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An Improved Protocol for the Synthesis of α-Trifluoromethylthio-Substituted Ketones by Copper-Mediated Trifluoromethylthiolation of α-Bromo Ketones

Yangjie Huang,[a] Xing He,[a] Haohong Li,*[a] and Zhiqiang Weng*[a]

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An efficient and practical approach to α-trifluoromethylthio-substituted ketones was developed. The trifluoromethylthiolation of (bpy)Cu(SCF_3) (bpy = 2,2′-bipyridyl) with various α-bromo ketones afforded the desired α-trifluoromethylthio-substituted ketones in good yields. The reaction tolerates more functionally than previously reported methods and demonstrates efficient scalability and practicality.

Introduction

The introduction of the trifluoromethyl group (CF_3) into an organic molecule often profoundly modifies the metabolic stability, lipophilicity, bioavailability, biological activity, and selectivity of lead compounds.[1] In this context, the development of efficient and operationally simple routes with which to access molecules containing the CF_3 group has potential for pharmaceutical and agrochemical applications.[2,3] Among them, carbonyl compounds bearing a trifluoromethyl group at the α position constitute an interesting class of synthons that are useful for the synthesis of biologically active compounds.[4–6]

Conventionally, α-trifluoromethyl carbonyl compounds are synthesized by the reactions of silyl enol ethers[7] and enolates[8] (premade by using a strong base such as lithium diisopropylamide)[9] or by electrophilic trifluoromethylation of β-keto esters[10] with a trifluoromethylating reagent. Alternatively, these compounds can be readily synthesized by oxidative trifluoromethylation of olefins with *S*-(trifluoromethyl)diphenylsulfonium triflate[11] or with CF_3SO_2Na.[12] Additionally, an excellent example of nucleophilic trifluoromethylation of α-halogenated ketones by using fluoroform-derived $CuCF_3$ under mild conditions was recently reported by Grushin and co-workers.[13]

However, despite this promising precedence for the synthesis of α-trifluoromethyl carbonyl compounds, methods to access α-trifluoromethylthio-substituted ketones have only scarcely been studied. Pioneering studies conducted by Bayreuther and Haas[14] and by Kolasa[15] have demonstrated that reactions of ketones or ethyl benzoylacetate with trifluoromethylsulfenyl chloride yielded the α-SCF_3-substituted ketones. Recently, the groups of Shen[16] and Rueping[17] reported the electrophilic trifluoromethylthiolation of β-keto esters to give the corresponding α-trifluoromethylthiolated carbonyl compounds in good to excellent yields. Li and Zard showed that α-trifluoromethylthio-substituted ketones can be synthesized from trifluoromethylthiolation of α-bromo ketones with *O*-octadecyl-*S*-trifluorothiolcarbonate.[18]

Looking at the importance of CF_3S substituents in pharmaceutical, agricultural, and advanced material products,[19,20] the preparation of α-trifluoromethylthio-substituted ketones from readily available starting materials by a simple and convenient approach is consequently highly desirable. To this end, we recently reported the copper-catalyzed trifluoromethylthiolation of α-bromo ketones with elemental sulfur and CF_3SiMe_3 to generate α-trifluoromethylthio-substituted ketones.[21] The catalyst system was particularly effective for the trifluoromethylthiolation of α-bromo ketones having either electron-donating groups or electron-neutral groups on the aromatic rings. Nevertheless, trifluoromethylthiolation of α-bromo ketone derivatives with a copper catalyst remained difficult for α-bromo ketones possessing electron-withdrawing groups on the phenyl ring (Scheme 1). For instance, under catalytic conditions, 4-(2-bromoacetyl)benzonitrile afforded the trifluoromethylthiolated product in 13% yield, whereas reaction of 4-(2-bromoacetyl)anisole afforded the product in 88% yield. Consequently, there remains a clear need for further development of efficient synthetic methods for the trifluoromethylthiolation of α-halo ketones that demonstrate a broad substrate scope.

