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Note

Acid-catalysed rearrangement of glycosyl trichloroacetimidates: a novel route to glycosylamines

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Abstract—A novel route to glycosylamines has been developed. Treatment of glycosyl trichloroacetimidates with TMSOTf under glycosylation conditions, but in the absence of an acceptor, resulted in complete rearrangement of the trichloroacetimidates into the corresponding N-protected-glycosylamines. Reductive cleavage of the trichloroacetyl groups using sodium borohydride provided the desired glycosylamine products.

Keywords: Chapman rearrangement; Glycosylamine; Reduction; Trichloroacetimidate

Glycosylamines are of biological and pharmaceutical importance,[1] with many of them considered to be active-site-directed reversible inhibitors of glycosidases, and some have been reported as oral antidiabetic agents.[2–4] The majority of cell-surface and secreted proteins are decorated with covalently linked carbohydrate residues bonded via their anomeric carbon atoms to either nitrogen atoms (hence, glycopeptides carrying N-linked saccharides) or oxygen atoms (hence, glycopeptides carrying O-linked saccharides).[5] The carbohydrate moieties of glycoproteins are thought to participate directly in recognition events, but may also influence protein properties[6–10] such as their catalytic activities,[11] protection from proteolytic degradation[12] and backbone conformation and folding.[13] A glycoprotein is characterised by its peptide backbone and a defined set of glycosylation sites, but the carbohydrate side chains may change in composition. Accordingly, the elucidation of structure and function of individual glycoproteins is complicated. Only in a few studies have the isolations of pure glycoforms been accomplished, and then only after extensive chromatographic separations.[14] To study biological processes mediated by the carbohydrate moieties, single glycoforms which have the same mono- or oligosaccharides attached to specific proteins are desirable.

For chemical synthesis of N-glycopeptides, the formation of glycosylamine bonds is a crucial step, and several methods for the preparation of glycosylamines (**2**) have been reported (Scheme 1).[1,15–19] These include treatment of unprotected sugars (**1**) with either methanolic ammonia[16] or a saturated solution of ammonium hydrogen carbonate[17] (**1**→**2**) or reduction of anomeric glycosyl azides (**3**→**2**),[18] the latter obtained by reaction of 1-*O*-acyl saccharides with $TMSN_3$ or from glycosyl halides by nucleophilic substitution with azide ions.[19] Herein we describe a novel alternative route to the glycosylamines (Scheme 1, **1**→**4**→**5**→**2**).

The method is efficient and is dependent on observations made during trichloroacetimidate-based glycosylaions[20] in which the appearance of unexpected

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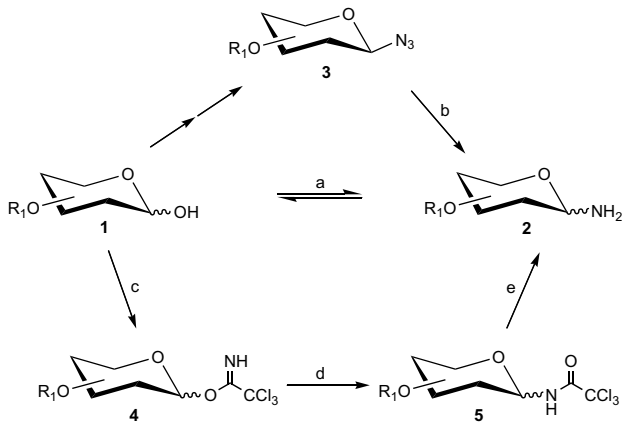


Scheme 1. Synthetic routes to glycosylamines. Reagents: (a) aq NH_3; (b) Reduction; (c) Ref. 26; (d) TMSOTf, DCM; (e) $NaBH_4$, EtOH.

