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Structural Study of Three 1,2,4-triazole Derivatives Prepared by Oxidative Cyclization of Thiosemicarbazides †

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Abstract: In the present research, 5,5-dimethyl-4-phenyl-4,5-dihydro-3H-1,2,4-triazole-3-thione (**1**) was prepared by condensation from N-phenylhydrazinecarbothioamide, while 4-phenyl-5-(pyrazin-2-yl) -2,4-dihydro-3H-1,2,4-triazole-3-thione (**2**) and 2-((5-(pyridin-2-yl) -4H-1,2,4-triazol-3-yl)thio)acetic acid (**3**) was prepared by oxidative cyclization from 2-(amino(pyrazin-2-yl)methylene)-N-phenylhydrazine -1-carbothioamide and 2-(amino(pyridine-2-yl)methylene)hydrazine-1-carbothioamide, respectively. The three compounds have been well characterized and their molecular structures studied by single-crystal X-ray diffraction. The supramolecular assembly of each crystal has also been analyzed and discussed.

Keywords: thiosemicarbazones; 1,2,4-triazole; oxidative cyclization; supramolecular architectures; hydrogen bond

1. Introduction

Heterocyclic chemistry is an integral part of the chemical sciences and constitutes a considerable part of the modern research that is being carried out at present throughout the world. The chemistry of heterocyclic compounds is as logical as the chemistry of aliphatic or aromatic compounds, and the study of heterocyclic systems is of great interest both from the theoretical and practical point of view. Heterocycles also play an important role in the design and discovery of new physiologically and pharmacologically active compounds [1].

Thiosemicarbazones have been used as intermediates for the preparation of many heterocyclic compounds. In the literature, many researchers have reported S/N regioselective nucleophilic completion in the synthesis of heterocyclic compounds by intramolecular cyclization reactions. Changes in reaction conditions can induce S-attack or N-attack to eventually afford different cyclic products from a single starting material. Moreover, thiosemicarbazones bearing an aromatic heterocyclic moiety seem to possess enhanced biological activities [2].

The use of thiosemicarbazides in organic synthesis has become a classic strategy for the synthesis of several heterocycles. Among the increasing number of heterocyclic sulphur and nitrogen-containing compounds, which are being pursued in both industry and academia, 1,3,4-thiadiazole and 1,2,4-triazole derivatives are also interesting targets for drug design. Therefore, there have been intense investigations into 1,4-disubstituted thiosemicarbazide, 1,3,4-thiadiazole and 1,2,4-triazole-thione compounds [3,4].

As part of our studies into thiocarbonyl chemistry, the reactivity of derived thiosemicarbazones, herein, we report an efficient and convenient method to synthesize 1,2,4-triazole-3-thiones. The structures of products have also been fully characterized by infrared spectroscopy (IR), ^{1}H and ^{13}C nuclear magnetic resonance (^{1}H- and ^{13}C-NMR), mass spectrometry (MS), elemental analysis, and single-crystal X-ray diffraction analysis.

2. Materials and Methods

All reagents and solvents were commercial products that were used as received, without further purification. The compounds were prepared as follows:

Synthesis of (5,5-dimethyl-4-phenyl-4,5-dihydro-3H-1,2,4-triazole-3-thione (**1**). Single crystals of this compound were obtained serendipitously from a solution of 4-phehyl-3-thiosemicarbazide (9.0 g, 34.19 mmol) in acetone (50 mL) exposed to air for several weeks.

Synthesis of 4-phenyl-5-(pyrazin-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**2**). 2-Cyanopyrazine (5 g, 48 mmol) was dissolved in a solution of sodium (0.18 g, 7.8 mmol) in dry MeOH (100 mL). The N-(4)-thiosemicarbazide (8 g, 48 mmol) was added slowly to the resulting solution with stirring. The mixture was heated under reflux for 5 h and the resulting yellow solid was filtered off, washed and recrystallized from methanol. Yield: 47%.

Elemental analysis. Found: C, 47.5; H, 3. 7; N, 27.5; S, 12.5%. Calc. for $C_{12}H_9N_5S$ (255.31): C, 56.4; H, 3.6; N, 27.4; S, 12.6%. Mp 227 ºC. IR(νmax/cm^{-1}): 3109–3058 ν(NH), 1734 ν(C=O), 893 ν(C–S), 1589, 1569 ν(C=N) + ν(C=C), 1071 ν(NN). EI MS, m/z, assignment: 255.8 $[M]^+$, 193.8 $[C_{12}H_9N_3]^+$, 117.8 $[C_6H_5N_3]^+$, 105.0 $[C_6H_5N_2]^+$, 90.9 $[C_6H_6N]^+$, 79.0 $[C_5H_5N]^+$. ^{1}H NMR (DMSO-d_6, ppm): 14.2 (1H, s, N3H); 8.2 (1H, d, H1); 7.9 (1H, d, H4); 7.8 (1H, td, H3); 7.4 (3H, t, Hb, Hd); 7.3 (3H, m, Hc, H2); 4.0 (2H, s, H8). ^{13}C RMN (DMSO-d_6, ppm): 169.6 (C7); 153.7 (C6); 152.9 (C9); 149.4 (C1), 146.5 (C5), 137.6 (C3); 134.8 (Ca); 129.8 (Cd); 129.7 (Cb); 127.6 (Cc): 124.8 (C2); 123.9 (C4); 34.5 (C8).

