Reductive Cyclization of δ-Hydroxy Nitriles: A New Synthesis of Glycosylamines †

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Reductive Cyclization of δ-Hydroxy Nitriles: A New Synthesis of Glycosylamines†

Andrew D. Dorsey, Jennifer E. Barbarow, and Dirk Trauner*

Center for New Directions in Organic Synthesis, Department of Chemistry, University of California−Berkeley, Berkeley, California 94720

trauner@cchem.berkeley.edu

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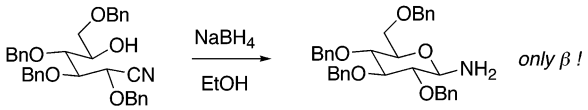
ABSTRACT



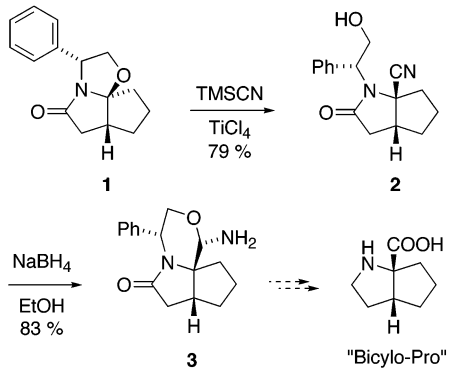
The stereoselective cyclization of δ-hydroxy nitriles to afford *N*,*O*-acetals and the application of this reaction toward the synthesis of glycosylamines is described.

Glycosylamines are a central motif in *N*-linked glycopeptides and glycoproteins.[1] Their importance in biology has sparked the development of numerous strategies for their synthesis involving, among others, glycosyl azides, glycals, and unprotected reducing oligosaccharides as precursors. Many of these methods, however, lack generality or suffer from low diastereoselectivities. The development of new methodology for the synthesis of glycosylamines, therefore, remains an important goal.

In the course of our ongoing program directed at conformationally restricted proline derivatives and novel ligands for metabotropic glutamate receptors, we have encountered a reaction useful to this end (Scheme 1). Exposure of Meyers' lactam **1**[2] to TMSCN in the presence of a Lewis acid led to *N*-acyl aminonitrile **2**.[3] In an attempt to selectively reduce its nitrile function via intramolecular participation of the primary hydroxy group, **2** was exposed to excess sodium borohydride in ethanol. To our surprise, the stable *N*,*O*-acetal **3** was obtained in good yield as a single diastereomer. The X-ray crystal structure of compound **3** is shown in Figure 1.

In principle, the reductive cyclization of hydroxynitriles to afford cyclic *N*,*O*-acetals is a known reaction.[4] The few reported examples, however, were observed as unexpected side reactions, which have never been further evaluated for their synthetic potential. We therefore decided to investigate the applicability of this reaction to the synthesis of glycosylamines, arguably the most important class of *N*,*O*-acetals.

Scheme 1



† This paper is dedicated to the memory of Andrew D. Dorsey (November 2, 1977−August 13, 2001).

(1) (a) Dwek, K. *Chem. Rev.* **1996**, *96*, 683. (b) Arsequell, G.; Valencia, G. *Tetrahedron: Asymmetry* **1999**, *10*, 3045. (c) Grogan, M. J.; Pratt, M. R.; Marcaurelle, L. A.; Bertozzi, C. R. *Annu. Rev. Biochem.* **2002**, *71*, 593.

(2) (a) Ragan, J. A.; Claffey, M. C. *Heterocycles* **1995**, *41*, 57. (b) Ennis, M. D.; Hoffman, R. L.; Ghazal, N. B.; Old, D. W.; Mooney, P. A. *J. Org. Chem.* **1996**, *61*, 5813.

(3) Apparently, reactions of TMSCN and Meyers' lactams have not been reported. For a review of the chemistry of Meyers' lactams, see: Meyers, A. I.; Brengel, G. P. J. *Chem. Commun.* **1997**, 1.

(4) For examples, see: (a) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042. (b) Deprez, P.; Royer, J.; Husson, H.-P. *Tetrahedron* **1993**, *49*, 3781.

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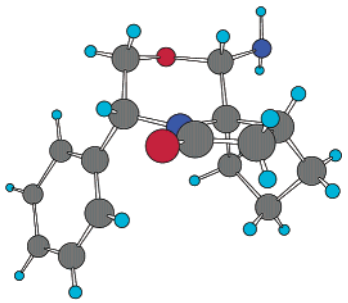
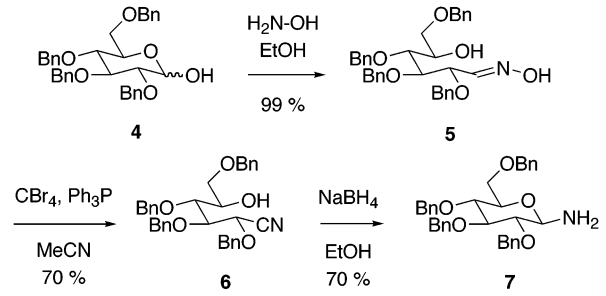


Figure 1. X-ray structure of compound **3**.

