ORIGINAL ARTICLE

5-ARYLAMINO-1,3,4-THIADIAZOL-2-YL ACETIC ACID ESTERS AS INTERMEDIATES FOR THE SYNTHESIS OF NEW BISHETEROCYCLIC COMPOUNDS

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Abstract

A series of 5-arylamino-1,3,4-thiadiazol-2-yl acetic acid esters have been synthesized by the cyclization of the corresponding thiosemicarbazides with concentrated sulphuric acid followed by the esterification of the amide group. The thiosemicarbazides derivatives were obtained by nucleophilic addition of cyanoacetic acid hydrazide to different arylisothiocyanates. The newly synthesized compounds were characterized by their physical parameters and the structures were elucidated by spectral data and elemental analysis.

Rezumat

Au fost sintetizaţi o serie de esteri ai acidului 5-arilamino-1,3,4-tiadiazol-2-il acetic prin ciclizarea tiosemicarbazidelor corespunzătoare cu acid sulfuric concentrat, urmată de hidroliza grupării amidice. Derivaţii tiosemicarbazidici au fost obţinuţi prin adiţia nucleofilă a cianacethidrazidei la diverşi arilizotiocianaţi. Noii compuşi sintetizaţi au fost caracterizaţi prin constantele lor fizice, iar structurile au fost elucidate pe baza datelor spectrale şi analizei elementale.

Keywords: 1,3,4-thiadiazoles; cyanoacetic acid hydrazide; thiosemicarbazides; ring closure reaction

Introduction

A wide variety of pharmacological properties have been shown to be associated with 1,3,4-thiadiazole derivatives which include antimicrobial [1, 6, 14], analgesic [15], antidepressant and anxiolytic [5], antihypertensive, anticonvulsant, anti-inflammatory [10, 13], local anaesthetic [11], antituberculosis [12], antiviral activities [3], etc. As a part of our strategy to synthesize heterocyclic molecules of medicinal relevance, our research group recently reported some results in the field of synthesis of 1,3,4-thiadiazole compounds [8, 9, 17, 18]. On the other hand, some heterocycles incorporating C=O or C=S groups (e.g. coumarins, 1,2,4-triazoline-5-thiones, etc.) have also been reported to possess a wide spectrum of biological effects like antitumor, antiviral, anticonvulsant or antibacterial [2, 4, 7, 16]. Therefore, coupling of these two biologically active moieties would be expected to afford interesting series of compounds having enhanced biological properties. Due to their diverse biological activities it was considered worthwhile to synthesize some new 1,3,4-thiadiazole derivatives as intermediates for new bisheterocyclic compounds.

Materials and Methods

The melting point determinations were carried out using the open capillary tube method on Schmelzpunkt Bestimmer Apotec apparatus. The thin layer chromatography (TLC) analysis was performed on Silica gel 60 F_{254} Merck plates. The IR spectra were recorded using a JASCO FTIR-615 spectrophotometer. The ^{1}H-NMR spectra in deuteriochloroform were recorded by a Varian Mercury-300 spectrometer with tetramethylsilane as internal standard (δ 0.0). The fast atom bombardment mass spectrometry (FAB-MS) spectra were recorded on an analytical VG-70SE mass spectrometer. The elemental analysis was performed using a Vario El CHNS analyser. All other chemicals and solvents were of commercial grade without further purification and were purchased from Farmachim Ploieşti, Reactivul Bucureşti, Chimprod, Fluka Chemie and Merck.

