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Chiral 2-Thioxotetrahydro-1,3-*O*,*N*-heterocycles from Carbohydrates

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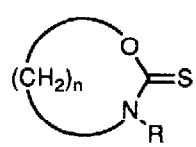
Key Words: Oxazolidine-2-thiones; 2-thioxotetrahydro-1,3-oxazines; sugar isothiocyanates; cyclic thiocarbamates; carbohydrates as chiral templates

Abstract: Triethylamine-induced cyclization of methyl 6-desoxy-6-isothiocyanato-α-D-glucopyranoside (**2**) yields the fused 2-thioxotetrahydro-1,3-oxazine derivative **4**. In contrast, 6-deoxy-1,2:3,4-di-*O*-isopropyliden-6-isothiocyanato-α-D-galactopyranose (**5**) undergoes, on deprotection, spontaneous cyclization involving the OH-5 of the galactofuranose tautomer to give the oxazolidine-2-thione derivative **7**. The chirality of the resulting substituted heterocycles is determined by the sugar configuration.

1,3-Oxazolidine-2-thiones (**1**, n = 2) are of interest because some of the naturally occurring members[1] show antithyroid activity. The six-membered analogues tetrahydro-1,3-oxazine-2-thiones (**1**, n = 3) have shown antidepressant, anticholinergic, analgesic, and antiinflammatory activity[2]. Furthermore, starting from 2-thioxo-1,3-heterocycles (**1**, R = H), a number of variously fused heterocycles can be prepared, which are interesting from both chemical and pharmacological points of view[3,4,5].



1, n = 2, 3

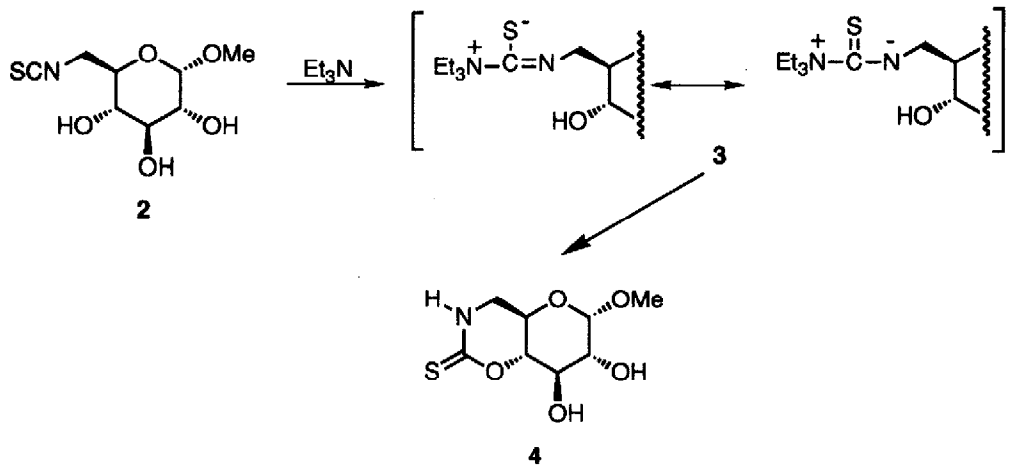
A few examples of the preparation of fused- and spiro-oxazolidine-2-thiones from sugars have been reported. The procedures imply either the reaction of a free sugar with thiocyanic acid[6,7] or the reaction of an aminosugar with carbon disulphide[8]. In both cases the anomeric hydroxyl group is involved in the heterocyclic ring closure. Different tautomers can thus react with a corresponding loss of selectivity.

It has been reported[9,10] that β- and γ-hydroxyisothiocyanates undergo spontaneous or based-induced cyclization to give the title compounds. Unprotected 6-deoxy-6-isothiocyanato aldoses fulfil this structural requirement and now we have explored its use as chiral templates in the synthesis of 2-

thioxotetrahydro-1,3-*O*, *N*-heterocycles. Hitherto, only one example of 6-deoxy-6-isothiocyanato has been reported in the literature[11], namely 6-deoxy-6-isothiocyanato-D-glucose, and a bicyclic seven-membered thiocarbamate has been detected as a by-product in the reaction of a partially protected galactopyranosyl isothiocyanate with tri-*n*-butyltin hydride[12].

Starting from methyl α-D-glucopyranoside and 1,2:3,4-di-*O*-isopropyliden-α-D-galactopyranose, we have prepared the corresponding 6-deoxyisothiocyanates **2**[13] and **5**[13], *via* 6-deoxy-6-iodo, 6-azido-6-deoxy, and 6-amino-6-deoxy derivatives, by reaction of the latter with thiophosgene[14] (85-90% yield).

