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EFFICIENT SYNTHESIS OF GLYCOSYL ENAMINOESTERS DIRECTLY FROM GLYCOSYL AZIDES [§]

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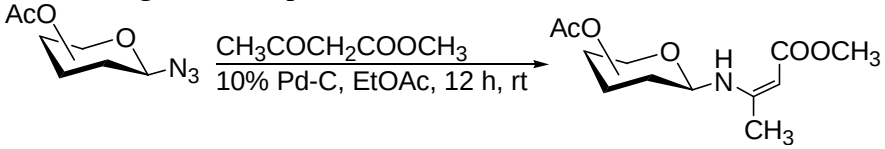
ABSTRACT

A convenient methodology has been developed for the synthesis of glycosylenaminoesters directly from glycosyl azides under hydrogenetion condition. Yields were moderate to good in all cases.

Keywords: Carbohydrate, glycosyl azide, glycosyl enaminoester, hydrogenetion, one-pot.

INTRODUCTION

Enaminoesters or vinylogous carbamates are useful intermediates for the synthesis of several bioactive natural products [1] and heterocyclic frameworks.[2] They are also in use for the preparation of and peptidomimetics[3] and β-aminoacid.[4] Glycosylenamines have been used for the synthesis of thioglycosides of azasugars,[5] iminocyclitols,[6] chiral pyrrolidines[7] and 4-aminoaldoses.[8] In general, enaminoesters are prepared by condensation of amines with β-ketoesters in presence of a catalyst under anhydrous condition.[9] Although these reactions are suitable for aliphatic amines, they are not very useful for the preparation glycosylenamines due to the reactive nature of glycosyl amines. A suitable alternative to overcome this problem could be the reduction of glycosyl azide and reaction of *in situ* generated glycosyl amines with β-ketoesters in a one-pot reaction condition. Recently, we noted a report for the preparation of vinylogous carbamates of simple alkyl azides under hydrogenetion condition.[10] We sought to explore this protocol for the preparation of glycosyl vinylogous carbamates from glycosyl azides and disclosing our findings in this report.



Scheme 1

[§] C.D.R.I. communication no. 7055.

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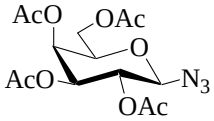
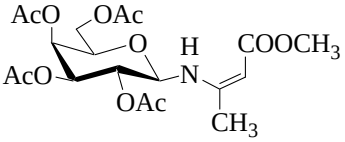
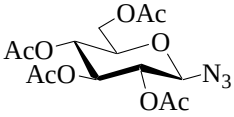
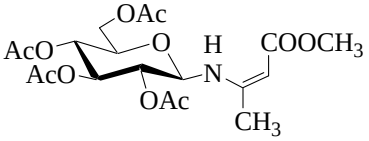
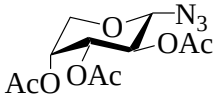
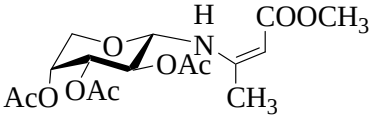
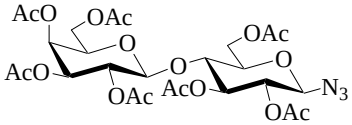
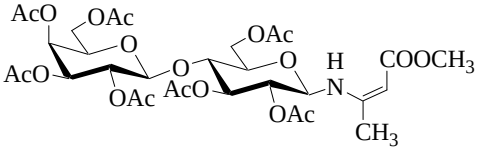
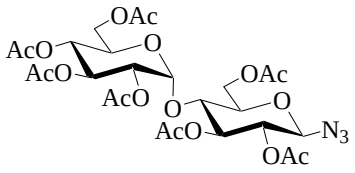
RESULTS AND DISCUSSION

To begin with, 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide was treated with a varied quantity of methyl acetoacetate and 10% Pd-C in different solvents under hydrogen. After some experimentation, it was observed that use of 3.0 equiv. of methyl acetoacetate, 10% Pd-C (10% w/w) in ethyl acetate as solvent furnished good yield of per-*O*-acetylated glucosyl enamino ester as a single isomer (Scheme 1). Following the similar reaction condition a series of glycosyl azides [11] were directly converted to glycosyl enamino esters (Table 1). Interglycoside bonds remained unaffected under the reaction condition. It is noteworthy that 1,2-*trans* isomers were obtained exclusively, which were confirmed from the NMR spectral analysis of glycosyl enaminoesters (doublet of doublet or triplet for anomeric protons, J = 9.4-10 Hz). Although, there was possibility for the formation of Z- and E-isomers, X-ray crystallographic study of compound **2** showed that only Z-isomers were formed, which may be due to the presence of intramolucular hydrogen bonding. Although, other products (**4**, **6**, **8** and **10**) were not crystallized, it is presumed that they exist as Z-isomers due to the presence of a intramolecular hydrogen bonding. Products were well characterized with the help of NMR and mass spectral analysis. Use of other solvents, such as, toluene, methanol, and ethanol did not produce satisfactory yield of enamino ester and glycosyl amines were isolated as major product.

