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HSCN condensation with ulosides: preferred formation of carbohydrate-fused hemiaminals of the 4-hydroxy-1,3-oxazolidine-2-thione type

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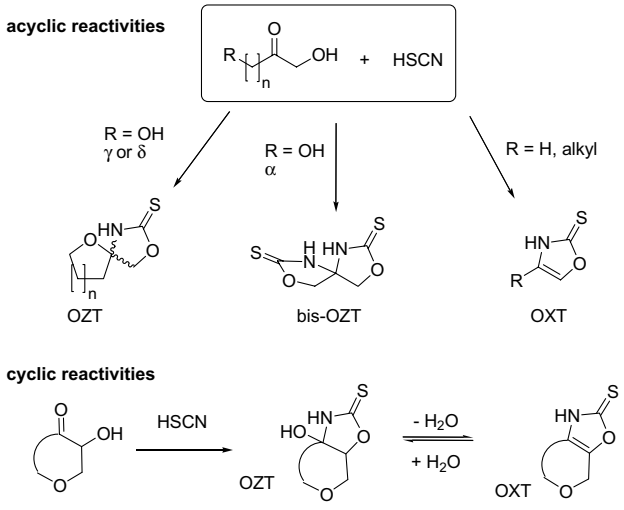
Abstract

Selected ulofuranosides and ulopyranosides react with thiocyanic acid to give good yields of stable carbohydrate-fused hemiaminal 1,3-oxazolidine-2-thiones.

Keywords: Hydroxyketone; Uloside; 1,3-Oxazolidine-2-thione; Thiocyanic acid; Hemiaminal

1,3-Oxazoline-2-thiones (OXTs) delineate a simple heterocyclic frame which has been scarcely explored compared to the non-aromatic counterpart 1,3-oxazolidine-2-thione (OZT) structure, which has aroused renewed interests in the past decade[1] for its applications in asymmetric synthesis.[2] Surprisingly for this simple heterocycle, only basic structures related to acetol have been converted into OXTs.[3] Syntheses of OXTs were reported using either condensation of thiocyanic acid[4] or isothiocyanates[5] with an α-hydroxycarbonyl, or condensation of thiophosgen with an aminoketone.[6] Using the largely preferred HSCN approach, we have recently shown the possible balance of reactivity of α-hydroxycarbonyl systems with thiocyanic acid toward the formation of either an OZT or an OXT (Scheme 1, acyclic reactivities).[7] In the present study, we have investigated the reactivity of carbohydrate-based α-hydroxyketone arrays with HSCN (Scheme 1, cyclic reactivities) to decipher the influence of the oxacycle on the formation of either an OZT or an OXT on a carbohydrate template and to investigate the



Scheme 1.

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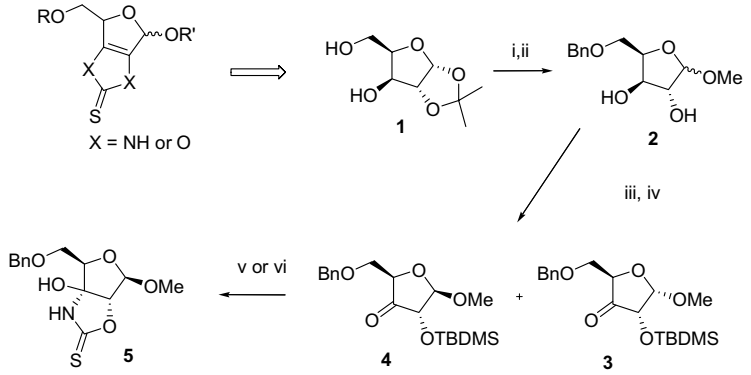
relationship of configurations and protective groups with the building up of the heterocyclic system.

First to be considered was the case of an α-hydroxyketo segment inserted in a furano-type structure: indeed, a pentofuranose-based approach seemed to be the most appropriate to establish such functional relationship between positions 2 and 3 and therefore D-arabinose and D-xylose were first targeted.

