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Efficient copper-catalyzed coupling of aryl iodides and thiobenzoic acid

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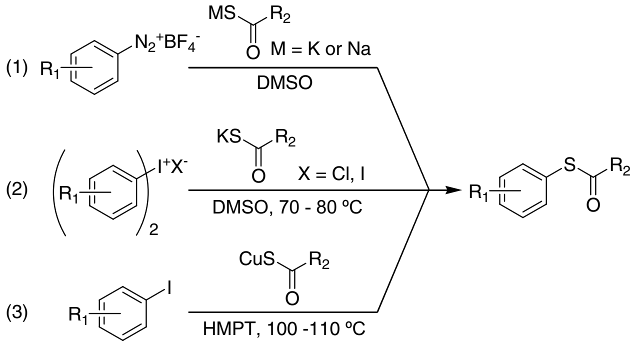
Abstract—A highly efficient copper-catalyzed coupling reaction of aryl iodides and thiobenzoic acid, using 10 mol % of copper iodide, 20 mol % of 1,10-phenanthroline, and $^{i}Pr_2NEt$ in toluene, was developed. This methodology is applicable to a variety of aryl iodides.

Aryl thiols are essential building blocks in the synthesis of sulfur-containing natural products and biologically active compounds. Traditional methods for constructing aryl–sulfur bonds include thermal rearrangement of *N*,*N*-dialkylthiocarbamates[1] or substitution via an addition–elimination mechanism.[2] However, these reactions often require harsh conditions (∼280 °C, or long reaction times). Since 1980, coupling reactions catalyzed by transition metals (Pd, Ni, Cu) have been developed as an efficient method for aryl–sulfur bond formation,[3–5] using alkyl thiols as a sulfur source. The desired aryl thiols are obtained after cleavage of the alkyl–sulfur bond, which typically requires harsh conditions.[6]

For this reason, the development of efficient methods for the synthesis of *S*-aryl thiocarboxylates has been the subject of much interest, since acyl groups may be removed under milder conditions than alkyl groups.[7] Various methods have already been reported (Scheme 1): the reaction of arenediazonium tetrafluoroborates with alkali metal thiocarboxylates (Eq. 1),[8] the reaction of diaryliodonium salts with potassium thiocarboxylates (Eq. 2),[9] and the reaction of aryl halides with the copper salt of thiobenzoic acid (Eq. 3).[10] However, all of these methods require hazardous reagents, uncommon starting materials or undesirable solvents such as HMPT, and thus are not suitable for the preparation of more functionalized *S*-aryl thiocarboxylates. We envisioned that transition-metal-catalyzed coupling reactions would proceed under milder conditions, under which many functional groups are tolerated. To the best of our knowledge, there have yet been no reports of transition-metal-catalyzed coupling reactions of aryl halides and thiobenzoic acid. Herein, we report an efficient copper-catalyzed synthetic method for *S*-aryl thiocarboxylates from aryl iodides and thiobenzoic acid.



Scheme 1. Reported methods for synthesis of *S*-aryl thiocarboxylates.

Iodobenzene was selected as a model substrate for optimization of the copper-catalyzed coupling reaction (Table 1). As expected, the reaction did not proceed at all under simple addition–elimination conditions (entry 1). Buchwald reported high-yield copper-catalyzed carbon–oxygen bond formation from aryl iodides, using 10 mol % of copper iodide, 20 mol % of 1,10-phenanthroline, and Cs_2CO_3;[11] this system, however, was less effective in our case, giving only trace amounts of *S*-aryl thiobenzoate (entry 2).

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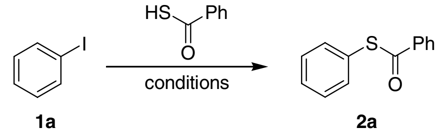
Table 1. Evaluation of various reaction conditions



Entry	Conditions[a]	Yield[b] (%)
1	^{t}BuONa, DMI, 120 °C	Nd
2	CuI, 1,10-phen, Cs_2CO_3, toluene, 110 °C	Trace
3	CuI, 1,10-phen, ^{t}BuONa, toluene, 110 °C	Nd
4	CuI, 1,10-phen, K_3PO_4, toluene, 110 °C	63
5	CuI, 1,10-phen, ^{i}Pr$_2$NEt, toluene, 110 °C	99
6	CuI, 1,10-phen, ^{i}Pr$_2$NEt, DMI, 120 °C	51
7	CuI, ^{i}Pr$_2$NEt, toluene, 110 °C	6
8	CuI, DMEDA, ^{i}Pr$_2$NEt, toluene, 110 °C	4
9	CuI, HO(CH$_2$)$_2$OH, ^{i}Pr$_2$NEt, toluene, 110 °C	4

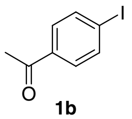
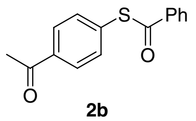
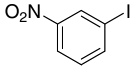
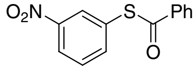
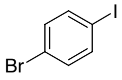
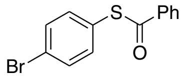
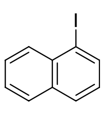
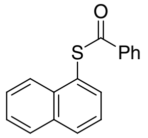
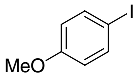
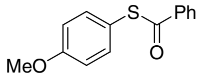
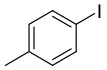
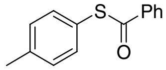
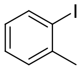
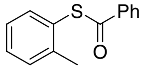
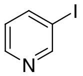
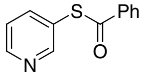
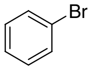
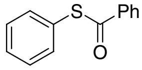
[a] All reactions were conducted using 2.45 mmol of iodobenzene, 10 mol % of CuI, 20 mol % of 1,10-phenanthroline, 1.2 equiv of thiobenzoic acid, 2.0 equiv of base, and 5 mL of solvent for 24 h.

