Synthesis of 1-Nonyl-4-[(6-Deoxy-1,2:3,4-Di-*O*-Isopropylidene-α-D-Galactos-6-yl)oxymethyl]1*H*-1,2,3-Triazole *Via* Click Chemistry

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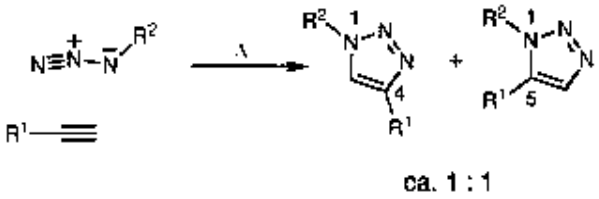
Abstract

The S_N2 reaction of nonyl bromide with sodium azide in DMF afforded Nonyl azide (1).D-galactose has been protected by acetone in acidic medium gave 1,2:3,4-di-O-isopropylidene-α-D-galactose (2). Williamson etherfication of (2) with propargyl bromide and sodium hydroxide yielded 6-O-(2-Propynyl)-1,2:3,4-di-O-isopropylidene-α-D-galactose(3). [2+3] Cycloaddition of (3) to nonyl azide using Click conditions afforded1-Nonyl-4-[(6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactose-6-yl)oxymethyl]1H-1,2,3-triazole(4). All prepared compounds have been characterized by FT-IR ,^{1}H NMR and ^{13}CNMR.

Keywords: triazoles, click chemistry, isopropylidene-α-D-galactose.

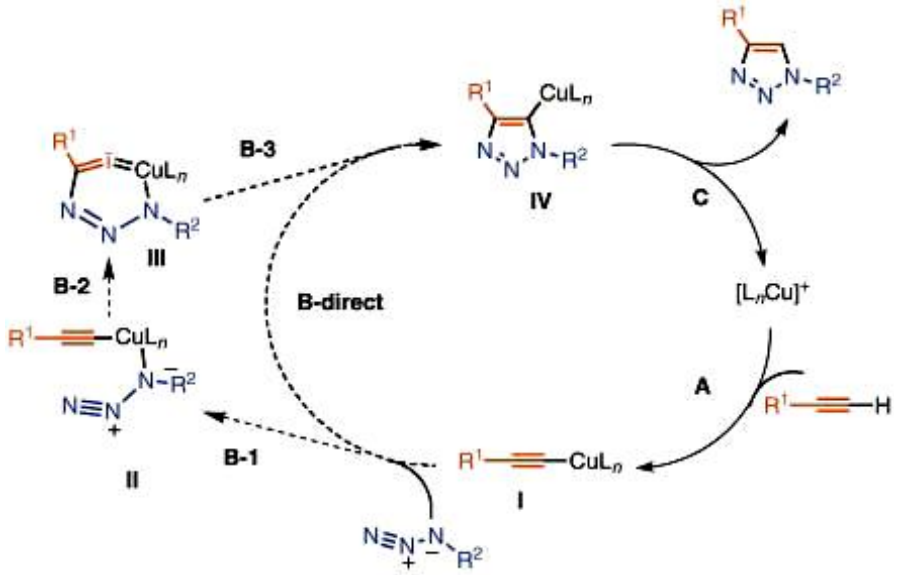
Introduction

1,2,3-Triazoles are an important class of heterocycles due to their wide range of applications as synthetic intermediates and pharmaceuticals. Several therapeutically interesting 1,2,3-triazoles have been reported, including anti-HIV agents [1], antimicrobial compounds, kinase inhibitors and other enzyme inhibitors [2]. The 1,3-dipolar cycloaddition reaction of alkyl azides and acetylenes always gives 1,4- and 1,5-disubstituted 1,2,3-triazoles in approximately 1:1 ratio (Scheme (1)) [3].



Scheme (1) 1,3-dipolar cycloaddition of organic azides to alkynes.

V. Rostovtsev [4] *etal.* reported the term "click" when prepared only 1,4-disubstituted 1,2,3-trizoles from organic azides and terminal acetylenes using Cu(I) as a catalyst. The proposed mechanism of click chemistry shown in Scheme (2):



Scheme (2) Cu(I) catalyzed synthesis of 1,2,3-triazoles "'click mechanism" [4].

Chiral macrocycles containing the sucrose skeleton were prepared by click chemistry in high selectivity and in good yields [5]. Y. Ali *etal* prepared high yield water soluble 1,2,3-trizole starting from D-mannose using Cu(I) as a catalyst [6]. Novel one-pot three- and four-component transformations of D-glucal to furan-based hydroxy triazoles glycoconjugates have been synthesized by sequential addition of reagents in the presence of $Cu(OTf)_2$-Cu powder as catalysts [7]. 5-azido-5-deoxy glycofuranoses clicked with different alkynes gave the corresponding sugar triazoles in very good yields. The synthesized sugar triazoles were evaluated for their antitubercular activity against Mycobacterium tuberculosis H37Rv, where one of the compounds displayed mild antitubercular activity in vitro with MIC12.5 lμg/mL [8]. Different thymidine derivatives have been efficiently synthesized as precursors for carbon-11 or fluorine-18 labeling compounds. Furthermore, iodoarylated thymidine derivatives have been incorporated (via 1,2,3-triazole ring) into oligonucleotides giving an original way to label them with carbon-11.[9]. In our work we prepared 1,2,3-triazole derivative starting from D-galactose, all the prepared compounds have been fully characterized.

Experimental Part

Chemicals and Instruments

Chemical reagents and starting materials were obtained from Ajax and Sigma-Aldrich. Infrared spectra were recorded using AVATAR 320 FT-IR. ^1H and ^{13}C NMR spectra were recorded using 300 MHz Bruker DPX spectrometers at The University of New South Wales, Sydney, Australia. Microelemental analysis was performed with Elemental Analyzer EA-300 Eurovector. 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.

Synthesis of Nonyl Azide (1)

Sodium azide (1.95 g, 30 mmol) was added to a solution of nonyl bromide (1.69 g, 10 mmol) in DMF (50 mL). The suspension was stirred at 70°C overnight. The reaction mixture was diluted with water (100 mL), extracted with Et_2O (3×50 mL). The combined organic layers were washed with brine (2×25 mL), dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was chromatographed (silica gel, light petroleum) to give nonyl azide as a colorless oil (1.62 g, 96%), R_f = 0.61 (light petroleum).

