Tetrahedron Letters, Vol. 34, No. 8, pp. 1359-1362, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A NOVEL, REGIO- AND HIGHLY STEREOSELECTIVE ANOMERIC DEACETYLATION OF 2-AMINOSUGAR DERIVATIVES.

Martin Avalos, Reyes Babiano, Pedro Cintas, José L. Jiménez, Juan C. Palacios*, and Concepción Valencia.

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Extremadura, 06071-Badajoz, Spain.

Abstract: Silica gel-mediated anomeric deacetylation of per-acetylated 2-amino-2-deoxy-glycopyranose derivatives in methanol constitutes a mild and inexpensive protocol for the selective deprotection of these relevant carbohydrate templates. The reaction proceeds with high stereoselectivity and with an almost complete avoidance of by-products.

The selective deprotection at the anomeric centre of carbohydrates is often an important prerequisite for the functionalisation and further use of these substances in organic synthesis. Moreover, the resulting deprotected compounds could serve as the anchoring point of the carbohydrate chain in *N*-glycoproteins, oligosaccharides, and other glycoconjugates.[1,2] These structures present an increasing interest, since it is well-established that those supramacromolecules are intimately associated with the immunological response. In addition, the vast number of naturally occurring and biologically active aminosugars makes general routes to these substances an area of considerable importance.[3]

In conjunction with a synthetic programme underway in our laboratory, we needed to carry out a selective deprotection at the anomeric centre of some per-*O*-acylated 2-aminosugar derivatives. There are numerous methods to achieve without difficulty the selective deprotection of an acyl group at the anomeric position of sugars.[4-9] In relation with 2-aminosugar derivatives, the protocols involve the use of metal salts,[5] Lewis acids,[6] nitrogen bases,[5e,7] electrolysis,[8] and enzymatic methods.[9] However, anomeric mixtures are frequently obtained which constitutes a severe limitation of these procedures. Thus far, the best stereodifferentiation has been observed using ammonia in aprotic organic solvents, such as THF or acetonitrile.[7e]

We have now studied a useful, facile alternative for the mild anomeric deprotection of per-*O*-acetylated 2-amino-2-deoxy-glycopyranose derivatives. Interestingly, the method proceeds with total or high stereoselectivity and α-anomers are exclusively obtained.

In the standard procedure, methanolic solutions of substrates were treated with silica gel and the resulting suspensions were stirred mechanically. The transformation proceeded slowly and variable amounts of the starting material remained in the reaction mixture. Reactions at room temperature (~30º) proceeded slower than at reflux, but in contrast cleaner processes take place with an almost complete avoidance of side products. Prolonged reaction times for enhancing the yields of products resulted in further deacetylations. Deacetylations are faster in methanol than in ethanol or aqueous methanol, whereas the reaction failed entirely in *n*-propanol

and in aprotic solvents such as THF, dioxane, or chloroform.

This protocol was successfully applied to various 2-aminosugar derivatives, and thus we have examined the natural *N*-acetyl protecting group, as well as ureido and enamino groups. The latter is an important temporary protective group of aminosugars.

Table

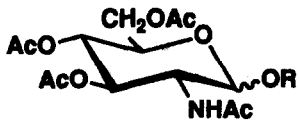
				Conversion		Isolation		
Entry [a]	Comp.	Anomer [10]	Product [11]	Time [c]	(%)[d]	Time [c]	Yield(%) [e]	Yield(%) [f]
1	**1**	α	**2α**	1	78	2	82	82
2	**1**	β	**2α**	2	53	3	46	72
3	**3**	α	**4α**	1	95	2	84	84
4	**3**	β	**4α**	2	50	3	40	57
5	**5**	α	**6α**	1	77	2	66	66
6	**5**	α	**6α**	2	83	-	-	-
7[b]	**5**	α	**6α**	2	62	-	-	-
8	**5**	β	**6α**	2	57	3	42	67
9	**7**	α	**8α**	1	78	2	55	71
10	**7**	β	**8α**	2	63	3	40	72
11	**9**	α	**10α**	-	-	3	31	61
12	**11**	α	**12α**	2	48	3	34	52
13[b]	**11**	α	**12α**	2	32	-	-	-
14	**13**	α	**14α**	2	36	3	45	81

[a] Reactions are performed in absolute methanol at r.t. unless otherwhise noted. [b] In aqueous methanol (80%). [c] In days. [d] Determined by NMR measurements. Only starting material and anomerically deacetylated product (%) were detected. [e] The yields of isolated products were determined after purification by crystallisation or flash chromatography. [f] These yields are calculated on the basis of unreacted starting material.

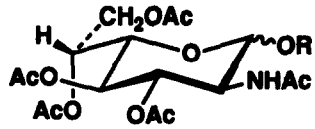
In the case of enamines **9**, **11**, and **13** only α-anomers were utilised for selective deacetylations because they are easily prepared in a two-stage procedure from the corresponding deprotected 2-aminosugars.[12,13] Anomerically deprotected 2-enaminosugars such as **10**, **12**, and **14** can be synthetic equivalents of the corresponding 2-azidosugar derivatives[14] among others, which have been employed in oligosaccharide synthesis.

