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Microwave-Assisted Synthesis of Diaryl Ethers without Catalyst

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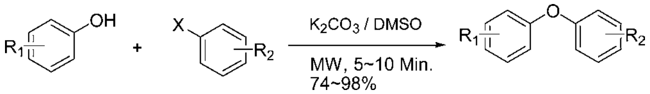
ABSTRACT



Diaryl ethers have been prepared by direct coupling of phenols including those that bear a strong electron-attracting substituent to electron-deficient aryl halides through S$_N$Ar-based addition reactions with assistance of microwave irradiation in high to excellent yields within 5–10 min. No catalysts were required under our conditions.

Diaryl ether motifs are known to be a presence in a variety of natural products and biologically interesting compounds[1] and consequently provide a strong incentive for synthesis. Central to this would be the assembly of the ether linkage. Over the past years, tremendous effort has been devoted to supplanting the classical Ullmann reaction[2] and many valuable new methodologies for diaryl ether formation have been developed.[3,4] An important alternative to the Ullmann method is the nucleophilic S$_N$Ar reaction of activated aryl halides, preferentially in a 1,2- and/or 1,4-substitution pattern, with phenols under basic conditions.[5,6] The other variant, which is more prevalent, features direct coupling of phenols with aryl halides under catalytic effects of Cu(I) or Pd(I) species. Although these advances have largely augmented the synthetic scope, there are still some limitations. For example, phenols can smoothly be converted to diaryl ethers only if no strong electron-withdrawing group is present or if exceedingly strenuous conditions (considerably prolonged reaction time, elevated reaction temperature) are employed, thus limiting the substrates employed and substituents in the products.

Microwave heating has been widely recognized as an efficient synthetic tool and its benefits have been well-documented.[7,8] Loupy has described a solvent free/microwave method for the synthesis of aromatic ethers by the S$_N$Ar reaction of 4-nitro-substituted halogenobenzenes or 2-halonaphthylenes, but only phenol was employed.[8a] Similar results have been achieved by Bogdal, who prepared a range of aromatic ethers by reaction of phenols with primary alkyl halides under microwave heating, however, in the presence of TBAB.[8b] Also Fan has employed the same strategy for the reaction of 1-chloro-4-nitrobenzene and phenolates, affording 4-nitrodiphenyl ethers.[8c] In this Letter, we wish to

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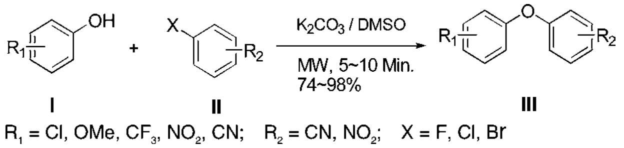
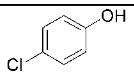
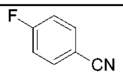
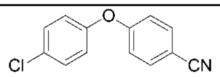
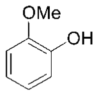
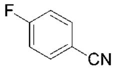
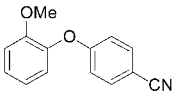
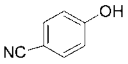
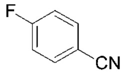
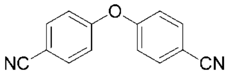
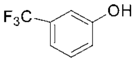
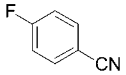
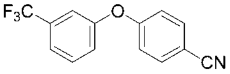
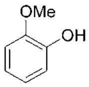
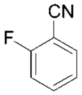
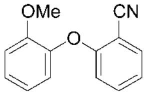
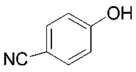
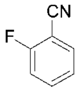
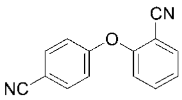
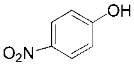
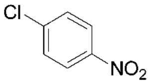
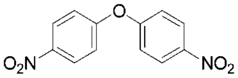
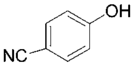
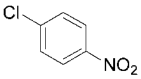
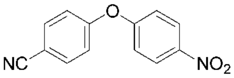
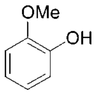
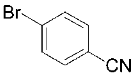
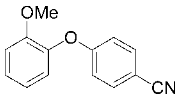
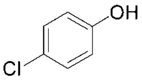
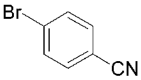
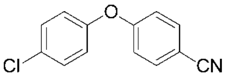
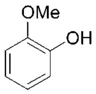
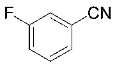
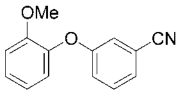
10.1021/ol0346436 CCC: $25.00

Scheme 1



report the microwave-assisted coupling of phenols, including those having a strong electron-withdrawing group, with aryl halides in the presence of potassium carbonate providing diverse diaryl ethers within a few minutes (Scheme 1).[9] A range of phenols were employed to couple with the electron-deficient aryl halides such as mono-halogen substituted benzonitrile and 1-chloro-4-nitrobenzene in the presence of 2 equiv of potassium carbonate under microwave irradiation in DMSO medium and the results are shown in Table 1. In all examples tested, fairly good to excellent yields could be achieved in less than 10 min. This indicates a dramatic reduction in reaction time as compared with the conventional thermal process.[10] For example, under the usual heating conditions, the $KF-Al_2O_3$/18-crown-6-catalyzed coupling of

