SYNTHESIS OF NEW 2-PHENYLAMINO-5-[(α-ACYLAMINO)-*p*-X-STIRYL]-1,3,4-THIADIAZOLE COMPOUNDS

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Abstract

Cyclization of 4-phenyl-1-[α-acylamino-β-(*p*-X-phenyl)]acriloyl thiosemicarbazides **2a-h** with concentrated sulfuric acid conduCted to 2-phenylamino-5-[(α-acylamino)-*p*-X-stiryl]-1,3,4-thiadiazole **3a-h**. The newly synthesized compounds structures were elucidated by elemental analysis and spectral data.

Rezumat

Ciclizarea 4-fenil-1-[α-acilamino-β-(*p*-X-fenil)]acriloil tiosemicarbazidelor **2a-h** cu acid sulfuric concentrat a dus la obţinerea compuşilor 2-fenilamino-5-[(α-acilamino)-*p*-X-stiril]-1,3,4-tiadiazolici **3a-h**. Structurile noilor compuşi sintetizaţi au fost elucidate pe baza analizei elementale şi datelor spectrale.

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

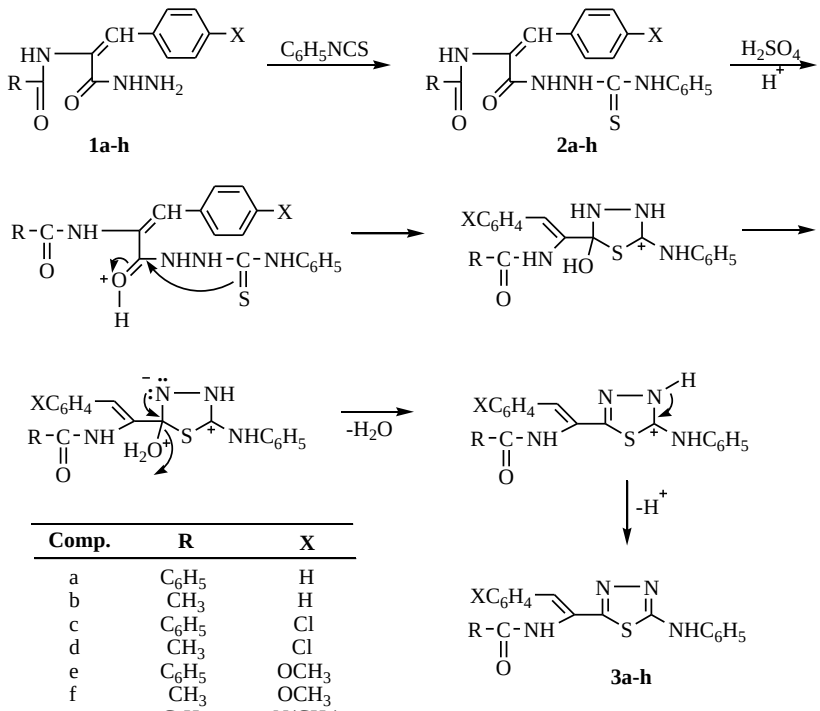
Introduction

The chemical research in the field of 1,3,4-thiadiazole derivatives have received significant attention since many scientists, investigating this kind of compounds, have revealed their broad spectrum of biological activities. Thus, the 1,3,4-thiadiazole core constitutes the active part of several biologically active compounds, including antibacterial [1, 2, 7, 16, 17, 24], antimycotic [6, 10], antiviral [3], antihypertensive [22, 23], anticonvulsant [4, 5], hypoglicemic [8, 15], antileukemic [12], local anesthetic agents [11], etc.

Literature survey revealed that slight modifications in the structure can result in qualitative as well as quantitative changes in the activity. Taking into account these findings and by continuing to our interest on the synthesis of 1,3,4-thiadiazoles [18-21], our research has been focused in the synthesis of some 2-amino-5-substituted-1,3,4-thiadiazole derivatives with the aim to obtain new biologically active compounds.

Materials and Methods

In a previous paper [9] we reported the synthesis of 4-phenyl-1-[α-acylamino-β-(*p*-X-phenyl)]acriloyl thiosemicarbazides **2a-h** by the nucleophilic addition of corresponding acid hydrazides **1a-h** to phenyl isothiocyanate. Literature survey reveals several procedures for dehydrative cyclization of 1,4-disubstituted thiosemicarbazides to their 1,3,4-thiadiazole analogues using a variety of dehydrating agents, including sulfuric acid, phosphorus oxychloride, polyphosphoric acid and methane sulphonic acid [1, 13, 14]. The 2-phenylamino-5-[(α-acylamino)-*p*-X-stiryl]-1,3,4-thiadiazole derivatives **3a-h** were succesfully obtained by the reaction of thiosemicarbazides **2a-h** with concentrated sulfuric acid under stirring at room temperature as the result of a ring closure reaction. The synthetic pathway of the compounds **3a-h** is presented in Figure 1.



