Synthesis of Diaryl Ethers, Diaryl Sulfides, Heteroaryl Ethers and Heteroaryl Sulfides under Microwave Dielectric Heating

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Abstract: This paper describes the synthesis of diaryl ethers and sulfides by utilizing microwave heating methodology. The methodology is shown to be rapid and efficient for the coupling of phenols or thiophenol with electron-deficient aryl halides through a SNAr reaction. The scope of the protocol can be expanded to six-membered heterocycles bearing a hydroxyl group as well as to the reaction of 2-pyrimidinethiol with mildly activated aryl halides, providing heteroaryl ethers and sulfides, respectively. The advantages of the present method include the wide substrate scope, the obviation of metal catalysts, ease of product isolation, and high purity of products.

Key words: dielectric heating, diaryl ether, diaryl sulfide, synthesis

The diaryl ether moiety is found in a variety of naturally occurring and medicinally significant compounds and the synthesis of this framework has aroused considerable interest.² The classic Ullmann ether synthesis from aryl halides and phenols provides one of the most direct methods for the formation of a diaryl ether linkage,³ the reactivity order is typical of that for nucleophilic substitution, despite the presence of arlyoxycopper(I) reagents ArOCu as intermediates. Although the Ullmann ether synthesis is not fully hampered by electron-donating groups, electron-deficient aryl halides proved to be superior substrates for ether formation. There are some other limitations incurred with the Ullmann ether synthesis, such as the need for harsh reaction conditions and metal catalysts. As such, development of improved conditions has received an ever-increasing interest in recent years,³,⁴ and a need for devising widely applicable and operationally simple variations toward the diaryl ether motif remains.

Significant alternatives to the Ullmann method⁵ may be classified into two categories. One is the aromatic nucleophilic substitution reaction (SNAr) of activated aryl halides with phenols under basic conditions, especially at positions ortho and para to the leaving group. Simple aryl halides behave like vinylic halides, and an electron-attracting group at the meta position does not produce evident activating effect. Sawyer has employed this strategy for the assembly of diaryl ethers in the presence of stoichiometric quantities of KF-alumina together with catalytic quantities of 18-crown-6.⁶ The other useful strategy involves catalytic metal salt mediated coupling of phenols with aryl halides or arylboronic acids as electrophiles, with efforts particularly being concentrated on copper⁴a–⁴e and palladium⁴f–⁴h salts. The second strategy seems to be more flexible in that activating groups on aryl halides are not required, but the reactivity order is still typical of that for nucleophiles despite the presence of the metal salts, however, harsher reaction conditions are required.

The use of microwave heating as a tool for organic synthesis has been a very promising area and microwave-promoted reactions have provided the focus for many research activities.⁷,⁸ The advantages of the microwave method over conventional techniques include the much shortened reaction time, more eco-friendly technique and, in some cases, higher purity of final products than conventional reactions. In our initial communication, we reported a general microwave-assisted preparation of diaryl ethers that constitutes a useful complement to the SNAr strategy.⁹ The microwave enhanced combination of phenols and aryl halides are a desirable extension of other recently reported diaryl ether synthesis techniques¹⁰ in which the substrate scope was restricted to phenols containing no strong electron-accepting groups. Moreover, the reported procedure usually required a metal catalyst.

Heterocyclic analogs of diaryl ethers like Fluazifop-butyl,¹¹ useful as an herbicide in agriculture, are also of much synthetic interest, but reports about this can only occasionally be found in the literature. In 1990, Hwang reported the successful synthesis of phenyl pyridyl ethers promoted by the fluoride ion.¹² Brandsma and co-workers have investigated the reaction of halogenated benzenes or heterocycles with sodium alkoxides using CuBr as a catalyst, by which a number of alkyl aryl and alkyl heteroaryl ethers were formed.¹³ In addition, Wang has described the synthesis of 8-quinolinolyl ethers from 8-hydroxy quinolines and organic halides under PTC and dielectric heating conditions, but only activated alkyl halides were examined.¹⁴ A similar procedure for rapid microwave-assisted synthesis of several 2-hydroxypyphenyl heteroaryl ethers has been reported recently by Kumar.¹⁵

In the present paper, we wish to report the microwave-mediated synthesis of a range of diaryl ethers, diaryl sulfides, heteroaryl ethers, and heteroaryl sulfides. It has been demonstrated that under our conditions, electron-deficient, electronically neutral as well as electron-rich phenols and thiophenols, and also heterocyclic counterparts can successfully be coupled with a variety of activated aryl halides in the absence of a metal catalyst. We have shown
that within a few minutes high conversion rates were obtained under microwave heating in comparison to hours with traditional methods, thereby increasing the substrate scope of the methodology significantly.

