SYNTHESIS OF 1-METHYL-3,7-DISUBSTITUTED PHENOTHIAZINES

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Abstract : Synthesis of title compounds by the Smiles rearrangement has been reported. 1-Methyl-3,7-disubstituted phenothiazines have been prepared by the Smiles rearrangement of 2-formamido-3-methyl-2'-nitro-5,4'-disubstituted disulides. The latter were obtained by the condensation of 2-amino-3-methyl-5-substituted benzenethiols with o-halonitrobenzenes. However, halonitrobenzenes containing a nitro group at both ortho positions to the reactive halogen atom on condensation with 2-amino-3-methyl-5-substituted benzenethiols 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.

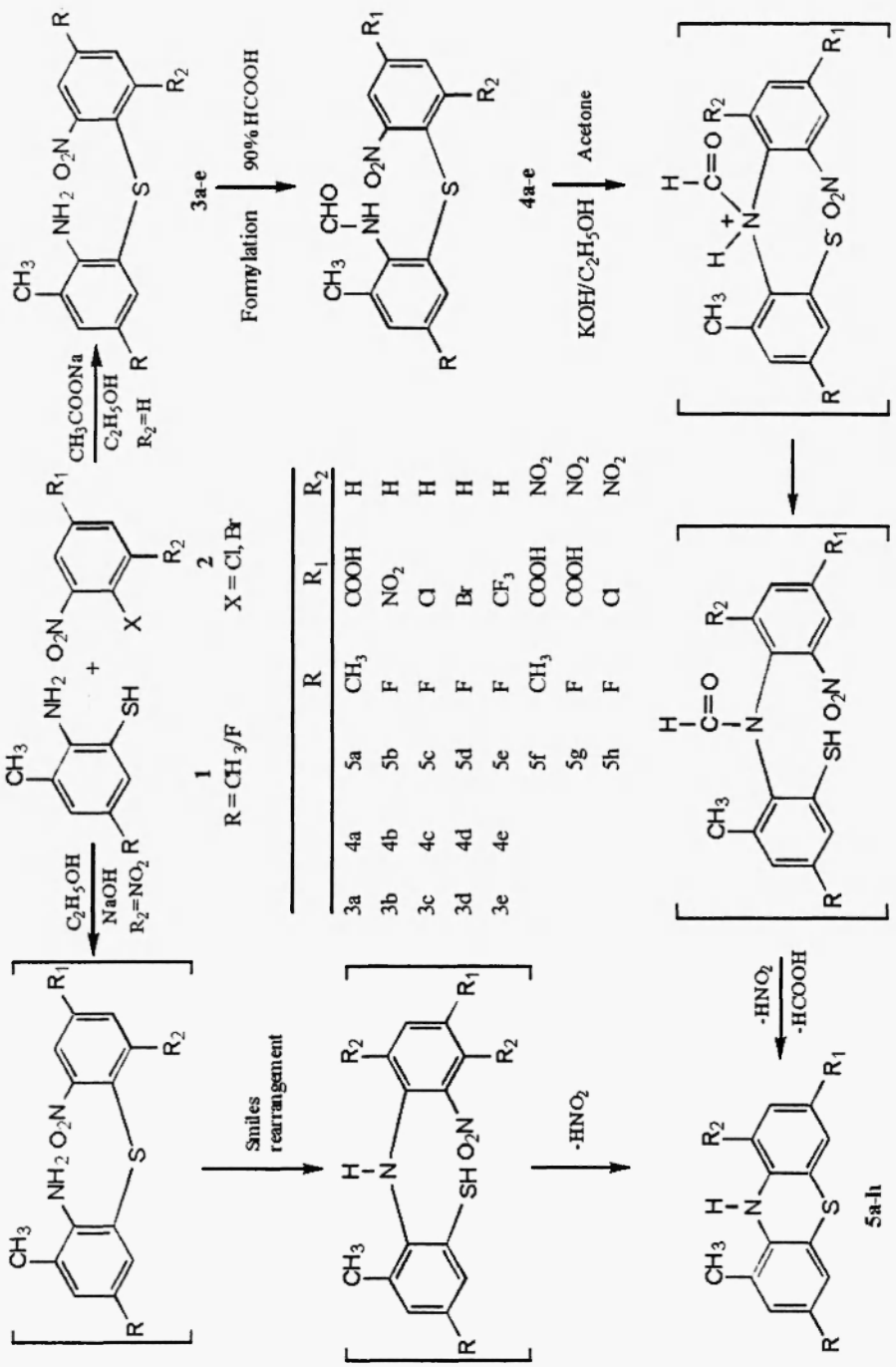
INTRODUCTION

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

RESULTS AND DISCUSSION

2-Amino-3-methyl-5-substitutedbenzenethiols 1 required in the synthesis of title phenothiazines has been prepared by the hydrolytic cleavage of 2-amino-4-methyl-6-substituted benzothiazoles adopted the method reported elsewhere (5,6).

