A CONVENIENT AND SINGLE STEP SYNTHESIS OF SUBSTITUTED 4H [1,4]-BENZOTHIAZINES.

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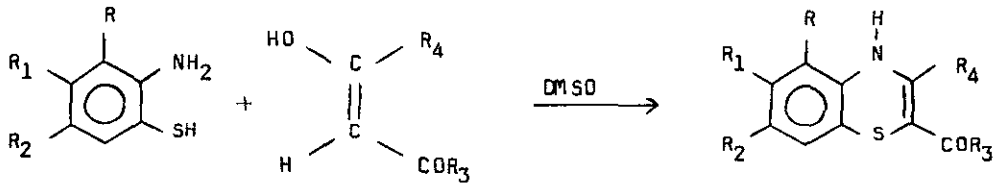
ABSTRACT

A simple one step synthesis is reported for substituted 4H[1,4]- benzothiazines involving the condensation of 5-(chloro, bromo, methyl, methoxy, ethoxy)-, 4-methyl- and 3-(chloro and methoxy)-2-aminobenzenethiols with acetylacetone/ethyl acetoacetate/dibenzoylmethane in DMSO.

Structural specificity responsible for tranquilizing activity in phenothiazines[1-5] is also present in 4H[1,4]-benzothiazines and one can anticipate tranquilizing activity in benzothiazines also. Such a close similarity of specific structural requirements in phenothiazines and 4H[1,4]-benzothiazines have stimulated our interest in the synthesis of substituted 4H[1,4]-benzothiazines. Unsubstituted 4H[1,4]-benzothiazines have been prepared[6] by the reaction of 2-aminobenzenethiol with active methylene compounds in the presence of dimethyl sulphoxide (DMSO) which causes oxidative cyclisation. We have extended this reaction to substituted o-aminobenzenethiols in order to synthesise substituted 4H[1,4]-benzothiazines with a view to make available drug of this series to develop a structural activity reactionship in order to search tranquilizers with maximum activity and minimum side effects. In this paper we are reporting the synthesis of some substituted 4H[1,4]-benzothiazines by condensation and oxidative cyclisation of 5-(chloro, bromo, methyl, methoxy, ethoxy)-, 4-methyl-, and 3-chloro/methoxy-2-aminobenzenethiols with acetylacetone, ethyl acetoacetate and dibenzoylmethane in DMSO (scheme-I).



R = Cl, OCH_3, H

R_1= CH_3, H

R_2= Cl, Br, CH_3, OCH_3, OC_2H_5, H

R_3= CH_3, OC_2H_5, C_6H_5

R_4= CH_3, C_6H_5

Scheme-I

EXPERIMENTAL

All the melting points are uncorrected. Purity of the compounds was checked on thin layer of silica gel in various non-aqueous solvent systems. The IR spectra of all these benzothiazines invariably show a single sharp peak in the region 3200-3310 cm^{-1} (νNH). Molecular ion peaks in their mass spectra are in accordance to their molecular weights.

(i) Preparation of 5-substituted-2-aminobenzenethiols:

2-Amino-6-(chloro, bromo, methyl, methoxy, ethoxy)benzothiazoles were prepared from the corresponding anilines by the reported method[7-9]. The benzothiazoles (25 g) were converted into o-aminobenzenethiols by refluxing with sodium hydroxide (125 g) in water (250 ml) until ammonia was no longer evolved. The solution was neutralised with 5N-acetic acid. The precipitate was washed with water and crystallised from ethanol.

Thiols	M.P. (°C)	Lit. M.P. (°C)
2-Amino-5-chlorobenzenethiol	110	110[8]
2-Amino-5-bromobenzenethiol	113	113-15[8]
2-Amino-5-methylbenzenethiol	90	90[7]
2-Amino-5-methoxybenzenethiol	105	103-105[8]
2-Amino-5-ethoxybenzenethiol	104	104[9]

(ii) Preparation of 2-amino-4-methylbenzenethiol hydrochloride

Sodium tetrasulphide was obtained by dissolving sulphur (48 g) in molten $Na_2S.9H_2O$ (120 g). The hot liquid is added dropwise to 4-chloro-3-nitrotoluene (171 g) in 95% ethanol (700 ml). After exothermic reaction had ceased, the mixture was refluxed (2 h) and filtered while hot and the precipitate, washed with water (200 ml) and ethanol (100 ml) to give 155 g of trisulphide (mp after crystallisation from glacial acetic acid, 195°C). Conc. hydrochloric acid (360 ml) was added at 70°C (4 h) to a well stirred suspension of the trisulphide (100 g), ethanol (600 ml) and tin (260 g). After filtration of hot solution, filtrate was allowed to stand overnight at room temperature. Precipitate was dissolved in hot methanol:Hydrochloric acid (50:50). On cooling the Sn-salt precipitated immediately, was removed by filtration. From the filtrate, after several hours (2 days) deposited yellowish needles 2-amino-4-methylbenzenethiol hydrochloride (yield 50%), mp 190°C (lit.[10] 189-191°C).

