SYNTHESIS OF 1- AND 3-CHLORO-PHENOTHIAZINES

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ABSTRACT

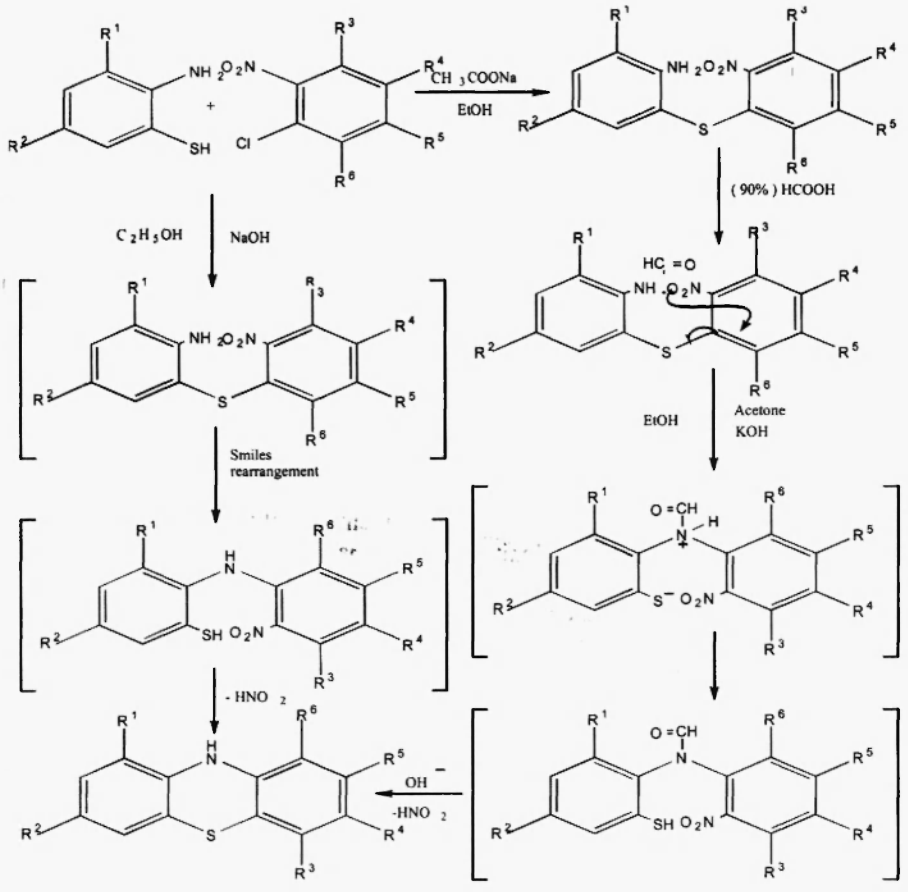
Phenothiazines have been synthesized via Smiles rearrangement by the reaction of 2-amino-3/5-chlorobenzenethiols with halonitrobenzenes. Halonitrobenzenes having a nitro group at both ortho positions to halogen yields directly phenothiazines as Smiles rearrangement occurs insitu. Halonitrobenzenes having a nitro group at ortho position to halogen give 2-amino-2'-nitrodiphenylsulfides which on formylation with 90% formic acid yields 2-formamido-2'-nitrodiphenylsulfides, which undergo Smiles rearrangement to provide phenothiazines.

INTRODUCTION

Phenothiazines show remarked pharmacological / biological activities (1,2). These are used as neuroleptics (3), sedative (4), analgesics (5), antihistamines (6) etc. They have also shown significant antitumor activities (7,8,9,10). A slight alteration in substitution pattern in phenothiazine nucleus causes a marked difference in biological activities. So it stimulate our interest to synthesize hitherto unknown phenothiazines in search of better medicinal agents.

