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An efficient method for the *N*-arylation of phenylurea *via* copper catalyzed amidation

Sandip N. Gavade [a], Ravi S. Balaskar [a], Madhav S. Mane [a], Pramod N. Pabrekar [c], Murlidhar S. Shingare [b], Dhananjay V. Mane [a,*]

[a] *Organic Research Laboratory, S.C.S. College, Omerga-413 606, MS, India*
[b] *Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431 004, MS, India*
[c] *V.G. Vaze College, Mulund (E), Mumbai-400081, MS, India*

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Abstract

The coupling reaction of phenylurea with different functionalized aryl halides in the presence of air stable CuI, *N*,*N*-dimethylethylenediamine as a ligand, and K_3PO_4 as a base gives symmetrical and unsymmetrical diarylureas in relatively high yields. This method is milder than the palladium catalyzed arylation and avoids the use of toxic phosphine ligands.

Keywords: Copper catalyst; Urea; Aryl halides; Amidation

The transition metal-catalyzed formation of carbon-nitrogen bonds *via* cross-coupling reactions plays an important role in the preparation of numerous important products in biological, pharmaceutical and material sciences [1]. *N*-Aryl- and *N*-heteroaryl-substituted ureas are important subunits present in a number of naturally occurring compounds and have found numerous applications such as drugs, pesticides [2], antioxidants [2] and anion binding receptors [3]. The most straightforward route for the synthesis of diarylureas include the reaction of aromatic amines with isocyanates, phosgene or carbon monoxide, although widely used, this methodology has numerous deficiencies: most notably, in low reaction yields resulting from instability of the isocyanates, disproportionation leading to symmetrical ureas, and highly toxic reagents [2]. The development of palladium-catalyzed C–N bond-forming processes [4] has supplanted classical amination reactions such as the Ullmann [5] and related Goldberg reactions [6], which require very high temperatures, highly polar solvents, and a large excess of the alkoxides [7]. 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 [8].

Brian has reported the palladium catalyzed amidation of urea with different aryl halides and bippyphos 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

* Corresponding author.
E-mail address: dr_dvmane@rediffmail.com (D.V. Mane).

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phenyl group of the bippyphos [9]. Belestkaya 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 [10]. An attempt by the same group for the arylation of urea using a copper catalyst was unsuccessful [10]. There have been many reports recently on the arylation of different compounds such as amines [8], amides [11], and hydrazides [12], *etc.* using copper catalysts in the presence of suitable ligands. It accelerates a variety of synthetic transformations *via* time and energy saving protocols. 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 phenylurea.

1. Experimental

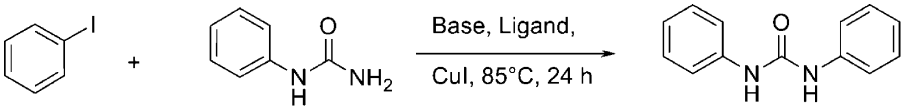
General procedure: A screw-capped tube was charged with phenylurea (1 mmol), aryl halide (1.2 mmol), K_3PO_4 (2 mmol), CuI (10 mol%), *N*,*N*′-dimethylethylenediamine (20 mol%) and DMF (3 mL) at room temperature. After closing, the tube was heated to 85 °C for specified time, allowed to cool to room temperature and the resulting mixture was extracted with ethyl acetate. The organic layers were washed with water, dried over anhydrous sodium sulfate and concentrated in vacuo; the crude product was purified by column chromatography on silica gel using EtOAc–hexane (1:2) as eluent to afford the coupled product. The identity and purity of the known products was confirmed by ^{1}H and ^{13}C NMR spectroscopic analysis, and the new products were fully characterized.

