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Trifluoromethanesulfonyl Hypervalent Iodonium Ylide for Copper-Catalyzed Trifluoromethylthiolation of Enamines, Indoles, and β-Keto Esters

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Supporting Information

ABSTRACT: A novel electrophilic-type trifluoromethylthiolation reagent, a trifluoromethanesulfonyl hypervalent iodonium ylide, was designed and reacted well with various nucleophiles to afford the desired CF_3S-substituted products. In situ reduction of the trifluoromethanesulfonyl group to give the trifluoromethylthio group, which is the key step in this process, was realized in the presence of copper(I) chloride.

Currently, more and more attention is being focused on fluorine chemistry because of the potential improvement in lipophilicity and bioactivity when a fluorine or fluorinated functional group is introduced into the parent molecule.[1] Fluorinated molecules are widely used in various fields, particularly in the pharmaceutical, agrochemical, and material sciences. As an important member in this family, the trifluoromethylthio group (CF_3S-) has attracted special interest because of its high electron-withdrawing effect and admirable lipophilicity (π_R = 1.44). Consequently, compounds bearing this group are potentially important targets in the pharmaceutical and agrochemical fields.[1,2]

In the last few decades, numerous methods for the introduction of a trifluoromethylthio group into organic compounds have been developed.[3] The main strategies are indirect methods, including halogen−fluorine exchange[4] and trifluoromethylation of sulfur-containing compounds such as disulfides,[5] thiols, and thiolates.[6] Obviously, the most attractive and ideal route to the CF_3S moiety is the direct introduction of this functional group.[7] However, in this approach, some limitations are usually encountered, including the use of gaseous and highly toxic reagents (e.g., CF_3SCl) or unstable reagents and modest substrate scope.[7d−j] Although several transition-metal-mediated or -catalyzed trifluoromethylthiolation methods have been developed, the substrates are mostly limited to aromatic compounds.[7a,c,d,8] Recently, Billard and coworkers reported that trifluoromethanesulfanylamides are effective for trifluoromethylthiolation of alkenes, alkynes, indoles, and organometallic species.[9] More recently, Lu and Shen also developed a novel hypervalent iodine reagent for the trifluoromethylthiolation of aryl and vinyl boronic derivatives, alkynes, and β-keto esters.[10] Even though these direct trifluoromethylthiolation reagents are shelf-stable, a more critical issue is the fact that these CF_3S regents must be prepared in advance by *trifluoromethylthiolations or related trifluoromethylations*! Because of these limitations and negative aspects, it is still necessary to develop an efficient and easily available reagent to introduce the CF_3S moiety directly.

In contrast to the CF_3S unit, a trifluoromethanesulfonyl (CF_3SO_2) unit is stable and often found in commonly used organic reagents such as CF_3SO_2Cl, CF_3SO_2Na, CF_3SO_2H, and $(CF_3SO_2)_2$. In this context, we came up with the novel idea of using ubiquitous CF_3SO_2 compounds as reagents for introducing the CF_3S unit under reductive conditions (Figure 1a). As a part of our recent work on the chemistry of

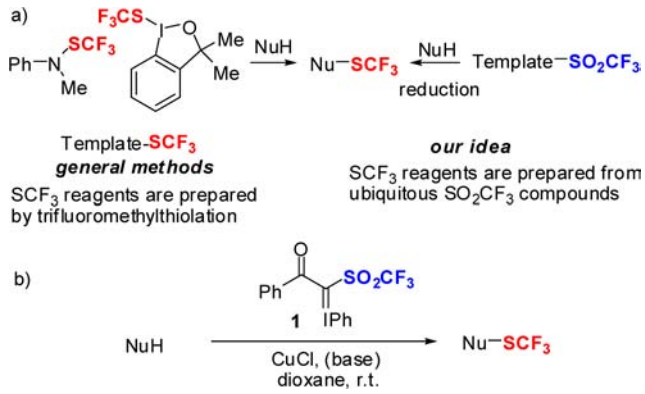

Figure 1. (a) General methods vs our strategy for electrophilic trifluoromethylthiolation. (b) Copper(I)-catalyzed trifluoromethylthiolation by trifluoromethanesulfonyl hypervalent iodonium ylide **1**.

trifluoromethanesulfonyl compounds (triflones),[11] we herein disclose the novel trifluoromethanesulfonyl hypervalent iodonium ylide **1** as a shelf-stable reagent for electrophilic-type trifluoromethylthiolation.[12] In the presence of a catalytic amount of copper(I) chloride, **1** nicely converts a wide variety of nucleophiles into the corresponding trifluoromethylthiolated products (Figure 1b).

