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Synthesis, structure and reactivity of 5-pyranosyl-1,3,4-oxathiazol-2-ones

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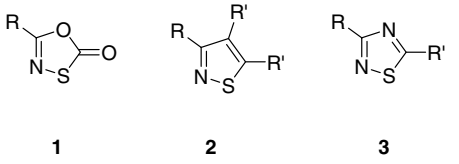
Abstract—5-(1,2,3,4-Tetra-*O*-acetyl-α-D-xylopyranos-5*S*-*C*-yl)-1,3,4-oxathiazol-2-one (**8**) has been prepared from glucuronamide in two steps and 73% overall yield by conversion to the tetra-*O*-acetyl derivative **7** followed by reaction with chlorocarbonylsulfenyl chloride. 5-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxathiazol-2-one (**12**) was synthesised from D-xylose by a four-step sequence involving conversion to the xylopyranosylnitromethane derivative **9**, reaction with PCl_3 to afford nitrile **10**, hydrolysis to amide **11**, and finally treatment with ClCOSCl. D-Glucose-derived analogue **13** was prepared similarly. The structure of oxathiazolone **8** was established by X-ray crystallography. Thermolysis of the oxathiazolones **8** and **12** at 130–160 °C resulted in decarboxylation and desulfuration to yield the corresponding nitriles. Attempts to trap the putative nitrile sulfide intermediates by repeating the thermolysis in the presence of dipolarophiles, such as ethyl cyanoformate, afforded only traces of the 1,3-dipolar cycloadducts; however, under microwave irradiation oxathiazolone **8** and ethyl cyanoformate afforded ethyl 3-(1,2,3,4-tetra-*O*-acetyl-α-D-xylopyranos-5*S*-*C*-yl)-1,2,4-thiadiazole-5-carboxylate **22** in good yield.

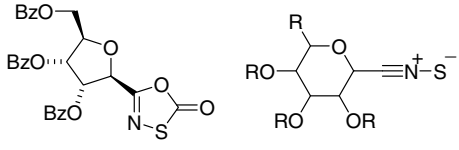
Keywords: *C*-Glycosyl compounds; 1,3,4-Oxathiazol-2-ones; Nitrile sulfides; X-ray crystallography; Microwave-assisted synthesis

1. Introduction

Various 1,3,4-oxathiazol-2-ones **1** have been shown to have biological activity, for example, as fungicides.[1] The principal use of these compounds, however, is as shelf-stable precursors of nitrile sulfides (R–C≡N^+–S^-),[2,3] which are usually generated by thermal decarboxylation at 120–160 °C. The cycloaddition reactions of this rare class of 1,3-dipoles can provide access to five-membered heterocycles incorporating the C=N–S unit, including isothiazoles **2** and 1,2,4-thiadiazoles **3**. Various substituents can be incorporated at the 5-position, including esters, amides and phenols in addition to simple alkyl and aryl groups. Little attention, however, has been paid to carbohydrate analogues, the furanosyl derivative **4** being are a rare exception.[4] We now report the first syntheses of pyranosyl oxathiazolones as potential precursors of pyranosyl nitrile sulfides **5**.



1 **2** **3**



4 **5**

2. Results and discussion

The most widely used synthetic approach to 1,3,4-oxathiazol-2-ones **1** involves treatment of the corresponding

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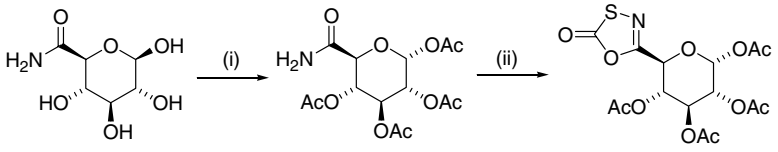
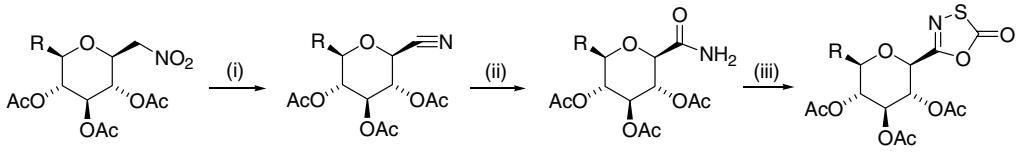


Scheme 1. Reagents: (i) Ac_2O, pyridine; (ii) ClCOSCl.

carboxamide with chlorocarbonylsulfenyl chloride.[1,3,5] For the present work sources of pyranosyl carboxamides were therefore required. For initial study glucuronamide **6** was selected as a readily accessible starting material, which would afford a pyranose bearing an oxathiazolone substituent at the 5-position. The glucuronamide was first converted to its tetra-*O*-acetyl derivative **7** (92%) by treatment with acetic anhydride/pyridine, and the product then reacted with ClCOSCl in toluene at reflux for 6 h (Scheme 1). Work-up of the reaction mixture afforded 5-(1,2,3,4-tetra-*O*-acetyl-α-D-xylopyranos-5*S*-*C*-yl)-1,3,4-oxathiazol-2-one (**8**) in 79% yield. The product was initially identified by its spectroscopic properties: in addition to the expected ^1H and ^{13}C NMR signals for the carbohydrate moiety there were characteristic peaks in the carbon spectrum at 170.3 and 155.4 ppm for C-2 and C-5, respectively, of the 1,3,4-oxathiazol-2-one ring. The structure was confirmed by X-ray crystallography (vide infra).

