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Synthesis and characterization of some 1,2,4-triazole-3-thiones obtained from intramolecular cyclization of new 1-(4-(4-X-phenylsulfonyl)benzoyl)-4-(4-iodophenyl)-3-thiosemicarbazides

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Abstract: This paper presents new heterocyclic compounds from the class of 1,2,4-triazole-3-thione which were obtained by intramolecular cyclization, in basic media of some acylthiosemicarbazides containing diphenyl sulfone moieties. The new 1-(4-(4-X-phenylsulfonyl)benzoyl)-4-(4-iodophenyl)-3-thiosemicarbazides (**7a**–**c**) were obtained by the reaction of 4-(4-X-phenylsulfonyl)-benzoic acid hydrazides (**6a**–**c**) (X = H, Cl or Br) with 4-iodophenylisothiocyanate. The cyclization of the acylthiosemicarbazides **7a**–**c** in the presence of an 8 % NaOH solution resulted in the formation of the new 5-(4-(4-X-phenylsulfonyl)phenyl)-4-(4-iodophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones (**8a**––**c)**. The structures of the newly synthesized compounds were elucidated by spectral methods (IR, UV–Vis, ^{1}H-NMR, ^{13}C-NMR and MS spectroscopy) and elemental analysis.

Keywords: 1-acylthiosemicarbazide; intramolecular cyclization; 1,2,4-triazole--3-thione.

INTRODUCTION

The synthesis of compounds containing 1,2,4-triazole rings in their structure has attracted widespread attention, mainly in connection with their wide range of pharmacological properties. A variety of biological activities, such as anti-inflammatory,[1] analgesic,[1,2] antibacterial,[3,4] antifungal,[3] antitubercular,[5] antiviral,[5]

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antitumoral,[6] anticonvulsant[7] and antidepressant,[8] have been reported for mercapto- and thione-substituted 1,2,4-triazole systems.

1,2,4-Triazole-3-thiones have been prepared by different methods. One of the most common routes to these compounds involves cyclodehydration of acylthiosemicarbazides with a variety of basic reagents, such as sodium hydroxide,[9–11] potassium hydroxide,[12] sodium carbonate,[13] triethylamine,[14] *etc*.

In addition, it is known that acylthiosemicarbazides, the key intermediates used in the synthesis of 1,2,4-triazoles, are compounds with various pharmacological activities: analgesic,[15] antibacterial,[16] antifungal,[17,18] antitubercular[19] and antitumoral.[17] Moreover, a literature survey revealed that diphenyl sulfone derivatives possess antibacterial activities.[20,21]

In view of the above-mentioned findings and in continuation of our research in the domain of heterocyclic compounds of the 1,2,4-triazole class with expected biological activity,[22–25] herein, the syntheses of some new acylthiosemicarbazides and their cyclization compounds from the 1,2,4-triazole class containing the diphenylsulfone moiety with potential biological activity are described. The new synthesized compounds were characterized by IR, UV-Vis, ^{1}H--NMR, ^{13}C-NMR and mass spectrometry and elemental analysis.

EXPERIMENTAL

Materials, methods and instruments

All chemicals used in this study were supplied by Sigma-Aldrich and Merck. Melting points were determined using a Böetius apparatus and are uncorrected. The infrared spectra were registered with a Vertex 70 Bruker spectrometer using potassium bromide disc technique and the results are expressed in wave number (cm^{-1}). The nuclear magnetic resonance (^{1}H-NMR and ^{13}C-NMR) spectra were registered on a Varian Gemini 300 BB spectrometer working at 300 MHz for ^{1}H- and 75 MHz for ^{13}C-NMR, using DMSO-d_6 as the solvent. Chemical shifts are expressed in δ (ppm) using TMS as the internal standard. The mass spectra were obtained with a triple quadrupole mass spectrometer Varian 1200 L/MS/MS, with an electrospray interface (ESI), coupled with a high performance liquid chromatograph with a Varian ProStar 240 SDM ternar pump. The sample solution (2 μg ml^{-1} in chloroform/methanol 1/1, v/v) was introduced into the ESI interface by direct infusion, after a hundred-fold dilution with methanol, at a flow rate of 20 μl min^{-1}. The instrument was operated in the negative ion mode. For negative ionization, a 10 % ammonia solution was added. The ESI needle was subjected to a DC voltage of ±5 kV, and for dispersion, nitrogen at a pressure of 42 psi (14 psi ≈ 1 atm) was used. The drying gas was air at 200 °C and 19 psi and the collision gas was argon (Linde, 99.9999 %) at a pressure of about 1 mTorr. The UV–Vis spectra were recorded on a Specord 40 Analytik Jena spectrometer, in methanol (2.5×10^{-5} M) in the wavelength range 200–600 nm. The elemental analyses were realized with a Perkin-Elmer 2400 instrument.

