A facile and stereoselective synthesis of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride

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Acetylation of D-glucosamine catalysed by sulfuric acid and *N*-phthaloylation of the glucosyl acetate yielded 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-α-D-glucopyranose. This gave the corresponding pure β-glucosyl chloride upon treatment with PCl_5-BF_3. An anomeric chlorination with thionyl chloride combined with the Lewis acids ($ZnCl_2$, $SnCl_4$ and $BiCl_3$) resulted in an α/β anomer mixture.

Keywords: 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride, anomeric chlorination, glucosyl chloride, stereoselective synthesis

2-Deoxy-2-amino glucosides and other amino sugar glycosides are common structural units found in various oligosaccharides.[1,2] *N*-Phthalimido-protected glycosyl donors have been extensively studied, and their use has become a method of choice for the synthesis of 1,2-*trans* glycosides and oligosaccharides of the 2-amino-2-deoxysugar(**1**).[3–5] Phthalimido-protecting groups play a key role in the stereoselective synthesis of 1,2-*trans* glycoside through neighbouring-group participation.[6] However, phthaloylation of **1** with phthalic anhydride followed by acetylation with acetic anhydride resulted in low yields of mixture of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-α-D-glucopyranose (**3**) and its β anomer.[7] Kochetkov[8] even developed a method of preparation **3** from the anomeric mixtures via fractional crystallisation. Subsequent treatment of **3** with HCl or $AlCl_3$ gave the corresponding β-glucosyl halides (**4b**).[9,10] However, this method is time-consuming and results in a very low yield.

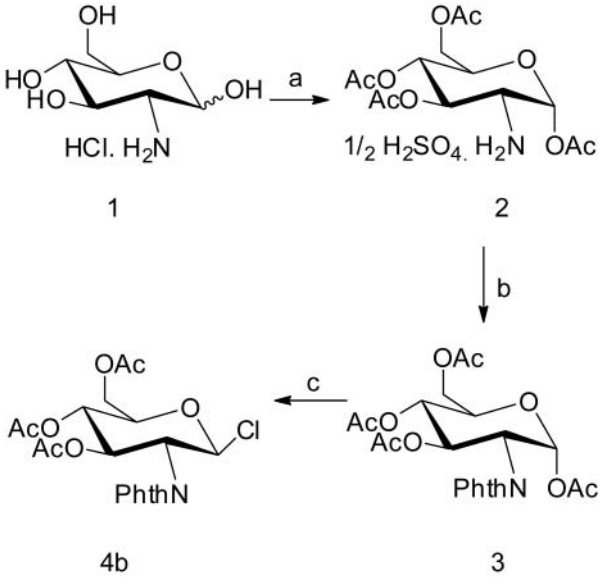
Compound **3** and 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride (**4b**) are important glycosyl donors.[11–14] In this study, we used a facile, two-step method to synthesise pure α-anomeric **3** directly from **1**, which gave the corresponding pure β-glucosyl chloride **4b** upon treatment with PCl_5-BF_3 in high yield. The effect of the chlorination reagent on stereoselective chlorination of the anomeric center of **3** was also investigated.

Results and discussion

Our strategy is based on acetylation of all of the hydroxyl groups of **1** before phthaloylation of the 2-amino group. Pure compound **3** can be easily synthesised from 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose (Scheme 1). Previous methods for the synthesis of 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-D-glucopyranose included *N*-protection of **1** with propargyloxycarbonyl[15] or diethyl ethoxymethylene malonate[16,17] and hydrolysis of *N*-acetyl-D-glucosamine oxazoline.[18] However, these methods are multistep processes involving lengthy protection and deprotection steps. Therefore, in this study, we used a simple and efficient method for synthesising 1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose hemisulfate (**2**) directly from **1** by acetylation with sulfuric acid as a catalyst.

Sulfuric acid is commonly used in the synthesis of sugar acetates[19] and in the catalysis of the anomerisation of glucose pentacetates into α-anomer.[20] Selective acetylation of the hydroxyl group of glucosamine **1** was achieved by sulfuric acid catalysis, which blocks the amino group by salt formation. In our experiment, 1.0 equiv of concentrated sulfuric acid was used to catalyse acetylation and facilitate the conversion of the glucosamine hydrochloride salt into its hemisulfate (**2**). α-Glucosyl acetate **2** was preferentially formed because of its higher thermodynamic stability. Ethanol was subsequently added to the reaction solvent to decompose the excess acetic anhydride and precipitate the product. Compound **2** was identified as an α-anomer because of the small $J_{1,2}$ anomeric coupling constant (3.3 Hz) in its ^{1}H NMR spectra.[16,21] The amino proton signals were observed at δ (H) 8.72 ppm. The hemisulfate **2** is very sensitive to moisture and it must be stored under anhydrous conditions.

