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Deoxygenative Tri- and Difluoromethylthiolation of Carboxylic Acids with Benzothiazolium Reagents

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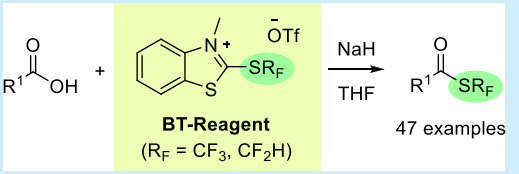
ABSTRACT: Deoxygenative syntheses of fluorinated thioesters directly from carboxylic acids have been developed employing benzothiazolium reagents. The process using BT-SCF_3 represents an attractive approach toward these SCF_3-containing compounds that avoids the use of metal $^-SCF_3$ salts or preactivated acyl electrophiles. Moreover, the *in situ* activation of BT-SCF_2H allows for an unprecedented nucleophilic difluoromethylthiolation reaction. DFT calculations support a mechanistic scenario involving a four-membered transition state where acyl substitution occurs without the formation of an unstable free $^-SCF_2H$ anion.



Fluorinated compounds play an important role in the agrochemical and pharmaceutical industry.[1] However, due to a scarcity of naturally occurring fluorinated molecules, the production of fluorinated targets relies heavily on synthetic organic chemistry. Among the various fluorine-containing functional groups, fluoroalkylthio groups such as the SCF_3 moiety have attracted considerable attention recently due to their lipophilic yet polar nature and several fluoroalkylthiolated pharmaceuticals and agrochemicals have been developed.[2]

The renewed interest in the SCF_3 group in particular has been spurred to a large extent by the development of new electrophilic trifluoromethylthiolating reagents capable of operating under mild conditions, which have supplanted the previously available toxic gases F_3CS-Cl and F_3CS-SCF_3.[2b,d,3] In contrast, nucleophilic trifluoromethylthiolation relies on a few comparatively expensive salts such as $AgSCF_3$, $CuSCF_3$, and $[Me_4N]SCF_3$. In 2019, we reported a new purely organic reagent for nucleophilic trifluoromethylthiolation suitable for the deoxygenative functionalization of aliphatic alcohols: the benzothiazolium salt BT-SCF_3.[4] This solid reagent can be easily prepared on a multigram scale in two steps from the inexpensive starting material 2-mercaptobenzothiazole (MBT) and is bench stable at least over several months. In the presence of an alcohol and the amine base $NEt(iPr)_2$, however, addition/elimination at the C2 carbon releases $^-SCF_3$, which then reacts with the intermediate 2-alkoxybenzothiazolium salt to afford a wide range of trifluoromethylthioethers under mild conditions.[5] This "*in situ* activation" approach is particularly attractive for nucleophilic trifluoromethylthiolation as the free $^-SCF_3$ anion is unstable toward β-fluoride elimination.[6] Using BT-SCF_3, this anion is generated in a controlled fashion together with a highly reactive electrophile. As such, nucleophilic trifluoromethylthiolation is expected to proceed rapidly while the concentration of $^-SCF_3$ in the reaction mixture remains low (Scheme 1a).

