Direct Electrophilic Trifluoromethylthiolation of *N*-Benzyl Indoles Using $AgSCF_3$

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Direct Electrophilic Trifluoromethylthiolation of *N*-Benzyl Indoles Using $AgSCF_3$

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ABSTRACT

A novel electrophilic trifluoromethylthiolation reaction system has been developed with $AgSCF_3$ used directly as the SCF_3 source, in the presence of $KI/K_2S_2O_8/I_2$**.** Various *N*-benzylindoles have been trifluoromethylthiolated successfully with this system, and the mechanism investigation showed an eletrophilic reagent was generated in situ.

Keywords:
Trifluoromethylthiolation
Indole
$AgSCF_3$
Electrophilic reaction

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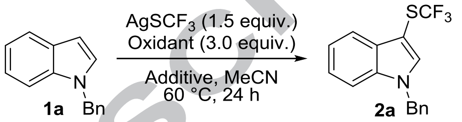
The selective introduction of fluorine-containing groups into organic molecules has attracted increasing interests and is emerging as a new and valuable strategy in drug design and screening, for the fluorinated compounds usually showed unprecedented physical and chemical properties, such as increasing hydrolytic stability and block metabolism, compared with the parent molecules.[1] Among all intriguing fluorine-containing moieties, the trifluoromethylthio group (SCF_3) 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 trifluoromethythiolating 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 regent.[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 CF_3SO_2Na 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 $AgSCF_3$ 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 $AgSCF_3$ as the SCF_3 source in presence of $K_2S_2O_8/KI/I_2$, 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 $F_3CS\bullet$ radical with $AgSCF_3/K_2S_2O_8$ 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 $AgSCF_3$ (1.5 equiv.) and $K_2S_2O_8$ (3.0 equiv.) in CH_3CN 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 reports[12] that addition of KI or tetra-n-butylammonium iodide (TBAI) into $AgSCF_3$ in acetonitrile can release SCF_3 moiety more easily via the formation of intermediate $[Ag(SCF_3)I]^-$, 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 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 $AgSCF_3$ with $CuSCF_3$ gave only 33% yield of **2a**, which clearly showed the importance of silver species in this trifluoromethylthiolation system (entry 13). Considering that I_2 could be generated in situ through the oxidation of $K_2S_2O_8$ to KI, 1.25 equivalents of I_2 has also been examined in place of KI/ $K_2S_2O_8$, in which the desired trifluoromethylthiolated product **2a** was obtained smoothly in 89% yield (entry 14). Notably, the addition of both I_2 (2.5 equiv.) and KI (1.5 equiv.) to $AgSCF_3/K_2S_2O_8$ system could afford the best isolated yield (82%, entry 18).

