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Synthesis and isomerism of hydrazones of 2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetohydrazide

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Abstract: New hydrazones of 2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetohydrazide have been obtained and the percentages of *anti/syn* - conformers were determined. Based on the analyses of ^{1}H NMR spectra, it was concluded that for hydrazones obtained from the 2- hydroxybenzaldehydes and 2'-hydroxycetophenones the ratio between the *anti-* and *syn-* conformers depends on the strength of intramolecular hydrogen bond (IMHB) between the nitrogen atom of the imino group and the proton of the 2-hydroxy group. It was shown that increase in IMHB strength results in stabilization of the *anti-* conformer in solution.

Keywords: Hydrazones, conformational isomers, intramolecular hydrogen bond, ^{1}H NMR spectroscopy.

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1 Introduction

Pyridoxal isonicotinoyl hydrazone and its analogues are proposed chemotherapeutics functioning as iron chelators for the treatment of iron overload disease [1, 2]. Pyridoxal isonicotinoyl as well as 2-hydroxybenzaldehyde benzoyl hydrazones are tridentate ligands and form monomeric structures upon complexation with iron(III) [3–5]. It was demonstrated [6–8] that these iron-binding tridentate ligands are also useful for inhibiting the growth of tumors.

Due to geometric isomerism with respect to the imino group (E, Z isomers) and rotational isomerism as a result of hindered rotation about the amide linkage (*anti/syn* - conformers), hydrazones can exist as four isomers. X-ray spectroscopic studies revealed

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that in the solid state acyl and aroylhydrazones form only E isomers [9]. It was demonstrated [9] that in the solid state, acylhydrazones of benzaldehyde form *syn* - conformers that aggregate to centrosymmetric dimers due to their intermolecular hydrogen bonding. Only *syn*, E - isomers possess C=O and N-N groups in a trans conformation that permits the formation of dimers. Calculations performed with the semiempirical MNDO method demonstrated that conjugation effects are also more pronounced in *syn*, E - isomers compared with *anti*, E - isomers [9]. In DMSO solutions acyl and aroylhydrazones form mostly (up to 100%) E - isomers [10]. In solution, the ratio between the *anti*- and *syn* - conformers of acylhydrazones depends on the solvent. Because of the high degree of intermolecular hydrogen bonding between the hydrazones, it is expected that in solution acylhydrazones exist mostly as the conglomerates of *syn* - conformers [9]. Indeed, in non-polar solvents such as chloroform, about 86% of acylhydrazone molecules were found to be in *syn* - conformer state. In contrast, the polar solvent DMSO, which disfavors aggregation of hydrazones through the hydrogen bonding, because of strong competitive interaction with the NH groups, still about 60% of molecules were in *syn* - conformations [10]. It was shown that aroylhydrazones form only *anti* - conformers, both, in the solid state [9] and in solution [10].

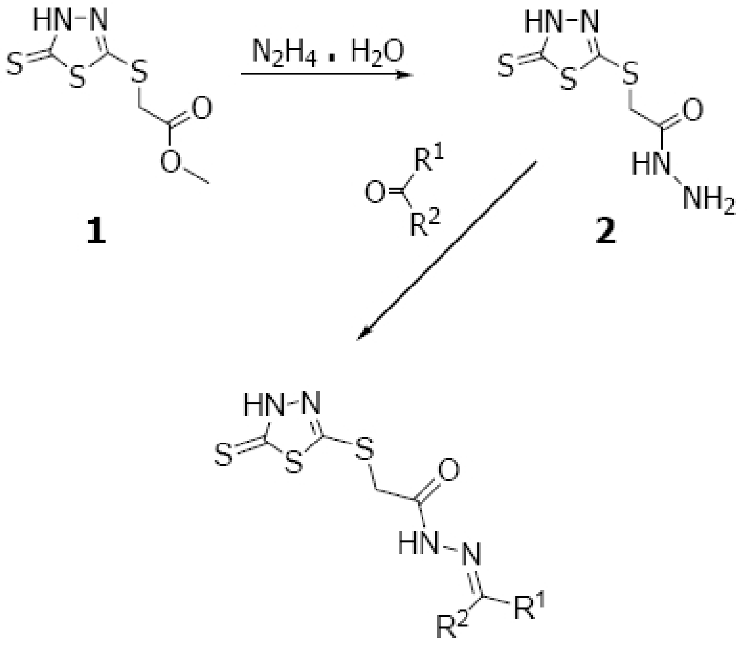
2-Hydroxybenzaldehyde benzoylhydrazone, as a representative of aroylhydrazones, forms only *anti*-conformers in solution [11], whereas 2-hydroxybenzaldehyde acylhydrazones form *anti* - and *syn* - conformers. *Syn* - conformers can have two complexation sites and should form dimeric or polymeric structures upon complexation with iron(III), but not monomeric complexes. It was noticed that the percentage of *anti* - conformer in the DMSO solution of hydrazone prepared from 2,5-dimercapto-1,3,4-thiadiazole and 2-hydroxybenzaldehyde has increased compared to that of hydrazones obtained from benzaldehydes [12, 13]. It was suggested that formation of intramolecular hydrogen bonds (IMHB) with the participation of the imino nitrogen lone electron pair and the proton of the 2-hydroxy group is responsible for this effect [11, 12].

