Preparation of 2-*C*-Cyano-glycals

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Treatment of certain glycals with chlorosulphonyl isocyanate, followed by triethylamine, gives 2-*C*-cyano-glycals.

THE reaction [1] whereby 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (tri-*O*-acetyl-D-glucal) (2) and chlorosulphonyl isocyanate (CSI) gave the dimer, 1,3,4,6-tetra-*O*-acetyl-2-*C*-(4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranosyl)-2-deoxy-β-D-glucopyranose (14), can only be rationalised by a reaction mechanism similar to that given by Ferrier and Prasad [2] for the

[1] R. H. Hall, A. Jordaan, and G. J. Lourens, *J.C.S. Perkin I*, 1973, 38.
[2] R. J. Ferrier and N. Prasad, *J. Chem. Soc.* (*C*), 1969, 581.

boron trifluoride-catalysed dimerisation of the glucal. This mechanism has since been supported by the work of Szczerek *et al.*,[3] who obtained the dimer (14) when the glucal (2) was treated with iodine. Ferrier suggested that the initial step is an isomerisation of the glucal (2) to 1,4,6-tri-*O*-acetyl-2,3-dideoxy-D-*erythro*-hex-2-enopyranose (12). Addition of the stabilised carbonium ion (13) derived from (12) to another, un-ionised molecule gives the unsaturated dimer (14).

For the initial isomerisation to take place there must be a good leaving group at C-3 and also anchimeric assistance by the group at C-4. Both these requirements are met in the glucal (2), with the C-3 and C-4 acetoxy-groups being *trans*.

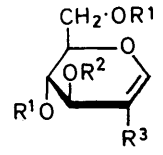
This suggested to us that replacement of the C-3 acetoxy-group in (2) by a poorer leaving group would inhibit the isomerisation, so that the resulting glycal might react with CSI as an enol ether in the known manner[4] to give an unsaturated *N*-chlorosulphonyl carboxamide. Again, with 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol (tri-*O*-acetyl-D-galactal) (8), although there is a good leaving group at C-3, there can be no anchimeric assistance as the C-3 and C-4 acetoxy-groups are *cis* to one another, and it might be expected that compound (8) would also react as an enol ether.

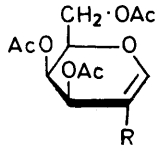
1,5-Anhydro-2-deoxy-3,4,6-tri-*O*-methyl-D-*arabino*-hex-1-enitol (tri-*O*-methyl-D-glucal) (3)[5] was prepared and treated with CSI as has been described[1] for hex-2-enopyranosides. Chromatography of the product gave a clear syrup (15%), $C_{10}H_{15}NO_4$, *m/e* 213. Its i.r. spectrum showed peaks at $\nu_{max.}$ 2220 (conjugated CN) and 1630 cm^{-1} (conjugated C=C). Comparison of its n.m.r. spectrum with that of the starting material (3) showed that the H-2 signal had disappeared and the H-1 signal had become simplified to a singlet at lower field. The H-3 signal had also shifted downfield. These data established that the compound was 1,5-anhydro-2-*C*-cyano-2-deoxy-3,4,6-tri-*O*-methyl-D-*arabino*-hex-1-enitol (4). Similar treatment of the galactal (8) gave crystalline 3,4,6-tri-*O*-acetyl-1,5-anhydro-2-*C*-cyano-2-deoxy-D-*lyxo*-hex-1-enitol (9) (17%).

Only one instance where the mixture of products obtained from the reaction of CSI with an olefin in the absence of solvents reacts further to give an unsaturated nitrile is quoted in a recent review.[6] Our results now furnish other examples where unsaturated nitriles are formed by reaction of CSI with enol ethers in the presence of solvent. The mechanism can be rationalised as before.[6]

A like reaction which has been described in more detail gave unsaturated nitriles in good yield by elimination of chlorosulphuric acid from *N*-chloro-sulphonamides in the presence of dimethylformamide[7] or triethylamine.[8]

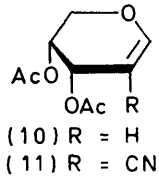
A procedure similar to these, adapted for the preparation of 2-*C*-cyano-glycals, proved superior to the method described above where the formation of the cyano-compound depended on further reaction of the primary products from reaction of CSI and a glycal. Thus, reaction of the galactal (8) and of the D-arabinal (10) with



