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Study of Direction of Cyclization of 1-Azolil-4-Aryl/Alkyl-Thiosemicarbazides

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ABSTRACT: *On a four series of 1-azolil-4-aryl/alkyl-thiosemicabazides, a study on the influence of azole moiety on the capability for intramolecular cyclization and its direction was carried out. It was found that for 4-aryl/alkyl-thiosemicabazides with triazole, imidazole, or pyrrole moiety at N-1 nitrogen atom possible products were only s-triazoles, both in alkaline and acidic medium. Successful dehydrocyclization of 1-azolil-4-aryl/alkyl-thiosemicarbazides leading to a thiadiazole has been documented only for a series of 1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-4-aryl/alkyl-thiosemicarbazides. It can be speculative that the determination of pK_a value of oxygen atom of 1-azolil-4-aryl/alkyl-thiosemicarbazide can be a very valuable parameter in the prediction of the possibility of dehydrocyclization to form thiadiazole.* © 2010 Wiley Periodicals, Inc. Heteroatom Chem 21:521–532, 2010; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20643

INTRODUCTION

Reactions of dehydrocyclization of 1,4-disubstituted thiosemicarbazides are of growing interest in synthetic organic chemistry because they allow rapid construction of several biologically active heterocycles such as 1,2,4-triazoles, 1,3,4-thiadiazoles, 1,3,4-oxadiazoles, or 2-thiohydantoines in a single operation [1]. The compounds have been studied as antimicrobial [2], antiviral [3], antitumor [3f,4], antidepressant [1f,5], antiinflammatory [2b,5a,6], analgesic [2b,6d,7], anti-Parkinson's [8], and antiasthmatic [9] agents.

It is well recognized that the cyclization of 1,4-disubstituted thiosemicarbazides in an alkaline medium results in the formation of *s*-triazoles, whereas in acidic medium 1,3,4-thiadiazoles are formed [1a-1f]. Results from our laboratory, however, show that in such reactions possible products are only *s*-triazoles, both in alkaline and acidic medium. In continuation of our interest in the synthesis of novel *s*-triazoles and thiadiazoles of potential biological importance, we report here the influence of azole moiety on the direction of ring closure of 1-azolil-4-aryl/alkyl-thiosemicarbazides.

RESULTS AND DISCUSSION

The influence of azole moiety on the direction of ring closure of 4-aryl/alkyl-thiosemicarbazides was studied for four series of 1-azolil-4-aryl/alkyl-thiosemicarbazides (**1–6, 13–18, 23–26**, and **31–36**). The rational design of these compounds was planned by the acidic-base properties of the azole ring, and the following heterocarboxylic acid hydrazides

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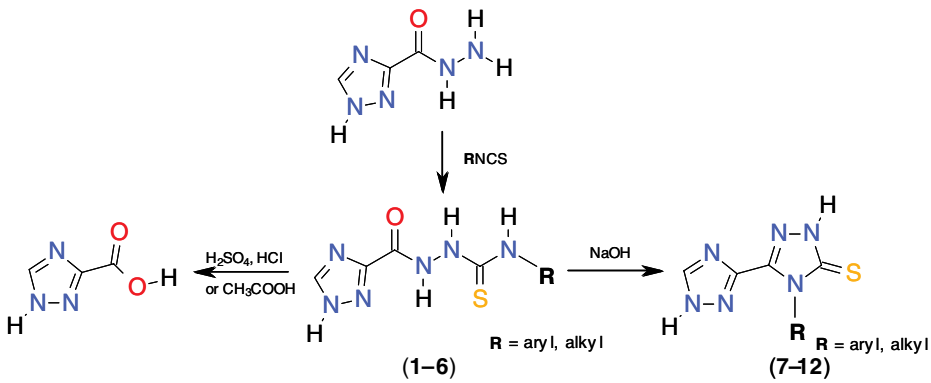
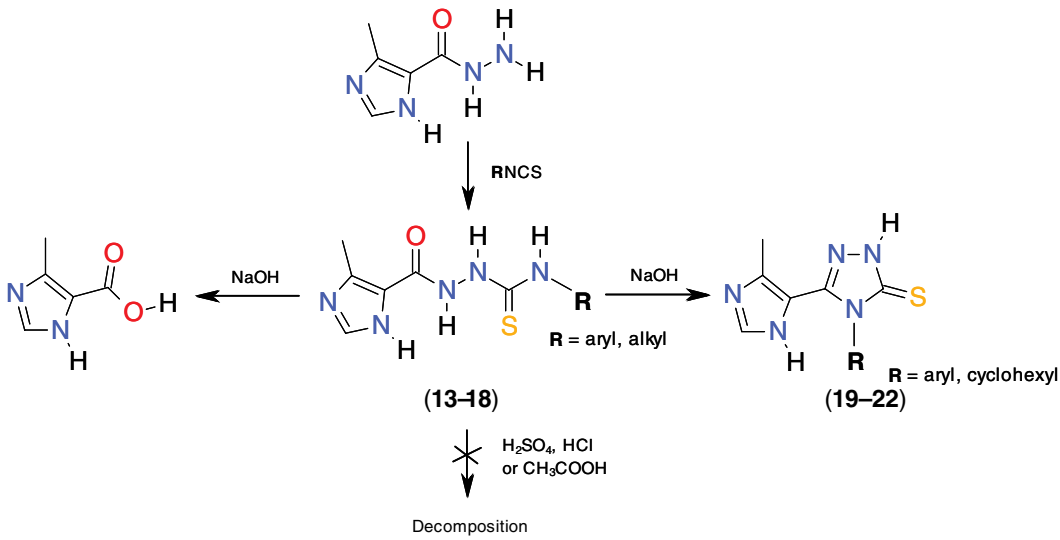


SCHEME 1 Direction of reaction of 1-(1,2,4-triazol-3-yl-carbonyl)-4-aryl/alkyl-thiosemicarbazides (**1–6**) in alkaline and acidic medium.

were used as starting materials: 1,2,4-triazole-3-carboxylic acid hydrazide, 4-methyl-imidazole-5-carboxylic acid hydrazide, pyrrole-2-carboxylic acid hydrazide, and 4-methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide. The compounds in the reaction with aromatic or aliphatic isothiocyanates gave 1-azolil-4-aryl/alkyl-thiosemicarbazides (**1–6, 13–18, 23–26**, and **31–36**). Next, acid/base-catalyzed dehydrocyclization of the compounds was examined. Thus, the compounds **1–6, 13–18, 23–26**, and **31–36** were treated with aqueous sodium hydroxide, aqueous hydrochloric acid, glacial acetic acid, or concentrated sulfuric acid.

As first, the influence of the 1,2,4-triazole moiety at N-1 nitrogen atom of 4-aryl/alkyl-thiosemicarbazides (**1–6**) on the direction of ring closure was tested. As shown in Scheme 1, base-catalyzed dehydrocyclization of 1-(1,2,4-triazol-3-yl-carbonyl)-4-aryl/alkyl-thiosemicarbazides (**1–6**) leads to the formation of *s*-triazoles (**7–12**), whereas in acidic medium unexpected product 1,2,4-triazole-3-carboxylic acid was formed.

