SINGLE STEP SYNTHESIS OF SUBSTITUTED 4H-1,4-BENZOTHIAZINES

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Abstract: The present work deals with one pot synthesis of substituted 4H-1,4-benzothiazines by the condensation and oxidative cyclisation of 2-amino-5-bromo-3-methylbenzenethiol with β-diketones/β-ketoesters in dimethyl sulfoxide. The structure of all the synthesized compounds have been characterized by elemental analyses and spectral studies.

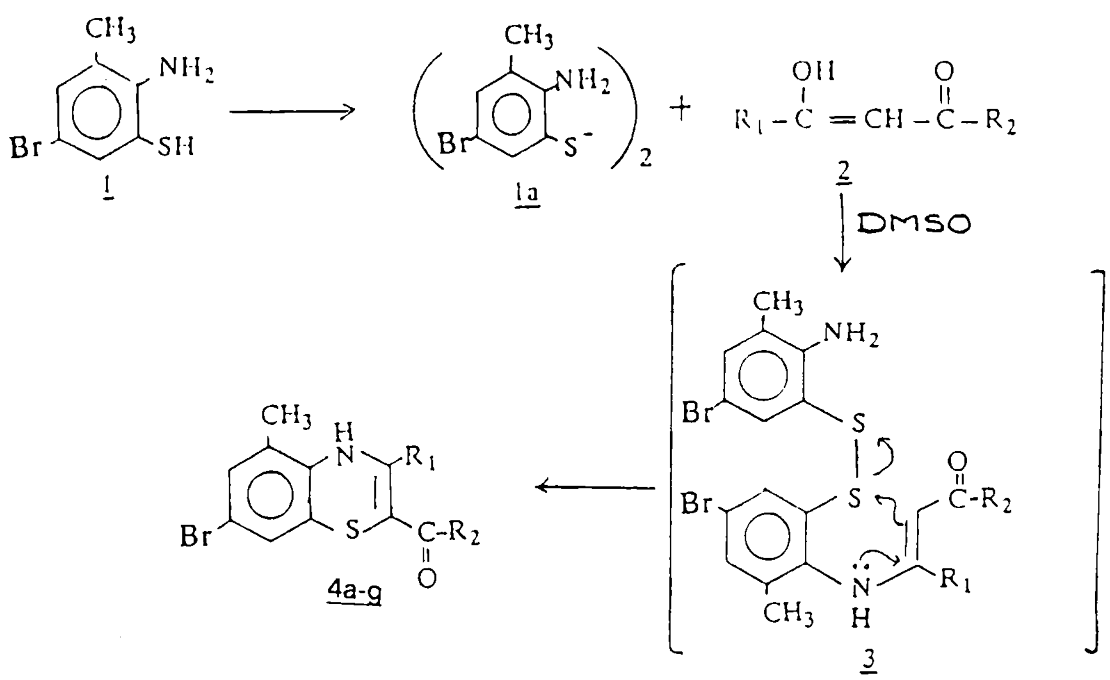
Introduction

4H-1,4-Benzothiazines resemble structurally to phenothiazines (1,2) in having a fold along nitrogen-sulphur axis which is one of the structural specificity to impart biological activities (3-6) to phenothiazines. As such 4H-1,4-benzothiazines are anticipated to possess a wide spectrum of biological activities similar to that of phenothiazines.

Results and Discussion

Substituted 4H-1,4-benzothiazines have been synthesized by one pot reaction involving condensation and oxidative cyclisation of 2-amino-5-bromo-3-methylbenzenthiol 1 with β-diketones/β-ketoesters 2 in dimethyl sulfoxide. The reaction is believed to proceed through the formation of an imtermediate enaminoketone 3 (7,8). Under the above experimental conditions 2-amino-5-bromo-3-methylbenzenethiol 1 is readily oxidized to bis-(2-aminophenyl) disulphide **Ia** (9,10) which cyclizes to 4H-1,4-benzothiazines 4 by scission of sulphur-sulphur bond due to high reactivity of α-position of enaminoketone system 3 towards nucleophilic attack **(Scheme-1)**.

The IR spetra of all the synthesized 4H-1,4-benzothiazines exhibit a single sharp peak in the region 3220-3380cm^{-1} due to N-H stretching vibrations. The sharp band in the region 1650-1700cm^{-1} is due to C=0 stretching vibrations. The compounds **4a-g** exhibit absorption bands 1330-1460cm^{-1} due to C-H deformation vibration of CH_3 group. In compound 4e - f bands appearing in the region 1220-1250 cm^{-1} and 1030-1060cm^{-1} are attributed to C-O-C asymmetric and symmetric vibrations respectively. Compound **4c** exhibits a single band in the region 780cm-1 due to C-Cl stretching vibrations. Compounds **4a - g** exhibit a single peak in the region 500-600cm^{-1} due to C-Br stretching Vibrations.



