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SYNTHESIS OF NEW FIVE MEMBERED NITROGEN CONTAINING HETEROCYCLES BEARING D-GALACTOSE SIDE CHAINS

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ABSTRACT: The synthesis of 5-[6'-deoxy-(1',2':3',4'-di-*O*-isopropylidene-α-D-galactopyranos-6'-yl)]tetrazole and its reaction with acetic anhydride and 1,2:3,4-di-*O*-isopropylidene-6-*O*-(4-toluenesulfonyl)-α-D-galactopyranose are described.

Among the heterocyclic compounds the tetrazoles have received considerable attention specially due to their phosphodiesterase[1], *O*-acyltransferase[2,11-12] and glycosidase[3]

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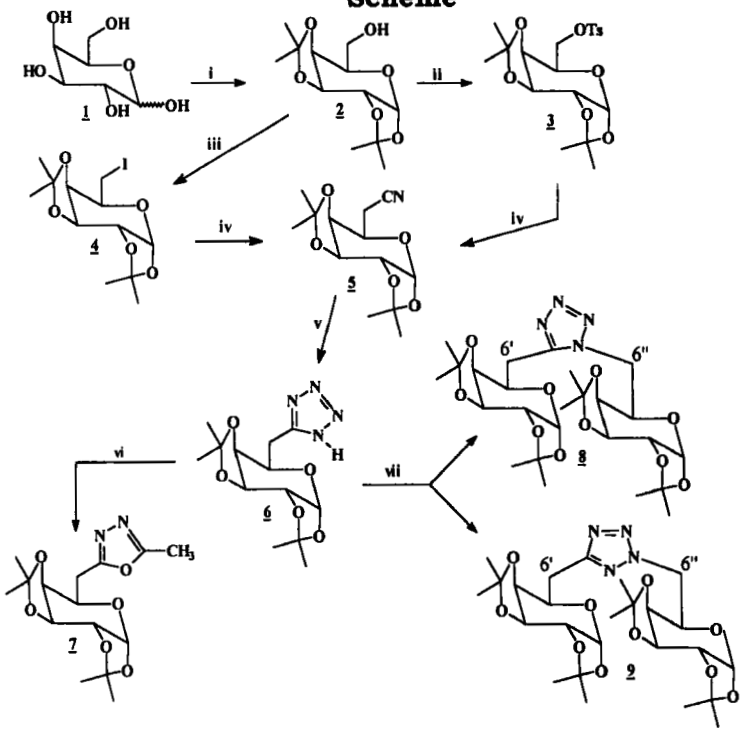
inhibitory activities. Some recent investigations indicate that oxadiazoles possess anti-inflammatory activity[14] and have been explored as potential monoamine oxidase inhibitors[13]. Besides these activities, the oxadiazoles are indicated as potential electron-transporting materials in electroluminescent devices[4]. In this article we wish to report the synthesis of four new nitrogen containing heterocycles from D-galactose **1**. The synthetic routes are shown in the scheme.

Scheme



i: H_2SO_4, acetone, $CuSO_4$; **ii:** TsCl, pyridine; **iii:** I_2, triphenylphosphine, imidazole, toluene, reflux; **iv:** DMF, KCN, 105°C; **v:** DMF, NaN_3, 105°C; **vi:** acetic anhydride, 110°C; **vii:** DMF, K_2CO_3, 110°C, compound **3**.

The first three steps included the protection of D-galactose **1** in the isopropylidene form **2** and its conversion to the 6-(4-toluenesulfonyl) and 6-iodo derivatives **3** and **4**, respectively, following the usual techniques described in the literature[5,6,7]. The convertion of the 6-iodo derivative **4** to the 6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-heptopyranurononitrile **5** was performed by nucleophilic displacement with potassium cyanide[8]. The reaction conditions were improved as shown in the table.

