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Trifluoromethylthiolation

Silver-Catalyzed Decarboxylative Trifluoromethylthiolation of Aliphatic Carboxylic Acids in Aqueous Emulsion**

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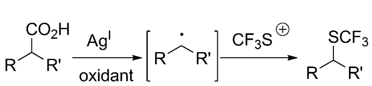
Abstract: *A silver-catalyzed decarboxylative trifluoromethylthiolation of secondary and tertiary carboxylic acids under mild conditions tolerates a wide range of functional groups. The reaction was dramatically accelerated by its performance in an aqueous emulsion, which was formed by the addition of sodium dodecyl sulfate to water. It was proposed that the radical, which was generated from the silver-catalyzed decarboxylation in the "oil-in-water" droplets, could easily react with the trifluoromethylthiolating reagent to form the product.*

As the most electronegative element, fluorine has played a pivotal role in agrochemistry and pharmaceutical chemistry, with an increasing number of fluorinated drugs on the market and drug candidates under development at different stages.[1] Among the different fluorinated functional groups, the trifluoromethylthio group (CF_3S) is highly valuable because of its advantageous effects, as the incorporation of the trifluoromethylthio group often improves the lipophilicity of a compound and suppresses metabolic detoxification processes to increase the in vivo lifetime of a drug.[2] This fact has stimulated a growing interest in the development of new reagents and methods for the direct introduction of the trifluoromethylthio group under mild conditions.[3] For instance, several electrophilic trifluoromethylthiolating reagents have been developed, which allow the trifluoromethylthiolation of common nucleophiles, such as β-ketoesters, alkynes, aryl or alkyl Grignard reagents, and lithium reagents.[4,5a–j] In addition, significant advances have been achieved recently in the transition-metal-mediated trifluoromethylthiolation, with functional groups such as aryl boronic acids and halides undergoing efficient trifluoromethylthiolation under palladium, nickel, or copper catalysis.[5k–p]

Despite these recent great achievements in this area, methods for the general and site-specific formation of sp^3-hybridized secondary or tertiary carbon–SCF_3 bonds are limited.[7,8] Billard and co-workers reported the electrophilic addition of a trifluoromethylthiolated reagent to olefins in excellent yields.[5b] Qing and co-workers reported reactions of allylsilane or tryptamine derivatives with Billard's reagent to form secondary or tertiary alkyl trifluoromethylthioethers.[5d,f] The groups of Shen and Shibata independently reported the trifluoromethylthiolation of β-ketoesters with two different electrophilic trifluoromethylthiolating reagents.[6a,b,5i] More recently, the groups of Rueping and Shen reported the asymmetric trifluoromethylthiolation of β-ketoesters.[5j,6b] Reactions using Billard's reagent generally required the use of a strong Lewis or Brønsted acid to activate the CF_3S reagent. Other reactions only proceeded in high yields with α-substituted β-ketoesters. Thus, the development of new methods for the direct introduction of the trifluoromethylthio group at sp^3-hybridized secondary or tertiary carbon centers with broad substrate scope and functional-group tolerance is highly desirable.

Aliphatic carboxylic acids are air- and water-stable, readily available, and cheap raw materials that can be easily converted into derivatives with different functional groups. One of the fundamental functional-group transformations in organic chemistry is the decarboxylative halogenation of carboxylic acids mediated by a silver salt (Hunsdiecker reaction), which has been well developed since 1930s.[9] More recently, Hunsdiecker-type reactions using catalytic amounts of silver salts have also been developed.[10]

Inspired by these advances and considering that the CF_3S group is generally referred to as a pseudohalide, we reasoned that a Hunsdiecker-type decarboxylative trifluoromethylthiolation (Scheme 1) may be possible if the alkyl radical generated from the well-known oxidative decarboxylation could be efficiently trapped by the electrophilic trifluoromethylthiolating reagent **1**, which we recently developed in our lab.[6]



Scheme 1. Proposed radical trifluoromethylthiolation.