3-Diphenylurea (*carbanilide*) (Table 2, *entry 1*): White solid in 95% isolated yield. M.p. 237.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.63 (s, 2H), 7.45 (d, 4H, J = 8.6, Hz), 7.27 (t, 4H, J = 7.9 Hz), 6.96 (t, 2H, J = 7.3 Hz). ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.9, 139.1, 128.2, 121.3, 117.7. HRMS (EI, *m*/*z*) calcd. for $C_{13}H_{12}N_2O$ (M^+) 212.25, found 212.21. *N-(4-Nitrophenyl)-N′-phenyl-urea* (Table 2, *entry 5*): Orange solid in 99% isolated yield. M.p. 210–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.40 (s, 1H), 8.89 (s, 1H), 8.18 (d, 2H, J = 9.3 Hz), 7.68 (d, 2H, J = 9.3 Hz), 7.47 (d, 2H, J = 8.6 Hz), 7.30 (t, 2H, J = 7.9 Hz), 7.01 (t, 1H, J = 7.4 Hz). ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.3, 145.8, 140.4, 138.4, 128.3, 124.6, 122.0, 118.2, 117.0. HRMS (EI, *m/z*) calcd. for $C_{13}H_{11}N_2O_3$ (M^+) 257.25, found 257.23. *N-(1-Naphthalenyl)-N′-phenyl-urea* (Table 2, *entry 9*): White solid in 85% isolated yield. M.p. 221–223 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.08 (s, 1H), 8.79 (s, 1H), 8.15 (d, 1H, J = 8.7 Hz), 8.05 (d, 1H, J = 7.6 Hz), 7.93 (d, 1H, J = 7.6 Hz), 7.45–7.72 (m, 6H), 7.32 (t, 2H, J = 7.9 Hz), 6.96–7.09 (m, 1H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 153.38, 140.23, 134.75, 134.16, 129.31, 128.88, 126.37, 126.33, 126.24, 126.14, 123.37, 122.30, 121.75, 118.57, 117.84. HRMS (EI, *m*/*z*) calcd. for $C_{17}H_{14}N_2O$ (M^+) 262.31, found 262.34. *N-(2-Pyridinyl)-N′-phenylurea* (Table 2, *entry 18*): White solid in 55% isolated yield. M.p. 186–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.49 (s, 1H), 9.42 (s, 1H), 8.27 (d, 1H, J = 3.9 Hz), 7.77–7.70 (m, 1H), 7.55–7.45 (m, 3H), 7.34–7.26 (m, 2H, J = 4.1, 11.7 Hz), 7.05–6.97 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 152.2, 151.5, 146.3, 138.4, 138.0, 128.4, 122.0, 118.3, 117.0, 111.5. HRMS (EI, *m*/*z*) calcd. for $C_{12}H_{11}N_3O$ (M^+) 213.24, found 213.28. *N-(4-Fluorophenyl)-N′-phenylurea* (Table 2, *entry 22*): White solid in 23% isolated yield; M.p. 240–242 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.68 (s, 1H), 8.64 (s, 1H), 7.41–7.52 (m, 4H), 7.27 (t, 2H, J = 7.9 Hz), 7.06–7.17 (m, 2H), 6.92–7.01 (m, 1H). ^{13}C NMR (300 MHz, DMSO-d_6): δ 159.35, 156.2, 153.07, 140.07, 136.45, 129.2, 122.28, 120.46, 118.69, 115.83. HRMS (EI, *m*/*z*) calcd. for $C_{13}H_{11}FN_2O$ (M^+) 230.24, found 230.22.

2. Results and discussion

To find the optimum conditions for the coupling of phenylurea with aryl halide, the *N*-arylation of phenylurea (1 mmol) with 4-iodobenzene (1.2 mmol) was investigated with different solvents, bases and various ligands (20 mol%) in the presence of CuI (10 mol%) at various temperatures for 24 h. Of the ligands tested, *N*,*N*′-dimethylethylenediamine (DMEDA) (Table 1, entry 4), tetramethylethylenediamine (TMEDA) (Table 1, entry 1), 2, 4-pentanedione (Table 1, entry 5), 1, 2-ethanediol (Table 1, entry 2), 1, 10-phenanthroline (Table 1, entry 3), the former proved to be the best ligand. Among the solvents examined, dioxane (Table 1, entry 8), toluene (Table 1, entry 7), DMF (Table 1, entry 4), and THF (Table 1, entry 6), DMF was the most effective for the coupling reaction; in other solvent yield was low. Reaction was done at higher temperature 100 °C (Table 1, entry 11), yield was low. Among the bases examined, K_3PO_4 (Table 1, entry 4), Cs_2CO_3 (Table 1, entry 9) and *t*-BuONa (Table 1, entry 10), K_3PO_4 was suitable base. As shown in Table 1, the reaction between phenylurea and iodobenzene gave an excellent yield of *N*,*N*′-diphenylurea after 24 h (Table 1, entry 4).

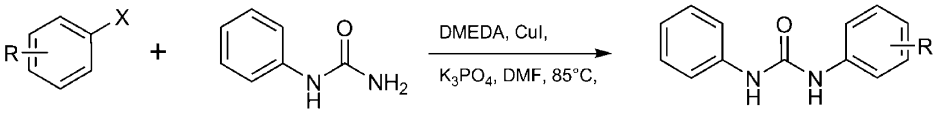
Table 1
The copper-catalyzed *N*-arylation of phenylurea with phenyl iodide with different solvent, bases and various ligands.



Entry	Base	Ligand	Solvent	Yield[a] (%)
1	K_3PO_4	TMEDA	DMF	60
2	K_3PO_4	1,2-Ethanediol	DMF	No reaction
3	K_3PO_4	1,10-Phenanthroline	DMF	40
4	K_3PO_4	DMEDA	DMF	95
5	K_3PO_4	2,4-Pentanedione	DMF	Trace
6	K_3PO_4	DMEDA	THF	33
7	K_3PO_4	DMEDA	Toluene	40
8	K_3PO_4	DMEDA	Dioxane	52
9	Cs_2CO_3	DMEDA	DMF	70
10	*t*-BuONa	DMEDA	DMF	50
11	K_3PO_4	DMEDA	DMF	75[b]

[a] Isolated yields.
[b] Temp. 100 °C.

