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Mild benzhydrylation and tritylation of saccharidic hydroxyls promoted by acid washed molecular sieves

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Abstract—Commercially available 4 Å acid washed molecular sieves (AW 300 MS) promote the protection of primary and secondary saccharidic alcohols through a dehydration mechanism and in the absence of any strong protic or Lewis acid. © 2003 Elsevier Science Ltd. All rights reserved.

The availability of a wide range of protecting groups is very important for the differentiation in the reactivity of saccharidic hydroxyl functions. Therefore the access to mild and convenient procedures for the installation and the removal of protecting groups represents an important target in the field of carbohydrate chemistry and, more in general, in organic synthesis.

Conversion of hydroxyl functionalities into the corresponding benzhydryl or diphenylmethyl (DPM) ethers is a common approach for the protection of alcohols. The installation can be performed with diphenylmethyl bromide or chloride in the presence of a base,¹ diazodiphenylmethane in boiling acetonitrile,² diphenyl methyl dialkyl phosphates and a protic acid as the catalyst,^{3,4} or by reacting the alcohol with diphenylmethanol in the presence of protic or Lewis acids such as sulphuric acid,⁵ toluensulfonic acid,⁶ Yb(OTf)₃ or FeCl₃,⁷ Nafion H,⁸ Fe(NO)₃·10 H₂O.⁹ Diphenylmethyl ethers flanked by a free hydroxyl group can be also obtained by reductive opening of diphenyl ketals installed on saccharidic diols.¹⁰

Application of these protocols is rather unusual in carbohydrate chemistry,^{2,7,10} and in many cases these approaches were found to be synthetically useful only for protection of structurally simple primary alcohols.

Prompted by our recent findings on the use of acid washed molecular sieves as useful coreagents in glyco-

sylation reactions,¹¹ we have examined the potential of such agents in synthetically useful dehydrative transformations in the absence of strong protic or Lewis acids. As mentioned above, acid promoted dehydration of diphenylmethanol is often employed in the benzhydrylation of alcohols.^{5–9}

In a first experiment, the treatment of model compound 1 in toluene with 4 Å AW 300 MS and diphenylmethanol at room temperature resulted in the high yielding protection of the primary hydroxyl functionality (Table 1, entry 1). Interestingly, ordinary non acid washed 4 Å molecular sieves were found inefficient for the same transformation (entry 2). The scope of the approach was then tested for protection of less reactive secondary hydroxyl groups of saccharidic derivatives 2-4 and also in these cases synthetically useful yields could be achieved (entries 3-5). In order to minimize undesired reactions such as self coupling⁶ or Friedel-Crafts alkylation of toluene,¹³ diphenylmethanol was added portionwise to the reaction mixture.¹² In the examples shown in Table 1, satisfying yields were achieved at room temperature even with less reactive alcohols adopting up to 2.5 equivalents of diphenylmethanol. The excess of benzhydryl alcohol was consumed in the formation of dibenzhydryl ether and diphenylmethyltoluenes (in the approximate 4:3 ratio). These by-products were easily separated from saccharidic compounds by chromatography. The installation procedure succeeds also with alcohols flanked by acetyl groups (entries 4 and 5) which are deactivating for their electron withdrawing nature and generally amenable to rearrangement. As expected, acid labile acetal and ketal protecting groups survive unaffected under these conditions.

Keywords: carbohydrates; protecting groups; molecular sieves.

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Encouraged by these results, we have investigated a dehydration approach to carry out the installation of the acid labile trityl protecting group, that is routinely accomplished by reacting the alcohol with trityl chloride and a base.¹⁴ Alternative approaches, requiring the preliminary preparation of a suitable tritylating agent, are, however, available in the literature.^{15–17} To the best of our knowledge there are no reports describing tritylations of alcohols through the direct dehydration of the cheap triphenylmethanol.

The efficiency of the proposed dehydration approach for tritylation of primary alcohols with a slight stoichiometric excess of triphenylmethanol¹² is shown in entries 6 and 7 of Table 1. Entry 7 displays the feasible exploitation of the methodology to achieve a selective protection for a primary alcohol in a saccharidic diol. The regioselective benzydrylation of diol **5** afforded a less satisfactory, although interesting, result. Besides 6-*O*-protected product **12** (52% yield), some amount of the 4,6-di-*O*-benzhydrylated product (15% yield) was also isolated.

