

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

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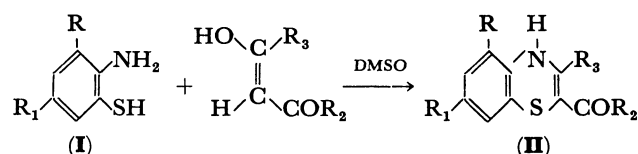
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(Received October 15, 1983)

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*-amino-benzenethiol with ethyl 2-chloroacetoacetate⁸) 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; R₁ = 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).

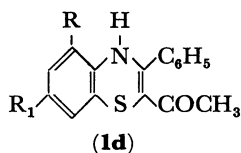
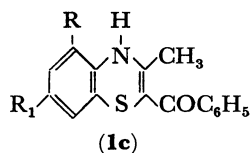
R = H, CH₃, OCH₃, Cl; R₁ = CH₃, Cl, HR₂ = C₆H₅, CH₃, OC₂H₅, *p*-ClC₆H₄R₃ = CH₃, C₆H₅

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—CH₃ 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 OCH₃ 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+C₆H₅, base peak), and 77 (C₆H₅⁺) by the loss of a benzoyl group, but did not show any peak corresponding to the M⁺—COCH₃ or COCH₃⁺ moiety, proving the structure of these benzothiazines to be **1c**. The 3,5-dimethyl-2-ethoxycarbonyl derivative gave peaks at m/z = M⁺—C₂H₄, M⁺—OC₂H₅, and M⁺—C₂H₅.

TABLE 1. PHYSICAL DATA OF SUBSTITUTED 4*H*-1,4-BENZOTHAZINES

Compound				Mp $\theta_m/^\circ\text{C}$	Yield %	Molecular formula	Found %			Calcd %		
R	R ₁	R ₂	R ₃				C	H	N	C	H	N
Cl	H	C ₆ H 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 ₆ H ₄ Cl	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 ₆ H ₄ Cl	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 ₆ H ₄ Cl	CH ₃	160	58	C ₁₇ H ₁₄ NSO ₂ Cl	61.70	4.30	4.25	61.53	4.22	4.22
OCH ₃	H	C ₆ H 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 ₂ H 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 ₆ H ₅	C ₆ H 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 ₆ H 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 ₆ H 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 ₆ H ₅	CH ₃	247	72.5	C ₁₆ H ₁₂ NSOCl	63.49	3.97	4.68	63.68	3.98	4.64



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 4H-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 μ A ionizing current.

Preparation of Substituted 4H-1,4-Benzothiazines(II). The substituted 2-aminobenzenethiol¹⁰⁻¹² (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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