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Synthetic Methods

An Electrophilic Hypervalent Iodine Reagent for Trifluoromethylthiolation**

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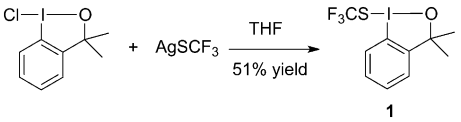
The trifluoromethylthio group (CF_3S-) is one of the most lipophilic substituents.[1] It is well known that incorporation of trifluoromethylthio group into small molecules greatly enhances their ability to cross lipid membranes and their in vivo absorption rate.[2] Moreover, the high electronegativity of the trifluoromethylthio group significantly improves the stability of small molecules in acidic environments.[3] Thus, the trifluoromethylthio group has been of interest to the pharmaceutical and agrochemical industries for its use in isosetere-based drug design.[4,5] For example, the trifluoromethylthio group has been utilized as a halogen isostere in Losartan analogues that are used clinically for the treatment of cardiovascular diseases.[6]

Classic methods[5,7] for the introduction of the trifluoromethylthio group into small molecules typically involve halogen–fluorine exchange reactions of polyhalogenomethyl thioethers[8] or the trifluoromethylation of sulphur-containing compounds such as disulfides, thiocyanates, and thiols by a single-electron transfer (SET) mechanism.[9] However, both of these methods suffer from harsh reaction conditions and/or limited substrate scope. A more straightforward strategy would be the direct formation of a new $C-SCF_3$ bond.[10] In recent years, several elegant methods employing transition-metal catalysts[11] or metal-free conditions[12] have emerged for the direct trifluoromethanesulfanylation of aryl halides, boronic acids, or alkynes with a nucleophilc trifluoromethylthio reagent under mild conditions. Despite their great advantages, these reactions typically involved the formation of $C_{sp^2}-SCF_3$ or $C_{sp}-SCF_3$ bonds, whereas processes that facilitate the construction of $C_{sp^3}-SCF_3$ bonds remain largely unexplored.

One attractive strategy for the construction of $C_{sp^3}-SCF_3$ bonds is to use an electrophilic trifluoromethylthio reagent. In contrast to the well-developed electrophilic trifluoromethyl reagents such as Umemoto's reagent or Togni's reagent,[13–16] electrophilic trifluoromethylthio reagents are far less studied.[5] The only known electrophilic trifluoromethylthio reagents include CF_3SCl and $CF_3NR^1R^2$ (R^1,R^2 = alkyl or aryl). CF_3SCl has been used to react with some nucleophiles.[5] However, it is gaseous and highly toxic. $CF_3SN(Me)Ph$, developed by Billard and co-workers, reacted with alkyl Grignard reagents to give the trifluoromethylthiolated products in good yields, but with limited functional group tolerance.[14] A general method for the introduction of a trifluoromethylthio group into the α position of a carbonyl group is highly desirable.

Toward this end, inspired by our own and Togni's recent study on electrophilic trifluoromethylated hypervalent iodine reagents,[15,16] we have now developed an air and moisture stable trifluoromethylthiolated hypervalent iodine reagent **1**. Herein, we report the preparation of this new reagent and its reaction with a variety of enolate nucleophiles to form highly selectively and efficiently $C_{sp^3}-SCF_3$ bonds. Moreover, it was discovered that the trifluoromethylthiolated hypervalent iodine reagent reacted with aryl and vinyl boronic acids to form $C_{sp^2}-SCF_3$ or with alkynes to form $C_{sp}-SCF^3$ bonds under mild conditions.

$$AgF + CS_2 \xrightarrow[85\ \%\ \text{yield}]{CH_3CN,\ 80\ ^\circ C} AgSCF_3 \quad (1)$$



(2)

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In an attempt to prepare the electrophilic trifluoromethylthiolated hypervalent iodine reagent **1**, we initially tried the reaction of 1-chloro-1,3-dihydro-3,3-dimethyl-1,2-benziodoxole with $AgSCF_3$ in different solvents. It turns out that the reaction is quite challenging, as it is well known that the sulfide can be easily converted into disulfide under oxidative conditions. Indeed, CF_3SSCF_3 was observed as the major product when hexane, NMP, CH_3CN, or DMF was used as the solvent. However, when THF was used as the solvent, the desired trifluoromethylthiolated hypervalent iodine reagent **1** was formed in 50% yield, as determined by ^{19}F NMR spectroscopy. The reaction can be scaled up to a 6.0 g scale and compound **1** was isolated by flash chromatography on silica gel as a colorless liquid in 51% yield. Compound **1** was characterized by ^1H, ^{13}C, and ^{19}F NMR spectroscopy and by elemental analysis.