Next, the direction of cyclization of 1-(4-methyl-imidazol-5-yl-carbonyl)-4-aryl/alkyl-thiosemicarbazides (**13–18**) was studied (see Scheme 2). *s*-Triazoles (**19–22**) were obtained as a product of dehydrocyclization of 1-(4-methyl-imidazol-5-yl-carbonyl)-4-aryl/cyclohexyl-thiosemicarbazides (**13–16**) in alkaline medium. Under the same experimental conditions,4-methyl-imidazole-5-carboxylic acid was obtained when 1-(4-methyl-imidazol-5-yl-carbonyl)-4-alkyl-thiosemicarbazides



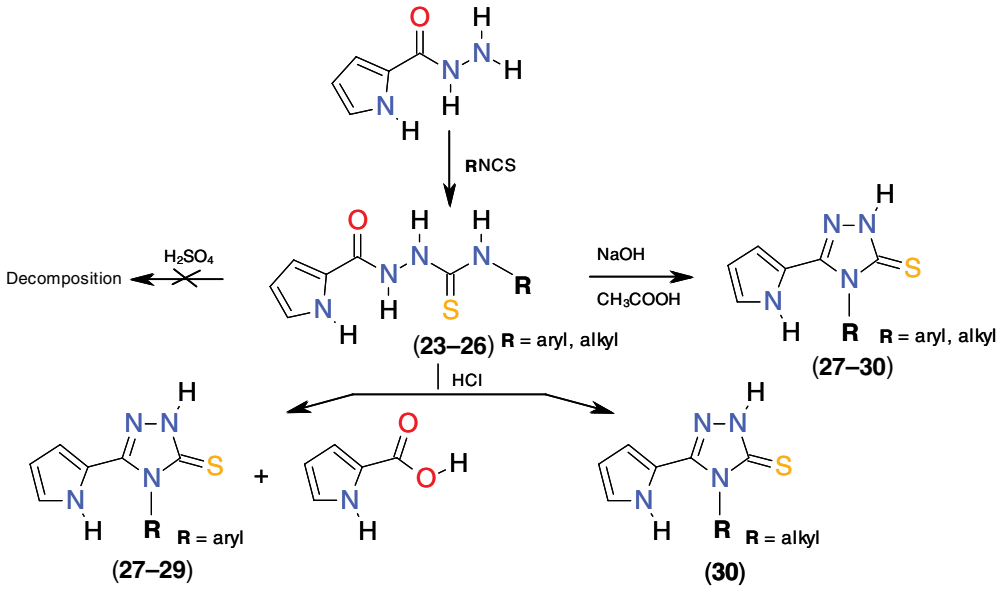
SCHEME 2 Direction of reaction of 1-(4-methyl-imidazol-5-yl-carbonyl)-4-aryl/alkyl-thiosemicarbazides (**13–18**) in alkaline and acidic medium.

(**17**) and (**18**) were used in the reaction. In acidic conditions for all thiosemicarbazides (**13–18**), the process of decomposition has taken place.

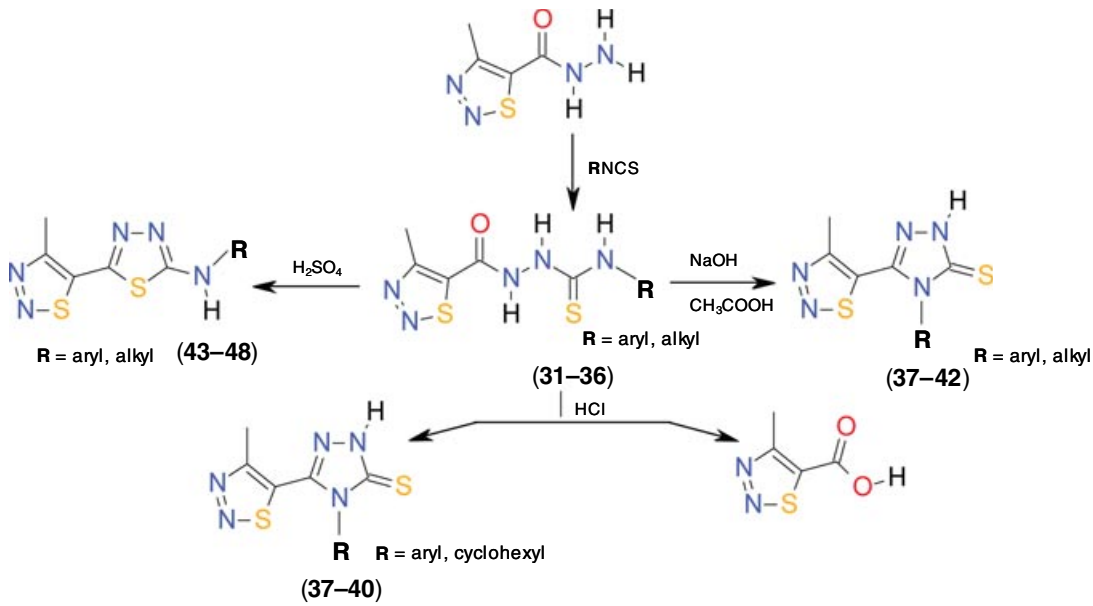
The influence of the pyrrole moiety at N-1 nitrogen atom of 4-aryl/alkyl-thiosemicarbazides (**23–26**) on the direction of ring closure was studied next (see Scheme 3). Both base-catalyzed and acid-catalyzed (hydrochloric acid or glacial acetic acid) dehydrocyclization of 1-(pyrrol-2-yl-carbonyl)-4-aryl/alkyl-thiosemicarbazides (**23–26**) gave compounds with *s*-triazole ring (**27–30**). When 1-(pyrrol-2-yl-carbonyl)-4-aryl-thiosemicarbazides (**23–25**) were refluxed with aqueous hydrochloric acid, pyrrole-2-carboxylic acid was obtained as a side product, which was removed by dissolving in sodium hydrocarbonate. The process of decomposition took place during dehydrocyclization of all thiosemicarbazides (**23–26**) in the presence of concentrated sulfuric acid.

The first successful intramolecular cyclization of 1-azolil-4-aryl/alkyl-thiosemicarbazides leading to a thiadiazole has been documented for a series of 1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-4-aryl/alkyl-thiosemicarbazides (**31–36**); see Scheme 4. Compounds with thiadiazole ring (**43–48**) were obtained then 1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-4-aryl/alkyl-thiosemicarbazides (**31–36**) were treated with concentrated sulfuric acid. Refluxing of thiosemicarbazides (**31–36**) with aqueous sodium hydroxide or glacial acetic acid gave *s*-triazoles (**37–42**). Compounds with *s*-triazole ring (**37–40**) were also obtained than 1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-4-aryl/cyclohexyl-thiosemicarbazides (**31–34**) were treated with aqueous hydrochloric acid. Under the same experimental conditions, 4-methyl-1,2,3-thiadiazol-5-carboxylic acid was obtained when 1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-4-alkyl-thiosemicarbazides (**35**) and (**36**) were used in the reaction.

The characterization of the all synthesized compounds was based on the elementary analysis, IR, and ^{1}H NMR spectra. The infrared spectra of thiosemicarbazides (**1–6, 13–18, 23–26**, and **31–36**) exhibited a characteristic strong absorption at 1353–1166 cm^{-1}attributable to the C=S. The carbonyl absorption in these compounds was observed at 1679–1620 cm^{-1}, which was eliminated by the formation of their cyclic analogs, *s*-triazoles (**7–12, 19–22, 27–30**, and **37–42**), and thiadiazoles (**43–48**). In the IR spectra of *s*-triazoles (**7–12, 19–22, 27–30**, and **37–42**), the presence of C=S in the region 1335–1220 cm^{-1} and NH at 3462–3220 cm^{-1}indicates that the compounds are in their thione rather than the thiol form. The ^{1}H NMR spectra of thiosemicarbazides (**1–6, 13–18, 23–26**, and **31–36**) displayed the NH—NH—C(=S)—NH resonances in the range 10.92–7.30 ppm. The ^{1}H NMR spectra of *s*-triazoles (**7–12, 19–22, 27–30**, and **37–42**) and thiadiazoles (**43–48**) gave proton signal typical for NH in the



SCHEME 3 Direction of reaction of 1-(pyrrol-2-yl-carbonyl)-4-aryl/alkyl-thiosemicarbazides (**23–26**) in alkaline and acidic medium.



