SYNTHESIS OF 6-CHLORO-9-METHYL-/7-METHOXYPHENOTHIAZINES VIA SMILES REARRANGEMENT

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Abstract

6-Chloro-9-methyl-/7-methoxyphenothiazines have been synthesized via Smiles rearrangement of 6-chloro-3-methyl-/5-methoxy-2-formamido-2′-nitrodiphenyl sulfides. The formyl derivatives were obtained by the formylation of diphenyl sulfides which were prepared by the condensation of 2-amino-6-chloro-3-methyl-/5-methoxybenzenethiols with o-halonitrobenzenes. With halonitrobenzene having nitro group at both the ortho positions to the reactive halogen atom, 1-nitrophenothiazines are obtained in a single step as Smiles rearrangement occurs in situ.

Introduction

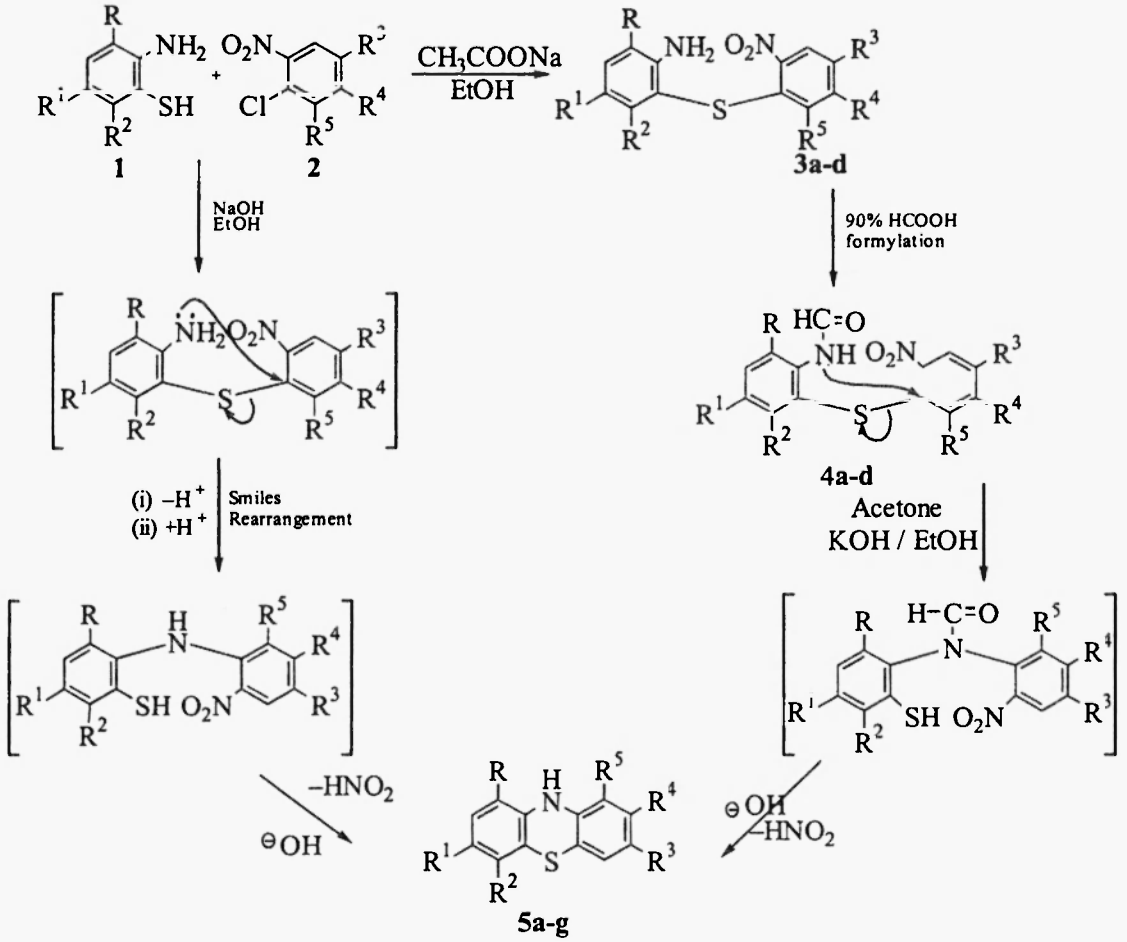
Phenothiazines and their analogues are well known for their biological / pharmacological activities[1,2] and find their uses as antihistamines[3], anti-inflammatory[4], CNS-depressants[6] and antipsychotics[7] tuberculostatics[5],. Phenothiazines have also shown significant antitumor activity[8,9]. In view of such a wide spectrum of medicinal applications of phenothiazines with a slight change in the substitution pattern, we have focussed our attention to synthesize phenothiazines with a hope to obtain better medicinal agents.

