Synthesis of New Sugar Based Triazoles and Bis-Triazoles via Click Chemistry

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ABSTRACT
Two types of new triazoles have been synthesized from two essential sugars D-glucose and D-mannitol. The reaction of D-mannitol with acetone in acidic media gave 1,2:5,6-di-O-isopropylidene-D-mannitol (1), Williamson etherification of (1) with propargyl bromide catalyzed by NaOH yielded (2). The [2+3] cycloaddition of compound (2) with glycosyl azide (5) using click conditions gave the targeted 1,4-disubstituted triazoles (6) and (7).

INTRODUCTION
The reaction of a terminal alkyne with a substituted azide was discovered by Arthur Michael 116 years ago (Figure 1). Later, R. Huisgen carried out systematic studies of this particular reaction and other 1,3-dipolar cycloadditions.(1) However, it was only after the publication of the copper(I)-catalyzed variant that the potential of the transformation could be fully exploited. The chemistry was subsequently further developed in parallel by the groups of Meldal(2) and Sharpless(3) and became synonymous with the broader concept of ‘Click chemistry’, also known as copper(I) catalyzed cycloaddition of an alkyne and azide (Figure 2).

Figure - 1: Traditional triazole formation 1,4 and 1,5 regioisomers
The 1,2,3-triazole system has widespread uses, and it has been considered as an interesting component in terms of biological activity (5,6). Although the use of heterocyclic moieties in peptidomimetics has been widely reported, the application of 1,2,3-triazoles in the field of conformational studies has occurred only recently (7). The generation of N-glycosyl-triazoles from simple acetylenes, sugar, amino acid and steroid-derived terminal acetylenes (C-linked alkynes, O-propargyl ethers, ynamides) has been reported (8,9). Recently, new methods technologies have been used for the synthesis of triazoles like; ultrasound (10) and microwave (11). In this work we prepared two new triazoles starting from D-glucose using click conditions.

**MATERIALS AND METHODS**

**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 spectrometers. Microelemental analysis was performed with Elemental Analyzer EA-300 Eurovector. Mass spectra were recorded using Waters 996 Micromass. 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 1,2:5,6-di-O-isopropylidene-d-mannitol[1] (12)
To a suspension of zinc chloride (60 g) in (300 mL) of anhydrous acetone, finely powdered D-mannitol (10 g, 55 mmol) was added. The mixture was stirred vigorously at room temperature until the D-mannitol dissolved (3 hr) then allowed to stand for (16 hr). the reaction mixture was poured into a solution of K$_2$CO$_3$(50g in 100 mL water) and stirred for (30 min) then extracted with ether (3x100 mL), dried and evaporated under reduced pressure to give a solid residue. Recrystallization of the solid from light petroleum (40-60 °C) gave the product as a white solid (9.0 g, 63%), mp 122-124° C. Microelemental analysis for C$_{12}$H$_{22}$O$_6$ calculated: C, 54.95; H, 8.45, found: C, 54.90; H, 8.43.

Synthesis of 3,4-O-Dipropargyl-1,2:5,6-di-O-isopropylidene-d-mannitol [2]
1,2:5,6-Di-O-isopropylidene-d-mannitol (1) (1.018 g, 3.00 mmol) was dissolved in DMF (30 mL), to this was added crushed NaOH (0.48 g, 12 mmol) and the mixture was stirred for 10 minutes. Propargyl bromide (1.77 mL, 8.54 mmol) was added and the mixture was stirred for a further 24 hours. The reaction was quenched with water (30 mL) and and extracted with ether (3 x 30 mL). The combined organic layers were washed sat. NH$_4$Cl (3 x 20 mL), water, dried over Na$_2$SO$_4$, filtered and the solvent was evaporated under reduced pressure to yield a pale yellow oil. Purification by column chromatography (Alumina, 3:1 light petroleum: ether) yielded 3,4-O-propargyl-1,2:5,6-di-O-isopropylidene-d-mannitol as needle crystals (1.15 g, 83 %) mp 95-97° C. Microelemental analysis for C$_{18}$H$_{26}$O$_6$ calculated: C, 63.89; H, 7.74, found: C, 63.85; H, 7.70.

