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Single Step Synthesis of 4*H*-1,4-Benzothiazines

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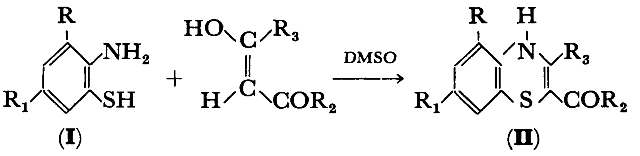
Synopsis. Single step synthesis of substituted 4*H*-1,4-benzothiazines is reported by the condensation and oxidative cyclization of substituted 2-aminobenzenethiol with β-dicarbonyl compounds in DMSO. The structures of the synthesized compounds have been confirmed by their elemental analyses and spectral studies.

4*H*-1,4-Benzothiazines resemble structurally with phenothiazines in having a fold along nitrogen sulfur axis and can be anticipated to possess biological activities like phenothiazines.[1–7] 4*H*-1,4-Benzothiazines have been prepared by the reaction of *o*-aminobenzenethiol with ethyl 2-chloroacetoacetate[8] or β-bromoketones/α,α-dimethoxy-β-bromoethane.[9] In these methods halogenated ethylacetoacetate and ketones are required, and therefore it is considered worthwhile to develop a convenient method for synthesis of 4*H*-1,4-benzothiazines involving the use of ethylacetoacetate or β-dicarbonyl compounds as such without converting them into halogenated form.

In the present communication a single step method is reported for the synthesis of hitherto unknown substituted 4*H*-1,4-benzothiazines which involve the condensation followed by oxidative cyclization of substituted 2-aminobenzenethiol with β-dicarbonyl compounds in DMSO (Scheme 1). We have used 3- and 5-substituted 2-aminobenzenethiols (1 : R=Me, Cl, MeO; R_1=Cl, Me) and β-dicarbonyl compounds such as ethylacetoacetate, dibenzoylmethane, benzoylacetone, and *p*-chlorobenzoylacetone. Two isomeric products of 4*H*- 1,4-benzothiazine may be formed theoretically, but compound (**1c**) predominates over the compound (**1d**) (identified by mass spectral studies).



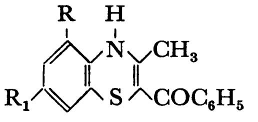
R=H, CH_3, OCH_3, Cl; R_1=CH_3, Cl, H
R_2=C_6H_5, CH_3, OC_2H_5, *p*-ClC_6H_4
R_3=CH_3, C_6H_5

Scheme 1.

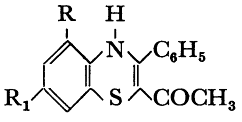
The infrared spectra of all the benzothiazines invariably showed an NH absorption in the region of 3200—3390 cm^{-1} and carbonyl absorption in the region of 1570—1615 cm^{-1}. The weak absorption bands in the region of 1355—1485 cm^{-1} are attributed to C–CH_3 vibrations in substituted 4*H*-1,4-benzothiazines. The bands in the region of 1600—1510 cm^{-1} are attributed to C=C stretching vibrations. A broad signal in the region of τ 1.25—1.45 was observed in all the compounds arising due to an NH proton and the multiplets in the region of τ 2.2—3.6 are due to aromatic ring protons. A singlet peak centered at τ 6.2 arising due to an OCH_3 group in methoxy derivatives was also observed. All benzoyl 4*H*-1,4-benzothiazines showed peaks at m/z=M^+−105 (with high intensity), 105 ($CO^+C_6H_5$, base peak), and 77 ($C_6H_5^+$) by the loss of a benzoyl group, but did not show any peak corresponding to the M^+–$COCH_3$ or $COCH_3^+$ moiety, proving the structure of these benzothiazines to be **1c**. The 3,5-dimethyl-2-ethoxycarbonyl derivative gave peaks at m/z=M^+–C_2H_4, M^+–OC_2H_5, and M^+–C_2H_5.

Table 1. Physical data of substituted 4*H*-1,4-benzothiazines

Compound				Mp	Yield	Molecular formula	Found %			Calcd %		
R	R_1	R_2	R_3	θ_m/°C	%		C	H	N	C	H	N
Cl	H	C_6H_5	CH_3	120	45	$C_{16}H_{12}NSOCl$	64.00	3.95	4.75	63.68	3.98	4.65
Cl	H	C_6H_4Cl	CH_3	127	60	$C_{16}H_{11}NSOCl_2$	57.20	3.30	4.25	57.14	3.28	4.17
CH_3	H	C_6H_4Cl	CH_3	205	55	$C_{17}H_{14}NSOCl$	64.82	4.45	4.48	64.65	4.44	4.44
OCH_3	H	C_6H_4Cl	CH_3	160	58	$C_{17}H_{14}NSO_2Cl$	61.70	4.30	4.25	61.53	4.22	4.22
OCH_3	H	C_6H_5	CH_3	142	40	$C_{17}H_{15}NSO_2$	68.75	5.10	4.75	68.68	5.05	4.71
CH_3	H	OC_2H_5	CH_3	162	69.5	$C_{13}H_{15}NSO_2$	62.15	6.05	5.60	62.65	6.02	5.62
CH_3	H	CH_3	CH_3	169	72.5	$C_{12}H_{13}NSO$	65.35	5.95	6.43	65.75	5.93	6.39
CH_3	H	C_6H_5	C_6H_5	105	66.0	$C_{22}H_{17}NSO$	76.50	4.98	4.13	76.96	4.95	4.08
CH_3	H	C_6H_5	CH_3	137	68.4	$C_{17}H_{15}NSO$	72.11	5.36	5.02	72.59	5.33	4.98
H	CH_3	C_6H_5	CH_3	208	71.8	$C_{17}H_{15}NSO$	73.02	5.34	5.01	72.59	5.33	4.98
H	Cl	C_6H_5	CH_3	247	72.5	$C_{16}H_{12}NSOCl$	63.49	3.97	4.68	63.68	3.98	4.64



(**1c**)



(**1d**)

Experimental

All the melting points are uncorrected. The purity of the synthesized compounds was tested on the elemental analysis and thin-layer chromatography of silica gel in various non-aqueous solvents. Infrared spectra of 4*H*-1,4-benzothiazines have been scanned in KBr on Perkin-Elmer 577 grating spectrophotometer and their NMR spectra were recorded on a Perkin-Elmer R12 B spectrometer using tetramethylsilane as an internal standard. The mass spectra were recorded on a JEOL, JMSD-300 mass spectrometer at 70 eV with 100 μA ionizing current.

*Preparation of Substituted 4*H*-1,4-Benzothiazines(II)*,

The substituted 2-aminobenzenethiol[10–12] (1, 0.01 mol) was added to the stirred suspension of *β*-dicarbonyl compound (0.01 mol) (acetylacetone, ethylacetoacetate, dibenzoylmethane, benzoylacetone, or *p*-chlorobenzoylacetone) in DMSO (5 ml) and the resulting mixture was refluxed for 1 h. The mixture was cooled down to room temperature and a solid substance separated was filtered and crystallized from methanol. The physical data are given in Table 1.

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