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Communication

Facile syntheses of 3-trifluoromethylthio substituted thioflavones and benzothiophenes *via* the radical cyclization

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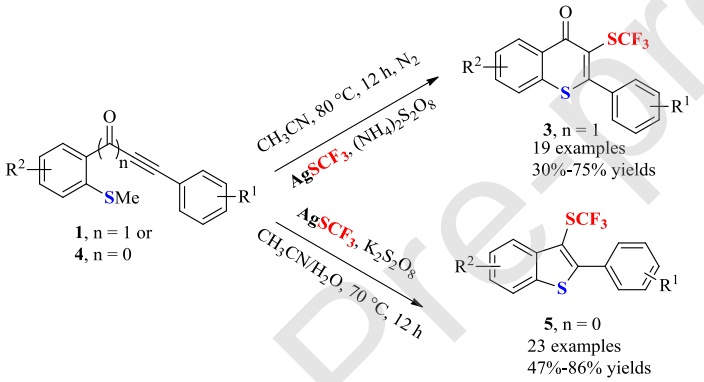
Graphical Abstract



An efficient and practical protocol for preparation of 3-CF_3S substituted thioflavones and benzothiophenes was developed. This protocol possesses good functional group tolerance and high yields. Mechanistic studies suggested that a classic two-step radical addition and cyclization process was involved.

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ABSTRACT

3-CF_3S substituted thioflavones and benzothiophenes were achieved *via* the reactions of $AgSCF_3$ with methylthiolated alkynones and alkynylthioanisoles, respectively, promoted by persulfate. This protocol possesses good functional group tolerance and high yields. Mechanistic studies suggested that a classic two-step radical process was involved, which includes addition of CF_3S radical to triple bond and cyclization with SMe moiety.

Organosulfur heterocycles are important compounds due to their unique physical properties and versatile biological activity. Thioflavones and benzothiophenes are two class of representative organosulfur heterocycles, and have been widely used as pharmaceuticals, functional materials, and synthetic intermediates [1-7]. Studies have shown that thioflavones are easy to pass through the cell membrane of fungi, changing the ultrastructure of fungal cells, thereby exhibit antibacterial [8] and

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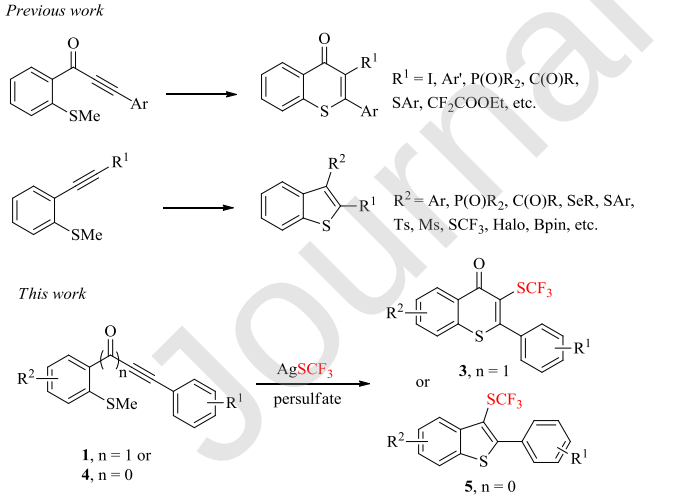
antiviral activities [9]. So the development of efficient synthetic methods for construction of thioflavone and benzothiophene skeletons has retained the interest of organic researchers along decades of historical development of chemistry [10,11]. For instance, Schneller's group reported the synthesis of thioflavones by reacting thiophenols and keto esters in 1975 [12]. In 2014, Seijiro's group developed a nickel-catalyzed decarbonylative cyclo-addition reaction of thioisatins and alkynes to form thioflavones [13,14]. In 2009, Takimiya's group reported a one-pot procedure for the synthesis of benzothiophene derivatives from readily available *o*-halo-ethynylbenzene precursors [15].

