SYNTHESIS OF 1- AND 3-METHYL PHENOTHIAZINES

Leby Thomas, Archana Gupta and Vandana Gupta*
Department of Chemistry, University of Rajasthan, Jaipur-302 004, India.
E-mail: -rrg_vg@yahoo.co.in; rrgupta@datainfosys.net

ABSTRACT : Synthesis of 1-methyl/3-methyl phenothiazines is reported by Smiles rearrangement of 2-formamido-3-methyl/5-methyl-2′-nitro diphenylsulfides. The latter were obtained by the condensation of 2-amino-3-methyl/5-methylbenzenethiols with o-halonitrobenzenes followed by formylation. However 2-amino-3-methyl/5-methylbenzenethiols on condensation with halonitrobenzenes containing a nitrogroup at ortho positions to the reactive halogen atom directly yields 9-nitrophenothiazines as Smiles rearrangement and ring closure occur simultaneously in situ due to combined resonance and inductive effect reinforced by two nitrogroups.

INTRODUCTION

Phenothiazines possess a wide spectrum of pharmacological/biological activities (1,2). These are used as antihistamines(3), diuretics(4), antimalarials(5), analgesics(6), neuroleptics(7) etc. They have also shown significant effects against cancer (8,9). A slight modification in the substitution pattern in phenothiazine nucleus causes a marked difference in biological activities, therefore, it is considered worthwhile to synthesize hitherto unknown phenothiazines in order to make them available for biomedical screening in search of better medicinal agents.

RESULTS AND DISCUSSION

1-Methyl/3-methyl phenothiazines **5a-f** have been prepared by Smiles rearrangement of substituted 2-formamido-3-methyl/ 5-methyl-2′-nitrodiphenylsulfides **4a-f** in alcoholic potassium hydroxide solution. The formyl derivatives were prepared by the formylation of diphenylsulfides **3a-f** obtained by the condensation of 2-amino-3-methyl/ 5-methylbenzenethiols **1**

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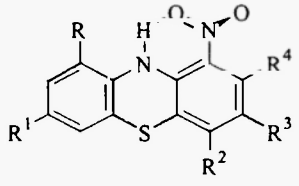
with substituted o-halonitrobenzenes **2** in ethanolic sodium acetate solution. 9-Nitrophenothiazines **5g-j** have been prepared by the condensation of 2-amino-3-methyl/5-methylbenzenethiols **1** with appropriately substituted halonitrobenzenes **2** containing a nitro group at ortho positions to the reactive halogen atom in ethanolic sodium hydroxide solution where the Smiles - rearrangement and ring closure occur simultaneously in situ due to nitro groups (Scheme 1).

2-Amino-3-methyl/5-methylbenzenethiols required in the synthesis of phenothiazines have been prepared by the hydrolytic cleavage of 2-amino-4-methyl/6-methylbenzothiazoles respectively adopting the method reported elsewhere (10,11).

The IR spectra of all phenothiazines exhibit a sharp peak in the region 3290-3420 cm^{-1} due to NH stretching vibrations. Phenothiazines **5a-f** containing no nitro group at 9-position exhibit this band in the region 3330-3420 cm^{-1} while in 9-nitrophenothiazines **5g-j** appears at 3290-3390 cm^{-1}. This shifting to lower frequency suggests a six membered chelate through (NH---O=N) hydrogen bonding (fig. 1).