(Scheme- 1)

$R_1=CH_3$

R_2 = - OCH_3, - OC_2H_5, - $C_6H_4Cl(p)$, - $C_6H_4Br(p)$, - C_6H_4 $CH_3(p)$, - $C_6H_4OCH_3(m)$, - $C_6H_4OCH_3(o)$,

The NMR spectra of the compounds **4a - g** exhibit a single sharp peak in the region δ 7.79-8.30 due to **NH** proton. The multiplets observed in the region δ 6.49-7.76 are due to aromatic protons. In compound **4a** singlet at δ 3.39 arises due to $\mathbf{OCH_3}$ protons at C_2. In compound 4g a singlet is observed at δ 2.88 due to $\mathbf{CH_3}$ protons at para position in benzoyl side chain at C_2. Compounds **4e** and **4f** exhibit a singlet at δ 2.85 and δ 2.47 due to $\mathbf{OCH_3}$ protons at ortho and meta positions respectively in benzoyl side chain at C_2. The singlet observed in the region δ 2.06-2.69 in the compounds **4a - g** is assigned to $\mathbf{CH_3}$ protons at C_3. Compound **4b** exhibits quartets andtriplets in the region δ 2.25-2.37 and δ 1.80-1.96 due to $\mathbf{CH_2}$ and $\mathbf{CH_3}$ protons of $OC_2\mathbf{H_5}$ group at C_2. A singlet is observed in the region δ 1.16-2.12 due to $\mathbf{CH_3}$ protons at C_5.

The mass spectra of all the synthesized 4H-1,4-benzothiazines showed molecular ion peaks corresponding to their molecular weight. In all cases side chain at C_2 appears as base peak.

Experimental

All the melting points are uncorrected. The purity of synthesized compounds has been checked by thin layer chromatography and the structures have been characterized by elemental analysis and spectral data. Infrared spectra of all the compounds have been scanned in KBr on a Nicolet Spectrophotometer model 544. The NMR spectra have been recorded at 90 MHz on a Jeol FX 90 Q FT NMR using TMS as an internal standared in DMSO-d_6. Mass spectra were recorded on Kratos MS-30,MS-50 at 70 eV.

Preparation of substituted 4H-1,4-benzothiazines

To the stirred suspension of β-diketones/β-ketoesters (2; 0.01M) in dimethylsulfoxide (5 ml) was added 2-amino-5-bromo-3-methylbenzenethiol (1; 0.01M) and the resulting mixture was refluxed for 20-30 minutes. The reaction mixture was concentrated and cooled down to room teperature and filtered. The product obtained was washed with petroleum ether and crystallized from methanol. The physical and analylical data of 4H-1,4-benzathiazines are given in Table 1.

Table 1 : Physical and analytical data of 4H-1,4-benzothiazines **4a-g**

Compd. 4	R_1	R_2	M.P. (°C)	Yield (%)	Molecular Formula	% Found/Calcd C	H	N
a	CH_3	OCH_3	160	48	$C_{12}H_{12}BrNO_2S$	45.55 45.85	3.81 3.82	4.44 4.45
b	CH_3	OC_2H_5	145	42	$C_{13}H_{14}BrNO_2S$	47.87 47.56	4.27 4.26	4.25 4.26
c	CH_3	C_6H_4-Cl(p)	180	58	$C_{17}H_{13}BrClNOS$	52.04 51.71	3.28 3.29	3.55 3.54
d	CH_3	C_6H_4-Br(p)	178	55	$C_{17}H_{13}Br_2NOS$	46.58 46.46	2.97 2.96	3.17 3.18
e	CH_3	C_6H_4-OCH_3(m)	155	48	$C_{18}H_{16}BrNO_2S$	55.05 55.38	4.12 4.10	3.60 3.58
f	CH_3	C_6H_4-OCH_3(o)	135	45	$C_{18}H_{16}BrNO_2S$	55.10 55.38	4.11 4.10	3.61 3.58
g	CH_3	C_6H_4-CH_3(p)	185	50	$C_{18}H_{16}BrNOS$	57.35 57.75	4.28 4.27	3.72 3.74

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References

(1) R.R. Gupta (Ed.), "Phenothiazines and 1,4-Benzothiazines–Chemical and Biomedical Aspects", Elsevier, Amsterdam, 1988

(2) H. Keyzer, G.M. Eckert, I.S. Forrest, R.R. Gupta, F. Gutmann and J. Molnar (Eds.), "Thiazines and Structurally Related Compounds", (Proceeding of Sixth International Conference on Phenothiazines and Structurally Related Psychotropic Compounds, Pasadena, California, September 11-14, 1990), Kriger Publishing Company, Malabar, Florida, USA, 1992

(3) S.K. Mukherji, M. Jain, A. Gupta, V. Saraswat and R.R. Gupta, Ind. J. Chem. 33B 990 (1994)

(4) R.R. Gupta, M. Jain, R.S. Rathore and A. Gupta, J. Fluor. Chem. 62, 191 (1993)

(5) R.R. Gupta, R.S. Rathore, M. Jain and V. Saraswat, Pharmazie 47, 229 (1992)

(6) V. Gupta and R.R. Gupta, J. Prakt. Chem. 333, 153 (1991)

(7) D.D. Bhatnagar, K.K. Gupta, V. Gupta and R.R. Gupta, Curr. Sci. 58, 1091 (1989)

(8) R.R. Gupta, R.K. Rathore, V. Gupta and R.S. Rathore, Pharmazie 46, 602 (1991)

(9) R.R. Gupta and Rakesh Kumar, J. Fluor. Chem. 31(1), 19 (1986)

(10) M. Marziano, G. Montavdo and R. Passerini, Ann. Chim 52, 121 (1962)

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