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SYNTHETIC APPLICATION OF MICELLAR CATALYSIS. WILLIAMSON'S SYNTHESIS OF ETHERS

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Abstract - A simple, rapid and efficient procedure for the preparation of di-alkyl, simple phenyl-alkyl and hindered phenyl-alkyl ethers has been developed. Based on the principle of micellar catalysis the method involves alkylation of the alkoxide or the phenoxide ion with an alkyl chloride at 80°C in the presence of cationic micelles. For the preparation of phenyl--alkyl ethers normal micelles were used, while for the di-alkyl ethers reverse micelles were more effective. By increasing the ionic strength of the solution the rate of formation of phenyl-alkyl ethers could be increased.

Preparation of ethers is an important synthetic reaction for which a wide variety of procedures has been developed during the last hundred years. The Williamson reaction, discovered in 1850, is still the best general method for the preparation of unsymmetrical as well as symmetrical ethers.[1] However, this method is not satisfactory for ethers containing a tertiary group (because of elimination) while with secondary groups low yields are obtained.[2] By the use of phase-transfer catalysis an improvement of the Williamson reaction was achieved.[3] A number of very useful synthetic applications of micellar catalysis has been reported,[4] but to our knowledge, no detailed studies on the application of this technique to the synthesis of ethers.

There are few available procedures for the conversion of phenols or alcohols into ethers which do not comprise the initial formation of the corresponding phenoxide or alkoxide ions. Among these the most widely used is the direct alkylation with diazomethane or diazoalkane[5] which is mostly limited to methyl ethers and seldom used because of the obnoxious nature of the reagent. Alkylation has also been accomplished with orthocarbonate esters,[6] dialkyl oxalate esters,[7] onium salts,[8] and by treating phenols with alcohols in the presence of dicyclohexylcarbodiimide.[9] However, none of these methods can be considered as a general method for the preparation of ethers.

In our work we used aqueous micelles to achieve perturbations which are synthetically favourable and succeeded in controlling the aromatic bromination[10] and enone reduction.[11] In this paper a new synthesis of ethers performed under mild conditions in the presence of normal and reverse micelles is reported.

RESULTS AND DISCUSSION

As already mentioned cationic micelles (CTAB)* are more effective than anionic ones (SDS)** in the synthesis of phenyl ethers (see Table 1). So the alkylation rate of phenol in SDS is lower by a factor of 100-1000 than in CTAB micelle. Cetyltrimethyl ammonium phenoxide, formed by the reaction of CTAB

*cetyltrimethylammonium bromide

**sodium dodecyl sulfate

Table 1. Yields of alkyl phenyl ethers PhOR prepared from phenol and alkyl halide in the presence of CTAB as micelle

RX	PhOR	Yield, %[a]	RX	PhOR	Yield, %[a]
CH_3I	$PhOCH_3$	97	$CH_2=CH-CH_2Cl$	$PhOCH_2CH=CH_2$	96
CH_3CH_2Br	$PhOCH_2CH_3$	93	$PhCH_2Cl$	$PhOCH_2Ph$	95
$CH_3CH_2CH_2Br$	$PhOCH_2CH_2CH_3$	95	$PhCH_2CH_2Cl$	$PhOCH_2CH_2Ph$	87
$n\text{-}C_4H_9Cl$	$PhOC_4H_9$	87	$Cl(CH_2)_2Cl$	$PhO(CH_2)_2OPh$	89
$n\text{-}C_5H_{11}Cl$	$PhOC_5H_{11}$	91	$Cl(CH_2)_3Cl$	$PhO(CH_2)_3OPh$	86
$n\text{-}C_{10}H_{21}Cl$	$PhOC_{10}H_{21}$	89	$Cl(CH_2)_4Cl$	$PhO(CH_2)_4OPh$	91
$n\text{-}C_{12}H_{25}Cl$	$PhOC_{12}H_{25}$	86	$Cl(CH_2)_5Cl$	$PhO(CH_2)_5OPh$	93
$n\text{-}C_{16}H_{33}Br$	$PhOC_{16}H_{33}$	83	$Br(CH_2)_6Br$	$PhO(CH_2)_6OPh$	90

[a] Refers to isolated material.

and sodium phenolate in water is a surface active compound which dissolves alkyl halides. The phenoxy ion, as evidenced by ^1H NMR spectroscopy,[12] resides on the Stern layer of the normal micelle so the nucleophilic displacement of phenoxy ion on primary alkyl chloride takes place on the interface of micelle (Figure 1).

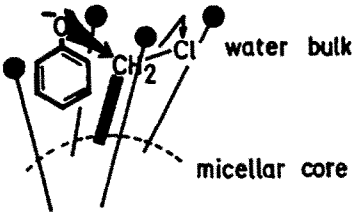


Figure 1

Table 2. Etherification of hindered phenols with butyl chloride in the presence of CTAB as micelle

ArOH	Yield, %[a]
2,6-Dimethylphenol	95
2,6-Dimethyl-4-t-butylphenol	82
2,6-Dimethoxyphenol	91
2,6-Di-t-butylphenol	80

[a] Refers to isolated material.

