ORGANIC LETTERS

2006
Vol. 8, No. 7
1303−1306

Desulfonylation with Mg–MeOH–$NiBr_2$: An Expedient Reagent System for the Synthesis of 2-Amino-2,3-dideoxy Furanosides

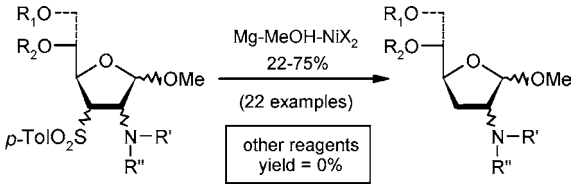
Indrajit Das and Tanmaya Pathak*

Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

tpathak@chem.iitkgp.ernet.in

Received December 20, 2005

ABSTRACT



A catalytic amount of $NiBr_2$ with Mg–MeOH increases the efficiency of reductive desulfonylation of the β-sulfonylated aminosugars. The Mg–MeOH–$NiBr_2$ system has been utilized in the synthesis of 2-amino-2,3-dideoxypentofuranosides and 2-amino-2,3-dideoxyhexofuranosides. The yield of the desulfonylation improved dramatically from 0% with the known reagents to 44–75% with Mg–MeOH–$NiBr_2$.

To circumvent the problem of resistance to aminoglycoside antibiotics among resistant bacteria, several semisynthetic aminoglycoside antibiotics have been designed where either the hydroxyl groups undergoing enzymatic phosphorylation have been removed and/or the amino groups susceptible to acetylation have been masked by acylation or alkylation.[1] We therefore considered it to be of interest to design general methodologies for the synthesis of modified new aminosugars having one or more deoxygenated centers and mono- or dialkylated amino groups at specific sites. In addition, an epimeric variation in the stereochemistry of the C−N bond might also lead to different types of responses by a biological system.[2]

As part of an ongoing project for developing a general methodology for the synthesis of deoxyaminosugars, we reacted various amines with vinyl sulfone-modified hex-2-enopyranosides **1**α and **1**β (Figure 1). It emerged from these

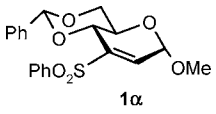


Figure 1. Vinyl sulfone modified hex-2-enopyranosides.

studies that the addition of primary amines to C-2 of both **1**α and **1**β exclusively produced C-2 equatorial (gluco) products. Secondary amines, on reaction with β-anomeric glycosides **1**β produced only gluco derivatives but with **1**α produced mixtures in which the gluco product was still the predominant isomer.[2a,c]

The successful application of vinyl sulfone modified carbohydrates in the synthesis of deoxyaminosugars crucially depends on the following factors: (i) the efficiency of Michael addition of amines; (ii) the diastereoselectivity of

(1) (a) Kondo, S.; Hotta, K. *J. Infect. Chemother*. **1999**, *5*, 1. (b) Jana, S.; Deb, J. K. *Current Drug Targets* **2005**, *6*, 353. (c) Kim, C.; Mobashery, S. *Bioorg. Chem*. **2005**, *33*, 149. (c) Busscher, Guuske F.; Rutjes, Floris P. J. T.; Van Delft, Floris L. *Chem. Rev*. **2005**, *105*, 775.

(2) (a) Ravindran, B.; Sakthivel, K.; Suresh, C. G.; Pathak, T. *J. Org. Chem*. **2000**, *65*, 2637. (b) Ravindran, B.; Deshpande, S. G.; Pathak, T. *Tetrahedron* **2001**, *57*, 1093 and references therein. (c) Suresh, C. G.; Ravindran, B.; Pathak, T.; Narasimha Rao, K.; Sasidhar Prasad, J. S.; Lokanath, N. K. *Carbohydr. Res*. **2002**, *337*, 1507.

