# A Short Synthesis of *C*-Glycosyl Pyrazoles and Pyrroles



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The sodium salt of TOSMIC reacted with (*E*)-3,4,5,6,7-penta-*O*-acetyl-1,2-dideoxy-1-*C*-nitro-D-*galacto*- (**1**) and -D-*manno*-hept-1-enitol (**2**) to give 3-(D-*galacto*- (**3**) and 3-(D-*manno*-penta-*O*-acetylpentitol-1-yl)-4-nitropyrrole (**4**), respectively. Compound **1** reacted with diaryl nitrile imines, affording 1,3-diaryl-4-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)pyrazoles **5** and **6**.

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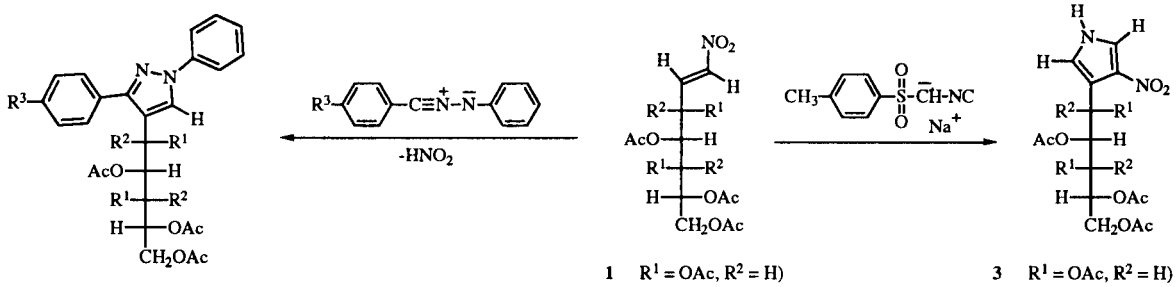
*C*-Nucleosides are a worthwhile research field because of their antiviral or cytostatic properties [1]. In this field, the 1-nitroalkenes derived from carbohydrates have been successfully employed as precursors of *C*-nucleosides [2] because of the ready availability of the starting materials and the high interest of the products obtained. For instance, 5-*C*-glycosylpyrazoles are obtained by reacting sugar nitroalkenes with aldehyde methyl- or phenylhydrazones [3]. When formaldehyde phenylhydrazone is employed, the 4-*C*-glycosylpyrazole is obtained [3]. The 1,3-dipolar cycloaddition of diazoalkanes to sugar nitroalkenes affords 4-*C*-glycosylpyrazoles as the main products [4-6]. In addition, the 1,3-dipolar cycloaddition of 1-nitroalkenyl sugars and mesoionic 1,3-oxazolium-5-olate [7] affords 3-*C*-glycosylpyrroles. Although many cycloadditions of tosylmethylisocyanide (TOSMIC) [8] to activated alkenes and sugar nitrile imines [9] to alkenes are known, the reactions of 1-nitroalkenyl sugars with TOSMIC or nitrile imines have not been studied. In this paper, we report on a new cyclization and 1,3-cycloaddition reactions of (*E*)-3,4,5,6,7-penta-*O*-acetyl-1,2-dideoxy-1-*C*-nitro-D-*galacto*-hept-1-enitol (**1**) and (*E*)-3,4,5,6,7-penta-*O*-acetyl-1,2-dideoxy-1-*C*-nitro-D-*manno*-hept-1-enitol (**2**) with TOSMIC and diaryl nitrile imines, which afford new *C*-glycosylpyrroles and pyrazoles.

Thus, when the sodium salt of TOSMIC was reacted with **1** in DMSO for 5 minutes at 0°, after working up, the new 3-(D-*galacto*-penta-*O*-acetylpentitol-1-yl)-4-nitropyrrole (**3**) was obtained in 51% yield. When compound **2** was reacted with the sodium salt of TOSMIC, under the same conditions, the corresponding 3-(D-*manno*-penta-*O*-acetylpentitol-1-yl)-4-nitropyrrole (**4**) was obtained in 50% yield. Both reactions are shown in the Scheme. In the $^1$H nmr spectra of compounds **3** and **4**, besides the sugar moiety signals, three singlet signals at δ 10, δ 6.7-6.9 and δ 7.6, due to the pyrrole nucleus, were detected. In addition, four new signals in $^{13}$C nmr spectra of **3** and **4**, in the δ 115-135 region, were assigned to the pyrrole nucleus which was formed. Other analytical data confirmed the assigned structures. Coupling constants in $^1$H nmr and chemical shifts in $^1$H and $^{13}$C nmr for compounds **3** and **4** are shown in Table I. Attempt to react **1** or **2** with methyl isocyanoacetate in the presence of DBU, or the sodium salt of *p*-nitrobenzylisocyanide were unsuccessful, and only the starting material was recovered after working up the reactions. On the other hand, the reaction of compound **1** with diphenyl nitrile imine, generated *in situ* from *N*-phenylbenzhydrazidoyl chloride, in refluxing xylene for 2 days, was not totally regioselective. This reaction afforded, after repeated column chromatography, the 1,3-diphenyl-4-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)pyrazole (**5**), which was accompanied by the 5-glycosyl-1,3-diphenylpyrazole isomer of **5**, in an 8:1 ratio. These relative amounts were measured by integrating the $^1$H nmr




