Synthesis of novel Schiff bases from the reaction of 3-O-methyl-4, 6-O-benzylidene-β-D-glucopyranosylamine with substituted aldehydes

Chao Shen, Qing Zhao, Hui Zheng and Pengfei Zhang*

College of Material, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, P.R. China

The synthesis of novel sugar derived Schiff base derivatives from reaction of 3-O-methyl-4, 6-O-benzylidene-β-D-glucopyranosylamine with several substituted aldehydes is described.

Keywords: sugar derived Schiff base, 3-O-methyl-4, 6-O-benzylidene-β-D-glucopyranosylamine, substituted aldehydes

Owing to the remarkable biological relevance of carbohydrate, the synthesis of oligosaccharides or carbohydrate derivatives has attracted much attention.[1] The sugar derived Schiff base are important intermediates in the synthesis of N-nucleosides and glycosylamino heterocycles.[2] The active site on carbohydrate structure directed reversible inhibitors of glycosidases and played important roles in various biological processes.[3] Carbohydrates are widespread chiral natural products, generally cheap and easily obtainable and stereogenic centres allows the regional and stereoselective introduction of different functionalities. These features are well-suited for developing catalysis in non-conventional conditions with a reduced environmental impact. Carbohydrates have recently received much attention as sources of chiral ligands for asymmetric catalysis.[4] A variety of iminic chiral ligands constituted by a chiral amino part and an aldehydic or acidic part can be found in literature.[5] However the complexity and diversity of carbohydrates found in nature makes the synthesis of carbohydrates a challenging task despite the numerous efforts documented.[6] One reason is that different carbohydrate scaffolds often manifest moderate to drastic different reactivity in various reactions.[7]

Several glycosylamines are known, but as far as the glycosylamine derived Schiff base molecules are concerned, the literature is scarce.[8] Recently, we have demonstrated that carbohydrates have emerged as versatile auxiliaries and reagents in regio- and stereoselective chemical reactions, and which can be straightforwardly prepared by suitable modification of common and inexpensive sugars such as D-glucose.[10] In connection with a program directed to broaden the application of carbohydrates in organic chemistry, we have focussed our attention on the development of new chiral Schiff bases for biological products and asymmetric catalysis. Here, we describe the efficient synthesis of chiral Schiff base from glucosamine and a series of substituted aldehydes.

Results and discussion

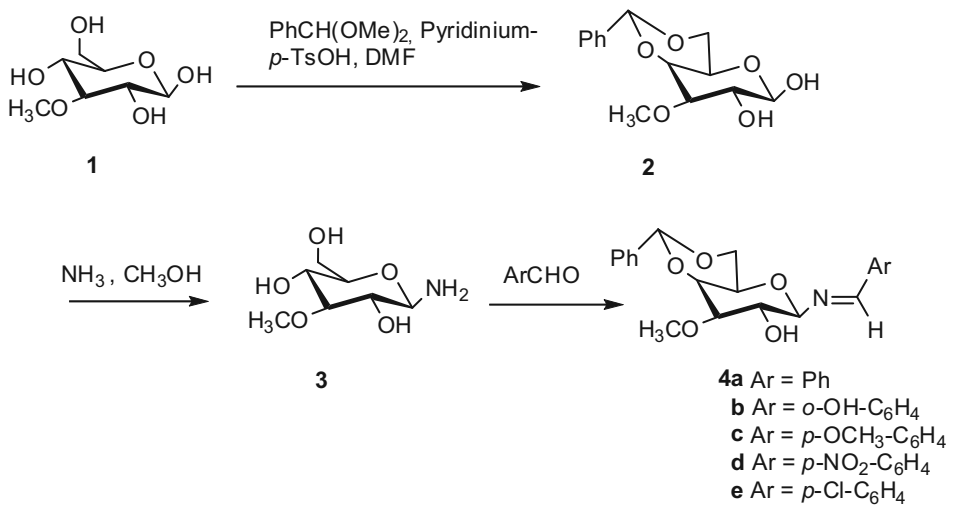
In this paper, we shall report multiple chemical modifications that were carried out on D-glucose to produce the corresponding Schiff bases. Such modifications performed on D-glucose not only helped in increasing the solubility of the products in nonaqueous solvents, but also restricted the anomerisation of the saccharide moiety in solution.

