5-ARYLAMINO-1,3,4-THIADIAZOL-2-YL-ACETAMIDE. SYNTHESIS AND SPECTRAL STUDIES

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Abstract

Considering the broad spectrum of pharmacological properties exhibited by various 1,3,4-thiadiazole derivatives and in continuation of our work in the field of biologically active heterocyclic compounds, we describe the synthesis of some 5-arylamino-1,3,4-thiadiazol-2-yl-acetamides.

The desired 1,3,4-thiadiazole compounds bearing different substituents were obtained by the cyclization of the corresponding thiosemicarbazides with concentrated sulphuric acid at room temperature.

The newly synthesized compounds were obtained in good yields and their structures were elucidated by spectral data and elemental analysis.

Keywords: 1,3,4-thiadiazoles, acetamide, thiosemicarbazides, ring closure reaction.

5-ARILAMINO-1,3,4-TIADIAZOL-2-IL-ACETAMIDA. SINTEZA ŞI STUDIUL SPECTRAL

Rezumat

Ţinând cont de varietatea de proprietăţi farmacologice manifestate de diverşi derivaţi 1,3,4-tiadiazolici şi în continuarea preocupărilor noastre în domeniul compuşilor heterociclici biologic activi, în lucrarea de faţă este prezentată sinteza unor amide ale acidului 5-arilamino-1,3,4-tiadiazol-2-il-acetic.

Compuşii 1,3,4-tiadiazolici doriţi, divers substituiţi, au fost obţinuţi prin ciclizarea tiosemicarbazidelor corespunzătoare, sub acţiunea acidului sulfuric concentrat, la temperatura camerei.

Noii compuşi sintetizaţi au fost obţinuţi cu randamente bune, iar structurile lor au fost elucidate pe baza datelor spectrale şi analizei elementale.

Cuvinte cheie: 1,3,4-tiadiazoli, acetamida, tiosemicarbazide, reacţie de ciclizare.

INTRODUCTION

Thiadiazoles are important classes of nitrogen-sulphur containing heterocycles. They have extensive applications as structural units of various biologically important molecules and as useful intermediates in medicinal chemistry. It is well established that various 1,3,4-thiadiazole derivatives exhibit a broad spectrum of pharmacological properties such as antibacterial, antifungal [1-3], analgesic [4], antitumor [5-6], anticonvulsant [7], anxiolytic [8], antidiabetic, anti-inflammatory [9-10], etc. In view of the above mentioned facts and in continuation of our work in the field of biologically active heterocyclic compounds [11-13], in this paper we describe the synthesis of some 5-arylamino-1,3,4-thiadiazol-2-yl-acetamides.

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MATERIAL AND METHODS

General

Melting points were measured using open capillary tube method on Schmelzpunkt Bestimmer Apotec apparatus and were uncorrected. The purity of the synthesized compounds was checked by thin layer chromatography on Silicagel 60 F_{254} 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 ^{1}H-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 spectra were obtained using a VG-70SE spectrometer. The elemental analysis was performed using Vario El CHNS analyzer. All chemicals and solvents were purchased from Farmachim Ploieşti, Reactivul Bucureşti, Chimprod, Fluka Chemie and Merck.

General procedure for the synthesis of 4-aryl-1-cyanoacetylthiosemicarbazides 5

To a solution of cyanoacetic acid hydrazide **3** (12 mmol) in 10 mL of ethanol, 15 mmol of the appropriate arylisothiocyanate **4** was added. The mixture was refluxed on a water bath for 5-10 min when the product started to separate. Cooling the reaction mixture, the solid product separated in a big amount, then it was collected by filtration, washed with aqueous ethanol and recrystallized from ethanol to obtain the desired product **5**.

General procedure for the synthesis of 2,5-disubstituted 1,3,4-tiadiazoles (6a-g)

A fine powder of the corresponding thiosemicarbazides **5** (4 mmol) was gradually added to cold concentrated sulphuric acid (3 mL, 0ºC) and the mixture was stirred at room temperature for 30 min. Then the reaction mixture was poured into ice-water mixture, filtrated after the ice melting and the filtrate made alkaline to pH 8 with ammonia. The precipitated product was filtered, washed with cold water, dried and recrystallized from ethanol to afford the desired product **6**.

