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Methylation of Alcohols and Phenols Adsorbed on Silica Gel with Diazomethane

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Alcohols and phenols adsorbed on silica gel react with diazomethane and quantitatively afford the corresponding methyl ethers. Alumina and titanium dioxide are also effective adsorbents for the reaction.

Carboxylic acids are easily *O*-methylated with diazomethane to give the corresponding esters. Alcohols, however, do not react with diazomethane because of their weak acidity. The methylation of alcohols with diazomethane requires a Lewis acid catalyst such as boron trifluoride,[1] tetrafluoroboric acid,[2] zinc chloride[3] and aluminum chloride[4] in solution. Mineral acids are not suitable for the catalyst because they react with the reagent. Recently, silica gel suspended in ether was found to be effective for the methylation of unstable alcohols with diazomethane.[5] However, these types of catalysts are not always effective for a complete methylation of alcohols.

The use of solid adsorbents as a reaction medium is becoming increasingly widespread in organic syntheses[6] involving oxidation,[7] alkylation,[8] and condensation.[9] We have successfully utilized solid adsorbents in the acetylation of alcohols and phenols by ketene,[10] and a selective monomethyl esterification of dicarboxylic acids by diazomethane[11] or by dimethyl sulfate.[12] The advantages of solid adsorbents are simpler work-ups, milder reaction conditions and higher selectivities.

Recent spectroscopic studies[13] have proved that alcohols are chemisorbed on alumina or silica as alkoxides or a species in which O-H bonds are strongly polarized. These facts persuaded us to use these oxides as a reaction medium as well as the catalyst for the methylation of alcohols with diazomethane. We report here that gaseous diazomethane easily reacts with alcohols and phenols adsorbed on oxides to quantitatively give the corresponding methyl ethers.

Results and Discussion

Methylation of 1-Decanol. 1-Decanol, which had been adsorbed on silica gel, was treated with gaseous diazomethane. The reaction profile of the methylation of 1-decanol is shown in Fig. 1. 1-Decanol was methylated in proportion to the amounts of diazomethane introduced, and 1-methoxydecane was quantitatively obtained when about 20 molar equivalents of diazomethane were used.

In the absence of silica gel, 1-decanol in ether was hardly methylated even by the addition of 200 molar equivalents of diazomethane. Clearly, silica gel is essential for this reaction.

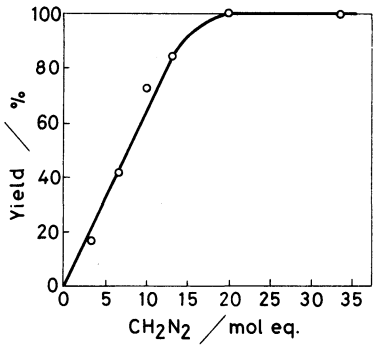

Fig. 1. Reaction profile of methylation of 1-decanol on silica gel.

Table 1. Methylation of Alcohols and Phenols on Silica Gel[a]

Substrate	CH_2N_2/mol equiv	Yield/%[b]
1-Decanol	34	99
1-Decanol[c]	159	83
1-Decanol[d]	200	< 1
Geraniol	34	96
Benzyl alcohol	34	99
1-Methyl-1-hexanol	68	99
Cyclohexanol	68	99
2-Methyl-2-hexanol	68	99
2-Methyl-2-butanol	68	99
Phenol	34	99
2-*t*-Butylphenol	34	93
2,6-Diisopropylphenol	34	79
2,6-di-t-Butylphenol	68	< 1
1-Naphthol	34	98
2-Naphthol	34	93

a) To a 1.0 g of silica gel 0.32 mmol of alcohol or phenol was added. b) Determined by GLC and/or HPLC. c) Silica gel suspended in ether. d) In an ether solution in the absence of silica gel.

Methylation of Alcohols and Phenols. Various kinds of alcohols and phenols were tested; the results are summarized in Table 1. As well as primary and secondary alcohols and phenol, tertiary alcohols and hindered phenols were quantitatively methylated. Geraniol, which holds two olefinic double bonds, was also methylated in a high yield with the bonds intact. However, 2,6-di-*t*-butylphenol was not methylated, even with 300 molar equivalents of diazomethane. On the basis of molecular models, 2,6-di-*t*-butylphenol could not be adsorbed on the silica gel surface with the hydroxyl group on account of a steric hindrance

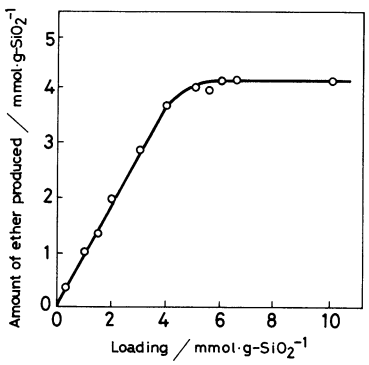

Fig. 2. Formation of 1-methoxydecane from the different amount of 1-decanol adsorbed on silica gel. The reaction was carried out with 34 molar equivalents of diazomethane.

involving the two *t*-butyl groups. These results suggest that the methylation requires the adsorption of hydroxyl group on the oxide.

While using silica gel suspended in ether, 1-decanol could not be quantitatively methylated and the product, 1-methoxydecane, was obtained in an 83% yield with a large excess of diazomethane (159 molar equivalents). Ohno et al.[5] reported that the maximum values of conversion for some alcohols such as geraniol, benzyl alcohol, and 2-methyl-2-butanol were no more than 25—54%. These less reactive alcohols could be exhaustively methylated by using our method.