RESULTS AND DISCUSSION

The entitle phenothiazines have been synthesized by 2-amino-3/5-chlorobenzenethiols which were prepared by the hydrolytic cleavage of 2-amino-4/6-chlorobenzothiazols adopting the method reported elsewhere (11,12).Substituted 1/3-Chlorophenothiazines (5a-d) were prepared by the Smiles rearrangement of substituted 2-formamido-3/5-chloro-2'nitrodiphenylsulfides (4a-d) in alcoholic potassium hydroxide solution. The formyl derivatives were prepared by the formylation of resultant diphenylsulfides (3a-d), obtained by the condensation of 2-amino-3/5-chlorobenzenethiols with o-halonitrobenzenes in ethanolic sodium acetate solution. 2-Amino-3/5-chlorobenzenethiols when react with halonitrobenzene containing nitro a group at both ortho position to halogen yield directly 9-nitrophenothiazines (5e-h) in single step as Smiles rearrangement occurs insitu due to combined resonance and inductive effect of two nitro groups (scheme-1).Phenothiazines (5a-d) and (5e-h) exhibit in IR spectra a sharp peak in the region 3320-3410 and 3200-3400 cm^{-1} due to N-H stretching vibrations respectively. The shifting towards lower frequency in 9-nitrophenothiazines (5e-h) suggest a six member chelate formation by (N-H----O=N) hydrogen bonding (fig. A). 9-Nitrophenothiazines (5e-h) exhibit two sharp peaks of medium intensity in the region 1320-1330 cm^{-1} and 1550-1560 cm^{-1} due to asymmetric and symmetric stretching vibration of aromatic nitro group. In all compounds (5a-h) a single sharp peak in the region 640-820 cm^{-1} is due to C-Cl stretching vibration. In compound 5e and g two sharp peaks are observed in the region 1120-1140 cm^{-1} and 1210-1240 cm^{-1} due to C-F stretching vibration of CF_3 group. The ^{1}HNMR spectra of phenothiazines (5a-d) exhibit a singlet in the region δ9.25-9.86 ppm due to N-H protons, however in 9-nitrophenothiazines (5e-h) the N-H protons give rise to singlet at δ 9.80-10.45 ppm. This down field shifting in 9-nitrophenothhiazines (5e-h) suggest hydrogen bonding between the nitro and a secondary amino groups as (N-H-----O=N). which has also been indicated by IR spectral data. The ^{1}HNMR spectra of all phenothiazines exhibit a multiplet in the region δ 6.35-8.32 ppm due to aromatic protons. In mass spectra of all phenothiazine, molecular ion peaks are in accordance with their molecular weights. 9-Nitrophenothiazines undergo fragmentation yielding M^+-17 due to loss of –OH redical due to Mc-Lafferty rearrangement (scheme-2).



Scheme-1

Compound			R^1	R^2	R^3	R^4	R^5	R^6
3_a	4_a	5_a	Cl	H	H	Cl	H	H
3_b	4_b	5_b	H	Cl	H	Cl	Cl	H
3_c	4_c	5_c	H	Cl	H	H	H	Cl
3_d	4_d	5_d	H	Cl	H	Cl	H	H
		5_e	H	Cl	H	CF_3	H	NO_2
		5_f	H	Cl	Cl	Cl	H	NO_2
		5_g	Cl	H	H	CF_3	H	NO_2
		5_h	Cl	H	Cl	Cl	H	NO_2

Scheme–I: Synthesis of phenothiazines via Smiles rearrangement

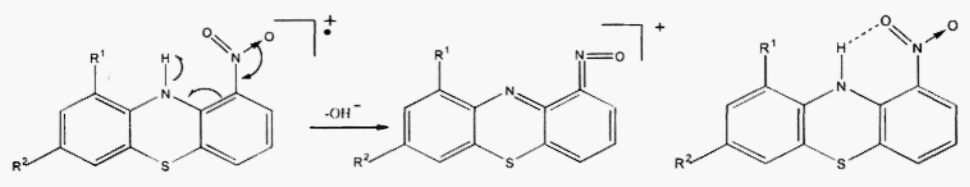


Fig. A

Scheme-2: Mc –Lafferty rearrangement in phenothiazines

EXPERIMENTAL

All the melting points are uncorrected. The purity was checked by thin layer chromatography and characterized by their spectral studies. The IR spectra have been recorded on FT IR spectrometer, MAGNA IR 550 NICOLET using KBr discs. NMR spectra were recorded on FT Bruker DRX-300 MHz in DMSO-d_6 and $CDCl_3$, using TMS as an internal standard. Mass spectra have been scanned on Jeol D-300 (EI) and JEOL SX 102 / DA-6000 Mass spectrometer / data system using Argon / Xenon (6kV, 10mA) as the FAB gas. Physical data of synthesized compounds are summarized in table-I.