Having identified BT-SCF_3 as a convenient reagent for the trifluoromethylthiolation of alcohols, we considered whether other important classes of fluoroalkylthiolated compounds could be similarly prepared in a deoxygenative fashion from readily available substrates. For example, deoxytrifluoromethylthiolation of carboxylic acids with BT-SCF_3 would provide facile access to trifluoromethylthioesters. Whereas trifluoromethylthioethers have been widely studied, the corresponding esters remain relatively underexplored despite the potential for applications in pharmaceuticals and agrochemicals.[2] Most reported synthetic routes toward trifluoromethylthioesters involve addition/elimination of $^-SCF_3$ salts to acid chlorides, which in addition to employing expensive, relatively unstable, or even toxic $^-SCF_3$ sources, require preformation of the acyl electrophile and generate stoichiometric amounts of metal chloride waste.[7] A selection of recent reports have instead employed electrophilic trifluoromethylthiolating reagents such as Phth-SCF_3 (Phth = phthalimide) or $PhSO_2SCF_3$, which while still expensive, are bench stable and easily handled. The groups of Glorius,[8] Shen,[9] and Wang[10] have developed radical methodologies involving SCF_3 group transfer onto acyl radicals generated via hydrogen atom transfer (HAT) from aldehydes.[11] The only synthesis of trifluoromethylthioesters directly from carboxylic acids was reported recently by Hu and co-workers.[12] This method uses an umpolung approach that employs Phth-SCF_3 as an electrophilic trifluoromethylthiolating reagent together with triphenylphosphine as a stoichiometric reductant and an iron(III) catalyst.

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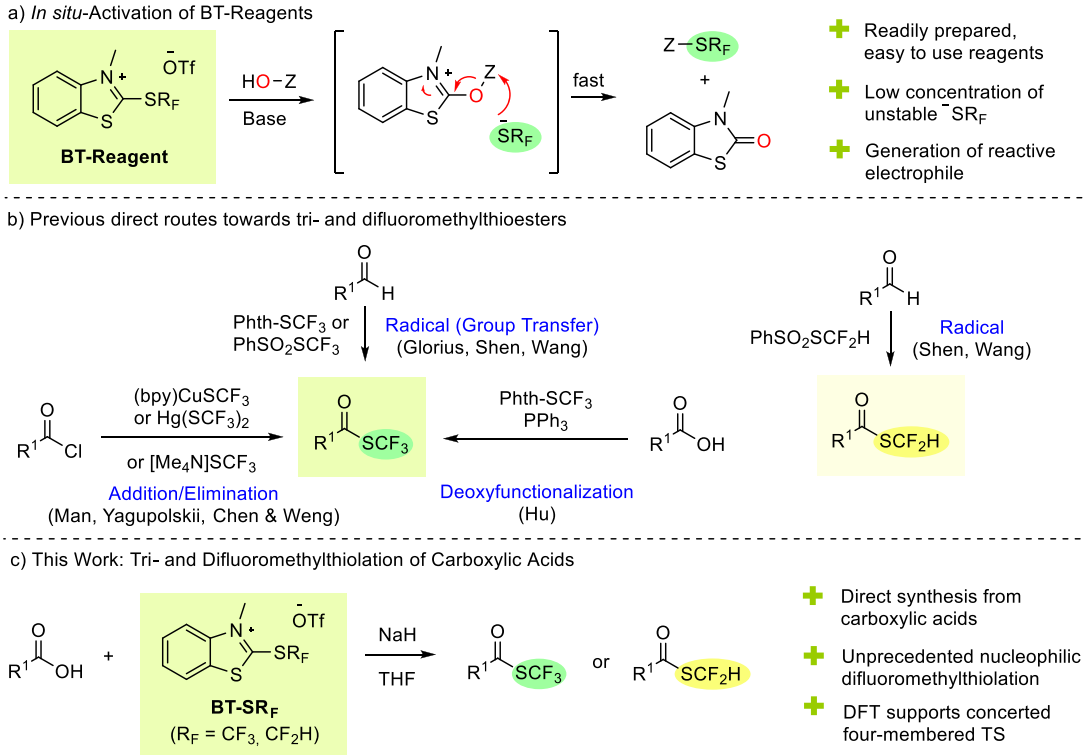
Scheme 1. Previous Direct Syntheses of Tri- and Difluoromethylthioesters and In Situ Activation of BT Reagents