Synthesis of 1,2:3,4-di-O-isopropylidene-α-D-galactose(2)[10]

Zinc chloride (8.87 g, 0.088 mol) was partially dissolved in acetone (125 mL) and conc. sulfuric acid (0.4 mL) was added at room temperature to give a clear solution. D-galactose (10 g, 0.056 mol) was added in one portion and the resulting white suspension was stirred for 6 h at room temperature. A suspension of sodium carbonate (20 g, 0.189 mol) in water (30 mL) was added to the yellow reaction mixture at 0 ºC in medium sized portions. The suspension was allowed to stir for 30 min before filtration and solvent removal in vacuo to give the crude product as yellow oil below the aqueous layer. The organic fraction was separated from the aqueous layer, followed by further extraction with diethyl ether (3 × 50 mL). The organics were dried over sodium sulfate, and the solvent removed in vacuo to yield 1,2:3,4-di-O-isopropylidene-α-D-galactose(2) as a pale yellow oil (20 g, 87 %), R_f = 0.23 (Et_2O).

Synthesis of 6-O-(2-Propynyl)-1,2:3,4-di-O-isopropylidene-α-D-galactose(3)

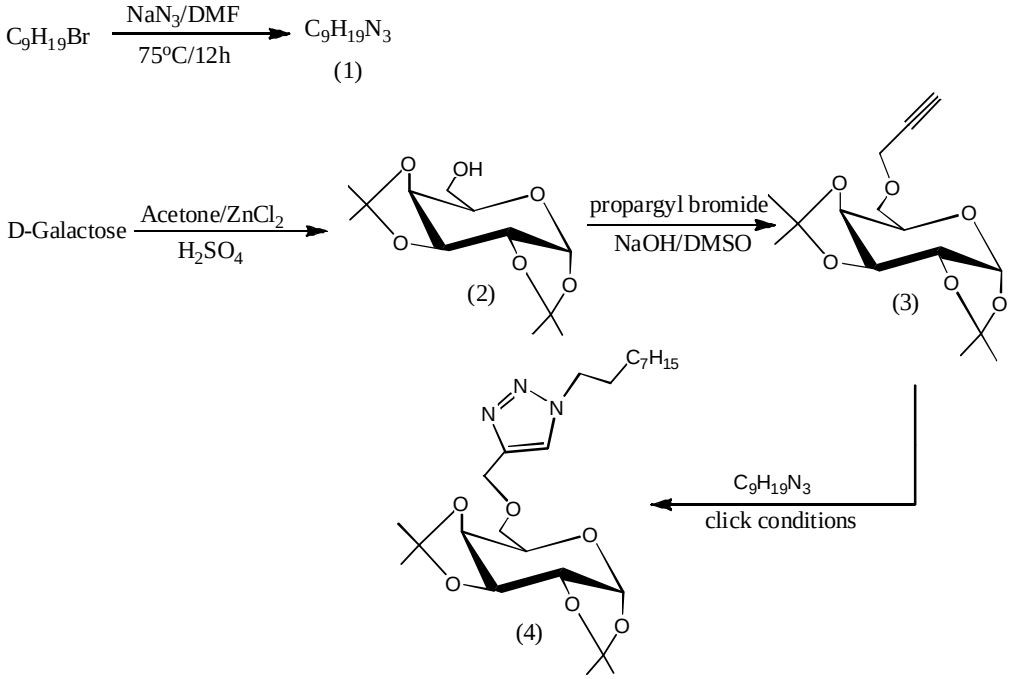
Alcohol **(2)** (6.0 g, 23.5 mmol) was dissolved in DMSO (50 mL) and powdered NaOH pellets (3.2 g, 80 mmol) were added. The contents were stirred in a salt-ice bath for 10 min then propargyl bromide (2.5 mL, 28.2 mmol) was added dropwise. The reaction mixture allowed to stir for 24 h, gradually warming to r.t. The reaction mixture was partitioned between Et_2O (100 mL) and water (150 mL) and the aqueous layer extracted with more Et_2O (3 × 50 mL). The combined organic extracts were dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was chromatographed (silica gel, Et_2O/light petroleum 1:1) to give 6-O-(2-Propynyl)-1,2:3,4-di-O-isopropylidene-α-D-galactose(3) as needles (5.5 g, 80%), R_f = 0.43 (hexane:Et_2O, 1:1), m.p. 75-77°C.

Synthesis of 1-Nonyl-4-[(6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactose-6-yl)oxymethyl]1*H*-1,2,3-triazole(4)

Alkyne **(3)** (2.98 g, 10 mmol) was added dropwise to a solution of sodium ascorbate (0.178 g, 0.90 mmol) and $CuSO_4$•$5H_2O$ (0.112 g, 0.45 mmol) in DMF/H_2O 2:1 (30 mL). The bright yellow-green solution was stirred for 1 min before nonyl azide **(1)** (1.70 g, 10 mmol) was added dropwise, then stirring was continued in a bath at 75°C for 30 h. The reaction mixture was diluted with water (75 mL), extracted with Et_2O (3 × 50 mL), the combined organic layers were washed with brine (2 × 25 mL), dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was chromatographed (silica gel, Et_2O/hexane 1:1) to give 1-Nonyl-4-[(6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactose-6-yl)oxymethyl] 1H-1,2,3-triazole**(4)** as pale yellow syrup (3.5 g, 75%), R_f = 0.31 (hexane:Et_2O, 1:1) (Found: C, 61.43, H, 8.70; N, 8.86. $C_{24}H_{41}N_3O_6$ requires C, 61.65; H, 8.84; N, 8.99 %)

Results and Discussion

The work started by conversion of nonyl bromide to nonyl azide (1) using S_N2 reaction followed by three steps to get the target compound, the overall work steps shown in scheme below:



Scheme (3) Synthetic route of galactosyl triazoles.

FT-IR spectrum of (1) showed the following band cm^{-1}(neat): 2987, 2916 and 2848 **(C-H)** stretching, 2105 **(-N_3)** stretching, 1454 **(C-H)** bending, 1382 **(C-H)** bending. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.88 (t, *J* 6.9 Hz, 3H, H9), 1.27 (m, 12H, H3-H8), 1.59 (m, 2H, H2), 3.25 (t, *J* 6.9 Hz, 2H, H1). ^{13}C NMR (75 MHz, $CDCl_3$)δ ppm: 13.9 (C9), 22.5 (C8), 26.6 (C7), 28.7(C6), 29.04 (C5), 29.09 (C4), 29.3 (C3), 31.7 (C2) and 51.3 (C1).

