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Copper-Catalyzed Synthesis of α-Trifluoromethylthio-Substituted Ketones

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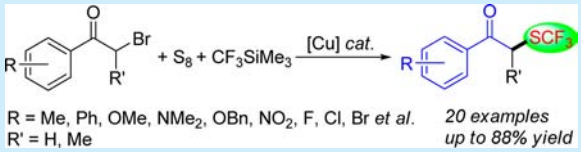
Supporting Information

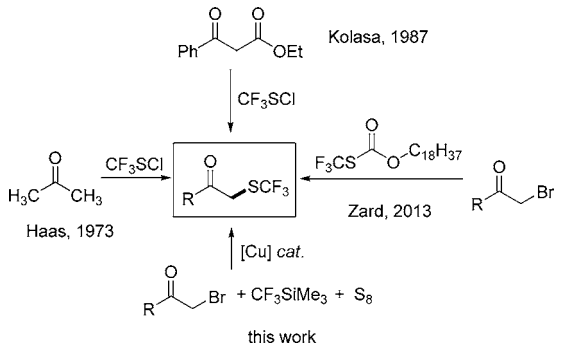
ABSTRACT: The CF_3S-substituted moiety serves as an important structural element in many bioactive molecules. A versatile copper catalyst that allowed for trifluoromethylthiolation of primary and secondary α-bromoketones is described. The reaction with readily available elemental sulfur and CF_3SiMe_3 afforded a broad scope and moderate to good yields of α-trifluoromethylthio-substituted ketones. This procedure represents a very operationally simple yet powerful strategy for the synthesis of α-trifluoromethylthio-substituted ketones, a useful and versatile class of synthetic synthons.



α-Trifluoromethyl-substituted carbonyl compounds are valuable synthons for the preparation of numerous derivatives containing the CF_3 group that are of increasing interest in pharmaceutical, agricultural, and material sciences.[1] With their broad application considered, the development of novel and more efficient synthetic methods for α-CF_3-substituted carbonyl compounds has been the focus of extensive research interest.[2,3]

However, whereas efficient methods for synthesis of α-CF_3-substituted carbonyl compounds have been reported,[4] the development of preparation of α-CF_3S-substituted analogues is much less explored (Scheme 1). Compared to other fluorinated

Scheme 1. Methods for Synthesis of α-CF_3S-Substituted Ketones



alkyl groups (SF_5−, π_x = 1.23; CF_3O−, π_x = 1.04; CF_3−, π_x = 0.88), the CF_3S− group shows the highest lipophilicity value (π_x = 1.44).[5,6] It is well-known that the introduction of trifluoromethylthio group into organic molecules such as pharmaceuticals and agrochemicals greatly enhances their bioavailability.[7−10]

Therefore, new methods for incorporation of CF_3S− substituents into carbonyl compounds would be broadly useful in synthetic chemistry. Haas and Kolasa initially reported the reactions of ketone or benzoylacetic ethyl ester with trifluoromethylsulfenyl chloride to give the α-CF_3S-substituted ketones.[11,12] Recently, the Shen and the Rueping groups independently described the electrophilic trifluoromethylthiolation of β-ketoesters to afford the corresponding α-trifluoromethylthiolated carbonyl compounds.[6,13] Most recently, Li and Zard reported trifluoromethylthiolation of α-bromoketones with O-octadecyl-S-trifluorothiolcarbonate.[14] However, some of these methods show modest substrate scope and require extremely toxic and corrosive CF_3SCl or electrophilic-type trifluoromethylthiolation reagent and are limited in their functional group compatibility.

Nonetheless, elegant work from the Qing group on copper-catalyzed oxidative trifluoromethylthiolation of aryl boronic acids with CF_3SiMe_3 and elemental sulfur[10a,15] has raised anticipation that efficient trifluoromethylthiolation could be realized by using readily available and inexpensive catalysts and fluorinated reagents.

As part of our ongoing interest in the development of efficient methods for trifluoromethylthiolation[16] and trifluoromethylselenolation,[17] we herein report copper-catalyzed trifluoromethylthiolation of α-bromoketones with elemental sulfur and CF_3SiMe_3 to synthesize α-trifluoromethylthio-substituted ketones.

Our initial investigation commenced with the treatment of 2-bromo-1-*p*-tolylethanone **1a**, elemental sulfur, and CF_3SiMe_3 and KF with CuI (20 mol %)/phen (20 mol %) as catalyst in CH_2Cl_2 as the solvent at 40 °C (Table 1). The reaction occurred leading to the formation of the trifluoromethylthiolated ketone **2a** in 25% yield (entry 1).

