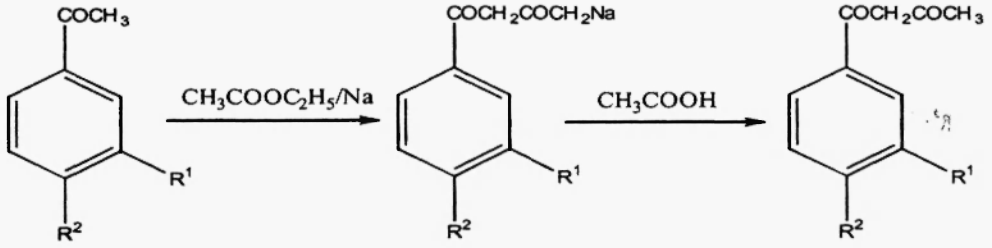
A CONVENIENT SYNTHESIS OF 5/7-CHLORO-4H-1, 4-BENZOTHIAZINES

Gulshan Kumar, Vandana Gupta, D.C. Gautam and R.R. Gupta*
Department of Chemistry, University of Rajasthan, Jaipur-302004
E-mail : rrg_vg@yahoo.co.in ;dr_vandana27@yahoo.co.in

ABSTRACT
5/7-Chloro-4H-1,4-benzothiazines have been synthesized by the condensation of sustituted 2-amino-3/5-chlorobenzenethiol with compounds containing active methylene group in dimethylsulfoxide which causes oxidative cyclization via enaminoketone intermediate. The IR, NMR and Mass spectra have been also included.

INTRODUCTION
4H-1,4-Benzothiazines possess a fold along nitrogen and sulfur axis, which is responsible for pharmacological and biological activities (1,2). 4H-1,4-Benzothiazines are being used as tranquilizers, antiemetics, sedative(3), antihistamines(4), antipsychotics, antiinflammatory, anthelmintics, diuretics etc. They have also shown antitumor activities(5,6). They have been used in industries as antioxidant, heatstabiliser, photosensitizers, dyes, indicators and lubricants. All these pharmacological, biological and industrial applications have stimulated our interest in synthesizing hitherto unknown benzothiazines.

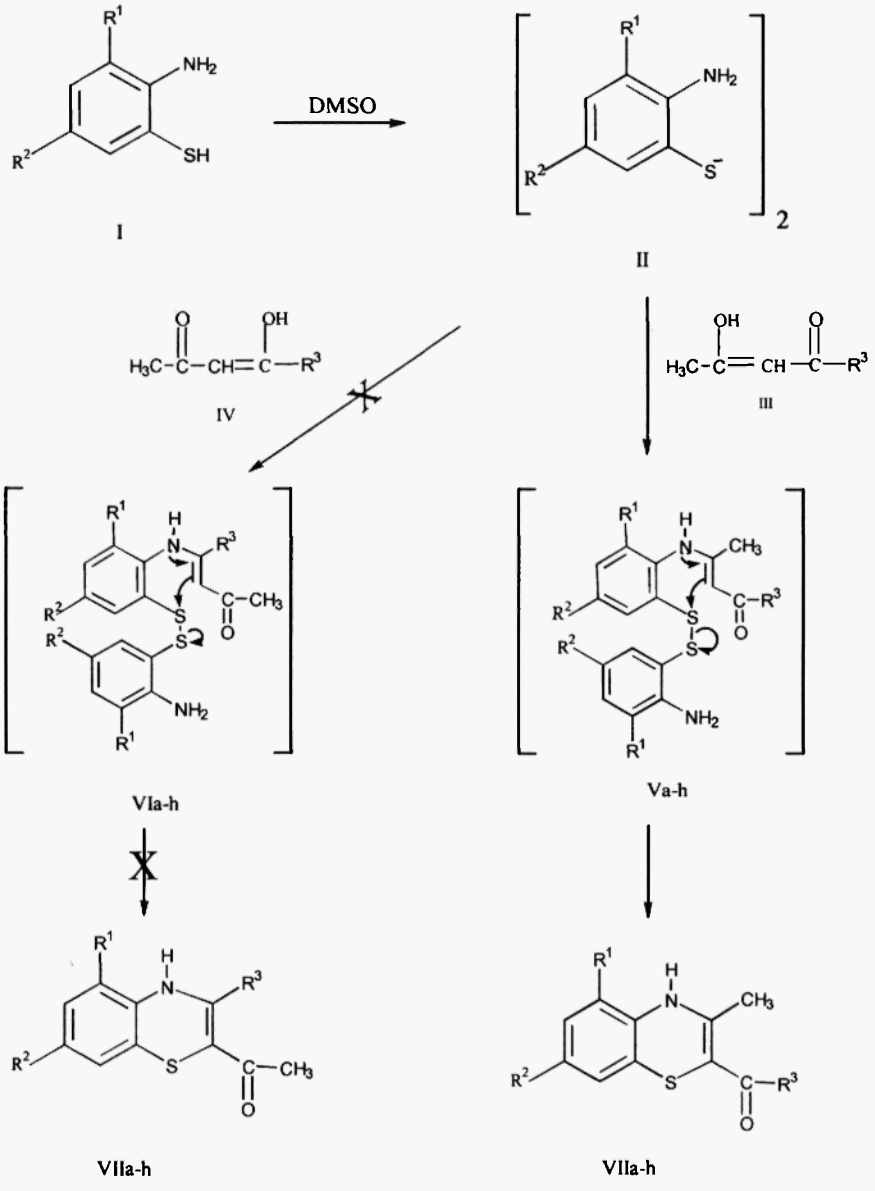
RESULTS AND DISCUSSION
5/7-Chloro-4H-1,4-benzothiazines have been synthesized by the condensation of 2-amino-3/5-chlorobenzenethiols and β- diketones. The 2-amino-3/5-chlorobenzenethiols have been synthesized by the hydrolytic cleavage of 2-amino-4/6-chlorobenzothiazole respectively by adopting the method reported elsewhere (7). β-Diketones has been prepared by Claisen condensation of ethylacetate with substituted acetophenones (scheme-1).