N-trichloroacetylglycosylamines (**5**), which are rearranged products of the trichloroacetimidate glycosyl donors (**4**), were observed.[21] The imidate to *N*-acylamide rearrangement is long established and normally occurs at higher temperatures[22] and/or in the presence of Lewis acids such as BF_3.[23] It has also been seen when glycosyl trichloroacetimidates are treated with unreactive glycosyl acceptors,[24] and can be promoted when glycosyl trichloroacetimidates are subjected to glycosylation conditions but without active glycosyl acceptors as described by Shohda et al.[24c]

Trihaloacetyl protections of amine functionalities have been used for some years in peptide chemistry. In the present work a reductive cleavage of the trichloroacetyl groups of the amides (**5**) with sodium borohydride in ethanol released the free amines (**2**), and hence it became possible to produce the corresponding glycosylamines from the free sugars under mild, controlled conditions following the pathway outlined in Scheme 1 (**1**→**4**→**5**→**2**).[25]

The procedure was tested on the mixed anomers of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl trichloroacetimidate (**6a**),[26] 2,3,4,6-tetra-*O*-benzyl-D-mannopyranosyl trichloroacetimidate (**6b**),[27] and 2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-D-glucopyranosyl trichloroacetimidate (**6c**),[28] all prepared according to the literature methods. The TMSOTf induced rearrangements occurred within one hour, and TLC indicated that, in each case, two products (presumably the anomeric amido compounds) were formed that migrates on the plates between the starting materials and the corresponding free sugars. The rearrangements were readily monitored by ^{1}H NMR spectroscopy since the H-1 doublets observed for the trichloroacetimidates were replaced by doublets of doublets (β-anomers) or triplets (α-anomers) consistent with the introduction of the amide protons (Table 1, compounds **5a**–**c**). In the ^{13}C NMR spectra the chemical shifts for C-1 are moved to higher fields reflecting the changed chemical environments of the anomeric carbon atoms. The yields of the reactions ranged from 67% to 94% (see Scheme 2).

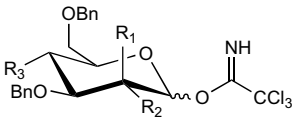
The reductive removal of the trichloroacetyl group proceeded smoothly and gave in 15–30 min new products with TLC mobilities lower than those of both the parent trichloroacetamides and the corresponding free sugars. To limit mutarotation of the free glycosylamines,[16b] it is important to keep the isolation environments neutral or weekly basic. The ^{1}H NMR assignment of the anomeric protons became more complex reflecting the coupling of H-1 with the two amine protons. The ^{13}C NMR chemical shifts moved downfield slightly in consequence of the removal of the trichloroacetyl groups. Concurrently the carbon resonances from the trichloroacetyl functions were removed. Yields were within the range 78–93%. All of the above results are supported by correct molecular weight determinations (Table 1).

In conclusion, we have utilised a known rearrangement reaction and applied it to glycosyl trichloroacetimidates in a mild method for the preparation of glycosylamines. When phenylthio glycosides are used during complex carbohydrate syntheses, as often occurs,[28] the sulfur-containing group may be removed hydrolytically at any appropriate stage and the liberated free sugars converted to the corresponding glycosylamines by the above procedures. Accordingly, the reaction sequence here described allows the synthesis of

Table 1. Yields and ^{1}H and ^{13}C NMR data for the anomeric positions of **7** and **8**

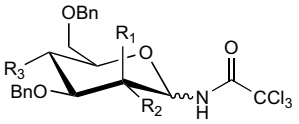
Compound no.	Yield (α/β-ratio[a])	^{1}H NMR H-1 (ppm)	^{13}C NMR C-1 (ppm)	MS (FAB) (*m*/*z*)
7a	94% (pure α)	5.60 t (α)	76.9 (α)	706.3 $[M+Na]^+$
7b	79% (1:2)	5.64 dd (α)	75.3 (α)	706.4 $[M+Na]^+$
		5.16 dd (β)	78.1 (β)	
7c	67% (3:1)	5.67 dd (α)	75.8 (α)	1138.4 $[M+Na]^+$
		5.20 dd (β)	80.6 (β)	
8a	91% (1:1)	5.84 dd (α)	73.7 (α)	540.3 $[M+H]^+$
		5.13 dd (β)	77.5 (β)	562.3 $[M+Na]^+$
8b	93% (pure α)	4.13 dd (α)	83.3 (α)	562.4 $[M+Na]^+$
8c	78% (1:1)	5.88 dd (α)	76.2 (α)	994.6 $[M+Na]^+$
		5.20 dd (β)	79.5 (β)	

[a] Calculated from integrated ^{1}H NMR spectra.