We first prepared 3-O-methyl-4, 6-O-benzylidene-β-D-glucopyranosylamine from D-glucose by several steps, followed by treatment with a series of substituted aldehydes to afford the corresponding Schiff base (**4a–e**) (Scheme 1). The results are reported in Table 1. It is well known that under mild conditions aldoses react with primary or secondary amines to form glycosylamines where the hydroxyl group on C-1 is replaced by the amine in order to produce C-1-NRR by condensation. The peak corresponding to C-1-NH_2 observed

Table 1 Synthesis of sugar derived Schiff base[a]

Entry	Ar	Product	Time/h	Yield/%[b]
1	Ph	**4a**	2.0	82.9
2	*o*-OH-C_6H_4	**4b**	2.0	72.7
3	*p*-OCH_3-C_6H_4	**4c**	2.5	75.7
4	*p*-NO_2-C_6H_4	**4d**	2.5	86.9
5	*p*-Cl-C_6H_4	**4e**	2.0	80.6

[a]Reagent and conditions: amine (1.0 mmol), substituted aldehydes (1.1 mmol) reflux in MeOH;
[b]Isolated yields.



Scheme 1

* Correspondent. E-mail: pfzhang@hznu.edu.cn

in **3** at 2.32 ppm disappears in **4** and a new peak appears at around 8.432 ppm arising from –CH=N indicating that the $–NH_2$ group present in the former was converted to its Schiff base in **4**.

Conclusions

In conclusion, D-glucose was successfully modified into the corresponding Schiff base through partial protection and glycosyl amination, followed by condensation with substituted aldehydes. All the compounds were characterised by analytical and spectral methods. Such modifications facilitate the solubility of the resulting Schiff base products in nonaqueous solvents and lock the saccharide in the anomeric form. Futher research of other Schiff base is taking place in our laboratory and the results will be reported later.

Experimental

All chemicals were reagent-grade quality. All reactions were carried out under an nitrogen atmosphere in oven-dried glassware with magnetic stirring. Column chromatography was performed on silical gel, Merck grade 60 (230–400 mesh). Reactions were monitored by TLC performed on a Merck precoated TLC (silica gel 60 F254) plate. Melting points were determined on an X4-Data microscopic melting point apparatus; IR spectra were determined on a Nicolet NEXUS-470FT-IR spectrometer as KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker AVANCE DRX-400 NMR spectrometer, using TMS as the internal standard.

General procedure for preparation of **1**

3-O-Methyl-D-glucose[11-12] (10.0 g, 52 mmol) was dissolved in dry dimethylformamide (50 mL, 90 °C) and pyridinium *p*-toluenesulfonate (100 mg) added. α,α-Dimethoxytoluene (9.0 g, 60 mmol) in dimethylformamide (50 mL) was then added dropwiseunder a stream of dry nitrogen (2 h, 90 °C). Evaporation and recrystallisation of the residue gave 3-O-methyl-4, 6-O-benzylidene-D-glucose as needles (12.65 g, 86.3%). M.p.129–131 °C. MS: *m/z* (EI): 282 (M^+). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.52–7.27 (m, 5 H, ArH), 5.62 (d, 1 H, J = 5.7 Hz, SacOH), 5.54 (s, 1 H, CHPh), 4.81 (d, 1 H, J = 3.9 Hz), 4.30 (dd, 1 H, J = 4.2 Hz, 9.7 Hz), 3.92 (d, 1 H, J = 5.7 Hz, SacOH), 3.37 (s, 3 H), 3.18–3.80 (m, 5 H, Sac). ^{13}C NMR ($CDCl_3$, 100 MHz) δ–129.0, 128.2, 126.0, 125.9, 101.2, 92.9, 81.9, 80.1, 77.3, 77.2, 76.9, 72.3, 68.9, 66.6, 61.0.