In order to increase the number of hydrazones able to form strong iron(III) complexes, the conditions for formation of acylhydrazones *anti* - conformer in solution should be investigated thoroughly. The present work has employed ^{1}H NMR spectroscopic studies to quantify the *anti*- and *syn*- conformers of newly synthesized hydrazones.

2 Results and discussion

Conformational isomerism of hydrazones obtained from 2,5-dimercapto-1,3,4-thiadiazole has been studied previously [12, 13]. Hydrazones in solution exist as a mixture of two conformers (*anti*/*syn*), as exemplified by doubled proton resonances assigned to the CH_2CO, =CH and NH groups in ^{1}H NMR spectra. The proton signals of assigned to the *anti* - conformer CH_2CO and =CH groups are upfield and downfield, respectively, as compared with the signals of the *syn* - conformer. The percentages of *anti* - and *syn* - conformers are calculated from the ratio of integral intensities of these signals. It was found that *syn* - conformers dominate in DMSO solution [12–14].

To continue the investigation of hydrazones obtained from 2,5-dimercapto-1,3,4-thiadiazole, the non-symmetric hydrazones 3 – 12 were synthesized (Figure 1).



3-12

3 R^1 = H, R^2 = 4-CH_3O-C_6H_4;
4 R^1 = H, R^2 = 2-HO-5-Br-C_6H_3;
5 R^1 = H, R^2 = 2-HO-3-CH_3O-C_6H_3;
6 R^1 = H, R^2 = 2-HO-C_6H_4;
7 R^1 = H, R^2 = 2,4-HO-C_6H_3;
8 R^1 = CH_3, R^2 = C_6H_5;
9 R^1 = CH_3, R^2 = 4-HO-C_6H_4;
10 R^1 = CH_3, R^2 = 2-CH_3O-C_6H_4;
11 R^1 = CH_3, R^2 = 2-HO-C_6H_4;
12 R^1 = CH_3, R^2 = 2,4-HO-C_6H_3;

Fig. 1 General pathway for the synthesis of hydrazones 3 – 12.

Analysis of ^{1}H NMR spectra revealed that the 2-OH is represented by two signals. The possible reason for such signal splitting is participation of the part of the 2-hydroxy group protons in an intramolecular hydrogen bond with the nitrogen atom of the imino group. It was demonstrated that the signal from hydroxy group shifts downfield upon formation of hydrogen bond and the extent of the shift increases with the strength of the hydrogen bonding interaction [15]. Apparently, the ^{1}H resonance of hydrazones 4 – 6 in the 9.36 – 10.4 ppm interval is associated with the 2-OH which does not participate in the formation of IMHB, while the resonance in the 10.54 – 10.99 ppm interval is associated with the 2-OH participating in the formation of IMHB (Figure 2, 3).

