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RESEARCH ARTICLE

PHARMACEUTICAL ANALYSIS

SYNTHESIS OF SOME NEW HETEROCYCLIC COMPOUNDS

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ABSTRACT

Synthesis of substituted heterocyclic compounds has been done by smiles rearrangement by substituted 2-amino-2'-nitrodiphenylsulphides.The later are produced by the formylation of substituted 2-amino-2'-nitrodiphenylsulphides, which are prepared by the condensation of 2-aminobenzenethiols with substituted o-halonitrobenzenes.

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KEYWORDS

Phenothiazines / Smiles Rearrangement / Formylation / Benzenethiol / o-halonitrobenzene.

INTRODUCTION

Heterocyclic compounds, specially phenothiazines are well known for biological and pharmacological activitites and their several derivatives are in clinical use[1], such as neuroleptics[2], diuretics[3], sedatives[4], antihistamines[5], analgesics[6] etc. A slight change in substitution of phenothiazines causes a marked difference in pharmacological and biological activities. Now a day a great interest has arisen to synthesize phenothiazines to screen anticancer activities[7-8]. In this paper, we have reported the synthesis of some new substituted phenothiazines.

MATERIALS AND METHOD

The purity of all the synthesized compounds has been checked by thin layer chromatography using silica gel G with different non aqueous solvent systems. The infrared spectra were recorded on Nicolet – Magna FTIR spectrophotometer model 550 in KBr discs. The ^{1}HNMR spectra have been recorded on 90 MHz Jeol FX90QFT 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 100µA ionization current. The melting points were determined by using capillary method and are uncorrected.

Procedure for the preparation of substituted heterocyclic compounds

Step 1: Synthesis of substituted 2- amino- 2'-nitrodiphenyl sulfides (III);

2-Amino-3-chloro-6-trifluoromethyl benzenethiols (I, 0.01mole) was taken in 50 ml round bottom flask and dissolved in ethanol (20ml) and o-halonitrobenzene (II, 0.01mole) then ethanol (10ml) was added. The reaction mixture was refluxed for 4-5hours, concentrated and cooled in an ice chamber overnight. The solid separated out was filtered and washed with 30% ethanol, crystallization from methanol afforded the desired compounds (scheme 1).

Step 2; Synthesis of substituted 2-formamido-2'-nitrodiphenyl sulfides (IV);

A mixture of diphenyl sulfides (III, 0.01) and 90 % formic acid (20 ml) was refluxed for 4 hours. The contents were poured into a beaker containing crushed ice. The solid was separated, filtered and washed with water until the filtrate was neutral and then crystallized with benzene.

Step 3; Preparation of substituted 10H-phenothiazines;

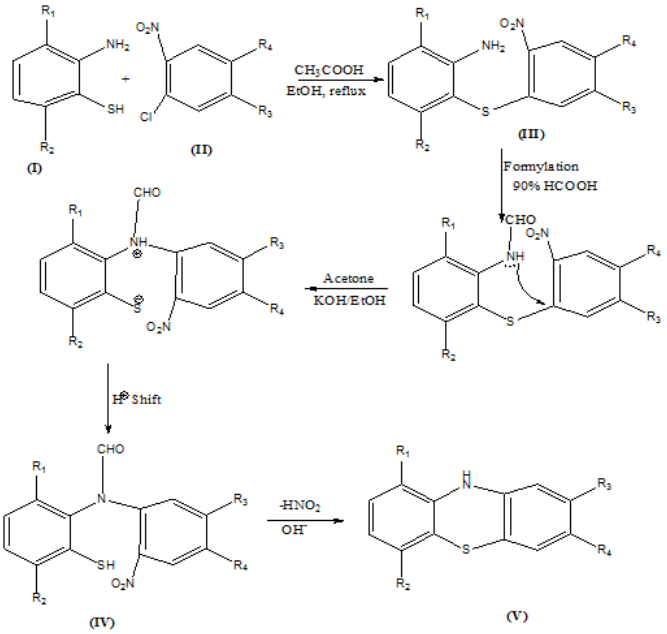
To refluxing solution of formyl derivatives (IV, 0.01 mole) in acetone (15 ml) , an ethanolic solution of potassium hydroxide (0.2 gm in 5 ml ethanol) was added. The contents were heated for half an hour. To this refluxing solution a second lot of potassium hydroxide (0.2 gm in 5ml ethanol) was added and refluxed for 2 hours. The contents were poured into a beaker containing crushed ice. The solid was separated filtered and washed with cold water, finally with 30% ethanol and recrystallized from benzene/methanol.

