N-Arylation of *N-H* Heterocycles with Aryl Bromides and Aryl Iodides Using CuI and KF/Al_2O_3

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

[a]Faculty of Chemistry, Department of Organic Chemistry, Mazandaran University, Babolsar, Iran,
[b]Faculty of Basic Science, Department of Biology, Mazandaran University, Babolsar, Iran
[c]Islamic Azad University, Ilam, Iran
r.hosseinzadeh@umz.ac.ir

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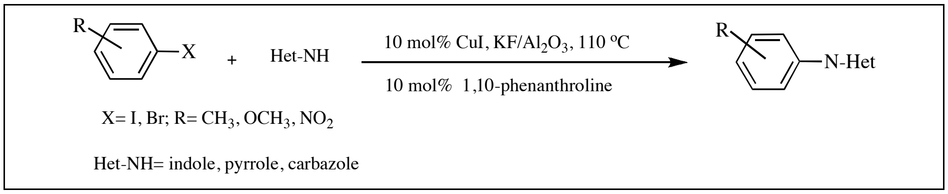

Copper-catalyzed system for *N*-arylation of *N-H* group in heterocycles such as indole, pyrrole and carbazole with aryl iodides and aryl bromides using potassium fluoride supported on alumina as a base is described. This is a simple and efficient method for the coupling of aryl iodides and bromides with *N-H* heterocycles. Different functionalized iodo and bromo arenes were coupled with *N-H* heterocycles using this system.

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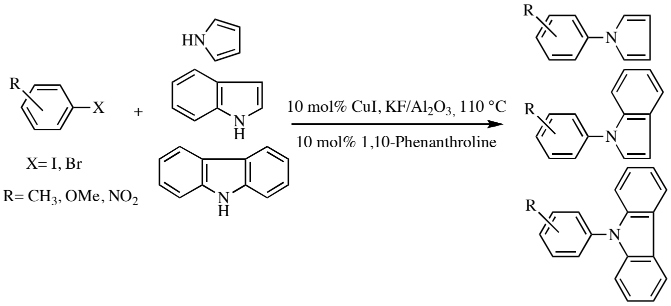
INTRODUCTION

Copper-catalyzed Ullmann-type coupling of aryl halides with *N-H* heterocycles is a traditional choice for preparing *N*-arylpyrroles, *N*-arylindoles, *N*-arylimidazoles and *N*-arylpyrazoles which are important compounds for both pharmaceutical and material sciences [1-3]. For a long time, these reactions had been carried out at high temperatures, and many functional groups could not be tolerated. Therefore, their usage was greatly limited. In addition, these reactions often require the use of stoichiometric amount of copper reagents, long reaction time, which on scale leads to problems of waste disposal [4,5]. Another limitation is that, to date, no single method has found success with each of the major classes of *N-H* heterocycles (imidazoles, pyrroles, pyrazoles, *etc*.). Moreover, several palladium-catalyzed C-N formation methods discovered so far upon using some sterically hindered phosphine ligands, allowed many coupling reactions of aryl halides with N-containing compounds to proceed under relatively mild conditions and low temperature [6,7]. 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 air and moisture, as well as the higher costs have lessened the utility of this method [8,9]. Buchwald *et al*. and other groups reported the copper-based protocol for *N*-arylation using cesium carbonate, potassium phosphate, potassium carbonate, *etc*. as a base in this method [4b,c,6c,8,10-13]. In our procedure we have used potassium fluoride supported on alumina as a base for *N*-arylation of indole, pyrrole and carbazole with aryl bromides and iodides (Scheme 1).

Scheme1



The application of potassium fluoride supported on alumina to organic synthesis has provided new methods for a wide array of organic reactions, many of which are staples of synthetic organic chemistry [14]. Its benefits have been achieved by taking advantages of the strongly basic nature of potassium fluoride supported on alumina which has allowed it to replace organic bases in a number of reactions [15]. In many cases, the use of this base afforded milder conditions and simpler procedures than previously reported methods.

RESULTS AND DISCUSSION

The reaction conditions were optimized using the cross-coupling reaction of iodobenzene and indole in the presence of 1,10-phenanthroline, potassium fluoride supported on alumina and copper iodide in toluene as solvent at 110 °C. The yield of *N*-phenylindole after 7 houre was 90%.

1,10-Phenanthroline as ligand and potassium fluoride supported on alumina as base in the presence of copper iodide were chosen as we have recently used this system for C-N and C-O bond formation in arylation of amides, alcohols, phenols and diazoles [16].