Partially fluorinated difluoromethylthioesters have been even less studied. In addition to the lipophilic and electron-withdrawing characteristics typical for fluoroalkylthio groups, the SCF_2H moiety can engage in hydrogen bonding interactions in biological systems.[13] These beneficial properties have duly led to the development of SCF_2H containing pharmaceuticals and agrochemicals such as flomoxef sodium and pyriprole. While there are currently no difluoromethylthioester-containing pharmaceuticals, a structurally similar monofluoromethylthioester motif is found in the corticosteroid medication fluticasone. Synthetic routes toward SCF_2H-substituted compounds are comparatively limited with most approaches involving difluoromethylation of a sulfur-containing substrate. In recent years, a few direct methods for installing the entire SCF_2H group onto organic molecules have been introduced, employing a selection of mostly electrophilic or radical difluoromethylthiolating reagents.[14] To date, however, only two methods both involving group transfer from $PhSO_2SCF_2H$ onto aldehyde-derived acyl radicals have been reported for the synthesis of difluoromethylthioesters (Scheme 1b).[9,14]

Herein, we report a transition metal free methodology for the direct deoxygenative fluoroalkylthiolation of readily available carboxylic acids via *in situ* activation of BT-SR_F reagents. The method using BT-SCF_3 provides aryl and alkyl trifluoromethylthioesters without any additives other than an inorganic base. The similarly efficient synthesis of difluoromethylthioesters using the novel reagent BT-SCF_2H is especially noteworthy. Not only is this method the only reported approach toward these partially fluorinated compounds from simple carboxylic acids, it also constitutes a rare example of a formally nucleophilic difluoromethylthiolation reaction. The success of this method despite the well-known instability of the $^-SCF_2H$ anion suggests that *in situ* activation of BT reagents could provide a strategy for conducting nucleophilic reactions of otherwise unstable fluorinated or nonfluorinated anions (Scheme 1c).

We began our study by reacting preformed cesium 4-methylbenzoate with BT-SCF_3 (1.25 equiv)[4,15] in MeCN. After 2 h at rt, we were pleased to observe the formation of the desired trifluoromethylthioester **2a** in 39% NMR yield. With the aim of developing an efficient set of conditions for the direct deoxyfunctionalization of the free carboxylic acid **1a**, a survey of different bases and solvents was conducted. The combination of NaH (3 equiv) and THF proved to be optimum, while dilution to 0.033 M, dropwise addition of the acid, and a lower reaction temperature of −78 °C suppressed the formation of side products resulting from nucleophilic attack of a second carboxylate anion or ring-opening of THF.[16]

With a set of optimized conditions established, an investigation into the reaction scope with variously substituted carboxylic acids **1** was conducted (Scheme 2). A wide range of aryl derivatives could be successfully converted into the corresponding thioesters in generally moderate to good yields. Electronically diverse functional groups such as −OMe and $-NO_2$ were well tolerated, while halogen-substituted products that are potentially amenable to further functionalization through cross-coupling methodologies were efficiently provided. As demonstrated by Hu and co-workers, aromatic trifluoromethylthioesters can be converted into the corresponding aryl thioethers via palladium-catalyzed decarbonylation.[12,17] As such, the deoxygenative trifluoromethylthiolation could serve as the first part of a facile two-step synthesis of valuable trifluoromethylthioethers from readily available carboxylic acids. The standard reaction conditions with BT-SCF_3 could also be applied to a series of alkyl carboxylic acids with the corresponding thioesters being formed in isolated yields up to 73%.

