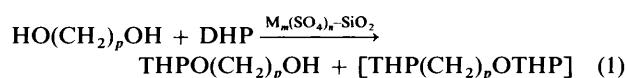


Highly Selective Monoetherification of Symmetrical Diols Catalysed by Metallic Sulfate Supported on Silica Gel

Takeshi Nishiguchi,* Katsumi Kawamine and Tomoko Ohtsuka
Faculty of Liberal Arts, Yamaguchi University, Yamaguchi 753, Japan

Several symmetrical primary and secondary diols from C₂ to C₁₆ have been protected in high selectivity by tetrahydropyranyl ether formation catalysed by metallic sulfates supported on silica gel. This selective etherification is simple and practical. The selectivity of monoether formation depends upon the composition and the volume of solvents. The selectivity can be explained by preferential adsorption of diols to monoethers and the formation of thin liquid films of diols on the surface of catalysts caused by the limited dissolution of the diols in DHP-hexane mixtures.

It is important for organic synthesis to offer general methods for selective protection of multiple identical functional groups in a similar chemical environment.¹ The use of reagents or reactants on insoluble inorganic supports, compared with that of their homogeneous counterparts, often has the advantage of ease of set-up and work-up, mild reaction conditions, increased yields, and greater selectivity.² We have already reported the highly-selective monoacylation of symmetrical diols by transesterification catalysed by metallic sulfates supported on chromatographic silica gel [M_m(SO₄)_n-SiO₂].³ This study suggests that selective reactions such as monoetherification of diols may occur when polarity and solubility successively decrease from starting material to the final product and the polarity of solvents is suitable. Protection of hydroxy groups by etherification is common in organic syntheses⁴ and we have already reported selective formation of monotetrahydropyranyl (THP) ethers in the reaction of symmetrical diols with 3,4-dihydro-2H-pyran (DHP) catalysed by M_m(SO₄)_n-SiO₂ in a preliminary communication.¹ Here we report on reaction (1) in more detail.



Results and Discussion

Selective Monoetherification of Symmetric Diols.—The monoetherification in this study was carried out by stirring a diol (1 mmol) and compound M_m(SO₄)_n-SiO₂ (3 mmol g⁻¹ of SiO₂) in a mixture of DHP and an alkane with monitoring by TLC and GLC. For synthetic purposes, the reactions were terminated by removing the catalysts by filtration when diethers began to be detected clearly by TLC. Table 1 shows that all the symmetrical primary and secondary diols examined from C₂ to C₁₆ gave the corresponding monoethers in acceptable yields, confirming the general applicability and practical utility of this method.* Reducing the quantity of catalyst raised the selectivity, although reaction periods became longer. The selectivity to monoethers was little affected by metallic sulfates on silica gel, so long as the activity of the salts was high (Table 2). This result suggests that the sulfates work as simple Lewis or protonic acids. The inference that sodium and potassium hydrogen sulfates function as protonic acids is supported by the fact that the corresponding sulfates showed no catalytic activity, as in the dehydration of alcohols.⁵

Rationalization of the Selectivity.—Fig. 1 shows an example of the time dependence of product yield in the etherification of

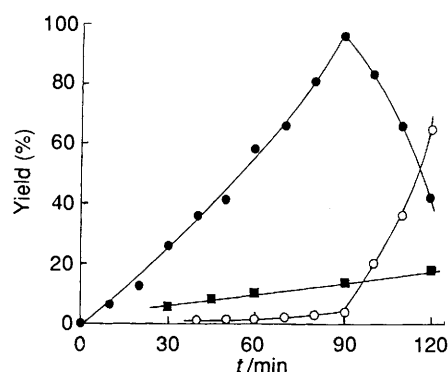


Fig. 1 Yield vs. reaction time. Butane-1,4-diol (1 mmol) and Al₂(SO₄)₃-SiO₂ (0.01 mmol) were stirred at room temperature in DHP-hexane (1:1; 2 cm³); monoether (●); diether (○). Yields of the monoether (■) in the reaction catalysed by unsupported Al₂(SO₄)₃ (0.01 mmol).

