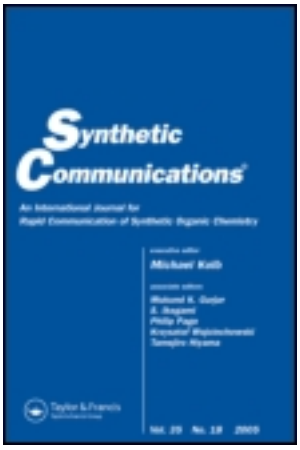

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A Facile Synthesis of Glycosyl Hydroxylamines

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A FACILE SYNTHESIS OF GLYCOSYL HYDROXYLAMINES

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Abstract: Condensation of N-benzylhydroxylamine with furanoses and pyranoses in the presence of zinc dichloride leads to novel anomeric glycosyl hydroxylamines.

The introduction of a nitrogen atom into the anomeric position of a carbohydrate unit is a crucial operation for the synthesis of a vast number of biologically interesting compounds. In this context, several approaches have been described for the preparation of optically active glycosyl amines[1] **1**; these compounds have been widely employed as versatile chiral auxiliaries and intermediates in Organic Synthesis.[2] Glycosyl azides **2** are also important intermediates and methods for their synthesis are well-documented in the literature.[3] In addition, a number of reports on the preparation of some other derivatives including glycoamidines **3a** or N-thioformyl and N-thioacetyl glycosyl amines **3b** have been described.[4] By contrast, less attention have been paid to glycosyl hydroxylamines despite the interest that represents to posses an intermediate oxidation state in the nitrogen atom.

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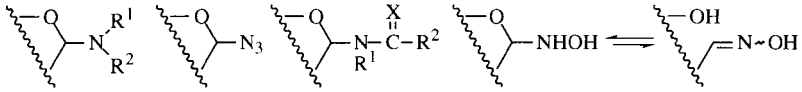
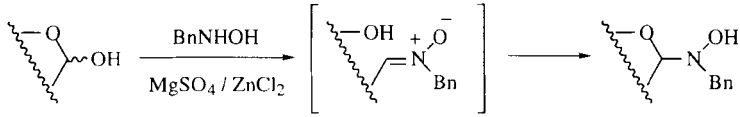


1 **2** **3a** X = NR^3 **4a** **4b**

3b X = S

To our knowledge the only report concerning the synthesis of glycosyl hydroxylamines consists of a condensation between the corresponding aldose and hydroxylamine hydrochloride;[5] the use of the latter makes that the obtained N-hydroxy glycosyl amines **4a** are not configurationally stable at the anomeric center due to the equilibrium with the corresponding aldoximes **4b**.[6] In this communication we wish to report a convenient synthesis of glycosyl hydroxylamines, based on the reaction of N-benzylhydroxylamine with an aldose in the presence of a drying agent and a Lewis acid as an activating agent (Scheme 1).

Scheme 1



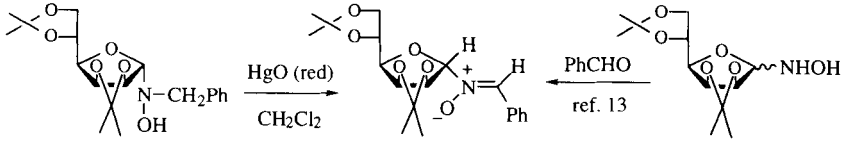
5a-e **6a-e**

Treatment of the readily available mannose diacetal[7] **5a** with benzylhydroxylamine[8] under the conditions previously described by us[9] for the preparation of aldehyde-derived nitrones only led to a 10% yield of the expected product, a substantial amount of the starting material being recovered after 3 days of reaction. On the other hand, having found zinc dichloride to be useful in the preparation of ketonitrones[10] we investigated the application of this reagent to the synthesis of the targeted glycosyl hydroxylamines. Thus, when the reaction was conducted in the presence of 1.5 equivalents of zinc dichloride it was accomplished with almost complete conversion of the starting product.[11] The use of either catalytic amounts or higher excess of zinc dichloride did not affect the observed yields. A variety of

Lewis acids ($SnCl_4$, $MgBr_2$, $AlCl_3$) and solvents (toluene, methanol, acetonitrile) were also examined and no better results were observed in any case.

