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Synthesis of benzyoylated β-D-glucosamine derivatives

Claudia Di Salvo\textsuperscript{a}, Karen A. Fox\textsuperscript{a}, Jens Langhanki\textsuperscript{b,†}, Paul V. Murphy\textsuperscript{a,*}

\textsuperscript{a}School of Chemistry, National University of Ireland Galway, University Road, Galway, Ireland. \textsuperscript{b}Institute of Organic Chemistry, University of Mainz, Duesbergweg 10–14, D-55128 Mainz, Germany

The preparation of intermediates for synthesis of \textit{D}-glucosamine (2-amino-2-deoxy-\textit{D}-glucopyranose) derivatives is of interest. The synthesis of 1,3,4,6-tetra-\textit{O}-acetyl-2-amino-2-deoxy-\textit{β}-\textit{D}-glucopyranose hydrochloride, described originally by Bergmann and Zervas\textsuperscript{1} in 1931, is often used to prepare glucosamine derivatives\textsuperscript{2,3}. This includes preparation of compounds for screening for medical applications where \textit{D}-glucosamine is a core scaffold\textsuperscript{4}. The analogous preparation of 2-amino-2-deoxy-1,3,4,6-tetra-\textit{O}-benzoyl-\textit{β}-\textit{D}-glucopyranose hydrochloride 4 and its acetamide derivative 5, is also of interest. For example, the use of benzoates instead of acetate protecting groups in carbohydrate chemistry can lead to an enhancement in the rate of anomerisation reactions\textsuperscript{5} and lead to increased yields from such

\textsuperscript{†} Checker under the supervision of Prof. Dr. Till Opatz; e-mail: opatz@uni-mainz.de

\textsuperscript{*} Corresponding author; e-mail: paul.v.murphy@nuigalway.ie
reactions. It can therefore be envisaged that 4 and 5 will be useful intermediates and we describe their preparation on multi-gram scale herein.

The treatment of 1 with 4-methoxybenzaldehyde as described previously by Bergmann and Zervas gave 2. Next the benzylation of 2 using benzoyl chloride in pyridine gave 3. The imine in 3 was hydrolysed under acidic conditions to give the salt 4, which is prepared without the need for chromatography in any of the steps starting from 1. Finally, the amine is acetylated with acetyl chloride to give the perbenzoyated-GlcNAc. All products crystallized readily and were fully characterized and the sequence was carried out in multigram scale. Only in the final step was chromatography used in order to obtain a sample for analytical purposes.

**Experimental**

**General Methods.** NMR spectra were recorded using Agilent Spectrometers at the indicated frequencies. Chemical shifts in $^1$H-NMR spectra are reported relative to internal Me$_4$Si (δ 0.00) in CDCl$_3$ or DMSO-d$_6$ (δ 2.49) and CDCl$_3$ (δ 77.00) or DMSO-d$_6$ (δ 39.97 ppm) for $^{13}$C. NMR spectra were processed and analysed using MestReNova software. $^1$H-NMR signals were assigned with the aid of gDQCOSY. $^{13}$C NMR signals were assigned with the aid of gHSQCAD, DEPT and APT experiments. Coupling constants are reported in Hertz. Mass spectral data were obtained using a Waters LCT Premier XE Spectrometer, measuring in both positive and/or negative mode as, using MeCN as solvent. Optical rotations were determined at the sodium D line at 20 °C with a Schmidt & Haensch Unipol L 1000 polarimeter, using chloroform and DMSO as solvents. The solvents ethanol, methanol, acetone and Et$_2$O were used as obtained from Sigma-Aldrich. Solutions in organic solvents were dried with anhydrous Na$_2$SO$_4$ and concentrated at reduced pressure.