In connection with our recent studies on fluorinated copper reagents, we initiated an investigation on the nucleophilic trifluoromethylthiolation of aryl halides,[22] alkyl halides,[23] and allylic bromides[24] with (bpy)Cu(SCF_3) (**1**, bpy = 2,2′-bipyridine). In this paper, we report an improved

[a] Department of Chemistry, Fuzhou University, Fuzhou China, 350108
E-mail: zweng@fzu.edu.cn
http://chem.fzu.edu.cn/szdw/teacherinfo.aspx?id=99
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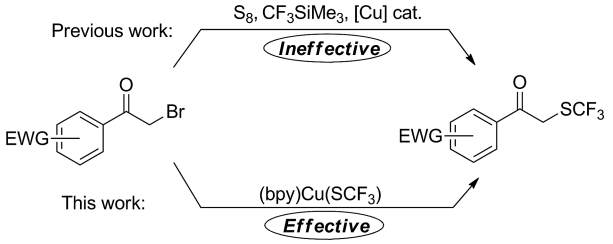


Scheme 1. Methods for the synthesis of α-SCF_3-substituted ketones. EWG = electron-withdrawing group.

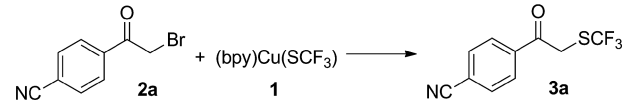
synthetic procedure for the preparation of α-trifluoromethylthio-substituted ketones by using **1** as the trifluoromethylthiolation reagent.

Results and Discussion

Initially, the trifluoromethylthiolation of (bpy)Cu(SCF_3) (**1**, 1.2 equiv.) with 4-(2-bromoacetyl)benzonitrile (**2a**) was selected as the model reaction to determine the optimum reaction parameters (Table 1). Upon performing the reaction at 25 °C in CH_3CN, an acceptable yield of 4-[2-(trifluoromethylthio)acetyl]benzonitrile (**3a**, 66%) was obtained in 16 h (Table 1, Entry 1). Further experiments indicated that raising the reaction temperature to 80 °C did not increase the yield of **3a** (49%; Table 1, Entry 2). The use of THF as a solvent at 80 °C for 16 h resulted in an improved yield of the product (76%; Table 1, Entry 3). Using DMF or *N*-methylpyrrolidone (NMP) as the solvent at 120 °C for 16 h generated a modest yield of **3a** (47 and 56%, respectively; Table 1, Entries 4 and 5). A rather low conversion was observed with CH_3OH and DMSO as the solvent (Table 1, Entries 6 and 7). Surprisingly, if a noncoordinating solvent such as CH_2Cl_2 was used at 25 °C for 16 h, the yield of **3a** increased to 81% (Table 1, Entry 8). Therefore, CH_2Cl_2 was determined to be the superior solvent for the reaction, and the yield of desired trifluoromethylthiolated product **3a** was further improved to 88% by raising the reaction temperature to 50 °C (Table 1, Entry 9). These findings show that the present protocol greatly improved the efficiency of the trifluoromethylthiolation in comparison to our previous synthesis,[21] with respect to substrates bearing electron-withdrawing groups.

We further investigated the trifluoromethylthiolation of (bpy)Cu(SCF_3) (**1**) with several α-bromo ketones to examine the scope and limits of the process. The results are summarized in Table 2. In general, the reactions of **1** with α-bromo ketones **2a**–**f** possessing electron-withdrawing substituents (e.g., CN, NO_2, CF_3, and CO_2Me) in the *para* and *meta* positions proceeded smoothly to afford corresponding products **3a**–**f** in good yields (77–83%; Table 2, Entries 1–6). Notably, these functional groups, which were problematic in our previous method, were well tolerated by the present reaction conditions. Electron-donating *para*-, *meta*-, and *ortho*-methoxy- or -amino-substituted aromatic α-bromo ketones **2g**–**k** were also found to react successfully, and desired ketones **3g**–**k** were produced in 82–93% yields

Table 1. Optimization of the Cu-mediated trifluoromethylthiolation of 4-(2-bromoacetyl)benzonitrile.[a]



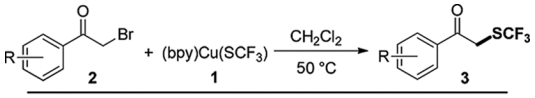
Entry	Solvent	Temp. [°C]	Time [h]	Yield [%][b]
1	CH_3CN	25	16	66
2	CH_3CN	80	16	49
3	THF	80	16	76
4	DMF	120	16	47
5	NMP	120	16	56
6	CH_3OH	80	16	4
7	DMSO	120	16	7
8	CH_2Cl_2	25	16	81
9	CH_2Cl_2	50	16	88
10	CH_2Cl_2	50	10	83

[a] Reaction conditions: **1** (0.060 mmol), **2a** (0.050 mmol), solvent (1.0 mL), N_2 atmosphere. [b] Yields were determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as an internal standard.