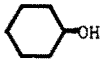
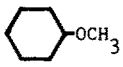
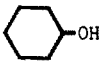
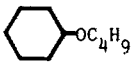
It was of interest to examine the applicability of the presented method to the esterification of highly hindered phenols, where generation of the phenoxide ions was reported to be difficult.[13] A number of highly hindered phenols were therefore treated with butyl chloride under micellar conditions with 20% sodium hydroxide. Excellent yields of the corresponding aryl butyl ethers were obtained (Table 2). As expected, there was no reaction in the absence of CTAB, which was confirmed (by gas chromatography) for the etherification of 2,6-dimethylphenol with butyl chloride.

This synthesis of aryl ethers is very convenient because the work-up is simple and involves saturation of the reaction mixture with sodium chloride, filtration, extraction and purification either by distillation or crystallization. The products obtained are 98% pure as determined by gas chromatography and ^1H NMR analysis.

Preparation of mixed n-alkyl ethers from the corresponding alcohols and n-alkyl chlorides in 20% or 50% aqueous sodium or potassium hydroxide in the presence of normal micelles is not so effective, rather low yields were obtained and a certain amount of symmetric ether was formed (~10%). This yield was raised to 40% when a large excess of alkyl chloride was used. The reaction of benzyl alcohol with a two-fold excess of 1-pentyl chloride in 50% potassium hydroxide in the presence of CTAB resulted in a very poor yield (30%) of the expected benzyl ether: the major product was diphenyl ether. However, the desired benzyl pentyl ether was obtained in an excellent yield when the reaction was performed under the liquid-solid[14] reverse micellar conditions. The experimental conditions for the solid-liquid reverse micellar ("water-pool") process are exceedingly simple. Etherification is usually carried out in the presence of the organic phase (alkyl chloride and alcohol) and with a two-fold excess of sodium or potassium hydroxide as the solid phase. In cases where solid products were formed a tetrahydrofuran solution of alkyl chloride and alcohol was used as a liquid phase. The results are presented in Table 3. The amount of water plays an important

role in the solid-liquid reverse micellar catalysis: in the absence of water no nucleophilic displacement reaction (etherification) takes place. This finding is similar to that valid for phase transfer systems.[15]

Table 3. Yields of dialkyl ethers prepared from alkyl halides and alcohols in the presence of CTAB as reverse micelle

R'OH	RX	R'OR	Yield, %[a]
CH_3OH	$n\text{-}C_5H_{11}Cl$	$CH_3OC_5H_{11}$	82
C_2H_5OH	$n\text{-}C_5H_{11}Cl$	$C_2H_5OC_5H_{11}$	85
$n\text{-}C_3H_7OH$	$n\text{-}C_5H_{11}Cl$	$C_3H_7OC_5H_{11}$	86
$n\text{-}C_5H_{11}OH$	$n\text{-}C_3H_7Br$	$C_3H_7OC_5H_{11}$	81
$(CH_3)_2CHOH$	$n\text{-}C_5H_{11}Cl$	$(CH_3)_2CHOC_5H_{11}$	91
$n\text{-}C_4H_9OH$	$n\text{-}C_5H_{11}Cl$	$C_4H_9OC_5H_{11}$	87
$n\text{-}C_5H_{11}OH$	$n\text{-}C_4H_9Cl$	$C_4H_9OC_5H_{11}$	85
$CH_3CH_2CH(CH_3)OH$	$n\text{-}C_5H_{11}Cl$	$CH_3CH_2CH(CH_3)OC_5H_{11}$	82
$(CH_3)_3COH$	CH_3I	$(CH_3)_3COCH_3$	85
$(CH_3)_3COH$	CH_3CH_2Br	$(CH_3)_3COCH_2CH_3$	83
$(CH_3)_3COH$	$n\text{-}C_3H_7Br$	$(CH_3)_3COC_3H_7$	87
$(CH_3)_3COH$	$n\text{-}C_4H_9Cl$	$(CH_3)_3COC_4H_9$	86
$(CH_3)_3COH$	$n\text{-}C_5H_{11}Cl$	$(CH_3)_3COC_5H_{11}$	87
$PhCH_2OH$	$CH_2=CH\text{-}CH_2Cl$	$PhCH_2OCH_2CH=CH_2$	91
$n\text{-}C_4H_9OH$	$CH_2=CH\text{-}CH_2Cl$	$C_4H_9OCH_2CH=CH_2$	95
$n\text{-}C_5H_{11}OH$	$CH_2=CH\text{-}CH_2Cl$	$C_5H_{11}OCH_2CH=CH_2$	96
$n\text{-}C_{12}H_{25}OH$	$CH_2=CH\text{-}CH_2Cl$	$C_{12}H_{25}OCH_2CH=CH_2$	90
	CH_3I		81
	$n\text{-}C_4H_9Cl$		87

[a] Refers to isolated material.

