SYNTHESIS OF 3-BROMO-1-METHYLPHENOTHIAZINES BY SMILES REARRANGEMENT

Naveen Gautam, Rajni Gupta, D.C. Gautam and R.R. Gupta*
Department of Chemistry, University of Rajasthan, Jaipur-302004. (INDIA)

Abstract

Synthesis of 3-bromo-1-methyl phenothiazines is prepared by the Smiles rearrangement of 5-bromo-2-formamido-3-methyl-2'-nitro -4'-substituted diphenyl sulfides. The formyl derivatives were prepared by the formylation of the resultant diphenyl sulfides obtained by the condensation of 2-amino-5-bromo-3-methylbenzenethiol with *o*-halonitrobenzene in ethanolic acetate solution. However, halonitrobenzenes containing a nitro group at both ortho positions to the reactive halogen atom on condensation with 2-amino-5-bromo-3-methylbenzenethiol directly yielded 9-nitrophenothiazine as Smiles rearrangement and ring closure occur simultaneously in situ due to combined resonance and inductive effects reinforced by two nitro groups. The IR, NMR and Mass-spectral studies are also included.

Introduction

Phenothiazines possess a wide spectrum of pharmacological and biological activites (1-4). They have been used as tranquilisers, antiemetics, anthelmintics, antiinflammatory, diuretics, antihistamines, sedatives, fungicides, bactericides, insecticides etc. Recently some substituted phenothiazines have shown significant anticancer activities (5-8). A slight variation in substitution pattern in phenothiazine nucleus causes a marked difference in their activities and has stimulated our interest to synthesize title phenothiazines to made them available for biological screening in search of better medicinal agents.

Results and Discussion

3-Bromo-1-methyl-7-substituted phenothiazines 5a-d have been prepared by Smiles rearrangement of 5-bromo-2-formamido-3-methyl-2'-nitro-4'-substituted diphenylsulfides 4a-d in alcoholic potassium hydroxide solution. The formyl derivatives were prepared by the formylation of resultant diphenylsulfies 3a-d obtained by the condensation of 2-amino-5-bromo-3-methylbenzenethiols 1 with substituted *o*-halonitrobenzenes 2 in alcoholic sodium acetate solution (Scheme-1). 9-Nitrophenothiazine have been prepared by the condensation of 2-amino-5-bromo-3-methyl benzenethiols 1 with 2,6-dinitro-4-trifluoromethyl chlorobenzene 2 containing a nitro group at both ortho positions to the reactive halogen atom in ethanolic sodium hydroxide solution where the Smiles rearrangement occurs *in situ* due to combined resonance and inductive effects of nitro group at both ortho positions **(Scheme-1)**.

The IR spectra of all the phenothiazines except 9-nitro, exhibit a sharp peak in the region 3445-3420 cm^{-1} due to NH stretching vibrations. The IR spectra of 9-nitrophenothiazine 5e exhibits a single sharp peak in the region 3370 cm^{-1} corresponding to the N-H stretching vibrations. This large shifting to a lower frequency region in 9-nitrophenothiazine suggests a six membered chelation of high stability through a strong (-NH---O=N) intramolecular hydrogen bonding **(Fig. 1)**.

IR spectra of the synthesized 9-nitrophenothiazine exhibits two sharp and intense bands at 1580 cm^{-1} and 1320 cm^{-1} due to asymmetric and symmetric vibrations of the aromatic nitro group. Two peaks observed in the region 1465-1450 cm^{-1} and 1355-1340 cm^{-1} which may be

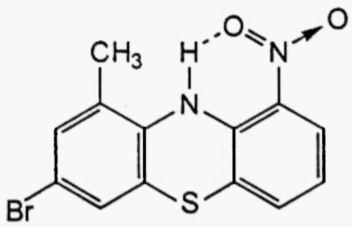


Fig. 1

assigned to C-H deformation vibrations of CH_3 group. Compounds 5c and 5e exhibit two peaks in the region 1340-1310 cm^{-1} and 1120-1100 cm^{-1} due to C-F stretching vibrations of CF_3 group. In compound 5d two peaks are observed in the region 1230 cm^{-1} and 1020 cm^{-1} due to C-O-C asymmetric and symmetric vibrations. In compounds 5a-e a single sharp peak is observed in the region 700-550 cm^{-1} due to C-Br stretching vibrations.

