Efficient Copper-Catalyzed N-Arylation of Amides and Imidazoles with Aryl Iodides

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Received 22 October 2009

Abstract: The C–N cross-coupling of amides and imidazoles with aryl iodides is described using CuI in tetrabutylammonium bromide (TBAB) under ligand-free conditions. The reaction is simple, general, and efficient affording the C–N cross-coupled products in shorter time and in high yield.

Key words: N-arylation, amides, imidazoles, copper iodide, TBAB

N-Arylamides and *N*-arylimidazoles are prevalent in numerous compounds that are of biological, material, and pharmaceutical interest (Figure 1).[1] The common classical methods used for their preparation, however, require high temperature (>150 °C) and stoichiometric amount of copper that, on scale-up, leads to the problem of waste disposal.[2] To overcome these limitations, palladium,[3] copper,[4] and iron[5] based catalytic systems have been recently studied for the cross-coupling of aryl halides with amides and imidazoles. These studies usually involve homogeneous processes and the ligands bound with the metals play a crucial role in the catalysis.

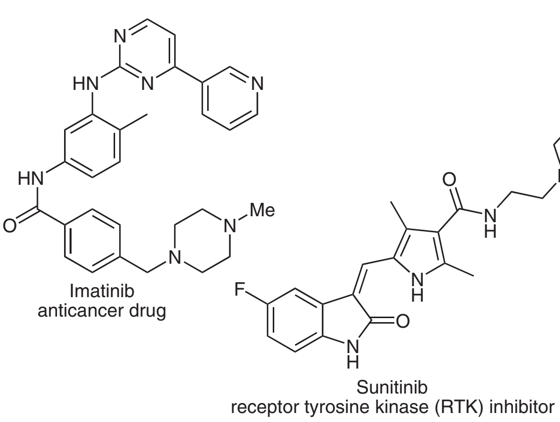


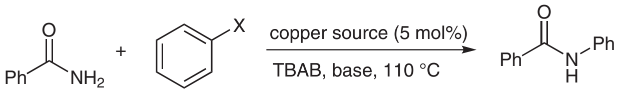
Figure 1 Examples of biologically active molecules

The use of molten salt for organic reactions has been active in recent years due to their excellent thermal stability and low vapor pressure.[6] In addition, the reactions in molten salts provide the advantages of high reactivity and simplified product isolation. More recently, tetrabutylammonium bromide (TBAB) has been found to be an effective reaction medium[7] as well as an additive[8] for the C–C and C–S cross-coupling reactions in the presence of transition metal salts. Since TBAB is cheap and readily available, we became further interested to investigate its application in organic synthesis. Herein, we report the C–N cross-coupling of amides and imidazoles with aryl halides using CuI in TBAB under air. The procedure is general, simple, and efficient to avail the cross-coupled products under ligand-free conditions. Substrates having either an electron-withdrawing or an electron-donating group are compatible with this protocol to afford the C–N cross-coupled products in shorter time in high yield.

SYNTHESIS 2010, No. 6, pp 0908–0910
Advanced online publication: 08.01.2010
DOI: 10.1055/s-0029-1218643; Art ID: P14609SS

First, the reaction condition was optimized studying the coupling of benzamide with aryl iodide as the model substrate. The reaction occurred to afford the C–N cross-coupled *N*-phenylbenzamide in 75% yield when the substrates were stirred at 110 °C for five hours using 5 mol% CuI and two equivalents of KOH in TBAB under air (Table 1). Bases such as Cs_2CO_3 and K_2CO_3 were inferior to KOH providing the cross-coupled product in 18% and 12% yield, respectively. The reaction using CuI was more effective in comparison with $CuCl_2·2H_2O$, $CuSO_4·5H_2O$, $Cu(OAc)_2·H_2O$ and CuO nanoparticle. Of the aryl halides,

Table 1 Optimization of the Reaction Conditions[a,b]



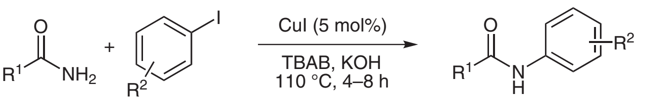
Entry	Catalyst	X	Base	Time (h)	Yield (%)
1	CuI	I	KOH	5	75
2	CuI	I	Cs_2CO_3	7	18
3	CuI	I	K_2CO_3	9	12
4	CuI	Br	KOH	25	50
5	CuI	Cl	KOH	12	n.r.[c]
6	$CuCl_2·2H_2O$	I	KOH	6	57
7	$CuSO_4·5H_2O$	I	KOH	6	61
8	$Cu(OAc)_2·H_2O$	I	KOH	6	52
9	CuO nano	I	KOH	6	48

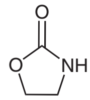
[a] Reaction conditions: catalyst (5 mol%), benzamide (1.1 mmol), aryl halide (1 mmol), and base (2 mmol) were stirred at 110 °C in TBAB (2 mmol).
[b] Isolated yield.
[c] n.r. = no reaction.

aryl iodide exhibited greater reactivity. The reaction with aryl bromide required longer time to give the cross-coupled product in 50% yield. In contrast, chlorobenzene showed no reaction. Similarly, the control experiment without either CuI or KOH exhibited no reaction.

