



Short Communication

Simple and efficient CuI/PEG-400 system for hydroxylation of aryl halides with potassium hydroxide

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ABSTRACT

This work reports a simple and efficient CuI/PEG-400 system for hydroxylation of aryl halides with potassium hydroxide. This protocol offers a direct transformation of aryl iodides or bromides to substituted phenols in great diversity. A very wide variety of functional groups are tolerated on aryl halides partners such as carboxyl, aldehyde and hydroxyl group.

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1. Introduction

Phenols are structural constituents of pharmaceuticals, polymers, and naturally occurring compounds in addition to serving as versatile synthetic intermediates [1]. Therefore, effective methods for the synthesis of phenols would be valuable [2]. Classical methods for phenol synthesis include [3,4] (1) nucleophilic substitution of activated aryl halides; (2) transformation of arene diazonium salts in the presence of copper complexes; (3) anodic oxidation of arenes in trifluoroacetic acid; (4) benzyne synthetic route; (5) C–H activation/hydroxylation. However, these methods have strong limitations due to the limited availability of starting materials and, in some cases, the requisite harsh reaction conditions [5–7]. A milder method of the preparation of non-orthosubstituted phenols has been achieved in two steps: C–H activation/borylation and oxidation in the presence of iridium–phosphine complexes [8]. Recently, some efficient catalytic systems based on palladium–phosphine complexes were developed by the groups of Buchwald [9], Kwong [10], Diaconescu [11], and Beller [12,13], which led to hydroxylation of aryl halides under mild reaction conditions. More recently, an iron-catalyzed method has been reported for conversion of aryl halides to phenols in water at 180 °C [14]. Although copper has led to a resurgence of interest in an Ullmann-type coupling reaction from an economic and industrial point of view [15–20], the copper-mediated direct hydroxylation of aryl halides using hydroxide salts as nucleophiles is less developed [21–28]. They use either neat water [25–28] or a water/DMSO solvent mix [21–24], copper (I) iodide as a catalyst, a range of aryl iodides and

bromides can be used as substrates and reactions are complete within 20–48 h at 100–130 °C. However, some supporting ligands were needed for obtaining high yields. Kormos and Leadbeater attempted the direct conversion of aryl halides to phenols in water with microwave heating, unfortunately, high temperatures (200–300 °C) were required, and the resulting yields were very low [29]. Thus, a more simple and efficient catalytic system for hydroxylation of aryl halides is desired in view of green and sustainable chemistry. As a non-toxic, inexpensive, thermally stable and recoverable reagent, polyethylene glycol (PEG) represents a very attractive medium for organic reactions [30–34]. To the best of our knowledge, the copper-catalyzed hydroxylation of aryl halides and hydroxide salts in PEG-400 has not so far been reported. In this paper, we wish to report a highly efficient copper-catalyzed protocol for a coupling of aryl iodides or aryl bromides with potassium hydroxide in PEG-400.

2. Experimental

2.1. General

All commercially available reagents and PEG-400 were used as received without further purification. All reactions were performed under argon atmosphere in glassware, ¹H NMR spectra were recorded on a Bruker AC-400 (400 MHz) spectrometer with TMS as an internal standard.

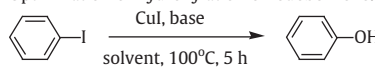
2.2. General procedure for the synthesis of substituted phenols

A 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with CuI (0.1 mmol, 19 mg), KOH (6 mmol, 336 mg), PEG-

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Table 1
Optimization of hydroxylation of iodobenzene.



