J|A|C|S
COMMUNICATIONS

Published on Web 04/29/2004

A New Method for the Stereoselective Synthesis of α- and β-Glycosylamines Using the Burgess Reagent

K. C. Nicolaou,* Scott A. Snyder, Annie Z. Nalbandian, and Deborah A. Longbottom

Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, and Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California 92093

Received February 9, 2004; E-mail: kcn@scripps.edu

Even though our knowledge concerning many classes of carbohydrates has expanded dramatically over the past decade, glycosylamines persist as an understudied group, especially in light of their prominence in glycopeptides and glycoproteins and their potential as selective RNA-binding agents.[1] This state of affairs primarily reflects the difficulty in achieving their synthesis, as available methods, based on the use of glycosyl azides, glycals,[2] Kochetkov aminations,[3] and α-hydroxy nitriles,[4] among others,[5] lack substrate generality and often result in variable stereoselectivity, especially in complex contexts. In this communication, we report an operationally simple method for the synthesis of both α- and β-glycosylamines that overcomes many of these limitations in a bare minimum of synthetic steps.

Drawing insight from our recent explorations[6] into the novel chemistry that can be achieved with Burgess-type reagents (**1**, **2**, or **3**, Scheme 1), we anticipated that exposing a carbohydrate of general structure **4** to an excess amount of one of these salts would lead to the formation of a sulfamidate product (**6**) with complete regio- and stereocontrol. Such an outcome is in accordance with the established preference[6a] of the more activated hydroxyl group to depart in the cyclization event, either by the indicated S_N2 mechanism or via an oxonium alternative, with the C-2 group orchestrating the stereoselective delivery of nitrogen. Once constructed, the newly installed sulfamidate ring could then be opened with a variety of heteroatomic nucleophiles to afford 1,2-*trans*-difunctionalized glycosylamine products.[6a,7] Thus, based on this model, a starting material derived from D-glucose would provide

Scheme 1

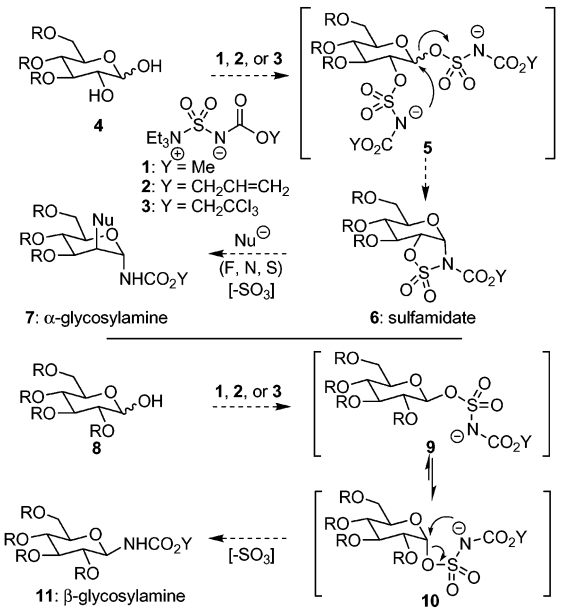
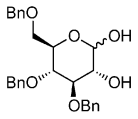
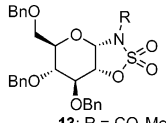
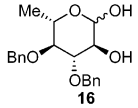
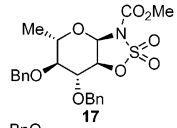
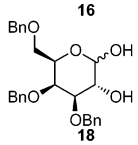
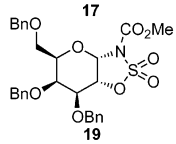
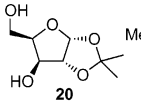
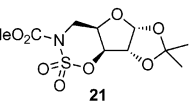
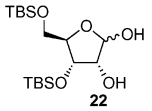
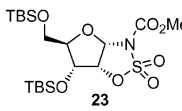


Table 1. Synthesis of Sulfamidates on Carbohydrate Templates[a]

Entry	Starting Material	Product	Ratio α:β	Yield (%)
1	 **12**	 **13**: R = CO_2Me **14**: R = Troc **15**: R = Alloc	8:1	88
2			15:1	75
3			15:1	83
4	 **16**	 **17**	10:1	82
5	 **18**	 **19**	>20:1	79
6	 **20**	 **21**	-	91
7	 **22**	 **23**	>20:1	74

