

SYNTHESIS OF SOME 1,4-DISUBSTITUTED THIOSEMICARBAZIDES AS INTERMEDIATES FOR THE SYNTHESIS OF 1,3,4-THIADIAZOLE DERIVATIVES

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Abstract

The 4-phenyl-1-[(α -acylamino- β -(*p*-X-phenyl)]acriloyl thiosemicarbazides **3a-h** were synthesized using 2-R-4-(*p*-X-benzylidene)-oxazol-5-ones **1a-h** as starting materials. The reaction of compounds **1a-h** with hydrazine hydrate led to the formation of acid hydrazides **2a-h**. The thiosemicarbazide derivatives **3a-h** were obtained by nucleophilic addition of corresponding acid hydrazides **2a-h** to phenylisothiocyanate. The newly synthesized compounds structures were elucidated by spectral data and elemental analysis.

Rezumat

Au fost sintetizați derivații 4-fenil-1-[(α -acilamino- β -(*p*-X-fenil)]acriloil tiosemicarbazidici **3a-h** folosind 2-R-4-(*p*-X-benziliden)-oxazol-5-onele **1a-h** drept materii prime. Reacția compușilor **1a-h** cu hidratul de hidrazină a dus la formarea hidrazidelor **2a-h**. Derivații tiosemicarbazidici **3a-h** au fost obținuți prin adiția nucleofilă a hidrazidelor corespunzătoare **2a-h** la fenilizotiocianat. Structura compușilor sintetizați a fost elucidată pe baza datelor spectrale și analizei elementale.

Keywords: acid hydrazides; thiosemicarbazides; 1,3,4-thiadiazoles

Introduction

Scientific studies reported that some substituted thiosemicarbazides possess significant anticancer, anticonvulsant, antihypoglycemic or anti-inflammatory activities [3, 5, 8]. On the other hand, thiosemicarbazides are valuable „building blocks” for the construction of larger molecules. Being easily cyclized by the action of acids, bases or oxidants, thiosemicarbazides are useful versatile reagents for the preparation of heterocyclic ring systems (e.g. 1,2,4-triazole, 1,3,4-thiadiazole, 1,3,4-oxadiazole, 1,3,4-triazine derivatives, etc.) [1, 2, 4, 6, 8, 10, 12, 13].

Continuing our research in the field of biologically active heterocyclic compounds [10-13], in this paper we describe the synthesis of some 1,4-disubstituted thiosemicarbazides as starting materials for the preparation of some 2,5-disubstituted 1,3,4-thiadiazoles.

Materials and Methods

General: Melting points were measured using the open capillary tube method on Schmelzpunkt Bestimmer Apotec apparatus and are uncorrected. The purity of the synthesized compounds was checked by thin layer chromatography on Silicagel 60 F₂₅₄ Merck plates and visualized by exposure in UV light. The IR spectra were recorded as potassium bromide pellets using a JASCO FTIR-615 spectrophotometer. The ¹H-NMR spectra in deuteriochloroform were recorded by a Varian Mercury-300 spectrometer. The NMR spectral data are reported in parts per million downfield from the internal standard (tetramethylsilane, δ 0.0). The FAB-MS (Fast atom bombardment mass-spectrometry) spectra were obtained using a VG-70SE spectrometer. The elemental analysis was performed using a Vario El CHNS analyzer. All chemicals and solvents were purchased from Reactivul București, Chimprod and Merck.

General procedure for the synthesis of acrylic acid hydrazides **2**

A fine powder of the corresponding compound **1** (0.04 mol) was suspended in 65 mL of methanol and cooled in an ice bath for 10-15 min, then 10 mL (0.28 mol) of 90% hydrazine hydrate was added under stirring when the reaction mixture become colorless and the compound **1** was completely dissolved. The reaction mixture was kept under stirring at 0°C for another 10 min and then allowed to warm up to room temperature and stirred at this temperature for another 30 min when a white solid appeared. The crude product was collected by filtration, washed with cold 50% methanol, dried *in vacuo* and recrystallized from methanol to provide the desired product **2**.