butane-1,4-diol in DHP-hexane. The yield of the diether was 4% until that of the monoether reached 96%, but rapidly increased after this stage of reaction. These results show that the monoether reacted further after most of the diol had been consumed. The yield of monoether increased nearly linearly over a lengthy time period, which suggests that adsorption of the diol on the catalyst takes place. Since similar results were obtained in the reactions of other diols and catalysts the generality of these phenomena was confirmed. The formation of monoether was promoted when diol consumption took place and the maximum rate of formation of the diether was higher than that of the monoether. These facts suggest that the affinity of diols for the catalyst is high enough for the adsorption of DHP to be strongly hindered by diols.

The selectivity for monoether formation may be explained at least partly by assuming that as long as the diol (which is more polar and more likely to be adsorbed on the surface of the

* It has been reported that the reaction of butane-1,3-diol with DHP catalysed by hydrochloric acid in dimethyl sulfoxide or by pyridinium *p*-toluenesulfonate in CHCl₃ gives the usual THP-ethers whereas the reaction catalysed by HCl, CH₃SO₃H, and *p*-toluenesulfonic acid in CHCl₃ gives the isomerized compounds possessing a 1,3-dioxane ring. (See R. Nouquier, *Tetrahedron Lett.*, 1982, 23, 2951). However, the monoether obtained in the reaction of propane-1,3-diol with DHP-catalysed Al₂(SO₄)₃-SiO₂ in DHP-hexane, pyridinium *p*-toluenesulfonate in CHCl₃, *p*-toluenesulfonic acid in CHCl₃, and pyridinium *p*-toluenesulfonate in dimethyl sulfoxide was found to be the same by ¹H NMR spectroscopic and GLC analysis. The corresponding reactions of ethane-1,2-diol also gave similar results.

Table 1 Selective monoetherification of diols^a

Diol	Amount of catalyst/mmol	DHP (%)	<i>T</i> /°C	<i>t</i> /min	Yield (%)	
					Monoether	Diether
Ethane-1,2-diol	0.04	20	Rt ^b	150	94	5
Propane-1,3-diol	0.01	70	Rt ^b	120	91	3
Propane-1,3-diol	0.04	20	Rt ^b	150	95	7
Butane-1,4-diol	0.01	50	Rt ^b	90	96	4
Pentane-1,5-diol	0.04	20	Rt ^b	150	78	8
Hexane-1,6-diol	0.01	20	45	85	74	10
Hexane-2,5-diol	0.01	20	40	600	82	3
Cyclohexane-1,4-diol	0.04	20	Rt ^b	480	71	9
Octane-1,8-diol	0.01	15	65	90	76	9
Decane-1,10-diol	0.005	10	78	150	76	10
Dodecane-1,12-diol ^c	0.01	12	85	300	76	8
Dodecane-1,12-diol ^{c,d}	0.015	12	85	240	79	8
Hexadecane-1,16-diol ^c	0.01	12	95	240	72	9

^a A diol (1 mmol) and Al₂(SO₄)₃-SiO₂ were stirred in DHP-hexane (2 cm³). Yields were determined by GLC. ^b Room temperature. ^c The reaction was carried out in DHP-octane (2 cm³). ^d SnSO₄ was used instead of Al₂(SO₄)₃.

Table 2 Selective monoetherification of butane-1,4-diol catalysed by M_n(SO₄)_n-SiO₂^a

<i>M</i>	Amount/mmol	<i>t</i> /min	Yield (%)	
			Monoether	Diether
Ti ^{IV}	0.0025	60	91	5
Ce ^{III}	0.005	70	93	6
NaH	0.005	110	95	7
Fe ^{III}	0.005	172	92	5
Al ^{III}	0.01	210	94	7
KH	0.02	50	91	6
Sn ^{II}	0.02	95	94	6
Zn ^{IIb}	0.01	220	94	4

^a Butane-1,4-diol (1 mmol) and a catalyst were stirred at room temperature in DHP-hexane (1:1; 2 cm³). ^b Reaction temperature 75 °C.