Table

Reaction	Molar ratio **4** : KCN	Reaction time (h)	Solvent/ temperature	Catalysis	Yield (%)
1	1:2.25	5	DMF-105°	-	34.3
2	1:2.25	12.5	DMF-105°	-	41.6
3	1:4.5	12	DMF-105°	-	48.5
4	1:2.25	4	DMF-105°	18-crown-6	60.6
5	1:2.25	6	DMF-105°	18-crown-6	60.6
6	1:2.25	12	DMF-105°	18-crown-6	57.0
7	saturated $KCN_{(aq)}$	17	Benzene-reflux	$(Bu)_4NHSO_4$	-
8	saturated $KCN_{(aq)}$	21.5	Xylene-105°	$(Bu)_4NHSO_4$	4.0

The use of 18-crown-6 ether allowed to achieve yields around 60 %, comparing to the 28 % yield reported[8]. When the 4-toluenesulfonate derivative **3** was substituted for the 6-iodo derivative **4**, the nitrile **5** was obtained in very low yield (< 1%) even after prolonged heating.

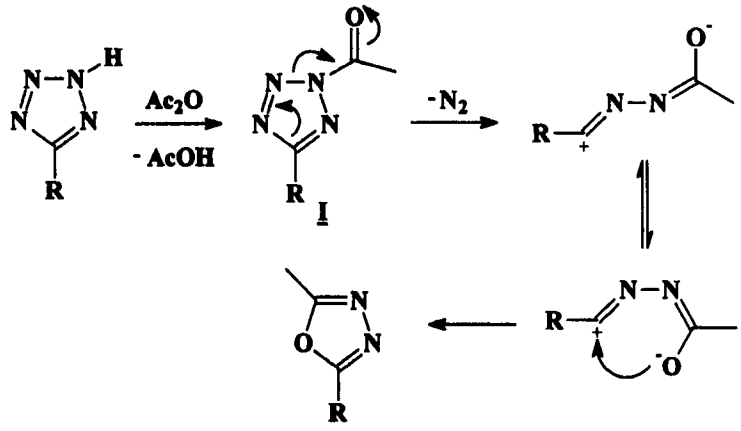
The 1,3-dipolar cycloaddition reaction[9] of nitrile **5** with sodium azide provided the desired product 5-[6'-deoxy-(1',2':3',4'-di-*O*-isopropylidene-α-D-galactopyranos-6'-yl)]tetrazole **6**. The reaction of tetrazole **6** with 1,2:3,4-di-*O*-isopropylidene-6-*O*-(4-toluenesulfonyl)-α-D-galactopyranose **3** in a slightly basic media (see Experimental) furnished the two possible alkylated heterocyclic derivatives 1H-1,5-bis-[6'-deoxy-(1',2':3',4'-di-*O*-isopropylidene-α-D-galactopyranos-6'-yl)]tetrazole **8** and 2-H-2,5-bis-[6'-deoxy-(1',2':3',4'-di-*O*-isopropylidene-α-D-galactopyranos-6'-yl)]tetrazole **9** in a 1:3 ratio. Besides the effect of the axial oxygen[9,10] at C4 of compound **3** that might be expected to hamper an efficient nucleophilic displacement[9] of the 4-toluenesulfonyl group by the heterocyclic nitrogen, there will be a more pronounced steric hindrance by the proximity of two protected α-D-galactopyranosyl units in the transition state leading to product **8** that probably explains the observed

regioselectivity[15]. When the 6-iodo derivative **4** was substituted for the 4-toluenesulfonate **3** no alkylation occurred. Although the reasons for this result and that for the reaction of the 4-toluenesulfonate **3** with potassium cyanide are not fully understood, they are believed to be related to conformational features of these compounds.

For the unequivocal characterization of the isomeric tetrazoles **8** and **9**, the HMBC experiment proved to be decisive. So, the HMBC contour plot of both tetrazoles showed strong cross correlations between the tetrazole carbon and each CH_2 group directly linked, due to ^2J coupling constants. Only for the *vic*-isomer **8**, the HMBC contour plot showed cross correlation between the tetrazole carbon and the CH_2 group linked to the vicinal nitrogen, due to a ^3J coupling constant.

Oxadiazoles can be prepared by the reaction of tetrazoles with carboxylic acid derivatives[16]. According to mechanistic proposition from literature[15], the more nucleophilic nitrogen atom is first acylated to give the intermediate **I** (usually not isolated) which, by extrusion of a nitrogen molecule furnishes the oxadiazole as shown in the figure.

