A Mild and Efficient Method for N-Arylation of Nitrogen Heterocycles with Aryl Halides Catalyzed by Cu(II)-NaY Zeolite

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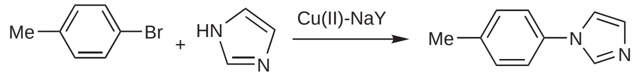
Abstract: A mild and efficient method for N-arylation of nitrogen-containing heterocycles with aryl halides to afford *N*-arylheterocycles in excellent yields using a Cu(II)-NaY catalyst in the presence of K_2CO_3 base is reported.

Key words: N-arylation, nitrogen heterocycles, aryl halides, Cu(II)-NaY zeolite

N-Arylheterocycles are common motifs in pharmaceutical research and can be prepared either by nucleophilic aromatic substitution[1] or by Ullmann-type coupling.[2] The former method requires substrates bearing electron-withdrawing substituents and the latter coupling reaction requires the use of stoichiometric amounts of copper and gives low to moderate yields. Milder methods involving various arylating agents are also reported[3] but only a few use aryl halides as the arylating agent.[4] Buchwald et al. employed copper(I) iodide and racemic *trans-N,N*-dimethyl-1,2-cyclohexanediamine in the N-arylation of nitrogen heterocycles[4f] and Cristau et al. reported N-arylation of azoles by using cuprous oxide and oxime ligands under mild conditions.[4g,4h] Dawei Ma et al. reported amino acid promoted, CuI-catalyzed C–N bond formation of aryl halides and amines or nitrogen heterocycles.[4i] All these reactions require additives or ligands. Recently we reported that copper basic apatites are potential catalysts for N-arylation of heterocycles using fluoro- and chloroarenes in the absence of any additive.[5] Zeolites are very useful catalysts in a large variety of reactions, including acid, base and redox catalysis.[6] Hutchings et al. reported that bis(oxazoline)-modified Cu(II)-HY catalysts are effective for asymmetric carbonyl- and imino-ene reactions and aziridination of styrene.[7] Recently Djakovitch and Kohler[8] found that Pd(II)-NaY zeolite activates aryl halides towards Heck olefination, α-arylation of malonate and amination reactions. It is well known that alkali-exchanged faujasite zeolites are solid base catalysts.[9] We conceived the use of a basic support, NaY zeolite to make an electron-rich copper catalyst that activates C–Cl, C–Br and C–I bonds. We herein report the N-arylation of nitrogen heterocycles with aryl halides to afford *N*-arylheterocycles in excellent yields under mild conditions using Cu(II)-modified alkali exchanged zeolite Y without the use of any additive.

Table 1 Cu(II)-NaY Catalyzed Coupling of 4-Bromotoluene and Imidazole[a]



Entry	Base	Solvent	Time (h)	Yield[b] (%)
1	K_2CO_3	DMF	20 (36)	62 (95)
2	K_3PO_4	DMF	20	65
3	Cs_2CO_3	DMF	20	68
4	Et_3N	DMF	20	trace
5	NaO^tBu	DMF	20	14
6	K_2CO_3	DMSO	20	60
7	K_2CO_3	NMP	20	52
8	K_2CO_3	1,4-Dioxane	20	10

[a] Reaction conditions: 4-bromotoluene (1 mmol), imidazole (1.2 mmol), base (2 mmol), Cu(II)-NaY (100 mg) in 3 mL of solvent.
[b] GC yields.