One challenge associated with this approach is the possible oxidation of the product alkyltrifluoromethylthioether by the oxidant that is used to reoxidize the silver(I) salt. To facilitate the formation of the alkyltrifluoromethylthioether and minimize the side reaction, we used a biphasic system that could physically separate the alkyltrifluoromethylthioether from the oxidant, as inspired by the emulsion

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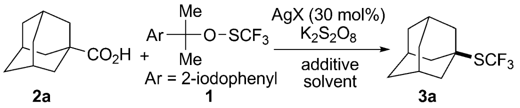
radical polymerization process.[11] We herein report the use of an aqueous emulsion, which was formed by the addition of sodium dodecyl sulfate (SDS) in water and dramatically accelerated a silver-catalyzed decarboxylative trifluoromethylthiolation of secondary and tertiary alkyl carboxylic acids under mild conditions. Radical-clock and radical-cyclization experiments suggested that the reaction proceeded through a free-radical process.

In order to test if the alkyl radical could be trapped by reagent **1**, we initially studied the conversion of 1-adamantane carboxylic acid to trifluoromethylthiolated adamantine using reagent **1** in the presence of catalytic amounts of different silver salts (20 mol%) and 1.0 equivalent of $K_2S_2O_8$ as the oxidant in different solvents.[12] As expected, the desired product was obtained in less than 12% yield when silver salts such as $AgNO_3$, AgOTf, $AgBF_4$, or AgOAc were used in different solvents, such as THF, CH_3CN, DMF, CH_2Cl_2, and acetone, at room temperature or at 50 °C (results not shown in the table). Furthermore, no significant improvement was observed when the reaction was conducted in a solvent mixture such as CH_3CN/H_2O (1/1; Table 1, entry 2), acetone/H_2O (1/1), or THF/H_2O (1/1). In contrast, the reaction generated the desired product in 60% yield when it was conducted in the presence of 1.0 equivalent of sodium dodecyl sulfate (SDS) in CH_3CN/H_2O (1/1; Table 1, entry 4). Decreasing the amount of SDS to 0.2 equivalent led to a higher yield (84%; Table 1, entry 5). Reactions in the presence of 0.2 equivalent of SDS conducted in acetone/H_2O (1/1) generated the product in 83% yield, while reactions in other mixed solvents, such as DMF/H_2O, THF/H_2O, or CH_2Cl_2/H_2O, were not effective at all (Table 1, entries 7–9). Interestingly, a higher percentage of water in the mixed solvent led to an increased yield of the product (92%; Table 1, entry 6). When the reaction was conducted in pure water with 0.2 equivalent of SDS, the desired product was generated in 98% yield as determined by ^{19}F NMR spectroscopy with an internal standard (Table 1, entry 10).[13] The yield decreased to 81% when 0.1 equivalent of SDS was used (Table 1, entry 11). The use of other surfactants, such as sodium methylsulfonate or sodium 4-dodecylbenzenesulfonate, under otherwise the same conditions resulted in much lower yields (Table 1, entries 12–14). Likewise, the use of other silver salts as the catalyst also led to lower yields (Table 1, entries 15–17). In the absence of the silver salt, no product was observed (Table 1, entry 18).

Table 1: Optimization of reaction conditions for silver-catalyzed decarboxylative trifluoromethylthiolation.[a]



