SYNTHESIS OF PHENOTHIAZINES VIA SMILES REARRANGEMENT

P R. Sharma, Vandana Gupta, D.C. Gautam and R.R. Gupta*
Department of Chemistry, University of Rajasthan, Jaipur - 302 004, INDIA
E-mail : rrg_vg@yahoo.co.in; dr_vandana27@yahoo.co.in

ABSTRACT

Synthesis of 3-bromo/1,2-dimethylphenothiazines is reported by Smiles rearrangement of 5-bromo/3,4-dimethyl-2-formamido-2′-nitrodiphenylsulfides. The later were obtained by the formylation of 2-amino-5-bromo/3,4-dimethyl-2′-nitrodiphenylsulfides which were prepared by the condensation of 2-amino-5-bromo/3,4-dimethylbenzenethiols with *o*–halonitrobenzenes.

INTRODUCTION

Phenothiazines possess a wide spectrum of pharmacological activities (1, 2). These are used as neuroleptics (3), diuretics (4), sedatives (5), antihistamines (6), analgesics (7) etc. They have also shown significant effects against cancer (8, 9). With a slight alteration in substitution pattern, their activity can be modified to a large extent. It is considered worthwhile to synthesize hitherto unknown phenothiazines in order to make them available for biomedical screening in search of better medicinal agents.

