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Copper-catalyzed arylation of phenylurea using KF/Al_2O_3

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Abstract

A mild and efficient method for the copper-catalyzed arylation of phenylurea is described. The coupling reaction of phenylurea with different functionalized aryl iodides in the presence of air stable CuI, *N*,*N*′-dibenzylethylenediamine as a ligand, and KF/Al_2O_3 as a base gives symmetrical and unsymmetrical diarylureas in relatively high yields.

Keywords: Copper catalyst; Urea; Aryl iodides; Coupling; KF/Al_2O_3

N,*N*′-Diarylureas are valuable subunits for organic synthesis and have found numerous applications as drugs, pesticides,[1] and anion binding receptors.[2] Traditional methods for the synthesis of diarylureas include the reaction of aromatic amines with isocyanates, phosgene or carbon monoxide, which are highly toxic reagents.[1,3] 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] However, despite great advances in this area, there are still some limitations for the preparation of compounds possessing C–N bonds, for example, the high cost of palladium complexes and the removal of trace palladium from late stage synthetic intermediates can be challenging.[8] Moreover, the coupling of electron-rich or *ortho*-substituted aryl halides is difficult.[9] Beletskaya has reported a palladium-catalyst system for the conversion of aryl halides to diarylureas using Xantphos as an effective ligand for this coupling reaction.[10] The drawbacks to this methodology include the cost of the reagents, the use of toxic ligands, and the formation of considerable amounts of *N*-phenylation byproducts in the arylation of ureas with unactivated aryl halides arising from the exchange of the aryl group bound to palladium and the phenyl group of the ligand. Recently, Nandakumar reported a copper catalyst system for the amidation of aryl halides with urea.[11] This method requires a diamine ligand and K_3PO_4 as a base to afford symmetrical *N*,*N*′-diarylureas in moderate yields.

We have recently used KF/Al_2O_3, 1,10-phenanthroline, and CuI, for C–N and C–O bond formation in the amidation and etherification of aryl iodides.[12] Here we report the CuI-catalyzed N-arylation of aryl iodides with *N*-phenylurea using KF/Al_2O_3 as a suitable base and *N*,*N*′-dibenzylethylenediamine as an effective ligand (Scheme 1).

To find the optimum conditions for the coupling of phenylurea with the aryl iodide, the N-arylation of phenylurea with 4-iodoanisole was investigated with different solvents, and various ligands in the presence of different amounts of KF/Al_2O_3 and CuI at various temperatures. Of the ligands tested, *N*,*N*′-dibenzylethylenediamine, *N*,*N*′-bis(2-pyridylmethyl)ethylenediamine, and 1,10-phenanthroline, the former proved to be the best ligand. This ligand was easily prepared according to the procedure reported.[13] Among the solvents examined, (dioxane, toluene, DMF, and

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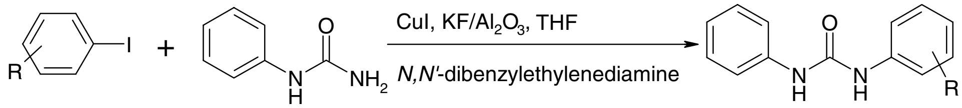
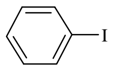
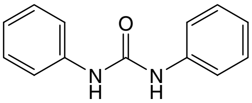
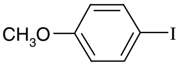
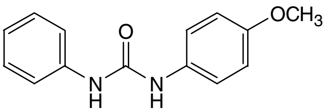
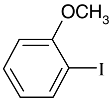
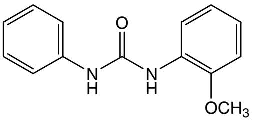
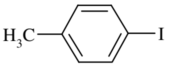
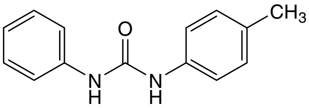
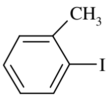
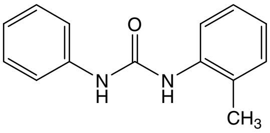
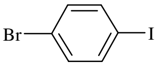
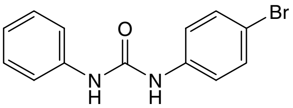
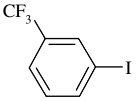
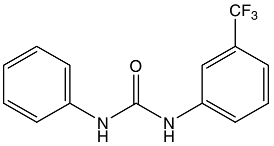
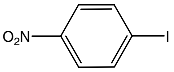
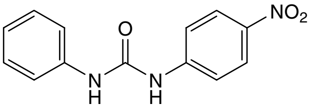


Scheme 1.

THF), THF was the most effective for the coupling reaction; in other solvents we observed the formation of substantial amounts of *N*,*N*′-diphenylurea as a side product. Ureas are very stable compounds and are sometimes prepared as derivatives of amines for characterization purpose. They can dissociate into the corresponding isocyanates and aniline derivatives at high temperature,[14] therefore, the formation of *N*,*N*′-diphenylurea may be explained by the dissociation of *N*-phenylurea to phenyl isocyanate at high temperature (reflux temperature of the solvents). To confirm this, we

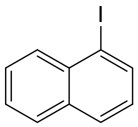
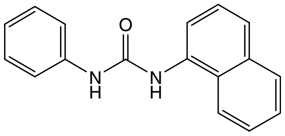
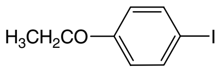
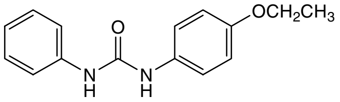
Table 1

The copper-catalyzed N-arylation of phenylurea with aryl iodides in the presence of KF/Al_2O_3 and *N*,*N*′-dibenzylethylenediamine

Entry	Aryl halide	Product[a]	Time (h)	Yield[b] (%)
1			4	83
2			4	78
3			4	75
4			4	70
5			5	77
6			3	88
7			4	73
8			3	71

(*continued on next page*)

Table 1 (*continued*)

Entry	Aryl halide	Product[a]	Time (h)	Yield[b] (%)
9			6	67
10			4	70

[a] Reactions were carried out with 1 mmol of aryl iodide, 1 mmol of phenylurea, 15 mol % of CuI, 15 mol % of *N*,*N*′-dibenzylethylenediamine, and 5 mmol of KF/Al_2O_3 in THF at 65–70 °C.

