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An easy approach for the acetylation of saccharidic alcohols. Applicability for regioselective protections

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Abstract—Cheap 4 Å molecular sieves can promote acetylation of carbohydrate hydroxyl functions with Ac_2O in absence of any co-reagent. The procedure is compatible with the presence of a variety of acid labile protecting groups and can be exploited for regioselective protections. © 2003 Elsevier Science Ltd. All rights reserved.

Acetylation represents a very common approach for the protection of hydroxyl groups in carbohydrate chemistry and, more in general, in organic synthesis. Installation of acetyl groups is routinely carried out by reacting the alcoholic functions with acetic anhydride or acetyl chloride in the presence of a base such as pyridine or triethylamine.[1] DMAP was disclosed to increase sensibly the rates of the reaction due to its ability to act as a nucleophilic catalyst.[2] In the last decade many other procedures were developed for this reaction, some of which make use of phosphor-based nucleophilic catalysts (Bu_3P[3] and aminophosphane base[4]), while others are based on the activation of the acylating agent with a variety of Lewis acids such as $CoCl_2$,[5] $Sc(OTf)_3$,[6,7] $Sc(NTf_2)_3$,[8] $TiCl_4/AgClO_4$,[9] $TiCl(OTf)_3$,[10] $Sn(OTf)_2$,[11] $Cu(OTf)_2$,[12] $In(OTf)_3$,[13] NBS,[14] TMSOTf,[15] $Bi(OTf)_3$,[16] I_2.[17] In recent years there has been wide interest in the development of easily removable acetylation promoters. Some solid acids such as Montmorillonite K-10,[18,19] Zeolite HSZ-360,[20] silica gel supported $NaHSO_4$,[21] silica gel supported $TaCl_5$,[22] Nafion H,[23] and WO_3-ZrO_2[24] turned out to be suitable for that purpose.

Acetylation of primary alcohols in the presence of secondary ones is often problematic, and typically it implies specific procedures. Regioselective acetylations can be promoted by alumina in refluxing ethyl acetate,[25,26] silica gel supported lanthanide chlorides and methylorthoacetate,[27] an hindered base and acetyl chloride at low temperature,[28] iminophosphorane bases and vinylacetate,[29] distannoxane and enolacetates,[30] NaH and 3-acetyl-thiazolidine-2-thiones,[31] PPh_3/CBr_4 in ethyl acetate at high temperatures.[32] These procedures can suffer from some drawbacks such as the employment of moisture sensitive reagents, the recourse to strictly controlled experimental conditions, the preliminary preparation of commercially unavailable reagents, and slow reaction rates.

In this paper we wish to report a very mild and experimentally simple acetylation procedure which can be advantageously applied to the regioselective protection of saccharidic alcohols.

Starting from the idea of exploiting the surface sites of commercially available molecular sieves to promote synthetically useful transformations in carbohydrate chemistry,[33] we firstly considered the acetylation reaction. In order to reveal a possible catalytic ability of molecular sieves in this reaction, model compound **1a** (Table 1) was treated with neat acetic anhydride in the presence and in absence of 4 Å molecular sieves. In the former case (entry 1) the protection went to completion (98% yield) within 4 h at room temperature, while in the second case (entry 2) appreciably high yields (85%) could be achieved but sensibly longer times were required. A model secondary saccharidic alcohol (**2a**) was acetylated more slowly with acetic anhydride and 4 Å molecular sieves and the reaction took 24 h to achieve a high yield (entry 3).

The application of this procedure was next examined for the protection of several saccharidic polyols (**3a**–**6a**)

Keywords: carbohydrates; protecting groups; acetylation; regioselectivity; molecular sieves.

