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Synthesis of Diaryl Ethers, Diaryl Thioethers, and Diarylamines Mediated by Potassium Fluoride–Alumina and 18-Crown-6[1]

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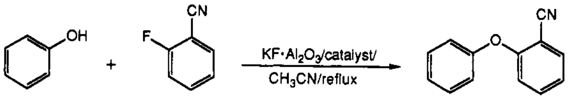
Summary: An efficient alternative to the copper-catalyzed synthesis (Ullmann ether synthesis) of diaryl ethers, diaryl thioethers, and diarylamines involving the potassium fluoride–alumina-mediated addition of a phenol, thiophenol, or an aniline to 2- or 4-fluorobenzonitriles catalyzed by 18-crown-6 is described.

The presence of oxidatively coupled aromatic groups in a number of synthetically challenging and medicinally important natural products (e.g. piperazinomycin,[2] K-13,[3] deoxybouvardin,[4] and combretastatin D-2[5]) has recently prompted an intense reexamination of the standard Ullmann ether synthesis. While the architecturally complex features of these compounds are diverse, methodology development has focused on efficient construction of the diaryl ether subunit. Similarly, the development of diaryl thioether- and diarylamine-containing medicinals such as the 5-HT uptake inhibitor moxifetin[6] and the LTD_4 receptor antagonist SR2640[7] demonstrates the need for further exploration beyond the existing Ullmann-based synthetic repertoire. While the combination of reagents and reaction conditions of the Ullmann ether synthesis often leads to formidable purification problems (accompanied by low and variable yields), nucleophilic addition occasionally provides an effective alternative strategy for diaryl ether,[8] diaryl thioether,[6,9] and diarylamine[10] synthesis. We were intrigued with a recent report detailing the condensation of phenols with a highly activated aryl chloride (2,4-dinitrochlorobenzene) mediated by potassium fluoride–alumina and various phase-transfer catalysts.[11] We have further investigated the nature of this reaction and now report that stoichiometric quantities of potassium fluoride–alumina,[12] together with catalytic quantities of 18-crown-6, effect coupling of phenols, thiophenols, and anilines to 2- and 4-fluorobenzonitriles to produce diaryl ethers, diaryl thioethers, and diarylamines in high yields.

Our initial examination of the condensation of phenol with 2-fluorobenzonitrile entailed the use of 1 wt equiv (based on phenol) of 37% w/w potassium fluoride supported on basic alumina in refluxing acetonitrile together with a catalytic amount (10 mol%) of tetra-*n*-butylammonium bromide (eq 1). 2-Phenoxybenzonitrile was cleanly isolated in 94% chromatographed yield after a reaction time of 168 h (7 days). In contrast, employment of 10 mol% 18-crown-6 (Table I, entry 1) afforded a 98% yield of product in only 48 h. In the latter example, the reaction mixture was simply cooled to room temperature, poured into a separatory funnel with ether, and washed once with water and (after drawing off the sediments) once with saturated potassium chloride solution. Drying of the organic layer (sodium sulfate), filtration, and concentration under reduced pressure provided analytically pure product directly. While the coupling proceeded in the absence of either tetra-*n*-butylammonium bromide or 18-crown-6, the time required to force reaction completion was lengthened significantly. Substitution of an electron-donating group, as in entry 3, again led to near quantitative yield of diaryl ether when catalytic amounts of 18-crown-6 were utilized (the corresponding yield from the standard Ullmann coupling of 3-methoxyphenol and 2-bromobenzonitrile was 43%[13]). As expected, while 2-fluorobenzonitrile and 4-fluorobenzonitrile (entries 2 and 4) provided high yields of product, the use of 3-fluorobenzonitrile generally led to recovered starting materials. Addition of electron-donating and/or electron-withdrawing groups to the fluorobenzonitrile electrophile resulted in a remarkable lack of deviation from the high yield observed for entry 3 (compare to entries 5–9). Even in entry 10, where both an electron-donating and an additional electron-withdrawing group are present on the electrophile, the expected diaryl ether was secured in high yield.



(1)

Variations on the nucleophilic component of the reaction further demonstrated the utility and limitations of potassium fluoride–alumina/18-crown-6 as a mediator of diaryl ether formation. The reaction of 2-*tert*-butylphenol (entry 11) was particularly noteworthy as such sterically crowded substrates are notoriously uncooperative when

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[1] This work has been presented previously: *Abstracts of Papers*, 205th National Meeting of the American Chemical Society, Denver, CO, March 28-April 2, 1993; American Chemical Society: Washington, D.C. Abstract 306.