In the spectrum of hydrazone 7 obtained from 2,4-dihydroxybenzaldehyde, there are three signals associated with different hydroxy groups. The signals at 9.83, 9.98 and 11.06 ppm correspond to the 2-OH, 4-OH, and the 2-OH group forming an IMHB, respectively. In the ^{1}H NMR spectrum of hydrazone 11 obtained from 2'-hydroxyacetophenone two signals were observed, while three signals were resolved in the spectrum of hydrazone 12 obtained from 2',4'-dihydroxyacetophenone (Figure 3). Experiments performed with different hydrazone concentrations revealed that the chemical shifts and the ratios between integral intensities of the signals did not change in the concentration region of 0.01 − 0.5 M.

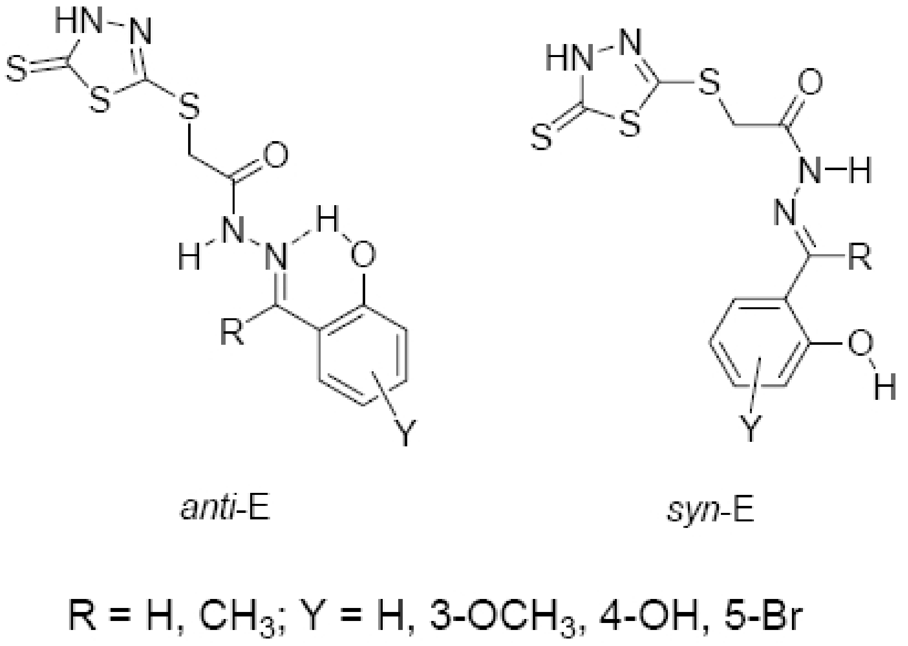


Fig. 2 *Anti* - and *syn* - conformers of hydrazones containing 2-OH group.

Table 1 summarizes the percentages of *anti* - conformers calculated from the integrated intensities of the corresponding signals. As expected, the portion of *anti* - conformers of the new hydrazones 4, 7, 11, and 12 possessing 2-hydroxy groups that can form IMHB in DMSO solution is larger (as judged from the ^{1}H NMR spectra) compared with that of hydrazones 3 and 8 − 10 which lack the possibility to form such bonds. As seen in Table 1, the percentage of *anti* - conformers for hydrazones 4 − 7 is consistent with the fraction of 2-OH group participation in IMHB. Thus, 2-OH participation in IMHB should be ascribed to the *anti* - conformer, while non-IMHB 2-OH groups should be ascribed to the *syn* - conformer.

It should be noted that in the ^{1}H NMR spectra of hydrazones 4 − 7 and 10 containing 2-substituted phenyl rings, the hydrogen at the sixth position of the phenyl ring (H-6) is represented also by two signals. We found that the ratio between the integrated intensities of these signals coincides with the ratio of *anti/syn* - conformers. The spectra of hydrazones 11 and 12 contained only one H-6 doublet, while the H-2 and H-6 signals of hydrazones 3, 8 and 9 are observed as multiplets or as two overlapped doublets. Due to the *anti/syn* - isomerism, methyl groups of hydrazones 9 − 12 obtained from methylketones are also appear as two singlets (Table 2) in the ^{1}H NMR spectra.