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

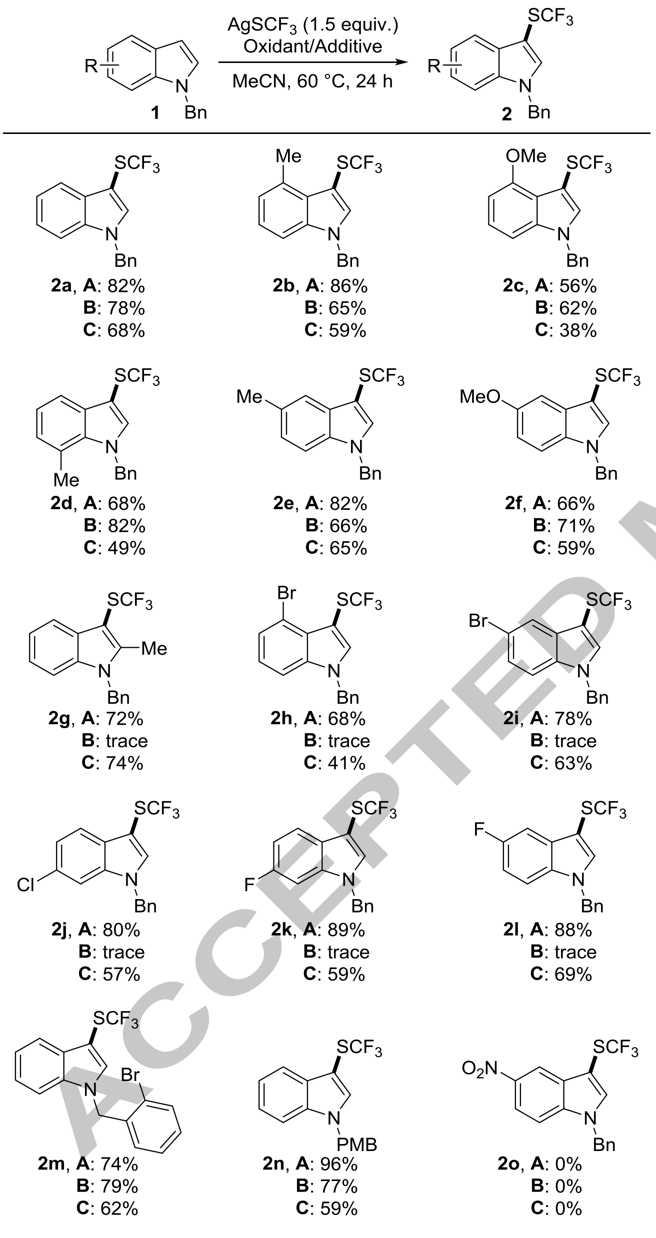


Entry	Oxidant	Additive (eq.)	Yield (%)
1	$K_2S_2O_8$	-	22
2	$PhI(OAc)_2$	-	6
3	NCS	-	trace
4	$K_2S_2O_8$	KI (1.5)	60
5	$K_2S_2O_8$	NaI (1.5)	46
6	$K_2S_2O_8$	TBAI (1.5)	trace
7	$K_2S_2O_8$	NIS (1.5)	trace
8	$K_2S_2O_8$	KCl (1.5)	0
9	$K_2S_2O_8$	KBr (1.5)	0
10[c]	$K_2S_2O_8$	KI (1.5)	20
11[d]	$K_2S_2O_8$	KI (1.5)	0
12	$K_2S_2O_8$	KI (2.0)	85 (78)
13[e]	$K_2S_2O_8$	KI (2.0)	33
14		I_2 (1.25)	89 (68)
15		I_2 (2.0)	53
16	$K_2S_2O_8$	KI (1.5)/I_2 (1.5)	90 (74)
17	$K_2S_2O_8$	KI (1.5)/I_2 (1.5)	86 (62)
18	$K_2S_2O_8$	KI (1.5)/I_2 (1.5)	98 (82)

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), $AgSCF_3$ (1.5 equiv.), Oxidant (3.0 equiv.), Additive (1.5 equiv.), CH_3CN (3 mL), 60 ˚C, 24 h.
[b] GC yield. Isolated yield is displayed in parentheses.
[c] MeOH was used as solvent.
[d] DMSO was used as solvent.
[e] $CuSCF_3$ (1.5 equiv.) was used instead of $AgSCF_3$.

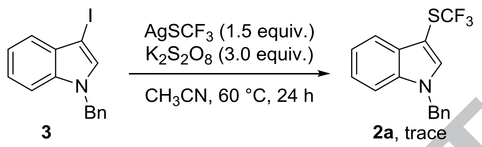
With the optimized reaction conditions in hand, we next investigated the scope of *N*-benzyl indoles. As shown in Table 2, a variety of *N*-benzyl indoles were trifluoromethylthiolated smoothly at 3-position in moderate to good yields. Initially, the examination of N-protecting groups indicated that 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, 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 I_2. Fortunately, the corresponding trifluoromethylthiolated products **2** could be obtained successfully when the additives were changed to KI (1.5 equiv.) and I_2 (2.5 equiv.) (Condition **A**) or I_2 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 (NO_2, **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.

