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Acetylation of Unsymmetrical Diols in the Presence of Al_2O_3

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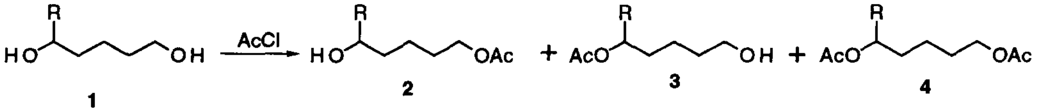
Abstract: The effect of the presence of chromatographic grade Al_2O_3 on the acetylation of a series of unsymmetrical 1,5-diols was investigated. For diols containing both a primary and a secondary hydroxyl group, it was observed that higher yields of the more hindered secondary acetates were formed in the presence of Al_2O_3 than the corresponding reactions in solution. © 1997 Elsevier Science Ltd.

Chromatographic grade Al_2O_3 has many applications as a heterogeneous catalyst either by itself, or (more commonly) as a support for other reagents.[1] There have been only a few reports, however, on the use of Al_2O_3 as a support for *substrates*, despite the fact that novel, synthetically useful, reactivities have been observed under these conditions.[2] Symmetrical difunctional substrates adsorb to the surface of Al_2O_3 via a single functional group when applied in saturating quantities.[2b,3] Adsorption of a group to the surface creates a sterically congested environment about that group which shields it from added reagents leaving only the non-adsorbed group available for reaction.[1,4] We anticipated that unsymmetrically substituted difunctional substrates would be adsorbed to the surface of Al_2O_3 primarily via the less sterically hindered functional group.[4] This would allow selective reaction at the more sterically hindered, non-adsorbed, site. Such regioselectivity would conveniently complement the corresponding reactions in solution in which the less sterically hindered site is typically the more reactive. We chose the acetylation of unsymmetrical diols for our initial investigations because of the synthetic importance of this procedure.[5] Whereas several methods have been developed for enhancement of the kinetically favored preference for acylation at the less hindered hydroxyl group of an unsymmetrical diol,[6] few methods allow for the direct acylation of the more hindered site.[7] Herein we report the effect that adsorption of unsymmetrical diols to the surface of Al_2O_3 has on the regioselectivity of acetylation.

Addition of one equivalent of acetyl chloride (AcCl) to unsymmetrical 1,5-diols **1a–e** under traditional



a, R = Me; **b**, R = Et; **c**, R = *n*–Bu; **d**, R = *sec*–Bu; **e**, R= *tert*–Bu

solution–phase conditions results in the formation of a mixture of monoacetates **2** and **3** (43–66% yield), and

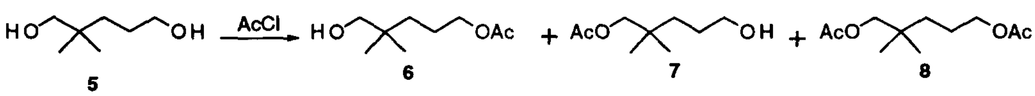
Table 1. Acetylation of Unsymmetrical Diols[a,b]

entry	substrate	Al_2O_3	yield of bisacetate (% yield)	yield of monoacetates (% yield)[c]
1	**1a**	no	24	45
2	**1a**	yes	25	53
3	**1b**	no	29	43
4	**1b**	yes	17	54
5	**1c**	no	18	57
6	**1c**	yes	19	59
7	**1d**	no	16	64
8	**1d**	yes	19	57
9	**1e**	no	17	66
10	**1e**	yes	19	50
11	**5**	no	23	41
12	**5**	yes	19	51

[a] Conducted according to the general procedure described in reference 11. [b] Isolated yields. Values from reactions over Al_2O_3 represent the average of two or more runs. [c] Combined yield of both isomeric monoacetates.