Synthesis of Glucopyranose pentaacetate [3]
A solution of pyridine (75 ml)/acetic anhydride (50 ml) 3:2 (v/v) was cooled in an ice bath under nitrogen. D-glucose (10 g, 45 mmol) was added, the suspension was stirred until the sugar dissolved then allowed to warm to room temperature and stirred for a further 16 h under nitrogen. After this time, the solution was poured into ice water (200 mL); α-D-glucopyranose pentaacetate was crystallized out rapidly, filtered, washed with cooled water and dried under vacuum (19.4 g, 90%); mp 113-114°C; later crops yielded β-D-glucopyranose pentaacetate.;[$\alpha$]$_D$ +105 (c 1.0, CHCl$_3$). Microelemental analysis for C$_{16}$H$_{22}$O$_{11}$ calculated: C, 49.23; H, 5.68, found: C, C, 49.27; H, 5.65.

Synthesis of 2,3,4,6-Tetra-O-acetyl-α-D-glucopyranosyl bromide [4]
1,2,3,4,6-penta-O-acetyl-α-D-glucopyranose (10 g, 25.40 mmol) portion wise (0.5 g at a time) to a stirred solution of HBr (33%) in glacial acetic
Synthesis of New Sugar Based Triazoles and Bis-Triazoles via Click Chemistry

Adnan

Acid (25 mL) at 0 °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 NaHCO₃ (aq., sat., 2 x 50 mL), dried with Na₂SO₄, filtered and then concentrated in vacuo. The residue was crystallizes from ether/petrol to afford 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl bromide (8.80 g, 83%) as a white crystalline solid, mp 87–89 oC; [α]D +202 (c 0.5 in CHCl₃). Microelemental analysis for C₁₄H₁₉BrO₉ calculated: C, 40.89; H, 4.66; Br, 19.43, found: C, 40.91; H, 4.70; Br, 19.47.

Synthesis of 2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl azide [5]

Sodium azide (1.95 g, 30 mmol) was added to the stirred solution of glycosyl bromide (5) (4.10 g, 10 mmol) in DMF (50 mL), the mixture was heated to 70 °C for (3hrs), the reaction was quenched with water (50 mL) and extracted with ether (3 x 50 mL), the combined organic layers was washed with brine (50 mL), water (50 mL), dried over Na₂SO₄ and evaporated under reduced pressure to give the titled compound (1.73 g, 98%) as a white crystalline solid, mp 102-104; [α]D -18 (c 0.5 in CHCl₃). Microelemental analysis for C₁₄H₁₉N₃O₉ calculated: C, 45.04; H, 5.13; N, 11.26, found: C, 45.08; H, 5.15; N, 11.30.

Synthesis of Triazoles [6] and [7]

A solution of compound (2) (2.05 mmol) in DMF (2 mL) was added to the suspension of CuI (3.1 mmol) and diethylisopropylamine (DEIPA) (3.15 mmol) in DMF (5 mL). Glycosyl azide (3.00 mmol) was added and the mixture was heated at 70 °C for (24 h). The solution was diluted with water (20 mL) and extracted with EtOAc (3x25 mL), the combined organic layers dried over Na₂SO₄ and evaporated under reduced pressure. Flash chromatography of the residue (Silica, 3:1 ether, light petroleum) produced the titled compounds.

Compound (6), white solid (0.50 g, 46%), mp 141-143. Microelemental analysis for C₄₆H₆₄N₆O₂₄ calculated: C, 50.92; H, 5.95; N, 7.75, found: C, 50.91; H, 5.97; N, 7.78, MS (FAB) m/z: 1107 ([M + Na⁺]).

Compound (7), white solid (0.26 g, 37%), mp 127-129. Microelemental analysis for C₃₂H₄₅N₃O₁₅ calculated: C, 54.00; H, 6.37; N, 5.90, found: C, 54.05; H, 6.41; N, 5.93. MS (FAB) m/z: 734 ([M + Na⁺]).
RESULTS AND DISCUSSION

The triazoles (6) and (7) were prepared according to the following scheme:

![Diagram of the reaction scheme]

Reagents and conditions: (a) Acetone, ZnCl₂ rt 3 hrs; (b) propargyl bromide, NaOH, DMF rt 24 h; (c) Ac₂O, pyridine rt 16 h; (d) 33% HBr/AcOH 0-rt 1 h; (e) NaN₃, DMF 70°C 3 hrs; (f) CuI, DEIPA, DMSO, 24 h 70°C.

