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Solvent-Free Williamson Synthesis: An Efficient, Simple, and Convenient Method for Chemoselective Etherification of Phenols and Bisphenols

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Abstract: Etherification of phenols with dimethyl- and diethylsulfates and benzyl chloride was performed efficiently in the presence of a suitable solid base, $NaHCO_3$ or K_2CO_3, under solvent-free conditions. The reaction proceeded rapidly at low temperature, and the corresponding ethers were obtained with high purity and excellent yield. Selective etherification of electron-poor phenols in the presence of electron-rich ones and also selective mono-etherification of bisphenols are the noteworthy advantages of this method. This method is environmentally friendly.

Keywords: chemoselective, bisphenols, etherification, phenols, solvent-free

Aromatic ethers are ubiquitous structural units in biologically important molecules such as cyclooxygenase inhibitors,[1] β-galactosidase inhibitors,[2]

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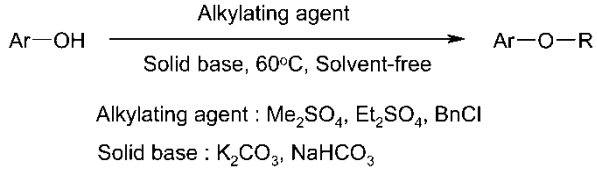
and anticancer porphyrines[3,4] and thus are very important for synthetic organic chemistry.[5]

Direct nucleophilic substitution of an alkyl halide or other alkylating agent with phenols and a base in an aprotic solvent are the most useful methods for the synthesis of aryl ethers.[6–12] Several Ni-,[13,14] Cu-,[15–17] pd-,[18–20] or Fe-catalyzed[21] substitutions of aryl halide with an alcohol were reported. However, these methodologies suffer from one or more disadvantages, such as long reaction times, elevated temperatures, and low yields. Furthermore, selective monoetherification of bisphenols is not easy in the reactions with solvents and is always inevitably accompanied by bietherified products. Recently, Fu and coworkers reported the highly selective vapor-phase O-methylation of catechol with methanol over $ZnCl_2$-modified γ-Al_2O_3catalysts. The reaction was carried out in a fixed-bed reactor at 553 K and under the optimum reaction conditions; the conversion of cathechol and the selectivity for *o*-methoxy phenol were up to 82 and 91% respectively.[22]

Solvent-free organic synthesis for the preparation of small molecule libraries is now routinely applied in pharmaceutical research for the discovery and optimization of lead compounds.[23–26] Solvent-free etherification of phenols that were catalyzed by solid–liquid phase-transfer PEG_{400} has been reported.[27] In this method, the hydroxyl groups of PEG were alkylated, and it is more difficult to remove the ethers of PEG. Also, the long reaction time and high temperature of the reaction are other limitations of this method. Therefore, introduction of an efficient and selective method for etherification of phenols and bisphenols is of practical importance and is still in demand. In this article, we report the results that successfully led to the development of a novel, simple, and convenient method for the transformation of phenols, naphthols, and bisphenols to their corresponding ethers.

A variety of aromatic ethers were synthesized from phenols and naphthols in a solid base at 60°C. Dimethylsulfate, diethylsulfate, and benzyl chloride were used as alkylating agent (Scheme 1). The process in its entirety involves a simple mixing of phenols with solid base under vigorous stirring at 60°C. Then, an alkylating agent was added, and the progress of the reaction was monitored by thin-layer chromatography (TLC). The product was purified by short column chromatography, but in most cases the ethers were obtained very pure.



Scheme 1.

To optimize the best reaction conditions, 4-hydroxy benzaldehyde was treated with diethylsulfate in the presence of various solid bases in the absence of any solvent. Complete conversion took place in 20 min when K_2CO_3 was used as base. One of the other important factors is the rate of mixing of the reaction mixture. However, if the rate of mixing is not high enough, the yield of product decreases and the reaction time increases.

A series of aromatic ethers were synthesized in the presence of K_2CO_3 as base to study the steric and electronic effects of substituent on phenols and naphthols during the reaction. The results are summarized in Table 1. Several points from this table are worth comment. Under the optimized conditions, the etherification reaction was found to be uniformly successful, and expected ethers were furnished in good yields and purity. The reaction proceeds well for both electron-rich and electron-poor phenols. However, quantitative yields of ethers were obtained at lower time during the reaction of phenols with electron-withdrawing substituents such as 2-bromophenol, 3-nitrophenol, and 4-hydroxy benzaldehyde (Table 1, entries 13–20). It must be noted that the competing alkylation of the ring did not occur, and no ring-alkylated by-product in these reactions was seen.