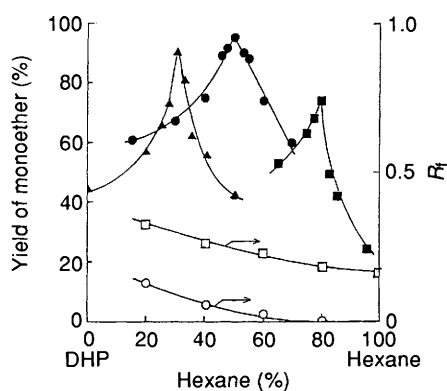


Fig. 2 Yield and *R_f* value vs. solvent composition. A diol (1 mmol) and Al₂(SO₄)₃-SiO₂ (0.01 mmol) were stirred at room temperature or 45 °C (hexane-1,6-diol) in DHP-hexane (2 cm³). Yields of the monoethers: in the reactions of propane-1,3-diol (▲), butane-1,4-diol (●), and hexane-1,6-diol (■) at 3%, 5% and 10% yields of the corresponding diethers. *R_f* values: hexane-1,6-diol (○) and its monoether (□).

supported catalysts than the monoether) remains it will react preferentially. The preferential adsorption of diols is inferred from the lower *R_f* values of hexane-1,6-diol than those of the corresponding monoether on silica gel TLC plates (Fig. 2). As described earlier, using smaller amounts of the catalyst generally raised the selectivity. This may be due to reduced

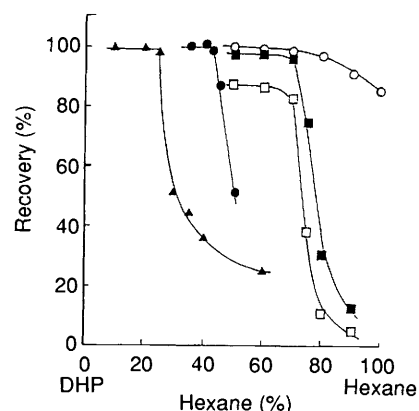


Fig. 3 Recoveries from supernatant solutions after stirring the diols and their monoethers (1 mmol) in DHP-hexane (2 cm³) at room temperature vs. solvent composition. Recoveries: propane-1,3-diol (▲); butane-1,4-diol (●); hexane-1,6-diol (■) and its monoether (○); hexane-1,6-diol (□) in the presence of silica gel. Hexane-1,6-diol and its monoether were recovered from the solution at 45 °C (see Experimental section).

adsorption of the monoether even in the presence of small amounts of the diol. The catalytic activity of unsupported Al₂(SO₄)₃ was much lower than that of the supported sulfate (Fig. 1).*

The selectivity in the monoacylation of diols seems to be partly explained by the separation of diols from ester-alkane mixtures (solvents) in addition to the preferential adsorption.† A similar explanation seems also to be applicable to the selective monoetherification. When the percentage of hexane in the solvent systems was gradually increased in the reactions of propane-1,3-diol, butane-1,4-diol, and hexane-1,6-diol, yields of the monoethers at which yields of the corresponding diesters were 3%, 5% and 10% showed maximum values. The maxima were realized when the percentages of hexane were 30%, 50% and 80%, respectively (Fig. 2). When these diols were stirred in DHP-hexane mixtures for a short while, the percentages of the diols detected again in the supernatant solutions, namely recovery, depended on the composition of the solvent (Fig. 3, see Experimental section). When the percentages of hexane

* When metallic sulfates were not supported, the etherification was slow but considerable selectivity was observed. A study to explain the selectivity in the absence of silica gel is planned.

† Unpublished results.

