SYNTHESIS OF FLUOROPHENOTHIAZINES BY SMILES REARRANGEMENT

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Abstract : 1-Chloro-3-fluorophenothiazines have been prepared by Smiles rearrangement of 3-chloro-5-fluoro-2-formamido-2′-nitrophenylsulfides in alcoholic potassium hydroxide solution. The formyl derivatives were prepared by the formylation of the resultant diphenyulsulfides obtained by the condensation of 2-amino-3-chloro-5-fluorobenzenethiol with *o*-halonitrobenzenes in ethanolic acetate solution. 9-Chloro-7-floronitrophenothiazines have been prepared by the condensation of 2-amino-3-chloro-5-fluorobenzenethiol with *o*-halonitrobenzenes containing nitro group (s) or one nitro and halogen atom at both ortho positions to the reactive halogen atom in ethanolic sodium hydroxide solution where Smiles rearrangement occures in situ.

Introduction

Phenothiazines possess a wide spectrum of pharmacological and biological activities and their several derivatives are in clinical use (**1**). A slight alteration in the substitution pattern in phenothiazines nucleus causes a marked difference in their biological activities. Recently great interest has arisen in the anticancer activities of phenothiazines (**2-8**). It is considerd worthwhile to synthesize the title compounds in our research programms to develop better medicinal agents .

Experimental

Melting points of the synthesized compounds are uncorrected. Their purity has been checked by thin layer chromatography. Characterization of the synthesized compounds was done by their spectral data. The infrared spectra were recorded on Nicolet-Magna FT IR spectrophotometer model 550 in KBr discs. NMR Spectra were recorded at 90 MHz on Jeol FX 90Q FT NMR spectrometer in DMSO-d_6 using TMS as an internal standard. ^{19}F NMR Spectra were recorded with respect to hexafluorobenzene with ^{19}F signal at -162.900 ppm.

1. Preparation of 2-amino-3-chloro-5-fluoro-2′-nitro-4′-substituted diphenylsulfides (4a,b)

To a refluxing solution of 2-amino-3-chloro-5-fluorobenzenethiol **1** in ethanol (20 ml) and anhydrous sodium acetate in (5 ml) ethanol, an alcoholic solution of 2-halonitrobenzenes **2** in ethanol (12 ml) was added and refluxed for 3 hrs. The reaction mixture was concentrated and cooled overnight in an ice chamber. The solid separated out was filtered, washed with 30% ethanol and crystallized from methanol (Scheme-1). Physical data of the synthesized compounds (**4a,b**) are recorded in Table-1. Their IR data are recorded in Table-2.

Table-1 : Physical data

Compound	Molecular Formula	M.P. °C	Yield %	% C, H, N Found (Calcd.)		
				Found (Calcd.)	Found (Calcd.)	Found (Calcd.)
4a	$C_{12}H_8N_2O_2FClS$	68	23.9	-	-	9.37 (9.38)
4b	$C_{13}H_8N_2O_4FClS$	98	33.4	-	-	8.20 (8.17)
5a	$C_{13}H_8N_2O_3FClS$	72	71.5	-	-	8.58 (8.57)
5b	$C_{14}H_8N_2O_5FClS$	110	53.5	-	-	7.53 (7.55)
6a	$C_{12}H_7NClFS$	123	78.7	57.28 (57.25)	2.77 (2.78)	5.57 (5.56)
6b	$C_{13}H_7NClFO_2S$	134	21.3	52.76 (52.79)	2.35 (2.36)	4.72 (4.73)
7a	$C_{12}H_5Cl_2FN_2O_2S$	114-115	63.5	43.52 (43.50)	1.50 (1.51)	8.47 (8.46)
7b	$C_{12}H_5ClFN_3O_4S$	78	68.8	42.18 (42.16)	1.45 (1.46)	12.28 (12.29)
7c	$C_{12}H_5Cl_2FN_2O_2S$	117	32.2	43.52 (43.50)	1.50 (1.51)	8.45 (8.46)

Table-2 : Infrared data

Compound	NH_2	NH	NO_2	C=O	C-Cl	C-F
4a	3490 3380	-	1520 1395	-	725	1015
4b	3450 3380	-	1545 1375	-	780	1020
5a	-	3410	1510 1305	1605	730	1020
5b	-	3430	1520 1310	1610	785	1025
6a	-	3425	-	-	725	1025
6b	-	3420	-	-	785	1030
7a	-	3360	1545 1365	-	740	1045
7b	-	3370	1570 1360	-	735	1040
7c	-	3430	1585 1375	-	745	1080