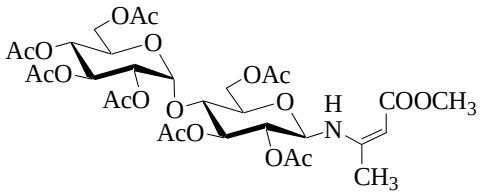
Table 1. Preparation of glycosyl enaminoesters directly from glycosyl azides.

Entry	Glycosyl azide	Glycosyl enaminoester	Yield[a] (%)
1	 **1**	 **2**	72
2	 **3**	 **4**	70
3	 **5**	 **6**	65
4	 **7**	 **8**	65

5 62



9



10

[a] Isolated yield.

In order to confirm the Z-stereoselectivity, single crystal X-ray crystallographic study of compound **2** was carried out. [12] The configuration, conformation and atom numbering of compound **2** are shown in Figure 1. The crystal of compound **2** has one molecule in the crystal unit cell and the pyranose ring exists in $^4C_1$ conformation, however due to crystal packing it is slightly distorted. The Cremer-Pople puckering parameters [13] for the pyranose ring are as follows: Q= 0.567°, θ = 5.29° and φ = 334.82°. Crystal packing studies of compound **2** reveals the presence of a strong intramolecular N-H…O=C interaction occurs between N1H1A…O2 (*D*…*A* = 2.716 Å, H…*A* = 2.11 Å, ∠*D*-*H*-*A* =127°). In addition, numerous weak intra and intermolecular C-H…O interactions were also observed, which are tabulated below (Table 2).[14] Presence of intramolecular hydrogen bonding may explain the formation of Z-isomer.

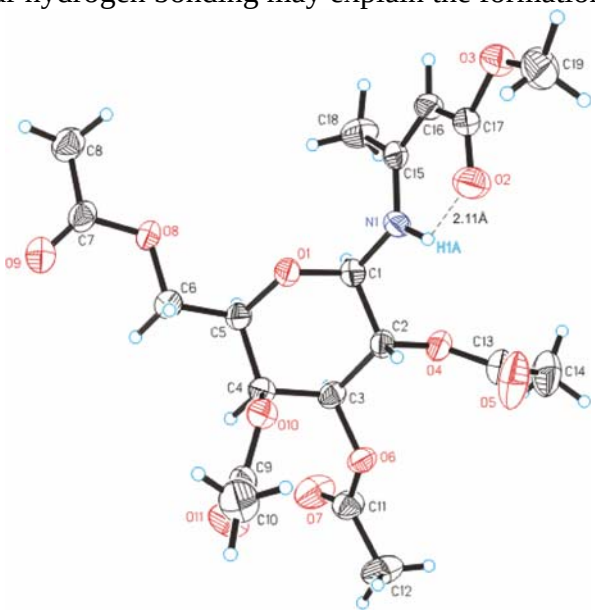


Figure 1: ORTEP diagram of compound **2** (30% probability)

Table 2: Weak C-H…O hydrogen bondings in compound **2**.

D*-H…*A	***Symm. code***	D…A ***(Å)***	**H…*A*** (Å)	**∠*D*-H-*A*** (°)
C2-H2…O5[i]	-	2.7012	2.29	104
C4-H4…O11[i]	-	2.6769	2.31	101
C4-H4…O9[ii]	1-x,-1/2+y, 1-z	3.3133	2.51	139
C5-H5…O3[ii]	-x, -1/2+y, 1-z	3.4801	2.52	168
C10-H10A…O7[ii]	x, 1+y, z	3.4559	2.55	158
C10-H10B…O5[ii]	-x, ½+y, -z	3.4463	2.51	164
C12-H12A…O11[ii]	1-x, -1/2+y, -z	3.4376	2.50	164

[i] :intramolecular, [ii]: intermolecular.

In summary, we have developed an efficient method for the preparation of glycosyl enaminoesters directly from glycosyl azides under hydrogenation condition. This environmentally benign reaction protocol will find application in the synthetic carbohydrate chemistry.

EXPERIMENTAL

General experimental protocol for the preparation of glycosyl enaminoesters: A solution of glycosyl azide (1.0 mmol), methyl acetoacetate (3.0 mmol) and 10% Pd-C (10% w/w) in EtOAc (5 mL) was stirred under 40 psi of hydrogen at room temperature for 12 h. The reaction mixture was filtered through a Celite® bed and concentrated under reduced pressure. Column chromatography of the crude product over SiO_2 using hexane-EtOAc (3:1) as solvent furnished pure glycosyl enaminoester.

