Synthesis and Characterization of Some Heterocyclic Derivatives by Cyclization of Carbohydrate Thiosemicarbazone - Part II

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Dedicated to the memory of Professor Raymond N. Castle

The syntheses of 2,3-dihydro-1,3,4-thiadiazoles and 1,3,4-thiadiazoles from 1,2-*O*-isopropylidene-α-D-*xylo*-1,5-pentadialdo-1,4-furanose thiosemicarbazone are described. The new compounds as well as the intermediate products are physically and spectroscopically characterized. We discuss a possible mechanistic pathway for heterocyclization in this particular substrate, using computational calculation.

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In our previous work [1], we reported the syntheses of heterocyclic analogous from 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,6-hexodialdo-1,5-pyranose thiosemicarbazone by intramolecular cyclization. In the present paper we extend those reactions to 1,2-*O*-isopropylidene-α-D-*xylo*-1,5-pentadialdo-1,4-furanose thiosemicarbazone an attempt to establish the possible influence of the carbohydrate configuration on the reaction products.

Reaction of 1,2-*O*-isopropylidene-α-D-*xylo*-1,5-pentadialdo-1,4-furanose [2] with thiosemicarbazide gave 1,2-*O*-isopropylidene-α-D-*xylo*-1,5-pentadialdo-1,4-furanose thiosemicarbazone (**1**), which was characterized physically and spectroscopically. When thiosemicarbazone **1** was treated with an acylating mixture in basic media, we isolated two new heterocyclic compounds: 2(*R*)- and 2(*S*)-5-acetamido-3-*N*-acetyl-2-[4'-(3'-*O*-acetyl-1',2'-*O*-isopropylidene-α-D-xylofuranosyl)]-2,3-dihydro-1,3,4-thiadiazole (**2** and **3**) and we had chromatographic evidence of a third, later characterized as 5-acetamido-2-[4'-(3'-*O*-acetyl-1',2'-*O*-isopropylidene-α-D-xylofuranosyl)]-1,3,4-thiadiazole (**4**).

The treatment of compound **1** with ferric chloride in pyridine, led us to 5-amino-2-[4'-(1',2'-*O*-isopropylidene-α-D-xylofuranosyl)]-1,3,4-thiadiazole (**5**). The acetylation of compound **5** yielded compound **4** in quantitative amounts. The synthetic routes applied are shown in Figure 1.

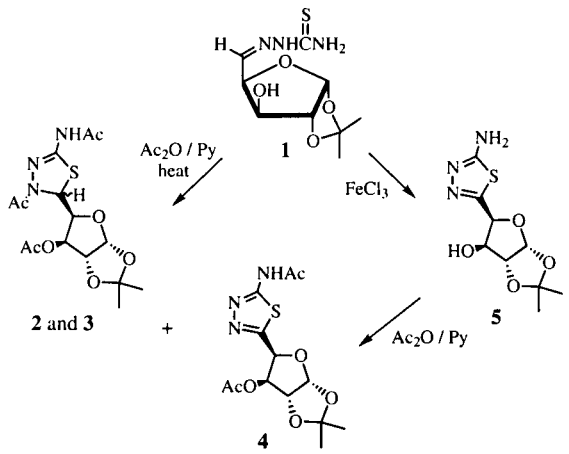

Figure 1

The ^{1}H nmr spectra of compounds **1** - **5** were performed at 500 MHz and permitted a first order analysis, and in Table 1 and 2 we present the chemical shifts and coupling constants, respectively. All ^{13}C nmr spectra were recorded on the same apparatus at 125 MHz, and the assignment of signals is shown in Table 3.

Compound **1** was isolated as a single isomer, and in order to determine if this fact was a consequence of the purification procedure, we performed the corresponding ^{1}H nmr analysis on the unpurified product and no trace of the other isomer was detected. As a consequence of that, we could not determine if compound **1** was the *syn* or *anti* isomer [3] because no comparison between either displacement could be made. Some calculations were made using PCMODEL™ [4], indicated that the *syn* and the *anti* form of compound **1** are stabilized by internal hydrogen bonding as shown in Figure 2.

