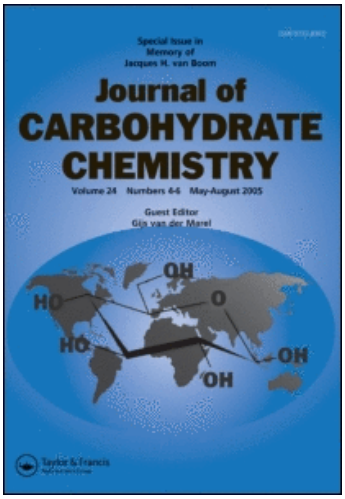

Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

Reductive Dephthalimidation: A Mild and Efficient Method for The *N*-Phthaumido Deprotection During Ougosaccharide Synthesis

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To cite this Article Dasgupta, Falguni and Garegg, Per J.(1988) 'Reductive Dephthalimidation: A Mild and Efficient Method for The *N*-Phthaumido Deprotection During Ougosaccharide Synthesis', Journal of Carbohydrate Chemistry, 7: 3, 701 — 707

To link to this Article: DOI: 10.1080/07328308808057560
URL: http://dx.doi.org/10.1080/07328308808057560

J. CARBOHYDRATE CHEMISTRY, 7(3), 701-707 (1988)

COMMUNICATION

REDUCTIVE DEPHTHALIMIDATION : A MILD AND EFFICIENT METHOD FOR THE *N*-PHTHALIMIDO DEPROTECTION DURING OLIGOSACCHARIDE SYNTHESIS

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Received January 22, 1988 - Final Form February 18, 1988

Synthesis of biologically active oligosaccharides, haptens and their protein conjugates is a major area of interest because of their role in antigen-antibody interaction and receptor effects[1]. A number of these molecules contain α- or β- linked 2-acetamido-2-deoxy-D-glucosamine (GlcNAc) moieties. Most commonly, during the oligosaccharide synthesis, introduction of the β-glycosidically linked GlcNAc residue is achieved by either the oxazoline[2] or the phthalimido method[3]. Of these, the latter is preferred because 2-*N*-phthalimido protected glycosamine units having a halogen or a thioalkyl group at C-1 have consistently proved to be more efficient donors than are the oxazolines. However, time and again, subsequent conversion of the *N*-phthalimido to amine by hydrazinolysis has proved inadequate. This has often resulted in a poor overall yield after an otherwise efficient synthesis. Recently it was shown that the phthalimido function could be removed under mild conditions from a number of amino acids[4]. We now report that this technique can be efficiently used for the deprotection of the phthalimido function in suitably protected carbohydrate compounds (**2**,**3** and **5**).

