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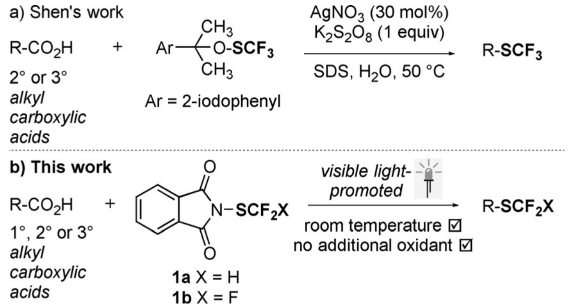
Visible Light-Promoted Decarboxylative Di- and Trifluoromethylthiolation of Alkyl Carboxylic Acids

Lisa Candish[+], Lena Pitzer[+], Adrián Gómez-Suárez, and Frank Glorius*[a]

Abstract: Described herein is a new and straightforward decarboxylative di- and trifluoromethylthiolation of alkyl carboxylic acids promoted by visible light. This approach enables the synthesis of biologically relevant alkyl SCF_2H and SCF_3 compounds from cheap and abundant carboxylic acids. The method is operationally simple, using irradiation from household light sources, and its mild reaction conditions make it tolerant of a range of functional groups. The strategy employs electrophilic phthalimide-derived di- and trifluoromethylthiolation reagents and exploits the ability of the imidyl radical to carry a radical chain.



Scheme 1. Di- and trifluoromethylthiolation of alkyl carboxylic acids. SDS = sodium dodecyl sulfate.

The incorporation of fluorine atoms into molecules can profoundly influence their physical, chemical, and biological properties.[1] Accordingly, the systematic derivatization of drug candidates through the inclusion of different fluorine-containing functional groups has become common practice in drug discovery. For example, the incorporation of the trifluoromethylthio group is known to increase a molecule's lipophilicity and metabolic stability.[2] In addition, the difluoromethylthio group has recently been found to be a highly lipophilic hydrogen bond donor, and is a potential lipophilic OH or NH surrogate.[3] Therefore, the development of mild and straightforward methodologies, capable of tolerating a wide range of functional groups, for the incorporation of SCF_2X (where X = H or F) moieties would be highly desirable.

Arguably, the most efficient method for the synthesis of alkyl di- and trifluoromethylthiolated compounds is through the direct formation of the $C{-}SCF_2X$ bond, as this circumvents the need for initial thiol formation. To date, however, there is only one reported method, from the group of Shen, for the direct formation of $C(sp^3_{alkyl}){-}SCF_2H$ bonds in β-ketoesters and 2-oxindoles, utilizing the phthalimide electrophilic reagent **1a** (see Scheme 1) developed by the same group.[4] In comparison, there has been considerably more chemistry developed for the direct formation of $C(sp^3_{alkyl}){-}SCF_3$ bonds. For example, several methodologies have been reported for the reaction of alkyl halides with nucleophilic SCF_3 transfer reagents,[5] the electrophilic trifluoromethylthiolation of organometallic nucleophiles,[6] or the activation of C–H bonds adjacent to carbonyl compounds.[7] Moreover, incorporation of the SCF_3 group can also be achieved through radical pathways, either via the formation of the SCF_3 radical[5b,8] or through the single electron oxidation of C–H bonds and reaction of the generated alkyl radical with the highly toxic gas SCF_3Cl,[8a,9] or, more recently, $AgSCF_3$.[10] Controlling the regioselectivity of such reactions is often challenging, and the product formed is generally dictated by radical stability.

Due to their cheap and abundant nature, alkyl carboxylic acids are desirable starting materials for the synthesis of valuable compounds. In addition, their decarboxylation, which yields the traceless by-product CO_2, is an excellent method for accessing alkyl radicals, which can be readily functionalized. Recently, Shen and co-workers reported the silver(I)-catalyzed decarboxylative trifluoromethylthiolation of alkyl carboxylic acids using $AgNO_3$ and $K_2S_2O_8$ as oxidant (Scheme 1 a).[11] While Shen's method was effective for the synthesis of 2° and 3° alkyl products, it was found to be inefficient for the preparation of 1° alkyl-SCF_3 species. Since 2013, visible light-promoted[12] decarboxylation has emerged as a very mild approach for the generation of alkyl radicals from carboxylic acids.[13] As a result, several decarboxylative processes, such as reductions,[14a,b] arylations,[14c,d] vinylations,[14e,f] alkylations,[14h,i] oxidative amidation,[14j] fluorinations,[14k–m] and alkynylations[14n,o] have been reported.

