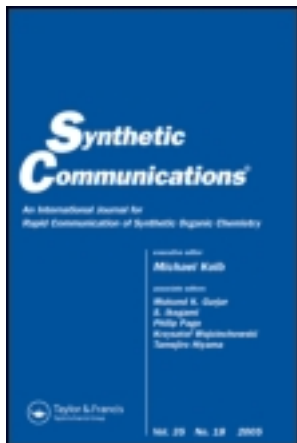


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### Etherification of Phenols Catalysed by Solid-Liquid Phase Transfer Catalyst PEG400 without Solvent

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**ETHERIFICATION OF PHENOLS CATALYSED BY SOLID-LIQUID  
PHASE TRANSFER CATALYST PEG400 WITHOUT SOLVENT**

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**ABSTRACT:** Aromatic ethers were synthesised in excellent yields (above 86 %) and purity by the etherification of phenols with dimethyl sulfate or alkyl halides, catalysed by phase transfer catalyst PEG400 under solvent-free conditions, and the effects of some key reaction conditions were also studied.

Aromatic ethers are useful compounds and extensively used for different purposes. Many methods for their synthesis have appeared. The direct etherification of phenols by using an alkylating agent and a base, in a solvent, water or an organic solvent, is the most useful way.<sup>1-6</sup> But major drawbacks have to be noted. Aprotic solvents were needed for the etherification of nitrophenols, otherwise a large amount of alkylating agents would be required.<sup>7</sup> For the benzyl-etherification of phenol, some special solvents, e.g. DME, had to be used to avoid alkylation of benzene ring.<sup>8</sup> Nevertheless, using large amounts of organic solvents is dangerous and costly in a laboratory or in industry. Furthermore, to obtain selectively monoetherified products of bisphenols is not easy in the

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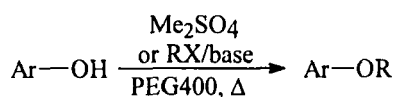
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solvent-employed reactions and is always inevitably accompanied by bietherified products. So alternative methods have been developed in this case.<sup>9-12</sup>

Organic synthesis in the absence of solvents is a powerful tool for the generation of structurally diverse molecules, due to higher selectivity and ease of set-up and work-up, and arouses a growing interest.<sup>13-14</sup>

Polyethylene glycols (PEG) of low molecular weight, especially PEG400 and PEG600, due to their low cost, stability, and easy availability, have been widely used as catalysts in many organic reactions which were conducted in liquid-liquid, gas-liquid, gas-solid or solid-liquid phases.<sup>15-18</sup>

We wish to report our research on the facile etherification of monophenols with excellent yields and highly selective monoetherification of bisphenols catalysed by PEG400 in the absence of solvents.



**Scheme**

The HPLC results showed that PEG400 performed similarly to PEG600 in catalysis with sodium 2-naphthalate as substrate, but the hydroxy groups of PEG were alkylated under etherification conditions of phenols, so that it is more difficult to remove the ethers of PEG600 by washing with water than those of PEG400, and more products will be lost simultaneously. So, we chose PEG400 as the catalyst in our experiment. As shown in **Table 1**, the desired amount of PEG400 is between 4-5mole % of the substrate in the 2-naphthol case. A longer reaction time will be necessary with less PEG400 (below 3 %) and lower yields

are observed in this case due to oxidation of sodium naphthalate exposed to air. The more amount of PEG employed, the more product was lost during the washing procedure with water.