Spectral data of glycosyl enaminoesters:

Compound 2: White solid, m.p. 149-151 °C; $[\alpha]_D$ +124 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.92 (d, *J* = 9.0 Hz, 1 H, NH), 5.38 (d, *J* = 3.0 Hz, 1 H, H-4), 5.25 (dd, *J* = 9.0 Hz each, 1 H, H-2), 5.10 (dd, *J* = 9.0 and 3.0 Hz, 1 H, H-3), 4.72 (t, *J* = 9.4 Hz each, 1 H, H-1), 4.66 (s, 1 H, olefinic H), 4.11-4.08 (m, 2 H, H-$6_{a,b}$), 3.95-3.90 (m, 1 H, H-5), 3.66 (s, 3 H, OCH_3), 2.19 (s, 3 H, CH_3), 2.07, 2.05, 2.02, 2.0 (4s, 12 H, 4 COCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.9, 169.8, 169.6 (2 C), 169.3, 158.1 (C-1′), 89.1 (C-3′), 82.7 (C-1), 71.8, 71.3, 68.5, 67.3, 61.5 (C-6), 50.4 (COO*C*H_3), 20.7 (2 C), 20.6 (2 C), 18.9; ESI-MS: 468.2 $[M+Na]^+$; Anal. Calcd. for $C_{19}H_{27}NO_{11}$ (445): C, 51.23; H, 6.11%; found: C, 50.95; H, 6.38%.

Compound 4: Colourless oil; $[\alpha]_D$ +75 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.80 (d, *J* = 9.0 Hz, 1 H, N*H*), 5.40-5.38 (t, *J* = 9.6 Hz each, 1 H, H-3), 5.22 (t, *J* = 9.4 Hz each, 1 H, H-2), 5.18-4.98 (m, 1 H, H-4), 4.73 (t, *J* = 10.0 Hz each, 1 H, H-1), 4.64 (s, 1 H, olefinic H), 4.26-4.02 (m, 2 H, H-$6_{a,b}$), 3.73-3.68 (m, 1 H, H-5), 3.62 (s, 3 H, COOCH_3), 2.12, 2.08, 2.07, 2.04, 2.0 (5 s, 15 H, CH_3, 4 COCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.4, 170.2, 169.8, 169.3, 169.2, 157.9 (C-1′), 89.8 (C-3′), 82.1 (C-1), 73.8, 71.9, 68.3, 66.9, 61.8 (C-6), 50.4 (COO*C*H_3), 20.6 (2 C), 20. 5 (2 C), 19.5; ESI-MS: 468 $[M+Na]^+$; Anal. Calcd. for $C_{19}H_{27}NO_{11}$ (445): C, 51.23; H, 6.11%; found: C, 50.96; H, 6.36%.

Compound 6: Colourless oil; $[\alpha]_D$ – 39 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.08 (d, *J* = 9.3 Hz, 1 H, N*H*), 5.29-5.26 (m, 1 H, H-4), 5.24 (t, *J* = 9.0 Hz each, H-2), 5.18 (dd, *J* = 9.6 and 3.0 Hz, 1 H, H-3), 4.73 (dd, *J* = 9.8 Hz each, 1 H, H-1), 4.67 (s, 1 H, olefinic H), 3.95 (dd, *J* = 11.9, 3.9 Hz, 1 H, H-5_a), 3.67 (dd, *J* = 12.0, 2.1 Hz, 1 H, H-5_b), 3.65 (s, 3 H, COOCH_3), 2.13, 2.11, 2.08, 1.99 (4 s, 12 H, CH_3, 3 COCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.6, 170.3, 170.0, 169.8, 158.9 (C-1′), 88.8 (C-3′), 81.9 (C-1), 70.1, 69.2, 67.7, 63.0 (C-5), 50.6 (COO*C*H_3), 21.2, 21.0 (2 C), 19.1; ESI-MS: 396 $[M+Na]^+$; Anal. Calcd. for $C_{16}H_{23}NO_9$ (373.1): C, 51.47; H, 6.21%; found: C, 51.18; H, 6.40%.