Nowadays, radical cascade reactions have become one of the most efficient synthetic strategy for the construction of organosulfur heterocycles. Thereinto, thioanisole derivatives have been widely used in the radical cyclization process with the release of a methyl group for the construction of thioflavone and benzothiophene skeletons. Most recently, Song and co-workers reported a radical-promoted cyclization of methylthiolated alkynones with diverse radical precursors, and allows an efficient synthesis of a variety of phosphoryl-, sulfenyl-, $EtOOCCF_2$-, and acyl-containing thioflavone derivatives under mild conditions (Scheme 1) [16]. Methylthiolated alkynones can also be transferred into 3-aryl [17] and 3-phosphorylated [18] thioflavones by visible-light induced radical reactions with arenediazonium salts and phosphine oxides, respectively. On the other hand, 2-alkynylthioanisoles as versatile building blocks have been widely used in the synthesis of 3-substituted benzothiophenes [19-28].

For example, Wu and co-workers disclosed a radical relay strategy for the preparation of 3-(methylsulfonyl)benzothiophenes through a reaction of 2-alkynylthioanisoles with sodium metabisulfite (Scheme 1) in the presence of a photocatalyst under visible light irradiation [29]. Gao and co-workers developed a direct synthetic method for 3-phosphinoylbenzothiophenes through an Ag-mediated radical addition−cyclization of 2-alkynylthioanisoles with secondary phosphine oxides [20].

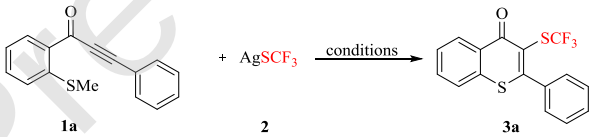


Scheme 1. Syntheses of 3-substituted thioflavones and benzothiophenes.

At the meantime, the special properties of trifluoromethylthio group have led to the widespread use of trifluoromethylthio-containing compounds in many fields, particularly in pharmaceutical and pesticide chemistry [30]. The development of efficient methods for introducing trifluoromethylthio groups into target molecules have attracted much attentions in the field of organic chemistry [31-33]. To date, through the efforts of chemists, direct trifluoromethylthiolation to construct C-SCF_3 has achieved rapid development [34-36]. According to the source of trifluoromethylthio group, the direct trifluoromethylthiolation is classified into nucleophilic, electrophilic and free radical pathways [37-54]. In 2014, Wu and co-workers synthesized several 3-trifluoromethylthiobenzothiophenes through the reactions of trifluoromethanesulfanylamide with 2-alkynylthioanisoles promoted by $BiCl_3$ [52]. As part of our ongoing interest in development of synthetic methods for fluorinated compounds, we envisioned that 3-trifluoromethylthio substituted thioflavones and benzothiophenes can be constructed by a radical addition of trifluoromethylthio radical ($CF_3S\cdot$) generated from $AgSCF_3$ to methylthiolated alkynones and 2-alkynylthioanisoles, respectively, followed by an intramolecular radical cyclization reaction (Scheme 1).

Initially, *tert*-butyl hydroperoxide (TBHP) or benzoyl peroxide (BPO) was chosen as the oxidant, and the reaction of 1-(2-(methylthio)phenyl)-3-phenylprop-2-yn-1-one (**1a**) with $AgSCF_3$ (**2**) was conducted in the presence of $AgNO_3$ in CH_3CN. But no desired 3-CF_3S substituted thioflavone **3a** was detected (Table 1, entries 1 and 2). When $K_2S_2O_8$ was chosen as an oxidant, **3a** was formed in 60% yield in the presence of $AgNO_3$ (Table 1, entry 3). However, the yield of **3a** was slightly increased in the absence of $AgNO_3$, which indicated that extra transition metal catalyst was not necessary for this reaction (Table 1, entry 4).

Table 1
Optimization of the reaction conditions.[a]



