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Synthesis of pyranosyl amidoximes by addition of amines to pyranosyl nitrile oxides

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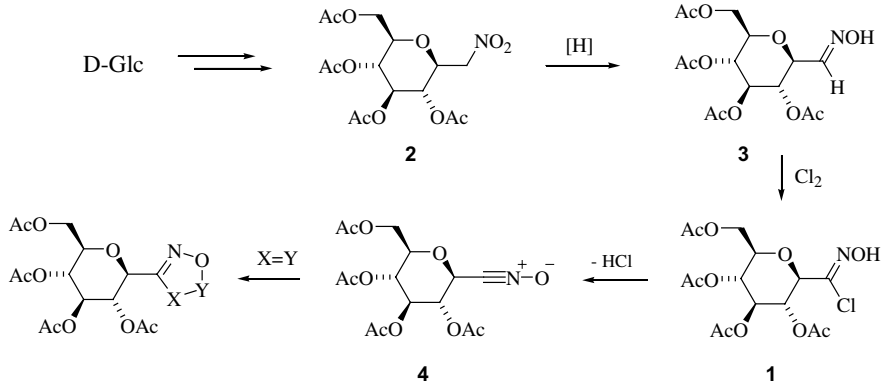
Abstract—Addition of amines to pyranosyl nitrile oxides, generated by base-induced dehydrochlorination of the corresponding hydroximoyl chloride, affords pyranosyl *N*-alkyl/aryl-formamide oximes (41–90%). Reaction with amino acid esters yields the corresponding amidoximes and/or 3-pyranosyl-1,2,4-oxadiazin-6-ones. The structure of *N*-phenyl-*C*-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)formamide oxime was established by X-ray crystallography.

We have recently reported a short and efficient synthetic route from monosaccharides to pyranosyl hydroximoyl chlorides.[1–3] The approach, which is illustrated in Scheme 1 for the D-glucose-derived compound **1**, involves addition of nitromethane to D-glucose and acetylation to afford the pyranosylnitromethane **2**, followed by reduction to oxime **3**, and finally reaction with chlorine. The hydroximoyl chorides were then used as a source of the corresponding nitrile oxide, for example, **4**, from which a variety of novel *C*-glycosides were prepared by cycloaddition to dipolarophiles X=Y.

We now report that dehydrochlorination of these hydroximoyl chlorides in the presence of a primary or secondary amine provides easy access to a range of novel pyranosyl amidoximes (Scheme 2). 1,3-Addition of amines to arene nitrile oxides has been known for many years[4,5] and the resulting amidoximes have been shown to have a variety of useful properties. These include metal ligation[6–8] and biological activity, for example, as nitric oxide donors[9] and amidine prodrugs.[10] Less attention, however, has been paid to carbohydrate analogues; rare examples include cyclic amidoximes as



Scheme 1.

Keywords: *C*-Glycosides; Nitrile oxides; Amidoximes; 1,2,4-Oxadiazin-6-ones.
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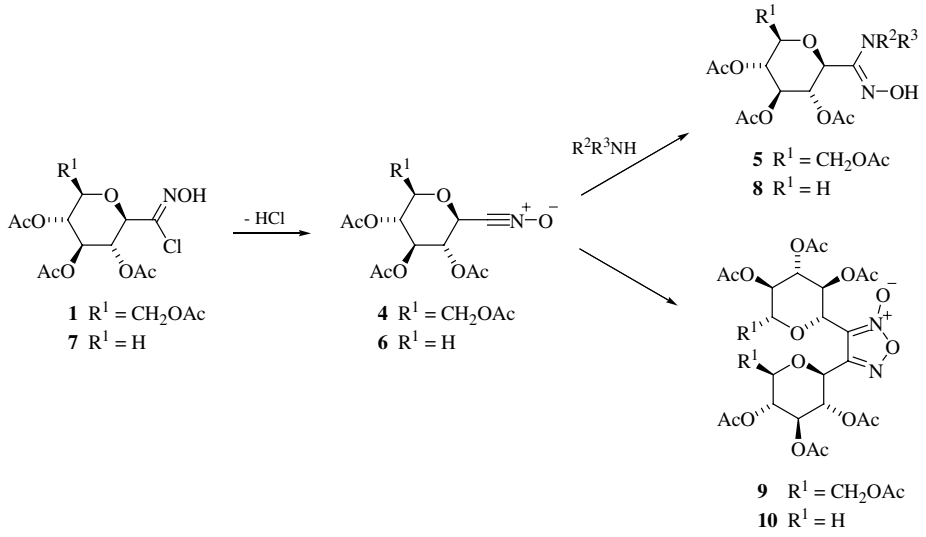


Scheme 2.