bisacetates **4** (16–29%) (Table 1). The less sterically hindered primary hydroxyl group sites are selectively acetylated under these conditions as is typically observed (see Figure 1).[5] However, when AcCl was added to a rapidly stirred suspension of a saturating amount of diols **1a–e** which had been preadsorbed to the surface of Al_2O_3 (approximately 1 mmol of diol per 2.5 g Al_2O_3) in CH_2Cl_2, a significant increase in selectivity for acetylation at the secondary site relative to that obtained in solution was observed (Figure 1).[8-11] Diol **1c**, for example, afforded a 59% yield of a mixture of monoacetates **2c** and **3c** in a ratio of 38:62, respectively, compared to a ratio of 79:21 in solution. The amount of the more sterically hindered monoacetate **3c** formed over Al_2O_3 was therefore increased by a factor of 3 relative to the corresponding solution–phase reaction (37% yield over Al_2O_3 vs. 12% yield in solution). Generally, the overall yields of monoacetates (**2** and **3**) and bisacetates (**4**) remained approximately the same between the solution–phase and surface–mediated reactions, but the yield of monoacetates **3** dramatically increased in the presence of Al_2O_3 at the expense in yield of **2**. In addition, as is evident from Figure 1, a gradual increase in selectivity for acetylation at the secondary hydroxyl group site was observed in the series methyl (**1a**), 46%; ethyl (**1b**), 54%; *n*–butyl (**1c**), 62%; *sec*–butyl (**1d**), 65%; and *tert*-butyl (**1e**), 66%. Increasing steric bulk at the secondary site had the effect of *increasing* the selectivity for acetylation at that site!

Solution–phase acetylation of 2,2–dimethyl–1,5–pentanediol (**5**), a diol containing two nonequivalent



primary hydroxyl groups, afforded only marginal preference for acetylation at the less sterically hindered C–5 hydroxyl group (54:46 for **6**:**7**, respectively), while over Al_2O_3 a more decisive preference for reaction at the

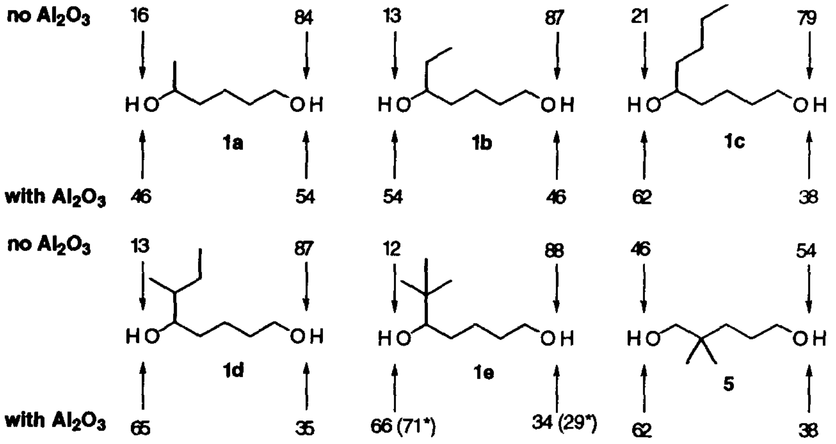


Figure 1. Percent acetylation (of total monoacetates formed) at each of the available hydroxyl groups in the absence (values above figures) and in the presence (values below figures) of Al_2O_3. *Values in parenthesis were obtained using hexane as solvent.

more hindered C–1 site was observed (38:62 for **6**:**7**).

Several relevant features of the reaction should be mentioned: i) the yields and product ratios obtained were found to be highly reproducible even over different bottles of Al_2O_3 (Fisher A540), ii) the use of a less polar solvent (i.e., hexane) or a more polar solvent (i.e., ethyl acetate) in lieu of methylene chloride generally afforded poorer selectivity except in the case of diol **1e** (see Figure 1), and iii) reversing the order of addition of reagents (i.e., addition of a solution of the diol to AcCl which had been preadsorbed to Al_2O_3) afforded selectivity comparable to the corresponding solution-phase reaction (e.g., 77:23 ratio for **2a**:**3a**, respectively, from diol **1a**). Thus, it is necessary for the diol to be adsorbed to the surface prior to the addition of acetylating agent in order to induce the desired regioselectivity.

