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Copper-catalyzed Ullmann coupling under ligand- and additive-free conditions. Part 2: S-Arylation of thiols with aryl iodides

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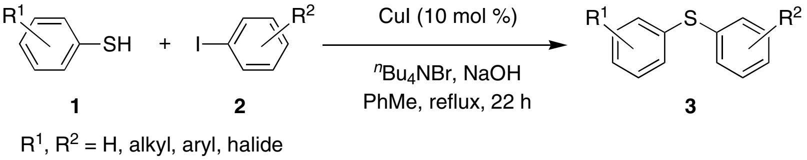
Abstract

S-Arylation of a wide variety of substituted aryl and aliphatic thiols with aryl halides catalyzed by copper iodide under mild ligand- and additive-free conditions (^{n}Bu$_4$NBr, PhMe, NaOH, reflux, 22 h) is accomplished in good to excellent product yields (up to 96%).

In the preceding Letter,[1] we described an efficient copper iodide-catalyzed process for the O-arylation of phenols and alcohols with equimolar amounts of aryl halides under mild ligand- and additive-free conditions. In an extension of this work, we wondered if a similar catalytic system could be developed for S-arylations. Indeed, we were keen to explore whether such an approach could provide a convenient route to aryl sulfides, a class of compounds commonly used in organic synthesis as building blocks and a prevalent structural unit found in many natural products and compounds of biological and materials importance.[2,3] Recently, a number of groups have been reported that the copper-catalyzed Ullmann S-arylation of thiols in the presence of a ligand or additive could overcome some of the problems traditionally associated with this reaction, which include high temperatures (typically above 140 °C), prolonged reaction times, the need for polar solvents such as HMPA, stoichiometric amounts of the metal catalyst, and low yields.[3–11] Despite these advances, examples of analogous reactions that do not require a ligand or additive in tandem with aryl halides as starting materials have remained sparse, which would be desirable from an economical perspective. Herein, we report the copper iodide-catalyzed S-arylation of a wide variety of thiols with equimolar amounts of aryl iodides in yields of up to 96% under ligand- and additive-free conditions (Scheme 1). It is noteworthy to highlight that in all instances, the present procedure was found to proceed in



Scheme 1.

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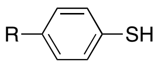
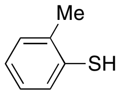
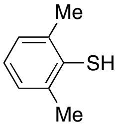
Table 1
CuI-catalyzed S-arylation of aryl thiols **1a**–**e** with aryl iodides **2a**–**i**[a]



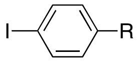
1a, R = Me
1b, R = OMe
1c, R = Cl



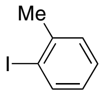
1d



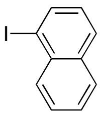
1e



2a, R = H
2b, R = Cl
2c, R = Br
2d, R = F
2e, R = NO_2
2f, R = Me
2g, R= OMe



2h



2i

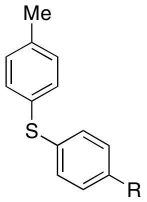
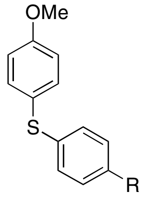
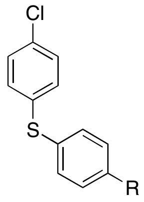
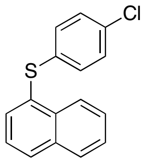
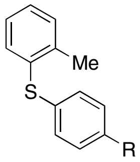
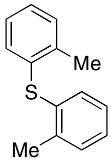
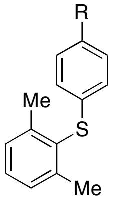
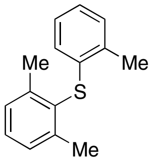
Entry	Substrates	Product		Yield[b] (%)
1	**1a** + **2a**		**3a**, R = H	95
2	**1a** + **2b**		**3b**, R = Cl	96
3	**1a** + **2c**		**3c**, R = Br	96
4	**1a** + **2d**		**3d**, R = F	96
5	**1a** + **2e**		**3e**, R = NO_2	80
6	**1a** + **2f**		**3f**, R = Me	94
7	**1b** + **2b**		**3g**, R = Cl	90
8	**1b** + **2e**		**3h**, R = NO_2	78
9	**1b** + **2g**		**3i**, R = OMe	78
10	**1c** + **2b**		**3j**, R = Cl	80
11	**1c** + **2e**		**3k**, R = NO_2	80
12	**1c** + **2f**		**3b**, R = Me	81
13	**1c** + **2g**		**3g**, R = OMe	62
14	**1c** + **2i**		**3l**	80
15	**1a** + **2h**		**3m**, R = Me	96
16	**1d** + **2f**			94
17	**1d** + **2b**		**3n**, R = Cl	95
18	**1d** + **2e**		**3o**, R = NO_2	90
19	**1d** + **2h**		**3p**	95

