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Practical copper-catalyzed *N*-arylation of amines with 20% aqueous solution of *n*-Bu_4NOH

Hamidreza Molaei, Mohammad Mehdi Ghanbari *

Department of Chemistry, Sarvestan Branch, Islamic Azad University, Sarvestan, Iran

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Abstract

N-Arylation of a wide variety of amines with phenylboronic acid catalyzed by copper acetate under 20% aqueous solution of *n*-Bu_4NOH was accomplished in good to excellent yields (up to 92%) and substrate conversions (up to 96%).

Keywords: Copper-catalyzed; *N*-Arylation; Phenylboronic acid; Amines

Transition-metal-catalyzed C–N bond formation is considered to be an important approach which has wide applications in the synthesis of many compounds such as drugs and natural products [1]. Among metals that are able to perform such transformations, copper stands out as a convenient alternative for palladium catalysts, because copper salts are often cheap and environmental friendly [2]. In the recent years, several reviews have been published showing some recent progresses of copper-catalyzed coupling reactions [3,4], but different ligands should be applied in most of these successful examples. And some ligand-free copper-catalyzed *N*-arylation reactions have been reported [5,6]. Reactions in aqueous media are of great interest for industrial processes for economic and safety reasons. These procedures have already been applied successfully which replace partially or fully organic solvents by water [7]. Among the different cross-coupling procedures known today, protocols involving boronic acids as coupling partners are becoming increasingly popular [8]. Because of this fact that most of the boronic acids are air and moisture-stable, using these reagents is highly attractive [9]. There has been reported *N*-arylation in aqueous media in the absence of ligands in which copper acetate and in organic solvent in the present of ligands is used as a catalyst in the microwave conditions [10]. Another paper has reported previously a method for the construction of C–N bond with *n*-Bu_4NOH as a base in organic solvent [11]. As part of our current studies on the development of new compounds synthesis [12], we wish to report *N*-arylation reaction of the primary and secondary amines with phenyl boronic acid catalyzed by copper acetate in 20% aqueous solution of *n*-Bu_4NOH at room temperature. Schemes 1 and 2 illustrate the synthesis of these amines.

In order to optimize the reaction conditions, we chose the reaction of indole with phenyl boronic acid as a model reaction. As shown in Table 1, different copper sources and bases have been applied for the reaction. No reaction was

* Corresponding author.
E-mail address: m.mehdi.ghanbari@gmail.com (M.M. Ghanbari).

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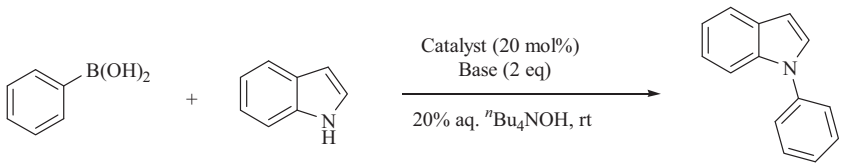
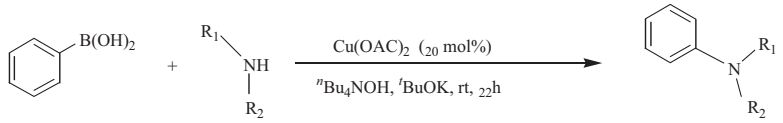


Scheme 1.



Scheme 2.

Table 1
Evaluation of bases and catalysts.

Entry	Catalyst	base	Isolated yield (%)
1	$Cu(OAC)_2$[a]	*t*-BuOK	62
2	$Cu(OAC)_2$[b]	*t*-BuOK	76
3	$Cu(OAC)_2$	*t*-BuOK	92
4	$Cu(OAC)_2H_2O$	*t*-BuOK	88
5	$CuSO_4$	*t*-BuOK	82
6	$CuCl_2$	*t*-BuOK	78
7	CuI	*t*-BuOK	55
9	$Cu(OAC)_2$	–	47
10	$Cu(OAC)_2$	NaOH	61
11	$Cu(OAC)_2$	K_2CO_3	64
12	$Cu(OAC)_2$	Et_3N	51
13	$Cu(OAC)_2$	Cs_2CO_3	72
14	–	*t*-BuOK	–

[a] 10 mol% of the copper acetate was used.
[b] 15 mol% of the copper acetate was used.

observed without any copper source (Table 1, entry 14). The yields of the product improved when the amount of the copper increased. The amounts of the byproduct increased when we rose the reaction temperature. We applied these optimized conditions for the rest of the substrates.

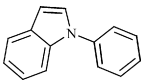
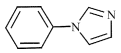
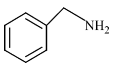
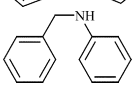
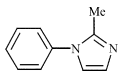
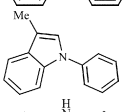
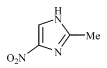
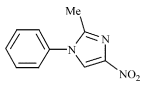
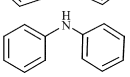
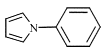
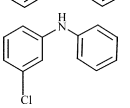
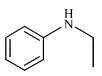
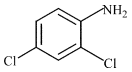
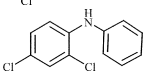
Thus, the reaction of amine and phenylboronic acid in the presence of $Cu(OAC)_2$, *n*-Bu_4NOH and *t*-BuOK leads to products in good yields (Scheme 2 and Table 2). The ^1H and ^{13}C NMR spectra of the aliphatic and aromatic amines clearly indicated the formation of them. The structures of these compounds were deduced from their elemental analyses and their IR, ^1H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate *m*/*z* values. Any product other than these products could not be detected by NMR spectroscopy.

