Synthesis of Diaryl Ethers, Diaryl Thioethers, and Diarylamines Mediated by Potassium Fluoride−Alumina and 18-Crown-6: Expansion of Scope and Utility[1]

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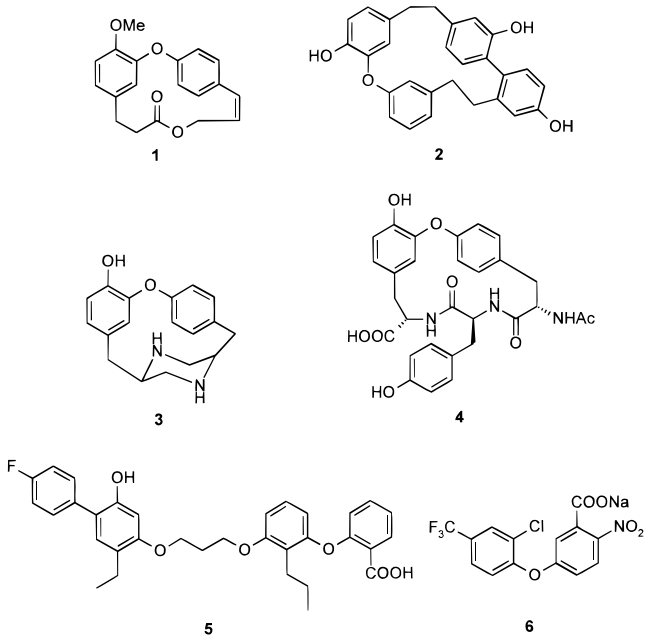
An efficient alternative to the Ullmann ether synthesis of diaryl ethers, diaryl thioethers, and diarylamines involving the S_NAr addition of a phenol, thiophenol, or aniline to an appropriate aryl halide, mediated by potassium−fluoride alumina and 18-crown-6 in acetonitrile or DMSO, is described. Expansion of the reaction conditions to include DMSO as solvent has resulted in a far greater range of substitution patterns permitted on the electrophile. For example, it was found that electronically unfavorable 3-chlorobenzonitrile could be condensed with 3-methoxyphenol to form the corresponding diaryl ether in 66% yield, a combination not normally amenable to Ullmann coupling. Electron-withdrawing groups present on the electrophile may be as diverse as nitro, cyano, formyl, acetyl, ester, amide, and even aryl. The method features a simple reaction procedure that provides products in generally good to excellent purified yields.

Introduction

The presence of the diaryl ether subunit in a number of synthetically challenging and medicinally important natural products (Chart 1) such as combretastatin D-2[2] (**1**, antifungal), riccardin C[3] (**2**, cytotoxin), piperazinomycin[4] (**3**, antifungal), and (−)-K-13[5] (**4**, ACE inhibitor), as well as purely synthetic bioactive agents such as LY293111[6] (**5**, LTB_4 receptor antagonist) and RH6201[7] (**6**, herbicidal), has renewed efforts in the development of versatile methodology for its construction. Examination of the classic Ullmann ether synthesis[2,8] has been complemented by additional strategies including Pummerer-type rearrangements,[9] inter- and intramolecular S_NAr reactions,[10] arene−metal complexes,[11] thallium-promoted oxidative couplings,[12] phenolic additions to cyclohexenone oxides,[13] and Diels−Alder cyclizations.[14] Related methods have been successfully employed in the synthesis of important diaryl thioethers[15] and diaryl-

Chart 1



1 2 3 4 5 6

(1) Portions of this work have been presented at the following conferences: (a) Schmittling, E. A.; Sawyer, J. S. Presented at the 205th National Meeting of the American Chemical Society, Denver, CO, March 28−April 2, 1993. (b) Schmittling, E. A.; Palkowitz, J. A.; Smith, W. J., III.; Sawyer, J. S. *Abstracts of Papers*, 208th National Meeting of the American Chemical Society, Washington, DC, August 21−26, 1994; American Chemical Society: Washington, DC, 1994; ORGN 64. (c) Smith, W. J., III.; Schmittling, E. A.; Sawyer, J. S. *Abstracts of Papers*, 208th National Meeting of the American Chemical Society, Washington, DC, August 21−26, 1994; American Chemical Society: Washington, DC, 1994; ORGN 65.

(2) (a) Deshpande, V. E.; Gohkhale, N. J. *Tetrahedron Lett.* **1992**, *33*, 4213−4216. (b) Boger, D. L.; Sakaya, S. M.; Yohannes, D. *J. Org. Chem.* **1991**, *56*, 4204−4207.

(3) Gottsegen, A.; Vermes, B.; Kajtarperedy, M.; Bihatsikarasai, E.; Nogradi, M. *Tetrahedron Lett.* **1988**, *29*, 5039−5040.

(4) Jung, M. E.; Rohloff, J. C. *J. Org. Chem.* **1985**, *50*, 4909−4913.

(5) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1989**, *54*, 2498−2502.

(6) (a) Sawyer, J. S. *Drugs Future* **1996**, *21*, 610−614. (b) Sawyer, J. S. *Expert Opin. Invest. Drugs* **1996**, *5*, 73−77.

(7) Johnson, W. O.; Kollman, G. E.; Swithenbank, C.; Yih, R. Y. *J. Agric. Food Chem.* **1978**, *26*, 285−287.

(8) (a) Couladouros, E. A.; Soufli, I. C. *Tetrahedron Lett.* **1995**, *36*, 9369−9372. (b) Rao, A. V. R.; Chakraborty, T. K.; Reddy, K. L.; Rao, A. S. *Tetrahedron Lett.* **1992**, *33*, 4799−4802. (c) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1991**, *56*, 1763−1767. (d) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1990**, *55*, 6000−6017. (e) Jung, M. E.; Jachiet, D.; Rohloff, J. C. *Tetrahedron Lett.* **1989**, *30*, 4211−4214. (f) Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063−1072. (g) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1988**, *53*, 487−499.

