SYNTHESIS OF SUBSTITUTED 4H-1,4-BENZOTHIAZINES AND THEIR CONVERSION INTO SULFONES

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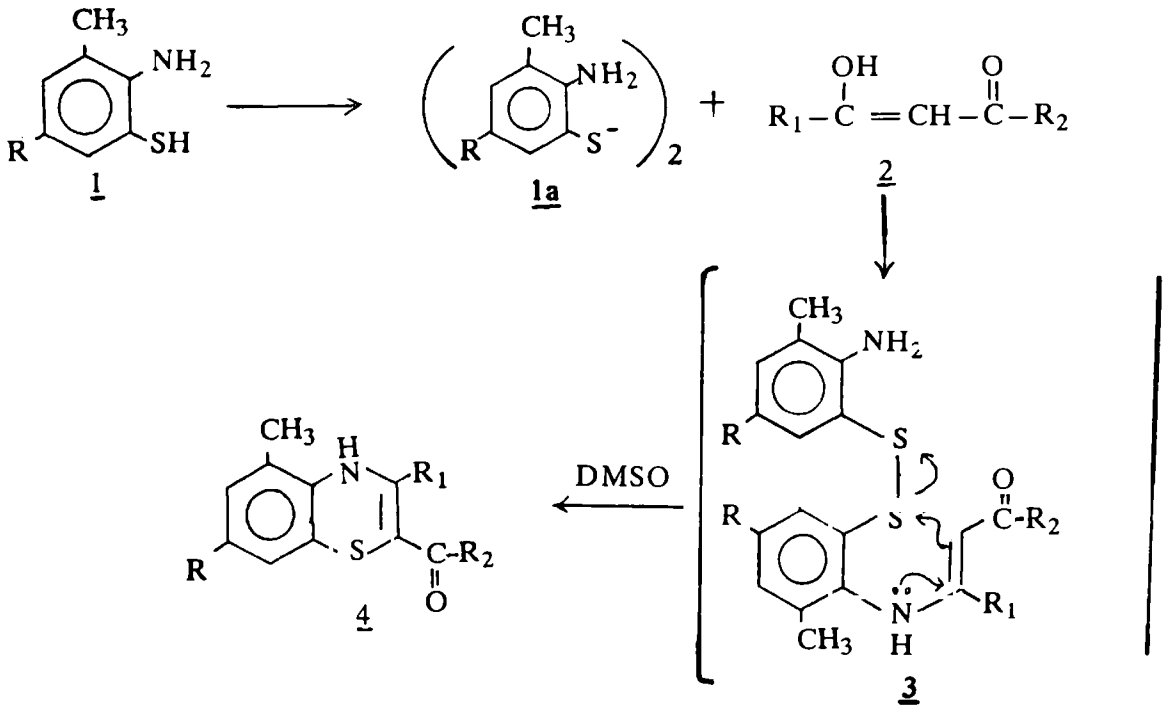
Abstract : The present work consists of one-pot synthesis of substituted 4H-1,4-benzothiazines by the condensation and oxidative cyclization of substituted 2-aminobenzenethiols with β- diketones/β-ketoesters in dimethyl sulfoxide and oxidation behaviour of 4H-1,4-benzothiazines by 30% hydrogen peroxide in glacial acetic acid to 1,4-benzothiazine sulfones. The structure of all the synthesized compounds has been confirmed by elemental analysis and spectral studies.

Introduction

4H-1,4-Benzothiazines possess a wide specturm of pharmacological/biological activities similar to phenothiazines (1,2) due to the presence of a fold along nitrogen and sulfur axis which is one of the structural specificity to impart pharmaceutical/biological activities (3-10). The oxidation of sulfide linkage in 4H-1,4-benzothiazines to dioxide leads to an interesting class of heterocyclic sulfones not only from medicinal (11-14) and industrial (15) point of view, but also structural aspects. It has stimulated our interest to convert benzothiazines to sulfones to understand oxidation behaviour of 4H-1,4-benzothiazines and to investigate changes in infrared and nuclear magnetic resonance spectra caused by the conversion of sulfide linkage to sulfone.

