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A Facile and General Approach to 3-((Trifluoromethyl)thio)-4*H*-chromen-4-one

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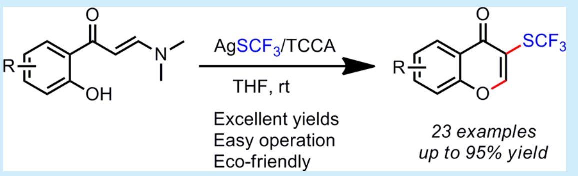
Supporting Information

ABSTRACT: A facile and efficient synthetic strategy to 3-((trifluoromethyl)thio)-4*H*-chromen-4-one was developed. $AgSCF_3$ and trichloroisocyanuric acid were employed here to generate active electrophilic trifluoromethylthio species in situ. This reaction could proceed under mild conditions in a short reaction time and be insensitive to air and moisture.



Fluorinated organic compounds have attracted considerable attention within organic synthesis, because of their desirable electronegativity, lipophilicity, and metabolic stability properties.[1] Among these fluorine-containing groups, the trifluoromethylthio (SCF_3) group possesses a higher Hansch parameter (π = 1.44), while the trifluoromethyl group has a lower Hansch parameter (π = 0.88).[1d,2] Therefore, medicinal chemists often incorporate the SCF_3 group into organic compounds to enhance their transmembrane permeation, thus enhancing their bioavailability.[3] As a consequence, there are many bioactive products bearing the SCF_3 group, such as anticoccidial drug Toltrazuril,[4] insecticide Fipronil,[5] and hypotensive agent analogues of Losartan and Nifedipine[6] (Figure 1).

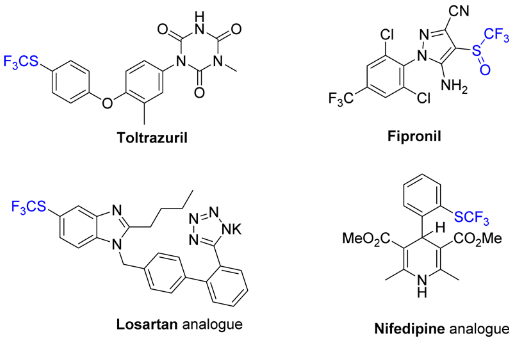


Figure 1. Bioactive agents containing an SCF_3 group.

As a result, an explosion of research efforts has been triggered in developing new and efficient methods to introduce the SCF_3 group.[3,7] Traditional indirect strategies for the introduction of the SCF_3 group need additional steps, including halogen–fluorine exchange reactions of trihalogenomethyl thioethers[8] and trifluoromethylations of sulfur-containing compounds.[9] However, the direct introduction of the SCF_3 group into organic molecules has been poorly investigated until recently. Thus, various modern direct trifluoromethylthiolation methods were developed.[7a] In 2011, Buchwald et al. reported a general method for the trifluoromethylthiolation of aryl halides with $AgSCF_3$, catalyzed by Pd species.[10] Afterward, another Ni-catalyzed trifluoromethylthiolation of aryl halides with Me_4NSCF_3 was reported by Vicic et al.[11] More recently, Liu et al. discovered a Cu-catalyzed trifluoromethylthiolation of aryl halides with diverse directing groups, using $AgSCF_3$ as a nucleophilic SCF_3 reagent.[12] Additionally, Cu-catalyzed oxidative trifluoromethylthiolations have been developed by Qing[13] and Vicic.[14] On the other hand, a series of elegant electrophilic SCF_3 reagents were also disclosed and employed for direct construction of the SCF_3 moiety into organic compounds. In 2009, two trifluoromethanesulfenamides were reported as effective electrophilic SCF_3 sources for the trifluoromethylthiolation of various substrates, and these reagents could be easily synthesized from CF_3TMS, diethylaminosulfur trifluoride (DAST), and aniline.[15] Another shelf-stable electrophilic SCF_3 reagent, *N*-(trifluoromethylthio)-phthalimide, the reactivity of which was further well studied by Rueping et al.,[16] was initially developed by Munavalli.[17] Following, a Pd-catalyzed trifluoromethylthiolation of aryl C–H bonds with a similar reagent, *N*-(trifluoromethylthio)-butanimide, was published by Shen et al.[18] In 2013, Shibata et al. reported a Cu-catalyzed trifluoromethylthiolation of enamines, indoles, and β-keto esters with a hypervalent iodonium ylide reagent.[19] Additionally, a novel trifluoromethylthiolated thioperoxy reagent with interesting reactivity was designed by Shen's group.[20]

