ONE - POT SYNTHESIS OF 3,5-DIMETHYL/ 3,7-DIMETHYL-4H-1, 4-BENZOTHIAZINES

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ABSTRACT: Synthesis of 3,5-dimethyl / 3,7-dimethyl-4H-1,4-benzo-thiazines is reported by the condensation and oxidative cyclization of 2-amino-3-methyl / 5-methylbenzenethiols with compounds containing active methylene group in dimethylsulfoxide. The reactions proceed through the formation of intermediate enaminoketones. The compounds containing active methylene group viz. benzoylacetones have been prepared by the Claisen condensation of acetophenones with ethylacetate. The IR, NMR and Mass spectral studies are also included.

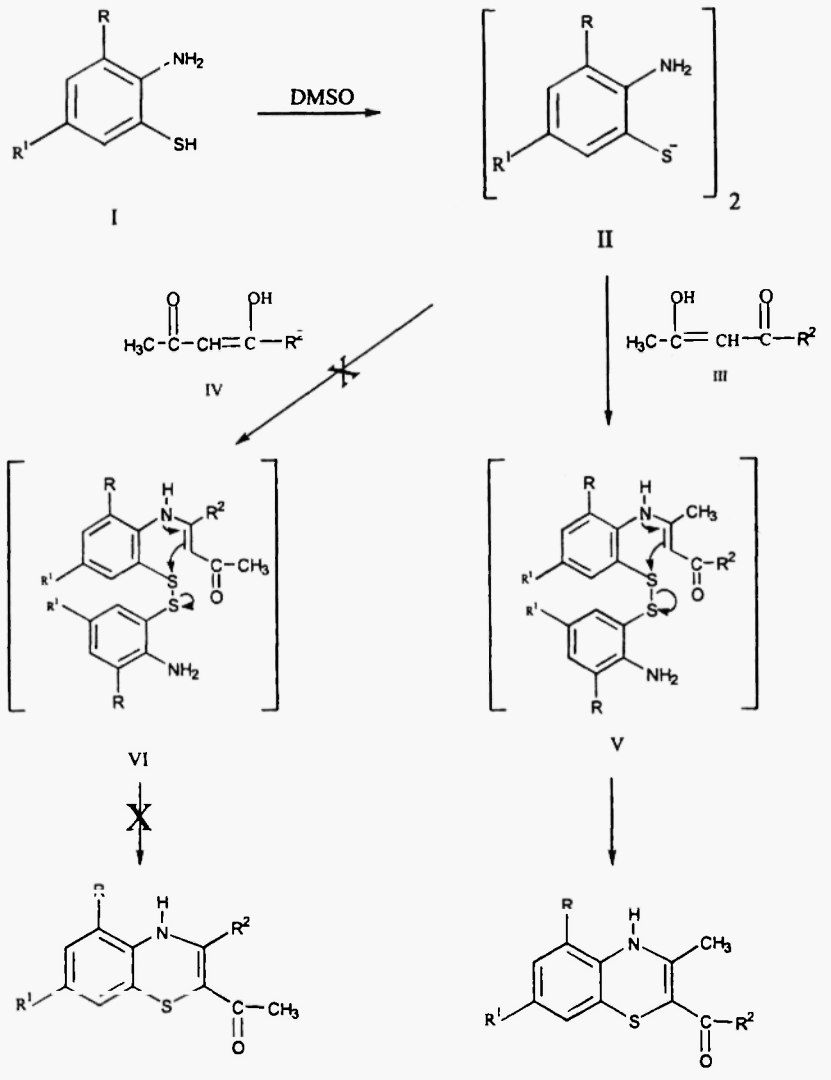
INTRODUCTION

4H-1,4-Benzothiazines constitute an interesting class of heterocycles. They are anticipated to exhibit pharmacological activities (1,2). These are used as central nervous system depressants, antispasmodics, antiulcer, antidermatosis, antiinflammatories, antihistaminics etc. Besides pharmacological activities, they are having industrial applications (3). Some benzothiazines have shown significant effects against cancer (4,5). A slight change in substitution pattern in benzothiazine nucleus causes marked difference in their activities. Therefore, we have synthesized some hitherto unknown title benzothiazines to make them available for biological screening.