Compound 8: Colourless oil; $[\alpha]_D$ + 5 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.82 (d, *J* = 9.2 Hz, 1 H, N*H*), 5.25 (t, *J* = 9.0 Hz each, 1 H, H-3), 5.05 (dd, *J* = 10.2 and 7.8 Hz, 1 H, H-2), 4.97-4.91 (m, 2 H, H-2′ and H-4′), 4.73 (t, *J* = 9.1 Hz each, 1 H, H-1), 4.64 (s, 1 H, olefinic H),

4.48 (d, *J* = 7.7 Hz, 1 H, H-1′), 4.38 (dd, *J* = 10.3 and 1.4 Hz, 1 H, H-3′), 4.11-4.05 (m, 3 H, H-4 and H-$6_{a,b}$), 3.90-3.87 (m, 1 H, H-5), 3.77-3.68 (m, 2 H, H-6′$_{a,b}$), 3.66-3.64 (m, 1 H, H-5′), 3.63 (s, 3 H, COOCH_3), 2.16 (s, 3 H, CH_3), 2.12, 2.10, 2.07, 2.06, 2.04, 2.01, 1.96 (7 s, 21 H, 7 COCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.2 (2 C), 170.1 (2 C), 169.9 (2 C), 169.7, 169.1, 158.5 (C-1″), 101.5 (C-1′), 89.2 (C-3″), 82.2 (C-1), 76.8, 74.5, 73.2, 77.4, 71.3, 71.0, 69.4, 66.9, 62.7 (C-6′), 61.1 (C-6), 50.8 (COO*C*H_3), 21.1 (2 C), 20.9 (3 C), 20.8 (2 C), 19.1; ESI-MS: 756 $[M+Na]^+$; Anal. Calcd. for $C_{31}H_{43}NO_{19}$ (733.2): C, 50.75; H, 5.91%; found: C, 50.52; H, 6.20%.

Compound 10: Colourless oil; $[\alpha]_D$ + 51 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.85 (d, *J* = 9.0 Hz, 1 H, N*H*), 5.39 (d, *J* = 3.9 Hz, 1 H, H-1′), 5.35-5.27 (dt, *J* = 9.6 Hz each, 2 H, H-2 and H-3), 5.04-4.96 (t, *J* = 9.8 Hz, 1 H, H-2′), 4.85-4.79 (ddt, *J* = 9.8 Hz each, 3 H, H-1, H-3′ and H-4′), 4.64 (bs, 1 H, olefinic H), 4.38 (dd, *J* = 12.0 and 2.6 Hz, 1 H, H-6_a), 4.25-4.16 (m, 3 H, H-4, H-5 and H-6_b), 4.0-3.92 (m, 3 H, H-5′ and H-6′$_{a,b}$), 3.62 (s, 3 H, COOCH_3), 2.15 (s, 3 H, CH_3), 2.10, 2.05, 2.04 (3 s, 9 H, 3 COCH_3), 2.03 (s, 6 H, 2 COCH_3), 2.02, 2.0 (2 s, 6 H, 2 COCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.4, 170.3 (2 C), 170.1, 169.9, 169.7, 169.5, 169.3, 158.3 (C-1″), 95.6 (C-1′), 89.1 (C-3″), 81.8 (C-1), 75.9, 75.6, 73.3, 73.1, 70.2, 69.5, 68.7, 68.2, 63.4 (C-6′), 61.7 (C-6), 50.5 (COO*C*H_3), 20.8 (2 C), 20.7 92 C), 20.6 (2 C), 20.5, 18.7; ESI-MS: 756.2 $[M+Na]^+$; Anal. Calcd. for $C_{31}H_{43}NO_{19}$ (733.2): C, 50.75; H, 5.91%; found: C, 50.52; H, 6.15%.

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[12] **Crystallography data of compound 2**: $C_{19}H_{27}NO_{11}$, M = 445.42, monoclinic, $P2_1$, a = 11.501(2), b = 8.602(1), c = 12.070(2) Å, β = 95.32(2)°, V = 1189.0(3) Å^3, T = 293(2)K, Z = 2, D_c= 1.244 gcm^{-3}, μ = 0.10mm^{-1}, $F_{(000)}$ =472, λ (Mo K_α) = 0.71073 Å, colourless block, crystal size 0.200 x 0.050 x 0.225 mm, 2928 reflections measured (R_{int} = 0.0480), 2536 unique, $R1$= 0.0473 for 1388 $Fo > 4\sigma(Fo)$ and 0.1134 for all 2536 data, S= 1.020 for all data and 286 parameters. Unit cell determinations and intensity data collection (2θ = 49.16°) was performed on a Bruker P4 diffractometer at 293(2)K. Structure solutions by direct methods and refinements by full-matrix-least-squares methods on F^2. Programs: *XSCANS* [(Siemens Analytical X-ray Instruments Inc.: Madison, Wisconsin, USA 1996) were used for data collection and data processing], *SHELXTL-NT* [(Bruker AXS Inc.: Madison, Wisconsin, USA 1997) was used for structure determination, refinements and molecular graphics]. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK (**CCDC deposit No. 615797**).

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