SYNTHESIS OF SUBSTITUTED 1,4-DIMETHYLPHENOTHIAZINES

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Abstract : Synthesis of title compounds by the Smiles rearrangement has been reported. 1,4-Dimethyl-7-substituted phenothiazines have been prepared by the Smiles rearrangement of 2-formamido-3,6-dimethyl-2'-nitro-4'-substituted diphenylsulphides. The latter were obtained by the condensation of 2-amino-3,6-dimethylbenzenethiol with o-halonitrobenzenes. However, halonitrobenzenes containing a nitro group at both ortho positions to the reactive halogen atom on condensation with 2-amino-3,6-dimethyl benzenethiol directly yielded 9-nitrophenothiazines as Smiles rearrangement and ring closure occurs in situ due to combined resonance and inductive effects reinforced by two nitro groups. The IR, NMR and Mass spectral studies are also included.

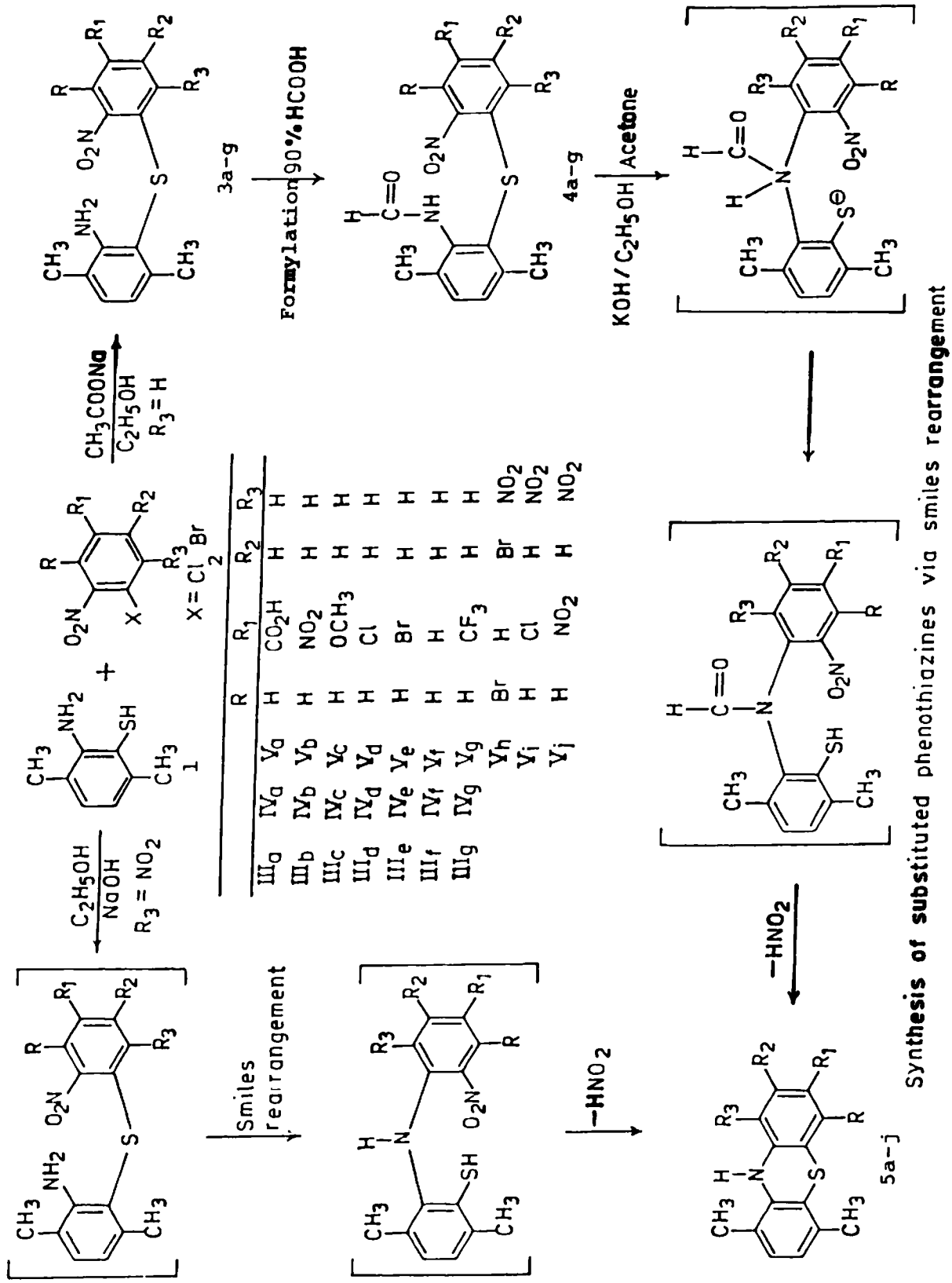
Introduction

Phenothiazines possess a wide spectrum of pharmacological/biological activities (1,2). These are widely used as tranquilizers, antiemetics, anthelmintics, antiinflammatory etc. Recently some substituted phenothiazines have shown significant effects against cancer (3,4). A slight change in substitution pattern in phenothiazines nucleus causes a marked difference in their activities and has stimulated our interest to synthesize title phenothiazines to make them available for biological screening in search of better medicinal agents.

Results and Discussion

2-Amino-3,6-dimethylbenzenethiol 1 required in the synthesis of title phenothiazines has been prepared by the hydrolytic cleavage of 2-amino-4,7-dimethylbenzothiazole adopting the method reported elsewhere (5,6).

