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Electrophilic Trifluoromethylthiolation/Semipinacol Rearrangement: Preparation of β-SCF_3 Carbonyl Compounds with α-Quaternary Carbon Center

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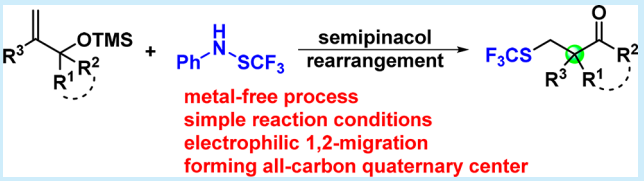
Supporting Information

ABSTRACT: A new and modular electrophilic trifluoromethylthiolation/semipinacol rearrangement of allylic silyl ethers has been developed under mild conditions. This approach allows the formation of a number of β-SCF_3 carbonyl compounds with a cyclic and all-carbon quaternary center framework in moderate to good yields. It should be noted that this achievement is a metal-free process and just requires the use of simple acetyl chloride as an acidic promoter. Additionally, an interesting H-migration in competition with aryl-migration process was revealed.



Among the numerous fluoroalkyl groups, the trifluoromethylthio group (SCF_3) reveals the highest constant (π = 1.44) and strong electron-withdrawing power. This property can significantly improve the transmembrane permeability and enhance the metabolic stability of drug candidates.[1] Therefore, trifluoromethylthiolated compounds play a unique and important role in pharmaceuticals, agrochemicals, and materials science (Figure 1).[2] Consequently, great efforts

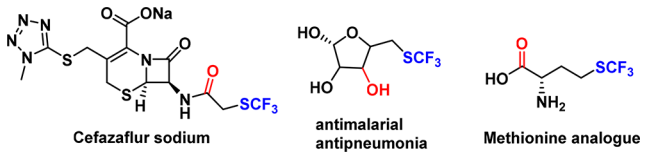
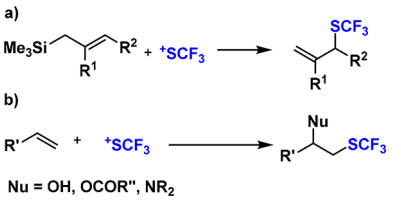


Figure 1. Examples of SCF_3-containing biologically active compounds.

have been dedicated to exploring efficient and practical strategies for incorporation of the SCF_3 into organic frameworks.[3,4] Traditionally, halogen−fluorine exchange reactions and trifluoromethylation of thiols are indirect pathways.[5] Recently, a number of radical,[6] nucleophilic,[7] electrophilic,[8] and oxidative[9] trifluoromethylthiolations have been reported. Among them, the electrophilic trifluoromethylthiolation with alkenes represents a powerful synthetic approach. This method not only directly constructs the C_{sp^3}−SCF_3 bond but also introduces chloro-,[10] amine-,[11] oxy-,[12] and allyl-functional groups,[13] etc. (Scheme 1), affording a series of aliphatic SCF_3-compounds. Despite these great achievements in the structurally diverse synthesis of SCF_3-compounds, however, there has been no direct method using an

Scheme 1. Previous Electrophilic Reactions Introducing SCF_3



electrophilic SCF_3 reagent reported to synthesize the β-SCF_3 substituted ketones compounds, in particular those with an all-carbon α-quaternary center and aliphatic/aromatic multicyclic frameworks. As shown in Figure 1, a parenteral cephalosporin Cefazaflur sodium and a promising lead for an amebiasis Methionine analogue are SCF_3-containing carbonyl derivatives. So such a β-SCF_3 carbonyl compound would be valuable for bioactive or pharmaceutical study, but are difficult to access by typical electrophilic substitution from a ketone substrate.

