ORGANIC LETTERS

2008
Vol. 10, No. 7
1361−1364

Convenient Synthesis of Branched-Chain Glycosamines by Radical Addition of Nitromethane to Glycals

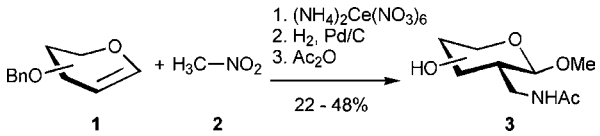
Elangovan Elamparuthi and Torsten Linker*

Department of Chemistry, University of Potsdam, Karl-Liebknecht-Strasse 24-25, D-14476 Potsdam, Germany

linker@chem.uni-potsdam.de

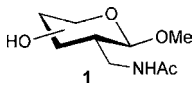
Received January 4, 2008

ABSTRACT



Radical addition–reduction–acetylation is the simple three-step sequence for the synthesis of branched-chain glycosamines 3 from glycals 1 and nitromethane (2). The intermediary formed 2-*C*-nitromethyl-pyranosides are valuable precursors for the synthesis of C-2 branched disaccharides.

Glycosamines represent important biomolecules, which have been discussed as potential drugs for the treatment of arthritis.[1] In the *N*-acetylated or -sulfated form they are constituents of the naturally occurring polysaccharides chitin[2] and heparin.[3] More recently, glycosamine analogs have been investigated as promising candidates for enzyme inhibition.[4] Attractive structures are C-2 branched glycosamines **1**, which have been incorporated into unnatural sialic acids.[5]



However, very few synthetic procedures for preparing such analogs **1** exist in the literature. The epoxide opening of 2,3-anhydropyranosides by nitrile containing reagents and subsequent reduction is not always applicable for their construction, due to the formation of the wrong regioisomer.[6] In contrast, the selective syntheses of C-2 branched glycosamines **1** from 2-uloses require many steps.[5,7] The best approach until now is Chmielewski's [2 + 2] cycloaddition to glycals, which affords the D-*gluco* and D-*galacto* configured products in moderate yields.[8]

Herein we describe a convenient and general two-step entry into branched-chain glycosamines **1** by radical addition of nitromethane (**2**) to glycals **3** and subsequent reduction. The new method is applicable to hexoses, pentoses, and disaccharides, and provides 2-deoxy-2-*C*-nitromethyl-pyranosides **4** as intermediates, which allow access to further functionalized carbohydrate 2-*C*-analogs.

Cerium(IV) ammonium nitrate (CAN) is a versatile one-electron oxidant for radical generation with manifold uses

(1) (a) Clouatre, D. *Glucosamine Sulfate and Chondroitin Sulfate*; Keats: Lincolnwood, IL, 1999. (b) Elkins, R. *Glucosamine/Chondroitin*; Woodland Publishing: Orem, UT, 2003. (c) Theodosakis, J.; Adderly, B.; Buff, S. *The Arthritis Cure*; St. Martin's Press: New York, 2004.

(2) (a) Roberts, G. A. F. *Chitin Chemistry*; The Macmillan Press Ltd.: London, 1992. (b) Brine, C. J.; Sandford, P. A.; Zikakis, J. P. *Advances in Chitin and Chitosan*; Elsevier: London, 1992. (c) Uragami, T.; Kurita K.; Fukamizo, T. *Chitin and Chitosan*; Kodansha Scientific Ltd.: Tokyo, 2001.

(3) (a) *Heparin and Related Polysaccharides*; Lane, D. A., Björk, I., Lindahl, U., Eds.; Springer: Berlin, 1992. (b) *Chemistry and Biology of Heparin and Heparan Sulfate*; Garg, H. G., Linhardt, R. J., Hales, C. A., Eds.; Elsevier: New York, 2005.

(4) (a) Islam, T.; Linhardt, R. J. *Carbohydrate-Based Drug Discovery*; Wiley-VCH: Weinheim, 2003, 407. (b) Lazarevic, D.; Thiem, J. *Carbohydr. Res.* **2006**, *341*, 569. (c) Chen, H.-M.; Withers, S. G. *Carbohydr. Res.* **2007**, *342*, 2212.

