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Short and General Procedure for Synthesizing Cis-1,2-Fused 1,3-Oxathiolan-, 1,3-Oxaselenolan-, and 1,3-Oxazolidin-2-imine Carbohydrate Derivatives

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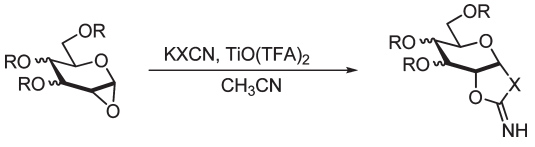

Novel cis-1,2-fused 1,3-oxathiolan-, 1,3-oxaselenolan-, and 1,3-oxazolidin-2-imine carbohydrate derivatives have been prepared by treatment of the corresponding 1,2-anhydrosugars with potassium thiocyanate, potassium selenocyanate, and sodium cyanamide, respectively. The procedure is compatible with several protecting groups such as acyl, benzyl, and silyl and also with sugars of different configurations.

Carbohydrate-fused heterocycles form a diverse family of compounds that exhibit interesting biological effects, including fructose transport inhibition,[1] as well as antitumor[2] and clinically useful antibacterial activity.[3] Since the heterocyclic moiety is directly involved in the binding process in the enzyme pocket,[4] much effort in recent years has focused on the synthesis of new and more potent analogous compounds.[5] In addition, heterocycles can be useful as simultaneous protecting groups of anomeric and C-2 substituents[6] and as precursors for glycoside and nucleoside asymmetric syntheses[7] as well as potential glycosidating agents.[8]

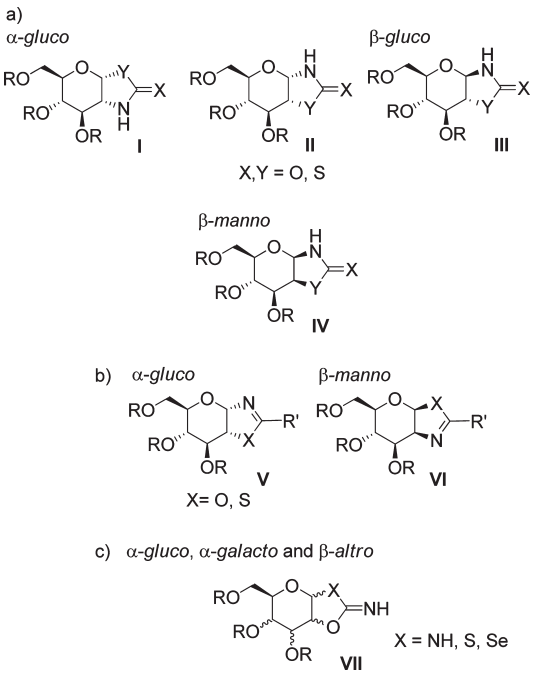

FIGURE 1. Sugars containing 1,2-fused five-membered heterocycles saturated (a) and unsaturated (b), previously reported, as well as those described in this work (c).

Figure 1 shows the main structures of carbohydrates incorporating saturated (a) or unsaturated (b) 1,2-fused five-membered heterocyclic rings previously reported in the literature. The first syntheses of carbohydrates with saturated five-membered heterocycles fused at the 1,2 positions containing carbamates, thiocarbamates, and related functions (**I**−**IV**, Figure 1a) consisted of the treatment of unprotected reducing sugars with potassium cyanate or thiocyanate in acidic media.[9] Fused glycofuranosyl and glycopyranosyl derivatives are also usually prepared by the treatment of unprotected sugars with carbonylating agents like phosgene[5c,10] or thiophosgene.[5a] Kovács et al. reported a

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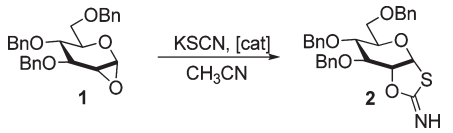
similar process by treating the corresponding glycopyranosyl azides with triphenylphosphine and then with carbon dioxide.[11] In addition, bicyclic oxazolines and thiazolines (**V**, **VI**, Figure 1b) can be prepared by cyclization of 1,2-*trans*-2-deoxy-2-iodoglycopyranosyl derivatives[12] and from 2-deoxy-2-amidoglycosides.[13]

Herein, we show a general, short and efficient procedure for synthesizing a new family of carbohydrate derivatives with fused heterocycles of general formula **VII** (Figure 1c).

