Journal of Kerbala University , Vol. 9 No.1 Scientific . 2011

Synthesis and NMR Study of Some Important Glucopyranosyl Derivatives

Adnan Ibrahim Mohammed* and Rasha Saad Jwad**
*Department of Chemistry/ College of Science/ University of Kerbala
Kerbala-Iraq
adnanimchem@yahoo.com

** Department of Chemistry/ College of Science/ AL-Nahrain University
Baghdad-Iraq

Abstract

Acetylation of D-glucose using acetic anhydride and sodium acetate gave 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (1). Reaction of (1) with hydrobromic acid in glacial acetic acid gave 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2). S_N2 reaction of (2) with sodium azide in DMF yielded 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (3). Glycosidation of (1) in the presence of tin (IV) chloride afforded 2-Propynyl (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside) (4). All of prepared compounds have been characterized by TLC, FT-IR, ^{1}H NMR, ^{13}C NMR and two dimensional NMR (COSY and HSQC) in order two assign the exact protons and carbons of the glupyranosyl ring.

الخلاصة

تمت عملية أسيلة الكلوكوز بأستخدام حامض الخليك اللامائي وخلات الصوديوم وأعطت المركب الكلوكوز خماسي الخلات(1). فوعل المركب (1) مع حامض الهايدروبروميك المذاب في حامض الخليك الثلجي أنتج بروميد السكر (2). تفاعل التعويض الباحث عن النواة ثنائي الجزيئة للمركب (2) مع أزيد الصوديوم في ثنائي مثيل فورمأمايد أعطى الأزيد السكري (3). تفاعل تكوين الرابطة الكلايكوسيدية للمركب (1) بوجود كلوريد القصدير الرباعي أنتج بروبارجيل السكر(4). شخصت جميع المركبات بأستخدام كروماتوغرافيا الطبقة الرقيقة , طيف الاشعة تحت الحمراء, الرنين النووي المغناطيسي أحادي وثنائي الابعاد.

Introduction

The acetylation of alcohols is an important organic transformation used in the laboratory to protect hydroxyl functionality in a multistep organic synthesis and to promote the isolation and identification of natural products bearing saccharide moiety. It is also used in industry to prepare special chemicals. In carbohydrate chemistry, acetylated sugars are important starting materials for the synthesis of complex oligosaccharides and glycoconjugates [1]. *i.e.* acetobromoglucose has been utilized to produce glycosyl azide [2], *C*-glycosides [3-5], *N*-glycosides [6], nucleosides …..etc.,

C-Glycosidation is of great significance in the organic synthesis of optically active materials, since it allows the introduction of carbon chains to sugar chirons and the use of sugar nuclei as a chiral pool as well as a carbon source [7], while glycosyl azide is widely used in the synthesis of nucleosides [8], aminosugars [9], synthesis of tetrazoles [10] and click chemistry [11-13]. Terminal propargyl glycosides of

glucose, galactose, and mannose also used in click chemistry and as donors in the synthesis of other type of glycosides [14].

Many of literature used the above derivatives do not assigned the protons and carbons of the sugar ring exactly. In the research we synthesized for glucopyranosyl derivatives and characterized them using spectroscopic methods FT-IR, ^{1}H NMR, ^{13}C NMR and two dimensional NMR (COSY and HSQC).

Experimental Part

Materials

Chemical reagents and starting materials were obtained from Ajax and Sigma-Aldrich Chemical.

Instrumentations

Infrared spectra were recorded using AVATAR 320 FT-IR. ^{1}H and ^{13}C NMR spectra were recorded using 300 MHz Bruker DPX spectrometer at the School of Chemistry, University of New South Wales, Australia. Silica TLC plates were used with an aluminum backing (0.2 mm, 60 F_{254}). The reactions were monitored by TLC and visualized by development of the TLC plates with an alkaline potassium permanganate dip.

1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (1) [15]

Acetic anhydride (25 mL, 260 mmol) was added to the mixture of a finely grinded anhydrous sodium acetate (4.0 g, 48.8 mmol) and D-glucose (5.0 g, 28 mmol). The mixture was heated at 50^{o} C with occasion stirring until a clear solution was obtained. The heating was continued for further 2h at the same temperature. The reaction mixture was poured on ice water (250 mL) with stirring gave a white solid, the solid was filtered off, washed with cold water (200 mL) and recrytallized from methanol to give 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (1) (8.80 g, 81 %) as a white solid, mp 132-134 ^{o}C, R_f =0.46 (hexane, EtOAc 1:1), $[\alpha]_D$= +4.1 (*c* 4.5, $CHCl_3$).