SCHEME 4 Direction of reaction of 1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-4-aryl/alkyl-thiosemicarbazides (**31**–**36**) in alkaline and acidic medium.

range 14.78–13.13 ppm and 10.85–8.32 ppm, respectively. All signals derived from NH groups disappeared after D_2O exchange.

The dominance of C=S form for *s*-triazoles (**7–12, 19–22, 27–30**, and **37–42**) and structures of obtained thiadiazoles (**43–48**) were confirmed on the basis of the X-ray analysis of two compounds **42** and **47** that were prone to crystallization. A perspective view of **42** and **47** including the atomic numbering scheme is shown in Figure 1.

All series of thiosemicarbazides tested (**1–6, 13–18, 23–26**, and **31–36**) possessed an azole subunit at N-1 nitrogen atom and aryl or alkyl moiety at N-4 nitrogen atom. Only 1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-4-aryl/alkyl-thiosemicarbazides (**31–36**), however, could be cyclized to form thiadiazoles (**43–48**). Thus, it can be suggested that the direction of cyclization of 1-azolilo-4-aryl/alkyl-thiosemicarbazides is highly dependent on the acidic-base properties of the azole subunit. To test this hypothesis, pK_a values of oxygen, sulfur, and nitrogen atoms of thiosemicarbazides (**1–6, 13–18, 23–26**, and **31–36**) were determined using the same procedure as described previously [1k]. As illustrated in Table 1, among four series of thiosemicarbazides, 1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-4-aryl/alkyl-thiosemicarbazides (**31–36**) possessed the lowest pK_a values at the oxygen atom, whereas

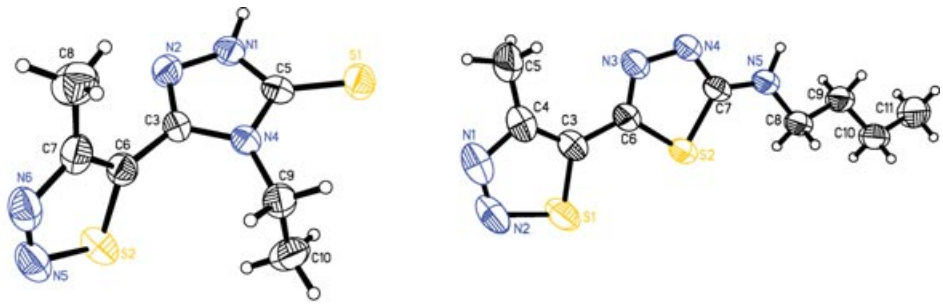
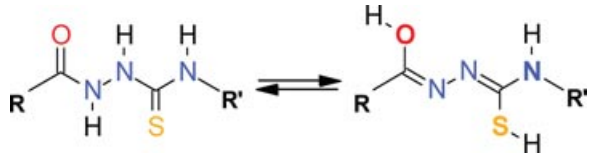


FIGURE 1 Molecular structures of **42** and **47**; both compounds (**42** and **47**) crystallize in the monoclinic system, space group $P2_1/n$; for **42**: $a = 10.433(2)$, $b = 7.975(2)$, $c = 13.100(3)$ Å, $\alpha = 90$, $\beta = 110.70(3)$, $\gamma = 90^\circ$, for **47**: $a = 5.222(1)$, $b = 15.010(3)$, $c = 15.343(3)$ Å, $\alpha = 90$, $\beta = 93.30(3)$, $\gamma = 90^\circ$.

TABLE 1 pK_a Values of Oxygen, Sulfur, and Nitrogen Atoms of 1-Azolil-4-aryl/alkyl-thiosemicarbazides (**1–6, 13–18, 23–26**, and **31–36**)



Comp. No	*OH*	*SH*	*NH*
1	5.0	7.6	12.2
2	4.7	7.5	12.8
3	4.5	7.3	12.1
4	5.1	7.8	20.7
5	5.0	7.8	20.7
6	4.9	7.7	20.6
13	6.9	7.7	12.3
14	6.8	7.7	12.7
15	6.4	7.5	10.1
16	7.0	7.9	20.7
17	6.8	7.9	20.6
18	6.8	7.8	20.6
23	7.0	7.7	12.8
24	6.7	7.5	12.1
25	6.8	7.5	10.1
26	7.3	8.0	20.6
31	2.9	7.4	12.3
32	3.0	7.4	12.5
33	2.5	7.2	10.1
34	3.0	7.6	20.7
35	2.9	7.6	20.7
36	2.7	7.5	20.6

pK_a values at sulfur and nitrogen atom were comparable for all thiosemicarbazides tested.

CONCLUSION

Based on our experiments, it can be hypothesized that the determination of pK_a values of an oxygen atom of 1-azolil-4-aryl/alkyl-thiosemicarbazide can be a very valuable parameter in the prediction of possibility of its cyclization to form thiadiazole. It will be interesting to examine this hypothesis for 4-aryl/alkyl-thiosemicarbazides with six/condensed-heterocycle ring at N-1 nitrogen atom.

EXPERIMENTAL

Chemistry

All commercial reactants and solvents were purchased from either Sigma-Aldrich or Lancaster with the highest purity and used without further purification. Melting points were determined on a Fischer–Johns block and are uncorrected. Elemental analyses were determined by a AMZ-CHX elemental analyzer (are within ± 0.4% of the theoretical values). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker Avance (300 MHz) spectrometer. All spectra were recorded at 25°C in DMSO-d_6 using solvent methyl group signal as the internal standard (δ_H 2.50). Splitting patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet. Analytical thin layer chromatography (TLC) was performed with Merc 60F_{254} silica gel plates and visualized by UV irradiation (254 nm). The structures of 4-phenyl-1-(1,2,4-triazol-3-yl-carbonyl)-thiosemicarbazide (**1**), 4-ethyl-1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-thiosemicarbazide (**36**), 4-ethyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)-*s*-triazole-3-thione (**42**), and 4-methyl-imidazole-5-carboxylic acid were confirmed by the results of elemental analysis, melting points, and spectroscopic data compared to literature values [10]. 1,2,4-Triazole-3-carboxylic acid, pyrrole-2-carboxylic acid, and 4-methyl-1,2,3-thiadiazole-5-carboxylic acid are commercially available.

*Synthesis of 1-Azolil-4-alkyl/aryl-thiosemicarbazides (***1–6, 13–18, 23–26***, and* **31–36***)*

Method for Compounds **1–6** *and* **31–36**. A reaction mixture of 1,2,4-triazole-3-carboxylic acid hydrazide (0.01 mol) or 4-methyl-1,2,3-thiadiazole-5-carboxylic acid hydrazide (0.01 mol) and related isothiocyanate (0.01 mol) in diethyl ether was stirred at room temperature and progress of the reaction was monitored by TLC. After two weeks, the reaction was completed, and crude reaction mixture was washed with diethyl ether and crystallized from ethanol.

Method for Compounds **13–18** *and* **23–26**. A reaction mixture of 4-methyl-imidazol-5-carboxylic acid hydrazide (0.01 mol) or pyrrole-2-carboxylic acid hydrazide (0.01 mol) and related isothiocyanate (0.01 mol) was heated in an oil bath at 80°C, and the progress of reaction was monitored by TLC. After 12 h, the reaction was completed and crude reaction mixture was washed with diethyl ether and crystallized from ethanol.

