Use of Hydrazine Acetate as a Mild and Efficient Reagent for Anomeric Denitration of Carbohydrates

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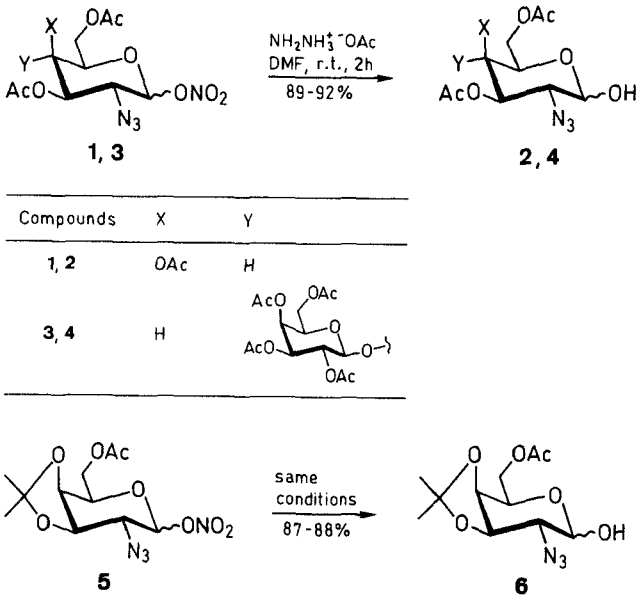
Treatment of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α,β-D-galactopyranosyl nitrate (**1**), 3,6-di-*O*-acetyl-2-azido-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α,β-D-glucopyranosyl nitrate (**3**), and 6-*O*-acetyl-2-azido-2-deoxy-3,4-*O*-isopropylidene-α,β-D-galactopyranosyl nitrate (**5**) with a slight excess of hydrazine acetate in anhydrous dimethylformamide at room temperature for 2 hours gave the corresponding hemiacetals, **2**, **4**, and **6** in the range of an 87–92% yield.

The 2-azido-2-deoxy derivatives of galactopyranose, glucopyranose, and lactose are versatile building blocks for the synthesis of biologically important galactosamine- and glucosamine-containing glycosides,[1] including cell-surface carbohydrate ligands of the vascular selectins,[2] tumor-associated carbohydrate antigens,[3] human blood-group determinants,[4] and bacterial cell-wall peptidoglycans.[5] The azidonitration of *O*-protected glycals, introduced by Lemieux and Ratcliffe in 1977,[6] continues to provide a useful route to 2-azido-2-deoxy sugars. The reaction yields 2-azido-1-nitrate adducts, which are subsequently converted into various glycosyl donors by either direct displacement of an anomeric nitrate with halide ions[6] and potassium *O*-ethyl dithiocarbonate,[7] or denitration followed by trichloroacetimidation[8] and fluorination.[9]

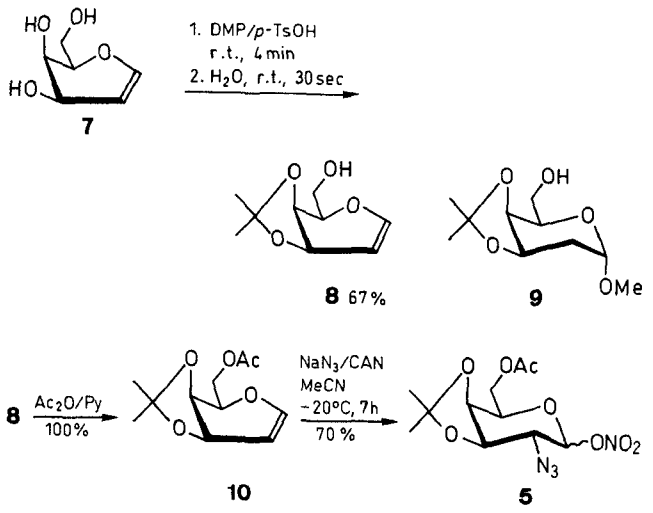
In the course of our study on a synthetic tumor vaccine[10] based on Tn (GalNAcα1 → *O*-Ser/Thr), T (Galβ1 → 3GalNAcα1 → *O*-Ser/Thr), and their sialylated antigens,[3] we have found that hydrazine acetate effectively cleaves nitrate groups from 2-azido-2-deoxy-α,β-glycopyranosyl nitrates in mild and near-neutral conditions, and hence can be used in the presence of both acid- and base-sensitive protecting groups. Hydrazine acetate has been used for regioselective 1-*O*-deacetylation of peracetylated glycopyranoses[11] and for deprotection of *N*-phthaloyl groups in the synthesis of base-sensitive peptides.[12] There have been some reports in the literature[13] that hydrazine reduces sugar nitrates into the corresponding sugar

alcohol in the presence of a platinum or palladium catalyst.