Synthesis of 2-((5-(pyridin-2-yl)-4H-1,2,4-triazol-3-yl)thio)acetic acid (**3**). The thiosemicarbazone HPyAm4DH (1.93 g, 8.15 mmol) in toluene (75 mL) with several drops of triethylamine was warmed and stirred for 1 h and a solution of chloracetic acid (0.77 g, 8.15 mmol) in toluene (25 mL) was added slowly. The mixture was heated under reflux for about 5 h and the white precipitate was filtered off and washed with fresh toluene. The precipitate was recrystallized from methanol to give pure 3 as colorless crystals. Yield: 57%.

Elemental analysis. Found: C, 45.5; H, 3.7; N, 23.5; S, 13.5%. Calc. for $C_9H_8N_4O_2S$ (236.26): C, 45.7; H, 3.4; N, 23.7; S, 13.6%. Mp 235 ºC. IR(νmax/cm^{-1}): 3475–3413 ν(NH), 1734 ν(C=O), 893 ν(C–S), 1589, 1569 ν(C=N) + ν(C=C), 1071 ν(NN). EI MS, m/z, assignment: 236 $[M]^+$, 118 $[C_6H_5N_3]^+$, 105 $[C_6H_5N_2]^+$, 79 $[C_5H_5N]^+$. ^{1}H NMR (DMSO-d_6, ppm): 14.4 (1H, s, N4H); 8.3 (1H, dc, H1); 7.9 (1H, td, H3); 7.8 (1H, d, H4); 7.3 (1H, m, H2);. ^{13}C RMN (DMSO-d_6, ppm): 169.5 (C7); 149.9 (C5); 149.59 (C1); 145.5 (C6), 137.7 (C3); 135.5 (Ca); 129.2 (Cc, Cd); 128.7 (Cb); 125.4 (C2): 124.4 (C4).

Suitable crystals of **2** and **3** for X-ray diffraction were grown by slow evaporation of the mother liquors from the recrystallization after two weeks.

Microanalyses (C, H and N) were carried out in a Carlo-Erba 1108 elemental analyzer. FT-IR spectra were recorded from KBr pellets over the range 400–4000 cm^{-1} on a Bruker IFS-66v spectrometer. For X-ray analysis, intensity data were collected at 100 K on a Bruker X8 KappaAPEXII diffractometer. Structures were solved by direct methods followed by difference Fourier calculations and were refined by a full-matrix least-squares procedure using SHELXLTL. The structures of **1** to **3** were deposited with the Cambridge Crystallographic Data Centre with CCDC Nos. 1878274–1878276, respectively.

3. Results and Discussion

The preparation of the thiosemicarbazones was carried out by the reaction of 2-cyanopyrazine with the corresponding thiosemicarbazide, as described previously for 2-pyridinethiosemicarbazones [5]. Compounds **2** and **3** were characterized by elemental analysis mass spectrometry, IR and ^{1}H (Figure 1) and ^{13}C NMR spectroscopy and the structures of all compounds were analyzed by X-crystallography.

