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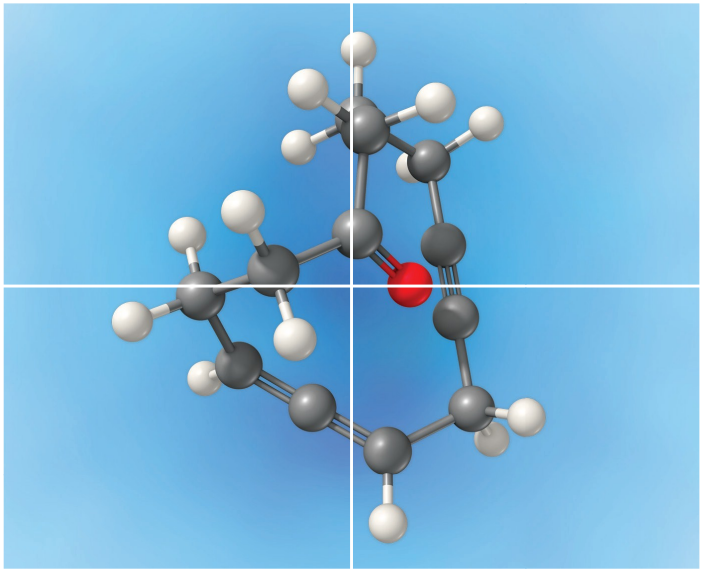

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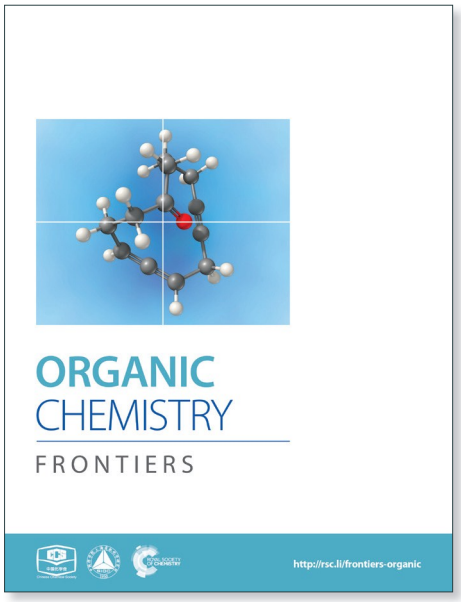

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Journal Name

COMMUNICATION

Direct Radical Trifluoromethylthiolation and Thiocyanation of Aryl Alkynoate Esters: Mild and Facile Synthesis of 3-Trifluoromethylthiolated and 3-Thiocyanated Coumarins

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Yao-Fu Zeng, Dong-Hang Tan, Yunyun Chen, Wen-Xin Lv, Xu-Ge Liu, Qingjiang Li, Honggen Wang*

A mild and convenient oxidative radical cyclization of aryl alkynoate esters for the synthesis of 3-trifluoromethylthiolated and 3-thiocyanated coumarins has been developed using $AgSCF_3$ and AgSCN as the corresponding radical sources, respectively. This protocol is characterized by readily available starting materials, excellent functional group tolerance and good yields.

Introduction

Coumarins represent a privileged class of structural scaffolds in medicinal chemistry due to their wide spectrum biological activities, such as anti-HIV,[1] antibacterial,[2] anti-inflammatory,[3] antitumor,[4] and antimalarial[5]. As such, the development of efficient methods to construction of structurally diverse coumarins bearing valuable functional group from easily accessible starting materials is highly demanding. Recently, the tandem functionalization/cyclization of aryl alkynoate ester has emerged as powerful strategies to synthesize 3-functionalized coumarins.[6] For instance, it was reported that 3-trifluoromethylated coumarins could be prepared by the reaction of aryl alkynoate esters with Togni's reagent following a radical addition/cyclization mechanism.[6a] Similarly, various 3-substituted coumarins have been accessed via radical alkyne sulfonation,[6b] phosphorylation,[6c] acylation,[6d-f] difluoroacetylation[6f]/cyclization pathways under oxidative or redox-neutral reaction conditions. Herein, we report our realization of a mild and facile synthesis of 3-trifluoromethylthiolated and thiocyanted coumarins by using $AgSCF_3$ and AgSCN as the radical sources, respectively. Broad substrate scope, good functional group tolerance were observed.