(9) Jung, M. E.; Jachiet, D.; Khan, S. I.; Kim, C. *Tetrahedron Lett.* **1995**, *36*, 361−364.

(10) (a) Zhu, J. *Synlett* **1997**, 133−144 and references therein. (b) Boger, D. L.; Borzilleri, R. M.; Nukui, S.; Beresis, R. T. *J. Org. Chem.* **1997**, *62*, 4721−4736. (c) Boger, D. L.; Zhou, J. C.; Borzilleri, R. M.; Nukui, S.; Castle, S. L. *J. Org. Chem.* **1997**, *62*, 4721−4736. (d) Beugelmans, R.; Zamora, E. G.; Roussi, G. *Tetrahedron Lett.* **1997**, *38*, 8189−8192. (e) Rao, A. V. R.; Gurjar, M. K.; Lakshmipathi, P., Reddy, M. M.; Nagarajan, M.; Pal, S.; Sarma, B. V. N. B. S.; Tripathy, N. K. *Tetrahedron Lett.* **1997**, *38*, 7433−7436. (f) BoisChoussy, M.; Vergne, C.; Neuville, L.; Beugelmans, R.; Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 5795−5798. (g) Roussi, G.; Zamora, E. G.; Carbonnelle, A.-C., Beugelmans, R. *Tetrahedron Lett.* **1997**, *38*, 4401−4404. (h) Roussi, G.; Zamora, E. G.; Carbonnelle, A.-C., Beugelmans, R. *Tetrahedron Lett.* **1997**, *38*, 4405−4406. (i) Vergne, C.; BoisChoussy, M.; Beugelmans, R., Zhu, J. *Tetrahedron Lett.* **1997**, *38*, 1403−1406. (j) Janetka, J. W.; Rich, D. H. *J. Am. Chem. Soc.* **1997**, *119*, 6488−6495. (k) Boger, D. L.; Zhou, J. *J. Org. Chem.* **1996**, *61*, 3938−3939.

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amines.[16] The genesis of the non-Ullmann methods listed above is rooted in the insidious nature of the copper-catalyzed addition of phenols or phenoxides to an appropriate aryl halide. Frequently in the Ullmann sphere one is confronted with elevated reaction temperatures, formidable purification problems, and low yields, although there are spectacular exceptions to this generalization when considering select intermolecular versions.[8f]

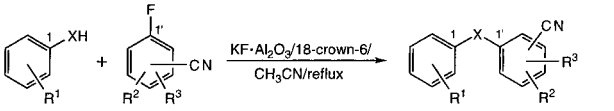
With respect to the S_NAr strategy for the formation of simple diaryl ethers, a survey of the literature reveals a plethora of variations on a very singular theme: the base-catalyzed addition of a phenol to an electron-deficient (usually nitro-containing) electrophile, preferably in a 1,2- or 1,4-substitution pattern. Our interest in this field grew out of a profound dissatisfaction with the Ullmann paradigm and a desire to create a general S_NAr method for the synthesis of diaryl ethers, diaryl thioethers, and diarylamines which would exhibit broad versatility with maximum toleration for sensitive functionality. Originally, we communicated that stoichiometric quantities of potassium fluoride−alumina, together with catalytic quantities of 18-crown-6, effect coupling of phenols, thiophenols, and anilines to 2- and 4-fluorobenzonitriles in refluxing acetonitrile in good to excellent yields.[17] Encouraged by the ease of construction of simple diaryl ethers,[18] we decided to further delineate the scope of our general protocol, particularly in regard to the nature of the solvent and reaction temperature. We now report a full study of the original work together with an extension of the method to encompass new nucleophiles and electrophiles containing diverse functional groups, often in electronically unfavorable patterns.

Results and Discussion

Acetonitrile was the solvent examined in our initial foray. It was found that 1−2.5 wt equiv (based on the nucleophile) of 37% w/w potassium fluoride supported on basic alumina[19] in refluxing acetonitrile is an efficient mediator for promoting the S_NAr addition of phenol to 2-fluorobenzonitrile. In the presence of 10 mol % tetra-*n*-butylammonium bromide, this process resulted in a 94% chromatographed yield of 2-phenoxybenzonitrile after a total reaction time of 7 days. While the rate of the reaction was even slower in the absence of tetra-*n*-butylammonium bromide, a brief survey of readily available reagents quickly led to the selection of 18-crown-6 as the phase transfer catalyst of choice. Under our now standard acetonitrile conditions, the yield of 2-phenoxybenzonitrile was near quantitative after a reaction time of 2 days (Table 1, entry 1). In the case of electronically favorable 2- and 4-fluorobenzonitrile, substitution of the mildly σ electron-withdrawing 3-methoxy group on the nucleophile resulted in high yields of diaryl ether accompanied by somewhat lengthened reaction times (entries 3 and 5). Unsurprisingly, 3-fluorobenzonitrile was inert under these nonforcing conditions (entry 4).[20] It is also interesting to note that the yield of 2-(3-methoxyphenoxy)benzonitrile derived from the classic Ullmann coupling of 3-methoxyphenol with 2-bromobenzonitrile (43%) is substantially inferior to that illustrated in entry 3.[21]

In entries 6−11, 2-fluorobenzonitriles substituted with a variety of electron-donating and/or electron-withdrawing groups were reacted with 3-methoxyphenol over varying (mostly moderate) reaction times. A remarkable lack of deviation from the high yield observed for entry 3 is evident. The utility of the method is further demonstrated by entry 12, where 4-fluorobenzonitrile was successfully condensed with 2-*tert*-butylphenol, a sterically crowded nucleophile notoriously uncooperative when subjected to normal Ullmann conditions. Coupling of a moderately electron-deficient phenol (methyl 4-hydroxybenzoate) with 2-fluorobenzonitrile (entry 13) also re-

Table 1. Coupling of Phenols, Thiophenols, and Anilines to Fluorobenzonitriles in Acetonitrile[17]



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

[a] No reaction observed. [b] Using 5 wt equiv (based on 4-nitrophenol) of $KF{\cdot}Al_2O_3$. Remainder was recovered starting materials.