In most of the cases mentioned above, trifluoromethylthiolation occurs at preformed arenes. As an alternative, a conceptually novel approach, in which the new heterocyclic cores are constructed during the trifluoromethylthiolation process, is high desirable, from the point of view of atom and step economy. Therefore, the trifluoromethylthiolation–cyclization reactions were applied recently into constructing various significant SCF_3-contaning heterocycles, on the basis of the previous works.[21] These useful strategies provided a novel route to assemble the

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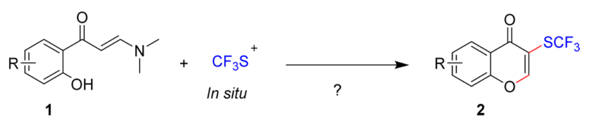
SCF_3 group into organic molecules. Various important heterocycles, such as indoles,[22] isocoumarins,[23] benzofurans, and benzothiophenes,[24] bearing an SCF_3 substituent were synthesized through a Lewis acid mediated electrophilic cyclization reaction with trifluoromethanesulfanylamide, whereas the SCF_3 reagents used here must be prepared in advance and additional Lewis acids were needed to promote these transformations. Meanwhile, Tan reported a practical and easily handled method for the generation of the active electrophilic trifluoromethylthio species in situ from trichloroisocyanuric acid (TCCA) and $AgSCF_3$.[25] Our group has concentrated on developing novel strategies to construct a variety of bioactive heterocyclic scaffolds for a long time.[26] Chromone and its derivatives, which are found in many natural products and pharmaceuticals with a wide range of physiological and biological activities,[27] are greatly versatile building blocks for constructing various heterocycles.[28] Therefore, introduction of the SCF_3 group to chromones might be very desirable and result in further advances in the pharmacological applications. Inspired by pioneering works, we envisioned that compounds **1** could covert directly to 3-((trifluoromethyl)thio) chromones under mild conditions through an electrophilic triflluoromethylthiolation–cyclization reaction (Scheme 1). Therefore, we herein first

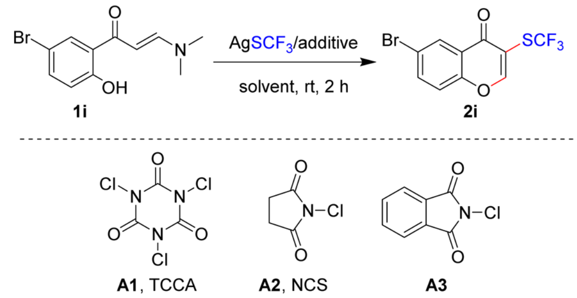
Scheme 1. Construction of 3-SCF_3-Chromones



demonstrated a facile and general synthetic route to 3-((trifluoromethyl)thio) chromones via in situ generation of electrophilic trifluoromethanesulfanyl cation from TCCA and $AgSCF_3$.

Initially, we screened parameters to find the optimal conditions (Table 1). Based on the reaction conditions adopted by Tan,[25] our present study commenced with mixing the commercially available TCCA (**A1**) and $AgSCF_3$ in MeCN. After the mixture was stirred at rt for 30 min, **1i** was added, which was easily prepared according to literature procedures.[29] We performed a solvent screening at first (Table 1, entries 1–7). Obviously, the reaction was highly solvent-dependent with good and moderate yields obtained in THF and DMF respectively (Table 1, entries 3, 4), while no desired products were detected in MeCN, DCM, DMSO, MTBE, or toluene (Table 1, entries 1–2, 5–7). Following, we surveyed the effect of the additive TCCA on the reaction, revealing that TCCA was indispensable for in situ generation of the electrophilic SCF_3 cation. Subsequently, we found that a similar yield was obtained when the reaction was conducted under an argon atmosphere, suggesting that this reaction was insensitive to air and moisture (Table 1, entry 8). Other additives **A2** and **A3** were ineffective in the current reaction, but with major byproduct of 6-bromo-3-chloro-4*H*-chromen-4-one (Table 1, entries 9, 10). And no reaction took place at all without any additive (Table 1, entry 11). Afterward, the feeding order of compound **1i** was also taken into consideration. No corresponding product was detected when compound **1i** was added along with TCCA and $AgSCF_3$ at the beginning of the reaction (Table 1, entry 12). Finally, we increased the amount of TCCA and $AgSCF_3$ to 1.5 and 3.0 equiv, respectively, and the yield of the reaction increased into 90% (Table 1, entry 13). And the yield of the desired product has not

Table 1. Investigation of Reaction Conditions[a]



