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A Novel and Selective Method for the N-Arylation of Indoles Mediated by KF/Al_2O_3[1]

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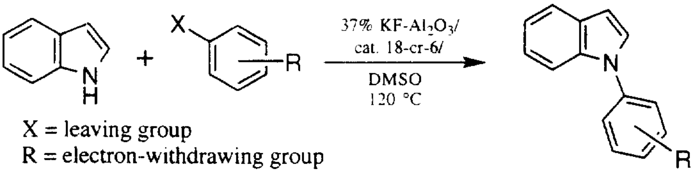
Abstract: *Indole was reacted with aryl electrophiles in the presence of 37% KF/Al_2O_3 and catalytic 18-crown-6 in DMSO at 120 °C to give selectively 1-arylindoles in fair to excellent yield. Electrophiles containing electronically unfavorable substitution patterns or leaving groups, such as 3-chlorobenzonitrile, coupled effectively under the reaction conditions.*

The presence of the N-arylindole subunit in a number of synthetically challenging and medicinally important agents, such as those displaying antiestrogen,[2] analgesic,[3] antidiabetic,[4] antimicrobial,[5] neuroleptic,[6] and antiallergy activity,[7] has renewed efforts in the development of methodology for its synthesis. Strategies for the construction of the N-arylindole moiety include the Ullmann coupling reaction,[8] transition metal-mediated arylation of indoles,[9,10] formation of the indole nucleus with N-aryl containing intermediates,[11] and nucleophilic aromatic substitution.[12,13] The copper-catalyzed coupling of an aryl halide with a heteroatom-based nucleophile, the Ullmann coupling reaction, has remained a standard method for the construction of N-arylindoles. Unfortunately, the use of Ullmann conditions usually leads to difficult purification issues, with concomitant low yields. The Nenitzescu reaction,[11d] and other syntheses based on cyclization, requires difficult and sometimes lengthy processes. Nucleophilic aromatic substitution has been demonstrated to be an effective method for the arylation of indoles. Generally, the method usually requires strong base, and is limited to aryl fluorides with strongly electron-withdrawing ortho and/or para groups.

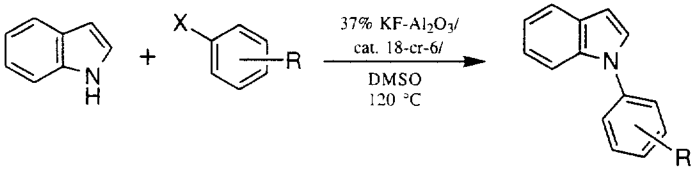
Our laboratory recently reported an alternative to the Ullmann ether synthesis involving the addition of a phenol to 2- or 4-fluorobenzonitriles mediated by potassium fluoride absorbed onto basic alumina, in the presence of a catalytic amount of 18-crown-6, using acetonitrile as solvent.[14] We now wish to report a general and synthetically useful variation of this method for the N-arylation of indoles using DMSO as solvent (Scheme 1). For example, addition of indole to 3-chlorobenzonitrile gave 1-(3-benzonitrile)indole in 60% purified yield (Table, example 4), which demonstrated the ability of the indole nitrogen to displace halogens other than fluoride. Also worth noting is the meta substitution of the cyano group, which inductively activates

Scheme 1



the chlorine towards displacement, yet offers no resonance contribution. In the case of 3-fluorobenzonitrile, KF/Al_2O_3 effectively mediated coupling to the N-1 position of indole (example 2), whereas employment of the conditions of Stabler (potassium carbonate in DMSO),[12] known to be successful with 2- or 4-fluoro-substituted electrophiles, resulted in no reaction. Examination of other electrophile substitution patterns revealed that most functional groups were well tolerated, with the exception of aldehyde (example 15). Esters and nitriles, on occasion, underwent partial hydrolysis, presumably due to small amounts of water present in the reaction medium.

Table. Reaction of indole with substituted aryl electrophiles catalyzed by 37% KF/Al_2O_3 and 18-crown-6 in DMSO at 120 °C.

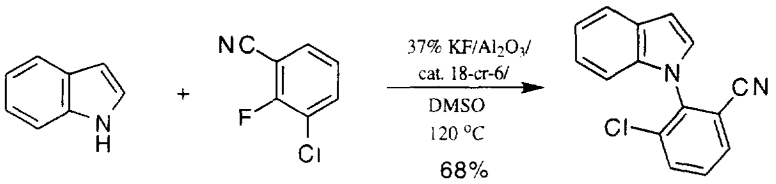


Example	X	R	% Yield
1	F	2-CN	93
2	F	3-CN	78
3	F	4-CN	94
4	Cl	3-CN	60
5	Cl	4-CN	80
6	Br	4-CN	48
7	I	4-CN	27
8	NO_2	4-CN	63
9	CN	4-CN	34
10	OMe	4-CN	8
11	F	4-NO_2	98
12	F	4-SO_2Ph	79
13	F	4-COPh	70
14	F	4-CO_2Et	74
15	F	4-CHO	trace
16	F	4-Ph	62
17	F	4-Br	55
18	F	4-H	33
19	F	4-$CONH_2$	88
20	F	4-COEt	80
21	F	4-CF_3	72

In all cases reaction took place exclusively at the indole N-1 position. It is unlikely that the observed reactivity can be explained solely in terms of a general base-catalyzed process, despite literature precedence demonstrating the various basic species formed within the KF/Al_2O_3 matrix.[15] The operative mechanism may in fact involve the hydrogen bonding of fluoride ion to the indole N-1 hydrogen, allowing for the partial ionization and subsequent nucleophilic aromatic displacement of the leaving group.[16] The qualitative order of reactivity for the leaving group of the electrophile is: fluoro > chloro ~ nitro > bromo > iodo ~ cyano >

methoxy, and is more consistent with nucleophilic aromatic substitution (S_NAr) than a single electron transfer mechanism. In cases where the leaving group is not fluoro, exchange with fluoride is a possible reaction path, however, direct displacement cannot be discounted. Further evidence for an S_NAr mechanism over a benzyne pathway is demonstrated by the observance of a single isomeric product for all examples in the Table, and the result illustrated in Scheme 2, where the di-ortho substituted fluorobenzene is incapable of producing the correct benzyne intermediate.

Scheme 2



In summary, an efficient alternative for the synthesis of N-arylindoles has been developed which features a simple procedure, inexpensive starting materials, general work-up, good to excellent yields, and clearly complements existing strategies.[17] Further research on the scope and limitations of the procedure are ongoing and will be reported shortly.

General Procedure for the N-Arylation of Indoles. The indole (0.33 M) and the aryl halide (0.33 M) in DMSO were heated to 120 °C in the presence of 18-crown-6 (0.03 M) and 37% potassium fluoride absorbed onto basic alumina[18] (1 weight equivalent based on the indole). The reaction progress was monitored by thin layer chromatography. Upon completion, the reaction mixture was filtered and partitioned between water and ethyl acetate. The organic layer was washed with saturated sodium chloride solution, dried over an appropriate desiccant, and concentrated in vacuo. The crude reaction mixture isolated in this manner often required additional purification by silica gel column chromatography.

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