Table 1. Microwave-Enhanced Synthesis of Diaryl Ethers

entry	phenol (I)	aryl halide (II)	diaryl ether (III)	I:II	reaction time (min.)	isolated yield (%)
1				1 : 1	5	93
2				1 : 1	5	85
3				1.2 : 1	10	87
4				1 : 1	5	86
5				1 : 1	5	94
6				1.2 : 1	10	98
7				1.2 : 1	10	83
8				1.2 : 1	5	95
9				1.2 : 1	10	78
10				1.2 : 1	10	87
11				1.2 : 1	10	74

phenols with 2- or 4-flourobenzonitrile has been reported to require 18−336 h in refluxing acetonitrile and etherification of 2-hydroxybenzonitrile with 4-fluorobenzonitrile requires 36 h for completion of the reaction in DMSO at 140 °C.[5]

Our experiments exhibited that a wide variety of phenols, including highly electron-deficient ones, could be smoothly coupled with aryl halides. As shown in Table 1, treatment of 2- or 4-fluorobenzonitrile with diversely substituted phenols in 10 min under microwave heating led to the formation of the desired aryoxy-substituted benzonitrile in 85% to 98% yields (entries 1−6).

It should be recalled that phenols bearing an electron-withdrawing substituent behave poorly or are completely inert toward diaryl formation. However, under our conditions even the coupling of 1-chloro-4-nitrobenzene with the extremely electron-poor 4-nitrophenol proceeded smoothly leading to satisfactory yields of 4,4′-dinitrodiphenyl ether (entry 7). To the best of our knowledge, 4-nitrophenol has only scarcely been used as the coupling partner affording extremely low yields.[5] Again, the reaction with 4-hydroxybenzonitrile afforded 4-(4-nitrophenoxy)benzenecarbonitrile in a high yield of 95% in 5 min (entry 8).

DMSO is the solvent of choice mainly due to its relatively high boiling point and a high tanδ of the solvent and hence resulting in rapid microwave heating.[11] The effected high temperature may account for the prominent acceleration in the present S_NAr reaction.[12]

Instead of 2- or 4-fluorobenzonitrile, the more readily available 4-bromobenzonitrile can also be employed in the coupling. Thus, the reaction with guaiacol (entry 9) furnished the same diaryl ether as entry 2 and the yields are comparable. Likewise, coupling with 4-chlorophenol led to the formation of the corresponding diaryl ether in 87% yield in 10 min (entry 10).

As can be seen from Table 1, not only 2- or 4-fluorine of aryl halides acted as an ideal leaving group in the coupling reaction (entries 1−6), 3-fluorine did equally well as demonstrated by the reaction between guaiacol and 3-fluorobenzonitrile giving 3-(2-methoxyphenoxy)benzenecarbonitrile as the sole product in 74% yield (entry 11).

Phenols bearing an electron-donating substituent are known to be more favored toward the S_NAr reaction. However, our results using guaiacol are slightly controversial. This might reflect the leveling action of the microwave heating.

It is worth mentioning that all the diaryl ethers formed are stable at high temperature and therefore the dielectric heating has not caused any decomposition problem.

Rather, the reaction under microwave irradiation is very clean and no byproducts have been detected. Therefore, the workup procedure involves only a simple filtration of the precipitation followed by washing with water. In all instances, the products can be obtained in a purity higher than 98% as indicated by GC-MS and ^{1}H NMR analysis.

In conclusion, we have developed a convenient microwave-assisted version of diaryl ether synthesis. The electron-deficient phenols have been shown to be well-tolerated in the coupling process. The simplicity of this short and clean procedure, no use of any catalyst, and generally satisfactory yields render this method particularly attractive. The presence of a diverse range of substituents and functional groups in the diaryl ethers suggests also an opportunity to acquire many other derivatives from these initial diaryl ethers.

Acknowledgment. Financial support from the Foundation for University Key Teacher by the Ministry of Education and the Key Organic Synthesis Laboratory of Jiangsu Province is gratefully acknowledged.

Supporting Information Available: Experimental details concurrent with ^{1}H NMR and GC-MS data of the synthesized diaryl ethers. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) **Typical procedure.** The appropriate aryl halide (10 mmol), the phenol (10−12 mmol), and anhydrous potassium carbonate (20 mmol) were sequentially added to 50 mL of DMSO (A.R. grade without any previous workup). The reaction was found not to be sensitive to air and moisture, hence there was no need for inert atmosphere. With use of a microwave power of 300 W, the reaction mixture was ramped from room temperature to the boiling point of DMSO over 30−40 s, and then held at this refluxing temperature for another 5−10 min until complete consumption of starting material (GC monitoring). After being cooled to room temperature, the resulting mixture was mixed with an ample amount of ice water to precipitate the products and the solution was stirred for 30 min. Normal workup afforded the pure diaryl ether.

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