

# CsOH·H<sub>2</sub>O-Promoted Synthesis of Aryl Sulfides via Direct Coupling of Aryl Halides and Thiols<sup>1</sup>

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We report here our observation that, using appropriate reaction conditions, CsOH·H<sub>2</sub>O-promoted coupling of aryl halides with thiols can be performed in moderate to good yields without a transition metal catalyst.

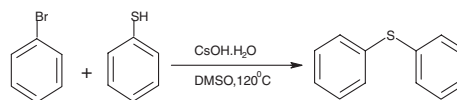
Lately, both the scope and application of organosulfur chemistry have received considerable attention in synthetic organic chemistry because sulfur-containing moieties serve as an important auxiliary function in synthetic sequences in organic chemistry. In addition, aryl sulfides are very useful intermediates in organic synthesis.<sup>2</sup> Furthermore, aryl sulfides also find important applications as pharmaceuticals as many aryl sulfide containing compounds show significant pharmacological activity.<sup>3</sup>

After early reports by Murahashi<sup>4</sup> and Migita,<sup>5</sup> only a few new synthetic methods of carbon-sulfur bond-forming reactions have appeared in the literature. The conversion of unactivated aryl halides or triflates to aryl sulfides has been realized by using stoichiometric amounts of copper salts<sup>6</sup> and using palladium complexes as catalysts.<sup>7</sup> Guy et al. has developed an elegant synthesis of aryl sulfides through copper-mediated cross-coupling of aryl boronic acids and thiols.<sup>8</sup> Buchwald et al.<sup>9</sup> has reported copper(I)-catalyzed coupling of aryl iodides and thiols using K<sub>2</sub>CO<sub>3</sub> as a base and ethylene glycol as an additive in 2-propanol at 80 °C. Recently, there is a report of coupling of aryl halides and thiols by using copper catalysts under microwave conditions.<sup>10</sup> Even though these reported methods are very efficient and provide good conversion for the synthesis of aryl sulfides, these synthetic methodologies require use of transition metal complexes, and suffer from long reaction times, and have a relatively narrow application scope for substrates. Furthermore, use of transition metal complexes leads to the generation of hazardous waste, which has a number of environmental health problems associated with it.<sup>11</sup> Very recently, a convenient one-pot synthesis of alkyl aryl sulfides from thiols and alkyl halides using cesium carbonate, tetrabutyl ammonium iodide, and DMF is reported.<sup>12</sup> Thus, development of improved synthetic methods for the synthesis of aryl sulfides still remains an active research area.

In the last few years, CsOH·H<sub>2</sub>O-promoted synthetic protocols have been widely applied to the formation of a variety of carbon-hetero atom and carbon-carbon bond.<sup>13</sup> Herein, we present our preliminary findings in the development of transition metal-free coupling of aryl halides and thiols using CsOH·H<sub>2</sub>O as efficient base for various structurally divergent benzene thiols and aryl halides.

First, we evaluated the feasibility of direct cross-coupling of bromobenzene (1.0 mmol) and thiophenol (1.2 mmol) in DMSO using 2 mmol of CsOH·H<sub>2</sub>O in a sealed tube (Scheme 1).<sup>14</sup> At ambient temperatures, no reaction between the coupling partners was observed, but heating the reaction mixture to 120 °C for 10 min afforded diphenyl sulfide in 64% yield after purification





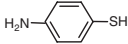
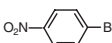
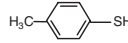
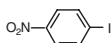
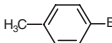
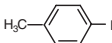
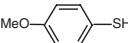
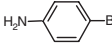
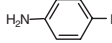
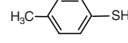
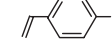
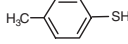
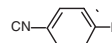
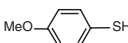

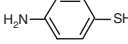





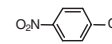

of the crude product using silica gel flash chromatography (Table 1, Entry 1). As a control experiment, the same reaction was carried out in the absence of CsOH·H<sub>2</sub>O at 120 °C, when no cross-coupled product was observed even after heating for a longer period of time. The optimum yield of the product is obtained when a ratio of aryl halide to thiol of 1:1.2 is used. Of the solvents tested for this reaction (DMSO-THF, H<sub>2</sub>O/TBAB, NMP, and DMSO), DMSO was found to be the most efficient, perhaps because thiolate anions are more reactive in aprotic solvents such as DMSO than in protic solvents. In the absence of DMSO, no product could be isolated from the crude reaction mixture, thus solvent plays a vital role in this reaction.



Scheme 1.