General procedure for the synthesis of acriloyl thiosemicarbazides **3**

A mixture of corresponding acid hydrazide **2** (0.02 mol) in 50 mL of ethanol (hydrazide **2** solved in ethanol by heating) and phenyl isothiocyanate (0.025 mol) was heated under reflux on a water bath for 5 min. The reaction mixture was filtered still hot. After cooling to room temperature, a white solid appeared. The crude product was collected by filtration, washed with cold ethanol and recrystallized from ethanol to obtain the desired product **3**.

Results and Discussion

Even if some isothiocyanates are difficult to handle and store, published preparations of thiosemicarbazides include reaction of acid hydrazides with isothiocyanates as the most frequently used method [2, 3, 4, 7, 9].

The synthesis of 4-phenyl-1-[α -acylamino- β -(*p*-X-phenyl)]acriloyl thiosemi carbazides **3a-h** was achieved through the versatile and efficient synthetic route outlined in Figure 1.

Thus, the reaction of 2-R-4-(*p*-X-benzylidene)-oxazol-5-ones **1a-h** with hydrazine hydrate in methanol at 0°C led to the formation of the acid hydrazides **2a-h**. The thiosemicarbazide derivatives **3a-h** were obtained by the nucleophilic addition of corresponding acid hydrazides **2a-h** to phenyl isothiocyanate in ethanol under reflux and in reasonable good yields.

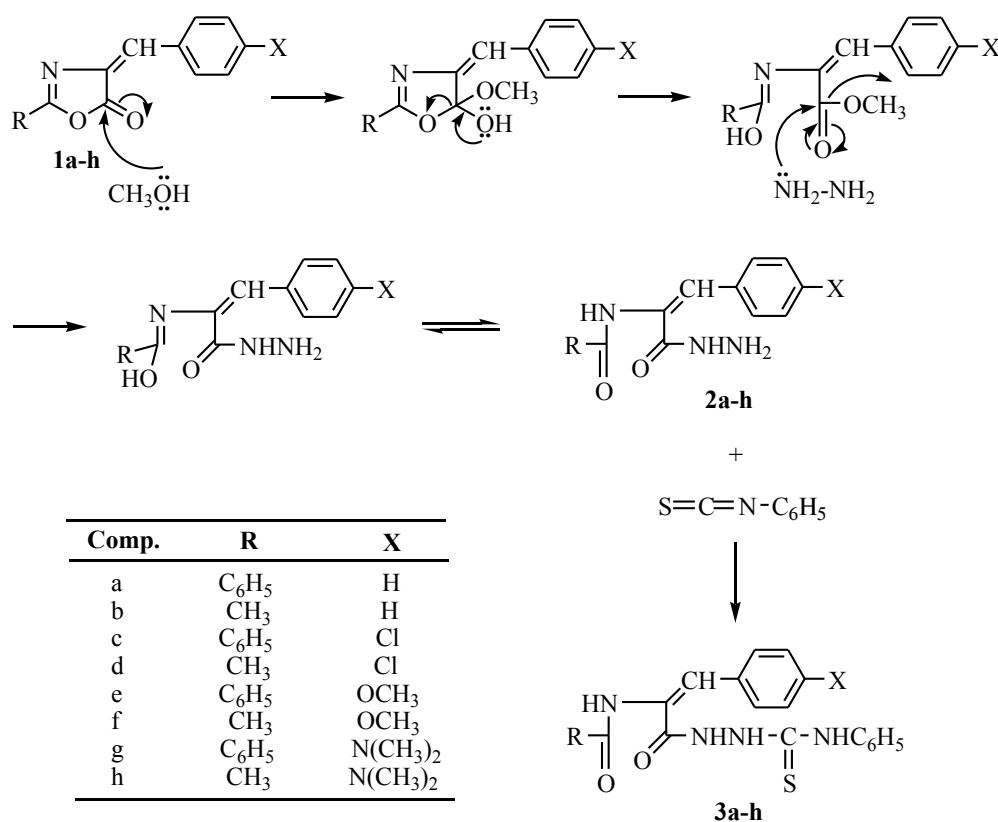


Figure 1

The synthesis of 4-phenyl-1-[α -acylamino- β -(*p*-X-phenyl)]acriloyl thiosemicarbazides **3a-h**

Following this synthetic procedure we obtained 8 new thiosemicarbazide derivatives (3a-h), white crystalline powders, soluble in ethanol, less soluble in water. The compounds structures were elucidated by elemental analysis and IR, MS and ^1H -NMR spectral data. The IR spectra revealed the presence of C=O and C=S groups in the thiosemicarbazide moiety, the protons signals in ^1H -NMR spectra and the molecular peaks in the mass spectra were in agreement to the synthesized compounds structures.