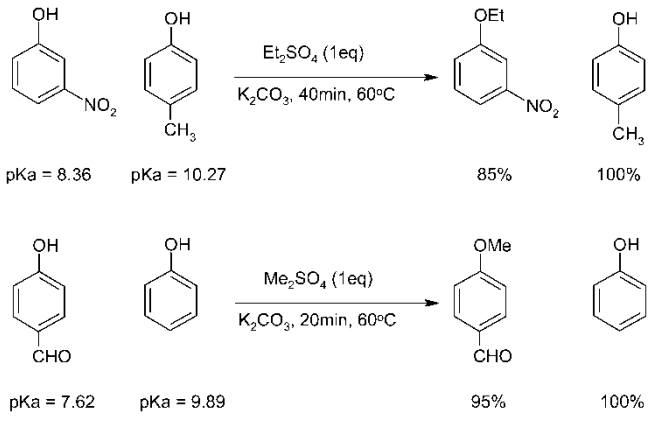
Based on this observation, we conducted a set of competitive etherification reactions between electron-rich and electron-poor phenols, the results of which are shown in Scheme 2. These results show that the presented method is potentially applicable for chemoselective etherification of electron-withdrawing substituted phenols in the presence of electron-donating substituted ones. To show the chemoselectivity of the method for the etherification of different hydroxyl groups, in multifunctional molecules, a number of competitive reactions were performed on some bisphenols (Table 2). According to the obtained results, the hydroxyl with stronger acidity was alkylated better, when the two hydroxyl groups of a bisphenol differ in acidity. For example, the pKa_1 of 2,2′-bisphenol is 8.0 and with a base such as $NaHCO_3$, the corresponding phenoxide was produced (entry 6). For the conversion of the second hydroxyl group ($pKa_2 = 11.32$) to anion, we used K_2CO_3 as a stronger base. In this case, the reaction time of the second step was higher than the first step (entries 7, 8). This is further supported by the fact that we observed a small amount of 2,2′-dimethoxy biphenyl when we used K_2CO_3 as base (Scheme 3). Methylation of 4-hydroxybenzylalcohol showed that only phenolic hydroxyl group was etherified, and the benzyl hydroxyl group did not react even in the presence of extra dimethylsulfate, in agreement with acidity power of hydroxyl groups (entry 5).

In conclusion, a facile route to the etherification of phenols has been demonstrated. This methodology offers significant advantages over other current procedures with regard to yields, mild reaction conditions, excellent chemoselectivity, and easy work-up. The low cost of reagent and the solvent-free reaction conditions are consistent with increasing environmental concerns and will make the present method potentially useful for industrial applications.

Table 1. Etherification results of some phenols in K_2CO_3 at 60°C[a]

Entry	ArOH	ArOR	Time (h)	Yield (%)[b]	Mp (bp)°C	
					Obs.	Lit.[27–29]
1	Phenol	Methoxy benzene	3.5	90	(156)	(156)
2	Phenol	Ethoxy benzene	5.0	87	(172–174)	(171–173)
3	1-Naphthol	1-Methoxy naphthalene	1.5	88	(264–266)	(265–266)
4	1-Naphthol	1-Ethoxy naphthalene	2.0	83	118–119	118–119
5	2-Naphthol	2-Methoxy naphthalene	1.0	90	73–74	72
6	2-Naphthol	2-Ethoxy naphthalene	1.5	86	37–38	37–38
7	4-Methyl phenol	1-Ethoxy-4-methyl benzene	5.0	87	(188–190)	(188–189)
8	3-Methyl phenol	1-Ethoxy-3-methyl benzene	4.5	88	(190–192)	192
9	1,2-Dihydroxy benzene	1,2-Dimethoxy benzene	1.0	82	(206–207)	(206–207)
10	1,1′-Dihydroxy biphenyl	1,1′-Dimethoxy biphenyl	1.5	95	153–155	155
11	1,1′-Dihydroxy binaphthyl	1,1′-Dimethoxy binaphthyl	2.0	92	190–192	190
12	1,4-Dihydroxy benzene	1,4-Dimethoxy benzene	1.5	80	54–56	55–56
13	2-Bromro phenol	1-Bromo 2-methoxy benzene	0.3	94	(210–211)	(210)
14	2-Bromo phenol	1-Bromo 2-ethoxy benzene	0.5	92	(221–223)	(221–223)
15	3-Nitro phenol	1-Methoxy-3-nitro benzene	0.5	90	37–38	38–39
16	3-Nitro phenol	1-Ethoxy-3-nitro benzene	0.75	87	34–36	34
17	3-Nitro phenol	1-Benzyloxy-3-nitro benzene	8.0	78	150–151	150
18	4-Hydroxy benzaldehyde	4-methoxy benzaldehyde	0.3	98	(247–248)	(248)
19	4-Hydroxy benzaldehyde	4-Ethoxy benzaldehyde	0.5	96	(249)	(249)
20	4-Hydroxy benzaldehyde	4-Benzyloxy benzaldehyde	6.0	82	71–73	72–74

[a]The molar ratio of alkylating agent to phenols, naphthols, or bisphenols was 1.5 for entries 1–8, 2.5 for entries 9–12, and 1.0 for entries 13–20.
[b]Isolated yield.



