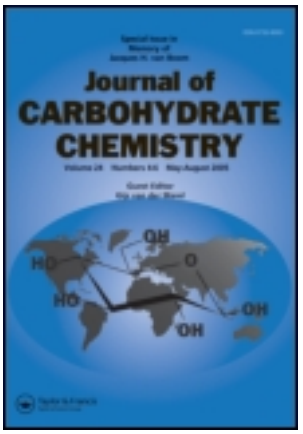

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Communication: Synthesis and Characterization of Some 3-Glycosyl-5-Substituted Isoxazoles with Potential Biological Activities.

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COMMUNICATION

SYNTHESIS AND CHARACTERIZATION OF SOME 3-GLYCOSYL-5-SUBSTITUTED ISOXAZOLES WITH POTENTIAL BIOLOGICAL ACTIVITIES.

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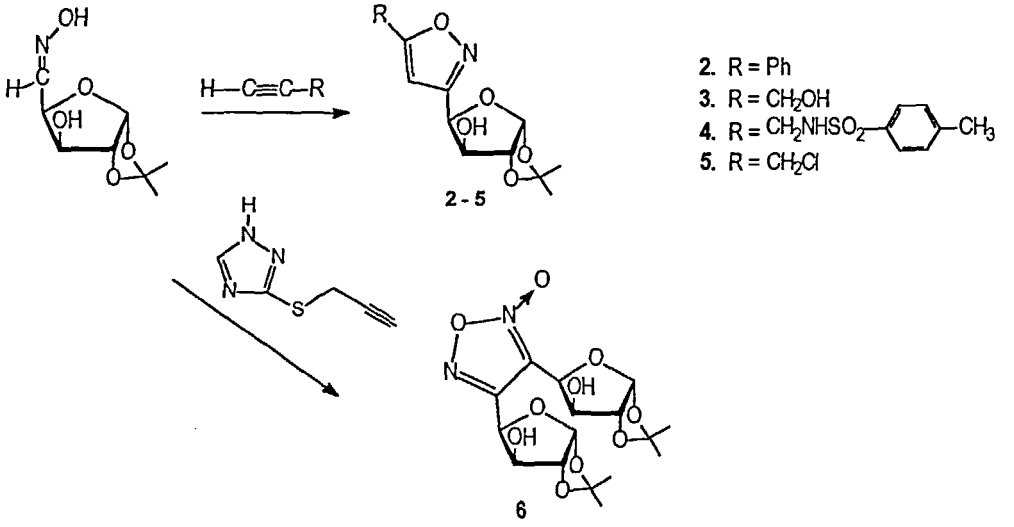
Isoxazoles are a family of heterocycles of great interest due to their diverse medicinal, agricultural and industrial applications.[1] Isoxazole derivatives are used as improved fluorescent probes for studying natural and synthetic lipids;[2] as muscle relaxants,[3] for the treatment of hypercholesteremia, arteriosclerosis, and hyperlipidemia,[4] as organic electrolytes for nonaqueous batteries,[5] in photographic emulsions,[6] and as synthetic intermediates.[7] The 1,3-dipolar cycloaddition of nitrile oxides to alkynes provides a general synthetic method for these compounds.[8]

In previous papers we reported the synthesis of 3-glycosyl-5-substituted-2-isoxazolines from unprotected[9] and protected[10] carbohydrate derivatives. Tronchet and coworkers[11] reported the synthesis of 2-isoxazolines and 3-glycosyl-5-phenylisoxazole from hydroxyl protected carbohydrate hydroximoyl chlorides.

In this work, we describe the synthesis of some 3,5 disubstituted isoxazoles using the following scheme.



