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CYANOSUGARS—II[1]

SYNTHESIS OF HEXOPYRANOSYL CYANIDES BY REACTION OF GLYCALS WITH TRIMETHYLSILYL CYANIDE

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Abstract—3,4,6-Tri-O-acetyl-O-glucal and 2,3,4,6-tetra-O-acetyl-2-hydroxy-D-glucal reacted with Me_3SiCN in the presence of a Lewis acid ($SnCl_4$, BF_3) as catalyst to give anomeric pairs of 2,3-dideoxy-hex-2-enopyranosyl cyanides and 3-deoxy-hex-2-enopyranosyl cyanides. These 2,3-unsaturated glycopyranosyl cyanides were hydrogenated over Pd/C to afford the corresponding 2,3-dideoxy- and 3-deoxy-hexopyranosyl cyanides.

Glycosyl cyanides are useful, versatile intermediates for the synthesis of C-glycosyl derivatives,[2,3] since the cyano group can be readily transformed into a variety of other functional groups. In fact, glycosyl cyanides have been used as starting products for the synthesis of most naturally occurring C-nucleoside antibiotics[2,3] and many analogs.[2-4] Glycosyl cyanides can be obtained by reaction of peracylated glycosyl halides with silver or mercury (II) cyanide.[2] In this reaction can also be obtained variable yields of other products such as isocyanides,[5] unsaturated sugars[6] and 1,2-O-(cyanoalkylidene) glycosyl derivatives.[7] Recently, we reported[1] a new procedure for the synthesis in high yields of glycosyl cyanides by reaction of acylated sugars with trimethylsilyl cyanide[8-10] in the presence of a Lewis acid as catalyst. Also recently, carbohydrates, and particularly unsaturated pyranosides, have been used as starting compounds, providing both useful functional groups as well as suitable chirality, for the total synthesis of a variety of natural products.[11,12]

According to this we considered of interest to study the reactions of glycals with Me_3SiCN under Lewis acid catalysis.† In these conditions, the CN group of Me_3SiCN acts as an anion stabilized by the adjacent Si atom[9] and should react with the electrophylic center(s) of glycals to give hexenopyranosyl cyanides. These compounds have two reactive functional groups and can be useful chiral synthons.

Reaction of 3,4,6-tri-O-acetyl-D-glucal with Me_3SiCN in nitromethane and in the presence of boron trifluoride etherate afforded the two 2,3-unsaturated pyranosyl cyanide α- and β-anomers **1** and **3** in excellent total yield (57 and 42%, respectively). Like in other reactions of glycals[13] and nucleophyles, the attachment of the cyano group to the anomeric position of the glycal occurred, together with the elimination of the 3-acetoxyl group and migration of the 1,2-double bond to the 2,3-positions. Hex-2-enopyranoxyl cyanides **1** and **3** were also obtained in lower yields (41 and 27% respectively) by reaction of triacetylglucal with cheap sodium cyanide using the same solvent and Lewis acid catalyst as before.

In the same way, we carried out the reaction of triacetylglucal with trimethylsilylazide in anhydrous acetonitrile using $SnCl_4$ as catalyst. The reaction yielded a mixture of the two anomeric 4,6-di-O-acetyl-2,3-dideoxy-α- and -β-D-*erythro*-hex-2-enopyranosyl azides **5** and **6** and the two epimeric 4,6-di-O-acetyl-3-azido-1,2,3-trideoxy-D-*ribo*- and -*arabino*-hex-1-enopyranoses **7** and **8** with 20, 5, 30, and 25% yield, respectively. Similar results have been obtained by Heyns[16] from the reaction of triacetylglucal with sodium azide.

