Communication

Trifluoromethanesulfonyl Hypervalent Iodonium Ylide for Copper-Catalyzed Trifluoromethylthiolation of Enamines, Indoles and beta-Ketoesters

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

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Supporting Information Placeholder

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

Currently, more and more attention is focused on fluorine chemistry due to the potential improvement in lipophilicity and bioactivity when a fluorine or fluorinated functional group is introduced into the parent molecules.[1] Fluorinated molecules are widely used in various fields, in particular 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 constitute 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, such as CF_3SCl, or unstable reagents, and the modest scope of substrates.[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 co-workers reported that trifluoromethanesulfanylamides were 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 trifuoromethylthiolation of aryl and vinyl boronic derivatives, alkynes and β-ketoesters.[10] Even though these direct trifluoromethylthiolation reagents are shelf-stable, a more critical issue is the fact that these CF_3S regents should be prepared in advance by *trifluoromethylthiolations or related trifluoromethylations*! Due to these limitations and negative aspects, it is thus still necessary to develop an efficient and easily available reagent to introduce the CF_3S moiety directly.

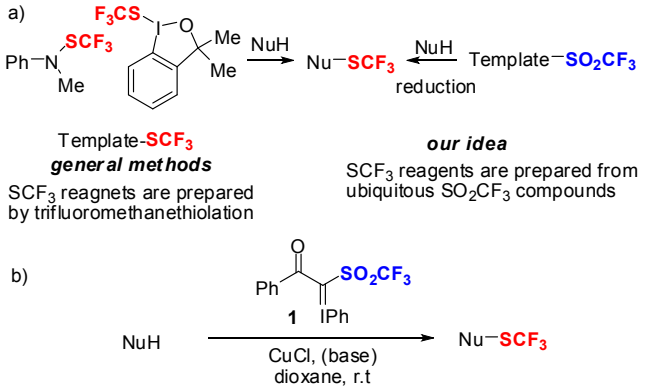


Fig. 1. a) The general method *versus* our strategy for electrophilic trifluoromethylthiolation. b) Copper-catalyzed trifluoromethylthiolation by trifluoromethanesulfonyl hypervalent iodonium ylide **1**.

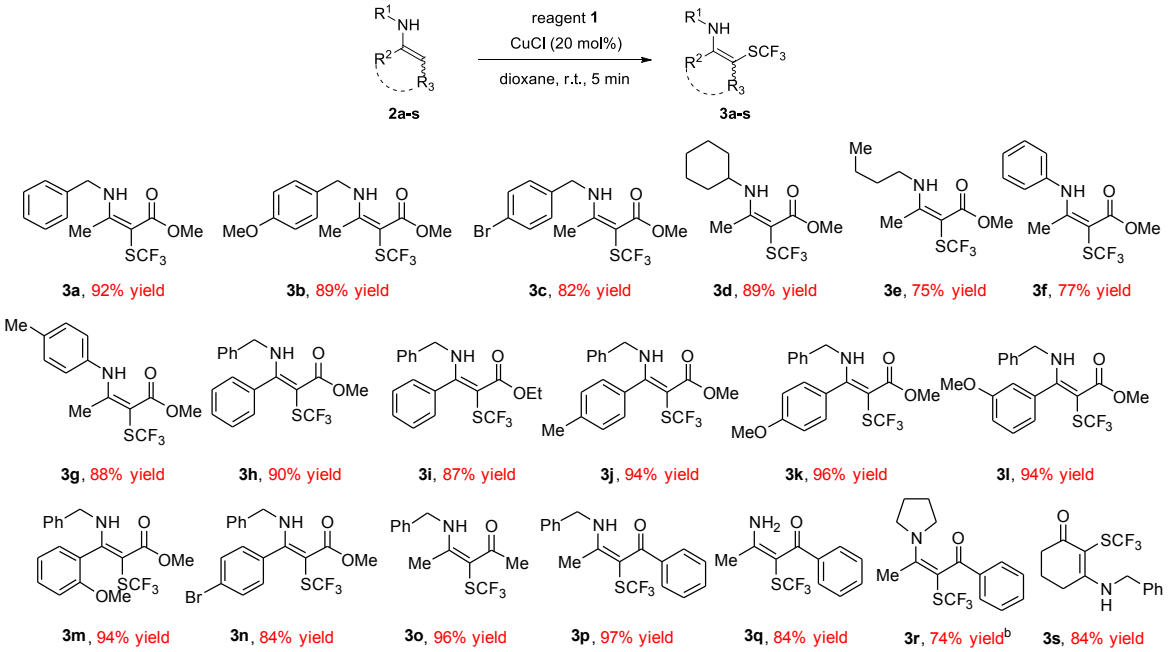
In contrast to the CF_3S unit, a trifluoromethanesulfonyl (CF_3SO_2) unit is stable and often found in commonly used organic reagents such as CF_3SO_2Cl, CF_3SO_2Na, CF_3SO_2H and $(CF_3SO_2)_2$. In this context, we came up with a novel idea of using ubiquitous CF_3SO_2 compounds as reagents for introducing the CF_3S unit under reductive conditions (Fig. 1a). As a part of our recent work on the chemistry of trifluoromethanesulfonyl compounds (triflones),[11] we herein disclose a 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 chloride, a wide variety of nucleophiles are nicely converted into the corresponding trifluoromethylsulfanyl products by **1** (Fig. 1b).