The pyranosyl carboxamide precursors that were required for the synthesis of pyranoses with the oxathiazolone linked to the anomeric position were prepared from the readily-accessible nitromethyl compounds (Scheme 2). For example, D-xylose was converted into the peracetylated nitromethyl derivative **9** using the general procedure of Köll and co-workers.[6] This involves reaction with nitromethane and sodium methoxide in methanol, heating the resulting adduct to achieve dehydration and cyclisation, and finally acetylation using Ac_2O/CF_3SO_3H. The nitromethyl compound **9** was then converted into the nitrile **10** by treatment with phosphorus trichloride in pyridine,[7] and the product hydrolysed ($TiCl_4/AcOH/H_2O$) using the general method of BeMiller et al.[8] to afford the carboxamide **11**. In the final stage the carboxamide was reacted with ClCOSCl using the procedure that had been successfully employed for the glucuronamide analogue described above to yield 5-(2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxathiazol-2-one (**12**) (74%). The overall yield for the three steps from nitromethyl compound **9** to oxathiazolone **12** was 25%. The D-glucose-derived oxathiazolone **13** was prepared similarly from the peracetylated nitromethyl-D-glucose compound **14** via nitrile **15** and carboxamide **16** in 20% overall yield. The ^{13}C NMR data for the oxathiazolone ring carbons of pyranosyl compounds **12** and **13** were very similar to those of the pyranos-5-*C*-yl analogue **8**, with distinctive signals at ~170 ppm for C-2 and ~155 ppm for C-5.

The structure of the glucuronamide-derived oxathiazolone **8** was determined by X-ray crystallography (Fig. 1). The Cremer and Pople[9] puckering parameters for the glucopyranose and oxathiazolone rings are shown in Table 1. The pyranoid ring has 91% of the puckering of an ideal cyclohexane chair conformation with $Q = 0.577$ Å and $\theta = 4.4°$, compared to $Q = 0.630$ Å and $\theta = 0°$ for the ideal chair. Such values are typical of pyranoid rings in the $^4C_1$ conformation. The chair arrangement is also evident from the proton–proton ^1H NMR couplings for the glucose ring [$J_{1,2}$ 3.6, $J_{2,3}$ 10.3, $J_{3,4}$ 9.9, $J_{4,5}$ 10.1 Hz], which are characteristic of β-glucopyranosides. The H–C–C–H torsion angles from the X-ray data are compared with the observed and calculated[10] ^3J values in Table 2; good agreement is observed in all cases. The atoms of the oxathiazole ring O-1, C-2, S-3, N-4, C-5 are near coplanar (maximum deviation 0.020 Å) with no atom more than 0.032 Å from the best plane, and the plane of the oxathiazole ring is near orthogonal to that involving C-1′, C-3′ and C-5′ of the glucopyranosyl moiety [dihedral angle between planes = 89.62(7)°]. Selected bond lengths and bond angles for the oxathiazolone unit are compared in Table 3 with the corresponding values for the non-carbohydrate oxathiazolone structures **17**–**20**.[11–14] The C=N bond length [N-4–C-5 = 1.262(3) Å] is somewhat shorter than the average value reported for compounds **17**–**20** (1.277 Å), but still con-



Scheme 2. Reagents: (i) PCl_3, pyridine; (ii) $TiCl_4$, AcOH, H_2O; (iii) ClCOSCl.

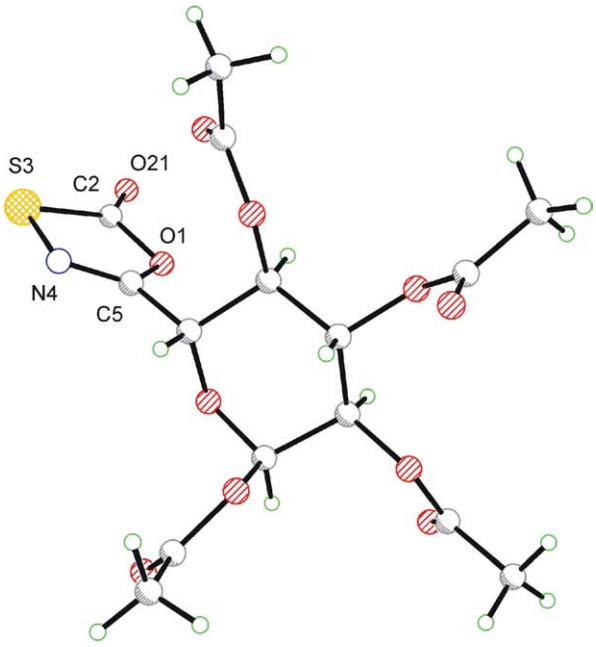
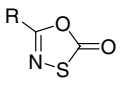


Figure 1. Crystal structure of 5-(1,2,3,4-tetra-*O*-acetyl-α-D-xylopyranos-5*S*-*C*-yl)-1,3,4-oxathiazol-2-one (**8**).

sistent with a localised C(sp^2)=N π-bond [1.28 Å].[15] The sulfur–nitrogen bond distance in compound **8** [S-3–N-4 = 1.689(2) Å] is also typical for heterocycles of this class, being slightly shorter than the accepted S–N single bond length [1.75 Å].[15] The average length [1.375 Å] for the two endocyclic carbon–oxygen bonds is significantly greater than that expected for C(sp^2)–O [1.34 Å] and, furthermore, O-1–C-5 is shorter than O-1–C-2 [Δd = 0.017 Å]. A similar effect has been reported for the 5-alkyl-substituted oxathiazolones **17** [Δd = 0.024 Å][11] and **18** [Δd = 0.015 Å],[12] whereas for the aryl analogues **19** and **20** these bonds are of similar length [Δd = 0.004 Å].[13,14]