Results and Discussion

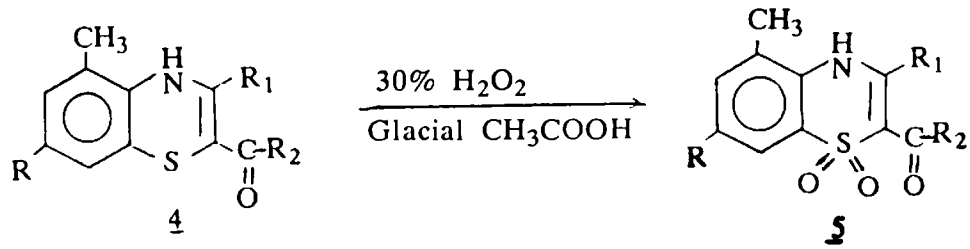
The title compounds have been synthesized by one-pot reaction involving condensation and oxidative cyclization of substituted 2-aminobenzenethiols 1 with β-diketones/β-ketoesters 2 in dimethyl sulfoxide. The reaction is believed to proceed through the formation of an intermediate enaminoketone 3 (16,17). Under the experimental conditions substituted 2-aminobenzenethiols 1 are readily oxidized to bis(2-aminophenyl) disulfides 1a (17,18) which cyclize to 4H-1,4-benzothiazines 4 by scission of sulfur-sulfur bond due to high reactivity of α-position of enaminoketone system 3 towards nucleophilic attack (Scheme 1).



R = CH_3, Cl
R_1 = CH_3, C_6H_5
R_2 = OC_2H_5, OCH_3, $C_6H_4Cl(p)$, $C_6H_4Br(p)$, $C_6H_4CH_3(p)$, $C_6H_5OCH_3(p)$, $C_6H_4F(p)$

Scheme 1

4H-1,4-Benzothiazines sulfones 5 have been prepared by the oxidation of 4H-1,4-benzothiazines 4 with 30% hydrogen peroxide in glacial acetic acid (Scheme 2).



Scheme 2

2-Aminobenzenthiols 1 required in the synthesis of title compounds have been prepared by the method reported by us earliar (5).

Experimental

All the melting points are uncorrected. The purity of the synthesized compounds was checked by thin layer chromatography. Infrared spectra of benzothiazines and their sulfones have been recorded on a Perkin-Elmer spectrophotometer model 577 in KBr discs as well as in chloroform. ^{1}H NMR spectra were scanned on 90 MHz Jeol FX 90Q FT NMR spectometer in DMSO-d_6 containing TMS as an internal standard and their mass spectra were recorded on Jeol JMSD-300 mass spectrometer at 70ev with 100 μamp ionising current.

Preparation of substituted 4H-1,4-benzothiazines 4a-q

To the stirred suspension of β-diketones/β-ketoesters (2; 0.01M) in dimethyl sulfoxide (5 ml) was added 2-aminobenzenethiol (1; 0.01M) and the resulting mixture was refluxed for 20-30 minutes. The reaction mixture was concetrated and cooled down to room temperature and filtered. The product obtained was washed with petroleum ether and crystallized from methanol. The physical and analytical data of 4H-1,4-benzothiazines are given in Table 1.

Preparation of substituted 4H-1,4-benzothiazine sulfones 5a-q

30% Hydrogen peroxide (5 ml) was added to a solution of substituted 4H-1,4-benzothiazines (4; 0.01M) in glacial acetic acid (15 ml) and refluxed for fifteen minutes. Heating was stopped and another lot of hydrogen peroxide (5 ml) was added. The reaction mixture was again refluxed for 4 hours. The excess of solvent was removed by distillation under reduced pressure and poured into a beaker containing crushed ice. The residue obtained was filtered off, washed with water and crystallised from ethanol. Physcial and analytical data of 4H-1,4-benzothiazine sulfones are given in Table 2.

