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

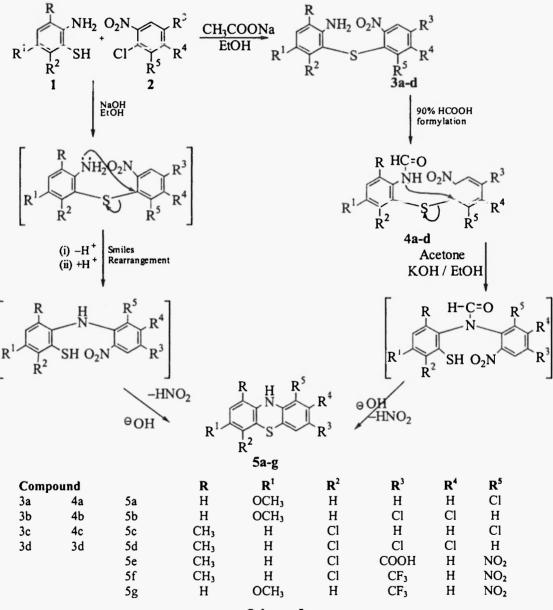
Phenothiazines and their analogues are well known for their biological / pharmacological activities^{1,2} and find their uses as antihistamines³, anti-inflammatory⁴, CNS-depressants⁶ and antipsychotics⁷ tuberculostatics⁵, Phenothiazines have also shown significant antitumor activity^{8,9}. In view of 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 $3420-3360 \text{ cm}^{-1}$ due to N-H stretching vibrations. But in 1-nitrophenothiazines (5e-g) this band appears at $3265-3250 \text{ cm}^{-1}$. 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 $1540-1535 \text{ cm}^{-1}$ and

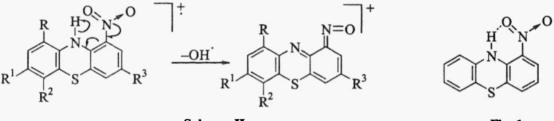
1430-1295 cm⁻¹ due to asymmetric and symmetric stretching vibrations of the aromatic ring nitro group. Two absorption bands observed at 1460-1450 cm⁻¹ and 1360-1310 cm⁻¹ are due to C–H deformation vibrations of CH₃ group in the compound (5c-f). The absorption bands in the region 1260-1240 cm⁻¹ and 1050-1040 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).



Scheme-I

The ¹H 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 1nitrophenothiazines. 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 OCH₃ 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 ¹H NMR spectra were scanned on 90 MHz Jeol FX 90Q FT NMR using TMS as an internal standard in CDCI₃. 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 2aminobenzenethiol (1, 0.01 mole) were dissolved in ethanol (20 ml) and to it ohalonitrobenzene (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

