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Silver-Mediated Oxidative Decarboxylative Trifluoromethylthiolation of Coumarin-3-carboxylic Acids

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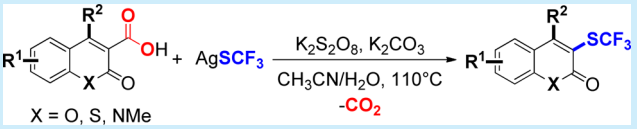
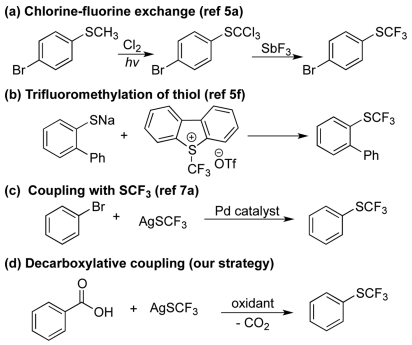
Supporting Information

ABSTRACT: The introduction of trifluoromethylthio groups into organic compounds, in particular heterocycles, is important because of the prevalence of these structures in medicinally and agriculturally relevant molecules. Herein, the silver-mediated oxidative decarboxylative trifluoromethylthiolation of coumarin-3-carboxylic acids is reported. This methodology utilizes existing carboxylic acid functionalities for the direct conversion to CF_3S groups and results in a broad scope of 3-trifluoromethylthiolated coumarins, including analogues of natural products, in moderate to excellent yields.



Fluorine is prevalent in numerous agrochemicals and pharmaceuticals.[1] In medicinal chemistry, the introduction of fluorine-containing groups into organic molecules can significantly improve the bioavailability, lipophilicity, and metabolic stability of a drug.[2] In particular, the trifluoromethylthio (CF_3S) group has received attention due to its strong electronegativity and high lipophilicity.[3] Although methods for the direct fluorination (F) and trifluoromethylation (CF_3) of organic molecules have received considerable recent attention, synthetic strategies for the late stage trifluoromethylthiolation are rare.[4] Traditional methods to introduce the CF_3S group rely on the fluorination of sulfur-containing substrates either by halogen−fluorine exchange of chloro- or bromomethyl sulfides (Scheme 1a) or the trifluoromethylation of thiols (Scheme 1b).[5]

Scheme 1. General Strategies To Generate Trifluoromethylthioarenes



Unfortunately, these methodologies require additional steps and reagents in addition to harsh reaction conditions. Alternatively, the direct installation of the CF_3S group into organic compounds could enable the more efficient construction of CF_3S containing compounds (Scheme 1c). A number of reactions that follow this reactivity pattern have been reported (Scheme S1). For example, such reactivity has recently been accomplished by addition of electrophilic CF_3S^+ reagents (Scheme S1a),[6] coupling with CF_3S^- salts (Scheme S1b-d),[7] and $CF_3S^\bullet$ triggered cyclization reactions (Scheme S1e)[8] that form the desired C-SCF_3 bond. Unfortunately, most of these methods require complex substrate synthesis or prefunctionalization steps to generate the required starting materials or CF_3S reagents.

An ideal transformation would be the direct conversion of an ester or carboxylic acid to a CF_3S group because esters are often introduced during heterocycle syntheses. For example, in the Feist−Benary furan synthesis, the Knorr pyrrole synthesis, and the Hantzsch dihydropyridine synthesis, the ester functionalities result from construction of the heterocyclic cores. The corresponding carboxylic acids are easily accessed from hydrolysis of these esters, making the acids ideal coupling partners to install the desired CF_3S group (Scheme 1d).