To determine the efficient copper catalyst for this one-pot synthesis, we then examined a variety of copper salts. When CuSCN was used as a catalyst, a small improvement in the yield (39%) was observed (entry 2). When $Cu(MeCN)_4PF_6$, CuF_2,

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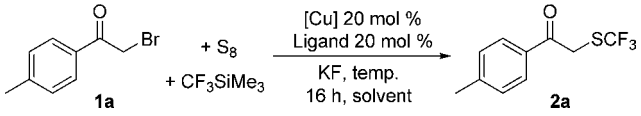
Table 1. Optimization of Copper-Catalyzed Trifluoromethylthiolation of 2-Bromo-4′-methylacetophenone[a]



entry	[Cu]	ligand	solvent	temp (°C)	time (h)	yield[b] (%)
1	CuI	phen	CH_2Cl_2	40	16	25
2	CuSCN	phen	CH_2Cl_2	40	16	39
3	$Cu(MeCN)_4PF_6$	phen	CH_2Cl_2	40	16	63
4	CuF_2	phen	CH_2Cl_2	40	16	68
5	$Cu(TFA)_2$	phen	CH_2Cl_2	40	16	63
6	$Cu(OTf)_2$	phen	CH_2Cl_2	40	16	92
7			CH_2Cl_2	40	16	2
8	$Cu(OTf)_2$	bpy	CH_2Cl_2	40	16	58
9	$Cu(OTf)_2$	tmeda	CH_2Cl_2	40	16	0
10	$Cu(OTf)_2$	dmcda	CH_2Cl_2	40	16	9
11	$Cu(OTf)_2$	Me_3py	CH_2Cl_2	40	16	1
12	$Cu(OTf)_2$	phen	CH_3CN	40	16	5
13	$Cu(OTf)_2$	phen	CH_3OH	40	16	0
14	$Cu(OTf)_2$	phen	DMF	40	16	1
15	$Cu(OTf)_2$	phen	DMF	80	16	1
16	$Cu(OTf)_2$	phen	DMSO	40	16	1
17	$Cu(OTf)_2$	phen	THF	40	16	9
18	$Cu(OTf)_2$	phen	toluene	40	16	0
19	$Cu(OTf)_2$	phen	CH_2Cl_2	30	16	57
20	$Cu(OTf)_2$	phen	CH_2Cl_2	50	16	74
21	$Cu(OTf)_2$	phen	CH_2Cl_2	40	8	48

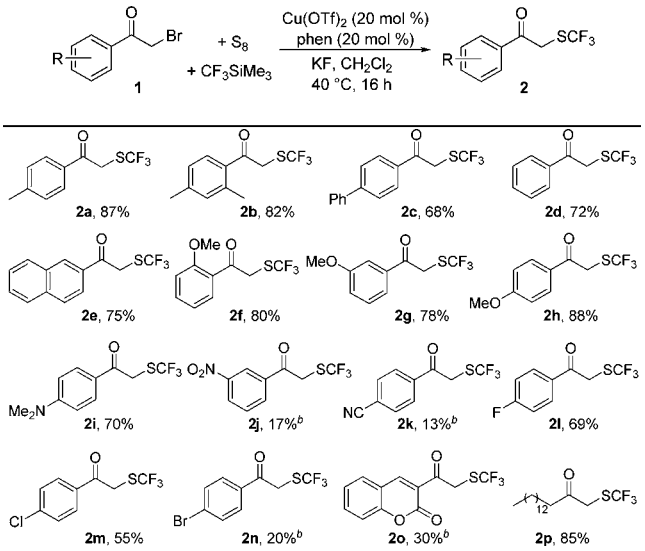
[a]Reaction conditions: [Cu] (0.010 mmol), ligand (0.010 mmol), 2-bromo-4′-methylacetophenone (0.050 mmol), CF_3SiMe_3 (0.20 mmol), S_8 (0.20 mmol), KF (0.20 mmol), solvent (1.0 mL), N_2; phen = 1,10-phenanthroline, bpy = 2,2′-bipyridine, tmeda = *N,N,N′,N′*-tetramethylethylenediamine, dmcda = *trans-N,N′*-dimethyl-1,2-cyclohexanediamine, Me_3py = 2,4,6-trimethylpyridine. [b]The yield was determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as internal standard.

and $Cu(TFA)_2$ (with phen as ligands) were employed, a moderate yield of product was obtained (entries 3−5). Notably, the use of $Cu(OTf)_2$ with phen as ligand produced the best results (92% yield; entry 6). It is also noteworthy that the products derived from the addition of the CF_3 to the carbonyl group[1a,18] were not detected by using these conditions. $Cu(OTf)_2$ was therefore established as the preferred Cu source for the copper-catalyzed trifluoromethylthiolation. Only a trace amount of product was formed in the absence of a copper source and ligand (entry 7). The result clearly demonstrated the importance of both the catalyst and ligands in this transformation.