With the aim of further expanding the field of visible light-promoted decarboxylative functionalization, improving the scope of radical trifluoromethylthiolation methodologies, and

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[a] *Dr. L. Candish,[+] L. Pitzer,[+] Dr. A. Gómez-Suárez, Prof. Dr. F. Glorius*
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstrasse 40, 48149 Münster (Germany)
E-mail: glorius@uni-muenster.de

[+] *These authors contributed equally to this work.*

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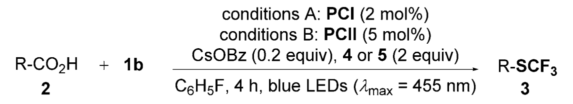
thus provide a new method for the underdeveloped field of difluoromethylthiolation, herein we disclose a visible light-promoted decarboxylative di- and trifluoromethylthiolation of alkyl carboxylic acids (Scheme 1 b). The method utilizes phthalimide derived electrophilic di-[4] and trifluoromethylthiolation[15] reagents **1 a** and **1 b** and is efficient for the transformation of 1°, 2°, and 3° carboxylic acids, under very mild (reactions run at room temperature using low-energy visible-light irradiation) and redox neutral conditions, thus not requiring the use of additional oxidants.

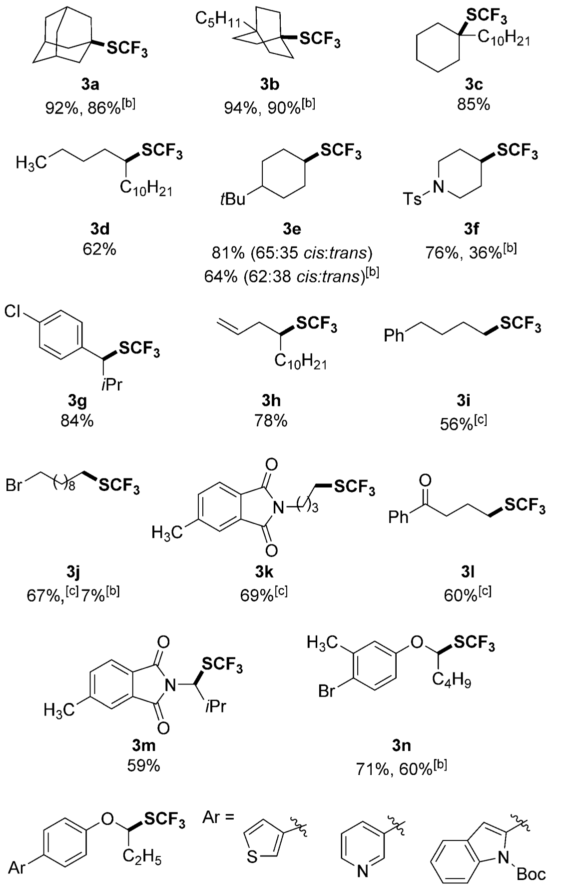
Investigations commenced with the reaction of tertiary 1-adamantanecarboxylic acid and electrophilic SCF_3-reagent **1 b** (2 equiv) in the presence of Cs_2CO_3 (1.5 equiv) and 2 mol % of photocatalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (**PCI**, $dF(CF_3)ppy = 2$-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine, dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) in 1,2-dichloroethane (DCE) under irradiation with blue LEDs ($\lambda_{max} = 455$ nm). Pleasingly, we observed the formation of the desired trifluoromethylthiolated adamantyl product **3 a** in 45 % yield (see the optimization table in Section 3 of the Supporting Information). Changing the solvent to chlorobenzene afforded the product in 66 % yield, whereas using either 1.0 or 0.2 equiv of cesium benzoate (CsOBz) gave improved, comparable yields of 70 % and 71 % respectively. At this point, alternative trifluoromethylthiolation reagents were explored; however, the phthalimide reagent **1 b** provided the product in highest yield (for details, see the Supporting Information). The reaction displayed a high solvent dependency, with fluorobenzene found to give the highest yield (92 %).

Over the course of the optimization, *bis*-trifluoromethylthiolation was observed under a number of conditions, presumably resulting from hydrogen atom abstraction from the product by the intermediate phthalimidyl radical, and subsequent SCF_3-transfer from reagent **1 b** to the resultant alkyl radical (for further details, see the Supporting Information). To suppress this undesired pathway, the addition of a sacrificial hydrogen atom donor, mesitylene (**4**) or 3-(methyl) toluate (**5**), was investigated. Both additives were found to modestly increase the yield of the trifluoromethylthiolated adamantyl product **3 a** (Table 1, conditions A). However, these additives were found to have a much more significant effect for other substrates and thus were used when exploring the reaction scope.

