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Synthesis of SCF_3-Substituted Sulfonium Ylides from Sulfonium Salts or α-Bromoacetic Esters

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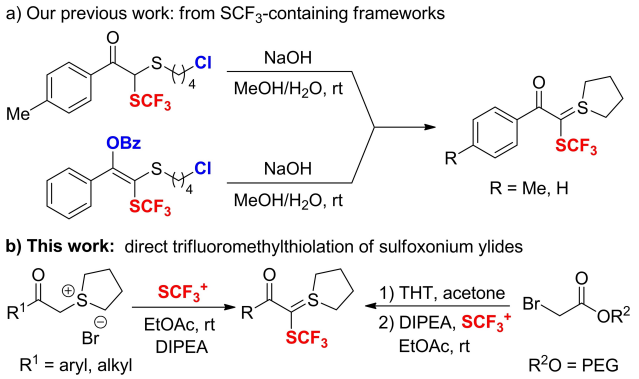
Abstract: A metal-free direct trifluoromethylthiolation of sulfonium ylides with an electrophilic trifluoromethylthiolating reagent has been established, in which sulfonium salt or α-bromoacetic ester is employed as sulfonium ylide precursors. This trifluoromethylthiolation enables the straightforward construction of SCF_3-substituted sulfonium ylides from a wide range of substrates, including ketones, esters, and even PEGylated substrates. Moreover, the application of this approach in large-scale preparation and the fluorescence and fluorine-19 magnetic resonance imaging capabilities of the product are also explored.

Keywords: Fluoroalkylation; Trifluoromethylthiolation; Sulfonium ylides; Sulfonium salts; Polyethylene glycols (PEGs)

The fluoroalkyl groups are significant structural motifs with diverse applications in advanced materials, drug discoveries and agrochemical developments.[1] Owing to its peculiar features, such as high dissociation energy of C–F bond, strong electronegativity, and extremely high Hansch lipophilicity parameter ($\pi = 1.44$), the trifluoromethylthio group (SCF_3) can substantially modify drug candidates' pK_a, lipophilicity, and metabolic stability.[2] However, SCF_3 group is not present in natural products even though a dozen fluorinated organic molecules have been isolated in nature.[3] Consequently, the rapid and highly efficient synthesis of organic compounds containing SCF_3 group has attracted considerable interest in the past decade.[4] As a consequence, many strategies to introduce SCF_3 into organic moieties, such as (alkanes)arenes,[5] alkenes,[6] alkynes,[7] boronic acids,[8] ketones,[9] diazo compounds,[10] halides,[11] alcohols,[12] and amines,[13] have been developed by nucleophilic, electrophilic, or free radical trifluoromethylthiolation.

Sulfoxonium ylide is a safe carbene precursor, identified as a potential surrogate of the diazo compound in synthetic organic chemistry. Their synthetic applications have also been extensively demonstrated, including annulation reactions, olefinations, rearrangements, cross-coupling reactions, and X–H (X=C, N, O, B, S) insertions.[14] Thus, it would be valuable to develop a general transformation for synthesizing SCF_3-containing sulfoxonium ylides through a one-pot strategy. In addition, the processes for constructing a SCF_3 group on the α position of sulfoxonium ylide-derived building block are minimal. We previously reported two examples for preparing SCF_3-substituted sulfoxonium ylides via the intramolecular nucleophilic substitution/elimination of SCF_3-containing ω-chloroalkyl thioethers.[15] However, the structural variation of these SCF_3-containing sulfides was hindered by the required multistep synthesis procedure (Scheme 1a). The development of a facile protocol for the efficient construction of functionalized α-trifluoromethylthiolated sulfonium ylides is still demanding, especially substrates start from non-SCF_3-containing frameworks. With our continuous interest in fluoroalkylation of unsaturated compounds,[16] we report herein a metal-free direct trifluoromethylthiolation of sulfoxonium ylides with an electrophilic SCF_3 reagent (Scheme 1b). This method features the formation of SCF_3-containing disubstituted sulfoxonium ylides using a sulfonium salt and even α-