17 R = Me
18 R = adamant-1-yl
19 R = Ph
20 R = 4-MeOC$_6$H$_4$

Having established an efficient and general synthetic route to 5-pyranosyl-1,3,4-oxathiazol-2-ones the feasibility of using these compounds as sources of pyranosyl nitrile sulfides was examined. The usual conditions for generating nitrile sulfides is to heat the oxathiazolone at 120–160 °C in an inert solvent such as toluene, chlorobenzene or mesitylene until the starting material has been consumed, typically 5–60 h. Nitrile sulfides are short-lived intermediates that are known to decompose to sulfur and the corresponding nitrile.[3] In order to provide initial evidence for nitrile sulfide formation, a solution of glucopyranos-5-*C*-yloxathiazolone **8** in mesitylene was therefore heated at reflux (~165 °C). The oxathiazolone proved to be unusually stable and it required 12 h for it to decompose completely. Work-up of the reaction mixture afforded the corresponding nitrile **21** (97%), which was identified by comparison with an authentic sample prepared by reaction of carboxamide **7** with thionyl chloride. Similarly, heating a solution xylopyranosyl oxathiazolone **12** in xylene at reflux for 36 h yielded the expected nitrile **10**. These results are consistent with the formation of nitrile sulfides as intermediates. To prove their involvement, however, required trapping with a dipolarophile. Ethyl cyanoformate (ECF) and dimethyl acetylenedicarboxylate (DMAD) were selected for this purpose as both are known to be reactive towards nitrile sulfides.[3] However, heating D-xylose-derived oxathiazolone **12** with an excess of ECF (1:9) in xylene afforded only the nitrile decomposition product **10** together with unreacted starting material. Likewise, only the nitrile was isolated from the corresponding reaction with DMAD. However, the reaction of glucuronamide-derived oxathiazolone **8** with ECF in mesitylene at reflux for 24 h afforded a mixture of nitrile **21** (44%) and ethyl 3-(1,2,3,4-tetra-*O*-acetyl-α-D-xylopyranos-5*S*-*C*-yl)-1,2,4-thiadiazole-5-carboxylate **22** (5%), from which traces (1%) of the cycloadduct were isolated in pure form by preparative TLC (Scheme 3). The product was identified from its analytical and spectroscopic properties. A full assignment of the proton and carbon NMR spectra was achieved using from the COSY, HMQC and HMBC techniques. There are, in addition to the expected proton and carbon peaks for the xylopyranos-5-*C*-yl unit, characteristic signals for the ethyl 1,2,4-thiadiazole-5-carboxylate moiety [δ_H

Table 2. Selected torsion angles involving hydrogen [H(X)–C(X)–C(Y)–H(Y)] for oxathiazolone **8** with observed and calculated coupling constants

H_x, H_y	Angle θ_{obs}/° [a]	J_{calc}/Hz[b]	J_{obs}/Hz
1′, 2′	+54.9	3.3	3.6
2′, 3′	−174.1	10.2	10.3
3′, 4′	+170.8	10.1	9.9
4′, 5′	−169.0	10.0	10.1

[a] H–C–C–H torsion angle (θ) from X-ray data.
[b] $J_{calc} = 7.76\cos^2\theta - 1.1\cos\theta + 1.4$ (see Ref. 10).

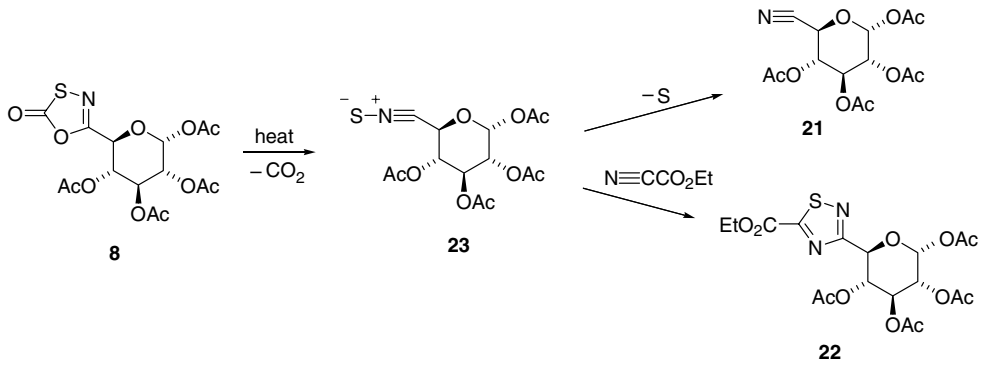
Table 1. Cremer and Pople puckering parameters[a] for oxathiazolone **8**

Ring		Q/Å	θ/°	ϕ/°
Pyranose	C-1′–C-2′–C-3′–C-4′–C-5′–O-6′	0.577	4.4	55.4
Oxathiazolone	O-1–C-2–S-3–N-4–C-5	0.051	—	308.0

[a] Ref. 9.

