Short Note

(4aS, 5S, 6aR, 10aR, 10bR)-5-Methoxy-9,9-Dimethyl-4a, 5,6a, 7,10a, 10b-Hexahydro-12H-[1,3]dioxino[4′, 5’:5,6]pyrano[4,3-b][1,2, 3]triazolo[1,5-d][1,4]oxazine

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Abstract: A new tetracyclic morpholine-fused [5,1-*c*]-triazole, (4a*S*,5S,6a*R*,10a*R*,10b*R*)-5-methoxy-9,9-dimethyl-4a,5,6a,7,10a,10b-hexahydro-12*H*-[1,3]dioxino[4',5':5,6]pyrano[4,3-b][1,2,3]triazolo[1,5-d][1,4]oxazine, was synthesized *via* a five-step sequence starting from methyl *α*-D-glucopyranoside by using as a key step an intramolecular copper(I) catalyzed alkyne-azide cycloaddition (CuAAC). The synthesized compound was fully characterized by ^{1}H and ^{13}C NMR, FT-IR, and HRMS.

Keywords: 1,2,3-triazoles; click chemistry; carbohydrates; morpholine-fused [5,1-*c*]-triazole

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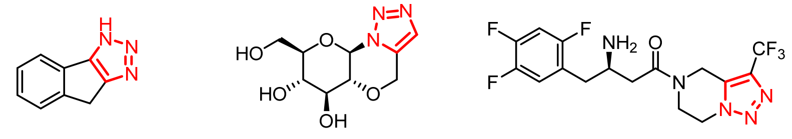
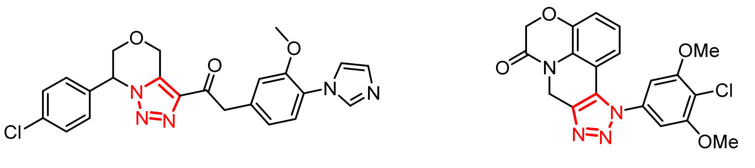
1. Introduction

The development of fused heterocyclic systems has gained great attention in the field of medicinal chemistry [1] and materials science [2]. Fused heterocycles are found in many natural products, pharmaceutical and synthetic compounds. Particularly, compounds containing fused 1,2,3-triazoles have shown some interesting biological applications. For example, as an antidiabetic [3], in the treatment of Alzheimer's disease [4], as anticancer [5] or antitumor agents [6], etc. (Figure 1). Therefore, developing efficient strategies for the access to fused 1,2,3-triazoles continues to be of great interest [7].



Indene fused 1,2,3-triazole Sugar fused 1,2,3-triazole Piperidine fused 1,2,3-triazoles



Morpholine fused 1,2,3-triazole Oxazinoquinolinone fused 1,2,3-triazole

Figure 1. Examples of pharmacology active fused 1,2,3-triazoles.