*General procedure for the preparation of 1-(4-(4-X-phenylsulfonyl)benzoyl)-4-(4-iodophenyl)-3-thiosemicarbazides (**7a**–**c**)*

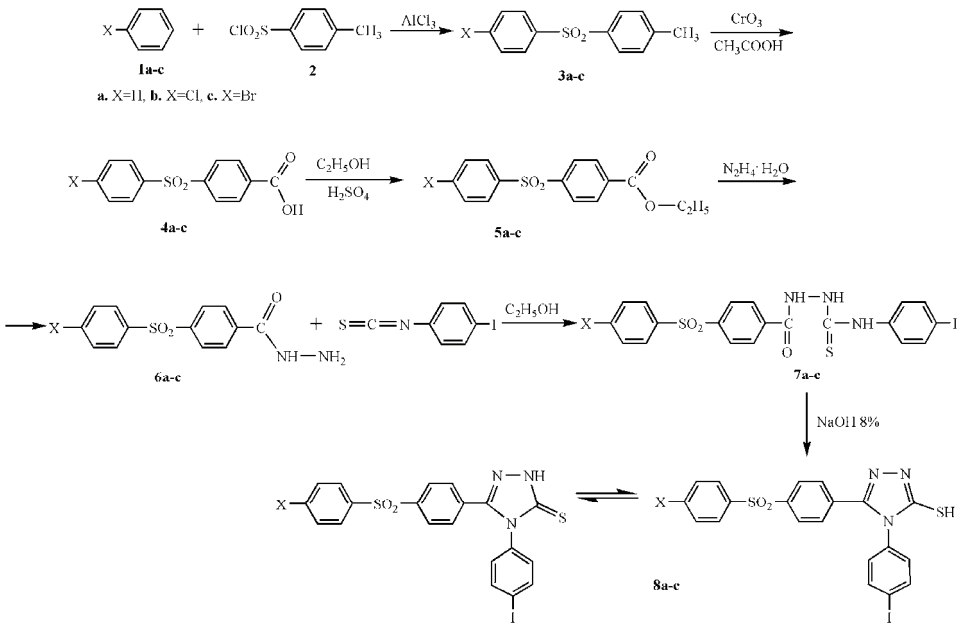
Equimolar quantities of hydrazide **6** (1.0 mmol) and 4-iodophenyl isothiocyanate (1.0 mmol) in absolute ethanol (3.0 mL) were refluxed for 10 h. The formed precipitate was filtered off and washed with a few mL of cold ethanol. The resulting solid was dried in air and recrystallized from ethanol.

*General procedure for the preparation of the 5-(4-(4-X-phenylsulfonyl)phenyl)-4-(4-iodophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones (**8a–c**)*

A mixture of acylthiosemicarbazide **7** (1.0 mmol) and sodium hydroxide solution (8 %, 8.0 mL) was heated under reflux for 4 h. The obtained solution was filtered, allowed to cool and then adjusted to pH 5.5–6.0 with a dilute solution of HCl. The crude product was filtered off, washed with water and recrystallized from $CHCl_3$/petroleum ether (1:1, v/v).