The coupling of phenol with 4-fluorobenzonitrile was investigated in our initial foray. The reaction was performed on a 10 mmol scale in an open vessel with heating. DMSO, a typical dipolar aprotic organic solvent, was chosen as the reaction medium due to its high dielectric constant (ε = 46.68 at 25 °C). We found that the reaction proceeds rapidly under microwave irradiation (300 W) using 2 equivalents of anhydrous potassium carbonate as the base and 96% yield of the coupled product 4-phenoxynbenzonitrile was obtained in 5 minutes. To explore the solvent scope, acetonitrile was also tested in this reaction, but it proved to be deleterious, resulting in only a 40% conversion after 10 minutes (GC) and 65% after 20 minutes. Even after 30 minutes, the reaction does not reach completion. With its relatively high boiling point and a high tan δ value, DMSO was adopted as the solvent throughout the present investigations. Microwave heating has resulted in far shorter reaction times than traditional heating for a great range of organic reactions though its nature is not fully understood. The high temperature may account for the prominent acceleration in the present S_NAr reaction.

Synthesis of Aryloxybenzonitrile Using Fluorobenzonitrile

Under our optimal microwave-promoted conditions, the reaction of phenol and 4-fluorobenzonitrile gave almost a quantitative yield of 4-phenoxynbenzonitrile in only five minutes (Table 1, entry 1). This indicates a dramatic reduction in reaction time when compared with conventional heating methodology. Thus, for example, under usual heating conditions, the KF-Al_2O_3 catalyzed coupling of phenols with 2- or 4-fluorobenzonitrile has been reported to require 18–336 hours in refluxing acetonitrile and the etherification of 2-hydroxybenzonitrile with 4-fluorobenzonitrile was not detected from the reaction mixture (Table 1, entry 4). For phenols containing a weak to mildly electron-withdrawing group like -Cl or -Ph on the aromatic ring the reaction proceeds with no difficulty to give the diaryl ether product could be obtained from pentachlorophenol even after microwave irradiation for 15 minutes because the combination of the five chloro atoms diminished the reactivity, thereby reducing the reaction time to 5 minutes. It is not surprising that no coupled product is formed 5 minutes after microwave irradiation for 15 minutes because the substrate affording the respective product in high yield (Table 1, entries 5–7).

<table>
<thead>
<tr>
<th>Entry</th>
<th>R^1</th>
<th>Position of CN</th>
<th>Reaction time (min)</th>
<th>Isolated yield (%)</th>
</tr>
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<td>H</td>
<td>4'</td>
<td>5</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>4-tert-Butyl</td>
<td>4'</td>
<td>5</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>2-tert-Butyl</td>
<td>4'</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>2,6-Di-tert-butyl</td>
<td>4'</td>
<td>15</td>
<td>NR^b</td>
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<tr>
<td>5</td>
<td>2-OMe</td>
<td>4'</td>
<td>5</td>
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<tr>
<td>6</td>
<td>2-OMe</td>
<td>2'</td>
<td>5</td>
<td>94</td>
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<td>9</td>
<td>2-Cl-4-Ph</td>
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<td>4-NO_2</td>
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</tr>
<tr>
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<td>4-CF_3</td>
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<td>62^c</td>
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<tr>
<td>15</td>
<td>2-NO_2</td>
<td>4'</td>
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<td>NR^b</td>
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<tr>
<td>16</td>
<td>3-CF_3</td>
<td>4'</td>
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<td>86</td>
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<tr>
<td>17</td>
<td>2-OMe</td>
<td>3'</td>
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<td>74</td>
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<tr>
<td>18</td>
<td>4-Cl</td>
<td>3'</td>
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<td>81</td>
</tr>
<tr>
<td>19</td>
<td>4-(imidazol-1-yl)</td>
<td>2'</td>
<td>5</td>
<td>98</td>
</tr>
</tbody>
</table>

^a Fluoro-substituted benzonitrile (1 mmol), phenol (1–1.2), K_2CO_3 (2 mmol), DMSO (5 mL), using microwave power of 300 W. The temperature is ramped to the boiling point of DMSO and held there for the time indicated.

^b No reaction observed.

^c Yield by GC.