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 and nitro groups. Interestingly, the phenyl sulfonyl group of phenyliodonium bis(phenylsulfonyl) methylide can be reduced to a phenylthio moiety when it is placed under photo 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-) compounds by carbene-mediated *in-situ* reduction catalyzed by copper salts. 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 Supporting Information).

With reagent **1** in hand, we began our attempt with enamines which are versatile intermediates for a wide range of organic synthesis and not achieved by other methods.[15] Initially, we tested various substitutions on the amino groups. Both electron-rich and electron-deficient substitutes gave high yields under the same conditions (**3b** and **3c**). When other aliphatic substituents such as cyclohexyl and *n*-butyl were attempted, 89% and 75% yields were afforded, respectively (**3d** and **3e**). *N*-Aromatic substrates were identified as being suitable for this reaction, as well. The 77% yield was found for *N*-phenyl enamine and higher yield was obtained when an electron-rich substitute was used (**3f** and **3g**). When the R^2 were aromatics, the electron nature of substituents on the rings affected the yields slightly although position on the benzene ring had no obvious influence (**3h-n**). Not only β-enamine esters but also β-enamine ketones were efficiently trifluoromethylthiolated under the current condition. Excellent yields were obtained for both aliphatic and aromatic substitutes (**3o** and **3p**). Desired product **3q** in 84% yield was also given without any problem when unprotected enamine was used. For di-substituted enamine, 15 min was required to complete the conversion to provide **3r** in 74% yield. Cyclic enamine **2s** was also tested and **3s** was afforded in 84% yield. Information gleaned from ^{1}H NMR, ^{19}F NMR, ^{13}C NMR, IR and MS spectra led to formulation of structure **3**, and this was confirmed unambiguously by a single-crystal X-ray structure of **3c** (CCDC 926214, see Fig. S1 in Supporting Information).

Table 1. Trifluoromethylthiolation of enamine **2**[a]

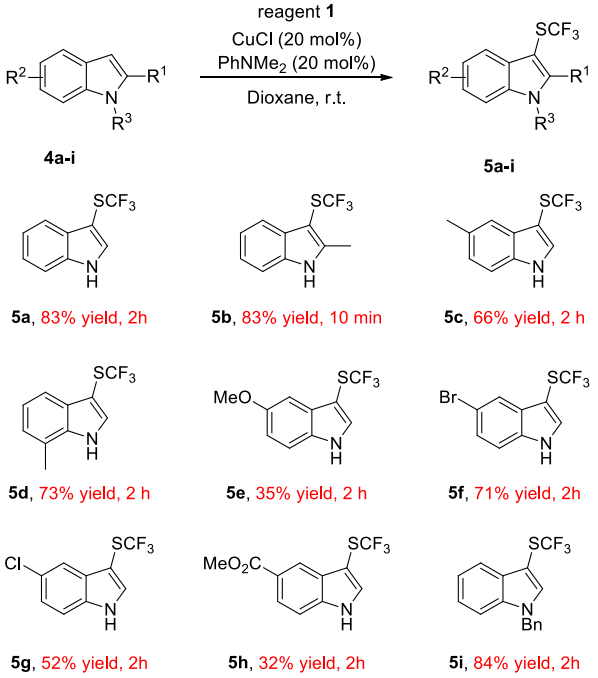


[a]Conditions: 2 (0.15 mmol), 1 (0.3 mmol), CuCl (20 mol%), dioxane (0.75 mL), room temperature, 5 min, isolated yields.