glycosidase and glycosyl transferase inhibitors[11,12] and amidoxime-linked nucleosides.[13]

In the present work the pyranosyl nitrile oxides were generated by dehydrochlorination of the corresponding hydroximoyl chlorides in situ in order to minimise dimerisation to 1,2,5-oxadiazole *N*-oxides (furoxans), which are often formed as by-products in reactions involving nitrile oxides.[3,14] In a typical experiment a solution of the glucopyranosyl-hydroximoyl chloride **1** (0.44 mmol) in dry chloroform (40 ml) was added dropwise over 3 h to a cooled (0 °C) vigorously stirred solution of benzylamine (1.32 mmol) and dry triethylamine (7.1 mmol) in dry chloroform (5 ml) under nitrogen. Removal of the solvent and chromatography of the residue (silica, hexane–EtOAc) afforded the *N*-benzyl amidoxime **5** (R^2 = Bn, R^3 = H) in 80% yield. The furoxan dimer **9** was not detected. D-Xylopyranosyl nitrile oxide **6**, generated from the hydroximoyl chloride **7**, reacted similarly to yield amidoxime **8** (R^2 = Bn, R^3 = H) (67%). The structures of the products were assigned on the basis of their spectroscopic properties; for example, in the NMR spectrum of D-xylose-derived amidoxime **8** (R^2 = Bn, R^3 = H) there are, in addition to the expected signals for the carbons and protons of the pyranosyl and benzene rings,[15] distinctive peaks for the oxime unit [δ_C 148.9 ppm (C=N)] and the attached $NHCH_2$ group [δ_H 4.38 (CH_a), 4.39 ppm (CH_b), 5.22 (NH); J_{NH-CH_a} 5.5, J_{NH-CH_b} 6.8, $J_{CH_a-CH_b}$ 14.6 Hz; δ_C 46.4 ppm (CH_2)].

Nitrile oxide **6** also reacted readily with 1-aminobutane, morpholine and allylamine to afford the corresponding adducts (**8** R^2 = Bu, R^3 = H; 63%), (**8** R^2R^3 = $CH_2CH_2OCH_2CH_2$; 67%) and (**8** R^2 = $CH_2CH{=}CH_2$, R^3 = H; 41%). It is noteworthy that in the latter case the isolated product results from addition of the nitrile oxide to the amine moiety in allylamine rather than cycloaddition to the alkene.

More forcing conditions were used for the corresponding reactions with aniline. Heating a 2:1 mixture of aniline and D-glucopyranosyl-hydroximoyl chloride **1** in ethanol at reflux for 5 h afforded amidoxime **5** (R^2 = Ph, R^3 = H) in 80% yield. The corresponding reaction with D-xylopyranosyl nitrile oxide **6** gave amidoxime **8** (R^2 = Ph, R^3 = H) (90%). In neither case was there any evidence for the formation of the furoxan dimer (**9**,**10**). However, reaction with aniline in the presence of triethylamine as dehydrochlorinating agent afforded a mixture (~1:3) of the amidoxime and the furoxan.

The structure of the adduct **8** (R^2 = Ph, R^3 = H) formed by 1,3-addition of aniline to nitrile oxide **6** was established by X-ray crystallography (Fig. 1).[16] Of particular note are the *Z*-configuration of the oxime moiety and the *s-trans* conformation about the amidic nitrogen with the H of the NHR facing the oxime OH. These results are in accord with previous studies indicating that such additions occur in a concerted, but nonsynchronous manner.[17] The near planarity of the NH–C=N–O unit [torsion angle 2.6(3)°] and the short nonbonded distance between the amidic N and the oxime O [N to O = 2.508(3) (Å)] are consistent with the existence of an intramolecular H-bond between these atoms.[17,18]

