

A General and Efficient Approach to Aryl Thiols: CuI-Catalyzed Coupling of Aryl Iodides with Sulfur and Subsequent Reduction

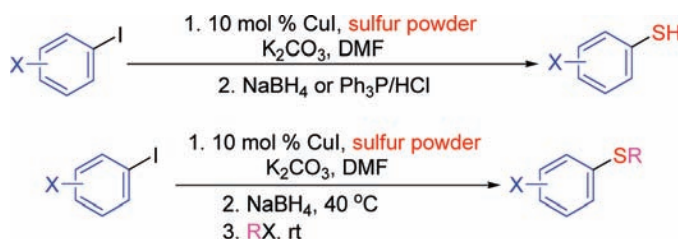
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ABSTRACT



A CuI-catalyzed coupling reaction of aryl iodides and sulfur powder takes place in the presence of K₂CO₃ at 90 °C. The coupling mixture is directly treated with NaBH₄ or triphenylphosphine to afford aryl thiols in good to excellent yields. A wide range of substituted aryl thiols that bear methoxy, hydroxyl, carboxylate, amido, keto, bromo, and fluoro groups can be assembled through this procedure.

Aryl thiols are important building blocks in the synthesis of sulfur-containing natural products and pharmaceutically important compounds. Among the existing approaches for preparation of aryl thiols,^{1–4} reductive cleavage of aryl disulfides has been well investigated.⁴ The suitable reductive agents include triphenylphosphine^{4a,c–e} and sodium borohydride.^{4b} Apart from the oxidation of aryl thiols, the

typical method for preparing aryl disulfides is through diazotization of anilines and subsequent reaction with sodium disulfide.^{4b} Recently, Knochel and Korn reported that direct preparation of aryl disulfides could be achieved via reaction of zinc reagents with sulfur monochloride,⁵ while Taniguchi found that the coupling reaction of aryl iodides and sulfur under the catalysis of Cu-bpy and Al worked at 110 °C to afford aryl disulfides, together with diaryl sulfides in some cases.⁶ Inspired from Taniguchi's report, we discovered that CuI alone could catalyze the coupling reaction of aryl iodides

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(1) By dealkylation of alkyl aryl sulfides, see: (a) Itoh, T.; Mase, T. *J. Org. Chem.* **2006**, *71*, 2203. (b) Shaw, J. E. *J. Org. Chem.* **1991**, *56*, 3728. (c) Testaferri, L.; Tingoli, M.; Tiecco, M.; Chianelli, D.; Montanucci, M. *Phosphorus Sulfur* **1983**, *15*, 263. (d) Cabiddu, S.; Melis, S.; Piras, P. P.; Sotgiu, F. *Synthesis* **1982**, 583.

(2) By hydrolysis of Ni-catalyzed coupling products of aryl iodides and thiourea, see: Takagi, K. *Chem. Lett.* **1985**, 1307.

(3) By hydrolysis of Cu-catalyzed coupling products of aryl iodides and thiobenzoic acid, see: Sawada, N.; Itoh, T.; Yasuda, N. *Tetrahedron Lett.* **2006**, *47*, 6595.

(4) For selected examples, see: (a) Jarkas, N.; Voll, R. J.; Williams, L.; Votaw, J.; Owens, M.; Goodman, M. M. *J. Med. Chem.* **2008**, *51*, 271. (b) Shinkai, H.; Maeda, K.; Yamasaki, T.; Okamoto, H.; Uchida, I. *J. Med. Chem.* **2000**, *43*, 3566. (c) Amos, R.; Fawcett, S. *J. Org. Chem.* **1984**, *49*, 2637. (d) Overman, L. E.; Petty, S. T. *J. Org. Chem.* **1975**, *40*, 2779. (e) Overman, L. E.; Smoot, J.; Overman, J. D. *Synthesis* **1974**, 59.