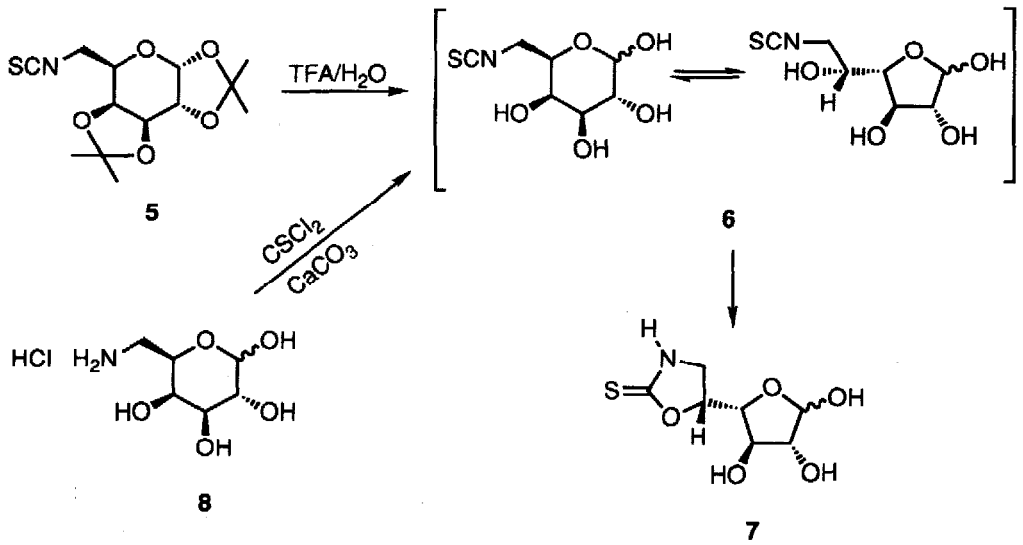
The *gluco*-isothiocyanate **2** is a crystalline, stable compound. No reaction was observed even after heating at 125° in DMF for 2 h. However, it readily underwent intramolecular cyclization on addition of a catalytic amount of Et_3N, to give the bicyclic (5R,6R)-*trans* -2-thioxotetrahydro-1,3-oxazine derivative **4**[13] in 78% yield. The reaction takes place through the complex (**3**) between the amine and the isothiocyanate[12], which undergoes nucleophilic displacement by the γ-located OH-4 of the glucopyranose ring (Scheme 1).



Scheme 1

In contrast, on deprotection, the *galacto*-isothiocyanate **5**[13] experienced spontaneous cyclization to yield the (5R)-1,3-oxazolidine-2-thione derivative **7**[13] in 73% yield. The reaction in this case involves the β-located OH-5 of the galactofuranose tautomer of **6**. The ^{13}C-NMR data[13] of **7** confirmed the furanoid structure, showing an α:β ratio ~1:2. The transient isothiocyanate **6** could be detected by IR spectroscopy (NCS band at 2133 cm^{-1}) but not isolated. Compound **7** was also obtained by reaction of unprotected 6-amino-6-deoxy-D-galactose hydrochloride (**8**) with thiophosgene (Scheme 2). This behaviour differs from that reported[11] for the stable *gluco*-

isothiocyanate analogue, probably due to the higher proportion of the furanoid form in the tautomeric equilibrium of reducing galactose derivatives[15].



Scheme 2

An isothiocyanate has also been postulated as intermediate in the reaction of 1-amino-1-deoxy-D-fructose with carbon disulphide[8]. The formation in that case of a spiro- oxazolidine-2-thione and not a tetrahydro-1,3-oxazine derivative agrees with our present result.

In conclusion, our results show that 6-deoxy-6-isothiocyanto aldoses can be used as chiral templates in the synthesis of optically pure substituted 2-thioxotetrahydro-1,3-*O,N* -heterocycles. The extension of this reaction to other sugar configurations as well as some transformations on the resulting heterocyclic derivatives are currently under study in our laboratory.

Acknowledgements

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13. Data for **2**: M.p. 52-53° (from ether), $[\alpha]_D^{20}$+117° (*c* 1, acetone); IR 2101 cm^{-1} (NCS); ^{13}C-NMR data (50.3 MHz, acetone-d_6): 131.1 (NCS). Data for **4**: M.p. 173-174° (from ethanol-ether), $[\alpha]_D^{20}$+16° (*c* 1.2, methanol); IR 1555 cm^{-1} (NH); ^{13}C-NMR data (50.3 MHz, CD_3OD): 188.1 (CS). Data for **5**: $[\alpha]_D^{20}$ -83° (*c* 1.4, chloroform); IR 2101 cm^{-1} (NCS); ^{13}C-NMR data (50.3 MHz, $CDCl_3$): 132.4 (NCS). Data for **7**: $[\alpha]_D^{20}$ -69° (*c* 1.2, water); IR 1545 cm^{-1} (NH); ^{13}C-NMR data (50.3 MHz, CD_3OD): 190.5, 190.4 (CS), 103.1 (C-1 β-Gal*f*), 97.2 (C-1 α-Gal*f*). Compounds **2**, **4**, **5**, and **7** gave satisfactory microanalysis (C, H, N, S).
14. The thiophosgene reaction was performed in water-acetone (**2**) or chloroform (**5**). For a typical procedure see, for instance: Fuentes Mota, J.; García Fernández, J.M.; Ortiz Mellet, C.; Pradera Adrián, M.A.; Babiano Caballero, R., *Carbohydr. Res.* **1989**, *188*, 35-44.
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