For phenols containing a weak to mildly electron-withdrawing group like -Cl or -Ph on the aromatic ring the reaction proceeds with no difficulty to give the diaryl ether in high to excellent yields (Table 1, entries 8 and 9) in only five minutes. It is not surprising that no coupled product could be obtained from pentachlorophenol even after microwave irradiation for 15 minutes because the combined effects of the five chloro atoms diminished the
nucleophilicity of the aryloxy considerably (Table 1, entry 10).

To explore the substrate scope of the reaction, we continued the study to encompass phenols containing a strong electron-withdrawing group. This is of much interest considering electron-poor phenols behave sluggishly or are ineffective in $S_N$Ar reactions under conventional heating conditions. Thus, phenols having a cyano, nitro, or trifluoromethyl group were investigated and the results are promising (Table 1, entries 11–16), although somewhat prolonged reaction times (ten minutes) were required to drive the reaction to completion. In the case of 4-cyanophenol the reaction with 2- or 4-fluorobenzonitrile were run with no difficulty to give the coupled diaryl ethers 4-(4'-cyanophenoxy)benzonitrile and 4-(2'-cyanophenoxy)benzonitrile in 87% and 98% yields, respectively (Table 1, entries 11 and 12). The reaction using nitrophenol with 4-fluorobenzonitrile seems to be slightly inconsistent (Table 1, entry 13). When 4-nitrophenol was allowed to react with 4-fluorobenzonitrile under microwave heating for 10 minutes, two more reaction products were isolated besides the desired product 4-(4-nitrophenoxy)benzonitrile (52% yield), namely 4-(4-nitrophenoxy)benzoic acid (5.8%), presumably a hydrolyzed product of the target molecule, and 4-(4'-cyanophenoxy)benzonitrile (8.6%), which is likely to have formed by initial defluorohydroxylation of 4-fluorobenzonitrile and subsequent coupling with itself (Scheme 1). To our knowledge, 4-nitrophenol has only been rarely employed for diaryl ether synthesis and in the reported procedure the reaction did not reach completion affording low product yield.

There was a similar occurrence when 4-fluorobenzonitrile was coupled with 4-trifluoromethylphenol. The reaction was finished in 10 minutes producing a 62% yield of 4-(4-trifluoromethylphenoxy)benzonitrile (GC) and 18% yield of 4-(4-trifluoromethylphenoxy)benzoic acid (GC) (Table 1, entry 14; Scheme 2). The precise factors that govern the abnormal behavior in such instances are unclear.

In marked contrast, the reaction with 2-nitrophenol did not occur under our conditions (Table 1, entry 15). Steric hindrance may be one reason, but here intramolecular hydrogen bonding may also come into play. The solubility of potassium carbonate in DMSO is not sufficiently great and hence the alkalinity of the solution is not strong enough to destroy the hydrogen bond.

On the other hand, when 3-trifluoromethylphenol was subjected to reaction with 4-fluorobenzonitrile, the expected 4-(3-trifluoromethylphenoxy)benzonitrile could be readily obtained in 86% yield in 5 minutes (Table 1, entry 16).

Next we were keen to know if a fluoro group at the meta position on the benzonitrile ring could serve as a leaving group, and so we screened the reaction of 3-fluorobenzonitrile with guaiacol as well as 4-chlorophenol as representatives of phenols possessing diverse groups. We were pleased to find that 3-fluorine substituted benzene reacted equally well under our microwave-DMSO protocol producing the diaryl ethers in moderate to high yields (Table 1, entries 17 and 18).

The wide range of functional group tolerance in this method was further evidenced by the reaction of 4-(imidazol-1-yl)phenol with 2-fluorobenzonitrile, producing 2-[4-(imidazol-1-yl)]phenoxybenzonitrile in almost quantitative yield (Table 1, entry 19).

### Coupling of Phenols with 4-Bromobenzonitrile or 1-Chloro-4-nitrobenzene

Having established that a fluorine atom on the benzene ring works well as a leaving group for the diaryl ether synthesis we were next interested in looking at the possibility of using other kinds of substrates, in considering the fact that fluorobenzenes are generally more expensive than their bromo and chloro counterparts. For this purpose, we...
employed the electron-deficient 4-bromobenzenonitrile and 1-chloro-4-nitrobenzene as substrates to couple with phenols bearing different functional groups. As shown in Table 2, under microwave irradiation for a couple of minutes, both substrates reacted with either electron-rich or electron-poor phenols to produce the expected diaryl ethers in moderate to good yield (Table 2, entries 1–6). The utility of the strategy is further demonstrated by entry 7, where 1-chloro-4-nitrobenzene successfully coupled with 4-nitrophenol leading to 4,4'-dinitrodiphenyl ether in 83% yield after microwave heating for ten minutes. It should be recalled that the results using 4-nitrophenol as a reaction partner in diaryl ether synthesis is generally less satisfactory under conventional classical heating.