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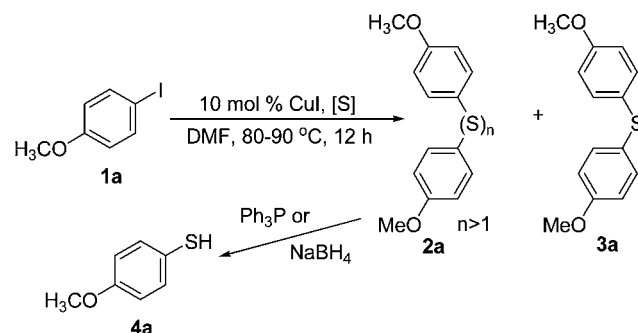
(6) Taniguchi, N. *Synlett* **2005**, 1687.

with sulfur. This reaction proceeded smoothly at 90 °C to give aryl disulfides exclusively, which underwent reductive cleavage when treated with triphenylphosphine or sodium borohydride to afford aryl thiols. Although two metal-catalyzed methods for the synthesis of aryl thiols have been reported,^{2,3} our method has the advantages in generality and using an inexpensive coupling reagent. Herein, we wish to detail our results.

Recently, we found that under the catalysis of CuI, metal sulfides such as Na₂S·9H₂O or K₂S could couple with 2-haloanilides to produce substituted benzothiazoles, after treatment with HCl.⁷ Inspired by this encouraging result, we decided to explore if aryl thiol synthesis could be achieved via direct coupling reaction of metal sulfides with simple aryl halides.⁸ Accordingly, a reaction of 4-iodoanisole with K₂S in the presence of 10 mol % of CuI was conducted. The reaction was found to be completed after 12 h at 80 °C in DMF, providing a mixture of 4-methoxybenzenethiol **4a** (80% yield) and bis(4-methoxyphenyl)sulfane **3a** (11% yield) upon direct reduction of the coupling mixture with triphenylphosphine and 12 N HCl (Table 1, entry 1). Changing the reducing agent to NaBH₄ gave a similar result (entry 2). To inhibit the formation of the diaryl sulfide **3a**, we attempted to introduce sulfur to the coupling reaction system because it can promote the formation of metal disulfides. To our delight, this measure led to isolation of the aryl thiol **4a** as a single product with an increased yield (entry 3). Further investigations indicated that a combination of sulfur with Na₂CO₃ or K₂CO₃ could give a similar outcome (entries 4 and 5). The presence of both base and copper catalyst is essential for this transformation because no coupling occurred if they were removed from the reaction system, respectively (entries 6 and 7). Noteworthy is that after quenching the coupling reaction with HCl, **2a** could be obtained as an inseparable mixture, indicating that several polysulfides with different numbers of sulfur were formed.

After the optimized reaction conditions were established, a number of aryl iodides were examined to explore the scope and limitation of this method. As summarized in Table 2, both electron-rich and electron-deficient aryl iodides worked well for this process, giving the corresponding aryl thiols in good to excellent yields. Noteworthy is that sterically hindered substrates also provided high yields of aryl thiols

Table 1. CuI-Catalyzed *S*-Arylation of 4-Iodoanisole and Subsequent Reduction under Different Conditions^a



entry	sulfur source	base	temp (°C)	reduction condition ^b	yield (%) ^c
1	K ₂ S		80	A	80 ^d
2	K ₂ S		80	B	79 ^d
3	K ₂ S/S		80	B	89
4	S	Na ₂ CO ₃	90	B	89
5	S	K ₂ CO ₃	90	B	90
6 ^e	S		90		— ^e
7 ^g	S	K ₂ CO ₃	90		— ^e

^a Reaction conditions: **1a** (1 mmol), K₂S or sulfur powder (3 mmol), CuI (0.1 mmol), base (2 mmol), DMF (2 mL), 80–90 °C, 12 h. ^b Condition A: PPh₃ (3 mmol), HCl (12 M, 0.2 mL), dioxane (3 mL), H₂O (1 mL), 40 °C, 5 h. Condition B: NaBH₄ (3 mmol), 40 °C, 5 h. ^c Isolated yield for **4a**. ^d **3a** was isolated in about 11% yield. ^e No coupling reaction occurred as monitored by TLC. ^f K₂CO₃ was not used. ^g CuI was not used

(entries 1 and 3), and a wide range of functional groups are tolerated in this process. The groups include methoxy, hydroxyl, carboxylate, amido, keto, bromo, fluoro, and nitro moieties. Thus, we concluded that this method provided a general approach to prepare aryl thiols.