RESULTS AND DISCUSSION

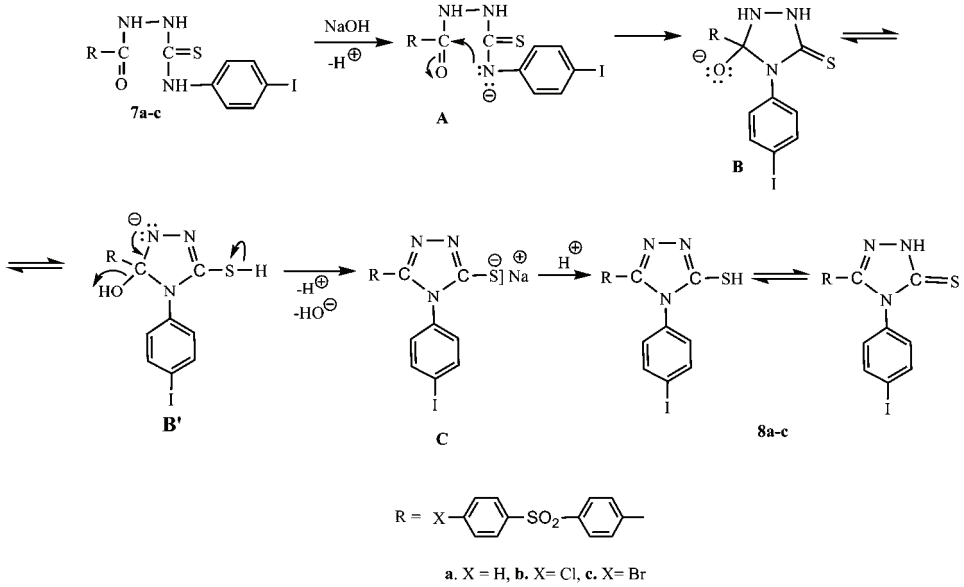
The synthetic pathway followed for the preparation of the title compounds was accomplished as shown in Scheme 1. 4-(4-X-Phenylsulfonyl)benzoic acid hydrazides **6a**–**c** (X = H, Cl or Br), the key intermediates used in the synthesis of the 1-acylthiosemicarbazides **7a**–**c**, were synthesized according to a literature method.[26] Thus, the diaryl sulfones **3a**–**c** were obtained by a Friedel–Crafts reaction between benzene or halobenzene **1a**–**c** (X = Cl or Br) and *p*-toluenesulfonyl chloride **2**. The diaryl sulfones **3a**–**c** were converted into the 4-(4-X-phenylsulfonyl)benzoic acids **4a**–**c** by oxidation in presence of chromic acid and acetic acid. The acids **4a**–**c** were reacted with ethanol in sulfuric acid media to yield the corresponding esters **5a**–**c**. The latter were converted to the desired 4-(4-X-phenylsulfonyl)benzoic acid hydrazides **6a**–**c** upon treatment with hydrazine hydrate in ethanol.[26] The new 1-(4-(4-X-phenylsulfonyl)benzoyl)-4-(4-iodophenyl)-3--thiosemicarbazides **7a**–**c** were obtained by nucleophilic addition of 4-(4-X-phenylsulfonyl)benzoic acid hydrazides **6a**–**c** to 4-iodophenyl isothiocyanate. For the



Scheme 1. The synthetic route of the title compounds.

synthesis of the new 5-(4-(4-X-phenylsulfonyl)phenyl)-4-(4-iodophenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **8a**–**c**, the acylthiosemicarbazides **7a**–**c** were subjected to intramolecular cyclization in 8 % sodium hydroxide solution under reflux.

The cyclization of the acylthiosemicarbazides **7a**–**c** to the 1,2,4-triazoles **8a**–**c** could be explained by the following mechanism (Scheme 2).[27]



Scheme 2. Proposed mechanism for the formation of the 1,2,4-triazoles **8a**–**c**.

The intermediate tautomer anion **B** was formed by cyclization of the initially obtained anion **A** in basic media from the acylthiosemicarbazides **7a**–**c**. The tautomer anion **B'** was converted into the sodium salt **C** of 1,2,4-triazole **8a**–**c** by elimination of water.