Finally, the procedure was successfully applied to other substrates (*i.e.* ribo, xylo, galacto and gluco). Hexoses **5d** and **5e** needed longer times of reaction and lower yields were obtained; in addition, those compounds afforded anomeric mixtures thus indicating pentoses as more suitable substrates for the described N-glycosilation.[12] The nitrone intermediate arising from the initial step was not observed in any case.

Scheme 2



6a **7** **8**

The presumed structure is consistent with the chemical properties of the products which were easily oxidized to the corresponding C-phenyl nitrones. For instance, hydroxylamine **6a** afforded nitrone **7** after treatment with HgO (red) in dichloromethane at ambient temperature (Scheme 2). The structure of nitrone **7** was confirmed by an independent synthesis as described by Huber and Vasella.[13] Assignments of the configurations at the anomeric centers of the isolated products were based on their spectroscopic properties. The anomeric signals for **6a** are diagnostic for an α-anomer ($J_{1,2}$ = 0 Hz) whereas for **6b** ($J_{1,2}$ = 5.4 Hz) and **6c** ($J_{1,2}$ =

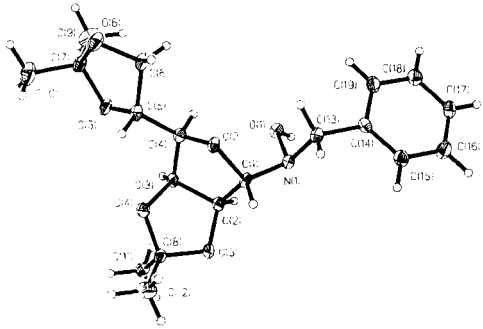


FIG. 1. ORTEP representation of **6a**

8.8 Hz) are diagnostic for β-anomers according to the known spectral properties of α- and β-glycosyl derivatives.[14] For **6d** and **6e** two anomers, which were not separated, were obtained. In the case of hydroxylamine **6a** confirmation of the anomeric configuration comes from X-ray diffraction analysis (Figure 1).[15]

In conclusion we have shown that glycosyl hydroxylamines can be easily prepared in good yields from the corresponding aldoses. Further studies with other substrates, including disaccharides are in progress.

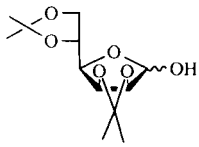
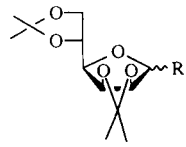
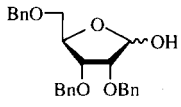
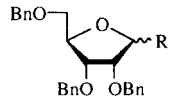
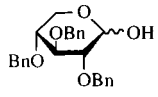
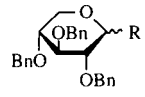
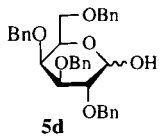
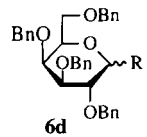
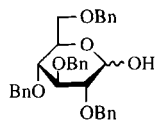
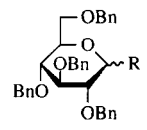
Experimental

General: Melting points were determined on a Büchi 510 apparatus and are uncorrected. Optical rotations were measured using a Perkin Elmer Model 214 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 300 Unity instrument. NMR spectra were taken in $CDCl_3$, and chemical shifts are expressed in ppm (δ) relative to TMS.