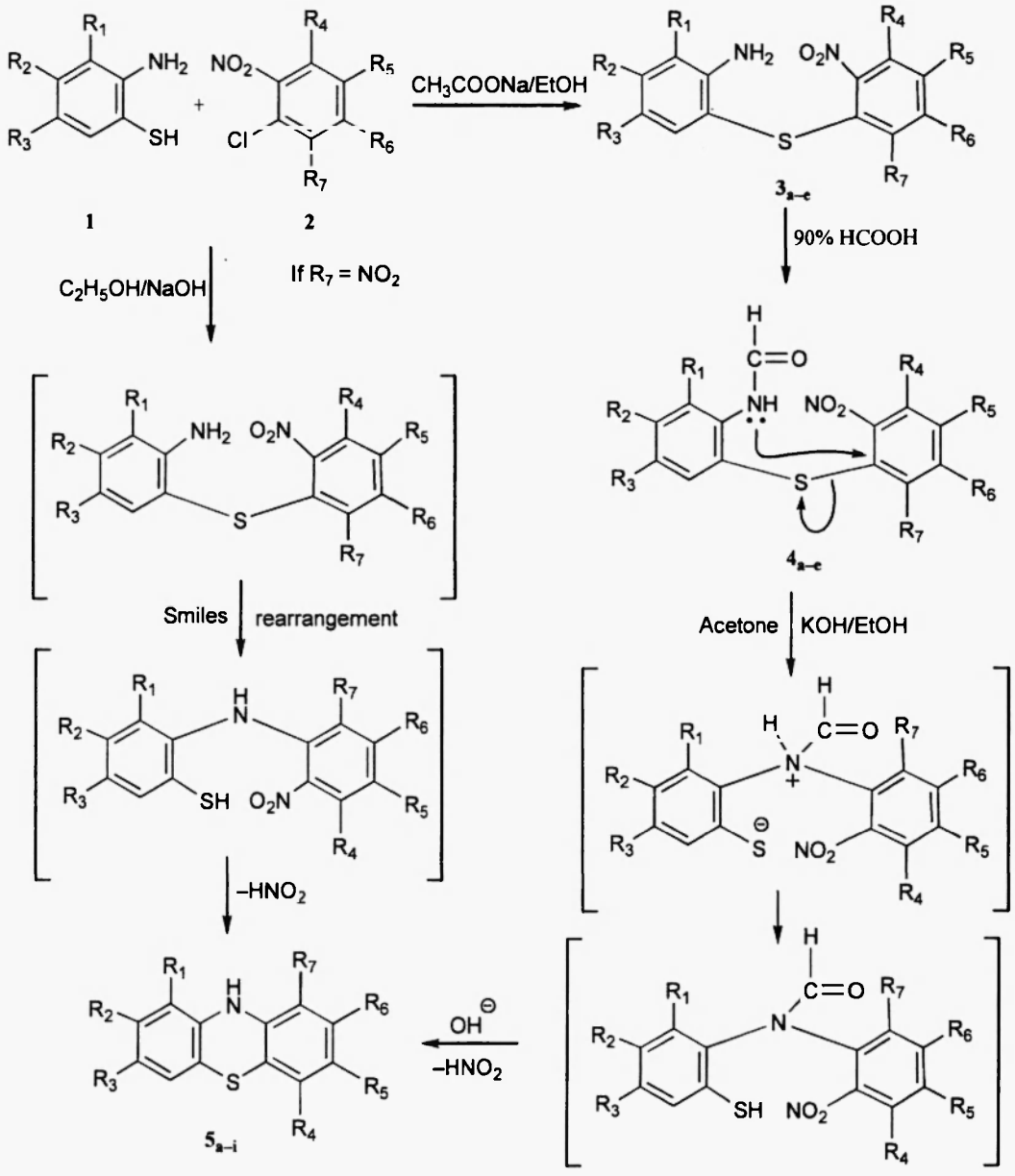
RESULT AND DISCUSSION

5-Bromo/3,4-dimethyl-2-formamido-2′-nitrodiphenylsulfides (4_{a-e}) obtained by formylation of 2-amino-5-bromo/3,4-dimethyldiphenylsulfides (3_{a-e}) undergo Smiles rearrangement in alcoholic potassium hydroxide solution yielding 3-bromo/1,2-dimethylphenothiazines 5_{a-e}. 2-Amino-5-bromo/3,4-dimethyldiphenylsulfides have been obtained by the condensation of 2-amino-5-bromo/3,4-dimethylbenzenethiols **1**, prepared by the hydrolytic cleavage of 2-amino-6-bromo/4,5-dimethylbenzothiazoles adopting the method reported elsewhere (10, 11) with *o*–halonitrobenzens **2** in ethanolic sodium acetate solution. 2-Amino-5-bromo/3,4-dimethylbenzenethiols **1** with halonitrobenzenes **2** containing a nitro group at ortho positions to halogen yields directly 3-bromo/1,2-dimethylphenothiazines 5_{f-j} in a single step as Smiles rearrangement occur in situ due to combined resonance and inductive effect of two nitro groups (Scheme–I).

Phenothiazines (5_{a-e}) exhibit in IR spectra a sharp peak in the region 3385–3250 cm^{-1} due to NH stretching vibrations while this sharp peak in phenothiazines (5_{f-j}) which contains a nitro group at 9 position appear in the region 3310–3215 cm^{-1}. This shifting to lower frequency suggests a six membered chelate through (NH·····O=N) hydrogen bonding (**Fig. 1**). 9-Nitrophenothiazines 5_{f-j} exhibit two peaks of medium intensity in the region 1570–1540 cm^{-1} and 1370–1340 cm^{-1} due to to asymmetric and symmetric vibrations of aromatic nitro group. In compounds $5_{a,b,f,g}$ two peaks are observed in the region 1470–1440 cm^{-1} and 1375–1335 cm^{-1} due to asymmetric and symmetric C–H deformation vibrations of CH_3 groups. A single sharp peak in the region 780–715 cm^{-1} in compounds $5_{c,d,f,h}$ is due to C–Cl stretching vibrations. In compounds $5_{g,i}$ two sharp peaks are observed in the region 1330–1310 cm^{-1} and 1150–1120 cm^{-1} due to C–F stretching vibrations of CF_3 group.

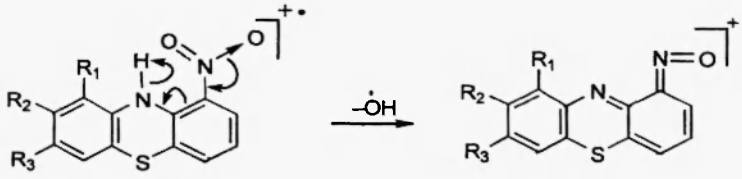
The ^1H NMR spectra of all phenothiazines exhibit a multiplet in the region δ 8.60–5.31 ppm due to aromatic protons. Phenothiazines 5_{a-e}, exhibit a singlet in the region δ 9.70–8.43 ppm due to NH protons, however in 9–nitrophenotiazines 5_{f-j} the NH proton gives rise to a singlet at δ 9.82–9.13 ppm and this downfield shift suggests hydrogen bonding between the nitro and a secondary amino groups as NH·····O=N which has also been indicated by the IR spectral data. Phenothiazines $5_{a\ b\&f,g}$ show two singlets in the region δ 3.60–2.22 ppm and 1.34–1.20 ppm due to CH_3 protons at C-1 and C-2 respectively.

