ONE POT SYNTHESIS OF 7-METHOXY/6-SULFONYL-4H-1, 4-BENZOTHIAZINES

Kalpana Gupta, Vandana Gupta, Rajni Gupta and M.Kumar *
Department of Chemistry, University of Rajasthan, Jaipur – 302004, India

Abstract

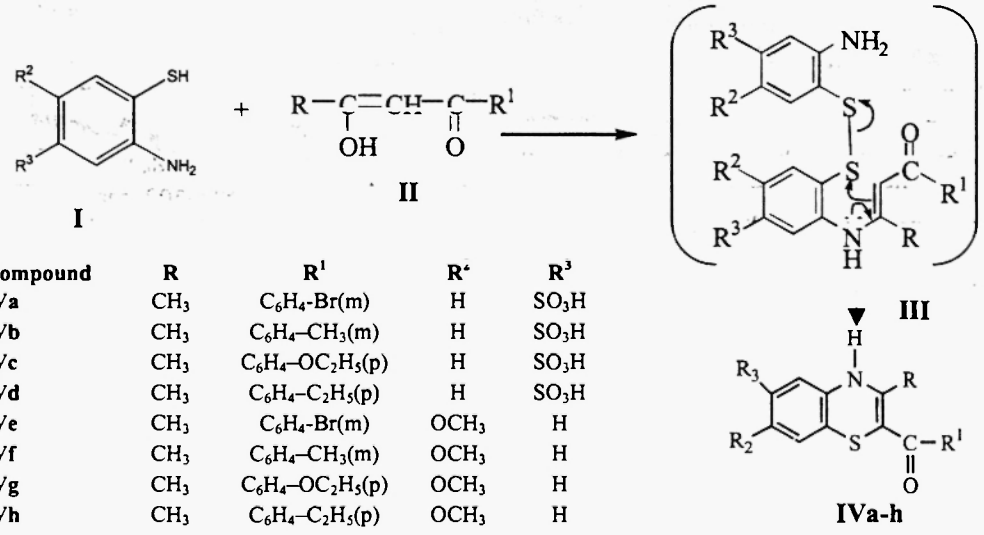
7-Methoxy/6-sulfonyl-4H-1,4-benzothiazines have been prepared by the condensation and oxidative cyclization of substituted 2-aminobenzenthiols (I) with β-diketones in the presence of dimethyl sulfoxide. The reaction is considered to proceed through the formation of an intermediate enaminoketone. The IR, ^{1}H NMR and mass spectra are also included.

Introduction

4*H*–1,4–benzothiazines[1,2] form an interesting class heterocycles.The structural resemblance of 1,4–benzothiazines with phenothiazines[3-8] has stimulated our interest to synthesize hither to unknown 1,4-benzothaizines.It is considered worthwhile to make them available for screening their biological/pharmacological activities in order to search better drugs of this series.

Results and Discussion

In the present investigation, 7-methoxy/6-sulfonyl-4*H*–1,4–benzothiazines have been synthesized by the condensation of β-diketones with 2-amino-7-methoxy/6-sulfonylbenzenethiol(I) in the presence of dimethyl sulfoxide which causes oxidative cyclization. The reaction proceeds with the formation of an intermediate enaminoketone (III). 2–Aminobenzenethiol (I) is readily oxidized to bis (2–aminophenyl) disulfide which is cyclized to the corresponding 4*H*–1,4–benzothiazine (IV) by the scission of sulfur–sulfur bond due to high reactivity of α–position of enaminoketone system (III) towards nucleophilic attack (Scheme-1).



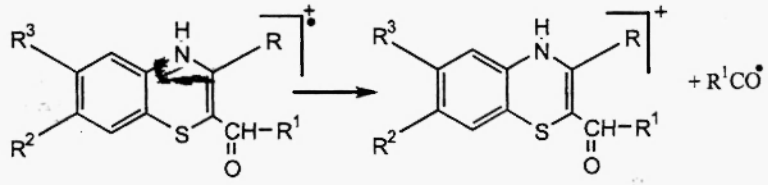
Compound	R	R^1	R^4	R^3
IVa	CH_3	C_6H_4-Br(m)	H	SO_3H
IVb	CH_3	C_6H_4–CH_3(m)	H	SO_3H
IVc	CH_3	C_6H_4–OC_2H_5(p)	H	SO_3H
IVd	CH_3	C_6H_4–C_2H_5(p)	H	SO_3H
IVe	CH_3	C_6H_4-Br(m)	OCH_3	H
IVf	CH_3	C_6H_4–CH_3(m)	OCH_3	H
IVg	CH_3	C_6H_4–OC_2H_5(p)	OCH_3	H
IVh	CH_3	C_6H_4–C_2H_5(p)	OCH_3	H

Scheme–1

All the synthesized 4*H*–1,4–benzothiazines exhibit a single sharp peak in the region 3385–3270 cm^{-1} due to N–H stretching vibrations. The sharp band observed in the region 1665–1600 cm^{-1} is attributed to C=O stretching vibrations of carbonyl group. 4H-1,4-benzothiazines containing methyl group exhibit two bands due to C–H deformation vibrations of CH_3 group at 1480–1420 cm^{-1} and 1395–1320 cm^{-1}. In the compounds (IVe–h) and (IVc) the absorption bands appearing in the regions 1265–1225 cm^{-1} and 1050–1030 cm^{-1} are attributed to C–O–C asymmetric and symmetric vibrations. In the compounds (IVa) and (IVe), a single absorption band is observed in the region 590–580 cm^{-1} due to C–Br stretching vibrations.