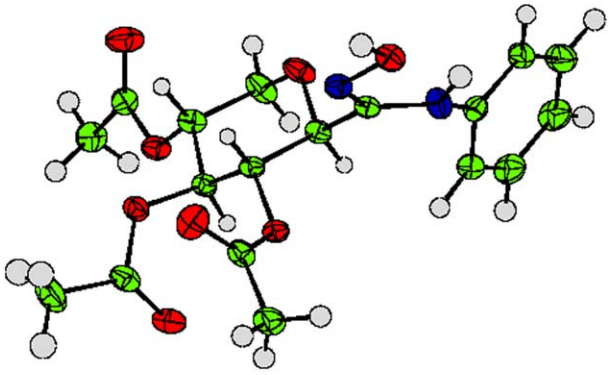
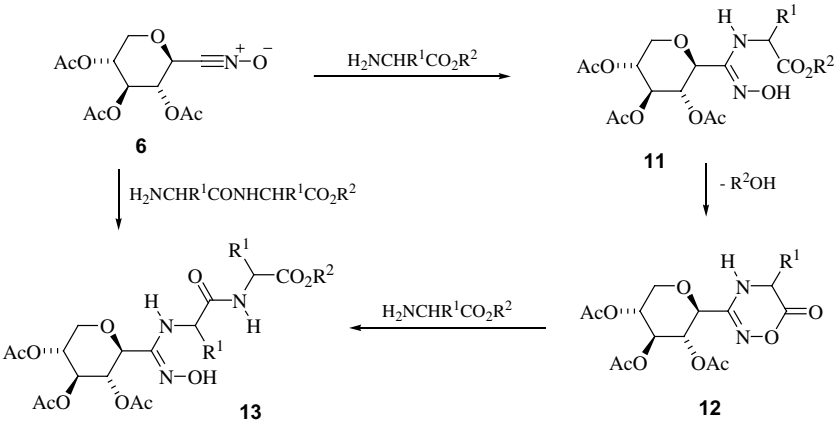


Figure 1. X-ray crystal structure of amidoxime **8** (R^2 = Ph, R^3 = H) showing the *Z-s-trans* arrangement.



Scheme 3.

Having established that simple amines such as aniline and benzylamine add readily to the pyranosyl nitrile oxides, the corresponding reactions with amino acid esters were examined. The resulting adducts were considered of interest as they would contain an unusual amidoxime sugar/amino acid linkage, and extension of the reaction to oligopeptides might provide access to novel glycopeptide analogues.

Reaction of hydroximoyl chloride **7** with glycine ethyl ester hydrochloride and triethylamine (1:1.5:15 molar ratio) at 0 °C afforded a mixture of three products, two of which were isolated and characterised (Scheme 3). The first (40%) proved to be the amidoxime **11** (R^1 = H, R^2 = Et)[19] resulting from the expected addition of glycine ethyl ester to nitrile oxide **6**; the other major product was identified from its spectroscopic properties[20] as the 1,2,4-oxadiazin-6-one **12** (R^1 = H) [δ_H 3.95 (CH_2), 5.61 ppm (NH); δ_C 40.2 (CH_2), 150.4 (C=N), 164.6 ppm (C=O)], and the third was provisionally assigned structure **13** (R^1 = H, R^2 = Et) on the basis of its NMR and mass spectra. In contrast, when the reaction was repeated under the same conditions with glycine *t*-butyl ester the amidoxime **11** ($R^1 = Pr^i$, $R^2 = Bu^t$) (88%) was the only isolated product. The corresponding reaction with L-leucine ethyl ester afforded 53% of amidoxime **11** ($R^1 = CH_2CHMe_2$, R^2 = Et) (53%) as the main product, which readily cyclised to oxadiazinone **12** ($R^1 = CH_2CHMe_2$) (71%). Reaction with β-alanine ethyl ester, for which cyclisation would result in a seven-membered ring, afforded only the expected amidoxime **8** ($R^2 = CH_2CH_2CO_2Et$, R^3 = H) (50%).

These results are consistent with nucleophilic addition of the amino acid ester to nitrile oxide **6** forming adduct **11**, followed by intramolecular cyclisation with expulsion of ethanol to afford oxadiazinone **12**, and finally nucleophilic ring opening to form dipeptide amidoxime **13** (Scheme 3). Similar facile cyclisations of amino acid amidoximes have been reported previously for adducts from benzonitrile oxide,[21] and for oligopeptides incorporating amidoxime links.[22]

Support for the pathway shown in Scheme 3 was the observation that, in the presence of silica, amidoxime **11** (R^1 = H, R^2 = Et) was smoothly converted to oxadiazinone **12** (R^1 = H) (~6 h in $CHCl_3$ at reflux, 2–3 days at room temperature). Furthermore, reaction of nitrile oxide **6** with glycylglycine ethyl ester afforded the dipeptide amidoxime **13** (R^1 = H, R^2 = Et) directly (43%), thus confirming the identity of the 2:1 adduct in the glycine ethyl ester reaction described above.

In conclusion, an efficient route to pyranosyl amidoximes has been established based on 1,3-addition of amines to pyranosyl nitrile oxides, which were generated from readily accessible hydroximoyl chlorides. The adducts resulting from the addition of amino acid esters cyclised to afford 3-pyranosyl-1,2,4-oxadiazin-6-ones; the feasibility of using the oxadiazinones as precursors for pyranosyl oligopeptides is currently under investigation.

