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REGULAR ARTICLE

Dimethylglyoxime as an efficient ligand for copper-catalyzed hydroxylation of aryl halides

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Abstract. The CuI/dimethylglyoxime (CuI/DMG) catalyzed direct hydroxylation of aryl iodides with CsOH takes place at 120 °C in a mixed solvent system (DMSO–H_2O,1:1), afforded the corresponding phenols in good to excellent yield. Aryl bromides are found to be less reactive than aryl iodides under these reaction conditions.

Keywords. Aryl halide; C-O coupling; dimethyl glyoxime; hydroxylation; phenol.

1. Introduction

Phenols play key role in production of natural products, pharmaceutical and medicinal compounds, as well as in polymers and other materials. These days, about more than 90% of the world's phenol requirement is satisfied by the Hock process, which entail the peroxidation of cumene, itself obtained from benzene propylation.[1–4] The conventional methods used in synthesis of phenols are nucleophilic aromatic substitution of activated aryl halides,[5] benzyne procedure,[6] and copper-mediated transformation of arene diazonium salts.[7] Recently, various efficient palladium/phosphine-catalyzed protocols have been developed for the formation of phenols.[8,9] However, less expensive copper (I) salt as catalyst would be most attractive option for economic benefits and low toxicity issues. The usage of a cheaper system facilitates the hydroxylation[10,11] of aryl halides have turn out to be an important objective. In organic synthesis the development of a mild, general and highly efficient method for the preparation of phenols is a challenging task. At present the availability of starting materials and the direct nucleophilic substitution of a halogen atom in aryl halides are interesting strategies for the preparation of substituted phenols. These days copper-catalyzed hydroxylation of aryl halides has gained considerable attention. In the past it was reported that direct crosscoupling of hydroxide salts and aryl iodides using CuI and either 1, 3-diketone[3] or 1, 10-phenanthroline[12] in aqueous DMSO can be used for synthesis of phenols. In addition to this several other ligands such as lithium pipecolinate, tetrabutylammonium hydroxide pentahydrate, 8-hydroxyquinoline-N-oxide and D-glucose[11,13–15] were used, which shows that ligands play important role in the activity of catalyst. However, in spite of these advancements, there is a need for economical and easily available ligands which have general applicability. Copper catalyzed route is essential from an industrial perspective, owing to the availability of reagents, low cost and low toxicity.[16,17]

This paper reports a simple, practical and efficient copper-catalyzed synthesis of substituted phenols from aryl halides by using dimethyl glycoxime (Butane-2, 3-dione dioxime) as an inexpensive, simple, and efficient ligand in presence of CsOH base. Thus, dimethylglyoxime has drawn considerable interest from both the chemical and biological sciences. The oxime group (>C=N–OH), which perhaps considered to be derived from oxy-imine, is amphoteric since it contains slightly basic nitrogen and mildly acidic hydroxyl groups.[18]

2. Experimental

All reagents were commercially purchased and used without further purification. The reation products were identified by comparing observed and reported ^{1}H-NMR spectra and melting point. ^{1}H NMR spectra were recorded on a Bruker AC-400 (400 MHz) spectrometer with TMS as an internal Standard.

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Electronic supplementary material: The online version of this article (https://doi.org/10.1007/s12039-017-1416-x) contains supplementary material, which is available to authorized users.

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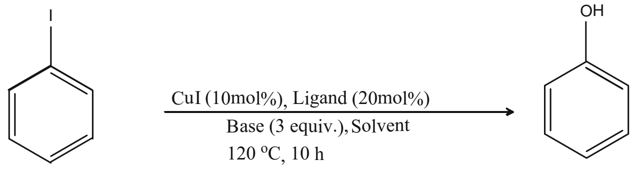


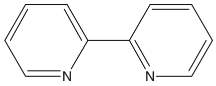
Scheme 1. Copper catalyzed Hydroxylation of Aryl Halides.

2.1 *General procedure for the synthesis of substituted phenols*

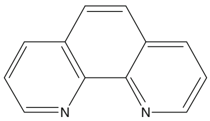
The appropriate aryl halide (1 mmol), CsOH (3 mmol), and H_2O (1 mL) were added over 0.1 h, to a stirred solution of CuI (19.0 mg, 10 mol%) and Dimethylglyoxime (L6; 23.2 mg, 20 mol%) in DMSO (1 mL), and the reaction mixture was stirred at 120 °C (aryl iodides) or (aryl bromides). The progress of the reaction was monitored by TLC (EtOAc–hexane). The reaction mixture was then cooled to room temperature and acidified with 0.5 M HCl (0.5 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and dried (Na_2SO4). Evaporation of the solvent gave a residue that was purified by column chromatography.