The analytical and spectral data for the newly prepared acylthiosemicarbazides **7a**–**c** are given below.

*4-(4-Iodophenyl)-1-(4-(phenylsulfonyl)benzoyl)-3-thiosemicarbazide (**7a**)*. Yield: 90 %; m.p. 228–230 °C. Anal. Calcd. for $C_{20}H_{16}IN_3O_3S_2$ (FW 537.39): C, 44.70; H, 3.00; S, 11.93; N, 7.82 %. Found: C, 44.77; H, 2.92; S, 11.89; N, 7.76 %. IR (KBr, cm^{-1}): 3365, 3291 (N–H stretching), 3085, 3064, 3038 (C–H stretching of aromatic ring), 1667 (C=O stretching), 1572, 1545, 1523, 1486 (C=C stretching of aromatic ring), 1326, 1295, 1156 (SO_2 stretching), 1226 (C=S stretching), 502 (C–I stretching). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 10.80 (1H, *s*, NH), 9.90 (1H, *br s*, NH), 9.80 (1H, *br s*, NH), 8.11 (4H, *s*, aromatic), 7.99 (2H, *dd*, aromatic, J = 7.9 and 1.2 Hz), 7.65 (5H, *m*, aromatic), 7.26 (2H, *br*

s, aromatic). ^{13}C-NMR (75 MHz, DMSO-d_6, δ / ppm): 181.32 (C=S), 164.90 (C=O), 143.93, 140.69, 139.17, 137.18, 136.95, 134.21, 130.04, 129.38, 128.33, 127.64, 127.59, 89.84 (aromatic ring). MS (APCI, *m*/*z*): 536 [M–H]$^-$, 1073 [2M––H]$^-$. UV–Vis (CH_3OH) (λ_{max} / nm (log ε)): 204 (4.55), 246 (4.47).

1-(4-(4-Chlorophenylsulfonyl)benzoyl)-4-(4-iodophenyl)thiosemicarbazide ***(7b)***. Yield: 83 %; m.p. 213–215 °C. Anal. Calcd. for $C_{20}H_{15}ClIN_3O_3S_2$ (FW 571.84): C, 42.01; H, 2.64; S, 11.21; N, 7.35 %. Found: C, 42.10; H, 2.59; S, 11.15; N, 7.43 %. IR (KBr, cm^{-1}): 3325, 3166 (N–H stretching), 3091, 3070, 3050 (C–H stretching of aromatic ring), 1687 (C=O stretching), 1578, 1541, 1525, 1484 (C=C stretching of aromatic ring), 1321, 1260, 1159 (SO_2 stretching), 1224 (C=S stretching), 761 (C–Cl stretching), 509 (C–I). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 10.81 (1H, *br s*, NH), 9.90 (1H, *br s*, NH), 9.80 (1H, *br s*, NH), 8.12 (4H, *s*, aromatic), 8.01 (2H, *d*, aromatic, *J* = 8.8 Hz), 7.66 (2H, *d*, aromatic, *J* = 8.8 Hz), 7.65 (2H, *d*, aromatic, *J* = 8.8 Hz), 7.28 (2H, *br s*, aromatic). ^{13}C-NMR (75 MHz, DMSO-d_6, δ / ppm): 181.53 (C=S), 164.60 (C=O), 143.26, 139.84, 139.08, 139.25, 137.26, 136.78, 130.03, 129.51, 129.29, 127.97, 127.53, 89.92 (aromatic ring). MS (APCI, *m*/*z*): 570 [M–H]$^-$, 572 [M–H]$^-$. UV––Vis (CH_3OH) (λ_{max} / nm (log ε)): 203 (4.69), 249 (4.55).