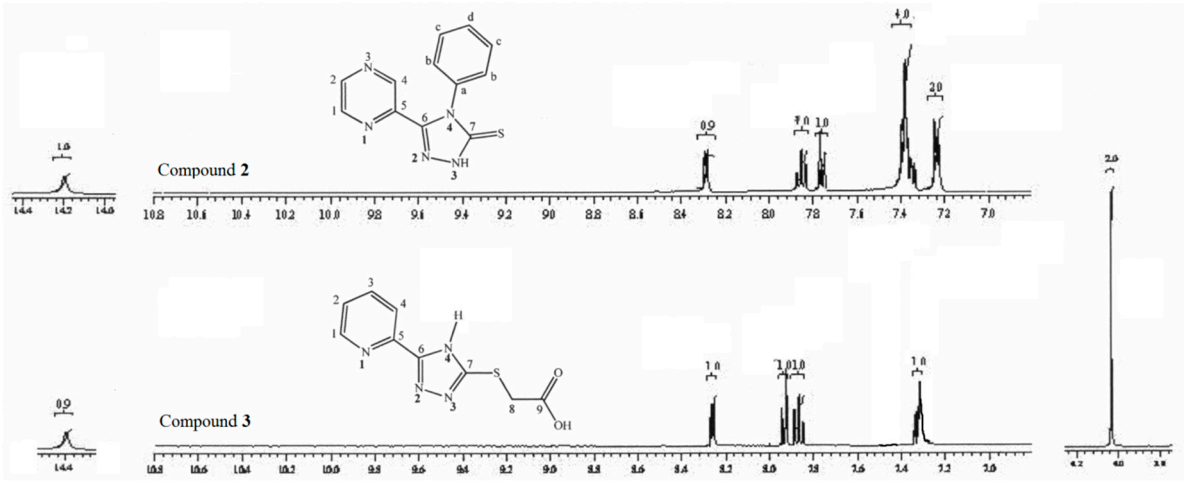
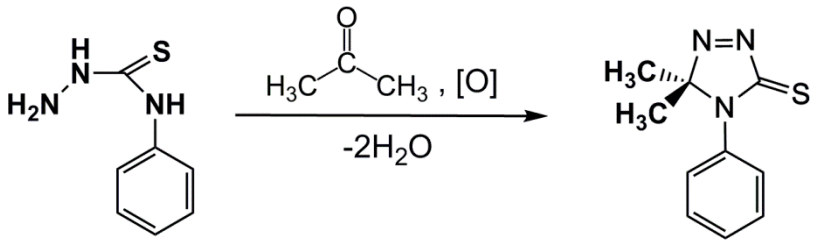


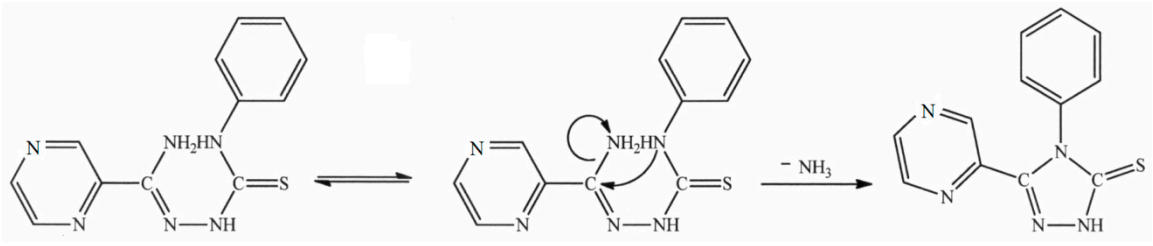
Figure 1. ^{1}H NMR spectra of Compounds **2** and **3**.

Compound **1** was obtained in good yield serendipitously by the tandem addition-oxidative cyclization achieved by the use of molecular oxygen, at room temperature, as the oxidant, which produces water as the sole theoretical byproduct, as indicated in Scheme 1.



Scheme 1. Compound **1** (Figure 2a) crystallizes in the $P2_1/n$ monoclinic space group and unit cell dimensions a = 9.03990(10) Å, b = 8.18110(10) Å, c = 14.0556(2) Å, β = 98.9500(10)°, and V = 1026.84(2) $Å^3$.

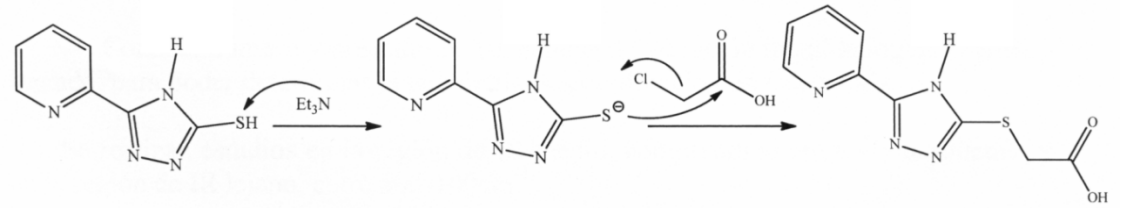
For Compound **2**, the proposed cyclization mechanism to form 1,2,4-triazole-5-thione suggests the nucleophilic attack of the N4 thioamide of the formamide thiosemicarbazone on the azomethine carbon, with the elimination of a molecule of NH_3 (Scheme 2). This cyclization was also observed in 2-pyridinethiosemicarbazone derivatives in the presence of Ag(I) [6,7].



Scheme 2. Proposed mechanism for the transformation of 2-(amino(pyrazin-2-yl)methylene)-N-phen ylhydrazine-1-carbothioamide to (**2**).

