

## Short Communication

# Selective acylation of a sterically hindered hydroxyl group of unsymmetrical diols containing a primary hydroxyl group such as 1,5-hexanediol in the presence of silica gel with acetyl chloride

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**ABSTRACT:** The more hindered monoacetates were selectively formed in the presence of silica gel with acetyl chloride by refluxing a suspension of unsymmetrical diols containing a primary hydroxyl group such as 1,5-hexanediol preadsorbed on silica gel. Such regioselectivity was observed through preferential adsorption via a primary hydroxyl group of the diols. Copyright © 2003 John Wiley & Sons, Ltd.

**KEYWORDS:** monoacylation; monoacetylation; unsymmetrical diol; 1,5-hexanediol; silica gel; acetyl chloride; adsorption isotherm

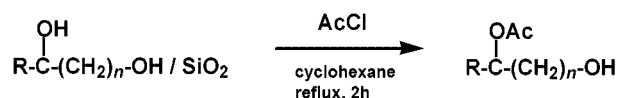
The application of solid adsorbents such as alumina and silica gel (SiO<sub>2</sub>) as solid supports in organic synthesis affords new procedures for selective reactions<sup>1–3</sup> involving oxidation,<sup>4</sup> alkylation,<sup>5</sup> condensation,<sup>6</sup> monomethyl esterification<sup>7</sup> and acetylation.<sup>8</sup> The significant potential of adsorbents can be recognized more fully for milder reactions conditions and selective organic transformations. It is important for organic chemists to develop methods that permit the selective protection or functionalization of one functional group of a bi- or multiple-functional molecule. Protection of hydroxyl groups by acylation is common in organic syntheses. In the case of polyols, monoprotection is achieved in some cases by carefully controlled reaction conditions,<sup>9</sup> continuous extraction,<sup>10</sup> the use of SiO<sub>2</sub>,<sup>11</sup> alumina,<sup>12</sup> phase-transfer catalysts<sup>13</sup> and insoluble polymer supports,<sup>14</sup> or via the formation of cyclic compounds.<sup>15</sup> We have previously reported selective monoacylation of symmetrical diols on SiO<sub>2</sub>,<sup>11c</sup> and we chose here the acylation of unsymmetrical diols because of the synthetic importance of this procedure.<sup>9b</sup> Recently, several methods have been developed for the selective acylation at the less hindered site<sup>16</sup> or at the more hindered site<sup>17</sup> of an unsymmetrical diol. We report here the direct and notably preferential acetylation of sterically hindered hydroxyl groups of diols on SiO<sub>2</sub> and the relationship between the adsorption

of the diol 1,5-hexanediol and its reactivity for selective acetylation.

Acetylation of unsymmetrical diols adsorbed on SiO<sub>2</sub> was performed via the following method (adsorption method) (Scheme 1). Alcohols were adsorbed on SiO<sub>2</sub> (C-200, Wako Chemicals) as follows: 1 g of SiO<sub>2</sub> was added to an Et<sub>2</sub>O solution of the alcohol; solvent was then eliminated under reduced pressure. The solid obtained (adsorption sample) and acetyl chloride (AcCl) were added to 50–100 ml of cyclohexane and refluxed for 2 h. The reaction period of 2 h was sufficient for the reaction to reach completion. After the reaction the mixture had been filtered the solid was washed with distilled water and DMF. The washings plus the filtrate were concentrated and the products were analyzed by GLC with triphenylmethane as an internal standard. The products were identified spectrometrically via comparison with authentic samples.