1-(4-(4-Bromophenylsulfonyl)benzoyl)-4-(4-iodophenyl)thiosemicarbazide ***(7c)***. Yield: 89 %; m.p. 228–230 °C. Anal. Calcd. for $C_{20}H_{15}BrIN_3O_3S_2$ (FW 616.29): C, 38.98; H, 2.45; S, 10.41; N, 6.82 %. Found: C, 39.06; H, 2.50; S, 10.49; N, 6.75 %. IR (KBr, cm^{-1}): 3329, 3309, 3163 (N–H stretching), 3090, 3046, 3013 (C–H stretching of aromatic ring), 1689 (C=O stretching), 1576, 1542, 1522, 1484 (C=C stretching of aromatic ring), 1320, 1261, 1160 (SO_2 stretching), 1225 (C=S stretching), 573 (C–Br stretching), 505 (C–I stretching). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 10.81 (1H, *br s*, NH), 9.90 (1H, *br s*, NH), 9.87 (1H, *br s*, NH), 8.12 (4H, *s*, aromatic), 7.92 (2H, *d*, aromatic, *J* = 8.8 Hz), 7.84 (2H, *d*, aromatic, *J* = 8.8 Hz), 7.66 (2H, *d*, aromatic, *J* = 8.8 Hz), 7.28 (2H, *br s*, aromatic). ^{13}C-NMR (75 MHz, DMSO-d_6, δ / ppm): 180.03 (C=S), 164.88 (C=O), 143.26, 139.44, 139.05, 137.23, 136.76, 132.96, 129.50, 129.28, 128.48, 128.28, 127.51, 89.76 (aromatic ring). MS (APCI, *m*/*z*): 614 [M–H]$^-$, 616 [M–H]$^-$. UV–Vis (CH_3OH) (λ_{max} / nm (log ε)): 203 (4.59), 252 (4.43).

The analytical spectral data for the newly prepared 1,2,4-triazole-3-thiones **8a**–**c** are given below.

*4-(4-Iodophenyl)-5-(4-(phenylsulfonyl)phenyl)-2,4-dihydro-3*H*-1,2,4-triazole-3-thione* ***(8a)***. Yield: 75 %; m.p. 300 °C. Anal. Calcd. for $C_{20}H_{14}IN_3O_2S_2$ (FW 519.38): C, 46.25; H, 2.72; S, 12.35; N, 8.09 %. Found: C, 46.36; H, 2.64; S, 12.30; N, 8.15 %. IR (KBr, cm^{-1}): 3411 (N–H stretching), 3091, 3059 (C–H stretching of aromatic ring), 1616 (C=N stretching of triazole ring), 1579, 1536, 1490 (C=C stretching of aromatic ring); 1323, 1290, 1159 (SO_2 stretching), 1239 (C=S stretching), 531 (C–I). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 7.96 (2H,

d, aromatic, *J* = 8.8 Hz), 7.94 (2H, *dd*, aromatic, *J* = 7.7; 1.7 Hz), 7.85 (2H, *d*, aromatic, *J* = 8.8 Hz), 7.68 (1H, *tt*, aromatic, *J* = 7.7; 1.7 Hz), 7.60 (2H, *t*, aromatic, *J* = 7.7 Hz), 7.54 (2H, *d*, aromatic, *J* = 8.8 Hz), 7.17 (2H, *d*, aromatic, *J* = = 8.8 Hz). ^{13}C-NMR (75 MHz, DMSO-d_6, δ / ppm): 169.04 (C3), 149.00 (C5), 142.61, 140.39, 138.51, 134.05, 130.91, 130.51, 130.44, 130.02, 129.58, 127.81, 127.68, 96.53. MS (APCI, *m*/*z*): 518 $[M–H]^-$. UV–Vis (CH_3OH) (λ_{max} / nm (log ε)): 204 (4.69), 240 (4.51), 249 (4.48), 323 (3.91).

