Tetrahedron Letters No. 38, pp 3251 - 3254, 1975. Pergamon Press. Printed in Great Britain.

AN IMPROVED WILLIAMSON ETHER SYNTHESIS USING PHASE TRANSFER CATALYSIS

H. H. Freedman* and R. A. Dubois
The Dow Chemical Company, New England Laboratory, Box 400, Wayland, Mass.

(Received in USA 18 June 1975; received in UK for publication 11 August 1975).

The use of phase transfer catalysis[1] (PTC) for a practical synthesis of mixed ethers has thus far been limited to the methylation of alkoxides, generated from alcohols in 50% aqueous sodium hydroxide by dimethyl sulphate in the presence of a phase transfer catalyst.[2] We now report that good to excellent yields of a variety of unsymmetrical ethers can be obtained using inexpensive, primary alkyl chlorides. This greatly extends the utility of the PTC method as a convenient substitute for the rigorous conditions usually required for the standard Williamson ether synthesis.[3]

Optimum PTC conditions are realized when the two phase system consisting of at least a five-fold excess of 50% aqueous sodium hydroxide over alcohol, an excess of alkyl chloride (conveniently used as solvent) and 3-5 mole % of tetrabutylammonium bisulphate (TBAB) as catalyst are stirred at temperatures of 25-70°C. Primary alcohols are thus completely alkylated by aliphatic chlorides in 3-4 hours while secondary alcohols require longer times or greater amounts of catalyst. In the absence of phase transfer catalyst, or with secondary halides, the yields are no longer preparatively useful. These data are summarized in Table I.

The results of a detailed investigation of the formation of n-butyl benzyl ether from n-butanol and benzyl chloride are completely consistent with a PTC mechanism. Under pseudo first-order conditions (1 equiv. of alkyl chloride in THF, excess alcohol, excess NaOH saturated with NaCl) the reaction is first order in catalyst and in benzyl chloride, while with equivalent amounts of reactants, clean second order kinetics are obtained through 80% of the reaction. The bimolecular nature of the process is also reflected[4] in its low activation energy (13.9 ± 0.5 kcal/mole) and entropy (-26.5 ± 1.6 e.u.).[5]

Only a minor amount of symmetrical ether is formed (<10%) even with a large excess of alkyl chloride and the bulk of this is formed during the last 20% of the reaction, when the ratio of OH^- to RO^- becomes large. A similar slow alkyl chloride solvolysis and relatively rapid ether formation has been observed by Herriot.[6] These results are consistent with the data in Table II which were obtained by titrating for total base and Cl^-, a THF layer which had been equilibrated with NaCl—saturated 50% aqueous sodium hydroxide. In the absence of quaternary ammonium cation (Q^+) an insignificant concentration of any ionic species is extracted. With Q^+, but without a source of $n\text{-}BuO^-$, 92% of the Q^+ is in the THF with a 9:1 preference of Cl^- over OH^- as counterion. With addition of excess n-BuOH we can account for all of the Q^+ in the organic layer, but now only 6% of the anion is Cl^- and the remainder must be butoxide. This preferential extraction of $n\text{-}BuO^-$ over either Cl^- or OH^- by the Q^+ catalyst is responsible for the efficiency of this process.

The initial Q^+ counter ion has a pronounced effect on the rate of alkylation. Thus, under our standard conditions after 1.5 hours, the % conversion for the benzylation of butanol using 5 mol % of $(n\text{-}Bu)_4N^+X^-$ drops from 92% for X = HSO_4 to 62% for X = I and to 40% for X = ClO_4. This agrees well with the chloroform extraction constants, $E_{QX}(Q = (n\text{-}Bu)_4N^+)$ of Modin and Schill;[7] log E_{QX} = 3.01 for I^- and 3.48 for ClO_4^-. The inhibition of PTC reactions by preferentially extractable anions produced during the reaction has been reported[1a] and our results document an analogous inhibition by the original quaternary counter ion. It follows that for maximum efficiency in PTC processes where a "hard" anion is the nucleophile, "soft" catalyst anions (as well as leaving groups) should be avoided.

