

Selective Monoacetylation of Unsymmetrical Diols Catalyzed by Silica Gel-Supported Sodium Hydrogen Sulfate

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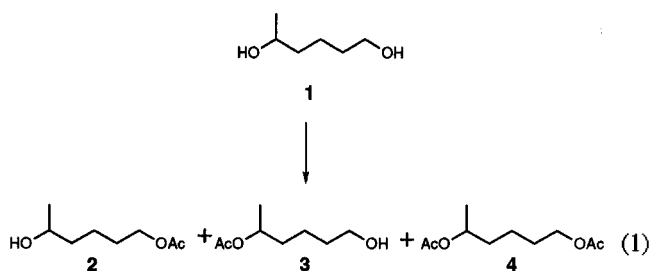
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Selective monoacetylation of unsymmetrical diols is an important procedure in organic synthesis as is reflected by the number of methods that have been developed to effect this transformation.^{1,2} Acetylation via the process of transesterification employing heterogeneous catalysts is of particular convenience since starting esters (e.g., ethyl acetate) are readily available and the catalyst may be easily separated from the product mixture through simple filtration.^{1c,3,4} High selectivity for acetylation of primary hydroxyl group sites in the presence of secondary sites has been previously reported with the use of alumina as catalyst.^{1c,3} This method suffers, however, from the large amounts of catalyst required (10 g of Al₂O₃/mmol of diol) as well as relatively high reaction temperatures (75–80 °C).

We were attracted to a heterogeneous silica gel-supported NaHSO₄ catalyst (NaHSO₄·SiO₂) that has been reported to readily acetylate simple alcohols via transesterification from EtOAc and also to selectively monoacetylate symmetrical diols.⁴ Small amounts of catalyst (57 mg/mmol of diol) at reasonable temperatures (60 °C) effectively catalyzed the transesterification process. To our knowledge no attempt has been made to employ this catalyst for the esterification of unsymmetrical diols.⁵ Herein we report our findings that NaHSO₄·SiO₂ is an excellent catalyst for the selective acetylation of unsymmetrical diols.

Upon warming a solution of 1 mmol of 1,5-hexanediol (1; eq 1) in 15 mL of a 30% solution of ethyl acetate in



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(2) *Protective Groups in Organic Synthesis*; Greene, T. W., Wuts, P. G. M., Eds.; Wiley: New York, 1991; pp 88–92.

(3) Posner, G. H.; Oda, M. *Tetrahedron Lett.* **1981**, *22*, 5003–5006.

(4) (a) Nishiguchi, T.; Kawamine, K.; Ohtsuka, T. *J. Org. Chem.* **1992**, *57*, 312–316. (b) Nishiguchi, T.; Taya, H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 172–173.

(5) Nishiguchi reported that attempted acetylation of symmetrical secondary diols resulted in the formation of substantial quantities of olefins along with the expected esters as a result of competing acid-catalyzed dehydration (ref 4). We speculate, therefore, that the reason the acetylation of unsymmetrical diols containing secondary sites was not investigated was the anticipation that they would similarly undergo dehydration.

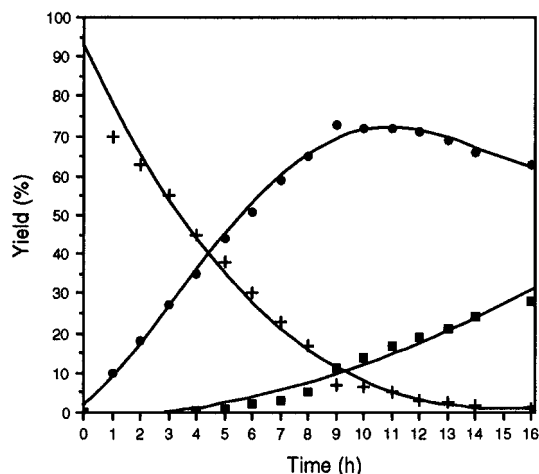


Figure 1. Plots of yield vs time for the NaHSO₄·SiO₂-catalyzed acetylation of **1** in a 30% solution of ethyl acetate in hexane at 50 °C: diol **1** (+), monoester **2** (●), and diester **4** (■). Monoester **3** is not shown in the figure for purposes of clarity; however, a maximum yield of 4% at 9 h was observed.