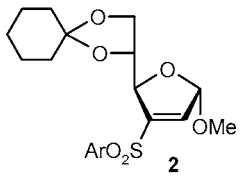
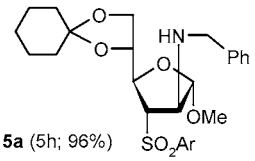
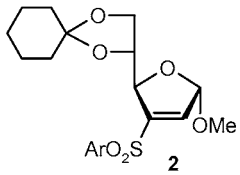
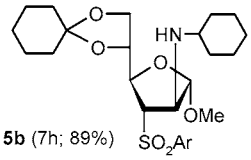
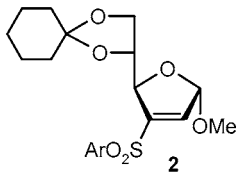
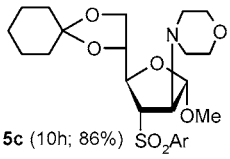
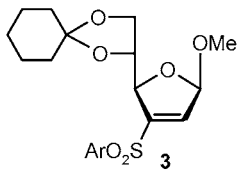
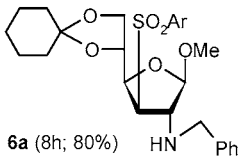
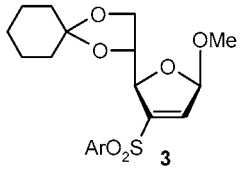
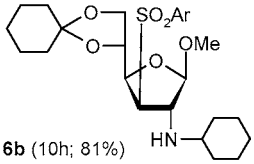
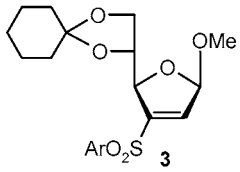
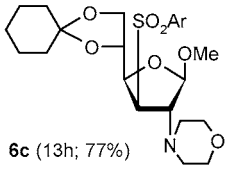
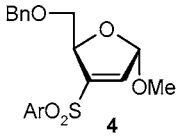
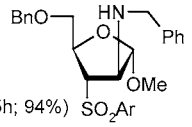
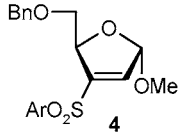
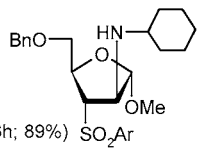
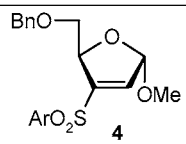
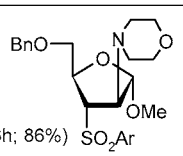
10.1021/ol053082a CCC: $33.50
Published on Web 03/03/2006

addition of amines; and (iii) the efficiency of desulfonylation under suitable reductive conditions.[3] Since all of our efforts to deliver primary amines from the β-face of the pyranose ring (**1**α and **1**β) failed,[2] we directed our attention to vinyl sulfone-modified pent-2- and hex-2-enofuranosyl systems such as **2**−**4**. From our previous experience[2,3] and the previously reported reactions of various nucleophiles with vinyl sulfone-modified pentofuranosyl nucleosides,[4] we were sure that amines would add efficiently in diastereoselective fashion to **2**−**4**. Thus, compound **2** on reaction with benzylamine, cyclohexylamine, and morpholine produced compounds **5a**−**c**, respectively, in diastereoselective fashion and high yield. Similarly, **3** and **4** also produced the expected aminosugars **6a**−**c** and **7a**−**c**, respectively (Table 1).[5]

Since the success of a scheme for the synthesis of deoxyaminosugars using carbohydrate vinyl sulfones would depend crucially on the desulfonylation step,[6] we experimented with a large variety of desulfonylating agents available in the literature. The Na−Hg-mediated reduction is the most widely used radical-based method for the desulfonylation of organic molecules and has been used extensively for the desulfonylation of β-amino sulfones[7] and γ-amino sulfone derivatives.[8] Another electron-transfer method that uses Mg metal in methanol has also been reported[9] with there being at least one report where Mg in methanol was successfully used for the desulfonylation of a β-amino sulfone compound.[7a] However, none of these reagents were able to efficiently desulfonylate the amine Michael addition products of vinyl sulfone modified nucleosides; the desired desulfonylated nucleosides were always obtained in moderate to very poor yields.[4]

After successfully introducing the amino groups to the α- or β-face of the hexofuranose and pentofuranose systems to obtain the products **6a**−**c** and **5a**−**c**/**7a**−**c**, respectively, three of these compounds **5a**, **6a**, and **7a** were subjected to desulfonylation using Na−Hg or Mg in methanol. None of these two reagent systems was suitable for the removal of the tolylsulfonyl group from these modified carbohydrates with amino groups at the β-position. All of the reactions produced inseparable mixtures of compounds, and the desired products **8a**, **9a**, or **10a** (Table 2) could not be isolated. A perusal of the literature revealed that reagents such as