### Table 2  Coupling of Phenols to 4-Bromobenzenonitrile or 1-Chloro-4-nitrobenzene

<table>
<thead>
<tr>
<th>Entry</th>
<th>R₁</th>
<th>X</th>
<th>R₂</th>
<th>Reaction time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-OMe</td>
<td>Br</td>
<td>4'-CN</td>
<td>10</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>4-Cl</td>
<td>Br</td>
<td>4'-CN</td>
<td>10</td>
<td>87</td>
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<tr>
<td>3</td>
<td>3-CF₃</td>
<td>Br</td>
<td>4'-CN</td>
<td>10</td>
<td>67</td>
</tr>
<tr>
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<td>4-CN</td>
<td>Br</td>
<td>4'-CN</td>
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<td>65</td>
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<td>4'-NO₂</td>
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<td>7</td>
<td>4-NO₂</td>
<td>Cl</td>
<td>4'-NO₂</td>
<td>10</td>
<td>83</td>
</tr>
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</table>

* Aryl halide (1 mmol), phenol (1–1.2 mmol), K₂CO₃ (2 mmol), DMSO (5 mL), using microwave power of 300 W. The temperature is ramped to the boiling point of DMSO and held there for the time indicated.

**Synthesis of Diaryl Sulfides**

In an attempt to widen the scope of the microwave heating protocol we next examined the behavior of thiophenol in place of phenols. We found that thiophenol can also be coupled with an electron-deficient aryl halide yielding the diaryl sulfide in moderate to high yields under our standard microwave irradiation conditions, as exemplified by the reaction with 2-fluorobenzenonitrile, 4-bromobenzenonitrile, and 1-chloro-4-nitrobenzene. The results are presented in Table 3.

### Table 3  Coupling of Thiophenol with Electron-Deficient Aryl Halides

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R₂</th>
<th>Reaction time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>2'-CN</td>
<td>5</td>
<td>91</td>
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<tr>
<td>2</td>
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<td>4'-CN</td>
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<td>83</td>
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<tr>
<td>3</td>
<td>Cl</td>
<td>4'-NO₂</td>
<td>10</td>
<td>78</td>
</tr>
</tbody>
</table>

* Aryl halide (1 mmol), thiophenol (1–1.2 mmol), K₂CO₃ (2 mmol), DMSO (5 mL), using microwave power of 300 W. The temperature is ramped to the boiling point of DMSO and held there for the time indicated.

**Expansion of the Substrate Scope of the Reaction to Incorporate Hydroxy-Substituted Heterocycles**

Due to the ease of construction of simple diaryl ethers under microwave heating, we decided to widen the scope of our general protocol further. Our study was directed toward introducing an aryloxy group onto some heterocyclic compounds. In comparison to the methods for assembling diaryl ethers such a topic remains a relatively unexplored field. As we have stated, aryloxy-substituted heterocycles are of biological significance. There is, therefore, a distinct need for useful methods that allow the efficient transformation of an OH group to an aryloxy group on heterocyclic rings.

Much to our delight, all the hydroxy-containing heterocycles at hand can couple with a range of electron-deficient aryl halides and the results are garnered in Table 4. The investigations demonstrated that the reaction with suitably activated aryl halides results in the formation of the corresponding aryloxyalkylated heterocycles. The reaction conditions are almost the same as for phenols.

When 7-hydroxy-4-methylcoumarin reacted with 2-fluorobenzenonitrile, the desired product was obtained in 86% yield (Table 4, entry 1). Likewise, 8-hydroxyquinoline can be coupled with different kinds of aryl halides, yielding the aryloxyalkylated compounds in moderate to high yields after 5–10 minutes of microwave heating (Table 4, entries 2–5). We can see from entry 5 that 3-fluorobenzenonitrile can also be coupled with 8-hydroxyquinoline, but this proved less reactive affording lower product yield.

