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Copper-catalyzed direct preparation of diaryl sulfides from aryl iodides using potassium thiocyanate as a sulfur transfer reagent

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ABSTRACT

A method for direct preparation of diaryl sulfides from aryl iodides using potassium thiocyanate as a sulfur-transfer agent is reported. A catalyst system comprising of a simple copper salt, tetrabutylammonium bromide as a phase-transfer agent and water as the solvent is used. Microwave heating at 200 °C for 60 min allows for the conversion of a range of aryl iodides to the corresponding diaryl sulfides.

Transition metal catalyzed carbon-heteroatom bond-forming reactions have proven to be very versatile in the preparation of a range of key compounds.[1,2] A review of the literature shows that, compared to C–O and C–N bond-forming reactions, couplings involving sulfur are far less prevalent.[3] This is due, at least in part, to the fact that sulfur compounds can often poison transition-metal complexes through irreversible ligation. Indeed, immobilized thiols are often used as post-reaction scavengers for a number of transition metal-mediated reactions. This being said, there are a number of routes to diaryl and aryl–alkyl thiols[4] involving the use of copper,[5] palladium,[6] or nickel complexes.[7] The majority of these routes involve coupling of a thiol with an aryl halide in an Ullmann-like reaction. Here we report a methodology for the preparation of symmetrical diaryl sulfides from aryl iodides using KSCN as the source of the sulfur bridging atom, copper(I) oxide as the catalyst, and water as the solvent.

In our laboratory we have become interested in developing methods for performing metal-mediated carbon-heteroatom bond forming reactions using a range of nucleophilic coupling partners. These include $K_4Fe(CN)_6$ and $Cu_2Fe(CN)_6$ for cyanation,[8,9] water for formation of phenols[10] and phenoxides and alkoxides for the synthesis of aryl ethers.[9] Most recently, our attention has turned to the reaction chemistry of thiocyanates with aryl halides. Aryl thiocyanates are versatile starting materials for a range of sulfur-containing compounds, particularly heterocycles. Suzuki and Abe reported a methodology for conversion of aryl iodides to the corresponding thiocyanates using the cuprate complex $K[Cu(SCN)_2]$, prepared in-situ from CuSCN and KSCN.[14] The reaction is performed in DMF and requires stoichiometric quantities of the cuprate complex.

Our starting point was to screen reaction conditions that built upon our work with other nucleophilic coupling partners. To this end, we decided to focus attention on the use of water as a solvent, tetrabutylammonium bromide (TBAB) as phase-transfer agent, and simple copper salts as the catalyst in conjunction with KSCN as the thiocyanate source. Using a scientific microwave unit as a convenient heating tool, 4-iodotoluene as a test substrate, and performing the reaction at 170 °C in a sealed vessel employing a stoichiometric quantity of CuI and 2 equiv KSCN we observed a 25% conversion to the corresponding thiocyanate after 20 min. We also observed a small quantity of di-*p*-tolyl sulfide (**1**) formed as a byproduct (Scheme 1). Further assessment of copper salts and reaction conditions showed us that the formation of the diaryl sulfide was more favorable than that of the corresponding aryl thiocyanate, especially when using Cu_2O. This interested us in light of the very recent report by Zhou and co-workers who have shown that when using $CuCl_2$ as a catalyst, 1,10-phenanthroline as ligand, tetrabutylammonium fluoride (TBAF) as additive and cesium carbonate as base, it is possible to perform copper-catalyzed C–S bond formation between aryl halides and potassium thiocyanate leading to diaryl sulfides.[11] Reactions were performed at 130 °C for 48 h. Our attention therefore turned to developing a more expedient and simple route to symmetrical diaryl sulfides.

Using 4-iodotoluene as the substrate and employing a stoichiometric quantity of copper(I) oxide and 2 equiv KSCN, we were able to generate **1** in 88% conversion (Table 1, entry 1). Interesting,

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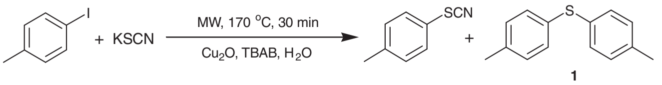
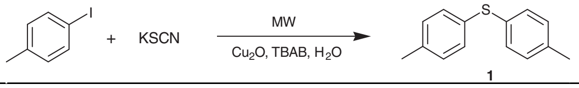


Scheme 1.

