

Synthesis of Some 1,3,4-Thiadiazoline Derivatives

S. KABILAN*, C. RAMALINGAN and S. BALASUBRAMANIAN
Department of Chemistry, Annamalai University, Annamalai Nagar-608 002, India
E-mail: kabilan@satyam.net.in

Some 4-acetyl-2-(acetylamino)- Δ^2 -1,3,4-thiadiazoline derivatives have been synthesised by cyclisation of thiosemicarbazones of some acyclic and cyclic betones using acetic anhydride and are fully characterised by their physical properties and spectral data.

Key Words: Synthesis, Spectra, 1,3,4-Thiadiazoline, Derivatives.

INTRODUCTION

Thiosemicarbazones were shown to exhibit potent activity against bacteria, leprosy, viral infection etc¹. The discovery of tibione² [*p*-acetamido benzaldehyde thiosemicarbazone] as a reputed clinically active tuberculostat brought to fore front thiosemicarbazones as a group of antitubercular agents. Aldehyde and ketone thiosemicarbazones were reported to give 1,3,4-thiadiazoline upon oxidative cyclisation with NaOH/K₃[Fe(CN)₆]³. Synthesis of 5 α -cholestan-3-spiro-3,4-acetyl-2-(acetylamino)- Δ^2 -1,3,4-thiadiazoline from 5 α -cholestan-3-one was reported⁴. But in many cases unsubstituted thiosemicarbazones do not cyclise in to 2-amino- 1,3,4-thiadiazoline.

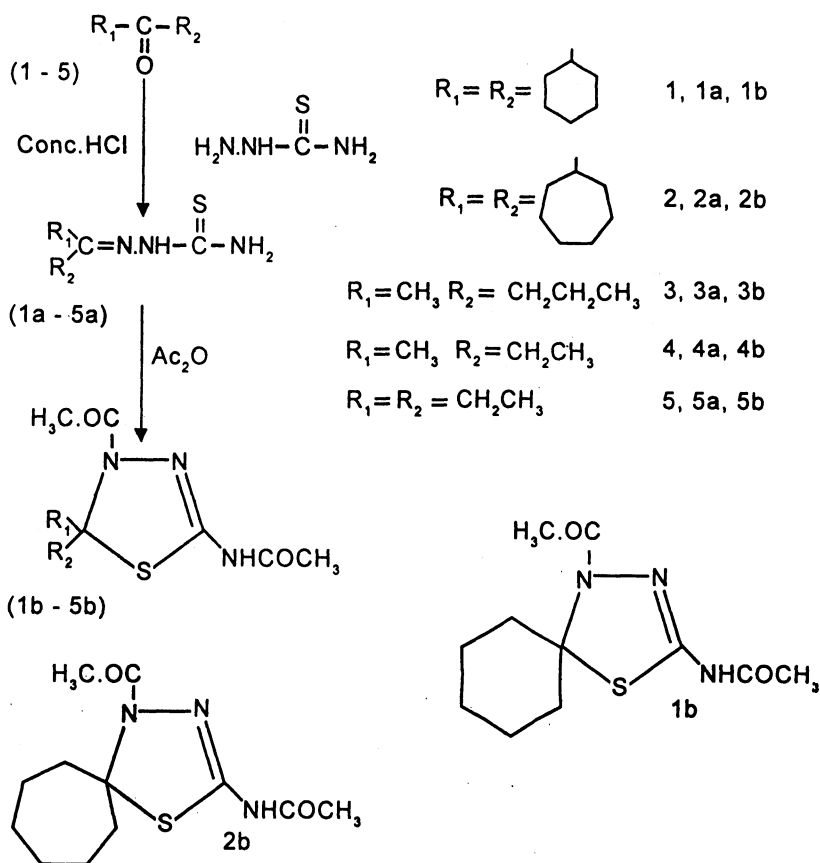
A relatively recent method of conversion of unsubstituted aldehyde and ketone thiosemicarbazones into 1,3,4-thiadiazoline involved acetylation of thiosemicarbazones⁵⁻⁷. 1,3,4-Thiadiazoline derivatives were shown to be potent medicinally active compounds⁸. We report here the synthesis of some 4-acetyl-2-(acetylamino)- Δ^2 -1,3,4-thiadiazolines.

