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Synthesis of 7-Chloro-9-trifluoromethyl-/7-fluorophenothiazines

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ABSTRACT: *Synthesis of 7-chloro-9-trifluoromethyl-/7-fluorophenothiazines is reported by Smiles rearrangement of 5-chloro-3-trifluoromethyl-/5-fluoro-2-formamido-2′-nitrodiphenyl sulfides. The later were obtained by the formylation of 2-amino-5-chloro-7-trifluoromethyl-/5-fluoro-2′-nitrodiphenyl sulfides, which were prepared by the condensation of 2-amino-5-fluoro-/5-chloro-3-trifluoromethyl benzenethiols with o-halonitrobenzenes. 1-Nitrophenothiazines have also been synthesized by the condensation of 2-aminobenzenethiols with o-halonitrobenzenes, involving Smiles rearrangement in situ.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:81–86, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20235

INTRODUCTION

Phenothiazines and their analogues, nitrogen and sulfur, containing heterocycles, particularly with thiazine ring system, are well known for their pharmacological activities due to their structural specificity. They have been used as antihistaminics [1], analgesics [2], antiemetics [3], diuretics [4], neuroleptics [5], sedatives [6], tuberculostatics [7], tranquilizers [8], etc. Significant anticancer activities have also been shown by phenothiazines [9–11]. In view of such a wide spectrum of medicinal and biological applications of phenothiazines [12], it is considered worthwhile to synthesize hitherto unknown phenothiazines with certain structural specificity, including thiazine moiety for effective drug–receptor interactions. Synthesized phenothiazines have been characterized by their IR, ^{1}H NMR, and mass spectral studies.

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EXPERIMENTAL

Melting points of all the substituted phenothiazines are uncorrected. The purity of all the synthesized compounds has been checked by thin-layer chromatography. Their structures have been assigned by elemental and spectral studies. The infrared spectra were recorded on FT-IR spectrometer MAGNA IR 550 NICOLET using potassium bromide discs. ^{1}H NMR spectra were recorded on FT NMR Bruker DRX-300 MHz in DMSO-d_6 using TMS as an internal standard. Mass spectra have been recorded on Jeol D-300 (EI).

Synthesis of Phenothiazines

Synthesis of phenothiazines involves the following three steps.

Preparation of 2-Amino-2′-nitrodiphenyl Sulfides **IIIa–d**. Substituted 2-aminobenzenethiol **I** (0.01 mol) was dissolved in ethanol (20 mL) in a 50 mL round bottom flask and halonitrobenzene **II** (0.01 mol) dissolved in 10 mL ethanol containing anhydrous sodium acetate (0.01 mol) was added. The contents of reaction mixture were refluxed for 4 h with stirring, concentrated and cooled in an ice bath overnight. The solid separated out was filtered and washed well with 30% ethanol solution. The product

