (Table 1, entry 9-11). Interestingly, DBU catalyzed the reation to give **3a** in 51% yield (Table 1, entry 12). Inorganic bases such as Cs_2CO_3, and K_2CO_3, showed low efficiency (Table 1, entry 13-14). A brief evaluation of reaction media revealed thattoluene is the best choice with respect to reaction yield (Table 1, entry 15-21). Using HOAt, HATu and HFIP as cocatalyst resulted in decreased yield (Table 1, entry 22-24). Reversing the molar ratio of substrates or raising reaction temperature cannot improve the yield (Table 1, entry 25-26). Pleasingly, when N-benzoyl sulfonimidoyl was used for the reaction, HOBt was not needed and NHC can independently catalyze the reaction in quantitative yield within one hour (Table 1, entry 27).

With the optimal optimized reaction conditions in hand, we then examined the substrate scope and the results are summarized in **Table 2**. Both electron-withdrawing and -donating substituents substituted phenols underwent the SuFEx to give the corresponding products in high yields (**3b-3g**). In addition, different positions of the substituents on the aromatic rings of phenols had no apparent effects on the reaction yield (**3h-3l**). Pinacol boronic ester substituted phenol **2m** participated in the reaction to afford **3m** in 83% yield. The Bpin group provides good opportunities for further derivation through classical coupling reactions.

O-phenylphenol and naphthol underwent the reaction to provide the corresponding sulfonimidate esters in excellent yields (**3n** and **3o**). Pyridinol performed the reaction to give **3p** in 91% yield. Notably, a variety of naturally occurring phenols, such as estone, pterostilbene, eugenol and thymol were proved to be good reactants for the click reaction, affording the corresponding products in high yields (**3q, 3r, 3s, 3t**). Maltol can also couple with **1a** to furnish the desired sulfonimidate ester **3u** in 55% yield. Interestingly, under the relay catalysis of 10 mol% NHC and 10 mol% HOBt, N-alkyl sulfonimidoyl fluorides reacted with phenols to give the corresponding products in good yields (**3v** and **3w**).

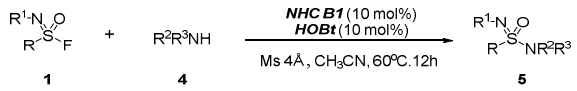
Table 2. Substrate scope for the synthesis of sulfonimidate esters



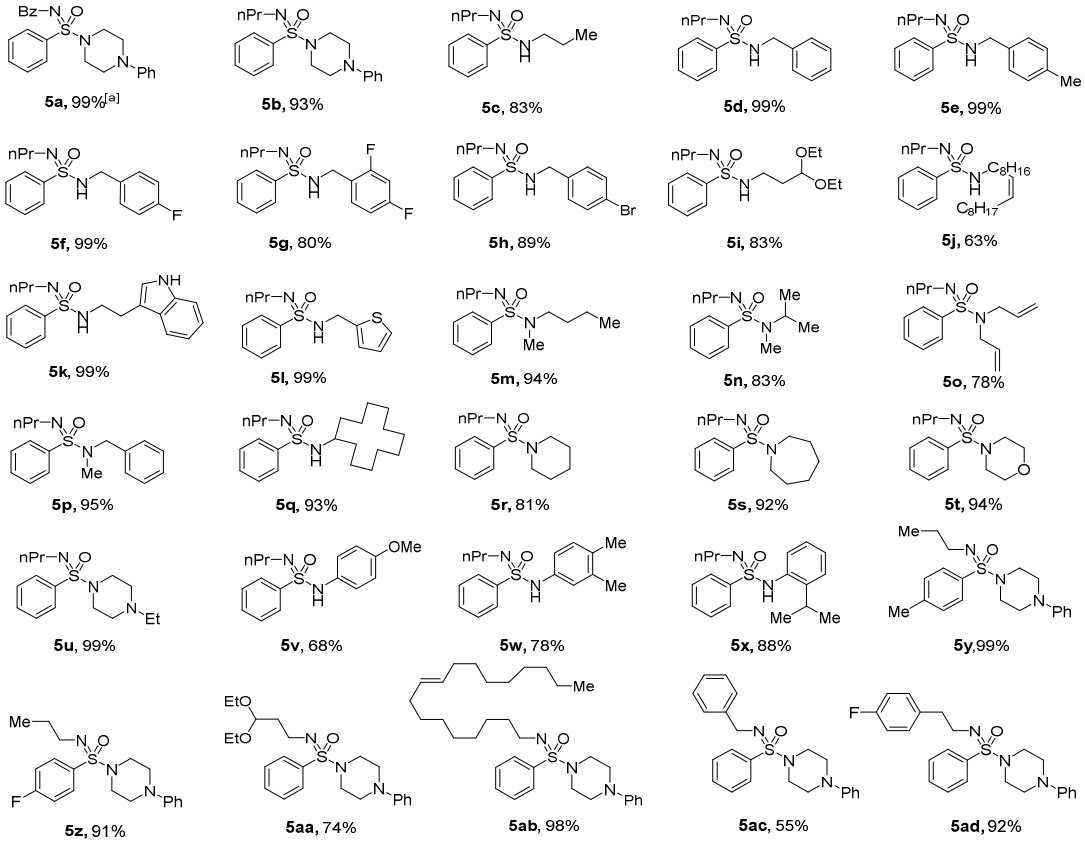
[a] **1** (0.30 mmol), **2** (0.20 mmol), IMes (11 mol%, 7.5 mg), DBU (10 mol%, 3 mg), MS 4Å (200 mg), toluene (0.5 ml), room temperature,1h.[b] **1** (0.30 mmol), **2** (0.20 mmol), IMes (11 mol%, 7.5 mg), DBU (10 mol%, 3 mg), HOBt (10 mol%, 2.7 mg) MS 4Å (200 mg), toluene (0.5 ml), room temperature,24h.

