

## TRIMETHYLSILYLDIAZOMETHANE : A CONVENIENT REAGENT FOR THE O-METHYLATION OF ALCOHOLS<sup>1</sup>

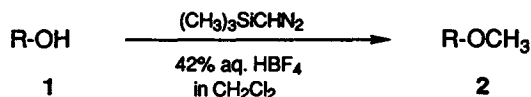
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**Abstract:** Trimethylsilyldiazomethane smoothly reacts with alcohols in dichloromethane in the presence of 42% aqueous fluoroboric acid to give methyl ethers in good to high yields.

Although a number of the methods for the O-methylation of alcohols are already known,<sup>2</sup> a novel general method is still required since the known methods have some drawbacks and limitations. We have already demonstrated that trimethylsilyldiazomethane (TMSCHN<sub>2</sub>) is quite useful as a reagent for the methyl esterification of carboxylic acids<sup>3</sup> and the O-methylation of phenols and enols.<sup>4</sup> As an extension of these works, we now wish to report that TMSCHN<sub>2</sub> can be also used for the O-methylation of alcohols.

We have found that TMSCHN<sub>2</sub> smoothly reacts with alcohols **1** in dichloromethane in the presence of 42% aqueous fluoroboric acid (FBA) to give the corresponding methyl ethers **2**.

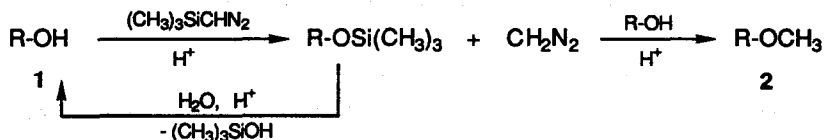


A typical experimental procedure is as follows : To a vigorously stirred mixture of **1** (1mmol) and FBA (209mg, 1mmol) in dichloromethane (4ml) was added dropwise TMSCHN<sub>2</sub><sup>5</sup> (1.8M hexane solution, 0.56ml, 1mmol) at 0°C during 4 min. The yellow color of TMSCHN<sub>2</sub> immediately disappeared in contact with the reaction mixture with evolution of nitrogen. The stirring was continued at 0°C, and three further portions of TMSCHN<sub>2</sub> (0.28ml (0.5mmol), 0.14ml (0.25mmol), and 0.14ml (0.25mmol)) were added dropwise at intervals of 20 min. The mixture was stirred at 0°C for further 30 min, poured into water, and extracted with dichloromethane. The organic layer was washed with water, dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (BW-820MH, Fuji Davison) to give **2**.

The results are summarized in Table. Various alcohols including primary, secondary, and tertiary ones smoothly react with TMSCHN<sub>2</sub> to give **2**. 2-Hydroxymethylcyclohexanone and 10-undecene-1-ol give the corresponding methyl ethers without any change of their ketone and carbon-carbon double bond functions, respectively. Monosaccharide such as methyl 2,3,6-tri-O-benzoyl- $\alpha$ -D-glucopyranoside also undergoes the O-methylation though sluggishly. Interestingly, in the case of N-benzylethanolamine, the selective N-methylation proceeds to give N-benzyl-N-methylethanolamine in 38% yield. Dichloromethane seems to be the reaction solvent of choice. The use of diethyl ether, benzene, or acetonitrile as the solvent gives poorer results.

Although 2-(1-naphthyl)ethanol reacts with TMSCHN<sub>2</sub> in the presence of one equivalent of FBA (contained 6.7 equivalents of water) to give the methyl ether in 93% yield, the use of 0.05 equivalents of

FBA (contained 0.33 equivalents of water) gives a mixture of the methyl ether (44%) and 2-(1-naphthyl)ethyl trimethylsilyl ether (32%). These results suggest the reaction mechanism as follows :



Diazomethane is known to react with alcohols in the presence of catalytic amounts of concentrated FBA to give the methyl ethers.<sup>6</sup> However, this method is very tedious and all manipulations should be carried out with great care. The present method using commercially available TMSCHN<sub>2</sub> is easy to conduct, appears to be general, and will provide a convenient method for the O-methylation of alcohols.

Table<sup>a</sup>) O-Methylation of Alcohols with TMSCHN<sub>2</sub>

Run	Starting Alcohol	Yield of product (%)	bp(°C)/mmHg <sup>b</sup> or mp(°C)
1	2-(1-Naphthyl)ethanol	93	165-170/17
2	1-Dodecanol	92	120-125/12
3	4- <i>n</i> -Butoxybenzylalcohol	76 <sup>c</sup> )	115-125/3
4	1-Methyl-1-dodecanol	84	90-95/1.5
5	Dihydrocholesterol	85	82-83 <sup>d</sup> )
6	1,1-Dimethyl-1-decanol	74	75-80/0.9
7	10-Undecene-1-ol	88	100-105/12
8	Geraniol	67	105-110/30
9	Ethyl 12-Hydroxydodecanoate	90	125-130/4
10	2-Hydroxymethylcyclohexanone	84	110-115/26
11	Methyl 2,3,6-Tri-O-benzoyl- $\alpha$ -D-glucopyranoside	32(93) <sup>e</sup> )	
12	N-Benzylethanolamine	-f, g)	

a) All products gave satisfactory spectral data and elemental analysis. b) By Kugelrohr distillation. c) Bis(4-*n*-butoxybenzyl) ether was also obtained in 12% yield. d) Lit.,<sup>6</sup> mp 84-85°C. e) Yield in parentheses is based on recovered starting alcohol. f) Two equivalents of FBA was used, and the reaction was carried out in the presence of sodium chloride (50mg) for the purpose of salting-out. g) N-Benzyl-N-methylethanolamine was obtained as a sole isolable product in 38% yield.

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