Synthesis and Characterization of some Heterocyclic Derivatives by Cyclization of Carbohydrate Thiosemicarbazones. Part I

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We report the synthesis of 2,3-dihydro-1,3,4-thiadiazoles and 1,3,4-thiadiazoles from 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose thiosemicarbazone. The physical and spectroscopic characterizations of the heterocyclic derivatives as well as the intermediate product are described. We present the prefered conformation in solution using computational calculations and spectroscopic data. The possibilities of chiral induction of the cyclization reaction are discussed.

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The synthesis of heterocyclic rings containing sulfur and nitrogen atoms are of interest because of wide application in the pharmacological field [1]. Somogyi [2] obtained 5-acetamido-3-*N*-acetyl-2,3-dihydro-1,3,4-thiadiazoles derived from penta-*O*-acetyl-D-galactose thiosemicarbazone using an acetylating mixture. In that work the authors applied successive protection and deprotection steps. El Ashry, *et al.* [3] obtained the same products by direct acylation of D-galactose thiosemicarbazone.

In previous work [4], we reported the synthesis of heterocyclic carbohydrates by nucleophilic substitution, in which we obtained nucleoside analogues with a sulfur bridge. In this paper we report the preparation of heterocyclic rings containing nitrogen and sulfur from 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose thiosemicarbazone by intramolecular cyclization.

Reaction of 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose [5] with thiosemicarbazide yields 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose thiosemicarbazone **1**, which was characterized physically and spectroscopically (see Experimental). When thiosemicarbazone derivative **1** was treated with an acylating mixture in basic media, we isolated three heterocyclic compounds: 2(*R*)- and 2(*S*)-5-acetamide-3-*N*-acetyl-2-[5'-(1',2':3',4'-di-*O*-isopropylidene-α-L-arabinopyranosyl)]-2,3-dihydro-1,3,4-thiadiazole **2** and **3** and 5-acetamide-2-[5'-(1',2':3',4'-di-*O*-isopropylidene-α-L-arabinopyranosyl)]-1,3,4-thiadiazole (**4**).

When compound **1** was treated with ferric chloride in pyridine, we obtained 5-amino-2-[5'-(1',2':3',4'-di-*O*-isopropylidene-α-L-arabinopyranosyl)]-1,3,4-thiadiazole (**5**), which was acetylated to obtain compound **4** in quantitative yield. In Figure 1 we show the synthetic routes used.

The ^{1}H nmr spectra of compounds **2-5** were performed at 200 MHz and permitted a first order analysis. In Tables 1 and 2 we present the chemical shifts and coupling constants, respectively.

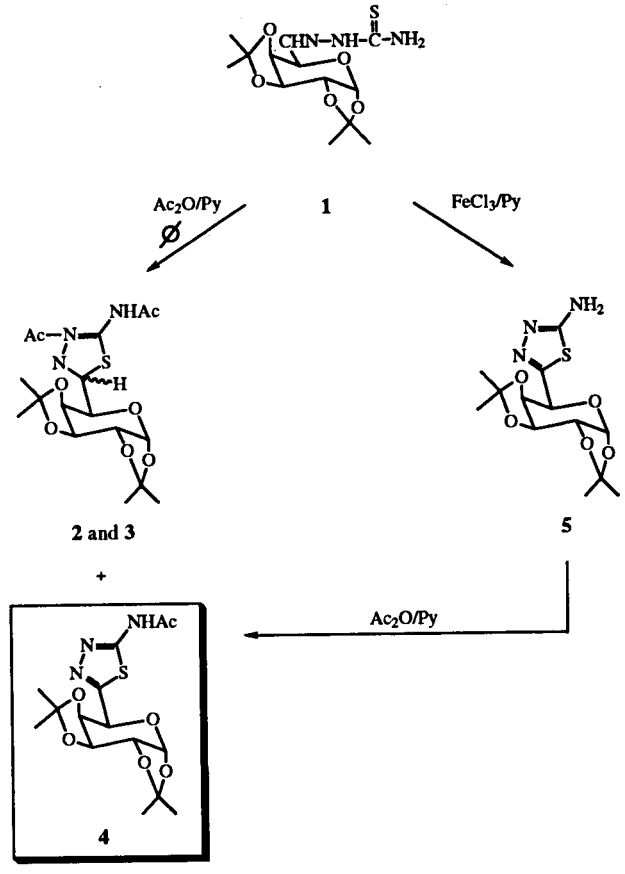


Figure 1.