The reaction of D-galactose with acetone in the presence of zinc chloride and sulfuric acid afforded compound (2) in very good yield.

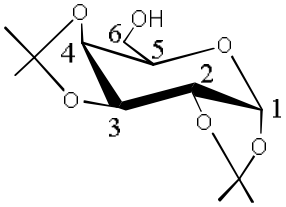


Fig.(1) Numbering of carbons in compound (2).

FT-IR spectrum of (2) showed the following band cm^{-1}(neat): 3311 (**O-H**) stretching, 2923 and 2854 (**C-H**) stretching, 1459 and 1376 (**C-H**) bending, 1219-1066 **(C-O)** stretching. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 1.32 (s, 6H, $2CH_3$), 1.44,

1.52 (s, 6H, $2CH_3$), 2.37 (broad s, 1H, OH), 3.73 (m, 1H, Ha6), 3.83 (m, 2H, Hb6 and H5), 4.27 (dd, *J* 7.92, 1.6 Hz, 1H, H4), 4.32 (dd, *J* 5.0, 2.4 Hz, 1H, H2), 4.61 (dd, *J* 7.92, 2.4 Hz, 1H, H3), 5.56 (d, *J* 5.0 Hz, 1H, H1). ^{13}C NMR (75 MHz, $CDCl_3$)δ ppm: 24.3, 24.9, 25.9, 26.0 (4C, CH_3), 62.3 (C6), 68.1 (C5), 70.5 (C2), 70.7 (C3), 71.5 (C4), 96.3 (C1), 108.6, 109.4 (2C, isopropylidene).Williamson etherification of compound (2) with propargyl bromide in DMSO in the presence of sodium hydroxide as a catalyst yielded compound (3) in very good yield.

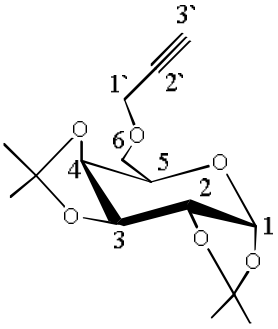


Fig.(2) Numbering of carbons in compound (3).

FT-IR spectrum Fig.(4) of (3) showed the following band cm^{-1}(nujol): 3251 (**C-H** acetylenic) stretching 2921, 2853 (**C-H**) stretching of paraffin [11], 2114 (**C≡C**) stretching, 1458, 1376 (**C-H**) bending paraffin, 1220-1057 (**C-O**) stretching. The appearance of the band at 3251 and 2114 is very good evidence of formation of the alkyne. The (**C-H**) stretching and bending bands of the sugar overlap with mineral oil bands. ^{1}H NMR Fig.(5) (300 MHz, $CDCl_3$) δ ppm: 1.32, 1.34, 1.45, 1.54 (s, 12H, $2CH_3$), 2.42 (t, *J* 2.4 Hz, 1H, H3`), 3.66 (dd, *J* 10.1, 7.1 Hz, 1H, Ha6), 3.76 (dd, *J* 10.1, 5.3 Hz, 1H, Hb6), 3.99 (m, 1H, H5), 4.22 (dd, *J* 15.9, 2.4 Hz, 1H, Ha1`), 4.24 (dd, *J* 15.9, 2.4 Hz, 1H, Hb1`), 4.27 (dd, *J* 8.0, 2.0 Hz, 1H, H4), 4.32 (dd, *J* 5.0, 2.4 Hz, 1H, H2), 4.61 (dd, *J* 7.9, 2.4 Hz, 1H, H3), 5.54 (d, *J* 5.0 Hz, 1H, H1). $^{13}$C NMR fig (7) (75 MHz, $CDCl_3$)δ ppm: 24.4, 24.9, 25.9, 26.0 (4C, $CH_3$), 58.5 (C1`), 66.7 (C5), 68.7 (C6), 70.4 (C2), 70.6 (C3), 71.2(C4), 74.6 (C3`), 79.6 (C2`), 96.3 (C1), 108.6, 109.3 (2C, isopropylidene).

[2+3] Cycloaddition of alkyne (3) to nonyl azide using Click conditions afforded1-Nonyl-4-[(6-deoxy-1,2:3,4-di-O-isopropylidene-α-D-galactose-6-yl)oxymethyl]1H-1,2,3-triazole(4) as a syrup in good yield and exclusively in 1,4-disubstiuted 1,2,3-triazole. Simply, click conditions depend on formation of copper acetylide which yield from the reaction of terminal acetylenes and Cu $^{1+}$ ion, the Cu $^{1+}$ ion either generates in situ from sodium ascorbate and one of Cu^{2+} salts like copper sulfate pentahydarte, cooper acetate,…etc. or using one of the Cu^{1+} salts like CuI, CuCl,...etc. with base. We followed the first type of conditions (as mechanism that mentioned in introduction).

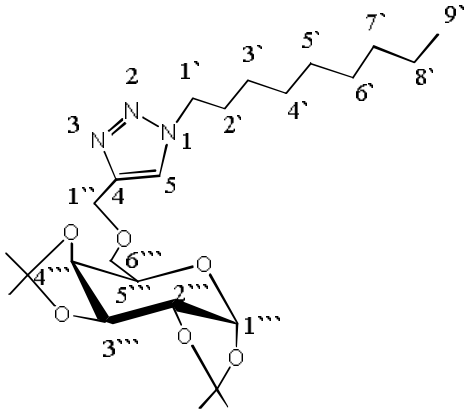


Fig.(3) Numbering of carbons in compound (4).

FT-IR spectrum Fig. (9) of comp (4) showed the following band cm^{-1}(neat): 3138 (**C-H $_{triazole}$**) stretching, 2925, 2856 (**C-H $_{aliphatic}$**) stretching, 1460, 1380, and 1307 (**C-H $_{aliphatic}$**) bending 1212-1005 (**C-O**) stretching, 918 and 891 (**C-H $_{triazole}$**) bending out of plane (oop). ^{1}H NMR Fig.(10) (300 MHz, $CDCl_3$) δ ppm: 0.85 (t, *J* 6.8 Hz, 3H, H9`), 1.22-1.51 (m, 12H, H3`-H8` and s, 12H, $CH_3$), 1.88 ( broad m, 2H, H2`), 3.69 (m, 2H, H6```), 3.99 (t, 2H, H1`), 4.21-4.34 (m, 3H, H5```, H4```, H2```), 4.59 (dd, *J* 7.9, 2.4 Hz, 1H, H3```), 4.71 (s, 2H, H1``), 5.52 (d, *J* 5.1 Hz, 1H, H1```), 7.57 (s, 1H, H5 $_{triazole}$). ^{13}C NMR Fig. (12) (75 MHz, $CDCl_3$)δ ppm: 14.0-31.7 (8C, C2`-C9` and 4C, CH_3), 50.5 (C5```), 64.7 (C1``), 66.7 (C1`), 69.3 (C6```), 70.4 (C4```), 70.6 (C3```), 71.1 (C2```), 96.3 (C1```), 108.5, 109.2 (2C, isopropylidene), 122.4 (C5), 144.9 (C4).