The OH group may also reside on the nitrogen-containing ring of quinoline systems, although the reaction seems to call for an electron-donating group like methyl to enhance the reactivity of the involved heterocyclic O-nucleophile. This was illustrated by the reaction of 2-methyl-4-quinolinol with activated aryl halides (Table 4, entries 6–8). Comparable results were also obtained by using 6-methyl-3-pyridinol affording the expected products in satisfactory yields (Table 4, entries 9–12). Our investigation suggests that the reaction using OH-substituted six-membered heterocycles or fused analogs works equally well with only moderate sensitivity towards electron effects and steric hindrance.
Table 4  Coupling of Hydroxy-Containing Heterocycles with Electron-Deficient Aryl Halides

<table>
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<th>Entry</th>
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<th>Yield (%)</th>
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<td>O</td>
<td>F</td>
<td>O</td>
<td>5</td>
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<td>F</td>
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<td>15</td>
<td>67</td>
</tr>
</tbody>
</table>

* Aryl halide (1 mmol), hydroxylated heterocycle (1–1.2 mmol), K₂CO₃ (2 mmol), DMSO (5 mL), using a microwave power of 300 W. The temperature is ramped to the boiling point of DMSO and held there for the time indicated.

* Yields are given for isolated, purified compounds.
Synthesis of 2-Arylthio-Substituted Pyrimidines

Finally, we extended the protocol to the synthesis of phenylthio-substituted pyrimidines from which interesting biological activities are solicited. Thus, we screened the reaction of 2-pyrimidinethiol with the following three aryl halides: 2-fluorobenzonitrile, 4-bromobenzonitrile, and 1-chloro-4-nitrobenzene. Again, its reaction proved to be quite successful despite the combined unfavorable electron-withdrawing effects of two pyridine-like nitrogen atoms. The respective 2-arylthio substituted pyrimidines were formed in moderate yields (Table 5).

Table 5 Coupling of 2-Mercaptopyrimidine to Electron-Deficient Aryl Halides

<table>
<thead>
<tr>
<th>Entry</th>
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<th>R</th>
<th>Reaction time (min)</th>
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<tbody>
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<td>1</td>
<td>F</td>
<td>2-CN</td>
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<td>4-CN</td>
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<tr>
<td>3</td>
<td>Cl</td>
<td>4-NO2</td>
<td>10</td>
<td>78</td>
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- Aryl halide (1 mmol), 2-pyrimidinethiol (1–1.2 mmol), K2CO3 (2 mmol), DMSO (5 mL), using a microwave power of 300 W. The temperature is ramped to the boiling point of DMSO and held there for 10 min.
- Yields are given for isolated, purified compounds.

In conclusion, we have reported in this paper a useful method for the rapid preparation of diaryl ethers. The electron-deficient phenols are shown to be well tolerated in the coupling process. The method has been extended to include the synthesis of diaryl sulfides, heteroaryl-aryl ethers and heteroaryl-aryl sulfides, while it was observed that a meta-cyano group in 3-fluorobenzonitrile produces a similar activating effect. Furthermore, the simplicity of this short and clean procedure and generally along with the satisfactory yields render this method particularly attractive. The eradication of any catalysts, especially the heavy metals from the reaction offers another advantage since their contamination of the product is always undesirable and the purification procedure as well as their preparation can be very costly. The presence of a diverse range of substituents and functional groups in the products suggests also an excellent opportunity to acquire many other derivatives from these initial compounds. The present protocol represents an operationally simple substitute for conventional heating methods.

All materials were of commercial quality and were used as received. The product purities were determined by GC-MS analysis. GC-MS data was acquired on a TOP series GC8000 with a FINNIGAN VOYAGER mass selective detector. NMR data were acquired on a Bruker 500 or a Varian 400 spectrometer. 1H and 13C NMR chemical shifts (δ) are reported in ppm relative to TMS as internal standard. Coupling constants (J) are given in Hz. The elemental analyses for C, H, and N were performed on a Carlo Erba 1106 elemental analyzer. Melting points were uncorrected. All reactions were carried out in a domestic microwave oven that had been modified according to Mingsos and Baghurst’s technique to allow safe refluxing without a build-up of pressure and allow for the escape of volatiles. The upper wall of the oven was holed for connecting the condenser and the reaction vessel. The key lay in that the water-cooled reflux condenser was located completely outside the microwave cavity since the circulating water coolant could absorb microwaves strongly. The reactions were monitored by TLC coated with silica gel. Separations and purifications (if necessary) were performed by flash chromatography on silica gel (200–300 mesh) columns. All new compounds were characterized by 1H and 13C NMR spectroscopy, MS spectroscopy, and elemental analyses.