Here $R^1 = Br, R^2 = H$; $R^1 = CH_3, R^2 = H$; $R^1 = H, R^2 = C_2H_5$; $R^1 = H, R^2 = OC_2H_5$

Scheme-1

5/7-Chlorobenzothiazines have been synthesized by the condensation of β- diketones (viz. 3-bromobenzoylacetone, 3-methylbenzoylacetone, 4-ethylbenzoylacetone, 4-ethoxybenzoylacetone) with 2-amino-3/5-chlorobenzenethiol in dimethylsulfoxide, which causes oxidative cyclization. The reaction proceeds through an intermediate enaminoketone. Under the experimental conditions 2-aminobenzenethiols are readily oxidized to bis (2-aminophenyl) disulfides. High reactivity at α-position of enaminoketone system towards nucleophilic attack causes cyclization of bis (2-aminophenyl) disulfides to 4H-1, 4-benzothiazine by cleavage of sulfur-sulfur bond (scheme-2).
The IR spectra of all benzothiazines exhibit a shark peak in the region 3235-3270 cm^{-1} due to N-H stretching vibrations. The two sharp bands due to symmetric and asymmetric C-H deformation vibrations of CH_3 group are observed in the region 1300-1430 cm^{-1} and 1480-1510 cm^{-1} respectively. The sharp band



Scheme-2

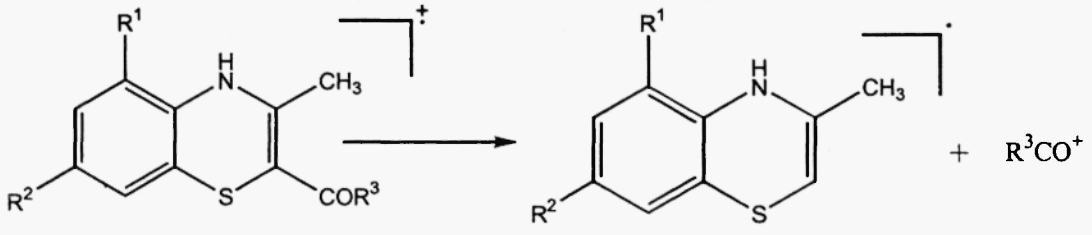
Compounds	R^1	R^2	R^3
VII_a	Cl	H	C_6H_4-Br (m)
VII_b	Cl	H	C_6H_4-CH_3 (m)
VII_c	Cl	H	C_6H_4-OC_2H_5 (p)
VII_d	Cl	H	C_6H_4-C_2H_5 (p)
VII_e	H	Cl	C_6H_4-Br (m)
VII_f	H	Cl	C_6H_4-CH_3 (m)
VII_g	H	Cl	C_6H_4-OC_2H_5 (p)
VII_h	H	Cl	C_6H_4-C_2H_5 (p)

Synthesis of 4H-1, 4-Benzothiazines (VII_{a-h}) (Scheme-2)

observed in the region 1560-1670 cm^{-1} are due to C=O stretching vibrations. The bands in the region 1050-1150 cm^{-1} and 1210- 1260 cm^{-1} appear in the compounds VII c and g having OC_2H_5 group due to C-O-C symmetric and asymmetric vibration respectively. All compounds show a single peak in the region 700-820 cm^{-1} due to C-Cl stretching vibration. Compounds VII a and e having bromine atom shows a single peak at 690 and 700 cm^{-1} respectively due to C-Br stretching vibration.