Table 1: Effects of the Amounts of PEG400

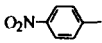
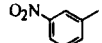
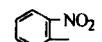
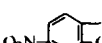
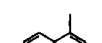
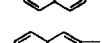
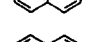
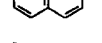
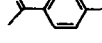
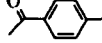
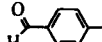
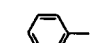


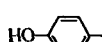
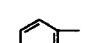

Amount <sup>a</sup> /%	1	2	3	4	5	6	7	8
Time <sup>b</sup> /h	16	11	8	6	5	4.5	4	4
Yield/%	83	88	91	93	92	90	87	85

<sup>a</sup>Mole ratio of PEG to sodium 2-naphthalate with Me<sub>2</sub>SO<sub>4</sub> as alkylating agent. <sup>b</sup>The time needed to complete conversion of 2-naphthol

As shown in Table 2, the monophenols which are difficult to volatilise upon heating gave the corresponding etherified products in excellent yields (87-99 %, **1a-3a**, **5a-13a**). For the bisphenols, highly selective monoetherified products were obtained in satisfactory yields (86-91 %, **4a**, **14a**, **15a** and **17a**) and no bietherified products were isolated. The difference in yields of the etherified products are related to their solubility in water and the stability of the corresponding sodium salts towards air under heating.

The high yields of isolated benzyl phenyl ethers in our method and the absence of C-alkylated product showed that the sodium phenolates could be considered as a close ion-pair in the reaction system. Otherwise, alkylation of the benzene ring would occur during etherification of phenol.<sup>8</sup> In addition, the selective monoetherification of bisphenols may be explained by this. Proton exchange would have induced bietherification of bisphenolates. If Na<sub>2</sub>CO<sub>3</sub> was used as base, quite an amount of bietherified product was formed during etherification of bisphenol (**16a**). In this case, the yield of monoetherified phenol was much lower (62 %) than using NaOH as base (**15a**, 86 %).

**Table 2:** Etherification Results of Some Phenols.

Entry	ArOH Ar-	ArOR R-	Agent/ base	Time/ h	Yield/ %	Mp or bp/°C	
						Observed	Lit. <sup>19,20</sup>
1a		Me(1b)	Me <sub>2</sub> SO <sub>4</sub> / NaOH	8.0	95 <sup>a</sup>	53	52-54
2a		Me(2b)	Me <sub>2</sub> SO <sub>4</sub> / NaOH	6.0	96 <sup>a</sup>	38	38-39
3a		Me(3b)	Me <sub>2</sub> SO <sub>4</sub> / NaOH	8.0	93 <sup>a</sup>	140-142/ 400Pa	121-123/ 133Pa
4a		Me(4b)	Me <sub>2</sub> SO <sub>4</sub> / NaOH	6.0	91 <sup>b</sup>	115	116-117
5a		Me(5b)	Me <sub>2</sub> SO <sub>4</sub> / NaOH	6.0	92 <sup>a</sup>	134-137/ 400Pa	135-137/ 400Pa
6a		Me(6b)	Me <sub>2</sub> SO <sub>4</sub> / NaOH	5.5	93 <sup>a</sup>	71.5	72-73
7a		Me(7b)	Me <sub>2</sub> SO <sub>4</sub> / Na <sub>2</sub> CO <sub>3</sub>	8.0	99 <sup>a</sup>	71.5	72-73
8a		Me(8b)	Me <sub>2</sub> SO <sub>4</sub> / Na <sub>2</sub> CO <sub>3</sub>	10	96 <sup>b</sup>	36.5	36-38
9a		Me(9b)	Me <sub>2</sub> SO <sub>4</sub> / NaOH	6.5	92 <sup>b</sup>	36.5	36-38
10a		Me(10b)	Me <sub>2</sub> SO <sub>4</sub> / NaOH	6.5	91 <sup>b</sup>	121-124/ 400Pa	285
11a		Bn(11b)	BnCl/ NaOH	7.0	94 <sup>a</sup>	38.5	38-39
12a		Bn(12b)	BnCl/ Na <sub>2</sub> CO <sub>3</sub>	11.0	87 <sup>a</sup>	38.5	38-39
13a		n-Bu(13b)	n-BuBr/ NaOH	6.0 <sup>c</sup>	94 <sup>a</sup>	76-78/ 400pa	210
14a		n-Bu(14b)	n-BuBr/ NaOH	9.0 <sup>d</sup>	92 <sup>b</sup>	64.5	65-67
15a		Me(15b)	Me <sub>2</sub> SO <sub>4</sub> / NaOH	4.0	86 <sup>b</sup>	27	27-29
16a		Me(16b)	Me <sub>2</sub> SO <sub>4</sub> / Na <sub>2</sub> CO <sub>3</sub>	10.0 <sup>d</sup>	62 <sup>b</sup>	27.5	27-29
17a		Et(17b)	EtBr/ NaOH	14.0 <sup>c</sup>	89 <sup>b</sup>	27	27-29