The ^1H NMR spectra of all the phenothiazines 5a-d except those having nitro group at 9-position exhibits a singlet at δ 9.45-8.27 due to NH-proton. In the 9-nitrophenothiazine 5e the NH-proton give rise to a singlet at δ 9.50 and this downfield shift suggests hydrogen bonding between the nitro and a secondary amino group through -NH--O=N (**Fig. 1**) which has been also indicated by the IR spectral data. Compound 5d exhibit a singlet in the region δ 5.37 due to OCH_3 protons at C_7. In all the compounds a singlet is observed in the region δ 2.12-2.08 due to CH_3 protons of C_1.

In mass spectra of all phenothiazines, molecular ion peaks are in accordance with their molecular weights. 9-Nitrophenothiazines undergo fragmentation yielded M^+-17 due to the loss of OH redical according to Mc-Lafferty rearrangement (**Fig. 2**).

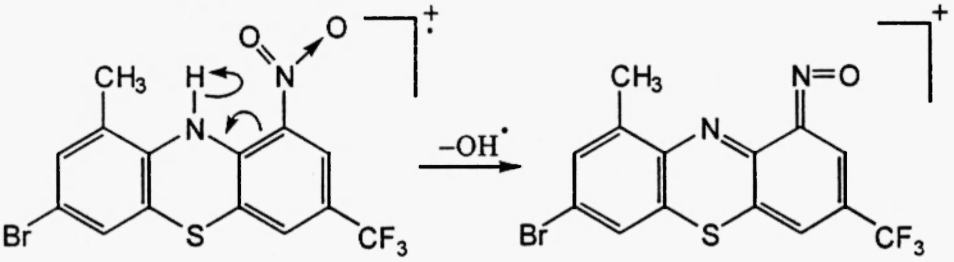
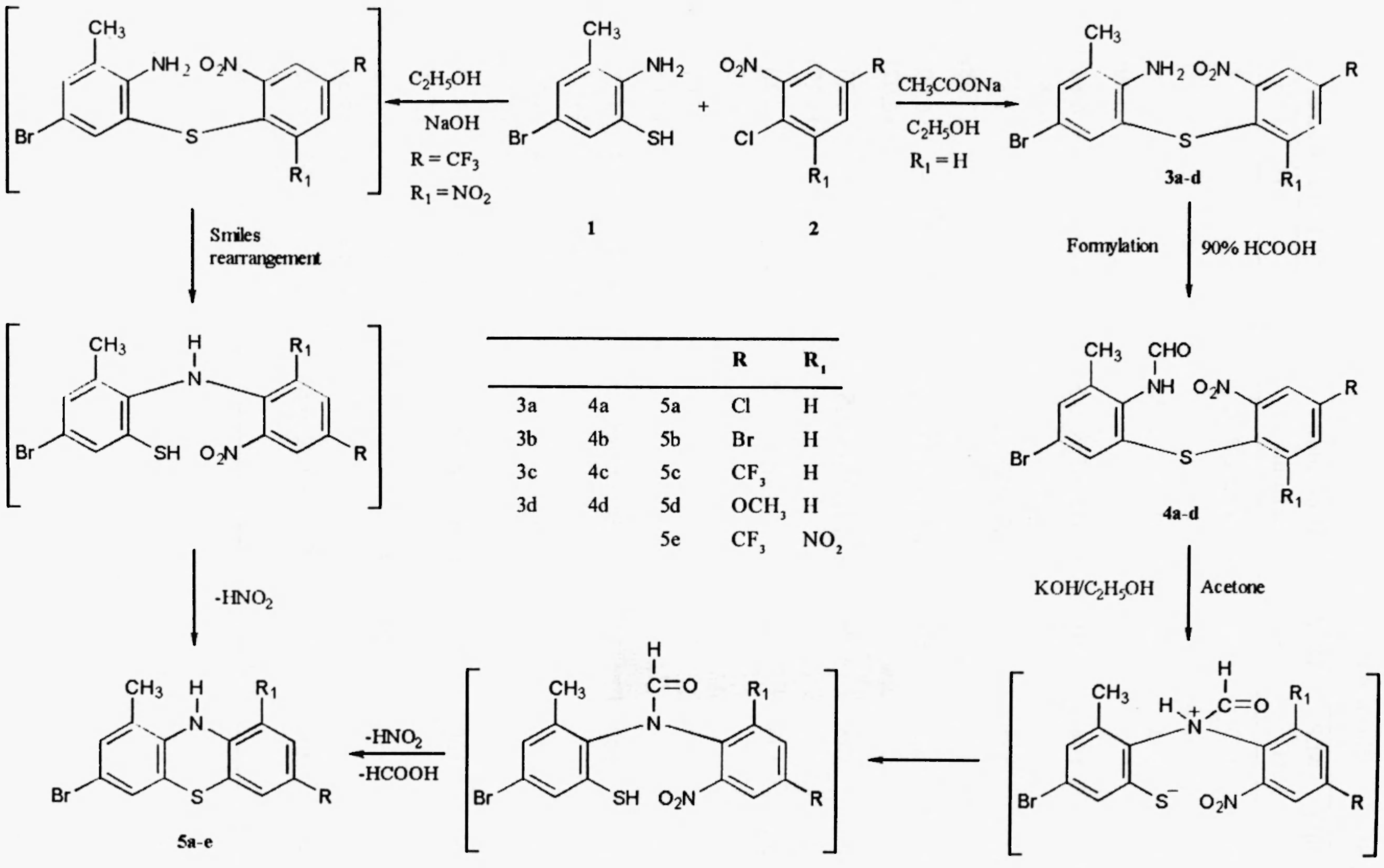