Finally, as found by Starks[1a] for the PTC cyanation of octyl bromide, the absence of interfacial effects is confirmed by the lack of dependence of k' on the stirring rate beyond that needed to maintain homogeneity of reactants in each layer (~80 r.p.m.). This is in contrast to the findings of Merz[2] and suggests that in his case factors other than simple phase transfer principles are involved. This is being investigated.

Acknowledgement: The authors are grateful to Profs. C.P. Lillya and W. E. McEwen for their suggestions and interest and for the opportunity for R. A. Dubois to apply portions of this research toward partial fulfillment of the Ph.D. requirements at the University of Massachusetts, Amherst.

TABLE I: PREPARATION OF UNSYMMETRICAL ETHERS BY PTC

$$\mathrm{ROH + R'Cl \xrightarrow[\text{cat.}]{50\%\ NaOH} ROR' + NaCl + H_2O}$$

R	R'	Mole % TBAB	Temp. °C	Time Hrs.	Yield[a]
n-C_4H_9-	$C_6H_5CH_2$-	5	35	1.5	92
"	"	0	45	6	4
n-$C_4H_9OCH_2CH_2$-	n-C_4H_9	5	65	6	82[b]
"	"	0	70	23	47
$CH_3(CH_2)_7$-	"	6	65	4	95
$CH_2=CHCH_2$-	$C_6H_5CH_2$	5[c]	30	over-night	72[b]
-$(CH_2)_4$-	CH_3CH_2	6	65	4	93[d]
$CH_3OCH_2CH(CH_3)$-	n-C_4H_9	23	65	3	97
n-$C_4H_9OCH_2CH_2$-	cy-C_6H_{11}	6	70	7	e

---

[a] Quantitative glc with internal standard.

[b] Distilled yield of pure product.

[c] Benzyltriethylammonium chloride as catalyst.

[d] Plus 3% monoethyl ether.

[e] 50% of cyclohexene only.

TABLE II: EXTRACTABILITY OF n-BuO$^-$, OH$^-$ AND Cl$^-$ FROM 50% NaOH (SATURATED WITH NaCl) INTO THF

n-BuOH (M)	TBAB (M x 10^2)	BASE IN THF (M x 10^2)[a]	Cl$^-$ IN THF (M x 10^2)[b]	BASE:Cl
1.0	—	<0.1	0.0	—
—	1.3	0.12	1.0	1:9
1.0	1.3	1.23	0.07	19:1

---

a. Determined by potentiometric titration with standard aqueous HCl.

b. Determined by potentiometric titration with standard $AgNO_3$.

References

1. a) C. M. Starks, *J. Amer. Chem. Soc.*, **93**, 195 (1971); **95**, 3613 (1973).
   b) M. Makosza, *Pure and Applied Chem.*, in press.
2. A. Merz, *Angew. Chem., Internat. Ed.*, **12**, 846 (1973).
3. Houben-Weyl, 4th ed., Vol. 613, 1965, pp. 26-37.
4. C. K. Ingold, "Structure and Mechanisms in Organic Chemistry", Cornell University Press, 2nd ed., 1969, pp. 471-2.
5. The activation energy was derived from an Arrhenius plot of the pseudo first order rate constants obtained at 31.5°, 41.5° and 51.5°. The entropy of activation at 41.5° was calculated from the experimentally determined activation energy and the second order specific rate constant, k_2, which was in turn derived by use of the equation, $k' = k_2[Q^+ n\text{-}BuO^-]$ where k' is the pseudo first order rate constant.
6. A. W. Herriot and D. Picker, *Tetrahedron Lett.*, 4521 (1972).
7. R. Modin and G. Schill, Act. Pharm. Suecica, 7, 585 (1970). We note that under our conditions, HSO_4^- is converted to the very unextractable $SO_4^=$.