3-C-Cyano-hex-1-enopyranosyl derivatives, such as **9** or **10**, analogs of 3-azido compounds **7** or **8**, were not obtained either from the above reactions, or by attempts of isomerisation from **1** and **3**. These reactions were carried out by heating the reagents to 100° for up to 3 days in polar aprotic solvents (acetonitrile, dimethylformamide, hexamethylphosphoric triamide) with protonic (trifluoracetic acid, *p*-toluensulfonic acid) and Lewis acid ($SnCl_4$, BF_3) catalysis. These conditions favour the formation of allylic carbonium ion **11**, which we have shown to be the intermediate[14,15] in the equilibrium transformation

$$\begin{matrix}\text{hex-2-enopyranosyl} \\ \text{derivatives}\end{matrix} \rightleftarrows \begin{matrix}\text{hex-1-enopyranosyl} \\ \text{derivatives}\end{matrix}$$

at least in those cases in which no sigmatropic allylic rearrangement[16-18] can be invoked to explain such conversion.

Treatment of 2,3,4,6-tetra-O-acetyl-2-hydroxy-D-glucal with Me_3SiCN and boron trifluoride etherate in anhydrous nitromethane afforded a mixture of 2,4,6-tri-O-acetyl-3-deoxy-α- and -β-D-*erythro*-hex-2-enopyranosyl cyanide anomers **12** and **14** in 46 and 34% yield, respectively.

Structures of the above hex-2-enopyranosyl cyanides **1**, **3**, **12** and **14** were demonstrated by analytical and NMR spectroscopic methods (Table 1). H1 half chair conformations were determined from $J_{4,5} = 8.5$–9 Hz for **1**, **2** and **12**, which indicated the axial-axial relationship of H-4 and H-5. However, the value of $J_{4,5} = 7.1$ Hz and the values of $J_{3,4} = 3.0$ and $J_{1,2} = 2.1$ Hz for β-cyanide **14**, are somewhat different of those expected ($J_{4,5} = 8.5$–9.0 Hz, $J_{3,4} = 1.5$–2, $J_{1,4} = 2.5$ Hz) for β-D-*erythro*-hex-2-enopyranosyl derivatives in H1 half chair conformation.[19,21,22] In fact, those coupling constants are in between the

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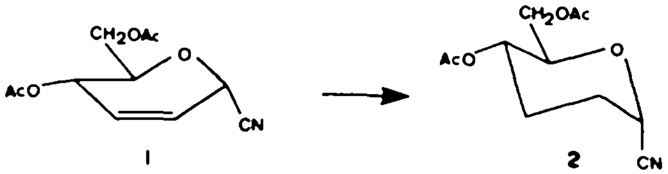
†During the preparation of this manuscript it came to our attention that a related work is being carried out by G. Grynkievicz and J. N. BeMiller. See Abstract I-18, XIth International Carbohydrate Symposium, Vancouver, Canada, 22–28 August 1982.



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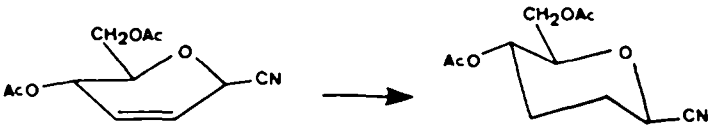

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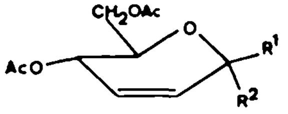
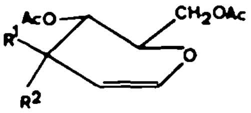


5 , $R^1 = H$; $R^2 = N_3$

6 , $R^1 = N_3$; $R^2 = H$

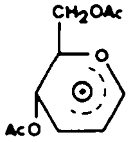


7 , $R^1 = H$; $R^2 = N_3$

8 , $R^1 = N_3$; $R^2 = H$

9 , $R^1 = H$; $R^2 = CN$

10 , $R^1 = CN$; $R^2 = H$



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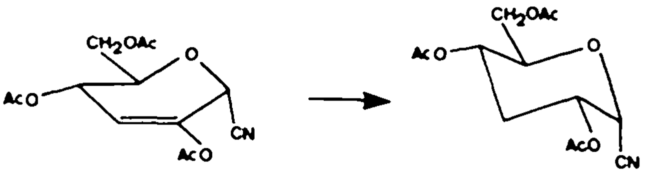
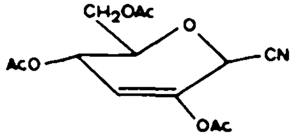