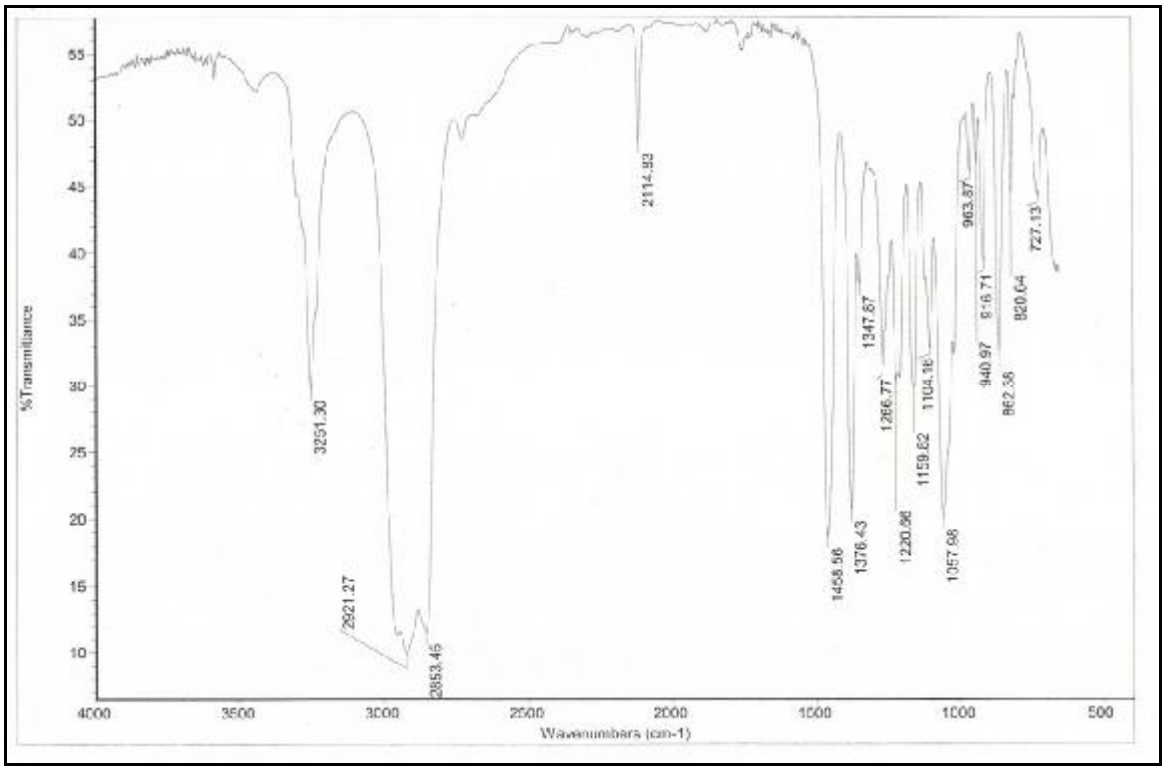


Fig.(4) FT-IR spectrum of compound (3).

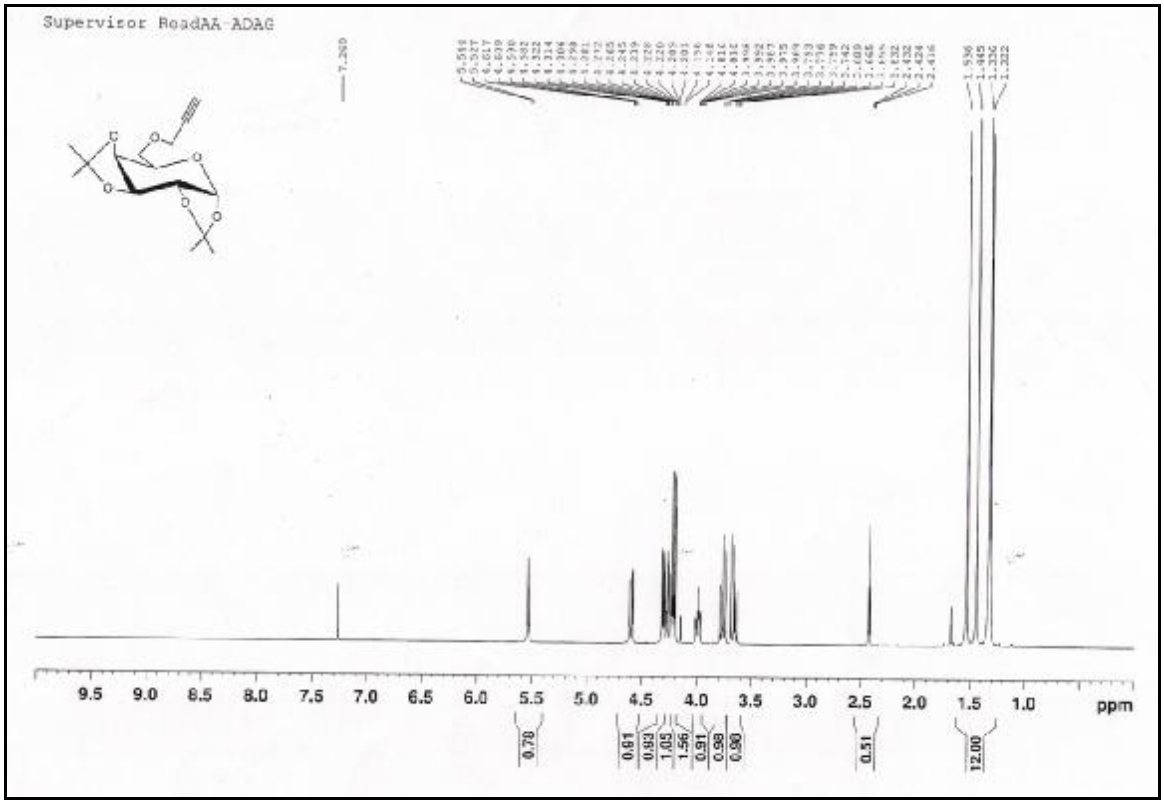


Fig.(5) ^{1}H NMR spectrum of compound (3).