(11) (a) Pearson, A. J.; Zhang, P. L.; Bignan, G. *J. Org. Chem.* **1997**, *62*, 4536−4538. (b) Pearson, A. J.; Zhang, P.; Lee, K. *J. Org. Chem.* **1996**, *61*, 6581−6586. (c) Pearson, A. J.; Bignan, G.; Zhang, P.; Chelliah, M. *J. Org. Chem.* **1996**, *61*, 3940−3941. (d) Pearson, A. J.; Bignan, G. *Tetrahedron Lett.* **1996**, *37*, 735−738. (e) Pearson, A. J.; Park, J. G.; Zhu, P. Y. *J. Org. Chem.* **1992**, *57*, 3583−3589. (f) Pearson, A. J.; Bruhn, P. R. *J. Org. Chem.* **1991**, *56*, 7092−7097.

(12) (a) Konishi, H.; Okuno, T.; Nishiyama, S.; Yamamura, S.; Koyasu, K.; Terada, Y. *Tetrahedron Lett.* **1996**, *37*, 8791−8794. (b) Inoue, T.; Sasaki, T.; Takayanagi, H.; Harigaya, Y.; Hoshino, O.; Hara, H.; Inaba, T. *J. Org. Chem.* **1996**, *61*, 3936−3937. (c) Suzuki, Y.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 6043−6046. (d) Evans, D. A. Ellman, J. A.; DeVries, K. M. *J. Am. Chem. Soc.* **1989**, *111*, 8912−8914.

(13) (a) Jung, M. E.; Starkey, L. S. *Tetrahedron* **1997**, *53*, 8815−8824. (b) Jung, M. E.; Starkey, L. S. *Tetrahedron Lett.* **1995**, *36*, 7363−7366.

(14) (a) Olsen, R. K.; Feng, X.; Campbell, M.; Shao, R.; Math, S. K. *J. Org. Chem.* **1995**, *60*, 6025−6031. (b) Feng, X.; Olsen, R. K. *J. Org. Chem.* **1992**, *57*, 5811−5812.

(15) (a) Protiva, M. *Drugs Future* **1991**, *16*, 911−916. (b) Hobbs, D. W.; Still, D. W. *Tetrahderon Lett.* **1987**, *28*, 2805−2808.

(16) (a) Gorvin, J. H. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1331−1335. (b) Kulagowski, J. J.; Rees, C. W. *Synthesis* **1980**, 215.

(17) Schmittling, E. A.; Sawyer, J. S. *J. Org. Chem.* **1993**, *58*, 3229−3230.

(18) For pioneer reports detailing the condensation of phenols with highly activated aryl chlorides mediated by potassium fluoride−alumina, see: (a) Kang, R. H.; Zhu, J. S.; Li, W. Z.; Liu, S. R. *Chin. Chem. Lett.* **1990**, *1*, 55−56. (b) Hwang, K.-J.; Park, S. K. *Synth. Commun.* **1990**, *20*, 949−954.

(19) (a) Schmittling, E. A.; Sawyer, J. S. *Tetrahedron Lett.* **1991**, 7207−7210. (b) For a review of organic reactions on alumina, see: Kabalka, G. W.; Pagni, R. M. *Tetrahedron* **1997**, *53*, 7999−8065.

(20) Under the standard acetonitrile conditions, no reaction was also observed when 3-methoxyphenol was reacted with either 2- or 4-chlorobenzonitrile, even after prolonged periods (9 days) and in the presence of large quantities of potassium fluoride−alumina (2.5 wt equiv based on 3-methoxyphenol).

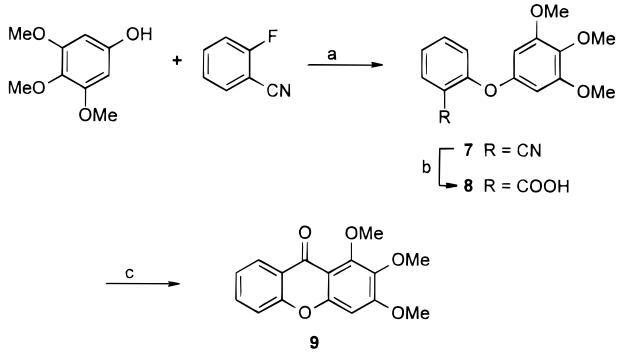
(21) Jackson, W. T.; Froelich, L. L.; Gapinski, D. M.; Mallett, B. E.; Sawyer, J. S. *J. Med. Chem.* **1993**, *36*, 1726−1734.

sulted in smooth product formation, although prolonged reaction time was necessary to secure the maximum yield. Unfortunately, nucleophiles containing strongly electron-withdrawing groups, such as 4-nitrophenol, proved to react sluggishly in acetonitrile even after extended reaction time and utilization of 5 wt equiv of potassium fluoride−alumina (entry 14). Since enhanced phenoxide stabilization by the nitro group would normally be expected, it is unlikely that full deprotonation by the potassium fluoride−alumina matrix[22] is operative in phenolic condensations. Rather, comparison of entries 1, 3, 13, and 14 suggests that, with phenols, nucleophilicity is decreased through the addition of electron-withdrawing groups and that 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 chemistry.