12 13



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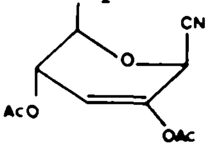

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expected values for H1 (**14**) and 1H (**15**) conformations, which suggests the existence of a conformational equilibrium between both conformations in which the former predominated. The preference of related 3-deoxy-β-D-hex-2-enopyranosyl esters to exist in 1H conformation has already been reported in contrast to the corresponding α-anomers which exist in H1 conformation.[20,21] Anomeric configurations were assigned on the basis of the values of $J_{1,2}$ and the homoallylic coupling $J_{1,4}$. The compounds showing the largest homoallylic coupling ($J_{1,4} \sim 2$–2.5) have been identified as the β-anomers, having a *quasi*-axial-*quasi*-axial relationship between H-1 and H-4, in agreement with previous assignments for anomeric pairs of related 2,3-dideoxy-α- and -β-D-*erythro*-hex-2-enopyranosyl- and 3-deoxy-α- and -β-D-*erythro*-hex-2-enopyranosyl derivatives.[15,19–22] Furthermore, all the chemical shifts and coupling constants of cyanides **1**, **3**, **12** and **14** were very similar to those reported for the mentioned 2,3-unsaturated hexopyranoside analogs,[15,19,22] thus providing additional evidences of their conformations

Table 1. NMR Parameters of hex-2-enopyranosyl cyanides **1**, **3**, **12**, **14** ($CDCl_3$)

Chemical shifts (δ)

Comp.	H-1	H-2	H-3	H-4	H-5	H-6
1	5.08	5.89	6.03	5.36	4.03	4.27
3	5.13	5.91	6.03	5.32	3.83	4.29
12	5.12		5.94	5.50	4.08	4.30
14	5.36		5.87	5.40	3.91	4.26

Coupling constants (Hz)

Comp.	$J_{1,2}$	$J_{1,3}$	$J_{1,4}$	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,5}$
1	2.9	1.3	1.8	10.2	1.4	1.3	9.0
3	1.8	1.8	2.3	10.2	1.8	1.8	8.5
12		1.3	1.6			2.4	8.5
14		1.9	2.1			3.0	7.1

and configurations. The main differences were in the chemical shifts of the anomeric protons, which, as expected, in the case of cyanides, appeared at higher fields δ 5.08–5.36 ppm.

These assignments were confirmed by chemical means. Catalytic hydrogenation of 2,3-unsaturated cyanides **1**, **3** and **12** with 10% Pd–C gave in excellent yields hexopyranosyl cyanides **2**, **4** and **13**, respectively. The C1 conformations of **2**, **4** and **13** were deduced from the corresponding NMR spectra[24] (Table 2), which showed $J_{4,5}$ = 10.0–10.2 Hz, which clearly established the diaxial coupling between these protons. The NMR spectra of compounds **2** and **4** showed a broad signal at δ1.5–2.6 ppm assigned to the H-2a, H-2e, H-3a and H-3e protons. The close chemical shifts of these protons and the fact that their signals were partially overlapped by those of the acetoxy groups precluded any attempt to determine the corresponding magnetic parameters. Thus, anomeric configurations were determined from the sum $J_{1,2a} + J_{1,2e}$ measured on proton H-1, which was 6.5 Hz for the α-anomer **2** and 11.1 Hz for the β-anomer **4**. These values indicated the equatorial and axial disposition of the corresponding anomeric protons. The α-anomeric configuration of **13** could not be unequivocally deduced from $J_{1,2}$ = 3 Hz. However, since no anomerisation is expected, and have not been observed in previous catalytic hydrogenations of related 2,3-unsaturated hexopyranosides,[24] it was assigned as α, identical to the starting unsaturated cyanide. The equatorial disposition of the 2-acetoxyl group of **13** was determined from the sum $J_{1,2} + J_{2,3a} + J_{2,3e}$ = 17 Hz measured on the signal of H-2, since, again, the chemical shifts of H-3a

Table 2. NMR Parameters of hexopyranosyl cyanides **2**, **4** and **13** ($CDCl_3$)