**2-Amino-2-deoxy-N-(4-methoxybenzylidene)-D-glucopyranose (2).** D-Glucosamine·HCl 1 (15.3 g, 71.0 mmol) was added to 1 M NaOH (80 mL) and the mixture was stirred vigorously
while anisaldehyde (8.7 mL, 71.5 mmol) was added dropwise. When a precipitate formed after ~1 h, the reaction was stored at -18 ºC overnight.\(^7\) The mixture, which had frozen, was then thawed and the precipitate was filtered off and washed with water (2 x 100 mL) and then washed with MeOH-Et\(_2\)O (1:1, 2 x 100 mL). The white solid obtained was then dried under diminished pressure to give 2 (16.9 g, 69 %); mp 162.3-162.6 ºC dec. (lit\(^1\) 164-168 ºC, dec.); \([\alpha]_D^0 = +22.8\) (c 1, DMSO) (lit\(^1\) +28.0 (c 0.84, DMSO)). The \(^1\)H and \(^{13}\)C-NMR data were in good agreement with reported literature data:\(^8\) \(^1\)H-NMR (DMSO-d\(_6\), 500 MHz) \(\delta\) 8.10 (1H, s, CH=N), 7.67 (2H, d, J = 8.7, Ar-H), 6.97 (2H, d, J = 8.6, Ar-H), 6.49 (1H, d, J=6.8, OH-1), 4.88 (1H, d, J = 5.3, OH-4), 4.77 (1H, d, J = 5.7, OH-3), 4.67 (1H, t, J = 7.3, H-1), 4.51 (1H, t, J = 5.8, OH-6), 3.78 (3H, s, OMe), 3.71 (1H, ddd, J = 11.8, 5.5, 2.1, H-6a), 3.47 (1H, ddd, J = 11.8, 5.5, 2.1, H-6a), 3.12 (1H, td, J = 9.1, 5.3, H-4), 2.80 - 2.74 (1H, m, H-2); \(^{13}\)C-NMR (126 MHz, DMSO-d\(_6\)) \(\delta\) 161.63 (ArCH=N), 161.47, 130.04, 129.55, 114.33 (each Ar-C), 96.07 (C-1), 78.62 (C-2), 77.30 (C-5), 75.03 (C-3), 70.80 (C-4), 61.72 (C-6), 55.71 (OMe); HRMS (ESI): [M+H]\(^+\) calcd. for C\(_{14}\)H\(_{20}\)NO\(_6\), 298.1291; found 298.1291; FT-IR 3483, 3310, 2933, 1604, 1515, 1267, 1104, 1061, 1023, 834 cm\(^{-1}\). Anal. calcd for C\(_{14}\)H\(_{19}\)NO\(_6\): C, 56.6; H, 6.4; N, 4.7. Found: C, 56.4; H, 6.24; N, 4.56.

2-Amino-2-deoxy-N-(\(p\)-methoxybenzylidene)-1,3,4,6-tetra-O-benzoyl-\(\beta\)-D-glucopyranose (3). Benzoil chloride (9.7 mL, 84.0 mmol) was added slowly at 0ºC to a solution of the benzylidene derivative 2 (5.00 g, 16.8 mmol) in pyridine (50 mL). The mixture was then allowed to attain room temperature and stirred for 12 h. EtOAc was added and the mixture was washed with 1.0 M HCl (x 2), satd aq NaHCO\(_3\), and brine. After drying and concentration the title compound was crystallized from EtOH (10.26 g, 86 %), mp 190.7-191.5 ºC (lit\(^8\) 190-191 ºC); \([\alpha]_D^{20}\) +56.6 (c 1, CHCl\(_3\)) (lit\(^8\) \([\alpha]_D^{24}\) +59.3, (c 1, CHCl\(_3\)) \; \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 8.28 (s, 1H, ArCH=N), 8.02 (m, Ar-H), 7.94-7.90 (m, 2H, Ar-H), 7.85-7.81 (m, 2H, Ar-H),
7.56-7.47 (m, 5H, Ar-H), 7.46-7.42 (m, 1H, Ar-H), 7.41 – 7.33 (m, 7H, Ar-H), 7.30 (m, 2H, Ar-H), 6.79 (m, 2H, Ar-H), 6.40 (d, J = 8.0, 1H, H-1), 6.02 (t, J = 9.5, 1H, H-3), 5.78 (t, J = 9.7, 1H, H-4), 4.66 (dd, J = 12.2, 2.9, 1H, H-6b), 4.52 (dd, J = 12.2, 5.0, 1H, H-6a), 4.45 (ddd, J = 10.0, 5.0, 3.0, 1H, H-5), 3.92 (dd, J = 9.5, 8.0, 1H, H-2), 3.76 (s, 3H, OMe); ¹³C NMR (126 MHz, CDCl₃): δ 166.1, 165.45, 165.17, 164.38 (each C=O), 164.34 (ArCH=N), 162.07 (Ar-COCH₃), 133.48, 133.34, 133.00, 132.95, 130.16, 129.93, 129.83, 129.80 (each Ar-CH), 129.70 (Ar-C), 129.52 (Ar-CH), 129.27, 129.10, 128.91 (each Ar-C), 128.37 (Ar-CH), 128.33 (Ar-C), 128.26, 128.23, 113.84, (each Ar-CH), 93.99 (C-1), 73.82 (C-3), 73.51 (C-2), 73.07 (C-5), 69.38 (C-4), 63.14 (C-6), 55.29 (OMe); HRMS (ESI): [M+H]+ calcd. for C₄₂H₃₅NO₁₀, 714.2333; found 714.2330; Anal. Calcd for C₄₂H₃₅NO₁₀: C, 70.68; H, 4.94; N, 1.96; Found: C, 71.08; H, 5.09; N, 2.03.