Decarboxylative coupling reactions have become reliable methodologies for the direct and selective functionalization of (hetero)aromatic acids.[9] Early work pioneered by Goossen and co-workers focused on the redox-neutral decarboxylative coupling of benzoic acids with aryl halides.[9a,10] Oxidative variants, pioneered by Myers[11] and others,[12] have also been developed and enable coupling with reaction partners such as alkenes,[11] indoles,[12b] benzoxazoles,[12d] anilines,[12e] and thiophenols.[12f] However, the oxidative decarboxylative trifluoromethylthiolation of (hetero)-aromatic acids has not been reported.[13]

We sought to exploit this decarboxylative trifluoromethylthiolation approach with the synthesis of CF_3S-substituted coumarins because the coumarin-3-carboxylic acids are easily accessed in a single step from Meldrum's acid and the corresponding salicylaldehyde.[14] Coumarins are privileged heterocycles and appear in numerous natural products and pharmaceuticals that show remarkable biological activities, such as anti-HIV,[15a] anti-inflammatory,[15b] anticancer,[15c] antioxidant,[15d] and antimutagenic activities (Figure 1).[15e]

Despite the importance of the CF_3S group, there are limited examples of the synthesis of trifluoromethylthiolated coumarins. Current examples require additional prefunctionalization steps

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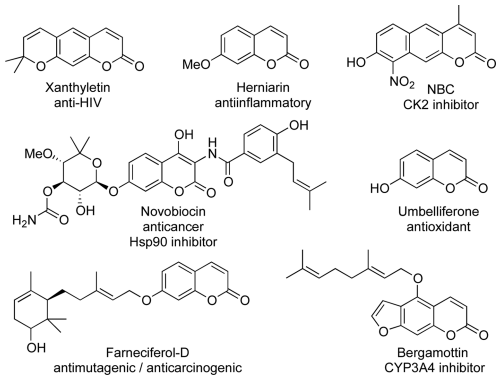


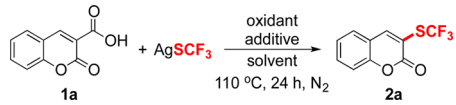
Figure 1. Selected coumarin derivatives with biological activities.

or complex substrate synthesis. For example, Wang and co-workers reported a CF_3S radical-triggered cyclization of alkynes to construct the coumarin core and simultaneously introduce CF_3S (Scheme S2a).[8e] This reaction requires the use of internal alkynes and results in unselective cyclization at both *ortho* C−H bonds. Recently Schoenebeck and co-workers developed the nickel catalyzed cross-coupling of coumarin triflates with $AgSCF_3$ (Scheme S2b),[7i] and Billard and co-workers reported the nucleophilic substitution of 4-hydroxycoumarin with *N*-trifluoromethylthiosulfonamide (Scheme S2c).[16] Although these late-stage trifluoromethylthiolation methods are attractive from a medicinal chemistry perspective, they are limited in substrate scope and by the need for prefunctionalized substrates and expensive or specialized catalysts. We report here an alternative approach to generate 3-trifluoromethylthio-coumarins efficiently and in a broad scope via a silver-mediated oxidative decarboxylative coupling reaction (Scheme S2d).

We began our studies by exploring the oxidative decarboxylative coupling of coumarin-3-carboxylic acid (**1a**) and $AgSCF_3$ with $K_2S_2O_8$ as the terminal oxidant (Table 1). Solvents such as DMSO, DMF, and anisole are commonly used in decarboxylative coupling reactions;[9] however, for this transformation these solvents led to little or no formation of the desired trifluoromethylthiolation product (**2a**) (entries 1−3), and in all cases, coumarin was obtained from unwanted protodecarboxylation (Table S1). We were pleased to find that 10% yield of **2a** was formed using CH_3CN as the solvent (entry 6). The yield of desired product increased with the addition of water, and a 1:1 ratio of CH_3CN:H_2O was found to provide the best yield (entries 7−9). Ligands, such as HMPA, have been shown to improve the yields of related reactions employing $AgSCF_3$;[8a−d] however, for our reaction both HMPA and imine-derived ligands led to decreased reaction yields (entries 10−12). A survey of inorganic bases (Table S3) revealed K_2CO_3 to improve the reaction yield (52% yield, Table 1, entry 13). Decreasing the loading of $K_2S_2O_8$ from 5.0 to 3.0 equiv resulted in a further improvement in yield (entry 14). While $(NH_4)_2S_2O_8$ could be used in place of $K_2S_2O_8$ (entry 15), organic peroxides such as TBHP and DTBP gave no desired product (entries 16 and 17). Thus, the optimized conditions employ $K_2S_2O_8$ (3.0 equiv) and K_2CO_3 (1.0 equiv) in CH_3CN/H_2O (1:1) at 110 °C to generate the trifluoromethylthiolated coumarin **2a** in 70% isolated yield.

