Synthesis of *C*-Disaccharides using Nitrile Oxide Cycloaddition Chemistry

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The xylose–mannose and xylose–glucose carbon-linked disaccharides **7** and **9** have been synthesised by a sequence in which the key steps are face selective 1,3-dipolar cycloaddition of xylose nitrile oxide (**1**) to the glucose-derived alkene (**2**) and reductive hydrolytic cleavage of the resulting 2-isoxazolines.

The synthesis of carbon–carbon linked disaccharides (*C*-disaccharides) is the subject of widespread current interest.[1] In order to develop a general route which would provide pyranose *C*-disaccharides with control of both position and stereochemistry of the interunit linkage we have made use of nitrile oxide cycloaddition chemistry.[2]

Our synthetic approach is based on cycloaddition of a sugar nitrile oxide to a sugar alkene and reductive hydrolytic cleavage of the resulting 2-isoxazoline (Scheme 1).† To test the method we selected the β-D-xylose nitrile oxide (**1**) and the D-glucose-derived alkene (**2**)[3] as representative 1,3-dipole and dipolarophile respectively. The nitrile oxide was generated *in situ* in the presence of the alkene by a modification of the Mukaiyama[4] procedure involving a dehydration of nitromethylxylose (**3**).[5] Slow addition of a solution of precursor (**3**) to an excess of the alkene ensures a low concentration of the nitrile oxide thus minimising the competing dimerisation to furazan *N*-oxide.[6] The use of tolylene di-isocyanate (rather than phenyl isocyanate) as dehydrating agent, and quenching the reaction with 1,2-diaminoethane, facilitates isolation of the cycloadducts.

Only two, (**4**) and (**5**), of the four possible isoxazolines were detected by t.l.c. and ^{13}C n.m.r. spectroscopy and were isolated as a *ca.* 1 : 1 mixture in a combined yield of 66%. The isomers were separated by chromatography and characterised

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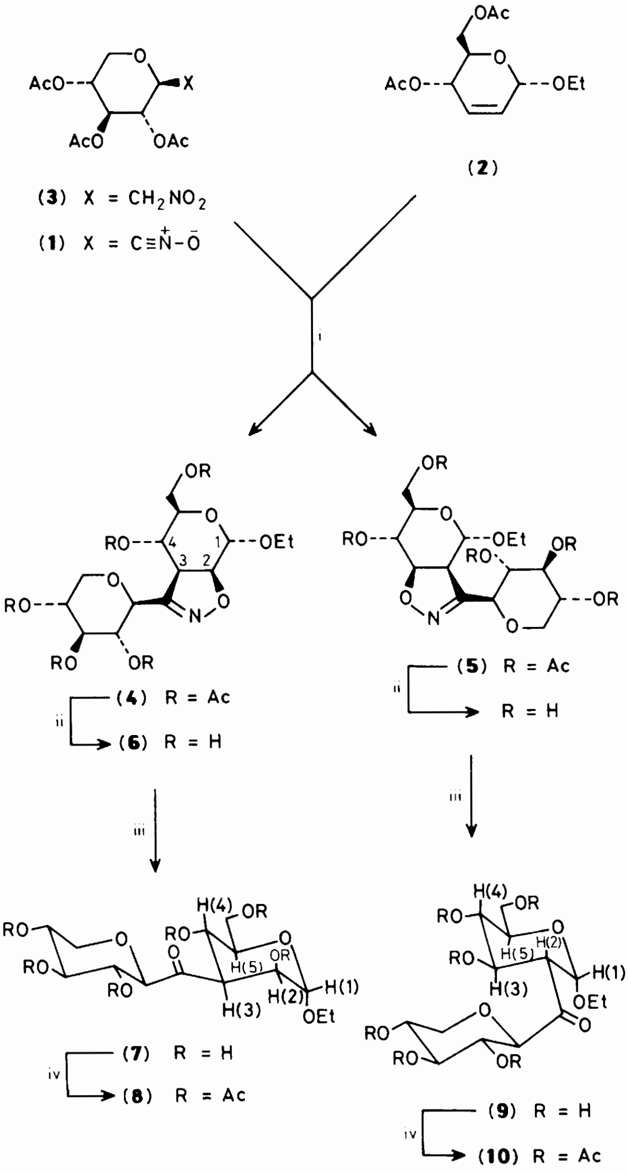
† 4,5-Dihydroisoxazoles.



