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

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Synthesis of (3'*R*) 2-acetamido-4-*N*-acetyl-3'-spiro-[1',2':5',6'-di-*O*-isopropylidene-α-D-glucofuranosyl]-1,3,4-thiadiazoline diastereomerically pure is described. We report the physical and spectroscopic characterization of the new heterocyclic compound as well as its immediate precursors. We discuss also the possibilities for cyclization and established the stereochemistry of the new stereogenic center.

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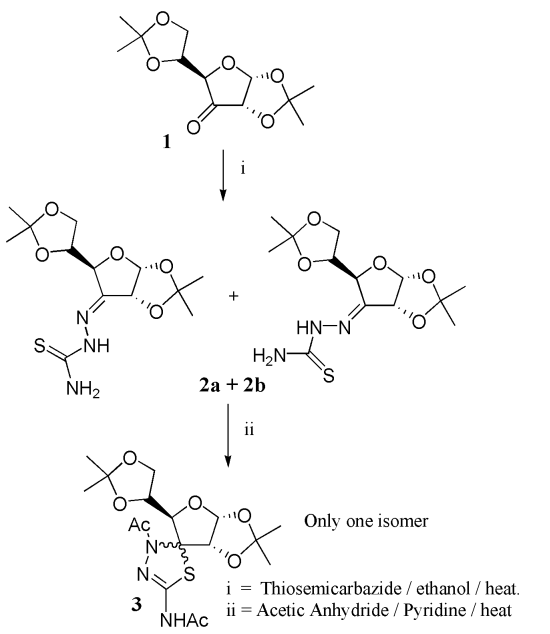
In our previous works [1], we reported the syntheses of heterocyclic derivatives from 1,2:3,4-di-*O*-isopropylidene-α-D-*galacto*-1,6-hexodialdo-1,5-pyranose and 1,2-*O*-isopropylidene-α-D-*xylo*-1,5-pentadialdo-1,4-furanose thiosemicarbazones by intramolecular cyclization, looking for a potential chiral induction of carbohydrate moiety, either by defined stereochemistry or by stabilization of an hypothetic carbocation, without success. In the present paper we extend that reaction to thiosemicarbazone derivative of 1,2:5,6-di-*O*-isopropylidene-α-D-*gluco*-1,5-furano-3-ulose in an attempt to synthesize a single spiro heterocycle.

Reaction of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofurano-3-ulose (**1**) [2] with thiosemicarbazide gave 1,2:5,6-di-*O*-isopropylidene-α-D-glucofurano-3-ulose thiosemicarbazones that were obtained as a mixture of two isomers (**2a** and **2b**) in a 3:2 ratio, determined by ^{1}H nmr. These isomers were separated and characterized physically and spectroscopically. When thiosemicarbazone **2** (as a mixture of both isomers) was treated with an acylating mixture in basic media, we isolated only one new heterocyclic compound. The synthetic route applied is shown in Figure 1.



The ^{1}H and ^{13}C nmr spectra of compounds **2a, 2b** and **3** were first performed at 200 MHz (which allowed a first order analysis) and 50 MHz respectively. In order to confirm our first assignment, we submitted all compounds to heteronuclear correlation analysis (HETCOR) in a 500

Table 1

^{1}H nmr Chemical Shifts (δ) for Compounds **2a**, **2b** Measured at 200 MHz in Deuteriochloroform; Data for Compound **3** were Recorded in Pyridine-d_5

Comp.	H-1	H-2	H-4	H-5	H-6a	H-6b	-NH	-NH_2
2a	6.05	5.06	4.73	4.35	4.10	3.96	9.44	7.17 and 6.59
2b	5.87	4.96	4.59	3.99	4.23	4.12	11.02	7.26 and 6.33
	H-1'	H-2'	H-4'	H-5'	H-6'a	H-6'b		
3	6.08	5.03	6.54	4.72	4.32	4.28		

Table 2

Measured Coupling Constants (Hz) for Compound **2a, 2b** and **3**

Comp.	$J_{1,2}$	$J_{2,4}$	$J_{4,5}$	$J_{5,6a}$	$J_{5,6b}$	$J_{6a,6b}$
2a	4.7	1.4	2.6	6.9	6.6	8.6
2b	4.2	1.2	9.4	6.2	5.2	9.2
	$J_{1',2'}$	$J_{2',4'}$	$J_{4',5'}$	$J_{5',6'a}$	$J_{5',6'b}$	$J_{6'a,6'b}$
3	3.9	-	6.5	5.9	6.2	12.4

