Direct Electrophilic Trifluoromethylthiolation of *N*-Benzyl Indoles Using AgSCF₃Lan Ma^a, Xiu-Fen Cheng^a, Yan Li^{a,*} and Xi-Sheng Wang^{a,*}^aDepartment of Chemistry, University of Science and Technology of China, Hefei 230026, China

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ABSTRACT

A novel electrophilic trifluoromethylthiolation reaction system has been developed with AgSCF₃ used directly as the SCF₃ source, in the presence of KI/K₂S₂O₈/I₂. Various *N*-benzylindoles have been trifluoromethylthiolated successfully with this system, and the mechanism investigation showed an electrophilic reagent was generated in situ.

Keywords:

Trifluoromethylthiolation

Indole

AgSCF₃

Electrophilic reaction

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The selective introduction of fluorine-containing groups into organic molecules has attracted increasing interests and is emerging as a new and valuable strategy in drug design and screening, for the fluorinated compounds usually showed unprecedented physical and chemical properties, such as increasing hydrolytic stability and block metabolism, compared with the parent molecules.¹ Among all intriguing fluorine-containing moieties, the trifluoromethylthio group (SCF₃) has been widely used in pharmaceuticals, agrochemicals, and material sciences owing to its strong electron-withdrawing effect and high lipophilicity ($\pi = 1.44$).^{1,2}

Indole and its derivatives are important structural motifs in various fields including materials, pharmaceuticals, agrochemicals, and dyes.³ It was noted that fluorine-containing indoles have emerged as biologically and medicinally beneficial compounds due to its various bioactive properties,⁴ and thus considerable efforts have been devoted to developing new methods to make such structure motifs. Based on the development of electrophilic trifluoromethylthiolating reagents in the last few years, several newly-developed reagents have also been used to realize the trifluoromethylthiolation of indoles. In 2012, Billard and Langlois reported the first example of Brønsted acid-mediated trifluoromethylthiolation of indoles using the electrophilic trifluoromethanesulfanylamide reagent.⁵ Shibata and co-workers developed the trifluoromethylthiolation of indoles with electrophilic-type trifluoromethanesulfonyl hypervalent iodonium ylide catalyzed by copper(I) chloride.⁶ Shen group has also trifluoromethylthiolated indoles successfully using their own developed hypervalent iodine reagent.⁷ Most recently, Glorius and _____ coworkers reported transition-metal-free

trifluoromethylthiolation of *N*-heteroarenes with the *N*-(trifluoromethylthio)phthalimide.⁸ Zhang group has also developed a new method using CF₃SO₂Na for direct trifluoromethylthiolation of indoles.⁹ In view of our continuous interests in trifluoromethylthiolation of organic molecules, we envisioned that the stable and readily available AgSCF₃ can be used as a trifluoromethylthiolating reagents on the combination of suitable oxidant,¹⁰ which will avoid the preparation of electrophilic reagents. Herein, we report a novel electrophilic trifluoromethylthiolation system using AgSCF₃ as the SCF₃ source in presence of K₂S₂O₈/KI/I₂, with which a variety of *N*-benzyl indoles were trifluoromethylthiolated at 3-position of pyrrole ring.

In 2014, we have developed a practical and easy-handling method to trigger F₃CS• radical with AgSCF₃/K₂S₂O₈ system,¹⁰ which has now been widely used in various trifluoromethylthiolation reactions by several groups.¹¹ Herein, we commenced our study with *N*-benzylindole (**1a**) as a model substrate in the presence of AgSCF₃ (1.5 equiv.) and K₂S₂O₈ (3.0 equiv.) in CH₃CN at 60°C. To our delight, the desired trifluoromethylthiolated product **2a** was obtained successfully, albeit with relatively low yield (22%, Table 1, entry 1). Not surprisingly, the other oxidants, including PhI(OAc)₂, and NCS gave none of the desired product in this reaction system (entries 2–3). As directed by Clark's and Buchwald's reports¹² that addition of KI or tetra-*n*-butylammonium iodide (TBAI) into AgSCF₃ in acetonitrile can release SCF₃ moiety more easily via the formation of intermediate [Ag(SCF₃)I]⁺, we next investigated different halide sources. To our excitement, KI and NaI enhanced the yield dramatically to 60% and 46% (entries 4, 5), while no