The results of acylation of unsymmetrical diols are listed in Table 1. Selectivity for the formation of monoacetates is defined by







$$S_{\text{mono}} = 100[\text{yields of monoacetates} / (\text{yields of monoacetates} + \text{yield of diacetate})]$$



**Scheme 1**

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**Table 1.** Selective monoacetylation of unsymmetrical diols on SiO<sub>2</sub><sup>a</sup>

Entry	Substrate	Yield <sup>b</sup> (%)	Selectivity (%)	
			S <sub>mono</sub> <sup>c</sup>	S <sub>hind</sub> <sup>d</sup>
1		60.2 <sup>e</sup>	78.0	69.8
2		56.0	64.2	48.9
3	(0 °C) <sup>f</sup>	69.2	87.3	89.6
4	(Kieselgel) <sup>g</sup>	56.6	78.2	71.4
5	(Mixing) <sup>h</sup>	52.8	69.1	36.0
6	(Homogeneous) <sup>i</sup>	51.9	54.0	35.1
7		83.3	87.4	38.4
8		99.9	99.9	71.8
9		78.1	88.8	32.6
10		51.9	74.7	96.5
11		58.2	99.2	73.4

<sup>a</sup> An adsorption sample containing 0.3 mmol g<sup>-1</sup> SiO<sub>2</sub> of each alcohol was refluxed for 2 h in cyclohexane with AcCl (1.5 equiv.). SiO<sub>2</sub> [Wakogel C-200, specific surface area (s) = 371 m<sup>2</sup> g<sup>-1</sup>].

<sup>b</sup> Combined yield of both isomeric monoacetates.

<sup>c</sup> Selectivity for monoacetates: S<sub>mono</sub> = [monoacetates/(monoacetates + diacetate)] × 100.

<sup>d</sup> Selectivity for sterically hindered monoacetate: S<sub>hind</sub> = (sterically hindered monoacetate/monoacetates) × 100.

<sup>e</sup> An adsorption sample containing 2.0 mmol g<sup>-1</sup> SiO<sub>2</sub> of 1,5-hexanediol was used.

<sup>f</sup> Reaction period was 18 h.

<sup>g</sup> SiO<sub>2</sub> (Merck Kieselgel 60, s = 357 m<sup>2</sup> g<sup>-1</sup>).

<sup>h</sup> Mixing method: SiO<sub>2</sub> (100 mg) was added to a 1,4-dioxane solution (5.8 ml) of 1,5-hexanediol (23.6 mg, 0.20 mmol), and the suspension obtained was refluxed for 2 h. A 0.20 mmol amount of 1,5-hexanediol corresponds to 2.0 mmol g<sup>-1</sup> of SiO<sub>2</sub> loaded amount if all the diol adsorbs on SiO<sub>2</sub>.

<sup>i</sup> 0.034 mol l<sup>-1</sup> solution of 1,5-hexanediol in 1,4-dioxane in the presence of pyridine (1 equiv.) was refluxed.

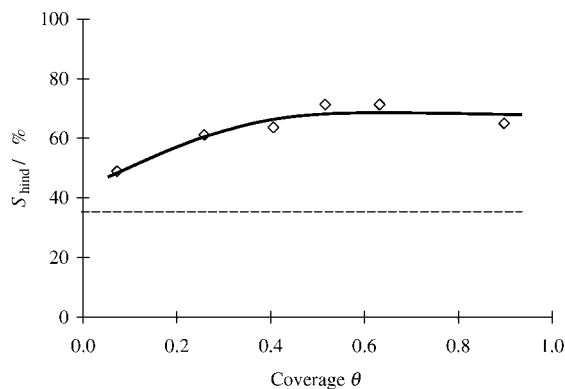
Selectivity for the formation of sterically hindered monoacetate is defined by

$$S_{\text{hind}} = 100(\text{yield of sterically hindered monoacetate} / \text{yields of monoacetates})$$

According to the adsorption method, high selectivities of S<sub>mono</sub> were observed for the diols, and the corresponding monoacetates were selectively formed. High selectivities of S<sub>hind</sub> were also observed, and the corresponding sterically hindered monoacetates were selectively obtained except for the cases of 1,3-butanediol and 1,2-hexanediol (entries 7 and 9). In the case of 1,5-hexanediol as a model compound, both S<sub>mono</sub> and S<sub>hind</sub> were notably improved compared with those in a homogeneous reaction conditions (entry 6). The selectivities were not significantly improved by the mixing method (entry 5). Higher S<sub>mono</sub> and S<sub>hind</sub> were observed with higher loading amounts and lower temperatures (entries 1 and 3). Merck Kieselgel was also an effective adsorbent for this method (entry 4). The highest selectivities were observed at a reaction temperature of 0 °C to give 87.3% for S<sub>mono</sub> and