Evaluation of the reactivity of thiophenols and anilines toward 2- or 4-flourobenzonitriles indicated some divergence from purely phenolic couplings. In general, it was found that thiophenols were more reactive as reflected in lower overall reaction times (entries 15−19), a result almost certainly due to the greater nucleophilicity of the mercapto group. For example, unlike 3-methoxyphenol, 3-methoxythiophenol coupled quantitatively with 2-fluorobenzonitrile to provide the expected diaryl thioether in only 18 h at reflux (entry 16, compare to entry 3); a similar result was observed for coupling with 4-fluorobenzonitrile (entry 17, compare to entry 5). A longer reaction time and slightly lower yield was realized with 2-chlorothiophenol, a nucleophile substituted with a mildly electron-withdrawing group (entry 19). While *N*-methylaniline could be successfully coupled to an activated electrophile (entry 20), additions involving 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 21) did provide the expected diarylamine in reasonable yield. Considering the reluctance of aniline to add cleanly to 2-fluorobenzonitrile 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 14).

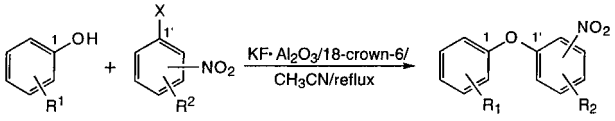
While the examples shown in Table 1 are not exhaustive, the nitrile-substituted products obtained represent useful intermediates suitable for further synthetic manipulation. In a specific example, we have used our basic acetonitrile method in an efficient construction of the key diaryl ether fragment of LY293111 (**5**), a synthesis which originally incorporated an obstreperous Ullmann ether coupling.[23] A further demonstration in the field of xanthanoid synthesis is given in Scheme 1, where 3,4,5-trimethoxyphenol was smoothly added to 2-fluorobenzonitrile to provide diaryl ether **7** in 82% yield. Hydrolysis to acid **8** and subsequent Friedel−Crafts cyclization provided 1,2,3-trimethoxyxanthone, a natural product isolated from the stems and roots of *Polygala arillata*.[24]

Scheme 1[a]



[a] Reaction conditions, reagents and yields: (a) KF·Al_2O_3 (1 wt equiv), 18-crown-6 (10 mol %), acetonitrile, reflux, 96 h, 82%; (b) KOH, 30% H_2O_2, MeOH, EtOH, reflux, 18 h, 87%; (c) P_2O_5, CH_3SO_3H, 18 h, 92%.

Table 2. Coupling of Phenols to Nitrobenzenes in Acetonitrile



entry	R^1	X	R^2	position of NO_2	reaction time (hours)	yield (%)
22	3-OMe	F	H	4'	6	80
23	4-OMe	F	H	4'	18	84
24	H	F	H	4'	1	98
25	4-NO_2	F	H	4'	40	68
26	2-*tert*-butyl	F	H	4'	84	98
27	2-*tert*-butyl	F	H	2'	68	97
28	2-Me	F	H	4'	7.5	97
29	3-Me	F	H	2'	18	86
30	4-OMe	F	4'-Me	2'	30	73
31	4-OMe	F	4'-CF_3	2'	16	56
32	4-OMe	F	5'-F	2'	116	50[a]
33	4-OMe	Cl	H	4'	218	80
34	4-OMe	Br	H	4'	192	72
35	4-OMe	I	H	4'	168	61
36	H	NO_2	H	4'[b]	18	83
37	3-OMe	NO_2	H	3'[c]	84	NR[d]

[a] Major product derives from displacement of the 2-fluoro atom. Remainder (19%) is the bis-substituted product. [b] Electrophile is *p*-dinitrobenzene. [c] Electrophile is *m*-dinitrobenzene. [d] No reaction observed.

The acetonitrile conditions have been conveniently employed to mediate the coupling of phenols to nitrobenzenes containing a variety of leaving groups (Table 2). Reactions carried out with generally neutral phenols and 4-fluoronitrobenzene proceeded with reasonable reaction times and in high yields (entries 22−24). The extreme electrophilicity of 2- and 4-halonitrobenzenes is well documented, and indeed there have been a number of reagents of varying basicity applied to phenolic condensations with great success.[25] However, these examples

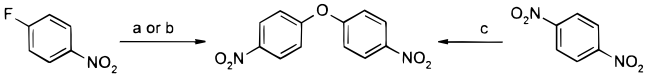
(22) The exact nature of the active basic species present in potassium fluoride−alumina reagents has been the subject of some controversy, see: (a) Ando, T.; Clark, J. H.; Cork, D. G.; Hanafusa, T.; Ichihara, J.; Kimura, T. *Tetrahedron Lett.* **1987**, *28*, 1421−1424. (b) Weinstock, L. M.; Stevenson, J. M.; Tomellini, S. A.; Pan, S.-H.; Utne, T.; Jobson, R. B.; Reinhold: D. F. *Tetrahedron Lett.* **1986**, *27*, 3845−3848.

(23) Sawyer, J. S.; Bach, N. J.; Baker, S. R.; Baldwin, R. F.; Borromeo, P. S.; Cockerham, S. L.; Fleisch, J. H.; Floreancig, P.; Froelich, L. L.; Jackson, W. T.; Marder, P.; Palkowitz, J. A.; Roman, C. R.; Saussy, D. L., Jr.; Schmittling, E. A.; Silbaugh, S. A.; Spaethe, S. M.; Stengel, P. W.; Sofia, M. J. *J. Med. Chem.* **1995**, *38*, 4411−4432.

(24) Ghosal, S.; Banerjee, S.; Chauhan, R. B. P. S.; Srivastava, R. S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 740−743.

(25) (a) Kajimoto, T.; Yahiro, K.; Nohara, T. *Chem. Lett.* **1988**, 1113−1114. (b) Fuchigami, T.; Awata, T.; Nonaka, T.; Baizer, M. M. *Bull. Soc. Chem. Jpn.* **1986**, *59*, 2873−2879. (c) Brunelle, D. J.; Singleton, D. A. *Tetrahedron Lett.* **1984**, *25*, 3383−3386. (d) Wright, J.; Jorgensen, E. C. *J. Org. Chem.* **1968**, *33*, 1245−1246.