(Table 2, Entries 7–11). Even if a free phenolic hydroxy group was present as an electron-donating substituent in the *para* position of the aromatic ring, desired ketone **3l** was formed in 32% yield (as determined by ^{19}F NMR spectroscopy; Table 2, Entry 12). Additionally, halide functional groups (F, Cl, and Br) in aromatic α-bromo ketones **2m**–**p** were well tolerated, and these substrates reacted smoothly to afford the corresponding products in 60–90% yields (Table 2, Entries 13–16). This particular feature shows one important advantage of this protocol, because the halogenated products can be further utilized in well-established cross-coupling reactions. 3-Bromoacetylpyridine **2q** and 3-(2-bromoacetyl)-2*H*-chromen-2-one **2r** as heterocyclic α-bromo ketones also reacted to give desired products **3q** and **3r** in yields of 71 and 61%, respectively (Table 2, Entries 17 and 18). Interestingly, this transformation is not limited to aromatic α-bromo ketones. Aliphatic α-bromo ketone **2s** also participated in trifluoromethylthiolation to furnish **3s** in 87% yield (Table 2, Entry 19). Additionally, the reaction of *N*-methyl-2-bromoacetanilide (**2t**) also proceeded smoothly, and desired product **3t** was isolated in 72% yield (Table 2, Entry 20). Notably, α-chloro ketones **2u** and **2v** also underwent trifluoromethylthiolation to afford corresponding products **3u** and **3v** in good yields (80 and 76%, respectively, as determined by ^{19}F NMR spectroscopy) if Bu_4NI (2.0 equiv.) was used to activate the substrates (Table 2, Entries 21 and 22). This method was also expanded to the trifluoromethylthiolation of secondary α-bromo ketones **2w** and **2x**. A chloro group or a bromo group in the *meta* or *ortho* position was tolerated, and corresponding product **3w** or **3x** was afforded in 74 or 76% yield, respectively (Table 2, Entries 23 and 24).

To demonstrate the practical utility, the reaction of **1** and **2a** was performed on a 2.23 mmol scale. As shown in Scheme 2, desired product **3a** was obtained in 82% yield (0.450 g).

Table 2. Trifluoromethylthiolation of α-bromo ketones **2** by (bpy)Cu(SCF_3) (**1**).[a]



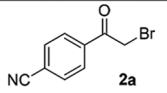
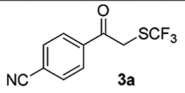
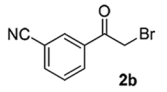
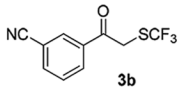
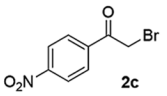
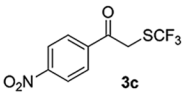
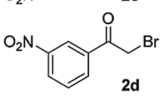
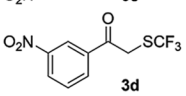
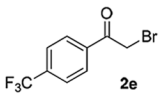
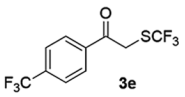
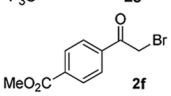
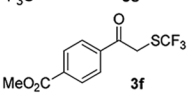
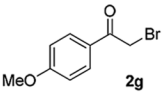
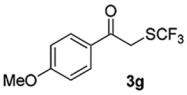
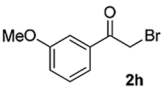
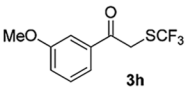
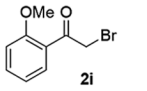
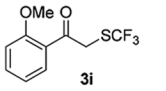
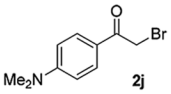
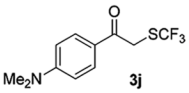
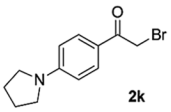
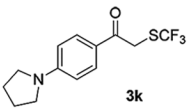
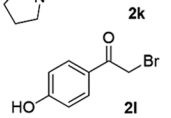
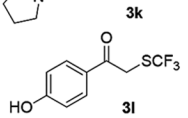
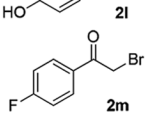
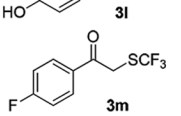
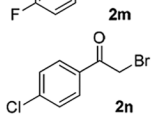
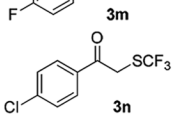
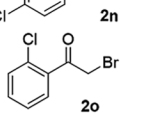
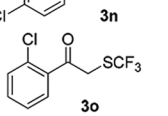
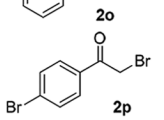
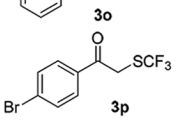
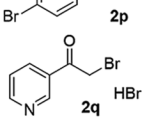
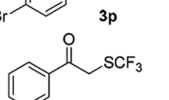
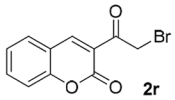
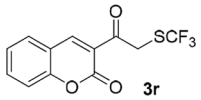
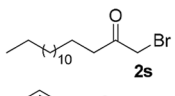
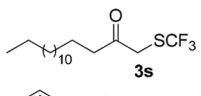
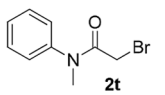
Entry	α-Halo ketone	Product	Yield [%][b]
1	 **2a**	 **3a**	80
2	 **2b**	 **3b**	83[c]
3	 **2c**	 **3c**	77
4	 **2d**	 **3d**	79
5	 **2e**	 **3e**	80
6	 **2f**	 **3f**	78
7	 **2g**	 **3g**	86
8	 **2h**	 **3h**	82
9	 **2i**	 **3i**	87
10	 **2j**	 **3j**	90
11	 **2k**	 **3k**	93
12	 **2l**	 **3l**	32[c]
13	 **2m**	 **3m**	86
14	 **2n**	 **3n**	90
15	 **2o**	 **3o**	60
16	 **2p**	 **3p**	82
17	 HBr **2q**	 **3q**	71[d]