Results and Discussion

In the present communication, phenothiazines have been prepared via Smiles rearrangement involving the migration of an aromatic ring from one heteroatom to another heteroatom by intramolecular nucleophilic aromatic substitution. The reaction of 2-amino-6-chloro-3-methyl-/5-methoxybenzenethiol (1) with halonitrobenzenes (2) provided the corresponding diphenyl sulfides (3). The formylation of diphenyl sulfides with 90% formic acid yielded 2-formamido-2′-nitrodiphenyl sulfides (4) which on treatment with alcoholic potassium hydroxide underwent Smiles rearrangement yielding phenothiazines (5). 1-Nitrophenotiazines have also been prepared by the condensation of 2-amino-6-chloro-3-methyl-/5-methoxybenzenethiol (1) with halonitrobenzenes (2), containing nitro groups at both the ortho positions to reactive halogen atom, in ethanolic sodium hydroxide solution where the Smiles rearrangement and ring closure occur simultaneously in situ due to increased resonance effects of nitro groups (Scheme-1).

The IR spectra of phenothiazines (5a-d) exhibit a single intense band in the region of 3420-3360 cm^{-1} due to N-H stretching vibrations. But in 1-nitrophenothiazines (5e-g) this band appears at 3265-3250 cm^{-1}. The large shifting to lower frequency region has been attributed to high stability through a strong (–NH----O=N) intramolecular hydrogen bonding (Fig. 1). 1-Nitrophenothiazines exhibit two sharp and intense bands at 1540-1535 cm^{-1} and

1430-1295 cm^{-1} due to asymmetric and symmetric stretching vibrations of the aromatic ring nitro group. Two absorption bands observed at 1460-1450 cm^{-1} and 1360-1310 cm^{-1} are due to C–H deformation vibrations of CH_3 group in the compound (5c-f). The absorption bands in the region 1260-1240 cm^{-1} and 1050-1040 cm^{-1} are observed due to C–O–C asymmetric and symmetric vibrations in the compounds (5a,b & g). All the phenothiazines show a single sharp peak in the region 790-675 cm^{-1} due to C–Cl stretching vibrations. Two sharp bands in the regions 1340-1305 cm^{-1} and 1130-1120 cm^{-1} are assigned to C–F stretching vibrations in the compounds (5f,g).



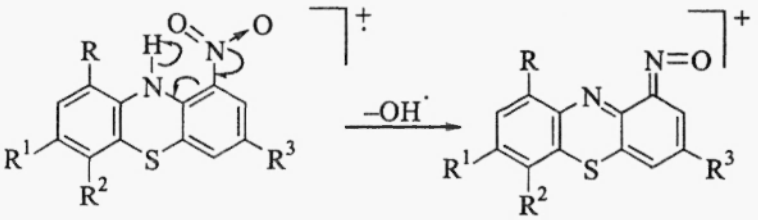
1 **2** **3a-d** **4a-d** **5a-g**

Compound			R	R^1	R^2	R^3	R^4	R^5
3a	4a	5a	H	OCH_3	H	H	H	Cl
3b	4b	5b	H	OCH_3	H	Cl	Cl	H
3c	4c	5c	CH_3	H	Cl	H	H	Cl
3d	3d	5d	CH_3	H	Cl	Cl	Cl	H
		5e	CH_3	H	Cl	COOH	H	NO_2
		5f	CH_3	H	Cl	CF_3	H	NO_2
		5g	H	OCH_3	H	CF_3	H	NO_2

Scheme-I

The ^{1}H NMR spectra of phenothiazines (5a-d) exhibit a singlet in the region δ 8.85-9.28 ppm due to N-H proton, which is shifted to δ 10.08-10.24 ppm downfield in 1-nitrophenothiazines. The downfield shifting is ascribed to the intramolecular hydrogen bonding (-NH---O=N). All the phenothiazines exhibit multiplet in the region δ 6.40-8.30 ppm due to aromatic ring protons. A singlet is observed in the region δ 2.15-2.18 in the compounds (5c-f) due to the protons of methyl group, while a singlet in the region δ 3.58-3.80 ppm is observed due to the protons of OCH_3 group in the compounds (5a,b & g). A singlet is also observed at δ 10.38 ppm due to the proton of COOH group in compound (5e).

In the mass spectra of all the phenothiazines, molecular ion peaks are in accordance with their molecular weights. 1-Nitrophenothiazines undergo fragmentation yielding $M^+ -17$ due to loss of OH radical by Mc Lafferty rearrangement (Scheme-II).



Scheme-II

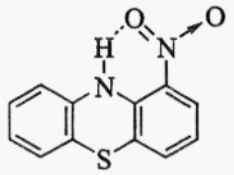


Fig. 1

Experimental

All the melting points are uncorrected. The purity of all the synthesized compounds was checked by thin layer chromatography and their structures have been assigned by their elemental analyses and spectral data. The infrared spectra were recorded by NICOLET-MAGNA FT IR spectrometer model 550 in KBr discs. The ^{1}H NMR spectra were scanned on 90 MHz Jeol FX 90Q FT NMR using TMS as an internal standard in $CDCl_3$. Mass spectra were scanned on VG 70-70H Mass spectrometer. Physical data of all the synthesized compounds are summarized in Table-1.