*4-(4-Methoxyphenyl)-1-(1,2,4-triazol-3-yl-carbonyl)-thiosemicarbazide (***2***)*. Yield 55%, mp 231–233°C; IR (KBr, ν in cm^{-1}): 3301, 3217 (NH), 3112, 1591, 1511, 1462, 855 (ArH), 1445 (Aliph.), 1674 (C=O), 1178 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.75 (s, 3H, OCH_3), 6.85–6.91 (m, 2H, 2×CH), 7.36–7.46 (m, 2H, 2×CH), 8.63 (s, 1H, CH), 9.55,

9.70, 14.39 (3s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_{12}N_6O_2S$: C, 45.20; H, 4.14; N, 28.75. Found: C, 45.12; H, 3.84; N, 28.96.

*4-(4-Bromophenyl)-1-(1,2,4-triazol-3-yl-carbonyl)-thiosemicarbazide (***3***).* Yield 62%, mp 183–185°C; IR (KBr, ν in cm^{-1}): 3300, 3225 (NH), 3100, 1596, 1510, 1461, 860 (ArH), 1670 (C=O), 1166 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 7.43–7.53 (m, 4H, 4×CH), 8.74 (s, 1H, CH), 9.82, 10.48, 14.56 (3s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_{10}H_9BrN_6OS$: C, 35.20; H, 2.66; N, 24.63. Found: C, 34.72; H, 2.33; N, 24.81.

*4-Cyclohexyl-1-(1,2,4-triazol-3-yl-carbonyl)-thiosemicarbazide (***4***).* Yield 58%, mp 231–233C; IR (KBr, ν in cm^{-1}): 3301, 3241 (NH), 2931, 2852, 1479 (Aliph.), 1674 (C=O), 1267 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 1.07–1.80 (m, 10H, 5×CH_2), 4.07 (s, 1H, CH), 8.43 (s, 1H, CH), 7.35, 9.17, 9.81, 14.49 (4s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_{10}H_{16}N_6OS$: C, 44.76; H, 6.01; N, 31.32. Found: C, 44.38; H, 6.14; N, 31.55.

*4-Butyl-1-(1,2,4-triazol-3-yl-carbonyl)-thiosemicarbazide (***5***).* Yield 49%, mp 233–235°C; IR (KBr, ν in cm^{-1}): 3300, 3222 (NH), 2955, 2920, 2860, 1470, 1395 (Aliph.), 1670 (C=O), 1180 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 0.80–0.91 (t, 3H, CH_3), 1.14–1.54 (m, 4H, 2×CH_2), 3.38–3.45 (m, 2H, CH_2), 8.43 (s, 1H, CH), 7.40, 9.21, 9.85, 14.50 (4s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_8H_{14}N_6OS$: C, 39.66; H, 5.82; N, 34.68. Found: C, 39.51; H, 6.03; N, 34.47.

*4-Ethyl-1-(1,2,4-triazol-3-yl-carbonyl)-thiosemicarbazide (***6***).* Yield 44%, mp 240–242°C; IR (KBr, ν in cm^{-1}): 3333, 3189 (NH), 2953, 2961, 2861, 1469, 1390 (Aliph.), 1671 (C=O), 1186 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 1.05–1.10 (t, 3H, CH_3), 3.40–3.52 (q, 2H, CH_2), 8.44 (s, 1H, CH), 7.30, 9.22, 9.85, 14.46 (4s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_6H_{10}N_6OS$: C, 33.64; H, 4.70; N, 39.23. Found: C, 33.39; H, 4.51; N, 39.20.

*1-(4-Methyl-imidazol-5-yl-carbonyl)-4-phenyl-thiosemicarbazide (***13***).* Yield 62%, mp 204–206°C; IR (KBr, ν in cm^{-1}): 3202 (NH), 3100, 1595, 1520, 899, 735, 690 (ArH), 2980, 1470, 1390 (Aliph.), 1675 (C=O), 1215 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 2.45 (s, 3H, CH_3), 7.09–7.14 (t, 1H, CH), 7.28–7.33 (m, 2H, 2×CH), 7.49–7.53 (m, 2H, CH), 7.62 (s, 1H, CH), 9.57, 9.75, 12.38 (3s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_{13}N_5OS$: C, 52.35; H, 4.76; N, 25.44. Found: C, 52.17; H, 4.54; N, 25.52.

*1-(4-Methyl-imidazol-5-yl-carbonyl)-4-(4-methyl-phenyl)-thiosemicarbazide (***14***).* Yield 65%, mp 205–207°C; IR (KBr, ν in cm^{-1}): 3194 (NH), 1591, 1541, 1518, 819 (ArH), 2962, 1417, 1383 (Aliph.), 1673 (C=O), 1192 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 7.09–7.12 (d, 2H, 2×CH), 7.34–7.36 (d, 2H, 2×CH), 7.61 (s, 1H, CH), 9.49, 9.71, 12.37 (3s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_{13}H_{15}N_5OS$: C, 53.96; H, 5.23; N, 24.20. Found: C, 54.14; H, 5.05; N, 24.16.

*4-(2-Fluorophenyl)-1-(4-Methyl-imidazol-5-yl-carbonyl)-Thiosemicarbazide (***15***).* Yield 71%, mp 218–220°C; IR (KBr, ν in cm^{-1}): 3171 (NH), 1620, 1588, 1504, 1452, 733 (ArH), 2926, 1415 (Aliph.), 1660 (C=O), 1206 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 2.45 (s, 3H, CH_3), 7.13–7.52 (m, 4H, 4×CH), 7.61 (s, 1H, CH), 9.31, 9.69, 9.82, 12.38 (4s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_{12}FN_5OS$: C, 49.14; H, 4.12; N, 23.88. Found: C, 49.32; H, 3.95; N, 23.51.

*4-Cyclohexyl-1-(4-methyl-imidazol-5-yl-carbonyl)-thiosemicarbazide (***16***).* Yield 73%, mp 150–152°C; IR (KBr, ν in cm^{-1}): 3227 (NH), 2931, 2854, 1450, 1391, 732 (Aliph.), 1658 (C=O), 1197 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 1.03–1.80 (m, 10H, 5×CH_2), 2.43 (s, 3H, CH_3), 4.06 (s, 1H, CH), 7.60 (s, 1H, CH), 7.37, 9.11, 9.54, 12.37 (4s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_{19}N_5OS$: C, 51.22; H, 6.81; N, 24.89. Found: C, 51.14; H, 6.42; N, 24.97.

*4-Ethyl-1-(4-methyl-imidazol-5-yl-carbonyl)-thiosemicarbazide (***17***).* Yield 71%, mp 259–261°C; IR (KBr, ν in cm^{-1}): 3300 (NH), 2930, 2874, 1455, 1375, 731 (Aliph.), 1651 (C=O), 1200 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 1.02–1.07 (t, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.40–3.49 (m, 2H, CH_2), 7.60 (s, 1H, CH), 7.77, 9.06, 9.55, 12.36 (4s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_8H_{13}N_5OS$: C, 42.27; H, 5.77; N, 30.81. Found: C, 41.83; H, 5.19; N, 30.96.