RESULT AND DISCUSSION

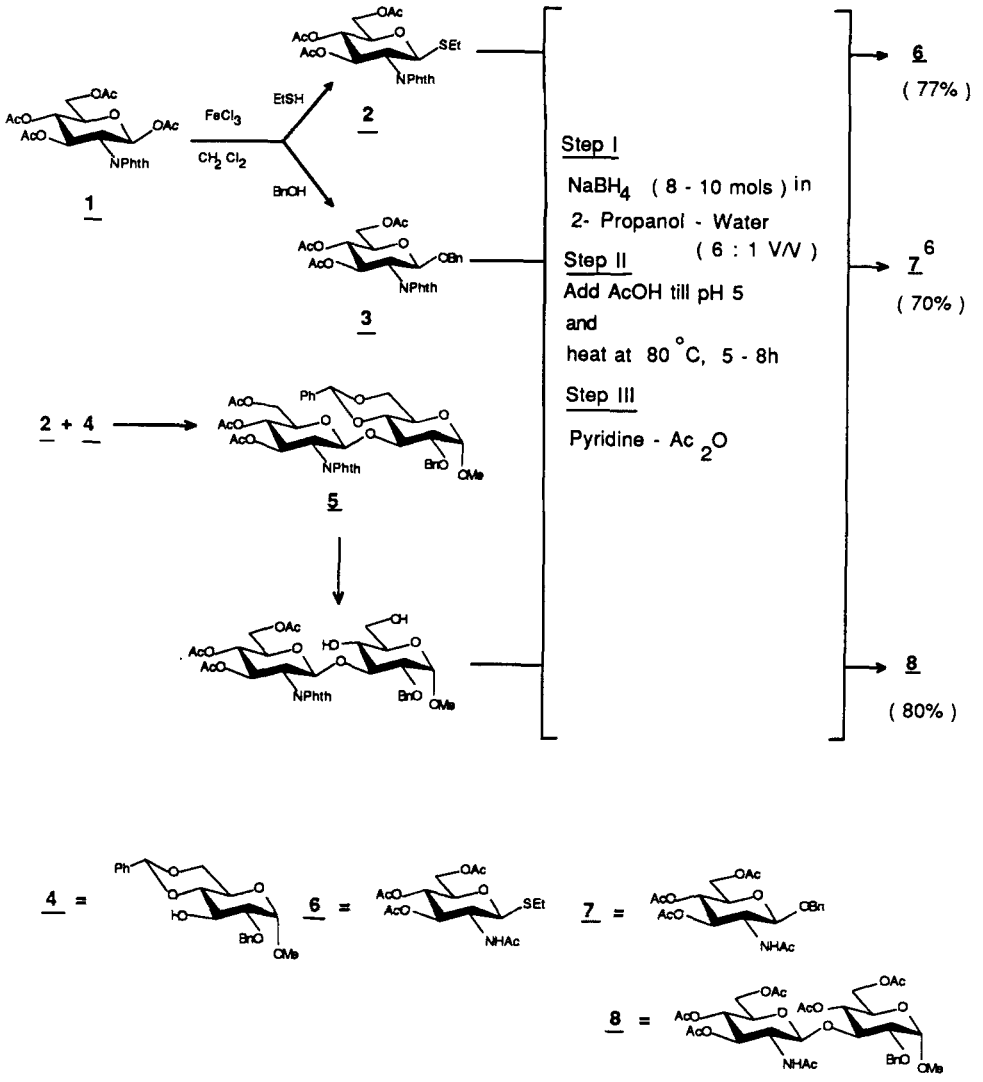
The method follows the same steps as those reported earlier[4]. However, the best results were obtained when eight to ten molar excess of sodium borohydride was used for the reductive opening of the phthalimido group. Thus, using the general method (scheme), in a one-pot reaction, deprotection of the phthalimido function could be consistently achieved in 75-85% yield (each reaction was repeated three times).

Compound **1** was made by a procedure different from the one known[3]. The new method (described in the experimental), gave **1** in 40-50% overall yield, consistently. Thus prepared, compound 1 showed sharp melting point at 74-75°C after crystallization from ethanol. Recrystallization from ethyl acetate or dichloromethane-hexane afforded crystals which softened at 74-75°C and melted at 79-80°C. The thioglycoside **2**[5] and the benzyl glycoside **3**[6] could be prepared from **1** by ferric chloride mediated glycosidation[7]. In the instance of the disaccharide (**5**), which was prepared from the appropriate precursors using dimethyl(methylthio)sulfonium triflate (DMTST) promoter[8], the 4,6-*O*-benzylidene group was removed before the dephthalimidation step (scheme).

Efficient removal of the phthaloyl group from a thioglycoside (**2**), opens up a new approach for oligosaccharide synthesis. Thus, the disaccharide donors as their thioglycosides and containing *N*-phthalimido at the non-reducing end can be first converted into their *N*-acetylated derivatives and subsequently used as donors. Such work and the application of this method for the conversion of *N*-phthalimido into *N*-acetyl function in higher oligosaccharides is in progress.

EXPERIMENTAL

General Procedures. Melting points are corrected. Specific rotations were determined as chloroform solutions with a Perkin-Elmer polarimeter model 141, using the sodium D line. ^{1}H- and ^{13}C- NMR spectra were recorded with a JEOL GSX270 spectrometer. All reactions were carried out under a nitrogen atmosphere and the chromatographic purifications were executed on dry silica gel 60 (Merck, 230-400 mesh) columns. Satisfactory separations were achieved by first eluting with toluene-



SCHEME

acetone (2:1 v/v, one-half column volume) and then completing the elution with toluene-acetone (4:1 v/v). Organic solutions, obtained after extraction and work-up procedures, were dried over $MgSO_4$. All evaporations were conducted *in vacuo*.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranose (1). D(+)-Glucosamine hydrochloride (10.8 g, 50.1 mmol) was dispersed in *N*,*N*-dimethylformamide (70 ml) containing triethylamine (17.2 ml,