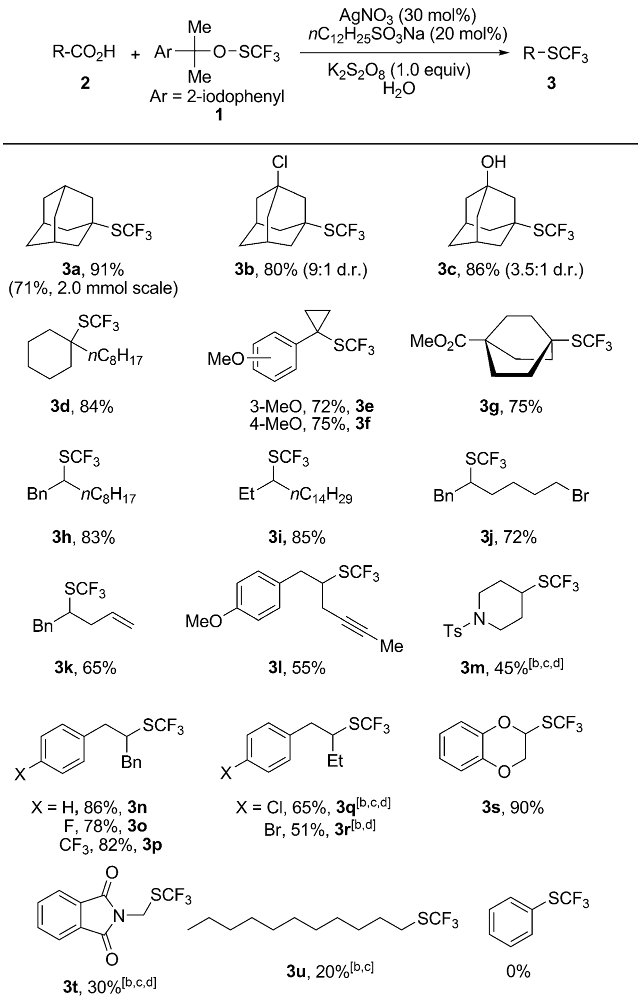
Entry	AgX	Additive	Solvent	Yield [%][a]
1	$AgNO_3$	–	CH_3CN	11
2	$AgNO_3$	–	CH_3CN/H_2O	12
3	$AgNO_3$	–	H_2O	<2
4	$AgNO_3$	$n\mathrm{C}_{12}\mathrm{H}_{25}\mathrm{SO}_3\mathrm{Na}$[c]	CH_3CN/H_2O	60
5	$AgNO_3$	$n\mathrm{C}_{12}\mathrm{H}_{25}\mathrm{SO}_3\mathrm{Na}$	CH_3CN/H_2O	84
6	$AgNO_3$	$n\mathrm{C}_{12}\mathrm{H}_{25}\mathrm{SO}_3\mathrm{Na}$	CH_3CN/H_2O[d]	92
7	$AgNO_3$	$n\mathrm{C}_{12}\mathrm{H}_{25}\mathrm{SO}_3\mathrm{Na}$	acetone/H_2O	66
8	$AgNO_3$	$n\mathrm{C}_{12}\mathrm{H}_{25}\mathrm{SO}_3\mathrm{Na}$	DMF/H_2O	<2
9	$AgNO_3$	$n\mathrm{C}_{12}\mathrm{H}_{25}\mathrm{SO}_3\mathrm{Na}$	CH_2Cl_2/H_2O	<2
10	$AgNO_3$	$n\mathrm{C}_{12}\mathrm{H}_{25}\mathrm{SO}_3\mathrm{Na}$	H_2O	98 (91)[e]
11	$AgNO_3$	$n\mathrm{C}_{12}\mathrm{H}_{25}\mathrm{SO}_3\mathrm{Na}$[f]	H_2O	81
12	$AgNO_3$	CH_3SO_3Na	H_2O	–
13	$AgNO_3$	4-($n\mathrm{C}_{12}\mathrm{H}_{25}$)$C_6H_4SO_3Na$	H_2O	70
14	$AgNO_3$	$n\mathrm{Bu}_4\mathrm{NHSO}_4$	H_2O	3
15	$AgSbF_6$	$n\mathrm{C}_{12}\mathrm{H}_{25}\mathrm{SO}_3\mathrm{Na}$	H_2O	11
16	AgOTf	$n\mathrm{C}_{12}\mathrm{H}_{25}\mathrm{SO}_3\mathrm{Na}$	H_2O	71
17	AgOAc	$n\mathrm{C}_{12}\mathrm{H}_{25}\mathrm{SO}_3\mathrm{Na}$	H_2O	59
18	–	$n\mathrm{C}_{12}\mathrm{H}_{25}\mathrm{SO}_3\mathrm{Na}$	H_2O	–