Scheme 2[a]

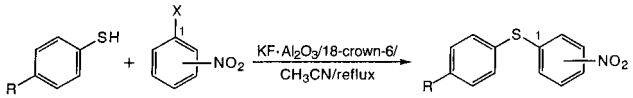


[a] Reaction conditions, reagents and yields: (a) KF·Al_2O_3 (2 wt equiv), 18-crown-6 (10 mol %), acetonitrile, reflux, 110 h, 10%; (b) KF·Al_2O_3 (2 wt equiv), 18-crown-6 (10 mol %), water (4 equiv), acetonitrile, reflux, 144 h, 40%; (c) KF·Al_2O_3 (2 wt equiv), 18-crown-6 (10 mol %), acetonitrile, reflux, 40 h, 11%.

are usually conducted with neutral or electron-rich phenols. In refluxing acetonitrile, potassium fluoride−alumina was found to effectively mediate the addition of 4-nitrophenol, an electron-deficient nucleophile, to 4-fluoronitrobenzene (entry 25). As with entry 13 (Table 1), this is the exact reverse of the nucleophilic electronic demand featured in conventional Ullmann ether syntheses. Similar to fluorobenzonitrile additions, sterically challenged nucleophiles couple well to halonitrobenzenes provided sufficient reaction times are employed (entries 26−27). Entries 28−32 illustrate further examples involving substitutions on the electrophile, including the observation of partial bis coupling of 4-methoxyphenol to 2,5-difluoronitrobenzene (entry 32). Unlike our experience with benzonitriles, nitrobenzenes may be augmented with halogen leaving groups other than fluorine. 4-Chloro-, 4-bromo-, and 4-iodonitrobenzene all reacted with 4-methoxyphenol to produce the expected diaryl ether in good yields, although long reaction times were needed (entries 33−35, compare to entry 23). While addition of phenol to *p*-dinitrobenzene provided easy access to 4-phenoxynitrobenzene (entry 36),[26] the addition of 3-methoxyphenol to electronically unfavorable *m*-dinitrobenzene resulted in no reaction (entry 37). Many different conditions have been used in such nitro displacements for the preparation of diaryl ethers and diarylamines.[27]

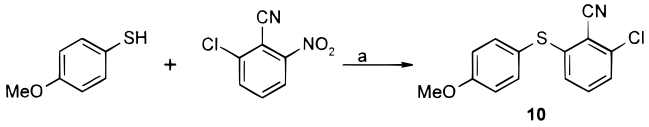
The exact mechanism operative in the case of electrophiles such as 4-chloronitrobenzene is unclear. Clark et al.[28] have demonstrated that over a 24 h period at room temperature 2-chloronitrobenzene undergoes a slow halogen exchange when exposed to a dry fluoride source, in marked contrast to the fast fluorodenitration process that occurs with dinitrobenzenes. This result may explain the lengthy reaction times observed for entry 33 (and possibly entries 34−35), but considering the reaction conditions, a slow, direct nucleophilic displacement of chloro by 4-methoxyphenol cannot be ruled out. Our own attempts to examine potassium fluoride−alumina as a fluoridation agent on 4-chloronitrobenzene were complicated by the observation that 4-fluoronitrobenzene will react under the standard acetonitrile conditions to produce 4-(4-nitrophenoxy)nitrobenzene in low (no added water) to moderate (with added water) yield (Scheme 2). Similar results were observed with *p*-dinitrobenzene. The production of diaryl ethers through the action of metal carbonates and phase transfer catalysts on activated electrophiles such as 2-fluoronitrobenzene has been reported previously.[29] The oxygen source in that example was derived from carbonate, whereas with the potassium fluoride−alumina/acetonitrile conditions it probably originates from potassium hydroxide. While water may effect direct nucleophilic displacement of fluoride from 4-fluoronitrobenzene to form 4-nitrophenol, its role as a simple potassium hydroxide solublizing agent cannot be discounted. In the case of *p*-dinitrobenzene, another mechanism may be operative involving a single fluorodenitration followed by attack of free nitrite anion and subsequent disproportionation to give 4-nitrophenol.[30]

Table 3. Coupling of 4-Substituted Thiophenols to Halonitrobenzenes in Acetonitrile



entry	R	X	position of NO_2	reaction time (hours)	yield (%)
38	*tert*-butyl	F	2	3	99
39	OMe	F	2	2.5	82
40	F	F	2	2	87
41	*tert*-butyl	Br	4	27	81
42	OMe	Br	4	216	81
43	*tert*-butyl	I	4	144	60

Scheme 3[a]



[a] Reaction conditions, reagents and yield: (a) KF·Al_2O_3 (2 wt equiv), 18-crown-6 (10 mol %), DMSO, 60 °C, 5 h, 82%.

Examples of the addition of thiophenols to halonitrobenzenes in refluxing acetonitrile are presented in Table 3. In general, the combination of superb nucleophiles (thiophenols) and electrophiles (halonitrobenzenes) resulted in high yields over short reaction times, as is evidenced by entries 38−40. Good yields could also be realized when using less active electrophiles such as 4-bromo- and 4-iodonitrobenzene over longer reaction periods (entries 41−43). Although several other bases may be used to successfully prepare nitro-substituted diaryl thioethers, few feature the simple reaction conditions and workup inherent with potassium fluoride−alumina in acetonitrile. However, in one subsequent example (the addition of 4-methoxythiophenol to 2-chloro-6-nitrobenzonitrile) it was apparent that use of refluxing acetonitrile, while effective, resulted in a sluggish reaction rate. We therefore turned to DMSO in an attempt to shorten the reaction time of this particular addition and possibly extend the scope of our general method. Using 2 wt equiv of potassium fluoride−alumina in DMSO at 60 °C, coupling smoothly proceeded to completion in only 5 h to give compound **10** (Scheme 3), an intermediate used in the preparation of analogues of the antischistosomal and antitumor agent hycanthone.[31] The preference for displacement of the nitro group is consistent with studies involving the fluorodenitration of

(26) For a discussion of the radical nature of the addition of phenolate to *p*-dinitrobenzene, see: Mir, M.; Espin, M.; Marquet, J.; Gallardo, I.; Tomasi, C. *Tetrahedron Lett.* **1994**, *35*, 9055−9058.