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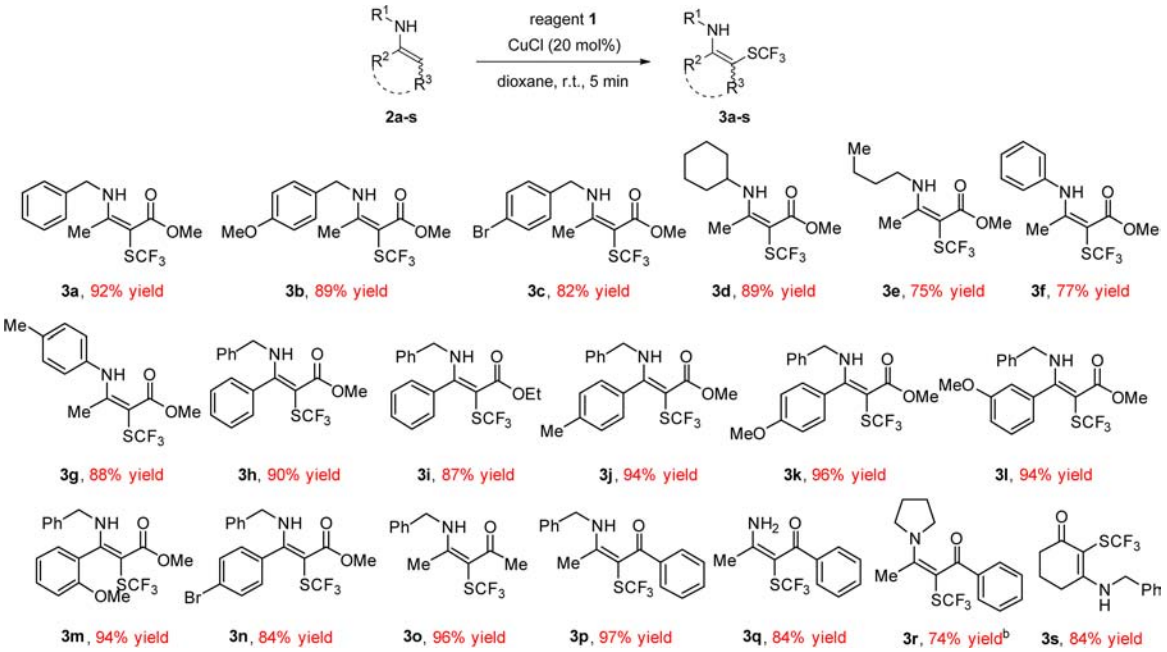
Table 1. Trifluoromethylthiolation of Enamines 2[a]



[a]Conditions: **2** (0.15 mmol), **1** (0.3 mmol), CuCl (20 mol %), dioxane (0.75 mL), r.t., 5 min. Isolated yields are shown. [b]The mixture was stirred for 15 min at r.t.

Iodonium ylides serve as excellent progenitors for the generation of carbenes and react with a wide range of substrates under thermal, catalytic, or photochemical conditions.[13] They are easily synthesized and usually stabilized by two strong electron-withdrawing groups such as carbonyl, sulfonyl, cyano, or nitro groups. Interestingly, the phenylsulfonyl group of phenyliodonium bis(phenylsulfonyl)methylide can be reduced to a phenylthio moiety when it is placed under illumination or thermal conditions in the presence of copper salts.[14] Inspired by this report, we hypothesized that a reactive trifluoromethylthio (CF_3S-) species might be generated from a stable trifluoromethanesulfonyl (CF_3SO_2-) compound by carbene-mediated in situ reduction catalyzed by a copper(I) salt. Reagent **1** was easily synthesized in quantitative yield by the reaction of α-trifluoromethanesulfonyl phenyl ketone and phenyliodine(III) diacetate (PIDA) [see Scheme S1 in the Supporting Information (SI)].

