Organic Reactions at Alumina Surfaces: An Extremely Simple, Mild and Convenient Method for Acetylating Primary Alcohols

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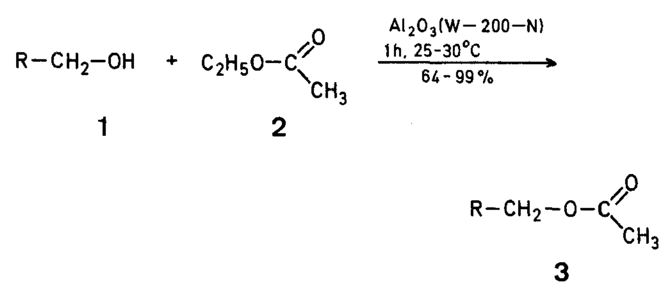
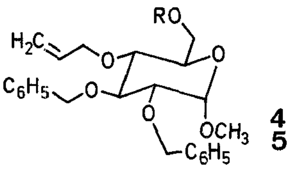
Esterification of an alcohol is achieved by treating the alcohol with an acylating agent in the presence of a base or an acid. Many different bases (e.g., sodium acetate, tertiary amines) and acids (e.g., Lewis acids, mineral acids) and many different acylating agents (e.g., acyl halides, acyl anhydrides, mixed acyl sulfonyl anhydrides, carboxylic acids, and acid derivatives) have been used[2]. Often these esterification procedures require chromatography for purification of the esters, and often they fail with base-sensitive or acid-sensitive compounds.

We report here a neutral, mild, simple, and *extremely convenient* new method for effective acetylation of primary alcohols **1** even in some base-sensitive (e.g. chlorohydrin) and acid-sensitive (e.g., ethylenic, pyridyl) primary alcohols. This heterogeneous procedure involves efficiently stirring a primary alcohol **1** (~ 100 mg) in ethyl acetate (**2**; ~ 10 ml) solvent over commercially available Woelm-200-neutral chromatographic alumina[3] at room temperature for one hour. Filtration and rotary evaporation of the ethyl acetate directly (i.e., without chromatography) provides the corresponding acetylated alcohol **3** in 64–99% yield and usually in excellent purity[4]. The Table lists the specific primary alcohols **1** which have been transesterified via this method.



Several features of the results shown in the Table 1 deserve comment. First, in many cases, the "crude" product acetate isolated simply by filtration and evaporation of ethyl acetate solvent is obtained in virtually complete purity (i.e., ratio of **3**:**1** ≈ 100). Second, 1,10-decanediol (**1j**) is converted effectively into the corresponding pure 1,10-diacetate (**3j**). Third, this heterogeneous acetylation reaction proceeds very well even in the presence of such base-sensitive functional groups as those of chlorohydrin (**1h**) and β-mercaptoethanol (**1g**) and such acid-sensitive groups as the pyridyl ring (**1i**) and carbon-carbon double bonds (**1b, c, f**). Even such a highly functionalized polyether primary alcohol as the carbohydrate **4** was converted into the corresponding pure acetate **5** in 81% yield by stirring in ethyl acetate over alumina at 75 °C for 12 hours.



4 R=H
5 R=CO–CH3

The best conditions generally involve about 10 g of alumina per 100 mg of primary alcohol. This procedure also works well on g scale; 1 g of cyclohexylmethanol (**1d**) was easily converted into its acetate by stirring over 100 g of alumina. In the absence of alumina, no transesterification occurs between 1-octadecanol (**1a**), for example, and ethyl acetate at room temperature even after 24 h. Similarly, with silica gel instead of alumina, no acetylation of cyclohexylmethanol (**1d**), for example, is observed.