1,3,4,6-Tetra-O-benzoyl-2-deoxy-2-amino-β-D-glucopyranose hydrochloride (4). 5 M HCl (3.5 m) was added dropwise at reflux temperature to a solution of 3 (9.18 g, 12.8 mmol) in acetone (50 mL). When a white precipitate was formed after ~10 min the mixture was allowed to cool to room temperature. The precipitate formed was filtered and washed with successively with acetone (20 mL) and Et₂O (2 x 50 mL), and the solid was crystallized (3 crops) and subsequently recrystallized from MeOH. After drying under vacuum the title compound (6.86 g after three crops, 85 %) showed mp 179.7-180.9 °C dec. (lit⁸ 200-201 °C, dec); [α]D = +22.6 (c 1, DMSO); ¹H NMR (500 MHz, DMSO-d₆) δ 8.72 (s, 3H, NH₃Cl), 8.18-8.13 (m, 2H, Ar-H), 7.88 (m, 4H, Ar-H), 7.82-7.77 (m, 2H, Ar-H), 7.75-7.70 (m, 1H, Ar-H), 7.60 (m, 5H, Ar-H), 7.46 (m, 6H, Ar-H), 6.41 (d, J = 8.5, 1H, H-1), 5.96 (t, J = 9.7, 1H, H-3), 5.59 (t, J = 9.6, 1H, H-4), 4.57 (dt, J = 10.1, 3.5, 1H, H-5), 4.47 (m, 2H, H-6), 4.12 (t, J = 9.5, 1H, H-2); ¹³C NMR (126 MHz, DMSO-d₆): δ 165.72, 165.59, 165.17, 164.26 (C=O), 134.77, 134.26, 134.00, 133.94, 130.63, 129.97, 129.72, 129.69 (each Ar-CH), 129.62, 129.60 (each Ar-C), 129.22,
129.17, 129.14, 128.94 (each Ar-CH), 128.89, 128.64 (each Ar-C), 91.97 (C-1), 72.25 (C-5), 71.90 (C-3), 69.55 (C-4), 62.67 (C-6), 52.75 (C-2); HRMS (ESI): [M+H]+ calcd. for C_{34}H_{30}ClNO_{9}, 596.1914; found 596.1909. Anal. Calcd for C_{34}H_{30}ClNO_{9}: C, 64.61; H, 4.78; N, 2.22. Found: C, 64.84; H, 4.87; N, 2.33.

2-Acetylamino-1,3,4,6-tetra-O-benzoyl-2-deoxy-β-D-glucopyranose (5). Triethylamine (3.15 mL, 22.6 mmol) was added at 0 °C to a solution of 4 (6.13 g, 9.7 mmol) in CH$_2$Cl$_2$ (80 mL) and the mixture was stirred until a clear solution was obtained. Acetyl chloride (0.80 mL, 11.2 mmol) was added with cooling (tap water), the mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was washed with water and brine, concentrated, and chromatography (6:4 petroleum ether–EtOAc,) gave a colorless foam (4.9 g, 80%); [α]$_D$ = -25.6 (c 2, CHCl$_3$), (lit$^8$ [α]$_D$)$^{24}$ -19.3 (c 2, CHCl$_3$); $^1$H-NMR (500 MHz, CDCl$_3$): δ 8.10 (m, J = 7.7, 2H, Ar-H), 8.03 (m, J = 7.7, 2H, Ar-H), 7.96 (m, J = 7.7, 2H, Ar-H), 7.88 (m, J = 7.7, 2H, Ar-H), 7.58 (m, J = 7.5, 1H, Ar-H), 7.56 – 7.49 (m, 2H, Ar-H), 7.49 – 7.44 (m, 2H, Ar-H), 7.45 – 7.35 (m, 5H, Ar-H), 7.35 – 7.30 (m, 2H, Ar-H), 6.09 (d, J = 8.7, 1H, H-1), 5.84 (d, J = 9.6, 1H, NH), 5.80 (t, J = 9.7, 1H, H-4), 5.66 (dd, J = 10.8, 9.4, 1H, H-3), 4.80 (ddd, J = 10.8, 9.4, 8.7, 1H, H-2), 4.63 (dd, J = 12.4, 2.8, 1H, H-6a), 4.48 (dd, J = 12.4, 4.6, 1H, H-6b), 4.29 (ddd, J = 9.8, 4.6, 2.9, 1H, H-5), 1.80 (s, 3H,NHAc); $^{13}$C NMR (126 MHz, CDCl$_3$): δ 170.14, 167.02, 166.11, 165.15, 164.97 (each C=O), 133.84, 133.71, 133.49, 133.09, 130.30, 129.95, 129.82, 129.73 (each Ar-CH), 129.49, 128.68 (each Ar-C), 128.59, 128.57, 128.53 (each Ar-CH), 128.45 (Ar-C), 128.42, 128.33 (each Ar-CH), 93.59 (C-1), 73.16 (C-2), 73.10 (C-3), 68.71 (C-4), 62.65 (C-5), 53.29 (C-6), 23.19 (OAc); HRMS (ESI): [M+H]$^+$ calcd. for C_{36}H_{31}NO_{10}Na$^+$ 660.1840; found 660.1840; Anal. Calcd for C_{36}H_{31}NO_{10}: C, 67.81; H, 4.90; N, 2.20. Found: C, 68.03; H, 5.07; N, 2.29.
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