1,4-Dimethyl-7-substituted phenothiazines 5a-b have been prepared by the Smiles rearrangement of 2-formamido-3,6-dimethyl-2'-nitro-4'-substituted diphenylsulfides 4a-g in alcoholic potassium hydroxide solution. The formyl derivatives were prepared by the formylation of resultant diphenylsulfides 3a-g obtained by the condensation of 2-amino-3,6-dimethylbenzenethiol 1 with substituted o-halonitrobenzenes 2 in ethanolic sodium acetate solution (Scheme-1). 9-Nitrophenothiazines have been prepared by the condensation of 2-amino-3,6-dimethylbenzenethiol 1



	R	R1	R2	R3
IIIa IVa Va	H	CO_2H	H	H
IIIb IVb Vb	H	NO_2	H	H
IIIc IVc Vc	H	OCH_3	H	H
IIId IVd Vd	H	Cl	H	H
IIIe IVe Ve	H	Br	H	H
IIIf IVf Vf	H	H	H	H
IIIg IVg Vg	H	CF_3	H	H
Vh	Br	H	Br	NO_2
Vi	H	Cl	H	NO_2
Vj	H	NO_2	H	NO_2

Synthesis of substituted phenothiazines via smiles rearrangement

Scheme 1

with appropriately substituted halonitrobenzenes 2 containing a nitro group at both ortho positions to the reactive halogen atom in ethanolic sodium hydroxide solution where the Smiles rearrangement occurs in situ due to nitro group (Scheme-1).

The IR spectra of all phenothiazines except 9-nitro, exhibit a sharp peak in the region 3100-3370 cm^{-1} due to NH stretching vibrations. But 9-nitrophenothiazines show a large shift in the secondary NH vibrational frequency. This shifting to lower frequency suggests a six membered chelate through NH---O——N bonding (Fig.1).

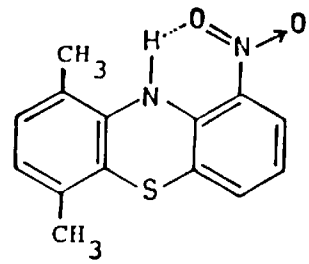


Fig.1

9-Nitro 5h-j and 7-nitrophenothiazines 5b exhibit two peaks of medium intensity in the region 1530-1580 cm^{-1} and 1380-1385 cm^{-1} due to asymmetric and symmetric vibrations of aromatic nitro group. The peak in the region 1420-1530 cm^{-1} and 1305-1385 cm^{-1} are due to C-H asymmetric and symmetric deformation vibrations of CH_3 group. Peaks corresponding to the chlorine atom in 5d has been observed at 745 cm^{-1}. In phenothiazine 5c two peaks at 1235 cm^{-1} and 1020 cm^{-1} are due to C-O-C asymmetric and symmetric vibrations.