General procedure for the synthesis of 5-arylamino-1,3,4-thiadiazol-2-yl acetic acid esters 8a-g

Procedure A. To a solution of 2 mmol of 5-arylamino-1,3,4-thiadiazol-2-yl acetamides **6a-g** in 50 mL of anhydrous methanol was added concentrated sulphuric acid (80 mmol). The mixture was refluxed on a water bath for 3-4h. After cooling, the reaction content was poured into ice-water mixture. The precipitated solid was collected by filtration, washed with water and

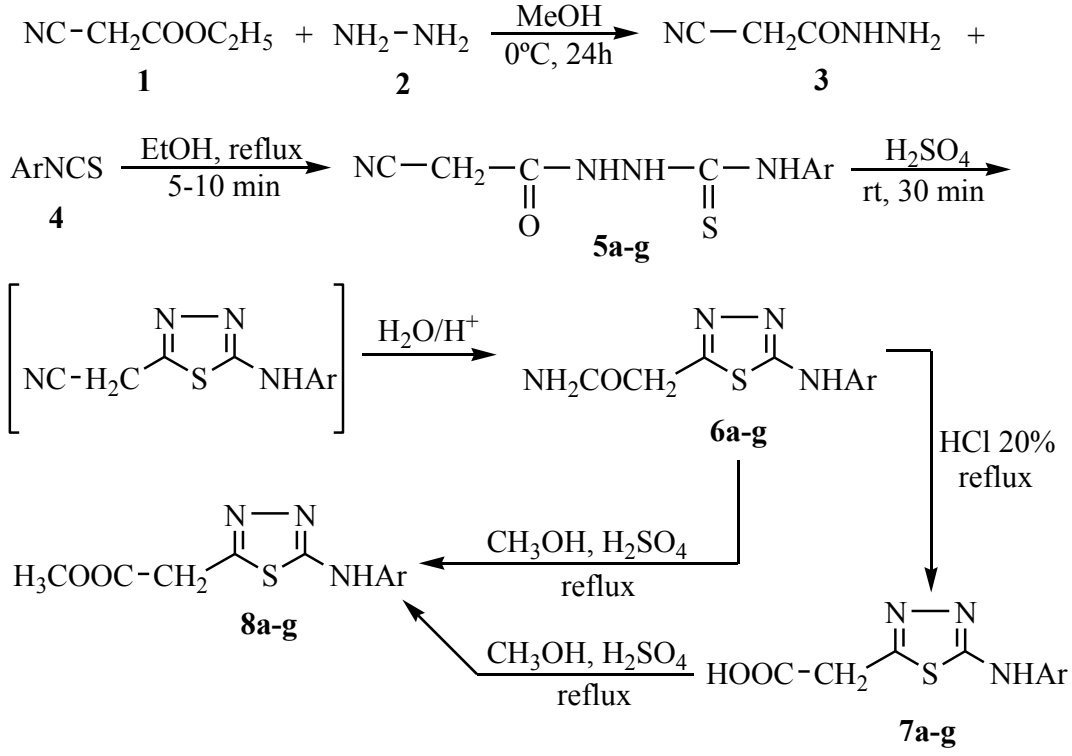
recrystallized from methanol to obtain the desired products **8a-g**.

Procedure B. To 2 mmol of 5-arylamino-1,3,4-thiadiazol-2-yl acetamides **6a-g** was added 20% hydrochloric acid (10 mL) and the mixture was refluxed for 2.5h. After cooling, water was added and the reaction mixture was alkalinised with concentrated ammonia and filtrated. The filtrate was then acidulated with diluted hydrochloric acid and the separated product was collected, washed with water and recrystallized from an appropriate solvent to obtain the desired products **7a-g**.

To a solution of 4 mmol of 5-arylamino-1,3,4-thiadiazol-2-yl acetic acids **7a-g** in 60 mL of anhydrous methanol was added concentrated sulphuric acid (40 mmol). The mixture was refluxed on a water bath for 4-4.5h, after that the reaction content was poured into water. The precipitated solid was collected by filtration, washed with water and recrystallized from methanol to afford the desired products **8a-g**.

The synthesis of 5-arylamino-1,3,4-thiadiazol-2-yl acetic acid esters **8a-g** was accomplished by the synthetic sequences outlined in Figure 1. Thus, the reaction of ethylcyanoacetate **1** with hydrazine hydrate **2** in methanolic ice-cooled solutions, followed by nucleophilic addition of the formed cyanoacetic acid hydrazide **3** to the aromatic isothiocyanates **4** in ethanol under reflux, gave the thiosemicarbazides derivatives **5a-g** in reasonable good yields. In the case of the aromatic isothiocyanates bearing electron withdrawing groups (e.g. chlorine, bromine) on the *para* position of the aromatic ring, the reaction with cyanoacetic acid hydrazide was faster and the products were obtained with very high yields (90-95%).