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2) (modified procedure) [16]

1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (10 g, 24 mmol) portion wise (0.5 g at a time) to a stirred solution of HBr (33%) in glacial acetic acid (25 mL) at 0 ^{o}C. After all the sugar has been added, the reaction mixture was allowed to warm to room temperature. After 45 min, TLC analysis (hexane:ethyl acetate, 1:1) indicated formation of product (Rf 0.5). The reaction was quenched with ice water (50 mL), extracted with DCM (2 x 60 mL), the combined organic extracts were washed with a solution of $NaHCO_3$ (aq., sat., 2 x 50 mL), dried with Na_2SO_4, filtered and then concentrated in vacuo. The residue was crystallizes from (ether/ light petroleum) to afford 2,3,4,6-tetra-O-acetyl-a-D-glucopyranosyl bromide (2) (9.50 g, 90.0%) as a white crystalline solid, mp 88–90 ^{o}C, R_f =0.73(hexane, EtOAc 1:1). $[\alpha]_D$= +202 (*c* 0.5, $CHCl_3$).

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl azide (3)

Sodium azide (1.95 g, 30 mmol) was added to the stirred solution of glycosyl bromide **(5)** (4.11 g, 10 mmol) in DMF (50 mL), the mixture was heated to 70 ^{o}C for 3 h , the reaction was quenched with water (50 mL) and extracted with ether (3 x 50 mL), the combined organic layers was washed with saturated NaCl (50 mL), water (50 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give the titled compound (3) (3.60g, 97%) as needle crystals, mp. 126-128^{o} C. R_f =0.60 (hexane, EtOAc 1:1), $[\alpha]_D$= -6.1 (*c* 0.5, $CHCl_3$).

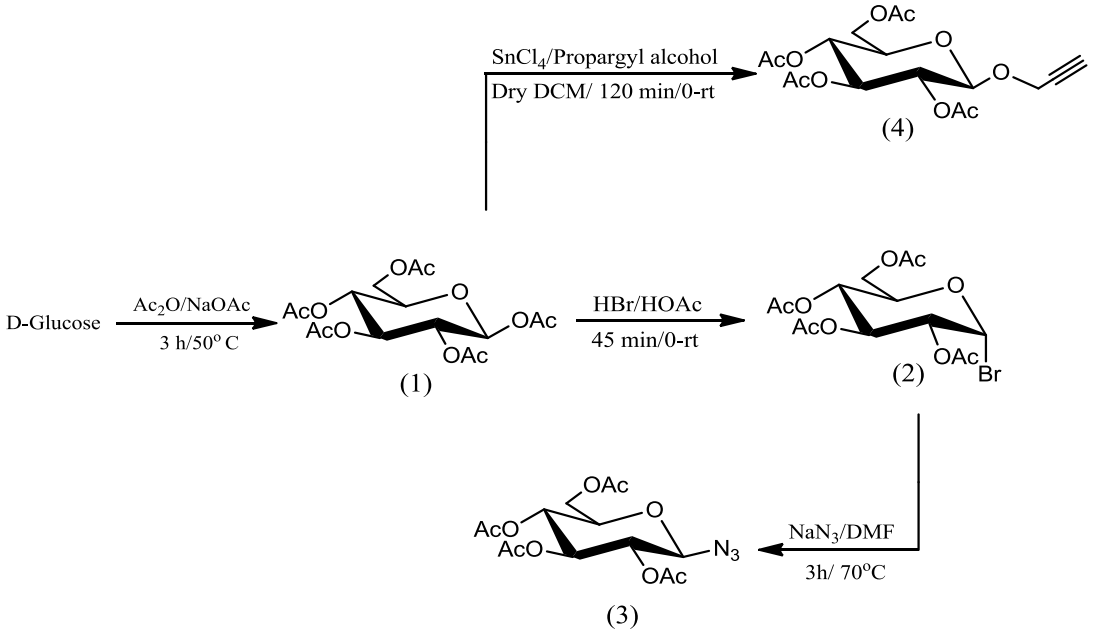
2-Propynyl (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside) (4)

A solution of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (1.95 g, 5 mmol) in dry DCM (50 mL) was cooled to 0 ^{o}C. Stannic chloride (5 mL, 5mmol) was added dropwise, the solution was stirred at 0 ^{o}C

for (15 min) then propargyl alcohol (5.05 mmol) was added, the solution was allow to warm to rt and the stirring was continued for (1.5 h). After which time the solution was diluted with (100 mL) DCM then poured on cooled water (100 mL), the organic layer was separated and washed with a solution of $NaHCO_3$ (aq., sat., 3 x 50 mL) then with water, dried with Na_2SO_4 and concentrated under reduced pressure. Flash chromatography of the residue using silica gel and (hexane, EtOAc 2:1) gave the alkyne (1.55 g, 80%) as needle crystals, mp 114-116^o C. R_f =0.48 (hexane, EtOAc 1:1).

