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Oxidative Trifluoromethylthiolation of Terminal Alkynes with AgSCF₃: A Convenient Approach to Alkynyl Trifluoromethyl Sulfides

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A new method for the efficient synthesis of alkynyl trifluoromethyl sulfides was developed. By combining AgSCF₃ and NCS in N_1N -dimethylacetamide, an electrophilic active intermediate was produced, which was then treated with a

Introduction

The trifluoromethanesulfenyl group (SCF_3) is one of the most important fluorine-containing groups. Its unique properties, such as its strong electron-withdrawing effects and extremely high lipophilicity,^[1] have received increasing attention from the pharmaceutical and agrochemical industries.^[2] Thus, numerous methods have been reported for the preparation of trifluoromethylated compounds.^[3] Especially over the past several years, significant progress has been made in SCF₃ chemistry. A lot of effort has been devoted to the direct trifluoromethylation of different substrates. Typical examples involve the development of new trifluoromethylthiolating reagents^[4-9] and transition-metal-mediated/catalyzed trifluoromethylthiolation reactions.^[10,11] Despite the fact that great achievements have been made in the direct formation of C-SCF₃ bonds, the construction of Csp-SCF3 bonds has been rarely described. Lu and Shen developed a copper-catalyzed trifluoromethylthiolation of terminal alkynes by using a novel thioperoxy reagent developed by their group [Scheme 1, Equation (a)].^[5a] Billard reported a base-catalyzed trifluoromethylthiolation of terminal alkynes by using a trifluoromethanesulfenamide reagent [Scheme 1, Equation (b)].^[4e] Although both of these methods supplied alkynyl trifluoromethyl sulfides in good to excellent yields, they suffered from the pre-preparation of electrophilic trifluoromethylthiolation reagents. In 2012, our group described the oxidative trifluoromethylthiolation

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variety of terminal alkynes to afford the corresponding trifluoromethanesulfenylated products in moderate to excellent vields.

of terminal alkynes by the combination of commercially available TMSCF₃ and S₈ [Scheme 1, Equation (c)].^[10e] This method represented a straightforward approach to a broad range of alkynyl trifluoromethyl sulfides. However, an excess amount of expensive TMSCF3 was required. Considering the fact that alkynes are of paramount importance in organic chemistry,^[12] alkynyl trifluoromethyl sulfides should become a type of useful building block that can potentially be used in medicinal and material chemistry.^[13] Thus, it is highly desirable to develop other more convenient and efficient methods for the preparation of alkynyl trifluoromethyl sulfides. In continuation of our recent research interest in oxidative trifluoromethylation^[14] and trifluoromethylthiolation reactions,[10b,10e] we herein report another type of oxidative trifluoromethylthiolation^[15] with AgSCF₃ for the preparation of alkynyl trifluoromethyl sulfides [Scheme 1, Equation (d)]. Compared to previous methods, the current one avoids the use of pre-prepared electrophilic reagents and an excess amount of TMSCF₃.^[16]



Scheme 1. Different strategies to alkynyl trifluoromethyl sulfides; bpy = 2,2'-bipyridyl, LiHMDS = lithium hexamethyldisilazane.

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Results and Discussion

Shen's electrophilic trifluoromethylthiolation reagent [Scheme 1, Equation (a)] was prepared from AgSCF₃ and a hypervalent iodine compound.^[5a,5c] Inspired by this excellent work, we wondered if the electrophilic trifluoromethylthiolation reagent could be generated in situ from a nucleophilic trifluoromethylthiolation reagent and an oxidant and then treated with different nucleophiles. Initially, phenylacetylene (1a) was chosen as the test substrate by using AgSCF₃ as the trifluoromethylthio (CF_3S_{-}) source to optimize the reaction conditions (Table 1). To our disappointment, only a trace amount of desired product 2a was obtained if PhI(OAc)₂ was added to the reaction mixture (Table 1, entry 1). Neither PhICl₂ nor (NH₄)₂S₂O₈ gave better results (Table 1, entries 2 and 3). The important breakthrough happened upon using NBS and its derivatives as oxidants (Table 1, entries 4-7).^[11c,17] Among them, NCS was the best one; it gave 2a in 52% yield (Table 1, entry 5). Then, the reaction conditions were screened with different bases (Table 1, entries 8-13). A lower yield of 2a was obtained if NaOAc was used, whereas a trace amount of 2a was obtained if the organic base NEt₃ was used (Table 1,