Chemical shifts (δ)

Comp.	H-1	H-2	H-3	H-4	H-5	H-6
2	4.88	1.68–2.38		4.68	3.95	4.22
4	4.27	1.83–2.63		4.69	3.53	4.15
13	5.00	4.75	2.53	4.87	3.97	4.17

Coupling constants (Hz)

Comp.	$J_{1,2a}+J_{1,2e}$	$J_{2,3a}+J_{2,3e}$	$J_{3a,4}+J_{3e,4}$	$J_{4,5}$
2	6.5		15.2	10.0
4	11.1		15.2	10.2
13	3	14		10.1

and H-3e were very close. The value of that sum is enough to include a diaxial $J_{2,3a}$ coupling constant. This assignment is reasonable from the stereochemical point of view since the addition of hydrogen should take place from the less hindered upper side of the molecule, opposite to the *quasi*-axial anomeric cyano group.

EXPERIMENTAL

M.ps were measured with a kofler hot-stage apparatus. ^1H NMR spectra were recorded with a Varian XL-100 or a Varian EM-390 spectrometer operating at 100 or 90 MHz, respectively, with Me_4Si as internal standard. IR spectra were recorded with a Perkin–Elmer 257 spectrophotometer. Optical rotations were determined with a Perkin–Elmer 141 polarimeter. Analytical TLC was performed on Al-sheets coated with a 0.2 mm layer of silica gel 60 F_{254} (Merck), and preparative layer chromatography was performed on 20 × 20 cm glass plates coated with a 2 mm layer of silica gel PF_{254} (Merck).

Reaction of 3,4,6-tri-O-acetyl-D-glucal with Me_3SiCN. To a soln of 3,4,6-tri-O-acetyl-D-glucal (1 g, 3.67 mmole) in anhydr nitromethane (15 ml), Me_3SiCN (1 ml) was added dropwise. The mixture was stirred at room temp for 15 min and BF_3 (4 drops) was added. The stirring continued until disappearance of the starting sugar. The rn mixture was purified by repeated chromotographies on preparative TLC plates using EtOAc–hexane (1:4) to give two compounds. The faster running band gave 0.50 g (57%) of *4,6-di-O-acetyl-2,3-dideoxy-α-D-*erythro-*hex-2-enopyranosyl cyanide* **1** as a white solid, m.p. 90–91° (from water), $[\alpha]_D - 14.6°$ (*c* 1, $CHCl_3$) (Found: C, 55.44; H, 5.52; N, 5.91. $C_{11}H_{13}NO_5$ requires: C, 55.22; H, 5.47; N, 5.85%). The slower running band afforded 0.368 g (42%) of *4,6-di-O-acetyl-2,3-dideoxy-β-D-*erythro-*hex-2-enopyranosyl cyanide* **3** as a syrup which decomposed on standing, $[\alpha]_D$ 197.5° (*c* 1, $CHCl_3$) (Found: C, 54.88; H, 5.72; N, 5.80. $C_{11}H_{13}NO_5$ requires: C, 55.22; H, 5.47; N, 5.85).

Reaction of 3,4,6-tri-O-acetyl-D-glucal with sodium cyanide. To a cooled soln (− 15°) of triacetylglucal (1.36 g, 5 mmole) in anhydr acetonitrile (250 ml), BF_3 (10 drops) was added. The mixture was stirred for 10 min, and NaCN (1.22 g, 24.8 mmole) was added. The stirring continued at − 15° for 15 min, then, at intervals of 30 min, aliquots of BF_3 (1 ml) were added up to a total of 5 ml and the reaction proceeded until disappearance of the starting sugar. The rn mixture was evaporated to dryness and the residue partitioned between CH_2Cl_2 (200 ml) and Na_2CO_3 aq (100 ml). The organic phase was washed with water dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed as before to give **1** (0.49 g, 41%) and **3** (0.32 g, 27%) identical in all respects to **1** and **3** obtained before.