Although bipyridine has been shown previously to be a powerful ligand for copper-mediated trifluoromethylthiolation with aryl halides,[16a] bpy was not so efficient as a ligand in this case, affording a less satisfactory yield (entry 8). Changing to other nitrogen ligands, such as tmeda, dmcyda, or Me_3py, only retarded the reaction (entries 9−11). Additionally, the choice of solvent influenced the yield. The use of other solvents, e.g., CH_3CN, CH_3OH, DMF, DMSO, THF, or toluene (entries 12−18), was found to be detrimental. The effect of temperature was also investigated. Reactions performed either at lower temperatures (30 °C) or elevated temperature (50 °C) produced lower yields (entries 19 and 20). Furthermore, reducing the reaction time to 8 h resulted in incomplete conversion (entry 21).

Having identified these optimal conditions, we next examined the substrate scope for this new reaction. A variety of aromatic α-bromoketones were surveyed to synthesize different trifluoromethylthiolated ketones (Scheme 2).

Scheme 2. Copper-Catalyzed Trifluoromethylthiolation of α-Bromoketones[a]



[a]Reaction conditions: $Cu(OTf)_2$ (0.050 mmol), phen (0.050 mmol), α-bromoketones (0.25 mmol), CF_3SiMe_3 (1.0 mmol), S_8 (1.0 mmol), KF (1.0 mmol), CH_2Cl_2 (1.0 mL), N_2. Yields of isolated products are shown. [b]The yield was determined by ^{19}F NMR spectroscopy with $PhOCF_3$ as internal standard.

α-Bromoketones bearing methyl, dimethyl, and phenyl substitutions at the aromatic rings reacted with S_8 and CF_3SiMe_3 to give the products **2a−c**, respectively, in 68−87% yields. The unfunctionalized aromatic α-bromoketones, 2-bromo-1-phenylethanone, and 2-bromo-1-(naphthalen-2-yl)-ethanone also underwent trifluoromethylthiolation to afforded the desired products **2d** and **2e** in good yields (72% and 75%, respectively).

Variation of electronic properties of the aryl substitutents in the aromatic α-bromoketones had a dramatic effect on the reaction efficiency. α-Bromoketone substrates with a methoxy substituent at the *ortho-*, *meta-*, or *para*-position of the aromatic rings provided the corresponding products **2f−h** in good yields (80%, 78% and 88%, respectively). Furthermore, α-bromoketone possessing a dimethylamino substituent in the *para*-position of the aryl groups also provided the desired product **2i**, exclusively (70% yield). Additionally, α-bromoketone having nitro or nitrile substituents at the *meta-* or *para*-position of the aryl groups could also be transferred through this protocol, although reduced yields of the corresponding products **2j,k** were observed (17% and 13%, respectively), with the trifluoromethylated alcohol resulting from the addition of CF_3 to the carbonyl group as side product. Notably, substrates bearing halogenated arenes were also accommodated and furnished the desired products **2l−n** in moderate yields (20−69%), thereby providing possibilities for subsequent chemical transformations. Heteroaryl groups, such as coumarin group, could also be tolerated to give the trifluoromethylthiolated

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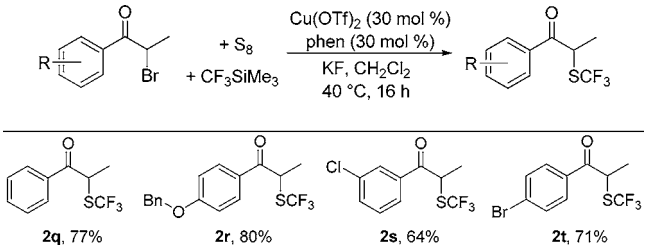
product **2o** in 30% yield (^{19}F NMR). Interestingly, the trifluoromethylthiolation of an aliphatic α-bromoketone was possible and proceeded in excellent yield (**2p**, 85%), thus enhancing the scope of our reaction.