Table 1. Optimization of the reaction conditions.^[a]

	H + AgSCF (1.2 equi 1a	oxidant (1. base (1.5 v.) r.t., ove	2 equiv.) equiv.) ent rnight	SCF ₃
Entry	Oxidant	Base	Solvent	Yield ^[b] [%]
1	PhI(OAc) ₂	KOAc	DMF	trace
2	PhICl ₂	KOAc	DMF	3
3	$(NH_4)_2S_2O_8$	KOAc	DMF	0
4	NBS	KOAc	DMF	46
5	NCS	KOAc	DMF	52
6	NIS	KOAc	DMF	20
7 ^[c]	TCCA	KOAc	DMF	24
8	NCS	NaOAc	DMF	36
9	NCS	NEt ₃	DMF	trace
10	NCS	K_2CO_3	DMF	58
11	NCS	K_3PO_4	DMF	67
12	NCS	K_2HPO_4	DMF	53
13	NCS	KO <i>t</i> Bu	DMF	39
14	NCS	K_3PO_4	DMA	88
15	NCS	K ₃ PO ₄	CH ₃ CN	trace
16 ^[d]	NCS	K ₃ PO ₄	DMA	94
17 ^[e]	NCS	K ₃ PO ₄	DMA	98
18 ^[e]	PhICl ₂	K ₃ PO ₄	DMA	35
19 ^[f]	NCS	K_3PO_4	DMA	7

[a] Reaction conditions: 1a (0.5 mmol), AgSCF₃ (0.6 mmol, 1.2 equiv.), oxidant (0.6 mmol, 1.2 equiv.), base (0.75 mmol, 1.5 equiv.), solvent (10.0 mL), r.t., overnight, under an atmosphere of N₂. DMF = N,N-dimethylformamide, DMA = N,N-dimethylacetamide, NBS = N-bromosuccinimide, NCS = N-chlorosuccinimide, NIS = *N*-iodosuccinimide, TCCA = trichloroisocyanuric acid. [b] Yields were determined by ¹⁹F NMR spectroscopy by using trifluoromethoxybenzene as an internal standard. [c] TCCA [d] K₃PO₄ (0.2 mmol,0.4 equiv.). (1.2 mmol, 2.4 equiv.). [e] AgSCF₃ (0.75 mmol, 1.5 equiv.), oxidant (0.75 mmol, 1.5 equiv.), K₃PO₄ (1.2 mmol, 2.4 equiv.). [f] CuSCF₃ (0.75 mmol, 1.5 equiv.), NCS (0.75 mmol, 1.5 equiv.), K₃PO₄ (1.2 mmol, 2.4 equiv.).

entries 8 and 9). K_3PO_4 was selected from the several potassium salts, and the yield slightly improved to 67% (Table 1, entry 11). The solvent was crucial to the reaction yield. If the reaction was performed in DMA, the yield sharply improved to 88% (Table 1, entry 14). In contrast, only a trace amount of **2a** was obtained in CH₃CN (Table 1, entry 15). The reaction yield was further improved by increasing the amount of base, AgSCF₃, and oxidant, and it finally reached as high as 98% (Table 1, entries 16 and 17). Notably, **2a** was obtained in 35% yield if PhICl₂ was used as the oxidant under the optimal reaction conditions (Table 1, entry 18). Upon using CuSCF₃ as the trifluoromethylthio source, **2a** was obtained in only 7% yield (Table 1, entry 19).

The substrate scope of the oxidative trifluoromethylthiolation reaction was then investigated with various terminal alkynes under the optimal reaction conditions (Table 2). A series of electron-rich and electron-deficient terminal alkynes were transformed into their corresponding alkynyl trifluoromethyl sulfides in moderate to excellent yields. Different functional groups, including F and Br, were compatible with the reaction conditions. Thiophene derivative 1k was trifluoromethylthiolated under the standard conditions to give 2k in 65% yield. Aliphatic alkynes also reacted under these conditions to afford desired products 2l and 2m in moderate to good yields.