In the framework of developing new methodologies for the synthesis of thiosugars, we explored the reaction of 1,2-anhydrocarbohydrates with reagents typically used for transforming epoxides into episulfides. Initially, the reaction of 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose[14] (**1**) with thiourea was tested but afforded a complex mixture of products. When **1** was treated with KSCN (3 equiv) in dry acetonitrile, the reaction also afforded a complex mixture (Table 1, entry 1). Then, different Lewis acid catalysts were tested; however, when $BF_3 \cdot OEt_2$ was used (Table 1, entry 2) the results did not improve. When the reaction was conducted in the presence of trimetylsilyl triflate, no thiirane was detected; instead, compound **2** was isolated in 40% yield (Table 1, entry 3). The use of titanium catalysts, such as titanium isopropoxide, afforded **2** with low conversion but with almost complete selectivity (Table 1, entry 4). The highest conversions and selectivities were obtained when $TiCl_4$ and $TiO(CF_3CO_2)_2$ were used as catalysts (Table 1, entries 5 and 6) and with $TiO(CF_3CO_2)_2$ the yield was quantitative.[15] A strong oxophile catalyst is necessary in this case in order to activate the epoxide without interacting with the soft thiocyanate reagent.[16]

The structure of compound **2**, incorporating a 1,3-oxathiolan-2-imine moiety, was determined by NMR and IR spectroscopy, as well as by exact mass spectrometry. The presence of the imidoyl group was determined by ^{13}C NMR (C=NH at roughly 189 ppm) and by the presence of two strong signals at 1495 and 1453 cm^{-1} in the IR spectrum, which are characteristic of the imidoyl functional group. The presence of a broad singlet at 8 ppm in the ^1H NMR spectrum is assigned to an imine hydrogen, which completes the characterization of this group. Furthermore, the ^1H NMR spectrum showed a doublet at 5.66 ppm ($J_{1,2}$ = 6.4 Hz) that correlated with a carbon at 82.2 ppm (C-1), which was assigned to an unshielded anomeric hydrogen. The chemical shift for C-1 indicated that it is bonded to sulfur and oxygen and not to two oxygens (δ ~100 ppm). The coupling constant $J_{1,2}$ ~6−7 Hz is characteristic for H-1 in an equatorial position,[5a,d,9e,10,11a,12a] indicating that the oxathiolane cycle is fused cis with the carbohydrate. A trans fusion would provide larger coupling constants (~9 Hz).[5c,11a,b] Vicinal coupling constants $J_{2,3}$ (3.2 Hz) and $J_{3,4}$ (3.2 Hz) have unexpected small values, which suggests a distorted pyranose ring with a preferential $^0S_2$ pyranose conformation, as previously reported for structurally related bicyclic structures in solution.[10,12a,13]

TABLE 1. Reaction of 1,2-Anhydroglucopyranose 1 with KSCN in the Presence of Lewis Acids as Catalysts[a]



entry	[cat.]	conversion[b] (%)	selectivity[b] (%)
1		100	mixture
2	$BF_3 \cdot OEt_2$	100	mixture
3	TMSOTf	100	40
4	$Ti(OCH(CH_3)_2)_4$	40	95
5	$TiCl_4$	100	95
6	$TiO(CF_3CO_2)_2$	100	99

[a]Conditions: **1** (1 mmol), KSCN (3 mmol), $TiO(CF_3CO_2)_2$ (2% mol), CH_3CN (5 mL), reaction time (3 h), reflux. [b]Conversion and selectivity were determined by integration of H-1 protons in the reaction crude.