Infrared Spectra

IR Spectra of all the 4H-1,4-benzothiazines exhibit a sharp peak in the region 3240-3380 cm^{-1} due to NH stretching vibrations which shifts to higher frequencies region 3340-3460 cm^{-1} in corresponding sulfones. A sharp peak observed in the region 1550-1640 cm^{-1} due to C=O stretching vibrations in 4H-1,4-benzothiazines shifts to higher frequency 1675-1720 cm^{-1} in corresponding sulfones. This is an agreement with increased

Table 1 : Physical data of 4H-1,4-benzothiazines 4a-q

Compd.	R	R_1	R_2	M.P. (°C)	Yield (%)	Molecular Formula	% Found/Calcd.		
							C	H	N
4a	CH_3	CH_3	OC_2H_5	114	57	$C_{14}H_{17}NO_2S$	63.57	6.45	5.30
							63.87	6.46	5.32
4b	CH_3	CH_3	OCH_3	118	52	$C_{13}H_{15}NO_2S$	62.90	6.04	5.61
							62.65	6.02	5.62
4c	CH_3	CH_3	C_6H_5	135	60	$C_{18}H_{17}NOS$	73.50	5.75	4.73
							73.22	5.76	4.74
4d	CH_3	CH_3	CH_3	139	45	$C_{13}H_{15}NOS$	67.17	6.42	6.02
							66.95	6.43	6.00
4e	CH_3	C_6H_5	C_6H_5	74	40	$C_{23}H_{19}NOS$	77.03	5.31	3.93
							77.31	5.32	3.92
4f	CH_3	CH_3	C_6H_4–Cl(p)	170	62	$C_{18}H_{16}ClNOS$	65.69	4.84	4.23
							65.55	4.85	4.24
4g	CH_3	CH_3	C_6H_4–Br(p)	205	43	$C_{18}H_{16}BrNOS$	58.01	4.26	3.75
							57.75	4.27	3.74
4h	CH_3	CH_3	C_6H_4–CH_3(p)	128	65	$C_{19}H_{19}NOS$	74.02	6.15	4.52
							73.78	6.14	4.53
4i	CH_3	CH_3	C_6H_4–OCH_3(p)	157	39	$C_{19}H_{19}NO_2S$	70.53	5.85	4.31
							70.15	5.84	4.30
4j	Cl	CH_3	OC_2H_5	112	43	$C_{13}H_{14}ClNOS$	55.33	4.95	4.91
							55.02	4.93	4.93
4k	Cl	CH_3	C_6H_5	128	61	$C_{17}H_{14}ClNOS$	64.38	4.41	4.44
							64.65	4.43	4.43
4l	Cl	CH_3	CH_3	124	48	$C_{12}H_{12}ClNOS$	56.43	4.75	5.53
							56.80	4.73	5.52
4m	Cl	CH_3	OCH_3	132	51	$C_{12}H_{12}ClNO_2S$	53.10	4.47	5.22
							53.43	4.45	5.19
4n	Cl	CH_3	C_6H_4–Cl(p)	170	64	$C_{17}H_{13}Cl_2NOS$	58.62	3.70	4.02
							58.28	3.71	4.00
4o	Cl	C_6H_5	C_6H_5	152	30	$C_{22}H_{16}ClNOS$	69.69	4.21	3.71
							69.93	4.23	3.70
4p	Cl	CH_3	C_6H_4–Br(p)	162	54	$C_{17}H_{13}BrClNOS$	52.03	3.28	3.53
							51.71	3.29	3.54
4q	Cl	CH_3	C_6H_4–CH_3	182	51	$C_{18}H_{16}ClNOS$	65.06	4.88	4.21
							65.55	4.85	4.24

