Tetrahedron. Vol. 30, pp. 1379 to 1382. Pergamon Press 1974. Printed in Great Britain

THE USE OF PHASE-TRANSFER CATALYSIS FOR THE SYNTHESIS OF PHENOL ETHERS

A. McKillop,* J.-C. Fiaud and R. P. Hug
School of Chemical Sciences, University of East Anglia, Norwich, England

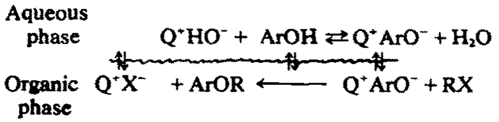
(*Received in the UK* 13 *December* 1973; *Accepted for publication* 1 *February* 1974)

Abstract—A simple, rapid and efficient procedure has been developed for the preparation of ethers of both simple and highly hindered phenols. Based on the principle of phase-transfer catalysis, the method involves alkylation of the phenoxide ion with an alkyl halide or sulphate ester in a methylene chloride-water system at room temperature, using a quaternary ammonium salt as the effective reagent for transport of the phenoxide ion between the two phases. In contrast to certain other processes in which phase-transfer "catalysis" is involved, the present procedure is truly catalytic with respect to the quaternary ammonium salt when alkyl bromides or sulphates are employed as alkylating agents.

Preparation of phenol ethers is an important synthetic reaction for which a wide variety of procedures has been developed during the last hundred years.[1] Most of the commonly used methods involve alkylation of the parent phenol or derived phenoxide ion, with the latter type of reaction being by far the more important. Use of dialkyl sulphate esters as alkylating agents often allows both generation and alkylation of the phenoxide ion to be carried out in aqueous solution, and generally leads to excellent yields of the desired ethers. Use of the more readily accessible alkyl halides as alkylating agents, on the other hand, almost always necessitates operation in organic solvents. The phenoxide ion is generated by treatment of the phenol with a base such as sodium, sodium hydride or sodium amide in a solvent such as benzene, toluene or dioxane; alkylation with the appropriate alkyl halide is then normally carried out in the same solvent. This method is again usually highly efficient, although some care must be exercised in the choice of solvent in order to avoid formation of both C- and O-alkylated products.[2,3]

There are few useful procedures available for the conversion of phenols into phenol ethers which do not necessitate initial formation of the corresponding phenoxide ion. Direct alkylation with diazomethane is the most widely used of these,[1] but is seldom the method of choice because of the obnoxious nature of the reagent. Alkylation has also been accomplished with alkyl orthocarbonate esters,[4] with dialkyl oxalate esters,[5] and by treatment of phenols with alcohols in the presence of dicyclohexylcarbodiimide.[6] None of these methods is, however, very general with respect to the variety of alkyl groups which can be introduced into the alkyl aryl ether, and hence they have usually been employed under special circumstances.

In the present paper we describe the results of an investigation into the use of phase-transfer catalysis for the preparation of phenol ethers. Phase-transfer catalysis, also often referred to as "ion pair partition" or "extractive alkylation", is a technique which has been the subject of much interest in recent years largely as a result of the work of Brändström, Makosza and Starks.[7] A number of very useful synthetic applications of the method have been reported, but there are no detailed studies of which we are aware on application of the technique to the synthesis of aryl ethers.[8] As applied to the alkylation of phenols, the process can be represented schematically as shown in the Figure ($Q^+ = R_4N^+$). In practice, the phenol is added to a two-phase system consisting of an aqueous solution of the quaternary ammonium hydroxide and a methylene chloride solution of the alkylating agent. The phenol, which in most cases is partitioned naturally between the two phases, is converted into the corresponding quaternary ammonium phenoxide in the aqueous phase. This latter salt has a discrete solubility in the organic phase; consequently, transport of the phenoxide ion into the methylene chloride solution is followed by rapid irreversible alkylation and formation of the phenol ether.



The procedure outlined above has been found to be highly effective for the preparation of a variety of phenol ethers. Data for representative conversions are summarised in Table 1, from which it can be seen that yields of ethers are generally excellent and compare favourably with those obtained by classical methods. This is particularly true in the