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product was observed with other iodides, bromides and chlorides used as additives (entries 6–9, see also Table S2 in the supporting information). To improve the yield further, a careful survey of solvents was then performed. Unfortunately, the reaction was almost quenched in most organic solvents except for MeOH, but only with low yield (entries 10–11, see also Table S3 in the supporting information). Increasing the amounts of KI to 2.0 equivalents led to a higher yield of 85% (entry 12). To our interest, the replacement of AgSCF₃ with CuSCF₃ gave only 33% yield of **2a**, which clearly showed the importance of silver species in this trifluoromethylthiolation system (entry 13). Considering that I₂ could be generated in situ through the oxidation of K₂S₂O₈ to KI, 1.25 equivalents of I₂ has also been examined in place of KI/ K₂S₂O₈, in which the desired trifluoromethylthiolated product **2a** was obtained smoothly in 89% yield (entry 14). Notably, the addition of both I₂ (2.5 equiv.) and KI (1.5 equiv.) to AgSCF₃/K₂S₂O₈ system could afford the best isolated yield (82%, entry 18).

Table 1. Trifluoromethylthiolation of *N*-benzyl indole: optimization of reaction conditions^a

Entry	Oxidant	Additive (eq.)	Yield (%)
1	K ₂ S ₂ O ₈	-	22
2	PhI(OAc) ₂	-	6
3	NCS	-	trace
4	K ₂ S ₂ O ₈	KI (1.5)	60
5	K ₂ S ₂ O ₈	NaI (1.5)	46
6	K ₂ S ₂ O ₈	TBAI (1.5)	trace
7	K ₂ S ₂ O ₈	NIS (1.5)	trace
8	K ₂ S ₂ O ₈	KCl (1.5)	0
9	K ₂ S ₂ O ₈	KBr (1.5)	0
10 ^c	K ₂ S ₂ O ₈	KI (1.5)	20
11 ^d	K ₂ S ₂ O ₈	KI (1.5)	0
12	K ₂ S ₂ O ₈	KI (2.0)	85 (78)
13 ^e	K ₂ S ₂ O ₈	KI (2.0)	33
14		I ₂ (1.25)	89 (68)
15		I ₂ (2.0)	53
16	K ₂ S ₂ O ₈	KI (1.5)/I ₂ (1.5)	90 (74)
17	K ₂ S ₂ O ₈	KI (1.5)/I ₂ (1.5)	86 (62)
18	K ₂ S ₂ O ₈	KI (1.5)/I ₂ (1.5)	98 (82)

^aReaction conditions: **1a** (0.1 mmol, 1.0 equiv.), AgSCF₃ (1.5 equiv.), Oxidant (3.0 equiv.), Additive (1.5 equiv.), CH₃CN (3 mL), 60 °C, 24 h.

^bGC yield. Isolated yield is displayed in parentheses.

^cMeOH was used as solvent.

^dDMSO was used as solvent.

^eCuSCF₃ (1.5 equiv.) was used instead of AgSCF₃.

With the optimized reaction conditions in hand, we next investigated the scope of *N*-benzyl indoles. As shown in Table 2, a variety of *N*-benzyl indoles were trifluoromethylthiolated smoothly at 3-position in moderate to good yields. Initially, the examination of *N*-protecting groups indicated that benzyl group (**1a**) and its derivatives (**1m–1n**) were still the optimal choice. Next, the substituent effects of the aryl ring (**1b–1l**) were also investigated. Not surprisingly, a series of *N*-benzyl indoles (**1b–1g**) with electron-donating substituents, including Me and MeO,

Table 2. Scope of *N*-benzyl indoles^{a,b}

<div>AgSCF₃ (1.5 equiv.) Oxidant/Additive MeCN, 60 °C, 24 h</div> <div> 1</div>					
<div> 2a, A: 82% B: 78% C: 68%</div>	<div> 2b, A: 86% B: 65% C: 59%</div>	<div> 2c, A: 56% B: 62% C: 38%</div>			
<div> 2d, A: 68% B: 82% C: 49%</div>	<div> 2e, A: 82% B: 66% C: 65%</div>	<div> 2f, A: 66% B: 71% C: 59%</div>			
<div> 2g, A: 72% B: trace C: 74%</div>	<div> 2h, A: 68% B: trace C: 41%</div>	<div> 2i, A: 78% B: trace C: 63%</div>			
<div> 2j, A: 80% B: trace C: 57%</div>	<div> 2k, A: 89% B: trace C: 59%</div>	<div> 2l, A: 88% B: trace C: 69%</div>			
<div> 2m, A: 74% B: 79% C: 62%</div>	<div> 2n, A: 96% B: 77% C: 59%</div>	<div> 2o, A: 0% B: 0% C: 0%</div>			