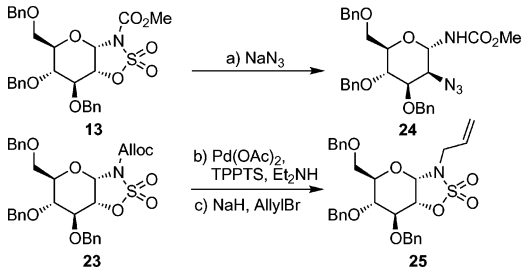
[a] All reactions were performed using 2.5 equiv of the appropriate Burgess-type reagent (**1**, **2**, or **3**) in THF/CH_2Cl_2 (4:1) with heating at reflux for 6 h.

an α-glycosylamine product (**7**), arguably the more difficult glycosylamine anomer to synthesize in a controlled manner. Alternatively, if lactols bearing C-2 protection (**8**) were exposed to the same general reaction conditions, it would be reasonable to expect that these materials would afford *N*,*O*-acetal products instead of sulfamidates through the indicated mechanism, with stereocontrol in this "self-displacement" reaction arising from the established preference for anomeric triflates to exist as α-anomers (**10**) over their β-disposed counterparts (**9**).[8] As such, D-glucose-based materials would afford only β-glycosylamine products (**11**) in this reaction paradigm.

Gratifyingly, when these propositions were tested in the laboratory, they proved to be highly accurate. Indeed, as shown in Table 1, a variety of diols on diverse carbohydrate templates (D-glucose, D-galactose, L-rhamnose) were smoothly converted into their α-disposed sulfamidate counterparts over the course of 6 h upon the action of 2.5 equiv of **1**, **2**, or **3** in refluxing THF/CH_2Cl_2 (4:1). As revealed through the selected examples in Scheme 2, these products could be subsequently opened with nucleophiles to afford α-disposed glycosylamines such as **24** or, alternatively, converted into functionalized sulfamidates such as **25** simply by removing

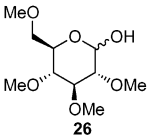
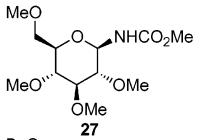
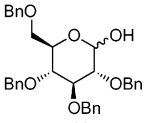
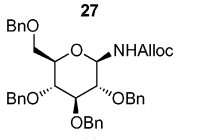
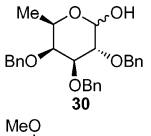
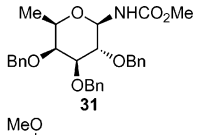
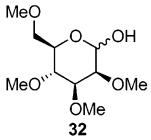
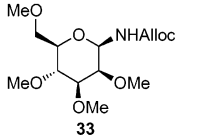
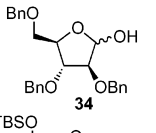
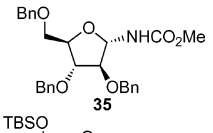
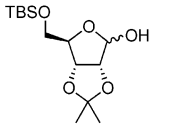
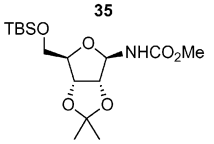
10.1021/ja049293c CCC: $27.50

Scheme 2 [a]



[a] Reagents and conditions: (a) NaN_3 (5.0 equiv), DMF, 60 °C, 5 h, 83%; (b) $Pd(OAc)_2$ (0.1 equiv), TPPTS (0.2 equiv), Et_2NH (40 equiv), $MeCNH_2O$ (1:1), 25 °C, 30 min; (c) NaH (5.0 equiv), DMF, 25 °C, 5 min, then allyl bromide (4.0 equiv), 25 °C, 15 min, 73% over two steps.

Table 2. Direct Conversion of Anomeric Alcohols to Amines[a]

Entry	Starting Material	Product	Ratio β:α	Yield (%)
1	 **26**	 **27**	>20:1	68
2	 **28**	 **29**	>20:1	78
3	 **30**	 **31**	>20:1	72
4	 **32**	 **33**	>20:1	73
5	 **34**	 **35**	8:1	72
6	 **36**	 **37**	3:1	70

[a] All reactions were performed using 1.5 equiv of the appropriate Burgess-type reagent (**1**, **2**, or **3**) in THF/CH_2Cl_2 (4:1) with heating at reflux for 6 h.