The data of the Table reveal important conclusions. In general, reactions with α-anomers are faster than with β-anomers (entries 1 and 2, 3 and 4, 5 and 8, 9 and 10). In contrast, reactions with α-enamines proceeded slower. As the time increases yield increases only slightly (entries 5 and 6). By increasing the water amount, lower yields were obtained (entries 7 and 13).

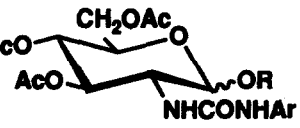
Starting materials having either α- or β-configuration gave exclusively 1-*O*-deacetylated α-anomers,[15] and no presence of β-anomers could be detected. According to our experimental results, the mechanism could involve a transesterification on the silica gel surface.[16] This feature offers a plausible explanation on the different reaction rates observed with α- and β-anomers. α-Anomers can interact easily with acidic centres of silica gel (Scheme). However, the approach of β-anomers to the support will be markedly impeded by axial interactions. A similar effect can be invoked for α-enamines having a bulky, planar substituent at C-2 position.



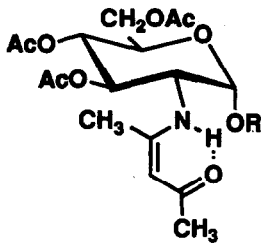
1 R = Ac
2 R = H



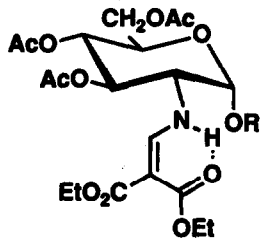
3 R = Ac
4 R = H



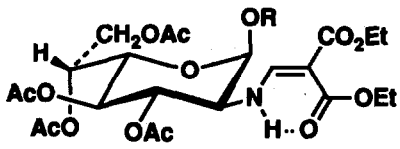
5 Ar = C $_6$H$_5$, R = Ac
6 Ar = C $_6$H$_5$, R = H
7 Ar = 4-ClC $_6$H$_4$, R = Ac
8 Ar = 4-ClC $_6$H$_4$, R = H



9 R = Ac
10 R = H

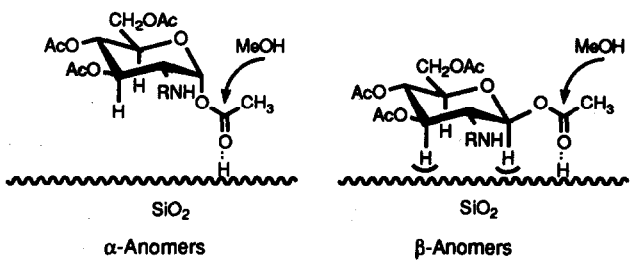


11 R = Ac
12 R = H



13 R = Ac
14 R = H

On the other hand, the extreme stereoselectivity of the process cannot be attributed to the mechanism since comparable stereoselectivity has been previously observed under very different reaction conditions.[7e] The stereodifferentiation should be rather a consequence of a very fast mutarrotation in the polar reaction medium. The deacetylation would be therefore stereospecific initially, but the anomeric effect[17] had favoured the exclusive formation of the thermodynamically more stable α-anomers.



α-Anomers β-Anomers

Scheme

In conclusion, we have demonstrated an efficient and completely stereoselective route to 1-*O*-deacetylated aminosugar derivatives. These compounds would provide a rapid entry to important biological compounds such as oligosaccharides, glycoproteins, and glycoconjugates in general. Convenience and low cost are also among the method's great advantages. Silica gel is available commercially and is inherently less expensive than other reagents used commonly for anomeric deacylations. Additionally, the process can be performed on a large scale (multigram) synthesis under mild and neutral conditions, which provide a desired medium for many functional groups sensitive to acid or basic conditions. Further applications are currently in progress in our laboratories.

General procedure for selective anomeric deacetylation.- A suspension of per-*O*-acetylated 2-amino-2-deoxy-glycopyranoses (2.0 mmol) and silica gel (Merck GF_{254}, 1.0 g) in dry methanol (100 mL) was

vigorously stirred at room temperature for the appropriate time (see table). The silica gel was filtered and washed with methanol (2 x 40 mL). The combined organic extracts were evaporated to provide a white foam, which was crystallised from the appropriate solvent, or purified previously by flash chromatography using benzene-acetone (3:1) or benzene-methanol (9:1) as eluents.

Acknowledgements

We express our sincere appreciation to DGICYT (PB89-0492) for financial support of our research on the subject matter in this article.

