Highly Efficient Copper-Catalyzed Formation of *N*-Aryl Diazoles Using KF/Al_2O_3

Rahman Hosseinzadeh,*[a] Mahmood Tajbakhsh,[a] Mohammad Alikarami[a,b]

[a] Faculty of Basic Science, Mazandaran University, Babolsar, Iran

[b] Islamic Azad University, Ilam, Iran
Fax +98(11252)42002; E-mail: r.hosseinzadeh@umz.ac.ir

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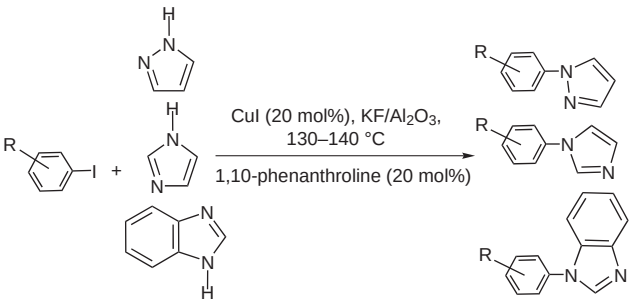
Abstract: A simple and efficient method for the coupling of aryl iodides with heterocyclic compounds such as diazoles that does not require the use of alkoxide bases is described. The C–N bond forming procedure shows that the combination of air stable CuI and 1,10-phenanthroline in the presence of KF/Al_2O_3 comprises an extremely efficient and general catalyst system for the N-arylation of aryl iodides. Different functionalized aryl iodides were coupled with diazoles using this method.

Key words: diazole, aryl iodides, copper iodide, coupling reaction, potassium fluoride on alumina

Nitrogen-containing heterocycles such as *N*-arylamines, *N*-arylpyrroles, *N*-arylindoles, *N*-arylimidazoles and *N*-arylpyrazoles are subunits found in numerous natural products and in many biologically active pharmaceuticals and recently, in the area of N-heterocyclic carbene chemistry.[1–4] It is therefore important that general methods to synthesize or to modify such compounds are developed. Certain classes of compounds available through these processes include N-arylated azoles,[5] N-arylated oxazolidin-2-ones,[6,7] which are industrially important synthetic targets. One such reaction is the cross-coupling of NH-containing heterocycles with aryl halides to form the respective N-arylated heterocycle (Ullmann coupling). To date, there have been numerous copper-mediated or copper-catalyzed methods published to allow for such a transformation.[8] However, these reports, while significant contributions, generally suffer from important limitations such as high reaction temperatures (often 140 °C or higher), sometimes requiring stoichiometric amounts of copper reagents, long reaction times and showing poor substrate generality.[9,10] Another limitation is that, to date, no single method has found success with each of the major classes of nitrogen heterocycles (imidazoles, pyrroles, pyrazoles, etc.). Recently, the use of C–H bond functionalization via palladium and ruthenium catalysis has been applied to the arylation of several azoles.[11] Those methods provide access to a wide range of azole derivatives, but high temperatures are necessary. Palladium-catalyzed cross-coupling of N–H heterocycles with aryl halides has been moderately successful, but limitations in terms of generality, sensitivity of palladium to the air and moisture, as well as the higher costs have lessened the utility of this method.[12] Buchwald et al. reported the copper-based protocol for the formation of *N*-aryl.[13,14] Most of these methods require Cs_2CO_3, K_3PO_4, K_2CO_3, etc. as a base in a sealed tube. The fact that Cs_2CO_3 has a high sensitivity to moisture reduces its capability 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 array of organic reactions, many of which are staples of synthetic organic chemistry.[15] Its benefits have been achieved by taking advantage of the strongly basic nature of KF/Al_2O_3 which has allowed it to replace organic bases in a number of reactions.[16] In many cases, the use of this base provides milder conditions and simpler procedures than previously reported methods.

We have explored the CuI-catalyzed N-arylation of aryl iodides with imidazole, 4-methylimidazole, pyrrazole and benzimidazole using 1,10-phenanthroline (20 mol%) as a simple ligand and KF/Al_2O_3 as a suitable base in the presence of CuI (20 mol%, Scheme 1).



Scheme 1

The choice of 1,10-phenanthroline as ligand and KF/Al_2O_3 as base in the presence of CuI (20 mol%) was made because we have recently used this system for C–N and C–O bond formation.[17,18]

To find the optimum conditions, we chose the cross-coupling reaction of iodobenzene and imidazole in the presence of 1,10-phenanthroline, KF/Al_2O_3 and CuI in xylene and toluene as solvents at reflux. The yield of *N*-phenylimidazole in xylene after 13 hours was 97% while in toluene after 13 hours the yield was 92%.