123.4 mmol) and phthalic anhydride (11.25 g, 75.9 mmol). The slurry was stirred at room temperature (20-30 min) and then heated (70 °C, 15 min). Anhydrous sodium acetate (~10 g) and acetic anhydride (80-100 ml) were quickly transferred into the flask and the mixture was stirred (4-5 h) at 100 °C. The dark solution obtained was allowed to attain room temperature and poured into crushed ice-water (1 L). A dark, gummy mass separated, which was dissolved in dichloromethane (250 ml). The organic layer was separated, washed successively with water, sodium hydrogencarbonate (aqueous, 10% w/v) and water, dried, filtered and evaporated. The crude product, which contained the β- anomer (major) and some (minor) α-anomer, was purified by column chromatography (silica gel, 500 g) using toluene-ethyl acetate (4:1 v/v). Pure β-product (1, 11 g, 44%) was recrystallized from ethanol; m.p. 74-75 °C; $[\alpha]_D^{25}$ + 70.5° (c 1.3), lit.[3,9] m.p. 90-94 °C, $[\alpha]_D^{22}$ + 65.5° (c 1, chloroform). ^{1}H-NMR ($CDCl_3$-TMS) : δ 7.9-7.7 (m, 4H, aromatic), 6.5 (d, 1H, J 8.8 Hz, H-1), 5.9, 5.2 (2t, 2 H, H-3,4), 3.7 (dd, 1H, H-2), and 2.1-1.9 (4s, 12H, 4 AcO). ^{13}C NMR : δ 170.6, 170, 169.5, 168.6, 167.4 (C=O), 134.5, 123.8 (aromatic), 89.8 (C-1), 72.7, 70.5, 68.3 (C-3,4,5), 61.5 (C-6), 53.5 (C-2) and 20.7, 20.6, 20.4 ($COCH_3$).

Anal. Calcd for $C_{22}H_{23}NO_{11}$: C, 55.35; H, 4.86; N, 2.93. Found : C, 55.1; H, 4.8; N, 2.8.

Methyl 3-*O*-(3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-phthalimido-β-D-glucopyranosyl)-2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (5). Compounds 4[10] (95 mg, 0.26 mmol) and **2** (154 mg, 0.32 mmol) were dissolved in dichloromethane (5 ml) containing powdered molecular sieve 4Å (0.5 g) and stirred at room temperature (1 h). The reaction mixture was cooled to 5 °C and DMTST (120 mg, 0.46 mmol) was added. After stirring for 2 h, some more DMTST (60 mg, 0.23 mmol) was added and the reaction terminated, after another 2 h, by the addition of triethylamine (0.5 ml, 3.58 mmol). The reaction mixture was filtered through Celite, the organic layer washed with sodium hydrogencarbonate and water, dried, filtered and concentrated to a syrup. Column (silica gel, 50 g) chromatography of the crude product, using toluene-acetone 4:1 (v/v), afforded **5** (502 mg, 79%). This was recrystallized from ethanol to give the pure compound, m.p. 186-187 °C, $[\alpha]_D^{23}$ + 11.8° (c 1.97).^{1}H NMR ($CDCl_3$-TMS): δ 7.76-7.07 (m, 14H, aromatic),

5.76 (dd, 1H, H-3′), 5.60 (d, 1H, H-1′), 5.51 (s, 1H, PhC*H*), 5.16 (dd, 1H, H-4′), 4.2 (d, 1H, H-1), 3.34 (dd, 1H, H-2), 3.17 (s, 3H, MeO) and 2.0, 1.96, 1.83 (3s, 9H, 3AcO).

Anal. Calcd for $C_{41}H_{43}NO_{15}$: C, 62.35; H, 5.49; N, 1.77. Found: C, 62.1; H, 5.4; N, 1.7.