According to these calculations, the *syn* form is near 3 kcal more stable than the *anti*, having a hydrogen bond between the hydroxyl group in C-3 and the electron pair on the nitrogen atom. This stabilization may be the reason for attainment of a single isomer, which was assigned as a *syn* form.

On the other hand, the chemical shifts data of compounds **2** and **3** were similar, the only difference being chemical shifts observed for H-3' and H-2. The influence on H-2 displacement was attributed to the configurational inversion, meanwhile the effect on H-3' was assigned to an interaction through the space. The rest of the signals remained virtually unchanged. Even in the case where very different $J_{4',2}$ was observed for compounds **2** and **3**, we could not determine the absolute configuration of this center using these spectroscopic data.

All protons of compounds **4** and **5** correlated well, and the main difference was located on H-3', due to the presence of an acetyl group in compound **4**. However, the H-3' displacement was in agreement with that observed for **2** and **3**. As it was expected for 1,2-*O*-isopropylidene derivatives of α-D-xylofuranose [2], the observed $J_{2',3'}$ was almost zero for all the reported compounds.

Table 1

^{1}H nmr chemical shifts (δ) for compounds **1** to **4**, measured at 500 MHz in acetone-d_6. Data for compound **5** were recorded in dimethyl sulfoxide-d_6.

Compound	H-1	H-2	H-3	H-4	H-5
1	5.01	3.64	3.32	3.64	6.54
	H-1'	**H-2'**	**H-3'**	**H-4'**	**H-2**
2	5.99	4.62	5.24	4.53	6.25
3	5.98	4.63	5.14	4.60	6.22
4	6.17	4.86	5.44	5.73	-
	H-1'	**H-2'**	**H-3'**	**H-4'**	**-OH**
5	5.95	4.57	4.13	5.81	5.20

Table 2

Measured coupling constants (Hz) for compound **2** to **5**.

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$
1	3.6	0	2.9	6.6
	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',2}$
2	3.8	0	3.2	8.5
3	3.6	0	3.8	4.4
4	3.6	0	3.2	-
	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{3',OH}$
5	3.6	0	5.3	2.8

Table 3

^{13}C nmr Chemical shifts for compounds **1** to **4**, measured at 50 MHz in acetone-d_6. Data for compound **5** were recorded in dimethyl sulfoxide-d_6.

Compound	C-1	C-2	C-3	C-4	C-5	C=S
1	105.5	85.7	76.8	80.6	142.5	180.0
	C-1'	**C-2'**	**C-3'**	**C-4'**	**C-2**	**C-5**
2	105.7	83.3	76.2	79.9	62.1	148.3
3	105.4	83.9	75.9	79.0	64.0	148.4
4	105.5	83.0	77.3[a]	77.7[a]	159.8	160.5
5	104.3	85.0	74.6	78.7	154.6	170.3

[a] This pair of values might be interchanged.

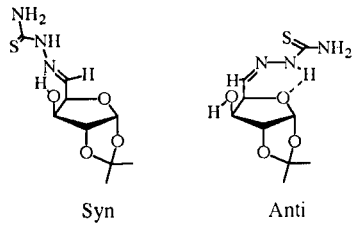

Figure 2

As described above, ^{13}C nmr spectra of compound **1** confirmed the presence of a single isomer, and displacement for compounds **1-5** correlated well. The major differences were located at C-2: between **2** and **3** due to the configurational inversion, as it was noted earlier in ^{1}H nmr spectra, and between **2** and **3** respect to **4** and **5** due to the aromatization of this carbon in the last compounds. Acetylation of C-3' did not affect very much the displacement of this carbon as well as the vicinal positions, despite what was previously observed for peracetylated derivatives of saccharides [5].