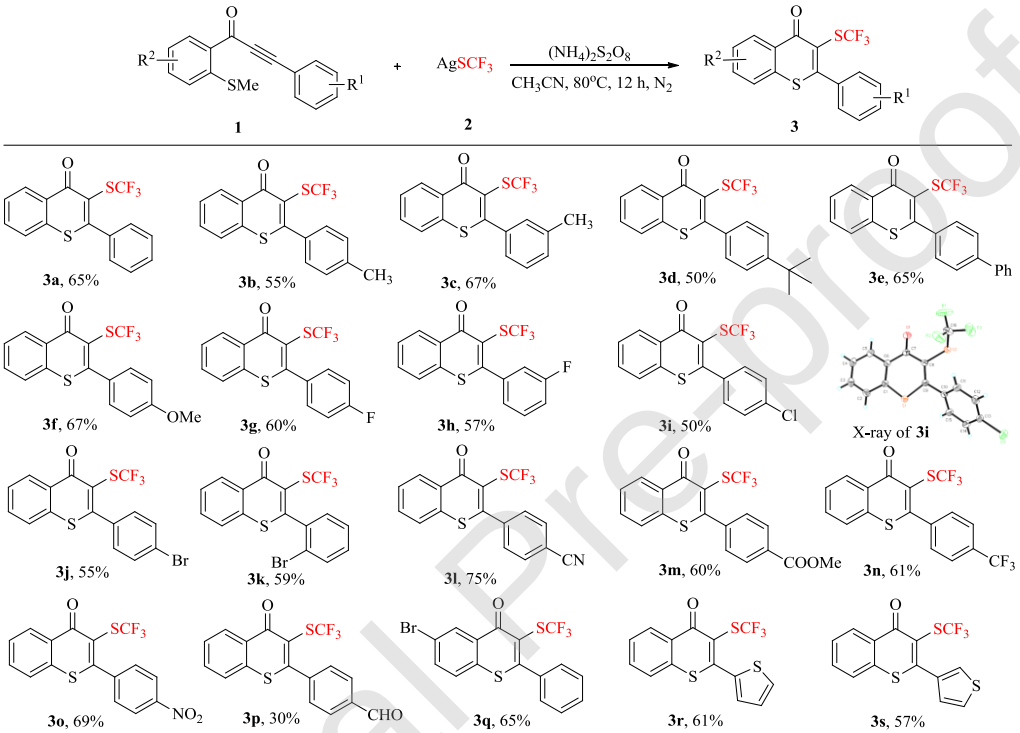
Entry	Ag salt	Oxidant	Temp (°C)	Solvent	Yield (%)[b]
1	$AgNO_3$	TBHP	80	CH_3CN	0
2	$AgNO_3$	BPO	80	CH_3CN	0
3	$AgNO_3$	$K_2S_2O_8$	80	CH_3CN	60
4	—	$K_2S_2O_8$	80	CH_3CN	67
5	—	$Na_2S_2O_8$	80	CH_3CN	65
6	—	$(NH_4)_2S_2O_8$	80	CH_3CN	75
7[c]	—	$(NH_4)_2S_2O_8$	80	CH_3CN	67
8[d]	—	$(NH_4)_2S_2O_8$	80	CH_3CN	57
9	—	$(NH_4)_2S_2O_8$	90	CH_3CN	63
10	—	$(NH_4)_2S_2O_8$	70	CH_3CN	46
11	—	$(NH_4)_2S_2O_8$	80	DMSO	54
12[e]	—	$(NH_4)_2S_2O_8$	80	CH_3CN/H_2O	18
13[f]	—	$(NH_4)_2S_2O_8$	80	$DMSO/H_2O$	25

[a] Unless otherwise specified, the reactions were carried out in the presence of **1a** (0.2 mmol), **2** (0.4 mmol), oxidant (0.3 mmol), solvents (2.0 mL), N_2, 80 °C, 12 h.
[b] Yields were determined by ^{19}F NMR spectroscopy using trifluoromethylbenzene as an internal standard.
[c] oxidant (0.2 mmol).
[d] oxidant (0.4 mmol).
[e] CH_3CN/H_2O = (1 mL/1 mL).
[f] $DMSO/H_2O$ = (1 mL/1 mL).