With the optimized conditions in hand, the generality of our light-mediated decarboxylative trifluoromethylthiolation protocol was investigated (Table 1). The reaction was found to proceed well when employing tertiary, secondary, and benzylic carboxylic acids (**3 a**–**h**). Gratifyingly, the trifluoromethylthiolation of primary acids was also found to proceed smoothly when 3 mol % of the photocatalyst was used, providing the products in moderate to good yields (**3 i**–**l**). The reaction was found to be tolerant of protected amines (**3 f** and **3 k**), aryl and alkyl halides (**3 g** and **j**), terminal alkenes (**3 h**), and ketones (**3 l**). Following this, the trifluoromethylthiolation of α-amino and α-oxo acids was also explored, with the products isolated in acceptable yields of 59 % and 71 %, respectively (**3 m** and **3 n**). Given the mild nature of visible light-promoted processes, they have the potential to become an important tool for the late-stage functionalization of advanced synthetic intermediates.[16] Heteroarenes are prevalent in many biologically relevant molecules, though they are also susceptible to nucleophilic radical addition.[17] Therefore, to determine whether our protocol was tolerant of heteroarenes, carboxylic acids containing thiophene, pyridine, and indole motifs were subjected to the reaction conditions. Gratifyingly, they provided the desired products in moderate to high yields (**3 o**–**q**) with no by-products resulting from radical addition to the heteroarenes observed.

Table 1. Scope of the visible light-promoted decarboxylative trifluoromethylthiolation.[a]





3a 92%, 86%[b]
3b 94%, 90%[b]
3c 85%
3d 62%
3e 81% (65:35 *cis:trans*) 64% (62:38 *cis:trans*)[b]
3f 76%, 36%[b]
3g 84%
3h 78%
3i 56%[c]
3j 67%,[c] 7%[b]
3k 69%[c]
3l 60%[c]
3m 59%
3n 71%, 60%[b]
3o 76%
3p 49%
3q 83%

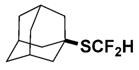
[a] Reaction conditions: alkyl carboxylic acid **2** (0.3 mmol), reagent **1 b** (2 equiv), **PCI** (2 mol %), **4** or **5** (2 equiv) CsOBz (0.2 equiv) fluorobenzene (6 mL), RT, 4 h, blue LEDs ($\lambda_{max} = 455$ nm). Percentage values show yields of isolated products. [b] Conditions B, same conditions as [a] but using **PCII** (5 mol %) instead of **PCI**. [c] Reaction performed with 3 mol % **PCI**.

During optimization of the photocatalyst, we found that metal-free trifluoromethylthiolation of carboxylic acids could be achieved employing the strongly oxidizing organic dye 9-mesityl-10-methylacridinium perchlorate (**PCII**). Organic dyes are inexpensive photosensitizers that have found application in several visible light-promoted decarboxylative processes.[14a,b,18] Using the standard reaction conditions, but with 5 mol% of **PCII** instead of **PCI**, 1-adamantyl carboxylic acid (**2a**) was converted to the corresponding SCF_3-product **3a** in 86% yield after 4 h (cf. 92% with **PCI**) (Table 1, conditions B). With these metal-free conditions, the trifluoromethylthiolation protocol was examined using 1°, 2°, and 3° carboxylic acids. Gratifyingly, using **PCII**, the tertiary SCF_3 product **3b** was isolated in 90% yield (cf. 94% with **PCI**). Secondary and α-oxo acids also afforded the corresponding products **3e**, **3f**, and **3n** in 64%, 36%, and 60% isolated yield, respectively (cf. 81%, 76%, and 71% with **PCI**). Unfortunately, **PCII** failed to effect formation of the primary trifluoromethylthiolated product (**3j**), which was isolated in only 7% yield.

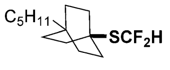
Having explored the scope of the trifluoromethylthiolation protocol, we turned our attention to the decarboxylative difluoromethylthiolation (Table 2). We were pleased to find that employing the reaction conditions A, although with longer reaction times (14 h), the desired products were isolated in similar yields to the corresponding alkyl-SCF_3 analogs. Tertiary difluoromethylthiolated products were isolated in excellent yields (**6a** and **6b**), whereas secondary (**6c**), primary (**6d**), and α-oxo products (**6e**) were afforded in good yields. As expected, the mild reaction conditions were found to be tolerant of a number of functional groups, highlighting the value of this process to the underdeveloped field of $C(sp^3_{alkyl})–SCF_2H$ bond formation.