Analysis of the mass spectra showed the typical fragmentation of isopropylidene group, like losses of methyl group, acetone, ketene and its combinations; peaks corresponding to the heterocyclic moiety were also observed [1]. The most representative peaks are shown in the Experimental.

Taking into account the influence of the hydroxyl group on thiosemicarbazone **1**, we expected some kind of interaction with the acetyl group at C-3' during the cyclization process, and a possible chiral induction as a consequence. As it was previously reported [6], heterocyclization of thiosemicarbazone could be the result of an ionic or a concerted mechanism. In both cases, the reaction starts with the development of a formal positive charge (after N-acetylation) or a positive charge density on the C=N carbon. This positive charge or positive density can be stabilized by the acetate at C-3',

so cyclization may only occur from a single side as it is shown in Figure 3, exemplified for an ionic process. If

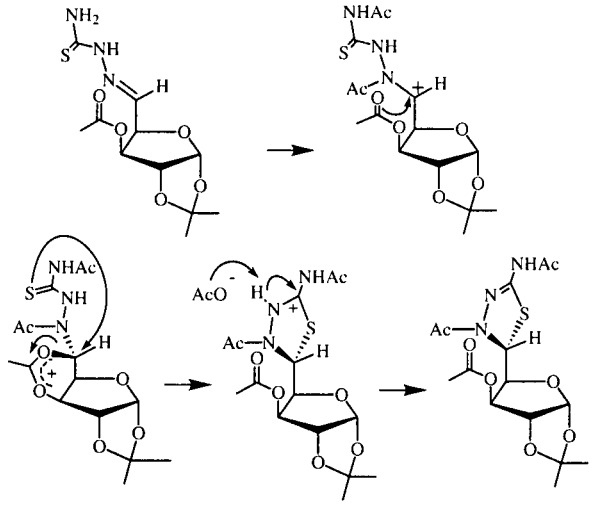

Figure 3

this hypothesis is true, the reaction would lead only to the 2*R* isomer.

As was reported above, we isolated both thiadiazolines, so the expected chiral induction did not occur. Hence if the assistance of C-3' acetyl group is involved in the cyclization process, its effect is lost on the successive steps. We observed by tlc that compound **2** was formed first, therefore taking into account the results obtained for 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,6-hexodialdo-1,5-pyranose thiosemicarbazone [1], we assumed that this compound was the kinetic product (**2**) and could be converted into the thermodynamic one (**3**) [7].

Even in the case that assistance of C-3' acetate does not exist, this group could block this side making the *exo* attack faster.Thus, compound **2** might be associated with the 2*R* configuration meanwhile **3** with the 2*S*.

This reaction on 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,6-hexodialdo-1,5-pyranose thiosemicarbazone using different heating times showed a variation on the distribution of heterocyclic compounds, and the acetylated thiadiazole became the main product when longer times were used. However, when we performed the same procedure on compound **1**, we found that the conversion into **4** was not quantitative. Even so when the ratio among compounds **2**:**3**:**4** changes from 26:29:1 (one hour of heating) to 14:15:1 (ten hours of heating) in both experiments the amounts of compound **4** are small and this reaction is not a suitable method for its synthesis.

In conclusion, all these results indicate that the behavior of the heterocyclization reaction strongly depends on the starting carbohydrate thiosemicarbazone.

EXPERIMENTAL

General Methods.

The melting points were measured on a Thomas Hoover melting point apparatus and are uncorrected, and the $[\alpha]_D$ were determined using a Perkin Elmer 341 Polarimeter. All ^1H nmr spectra were recorded on a Bruker Spectrometer at 500 MHz in acetone-d_6 or dimethyl sulfoxide-d_6, using tetramethyl silane as internal standard. The ^{13}C nmr were recorded at 125 MHz on the same apparatus. Mass spectra were performed with a Shimadzu QP-5000 by electron impact ionization.

