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A Straightforward Route to *N*-Acetyl-D-glucosamine-derived *C*-β-D-Glycosyl Synthons

Mária Petrušová§, James N. BeMiller¶*, and Ladislav Petruš§*

§Institute of Chemistry, Slovak Academy of Sciences, 84238 Bratislava, Slovakia

¶The Whistler Center for Carbohydrate Research, Purdue University, West Lafayette, IN 47907-1160, USA

Abstract: A practical synthesis of formaldehyde, nitroethene, and nitroethane *C*-glycosylated with a 2-acetamido-2-deoxy-β-D-glucopyranosyl group is described. Synthesis follows the nitromethane route and involves an unusual, intramolecularly catalyzed β-elimination of acetic acid and pH-controlled ozonolysis of nitronate salts. Copyright © 1996 Elsevier Science Ltd

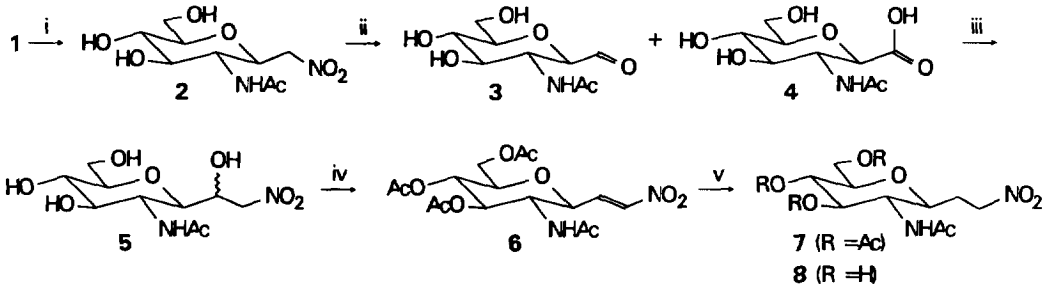
2-Acetamido-2-deoxy-β-D-glucose (*N*-acetyl-D-glucosamine, **1**) is the most often occurring carbohydrate unit of glycoproteins[1] and occurs as single glycosyl units in nucleoplasmic and cytoplasmic proteins.[2] In these natural materials with crucial roles in biological recognition and regulation phenomena, **1** occurs solely as β-D-pyranosyl units glycosidically linked to a serine, threonine, or another glycosyl unit or attached through a glycosylamine linkage to asparagine. *C*-Glycosyl derivatives of **1** can serve as stable analogs for studies of biological recognition and regulation and as biologically active agents.[3] Efficient methods for the synthesis of C-glycosyl compounds derived from **1** are therefore necessary for the generation of carbohydrate mimics.

Several routes to *C*-glycosyl compounds involving catalyzed additions to activated carbohydrate derivatives have been elaborated.[4] However, these methods are incompatible with Lewis acidic and anionic conditions, when applied to derivatives with an amino or amido functionality. As a result, azides as amine equivalents have been utilized.[5]

However, the availability of *C*-(β-D-glycopyranosyl)nitromethanes,[6,7] together with the ozonolysis of their nitronate salts,[8,9] offered a straightforward route to a series of *C*-glycosyl compounds with the acetamido functionality. This communication reports a concise synthesis of such a series of versatile derivatives of **1**.

Treatment of **2** (Scheme 1) in its nitronate form, generated in aqueous solution containing 1.2 equivalents[10] of 0.3 M NaOH, with 0.4 equiv/min of ozone at room temperature until the reaction mixture reached pH 7 afforded a 4:1 mixture of aldehyde **3** and acid **4**. As **3** is an unstabilized aldehyde and easily oxidized to acid **4**, the subsequent workup was done under an atmosphere of nitrogen, and crude syrupy **3** was used without purification.[11]

Scheme 1



Conditions: i, 2 steps,[6g] ii, NaOH, H_2O, O_3, r.t.; iii, 1. $MeNO_2$, NaOMe, MeOH; 2. H^+ resin, HCO_3^- resin, H_2O; iv, Ac_2O, H_2SO_4; v, 1. H_2, Pd/C, EtOAc; 2. NaOMe, MeOH.

Compound **3** (0.2 M solution in MeOH) was reacted with 10 equiv of $MeNO_2$ and 12 equiv of 1.5 M NaOMe in the dark at room temperature for 5 h. Treatment of the reaction mixture with ion-exchange resins in the H^+ and HCO_3^- forms[12] afforded a pure 2:1 mixture of epimeric nitrohydrols **5** in 58% overall yield from compound **2**. Acetylation of a 30% methanolic solution of syrupy **5** was accomplished with Ac_2O and a catalytic amount of H_2SO_4 with temperature control, as sensitive product **6** was formed spontaneously under the acidic conditions. Careful extractive workup of the acetylation mixture[13] afforded nitroalkene **6** as the only product in 89% yield (isomer ratio $E:Z \geq 95:5$).[14] The unusual behavior of acetylated nitrohydrols **5** is apparently connected with the presence of the acetamido functionality in the molecule, which catalyzes β-elimination of an HOAc molecule intramolecularly.[15] Analogous per-*O*-acetylated epimeric mixtures of nitrohydrols derived from D-glucose, D-galactose, and D-mannose were stable under the acetylation and isolation conditions and were obtained in 85–90% yields.[16]