Figure



Thus, when the tetrazole **6** was reacted with acetic anhydride, the oxadiazole **7** was obtained, as expected.

Experimental

General Procedures

A Perkin-Elmer 240-A microanalyses apparatus was used to perform the elemental analyses. The specific optical rotations were measured in a P 20 Bellingham-Stanley polarimeter. The melting points were measured in a MQAPF-301 Microquímica melting point apparatus and are uncorrected. Thin layer chromatography (tlc) was performed with silica Gel 60 Merck as adsorvent. Column chromatography was performed with silica

Gel 60 G Merck 70-230 mesh unless otherwise specified. The 1D NMR spectra were recorded on a *AVANCE* DPX 200 and *AVANCE* DRX 400 Bruker Spectrometers using tetramethylsilane as the internal standard (δ 0.00). The 2D NMR spectra were recorded on a *AVANCE* DRX 400 Bruker Spectrometer with the same internal standard. The samples (40 mg) were dissolved in $CDCl_3$, filtered, and spun at 20 Hz to record proton and carbon NMR spectra. The other experiments were done non-spinning. Eventually, exponential multiplications were applied for processing 1D proton spectra. The main assignments were supported by 2D experiments like COSY with homospoil gradients, HMQC and HMBC. For the HMQC experiment a 3.45 ms delay for creation of anti-phase magnetization were used and for the HMBC, an evolution delay was set to 70 ms.

Synthesis

5-[6'-deoxy-(1',2':3',4'-di-O-isopropylidene-α-D-galactopyranos-6'-yl)]tetrazole (6)

A mixture of nitrile **5** (0.8 g, 2.97 mmol), ammonium chloride

(2.23 g, 41.68 mmol) and sodium azide (2.71 g, 41.69 mmol) in 30 mL of anhydrous dimethylformamide was stirred and heated at 105°C in an oil bath for 120 hours. The reaction was monitored by tlc (ethyl acetate). Then the reaction mixture was concentrated under reduced pressure and extracted with dichlorometane (3 portions of 50 mL) after the addition of 10 mL of water. The organic layer was dried over anhydrous sodium sulfate and concentrated. The crude product was purified by column chromatography using *n*-hexane/ethyl acetate 7:3 and ethyl acetate as eluents. The pure product was crystallized from ethyl ether/petroleum ether 1:1, 0.61 g, 66.3 % yield, mp 135-138°C, $[\alpha]_D$ -90.3° (c 0.86, $CHCl_3$), ^1H NMR (δ, $CDCl_3$) : 5.55 (d, $J_{1',2'}$ = 4.9 Hz, H1'), 4.67 (dd, $J_{3',4'}$ = 7.8 Hz, $J_{3',2'}$ = 2.4 Hz, H3'), 4.37 (dd, $J_{2',3'}$ = 2.4 Hz, $J_{2',1'}$ = 4.9 Hz, H2'), 4.25 (dd, $J_{4',3'}$ = 7.8 Hz, $J_{4',5'}$ = 1.7 Hz, H4'), 4.18 (dt, $J_{5',4'}$ =1.7 Hz, $J_{5',6'}$ or $J_{5',6''}$ = 6.4 Hz, H5'), 3.34 (d, $J_{6',5'}$ or $J_{6'',5'}$ = 6.4 Hz, H6' and H6''), 1.43, 1.34, 1.32, 1.25 (s, $C\underline{H}_3$ groups), ^{13}C NMR (δ, $CDCl_3$): 96.32 (C1'), 71.98 (C3'), 70.66 (C2'), 70.24 (C4'), 65.78 (C5'), 25.77, 25.13, 25.73, 24.23 ($\underline{C}H_3$), 109.66, 109.12 (C, isopropylidene), 153.66 (C, tetrazole).

Anal. Calcd for $C_{13}H_{20}N_4O_5$: C, 50.00, H, 6.41, N, 17.95.

Found: C, 50.00, H, 6.35, N, 17.98.