1-Methyl-3,7-disubstituted phenothiazines 5a-e have been prepared by Smiles rearrangement of 2-formamido-3-methyl-2'-nitro-5,4'-disubstituted diphenylsulfides 4a-e in alcoholic potassium hydroxide solution. The formyl derivatives were prepared by the formylation of resultant diphenylsulfies 3a-e obtained by the condensation of 2-amino-3-methyl-5-substituted benzenethiols 1 with substituted o-halonitrobenzenes 2 in alcoholic sodium acetate solution (Scheme-1). 9-Nitrophenothiazines have been prepared by the condensation of 2-amino-3-methyl-5-substituted benzenethiols 1 with appropriately substituted halonitrobenzens 2 containing a nitro group at both orth positions to the reactive halogen atom in ethanolic sodium hydroxide solution where the Smiles rearragement occurs in situ due to combined resonance and inductive effects of nitro group at both ortho positions (Scheme-I).



Synthesis of substituted phenothiazines via Smiles rearrangement

Scheme-1

The IR spectra of all the phenothiazines except 9-nitro, exhibit a sharp peak in the region 3440-3380 cm^{-1} due to NH stretching vibrations. But 9-nitrophenothiazines show a large shift in the secondary NH vibrational frequency. This shift to lower frequency suggests a six membered chelate through NH--O-N bonding (fig-1).

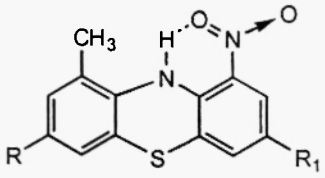


Fig. 1

9-Nitro 5f-h and 7-nitrophenothiazines 5b exhibit two peaks of medium intensity in the region 1585-1595 cm^{-1} and 1340-1380 cm^{-1} due to asymmetric and symmetric vibrations of aromatic nitro group. The peak in the region 1450-1470 cm^{-1} and 1305-1340 cm^{-1} are due to C-H asymmetric and symmetric deformation vibrations of CH_3 group. Peaks corresponding to the chlorine atom in 5c, 5g have been observed at 780 and 770 cm^{-1} respectively. Each of compounds 5b,c,d,e,g,h exhibits band in the region 805-815 cm^{-1} due to C-F stretching vibrations and the compound 5e exhibits two bands at 900 cm^{-1} and 800 cm^{-1} due to C-F_3 linkage at C_7.

The ^1H NMR spectra of all the phenothiazines exhibit a multiplet in the region δ 9.29-6.59 due to aromatic protons. All the phenothiazines 5a-e except those having a nitro group at 9-position exhibit a singlet at δ 8.50-7.89 due to N-H proton. In the 9-nitrophenothiazines 5f-h the N-H proton gives rise to a singlet at δ 9.29-8.27 and this downfield shift suggests hydrogen bonding between the nitro and a secondary amino group through -NH--O=N (fig 1) which has been also indicated by the IR spectral data. In all the compounds a singlet is observed in the region δ 2.31-2.02 due to CH_3 protons of C_1. The compounds 5a and 5f exhibites a peak in the region δ 2.07-1.82 due to CH_3 protons at C_3. In compound 5a,f,g a singlet is observed between δ 9.78-9.1 due to OH proton as COOH group present on C_7 position.

^{19}F NMR of the fluorophenothiazines have been recorded relative to hexaflurobenzene with ^{19}F signal at -162.9 ppm. Each compound 5b-e,g,h exhibits ^{19}F signal at -115.60 ppm, 117.63 ppm, 109.29 ppm and -109.46 ppm, -115.68 ppm and -117.05 ppm respectively due to fluorine present at C_3 position. Compound 5e exhibits an another ^{19}F signal at -122.73 ppm due to fluorine of CF_3 group present at C_7 position.

In mass spectra of all phenothiazines, molecular ion peaks are in accordance with their molecular weights. 9-Nitrophenothiazines undergo fragmentation yielded M^+-17 due to the loss of OH redical according to Mc. lafferty rearrangement (fig. 2).

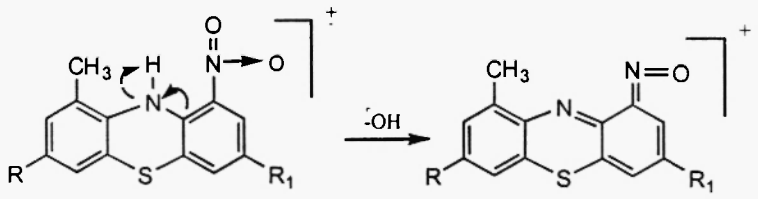


Fig. 2

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 Nicolet-Magna FTIR spectrophotometer model 550 in KBr discs. The ^{1}H NMR spectra have been recorded on 300 MHz on Brucker DRX-300 MHZ FTIR NMR using TMS as an internal standard in $DMSOd_6$. Mass spectra were recorded on Jeol JMSD-300 mass spectrometer at 70ev with 100 μ amp ionization current. Physical data of newly synthesized compounds are summarized on Table-1.

