

N-Heterocyclic carbene catalyzed SuFEx reactions of functionalized secondary alcohols

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Abstract:

An organocatalytic Sulfur (VI)-fluoride exchange (SuFEx) reaction of secondary alcohols is reported. Under the catalysis of 10mol% NHC/MS 4Å, both trifluoromethyl and difluoromethyl benzyl alcohols reacted with aryl sulfonyl fluorides to produce the corresponding sulfonates in moderate to high yields.

Introduction:

Sulfonates are important structural motifs found in biologically active molecules, pharmaceuticals and functional materials.¹ Owing to their synthetic importance, considerable efforts have been exerted to develop new methods for the synthesis of these valuable organosulfur compounds. The esterification of sulfonyl chlorides,² photo-induced oxidation of thiophenols³ and transition-metal catalyzed multicomponent reactions⁴ provide different methods for the preparation of sulfonic esters. However,

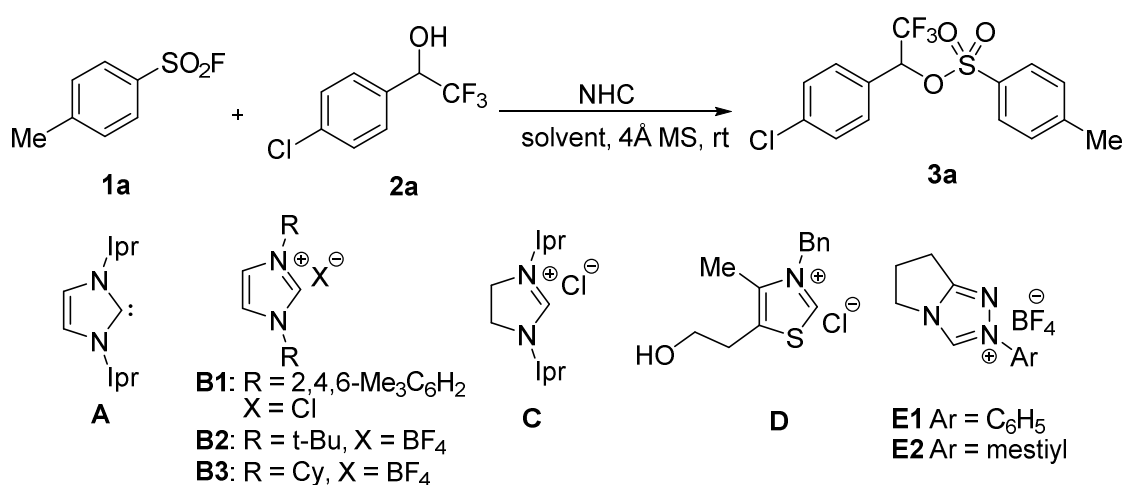
these methods suffers from drawbacks, such as the instability and moisture sensitive of sulfonyl chlorides, the unpleasant odors of thiophenols. Therefore, the development of new method for the synthesis of sulfonates is still significant. Compared to Sulfonyl chlorides, sulfonyl fluorides show remarkable thermodynamic tunable stability. Based on these unique properties, Sharpless and coworkers developed Sulfur(VI)-fluoride exchange (SuFEx) chemistry in 2014.⁵ This new generation click chemistry provides a robust method for the construction of sulfur-heteroatom bonds. As a result, a broad spectrum of sulfonyl-containing compounds such as sulfonates, sulfonamides, sulfamates, sulfamides and so on, can be synthesized through SuFEx reactions.⁶ In the past ten years, SuFEx click chemistry has been applied in organic synthesis,⁷ chemical biology,⁸ drug discovery⁹ and synthesis of polymers.¹⁰

