Copper-Catalyzed N-Arylation of Amines/Amides in Poly(ethylene glycol) as Recyclable Solvent Medium

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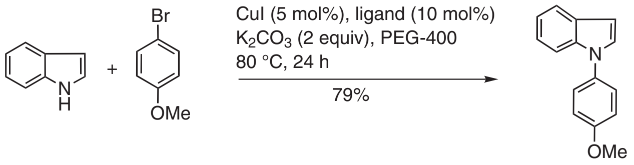
Abstract: The Buchwald N-arylation of amines and amides is achieved efficiently in PEG (400 Daltons) as solvent medium. The solvent and catalyst recyclability is studied. Interestingly amides underwent N-arylation with better yields.

Key words: N-arylation, copper iodide, poly(ethylene glycol), reusability

The synthesis of nitrogen-containing heterocycles continues to attract medicinal and synthetic chemists due to the excellent biological activity[1] profiles they exhibit against various targets. Also several natural products,[2] especially alkaloids, incorporate nitrogen heterocycles.[3] These natural products have become drugs and drug candidates after derivatization. Owing to this important feature, various research groups have developed general methods for N-arylation of amines/amides.[4,5] Most of these reports suffer from limitations such as high reaction temperature and poor substrate versatility. Recently, Buchwald and coworkers reported a versatile method wherein copper-diamine complex has been used as a catalyst for N-arylation of pyrroles, pyrazoles, imidazoles, indazoles and triazoles.[6] Encouraged by these findings, we have initiated a program to explore the possibility of developing a recyclable system for both the copper catalyst and the solvent medium used for the reaction.

In our earlier efforts, we demonstrated efficiently the functional-group transformations in PEG as a solvent, *viz.* Heck reaction,[7] asymmetric dihydroxylation,[8] aldol[9] and hydrogenation reactions,[10] wherein both the catalyst and solvent (PEG) were efficiently recycled for several runs. This communication describes the first PEG (400 Daltons) as solvent medium for Buchwald N-arylation of amines/amides wherein both PEG and CuI are recycled with equal ease (Scheme 1).



Scheme 1

In the first instance, indole was N-arylated with 1-bromonaphthalene by stirring the two substrates in the presence of CuI, ethylenediamine ligand and potassium carbonate in PEG (400 Daltons) at 80 °C. The reaction was complete in 24 hours with isolation of the product **1b** in over 92% yield (Table 1, entry 1). In the next case electron-rich 4-bromoanisole was taken as arylating species to observe the formation of 1-(4-methoxyphenyl)indole (**2b**) in 79% yield (entry 2). In order to study the recycling of the catalytic system and the solvent, this reaction (entry 2) was repeated six times using the same solvent medium containing catalyst (after extracting the product with cold diethyl ether) (Table 2). It was observed that the solvent recovery was efficient, but due to loss of catalyst in smaller quantities during every extraction, the yields of the product declined gradually. To overcome this limitation, after the third run, 2 mol% of catalyst is additionally added (Table 2).

For checking the generality of the protocol, other aryl halides, such as iodobenzene (Table 1, entry 3), *o*-iodoaniline (entry 4), *o*-bromoaniline (entry 5), and 3,4-methylenedioxybromobenzene (entry 6), were subjected to the reaction conditions. The yields of the products **3b**, **4b** and **6b** obtained were in the range of 60–86%. To check the compatibility of the amine partner, piperidine was subjected to Buchwald arylation with 4-bromoanisole (entry 7) and 1-bromonaphthalene (entry 8) to isolate the products **7b** and **8b** in 69 and 60% yields respectively. In a different series, benzamide was subjected to N-arylation with iodobenzene (entry 10), 4-bromoanisole (entry 11) and 1-bromonaphthalene (entry 12). In all the three cases studied, the product was isolated in good yields (Table 1).

In summary, this paper describes an alternative and practically viable methodology for N-arylation of aromatic and aliphatic amines/amides with equal ease. Extension of this methodology to more functional amines including supported ones is currently under progress.

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Table 1 Copper-Catalyzed N-Arylation of Amines/Amides in PEG

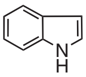
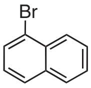
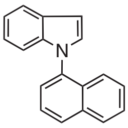
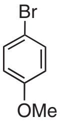
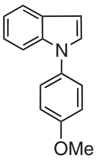
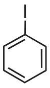
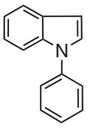
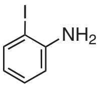
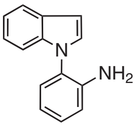
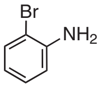
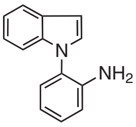
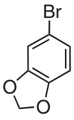
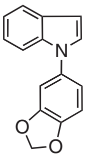
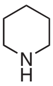
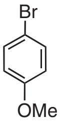
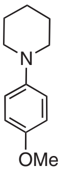
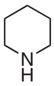
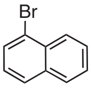
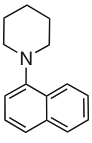
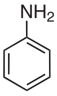
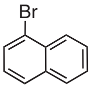
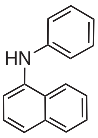
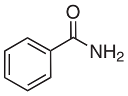
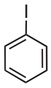
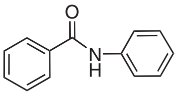
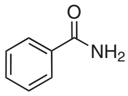
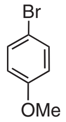
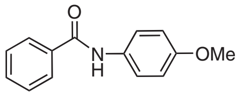
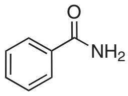
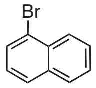
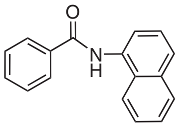
Entry	Amines/Amides	R–X	Product[a]	Time (h)	Yield (%)[b]
1	 **1a**		 **1b**	24	92
2	**1a**		 **2b**	24	79
3	**1a**		 **3b**	12	86
4	**1a**		 **4b**	18	84
5	**1a**		 **4b**	24	79
6	**1a**		 **6b**	24	60
7			 **7b**	24	69
8			 **8b**	24	60
9			 **9b**	24	58