During the past two decades, we have been making efforts to engage in the research of semipinacol rearrangements. This reaction has become a remarkable strategy in the construction of a variety of natural and non-natural compounds with features of an α-quaternary carbon center,[14] e.g., semipinacol rearrangement of α-hydroxy epoxides, tandem aziridination/semipinacol rearrangement, and halogenation/semipinacol rearrangement for the formation of α-quaternary β-hydroxy, amino, and haloketo compounds.[15] With this concept, we

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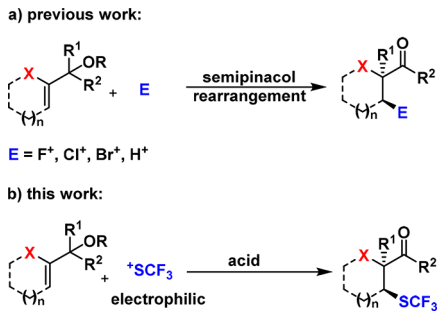
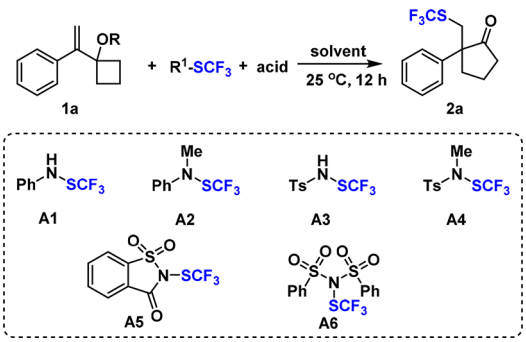
hypothesize that the SCF_3 reagent could be used as an electrophile to promote a semipinacol rearrangement (Scheme 2), which could provide a straightforward strategy for the synthesis of a broad range of β-SCF_3 carbonyl compounds containing the multiunits mentioned above. Herein, we report our preliminary research results.

Scheme 2. Design of the Electrophilic Trifluoromethylthiolation/Semipinacol Rearrangement



To initiate our investigation, allylic alcohol **1a** was chosen as a model substrate with $PhNHSCF_3$ (**A1**) which developed by Billard and Langlois as an electrophilic SCF_3 reagent,[16] and dichloromethane as solvent at room temperature (Table 1). First, the commonly used Bronsted acid TfOH and Lewis acid $BF_3{\cdot}Et_2O$ were selected as acidic initiators for this transformation, respectively. Unfortunately, the allylic alcohol rapidly converted to a complex mixture and no desired product was obtained in both cases (entries 1−2). We thought a weaker acid might be suitable for the transformation. The desired product **2a** was obtained in 43% yield when HCl was used as an acidic promoter (entry 3). Inspired by this result, some other weaker acids were carefully examined. To our delight, the desired product was produced in 53% yield using AcCl as the initiator while TMSCl exhibited only a 40% yield (entries 4−5). The yield was further improved to 65%, when allylic trimethylsilyl ether **1a** was used as the substrate (entry 6). However, the reaction time required 3 days. To further improve the reaction outcome, we screened other solvents such as $MeNO_2$, MeCN, and DMF (entries 7−9), which showed that MeCN performed the best with an increase in the yield to 81%; simultaneously, the reaction time reduced to 12 h (entry 8). Ultimately, optimization of the reaction by screening more SCF_3 reagents and other different reagents such as the derivatives of **A1** (**A2**−**A4**),[17] *N*-trifluoromethylthiosaccharin **A5** pioneered by the work of Shen,[13b] and $(PhSO_2)_2NSCF_3$ **A6** developed by Shen and Zhao[8g,18] failed to give any better result. Regarding the role of AcCl in this transformation, we surmised that $PhNHSCF_3$ (**A1**) reacted with AcCl to form more active reagent CF_3SCl in situ.[19]

Table 1. Conditions Optimization[a]



entry	R^1−SCF_3	solvent	acid	yield[b] (%)
1	**A1**	CH_2Cl_2	TfOH	N.D.
2	**A1**	CH_2Cl_2	$BF_3{\cdot}Et_2O$	N.D.
3	**A1**	CH_2Cl_2	HCl	43
4	**A1**	CH_2Cl_2	TMSCl	40
5	**A1**	CH_2Cl_2	AcCl	53
6[c,d]	**A1**	CH_2Cl_2	AcCl	65
7[d]	**A1**	$MeNO_2$	AcCl	63
8[d]	**A1**	MeCN	AcCl	81
9[d]	**A1**	DMF	AcCl	trace
10[d]	**A2**	MeCN	AcCl	69
11[d]	**A3**	MeCN	AcCl	trace
12[d]	**A4**	MeCN	AcCl	trace
13[d]	**A5**	MeCN	AcCl	44
14[d]	**A6**	MeCN	AcCl	62