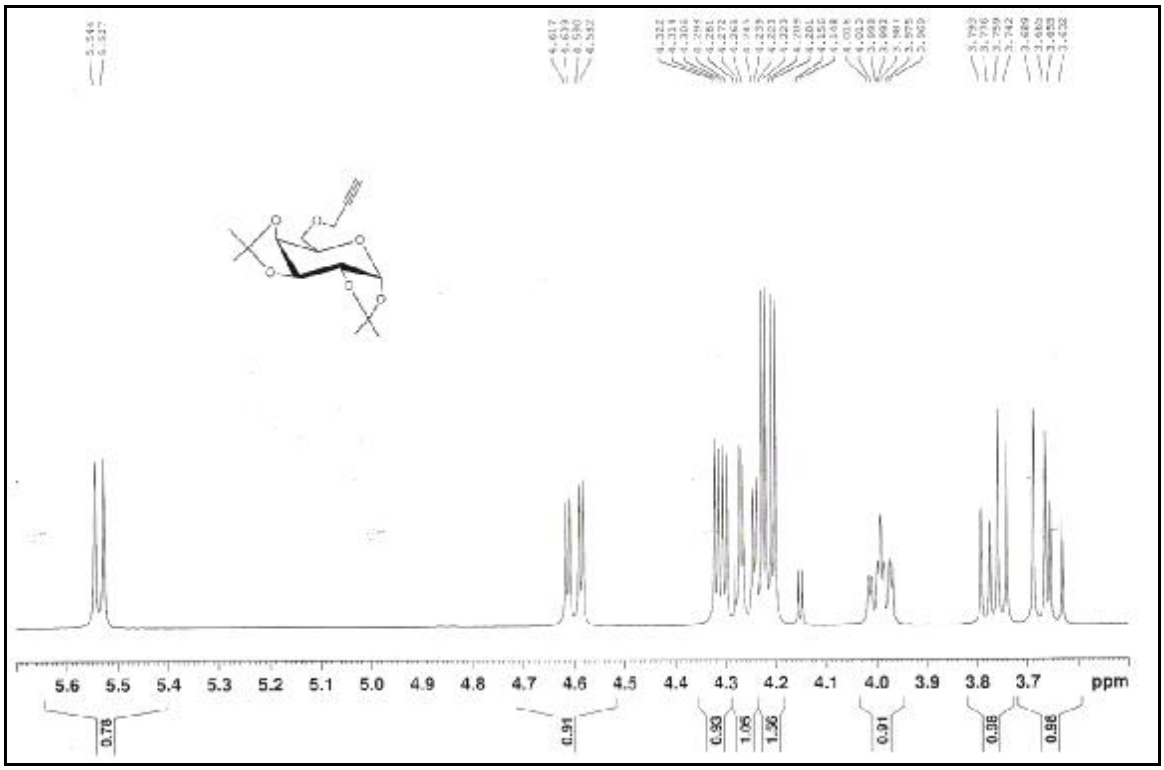


Fig. (6) ^{1}H NMR expansion of compound (3).

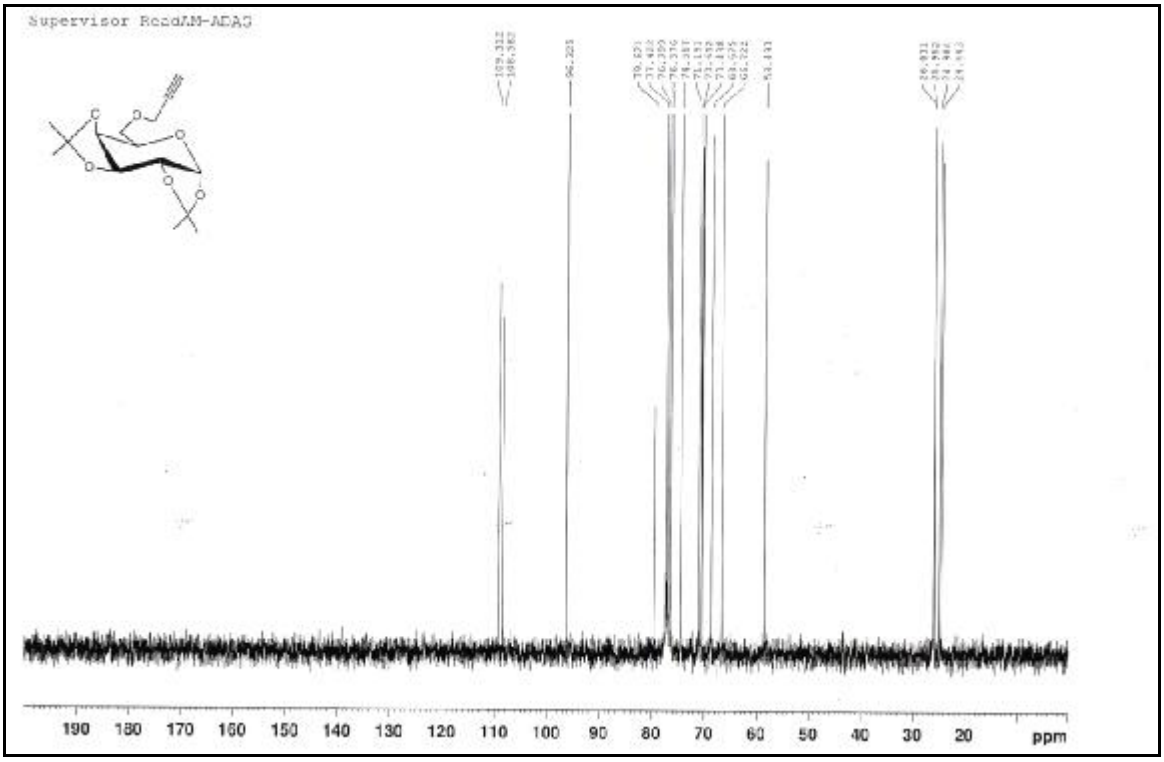


Fig.(7) ^{13}C NMR spectrum of compound (3).

