

SYNTHESIS OF 2-AMINO-3-ETHOXYBENZENETHIOL AND ITS CONVERSION INTO 4H-1,4-BENZOTHAZINES

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Abstract - Synthesis of 2-amino-3-ethoxybenzenethiol and 5-ethoxy-4H-1,4-benzothiazines is reported for the first time. Synthesis of 4H-1,4-benzothiazines involves the condensation and oxidative cyclisation of 2-amino-3-ethoxybenzenethiol with β -diketones in DMSO.

Benzothiazine derivatives find a number of medicinal and industrial applications such as anti-inflammatory¹, anti-depressant², anti-histamine³, dyes⁴ and excellent antiozonates for rubber⁵. Therefore, such a wide spectrum of applications of benzothiazines has stimulated our interest to synthesise substituted 4H-1,4-benzothiazines.

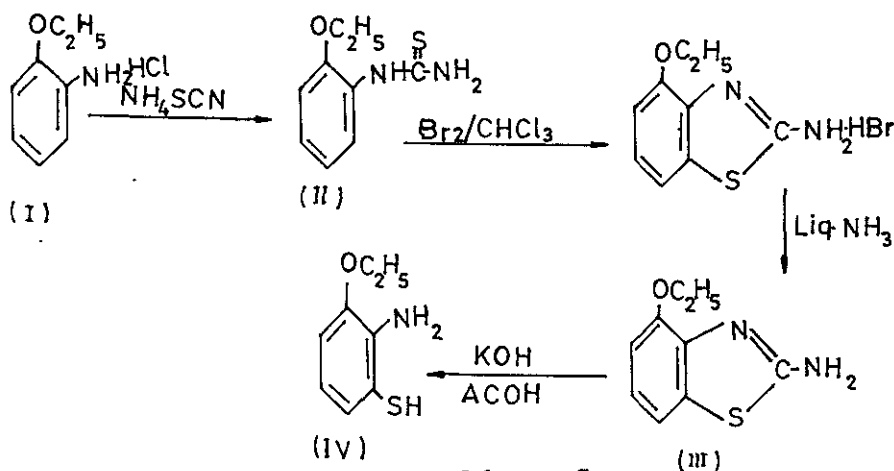
In this paper we wish to report a convenient method for synthesis of 2-amino-3-ethoxybenzenethiol and synthesis of 5-ethoxy-4H-1,4-benzothiazines by the condensation and oxidative cyclisation of 2-amino-3-ethoxybenzenethiol with β -diketones in presence of DMSO.

The substituted 2-aminobenzenethiols required for the synthesis of benzothiazines are generally prepared by alkaline hydrolysis of the Herz compound.

The Herz reaction⁶, however, is subjected to various limitations and cannot be available to prepare 2-aminobenzenethiols with a free 5-position. It has been reported that aryl amines, unsubstituted at the para-position, undergo nuclear chlorination during Herz reaction.

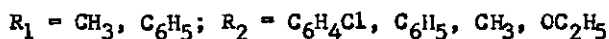
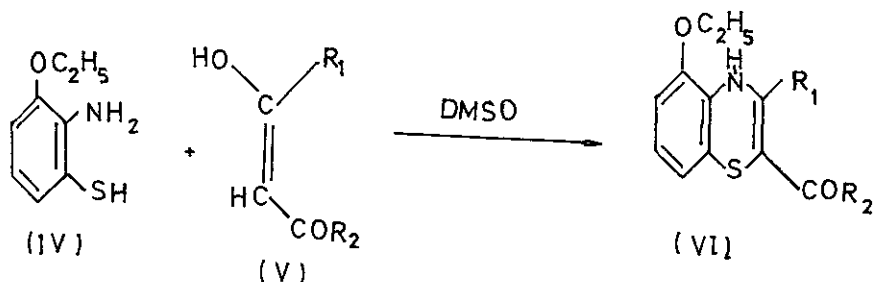
2-Aminobenzenethiols have also been prepared by hydrolytic fission of 2-aminobenzothiazoles. The benzothiazoles are prepared by thiocyanation of aryl amines. This process of thiocyanation also suffers from various limitations e.g. when para-position in aryl amine is free, thiocyanation occurs at both positions; ortho and para. Therefore, it is not possible by this method to convert arylamines (with free para-position) into benzothiazoles. To overcome these limitations we are reporting a convenient method to prepare 2-amino-3-ethoxybenzenethiol (with 5-position free) and its conversion into 5-substituted

4H-1,4-benzothiazines. 2-Amino-4-ethoxybenzothiazole(III) has been prepared from 2-ethoxyphenylthiourea(II) by treating it with bromine in chloroform in order to effect cyclisation. The benzothiazole(III) on alkaline hydrolysis yielded 2-amino-3-ethoxybenzenethiol(IV) (Scheme-I).