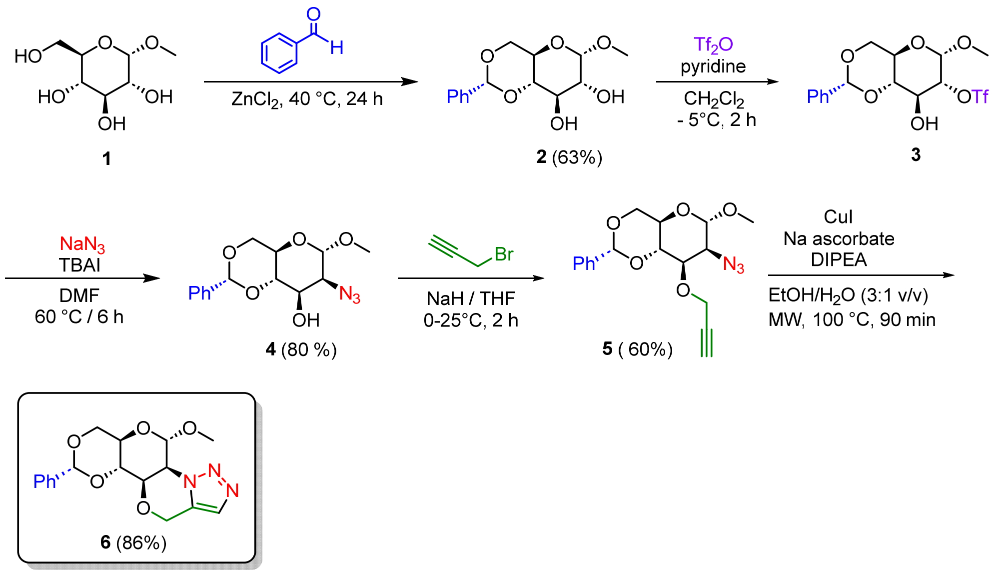
In the field of click chemistry, the copper(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction is a powerful, highly reliable, selective, and atom-efficient reaction that allows easy access to 1,4-disusbtituted 1,2,3-triazoles [8]. Often, this reaction involves the use of mild reaction conditions and readily available starting materials and reagents, so it is not surprising that triazoles have been extensively used in many fields of interest such as medicinal chemistry [9], materials science [10], and catalysis [11]. On the other hand, the synthesis of 1,5-disubstituted 1,2,3-triazoles and their applications have been much less studied in comparison to their regioisomeric counterpart. The Ru-catalyzed azide-alkyne cycloaddition (RuAAC) reaction is one of the most widely used strategies for preparing 1,5-disubstituted triazoles [12]. However, the cost of the catalyst and the potential toxicity of ruthenium salts have forced the search for new synthetic strategies to accessing these triazoles. Due to the widespread applicability of 1,2,3-triazole-containing heterocycles, and by taking advantage of the inherent strain in the 1,2,3-triazole fused cyclic system, organic chemists have been able to develop methodologies for the synthesis of 1,5-disubstituted-1,2,3-triazole fused heterocycles via intramolecular azide-alkyne cycloaddition reactions [13] Nucleotides and carbohydrates are substrates that stand out for their versatility in synthesizing fused triazoles [14]. Several oxa- [15], aza- [16] and carba-ring [17] fused triazoles from carbohydrates have been reported utilizing thermal- or Cu(I)-catalyzed intramolecular azide-alkyne cycloaddition reactions, where the key intermediate for its synthesis is the formation of an azido alcohol.

Organic azides have been extensively used in organic synthesis as precursors for numerous nitrogen-containing molecules [18]. Particularly, 1,2-azido alcohols have been widely employed in organic synthesis for the preparation of 1,2-amino alcohols as well as 1,2,3-triazole fused heterocycles. For example, glycosyl 1,2-azido alcohols have been used as starting materials for preparing fused bicyclic molecules containing a morpholine-fused triazole [19]. Triazolo-morpholine 0moiety is a highly attractive bicyclic system due to its wide range of biological applications, especially when conjugated to carbohydrates, as their presence has been shown to enhance enzyme inhibitory activity by increasing interactions with the biomolecular target [20]. Herein, we report the synthesis of a new morpholino-fused [5,1-*c*]-triazole **6**, by a five-step sequence starting from methyl *α*-ᴅ-glucopyranoside **1**. This is the first tetracyclic morpholino-fused triazole system containing a hexose.

2. Results and Discussion

Tiwari *et.al.*, reported the synthesis of bicyclic compounds based on morpholine-fused triazole *via* a thermal intramolecular azide–alkyne cycloaddition reaction from glycosyl 1,2-azido alcohols and propargyl bromide [21]. Based on their synthetic pathway, the replacement of monosaccharides of five carbon atoms (pentoses) with methyl-4,6-*O*-benzylidene-α-ᴅ-glucopyranoside **2** (a hexose) to obtain a tetracyclic morpholine-fused triazole was envisioned (Scheme 1).