R^2 R^4 R^4 R^4 R^4 R^4 R^4 R^4 X				Compound	pun			M.P. °C	Yield %	Molecular	H %	% Found (Calcd.)	cd.)
II III IV V VII VII IX X XI I OCH1 H H H CI 47 55 C _H I,NO ₀ SCI 5323 5024 5031 I OCH1 H C CI H 52 59 C _H I,NO ₀ SCI 4481 I H CI H H CI H 52 59 C _H I,NO ₀ SCI 4481 I H CI H H CI H 52 54 44.81 5533 I OCH1 H CI H CI H S2 54 44.81 655 54.41.NO ₆ SCI 47.53 67.5533 I OCH1 H CI I H CI H S2 54.41.NO ₆ SCI 47.93 67.93 67.93 67.93 67.93 67.93 67.93 67.93 67.93 67.93 67.93 67.93 67.93		R	R ¹	R ²		R4	R ⁵			formula	c	H	N
H OCH, H H Cl. 47 65 C ₁ H ₁ N ₂ O ₅ CCl 5991 H OCH, H C Cl H 52 59 C ₁ H ₁ N ₂ O ₅ CCl 5953 CH, H Cl H H Cl 45 5552 4533 CH, H Cl H H Cl 45 56 C ₁ H ₁ N ₂ O ₅ SCl ₃ 4533 CH, H Cl H Cl H Cl 45 4533 CH, H Cl H Cl H Cl 4533 CH, H Cl Cl H Cl H Cl 4733 CH, H Cl H H Cl H 4732 CH, H H Cl H H Cl 4703 CH, H Cl H H Cl H 4373 CH,	I	п	ш	IV	V	M	IIV	VIII	IX	X	XI	ХП	XIII
	3a	E	OCH	н	н	н	Ū	47	65	CI3H1N2O3SC	50.91	3.58	8.96
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$											(50.24)	(3.54)	(10.9)
	3b	Н	OCH.	Η	Ū	ū	Η	52	59	CI3H1,N2O,SCI2	44.81	2.83	8.18
											(45.23)	(2.92)	(8.11)
	3c	CH	Н	ប	Н	Η	Ū	45	68	CI3HI0N2O2SCI2	46.95	3.02	8.55
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$											(47.42)	(3:05)	(8.51)
	3d	CH	н	ວ	Ū	C	Н	60	01	C ₁ ,H ₉ N ₂ O ₂ SCl ₃	43.58	2.45	7.73
H OCH, H H Cl 116 65 $C_{44}H_{10}N_{20}SCl_{1}$ 4883 H OCH, H Cl H Cl H 89 57 $C_{44}H_{10}N_{20}SCl_{2}$ 4587 CH, H Cl H Cl H Cl 49 57 $C_{44}H_{10}N_{20}SCl_{2}$ 4535 CH, H Cl Cl H Cl 39 78 $C_{44}H_{10}N_{20}SCl_{2}$ 4535 CH, H Cl Cl H H Cl 410 470 4703 CH, H Cl Cl H H Cl 41 470 4703 H OCH, H H Cl 29 Cl_{4}H_{10}NOSCl_{3} 4703 4703 CH, H H H Cl 29 514 4703 5310 CH, H H Cl H H Cl 41 4											(42.93)	(2.49)	(01.70)
H OCH, H C C H 89 57 C ₄ H ₁₀ N ₂ OSC ₁ 45.87 CH, H C H C H C 39 57 C ₄ H ₁₀ N ₂ OSC ₁ 45.87 CH, H CI H CI 39 78 C ₄ H ₁₀ N ₂ OSC ₁ 47.92 CH, H CI CI H CI 39 78 C ₄ H ₁₀ N ₂ OSC ₁ 47.92 H OCH, H H CI 29 72 C ₄ H ₁₀ N ₂ OSC ₁ 47.92 H OCH, H H CI 98 59 C ₁₁ H ₁₀ NOSC ₁ 47.92 CH, H CI CI H CI 89 59 53.10 CH, H CI CI H CI 92 C ₁₁ H ₁₀ NOSC ₁ 47.92 CH, H CI H CI H CI 47 C ₁₁ H ₁₀ N ₁₀ N ₂ C ₁ 47.93 <	4a	H	OCH1	Н	H	Η	ธ	116	65	C ₁₄ H ₁₁ N ₁ O ₄ SC	48.83	3.24	8.30