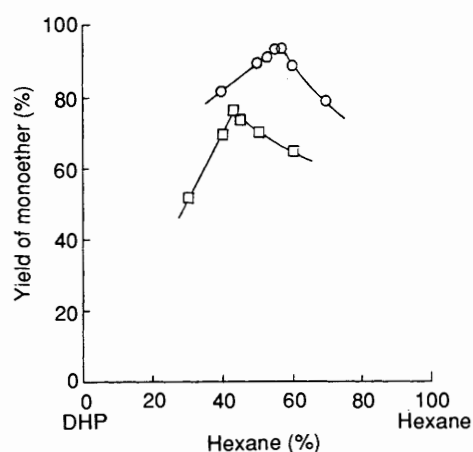


Fig. 4 Yields of the monoether at 5% yield of the diether in the reaction of butane-1,4-diol (1 mmol) and $\text{Al}_2(\text{SO}_4)_3\text{-SiO}_2$ (0.01 mmol) in 1 cm^3 (O) and 4 cm^3 (□) of DHP-hexane at room temperature vs. solvent composition

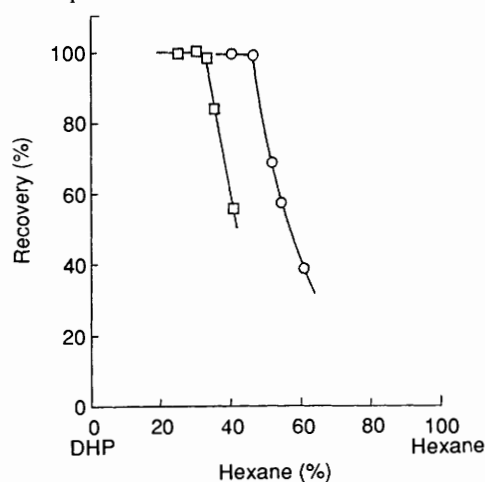


Fig. 5 Recoveries of butane-1,4-diol after stirring the diol (1 mmol) in 1 cm^3 (□) and 4 cm^3 (O) of DHP-hexane vs. solvent composition (see Experimental section)

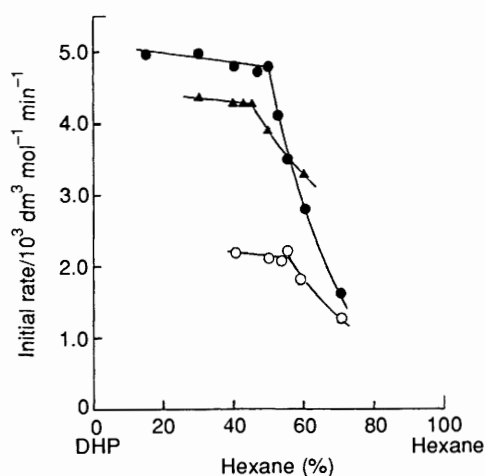


Fig. 6 Initial rate vs. solvent composition. Butane-1,4-diol (1 mmol) and $\text{Al}_2(\text{SO}_4)_3\text{-SiO}_2$ (0.01 mmol) were stirred at room temperature in 1 cm^3 (▲), 2 cm^3 (●), and 4 cm^3 (O) of DHP-hexane.

reached 25%, 43% and 75%, the recoveries began to decrease sharply at hexane percentages of 25%, 43% and 75%. These results suggest that a proportion of the diols separated without dissolving completely in solvents of high hexane content. Probably the separated diols form thin liquid films on the

surface of solid catalysts when they are present. In contrast, the recovery of the monotetrahydropyranyl ether of hexane-1,6-diol decreased little at any composition of the solvent, showing that the monoether scarcely separated (Fig. 3). It is inferred that (a) the monoethers are formed in the thin diol layers on the surface of the catalysts, then (b) move away into the DHP-hexane layers by a process resembling continuous extraction, and (c) remain without reacting further in the DHP-hexane layers which contain no solid catalysts. Fig. 3 also shows that the recovery of hexane-1,6-diol decreased by ca. 10% by the addition of silica gel. This suggests that adsorption of the diol to supported catalysts occurs. The inference that the formation of thin diol layers increases the selectivity of the etherification is also supported by the result that the selectivity decreased considerably when the reaction temperatures were lower than the melting points of the diols. The assumption that the excessive addition of hexane makes the diol layer too thick and lowers the selectivity by reducing the reaction rate of diols in the diol layer will be described later.