2. Preparation of 3-chloro-5-fluoro-2-formamido-2′-nitro-4′-substituted diphenylsulfides(5a,b)

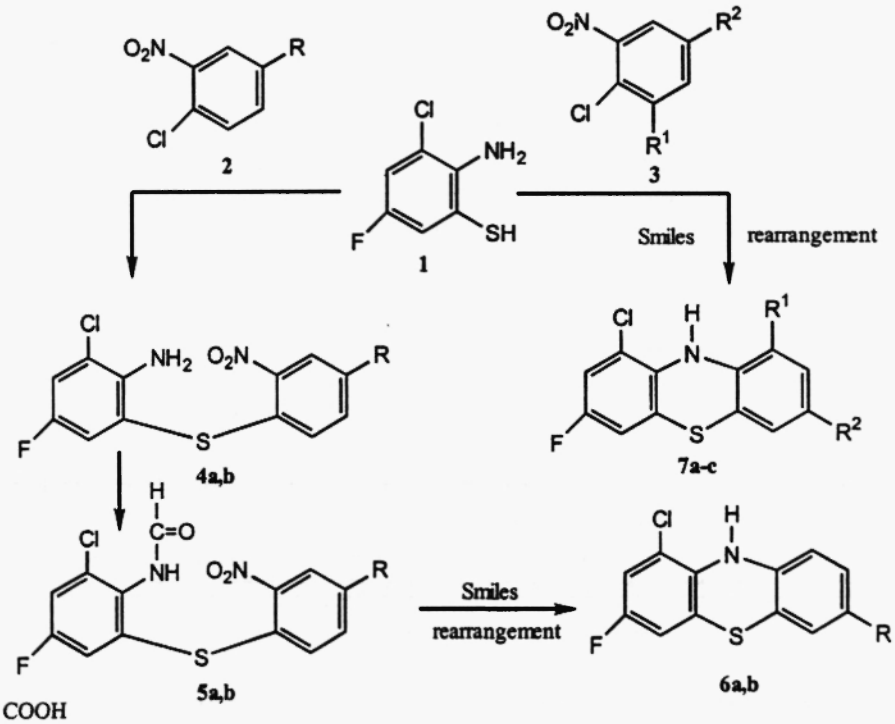
A mixture of diphenylsulfides(**4a,b**) and 90% formic acid (20 ml) was refluxed for 4 hrs. The contents were poured into crushed ice. The solid separated out was filtered, washed with water till neutralization is obtained and crystallized from benzene (Scheme-1). The physical and IR data of the synthesized compounds (**5a,b**) are tabulated in Table-1 and Table-2 respectively.

3. Preparation of 1-chloro-3-fluorophenothiazies (6a,b)

To a refluxing solution of formyl derivatives (**5a,b**) in acetone (15 ml), alcoholic solution of potassium hydroxide in (5 ml) ethanol was added. The contents were refluxed for half an hr. To this refluxing solution, a second lot of potassium hydroxide in (5 ml) ethanol was added and refluxed for two hrs. The contents were poured into crushed ice, the solid separated out was filtered, washed with cold water and finally with 30% ethanol and recrystallized from benzene (Scheme-1). The physical, IR and NMR data of the synthesized compounds (**6a,b**) are recorded in Table-1, 2 and 3 respectively.

4. Preparation of 9-chloro-7-fluoronitrophenothiazines (7a-c)

A mixture of halonitrobenzene, 2-amino-3-chloro-5-fluorobenzenethiol, sodium hydroxide and absolute alcohol (20 ml) was refluxed for 2 hrs. The mixture was concentrated, cooled, filtered, washed with hot water and 30% ethanol and crystallized from acetone (Scheme-1). The physical, IR and NMR data of the synthesized compounds (**7a-c**) are tabulated in Table-1, 2 and 3 respectively.



R = H or COOH
a: $R^1 = NO_2$; $R^2 = Cl$
b: $R^1 = NO_2$; $R^2 = NO_2$
c: $R^1 = Cl$; $R^2 = NO_2$

Scheme-1

Table-3 : NMR Data

Compound	δ(ppm)	Hydrogen	Multiplicity	Assignment	^{19}F Signal
6a	7.73	1	singlet	NH proton	-120.93
	7.48-6.84	6	multiplet	aromatic protons	
6b	10.30	1	singlet	COOH proton at C_7	
	8.68	1	singlet	NH proton	-121.70
	8.21-7.35	5	multiplet	aromatic protons	
7a	7.98	1	singlet	NH proton	-111.60
	7.57-6.56	4	multiplet	aromatic protons	
7b	8.78	1	singlet	NH proton	-109.70
	7.67-6.65	4	multiplet	aromatic protons	
7c	7.73	1	singlet	NH proton	-122.80
	7.57-6.97	4	multiplet	aromatic protons	

Results and discussion

The reaction of 2-amino-3-chloro-5-fluorobenzenethiol **1** with 2-halonitrobenzenes **2** containing nitro group ortho to the halogen atom has yielded the diphenylsulfides **4a,b**. The latter on formylation has yielded the 2-formamido-2′-nitrodiphenylsulfides **5a,b.** In the presence of alkali, imido nitrogen donates its lone pair of electrons for intramolecular nucleophilic attack on the carbonium ion (carbon carrying the halogen atom) as a result, sulfur parts away with its electron pair and the positively charged nitrogen provides the proton which attaches with $\bar{S}$ yielding mercaptodiphenylamine. The latter on cyclization losses nitrous acid and with the simultaneous hydrolysis of acyl group on nitrogen undergoes Smiles rearrangement yielding phenothiazines **6a,b**. The condensation of 2-amino-3-chloro-5-fluorobenzenethiol **1** with halonitrobenzenes **3** containing a nitro group at para and ortho or both ortho positions to the halogen atom in which the increased resonance effect of both nitro groups due to their ortho positions and combined resonance and inductive effect reinforced by the same nitro groups, activates Smiles rearrangement as well as the ring closure to such an extant that both the porcess occured instantaneously and in situ yielding nitrophenothiazines **7a-c.**

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