Scheme 1

The 1,3-dipolar cycloaddition of 1,2-*O*-isopropylidene-α-D-*xylo*-pentadialdo-1,4-furanose oxime[10] to phenylacetylene, 2-propyn-1-ol, *N*-(2-propynyl)-*p*-toluenesulfonamide (**1**) and 3-chloro-1-propyne, all in the presence of chloramine-T, yielded, respectively, 3-(1,2-*O*-isopropylidene-α-D-threofuranos-4-yl)-5-phenylisoxazole (**2**), 5-hydroxymethyl-3-(1,2-*O*-isopropylidene-α-D-threofuranos-4-yl)isoxazole (**3**), 3-(1,2-*O*-isopropylidene-α-D-threofuranos-4-yl)-5-[(*N*-*p*-toluenesulfonylamide)methyl]isoxazole (**4**) and 5-chloromethyl-3-(1,2-*O*-isopropylidene-α-D-threofuranos-4-yl)isoxazole (**5**). However, the reaction with 3-(2-propynylthio)-1H-1,2,4-triazole[12] under same conditions, did not give the corresponding isoxazole. The main product was identified as 3,4-bis-(1,2-*O*-isopropylidene-α-D-threofuranos-4-yl)-1,2,5-oxadiazole-2-oxide (**6**). The formation of compound **6** can be attributed to the dimerization to furoxanes of nitrile oxides, which is the normal mode of decay of these kind of compounds.

The 1,3-dipolar cycloaddition of 1,2-*O*-isopropylidene-α-D-*xylo*-pentadialdo-1,4-furanose oxime as stable precursor of nitrile oxide to these alkynes, gave us isoxazoles (**2** -

5) in moderate yields. When the dipolarophilic activity decreased, we could only isolate the furoxane 6 as the main product.

EXPERIMENTAL

General methods. Melting points were determined on a Unimelt apparatus and are uncorrected. Optical rotations were measurred at 20 °C using a Perkin-Elmer 141 Polarimeter. NMR spectra were recorded with a Bruker AC 200 instrument (200.01 MHz for ^1H and 25 MHz for ^{13}C), in $CDCl_3$ solution. Chemical shifts are given in ppm downfield from internal TMS. Mass spectra were performed with a Shimadzu QP-5000 spectrometer by EI technique. For TLC, silica gel 60 F_{254} (Merck) coated plates were used, detection by UV light (254 nm) and spraying with a 10% solution of concentrated sulfuric acid in ethanol followed by heating.

***N*-(2-propynyl)-*p*-toluenesulfamide (1).** To a solution of 1.5 mL (23.5 mmol) of 2-propynylamine in 8 mL of 15% DMF-water (v/v) , three portions of 1.46 g (7.6 mmoles) of *p*-toluenesulfonyl chloride were added, adjusting to alkalinity with aq NaOH (20%) each time. Finally the reaction mixture was stirred for another 30 min during which time the pH remained approximately constant. The stirred reaction mixture was then acidified with HCl (c), cooled in an ice bath, filtered and washed with water until neutral. The solid was dissolved in ethanol and the salt eliminated by filtration. The product was purified by silica gel G column chromatography using toluene-ethyl acetate mixtures. Compound **1** (83.5 mg, 4 mmol, 17 %) was obtained as a yellow solid; mp 63 - 64 °C. ^1H NMR ($CDCl_3$) δ 2.11 (t, 1 H, *J*= 2.5 Hz, CH), 2.43 (s, 3 H, Me), 3.83 (dd, 2 H, *J*= 2.5 Hz, 6.1Hz, CH_2), 4.60 (wide s, 1H, NH), 7.31 (d, 2H, *J*= 8.2 Hz)), 7.77 (d, 2H, *J*= 8.2 Hz) . ^{13}C NMR ($CDCl_3$) δ 21.2 (Me), 32.5 (CH_2), 72.7 (CH), 78.0 (C), 127.1-129.4-136.3-143.5 (aromatic carbons).

Anal. Calcd for $4(C_{10}H_{11}NO_2S).H_2O$: C, 56,21; H, 5,39. Found: C, 55,92; H, 5,28.

General Procedure. 3-(1,2-*O*-Isopropylidene-α-D-threofuranos-4-yl)-5-substituted isoxazole. To a solution of 1,2-*O*-isopropylidene-α-D-*xylo*-pentadialdo-1,4-furanose oxime[10] (1.0 mmol) in minimum volume of ethanol at 0 °C, a solution of dipolarophile (in excess) in ethanol was added. Additional ethanol, was sometimes required for complete dissolution. The stirred reaction mixture was placed in an ice bath

and 1.5 mmol of chloramine-T was added slowly. Once the reaction reached room temperature, it was heated between 60 - 80 °C. The course of the reaction was followed by TLC [toluene:ethyl acetate (1:1)] until the oxime had dissapeared. The salts were filtered, the solvent was evaporated and the syrup was purified by column chromatography on silica gel G, using toluene and toluene-ethyl acetate (95:5) as eluents.