Table–1 Physical data (compounds 3–5)

							M.P.	Yield	Molecular	% found (Calcd.)		
Compd.	R^1	R^2	R^3	R^4	R^5	R^6	°C	%	formula	C	H	N
3a	Cl	H	H	Cl	H	H	70	71	$C_{12}H_8N_2SO_2Cl_2$	(45.71) 45.70	(2.53) 2.51	(8.88) 8.86
3b	H	Cl	H	Cl	Cl	H	66	71	$C_{12}H_7N_2SO_2Cl_3$	(41.20) 41.19	(2.00) 1.98	(8.01) 8.00s
3c	H	Cl	H	H	H	Cl	70	76	$C_{12}H_8N_2SO_2Cl_2$	(45.71) 45.68	(2.53) 2.52	(8.88) 8.85
3d	H	Cl	H	Cl	H	H	98	80	$C_{12}H_8N_2SO_2Cl_2$	(45.71) 45.69	(2.53) 2.48	(8.88) 8.87
4a	Cl	H	H	Cl	H	H	198-202	69	$C_{13}H_8N_2SO_3Cl_2$	(45.48) 45.45	(2.33) 2.31	(8.16) 8.12
4b	H	Cl	H	Cl	Cl	H	62	55	$C_{13}H_7N_2SO_3Cl_3$	(41.32) 41.30	(1.85) 1.83	(7.41) 7.40
4c	H	Cl	H	H	H	Cl	108	73	$C_{13}H_8N_2SO_3Cl_2$	(45.48) 45.47	(2.33) 2.30	(8.16) 8.14
4d	H	Cl	H	Cl	H	H	164	50	$C_{13}H_8N_2SO_3Cl_2$	(45.48) 45.47	(2.33) 2.32	(8.16) 8.15
5a	Cl	H	H	Cl	H	H	83	71	$C_{12}H_7NSCl_2$	(53.73) 53.70	(2.61) 2.60	(5.22) 5.20
5b	H	Cl	H	Cl	Cl	H	172	41	$C_{12}H_6NSCl_3$	(47.60) 47.58	(1.98) 1.95	(4.62) 4.61
5c	H	Cl	H	H	H	Cl	160	48	$C_{12}H_7NSCl_2$	(53.73) 53.72	(2.61) 2.58	(5.22) 5.21
5d	H	Cl	H	Cl	H	H	90	46	$C_{12}H_7NSCl_2$	(53.73) 53.71	(2.61) 2.59	(5.22) 5.19
5e	H	Cl	H	CF_3	H	NO_2	123	63	$C_{13}H_6N_2SO_2F_3Cl$	(45.02) 45.00	(1.73) 1.70	(8.08) 8.06
5f	H	Cl	Cl	Cl	H	NO_2	>360	51	$C_{12}H_5N_2SO_2Cl_3$	(41.43) 41.42	(1.43) 1.40	(8.05) 8.03
5g	Cl	H	H	CF_3	H	NO_2	150	44	$C_{13}H_6N_2SO_2F_3Cl$	(45.02) 45.01	(1.73) 1.71	(8.08) 8.05
5h	Cl	H	Cl	Cl	H	NO_2	>360	36	$C_{12}H_5N_2SO_2Cl_3$	(41.43) 41.40	(1.43) 1.41	(8.05) 8.01

Preparation of 2-amino-3/5-chloro-2'-nitrodiphenylsulfides (3a-d)

To a refluxing solution of 2-amino-3/5-chlorobenzenethiols (.01 mole) in ethanol (20 ml) and anhydrous sodium acetate (01 mole in 5 mole ethanol) was added an alcoholic solution of o-halonitrobenzene (.01

mole) in ethanol (12 ml) and refluxed for four hours. The reaction mixture was kept overnight in an ice chamber. The solid separate out was filtered and washed with 30 % ethanol and crystallized from methanol.

Preparation of 3/5-chloro-2-formamido-2'-nitrodiphenylsulfides (4a-d)
A mixture of diphenylsulfides (.01 mole) and 20 ml 90 % formic acid was taken in R.B. flask and refluxed for four hours. The content were poured into a beaker containing crushed ice. The solid separate out was filtered, washed with water and crystallized from benzene / methanol.

Preparation of 3/5-chlorophenothiazines (5a-d)
A solution of formyl derivatives (.01 mole) in acetone (15 ml) and an alcohclic potassium hydroxide (.02 gm in 5 ml ethanol) was refluxed half an hour. Another lot of an alcoholic potassium hydroxide (.02 gm in 5 ml ethanol) was added. The contents were refluxed for two hours and poured in a beaker containing crushed ice. The solid separated out was filtered, washed with cold water, finally with 30 % ethanol and crystallized from methanol.

Preparation of 9-nitrophenothiazines (5e-h)
A mixture of halonitrobenzene (.01 mole), 2-amino-3/5-chlorobenzenethiol (.01 mole), sodium hydroxide (.01 mole) and ethyl alcohol (20 ml) was refluxed for 2-3 hours. The reaction mixture was concentrated, cooled and filtered. The solid separate out was washed with hot water and finally with 20 % ethanol and crystallized from acetone / benzene.

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