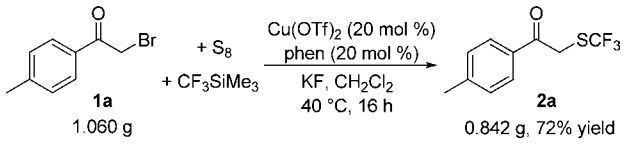
The scope was then extended to the use of secondary bromides (Scheme 3). The reaction with 2-bromopropiophenone, 4′-(benzyloxy)-2-bromopropiophenone, and 2-bromo-1-(3-chlorophenyl)-1-propanone led to the formation of desired products **2q−s** in good yields (77%, 80%, and 64%, respectively), albeit with the higher catalyst loading of CuI (30 mol %)/phen (30 mol %). Moreover, 2-bromo-1-(4-bromophenyl)-1-propanone smoothly underwent trifluoromethylthiolation to afford product **2t** in 71% yield with remarkable chemoselectivity, leaving the C(sp^2)−Br bond untouched.

Scheme 3. Copper-Catalyzed Trifluoromethylthiolation of Secondary α-Bromoketones[a]



[a]Reaction conditions: $Cu(OTf)_2$ (0.075 mmol), phen (0.075 mmol), α-bromoketones (0.25 mmol), CF_3SiMe_3 (1.0 mmol), S_8 (1.0 mmol), KF (1.0 mmol), CH_2Cl_2 (1.0 mL), N_2. Yields of isolated products are shown.

Scheme 4. Gram-Scale Synthesis of α-Trifluoromethylthio-Substituted Ketones

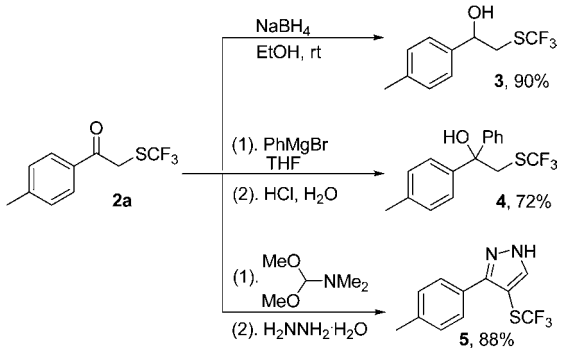


In a synthetic application of the present reaction, we attempted to prepare alcohol and pyrazole derivatives, and the results are summarized in Scheme 5. The trifluoromethylthiolated ketone **2a** was treated with $NaBH_4$ to deliver alcohol **3** in 90% yield or alternatively reacted with PhMgBr to generate tertiary alcohol **4** in 72% yield.

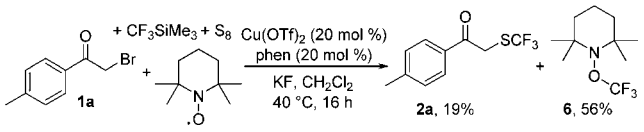
The utility of the reaction is further illustrated by the synthesis of trifluoromethylthio-substituted pyrazoles, which is of great interest in medicinal chemistry.[4b,19] Reaction of **2a** with dimethylformamide acetal followed by hydrazine gave the desired trifluoromethylthio-substituted pyrazole **5** in 88% overall yield, thus demonstrated herein that this new protocol provides a convenient methodology to access these biologically interesting scaffolds (Scheme 5).

In an attempt to find out whether any radical intermediates are formed in trifluoromethylthiolation, a radical scavenger, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), was added to the reaction under the optimized conditions (Scheme 6). Suprisingly, the reaction produced the desired product **2a** in only 19% yield together with the TEMPO−CF_3 adduct **6** in 56% yield by ^{19}F NMR analysis. This observation indicated that a CF_3 radical intermediate might be involved in the reactions.

Scheme 5. Synthetic Utility of 2a



Scheme 6. Inhibition Experiment with TEMPO



In summary, a new approach to the direct construction of α-trifluoromethylthio-substituted ketones from readily available α-bromoketones, elemental sulfur, and CF_3SiMe_3 has been achieved using copper catalysis. This method provides a broad scope and moderate to good yields of the trifluoromethylthiolated products, and a variety of functional groups are compatible with these reaction conditions. The present reaction, therefore, is anticipated to be a powerful protocol for the synthesis of α-trifluoromethylthio-substituted ketones, which are important synthons for the preparation of numerous derivatives containing the CF_3S− group. Further studies of this and related copper-catalyzed chemistry are in progress.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for products and mechanistic study experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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