We now report a general strategy for the synthesis of protected pyranosylamines via reductive cyclization of δ-hydroxynitriles.

Our method is exemplified by the synthesis of β-tetra-*O*-benzylglucosylamine **7** shown in Scheme 2.[5] Quantitative

Scheme 2



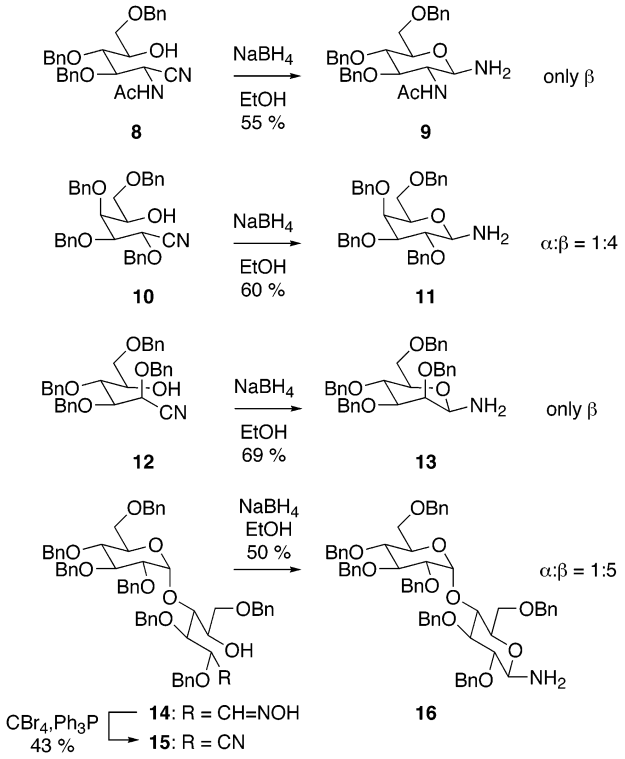
conversion of 2,3,4,6-tetra-*O*-benzylglucose **4** into the corresponding oxime **5** was followed by dehydration under the conditions described by Vasella.[6] Exposure of the resulting known hydroxynitrile **6** to sodium borohydride in ethanol led to reductive cyclization and precipitation of glycosylamine **7** as a single β-anomer in good yield.

The extension of this methodology to other glycosylamines is shown in Scheme 3. All substrates are readily available from the corresponding reducing sugars and are, with the exception of maltose-derivative **15**, known compounds.[6,7] Nitrile **15** was obtained from the known oxime **14**[8] under standard dehydration conditions.

Upon exposure to sodium borohydride in ethanol, the δ-hydroxynitriles cyclized to afford the corresponding glycosylamines in moderate to good yields. In all cases, the reductive cyclization resulted in preferential formation of the β-anomer. No attempts were made to separate anomeric mixtures. *N*-Acetylglucosamine derivative **8** afforded β-

(5) Aebischer, B.; Hanssen, H.; Vasella, A.; Schweizer, W. *J. Chem. Soc., Perkin Trans. 1* **1982**, *6*, 2139.
(6) Ermert, P.; Vasella, A. *Helv. Chim. Acta* **1991**, *74*, 2043.
(7) Heightman, T.; Ermert, P.; Klein, D.; Vasella, A. *Helv. Chim. Acta* **1995**, *78*, 514.
(8) Yokoyama, M.; Irie, M.; Sujino, K.; Kagemoto, T.; Togo, H.; Funabashi, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, *16*, 2127.

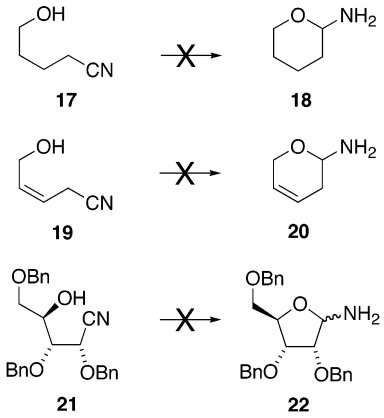
Scheme 3



glycosylamine **9**, a building block for N-linked glycoproteins, as the only observed diastereomer. Galactonitrile **10** gave a 1:4 mixture favoring the β-anomer **11**, whereas mannonitrile **12** only gave β-glycosylamine **13**. In the case of maltonitrile **15**, formation of a 1:5 mixture favoring the β-anomer **16** was observed.