The ^{1}HNMR spectra of all the synthesized 4H-1, 4-benzothiazines exhibit a single sharp peak in the region δ 8.89-9.63 ppm due to N-H proton. The multiplets observed in the region δ 6.40-8.33 ppm are attributed to the aromatic protons. All synthesized compounds show singlet in the region δ 2.01-2.48 ppm due to allylic protons(C=C-CH_3) at C_3. Compounds VII c and g exhibit quartets and triplets in the region δ 3.23-4.20 ppm and δ 1.23-2.01 ppm due to CH_2 and CH_3 protons of OC_2H_5 group at 4- position of benzoyl side chain at C_2. Compounds VII b and f exhibit a singlet in the region 1.62-1.80 ppm due to CH_3 protons at 3-position of benzoyl side chain at C_2.The quartets and triplets observed in the region 2.50-3.52 ppm and 1.10-1.90 ppm in the compound VII d and h can be assigned to C_2H_5 group at 4-position of benzoyl side chain at C_2.

In the mass spectra of benzothiazines , moleculer ion peaks are in accordance with their molecular weight. The formation of R^3CO^+ ions indicates that under experimental conditions β- diketones participate in the reactions as tautomeric form III to give benzothiazines VII (scheme-3).



Scheme-3

EXPERIMENTAL

All the melting points were checked in open glass capillaries and are uncorrect. The purity of synthesized compounds was tested by TLC using different proportion of various polar and nonpolar nonaqueous solvents and characterized by their spectral studies. The infrared spectra have been recorded on FT IR spectrometer, MAGNA IR 550 NICOLET using potassium bromide discs. NMR spectra were recorded on FT NMR Bruker DRX-300 MHz in DMSO-d_6 using TMS as an internal standard. Mass spectra have been scanned on Jeol D-300 (EI) and JEOL SX 102 / DA-6000 Mass spectrometer / data system using Argon / Xenon (6kV, 10mA) as the FAB gas. Physical data of synthesized compounds are summarized in Table–1.

Table-I : Physical data (compounds VII_{a-h})

Compounds				M.P.	Yield	Molecular	% found (Calcd.)		
	R^1	R^2	R^3	°C	%	formula	C	H	N
VII_a	Cl	H	C_6H_4-Br(m)	Above 360	55	$C_{16}H_{11}BrClNS$	(50.47) 50.44	(2.89) 2.86	(3.68) 3.67
VII_b	Cl	H	C_6H_4-CH_3(m)	72	49	$C_{17}H_{14}ClNOS$	(64.65) 64.63	(4.43) 4.40	(4.43) 4.39
VII_c	Cl	H	C_6H_4-OC_2H_5(p)	182	26	$C_{18}H_{16}ClNO_2S$	(62.51) 62.49	(4.63) 4.60	(4.05) 4.00
VII_d	C	H	C_6H_4-C_2H_5(p)	76	32	$C_{18}H_{16}ClNOS$	(65.75) 65.72	(4.56) 4.54	(4.26) 4.20
VII_e	H	Cl	C_6H_4-Br(m)	90	44	$C_{16}H_{11}BrClNS$	(50.47) 50.40	(2.89) 2.83	(3.68) 3.65
VII_f	H	Cl	C_6H_4-CH_3(m)	160	49	$C_{17}H_{14}ClNOS$	(64.65) 64.64	(4.43) 4.41	(4.43) 4.37
VII_g	H	Cl	C_6H_4-OC_2H_5(p)	98	50	$C_{18}H_{16}ClNO_2S$	(62.51) 62.48	(4.63) 4.61	(4.05) 4.03
VII_h	H	Cl	C_6H_4-C_2H_5(p)	118	48	$C_{18}H_{16}ClNOS$	(65.75) 65.70	(4.56) 4.53	(4.26) 4.24

Preparation of substituted benzoylacetone

In a 500 ml three necked RB flask fitted with a reflux condenser, mechanical stirrer and dropping funnel, sodium wire (11.5 gm) was suspended in dry ice cold ethylacetate (200 ml). Substituted acetophenone was added in small lots from the dropping funnel to the ice cold reaction mixture with continuous stirring for two to four hours and then allowed to stand over night in an ice box. The sodium salt of substituted benzoylacetone was filtered, washed with benzene and dried in air. The product was then dissolved in cold water and neutralized with dilute acetic acid. The product was extracted with ether and ether was evaporated. Then solid obtained was crystallized from ethanol.

Preparation of 4H-1, 4- benzothiazines

To a stirred suspension of β- diketones (0.01 mole) in DMSO (5 ml) 2-amino-3/5-chlorobenzenethiol (0.01 mole) was added and the resulting mixture was refluxed for 40-60 min. The resulting mixture was cooled down to room temperature and solid separated out was filtered, washed with petroleum ether and crystallized from methanol.

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