Compound **6** [2-(2'-acetamido-3',4',6'-tri-*O*-acetyl-2'-deoxy-β-D-glucopyranosyl)nitroethene] may be employed in various syntheses of *C*-(*N*-acetyl-β-D-glucosaminyl) compounds by Michael additions. Catalytic hydrogenation[17] of **6** in EtOAc over Pd/C within a 10 min period led to the selective reduction of its alkene double bond to give **7** in 86% yield. Its deacetylation under Zemplen conditions afforded nitroalkane **8**,[18] convenient for the synthesis of the *C*-glycosyl analog of GlcNAc-Asn by the nitromethane methodology.[19]

Acknowledgment

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10. Optimized excess for the conditions used. An excess of NaOH was necessary to assure complete disappearance of starting **2** (*cf.* note 12), as a part of **3** formed was subsequently oxidized to acid **4**, which consumed the extra base.

11. Quantitative estimation of the ^{13}C NMR signals of *C*HO (δ, 172.3 ppm) and *C*H(OH)$_2$ (δ, 89.6 ppm) of two forms of compound **3** revealed that it occurs in aqueous solution prevalently as aldehydrol (**3** : **3**·H_2O ≈ 1:4); the ^{13}C NMR signal of *C*OONa of the Na salt of **4** was observed at δ 178.3 ppm.

12. Treatment was done batchwise with mixed resins. In addition to a strongly acidic cation-exchange resin (H^+ form) used for decationization, a strongly basic anion-exchange resin (HCO_3^- form) removed HNO_3 (a side product of the ozonolysis of sodium nitronates) and acid **4**. If **2** was not completely reacted in the ozonolysis step, it contaminated intermediate **5** and the other products, from which it was difficult to separate by both recrystallization and column chromatography.

13. Soon after pouring the reaction mixture onto an ice-water mixture, crystals of **6** appeared. For their efficient isolation, $NaHCO_3$ equivalent to the amount of H_2SO_4 used as catalyst had to be added to the ice-water mixture; otherwise only underacetylated species were isolated.

14. Analytical and spectroscopic data for **6** (*E* isomer): Mp 179–181° (1:1 EtOAc–hexane); $[\alpha]_D^{25}$ – 36.5° (*c* 0.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.20 (dd, 1 H, $J_{1,2}$ 13.3 Hz, H-1), 7.14 (dd, 1 H, $J_{2,3}$ 3.3 Hz, H-2), 5.73 (bd, 1 H, $J_{4,NH}$ 8.8 Hz, NH), 5.19 (t, 1 H, $J_{5,6}$ 9.4 Hz, H-5), 5.12 (t, 1 H, $J_{6,7}$ 9.6 Hz, H-6), 4.23 (dd, 1 H, $J_{8,8'}$ 12.4 Hz, H-8), 4.22 (ddd, 1 H, $J_{3,4}$ 10.3 Hz, H-3), 4.18 (dd, 1 H, H-8'), 3.99 (td, 1 H, $J_{4,5}$ 10.2 Hz, H-4), 3.74 (ddd, 1 H, $J_{7,8}$ 2.4, $J_{7,8'}$ 4.8 Hz, H-7), 2.12, 2.08, 2.07 1.99 (4 s, 12 H, 4 CH_3 of Ac); ^{13}C NMR ($CDCl_3$): δ 171.4, 170.6, 170.5, 169.2 (4 CO of Ac), 140.8 (C-1), 136.1 (C-2), 75.9 (C-3), 75.0 (C-7), 73.3 (C-5), 67.9 (C-6), 61.9 (C-8), 53.7 (C-4), 23.2, 20.7, 20.6, 20.5 (4 s, 12 H, 4 Me of Ac). Anal. Calcd for $C_{16}H_{22}N_2O_{10}$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.39; H, 5.58; N, 6.79.

15. A series of model compounds with the acetamido functionality was prepared to support the interpretation (to be published separately). It was indicated that a strain influencing the acetyl group to be eliminated had to be present. In this case, a parallel interaction with an unbonded electron pair of the ring oxygen atom seemed to provide the necessary strain.

16. $CHCl_3$ extracts of per-*O*-acetylated nitrohydrols derived from D-glucose, D-mannose, and D-galactose were washed with water only, instead of with aqueous $NaHCO_3$, because of a partial formation of nitroalkenes and their subsequent decomposition. For preparation of nitroalkenes from these nitrohydrols, treatment with an external base under anhydrous conditions was necessary, usually 5 h reflux in a benzene solution over $NaHCO_3$, *e.g.*, according to: Sowden J. C.; Fischer, H. O. L. *J. Am. Chem. Soc.*, **1947**, *69*, 1048–1050.

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18. Analytical and spectroscopic data for compound **8**: Mp 187–188°; $[\alpha]_D^{25}$ – 40.2° (*c* 0.6, H_2O); ^{13}C NMR (D_2O): δ (ppm) 177.4 (CO of Ac), 82.3 (C-7), 78.3 (C-3), 77.9 (C-5), 75.0 (C-1), 72.9 (C-6), 63.7 (C-8), 57.9 (C-4), 31.7 (C-2), 25.0 (Me of Ac). Anal. Calcd for $C_{10}H_{18}N_2O_7$: C, 43.16; H, 6.52; N, 10.07. Found: C, 42.86; H, 6.77; N, 9.84.

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