89.6% for S<sub>hind</sub> (entry 3). Breton *et al.* reported a successful investigation using Al<sub>2</sub>O<sub>3</sub> in 1,5-hexanediol, recording values of 53% as the yield of monoacetates, 68% for S<sub>mono</sub> and 46% for S<sub>hind</sub>.<sup>17a</sup> In our adsorption method using Merck neutral Al<sub>2</sub>O<sub>3</sub> (specific surface area = 108 m<sup>2</sup> g<sup>-1</sup>), we obtained a 40.5% yield of monoacetates, 62.4% for S<sub>mono</sub> and 25.8% for S<sub>hind</sub>. Different surface coverages of 1,5-hexanediol on Al<sub>2</sub>O<sub>3</sub> would cause the different selectivities. SiO<sub>2</sub> was an effective adsorbent in our method to achieve direct and notably selective acetylation of the sterically hindered site of the diols.

The dependence of the surface coverage  $\theta$  of 1,5-hexanediol on SiO<sub>2</sub> on S<sub>hind</sub> was investigated (Fig. 1). The saturation amount ( $\theta = 1$ ) was estimated as 3.9 mmol g<sup>-1</sup> SiO<sub>2</sub> by measurement of the adsorption isotherm, discussed later. High selectivities were obtained, on the whole, compared with that under homogeneous reaction conditions. A slight increase in S<sub>hind</sub> was observed with increase in  $\theta$ , and S<sub>hind</sub> showed a constant value of ca. 70% in the range of  $\theta$  values exceeding ca 0.3. The inherent reactivities of the hydroxyl groups of alcohols were evaluated under homogeneous reaction conditions by competitive acylation of appropriate monofunctional alcohols, 1-hexanol (primary), 2-hexanol (secondary) and 3-methyl-3-pentanol (tertiary), in the absence of pyridine. In general, a base such as pyridine is frequently added to combine with the HCl formed during the reaction, but it is not essential and is not always needed for the reaction.<sup>18</sup> The resulting reactivities decreased in the order *prim*-OH > *sec*-OH, *tert*-OH (Table 2). The reactivities changed on adsorption on SiO<sub>2</sub> to the following order: *sec*-OH, *tert*-OH > *prim*-OH. SiO<sub>2</sub> suppressed the reactivity of primary OH. The relatively weak adsorption of a counterpart of OH to *prim*-OH would affect S<sub>hind</sub> in unsymmetrical diols. This seems to lead to preferential acylation of sterically hindered OH groups. Acetylation has the possibility of intramolecular transfer of an acetyl group in the case of a 1,2-diol



**Figure 1.** Dependence of surface coverage of 1,5-hexanediol on selectivity S<sub>hind</sub>. The dashed line shows the value of S<sub>hind</sub> in homogeneous reaction. S<sub>hind</sub> shows high selectivities, on the whole, with a slight increase with increase in  $\theta$

**Table 2.** Competitive acetylation of mono-ols<sup>a</sup>

Method <sup>b</sup>	Substrate <sup>c</sup>	Relative reactivity <sup>d</sup>		
		primary:	secondary:	tertiary
Homogeneous	1° + 2°	1 <sup>e</sup> :	0.75	
Homogeneous	1° + 3°	1 <sup>f</sup> :		0.67
Adsorption	1° + 2°	1 <sup>g</sup> :	1.69	
Adsorption	1° + 3°	1 <sup>h</sup> :		1.38

<sup>a</sup> Each experiment was carried out under reflux for 2 h with AcCl (1 equiv.) in the absence of pyridine.

<sup>b</sup> Homogeneous: homogeneous reaction (0.03 mol l<sup>-1</sup> solution of each alcohol in 1,4-dioxane). Adsorption: adsorption method (3.0 mmol g<sup>-1</sup> SiO<sub>2</sub> of each alcohol,  $\theta = 0.8$ ).