General procedure for preparation of **3**

3-O-methyl-4, 6-O-benzylidene-D-glucose (10.0 g., 35 mmol) was added to a chilled (ice-salt) solution of ammonia (35–40 g.) in methanol (120 mL), contained in a steel bomb. The bomb was closed, and with shaking the temperature was raised gradually and maintained at 60 °C for 3 h. At the end of this period, the bomb was allowed to reach room temperature and then cooled to 0 °C. Upon careful removal of the excess of ammonia by means of a water-pump, compound **3**, which had already begun to crystallise, separated out in a mass. It was kept at 0 °C overnight, filtered off, washed with small portions of methanol and dried over calcium chloride and potassium hydroxide; yield (6.5 g. 66.3%), M.p. 129–131 °C. IR (KBr, cm^{-1}): 1627 (NH_2). MS: *m/z* (EI): 281 (M^+). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.54–7.26 (m, 5 H, ArH), 5.55 (d, 1 H, J = 5.7 Hz, SacOH), 5.31 (s, 1 H, CHPh), 4.81 (d, 1 H, J = 3.9 Hz), 4.30 (d, 1 H, J = 4.2 Hz), 3.37 (s, 3 H), 3.18–3.80 (m, 5 H, Sac), 2.32 (br., 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 137.9, 128.9, 128.2, 126.3, 100.2, 87.7, 83.4, 81.4, 79.3, 79.2, 73.7, 68.6, 67.2, 60.3. Anal. Calcd for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.80; N, 4.95. Found: C, 59.80; H, 6.90; N, 4.98%.

General procedure for preparation of **4**

To a suspension of 3-O-methyl-4, 6-O-benzylidene-β-D-glucopyranosylamine (0.281 g, 1.0 mmol) in MeOH (15 mL) was added substituted aldehyde (1.1 mmol), and the reaction mixture was refluxed for 2.0 h to produce a clear orange solution. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue was dissolved in 5 mL diethyl ether and excess hexane was added to the solution while stirring to afford the light yellow solid product which was isolated through filtration and dried under vacuum. The crude product was recrystallised from ethanol–water to give a pure sample. The physical and spectra data of the compounds (**4a–e**) are as follows.

N-benzylidene-3-O-methyl-4, 6-O-benzyliden -β-*D-glucopyranosylamine* (**4a**): Yield: 0.306 g, 82.9% M.p. 152–154 °C. IR (KBr, cm^{-1}): 1634 (CH=N). MS: *m/z* (EI): 369 (M^+). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.56 (s, 1 H, HC=N), 7.30–7.62 (m, 8 H, ArH), 6.78–6.94 (m, 2 H, ArH), 5.62 (d, 1 H, J = 3.2 Hz, SacOH), 5.51 (s, 1 H, CHPh), 4.71 (1 H, J = 4.4 Hz), 4.24 (1 H, J = 12.2 Hz), 3.37 (s, 3 H), 3.18–3.80 (m, 5 H, Sac). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 159.6, 138.2, 136.5, 135.6, 130.4, 129.1, 129.1, 128.2, 126.8, 101.1, 97.0, 81.1, 75.0, 74.2, 68.7, 57.9, 20.2. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.41; H, 6.20; N, 3.82%.

N-(2-hydroxybenzylidene)-3-O-methyl-4, 6-O-benzylidene-β-*D-glucopyranosylamine* (**4b**): Yield: 0.280 g, 72.7%. M.p. 172–174 °C. IR (KBr, cm^{-1}): 1624 (CH=N). MS: *m/z* (EI): 385 (M^+). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.95 (s, 1 H, ArOH), 8.62 (s, 1 H, HC=N), 7.22–7.62 (m, 7 H, ArH), 6.80–7.1 (m, 2 H, ArH), 5.62 (d, 1 H, J = 3.2 Hz, SacOH), 5.51 (s, 1 H, CHPh), 4.56 (1 H, J = 6.2 Hz), 4.10 (1 H, J = 4.8 Hz), 3.37 (s, 3 H), 3.70–3.52 (m, 5 H, Sac). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 165.7, 160.7, 138.2, 133.4, 132.8, 129.3, 128.5, 126.8, 119.3, 118.8, 116.9, 101.1, 95.9, 81.0, 75.1, 73.7, 68.3. 20.1. Anal. Calcd for $C_{21}H_{23}NO_6$: C, 65.41; H, 6.01; N, 3.60. Found: C, 65.15; H, 6.22; N, 3.71%.