Table 2. *(Continued)*

Entry	α-Halo ketone	Product	Yield [%][b]
18	 **2r**	 **3r**	61
19	 **2s**	 **3s**	87
20	 **2t**	**3t**	72
21	**2u**	**3u**	80[c,e]
22	**2v**	**3v**	76[c,e]
23	**2w**	**3w**	74
24	**2x**	**3x**	76

[a] Reaction conditions: **1** (0.30 mmol), **2** (0.25 mmol), CH_2Cl_2 (5.0 mL), 50 °C, 16 h, N_2. [b] Yield of isolated product. [c] The yield was determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as an internal standard. [d] Addition of KF (0.50 mmol, 2 equiv.). [e] Addition of Bu_4NI (0.50 mmol, 2.0 equiv.).

Scheme 2. Scalability of the trifluoromethylthiolation of **2a**.

Conclusions

We disclosed herein the copper-mediated trifluoromethylthiolation of readily available α-bromo ketones as an improved protocol for the synthesis of various α-trifluoromethylthio-substituted ketones, useful and versatile synthons for further synthetic transformations, in good-to-high yields. The reaction conditions appeared to be highly compatible with a wide range of functional groups, and the ease of the protocol is highly convenient for synthetic chemistry.

Experimental Section

General Information: ^1H NMR, ^{19}F NMR, and ^{13}C NMR spectra were recorded by using a Bruker AVIII 400 spectrometer. ^1H NMR and ^{13}C NMR chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane, and ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as the external standard. The residual solvent peak was used as an internal reference

($CHCl_3$: δ_H = 7.26 ppm, δ_C = 77.0 ppm). HRMS were obtained with a Waters GCT-TOF at the Shanghai Institute of Organic Chemistry. (bpy)Cu(SCF_3) (**1**)[22] and α-bromo ketones **2f**[25] and **2t**[26] were prepared according to published procedures. Other reagents were received from commercial sources. Solvents were freshly dried and degassed according to published procedures[27] prior to use. Column chromatography purifications were performed by flash chromatography by using Merck silica gel 60.

General Procedure for the Trifluoromethylthiolation of α-Bromo Ketones with (bpy)Cu(SCF_3): α-Bromo ketone **2** (0.50 mmol), [(bpy)Cu(SCF_3)] (**1**; 192 mg, 0.60 mmol, 1.2 equiv.), and CH_2Cl_2 (5.0 mL) were added to a reaction tube with Teflon screw cap equipped with a stir bar. The mixture was stirred at 50 °C for 16 h. The mixture was filtered through a pad of Celite. Water (3 × 10 mL) was added to the filtrate at 0 °C. The resulting mixture was extracted with Et_2O (3 × 15 mL), and the combined organic layers were washed with water and then dried with $MgSO_4$. The solvent was removed under reduced pressure while cooling with an ice bath, and the resulting product was purified by column chromatography on silica gel with pentane/Et_2O.

Supporting Information (see footnote on the first page of this article): Copies of the ^1H NMR, ^{19}F NMR, and ^{13}C NMR spectra of all products.

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