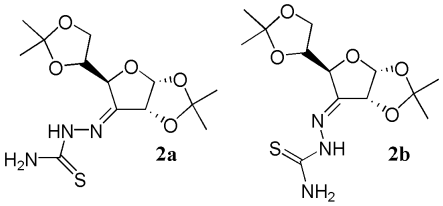
MHz apparatus, and obtained the same results. In Table 1 and 2 we present the chemical shifts and coupling constants for compounds **2a, 2b** and **3** respectively, and the assignment of ^{13}C nmr signals is shown in Table 3. For compounds **2a** and **2b** a small "long distance" coupling constant was observed between H-2 and H-4. This fact was attributed to the presence of C-N double bond (noted that this coupling is not observed for compound **3**).

Table 3

^{13}C nmr Chemical Shifts for Compounds **2a** and **2b**, Measured at 50 MHz in Deuteriochloroform; Data for Compound **3** were Recorded in Pyridine-d_5

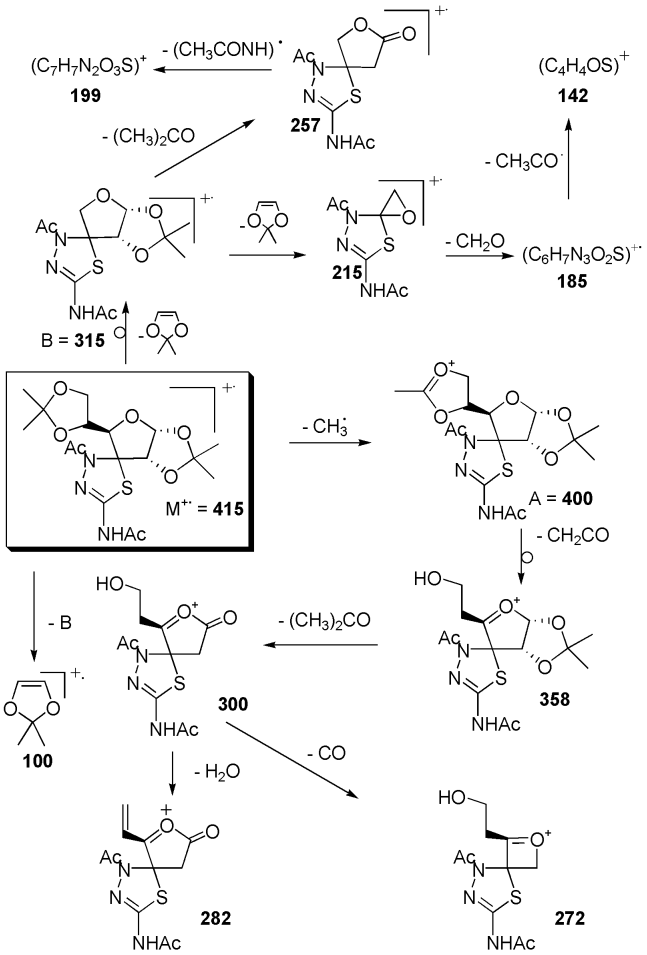
Comp.	**C-1**	**C-2**	**C-3**	**C-4**	**C-5**	**C-6**	**C=S**
2a	104.8	75.7	152.5	79.6	77.1	64.7	179.8
2b	103.2	80.2	149.6	78.5	74.8	68.0	180.4
	C-1'	**C-2'**	**C-3'**	**C-4'**	**C-5'**	**C-6'**	**C=N**
3	103.8	86.8	75.9	86.2	75.1	67.3	144.7

Based on nmr analysis, we attempt to determine which structure best fits with experimental data for compound **2a** and **2b**. In our previous works [1], we used the observations of Karabatsos and Taller [3] for nitrogen derivatives of ketones to determine the relative position of substituents. According with that supposition, the substituent that was in the same side of -NHCSNH$_2$ (*syn* form), must be less shielded, so, following this reasoning, we can observe that ^{13}C nmr displacement of C-2 for compound **2a** is, in chemical shift, lower than the corresponding signal for **2b**. For C-4 the inverse relationship can be observed, so we conclude that **2b** is the *syn* form and **2a** is the *anti* (Figure 2).