RESULTS AND DISCUSSION

The title benzothiazines have been synthesized by 2-amino-3-methyl / 5-methylbenzenethiols which were prepared by the hydrolytic cleavage of 2-amino-4-methy / 6-methylbenzothiazoles respectively by adopting the method reported elsewhere (6).

3,5-Dimethyl / 3,7-dimethyl-4H-1,4-benzothiazines (**VIIa-h**) have been synthesized by the condensation of β-diketones (**III**) (viz. 3-bromo-benzoylacetone, 3-methylbenzoylacetone, 4-ethoxybenzoylacetone or 4-ethylbenzo-ylacetone) with 2-amino-3-methyl / 5-methylbenzenethiol (**I**) (Scheme 1) in dimethyl-sulfoxide which causes oxidative cyclization. Each reaction involves the formation of an intermediate enaminoketone (**V**). Under the experimental conditions 2-aminobenzenethiols (**I**) are readily oxidised to bis(2-aminophenyl)disulfides(**II**) which cyclizes to 4H-1,4-benzothiazines (**VII**) by scission of sulphur-sulphur bond due to high reactivity of α-position of enaminoketone systems (**III**) towards nucleophilic attack.



Compound	R	R^1	R^2
VIIa	CH_3	H	C_6H_4-Br(m)
VIIb	CH_3	H	C_6H_4-CH_3(m)
VIIc	CH_3	H	C_6H_4-OC_2H_5(p)
VIId	CH_3	H	C_6H_4-C_2H_5(p)
VIIe	H	CH_3	C_6H_4-Br(m)
VIIf	H	CH_3	C_6H_4-CH_3(m)
VIIg	H	CH_3	C_6H_4-OC_2H_5(p)
VIIh	H	CH_3	C_6H_4-C_2H_5(p)

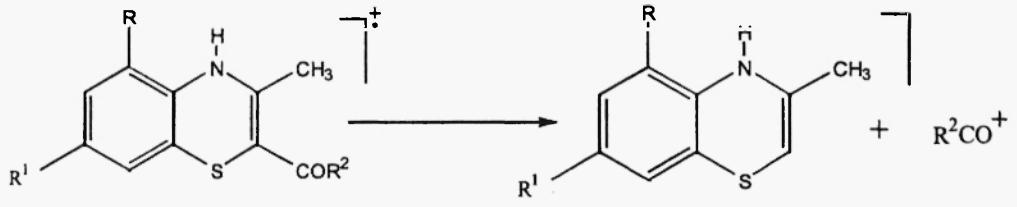
Synthesis of substituted 4H-1,4-Benzothiazines (VIIa-h)

Scheme 1

The IR spectra of all benzothiazines exhibit a sharp peak in the region 3260-3360 cm^{-1} due to N-H stretching vibrations. The sharp band observed in the region 1580-1610 cm^{-1} are due to C=O stretching vibrations. The two sharp bands due to symmetric and asymmetric C-H deformation vibrations of CH_3 group are observed in the region 1380-1390 cm^{-1} and 1470-1480 cm^{-1} respectively. The bands in the region 1100-1110 cm^{-1} and 1250-1260 cm^{-1} appear in the compounds **VII c and g** having OC_2H_5 group due to C-O-C symmetric and asymmetric vibrations. Compounds **VII a and e** having bromine atom shows a single peak at 690 and 640 cm^{-1} respectively due to C-Br stretching vibrations.