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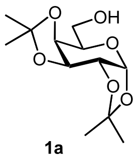
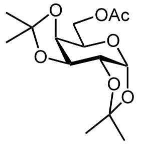
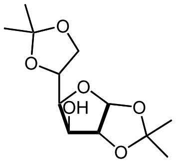
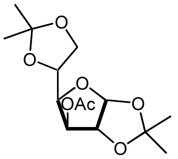
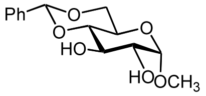
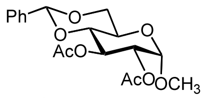
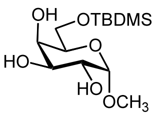
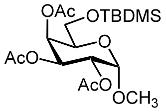
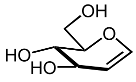
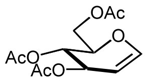
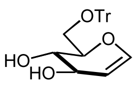
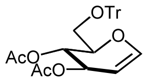
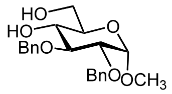
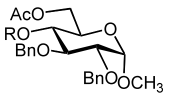
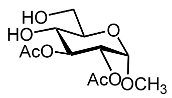
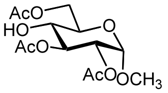
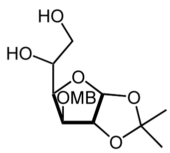
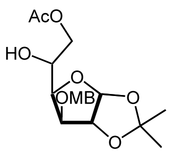
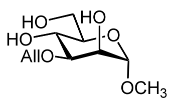
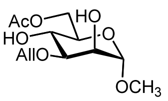
Table 1. Acetylation of saccharidic compounds promoted by 4 Å molecular sieves

Entry	Reagent	T(°C)	time (h)	Product[a]	Yield
1	 **1a**	r.t.	4	 **1b**	98
2[b]	**1a**	r.t.	24	**1b**	85
3	 **2a**	r.t.	24	 **2b**	90
4	 **3a**	60	6	 **3b**	93
5	 **4a**	60	20	 **4b**	87
6	 **5a**	60	20	 **5b**	85
7	 **6a**	r.t.	20	 **6b**	82
8	 **7a**	60	8	 **7b** R = Ac	91
9	**7a**	0	6	**7c** R = H	90
10	 **8a**	0	5	 **8b**	90
11	 **9a** MB = p-methoxybenzyl	0	1	 **9b**	82
12	 **10a**	5	13	 **10b**	56

[a] All saccharides were identified by ^{1}H and ^{13}C NMR. The acetylated positions in the products have been established by chemical shift analysis and decoupling experiments. [b] Without molecular sieves.

equipped with acid labile functionalities. In all cases acetylations occurred in high yields at room temperature or at 60°C (entries 4–7). Interestingly, the results listed on Table 1 show that the acetylation conditions are compatible with the stability of several acid labile groups such as primary acetonides, TBDMS ethers, benzylidenes, enol ethers, trityl ethers. In contrast, in some examples of the above cited acid Lewis promoted acetylations the cleavage of acid labile acetal and silyl ether functionalities has been reported.[15,32]

The different reactivity of primary and secondary hydroxyl functions observed in these first experiments suggested the potentiality of the protocol for regioselective protections of polyols. As shown in entries 9–12 of Table 1, substrates **7a**–**10a** could be acetylated at their primary position in short reaction times and generally in high yield. Representative experiments are constituted by entries 8 and 9, showing that compound **7a** can be alternatively converted into the mono acetylated derivative **7c** or the peracetylated derivative **7b** by simply changing the reaction temperature.

It should be outlined the simplicity of the proposed procedure, cheap commercially available reagents being used without resorting to particular experimental precautions. The molecular sieves can be used without any preliminary activation and removed by simple filtration. In many cases pure products were often obtained by a simple dilution with dichloromethane and washings with aqueous Na_2CO_3.

In conclusion we have shown that commercially available 4 Å molecular sieves can promote the acetylation of both primary and secondary alcoholic functionalities. The proposed procedure is based on commercially available and inexpensive reagents, and is experimentally very simple.[34] In addition, the procedure was shown to be perfectly compatible with a variety of functional and protecting groups adopted in carbohydrate chemistry and can even be usefully employed to perform regioselective acetylations of saccharidic diols.

Acknowledgements

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34. Typical procedure: compound **3a** (724 mg) is suspended in acetic anhydride (15 mL) and 4 Å molecular sieves (1.5 g; Fluka Chemie GmbH, catalogue number 69834) are added. The mixture is stirred at 60°C and after completion of the reaction (TLC) the mixture is diluted with dichloromethane and the organic phase washed several times with a saturated Na_2CO_3 aqueous solution. Combined aqueous phases are extracted with dichloromethane, and the combined organic phases are concentrated under vacuum and purified on a short silica gel column to yield **3b** (875 mg, 93%).