^{1}H NMR spectra of all the synthesized 4H-1,4-benzothiazines exhibit multiplet in the region δ 6.37–8.24 ppm due to aromatic protons. A singlet observed in the region δ 8.38–9.35 ppm in all the compounds can be assigned to NH proton. The CH_3 protons in the allylic linkage exhibit resonance signal in the region δ 1.80–2.53 ppm. A triplet centered at δ 1.20 ppm and quartet centered in the region δ 2.63–2.59 ppm are observed in the compound (IVd,h) due to CH_3 and CH_2 protons of ethyl group at para position in benzoyl side chain at C_2. A singlet is observed in the region δ 1.80–1.83 ppm due to CH_3 protons at meta–position in benzoyl side chain at C_2 in the compounds (IVb) and (IVf). The compounds (IVc) and (IVg), exhibit a quartet and a triplet in the region δ 3.79–4.15 ppm and δ 1.35 ppm due to CH_2 and CH_3 protons respectively of OC_2H_5 group at para position in benzoyl side chain at C_2.

The molecular ion peaks in the mass spectra of all the synthesized benzothiazines are in accordance with their molecular weights. In all cases, the side chain at C_2 appears as base peak (Scheme–2).



Scheme-2

Experimental

All the melting points are uncorrected. The purity of all the synthesized compounds was checked by thin layer chromatography. The infrared spectra have been recorded on NICOLET–MAGNA FT IR spectrophotometer model 550 in KBr over the range of 4000–400 cm^{-1}. ^{1}H NMR spectra were scanned on Jeol FX–90Q FT NMR spectrometer at 90 MHz and at 300 MHz on FT NMR Bruker DRX in DMSO–d_6 using TMS as internal standard. Mass spectra were recorded on Jeol JMSD–300 mass spectrometer at 70 eV with 100μ amp ionising current. The physical data are given in Table-1.

Table-1 : Physical and analytical data of substituted 4H–1,4–benzothiazines (IVa–h)

Compound				M.P. °C	Yield %	Molecular formula	% Found (Calcd.)		
	R^1	R^2	R^3				C	H	N
I	II	III	IV	V	VI	VII	VIII	IX	X
IVa.	C_6H_4–Br(*m*)	H	SO_3H	79	30	$C_{16}H_{12}NO_4S_2Br$	45.72 (45.07)	2.85 (2.83)	3.33 (3.28)
IVb	C_6H_4–CH_3(m)	H	SO_3H	158	71	$C_{17}H_{15}NO_4S_2$	56.97 (56.49)	4.20 (4.18)	3.89 (3.87)
IVc.	C_6H_4–OC_2H_5(*p*)	H	SO_3H	85	35	$C_{18}H_{17}NO_5S_2$	54.79 (55.22)	4.35 (4.37)	3.53 (3.57)
IVd.	C_6H_4–C_2H_5(*p*)	H	SO_3H	122	45	$C_{18}H_{17}NO_4S_2$	57.92 (57.58)	4.58 (4.56)	3.76 (3.73)
IVe.	C_6H_4–Br(*m*)	OCH_3	H	75	25	$C_{17}H_{14}NO_2SBr$	53.98 (54.26)	3.71 (3.75)	3.68 (3.72)
IVf.	C_6H_4–CH_3(*m*)	OCH_3	H	115	65	$C_{18}H_{17}NO_2S$	69.94 (69.42)	5.54 (5.50)	4.56 (4.50)
Ivg.	C_6H_4–OC_2H_5(*p*)	OCH_3	H	90	70	$C_{19}H_{19}NO_3S$	67.02 (66.84)	5.63 (5.60)	4.15 (4.10)
IVh.	C_6H_4–C_2H_5(*p*)	OCH_3	H	119	50	$C_{19}H_{19}NO_2S$	69.82 (70.12)	5.85 (5.88)	4.26 (4.30)

Synthesis of benzoylacetones

Sodium wire (11.5 gm) was suspended in cold dry ethylacetate (200 ml) contained in a 500 ml three necked R.B. flask fitted with a reflux condenser, mechanical stirrer and a dropping funnel. It was immersed it in an ice bath and substituted acetophenone (0.25 mole) was added in small lots from the dropping funnel to the ice cold reaction mixture over a period of 3–4 hours with continuous stirring and allowed to stand overnight. The sodium salt of substituted benzoylacetone was filtered and washed with benzene and dried. It was dissolved in minimum amount of water and then decomposed by dilute acetic acid. The product was extracted with ether. The ether was evaporated and was dried over anhydrous sodium sulphate and liquid obtained was distilled.

Preparation of 4*H*–1,4–benzothiazines (IVa–h)

To the stirred suspension of β–diketone (II, 0.01 mole) in DMSO (6ml) was added 2–amino–5–methoxy/4–sulfonylbenzenethiol (I, 0.01 mole) and the resulting mixture was refluxed for one hour (15–20 minutes in case of sulfonic acid group derivative). The mixture was cooled down to room temperature and a solid substance separated was filtered and crystallized from methanol/solvent ether.

Acknowledgement

We express our thanks to CDRI, Lucknow for scanning ^{1}H NMR and mass spectra.

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Received on July 7, 2002