Due to the typically desirable strong electron-withdrawing effect and high lipophilicity properties, trifluoromethylthio group is frequently incorporated into bioactive compounds.[7] Therefore, numerous trifluoromethylthiolation approaches have been developed by using either nucleophilic[8] or electrophilic SCF_3 reagents.[9] Nevertheless, the introduction of SCF_3 group through a radical pathway has been relatively less explored.[10-15] Recently, Wang disclosed the synthesis of SCF_3-containing oxindoles through a $.SCF_3$ addition/cyclization pathway.[11] Wang and Xu reported an intramolecular oxytrifluoromethylthiolation of alkenes is feasible under the catalysis of copper.[12] Silver-meditated direct trifluoromethylthiolation of $C(sp^3)$-H bonds have been developed by Tang[13] and Chen[14], respectively. Very recently, Liang disclosed a $AgSCF_3$-mediated radical cascade cyclization/trifluoromethylthiolation of 1,6-enynes.[15]

On the other hand, thiocyano group is a versatile synthon which could be readily converted to other functional groups, such as sulfide,[16] thiocarbamate,[17] trifluoromethylthio[18] and thiotetrazole[19]. A variety of thiocyanation methods with the involvement of ·SCN were known.[20] However, the tandem thiocyanation/cycliaztion reactions of unsaturated C-C bonds remain less explored.[21] In particular, no precedent exists for thiocyanation/cycliaztion reaction of alkynes.

Results and discussion

Initially, we investigated the reaction of phenyl 3-phenylpropiolate (**1a**) with $AgSCF_3$ using $K_2S_2O_8$ as the oxidant in the presence of HMPA at 75 °C under argon (Table 1, entry 1).[11] To our delight, the desired cyclized 3-trifluoromethylthiolated coumarin **2a** was obtained in 25% yield. Further screening of solvent showed that DMSO was superior to others, increasing the yield to 42% (entries 1-5). When HMPA was removed from the reaction mixture, the yield was improved to 57% (entry 6). The increasing of reaction temperature to 100 °C gave a similar yield (entry 7). However, a lower temperature of 30 °C gave an increased yield of 71% (entry 8). Next, the effects of various oxidants such as Oxone, $PhI(OAc)_2$, and

School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China.
Email: wanghg3@mail.sysu.edu.cn.
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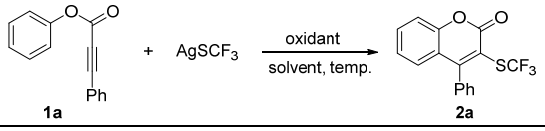
$Cu(OAc)_2{\cdot}H_2O$ were investigated (entries 9-11). Disappointedly, none of them were effective for the reaction. By increasing the loading of $K_2S_2O_8$ (4.0 equiv) and $AgSCF_3$ (2.0 equiv), the yield was further improved to 78% (entry 12). A slightly lower yield of 74% was observed when the reaction was performed under air (entry 13). Additional control experiments demonstrated $K_2S_2O_8$ was essential for the reaction as its omission gave no desired product (entry 14).

Table 1 Optimization of the reaction conditions[a]