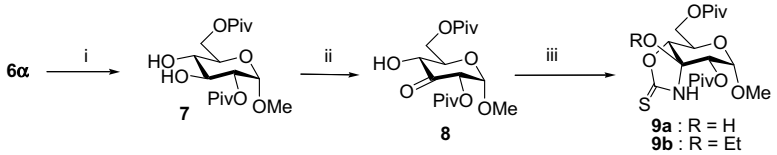
After having experienced low selectivities and moderate yields in the sequence when addressing the D-arabino series, we then moved to the D-xylo series to elaborate our α-hydroxyketo substrate. Starting from 1,2-*O*-isopropylidene-α-D-xylofuranose **1**,[8] selective benzylation of the primary hydroxyl via the 3,5-*O*-stannylidene intermediate,[9] followed by acid-catalyzed methanolysis led in an overall yield of 35–40% to methyl D-xylofuranosides **2** (Scheme 2).[10] On the basis of our previous profitable use of an acid-sensitive protection in direct OZT formation,[11] compounds **2** were protected by a TBDMS group, affording in an overall yield of 89% and with high regioselectivity the 2-O-silylated α- and β-xylofuranosides, which could be separated by chromatography (α/β diastereomeric ratio 1.6:1). PDC oxidation at the 3-position gave α- and β-ulosides **3** and **4** in 92% and 93% yield, respectively. Before applying our routine conditions (KSCN, EtOH, HCl) some slight modifications should be effected (a) to ensure in situ de-O-silylation, which allows OXT formation (b) to prevent partial anomeric hydrolysis or transacetalation. Using TsOH catalysis in solution helped optimizing the chemical yield (81% only under routine conditions): thiocyanic acid efficiently condensed in 92% yield on β-uloside **4** whereas no reaction was observed in the case of **3**. Furthermore, β-isomer **5** obtained was not the expected OXT but a hydrated form displaying a hemi-aminal-type function in position 3.[5,12] No water elimination was observed and the stereochemistry of **5** was controlled by the hydroxyl group. The pronounced difference of reactivity between α-anomer **3** and β-anomer **4** can be attributed to sterical hindrance caused by the *cis*-orientation of the OMe group in **3**, which prevents the hydrolytic attack on the TBDMS group. Acidic conditions led to degradation of the starting material.

To extend our knowledge of this balance between OXT or OZT formation, we have developed α-hydroxyketo segments inserted in pyrano-type structures derived from methyl D-glucopyranosides. Two approaches were selected to generate accessible hydroxyketones. In the first approach the α-hydroxyketone was readily obtained from glucopyranoside **6α** using a chemoselective sequence of two reactions (Scheme 3). Selective 2,6-bis-O-pivaloylation afforded in 75% yield the partially protected diol **7**, which was regioselectively oxidized by PDC at position 3 to furnish ketol **8** in 87% yield.[13] The reaction of **8** with thiocyanic acid was explored in various conditions (Table 1).

When run in refluxing ethanol, the reaction gave a good overall transformation yield of 83%: two OZTs were formed in 22% and 61% yield, respectively (entry 1). The minor OZT **9a** was a hemi-aminal of the same type as OZT **5**, whereas OZT **9b** resulted from subsequent



Scheme 2. Reagents and conditions: (i) Bu_2SnO, BnBr, Bu_4NI, toluene, △; (ii) cat. H_2SO_4, MeOH; (iii) TBDMSCl (1.1 equiv), imidazole (2 equiv) DMF; (iv) PDC (0.8 equiv), Ac_2O (4 equiv), DCM; (v) KSCN (4.1 equiv), 12 M HCl (2.1 equiv), EtOH, 24 h, △; (vi) KSCN (2.4 equiv), $TsOH{\cdot}H_2O$ (2.1 equiv), THF–DMF, 24 h, △.



