Oxidative decarboxylative radical trifluoromethylthiolation of alkyl carboxylic acids with silver(i) trifluoromethanethiolate and selectfluor†

Bin He, Zhiwei Xiao, Hao Wu, Yong Guo, Qing-Yun Chen* and Chao Liu*

A straightforward silver-mediated oxidative decarboxylative radical trifluoromethylthiolation reaction of aliphatic carboxylic acid is described. This reaction operates under mild conditions and allows the synthesis of various valuable alkyltrifluoromethylthioethers from alkyl carboxylic acids and convenient nucleophilic AgSCF₃ reagent. It provides a practical and efficient approach for the preparation of alkyltrifluoromethylthioethers.

Introduction

The selective introduction of fluorine and fluorine-containing groups into organic molecules can dramatically alter their physical, chemical and biological properties.¹ As a star group in organofluorine chemistry in recent years, the trifluoromethylthio group (CF₃S) has attracted much attention because of its electron-withdrawing nature, unique high lipophilicity and metabolic stability. Compounds containing CF₃S are frequently found in pharmaceuticals and agrochemicals.² Many methods are now available to efficiently synthesize various organic substrates containing CF₃S on the basis of electrophilic, nucleophilic, radical, and oxidative direct trifluoromethylthiolation.³ Among them, more popular strategy of choice for the introduction of the CF₃S group into organic substrates is the direct formation of the C–SCF₃ bond. Compared with numerous methods for the efficient formation of C(sp³)–SCF₃ and C(sp)–SCF₃ bonds, relatively limited methods are currently available for the general and site-specific formation of various C(sp³)–SCF₃ bonds. The resulting alkyltrifluoromethylthioethers are mainly accessible by the nucleophilic, electrophilic, or radical trifluoromethylthiolation of the corresponding alkanes or olefins. For examples, a direct dehydroxytrifluoromethylthiolation of alkyl alcohols using AgSCF₃ and n-Bu₄NI has been reported to efficiently form C(sp³)–SCF₃ bonds.⁴ A direct nucleophilic trifluoromethylthiolation of various alkyl chlorides, bromides and tosylates with AgSCF₃ was described in the presence of n-Bu₄NI or a combination of n-Bu₄NI/nBu₄NBr.⁵ Several electrophilic trifluoromethylthiolation reagents have been reported for effective trifluoromethylthiolation of organometallic nucleophilic or direct z-SCF₃ of carbonyl compounds.⁶ Recently, the direct trifluoromethylthiolation of unactivated C(sp³)–H by AgSCF₃/K₂S₂O₈ was described via a radical pathway.⁷

Aliphatic carboxylic acids are cheap and abundant raw materials, and have been widely used as desirable starting materials for the preparation of many important and valuable compounds with different functional groups. The fundamental transformation process involves decarboxylation with the release of traceless by-product CO₂ to generate alkyl radicals, and their subsequent reactions with a variety of reagents lead to efficient formation of many functionalized compounds. This important transformation process has been applied in several elegant decarboxylative fluorinations.⁸ Shen and co-workers described the silver-catalyzed oxidative decarboxylative trifluoromethylthiolation of alkyl carboxylic acids with electrophilic trifluoromethylthiolating reagent I in an aqueous emulsion (Scheme 1a).⁹ Very recently, Glorius group reported the visible-light-promoted decarboxylative trifluoromethylthiolation of alkyl carboxylic acids with electrophilic trifluoromethylthiolating reagent II under mild conditions (Scheme 1b).¹⁰ Although these methods are effective for the site-selective formation of C(sp³)–SCF₃, they utilize relatively expensive electrophilic trifluoromethylthiolating reagents as the CF₃S source, which are commonly prepared from readily available AgSCF₃.

Recently, we developed a practical and efficient method for the direct trifluoromethylthiolation of unactivated C(sp³)–H bonds by AgSCF₃/K₂S₂O₈ under mild conditions.¹¹ However, the regioselectivity of the reaction generally depends on the alkyl radical stability in situ formed, and several regioselective isomers are often generated in many cases. With the aim of overcoming the issue and further expanding the scope of the oxidative radical trifluoromethylthiolation methodologies,
herein we report an efficient and general site-selective preparation of alkyltrifluoromethylthioethers by means of oxidative decarboxylative radical trifluoromethylthiolation of various aliphatic carboxylic acids by AgSCF₃/selectfluor (Scheme 1c).