Table 1. Preparation of alkyl aryl ethers ArOR

ArOH	RX	Yield,%[a]
C_6H_5OH	CH_3I	95
	$CH_2=CHCH_2Br$	77
	$\underset{\setminus\ O\ /}{CH_2-CH}-CH_2Cl$	77
	n-C_4H_9Br	85
	cyclo-$C_5H_{11}Br$	73
	$C_6H_5CH_2Cl$	86
	$C_6H_5CH(CH_3)Br$	91
	$BrCH_2COOEt$	86
4-t-$C_4H_9C_6H_4OH$	CH_3I	96
	$CH_2=CHCH_2Br$	77
	$C_6H_5CH_2Br$	83
4-$CH_3OC_6H_4OH$	$(CH_3)_2SO_4$	91
1-$C_{10}H_7OH$	$\underset{\setminus\ O\ /}{CH_2-CH}-CH_2Cl$	42[b]
2-$C_{10}H_7OH$	CH_3I	92
	$(CH_3)_2SO_4$	92
	$(C_2H_5)_2SO_4$	81
	$\underset{\setminus\ O\ /}{CH_2-CH}-CH_2Cl$	41
2-$C_6H_5C_6H_4OH$	$(CH_3)_2SO_4$	81
2-$OHCC_6H_4OH$	$(CH_3)_2SO_4$	78
	$(C_2H_5)_2SO_4$	83
2-$HOOCC_6H_4OH$	$(CH_3)_2SO_4$	78[c]
	$(C_2H_5)_2SO_4$	85[c]
2-$O_2NC_6H_4OH$	CH_3I	81
3-$O_2NC_6H_4OH$	CH_3I	79
4-$O_2NC_6H_4OH$	CH_3I	83

[a] Refers to isolated material.

[b] Accompanied by 20% of di-1-naphthoxymethane.

[c] Refers to formation of ester, 2-$ROOCC_6H_4OR$.

cases of the isomeric nitrophenols and of salicylaldehyde, phenolic O-alkylation of which can be difficult and normally requires the use of special techniques. The results with 1- and 2-naphthol are also of interest. Kornblum[3] has reported that benzylation of sodium 2-naphthoxide gives mainly 1-benzyl-2-naphthol in hydrogen bonding solvents such as water or alcohol, but that the extent of C-alkylation does decrease with increase in the size of the cation associated with the naphthoxide ion from Li^+ through R_4N^+. The exclusive O-alkylation observed in the present study thus provides supporting evidence for the kinetic data reported by Starks,[9] which indicate that the alkylation step in phase-transfer catalysis normally takes place in the organic phase and not in the aqueous phase or at the interface.

With the notable exceptions of the reactions of 1- and 2-naphthol with epichlorohydrin and of p-t-butylphenol with benzyl chloride, the above method is remarkably free of side reactions and isolation of pure products is simple and straightforward. Under the standard reaction conditions, however, both 1- and 2-naphthol reacted with epichlorohydrin to give brilliantly blue coloured reaction mixtures from which the expected alkyl aryl ethers were isolated in poor yield. Exclusion of oxygen during reaction failed either to remove the coloured species or to improve the yields of ethers. In the case of 1-naphthol, however, a 20% yield of di-1-naphthoxymethane was isolated. In the case of p-t-butylphenol, treatment with benzyl chloride and a catalytic (5%) amount of quaternary ammonium salt led to formation of the expected benzyl ether in very poor yield; the major product was di-p-t-butylphenoxymethane. The desired benzyl ether was, however, obtained in excellent yield when a stoichiometric amount of ammonium salt was employed. From these preliminary experiments it appears that alkylations involving relatively unreactive alkyl chlorides are best carried out using a stoichiometric amount of quaternary ammonium salt, in order to avoid competition between methylene chloride and the alkyl chloride as alkylating agents.

All of the transformations shown in Table 1 can be adequately explained on the basis of the equilibria shown in the Figure, i.e. initial formation of Q^+ArO^- in the aqueous phase, transport of this species into the methylene chloride layer, and finally alkylation. It was of interest therefore to examine the utility of the present method for the etherification of highly hindered phenols, where generation of the phenoxide ions is reported to be difficult. 2,6-Di-t-butylphenol, for example, is reported not to react with either diazomethane or with sodium in boiling ligroin, and one procedure for the preparation of the methyl ether involves initial formation of the sodium salt by treatment of the phenol with sodium in liquid ammonia followed by methylation with methyl iodide under pressure.[10] A number of highly hindered phenols were therefore treated with either methyl iodide or dimethyl sulphate under phase-transfer catalysis conditions: in each case an excellent yield of the corresponding methyl ether was obtained and the data are summarised in Table 2. All reactions were carried out at

Table 2. Methylation of hindered phenols, ArOH, with dimethyl sulphate

ArOH	Yield, %[a]
2,6-Dimethylphenol[b]	92
2,6-Dimethyl-4-t-butylphenol	79
2,6-Dimethoxyphenol	91
2,6-Diisopropylphenol	84
2,6-Di-t-butylphenol	83
2,6-Di-t-butyl-4-methylphenol	84
2,6-Di-t-butyl-4-methoxyphenol	85
2,4,6-Tri-t-butylphenol	93

[a] Refers to isolated material.