[a]Conditions: compound **1a** (0.1 mmol), R = H, R^1−SCF_3 (0.2 mmol), acid (0.3 mmol) in solvent (2 mL) stirred at 25 °C for 12 h under Ar. [b]Isolated yield. [c]Reaction time is 3 days. [d]R = TMS.

Having established the optimized reaction conditions (Table 1, entry 8), the scope of allylic silyl ethers was expanded (Table 2). In general, the desired β-SCF_3 carbonyl compounds were obtained with moderate to good yields. Compared with the model substrate (**1a**), the *meta*- or *para*-substitutions did not have evident effect (**2b** and **2c**), whereas the *ortho*-substitution led to a decrease in yield (**2d**). Substrates with an electron-rich aryl group performed better than those with an electron-withdrawing aryl group (**2e** vs **2f**, **2j**). Meanwhile, multi-substituted aryl substrates were also tolerable to this reaction affording the desired products in good yields (**2h** and **2i**). It was found that the biphenyl and 2-naphthyl-substituted substrates reacted smoothly and delivered the corresponding products in moderate yields (**2k** and **2l**). It was worth mentioning that nonactivated alkene substrates, **1m** and **1n**, were well-incorporated, giving the corresponding products **2m** and **2n** in 60% and 39% yields, respectively. The transformation also tolerated a number of substrates containing different substituents at the cyclobutanol group affording the products in moderate to good yields (**2o**−**q**). Next, cyclopropanol and cyclopentanol were subjected to the standard conditions to give **2r** and **2s** in 83% and 21% yield, respectively. The great disparities might result from the expansion abilities of a three- and five-member ring. Unfortunately, the trisubstituted alkene substrate was not well-tolerated, resulting in a significant decrease of the yield (**2t**). In particular, an acyclic tertiary alcohol also worked well under the conditions, with aryl-migration product **2u** generated exclusively in 53% isolated yield.

To further broaden the scope of the substrates, we investigated various secondary alcohol substrates (Table 3). It is noteworthy that two different migration products could be simultaneously obtained under the standard conditions. One was the aldehyde generated from aryl-migration, the other was the ketone formed from H-migration. When we carried out the reaction with substrates bearing *para*-OMe instead of the $-CF_3$ substituent (**1v**−**y**), the ratio of (**2**:**2′**) enhanced from 9:1 to 1:28, meanwhile, the total yields of the two products ranged from 83% to 44%. Based on the previous literature, the electron-rich aryl groups migrate prior to the electron-poor aryl group in cationic rearrangement. The results suggested that the