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

Table 1

The copper-catalyzed *N*-arylation of *N-H* heterocyles in the presence of potassium fluoride supported on alumina

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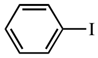
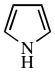
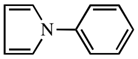
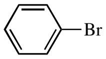
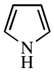
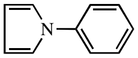
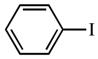
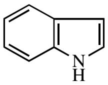
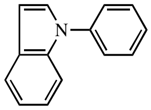
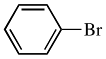
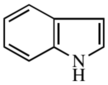
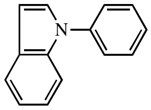
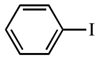
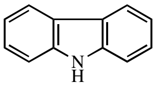
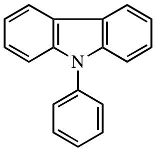
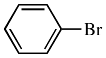
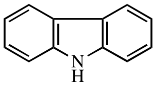
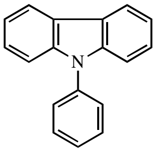
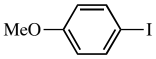
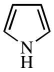
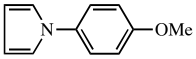
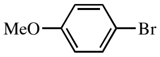
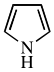
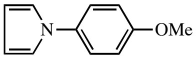
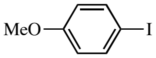
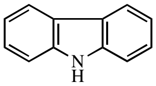
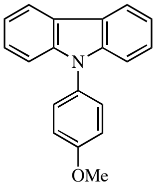
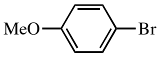
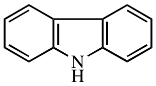
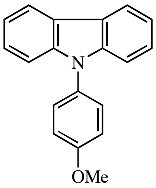
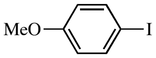
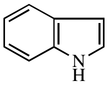
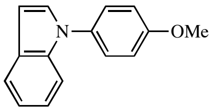
1				8	58-60(62)[4b]	85
2				9	58-60(62)[4b]	81
3				7	Liquid[4b]	90
4				8	Liquid[4b]	86
5				7	87-89(89-90)[19a]	90
6				8	86-89(89-90)[19a]	84
7				9	108-110(112-113) [19b]	85
8				10	108-110(112-113) [19b]	80
9				8	151-153(155-156) [8]	89
10				10	151-153(155-156) [8]	83
11				8	57-59(59.5-60.5) [18]	87

Table 1 (continued)

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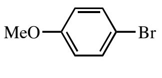
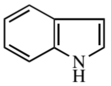
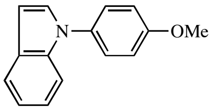
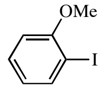
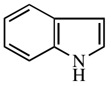
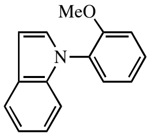
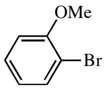
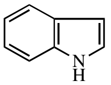
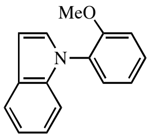
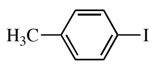
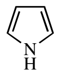
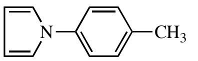
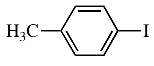
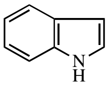
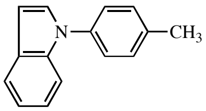
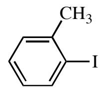
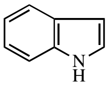
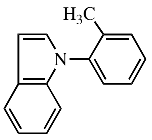
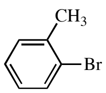
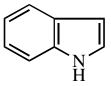
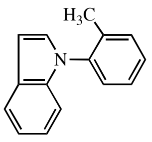
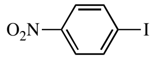
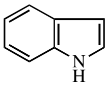
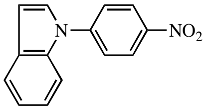
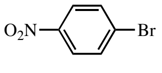
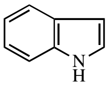
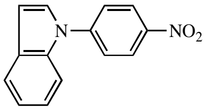
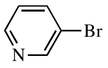
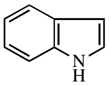
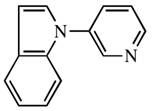
12				9	57-59(59.5-60.5) [18]	84
13				11	Liquid[19c]	78
14				12	Liquid[19c]	73
15				8	81-83(81.5-83)[18]	84
16				7	Liquid[18]	89
17				9	Liquid[19c]	81
18				10	Liquid[19c]	76
19				8	129-131(131-132) [19d]	94
20				9	129-131(131-132) [19d]	89
21				7	Liquid[7d]	91

a] Reaction was performed using 10 mol% of 1,10-phenanthroline as ligand, 1.0 equivalent of aryl halides, 2 equivalent of heterocycle and 5 equivalent of potassium fluoride supported on alumina as base in toluene as solvent at 110 °C .[b] Isolated yields; products were characterized by ^{1}H NMR and from mps.