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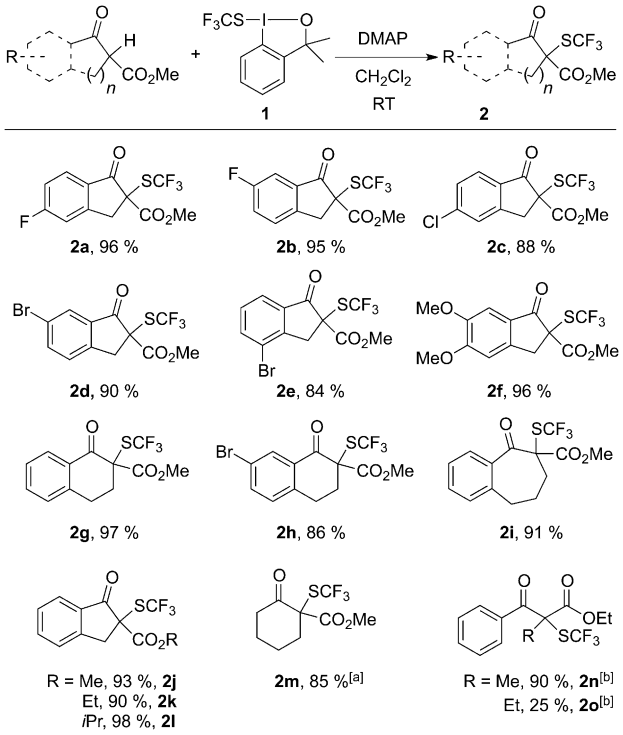
Compound **1** is stable in solvents such as THF, CH_2Cl_2, toluene, Et_2O, and CH_3CN at room temperature for at least 72 h, as determined by ^{19}F NMR spectroscopy. No decomposition was observed at 80 °C for 12 h for a solution of compound **1** in toluene. Compound **1** is less stable in more polar solvents such as DMF and DMSO, wherein 50 % of the compound was decomposed after 48 h at room temperature or completely decomposed after 12 h at 80 °C, as determined by ^{19}F NMR spectroscopy.

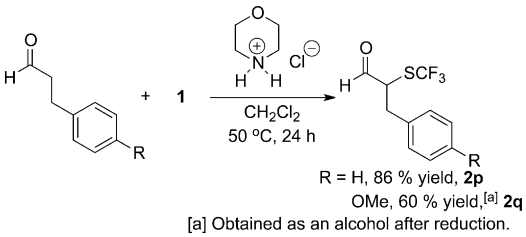
With this new reagent in hand, we then explored its reactivity with a variety of nucleophiles. Carbonyl compounds, such as β-ketoesters, reacted with **1** in CH_2Cl_2 at room temperature to give the corresponding α-trifluoromethylthiolated derivatives in good to excellent yields when 4-dimethylaminopyridine (DMAP) was used as the base. Various β-ketoesters derived from indanone, tetralone, or 1-benzosuberone gave the corresponding products in good to excellent yields (Scheme 1, **2a**–**l**). Reaction of methyl



Scheme 1. Electrophilic α-trifluoromethylthiolation of β-ketoesters. Reaction conditions: β-ketoester (0.5 mmol), **1** (1.0 mmol), DMAP (0.55 mmol) in CH_2Cl_2 (2.5 mL) at room temperature for 12 h. Yields shown are of isolated products. [a] Reaction conducted at 40 °C for 36 h. [b] Reaction conducted at 60 °C for 24 h.

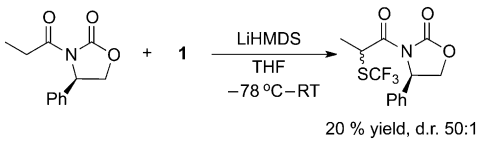
2-oxocyclohexanecarboxylate with reagent **1** also gave the desired product in 85 % yield (Scheme 1, **2m**). Under the optimized conditions, the reaction of open-chain β-ketoesters was much slower. Nevertheless, the corresponding product was obtained in 90 % and 25 % yield after 24 h at 60 °C for methyl or ethyl esters, respectively (Scheme 1, **2n, 2o**). Reactions of β-ketoesters with an active methylene moiety, however, gave no desired products under these conditions.

Encouraged by the excellent results with β-ketoesters, we next studied reactions with other nucleophiles, such as aldehydes and chiral amide enolates derived from an Evans type oxazolidinethione auxiliary with reagent **1**. It was found that when morpholine hydrochloride was used as the catalyst for the reaction of aldehydes with **1**, the desired α-trifluoromethylthiolated products were obtained in good yields, whereas other hydrochloride salts of secondary amines such as pyrrolidine or piperidine were used, the reaction was much slower [Eq. (3)]. On the other hand, a lithium enolate derived