(5) Koppert, K.; Brossmer, R. *Tetrahedron Lett.* **1992**, *33*, 8031.

(6) (a) Davison, B. E.; Guthrie, R. D. *J. Chem. Soc., Perkin I* **1972**, 658. (b) Hall, R. H.; Bischofberger, K.; Brink, A. J.; de Villiers, O. G.; Jordaan, A. *J. Chem. Soc., Perkin I* **1979**, 781.

(7) (a) Sarda, P.; Olesker, A.; Lukacs, G. *Carbohydr. Res.* **1992**, *229*, 161. (b) Kazmir, S. N.; Ahmed, Z.; Malik, A.; Afza, N.; Voelter, W. *Z. Naturforsch. B* **1994**, *50*, 294.

(8) (a) Mostowicz, D.; Belzecki, C.; Chmielewski, M. *J. Carbohydr. Chem.* **1988**, *7*, 805. (b) Mostowicz, D.; Zegrocka, O.; Chmielewski, M. *Carbohydr. Res.* **1991**, *212*, 283.

10.1021/ol703062s CCC: $40.75
Published on Web 03/11/2008

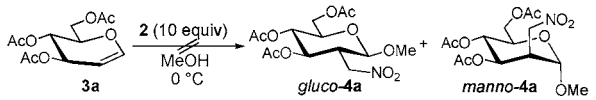
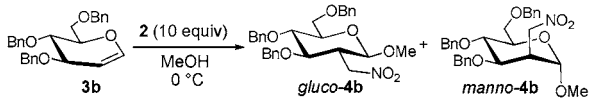
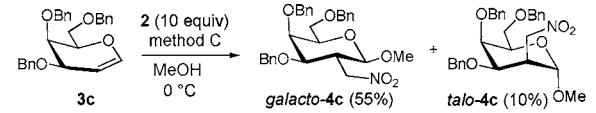
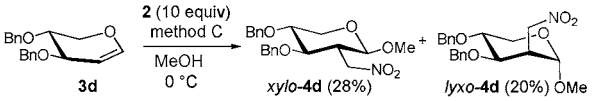
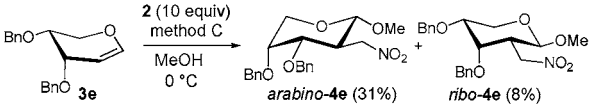
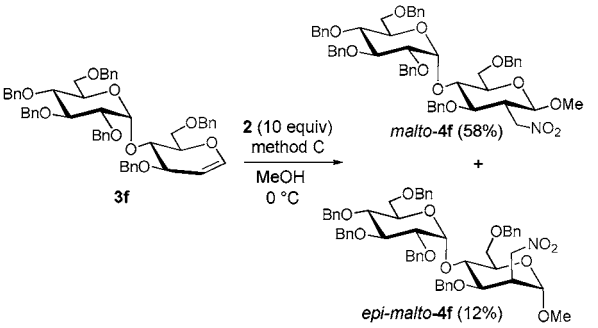
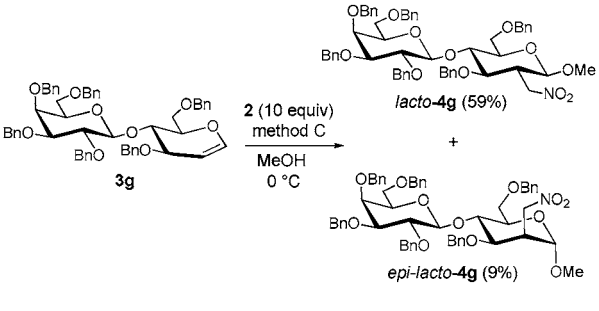
in organic synthesis that were summarized in a recent review.[9] We developed the first C−C bond formation with this reagent in carbohydrate chemistry, with a special emphasis on the addition of malonates to glycals.[10] More recently, we became interested in the reaction of other CH acidic substrates[11] and the transformation of the addition products.[12] However, two adjacent acceptor groups were essential in the precursors, for the radical generation with CAN under mild conditions.