As can be seen in Table 1, indole, pyrrole and carbazole were successfully transformed to the corresponding *N*-aryl compounds. The reactions between pyrrole and iodo- and bromobenzenes under optimum reaction conditions gave excellent yields of the corresponding *N*-aryl compounds (entries **1, 2**). Under similar reaction conditions indole and carbazole reacted with iodo- and bromobenzenes to give high yields of the *N*-phenylindole and *N*-phenylcarbazole, respectively (entries **3-6**). Aryl halides possessing electron-releasing groups such as methoxy (entries **7-14**), and methyl (entries **15-18**) in the *ortho*- and *para*-positions of the aromatic ring also gave good to excellent yields of the corresponding *N*-aryl compounds. Aryl halides with electron-withdrawing groups such as NO_2 in *para*-position on the reaction with indole also gave a satisfactory yields of the corresponding *N*-aryl compound (entries **19, 20**). 3-Bromopyridine reacted with indole to give a high yield of the *N*-(pyridin-3-yl) compound (entry **21**).

In summary, we have developed an experimentally simple, efficient and inexpensive catalyst system for the *N*-arylation of *N-H* heterocycles. With this protocol both of bromo- and iodo arenes coupled with indole, pyrrole and carbazole successfully. We believe that potassium fluoride supported on alumina provides an excellent complement to other bases such as cesium carbonate, in copper-catalyzed coupling reactions which have already been utilized in a number of applications.

EXPERIMENTAL

General procedure. To a solution of heterocyclic compounds (2 mmol) and aryl bromides or iodides (1 mmol) in toluene (5 mL) under an argon atmosphere were added copper iodide (19 mg, 10 mol%) and 1,10-phenanthroline (20 mg, 10 mol%) and then by potassium fluoride supported on alumina [17] (5 equivalents, 780 mg). The reaction mixture was stirred at 110 °C for the specified time (Table 1). The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allowed to cool to room temperature, filtered and was then partitioned between dichloromethane (30 mL) and saturated aqueous ammonium chloride solution (3×10 mL). The organic fraction was washed with water (3×10 mL), dried (sodium sulfate), filtered and concentrated. The crude product was purified by column chromatography on silica gel using hexane : ethyl acetate (9:1) as eluent to afford the pure product. The spectroscopic data for the known products was identical with the reported data and melting points.

***N*-phenyl indole (Table1, Entry 4).** An oily liquid; [^{1}H nmr (deuteriochloroform), 500 MHz): δ 7.66 (br d, J= 7.3 Hz, 1H), 7.53 (br d, J= 8.1 Hz, 1H), 7.43-7.40 (m, 4H), 7.27-7.24 (m, 2H), 7.20-7.12 (m, 2H), 6.63 (d, J= 3.2 Hz, 1H).

9-(4-methoxy phenyl) carbazole (Table1, Entry 9). A white solid; mp 151–153 °C (Lit.[8] 155-156 °C); [^{1}H nmr (deuteriochloroform), 500 MHz): δ 8.14 (d, J= 7.7 Hz, 2H), 7.46-7.43 (m, 2H), 7.41-7.37 (m, 2H), 7.32 (d, J= 8.1 Hz, 2H), 7.28-7.24 (m, 2H), 7.12-7.08 (m, 2H), 3.91(s, 3H).

***N*-(4-methyl phenyl) pyrrole (Table1, Entry 15).** A solid, mp 81–83 °C (Lit.[18] 81.5-83 °C); [^{1}H nmr (deuteriochloroform), 90 MHz) δ 7.30 (s, 4H), 7.05 (pseudo t, 2H), 6.36 (pseudo t, 2H), 2.40 (s, 3H).

***N*-(4-methyl phenyl) indole (Table1, Entry 16).** A liquid; [^{1}H nmr (deuteriochloroform), 500 MHz): δ 7.67 (br d, J= 7.8 Hz, 1H), 7.51 (d, J= 8.2 Hz, 1H), 7.32 (d, J= 8.2 Hz, 2H), 7.24 (d, J= 3.2 Hz, 1H), 7.23-7.14 (m, 4H), 6.64 (d, J= 3.2 Hz, 1H), 2.43 (s, 3H).

***N*-(3-pyridyl) indole (Table1, Entry 21).** yellow oil, [^{1}H nmr (deuteriochloroform), 90 MHz): δ 8.82 (m, 1H), 8.57 (m, 1H), 7.88-7.12 (m, 7H), 6.72 (d, 1H).

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