5-Methyl-3-[6'-deoxy-(1',2':3',4'-di-*O*-isopropylidene-α-D-galactopyranos-6'-yl)]-1,2,4-oxadiazole (7)

Tetrazole **6** (0.35 g, 1.12 mmol) was dissolved in a mixture of 10 mL of freshly distilled acetic anhydride and 5 mL of pyridine. The solution was stirred and heated at 110°C for 24 hours and the reaction was monitored by tlc (*n*-hexane:ethyl acetate 1:1). The reaction was stopped by the addition of ice and water (100 mL) and stirred for further 15 min. The mixture was extracted with dichlorometane (2 portions of 75 mL) and the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The product was purified by column chromatography using *n*-hexane and *n*-hexane/ethyl acetate 1:1 as eluents. The product was obtained as an oil, 0.15 g, 42.4 % yield. For analytical purposes a sample was submitted to a new column chromatography (*n*-hexane/ethyl acetate 7:3, silica Gel 60 G Merck 230-400 mesh) and crystallized from petroleum ether. The pure product was obtained as a solid, mp 99.3-100.8°C, $[\alpha]_D$ -61.8° (c 2.7, $CHCl_3$), ^1H NMR (δ, $CDCl_3$): 5.49 (d, $J_{1',2'}$ = 4.9 Hz, H1'), 4.65 (dd, $J_{3',4'}$ = 7.7 Hz, $J_{3',2'}$ = 2.4 Hz, H3'), 4.32 (m, H2', H4' and H5'), 3.14 (dd, $J_{5',6'}$ or $J_{5',6''}$ = 1.3 Hz, $J_{6',6''}$ = 7.2 Hz, H6' and H6''), 2.50, 1.53, 1.47, 1.35, 1.32 (s, CH_3), ^{13}C

NMR (δ, $CDCl_3$): 96.27 (C1'), 71.71 (C3'), 70.73 (C2'), 70.29 (C4'), 65.39 (C5'), 26.86 (C6'), 25.88, 25.82, 24.86, 24.39, 10.86 (s, $\underline{C}H_3$), 108.79, 109.48 (C, isopropylidene), 163.73 [N=$\underline{C}(CH_3)$-O], 164.29 [N=$\underline{C}(CH_2)$-O].

Anal. Calcd. for $C_{15}H_{22}N_2O_6$: C, 55.20, H, 6.75, N, 8.59.

Found: C, 54.80, H, 6.74, N, 8.42.

1-H-1,5-bis-[6'-deoxy-(1',2':3':4'-di-*O*-isopropylidene- α-D-galactopyranos-6'-yl)]tetrazole (8) and 2-H-2,5-bis-[6'-deoxy-(1',2':3':4'-di-*O*-isopropylide-ne-α-D-galactopyranos-6'-yl)]tetrazole (9)

A mixture of tetrazole **6** (0.2 g, 0.64 mmol), 4-toluenesulfonate **3** (0.52 g, 1.26 mmol) and anhydrous potassium carbonate (0.35 g, 2.53 mmol) in 10 mL of anhydrous dimethylformamide was stirred and heated at 110°C for 120 hours. The reaction was monitored by tlc (*n*-hexane:ethyl acetate 7:3). After the addition of 5 mL of water the reaction mixture was extracted with ethyl ether (3 portions of 50 mL). The organic layer was separated, dried over anhydrous sodium sulfate, concentrated and the crude mixture was separated by gradient column chromatography (*n*-hexane/ethyl acetate), the regioisomer **9**