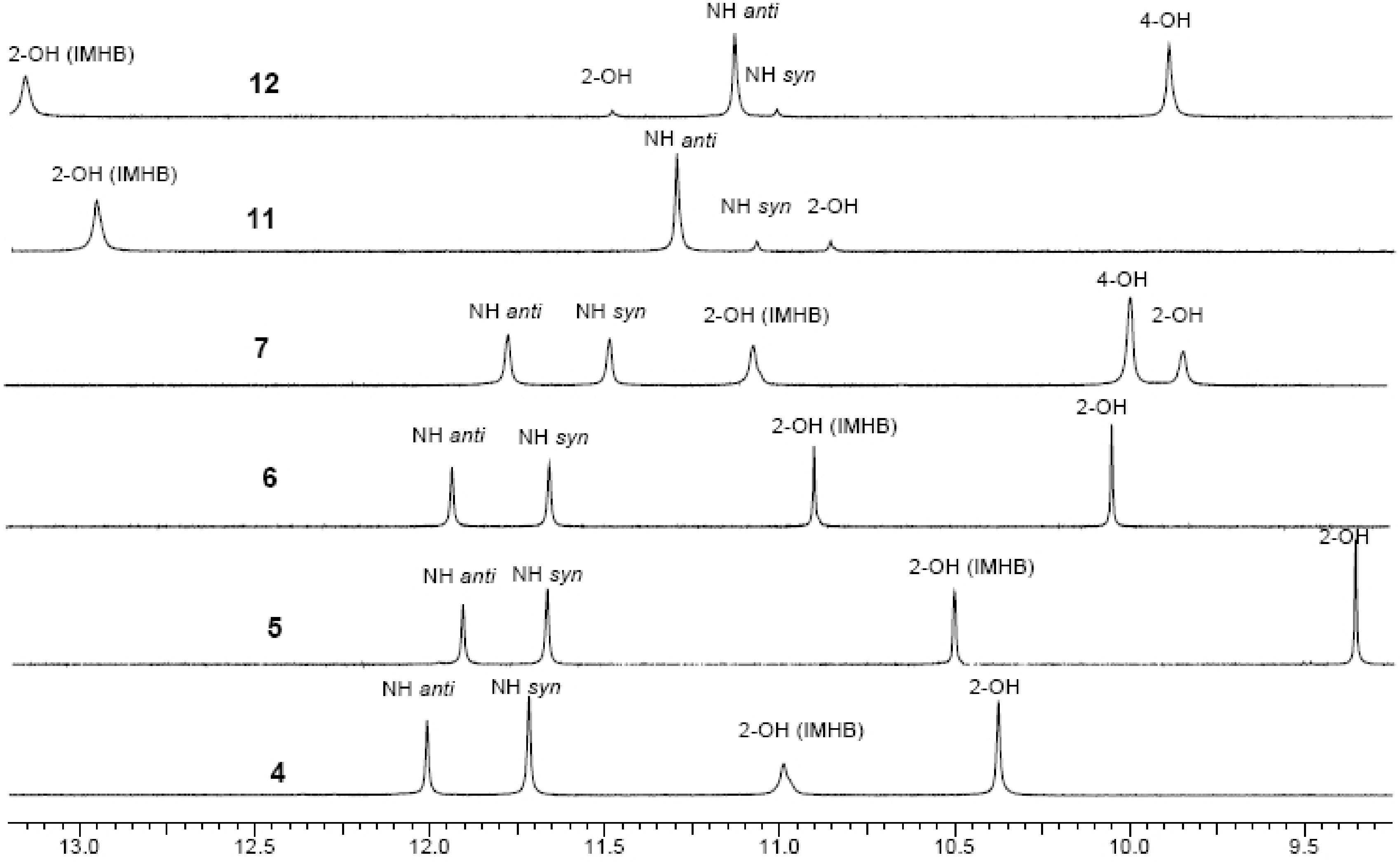


Fig. 3 Signals of OH and NH groups in ^{1}H NMR spectra of 4 – 7, 11, and 12 hydrazones in DMSO-d_6 solvent.

Table 1 Percentage of 2-OH group (participating in IMHB), H-6, and *anti* - conformers of hydrazones 3 – 12 in DMSO-d_6 solvent (29°C) determined from ^{1}H NMR integrations, and Mulliken charges of imino group nitrogen atoms.