RESULTS AND DISCUSSION

As shown in Scheme-1, first the respective ketone thiosemicarbazones (**1a–5a**) were prepared in high yields by condensing thiosemicarbazide with appropriate ketones (**1–5**) in the presence of trace amount of Conc. HCl. The reaction progress was monitored by conducting TLC. The formation of ketone thiosemicarbazone were proved beyond doubt by IR bands at 1680–1639 and 3494–3139 cm⁻¹ for $\nu(\text{C}=\text{N})$ and $\nu(-\text{NH}/\text{NH}_2)$ groups respectively, whereas $\nu(\text{C}=\text{S})$ was ascertained by its characteristic band at 1282–1078 cm⁻¹. The IR spectral data and physical constants of ketone thiosemicarbazones (**1a–5a**) are given in Table-1.

The corresponding acylated 1,3,4-thiadiazolines (**1b–5b**) with appropriate yields (40–85%) were prepared by refluxing ketone thiosemicarbazones with acetic anhydride. The reaction progress was monitored by performing TLC. The formation of respective 1,3,4-thiadiazoline were ascertained by IR, ¹H NMR and mass spectral data for all the compounds. For all the compounds (**1b–5b**), the IR

bands at 1708–1701, 3156–3153, 1260–1235 and 799–717 cm^{-1} were assigned for $\nu(\text{C}=\text{O})$, $\nu(-\text{NH})$, $\nu(\text{C}=\text{N})$ and $\nu(\text{C}-\text{S})$ groups respectively. The characteristic infrared band for $\nu(\text{C}=\text{S})$, as ketone thiosemicarbazones were not seen in IR spectra of 1,3,4-thiadiazolines. The absence of IR band for $\nu(\text{C}=\text{S})$ and



SCHEME-1

TABLE-I
PHYSICAL CONSTANTS AND IR DATA OF KETONE
THIOSEMICARBAZONES (1a-5a)

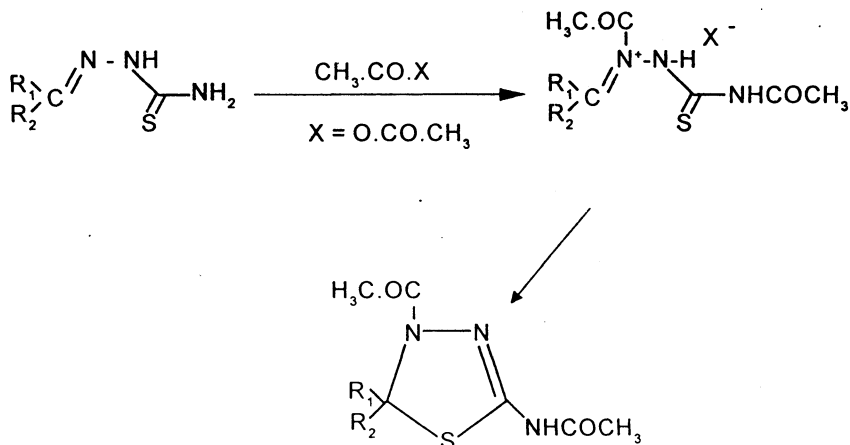
Compound	Yield (%)	m.p. ($^{\circ}\text{C}$)	IR (cm^{-1})
1a	75	123	3479 $\nu(\text{NH}_2)$, 3196 $\nu(\text{NH})$, 1639 $\nu(\text{C}=\text{N})$, 1078 $\nu(\text{C}=\text{S})$
2a	68	126	3494 $\nu(\text{NH}_2)$, 3109 $\nu(\text{NH})$, 1688 $\nu(\text{C}=\text{N})$, 1182 $\nu(\text{C}=\text{S})$
3a	43	61	3380 $\nu(\text{NH}_2)$, 3162 $\nu(\text{NH})$, 1670 $\nu(\text{C}=\text{N})$, 1087 $\nu(\text{C}=\text{S})$
4a	58	152	3310 $\nu(\text{NH}_2)$, 3249 $\nu(\text{NH})$, 1685 $\nu(\text{C}=\text{N})$, 1282 $\nu(\text{C}=\text{S})$
5a	77	165	3421 $\nu(\text{NH}_2)$, 3343 $\nu(\text{NH})$, 1670 $\nu(\text{C}=\text{N})$, 1090 $\nu(\text{C}=\text{S})$

presence of new bands for $\nu(\text{C—N})$ and $\nu(\text{C—S})$ confirms the formation of 1,3,4-thiadiazolines.

