Carbohydrate Research, 53 (1977) 129–133

Note

Synthesis of phenyl 4-*O*-acetyl-2-*O*-benzyl-3-deoxy-3-nitro-β-D-glucopyranoside derivatives and amination at C-4*

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(Received April 2nd, 1976; accepted for publication May 24th 1976)

It is well known that α-nitroalkenes undergo nucleophilic addition to give β-substituted nitroalkanes[1]. In carbohydrate chemistry, this has been demonstrated with alditols[2], pyranosides[3–8], and furanosides[9,10]. β-Acetoxynitroalkanes[3,11–13] generally react with nucleophiles to give the same products through a base-catalyzed elimination–addition process, although certain complications[4–7] may occur. Previous studies of these synthetically useful reactions on 3-nitro aldopyranosides dealt mostly with functionalization at C-2, but the preparation[12,14,15] of several 4-acetates and 3,4-unsaturated derivatives, as well as amination[12–14] at C-4, has been reported.

As an extension of such studies, we now describe the synthesis of the title compounds in which O-2 is blocked with a benzyl group, and amination at C-4 is achieved with benzylamine.

Direct benzylation of phenyl 4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside[4] (**1**) by use of a published[16] procedure proved unsuccessful as most of **1** was recovered unchanged. Likewise, treatment of the 2-acetate (**2**) of **1** with benzyl alcohol and triethylamine in tetrahydrofuran under a variety of conditions gave only low yields of the desired benzyl ether (**4**). However, satisfactory yields of **4** were obtained when phenyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (**3**) was refluxed in toluene solution with benzyl alcohol and triethylamine (Table I). Presence of the amine proved advantageous in that it afforded higher yields and shorter reaction-times**. The β-D-*gluco* configuration of **4** was deduced from p.m.r. data (Table II) and agrees with expectations for a thermodynamically controlled process of addition of a nucleophile to **3**.

Debenzylidenation of **4** occurred readily in 70% acetic acid[17] (1 h at 90–95°) and gave phenyl 2-*O*-benzyl-3-deoxy-3-nitro-β-D-glucopyranoside (**5**) in 96% yield. Under more drastic conditions of hydrolysis, the preponderant product was the

*Studies on Nitro Sugars, Part VIII. For Part VII, see Ref. 10.

**Effective base-catalysis for similar additions has been noted previously[5]. When the methyl glycoside analog of 3 was treated with benzyl alcohol in refluxing toluene, the yield of benzyl ether was 47.5% after 2 days[5].

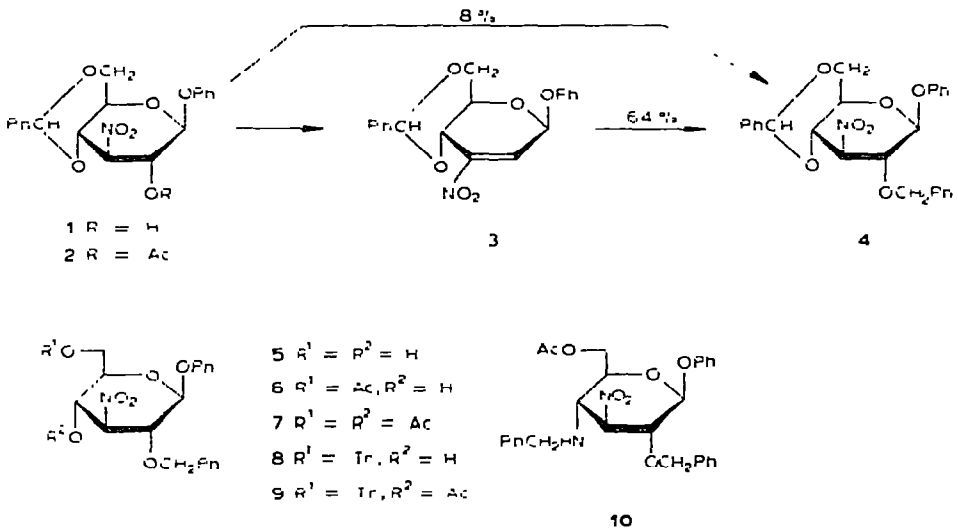

TABLE I

CONDITIONS AND YIELDS IN THE REACTION OF **3** WITH BENZYL ALCOHOL UNDER REFLUX

Molar ratio of **3** . Et_3N . $PhCH_2OH$	*Solvent*	*Time*	*Yield of* **4** (%)
1 : 3 : 2	Tetrahydrofuran	2 h	23
1 : 3 : 2	Benzene	1 h	42
1 : 3 : 3	Toluene	20 min	53
1 : 3 : 5	Toluene	20 min	60
1 : 5 : 5	Toluene	20 min	64

6-*O*-acetyl derivative (**6**) of **5**. It was found that **5** underwent selective monoacetylation at position 6 under the conditions used, whether or not benzaldehyde was present. The location of the acetyl group was revealed by a downfield shift of the H-6,6' signals in the p.m.r. spectrum of **6**.