Results and Discussion

The following scheme shows the overall synthetic route of compounds (1), (2), (3) and (4):



Scheme (1) Synthetic route of glucopyranosyl derivatives

The synthesis started by conversion of D-glucose to 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (1) using the traditional acetylaing agent acetic anhydride and sodium acetate gave the β-anomer only in very good yield. FT-IR spectrum of **(3)** showed the following bands in cm^{-1}(nujol): 2923 and 2854 (**C-H**) stretching of nujol [17], 1745 **(C=O)** stretching , 1456 and 1376 (**C-H**) bending nujol, the (**C-H**) stretching and bending bands of the sugar overlap with mineral oil bands, 1229-1044 **(C-O)** stretching. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.01, 2.02, 2.03, 2.08, 2.11 (s, 15H, $CH_{3\ acetate}$), 3.85 (ddd, *J* 9.9, 6.7, 2.2 Hz, 1H, H5), 4.12 (dd, *J* 12.5, 2.2 Hz, 1H, Ha6), 4.26 (dd, *J* 12.5, 4.5 Hz, 1H, Hb6), 5.12 (t, *J* 9.4 Hz, 1H, H4), 5.13 (t, *J* 9.4 Hz, 1H, H2), 5.25 (t, *J* 9.3 Hz, 1H, H3), 5.77 (d, *J* 8.2 Hz, 1H, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.5, 20.7, 20.8 (5C, $CH_{3\ acetate}$), 61.4 (C6), 67.7 (C4), 70.2 (C2), 72.7 (C3), 72.8 (C5), 91.7 (C1), 168.7, 169.2, 169.4, 170.1, 170.6 (5C=O $_{acetate}$).

Table (1) ^{1}H NMR, ^{13}C NMR, COSY and HSQC data of compound (1)

^{1}H NMR ($CDCl_3$)	COSY	^{13}C NMR	HSQC
2.01, 2.02, 2.03, 2.08, 2.11 (s, 15H, CH_3)	-	20.5, 20.7, 20.8	2.01-2.11
3.85 (ddd, *J* 9.9, 6.7, 2.2 Hz, 1H, H5)	4.26	61.4	4.12, 4.26
4.12 (dd, *J* 12.5, 2.2 Hz, 1H, Ha6)	4.26	67.7	5.12
4.26 (dd, *J* 12.5, 4.5 Hz, 1H, Hb6)	3.85, 4.12	70.2	5.13
5.12 (t, *J* 9.4 Hz, 1H, H4)	3.85, 5.25	72.7	5.25
5.13 (t, *J* 9.4 Hz, 1H, H2)	5.25, 5.77	72.8	3.85
5.25 (t, *J* 9.3 Hz, 1H, H3)	5.12, 5.13	91.7	5.77
5.77 (d, *J* 8.2 Hz, 1H, H1)	5.13	168.7, 169.2, 169.4, 170.1, 170.6	-

The treatment of compound **(1)** with HBr/HOAc in dry conditions for 45 min produced acetobromoglucose **(2)** also in very good yield. FT-IR spectrum of **(2)** showed the following bands in cm^{-1}(nujol): 1743 **(C=O $_{acetate}$)** stretching and 1165 (**CH-Br**) bending (wagging). The (**C-Br**) stretching band should be out of spectrum because it appears around 550 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.02, 2.03, 2.08, 2.08 (s, 12H, $CH_{3\ acetate}$), 4.14 (ddd, *J* 13.9, 3.5, 1.5 Hz, 1H, Ha6), 4.26 (m, 1H, H5), 4.29 (dd, *J* 13.6, 3.6 Hz, 1H, Hb6), 4.84 (dd, *J* 10.0, 4.1 Hz, 1H, H2), 5.14 (tt, *J* 10.2, 1.5, 1H, H4), 5.54 (t, *J* 9.7 Hz, 1H, H3), 6.60 (d, *J* 4.1 Hz, 1H, H1). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.5, 20.6, 20.6, 20.6 (4C, $CH_{3\ acetate}$), 60.9 (C6), 67.1 (C4), 70.1 (C3), 70.5 (C2), 72.1 (C5), 86.5 (C1), 169.4, 169.7, 169.8, 170.5 (4C=O $_{acetate}$).

