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Methylation of Alcohols, Phenols, and Carboxylic Acids, and Selective Monomethylation of Diols and Dicarboxylic Acids with Dimethyl Sulfate by Use of Alumina

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Alcohols in cyclohexane give their methyl ethers in high yields by the use of a combination of dimethyl sulfate and alumina. Some diols and dicarboxylic acids adsorbed on alumina react with dimethyl sulfate and produce the corresponding monomethyl ethers and esters in high selectivities.

The utilization of solid adsorbents such as alumina and silica gel as a reaction media represents one of the recent advances of organic syntheses.[1–3] The use of solid adsorbents is advantageous to milder reaction conditions, simpler work-ups and higher selectivities. We have successfully applied solid adsorbents to the acetylation of alcohols and phenols,[4] the selective monomethyl esterification of dicarboxylic acids,[5] and the selective reduction of dicarbonyl compounds.[6] We then extended this approach to the methylation of various compounds containining hydroxyl groups.

Alcohols, phenols and carboxylic acids are methylated with dimethyl sulfate in the presence of alkali. Sodium hydroxide is used for the methylation of glucose,[7,8] 1-(2,5-dihydroxyphenyl)ethanone,[9] *m*-hydroxybenzaldehyde[10] and gallic acid.[11] Potassium hydroxide and potassium carbonate are also used for the methylation of benzoic acid derivatives.[12,13] We report here the successful methylation of alcohols with dimethyl sulfate in which the alcohols were converted to the ethers in high yields by the addition of alumina instead of alkali to the reaction system. Diols and dicarboxylic acids were selectively monomethylated by a modified method. Details of these reactions are described in this paper.

Results and Discussion

Methylation of Alcohols, Phenols and Carboxylic Acids. Primary, secondary and tertiary alcohols were quantitatively converted to the corresponding methyl ethers as shown in Table 1. Phenols were converted in lower yields, and further low yields were found for carboxylic acids. The yields of methylated compounds of phenols and carboxylic acids hardly increased even though a large amount of dimethyl sulfate was used. In the absence of alumina alcohols, phenols, and carboxylic acids were not methylated with dimethyl sulfate at all.

In the methylation of benzyl alcohol Merck's neutral aluminum oxide and silica alumina (28.6% Al_2O_3) were also effective, and gave benzyl methyl ether in yields of 52 and 41%, respectively, under the same reaction conditions described in Table 1.

Selective Monomethylation of Diols and Dicarboxylic Acids. Table 2 shows the reactions that proceeded to give, selectively, monomethylated compounds in high yields. It was confirmed that no reactions took place in the absence of alumina. In the conventional method using potassium carbonate,[13] 55% methyl hydrogen terephthalate and 24% dimethyl terephthalate were formed at the point of a 79% conversion of terephthalic acid. It shows a typical example of a two-stage reaction proceeding via the intermediate methyl hydrogen terephthalate.

It is reasonable to assume that dicarboxylic acids are chemisorbed on alumina as monocarboxylate anions and that there carboxyl groups are left in positions

Table 1. Methylation of Alcohols, Phenols, and Carboxylic Acids[a)]

Substrate	Me_2SO_4/mol eq	Yield/%[b)]	Substrate	Me_2SO_4/mol eq	Yield/%[b)]
1-Heptanol	1.5	66	o-*t*-Butylphenol	1.5	7.1
1-Heptanol	3	85	2,6-Dimethylphenol	1.5	10
1-Heptanol	6	95	2,6-Diisopropylphenol	1.5	0.1
1-Heptanol	12	99	2,6-Di-*t*-butylphenol	1.5	0.1
1-Decanol	12	92	1-Naphthol	1.5	38
Benzyl alcohol	12	99	2-Naphthol	1.5	44
2-Heptanol	12	76	Benzoic acid	1.5	12
Cyclohexanol	12	75	Benzoic acid	10	13
2-Methyl-2-hexanol	12	97	Heptanoic acid	1.5	8.0
Phenol	1.5	36	Undecanoic acid	1.5	7.0
Phenol	12	36			

a) Substrate (0.467 mmol), alumina (1.0 g), and cyclohexane (8 mL) were refluxed for 2 h. b) Determined by GLC, GSC, and/or HPLC.

Table 2. Selective Monomethylation of Diols and Dicarboxylic Acids[a]

Substrate	Yield of methylated compound/%[b]	
	mono-	di-
1,4-Benzenedimethanol	73	9.2
1,4-Benzenedimethanol[e]	0.0	0.0
1,10-Decanediol	86	13
Terephthalic acid	72	12
Terephthalic acid[c]	6.5	0.0
Terephthalic acid[d]	4.1	0.2
Terephthalic acid[e]	0.0	0.0
Terephthalic acid[f]	55	24
Isophthalic acid	63	19
Phthalic acid	80	8.0
Adipic acid	93	6.7
Suberic acid	99	0.0
Suberic acid[e]	0.0	0.0
1,12-Dodecanedioic acid	97	3.2

a) Each experiment was carried out at room temperature in cyclohexane (8 mL) using the adsorbed sample (1 g), which held diol (0.467 mmol/g-alumina) or diarboxylic acid (0.400—0.467 mmol/g-alumina). In the case of diols 12 mol eq of dimethyl sulfate, and in the case of dicarboxylic acid 1.5 mol eq of dimethyl sulfate was used. b) Determined by GLC, GSC, and/or HPLC. c) In 1,4-dioxane. d) In formamide. e) In DMF solution in the absence of alumina. f) Using potassium carbonate according to the usual method[13] in the absence of alumina.

remote from the alumina surface.[5] A low yield (12%; see Table 1) for methyl esterification of benzoic acid, which is strongly adsorbed on alumina,[14] indicates that the carboxylate anion has a very low reactivity toward dimethyl sulfate. The high selectivities for monomethyl esterification of dicarboxylic acids adsorbed on alumina might be due to the much higher reactivities of free carboxyl groups than those of carboxylate anions.