Zhou and coworkers reported that copper(I) oxide was an ineffective catalyst for diaryl sulfide formation but under our conditions it performs better than all other copper salts screened. The reaction required heating to 200 °C for 1 h using water as the solvent and 1 equiv TBAB as the phase-transfer agent. Increasing the quantity of KSCN to 2.5 equiv while keeping all other conditions the same led to a quantitative conversion to **1** (Table 1, entry 2). Our next objective was to reduce the quantity of Cu_2O required, turning the process from stoichiometric to catalytic in copper. We found that we could reduce the loading to 30 mol % without a deleterious effect on product conversion (Table 1, entry 3). At catalyst loadings below 30 mol %, a significant drop in conversion was observed (Table 1, entries 4 and 5). We were also able to reduce the quantity of TBAB required to 30 mol % (Table 1, entry 6). Interestingly, addition of a base (Cs_2CO_3) which was deemed essential by Zhou and co-workers in their methodology,[11] led to competitive formation of 4-methylphenol in our case (Table 1, entry 7). Attempts to perform the reaction using either aqueous acetonitrile or polar aprotic organic solvents were either less successful or else yielded no product (Table 1, entries 8–10), showing that water was the optimal solvent. Therefore, our optimized conditions were: Cu_2O (30 mol %) as catalyst, KSCN (2.5 equiv), 30 mol % TBAB as phase-transfer agent, water as solvent, heating at 200 °C for 60 min. As was the case with our methodologies for cyanation of aryl halides, we found here that, while we observed high conversions to **1**, the method used to isolate the product was critical to obtaining good yields. Our optimized work-up used ethyl acetate as solvent in an aqueous-organic extraction, this leading to a 75% yield of **1** (Table 1, entry 11).

With optimized conditions in hand, we next screened a representative range of aryl halide substrates.[12,13] The results are shown in Table 2. The aryl iodides screened could be converted to the corresponding diaryl sulfides in good yields (Table 2, entries 1–8). An exception was 3-iodopyridine where only a trace of the desired product was formed (Table 2, entry 9). Extending the methodology to aryl bromides was not as successful as with the corresponding aryl iodides (Table 2, entries 10 and 11).

Table 1
Optimization of conditions for the direct conversion of 4-iodotoluene to di-p-tolyl sulfide, **1**



Entry	Reaction conditions[a,b]	Conv (%)[c]
1	1 equiv Cu_2O, 2 equiv KSCN, 1 equiv TBAB, water	88
2	1 equiv Cu_2O, **2.5 equiv KSCN**, 1 equiv TBAB, water	100
3	**30 mol % Cu_2O**, **2.5 equiv KSCN**, 1 equiv TBAB, water	100
4	**20 mol % Cu_2O**, **2.5 equiv KSCN**, 1 equiv TBAB, water	63
5	**10 mol % Cu_2O**, **2.5 equiv KSCN**, 1 equiv TBAB, water	55
6	**30 mol % Cu_2O**, **2.5 equiv KSCN**, **30 mol % TBAB**, water	100
7	**30 mol % Cu_2O**, **2.5 equiv KSCN**, **30 mol % TBAB**, **1 equiv Cs_2CO_3**, water	0
8	**30 mol % Cu_2O**, **2.5 equiv KSCN**, **30 mol % TBAB**, **9:1 acetontrile/water**	33
9	**30 mol % Cu_2O**, **2.5 equiv KSCN**, **30 mol % TBAB**, **acetonitrile**	0
10	**30 mol % Cu_2O**, **2.5 equiv KSCN**, **30 mol % TBAB**, **NMP**[d]	0
11	**30 mol % Cu_2O**, **2.5 equiv KSCN**, **30 mol % TBAB**, water	75[e]

[a] *Conditions:* reactions performed on the 1 mmol scale using 1 mL solvent. Reaction mixture heated to target temperature and held for 60 min.