Table 1

^{1}H NMR Chemical Shifts (δ) for Compounds **2** to **4** (200 MHz, deuteriochloroform). Data for Compound **5** Recorded in Dimethyl-d_6 Sulfoxide

Compound	H-1'	H-2'	H-3'	H-4'	H-5'	H-2
2	5.55	4.32	4.61	4.30	4.40	5.98
3	5.52	4.30	4.62	4.43	4.13	6.32
4	5.65	4.43	4.76	4.55	5.33	-
5	5.57	4.47	4.74	4.43	5.00	-

Table 2
Measured Coupling Constants (Hz) for Compound **2** to **5**

Compound	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',2}$
2	5.0	2.6	7.9	2.1	< 1
3	4.9	2.5	7.8	1.8	9.0
4	4.9	2.5	7.8	1.9	-
5	4.9	2.3	7.8	1.7	-

The comparison between chemical shift data of compounds **2** and **3** shows the main differences on H-5' and H-2, which was attributed to configurational inversion. The rest of the signals remain virtually unchanged. Even in the case that we observe very different values for $J_{5',2}$ for compounds **2** and **3**, we could not determine the absolute configuration of this center using these spectroscopic data.

The most important difference between the spectra of compounds **2-3** and **4-5** is the loss of the H-2 signal for the latter compounds. The analysis of coupling constants of the carbohydrate moiety for all compounds allow us to propose the $^{O}T_2$ as a main conformation in solution. The same conformation was observed in other di-*O*-isopropylidene-α-D-galactopyranose derivatives [4].

Assignment of the ^{13}C nmr data for compounds **2** to **5** was made using 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose [6] as a model compound (Table 3). In a general way we observe slight differences for C-1' to C-3' with the model compound, and with increases for C-4' to C-2 (C-6 for the model compound).

Table 3
^{13}C NMR Chemical Shifts for Compounds **2** to **4**, (50 MHz, deuteriochloroform). Data for Compound **5** Recorded in Dimethyl-d_6 Sulfoxide

Compound	C-1'	C-2'	C-3'	C-4'	C-5'	C-2	C-5
2	96.5	70.8	70.2	67.3	71.1	66.2	148.9
3	96.6	70.0*	69.9*	68.8	70.9	62.2	150.0
4	96.6	70.9*	70.6*	67.8	72.9	168.9	162.0
5	96.2	70.3*	69.9*	67.1	72.0	169.8	155.4

*This pair of values could be interchanged.

Comparison of the assignments for compounds **2** and **3** show the consequences of configurational inversion on C-2. The influence of this change is the most important on C-2 (4.0 ppm), decreasing in C-4' and C-2' (-1.5 and 0.8 ppm respectively), and can be attributed to an 1,3-interaction of C-2 with the pseudoaxial positions in C-2' and C-4'.

A similar comparison was made for compounds **4** and **5**. We observed that these compounds correllated well between them, and the main difference appears at C-5 (6.6 ppm) by acetylation of the amino group (6.6 ppm).

Mass spectra of compounds **1** to **5** show typical fragmentation of di-*O*-isopropylidene-α-D-galactopyranose derivatives as was described earlier [4], which include loss of methyl group, acetic acid, acetone, ketene and its combinations and other characteristic peaks for each heterocycle (see Experimental).

A possible mechanism for the formation of related heterocyclic compounds with **2** and **3** has been reported [7]. This reaction generates a new chiral center by heterocyclization on a flat site in the molecule. The attack should take place on both sides of an sp^2 carbon, the ratio of two possible isomers could be approximately 1:1.

The spectroscopic evidence (Tables 4-6) indicated that compound **1** was characterized as a mixture of two isomers: *syn* (-$NHCSNH_2$ group *cis* to hydrogen) and *anti* (-$NHCSNH_2$ group *trans* to hydrogen), according to the definition used by Karabatsos *et al.* [8]. One of the isomers is the principal compound (approximate ratio 15:1 by ^{13}C nmr data). Even though the existence of a main isomer and the presence of a bulky group with many chiral centers permits us to propose the existence of a potential asymmetric induction, similar yields were found for both diasteroisomers, compounds **2** and **3**.