The ^1H NMR spectra of all synthesized 4H-1,4-benzothiazines exhibit a single sharp peak in the region δ 9.854-8.27 ppm due to N-H proton. The multiplets observed in the region δ 8.620-5.08 ppm are attributed to the aromatic protons. All the compounds show resonance signal in the region δ 2.485-2.039 ppm due to allylic protons (C=C-CH_3) at C_3. Compounds **VIIa-d** exhibit a singlet in the region δ 2.094-1.213 ppm due to CH_3 protons at C_5 and compounds **VIIe-h** exhibit a singlet in the region δ 2.11-1.72 ppm due to CH_3 protons at C_7. Compounds **VII b and f** exhibit a singlet at δ 2.122 ppm & δ 2.12 ppm respectively due to CH_3 protons at 3-position of benzoyl side chain at C_2. Compounds **VII c and g** exhibit quartets and triplets in the region δ 4.60-3.65 ppm and δ 1.75-1.10 ppm due to CH_2 and CH_3 protons of OC_2H_5 group at 4-position of benzoyl side chain at C_2. The quartets and triplets observed in the region δ 3.33-2.569 ppm and δ 1.811-1.214 ppm in the compounds **VII d and h** can be assigned to C_2H_5 group at para position of benzoyl side chain at C_2.

In the mass spectra of benzothiazines, molecular ion peaks are in accordance with their molecular weights. The peaks observed by the formation of R^2CO^+ ions clearly indicate that under experimental conditions β-diketones/β-ketoesters participate in the reactions as tautomeric form **III** rather than **IV** to give benzothiazines **VII** rather than **VIII** (Scheme 3).



Scheme 3

EXPERIMENTAL

All the melting points are uncorrected. The purity of synthesized compounds was tested by thin layer chromatography using various non-aqueous solvents and characterised by spectral studies. The infrared spectra were recorded on FT IR spectrometer, MAGNA IR 550, NICOLET using potassium bromide discs. NMR spectra were recorded on FT NMR Bruker DRX-300MHz in DMSO-d_6 using TMS as an internal standard. Mass spectra were scanned on Jeol D-300 (EI). Physical data of newly synthesized compounds are summarized in Table 1.

Preparation of 4H-1,4-benzothiazines (VIIa-h)

To a stirred suspension of β-diketone / β-ketoester (**II**, 0.01 mole) in DMSO (5 ml) was added 2-amino-3-methyl / 5-methylbenzenethiol (**I**; 0.01 mole) and the resulting mixture was refluxed for 30-40 min. The reaction mixture was concentrated, cooled and filtered. The product obtained was washed with petroleum ether and crystallized from methanol / solvent ether.

Table 1 : Physical data (Compounds VIIa-h)

	Compound			M.P.	Yield	Molecular	% found (Calcd.)		
	R	R^1	R^2	°C	%	formula	C	H	N
I	II	III	IV	V	VI	VII	VIII	IX	X
VIIa	CH_3	H	C_6H_4-Br(m)	84	45	$C_{17}H_{14}NOSBr$	56.77 (56.67)	3.94 (3.92)	3.92 (3.89)
VIIb	CH_3	H	C_6H_4-CH_3(m)	114	38	$C_{18}H_{17}NOS$	73.28 (73.19)	5.79 (5.80)	4.76 (4.74)
VIIc	CH_3	H	C_6H_4-OC_2H_5(p)	76	30	$C_{19}H_{19}NO_2S$	70.21 (70.12)	5.88 (5.89)	4.26 (4.31)
VIId	CH_3	H	C_6H_4-C_2H_5(p)	73	10	$C_{19}H_{19}NOS$	73.79 (73.75)	6.23 (6.19)	4.51 (4.53)
VIIe	H	CH_3	C_6H_4-Br(m)	184	40	$C_{17}H_{14}NOSBr$	56.72 (56.67)	3.91 (3.92)	3.87 (3.89)
VIIf	H	CH_3	C_6H_4-CH_3(m)	99	82	$C_{18}H_{17}NOS$	73.16 (73.19)	5.79 (5.80)	4.76 (4.74)
VIIg	H	CH_3	C_6H_4-OC_2H_5(p)	171	40	$C_{19}H_{19}NO_2S$	69.90 (70.12)	5.91 (5.89)	4.28 (4.31)
VIIh	H	CH_3	C_6H_4-C_2H_5(p)	108	13	$C_{19}H_{19}NOS$	73.78 (73.75)	6.17 (6.19)	4.57 (4.53)

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