*4-Methyl-1-(4-methyl-imidazol-5-yl-carbonyl)-thiosemicarbazide (***18***).* Yield 64%, mp 302–304°C; IR (KBr, ν in cm^{-1}): 3280 (NH), 2962, 2851, 1455, 1375 (Aliph.), 1656 (C=O), 1235 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 2.43 (s, 3H, CH_3), 2.85 (s, 3H, CH_3), 7.59 (s, 1H, CH), 7.76, 9.12, 9.57, 12.35 (4s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for

$C_7H_{11}N_5OS$: C, 39.42; H, 5.20; N, 32.84. Found: C, 39.11; H, 5.55; N, 32.91.

*4-(4-Methoxyphenyl)-1-(pyrrol-2-yl-carbonyl)-thiosemicarbazide (**23**).* Yield 88%, mp 164–166°C; IR (KBr, ν in cm^{-1}): 3255 (NH), 2872, 1459 (Aliph.), 1620 (C=O), 1582, 1499, 822 (ArH), 1331 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.74 (s, 3H, OCH_3), 6.11–6.14 (m, 1H, CH), 6.82–7.39 (m, 6H, 6×CH), 9.51, 9.65, 10.00, 11.62 (4s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_{13}H_{14}N_4O_2S$: C, 53.78; H, 4.86; N, 19.30. Found: C, 53.52; H, 4.55; N, 19.03.

*4-(4-Bromophenyl)-1-(pyrrol-2-yl-carbonyl)-thiosemicarbazide (**24**).* Yield 87%, mp 199–201°C; IR (KBr, ν in cm^{-1}): 3300, 3202 (NH), 3098, 1620, 1589, 1510, 828 (ArH), 1645 (C=O), 1344 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.13–6.16 (m, 1H, CH), 6.92–6.97 (m, 2H, 2×CH), 7.44–7.52 (m, 4H, 4×CH), 9.75, 9.84, 10.06, 11.66 (4s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_{11}BrN_4OS$: C, 42.49; H, 3.27; N, 16.52. Found: C, 42.18; H, 3.18; N, 16.77.

*4-(2-Fluorophenyl)-1-(pyrrol-2-yl-carbonyl)-thiosemicarbazide (**25**).* Yield 92%, mp 196–198°C; IR (KBr, ν in cm^{-1}): 3320, 3280 (NH), 3057, 1602, 1510, 1459, 740 (ArH), 1623 (C=O), 1353 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.11–6.14 (m, 1H, CH), 6.92–6.95 (m, 2H, 2×CH), 7.13–7.34 (m, 4H, 4×CH), 9.58, 9.78, 10.12, 11.66 (4s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_{11}FN_4OS$: C, 51.79; H, 3.98; N, 20.13. Found: C, 51.50; H, 4.05; N, 19.96.

*4-Ethyl-1-(pyrrol-2-yl-carbonyl)-thiosemicarbazide (**26**).* Yield 79%, mp 214–216°C; IR (KBr, ν in cm^{-1}): 3359, 3253 (NH), 2977, 1443 (Aliph.), 1642 (C=O), 1341 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.02–1.07 (t, 3H, CH_3), 3.40–3.50 (m, 2H, CH_2), 6.10–6.13 (m, 1H, CH), 6.88–6.94 (m, 2H, 2×CH), 8.02, 9.14, 9.82, 11.60 (4s, 4H, 4×NH, D_2O exchangeable). Anal. Calcd for $C_8H_{12}N_4OS$: C, 45.27; H, 5.70; N, 26.39. Found: C, 45.34; H, 5.26; N, 26.79.

*4-Phenyl-1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-thiosemicarbazide (**31**).* Yield 89%, mp 163–165°C; IR (KBr, ν in cm^{-1}): 3270 (NH), 3096, 1585, 1490, 1485, 900, 752, 700 (ArH), 2970, 2882, 1462, 1371 (Aliph.), 1673 (C=O), 1240 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.85 (s, 3H, CH_3), 7.16–7.44 (m, 5H, 5×CH), 9.87, 9.95, 10.85 (3s, 3H, 3×NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_{11}N_5OS_2$: C, 45.03; H, 3.78; N, 23.87. Found: C, 44.86; H, 3.70; N, 23.55.

*4-(2-Methylphenyl)-1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-thiosemicarbazide (**32**).* Yield 92%, mp 108–110°C; IR (KBr, ν in cm^{-1}): 3266 (NH), 3089, 1586, 1494, 1459, 736 (ArH), 2946, 2873, 1378 (Aliph.), 1678 (C=O), 1242 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.19 (s, 3H, CH_3), 2.82 (s, 3H, CH_3), 7.16–7.26 (m, 4H, 4×CH), 9.71, 9.79, 10.83 (3s, 3H, 3×NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_{13}N_5OS_2$: C, 46.89; H, 4.26; N, 22.78. Found: C, 46.51; H, 3.95; N, 22.93.

*4-(2-Fluorophenyl)-1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-thiosemicarbazide (**33**).* Yield 91%, mp 101–103°C; IR (KBr, ν in cm^{-1}): 3256 (NH), 3030, 1622, 1600, 1487, 1478, 739 (ArH), 2950, 1433, 1390 (Aliph.), 1660 (C=O), 1236 (C=S); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.83 (s, 3H, CH_3), 7.17–7.32 (m, 4H, 4×CH), 9.77, 10.03, 10.92 (3s, 3H, 3×NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_{10}FN_5OS_2$: C, 42.43; H, 3.24; N, 22.49. Found: C, 42.42; H, 3.58; N, 22.32.

*4-Cyclohexyl-1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-thiosemicarbazide (**34**).* Yield 85%, mp 120–122°C; IR (KBr, ν in cm^{-1}): 3225 (NH), 2975, 2880, 1462, 1395 (Aliph.), 1659 (C=O), 1241 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.06–1.81 (m, 10H, 5×CH_2), 2.82 (s, 3H, CH_3), 4.10 (s, 1H, CH), 7.89, 9.35, 10.54 (3s, 3H, 3×NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_{17}N_5OS_2$: C, 44.12; H, 5.72; N, 23.39. Found: C, 43.88; H, 5.96; N, 23.50.

*4-Butyl-1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)- thiosemicarbazide (**35**).* Yield 74%, mp 118–120°C; IR (KBr, ν in cm^{-1}): 3212 (NH), 2970, 2922, 2861, 1449, 1391 (Aliph.), 1662 (C=O), 1233 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.80-.0.91 (t, 3H, CH_3), 1.14–1.54 (m, 4H, 2×CH_2), 2.81 (s, 3H, CH_3), 3.38–3.45 (m, 2H, CH_2), 8.23, 9.40, 10.57 (3s, 3H, 3×NH, D_2O exchangeable). Anal. Calcd for $C_9H_{15}N_5OS_2$: C, 39.54; H, 5.53; N, 25.62. Found: C, 39.63; H, 5.47; N, 25.60.

*4-Ethyl-1-(4-methyl-1,2,3-thiadiazol-5-yl-carbonyl)-thiosemicarbazide (**36**).* Yield 72%, mp 177–179°C; IR (KBr, ν in cm^{-1}): 3240, 3201 (NH), 2975, 1444, 1378 (Aliph.), 1679 (C=O), 1211 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.05–1.10 (t, 3H, CH_3), 2.81 (s, 3H, CH_3), 3.40–3.52 (q, 2H, CH_2), 8.26, 9.43, 10.59 (3s, 3H, 3×NH, D_2O exchangeable). Anal. Calcd for $C_7H_{11}N_5OS_2$: C, 34.27; H, 4.52; N, 28.55. Found: C, 33.86; H, 4.57; N, 28.24.