Comp.	R	X
a	C_6H_5	H
b	CH_3	H
c	C_6H_5	Cl
d	CH_3	Cl
e	C_6H_5	OCH_3
f	CH_3	OCH_3
g	C_6H_5	$N(CH_3)_2$
h	CH_3	$N(CH_3)_2$

Figure 1.
Synthetic pathway for the preparation of 2-phenylamino-5-[(α-acylamino)-*p*-X-stiryl]1,3,4-thiadiazole derivatives **3a-h**

Following this cyclization procedure we obtained 8 new 1,3,4-thiadiazole derivatives, white or yellowish crystalline powders, soluble in ethanol, less soluble in water. The compounds structures were elucidated by elemental analysis and IR, MS and ^{1}H-NMR spectral data. The IR spectra revealed the presence of C=N group in the 1,3,4-thiadiazole ring and the exocyclic C=O and NH groups. The protons signals in ^{1}H-NMR spectra and the molecular peaks showed by the mass spectra were in agreement with the synthesized compounds structures.

Experimental

General: Melting points were measured using the open capillary tube method using a Schmelzpunkt Bestimmer Apotec apparatus and are 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 deuterated chloroforme were recorded using 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 fast atom bombardament – mass spectrometry (FAB-MS) 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 Bucureşti, Chimprod and Merck.

General procedure for the synthesis of 1,3,4-thiadiazole derivatives 3a-h

A fine powder of the corresponding thiosemicarbazides **2** (3.6 mmol) was added drop wise to cold concentrated sulfuric acid (10 mL, 0ºC) and the mixture was stirred for 10 min. Then the mixture was allowed to warm up to room temperature. After stirring for 30 min, the resulting solution was poured onto crushed ice and alkalinised to pH 8 with ammonia. The precipitated product was filtered, washed with cold water, dried and recrystallized from ethanol to obtain the desired product **3**.

Results and Discussion

2-Phenylamino-5-(α-benzoylamino)stiryl-1,3,4-thiadiazole (3a). White crystals, mp 159-160°C, 71% yield. IR (KBr) cm^{-1}: 3328-3150 (NH), 1710 (C=O), 1575 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.27 (s, 1H, =CH), 6.46-7.01 (m, 5H, Ar-H), 7.14-7.30 (m, 5H, Ar-H), 7.44-7.95 (m, 5H, Ar-H), 7.81 (s, 1H, -NH), 9.76 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z*

399 [M+H$^+$]. *Anal.* Calcd for $C_{23}H_{18}N_4OS$: C, 69.32; H, 4.55; N, 14.06; S, 8.05. Found: C, 69.52; H, 4.75; N, 13.81; S, 7.98. MW 398.5.

2-Phenylamino-5-(α-acetylamino)stiryl-1,3,4-thiadiazole (3b). White crystals, mp 118-120°C, 68% yield. IR (KBr) cm^{-1}: 3316-3140 (NH), 1695 (C=O), 1550 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.02 (s, 3H, -CH_3), 6.35 (s, 1H, =CH), 6.48-7.05 (m, 5H, Ar-H), 7.27-7.35 (m, 5H, Ar-H), 7.85 (s, 1H, -NH), 10.50 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z* 337 [M+H$^+$]. *Anal.* Calcd for $C_{18}H_{16}N_4OS$: C, 64.26; H, 4.79; N, 16.65; S, 9.53. Found: C, 64.15; H, 4.71; N, 16.87; S, 9.71. MW 336.4.

2-Phenylamino-5-[(α-benzoylamino)-p-chlorostiryl]-1,3,4-thiadiazole (3c). Light yellow crystals, mp 187°C, 73% yield. IR (KBr) cm^{-1}: 3326-3140 (NH), 1699 (C=O), 1581 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.32 (s, 1H, =CH), 6.47-7.01 (m, 5H, Ar-H), 7.22-7.24 (m, 4H, Ar-H), 7.40-7.95 (m, 5H, Ar-H), 7.75 (s, 1H, -NH), 9.85 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z* 433 [M+H$^+$]. *Anal.* Calcd for $C_{23}H_{17}ClN_4OS$: C, 63.81; H, 3.96; N, 12.94; S, 7.41. Found: C, 63.97; H, 4.05; N, 12.78; S, 7.65. MW 432.9.