Table 1. Amination of Vinyl Sulfone Modified Carbohydrates **2**−**4** with Benzylamine, Cyclohexylamine, and Morpholine[a]

Starting material[b]	Product[b]
 **2**	 **5a** (5h; 96%)
 **2**	 **5b** (7h; 89%)
 **2**	 **5c** (10h; 86%)
 **3**	 **6a** (8h; 80%)
 **3**	 **6b** (10h; 81%)
 **3**	 **6c** (13h; 77%)
 **4**	 **7a** (5h; 94%)
 **4**	 **7b** (6h; 89%)
 **4**	 **7c** (8h; 86%)

[a] All reactions were carried out at room temperature using neat amines (5 mL/mmol). [b] Ar = *p*-Tol.

(3) The strategy has been implemented in the synthesis of D-lividosamine (2-amino-2,3-dideoxy-D-glucose), a constituent of aminoglycosides lividomycin-A, lividomycin-B, etc. Diastereoselective equatorial addition of ammonia to **1**α (Figure 1) followed by the desulfonylation of the product at the C-3 site produced a known intermediate for accessing D-lividosamine. Several partially and fully protected analogues of D-lividosamine could be synthesized using *N*-monoalkylated and *N*-dialkylated amines in a similar approach. See ref 2b.

(4) Wu, J.-C.; Pathak, T.; Tong, W.; Remaud, G.; Chattopadhyaya, J. *Tetrahedron* **1988**, *44*, 6705.

(5) All aminosugars **5a**−**c**, **6a**−**c**, and **7a**−**c** described in Table 1 are single compounds. Structures of all compounds have been assigned on the basis of X-ray structural analysis and comparison of NMR data. These data will be reported elsewhere.

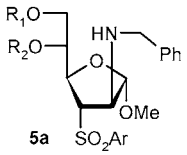
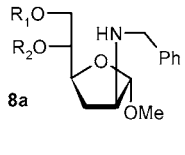
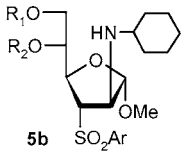
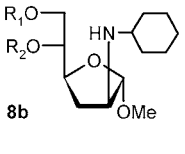
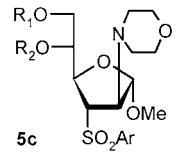
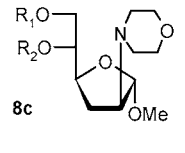
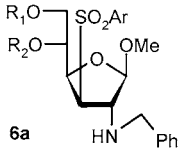
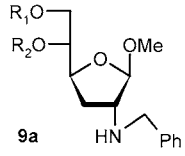
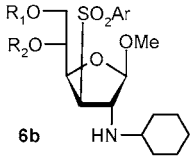
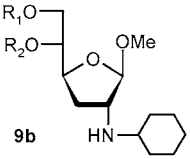
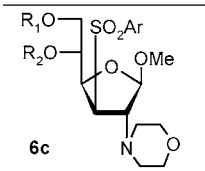
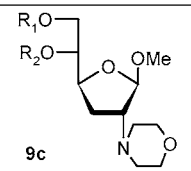
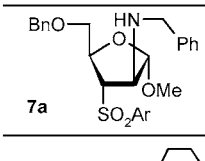
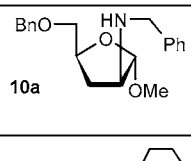
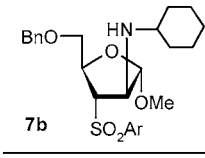
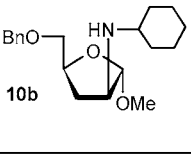
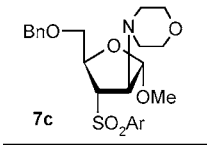
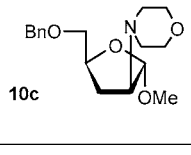
(6) For a review on desulfonylation, see: Najera, C.; Yus, M. *Tetrahedron* **1999**, *40*, 10547.

(7) (a) Ku, Y. Y.; Patel, R. R.; Roden, B. A.; Sawick, D. P. *Tetrahedron Lett.* **1994**, *35*, 6017. (b) Eiji, A.; Masahiro, H. *Synlett* **1996**, 100. (c) Giblin, G. M. P.; Jones, C. D.; Simpkins, N. S. *Synlett* **1997**, 589. (d) Balasubramanian, T.; Hassner, A. *Tetrahedron: Asymmetry* **1998**, *9*, 2201.