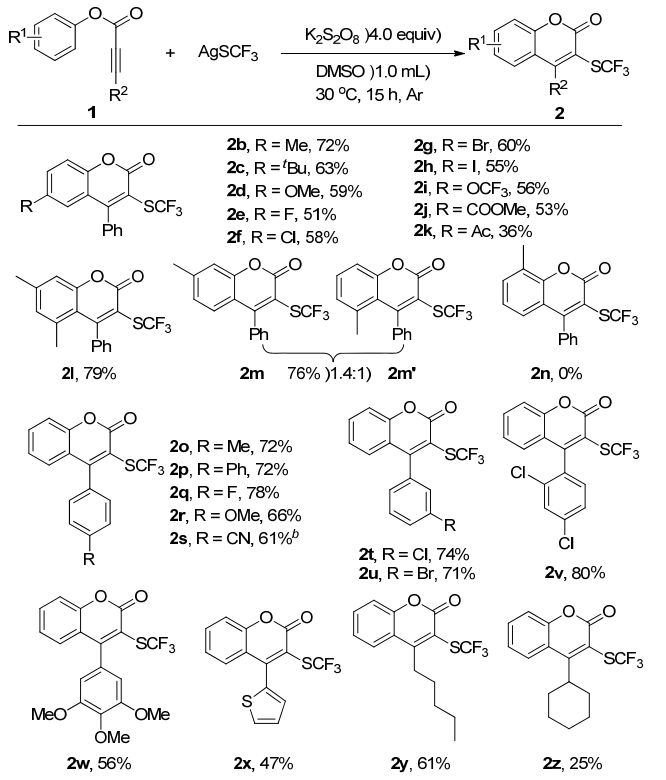
1a 2a

entry	oxidant (equiv)	solvent	additive (equiv)	temp (°C)	Yield (%)[b]
1	$K_2S_2O_8$ (3.0)	CH_3CN	HMPA (0.5)	75	25[c]
2	$K_2S_2O_8$ (3.0)	DMSO	HMPA (0.5)	75	42
3	$K_2S_2O_8$ (3.0)	toluene	HMPA (0.5)	75	0
4	$K_2S_2O_8$ (3.0)	DCE	HMPA (0.5)	75	trace
5	$K_2S_2O_8$ (3.0)	DMF	HMPA (0.5)	75	20
6	$K_2S_2O_8$ (3.0)	DMSO	-	75	57
7	$K_2S_2O_8$ (3.0)	DMSO	-	100	58
8	$K_2S_2O_8$ (3.0)	DMSO	-	30	71
9	Oxone (3.0)	DMSO	-	30	trace
10	PhI(OAc) (3.0)	DMSO	-	30	trace
11	$Cu(OAc)_2{\cdot}H_2O$ (3.0)	DMSO	-	30	0
12[d]	**$K_2S_2O_8$ (4.0)**	**DMSO**	**-**	**30**	**78**[c]
13[d, e]	$K_2S_2O_8$ (4.0)	DMSO	-	30	74
14	-	DMSO	-	30	0

[a] Unless otherwise noted, all reactions were conducted with **1a** (0.1 mmol), $AgSCF_3$ (1.5 equiv), and oxidant (3.0 euqiv) in solvent (1.0 mL) at 30 °C for 15 h under Ar. [b] ^1H NMR yield based on **1a** using methyl 4-bromobenzoate as internal standard. [c] Isolated yield. [d] Oxidant (4.0 equiv), $AgSCF_3$ (2.0 equiv). [e] The reaction was performed under air.

With the optimized conditions in hand, various substituted aryl alkynoates **1a-z** were synthesized and subjected to evaluate the scope and limitation of this transformation. As depicted in Table 2, alkynoates with different substituents on the phenoxy ring, regardless of electron-withdrawing or -donating properties, could be converted to the corresponding products in moderate to good yields (**2a-m**). A variety of functional groups, such as methoxyl (**2d**), halogen (**2e-h**), trifluoromethoxyl (**2i**), ester (**2j**), acetyl (**2k**) were well tolerated under the reaction conditions. Interestingly, the di-*meta*-substituted substrate did not hamper the reactivity, giving a good yield of 79% (**2l**). Two regioisomers **2m** and **2m'** were obtained in a ratio of 1.4:1 when *meta*-methyl substituted phenoxy ring was employed. No desired product was detected with a methyl group substituted at the *ortho*-position of the phenoxy (**2n**). Next, the compatibility of the substituents on the alkynyl moiety were also investigated (**2o-w**). Arylpropilates with substituents at *ortho*, *meta*, or *para*-position of the phenyl ring were all well tolerated in the reaction, affording the products in moderate to good yields. The heterocyclic 2-thienyl group was also compatible (**2x**). Delightedly, phenyl 2-octynoate (**2y**) and phenyl 3-cyclohexylpropiolate (**2z**) bearing an alkyl substituent were also suitable substrates, thus greatly extending the scope of this transformation.