α -Benzoylamino- β -phenylacrylic acid hydrazide (2a). White crystals, mp 161°C, 60% yield. IR (KBr) cm^{-1} : 3296-3245 (2NH + NH₂), 1685 (benzoyl C=O), 1665 (hydrazide C=O). MS (FAB, positive ion mode) m/z 282 [M+H⁺]. *Anal.* Calcd for C₁₆H₁₅N₃O₂: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.55; H, 5.21; N, 15.02. MW 281.31.

α -Acetylamino- β -phenylacrylic acid hydrazide (2b). White crystals, mp 154-156°C, 67% yield. IR (KBr) cm^{-1} : 3301-3178 (2NH + NH₂), 1678 (acetyl C=O), 1658 (hydrazide C=O). MS (FAB, positive ion mode) m/z 220 [M+H⁺]. *Anal.* Calcd for C₁₁H₁₃N₃O₂: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.02; H, 5.77; N, 19.37. MW 219.24.

α -Benzoylamino- β -(*p*-chlorophenyl)acrylic acid hydrazide (2c). White crystals, mp 186-187°C, 57% yield. IR (KBr) cm^{-1} : 3305-3172 (2NH + NH₂), 1687 (benzoyl C=O), 1651 (hydrazide C=O). MS (FAB, positive ion mode) m/z 316 [M+H⁺]. *Anal.* Calcd for C₁₆H₁₄ClN₃O₂: C, 60.86; H, 4.47; N, 13.31. Found: C, 60.71; H, 4.75; N, 13.02. MW 315.75.

α -Acetylamino- β -(*p*-chlorophenyl)acrylic acid hydrazide (2d). White crystals, mp 132-134°C, 58% yield. IR (KBr) cm^{-1} : 3289-3167 (2NH + NH₂), 1691 (acetyl C=O), 1653 (hydrazide C=O). MS (FAB, positive ion mode) m/z 254 [M+H⁺]. *Anal.* Calcd for C₁₁H₁₂ClN₃O₂: C, 52.08; H, 4.77; N, 16.56. Found: C, 51.79; H, 4.51; N, 16.82. MW 253.68.

α -Benzoylamino- β -(*p*-methoxyphenyl)acrylic acid hydrazide (2e). White crystals, mp 155-156°C, 63% yield. IR (KBr) cm^{-1} : 3301-3187 (2NH + NH₂), 1685 (benzoyl C=O), 1667 (hydrazide C=O). MS (FAB, positive ion mode) m/z 312 [M+H⁺]. *Anal.* Calcd for C₁₇H₁₇N₃O₃: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.27; H, 5.41; N, 13.67. MW 311.34.

α -Acetylamino- β -(*p*-methoxyphenyl)acrylic acid hydrazide (2f). White crystals, mp 136-138°C, 70% yield. IR (KBr) cm^{-1} : 3287-3198 (2NH + NH₂), 1675 (acetyl C=O), 1653 (hydrazide C=O). MS (FAB, positive ion mode) m/z 250 [M+H⁺]. *Anal.* Calcd for C₁₂H₁₅N₃O₃: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.97; H, 6.02; N, 16.57. MW 249.27.

α -Benzoylamino- β -(*p*-dimethylaminophenyl)acrylic acid hydrazide (2g). White crystals, mp 250-251°C, 65% yield. IR (KBr) cm^{-1} : 3284-

3187 (2NH + NH₂), 1692 (benzoyl C=O), 1665 (hydrazide C=O). MS (FAB, positive ion mode) *m/z* 325 [M+H⁺]. *Anal.* Calcd for C₁₈H₂₀N₄O₂: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.87; H, 6.02; N, 17.57. MW 324.38.