*Synthesis of 5-Azole-4-alkyl/aryl-s-triazole-3-thiones (***7–12, 19–22, 27–30***, and* **37–42***)*

Method for Compounds **7–12, 19–22, 27–30**, *and* **37–42**. A solution of appropriate thiosemicarbazide (**1–6, 13–18**, and **23–26**, or (**31–36**) (0.01 mol) in 2% sodium hydroxide (10 mL) was refluxed for 2 h. After cooling, the reaction mixture was filtered and the isolated solution was acidified with 3 M HCl, whereupon a solid separated out. The precipitate was filtered, dried, and crystallized from ethanol.

Method for Compounds **27–30** *and* **37–40**. A solution of thiosemicarbazide (**23–26** or **31–34**) (0.01 mol) in 3 M hydrochloric acid (30 mL) was refluxed for 5 h. Hot solution was filtered and concentrated to one fourth of the initial volume. Then it was kept at room temperature until precipitation of the final product was completed. The precipitate was filtered, dried, and crystallized from ethanol. During dehydrocyclization of compounds (**23–25**), the mixture of related *s*-triazole (**27–29**) and 4-methyl-imidazole-5-carboxylic acid was obtained. The latter was removed by dissolving in sodium hydrocarbonate.

Method for Compounds **27–30** *and* **37–42**. A solution of thiosemicarbazide (**23–26**) or (**31–36**) (0.01 mol) in glacial acetic acid (30 mL) was refluxed for 5 h. The reaction mixture was kept for 12 h at room temperature. The precipitate was filtered, dried, and crystallized from ethanol.

*4-Phenyl-5-(1,2,4-triazol-3-yl)-s-triazole-3-thione (***7***)*. Yield 46%, mp 210–212°C; IR (KBr, ν in cm^{-1}): 3460, 3200 (NH), 3092, 1600, 1511, 1450, 910, 752, 690 (ArH), 1611 (C=N), 1323 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.88–7.61 (m, 6H, 6×CH), 8.33, 13.33 (2s, 2H, 2×NH, D_2O exchangeable). Anal. Calcd for $C_{10}H_8N_6S$: C, 49.17; H, 3.30; N, 34.40. Found: C, 48.82; H, 2.96; N, 34.53.

*4-(4-Methoxyphenyl)-5-(1,2,4-triazol-3-yl)-s-triazole-3-thione (***8***)*. Yield 33%, mp 220–222°C; IR (KBr, ν in cm^{-1}): 3333, 3220 (NH), 3100, 1625, 1510, 1455, 800 (ArH), 2846, 1469, 1440 (Aliph.), 1610 (C=N), 1322 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.69 (s, 3H, OCH_3), 6.80–7.40 (m, 5H, 5×CH), 8.04, 13.13 (2s, 2H, 2×NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_{10}N_6OS$: C, 48.16; H, 3.67; N, 30.64. Found: C, 47.88; H, 3.54; N, 30.95.

*4-(4-Bromophenyl)-5-(1,2,4-triazol-3-yl)-s-triazole-3-thione (***9***)*. Yield 41%, mp 270–272C; IR (KBr, ν in cm^{-1}): 3372, 3292 (NH), 3021, 1587, 1488, 810 (ArH), 1615 (C=N), 1321 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.39–7.80 (m, 5H, 5×CH), 8.58, 13.41 (2s, 2H, 2×NH, D_2O exchangeable). Anal. Calcd for $C_{10}H_7BrN_6S$: C, 37.16; H, 2.18; N, 26.00. Found: C, 36.78; H, 2.20; N, 26.25.

*4-Cyclohexyl-5-(1,2,4-triazol-3-yl)-s-triazole-3-thione (***10***)*. Yield 38%, mp 152–154°C; IR (KBr, ν in cm^{-1}): 3354 (NH), 2920, 2844, 1480, 722 (Aliph.), 1613 (C=N), 1275 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.18–1.93 (m, 10H, 5×CH_2), 4.33 (s, 1H, CH), 8.28 (s, 1H, CH), 13.96 (s, 2H, 2×NH, D_2O exchangeable). Anal. Calcd for $C_{10}H_{14}N_6S$: C, 47.98; H, 5.64; N, 33.57. Found: C, 48.22; H, 5.36; N, 33.80.

*4-Butyl-5-(1,2,4-triazol-3-yl)-s-triazole-3-thione (***11***)*. Yield 45%, mp 224–226°C; IR (KBr, ν in cm^{-1}): 3300 (NH), 2950, 2915, 2892, 1470, 1445, 1371 (Aliph.), 1600 (C=N), 1275 (C=S); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 0.84–0.89 (t, 3H, CH_3), 1.21–1.31 (m, 2H, CH_2), 1.61–1.71 (m, 2H, CH_2), 4.35–4.40 (t, 2H, CH_2), 8.81 (s, 1H, CH), 14.06, 14.78 (2s, 2H, 2×NH, D_2O exchangeable). Anal. Calcd for $C_8H_{12}N_6S$: C, 42.84; H, 5.39; N, 37.47. Found: C, 42.80; H, 5.32; N, 37.05.

*4-Ethyl-5-(1,2,4-triazol-3-yl)-s-triazole-3-thione (***12***)*. Yield 36%, mp 311–313°C; IR (KBr, ν in cm^{-1}): 3421 (NH), 2931, 1449, 1371 (Aliph.), 1598 (C=N), 1276 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.24–1.29 (t, 3H, CH_3), 4.38–4.42 (q, 2H, CH_2), 8.80 (s, 1H, CH), 14.34 (s, 2H, 2×NH, D_2O exchangeable). Anal. Calcd for $C_6H_8N_6S$: C, 36.72; H, 4.11; N, 42.83. Found: C, 36.51; H, 4.45; N, 42.80.

*5-(4-Methyl-imidazol-5-yl)-4-phenyl-s-triazole-3-thione (***19***)*. Yield 45%, mp 299–301°C; IR (KBr, ν in cm^{-1}): 3222 (NH), 3096, 1591, 1522, 900, 729, 691 (ArH), 2980, 1470, 1390 (Aliph.), 1661 (C=N), 1280 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H, CH_3), 7.22–7.42 (m, 6H, 6×CH), 12.27, 13.90 (2s, 2H, 2×NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_{11}N_5S$: C, 56.01; H, 4.31; N, 27.22. Found: C, 55.83; H, 4.56; N, 27.20.

*5-(4-Methyl-imidazol-5-yl)-4-(4-methylphenyl)-s-triazole-3-thione (***20***)*. Yield 40%, mp 221–223°C; IR (KBr, ν in cm^{-1}): 3225 (NH), 3035, 1562, 1515, 1494, 820 (ArH), 1440, 1395 (Aliph.), 1635 (C=N), 1220 (C=S); ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.27 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 7.09–7.12 (d, 2H, 2×CH), 7.19–7.22 (d, 2H, 2×CH), 7.41 (s, 1H, CH), 12.26, 13.85 (2s, 2H, 2×NH, D_2O exchangeable).

Anal. Calcd for $C_{13}H_{13}N_5S$: C, 57.54; H, 4.83; N, 25.81. Found: C, 57.41; H, 5.12; N, 25.67.

*4-(2-Fluorophenyl)-5-(4-methyl-imidazol-5-yl)-s-triazole-3-thione (***21***).* Yield 39%, mp 216–218°C; IR (KBr, ν in cm^{-1}): 3387, 3268 (NH), 3058, 1596, 1572, 1505, 1480, 759 (ArH), 2921, 2882, 1462, 1383 (Aliph.), 1625 (C=N), 1240 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 2.38 (s, 3H, CH_3), 7.23–7.53 (m, 5H, 5×CH), 12.34, 13.95 (2s, 2H, 2×NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_{10}FN_5S$: C, 52.35; H, 3.66; N, 25.44. Found: C, 52.06; H, 3.58; N, 25.33.