When 4-bromiodobenzene was utilized, aryl thiol **4m** was isolated in 90% yield (entry 12), which indicated that disulfide and polysulfides were formed exclusively in the coupling reaction step. This observation is inconsistent with Taniguchi's report in which this substrate gave rise to the corresponding aryl disulfide as a major product. Obviously, the different coupling reaction conditions could be used to account for this phenomenon.

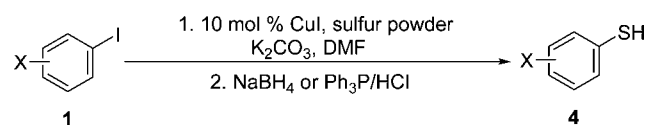
When some aryl iodides bearing a strong withdrawing group were used, it was found that simple nucleophilic substitution could take place easily and the presence of the catalyst was not required. For example, in the absence of CuI, 1-(4-iodophenyl)ethanone and 4-nitroiodobenzene produced thiol **4t** and **4u** in 73–84% yields at 60 °C (entries 19 and 20). However, for other electron-deficient aryl iodides, CuI is still helpful as a catalyst, as evident from that for both 3-nitroiodobenzene and 4-iodobenzoic acid, where better yields were observed if CuI was added (entry 21 vs. entry 22, entry 17 vs. entry 23).

We next attempted to use aryl bromides as coupling partners and observed low conversion for electron-rich aryl bromides in the coupling step even though the reaction temperature was increased to 140 °C. Only 1-(4-bromophe-

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Table 2. Synthesis of Aryl Thiols via a One-Pot Coupling-Reduction Procedure^a



entry	X	temp (°C)/ time (h)	product	yield (%)
1	2-OMe	90/12	4b	90
2	3-OMe	90/12	4c	89
3	2-Me	90/12	4d	90
4	3-Me	90/12	4e	92
5	4-Me	90/12	4f	90
6	3,5-dimethyl	90/12	4g	93
7	4-phenyl	90/12	4h	84
8	2-CH ₂ CO ₂ H	90/12	4i	82 ^c
9	4-NHAc	90/12	4j	90 ^c
10	4-CH ₂ OH	90/12	4k	89
11	4-CH(CH ₃)OH	90/12	4l	88 ^c
12	4-Br	90/12	4m	90
13	3-F	90/8	4n	92
14	4-F	90/8	4o	88
15	2-CO ₂ H	90/12	4p	88 ^c
16	3-CO ₂ H	90/12	4q	91 ^c
17	4-CO ₂ H	90/16	4r	87 ^c
18	3-CF ₃	90/8	4s	90
19	4-COCH ₃	60/12	4t	84 ^b
20	4-NO ₂	60/4	4u	73 ^b
21	3-NO ₂	90/12	4v	53 ^b
22	3-NO ₂	90/5	4v	84
23	4-CO ₂ H	90/12	4r	5 ^b