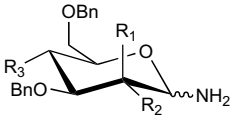
6a-c

i



7a-c

ii



8a-c

	R_1	R_2	R_3
a	H	OBn	OBn
b	OBn	H	OBn
c	H	OBn	$(BnO)_4Glc\alpha$*

Scheme 2. *$(BnO)_4Glc\alpha$ corresponds to 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl. Synthesis of glycosylamines building blocks. Reagents and conditions: (i) TMSOTf (0.2 equiv), CH_2Cl_2, 4 Å MS (activated powder), −20 to 22 °C, 45–60 min; (ii) $NaBH_4$, EtOH, rt, 15–30 min.

glycosylamines at any stage in the synthesis of complex carbohydrates in which phenyl thioglycosides are involved. The deprotection of the trichloroacetamides can be delayed until many other chemical manipulations have been completed, and finally conducted concurrently with, for example, catalytic hydrogenation of benzyl protection functions or deacylations.

1. Experimental

1.1. General methods

Optical rotations were measured at 21 ± 2 °C with an Optical Activity Ltd AA-100 Polarimeter. Reactions were monitored by TLC on aluminium sheets coated with silica gel $60F_{254}$ (0.2-mm thickness, E Merck, Darmstadt, Germany) and the compounds were detected by charring with 10% H_2SO_4 in MeOH. Column chromatography was carried out using Silica Gel 60 (particle size 0.040–0.063, 230–400 mesh ASTM, E Merck, Darmstadt, Germany). Solvent extracts were dried with anhydrous $MgSO_4$ unless otherwise specified. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 instrument at 400 and 101 MHz, respectively. $CDCl_3$ was used as solvent, δ_H-values are relative to internal Me_4Si and δ_C-values are referenced to the solvent [δ_C ($CDCl_3$, central resonance) = 77.08]. FAB spectra were recorded on a Joel A505W mass spectrometer. All the chemicals used in this study were commercially available.

1.2. General procedure for the rearrangement of glycosyl trichloroacetimidates

TMSOTf (66.6 μL, 0.36 mmol) was added to solutions of the trichloroacetimidate derivatives **6a–c**[20,26,27] (1.8 mmol) together with 4 Å molecular sieve powder in dry dichloromethane (50 mL) at −20 °C. After 10 min the reactions were stopped by addition of solid $NaHCO_3$ and the mixtures were filtered through a layer of sand and silica gel. The filtrates were washed with satd aq $NaHCO_3$ and water until neutral. The organic phases were dried, concentrated and the residues purified by column chromatography.

1.2.1. *N*-Trichloroacetyl-2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosylamine (7a). The residue was chromatographed on silica gel (85 g) with EtOAc (20%) in *n*-pentane to give compound **7a** (440 mg, colourless syrup, 94%, pure α); $[\alpha]_D$ +35.3° (*c* 8.5×10^{-3} $CHCl_3$) ^1H NMR data ($CDCl_3$): δ, 7.37–7.12 (m, 21H, Ar, N*H*, α-anomer, *Ph*CH_2), 5.60 (dd, 1H, *J* 5.7 Hz, H-1, α-anomer), 4.92–4.47 (m, 8H, *CH*$_2$Ph), 3.88 (dd, 1H, *J* 5.2 Hz, *J* 9.0 Hz, H-6b), 3.81–3.73 (m, 2H, H-3, H-6a), 3.70–3.63 (m, 3H, H-2, H-4, H-5); ^{13}C NMR ($CDCl_3$): For the α-anomer: δ 162.1 (*C*=O), 138.1–127.2 (C-arom, *Ph*CH_2), 92.3 (*C*Cl_3), 81.6 (C-3), 77.2 (C-2), 76.9 (C-1), 76.5 (C-5), 75.5, 75.1, 73.6, 72.9 (4 *C*H_2Ph), 71.8 (C-4), 68.0 (C-6). MS (FAB): *m*/*z* = 706.3 $[M+Na]^+$.