Using the above protocol, we subjected a series of aryl iodides to these reaction conditions (Table 1).[19]

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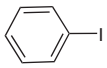
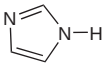
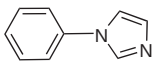
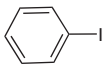
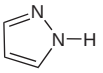
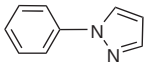
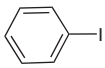
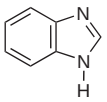
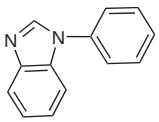
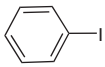
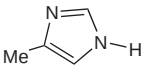
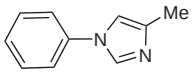
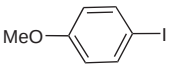
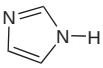
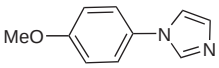
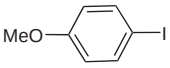
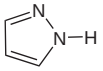
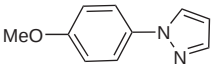
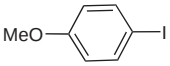
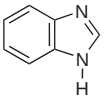
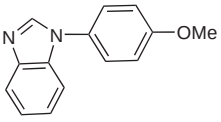
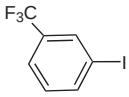
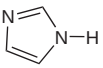
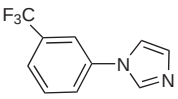
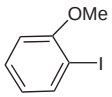
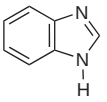
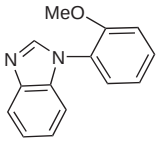
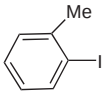
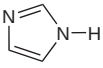
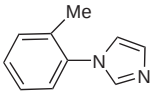
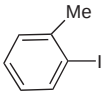
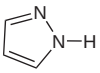
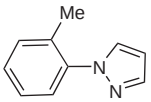
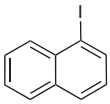
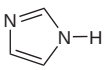
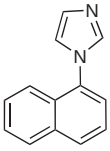
Table 1 The Copper-Catalyzed N-Arylation of Aryl Iodides in the Presence of KF/Al_2O_3

Entry	Aryliodide	Diazole	Product[a]	Time (h)	Yield (%)[b]
1				13	97
2				13	95
3				13	94
4				13	95
5				15	94
6				15	94
7				15	86
8				11	98
9				17	76
10				17	80
11				17	82
12				15	74

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

[b] Isolated yields; products were characterized by ^1H NMR spectroscopy and melting point.

As can be seen in Table 1, imidazole, 4-methylimidazole, pyrrazole and benzimidazole were successfully transformed to their corresponding *N*-aryl compounds. The reaction between these diazoles with iodobenzene gives excellent yields after 13 hours (entries 1–4). Substrates possessing electron-withdrawing groups such as CF_3 in *meta*-position (entry 8) and electron-releasing groups such as OMe (entries 5–7, 9), and Me (entries 10, 11) in the *ortho*- and *para*-position of the aromatic ring also give excellent yield of the corresponding *N*-aryl compounds. The fused compounds such as 1-iodonaphtalene with imidazole also gives excellent yield of the corresponding *N*-aryl compound (entry 12).

In summary, we have developed an experimentally simple and inexpensive catalyst system for the N-arylation of diazoles. We believe that potassium fluoride supported on

alumina (KF/Al_2O_3) provides an excellent complement to the other bases such as Cs_2CO_3 in copper-catalyzed methodology that has already been utilized in a number of applications.

General Procedure

To a solution of diazole (3 mmol) and aryl iodides (1 mmol) in xylene (3 mL) under argon atmosphere were added CuI (38 mg, 20 mol%) and 1,10-phenanthroline (40 mg, 20 mol%) followed by KF/Al_2O_3[20] (5 equiv, 780 mg) and stirred at 130–140 °C for specified times (Table 1). The progress of the reaction was monitored by TLC. The reaction mixture allowed to cool to r.t. and was then partitioned between CH_2Cl_2 (30 mL) and sat. aq NH_4Cl (3×10 mL). The organic phase was washed with H_2O (3×10 mL), dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography on silica gel using hexane–EtOAc as eluent (9:1).

Acknowledgment

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(19) Satisfactory physical and spectral data were obtained in accordance with the structure. Selected physical and spectral data are as follows.
Entry 3: colorless solid; mp 96–98 °C (Lit.[21] 98 °C). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 8.1 (1 H, s), 7.8 (1 H, m), 7.6–7.3 (8 H, m). Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.38; H, 5.20; N, 14.42. Found: C, 80.43; H, 5.14; N, 14.41.
Entry 5: brown solid; mp 60–62 °C (Lit.[9b] 60–61 °C). ^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.7 (1 H, br s), 7.3–7.1 (4 H, m), 7.12 (1 H, s), 6.8 (1 H, s), 3.9 (3 H, s). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.78; N, 16.08. Found: C, 68.71; H, 5.67; N, 16.01.
Entry 6: liquid. ^{1}H NMR (90 MHz, $CDCl_3$): δ = 7.8–7.5 (4 H, m), 7.2–6.9 (2 H, m), 6.5 (1 H, s), 3.9 (3 H, s). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.94; H, 5.78; N, 16.08. Found: C, 68.81; H, 5.56; N, 16.19.
Entry 10: yellow oil. ^{1}H NMR (90 MHz, $CDCl_{3:}$) δ = 7.5 (1 H, s), 7.4–7.1 (5 H, m), 7.1 (1 H, s), 2.2 (3 H, s). Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.73; H, 6.47; N, 17.70. Found: C, 75.91; H, 6.35; N, 17.80.

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