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Rapid microwave-assisted synthesis of phenyl ethers under mildly basic and nonaqueous conditions

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Abstract—A mild method for *O*-alkylation of phenols has been developed using stoichiometric amounts of K_2CO_3 as a base and microwave irradiation. The method is suitable for substrates that are sensitive towards strong bases or hydrolysis, or difficult to extract from an aqueous medium.

Since its first application in 1986,[1] microwave irradiation has found increasing use in organic synthesis.[2] This is not only due to the fact that many reactions proceed significantly faster and more selectively than under thermal conditions, but also because of the ease with which protocols suitable for automated processes used in high throughput schemes or combinatorial chemistry can be adopted.[3]

Typically, ethers are prepared according to the classical Williamson synthesis from an alkyl halide and an alkoxide or phenoxide salt. Hitherto, most microwave protocols developed for the preparation of aliphatic ethers involve a large excess of KOH as a comparatively strong base to deprotonate the poorly acidic alcohol group.[4] Phenols are more acidic than aliphatic alcohols, and therefore a milder base can be applied to bring about the reaction. Under thermal conditions, use of K_2CO_3 was occasionally reported, although these reactions often suffer from long reaction times (up to 72 h).[5] Surprisingly, almost all protocols previously described for alkylation of phenols under microwave irradiation employ a large excess of sodium or potassium hydroxide,[6] often in aqueous medium.[7] Since the hydroxide ion is not only basic but also considerably nucleophilic, side reactions, such as degradation of the alkylating reagent to the corresponding alcohol, can interfere. The reactions are therefore often run as a two-step process with pre-formation of the phenoxide salt and subsequent addition of the alkyl halide. Also many sensitive functional groups present in the substrates can undergo unwanted side reactions (e.g., hydrolysis of nitriles). As a consequence, only substrates that do not contain any functional groups prone to hydrolysis or reaction with bases were used. Other protocols employ high boiling solvents that are difficult to remove (e.g., DMF or glycols),[8] and this can cause problems if the reaction product is not compatible with an aqueous work-up, for example, due to considerable solubility in water. Often, addition of organic phase transfer catalysts is necessary to mediate the reaction.[9] This can lead to contamination of the product or the need for more sophisticated and time consuming work-up procedures, together with overall enhanced process costs.

In our attempts to extend the application range of microwave-assisted methods to more sensitive substrates, and partially water-soluble products bearing glycol-derived side chains, we have found that phenols can be alkylated under microwave conditions in the presence of a stoichiometric amount of the mild base K_2CO_3, and methanol as solvent, in nonaqueous conditions and without the need of a phase transfer catalyst. A typical procedure is described in the References and notes;[10] reaction conditions are given in Table 1 and ^1H and ^{13}C NMR data of the products in Table S1 of the Supplementary data. The target compounds chosen for this work are frequently used as precursors of pharmaceutically relevant compounds,[11] liquid crystalline[12] or polymer materials.[13d,e]

Keywords: Microwave irradiation; Ether synthesis; *O*-alkylation; Potassium carbonate.
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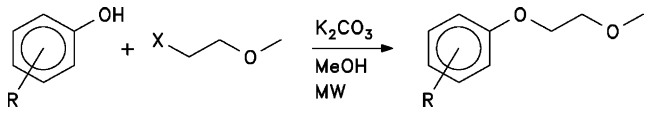
Table 1. Reaction conditions and yields



Entry	R =	pK_a[14]	X = Br			X = Cl		
			T (°C)	Time (min)	Yield (%)	*T* (°C)	Time (min)	Yield (%)
1	4-CHO	7.61	100	15	45	140	30	65
2	3-CHO	8.98	100	15	78	140	30	74
3	2-CHO	8.37	100	15	81	140	30	76
4	4-C≡N	7.97	120	30	87	140	30	96
5	3-C≡N	8.61	120	30	89	140	30	73
6	2-C≡N	6.86	120	30	80	140	30	91

In a recent paper on microwave-assisted methylation of phenols, the use of excess K_2CO_3 in refluxing acetone was suggested.[15] However, at the high temperatures required with the alkylating agents used in our work, acetone undergoes competing aldol reactions with the aromatic aldehyde present in our substrates. Thus, microwave heating of a mixture of 4-hydroxybenzaldehyde and 0.6 equiv of K_2CO_3 in acetone at 140 °C for 30 min produced 24% of *E*-4-(4-hydroxyphenyl)-3-buten-2-one.

