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Copper-catalyzed N-arylation of diazoles with aryl bromides using KF/Al_2O_3: an improved protocol

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Abstract—Copper-catalyzed N-arylation of diazoles can be accomplished using air-stable CuI as a copper source and 1,10-phenanthroline in the presence of KF/Al_2O_3 as a base. This is a simple and efficient method for the coupling of aryl bromide with diazoles. Different functionalized aryl bromides were coupled with diazoles using this system.

N-Arylamines, N-arylpyrroles, N-arylindoles, N-arylimidazoles and N-arylpyrazoles are prevalent in compounds that are of biological, pharmaceutical and material interest.[1–3] These compounds have been synthesized via S_NAr substitution of azoles with aryl halides bearing electron-withdrawing substituents.[4] Copper-catalyzed Ullmann-type reactions are traditional methods for preparing these compounds.[5] These reactions have been carried out at high temperatures and many functional groups are not tolerated, and therefore their use is greatly limited.[5] In addition, these reactions often require the use of stoichiometric amounts of copper reagents, which, on scale-up, leads to problems of waste disposal.[6] To overcome these drawbacks, several Pd-catalyzed C–N bond formation methods have been developed, which, together with sterically hindered phosphine ligands, allow many coupling reactions of aryl halides with N-containing compounds to proceed under relatively mild conditions and at low temperature.[7] However, industrial use of these methods is problematic in many cases due to their air and moisture sensitivity, as well as the higher costs of Pd catalysts and the ligands.[8] Buchwald et al. and others have reported a copper-based protocol for the formation of N-aryl bonds.[9–12] Most of these methods require long reaction times and bases such as Cs_2CO_3, K_3PO_4, K_2CO_3, etc. Cs_2CO_3 is very sensitive to moisture and this problem reduces its ability as a base in moisture sensitive reactions. On the other hand, the application of KF/Al_2O_3 to organic synthesis has provided new methods for a wide range of organic reactions, many of which are staples of synthetic organic chemistry.[13] Its benefits include its strongly basic character which has led to its replacing organic bases in a number of reactions.[14] In many cases, the use of this base provides milder conditions and simpler procedures than previously reported methods. We have modified the copper-catalyzed N-arylation reaction of aryl bromides using KF/Al_2O_3 as a base.

We have explored the CuI-catalyzed N-arylation of imidazole, pyrazole and benzimidazole with aryl bromides using 1,10-phenanthroline (20 mol %) as a simple ligand and KF/Al_2O_3 as base in the presence of CuI (20 mol %) (Scheme 1).

1,10-Phenanthroline as ligand and KF/Al_2O_3 as base in the presence of CuI (20 mol %) were chosen as we have recently used this system for C–N and C–O bond formations in N-amidation and O-arylation.[15,16]

The reaction conditions were optimized using the cross-coupling reaction of bromobenzene and imidazole in the presence of 1,10-phenanthroline, KF/Al_2O_3 and CuI in xylene or toluene as solvent at 110–140 °C. The yield of *N*-phenylimidazole in xylene after 15 h was 92% while in toluene after 15 h it was 87%.

Using the above protocol, we subjected a series of aryl bromides to these reaction conditions (Table 1).

Keywords: Copper-catalyzed; Coupling; N-arylation; Diazoles; Aryl bromide.