*4-Cyclohexyl-5-(4-methyl-imidazol-5-yl)-s-triazole-3-thione (***22***).* Yield 36%, mp 234–236°C; IR (KBr, ν in cm^{-1}): 3220 (NH), 2930, 1470, 1452, 1391, 730 (Aliph.), 1620 (C=N), 1220 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 1.03–1.77 (m, 10H, 5×CH_2), 2.26 (s, 3H, CH_3), 4.85 (s, 1H, CH), 7.74 (s, 1H, CH), 12.43, 13.68 (2s, 2H, 2×NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_{17}N_5S$: C, 54.73; H, 6.51; N, 26.59. Found: C, 54.49; H, 6.56; N, 26.25.

*4-(4-Methoxyphenyl)-5-(pyrrol-2-yl)-s-triazole-3-thione (***27***).* Yield 85%, mp 257–259°C; IR (KBr, ν in cm^{-1}): 3426, 3318, 3233 (NH), 3083, 1588, 1516, 831 (ArH), 2835, 1451, 1416 (Aliph.), 1606 (C=N), 1334 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 3.85 (s, 3H, OCH_3), 5.26–5.27 (m, 1H, CH), 5.92–5.94 (m, 1H, CH), 6.87–6.89 (m, 1H, CH), 7.10–7.13 (dd, 2H, 2×CH), 7.28–7.31 (dd, 2H, 2×CH), 11.73, 13.85 (2s, 2H, 2×NH, D_2O exchangeable). Anal. Calcd for $C_{13}H_{12}N_4OS$: C, 57.34; H, 4.44; N, 20.57. Found: C, 57.37; H, 4.44; N, 20.23.

*4-(4-Bromophenyl)-5-(pyrrol-2-yl)-s-triazole-3-thione (***28***).* Yield 88%, mp 274–276°C; IR (KBr, ν in cm^{-1}): 3462, 3315 (NH), 3089, 1519, 1490, 828 (ArH), 1607 (C=N), 1328 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 5.28–5.31 (m, 1H, CH), 5.95–5.98 (m, 1H, CH), 6.89–6.91 (m, 1H, CH), 7.37–7.42 (m, 2H, 2×CH), 7.78–7.83 (m, 2H, 2×CH), 11.77, 13.95 (2s, 2H, 2×NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_9BrN_4S$: C, 44.87; H, 2.82; N, 17.44. Found: C, 45.03; H, 2.51; N, 17.05.

*4-(2-Fluorophenyl)-5-(pyrrol-2-yl)-s-triazole-3-thione (***29***).* Yield 91%, mp 240–242°C; IR (KBr, ν in cm^{-1}): 3273 (NH), 3089, 1510, 1449, 732 (ArH), 1607 (C=N), 1335 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 5.29–5.32 (m, 1H, CH), 5.95–5.98 (m, 1H, CH), 6.92–6.94 (m, 1H, CH), 7.43–7.73 (m, 4H, 4×CH), 11.87, 14.06 (2s, 2H, 2×NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_9FN_4S$: C, 55.37; H, 3.49; N, 21.52. Found: C, 54.98; H, 3.77; N, 21.30.

*4-Ethyl-5-(pyrrol-2-yl)-s-triazole-3-thione (***30***).* Yield 77%, mp 210–212°C; IR (KBr, ν in cm^{-1}): 3354 (NH), 2979, 1471, 1444, 1391 (Aliph.), 1663 (C=N), 1327 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 1.22–1.26 (t, 3H, CH_3), 4.16–4.23 (q, 2H, CH_2), 6.24–6.26 (m, 1H, CH), 6.68–6.70 (m, 1H, CH), 6.99–7.02 (m, 1H, CH), 11.72, 13.78 (2s, 2H, 2×NH, D_2O exchangeable). Anal. Calcd for $C_8H_{10}N_4S$: C, 49.46; H, 5.19; N, 28.84. Found: C, 49.45; H, 5.19; N, 28.84.

*4-Phenyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)-s-triazole-3-thione (***37***).* Yield 68%, mp 266–268°C; IR (KBr, ν in cm^{-1}): 3263 (NH), 3091, 1588, 1493, 1485, 901, 754, 705 (ArH), 2971, 2876, 1463, 1392 (Aliph.), 1633 (C=N), 1244 (C=S); ^1H NMR (300 MHz, DMSO-d_6): δ 2.82 (s, 3H, CH_3), 7.46–7.50 (m, 2H, 2×CH), 7.56–7.64 (m, 3H, 3×CH), 14.55 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_9N_5S_2$: C, 47.98; H, 3.92; N, 25.43. Found: C, 48.03; H, 3.21; N, 25.24.

*4-(2-Methylphenyl)-5-(4-methyl-1,2,3-thiadiazol-5-yl)-s-triazole-3-thione (***38***).* Yield 55%, mp 263–265°C; IR (KBr, ν in cm^{-1}): 3225 (NH), 3050, 1586, 1490, 740 (ArH), 2933, 2871, 1395 (Aliph.), 1613 (C=N), 1234 (C=S); ^1H NMR: δ 2.02 (s, 3H, CH_3), 2.93 (s, 3H, CH_3), 7.40–7.49 (m, 2H, 2×CH), 7.51–7.54 (m, 1H, CH), 7.59–7.64 (m, 1H, CH), 14.66 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_{11}N_5S_2$: C, 49.81; H, 3.83; N, 24.20. Found: C, 49.75; H, 4.54; N, 23.90.

*4-(2-Fluorophenyl)-5-(4-methyl-1,2,3-thiadiazol-5-yl)-s-triazole-3-thione (***39***).* Yield 50%, mp 261–263°C; IR (KBr, ν in cm^{-1}): 3256 (NH), 3087, 1616, 1600, 1515, 742 (ArH), 2876, 1451, 1366 (Aliph.), 1627 (C=N), 1246 (C=S); ^1H NMR: δ 2.85 (s, 3H, CH_3), 7.45–7.58 (m, 2H, 2×CH), 7.66–7.77 (m, 2H, 2×CH), 14.74 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_8FN_5S_2$: C, 45.04; H, 2.75; N, 23.87. Found: C, 45.25; H, 2.97; N, 23.91.

*4-Cyclohexyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)-s-triazole-3-thione (***40***).* Yield 41%, mp 242–244°C; IR (KBr, ν in cm^{-1}): 3252 (NH), 2852, 1476, 730 (Aliph.), 1624 (C=N), 1248 (C=S); ^1H NMR: δ 0.89–1.94 (10H, 5×CH_2), 2.66 (s, 3H, CH_3), 4.19 (s, 1H, CH), 14.31 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_{15}N_5S_2$: C, 46.95; H, 5.37; N, 24.89. Found: C, 46.58; H, 5.44; N, 24.70.

*4-Butyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)-s-triazole-3-thione (***41***).* Yield 46%, mp 123–125°C; IR (KBr, ν in cm^{-1}): 3290 (NH), 2952, 2918, 2869,

1468, 1449, 1380 (Aliph.), 1620 (C=N), 1244 (C=S); ^{1}H NMR: δ 0.78-.0.83 (t, 3H, CH_3), 1.15–1.27 (m, 2H, CH_2), 1.45–1.55 (m, 2H, CH_2), 2.76 (s, 3H, CH_3), 3.92–3.97 (t, 2H, CH_2), 14.36 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_9H_{13}N_5S_2$: C, 42.33; H, 5.13; N, 27.42. Found: C, 42.34; H, 4.91; N, 26.98.