3-(1,2-*O*-Isopropylidene-α-D-threofuranos-4-yl)-5-phenylisoxazole (2). The general procedure was applied using phenylacetylene (0.2 mL) as the dipolarophile yielding compound **2** (45%) as a crystalline solid which was recrystallized from 2-propanol: mp 159-160 °C; $[\alpha]_D$ -47.4 (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.36, 1.56 (two s, 6H, Me), 6.69 (s, 1 H, H-4), 6.09 (d, $J_{1',2'}$ = 3.6 Hz, 1 H, H-1'), 4.68 (d, $J_{2',3'}$ = 0 Hz, 1 H, H-2'), 4.56 (d, $J_{3',4'}$ = 2.3 Hz, 1 H, H-3'), 5.31 (d, 1 H, H-4'), 7.41-7.76 (m, 5 H, aromatic proton). ^{13}C NMR ($CDCl_3$) δ 26.1, 26.8 (Me), 161.3 (C-3), 99.9 (C-4), 170.3 (C-5), 105.1(C-1'), 84.8 (C-2'), 76.1 (C-3', C-4'), 112.1 ($C(Me)_2$), 125.8-129.0-130.4 (aromatic carbons). Mass spectrum (EIMS): *m/z* (%) 303 (7.9, M^+), 288 (11.4, M^+ - CH_3), 244 (6.0), 228 (27.2), 203 (7.8), 188 (10.9), 175 (27.2), 174 (100), 158 (11.2), 100 (51.5). HRMS Calcd for $C_{16}H_{17}NO_5$: 303.1107. Found: 303.1109.

Anal. Calcd for $C_{16}H_{17}NO_5$: C, 63.37; H, 5.61. Found: C, 63.03; H, 5.72

5-Hydroxymethyl-3-(1,2-*O*-isopropylidene-α-D-threofuranos-4-yl)isoxazole (3). The general procedure was applied using 2-propyn-1-ol (0.2 mL) as the dipolarophile yielding compound **3** (55%) as a syrup; $[\alpha]_D$ -49.8 (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.36, 1.54 (two s, 6 H, Me), 6.37 (s, 1 H, H-4), 6.05 (d, $J_{1',2'}$ = 3.6 Hz, 1 H, H-1'), 4.65 (d, $J_{2',3'}$ = 0 Hz, 1 H, H-2'), 4.45 (d, $J_{3',4'}$ = 2.4 Hz, 1 H, H-3'), 5.25 (d, 1 H, H-4'), 4.72 (s, 2 H, CH_2), 3.25 (wide s, 1 H, OH). ^{13}C NMR ($CDCl_3$) δ 26.0, 26.6 (Me), 160.6 (C-3), 102.2 (C-4), 171.7 (C-5), 104.9 (C-1'), 84.8 (C-2'), 75.9 (C-3'), 76.0 (C-4'), 112.2 ($C(Me)_2$), 55.8 (CH_2) . Mass spectrum (EIMS): *m/z* (%) 257 (0.6, M^+), 242 (26.5), 198 (3.8), 182 (54.0), 157 (4.3), 142 (13.9), 129 (48.0), 128 (100), 112 (15.5), 100 (30.6). HRMS Calcd for $C_{10}H_{12}NO_6$: 242.0665. Found: 242.0668.

Anal. Calcd for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.84. Found: C, 51.27; H, 5.85.

3-(1,2-*O*-Isopropylidene-α-D-threofuranos-4-yl)-5-[(*N*-*p*-toluenesulfonylamide)methyl]isoxazole (4). The general procedure was applied using *N*-(2-propynyl)-*p*-toluenesulfamide (0.43 g) as the dipolarophile yielding compound **4** (33%) as a syrup,

