

One Pot Synthesis of Methyl 3-Methyl-4H-1,4-benzothiazine 2-carboxylates

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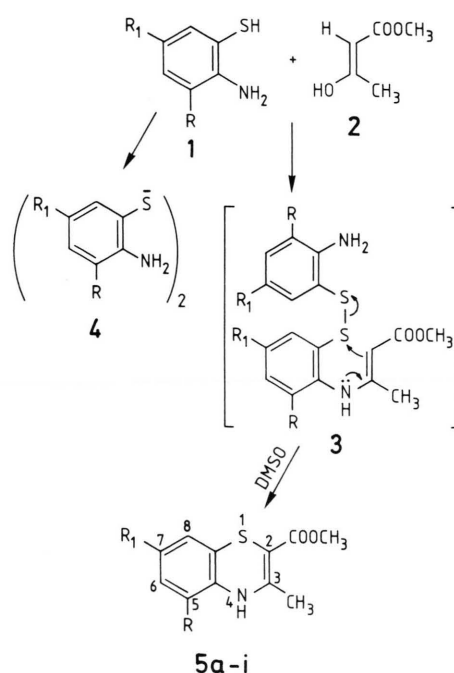
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One Pot Synthesis, 1,4-Benzothiazines, 2-Aminobenzenethiols, Methyl Acetoacetate, Methyl 3-Methyl-4H-1,4-benzothiazines 2-Carboxylate

A one pot synthesis of methyl 3-methyl-4H-1,4-benzothiazine 2-carboxylates is reported by the condensation and oxidative cyclization of substituted 2-aminobenzenethiols with methyl acetoacetate in DMSO.

1,4-Benzothiazines resemble phenothiazines in having a fold along nitrogen and sulphur axis [1] which is one of the structural specificity which imparts a wide spectrum of biological activities to phenothiazines [2] and 1,4-benzothiazines analogously possess biological activities [3–9]. In continuation our program to synthesize novel pharmaceutical heterocycles, we are presenting one pot synthesis of the title compounds. It involves the condensation and oxidative cyclization of 2-aminobenzenethiols (**1**) and methyl acetoacetate (**2**) in DMSO. The reaction is believed to proceed through the formation of an intermediate enamino-ketone (**3**) [1, 10, 11]. 2-Aminobenzenethiols (**1**) are readily oxidized to bis(2-aminophenyl) disulphides (**4**) under the experimental conditions [1, 11, 12]. Disulphides (**4**) cyclize to 1,4-benzothiazines (**5**) by scission of the sulphur–sulphur bond [1, 11, 13] upon attack by nucleophilic enamino ketone system (Scheme 1).



- | | |
|--|---|
| a : R = R ₁ = H | f : R = H, R ₁ = Br |
| b : R = Cl, R ₁ = H | g : R = H, R ₁ = CH ₃ |
| c : R = CH ₃ , R ₁ = H | h : R = H, R ₁ = OCH ₃ |
| d : R = OCH ₃ , R ₁ = H | i : R = H, R ₁ = OC ₂ H ₅ |
| e : R = H, R ₁ = Cl | |

Scheme 1.

Experimental

All the melting points are uncorrected. The purity of the synthesized compounds has been checked by thin layer chromatography. Infrared spectra of all the compounds have been scanned in KBr on Perkin-Elmer spectrophotometer model 577. The IR spectra of all the 4H-1,4-benzothiazines exhibit a single sharp intense peak in the region 3240–3380 cm⁻¹ which corresponds to NH stretching vibrations. The sharp band in the region 1620–1670 cm⁻¹ is due to carboxylate C=O stretching vibrations. All the compounds exhibit sharp bands in the region 1370–1475 cm⁻¹ due to C–H deformation vibrations of CH₃ group.

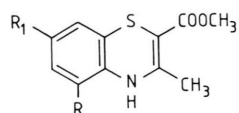
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All the NMR spectra have been recorded at 90 MHz on Jeol. FX 90 Q FT NMR using TMS as an internal standard in polysol/DMSO-d₆. The NMR spectra of all the benzothiazines exhibit a singlet at 2.18–2.47 δ due to allylic linkage (C=C–CH₃) at C₃ in the heterocyclic ring. Protons of methyl group of carboxylate linkage (COOCH₃) at C₂ in the heterocyclic ring gives rise to a singlet at 3.55–4.43 δ. Multiplets appear due to aromatic protons in the region 6.27–7.67 δ. A singlet is exhibited

in all the benzothiazines in the region 8.55–9.93 δ which is ascribed to N–H proton. Benzothiazine **5c**, **5d**, **5g–i** exhibit resonance signals due to the groups present in the benzene ring and NMR spectral data is presented in Table I.

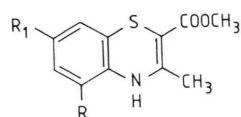
Mass spectra of all the compounds were recorded on Jeol. JMSD-300 mass spectrometer at 70 eV with 100 amp ionizing current. The mass spectra of all the compounds showed molecular ion peaks corresponding to their molecular weights.