(27) (a) Shevelev, S. A.; Dutov, M. D.; Vatsadze, I. A.; Seruchkina, O. V.; Korolev, M. A.; Rusanov, A. L. *Russ. Chem. Bull.* **1995**, *44*, 384−385. (b) Sammes, P. G.; Thetford, D.; Voyle, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3229−3231. (c) Clark, J. H.; Owen, N. D. S. *Tetrahedron Lett.* **1987**, *28*, 3627−3630. (d) Gorvin, J. H. *J. Chem. Soc., Chem. Commun.* **1985**, 238−239. (e) Williams, F. J.; Donahue, P. E. *J. Org. Chem.* **1977**, *42*, 3414−3419.

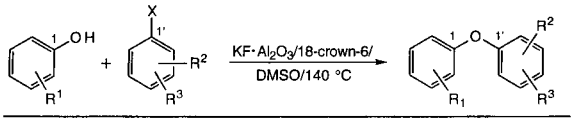
(28) Clark, J. H.; Smith, D. K. *Tetrahedron Lett.* **1985**, *26*, 2233−2236.

(29) Cella, J. A.; Bacon, S. W. *J. Org. Chem.* **1984**, *49*, 1122−1125.

(30) Maggini, M.; Passudetti, M.; Gonzales-Trueba, G.; Prato, M.; Quintily, U.; Scorrano, G. *J. Org. Chem.* **1991**, *56*, 6406−6411.

(31) Archer, S.; Pica-Mattoccia, L.; Cioli, D.; Seyed-Mozaffari, A.; Zayed, A.-H. *J. Med. Chem.* **1988**, *31*, 254−260.

Table 4. Coupling of Phenols to Halobenzenes in DMSO

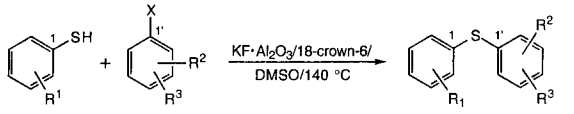


entry	R^1	X	R^2	R^3	reaction time (hours)	yield (%)
44	H	F	4'-CHO	H	16	81
45	3-OMe	F	4'-Ac	H	16	70
46	H	F	4'-COOEt	H	124	82
47	3-OMe	F	4'-COOEt	H	18	65
48	H	F	2'-$CONH_2$	H	48	66
49	3-OMe	F	4'-Br	H	48	36
50	4-OMe	F	3'-CF_3	H	140	38
51	3-OMe	F	4'-Ph	H	172	19
52	H	F	2'-CN	3'-Cl	20	90
53	3-OMe	F	3'-CN	H	6	66
54	2-CN	F	4'-CN	H	18	84
55	2-CN	F	2'-CN	H	36	88
56	4-OMe	Br	4'-CN	H	2	78
57	4-OMe	Cl	4'-CN	H	3	84
58	3-OMe	Cl	3'-CN	H	6	66
59	3-OMe	Cl	4'-CN	H	18	82
60	H	Cl	2'-CN	H	18	68
61	4-OMe	Cl	3'-CN	4'-CF_3	3	69
62	4-OMe	Cl	2'-Cl	4'-CN	16	72

methyl 4-chloro-2-nitrobenzoate (electronically similar to 2-chloro-6-nitrobenzonitrile), where unsupported potassium fluoride was used in DMSO at 130 °C.[32]

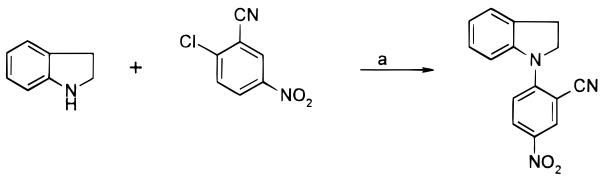
Further exploration of DMSO as a forcing solvent quickly broadened the utility of potassium fluoride−alumina as a mediator of diaryl ether synthesis. By routinely running reactions in DMSO at 140 °C, we were able to couple electrophiles containing electron-withdrawing groups other than cyano or nitro (Table 4). The reactivity of aryl fluorides substituted with formyl (entry 44) or acetyl (entry 45) groups is especially interesting as these may be oxidized to ultimately produce phenols, a transformation which represents a formal coupling of a phenol with an oxygenated electrophile.[33] Addition of phenols to aryl fluorides substituted with esters or amides was also feasible provided sufficient reaction times were allowed and an *ortho* or *para* substitution pattern employed (entries 46−48). Although these diaryl ether products are accessible through the corresponding nitriles, a more direct approach may be preferred synthetically in some instances. We were surprised to find that under the DMSO protocol electrophiles possessing less favorable electron-withdrawing groups and substitution patterns still provided low yields of diaryl ethers (entries 49−50), including the expected product from addition of 3-methoxyphenol to 4-fluorobiphenyl (entry 51). Fluorobenzonitriles were effective electrophiles when exhibiting both favorable (entry 52) and unfavorable (entry 53, compare to Table 1, entry 4) substitution patterns, while 2- and 4-fluorobenzonitrile underwent smooth coupling with electronically unfavorable 2-cyanophenol (entries 54−55). Additions of phenols to bromo- and chlorobenzonitriles were equally effective (entries 56−62), including that of 3-methoxyphenol to 3-chlorobenzonitrile, which produced the expected product in 66% yield (entry 58). The only apparent downside to the substitution of DMSO for acetonitrile in diaryl ether or thioether formation is the higher temperature