[a] Reaction conditions: 1-adamantane carboxylic acid (0.3 mmol), reagent **1** (0.45 mmol), AgX (30 mol%), additive (20 mol%), $K_2S_2O_8$ (0.3 mmol), solvent (2.0 mL, 1:1 (v/v) for mixed solvent) at 50 °C for 12 h. [b] Yields were determined by ^{19}F NMR spectroscopy with 1-fluoronaphthalene as the internal standard. [c] 1.0 equiv of SDS was used. [d] 1:2 (v/v). [e] Yield of isolated product. [f] 10 mol% of SDS was used.

With an efficient protocol for the decarboxylative trifluoromethylthiolation in hand, we next investigated its scope with aliphatic carboxylic acids (Table 2). The reaction conditions were quite general for tertiary and secondary alkyl carboxylic acids. A wide range of substrates with different functional groups, such as chloride, bromide, esters, and electron-rich arenes, underwent the efficient decarboxylative trifluoromethylthiolation to afford the corresponding products in good to excellent yields (Table 2, **3b–c**, **3j**, **3q–s**). A cyclopropyl carboxylic acid also underwent the decarboxylative trifluoromethylthiolation to give the corresponding product in good yields (Table 2, **3e–f**). Notably, no competing electrophilic trifluoromethylthiolation of electron-rich arenes was observed (Table 2, **3e–f**, **3l**, **3s**). In addition, the reaction was compatible with alkene and alkyne groups, thus illustrating an orthogonal reactivity of the silver-catalyzed decarboxylative trifluoromethylthiolation to classical electrophilic addition reactions (Table 2, **3k–l**). Reactions of primary alkyl carboxylic acids, however, occurred much slower and in lower yield than those of tertiary and secondary alkyl carboxylic acids. The desired products were obtained in only 20–30% yield in a mixture of CH_3CN/H_2O (Table 2, **3t–u**). The reaction of benzoic acid with reagent **1** under the optimized conditions did not generate the trifluoromethylthiolated product at all. With regard to a possible scale-up of the reaction, the yield of **3a** dropped slightly to 71% when the reaction was conducted on a 2.0 mmol scale (Table 2).

In general, silver-mediated oxidative decarboxylative functionalization was suggested to proceed through a radical pathway. The reactivity of the carboxylic acids in Table 2 decreases in the order of tertiary, secondary $>$ primary $\gg$ aromatic, which also indicates that a radical pathway is likely. In order to gain experimental evidence to support this assertion, two sets of experiments were conducted. In the first experiment, cyclopropyl carboxylic acid **4** was prepared as a radical clock and subjected to the reaction conditions. The ring-opening products were generated in 87% yield as a mixture of stereoisomers in a ratio of 3:1 [Eq. (1)]. No trifluoromethylthiolated cyclopropane derivative was observed by ^1H and ^{19}F NMR spectroscopy of the crude reaction mixture.

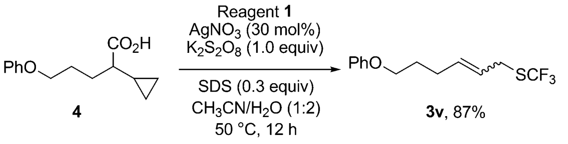
Table 2: Scope of silver-catalyzed decarboxylative trifluoromethylthiolation.[a]