With the optimized conditions established, we turned our attention to the substrate scope and limitations of this approach. As shown in Scheme 2, both electron-deficient and electron-rich substrates undergo efficient trifluoromethylthiolation with electron-donating substituents providing slightly higher yields (**2h** and **2o**). Substrates bearing halogen (**2b**, **2c**, **2g**),

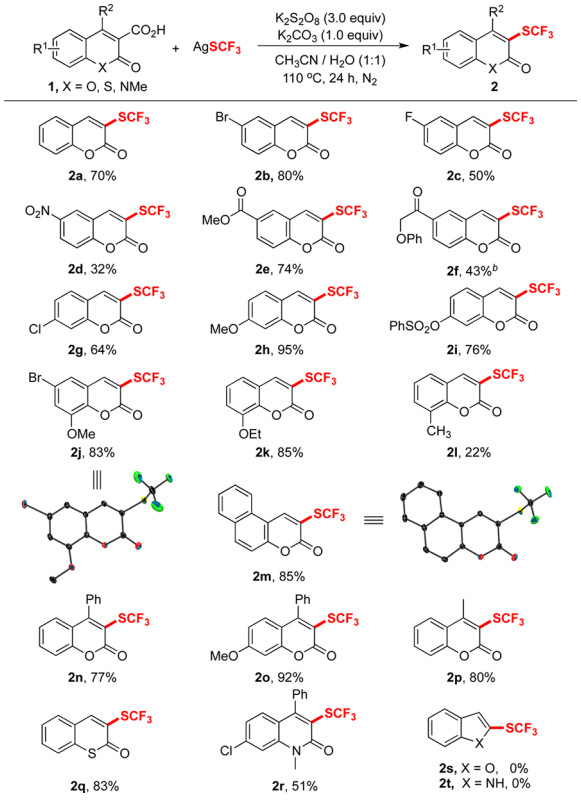
Table 1. Optimization of the Reaction Conditions[a]



entry	oxidant	solvent	additive[b]	% yield[c]
1	$K_2S_2O_8$	DMSO		2
2	$K_2S_2O_8$	DMF		N.D.
3	$K_2S_2O_8$	anisole		N.D.
4	$K_2S_2O_8$	DCE		N.D.
5	$K_2S_2O_8$	1,4-dioxane		N.D.
6	$K_2S_2O_8$	CH_3CN		10
7	$K_2S_2O_8$	CH_3CN/H_2O (4:1)		15
8	$K_2S_2O_8$	CH_3CN/H_2O (1:1)		40
9	$K_2S_2O_8$	H_2O		28
10	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	bipy	30
11	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	phen	8
12	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	HMPA	N.D.
13[d]	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	K_2CO_3	52
14[d,e]	**$K_2S_2O_8$**	**CH_3CN/H_2O (1:1)**	**K_2CO_3**	**73 (70)**[f]
15[d,e]	$(NH_4)_2S_2O_8$	CH_3CN/H_2O (1:1)	K_2CO_3	75
16[d,e]	TBHP	CH_3CN/H_2O (1:1)	K_2CO_3	N.D.
17[d,e]	DTBP	CH_3CN/H_2O (1:1)	K_2CO_3	N.D.

[a]Reaction conditions: **1a** (0.2 mmol), $AgSCF_3$ (0.4 mmol) in a solvent (5.0 mL). [b]Additive (0.5 equiv). [c]^1H NMR yield with 1,3,5-trimethoxybenzene as an internal standard. [d]K_2CO_3 (1.0 equiv). [e]3.0 equiv of oxidant. [f]Isolated yield in parentheses.