N- (*4-methoxybenzylidene)-3-O-methyl-4, 6-O-benzylidene*-β-*D-glucopyranosylamine* (**4c**): Yield: 0.302 g, 75.7%. M.p. 162–164 °C. IR (KBr, cm^{-1}):1612 (CH=N). MS: *m/z* (EI): 399 (M^+). ^{1}H NMR (DMSO-d_6, 400 $MHz_)$ δ: 8.56 (s, 1 H, HC=N), 7.58–7.62 (m, 7 H, ArH), 6.85–6.96 (m, 2 H, ArH), 5.52 (d, 1 H, J = 5.2 Hz, SacOH), 5.30 (s, 1 H, CHPh), 4.70 (1 H, J = 6.4 Hz), 4.24 (1 H, J = 6.5 Hz), 3.79 (s, 3 H, $ArCH_3$), 3.37 (s, 3 H), 3.11–3.75 (m, 5 H, Sac).^{13}C NMR (DMSO-d_6, 100 MHz) δ: 161.8, 159.2, 135.1, 134.5, 132.5, 131.8, 128.3, 126.9, 125.9, 101.6, 85.2, 78.6, 77.2, 70.4, 67.1, 50.6,39.5, 20.2. Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.20; H, 6.32; N, 3.64. Found: C, 66.35; H, 6.43; N, 3.70%.

N-(*4-nitrobenzylidene)-3-O-methyl-4, 6-O-benzylidene* -β-*D-glucopyranosylamine* (**4d**): Yield: 0.356 g, 86.9%. M.p.142–144 °C. IR (KBr, cm^{-1}): 1646 (CH=N). MS:*m/z* (EI): 414 (M^+). ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.82 (s, 1 H, HC=N), 8.54–7.85 (m, 7 H, ArH), 7.21–7.03 (m, 2 H, ArH), 5.66 (d, 1 H, J = 5.5 Hz, SacOH), 5.51 (s, 1 H, CHPh), 4.71 (1 H, J = 5.1 Hz), 4.24 (1 H, J = 8.4 Hz), 3.37 (s, 3 H), 3.18–3.80 (m, 5 H, Sac). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 166.8, 162.5, 137.5, 128.3, 118.6, 129.0, 128.2, 126.8, 101.7, 96.6, 81.8, 75.6, 71.5, 68.7. 20.1. Anal. Calcd for $C_{21}H_{22}N_2O_7$: C, 60.91; H, 5.35; N, 6.78. Found: C, 60.72; H, 5.47; N, 6.83%.

N-(*4-Chlorobenzylidene)-3-O-methyl-4, 6-O-benzylidene*-β-*D-glucopyranosylamine* (**4e**): Yield: 0.325 g, 80.6%. M.p.170–172 °C. IR (KBr, cm^{-1}): 1645 (CH=N). MS *m/z* (EI): 403 (M^+); ^{1}H NMR (DMSO-d_6, 400 $MHz_)$ δ: 8.43 (s, 1 H, HC=N), 7.83–7.75 (m, 7 H, ArH), 7.37–7.26 (m, 2 H, ArH), 5.56 (d, 1 H, J = 5.7 Hz, SacOH), 5.16 (s, 1 H, CHPh), 4.70 (1 H, J = 8.6 Hz), 4.19 (1 H, J = 12.3 Hz), 3.37 (s, 3 H), 3.17–3.80 (m, 5 H, Sac). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 160.5, 13.6, 137.1, 133.6, 130.8, 129.9, 128.9, 128.2, 125.9, 101.2, 95.4, 87.7, 82.8, 77.3, 73.8, 68.3, 60.9. Anal. Calcd for $C_{21}H_{22}ClNO_5$: C,62.40; H, 5.61; N, 3.52.86 Found: C,62.52; H, 5.74; N, 3.62%.

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