With reagent **1** in hand, we began our attempt with enamines, which are versatile intermediates for a wide range of organic syntheses.[15] We initially tested various substitutions on the amino groups (Table 1). Both electron-rich and electron-deficient substituents gave high yields under the same conditions (**3b** and **3c**). Other aliphatic substituents such as cyclohexyl and *n*-butyl afforded yields of 89% and 75%, respectively (**3d** and **3e**). *N*-Aryl-substituted substrates were identified as being suitable for this reaction as well. A 77% yield was found for *N*-phenylenamine (**3f**), and a higher yield was obtained when an electron-rich substituent was used (**3g**). For R^2 = aryl, the electronic nature of the substituents on the ring affected the yield slightly, although the position on the aryl ring had no obvious influence (**3h**–**n**). Not only β-enamine esters but also β-enamine ketones were efficiently trifluoromethylthiolated under the current conditions. Excellent yields were obtained for both aliphatic and aromatic substituents (**3o** and **3p**). The desired product **3q** was also obtained in 84% yield without any problem when an unprotected enamine was used. For a disubstituted enamine, 15 min was required to complete the conversion to provide **3r** in 74% yield. Cyclic enamine **2s** was also tested, and **3s** was obtained in 84% yield. Information gleaned from ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, IR, and mass spectra led to the formulation of the structures of **3**, and the structure of **3c** was was confirmed unambiguously by single-crystal X-ray structure analysis (CCDC 926214; see Figure S1 in the SI).

Encouraged by these good results, we next tried to extend this reaction to other substrates. Since indole and its derivatives are important structural units in a diverse array of fields such as pharmaceuticals, agrochemicals, and dyes,[16] they were chosen as our next attempt. Although only a 25% yield of the trifluoromethylthiolated product from indole (**4a**) was detected by ^{19}F NMR spectroscopy under the same conditions, the addition of a catalytic amount of $PhNMe_2$ afforded the desired products with various indoles in moderate to high yields within 2 h (Table 2). No desired product was found when 3-methylindole was studied under these conditions.

β-Keto esters were also tested under similar conditions. Trifluoromethylthiolated 1-indanone-2-carboxylate **7a** having a quaternary sp^3 carbon center was obtained in 54% yield when cyclic ester **6a** was reacted in the presence of catalytic amount of 2,4,6-collidine and copper(I) chloride (Scheme 1). Also, it is noteworthy that even though no trifluoromethylthiolation product was found in the reaction of acylic β-keto esters with Shen's SCF_3 reagent according to the literature,[10] a 48% yield of **7b** was obtained in our attempt with reagent **1** and ester **6b** (Scheme 1).

Although the details of the reaction process are not clear, we hypothesize the mechanism shown in Scheme 2 on the basis of the experimental results, references, and mass spectral data (see Figures S2 and S3 for the mass spectra). The process for reduction of the sulfonyl group via a carbene species is based on previous reports.[14,17] Two potential paths may achieve this result. As shown in path I, copper carbenoid **9** may initially be

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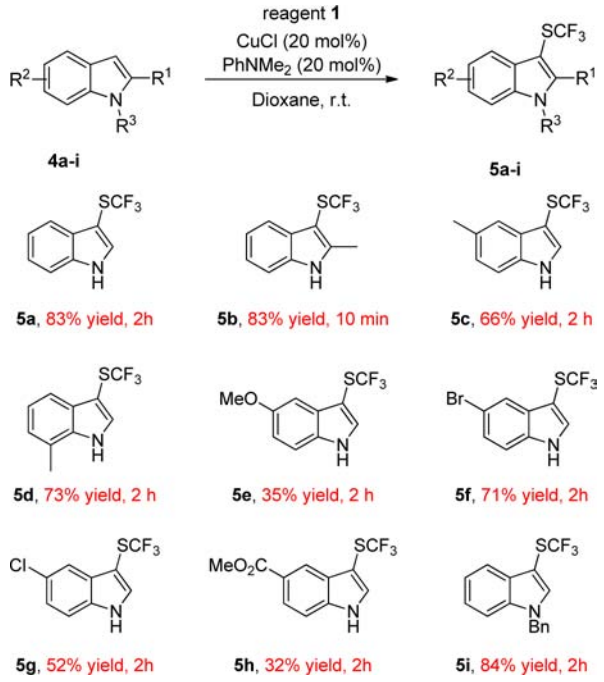
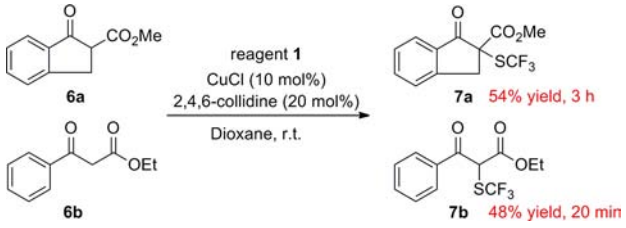
Table 2. Trifluoromethylthiolation of Indoles 4[a]



[a]Conditions: **3** (0.2 mmol), **1** (0.4 mmol), CuCl (20 mol %), $PhNMe_2$ (20 mol %), dioxane (1.5 mL), r.t. Isolated yields are shown.