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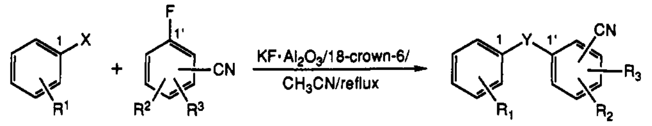
Table I. Coupling of Phenols, Thiophenols, and Anilines to Fluorobenzonitriles



entry	X	R¹	R²	R³	position of CN	reaction time (h)	Y	yield (%)
1	OH	H	H	H	2′	48	O	98
2	OH	H	H	H	4′	72	O	91
3	OH	3-OMe	H	H	2′	72	O	99
4	OH	3-OMe	H	H	4′	72	O	99
5	OH	3-OMe	3′-OMe	H	2′	36	O	99
6	OH	3-OMe	3′-(1-pyrrolyl)	H	2′	18	O	98
7	OH	3-OMe	5′-NO_2	H	2′	18	O	97
8	OH	3-OMe	3′-(4-methylthiophenoxy)	H	2′	18	O	99
9	OH	3-OMe	6′-Cl	H	2′	18	O	98
10	OH	3-OMe	3′-NMe_2	6′-CHO	2′	96	O	91
11	OH	2-*tert*-butyl	H	H	4′	120	O	83
12	OH	4-COOMe	H	H	2′	168	O	83
13	OH	4-NO_2	H	H	2′	336	O	13[a]
14	SH	4-*tert*-butyl	H	H	2′	5	S	93
15	SH	3-OMe	H	H	2′	18	S	99
16	SH	3-OMe	H	H	4′	18	S	95
17	SH	3-OMe	3′-(4-methylthiophenoxy)	H	2′	18	S	98
18	SH	2-Cl	H	H	2′	84	S	91
19	NHMe	H	5′-NO_2	H	2′	18	NMe	71
20	NH_2	4-NO_2	H	H	2′	18	NH	70

[a] Using 5 wt equiv (based on 4-nitrophenol) of $KF·Al_2O_3$. Remainder was recovered starting materials.

normal Ullmann conditions are employed. Coupling of a moderately electron-deficient phenol (methyl 4-hydroxybenzoate) with 2-fluorobenzonitrile (entry 12) also resulted in smooth product formation, although prolonged reaction time was necessary to obtain the highest yield. Unfortunately, 4-nitrophenol proved to be a sluggish reactant even after extended reaction time and utilization of 5 wt equiv of potassium fluoride–alumina (entry 13). Since enhanced phenoxide stabilization by the nitro group would normally be expected (vide infra), it is unlikely that full deprotonation by the potassium fluoride–alumina matrix[14] is operative in phenolic condensations. Rather, comparison of phenol entries 1, 3, 12, and 13 suggests that, with phenols, nucleophilicity is decreased through the addition of electron-withdrawing groups, and that the potassium fluoride–alumina functions more as a proton sponge effecting only partial deprotonation. These results are especially interesting in light of the known preference for nonhindered electron-rich phenols and electron-deficient aryl halides as reactants in Ullmann-type reactions.

We next evaluated the reactivity of thiophenols and anilines toward 2- or 4-fluorobenzonitriles. In general, it was found that thiophenols were more reactive than phenols as reflected in overall reaction times (entries 14–18), a result almost certainly due to the greater nucleophilicity of sulfur. For example, unlike 3-methoxyphenol, 3-methoxythiophenol coupled quantitatively with 2-fluorobenzonitrile to provide the expected product in only 18 h at reflux (entry 15); a similar result was observed for coupling with 4-fluorobenzonitrile (entry 16). A longer reaction time and slightly lower yield was realized with 2-chlorothiophenol, a nucleophile substituted with a mildly electron-withdrawing group (entry 18). While *N*-methylaniline could be successfully coupled to an activated electrophile (entry 19), addition to unactivated electrophiles generally led to complex mixtures, as did the reaction of aniline with 2-fluorobenzonitrile. The addition of 4-nitroaniline to 2-fluorobenzonitrile (entry 20) did provide the expected diarylamine in reasonable yield. Considering the reluctance of aniline to add cleanly to 2-fluorobenzonitrile (vide supra) compared to phenol (entry 1), it is interesting to note that the addition of 4-nitroaniline is a much more facile process than that of 4-nitrophenol (entry 13). Whether or not the addition of electron-deficient anilines to fluorobenzonitriles involves full proton transfer leading to stabilized nitranion formation remains to be confirmed.[10b,15] We did not observe formation of triaryl amines under the reaction conditions employed, a result noted for other base-mediated systems where the concentration of electrophile is relatively low.[10b]

In summary, an efficient alternative to the Ullmann ether synthesis has been developed which features a simple reaction procedure, facile workup, and generally high yields. A further exploration of the scope and limitations of this procedure are in progress and will be reported shortly.

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Supplementary Material Available: Procedures, characterization of data, and copies of selected NMR spectra (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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