The ^1H NMR spectra of all the phenothiazines exhibit a multiplet in the region δ 6.25-8.55 due to aromatic protons. All the phenothiazines 5a-q except those having a nitro group at 9-position exhibit a singlet at δ 7.75-11.46 due to N-H proton. In the 9-nitrophenothiazines 5h-j the N-H proton gives rise to a singlet at δ 11.51-11.70 and this down field shift suggests hydrogen bonding between the nitro and a secondary amino groups as -NH..O=N which has been also indicated by the IR spectral data. In all the phenothiazine 5a-j singlets are observed in the region δ 1.59-2.49 and δ 1.50-2.40 due to CH_3 protons at C-1 and C-4. Compound 5c exhibit a singlet at δ 2.70 due to OCH_3 protons at C-7.

In mass spectra of all phenothiazines, molecular ion peaks are in accordance with their molecular weights. 9-Nitrophenothiazines undergo

fragmentation yielding M^+-17 due to the loss of OH radical according to McLafferty rearrangement (Fig. 2).

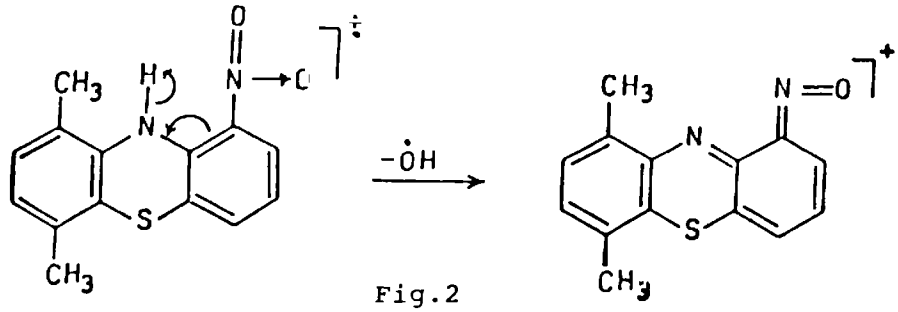


Fig.2

Experimental

All the melting points are uncorrected. The purity was checked by thin layer chromatography and characterized by spectral studies. The infrared spectra were recorded on Perkin-Elmer spectrophotometer model 577 using potassium bromide discs. NMR Spectra were recorded on 90 MHz Jeol FX 90Q FT NMR using TMS as internal standard. Mass spectra were scanned on Jeol JMSD-300 mass spectrometer at 70 eV with 100 μ amp ionization current. Physical data of newly synthesized compounds are summarized in Table-1.

Preparation of 2-amino-3,6-dimethyl-2'-nitro-4'-substituted diphenyl-sulfides 3a-g

To a refluxing solution of 2-amino-3,6-dimethylbenzenethiol (1,0.01 mol) in ethanol (20 ml) and anhydrous sodium acetate (0.01 mol in 5 ml of ethanol) was added an alcoholic solution of 2-halonitrobenzene (2,0.01 mol) in ethanol (12ml) and refluxed for three hours. The reaction mixture was concentrated and cooled overnight in an ice chamber. The solid which separated out was filtered and washed with 30% ethanol. Crystallization from methanol afforded the desired products.

Preparation of 2-formamido-3,6-dimethyl-2'-nitro-4'-substituted diphenyl-sulfides 4a-g

A mixture of diphenylsulfide (4a-g, 0.01 mol) and 90% formic acid (20 ml) was refluxed for four hours. The contents were poured into a beaker containing crushed ice. The solid separated out was filtered and washed with water until the filterate was neutral and crystallized from benzene/methanol.