^1H NMR spectrum of **1b** and their frequency values of ring hydrogens clearly indicates the conformation of cyclohexane ring may be in the chair form. A signal at 2.05 ppm for *gem* equatorial hydrogen orientations (H_{2e} & H_{6e}) (12Hz) and a signal at 1.44 ppm for *gem* axial hydrogen orientation (H_{3a} & H_{5a}) (40Hz). A signal at 1.66 ppm for H_{4e} hydrogen (16Hz), a signal at 1.88 ppm for H_{3e} & H_{5e} and at 3.00 ppm for H_{2a} & H_{6a} hydrogen of cyclohexane ring. In ^1H NMR spectrum of **2b**, a signal at 2.90 ppm and 2.84 ppm is for H_{2a} and H_{7a} hydrogens and signal at 2.14 ppm and 2.12 ppm is for H_{2e} and H_{7e} hydrogens respectively. Other ring protons were appeared at 1.80–1.57 ppm. However, the individual signals cannot be distinguished because only few lines were obtained in the spectrum.

To confirm further the formation of 1,3,4-thiadiazolines, ^{13}C NMR spectra of **5b** was recorded as a representative of all the compounds under study. The carbonyl carbons ($-\text{NCOCH}_3$, $-\text{NHCOCH}_3$) resonates at 169.93 and 168.83 ppm. The ($\text{C}=\text{N}$) carbon absorbed at 143.75 ppm. The methyl carbons of the acetyl groups are observed at 24.49 and 24.23 ppm. The signals at 24.73 and 24.61 ppm are assigned for methylene and methyl carbons of two ethyl groups respectively. The quaternary carbon appeared at 35.99 ppm.

In EI mass spectra, molecular ion peak was obtained for all the compounds (**1b–5b**). The physical and spectral data of all the five thiadiazolines are given in Table-2. All the investigations clearly indicates the formation of 1,3,4-thiadiazolines. For the formation of above compounds a plausible mechanism (**Scheme-2**) is proposed on the basis of hard and soft acid base (HSAB) principle. The harder acetylating reagent reacts with harder nitrogen atom rather than softer sulfur atom and this acylation mostly favours the cyclisation of thiosemicarbazones to the expected 1,3,4-thiadiazolines.



SCHEME-2

TABLE 2
 PHYSICAL CONSTANTS AND SPECTRAL DATA OF 1,3,4-THIADIAZOLINES (1b-5b)