In the mass spectra of phenothiazines molecular ion peaks are in accordance with their molecular weights. 9-Nitrophenothiazines undergo fragmentation yielding M^+–17 due to loss of OH radical due to Mc Lafferty rearrangement (Scheme–II).



Compound			R^1	R^2	R^3	R^4	R^5	R^6	R^7
3_a	4_a	5_a	CH_3	CH_3	H	H	Cl	Cl	H
3_b	4_b	5_b	CH_3	CH_3	H	H	Cl	H	H
3_c	4_c	5_c	H	H	Br	H	Cl	Cl	H
3_d	4_d	5_d	H	H	Br	H	Cl	H	H
3_e	4_e	5_e	H	H	Br	H	H	H	Cl
		5_f	CH_3	CH_3	H	Cl	Cl	H	NO_2
		5_g	CH_3	CH_3	H	H	CF_3	H	NO_2
		5_h	H	H	Br	Cl	Cl	H	NO_2
		5_i	H	H	Br	H	CF_3	H	NO_2

Scheme–I : Synthesis of phenothiazines via Smiles rearrangement



Scheme–II

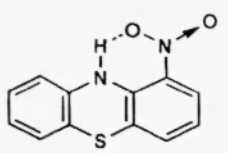


Fig. A

EXPERIMENTAL

All the melting points are uncorrected. The purity was checked by thin layer chromatography and characterized by their spectral studies. The infrared spectra have been recorded on FT IR spectrometer, MAGNA IR 550 NICOLET using KBr discs. NMR specta were recorded on FT NMR Bruker DRX-300 MHz in DMSO-d_6 using TMS as an internal standard. Mass spectra have been scanned on Jeol D-300 (EI). Physcial data of synthesized compounds are summarized in Table–1.

Table–1 Physical data (compounds 3–5)