Our method involves simply stirring the azido nitrates, which were prepared by azidonitration of properly protected glycals, in anhydrous dimethylformamide with a slight excess of hydrazine acetate at room temperature and then extracting the corresponding hemiacetals with ethyl acetate (Scheme 1). The reaction is often complete within 2 hours and the yield is, after column chromatography on silica gel, in the range of 87–92%. The method proved especially useful for conversion of acid-sensitive derivative **5** into hemiacetal **6**. Usual denitration[8] of **5** with sodium nitrite in aqueous 1,4-dioxane at 80 °C for 6 hours was accompanied by extensive de-*O*-isopropylidenation. A similar decomposition of an acid-sensitive protecting group has been reported for denitration of 2-azido-6-*O*-benzyl-2-deoxy-3,4-*O*-isopropylidene-α-D-galactopyranosyl nitrate with sodium nitrite.[14]



Scheme 1



Scheme 2

Compound **5**, which is a key intermediate for the synthesis of sialyl Tn antigen as well as for the modification of Tn antigen,[15] was readily prepared from D-galactal[16] **7** through **8** and **10**[17] in a total yield of 47% as an α and β mixture (Scheme 2). A modified Liptak method[18] of isopropylidenation produced no significant amount of degradation products of acid-sensitive[19] **7**. However, the longer reaction time led to the formation of methanol-adduct[19] **9**.

Very recently, thiophenol has been employed in the presence of *N,N*-diisopropylethylamine to achieve anomeric denitration.[14] Although the thiophenol method is effective for both acid- and base-sensitive compounds, its malodor is undesirable from a practical standpoint. We, therefore, feel that our method with hydrazine acetate should be of general utility for the denitration of azido nitrates, particularly for those possessing acid-sensitive protecting groups.

Melting points were measured with a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WM-500 spectrometer in $CDCl_3$ with TMS as an internal standard. High resolution mass spectrometry (HRMS) was obtained on a JEOL JMS-HX 110 mass spectrometer, operating in the FAB mode, using a matrix of *m*-nitrobenzyl alcohol. Optical rotations were determined at 23 °C with a Perkin-Elmer 241MC polarimeter. Silica gel used for flash column chromatography[20] was purchased from EM Science (Gibbstown, NJ; particle mesh size 0.040–0.063 mm). Compounds **1** and **3** were prepared according to the method developed by the Lemieux's group.[6] Hydrazine acetate is commercially available from Aldrich (Milwaukee, WI) and is also readily prepared by mixing equivalent amounts of hydrazine and AcOH under N_2. The structures of the known compounds were verified by ^{1}H NMR spectroscopy.

General Procedure for Denitration:

Five 8 mmol portions of hydrazine acetate (total 40 mmol) were added to a stirred solution of azido nitrates (37 mmol) in dry DMF (120 mL) at 4 min intervals at r.t. in N_2. The mixture was stirred at r.t. for 2 h, poured into saturated brine (800 mL), and extracted with EtOAc (3 × 300 mL). The combined EtOAc layer was washed with H_2O (3 × 100 mL) and dried (Na_2SO_4). After concentration, the residue was purified by flash column chromatography.

3,4,6-Tri-O-acetyl-2-azido-2-deoxy-α,β-D-galactopyranose[22] **(2)**:

Denitration of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl nitrate[6] **(1α)** and its β-anomer[6] **1β** gave, after flash column chromatography (hexane/EtOAc, 4:3), **2** in 90% and 92% yields, respectively.