Scheme 3. Reagents and conditions: (i) PivCl (2.2 equiv), pyridine, DCM (−15 °C); (ii) PDC (3 equiv), DCM, Ac_2O (1 equiv), 2.5 h, rt, 87%; (iii) see Table 1.

Table 1
Formation of OZTs **9a** and **9b** using KSCN (4 equiv), HCl (1.8 equiv) at 75 °C

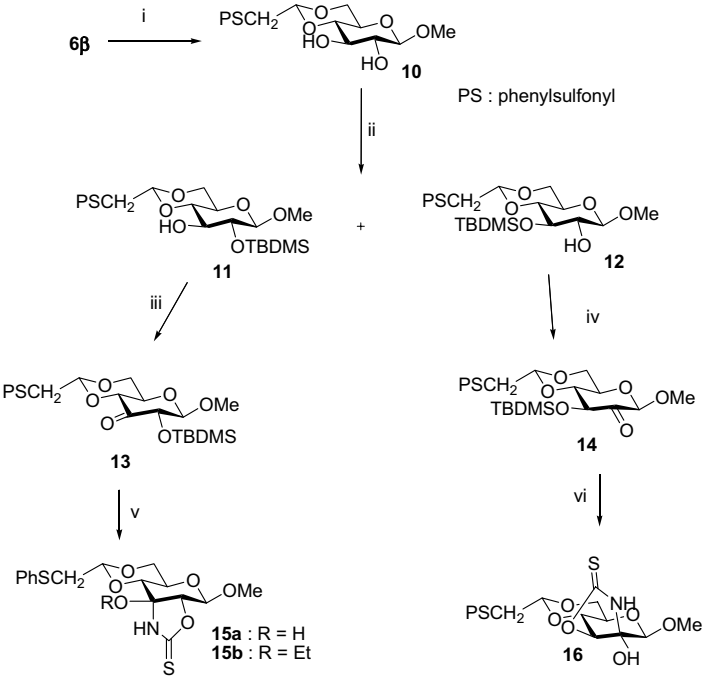
Entry	Solvent	Time (h)	**9a** (%)	**9b** (%)
1	EtOH	30	22	61
2	H_2O	48	33	—
3	DMF	25	23	—
4	THF–DMF (1:1)	64	79	—

acetalation of **9a** by ethanol. Performing the reaction in water allowed to avoid this secondary transformation, but the yield of **9a** was poor. Finally, the synthesis of OZT **9a** was optimized to a 79% yield by running the experiment for more than 2.5 days in a mixture of aprotic solvents (entry 4).

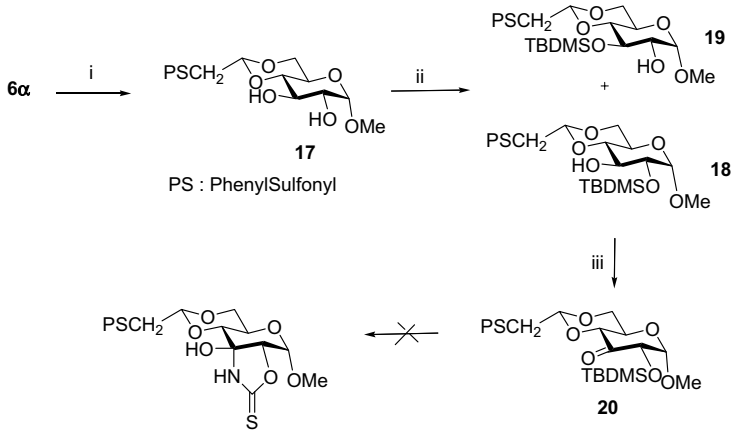
The second approach (Scheme 4) involved initial protection of the glucopyrano template by a PSE acetal—an atypical acid-resistant functional array developed in our laboratory.[14] Reacted with *Z*-1,2-bis(phenylsulfonyl)-ethylene (BPSE) under basic conditions, methyl β-D-glucopyranoside **6β** was converted into the PSE acetal **10** in 77% yield. Attempted regioselective PDC oxidation of **10** under previously described conditions unfortunately failed. Masking hydroxyl groups on either position 2 or 3 was therefore undertaken. Non-regioselective O-silylation of **10** led to a separable mixture of isomers **11** (45% yield) and **12** (43% yield). Subsequent oxidation of both compounds was performed using TPAP–NMO system, which had proven more efficient than PDC, with 87–100% yield on position 3 and 41–58% yield on position 2 to furnish uloses **13** and **14**, respectively. Reacting precursors **13** and **14** with thiocyanic acid in standard conditions (KSCN, 12 M HCl, EtOH) led to the formation of the OZTs **15** and **16** in 44% and 69% yield, respectively. Subsequent acetalation of **15a** was also observed to produce **15b** in 49% yield and therefore aprotic solvents and $TsOH{\cdot}H_2O$ were employed producing **15a** and **16** in 83% and 88% yield, respectively.[15]

