



A ligand-free copper(I) oxide catalyzed strategy for the N-arylation of azoles in water

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ARTICLE INFO

Article history:

Received 27 October 2010

Revised 13 December 2010

Accepted 4 January 2011

Available online 12 January 2011

ABSTRACT

A simple and practical protocol has been developed for the cross-coupling of azoles and aryl iodides under ligand-free copper(I) oxide catalyzed conditions in water. The protocol uses tetrabutylammonium bromide (TBAB) as the phase-transfer catalyst, and water as the solvent, and shows good tolerance towards various functional groups.

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Nitrogen-containing heterocycles are found in numerous natural products and biologically active pharmaceutical compounds.¹ N-Arylindoles are an important class of structural elements in a multitude of synthetically and medicinally relevant compounds due to their interesting biological activities. They are important as antipsychotic agents,² antiallergic,³ antiestrogen,⁴ analgesic,⁵ cyclooxygenase (COX)-1 inhibitors,⁶ COX-2 inhibitors,⁷ neuroleptic,^{2a} angiotensin II antagonists,⁸ melatonin receptor MT1 agonists,⁹ 5-HT₆ receptor antagonists,¹⁰ FTase inhibitors (FTIs),¹¹ anti HIV-1 agents¹², and herbicides.¹³

Traditionally, N-arylindoles have been prepared by the Ullmann-type coupling of indoles with aryl halides, which is a straightforward and inexpensive approach. However, this classical copper-catalyzed coupling has drawbacks, for example, high reaction temperature (generally 140 °C or greater) and the requirement of strong bases and stoichiometric amounts of copper reagents, which limits the synthetic utility of this method.¹⁴ Therefore, it is highly desirable to develop mild and efficient methods for the assembly of N-arylated nitrogen-containing heterocycles. Notably, the addition of ligands has increased the economic attractiveness of copper salts in the N-arylation of nitrogen heterocycles with aryl halides. Indeed, several efficient ligands have been disclosed, which increase significantly the rate of the reaction, and lower the reaction temperature.¹⁵ On the other hand, the addition of ligands to the reaction protocols entails additional costs.

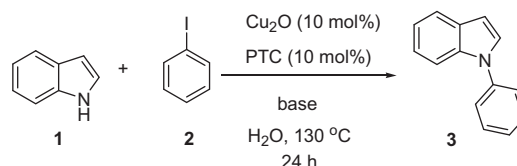
Although much progress has been achieved on the aforementioned transformation, it is still advantageous to develop economical and sustainable protocols that operate under ligand-free and environmentally friendly conditions.¹⁶ Water is the most economical and environmentally friendly solvent and has stimulated research in the development of new strategies for N-arylations in water.¹⁷ However, the synthesis of organic molecules in water involves the additional challenges of water tolerance for the catalyst/

ligand system and the associated problems of substrate solubility and reactivity.¹⁸ Yadav demonstrated a ligand-free copper-catalyzed N-arylation procedure in aqueous media which required the use of microwave irradiation.¹⁹ The use of microwaves limits the practicality of the protocol especially on an industrial scale. Che reported the ligand-free copper-catalyzed N-arylation of aliphatic amines and pyrrole in aqueous media using the phase-transfer catalyst (PTC) ⁿBu₄N⁺OH[−] (40% aqueous), but the scope of the azole substrates was limited.²⁰

In continuation of our endeavors to develop ligand-free copper cross-couplings in aqueous media, herein we report a simple, practical and efficient ligand-free Cu₂O-catalyzed N-arylation of a series of nitrogen-containing heterocycles using tetrabutylammonium

Table 1

Optimization studies on the ligand-free copper-catalyzed cross-coupling of indole and iodobenzene^a



Entry	Base	PTC	Yield (%) ^b
1	K ₃ PO ₄	TBAC	78
2	Cs ₂ CO ₃	TBAC	76
3	KOH	TBAC	70
4	K ₃ PO ₄	TBAC	78 ^c
5	K ₃ PO ₄	TPAB	71 ^c
6	K ₃ PO ₄	TBAB	79 ^c
7 ^d	K ₃ PO ₄	TBAB	Trace

^a The reaction was carried out with indole (1.47 mmol), iodobenzene (2.21 mmol), base (2.94 mmol), Cu₂O (10 mol %), H₂O (0.75 ml) at 130 °C for 24 h.

^b Isolated yield after column chromatography.

^c The reaction was performed with indole (1.47 mmol), aryl halide (1.76 mmol).

^d Control experiment in the absence of Cu₂O.

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Table 2N-Arylation of indole with various aryl halides catalyzed by ligand-free Cu₂O in water^a


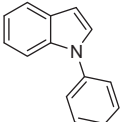

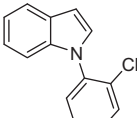

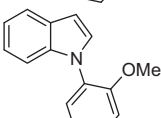
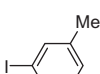
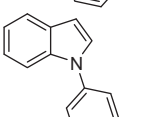

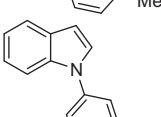
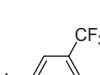
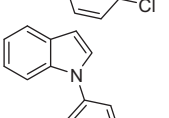
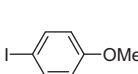
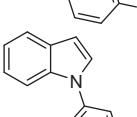
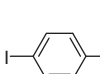
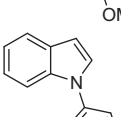

