SINGLE STEP SYNTHESIS OF 2-(3-METHOXYBENZOYL)-3-METHYL-4H-1,4-BENZOTHIAZINES

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Abstract : One pot synthesis of title compounds is reported by the condensation and oxidative cyclization of 2-aminobenzenethiols with 3-methoxybenzoylacetone in DMSO. The product have been characterised by analytical, IR, NMR and mass spectral data.

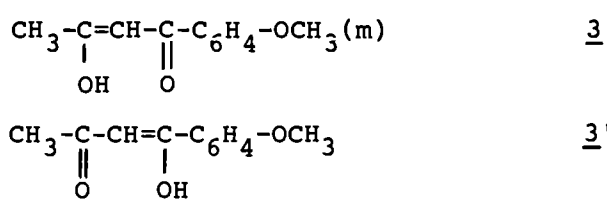
Introduction

4H-1,4-Benzothiazines resemble structurally to phenothiazines in having a fold along nitrogen-sulphur axis which is one of the structural specificity to impart biological activities to phenothiazines (1). As such 1,4-benzothiazines are anticipated to possess a wide spectrum of biological activities similar to that of phenothiazines. In continuation of our programme to synthesize novel pharmaceutical heterocycles, we report a single step synthesis of title compounds.

Results and Discussion

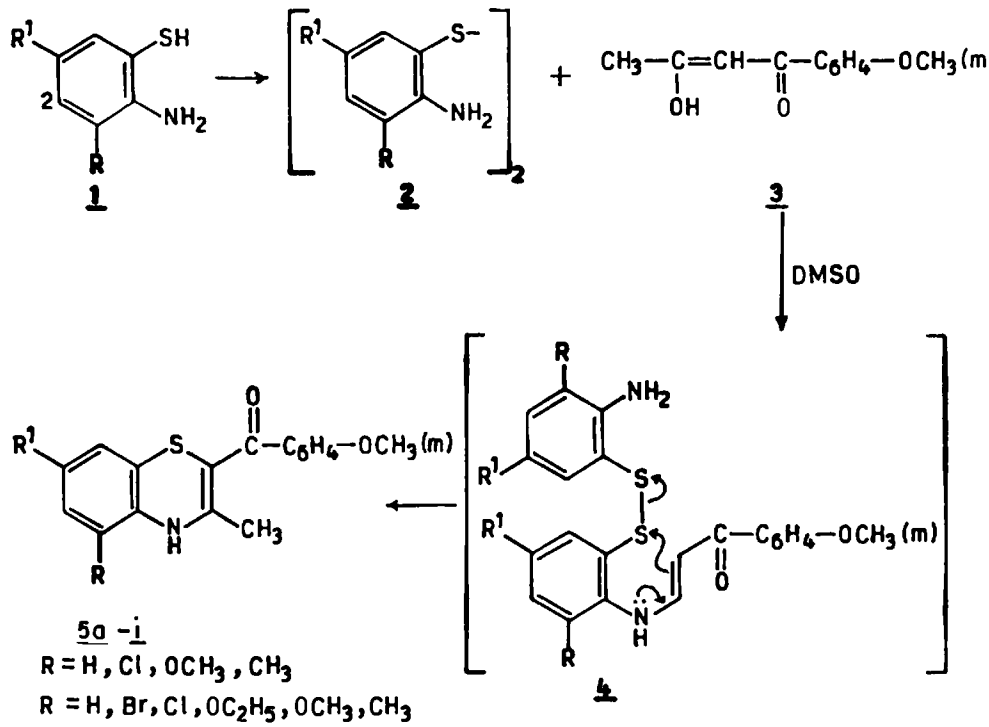
Substituted 2-(3-methoxybenzoyl)-3-methyl-4H-1,4-benzothiazines 5 have been synthesized by the condensation and oxidative cyclization of 3- and 5-substituted 2-aminobenzenethiols 1 and 3-methoxybenzoylacetone 3 in dimethylsulphoxide. The reaction is believed to proceed through the formation of an intermediate enaminoketone 4. Under the experimental conditions, 2-aminobenzenethiols 1 are rapidly oxidised to bis-(2-aminophenyl) disulphides 2 (2-5). Disulphides 2 cyclise to 1,4-benzothiazines 5 by scission of sulphur-sulphur bond (2,6) upon attack by nucleophilic enaminoketone system (Scheme 1).

3-Methoxybenzoylacetone can exist in two enolic forms 3 and 3' and there is possibility for the formation of two types of benzothiazines. Only



3

3'



Scheme 1

benzothiazine 5 with methoxybenzoyl group is formed as shown by mass spectral investigations.

3-Methoxybenzoylacetone 3 has been prepared by Claisen condensation of ethyl acetate with 3-methoxy acetophenone.

The IR spectra of all the 4H-1,4-benzothiazines exhibit a single sharp peak in the region 3220-3360 cm^{-1} due to NH stretching vibrations. The sharp band in the region 1600-1605 cm^{-1} is due to C=O stretching vibrations. The absorption bands in the region 1370-1465 cm^{-1} are attributed to C-H deformation vibration of CH_3 group. All the compounds exhibit bands in the region 1230-1250 cm^{-1} and 1020-1050 cm^{-1} due to C-O-C asymmetric and symmetric vibrations. In IR spectra of 3-methoxybenzoylacetone an intense peak at 1600 cm^{-1} appears due to C=O stretching vibrations. The peak obtained at 1260 cm^{-1} and 1020 cm^{-1} are attributed to C-O-C asymmetric and symmetric vibrations. The aromatic C-H stretching bands are obtained at 3080 cm^{-1}.