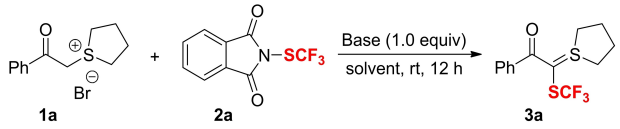


Scheme 1. Synthesis of α-SCF_3 sulfonium ylides.

bromoacetic esters as the starting materials. In the reaction sequence, sulfoxonium ylide serves as a strong nucleophile that might react with an electrophilic SCF_3 reagent to provide the α-SCF_3 substituted sulfonium salt, which then readily undergoes deprotonation under alkaline conditions to furnish the SCF_3-substituted sulfonium ylide.

At first, we proceeded with reaction condition optimization by employing acetophenone derived sulfonium salt **1a** as a model substrate for the direct trifluoromethylthiolation with Munavalli's[17] SCF_3 reagent **2a**. We speculated that the sulfonium salt could readily be converted into sulfonium ylide *in situ* under an alkaline environment. To our delight, when the reaction was performed in ethyl acetate at room temperature for 12 hours adopting KF as a base, 43% yield of the trifluoromethylthiolated sulfonium ylide product **3a** could be observed (Table 1, entry 1). To further improve this transformation, a number of inorganic and organic bases were subsequently evaluated, and it was found that bases have a significant influence on the reactivity (Table 1, entries 2–7). Potassium acetate could increase the yield slightly, while potassium *tert*-butoxide did not improve the result (Table 1, entries 2–3). Notably, this reaction was significantly accelerated in the presence of NaOH or Cs_2CO_3 as a base to afford the expected product **3a** in 89% and 97% yields, respectively (Table 1, entries 4–5). For comparison, when the organic bases Et_3N and DIPEA were employed, the same reaction occurred smoothly, the latter providing the desired product **3a** almost quantitatively (Table 1, entry 7). Subsequently, other commonly used solvents, including $CHCl_3$, DMF, THF, toluene, CH_3CN, and dioxane have also been investigated, almost all raw materials were converted quantitatively, which implies that the current reaction exhibits a relatively wide tolerance for solvents (Table 1, entries 8–13). Interestingly, no corresponding O-trifluoromethylthio by-product was observed when the reaction was even carried out in the protonic solvent methanol (Table 1, entry 14). Finally,

Table 1. Screening of the reaction conditions.[a]



1a 2a 3a

Entry	Base	Solvent	Yield[b]
1	KF	EtOAc	43
2	KOAc	EtOAc	54
3	KO*t*Bu	EtOAc	43
4	NaOH	EtOAc	89
5	Cs_2CO_3	EtOAc	97
6	Et_3N	EtOAc	94
7	DIPEA	EtOAc	>99
8	DIPEA	$CHCl_3$	>99
9	DIPEA	DMF	>99
10	DIPEA	THF	>99
11	DIPEA	Toluene	>99
12	DIPEA	CH_3CN	>99
13	DIPEA	Dioxane	>99
14	DIPEA	MeOH	>99