been eluted first. Then each isolated compound was purified by three further column chromatography (*n*-hexane/ethyl acetate 6:4, silica Gel 60 G Merck 230-400 mesh) to remove remaining starting materials and alcohol **2** which is a side product of the reaction. Compound **9** was obtained as a solid product, 0.135 g, 38.8% yield, mp 193.6-194.6°C, $[\alpha]_D$ - 43,8° (c 3.6, CH_2Cl_2), ^1H NMR (δ, $CDCl_3$): 5.50 (d, $J_{1'',2''}$ = 4.8 Hz, H1''), 5.45 (d, $J_{1',2'}$ = 4.8 Hz, H1'), 4.82 (dd, $J_{6a'',5''}$ = 8.4 Hz, $J_{6a'',6b''}$ = 13.6 Hz, H6a''), 4.72 (dd, $J_{6b'',5''}$ = 4.8 Hz, $J_{6b'',6a''}$ = 14 Hz, H6b''), 4.64 (dd, $J_{3'',2''}$ = 2.4 Hz, $J_{3'',4''}$ = 7.8 Hz, H3''), 4.61 (dd, $J_{3',2'}$ = 2.0 Hz, $J_{3',4'}$ = 8.0 Hz, H3'), 4.45-4.42 (m, H5''), 4.33-4.29 (m, H5', H2' and H2''), 4.24 (dd, $J_{4'',5''}$ = 1.2 Hz, $J_{4'',3''}$ = 9.0 Hz, H4''), 4.22 (dd, $J_{4',5'}$ = 1.2 Hz, $J_{4',3'}$ = 9.0 Hz, H4'), 3.24 (d, $J_{6a',5'}$ or $J_{6b',5'}$ = 6.4 Hz, H6a' and H6b'), 1.52, 1.50, 1.49, 1.48, 1.36, 1.34, 1.31, 1.29 (s, $C\underline{H}_3$), ^{13}C NMR (δ, $CDCl_3$): 96.84 (C1''), 96.58 (C1'), 72.27 (C2''), 72.18 (C2'), 71.23 (C3''), 71.14 (C3'), 70.90 (C4''), 70.80 (C4'), 66.97 (C5''), 66.78 (C5'), 53.33 (C6''), 27.35 (C6'), 26.42, 26.35, 25.41, 25.37, 24.87, 24.82 ($\underline{C}H_3$), 109.92, 109.30, 108.96, 108.61 (C, isopropylidene), 163.51 (C, tetrazole).

Anal. Calcd. for $C_{25}H_{38}N_4O_{10}$: C, 54.15; H, 6.86; N, 10.11.

Found: C, 54.34; H, 6.82; N, 9.95.

Compound **8** was obtained as an oil that crystallized under reduced pressure, 0.031 g, 8.6 % yield, mp 114-117°C, $[\alpha]_D$ – 50.8° (c 1.5, CH_2Cl_2), ^1H NMR (δ, $CDCl_3$): 5.42 (dd, $J_{1",2"}$ = 5.6 Hz, H1"), 5.41 (dd, $J_{1',2'}$ = 5.6 Hz, H1'), 4.64 (dd, $J_{3",2"}$ = 2.8 Hz, $J_{3",4"}$ = 2.8 Hz, H3"), 4.62 (dd, $J_{3',2'}$ = 2.8 Hz, $J_{3',4'}$ = 2.8 Hz, H3'), 4.57 (dd, $J_{6a",5"}$ = 9.0 Hz, $J_{6a",6b"}$ = 14.6 Hz, H6a"), 4.48 (dd, $J_{6b",5"}$ = 3.4 Hz, $J_{6b",6a"}$ = 14.6 Hz, H6b"), 4.30-4.27 (m, H5", H2' and H2"), 4.25-4.15 (m, H5', H4', H4"), 3.28 (dd, $J_{6a',5'}$ = 9.0 Hz, $J_{6a',6b'}$ = 15.4 Hz, H6a'), 3.17 (dd, $J_{6b',5'}$ = 4.4 Hz, $J_{6b',6a'}$ = 15.4 Hz, H6b'), 1.475, 1.47, 1.42, 1.38, 1.34, 1.26, 1.24 (s, $C\underline{H}_3$), ^{13}C NMR (δ, $CDCl_3$): 96.12 (C1"), 95.96 (C1'), 72.13 (C5"), 71.78 (C5'), 71.01 (C3"), 70.85 (C3'), 70.77 (C2"), 70.23 (C2'), 67.37 (C4"), 67.14 (C4'), 47.43 (C6"), 24.60 (C6'), 26.03, 25.95, 25.88, 25.84, 24.87, 24.48, 24.43 ($\underline{C}H_3$), 109.86, 109.43, 109.06, 108.94 (C, isopropylidene), 153.96 (C, tetrazole).

Anal. Calcd. for $C_{25}H_{38}N_4O_{10}$: C, 54.15; H, 6.86; N, 10.11.

Found: C, 54.52; H, 7.19; N, 9.99.

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