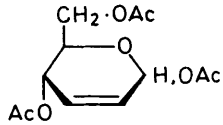


(8) R = H
(9) R = CN

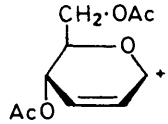
(1) $R^1 = R^2 = R^3 = H$
(2) $R^1 = R^2 = Ac, R^3 = H$
(3) $R^1 = R^2 = Me, R^3 = H$
(4) $R^1 = R^2 = Me, R^3 = CN$
(5) $R^1 = Ac, R^2 = CH_2Ph, R^3 = H$
(6) $R^1 = Ac, R^2 = CH_2Ph, R^3 = CN$
(7) $R^1 = R^2 = Ac, R^3 = OAc$



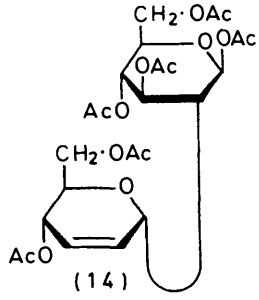
(10) R = H
(11) R = CN



(12)



(13)



(14)

CSI and subsequent treatment with triethylamine, gave the corresponding 2-*C*-cyano-compounds (9) (60%) and 3,4-di-*O*-acetyl-1,5-anhydro-2-*C*-cyano-2-deoxy-D-*erythro*-pent-1-enitol (11) (46% yield), respectively.

CSI was also treated with a glucal bearing a poor leaving group, other than methoxy, on C-3. 4,6-Di-*O*-acetyl-1,5-anhydro-3-*O*-benzyl-2-deoxy-D-*arabino*-hex-1-enitol (5) was prepared from 2,4,6-tri-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranosyl bromide[9] by a modified Fischer and Zach method and treated with CSI and then triethylamine to give 4,6-di-*O*-acetyl-1,5-anhydro-3-*O*-benzyl-2-*C*-cyano-2-deoxy-D-*arabino*-hex-1-enitol (6) (36%).

Although *O*-acetyl-glycals with no substituents at C-2 do not give molecular ions in their mass spectra,[10,11]

[3] I. Szczerek, J. S. Jewell, R. S. G. Richie, W. A. Szarek, and J. K. N. Jones, *Carbohydrate Res.*, 1972, **22**, 163.
[4] F. Effenberger and R. Gleiter, *Chem. Ber.*, 1964, **97**, 1576.
[5] (*a*) R. Kuhn, I. Lõw, and H. Trischmann, *Chem. Ber.*, 1957, **90**, 203; (*b*) E. L. Hirst and C. S. Woolvin, *J. Chem. Soc.*, 1931, 1311.
[6] R. Graf, *Angew. Chem. Internat. Edn.*, 1968, **7**, 172.
[7] G. Lohaus, *Chem. Ber.*, 1967, **100**, 2719.
[8] H. Vorbrüggen, *Tetrahedron Letters*, 1968, 1631.
[9] P. A. Finan and C. D. Warren, *J. Chem. Soc.*, 1962, 3089.
[10] A. Rosenthal, *Carbohydrate Res.*, 1968, **8**, 61.
[11] V. Kováčik, V. Bílik, and Š. Kučár, *Chem. Zvesti*, 1970, **24**, 52.

those of the 2-*C*-cyano-glycals (4), (6), (9), and (11) all exhibited molecular ions and $M + 1$ peaks of varying prominence. This is in accord with Rosenthal's[10] observation that the 2-substituted glycal (7) shows a molecular ion and readily captures a proton in the mass spectrometer. The initial fragmentation of (4), (6), (9), and (11) involved only the loss of the 3-, 4-, or 6-substituents; fragmentation by decomposition of the ring, as has been shown[11] for glycals with no substituent at C-2, did not take place.