Table 1 Copper-Catalyzed N-Arylation of Amines/Amides in PEG (continued)

Entry	Amines/Amides	R–X	Product[a]	Time (h)	Yield (%)[b]
10			 **10b**	8	75
11			 **11b**	8	70
12			 **12b**	8	73

[a] All products were characterized by ^{1}H NMR and mass spectral data.

[b] Isolated yields after column chromatography.

Table 2 Recycling Studies of Copper-Catalyzed N-Arylation of Indole with 4-Bromoanisole

Run	1	2	3	4	5	6
Isolated Yield	79	75	71	68	63	60
Isolated Yield[a]	–	–	–	76	75	75

[a] After addition of 2 mol% extra catalyst.

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. IR spectra were recorded on Perkin-Elmer 683 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a Varian Gemini 200, Bruker 300 or Varian Unity 400 NMR spectrometers. Chemical shifts were reported in ppm with respect to internal TMS. Coupling constants (*J*) are quoted in Hz. Mass spectra were obtained on a Finnegan MAT 1020B or a Micromass VG 70-70H spectrometer operating at 70 eV using direct inlet system.

Copper-Catalyzed N-Arylation of Amines/Amides in PEG-400; 1-(4-Methoxyphenyl)indole (2b); Typical Procedure

A mixture of indole (0.117 g, 1.0 mmol), 4-bromoanisole (0.224 g, 1.2 mmol), PEG-400 (1.0 g), CuI (0.0095 g, 5 mol%), ethylenediamine (66 μL, 10 mol%) and K_2CO_3 (0.196 g, 2 mmol) was placed in a 10 mL round bottomed flask and heated at 80 °C for 24 h. After completion of the reaction (monitored by TLC), the mixture was cooled and extracted with cold Et_2O (3 × 10 mL) and purified by column chromatography; yield: 79% (Table 1, entry 2).

Colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (m, 2 H), 7.5 (m, 2 H), 7.1–7.4 (m, 4 H), 6.70 (d, *J* = 5.2 Hz, 2 H), 3.9 (s, 3 H).

EI-MS: *m*/*z* = 223 (M^+), 208 (M^+ – 15), 181, 153.

Analytical and spectral data for some selected compounds are given below (Table 1).

1-Naphthylindole (1b)

Colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 7.5 Hz, 2 H), 7.83–7.75 (m, 1 H), 7.67 (d, *J* = 7.5 Hz, 1 H), 7.59–7.36 (m, 4 H), 7.30 (d, *J* = 3.0 Hz, 1 H), 7.15–6.95 (m, 3 H), 6.71 (d, *J* = 3.0 Hz, 1 H).

EI-MS: *m*/*z* = 243 (M^+), 242 (M^+ – 1), 215, 154, 127.

1-Phenylindole (3b)

Yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61 (d, *J* = 7.5 Hz, 1 H), 7.54–7.43 (m, 6 H), 7.34–7.26 (m, 2 H), 7.13 (t, *J* = 8.3 Hz, 1 H), 6.62 (d, *J* = 2.26 Hz, 1 H).

EI-MS: *m*/*z* = 193 (M^+), 116, 77.

1-(2-Aminophenyl)indole (4b)

Light yellow oil.

IR (neat): 3380, 1600, 1582, 1464, 1332, 1212, 780, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (m, 1 H), 7.18 (m, 6 H), 6.82 (m, 2 H), 6.67 (d, *J* = 6 Hz, 1 H), 3.52 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 136.3, 129.1, 128.6, 128.5, 124.8, 122.2, 120.9, 120.1, 118.5, 116.2, 110.7, 103.2, 102.0.

EI-MS: *m*/*z* = 208 (M^+), 207 (M^+ – 1), 181, 142, 104, 89.

1-(4-Methoxyphenyl)piperidine (7b)

Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (d, *J* = 8.9 Hz, 2 H), 6.75 (d, *J* = 8.9 Hz, 2 H), 3.75 (s, 3 H), 3.01 (t, *J* = 5.2 Hz, 4 H), 1.69–1.80 (m, 4 H), 1.51–1.59 (m, 2 H).

EI-MS: *m*/*z* = 191 (M^+), 190 (M^+ – 1), 176, 41.

N-Phenylbenzamide (10b)
Viscous liquid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, J = 7.5 Hz, 2 H), 7.76 (br s, 1 H), 7.61 (d, J = 7.5 Hz, 2 H), 7.56–7.42 (m, 3 H), 7.34 (t, J = 7.55 Hz, 2 H), 7.11 (t, J = 7.5 Hz, 1 H).

EI-MS: m/z = 197 (M^+), 141, 105, 77.

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