[b] Isolated yields; products were characterized by ^{1}H NMR and mp.[16]

heated phenylurea in the absence of aryl halide and catalyst system in refluxing toluene or in the presence of 2 equiv of aniline and *N*,*N*′-diphenylurea was formed as sole product in both reactions.

Thus, the optimized reaction conditions utilized 15 mol % of CuI, 15 mol % of *N*,*N*′-dibenzylethylenediamine as ligand, and 5 equiv KF/Al_2O_3 as base in refluxing THF under argon.

These optimized reaction conditions were applied to the coupling of various aryl iodides and phenylurea (Table 1).[15] As shown in Table 1, the reaction between phenylurea and iodobenzene gave an excellent yield of *N*,*N*′-diphenylurea after 3 h (entry 1).

No significant electronic effects were observed for substituted aryl iodides based on the yields of reactions and reaction times. Substrates possessing electron withdrawing substituents such as CF_3, in the *meta*-position (entry 7), bromine and nitro in the *para*-position (entries 6 and 8) and electron-releasing substituents such as OEt (entry 10) in the *para*-position, OMe (entries 2 and 3) and Me (entries 4 and 5) in the *ortho* and *para*-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 (entry 9). Unfortunately, attempts to perform the analogous coupling reaction using aryl bromides and phenylurea in this catalytic system were unsuccessful.

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 iodides with phenylurea using *N*,*N*′-dibenzylethylenediamine as ligand and KF/Al_2O_3 as base. We believe that this protocol is an excellent complement to palladium-catalyzed methods.

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15. General procedure for the copper-catalyzed N-arylation of phenylurea in the presence of KF/Al_2O_3 (Table 1). To a solution of phenylurea (1 mmol) and aryl iodide (1 mmol) in dry THF (3 ml) under an argon atmosphere were added CuI (28.5 mg, 15 mol %) and *N*,*N*′-dibenzylethylenediamine (36 mg, 15 mol %) followed by KF/Al_2O_3 (5 equiv, 780 mg). The reaction was carried out with stirring at 65–70 °C for the

specified times (Table 1). The progress of the reaction was monitored by TLC. On completion, the reaction mixture was cooled to room temperature and was then filtered and the filtrate was concentrated under vacuum. The residue was purified by column chromatography on silica gel using *n*-hexane–ethyl acetate (3:2) as eluent to afford the coupled product.

16. The spectroscopic data and melting points for known products compared well with the reported data. Selected physical and spectral data: *N*-(4-methoxyphenyl)-*N*′-phenylurea (Table 1, entry 2). White solid; mp 195–196 °C (lit.[17] 193–194 °C); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.00 (s, 1H), 7.90 (s, 1H), 7.52 (d, $J = 8.1$ Hz, 2H), 7.43 (d, $J = 9.8$ Hz, 2H), 7.25 (t, $J = 7.5$ Hz, 2H), 6.95 (t, $J = 7.4$ Hz, 1H), 6.86 (d, $J = 9.8$ Hz, 2H), 3.76 (s, 3H). *N*-(2-Methoxyphenyl)-*N*′-phenylurea (Table 1, entry 3). White solid; mp 149–150 °C (lit.[18] 146.2–146.8 °C); ^{1}H NMR (500 MHz, acetone-d_6) δ 8.59 (s, 1H), 8.30 (d, $J = 7.7$ Hz, 1H), 7.86 (s, 1H), 7.55 (d, $J = 8.1$ Hz, 2H), 7.27 (t, $J = 7.5$ Hz, 2H), 6.98–6.90 (m, 4H), 3.87 (s, 3H). *N*,*N*′-Diphenylurea (Table 1, entry 1). White solid; mp 237.5 °C (lit.[11] 238 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.67 (s, 2H), 7.47 (d, $J = 8.4$ Hz, 4H), 7.29 (t, $J = 7.7$ Hz, 4H), 6.97 (t, $J = 7.2$ Hz, 2H). *N*-(4-Methylphenyl)-*N*′-phenylurea (Table 1, entry 4). White solid; mp 219–220 °C (lit.[19] 222–223 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.57 (s, 1H), 8.50 (s, 1H), 7.42 (d, $J = 7.9$ Hz, 2H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.25 (t, $J = 7.9$ Hz, 2H), 7.07 (d, $J = 7.9$ Hz, 2H), 6.94 (t, $J = 7.3$ Hz, 1H), 2.23 (s, 3H). *N*-(4-Nitrophenyl)-*N*′-phenylurea (Table 1, entry 8). Orange solid; mp 210–211 °C (lit.[20] 208 °C); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.41 (s, 1H), 8.90 (s, 1H), 8.18 (d, $J = 9.1$ Hz, 2H), 7.68 (d, $J = 9.1$ Hz, 2H), 7.46 (d, $J = 7.2$ Hz, 2H), 7.30 (t, $J = 7.8$ Hz, 2H), 7.01 (t, $J = 7.4$ Hz, 1H).
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