The synthesis of the *N*-phthalimido derivative from the α-tetraacetate **2** was accomplished using a modified method.[7] Acetylation of the anomeric hydroxyl group makes phthaloylation of the 2-amino group difficult by decreasing the nucleophilicity of the amino group. In this study, **3** was efficiently prepared using 4-dimethylaminopyridine (DMAP) as a powerful catalyst for *N*-acylation by neutralisation of the hemisulfate **2** with triethylamine and then phthaloylation with phthalic anhydride. Data from ^{1}H NMR showed that the α-configuration was maintained at the anomeric center during *N*-phthaloylation.



Scheme 1 Reagent and condition: (a) Ac_2O, concentrated sulfuric acid, rt; (b) (i) phthalic anhydride, triethylamine, DMAP, CH_2Cl_2 rt; (ii) Ac_2O, rt; (c) PCl_5/BF_3.

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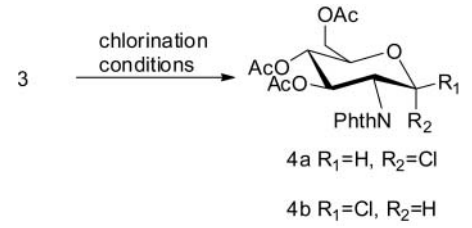
Table 1 Yelds and α/β rations of chlorination product of *N*-phthalimido derivatives[a]



Entry	Chlorination agent[b]	Time/h	Yield/%	α/β ratio[c]
1	$SOCl_2/BiCl_3$	12	86	41:59
2	$SOCl_2/SnCl_4$	4	90	55:45
3	$SOCl_2/ZnCl_2$	2	81	44:56
4	PCl_5/BF_3	0.5	95	β only

[a] All reactions performed in CH_2Cl_2 at room temperature. [b] $SOCl_2$ (2.0 equiv.), $BiCl_3$ (0.1 equiv.).[26] $SOCl_2$ (2.0 equiv.), $SnCl_4$ (2.0 equiv.).[25] $SOCl_2$ (2.0 equiv.), $ZnCl_2$ (4.0 equiv.).[24] PCl_5 (1.2 equiv.), BF_3 (0.1 equiv.).[23] [c] ^{1}H NMR ratio.

Shoda[22] has reviewed the glycosyl chloride synthesis. Phosphorus pentachloride (PCl_5) or thionyl chloride combined with Lewis acids, such as BF_3,[23] $ZnCl_2$,[24] $SnCl_4$,[25] and $BiCl_3$,[26] are excellent chlorinating reagents which have been widely used for the preparation of anomerically pure α or β-glucosyl chlorides. However, there are few studies on the chlorination of D-glucosamine using these reagents. Hence, we investigated the chlorination reaction of *N*-phthalimido glucosamine acetate based on the previously studied methods. The anomeric composition of the chloride products was then determined by ^{1}H NMR spectroscopy.

Table 1 shows that treatment of **3** with PCl_5 or thionyl chloride combined with Lewis acids provided good yields of glucosyl chlorides. Among the reagents that were screened, only PCl_5 gave the pure β-anomeric product **4b**. Chlorination with thionyl chloride/Lewis acid resulted in an α/β anomer mixture with ratios ranging from 4:6 to 6:4.

The proposed mechanism for the β-selective chlorination with PCl_5 involves the formation of a bicyclic *N*-acyloxonium ion intermediate (Scheme 2).[23] Although it had been demonstrated earlier the chlorination was limited to 1,2-*trans* acetate, the α-glucosyl acetate **3** can also readily react with PCl_5. Thionyl chloride-mediated chlorination of *N*-phthalimido glucosamine acetates exhibited poorer α-stereoselectivity compared with the glycosyl acetates. This result demonstrates that the stereoselective chlorination of the anomeric group is greatly affected by the phthaloyl group on the nitrogen atom regardless of whether the reaction proceeds via the S_N1 or S_N2 mechanism.