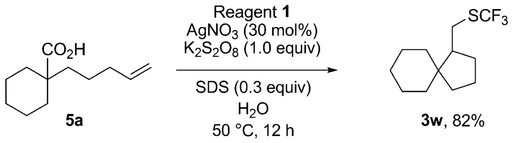
3a, 91% (71%, 2.0 mmol scale)
3b, 80% (9:1 d.r.)
3c, 86% (3.5:1 d.r.)
3d, 84%
3-MeO, 72%, 3e
4-MeO, 75%, 3f
3g, 75%
3h, 83%
3i, 85%
3j, 72%
3k, 65%
3l, 55%
3m, 45%[b,c,d]
X = H, 86%, 3n
F, 78%, 3o
CF_3, 82%, 3p
X = Cl, 65%, 3q[b,c,d]
Br, 51%, 3r[b,d]
3s, 90%
3t, 30%[b,c,d]
3u, 20%[b,c]
0%

[a] Reaction conditions: alkyl carboxylic acid (0.3 mmol), reagent 1 (0.45 mmol), $AgNO_3$ (30 mol%), $K_2S_2O_8$ (0.3 mmol), SDS (20 mol%), H_2O (2.0 mL) at 50°C for 12 h, yields of isolated products are given. [b] The reaction was conducted in CH_3CN/H_2O (1:2). [c] 24 h. [d] $CH_3(CH_2)_{11}SO_3Na$ (0.3 mmol) was used.

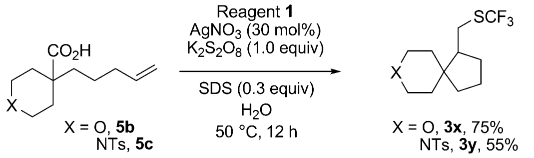
In the second set of experiments, compounds **5a–c** were synthesized and subjected to the silver-catalyzed reactions with reagent **1** in water to generate the ring-closed trifluoromethylthiolated spiro products **3w–y** in 82%, 75%, and 55% yield, respectively [Eq. (2),(3)]. We reasoned that the radicals generated from the silver-mediated oxidative decarboxylation undergo irreversible intramolecular 5-*exo*-cyclization at a much faster rate than those of the bimolecular radical quenching process. Both sets of experiments strongly suggested the involvement of a free-radical mechanism in the silver-catalyzed decarboxylative trifluoromethylthiolation. The experiments further suggested that the formation of primary alkyl radicals from primary alkyl carboxylic acids was difficult under the current conditions.[10] Once the primary alkyl radical was formed, it could easily react with reagent **1** to form the trifluoromethylthioether.



4
3v, 87%
(1)

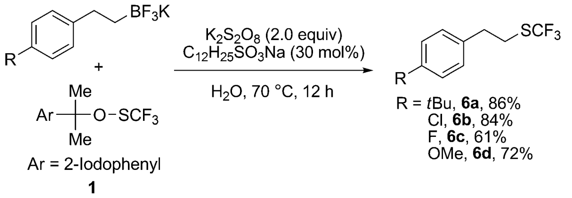


5a
3w, 82%
(2)



X = O, 5b
NTs, 5c
X = O, 3x, 75%
NTs, 3y, 55%
(3)

To probe if a free alkyl radical can easily react with reagent **1** to form alkyl trifluoromethylthioether, we studied the reaction of alkyl trifluoroborate potassium salts with reagent **1** in the absence of a silver catalyst, as it is well-known that alkyl radicals can be easily formed from alkyl trifluoroborates in the presence of an oxidant.[14] Reactions of four different primary alkyl trifluoroborate salts with reagent **1** formed the corresponding alkyl trifluoromethylthioether in good yields [Eq. (4)]. The reactions occurred in much lower yields in the absence of SDS. These results supported our assertion that free primary alkyl radicals can easily react with reagent **1** to form the products.