The synthesis of the branched-chain glycosamines **1** required the addition of nitromethane (**2**), which reacts with cerium(IV) ammonium nitrate (CAN) much slower than dimethyl malonate or other nitroalkanes.[9,13] Furthermore, applications of nitroalkyl radicals in carbohydrate chemistry were hitherto unknown. Therefore, we first optimized the conditions for the reaction of nitromethane (**2**) with the *gluco* configured glycals **3a** and **3b** (Table 1, entries 1−6). No conversion of tri-*O*-acetyl-D-glucal (**3a**) was observed with the conventional CAN protocol (method A), even with 10 equiv of the CH acidic precursor (entry 1).

In contrast, tri-*O*-benzyl-D-glucal (**3b**) afforded decomposition products under such conditions (entry 4), due to undesired deprotections and Ferrier rearrangements.[14] Therefore, we added sodium hydrogen carbonate to the reaction mixture (method B), which was advantageous for the addition of malonates,[12] but no conversion was observed (entries 2 and 5). Thus, stronger bases for the deprotonation of nitromethane (**2**) were required, since the corresponding nitronate anion is oxidized by cerium(IV) ammonium nitrate (CAN) much faster.[13] Best conditions were found with 10 equiv of nitromethane (**2**), 2 equiv of KOH, and 4 equiv of CAN (method C). Although tri-*O*-acetyl-D-glucal (**3a**) underwent deprotection, the benzylated glucal **3b** reacted smoothly at 0 °C. Finally, the 2-deoxy-2-*C*-nitromethyl-pyranosides **4b** were isolated in 71% yield in analytically pure form (entry 6, Supporting Information). The diastereoselectivity of the addition of nitromethane was clearly in favor of the equatorial attack (*gluco*/*manno* 5:1), but somewhat lower than the corresponding reaction of malonates (*gluco*/*manno* 6:1).[12] This result can be rationalized by the sterically less demanding nitroalkyl in comparison to malonyl radicals.

The successful method C was applied to other benzyl glycals **3c-g**, which are easily available on a large scale.[15] Thus, tri-*O*-benzyl-D-galactal (**3c**) afforded the 2-deoxy-2-*C*-nitromethyl-pyranosides **4c** in similar yields and stereoselectivities (Table 1, entry 7). The products **4b**, **4f**, and **4g** were obtained in almost identical diastereomeric ratios (entries 6, 10, and 11), since the unsaturated rings have always the *gluco* configuration. In contrast, for the *arabino* isomer **3e** the 2-deoxy-2-*C*-nitromethyl-pyranoside *arabino*-**4e** was the main product (entry 9), due to the *pseudoaxial* *O*-benzyl group in the 3-position. This *anti* attack of the

Table 1. Addition of Nitromethane (**2**) to Various Glycals **3a−g**

entry	method[a]	nitromethyl pyranoside **4**[b]
		
1	method A	no conversion
2	method B	no conversion
3	method C	deprotection
		
4	method A	decomposition
5	method B	no conversion
6	method C	59% 12%
		
7	method C	galacto-**4c** (55%) talo-**4c** (10%)
		
8	method C	xylo-**4d** (28%) lyxo-**4d** (20%)
		
9	method C	arabino-**4e** (31%) ribo-**4e** (8%)
		
10	method C	malto-**4f** (58%) + epi-malto-**4f** (12%)
		
11	method C	lacto-**4g** (59%) + epi-lacto-**4g** (9%)

[a] Method A: 4 equiv CAN. Method B: 4 equiv CAN, 4 equiv $NaHCO_3$. Method C: 2 equiv KOH, then 4 equiv CAN, MeOH, 0 °C. [b] Yields of isolated products after column chromatography.

(9) Recent review: Nair, V.; Deepthi, A. *Chem. Rev.* **2007**, *107*, 1862.