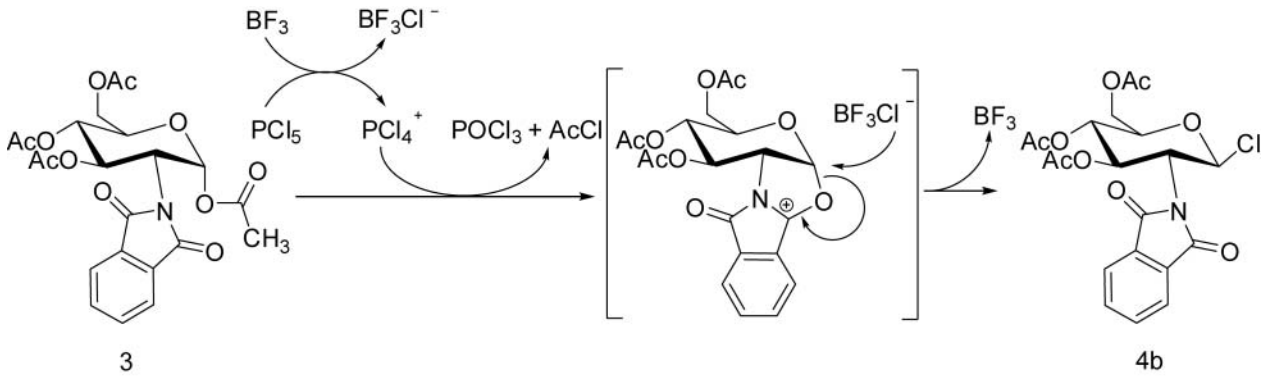
In conclusion, we have developed a new procedure for the efficient synthesis of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride (**4b**) from the 2-amino-2-deoxy-sugar D-glucosamine in 61% yield over three steps. Key intermediates, 1,3,4,6-tetra-*O*-acetyl-2-amino-2-deoxy-α-Dglucopyranose hemisulfate and its *N*-phthalimido derivative, were also stereoselectively synthesised. PCl_5–BF_3 was shown to be an effective chlorination reagent for the β-stereoselective chlorination of the anomeric centre of *N*-phthalimido glucosamine acetate.

Experimental

Melting points were determined using a Tianjin Skylight XT4A micro melting point apparatus and are reported uncorrected. NMR spectra were measured using a Bruker Avance (300 MHz) spectrometer with tetramethylsilane as the internal standard. Microanalysis was carried out using a Perkin Elmer 2400 analyser. Optical rotation measurements were carried out on a WZZ-2S automatic polarimeter at 589.4 nm (Na D-line). A silica gel GF254 plate (Qingdao Haiyang Chemical Plant, Qingdao, China) was used for TLC under UV light (λ 254 nm). All other chemicals for synthesis were purchased from TCI (Tokyo, Japan) unless otherwise specified.

1,3,4,6-Tetra-O-acetyl-2-amino-2-deoxy-α-Dglucopyranose hemisulfate (**2**): D-Glucosamine hydrochloride (5.0 g, 23.2 mmol) was dissolved into acetic anhydride (18.0 mL, 190 mmol). The mixture was cooled in an ice-salt bath and stirred for 10 min. Then, concentrated sulfuric acid (1.3 mL, 23.2 mmol) was carefully added into the mixture. The cooling bath was removed, and the mixture was again stirred at room temperature for 12 h, during which time the reaction solution became clear. Ethanol (30 mL) was added to the solution, causing the formation of a white precipitate. The solution containing the precipitate was vigorously stirred for another 30 min. Then, the precipitate was filtered, washed with ethyl acetate, and dried to yield 7.98 g (86.8%) of **2**. M.p. 186–188 °C; $[a]_D^{24}$ + 116.2° (c 0.2, H_2O); IR (KBr) (ν_{max}, cm^{-1}): 3442, 3291, 1702, 1644, 1562, 1412, 1331, 1166, 1021, 795, 642; ^{1}H NMR (300 MHz, DMSO) δ 8.72 (bs, 3H, -NH_3SO_4), 6.22 (d, $J_{1,2}$ = 3.3 Hz, 1H, H-1), 5.25 (t, 1H, $J_{3,4}$ = $J_{2,3}$ 9.6 Hz, H-3), 5.01 (t, $J_{4,5}$ = $J_{3,4}$ 9.6 Hz, 1H, H-4), 4.23–4.08 (m, 2H, H-6a, H-5), 3.99 (d, $J_{6a,6b}$ 10.7 Hz, 1H, H-6b), 3.83 (dd, $J_{2,3}$ 10.7 Hz, $J_{1,2}$ 3.0 Hz, 1H, H-2), 2.19, 2.05, 2.00, 1.98 (4s, 12H, $OCOCH_3$); ^{13}C NMR (75 MHz, DMSO) δ 169.93, 169.17, 168.64 (C=O), 88.23 (C-1), 68.97 (C-2), 68.81 (C-5), 67.41 (C-3), 61.04 (C-4), 50.22 (C-6), 20.81, 20.71, 20.44, 20.26 (CH_3). Anal. Calcd for $C_{28}H_{44}N_2O_{22}S$: C, 42.42; H, 5.59; N, 3.53. Found: C, 42.70; H, 5.66; N, 3.59%.