[b] Methyl iodide used as alkylating reagent.

room temperature, and were complete in 2–12 h; as expected, there was no reaction in the absence of quaternary salt, while no evidence was obtained (TLC, GLC) in the reactions of either 2,6-dimethyl- or 2,6-di-t-butylphenol for the formation of C-alkylated products. Not unexpectedly, virtually no reaction was observed when either ethyl or isopropyl iodide was substituted for methyl iodide. These results are to some extent complementary to those obtained recently by Stoochnoff and Benoiton,[11] who found that 2,6-di-t-butyl-p-cresol could be methylated in excellent yield simply on treatment at room temperature with sodium hydride and methyl iodide in either tetrahydrofuran or tetrahydrofuran-dimethylformamide. Hence it appears probable that many of the "difficulties" reported in attempts to generate and react the anions derived from highly hindered phenols have arisen simply as a result of incorrect selection of experimental conditions.

One particularly attractive feature of phase-transfer catalysis is that the method is theoretically catalytic with respect to the quaternary ammonium salt, provided that sufficient base is present in the aqueous layer to regenerate the quaternary ammonium hydroxide from the halide which is formed in the irreversible alkylation step. The results obtained from a study of the rate of methylation of 4-t-butylphenol with dimethyl sulphate in the presence of varying amounts of quaternary ammonium salt are summarised in Table 3, from which it can be seen that there are no significant experimental advantages in using stoichiometric amounts of catalyst rather than 10 mole% or even 1 mole%. In contrast to the situation with alkyl bromides and sulphates, however, use of benzyl chloride (*loc. cit.*) or alkyl iodides as alkylating agents necessitated use of stoichiometric amounts of quaternary ammonium salt. Use of catalytic amounts of ammonium salt in the case of alkyl iodides resulted in poor conversions (30–40%) due to the known role of iodide ion as a "catalyst poison" in phase-transfer catalysis.[7]

Quaternary ammonium salts have been used previously for the preparation of phenol ethers. Baw[12] reported in 1926 that benzyl phenyl ethers were obtained when phenols were heated with benzyldimethylaniline chloride for several hours in the presence of either sodium hydroxide or sodium carbonate. This type of reaction has subsequently been used on a number of occasions for the preparation of methyl, ethyl, butyl and benzyl ethers, especially those of phenolic alkaloids and hydroxypyridines.[13–17] In contrast to the very mild conditions used in the present method, however, (a) the above procedures involve heating of a mixture of the preformed quaternary ammonium phenoxide in a high boiling solvent such as dimethylformamide or xylene, and yields of ethers are in most cases moderate; and (b) the generality of these techniques with respect to the variety of alkyl groups which can be introduced to the product ether has not been demonstrated.

Table 3. Effect of quantity of catalyst Q^+Br^- on rate of methylation of 4-t-butylphenol with dimethyl sulphate at 20°

Q^-Br^-, mole %	$t_{\frac{1}{2}}$, min
100	$\ll 1$
10	$3 \pm 0{\cdot}5$
1	40 ± 3
0	160 ± 10

EXPERIMENTAL

M.ps were determined on a Kofler hot-stage microscope apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 257 Grating Infrared Spectrophotometer using the standard liquid film and Nujol mull techniques. Nuclear magnetic resonance spectra were recorded on a Perkin-Elmer R12 60 MHz Spectrometer as solutions in carbon tetrachloride or deuterochloroform, using tetramethylsilane as internal standard. Where possible, identity of products was confirmed by comparison if IR and NMR spectra with those of commercial samples. Analytical gas–liquid chromatograms were carried out using a Perkin-Elmer Model F11 Gas Chromatograph with standard one metre Carbowax 20M columns. Quantitative work was carried out using anisole as internal standard; product ratios were determined with a Vitatron UR 400 digital readout integrator.

Quaternary ammonium salts. Benzyltri-n-butylammonium salts were used throughout, due to the high crystallinity and ease of manipulation of the chloride, bromide and iodide derivatives. Solutions of the quaternary ammonium hydroxide were prepared either by: (a) passage of an aqueous solution of benzyltri-n-butylammonium bromide through a basic ion exchange resin (Deacidite FF-1P 8RA66, preactivated by through percolation of 25 ml of 3N KOH solution) followed by concentration of the eluate under reduced pressure (bath temperature ~ 60°); and standardisation of the final solution by titration against standard hydrochloric acid; or (b) by dissolving equimolar amounts of sodium hydroxide and the quaternary ammonium bromide in water. Methylation of 4-t-butylphenol was used in standard control experiments to show that the yield of 4-t-butylanisole was independent of the method of preparation of the quaternary ammonium hydroxide.

