SYNTHESIS OF 7-ETHOXY-3-METHYL-4H-1,4-BENZOTHIAZINES

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Abstract

Synthesis of 4H-1,4-benzothiazines is reported by the condensation of 5-ethoxy-2-aminobenzethiol with β-diketones in DMSO. 2-Aminobenzenethiol readily oxidized to bis-(2-aminophenyl)disulfide which on reaction with β-diketones cyclizes to 4H-1,4-benzothiazines via intermediate formation of enaminoketones.

Introduction

4H-1,4-benzothiazines derivatives possess a wide spectram of biological activities similar to phenothiazines[1,2] due to the presence of a fold along nitrogen-sulfur axis which is structural specificity to impart pharmacological activities[3-10]. It is considered worthwhile to synthesize hitherto unknown benzothiazines to make them for pharmacological activities[11-17].

Result and Discussions

In the present work hitherto unknown 4H-1,4-benzothiazines have been synthesized by the condensation and oxidative cyclization of 2-amino-5-ethoxybenzenethiol **I** and active methylene compounds **III** in DMSO. Under the experimental conditions 2-aminobenzenethiol I is readily oxidized to bis-(2-aminophenyl)disulphide **II**. The reaction proceeds through the formation of an intermediate enaminoketones **V**. Due to high reactivity of α-position of enaminoketones system **V** towards nucleophilic attack, they are cyclized to 4H-1,4-benzothiazines **VII** by the scission of sulphur-sulphur bond. 2-Amino-5-ethoxybenzenethiol required in the synthesis of benzothiazines has been synthesized by the hydrolytic cleavage of 2-amino-6-ethoxybenzenethiazole which was in turn prepared by the action of ammonium thiocyanate and bromine on p-phenitidine.

β-Diketones exhibit keto- and enol tautomerism and two enolic forms **III** and **IV** are possible. Hence there is a possibility for the formation of two types of benothiazines **VII** and **VIII** but only benzothiazine **VII** is obtained. Mass spectral investigation shows that the benzotiazines obtained contain $R-\overset{\overset{O}{\|}}{C}-$ linkage (**Fig. 1**) which suggests the existence of tautomer **III** under the experimental

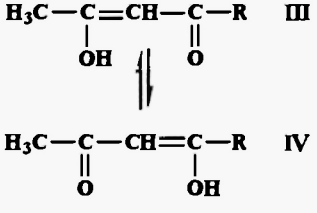
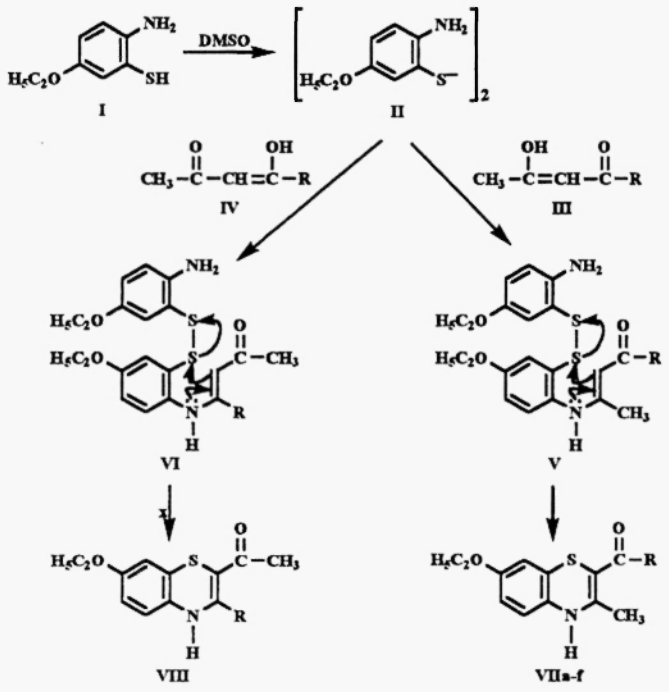


Fig. 1

conditions (employing DMSO a polar solvent) resulting in the formation of benzothiazines **VIIa-f** instead of **VIII** via the formation of an intermediate **V** (**Scheme-1**). All the synthesized benzothiazines show that molecular ion peaks are in accordance with their molecular weights.



VIIa R = $C_6H_4CH_3$(m), **VIIc** R = $C_6H_4OC_2H_5$(p), **VIIe** R = C_6H_4Br(m)

VIIb R = $C_6H_4C_2H_5$(p), **VIId** R = C_6H_4Cl(p), **VIIf** R = C_6H_4Br(p)

Scheme 1.