α -Acetylamino- β -(*p*-dimethylaminophenyl)acrylic acid hydrazide (2h). White crystals, mp 199-200°C, 67% yield. IR (KBr) cm⁻¹: 3321-3215 (2NH + NH₂), 1671 (acetyl C=O), 1657 (hydrazide C=O). MS (FAB, positive ion mode) *m/z* 263 [M+H⁺]. *Anal.* Calcd for C₁₃H₁₈N₄O₂: C, 59.53; H, 6.92; N, 21.36. Found: C, 59.47; H, 7.12; N, 21.55. MW 262.31.

4-Phenyl-1-(α -benzoylamino- β -phenyl)acriloyl thiosemicarbazide (3a). White crystals, mp 141-142°C, 70% yield. IR (KBr) cm⁻¹: 3378-3301 (4NH), 1695 (benzoyl C=O), 1680 (C=O), 1340 (C=S). ¹H-NMR (300 MHz, CDCl₃) δ : 6.57 (s, 1H, =CH), 7.32-7.42 (m, 5H, Ar-H), 7.44-7.58 (m, 10H, Ar-H), 9.37 (s, 1H, -NH), 9.46 (s, 1H, -NH), 9.72 (s, 1H, -NH), 11.25 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z* 417 [M+H⁺]. *Anal.* Calcd for C₂₃H₂₀N₄O₂S: C, 66.33; H, 4.84; N, 13.45; S, 7.70. Found: C, 66.52; H, 4.75; N, 13.21; S, 7.53. MW 416.5.

4-Phenyl-1-(α -acetylamino- β -phenyl)acriloyl thiosemicarbazide (3b). White crystals, mp 183-184°C, 75% yield. IR (KBr) cm⁻¹: 3389-3305 (4NH), 1699 (acetyl C=O), 1685 (C=O), 1341 (C=S). ¹H-NMR (300 MHz, CDCl₃) δ : 2.51 (s, 3H, -CH₃), 6.49 (s, 1H, =CH), 7.35-7.48 (m, 10H, Ar-H), 9.38 (s, 1H, -NH), 9.51 (s, 1H, -NH), 9.95 (s, 1H, -NH), 10.75 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z* 355 [M+H⁺]. *Anal.* Calcd for C₁₈H₁₈N₄O₂S: C, 61.00; H, 5.12; N, 15.81; S, 9.05. Found: C, 60.89; H, 5.21; N, 15.75; S, 8.97. MW 354.43.

4-Phenyl-1-(α -benzoylamino- β -(*p*-clorophenyl)acriloyl thiosemicarbazide (3c). White crystals, mp 142-143°C, 67% yield. IR (KBr) cm⁻¹: 3295-3208 (4NH), 1701 (benzoyl C=O), 1690 (C=O), 1315 (C=S). ¹H-NMR (300 MHz, CDCl₃) δ : 6.76 (s, 1H, =CH), 7.42-7.57 (m, 8H, Ar-H), 8.01-8.07 (m, 6H, Ar-H), 9.38 (s, 1H, -NH), 9.67 (s, 1H, -NH), 9.96 (s, 1H, -NH), 10.75 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z* 452 [M+H⁺]. *Anal.* Calcd for C₂₃H₁₉ClN₄O₂S: C, 61.26; H, 4.25; N, 12.42; S, 7.11. Found: C, 61.32; H, 4.71; N, 12.54; S, 7.02. MW 450.9.

4-Phenyl-1-(α -acetylamino- β -(*p*-clorophenyl)acriloyl thiosemicarbazide (3d). White crystals, mp 202-204°C, 72% yield. IR (KBr) cm⁻¹: 3378-3298 (4NH), 1697 (acetyl C=O), 1682 (C=O), 1305 (C=S). ¹H-NMR (300 MHz, CDCl₃) δ : 2.35 (s, 3H, -CH₃), 7.27 (s, 1H, =CH), 7.56-7.72 (m, 9H, Ar-H), 9.65 (s, 1H, -NH), 9.76 (s, 1H, -NH), 10.21 (s, 1H, -NH), 10.87 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z* 389

[M+H⁺]. *Anal.* Calcd for C₁₈H₁₇ClN₄O₂S: C, 55.59; H, 4.41; N, 14.41; S, 8.25. Found: C, 55.71; H, 4.71; N, 14.12; S, 8.37. MW 388.8.