Scheme 2.

EXPERIMENTAL

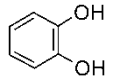
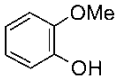
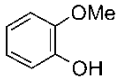
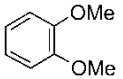
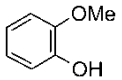
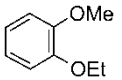
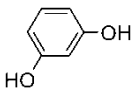
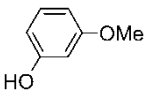
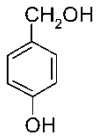
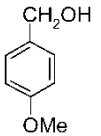
All chemicals were purchased from Merck and Fluka chemical companies. Infrared spectra were recorded on Nicolet (impact 400D model) spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker DRX 500 Avance spectrometer. MS analysis was performed using Saturn 2200 specterometer. Column chromatography was performed using silica gel 60 (230–400 mesh).

General Procedure

A phenol or naphthol (2 mmol) and anhydrous base (1 g) were ground altogether into fine powder and heated at 60°C under vigorous stirring. Alkylating agent (2 mmol) was added and heated under vigorous stirring, and the progress of reaction was monitored by thin-layer chromatography (TLC) (by dissolving the sample in ethyl acetate) until the conversion of phenol was completed. Then, water was added to the mixture, and the solid ether was filtrated and washed with additional water. In the case of liquid ethers, the products were extracted with diethyl ether. The solvent (diethyl ether) was evaporated, and the crude product was purified by short-column chromatography using petroleum ether–ethylacetate as eluent or by recrystallization in ethylacetate-n-hexan (in the case of solid ethers).

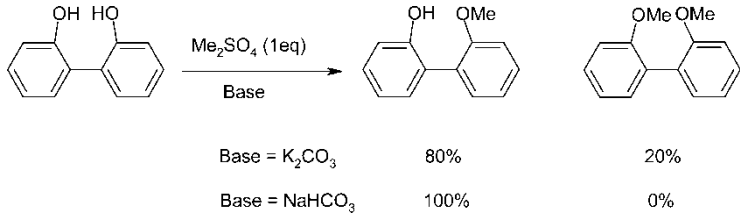
The products were characterized by comparison of their melting point, boiling point, IR, and ^{1}H NMR spectra with those of known compounds,[27–30] except 2-ethoxy 2′-methoxy biphenyl (Table 2, entry 8), which is a new compound. Its spectral analytical data is the following.

Table 2. Chemoselective etherification results of some bisphenols

Entry	ArOH	ArOR	Time (h)	Yield (%)[a]	Condition	Mp (bp)°C	
						Obs.	Lit.[27–30]
1			2.0	82	$NaHCO_3$, 50°C	32–34	32
2			1.0	78	K_2CO_3, 50°C	(206–207)	(206–207)
3			1.0	78	K_2CO_3, 50°C	(207–208)	(207–209)
4			1.0	80	$NaHCO_3$, 50°C	(244)	(244)
5			1.0	88	K_2CO_3, 50°C	(259)	(259)

6			1.0	92	$NaHCO_3$, rt	74–75	74–75
7			2.5	90	K_2CO_3, rt	154–155	155
8			4.5	85	K_2CO_3, rt	258–260	—
9			5.0[b]	75	K_2CO_3,/ $NaHCO_3$,[c] 10°C	152–153	152–153

[a]Isolated yield.
[b]Dimethylsulfate was added slowly over 5.0 h.
[c]0.1gr K_2CO_3 + 0.8gr Na HCO_3.



Scheme 3.

2-Ethoxy 2′-methoxy Biphenyl

White crystals; mp 258–260°C. IR (KBr): 1592, 1482, 1445, 1378, 1253, 1225, 758 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.31$ (t, 3H, $J = 7.0$ Hz), 3.82 (s, 3H), 4.07 (q, 2H, $J = 7.0$ Hz), 7.01 (dd, 2H, $J_1 = 8.4$, $J_2 = 1.4$ Hz), 7.05 (t, 2H, $J = 7.5$ Hz), 7.3 (dd, 2H, $J_1 = 7.5$, $J_2 = 1.7$ Hz), 7.33–7.39 (m, 2H). ^{13}C NMR(125 MHz, $CDCl_3$): $\delta = 14.84$, 55.53, 64.03, 110.83, 112.59, 120.26, 120.39, 128.09, 128.36, 128.45, 128.55, 131.38, 131.56, 156.48, 157.11. MS (m/e): 228 [M^+], 213, 200, 185, 169, 77. Anal. calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06; O, 14.02. Found: C, 79.04; H, 7.12; O, 14.06.

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