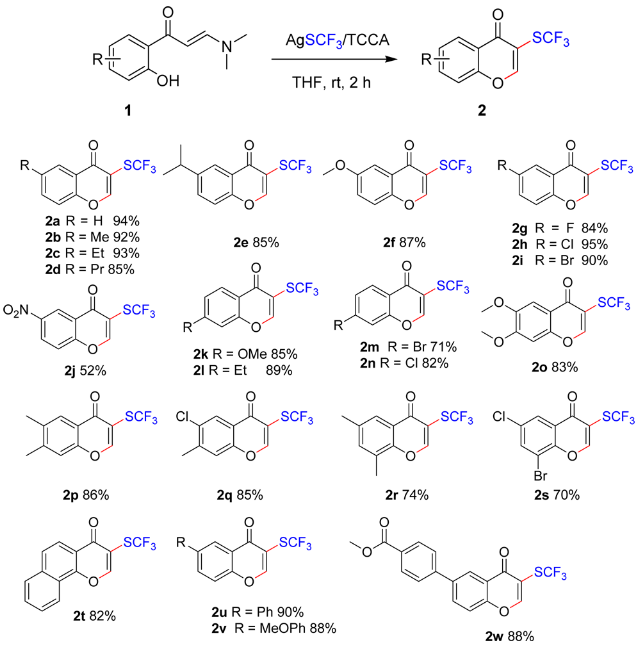
entry	solvent	additive	yield[b] (%)
1	MeCN	**A1**	n.d.
2	DCM	**A1**	n.d.
3	THF	**A1**	80
4	DMF	**A1**	57
5	DMSO	**A1**	n.d.
6	MTBE	**A1**	n.d.
7	toulene	**A1**	n.d.
8	THF	**A1**	78[c]
9	THF	**A2**	n.d.[d]
10	THF	**A3**	n.d.[d]
11	THF	**none**	n.r.
12	THF	**A1**	n.d.[e]
13	THF	**A1**	90[f]
14	THF	**A1**	87[g]

[a]Reaction conditions: additive (0.25 mmol) and $AgSCF_3$ (0.5 mmol) were mixed, THF (2 mL) was added and stirred for 30 min at rt, and then compound **1i** (0.2 mmol) was added and stirred for another 2 h. [b]Isolated yield; n.d. = no **2i** detected; n.r. = no reaction. [c]The reaction is carried out under an argon atmoshpere. [d]The major product was 6-bromo-3-chloro-4*H*-chromen-4-one. [e]TCCA (0.25 mmol), $AgSCF_3$ (0.5 mmol), and compound **1a** were mixed in solvent and stirred for 2 h. [f]0.3 mmol of TCCA and 0.6 mmol of $AgSCF_3$ were used. [g]0.4 mmol of TCCA and 0.8 mmol of $AgSCF_3$ were used.

been improved any more when we further increased the amount of TCCA and $AgSCF_3$ (Table 1, entry 14).

To study the scope and limitations of this approach, various (*E*)-3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-ones **1** were prepared and reacted under optimized reaction conditions ($AgSCF_3$ (0.6 mmol) and TCCA (0.3 mmol) in THF (2 mL) at rt for 30 min, then compounds **1** were added and stirred for another 2 h). The results are shown in Scheme 2. Generally, with both electron-donating and -withdrawing substituents on the benzene rings, the reaction proceeded smoothly and provided the corresponding products **2a–2w** in moderate to excellent yields. Simple alkyl, halo, and methoxy groups substituted at the *para*-position of the phenol groups of compound **1** all gave the corresponding 3-((trifluoromethyl)-thio)chromones **2a–2i** in excellent yields. We were pleased to find that the nitro-substituted compound **1j** was a suitable reactant as well under the standard conditions, leading to the desired product **2j** in 52% yield. The reactants **1** possessing electron-donating substituents at the *meta*-position of the phenol groups gave the desired products in better yields than those with electron-withdrawing substituents (Scheme 2, **2k–l** vs **2m–n**). It was also found that bearing substituents at the *meta*-position of the phenol groups of compound **1** gave 3-((trifluoromethyl)-thio)chromones in lower yields than those at the *para*-position for the electron-withdrawing groups (Scheme 2, **2h** vs **2n** and **2i** vs **2m**), while similar yields were achieved for the electron-

Scheme 2. Exploration of Substrate Scope[a,b]



[a]Reaction conditions: TCCA (0.3 mmol) and $AgSCF_3$ (0.6 mmol) were mixed, THF (2 mL) was added and stirred for 30 min at rt, and then compound **1** (0.2 mmol) was added and stirred for another 2 h. [b]Isolated yield.