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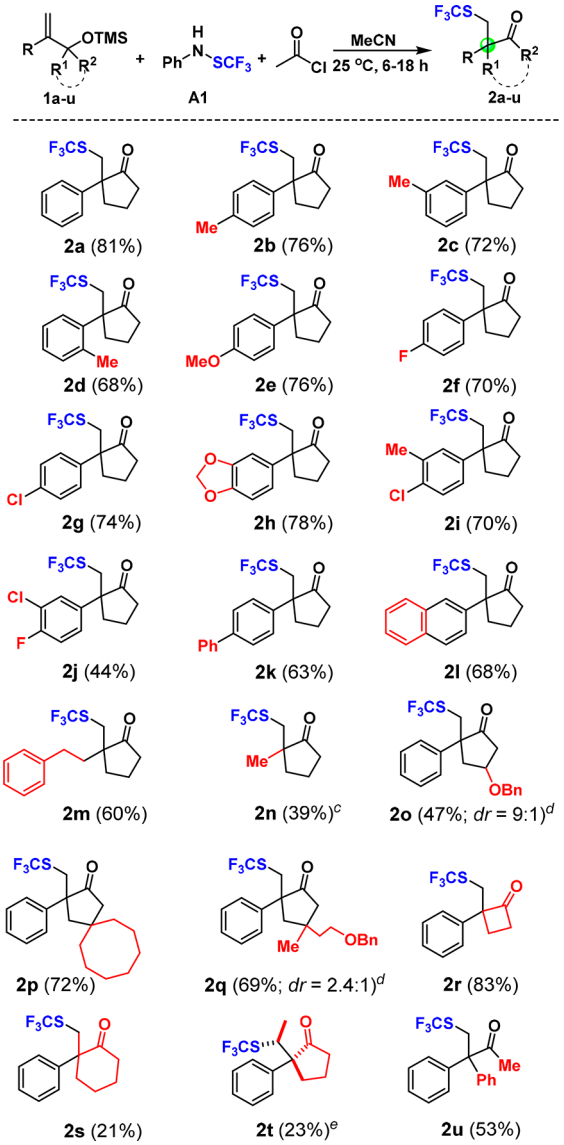
Table 2. Scope of Allylic Silyl Ethers[a,b]

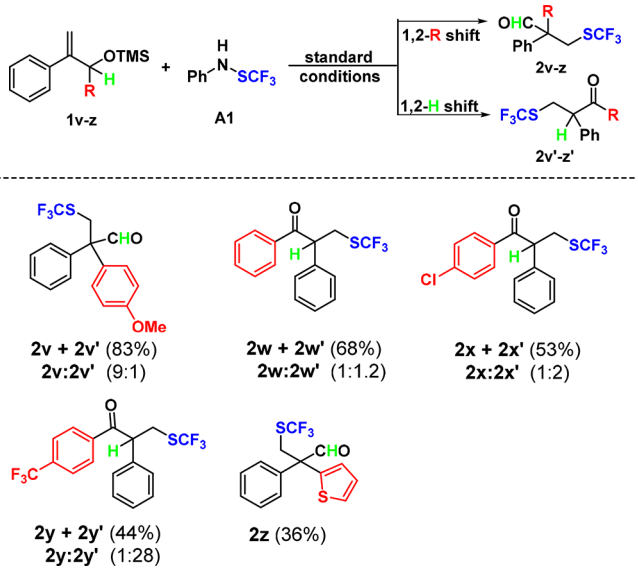


[a]Reaction conditions (also please see Supporting Information (SI)): compound **1** (0.2 mmol), **A1** (0.4 mmol), and AcCl (0.6 mmol) in MeCN (4 mL) stirred at 25 °C for 12 h under Ar. [b]Isolated yield. [c]Determined by crude ^{19}F NMR. [d]Determined by crude ^{1}H NMR. [e]For the relative stereochemistry of **2t**, please see SI.

reaction should undergo a cationic 1,2-migration process. The H-migration in competition with aryl-migration process was revealed in this case which is different from previous reports.[20] Surprisingly, heteroaromatic 2-thiofuran also performed well and only formed **2z** in 36% yield.

In summary, a novel and practical tandem electrophilic trifluoromethylthiolation/semipinacol rearrangement of allylic silyl ethers has been successfully developed, which expanded the types of trifluoromethylthiolation reactions. This tandem transformation is valuable since a broad range of cyclic β-SCF$_3$ carbonyl compounds with different substituents were obtained with moderate to good yields under mild conditions. This strategy enables the construction of an all-carbon quaternary center and a C_{sp^3}–SCF$_3$ bond in a single transformation. Further studies on the development of an enantioselective transformation are underway.

Table 3. Scope of Secondary Alcohols[a,b,c]



[a]Reaction conditions (also please see SI): compound **1** (0.2 mmol), **A1** (0.4 mmol), and AcCl (0.6 mmol) in MeCN (4 mL) stirred at 25 °C for 6 h under Ar. [b]Isolated yield. [c]Determined by crude ^{1}H NMR.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01627.

Experimental details, analytical data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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