TABLE 1 Physical Data of Compounds **III–V**

Compounds	R^1	R^2	R^3	R^4	R^5	R^6	M.p. (°C)	Yield (%)	Molecular Formula	% Found/(Calcd) C	H	N
IIIa	CF_3	Cl	H	Cl	H	H	148	37.2	$C_{13}H_7Cl_2F_3N_2O_2S$	40.74/(40.75)	1.85/(1.84)	7.30/(7.31)
IIIb	CF_3	Cl	H	Br	H	H	80	74.5	$C_{13}H_7BrClF_3N_2O_2S$	36.50/(36.51)	1.66/(1.65)	6.56/(6.55)
IIIc	CF_3	Cl	H	H	H	H	95	25.4	$C_{13}H_8ClF_3N_2O_2S$	44.76/(44.77)	2.29/(2.31)	8.04/(8.03)
IIId	CF_3	Cl	H	H	H	Cl	89	22.2	$C_{13}H_7Cl_2F_3N_2O_2S$	40.71/(40.75)	1.83/(1.84)	7.30/(7.31)
IVa	CF_3	Cl	H	Cl	H	H	194	52.3	$C_{14}H_7Cl_2F_3N_2O_3S$	40.87/(40.89)	1.73/(1.72)	6.80/(6.81)
IVb	CF_3	Cl	H	Br	H	H	72	57.5	$C_{14}H_7BrClF_3N_2O_3S$	36.91/(36.90)	1.54/(1.55)	6.14/(6.15)
IVc	CF_3	Cl	H	H	H	H	82	44.6	$C_{14}H_8ClF_3N_2O_3S$	44.63/(44.63)	2.12/(2.14)	7.42/(7.44)
IVd	CF_3	Cl	H	H	H	Cl	89	43.5	$C_{14}H_7Cl_2F_3N_2O_3S$	40.87/(40.89)	1.73/(1.72)	6.80/(6.81)
Va	CF_3	Cl	H	Cl	H	H	230	26.6	$C_{13}H_6Cl_2F_3NS$	46.43/(46.45)	1.81/(1.80)	4.16/(4.17)
Vb	CF_3	Cl	H	Br	H	H	180	21.23	$C_{13}H_6BrClF_3NS$	41.00/(41.02)	1.60/(1.59)	3.67/(3.68)
Vc	CF_3	Cl	H	H	H	H	106	29.9	$C_{13}H_7ClF_3NS$	51.73/(51.75)	2.36/(2.34)	4.63/(4.64)
Vd	CF_3	Cl	H	H	H	Cl	120	22.3	$C_{13}H_6Cl_2F_3NS$	46.44/(46.45)	1.78/(1.80)	4.15/(4.17)
Ve	CF_3	Cl	H	NO_2	H	NO_2	170	75.4	$C_{13}H_5ClF_3N_3O_4S$	39.85/(39.86)	1.30/(1.29)	10.72/(10.73)
Vf	CF_3	Cl	Br	H	Br	NO_2	108	68.7	$C_{13}H_4Br_2ClF_3N_2O_2S$	30.93/(30.95)	0.79/(0.80)	5.53/(5.55)
Vg	CF_3	Cl	H	Cl	H	NO_2	148	72.1	$C_{13}H_5Cl_2F_3N_2O_2S$	40.92/(40.96)	1.34/(1.32)	7.33/(7.35)
Vh	CF_3	Cl	H	Cl	H	NO_2	140	76.21	$C_{13}H_5Cl_2F_3N_2O_2S$	40.95/(40.96)	1.31/(1.32)	7.34/(7.35)
Vi	H	F	H	NO_2	H	NO_2	198	80.9	$C_{12}H_6FN_3O_4S$	46.89/(46.91)	1.96/(1.97)	13.65/(13.68)
Vj	H	F	Br	H	Br	NO_2	104	76.63	$C_{12}H_5Br_2FN_2O_2S$	34.30/(34.31)	1.21/(1.20)	6.65/(6.67)
Vk	H	F	H	Cl	H	NO_2	220	68.3	$C_{12}H_6ClFN_2O_2S$	48.57/(48.58)	2.10/(2.04)	9.41/(9.44)
Vl	H	F	H	Cl	H	NO_2	214	65.1	$C_{12}H_6ClFN_2O_2S$	48.59/(48.58)	2.03/(2.04)	9.43/(9.44)

was recrystallized from methanol. Physical data of all synthesized compounds are shown in Table 1.

Preparation of 2-Formamido-2′-nitrodiphenyl Sulfides **IVa–d**. The diphenyl sulfides **IIIa–d** (0.01 mol) obtained in the first step were refluxed for 4 h in 90% formic acid (20 mL). The contents were poured in a beaker containing crushed ice. The solid separated out was filtered, washed well with water, and crystallized from benzene. Physical data of synthesized 2-formamido-2′-nitrodiphenyl sulfides are shown in Table 1.

Preparation of Phenothiazines **Va–d**. To an alcoholic solution of potassium hydroxide (0.2 g in 5 mL ethanol), a solution of formyl derivative **IVa–d** (0.01 mol) in acetone (15 mL) was added. The contents of round bottom flask were heated for 30 min under reflux. A second lot of potassium hydroxide (0.2 g in 5 mL ethanol) was added to the reaction mixture and refluxed for 2 h. The contents of round bottom flask was then poured into a beaker containing crushed ice and filtered. The residue obtained was washed well with water, finally with 30% ethanol and crystallized from benzene. Physical data of synthesized phenothiazines are shown in Table 1.