Table 2 : Physical data of 4H-1,4-benzothiazine sulfones 5a-q

Compd.	R	R_1	R_2	M.P. (°C)	Yield (%)	Molecular Formula	% Found/Calcd.		
							C	H	N
5a	CH_3	CH_3	OC_2H_5	185	24	$C_{14}H_{17}NO_4S$	57.23	5.78	4.73
							56.94	5.76	4.74
5b	CH_3	CH_3	OCH_3	122	21	$C_{13}H_{15}NO_4S$	55.19	5.35	4.96
							55.51	5.33	4.98
5c	CH_3	CH_3	C_6H_5	152	18	$C_{18}H_{17}NO_3S$	65.82	5.21	4.27
							66.05	5.19	4.28
5d	CH_3	CH_3	CH_3	128	28	$C_{13}H_{15}NO_3S$	59.19	5.68	5.27
							58.86	5.66	5.28
5e	CH_3	C_6H_5	C_6H_5	79	32	$C_{23}H_{19}NO_3S$	70.61	4.90	3.58
							70.95	4.88	3.59
5f	CH_3	CH_3	C_6H_4–Cl(p)	202	14	$C_{18}H_{16}ClNO_3S$	59.41	4.43	3.88
							59.75	4.42	3.87
5g	CH_3	CH_3	C_6H_4–Br(p)	182	23	$C_{18}H_{16}BrNO_3S$	53.61	3.95	3.43
							53.20	3.94	3.44
5h	CH_3	CH_3	C_6H_4–CH_3(p)	172	32	$C_{19}H_{19}NO_3S$	55.94	5.59	4.09
							55.71	5.57	4.10
5i	CH_3	CH_3	C_6H_4–OCH_3(p)	136	25	$C_{19}H_{19}NO_4S$	64.19	5.31	3.91
							63.86	5.32	3.92
5j	Cl	CH_3	OC_2H_5	146	18	$C_{13}H_{14}ClNO_3S$	49.62	4.41	4.42
							49.44	4.43	4.43
5k	Cl	CH_3	C_6H_5	158	22	$C_{17}H_{14}ClNO_3S$	58.42	4.00	4.01
							58.70	4.02	4.02
5l	Cl	CH_3	CH_3	149	40	$C_{12}H_{12}ClNO_3S$	50.75	4.21	5.37
							50.43	4.20	5.39
5m	Cl	CH_3	OCH_3	136	38	$C_{12}H_{12}ClNO_4S$	47.48	3.99	4.65
							47.76	3.98	4.64
5n	Cl	CH_3	C_6H_4–Cl(p)	144	43	$C_{17}H_{13}Cl_2NO_3S$	53.78	3.42	3.67
							53.40	3.40	3.66
5o	Cl	C_6H_5	C_6H_5	82	12	$C_{22}H_{16}ClNO_3S$	64.88	3.89	3.40
							64.46	3.90	3.41
5p	Cl	CH_3	C_6H_4–Br(p)	208	24	$C_{27}H_{13}BrClNO_3S$	47.69	3.05	3.27
							47.83	3.04	3.28
5q	Cl	CH_3	C_6H_4–CH_3	196	33	$C_{18}H_{16}ClNO_3S$	59.93	4.44	3.88
							59.75	4.42	3.87