Microwave-Assisted Reactions; General Procedure

An aryl halide (ArX, 10 mmol), phenol, thiophenol, or hydroxylated heterocycle (Het-OH) (10–12 mmol) and K2CO3 (20 mmol) were sequentially added to DMSO (50 mL). The reaction was found to be not sensitive to air and moisture, hence there was no need for an inert atmosphere. Using microwave power of 300 W the temperature was ramped from r.t. to the bp of DMSO, which took 30–40 s, and was then held there for 5–15 min. A blast shield was used for protection. After completion of the reaction, it was cooled to r.t., put into ice water and stirred for 30 min to precipitate the product. Filtration of the precipitation followed by washing with distilled water afforded the desired products. In cases where further purification was required, recrystallization was performed.

4-Phenoxobenzonitrile (Table 1, entry 1)
Yield: 96%; white solid; mp 45–46 °C.
1H NMR (DMSO-d6): δ = 7.80 (dd, J = 6.8, 2.1 Hz, 2 H), 7.48 (m, 2 H), 7.28 (m, 1 H), 7.14 (m, 2 H), 7.10 (d, J = 6.8 Hz, 2 H).
GC-MS: m/z = 195 (M+).

4-(4-tert-Butyloxy)benzonitrile (Table 1, entry 2)
Yield: 93%; white solid; mp 89–90 °C.
1H NMR (DMSO-d6): δ = 7.83 (d, J = 8.6 Hz, 2 H), 7.48 (d, J = 8.6 Hz, 2 H), 7.08–7.06 (m, 4 H), 1.31 (s, 9 H, t-Bu).
GC-MS: m/z = 251 (M+).

4-(2-tert-Butyloxy)benzonitrile (Table 1, entry 3)
Yield: 77%; white solid; mp 101–102 °C.
1H NMR (DMSO-d6): δ = 7.81 (d, J = 8.7 Hz, 2 H), 7.45 (s, 1 H), 7.26 (m, 1 H), 7.19 (d, J = 7.8 Hz, 1 H), 7.04 (d, J = 8.7 Hz, 2 H), 6.92 (m, 1 H), 1.31 (s, 9 H, t-Bu).
GC-MS: m/z = 251 (M+).

4-(2-Methoxybiphenyl)benzonitrile (Table 1, entry 5)
Yield: 86%; white solid; mp 90–91 °C.
1H NMR (DMSO-d6): δ = 7.78 (dd, J = 6.8, 2.1 Hz, 2 H), 7.31 (t, J = 7.3 Hz, 1 H), 7.24–7.17 (m, 2 H), 7.03 (t, J = 1.0 Hz, 1 H), 6.94 (dd, J = 6.8, 2.1 Hz, 2 H), 3.72 (s, 3 H, OCH3).
GC-MS: m/z = 225 (M+).

2-(2-Methoxybiphenyl)benzonitrile (Table 1, entry 6)
Yield: 94%; white solid; mp 78–80 °C.
1H NMR (DMSO-d6): δ = 7.86–7.82 (m, 1 H), 7.57 (m, 1 H), 7.32–7.29 (m, 1 H), 7.25–7.18 (m, 3 H), 7.04 (t, J = 1.0 Hz, 1 H), 6.63 (d, J = 8.5 Hz, 1 H), 3.74 (s, 3 H, OCH3).
GC-MS: m/z = 225 (M+).

4-(4-Methoxybiphenyl)benzonitrile (Table 1, entry 7)
Yield: 85%; white solid; mp 108–109 °C.
1H NMR (DMSO-d6): δ = 7.86–7.80 (m, 1 H), 7.57 (m, 1 H), 7.32–7.29 (m, 1 H), 7.25–7.18 (m, 3 H), 7.04 (t, J = 1.0 Hz, 1 H), 6.63 (d, J = 8.5 Hz, 1 H), 3.74 (s, 3 H, OCH3).
GC-MS: m/z = 225 (M+).
1H NMR (DMSO-d$_6$): $\delta = 7.81$ (d, $J = 8.8$ Hz, 2 H), 7.12–7.10 (dd, $J = 7.0, 2.1$ Hz, 2 H), 7.03–7.01 (m, 4 H), 3.78 (s, 3 H, OCH$_3$).

GC-MS: $m/z = 225$ (M$^+$).