The work commenced by the reaction of D-mannitol with anhydrous acetone in the presence of zinc chloride as an acidic catalyst to give the diacetonomannitol (1), FT-IR bands in cm⁻¹ (nujol): 3461 and 3311 (O-
Synthesis of New Sugar Based Triazoles and Bis-Triazoles via Click Chemistry

Williamson etherification of compound (1) using propargyl bromide and crushed sodium hydroxide in DMF at room temperature yielded compound (2). FT-IR spectrum of (2) showed the following bands in cm\(^{-1}\) (nujol): 3251 (≡C-H) stretching, 2986 (C-H\textsubscript{propargyl}) stretching, 2935 and 2884 (C-H) stretching which overlapped with mineral oil bands, 2114 (C≡C) stretching, (C-H) bending at 1458, 1376 and 1347, and different (C-O) stretching 1266-1057. \(^1\)H NMR (300 MHz (CDCl\(_3\)) δ ppm: 4.36 (dd, J = 2.3, 1.9 Hz, 4H, CH\(_2\)C≡C), 2.45 (t, J = 1.7 Hz, 2H, C≡CH), the same coupling constant of the mentioned signals shows there is a long range coupling between the acetylenic proton and the other two protons, the other signals due to the rest of the sugar molecule. \(^1\)C NMR (300 MHz (CDCl\(_3\)) δ ppm: 79.7 (2C, CH\(_2\)-C≡CH), 74.6 (2C, CH\(_2\)-C≡CH), 59.4 (2C, CH\(_2\)-C≡CH). The two dimensional NMR spectrum HC Heteronuclear Single Quantum Coherence (HSQC) shown below supports the above signals assignment. The other signals are belong to the rest of the sugar molecule.

Figure – 3: Two dimensional NMR HSQC expansion of compound (2)
Keeping the D-glucose in the acetylation mixture acetic anhydride/pyridine for 16 h gave the glucose pentaacetate (3). FT-IR spectrum of (3) showed the following bands in cm\(^{-1}\)(nujol): 1745 (C=O) stretching and 1229-1044 (C-O) stretching. \(^1\)H NMR (300 MHz (CDCl\(_3\)) \(\delta\) ppm: 5.72 (d, \(J =7.9\) Hz, 1H, H-1), 5.25 (t, \(J =9.3\) Hz, 1H, H-4), 5.16 (t, \(J =9.0\) Hz, 1H, H-3), 5.13 (t, \(J =9.0\) Hz, 1H, H-2), 4.30 (dd, \(J =8.0\) Hz, \(J =4.5\) Hz 2H, H-6\(_a\) and b), 3.84 (ddd, \(J =9.9\) Hz, \(J =4.9\) Hz, \(J =2.3\) Hz, 1H, H-5), 2.12, 2.09, 203 and 2.01 (s, 15H, CH\(_3\) acetate). The signal at 1.56 ppm attributed to water in CDCl\(_3\).

\(^1\)H NMR (300 MHz (CDCl\(_3\)) \(\delta\) ppm: 6.60 (d, \(J =4.1\) Hz, 1H, H-1), 5.55 (t, \(J =10.1\) Hz, 1H, H-3), 4.83 (dd, \(J =10.0\) Hz, \(J =4.0\) Hz, 1H, H-2), 4.30 (m, 2H, H-5 and H-6\(_a\)), 4.12 (dt, \(J =9.2\) Hz, \(J =2.0\) Hz, 1H, H-6\(_b\)), 2.10, 2.09, 205 and 2.03 (s, 14H, CH\(_3\) acetate). The \(^1\)H NMR data gave an excellent confirmation for glycosyl bromide due to the shift of the anomeric proton signal downfield from 5.75 ppm to 6.60 ppm, also the change of integration of (CH\(_3\)) signals. The coupling constant value of the anomeric proton 4.1 Hz indicates that the bromide formed in \(\alpha\)-conformation only.

\(^1\)C NMR (300 MHz (CDCl\(_3\)) \(\delta\) ppm: 170.4, 169.7 and 169.4 (4C, C=O acetate), 86.4 (1C-C1), 72.0 (1C-C4), 70.4 (1C-C3), 69.9 (1C-C6), 60.8 (1C-C5) and 20.5 (4C-CH\(_3\) acetate).