The n.m.r. spectrum of one of the compounds discussed did not agree with published results[12] and detailed analyses will be published elsewhere. In all cases comparison of the spectrum of each 2-*C*-cyano-glycal with the spectrum of its parent glycal (see Table) showed that

Chemical shifts (τ scale) and coupling constants (Hz) of the glycals and 2-*C*-cyano-glycals

Compd.	H-1	H-2	H-3	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$
(3)	3·66	5·23	*ca.* 6·08	6·2	1·3	2·8
(4)	2·89		5·71			
(5)	3·59	5·10	6·04	6·2	1·3	3·8
(6)	2·83		6·04			
(8)	3·58	5·30	*ca.* 4·50	6·1	1·7	2·5
(9)	2·81		4·35		1·3	
(10)	3·51	5·17	4·57	6·1	0·8	5·0
(11)	2·78		4·37		0·7	

the H-2 signal had disappeared and that the signal due to H-1 had collapsed to a singlet (sometimes showing fine splitting due to coupling with H-3) and had moved 73—77 Hz downfield.

Although the synthesis and reactions of many glycals bearing a hetero-substituent on C-2 have been documented,[13] few examples of glycals bearing a carbon substituent on the 2-position are known (*cf.* refs. 14 and 15), and these substituents are of little synthetic value. However, it should be possible to convert the cyano-group on C-2 of the glycals which we have described into a variety of functional groups and it might be expected that the 2-*C*-cyano-glycals will prove useful in the synthesis of branched-chain carbohydrates and nucleosides.

EXPERIMENTAL

All solvent extracts were washed (ice–water, cold 0·5N-sulphuric acid, ice–water, cold saturated sodium hydrogen carbonate solution, and finally ice–water) and dried (Na_2SO_4) before evaporation; solvents were then removed below 50° *in vacuo*. T.l.c. and column chromatography were performed with silica gel (Merck GF_{254}) [100 g of silica gel per g of residue for column separations and ethyl acetate–hexane (1 : 1) as eluant, unless otherwise stated]. M.p.s were determined on a hot-stage apparatus. I.r. spectra were measured with a Perkin-Elmer 257 spectrophotometer and n.m.r. spectra were recorded on a Varian HA-100 instrument with tetramethylsilane as internal standard for $CDCl_3$ solutions. Mass spectra were determined with an A.E.I. MS9 spectrometer by use of the direct insertion technique. Samples of syrups for microanalysis were distilled under high vacuum by use of kugelröhre, unless otherwise stated.

[12] M. Fuertes, G. Garcia-Muñoz, R. Madroñero, M. Stud, and M. Rico, *Tetrahedron*, 1970, 4823.

1,5-*Anhydro*-2-*deoxy*-3,4,6-*tri*-O-*methyl*-D-arabino-*hex*-1-*enitol* (3).—Methylation of 1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol (1)[5] followed by two distillations gave compound (3) as a clear liquid (65%), b.p. 48—52° at 0·1 mmHg, $\nu_{max.}$ 1640 cm^{-1} (conj. C=C), M^+ 188.

1,5-*Anhydro*-2-C-*cyano*-2-*deoxy*-3,4,6-*tri*-O-*methyl*-D-arabino-*hex*-1-*enitol* (4).—Compound (3) (1 g, 5·3 mmol) and CSI (0·78 g, 5·5 mmol) in dry ether (15 ml) were treated as described earlier for hex-2-enopyranosides[1] to give a residue (*ca.* 500 mg). Chromatography gave the 2-C-*cyano-compound* (4) as a clear syrup (170 mg, 15%), $\nu_{max.}$ 2220 (conj. CN) and 1630 cm^{-1} (conj. C=C), M^+ 213 (Found: C, 56·0; H, 7·0; N, 6·4. $C_{10}H_{15}NO_4$ requires C, 56·3; H, 7·1; N, 6·6%).

3,4,6-*Tri*-O-*acetyl*-1,5-*anhydro*-2-C-*cyano*-2-*deoxy*-D-lyxo-*hex*-1-*enitol* (9).—*Method* (*a*). Tri-*O*-acetyl-1,5-anhydro-2-deoxy-D-*lyxo*-hex-1-enitol (8) and CSI in dry ether were treated as described for compound (3). Crystallisation of the residue from ethanol (96%) gave the 2-C-*cyano-compound* (9) as needles (17%), m.p. 108·5—110°, $\nu_{max.}$ ($CHCl_3$) 2215 (conj. CN), 1745 (CO), and 1631 cm^{-1} (conj. C=C), M^+ 297 (Found: C, 52·4; H, 5·1; N, 4·6. $C_{13}H_{15}NO_7$ requires C, 52·5; H, 5·1; N, 4·7%).

