

A General, Efficient, and Inexpensive Catalyst System for the Coupling of Aryl Iodides and Thiols

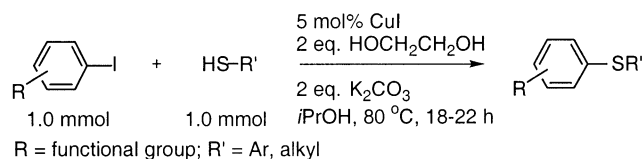
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Received August 4, 2002

ABSTRACT



An efficient copper-catalyzed carbon–sulfur bond formation reaction was developed. This method is particularly noteworthy given its experimental simplicity, high generality, and exceptional level of functional group toleration and the low cost of the catalyst system.

During the past few years, the efficiency of metal-catalyzed methods for the preparation of aryl ethers and, in particular, aniline derivatives using palladium catalysts has increased greatly.¹ More recently, our laboratory and others have begun to reinvestigate the use of copper catalysis for the preparation of these classes of important compounds.^{2,3}

In contrast, methods for the analogous formation of aryl sulfides, which are of great significance to the pharmaceutical

industry,⁴ have lagged behind. Transition metal-catalyzed and -mediated methods for the construction of aryl–sulfur bonds⁵ have usually required either forcing reaction conditions⁶ or substrates with ortho carbonyl groups that are both electron-withdrawing and capable of chelating copper.⁷ As in the case of C–N bond formation, the first report of a mild palladium-catalyzed carbon–sulfur bond formation came from Migita's laboratory.⁸ More recently, substantial contributions by the Merck group,⁹ Li,¹⁰ and Schopfer¹¹ have appeared.¹²

The use of copper catalysts for C–S bond-formation is attractive from an industrial perspective.¹³ Traditional copper systems have lacked the efficiency and wide applicability to polyfunctionalized substrates that is desirable.^{6,7,14} Of the catalytic processes that have appeared, the most attractive is that of Palomo and co-workers.¹⁵ However, their protocol

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utilizes 20% CuBr and the extremely expensive phosphazene bases.¹⁶ Our recent results on Cu-catalyzed C–N coupling chemistry suggested to us that similar catalysts for C–S couplings might be tolerant of a wide variety of functional groups.^{2c} Herein, we report a general, efficient, and operationally simple Cu-catalyzed C–S bond-forming reaction. During the completion of this work, Venkataraman reported an interesting Cu-catalyzed method for the combination aryl iodides with thiols in the presence of NaOt-Bu.¹⁷

5-Iodo-*m*-xylene and thiophenol was used as the prototypical substrate combination for preliminary optimization of the reaction conditions. Copper(I) complexes generally gave superior results compared to copper(II) sources in terms of conversion and yield of the desired product. A variety of these were efficient, but we chose to focus on the use of CuI due to its stability to air.¹⁸ Both K₃PO₄ and K₂CO₃ were found to be effective bases for this coupling reaction; the use of other bases such as DBU or Et₃N gave somewhat lower yields.¹⁹ As we recently reported for Cu-catalyzed amination,^{2c} the use of ethylene glycol (2 equiv) in 2-propanol provides an active and general catalyst system. Presumably, it serves as a cosolvent and ligand in the reaction. Its major function may be to get and keep the Cu(I) species in solution. In accordance with this notion, fairly good results were obtained using DME, DMF, or dioxane as a solvent in the absence of any additional ligand. In fact, in several cases, we found that DME was the solvent of choice. Presumably, it can function in much the same way that ethylene glycol does. Control experiments revealed that only a trace amount of aryl-aryl sulfide coupled product was observed from GC-MS in the absence of copper catalyst.

Thus, the optimized reaction conditions utilized 5 mol % CuI, K₂CO₃ (2 equiv), and ethylene glycol (2 equiv) in reagent-grade 2-propanol (without drying or degassing) at 80 °C under argon.²⁰ In the first part of this study, these reaction conditions were applied to the coupling of various functionalized aryl iodides and thiophenol counterparts, neither of which contained ortho substituents (Table 1). As can be seen, the process is extremely tolerant of a variety of

Table 1. Cu-Catalyzed Carbon–Sulfur Bond Formation^a

entry	ArI	ArSH	product	% yield ^b
1				92
2				86
3				92
4				84
5				91
6				85
7				83
8				90
9				91
10				88
11				82 ^c
12				87
13				93

(6) (a) Using stoichiometric Cu₂O reagent in a 1:4 pyridine/quinoline solvent at 160 °C: Pinchart, A.; Dallaire, C.; Gingras, M. *Tetrahedron Lett.* **1998**, 39, 543. (b) Using 5 mol % Cu in refluxing NMP: Sindelar, K.; Hrubantová, M.; Svátek, E.; Matousová, O.; Metysová, J.; Valchár, M.; Protiva, M. *Collect. Czech. Chem. Commun.* **1989**, 54, 2240. (c) Use of a stoichiometric amount of CuI to prepare S-arylated cysteine derivatives at 100 °C in ~30% yield: Hickman, R. J. S.; Christie, B. J.; Guy, R. W.; White, T. J. *Aust. J. Chem.* **1985**, 38, 899.