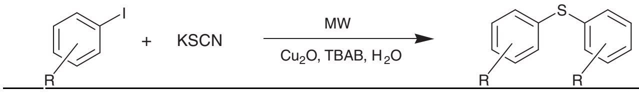
[b] For clarity, changes in reaction conditions from entry 1 are noted in bold.

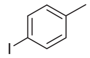
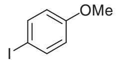
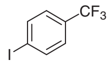
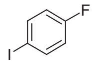
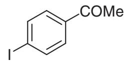
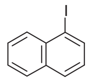
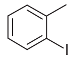
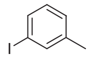
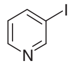
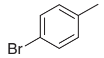
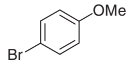
[c] Determined using ^1H NMR spectroscopy.

[d] *N*-methyl-2-pyrrolidone.

[e] Product yield.

Table 2
Copper-catalyzed preparation of diaryl sulfides from aryl halides[a]



Entry	Aryl halide	Yield (%)[b]
1		75 (48)[c]
2		65
3		60
4		63
5		61
6		60
7		58
8		56
9		trace
10		40[d]
11		36

[a] Reactions were performed on the 1 mmol scale using 30 mol % Cu_2O as catalyst, 2.5 equiv KSCN as sulfur source, 30 mol % TBAB as phase-transfer agent and 1 mL water as solvent. Reaction mixture was heated to 200 °C for 60 min.

[b] Determined using ^1H NMR spectroscopy by comparison with an internal standard.

[c] Isolated yield.

[d] Product conversion.

In conclusion, we present here a methodology for a direct and rapid preparation of diaryl sulfides from aryl iodides using potassium thiocyanate as the source of sulfur. The work complements the very recent report by Zhou and co-workers,[11] advantages of our approach being substantially shorter times (1 h rather than 48 h), no need for added base or ligand and the use of a substoichiometric quantity of TBAB as opposed to its more aggressive fluoride analog. Our catalyst system comprises a simple copper salt and heating at 200 °C for 60 min allows for the conversion of a range of aryl iodides to the corresponding dialkyl sulfides.

Acknowledgments

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12. General representative procedure: preparation of di-p-tolyl sulfide (Table 2, entry 1). In a 10 mL glass tube was placed 4-iodotoluene (219 mg, 1 mmol), potassium thiocyanate (243 mg, 2.5 mmol), copper(I) oxide (43 mg, 0.3 mmol), tetrabutylammonium bromide (97 mg, 0.3 mmol), and water (1 mL). The mixture was stirred for 1 min before sealing the tube with a septum and placing the reaction mixture into the microwave cavity (CEM Discover). An initial microwave power of 150 W was used, the temperature being ramped from rt to 200 °C where it was held for 60 min (*caution:* The water is heated well above its boiling point so all necessary precautions should be taken when performing such experiments. Vessels designed to withhold elevated pressures must be used. The microwave apparatus used here incorporates a protective metal cage around the microwave vessel in case of explosion. After completion of an experiment, the vessel must be allowed to cool to a temperature below the boiling point of the solvent before removal from the microwave cavity and opening to the atmosphere.). The reaction mixture was stirred continuously throughout. The reaction was run in triplicate. After allowing the three identical reaction mixtures to cool to rt, the vessels were opened and their contents poured into a separatory funnel and the tubes washed three times with ethyl acetate (approximately 3 mL each time) followed by two washes with water (5 mL each time). All washings were added to the separatory funnel along with an additional 20 mL of ethyl acetate. Typically an emulsion was formed after shaking; therefore brine (approximately 5 mL) was added to aid separation. The aqueous layer was extracted twice more with ethyl acetate (approximately 30 mL each time). The organic washings were combined, washed with deionized water (approximately 20 mL), collected, dried over $MgSO_4$, and then the ethyl acetate removed in vacuo. Purification was accomplished by column chromatography (100% hexanes) affording the product as a white solid (152 mg, 48%).^{1}H NMR ($CDCl_3$): δ/ppm 7.22 (4H, d), 7.08 (4H, d), 2.37 (6H, s). ^{13}C NMR ($CDCl_3$): δ/ppm 137.11, 132.97, 131.32, 130.16, 21.3.
13. All products prepared are known compounds and were characterized by comparison of NMR spectral data with that in the literature.
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