Table 3. Selected bond lengths and bond angles for oxathiazolones **8**, **17**–**20**

Length	**8**	**17**–**20**	Angle	**8**	**17**–**20**
O-1–C-2	1.387(3)	1.380–1.392	C-5–O-1–C-2	110.26(18)	111.2–112.0
C-2–S-3	1.753(3)	1.744–1.768	O-1–C-2–S-3	106.97(15)	106.4–107.2
S-3–N-4	1.689(2)	1.677–1.687	C-2–S-3–N-4	93.23(11)	92.9–93.5
N-4–C-5	1.262(3)	1.267–1.289	S-3–N-4–C-5	108.52(16)	109.1–110.5
C-5–O-1	1.365(3)	1.367–1.380	N-4–C-5–O-1	120.7(2)	117.9–119.3
C-2═O-21	1.186(3)	1.184–1.198	O-1–C2═O	122.8(8)	121.7–123.6
C-5–R	1.495(3)	1.457–1.491	O-1–C5–R	114.69(19)	115.0–116.6



Scheme 3.

1.44 (CH_3), 4.51 ppm (OCH_2), ^3J 7.1 Hz; δ_C 14.0 (CH_3), 63.4 (OCH_2), 157.8 (C═O), 171.6 (C-3), 179.9 (C-5)] that are very similar to those previously reported for ethyl 1,2,4-thiadiazole-5-carboxylates.[4,16] The nitrile **21** was identified by comparison with an authentic sample prepared by dehydration of carboxamide **7** using thionyl chloride. The formation of thiadiazole **22** provides unequivocal evidence for the formation of pyranos-5-*C*-yl nitrile sulfide **23** as an intermediate in the reaction. The very low cycloadduct yield indicates that the decomposition rate of pyranosyl nitrile sulfides is greater than the rate of trapping by the dipolarophiles employed for this purpose.

The failure to trap the pyranosyl nitrile sulfides in synthetically-useful yields is attributed, not only to the unusual thermal stability of the oxathiazolone precursors and to the short lifetime of the nitrile sulfides, but also the need to use high-boiling solvents and long reaction times. In an attempt to overcome these problems preliminary studies were undertaken using microwave irradiation in place of conventional thermolysis at reflux. This technique is finding widespread application[17] in organic synthesis and has been used to promote various cycloaddition reactions including those of nitrile imides[18] and nitrile oxides.[19] Initial experiments carried out in ethyl acetate at 160 °C (300 W, 10 min) gave only unreacted starting material. In order to perform the reactions at higher temperatures toluene, rather than ethyl acetate, was used in subsequent experiments. Irradiation of a solution of xylopyranos-5-*C*-yl oxathiazolone **8** in toluene for 10 min at 200 °C gave a mixture of the starting material and the target 3-xylopyranos-5-*C*-yl-1,2,4-thiadiazole **22**. However, after irradiation for 55 min at the same temperature all the starting material had been consumed and work-up of the reaction mixture afforded the thiadiazole **22** in good yield (63%).

3. Conclusion

In conclusion, 5-pyranosyl-1,3,4-oxathiazol-2-ones can be prepared in good yield by reaction of the corresponding carboxamide with chlorocarbonylsulfenyl chloride. They show unusual thermal stability and require temperatures in excess of 150 °C before they undergo decarboxylation to the nitrile sulfide. The latter either fragment to the corresponding nitrile or can be trapped by cycloaddition with ethyl cyanoformate to afford the 3-pyranosyl-1,2,4-thiadiazole. Only trace amounts of cycloadduct were isolated by conventional thermolysis; however, using microwave irradiation the thiadiazole is formed in good yield.

4. Experimental

4.1. General methods and materials

The analytical methods, instrumentation and procedures for preparative chromatography were as previously described.[20] Microwave experiments were conducted in closed vessels using a CEM Discoverer microwave with

ramp times of between 5 and 15 min and 20 min cooling. 2,3,4-Tri-*O*-acetyl-β-D-xylopyranosylnitromethane (**9**) and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylnitromethane (**14**) were prepared from D-xylose and D-glucose, respectively, by reaction with $MeNO_2$/NaOMe/MeOH and acetylation of the resulting β-D-pyranosylnitromethane as previously reported.[8]

4.2. 5-(1,2,3,4-Tetra-*O*-acetyl-α-D-xylopyranos-5*S*-*C*-yl)-1,3,4-oxathiazol-2-one (8)

4.2.1. 1,2,3,4-Tetra-*O*-acetyl-α-D-glucuronamide (7). Ac_2O (20 mL) was added to a suspension of glucuronamide (2.00 g, 10.4 mmol) in pyridine (20 mL) and stirred overnight under nitrogen at room temperature. The mixture was concentrated, azeotroped with toluene followed by Et_2O and the residue recrystallised from EtOH to afford the title compound **7** as colourless needles (3.43 g, 92%); mp 155–156 °C (lit.[21] 147–149 °C; lit.[22] 145–148 °C); $[\alpha]_D^{18}$ +10.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.04, 2.05, 2.08, 2.15 (4 × s, 12H, $COCH_3$), 4.27 (d, 1H, H-5), 5.06 (dd, 1H, H-2), 5.21 (dd, 1H, H-4), 5.51 (t, 1H, H-3), 6.35 (d, 1H, H-1), 6.41 (br s, 2H, $CONH_2$); *J*(*x*–*y*)/Hz 1–2 3.6, 2–3 10.1, 3–4 9.5, 4–5 10.1. ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.3, 20.5, 20.6 (4 × $CO\mathit{C}H_3$), 68.8, 70.1 (C-2, C-3, C-4, C-5), 88.1 (C-1), 168.7, 168.9, 169.6, 169.7 (4 × $\mathit{C}OCH_3$, $CONH_2$). HRFABMS: (*m*/*z*): $[M+H]^+$ calcd for $C_{14}H_{20}NO_{10}$, 362.1087; found, 362.1086.