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^a Reaction conditions: ArI (1.0 mmol), ArSH (1.0 mmol), 5 mol % CuI, 2.0 equiv of K₂CO₃, 2.0 equiv of HO(CH₂)₂OH, in *i*PrOH at 80 °C under argon. ^b Isolated yield (average of two runs). ^c DME used as a solvent.

common functional groups. Thus, aryl iodides containing a nitrile, nitro group, ketone, free anilino NH₂ and phenolic OH moieties, a carboxylic acid, an aldehyde, and a free alkylamino group were all efficiently converted to product. The presence of an ethyl ester could be accommodated by using DME as the reaction solvent (in the absence of ethylene glycol), under our normal conditions transesterification to

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the isopropyl ester occurs. These results speak to the importance of using mild bases for transformations of this type. Also of interest is the result in entry 8 in which chemoselective C–S bond formation occurs in the presence of a phenolic OH group.¹⁵

A second portion of this work involved the application of our protocol to the combination of ortho-substituted aryl and of heteroaryl iodide substrates (Table 2). The presence of

Table 2. Cu-Catalyzed Carbon–Sulfur Bond Formation of Ortho-Substituted and Heterocyclic Substrates^a

entry	ArI	ArSH	product	% yield ^b
1				90
2				91
3				88
4 ^c				86
5				93
6				88
7 ^d				94
8 ^d				91
9				85
10				90

^a Reaction conditions: ArI (1.0 mmol), ArSH (1.0 mmol), 5 mol % CuI, 2.0 equiv of K₂CO₃, 2.0 equiv of HO(CH₂)₂OH, in 2-propanol at 80 °C under argon. ^b Isolated yield in average of two runs. ^c DME solvent. ^d Reaction conditions: ArI (1.0 mmol), ArSH (1.2 mmol), 20 mol % CuI, 2.0 equiv of K₂CO₃, 2.0 equiv of HO(CH₂)₂OH in *tert*-amyl alcohol at 100 °C under argon for 24 h.

functional groups in the ortho position of the aryl iodide substrates are tolerated, including a hydroxymethyl group

and a free NH₂ group. As can be seen from the results in entry 4, a thiophenol with an ortho carboxymethyl group can be coupled in good yield. This demonstrates that the protocol can be applied even with electron-deficient thiols.

The process is also extremely tolerant of steric hindrance, although the reaction is, in some cases, slightly more demanding. For example, the coupling of 2-isopropylthiophenol with 2-iodotoluene takes place in 88% yield. In comparison, the reaction of *p*-methoxythiophenol with 2-isopropyl iodobenzene is carried out with 20% CuI at 100 °C in *tert*-amyl alcohol to give a 94% yield of the desired

Table 3. Cu-Catalyzed Carbon–Sulfur Bond Formation of Alkyl Thiols^a

entry	ArI	RSH	product	% yield ^b
1				71 ^c
2				95
3				91
4				92

^a Reaction conditions: ArI (1.0 mmol), alkyl-SH (1.0 mmol), 5 mol % CuI, 2.0 equiv of K₂CO₃, 2.0 equiv of HO(CH₂)₂OH, in 2-propanol at 80 °C under argon. ^b Isolated yield in average of two runs. ^c Isolated yield. Reaction only proceeded to 78% conversion.

product. The combination of substrates that both possess an ortho isopropyl group can be accomplished in 91% yield (entry 8) under the latter conditions. As seen in entries 9 and 10, 3-iodopyridine and 5-iodoindole are also excellent substrates for this method.

Alkanethiols were also found to be effective nucleophiles in these reaction conditions (Table 3). Butanethiol and

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 (b) Ishiyama, T.; Mori, M.; Suzuki, A.; Miyaura, N. *J. Organomet. Chem.* **1996**, *525*, 225. (c) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1995**, *36*, 4133.
 (13) Ullmann couplings: (a) Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2382. For a review, see: (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (c) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
 (14) For an alternative process using a stoichiometric amount of Cu(OAc)₂ and arylboronic acids as S-aryllating agents, see: Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019.
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 (16) Schwesinger's phosphazene P₂-Et base (\$ 260 for 5 mL from Aldrich) was used.

benzylmercaptan were S-arylated in excellent yield (Table 3, entries 2 and 3). The selective S-arylation was observed when 6-mercaptohexanol was used as the substrate (Table 3, entry 4).

In summary, we have developed a general and efficient Cu-catalyzed carbon–sulfur bond formation for both aromatic and alkanethiols under mild conditions. This method is particularly noteworthy given its experimental simplicity, high generality, and exceptional level of functional group toleration and the low cost of the catalyst system. Further

(17) The coupling of ArI with thiols, 10 mol % CuI, 10 mol % of the relatively expensive neocuproine ligand, and 1.5 equiv NaO*t*-Bu in toluene at 110 °C was reported. The authors indicated that K₃PO₄ may be used as the base, where needed, for functionalized substrates. No examples, however, were provided: Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803–2806.

(18) For examples, CuX (X = I, Br, Cl, OAc), CuX₂ (X = Cl (as hydrate), Br, F, OAc, acac) and Cu₂O all worked well. We are currently examining the latter as an industrially interesting precatalyst.

(19) % Conversion (% GC yield); DBU, 72 (70); Et₃N 68 (64).

studies of this and related Cu-catalyzed cross-coupling reactions are in progress.

Acknowledgment. We thank the NIH (GM 58160), Pfizer, Merck, and Bristol-Myers Squibb are acknowledged for support in the form of unrestricted funds. F.Y.K. is grateful to The Croucher Foundation for a postdoctoral fellowship.

Supporting Information Available: Detailed experimental procedures and characterization data of each compound. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0266673

(20) Control experiments revealed that (a) anhydrous 2-propanol (packed under argon from Aldrich in a Sure-Seal bottle) gave the same conversion and yield of the reaction and (b) the oxidative coupling product, diaryl disulfide (ArS–SAr), was the major product if the reaction was performed in air.