Although we have not yet established the mechanism of this reaction in an experimental manner, a possible explanation is proposed in Scheme 3.

In summary, we have developed a practical and simple approach for the *N*-arylations of amines with phenylboronic acid. The 20% aqueous solution of *n*-Bu_4NOH was used as a base solvent which plays the role of a phase transfer catalyst (PTC). We believe that the versatility, convenient operation, and environmental friendliness of this procedure without organic ligand such as diazabutadienes (DABs) make it easily transferable to industrial applications.

Typical experimental procedure: To stirred solution of the round bottomed flask containing the amine (1 mmol), $Cu(OAC)_2$ (20 mol%), *n*-Bu_4NOH (2 mmol) and *t*-BuOK (2 mmol) was added phenylboronic acid (1.5 mmol). The reaction mixture was stand for 22 h the product was filtered and the residue was purified by silica column chromatography (Merck 230–400 mesh) using *n*-hexane–AcOEt to afford the *N*-arylated product.

Table 2
Copper catalyzed synthesis of arylamines.

Entry	Amine	Product[a]	Yield (%)[b]	Entry	Amine	Product[a]	Yield (%)[b]
1			92	7			78
2			85	8			61
3			81	9			67
4			82	10			60
5			72	11			75
6			65				

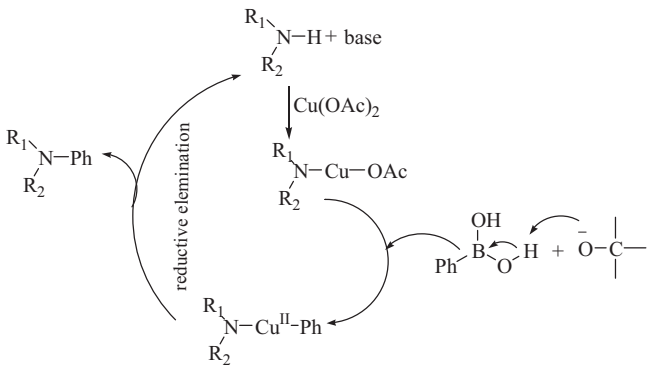
[a] All the products were characterized on the basis of their IR, ^{1}H NMR and ^{13}C NMR spectral analysis and compared with the literature data [1–7].
[b] Isolated yields.

2,4-Dichloro-N-phenylaniline (**6**): IR (KBr) (ν_{max}/cm^{-1}): 3405 (NH), 1494 (C=C); Anal. Calcd. (%) for $C_{12}H_9Cl_2N$ (238.11): C, 60.53; H, 3.81; N, 5.88. Found: C 60.28; H, 3.78; N, 5.91; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.66 (1H, s, NH), 6.92–7.97 (8H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.5 (2 CH), 122.4 (CH), 123.1 (CH), 127.2 (CH), 127.3 (CH), 127.5 (C), 128.8 (C), 129.3 (C), 129.6 (2 CH), 141.0 (C).

1-Phenyl-1H-imidazole (**7**): IR (KBr) (ν_{max}/cm^{-1}): 3408 (NH), 1496 (C=C); Anal. Calcd. (%) for $C_9H_8N_2$ (144.17): C, 74.98; H, 5.59; N, 19.43. Found: C 75.08; H, 5.48; N, 19.51; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71–7.92 (8H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 118.3 (CH), 121.5 (2 CH), 127.5 (CH), 129.9 (2 CH), 130.3 (CH), 135.6 (CH), 136.7 (C).

2-Methyl-1-phenyl-1H-imidazole (**8**): IR (KBr) (ν_{max}/cm^{-1}): 3400 (NH), 1498 (C=C); Anal. Calcd. (%) for $C_{11}H_{13}N_2$ (173.23): C, 76.27; H, 7.56; N, 16.17. Found: C 75.98; H, 7.62; N, 15.98; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17 (s, 3H, CH_3), 7.01–7.48 (m, 7H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.4 (CH_3), 106.5 (CH), 125.5 (2 CH), 126.4 (CH), 128.6 (CH), 129.4 (2 CH), 137.9 (C), 145.2 (C).

1-Phenyl-1H-pyrrole (**10**): IR (KBr) (ν_{max}/cm^{-1}): 3410 (NH), 1500 (C=C); Anal. Calcd. (%) for $C_{10}H_9N$ (143.19): C, 83.88; H, 6.34; N, 9.78. Found: C 84.02; H, 6.28; N, 9.85; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70–8.22 (9H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 110.4 (2 CH), 115.6 (2 CH), 119.3 (2 CH), 125.6 (CH), 129.5 (2 CH), 140.6 (C).



Scheme 3.

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