Table I. PMR Spectral data of methyl 3-methyl-4H-1,4-benzothiazine 2-carboxylates.



Compd.	R	R ₁	Solvent	(ppm)	Multiplicity	Assignments
5a	H	H	DMSO-d ₆	8.9 7.22–6.90 3.74 2.47	singlet multiplet singlet singlet	N–H proton aromatic protons CH ₃ protons as COOCH ₃ at C ₂ CH ₃ protons at C ₃
5b	Cl	H	Polysol	8.84 7.67–6.72 3.55 2.31	singlet multiplet singlet singlet	N–H proton aromatic protons CH ₃ protons as COOCH ₃ at C ₂ CH ₃ protons at C ₃
5c	CH ₃	H	Polysol	9.98 7.60–6.68 3.58 2.31 2.12	singlet multiplet singlet singlet singlet	N–H proton aromatic protons CH ₃ protons as COOCH ₃ at C ₂ CH ₃ protons at C ₃ CH ₃ protons at C ₅
5d	OCH ₃	H	Polysol	8.68 7.06–6.27 3.67 3.58 2.31	singlet multiplet singlet singlet singlet	N–H proton aromatic protons CH ₃ protons as COOCH ₃ at C ₂ OCH ₃ protons at C ₅ CH ₃ protons at C ₃
5e	H	Cl	Polysol	9.41 7.29–6.53 4.24 2.21	singlet multiplet singlet singlet	N–H proton aromatic protons CH ₃ protons as COOCH ₃ at C ₂ CH ₃ protons at C ₃
5f	H	Br	Polysol	9.03 7.38–6.72 4.43 2.44	singlet multiplet singlet singlet	N–H proton aromatic protons CH ₃ protons as COOCH ₃ at C ₂ CH ₃ protons at C ₃
5g	H	CH ₃	Polysol	8.81 7.22–6.46 3.93 2.50 2.40	singlet multiplet singlet singlet singlet	N–H proton aromatic protons CH ₃ protons as COOCH ₃ at C ₂ CH ₃ protons at C ₃ CH ₃ protons at C ₇
5h	H	OCH ₃	Polysol	8.55 6.72–6.37 3.77 3.64 2.18	singlet multiplet singlet singlet singlet	N–H proton aromatic protons CH ₃ protons as COOCH ₃ at C ₂ OCH ₃ protons at C ₇ CH ₃ protons at C ₃
5i	H	OC ₂ H ₅	DMSO-d ₆	8.68 6.91–6.37 4.05–3.74 3.58 2.21 1.39–1.1	singlet multiplet quartet singlet singlet triplet	N–H proton aromatic protons CH ₂ protons of OC ₂ H ₅ group at C ₇ CH ₃ protons as COOCH ₃ at C ₂ CH ₃ protons at C ₃ CH ₃ protons of OC ₂ H ₅ group at C ₇

Table II. Physical and analytical data of methyl 3-methyl-4H-1,4-benzothiazine 2-carboxylates.



Compd.	R	R ₁	M.P. °C	Yield	Molecular Formula	Found [%]			Calcd [%]		
						C	H	N	C	H	N
5a	H	H	157	56.10	C ₁₁ H ₁₁ NSO ₂	59.58	4.93	6.30	59.72	4.97	6.33
5b	Cl	H	132	13.46	C ₁₁ H ₁₀ NSClO ₂	51.35	3.94	5.50	51.66	3.91	5.47
5c	CH ₃	H	122	63.39	C ₁₂ H ₁₃ NSO ₂	58.55	5.69	5.25	58.86	5.66	5.28
5d	OCH ₃	H	85	27.88	C ₁₂ H ₁₃ NSO ₃	57.50	5.15	5.52	57.37	5.17	5.57
5e	H	Cl	165	74.8	C ₁₁ H ₁₀ NSClO ₂	51.35	3.93	5.50	51.66	3.91	5.47
5f	H	Br	164	49.67	C ₁₁ H ₁₀ NSBrO ₂	43.78	3.35	4.63	44.00	3.33	4.66
5g	H	CH ₃	160	65.10	C ₁₂ H ₁₃ NSO ₂	61.05	5.55	5.92	61.27	5.53	5.95
5h	H	OCH ₃	125	60.8	C ₁₂ H ₁₃ NSO ₃	57.15	5.20	5.60	57.37	5.17	5.57
5i	H	OC ₂ H ₅	122	63.39	C ₁₃ H ₁₅ NSO ₃	58.55	5.69	5.25	58.86	5.66	5.28

*Preparation of
methyl 3-methyl-4H-1,4-benzothiazine 2-carboxylates
(5a–i)*

To the stirred suspension of methyl acetoacetate (**2**; 0.01 mol) in DMSO (5 ml) was added to substituted 2-aminobenzenethiol (**1**; 0.01 mol) and the resulting mixture was refluxed for 30 minutes. The reaction mixture was cooled down to room temperature and the solid separated out was filtered, washed

with methanol and crystallized from methanol. The physical and analytical data have been recorded in Table II.

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