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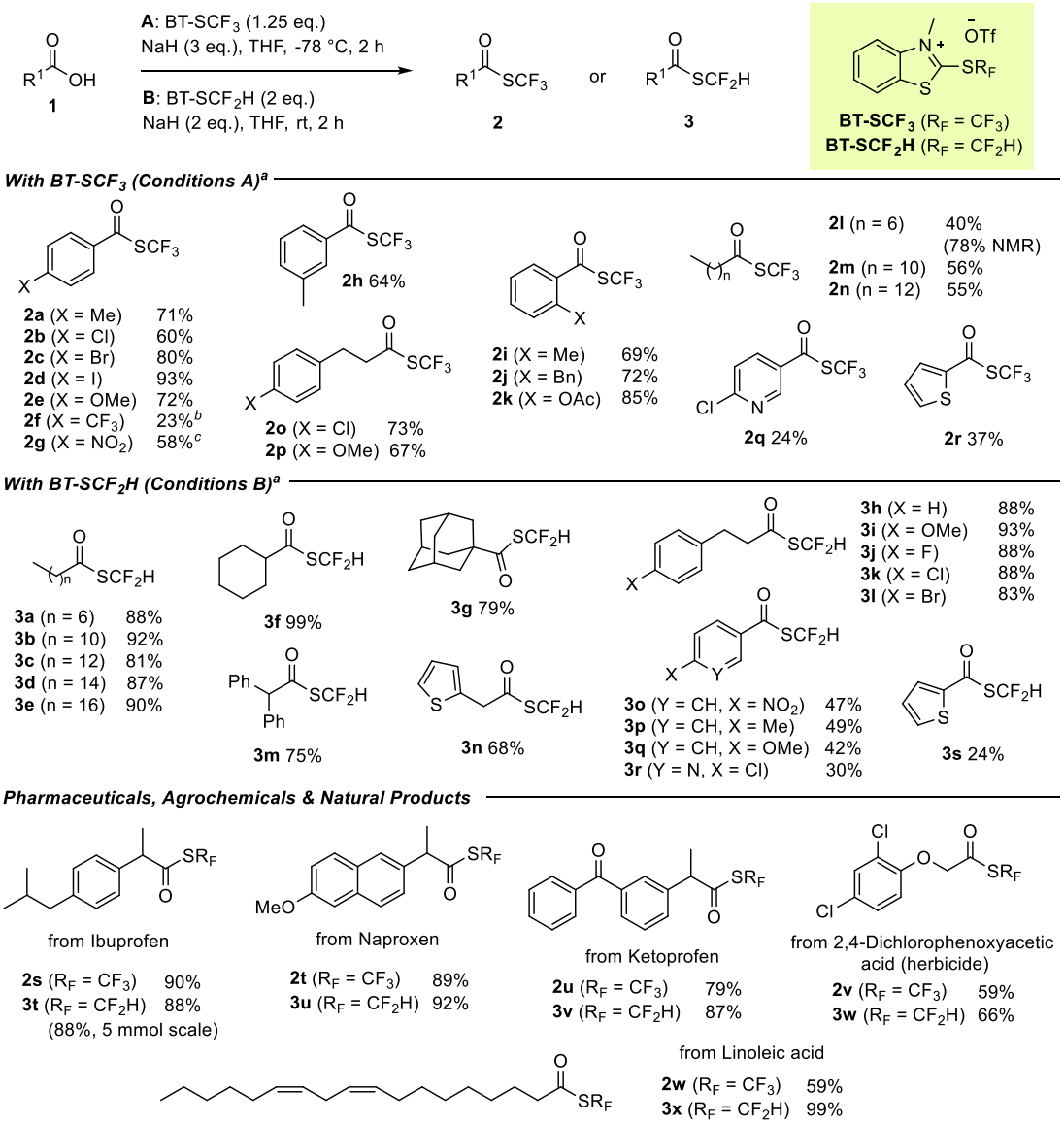
Scheme 2. Scope of Deoxygenative Tri- and Difluoromethylthiolation of Acids Using BT-SCF_3 and BT-SCF_2H



[a]Isolated yields, 0.5 mmol scale. For full conditions, see the SI. [b]No dropwise addition of acid, 0.1 M concentration, stirred for 2 h at rt. [c]No dropwise addition of acid, 0.033 M concentration, stirred for 2 h at rt.