When the amount of solvent was doubled in the reaction and halved in the recovery of butane-1,4-diol, Figs. 2 and 3, the percentage of hexane required to give the maximum yield of monoethers changed from 50% to 57% and to 43% (Fig. 4) and the percentage at which the recoveries of the diol began to decrease changed from 43% to 45% and 34%, respectively (Fig. 5). This result corresponds to the fact that the larger the carbon number of the diols, the higher the ratio of hexane in the solvents required to give maximum yields of monoethers, since an increase in amount of solvent has the same effect as an increase in the solubility of the diols. These results suggest that the solvents required to give maximum monoether selectivity can be prepared by adjusting the composition and the volume in such a way that the percentage of alkanes is 5–7% higher than the percentage at which the recovery of diols begin to fall.

Initial rates for the monoetherification of diol were readily obtained since no remarkable induction periods were observed (see, e.g., Fig. 1). The rate of reaction of butane-1,4-diol decreased slightly and then sharply according to the percentage increase of hexane present in the solvents (Fig. 6). This result suggests that the surface of the catalyst is almost covered with a monolayer of the diol, provided that thick diol layers are not formed and that the attachment of DHP to the surface of the catalyst is arrested after the formation of the thick diol layers (owing to the partial insolubility of the diol). By changing the amount of the solvent from 2 to 4 ml and 1 ml the percentage of hexane, at which the sharp decrease of the rate began, changed from 50% to 56% and 45%, respectively. These values are nearly the same as the percentage of hexane required to give maximum selectivity. This result suggests that the decrease in selectivity at high percentages of hexane is caused by a decrease in the reactivity of the diols, because the selectivity is determined by the relative reaction rates of the diols and the monoethers in the diol and in the DHP-hexane layers.

Experimental

Reagents, solvents and silica gel WB-300 (Fuji-Davison, 230–400 mesh) were purchased and used without purification. Solvents were stored over 3 Å molecular sieves. Supported reagents were prepared by the method reported in the previous paper.⁵ The loading amount of the metallic salts was 3 mmol g^{-1} of silica gel. $\text{Al}_2(\text{SO}_4)_3$ and $\text{Ce}(\text{SO}_4)_2\text{-SiO}_2$ were dried at 230°C for 1 h under vacuum ($4\text{--}10 \times 10^2 \text{ Pa}$). Supported NaHSO_4 and $\text{Ti}(\text{SO}_4)_2$ were dried for 1 h at 160 and 150°C , respectively. All the diethers for the calibration curves of GLC analyses were prepared by the conventional method using DHP and *p*-toluenesulfonic acid in CH_2Cl_2 .⁴ GLC

analyses were carried out using an apparatus comprising a direct injector equipped with a 25×0.53 mm i.d. fused silica capillary column, OV-1 or OV-1701. Analytical TLC was performed on pre-coated silica gel 60F₂₅₄ (E. Merck) glass-supported plates. ¹NMR (60 MHz) and IR spectra of all the products listed in Table 1 are satisfactory.

An Example of Selective Monoetherification of Diols for Analytical Purposes.—Butane-1,4-diol (88.6 mm³, 1 mmol), Al₂(SO₄)₃-SiO₂ (6.8 mg, 0.01 mmol), and benzyl ether (an internal standard, 10 mm³) were stirred at room temperature in a DHP-hexane mixture (2 cm³; 1:1, v/v). The reaction mixture was subjected to GLC analysis using OV-1 at appropriate time intervals. The retention times of the monoether and the diether in the reaction were identical with those of the authentic samples prepared in the conventional method. Yields of monoethers at the yields of diethers designated in Figs. 2 and 4 were derived from product yield *vs.* time plots (e.g. Fig. 1).