Fig. 1



9-Nitrophenothiazines **5g-j** exhibit two peaks of medium intensity in the region 1500-1580 cm^{-1} and 1340-1390 cm^{-1} due to asymmetric and symmetric vibrations of aromatic nitro group. The peak in the region 1430-1480 cm^{-1} and 1280-1360 cm^{-1} are due to asymmetric and symmetric C-H deformation vibrations of CH_3 group. A single sharp peak in the region 750-820 cm^{-1} in compounds **5a-f,h,j** is due to C-Cl stretching vibrations. In compounds **5j and l** two sharp peaks are observed in the region 1110-1165 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 8.58-6.007 ppm due to aromatic protons. All the phenothiazines **5a-f** except those having a nitro group at 9-position exhibit a singlet in the region δ 9.414-9.18 ppm due to N-H proton. In the 9-nitrophenothiazines **5g-j** the N-H proton gives rise to a singlet at δ 9.887-9.419 ppm and this downfield 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 phenothiazines **5a-j** singlets are observed in the region δ 2.636-2.15 ppm and δ 2.56-2.10 ppm due to CH_3 protons at C-1 and C-3 respectively.

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 due to Mc Lafferty rearrangement (Scheme 2).

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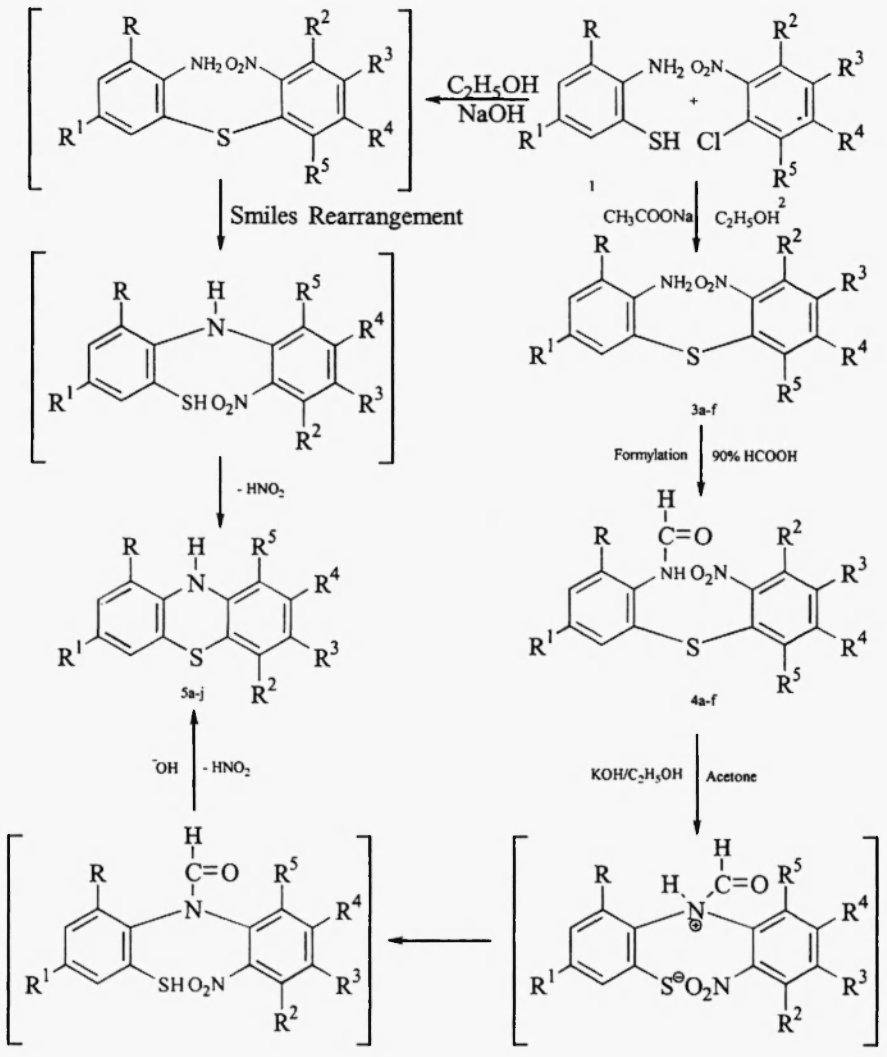