(a) Preparation of 2–amino-6-chloro-3-methyl-/5-methoxy–2'–nitrodiphenyl sulfides (3a–d)

In a 50 ml R.B. flask, anhydrous sodium acetate (0.01 mole) and substituted 2–aminobenzenethiol (**1**, 0.01 mole) were dissolved in ethanol (20 ml) and to it o–halonitrobenzene (**2**, 0.01 mole dissolved in 10 ml ethanol) was added and refluxed for four hours. The resulted solution was concentrated, cooled and kept overnight in ice chamber. The

Table-1 : Physical data of Synthesized compounds

	Compound						M.P. °C	Yield %	Molecular formula	% Found (Calcd.)		
	R	R^1	R^2	R^3	R^4	R^5				C	H	N
I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII
3a	H	OCH_3	H	H	H	Cl	47	65	$C_{13}H_{11}N_2O_3SCl$	50.91 (50.24)	3.58 (3.54)	8.96 (9.01)
3b	H	OCH_3	H	Cl	Cl	H	52	59	$C_{13}H_{11}N_2O_3SCl_2$	44.81 (45.23)	2.88 (2.92)	8.18 (8.11)
3c	CH_3	H	Cl	H	H	Cl	45	68	$C_{13}H_{10}N_2O_2SCl_2$	46.95 (47.42)	3.02 (3.05)	8.55 (8.51)
3d	CH_3	H	Cl	Cl	Cl	H	60	70	$C_{13}H_9N_2O_2SCl_3$	43.58 (42.93)	2.45 (2.49)	7.73 (7.70)
4a	H	OCH_3	H	H	H	Cl	116	65	$C_{14}H_{11}N_3O_4SCl$	48.83 (49.64)	3.24 (3.27)	8.30 (8.27)
4b	H	OCH_3	H	Cl	Cl	H	89	57	$C_{14}H_{10}N_2O_3SCl_2$	45.87 (45.05)	2.73 (2.70)	7.57 (7.50)
4c	CH_3	H	Cl	H	H	Cl	39	78	$C_{14}H_{10}N_2O_3SCl_2$	47.92 (47.07)	2.85 (2.82)	7.78 (7.84)
4d	CH_3	H	Cl	Cl	Cl	H	102	72	$C_{14}H_9N_2O_3SCl_3$	43.73 (42.93)	2.29 (2.32)	7.10 (7.16)
5a	H	OCH_3	H	H	H	Cl	98	59	$C_{13}H_{10}NOSCl$	60.04 (59.20)	3.85 (3.82)	5.36 (5.31)
5b	H	OCH_3	H	Cl	Cl	H	114	52	$C_{13}H_9NOSCl_2$	53.10 (52.36)	3.09 (3.04)	4.64 (4.69)
5c	CH_3	H	Cl	H	H	Cl	89	43	$C_{13}H_9NSCl_2$	54.85 (55.33)	3.19 (3.22)	4.92 (4.97)
5d	CH_3	H	Cl	Cl	Cl	H	120	47	$C_{13}H_8NSCl_3$	50.20 (49.31)	2.58 (2.55)	4.50 (4.43)
5e	CH_3	H	Cl	COOH	H	NO_2	165	38	$C_{14}H_9N_2O_4SCl$	50.49 (49.93)	2.65 (2.69)	8.37 (8.32)
5f	CH_3	H	Cl	CF_3	H	NO_2	137	56	$C_{14}H_8N_2O_2SClF_3$	45.85 (46.61)	2.27 (2.24)	7.81 (7.77)
5g	H	OCH_3	H	CF_3	H	NO_2	155	47	$C_{14}H_9N_2O_3SF_3$	49.83 (49.12)	2.63 (2.65)	8.11 (8.18)

solid separated out was filtered and washed with 30% ethanol and recrystallized from methanol.

(b) Preparation of 6-chloro-3-methyl-/5-methoxy-2–formamido–2'–nitrodiphenyl sulfides (4a–d)

The substituted diphenyl sulfide (**3**, 0.01 mole) dissolved in 20 ml of 90% formic acid was refluxed for 4 hours. The contents were poured into a beaker containing crushed ice. The solid separated out was filtered, washed with water until the filtrate was neutral and crystallized from benzene.

(c) Preparation of 6-chloro-9-methyl-/7-methoxyphenothiazines (5a–d)

To the refluxing solution of formyl derivative (**4**, 0.01 mole) in acetone (15 ml) was added an alcoholic solution of potassium hydroxide (0.2 gm in 5 ml alcohol). The contents were heated for half an hour. The second portion of potassium hydroxide (0.2 gm in 5 ml alcohol) was added and refluxed for 2 hours. The contents were poured into a beaker containing crushed ice and filtered. The residue obtained was washed with cold water and finally with 30% ethanol and crystallised from benzene/methanol.

(d) Preparation of 1-nitrophenothiazines (5e-g)

A mixture of 2-amino-6-chloro-3-methyl-/5- methoxybenzenethiol (**1**, 0.01 mole), ethanol (20 ml) and sodium hydroxide (0.01 mole) was added in alcoholic solution of reactive halonitrobenzene (**2**, 0.01 mole). The contents were refluxed for 1-2 hours concentrated, cooled and filtered. The solid separated out was washed with hot water and finally with 30% ethanol and crystallized from methanol / acetone.

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