Scheme 1. *Reagents and conditions*: i, (**1**) (10 mmol) in CH_2Cl_2 (50 ml) added over 12 h to (**3**) (40 mmol), tolylene di-isocyanate (16 mmol), Et_3N (5 mmol) in CH_2Cl_2 at reflux. Quenched at 0 °C with excess 1,2-diaminoethane; ii, KCN/MeOH, 20 °C, 24 h; iii, Pd/C or Raney Ni, H_2, $B(OH)_3$, H_2O, MeOH, 20 °C, 4 h; iv, Ac_2O/BF_3, 0 °C, 2 h.

by elemental analysis, mass spectrometry (*m/z* 559), and n.m.r. spectroscopy. The two regioisomers can readily be distinguished by the characteristic peaks for the isoxazoline ring protons; the CH adjacent to the isoxazoline oxygen invariably has the greater chemical shift. The absence in each case of discernible coupling between the anomeric proton [H(1)] in the dipolarophile-derived portion of the adduct and the adjacent isoxazoline ring proton [H(2)] is consistent with the indicated *trans*-stereochemistry.[7] The reaction thus appears to be totally face selective with the nitrile oxide approaching the alkene, as expected, from the less hindered side *anti* to the C(1) and C(4) subtituents.

Isoxazoline (**4**) was deacetylated[8] to (**6**) and then subjected to reductive hydrolysis[9] (Pd/H_2 or Raney Ni; boric acid/methanol/water). The product was identified by F.A.B. mass spectrometry (*m/z* 352) and by i.r. and n.m.r. spectroscopy as the *C*-glycosyl analogue of ethyl 3-*O*-β-D-xylopyranosyl-α-D-mannopyranoside (**7**) (97% overall yield), in which the interunit oxygen is replaced by a carbonyl. The presence of the carbonyl group is confirmed by an infrared absorption at 1720 cm^{-1} and a characteristic ^{13}C n.m.r. peak at 207 p.p.m. The 360 MHz ^{1}H n.m.r. spectrum of hexa-acetyl derivative (**8**)‡ showed couplings of 1.6, 2.7, 11.0, and 10.6 Hz for H(1) H(2), H(2) H(3), H(3) H(4), and H(4) H(5) respectively, consistent with the proposed structure with H(1) and H(2) equatorial and H(3) H(4) and H(5) axial.

When isoxazoline (**5**) was treated under the same conditions as isomer (**4**), compound (**9**) was formed in 90% yield. From the ^{1}H n.m.r. spectrum of (**9**), and particularly its hexa-acetate (**10**), which showed diagnostic couplings of $J_{H(1)H(2)}$ 3.8, $J_{H(2)H(3)}$ 11.1, $J_{H(3)H(4)}$ 9.3, and $J_{H(4)H(5)}$ 10.3 consistent with H(1) equatorial and H(2)H(5) all axial, it follows that a *C*-glycosyl analogue of ethyl 2-*O*-β-D-xylopyranosyl-α-D-glucopyranoside (**9**) had been formed rather than the expected mannose analogue (the latter could not be detected by t.l.c. or n.m.r.). The product presumably arises from epimerisation at C(2), either in the product (**9**) or its imine precursor, allowing the bulky acyl group to occupy the energetically favoured equatorial position. This result has significance for the scope of the synthetic sequence as *trans*- as well as the expected *cis*-substituted products may be prepared.

Our results demonstrate that *C*-disaccharides can be synthesised in good yield. The method is versatile and can be extended[10] to other sugar nitrile oxides and sugar alkenes. The isoxazoline intermediates should also provide *C*-disaccharides linked by aminomethine and hydroxymethine groups. These reactions are currently under investigation.

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‡ The structure of compound (**8**) has been confirmed by *X*-ray crystallography, details of which will be published in the full paper.