Acetylation of **5** with 1:1 acetic anhydride–pyridine at low temperature provided the 4,6-diacetate (**7**). Increasing the proportion of pyridine resulted in a mixture of **7** (ν_{NO_2} 1555 cm^{-1}) and a nitroalkenic product (ν_{NO_2} 1525 cm^{-1}). Tritylation of **5** followed by acetylation furnished the 6-trityl ether (**8**) and its 4-acetate (**9**) in yields of 96% and 72%, respectively.

For the purpose of introducing an amino group at C-4, the acetates **7** and **9** were treated with benzylamine in tetrahydrofuran. Compound **9** gave a product whose elemental analysis corresponded to that of the expected benzylamino derivative, but which was not homogeneous; it contained at least two components according to t.l.c. On the other hand, the diacetate **7** readily afforded in 77% yield a pure product

TABLE II

100-MHz P.M.R. DATA FOR PHENYL 2-*O*-BENZYL-3-DEOXY-3-NITRO-β-D-GLUCOPYRANOSIDE DERIVATIVES IN CHLOROFORM-*d* (Me_4Si AS THE INTERNAL STANDARD)

Compound	*Chemical shifts (p.p.m.)*							*Coupling constants (Hz)*						
	H-1	*H-2*	*H-3*	*H-4*	*H-5*	*H-6*	*H-6'*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$	$J_{5,6'}$	$J_{6,6'}$
4	5.14	4.24	4.81	4.13	3.59	4.37	3.80	7.5	10.0	10.0	10.0	4.5	10.0	10.0
5[a]	5.10	4.10	4.80	4.17	3.63	4.20	3.88	7.5	10.0	10.0	10.0	3.0	5.5	12.5
6	5.13	4.13	4.78	4.15	'	4.48	4.23	8.0	10.0	10.0	10.0	3.0	5.5	12.0
7	5.04	4.29	5.45	4.74	3.76	4.36	4.11	8.0	10.0	10.0	10.0	3.0	5.0	12.5
9	5.03	4.32	5.37	4.66	3.59	3.31	3.14	8.0	10.0	10.0	10.0	3.0	5.0	12.0
10	4.94	4.20	4.68	3.36	3.60	4.46	4.22	8.0	10.0	10.0	10.0	3.0	5.0	12.0

[a] In Me_2SO-d_6.

of elimination–addition, namely, phenyl 6-*O*-acetyl-2-*O*-benzyl-4-benzylamino-3,4-dideoxy-3-nitro-β-D-glucopyranoside (**10**). The configuration of **10** was confirmed by its p.m.r. spectrum (Table II).

EXPERIMENTAL

General methods. — Evaporations were performed under diminished pressure in a rotary evaporator. All melting points were determined in capillaries and are uncorrected. Optical rotations were measured with a Carl Zeiss photoelectric polarimeter. P.m.r. spectra were recorded at 100 MHz with a JEOL spectrometer (Type JNM-4H-100) and tetramethylsilane as an internal standard. T.l.c. was performed on silica gel (DC-Fertig platten Kieselgel 60, Merck Co. Darmstadt) with the solvent system (A) 9:1 benzene–methanol, or (B) benzene only.

Phenyl 2-O-benzyl-4,6-O-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (**4**). — A mixture of phenyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside[4] (**3**, 17.0 g), toluene (250 ml), triethylamine (25.0 g), and benzyl alcohol (25.8 g) was stirred for 20 min under reflux. After evaporation, the residue was triturated with methanol at 5° to give white crystals that were recrystallized from benzene; yield 14.2 g (64%), m.p. 208–209°, $[\alpha]_D^{20}$ −27.8° (*c* 1, chloroform); R_F 0.51 (solvent B).

Anal. Calc. for $C_{26}H_{25}NO_7$: C, 67.37; H, 5.44; N, 3.02. Found: C, 67.39; H, 5.45; N, 3.02.

Phenyl 2-O-benzyl-3-deoxy-3-nitro-β-D-glucopyranoside (**5**). — Compound **4** (7.0 g) was heated in 70% acetic acid (70 ml) for 1 h at 90–95°. Removal of the solvent gave a white solid that was recrystallized from ethanol; yield 5.0 g (96%), m.p. 197.5–199° (dec.), $[\alpha]_D^{20}$ −7.9° (*c* 1, ethanol); R_F 0.23 (solvent A); ν_{max}^{KBr} 3400, 3230 (ν_{OH}), 1560 cm^{-1} (ν_{asNO_2}).

