Cu(OAc)₂-Catalyzed Thiolation of Acyl C–H Bonds with Thiols Using TBHP as an Oxidant

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Abstract: Cu(OAc)₂-promoted TBHP oxidative coupling reaction of formamides with thiols successfully proceeded through direct C–H bond activation of formamides. The corresponding *S*-phenyl dialkyl thiocarbamate compounds were formed with high yield under solvent-free conditions.

Key words: TBHP, Cu(OAc)2, thiolation, thiols, formamide

Transition-metal-catalyzed C-S bond formation has been a subject of intense study due to the importance of sulfides and their derivatives in numerous biological and pharmaceutically active compounds.1 With the increasing requirements for environmentally benign and atom economic processes, over the last decades, the activation of C-H bonds has emerged as an active field in organometallic catalysis, which allows for superior step- and atomeconomic transformations.^{1a} Among these, much effort has been focused on C-C and C-heteroatom bonds.² However, few examples of the formation of a C-S bond through C-H bond cleavage have been reported before. In 2006, Yu and co-workers reported a Cu(OAc)₂-catalyzed thiolation of the 2-phenylpyridine with PhSH and MeSSMe under oxygen atmosphere.³ Subsequently, in 2009, Fukuzawa and co-workers demonstrated a coppercatalyzed direct thiolation of a benzoxazole C-H bond with diaryl disulfides and aryl thiols.⁴ Recently, Cheng and co-workers reported Cu-catalyzed thiolation of an arene C-H bond with diaryl disulfides.⁵ Very recently, Li described a free-metal reaction of an sp³ C-H bond with disulfides.6

Formamides such as DMF are normally used as solvents;⁷ a few reports are available on the direct activation of the formamide C–H bond.^{8,9} Inspired by the work of Chang^{8a} and Reddy,^{9a} herein, we report a high yielding protocol for





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the synthesis of *S*-aryl thiocarbamates via direct C–H bond activation of formamides (Scheme 1).

To determine the optimized reaction conditions, the initial efforts focused on the direct thiolation of morpholine-4-carbaldehyde (**1a**, 1.0 mmol) with 4-chloro thiophenol (**2a**, 1.2 mmol) by using TBHP (*tert*-butylhydroperoxide, 2.0 mmol) as oxidant at 120 °C under N₂ atmosphere

Table 1 Screening Optimal Conditions

O N H	+ CI	oxidant Cu	CI
Entry	Oxidant	Catalyst	Yield (%) ^a
1	TBHP	_	65
2	TBHP	_	76
3	DDQ	-	0
4	$K_2S_2O_8$	_	0
5	(NH4) ₂ S ₂ O ₈	_	65
6	CAN	_	75
7	TBHP	-	0
8	TBHP	Cu(OAc) ₂ ·H ₂ O	87
9	TBHP	Cu(OAc) ₂ ·H ₂ O	84
10	TBHP	Cu(OAc) ₂ ·H ₂ O	87
11	TBHP	Cu(OAc) ₂ ·H ₂ O	83
12	TBHP	Cu(OAc) ₂ ·H ₂ O	61
13	TBHP	Cu ₂ O	70
14	ТВНР	CuI	72
15	TBHP	CuBr	71
16	TBHP	FeCl ₂	61
17	TBHP	FeCl ₃	65
18	ТВНР	PdCl ₂	68
19	TBHP	$Pd(OAc)_2$	77

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^a Isolated yields.¹⁰

without solvent; the desired product was obtained in 65% isolated yield after 24 hours (Table 1, entry 1), and afforded 76% yield with four equivalents of TBHP (Table 1, entry 2). Encouraged by these preliminary results, we further investigated other oxidants with the aim of optimizing the reaction conditions. Oxidant screening established that TBHP was the most efficient oxidant providing the highest yield of the target product. No reaction was observed using the DDQ as oxidant (Table 1, entry 3), disulfide was the only product when the $K_2S_2O_8$ was added (Table 1, entry 4), and moderate isolated yields (65–75%) were isolated under (NH₄)₂S₂O₈ or CAN conditions (Table 1, entries 5 and 6). It is noteworthy that no reaction was observed without TBHP (Table 1, entry 7).

To our delight, $Cu(OAc)_2$ improved the reaction greatly: the yield of **3a** was enhanced to 87% with the use of 10 mol% of $Cu(OAc)_2$ ·H₂O in the presence of four equivalents of TBHP at 120 °C after 12 hours (Table 1, entries 8), a yield of 84% was obtained when 5 mol% of $Cu(OAc)_2$ ·H₂O were used, and a yield of 87% was observed with 20 mol% of $Cu(OAc)_2$ ·H₂O (Table 1, entries 9 and 10). The reaction temperature also affected the reaction: 83% yield at 130 °C and 61% yield at 100 °C were observed after 12 hours (Table 1, entries 11 and 12). Other transition metal catalysts were also employed in the reactions to compare their catalytic activities, using 10 mol%

Table 2 Reactions of 1a with Various Thiols^a

of catalyst: Cu₂O, CuI, CuBr, FeCl₂, FeCl₃, PdCl₂ and Pd(OAc)₂ only gave moderate yields after 12 hours (Table 1, entries 13 and 19), and Cu(OAc)₂·H₂O was proven to be the best catalyst, giving **3a** in 87% yield. Thus, we deduced that the weak base Cu(OAc)₂·H₂O may play a role to promote the TBHP to form the reaction intermediate.