With an excess of water two non-miscible liquid-phases are formed and the yield of the reaction is decreased. The schematic presentation of the proposed catalysis is given in Figure 2. The reverse micelle dissolves sodium hydroxide and removes it from the solid state to the organic bulk; the hydroxide ion is a very strong base and forms alkoxide ion thus enabling the displacement reaction with alkyl chloride on the interface of the reverse micelle.

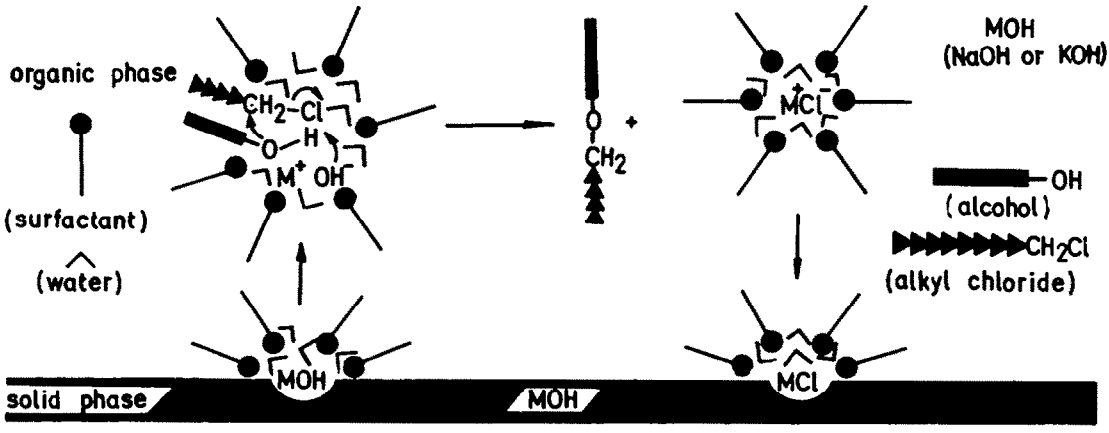


Figure 2. Schematic presentation of "water-pool" (reverse micelle) catalysis in the esterification of alcohols with alkyl chlorides

EXPERIMENTAL

Melting points 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 a standard liquid film and Nujol mull techniques. Nuclear magnetic resonance spectra were recorded on a JEOL 90 FXQ spectrometer, as solutions in deuteriochloroform, using tetramethylsilane as an internal standard. Where possible, the identity of products was confirmed by comparing their IR and NMR spectra with those of commercial samples. Analytical gas-liquid chromatography was done on a Varian Model 920 gas chromatograph with standard Carbowax 20 M columns. Commercially available (Fluka) sodium dodecyl sulfate (SDS) and cetyltrimethylammonium bromide (CTAB) were used without further purification.

Starting phenols, alcohols, and alkyl chloride were purchased commercially and, where necessary purified before use. Analytical and spectral data for the product ethers were consistent with the assigned structures. The products were 98% pure as determined by gas chromatography and ^{1}H NMR analysis.

General procedure for the preparation of phenolic ethers

To a 20% aqueous solution of sodium hydroxide (1000 mL) the corresponding phenol (0.1 mol) and cetyltrimethylammonium bromide (3.2 g; 0.1 mol) were added. The mixture was heated to 60°C for 0.5 hr and then allowed to cool to ambient temperature, after which the corresponding alkyl halide (0.12 mol) was added with stirring. After re-heating to 80°C for 5 hrs, the reaction mixture was saturated with sodium chloride and the aqueous layer separated by filtration from the solid sodium chloride. The aqueous solution was extracted with diethyl ether (x3). The ethereal extract was washed twice with 20% sodium hydroxide to remove unreacted phenol, and then with saturated sodium chloride solution. After drying with sodium sulfate, the solvent was evaporated and the residual ether purified by distillation or crystallization.

When methyl iodide was used as an alkylation agent, due to hydrolysis a notable excess of methyl iodide (x5) was required.

General procedure for the preparation of unsymmetrical alkyl ethers

A mixture of alkyl chloride (0.2 mol), alcohol (0.2 mol), water (1.0 mL), cetyltrimethylammonium bromide (3.64 g; 0.01 mol), sodium hydroxide (16 g; 0.4 mol), and, in the case of solid products, tetrahydrofuran (50 mL) was heated to 70°C and stirred vigorously overnight. The reaction suspension was then allowed to cool and the solid residue was separated by filtration. The residue was washed several times with ether or tetrahydrofuran, the organic solutions were combined and dried over anhydrous sodium sulfate. Ether or tetrahydrofuran was carefully evaporated and the oily residue purified by distillation or crystallization.

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