With optimized experimental conditions for thiophenol in hand, we then investigated the direct cross-coupling reactions of a wide range of substituted aryl halides and thiols. The results from this study are shown in Table 1. It is clear from Table 1 that most substrates underwent direct coupling reactions to afford the corresponding sulfides in moderate to good yields. Reaction time is also very short (5–20 min) for most of the substrates. However, the reaction of benzylmercaptan with 1-bromo-4-nitrobenzene required no heating at all, as the reaction takes place at room temperature in about 3 h in excellent yield, similarly, 4-methylthiophenol coupled with 1-bromo-4-nitrobenzene gave 72% yield (Entry 4). In general, benzyl mercaptans gave excellent yields compared to thiophenols. In general, electron donating groups like methyl, amino groups on the aryl halide gave poor yields than those of reactions carried out with electron withdrawing groups on aryl halides. For example, 4-bromotoluene and 4-bromoaniline on reacting with thiophenol gave 62, 57% in yields respectively (Entries 6 and 8). However, aryl halides that contain *p*-hydroxy and *p*-methoxy substituents do not undergo adduct formation at all under our experimental conditions. However, when methoxy substituents were present in the aromatic thiol fragments, no inhibition for direct coupling reactions were observed. As seen in Entry 11, 1-bromo-4-cyanobenzene and 4-methoxybenzenethiol gave coupled products in good yields. In a similar fashion, thiophenols containing amino groups do not inhibit the reaction as well. The coupling of 1-bromonaphthalene and 4-aminobenzenethiol gave coupled product in moderate yield 68% (Entry 12). In general, the use of aryl iodides for the coupling reactions gave higher yields of the desired sulfides than those of reactions involving corresponding bromides (Entries 2, 5, 7, and 9). This observation is consistent with earlier observation that aryl iodides are more reactive than corresponding bromo analogues.<sup>15</sup> Aliphatic thiols react readily with aryl halides to form corresponding sulfides in moderate

**Table 1.** CsOH·H<sub>2</sub>O promoted cross-coupling of aryl halides and thiols

Entry	Ar-X	Thiol	Time/min	Yield/% <sup>a</sup>
1		PhSH	10	64
		PhCH <sub>2</sub> SH	5	70
2		PhSH	10	72
		PhCH <sub>2</sub> SH	5	78
3			20	55
			15	45
4 <sup>b</sup>			300	72
		PhCH <sub>2</sub> SH	180	86
5 <sup>b</sup>		PhSH	240	80
		PhCH <sub>2</sub> SH	150	90
6		PhSH	15	62
7			15	65
8		PhSH	10	57
9			15	68
10			10	71
11			5	76
12			10	68
13		PhSH	20	42
14			5	62
15			5	67
16		PhSH	10	58
17		PhSH	15	62

<sup>a</sup>Isolated yields.<sup>b</sup>Room temperature.

yield. For example, hexanethiol on coupling with 1-bromonaphthalene gave 62% yield (Entry 14). Similarly, 2-sulfanylethanol and 1-bromonaphthalene gave corresponding sulfide in 67% yield (Entry 15). However, this type of coupling reaction does not seem to work well on aryl chlorides and fluorides.

Interestingly, we have observed the coupling of 1-chloro-4-nitrobenzene with thiophenol gave 58% yield and 1-cyano-2-fluorobenzene on coupling with thiophenol gave good yield of 62% respectively (Entries 16 and 17). Electron withdrawing groups containing chloro, fluorobenzenes only underwent smooth nucleophilic substitution with the thiols.

We evaluated the feasibility of direct cross-coupling of phenol triflate and benzenethiol using CsOH·H<sub>2</sub>O on heating the reaction mixture to 120 °C for 5 min as described in general procedure, afforded diphenyl sulfide in 70% yield after purification of the crude product using silica gel flash chromatography.

In summary, we have shown a rapid and direct method for the coupling of aryl halides with thiols without a transition-metal catalyst that could be performed in good yields using CsOH·H<sub>2</sub>O. An effort to expand the scope of the method is ongoing in our laboratory.

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- A mixture of arylhalide (1 mmol), thiol (1.2 mmol), and CsOH·H<sub>2</sub>O (2 mmol) in DMSO (3 mL) were taken in a sealed tube placed in preheated oil bath at the given temperature (Table 1) and then held at that temperature for the given time. Then the reaction mixture was cooled to rt, poured into water containing crushed ice, and stirred for 5 min. Sat. aq NH<sub>4</sub>Cl solution was added to this mixture, and the organic portion was extracted with Et<sub>2</sub>O (3 × 20 mL). The combined organic extracts were washed with a saturated NH<sub>4</sub>Cl solution and brine, and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After removal of the solvent the residue was purified by column chromatography on silica gel to furnish the product. All isolated compounds were fully characterized by comparing their spectral data (<sup>1</sup>H NMR and Mass Spectra) of authentic compounds.
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