Studies on the oximes and phenylhydrazones derived from 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose [9], indicated that the main isomer of all of these compounds is the *syn* form. From the ^1H nmr signals for compound **1** and those reported for related compounds, we have concluded that the main isomer of thiosemicarbazone derivative was the *syn* form.

Table 4
^1H NMR Chemical Shifts (δ) for Compounds **1** *syn* and **1** *anti*, (200 MHz in deuteriochloroform)

Compound	H-1	H-2	H-3	H-4	H-5	H-6	-NH	$-NH_2$
1 *syn*	5.57					7.22	9.72	
		4.36	4.66	4.47	4.40			7.23 and 7.21
1 *anti*	5.69					6.56	10.24	

Syn form: δ 1.35, 1.36, 1.47, 1.55 (CH_3-).
Anti form: 1.36, 1.47, 1.50, 1.59 (CH_3-).

Table 5
Measured Coupling Constants (Hz) for Compound **1** *syn* and **1** *anti*

Compound	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{5,6}$
1 *syn*	5.0	2.5	7.7	2.1	5.4
1 *anti*	5.0				3.4

From some molecular mechanics calculations [10] we found that the *anti* isomer of compound **1** is nearly 4 kcal more energetic than the *syn* isomer, thus the predominance of a main isomer. Tronchet [9] concluded that 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranoseoxime has six possible rotamers; the most stable were those eclipsed.

Table 6

^{13}C NMR Chemical Shifts for Compounds **1** *syn* and **1** *anti*, (50 MHz in deuteriochloroform)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C=S
1 *syn*	96.1	70.1	70.6	68.1	73.0	143.9 [a]	179.0
1*anti*	96.2		70.4	67.1	71.0	136.8 [a]	

Syn form: δ 24.4, 24.8, 25.9, 26.1 (CH_3-), δ 109.0, 109.9 (quaternary carbons)
Anti form: δ 24.4, 24.8, 25.9, 26.1 (CH_3-), δ 109.5, 110.2 (quaternary carbons)

[a] Intensities *syn*:*anti* = 15:1.

We propose as possible rotamers for compound **1** those shown in Figure 2.

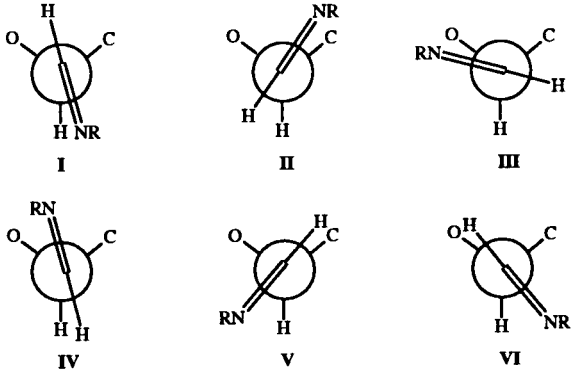


Figure 2.

In our calculations using PM3 [10] we found that the lowest energetic rotamer corresponds to rotamer **I** (dihedral angle between H-5 and H-6, 154.4°). When the calculations were made with MM+, the lowest energetic rotamer is near to rotamer **VI** (dihedral angle 113.8°). The calculated coupling constant $J_{5,6}$ for rotamer **I** and for rotamer **VI** do not agree with the experimental values. This fact can be attributed to the contribution of several local minima which differ only in a few calories with the absolute minimum in a rotation belonging to the C-5→C-6 linkage. All possible rotamers contribute to the main conformation in solution affecting the coupling constant value. If we consider rotamers **I** and **VI** as the main contributors to the conformational equilibrium, we can estimate the proportion of rotamers in solution on the basis of the coupling constants:

measured $J_{5,6} = 5.4$

calculated $J_{5,6}$ for I = 9.9, calculated $J_{5,6}$ for VI = 4.1

I+VI = 1 5.4 = I (9.9) + VI (4.1) I = 0.22 VI = 0.78

From these calculations we conclude that the main rotamer in solution was rotamer **VI**.

When the reaction was monitored by the tlc technique, we observed the formation of one isomer ($J_{5,6}$ = 9.0) faster than the other ($J_{5,6}$ <1). Like other cases [11] the existence of possible kinetic or thermodynamic control could explain this observation. When the reaction was carried out at different temperatures with the same reaction time, identical results were obtained; aproximate 1:1 ratio for both diasteromers, so we must discard that possibility. From the experimental data we must conclude that the faster formation of compound **3** must be attributed to other effects, such as steric hindrance.