Fig. 2

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 Nicolet-Magna FTIR spectrophotometer model 550 in KBr discs. The ^1H NMR spectral have been recorded on 90 MHz on Jeol FX 90Q FT NMR spectrometer using TMS as an internal standard in DMSO-d_6. Mass spectra were recorded on Jeol JMSD-300 mass spectrometer at 70ev with 100 μ amp ionization current. Physical data of newly synthesized compounds are summarized on Table-1.

Scheme-1



			R	R_1
3a	4a	5a	Cl	H
3b	4b	5b	Br	H
3c	4c	5c	CF_3	H
3d	4d	5d	OCH_3	H
		5e	CF_3	NO_2

Synthesis of 3-bromo-1-methyl phenothiazines via Smiles rearrangement

Table-1 : Physical data 3-5

Comp.	M.P. °C	Yield %	Molecular formula	% Found/Calcd. C	H	N
3a	120	45	$C_{13}H_{10}BrClN_2O_2S$	-	-	7.47 (7.49)
3b	154	40	$C_{13}H_{10}Br_2N_2O_2S$	-	-	6.71 (6.69)
3c	194	50	$C_{14}H_{10}BrF_3N_2O_2S$	-	-	6.84 (6.87)
3d	203	32	$C_{14}H_{13}BrN_2O_3S$	-	-	7.57 (7.58)
4a	165	50	$C_{14}H_{10}BrClN_2O_3S$	-	-	6.99 (6.97)
4b	198	45	$C_{14}H_{10}Br_2N_2O_3S$	-	-	6.23 (6.27)
4c	202	54	$C_{15}H_{10}BrF_3N_2O_3S$	-	-	6.40 (6.43)
4d	174	40	$C_{15}H_{13}BrN_2O_4S$	-	-	7.01 (7.05)
5a	180	52	$C_{13}H_9BrClNS$	47.95 (47.77)	2.74 (2.75)	4.29 (4.28)
5b	170	47	$C_{13}H_9Br_2NS$	42.29 (42.04)	2.43 (2.42)	3.76 (3.77)
5c	130	54	$C_{14}H_9BrF_3NS$	46.94 (46.66)	2.49 (2.50)	3.89 (3.88)
5d	154	40	$C_{14}H_{12}BrNOS$	52.37 (52.17)	3.73 (3.72)	4.36 (4.34)
5e	200	55	$C_{14}H_8BrF_3N_2O_2S$	41.36 (41.48)	1.98 (1.97)	6.93 (6.91)

