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Generation and cycloaddition reactions of pyranose-1-carbonitrile oxides

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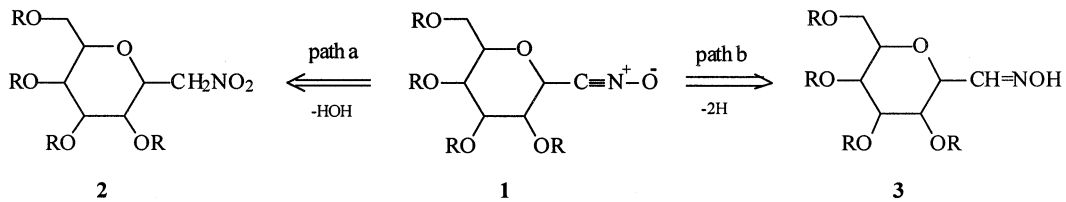
Abstract—Stannate(II) reduction of the β-D-glucopyranosylnitromethane derivative **4** affords aldoxime **5**, which provides access to the nitrile oxide **7**, either on treatment with aq. hypochlorite, or via conversion to the hydroximoyl chloride **11** followed by base-mediated dehydrohalogenation. D-Galactose-, D-mannose- and D-xylose-derived nitrile oxides are generated similarly. The nitrile oxides either dimerise to 3,4-dipyranosyl-1,2,5-oxadiazole *N*-oxides or are trapped as cycloadducts in the presence of dipolarophiles.

There is considerable current interest in the chemistry of *C*-glycosides,[1] and in methods for their synthesis in particular. One approach which has so far received little attention, but offers scope for the preparation of a variety of novel derivatives, makes use of nitrile oxide/isoxazoline chemistry,[2] and involves the generation of glycosyl nitrile oxides, their cycloaddition reactions with alkenes (or alkynes) and manipulation of the resulting isoxazoline (isoxazole) cycloadducts. In the literature there are occasional reports[3] of furanosyl nitrile oxide cycloadditions, and we have utilised[4,5] the pyranosyl analogues **1** as key intermediates in a synthetic sequence from readily accessible monosaccharide precursors to carbohydrate isoxazolines as precursors of carbon linked disaccharides (*C*-disaccharides). We previously employed[4,5] a modified Mukaiyama procedure[6] for generating pyranosyl nitrile oxides **1**, which involved tolylene diisocyanate-mediated dehydration of the corresponding nitromethyl compounds **2** (Scheme 1, path a). The Mukaiyama route, however, has several limitations. Firstly, the use of isocyanates as the dehydrating agent is incompatible with free hydroxyl groups in either reactant—a disadvantage in carbohydrate synthesis—and elevated temperatures (80–100°C) and/or prolonged reaction times (3–5 days) are often required to achieve high conversions, so the method is not ideal for low boiling and thermally unstable dipolarophiles. An alternative approach is therefore needed to overcome these deficiencies. We now report that carbohydrate nitrile oxides such as **1** can readily be generated form the corresponding oxime **3**, either by oxidation with aq. hypochlorite, or by base mediated dehydrohalogenation of its hydroximoyl chloride derivative (Scheme 1, path b).

The first requirement was to develop an effective route to the oximes.[7] The method selected was based on the observation[8] that primary aliphatic nitro compounds are reduced to aldoximes by stannate(II) complexes generated from $SnCl_2/PhSH/Et_3N$. Treatment of $SnCl_2$ (363 mg, 1.92 mmol) in dry THF (6 ml) at 0°C with Et_3N (648 mg, 6.40 mmol) and thiophenol (635 mg, 5.76 mmol) afforded a yellow solution of the stannate (II) complex $[Et_3NH][(PhS)_3Sn]$, to which was added a



Scheme 1.

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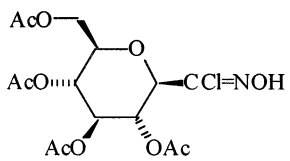
solution of β-D-glucopyranosyl-nitromethane derivative **4**[9] (500 mg, 1.28 mmol). After stirring for 16 h the solvent was removed in vacuo and the residue purified by chromatography (silica, hexane/Et_2O) and recrystallisation (hexane/Et_2O) to afford tetra-*O*-acetyl-β-D-glucopyranosylformaldoxime (**5**)[10] as a 4:1 mixture of *E*- and *Z*-isomers[11] in a 76% combined yield. In the ^1H NMR spectrum there are characteristic doublet signals (*J* 6.8 Hz) for the imino proton of the *E*- and *Z*-isomers at 7.30 and 6.7 ppm, respectively, and corresponding broad singlet peaks at 8.40 and 8.62 ppm for the OH groups. D-Galactose-, D-mannose- and D-xylose-derived oximes were prepared similarly in 80–90% yields from the corresponding pyranosylnitromethanes.