4.2.2. 5-(1,2,3,4-Tetra-*O*-acetyl-α-D-xylopyranos-5*S*-*C*-yl)-1,3,4-oxathiazol-2-one (8). Chlorocarbonylsulfenyl chloride (0.1 mL, 1.2 mmol) was added to a solution of carboxamide **7** (100 mg, 0.28 mmol) in Na-dried toluene (3 mL) and the mixture heated at reflux for 6 h. After concentration the residue was azeotroped with toluene and the residue recrystallised from EtOAc to afford the title compound as colourless crystals (92 mg, 79%); mp 212–214 °C; $[\alpha]_D^{18}$ +12.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.03, 2.04, 2.07, 2.23 (4 × s, 12H, $COCH_3$), 4.75 (d, 1H, H-5′), 5.16 (dd, 1H, H-2′), 5.30 (dd, 1H, H-4′), 5.58 (t, 1H, H-3′), 6.42 (d, 1H, H-1′); *J*(*x*–*y*)/Hz 1′–2′ 3.6, 2′–3′ 10.3, 3′–4′ 9.5, 4′–5′ 10.1. ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.8 (4 × $CO\mathit{C}H_3$), 68.9, 69.1, 69.2, 69.6 (C-1′, C-2′, C-3′, C-4′), 89.1 (C-5′), 155.4 (C-5), 168.8, 169.8, 169.9 (4 × $\mathit{C}OCH_3$), 170.3 (C-2). HRFABMS: (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{18}NO_{11}S$, 420.0601; found, 420.0600. The structure of compound **8** was established by X-ray crystallography (vide infra).

4.3. 5-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxathiazol-2-one (12)

4.3.1. 2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl cyanide (10). Percetylated nitromethyl-xylose derivative **9** (150 mg, 0.47 mmol) was dissolved in pyridine (3 mL) and cooled in an ice bath. To this PCl_3 (0.05 mL, 0.52 mmol) was added and the mixture stirred overnight at room temperature. Ice-cold aq 1 M HCl (20 mL) was added and the solution stirred for 20 min. The product was extracted into chloroform (3 × 10 mL) and the combined organic layers were washed with satd aq $NaHCO_3$ (2 × 10 mL) and with water (10 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed in vacuo, to give the title compound **10** as a white solid (113 mg, 84%); mp 128–129 °C (lit.[7] 131–132 °C); $[\alpha]_D^{18}$ −36.7 (*c* 0.90, $CHCl_3$); R_f 0.54 (Et_2O); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.03, 2.06, 2.07 (3 × s, 9H, CH_3), 3.56 (dd, 1H, H-5e), 4.18 (dd, 1H, H-5a), 4.46 (d, 1H, H-1), 4.83–4.90 (m, 1H, H-4), 5.04–5.07 (m, 2H, H-2, H-3); *J*(*x*–*y*)/Hz 1–2 6.9, 2–3 nd, 3–4 nd, 4–5a 4.0, 4–5e 6.8, 5a–5e 12.4; ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.3, 20.5 ($CO\mathit{C}H_3$), 65.1 (C-5), 65.3, 66.8, 67.6, 68.7 (C-1, C-2, C-3, C-4), 114.3 (CN), 168.8, 169.2, 169.4 (3 × $\mathit{C}OCH_3$). HRFABMS: (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{16}NO_7$, 286.0927; found, 286.0921.

4.3.2. 2,3,4-Tri-*O*-acetyl-β-D-xylopyranosylformamide (11). Titanium tetrachloride (0.13 mL, 1.19 mmol) was added to a solution of 2,3,4-tri-*O*-acetyl-β-D-xylopyranosyl cyanide (1.71 g, 5.96 mmol) in glacial acetic acid (5 mL) at 0 °C. After addition of H_2O (0.11 mL), the mixture was stirred at room temperature for 5 h. The mixture was then poured into ice-water (50 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and dried ($MgSO_4$). After removal of the solvent in vacuo the resulting solid was recrystallised from $CHCl_3$/Et_2O to afford the title compound (722 mg, 40%); mp 175 °C; $[\alpha]_D^{18}$ −38.0 (*c* 1.00, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.13, 2.14, 2.16 (3 × s, 9H, $COCH_3$), 3.48 (d, 1H, H-5a), 3.93 (dd, 1H, H-1), 4.30 (dd, 1H, H-5e), 5.08 (ddd, 1H, H-4), 5.22 (t, 1H, H-2), 5.36 (t, 1H, H-3), 6.28 (br s, 1H, $CONH_2$), 6.54 (br s, 1H, $CONH_2$); *J*(*x*–*y*)/Hz 1–2 9.6, 2–3 9.4, 3–4 9.2, 4–5a 10.3, 4–5e 5.5, 5a-5e 11.2. ^{13}C NMR (63 MHz, $CDCl_3$): δ 21.0 (3 × $CO\mathit{C}H_3$), 66.5 (C-5), 69.1, 69.7 72.9, 76.9 (C-1, C-2, C-3, C-4), 170.2, 170.3, 170.4 (3 × $\mathit{C}OCH_3$, $\mathit{C}ONH_2$). HRFABMS: (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{18}NO_8$, 304.1032; found, 304.1027. Anal. Calcd for $C_{12}H_{17}NO_8$: C, 47.5; H, 5.6; N, 4.6; found: C, 47.4; H, 5.6; N, 4.3.