The \(\text{SN}_2\) reaction between glycosyl bromide (4) and sodium azide in DMF for 3 hrs gave glycosyl azide (5) 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 (5) 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\(_3\)) \(\delta\) ppm: 5.20 (t, \(J =9.4\) Hz, 1H, H-4), 5.09 (t, \(J =9.3\) Hz, 1H, H-3), 4.94 (t, \(J =8.9\) Hz, 1H, H-2), 4.64 (d, \(J =8.8\) Hz, 1H, H-1), 4.20 (ddd, \(J =13.5\) Hz, \(J =9.0\) Hz, 3.1 2H, H-6\(_a\) and b), 3.84 (ddd, \(J =9.2\) Hz, \(J =4.1\)Hz, \(J =2.9\) Hz, 1H, H-5), 2.08, 2.06, 2.01 and 1.99 (s, 15H, CH\(_3\) acetate). \(^1\)C NMR (300 MHz (CDCl\(_3\)) \(\delta\) ppm: 170.5, 170.0, 169.2 and 169.1 (4C, C=O acetate),
Synthesis of New Sugar Based Triazoles and Bis-Triazoles via Click Chemistry

Adnan

87.8 (1C-C1), 73.9 (1C-C4), 72.4 (1C-C3), 70.51 (1C-C2), 67.7 (1C-C6), 61.5 (1C-C5), 20.5 and 20.4 (4C-CH$_3$ acetate).

![Figure 4: Numbering the final compounds](image)

The cycloaddition of glycosyl azide (5) to the diacetylene (2) using click conditions in DMF at 70°C for 24 h afforded the two targeted triazoles (6) and (7). FT-IR spectrum of (6) showed the following important bands in cm$^{-1}$ (nujol): 3069 (C-H triazole) stretching, 1754 and 1737 (C=O) stretching. To explain the NMR data we numbered the final compounds as follows:

$^1$H NMR (300 MHz (CD$_3$)$_2$SO) δ ppm: 8.40 (s, 2H, H-5), 6.32 (d, $J$ =8.8 Hz, 2H, H-1$^\text{iii}$), 5.67 (t, $J$ =8.9 Hz, 2H, H-4$^\text{iii}$), 5.53(t, $J$ =8.9 Hz, 2H, H-3$^\text{iii}$), 5.16 (t, $J$ =8.8 Hz, 2H, H-2$^\text{iii}$), 4.67 (q, $J$ =7.9 Hz, 4H, H-6$^\text{iii}$), 4.34 (dd, $J$ =7.8 Hz, $J$ =4.1 Hz, $J$ =2.0 Hz, 2H, H-5$^\text{iii}$), 4.07 (m, 6H, H-1$^\text{i}$, H-3$^\text{iii}$ and H-4$^\text{iii}$), 3.90 (t, $J$ =6.4 Hz, 2H, H-2$^\text{iii}$ and H-5$^\text{iii}$), 3.74 (dd, $J$ =6.1 Hz, $J$ =4.2 Hz, 4H, H-1$^\text{iii}$ and H-6$^\text{iii}$), 3.33 (water), 2.49 (m, DMSO$^{(14)}$, 2.07, 2.01, 1.97, 1.94, 1.26 and 1.24 (s, 36H, CH$_3$ acetate and isopropylidene).

The other compound produced from the above cycloaddition is compound (7), we will explain the major differences in spectra between the two compounds (6) and (7). FT-IR spectrum of (7) showed the following new band cm$^{-1}$ (nujol): 3278 (≡C-H) stretching, 3072 (C-H triazole) stretching, very week band at 2116 (C≡C) stretching and 1750 (C=O) stretching.

$^1$H NMR (300 MHz (CD$_3$)$_2$SO) δ ppm: 4.25 (t, $J$ =2.5 Hz, 2H, H-1$^\text{iii}$), 3.46 (t, $J$ =2.4Hz, 1H, H-3$^\text{iii}$) in addition to the same signals of compound (6) but with half integration. Also the $^{13}$C NMR (300 MHz (CD$_3$)$_2$SO) spectrum of (7) showed almost the same signals of (6) with the following changes δ ppm: (4C, C=O acetate) around 170.0, 76.4 (1C, C-3$^\text{iii}$), 107.8 (1C, C-1$^\text{iii}$). The two dimensional NMR (HSQC) spectrum figure (5) gives an excellent the above signals assignment.
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