

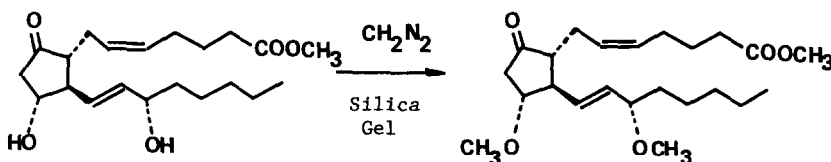
A MILD METHYLATION OF ALCOHOLS WITH DIAZOMETHANE  
CATALYZED BY SILICA GEL

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**ABSTRACT;** Alcohols including prostaglandins, geraniol, and carbohydrate, can easily be methylated with diazomethane in the presence of silica gel.

During the course of our synthetic study on PG analogs,<sup>1)</sup> we have been interested in the preparation of methyl ether analogs of prostaglandins in search of long duration of action. Since E-type prostaglandins(PGE<sub>1</sub>, PGE<sub>2</sub> etc.) are unstable in basic or acidic media,<sup>2)</sup> new technique was needed for direct methylation of them. We wish to describe herein a new methylation of alcohols with diazomethane catalyzed by silica gel.

A suspension of PGE<sub>2</sub> methyl ester and neutral silica gel in ether was treated with gaseous diazomethane to give the mixture of 11(O),15(O)-dimethyl, 11(O)-methyl, and 15(O)-methyl-PGE<sub>2</sub> methyl ester without any concomitant formation of PGA<sub>2</sub> or methylated products of PGA<sub>2</sub>. When PGE<sub>2</sub> methyl ester was treated with a large excess of gaseous diazomethane introduced, 11(O),15(O)-dimethyl-PGE<sub>2</sub> methyl ester was selectively obtained. The results are



summarized in Table 1 with other examples. As shown, primary, secondary, and even tertiary alcohols react smoothly with diazomethane to afford corresponding ethers in a high yield. No rearrangement was observed during the methylation of geraniol. Thus, geraniol afforded methyl ether as a sole product. Besides olefine and ketone, acetate which is partly removed during the benzylation of acetylated carbohydrates with benzyl bromide-Ag<sub>2</sub>O, survived the reaction conditions.<sup>3)</sup> Partial methylation of carbohydrates occurs in the reaction of them with diazomethane,<sup>4)</sup> while silica gel catalyzed reaction afforded completely methylated product.

In addition to neutral silica gel, silicic acid, neutral or acidic aluminum oxide and zeolite can also catalyze the methylation of alcohols. All of these solid catalysts seem to have nearly the same catalytic activity. Although no concrete kinetic studies have been carried out, the more polar substances feasible to be adsorbed on silica gel, reacted more rapidly than nonpolar substances(compare example 5 or 9 with example 8.).

In mechanism of silica gel catalyzed methylation, intermediate formation of methyl diazonium silicate and subsequent nucleophilic attack of alcohols(or alkoxides) were hypothe-

sized. During the reaction, the intermediate methyl diazonium silicate gradually decomposes into methylated silica gel and nitrogen, because of the weak nucleophilicity of silicate anion, so that the catalytic activity of silica gel slowly decreases.

Although alcohols can be methylated with diazomethane in the presence of Lewis acid such as  $ZnCl_2$ <sup>5)</sup> and  $BF_3$ <sup>6)</sup>, or  $HBf_4$ <sup>7)</sup>, silica gel catalyzed methylation will add a useful methodology to the alkylation of alcohols owing to mild and neutral reaction condition and simple manipulation of 'work up'.

TABLE 1 Methylation of Alcohols with Diazomethane Catalyzed by Silica Gel<sup>a</sup>

Example	Starting Material	Amount of Diazo-		Conversion (%)	Methyl Ethers (yield, %)			
		Silica Gel (wt.eq.)	methane (mol eq.)		mono-	di-	tri-	tetra-
1	PGE <sub>2</sub> methyl ester	60	180	100	42 <sup>b,c</sup>	38 <sup>b</sup>	-	-
2	"	60	600	100	0	100 <sup>b</sup>	-	-
3	PGE <sub>1</sub> methyl ester	37	92	100	36 <sup>b,c</sup>	22 <sup>b</sup>	-	-
4	PGF <sub>2</sub> α methyl ester	11	15	100	70 <sup>d,f</sup>	30 <sup>f</sup>	0	-
5	"	33	30	100	10 <sup>f</sup>	85 <sup>f</sup>	5 <sup>f</sup>	-
6	5-Iodo-PGI <sub>1</sub> methyl ester	65	100	100	52 <sup>b,e</sup>	24 <sup>b</sup>	-	-
7	Benzyl alcohols	92	66	49	100 <sup>g</sup>	-	-	-
8	Geraniol	100	60	25	100 <sup>g</sup>	-	-	-
9	Butane-2,3-diol	100	50	95	20 <sup>g</sup>	80 <sup>g</sup>	-	-
10	tert-Amyl alcohol	30	80	54	100 <sup>g</sup>	-	-	-
11	α-Methyl-D(+)-glucoside	66	840	100	0	0	0	98 <sup>b</sup>

a) To the mixture of starting material and silica gel in ether was introduced the diazomethane, generated from N-methyl-N-nitroso-p-toluene-sulfonamide, in the temperature range of 0-10°C.

b) Isolated yield. c) 11(O)-methyl:15(O)-methyl = 1:1. d) 9(O)-methyl:11(O)-methyl:15(O)-methyl = 1:4:2. e) 11(O)-methyl:15(O)-methyl = 4:6. f) Analytical yield (TLC Scanner, Shimadzu CS-900). g) Analytical yield (GLPC).

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