Catalysis by Solid Superacids[1]; 15. Facile Preparation of Methoxymethyl Ethers

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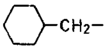
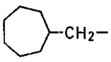
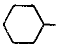
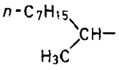
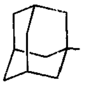
Methoxymethyl ethers are commonly used for protection of alcohols in natural product synthesis[2]. The reagent usually employed for methoxymethylation is chloromethyl methyl ether[3], which is, however, no longer suitable because of its extreme carcinogenicity.

Therefore, it was desirable to develop other reagents for this important synthetic transformation. For this purpose, condensation of dimethoxymethane with corresponding alcohols catalyzed by phosphorus pentoxide[4] or *p*-toluenesulfonic acid[5] seems most practical. However, these reactions necessitate an inconvenient aqueous basic workup. We have previously described perfluorinated solid superacidic Nafion-H-catalyzed preparations of acetals and ethylene dithioacetals from carbonyl compounds[6]. In continuation of our interest in Nafion-H catalyzed synthetic transformations, we now report the preparation of methoxymethyl ethers **3** (formaldehyde acetals) by reacting the corresponding alcohols **1** with dimethoxymethane (**2**; methylal) in the presence of Nafion-H catalyst (Table).

$$\underset{\textbf{1}}{R{-}OH} + \underset{\textbf{2}}{H_3C{-}O{-}CH_2{-}O{-}CH_3} \xrightarrow[-\,H_3C{-}OH]{\text{Nafion-H}\,,\,\nabla} \underset{\textbf{3}}{R{-}O{-}CH_2{-}O{-}CH_3}$$

Table. Methoxymethyl Ethers **3** prepared

R	Solvent	Reaction time [h]	Yield[a] [%]	m.p. [°C] or b.p. [°C]/torr found	m.p. [°C] or b.p. [°C]/torr reported
	**2**	10	90	42-46°/25	
	2	48[b]	87		
	**2**	10	90	73-76°/3.75	
n-C_9H_{19}–	**2**	10	93	40-43°/0.05	
n-C_7H_{15}–	**2**	10	96	35-36°/0.075	
n-$C_{11}H_{23}$–	**2**	10	93	80-82°/0.05	
	**2**+C_6H_6	16	65	32-34°/1.6	
	**2**+C_6H_6	16	57	110-115°/15	
	**2**+$CHCl_3$	24	75[c]	81-85°/3.75	66-68°/3
cholesterol	**2**+$CHCl_3$	16	70[d]	78.8°	76-78°[8]

[a] Yield of product isolated by distillation and characterized by I.R. and ^{1}H-N.M.R. spectroscopy. Purity ≥98% as determined by G.L.C. and ^{1}H-N.M.R. analysis.

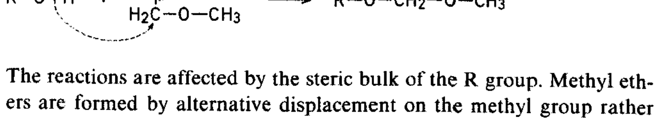
[b] Reaction at room temperature.

[c] Yield of 1-methoxyadamantane.

[d] Recrystallized from methanol.

The reaction is facile for primary alcohols, yielding the corresponding methoxymethyl ethers in almost quantitative yield. Excess dimethoxymethane (**2**) is also used as solvent and the reaction proceeds at a convenient rate at this reflux temperature (41 °C). (At room temperature, the reaction is more sluggish.) In the case of secondary alcohols, the reaction is slow under similar conditions. Therefore, benzene is used as a cosolvent to raise the reaction temperature and thus giving convenient reaction rates. The reaction takes a different course for bridgehead tertiary alcohols, which form methyl ethers, instead of methoxymethyl ethers. Ordinary tertiary alcohols yield only olefinic dehydration products under the acid-catalyzed reaction conditions.

These observations suggest that the reaction proceeds via protonated dimethoxymethane.



The reactions are affected by the steric bulk of the R group. Methyl ethers are formed by alternative displacement on the methyl group rather

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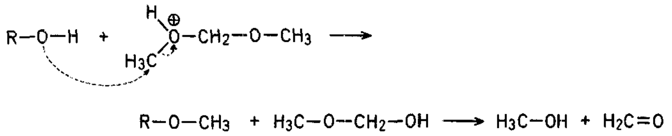
than the methylene group of protonated dimethoxymethane by the bulkier tertiary R group (which, in bridgehead systems, will not give elimination).



As mentioned, previously used phosphorus pentoxide- and *p*-toluenesulfonic acid-catalyzed preparations of methoxymethyl ethers, require tedious aqueous basic workup. As the present method necessitates only filtration of the Nafion-H resin, requires no aqueous workup, and gives good yields under mild conditions, it should be of practical utility.

Methoxymethyl Ethers 3; General Procedure:

A stirred solution of the corresponding alcohol **1** (10 mmol) in dimethoxymethane (**2**; 20 ml) is heated under reflux in the presence of Nafion-H (500 mg) under a dry atmosphere. The reaction is monitored by T.L.C. (silica gel/hexane) and G.L.C. (glass capillary column, 50 ft × 0.25 mm, OV-101, 60–100 °C). On completion of the reaction, the reaction mixture is filtered and the residue washed with dimethoxymethane (benzene in case of secondary alcohols) (2 × 5 ml). After evaporating the solvent, that crude product is purified by column chromatography on silica gel eluting with hexane.

In case of secondary alcohols, dimethoxymethane (5 ml) and benzene (40 ml, as a cosolvent) is used. Chloroform (40 ml) is used as a cosolvent for 1-adamantanol. Reactions are carried out at reflux temperature of the solvent.

Support of our work by the National Science Foundation and the National Institutes of Health is gratefully acknowledged.

Received: January 27, 1981

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