The first method utilised for nitrile oxide generation involved oxidation of the oximes with aqueous hypochlorite.[12] In a typical experiment, a solution of the oxime (1 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a well stirred mixture of the dipolarophile (3 mmol), Et_3N (0.1 ml), CH_2Cl_2 (30 ml) and 8% aq. NaOCl (15 ml) at 0°C. After 2 h TLC indicated complete consumption of the oxime, and the reaction was then worked up and the products separated by chromatography. To test the efficiency of nitrile oxide formation a reaction was first carried out in the absence of a dipolarophile. Under these conditions glucose oxime **5** gave diglucopyranosylfuroxan **6**[13,14] (88%), which was identified from its spectroscopic properties (Table 1, entry 1, Scheme 2). In both the ^1H and ^{13}C NMR spectra there are distinct and independent sets of signals for the two glucosyl fragments, and in the carbon spectrum peaks are observed at 111.6 (C-3) and 153.4 (C-4) ppm, which are characteristic of the 1,2,5-oxadiazole ring.[15] Further evidence is provided by the mass spectrum which shows, in addition to the parent ion, a significant peak at M−60 corresponding to loss of N_2O_2; this mode of fragmentation is typical for furoxans.[15] It is well established[16] that nitrile oxides readily dimerise to furoxans, and isolation of compound **6** provides unambiguous evidence for efficient generation of the nitrile oxide **7**. The oximes derived form D-galactose and D-xylose reacted similarly affording the corresponding furoxans (Table 1, entries 2 and 3). The pyranosylfuroxans are of interest in their own right, and they can be regarded as *C*-disaccharides with functionalised ethylene bridges between the two anomeric positions.

Generating nitrile oxide **7** in the presence of an excess of methylenecyclohexane (1:5) afforded a mixture of furoxan **6** (53%) and the isoxazoline **8** (32%) resulting from regiospecific cycloaddition to the alkene. The more reactive dipolarophiles styrene and norbornene afforded correspondingly greater yields of cycloadducts **9** (53%) and **10** (76%), respectively (Table 1, entries 6 and 7).

The second method for generating nitrile oxide **7** involved initial conversion of oxime **5** to the corresponding hydroximoyl chloride **11**. This was achieved by bubbling chlorine through a solution of the oxime (1 mmol) in CH_2Cl_2 (5 ml) at −78°C, and allowing the mixture to warm to room temperature. After stirring for 16 h the solvent was removed in vacuo to yield **11**

Table 1. Generation and reactions of pyranosyl nitrile oxides



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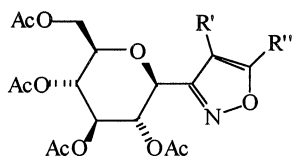
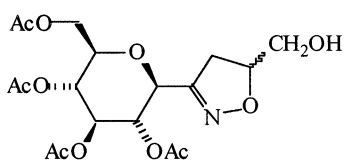


