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Carbohydrate Research 339 (2004) 729–732

Carbohydrate
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Note

Practical de-O-acylation reactions promoted by molecular sieves

K. P. Ravindranathan Kartha,[a,*] Balaram Mukhopadhyay[b] and Robert A. Field[b]

[a]Department of Medicinal Chemistry, National Institute of Pharmaceutical Education and Research, Sector 67, S.A.S Nagar, Punjab 160062, India

[b]Centre for Carbohydrate Chemistry, School of Chemical Sciences and Pharmacy, University of East Anglia, Norwich NR4 7TJ, UK

Received 29 November 2003; accepted 30 November 2003

Abstract—Methanol dried extensively over molecular sieves, or methanol in combination with powdered molecular sieves, serves as a good acceptor for acyl transfer reactions. Several O-acetylated and O-benzoylated sugar derivatives were efficiently de-O-acylated using this approach. In the case of per-O-acetylated *N*-acetylglucosamine, selective anomeric deprotection could be effected in high yield.

Keywords: Molecular sieves; Alcohols; Deacetylation

1. Introduction

Since the introduction of synthetic zeolites by Union Carbide nearly 50 years ago,[1] activated molecular sieves have found wide-ranging applications, including the purification and drying of hydrocarbons.[2] Organic chemists routinely employ activated molecular sieves as scavengers in reactions as well as for drying solvents;[3] storage of dry solvents over activated molecular sieves is a common practice. In the course of our work we noted that methanol stored over 4 Å molecular sieves[4] could effect de-O-acetylation of per-O-acetylated glycosides. For instance, O-acetylated 2-(trimethylsilyl)ethyl glycoside **1** was converted to the corresponding triol **2** in 30 min without the need for addition of sodium methoxide (Table 1, entry 1). Crude assessment of the pH of the methanol used (using wet pH paper) showed it to be in the range of 9.5–10.[5] From the known chemical composition of activated 4 Å molecular sieves {$1Na_2O{:}1Al_2O_3{:}2.0 \pm 0.1SiO_2$ with a molecular formula of $Na_{12}[(AlO_2)_{12}(SiO_2)_{12}]$[2,6] it seems likely that the alkaline pH caused formation of sodium methoxide on standing, albeit in small quantities, which was responsible for the trans-esterification reaction observed. Recent literature reports use of 3 Å molecular sieves to promote de-O-acetylation reactions[7] and, in the opposite sense, the use of 4 Å molecular sieves to promote acetylation chemistry.[8] Herein we report observations on partial and complete de-O-acylation of various sugars derivatives using methanol and molecular sieves.

Treatment of per-O-acetylated α- or β-D-glucopyranose, **3** and **5**, at room temperature for 45 min with methanol that had been stored over 4 Å molecular sieves gave D-glucose **4** in essentially quantitative yield (Table 1, entries 2 and 3). Likewise, de-O-acylation of tri-*O*-benzoyl-α-D-arabinofuranoside **6** (entry 4), which was accompanied by the formation of methyl benzoate with its characteristic odour, and hepta-*O*-acetyl lactoside **8** (entry 5) were also successful, giving deprotected glycosides **7** and **9**, respectively. Under similar conditions, de-O-acetylation of tetra-*O*-acetyl-α-D-mannosides **10** and **12** (entries 6 and 7), gave the corresponding alcohols **11** and **13**, respectively. Retention of a hindered *tert*-butyl ester on treatment with methanol and 3 Å molecular sieves has been noted;[7] here the more reactive benzyl ester function in **12** is also retained, which is significant since use of freshly prepared sodium methoxide in anhydrous methanol to de-O-acetylate benzyl

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[*] Corresponding author. Fax: +91-172-2214692; e-mail: rkartha@niper.ac.in

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doi:10.1016/j.carres.2003.11.021

Table 1. De-O-acylation of sugar derivatives using MeOH extensively dried over 4 Å molecular sieves—(Method A)

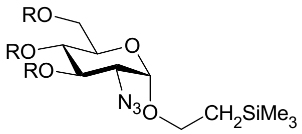
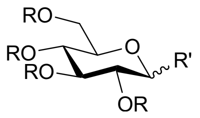
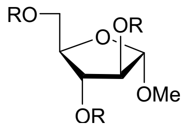
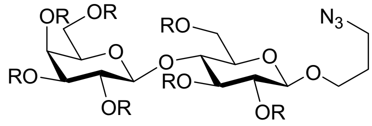
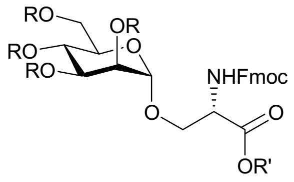
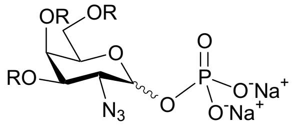
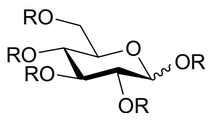
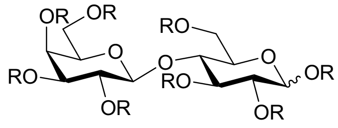
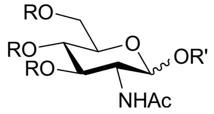
Entry	Structure	Reactant	Product
1		R = Ac, **1**	R = H, **2**
2		R = Ac R′ = α-OAc, **3**	R = H R′ = OH, **4**
3		R = Ac R′ = β-OAc, **5**	R = H R′ = OH, **4**
4		R = Bz, **6**	R = H, **7**
5		R = Ac, **8**	R = H, **9**
6		R = Ac R′ = Me, **10**	R = H R′ = Me, **11**
7		R = Ac R′ = Bn, **12**	R = H R′ = Bn, **13**
8		R = Ac, **14**	R = H, **15**