Entry ^a	Solvent (3 mL)	Base	Yield ^b (%)
1	H ₂ O	KOH	10
2	PEG-400	KOH	89
3	PEG-400/H ₂ O 1:4	KOH	78
4	PEG-400/H ₂ O 1:2	KOH	80
5	PEG-400/H ₂ O 1:1	KOH	82
6	PEG-400/H ₂ O 2:1	KOH	90
7	PEG-400/H ₂ O 4:1	KOH	98
8 ^c	PEG-400/H ₂ O 4:1	KOH	95
9 ^d	PEG-400/H ₂ O 4:1	KOH	75
10	PEG-400/H ₂ O 4:1	NaOH	84
11	PEG-400/H ₂ O 4:1	Na ₃ PO ₄	56
12	PEG-400/H ₂ O 4:1	Na ₂ CO ₃	trace
13	PEG-400/H ₂ O 4:1	K ₂ CO ₃	10
14	PEG-400/H ₂ O 4:1	NaOAc	24

^a Reactions performed at 100 °C with 6.0 equiv of base and 0.1 equiv of CuI unless otherwise noted.

^b Yield of isolated product.

^c At 80 °C.

^d CuI (0.05 equiv.).

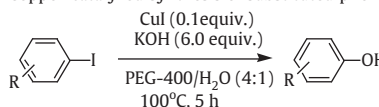
400 (2.4 mL), H₂O (0.6 mL) and aryl halide (1.0 mmol). The tube was evacuated twice and backfilled with nitrogen and the tube was sealed and put into a preheated oil bath at 100 °C under a positive pressure of nitrogen. After the reaction was completed, the resulting solution was cooled to RT, HCl (1 N, 2 ml) was added to acidify the solution (pH 2–3) and the solution was extracted with ethyl acetate (3 times). The combined organic phases were concentrated, and the remaining residue was purified by column chromatography on silica gel to provide the desired product.



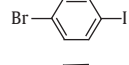
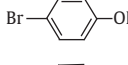
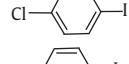
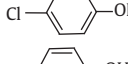
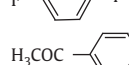
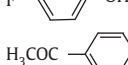
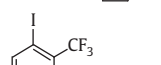
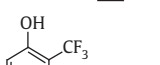




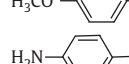
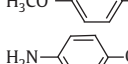
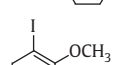
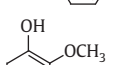




3. Results and discussion

We initially selected iodobenzene as a model substrate for optimization of the reaction conditions. Selected results from our screening experiments are summarized in Table 1. Our first test was performed in water alone using a catalytic amount of CuI (0.1 equiv), with KOH (6.0 equiv) as the nucleophile, only small amounts of Phenol were obtained (Table 1, Entry 1). To our delight, the desired product was obtained with excellent yield, when the same reaction was performed in neat PEG-400 (Table 1, Entry 2). Subsequently, we systematically tested mixed-solvent systems over a range of proportions using KOH as the nucleophile (Table 1, Entries 3–7), we were pleased to find that iodobenzene was quantitatively transformed into phenol with PEG-400/H₂O (4:1 ratio, Table 1, Entry 7). It is worth noting that the corresponding symmetric diaryl ether [35] was not detected in all cases. Under the same conditions, when the temperature was decreased to 80 °C, or when only 0.05 equivalents of CuI were used, the yields of phenol were both reduced (Table 1, Entries 8–9). Other bases were tested (Table 1, Entries 10–14); moderate yield was obtained using NaOH as base, while Na₃PO₄, Na₂CO₃, K₂CO₃ or NaOAc as a base afforded the phenol product in very low yield. Obviously, the reaction activity was closely related to the strength of base; alkaline stronger and the yield is higher. Thus, we selected KOH as the base in the following studies. Based on the result of the above screening experiment, we presume that PEG-400 is served not only as a solvent, but also as a ligand that stabilizes or solubilizes CuI.

We then explored the breadth of application of this new method using the above optimized experimental conditions (Table 1, Entry 7). Thus, in a mixed solvent system of PEG-400/H₂O (4:1), the CuI/PEG-400 system efficiently promotes cross-coupling reactions between KOH and aryl iodides with electron-withdrawing groups (EWGs), to afford the corresponding phenols in excellent yields (Table 2, Entries 2–7). However, in some cases, with activated substrates such as *o*-iodothi-

Table 2
Copper-catalyzed synthesis of substituted phenols by hydroxylation of aryl iodides.