Hydra -zone	2-OH, %[a] (IMHB)	H-6, %[a]	*Anti* – conformers, %[a] CH_2	CH	NH	Mulliken charges
3	-	-	32	32	-	−0.247820
4	43	43	43	43	43	−0.284151
5	44	44	44	45	45	−0.270750
6	48	48	48	48	48	−0.296148
7	56	56	56	55	55	−0.321991
8	-	-	30	-	30	−0.322894
9	-	-	32	-	32	−0.326432
10	-	32	32	-	32	−0.344677
11	91	-	91	-	91	−0.399575
12	93	-	93	-	92	−0.423371

[a] error – limits ± 1%

Table 2 Chemical shifts (δ/ppm) from ^{1}H NMR spectra (DMSO-d_6, 29°C) of *anti/syn* - conformers of hydrazones 3 – 12.

Hydr- azone	CH_3, s	CH_2, s	H-6, d (J Hz)	CH, s	2-OH, s	NH, s	Other chemical shifts
3 anti	-	4.02	-	8.12	-	11.58	6.98 (2d, J = 8.8 Hz, H-3,-5),
syn		4.44		7.98		11.58	7.62 (2d, J = 8.8 Hz, H-2,-6)
4 anti	-	4.04	7.75[a]	8.36	10.99	12.01	6.86 (m, H-3), 7.38 (m, H-4)
syn		4.48	7.81[a]	8.24	10.37	11.72	
5 anti	-	4.04	7.14 (7.9)	8.41	10.51	11.91	3.79, 3.80, (2s, OCH_3), 6.82
syn		4.45	7.27 (7.9)	8.34	9.36	11.67	(m, H-5), 7.00 (m, H-4)
6 anti	-	4.04	7.54 (7.7)	8.40	10.90	11.94	6.89 (m, H-3, -5),
syn		4.45	7.67 (7.7)	8.31	10.05	11.66	7.25 (m, H-4)
7 anti		4.03	7.30 (8.4)	8.26	11.06	11.76	6.31 (m, H-3, -5),
syn		4.43	7.45 (8.4)	8.18	9.86	11.47	9.98 (s, 4-OH)
8 anti	2.27	4.15	-	-	-	10.71	7.39 (m, H-3, -4, -5),
syn	2.25	4.50				10.98	7.78 (m, H-2, -6)
9 anti	2.20	4.11	-	-	-	10.56	6.77 (d, J = 8.8 Hz, H-3,-5),
syn	2.18	4.46				10.79	7.62 (2d, J = 8.8 Hz, H-2,-6), 9.76 (s, 4-OH)
10 anti	2.17	4.13	7.25 (7.5)	-	-	10.62	3.79 (s, OCH_3), 6.95 (m, H-5),
syn	2.15	4.39	-			10.88	7.05 (d, J = 8.2 Hz, H-3), 7.34 (m, H-4, -6[b])
11 anti	2.37	4.18	7.59 (8.2)	-	12.96	11.30	6.89 (m, H-3, -5),
syn	2.29	4.46	7.59 (8.2)		10.86	11.07	7.28 (m, H-4)
12 anti	2.29	4.14	7.39 (8.8)	-	13.15	11.13	6.24 (s, H-3), 6.30 (d, J = 8.8
syn	2.26	4.43	7.39 (8.8)		11.48	11.01	Hz, H-5), 9.89 (s, 4-OH)

[a] singlet

[b] *syn* - conformer

We have calculated the negative Mulliken charges of the nitrogen atom within the imino groups for the *anti* - conformers of hydrazones 3 – 12 by optimizing the structure with the PM6 method (Mopac2007 [16]). To account for the solvation effects, we have employed the COSMO approach [17] (DMSO $\varepsilon = 46.7$). A linear relationship was found between the calculated imino group nitrogen charges and the experimentally observed portion of *anti* - conformers for the 4 – 7, 11 and 12 hydrazones (Figure 4).