5-Phenylamino-1,3,4-thiadiazol-2-yl-acetamide (6a). White crystals, mp 230-232°C (ethanol), 71% yield. IR (KBr) cm^{-1}: 3315-3120 (νNH + $νNH_2$), 1690 (νC=O), 1606 (νC=N), 685 (νC–S–C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.15 (s, 2H, CH_2), 5.67 (s, 2H, NH_2), 7.08-7.25 (m, 5H, Ar-H), 10.5 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 235 [M+H$^+$]. *Anal.* Calcd for $C_{10}H_{10}N_4OS$: C, 51.27; H, 4.30; N, 23.91; S, 13.69. Found: C, 51.45; H, 4.12; N, 24.3; S 13.77. MW 234.28.

5-(4-Methylphenylamino)-1,3,4-thiadiazol-2-yl-acetamide (6b). Colourless needles, mp 240-241°C (ethanol), 73% yield. IR (KBr) cm^{-1}: 3350-3140 (νNH + $νNH_2$), 1699 (νC=O), 1605 (νC=N), 690 (νC–S–C). MS (FAB, positive ion mode) *m/z* 249 [M+H$^+$]. *Anal.* Calcd for $C_{11}H_{12}N_4OS$: C, 53.21; H, 4.87; N, 22.56; S, 12.91. Found: C, 53.44; H, 4.52; N, 22.25; S 13.06. MW 248.3.

5-(4-Bromophenylamino)-1,3,4-thiadiazol-2-yl acetamide (6c). Colourless needles, mp 258-259°C (ethanol), 75% yield. IR (KBr) cm^{-1}: 3314-3125 (νNH + $νNH_2$), 1695 (νC=O), 1605 (νC=N), 689 (νC–S–C), 570 (νC-Br). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.25 (s, 2H, CH_2), 5.82 (s, 2H, NH_2), 7.22-7.67 (m, 4H, Ar-H), 10.95 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 314 [M+H$^+$]. *Anal.* Calcd for $C_{10}H_9BrN_4OS$: C, 38.35; H, 2.90; N, 17.89; S, 10.24. Found: C, 38.23; H, 3.21; N, 18.22; S 10.35. MW 313.17.

5-(4-Chlorophenylamino)-1,3,4-thiadiazol-2-yl-acetamide (6d). Colourless prisms, mp 154-156°C (ethanol, decomp.), 70% yield. IR (KBr) cm^{-1}: 3322-3200 (νNH + $νNH_2$), 1695 (νC=O), 1605 (νC=N), 683 (νC–S–C), 674 (νC-Cl). MS (FAB, positive ion mode) *m/z* 269 [M+H$^+$]. *Anal.* Calcd for $C_{10}H_9ClN_4OS$: C, 44.70; H, 3.38; N, 20.85; S, 11.93. Found: C, 44.76; H, 3.56; N, 20.92; S 11.52. MW 268.7.

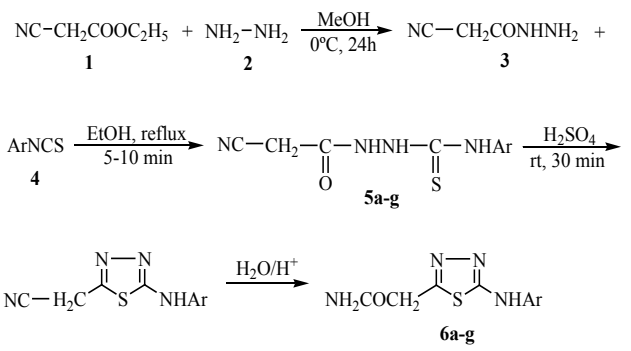
5-(4-Methoxyphenylamino)-1,3,4-thiadiazol-2-yl-acetamide (6e). White prisms, mp 210-212°C (ethanol), 70% yield. IR (KBr) cm^{-1}: 3247-3200 (νNH + $νNH_2$), 1692 (νC=O), 1609 (νC=N), 685 (νC–S–C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.8 (s, 3H, OCH_3), 4.21 (s, 2H, CH_2), 5.87 (s, 2H, NH_2), 7.15-7.31 (m, 4H, Ar-H), 10.41 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 265 [M+H$^+$]. *Anal.* Calcd for $C_{11}H_{12}N_4O_2S$: C, 49.99; H, 4.58; N, 21.20; S, 12.13. Found: C, 50.13; H, 4.33; N, 21.50; S 11.89. MW 264.3.