4.3.3. 5-(2,3,4-Tri-*O*-acetyl-β-D-xylopyranosyl)-1,3,4-oxathiazol-2-one (12). Chlorocarbonylsulfenyl chloride (0.08 mL, 0.94 mmol) was added to a solution of carboxamide **11** (117 mg, 0.39 mmol) in dry $CHCl_3$ (10 mL) and the mixture heated at reflux for 48 h. After concentration the residue was azeotroped with toluene (3 × 20 mL) and the resulting solid dissolved in CH_2Cl_2. The solution was passed through a silcica pad (~5 mm) and the eluant concentrated to afford the title compound

as white crystals (104 mg, 74%); mp 134–137 °C; $[\alpha]_D^{18}$ −41.7 (*c* 0.48, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 1.95, 1.98, 1.99 (3 × s, 9H, $COCH_3$), 3.36 (dd, 1H, H-5a′), 4.20 (dd, 1H, H-5e′), 4.25 (d, 1H, H-1′), 5.00 (ddd, 1H, H-4′), 5.16 (t, 1H, H-2′), 5.22 (t, 1H, H-3′); *J*(*x*–*y*)/Hz 1′–2′ 9.3, 2′-3′ 9.3, 3′–4′ 9.1, 4′–5′a 10.7, 4′–5′e 5.5, 5′a–5′e 11.4. ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.3, 20.5 (3 × $CO\mathit{C}H_3$), 66.8 (C-5), 68.1, 69.1 72.0 (C-2′, C-3′, C-4′), 74.5 (C-1′), 155.4 (C-5), 169.3, 169.5, 169.9 (3 × $\mathit{C}OCH_3$), 172.2 (C-2). HRFABMS: (*m*/*z*): $[M+H]^+$ calcd for $C_{12}H_{16}NO_9S$, 362.0547; found, 362.0546.

4.4. 5-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,3,4-oxathiazol-2-one (13)

4.4.1. 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl cyanide (15). Phosphorus trichloride (0.4 mL, 4.58 mmol) was added to an ice-cold solution of nitromethyl-glucose derivative **14** (1.50 g, 3.84 mmol) in pyridine under nitrogen; the reaction mixture was allowed to warm to room temperature and left stirring for 72 h. The resulting dark-brown mixture was quenched with ice-cold aq HCl (1 M, ca. 150 mL) and left stirring for 1 h then extracted with chloroform (3 × 150 mL). The organic extracts were combined, washed with satd aq $NaHCO_3$ (100 mL), H_2O (50 mL) and satd aq NaCl (50 mL). The organic layers were then dried ($MgSO_4$) and the solvent removed in vacuo to give an orange-brown oil. This was dissolved in CH_2Cl_2 (ca. 100 mL), passed through a silica pad and concentrated in vacuo to give the title compound as a white solid (812 mg, 59%); mp 110–111 °C (lit.[23] 114–115 °C); R_f 0.33 (petroleum ether/ethyl acetate, 1:1); ^1H NMR (250 MHz, $CDCl_3$): δ 2.03, 2.04, 2.11 (4 × s, 12H, $COCH_3$), 3.73 (m, 1H, 5-H), 4.20 (m, 2H, 6a-H, 6b-H), 4.33 (d, 1H, 1-H), 5.07–5.22 (m, 2H, 2-H, 4-H), 5.32 (t, 1H, 3-H); *J*(*x*–*y*)/Hz 1–2 10.1, 2–3 9.8, 3–4 9.8, 4–5 9.4, 5–6a 4.8, 5–6b 2.3, 6a–e 12.7; ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.3 (4 × $CO\mathit{C}H_3$), 61.3 (C-6), 66.3, 67.1, 68.8, 72.7, 76.7 (C-1. C-2, C-3, C-4, C-5), 114.0 (CN), 168.6, 169.0, 169.9, 170.4 (4 × $\mathit{C}OCH_3$); HRFABMS: (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{20}NO_9$, 358.1138; found, 358.1137.

4.4.2. 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylformamide (16). Titanium tetrachloride (0.05 mL, 0.46 mmol) and water (0.06 mL) were added to an ice-cold solution of 2,3,4,6-tetra-*O*-acetyl-β-D-glucpyranosyl cyanide (1.00 g, 2.80 mmol) in glacial acetic acid (5 mL) and the mixture stirred at 0 °C for 30 min. The mixture was allowed to warm to room temperature and then stirred for 5 days. It was then poured into ice-water (50 mL) and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (50 mL) and satd aq NaCl. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The resulting solid was recrystallised from $CHCl_3/Et_2O$ to afford the title compound as fine white crystals (478 mg, 46%); mp partially 112–114 °C, totally 146–147 °C (lit.[7] partially 112–114 °C, totally 146–147 °C); $[\alpha]_D^{25}$ +103.1 (*c* 0.98, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ 1.81, 1.85, 1.88, 1.93 (4 × s, 9H, $COCH_3$), 3.57–3.59 (m, 1H, H-5), 3.69 (d, 1H, H-1), 4.00 (m, 2H, H-6a, H-6b), 5.10 (t, 1H, H-2), 5.28 (t, 1H, H-4), 5.42 (t, 1H, H-3), 5.49 (br s, 1H, $CONH_2$); *J*(*x*–*y*)/Hz 1–2 9.6, 2–3 9.7, 3–4 9.7, 4–5 10.3, 5–5a 7.0, 5–6b 2.2, 6a–b 13.0. ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.2, 20.4, 20.5 (4 × $CO\mathit{C}H_3$), 61.8 (C-7), 66.4, 68.1 73.6, 75.0. 75.9 (C-1, C-2, C-3, C-4, C-5), 169.1, 169.8, 170.4, 170.5 (4 × $\mathit{C}OCH_3$, $\mathit{C}ONH_2$). HRFABMS: (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{22}NO_{10}$, 376.1244; found, 376.1244.