Method (*b*). CSI (5·24 g, 37 mmol) in dry ether (50 ml) was added during 30 min to a stirred solution of compound (8) (10 g, 36·67 mmol) in dry ether (100 ml) at 0° and the mixture was then kept at 0° for 5 h. Dry triethylamine (3·75 g, 3·7 mmol) in dichloromethane (25 ml) was added during 15 min at 0°. The mixture was allowed to come to room temperature and poured into water (500 ml); the organic solvents were removed with a stream of nitrogen, and the aqueous residue was extracted with dichloromethane (5 × 50 ml). Evaporation of the extracts gave a residue (*ca.* 10 g) which slowly crystallised. Recrystallisation from ethanol (96%) gave compound (9) (4·6 g, 42·2%), identical (m.p., mixed m.p., and spectral data) with the compound obtained by method (a). Chromatography of the mother liquors afforded, after recrystallisation (96% ethanol), more compound (9) (1·9 g, 17·4%; overall yield 59·6%).

3,4-*Di*-O-*acetyl*-1,5-*anhydro*-2-C-*cyano*-2-*deoxy*-D-erythro-*pent*-1-*enitol* (11).—3,4-Di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-pent-1-enitol (10) (8 g, 44·4 mmol) in dry ether was treated with CSI and then triethylamine as described for compound (8) [method (b)] to give a residue (6·6 g) which slowly crystallised. Recrystallisation from ethanol (96%) gave the 2-C-*cyano-compound* (11) as needles (4·2 g, 46·4%), m.p. 100—101°, $\nu_{max.}$ ($CHCl_3$) 2230 (conj. CN), 1750 (CO), and 1630 cm^{-1} (conj. C=C), *m/e* 226 ($M^+ + H^\cdot$) (Found: C, 53·4; H, 5·0; N, 6·2. $C_{10}H_{11}NO_5$ requires C, 53·3; H, 4·9; N, 6·2%).

4,6-*Di*-O-*acetyl*-1,5-*anhydro*-3-O-*benzyl*-2-*deoxy*-D-arabino-*hex*-1-*enitol* (5).—2,4,6-Tri-*O*-acetyl-3-*O*-benzyl-α-D-glucopyranosyl bromide (10 g), without purification to remove benzyl bromide,[9] was dissolved in 50% aqueous acetic acid (100 ml) and cooled to 0°. With vigorous stirring, activated zinc[16] (20 g) was added and the mixture was kept at 0° for 1 h, filtered, diluted with ice–water (300 ml), and extracted with chloroform. Evaporation of the extracts gave a residue (4·6 g) which was purified by chromatography

[13] R. J. Ferrier, *Adv. Carbohydrate Chem.*, 1969, **24**, 199.
[14] M. Sharma and R. K. Brown, *Canad. J. Chem.*, 1966, **44**, 2825; 1968, **46**, 757.
[15] J. B. Lee and B. Scanlon, *Chem. Comm.*, 1969, 955.
[16] F. Straus, *Annalen*, 1905, **342**, 190.

to give *compound* (5) as a clear syrup (1·49 g), $\nu_{max.}$ 1740 (CO) and 1645 cm^{-1} (conj. C=C), *m/e* 260 ($M^+ - CH_3 \cdot CO_2H$) (Found: C, 63·6; H, 6·1. $C_{17}H_{20}O_6$ requires C, 63·7; H, 6·3%).

4,6-*Di*-O-*acetyl*-1,5-*anhydro*-3-O-*benzyl*-2-C-*cyano*-2-*deoxy*-D-arabino-*hex*-1-*enitol* (6).—Compound (5) (1 g, 3·12 mmol) in dry ether at 25° was treated with CSI and triethylamine as described for compound (8) [method (b)] to give an oil (890 mg). Chromatography gave unchanged (5) (77 mg, 7·7%) and the 2-C-*cyano-compound* (6) as a clear syrup (284 mg, 26·4%), $\nu_{max.}$ 2220 (conj. CN), 1740 (CO), and 1625 cm^{-1} (conj. C=C), M^+ 345 (Found: C, 62·5; H, 5·6; N, 3·8 $C_{18}H_{19}NO_6$ requires C, 62·6; H, 5·6; N, 4·1%).

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