Other persulfate as an oxidant was then screened (Table 1, entries 5 and 6), and the results indicated that $(NH_4)_2S_2O_8$ was the best choice affording the desired product **3a** in 75% yield (Table 1, entry 6). The amount of $(NH_4)_2S_2O_8$ was then adjusted, and the results revealed that 1.5 equiv. of oxidant was optimal (Table 1, entries 7 and 8). The yield of product **3a** was decreased when the

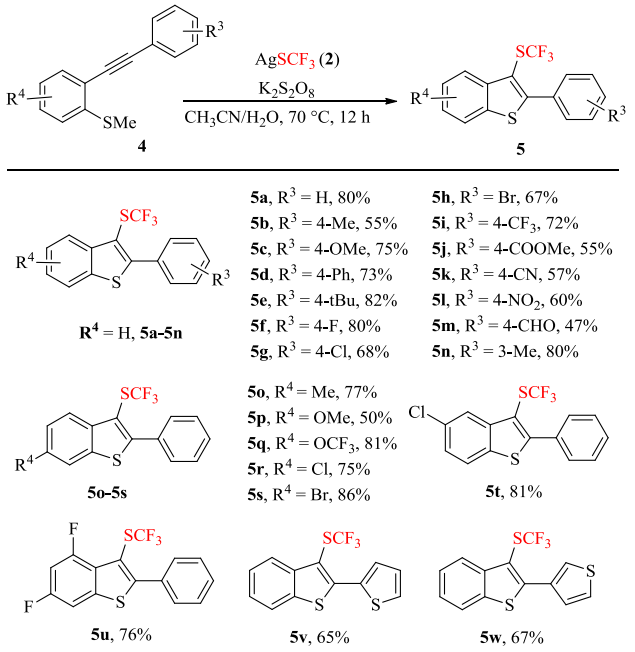
reaction temperature was increased to 90 °C or reduced to 70 °C (Table 1, entries 9 and 10). Subsequently, different solvents were investigated, and no better yield was observed when the reaction was carried out in different solvents other than CH_3CN (Table 1, entries 11-13).

With the optimized reaction conditions in hand (Table1, entry 6), the efficiency and generality of this reaction was explored, and the results were presented in Scheme 2. The R^1 group on the benzene ring of alkynones was first investigated and most of the functional groups were tolerated under the optimized conditions. With electron-donating substituents at the R^1 position, such as methyl, methoxy, *tert*-butyl, and phenyl groups, products **3b-3f** were obtained in yields of 55%-67%. Halogen atoms such as fluorine, chlorine, and bromine have little influences under the optimized reaction conditions to afford the corresponding products **3g-3k** in moderate yields. Electron-withdrawing substituents, such as cyano, trifluoromethyl and nitro groups, were also compatible with the reaction, affording the desired products **3l-3o** in yields of 60%-75%. Notably, formyl group as an electron-withdrawing substituent suppressed the radical cyclization significantly due to its high reactivity to radicals [55], the desired product **3p** was obtained only in yield of 30%. Substituent such as bromine group at the R^2 position were also amenable for this reaction, affording **3q** in 65% yield. Additionally, the thiophenyl group could be tolerated as well under the reaction conditions, and the corresponding products **3r** and **3s** were obtained in 61% and 57% yields, respectively. The structure of thioflavone **3i** was further unambiguously established by X-ray diffraction studies. The supplementary crystallographic data can be obtained free of charge from The Cambridge Cryatallographic Data Center (CCDC No. 1968769).



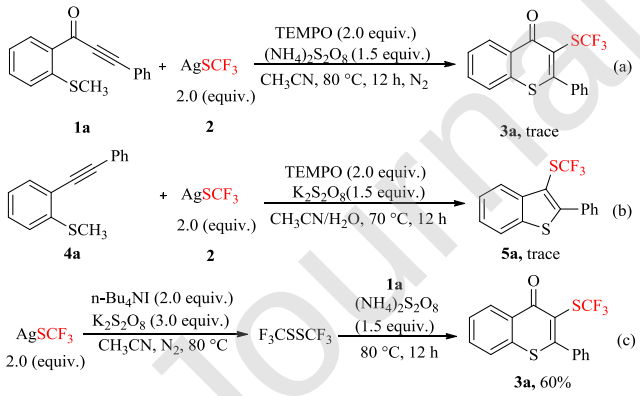
Scheme 2. Synthesis of 3-CF_3S substituted thioflavones. Reaction conditions: **1** (0.5 mmol), **2** (1.0 mmol), $(NH_4)_2S_2O_8$ (0.75 mmol), CH_3CN (5 mL), 80 ℃, N_2, 12 h. Isolated yields.