Entry ^a	Arl	ArOH	Yield ^b (%)
1			98
2			92
3			94
4			92
5			96
6 ^c			85
7 ^{c, d}			94
8 ^c			90
9 ^c			70
10 ^c			91
11			88

^a Reaction conditions: aryl iodide (1 mmol), CuI (0.1 mmol), KOH (6 mmol), solvent (3 mL in a ratio of 4:1), reaction for 6 h at 100 °C.

^b Isolated yield.





































^c Reaction for 8 h.

^d KOH (7.0 equiv.).

fluoromethylbenzene or *o*-iodocarbonylbenzene, reactions can also proceed efficiently at longer reaction time (8 h, Table 3, Entries 6–7). Subsequently, we performed the coupling reaction with aryl iodides deactivated by electron-donating groups (EDGs), and we obtained the desired products in good to excellent yields (8 h, Table 3, Entries 8–10). Interestingly, for *p*-iodobromobenzene, we observed the quantitative formation of the mono-substituted product (Table 2, Entry 2); on the other hand, 4-iodo-phenylamine as substrate gave the desired phenol in moderate yield with minor amination byproduct (4-Iodo-phenyl)-phenyl-amine (Table 2, Entry 9). It must to note that 7 equivalents of KOH were needed to achieve high conversion when iodobenzene containing carboxyl group was employed as a substrate, (Table 2, Entry 7). 2-Iodo-thiophene as substrate was also selectively converted into the corresponding phenol under these conditions (Table 2, Entry 11).

Then, we further tested the activity of aryl bromides under our reaction conditions, as shown in Table 3. However, low yield was found under the previously optimized reaction conditions (54%; Table 3, Entry 1). After careful optimization of the reaction conditions it was found that hydroxylation of bromobenzene was well performed with excellent yield at 120 °C for 8 h (93%, Table 3, Entry 1). This method was successfully extended to aryl bromides deactivated by electron-donating groups, such as methoxyl, methyl, 3,5-dimethyl (Table 3, Entries 11–16) or a electron-withdrawing groups such as chloro, fluoro, bromo, carboxyl (Table 3, Entries 2–8). Furthermore, Bromonaphthalene was also quantitatively converted into the corresponding naphthol for 12 h (89%, 96%, Table 3, Entries 17–18), respectively. It

Table 3
Copper-catalyzed synthesis of substituted phenols by hydroxylation of aryl bromides.

Entry ^a	ArBr	ArOH	Yield ^b (%)
1			54 ^c , 93
2			91
3			89
4			88
5			94
6			88
7 ^d			92
8 ^d			95
9			78
10 ^e			89
11 ^e			76
12 ^e			90
13 ^e			92
14			80
15			90
16			91
17 ^e			89
18 ^e			96

^a Reaction conditions: aryl bromides (1 mmol), CuI (0.1 mmol), KOH (6 mmol), solvent (3 mL in ratio of 4:1), reaction for 8 h at 120 °C.

^b Isolated yield.

^c Reaction for 5 h at 100 °C.

^d KOH (7.0 equiv.).

^e Reaction for 12 h.

was important to stress that the hydroxylation reactions above could tolerate various functional groups, including C–Cl bond (Table 3, Entries 2, 3), C–F bond (Table 3, Entry 4, 5), carboxyl groups (Table 3, Entries 7, 8), aldehyde group (Table 3, Entry 9), and hydroxyl group (Table 3, Entry 10) in aryl halides.

4. Conclusions

We have developed a general, economical and efficient protocol for copper-catalyzed synthesis of substituted phenols by hydroxylation of aryl iodides and even less reactive aryl bromides under mild conditions. This procedure avoids the otherwise typical formation of the related biaryl ether byproduct. This method is of particular value given its experimental simplicity, functional group compatibility, and the low cost of the catalytic system, which makes this method readily adaptable to production on an industrial scale, where safety and environmental factors are of particular concern. Further application of the CuI/PEG-400 catalytic system is currently under investigation in our laboratory.

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