Acknowledgements

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15. (*Z*)-*N*-benzyl-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)formamide oxime (**8**, R^2 = Bn, R^3 = H): mp 64–66 °C (from hexane–EtOAc). $[\alpha]_D^{20}$ −3.7 (c = 0.54 $CHCl_3$). δ_H (250 MHz, $CDCl_3$) 1.95, 1.96, 1.97 (9H, 3s, 3 × $COCH_3$), 3.19 (1H, dd, 5a′-H), 3.89 (1H, d, 1′-H), 4.07 (1H, dd, 5e′-H), 4.38 (1H, dd, Bn-H_a), 4.39 (1H, dd, Bn-H_b), 4.92 (1H, ddd, 4′-H), 5.11 (1H, dd, 3′-H), 5.22 (1H, t, NH), 5.29 (1H, dd, 2′-H); J(X-Y)/Hz 1′–2′ 10.0, 2′–3′ 9.2, 3′–4′ 9.5, 4′–5a′ 10.4, 4′–5e′ 5.6, 5a′–5e′ 11.2, Bna-Bnb 14.6, Bna-NH 5.5, Bnb-NH 6.8; δ_C (63 MHz, $CDCl_3$) 20.5 (3 × $COCH_3$), 46.4 ($BnCH_2$), 67.7 (C-5′), 68.6, 68.7, 73.5 (C-2′,C-3′,C-4′), 76.1 (C-1′), 127.3, 127.4, 128.6 (5 × PhCH), 138.8 (PhC), 148.9 (C=N), 169.5, 169.7, 170.2 (3 × C=O). FAB-HRMS $[M + H]^+$ calculated for $C_{19}H_{24}N_2O_8$: 409.16109; found: 409.16095.
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19. (*Z*)-*N*-Carbethoxymethyl-(2′,3′,4′-tri-*O*-acetyl-β-D-xylopyranosyl)formamide oxime (**11**, R^1 = H, R^2 = Et): δ_H (250 MHz, $CDCl_3$) 1.23 (3H, t, CH_3), 1.96, 1.97, 1.98 (9H, 3s, 3 × $COCH_3$), 3.28 (1H, dd, 5a′-H), 3.85 (1H, d, 1′-H), 4.07 (2H, d, CH_2), 4.06 (1H, dd, 5e′-H), 4.16 (2H, q, OCH_2), 4.85–5.02 (1H, m, 4′-H), 5.12–5.21 (2H, m, 2′-H & 3′H), 5.48 (1H, t, NH); J(X-Y)/Hz 1′–2′ 9.8, 2′–3′ 9.2, 3′–4′ nd, 4′–5a′ 10.2, 4′–5e′ 5.5, 5a′–5e′ 11.5, CH_2-NH 5.8; δ_C (63 MHz, $CDCl_3$) 14.5 (CH_3), 21.0 (3 × CH_3), 44.7 (CH_2), 61.7 (OCH_2), 67.1 (C-5′), 68.9, 69.1, 73.6 (C-2′,C-3′,C-4′), 76.9 (C-1′), 148.1 (C=N), 170.1, 170.2, 170.5, 170.7 (4 × C=O). FAB-HRMS $[M + H]^+$ calculated for $C_{16}H_{24}N_2O_{10}$: 405.15092; found: 405.15194.
20. 3-(2′,3′,4′-Tri-*O*-acetyl-β-D-xylopyranosyl)-1,2,4-oxadiazin-6-one (**12**, R^1 = H): mp 165 °C (decomp.) (from hexane–EtOAc). δ_H (250 MHz, $CDCl_3$) 1.98, 1.99, 2.00 (9H, 3s, 3 × $COCH_3$), 3.37 (1H, dd, 5a′-H), 3.94 (1H, d, 1′-H), 3.95 (2H, s, CH_2), 4.14 (1H, dd, 5e′-H), 4.93 (1H, ddd, 4′-H), 4.98 (1H, dd, 3′-H), 5.26 (1H, t, 2′H), 5.61 (1H, br s, NH); J(X-Y)/Hz 1′–2′ 9.7, 2′–3′ 9.4, 3′–4′ 9.9, 4′–5a′ 10.3, 4′–5e′ 6.2, 5a′–5e′ 11.6; δ_C (63 MHz, $CDCl_3$) 20.4 (3 × $COCH_3$), 40.2 (CH_2), 66.5 (C-5′), 68.4, 69.1, 71.7 (C-2′,C-3′,C-4′), 74.9 (C-1′), 150.4 (C=N), 164.6 (C=O), 169.7, 169.8, 170.1 (3 × C=O). FAB-HRMS $[M + H]^+$ calculated for $C_{14}H_{18}N_2O_9$: 359.10906; found 359.10950. The structure of oxadiazinone **12** has been confirmed by X-ray crystallography (Parsons, S.; Paton, R. M.; Smellie, I. A. S. unpublished observations).
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