Table (2) ^{1}H NMR, ^{13}C NMR, COSY and HSQC data of compound (2)

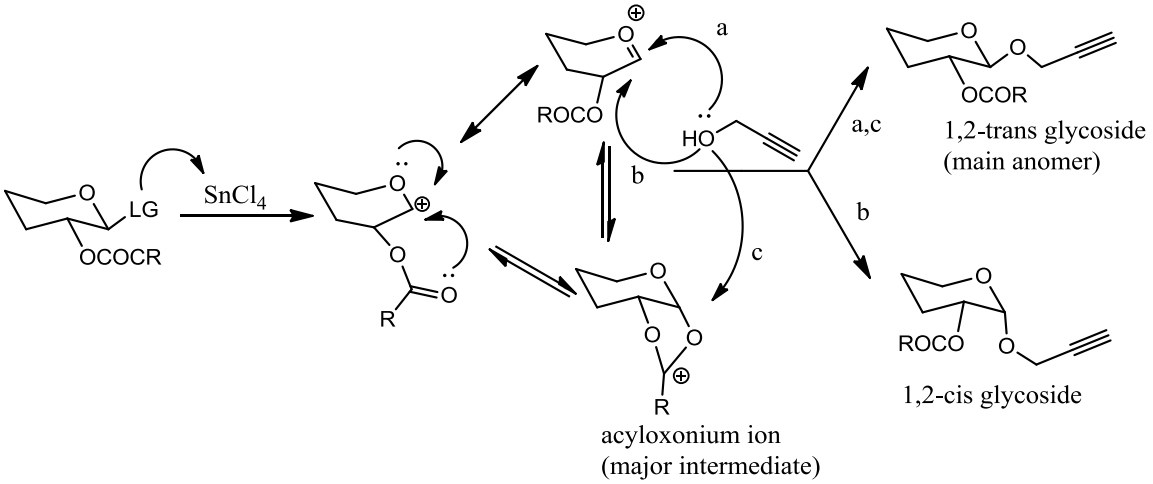
^{1}H NMR ($CDCl_3$)	COSY	^{13}C NMR	HSQC
2.02, 2.03, 2.08, 2.08 (s, 12H, CH_3)	-	20.5, 20.6, 20.6, 20.6	2.02-2.08
4.14 (ddd, *J* 13.9, 3.5, 1.5 Hz, 1H, Ha6)	4.29	60.9	4.14, 4.29
4.26 (m, 1H, H5)	4.29, 5.14	67.1	5.14
4.29 (dd, *J* 13.6, 3.6 Hz, 1H, Hb6)	4.14, 4.26	70.1	5.54
4.84 (dd, *J* 10.0, 4.1 Hz, 1H, H2)	5.54, 6.60	70.5	4.84
5.14 (tt, *J* 10.2, 1.5, 1H, H4)	4.26, 5.54	72.1	4.26
5.54 (t, *J* 9.7 Hz, 1H, H3)	4.84, 5.14	86.5	6.60
6.60 (d, *J* 4.1 Hz, 1H, H1)	4.84	169.4, 169.7, 169.8, 170.5	-

The S_N2 reaction between glycosyl bromide **(2)** and sodium azide in DMF for 3 hrs gave glycosyl azide **(3)** in quantitative yield due to the nucleophile strength (N_3^-) and the neighboring group participation of acetate in position **2** of the sugar. FT-IR spectrum of **(3)** showed the following important bands in cm^{-1}(nujol): 2118 (**-N_3**) stretching, 1754 and 1732 **(C=O $_{acetate}$)** stretching. ^{1}H NMR (300 MHz, $CDCl_3$) δ: δ: 1.99, 2.01, 2.06, 2.08 (s, 12H, $CH_{3\ acetate}$), 3.79 (ddd, *J* 9.8, 4.8, 2.3 Hz, 1H, H5), 4.17 (dd, *J* 12.5, 2.4 Hz, 1H, Ha6), 4.27 (dd, *J* 12.5, 4.5 Hz, 1H, Hb6), 4.65 (d, *J* 8.8 Hz, 1H, H1), 4.94 (t, *J* 9.4, 1H, H2), 5.09 (t, *J* 9.9 Hz, 1H, H4), 5.21 (t, *J* 9.4 Hz, 1H, H3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.5, 20.5, 20.7 (4C, $CH_{3\ acetate}$), 61.6 (C6), 67.8 (C4), 70.6 (C2), 72.5 (C3), 73.9 (C5), 87.9 (C1), 169.2, 169.3, 170.1, 170.6 (4C=O $_{acetate}$).