1.2.2. *N*-Trichloroacetyl-2,3,4,6-tetra-*O*-benzyl-α/β-D-mannopyranosylamine (7b). The residue was chromatographed on silica gel (100 g) with 20% Et_2O in *n*-pentane to give **7b** (980 mg, colourless syrup, 79%, α/β 1:2); $[\alpha]_D$ +7.1° (*c* 5.6×10^{-3} $CHCl_3$); ^1H NMR data ($CDCl_3$): δ 7.38–7.16 (m, 20.7H, H-arom, N*H*, β-anomer, *Ph*CH_2), 6.91 (d, 0.3H, *J* 7.32, N*H*, α-anomer), 5.64 (dd, 0.3H, *J* 5.4, *J* 7.5, H-1, α-anomer), 5.16 (dd, 0.7H, *J* 1.5 Hz, *J* 8.7 Hz, H-1, β-anomer), 5.07–4.51 (m, 8H, *CH*$_2$Ph), 4.06–3.87 (m, 2H, H-2, H-4), 3.84–3.53 (m, 4H, H-3, H-5, 2 H-6); ^{13}C NMR ($CDCl_3$): For the α-anomer: δ 161.3 (*C*=O), 138.0–127.7 (C-arom, *Ph*CH_2), 93.2 (*C*Cl_3), 77.2 (C-5), 75.9 (C-3), 75.3 (C-1), 74.0 (C-2), 73.9 (C-4), 73.8–71.9 (4*C*H_2Ph), 68.4 (C-6). For the β-anomer: δ 161.1 (*C*=O), 138.0–127.6 (C-arom, *Ph*CH_2), 92.1 (*C*Cl_3), 83.2 (C-3), 78.6 (C-1), 77.2 (C-5), 75.0 (*C*H_2Ph), 74.6 (C-2), 74.5 (*C*H_2Ph), 74.2 (C-4),

73.5, 73.2 (2CH_2Ph), 68.6 (C-6). MS (FAB): $m/z = 706.4$ $[M+Na]^+$.

1.2.3. *N*-Trichloroacetyl-2,3,6-tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α/β-D-glucopyranosylamine (7c). The residue was chromatographed on silica gel (90 g) with 40% Et_2O in *n*-pentane to give **7c** (650 mg, colourless syrup, 67% yield, α/β 3:1); $[\alpha]_D$ +24.0° (*c* 10.0×10^{-3} $CHCl_3$) ^1H NMR data ($CDCl_3$): δ 5.67 (dd, 0.8H, *J* 3.2 Hz, *J* 6.6 Hz, H-1, α-anomer), 5.47 (d, 0.2H, *J* 3.82 Hz, H-1′, β-anomer), 5.35 (d, 0.8H, *J* 3.5 Hz, H-1′, α-anomer), 5.20 (dd, 0.2H, *J* 8.7 Hz, H-1, β-anomer). ^{13}C NMR ($CDCl_3$): For the α-anomer: δ 161.9 (*C*=O), 97.1 (C-1′), 92.4 (*C*Cl_3), 75.8 (C-1). For the β-anomer: δ 161.4 (*C*=O), 97.2 (C-1′), 92.2 (*C*Cl_3), 80.6 (C-1). MS (FAB): $m/z =$ 1138.4 $[M+Na]^+$.

1.3. General procedure for the reduction of the *N*-trichloroacetylglycosylamines

$NaBH_4$ powder (2.9 mmol) was added to a solution of the trichloroacetamide derivatives **7a**–**c** (0.73 mmol) in absolute EtOH (5 mL). After 15 min the reactions were stopped by addition of acetone (excess) and the reaction mixtures were stirred for additional 15 min. The mixtures were concentrated under vacuum and extracted with EtOAc. The organic phases were washed with water until neutral, dried, filtered and evaporated. The residues were purified by column chromatography.