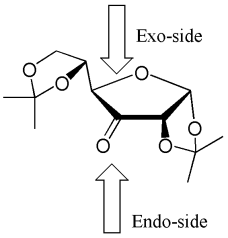


Spectroscopic characterization of compounds was concluded by mass spectrometry analysis and for all compounds we observed the molecular ion ($M^{+\bullet}$). We found a similar fragmentation pattern for compound **2a** and **2b** with losses of methyl group, acetone, ketene, carbon monoxide and its combinations. For compound **3**, we observed the typical fragmentations of isopropylidene derivatives and several differences with aldehyde thiadiazolines described by us [1,7]. The aldehyde derivatives showed important peaks at mass/charge relationship (m/z) 186 and 144, corresponding to protonated heterocycle fragment and its ketene loss. For compound **3** these peaks exist and may have originated by fragmentations with rearrangement, but the most important peak in that zone is m/z 185. A possible fragmentation pattern for compound **3** is proposed in Figure 3.

The resulting of a single spiro compound indicates a preferential side of attack, but we can not determine which is the absolute configuration of C-3' in the pyranose ring with the information previously discussed. Several number of spiro compounds were synthesized from compound **1**



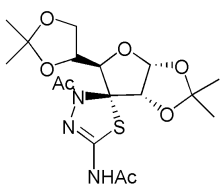
[4], and in each case, the assigned configuration of the new stereogenic center corresponds to an *exo* attack during the ring closure (Figure 4).



According to the literature, when 5-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*erythro*-pentofurano-3-ulose is treated with nitromethane anion, the attack occurs by the *exo*-side, giving the *allo* configuration. This was attributed to steric control exerted by the 1,2-isopropylidene group, however when this reaction was carried out on **1,** the attack proceeds by the *endo*-side [5].

In a further publication, Tronchet *et. al*. [6] reported that for nucleophilic attack a thermodynamic and a kinetic side can be defined, which coincides with the α and β side of the carbohydrate respectively. So, the characteristics of the reaction and the selection of reaction conditions can determine the achievement of one or either isomer. This conclusion is in agreement with those observed for heterocyclization of free sugar thiosemicarbazones [7]. Based on this fact, we performed the heterocyclization reaction over the 1,2:5,6-di-*O*-isopropylidene-α-D-glucofurano-3-ulose thiosemicarbazone using two different reaction conditions. Under the usual treatment (acetic anhydride/pyridine, 100 °C, 1 hour), we obtained only one heterocyclic product in a 60 % of purified non-optimized yield. This compound was characterized and identified as 2-acetamido-4-*N*-acetyl-3'-spiro-[1',2':5',6'-di-*O*-isopropylidene-α-D-glucofuranosyl]-1,3,4-thiadiazoline (**3**). When the reaction was accomplished with the same reagents at room temperature, we obtained **3** as the only heterocyclic product in a very low yield. Then, we can not use a difference of reactivity of compound **2** under different energetic conditions to determine whether **3** results from a thermodynamic or kinetic cyclization.

Finally, we performed a bidimensional nuclear Overhauser effect experiment (NOESY) on **3** and we found a long distance correlation between H-2' and a CH_3- from amide. This correlation only can be observed when the methyl group of N-4 is on the same face of the molecule as H-2'. So, we can conclude that cyclization takes place by the *endo* side, and C-3' for compound **3** have the *R* configuration (Figure 5).



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 200 MHz in deuteriochloroform (compound **2a** and **2b**) or pyridine-d_5, using tetramethyl silane as internal standard. The ^{13}C nmr spectra were recorded at 50 MHz on the same apparatus. HETCOR and NOESY experiments were performed in a Bruker Spectrometer at 500 MHz. Mass spectra were performed with a Shimadzu QP-5000 by electron impact ionization.

1,2:5,6-Di-*O*-isopropylidene-α-D-glucofurano-3-ulose Thiosemicarbazone (**2a** and **2b**).