References and Notes

1 C. C. Sweely and B. Siddiqui, in *The Glycoconjugates*, M. I. Horowitz and W. Pigman, Eds., Academic Press, New York, **1977**.
2 (a) H. Paulsen, *Angew. Chem. Int. Ed. Engl.*, **1990**, *29*, 823; (b) B. Lindberg, *Adv. Carbohydr. Chem. Biochem.*, **1990**, *48*, 279; (c) A. Lubineau, H. Bienaymé and J. Le Gallic, *J. Chem. Soc., Chem. Commun.*, **1989**, 1918.
3 (a) F. M. Hauser and S. R. Ellenberger, *Chem. Rev.*, **1986**, *86*, 35; (b) I. F. Pelyvás, C. Monneret and P. Herczegh, *Synthetic Aspects of Aminodeoxy Sugars of Antibiotics*, Springer-Verlag, Berlin, **1988**.
4 (a) A. Georg, *Helv. Chim. Acta*, **1932**, *15*, 924; (b) C. M. McCloskey, R. E. Pyle and G. H. Coleman, *J. Am. Chem. Soc.*, **1944**, *66*, 349; (c) W. A. Bonner, *J. Am. Chem. Soc.*, **1958**, *80*, 3372; (d) J. Honeyman, *Methods Carbohydr. Chem.*, **1963**, *2*, 95.
5 (a) D. R. Whitaker, M. E. Tate and C. T. Bishop, *Can. J. Chem.*, **1962**, *40*, 1885; (b) F. Micheel and W. Lengsfeld, *Chem. Ber.*, **1956**, *89*, 1246; (c) F. García González, A. Gómez Sánchez and U. Scheidegger, *Carbohydr. Res.*, **1967**, *3*, 486; (d) T. Itoh, H. Takamura, K. Watanabe, Y. Araki and Y. Ishido, *Carbohydr. Res.*, **1986**, *156*, 241; (e) K. Watanabe, K. Itoh, Y. Araki and Y. Ishido, *Carbohydr. Res.*, **1986**, *154*, 165.
6 A. Banaszek, X. B. Cornet and A. Zamojski, *Carbohydr. Res.*, **1985**, *144*, 342.
7 (a) R. M. Rowell and M. S. Feather, *Carbohydr. Res.*, **1967**, *4*, 486; (b) J. E. Hodge and C. E. Rist, *J. Am. Chem. Soc.*, **1952**, *74*, 1498; (c) G. Excoffier, D. Gagnaire and J. P. Utille, *Carbohydr. Res.*, **1975**, *39*, 368; (d) C. Ferrer Salat, P. Exero Agneseti and M. Bemporad Caniato, *Spanish Patent*, **1976**, 430 636 (*Chem. Abstr.*, **1977**, *87*, 23683; (e) J. Fiandor, M. T. García-López, F. G. de las Heras and P. P. Méndez-Castrillón, *Synthesis*, **1985**, 1121.
8 T. Imagawa, Y. Nakashima and M. Kawanishi, *Chem. Lett.*, **1980**, 1609.
9 W. J. Hennen, H. M. Sweers, Y. F. Wang and C. H. Wong, *J. Org. Chem.*, **1988**, *53*, 4939.
10 For comparative purposes between homomorphous sugars, α or β-descriptors denote the stereochemistry of the anomeric centre with respect to that at C-5.
11 Satisfactory elemental analyses and spectral data were obtained for all new compounds.
12 (a) F. García González, A. Gómez Sánchez and M. I. Goñi de Rey, *Carbohydr. Res.*, **1965**, *1*, 261; (b) A. Gómez Sánchez, M. Gómez Guillén and U. Scheidegger, *Carbohydr. Res.*, **1967**, *3*, 486; (c) A. Gómez Sánchez, M. Gómez Guillén, A. Cert Ventulá and U. Scheidegger, *An. Real Soc. Esp. Fís. Quím.*, **1968**, *64B*, 579.
13 The corresponding β-anomers require a lengthy multistep sequence: (a) A. Gómez Sánchez, A. Cert Ventulá and U. Scheidegger, *Carbohydr. Res.*, **1971**, *17*, 275; (b) *ibid.*, **1971**, *18*, 173.
14 (a) H. Paulsen and M. Paal, *Carbohydr. Res.*, **1983**, *113*, 203; (b) *ibid.*, **1984**, *135*, 71; (c) W. Kinzy and R. R. Schmidt, *Tetrahedron Lett.*, **1987**, *28*, 1981; (d) S. Nunomura, M. Mori, Y. Ito and T. Ogawa, *Tetrahedron Lett.*, **1989**, *30*, 5619; (e) C. Lamberth and M. D. Bednarski, *Tetrahedron Lett.*, **1991**, *32*, 7369.
15 1-H Protons at δ_H ~5 ppm have the normal values for axial-equatorial ($J_{1,2}$ ~3.4 Hz) dispositions, which indicate an α-anomeric configuration.
16 In solution, the transesterification and the saponification of cyclic compounds with equatorial ester groups are faster than with axial substituents. See for instance: F. A. Carey and R. J. Sundberg, *Advanced Organic Chemistry*, Part A, Plenum Press, New York, 3rd ed., **1990**; pp 152-155.
17 I. Tvaroska and T. Bleha, *Adv. Carbohydr. Chem. Biochem.*, **1989**, *47*, 45 and references cited therein.

(Received in UK 7 October 1992)