1.3.1. 2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosylamine (8a). The residue was chromatographed on silica gel (60 g) with 80% Et_2O in *n*-pentane to give N-substituted glycosylamine **8a** (230 mg, colourless syrup, 91% yield, α/β 1:1); $[\alpha]_D$ +66.9° (*c* 11.8×10^{-3} $CHCl_3$) ^1H NMR data ($CDCl_3$): δ 7.34–7.12 (m, 20H, H-arom, *Ph*CH_2), 6.83 (dd, 0.5H, NH), 6.46 (d, 0.5H, NH), 5.84 (dd, 0.5H, H-1, α-anomer), 5.13 (dd, 0.5H, H-1, β-anomer), 4.92–4.40 (m, 8H, *C*H_2Ph), 3.84–3.55 (m, 6H, H-2, H-3, H-4, H-5, 2 H-6); ^{13}C NMR ($CDCl_3$): for the α-anomer: δ 138.4–127.6 (C-arom, *Ph*CH_2), 81.6 (C-3), 77.8 (C-2), 76.8 (C-5), 75.4, 74.9 (2*C*H_2Ph), 73.7 (C-1), 73.5, 72.7 (2 *C*H_2Ph), 70.6 (C-4), 68.1 (C-6); for the β-anomer: δ 138.4–127.6 (C-arom, *Ph*CH_2), 81.8 (C-3), 78.2 (C-2), 77.5 (C-1), 76.9 (C-5), 75.6, 75.0, 73.5, 73.3 (4*C*H_2Ph), 71.4 (C-4), 68.2 (C-6). MS (FAB): $m/z =$ 540.3 $[M+H]^+$; 562.3 $[M+Na]^+$.

1.3.2. 2,3,4,6-Tetra-*O*-benzyl-α-D-mannopyranosylamine (8b). The residue, was chromatographed on silica gel (90 g) with 5% MeOH in CH_2Cl_2 to give N-substituted glycosylamine **8b** (370 mg, colourless syrup, 93% yield, pure α); $[\alpha]_D$ +10.0° (*c* 9.0×10^{-3} $CHCl_3$); ^1H NMR data ($CDCl_3$): δ, 7.39–7.13 (m, 20H, H-arom, *Ph*CH_2), 5.13–4.45 (m, 8H, *C*H_2Ph), 4.13 (m, 1H, H-1), 3.90 (dd, 1H, *J* 1.9 Hz, H-2), 3.82 (dd, 1H, *J* 9.5 Hz, H-4), 3.71 (dd, 1H, *J* 1.9 Hz, *J* 10.3 Hz, H-6a), 3.69–3.57 (m, 2H, H-3, H-6b), 3.46 (ddd, 1H, *J* 2.0 Hz, *J* 6.0, *J* 9.6 Hz, H-5); ^{13}C NMR ($CDCl_3$): δ 138.2–127.5 (C-arom, *Ph*CH_2) 84.4 (C-3), 83.3 (C-1α), 77.2 (C-2), 76.2 (C-5), 75.1 (*C*H_2Ph), 75.0 (C-4), 74.9, 73.4, 72.5 (3*C*H_2Ph), 69.5 (C-6). MS (FAB): $m/z = 562.4$ $[M+Na]^+$.

1.3.3. 2,3,6-Tri-*O*-benzyl-4-*O*-(2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl)-α/β-D-glucopyranosylamine (8c). To the 100% EtOH solution was added 2 mL of toluene to ensure total solubility of **7c**, which was chromatographed on silica gel (70 g) with 5% MeOH in CH_2Cl_2 to give N-substituted glycosylamine **9c** (380 mg, colourless syrup, 78% yield, α/β 1:1); $[\alpha]_D$ +43.2° (*c* 9.5×10^{-3} $CHCl_3$); ^1H NMR data ($CDCl_3$): δ 6.83 (dd, 0.5 H, NH), 6.46 (d, 0.5H, NH), 5.88 (dd, 0.5H, H-1, α-anomer), 5.47 (d, 0.5H, *J* 3.82 Hz, H-1′, β-anomer), 5.35 (d, 0.5H, H-1′, α-anomer), 5.20 (dd, 0.5H, H-1, β-anomer); ^{13}C NMR ($CDCl_3$): For the α-anomer: δ 96.4 (C-1′), 76.2 (C-1); for the β-anomer: δ 96.7 (C-1′), 79.5 (C-1). MS (FAB): $m/z = 994.6$ $[M+Na]^+$.

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