4.4.3. 5-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-1,3,4-oxathiazol-2-one (13). Chlorocarbonylsulfenyl chloride (0.1ml, 1.2 mmol) was added to a solution of carboxamide **16** (100 mg, 0.27 mmol) in Na-dried toluene (3 mL), and the mixture heated at reflux for 4 h. The reaction mixture was concentrated in vacuo, azeotroped with toluene and then passed through a silica pad [cyclohexane/ethyl acetate, 1:1 (50 mL)] and concentrated in vacuo to give the title compound as a white solid (88 mg, 75%); mp 112–113 °C; $[\alpha]_D^{25}$ +1.8 (*c* 1.64, $CHCl_3$); R_f 0.43 (petroleum ether/ethyl acetate, 1:1); ^1H NMR (250 MHz, $CDCl_3$): δ 2.02, 2.03, 2.07, 2.09 (4 × s, 12H, $COCH_3$), 3.70 (m, 1H, 5′-H), 4.18 (m, 2H, 6′a-H, 6b′-H), 4.48 (d, 1H, 1′-H), 5.17 (t, 1H, 2′-H), 5.30 (t, 1H, 4′-H), 5.52 (t, 1H, 3′-H); *J*(*x*–*y*)/Hz 1′–2′ 10.0, 2′–3′ 9.6, 3′–4′ 9.6, 4′–5′ 9.4, 5′–6′a nd, 5′–6′b nd, 6′a–6′b nd; ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.3, 20.4 (4 × $CO\mathit{C}H_3$), 61.5 (C-6′), 66.3, 67.9, 70.2, 72.8, 73.8 (C-1′, C-2′, C-3′, C-4′, C-5′), 156.1 (C-5), 168.9, 169.3, 169.7 (4 × $\mathit{C}OCH_3$) 170.0 (C-2); HRFABMS: (*m*/*z*): $[M+H]^+$ calcd for $C_{16}H_{20}NO_{11}S$, 434.0757; found 434.0752.

4.5. 1,2,3,4-Tetra-*O*-acetyl-α-D-glucuronic acid nitrile (21)

A solution of 1,2,3,4-tetra-*O*-acetyl-α-D-glucuronamide (**7**) (220 mg, 0.61 mmol) in thionyl chloride (1.0 mL) was heated at reflux for 72 h, then passed through a silica pad (eluting with 1:1 cyclohexane/EtOAc, 50 mL) and concentrated in vacuo to afford the title compound as a white (155 mg, 74%); mp 212–215 °C; $[\alpha]_D^{25}$ +83.9 (*c* 0.62, $CHCl_3$); R_f 0.65 (petroleum ether/ethyl acetate, 1:1); ^1H NMR (250 MHz, $CDCl_3$): δ 2.28, 2.30, 2.37, 2.47 (4 × s, 12H, $COCH_3$), 4.98 (d, 1H, 5-H), 5.35 (dd, 1H, 2-H), 5.54–5.70 (m, 2H, 3-H, 4-H), 6.62 (d, 1H, 1-H); *J*(*x*–*y*)/Hz 1–2 3.7, 2–3 9.5, 3–4 nd, 4–5 10.0; ^{13}C NMR (63 MHz, $CDCl_3$): δ 20.2, 20.6 (4 × $CO\mathit{C}H_3$),

61.0, 68.1, 68.5, 68.6 (C-1, C-2, C-3, C-4), 88.3 (C-5), 114.0 (C-6), 167.9, 168.6, 169.2, 169.8 ($4\times COCH_3$); HRFABMS: (m/z): $[M+H]^+$ calcd for $C_{14}H_{18}NO_9$, 344.0982; found 344.0979. Anal. Calcd for $C_{14}H_{17}NO_9$: C, 48.98; H, 4.99; N, 4.08; found: C, 48.97; H, 5.38; N, 3.68.

4.6. Generation and reactions of pyranosyl nitrile sulfides

4.6.1. Thermolyses of oxathiazolones 8 and 12. A solution of the oxathiazolone **8** (50 mg, 0.14 mmol) in dry mesitylene (5 mL) was heated at reflux under nitrogen for 12 h. The solvent was concentrated in vacuo and the remaining solvent removed by azeptroping with toluene. The resulting white solid was identified as the glucuronic acid nitrile **21** (40 mg, 97%) by comparison of its spectroscopic properties with those of an authentic sample. Similarly, thermolysis of a solution of oxathiazolone **12** in xylene at reflux for 36 h afforded only the nitrile **10**.