With a view to investigating the effect of the anomeric configuration in ulopyranosides on the formation of OZTs, the same sequence was repeated in the α-series (Scheme 5). Methyl α-D-glucopyranoside **6α** was first converted into the PSE acetal **17**.[14a] Non-regioselective O-silylation of **17** afforded a mixture of isomers **18** (36% yield) and **19** (38% yield), which were submitted to PDC oxidation. Whereas position 2 in **19** unexpectedly[16] showed reluctance to oxidation, in contrast **18** was readily converted (96% yield) into the ulopyranoside **20**. However, despite all the different conditions tested, the subsequent formation of the OZT was not observed.

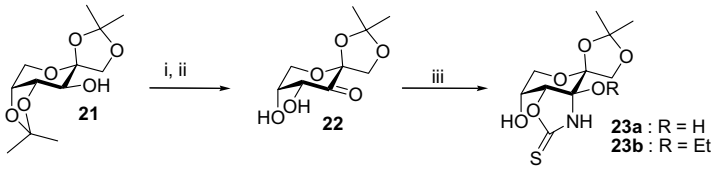
The reaction was then considered from another angle starting from a ketohexose frame bearing acid-sensitive ketal groups (Scheme 6): 1,2:4,5-di-*O*-isopropylidene-β-D-fructopyranose **21** was a candidate of choice to prepare a α-hydroxyketone via a short sequence. PDC oxidation of the free 3-OH[17] in **21** was followed by selective acid-catalyzed deprotection of the 4,5-isopropylidene ketal to afford ketol **22** in 94% overall yield. With regard to subsequent HSCN condensation, adapted acidic conditions had to be established so as to avoid 1,2-isopropylidene cleavage: because of major degradation observed when



Scheme 4. Reagents and conditions: (i) BPSE (1.1 equiv), *t*BuOK (2 equiv), DMF, 0 °C to rt; (ii) *t*BDMSCl (1.3 equiv), imidazole (2 equiv), DMF, rt; (iii) NMO (3 equiv), TPAP (0.1 equiv), DCM, rt, overnight; (iv) NMO (3 equiv), TPAP (0.2 equiv), DCM, rt, overnight; (v) KSCN (4 equiv), $TsOH{\cdot}H_2O$ (3 equiv), THF–DMF (8:1), △, overnight.



Scheme 5. Reagents and conditions: (i) BPSE (1.1 equiv), *t*BuOK (2 equiv), DMF, 0 °C to rt; (ii) *t*BDMSCl (1 equiv), imidazole (2 equiv), DMF, rt; (iii) PDC (0.6 equiv), Ac_2O (4 equiv), DCM.