Among different SuFEx reactions, the coupling of sulfonyl fluorides with aryl silyl ethers, phenols, or primary alcohols provides facile access to different sulfonates. However, owing to decreased reactivity, SuFEx reaction of secondary and tertiary alcohols are underdeveloped.¹¹ Recently, we reported an organocatalytic SuFEx chemistry of different SuFExable hubs under silicon-free conditions.¹² We found that phenols, primary alcohols and secondary alkyl alcohols are suitable reactants. However, when secondary benzylic alcohols and tertiary alcohols were used for the reaction, no desired products were formed. As a continuous study, we found that under the catalysis of NHC/MS 4Å, many functionalized secondary benzylic alcohols, such as trifluoromethyl and difluoromethyl benzyl alcohols can efficiently undergo this SuFEx reaction to produce sulfonates. Herein, we would like to report this result.

Results and Discussion:

At the outset, we commenced our study with sulfonyl fluoride **1a** and trifluoromethyl benzyl alcohol **2a** as the model substrates. To our delight, in the presence of molecular sieves 4Å (MS 4Å) and 10mol% stable NHC **A** ((1,3-bis-(2,6-dissopropylphenyl)-imidazole-2-ylidene, IPr),^{13a} the SuFEx reaction proceeded smoothly in acetonitrile at room temperature to produce the desired sulfonate **3a** in 90% yield (Table 1, entry 1). Encouraged by this result, several other NHCs were then examined for the reaction. NHCs generated from imidazolium and imidazolinium catalyzed the reaction in high yields (Table 1, entries 2-5). Owing to decreased basicity, NHC derived from thiazolium catalyzed the reaction in low yield (Table 1, entry 6). NHCs generated from triazolium salts catalyzed the reaction in good yields (Table 1, entries 7 and 8). A brief evaluation of the reaction media show that acetonitrile is the best choice with respect to the yield (Table 1, entries 9-13). Reduction of NHC to 5mol% led to dramatic decrease of the reaction yield (Table 1, entry 14). Control experiments showed that in the absence of NHC catalyst, no desired was formed (Table 1, entry 15). Without the addition of MS 4Å, only 15% yield of **3a** was obtained (Table 1, entry 16).