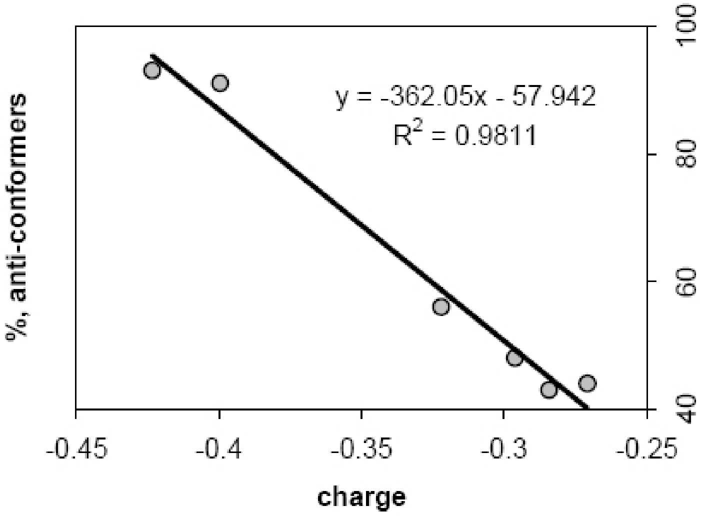


Fig. 4 Dependence of the percentage of hydrazones 4 – 7, 11, and 12 *anti* - conformers on the Mulliken charge on the imino group nitrogen atom.

The magnitude of the charge depends on the nature of substituents both on the phenyl ring and imino group. Replacement of a hydrogen by a methyl group at the imino site (11 and 12 hydrazones) results in an increased negative charge on the nitrogen atom and an increase of the portion of *anti* - conformers. In the case of the 3 and 8 – 10 hydrazones, the imino groups exhibit a charge on the nitrogen atom that depends on the nature of the substituents. However, the portion of *anti* - conformers (30 – 32%) is relatively unaffected for all the studied compounds. For hydrazones containing 2-OH substituents (4 – 7, 11, and 12) the strength of the IMHB must increase with the negative charge on the nitrogen atom of the imino group. Thus, based on the above considerations, we conclude that the stability of the *anti* - conformers in DMSO solution critically depends on the strength of the IMHB.

3 Conclusions

This work showed that by strengthening the intramolecular hydrogen bond the percentage of *anti* - conformer increases. This means that *anti* - conformers of hydrazones of 2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetohydrazide in DMSO are stabilized by IMHB. This bond is strengthened not only by substitution at the phenyl ring but also by the presence of a methyl group at the imino site. In DMSO solution, the *anti*-conformers of hydrazones (obtained from 2'-hydroxyacetophenones) that possess three complexation sites, i.e., then oxygen of amido group, the oxygen of the 2-OH group, and the nitrogen of the imino group predominate. These species should bind iron(III) cations by forming monomeric structures.

4 Experimental

4.1 General

^{1}H NMR spectra were recorded on a Varian Unity Inova NMR spectrometer operating at a ^{1}H frequency of 299.75 MHz. ^{1}H NMR spectra were acquired with 16 scans, 5999.25 Hz spectral width, 0.8 s relaxation decay. Data were zerofilled up to 32k, apodized with a 0.2 Hz exponential line broadening function and Fourier transformed. An auto phase and a baseline optimization were applied using the ACDLabs SpecManager 4.0 software [18]. The same software was used to integrate the signals. The integration range was determined manually. The compounds were identified by microanalysis. Methyl 2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetate (1) was obtained according to the procedure described in [19].

4.2 Synthesis of initial hydrazide

2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetohydrazide (2)

A mixture of 11.1 g 1 (0.05 mol), 7.5 g hydrazine hydrate (0.15 mol) and 100 mL 2-propanol was refluxed for 2 h. The solvent was evaporated. The residue was dissolved in 50 mL of water, filtered and acidified with dilute (1:1) HCl to pH∼5. The precipitate was filtered and washed with water to obtain 8.5 g (77%) of 2. M.p.: $145-146$°C. Found: C, 21.45; H, 2.94; N, 24.98%. Calcd. for $C_4H_6N_4OS_3$: C, 21.61; H, 2.72; N, 25.20%. ^{1}H NMR (DMSO-d_6): δ 3.83 (2H, s, CH_2) ppm.

4.3 General procedure for the synthesis of hydrazones (3-12)

A mixture of 5 mmoles of hydrazide 2, 30 mL of 1,4-dioxane, 10 mL of water, and 5 mmoles of aldehyde or ketone was stirred for 3 h at 85°C. The 1,4-dioxane was partially driven off, and then the crystals of products were filtered off and washed with water and 1,4-dioxane.