Cyclohexylmethyl Acetate (3d); Typical Procedure:

Woelm-200-N alumina (~ 100 g) is transferred from its commercial metal container inside a nitrogen-filled glove bag to a 500 ml 3-necked

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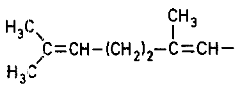
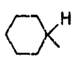
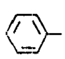
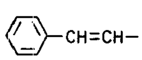
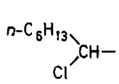
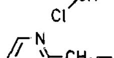
Table. Alumina-Promoted Acetylation of Primary Alcohols **1**

Product Acetate[a] No.	R	Yield [%]	Ratio of **3**:**1** in crude product[b]	m.p. [° C] or n_D (temp) of pure **3**	
				found	reported
3a	$n\text{-}C_{17}H_{35}$	96	33	32.5°[c]	34.5°[6]
3b	$n\text{-}C_8H_{17}\text{-}CH{=}CH\text{-}(CH_2)_7\text{-}$	99	~100	1.4528 (23 °C)	1.4528 (23 °C)[7]
3c	 $(H_3C)_2C{=}CH\text{-}(CH_2)_2\text{-}C(CH_3){=}CH\text{-}$	91	~100	1.4600 (25 °C)	1.4628 (15 °C)[8]
3d		85	~100	1.4440 (23 °C)	1.4451 (20 °C)[5]
3e		90	33	1.5200 (25 °C)	1.5232 (20 °C)[6]
3f		90	18[c]	1.5448 (25 °C)	1.5428 (20 °C)[9]
3g	$C_2H_6\text{-}S\text{-}CH_2\text{-}$	93	~100	1.4596 (24 °C)	1.4614 (18 °C)[10]
3h	 $n\text{-}C_6H_{13}\text{-}CH(Cl)\text{-}$	69	~100	—	—
3i		64[d]	—	1.4902 (26 °C)	1.4957 (20 °C)[11]
3j	$\text{-}(CH_2)_8\text{-}$	87	~100	1.4411 (22 °C)	—

[a] The product acetates were characterized by m.p., refractive index, and ^{1}H-N.M.R., in comparison with authentic samples.

[b] Determined by ^{1}H-N.M.R.

[c] Performed at 50 °C.

[d] Isolated by preparative T.L.C. from a 60 °C/27 h reaction using freshly dried ethyl acetate and only 5 g of alumina per 100 mg of 2-pyridineethanol, 10% of which was recovered.

round-bottomed flask which is then attached to an overhead mechanical stirrer via a stirring rod. Ethyl acetate solution (~150 ml) containing cyclohexylmethanol (1.021 g) is poured into the flask. Rapid stirring is performed for 1 h at 25-30 °C. Ethyl acetate (~100 ml) is then added, and the reaction mixture is poured into a sintered-glass funnel containing a pad (~2 cm) of Celite. Slow gravity filtration and rinsing with additional ethyl acetate is followed by rotary evaporation to produce spectroscopically pure cyclohexylmethyl acetate (**3d**); yield: 1.192 g (85%); n_D^{23}: 1.4440 (Ref.[5], n_D^{20}: 1.4451).

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.90$ ppm (d, 2H, $J = 6$ Hz).

Methyl 6-*O*-Acetyl-2,3-di-*O*-benzyl-4-*O*-(2-propenyl)-α-D-glucopyranoside (5):

To a 50 ml round-bottomed flask containing a magnetic stirring bar and Woelm-200-neutral alumina (6.6 g) is added methyl 2,3-di-*O*-benzyl-4-*O*-(2-propenyl)-α-D-glucopyranoside (**4**; 32 mg, 0.074 mmol) in ethyl acetate (**2**; 15 ml). After stoppering and heating the flask with magnetic stirring for 12 h at 75 °C, absolute methanol (5-10 ml) is added to the cooled flask, and the contents are poured into a 60 ml sintered glass funnel containing a 1 cm Celite pad. Suction filtration and repeated methanol washing gives a filtrate which is evaporated under vacuum. Preparative T.L.C. on silica gel plates (1 : 1 petroleum ether/diethyl ether) gives the starting alcohol **4** [yield: 6 mg (19%)] and the acetate **5** as an oil; yield: 28 mg (81%).

$C_{26}H_{32}O_7$	calc.	C 68.40	H 7.06
(456.5)	found	68.40	7.26

I.R. (neat): $\nu = 1740, 1240, 1130\text{-}100\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 2.10$ (s, 3H); 3.44 (s, 3H); 4.35 (d, 2H, $J = 4$ Hz); 7.48 ppm (s, 10H).

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