We first conducted the coupling reactions with 4-bromotoluene and imidazole using the Cu(II)-NaY catalyst.[10] The reaction proceeded well at 120 °C in DMF in the presence of K_2CO_3 to afford 1-(4-methylphenyl)-1H-imidazole in 62% yield in 20 hours and 95% yield in 36 hours (Table 1, entry 1). To our knowledge, there is no report of the N-arylation of nitrogen heterocycles with aryl halides using zeolite catalysts in the literature. Other bases including K_3PO_4 and Cs_2CO_3 afforded 65% and 68% yields respectively in 20 hours (Table 1, entries 2 and 3). We have screened different solvents and the results are summarized in Table 1 (entries 6–8). These results indicate that *N*-arylheterocycles can be prepared using a cheap and mild base (K_2CO_3) in DMF.[11]

After the reaction conditions were optimized, the reaction scope was extended to different aryl halides and imidazole. As summarized in Table 2, N-arylation of imidazole with chloroarenes containing electron-withdrawing groups such as nitro-, cyano-, and trifluoromethyl gave high yields (92%, 99% and 97%, respectively, Table 2,

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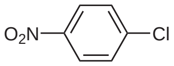
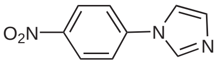
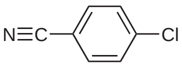
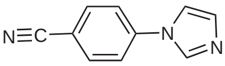
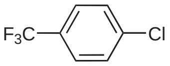
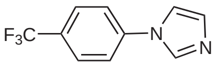
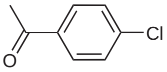
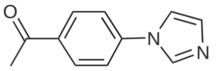
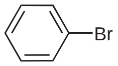
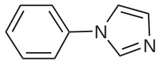
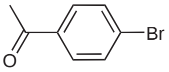
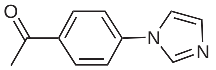
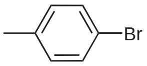
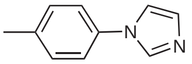
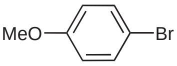
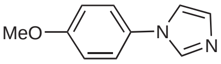
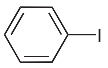
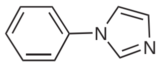
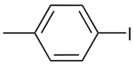
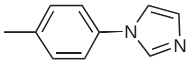
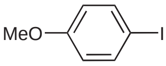
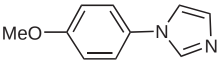
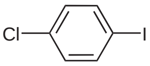
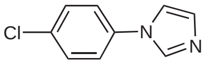
Table 2 Cu(II)-NaY-Catalyzed Coupling Reactions of Aryl Halides with Imidazole[a]

Entry	Aryl halide	Product	Time (h)	Yield[b] (%)
1			20	92[c]
2			24	99
3			30	97
4			48	95
5			30	99
6			20	99
7			36	90[c] (84)[d]
8			48	85
9			24	99
10			24	99
11			36	99
12			40	99

[a] Reaction conditions: aryl halide (1 mmol), imidazole (1.2 mmol), K_2CO_3 (2 mmol), Cu(II)-NaY (100 mg) in DMF (3 mL).

[b] GC yields; products were characterized by ^1H NMR and MS.

[c] Isolated yields.

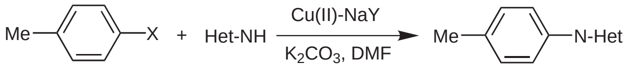
[d] Isolated yield after the third recycling.

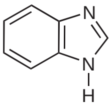
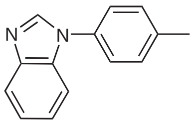
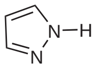
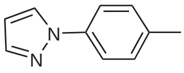
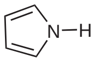
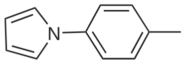
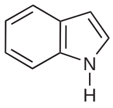
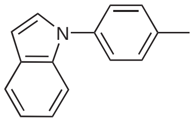
entries 1–3) in shorter reaction times when compared with 4-chloroacetophenone (Table 2, entry 4). Bromoarenes containing electron-donating groups afforded the corresponding N-arylated products in high yields after 36 h (entries 5–8). The reaction with iodoarenes resulted in complete conversion in shorter reaction times (Table 2, entries 9–11). Treatment of 1-chloro-4-iodobenzene with imidazole gave selectively *N*-(4-chlorophenyl)imidazole (Table 2, entry 12). The catalyst was used for four cycles successfully with minimal loss of activity (Table 2, entry 7). After completion of the reaction, the catalyst was separated by filtration and washed with DMF and acetone and then dried in an oven. Atomic absorption spectroscopy (AAS) results of the used Cu(II)-NaY catalyst indicate leaching of 1.8% of copper in the N-arylation reaction of imidazole with 4-bromotoluene after the first cycle and 6.2% after the fourth cycle. When a fresh reaction was conducted with the filtrate obtained at the end of the N-arylation reaction, no product formation was observed.

