Iodotrimethylsilane-Catalyzed Preparation of Methoxymethyl Ethers of Primary and Secondary Alcohols with Dimethoxymethane[1]

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The methoxymethyl moiety is a useful protecting group for alcohols and phenols[2,3,4]. It is stable to a variety of commonly used reagents, e.g., strong alkali, Grignard reagents, butyllithium, lithium, aluminum hydride, etc., and is readily removed by mild acid treatment. The commonly employed method for the preparation of methoxymethyl ethers is based on the reaction of the corresponding alkoxide anions with chloromethyl methyl ether[5]. However, chloromethyl methyl ether (and bis[chloromethyl] ether which is a usual contaminant in the former) is a powerful carcinogen and its use is seriously limited[6,7]. In order to overcome this limitation, a number of alternative methods have been introduced. These include condensation of dimethoxymethane with the corresponding alcohols catalyzed by phosphorus pentoxide[8] or *p*-toluenesulfonic acid[9]. We have recently reported an improved method for the acid-catalyzed preparation of methoxymethyl ethers using perfluorinated solid superacidic Nafion-H which eliminates the usual aqueous work-up of the reaction mixture[10]. There is, however, the need to frequently carry out the reaction under milder and less acidic reaction conditions. In our continuing interest in utilizing iodotrimethylsilane in synthetic transformations, we observed that methoxymethyl ethers can be conveniently prepared from the corresponding alcohols and dimethoxymethane by iodotrimethylsilane-catalyzed reactions. This method is related to the tetrahydropyranylation of alcohols in the presence of bis[trimethylsilyl] sulfate[11].

When a solution of an alcohol (**1**) in dimethoxymethane is stirred in the presence of a few drops of iodotrimethylsilane, the related methoxymethyl ether (**2**) is obtained in generally excellent yield.

$$\underset{\mathbf{1}}{R-OH} + H_3CO-CH_2-OCH_3 \xrightarrow{(H_3C)_3SiJ} \underset{\mathbf{2}}{R-O-CH_2-OCH_3}$$

Both primary and secondary alcohols (**1**) can thus be smoothly converted into the corresponding methoxymethyl ethers (**2**). Tertiary alcohols, however, do not give methoxymethyl ethers in any significant yield but instead are converted into the corresponding iodides. This is not unexpected as tertiary alcohols are known to react rapidly with iodotrimethylsilane to give alkyl iodides[12,13].

It should be noted that the reaction can also be carried out using the *in situ* analoges of iodotrimethylsilane, for example allyltrimethylsilane/iodine (see Table).

Alkyl Methoxymethyl Ethers (2); General Procedure:

To a solution of the alcohol (**1**; 20 mmol) in dimethoxymethane (30 ml), iodotrimethylsilane (a few drops) or allyltrimethylsilane/iodine (0.1 mmol) is added and the mixture is stirred under a nitrogen atmosphere while the progress of the reaction is monitored by G.L.C. (glass capillary column, 50 ft × 0.25 mm, OV-101; 80–180°C). After completion of reaction, the mixture was poured into a mixture of ether (30 ml), water (30 ml), and saturated sodium thiosulfate solution (~5 ml). The organic layer is washed with water (2 × 25 ml) and saturated sodium chloride solution (25 ml) and is dried with magnesium sulfate. Evaporation of solvents gives crude product **2** which is purified by column chromatography (silica gel, hexane/chloroform).

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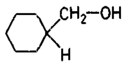
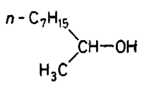
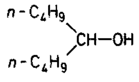
Table. Preparation of Alkyl Methoxymethyl Ethers (**2**) from Alcohols (**1**)

Alcohol	Catalyst[a]	Reaction time[b] [h]	Yield[c] [%]	m.p. or b.p./torr [°C] found	m.p. or b.p./torr [°C] reported[10]
	ITMS	1	95	b.p. 44-46°/25	b.p. 42-46°/25
n-C_7H_{15}—OH	ITMS	1	90	b.p. 33-36°/0.05	b.p. 35-36°/0.075
	ATMS / J_2	4	92		
n-C_9H_{19}—OH	ITMS	2	94	b.p. 41-43°/0.05	b.p. 40-43°/0.05
	ATMS / J_2	4	92		
n-$C_{11}H_{23}$—OH	ITMS	3	95	b.p. 80-81°/0.05	b.p. 80-82°/0.05
	ATMS / J_2	6	94		
	ATMS / J_2	2	80[d]	b.p. 110-115°/15	b.p. 110-115°/15
	ITMS	1	80[d]	b.p. 102-104°/15	
cholesterol	ATMS / J_2	5[e]	76[d]	m.p. 78.2°	m.p. 78.8°

[a] ITMS = iodotrimethylsilane; ATMS = allyltrimethylsilane.

[b] All reactions were carried out at room temperature unless otherwise noted.

[c] Yield of isolated purified products. Purified by column chromatography (silica gel; hexane/chloroform). All products gave satisfactory I.R and ^{1}H-N.M.R. spectra.

[d] Remaining starting material recovered unreacted.

[e] Refluxed in dry benzene.

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[1] Synthetic Methods and Reactions, Part 120. For Part 119 see G. A. Olah, A. Husain, B. P. Singh, A. K. Mehrotra, *J. Org. Chem.*, submitted.

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