SYNTHESIS OF DISUBSTITUTED 6-CHLORO-5-METHYL-4*H*-1,4-BENZOTHIAZINES: NOVEL HETEROCYCLES

Ram K. RATHORE[a] and Radha R. GUPTA[b]

[a] *Central Forensic Science Laboratory, Government of India, Sector 18A, Chandigarh-160 018, India*
[b] *Chemistry Department, Rajasthan University, Jaipur, India*

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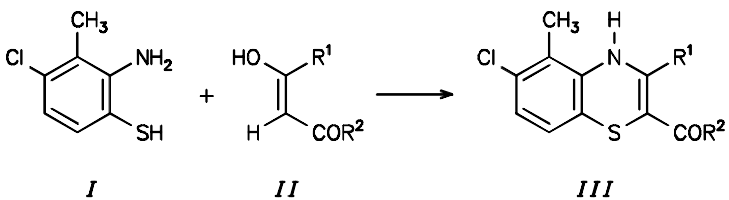
4*H*-1,4-Benzothiazines resemble structurally phenothiazines and possess a wide spectrum of biological and pharmacological activities[1]. In continuation to our research project (e.g. ref.[2]) concerning development of heterocyclic pharmaceuticals, we report here on the synthesis of 6-chloro-5-methyl-2, 3-disubstituted 4*H*-1,4-benzothiazines. For that purpose we used well-known[3] one-pot cyclocondenzation reaction of 2-amino-4-chloro-3-methylbenzenethiol (*I*) with 1,3-dicarbonyl compounds *II* (Scheme 1) in dimethyl sulfoxide. 4*H*-Benzothiazines *III* were formed in moderate yields.



I *II* *III*

II, *III*	R^1	R^2
a	CH_3	OCH_3
b	CH_3	OC_2H_5
c	CH_3	C_6H_5
d	CH_3	$4\text{-}ClC_6H_4$
e	CH_3	$4\text{-}CH_3C_6H_4$
f	CH_3	CH_3
g	C_6H_5	C_6H_5
h	CH_3	$4\text{-}BrC_6H_4$

SCHEME 1

The IR spectra (Table I) of the compounds *III* exhibited a single intense peak in the region 3 410–3 320 cm^{-1} which corresponded to ν(NH). The sharp band in the region 1 680–1 590 cm^{-1} was attributed to ν(CO). All compounds contain methyl group at C-3 position and exhibited sharp bands in the region 1 470–1 420 cm^{-1} and 1 370–1 320 cm^{-1} due to C–H asymmetric and symmetric deformation vibrations. The absorption bands in the region 780–720 cm^{-1} were assigned to C–Cl vibration.

The ^{1}H NMR spectra (Table II) of all 4*H*-1,4-benzothiazines *III* have –C=C–CH_3 grouping which exhibited resonance signals (singlets) in the region 2.31–2.97 ppm. A singlet in the region 8.49–9.10 ppm was assigned to NH proton in all compounds.

EXPERIMENTAL

Melting points are uncorrected. The purity of the samples was checked by thin layer chromatography using silica gel plates and acetone–benzene (1 : 3, v/v) as solvent system. IR spectra of the compounds were scanned in KBr discs on Perkin–Elmer 577 spectrophotometer. The ^{1}H NMR spectra were recorded at 90 MHz on Jeol FX 90Q FT NMR spectrometer in $CDCl_3$ solution using TMS as an internal standard. Mass spectra of all the compounds were recorded on Jeol JMSD-30Q mass spectrometer at 70 eV.

(3-Chloro-2-methylphenyl)thiourea

3-Chloro-2-methylaniline (14.15 g, 0.1 mol) was added to a mixture of concentrated hydrochloric acid (9 ml) and water (25 ml), and refluxed for about half an hour. The solution was allowed to cool and ammonium thiocyanate (8 g, 0.1 mol) was added. The reaction mixture was then refluxed for 4 h. The solid separated out on cooling was filtered, washed with water, dried and recrystallized from ethanol, m.p. 175 °C, yield 17.02 g (85%). For $C_8H_9ClN_2S$ (200.7) calculated: 47.88% C, 4.52% H; found: 47.75% C, 4.43% H.

2-Amino-5-chloro-4-methylbenzothiazole

3-Chloro-2-methylphenylthiourea (20.05 g, 0.1 mol) was dissolved chloroform (100 ml). Bromine (8.0 g, 0.1 mol) in chloroform (80 ml) was added dropwise with stirring. The temperature of the reaction mixture was maintained below 5 °C. After the complete addition of bromine the stirring was continued for half an hour and the reaction mixture was refluxed till the evolution of hydrogen bromide ceased. Chloroform was removed by distillation and resulting solid material was treated with aqueous sulfur dioxide solution and filtered. The filtrate was neutralized with aqueous ammonia and the precipitate was recrystallized from ethanol, m.p. 205 °C, yield 15.84 g (80%). For $C_8H_7ClN_2S$ (198.7) calculated: 48.36% C, 3.52% H; found: 48.22% C, 3.45% H.