The synthetic strategy begins with the commercially available methyl-α-D-glucofuranose **1**. First, compound **1** was subjected to a benzylidene acetal protection of the 1,3-diol by using powdered zinc chloride and benzaldehyde for 40 hours at room temperature to afford the methyl-4,6-O-benzylidene-α-ᴅ-glucopyranoside **2** in a 63% yield **[**24**].** Compound **2** was next reacted with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of pyridine at – 5°C for 2 hours to produce the trifluoromethanesulfonic ester **3** [25]. The subsequent azidation of the triflated sugar **3** with sodium azide and tetrabutylammonium iodide (TBAI) in dimethyl formamide (DMF) at 80 °C for 3 hours resulted in the methyl 2-azido-2-deoxy-4,6-O-benzylidene-*α*-ᴅ-mannopyranoside **4** in a moderate 48 % yield after purification using column chromatography [26]. Once the 1,2-azido alcohol **4** was achieved, the next step was the introduction of the terminal alkyne necessary for synthesizing the morpholine-fused triazole. The *O*-propargylation of the secondary hydroxyl group of the 1,2-azido alcohol **4** was performed using propargyl bromide and sodium hydride in dry tetrahydrofuran (THF) to afford the propargylated sugar **5** in a 60 % yield. Finally, for the synthesis of target compound **6** we used a copper(I) catalyzed intramolecular alkyne-azide cycloaddition by using the azido-alkyne **4**, copper iodide, sodium ascorbate, and diisopropylethylamine (DIPEA) at 100°C with microwave heating for 90 min in ethanol–water (3:1 v/v) as solvent. To our delight, under these conditions, the tetracyclic morpholine-fused [5,1-*c*]triazole **6** was satisfactorily obtained in 86% yield as a white solid.



Scheme 1. Synthetic route for the synthesis of tetracyclic morpholine-fused[5,1-*c*] triazole **6.**

The chemical structure of compound **6** was confirmed by NMR, IR, and HRMS analyses. The ^1H NMR spectrum of compound **6** exhibited a singlet of one proton observed at δ 7.60 ppm assigned to the triazole-proton. A broad singlet at δ 5.57 ppm confirmed the presence of the anomeric proton, while appearance of a quartet at δ 5.10 ppm is attributed to the OCH_2 protons of the triazolo morpholine ring. In addition, two triplet signals at δ 3.81 and δ 3.70 and the three multiplets from δ 4.74 to δ 3.95 ppm displayed the remaining carbohydrate protons, while the singlet at δ 3.57 ppm assigned to the methoxy group and two signals of aromatic protons at δ 7.50 and δ 7.40 ppm confirmed the occurrence of the intramolecular cycloaddition. ^{13}C NMR of compound **6** showed two resonances at δ 130.6 and δ 128.9 ppm corresponding to the triazole-carbons. Finally, the molecular ion peak at *m*/*z* 346.14321 $[M + H]^+$ confirms the synthesis of the morpholine-fused [5,1-*c*]triazole **6.**

3. Materials and Methods

All reagents were purchased from commercial suppliers and used without further purification. Solvents used in the syntheses were of technical grade and freshly distilled prior to use. Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. NMR spectra were recorded on Bruker Ascend-400 (400 MHz) and Bruker Avance DMX-400 (400 MHz) spectrometers in $CDCl_3$, and chemical shifts are given in ppm, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet), coupling constant (J) with TMS as the reference. Mass spectra were recorded on mass spectrometer model micrOTOF II (Bruker Daltonics Inc.) using the Compass platform (otofControl and DataAnalysis from Bruker Daltonics Inc.). Spectra were acquired in positive mode with a capillary voltage of 4500 V, nebulizer gas: 0.5 Bar, drying gas 4.0 L/min and a drying temperature of 150 C. Microwave irradiation experiments were performed using a Discover System (CEM Corporation, Matthews, NC, USA) single-mode microwave with standard sealed microwave glass vials. The precursor 2 [22] and 4 [23,24] were prepared according to the previously reported procedures.

Synthesis de Methyl 2-azido-4,6-O-benzyliden-2-deoxy-3-O-propargyl- a-D-glycopyranoside 5