(8) François, D.; Lallemand, M. C.; Selkti, M.; Tomas, A.; Kunesch, N.; Husson, H. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 104.

(9) For a review on Mg in MeOH, see: Lee, G. H.; Youn, I. K.; Choi, E. B.; Lee, H. K.; Yon, G. H.; Yang, H. C.; Pak, C. S. *Curr. Org. Chem.* **2004**, *8*, 1263.

Table 2. Desulfonylation of Aminosugars **5**−**7**[a]

Starting material[b]	Product[b]	NiX_2 (Yield %)
 **5a**	 **8a**	$NiCl_2$ (65) **$NiBr_2$ (73)** NiI_2 (53)
 **5b**	 **8b**	$NiCl_2$ (60) **$NiBr_2$ (70)**
 **5c**	 **8c**	$NiCl_2$ (36) **$NiBr_2$ (50)** NiI_2 (22)
 **6a**	 **9a**	$NiCl_2$ (62) **$NiBr_2$ (71)**
 **6b**	 **9b**	$NiCl_2$ (61) **$NiBr_2$ (65)** NiI_2 (51)
 **6c**	 **9c**	$NiCl_2$ (23) **$NiBr_2$ (44)**
 **7a**	 **10a**	$NiCl_2$ (61) **$NiBr_2$ (75)** NiI_2 (53)
 **7b**	 **10b**	$NiCl_2$ (52) **$NiBr_2$ (69)**
 **7c**	 **10c**	$NiCl_2$ (31) **$NiBr_2$ (50)**

[a] All reactions were carried out at room temperature using Mg−MeOH−NiX_2 in 6 h. [b] R_1, R_2 = cyclohexylidenyl; Ar = *p*-Tol.

$HgCl_2$, $CdCl_2$, and Pd−C have been used as additives with Mg−MeOH system,[9] although the exact role of these compounds in the reaction medium is not well delineated. However, Mg−EtOH−$HgCl_2$[9] also failed to produce the expected compounds from **6a** and **7a**. On treatment with Al−Hg,[6] **6a** also produced an inseparable mixture of compounds. Thereafter, **5a**, **6a**, and **7a** were reacted with either electron-transfer reagent SmI_2[10a] or hydride reagents ($LiAlH_4$) known for their abilities to induce desulfonylation.[6] Interestingly, a mixture of $NiBr_2$−DME, PPh_3, and $LiAlH_4$, which has previously been reported[10b] to be an efficient desulfonylating agent, was also found to be too harsh to be used for the desulfonation of **7a**. In all cases, compounds **5a**, **6a**, and **7a** were always converted to an inseparable mixture of compounds. Since most of the conventional reagents or combinations of reagents failed to deliver the desired products, we initiated a search for an alternative method for the desulfonylation of **5a**−**c**, **6a**−**c**, and **7a**−**c**.

Reaction systems generating Ni(0) in situ[11] or making direct use of Raney nickel[12] for the reduction of sulfones to the corresponding carbon−hydrogen bonds have been reported. However, compounds **5a** and **7a** were either inert to Raney-Ni or produced several products under the reaction conditions. At this point, our attention was drawn to a reported observation that the reduction of nickel halides with low-oxidation-potential metals such as magnesium produce finely divided Ni(0), which exhibits general, catalytic activity greater than commercial Raney nickel.[13] We therefore subjected compounds **5a**−**c**, **6a**−**c**, and **7a**−**c** to desulfonylation by the Mg−MeOH−NiX_2 system. Three nickel salts, namely $NiCl_2$, $NiBr_2$, and NiI_2, were employed for the present study. To our pleasant surprise, we could desulfonylate compounds **5a**−**c**, **6a**−**c**, and **7a**−**c** to obtain the dideoxyaminosugars **8a**−**c**, **9a**−**c**, and **10a**−**c,** respectively, in moderate to good yields. The results are summarized in Table 2. It is clear from the table that $NiBr_2$ is the most efficient of all nickel halides used for the desulfonylation. The use of $NiCl_2$ caused the yield to drop in all cases. NiI_2 was always the least efficient additive in all cases. However, it appears from Table 2 that the amino group that is present is also responsible in helping to determine the efficiency of the reaction. For example, benzylamino-containing analogues **5a**, **6a,** and **7a** were always desulfonylated by Mg−MeOH−$NiBr_2$ most efficiently to produce **8a**, **9a,** and **10a** in 73, 71, and 75% yields, respectively. The desulfonylation of the cyclohexylamino derivatives **5b**, **6b**, and **7b** to **8b** (70%), **9b** (65%), and **10b** (69%), respectively, was slightly less efficient, while for the morpholino analogues **5c**, **6c,** and **7c** the yields of desulfonylation to **8c** (50%), **9c** (44%), and **10c** (50%) dropped significantly. Interestingly, aminosugars **5a**,**b**, **6a**,**b**, and **7a**,**b** derived from primary amines required only 10 mol % of the nickel salts, whereas aminosugars **5c**, **6c**, and **7c** derived from secondary amines required 20 mol % of the nickel salts. The use of $NiBr_2$ or other nickel halides in stoichiometric amounts did not alter yields and in fact in some cases yields actually dropped.[14] A change of solvent