**5** $R^1$ = OAc, $R^2$ = H, $R^3$ = H)
**6** $R^1$ = OAc, $R^2$ = H, $R^3$ = $OCH_3$)

**1** $R^1$ = OAc, $R^2$ = H)
**2** $R^1$ = H, $R^2$ = OAc)

**3** $R^1$ = OAc, $R^2$ = H)
**4** $R^1$ = H, $R^2$ = OAc)

Table I

$^1$H NMR and $^{13}$C NMR Data for Compounds **3** and **4**

| $^1$H nmr | **3** | **4** | $^{13}$C nmr | **3** | **4** |
|---|---|---|---|---|---|
| H-1 | 10.08 (s, 1H) | 10.24 (s, 1H) | C-2 | 117.8 | 119.8 |
| H-2 | 6.66 (s, 1H) | 6.89 (s, 1H) | C-3 | 115.9 | 114.6 |
| H-5 | 7.59 (s, 1H) | 7.66 (s, 1H) | C-4 | 133.9 | 134.7 |
| H-1' | 6.48 (s, 1H) | 6.33 (d, 1H) | C-5 | 121.5 | 121.6 |
| | | $J_{1',2'}$ = 8.4 | | | |
| H-2' | 5.61 (dd, 1H) | 5.71 (dd, 1H) | C-1'-4' | 66.4 | 65.0 |
| | | | | 67.6 | 67.3 |
| | $J_{2',3'}$ = 9.9 | $J_{2',3'}$ = 2.0 | | 67.8 | 67.9 |
| | | | | 68.2 | 70.3 |
| H-3' | 5.50 (dd, 1H) | 5.58 (dd, 1H) | C-5' | 62.0 | 61.7 |
| | $J_{3',4'}$ = 1.7 | $J_{3',4'}$ = 8.9 | | | |
| H-4' | 5.35 (m, 1H) | 5.12 (m, 1H) | $CH_3$ | 20.0 | 20.0 |
| | | | | 20.3 | 20.3 |
| | $J_{4',5'}$ = 4.9 | $J_{4',5'}$ = 2.9 | | 20.5 | 20.4 |
| | $J_{4',5''}$ = 7.5 | $J_{4',5''}$ = 5.0 | | 21.1 | 20.5 |
| | | | | 21.3 | 20.7 |
| H-5' | 4.32 (dd, 1H) | 4.25 (dd, 1H) | C = O | 169.0 | 169.4 |
| | | | | 169.9 | 169.7 |
| | $J_{5',5''}$ = -11.6 | $J_{5',5''}$ = -12.5 | | 170.0 | 169.8 |
| | | | | 170.3 | 170.5 |
| | | | | 170.5 | 170.6 |
| H-5'' | 3.91 (dd, 1H) | 4.13 (dd, 1H) | | | |
| $CH_3$ | 1.88 (s, 3H) | 1.90 (s, 3H) | | | |
| | 2.00 (s, 3H) | 2.04 (s, 3H) | | | |
| | 2.03 (s, 3H) | 2.07 (s, 3H) | | | |
| | 2.15 (s, 3H) | 2.09 (s, 3H) | | | |
| | 2.17 (s, 3H) | 2.15 (s, 3H) | | | |