2-Amino-4-chloro-3-methylbenzenethiol (*I*)

2-Amino-5-chloro-4-methylbenzothiazole (19.85 g, 0.1 mol), sodium hydroxide (80 g, 2 mol) and water (200 ml) were refluxed until the evolution of ammonia gas ceased. The reaction mixture was dilluted by cold water and filtered. The filtrate was neutralized by 5 M acetic acid and the yellowish precipitate was extracted with ether, evaporated and crystallized from ethanol. The formed compound *I* had m.p. 91 °C,, yield 9.86 g (57%). For C_7H_8ClNS (173.7) calculated: 48.41% C, 4.61% H; found: 48.30% C, 4.55% H. IR spectrum (cm^{-1}): 3 455, 3 365 (NH_2); 2 350 (SH); 1 435, 1 360 (CH); 750

(CCl). ^{1}H NMR spectrum (ppm): 7.82–6.46 m, 2 H (arom.); 4.05 s, 2 H (NH_2); 2.21 s, 3 H (CH_3); 1.37 s, 1 H (SH).

6-Chloro-5-methyl-4*H*-1,4-benzothiazines *III*. General Procedure

Corresponding β-diketone or β-keto ester *III* (0.01 mol) was added to the stirred suspension of 2-amino-4-chloro-3-methyl benzenethiol (*I*, 1.73 g, 0.01 mol) in DMSO (5 ml) and heated for 10–15 min. The

TABLE I
IR spectral data of 4*H*-1,4-benzothiazines *III*

Compound	$\tilde{\nu}$, cm^{-1}			
	NH	CO	CH	C–Cl
IIIa	3 370	1 620	1 490, 1 340	750
IIIb	3 400	1 630	1 450, 1 360	780
IIIc	3 410	1 600	1 480, 1 340	740
IIId	3 390	1 680	1 480, 1 320	770
IIIe	3 320	1 590	1 490, 1 340	720
IIIf	3 360	1 590	1 440, 1 360	760
IIIg	3 320	1 595	1 470, 1 355	745
IIIh	3 340	1 620	1 480, 1 365	755

TABLE II
^{1}H NMR spectral data (δ, ppm) of 4*H*-1,4-benzothiazines *III*

Compound	NH[a]	arom.[b]	3-CH_3[a]	5-CH_3[a]	Other protons
IIIa	9.10	7.44–6.11	3.01	2.66	4.08 s (CH_3)
IIIb	8.92	7.48–6.91	2.38	2.17	4.10–3.90 q (CH_2); 1.40–1.23 t (CH_3)
IIIc	8.55	7.92–7.00	2.53	2.15	–
IIId	8.54	8.11–7.22	2.56	2.21	–
IIIe	8.49	8.08–7.32	2.63	2.31	2.85 s (CH_3)
IIIf	8.71	8.24–7.29	2.31	1.74	2.69 s (CH_3)
IIIg	8.93	7.69–6.60	–	2.35	–
IIIh	8.87	7.44–6.05	2.97	2.59	–

[a] Singlet. [b] Multiplet.

reaction mixture was cooled to room temperature and the separated solid was filtered and recrystallized from methanol. The physical and analytical data are given in Table III.

TABLE III
Physical and analytical data of 4*H*-1,4-benzothiazines *III*

Compound	Formula (M.w.)	M.p., °C Yield, %	Calculated/Found		
			% C	% H	% N
IIIa	$C_{12}H_{12}ClNO_2S$	112	53.43	4.45	5.19
	(269.15)	68	53.35	4.41	5.15
IIIb	$C_{13}H_{14}ClNO_2S$	185	55.02	4.93	4.93
	(283.5)	69	54.90	4.91	4.90
IIIc	$C_{17}H_{14}ClNOS$	166	64.65	4.43	4.43
	(315.5)	44	64.55	4.38	4.39
IIId	$C_{17}H_{13}Cl_2NOS$	120	58.28	3.71	4.00
	(350.0)	63	58.19	3.65	3.94
IIIe	$C_{18}H_{16}ClNOS$	136	65.55	4.85	4.24
	(329.5)	50	65.44	4.79	4.26
IIIf	$C_{12}H_{12}ClNOS$	110	56.80	4.73	5.52
	(253.5)	64	56.75	4.71	5.48
IIIg	$C_{22}H_{16}ClNOS$	64	69.93	4.23	3.70
	(377.5)	55	69.85	4.18	3.75
IIIh	$C_{17}H_{13}BrClNOS$	145	51.71	3.29	3.54
	(394.5)	61	51.66	3.25	3.51

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