3,6-Di-O-acetyl-2-azido-2-deoxy-4-O-(2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-α,β-D-glucopyranose[8] **(4)**:

Denitration of 3,6-di-*O*-acetyl-2-azido-2-deoxy-4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-α-D-glucopyranosyl nitrate[21] **(3α)** and its β-anomer[21] **3β** gave, after flash column chromatography (hexane/EtOAc, 1:1), **4** in 90% and 89% yields, respectively.

6-O-Acetyl-2-azido-2-deoxy-3,4-O-isopropylidene-α,β-D-galactopyranose **(6)**:

Denitration of **5α** and **5β** (see below for the preparation) gave, after flash column chromatography (hexane/EtOAc, 3:2), **6** in 88% and 87% yields, respectively.

^{1}H NMR: for the α-isomer: δ = 1.36 (s, 3H) and 1.52 (s, 3H), (CMe_2), 2.09 (s, 3H), OAc), 2.86 (d, 1H, *J* = 3.7 Hz, OH), 3.49 (dd, 1H, *J* = 7.9, 3.3 Hz, 2-H), 4.22 (dd, 1H, *J* = 5.4, 2.4 Hz, 4-H), 4.28 (dd, 1H, *J* = 11.9, 7.8 Hz, 6a-H), 4.38 (dd, 1H, *J* = 11.9, 3.6 Hz, 6b-H), 4.49 (dd, 1H, *J* = 7.9, 5.4 Hz, 3-H), 4.45 (m, 1H, 5-H), 5.30 (dd, 1H, and *J* = 3.7, 3.3 Hz, 1-H);

for the β-isomer: δ = 1.35 (s, 3 H) and 1.54 (s, 3 H) (CMe_2), 2.09 (s, 3 H, OAc), 3.29 (d, 1 H, J = 5.8 Hz, OH), 3.41 (dd, 1 H, J = 7.8, 7.7 Hz, 2-H), 4.01 (m, 1 H, 5-H), 4.02 (dd, 1 H, J = 7.8, 5.7 Hz, 3-H), 4.11 (dd, 1 H, J = 5.7, 2.2 Hz, 4-H), 4.30 (dd, 1 H, J = 12.9, 7.6 Hz, 6a-H), 4.39 (dd, 1 H, J = 12.9, 3.4 Hz, 6b-H), 4.58 (dd, 1 H, J = 7.8, 5.8 Hz, 1-H).

HRMS: calc. for $C_{11}H_{17}N_3O_6$ + Na: 310.1015; found: 310.1015.

1,5-Anhydro-2-deoxy-3,4-*O*-isopropylidene-D-*lyxo*-hex-1-enitol[17] (8):

p-TsOH · H_2O (5.0 mg, 26.3 μmol) was added to a stirred suspension of 1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol (D-galactal)[16] (**7**) (1.0 g, 6.8 mmol) in 2,2-dimethoxypropane (DMP) (10 mL, 79.7 mmol) at r.t. The mixture became homogeneous in 2 min. After an additional 2 min, H_2O (10 mL) was added and stirring was continued for another 30 s. The mixture was then diluted with sat. aq $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 layer was washed with H_2O (3 × 50 mL), dried (Na_2SO_4), and concentrated to a pale yellow syrup. Flash column chromatography (hexane/EtOAc, 2:1) afforded **8** (854 mg, 67%) as a colorless syrup.

$[\alpha]_D$ + 37.6° (*c* = 1.0, $CHCl_3$) [Lit.[17] $[\alpha]_D$ + 28° (*c* = 1.9, $CHCl_3$)].

When the acetalation mixture was stirred at r.t. for 1 h, methyl 2-deoxy-3,4-*O*-isopropylidene-α-D-*lyxo*-hexopyranoside (**9**) was obtained in a 38% yield as a colorless syrup along with **8** (27%).

$[\alpha]_D$ + 37.7° (*c* = 1.3, $CHCl_3$).