Scheme 6. Reagents and conditions: (i) PDC, Ac_2O, DCM (94%); (ii) AcOH, H_2O, rt (100%); (iii) KSCN (4 equiv), $TsOH{\cdot}H_2O$ (3 equiv), THF–DMF (8:1), △, overnight.

applying thermal conditions, **22** was reacted to give a 60% yield of OZT **23a**. When performed in ethanol, the reaction gave the acetal counterpart **23b** albeit in a lower yield.

Considering the contrasted results previously[7b] and presently obtained, some statements can be put into light: (a) condensation of thiocyanic acid on carbohydrate-based α-hydroxyketones favors the formation of a fused OZT over an OXT, whereas the opposite is observed on acyclic systems;[18] taking the different geometries into account, this is indicative of a thermodynamic effect in favor of the OZT formation (b) the position and orientation of the hydroxyl group involved is critical with regard to the stereochemistry of the OZT formed[19] (c) the anomeric configuration has a decisive influence on the formation of the OZT between positions 2 and 3 on the carbohydrate backbone: with α-D-xylofuranoside **3** and α-D-glucopyranoside **20**, which share the same 1,2-*cis* relationship, no reaction occurred, while on both β-anomers **4** and **13**, effective condensations occurred, giving, respectively, OZTs **5** and **15a**. Such behavior might appear as a consequence of two possible phenomena: (a) the approach of HSCN, which should take place on the ring face congested by the masked α-hydroxyl, might be blocked because of steric or electronic repulsion (b) unfavorable repulsive effects in the case of a 1,2-*cis* rela-

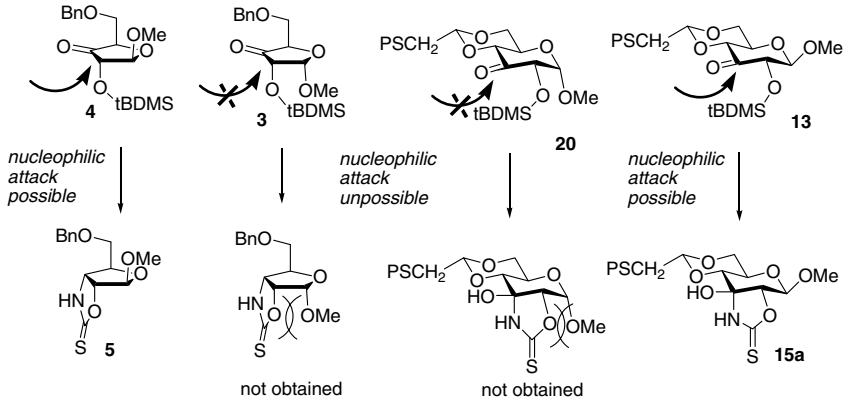


Fig. 1.

tionship to the anomeric oxygen (Fig. 1) might bring an additional limitation to the construction of a fused OZT.

In summary, we have reported for the first time the installation on carbohydrate templates of hemiaminals derived from the parent 4-hydroxy-1,3-oxazolidine-2-thione. Preliminary studies on the reactivity of these carbohydrate-fused OZT are ongoing and will be published in due course.