*5-(4-(4-Chlorophenylsulfonyl)phenyl)-4-(4-iodophenyl)-2,4-dihydro-3*H-*-1,2,4-triazole-3-thione (**8b**)*. Yield: 94 %; m.p. 293–295 °C. Anal. Calcd. for $C_{20}H_{13}ClIN_3O_2S_2$ (FW 553.82): C, 43.37; H, 2.37; S, 11.58; N, 7.59 %. Found: C, 43.29; H, 2.29; S, 11.51; N, 7.70 %. IR (KBr, cm^{-1}): 3409 (N–H stretching), 3088, 3061, 3027 (C–H stretching of aromatic ring), 1617 (C=N stretching of triazole ring), 1579, 1539, 1490 (C=C stretching of aromatic ring); 1322, 1284, 1158 (SO_2 stretching), 1237 (C=S stretching), 768 (C–Cl stretching); 534 (C–I). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 7.96 (2H, *d*, aromatic, *J* = 8.8 Hz), 7.95 (2H, *d*, aromatic, *J* = 8.5 Hz), 7.85 (2H, *d*, aromatic, *J* = 8.8 Hz), 7.67 (2H, *d*, aromatic, *J* = 8.5 Hz), 7.54 (2H, *t*, aromatic, *J* = 8.8 Hz), 7.17 (2H, *d*, aromatic, *J* = 8.5 Hz). ^{13}C-NMR (75 MHz, DMSO-d_6, δ / ppm): 169.06 (C3), 148.96 (C5), 142.14, 139.42, 139.19, 138.52, 134.05, 130.91, 130.69, 130.17, 129.69, 129.64, 127.88, 96.54; MS (APCI, *m*/*z*): 552 $[M–H]^-$, 554 $[M–H]^-$. UV–Vis (CH_3OH) (λ_{max} / nm (log ε)): 204 (4.62), 241 (4.47), 251 (4.30), 322 (3.84).

*5-(4-(4-Bromophenylsulfonyl)phenyl)-4-(4-iodophenyl)-2,4-dihydro-3*H-*-1,2,4-triazole-3-thione (**8c**)*. Yield: 70 %; m.p. 285–286 °C. Anal. Calcd. for $C_{20}H_{13}BrIN_3O_2S_2$ (FW 598.27): C, 40.15; H, 2.19; S, 10.72; N, 7.02 %. Found: C, 40.25; H, 2.31; S, 10.65; N, 6.97 %. IR (KBr, cm^{-1}): 3410 (N–H stretching), 3086, 3061, 3028 (C–H stretching of aromatic ring), 1617 (C=N stretching of triazole ring), 1572, 1540, 1490 (C=C stretching of aromatic ring), 1323, 1280, 1158 (SO_2 stretching), 1238 (C=S stretching), 574 (C–Br); 534 (C–I). ^{1}H-NMR (300 MHz, DMSO-d_6, δ / ppm): 7.95 (2H, *d*, aromatic, *J* = 8.8 Hz), 7.90 (2H, *d*, aromatic, *J* = 8.8 Hz), 7.84 (2H, *d*, aromatic, *J* = 8.5 Hz), 7.84 (2H, *d*, aromatic, *J* = 8.5 Hz), 7.54 (2H, *d*, aromatic, *J* = 8.5 Hz), 7.17 (2H, *d*, aromatic, *J* = 8.5 Hz). ^{13}C-NMR (75 MHz, DMSO-d_6, δ / ppm): 169.08 (C3), 149.00 (C5), 142.11, 139.64, 138.54, 134.08, 133.14, 130.92, 130.69, 129.73, 129.65, 128.56, 127.90, 96.56. UV–Vis (CH_3OH) (λ_{max} / nm (log ε)): 204 (4.67), 239 (4.42), 255 (4.40), 324 (3.83).

The spectral data of all the newly synthesized compounds from the 1,2,4-triazoles and thiosemicarbazides were in accordance with the proposed structures.