(10) (a) Serafinowski, P. J.; Barnes, C. L. *Synthesis* **1997**, 225. (b) Ho, K. M.; Lam, C. H.; Luh, T. Y. *J. Org. Chem.* **1989**, *54*, 4474.

(11) Chan, M. C.; Cheng, K. M.; Ho, K. M.; Ng, C. T.; Yam, T. M.; Wang, B. S. L.; Luh, T. Y. *J. Org. Chem.* **1988**, *53*, 4466.

(12) (a) Oikawa, M.; Oikawa, H.; Ichthara, A. *Tetrahedron Lett.* **1993**, *34*, 4797. (b) Oikawa, M.; Oikawa, H.; lchihara, A. *Tetrahedron* **1995**, *51*, 6237. (c) Gamble, M. P.; Giblin, G. M. P.; Taylor. R. J. K. *Synlett* **1995**, 779. (d) Sheehan, S. M.; Padwa, A. *J. Org. Chem.* **1997**, *63*, 4438.

(13) Mauret, P.; Alphonse, P. *J. Org. Chem.* **1982**, *47*, 3322.

from MeOH to EtOH did not improve the yield or the quality of the desulfonylation reactions.

Based on earlier reports,[13] we presume that under the reductive conditions employed, nickel halides are reduced to Ni(0). However, it is clear from our background work using Raney-Ni (discussed above) that mere conversion of Ni(II) to Ni(0) is not the sole reason for the controlled activity of the Mg−MeOH−NiX_2 reported here. It is also logical to presume at this stage that as suggested earlier, the "particle arrangement and aggregate textures",[13] may play an important role in determining the mechanism of action of Mg−MeOH−NiX_2 system. Several other issues such as (i) the role of counteranion of the nickel salts, (ii) stereoelectronic properties of the amino groups, and (iii) the ring conformation also appear to dictate the interactions of furanose systems with the Ni(0) surface and should also be considered when predicting the efficacy of the process.

In conclusion, we have developed a novel Mg−MeOH−$NiBr_2$ system for the reductive desulfonylation of the β-sulfonylated aminosugars that allows the synthesis of hitherto inaccessible 2-amino-2, 3-dideoxypentofuranosides and 2-amino-2,3-dideoxyhexofuranosides. The yields of desulfonylation step improve dramatically from 0% with the known reagents to 44−75% with Mg−MeOH−$NiBr_2$. Research is currently in progress to delineate the exact mechanism of desulfonylation and further synthetic applications of the new reagent system.

(14) One of the reviewers suggested that the drop in yield was possibly due to the amines irreversibly binding to the greater quantities of Ni(0) reagent present.

Acknowledgment. T.P. thanks the Department of Science and Technology, New Delhi, India, for financial support and Professor Muktimoy Chaudhury for discussions. I.D. thanks the Council of Scientific and Industrial Research, New Delhi, India, for a fellowship.

Supporting Information Available: Experimental procedures and spectral and analytical data of compounds **8**−**10**. ^1H and ^{13}C NMR spectra of all new compounds. Table 3 summarizes attempted desulfonylation of **5a**, **6a**, and **7a** with known reagents. This material is available free of charge via the Internet at http://pubs.acs.org.

OL053082A