SYNTHESIS OF 3-TRIFLUOROMETHYL-7-ALKOXY-9-NITROPHENOTHIAZINES VIA SMILES REARRANGEMENT

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Abstract : Synthesis of title compounds by Smiles rearrangement has been reported. 3-Trifluoromethyl-7-alkoxy-9-nitrophenothiazines have been prepared by Smiles rearrangement of 5-alkoxy-3-nitro-2-formamido-2-nitro-4-trifluoromethyldiphenyl sulfides. The later were obtained by the formylation of diphenyl sulfides which were prepared by the condensation of 5-alkoxy-3-nitro-2-aminobenzenethiol with 4-chloro-3-nitro-trifluoromethylbenzene.

Introduction

Phenothiazines possessess a wide spectrum of biological activities and its several derivatives are in clinical use (1-5). A slight variation in nucleur substitution causes a marked difference in the biological activities and therefore it has been considered worthwhite to synthesize title compounds.

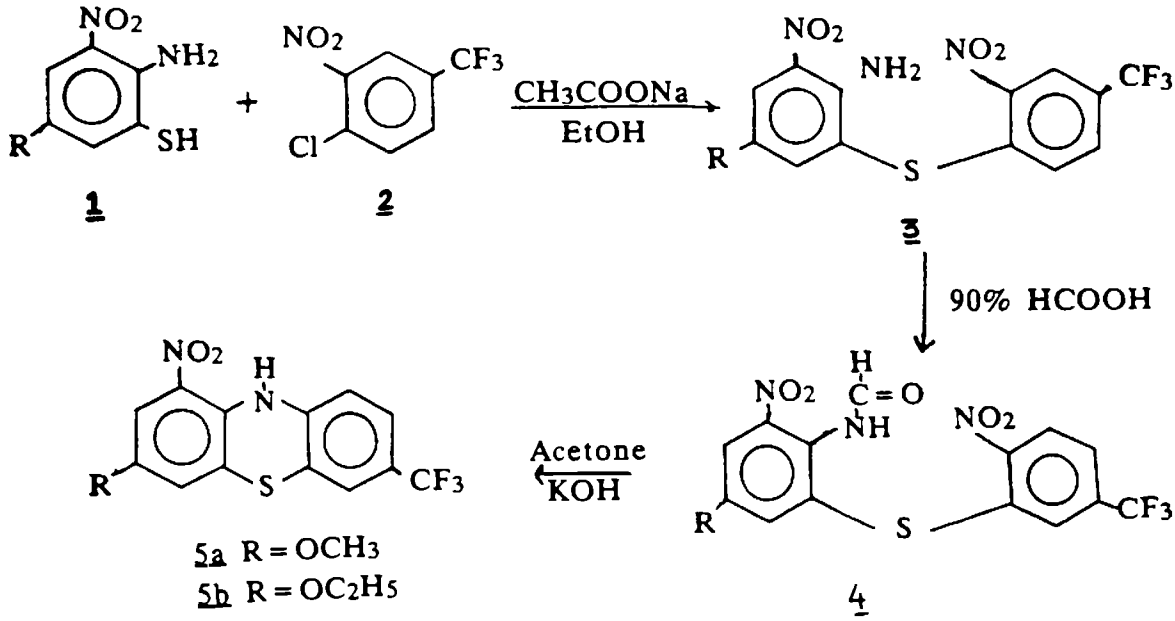
Result and Discussions

5-Alkoxy-3-nitro-2-aminobenzenethiol 1 required in the synthesis of title compounds has been prepared adopting the method reported earlier (6).

3-Trifluoromethyl-7-alkoxy-9-nitrophenothiazines 5a-b have been prepared by Smiles rearrangement of 5-alkoxy-3-nitro-2-formamido-2-nitro-4-trifluoromethyldiphenyl sulfides 4 in alcoholic potassium hydroxide solution. The formyl derivatives were prepared by the formylation of resultant diphenyl sulfides 3 obtained by the condensation of 5-alkoxy-3-nitro-2-aminobenzenethiol 1 with 4-chloro-3-nitrotrifluoromethylbenzene 2 in ethanolic sodium acetate solution (Scheme 1).

Experimental

All the melting points are uncorrected. The purity of the synthesized phenothiazines has been checked by TLC and characterized by elemental analyses and spectral studies (IR and Mass).



Scheme 1

Preparation of 2-amino-5-alkoxy-3-nitro-2-nitro-4-trifluoromethyldiphenyl sulfides 3a-b

To a refluxing solution of 2-amino-5-alkoxy-3-nitrobenzenethiol (1; 0.01 mol) in ethanol (20 ml) and anhydrous sodium acetate (0.01 mol in 5 ml alcohol) was added an alcoholic solution of 4-chloro-3-nitrotrifluoromethylbenzene (2; 0.01 mol) in ethanol (10 ml) and refluxed for 4 hours. The reaction mixture was concentrated and cooled overnight in an ice chamber. The solid separated was filtered and washed with 30 % ethanol and crystallization from methanol afforded the desired product. The physical data are summarized in Table 1.

Table 1 : Physical data of compound 3-5

Compd.	R	M.P. (°C)	Yield (%)	Molecular Formula	% Found / Cald. C	H	N
3a	OCH_3	148	60	$C_{14}H_{10}F_3N_3O_5S$	43.32 43.18	2.56 2.57	10.74 10.79
3b	OC_2H_5	155	72	$C_{15}H_{12}F_3N_3O_5S$	44.38 44.66	2.98 2.97	10.41 10.42
4a	OCH_3	157	68	$C_{15}H_{10}F_3N_3O_6S$	42.92 43.16	2.39 2.39	10.09 10.07
4b	OC_2H_5	171	75	$C_{16}H_{12}F_3N_3O_6S$	44.29 44.54	2.77 2.78	9.78 9.74
5a	OCH_3	184	69	$C_{14}H_9F_3N_2O_3S$	48.93 49.12	2.62 2.63	8.16 8.18
5b	OC_2H_5	165	74	$C_{15}H_{11}F_3N_2O_3S$	50.32 50.56	3.07 3.08	7.82 7.86

Preparation of 5-alkoxy-3-nitro-2-formamido-2-nitro-4-trifluoromethyldiphenyl sulfides 4a-b

The diphenyl sulfide (3; 0.01 mol) in 90 % formic acid (15 ml) was refluxed for 3 hours, poured into crushed ice, and the separated solid was filtered, washed with cold water till the filterate was neutral and crystallized from benzene. The physical data are summarized in Table 1.

Preparalion of 3-trifluoromethyl-7-alkoxy-9-nitrophenothiazines 5a-b

To a refluxing solution of formyl derivatives (4; 0.01 mol) in acetone (5 ml) was added an alcoholic solution of potassium hydroxide (0.2 gm in 5 ml of ethanol). The colour of the solution darkened immediately on addition of the alkaline alcoholic solution. The contents were heated for half an hour. To this solution a second lot of potassium hydroxide (0.2 gm in 5 ml of ethanol) was added and refluxing was continued for two hours and the contents were cooled down and poured into a beaker containing crushed ice. The solid separated out was filtered, washed with cold water and finally with 30% ethanol. Crystallization from methanol/benzene afforded desired phenothiazine. The physical data are summarized in Table 1.

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