3. Results and Discussion

Initially, the reaction conditions were optimized using iodobenzene as a model substrate and using different ligands, bases, copper salts and solvents (Table 1, entries 1–16). Among several ligands briefly screened, L6 (dimethylglyoxime) and L3 (N, N, N, N-Tetramethylethane-1,2-diamine) are effective. The ligand L6 gave 96% (Table 1, entry 6) yield of the corresponding product higher than ligand L3 (85%) (Table 1, entry 3). Hence the ligand L6 was identified as a competent ligand, whereas ligands L1(2,2-Bipyridine), L2(1,10-Phenanthroline), L4[N-(2-cyanophenyl)benzamide] and L5 (2,2′,2″,2‴-(ethane-1,2-diylbis(azanetriyl)tetraacetic acid) afforded lower yield (Table 1, entries 1, 2, 4 & 5) . In the absence of ligand, controlled experiments were carried out in order to check whether reaction proceeds in absence of ligand or not. It was found that only 15% yield of the desired product was obtained without the aid of the ligand (Table 1, entry 16).



L1



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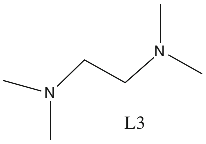

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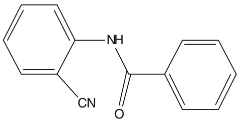

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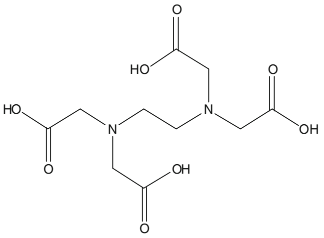
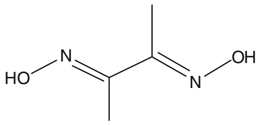


L5



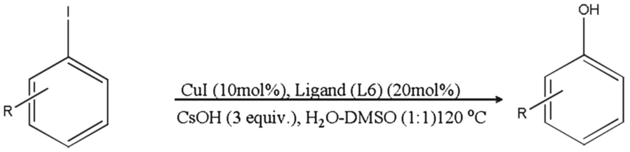
L6

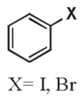
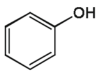
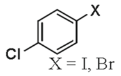
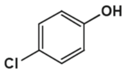
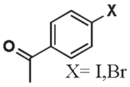
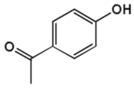
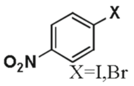
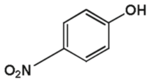
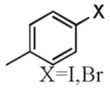
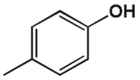
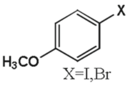
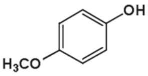
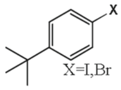
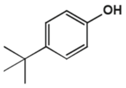
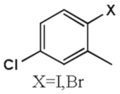
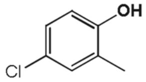
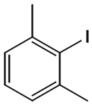
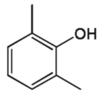
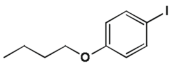
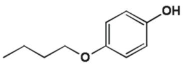
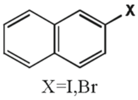
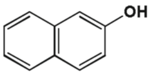
Table 1. Optimization of Hydroxylation of Aryl Halides[a].

Sr. no	Ligand	Solvent [2ml]	Base	[Cu] salts	Yield [b](%)
1	L1	DMSO/H_2O 1:1	CsOH	CuI	72
2	L2	DMSO/H_2O 1:1	CsOH	CuI	76
3	L3	DMSO/H_2O 1:1	CsOH	CuI	85
4	L4	DMSO/H_2O 1:1	CsOH	CuI	66
5	L5	DMSO/H_2O 1:1	CsOH	CuI	35
6	L6	DMSO/H_2O 1:1	CsOH	CuI	96
7	L6	DMSO/H_2O 1:1	KOH	CuI	82
8	L6	NMP	CsOH	CuI	20
9	L6	DMF/H_2O 1:1	CsOH	CuI	No Reaction
10	L6	H_2O	CsOH	CuI	05
11	L6	1,4-dioxane/H_2O	CsOH	CuI	32
12	L6	DMSO	CsOH	CuI	30
13	L6	DMSO/H_2O 1:1	CsOH	CuCl	62
14	L6	DMSO/H_2O 1:1	CsOH	CuSO4	42
15	L6	DMSO/H_2O 1:1	CsOH	$Cu(OAc)_2$	50
16	—	DMSO/H_2O 1:1	CsOH	CuI	15