Title compounds were prepared from 0.9 g of ketone **1** [2] dissolved in 15 ml of ethanol and 0.35 g of thiosemicarbazide. The mixture was refluxed with continuous stirring, 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 (cyclohexane:ethyl acetate), to yield **2a** and **2b** as a syrup, 0.86 g (75%). Compounds **2a** and **2b** are in a 3:2 ratio, determined by nmr; ms: m/z 331 ($M^{+\bullet}$), 316 ($M^{+\bullet}$-$CH_3^{\bullet}$= A^+), 273 ($M^{+\bullet}$-$(CH_3)_2CO$) = $B^{+\bullet}$), 274 (A^+-CH_2CO), 256 (A^+-AcOH), 215 ($B^{+\bullet}$-$(CH_3)_2CO$), 43 (base peak, CH_3CO^+).

Anal. Calcd. for $C_{13}H_{21}N_3O_5S\bullet 3C_4H_8O_2$: C, 50.42; H, 7.56; N, 7.06. Found: C, 50.43; H, 7.49; N, 7.13.

Certain fractions, which contain pure **2a** or **2b**, were used for individual characterization.

Compound **2a** has $[\alpha]_D$ = 335.1° (chloroform); ^1H nmr (deuteriochloroform): δ 1.33 (s, 6H, 2 CH_3), 1.45 (s, 3H, CH_3), 1.46 (s, 3H, CH_3); ^{13}C nmr: δ 114.7 and 110.5 (quaternary carbons), δ 24.9, 26.2, 27.3, 27.5 (methyl groups).

Compound **2b** has $[\alpha]_D$ = 270.8° (chloroform); ^1H nmr: δ 1.42, 1.45, 1.46 (three s, 9H, CH_3), 1.88 (s, 3H, CH_3); ^{13}C nmr: δ 113.1 and 111.9 (quaternary carbons), δ 25.1, 26.6, 27.4, 27.6 (methyl groups).

(3'*R*) 2-Acetamido-4-*N*-acetyl-3'-spiro-[1',2':5',6'-di-*O*-isopropylidene-α-D-glucofuranosyl]-1,3,4-thiadiazoline (**3**).

Compound **2**, (1.0 g) was suspended in a mixture of 5 ml of pyridine and 5 ml of acetic anhydride and was heated at 100° on a water bath with magnetic stirring. The reaction was stopped by addition of ethanol; evaporation to dryness under reduced pressure, and addition of some water and toluene to eliminate all acetic acid residues. The residue was purified by silicagel G flash column using mixtures of benzene:ethyl acetate and product **3** was obtained as a solid by recrystallization from ethyl acetate, 0.75 g, (60%), mp 234-236º, $[\alpha]_D$ = -104.5° (chloroform), ^1H nmr: δ 1.31, 1.34 (2s, 6H, $2CH_3$), 1.55 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 2.26, 2.29 (2s, 6H, $2CH_3$); ^{13}C nmr: δ 109.7 and 103.8 ppm (quaternary carbons); δ 23.1, 24.8, 25.3, 26.3, 26.6, 27.1 (methyl groups), ms: m/z 415 ($M^{+\bullet}$), 400 ($M^{+\bullet}$-$CH_3^{\bullet}$= A^+), 358 (A^+-CH_2CO), 315 ($M^{+\bullet}$-$C_5H_8O_2$= $B^{+\bullet}$), 300 (A^+-$(CH_3)_2CO$-CH_2CO, or A^+-$C_5H_8O_2$), 282 (A^+-$(CH_3)_2CO$-CH_2CO-H_2O), 272 (A^+-$(CH_3)_2CO$-CH_2CO-CO), 257 ($B^{+\bullet}$-$(CH_3)_2CO$), 215 ($B^{+\bullet}$- $C_5H_8O_2$), 199 ($B^{+\bullet}$-$(CH_3)_2CO$-$CH_3CONH^{\bullet}$), 185 ($M^{+\bullet}$-$2(C_5H_8O_2)$-H_2CO), 142 ($M^{+\bullet}$-$2(C_5H_8O_2)$-H_2CO-$CH_3CO^{\bullet}$), 100 ($C_5H_8O_2^{+\bullet}$), 43 (base peak, CH_3CO^+).

Anal. Calcd. for $C_{17}H_{25}N_3O_7S•3C_4H_8O_2$: C, 51.25; H, 7.07; N, 6.19. Found: C, 51.47; H, 6.72; N, 5.97.

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