Compound			R	R^1	R^2	R^3	R^4	R^5
3a	4a	5a	CH_3	H	H	H	H	Cl
3b	4b	5b	CH_3	H	H	Cl	Cl	H
3c	4c	5c	CH_3	H	H	Cl	H	H
3d	4d	5d	H	CH_3	H	H	H	Cl
3e	4e	5e	H	CH_3	H	Cl	Cl	H
3f	4f	5f	H	CH_3	H	Cl	H	H
		5g	CH_3	H	H	CF_3	H	NO_2
		5h	CH_3	H	Cl	Cl	H	NO_2
		5i	H	CH3	H	CF_3	H	NO_2
		5j	H	CH3	Cl	Cl	H	NO_2

Scheme1:Synthesis of phenothiazines via Smiles rearrangement

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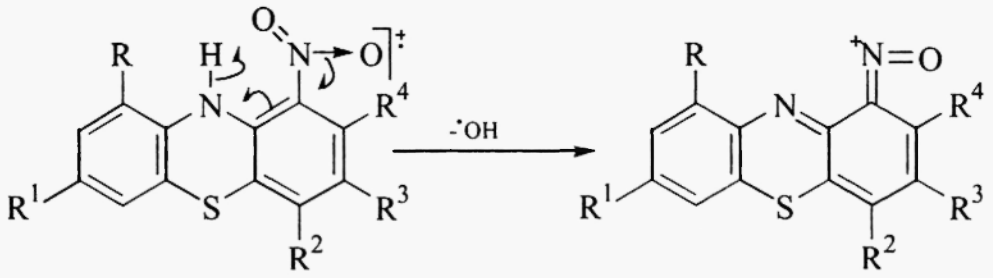

Scheme 2

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 FT IR spectrometer. MAGNA IR 550, NICOLET using potassium bromide discs. NMR spectra were recorded on FT NMR Bruker DRX-300 MHz in DMSO-d_6 using TMS as an internal standard. Mass spectra were scanned on Jeol D-300 (EI). Physical data of synthesized compounds are summarized in Table 1.

Preparation of substituted 2-amino-3-methy l/5-methyl-2'-nitrodiphenyl-sulfides 3a-f

To a refluxing solution of 2-amino-3-methyl/5-methyl benzenethiol (**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 2-halonitrobenzene (**2**, 0.01 mole) in ethanol (12 ml) and refluxed for three hours. The reaction mixture was concentrated and cooled overnight in an ice chamber. The solid separated out was filtered and washed with 30% ethyl alcohol. Crystallization from methanol afforded the desired diphenylsulfide.

Preparation of substituted 2-formamido-3-methyl/5-methyl-2'-nitrodi-phenylsulfides 4a-f

A mixture of diphenylsulfide (**3a-f**, 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 filtrate was neutral & crystallized from benzene/methanol.

Preparation of 1-methyl/3-methylphenothiazines 5a-f

To a refluxing solution of formyl derivative (4a-f, 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.

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Table 1 : Physical data (Compounds 3-5)