Table II

$^1$H NMR Data for **5** and **6** and $^{13}$C NMR Data for **5**

| $^1$H nmr | **5** | **6** | $^{13}$C nmr | **5** |
|---|---|---|---|---|
| H-5 | 7.95 (s, 1H) | 7.90 (s, 1H) | C-3 | 129.5 |
| H-1' | 6.27 (d, 1H) | 6.10 (s, 1H) | C-4 | 116.5 |
| | $J_{1',2'}$ = 3.4 | | | |
| H-2' | 5.32 (dd, 1H) | 5.94 (d, 1H) | C-5 | 118.9 |
| | $J_{2',3'}$ = 9.4 | $J_{2',3'}$ = 8.4 | | |
| H-3' | 5.43 (dd, 1H) | 5.61 (dd, 1H) | C-1'-4' | 65.9 |
| | $J_{3',4'}$ = 1.9 | $J_{3',4'}$ = 2.9 | | 67.7 |
| | | | | 68.2 |
| | | | | 69.3 |
| H-4' | 5.24 (m, 1H) | 5.44 (m, 1H) | C-5' | 61.9 |
| | $J_{4',5'}$ = 5.1 | $J_{4',5'}$ = 5.2 | | |
| H-5' | 4.23 (dd, 1H) | 4.26 (dd, 1H) | C-Aryl | 125.6-151.1 |
| H-5'' | 3.81 (dd, 1H) | 3.98 (dd, 1H) | $CH_3$ | 20.3 |
| | $J_{4',5''}$ = 7.4 | $J_{4',5''}$ = 6.9 | | 20.3 |
| | $J_{5',5''}$ = -11.6 | $J_{5',5''}$ = -11.7 | | 20.5 |
| | | | | 20.5 |
| | | | | 20.8 |
| H-Aryl | 7.19-7.81 | 6.74-7.92 | C = O | 169.0 |
| | (m, 10H) | (m, 9H) | | 169.6 |
| | | | | 169.7 |
| | | | | 170.1 |
| | | | | 170.3 |
| $CH_3$ | 1.89 (s, 3H) | 2.03 (s, 3H) | | |
| | 1.93 (s, 3H) | 2.04 (s, 3H) | | |
| | 1.98 (s, 3H) | 2.06 (s, 3H) | | |
| | 2.03 (s, 3H) | 2.08 (s, 3H) | | |
| | 2.09 (s, 3H) | 2.13 (s, 3H) | | |
| $CH_3O$ | | 3.82 (s, 3H) | | |

signals of the inseparable mixture. Product **5** showed a neat signal at δ 7.96, assigned to the H-5 of the pyrrole nucleus of **5**, in addition to a smaller and neat signal at δ 6.64, assigned to the H-4 of the isomer of **5**, whose integrals corresponded to the above proportion. The overall yield was 35%. When compound **1** was reacted with *C*-(4-methoxyphenyl)-*N*-phenylnitrile imine, under the same conditions, the corresponding 1-phenyl-3-(*p*-methoxyphenyl)-4-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)pyrazole (**6**) is obtained in 30% yield as the sole reaction product. The structure of compound **6** was unequivocally assigned on the basis of its $^1$H nmr spectrum. Other analytical data confirmed the structure. In this case the strong directive effect of the methoxy group dominates the regiochemistry of the reaction, thus, a unique product was obtained. Both products **5** and **6** are shown in the Scheme. Coupling constants and chemical shifts in the $^1$H nmr spectra for compounds **5** and **6**, and $^{13}$C nmr chemical shifts for **5**, are shown in Table II. Compound **2** did not react with both nitrile imines under the same conditions. In addition, compounds **1** and **2** did not react with *C*-phenyl-*N*-(*p*-nitrophenyl)nitrile imine, probably because of the electron withdrawing effect of the nitro group.

Many 3-*C*-glycosylpyrroles and related compounds have been investigated [7,10-11], even as precursors of Showdomycin [11] and acyclo-*C*-nucleosides [12], although the construction of the pyrrole moiety frequently implies many steps. Isocyanides have been scarcely used in carbohydrate chemistry [13,14]. Thus, the above reported reactions of **1** and **2** with TOSMIC expand the isocyanide methodology in *C*-nucleoside chemistry by opening a straightforward way to new and potentially useful 3-*C*-glycosyl-4-nitropyrroles. On the other hand, the observed regiochemistry of the reactions between **1** and diphenyl nitrile imines is the opposite to that reported for the reaction between **1** and benzaldehyde phenylhydrazone [3]. In this way, the above reported reactions of **1** and nitrile imines complete the known methods, making accessible some new 4-*C*-glycosyldiarylpyrazoles.

## EXPERIMENTAL

Melting points were determined with a Gallenkamp MFB-595 apparatus and are uncorrected. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter at 18°. The ir spectra were registered with Perkin-Elmer 399 and 1310 spectrophotometers. The $^1$H and $^{13}$C nmr spectra were recorded on a Bruker AC200-E spectrometer; chemical shifts are reported in ppm from tetramethylsilane as internal standard, coupling constants in Hz. Methyl, methylene and methine groups, and quaternary carbons, were discriminated in the $^{13}$C nmr spectra by DEPT experiments. Mass spectral data were taken at the Service of Spectroscopy, Imperial College of Science, Technology and Medicine, London (U.K.), at 70 eV. Elemental analyses were carried out on a Perkin Elmer 240-B apparatus.

General Procedure for the Synthesis of **3** and **4**.