2-(4-Chlorophenoxy)benzonitrile (Table 1, entry 8)

Yield: 85%; white solid; mp 101–102 °C.

1H NMR (DMSO-d$_6$): $\delta = 7.96$ (d, $J = 2.2$ Hz, 1 H), 7.87 (d, $J = 8.9$ Hz, 2 H), 7.76–7.73 (m, 3 H), 7.50–7.48 (m, 2 H), 7.43–7.41 (m, 2 H), 7.12 (d, $J = 8.9$ Hz, 1 H).

GC-MS: $m/z = 220$ (M$^+$).

4-(2-Chloro-4-phenyloxy)benzonitrile (Table 1, entry 9)

Yield: 95%; yellow solid; mp 154–155 °C.

1H NMR (DMSO-d$_6$): $\delta = 8.31$ (d, $J = 9.2$ Hz, 2 H), 7.96 (d, $J = 8.8$ Hz, 2 H), 7.36–7.26 (m, 4 H).

GC-MS: $m/z = 240$ (M$^+$).

4-(4-Chlorophenoxy)benzonitrile (Table 2, entry 6)

Yield: 95%; yellow solid; mp 154–155 °C.

1H NMR (DMSO-d$_6$): $\delta = 8.36–8.31$ (m, 4 H), 7.70–7.35 (m, 4 H).

GC-MS: $m/z = 260$ (M$^+$).

2-Phenythiobenzonitrile (Table 3, entry 1)

Yield: 91%; white solid; mp 57–58 °C.

1H NMR (DMSO-d$_6$): $\delta = 7.92$ (d, $J = 7.7$, 1.0 Hz, 1 H), 7.65 (t, $J = 1.1$ Hz, 1 H), 7.48–7.45 (m, 6 H), 7.24 (d, $J = 8.0$ Hz, 1 H).

GC-MS: $m/z = 211$ (M$^+$).

4-Phenythiobenzonitrile (Table 3, entry 2)

Yield: 83%; white solid; mp 52–53 °C.

1H NMR (DMSO-d$_6$): $\delta = 7.72$ (dd, $J = 8.7$, 3.0 Hz, 2 H), 7.54 (m, 2 H), 7.50 (m, 3 H), 7.24 (dd, $J = 8.7$, 3.0 Hz, 2 H).

GC-MS: $m/z = 211$ (M$^+$).

4-Nitrodiphenyl Ether (Table 2, entry 7)

Yield: 63%; yellow solid; mp 100–101 °C.

1H NMR (DMSO-d$_6$): $\delta = 8.75$ (d, $J = 7.8$ Hz, 1 H), 6.99 (s, 1 H), 7.14 (d, $J = 7.8$ Hz, 2 H), 7.10 (m, 2 H), 7.02 (m, 2 H), 6.81–6.77 (m, 2 H).

GC-MS: $m/z = 260$ (M$^+$).

7-(2-Cyanophenoxy)-4-methylcoumarin (Table 4, entry 1)

Yield: 86%; yellow solid; mp 164–165 °C.

1H NMR (DMSO-d$_6$): $\delta = 7.97$ (d, $J = 6.8$ Hz, 1 H), 7.85 (d, $J = 8.7$ Hz, 1 H), 7.75 (m, 1 H), 7.42 (m, 1 H), 7.21 (d, $J = 8.4$ Hz, 1 H), 7.14 (d, $J = 2.1$ Hz, 1 H), 7.12 (d, $J = 2.0$ Hz, 1 H), 6.37 (s, 1 H), 2.54 (s, 3 H, CH$_3$).

13C NMR (DMSO-d$_6$): $\delta = 160.09, 158.64, 157.59, 154.84, 153.45, 136.03, 134.86, 127.92, 125.60, 119.85, 118.87, 116.05, 115.37, 113.58, 106.85, 104.38, 18.64.

GC-MS: $m/z = 277$ (M$^+$).

Anal. Calcd for C$_{15}$H$_{14}$NO: (277.28): C, 73.64; H, 4.00; N, 5.05. Found: C, 73.26; H, 3.96; N, 4.85.

5-(2-Cyanophenoxy)quinoline (Table 4, entry 2)

Yield: 91%; yellow solid; mp 155–156 °C.