Starting phenols and product ethers. The phenols used were commercial samples and were purified, where necessary, prior to use. Analytical and spectral data for the product ethers were consistent with the assigned structures.

General procedure for the preparation of ethers. A mixture of 50 ml of dichloromethane, 50 ml of water, 10 mmoles of the phenol, 15 mmoles of sodium hydroxide, 20–30 mmoles of alkylating agent and 0·1–1 mmole of quaternary ammonium bromide was agitated with a vibromixer at room temperature for 2–12 h. The organic layer was then separated and the aqueous layer extracted twice with 20 ml portions of methylene chloride. The combined organic extracts were evaporated, the residue mixed with water, and the mixture extracted with ether or pentane.

The organic extract was washed twice with 2N ammonia solution to remove dimethyl sulphate if necessary (methanolic ammonia in the case of diethyl sulphate), then with 2N sodium hydroxide solution (Claisen's alkali in the case of hindered phenols) to remove unreacted phenol, and finally with saturated sodium chloride solution. After drying with sodium sulphate, the solvent was evaporated and the residual ether purified by distillation or crystallisation.

When methyl iodide was used as alkylating agent it was found that reaction proceeded most satisfactorily when a stoichiometric amount of the quaternary ammonium salt was used. Use of less than one equivalent of catalyst resulted in slow and incomplete reaction due to inhibition of the catalytic effect by iodide ion.[7] Reactions with benzyl chloride were carried out similarly (see Discussion).

Determination of $t_{\frac{1}{2}}$ for the reaction of 4-t-butylphenol with dimethyl sulphate in the presence of different amounts of quaternary ammonium salt. These reactions were carried out, at 20°, as described above, except that anisole (800 mg) was added as an internal standard. After addition of the dimethyl sulphate, aliquots were withdrawn from the organic phase after 1, 2, 5, 10, 20, 40, 80, ... etc min, and analysed directly by GLC to give the ratio of 4-t-butylanisole relative to anisole.

Acknowledgements—One of us (J.-C. F.) acknowledges receipt of a NATO Fellowship and another (R. P. H.) financial support from the Stiftung für Stipendien auf dem Gebiete der Chemie (Basel).

REFERENCES

[1] See e.g. C. A. Buehler and D. E. Pearson, *Survey of Organic Synthesis*, pp. 285–382. Wiley-Interscience, New York (1970)

[2] E. Wenkert, R. D. Youssefyeh and R. G. Lewis, *J. Am. Chem. Soc.* **82**, 4675 (1960)

[3] N. Kornblum, R. Seltzer and P. Haberfield, *Ibid.* **85**, 1148 (1963), and references therein

[4] B. Smith, *Acta. Chem. Scand.* **19**, 1006 (1956)

[5] E. E. Smissman, M. D. Corbett, S. El-Antably and K. C. Kroboth, *J. Org. Chem.* **37**, 3944 (1972)

[6] E. Vowinkel, *Chem. Ber.* **99**, 1479 (1966)

[7] For a recent review see J. Dockx, *Synthesis* 441 (1973)

[8] Application of phase-transfer catalysis to the preparation of certain dialkyl ethers has been described recently: A. Merz, *Angew. Chem.* **85**, 868 (1973)

[9] C. M. Starks and R. M. Owens, *J. Am. Chem. Soc.* **95**, 3613 (1973)

[10] L. A. Cohen, *J. Org. Chem.* **22**, 1333 (1957)

[11] B. A. Stoochnoff and N. L. Benoiton, *Tetrahedron Letters* 21 (1973)

[12] H. Baw, *J. Indian Chem. Soc.* **3**, 101 (1926)

[13] V. Rodionov, *Bull. Soc. Chim. Fr.* **39**, 305 (1926)

[14] B. R. Baker and F. J. McEvoy, *J. Org. Chem.* **20**, 118, 136 (1955)

[15] A. Cohen, J. W. Haworth and E. H. Hughes, *J. Chem. Soc.* 4374 (1952)

[16] J. Ugelstad, T. Ellingsen and A. Berge, *Acta. Chem. Scand.* **20**, 1593 (1966)

[17] R. L. Merker and M. J. Scott, *J. Org. Chem.* **26**, 5180 (1961)