Infrared spectra

All the 4H-[1,4]-benzothiazines exhibit a single sharp peak in the region 3400-3280 cm^{-1} due to N-H streching vibrations. The sharp bands observed in the region 1620-1585 cm^{-1} are attributed to C=O streching vibrations of carbonyl group. 4H-1,4-benzothiazines (**VIIIa-c**) exhibit two bands in the region 1480-1440 cm^{-1} and 1400-1370 cm^{-1} due to C-H deformation vibrations of CH_3 group. The bands in the region 1270-1240 cm^{-1} and 1050-1010 cm^{-1} appear in all benzothiazines having OC_2H_5 group due to C-O-C asymmetric and symmetric vibrations. In compound **VIIa-f** having bromine atom shows a single peaks in region 690-660 cm^{-1} due to C-Br streching vibrations.

Nuclear magentic resonance spectra

The ^1H NMR spectra of all synthesized substituted 7-ethoxy-3-methyl-4H-(1,4)-benzothiazines exhibit a single sharp peak in the region δ 9.725-8.12 ppm due to N-H proton. The multiplets observed in the region δ 8.530-5.37 ppm are attributed to the aromatic protons. All the benzothiazines exhibit resonance signal in the region δ 2.52-1.94 ppm due to allylic proton (C=C-CH_3) at C_3. Benzothiazines exhibit quartets and triplets in the region δ 4.52-3.76 ppm and 1.58-106 ppm due to CH_2 and CH_3 protons of OC_2H_5 group at C_7. Compound **VII** a exhibits a singlet at 2.09 due to CH_3 protons at 3-position of benzoyl side chain at C_2. The quartets and triplets observed in the region δ 3.22-2.527 ppm and 1.78-1.230 ppm in the compounds **VIIc** can be assigned to C_2H_5 group at para position of benzoyl side chain at C_2. Compound **VIId** exhibits quartets and triplets in the region δ 4.58-3.62 ppm and δ 1.69-1.08 ppm due to CH_2 and CH_3 protons of OC_2H_5 group at para position of benzoyl side chain at C_2.

Experimental

All the melting points are uncorrected. The purity of synthesized compounds was tested by thin layer chromatography and characterised by spectral data. ^{1}H NMR spectra were recorded on FT NMR Bruker DRX-300 MHz spectrometer in DMSO-d_6 containing TMS as internal standard. The IR spectra were recorded on a nicolet magna FT IR spectrophotometer model 550 in KBr over the range of 4000-400 cm^{-1}. Mass spectra were scanned on Jeol D-300 mass spectrometer (Electron Ionisation Technique). Physical data of synthesized compounds are summarised in Table-I.

Table 1 : Physical data of 4H-1,4-benzothiazines VIIa-f

Compound						% Found (Calcd.)		
	R	M.P. °C	Yield %	Molecular formula	Molecular Weight	C	H	N
I	II	III	IV	V	VI	VII	VIII	IX
VIIa	$C_6H_4CH_3$(m)	170°C	79	$C_{19}H_{19}NO_2S$	325.38	70.69	5.82	4.28
						(70.72)	(6.25)	(4.30)
VIIb	$C_6H_4C_2H_5$(p)	81-83°C	89	$C_{20}H_{21}NO_2S$	339	70.72	6.25	4.08
						(70.76)	(6.23)	(4.12)
VIIc	$C_6H_4OC_2H_5$(p)	89°C	66	$C_{20}H_{21}NO_3S$	354.39	67.54	5.92	3.92
						(67.58)	(5.95)	(3.94)
VIId	C_6H_4Cl(p)	81°C	80	$C_{18}H_{16}NSO_2Cl$	345.85	62.54	4.61	4.08
						(62.50)	(4.65)	(4.05)
VIIe	C_4H_4Br(m)	78°C	72	$C_{18}H_{16}NO_2SBr$	389.35	55.48	4.16	3.57
						(55.52)	(4.14)	(3.59)
VIIf	C_6H_4Br(p)	65°C	75	$C_{18}H_{16}NSO_2Br$	389.35	55.44	4.08	3.56
						(55.52)	(4.13)	(3.59)

Synthesis of 4H-1,4-benzothiazines

2-Amino-5-ethoxybenzenethiol (0.01 mole) was added to a stirred suspension of β-diketones (0.01 mole) in DMSO (5 ml). The resulting mixture was refluxed for 40-50 min. The reaction mixture was concentrated, cooled down to room temperature and filtered. The product obtained was washed with petroleum ether and crystallized from methanol / solvent ether.

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