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

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Abstract 3-Bromo-1-methyl phenothiazines have been 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 7- bromo - 9- methyl nitro phenothiazine as Smiles rearrangement occurs in situ.

Introduction

Phenothiazines possess a wide spectrum of pharmacological and biological activites[1,2]. Recently some substituted phenothiazines have shown significant anticancer activities[3,4]. 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[5-8] to made them available for biological screening in search of better medicinal agents.

Experimental

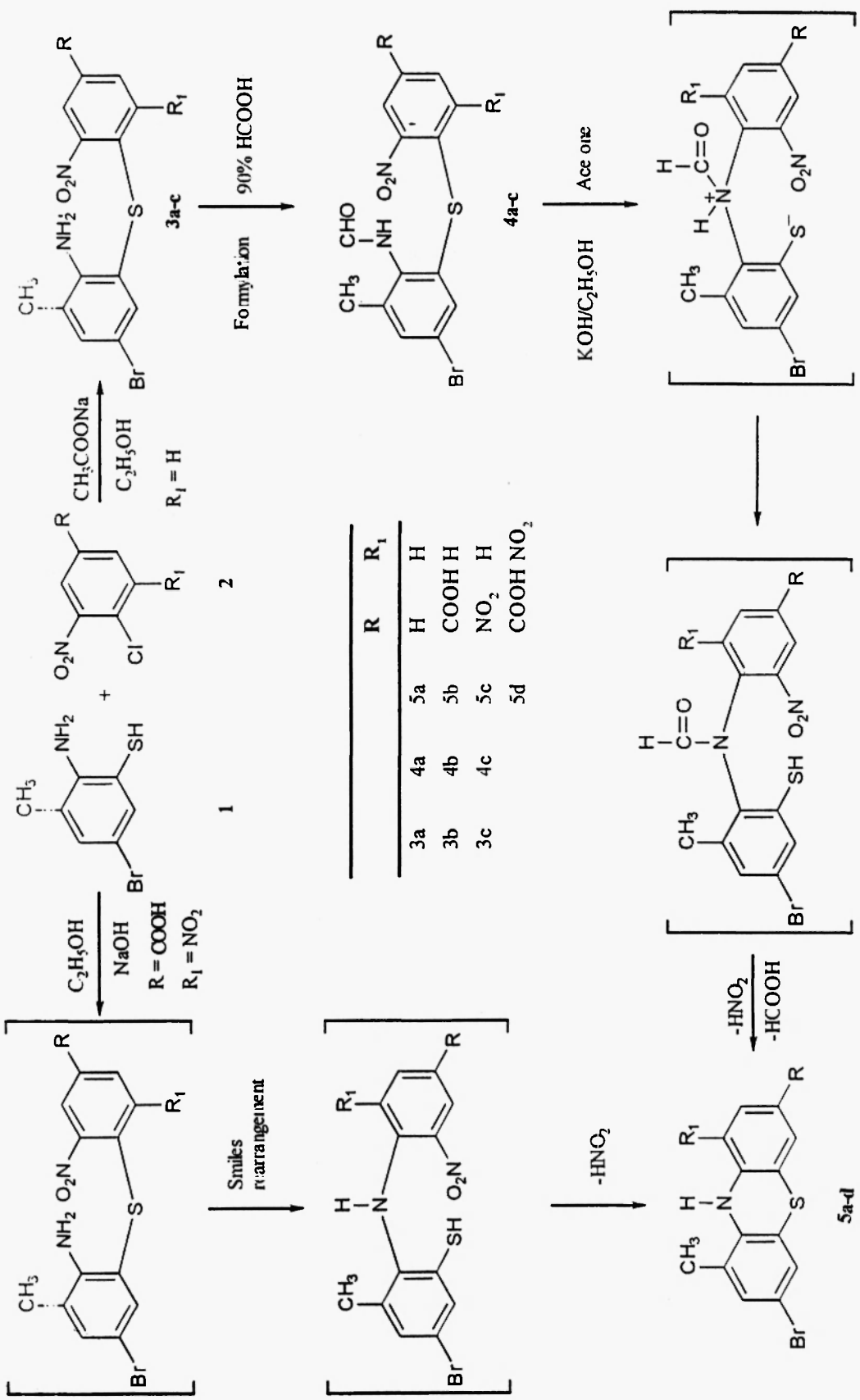
All the melting points are uncorrected. The purity was checked by thin layer chromatography and characterized by spectral studies. The infrared spectra were recorded on Nicolet-Magna FT IR spectrophotometer model 550 in KBr discs. The ^{1}H NMR spectral have been recorded on 90 MHz on Jeol FX 90Q FT 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.

(a) Preparation of 2-amino-5-bromo-3-methyl-2'-nitro-4'-substituted diphenylsulfides 3a-c

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. (Scheme - 1)

(b) Preperation of 5-bromo-2-formamido-3-methyl-2'-nitro-4'-substituted diphenylsulfides 4a-c

A mixture of diphenylsulfide (3a-c; 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. (Scheme -1)



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

Scheme-1

Table - 1 : Analytical, IR and NMR spectral data of substituted Phenothiazine.

Compd.	Molecular Formula	M. Pt.	IR spectral data in cm -1	PMR data in δ ppm
5a	$C_{13}H_{10}Br\ NS$	84	3440 (N-H Str.) 1440, 1320 (C-H def. of CH_3) 750 (C-Br. Str.)	8.24 (S,1H,NH), 7.60-6.29 (m, 6H, ArH), 1.90 (S,3H,CH_3)
5b	$C_{14}H_{10}Br\ NO_2S$	69	3460 (N-H Str.) 1430, 1340 (C-H def. of CH_3) 700 (C-Br. Str.)	7.90 (S, 1H, NH), 7.32-7.13 (m, 5H, ArH), 9.87 (S, 1H, COOH), 1.50, (S,3H, CH_3).
5c	$C_{13}H_9BrN_2O_2S$	76	3445 (N-H Str.) 1550, 1340 (NO_2) 1410, 1310 (C-H def. of CH_3) 740 (C-Br.)	8.83 (S, 1H, NH), 8.50-6.76 (m, 5H, ArH), 2.30 (S, 3H, CH_3).
5d	$C_{14}H_9Br\ N_2O_4S$	198	3360 (N-H) 1545, 1350 (NO_2) 1610 (C=O) 1440, 1300 (C-H def. of CH_3) 800 (C-Br.)	9.76 (S, 1H, NH), 7.69-6.88 (m, 4H, ArH), 9.85 (S, 1H, COOH), 2.07 (S, 3H, CH_3)

(c) Preparation of 3-bromo-1-methyl phenothiazines 5a-c

To a refluxing solution of formyl derivatives (4a-c; 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. (Scheme - 1). The analytical, IR and PMR data of synthesized compound (5a-c) are recorded in Table - 1.

Preparation of 7- bromo - 3 - carboxylic - 9-nitrophenothiazines 5d

A mixture of 3,5 -dinitro-4-chlorobenzoic acid (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. The analytical, IR, NMR data is included in Table - 1.

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).

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