R = *t*Bu, 6a, 86%
Cl, 6b, 84%
F, 6c, 61%
OMe, 6d, 72%
(4)

To gain some understanding about the effect of the surfactant on the silver-catalyzed decarboxylative trifluoromethylthiolation, we studied the kinetics of the reactions in the presence of different amount of SDS by monitoring the reaction with ^{19}F NMR spectroscopy. A comparison of the silver-catalyzed reactions of 1-adamantane carboxylic acid with reagent **1** in the presence of 0, 6, 10 and 20 mol% SDS is shown in Figure 1. The reaction in the absence of SDS occurred sluggishly with less than 15% conversion even after 6 hours. In contrast, the reaction occurred much faster in the presence of SDS. Interestingly, reactions in the presence of 10 mol% SDS or above were significantly faster and occurred in much higher yields than those using 6 mol% SDS. Notably, an emulsion was formed for reactions using 10 or 20 mol% SDS, which indicated the formation of "oil-in-water" droplets[15] (Figure 1, right). The size of the droplets was deter-

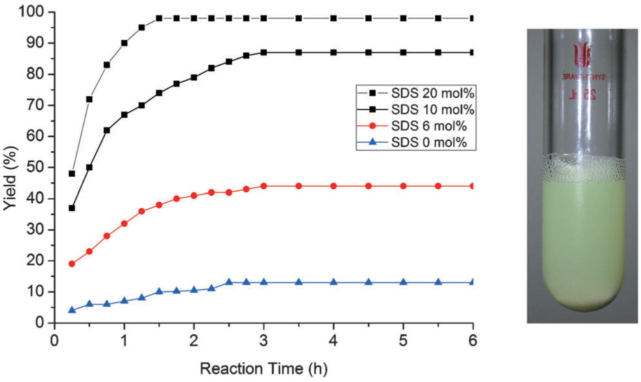
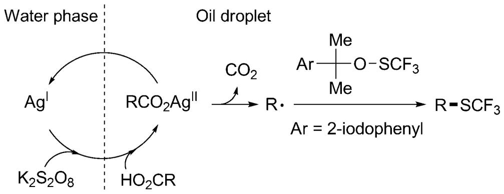


Figure 1. Left: A comparison of the silver-catalyzed decarboxylative trifluoromethylthiolation in the presence of 0, 6, 10, and 20 mol% of SDS. Right: Image of the reaction mixture.

mined to be 230–280 nm by dynamic light scattering (DLS) measurements.

Based on these experimental results, we proposed a working mechanism for the micelle-accelerated, silver-catalyzed decarboxylative trifluoromethylthiolation (Scheme 2). Initially, the organic compounds were emulsified in a solution of SDS and water to form "oil-in-water" droplets. Silver(II) carboxylates, which were generated from the reactions of silver(I) salts with the alkyl carboxylic acids in the presence of $K_2S_2O_8$, could penetrate into the droplets. The alkyl radical, generated from the silver(II) carboxylate through a concerted decarboxylation pathway,[16] then reacted with reagent **1** to form the corresponding product and a tertiary alkoxy radical. The alkoxy radical decomposed to form 1-(2-iodophenyl)-ethanone. This ketone was isolated in every silver-catalyzed decarboxylative trifluoromethylthiolation reaction, in agreement with the current mechanistic assumption. On the other hand, in the water phase, the silver(I) intermediate was easily reoxidized by $K_2S_2O_8$ to regenerate the active silver(II) catalyst.



Scheme 2. Proposed mechanism.

In summary, we have developed a silver-catalyzed decarboxylative trifluoromethylthiolation of secondary and tertiary alkyl carboxylic acids under mild conditions. The reaction tolerates a wide range of functional groups. In addition, the reactions were dramatically accelerated by their performance in an aqueous emulsion, which was formed by the addition of sodium dodecyl sulfate (SDS) to water. The use of water as the solvent for organic reactions is advantageous, as it is cheap, nontoxic, and nonflammable, and has extraordinary solvent effects.[13,17] Radical-clock and radical-cyclization experiments suggested that the reaction proceeded through a free-radical process. The effect of aqueous emulsions on other reactions is currently investigated in our laboratory.

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Keywords: decarboxylation · fluorine · radicals · silver · trifluoromethylthiolation

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