Table 1. Acetylation of Diol **1**^a

reaction conditions	% yield			ratio 2:3
	2	3	4	
NaHSO ₄ ·SiO ₂ , EtOAc/hexane, 50 °C, 9 h	71 ^b	4	12	95:5
Ac ₂ O (1 equiv), pyridine, CH ₂ Cl ₂ , 25 °C, 24 h	59	4	10	94:6
AcCl (1 equiv), CH ₂ Cl ₂ , 25 °C, 24 h	34	9	27	79:21
NaHSO ₄ , EtOAc/hexane, 50 °C, 8 h	65 ^c	3	20 ^b	96:4

^a Yields determined by GC analysis of the crude reaction mixtures. Values represent the average of at least three runs which agreed within ±1% unless otherwise specified. ^b Values of several runs agreed within ±2%. ^c Significant amounts of several unidentified volatile byproducts were observed in the GC analysis of the crude reaction mixture (see ref 6).

hexane in the presence of NaHSO₄·SiO₂ (100 mg, 3.0 mmol NaHSO₄/g) for 9 h followed by filtration, primary monoacetate **2** was afforded in 71% yield (Table 1). Only 4% of the secondary isomer **3** was formed under these conditions (ratio of 2:3 = 95:5). Some of the bisacetate **4** was also formed (12% yield). Figure 1 shows the progress of the reaction as a function of time. The yield of **2** was greatest at approximately 9 h, at which time the yield of **4** became significant. Reaction beyond this point was characterized by slow conversion of **2** to **4**. Selectivity for monoacetate **2** relative to **3** increased from 90:10 at 1 h to 95:5 at 9 h and finally to 97:3 at 10 h, after which it remained constant up to 14 h. A reaction temperature of 50 °C proved to be optimal for the reaction: higher temperatures (e.g., 65 °C) afforded lower yields of **2** (59% at 8 h), while lower temperatures (25 °C) resulted in impractically long reaction times. Results were reproducible within a few percent using the same catalyst over several months as well as with different batches of catalyst prepared in the same manner (see the Experimental Section).

The results obtained for acetylation over NaHSO₄·SiO₂ may be compared to those obtained using more conventional acetylating agents such as (1) Ac₂O, pyridine, (2) AcCl, and (3) transesterification over unsupported NaHSO₄ (Table 1). In all cases, lower yields and/or poorer selectivities were observed.⁶ Furthermore, the use of

Table 2. NaHSO₄·SiO₂-Catalyzed Acetylation of Unsymmetrical Diols^{a,b}

diol	% yield of primary monoacetate	ratio 1°:2°
	70	95:5 ^c
1 (R = Me)		
5 (R = Et)	72	98:2 ^c
6 (R = <i>n</i> -Bu)	70	95:5 ^d
7 (R = <i>sec</i> -Bu)	72	97:3 ^d
8	70	97:3 ^c
9	69 ^e	

^a Isolated yields. ^b Reaction conducted according to the general procedure described in the Experimental Section. ^c Ratio determined by gas chromatographic analysis of a mixture of isolated monoacetates. ^d Ratio determined by isolation of individual isomers. ^e 72 h of reaction time.

NaHSO₄·SiO₂ eliminates the need for corrosive reagents (i.e., Ac₂O and AcCl), allows for simple reaction workup via filtration, and does not require aqueous washings to remove catalysts or byproducts that characterize the more conventional methods.

Several acyclic diols were subjected to acetylation under these reaction conditions, and results similar to those of diol **1** were obtained (diols **5**–**8**, Table 2). Good yields of monoacetates and high selectivity for acetylation at the primary site (typically >95:5 for primary:secondary) were observed in each case. The progress of each of the reactions was followed by thin-layer chromatography, and the reaction halted (by cooling and filtration from the catalyst) upon disappearance of starting diol. In most cases 9 h was a sufficient reaction time. Allowing the reaction to proceed significantly beyond this point resulted in a decrease in yield of monoacetate and an increase in yield of the corresponding bisacetate (see Figure 1).

Acetylation of betulin (**9**) proceeded under these conditions to afford a 69% yield of the primary monoacetate although 72 h of reaction time was required. A 14% yield of the bisacetate was observed in addition to a trace amount of the secondary monoacetate. The lower reactivity of **9** relative to the acyclic diols may be attributed to the greater steric bulk encountered by this diol upon approach toward the surface of the silica gel.

(6) Interestingly, unsupported NaHSO₄ gave results similar in yield and selectivity to those of the supported reagent. However, gas chromatographic analysis of the reaction mixture revealed that upon attaining the highest yield (65%) of monoacetate **2** (at 8 h of reaction time) further conversion of **2** to **4** occurred at a much faster rate than was the case with the supported reagent (thus, a 70% yield of **2** was observed at 10 h using the supported reagent versus a 55% yield at 10 h over the unsupported reagent). In addition, appreciable amounts of unidentified volatile byproducts were produced from the reaction which were detected in only trace amounts using the supported reagent.