Next, the scope of the procedure with respect to other substrates was studied (Table 2). Benzamide could be cross-coupled with aryl iodide having 2-OMe, 4-Br, 4-OMe, 4-Me, and 2,4-$(Me)_2$ substituents in 72–91% yields. Similarly, the reactions of benzamide having 3-Br, 3-NO_2, 4-OMe, 4-Me, and 4-NO_2 substituents were investigated with aryl iodide. As above, the reactions occurred efficiently to give the corresponding cross-coupled products in 58–79% yields. Aliphatic amides, acetamide, hexanamide, and 2-oxazolidinone could be cross-coupled with aryl iodide in 75–87% yields. A similar result was obtained with (*E*)-cinnamamide and aryl iodide.

Table 2 Reaction of Amides with Aryl Iodides[a,b]



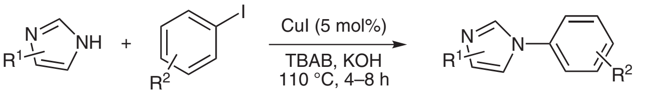
Entry	Amide	Iodobenzene (R^2)	Time (h)	Yield (%)
1	$PhCONH_2$	H	5	75
2	$PhCONH_2$	2-MeO	8	72
3	$PhCONH_2$	4-Br	5	76
4	$PhCONH_2$	4-MeO	6	82
5	$PhCONH_2$	4-Me	5	75
6	$PhCONH_2$	2,4-$(Me)_2$	6	91
7	3-$BrC_6H_4CONH_2$	H	6	69
8	3-$O_2NC_6H_4CONH_2$	H	7	63
9	4-$MeC_6H_4CONH_2$	H	5	76
10	4-$MeOC_6H_4CONH_2$	H	4	79
11	4-$O_2NC_6H_4CONH_2$	H	6	58
12	$MeCONH_2$	H	4	87
13	*n*-$C_5H_{11}CONH_2$	H	4	75
14	(*E*)-PhCH=CHCONH$_2$	H	5	52
15	 O NH	H	4	85

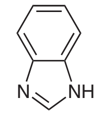
[a] Reaction conditions: CuI (5 mol%), amide (1.1 mmol), aryl iodide (1 mmol), and KOH (2 mmol) were stirred at 110 °C in TBAB (2 mmol).

[b] Isolated yield.

These reaction conditions are also suitable for cross-coupling of imidazoles with aryl iodides (Table 3). Imidazole could be cross-coupled with aryl iodide having 2-OMe, 4-OMe, 4-Me, and 2,4-$(Me)_2$ substituents in 55–95% yields. Similarly, 2-methylimidazole and benzimidazole underwent reactions with aryl iodide in 78% and 72% yield, respectively. The reactions required shorter time (4–8 h) and the cross-coupled products were obtained in high yield. Substituted aryl iodides as well as substituted amides and imidazoles were compatible with the procedure. These results clearly suggest that the reaction is general and can be used for the cross-coupling of amides and imidazoles with aryl iodides.

Table 3 Reaction of Imidazoles with Aryl Iodides[a,b]



Entry	Imidazole (R^1)	Iodobenzene (R^2)	Time (h)	Yield (%)
1	H	H	6	85
2	H	2-MeO	8	55
3	H	4-MeO	6	93
4	H	4-Me	8	70
5	H	4-O_2N	4	95
6	H	2,4-$(Me)_2$	7	65
7	2-Me	H	7	78
8	 N NH	H	6	72

[a] Reaction conditions: CuI (5 mol%), imidazole (1.1 mmol), aryl halide (1 mmol), and KOH (2 mmol) were stirred at 110 °C in TBAB (2 mmol).

[b] Isolated yield.

In summary, we have developed a simple and facile method for the C–N cross-coupling of amides and imidazoles with aryl iodides using CuI in TBAB under ligand-free conditions. The reactions are efficient affording the cross-coupled products in shorter time with high yield.

C–N Cross-Coupling Reactions; General Procedure

An oven-dried round-bottomed flask was charged with the amide or imidazole (1.1 mmol), CuI (5 mol%), KOH (2.0 mmol), aryl halide (1.0 mmol), and TBAB (2.0 mmol) and the contents were stirred at 110 °C for the appropriate time (Tables 2, 3). The reaction progress was monitored by TLC using EtOAc and hexane (30:70 for amides; 80:20 for imidazoles) as eluent. The reaction mixture was then cooled to r.t. and diluted with EtOAc (10 mL). The resulting solution was washed with brine (2 mL) and H_2O (2 × 2 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue, which was purified by column chromatography on silica gel (230–400 mesh) using EtOAc and hexane (30:70 for amides; 80:20 for imidazoles) as eluent to yield the C–N cross-coupled products (Tables 2, 3). Their identity and purity were confirmed by ^1H and ^{13}C NMR spectroscopic analyses.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

This work was supported by Department of Science and Technology, New Delhi and Council of Scientific and Industrial Research, New Delhi.

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