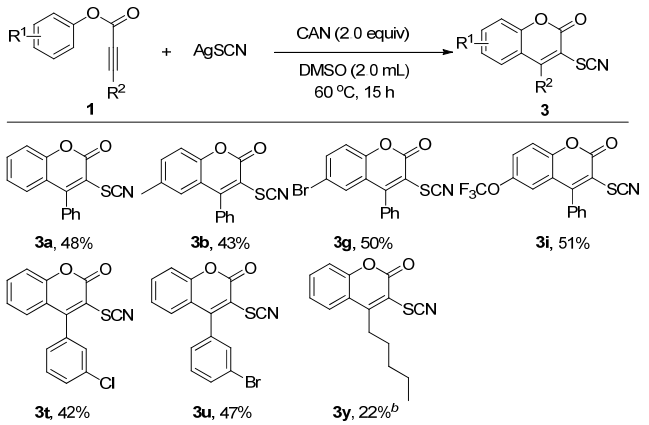
Table 2 Scope of the Trifluoromethylthiolation Reaction of Aryl Alkynoate Esters with $AgSCF_3$[a]



[a] Reaction conditions: **1** (0.2 mmol), $AgSCF_3$ (2.0 equiv), $K_2S_2O_8$ (4.0 equiv), DMSO (1.0 mL), 30 °C, under Ar, 15 h. [b] At 50 °C.

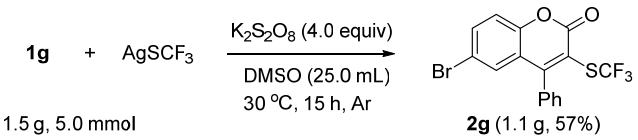
Encouraged by the above results, we then turned our attention to investigate of the feasibility of thiocyanation of alkynoates using a similar protocol (Table 3). To our disappointment, the desired 3-thiocyanated coumarin products were not produced under the above standard conditions using AgSCN as the thiocyano source. It was reported that the thiocyanate radical could be formed by the oxidation of thiocyanate anion with various oxidants, such as CAN (ammonium nitrate), hypervalent iodine reagents, oxone, and so on.[20] Therefore, screening of different oxidants and thiocyanate salts turned out that the combination of CAN ($Ce(NH_4)_2(NO_3)_6$, 2.0 equiv) and silver thiocyanate (2.0 equiv) in DMSO (2.0 mL) at 60 °C was effective for the reaction, affording the product in 48% yield (**3a**). Similar to the trifluoromethylthiolation reaction, aryl alkynoates with various substituents were also compatible with the reaction conditions to give the corresponding products in moderate yields. Phenyl 2-octynoate could also be converted to the cyclization product with CH_3CN as solvent, albeit in a low yield of 22% (**3y**).

Table 3 Scope of the Thiocyantion Reaction of Aryl Alkynoate Esters with AgSCN[a]



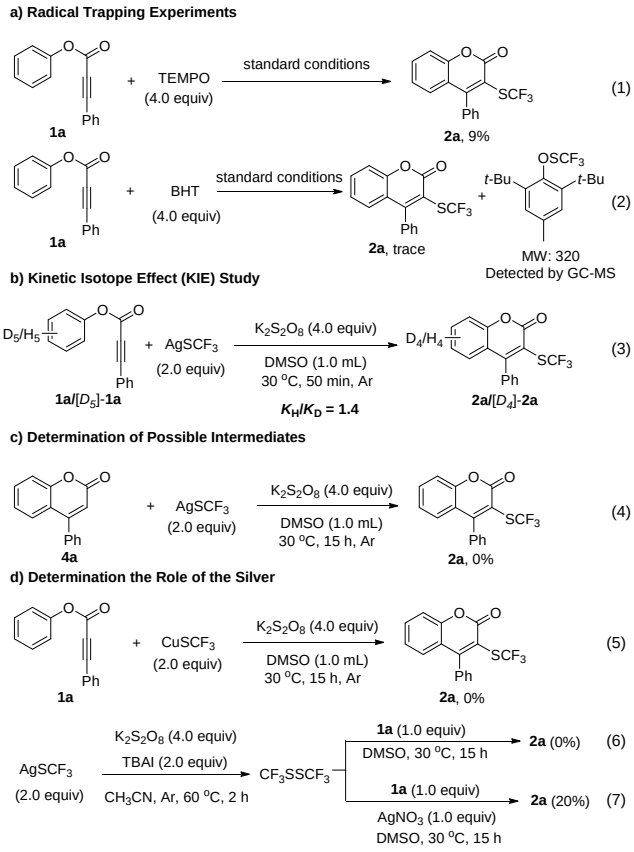
[a] Reaction conditions: **1** (0.2 mmol), AgSCN (2.0 equiv), CAN (2.0 equiv), DMSO (2.0 mL), 60 °C, 15 h, under air. [b] Solvent: CH_3CN (2.0 mL)