Table 1 Optimization of reaction conditions ^a

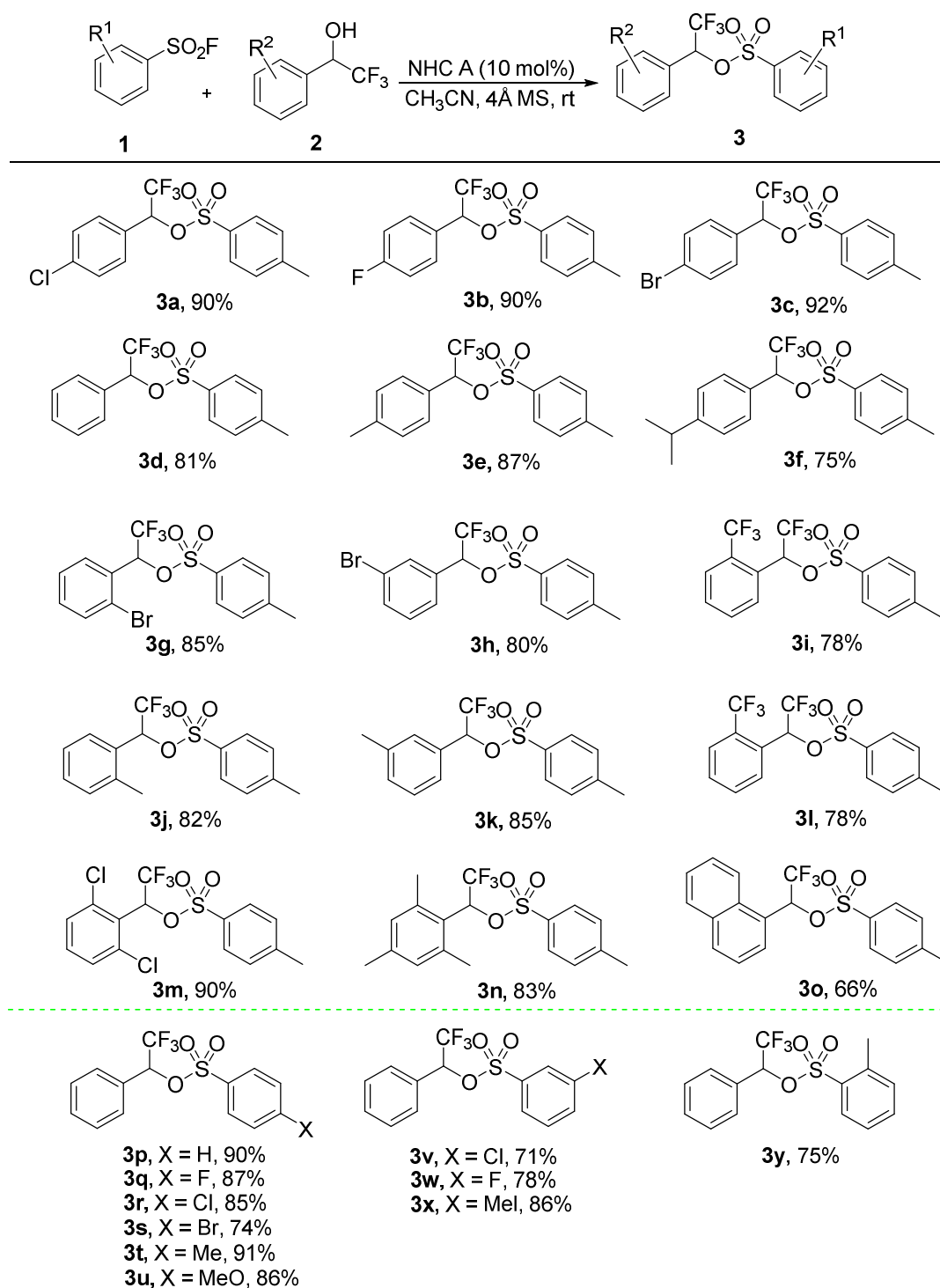


Entry	Catalyst	Solvent	Time (h)	Yield (%) ^b
1	A	CH ₃ CN	24	90
2	B1	CH ₃ CN	24	89
3	B2	CH ₃ CN	24	85
4	B3	CH ₃ CN	24	87
5	C	CH ₃ CN	24	85
6	D	CH ₃ CN	24	42
7	E1	CH ₃ CN	24	60
8	E2	CH ₃ CN	24	81
9	A	toluene	24	85
10	A	THF	24	80
11	A	CH ₂ Cl ₂	24	81
12	A	DCE	24	62
13	A	1,4-dioxane	24	66
14 ^c	A	CH ₃ CN	24	60
15 ^d	/	CH ₃ CN	48	trace
16 ^e	A	CH ₃ CN	48	15

^a **1a** (0.25 mmol), **2a** (0.20 mmol), NHC **A** (10 mol%) or NHC precursor (11 mol%), DBU (10 mol%), MS 4Å (200 mg), CH₃CN (1.0 mL), room temperature. ^b Isolated yield. ^c NHC **A** (5 mol%). ^d No catalyst. ^e No MS 4Å (200 mg).

With the optimized reaction conditions in hand, we then examined the scope of this SuFEx reaction. As shown in Table 2, both electron-withdrawing and electron-donating substituents substituted secondary alcohols reacted with aryl sulfonyl fluoride **1a** to produce the corresponding products in high yields. In addition, varied positions of the substituents have no apparent effects on the reaction efficiency (**3a-3m**). Sterically hindered alcohols **2n** and **2o** participated in the reaction to give the corresponding products **3n** and **3o** in 83% and 66% yields, respectively. On the other hand, different substituted aryl sulfonyl fluorides underwent the SuFEx reaction with trifluoromethyl benzyl alcohol to afford the corresponding sulfonates in high yields (**3p-3y**). Similarly, different electronic properties and varied positions of the substituents have no obvious effects on the reaction yields.