RESULT AND DISCUSSION

6-trifluoromethyl-3-chloro-2-formamido-2'-nitrodiphenyl sulfides (IV_{a-b}) obtained by the formylation of 2-amino-3-chloro-6-trifluoromethyl-

2'-nitrodiphenyl sulfides(III_{a-b}) undergo smiles rearrangement in alcoholic potassium hydroxide solution yielding substituted 7-chloro-10-trifluoromethyl phenothiazines (IV_{a-b}). 2-amino-3-chloro-6-trifluoromethylbenzinethiols (I) prepared by the hydrolytic cleavage of 2-amino-6-trifluoromethyl-3-chloro benzenethiols adopting the method reported elsewhere[9] with o-halo nitrobenzenes (II) in ethanolic sodium acetate solution. Physical data of synthesized compounds are listed in table1.The melting points reported there in are uncorrected values.

Phenothiazine exhibits sharp peak in the region 3460-3420 cm^{-1} due to N-H stretching vibration in IR spectra. Besides it, due to C-Cl stretching vibration observed at 795-790 cm^{-1}. Two bands are observed in the region 1330-1320 cm^{-1} and 1140-1110 cm^{-1} due to asymmetric and symmetric stretching vibrations of C-F in CF_3 group. The IR data of synthesized compounds are given in table 2. The ^{1}HNMR spectra of all the synthesized phenothiazines (V_{a-b}) (see table 3) exhibits a singlet at δ 8.55-8.52 ppm due to N-H proton. A multiplet exhibits in the region δ7.86- 7-84 ppm due to aromatic protons.



Scheme 1

Where,
R_1 = Cl
R_2 =CF_3
R_3 = H, F
R_4 =H, Cl,

Synthesized phenothiazines are:

1. **1,7-Dichloro-4-trifluoromethyl-10H-phenothiazine**
2. **1-Chloro-8-fluorotrifluoromethyl-10H-phenothiazine**

Table 1
Physical data of the synthesized phenothiazine compounds

Compounds	M.P. ^{0}C	Yield %	Molecular formula	Mol. Weight	% N found (Calc.)
III $_a$	58	45	$C_{13}H_7Cl_2F_3N_2O_2S$	383	7.30 (7.31)
III $_b$	45	57	$C_{13}H_7ClF_4N_2O_2S$	366.50	7.65 (7.63)
IV $_a$	102	45	$C_{14}H_7Cl_2F_3N_2O_3S$	411	6.80 (6.81)
IV $_b$	65	52	$C_{14}H_7ClF_4N_2O_3S$	394.50	7.10 (7.09)
V $_a$	320	45	$C_{13}H_6Cl_2F_3NS$	336	4.14 (4.16)
V $_b$	195	47	$C_{13}H_6ClF_4NS$	319.50	4.40 (4.38)

Table 2
***Infrared spectral data of synthesized phenothiazine compounds*:**

Compounds	NH_2	NH	NO_2	C=O	C-F	C-Cl
III $_a$	3460 3350	-	1570 1360	-	1320 1110	720
III $_b$	3400 3320	-	1560 1370	-	1310 1120	715
IV$_a$	-	3350	1580 1350	1705	1340 1110	740
IV $_b$	-	3320	1570 1380	1680	1350 1100	730
V $_a$	-	3340	-	-	1330 1140	790
V$_b$	-	3350	-	-	1320 1110	795

Table 3
[1]HNMR spectral data of substituted phenothiazines (δ in ppm)

Compounds	δ ppm	No. of Hydrogen	Multiplet	Assignment
V_a	8.55	1	Singlet	N-H Proton
	7.58-6.85	5	Maltiplet	Aromatic Protons
V_b	8.53	1	Singlet	N-H proton
	7.85-6.90	5	Maltiplet	Aromatic Protons

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