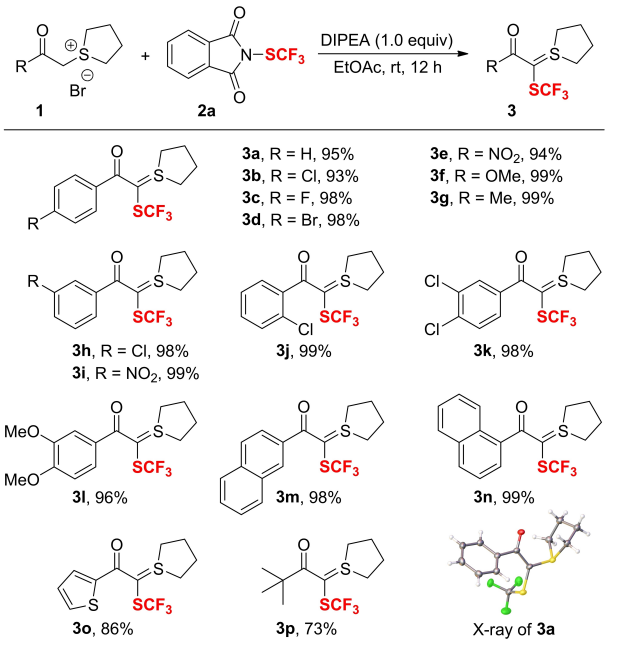
[a] Reaction conditions: sulfonium salt **1a** (0.1 mmol), SCF_3 reagent **2a** (1.0 equiv.), base (1.0 equiv.) in solvent (1.0 mL) at rt for 12 h.

[b] Yields were determined by crude ^{19}F NMR analysis using $PhCF_3$ as an internal standard.

the superior reaction conditions were identified as DIPEA (1.0 equiv.) in EtOAc at room temperature for 12 h.

With these optimized reaction conditions for the direct trifluoromethylthiolation, we first studied the generality of this reaction to different sulfonium salts (Table 2). When the reaction was carried out on a 0.5 mmol scale, the target product **3a** was delivered without loss of efficiency while maintaining a 95% isolated yield. Subsequently, the electronic effects of the substituents were evaluated. Sulfonium salts bearing a diverse array of substituents on the *para* position of the arene ring, including electron-releasing, electron-neutral, and electron-deficient substituents, were smoothly trifluoromethylthiolated to afford the desired products **3a–g** in high to excellent yields. A variety of functional groups, such as chlorine, fluorine, bromine, nitro, methoxy, and methyl, can be well tolerated under the reaction conditions. *Meta*-substitution in the phenyl ring was also well-tolerated in the cases of chlorine and nitro groups and provided the corresponding products **3h** and **3i** in 98% and 99% yields, respectively. Likewise, when *ortho*-substituted sulfonium salt was employed, no steric hindrance effect was observed and the desired product **3j** was isolated in 99% yield. Furthermore, the incorporation of disubstituents at the 3,4-positions of the aromatic ring had a slight influence on the reactivity of this transformation. The target products **3k–l** were detected in 96–98%

Table 2. Scope and limitations of the reaction using various sulfoxonium salts.[a]



[a] Standard conditions: sulfonium salt **1** (0.5 mmol), DIPEA (0.5 mmol, 1.0 equiv.) and Munavalli's SCF_3 reagent **2a** (0.5 mmol, 1.0 equiv.) in EtOAc (5.0 mL) at rt for 12 h. Isolated yields are indicated.