^aReaction conditions A: **1a** (0.1 mmol, 1.0 equiv.), AgSCF₃ (1.5 equiv.), K₂S₂O₈ (3.0 equiv.), KI (1.5 equiv.), I₂ (2.5 equiv.), CH₃CN (3 mL), 60 °C, 24 h. Reaction conditions B: **1a** (0.1 mmol, 1.0 equiv.), AgSCF₃ (1.5 equiv.), K₂S₂O₈ (3.0 equiv.), KI (2.0 equiv.), CH₃CN (3 mL), 60 °C, 24 h. Reaction conditions C: **1a** (0.1 mmol, 1.0 equiv.), AgSCF₃ (1.5 equiv.), I₂ (1.25 equiv.), CH₃CN (3 mL), 60 °C, 24 h. ^bIsolated yield.

afforded the desired products (**2b–2g**) in moderate to good yields, no matter where such substituted groups were placed on the phenyl ring. It seemed strange that no trifluoromethylthiolated products were obtained when F, Cl, Br-containing indoles (**1h–1l**) were used in condition B without the addition of I₂. Fortunately, the corresponding trifluoromethylthiolated products **2** could be obtained successfully when the additives were changed to KI (1.5

equiv.) and I₂ (2.5 equiv.) (Condition A) or I₂ only (Condition C). Notably, conditions A and C were also suitable for the steric hindrance substrate **1g**. While the acid sensitive PMB (*p*-methoxybenzyl) group could be well tolerated in this reaction system (**1n**), indole with strong electron-withdrawing substituent (NO₂, **1o**) on the phenyl ring gave none of the desired product under all three conditions. Comparing all conditions A, B and C, condition A demonstrated the best functional groups tolerance and gave the best results in almost all cases.

To understand the mechanism of this reaction, a series of experiments were carried out. First, as directed by GC-MS detection, 1-benzyl-3-iodoindole **3** has been observed in the reaction mixture. However, no desired product **2a** was obtained when 1-benzyl-3-iodoindole **3** was subjected to the standard conditions, which clearly indicated that iodoindole was not involved in the reaction as a possible intermediate (Scheme 1).

Scheme 1. Intermediate study.

To get more details of the reaction process, we tracked the reaction under the Condition A carefully using ¹⁹F NMR spectroscopy. It was found that [Ag(SCF₃)I][−] (δ -16.3 ppm) was formed immediately, and the signal of [Ag(SCF₃)I][−] decreased gradually while F₃CSSCF₃ (δ -46.8 ppm) increased accordingly. The desired product **2a** (δ -45.7 ppm) was observed after 2 hours, and thus increased gradually along with the reduction of F₃CSSCF₃.¹³ To investigate the exact role of F₃CSSCF₃, we next set out to perform a series of controlled experiments. Under the standard conditions without indole **1a**, ¹⁹F NMR monitoring showed only F₃CSSCF₃ could be detected after 5 hours. After filtration, no reaction occurred with the subjection of **1a** and K₂S₂O₈ (Eq. 2, Scheme 2), but addition of KI and K₂S₂O₈ or I₂ only together with **1a** afforded **2a** in 21% and 53% yield, respectively (Eq. 1 & 3). Meanwhile, stirring the mixture of 1.5 equiv. of AgSCF₃ and 0.75 equiv. of I₂ in CH₃CN at 60 °C in 1 hour gave a large amount of F₃CSSCF₃, and there was still I₂ remaining to be detected by starch in the reaction system. It was found **2a** was obtained with 73% GC yield with the subjection of **1a** (Eq. 4), which further confirmed the active trifluoromethylthiolating reagent could be generated in situ from F₃CSSCF₃ in presence of I₂ (or KI/K₂S₂O₈).

Scheme 2. Controlled experiments.

On the base of all observations mentioned above and previous reports, a possible mechanism is proposed (Scheme 3). The oxidation of KI by K₂S₂O₈ affords I₂, which generates ISCF₃ after the following reaction with AgSCF₃. As an intermediate detected in all cases, F₃CSSCF₃ is given via disproportionation of ISCF₃¹⁴ or reaction of AgSCF₃ and K₂S₂O₈, and would regenerate active ISCF₃. The electrophilic attack of 3-position on pyrrole ring by ISCF₃, followed by hydrogen elimination, yields the desired trifluoromethylthiolated indole **2a**.

Scheme 3. Proposed mechanism.

In conclusion, we have developed a novel method for electrophilic trifluoromethylthiolation of *N*-benzylindoles with AgSCF₃ used directly as the SCF₃ source, in which an electrophilic trifluoromethylthiolating reagent was generated in situ in the presence of KI/K₂S₂O₈/I₂. Further studies to understand the mechanism and application to modify more complex molecules are still underway in our laboratory.

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