A proposed mechanism for this transformation is shown in Scheme 1. The reaction is presumably initiated by the coordination of titanium catalyst to epoxide **1** with concomitant opening of the epoxide by KSCN to give **3**. Alternatively, the generation of oxocarbenium **4** could lead to the formation of either **3** or **5**. Since substituents at positions 1,2 in compound **3** have a cis relationship, compound **2** must isomerize to **5** through cation **4**. Further attack of the alcoholate to the thiocyanate group in **5** would render the final product. It has been reported that stoichiometric reactions with organometallic reagents (Zr, Zn or Al) afforded compounds of cis opening. Intermediates type **4′**, which have been postulated in these cases, can not be discarded.[17] There are few examples of epoxides present in natural products where their opening proceeds in a cis fashion.[18]

The reaction is compatible with other protecting groups such as acetates. Thus, 1,2-anhydro-3,4,6-tri-*O*-acetyl-α-D-glucopyranose (**6**)[14] was reacted following the optimized conditions to afford **7** in 66% yield (Table 2, entry 1). The reaction was then extended to other 1,2-anhydropyranoses, such as the galacto derivative **8**,[14] which afforded compound **9** in excellent yield when it was treated with KSCN under the optimized conditions (Table 2, entry 2). With the aim of investigating the possibility of obtaining compounds with opposite configuration at the 1,2-positions, the altro derivative **10**[19] was also treated with KSCN in the presence of $TiO(CF_3COO)_2$ to afford the expected product **11** in 75% yield (Table 2, entry 3).

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SCHEME 1. Possible Mechanism for Product 2 Formation

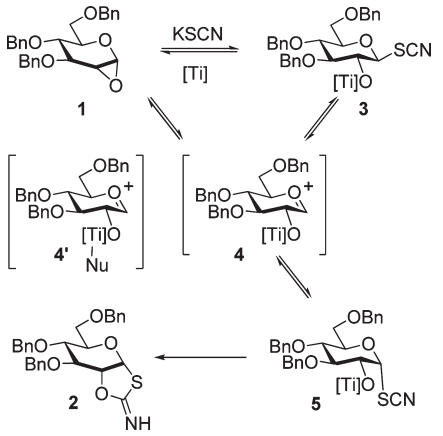
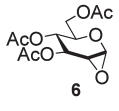
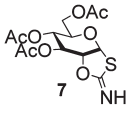
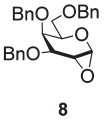
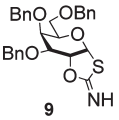
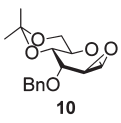
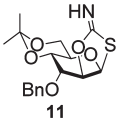


TABLE 2. Reaction of 1,2-Anhydroglucopyranoses 6, 8, and 10 with KSCN in the Presence of $TiO(CF_3CO_2)_2$[a]

Entry	Reactant	Product	t (h)	Yield (%)
1			2	66
2			3	87
3			3	75

[a]All reactions were carried out at reflux under argon with 1.0 equiv of substrate, 3.0 equiv of KSCN, 1 mol % of $TiO(CF_3COO)_2$, and CH_3CN.

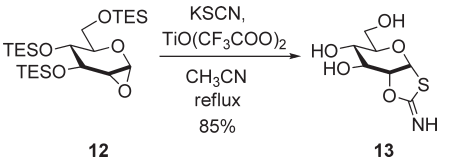
We then studied the reaction of the tri-*O*-silyl derivative **12** with $KSCN/TiO(CF_3COO)_2$ in the optimized conditions. To our delight, the unprotected 1,3-oxathiolan-2-imine derivative **13** was directly recovered from the aqueous solution in a 85% yield. The silylated product was not present in the organic phase, indicating that the deprotection was complete. TLC control indicated that deprotection takes place during the reaction and not in the workup. Deprotection tests of compound **7** (Zemplen conditions) were unsuccessful.