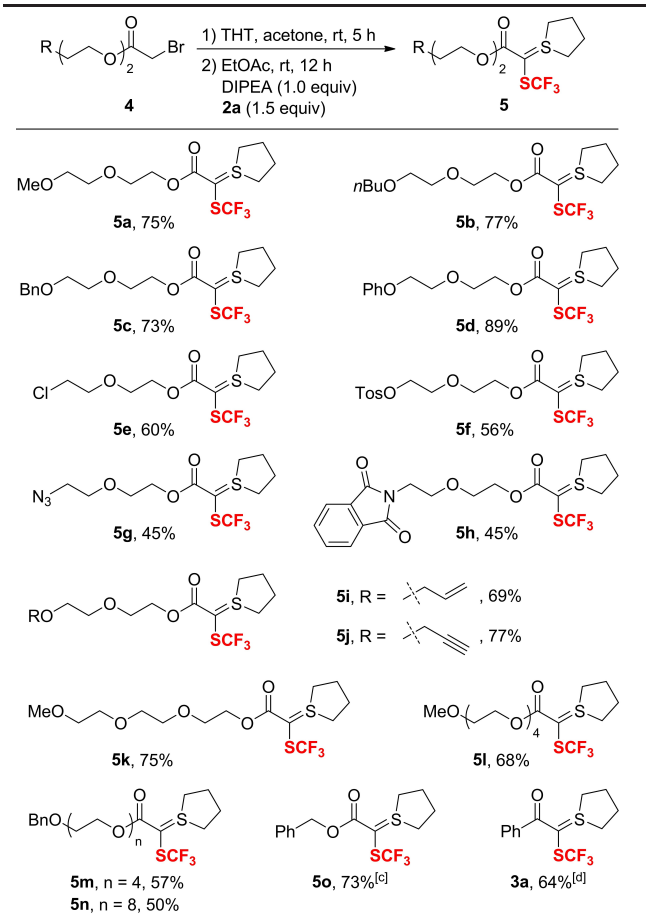
yields. It was found that the fused ring-derived substrates (R = 1- or 2-naphthyl) were suitable with the current reaction conditions, delivering the trifluoromethylthiolated sulfonium ylides **3m–n** almost quantitatively. Notably, the sulfonium salt with heteroaromatic ring substituent was amenable despite the efficiency being slightly reduced due to the thienyl group, thus providing the expected product **3o** in 86% yield. Besides, when an aliphatic ketone-containing substrate **1p**, a *tert*-butyl ketone sulfonium salt, was applied, smoothly delivered product **3p** in satisfactory yield. When a 3-methyl-2-butanone-derived sulfonium salt containing a α-hydrogen atom was also synthesized and subjected to the standard conditions, only trace amounts of the desired product were observed. Finally, the molecular structure of α-SCF_3 sulfonium ylide **3a** was unambiguously confirmed by single-crystal X-ray diffraction (CCDC 2101452).

Encouraged by the above successful results using ketone sulfonium salts, we next turned our attention to the preparation of SCF_3-containing PEGylated esteryl sulfonium ylides. As biocompatible, water-soluble, and stable polymers, polyethylene glycols (PEGs) are prevalent in life and materials sciences, which can substantially decrease immunogenicity and dosing frequency, and extend blood residence time. Three polyethylene glycol-derived sulfonium salts with different sulfide moieties were subjected to the above optimal reaction conditions, the corresponding products were obtained in poor to moderate yields because these sulfonium salts are difficult to purify and the relatively complicated synthesis procedure (see the Supporting Information for details). For convenience, the sulfonium salt was prepared *in situ* from the α-bromoacetic ester **4a**, and then treated with DIPEA and SCF_3 reagent **2a** in a one-pot process, in which the ylide underwent the direct trifluoromethylthiolation to generate the desired product **5a** in 75% isolated yield. With this idea in mind, the substrate scope of the one-pot transformation was studied and various functionalized polyethylene glycols were successfully transferred into resulting adducts with good to high yields. As shown in Table 3, the ω position of the diethylene glycol moiety can be substituted by alkoxy groups, such as MeO, *n*BuO, BnO and PhO and the targeted products **5a–d** were afforded in 73–89% yields. The diethylene glycol moiety bearing leaving groups like Cl or TosO at the ω position was well-tolerated and successfully converted to the expected products **5e–f** in moderate yields. Substituents containing nitrogen atoms such as azido and *N*-phthalimido at the ω position are also amenable for the current transformation, albeit with lower reactivity (**5g–h**, 45% yields). Interestingly, no [2 + 1] cycloaddition side products were observed, even in the case of allyl or propargyl substituted substrates **4i–j**. Substrates with different ethylene glycol numbers (3-mer, 4-mer and 8-mer) worked well under the same reaction conditions, providing the desired products **5k–n** in 50–75% yields. In addition, simple and commercially available α-bromoacetic esters, including benzyl 2-bromoacetate and 2-bromoacetophenone, were also suitable for this reaction to deliver the expected products **5o** and **3a** in 73% and 64% yields, respectively.