[b] Product yields are the average of two runs, determined by HPLC.

Several bases were screened for the coupling reaction using 10 mol % of copper iodide and 20 mol % of 1,10-phenanthroline as a ligand. When ^{t}BuONa was used as a base,[12] the coupling reaction did not proceed and gave none of the desired product (entry 3). Inorganic bases such as K_3PO_4, which are widely used in copper-catalyzed protocols for the formation of aryl–nitrogen, aryl–oxygen and aryl–sulfur bonds,[5] gave the desired *S*-aryl thiobenzoate only in moderate yield (63%, entry 4). ^{i}Pr$_2$NEt was eventually found to be the most effective base for this reaction. The use of less polar solvents such as toluene (99%, entry 5) was found to result in better yields than that of polar solvents such as DMI (51%, entry 6). The effects of various ligands were then investigated. The reaction did not proceed well in the absence of ligands (6%, entry 7). The reaction using *N*,*N*′-dimethylethylenediamine, which has been found to be an effective ligand for copper-catalyzed amidation of aryl halides,[13] failed in our case (4%, entry 8). Likewise, the use of diol-type ligands such as ethylene glycol gave the product in 4% yield (entry 9); thus, 1,10-phenanthroline was confirmed to be the most effective ligand for this reaction.

To investigate the scope of the copper-catalyzed coupling reaction, a variety of aryl iodides (**1b**–**i**) were used (Table 2). Electron-deficient aryl iodides (**1b**–**d**) were effectively converted into the desired *S*-aryl thiobenzoates in excellent yields (entries 1–3). High chemoselectivity was observed for *p*-bromoiodobenzene (**1d**) (entry 3). Even electron-rich aryliodides (**1f**–**h**) and an electron-neutral aryliodide (**1e**) were completely converted to the corresponding *S*-aryl thiobenzoates in almost quantitative yields (entries 4–7). It is notable that coupling proceeded even with a sterically hindered substrate such as *o*-iodotoluene (**1h**) (entry 6). A heteroaryl iodide (3-iodopyridine, **1i**) also underwent coupling with an excellent yield of 99% (entry 8). However, bromobenzene (**1j**) gave only trace amounts of *S*-aryl thiobenzoate under the conditions described (entry 9).

Table 2. Copper-catalyzed coupling of thiobenzoate with various substrates[a]

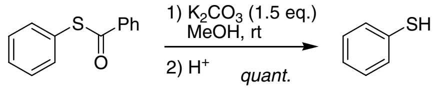
Entry	Substrate	Product	Yield[b] (%)
1	 **1b**	 **2b**	97
2	 **1c**	 **2c**	99
3	 **1d**	 **2d**	94
4	 **1e**	 **2e**	97
5	 **1f**	 **2f**	99
6	 **1g**	 **2g**	100
7	 **1h**	 **2h**	99
8	 **1i**	 **2i**	99
9	 **1j**	 **2a**	Trace

[a] All reactions were conducted using 2.45 mmol of aryl iodide, 10 mol % of CuI, 20 mol % of 1,10-phenanthroline, 1.2 equiv of thiobenzoic acid, 2.0 equiv of ^{i}Pr$_2$NEt, and 5 mL of toluene for 24 h at 110 °C. Reaction time was not optimized for each substrate.

[b] Product yields were the average of two runs, determined by HPLC.

Deprotection of the resulting *S*-aryl thiobenzoates proceeded smoothly under mild conditions, and the corresponding aryl thiols were obtained in quantitative yield (Scheme 2).

In conclusion, we have developed a highly efficient copper-catalyzed coupling reaction of aryl iodide and thiobenzoic acid in toluene using 10 mol % of copper iodide and 20 mol % of 1,10-phenanthroline. This method is applicable to both electron-deficient and electron-rich aryl iodides, and even to sterically hindered substrates,



Scheme 2. Deprotection of *S*-phenyl thiobenzoate.

giving *S*-aryl thiobenzoates in excellent yields as protected thiols.

General procedure

To a solution of aryl iodide (2.45 mmol), thiobenzoic acid (2.94 mmol), 1,10-phenanthroline (0.49 mmol), and $^i\mathrm{Pr}_2\mathrm{NEt}$ (4.90 mmol) in toluene (5 mL) was added CuI (0.25 mmol). The resulting mixture was degassed and then stirred under N_2 at 110 °C for 24 h. The reaction mixture was then cooled to rt and diluted to 50 mL with CH_3CN. The resulting mixture was analyzed by HPLC.[14]

Acknowledgements

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14. Compound **2a**–**2g** and **2i** are known compounds. Physical data for **2h**: ^{1}H NMR (500 MHz, $CHCl_3$, ppm) δ 8.05 (d, $J = 8.0$ Hz, 2H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.51–7.46 (m, 3H), 7.38–7.34 (m, 2H), 7.28–7.24 (m, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CHCl_3$, ppm) δ 189.6, 142.6, 136.8, 136.4, 133.5, 130.8, 130.2, 128.7, 127.5, 126.8, 126.6, 20.8. HRMS (EI positive) *m*/*z* calcd for $C_{14}H_{12}OS$ [M^+]: 229.0609, found: 229.0609.