Compd.	R^1	R^2	R^3	R^4	R^5	R^6	R^7	M.P. °C	Yield %	Molecular formula	% found (Calcd.)		
I	II	III	IV	V	VI	VII	VIII	IX	X	XI	C XII	H XIII	N XIV
3_a	CH_3	CH_3	H	H	Cl	Cl	H	88	41.6	$C_{14}H_{12}N_2SO_2Cl_2$	(48.98) 48.96	(3.50) 3.48	(8.16) 8.11
3_b	CH_3	CH_3	H	H	Cl	H	H	167	34.9	$C_{14}S_{12}N_2SO_2Cl$	(54.63) 54.33	(3.90) 3.70	(9.10) 9.12
3_c	H	H	Br	H	Cl	Cl	H	94	68.1	$C_{12}H_7N_2SO_2Cl_2Br$	(36.55) 36.57	(1.78) 1.75	(7.10) 7.09
3_d	H	H	Br	H	Cl	H	H	67	62.8	$C_{12}H_8N_2SO_2ClBr$	(40.05) 40.10	(2.22) 2.12	(7.79) 7.75
3_e	H	H	Br	H	H	H	Cl	44	37.4	$C_{12}H_8N_2SO_2ClBr$	(40.05) 40.05	(2.22) 2.21	(7.79) 7.73
4_a	CH_3	CH_3	H	H	Cl	Cl	H	72	45.3	$C_{15}S_{12}N_2SO_3Cl_2$	(48.52) 48.50	(3.23) 3.21	(7.55) 7.48
4_b	CH_3	CH_3	H	H	Cl	H	H	198	38.1	$C_{15}S_{12}N_2SO_3Cl$	(53.65) 53.62	(3.58) 3.57	(8.35) 8.37
4c	H	H	Br	H	Cl	Cl	H	48	42.6	$C_{13}H_7N_2SO_3Cl_2Br$	(36.97) 36.95	(1.66) 1.63	(6.64) 6.65
4_d	H	H	Br	H	Cl	H	H	62	72.1	$C_{13}H_8N_2SO_3ClBr$	(40.26) 40.22	(2.06) 2.06	(7.22) 2.21
4_e	H	H	Br	H	H	H	Cl	140	48.2	$C_{13}H_8N_2O_3SClBr$	(40.26) 40.24	(2.06) 2.05	(7.22) 2.22
5_a	CH_3	CH_3	H	H	Cl	Cl	H	175	68.5	$C_{14}H_{11}Cl_2NS$	(56.75) 56.71	(3.71) 3.73	(4.72) 4.71
5_b	CH_3	CH_3	H	H	Cl	H	H	120	64.2	$C_{14}H_{12}ClNS$	(64.24) 64.22	(4.58) 4.57	(5.35) 5.33
5_c	H	H	Br	H	Cl	Cl	H	113	48.3	$C_{12}H_6Cl_2BrNS$	(41.49) 41.50	(1.72) 1.71	(4.03) 4.02
5_d	H	H	Br	H	Cl	H	H	121	37.2	$C_{12}H_7ClBrNS$	(46.08) 46.06	(2.24) 2.22	(4.48) 4.49
5_e	H	H	Br	H	H	H	Cl	170	41.4	$C_{12}H_7ClBrNS$	(46.08) 46.09	(2.24) 2.24	(4.48) 4.50
5_f	CH_3	CH_3	H	Cl	Cl	H	NO_2	130	67.8	$C_{14}H_{10}N_2Cl_2O_2S$	(49.26) 49.24	(2.93) 2.93	(8.21) 8.22
5_g	CH_3	CH_3	H	H	CF_3	H	NO_2	98	71.3	$C_{15}H_{11}F_3N_2O_2S$	(52.94) 52.94	(3.23) 3.21	(8.23) 8.22
5_h	H	H	Br	Cl	Cl	H	NO_2	124	65.4	$C_{12}H_5N_2Cl_2BrO_2S$	(36.73) 36.71	(1.27) 1.26	(7.14) 7.15
5_i	H	H	Br	H	CF_3	H	NO_2	120	56.1	$C_{13}H_6N_2BrO_2SF_3$	(39.89)	(1.53)	(7.16)

Preparation of 2-amino-5-bromo/3,4-dimethyl-2'-nitrodiphenylsulfides (3_{a-e})

To a refluxing solution of 2- amino-5-bromo/3,4-dimethylbenzenethiol (**1**, 0.01 mole) in ethanol (20 ml) and anhydrous sodium acetate (0.01 mole in 5 ml of ethanol) was added an alcoholic solution of *o*–halonitrobenzene (**2**, 0.01 mole) in ethanol (12 ml) and refluxed for three hours. The reaction mixture was concentrated and kept overnight in an ice chamber. The solid separated out was filtered and washed with 30% ethanol. Crystallization from methanol afforded the desired diphenylsulfides.

Preparation of 5-bromo/3,4-dimethyl-2-formamido-2'-nitrodiphenylsulfides 4_{a-e}

A mixture of diphenylsulphide (3_{a-e} 0.01 mole) and 20 ml formic acid (90%) was taken in R.B. flask and refluxed for four hrs. The contents were poured into a beaker containing crushed ice. The solid separated out was flitred, washed with water and crystallized from benzene/methanol.

Preparation of 3-bromo/1,2-dimethylphenothiazines 5_{a-e}

A solution of formyl derivative (4_{a-e} 0.1 mole) in acetone (15 ml) and an alcoholic potassium hydroxide (0.2 gm in 5 ml ethanol) was refluxed for half an hour. Another lot of an alcoholic potassium hydroxide (0.2 gm in 5 ml ethanol) was added. The contents were refluxed for 2 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 benzene/methanol.

Preparation of 9–nitrophenothiazines 5_{f-i}

A mixture of halonitrobenzene (**2**, 0.01 mole), 5–bromo/3,4–dimethyl–2–aminobenzenethiol (**1**, 0.01 mole), sodium hydroxide (0.01 mole) and ethyl alcohol (20 ml) was refluxed for 1–2 hrs. The reaction mixture was concentrated, cooled and filtered. The solid separated out was washed well with hot water and finally with 20% ethanol and crystallized from acetone/benzene.

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