Table 5. Coupling of Thiophenols to Halobenzenes in DMSO



entry	R^1	X	R^2	R^3	reaction time (hours)	yield (%)
63	3-OMe	F	2'-CN	H	8	96
64	4-OMe	F	3'-CN	H	4	81
65	3-OH	F	2'-CN	H	12	91
66	4-OMe	Cl	4'-CN	H	12	91
67	4-OMe	Cl	2'-CN	3'-Me	8	72
68	4-OMe	Cl	2'-CN	4'-CF_3	4	88
69	4-OMe	F	2'-$CONH_2$	H	24	85
70	4-OMe	F	4'-$CONH_2$	H	60	66
71	4-OMe	F	4'-COOEt	H	48	81
72	4-F	F	4'-COOEt	H	4	36

Scheme 4[a]



11

[a] Reaction conditions, reagents and yield: (a) $KF·Al_2O_3$ (2 wt equiv), 18-crown-6 (10 mol %), DMSO, 140 °C, 18 h, 82%.

range afforded by the former, a potential problem with thermally sensitive substrates. This appears to be more than offset by the broadened scope of the reaction. Formation of diaryl thioethers was also found to be significantly accelerated in DMSO (Table 5), where little differentiation was seen between thiophenolic additions to 2-, 3-, or 4-halobenzonitriles (entries 63−68). As in the diaryl ether examples, ester and amide also served as a functional electron-withdrawing group on the electrophile (entries 69−72).

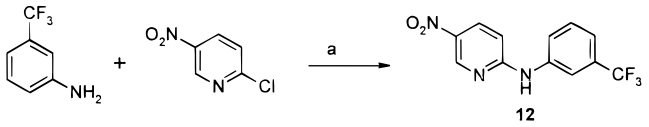
Attempts to extend the DMSO variation to anilines has met with mixed success. While the N-arylation of indole mediated by potassium fluoride−alumina has proven to be a facile process,[34] general diarylamine formation is still problematical. However, it was possible to add indoline to a highly activated electrophile using the DMSO variation to provide the expected product in good yield (Scheme 4). This result is consistent with entry 20 (Table 1), where an *N*-alkylaniline could be coupled in refluxing acetonitrile to an activated electrophile in good yield. Furthermore, we have found that primary anilines may be efficiently added to activated compounds such as 2-chloro-5-nitropyridine under DMSO conditions (Scheme 5), a result that fully compliments the original synthesis of 2-aryloxypyridines using potassium fluoride−alumina.[18b] We conclude that the challenges posed by diarylamine synthesis represent fertile ground ripe for further exploration.

Conclusions

In this paper we have described a useful method for the facile preparation of diaryl ethers, diaryl thioethers, and diarylamines. The method originally developed

(32) Beaumont, A. J.; Clark, J. H.; Boechat, N. A. *J. Fluorine Chem.* **1993**, *63*, 25−30.
(33) Yeager, G. W.; Schissel, D. N. *Synthesis* **1991**, 63−68.
(34) Smith, W. J., III.; Sawyer, J. S. *Tetrahedron Lett.* **1996**, *37*, 299−302.

Scheme 5[a]



[a] Reaction conditions, reagents and yield: (a) $KF{\cdot}Al_2O_3$ (1.0 wt equiv), 18-crown-6 (10 mol %), DMSO, 140 °C, 18 h, 86%.

involving the use of potassium fluoride−alumina, 18-crown-6, and refluxing acetonitrile has proven to be highly effective in mediating the condensation of phenols, thiophenols, and certain anilines with fluorobenzonitriles and halonitrobenzenes. The discovery that through the use of DMSO the method may be extended to include aromatic nucleophiles and electrophiles possessing unfavorable functionality and substitution patterns proved to be key in demonstrating its true scope. Furthermore, a simple reaction procedure combined with easy workup and generally good to excellent yields make for an attractive alternative to other S_NAr paradigms. Overall the potassium fluoride−alumina method appears to be of broad utility and may find particular application in the construction of synthetically challenging and biologically important diaryl ethers.

Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were determined on a GE QE-300 spectrometer. Analytical data was determined by the Physical Chemistry Department (MC525) of the Lilly Research Laboratories. All reactions were conducted under nitrogen atmosphere with stirring unless otherwise noted.

General Coupling Procedure in Acetonitrile. A mixture of the phenol, thiophenol, or aniline (20 mmol), the electrophile (20 mmol), 18-crown-6 (2.0 mmol), and 37% w/w potassium fluoride−alumina[19a] (1−2.5 g per g of nucleophile) in acetonitrile (35 mL) was refluxed and followed to reaction completion via TLC. The reaction mixture was cooled to room temperature, partitioned between equal parts ether and water, and shaken vigorously. The aqeous layer and alumina sediments were drawn from the funnel, and the resulting organic phase was washed once with a saturated potassium chloride solution. The organic phase was dried (sodium sulfate), filtered, and concentrated in vacuo to provide product. Analytically pure samples could usually be obtained through recrystallization. In cases where further purification was necessary, column chromatography on silica gel eluting with ethyl acetate/hexane mixtures was used.