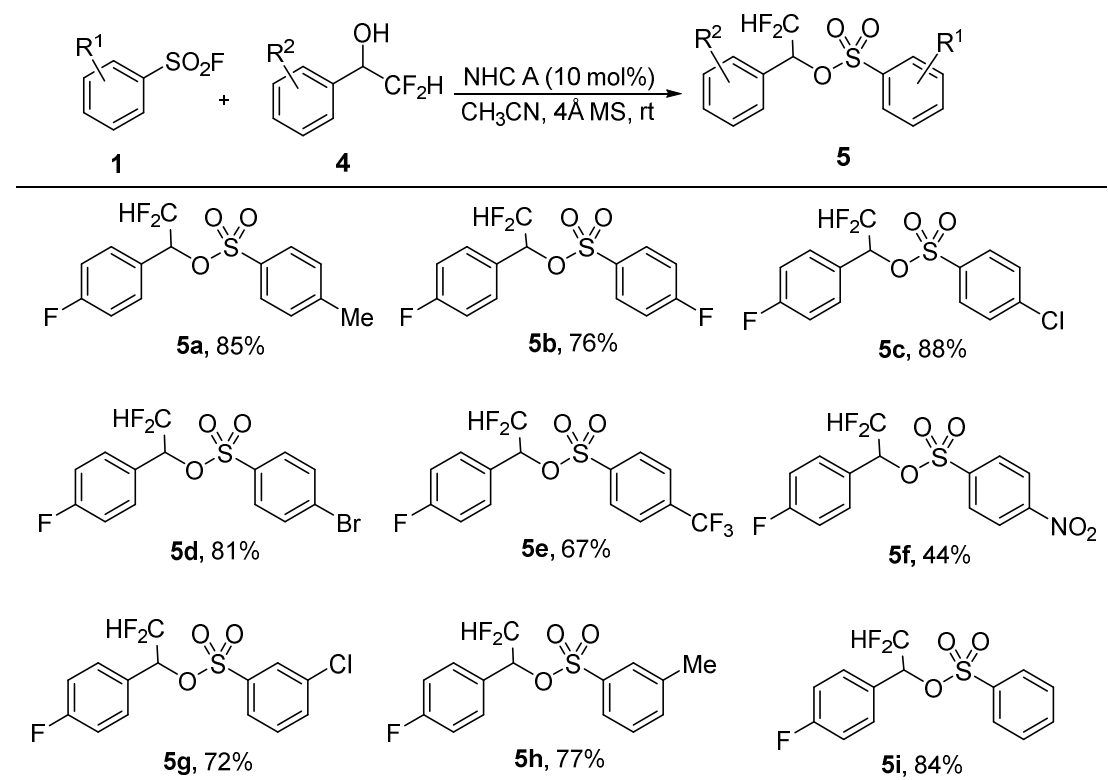
Table 2 SuFEx reaction of trifluoromethyl benzyl alcohols ^a



^a **1** (0.25 mmol), **4** (0.20 mmol), NHC A (10 mol%), MS 4Å (200 mg), CH₃CN (1.0 mL), room temperature, 24h, isolated yield.

Difluoromethyl benzyl alcohols were also tested for this organocatalytic SuFEx click reaction and the results were summarized in Table 3. Under standard reaction conditions, different substituted aryl sulfonyl fluorides underwent SuFEx reaction with difluoromethyl benzyl alcohol **4** to give the corresponding sulfonates in moderate to high yields (**5a-5i**).