(7) Tietze, L. F.; Heinzen, H.; Moyna, P.; Rischer, M.; Neunaber, H. *Liebigs Ann. Chem.* **1991**, 1245–1249.

Table 3. Selective Acetylation of Saturated Hydroxyl Groups^{a,b}

diol	% yield of saturated monoacetate
	88
10	
	91
11	
	59
12	

^a Isolated yields. ^b Conducted according to the general procedure described in the Experimental Section, but at a reaction temperature of 67 °C and for the following reaction times: **10**, 6 h; **11**, 18 h; **12**, 72 h.

Selective acetylation of aliphatic hydroxyl groups in the presence of phenolic hydroxyl groups was achieved and in good yields (compounds **10**–**12**, Table 3). Furthermore, the saturated secondary hydroxyl group of β -estradiol (**12**) was acetylated preferentially over the phenolic hydroxyl group. Therefore, a qualitative ranking of hydroxyl group reactivity toward acetylation under these conditions of primary > secondary > phenol may be made.

In summary, a convenient and selective method of acetylation of unsymmetrical diols has been devised. This method affords greater yields of monoacetate products and higher selectivity for primary hydroxyl groups over secondary and phenolic groups than more traditional methods of acetylation. Lesser amounts of catalyst are required than previously reported heterogeneous catalysts. Finally, corrosive acetylating reagents are avoided, and reaction workup is effected through a simple filtration process.

Experimental Section

General. All reactions were conducted in oven-dried glassware. Unless otherwise indicated, reagents were obtained from commercial suppliers and used without further purification. Column chromatography was conducted on Merck grade 60 (230–400 mesh) silica gel. ¹H NMR spectra were recorded in CDCl₃ at 60 MHz. Gas chromatography was conducted on a Hewlett-Packard 5890 instrument using a 6' × 1/8" stainless steel column packed with 10% carbowax 20M on 80/100 Chromosorb W AW at 130 °C. All products were identified by comparison of their physical and/or spectroscopic data (IR, ¹H NMR) with published data (as for the monoacetates of **9**,⁷ **11**,⁸ and **12**^{1e}) or by comparison with the data of corresponding materials independently synthesized according to published procedures [for compound **2**, monoacetates of **5**–**8**, and **10**, see refs 2 (acetylation via Ac₂O, pyridine) and 3].

Preparation of the NaHSO₄·SiO₂ Catalyst. The following procedure is a modification of Nishiguchi's method:⁹ To a

(8) *Dictionary of Organic Compounds*, 5th ed.; Buckingham, J., Ed.; Chapman and Hall: New York, 1982; Fourth Supplement, p 207.

(9) Nishiguchi, T.; Kamio, C. *J. Chem. Soc., Perkin Trans. 1* **1989**, 707–710.

solution of 4.14 g (0.03 mol) of $\text{NaHSO}_4 \cdot \text{H}_2\text{O}$ in 20 mL of water in a 100-mL beaker containing a stir bar was added 10 g of SiO_2 (column chromatographic grade, 60 Å, 200–400 mesh). The mixture was stirred for 15 min and then gently heated on a hot plate, with intermittent swirling, until a free-flowing white solid was obtained. The catalyst was further dried by placing the beaker in an oven maintained at 120 °C for at least 48 h prior to use.

General Procedure for the Acetylation of Diols. A solution of 1 mmol of diol was dissolved in 15 mL of a 30% solution by volume of ethyl acetate in hexane in a 25-mL round-bottomed flask containing a stir bar. To this solution was added 100 mg of $\text{NaHSO}_4 \cdot \text{SiO}_2$ prepared as described above. The flask was fitted with a condenser and drying tube, and the mixture was heated to 50 °C with stirring. The reaction was monitored

by TLC (SiO_2 plates, eluting with 3:2 hexane/ethyl acetate, aqueous phosphomolybdic acid stain) until diol was no longer apparent (typically 9 h). The mixture was cooled and gravity-filtered, and the recovered catalyst was washed with CH_2Cl_2 (50 mL). The combined organics were concentrated on a rotary evaporator, and the resulting residue was column-chromatographed (SiO_2 , eluting with 3:2 hexane/ethyl acetate) to afford pure materials. Deviations from this general procedure are detailed in the footnotes of the tables.

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