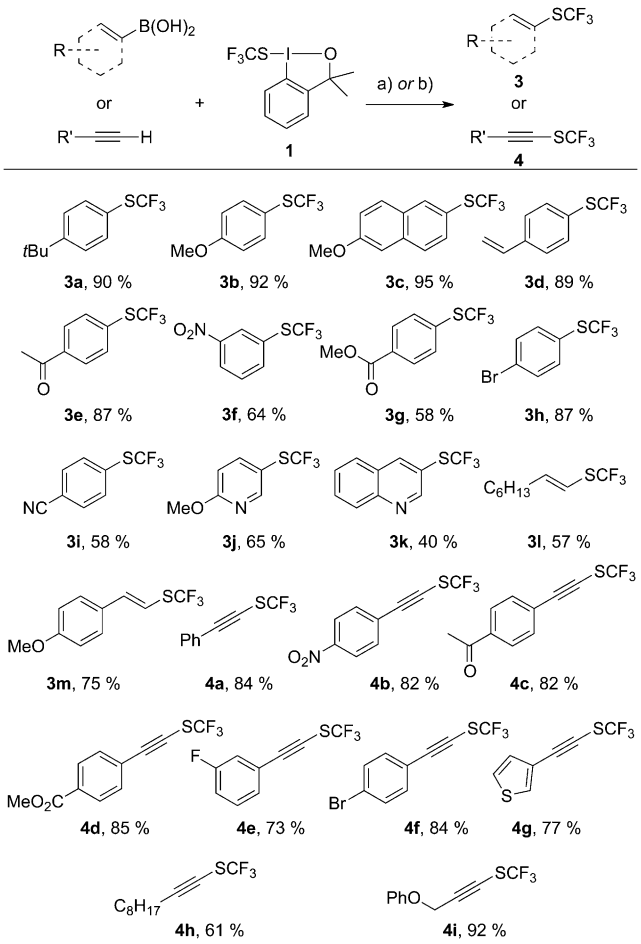
(3)

from an Evans type oxazolidinethione auxiliary reacted with reagent **1** at −78 °C and gave the corresponding product with high diastereoselectivity (d.r. = 50:1) in 20 % yield [Eq. (4)].



(4)

Arenes and alkynes with a trifluoromethylthio group are important structural motifs found in a variety of pharmaceuticals and agrochemicals. A number of reported transition-metal-catalyzed trifluoromethylthiolations of aryl halides or aryl boronic acids typically involved a nucleophilic trifluoromethylthio reagent.[11] Methods using a readily available electrophilic trifluoromethylthio reagent would be an attractive alternative. Initial attempts to extend our previously published work on the trifluoromethylation of arylboronic acids to the trifluoromethylthiolation of arylboronic acids with reagent **1** gave the desired product in only moderate yield.[16] After a quick screening of the reaction conditions (see the Supporting Information for details), it was found that reactions conducted with a combination of $Cu(MeCN)_4PF_6$ (10 mol %) and 2, 2′-bipyridine (bpy, 20 mol %) as the catalyst, and K_2CO_3 as the base in diglyme resulted in full conversion of arylboronic acids into trifluoromethylthiolated arenes. Both electron-rich and electron-deficient arylboronic acids reacted to give the corresponding products in high yields. Various functional groups, including ethers, alkynes, ketones, nitro groups, esters, bromides, and cyano groups, were tolerated under the standard reaction conditions (Scheme 2, **3b**–**i**). Notably, bromides and vinyl groups were not compatible with the palladium catalyst reported by Buchwald for trifluoromethylthiolation.[11a] Reactions of heteroarylboronic acids occurred smoothly to give the trifluoromethylthiolated products in moderate yields



Scheme 2. Copper-catalyzed trifluoromethylthiolation of aryl or vinyl boronic acids and alkynes. Reaction conditions: a) Aryl or vinyl boronic acid (0.65 mmol), reagent **1** (0.5 mmol), $Cu(MeCN)_4PF_6$ (10 mmol%), bpy (20 mmol%), K_2CO_3 (1.0 mmol) in diglyme (2.5 mL) at 35 °C for 15–24 h; b) Alkyne (0.60 mmol), **1** (0.3 mmol), $CuBr(SMe_2)$ (20 mmol%), bpy (40 mmol%), K_2CO_3 (0.60 mmol) in 1,2-dichloroethane (2.5 mL) at 80 °C for 14 h. Yields shown are of isolated products.

(Scheme 2, **3j** and **3k**). This trifluoromethylthiolation method was also suitable for the trifluoromethylthiolation of vinyl boronic acids. The reaction was stereospecific, with only the (*E*)-trifluoromethylthiovinylarene products observed (Scheme 2, **3l** and **3m**). Both of these types of substrates were not suitable for copper-catalyzed oxidative trifluoromethylthiolation.[11d]

Reactions of alkynes with reagent **1** in the presence of a copper catalyst was much slower than those of aryl or vinyl boronic acids and required heating to 80 °C for 15 h to obtain full conversion. A variety of electron-rich and electron-deficient terminal alkynes could be transformed into the corresponding alkynyl trifluoromethylsulfides in good yields. A wide range of functional groups, including nitro groups, enolizable ketones, esters, fluorides, and bromides were compatible with the reaction conditions (Scheme 2, **4b–f**). Aliphatic alkynes also reacted under these conditions to give the corresponding alkynyl-trifluoromethylthioethers in good to excellent yields (Scheme 2, **4h** and **4i**).

In summary, a new electrophilic hypervalent iodine reagent based on the 1,2-benziodoxole fragment for direct trifluoromethylthiolation has been developed. Reagent **1** is effective for the direct transfer of the trifluoromethylthio group (CF_3S^-) to various substrates, such as β-ketoesters, aldehydes, amides, aryl, or vinyl boronic acids, or alkynes, under mild conditions. The development of enantioselective methods for the construction of a stereocenter containing a trifluoromethylthio group is ongoing and will be reported in due course.

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