4-Phenyl-1-[α -benzoylamino- β -(*p*-methoxyphenyl)]acriloyl thiosemicarba zide (3e). White crystals, mp 178-180°C, 73% yield. IR (KBr) cm⁻¹: 3379-3308 (4NH), 1696 (benzoyl C=O), 1681 (C=O), 1309 (C=S). MS (FAB, positive ion mode) *m/z* 447 [M+H⁺]. *Anal.* Calcd for C₂₄H₂₂N₄O₃S: C, 64.56; H, 4.97; N, 12.55; S, 7.18. Found: C, 64.47; H, 4.78; N, 12.50; S, 7.02. MW 446.5.

4-Phenyl-1-[α -acetylamino- β -(*p*-methoxyphenyl)]acriloyl thiosemicarba zide (3f). White crystals, mp 187-188°C, 78% yield. IR (KBr) cm⁻¹: 3387-3310 (4NH), 1695 (acetyl C=O), 1680 (C=O), 1321 (C=S). ¹H-NMR (300 MHz, CDCl₃) δ : 2.31 (s, 3H, -CH₃), 3.82 (s, 3H, -OCH₃), 6.45 (s, 1H, =CH), 7.31-7.44 (m, 9H, Ar-H), 9.45 (s, 1H, -NH), 9.76 (s, 1H, -NH), 9.97 (s, 1H, -NH), 10.38 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z* 385 [M+H⁺]. *Anal.* Calcd for C₁₉H₂₀N₄O₃S: C, 59.36; H, 5.24; N, 14.57; S, 8.34. Found: C, 59.52; H, 4.97; N, 14.35; S, 8.37. MW 384.4.

4-Phenyl-1-[α -benzoylamino- β -(*p*-dimethylaminophenyl)]acriloyl thiosemi carbazide (3g). White crystals, mp 168-170°C, 70% yield. IR (KBr) cm⁻¹: 3298-3209 (4NH), 1695 (benzoyl C=O), 1681 (C=O), 1345 (C=S). MS (FAB, positive ion mode) *m/z* 460 [M+H⁺]. *Anal.* Calcd for C₂₅H₂₅N₅O₂S: C, 65.34; H, 5.48; N, 15.24; S, 6.98. Found: C, 65.27; H, 5.53; N, 15.07; S, 7.04. MW 459.5.

4-Phenyl-1-[α -acetylamino- β -(*p*-dimethylaminophenyl)]acriloyl thiosemi carbazide (3h). White crystals, mp 258-260°C, 74% yield. IR (KBr) cm⁻¹: 3375-3310 (4NH), 1705 (acetyl C=O), 1695 (C=O), 1325 (C=S). ¹H-NMR (300 MHz, CDCl₃) δ : 2.42 (s, 3H, -CH₃), 2.85 (s, 3H, -NCH₃), 2.97 (s, 3H, -NCH₃), 6.55 (s, 1H, =CH), 7.28-7.39 (m, 9H, Ar-H), 9.38 (s, 1H, -NH), 9.77 (s, 1H, -NH), 10.01 (s, 1H, -NH), 11.23 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z* 398 [M+H⁺]. *Anal.* Calcd for C₂₀H₂₃N₅O₂S: C, 60.43; H, 5.83; N, 17.62; S, 8.07. Found: C, 60.27; H, 5.92; N, 17.51; S, 7.87. MW 397.4.

Conclusions

New 1,4-disubstituted thiosemicarbazides were synthesized, their structures were elucidated and the compounds were characterized by their main physical properties. The synthesized compounds will be further investigated for their potential as starting materials in the cyclization reaction in order to obtain some 2,5-disubstituted 1,3,4-thiadiazoles.

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