1,2-*O*-isopropylidene-α-D-*xylo*-1,5-hexodialdo-1,4-furanose thiosemicarbazone (**1**).

Title compound was prepared from 0.43 g of 1,2-*O*-isopropylidene-α-D-*xylo*-1,5-hexodialdo-1,4-pyranose [2] dissolved in 10 ml of ethanol and 0.26 g of thiosemicarbazide. The mixture was heated at reflux checking the reaction by tlc (silicagel G, benzene:ethyl acetate 2:3). Evaporation under reduced pressure gave a yellow syrup which was purified using flash chromatography (benzene : ethyl acetate), 0.56 g (94%), mp 125-127°, $[\alpha]_D$ = -62.4° (ethanol); ms: m/z 261 ($M^{+\bullet}$), 246 ($M^{+\bullet}$-$CH_3^{\bullet}$= A^+), 243 ($M^{+\bullet}$-H_2O = $B^{+\bullet}$), 228 (A^+-H_2O), 186 (A^+ - AcOH), 185 ($B^{+\bullet}$-$(CH_3)_2CO$), 102 (base peak, $(C_2H_4N_3S)^+$).

Anal. Calcd. for $C_9H_{15}N_3O_4S$: C, 41.38; H, 5.75; N, 16.09. Found: C, 41.41; H, 5.71; N, 15.95.

2(*R*)- and 2(*S*)-5-Acetamido-3-*N*-acetyl-2-[4'-(3'-*O*-acetyl-1',2'-*O*-isopropylidene-α-D-xylofuranosyl)]-2,3-dihydro-1,3,4-thiadiazole (**2** and **3**).

Compound **1** (0.46 g) was dissolved in 4 ml of pyridine and 4 ml of acetic anhydride and the mixture was heated at 100° during 1 hour with magnetic stirring. The crude product was purified by flash chromatography, using benzene : ethyl acetate, to give compounds **2** and **3** which were obtained as white amorphous solids.

Compound **2**: 0.23 g, (33%), mp 121-123°, $[\alpha]_D$ = -310.0° (ethanol); ^1H nmr: δ 1.30, 1.45, 2.13, 2.14, 2.22 (s, 15H, CH_3-groups), δ 10.67 ppm (s, 1H, NH); ^{13}C nmr: δ 20.2, 21.3, 22.3, 25.8, 26.4 (CH_3-groups), δ 112.0 (quaternary carbon), δ 168.9, 169.1, 169.5 ppm (carbonyl groups); ms: m/z 387 ($M^{+\bullet}$), 372 ($M^{+\bullet}$-$CH_3^{\bullet}$= A^+), 330 (A^+-CH_2CO), 288 (A^+-2(CH_2CO)), 270 (A^+-CH_2CO-CH_3COOH), 228 (A^+-2(CH_2CO)-CH_3COOH), 186 (Het^+), 144 (Het^+-CH_2CO), 43 (base peak, CH_3CO^+).

Anal. Calcd. for $C_{15}H_{21}N_3O_7S$: C, 46.51; H, 5.43; N, 10.85. Found: C, 46.64; H, 5.19; N, 11.03.

Compound **3**: 0.22 g, (32%), mp: 99-101°, $[\alpha]_D$ = 303.9° (ethanol); ^1H nmr: δ 1.32, 1.45, 2.12, 2.14, 2.22 (s, 15H, CH_3-groups), δ 10.52 ppm (s, 1H, NH); ^{13}C nmr: δ 20.5, 21.6, 22.4, 25.9, 26.6 (CH_3-groups), δ 112.3 (quaternary carbon), δ 168.9, 169.2, 169.6 ppm (carbonyl groups); ms: m/z 387 ($M^{+\bullet}$), 372 ($M^{+\bullet}$-$CH_3^{\bullet}$= A^+), 330 (A^+-CH_2CO), 288 (A^+-2(CH_2CO)), 270 (A^+-CH_2CO-CH_3COOH), 228 (A^+-2(CH_2CO)-CH_3COOH), 186 (Het^+), 144 (Het^+-CH_2CO), 43 (base peak, CH_3CO^+).