(iii) Preparation of 2-amino-3-chloro/methoxybenzenethiols:

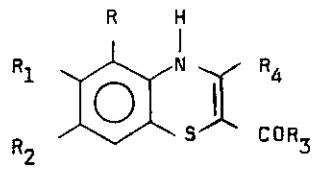
2-Chloro/methoxyphenylthiourea was prepared by refluxing 2-chloro/methoxyaniline hydrochloride (0.1 mol) with ammonium thiocyanate (0.1 mol) in 100 ml of water for 4 h. The solid separated on cooling was washed with water and recrystallised from ethanol. To substituted phenylthiourea (0.1 mol) in chloroform (25 ml) bromine (0.1 mol) in chloroform (20 ml) was added dropwise with stirring and temperature of reaction mixture was kept below 5°C. After addition of bromine, the reaction mixture was refluxed for 4 h. Contents were heated on a water-bath to remove the chloroform and solid was treated with sulphurous acid and filtered. Clear filtrate was neutralized with queous ammonia. Precipitate of 2-amino-4-chloro/methoxybenzothiazole was washed with water and crystallised from ethanol. Substituted benzothiazole was converted into respective thiol by alkaline hydrolysis followed by neutralization with 5N-acetic acid as described in method (I).

2-Amino-3-chlorobenzenethiol, mp 78°C, C = 45.40, H = 3.73, N = 8.70 and S = 20.18 (calculated C = 45.14, H = 3.76, N = 8.77 and S = 20.06).

2-Amino-3-methoxybenzenethiol hydrochloride, mp 110-12°C, C = 44.16, H = 5.26, N = 7.38 and S=16.65 (calculated C = 43.86, H = 5.22, N = 7.31 and

TABLE-I

physical data of substituted 4H 1,4 -benzothiazines.



Compound					M.P. °C	Yield %	Molecular Formula	N % Calc.	N % Found
R	R_1	R_2	R_3	R_4					
H	H	Cl	CH_3	CH_3	180	55	$C_{11}H_{10}ClNOS$	17.10	17.22
H	H	Cl	OC_2H_5	CH_3	180-82(D)	60	$C_{12}H_{12}ClNO_2S$	19.25	19.12
H	H	Cl	C_6H_5	C_6H_5	85	60	$C_{21}H_{14}ClNOS$	3.85	3.78
H	CH_3	H	CH_3	CH_3	172(D)	45	$C_{12}H_{13}NOS$	15.64	15.58
H	H	Br	CH_3	CH_3	108	60	$C_{11}H_{10}BrNOS$	20.28	20.45
H	H	OC_2H_5	OC_2H_5	CH_3	101	50	$C_{14}H_{17}NO_3S$	19.92	19.56
H	H	OCH_3	OC_2H_5	CH_3	116	45	$C_{13}H_{15}NO_3S$	18.90	19.12
H	H	OCH_3	C_6H_5	C_6H_5	171-72(D)	65	$C_{22}H_{17}NO_2S$	3.89	3.82
H	H	CH_3	OC_2H_5	CH_3	178	50	$C_{13}H_{15}NO_2S$	17.78	17.42
H	H	CH_3	CH_3	CH_3	185	75	$C_{12}H_{13}NOS$	15.64	15.84
H	H	CH_3	C_6H_5	C_6H_5	195(D)	60	$C_{22}H_{17}NOS$	4.08	4.10
Cl	H	H	O C_2H_5	CH_3	160	55	$C_{12}H_{12}ClNO_2S$	19.25	19.37
Cl	H	H	CH_3	CH_3	88-89	60	$C_{11}H_{10}ClNOS$	17.10	17.05
Cl	H	H	C_6H_5	C_6H_5	170	60	$C_{21}H_{14}ClNOS$	3.85	3.86
OCH_3	H	H	OC_2H_5	CH_3	140	68	$C_{13}H_{15}NO_3S$	18.90	18.82
OCH_3	H	H	CH_3	CH_3	168-70	70	$C_{12}H_{13}NO_2S$	16.69	16.75
OCH_3	H	H	C_6H_5	C_6H_5	167	65	$C_{22}H_{17}NO_2S$	3.89	3.85

S = 16.71).

(iv) Preparation of substituted 4H[1,4]benzothiazines:

To a stirred suspension of active methylene compound (0.01 mol, acetylacetone/ethyl acetoacetate/dibenzoylmethane) in DMSO (5 ml) was added substituted o-aminobenzenethiol (0.01 mol) and the solution refluxed for 1 h concentrated and cool to room temperature. The solid separated out was washed with small amount of methanol and recrystallised from methanol to give pure compounds. Their physical data are recorded in Table-I.

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