Preparation of 2-amino-3-methyl-2'-nitro-5,4'-disubstituted diphenylsulfides 3a-e

To a refluxing solution of 2-amino-3-methyl-5-substituted benzenethiols (1; 0.01 mole) in ethanol (20 mole) and anhydrous sodium acetete (0.01 mole in 5 ml of ethanol) was added in alcoholic solution of 2-halonitrobenzene (2; 0.01 mole) in ethanol (12ml) and refluxed for three hours. The reaction mixture was concentrated and cooled overnight in ice chamber. The solid seperated out was filtered and crytalization from methanol afforded the desired product.

Preparation of 2-foramido-3-methyl-2'-nitro-5,4'-disubstituted diphenylsulfides 4a-e

A mixture of diphenylsulfide (3a-e; 0.01 mole) and 90% formic acid (20 ml) was refluxed for four hours. The contents were poured into a beaker containg crushed ice. The solid seperated out was filtered and washed with water untill the filterate was neutral and crystalized from benzene or methanol.

Preparation of 1-methyl-3,7-disubstituted phenothiazines 5a-e

To a refluxing solution of formyl derivatives (4a-e; 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 beaker containing crushed ice. The solid seperated out was filtered, washed with cold water, finally with 30% ethanol and recrystallised from benzene or methanol.

Preparation of 9-nitrophenothiazines 5f-h

A mixture of halonitrobenzene (2; 0.01 mole), 2-amino-3-methyl-5-substituted benzenethiol (1, 0.01 mol) sodium hydroxide (0.01 mol) and absolute ethyl alcohol (20ml) was refluxed for two hours. The reactiom 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 or benzene.

Table-1 Physical data 3-5

Comp.	M.P. °C	Yield %	Molecular formula	% Found/Calcd C	H	N
IIIa	240	86.60	$C_{15}H_{14}N_2SO_4$	56.60 (56.70)	4.40 (4.41)	8.78 (8.80)
IIIb	94	82.63	$C_{13}H_{10}N_3SO_4F$	48.29 (48.27)	3.09 (3.08)	13.05 (13.00)
IIIc	120	70.33	$C_{13}H_{10}N_2SO_2FCl$	49.92 (49.90)	3.19 (3.18)	8.90 (8.96)
IIId	50	74.97	$C_{13}H_{10}N_2SO_2FBr$	43.69 (43.67)	2.80 (2.79)	7.85 (7.82)
IIIe	69	31.76	$C_{14}H_{10}N_2SO_2F_4$	48.55 (48.56)	2.89 (2.90)	8.00 (8.09)
IVa	120	64.67	$C_{16}H_{14}N_2SO_5$	55.49 (55.50)	4.04 (4.05)	8.10 (8.09)
IVb	140	70.37	$C_{14}H_{10}N_3SO_5F$	47.86 ((47.88)	2.84 (2.83)	11.95 (11.96)
IVc	95	58.99	$C_{14}H_{10}N_2SO_3FCl$	49.33 (49.30)	2.93 (2.92)	8.23 (8.22)
IVd	126	92.70	$C_{14}H_{10}N_2SO_3FBr$	43.63 (43.65)	2.59 (2.58)	7.25 (7.27)
IVe	80	81.78	$C_{15}H_{10}N_2SO_3F_4$	48.12 (48.10)	2.67 (2.66)	7.50 (7.48)
Va	230	21.42	$C_{15}H_{13}NSO_2$	66.41 (66.42)	4.78 (4.79)	5.14 (5.16)
Vb	249	34.23	$C_{13}H_9N_2SO_2F$	56.53 (56.52)	3.27 3.26)	10.15 (10.14)
Vc	205	42.79	$C_{13}H_9NSFCl$	58.76 (58.75)	3.39 (3.38)	5.28 (5.27)
Vd	180	51.00	$C_{13}H_9NSFBr$	50.33 (50.32)	2.91 (2.90)	4.52 (4.51)
Ve	185	10.00	$C_{14}H_9NSF_4$	56.17 (56.18)	3.00 (3.01)	4.67 (4.68)
Vf	310	87.15	$C_{15}H_{12}N_2SO_4$	56.95 (56.96)	3.78 (3.79)	8.85 (8.86)
Vg	320	68.68	$C_{14}H_9N_2SO_4F$	52.51 (52.50)	2.82 (2.81)	8.76 (8.75)
Vh	270	75.84	$C_{13}H_8N_2SO_2FCl$	50.3 (50.2)	2.58 (2.57)	9.02 (9.01)

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