Deprotection of the silyl groups in the presence of a strong oxophile catalyst can explain the direct synthesis of the unprotected compound **13** (Scheme 2).

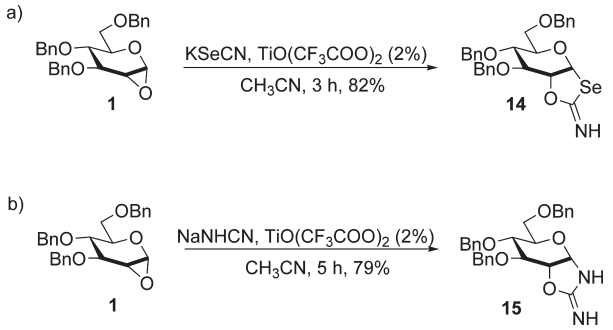
Finally, we studied the generality of the reaction using different cyanate reagents. The reaction of **1** with potassium selenocyanate gave the selenocarboimidate derivative **14** in very good yield after 3 h (Scheme 3a). The corresponding imino-oxazolidine derivative **15** was also obtained in excellent yield when **1** was reacted with sodium cyanamide (Scheme 3b).

In order to obtain the deprotected seleno and amino derivatives, the silyl derivative **12** was also treated with potassium selenocyanate and sodium cyanamide under similar reactions conditions, but in these cases the reaction proceeded with the decomposition of the products.

SCHEME 2. Synthesis of Compound 13 from 12



SCHEME 3. Synthesis of Compounds 13 and 14



In summary, 1,3-oxathiolan-2-imine heterocycles fused to the 1,2 positions of different pyranoses have been efficiently prepared by the reaction of 1,2-anhydrosugars with KSCN using $TiO(CF_3COO)_2$ as catalyst. The reaction is general and 1,2-anhydrosugars of gluco, galacto, and altro configurations afforded compounds with the same relative configurations, although the configuration of the anomeric position for the two first cases was α and for the altro derivative was β. The procedure can also be extended to the preparation of seleno and amino derivatives, such as compounds **14** and **15**, respectively, which demonstrates the generality of the procedure. Although fully deprotected sulfur derivative can be obtained in a one-pot process starting from triethylsilyl protected 1,2-anhydrosugars, more research is being carried out in order to generalize this deprotection to another cyanide reagents.

Experimental Section

General Procedure for Glycal Epoxydation.[14] The glycal (1.00 mmol) was dissolved in an ice bath cooled biphasic solution of CH_2Cl_2 (4 mL), acetone (0.4 mL), and saturated aqueous $NaHCO_3$ (6.5 mL). The mixture was vigorously stirred and a solution of Oxone (1.23 g, 2.00 mmol) in H_2O (5 mL) was added dropwise over 15 min. The crude reaction was vigorously stirred at 0 °C for 30 min and was then allowed to warm to room temperature until TLC indicated complete consumption of the glycal. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 4 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated to afford the 1,2-anhydropyranoses in the yields shown. The crude could not be purified due the decomposition of the 1,2-anhydro sugar.

General Procedure for the Synthesis of Cis-1,2-Fused 1,3-Oxathiolan-, 1,3-Oxaselenolan-, and 1,3-Oxazolidin-2-imine Carbohydrate Derivatives. To a stirred solution of the 1,2-anhydro sugar (1.00 mmol) and XCN (X = KS, KSe, NaNH) (3.00 mmol) in dry CH_3CN (5 mL) was added finely powdered $TiO(CF_3COO)_2$ (0.02 mmol) under an argon atmosphere, and the mixture was heated to boiling for an appropriate time. After completion of the reaction, followed by TLC, the mixture was cooled to room temperature, H_2O (10 mL) was added, and the resultant mixture was extracted with EtOAc. The combined

organic extracts were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel gave the products in the yields shown.

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Supporting Information Available: General experimental methods, experimental procedures, compound characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.