The methodology could be readily performed on a gram scale, demonstrating the synthetic potential for further transformations. Happily, 5.0 mmol of sulfonium salt **1a** (1.43 g) reacted with Munavalli's SCF_3 reagent **2a** under the aforementioned standard reaction conditions, delivering the desired product **3a** in 99% yield, which matches the result of the small-scale experiment (Scheme 2a). As a utility of the ylides, several derivatization experiments of the products were explored and shown in Scheme 2b. First, the treatment of **3a** with $SOCl_2$ and 4 Å M.S. in DMF, a dichlorinated trifluoromethylthiolated alkene **6** was obtained in 99% yield. Second, the reduction of **5g** with Pd/C and H_2 resulted in the formation of **7** in 45% yield and the ylide moiety was not affected. Third, when **3a** underwent hydrogenation with an excess of zinc powder in the presence of AcOH in CH_2Cl_2, only acetophenone **8** was given in 83% yield.

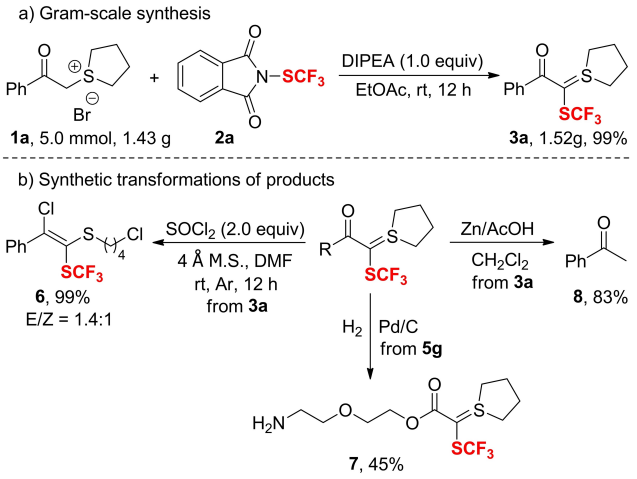
Moreover, these α-SCF_3 sulfonium ylides contain π-conjugated systems, which may be used as fluoro-

Table 3. Scope and limitations of the reaction using various α-bromoacetic esters.[a,b]



[a] Standard conditions: (1) α-bromoacetic ester **4** (0.5 mmol) and THT (0.5 mmol, 1.0 equiv.) in acetone (0.1 mL) at rt for 5 h; (2) Munavalli's SCF_3 reagent **2a** (0.75 mmol, 1.5 equiv.), DIPEA (0.5 mmol, 1.0 equiv.), EtOAc (5.0 mL) at rt for 12 h. Isolated yield.
[b] THT = tetrahydrothiophene, TosO = tosylate.
[c] From benzyl 2-bromoacetate.
[d] From 2-bromoacetophenone.

phores with potential applications in photophysics. Fluorescence emission spectra of **3a** in different solvents were obtained, indicating it is solvent polarity-responsive, which showed the strongest fluorescence emission in DMSO (Figure 1a). Significantly, introducing the SCF_3 unit is highly beneficial for improving the fluorescence emission (Figure 1b). Moreover, the ^{19}F MRI phantom experiment revealed that **3a** has a high ^{19}F MRI sensitivity, which was detected at a low concentration of 5 mM with a data collection time of 240 seconds. The ^{19}F MRI capability may facilitate sensitive detection of the α-SCF_3 sulfonium ylides without background interference and ionizing radiation.



Scheme 2. Large-scale synthesis and synthetic utility.