The NMR spectra of all the 4H-1,4-benzothiazines exhibit resonance signals in the region δ 1.7-1.9 due to allylic linkage ($C=C-CH_3$). A single peak in the region δ 8.4-9.3 is ascribed to NH proton. The multiplet in the

region δ 6.4-7.6 is due to aromatic ring protons. All the compounds show singlet at δ 3.8 due to OCH_3 protons at meta position of benzoyl side chain at C_2. In compounds 5c, 5h singlets at δ 4.05 and δ 3.86 arise due to OCH_3 protons at C_5 and C_7 respectively. In compounds 5d, 5i singlets appear at δ 4.05 and δ 2.1 due to CH_3 protons at C_5 and C_7 respectively. In compound 5g a quartet at δ 3.88-4.12 and a triplet at δ 1.26-1.37 are obtained due to CH_2 and CH_3 protons of OC_2H_5 group at C_7. The NMR spectra of 3-methoxybenzoylacetone shows a multiplet at δ 7.17-7.64 due to aromatic protons. A singlet at δ 3.89 appears due to OCH_3 protons at meta position. Singlets at δ 2.61 and δ 2.32 are ascribed to CH_2 and CH_3 protons of the group $COCH_2COCH_3$.

The mass spectra of all the compounds showed molecular ion peaks corresponding to their molecular weights and a base peak at m/z = 135 due to $[COC_6H_4\text{-}OCH_3]^+$ ion. The formation of this ion at m/z = 135 supports the formation of benzothiazines with methoxybenzoyl group 5 rather than acetyl group.

Experimental

All the melting points are uncorrected. The purity of synthesised compounds has been checked by TLC 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 Perkin-Elmer spectrophotometer model 577. All the NMR spectra have been recorded at 90 MHz on a Jeol FX 90Q FT NMR using TMS as an internal standard in DMSO-d_6/(DMSO-d_6+$CDCl_3$)/Polysol. Mass spectra of all the compounds were recorded on a Jeol JMSD-300 mass spectrometer at 70 eV with 100 μamp ionizing current.

Synthesis of 3-Methoxybenzoylacetone 3

Sodium wire was suspended in ice cold dry ethyl acetate (200 ml), contained in a 500 ml three necked flask, fitted with reflux condenser, mechanical stirrer and dropping funnel. 3-Methoxyacetophenone (0.25 mol) was added in small lots from the dropping funnel to the ice cold reaction mixture with continuous stirring for 3-4 hrs and allowed to stand over night. The sodium salt of 3-methoxybenzoylacetone was filtered and washed with benzene. It was dissolved in minimum amount of water and decomposed by dilute acetic acid. The separated oil was extracted with ether and etheral

solution after being washed with water was dried over anhydrous sodium sulphate. The ether was evaporated and residual liquid was distilled under reduced pressure and the fraction between 210-20°C at 15 mm was collected (Yield 65%, % Found : C 68.64%, H 9.90%, % Calcd : C 68.75%, H 9.89%.)

Synthesis of 2-(3-Methoxybenzoyl)-4H-1,4-benzothiazines 5a-i

3- And 5-substituted 2-aminobenzenethiols (1; 0.01 mol) were added to the stirred suspension of 3-methoxybenzoylacetone (3; 0.01 mol) in DMSO (5 ml). and the resulting mixture was refluxed for 30 minutes. The reaction mixture was cooled to room temperature and the solid substance separated out was filtered, dried and crystallised from methanol. The physical and analytical data are summarised in Table 1.

Table 1 : Physical and analytical data of substituted 2-(3-methoxybenzoyl)-4H-1,4-benzothiazines 5a-i

Comp. 5	R	R^1	M.P. (°C)	Yield (%)	Molecular Formula	% Found/Calcd. C	H	N
a	H	H	167	60.20	$C_{17}H_{15}NO_2S$	68.95 68.68	5.07 5.05	4.69 4.71
b	Cl	H	127	45.15	$C_{17}H_{14}ClNO_2S$	61.65 61.53	4.25 4.22	4.20 4.22
c	OCH_3	H	107	46.25	$C_{18}H_{17}NO_3S$	66.45 66.05	5.22 5.19	4.31 4.28
d	CH_3	H	129	48.45	$C_{18}H_{17}NO_2S$	69.15 69.45	5.49 5.46	4.53 4.50
e	H	Br	173	73.55	$C_{17}H_{14}BrNO_2S$	54.48 54.25	3.70 3.72	3.75 3.72
f	H	Cl	205	75.40	$C_{17}H_{14}ClNO_2S$	61.25 61.53	4.20 4.22	4.24 4.22
g	H	OC_2H_5	162	58.73	$C_{19}H_{19}NO_3S$	66.63 66.86	5.60 5.57	4.13 4.10
h	H	OCH_3	156	63.00	$C_{18}H_{17}NO_3S$	66.35 66.05	5.21 5.19	4.26 4.28
i	H	CH_3	190	70.45	$C_{18}H_{17}NO_2S$	69.70 69.45	5.49 5.46	4.52 4.50

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