General Coupling Procedure in DMSO. A mixture of the phenol, thiophenol, or aniline (20 mmol), the electrophile (20 mmol), 18-crown-6 (2.0 mmol), and 37% w/w potassium fluoride−alumina[19a] (2.5 g per g of nucleophile) in DMSO (50 mL) was heated at 140 °C and followed to reaction completion via TLC. The reaction mixture was cooled to room temperature, diluted with ether, and filtered. The resulting solution was placed in a separatory funnel and washed once with water and once with saturated potassium chloride solution. The organic phase was dried (sodium sulfate), filtered, and concentrated in vacuo. Products were purified either through recrystallization or by column chromatography on silica gel eluting with ethyl acetate/hexane mixtures.

2-(3,4,5-Trimethoxyphenoxy)benzonitrile (7). A mixture of 3,4,5-trimethoxyphenol (2.35 g, 12.8 mmol), 2-fluorobenzonitrile (1.55 g, 12.8 mmol), 37% potassium fluoride/alumina (2.4 g), and 18-crown-6 (338 mg, 1.28 mmol) in acetonitrile (25 mL) was refluxed with stirring for 96 h. The mixture was cooled to room temperature, filtered, and diluted with 1 N aqueous sodium hydroxide. The resulting mixture was extracted once with diethyl ether. The organic layer was washed once with saturated sodium chloride solution, dried (sodium sulfate), filtered, and concentrated in vacuo to provide 3.00 g (82%) of the title product as tan needles: mp 103−105 °C. Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30, N, 4.91. Found: 67.10; H, 5.32; N, 4.85.

2-(3,4,5-Trimethoxyphenoxy)benzoic Acid (8). Compound **7** (2.00 g, 7.01 mmol) was dissolved in a hot mixture of methanol (5 mL) and ethanol (20 mL). Potassium hydroxide (8.00 g, 143 mmol) and a 30% hydrogen peroxide solution (8 mL) was added, and the resulting mixture was refluxed with stirring for 18 h. The mixture was concentrated in vacuo, and the residue was dissolved in 5 N aqueous sodium hydroxide. This solution was washed once with ether, acidified with 5 N aqueous hydrochloric acid, and extracted with ethyl acetate. The ethyl acetate layer was separated, dried (sodium sulfate), filtered, and concentrated in vacuo to provide 1.86 g (87%) of the title product as an off-white powder. Anal. Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.40; H, 5.33.

1,2,3-Trimethoxyxanthone (9). Phosphorus pentoxide (3.00 g, 20.8 mmol) was dissolved in methanesulfonic acid (20 mL). Compound **8** (1.60 g, 5.26 mmol) was added, and the resulting solution was stirred at room temperature for 18 h. The mixture was carefully poured over crushed ice, and the resulting precipitate was (2.00 g) filtered. The filtrate was extracted with methylene chloride. The organic layer was separated, dried (sodium sulfate), and filtered to provide additional crude product (0.65 g). The combined crude material was recrystallized from acetone to give 1.38 g (92%) of the title product as a tan solid: mp 117−120 °C: ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 8 Hz, 1 H), 7.67 (t, J = 7 Hz, 1 H), 7.40 (d, J = 8 Hz, 1 H), 7.36 (t, J = 8 Hz, 1 H), 6.76 (s, 1 H), 4.05 (s, 3 H), 4.00 (s, 3 H), 3.93 (s, 3 H); MS−FD *m/e* 286 (p); IR ($CHCl_3$, cm^{-1}) 1651, 1465, 1310. Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.93. Found: C, 67.36; H, 4.99.

2-Chloro-6-(4-methoxythiophenoxy)benzonitrile (10): 82% yield, mp 114−116 °C; ^{1}H NMR ($CDCl_3$) δ 7.51 (d, J = 9 Hz, 2 H), 7.27 (d, J = 7 Hz, 1 H), 7.22 (t, J = 8 Hz, 1 H), 6.99 (d, J = 9 Hz, 2 H), 6.74 (d, J = 7 Hz, 1 H), 3.87 (s, 3 H); MS−FD *m/e* 275 (p), 277; IR ($CHCl_3$, cm^{-1}) 2230, 1592, 1174. Anal. Calcd for $C_{14}H_{10}NClOS$: C, 60.98; H, 3.65; N, 5.08; S, 11.63. Found: C, 61.11; H, 3.71; N, 5.09; S, 11.30.

2-(1-Indolinyl)-5-nitrobenzonitrile (11): 82% yield; ^{1}H NMR ($CDCl_3$) δ 8.51 (d, J = 2 Hz, 1 H), 8.22 (dd, J = 8, 2 Hz, 1 H), 7.65 (d, J = 8 Hz, 1 H), 7.32 (d, J = 7 Hz, 1 H), 7.18 (m, 2 H), 7.02 (t, J = 8 Hz, 1 H), 4.39 (t, J = 7 Hz, 2 H), 3.23 (t, J = 7 Hz, 2 H); MS−FD *m/e* 265 (p); IR ($CHCl_3$, cm^{-1}) 2228, 1571, 1338.

2-[*N*-(3-Trifluoromethylphenyl)amino]-5-nitropyridine (12): 86% yield; ^{1}H NMR (d_6-DMSO) δ 10.40 (s, 1 H), 9.09 (d, J = 2 Hz, 1 H), 8.36 (dd, J = 9, 2 Hz, 1 H), 8.09 (s, 1 H), 7.99 (d, J = 8 Hz, 1 H), 7.59 (t, J = 8 Hz, 1 H), 6.98 (d, J = 8 Hz, 1 H); MS−FD *m/e* 283 (p); IR ($CHCl_3$, cm^{-1}) 1603, 1330, 1292. Anal. Calcd for $C_{12}H_8N_3O_2F_3$: C, 50.89; H, 2.85; N, 14.84. Found: C, 50.70; H, 2.95; N, 14.89.

Acknowledgment. The authors wish to thank members of the Physical Chemistry Group, Lilly Research Laboratories, for providing analytical data.

Supporting Information Available: Spectroscopic data, melting points, and elemental analyses for compounds listed in the tables (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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