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Microwave-assisted Synthesis of Diaryl Ethers from Reactions of Phenols with Nitroaryl Fluorides under Solvent-free Conditions

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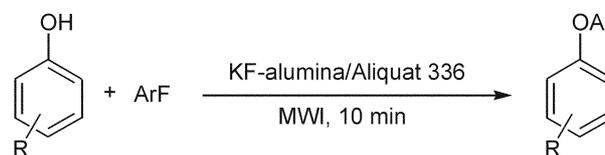
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Diaryl ethers are frequently found in substructures of many biologically important natural products.¹⁻³ Diaryl ethers can be commonly synthesized *via* two general ways which include Ullmann ether synthesis^{4,5} and aromatic nucleophilic substitution (S_NAr) based addition reactions.⁶ In general, classical Ullmann diaryl ether synthesis required high boiling solvents, stoichiometric amount of organocuprate catalyst, and long reaction times.⁷ In recent years, diaryl ether synthesis based on S_NAr addition reactions have received considerable attention.⁶ For example, various diaryl ethers have been synthesized from the method utilizing the reaction of phenols with electron deficient aryl halides in the presence of potassium fluoride-alumina and 18-crown-6.^{8,9} However, in this method the reactions usually required longer reaction times ranged from hours to several days in refluxing acetonitrile which limit its practical utilization.

Recently, microwave-assisted organic synthesis in various solvents as well as under solvent-free conditions have received tremendous investigation.^{10,11} By applying microwave irradiation to certain organic reactions, it is often possible to reduce reaction times from many hours to a few minutes. In addition, recent large demand for environmentally-friendly and less hazardous chemical reaction processes have stimulated the development of clean reactions that avoid use of excess amount of toxic and volatile organic reaction solvents. In particular, microwave-assisted reactions coupled with solvent-free conditions that involve the exposure of neat reactants to microwaves received great attention.¹² This eco-

friendlier technique has many practical advantages over conventional methods in terms of rapid reaction, operational simplicity, cleaner reaction, and increased yield.

A couple of methods for the preparation of diaryl ethers using refluxing solvents under microwave irradiation conditions are recently reported.^{13,14} However, to the best of our knowledge, the only previous example for the microwave-assisted synthesis of diaryl ethers *via* S_NAr based reaction under solvent-free conditions was reported briefly by the reaction of 4-fluoronitrobenzene with phenol in the presence of potassium hydroxide.¹⁵ As part of our ongoing program for the development of microwave-assisted organic reactions, we need to develop an efficient and facile synthetic method for diaryl ethers in solvent-free conditions using microwaves. Herein, we report our preliminary results on the microwave promoted synthesis of diaryl ethers under solvent-free phase transfer catalysis (PTC) conditions. Treatment of phenols with nitroaryl fluorides, KF-alumina and Aliquat 336 under microwave irradiation in a domestic microwave oven provided the corresponding diaryl ethers in high yields. When the reactions were conducted in the absence of the PTC catalyst, the negligible amounts of the diaryl ethers were detected. After careful screening of several phase transfer catalysts (TBAB, 18-crown-6, and



Scheme 1

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Table 1. Synthesis of diaryl ethers under microwave irradiation

Entry	R	Ar	Yield (%) ^a
1	H	4-NO ₂ -C ₆ H ₄	92
2	2-CH ₃	4-NO ₂ -C ₆ H ₄	92
3	2-CH ₃	4-NO ₂ -C ₆ H ₄	90
4	4-CH ₃ O	4-NO ₂ -C ₆ H ₄	92
5	2- <i>tert</i> -butyl	4-NO ₂ -C ₆ H ₄	90
6	2- <i>tert</i> -butyl	4-NO ₂ -C ₆ H ₄	91
7	4-Cl	4-NO ₂ -C ₆ H ₄	87
8	4-NO ₂	4-NO ₂ -C ₆ H ₄	76
9	H	2-NO ₂ -C ₆ H ₄	91
10	2-CH ₃	2-NO ₂ -C ₆ H ₄	90
11	3-CH ₃	2-NO ₂ -C ₆ H ₄	91
12	4-CH ₃ O	2-NO ₂ -C ₆ H ₄	88
13	2- <i>tert</i> -butyl	2-NO ₂ -C ₆ H ₄	88
14	4- <i>tert</i> -butyl	2-NO ₂ -C ₆ H ₄	87
15	4-Cl	2-NO ₂ -C ₆ H ₄	80
16	4-NO ₂	2-NO ₂ -C ₆ H ₄	72

^aIsolated yield.

Aliquat 336) together with various inorganic bases (K₂CO₃, CsF-Celite, and KF-alumina) in microwave promoted arylation reactions, reagents combination of 40% w/w potassium fluoride on alumina with Aliquat 336 (MeOCT₃N⁺Cl⁻) appeared to be the most useful in terms of yield and convenience. Whereas the same arylation reactions with KF-alumina/18-crown-6 in acetonitrile proceeded very sluggishly (1-84 h) as has been shown in the previous study,⁹ the reactions at the present reaction conditions exhibited dramatic rate acceleration. As can be seen in the Table 1, all of the reactions are completed in 10 min with very high yields. Noteworthy among these are very rapid and efficient reactions of bulky 2-*tert*-butylphenol with 2-fluoronitrobenzene and 4-fluoronitrobenzene, which required 68 h and 84 h of reaction times respectively in previous conventional method in solvents (entries **5** and **13**).⁹ Electron deficient phenols such as 4-chlorophenol and 4-nitrophenol were reacted smoothly with aryl fluoride to give the corresponding diaryl ethers (entries **7-8** and **15-16**), which would not proceeded effectively under classical Ullmann type diaryl ether synthesis. These results coupled with environmentally

benign conditions clearly demonstrate the advantage of the present new protocol. In a general reaction procedure, a mixture of the phenol (1.0 mmol), aryl fluoride (1.0 mmol), KF-Alumina (0.44 g), and Aliquat 336 (0.10 g) contained in a test tube placed inside a domestic microwave oven (Samsung RE-50M, 700W). The reaction contents were irradiated in full power intermittently for 60 sec irradiation with 30 sec intervals for ten times. After completion of reaction, the product was extracted with ethyl ether (2 × 30 mL), washed with brine (60 mL), water (3 × 40 mL), and dried over MgSO₄. After evaporation of solvent, the residue was purified by flash column chromatography on SiO₂ (ethyl acetate : hexane = 1 : 3) to afford desired pure diaryl ether.

In summary, diaryl ethers are efficiently prepared by the rapid reaction of phenols with nitroaryl fluorides using combination of microwave activation and solvent-free phase transfer catalysis conditions. We consider this new protocol should provide a better and practical alternative to the existing methods for the diaryl ether synthesis. We are currently investigating the scope of this method in the preparation of the other diaryl ether derivatives.

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