<sup>a</sup> The products were treated with NaOH solution and <sup>b</sup> with hot water. The reactions were processed at 110°C except <sup>c</sup> refluxing and <sup>d</sup> 50°C.

However, anhydrous  $\text{Na}_2\text{CO}_3$  may be used as base at higher temperatures (see general procedure) for the solid monophenols that are unstable under strongly basic conditions giving higher yields than when NaOH was used as base, see for example entries **7a**, **8a**. For phenol with low boiling point, e.g. entry **12a**, the lower yield could be attributed to the loss of phenol by evaporation or co-evaporation with water when heated above 140 °C. In this case, use of NaOH as base was satisfactory (**11a**, **13a**).

Accordingly, the etherification of some other phenols of which the melting points of the corresponding products are less than 150 °C were studied thoroughly. It is evident that the hydroxy with stronger acidity was converted into an anion and alkylated in favour (**4a**) when the two hydroxyl groups of a bisphenol differ in acidity. The reaction rates of both groupings are related to their pKa values and also the structure of the phenols. The hydroxyl group with larger pKa is favourable for O-alkylation while the spatial effects of *ortho* groups are unfavourable.

Meanwhile, HPLC showed that initial etherification was fast but got slower and slower when the reaction proceeded. This can be rationalised by the absorption of sodium halide or monomethyl sulfate to the surface of solid sodium phenolate leading to hindered diffusion of the reactants. The amount of alkylating agents should be excessive (about 10 %) to compensate for the consumption of PEG and to complete the reaction in a reasonable time.

In conclusion, this new method is safe, practical, highly selective and results in less pollution and easy work-up. The aromatic ethers are obtained in excellent yields and purity.

## EXPERIMENTAL SECTION

HPLC was performed on a TMC<sub>18</sub> 3.9 × 30 mm column, methanol(10 %) with NaH<sub>2</sub>PO<sub>4</sub>(0.1 M) as eluent. TLC was GF<sub>254</sub> thin layer chromatography with petroleum ether/diethyl ether(2/1) as eluent. Melting points were determined on a microscopy apparatus and uncorrected. Melting points and boiling points were compared with the literature values All the reagents and phenols were obtained from commercial suppliers and were used without further purification.

## GENERAL PROCEDURES

- a. A phenol(0.10 mol) was added to a solution of NaOH(40 %, 10 mL, 0.1 mol) and dissolved under heating. Water was evaporated under reduced pressure.
- b. A phenol(0.10 mol) and anhydrous Na<sub>2</sub>CO<sub>3</sub>(*ca.* 0.11 mol) were altogether ground into fine powder and heated in an oil bath(140-150°C) for 30 min under vigorous stirring.

PEG 400(1.6g, about 0.04mol) and alkylating agent(0.11 mol) were added slowly to the reaction system under vigorous stirring. The reaction was processed with heating and monitored with HPLC and TLC until the conversion of phenol was complete. Then the mixture was poured into a hot NaOH solution(5 %) or water(80-90°C, 100 mL) with stirring and allowed precipitation of product or layer separation. The precipitate or organic layer was washed with water (three portions of 50 mL). The purity of products in **Table 2** was above 96 % indicated by HPLC. If a higher purity is needed, recrystallisation with a suitable solvent or distillation in vacuum may be used.



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