Scheme - I

2-Amino-3-ethoxybenzenethiol(IV) was condensed with β -diketones(V) in DMSO to give 5-substituted 4H-1,4-benzothiazines(VI) (Scheme-II).



Scheme - II

EXPERIMENTAL

All the melting points are uncorrected. The purity of the samples was tested by thin layer chromatography using various non-aqueous solvent systems. The structures were confirmed by spectral studies. The ir spectra of all these newly synthesised 4H-1,4-benzothiazines exhibited a sharp NH-stretching peak

near 3450 cm^{-1} indicating a free NH group. 2-Amino-3-ethoxybenzenethiol exhibited two peaks in the region $3350\text{--}3475\text{ cm}^{-1}$ due to NH_2 group. The nmr spectra of these 4H-1,4-benzothiazines exhibit a signal at ppm 8.5-8.6 due to NH proton and the multiplets in the region ppm 6.4-7.9 are due to aromatic ring protons. The mass spectrum showed molecular ion peaks corresponding to their molecular weights.

Preparation of 2-ethoxyphenylthiourea(II)

2-Ethoxyphenylthiourea was prepared by refluxing 2-ethoxyaniline hydrochloride (I; 0.1M) with ammonium thiocyanate (0.1M) in 100 ml of water for 3 h. The solid, separated on cooling, was filtered, washed with water and recrystallised from ethanol (mp 115°C). Anal. Calcd. for $\text{C}_9\text{H}_{12}\text{N}_2\text{SO}$: C, 55.10; H, 6.12; N, 14.28 (Found C, 55.17; H, 6.16; N, 14.25).

Preparation of 2-amino-4-ethoxybenzothiazole(III)

To 2-ethoxyphenylthiourea (II; 0.1 M) in chloroform (100 ml) bromine (0.1 M) in chloroform (50 ml) was added dropwise and the temperature of the reaction mixture was kept below 5°C . After complete addition of bromine, the contents of the flask were refluxed for 2.5 h. The contents were heated to evaporate the excess of chloroform and the resulting solid was treated with aqueous SO_2 solution and filtered. The filtrate was precipitated by the addition of aqueous ammonia. The precipitate was filtered, washed with water and recrystallised from ethanol (mp 154°C). Anal. Calcd. for $\text{C}_9\text{H}_{10}\text{N}_2\text{SO}$: C, 55.67; H, 5.15; N, 14.43 (Found C, 55.73; H, 5.11; N, 14.40).

Preparation of 2-amino-3-ethoxybenzenethiol(IV)

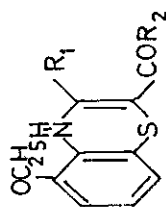
2-Amino-4-ethoxybenzothiazole(III) was refluxed with sodium hydroxide (7 times by weight of benzothiazole) and water (12 times by weight of benzothiazole) until an evolution of ammonia gas ceased (about 48 h). The contents were filtered and the resulting clear solution on acidification with acetic acid afforded the desired thiol. 2-Amino-3-ethoxybenzenethiol hydrochloride melts at 134°C . Anal. Calcd. for $\text{C}_8\text{H}_{12}\text{NSOCl}$: C, 46.82; H, 5.85; N, 6.82 (Found C, 46.78; H, 5.90; N, 6.85).

Preparation of 4H-1,4-benzothiazines(VIa-e)

2-Amino-3-ethoxybenzenethiol (IV; 0.01 M) was added to a stirred suspension of β -diketones (acetyl-benzoylmethane, acetyl-p-chlorobenzoylmethane, acetylacetone, ethyl acetoacetate and dibenzoylmethane (V; 0.01 M) in DMSO (6 ml) and the solution

Table - I

Physical data of substituted 4H-1,4-benzothiazines (VIa-e)



S.No.	Compound R ₁	Compound R ₂	m.p. (°C)	Yield %	Colour	Molecular Formula	% Found		% Calcd.	
							C	H	C	N
a	CH ₃	C ₆ H ₅	105	55	Orange	C ₁₈ H ₁₇ O ₂ NS	69.20	5.30	69.45	4.50
b	CH ₃	C ₆ H ₄ Cl	101	50	Yellow	C ₁₈ H ₁₆ O ₂ NSCl	62.65	4.55	62.60	4.05
c	CH ₃	CH ₃	115	45	Yellow	C ₁₃ H ₁₅ O ₂ NS	62.60	6.08	62.65	5.62
d	C ₆ H ₅	C ₆ H ₅	162	50	Turky	C ₂₃ H ₁₉ O ₂ NS	73.89	5.07	73.99	3.75
e	CH ₃	C ₂ H ₅	120	42	Yellow	C ₁₄ H ₁₇ O ₃ NS	60.35	6.08	60.20	5.01

was refluxed for 1.5 h, concentrated and cooled to room temperature. The contents were filtered and washed with a small quantity of methanol. They were recrystallised from methanol. Physical data are recorded in table-1.

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