12 R' = R'' = CO_2Me
13 R' = H, R'' = CO_2Et
14 R' = CO_2Et, R'' = H



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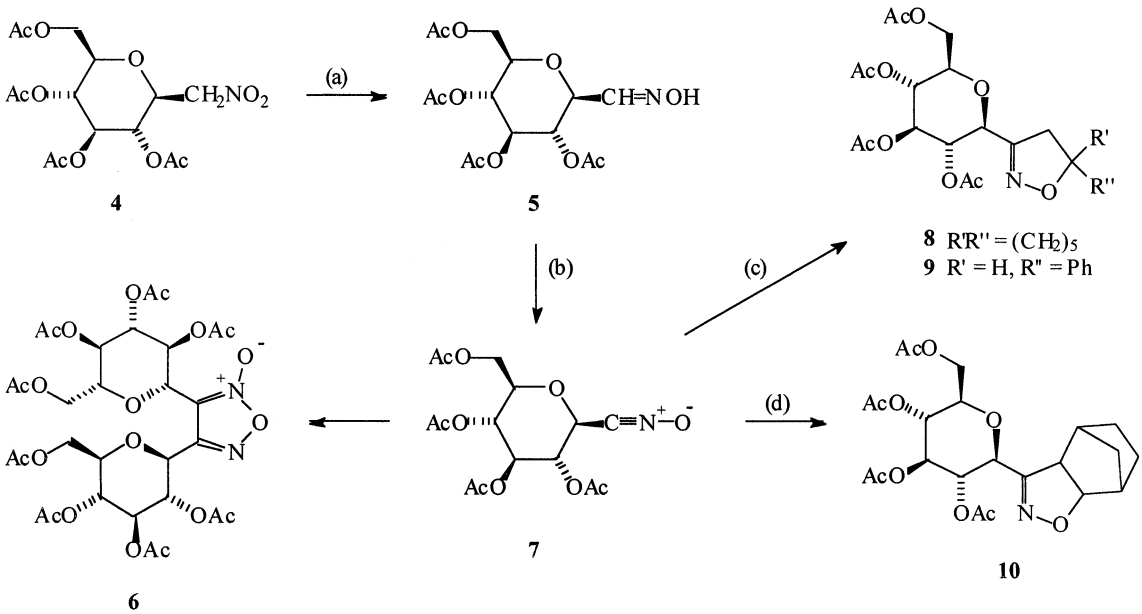
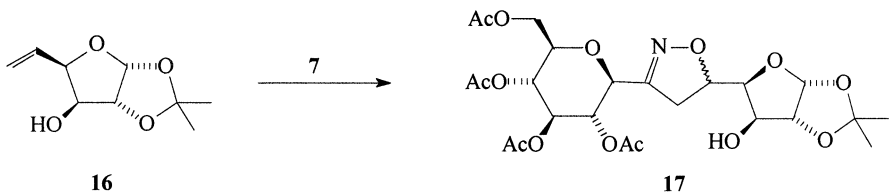
Entry	Nitrile oxide	Method[a]	Dipolarophile	Cycloadduct	Yield/% (d.r.)	Furoxan yield/%
1	D-Glc	A/B	None	–		88/96
2	D-Gal	A	None	–		90
3	D-Xyl	A	None	–		89
4	D-Man	B	None	–		95
5	D-Glc	A	Methylenecyclohexane	**8**	32	53
6	D-Glc	A	CH_2=CHPh	**9**	53 (55:45)	21
7	D-Glc	A	Norbornene	**10**	76 (61:39)	5
8	D-Man	A/B	CH_2=CHPh		85 (53:47)/95 (56:44)	Traces
9	D-Glc	B	MeO_2C=CO_2Me	**12**	98	6
10	D-Glc	B	HC≡CCO_2Et	**13**+**14**	69 (85:15)[b]	15
11	D-Man	B	CH_2=$CHCH_2OH$	**15**	30	14
12	D-Glc	B	**16**	**17**	40 (72:28)	26
13	D-Gal	B	**16**		36 (75:25)	33

[a] (A) RCH=NOH+aq. NaOCl; (B) RCCl=NOH+Et_3N.
[b] Ratio of regioisomers **13** and **14**.



Scheme 2. *Reagents*: (a) $SnCl_2/PhSH/Et_3N$, THF; (b) aq. $NaOCl_2$ CH_2Cl_2; (c) methylenecyclohexane or styrene; (d) norbornene.



Scheme 3.

(90%) as a white solid which was recrystallised from hexane/Et_2O. Similar yields (90–95%) were obtained for the hydroximoyl chlorides[14] derived from the D-Gal, D-Man and D-Xyl. The nitrile oxides were then generated from the hydroximoyl chlorides by base-mediated dehydrochlorination. Typically, the hydroximoyl chloride (1 mmol) and the dipolarophile (5 mmol) were dissolved in dry Et_2O (20 ml) and Et_3N (1.1 mmol) in dry CH_2Cl_2 (40 ml) added at 0°C via a syringe over 24 h. The solvent was then removed in vacuo and the products separated by chromatography. Improved yields were achieved by this method, which also allowed a wider range of dipolarophiles to be employed. Representative examples are shown in Table 1, entries 8–13, Scheme 3. The formation of **15** from allyl alcohol and *C*-disaccharide precursor[1c,5] **17** from D-Glc-derived alkene **16** represent examples of isoxazolines which could not be prepared directly from the nitromethyl compound by the Mukaiyama method.[5] The nitrile oxide derived from D-Gal reacted similarly (Table 1, entry 13). Dipyranosylfuroxans were also readily prepared by this approach (Table 1, entries 1 and 4).

In conclusion, hypochlorite oxidation of pyranose-1-carbaldoximes and base-induced dehydrochlorination of the corresponding hydroximoyl chlorides provide effective means of generating pyranosyl nitrile oxides suitable for the synthesis of a range of *C*-glycosides. This approach is complementary to the current literature procedure based on isocyanate-mediated dehydration of pyranosylnitromethanes, and also provides easy access to novel dipyranosylfuroxans.

Acknowledgements

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