Preparation of Substituted 1-Nitrophenothiazines **Ve–l**

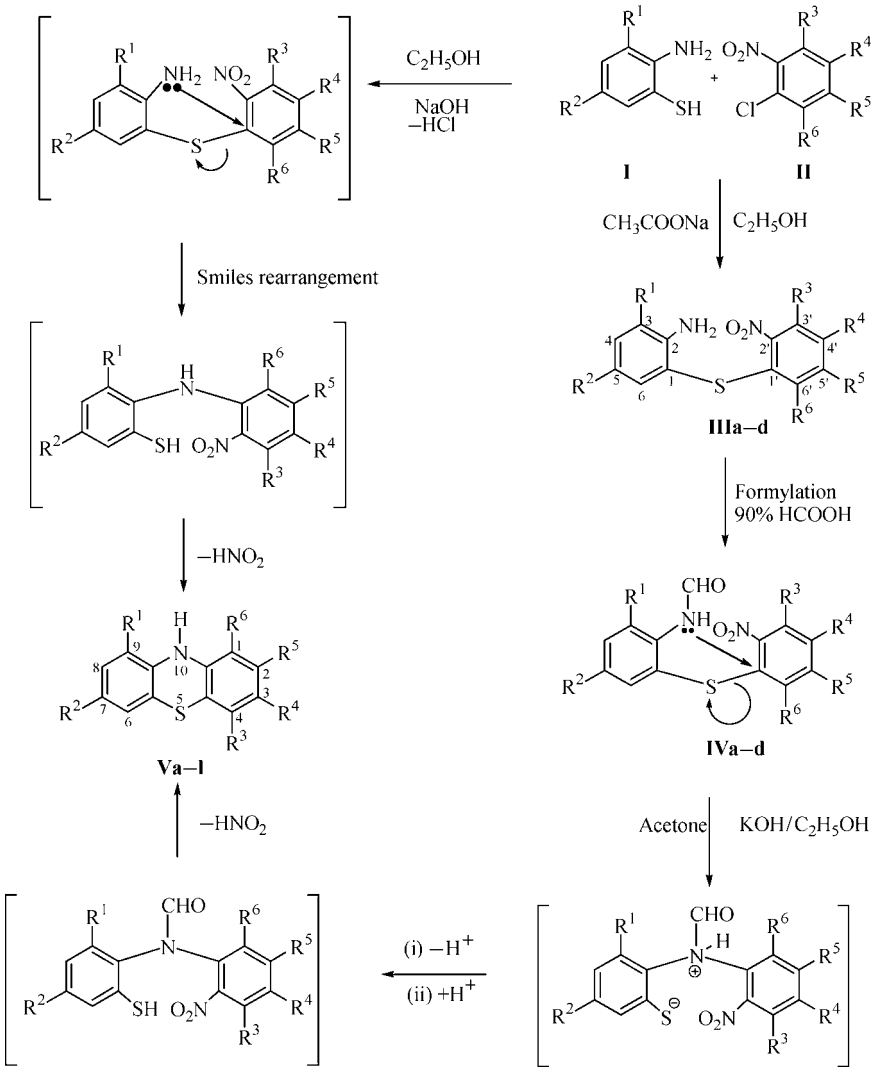
An alcoholic solution of reactive halonitrobenzene **II** (0.01 mol) was added to a stirred suspension of substituted 2-aminobenzenethiol **I** (0.01 mol), ethanol (20 mL), and sodium hydroxide (0.01 mol) contained in a round-bottomed flask (50 mL) fitted with reflux condenser. The color of the solution changed immediately. The contents were refluxed for 2 h, concentrated, cooled, and filtered. The separated solid was washed well with hot water and finally with 30% hot alcohol. The compounds were crystallized from methanol/acetone. Physical and analytical data of synthesized compounds are shown in Table 1.

RESULTS AND DISCUSSION

In the present investigation, 7-chloro-9-trifluoromethyl-/7-fluorophenothiazines **Va–l** have been synthesized by Smiles rearrangement [13–16] of 2-formamido-2′-nitrodiphenyl sulfides **IVa–d**, which were prepared by the formylation of corresponding 2-amino-2′-nitrodiphenyl sulfides **IIIa–d**. The 2-amino-2′-nitrodiphenyl sulfides **IIIa–d** were prepared by the condensation of 2-amniobenzenethiols **I** with *o*-halonitrobenzenes **II**.

A single-step synthesis of 1-nitrophenothiazines has been achieved by the condensation of 2-aminobenzenethiols **I** with halonitrobenzenes in the presence of NaOH, involving Smiles rearrangement and ring closure occurring in situ due to combined resonance and inductive effect of nitro group (Scheme 1).

The infrared spectral data of synthesized 2-amino-2′-nitrodiphenyl sulfides **IIIa–d**, 2-form-amido-2′-nitrodiphenyl sulfides **IVa–d**, and



SCHEME 1 Synthesis of phenothiazines via Smiles rearrangement.

phenothiazines **Va–l** are shown in Tables 2 and 3, respectively.

