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Novel Cyclization of D-Glucopyranosyl-(*Z*)-Thiohydroximates leading to New Anomeric Spiro Oxathiazole Derivatives

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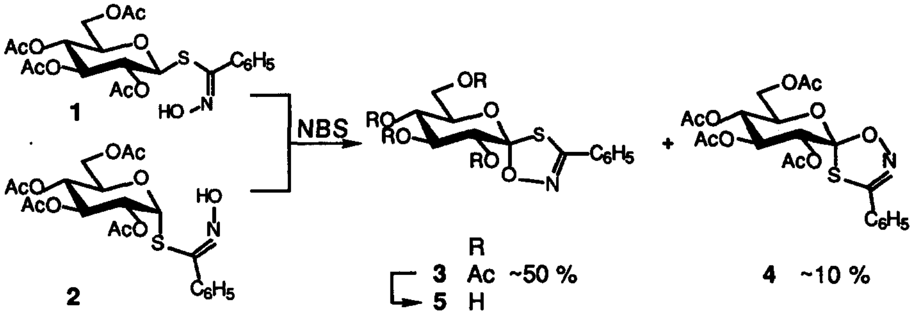
Abstract: Both α- and β- anomers of 2,3,4,6-tetra-*O*-acetyl-1-*S*-(*Z*)-benzhydroximoyl-1-thio-D-glucopyranose yielded, when treated with *N*-bromosuccinimide in refluxing carbon tetrachloride, the same mixture of new anomeric spiro oxathiazole derivatives in which the major epimer has a (*S*) configuration at the anomeric centre.

Earlier studies have shown that free-radical conditions allow the transformation of 2-hydroxyethyl-2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside into the corresponding anomeric spiro orthoester via a cyclization reaction which involves homolysis of the anomeric C-H bond via a 6-membered transition state[1,2]. Therefore, it was anticipated that the same methodology might be applicable for achieving the spirocyclization of the structurally related glucopyranosyl-(Z)-thiohydroximates **1** and **2**[3]. Although *S*-glycosidic bonds are readily cleaved by halonium-forming species[4], conditions exist which favour free-radical reactions, in particular homolysis of anomeric C-H bonds[5-7]. In order to design a possible route to sugar derivatives displaying an unusual anomeric linkage, the treatment of acetylated β- and α-D-glucopyranosyl-(Z)-thiohydroximates **1** and **2** with NBS was investigated.



A mixture of **1** (1 mmol) and NBS (1 mmol) in dry carbon tetrachloride was refluxed over a 150 W tungstene lamp for 10 min. After addition of another portion of NBS (1mmol), heating was continued until TLC monitoring (hexane-ethyl acetate 6:4 v/v) showed the complete transformation of the starting material (5-10 min)[8]. On silica gel 60 F_{254} plates, two faster moving compounds were visible under UV light. After workup, the reaction mixture was resolved by column chromatography on silica gel (hexane-ethyl acetate 7:3 v/v). Compounds **3** and **4**[9] were isolated in *ca.* 50% and 10% yield, respectively. Similar observations were made when using the α-anomer, which reacted within 20 min altogether to give a comparable mixture of products (TLC) from which **3** could be isolated in a 44% yield.

The absence of anomeric and hydroximino protons in the ^{1}H NMR spectra of both **3** and **4** and, simultaneously, the presence, in their ^{13}C NMR spectra, of downfield signals corresponding to quaternary anomeric carbons (δC1: 122.4 (**3**); ~127 (**4**)), proved that cyclization had indeed taken place. The deshielding effect observed for the H-3 and H-5 signals in the ^{1}H NMR spectra of **3** (~5.6, 4.43 ppm, respectively) as compared to **4** (5.11, 4.12 ppm) could not lead to a reliable assignment of their anomeric configuration[10]. Although both epimers gave crystalline solids, crystals obtained from various solvent mixtures were not found suitable for X-ray analysis. However, the deacetylated material **5** obtained from **3** under Zemplen conditions gave colourless prisms (80% yield) from methanol. The X-ray crystal analysis obtained for **5** clearly showed that the C-1—S and C-1—O bonds have, respectively, equatorial and axial orientations whereas the pyranose ring exists under the favoured $^4C_1$ chair conformation. Since anomerization can be excluded on the basis of the optical rotations measured for **3** and **5**[9], the major cyclized product obtained regardless of the α or β anomeric configuration of the substrates also displays an equatorial C-1—S bond. This infers that the formation of the C-1—O bond occurs preferentially from the α-side of the pyranose ring of both **1** and **2** as already observed under either free-radical[2] or ionic[11] conditions.

In conclusion, cyclization of both α and β anomers of 2,3,4,6-tetra-*O*-acetyl-1-*S*-*(Z)*-benzhydroximoyl-1-thio-D-glucopyranose has been carried out in the presence of NBS, under free-radical conditions to yield similar mixtures of epimeric spiro oxathiazoles. The *(S)* anomeric configuration of the major product was deduced from the crystal analysis of its deacetylated derivative. This cyclization process provides a ready access to an unprecedented class of spiro sugars attached to an oxathiazole ring by the anomeric carbon. The scope and limitations of this new spirocyclization reaction as well as the crystal structure determination of compound **3** will be reported in due course.

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8. The reaction was found to proceed also at room temperature, albeit at a slower rate.
9. Satisfactory elemental analyses have been obtained for compounds **3**, **4** and **5** which show the following constants: **3**: white crystals, mp: 119-120°C (diethyl ether-petroleum ether), $[\alpha]_D$ + 52° (c 0.7 chloroform), UV (ethanol): λmax (ε): 203.8 (18000), 243.2 (12000); **4**: white crystals, mp: 111-112°C (diethyl ether-petroleum ether), $[\alpha]_D$ + 179° (c 0.8 chloroform), UV (ethanol): λmax (ε): 203.4 (17000), 243.0 (11000); **5**: colourless prisms, mp: 180-183°C (dec., methanol), $[\alpha]_D$ + 56° (c 1.1 methanol).
10. In peracetylated α-D-glucopyranosides, the H-3 and H-5 signals are deshielded (0.2-0.3 ppm), as compared to the corresponding nuclei in β-anomers, by the axially oriented oxygen atom of the glycosidic residue. The deshieldings of H-3 an H-5 due to similarly located sulphur atoms are of comparable magnitude[12].
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