Although the methodology performs well in the synthesis of pyranosylamines, it appears to be somewhat limited to hydroxynitriles yielding electronically deactivated six-membered ring products. Attempts to prepare *N*,*O*-acetals **18** and **20** and furanosylamine **22** from the corresponding hydroxynitriles **17**, **19**, and **21**, respectively, through reductive cyclization failed (Scheme 4). Instead, complex mixtures

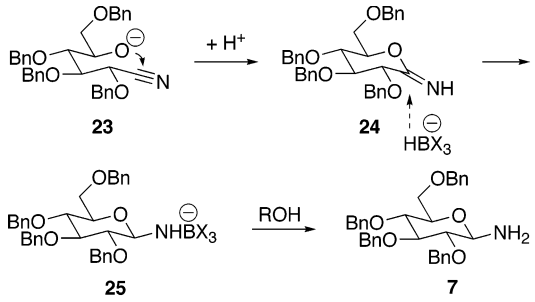
Scheme 4



of amino alcohols and products of reductive amination were obtained under these conditions. Note that the simple *N,O*-acetals **18** and **20** are unknown and appear to be unstable.

Mechanistically, the reaction presumably involves base-catalyzed cyclization of the δ-hydroxynitrile to the corresponding imidate (**24**), followed by reduction of the C=N double bond and alcoholysis (Scheme 5).[9] NMR studies in

Scheme 5



deuterated ethanol indicate that at the end of the reaction time, no boron species remains bound to the amino group. Nitriles per se have been reported to be insensitive toward sodium borohydride in alcoholic solvents.[10]

The stereoselectivity of the reaction can be explained by preferential axial attack of the borohydride onto the imidate. However, it is unclear whether the product ratio reflects kinetic or thermodynamic control since glycosylamines are known to epimerize readily in protic solvents. Due to a less pronounced anomeric effect, β-glycosylamines are generally more stable.[11] Furthermore, the products are isolated by precipitation in some cases.

The use of glycosylamines **7** and **9** in the synthesis of building blocks for N-linked glycopetides and glycoproteins is shown in Scheme 6. Coupling of pure β-anomer **7** with protected aspartic acid **26** under DCC/HOBt conditions gave a 5:1 mixture of *N*-acylglycosylamine **27** and its α-anomer.[12]

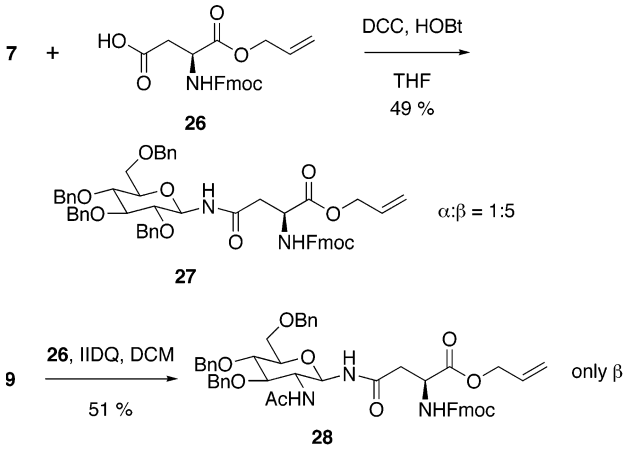
(9) Attempts to prepare these imidates through acid- or base-mediated cyclizations of the corresponding hydroxynitriles failed.

(10) Seyden-Peyne, J. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VCH: New York, 1991; p 129.

(11) Kozar, T.; Tvaroska, I. *Biopolymers* **1990**, *29*, 1531.

(12) Torres, O. L.; Haro, I.; Bardaoi, E.; Valencia, G.; Garcia-Anton, O. M.; Reig, F. *Tetrahedron* **1988**, *44*, 6131.

Scheme 6



By contrast, coupling of **9** with **26** using IIDQ afforded **28** as a single diastereomer.[13] No anomerizaton was observed under these conditions.

In summary, a new method for the stereoselective synthesis of glycosylamines has been developed. Since the δ-hydroxynitriles used as synthetic precursors can be obtained in two simple steps from the corresponding reducing sugars, the methodology appears to be practical for large-scale applications. Future investigations will address the optimization of yields, the stability of different protecting groups (silyl ethers, esters) toward the cyclization conditions, and mechanistic studies.

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Supporting Information Available: Spectroscopic and analytical data for compounds **1**−**3**, **7**, **9**, **11**, **13**, **15**, **16**, **21**, **27**, and **28**, as well as an X-ray structure of compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org. Crystallographic data for compound **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CDC 215332.

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(13) Danishefsky, S.; Hu, S.; Cirillo, P.; Eckhardt, M.; Seeberger, P. *Chem. Eur. J.* **1997**, *3*, 1617.