which crystallized in a mixture of ethanol: water; mp 156-157 °C; $[\alpha]_D$ -29.0 (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.35, 1.53 (two s, 6 H, Me), 2.42 (s, 3H, Me), 6.21 (s, 1 H, H-4), 6.01 (d, $J_{1',2'}$ = 3.6 Hz, 1 H, H-1'), 4.62 (d, $J_{2',3'}$ = 0 Hz, 1 H, H-2'), 4.39 (d, $J_{3',4'}$ = 2.6 Hz, 1 H, H-3'), 5.17 (d, 1 H, H-4'), 4.25 (d, $J_{NH\text{-}CH2}$= 6.3, 2H, CH_2), 5.69 (d, 1H, NH), 7.26 (d, 2 H, *J*= 8.3 Hz), 7.72 (d, 2 H, *J*= 8.3 Hz). ^{13}C NMR ($CDCl_3$) δ 26.1, 26.7 ($C(\underline{C}H_3)_2$), 21.5 (CH_3), 38.6 (CH_2), 160.7 (C-3), 103.1 (C-4), 168.2 (C-5), 104.9(C-1'), 84.8 (C-2'), 75.8 (C-3'), 76.0 (C-4'), 112.1 ($\underline{C}(Me)_2$), 144.0-136.3-129.8-127.1 (aromatic carbons). Mass spectrum (EIMS): *m/z* (%) 410 (3.5, $M^{+\cdot}$), 395 (6.6), 351 (1.9), 335 (8.6), 310 (1.0), 295 (1.2), 282 (5.8), 281 (19.9), 155 (33.0), 100 (15.8), 43 (100). HRMS Calcd for $C_{17}H_{19}N_2O_7S$: 395.0914. Found: 395.0916.

Anal. Calcd for $C_{18}H_{22}N_2O_7S$: C, 52.68; H, 5.37. Found: C, 52.94; H, 5.47.

5-Chloromethyl-3-(1,2-*O*-isopropylidene-α-D-threofuranos-4-yl)isoxazole (5). The general procedure was applied using propargylchloride (0.1 mL) as the dipolarophile yielding compound **5** (22%) as a syrup; $[\alpha]_D$ -13.1 (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.36, 1.55 (two s, 6 H, Me), 6.50 (s, 1 H, H-4), 6.07 (d, $J_{1',2'}$ = 3.6 Hz, 1 H, H-1'), 4.67 (d, $J_{2',3'}$ = 0 Hz, 1 H, H-2'), 4.53 (d, $J_{3',4'}$ = 2.5 Hz, 1 H, H-3'), 5.27 (d, 1 H, H-4'), 4.61 (s, 2 H, CH_2). ^{13}C NMR ($CDCl_3$) δ 26.1, 26.8 (Me), 161.1 (C-3), 104.3 (C-4), 167.7 (C-5), 105.1(C-1'), 84.8 (C-2'), 75.8 (C-3'), 76.1 (C-4'), 112.2 ($C(Me)_2$), 29.6 (CH_2) . Mass spectrum (EIMS): *m/z* (%) 276/278 (35, $(M+H)^+$), 260/262 (65, $M^{+\cdot}$ - $CH_3^{\cdot}$), 240 (22), 218/220 (42), 200/202 (100), 175/177 (9). HRMS Calcd for $C_{10}H_{11}NO_5Cl$: 260.0326. Found: 260.0325.

3,4-Bis-(1,2-*O*-isopropylidene-α-D-threofuranos-4-yl)-1,2,5-oxadiazole-2-oxide (6). The general procedure was applied using 3-(2-propynylthio)-1H-1,2,4-triazole (0.21 g) as the dipolarophile yielding compound **6** (41 %) as a white solid which was recrystallized from ethanol: water; mp 180 - 182 °C; $[\alpha]_D$ +42.5 (*c* 1, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.30-1.55 (two s,12 H, Me), 6.05 (d, 1H, H-1'), 6.06 (d, 1H, H-1''), 4.63 (d, 1H, H-2'), 4.65 (d, 1H, H-2''), 4.47 (d, 1H, H-3'), 4.59 (d, 1H, H-3''), 5.30 (d, 1H, H-4'), 5.53 (d, 1H, H-4''). ^{13}C NMR ($CDCl_3$) δ 26.2-26.3-26.9-27.0 (Me), 105.0-105.1 (C-1'), 74.0-76.0-76.6-77.0-78.0 (C-2' and C-3'), 84.6-84.8 (C-4'), 112.7-113.2(C), 154.6 (C-3),113.2 (C-4).

Anal. Calcd for $C_{16}H_{22}N_2O_{10}$: C, 47.76; H, 5.47. Found: C, 47.96; H, 5.48

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