Materials: Column chromatography was carried out on SiO_2 (silica gel 60, 40-63 μm). Dichloromethane was feshly distilled from calcium hydride. Magnesium sulfate and zinc dichloride were used in commercial grade (Aldrich) without further purification. N-Benzylhydroxylamine was prepared as described.[8] 2,3:4,5-Di-O-isopropylidene-D-mannofuranose[7] **5a**, 2,3,5-tri-O-benzyl-D-ribofuranose[16] **5b**, 2,3,4-tri-O-benzyl-D-xylopyranose[17] **5c**, 2,3,4,6-tetra-O-benzyl-D-gluco-pyranose[17] **5d**, and 2,3,4,6-tetra-O-benzyl-D-galactopyranose[17] **5e** were prepared as described.

Synthesis of Glycosyl Hydroxylamines. A solution of the corresponding aldose (10 mmol) in dichloromethane (50 mL) was treated sequentially with $MgSO_4$ (3.6 g, 30 mmol), N-benzyl-hydroxylamine (1.85 g, 15 mmol) and $ZnCl_2$ (2.03 g, 15 mmol). The resulting mixture was refluxed under argon atmosphere for

Table. Condensation of benzylhydroxylamine with furanoses or pyranoses

Aldose	Hydroxylamine R = N(OH)Bn	Time (h)	Yield (%)[a]	α/β ratio[b]
 **5a**	 **6a**	48	75	100 : 0
 **5b**	 **6b**	48	73	0 : 100
 **5c**	 **6c**	60	74	0 : 100
 **5d**	 **6d**	72	68	50 : 50
 **5e**	 **6e**	72	65	60 : 40

a Isolated yield after column chromatography. b Determined by ^{1}H NMR on the isolated anomeric mixture. c The anomers were not separated.

the time indicated in Table. After the mixture was cooled to room temperature, 50 mL of a saturated aqueous solution of the disodium salt of EDTA were added. The mixture was stirred vigorously for 30 min and the organic layer was then separated and washed with brine (2 x 25 mL). The organic extract was dried ($MgSO_4$) and

concentrated at reduced pressure to give a crude residue which was purified by flash column chromatography to afford the pure glycosylhydroxylamines **6** (eluent is given in brackets for each compound).

N-Benzyl-1-(hydroxyamino)-2:3,4:5-di-O-isopropylidene-α-D-mannofuranose (6a). (hexane : diethyl ether, 80:20); mp 116 °C; $[\alpha]_D$ = +10.4 (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.36 (s, 3H), 1.44 (s, 3H), 1.45 (s, 3H), 3.84 (d, 1H, J = 13.2 Hz), 3.96 (d, 1H, J = 13.2 Hz), 4.10 (m, 2H), 4.32 (m, 2h), 4.62 (s, 1H), 4.80 (dd, 1H, J = 6.1, 3.2 Hz), 4.92 (d, 1H, J = 6.1 Hz), 5.32 (bs, 1H, ex. D_2O), 7.28-7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.36, 25.18, 25.97, 26.80, 59.23, 66.81, 73.79, 80.73, 84.12, 84.22, 98.81, 109.07, 112.29, 127.52, 128.40, 129.56, 136.71.

Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.46; H, 7.45; N, 3.83. Found: C, 62.67; H, 7.30; N, 4.10.

N-Benzyl-1-(hydroxyamino)-2,3,5-tri-O-benzyl-β-D-ribofuranose (6b). (hexane : diethyl ether, 90:10); syrup; $[\alpha]_D$ = -9.5 (c 1.00 $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.74 (d, 1H, J = 13.5 Hz), 3.85 (d, 1H, J = 13.5 Hz), 3.94 (m, 2H), 4.03 (pseudo t, 1H, J = 5.3 Hz), 4.27 (dd, 1H, J = 5.2, 4.9 Hz), 4.36 (m, 1H), 4.42 (d, 1H, J = 12.1 Hz), 4.50 (d, 1H, J = 11.8 Hz), 4.56 (d, 1H, J = 12.1 Hz), 4.69 (d, 1H, J = 11.6 Hz), 4.73 (d, 1H, J = 11.8 Hz), 4.77 (d, 1H, J = 5.4 Hz), 4.83 (d, 1H, J = 11.6 Hz), 6.20 (bs, 1H, ex. D_2O), 7.23-7.42 (m, 20H); ^{13}C NMR ($CDCl_3$) δ 60.27, 64.32, 70.28, 71.84, 72.37, 76.12, 81.23, 81.50, 98.32, 127.50, 127.64, 127.82 (2C), 127.90, 128.12, 128.34 (2C), 128.43 (2C), 128.47, 128.50, 137.61, 137.90, 138.12, 138.35.