the Alloc protecting group and alkylating. Although both of these manipulations should prove important in future applications relevant to chemical biology and medicinal chemistry, compounds of type **25** offer several unique advantages as their sulfamidate ring provides untapped structural novelty and ensures that the disposition of the *N*-atom cannot anomerize (as often occurs with unprotected α-glycosylamines simply upon standing in solution). As indicated in Table 2, C-2 protected lactols reacted with Burgess-type reagents in a level of smoothness that matched their diol counterparts, affording a *β*-disposed, protected glycosylamine on every six-membered carbohydrate probed (entries 1−4), as verified by both X-ray crystallographic and ^1H NMR analyses. Five-membered furanose substrates performed equally well (entries 5 and 6), with anomeric stereochemistry in these products presumably controlled by the orientation of the C-2 substituent on a level commensurate to its bulk.[9] Finally, it is important to note that, in addition to generating highly predictable products within this reaction manifold, Alloc-protected amines were readily liberated to afford free glycosylamines for additional synthetic applications. For example, Alloc-protected **29** was transformed into 2,3,4,6-tetra-*O*-benzyl-*β*-D-glucosylamine in near quantitative yield (95%) using conditions[10] that did not initiate any anomerization.

In conclusion, we have developed a new approach for the synthesis of both α- and *β*-glycosylamines on a wide variety of carbohydrate scaffolds using a reaction protocol that is exceedingly mild, operationally simple, and tolerant of numerous functional and protecting groups.[11] In addition, these reactions appear to be applicable for large-scale syntheses (reactions up to 5 mmol have been performed with no drop in efficiency) and late-stage operations relevant to the synthesis of complex aminoglycosides and/or *N*-linked glycopeptides. Accordingly, this synthetic technology provides certain advantages over those currently available and should enhance our capability to study the chemical biology of both natural and designed glycosylamines. Equally important, this methodology continues to underscore the impressive power of the Burgess reagent (**1**) and its relatives (**2**, **3**) to effect transformations of critical importance in chemical synthesis.[12]

Acknowledgment. We thank Drs. D. H. Huang and G. Siuzdak for NMR spectroscopic and mass spectrometric assistance, respectively. Financial support for this work was provided by The Skaggs Institute for Chemical Biology, the National Institutes of Health (U.S.A.), predoctoral fellowships from the National Science Foundation, Pfizer, and Bristol-Myers Squibb (all to S.A.S.), and a grant from American Biosciences.

Supporting Information Available: Detailed experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) Arsequell, G.; Valencia, G. *Tetrahedron: Asymmetry* **1999**, *10*, 3045. (b) Grogan, M. J.; Pratt, M. R.; Marcaurelle, L. A.; Bertozzi, C. R. *Annu. Rev. Biochem.* **2002**, *71*, 593.
(2) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380.
(3) (a) Likhoshertov, L. M.; Novikova, V. A.; Dervitskaja, V. A.; Kochetkov, N. K. *Carbohydr. Res.* **1986**, *46*, C1. (b) Lubineau, A.; Auge, J.; Drouillat, B. *Carbohydr. Res.* **1995**, *266*, 211.
(4) Dorsey, A. D.; Barbarow, J. E.; Trauner, D. *Org. Lett.* **2003**, *5*, 3237.
(5) Damkaci, F.; DeShong, P. *J. Am. Chem. Soc.* **2003**, *125*, 4408.
(6) (a) Nicolaou, K. C.; Huang, X.; Snyder, S. A.; Rao, P. B.; Bella, M.; Reddy, M. V. *Angew. Chem., Int. Ed.* **2002**, *41*, 834. (b) Nicolaou, K. C.; Longbottom, D. A.; Snyder, S. A.; Nalbandian, A. Z.; Huang X. *Angew. Chem., Int. Ed.* **2002**, *41*, 3866.
(7) For a review, see: Melendez, R. E.; Lubell, W. D. *Tetrahedron* **2003**, *53*, 2581.
(8) Crich, D. *J. Carbohydr. Chem.* **2002**, *21*, 667.
(9) It is important to note that this protocol does not provide a general synthesis of aminals from lactols, as a number of conventional lactols gave inconsistent yields of the desired products.
(10) Genêt, J. P.; Blart, E.; Savignac, M.; Lemeure, S.; Paris, J.-M. *Tetrahedron Lett.* **1993**, *34*, 4189.
(11) The only incompatibility that we have identified is the presence of carbonyl-based protecting groups such as acetate or benzoate at the C-3 position.
(12) For reviews on the chemistry of the Burgess reagent, see: (a) Taibe, P.; Mobashery, S. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L.A., Ed.; John Wiley & Sons: Chichester, 1995; Vol. 5, pp 3345−3347. (b) Burckhardt, S. *Synlett* **2000**, 559.

JA049293C