Scheme 2. Substrate Scope of the Oxidative Decarboxylative Trifluoromethylthiolation[a]



[a]Isolated yields. Conditions: **1** (0.2 mmol), $AgSCF_3$ (0.4 mmol), $K_2S_2O_8$ (0.6 mmol), K_2CO_3 (0.2 mmol) in a mixture of CH_3CN (2.5 mL) and H_2O (2.5 mL) at 110 °C for 24 h. [b]K_3PO_4 (0.2 mmol) at 60 °C.

carboxylate (**2e**), sulfonate (**2i**), ketone (**2f**), and ether (**2k**, **2o**) groups were all tolerated and afforded the corresponding products

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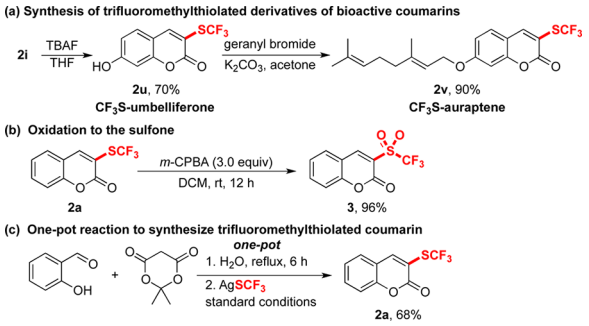
in good to excellent yields. It is worth mentioning that **2h**, the 3-trifluoromethylthio-derivative of the biologically active natural product herniarin,[15b] was isolated in excellent yield, indicative of the utility of this approach. Coumarin-3-carboxylic acids bearing multiple substituents also underwent efficient coupling, and the structures of the corresponding products (**2j** and **2m**) were confirmed by X-ray crystallographic analysis. Similar to other $K_2S_2O_8$ oxidized reactions,[8] the phenol and tertiary amine groups were not compatible and the 8-methyl substituted product (**2l**)[8e] could be obtained only in low yield. We were pleased that both 2-aryl and -alkyl substituted coumarin-3-carboxylic acids could be employed in this protocol, furnishing the trifluoromethylthiolated products (**2n**, **2o**, and **2p**) in good to excellent yields. The analogous thiocoumarin and quinolin-2(1*H*)-one carboxylic acids were also explored, and to our delight, both underwent efficient decarboxylative coupling to yield the corresponding 3-trifluoromethylthiolated products in good yields (**2q**, **2r**). Unfortunately, the five-membered-ring heterocyclic acids, such as benzofuran-2-carboxylic acid and indole-2-carboxylic acid did not undergo trifluoromethylthiolation under these conditions (**2s**, **2t**).

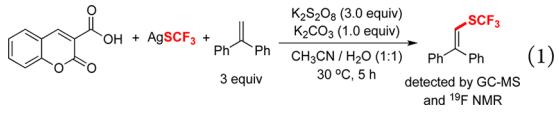
Several experiments were conducted in order to highlight the synthetic utility of this method. First, we generated the trifluoromethylthiolated analogues of two natural products, umbelliferone (**2u**) and auraptene (**2v**), from **2i** (Scheme 3a). Second, the

Scheme 3. Synthetic Utility of Silver-Mediated Oxidative Decarboxylative Trifluoromethylthiolation



trifluoromethylthiolated product was oxidized to the corresponding sulfone (**3**, Scheme 3b), another class of fluorine-containing scaffold with high bioavailability and biological activity.[4] Finally, **2a** was synthesized from the one-pot reaction of readily available salicylaldehyde and Meldrum's acid in 68% yield (Scheme 3c), similar to the yield obtained with our standard protocol (70%, Scheme 2).

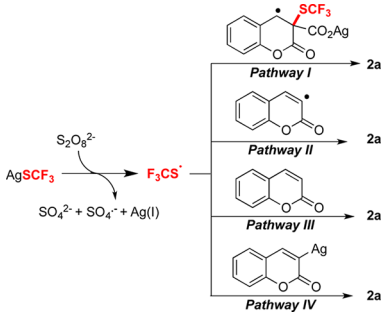
Based on literature precedent we suspected that $CF_3S^•$ may play a key role in product formation under our reaction conditions.[8] To explore this possibility, several radical trapping experiments were conducted. First, the reaction was completely quenched when 3.0 equiv of TEMPO or 9,10-dihydroanthracene was included under standard reaction conditions (Scheme S3). Furthermore, when 1,1-diphenylethylene was included in the reaction, the trifluoromethylthiolated alkene was detected, indicating the formation of $CF_3S^•$ (eq 1).