**Results and discussion**

Our study commenced by examining the oxidative decarboxylative trifluoromethylthiolation reaction of decanoic acid 1a with AgSCF₃ (ref. 9) (1.0 equiv.) at 60 °C for 4 hours in the presence of different oxidants and solvents (Table 1). Unfortunately, no desired trifluoromethylthiolation product was observed with K₂S₂O₈ as oxidant in CH₃CN (Table 1, entry 1). To our surprise, under similar conditions, Na₂S₂O₈ resulted in the formation of oxidative decarboxylative trifluoromethylthiolation products (Table 1, entry 2). However, after careful analysis and spectroscopic characterization, it was found that the products are not the desired product 2a, but a variety of di-trifluoromethylthiolation isomer mixture, which is presumably due to concurrent occurrence of both direct trifluoromethylthiolation of C(sp³)-H and the desired oxidative decarboxylative trifluoromethylthiolation of 1a (Scheme 2). In order to suppress the undesired direct trifluoromethylthiolation of C(sp³)-H, different solvents including DMSO, DMF, acetone, and CH₂Cl₂/CH₂CN/H₂O were screened. However, the reactions led to no formation of the desired products. When AgSCF₃ was used as the limiting reagent with 5 equiv. of 1a in CH₃CN in the presence of Na₂S₂O₈, a complex di-trifluoromethylthiolation isomer mixture was still obtained (Table 1, entry 3).

Next, we were delighted to find that when selectfluor was used as oxidant, the desired oxidative decarboxylative mono-trifluoromethylthiolation product 2a was obtained and no undesired di-trifluoromethylthiolation products were observed, demonstrating the successful suppression of the undesired direct trifluoromethylthiolation of C(sp³)-H (Table 1, entry 4). Notably, neither competitive oxidative decarboxylative fluorination reaction was observed, which was considered to presumably occur under the reaction conditions according to literature. These results demonstrate that oxidative decarboxylative trifluoromethylthiolation under the reaction conditions is the predominant process presumably because selectfluor would not activate the C(sp³)-H to give the corresponding key C(sp³)-centered radical intermediate. Among several common reaction solvents we screened, acetone was the best one and provided 31% yield of the desired product 2a (Table 1, entries 4–7). It is worth noting that water was harmful for the reaction and resulted in no formation of the desired product (Table 1, entry 8). Then various oxidants such as N-fluorobenzenesulfonimide (NFSI), and 1-fluoro-2,4-pentanediol (PF) were further tested, it turned out that worse results were observed (Table 1, entries 9 and 10). By changing the amount of AgSCF₃/selectfluor, the yield of the desired product 2a was further improved to 65% (Table 1, entries 11 and 12). The influence of several ligands were also estimated, 2,6-lutidine gave the best yield of 82% (Table 1, entry 13), which might coordinate with active Ag species to enhance their stability during the reaction. Furthermore, the replacement of AgSCF₃ with CuSCF₃ led to no formation of the desired product, demonstrating the key role of the free silver cation for the reaction (Table 1, entry 14). All these experimental results indicate that a combination of AgSCF₃ (2.0 equiv.)/selectfluor (4.0 equiv.)/2,6-lutidine (2.0 equiv.) in acetone at 60 °C for 4

![Scheme 2](image)

**Table 1** Optimization of reaction conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>AgSCF₃ (equiv.)</th>
<th>Oxidant (equiv.)</th>
<th>Solvent</th>
<th>Yield (%)</th>
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<tr>
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<td>CH₃CN</td>
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</tr>
<tr>
<td>4</td>
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<td>Selectfluor (2.0)</td>
<td>Acetone</td>
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<td>1.0</td>
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<td>CH₃CN</td>
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<tr>
<td>7</td>
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<td>Acetone/CH₃CN</td>
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<td>Acetone/H₂O</td>
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* Reaction conditions: decanoic acid (0.2 mmol, 1.0 equiv.), AgSCF₃ (1.0–2.0 equiv.), oxidant (2.0–4.0 equiv.), and solvent (2.0 mL) at 60 °C for 4 hours under Ar atmosphere. * Yields were determined by 19F NMR spectroscopy with benzotrifluoride as the internal standard. * A di-trifluoromethylthiolation isomer mixture was obtained. * Acetone/CH₃CN (1 : 1 v/v) was used. * Acetone/H₂O (4 : 1 v/v) was used. * 2,6-Lutidine (2.0 equiv.) was used as ligand. * CuSCF₃ was used instead of AgSCF₃.
hours is established as the optimal conditions for oxidative
decarboxylative trifluoromethylthiolation reactions of various
aliphatic carboxylic acids.