As shown in Figure 3, if we consider the rotamer **I**, the location of the reactive center (C-6) is relatively far from the steric influence of the isopropylidene groups, therefore ring closure may occur on both sides of C-6 of compound **1**, thus originating the 2*R*- and 2*S*-isomers in the same proportion.

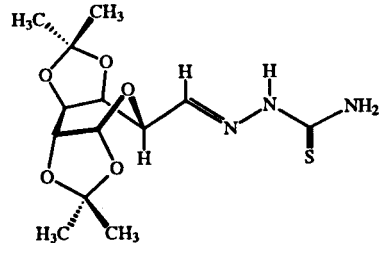


Figure 3.

When the heterocyclization reaction was analyzed for rotamer **VI**, we observed that attack of a bulky sulfur atom is easier at the α side because of the influence of electronic pairs of oxygen of pyranose ring and the oxygen of isopropylidene moiety (Figure 4). However we cannot discount an attack at the β side.

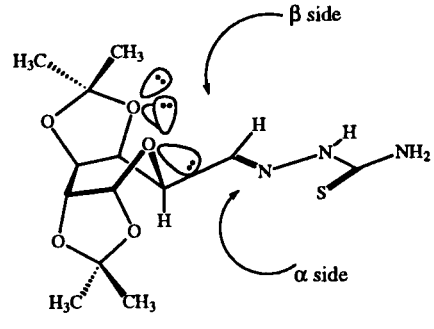
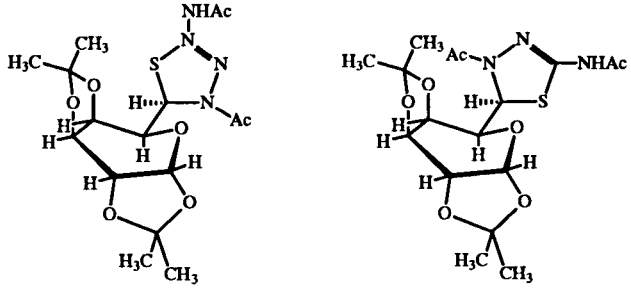


Figure 4.

If we suppose that rotamer **VI** is more easily attacked at the α side, the 2*S*-dihydrothiadiazole must be formed earlier than the 2*R*-rotamer. Thus from the observed behavior of this reaction we propose that compound **2** is the 2*R* and compound **3** is the 2*S* (Figure 5).

When the reaction was carried out at 100° but during a longer period of time, **4** was isolated as the main product. The increasing ratio of **4** was determined from the ^{13}C nmr spectrum by comparison of the intensities at C-5.



A B

Figure 5. A: 2(*R*)-5-Acetamide-3-*N*-acetyl-2-[5'-(1',2':3',4'-di-*O*-isopropylidene-α-L-arabinopyranosyl)]-2,3-dihydro-1,3,4-thiadiazole. B: 2(*S*)-5-acetamide-3-*N*-acetyl-2-[5'-(1',2':3',4'-di-*O*-isopropylidene-α-L-arabinopyranosyl)]-2,3-dihydro-1,3,4-thiadiazole.

Compound **4** appears to arise from compounds **2** and **3**, because the yield of heterocyclic products is virtually the same but their ratios were different. After 1 hour we isolated a 75% of heterocyclic products, and the distribution was 43% of compound **2**, 48% of compound **3** and 9.3% of compound **4**, meanwhile when the reaction was carried out during 10 hours, the total yield of heterocyclic compounds was 69% and the percent composition was 2.9:17:80 (**2**:**3**:**4**).

Compound **4** differs from **2** or **3** in a molecule of acetaldehyde, but a direct loss of this substance is not easy to be postulated. In our opinion, acetate formed during the reaction must be involved, because when pure compounds **2** and **3** were treated with acetic anhydride and pyridine the transformation into compound **4** takes place slowly and incompletely.

To confirm the identity of compound **4**, we acetylated compound **5** and obtained a product that its physical and spectroscopic properties was consistent with compound **4**.

EXPERIMENTAL

General Methods.