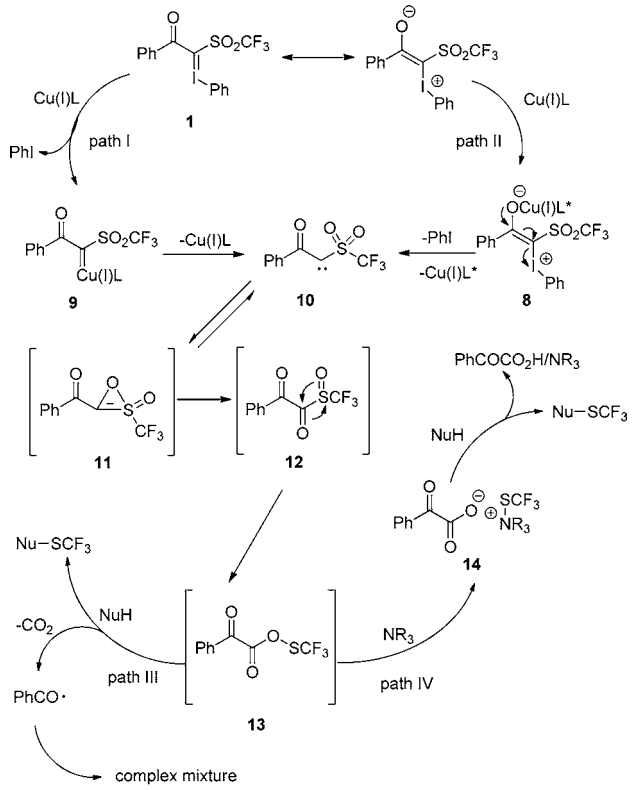
Scheme 1. Trifluoromethylthiolation of β-Keto Esters 6[a]



[a]Conditions: **6** (0.2 mmol), **1** (0.4 mmol), CuCl (10 mol %), 2,4,6-collidine (20 mol %), dioxane (1.5 mL), r.t. Isolated yields are shown.

generated and then decompose to form sulfonyl carbene **10**. Alternatively, reagent **1** could be activated by a copper(I) salt and generate zwitterionic intermediate **8**, which subsequently eliminates iodobenzene to form carbene **10** without a copper carbenoid intermediate (path II). Because metal carbenoids are usually formed with copper or rhodium in transition-metal-catalyzed decomposition of phenyliodonium ylides and a variety of metal salts could also catalyze our reaction (see Table S1 in the SI), we propose that path II is more likely to be responsible for this carbene generation process. The observation of carbene **10** (or its isomers) but no copper carbenoid (coordinated with a chloride anion or one more amine) by high-resolution electrospray ionization mass spectrometry (HR-ESI-MS) also implies the possibility of our surmise. Next, as proposed by Varvoglis,[14] oxirene **11** (which is in equilibrium with carbene **10**) would rearrange to give sulfoxide **12**, and subsequent intramolecular nucleophilic collapse would then form the true reactive species, thioperoxoate **13**. The transfer trifluoromethylthiolation from **13** to the nucleophile via a single-electron transfer process or an electrophilic path would yield the desired products (path III). Alternatively, when this reaction is carried out in the presence of an amine (Table 2 and

Scheme 2. Proposed Mechanism for Cu(I)-Catalyzed Trifluoromethylthiolation with 1



Scheme 1), the real reactive species might be trifluoromethylthiolated ammonium salt **14**, which is subsequently attacked by the nucleophile to afford the final product (path IV).[18] The salt **14** should be relatively stable, and the attack by the nucleophile might determine the rate of the whole reaction.

In conclusion, a novel electrophilic trifluoromethylation reagent has been developed. A wide scope of nucleophiles is efficiently trifluoromethylthiolated through this approach to give the corresponding CF_3S-substituted products in synthetically useful yields. Reagent **1** costs little and is stable. The stable CF_3SO_2 moiety is reduced to a reactive CF_3S species by intramolecular rearrangement, and an ammonium salt which is proposed to be responsible for the trifluoromethylthiolation might be generated in the presence of a amine. The formation of this salt species would potentially be valuable in the asymmetric reaction when a chiral amine is used. Our reagent not only affords success in trifluoromethylthiolation but also may serve as another potential organoiodine reagent.[13a,19] An investigation of the mechanism of this reaction and expansion of the new reagent **1** to other substrates is underway in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, NMR spectra, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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