(1)

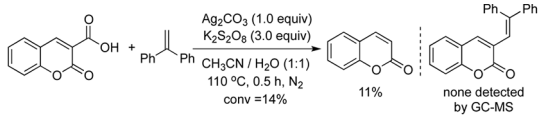
As summarized in Scheme 4,[17] we considered four distinct pathways for the formation of **2a** from $CF_3S^•$: (I) addition of

Scheme 4. Possible Pathways for the Formation of 2a

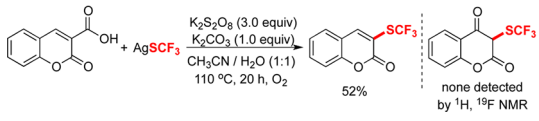


$CF_3S^•$ prior to decarboxylation, (II) decarboxylation to form a free coumarin radical, (III) protodecarboxylation to generate coumarin as an intermediate, and (IV) silver-mediated decarboxylation to form an organometallic intermediate.

We first considered Pathways I and II involving coumarin-derived radical intermediates. First, addition of $CF_3S^•$ may trigger the decarboxylation (Pathway I).[18a,b] Alternatively, Minisci-type decarboxylation[18c] may result in a coumarin radical, which combines with $CF_3S^•$ to form **2a** (Pathway II). Additional radical trapping experiments provided evidence against these pathways. When 1,1-diphenyl ethylene was included in the reaction mixture in the absence of $AgSCF_3$ (eq 2), no trapping

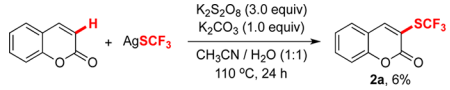


(2)



(3)

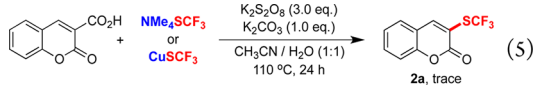
products of a coumarin-based radical were detected. In addition, the reaction occurred smoothly under an O_2 atmosphere (eq 3) and no oxygenated products were detected.[13b] These results disfavor a pathway involving a coumarin-derived radical intermediate. Related decarboxylative coupling reactions proceed through a sequential protodecarboxylation-dehydrogenative coupling pathway,[19] and silver-mediated protodecarboxylations are well-established.[20] Under our conditions a silver-mediated protodecarboxylation step (Pathway III) was excluded with control experiments employing coumarin. As shown in eq 4,



(4)

when coumarin is treated with $AgSCF_3$ under the standard conditions, only small amounts of **2a** are formed (6%), highlighting the importance of the acid functionality in the formation of **2a**.

Instead we favor a pathway in which a silver-mediated decarboxylation generates an organometallic intermediate that undergoes trifluoromethylthiolation (Pathway IV). The importance of silver in the formation of **2a** is evident when $AgSCF_3$ is replaced by $CuSCF_3$ or NMe_4SCF_3 (eq 5). Under these conditions only



(5)

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trace **2a** is formed. Further mechanistic studies are underway to fully elucidate the detailed reaction pathway.

In conclusion, we have developed a facile synthetic route to 3-trifluoromethylthiolated coumarins via a silver-mediated oxidative decarboxylative coupling reaction. This protocol is efficient for a broad substrate scope of readily available substituted coumarin-3-carboxylic acids in addition to the thiocoumarin and 3-quinolin-2(1*H*)-one derivatives. Trifluoromethylthiolated natural product analogues were also accessed using this method. We anticipate that this methodology will not only enrich the field of decarboxylative couplings reactions, but will also provide a new method for the late-stage synthesis of fluorine-containing biologically active molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03806.

Experimental procedures and characterization data for starting materials and products (PDF)
Crystallographic data for compound **2j** (CIF)
Crystallographic data for compound **2m** (CIF)

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Notes

The authors declare no competing financial interest.

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(17) Although the CF_3S radical appears to be a key intermediate under our conditions, it may not be the direct trifluoromethylthiolating agent as other CF_3S species such as CF_3SSCF_3 may form in situ as described in ref 8. See SI for experimental details of reactions with CF_3SSCF_3.

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