Effect of Surface Coverage on Methylation. Adsorbed samples of 1-decanol with various amounts of loading were prepared and treated with diazomethane. As shown in Fig. 2, the amount of produced 1-methoxydecane was proportional to the amount of loading. Beyond the value of 4.0 mmol g^{-1}-SiO_2, however, the amount of 1-methoxydecane did not increase even upon the addition of large excess amounts of diazomethane.

The limiting value of loading (4.0 mmol g^{-1}-SiO_2) appears to be the saturation amount of 1-decanol on the silica gel surface. The surface area of the silica gel used was found to be 371 $m^2 g^{-1}$ by a BET measurement. Thus, one molecule of 1-decanol occupies 0.15 nm^2 on the silica gel surface. The critical cross section for aliphatic alcohols determined from their monomolecular layers spread over a flat surface of water is 0.216 nm^2.[14] The agreement between these two cross-sectional values implies that 1-decanol molecules are adsorbed as a monomolecular layer on silica gel. The methylation seems to occur on the silica gel surface by a reaction of diazomethane with the 1-decanol adsorbed as the monomolecular layer.

Effective Adsorbents. Various kinds of solid adsorbents were tested in the methylation of 1-decanol. A small amount of diazomethane was introduced into the reaction vessel in order to estimate the effectiveness of each adsorbent. Table 2 shows that the yields of 1-methoxydecane decreased in the following order:

Table 2. Effect of Adsorbent[a]

Adsorbent[b]	Yield/%[c]	Relative value
SiO_2	41.4	1
Al_2O_3	11.5	0.28
TiO_2	6.5	0.16
Zeolite(Na-Y type)	2.1	0.05
SiO_2-Al_2O_3[d]	2.0	0.05
Celite 545	1.3	0.03
ZnO	0.4	0.01
MgO	0.0	0.00
Non	0.0[e]	0.00

a) To a 1.0 g of adsorbent 0.32 mmol of 1-decanol was added. b) Dried at 110°C for one hour in a stream of N_2 before adsorption of 1-decanol. c) Yield of 1-methoxydecane, when 6.8 molar equivalents of diazomethane was introduced at room temperature. d) 28.6% Al_2O_3. e) In an ethyl ether solution in the absence of any additives.

$$SiO_2 > Al_2O_3 > TiO_2.$$

A sufficient amount of diazomethane resulted in a complete conversion on Al_2O_3 and/or TiO_2. On zeolite, silica-alumina, Celite 545, and zinc oxide the methylation occurred slightly. Magnesium oxide did not cause a reaction.

IR and inelastic electron tunneling spectroscopy clearly showed that surface-bound alkoxides or strongly polarized O-H bonds were formed when alcohols were introduced to silica or alumina.[13] The chemisorption of alcohol on the oxides undoubtedly facilitates a dissociation of protons from the hydroxyl group. It has been reported that methylation of alcohols is initiated by the portonation of diazomethane with the aid of a Lewis acid.[4] Probably, the protonation of diazomethane occurs on the oxides by accepting protons released from the adsorbed alcohol and the protonated diazomethane attacks the resulting alkoxide to form the methyl ether.

Experimental

Materials. A modified method was adopted for the preparation of diazomethane from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide.[15] Diazomethane is toxic and potentially explosive. All the operations were performed in a well ventilated hood and behind a safety screen. The following preparation of diazomethane is illustrative. In a 25 ml distillation flask, 2 g of potassium hydroxide, 3.2 ml of water and 11 ml of diethylene glycol dimethyl ether were placed. A stream of dry nitrogen (10 ml min^{-1}) was passed through the flask and led to a drying tube containing potassium hydroxide pellets. The flask was kept at 30°C and 6.88 g (31 mmol) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide was added by small portions over 20 min. Nitrogen was passed for an additional 30 min in order to carry the diazomethane thoroughly into the reaction vessel for methylation. The total amount of dry diazomethane was measured to be 22 mmol (70% yield) by a GLC analysis instead of titration.[16] The amount of diazomethane was controlled by the amount of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide used.

Silica gel (Wako Chemicals; 200 mesh, for column chro-

matographic use), alumina (the reference catalyst of the Catalysis Society of Japan (JRC-ALO-5; 60—200 mesh) and titanium dioxide (JRC-TIO-1; powder), zeolite (JRC-Z-Y4.8; powder, Na-Y type), silica-alumina (JRC-SAH-1; powder, 38% alumina), Celite 545 (Johns-Manville), zinc oxide (Kokusan Chemicals), and Magnesium oxide (Kamishima Chemicals) were used. These solids were dried at 110 °C for a day and stored in a desiccator.

Other materials were commercial products and were used without further purification.

Reaction Procedure. Typically, 51 mg (0.32 mmol) of 1-decanol was added into a reaction vessel of a glass column (15-mm i.d.) containing 1.0 g of silica-gel powders. The reaction vessel was allowed to stand for a day, although lumps of silica gel usually disappeared within an hour. Then, a calculated amount of diazomethane was introduced into the reaction vessel in a stream of nitrogen at room temperature. After passage of the diazomethane through the vessel, the adsorbate was immediately eluted with ethyl acetate. The eluate was condensed and the product was analyzed by GLC and/or HPLC. 1-Methoxydecane was obtained in a 99% yield and no reaction other than methylation was observed.

The amount of diazomethane necessary for a complete methylation of 1-decanol could be reduced by the following method. The 3 molar equivalents of diazomethane were introduced into a reaction vessel maintained at −78 °C. The color of the silica gel near the entrance end of the reaction vessel changed to yellow. The vessel, sealed with septum, was allowed to stand for 12 h at room temperature to ensure a complete conversion.

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