To demonstrate the scalability of our protocol, the reaction of **1ag** in a 5 mmol scale was conducted under the standard conditions, giving 1.1 gram of the product in 57% yield (Scheme 1).



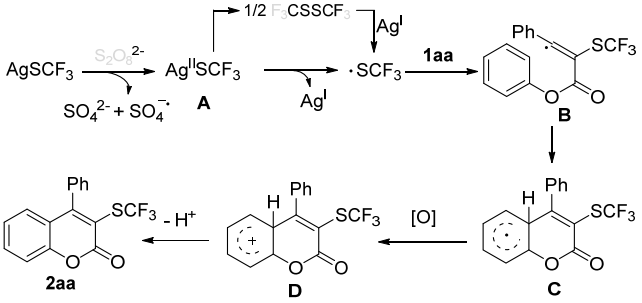
Scheme 1. Gram Scale Synthesis of **2g**.

To probe the possible reaction mechanism, a series of control experiments were carried out (Scheme 2). Firstly, radical trapping experiments were conducted. When 4.0 equiv of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added, only 9% yield was detected (eq 1). Additionally, BHT (butylhydroxytoluene) also inhibited the transformation significantly and the BHT-SCF_3 (MS = 320) adduct was detected by GC-MS analysis (eq 2), indicating a radical pathway involved and that $\cdot SCF_3$ radical might be generated in the reaction. An intermolecular kinetic isotope effect (KIE) value of 1.4 suggested the C-H bond cleavage step was not rate-determining (eq 3). To determine the possible intermediate of this transformation, coumarin **4a** was subjected the standard conditions. The trifluoromethylthiolation coumarin **2a** could not be obtained (eq 4). Finally, the role of silver in the reaction system was studied. No product was formed when $AgSCF_3$ was replaced by $CuSCF_3$, which indicated that silver was essential for the reactivity (eq 5). It was reported that F_3CSSCF_3 might act as $\cdot SCF_3$ source in some reactions.[11] Therefore, F_3CSSCF_3 was prepared according to a known procedure[22] and used for our reaction. In the presence of $AgNO_3$, the trifluoromethylthiolation product was obtained in 20% yield (eq 7), while no desired product was observed without silver (eq 6).



Scheme 2 Mechanistic Studies.

Based on the above observations and previous reports,[6,11-15,23] a plausible mechanism was outlined in Scheme 3. Initially, $AgSCF_3$ is oxidized by $K_2S_2O_8$ to generate a $[Ag^{II}SCF_3]$ species **A**, which could produce the $\cdot SCF_3$ radical through single electron transfer. Alternatively, F_3CSSCF_3, generated from $[Ag^{II}SCF_3]$, might be a possible source of $\cdot SCF_3$. Regio-selective addition of the $\cdot SCF_3$ to **1a** affords a vinyl radical **B**. Thereafter, an intramolecular cyclization gives a radical intermediate **C**, which is further oxidized by Ag^{II} to deliver the F-C reaction Wheland intermediate **D**. The deprotonation/rearomatization yields the final product **2a**.



Scheme 3. Proposed Mechanism.

Conclusions

In conclusion, we have developed a novel oxidative radical cyclization of aryl alkynoate esters. This method provides a

simple and efficient synthesis of various 3-trifluoromethylthiolated or 3-thiocyanated coumarins from readily accessible starting materials. Mild reaction conditions, excellent functional group tolerance, and generally good yields were observed. Preliminary mechanistic studies suggested a radical reaction pathway was involved.

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