[b]The mixture was stirred over 15 min at r.t.

Encouraged by this good result, we next tried to extend this reaction to other substrates. Since indole and its derivatives are important structural units in a diverse array of area such as pharmaceuticals, agrochemicals and dyes,[16] they were chosen as our next attempt. Although only 25% yield of the trifluoromethyltholated product from indole (**4a**) was detected by 19F NMR under the same condition, the addition of catalytic amount of amine, PhNMe2, could afford the desired products with various indoles in moderate to high yields within 2 h. No desired product was found when 3-methyl indole was studied under this condition.

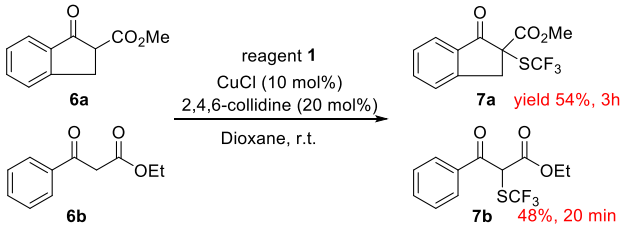
Table 2. Trifluoromethylthiolation of indoles **4**[a]



[a]Conditions: 3 (0.2 mmol), 1 (0.4 mmol), CuCl (20 mol%), PhNMe2 (20 mol%), dioxane (1.5 mL), room temperature, isolated yields.

β-Ketoesters were also tested under a similar condition. Trifluoromethylthiolated 1-indanon-2-carboxylate **7a** (54%) having a quaternary sp_3 carbon center was afforded when cyclic ester **6a** was performed in the presence of catalytic amount of 2,4,6-collidine and copper (I) chloride. It is noteworthy that no trifluoromethylthiolation was found in the reaction of acylic β-ketoester with Shen SCF3-reagent according to the literature,[10] 48% yield of **7b** was obtained in our attempt with reagent **1** and ester **6b** (Scheme 1).

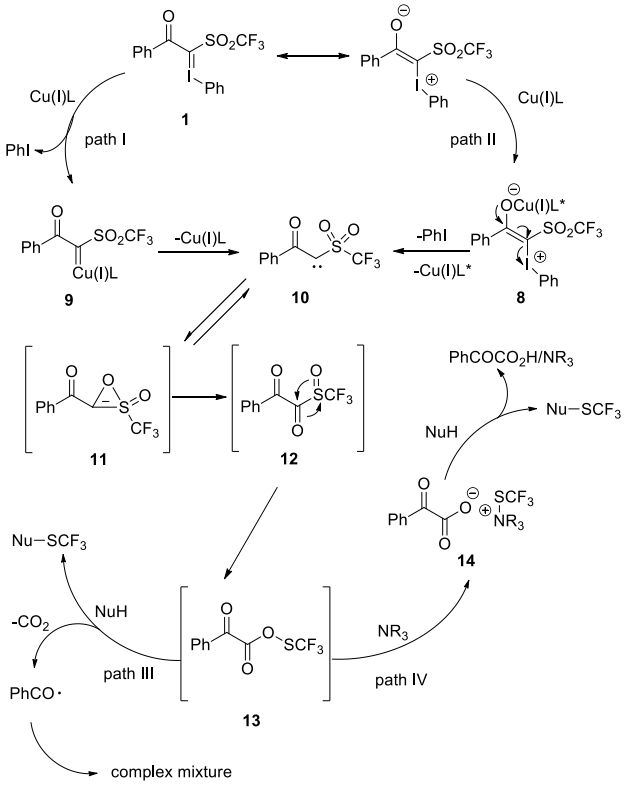
Scheme 1. Trifluoromethylthiolation of β-ketoesters **6**[a]



[a]Conditions: **6** (0.2 mmol), **1** (0.4 mmol), CuCl (10 mol%), 2,4,6-collidine (20 mol%), dioxane (1.5 mL), room temperature, isolated yields.