Table 2. Oxidative trifluoromethylthiolation of terminal alkynes under the optimal reaction conditions.



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Oxidative Trifluoromethylthiolation of Terminal Alkynes

To understand the reaction mechanism, ¹⁹F NMR spectroscopy was used to track the reaction (Table 3). It was found that after 10 min AgSCF₃ was completely converted into a new intermediate, which was consistent with known electrophilic trifluoromethylthiolation reagent **3** (resonance at $\delta = -48.1$ ppm, see the Supporting Information).^[11c,17] As time went on, resonances attributable to desired product **2a** gradually increased, whereas those for intermediate **3** decreased. Thus, it is concluded that intermediate **3** is the active species in our reaction system.

Table 3. Monitoring the reaction by ¹⁹F NMR spectroscopy.^[a]



[a] Reaction conditions: **1a** (0.5 mmol), AgSCF₃ (0.75 mmol), NCS (0.75 mmol), K₃PO₄ (1.2 mmol), DMA (10.0 mL), r.t., under an atmosphere of N₂. [b] Yields were determined by ¹⁹F NMR spectroscopy by using trifluoromethoxybenzene as an internal standard.

Several experiments were performed to obtain more details of the reaction process (Scheme 2). The reaction of phenylacetylene (1a) with reagent 3 under basic conditions did not give desired product 2a [Scheme 2, Equation (a)]. The addition of a sliver salt was necessary for the formation of 2a [Scheme 2, Equations (b) and (c)]. Although the exact reaction mechanism is still unclear, the above results show that the formation of the C_{sp} -SCF₃ bond does not pass through a typical S_N 2-type reaction, but rather a silver-mediated electrophilic reaction.



Scheme 2. The reaction of phenylacetylene (1a) with reagent 3.

Notably, the yields in Scheme 2 are lower than the yield obtained under the optimal reaction conditions in Table 2, which shows that our oxidative trifluoromethylthiolation system has some advantages over the normal electrophilic trifluoromethylthiolation reactions.

Conclusions

We demonstrated the novel oxidative trifluoromethylthiolation of terminal alkynes by mixing $AgSCF_3$ and NCS in DMA. Electrophilic intermediate **3** is believed to be formed in situ and involved in the silver-mediated trifluoromethylthiolation reaction. This protocol provides a convenient and efficient method for the synthesis of various alkynyl trifluoromethyl sulfides in high yields. Further investigation of this reaction system and its potential applications are in progress.

Experimental Section

General Procedure for the Oxidative Trifluoromethylthiolation of Terminal Alkynes 1: Terminal alkyne 1 (0.50 mmol) was added to a stirred solution of AgSCF₃ (156.7 mg, 0.75 mmol), NCS (100.1 mg, 0.75 mmol), and K_3PO_4 (254.8 mg, 1.20 mmol) in anhydrous DMA (10.0 mL) under a nitrogen atmosphere at room temperature. The reaction mixture was stirred at room temperature overnight, then diluted with H₂O and extracted with Et₂O. The combined organic layer was washed with brine, dried with Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give alkynyl trifluoromethyl sulfide 2.

Supporting Information (see footnote on the first page of this article): General methods, experimental procedures, and characterization data for all compounds.

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Trifluoromethylthiolation

			NCS (1.5 equiv.) K₃PO₄ (2.4 equiv.)	
R— — —H	+	AgSCF ₃ (1.5 equiv.)	DMA, r.t., overnight	RSCF3
R = alkyl, aryl		(110 04011)		13 examples 61–93 % yield

A new oxidative trifluoromethylthiolation system, AgSCF₃/NCS, is developed and applied in the efficient synthesis of alkynyl trifluoromethyl sulfides. Various desired compounds are obtained under mild conditions in moderate to excellent yields. DMA = N,N-dimethylacetamide.

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