Table 2. De-O-acylation of sugar derivatives using HPLC grade MeOH + powdered 4 Å molecular sieves—(Method B)

Entry	Structure	Reactant	Product (Time)
1		R = Ac, **3α**	R = H, **4** (36 h)
2		R = Ac, **16α**	R = H, **17** (48 h)
3		R = R′ = Ac, **18α**	R = Ac, R′ = H, **19α** (2 h)
4		R = R′ = Ac, **18α**	R = R′ = H, **20** (48 h)

ester **12** results solely in the formation of methyl ester **11**. Further, de-O-acetylation of anomeric phosphate **14**, to give **15**, with retention of the phosphate group (entry 8) is also significant since attempts to de-O-acetylate **14** under conventional Zemplen conditions gave only the unwanted methyl glycoside.

Although satisfactory results were obtained in the above reactions, the necessity to use methanol obtained by storage over molecular sieves for extended periods proved limiting. As an alternative, use of HPLC grade MeOH in combination with powdered molecular sieves was examined.[9] When a solution of the per-O-acetylated glucose **3** was stirred at room temperature in the presence of powdered, activated 4 Å molecular sieves (equal in weight to that of the sugar derivative) conversion to the fully deprotected **4** was complete in 36 h (Table 2, entry 1). Likewise, lactose octa-O-acetates **16** gave lactose **17** in excellent yield (entry 2). Per-O-acetylated *N*-acetyl glucosamine **18**, on the other hand, gave the hemiacetal **19** (entry 3), a useful precursor to the corresponding glycosyl trichloroacetimidate,[10] in 90% yield in around 2 h. Fully deprotected *N*-acetylglucosamine **20** was obtained on continuation of the reaction for 48 h.

In summary, we have shown that activated 4 Å molecular sieves can effect useful selective and complete de-O-acylation of sugar derivatives and that the process is notably milder than Zemplen conditions. Although in some contexts such trans-esterification reactions may be desirable, clearly the use of molecular sieves as drying agents in glycosylation reactions employing esterified building blocks needs to be considered with caution.

2. Experimental

2.1. General

All compounds described in this study have been reported previously: **1** and **2**[11], **3–5** and **16–20**[12], **6–7**[13], **8–9**[14], **10–13**[15], **14** and **15**[16]; several are commercially available.

2.2. Procedures for the preparation and use of methanolic sodium methoxide solution

2.2.1. Method A: MeOH extensively dried over activated 4 Å molecular sieves. MeOH was stored for at least 8 weeks over pelleted 4 Å molecular sieves. Methanolic sodium methoxide prepared in this fashion was used (approximately 2–4 ml per 100 mg of acetylated sugar) to effect deacylation. Reactions were carried out at room temperature and were typically complete in <45 min (Table 1, entries 1–5) and <2 h (Table 1, entries 6 and 7), respectively. Products were obtained in essentially quantitative yield, except entry 8 where the yield was 70%. All compounds were judged pure by proton NMR spectroscopy.

Alternatively, methanolic sodium methoxide was prepared from HPLC grade MeOH by refluxing over pelleted 4 Å molecular sieves for 10 h. Subsequent deacetylation reaction rates were somewhat slower (approximately 2-fold) than noted above.

2.2.2. Method B: HPLC grade MeOH + powdered, activated 4 Å molecular sieves. A mixture of the acylated sugar derivative and powdered, activated 4 Å molecular sieves (equal in weight to that of the sugar) in HPLC grade MeOH (approximately 2–4 ml per 100 mg of acetylated sugar) was stirred at room temperature. Following completion of the reaction (Table 2), filtration and concentration in vacuo gave the product in near quantitative yield. In the preparation of **19α**, the pure product was obtained in 90% yield after purification by chromatography on a column of silica gel using dichloromethane/MeOH (97:3) as eluent.

Acknowledgements

We thank the MRC, EPSRC and the Weston Foundation for financial support. We gratefully acknowledge the EPSRC Mass Spectrometry Service Centre, Swansea for invaluable support.

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