Table 1 (*continued*)

Entry	Substrates	Product		Yield[b] (%)
20	**1e** + **2b**		**3q**, R = Cl	96
21	**1e** + **2e**		**3r**, R = NO_2	81
22	**1e** + **2f**		**3s**, R = Me	95
23	**1e** + **2g**		**3t**, R = OMe	81
24	**1e** + **2h**		**3u**	96

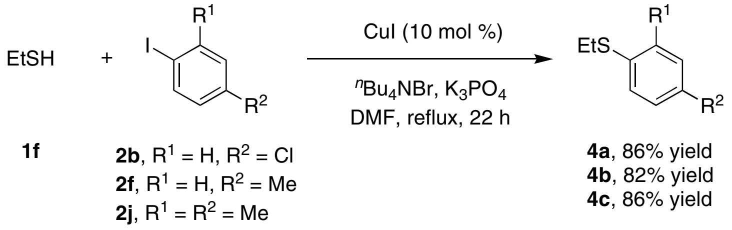
[a] All reactions were performed for 22 h with CuI: $^{n}Bu_4NBr$:**1**:**2**:NaOH, molar ratio = 1:1:10:10:20 in PhMe at reflux.

[b] Isolated yield.

good to excellent yields being comparable to those obtained for the analogous ligand or additive promoted reactions.[7b,11b,12]

Initially, we found that the conditions reported previously for the N-arylation of nitrogen heterocycles with aryl iodides also worked well for the coupling of a variety of substituted aryl thiols and aryl iodides (Table 1).[13] In the presence of 10 mol % of CuI as a catalyst, 10 mol % of $^{n}Bu_4NBr$ as a phase transfer catalyst, and NaOH (2 equiv) in toluene at reflux for 22 h, S-arylation of 4-methylbenzenethiol **1a** (1 equiv) with a variety of aryl iodides bearing either electron-withdrawing or electron-donating substituents (1 equiv) was shown to give the corresponding products in excellent yields of 80–96% (entries 1–6).[14] Notably, this included the ability to exploit the difference in reactivity of aryl halides (I ≫ Br > Cl > F) by coupling **1a** and the aryl iodide selectively in the presence of substrates containing aryl bromides, chlorides and fluorides. Similarly, the coupling of aryl thiols and aryl iodides containing various electron-withdrawing and electron-donating substrate combinations was found to proceed in good to excellent yields (entries 7–13). The present procedure was also shown to work well for the S-arylation of aryl thiols and aryl iodides in which either or both the starting materials contained sterically demanding *ortho*-substituents such as a methyl group or a fused benzene ring. In all the instances, the present procedure was found to proceed in good to excellent yields (entries 14–24).

To define the scope of the present reaction, the S-arylation of a representative aliphatic thiol, ethanethiol **1f**, with a variety of aryl iodides was also examined (Scheme 2). Analogous to our findings for the Cu-catalyzed O-arylation of alcohols, we found the reactivity of **1f** to be solvent and base dependent. When **1f** was treated with either 1 equiv of **2b** or **2f** in the presence of CuI (10 mol %) and $^{n}Bu_4NBr$ (10 mol %) in toluene at reflux for 22 h, the corresponding ethyl(aryl)sulfane adducts **4a** and **4b** were obtained in only



Scheme 2.

50% yield in both the cases. In contrast, repetition of these reactions but with DMF as a solvent and K_3PO_4 as a base was found to give **4a** and **4b** in yields of 86% and 82%, respectively. Under similar conditions, S-arylation of **1f** with **2j** was found to give **4c** in 86% yield.

In summary, we have developed a practical copper-catalyzed procedure for the S-arylation of thiols with aryl iodides that proceeded in good to excellent yields. The present protocol is applicable to a variety of thiols and aryl iodides containing electron-withdrawing, electron-donating and sterically demanding substrate combinations under mild conditions. Further investigation of the scope and applications of this reaction is currently underway and will be reported in due course.

Acknowledgement

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13. Chang, J. W. W.; Xu, X.; Chan, P. W. H. *Tetrahedron Lett.* **2007**, *48*, 245–248.
14. *Typical experimental procedure*: To a round bottom flask containing thiol **1** (2 mmol), aryl iodide **2** (2 mmol), CuI (0.2 mmol), $^n Bu_4NBr$ (0.2 mmol) and NaOH (4 mmol) under a N_2 atmosphere was added toluene (1.3 mL). The reaction mixture was vigorously refluxed for 22 h. On cooling to room temperature, saturated NH_4Cl (20 mL) was added and the organic layer was extracted with Et_2OAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography to afford the title compound.