Table 2. Scope of *N*-benzyl indoles[a,b]



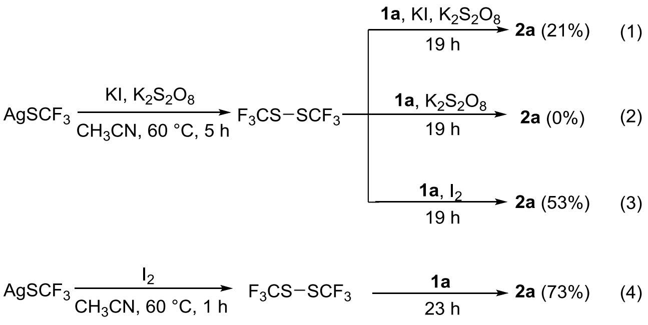
[a]Reaction conditions **A**: **1a** (0.1 mmol, 1.0 equiv.), $AgSCF_3$ (1.5 equiv.), $K_2S_2O_8$ (3.0 equiv.), KI (1.5 equiv.), I_2 (2.5 equiv.),CH_3CN (3 mL), 60˚C, 24 h. Reaction conditions **B**: **1a** (0.1 mmol, 1.0 equiv.), $AgSCF_3$ (1.5 equiv.), $K_2S_2O_8$ (3.0 equiv.), KI (2.0 equiv.), CH_3CN (3 mL), 60˚C, 24 h. Reaction conditions **C**: **1a** (0.1 mmol, 1.0 equiv.), $AgSCF_3$ (1.5 equiv.), I_2 (1.25 equiv.), CH_3CN (3 mL), 60˚C, 24 h. [b]Isolated yield.

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).



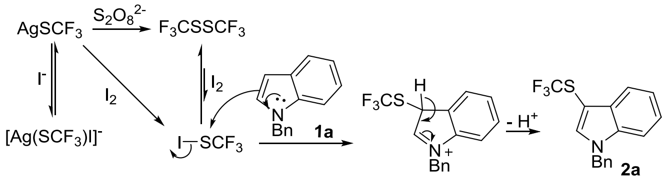
Scheme 1. Intermediate study.

To get more details of the reaction process, we tracked the reaction under the Condition A carefully using ^{19}F NMR spectroscopy. It was found that $[Ag(SCF_3)I]^-$ (δ -16.3 ppm) was formed immediately, and the signal of $[Ag(SCF_3)I]^-$ decreased gradually while F_3CSSCF_3 (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 F_3CSSCF_3.[13] To investigate the exact role of F_3CSSCF_3, we next set out to perform a series of controlled experiments. Under the standard conditions without indole **1a**, ^{19}F NMR monitoring showed only F_3CSSCF_3 could be detected after 5 hours. After filtration, no reaction occurred with the subjection of **1a** and $K_2S_2O_8$ (Eq. 2, Scheme 2), but addition of KI and $K_2S_2O_8$ or I_2 only together with **1a** afforded **2a** in 21% and 53% yield, respectively (Eq. 1 & 3). Meanwhile, stirring the mixture of 1.5 equiv. of $AgSCF_3$ and 0.75 equiv. of I_2 in CH_3CN at 60 ˚C in 1 hour gave a large amount of F_3CSSCF_3, and there was still I_2 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 F_3CSSCF_3 in presence of I_2 (or KI/ $K_2S_2O_8$).



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 $K_2S_2O_8$ affords I_2, which generates $ISCF_3$ after the following reaction with $AgSCF_3$. As an intermediate detected in all cases, F_3CSSCF_3 is given via disproportionation of $ISCF_3$[14] or reaction of $AgSCF_3$ and $K_2S_2O_8$, and would regenerate active $ISCF_3$. The electrophilic attack of 3-position on pyrrole ring by $ISCF_3$, 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 AgSCF$_3$ used directly as the SCF$_3$ source, in which an electrophilic trifluoromethylthiolating reagent was generated in situ in the presence of KI/$K_2S_2O_8$/I$_2$. Further studies to understand the mechanism and application to modify more complex molecules are still underway in our laboratory.

Acknowledgments

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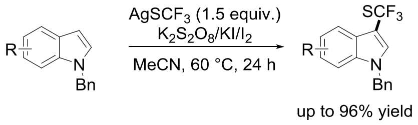

Highlights

1. $AgSCF_3/I_2/KI$ has been developed as a novel electrophilic trifluoromethylthiolating system.
2. Electrophilic trifluoromethylthiolation of N-benzylindoles has been developed.
3. Mechanistic studies indicate that $ISCF_3$ generated in situ played as the active SCF_3 reagent.