Anal. Calc. for $C_{19}H_{21}NO_7$: C, 60.79; H, 5.64; N, 3.73. Found: C, 60.38; H, 5.62; N, 3.63.

Phenyl 6-O-acetyl-2-O-benzyl-3-deoxy-3-nitro-β-D-glucopyranoside (**6**). — A solution of **4** (0.462 g) in 90% acetic acid (10 ml) was refluxed for 6 h, and then toluene was evaporated from it until the odor of acetic acid disappeared. Removal of **5** (13%) by fractional recrystallization (twice) from ethanol gave almost pure **6**, which was treated with active charcoal and then reprecipitated from chloroform; yield 0.25 g (60%), m.p. 127.5–128.5°, $[\alpha]_D^{20}$ −25.3° (*c* 1, chloroform); ν_{max}^{KBr} 3400 (ν_{OH}), 1720 ($\nu_{C=O}$), 1550 cm^{-1} (ν_{asNO_2}).

Anal. Calc. for $C_{21}H_{23}NO_8$: C, 60.42; H, 5.55; N, 3.36. Found: C, 60.54; H, 5.57; N, 3.23.

In this reaction, reflux for 3 h provided **5** (57%) and **6** (30%).

Phenyl 4,6-di-O-acetyl-2-O-benzyl-3-deoxy-3-nitro-β-D-glucopyranoside (**7**). — Compound **5** (1.95 g) was treated with acetic anhydride (1.38 g) in pyridine (1.4 g) for 1 h at 3–5°. Addition of water to the mixture gave crystals that were recrystallized from ethanol; yield 1.82 g (77%), m.p. 139–140°, $[\alpha]_D^{20}$ −12.7° (*c* 1, chloroform); ν_{max}^{KBr} 1755, 1735 ($\nu_{C=O}$), 1555 cm^{-1} (ν_{asNO_2}).

Anal. Calc. for $C_{23}H_{25}NO_9$: C, 60.12; H, 5.48; N, 3.05. Found. C, 60.28; H, 5.49; N, 3.04.

Phenyl 2-O-benzyl-3-deoxy-3-nitro-6-O-trityl-β-D-glucopyranoside (**8**). — To a solution of **5** (0.95 g) in pyridine (2 g) was added chlorotriphenylmethane (775 mg, 1.1 eq.) at room temperature. After 3 days, cooled water was added to the mixture to afford a solid that was reprecipitated from methanol: yield 1.45 g (93%), m.p. 93–95°, $[\alpha]_D^{20}$ +8.2° (*c* 1, ethanol); R_F 0.67 (solvent A), ν_{max}^{KBr} 3400 (ν_{OH}), 1560 cm^{-1} (ν_{asNO_2}).

Anal. Calc. for $C_{38}H_{35}NO_7$: C, 73.87; H, 5.71; N, 2.27. Found: C, 74.08; H, 5.98; N, 2.45.

Phenyl 4-O-acetyl-2-O-benzyl-3-deoxy-3-nitro-6-O-trityl-β-D-glucopyranoside (**9**). — Compound **8** (0.618 g) was treated with acetic anhydride (0.13 g, 1.3 eq.) in pyridine (0.6 g) for 45 min at 3–5°. Addition of water afforded a solid that was reprecipitated from ethanol: yield 0.475 g (72%), m.p. 160–161°, $[\alpha]_D^{20}$ +26° (*c* 1, chloroform); R_F 0.59 (solvent B); ν_{max}^{KBr} 1750 ($\nu_{C=O}$) and 1555 cm^{-1} (ν_{asNO_2}).

Anal. Calc. for $C_{40}H_{37}NO_8$: C, 72.82; H, 5.65; N, 2.12. Found: C, 72.87; H, 5.77; N, 2.52.

Phenyl 6-O-acetyl-2-O-benzyl-4-benzylamino-3,4-dideoxy-3-nitro-β-D-gluco-pyranoside (**10**). — Compound **7** (0.3 g) was dissolved in tetrahydrofuran (10 ml) and treated with benzylamine (0.18 g) for 1 h at 5°. After evaporation, water (5 ml) and ethanol (1 ml) were added successively to afford precipitate that was reprecipitated from ethanol: yield 0.255 g (77%), m.p. 151–152° (dec), $[\alpha]_D^{20}$ −11° (*c* 1, chloroform); R_F 0.81 (solvent A); ν_{max}^{KBr} 3325 (ν_{NH}), 1740 ($\nu_{C=O}$), 1555 cm^{-1} (ν_{asNO_2}).

Anal. Calc. for $C_{28}H_{30}N_2O_7$: C, 66.39; H, 5.97; N, 5.53. Found. C, 66.14; H, 5.84; N, 5.52.

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