4.6.2. Thermolysis of oxathiazolone 12 with ethyl cyanoformate (ECF). Xylopyranosyl-oxathiazolone **12** (100 mg, 0.28 mmol) and ECF (250 mg, 2.52 mmol) were dissolved in *m*-xylene under nitrogen and the solution heated at reflux for 72 h. The reaction mixture was cooled, the solvent was removed in vacuo and the resulting oil co-evaporated with toluene to remove the residual ECF to give a white solid (38 mg). ^{1}H NMR and mass spectroscopy indicated that the product was a 1:1 mixture of the starting material **12** and the nitrile **10**.

4.6.3. Thermolysis of oxathiazolone 12 with dimethyl acetylenedicarboxylate (DMAD). A solution of xylopyranosyl-oxathiazolone **12** (100 mg, 0.28 mmol) and DMAD (358 mg, 2.52 mmol) in *m*-xylene under nitrogen was heated at reflux for 48 h. The reaction mixture was cooled, the solvent was removed in vacuo and the resulting oil was co-evaporated with toluene to remove the residual DMAD. The only identifiable product was the nitrile **10**.

4.6.4. Thermolysis of oxathiazolone 8 with ethyl cyanoformate (ECF). A solution of oxathiazolone **8** (500 mg, 1.2 mmol) and ECF (2.0 mL, 20.2 mmol) in mesitylene (30 mL) was heated at reflux in a nitrogen atmosphere for 24 h. Having confirmed by TLC and MS analysis that no starting material remained, the reaction mixture was concentrated in vacuo and azeotroped with toluene to give a solid. Chromatography (silica; cyclohexane/EtOAc, gradient elution) to afford a mixed fraction (212 mg) containing nitrile **21** (44%) and ethyl 3-(1,2,3,4-tetra-*O*-acetyl-α-D-xylopyranos-5*S*-*C*-yl)-1,2,4-thiadiazole **22** (5%). Traces of thiadiazole **22** were isolated by preparative TLC as a white solid (6 mg, 1%); mp 193–194 °C; $[\alpha]_D^{20}$ +103 (c 1, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$): δ 1.44 (t, 3H, CH_3), 1.91, 2.03, 2.04, 2.22 ($4\times$s, 12H, $COCH_3$), 4.51 (q, 2H, OCH_2), 5.28 (dd, 1H, 2′-H), 5.35 (d, 1H, 5′-H), 5.50 (t, 1H, 4′-H), 5.65 (t, 1H, 3′-H), 6.47 (d, 1H, 1′-H); $J(x–y)$/Hz CH_3–CH_2 7.1, 1′–2′ 3.6, 2′–3′ 10.2, 3′–4′ 9.4, 4′–5′ 10.1; ^{13}C NMR (90 MHz, $CDCl_3$): δ 14.0 (CH_3), 20.2, 20.3, 20.6, 20.8 ($4\times CO\underline{C}H_3$), 63.4 ($OCH_2$), 68.9 (C-4′), 69.1 (C-5′), 70.1 (C-3′), 70.7 (C-2′), 88.9 (C-1′), 157.8 (C=O), 168.5, 169.1, 169.4, 170.0 ($4\times \underline{C}OCH_3$), 171.6 (C-3), 179.9 (C-5); HRFABMS: (m/z): $[M+H]^+$ calcd for $C_{18}H_{23}N_2O_{11}S$, 475.1023; found 475.1034. Anal. Calcd for $C_{18}H_{22}N_2O_{11}S$: C, 45.6; H, 4.6; N, 5.9; found: C, 45.3; H, 4.6; N, 5.7.

4.6.5. Microwave irradiation of oxathiazolone 8 with ethyl cyanoformate (ECF). A solution of oxathiazolone **8** (100 mg, 0.238 mmol) and ECF (0.24 mL, 2.38 mmol) in toluene (3 mL) was heated in the microwave at 200 °C and with a 300 W power input for 55 min. After cooling, the excess ECF and the solvent were removed under reduced pressure. The resulting residue was purified by flash chromatography (silica; 0–40% ethyl acetate/hexane) to yield a white solid, which was recrystallised from ethanol to afford the thiadiazole **22** as white crystals (71 mg, 63%). Similar experiments carried out at 200 °C for 10 min afforded a mixture of thiadiazole **22** and oxathiazolone **8**. After 10 min at 160 °C only starting material was recovered.

4.7. Crystal structure of oxathiazolone 8

Diffraction data were collected with graphite-monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) on a Bruker SMART Apex diffractometer equipped with an Oxford Cryosystems low-temperature device operating at 150 K. The structure was solved by direct methods (Shelxs) and refined by full-matrix least-squares against F^2 (Shelxl).[24] All non-H atoms were refined with anisotropic displacement parameters; H-atoms were placed in idealised positions. Crystal data: $C_{15}H_{17}N_1O_{11}S$, $M = 419.36$, orthorhombic, $a = 8.8149(7)$, $b = 12.787(1)$, $c = 16.4247(13)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$, $V = 1851.4(3)$ Å^3, space group $P2_12_12_1$ (the compound was known to be chiral); $T = 150$ K, $Z = 4$, $D_c = 1.504$ Mg m^{-3}, colourless block, $0.14\times0.23\times0.24$ mm^3. The final conventional R-factor (based on F and 4200 data with $F > 4\sigma(F)$ was 4.88%; $wR2$ (based on F^2 and all 4542 data used in refinement) was 10.88. The final difference map extremes were 0.42 and −0.28 e Å^{-3}. The Flack parameter[25] was −0.08(9)); this is sufficient to confirm the hand of the molecule as predicted from the synthesis.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as

supplementary publication number CCDC 287132. Copies can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033 or email: deposit@ccdc.cam.ac.uk).

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