The application of this catalytic system for the coupling of nitrogen-containing heterocycles with 4-bromo- and 4-iodotoluene was also explored and the desired N-arylated products were obtained in excellent yields (Table 3). However, the reaction of 4-chlorotoluene with nitrogen heterocycles provided the products in only trace amounts even after 48 hours.

In conclusion, we have demonstrated that Cu(II)-NaY catalyzes the N-arylation of nitrogen-containing heterocycles with chloro-, bromo-, and iodoarenes in excellent yields. The present reaction is applicable to bromo- and iodoarenes containing electron-donating and electron-withdrawing groups and chloroarenes containing electron-withdrawing groups under mild conditions without the use of any additive.

Table 3 N-Arylation of Various Nitrogen Hetrocycles[a]



Entry	Nitrogen hetrocycle	Product	X = Br		X = I	
			Time (h)	Yield[b] (%)	Time (h)	Yield[b] (%)
1			48	99	36	99
2			36	99	22	99
3			24	99	20	99
4			20	99	22	99

[a] Conditions as in Table 2.

[b] GC yields; products were characterized by ^{1}H NMR and MS.

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(10) *Catalyst preparation:* Cu(II)-NaY zeolite was prepared by ion-exchange of zeolite NaY (10 g) with a solution of copper(II) acetate (2.86 g, 15.75 mmol in deionized water (150 mL) at r.t. for 24 h. The material was recovered by filtration, dried (110 °C) and calcined (550 °C) in a flow of air. AAS analysis showed that the zeolite contained 6.84 wt% of Cu.

(11) **Typical Experimental Procedure:** A mixture of 4-bromotoluene (1 mmol), imidazole (1.2 mmol), K_2CO_3 (2 mmol) and Cu(II)-NaY (100 mg) in DMF (3 mL) was heated to 120 °C for the specified time (Table 2). The progress of the reaction was monitored by GC or TLC. The reaction mixture was filtered to separate the catalyst and the filtrate was quenched with aq $NaHCO_3$ and the product extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography to afford pure 1-(4-methylphenyl)-1*H*-imidazole.

1-(4-Methylphenyl)-1*H*-imidazole (Table 2, entry 7). ^{1}H NMR (CDCl$_3$): $\delta = 7.76$ (br s, 1 H), 7.24 (br s, 4 H), 7.19 (br s, 1 H), 7.13 (br s, 1 H), 2.39 (s, 3 H); MS (EI): *m*/*z* (%) = 158, 131, 104, 91 (100) 50; Anal. Calcd for $C_{10}N_2H_{10}$: C, 75.95; N, 17.72; H, 6.33. Found: C, 76.09; N, 17.75; H, 6.16.

1-(4-Nitrophenyl)-1*H*-imidazole (Table 2, entry 1): mp 203 °C; ^{1}H NMR (CDCl$_3$): $\delta = 8.37$ (d, $J = 9.0$ Hz, 2 H), 7.93 (br s, 1 H), 7.58 (d, $J = 9.0$ Hz, 2 H), 7.32 (br s, 1 H), 7.24 (br s, 1 H); MS (EI): *m*/*z* (%) = 189 (100), 159, 141, 116, 89, 50; Anal. Calcd for $C_9N_3O_2H_7$: C, 57.14; N, 22.2; H, 3.7; Found C, 57.42; N, 22.59; H, 3.19.

All products are reported compounds and have been identified by ^{1}H NMR and mass spectrometric data.[5]