Reaction of 3,4,6-tri-O-acetyl-D-glucal with Me_3SiN_3. To a cooled (0°), stirred mixture of triacetylglucal (2.72 g, 0.01 mole), anhyd acetonitrile (15 ml) and Me_3SiN_3 (2.30 g, 0.02 mole), $SnCl_4$ (2.61 g, 0.01 mole) was added dropwise. The stirring continued until disappearance of glucal. Then, the mixture was concentrated *in vacuo* under 25° and the residue washed with water, $NaHCO_3$ aq and water, dried over $CaCl_2$ and further concentrated *in vacuo* to give a syrup which was chromatographed on preparative TLC plates with EtOAc–hexane (1:3) to give **5**, **6**, **7** and **8** in 20, 5, 30 and 25% yield, respectively.[16]

Reaction of 2,3,4,6-tetra-O-acetyl-2-hydroxy-D-glucal with Me_3SiCN. A mixture of tetraacetyl-2-hydroxy-D-glucal (1 g, 3 mmole), Me_3SiCN (1 ml), BF_3 (4 drops) and anhyd nitromethane (15 ml) was stirred at room temp until disappearance of the starting sugar. The soln was concentrated *in vacuo* and the residue chromatographed several times on preparative TLC plates with EtOAc–hexane (1:3) to give two bands. The fastest band gave 0.41 g (46%) of *2,4,6-tri-O-acetyl-3-deoxy-α-D-*erythro-*hex-2-enopyranosyl cyanide* **12** as a solid, m.p. 71–72° (from water), $[\alpha]_D + 2°$ (*c* 1, $CHCl_3$) (Found: C, 52.70; H, 5.26; N, 4.34. $C_{13}H_{15}NO_7$ requires: C, 52.52; H, 5.03; N, 4.71). The slower band yielded 0.31 g (34%) of *2,4,6-tri-O-acetyl-3-deoxy-β-D-*erythro-*hex-2-enopyranosyl cyanide* **13** as an homogeneous syrup, $[\alpha]_D + 66°$ (*c* 1, $CHCl_3$) (Found: C, 52.38; H, 4.76; N, 4.52, $C_{11}H_{15}NO_7$ requires: C, 52.52; H, 5.03; N, 4.71).

*4,6-Di-O-acetyl-2,3-dideoxy-α-D-*erythro-*hexopyranosyl cyanide* **2**. A soln of **1** (0.5 g, 2.09 mmole) in EtOAc (25 ml) was hydrogenated with 10% Pd/C at 30–40° and ~ 2 atmospheres for 3.5 hr. Then, the mixture was filtered and evaporated to dryness to give 0.5 g (99%) of **2**, as a chromatographically homogeneous syrup, $[\alpha]_D + 84°$ (*c* 1, $CHCl_3$) (Found: C, 54.86; H, 6.43; N, 5.68. $C_{11}H_{15}NO_5$ requires: C, 54.76; H, 6.26; N, 5.80).

*4,6-Di-O-acetyl-2,3-dideoxy-β-D-*erythro-*hexopyranosyl cyanide* **4**. A soln of **3** (0.5 g, 2.09 mmole) in EtOAc (25 ml) was hydrogenated and worked up as before to give 0.5 g (99%) of **4** as a chromatographically homogeneous syrup, $[\alpha]_D + 39°$ (*c* 1, $CHCl_3$). (Found C, 54.62; H, 6.38; N, 5.50. $C_{11}H_{15}NO_5$ requires: C, 54.76; H, 6.26; N, 5.80).

*2,4,6-Tri-O-acetyl-3-deoxy-α-D-*ribo-*hexopyranosyl cyanide* **13**. A soln of **12** (0.25 g, 0.84 mmole) in EtOAc (12 ml) was hydrogenated as before. The rn mixture was filtered, concentrated *in vacuo* and chromatographed on TLC preparative plates with EtOAc–hexane (2:3) to give 0.215 g (85%) of **13** as a solid, m.p. 94° (from EtOAc–hexane), $[\alpha]_D + 90°$ (*c* 1, $CHCl_3$) (Found: C, 52.08; H, 5.94; N, 4.39. $C_{13}H_{17}NO_7$ requires: C, 52.17; H, 5.68; N, 4.68).

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