Synthesized 2-amino-2′-nitrodiphenyl sulfides **IIIa–d** exhibit absorption bands in the regions 3490–3444 and 3383–3333 cm^{-1} due to asymmetric and symmetric vibrations of NH_2 group. Two bands observed in the regions 1570–1539 and 1383–1329 cm^{-1} are due to asymmetric and symmetric stretching vibrations of NO_2 group. Asymmetric and symmetric C—F stretching vibrations of CF_3 group occur in the regions 1391–1317 and 1287–1282 cm^{-1}, respectively. The absorption band observed in the region 717–667 cm^{-1} is due to C—Cl stretching vibrations, while the absorption band at 575 cm^{-1} is due to C–Br stretching vibrations.

Synthesized 2-formamido-2′-nitrodiphenyl sulfides **IVa–d** exhibit an absorption band in the region 3433–3383 cm^{-1} due to N—H stretching vibrations. The intense absorption band observed in the region 1692–1666 cm^{-1} is due to >C=O stretching vibrations. Asymmetric and symmetric stretching vibrations of NO_2 group are observed in the regions 1567–1533 and 1380–1376 cm^{-1}, respectively. The absorption bands observed in the regions 1383–1333$^-$ and 1361–1267 cm^{-1} are due to asymmetric and symmetric C—F stretching vibrations of CF_3 group. The absorption band in the region 767–708 cm^{-1} is observed due to C—Cl stretching vibrations, while the absorption band at 567 cm^{-1} appears due to C—Br stretching vibrations.

All the synthesized phenothiazines **Va–l** exhibit an absorption band in the region 3492–3316 cm^{-1} due to N—H stretching vibrations. Two sharp absorption bands in the region 1384–1367 and 1276–1267 cm^{-1} are assigned to C—F stretching vibrations in CF_3 group. A sharp band observed in the region

TABLE 2 Infrared Spectral Data of Compounds **IIIa–d** and **IVa–d** (in cm^{-1})

Compounds	*A*	*B*	*C*	*D*	*E*	*F*	*G*
IIIa	3467, 3333	–	–	1533, 1383	1366, 1287	717	–
IIIb	3483, 3383	–	–	1545, 1355	1317, 1283	683	575
IIIc	3490, 3381	–	–	1543, 1334	1391, 1287	667	–
IIId	3444, 3381	–	–	1570, 1329	1381, 1282	690	–
IVa	–	3433	1667	1533, 1316	1383, 1250	767	–
IVb	–	3417	1666	1558, 1342	1367, 1260	708	567
IVc	–	3383	1692	1567, 1380	1333, 1267	733	–
IVd	–	3415	1690	1556, 1347	1370, 1254	715	–

A, asymmetric and symmetric stretching vibrations of primary amino group; B, N—H stretching vibrations; C, C═O stretching vibrations; D, asymmetric and symmetric stretching vibrations of nitro group; E, C—F stretching vibrations of CF_3 group; F, C—Cl stretching vibrations; G, C—Br stretching vibrations.

737–722 cm^{-1} is due to C—Cl stretching vibrations and the absorption band observed at 585–567 cm^{-1} is due to C—Br stretching vibrations.

IR spectra of synthesized 1-nitrophenothiazines **Ve–l** exhibit a broad band in the region 3406–3316 cm^{-1} (Table 3) corresponding to the N—H stretching vibrations, which appears at 3492–3428 cm^{-1} in phenothiazines having no nitro group at 1-position. This large shifting of N–H stretching vibrations to a lower frequency region in 1-nitrophenothiazines is attributed to the formation of six-membered chelate of high stability through strong intramolecular hydrogen bonding (—N—H···O═N—).

All 1-nitrophenothiazines exhibit two sharp and intense bands in the region 1580–1475 and 1358–1233 cm^{-1} due to asymmetric and symmetric vibrations of the aromatic nitro group. Compounds **Ve–h** exhibit two bands in the region 1366–1316 and 1166–1133 cm^{-1} due to asymmetric and symmetric stretching vibrations of CF_3 group, while the band due to C—Cl stretching vibrations was observed between 816 and 725 cm^{-1}. Compounds **Vf–j** exhibit a sharp band in the region 587–575 cm^{-1} due to C—Br stretching vibrations, while compounds **Vi–l** exhibit strong absorption band in the region 1097–1067 cm^{-1} due to C—F stretching vibrations.