The melting points were measured on a Thomas Hoover melting point apparatus and are uncorrected. The $[\alpha]_D$ were observed using a Perkin Elmer 141 polarimeter. All ^1H nmr spectra were recorded on a Bruker Spectrometer at 200 MHz in deuteriochloroform or d_6-dimethyl sulfoxide, using tetramethylsilane as internal standard. The ^{13}C nmr spectra were recorded at 50 MHz in the same apparatus. Mass spectra were obtained with a Shimadzu QP-5000 by electron impact ionization.

1,2:3,4-Di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose Thiosemicarbazone (**1**).

Title compound was prepared from 3.5 g of crude 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-1,6-hexodialdo-1,5-pyranose [5] dissolved in 50 ml of ethanol and 1.3 g of thiosemicarbazide. The mixture was heated at reflux monitoring the reaction using tlc (silica gel G, benzene:ethyl acetate 2:3). Evaporation under reduced pressure gave a yellow syrup which was purified using flash chromatography (benzene:ethyl acetate), 2.8 g, yield 63%, mp 118-120°, $[\alpha]_D$ = -139.5° (chloroform); ms: m/z 333 ($M^{+\bullet}$ +2H), 332 ($M^{+\bullet}$ +H), 331 ($M^{+\bullet}$), 316 ($M^{+\bullet}$ -$CH_3^\bullet$ = A^+), 274 (A^+ -CH_2CO), 273 ($M^{+\bullet}$ -$(CH_3)_2CO$), 258 (A^+ -$(CH_3)_2CO$), 256 (A^+ -CH_3COOH), 215 ($M^{+\bullet}$ -2$(CH_3)_2CO$), 102 (base peak, $(CH_3CO)_2O^{+\bullet}$ or $(C_2H_4N_3S)^+$.

Anal. Calcd. for $C_{13}H_{21}N_3O_5S\bullet C_4H_8O_2$: C, 48.69; H, 6.92. Found: C, 48.69; H, 7.01.

2(*R*)- and 2(*S*)-5-Acetamide-3-*N*-acetyl-2-[5'-(1',2':3',4'-di-*O*-isopropylidene-α-L-arabinopyranosyl)]-2,3-dihydro-1,3,4-thiadiazoles **2** and **3**.

Compound **1** (0.30 g) was dissolved in 2 ml of pyridine and 2 ml of acetic anhydride and the mixture was heated at 100° during 1 hour with magnetic stirring. The crude product purified by flash chromatography using benzene:ethyl acetate, compound **2** and **3** were obtained as white amorphous solids.

Compound **2** was obtained in 32% yield (0.12 g), mp 138-140°, $[\alpha]_D$ = 238.1° (chloroform); ^1H nmr: δ 1.28, 1.31, 1.43, 1.51, 2.15, 2.20 (s, CH_3-groups), δ 9.13 (s, NH) ppm; ^{13}C nmr: δ 22.1, 23.2, 24.4, 25.0, 25.5, 25.8 (CH_3-groups), δ 109.1, 110.3 (quaternary carbons), δ 169.2, 168.7 (carbonyl groups) ppm; ms: m/z 417 ($M^{+\bullet}$ +2H), 416 ($M^{+\bullet}$ +H), 415 ($M^{+\bullet}$), 400 ($M^{+\bullet}$ -$CH_3^\bullet$ = A^+), 358 (A^+ -CH_2CO), 342 (A^+ -$(CH_3)_2CO$), 314 (A^+ -$(CH_3)_2CO$-CO), 300 (A^+ -$(CH_3)_2CO$-CH_2CO), 215 ($C_7H_9N_3O_3S^{+\bullet}$), 186 (Het^+), 144 (base peak, Het^+ -CH_2CO).

Anal. Calcd. for $C_{17}H_{25}N_3O_7S\bullet C_4H_8O_2$: C, 50.1; H, 6.56. Found: C, 49.97; H, 6.71.