Having developed a practical protocol for the deoxytrifluoromethylthiolation of carboxylic acids, we next turned our attention to the deoxygenative synthesis of difluoromethylthioesters. According to the general mechanism outlined in Scheme 1a, addition of a carboxylate to the C2 carbon of the 2-difluoromethylthio-substituted benzothiazolium salt BT-SCF_2H would result in the generation of the $^-SCF_2H$ anion. Whereas nucleophilic pathways are often employed to install the SCF_3 group, direct difluoromethylthiolation reactions are almost exclusively electrophilic or radical in character. The scarcity of nucleophilic methods can be explained by the very low stability of $^-SCF_2H$ toward β-fluoride elimination. Despite many attempts over the years, only one stable $^-SCF_2H$ salt has been successfully isolated to date: the N-heterocyclic carbene (NHC)-stabilized silver complex [SIPrAg(SCF_2H)] (SIPr = 1,3-(2,6-diisopropylphenyl)imidazolinylidene). This compound, which was introduced in 2015 by Shen and coworkers,[18] has been employed as a stoichiometric source of SCF_2H groups in transition-metal-mediated cross-coupling reactions but, to the best of our knowledge, no applications in direct nucleophilic substitution reactions, including for the synthesis of difluoromethylthioesters, have been reported.[18,19]

In order to investigate the feasibility of nucleophilic difluoromethylthiolation using BT reagents, we first synthesized the new compound BT-SCF_2H. As for BT-SCF_3, BT-SCF_2H was efficiently prepared in a two-step protocol starting from MBT. Formal insertion of difluorocarbene obtained from HCF_2OTf into the S−H bond of MBT[20] followed by *N*-methylation with methyl triflate afforded the desired salt in high yields on scales up to at least 25 mmol. BT-SCF_2H was obtained as a pale yellow solid and, like BT-SCF_3, is bench stable over at least several months under ambient conditions (Scheme 3). In a test experiment, 1.25 equiv of BT-SCF_2H was then reacted with octanoic acid and NaH (3 equiv) in THF. After 2 h at rt, we were delighted to observe clean formation of the desired difluoromethylthioester **3a** in 72% NMR yield. The

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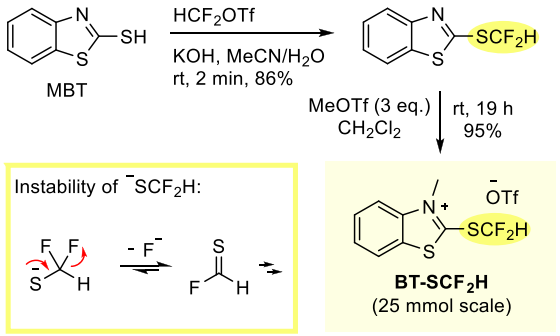
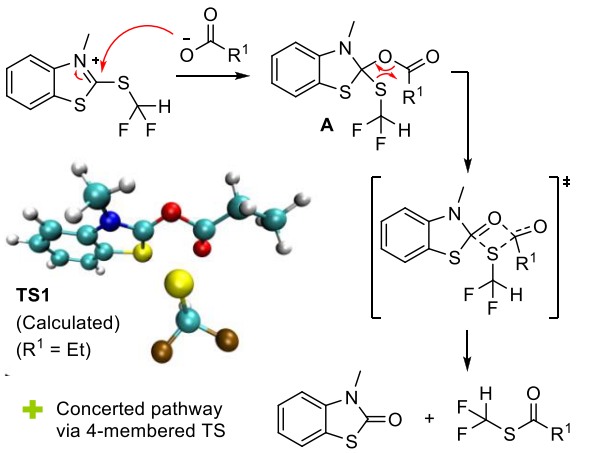
Scheme 3. Synthesis of BT-SCF$_2$H



Scheme 4. Proposed Mechanism via Four-Membered TS



success of this transformation suggests that *in situ* activation of BT reagents can enable unprecedented nucleophilic difluoromethylthiolation reactions and that BT-SCF$_2$H itself could serve as a practical formal "$^-$SCF$_2$H" source.