1,3,4,6-Tetra-O-acetyl-2-deoxy-2-phthalimido-a-D-glucopyranose (**3**): Phthalic anhydride (1.00 g, 6.75 mmol), triethylamine (1 mL), and DMAP (88.8 mg, 0.73 mmol) were added to a stirred solution of **2** (1.8 g, 4.54 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 1 h at room temperature. Then acetic anhydride (1 mL) was added and the mixture was again stirred for 24 h. The progress of the reaction was monitored by TLC (silica, ethyl acetate: petroleum ether 2:3), and ethanol (4 mL) was added after completion. The solvents evaporated after 20 min of stirring. The residue was extracted with ethyl acetate (10 mL), washed with water, dried ($MgSO_4$). After complete evaporation of the ethyl acetate, the residue was recrystallised from ethanol to



Scheme 2

yield 1.65 g (76.1%) of **3**. M.p. 128–129 °C (lit.[8] 128–131 °C); $[a]_D^{24}$ + 115.5° (c 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80–7.87 (m, 2H), 7.77–7.71 (m, 2H), 6.56 (dd, $J_{2,3}$ 11.5, $J_{3,4}$ 9.2 Hz, 1H, H-3), 6.28 (d, $J_{1,2}$ 3.3 Hz, 1H, H-1), 5.16 (t, $J_{3,4} = J_{4,5}$ 9.6 Hz, 1H, H-4), 4.71 (dd, $J_{2,3}$ 11.6, $J_{1,2}$ 3.3 Hz, 1H, H-2), 4.41–4.25 (m, 2H, H-6a, H-5), 4.17–4.09 (m, 1H, H-6b), 2.12, 2.08, 2.05, 1.87 (4s, 12H, $OCOCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.82, 169.92, 169.68, 169.47 (O–C=O), 167.54 (2C=O), 134.60 (2C-arom), 123.87 (2C-arom), 90.65 (C-1), 70.30 (C-5), 69.50 (C-3), 67.12 (C-4), 61.64 (C-6), 52.93 (C-2), 21.11, 20.87, 20.78 (CH_3).

3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride (**4b**): Phosphorus pentachloride (0.81 g, 3.89 mmol) and $BF_3{\cdot}Et_2O$ (40 μL) were added to a solution of **3** (1.54 g, 3.23 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 30 min at room temperature. CH_2Cl_2 (10 mL) was added into the reaction mixture after completion of the reacton, as monitored by TLC. The diluted reaction mixture was washed with water, saturated $NaHCO_3$ solution (2× 30 mL), and saturated NaCl in succession and then dried over $MgSO_4$. The residue was crystallised from ether after evaporation of the solvent under reduced pressure to produce 1.34 g (91.5%) of **4b**. M.p. 150–151 °C (lit.[10] 149 °C); $[a]_D^{24}$ + 63.2° (c 0.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93–7.78 (m, 2H), 7.78–7.69 (m, 2H), 6.18 (d, $J_{1,2}$ 9.3 Hz, 1H, H-1), 5.77 (dd, $J_{3,4}$ 10.4, $J_{2,3}$ 9.3 Hz, 1H, H-3), 5.24 (t, $J_{1,2} \approx J_{2,3}$ 9.4 Hz, 1H, H-2), 4.50 (dd, $J_{3,4}$ 10.4, $J_{4,5}$ 9.6 Hz, 1H, H-4), 4.36–4.11 (m, 2H, H-6a, H-5), 4.05–3.85 (m, 1H, H-6b), 2.11 (s, 3H), 2.02 (s, 3H), 1.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.99, 170.31(O–C=O), 169.67(2C=O), 134.93 (2C-arom), 124.20 (2C-arom), 85.88 (C-1), 76.03 (C-5), 70.92 (C-3), 68.48 (C-4), 62.01 (C-6), 57.84 (C-2), 21.08, 20.90, 20.70 (CH_3).

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