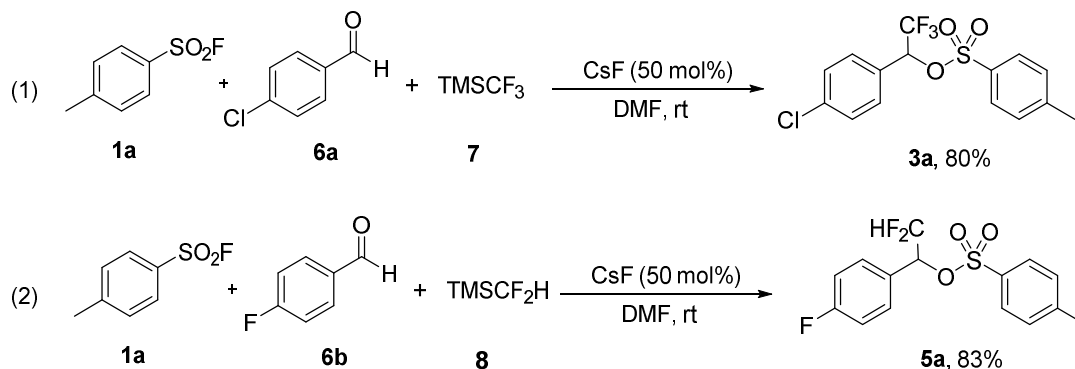
Table 3 SuFEx reaction of difluoromethyl benzyl alcohols ^a



^a **1** (0.25 mmol), **2** (0.20 mmol), NHC A (10 mol%), MS 4 Å (200 mg), CH₃CN (1.0 mL), room temperature, 24h, isolated yield.

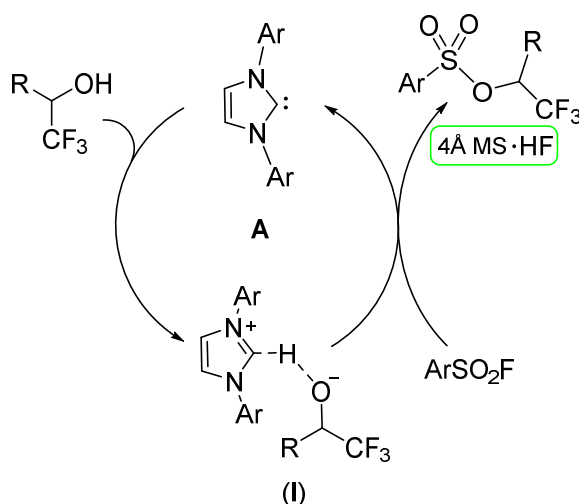
Considering that trifluoromethyl benzyl alcohol can be prepared via the addition of benzaldehyde and Ruppert-Prakash reagent,¹⁴ we next investigated the one-pot reaction of benzaldehyde, TMSCF₃ and sulfonyl fluoride. Pleasingly, under the mediation of CsF, the desired sulfonate **3a** was formed in 85% yield (Scheme 1, eq. 1). The analogous

multicomponent of TMSCF_2H , benzaldehyde and sulfonyl fluoride **2a** was also tested and the desired product **5a** was obtained 80% yield (Scheme 1, eq. 2).



Scheme 1 Synthesis of sulfonates through CsF-mediated multicomponent reactions

Based on our previous study of NHC-catalyzed SuFEx reaction,^{12a} a plausible mechanism was proposed in Scheme 2. NHC acts as a Brønsted base to activate alcohol via the formation of no-covalent hydrogen bonding to form an oxyanion intermediate **I**, which might trigger the subsequent SuFEx with sulfonyl fluoride to form sulfonate product with releasing of NHC.



Scheme 2 Proposed Mechanism

Conclusion:

In summary, an NHC/MS 4Å catalyzed SuFEx click reaction of secondary benzylic alcohols has been demonstrated. The mild and silicon-free conditions, simple procedure, generally high yield provide a new method for the synthesis of secondary alcohol derived sulfonates. Further study of a broader substrate scope, including different SuFExable hubs and other functionalized secondary and tertiary alcohols, are currently underway in our laboratory.

Notes

The authors declare no competing interests.

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