1H NMR (DMSO-d$_6$): $\delta = 8.85$ (d, $J = 4.0$, 1.6 Hz, 1 H), 8.49 (t, $J = 6.8$ Hz, 1 H), 7.97 (m, 1 H), 7.88 (d, $J = 1.5$ Hz, 1 H), 7.70–7.66 (m, 3 H), 7.47 (m, 1 H), 7.20 (t, $J = 7.6$ Hz, 1 H), 6.56 (d, $J = 8.5$ Hz, 1 H).

13C NMR (DMSO-d$_6$): $\delta = 160.55, 150.63, 149.28, 140.39, 136.39, 134.87, 133.76, 129.75, 126.86, 126.00, 122.54, 122.27, 120.80, 116.27, 115.72, 101.18.

GC-MS: $m/z = 248$ (M$^+$).
Anal. Found: C, 73.91; H, 4.96; N, 13.52.

5-(4-Nitrophenoxy)-2-picoline (Table 4, entry 11)
Yield: 80%; orange solid; mp 164–165 °C.
1H NMR (DMSO-d₆): δ = 8.38 (d, J = 8.5 Hz, 1 H), 7.91 (dd, J = 7.7, 1.5 Hz, 1 H), 7.67 (m, 1 H), 7.37–7.31 (m, 2 H), 6.97 (d, J = 8.5 Hz, 1 H), 2.50 (s, 3 H, CH₃).
13C NMR (DMSO-d₆): δ = 130.14, 155.15, 149.88, 141.30, 135.72, 134.66, 128.13, 124.67, 124.33, 117.41, 116.21, 103.16, 23.76.
GC-MS: m/z = 260 (M⁺).
Anal. Found: C, 68.16; H, 4.29; N, 9.89.

5-(2-Cyanophenoxy)-2-picoline (Table 4, entry 9)
Yield: 74%; yellow oil.
1H NMR (DMSO-d₆): δ = 8.38 (d, J = 2.7 Hz, 1 H), 7.91 (dd, J = 7.7, 1.5 Hz, 1 H), 7.67 (m, 1 H), 7.37–7.31 (m, 2 H), 6.97 (d, J = 8.5 Hz, 1 H), 2.50 (s, 3 H, CH₃).
13C NMR (DMSO-d₆): δ = 130.14, 155.15, 149.88, 141.30, 135.72, 134.66, 128.13, 124.67, 124.33, 117.41, 116.21, 103.16, 23.76.
GC-MS: m/z = 260 (M⁺).
Anal. Found: C, 73.91; H, 4.96; N, 13.52.

5-(4-Cyanophenoxy)-2-picoline (Table 4, entry 10)
Yield: 78%; incubamide solid; mp 78–79 °C.
1H NMR (DMSO-d₆): δ = 8.38 (d, J = 2.5 Hz, 1 H), 7.85 (d, J = 8.8 Hz, 2 H), 7.53 (d, J = 8.4, 2.7 Hz, 1 H), 7.36 (d, J = 8.4 Hz, 1 H), 7.12 (d, J = 8.8 Hz, 2 H), 2.50 (s, 3 H, CH₃).
13C NMR (DMSO-d₆): δ = 161.16, 155.25, 149.49, 149.12, 135.17, 128.88, 124.77, 119.08, 118.28, 105.90, 23.82.
GC-MS: m/z = 260 (M⁺).
Anal. Found: C, 68.16; H, 4.29; N, 9.89.
2-(2-Cyanophenylthio)pyrimidine (Table 5, entry 3)
Yield: 80% yield; incarnadine solid; mp 111–112 °C.

1H NMR (DMSO-d6): δ = 8.66 (d, J = 4.8 Hz, 2 H), 8.28 (d, J = 8.7 Hz, 2 H).
13C NMR (DMSO-d6): δ = 169.80, 158.88, 147.96, 138.57, 135.40, 124.44, 119.25.

GC-MS: m/z = 214 (M+).

Found: C, 61.52; H, 3.22; N, 19.43.

Yield: 87% yield; incarnadine solid; mp 111–112 °C.

2-(2-Cyanophenylthio)pyrimidine (Table 5, entry 1)
Yield: 83% yield; incarnadine solid; mp 114–115 °C.

1H NMR (DMSO-d6): δ = 8.66 (d, J = 4.8 Hz, 2 H), 8.28 (d, J = 8.7 Hz, 2 H).
13C NMR (DMSO-d6): δ = 169.80, 158.88, 147.96, 138.57, 135.40, 124.44, 119.25.

GC-MS: m/z = 214 (M+).

Found: C, 61.52; H, 3.22; N, 19.43.

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References

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