With the optimal reaction conditions in hand, the scope of both thiols and formamides was explored (Table 2 and Table 3). Firstly, we investigated the scope of the reaction using different substituted thiols with 1a. As depicted in Table 2, the results demonstrated that aryl thiols, bearing either electron-withdrawing group such as halo atom or electron-donating groups on the aromatic ring, were perfectly tolerated (Table 2, entries 1-8). For example, 4methoxy-substituted thiophene smoothly underwent the reaction with 1a to afford the corresponding product 3c in 89% yield. The steric hindrance of the ortho-substituted thiols had a quite limited effect on the yield of the reaction (Table 2, entries 9–13); the *ortho*-substituted 2-methoxythiophene also delivered 81% yield of 3g. Unfortunately, aryl thiols with very strong electron-withdrawing functionalities, such as 4-nitrobenzenethiol, 4-(trifluoromethyl)benzenethiol and pyridine-2-thiol, had no reaction with **1a** (Table 2, entries 14–16). In comparison to aryl thiols, diaryl disulfides performed with moderate yield (61-77%), Table 2, entries 1–6, and 9–12; see footnote c in Table 2).



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Table 2 Reactions of 1a with Various Thiols^a (continued)

^a Reaction conditions:¹⁰ **1a** (1.0 mmol), thiols (1.2 mmol), TBHP (4 mmol), Cu(OAc)₂ (10 mol%) at 120 °C for 12 h.

^b Isolated yields.

^c Isolated yield of disulfides with 1a.

Secondly, we examined the other formamides, such as piperidine-1-carbaldehyde (1b), and *N*,*N*-dimethyl formamide (1c) with different aryl thiols. As depicted in Table 3, a series of electron-donating groups on the phenyl ring of thiols, such as *para*-methyl, *ortho*-methyl, *para*-methoxy, *ortho*-methoxy, *ortho*-halo and *para*-halo, afforded the corresponding products in moderate to good yields (Table 3, entries 1–13 and 15–27). Disappointingly, the *N*-aryl formamide and formamide did not work under the current condition (Table 3, entries 14 and 28).

On the basis of above results and previous publications,^{9,11,12} a plausible catalytic cycle is presented in Scheme 2. This was attributed to the tendency of thiols to form intermediate **A** with Cu(OAc)₂; intermediate **A** decomposes TBHP to form hydroxyl and *tert*-butoxy radicals. The hydroxyl can react with intermediate **A** to form the trivalent copper salt (intermediate **B**). The *tert*-butoxy radicals can abstract hydrogen from the reacting formamide to generate the corresponding radical, which reacts with the copper complex affording the desired products. Furthermore, the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) was added to the above reaction system. The TEMPO prevented the desired direct C–S coupling reaction without any target product, supporting the proposed radical pathway.^{9a}

In conclusion, a high yielding, efficient, green methodology for the synthesis of *S*-phenyl dialkyl thiocarbamate compounds through direct oxidation of acyl C–H was developed. Moreover, this is a new methodology for the construction of C–S bonds.



Scheme 2







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 Table 3 Reactions of 1b and 1c with Various Thiols^a (continued)

^a Reaction conditions:¹⁰ **1b** (or **1c**; 1.0 mmol), thiols (1.2 mmol), TBHP (4 mmol), Cu(OAc)₂ (10 mol%) at 120 °C for 12 h. ^b Isolated yields.

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- (10) Typical Procedure: Under a N₂ atmosphere, a reaction vessel was charged with 1a (or 1b, 1c) (1.0 mmol), ArSH 2 (1.2 mmol), Cu(OAc)₂·H₂O (10 mol%), and 70% aq TBHP (4 mmol). The mixture was stirred at 120 °C and monitored by TLC. Upon completion of the reaction (approximately 12 h), the mixture was cooled to r.t. and mixed with H₂O (15.0 mL). The product was then extracted with CH₂Cl₂ (3 ×

10 mL). The organic layers were combined, dried over anhyd Na₂SO₄, concentrated under reduced pressure, and purified over a column of silica gel (EtOAc–hexane as eluent) to give product **3a** in 87% yield. ¹H NMR (300 MHz, CDCl₃): δ = 7.34–7.43 (m, 4 H), 3.72 (t, *J* = 5.1 Hz, 4 H), 3.59 (t, *J* = 4.8 Hz, 4 H). ¹³C NMR (75 MHz, CDCl₃): δ = 164.6, 135.9, 134.8, 128.2, 125.5, 65.4, 44.3. The identity and purity of other products were confirmed by ¹H NMR and ¹³C NMR spectroscopic analysis.

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