Preparation of 2-amino-5-bromo-3-methyl-2'-nitro-4'-substituted diphenylsulfides 3a-d

To a refluxing solution of 2-amino-5-bromo-3-methyl benzenethiols (1; ·0.01 mole) in ethanol (20 mole) and anhydrous sodium acetete (0.01 mole) in 5 ml of ethanol was added in 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 ice chamber. The solid seperated out was filtered, washed with 30% ethanol and crystalization from methanol afforded the desired product.

Preperation of 5-bromo-2-formamido-3-methyl-2'-nitro-4'-substituted diphenylsulfides 4a-d

A mixture of diphenylsulfide (3a-d; 0.01 mole) and 90% formic acid (20 ml) was refluxed for four hours. The contents were poured into a beaker containg crushed ice. The solid seperated out was filtered and washed with water untill the filterate was neutral and crystalized from benzene.

Preparation of 3-bromo-1-methyl phenothiazines 5a-d

To a refluxing solution of formyl derivatives (4a-d; 0.01 mole) 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. The contents were poured into beaker containing crushed ice. The solid seperated out was filtered, washed with cold water, finally with 30% ethanol and recrystallised from benzene.

Preparation of 9-nitrophenothiazines 5e

A mixture of 2,6-dinitro-4-trifluoromethyl chlorobenzene (2; 0.01 mole), 2-amino-5-bromo-3-methylbenzenethiol (1; 0.01 mole) sodium hydroxide (0.01 mole) and absolute ethyl alcohol (20 ml) was refluxed for two hours. The reaction mixture was concentrated on water bath, cooled and filtered. The precipitate was washed well with hot water and finally with 20% ethanol and crystallized from acetone.

References

1. R.R. Gupta (Ed.), "Phenothiazines and 1,4-Benzothiazines- Chemical and Biomedical Aspects", Elsevier, Amsterdam (1988).
2. H. Keyzer, G.M. Eckert, I.S. Forrest, R.R. Gupta, F. Gutmann, J. Molnar (Eds.), "Thiazines and Structurally Related Compounds" (Proceedings of the Sixth International Conference on Phenothiazines and Structurally Related Psychotropic Compounds, Pasadena, California, Septembar 11-14, 1990), Krieger Publishing Company, Malabar, Florida (1992).
3. N. Motohashi, Anticancer Res., 11, 1125 (1991).
4. A. Andreani, M. Rambaldi, A. Locatelli, P. Aresca, R. Bossa and I. Galatulas, Eur., J. Med. Chem., **26**, 113 (1991).
5. R.S. Rathore, M. Jain and V. Saraswat, V. Gupta and R.R. Gupta, Pharmazie, **47**, 1945 (1992).
6. R.R. Gupta, M. Jain, R.S. Rathore and A. Gupta, J. Fluor. Chem., **62**, 191 (1993).
7. M. Jain, S. Kumar, V. Saraswat and R.R. Gupta, Pharmazie, **49(9),** 689 (1994).
8. R. Gupta, V. Gupta, N. Sharma, M.Y. Hamadi, P.S. Verma and R.R. Gupta, Heterocycl. Commun. **5** 263 (1999).

Received on June 18, 2000