NMR spectra of phenothiazines show a singlet in the region δ 9.53–8.20 ppm due to NH proton. All the phenothiazines **Va–l** exhibit a multiplet in the region δ 7.88–6.71 ppm due to aromatic protons. NMR data of these compounds are shown in Table 4.

All the synthesized 1-nitrophenothiazines **Va–l** exhibit a sharp peak in the region δ 10.30–8.71 ppm due to N–H proton and peaks in the region δ 8.57–5.3 ppm due to aromatic protons. But phenothiazines without NO_2 group at 1-position exhibit a peak due to NH proton in the δ 9.93–8.20 ppm region (Table 4). This shifting towards downfield in 1-nitrophenothiazines **Ve–l** is attributed to intramolecular hydrogen bonding (—N—H···O═N—) (Fig. 1).

In mass spectra of all phenothiazines, molecular ion peaks are in accordance with their molecular weights. 1-Nitrophenothiazines undergo fragmentation with the loss of —OH radical by Mc-Lafferty

TABLE 3 Infrared Spectral Data of Compounds **Va–l** (in cm^{-1})

Compounds	*A*	*B*	*C*	*D*	*E*
Va	3467	1384, 1267	717	–	–
Vb	3492	1367, 1275	725	567	–
Vc	3428	1383, 1276	737	–	–
Vd	3387	1373, 1260	722	–	–
Ve	3358	1325, 1166	733	–	1516, 1308
Vf	3383	1333, 1150	683	575	1541, 1383
Vg	3365	1366, 1133	816	–	1566, 1233
Vh	3367	1316, 1158	725	–	1566, 1358
Vi	3316	1083	–	–	1580, 1350
Vj	3406	1067	–	585	1566, 1350
Vk	3376	1097	708	–	1483, 1316
Vl	3383	1092	758	–	1475, 1308

A, N—H stretching vibrations; B, C—F stretching vibrations of CF_3 group; C, C—Cl stretching vibrations; D, C—Br stretching vibrations; E, asymmetric and symmetric vibrations of NO_2 group.

TABLE 4 ^{1}H NMR Spectral Data of Compounds **Va–l** (in ppm on FT NMR Bruker DRX-300 MHz in DMSO-d_6 300 MHz)

Compounds	δ *(ppm)*	*Hydrogen*	*Multiplicity*	*Assignment*
Va	7.80–7.39	6	Multiplet	Aromatic protons
	9.93	1	Singlet	N—H proton
Vb	7.67–6.72	6	Multiplet	Aromatic protons
	8.86	1	Singlet	N—H proton
Vc	7.88–6.73	7	Multiplet	Aromatic protons
	8.78	1	Singlet	N—H proton
Vd	7.76–6.71	6	Multiplet	Aromatic protons
	8.20	1	Singlet	N—H proton
Ve	7.57–6.77	5	Multiplet	Aromatic protons
	9.11	1	Singlet	N—H proton
Vf	7.37–6.43	4	Multiplet	Aromatic protons
	8.73	1	Singlet	N—H proton
Vg	7.85–6.62	5	Multiplet	Aromatic protons
	9.50	1	Singlet	N—H proton
Vh	7.85–6.77	5	Multiplet	Aromatic protons
	9.32	1	Singlet	N—H proton
Vi	7.51–6.25	6	Multiplet	Aromatic protons
	8.65	1	Singlet	N—H proton
Vj	7.54–6.19	5	Multiplet	Aromatic protons
	9.07	1	Singlet	N—H proton
Vk	7.32–6.30	6	Multiplet	Aromatic protons
	10.30	1	Singlet	N—H proton
Vl	7.64–6.19	6	Multiplet	Aromatic protons
	9.13	1	Singlet	N—H proton

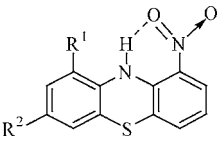
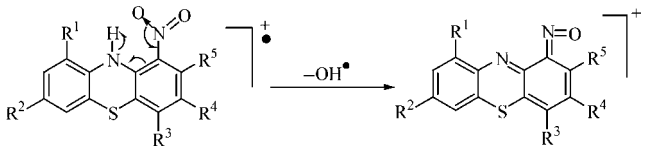


FIGURE 1



SCHEME 2

rearrangement [17] to form species with $M^+ - 17$ (Scheme 2).

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