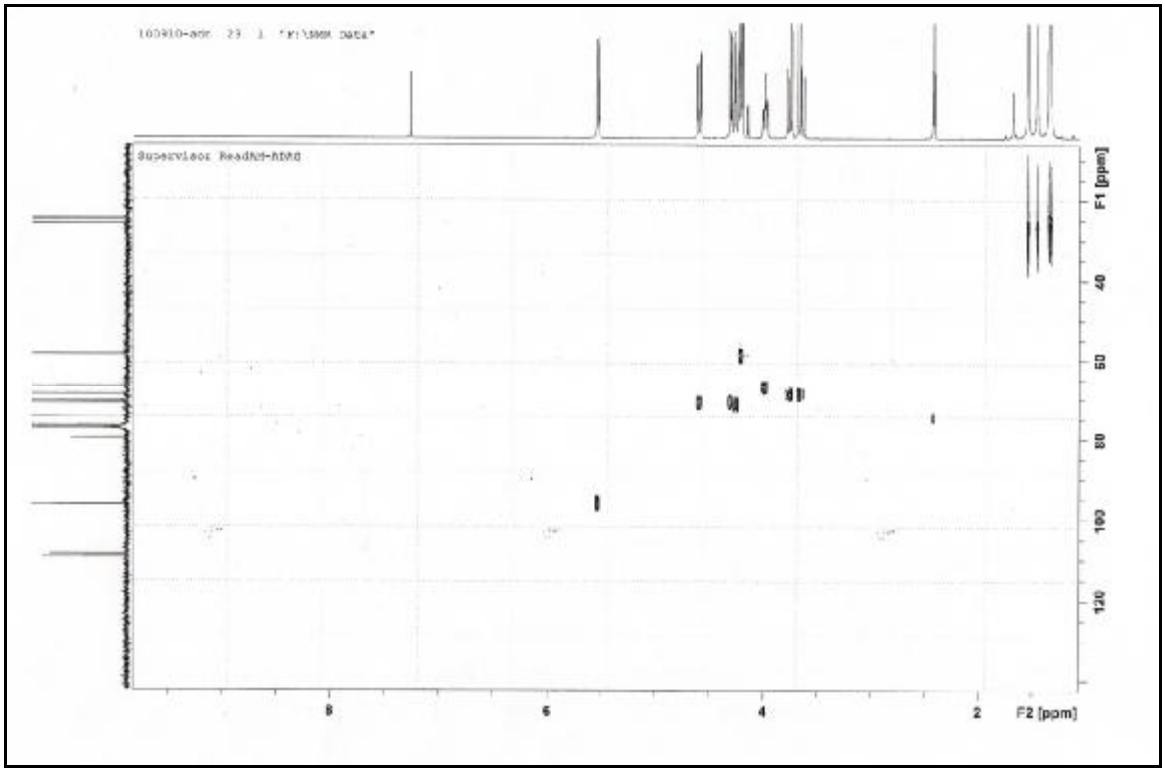


Fig. (8) Two dimensional NMR HSQC spectrum of compound (3).

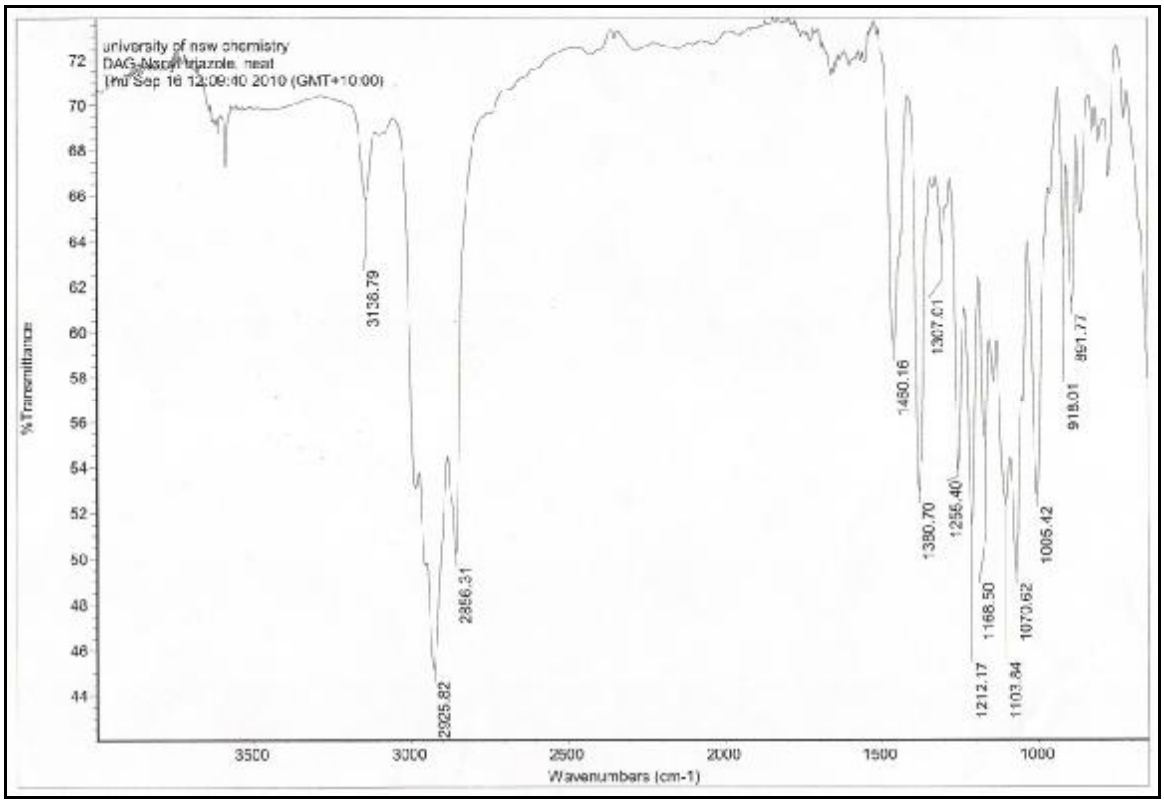


Fig.(9) FT-IR spectrum of compound (4).