4.3.1 N'-(4-methoxybenzylidene)-2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetohydrazide (3)

From 2 and 4-methoxybenzaldehyde; yield: 41%; m.p.: $202-203$°C. Found: C, 42.12; H, 3.43; N, 16.60%. Calcd. for $C_{12}H_{12}N_4O_2S_3$: C, 42.34; H, 3.55; N, 16.46%.

4.3.2 N'-(5-bromo-2-hydroxybenzylidene)-2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetohydrazide (4)

From 2 and 5-bromo-2-hydroxybenzaldehyde; yield 90%; m.p.: $225-226$°C. Found: C, 32.29; H, 2.12; N, 13.58%. Calcd. for $C_{11}H_9BrN_4O_2S_3$: C, 32.60; H, 2.24; N, 13.82%.

4.3.3 N'-(2-hydroxy-3-methoxybenzylidene)-2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetohydrazide (5)

From 2 and 2-hydroxy-3-methoxybenzaldehyde; yield 45%; m.p.: $219-220$°C. Found: C, 40.15; H, 3.20; N, 15.49%. Calcd. for $C_{12}H_{12}N_4O_3S_3$: C, 40.44; H, 3.39; N, 15.72%.

4.3.4 N'-(2-hydroxybenzylidene)-2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetohydrazide (6)

From 2 and 2-hydroxybenzaldehyde; yield: 80%; m.p.: $206-208$°C. Found: C, 40.31; H, 2.88; N, 16.95%. Calcd. for $C_{11}H_{10}N_4O_2S_3$: C, 40.48; H, 3.09; N, 17.16%.

4.3.5 N'-(2,4-dihydroxybenzylidene)-2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio) acetohydrazide (7)

From 2 and 2,4-dihydroxybenzaldehyde; yield: 24%; m.p.: $206-207$°C. Found: C, 38.36; H, 3.15; N, 16.18%. Calcd. for $C_{11}H_{10}N_4O_3S_3$: C, 38.58; H, 2.94; N, 16.36%.

4.3.6 N'-(1-phenylethylidene)-2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetohydrazide (8)

From 2 and acetophenone; yield 62%; m.p.: 228°C. Found: C, 44.60; H, 3.51; N, 17.00%. Calcd. for $C_{12}H_{12}N_4OS_3$: C, 44.42; H, 3.73; N, 17.27%.

4.3.7 N'-(1-(4-hydroxyphenyl)ethylidene)-2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetohydrazide (9)

From 2 and 4'-hydroxyacetophenone; yield 30%; m.p.: $216-217$°C. Found: C, 42.53; H, 3.41; N, 16.20%. Calcd. for $C_{12}H_{12}N_4O_2S_3$: C, 42.34; H, 3.55; N, 16.46%.

4.3.8 N'-(1-(2-methoxyphenyl)ethylidene)-2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetohydrazide (10)

From 2 and 2'-methoxyacetophenone; yield 57%; m.p.: $160-161$°C. Found: C, 44.26; H, 3.75; N, 15.63%. Calcd. for $C_{13}H_{14}N_4O_2S_3$: C, 44.05; H, 3.98; N, 15.81%.

4.3.9 N'-(1-(2-hydroxyphenyl)ethylidene)-2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetohydrazide (11)

From 2 and 2'-hydroxyacetophenone; yield 41%; m.p.: $237-238$°C. Found: C, 42.52; H, 3.68; N, 16.25%. Calcd. for $C_{12}H_{12}N_4O_2S_3$: C, 42.34; H, 3.55; N, 16.46%.

4.3.10 N'-(1-(2,4-dihydroxyphenyl)ethylidene)-2-(5-thioxo-4,5-dihydro-1,3,4-thiadiazol-2-ylthio)acetohydrazide (12)

From 2 and 2',4'-dihydroxyacetophenone; yield 34%; m.p.: $193-194$°C. Found: C, 40.61; H, 3.57; N, 15.89%. Calcd. for $C_{12}H_{12}N_4O_3S_3$: C, 40.44; H, 3.39; N, 15.72%.

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