<sup>c</sup> 1°, 1-hexanol; 2°, 2-hexanol; 3°, 3-methyl-3-pentanol.

<sup>d</sup> Relative reactivity of each alcohol based on a yield of primary acetate.

<sup>e-h</sup> Yields of 1-hexyl acetate correspond to

<sup>e</sup> 62.8%,

<sup>f</sup> 62.7%,

<sup>g</sup> 43.6% and

<sup>h</sup> 41.1%.

acetylation of 1-phenyl-1,2-ethanediol in homogeneous reaction conditions, as shown in entry 6 in Table 1 at a temperature 0 °C, showed values 55.3% for  $S_{\text{hind}}$ , and the value of  $S_{\text{hind}}$  was changed slightly by refluxing to 51.0%; the transfer would occur under homogeneous reaction conditions. Acetylation of 1-phenyl-1,2-ethanediol in a homogeneous reaction under the same reaction conditions as in entry 6 in Table 1 gave values of  $S_{\text{mono}}$  and  $S_{\text{hind}}$  of 50.8% and 51.4%, respectively, and moreover the reaction mixture was used in a reaction by the adsorption method in the absence of AcCl. The composition of the mixture did not change. This indicates that the transfer does not proceed by an adsorption method.

The adsorption isotherm of 1,5-hexanediol on SiO<sub>2</sub> in 1,4-dioxane showed Langmuir-type adsorption and reached a saturation  $E_{\infty}$  of 3.9 mmol g<sup>-1</sup> SiO<sub>2</sub> with an adsorption constant  $K_{\text{ad}} = 38 \text{ l mol}^{-1}$ . Table 3 summarizes the relative  $K_{\text{ad}}$  for appropriate monofunctional alcohols in addition to that for 1,5-hexanediol. A primary alcohol interacts more easily with the surface of SiO<sub>2</sub> and adsorbs more preferentially than secondary and tertiary alcohols. From molecular modeling, one molecule of 1,5-hexanediol, adsorbed on the surface via a single OH group with the free counterpart of the residue remote from the surface, occupies 0.16 nm<sup>2</sup>. The specific surface

**Table 3.** SiO<sub>2</sub> adsorption equilibria for alcohols<sup>a</sup>

Alcohol <sup>b</sup>	$K_{\text{ad}}(\text{alcohol})/K_{\text{ad}}(1\text{-hexanol})$
1,5-Hexanediol	1.2
1°	1 <sup>c</sup>
2°	0.78
3°	0.63

<sup>a</sup> Langmuir adsorption isotherms on SiO<sub>2</sub> (Wakogel C-200, surface area 371 m<sup>2</sup> g<sup>-1</sup>) in 1,4-dioxane suspension at 25 ± 0.2 °C.

<sup>b</sup> 1°, 1-hexanol; 2°, 2-hexanol; 3°, 3-methyl-3-pentanol.

<sup>c</sup> Adsorption constant  $K_{\text{ad}}$  equals 32 l mol<sup>-1</sup>.

area of the SiO<sub>2</sub> used is 371 m<sup>2</sup> g<sup>-1</sup> by BET measurement. Hence the saturation amount of 1,5-hexanediol gives an estimation of  $E_{\infty}$  of 3.9 mmol g<sup>-1</sup> SiO<sub>2</sub>, whereas  $E_{\infty}$  is estimated as 2.9 mmol g<sup>-1</sup> SiO<sub>2</sub> in the case of the compact adsorption of the alcohol in a bidentate fashion. The good agreement between the isotherm and the molecular modeling indicates that 1,5-hexanediol adsorbs on the surface via a single OH group. The results of a series of investigations imply that unsymmetrical diols adsorb on the surface of SiO<sub>2</sub> preferentially via a primary OH group, leaving the non-adsorbed OH group available for reaction. In addition, adsorption of the group on the surface would create a sterically congested environment which shields it from added reagents as suggested in recent papers.<sup>1-3,7a,16d,17a,19</sup> These would allow selective monoacylation at the more sterically hindered, non-adsorbed, site to give sterically hindered secondary and tertiary monoacetates.

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