(10) (a) Linker, T.; Hartmann, K.; Sommermann, T.; Scheutzow, D.; Ruckdeschel, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1730−1732. (b) Linker, T.; Sommermann, T.; Kahlenberg, F. *J. Am. Chem. Soc.* **1997**, *119*, 9377−9384. (c) Gyóllai, V.; Schanzenbach, D.; Somsák, L.; Linker, T. *Chem. Commun.* **2002**, 1294−1295. (d) Linker, T. *J. Organomet. Chem.* **2002**, *661*, 159−167.

(11) (a) Sommermann, T.; Kim, B. K.; Peters, K.; Peters, E.-M.; Linker, T. *Chem. Commun.* **2004**, 2624. (b) Kim, B. G.; Schilde, U.; Linker, T. *Synthesis* **2005**, 1507.

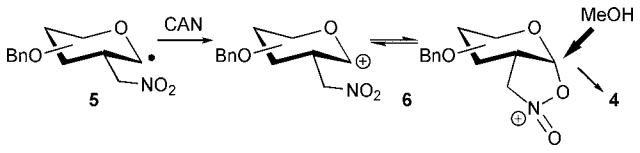
(12) (a) Yin, J.; Spindler, J.; Linker, T. *Chem. Commun.* **2007**, 2712. (b) Yin, J.; Sommermann, T.; Linker, T. *Chem.−Eur. J.* **2007**, *13*, 10152.

(13) Arai, N.; Narasaka, K. *Chem. Lett.* **1995**, 987. (b) Arai, N.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2525.

(14) Ferrier, R. J.; Prasad, N. *J. Chem. Soc. C* **1969**, 581.

radicals to functional groups in the 3-position is in accordance with our previous studies with dimethyl malonate.[10,12] The methyl glycosides are formed by CAN oxidation of the adduct radicals **5** to cations **6** and trapping with the solvent, exhibiting excellent 1,2 *trans* selectivity, which can be explained by a neighboring effect of the adjacent nitro group (Scheme 1).

Scheme 1. Mechanism for the Formation of the Methyl Glycosides **4** via Radicals **5** and Cations **6**

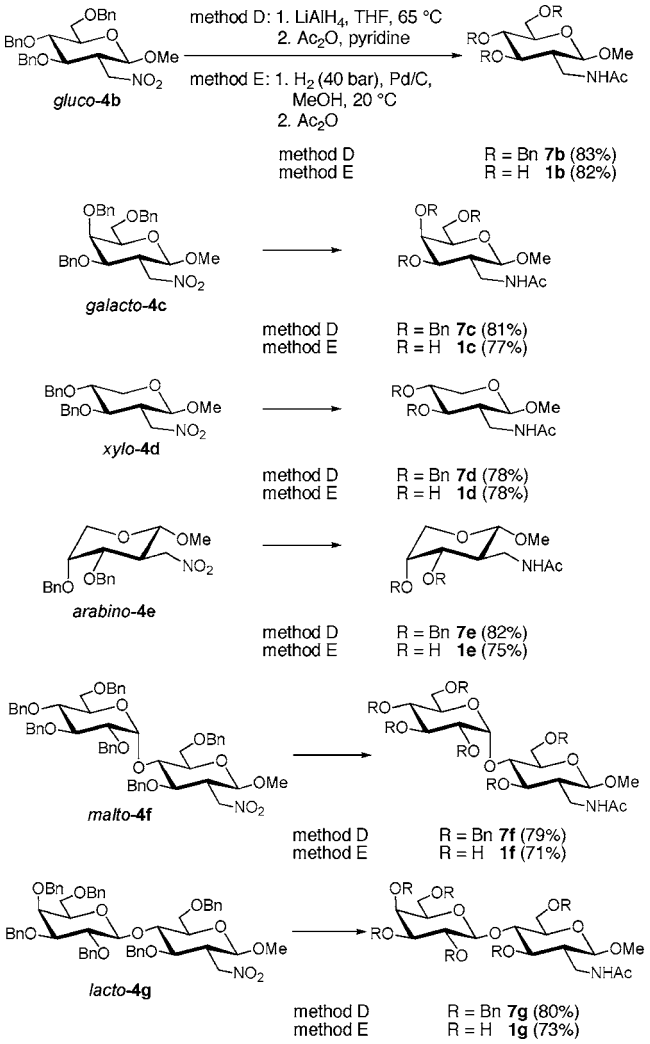


Pentoses **3d** and **3e** gave lower yields (entries 8 and 9), due to the formation of oxidative side-products. However, the desired *xylo* (**4d**) and *arabino* (**4e**) isomers were isolated in analytically pure form by column chromatography. Finally, disaccharides **3f** and **3g** reacted smoothly with nitromethane (**2**) to afford the 2-deoxy-2-*C*-nitromethyl-pyranosides **4f** and **4g** in good yields (Table 1, entries 10 and 11).