Table 2. Scope of the decarboxylative difluoromethylthiolation.[a]

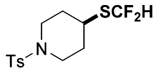
$$\underset{\mathbf{2}}{\text{R-CO}_2\text{H}} + \mathbf{1a} \xrightarrow[\text{blue LEDs } \lambda_{max} = 455\text{ nm}]{\mathbf{PCI}\text{ (2 mol\%), CsOBz (0.2 equiv), }\mathbf{4}\text{ or }\mathbf{5}\text{ (2 equiv), C}_6\text{H}_5\text{F, 14 h}} \underset{\mathbf{6}}{\text{R-}\mathbf{SCF_2H}}$$



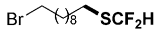
6a
88%



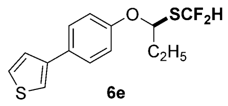
6b
90%



6c
73%



6d
74%[b]



6e
68%

[a] Reaction conditions: alkyl carboxylic acid **2** (0.3 mmol), reagent **1a** (2 equiv), **PCI** (2 mol%), **4** or **5** (2 equiv) CsOBz (0.2 equiv) fluorobenzene (6 mL), RT, 14 h, blue LEDs ($\lambda_{max} = 455$ nm). Percentage values show yields of isolated products. [b] Reaction performed with 3 mol% **PCI**.

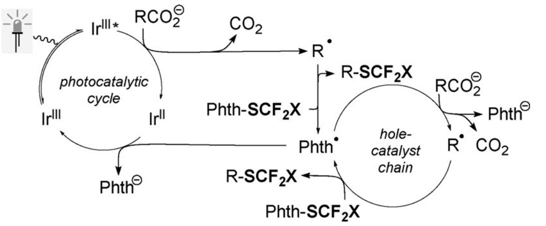


Figure 1. Proposed decarboxylative di- and trifluoromethylthiolation mechanism. Phth = phthalimide, counterions omitted for clarity.

Based on the mechanistic research previously reported for visible light-promoted decarboxylative functionalizations, and the results of Stern–Volmer luminescence quenching studies (see the Supporting Information), we propose a mechanism for the di- and trifluoromethylthiolation reactions as shown in Figure 1. Photoexcitation of the Ir^{III} photocatalyst produces a strong oxidant ($E^{red}_{1/2}([Ir^{III}*/Ir^{II}]) = +1.21$ V vs. SCE in CH_3CN) that should promote a thermodynamically favorable single-electron oxidation of the alkyl carboxylate (hexanoate ion $E^{red}_{1/2} = +1.16$ V vs. SCE in CH_3CN).[19] Decarboxylation of the carboxylate radical would afford the corresponding alkyl radical, and direct SCF_2X (X = H or F) transfer from the phthalimide reagents (**1a,b**) should provide the desired product and the phthalimidyl radical. Oxidation of the Ir(II) complex through single-electron transfer (SET) from the phthalimidyl radical would then regenerate the photocatalyst and furnish the phthalimide anion. Alternatively, given that imidyl radicals can act as competent chain carriers,[20] following photoinitiation, the phthalimidyl radical may participate in a hole-catalyst chain process,[21] whereby it oxidizes a second alkyl carboxylate to provide the alkyl radical following decarboxylation. Subsequent SCF_3 group transfer reforms the phthalimidyl radical and provides the desired product. A radical chain mechanism has not yet been proposed for a visible light-promoted decarboxylative process, hence, the reaction's quantum yield was measured (quantum yield: $\Phi = 1.7$, see the Supporting Information).[22] The quenching fraction (Q) was also measured to determine what fraction of the excited $Ir^{III}*$ complexes participate in productive electron transfer processes. Using the method described by Yoon,[22] the quenching fraction was found to be 0.14, suggesting that 86% of excited complexes relax through radiative decay. The chain length was therefore determined (by dividing the quantum yield by the quenching fraction (Φ/Q)) to be 12, suggesting a mechanism involving a smart initiated hole-catalyst chain.[21]

In conclusion, we have developed a new operationally simple methodology for the visible light-promoted di- and trifluoromethylthiolation of alkyl carboxylic acids. Mechanistic analysis suggests a smart photoinitiated hole-catalyst chain is operational. The method is efficient for tertiary, secondary, and primary alkyl carboxylic acids, and its mild nature makes it tolerant to a range of functionalities, including heteroarenes. In addition, an alternative metal-free protocol for the efficient trifluoromethylthiolation of secondary and tertiary carboxylic acids was also developed. Moreover, our decarboxylative difluoromethylthiolation process represents only the second reported method for the direct formation of $C(sp^3_{alkyl})–SCF_2H$ bonds and should act as an enabling tool for late-stage difluoromethylthiolation reactions.

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Keywords: decarboxylation · difluoromethylthiolation · photocatalysis · trifluoromethylthiolation · visible light

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