With the above investigation in hand, we assumed that the 2-alkynylthioanisoles would also be suitable for this transformation to afford 3-CF_3S substituted benzothiophenes. Thus, the exploration of the reaction of 2-alkynylphenylmethylsulfides **4** and $AgSCF_3$ (**2**) was conducted. The optimal reaction conditions were slightly adjusted with $K_2S_2O_8$ instead of $(NH_4)_2S_2O_8$ as the oxidant and CH_3CN/H_2O as a mixed solvent (Supporting information). As shown in Scheme 3, the reactions of 2-alkynylphenylmethylsulfides with an electron-donating group at R^3 position proceeded smoothly to provide the corresponding products **5a-5e** in moderate to good yields. Several sensitive functional groups such as fluoro, chloro, bromo, trifluoromethyl, ester, nitro, cyano, and formyl groups were all compatible. For example, the formyl-containing product **5m** was produced in 47% yield. Additionally, methyl substituent at the *meta*-position of the right benzene ring also presented good reactivity, and the corresponding product **5n** was obtained in 80% yield. Then, different substituents on the benzene ring of 2-methylthio-arylalkyne were studied. To our delight, the electronic effects of substituents including methyl, methoxy, trifluoromethoxy, chloro and bromo have no significant influence on the yields of the products, and the expected benzothiophenes **5o-5u** were generated in 50%-86% yields. Furthermore, the thiophenyl group could be tolerated as well under the reaction conditions, and the corresponding products **5v** and **5w** were generated in 65% and 67% yield, respectively. Compared to Wu's protocol reported in 2014 [52], the CF_3S source was different and wider substrate scope was investigated in this methodology.



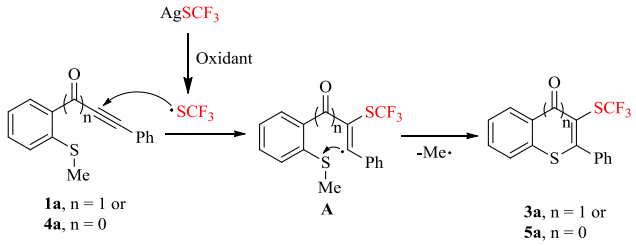
Scheme 3. Synthesis of 3-CF_3S substituted benzothiophenes. Reaction conditions: **4** (0.5 mmol), **2** (1.0 mmol), $K_2S_2O_8$ (0.75 mmol), CH_3CN/H_2O (v/v = 3:3, 6 mL), 70 ℃, 12 h. Isolated yields.

With a radical process hypothesized, control experiments were carried out to gain the detailed reaction mechanism. As demonstrated in Scheme 4, the formation of **3a** or **5a** was completely suppressed after adding 2,2,6,6-tetramethylpiperidine oxide (TEMPO) as a free radical scavenger, and a large amount of starting material **1a** or **4a** was recovered from the reaction system (Scheme 4, a and b). This result indicated that a radical process might be involved in this reaction. In order to verify whether CF_3S radical participated in the reaction, F_3CSSCF_3 was prepared from $AgSCF_3$ and then reacted with **1a**. The formation of product **3a** was detected in a yield of 60%, which confirmed that CF_3S radical was participated in the reaction (Scheme 4, c).



Scheme 4. Control experiments.

On the basis of these observations and previous reports [21,27, 28,56-61], a plausible mechanism for the cascade trifluoromethylthiolation cyclization reaction was described as shown in Scheme 5. Initially, $AgSCF_3$ reacts with oxidant ($(NH_4)_2S_2O_8$ or $K_2S_2O_8$) to form the CF_3S radical. Then, the triple bond in **1a** or **4a** is attacked by CF_3S radical to afford a vinyl radical intermediate **A**, which follows 6-exo-trig or 5-exo-trig cyclization with the SMe moiety to give the desired product **3a** or **5a** along with the release of a methyl radical.



Scheme 5. Proposed mechanism.

In summary, we have developed an efficient method for synthesis of 3-trifluoromethylthioflavones through a radical addition and cyclization of methylthio substituted arylalkynyl ketones with $AgSCF_3$. Besides, a facile and general route to 3-trifluoromethylthiobenzothiophenes *via* a reaction of 2-alkynylphenylmethylsulfides and $AgSCF_3$ was described. These protocols featured simple operation, mild conditions, good functional group tolerance and high yields.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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