With the optimal conditions in hand, we then explored the
generality of the oxidative decarboxylative trifluoromethyl
thiolation reactions with a variety of aliphatic carboxylic acids
(Scheme 3). It was found that various aliphatic carboxylic acids
including primary, secondary and tertiary carboxylic acids are
all suitable substrates for the oxidative decarboxylative trifluoromethylthiolation reactions. For example, a number of
primary alkyl carboxylic acids underwent smooth oxidative decarboxylative trifluoromethylthiolation to give the desired alkylthi
fluoromethylthioethers in isolated yields of 48–84% (2a–k).
Secondary aliphatic carboxylic acids could also be subjected to the
reactions to provide the corresponding products in modest to good
yields (2l–q). When tertiary alkyl carboxylic acids were employed
as the substrates, the desired oxidative decarboxylative trifluoromethylthiolation products were generated in acceptable yields (2r, s). It should be mentioned that reduced reaction time
should be applied to the aliphatic carboxylic acids 1j and 1l since
significant decrease in the yields of the corresponding desired
trifluoromethylthiolation products was observed under the
optimal reaction conditions,10 which might be due to the insta
bility of the corresponding products 2j and 2l under the reaction
conditions. With regard to the potential of the reaction in late
stage functionalization of valuable synthetic intermediates, a
structurally complicated biologically active steroid derivative was
applied to the oxidative decarboxylative trifluoromethylthiolation
reaction and the desired product 2k was produced smoothly in
good isolated yield. Its structure was unambiguously assigned by
various spectral analysis, including X-ray single-crystal analysis.

To gain some understanding on the reaction pathway,
a radical inhibitor (hydroquinone) or a radical scavenger
(2,2,6,6-tetramethyl-1-piperidinyloxy, TEMPO) were added to
the reaction of 1a, and a sharp decrease in the yield was observed
for both cases.10 These preliminary results combined with previous reports on silver-mediated oxidative decarboxylative functionalization7a–e indicate that the reaction proceeds
through a radical pathway.10 First, AgSCF3 is oxidized by selectfluor to generated Ag[n]SCF3 intermediate, CF3S radical or
CF3SSCF3, Ag[n] combines with alkyl carboxylic acids to
generate the corresponding alkyl radical via decarboxylation
pathway. Then, the produced alkyl radical attacks a CF3S radical, CF3SSCF3, or abstracts the CF3S ligand of Ag[n]SCF3
intermediate to provide the desired oxidative decarboxylative
trifluoromethylthiolation product (Scheme 4).

Conclusions

In conclusion, we developed a practical and effective silver
mediated oxidative decarboxylative trifluoromethylthiolation
reaction of aliphatic carboxylic acids using nucleophilic AgSCF3
as CF3S source and selectfluor as the oxidant. The reaction can
be applied to primary, secondary and tertiary alkyl carboxylic
acids under mild conditions and is tolerant of many functional
groups. It represents an alternative approach for site-selective
construction of C(sp3)–SCF3 bonds.

Acknowledgements

The authors gratefully acknowledge the financial support from
the National Basic Research Program of China (2012CB821600),
the National Natural Science Foundation of China (21032006,
21302207, 21421002).

Notes and references

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The exact molecular formula of silver(i) trifluoromethanethiolate prepared according to the literature (G. Teverovskiy, D. S. Surry and S. L. Buchwald, Angew. Chem., Int. Ed., 2011, 50, 7312) is 3AgSCF3·CH3CN.78 For simplicity, we used AgSCF3 instead of 3AgSCF3·CH3CN in the text.

See the ESI for details.