electron acceptor ability of heteroaromatic nucleus in sulfones as compared to parent nucleus. The lone pair of electrons on nitrogen is withdrawn more effectively with carbonyl group and results in higher frequency of carbonyl group frequencies. The -I effect of SO_2 group combined with a mesomeric effect which operates in the same direction, also hinders the conjugation of lone pair of electron of nitrogen with carbonyl group. All 4H-1,4-benzothiazine sulfones exhibit an intense peak in the region 1360-1395 cm^{-1} in chloroform due to asymmetric stretching mode of the sulfonyl group, which in solid state splits into three bands in the region 1351-1390, 1305-1322 and 1235-1285 cm^{-1}. Asmmetric stretching vibration in sulfones is strongly affected on passing from solution to crystalline state. Symmetrial stretching vibrations, give rise to a doublet and in some cases a broad signal in potassium bromide pellets in the region 1112-1180 cm^{-1} where as in solution it appears at 1110-1178 cm^{-1}. These frequencies are slightly affected by the state of aggregation. In 1,4-benzothiazines a medium intensity band appears at 1015-1080 cm^{-1} due to C-S stretching vibrations (19) and shifts to higher frequency region 1040-1090 cm^{-1} in corresponding sulfones. Peaks corresponding to C-Cl stretching vibrations appear at 710-780 cm^{-1} in benzothiazines (4f, 4i-q) as well as in sulfones (5f, 5f-q). Peaks corresponding to C-H deformation vibrations of CH_3 group appear at 1310-1385 and 1430-1470 cm^{-1} respectively in benzothiazines as well as in sulfones. The information about the electron donor and electron acceptor abilities of heteroaromatic rings (20) can be obtained from substituted vibrations.

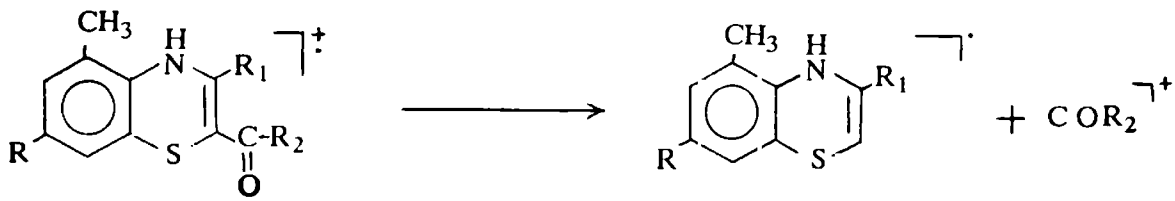
NMR Spectra

Resonance signal due to N-H proton in benzothiazines appears at δ 7.9-9.87 ppm and is shifted to downfield (δ 8.0-10.22 ppm) in corresponding sulfones. NMR Spectra of 4H-1,4-benzothiazines except (4e,4o) exhibit resonance signals in the region δ 2.12-2.63 ppm due to allylic protons ($C=C-CH_3$) and are also shifted to downfield (δ 2.20-2.70 ppm) in sulfones. A singlet due to CH_3 protons at C_5 observed in the region δ 1.52-2.25 ppm in benzothiazines is shifted to downfield δ 1.80-2.34 ppm in corresponding sulfones. The singlet is observed in the region δ 1.3-2.00 ppm due to CH_3 protons at C_7 (4a-i) in benzothiazines is shifted to downfield (δ 1.71-2.20 ppm) in corresponding sulfones. A singlet due to CH_3 protons of $COOCH_3$ group (4b,4m) at C_2 observed at

δ 2.13-2.30 ppm in benzothiazines is shifted to downfield (δ 2.54- 2.59 ppm) in corresponding sulfones (5b,5m). The singlet observed at δ 3.58 ppm due to OCH_3 protons at para position of benzoyl side chain at C_2 in benzothiazine (4i) is also shifted to downfield (δ 4.62 ppm) in corresponding sulfone (5i). Conversion of benzothiazines to sulfones involves conversion of sulfides linkage to sulfoxide and results in shifting resonance signals to downfields. It is due to decreased local diamagnetic shielding of the substituent anisotropic deshielding. In sulfones, thiazine nucleus contains large close loops of π-electrons in comparision to parent benzothiazine due to the conversion of sulfide linkage to dioxide, in which strong diamagnetic current is induced by the magnetic field. The effect results in an increased ring current effect causing the deshielding of aromatic protons and any group contained in the plane of the thiazine nucleus.

Mass Spectra

The mass spectrum of each benzothiazine shows molecular ion peak in accordance with its molecular weight and in all cases side chain at C_2 appears as base peak (Scheme-3)



Scheme 3

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