H OCH, H C C H 89 57 C,H,h,N,O,SCI_1 45.87 CH, H CI H H CI H CI 47.92 CH, H CI H CI 39 57 C,4H,h,O,SCI_1 47.92 CH, H CI CI H CI 39 57 C,4H,h,O,SCI_1 47.92 CH, H CI CI H CI 39 59 C,4H,h,O,SCI_1 47.93 CH, H CI CI H CI 98 59 C,4H,h,O,SCI_2 47.93 CH, H CI CI H CI 98 59 C,4H,h,O,SCI_3 53.10 CH, H CI CI H CI 98 59 51.44,00SCI_3 53.33 CH, H CI H CI CI H 100 112 10 114											(49.64)	(3.27)	(8.27)
		Η		Η	ū	บ	Н	89	57	C14H10N2O.SC12	45.87	2.73	7.57
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$											(45.05)	(0.70)	(7.50)
		CH		5	Н	Η	Ū	39	78	Cl4H10N2OISCI2	47.92	2.85	7.78
CH ₃ H CI CI H IO H CI CI H IO H3.73 H OCH ₁ H H H H CI 98 59 CI ₄ H ₆ NOSCI ₅ 43.73 H OCH ₁ H H CI 98 59 CI ₄ H ₆ NOSCI ₅ 53.10 CH ₃ H CI CI H II 52 CI ₄ H ₆ NOSCI ₅ 53.10 CH ₃ H CI H CI 89 43 CI ₃ H ₆ NOSC ₁ 53.33 CH ₄ H CI H H CI 53.33 CH ₄ H CI H II 52 C ₁ H ₆ NOSC ₁ 53.33 CH ₄ H CI H II 23 54.85 55.33 CH ₄ H II H II 120 47 C ₁₄ H ₆ NO ₅ CI ₅ 55.33 CH ₄ H NO ₁ 157 H											(47.07)	(2.82)	(7.84)
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		CH		5	ū	ວ	Η	102	72	Cl4H,N2O3SC 3	43.73	2.29	7.10
H OCH, H H C 98 59 C ₁₃ H ₁₀ NOSCI 60.04 H OCH, H C C H 114 52 C ₁₃ H ₁₀ NOSCI 53.10 CH ₃ H C C H H C 54.85 53.10 CH ₃ H C C C H H C 54.85 53.10 CH ₃ H C C C H H C 54.36 53.10 55.33 53.10 55.33 54.85 55.33 56.23 56.23 56.23 56.23 56.23 56.23 56.24 56.49 <td></td> <td>(42.93)</td> <td>(2:32)</td> <td>(7.16)</td>											(42.93)	(2:32)	(7.16)
H OCH1 H Cl H II4 S10 S310		Η		Н	Н	Ħ	G	98	59	C ₁₃ H ₁₀ NOSCI	60.04	3.85	5.36
H OCH1 H C C H II4 S2 $C_{1J}H_{3}NOSC_{12}$ S3.10 CH3 H CI H H CI H CI S4.85 S3.36 S3.35 S3.36											(59.20)	(3.82)	(5.31)
	5b	H	OCH	Η	Ū	Ū	Η	114	52	C ₁ JH,NOSC ¹ 2	53.10	3.09	4.64
CH ₃ H Cl H H Cl S4.85 CH ₃ H Cl H H Cl 54.85 CH ₃ H Cl Cl H I 50.20 CH ₄ H Cl Cl H I20 47 Cl ₃ H ₆ NSCl ₃ 50.20 CH ₄ H Cl Cl H NO ₂ 165 38 Cl ₄ H ₉ N ₂ O ₄ SCl 50.49 CH ₄ H Cl CF ₃ H NO ₂ 165 38 Cl ₄ H ₉ N ₂ O ₅ SCl 50.49 CH ₄ H Cl CF ₃ H NO ₁ 137 56 Cl ₄ H ₉ N ₂ O ₂ SClF ₃ 45.85 H OCH ₃ H CF ₃ H NO ₁ 155 47 Cl ₄ H ₉ N ₂ O ₃ SF ₃ (49.93)											(52.36)	(3.04)	(4.69)