donating groups (Scheme 2, **2c** vs **2l** and **2f** vs **2k**). Moreover, compounds **1** with multisubstituents were compatible with the reaction process as well, providing the corresponding products **2o**−**2s** in good yields. Replacing benzene moieties by naphthalene moieties for compounds **1** also afforded 3-((trifluoromethyl)thio)chromone **2t** in a good yield. Meanwhile, aryl-substituted compounds **1u**−**1w** were found to be suitable substrates. Additionally, the structure of **2a** was confirmed by X-ray crystallographic analysis (Figure 2).[30]

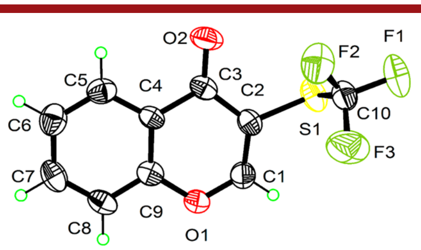
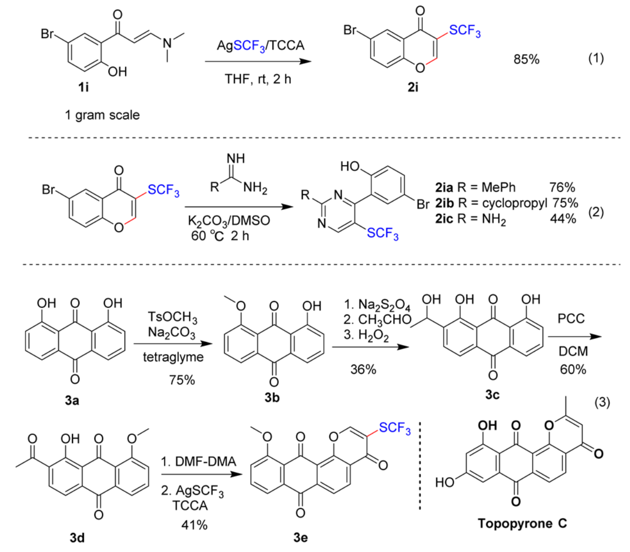


Figure 2. X-ray crystal structure of **2a**.

Notably, the reaction is operationally simple and amenable to gram-scale synthesis in 85% yield (Scheme 3, eq 1). To demonstrate the synthetic utility of the desired product, we treated 3-((trifluoromethyl)thio)chromone **2i** with amidines and guanidine,[26b,31] furnishing diverse SCF_3-group-containing and nitrogen-containing heterocycles (Scheme 3, eq 2). Moreover, this approach could be applied in the construction of (trifluoromethyl)thio-containing analogue **3e** of natural topopyrone C (Scheme 3, eq 3), which was isolated from the culture broth of a fungus and showed significant cytotoxic effects as topoisomerase I inhibitors.[32]

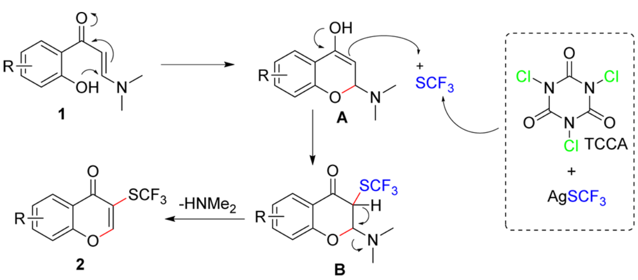
A possible mechanism was proposed in Scheme 4. We envisioned that an intramolecular Michael addition/cyclization of compound **1** would happen to produce intermediate **A**.

Scheme 3. Synthetic Utility of This Reaction[a]



[a]All of the reactions in eq 2 were not optimized.

Scheme 4. Proposed Mechanism



Subsequently, the enolate intermediate **A** would further react with the trifluoromethanesulfanyl cation generated in situ from TCCA and $AgSCF_3$[25] to form intermediate **B**. Finally, *N*,*N*-dimethylamine was eliminated from **B** to provide 3-((trifluoromethyl)thio)chromones **2**.

In conclusion, we first demonstrated a facile and general synthetic route to a range of 3-((trifluoromethyl)thio)-chromones via in situ generation of electrophilic trifluoromethylthio species from trichloroisocyanuric acid (**TCCA**) and $AgSCF_3$. This practical and easily handled reaction, which was insensitive to air and moisture, could occur under mild conditions in a short reaction time without any extra additive metal. Moreover, the reaction could be scaled-up easily. Additionally, the desired 3-((trifluoromethyl)thio)chromones could covert to diverse (trifluoromethyl)thio-substituted heterocycles. And this method also provides a new direction to optimize natural bioactive products.

■ ASSOCIATED CONTENT

Supporting Information

General experimental information and copies of ^{1}H and ^{13}C NMR of new compounds are also provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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