Acknowledgments

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12. *Method A*: uloside **4** (0.13 g, 0.35 mmol) and KSCN (0.14 g, 4.1 equiv) were dissolved in EtOH (10 mL). After cooling at −5 °C, 12 M aqueous HCl (0.06 mL, 2.1 equiv) was carefully added and the mixture was stirred under reflux for 4 h, then cooled by treating with crushed ice. After extraction with ethyl acetate (3 × 20 mL), the combined organic phases were washed first with saturated aqueous $NaHCO_3$, then water, brine, and finally dried over $MgSO_4$. After filtration and concentration in vacuo, the residue was purified by column chromatography (petroleum ether/AcOEt 7:3) to afford compound **5** (0.088 g, 81% yield) as a white solid. *Method B*: uloside **4** (0.1 g, 0.27 mmol) and KSCN (0.064 g, 2.4 equiv) were dissolved in 4:1 THF–DMF (10 mL). After cooling at −5 °C, $TsOH{\cdot}H_2O$ (0.107 g, 2.1 equiv) was added and the mixture was stirred overnight under reflux, then cooled by treating with crushed ice. After extraction with ethyl acetate (3 × 20 mL), the combined organic phases were processed as in method A: compound **5** (0.075 g, 89% yield) was obtained in the form of a white solid, mp 156–158 °C; $[\alpha]_D^{20}$ −4 (*c* 0.3, MeOH). ^{1}H NMR (400 MHz, MeOH) δ 3.36 (s, 3H, Me), 3.64–3.79 (m, 2H, $J_{5a-5b} = 10.6$ Hz, H-5a, H-5b), 4.31 (dd, 1H, $J_{4-5a} = 5.0$ Hz, $J_{4-5b} = 8.4$ Hz, H-4), 4.52–4.59 (AB system, 2H, $J_{6a-6b} = 12.0$ Hz, CH_2Ph), 4.72 (s, 1H, H-2), 4.99 (s, 1H, H-1), 7.28–7.36 (m, 5H, H-Ar). ^{13}C NMR (100 MHz, MeOH) δ 55.5 (OMe), 71.8 (C-5), 74.4 (CH_2Ph), 86.1 (C-4), 95.5 (C-2), 98.7 (C-3), 109.3 (C-1), 128.8, 129.1, 129.4 (CH-Ar), 139.3 (C_{IV}-Ar), 189.3 (C=S). MS (IS+): m/z = 280 $[M-MeOH+H]^+$, 312.5 $[M+H]^+$, 334.5 $[M+Na]^+$.
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15. Uloside **14** (0.62 g, 1.3 mmol) and KSCN (0.51 g, 4 equiv) were dissolved in 4:1 THF–DMF (30 mL). After cooling at −5 °C, $TsOH{\cdot}H_2O$ (0.74 g, 3 equiv) was carefully added and the mixture was stirred under reflux for 24 h, then cooled by treating with crushed ice. After extraction with ethyl acetate (3 × 50 mL), the combined organic phases were processed as in method A: compound **16** (0.48 g, 88% yield) was obtained as a white solid, mp 74–75 °C; $[\alpha]_D^{20}$ −118 (*c* 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (dt, 1H, $J_{5-6a} = 5.1$ Hz, $J_{5-6b} = 9.9$ Hz, $J_{5-4} = 10.0$ Hz, H-5), 3.47–3.51 (m, 2H, H-8), 3.54 (s, 3H, Me), 3.55–3.57 (m, 2H, H-6b, H-4), 4.20 (dd, 1H, $J_{6a-6b} = 10.7$ Hz, $J_{6a-5} = 5.1$ Hz, H-6a), 4.52 (d, 1H, $J_{3-4} = 7.5$ Hz, H-3), 4.62 (s, 1H, H-1), 4.86 (br s, 1H, OH), 5.00 (t, $J_{7-8} = 5.0$ Hz, H-7), 7.60–7.63 (m, 2H, *meta*-H-Ar), 7.66–7.70 (m, 1H, *para*-H-Ar), 7.91–7.93 (m, 2H, *ortho*-H-Ar), 8.11 (br s, 1H, N–H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 57.9 (OMe), 59.7 (C-8), 63.3 (C-5), 68.4 (C-6), 78.8 (C-4), 87.3 (C-3), 88.1 (C-2), 97.1 (C-7), 101.9 (C-1), 128.6 (CH-*ortho*-Ph), 129.5 (CH-*meta*-Ph), 134.3 (CH-*para*-Ph), 139.2 (C_{IV}-Ar), 189.0 (C=S). MS (IS+): m/z = 418.5 $[M+H]^+$, 440.5 $[M+Na]^+$.
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19. The configuration of hemiaminal stereogenic centers was assigned through NOESY experiments. All OZTs showed a strict cis relationship.