Anal. Calcd for $C_{33}H_{35}NO_5$: C, 75.41; H, 6.71; N, 2.66. Found: C, 75.52; H, 7.00; N, 2.84.

N-Benzyl-1-(hydroxyamino)-2,3,4-tri-O-benzyl-β-D-xylopyranose (6c). (hexane : diethyl ether, 80:20); syrup; $[\alpha]_D$ = +14.3 (c 1.00, $CHCl_3$); ^1H

NMR ($CDCl_3$) δ 3.20 (m, 1H), 3.60 (m, 2H), 3.80 (pseudo t, 1H, J = 8.8 Hz), 3.95 (d, 1H, J = 12.9 Hz), 4.03 (m, 2H), 4.18 (d, 1H, J = 12.9 Hz), 4.62 (d, 1H, J = 11.7 Hz), 4.72 (d, 1H, J = 11.7 Hz), 4.77 (d, 1H, J = 11.0 Hz), 4.89 (s, 2H), 4.93 (d, 1H, J = 11.0 Hz), 6.80 (bs, 1H, ex. D_2O), 7.24-7.40 (m, 20H). ;^{13}C NMR ($CDCl_3$) δ 60.06, 65.75, 73.37, 74.61, 75.71, 77.61, 77.78, 85.24, 93.68, 127.44, 127.60, 127.75, 127.86, 127.96, 128.31, 128.36 (2C), 128.41 (2C), 128.46, 129.11, 137.34, 138.16, 138.55, 138.71.

Anal. Calcd for $C_{33}H_{35}NO_5$: C, 75.41; H, 6.71; N, 2.66. Found: C, 75.23; H, 6.89; N, 2.88.

N-(2,3:5,6-Di-O-isopropylidene-α-D-mannofuranosyl)phenylmethanamine N-oxide (7). To a well-stirred solution of hydroxylamine **6a** (0.73 g, 2 mmol) in dichloromethane (35 ml) red HgO (0.455 g, 2.1 mmol) was added portionwise. The resulting suspension was stirred at ambient temperature for 16 h at which time the reaction mixture was filtered through a short pad of Celite™. The filtrate was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel (hexane : diethyl ether, 60:40) to give pure **7** (0.67 g, 92%) as a white solid; mp 184 °C ; $[\alpha]_D$ = +62.1 (c 1.50, $CHCl_3$) [Lit.[13] mp 182-183 °C ; $[\alpha]_D$ = +66.4 (c 1.50, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.36 (s, 3H), 1.43 (s, 3H), 1.50 (s, 3H), 4.10 (m, 2H), 4.36 (dt, 1H, J = 7.1, 5.3 Hz), 4.66 (dd, 1H, J = 7.1, 3.9 Hz), 4.92 (dd, 1H, J = 6.0, 3.9 Hz), 5.31 (d, 1H, J = 6.0 Hz), 5.44 (s, 1H), 7.35-7.43 (m, 3H), 7.53 (s, 1H), 8.18-8.23 (m, 2H);^{13}C NMR ($CDCl_3$) δ 24.26, 25.14, 25.96, 26.78, 66.52, 73.22, 80.30, 84.53, 85.60, 103.39, 109.32, 113.24, 128.59, 128.96, 129.47, 131.10, 133.26.

Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85. Found: C, 62.97; H, 7.02; N, 3.68.

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