Compound **2** (Figure 2b) crystallizes in the $P2_1/c$ monoclinic space group and unit cell dimensions a = 6.3188(4) Å, b = 18.4287(14) Å, c = 10.5545(8) Å, β = 107.357(4)°, and V = 1173.08(15) Å^3

The formation of Compound **3** involves the thiol tautomer, subsequent deprotonation mediated by triethylamine and attack on the carbon atom of the chloroacetic acid to form 2-(5-(pyridin-2-yl)-1H-1,2,4-triazol-3-ylthio)acetic acid and chloride (Scheme 3).



Scheme 3. Proposed mechanism for the transformation of 5-(pyridin-2-yl)-2,4-dihydro -3H-1,2,4-triazole-3-thione to (**3**).

Compound **3** (Figure 2c) crystallizes in the $P2_1/c$ monoclinic space group and unit cell dimensions a = 4.9288(5) Å, b = 14.9283(15) Å, c = 13.5497(14) Å, β = 90.286(6)°, and V = 996.96(18) Å^3

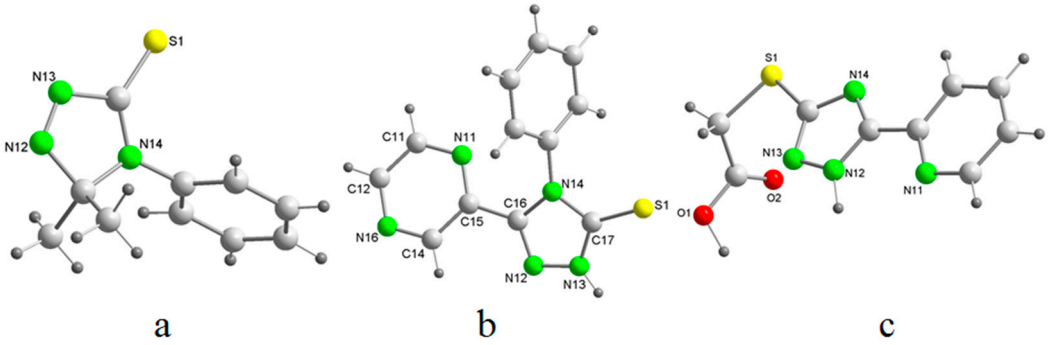


Figure 2. Perspective view of the asymmetrical unit of (**a**) Compound **1**, (**b**) Compound **2** and (**c**) Compound **3**.

In the crystal lattice of all three compounds, weak non-classical hydrogen bonding intermolecular interactions are observed. In Compound **1**, an intermolecular weak hydrogen bonding links the sulfur atom of one molecule to the NH group of the adjacent one [C-H··S: 3.846(1)]. In Compound **2**, a weak intermolecular hydrogen bond links the sulfur atom of one molecule to the NH group of the adjacent one [N–H···S: 3.284(1) Å], which generates a cyclic bimolecular homosynthon with an $R_2^2(8)$ graph-set motif. In addition, there are two intermolecular non-classical hydrogen bonds [C–H···S: 3.829(2) and 3.631(2) Å]. In the crystal structure of Compound **3**, an intermolecular hydrogen bond links the nitrogen atom (N_{py}) of one molecule to the $N_{trz}H$ group of the neighboring molecule generating a dimeric homosynthon with an $R_2^2(10)$ graph-set motif. These dimers link other nearest-neighbor molecules through a strong hydrogen bond O-H···N_{trz}. In the crystal lattice of **2** and **3**, in addition to non-classical hydrogen bonds, the packing is governed by intermolecular π-π stacking interactions between the pyridyl rings and triazole rings, with centroid-centroid separations of 3.65–3.96 Å reinforcing the 3D supramolecular network.

4. Conclusions

We have developed a controllable in situ generation of functionalized 4-substituted-1,2,4-triazole-3-thiones under mild reaction conditions from 2-pyridine- or 2-pyrazineformamide thiosemicarbazones. Three novel crystals (**1**–**3**) based on the oxidative cyclization of thiosemicarbazides were prepared. It was found that 1,2,4-triazole-3-thione are formed directly from the starting 2-pyrazineformamide thiosemicarbazone by heating to reflux for several

hours. The reaction between 2-pyridineformamide thiosemicarbazone and chloroacetic acid in toluene as the solvent by a conventional method is an efficient and rapid method to produce thioacetic acid derivatives of 1,2,4-triazol. Synthons involving $R_2^2(8)$ or $R_2^2(10)$ interactions are favourable for the formation of doubly hydrogen-bonded compounds, but other synthons can be taken into account for the formation of supramolecular systems of these compounds as well. Results also show that the π-π stacking interactions between the 1,2,4-triazole rings and pyrazine or pyridine rings contribute to their overall three-dimensional packing.

Conflicts of Interest: The authors declare no conflicts of interest.

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