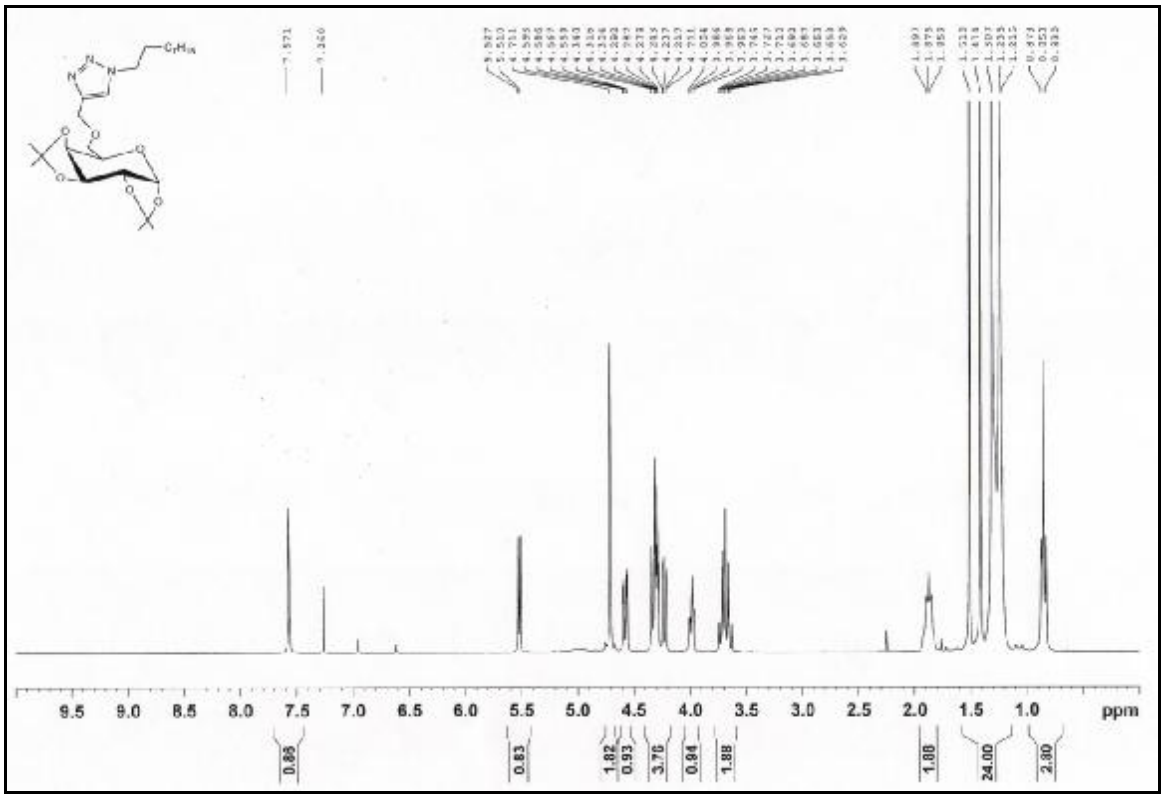


Fig. (10) ^{1}H NMR spectrum of compound (4).

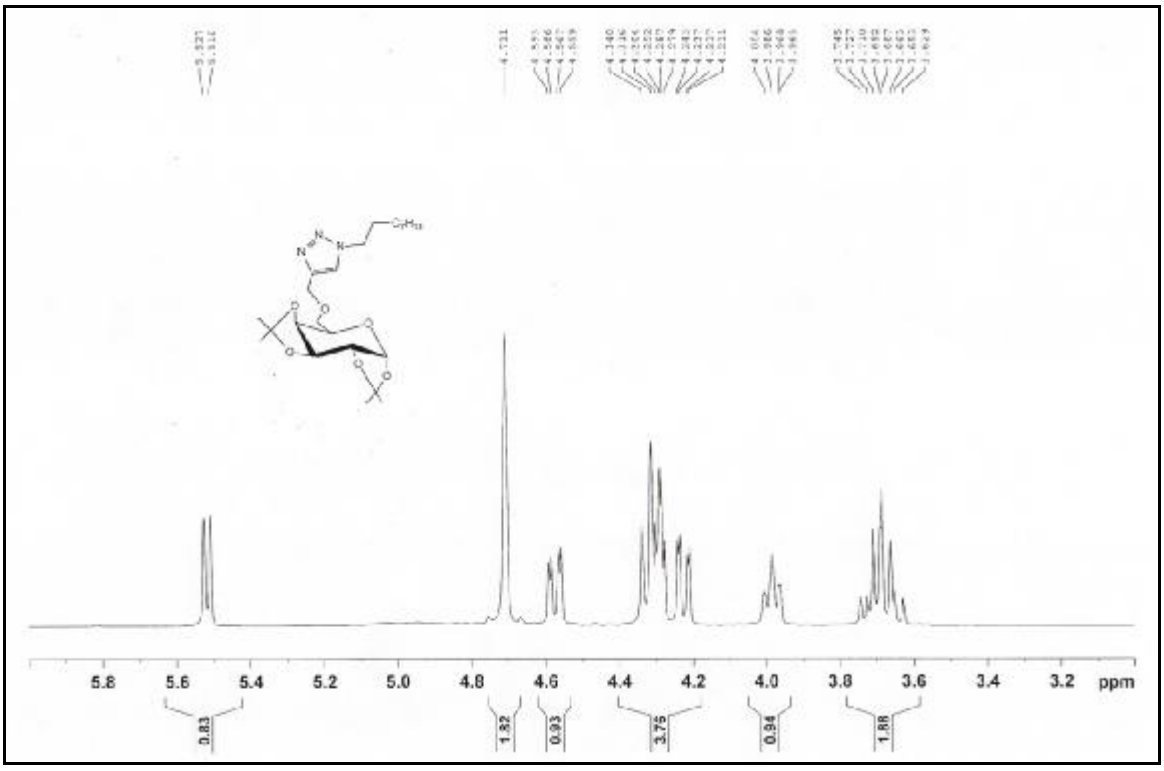


Fig.(11) ^{1}H NMR expansion of compound (4).