A solution of tosylmethylisocyanide (0.78 g, 4 mmoles) in dimethyl sulfoxide (40 ml) was added to a suspension of sodium hydride (0.17 g, 7.1 mmoles) in diethyl ether (40 ml) at 0° under a nitrogen atmosphere, and the mixture was stirred for 5 minutes at 0°. A solution of nitroalkenyl sugar **1** or **2** (1.73 g, 4 mmoles), prepared from D-galactose [15] or D-mannose [16], in dimethyl sulfoxide (50 ml) was added dropwise to the above mixture, maintaining the temperature at 0°. The resulting mixture was stirred at 0° for additional 2 hours, then poured into saturated aqueous ammonium chloride solution, and extracted with diethyl ether (3 x 100 ml). The combined ethereal extracts were washed with saturated sodium chloride aqueous solution, dried with magnesium sulfate and evaporated. Separations of products were obtained by using column chromatography (120 cm length, 5 cm diameter) filled with silica gel type 60 (Merck) and dichloromethane: methanol (50:1, v/v) as the eluent.

3-(D-*galacto*-Penta-*O*-acetylpentitol-1-yl)-4-nitropyrrole (**3**).

Compound **3** was obtained in 50% yield as colorless needles (ethanol), mp 175-176°; ir (potassium bromide): ν 3300, 1730, 1210, 1020 $cm^{-1}$; $[\alpha]_D$ +33.6°; $[\alpha]_{578}$ +34.3°; $[\alpha]_{546}$ +36.9°; (*c* 0.5, $Cl_3CH$); ms: m/z (%) 472 ($M^+$, 2), 281 (78), 84 (100).

*Anal.* Calcd. for $C_{19}H_{24}O_{12}N_2$: C, 48.31; H, 5.12; N, 5.93. Found: C, 48.37; H, 5.19; N, 5.88.

3-(D-*manno*-Penta-*O*-acetylpentitol-1-yl)-4-nitropyrrole (**4**).

Compound **4** was obtained in 51% yield as colorless needles (ethanol), mp 139-141°; ir (potassium bromide): ν 3320, 1730, 1200, 1020 $cm^{-1}$; $[\alpha]_D$ +23.1°; $[\alpha]_{578}$ +24.0°; $[\alpha]_{546}$ +26.0°; (*c* 0.5, $Cl_3CH$); ms: m/z (%) 472 ($M^+$, 3), 281 (75), 84 (100).

*Anal.* Calcd. for $C_{19}H_{24}O_{12}N_2$: C, 48.31; H, 5.12; N, 5.93. Found: C, 48.35; H, 5.17; N, 5.89.

General Procedure for the Synthesis of **5** and **6**.

Triethylamine (0.73 g, 0.87 mmole) was added to a solution of nitroalkenyl sugar **1** (1 g, 2.3 mmoles) and *N*-phenylbenzhydrazidoyl chloride [17] (0.58 g, 2.5 mmoles) or *N*-phenyl-*C*-(4-methoxyphenyl)hydrazidoyl chloride [18] (0.66 g, 2.5 mmoles) in xylene (100 ml) at room temperature. The resulting solution was refluxed for 2 days and then evaporated to dryness. Separations of products were obtained by using column chromatography (120 cm length, 5 cm diameter) filled with silica gel type 60 (Merck) and trichloromethane:methanol (100:1, v/v) as the eluent.

1,3-Diphenyl-4-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)pyrazole (**5**).

Compound **5** was obtained in 35% yield as a sticky solid; ir (potassium bromide): ν 1760, 1676, 1652, 1220, 1035 $cm^{-1}$; $[\alpha]_D$ +6.7°; $[\alpha]_{578}$ +7.1°; $[\alpha]_{546}$ +7.8°; $[\alpha]_{436}$ -29.0°; (*c* 3.0, $Cl_3CH$); ms: m/z (%) 580 ($M^+$, 0.5), 249 (99), 77 (28), 43 (100).

*Anal.* Calcd. for $C_{30}H_{32}O_{10}N_2$: C, 62.06; H, 5.56; N, 4.82. Found: C, 61.97; H, 5.49; N, 4.78.

1-Phenyl-3-(*p*-methoxyphenyl)-4-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)pyrazole (**6**).

Compound **6** was obtained in 30% yield as a sticky solid; ir (potassium bromide): ν 1720, 1668, 1606, 1259, 1212, 1027 $cm^{-1}$; $[\alpha]_D$ +0.1°; $[\alpha]_{578}$ +0.2°; $[\alpha]_{546}$ -0.1°; $[\alpha]_{436}$ -161.8°; (*c* 3.0, $Cl_3CH$); ms: m/z (%) 597 ($[M-CH]^+$, 0.5), 135 (100), 93 (63), 43 (93.5).

*Anal.* Calcd. for $C_{31}H_{34}O_{11}N_2$: C, 60.92; H, 5.61; N, 4.59. Found: C, 61.07; H, 5.69; N, 4.70.

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