Table (3) ^{1}H NMR, ^{13}C NMR, COSY and HSQC data of compound (3)

^{1}H NMR ($CDCl_3$)	COSY	^{13}C NMR	HSQC
1.99, 2.01, 2.06, 2.08 (s, 12H, CH_3)	-	20.5, 20.5, 20.7	1.99-2.08
3.79 (ddd, *J* 9.8, 4.8, 2.3 Hz, 1H, H5)	4.27, 5.09	61.6	4.17, 4.27
4.17 (dd, *J* 12.5, 2.4 Hz, 1H, Ha6)	4.27	67.8	5.09
4.27 (dd, *J* 12.5, 4.5 Hz, 1H, Hb6)	3.79, 4.17	70.6	4.94
4.65 (d, *J* 8.8 Hz, 1H, H1)	4.94	72.5	5.21
4.94 (t, *J* 9.4, 1H, H2)	4.65, 5.21	73.9	3.79
5.09 (t, *J* 9.9 Hz, 1H, H4)	3.79, 5.21	87.9	4.65
5.21 (t, *J* 9.4 Hz, 1H, H3)	4.94, 5.09	169.2, 169.3, 170.1, 170.6	-

Glycosidation of glucosepenaacetate (1) with propargyl alcohol in the presence of stannic chloride afforded the glycoside (4) in very good yield. $SnCl_4$ plays a great role in activation of the anomeric acetate beside the acetate group in position 2 as shown in the scheme below:



Scheme (2) Mechanism of formation of the glycoside bond (the role of $SnCl_4$ and neighboring group participation)

FT-IR spectrum of **(4)** showed the following important bands in cm^{-1}(nujol): 3273 **(C-H $_{alkyne}$)**, 2118 (**C≡C**) stretching, 1758 and 1732 **(C=O $_{acetate}$)** stretching. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.99, 2.00, 2.04, 2.07 (s, 12H, $CH_{3\ acetate}$), 2.46 (t, *J* 2.4 Hz, 1H, H3`), 3.72 (ddd, *J* 9.8, 4.8, 2.4 Hz, 1H, H5), 4.11 (dd, *J* 12.4, 2.4 Hz, 1H, Ha6), 4.25 (dd, *J* 12.4, 4.5 Hz, 1H, Hb6), 4.35 (d, *J* 2.4 Hz, 2H, H1`), 4.77 (d, *J* 7.9 Hz, 1H, H1), 4.99 (dd, *J* 9.4, 7.9 Hz, 1H, H2), 5.08 (t, *J* 9.9 Hz, 1H, H4), 5.23 (t, *J* 9.4 Hz, 1H, H3). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.6, 20.6, 20.7 (4C, $CH_{3\ acetate}$), 55.9 (C1`), 61.7 (C6), 68.2 (C4), 70.9 (C2), 71.8 (C5), 72.7 (C3), 75.5 (C3`), 78.0 (C2`), 98.1(C1), 169.4, 169.4, 170.2, 170.6 (4C=O $_{acetate}$).

Table (4) ^{1}H NMR, ^{13}C NMR, COSY and HSQC data of compound (4)

^{1}H NMR ($CDCl_3$)	COSY	^{13}C NMR	HSQC
1.99, 2.00, 2.04, 2.07 (s, 12H, CH_3)	-	20.6, 20.6, 20.7	1.99-2.07
2.46 (t, *J* 2.4 Hz, 1H, H3`)	4.35	55.9	4.35
3.72 (ddd, *J* 9.8, 4.8, 2.4 Hz, 1H, H5)	4.25, 5.08	61.7	4.11, 4.25
4.11 (dd, *J* 12.4, 2.4 Hz, 1H, Ha6)	4.25	68.2	5.08
4.25 (dd, *J* 12.4, 4.5 Hz, 1H, Hb6)	3.72, 4.11	70.9	4.99
4.35 (d, *J* 2.4 Hz, 2H, H1`)	2.46	71.8	3.72
4.77 (d, *J* 7.9 Hz, 1H, H1)	4.99	72.7	5.23
4.99 (dd, *J* 9.4, 7.9 Hz, 1H, H2)	4.77, 5.23	75.5	2.46
5.08 (t, *J* 9.9 Hz, 1H, H4)	3.72, 5.23	78.0	-
5.23 (t, *J* 9.4 Hz, 1H, H3)	4.99, 5.08	98.1	4.77
		169.4, 169.4, 170.2, 170.6	

Acknowledgement

Thanks for Austraining International, Department of Education, Employment and Workplace Relations (DEEWR) Australia for the postdoctoral research fellowship also to the School of Chemistry, The University of New South Wales (UNSW) Sydney especially to Associate Professor Dr. Roger Read for his support.

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