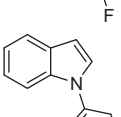
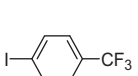
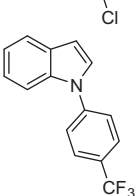
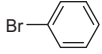
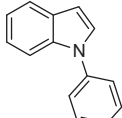
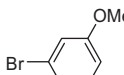
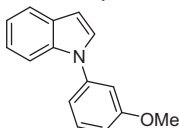
$ \begin{array}{c} \text{Cu}_2\text{O (10 mol\%)} \\ \text{TBAB (10 mol\%)} \\ \text{K}_3\text{PO}_4 \text{ (2 equiv)} \\ \text{H}_2\text{O, 130 }^\circ\text{C} \\ \text{24 h} \end{array} $			
Entry	ArX	Product	Yield (%) ^b
1			3a 79
2			3b 87
3			3c 64
4			3d 72
5			3e 70
6			3f 90
7			3g 77
8			3h 75
9			3i 83
10			3j 80

Table 2 (continued)

Entry	ArX	Product	Yield (%) ^b
11			3a 40
12			3k 33

^a The reaction was carried out with indole (1.47 mmol), aryl halide (1.76 mmol), K₃PO₄ (2.94 mmol), Cu₂O (10 mol %), TBAB (10 mol %), H₂O (0.75 ml) at 130 °C for 24 h.

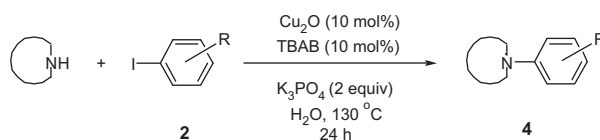
^b Isolated yield after column chromatography.

bromide (TBAB) as the phase-transfer catalyst and water as the solvent. This method is attractive for several reasons: (i) it employs an economical and sustainable Cu₂O catalytic system, without the need for additional ligands; (ii) it uses TBAB as the PTC, which is inexpensive and commercially available; (iii) it offers experimental simplicity, which excludes the need for an inert atmosphere and anhydrous solvent; (iv) it uses water as the reaction medium, which is abundant, cheap and, environmentally benign.

A systematic study was first undertaken using indole (**1**) and iodobenzene (**2**) as model substrates for the N-arylation reaction. Under ligand-free conditions, the reaction of indole (1 equiv) with iodobenzene (1.5 equiv), 10 mol % Cu₂O as catalyst, tetrabutylammonium chloride (TBAC) (10 mol %) and K₃PO₄ (2 equiv) in water gave a good 78% yield of the N-arylated product **3** (Table 1, entry 1). Encouraged by this result, optimization studies were initiated to evaluate the efficiency of various bases and PTCs for the arylation reaction. K₃PO₄ was found to be the most effective base. It is worth noting that decreasing the amount of iodobenzene to 1.2 equivalents relative to indole did not have any adverse effect on the yield of the product (entry 4). Next, a series of commonly used PTCs was tested with tetrabutylammonium bromide (TBAB) giving a comparable yield to TBAC (entry 6). TBAB was chosen as the PTC due to its ease of handling. To rule out the possibility that the catalysis was assisted by other contaminants that might be present in the system, control experiments revealed that a trace amount of the product was obtained in the absence of the copper source (entry 7). The optimized conditions for our ligand-free copper-catalyzed cross-coupling were as follows: Cu₂O (10 mol %), aryl iodide (1.2 equiv), TBAB (10 mol %) and K₃PO₄ (2 equiv) in water at 130 °C for 24 h.

To probe the effectiveness of this Cu-catalyzed protocol, a variety of *ortho*, *meta*, and *para*-substituted aryl halides were coupled with indole under the optimized conditions. As shown in Table 2, the desired aryl iodide amination products were observed in good to excellent yields (Table 2, entries 1–10). *Ortho*-substituted aryl iodides did not hamper significantly the cross-coupling reaction affording the products in good yields (Table 2, entries 2 and 3). In addition, good to excellent yields were obtained regardless of the electronic nature of the substituent on the aryl iodide, and no significant electronic effects were observed for both *meta*- and *para*-substituted aryl iodides (entries 4–10). Aryl iodides showed higher reactivity than aryl bromides (entries 11 and 12).

These promising results encouraged us to investigate the scope of the ligand-free copper(I) oxide catalyzed arylation with other nitrogen heterocycles. As shown in Table 3, indazole and imidazole were effective nucleophilic partners for the ligand-free catalytic conditions, which afforded the corresponding products **4** in good to excellent yields (Table 3, entries 1–5). Moderate yields were ob-

Table 3N-Arylation of indazole, imidazole, 7-azaindole, and pyrrole with aryl iodides catalyzed by ligand-free Cu₂O in water^a

Entry	Amine		Product	Yield (%) ^b
1				78
2				88
3				83
4				63
5				67
6				53
7				58
8				50
9				48
10				52
11				44

^a The reaction was carried out with amine (1.47 mmol), aryl iodide (1.76 mmol), K₃PO₄ (2.94 mmol), Cu₂O (10 mol %), TBAB (10 mol %), H₂O (0.75 ml) at 130 °C for 24 h.^b Isolated yield after column chromatography.

served in the coupling of 7-azaindole and pyrrole with various aryl iodides (entries 6–11).

In conclusion, we have developed a practical and simple protocol for the cross-coupling of various N-heterocycles with substituted aryl iodides using ligand-free copper(I) oxide in water. The reactions were efficient in affording the arylated

N-heterocyclic products in moderate to excellent yields. The economy, versatility, and environmental friendliness of this procedure should make it easily transferrable to industrial applications. Further study of this ligand-free Cu catalytic system in water on other cross-coupling reactions is ongoing.

Acknowledgments

The authors would like to thank the National Institute of Education and Nanyang Technological University for generous financial support.

Supplementary data

Supplementary data (experimental procedures and compound characterization) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.01.005.

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