Compound **3** was obtained in 36% yield (0.14 g), mp 131-133°, $[\alpha]_D$ = -357.7° (chloroform); ^1H nmr: δ 1.26, 1.29, 1.32, 1.48, 2.04, 2.20 (s, CH_3-groups), δ 9.41 (s, NH) ppm; ^{13}C nmr: δ 21.8, 23.3, 24.6, 24.8, 25.9, 25.9 (CH_3-groups), δ 108.7, 110.1 (quaternary carbons), δ 168.9, 170.0 (carbonyl groups) ppm; ms: m/z 416 ($M^{+\bullet}$ +H), 415 ($M^{+\bullet}$), 400 ($M^{+\bullet}$ -$CH_3^\bullet$ = A^+), 373 ($M^{+\bullet}$ -CH_2CO), 358 (A^+ -CH_2CO), 342 (A^+ -$(CH_3)_2CO$), 314 (A^+ -$(CH_3)_2CO$-CO), 300 (A^+ -$(CH_3)_2CO$-CH_2CO), 215 ($C_7H_9N_3O_3S^{+\bullet}$), 186 (Het^+), 144 (base peak, Het^+ -CH_2CO).

Anal. Calcd. for $C_{17}H_{25}N_3O_7S$: C, 49.16; H, 6.02. Found: C, 49.33; H, 6.33.

5-Acetamide-2-[5'-(1',2':3',4'-di-*O*-isopropylidene-α-L-arabinopyranosyl)]-1,3,4-thiadiazole (**4**).

Method 1.

Compound **4** was obtained by the procedure described for synthesis of compounds **2** and **3** after 10 hours reaction time. The syrup obtained was purified by flash chromatogaphy and recrystallized from ethyl acetate. Product **4** was obtained as a solid, 0.21 g, 55% yield, mp 210-212°.

Method 2.

Compound **5**, 0.20 g was suspended in a mixture of 1 ml of pyridine and 1 ml of acetic anhydride and allowed to stand over night with magnetic stirring. The reaction was stopped by addition of ethanol, evaporated to dryness under reduced pressure and gave a syrup which was recrystallized from ethyl acetate. Product **4** was obtained as a solid, 0.22 g, 97% yield, mp 211-212°, $[\alpha]_D$ = -104.9° (chloroform); ^1H nmr: δ 1.33, 1.38, 1.50, 1.60, 2.43 (s, CH_3- groups) ppm; ^{13}C nmr: δ 23.2, 24.4, 24.9, 26.0, 26.2 (CH_3- groups), δ 109.3, 110.1 (quaternary carbons), δ 162.8 (carbonyl group) ppm; ms: m/z 356 ($M^{+\bullet}$ -$CH_3^\bullet$ = A^+),

256 (A^+ -$C_5H_8O_2^{\bullet}$), 196 (A^+ -$C_5H_8O_2^{\bullet}$ -CH_3COOH), 142 (Het^+), 43 (base peak, CH_3CO^+).

Anal. Calcd. for $C_{15}H_{21}N_3O_6S \cdot C_4H_8O_2$: C, 49.67; H, 6.32. Found: C, 49.71; H, 6.40.

5-Amino-2-[5'-(1',2':3',4'-di-*O*-isopropylidene-α-L-arabino-pyranosyl)]-1,3,4-thiadiazole (**5**).

Compound **1** (0.9 g) was disolved in 90 ml of pyridine and heated at 100°, then 5 ml of 2 *M* ferric chloride hexahydrate was added dropwise and heated for an additional 10 minutes. The mixture was concentred, dissolved in ethanol and filtered through a silica layer. The solution was evaporated, the solid recrystallized from ethyl acetate, and gave product **5** as a solid, 0.34 g, 38% yield, mp 263-264°, $[\alpha]_D$ = -122.0° (chloroform); ^1H nmr: δ 1.30, 1.33, 1.40, 1.50 (s, CH_3- groups), δ 7.40 (s, NH) ppm; ^{13}C nmr: δ 24.3, 24.9, 25.9, 25.9 (CH_3- groups), δ 108.6, 109.0 (quaternary carbons) ppm; ms: m/z 331 ($M^{+\bullet}$ +2H), 330 ($M^{+\bullet}$ +H), 329 ($M^{+\bullet}$), 314 ($M^{+\bullet}$ -$CH_3^{\bullet}$ = A^+), 272 (A^+ -CH_2CO), 256 (A^+ -$(CH_3)_2CO$), 254 (A^+ -CH_3COOH), 100 (Het^+), 43 (base peak, CH_3CO^+).

Anal. Calcd. for $C_{13}H_{19}N_3O_5S$: C, 47.42; H, 5.78. Found: C, 47.79; H, 5.90.

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