The infrared spectra of the new acylthiosemicarbazides **7a**–**b** confirmed that the nucleophilic addition of hydrazides **6a**–**c** to 4-iodophenyl isothiocyanate occurred by the appearance of a new absorption band due to stretching vibration of C=S group at 1224–1226 cm^{-1}. In addition, the C=O and N–H stretching bands

were present at 1667–1689 and 3365–3163 cm^{-1}, respectively. In the 1,2,4-triazoles **8a**–**c**, the disappearance of the C=O stretching band from the acylthiosemicarbazides and the detection of the C=N stretching band at ≈1617 cm^{-1} is evidence for ring closure. 1,2,4-Triazoles **8a**–**c** may exist in the thiol and thione forms. According to the IR spectral data of compounds **8a**–**c** which have the triazole-3-thione structure, the observation of C=S stretching bands at 1237–1239 cm^{-1} and the absence of an absorption band in the 2300–2600 cm^{-1} region cited for the SH group [11,28] proved that, in the solid state, these new derivatives exist predominantly in the thionic form. The N–H stretching bands of 1,2,4-triazoles **8a**–**c** were observed at 3409–3411 cm^{-1}.

All protons were seen in the ^{1}H-NMR spectra with the expected chemical shifts and integral values. The NH protons of the acylthiosemicarbazides were observed as singlets at 9.80–10.81 ppm. The ^{13}C-NMR spectra of the newly synthesized compounds (**7a**–**c** and **8a**–**c**) showed the number of signals which were consistent with the number of carbon atoms in the molecule. The C=O carbon signal in the ^{13}C-NMR spectra of the acylthiosemicarbazides **7a**–**c** was observed at 164.60–164.90 ppm, whereas the C=S carbon signal appeared in the range 180.03–181.53 ppm. The ^{13}C-NMR spectra of compounds **8a**–**c** contained the resonance signals C3 and C5 of the triazole ring at ≈ 169 and ≈ 149 ppm, respectively. The presence of the signal at ≈ 169.00 ppm, characteristic for the carbon of a C=S group, indicated that these compounds from the 1,2,4-triazoles class existed in solution predominantly in the thione form.[29,30]

The mass spectra of compounds **7a**–**c** and **8a,b** showed an $(M–H)^-$ peak in agreement with their molecular formula. In the case of compounds which contain halogen, two molecular ion peaks were observed as expected, due to the isotopic chlorine or bromine atom in the molecule.

CONCLUSIONS

A series of novel heterocyclic compounds from the 1,2,4-triazole-3-thione class **8a**–**c** were synthesized by treatment of the corresponding acylthiosemicarbazides **7a**–**c** with a sodium hydroxide solution, at reflux. The new acylthiosemicarbazides were synthesized by nucleophilic addition of 4-(4-X-phenylsulfonyl)benzoic acid hydrazides **6a**–**c** to 4-iodophenyl isothiocyanate. The structures of these new compounds were determined by spectral data and elemental analyses. These new compounds will be tested for their biological activity.

ИЗВОД

СИНТЕЗА И КАРАКТЕРИСАЊЕ НЕКИХ 1,2,4-ТРИАЗОЛ-3-ТИОНА ДОБИЈЕНИХ ИНТРАМОЛЕКУЛСКОМ ЦИКЛИЗАЦИЈОМ НОВИХ 1-(4-(4-X-ФЕНИЛСУЛФОНИЛ)БЕНЗОИЛ)-4-(4-ЈОДФЕНИЛ)-3-ТИОСЕМИКАРБАЗИДА

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У раду су приказани нови деривати 1,2,4-триазол-3-тиона, добијени интрамолекулском циклизацијом, у базним условима, из неких ацилтиосемикарбазида који садрже дифенил-сулфонску структуру. Нови 1-(4-(4-X-фенилсулфонил)бензоил)-4-(4-јодфенил)-3-тиосемикарбазиди **7a**–**c** добијени су реакцијом хидразида 4-(4-X-фенилсулфонил)-бензоеве киселине **6a**–**c** (X = H, Cl, Br) са 4-јодфенил-изотиоцијанатом. Циклизацијом ацилтиосемикарбазида **7a**–**c** у присуству 8 % раствора NaOH добијени су 5-(4-(4-X-фенилсулфонил)фенил)-4-(4-јодфенил)-2,4-дихидро-3*H*-1,2,4-триазол-3-тиони **8a**–**c**. Структуре нових једињења утврђене су спектралним методама (IR, UV–Vis, ^{1}H-NMR, ^{13}C-NMR и MS спектри) и елементалном анализом.

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