After treating with concentrated sulphuric acid at room temperature, the intermediary thiosemicarbazides **5a-g** were cyclized 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 [19]. In the next step, the synthesis of the esters **8a-g** was afforded by two ways: acidic hydrolysis under reflux with 20% hydrochloric acid of the amides **6a-g** followed by the esterification in acidic conditions (10 eq conc. sulphuric acid) of the acids **7a-g** (procedure B) or by refluxing of the compounds **6a-g** in alcohol and sulphuric acid (methanol or ethanol, 40 eq conc. sulphuric acid) (procedure A).



Ar = C_6H_5 (**8a**), 4-$CH_3C_6H_4$ (**8b**), 4-BrC_6H_4 (**8c**), 4-ClC_6H_4 (**8d**), 4-$CH_3OC_6H_4$ (**8e**), 4-$C_2H_5OC_6H_4$ (**8f**), $C_{10}H_7$ (naphtyl, **8g**).

Figure 1.
Synthesis of 5-arylamino-1,3,4-thiadiazol-2-yl acetic acid esters **8a-g**

Results and Discussion

5-Phenylamino-1,3,4-thiadiazol-2-yl acetic acid methyl ester (8a). White crystals, mp 205-206°C (ethanol), 75% yield. IR (KBr) cm^{-1}: 3320 (NH), 1751 (C=O ester), 1610 (C=N), 687 (C–S–C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.5 (s, 3H, CH_3), 4.08 (s, 2H, CH_2), 7.1-7.4 (m, 5H, Ar-H), 10.48 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 250 [M+H$^+$]. *Anal.* Calcd for $C_{11}H_{11}N_3O_2S$: C, 53.00; H, 4.45; N, 16.86; S, 12.86. Found: C, 52.87; H, 4.21; N, 16.97; S 12.55. MW 249.29.

5-(4-Methylphenylamino)-1,3,4-thiadiazol-2-yl acetic acid methyl ester (8b). Colourless needles, mp 167-168°C (ethanol), 77% yield. IR (KBr) cm^{-1}: 3355 (NH), 1743 (C=O ester), 1609 (C=N), 690 (C–S–C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.3 (s, 3H, CH_3-Ar), 3.32 (s, 3H, CH_3OCO), 4.1 (s, 2H, CH_2), 7.21-7.67 (m, 4H, Ar-H), 10.42 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 264 [M+H$^+$]. *Anal.* Calcd for $C_{12}H_{13}N_3O_2S$: C, 54.74; H, 4.98; N, 15.96; S, 12.18. Found: C, 54.44; H, 4.76; N, 16.14; S 12.33. MW 263.32.

5-(4-Bromophenylamino)-1,3,4-thiadiazol-2-yl acetic acid methyl ester (8c). White needles, mp 192-195°C (ethanol), 71% yield. IR (KBr) cm^{-1}: 3318 (NH), 1745 (C=O ester), 1609 (C=N), 689 (C–S–C), 580 (C-Br). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.25 (s, 3H, CH_3), 4.05 (s, 2H, CH_2), 7.22-7.55 (m, 4H, Ar-H), 10.65 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 329 [M+H$^+$]. *Anal.* Calcd for $C_{11}H_{10}BrN_3O_2S$: C, 40.26; H, 3.07; N, 12.80; S, 9.77. Found: C, 40.42; H, 3.17; N, 13.13; S 9.89. MW 328.19.