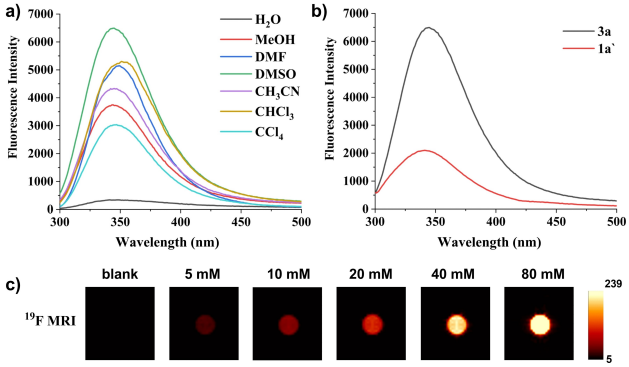
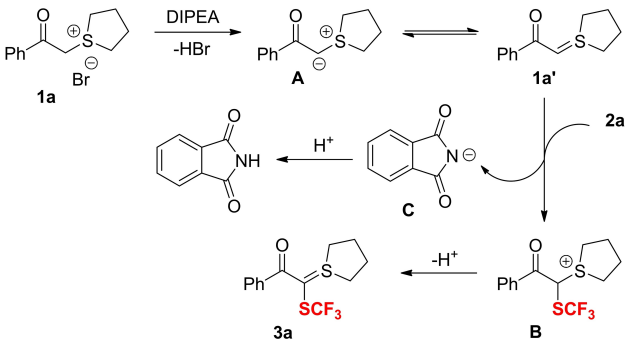


Figure 1. (a) Fluorescence emission spectra of **3a** at different solvents (0.1 mM). (b) Fluorescence emission spectra of **3a** and **1a'** (0.1 mM in DMSO). (c) ^{19}F MRI phantom images of **3a**.

Based on our previous observations and published work,[4–13] a possible reaction mechanism for the trifluoromethylthiolation of sulfonium ylides was proposed (Scheme 3). Initially, elimination of HBr on sulfonium salt **1a** with DIPEA generates the ylide **1a'**, which serves as a strong nucleophile. Then, SCF_3



Scheme 3. Proposed mechanism.

reagent **2a** reacts with the ylide **1a'** to afford the SCF_3-substituted sulfonium salt **B** and concomitant formation of nitrogen anion intermediate **C**. The final product **3a** is formed through the deprotonation of the sulfonium salt intermediate **B**, where the nitrogen anion intermediate **C** can capture a proton to produce phthalimide.

In summary, a metal-free direct trifluoromethylthiolation of stabilized sulfonium ylides has been described. The easily available sulfonium salts and α-bromoacetic esters have been employed as the starting materials, providing convenience for large-scale synthesis of desired products. This approach exhibits the potential to form trifluoromethylthiolated products with a wide variety of structures. In addition, the SCF_3-containing products were successfully converted into synthetic analogs by chemical transformations.

Experimental Section

General procedure for trifluoromethylthiolation of sulfonium salts: A dry reaction tube was charged with sulfonium salt **1** (0.5 mmol, 1.0 equiv.), Munavalli's SCF_3 reagent **2a** (0.5 mmol, 1.0 equiv.) and EtOAc (5.0 mL). DIPEA (0.5 mmol, 1.0 equiv.) was added to the reaction mixture in the end. The mixture kept stirring at the room temperature for 12 hours. After the reaction completion, the residue was directly purified by flash column chromatography on deactivation silica gel to afford the desired product **3**.

General procedure for trifluoromethylthiolation using α-bromoacetic esters: A dry reaction tube was charged with α-bromoacetic ester **4** (0.5 mmol, 1.0 equiv.), acetone (0.1 mL) and tetrahydrothiophene (THT, 0.5 mmol, 1.0 equiv.) was added to the reaction mixture in the end. The mixture kept stirring at the room temperature for 5 hours. The reaction mixture was concentrated under reduce pressure, and the residue was washed with ether (5 × 3.0 mL) and acetone (3 × 3.0 mL). After drying under reduced pressure, Munavalli's SCF_3 reagent **2a** (0.75 mmol, 1.5 equiv.), EtOAc (5.0 mL) and DIPEA (0.5 mmol, 1.0 equiv.) was added to the crude reactant. The mixture was allowed to stir at room temperature for 12 hours. After solvent was removed under reduced pressure, the crude residue was directly purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 1/1) to afford the compound **5**.

CCDC 2101452 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..

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