Table 2
The copper-catalyzed *N*-arylation of phenylurea with aryl halides in the presence of K_3PO_4 and *N*,*N*′-dimethylethylenediamine.



Entry	Aryl halide	Product[a]	Time (h)	Yield[b] (%)
1	C_6H_5I	$C_6H_5NHCONHC_6H_5$	24	95
2	4-$CH_3C_6H_4I$	4-$CH_3C_6H_4NHCONHC_6H_5$	24	96
3	4-$CH_3OC_6H_4I$	4-$CH_3OC_6H_4NHCONHC_6H_5$	24	90
4	4-FC_6H_4I	4-$FC_6H_4NHCONHC_6H_5$	16	98
5	4-$NO_2C_6H_4I$	4-$NO_2C_6H_4NHCONHC_6H_5$	18	99
6	2-$CH_3OC_6H_4I$	2-$CH_3OC_6H_4NHCONHC_6H_5$	24	87
7	3-PyridineI	3-PyridineNHCONHC$_6H_5$	17	93
8	3-$CF_3C_6H_4I$	3-$CF_3C_6H_4NHCONHC_6H_5$	16	90
9	1-NaphthylI	1-NaphthylNHCONHC$_6H_5$	24	85
10	C_6H_5Br	$C_6H_5NHCONHC_6H_5$	24	58
11	4-$CH_3C_6H_4Br$	4-$CH_3C_6H_4NHCONHC_6H_5$	24	60
12	4-$CH_3OC_6H_4Br$	4-$CH_3OC_6H_4NHCONHC_6H_5$	24	55
13	4-FC_6H_4Br	4-$FC_6H_4NHCONHC_6H_5$	24	69
14	4-$NO_2C_6H_4Br$	4-$NO_2C_6H_4NHCONHC_6H_5$	18	77
15	4-CNC_6H_4Br	4-$CNC_6H_4NHCONHC_6H_5$	16	79
16	2-$CH_3C_6H_4Br$	2-$CH_3C_6H_4NHCONHC_6H_5$	24	60
17	2-$CH_3OC_6H_4Br$	2-$CH_3OC_6H_4NHCONHC_6H_5$	24	57
18	2-PyridineBr	2-PyridineNHCONHC$_6H_5$	24	55
19	3-PyridineBr	3-PyridineNHCONHC$_6H_5$	24	70
20	4-PyridineBr	4-PyridineNHCONHC$_6H_5$	24	25
21	C_6H_5Cl	$C_6H_5NHCONHC_6H_5$	24	16
22	4-FC_6H_4Cl	4-$FC_6H_4NHCONHC_6H_5$	24	23
23	4-$NO_2C_6H_4Cl$	4-$NO_2C_6H_4NHCONHC_6H_5$	24	32
24	2-$CH_3OC_6H_4Cl$	2-$CH_3OC_6H_4NHCONHC_6H_5$	24	Trace

[a] Reactions were carried out with 1.2 mmol of aryl halide, 1.0 mmol of phenylurea, 20 mol% of CuI, 20 mol% of DMEDA, and 3 mmol of K_3PO_4 in DMF (1 mL per mmol) at 80–85 °C.
[b] Isolated yields; products were characterized by ^{1}H NMR and mp.

Thus, the optimized reaction conditions utilized 10 mol% of CuI, 20 mol% of DMEDA as ligand, and 2.0 equiv K_3PO_4 as base in DMF heated at 85 °C for specific time. These optimized reaction conditions were applied to the coupling of various aryl halides and phenylurea (Table 2).

The product was characterized on the basis of its spectral data and by comparison of its melting point with the literature [13–19].

No significant electronic effects were observed for substituted aryl halides based on the yields of reactions and reaction times. Substrate possessing electron withdrawing substituent such as CF_3, in the meta position (Table 2, entry 8), F, NO_2, CN in the para position (Table 2, entries 13–15) and electron releasing substituents such as Me and OMe in the para position (Table 2, entries 2 and 3), OMe (Table 2, entries 3 and 6) and Me (Table 2, entries 11 and 16) in the para and ortho-positions of the aromatic rings also gave good to excellent yields of the corresponding diarylureas. Reaction of the bulky aryl halides 1-iodonaphthalene with phenylurea gave *N*-(1-naphthyl)-*N*′-phenylurea in a good yield (Table 2, entry 9). Reaction of heteroaryl halides 3-iodopyridine, 3-bromopyridine, and 2-bromopyridine gave good yield, but 4-bromopyridine gave low yield. Reaction of aryl chlorides with phenylurea gave poor yield of the desired product (Table 2, entries 21–24).

3. Conclusion

In summary, we have developed an efficient and inexpensive catalytic system for the synthesis of symmetrical and unsymmetrical *N*,*N*′-diarylureas *via* the reaction of various aryl halides with phenylurea using DMEDA as ligand and K_3PO_4 as base. We believe that this protocol is an excellent complement to palladium-catalyzed methods.

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