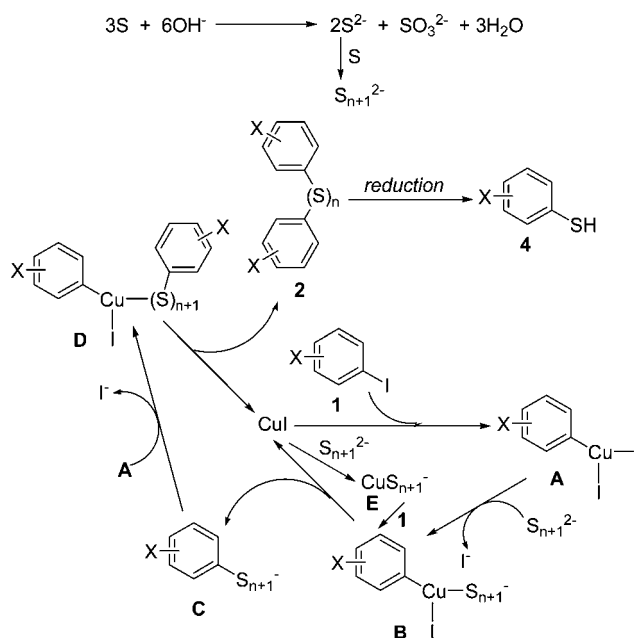
^a Reaction conditions: coupling step: **1** (1 mmol), sulfur powder (3 mmol), CuI (0.1 mmol), K₂CO₃ (2 mmol), DMF (2 mL); reduction step: NaBH₄ (3 mmol), 40 °C, 5 h (for entries 1–18 and 23); PPh₃ (3 mmol), HCl (12 M, 0.2 mL), dioxane (3 mL), H₂O (1 mL), 40 °C, 5 h (for entries 19–22).

^b Without addition of CuI. ^c Product purification was carried out by column chromatography. In the other entries, the products were unstable and therefore they were obtained directly via extract workup with about 95% purity.

nyl)ethanone was found to give the desired product through a simple nucleophilic substitution mechanism.

A possible mechanism for the CuI-catalyzed coupling reaction step is depicted in Scheme 1. It is known that sulfur could undergo a disproportionation reaction in the presence of the base to produce a sulfide and a sulfite. The former could further react with sulfur to deliver polysulfides. We assumed that these polysulfide ions might serve as the active species in the catalytic cycle. Accordingly, after oxidation addition of CuI to aryl iodide to afford complex **A**, ligand exchange with polysulfide ions might provide complexes **B**, which could undergo reductive elimination to give the initial coupling products **C** and regenerate CuI. Ligand exchange between the intermediate **C** and the complex **A** might take place to form complexes **D**. Reductive elimination of these intermediates could provide polysulfides **2** and regenerate CuI. Noteworthy is that another possible pathway for formation of complex **B** might be through the oxidative addition of

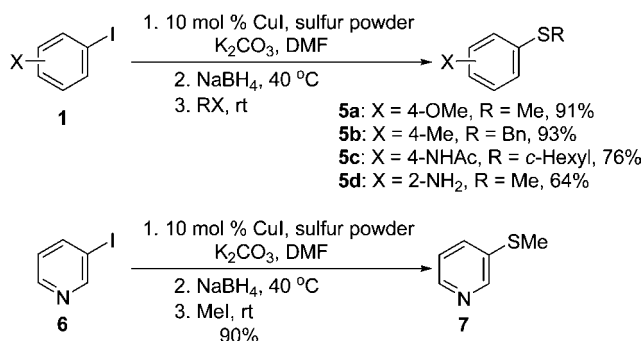
Scheme 1



copper polysulfides **E** to aryl iodides. Complex **E** might result from the reaction of CuI with polysulfides.

To further demonstrate the usage of the present process, we developed a one-pot procedure to synthesize thiol ethers by using a coupling reaction of aryl iodides with sulfur. As outlined in Scheme 2, after reduction of the coupling mixture, alkyl halides were added directly to afford the corresponding aryl alkyl thiol ethers in good to excellent yields.

Scheme 2



In conclusion, a novel procedure was developed for the preparation of aryl thiols from aryl iodides and sulfur, which relied on a CuI-catalyzed coupling reaction of aryl iodides with in situ generated polysulfide ions and the subsequent reduction. By adding alkyl halides to the reductive reaction mixture, aryl alkyl thiol ethers could be isolated with good yields. Considering the inexpensive catalyst and reagents, this method may find application in the synthesis of the related sulfur compounds.

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Supporting Information Available: Experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra for all new products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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