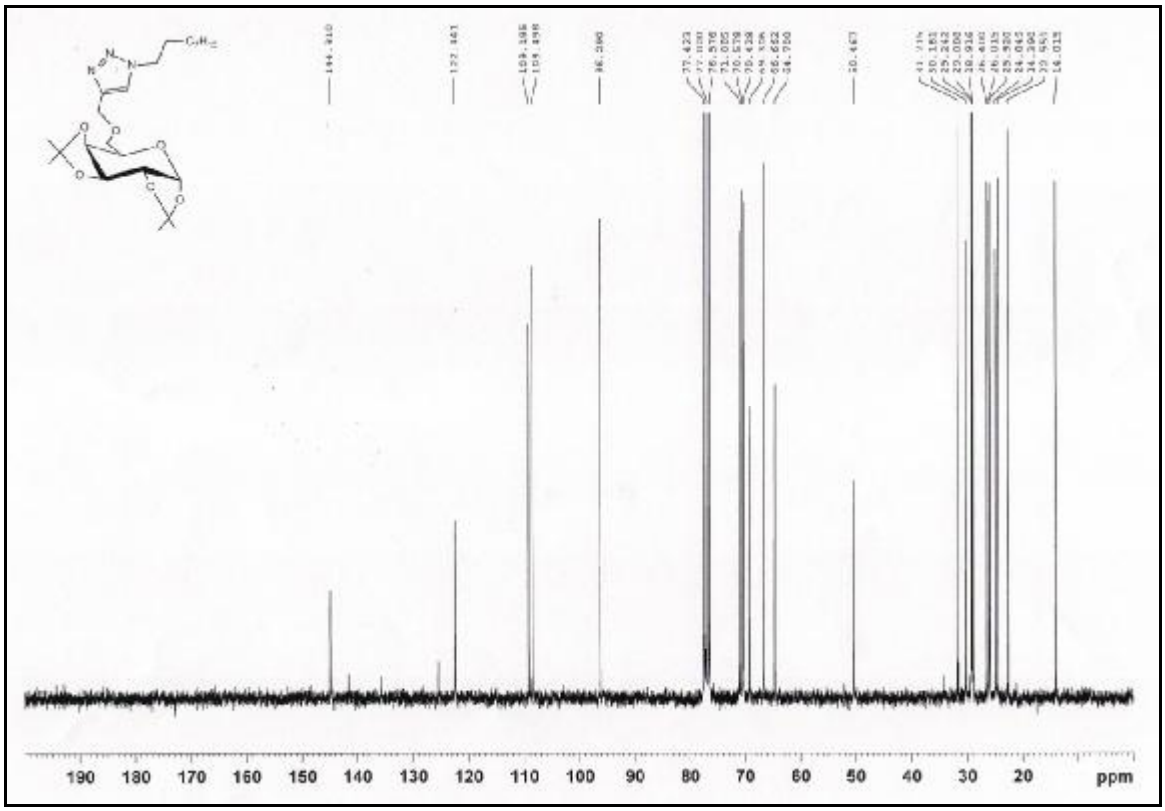


Fig. (12) ^{13}C NMR expansion of compound (4).

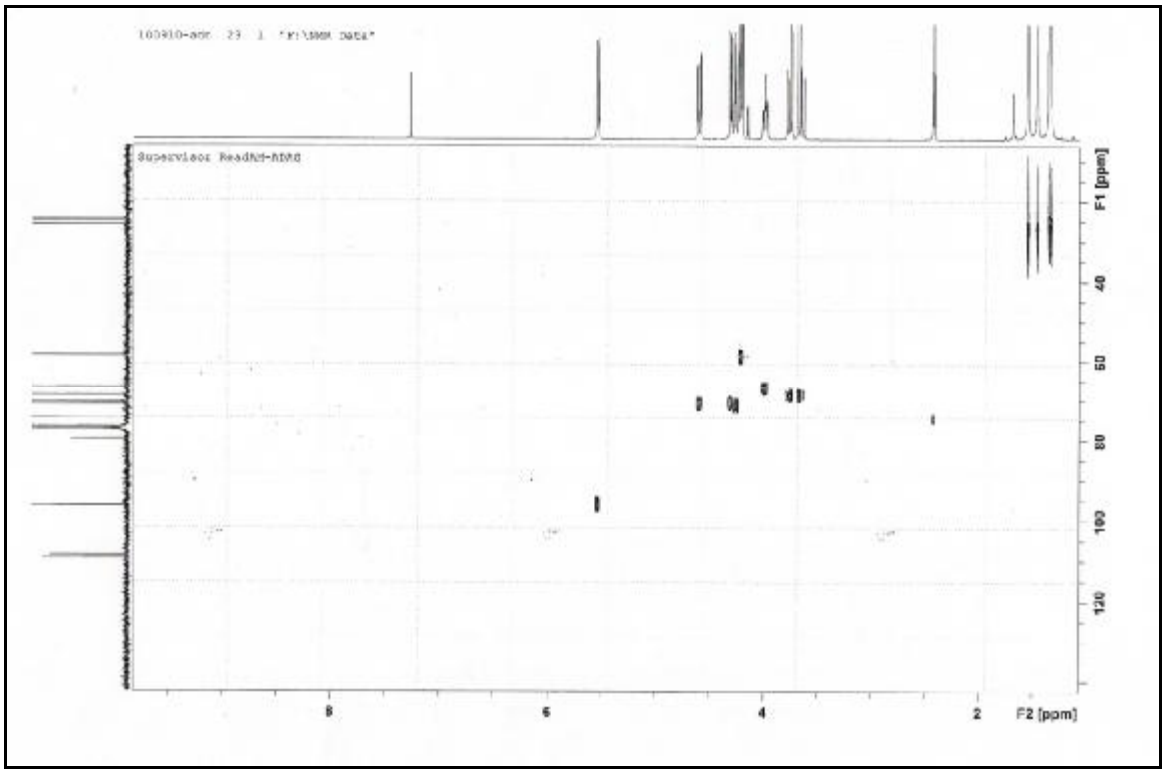


Fig. (13) Two dimensional NMR HSQC spectrum of compound (4).

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الخلاصة

تفاعل التعويض ثنائي الجزيئة لمركب بروميد النونيل مع أزيد الصوديوم في ثنائي مثيل فورماأميد أعطى أزيد النونيل (1).تم حماية د-كالكتوزبمفاعلته مع الاسيتون بالوسط الحامضي ليعطي 4,3:2,1-ثنائي-O–ايزوبروبايلدين د-كالكتوز(2).أجري تفاعل وليمسن لتكوين الايثر للمركب (2) مع بروميد البروبرجيل بوجود هيدروكسيد الصوديوم ليعطي 6-O-(2-بروباينيل)-4,3:2,1-ثنائي -o–ايزوبروبايلدين د-كالكتوز(3). الاضافة الحلقية للمركب (1) الى المركب (3) بأستخدام ظروف Click أعطت المركب 1-نونايل -4-((6-منقوص الاوكسجين-4,3:2,1-ثنائي -O–ايزوبروبايلدين د-كالكتوز-6-يل)أوكسي مثيل)-1,2,3- ترايزول(4). تم تشخيص جميع المركبات المحضرة بأستخدام طيف الاشعة تحت الحمراء وطيف الرنين النووي المغناطيسي .