Preparation of 1,4-dimethyl-7-substituted phenothiazines 5a-g

To a refluxing solution of formyl derivatives (4a-g, 0.01 mol) in acetone (15 ml) an alcoholic solution of potassium hydroxide (0.2 gm in 5 ml ethanol) was added. The contents were heated for half an hour. To

this refluxing solution, a second lot of potassium hydroxide (0.2 gm in 5 ml ethanol) was added and refluxed for two hours. The contents were poured into a beaker containing crushed ice. The solid separated out was filtered, washed with cold water, finally with 30% ethanol and recrystallised from benzene/methanol.

Preparation of 9-nitrophenothiazines 5h-j

A mixture of halonitrobenzene (2, 0.01 mol), 2-amino-3,6-dimethylbenzenethiol (1, 0.01 mol), sodium hydroxide (0.01 mol) and absolute ethyl alcohol (20 ml) was refluxed for two hours. The reaction mixture was concentrated on water bath, cooled, and filtered. The precipitate was washed well with hot water and finally with 20% ethanol and crystallized from acetone/benzene.

Table 1 : Physical data(compounds 3-5)

Compd.	M.P. (°C)	Yield (%)	Molecular Formula	% Found/Cald. C	H	N
3a	140	82	$C_{15}H_{14}N_2O_4S$	55.68 56.60	4.39 4.40	8.77 8.80
3b	43	91	$C_{14}H_{13}N_3O_4S$	53.60 52.66	4.07 4.06	13.19 13.16
3c	180	34	$C_{15}H_{16}N_2O_3S$	58.20 59.21	5.26 5.26	9.25 9.21
3d	142	45	$C_{14}H_{13}ClN_2O_2S$	54.40 54.45	4.20 4.21	9.02 9.07
3e	78	73	$C_{14}H_{13}BrN_2O_2S$	47.68 47.59	3.68 3.68	7.89 7.93
3f	81	28	$C_{14}H_{14}N_2O_2S$	60.00 61.31	5.09 5.10	10.25 10.21
3g	150	47	$C_{15}H_{13}F_3N_2O_2S$	51.36 52.63	3.80 3.80	8.22 8.18
4a	112	57	$C_{16}H_{14}N_2O_5S$	54.45 55.49	4.03 4.04	8.06 8.09
4b	69	47	$C_{15}H_{13}N_3O_5S$	52.87 51.87	3.73 3.74	12.15 12.10
4c	110	23	$C_{16}H_{16}N_2O_4S$	57.00 57.83	4.82 4.81	8.47 8.43
4d	146	19	$C_{15}H_{13}ClN_2O_3S$	53.45 53.49	3.85 3.86	8.31 8.32

cont'd...

4e	66	37	$C_{15}H_{13}BrN_2O_3S$	46.26 47.24	3.41 3.41	7.36 7.34
4f	83	25	$C_{15}H_{14}N_2O_3S$	58.60 59.60	4.63 4.63	9.26 9.27
4g	144	41	$C_{16}H_{13}F_3N_2O_3S$	50.80 51.89	3.52 3.51	7.53 7.56
5a	102	87	$C_{15}H_{13}NO_2S$	66.20 66.42	4.81 4.79	5.13 5.16
5b	97	70	$C_{14}H_{12}N_2O_2S$	61.50 61.76	4.41 4.41	10.26 10.29
5c	110	40	$C_{15}H_{15}NOS$	69.91 70.03	5.82 5.83	5.41 5.44
5d	149	69	$C_{14}H_{12}ClNS$	63.44 64.24	4.60 4.58	5.32 5.35
5e	60	95	$C_{14}H_{12}BrNS$	54.80 54.90	3.91 3.92	4.55 4.57
5f	92	41	$C_{14}H_{13}NS$	73.98 74.00	5.71 5.72	6.14 6.16
5g	150	86	$C_{15}H_{12}F_3NS$	60.85 61.01	4.05 4.06	4.71 4.74
5h	77	33	$C_{14}H_{10}Br_2N_2O_2S$	38.90 39.06	2.33 2.32	6.48 6.51
5i	85	25	$C_{14}H_{11}ClN_2O_2S$	54.98 54.81	3.60 3.58	9.15 9.13
5j	82	48	$C_{14}H_{11}N_3O_4S$	52.90 52.99	3.48 3.47	13.21 13.24

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