Experimental results suggested that the adsorbed molecules of aliphatic dicarboxylic acids align with their axis perpendicular to the adsorbent surface in a closed-packed rigid array.[5] Selective monomethyl esterification of aliphatic dicarboxylic acids is attributable to the characteristic adsorption mode which protects the carboxyl groups being adsorbed on alumina, but not those in the free state, from the attack of dimethyl sulfate. With the aid of this protecting effect, the terminal chlorination of octanoic acid adsorbed on alumina was attained.[15]

In contrast to the carboxylic acids, mono-alcohols adsorbed on alumina were methylated with dimethyl sulfate to produce the corresponding ethers almost quantitatively as shown in Table 1. This result means that the hydroxyl group became reactive with dimethyl sulfate by adsorption on alumina. IR and inelastic electron tunneling spectroscopy proved that alcohols are chemisorbed on alumina as alkoxides or the species in which O–H bonds are strongly polarized.[16,17] The selective monomethylation of diols is attributable to their adsorption states in which the hydroxyl groups at one end of the molecule are activated through chemisorption on alumina to react with dimethyl sulfate, and suggests that there free hydroxyl groups are left in positions remote from alumina surface.

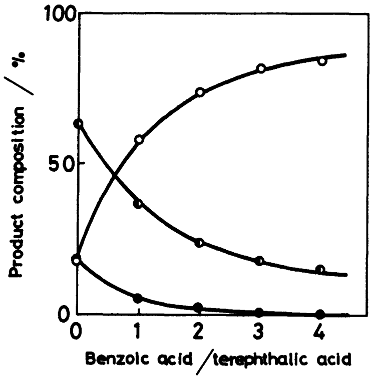

Fig. 1. Effect of benzoic acid addition on methylation of terephthalic acid on alumina. (○): Terephthalic acid, (◐): methyl hydrogen terephthalate, (●): dimethyl terephthalate. Dimethyl sulfate: Terephthalic acid=3:1 (mole).

Effect of Benzoic Acid Addition on Reactivity of Terephthalic Acid. Benzoic acid was added to cyclohexane suspension of alumina adsorbing terephthalic acid. The reactivity of terephthalic acid toward dimethyl sulfate decreased with increasing amounts of benzoic acid, as shown in Fig. 1. A desorption of terephthalic acid into cyclohexane was not detected.

Carboxylic acids exist stably in a dimer state in a solution as well as in a crystal. Benzoic acid in cyclohexane (98 mmol L^{-1}) was confirmed to be in a dimer state on the basis of the IR absorption spectrum, which has only a band at 1695 cm^{-1} assignable to dimeric acid in the reagion of C=O streching vibration. Benzoic acid added to the reaction system probably forms acid dimers by using the free carboxyl groups of terephthalic acid adsorbed on alumina. This gives rise to the decrease in the reactivities of terephthalic acid.

In 1,4-dioxane or formamide, the adsorbed terephthalic acid was hardly converted to methyl hydrogen terephthalate (see Table 2). This is, perhaps, due to the solvation of free carboxyl groups which impedes the attack of dimethyl sulfate.

Experimental

Materials. Alumina (the reference catalyst of the Catalysis Society of Japan; JRC-ALO-5), Merck's neutral aluminum oxide 90 for column chromatography and silica alumina (28.6% Al_2O_3: JRC-SAH-1) were dried at 110 °C for a day and stored in a desiccator. Cyclohexane was dried by refluxing with calcium hydride and distilled. Other materials were commercially available and used without further purification.

Preparation of Adsorbed Sample. Diols were adsorbed on alumina by the following procedure: One gram of alumina was added to an ether solution of diol in which 0.467 mmol of diol was contained; then, ether was eliminated under a reduced pressure.

Dicarboxylic acids were adsorbed on alumina according to a previously reported procedure: One gram of alumina powder was added to 10 mL of a 1% solution of acid in DMF, the mixture was allowed to stand for 8 h; then, the alumina was filtered off and dried.[5]

Reaction Procedure. Alcoholes, phenols, and benzoic acid: Typically, 1.0 g of alumina, 54.3 mg (0.467 mmol) of 1-heptanol and 706 mg (5.60 mmol) of dimethyl sulfate was added to 8 mL of cyclohexane, and refluxed for 2 h. Then, the alumina was filtered off and eluted with ethyl acetate. After the eluate was concentrated, the product was analyzed by GLC. The analysis showed that a 1-methoxyheptane product was obtained at about 99% yield.

Diols and Dicarboxylic Acids: About 6.4 mL (5 g) of cyclohexane and 0.5 g of the adsorbed sample were placed in a reaction vessel. A calculated amount of dimethyl sulfate was introduced and the reaction was started with vigorous stirring at room temperature. Subsequent procedures were the same as those for mono-alcohols, except for washing the eluate with an alkali solution. The products were analyzed by GLC, GSC and/or HPLC.

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