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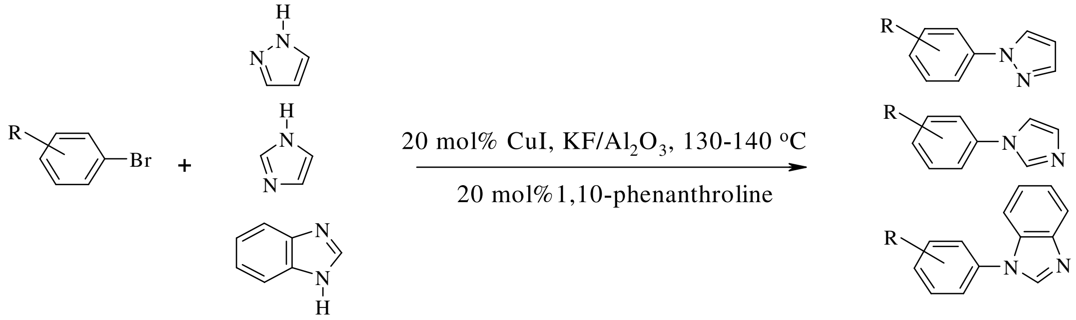
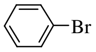
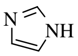
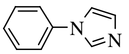
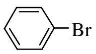
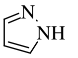
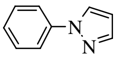
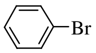
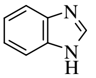
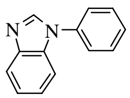
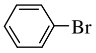
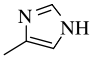
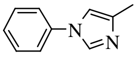
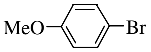
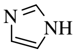
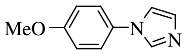
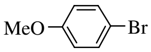
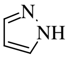
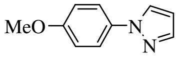
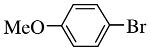
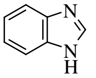
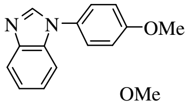
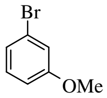
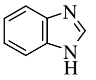
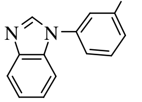
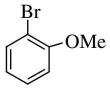
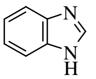
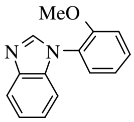
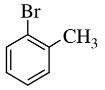
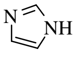
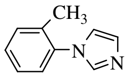
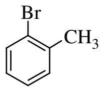
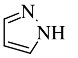
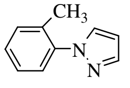
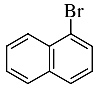
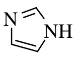
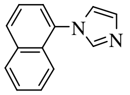
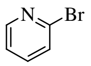
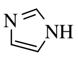
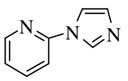


Scheme 1.

Table 1. The copper-catalyzed N-arylation of aryl bromides in the presence of KF/Al_2O_3

Entry	Aryl bromide	Diazole	Product[a]	Time (h)	Yield (%)[b]
1				15	92
2				15	92
3				15	90
4				15	91
5				16	89
6				16	88
7				17	80
8				16	91
9				18	71
10				18	80
11				18	81
12				17	71
13				15	90

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[a] Reaction performed using 20 mol % of 1,10-phenanthroline as ligand, 1.0 equiv of aryl bromide, 3 equiv of diazole and 5 equiv of KF/Al_2O_3 as base in xylene as solvent at 130–140 °C.

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

As can be seen in Table 1, imidazole, 4-methylimidazole, pyrazole and benzimidazole were successfully transformed to the corresponding *N*-aryl compounds. The reactions between these diazoles and bromobenzene gave excellent yields after 15 h (entries 1–4). Substrates possessing electron-releasing groups such as OMe (entries 5–9), and Me (entries 10 and 11) in the *ortho*-, *meta*- and *para*-positions of the aromatic ring also gave good to excellent yields of the corresponding *N*-aryl compounds. Fused compounds such as 1-bromonaphthalene on reaction with imidazole gave a satisfactory yield of the corresponding *N*-aryl compound (entry 12). 2-Bromopyridine reacted with imidazole to give an excellent yield of the corresponding *N*-pyrid-2-yl compound (entry 13).

This protocol can be successfully applied for the N-arylation of indoles and pyrroles and this is under investigation in our laboratory.

In summary, we have developed an experimentally simple and inexpensive catalyst system for the N-arylation of diazoles.[17] We believe that potassium fluoride supported on alumina (KF/Al_2O_3) provides an excellent complement to other bases such as Cs_2CO_3, in copper-catalyzed coupling reactions which have already been utilized in a number of applications.

Acknowledgements

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17. *General procedure for the copper-catalyzed N-arylation of aryl bromides in the presence of* KF/Al_2O_3 (Table 1). To a solution of diazole (3 mmol) and aryl bromide (1 mmol) in xylene (3 ml) under an argon atmosphere were added CuI (38 mg, 20 mol %) and 1,10-phenanthroline (40 mg, 20 mol %) followed by KF/Al_2O_3[18] (5 equiv, 780 mg) and the reaction was stirred at 130–140 °C for the specified time (Table 1). The progress of the reaction was monitored by TLC. The reaction mixture was allowed to cool to room temperature and was then partitioned between CH_2Cl_2 (30 ml) and saturated aqueous NH_4Cl solution (3 × 10 ml). The organic fraction was washed with water (3 × 10 ml), dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate (1:9) as eluent to afford the pure product.
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