The observed results are consistent with a model for the reaction in which adsorption of an unsymmetrical diol to the surface of Al_2O_3 occurs primarily via the least hindered hydroxyl group. Interaction of the adsorbed hydroxyl group with the surface effectively shields that site leaving only the non–adsorbed hydroxyl group available for reaction with the added acetylating agent. As the difference in steric environments between the two competing hydroxyl sites is magnified by introducing larger substituents, the preference for adsorption at the less sterically hindered hydroxyl group increases, and higher selectivity for acetylation at the more hindered (non–adsorbed) site is obtained.

While these results are very promising in that reactivity was successfully directed to an inherently less reactive site through simple physical adsorption of a substrate to the surface of Al_2O_3, the formation of significant amounts of bisacetylated products from the diols examined limits the synthetic usefulness of the methodology. Contributing to the formation of the bisacetates is the difference in solubility between the starting diols and the monoacetate products. Whereas the diols exhibit low solubility in CH_2Cl_2 (and, therefore, reside exclusively on the surface of Al_2O_3 at these loading levels),[10] the monoacetates show appreciable solubility. Following their formation, therefore, monoacetates may desorb from the surface of Al_2O_3 into solution which allows for further reaction with AcCl to yield bisacetates. As mentioned earlier, attempts at thwarting this behavior by decreasing the polarity of the solvent from CH_2Cl_2 to hexane generally afforded lower selectivities (with the exception of diol **1e**). Investigation of the reactivity of unsymmetrically disubstituted substrates with functional groups that exhibit a higher affinity for the surface (i.e., dicarboxylic acids, diamines),[12] and are, therefore, less likely to desorb from the surface upon reaction, are currently in progress.

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8. It is necessary to pretreat the Al_2O_3 prior to its use in order to eliminate surface–bound water which severely interferes with the acetylation reactions. The bulk of physically adsorbed water is removed by routine preheating of the Al_2O_3 prior to use (120 °C for at least 48 h). The more strongly adsorbed water which remains after the preheating process may be removed by treatment of the surface with oxalyl chloride (1 mmol per 2.5 g of Al_2O_3 in 5 mL of CH_2Cl_2) which, upon hydrolysis, yields CO, CO_2 and HCl as byproducts.[9] The result is an anhydrous surface containing approximately 1 mmol of acidic active sites per 2.5 g of Al_2O_3. Residual HCl and the carbon oxides may be removed by heating the treated adsorbent to moderate temperatures (~100 °C) under vacuum (1 mm Hg). Al_2O_3 treated in this manner in bulk quantities, and stored in a dessicator, maintains its activity for at least several months as determined by control studies.
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10. Adsorption studies indicated that surface saturation occurred at a compound loading level corresponding to 1 mmol of alcohol per 2.5 g of Al_2O_3. This was true for 1–hexanol as well as for 1,5–hexanediol indicating that the diol adsorbs to the surface via a single hydroxyl group.
11. **General Procedure**: To 2.5 g of Fisher A540 Al_2O_3 (which had been pretreated with $(COCl)_2$ as described above) was added a solution of diol (1.0 mmol) in 5 mL of CH_2Cl_2 via pipette. The mixture was stirred 0.5 h followed by the dropwise addition of a solution of AcCl (70 μL, 1.0 mmol) in 2 mL of CH_2Cl_2. The mixture was stirred 3 h, filtered, and the separated Al_2O_3 was washed with EtOAc (2 × 40 mL). The organics were washed with sat. aq. $NaHCO_3$ (1 × 40 mL), and the aqueous layer backwashed with EtOAc (1 × 30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude mixture was separated by column chromatography (SiO_2), eluting with a 3:2 hexane/ethyl acetate solvent mixture.
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