Methanol, in contrast, can be used without being alkylated. This is consistent with previous reports on unsuccessful attempts to alkylate aliphatic alcohols in the presence of carbonate as a base.[4a] Use of the weak base in only stoichiometric amounts further assures the mildest conditions and makes the method attractive for base sensitive substrates.

2-Bromoethylmethyl ether was used in close to an equimolar ratio (1.2 equiv), whereas the less reactive 2-chloroethylmethyl ether was applied in a 3-fold excess and required higher reaction temperatures. The hydroxybenzonitriles are slightly less reactive than the corresponding hydroxybenzaldehydes. However, there seemed to be no straightforward relationship between reactivity and pK_a values. This is plausible because the reactivity depends on a delicate balance between the ease of deprotonation and nucleophilicity of the resulting phenoxide. Electron withdrawing substituents in the 2- or 4-positions facilitate deprotonation, as reflected in a lower pK_a value. On the other hand the nucleophilicity of the phenoxide oxygen atom is decreased due to delocalisation of its negative charge into the aromatic ring.

The work-up procedure was designed to avoid water from which the products would have been extracted with difficulty, and only processes that are easily carried out by automated systems were applied. After evaporation of the solvent from the crude reaction mixture, hexane was used to extract selectively the product from the inorganic salts. Residual phenolic starting material is not released from the inorganic solid under these conditions. The hexane can also be recycled and reused. In all cases, the product was obtained in high yield and purity within less than 1 h.

Motivated by a previous report on the use of NaF/K_2CO_3 for alkylation of less sensitive substrates,[16] we also attempted the synthesis of our target compounds under solvent-free conditions on K_2CO_3 as solid support. However, both yield and purity of the products dropped significantly as compared to the reaction in methanol. Also substitution of methanol for the less toxic ethanol led to drastically reduced yields, presumably due to the lower solubility of the K_2CO_3 in the latter (MeOH: 16,500 ppm, EtOH: 904 ppm).

3- And 4-(2-methoxyethoxy)benzaldehydes were synthesised previously under thermal conditions from 2-chloroethylmethyl ether and the corresponding hydroxybenzaldehydes, using K_2CO_3 in refluxing DMF, in yields of 60–75%. However, no detailed information about the reaction conditions, reaction times and work-up procedure were given.[13b,c] Reaction of potassium 4-formylphenoxide with 2-bromoethylmethyl ether in ethanol in a sealed tube required a reaction time of 3 h at 160–170 °C, to provide the product in 50% yield.[13a] 2-(2-Methoxyethoxy)benzonitrile was prepared previously under similarly harsh conditions.[17] In our hands, the thermal reaction in refluxing methanol as solvent, and otherwise equivalent conditions to the ones used for the microwave experiments, required 96 h of reaction time and yielded 40% of 4-(2-methoxyethoxy)benzaldehyde. In the reaction with 4-hydroxybenzonitrile, formation of 4-(2-methoxyethoxy)benzonitrile was below the NMR detection limit under these conditions.

In conclusion, we have introduced a simple and rapid method of microwave-assisted alkylation of phenols using stoichiometric amounts of K_2CO_3 as a mild, cheap and environmentally compatible base. Both reaction and work-up procedures are easy to perform and potentially suited for automated synthesis in high-throughput schemes and combinatorial chemistry. The reaction can be run as a true one-step reaction, without the need of pre-formation of the phenoxide salt prior to addition of the halo compound, and without risk of degradation of the alkylating agent. The mild reaction conditions are compatible with functional groups that are sensitive towards strong bases or hydrolysis. The nonaqueous work-up allows for partially water-soluble products being obtained in high yield, without any loss due to

incomplete extraction. Overall, only a minimum of reagents is used, and there is no need for a phase transfer catalyst that complicates the work-up procedure. With this in mind, the process is also economically and environmentally acceptable.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.08.087. ^{1}H and ^{13}C NMR data of the products are given in Table S1 of the Supplementary data.

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