Anal. Calcd. for $C_{15}H_{21}N_3O_7S$: C, 46.51; H, 5.43; N, 10.85. Found: C, 46.49; H, 5.60, N, 10.64.

5-Acetamido-2-[4'-(3'-*O*-acetyl-1',2'-*O*-isopropylidene-α-D-xylofuranosyl)]-1,3,4-thiadiazole (**4**).

Compound **5**, 55 mg was suspended in a mixture of 0.5 ml of pyridine and 0.5 ml of acetic anhydride and was left overnight

with magnetic stirring. The reaction which was stopped by addition of ethanol, and evaporation to dryness under reduced pressure, gave a syrup which slowly crystallized from ethyl acetate.

Product **4** was obtained as a solid in almost quantitative yield, mp 168-169°, $[\alpha]_D$ = 74.3° (ethanol), ^{1}H nmr: δ 1.40, 1.60, 2.00, 2.36 (s, 12H, CH_3- groups), δ 11.56 ppm (s, 1H, NH); ^{13}C nmr: δ 20.3, 22.3, 26.0, 26.5 (CH_3- groups), δ 112.8 (quaternary carbon), δ 168.8, 169.1 ppm (carbonyl groups); ms: m/z 343 ($M^{+\bullet}$), 328 ($M^{+\bullet}$-$CH_3^\bullet$= A^+), 286 (A^+-CH_2CO), 226 (A^+-$(CH_3CO)_2O$ or A^+-CH_2CO-CH_3COOH), 186 (A^+-CH_2CO-$C_5H_8O_2$), 200 ($M^{+\bullet}$-(HetH)), 171 ($HetCHO^{+\bullet}$), 43 (base peak, CH_3CO^+).

Anal. Calcd. for $C_{13}H_{17}N_3O_6S$: C, 45.48; H, 4.96; N, 12.24. Found: C, 45.43, H, 5.22, N, 11.91.

5-Amino-2-[4'-(1',2'-*O*-isopropylidene-α-D-xylofuranosyl)]-1,3,4-thiadiazole (**5**).

Compound **1** (0.46 g) was dissolved in 20 ml of pyridine and heated at 100°, then 1.4 ml of 2 *M* iron (III) chloride hexahydrate ($FeCl_3.6H_2O$) was added dropwise and heated for another 10 minutes. The mixture was filtered through a silica layer and concentrated. The residue was purified by silicagel G flash column using ethyl acetate and product **5** was obtained as a solid, 0.13 g, (29%), mp 184-185°, $[\alpha]_D$ = -26.6° (ethanol), ^{1}H nmr: δ 1.29, 1.46 (s ,6H, CH_3- groups), δ 7.11 ppm (s, 2H, $-NH_2$); ^{13}C nmr: δ 26.2, 26.8 (CH_3- groups), δ 111.2 ppm (quaternary carbon); ms: m/z 259 ($M^{+\bullet}$), 244 ($M^{+\bullet}$-$CH_3^\bullet$= A^+), 202 (A^+-CH_2CO), 200 (A^+-$(CH_3)_2CO$-$H^\bullet$), 184 (A^+-CH_3COOH), 172 (A^+-$(CH_3)_2CO$-CO-$H^\bullet$), 142 (A^+CH_3COOH-HCCOH), 130 ($HetCH_2OH^{+\bullet}$), 100 (Het^+), 43 (base peak, $CH_3CO^\bullet$).

Anal. Calcd. for $C_9H_{13}N_3O_4S$: C, 41.70; H, 5.02; N, 16.22. Found: C, 41.48; H, 5.21; N, 15.97.

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