Compound	Yield (%)	m.p. (°C)	IR (cm ⁻¹)	¹ H NMR (δ) ppm	MS (m/z)
1a	72	177	3154 v(NH), 1708 v(C=O), 1510 v(C=N), 1235 v(C-N), 721, v(C-S)	8.5(s, 1H, NH), 1.44(H _{3a} , H _{5a} , 40Hz),	225(M ⁺), 213, 170, 157, 128, 115, 96, 71, 43(100%), 39, 27 M ⁺ stands for C ₁₁ H ₁₇ N ₃ O ₂ S
				1.66(H _{4c} , 16Hz), 2.05(H _{2e} , H _{6e} , 12Hz),	
				1.83(H _{3e} , H _{5e}), 3.0(H _{2a} , H _{6a}),	
				2.16(s, 3H, NCOCH ₃),	
				2.17(s, 3H, NHCOCCH ₃)	
2b	68	205	3154 v(NH), 1708 v(C=O), 1511 v(C=N), 1235 v(C-N), 717 v(C-S)	2.90, 2.84(H _{2a} & H _{7a}),	269(M ⁺), 227, 184, 170, 157, 115, 95, 55, 43(100%), 28, M ⁺ stands for C ₁₂ H ₁₉ N ₃ O ₂ S
				2.14, 2.12(H _{2e} & H _{7e}), 1.82-1.57 (ring H), 2.19 (s, 3H, NCOCH ₃),	
				2.17 (s, 3H, NHCOCCH ₃), 8.8 (s, 1H, NH).	
				8.13, (s, 1H, NH),	
				2.13-1.9 (t, 2H, C ₂ (CH ₂),	
3b	42	76	1705 v(C=O), 1509 v(C=N), 1239 v(C-N), 724 v(C-S)	1.60 (m, 5H, C ₃ (CH ₂)), 0.94 (t, CH ₃),	243(M ⁺), 215, 208, 186, 158, 116, 99, 71, 43(100%), 28, M ⁺ stands for C ₁₀ H ₁₇ N ₃ O ₂ S
				1.97 (s, 3H, C ₂ (CH ₃)),	
				2.16 (s, 3H, NCOCH ₃),	
				2.17 (s, 3H, NHCOCCH ₃)	
				8.0, (s, 1H, NH), 0.94 (t, 3H, C ₃),	
4b	56	124	3155 v(NH), 1701 v(C=O), 1500 v(C=N), 1260 v(C-N), 799 v(C-S)	1.97 (s, 3H, C ₂ (CH ₃)), 1.98 (q, 2H, C ₂)	229(M ⁺), 201, 172, 157, 130, 115, 71, 43(100%), 28 M ⁺ stands for C ₉ H ₁₅ N ₃ O ₂ S
				2.16 (s, 3H, NCOCH ₃),	
				2.17 (s, 3H, NHCOCCH ₃)	
				0.94 (t, 3H, C ₃); 1.01 (t, 3H, C ₃),	
				1.97 (q, 2H, C ₇); 1.96 (q, 2H, C ₂),	
5b	80	183.5	3153 v(NH), 1706 v(C=O), 1508 v(C=N), 1242 v(C-N), 796 v(C-S)	8.0 (s, 1H, NH), 2.16 (s, 3H, NCOCH ₃),	243(M ⁺), 215, 208, 158, 144, 116, 71, 59, 43(100%), 28 M ⁺ stands for C ₁₀ H ₁₇ N ₃ O ₂ S
				2.17 (s, 3H, NHCOCCH ₃)	

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. Silica gel (120 mesh) was used for TLC. ^1H NMR spectra of compounds were recorded at 23°C on "Jeol"—400 MHz spectrophotometer using CDCl_3 as solvent and TMS as internal standard. ^{13}C NMR spectrum was recorded at "DPX"—200 MHz spectrophotometer. The infrared spectra were run as KBr pellet forms on a "Bruker"—1 FS 66 V FT—IR spectrophotometer and mass spectra were recorded on "Bruker" mass spectral instrument. All chemicals used were of AnalaR grade.

Ketone thiosemicarbazones (1a–5a)

To a boiling solution of respective ketone (0.01 mole) in methanol (25 mL) with few drops of conc. HCl, the methanolic solution of thiosemicarbazide (0.01 mol) was added dropwise with stirring. The reaction mixture was refluxed for 2 h over water bath. After cooling, the solid products separated were filtered off and recrystallized from methanol.

Cyclohexane-5-spiro-4-acetyl-2-(acetylamino)- Δ^2 -1,3,4-thiadiazoline (1b)

Cyclohexanone thiosemicarbazone (0.0025 M) (1a) was treated with freshly distilled acetic anhydride (20 mL) and the mixture was refluxed for 3 h at 100–110°C. The removal of the solvent from the cooled reaction mixture in vacuum gave a solid mass which was purified by recrystallization from benzene. Cycloheptane-5-spiro-4-acetyl-2-(acetylamino)- Δ^2 -1,3,4-thiadiazoline (2b). 5-Methyl-5-propyl-4-acetyl-2-(acetylamino)- Δ^2 -1,3,4-thiadiazoline (3b), 5-ethyl-5-methyl-4-acetyl-2-(acetylamino)- Δ^2 -1,3,4-thiadiazoline (4b) and 5,5-diethyl-4-acetyl-2-(acetylamino)- Δ^2 -1,3,4-thiadiazoline (5b) were synthesised by adopting the same procedure from respective ketone thiosemicarbazones (2a–5a).

ACKNOWLEDGEMENT

Authors are thankful to Dr. Kaelvi Philaja, Professor of Physical Chemistry, University of Turkey, Finland for recording mass spectra.

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