2-Phenylamino-5-[(α-acetylamino)-p-chlorostiryl]-1,3,4-thiadiazole (3d). Light yellow crystals, mp 205-206°C, 70% yield. IR (KBr) cm^{-1}: 3316-3125 (NH), 1695 (C=O), 1599 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.12 (s, 3H, -CH_3), 6.27 (s, 1H, =CH), 6.47-7.03 (m, 5H, Ar-H), 7.25-7.27 (m, 4H, Ar-H), 7.85 (s, 1H, -NH), 9.75 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z* 371 [M+H$^+$]. *Anal.* Calcd for $C_{18}H_{15}ClN_4OS$: C, 58.30; H, 4.08; N, 15.11; S, 8.65. Found: C, 58.05; H, 4.12; N, 15.24; S, 8.87. MW 370.8.

2-Phenylamino-5-[(α-benzoylamino)-p-methoxystiryl]-1,3,4-thiadiazole (3e). White crystals, mp 212-214°C, 75% yield. IR (KBr) cm^{-1}: 3289-3170 (NH), 1705 (C=O), 1575 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.73 (s, 3H, -OCH_3), 6.25 (s, 1H, =CH), 6.46-7.19 (m, 9H, Ar-H), 7.44-7.95 (m, 5H, Ar-H), 7.81 (s, 1H, -NH), 10.29 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z* 429 [M+H$^+$]. *Anal.* Calcd for $C_{24}H_{20}N_4O_2S$: C, 67.27; H, 4.70; N, 13.07; S, 7.48. Found: C, 67.21; H, 4.37; N, 12.85; S, 7.45. MW 428.5.

2-Phenylamino-5-[(α-acetylamino)-p-methoxystiryl]-1,3,4-thiadiazole (3f). White crystals, mp 179-180°C, 77% yield. IR (KBr) cm^{-1}: 3288-3200 (NH), 1712 (C=O), 1581 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.02 (s, 3H, -CH_3), 3.88 (s, 3H, -OCH_3), 6.45 (s, 1H, =CH), 6.52-7.01 (m, 5H, Ar-H), 7.12-7.19 (m, 5H, Ar-H), 7.85 (s, 1H, -NH), 10.29 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z* 367 [M+H$^+$]. *Anal.* Calcd for $C_{19}H_{18}N_4O_2S$: C, 62.28; H, 4.95; N, 15.29; S, 8.75. Found: C, 62.21; H, 4.78; N, 15.35; S, 8.46. MW 366.4.

2-Phenylamino-5-[(α-benzoylamino)-p-dimethylaminostiryl]-1,3,4-thiadiazole (3g). White crystals, mp 264-266°C, 70% yield. IR (KBr) cm^{-1}:

3318-3255 (NH), 1702 (C=O), 1562 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.83 (s, 3H, -CH_3), 2.85 (s, 3H, -CH_3), 6.27 (s, 1H, =CH), 6.45-7.12 (m, 9H, Ar-H), 7.51-7.95 (m, 5H, Ar-H), 8.01 (s, 1H, -NH), 10.37 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z* 442 [M+H^+]. *Anal.* Calcd for $C_{25}H_{23}N_5OS$: C, 68.00; H, 5.25; N, 15.86; S, 7.26. Found: C, 67.78; H, 5.31; N, 15.72; S, 7.45. MW 441.5.

2-Phenylamino-5-[(α-acetylamino)-p-dimethylaminostiryl]-1,3,4-tiadiazole (3h). White crystals, mp 188-189°C, 72% yield. IR (KBr) cm^{-1}: 3291-3215 (NH), 1699 (C=O), 1556 (C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.05 (s, 3H, -CH_3), 2.81 (s, 3H, -NCH_3), 2.85 (s, 3H, -NCH_3), 6.41 (s, 1H, =CH), 6.47-7.12 (m, 9H, Ar-H), 8.15 (s, 1H, -NH), 10.67 (s, 1H, -NH). MS (FAB, positive ion mode) *m/z* 380 [M+H^+]. *Anal.* Calcd for $C_{20}H_{21}N_5OS$: C, 63.30; H, 5.58; N, 18.46; S, 8.45. Found: C, 63.41; H, 5.31; N, 18.72; S, 8.31. MW 379.5.

Conclusions

We have synthesized some 2,5-disubstituted 1,3,4-thiadiazole derivatives, their structures were elucidated and the compounds were characterized by their main physical properties. The synthesized compounds will be further investigated for their biological activity.

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