In summary, we could apply CH acidic radical precursors with only one acceptor group in carbohydrate chemistry for the first time. Since benzyl glycals **3b**−**g** can be easily synthesized on a large scale and nitromethane is a very inexpensive reagent, the one-step procedure offers an easy access to 2-*C*-nitromethyl substituted hexoses, pentoses and disaccharides in moderate to good yields. The regioselectivity is excellent for all additions, due to the electrophilic character of the nitroalkyl radicals and good to high stereoselectivities were observed. The experimental procedure is very convenient, since the excess of the radical precursor can be easily removed by distillation and all products were isolated in analytically pure form by column chromatography (Supporting Information). Finally, the nitro group allows various further transformations and the 2-deoxy-2-*C*-nitromethyl-pyranosides **4** may serve as precursors for the synthesis of *C*-disaccharides.[16]

To gain access to the required C-2 branched-chain glycosamines **1**, the nitro group had to be reduced and various methods for this transformation have been described in literature.[17] First we selected the reaction with lithium aluminum hydride (method D), which after acetylation afforded the protected amides **7** in good yields (Scheme 2). In contrast, catalytic hydrogenation (method E) reduced the

Scheme 2. Reductions of the Nitromethane Addition Products **4b**−**g** to the Branched-Chain Glycosamines **7** and **1**



nitro group and cleaved the benzyl protecting groups in the same step, and the C-2 branched glycosamines **1** were isolated in good yields in analytically pure form (Scheme 2, Supporting Information).

In conclusion, we have developed a rapid two-step entry into branched-chain glycosamines from glycals. For the first time, nitromethane was applied in transition-metal-mediated radical reactions in carbohydrate chemistry; these afforded 2-deoxy-2-*C*-nitromethyl-pyranosides in moderate to good yields with high stereoselectivities. The method is applicable to hexoses, pentoses, and disaccharides, and the addition products are valuable precursors for the synthesis of C-2 branched disaccharides. Reduction of the nitro group was accomplished by two different methods that allowed the direct synthesis of protected or unprotected branched-chain glycosamines. Future work will focus on various further transformations of the nitro group, like Henry reactions,

(15) (a) Tolstikov, A. G.; Khakhalina, N. V.; Spirikhin, L. V. *Synthesis* **1988**, 221. (b) Chmielewski, M.; Fokt, I.; Grodner, J.; Grynkiewicz, G.; Szeja, W. *J. Carbohydr. Chem.* **1989**, *8*, 735. (c) Messaoudi, S.; Anizon, F.; Pfeiffer, B.; Golsteyn, R.; Prudhomme, M. *Tetrahedron Lett.* **2004**, *45*, 4643. (d) Madhusudan, S. K.; Agnihotri, G.; Negi, D. S.; Misra, A. K. *Carbohydr. Res.* **2005**, *340*, 1373.

(16) (a) Martin, O. R.; Lai, W. *J. Org. Chem.* **1993**, *58*, 176. (b) Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1996**, *61*, 1894. (c) Spak, S. J.; Martin, O. R. *Tetrahedron* **2000**, *56*, 217. Recent Review: Yuan, X.; Linhardt, R. J. *Curr. Top. Med. Chem.* **2005**, *5*, 1393.

(17) (a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. $LiAlH_4$: Reddy, B. G.; Vankar, Y. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 2001. Catalytic hydrogenation: von Roedern, E.; Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 687.

which should provide access to a variety of C-2 branched saccharides.

Acknowledgment. This work was generously supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft (Li 556/7-3).

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

OL703062S