A short optimization study led to the set of conditions shown in Scheme 2 (conditions B). Preforming the carboxylate with NaH for 30 min before addition of BT-SCF$_2$H led to the highest yields of thioesters **3** while, in contrast to the deoxytrifluoromethylthiolation reaction, cooling of the reaction mixture to −78 °C was not required. A survey of carboxylic acid substrates allowed for the facile synthesis of a range of diverse difluoromethylthioesters in generally good to excellent yields up to 99%. The method proved to be tolerant of several commonly encountered functional groups, such as nitro groups, halogens, heterocycles, and alkoxy groups. The reagent also proved capable of efficiently converting sterically encumbered substrates with the thioester of adamantane carboxylic acid (**3g**) being afforded in 79% yield. In general, aliphatic carboxylic acids reacted most smoothly although aromatic and heteroaromatic substrates could also be successfully converted in moderate yields.

The scope of both the deoxytrifluoromethylthiolation and difluoromethylthiolation reactions was then tested further with a selection of pharmaceuticals, agrochemicals, and natural products (Scheme 2). CF$_3$- or CF$_2$H-thioesters of several blockbuster drugs such as ibuprofen or naproxen as well as naturally occurring species such as linoleic acid could be obtained directly from the parent compounds in excellent yields using BT-SCF$_3$ or BT-SCF$_2$H. Moreover, the practical utility of the deoxyfunctionalization process was demonstrated by the gram-scale synthesis of ibuprofen derivative **3t** in 88% isolated yield (5 mmol scale).

The remarkable success of the deoxydifluoromethylthiolation reaction led us to consider the reaction mechanism more closely. Given the well-documented instability of $^-$SCF$_2$H, we considered whether an alternative mechanistic scenario to that outlined in Scheme 1a that avoids the intermediate formation of a free anion could be operating. In particular, a concerted process involving a four-membered transition state from intermediate **A** (Scheme 4) could provide the thioester product and thiocarbamate byproduct directly. Similar concerted mechanisms have been previously proposed in deoxygenative fluorination reactions of phenols using the imidazolium-based reagent Phenofluor.[21] In order to test this hypothesis, DFT calculations (B3LYP/def2-SVP)[22] were carried out on model intermediate **A** (R^1 = Et). As predicted, a concerted mechanism proceeding through the four-membered transition state **TS1** (Scheme 4) was found to be the most favored pathway for the deoxydifluoromethylthiolation reaction (energy barrier = 12.3 kcalmol^{-1} cf. 34.1 kcalmol^{-1} for release of $^-$SCF$_2$H). Moreover, an albeit more asynchronous concerted pathway was also predicted for the analogous trifluoromethylthiolation (see the SI). These results suggest BT reagents could open up hitherto unfeasible nucleophilic reaction pathways by circumventing the generation of an unstable free anion nucleophile.

In conclusion, fluorine-containing benzothiazolium salts have been employed as efficient reagents for deoxygenative substitution reactions of unactivated carboxylic acids. A wide range of trifluoromethylthioesters could be conveniently prepared using BT-SCF$_3$, while the novel reagent BT-SCF$_2$H allowed for an unprecedented nucleophilic difluoromethylthiolation reaction. The success of this latter transformation can be explained by the involvement of a four-membered concerted transition state that avoids the formation of the unstable $^-$SCF$_2$H anion. As such, BT reagents could facilitate otherwise unachievable nucleophilic reaction pathways and further investigations of this concept for the formal installation of $^-$SCF$_2$H or other unstable anions are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03328.

Experimental procedures, characterization data, and computational details (PDF)

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Author Contributions

†M.T. and L.M.M. contributed equally to this work.

Notes

The authors declare the following competing financial interest(s): M.N.H. and S.D. are coinventors on a European and International Patent Application concerning the synthesis and use of benzothiazolium reagents for installing fluorine-containing functional groups (EP 3 677 576 A1; WO 2020141195 A1).

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