We next studied the SuFEx of sulfonimidoyl fluorides and amines for the preparation of sulfonimidamides (Table 3). Under slightly modified reaction conditions, both N-benzoyl and N-propyl sulfonimidoyl fluorides underwent the reaction to produce the corresponding sulfonimidanides in excellent yields (**5a** and **5b**). A broad variety of primary and secondary amines reacted with N-propyl sulfonimidoyl fluoride **la** efficiently to give

Table 3. Substrate Scope for the Synthesis of sulfonimidamides



1 4 5

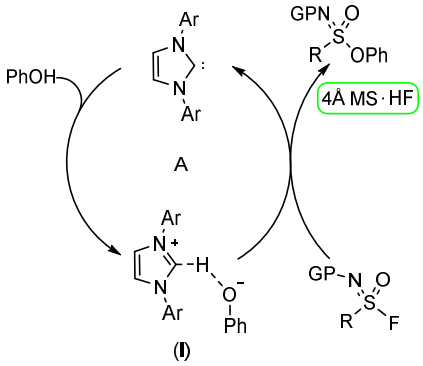


[a] **1** (0.20 mmol), **4** (0.30 mmol), IMes (11 mol%, 7.5 mg), DBU (10 mol%, 3.0 mg), HOBt (10 mol%, 2.7 mg) MS 4Å (200 mg), CH_3CN (0.5 ml), 60°C, 12h.

the corresponding products in high yields **(5a-5u)**. Many useful groups such as halogen atoms, olefins, ketal and heteroaryls were well tolerated for the SuFEx. Aromatic amines coupled with sulfonimidoyl fluoride smoothly to give the desired products in high yields (**5v-5x**). On the other hand, different N-alkyl sulfonimidoyl fluorides were proved to be very good electrophiles for the reaction, delivering the corresponding products in high yields (**5y-5ad**).

Based on our previous Studies on NHC-catalyzed SuFEx reactions,[17]

we proposed a possible mechanism for the reaction (Scheme 1). NHC acts as a Brønsted base to activate phenols or amines through the formation of hydrogen bond which might trigger the following SuFEx reaction with sulfonimidoyl fluoride to form the final product. In this process, MS 4Å function as a weak base to absorb the acidic HF efficiently.



Scheme 1 proposed mechanism

In summary, an organocatalytic SuFEx click reaction of sulfonimidoyl fluorides have been demonstrated. The mild and silicon-free conditions, broad substrate scope and a high reaction yield provide an efficient method for the synthesis of sulfonimidate esters and sulfonimidamides. Further study of chiral NHC-catalyzed asymmetric SuFEx reaction via kinetic resolution are ongoing in our lab.

Notes

The authors declare no competing interests.

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