CH ₃ H Cl Cl H I20 47 Cl ₃ H ₆ NSCl ₃ CH ₁ H Cl Cl H NO ₂ 165 38 Cl ₄ H ₉ N ₂ O ₄ SCl 50.49 CH ₁ H Cl COH H NO ₂ 165 38 Cl ₄ H ₉ N ₂ O ₄ SCl 50.49 CH ₁ H Cl CF ₃ H NO ₁ 137 56 Cl ₄ H ₉ N ₂ O ₂ SClF ₃ 45.85 H OCH ₃ H CF ₃ H NO ₁ 155 47 Cl ₄ H ₉ N ₂ O ₃ SF ₃ 49.83	Sc	СĤ	Н	ច	Н	H	บ	89	43	CIJI-NSC 2	54.85	3.19	4.92
CH ₃ H Cl Cl H I20 47 Cl ₃ H ₆ NSCl ₃ 50.20 CH ₄ H Cl Cl H NO ₂ 165 38 Cl ₄ H ₆ N2O ₄ SCl 50.49 CH ₄ H Cl COH H NO ₂ 165 38 Cl ₄ H ₆ N ₂ O ₄ SCl 50.49 CH ₄ H Cl CF ₃ H NO ₁ 137 56 Cl ₄ H ₆ N ₂ O ₂ SClF ₃ 45.85 H OCH ₃ H CF ₃ H NO ₁ 155 47 Cl ₄ H ₉ N ₂ O ₃ SF ₃ 49.83 H OCH ₃ H NO ₁ 155 47 Cl ₄ H ₉ N ₂ O ₃ SF ₃ 49.83											(55.33)	(3.22)	(4.97)
CH1 H Cl C00H H NO2 165 38 Cl4H5N2O4SCI 50.49 CH1 H Cl CF3 H NO1 137 56 Cl4H5N2O2SCIF5 45.85 (49.93) H CH3 H NO1 137 56 Cl4H5N2O2SCIF5 45.85 (49.93) H CF3 H NO1 155 47 Cl4H5N2O3SF3 49.83 (40.12) H NO1 155 47 Cl4H5N2O3SF3 49.83	Sd	СĤ	Н	5	ü	บ	Η	120	47	C13HeNSC13	50.20	2.58	4.50
CH, H CI C00H H NO2 165 38 CI4H5N204SCI 50.49 CH, H CI CF3 H NO1 137 56 CI4H5N202SCIF3 45.85 (49.93) H CI CF3 H NO1 137 56 CI4H5N202SCIF3 45.85 (1 OCH3 H CF3 H NO1 155 47 CI4H5N203SF3 49.83 (1 OCH3 H CF3 H NO1 155 47 CI4H5N203SF3 49.83											(49.31)	(2.55)	(4.43)
CH ₁ H CI CF ₃ H NO ₁ 137 56 C ₁₄ H ₈ N ₂ O ₂ SCIF ₃ 45.85 (46.61) H 0CH ₃ H CF ₃ H NO ₁ 155 47 C ₁₄ H ₉ N ₂ O ₃ SF ₃ 49.83 (46.61)	5e	CH,	Н	IJ	СООН	Η	NO	165	38	C ₁₄ H ₉ N ₂ O ₄ SC	50.49	2.65	8.37
CH, H CI CF3 H NO1 137 56 C14J4N2O2SCIF3 45.85 (46.61) H OCH3 H CF3 H NO1 155 47 C14H9N2O3SF3 49.83 (49.12)											(49.93)	(5.69)	(8.32)
H OCH ₃ H CF ₃ H NO ₁ 155 47 C ₁₄ H ₉ N ₂ O ₃ SF ₃ (46.61) (49.12)	Sf	CH	Н	ບ	CF3	Н	NO	137	56	C ₁₄ H ₈ N ₂ O ₂ SCIF ₃	45.85	2.27	7.81
H OCH3 H CF3 H NO1 155 47 C14H9N2O3SF3 49.83 (49.12)											(46.61)	(2.24)	(LLL)
(49.12) (2	5g	Ξ	0CH3	Н	CF3	H	Ň	155	47	C ₁₄ H ₉ N ₂ O ₃ SF ₃	49.83	2.63	8.11
											(49.12)	(2.65)	(8.18)

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Table-1 : Physical data of Synthesized compounds

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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