Entry	Reagent	time (h)	Product	Yield ^a
1		6		86
2 ^b	1	6	no reaction	
	Ph ToR^2oR^1OOCH	F	Ph 0 0 R ² 0 R ¹ 00	CH₃
3	2 R ¹ : Bn, R ² : H	24		81
4	3 R ¹ : H, R ² : Ac	24		61 (79) ^c
5		24	Aco BPMO 9 OAc	70 (85) ^c
6		6		95)))
	HO HO AcO AcOOCH ₃		HO Aco Aco	СН₃
7	5	8	11 R: Tr	70
8	5	8	12 R: DPM	52 (70) ^d

Table 1. AW 300 MS promoted benzhydrylation and tritylation of saccharidic alcohols under dehydrative conditions¹²

^aIsolated yields. All products were characterized by ¹H and ¹³C NMR; ^bOrdinary non acid washed 4Å molecular sieves were used in place of acid washed molecular sieves; ^cYields in parentheses are calculated on the base of recovered starting compound; ^d 15% of the 4,6-di-*O*-benzhydrylated product was also isolated.

In conclusion, commercially available and cheap 4 Å acid washed molecular sieves (300 AW MS) can promote the protection of primary and secondary saccharidic alcohols at room temperature following a dehydration mechanism in absence of any strong protic or Lewis acid. In this way even poorly reactive secondary functionalities can be protected as diphenylmethyl ethers under very mild conditions compatible with the stability of acid labile functionalities. In addition, the described protocol offers a further opportunity for the non trivial installation of ether protecting groups in the presence of base-sensitive functionalities such esters. Finally, tritylation of primary alcohols can be also conducted under analogous conditions.

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References

- 1. Dobson, D.; Todd, A.; Gilmore, J. Synth. Commun. 1991, 21, 611.
- Jackson, G.; Jones, H. F.; Petursson, S.; Webber, J. M. Carbohydr. Res. 1982, 102, 147.
- 3. Lapatsanis, L. Tetrahedron Lett. 1978, 19, 3943.
- 4. Kolovos, M.; Froussios, C. Tetrahedron Lett. 1984, 25, 3909.
- 5. Sugsawa, S.; Fujiwara, K. Org. Synth. Coll. 1963, 4, 72.
- 6. Paredes, R.; Perez, R. L. Tetrahedron Lett. 1998, 39, 2037.
- Sharma, G. V. M.; Rajendra Prasad, T.; Mahalingam, A. K. *Tetrahedron Lett.* 2001, 42, 759.

- Stanescu, M. A.; Varma, R. S. Tetrahedron Lett. 2002, 43, 7307.
- Mamboodiri, V. V.; Varma, R. S. *Tetrahedron Lett.* 2002, 43, 4593.
- 10. Hajko, J.; Borbas, A.; Szabovik, G.; Kojtar-Peredy, M.; Liptak, A. J. Carbohydr. Chem. **1997**, 16, 1123.
- 11. Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Tetrahedron Lett.* 2002, 43, 5573.
- 12. General benzhydrylation and tritylation procedure: a mixture of the saccaharidic compound (0.20 mmol) and diphenylmethanol (0.22 mmol) were co-evaporated in anhydrous toluene. The mixture was then dissolved in anhydrous toluene (1 mL) and activated 4 Å acid washed molecular sieves (250-300 mg) were added. The mixture was stirred at room temperature and after 3-4 h further diphenylmethanol (0.20 mmol) was added. For reactions in entries 3-5 another addition of diphenylmethanol (0.1 mmol) was made after a further 4 h. Finally, a few drops of triethylamine were added and the mixture was filtered on a short pad of silica gel. Molecular sieves were thoroughly washed and recovered for reactivation. Protected sugars were then isolated by silica gel chromatography (eluent: hexane/ethyl acetate mixtures). Tritylations were performed by an analogous procedure but adopting only a slight stoichiometric excess of triphenylmethanol (1.1 equiv.) and no further addition was required.
- 13. Different solvents such as acetonitrile and dichloroethane were quite unsuitable for the described reactions.
- (a) Reddy, M. P.; Rampal, J. B.; Baucage, S. L. *Tetra*hedron Lett. **1987**, 28, 23; (b) Hernandez, O.; Chaudary, S. K.; Cox, R. H.; Porter, J. *Tetrahedron Lett.* **1981**, 22, 1491.
- 15. Murata, S.; Notori, R. Tetrahedron Lett. 1981, 22, 2107.
- 16. Oikawa, M.; Yoshizaki, H.; Kusumoto, S. Synlett 1998, 757.
- Sharma, G. V. M.; Mahalingam, A. K.; Rajendra Prasad, T. Synlett 2000, 1479.