5-(4-Ethoxyphenylamino)-1,3,4-thiadiazol-2-yl-acetamide (6f). White prisms, mp 174-176°C (ethanol), 69% yield. IR (KBr) cm^{-1}: 3355-3270 (νNH + $νNH_2$), 1695 (νC=O), 1608 (νC=N), 690 (νC–S–C). MS (FAB, positive ion mode) *m/z* 279 [M+H$^+$]. *Anal.* Calcd for $C_{12}H_{14}N_4O_2S$: C, 51.78; H, 5.07; N, 20.13; S, 11.52. Found: C, 51.46; H, 5.15; N, 20.48; S 11.34. MW 278.33.

5-Naphtylamino-1,3,4-thiadiazol-2-yl-acetamide (6g). White crystals, mp 192-194°C (ethanol), 65% yield. IR (KBr) cm^{-1}: 3302-3212 (νNH + $νNH_2$), 1685 (νC=O), 1603 (νC=N), 660 (νC–S–C). MS (FAB, positive ion mode) *m/z* 361 [M+H$^+$]. *Anal.* Calcd for $C_{20}H_{16}N_4OS$: C, 66.65; H, 4.47; N, 15.54; S, 8.90. Found: C, 66.71; H, 4.32; N, 15.67; S 9.01. MW 360.43.

RESULTS AND DISCUSSIONS

The synthesis of 5-arylamino-1,3,4-thiadiazol-2-yl-acetamides **6a-g** was accomplished by the synthetic sequences outlined in Scheme 1.



Scheme 1. Synthesis of 5-arylamino-1,3,4-thiadiazol-2-yl-acetamides (6**a-g**).

Thus, ethyl cyanoacetate **1** reacted with hydrazine hydrate **2** in methanolic ice-cooled solution to yield the cyanoacetic acid hydrazide **3**. The nucleophilic addition of the compound **3** to the aromatic isothiocyanates **4** in ethanol under reflux gave, in reasonable good yields, the thiosemicarbazide derivatives **5a-g** which were cyclised in concentrated sulphuric acid at room temperature into the 5-arylamino-1,3,4-thiadiazol-2-yl-acetamides **6a-g** as the result of a ring closure reaction and hydrolysis of the nitrile group.

The amides **6a-g** are white or colourless crystals, soluble in ethanol and dimethylsulfoxide, slightly soluble in chloroform, less soluble in water. The compounds structures were elucidated by elemental analysis and spectral data. The IR spectra revealed the presence of C=N group and the C-S-C endocyclic bonds in the 1,3,4-thiadiazole ring and also the exocyclic C=O amide, NH_2 amide and secondary amine NH groups. Thus, the IR spectra showed absorption bands between 1609-1603 cm^{-1} characteristic of C=N group and between 1699-1685 cm^{-1} characteristic of C=O group. ^{1}H-NMR spectra showed characteristic signals for the aromatic protons as multiplet (δ 7.08-7.67 ppm) and also the signals for the exocyclic CH_2 (δ 4.15-4.25 ppm), NH_2 (δ 5.67-5.87 ppm) and NH (δ 10.41-10.95 ppm) groups as singlet. Mass spectra of the synthesized compounds showed the molecular peaks in agreement with their molecular formula.

CONCLUSIONS

A series of 5-arylamino-1,3,4-thiadiazol-2-yl-acetamides were synthesized by the cyclisation of the corresponding thiosemicarbazides with concentrated sulphuric acid, at room temperature. The compounds were characterized by their main physical properties and their structures were elucidated by elemental analysis and spectral data.

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