5-(4-Chlorophenylamino)-1,3,4-thiadiazol-2-yl acetic acid methyl ester (8d). White crystals, mp 168-170°C (ethanol, decomp.), 69% yield. IR (KBr) cm^{-1}: 3328 (NH), 1747 (C=O ester), 1608 (C=N), 700 (C-Cl), 683 (C–S–C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.28 (s, 3H, CH_3), 4.1 (s, 2H, CH_2), 7.18-7.43 (m, 4H, Ar-H), 10.77 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 284 [M+H$^+$]. *Anal.* Calcd for $C_{11}H_{10}ClN_3O_2S$: C, 46.56; H, 3.55; N, 14.81; S, 11.30. Found: C, 46.98; H, 3.48; N, 14.35; S 11.76. MW 283.73.

5-(4-Methoxyphenylamino)-1,3,4-thiadiazol-2-yl acetic acid methyl ester (8e). White prisms, mp 164-165°C (ethanol), 79% yield. IR (KBr) cm^{-1}: 3250 (NH), 1736 (C=O ester), 1605 (C=N), 680 (C–S–C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.3 (s, 3H, CH_3), 3.9 (s, 3H, CH_3O), 4.12 (s, 2H, CH_2), 7.12-7.39 (m, 4H, Ar-H), 10.45 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 280 [M+H$^+$]. *Anal.* Calcd for $C_{12}H_{13}N_3O_3S$: C, 51.60; H, 4.69; N, 15.04; S, 11.48. Found: C, 51.85; H, 4.32; N, 14.65; S 11.21. MW 279.31.

5-(4-Ethoxyphenylamino)-1,3,4-thiadiazol-2-yl acetic acid methyl ester (8f). White prisms, mp 177-178°C (ethanol), 70% yield. IR (KBr) cm^{-1}: 3360 (NH), 1750 (C=O ester), 1621 (C=N), 690 (C–S–C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.3 (t, 3H, CH_2-$\underline{CH_3}$), 3.2 (s, 3H, CH_3OCO), 4.15 (s, 2H, CH_2), 4.25 (q, 2H, $\underline{CH_2}$-CH_3), 7.2-7.43 (m, 4H, Ar-H), 10.42 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 294 [M+H$^+$]. *Anal.* Calcd for $C_{13}H_{15}N_3O_3S$: C, 53.23; H, 5.15; N, 14.32; S, 10.93. Found: C, 53.15; H, 5.33; N, 14.66; S 10.65. MW 293.34.

5-Naphtylamino-1,3,4-thiadiazol-2-yl acetic acid methyl ester (8g). White crystals, mp 123-124°C (ethanol), 67% yield. IR (KBr) cm^{-1}: 3311 (NH), 1745 (C=O ester), 1603 (C=N), 665 (C–S–C). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.42 (s, 3H, CH_3), 4.2 (s, 2H, CH_2), 7.41-7.89 (m, 7H, Ar-H), 10.7 (s, 1H, NH). MS (FAB, positive ion mode) *m/z* 300 [M+H$^+$]. *Anal.* Calcd for $C_{15}H_{13}N_3O_2S$: C, 60.18; H, 4.38; N, 14.04; S, 10.71. Found: C, 60.45; H, 4.70; N, 14.38; S 10.35. MW 299.35.

The synthesized compounds **8a-g** are colourless or white crystals, soluble in methanol, 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 C-S-C bonds belonging to 1,3,4-thiadiazole ring and also the exocyclic secondary amine NH and COO ester groups. Thus, the νCOO vibration produced a strong stretching band in the region 1751-1736 cm^{-1} and the heterocyclic C=N stretching vibrations were found in the area 1621-1603 cm^{-1}, which is in agreement with literature data. ^{1}H-NMR spectra displayed characteristic signals for the aromatic protons between 7.1-7.89 ppm. The signals belonging to -NH proton appeared between 10.42-10.77 ppm and the signals derived from ester group were observed at 4.05-4.2 ppm (-CH_2-) and 3.2-3.5 ppm (CH_3OCO-). 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 acetic acid esters were synthesized in good yields and their structures were elucidated by elemental analysis and spectral data. The synthesized compounds will be further investigated for their potential as starting materials in order to obtain some new bisheterocyclic compounds with potential biological activities.

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