^1H NMR: δ = 1.33 (s, 3 H) and 1.48 (s, 3 H) (CMe_2), 1.74 (ddd, 1 H, J = 14.8, 5.8, 4.0 Hz, 2ax-H), 2.18 (ddd, 1 H, J = 14.8, 5.3, 5.2 Hz, 2eq-H), 3.39 (s, 3 H, OMe), 3.79 (dd, 1 H, J = 10.4, 4.3 Hz, 6a-H), 3.81 (ddd, 1 H, J = 5.4, 4.3, 2.0 Hz, 5-H), 3.91 (dd, 1 H, J = 10.4, 5.4 Hz, 6b-H), 4.17 (dd, 1 H, J = 7.2, 2.0 Hz, 4-H), 4.48 (ddd, 1 H, J = 7.2, 5.2, 4.0 Hz, 3-H), 4.87 (dd, 1 H, J = 5.8, 5.3 Hz, 1-H).

HRMS: calc. for $C_{10}H_{18}O_5$ + Na: 241.1051; found: 241.1059.

6-*O*-Acetyl-1,5-anhydro-2-deoxy-3,4-*O*-isopropylidene-D-*lyxo*-hex-1-enitol[17] (10):

The conventional acetylation of **8** (404 mg, 2.2 mmol) with Ac_2O (2 mL) and pyridine (4 mL) gave, after flash column chromatography (hexane/EtOAc, 3:1), **10** (494 mg, 100%) as a colorless syrup.

$[\alpha]_D$ + 18.0° (*c* = 1.0, $CHCl_3$) [Lit.[17] $[\alpha]_D$ + 16° (*c* = 1.2, $CHCl_3$].

6-*O*-Acetyl-2-azido-2-deoxy-3,4-*O*-isopropylidene-α,β-D-galactopyranosyl Nitrate (5α,5β):

A solution of **10** (686 mg, 3 mmol) in anhydr. MeCN (15 mL) was added dropwise to a vigorously stirred mixture of NaN_3 (300 mg, 4.5 mmol) and cerium(IV) ammonium nitrate (CAN) (5 g, 9 mmol) at − 20 °C under N_2, and stirring was continued at − 20 °C for 7 h. The mixture was then diluted with cold Et_2O (150 mL), washed with cold H_2O (3 × 100 mL) unit it became neutral, and dried (Na_2SO_4). After concentration, the residue was subjected to flash column chromatography (hexane/EtOAc, 2:1, containing 0.3% Et_3N). The first fraction gave **5α** (490 mg, 49%) as a colorless solid. $[\alpha]_D$ + 144.5° (*c* = 1.01, $CHCl_3$).

^1H NMR: δ = 1.37 (s, 3 H) and 1.54 (s, 3 H) (CMe_2), 2.08 (s, 3 H, OAc), 3.87 (dd, 1 H, J = 7.5, 4.0 Hz, 2-H), 4.27 (dd, 1 H, J = 5.8, 2.3 Hz, 4-H), 4.31 (dd, 1 H, J = 13.3, 4.0 Hz, 6a-H), 4.33 (dd, 1 H, J = 13.3, 4.1 Hz, 6b-H), 4.37 (ddd, 1 H, J = 4.1, 4.0, 2.3 Hz, 5-H), 4.39 (dd, 1 H, J = 7.5, 5.8 Hz, 3-H), 6.23 (d, 1 H, J = 4.0 Hz, 1-H).

HRMS: calc. for $C_{11}H_{16}N_4O_8$ + Na: 355.0865; found: 355.0868.

The second fraction afforded **5β** (209 mg, 21%) as a colorless solid, which crystallized from Et_2O. mp 91–92 °C. $[\alpha]_D$ + 66.9° (*c* = 1.3, $CHCl_3$).

^1H NMR: δ = 1.37 (s, 3 H) and 1.56 (s, 3 H) (CMe_2), 2.08 (s, 3 H, OAc), 3.55 (dd, 1 H, J = 8.8, 7.3 Hz, 2-H), 4.15 (ddd, 1 H, J = 7.5, 4.3, 2.2 Hz, 5-H), 4.16 (dd, 1 H, J = 7.3, 5.8 Hz, 3-H), 4.19 (dd, 1 H, J = 5.8, 2.2 Hz, 4-H), 4.31 (dd, 1 H, J = 11.9, 7.5 Hz, 6a-H), 4.39 (dd, 1 H, J = 11.9, 4.3 Hz, 6b-H), 5.47 (d, 1 H, J = 8.8 Hz, 1-H).

HRMS: calc. for $C_{11}H_{16}N_4O_8$ + Na: 355.0865; found: 355.0854.

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