Although the detail of the reaction process is not clear, we hypothesize the mechanism in Scheme 2 based on the experimental results, references and MS spectral data (see Figs. S2 and S3 for MS spectra in Supporting Information). The process for reduction of the sulfonyl group via a carbene species was based on previous reports.[14,17] Two potential paths may achieve this result. As shown in path I, a copper-carbenoid **9** may be initially generated, this carbenoid intermediate is thereafter decomposed to form sulfonyl carbene **10**. Alternatively, reagent **1** could be activated by a copper (I) salt and generated a zwitterionic intermediate **8** which subsequently eliminated an iodobenzene to form carbene **10** without a copper-carbenoid intermediate (path II). Due to metal-carbenoids are usually formed with copper or rhodium in transition-metal-catalyzed decomposition of phenyliodonium ylides, besides, a variety of metal salts could also catalyze our reaction (see Table S1 in Supporting Information), we proposed path (II) is more possible responsible for this carbene generation process. The observation of carbene **10** (or its isomers) and that no copper-carbenoid (coordinated with a chloride anion or one more amine) was found in HRMS-ESI also imply the possibility of our surmise. Then, as proposed by Varvoglis,[14] oxirene **11** which was in equilibrium with carbene **10** would be rearranged into sulfoxide **12** followed by intramolecular nucleophilic collapse to form a true reactive species, thioperoxoate **13**. The transfer trifluoromethylthiolation from **13** to nucleophiles via a SET process or an electrophilic path would yield the desired products (path III). Alternatively, when this reaction was carried out in the presence of a amine (Tables 2 and Scheme 1), the real reactive species might become a trifluoromethylthiolated ammonium salt **14** and this intermediate was subsequently attacked by a nucleophile to afford the final product (path IV).[18] The salt **14** was supposed to be relative stable and the attack by a nucleophile might determine the rate of the whole reaction.

Scheme 2. A proposed mechanism for copper-catalyzed trifluoromethylthiolation with **1**.



In conclusion, a novel electrophilic trifluoromethylation reagent was developed. A wide scope of nucleophiles is efficiently trifluoromethylthiolated through this approach to give the corresponding CF_3S-products in synthetic useful yields. Reagent **1** costs little and is stable. The stable CF_3SO_2

moiety was reduced to a reactive CF_3S species by intramolecular rearrangement and an ammonium salt which was supposed to be responsible for the trifluoromethylthiolation might be generated in the presence of a amine. The formation of this salt species would be potential valuable in the asymmetrical reaction when a chiral amine was used. Our reagent affords not only a success of trifluoromethylthiolation, but also another potential of organo-iodine reagents.[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, and copies of ^1H, ^{19}F and ^{13}C NMR spectra. 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 interests.

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(18) The trifluoromethylthiolated salt **14** was also found in HRMS-ESI (see Support Information). When PhNH2 was added as a base in the trifluoromethylthiolation of indoles, PhNHSCF3 was detected by ^{19}F NMR in the crude mixture.

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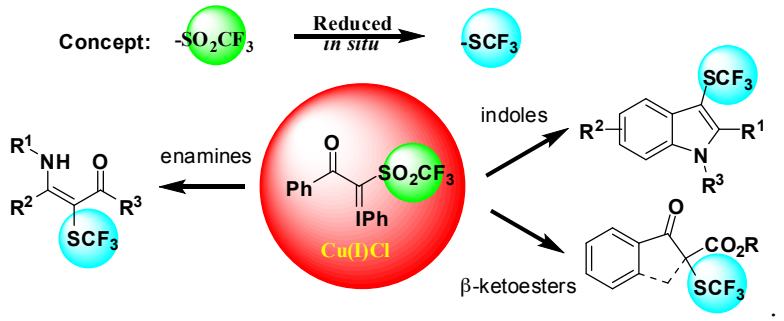
Concept:
-SO2CF3
Reduced
in situ
-SCF3
indoles
enamines
β-ketoesters
Ph
IPh
SO2CF3
Cu(I)Cl
SCF3
CO2R