An Example of Selective Monoetherification of Diols for Synthetic Purposes.—Butane-1,4-diol (0.50 cm³, 5 mmol) and Al₂(SO₄)₃-SiO₂ (44.1 mg, 0.07 mmol) were stirred at room temperature in a DHP-hexane mixture (10 cm³; 1:1, v/v). The reaction was monitored by TLC (1:1 EtOAc-hexane) and GLC. After being stirred for 3 h the presence of diether was clearly evidenced by TLC. The reaction mixture was filtered to remove the solid catalyst and the separated solid was washed with CCl₄ (5 cm³). The filtrate and washings were combined and evaporated. Chromatography (SiO₂, 1:4 EtOAc-hexane) gave the monoether (0.75 g, 86%), $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3400 (OH); $\delta_{\text{H}}(60 \text{ MHz; CCl}_4)$ 1.3–1.9 (10 H, m), 2.18 (1 H, s), 3.3–4.0 (6 H, m) and 4.49 (1 H, s).

An Example of Preparation of Authentic Samples of Monoethers and Diethers.—Into octane-1,8-diol (1.0 g, 6.85 mmol) and *p*-toluenesulfonic acid (0.02 g) in CH₂Cl₂ (25 cm³) and tetrahydrofuran (THF) (5 cm³) was added DHP (1 cm³, 11 mmol) dropwise over 10 min at room temperature with

stirring. The reaction was followed by TLC (1:3 EtOAc-hexane). After being stirred for 3.5 h the reaction mixture was washed with aqueous NaHCO₃ (5 cm³) and brine (5 cm³) and then solvent was evaporated. Chromatography (SiO₂, 1:9 EtOAc-hexane) gave the monoether (0.49 g, 31%) and the diether (0.95 g, 44%). For the monoether, $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3400 (OH); $\delta_{\text{H}}(60 \text{ MHz; CCl}_4)$ 1.2–1.7 (18 H, m), 2.10 (1 H, s), 3.0–3.9 (6 H, m) and 4.48 (1 H, s). For the diether, $\delta_{\text{H}}(60 \text{ MHz; CCl}_4)$ 1.2–1.7 (24 H, m), 3.0–3.9 (8 H, m) and 4.48 (2 H, s).

These ethers were used to make calibration curves for the GLC analysis using an internal standard.

An Example of Recovery of Diols.—Butane-1,4-diol (88.5 mm³, 1 mmol) were stirred at room temperature in a DHP-hexane mixture (2 cm³; 1:1, v/v) for 5 min and benzyl ether (10 cm³) was added as an internal standard. The reaction mixture was left for 5 min without stirring and the supernatant solution was submitted to GLC analysis using OV-1. The amounts of diols and solvents were the same as those used in the corresponding etherifications.

The recovery of butane-1,6-diol was also measured in the presence of SiO₂ (3.4 mg). The amount of SiO₂ was the same as that contained in Al₂(SO₄)₃-SiO₂ used in the corresponding etherification.

References

- 1 T. Nishiguchi and K. Kawamine, *J. Chem. Soc., Chem. Commun.*, 1990, 1766 and references cited therein.
- 2 *Preparative Chemistry Using Supported Reagents*, ed. P. Laszlo, Academic Press, San Diego, 1987.
- 3 T. Nishiguchi and H. Taya, *J. Am. Chem. Soc.*, 1989, **111**, 9102.
- 4 T. W. Greene, *Protecting Groups in Organic Synthesis*, Wiley, New York, 1981.
- 5 T. Nishiguchi and C. Kamio, *J. Chem. Soc., Perkin Trans. 1*, 1989, 707.

Paper 1/02728J

Received 7th June 1991

Accepted 1st October 1991