Conversion of 2 to ethyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-β-D-glucopyranoside (6). *N*-Phthalimido protected carbohydrate compound, **2** (80mg, 0.17 mmol) was dissolved in 2-propanol : water (6:1 v/v, 2ml) and sodium borohydride (66mg, 1.74 mmol) was added in four lots over a period of 4-6h at room temperature. After 8h (at the end of which, the reaction mixture may contain white powder), glacial acetic acid was added dropwise to adjust the pH to 4.5-5.0. The flask was fitted with a reflux condenser and the content was stirred while being heated at 80 °C (5-8h). The reaction mixture was dried by repeated co-concentration with methanol and toluene and acetylated with pyridine-acetic anhydride. Chloroform and ice-water were added. The organic layer was separated, washed with aqueous sodium hydrogencarbonate and water, dried, filtered and evaporated . The residue was purified by silica gel (30g) column chromatography to give **6** (52 mg, 77%). Recrystallization from ethanol afforded the pure material, m.p. 196-197 °C, $[\alpha]_D^{23}$ - 55° (c 1.5). ^{1}H NMR ($CDCl_3$-TMS): δ 5.87 (d, 1H, N*H*), 5.23-5.05 (2 t, 2H, H-3,4), 4.63 (d, 1H, $J_{1,2}$ =10.3 Hz, H-1), 4.27-4.08 (m, 3H, H-6,6′,2), 3.7 (m, 1H, H-5), 2.7 (m, 1H, SCH_2CH_3), 2.2-1.9 (4s, 12H, 3AcO, NAc) and 1.25 (t, 3H, SCH_2CH_3).

Anal. Calcd for $C_{16}H_{25}NO_8S$: C, 49.09; H, 6.44; N, 3.58; S, 8.19. Found : C, 49.2; H, 6.5; N, 3.5; S, 8.2.

Conversion of 3 to benzyl 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside (7). *N*-Phthalimido precursor **3** (800 mg, 1.5 mmol), aqueous propanol (10 ml) and sodium borohydride (400 mg, 10.58 mmol) were used to carry out the reductive dephthalimidation in the same manner as given above. Acetylation followed by column (silica gel, 50 g) chromatography afforded pure **7** (328 mg, 70%) which was recrystallized from ethanol, m.p. 164-165 °C, $[\alpha]_D^{23}$ - 47° (c 2.1), lit.[7] m.p. 164-165 °C, $[\alpha]_D^{25}$ - 54.4° (c 0.5, chloroform). Some starting material (40 mg, 8.5%) was recovered.

Conversion of 5 to methyl 3-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-4,6-di-*O*-acetyl-2-*O*-benzyl-α-D-glucopyranoside (8). Acetic acid (80%, 10 ml) was added into the flask containing compound **5** (120 mg, 0.15 mmol), the mixture was heated (80 ^{o}C) and stirred till tlc (toluene-acetone 2:1 v/v) indicated complete hydrolysis of the benzylidene group to give one product (R_f = 0.32). The reaction mixture was evaporated to dryness and the acid removed by repeated coevaporation with toluene. The residue (117 mg) was dissolved in aqueous propanol (3 ml) and dephthalimidation-acetylation sequence carried out, in the manner described earlier, using sodium borohydride (48 mg, 1.26 mmol). The product (R_f = 0.23, toluene-acetone 2:1 v/v) was purified by column chromatography (silica gel, 80 g) to afford **8** as a white solid (84 mg, 79%, overall). Recrystallization from ethanol gave pure **8**, m.p. 170-171 ^{o}C, $[\alpha]_D^{23}$ +13.2^{o} (*c* 1.9). ^{1}H NMR ($CDCl_3$-TMS): δ 7.2 (m, 5H, aromatic), 5.2 (d, 1H, N*H*), 4.87 (d, 1H, $J_{1',2'}$ = 10.6 Hz, H-1'), 4.55 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 3.56 (dd, 1H, H-2), 3.31 (s, 3H, MeO) and 2.07, 2.06, 2.03, 2.0, 1.98 (5s, 18H, 5AcO, NAc); ^{13}C NMR ($CDCl_3$-TMS): δ 170.8, 170.7, 170.56, 169.69, 169.48, 169.36 (C=O); 137.78, 127.4 (C-aromatic); 101.16 (C-1'); 97.45 (C-1); 23.14 (CH_3 of NAc).

Anal. Calcd for $C_{32}H_{43}NO_{16}$: C, 55.09; H, 6.21; N, 2.01. Found: C, 54.8; H, 6.2; N, 1.9.

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