	Compound						M.P.	Yield	Molecular	% found (Cald.)		
	R	R^1	R^2	R^3	R^4	R^5	°C	%	formula	C	H	N
I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
3a	CH_3	H	H	H	H	Cl	55	99	$C_{13}H_{11}N_2O_2SCl$	53.33 (52.97)	3.78 (3.76)	9.45 (9.51)
3b	CH_3	H	H	Cl	Cl	H	55	56	$C_{13}H_{10}N_2O_2SCl_2$	47.73 (47.43)	3.05 (3.06)	8.55 (8.51)
3c	CH_3	H	H	Cl	H	H	40	57	$C_{13}H_{11}N_2O_2SCl$	52.71 (52.97)	3.79 (3.76)	9.48 (9.51)
3d	H	CH_3	H	H	H	Cl	54	75	$C_{13}H_{11}N_2O_2SCl$	53.12 (52.97)	3.73 (3.76)	9.54 (9.51)
3e	H	CH_3	H	Cl	Cl	H	80	70	$C_{13}H_{10}N_2O_2SCl_2$	47.20 (47.43)	3.07 (3.06)	8.47 (8.51)
3f	H	CH_3	H	Cl	H	H	57	82	$C_{13}H_{11}N_2O_2SCl$	52.65 (52.97)	3.74 (3.76)	9.56 (9.51)
4a	CH_3	H	H	H	H	Cl	52	63	$C_{14}H_{11}N_2O_3SCl$	52.41 (52.10)	3.42 (3.44)	8.64 (8.68)
4b	CH_3	H	H	Cl	Cl	H	40	94	$C_{14}H_{10}N_2O_3SCl_2$	47.13 (47.07)	2.79 (2.82)	7.87 (7.84)
4c	CH_3	H	H	Cl	H	H	48	70	$C_{14}H_{11}N_2O_3SCl$	52.14 (52.10)	3.47 (3.44)	8.75 (8.68)
4d	H	CH_3	H	H	H	Cl	150	80	$C_{14}H_{11}N_2O_3SCl$	52.36 (52.10)	3.43 (3.44)	8.71 (8.68)
4e	H	CH_3	H	Cl	Cl	H	151	46	$C_{14}H_{10}N_2O_3SCl_2$	47.41 (47.07)	2.84 (2.82)	7.78 (7.84)
4f	H	CH_3	H	Cl	H	H	43	65	$C_{14}H_{11}N_2O_3SCl$	52.15 (52.10)	3.45 (3.44)	8.73 (8.68)
5a	CH_3	H	H	H	H	Cl	75	55	$C_{13}H_{10}NSCl$	62.68 (63.02)	4.08 (4.07)	5.62 (5.66)
5b	CH_3	H	H	Cl	Cl	H	88	86	$C_{13}H_9NSCl_2$	54.81 (55.33)	3.21 (3.22)	5.01 (4.97)
5c	CH_3	H	H	Cl	H	H	119	62	$C_{13}H_{10}NSCl$	63.29 (63.02)	4.08 (4.07)	5.69 (5.66)
5d	H	CH_3	H	H	H	Cl	142	49	$C_{13}H_{10}NSCl$	62.87 (63.02)	4.09 (4.07)	5.64 (5.66)
5e	H	CH_3	H	Cl	Cl	H	99	95	$C_{13}H_9NSCl_2$	55.69 (55.33)	3.20 (3.22)	4.98 (4.97)
5f	H	CH_3	H	Cl	H	H	110	80	$C_{13}H_{10}NSCl$	63.35 (63.02)	4.04 (4.07)	5.61 (5.66)
5g	CH_3	H	H	CF_3	H	NO_2	75	51	$C_{14}H_9N_2O_2SF_3$	51.15 (51.53)	2.80 (2.78)	8.56 (8.59)
5h	CH_3	H	Cl	Cl	H	NO_2	127	30	$C_{13}H_8N_2O_2SCl_2$	48.15 (47.72)	2.44 (2.47)	8.50 (8.57)
5i	H	CH_3	H	CF_3	H	NO_2	123	26	$C_{14}H_9N_2O_2SF_3$	51.88 (51.53)	2.77 (2.78)	8.61 (8.59)
5j	H	CH_3	Cl	Cl	H	NO_2	79	25	$C_{13}H_8N_2O_2SCl_2$	47.45 (47.72)	2.48 (2.47)	8.62 (8.57)

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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 recrystallized from benzene/methanol.

Preparation of 9-nitrophenothiazines 5g-j

A mixture of halonitrobenzene (**2**, 0.01 mol), 2-amino-3-methyl/5-methyl benzenethiol (**1**, 0.01 mol), sodium hydroxide (0.01 mol) and absolute ethylalcohol (20 ml) was refluxed for two hours. The reaction mixture was concentrated on waterbath, cooled and filtered. The precipitate was washed well with hot water and finally with 20% ethanol and crystallized from acetone/benzene.

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