[a] Iodobenzene (1 mmol), Ligand (20 mol%), CuI (10 mol%).
[b] Isolated yield.

Table 2. Copper(I)-Catalyzed Hydroxylation of Aryl Iodides and Bromides[a].



Entry	Aryl Halide	Product	Time (h)	Yield[b] %
1			10 17	96 85
2			12 16	89 78
3			7 20	94 80
4			7 13	95 86
5			11 16	85 88
6			12 20	96 87
7			10 19	96 91
8			12 18	85 78
9			12	87
10			10	94
11			12 20	90 81

[a] Reaction conditions: Aryl iodide (1 mmol), CuI (10 mol%), DMG(L6; 20 mol%), CsOH (3 equivalent), DMSO/H_2O (1:1; 2 mL), 120 °C. [b] Isolated yield.

Among the bases, potassium hydroxide and cesium hydroxide, the latter provided the best results (Table 1, entries 6 & 7). A 1:1 mixture of DMSO/H_2O was found to be the suitable solvent for this reaction. Solvents such as NMP, water, DMF/H_2O (1:1) and 1,4-dioxane/H_2O (Table 1, entries 8–12) were found to be less effective, providing the desired product in less than 32%. In addition, other copper salts such as CuCl, $CuSO_4$ and $Cu(OAc)_2$ were poorer. The optimum temperature was 120 °C (Scheme 1).

The scope of the CuI/DMG catalyzed synthesis of phenols was then investigated under above optimized conditions. Irrespective of the aryl iodides as electron-rich, electron-poor, or sterically bulky, all of them afforded good to excellent yields (Table 2, entries 1–11) of the corresponding products in presence of CsOH in DMSO/H_2O (1:1). The hydroxylation of iodobenzene went on smoothly in high yields (96%) (Table 2, entry 6). In case of the activated aryl iodides, such as Nitro, carbonyl (Table 2, entries 3 & 4) the reactions proceeded in 7 h providing the products in 94 & 95% yield. In addition to this, high yields observed in the reaction of 4-methoxyphenyl, 4-butoxyphenyl and 4-t-butylphenyl (Table 2, entries 6, 7 and 10). Furthermore, 2-Iodonaphthalene gave 90% yield in 12 h. However, chloro substituted iodobenzene provided 89% yield of the corresponding product (Table 2, entry 2).

The reaction conditions were further investigated for the hydroxylation of the less reactive aryl bromides, most of the aryl bromides were smoothly converted into the corresponding phenols (Table 2, entries 1–8). Bromobenzene underwent hydroxylation to give the phenol with 85% yield, but required 17 h (Table 2, entry 1). However, the CuI/DMG system were able to tolerate some functional groups such as t-butyl, carbonyl, methyl, t-butoxide, nitro, and methoxy groups but showed lower yield of the corresponding products, compared to aryl iodides (Table 2, entries 3–7 and 10). Moreover, 2-bromonaphathalene afforded 80% yield in 20 h (Table 2, entry11). This protocol has advantages such as short reaction time and low reaction temperature over earlier reported methods.

4. Conclusion

This paper reports use of dimethylglyoxime (L6) as a simple, efficient and economical ligand for the direct copper-catalyzed synthesis of phenols. This protocol tolerates various substituted and unsubstituted aryl iodides and aryl bromides. The present protocol could be used for synthesis of various substituted phenols. In general, the lower cost of copper and the use of readily available ligands offer undisputable advantages over the expensive metal/ligand systems. The reported protocol will attract much attention in research because of their wide applications in pharmaceuticals, polymers and natural products.

Supplementary Information (SI)

^{1}HNMR, ^{13}C NMR and GC-MS spectral data for compounds dealt in this article can be accessed at www.ias.ac.in/chemsci.

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