*4-Ethyl-5-(4-methyl-1,2,3-thiadiazol-5-yl)-s-triazole-3-thione (***42***).* Yield 47%, mp 182–184°C; IR (KBr, ν in cm^{-1}): 3287 (NH), 2950, 2923, 2865, 1471, 1371 (Aliph.), 1621 (C=N), 1239 (C=S); ^{1}H NMR: δ 1.12–1.17 (t, 3H, CH_3), 2.76 (s, 3H, CH_3), 3.95–4.02 (q, 2H, CH_2), 14.35 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_7H_9N_5S_2$: C, 36.99; H, 3.99; N, 30.81. Found: C, 36.74; H, 3.84; N, 30.54.

*Synthesis of 2-aryl/alkylamino-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-thiadiazoles (***43–48***).* The thiosemicarbazide (**31–36**) (0.01 mol) was dissolved in concentrated sulfuric acid (10 mL). The solution was kept at room temperature for 4 h and then poured into crushed ice to precipitate a crude solid. The precipitate was filtered, dried, and crystallized from ethanol.

*2-(Phenylamino)-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-thiadiazole (***43***).* Yield 74%, mp 225–227°C; IR (KBr, ν in cm^{-1}): 3242 (NH), 3088, 1586, 1484, 901, 758, 702 (ArH), 2971, 2887, 1451, 1374 (Aliph.), 1592 (C=N); ^{1}H NMR: δ 2.90 (s, 3H, CH_3), 7.05–7.10 (m, 1H, CH), 7.37–7.43 (m, 2H, 2×CH), 7.58–7.67 (m, 2H, 2×CH), 10.85 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_9N_5S_2$: C, 47.98; H, 3.29; N, 25.43. Found: C, 47.82; H, 3.20; N, 25.28.

*2-(2-Methylphenylamino)-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-thiadiazole (***44***).* Yield 64%, mp 133–135°C; IR (KBr, ν in cm^{-1}): 3255 (NH), 3021, 1625, 1622, 1519, 752 (ArH), 2957, 2877, 1436, 1382 (Aliph.), 1601 (C=N); ^{1}H NMR: δ 2.30 (s, 3H, CH_3), 2.87 (s, 3H, CH_3), 7.09–7.15 (m, 1H, CH), 7.24–7.30 (m, 2H, 2×CH), 7.79–7.84 (m, 1H, CH), 10.03 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{12}H_{11}N_5S_2$: C, 49.81; H, 3.83; N, 24.20. Found: C, 49.73; H, 4.25; N, 24.14.

*2-(2-Fluorophenylamino)-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-thiadiazole (***45***).* Yield 52%, mp 176–178°C; IR (KBr, ν in cm^{-1}): 3212 (NH), 3036, 1577, 1575, 744 (ArH), 2864, 1454, 1367 (Aliph.), 1607 (C=N); ^{1}H NMR: δ 2.90 (s, 3H, CH_3), 7.09–7.17 (m, 1H, CH), 7.23–7.36 (m, 2H, 2×CH), 8.33–8.39 (m, 1H, CH), 10.64 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_8FN_5S_2$: C, 45.04; H, 2.75; N, 23.87. Found: C, 44.71; H, 2.78; N, 23.91.

*2-Cyclohexylamino-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-thiadiazole (***46***).* Yield 48%, mp 163–165°C; IR (KBr, ν in cm^{-1}): 3220 (NH), 2970, 2883, 2859, 1461, 1395 (Aliph.), 1610 (=N); ^{1}H NMR: δ 1.18–2.01 (10H, 5×CH_2), 2.85 (s, 3H, CH_3), 3.60 (s, 1H, CH), 8.32 (s, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_{11}H_{15}N_5S_2$: C, 46.95; H, 5.37; N, 24.89. Found: C, 47.39; H, 5.60; N, 24.75.

*2-Butylamino-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-thiadiazole (***47***).* Yield 52%, mp 123–125°C; IR (KBr, ν in cm^{-1}): 3225 (NH), 2973, 2919, 2860, 1450, 1395 (Aliph.), 1602 (C=N); ^{1}H NMR: δ 0.89–0.94 (t, 3H, CH_3), 1.31–1.43 (m, 2H, CH_2), 1.54–1.64 (m, 2H, CH_2), 2.85 (s, 3H, CH_3), 3.33–3.39 (m, 2H, CH_2), 8.35–8.38 (t, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_9H_{13}N_5S_2$: C, 42.33; H, 5.13; N, 27.42. Found: C, 41.87; H, 5.23; N, 27.10.

*2-Ethylamino-5-(4-methyl-1,2,3-thiadiazol-5-yl)-1,3,4-thiadiazole (***48***).* Yield 58%, mp 144–146°C; IR (KBr, ν in cm^{-1}): 3201 (NH), 2972, 1446, 1391 (Aliph.), 1603 (C=N); ^{1}H NMR: δ 1.19–1.24 (t, 3H, CH_3), 2.85 (s, 3H, CH_3), 3.38–3.41 (q, 2H, CH_2), 8.34–8.37 (t, 1H, NH, D_2O exchangeable). Anal. Calcd for $C_7H_9N_5S_2$: C, 36.90; H, 3.99; N, 30.81. Found: C, 37.41; H, 4.12; N, 31.15.

Synthesis of 1,2,4-Triazole-3-carboxylic Acid

Method A. A solution of thiosemicarbazide (**1–6**) (0.01 mol) in 3 M hydrochloric acid (30 mL) was refluxed for 5 h. Hot solution was filtered and concentrated to one fourth of the initial volume. Then it was kept at room temperature until precipitation of the final product was completed. The precipitate was filtered, dried, and crystallized from ethanol.

Method B. A solution of thiosemicarbazide (**1–6**) (0.01 mol) in glacial acetic acid (30 mL) was refluxed for 5 h. The reaction mixture was kept for 12 h at room temperature. The precipitate was filtered, dried, and crystallized from ethanol.

Method C. The thiosemicarbazide (**1–6**) (0.01 mol) was dissolved in concentrated sulfuric acid (10 mL). The solution was kept at room temperature for 4 h, and then poured into crushed ice to precipitate a crude solid. The precipitate was filtered, dried, and crystallized from ethanol.

Synthesis of 4-Methyl-imidazole-5-carboxylic Acid. A solution of thiosemicarbazide (**17**) or (**18**) (0.01 mol) in 2% sodium hydroxide (10 mL) was refluxed for 2 h. After cooling, the reaction mixture

was filtered and the isolated solution was acidified with 3 M HCl, whereupon a solid separated out. The precipitate was filtered, dried, and crystallized from ethanol.

Synthesis of 4-Methyl-1,2,3-thiadiazole-5-carboxylic Acid. A solution of thiosemicarbazide (**35**) or (**36**) (0.01 mol) in 3 M hydrochloric acid (30 mL) was refluxed for 5 h. Hot solution was filtered and concentrated to one fourth of the initial volume. Then it was kept at room temperature until precipitation of the final product was completed. The precipitate was filtered, dried, and crystallized from ethanol.

Crystallographic Data of Compounds **42** *and* **47**

Diffraction data were collected on a KUMA KM4 diffractometer ($T = 293$ K, Cu Kα: $\lambda = 1.54178$ Å). Crystal structure was solved by direct methods (SHELXS-97 [11]) and refined by full-matrix least squares on F^2 using the program SHELXL-97 [12].

Computational Details

pK_a values of oxygen, sulfur, and nitrogen atoms of thiosemicarbazides (**1–6, 13–18, 23–26**, and **31–36**) were calculated by JChem's pK_a calculator plugin [13].

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