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Copper catalyzed arylation of urea

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Abstract—An efficient copper catalyzed amidation of aryl iodides with urea is described. This method is milder than the palladium catalyzed arylation and avoids the use of toxic phosphine ligands.

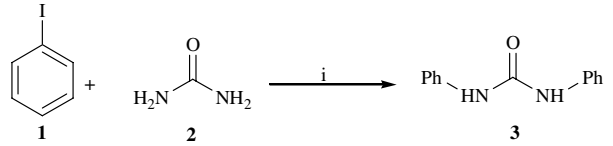
Biphenyl ureas are important subunits present in a number of naturally occurring compounds and have found numerous applications such as drugs, pesticides, and antioxidants.[1] The most straightforward route for the synthesis of biphenyl ureas involves the reaction of aryl amines with isocyanates or phosgene, which are highly toxic and require harsh reaction conditions. Recent developments in the palladium and copper catalyzed amination of aryl halides dramatically simplified classical amination reactions such as the Ullmann and Goldberg reactions, which require very high temperatures and toxic reagents.[2] Among these the palladium catalyzed reactions are very sensitive to functional groups such as –OH, $–NH_2$, exogenous air or moisture and also very expensive compared to the copper reagent.[3] Recently, Belestkaya has reported the palladium catalyzed amidation of urea with different aryl halides and Xantphos was found to be a suitable ligand for these coupling reactions. However, this method suffers from the following disadvantages: (1) the use of toxic phosphine ligands, (2) the palladium catalyst is expensive, and (3) the formation of substantial amounts of *N*-phenylation products arising from aryl group exchange between the aryl group bound to the palladium and the phenyl group of the Xantphos.[4] In a recent paper, the same group has reported that the electron poor ligand 3,5-$(CF_3)_2$-Xantphos is more effective than Xantphos and requires lower catalyst loading and gives higher yields of products than Xantphos. An attempt by the same group for the arylation of urea using a copper catalyst was unsuccessful.[5]

There have been many reports recently on the arylation of different compounds such as amines,[3] amides,[6] hydrazides,[7] etc. using copper catalysts in the presence of suitable ligands. As a part of our program to synthesize different biologically active molecules using copper catalyzed coupling reactions, we carried out the following investigations and preliminary results are given below. We report a simple and mild copper catalyzed amidation of aryl halides with urea. A preliminary screening of ligands showed that both 1,2-diaminocyclohexane and *N*,*N*′-dimethylethylenediamine afforded products in the coupling reactions, with the latter giving low yields. Efforts to use other ligands such as ethylenediamine, 1,2-ethanediol, etc. were not successful. We chose 1,2-diaminocyclohexane as the preferred ligand for the coupling reactions.

The reaction of iodobenzene with urea in presence of the CuI, 1,2-diaminocyclohexane catalyst system afforded the biphenyl urea **3** in good yield (see Scheme 1).

The product was characterized on the basis of its spectral data and by comparison of its melting point with the literature.[8]

Similar reactivity was also observed with other aryl iodides and the results are summarized in Table 1.[9]



1 **2** **3**

Scheme 1. (i) CuI, 1,2-diaminocyclohexane, K_3PO_4, DMF, 80 °C, 24 h.

Keywords: Copper; Urea; Amidation; Aryl iodides.
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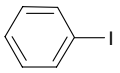
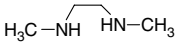
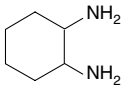
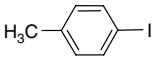
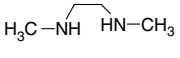
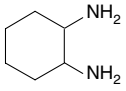
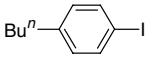
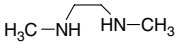
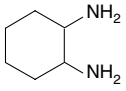
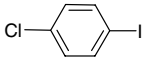
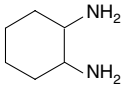
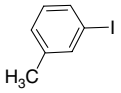
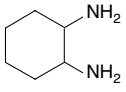
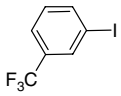
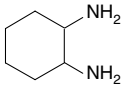
Table 1. CuI catalyzed *N*,*N*′-bisarylation of urea[a]

Entry	Iodobenzene	Ligand	Yield (%)[b]
1			43
			60
2			12
			56
3			28
			65
4			57
5			63
6			29

[a] Reaction conditions: 1 equiv urea, 2.2 equiv aryl iodide, 10 mol% CuI, 10 mol% 1,2-diaminocyclohexane (mixture of *cis* and *trans*), 3 mL DMF, 24 h, 80 °C.
[b] Isolated yield.

In summary, an efficient copper catalyzed amidation of aryl iodides with urea is described. In all the cases, 1,2-diaminocyclohexane as the ligand afforded good yields of coupled products.

Acknowledgements

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9. General procedure for coupling reactions: CuI (10 mol%) and K_3PO_4 (3 mmol) were added to a Schlenk tube with a Teflon cap. The tube was evacuated and back filled with argon three times. Urea (1 mmol), iodobenzene (2.2 mmol), 1,2-diaminocyclohexane (10 mol%), and 3 mL dry DMF were added. The tube was sealed and heated at 80 °C. The reaction mixture was cooled to room temperature after heating for the specified time. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography using EtOAc–hexane (1:2) as eluants to afford coupled products. *N*,*N*′-Biphenyl urea: (Table 1, entry 1): Following the general procedure, urea (60 mg, 1 mmol), iodobenzene (449 mg, 2.2 mmol), CuI (19 mg, 10 mol%), 1,2-diaminocylcohexane (11.4 mg, 10 mol%), K_3PO_4 (636 mg, 3 mmol), and 3 mL of dry DMF at 80 °C for 24 h gave the biphenyl urea **3** (127 mg, 60%) as white solid. Mp 238–240 °C.