To a solution of azide 4 (0.200 g, 0.650 mmol) in dry THF (5 mL), and under nitrogen atmosphere was added NaH (0.018 g, 0.780 mmol, 60% dispersion in oil) at 0 °C followed by the dropwise addition of propargyl bromide (0.058 mL, 0.650 mmol). The resulting mixture was allowed to warm up at room temperature and was kept under stirring for 2 hours. Finally, the reaction was quenched carefully with H_2O (5 mL), the solvent was evaporated, and the residue was diluted with EtOAc (30 mL), washed with brine (1x60 mL), dried with anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by flash chromatography on silica gel using eluents (7:1 Hex-EtOAc) to give propargylated product 5 (0.130 g, 60% yield) as a yellow oil. $[\alpha]_D^{20}$ -30 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.53 – 7.47 (m, 2H), 7.45 – 7.35 (m, 3H), 5.62 (s, 1H), 4.71 (d, *J* = 1.7 Hz, 1H), 4.50 (dd, *J* = 16.0, 2.4 Hz, 1H), 4.40 (dd, *J* = 15.9, 2.4 Hz, 1H), 4.31 – 4.20 (m, 2H), 4.14 (dd, *J* = 3.9, 1.5 Hz, 1H), 4.11 – 4.02 (m, 1H), 3.88 – 3.81 (m, 2H), 3.41 (s, 3H), 2.51 (d, J = 2.4 Hz, 1H). ^{13}C RMN (101 MHz, $CDCl_3$) δ 137.25, 128.93, 128.31(2C), 126.15(2C), 101.63, 101.11, 79.51, 78.06, 77.59, 75.65, 69.65, 68.87, 63.79, 58.13, 56.51. HRMS (ESI-TOF) Calculated for $C_{17}H_{21}N_3O_5$ $[M + 2H]^+$ 347.14812, found 347.14321.

Synthesis Morpholine-fused [5,1-c]triazole 6

the propargyl carbohydrate 5 (0.100 g, 0.289 mmol was placed in a microwave tube equipped with magnetic stirrer), and then was dissolved in 5 mL of a solution of EtOH-H_2O (2:1). After that, sodium ascorbate (0.011 g, 0.057 mmol), copper iodide (0.016 g, 0.086 mmol), and DIPEA (0.019 mL, 0.111 mmol) were added. The resulting mixture was heated under microwave irradiation (40 W, 100 °C) for 90 min. Finally, the reaction mixture was diluted with ethyl acetate and filtered through a short plug of silica, the resulting organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. The resulting residue was purified by flash chromatography on silica gel using a mixture of Hex-EtOAc (1:1) to give morpholine-fused [5,1-c]-triazole 6 (0.086 g, 86% yield) as a white solid, m. p. 198-200°C. $[\alpha]_D^{20}$ -70 (c 1, $CHCl_3$). ^{1}H RMN (400 MHz, $CDCl_3$) δ: 7.60 (s, 1 H), 7.50 (d, *J* =5.1, 1.6, Hz, 2 H), 7.40 (d, *J* = 5.0, 1.4, Hz, 3 H), 6.00 (s, 1H), 5.57 (br s, 1H), 5.10 (q, *J*= 1.5 Hz, 2 H), 4.74 – 4.66 (m, 2 H), 4.32 (dd, *J* = 10.2, 4.9, 1.5 Hz, 1 H), 4.08 – 3.95 (m, 1 H), 3.81 (t, *J* = 9.3 Hz, 1Hj), 3.70 (t, *J* = 10.4, 1.6 Hz, 1H), 3.57 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.87, 130.57, 129.51, 128.94, 128.52(2C), 126.37(2C), 102.31, 98.16, 72.76, 69.34, 68.79, 62.13, 58.38, 57.02, 55.71. HRMS (ESI-TOF) Calculated for $C_{17}H_{20}N_3O_5$ $[M + H]^+$ 346.1397, found 346.1398.

4. Conclusions

The synthesis of a new tetracyclic morpholine-fused [5,1-*c*]-triazole was performed successfully through a five-step sequence starting from methyl *α*-D-glucopyranoside by using as a key step an intramolecular copper(I) catalyzed alkyne-azide cycloaddition with a 28% overall yield. The title product could be used as a starting point for the synthesis of morpholine-fused [5,1-*c*]-triazolyl glycoconjugates, since hydrolysis of the benzylidene acetal will allow regeneration of the 1,3-diol, which can be functionalized in several ways. In addition, the reported morpholine-fused [5,1-*c*]-triazole could be consider for further *in vitro* studies because it contains a pharmacophoric moiety.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. Copies of ^{1}H-NMR, ^{13}C-NMR spectra for the new product **6**.

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