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Synthesis of chloro pyrazolone derivatives and their biological activities

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ABSTRACT

3-Methyl-5-chloro-1-phenylpyrazol and its derivatives were prepared by the reaction with 3-methyl -1-phenylpyrazol-5-one, phosphorous oxytrichloride and N-N dimethyl aniline respectively using catalyst. These compounds were further treated with alcohols and sodium hydroxide to form ether linkage. Ethyl acetoacetate reacted with phenylhydrazine at reflux temprature to give 3-methyl-1-phenylpyrazol-5-one crude and recrystlized from diluted ethanol to give pure 3-methyl-1-phenylpyrazol-5-one. Different pyrazolone derivatives were prepared by using different phenylhydrazine derivatives. These derivatives converted in to chloro and ethereal derivatives. The structure of the compounds was also elucidated. The synthesized compounds were found to have significant effect against the tested microorganisms.

Key words : chloro pyrazolone , antibacterial, antifungal.

INTRODUCTION

An intensive literature survey including the methods of synthesis for various pyrazolone derivatives has been carried out, as the derivatives of pyrazolone have been of interest to medicinal chemists for their wide range of biological activity[1]. Here pyrazolone derivatives of 5- chloro and 5-methoxy and other ethereal pyrazolone derivatives were synthesized by the Vogel A I. A textbook of practical organic chemistry, 4th edn.[11]. The presence of C=O group is of great importance, considering the fact that it can be transformed into chloro compounds[2-9]. The availability of the present and significant biological properties of the members known so far prompted to extend moieties like ether linkage derivatives. In this context, the synthesis of chloro of pyrazolone was carried out. The synthesis and IR characterization of some chloro derivatives from 3-Methyl-1-R pyrazol-5-one have been reported. Applications of this includ some chloro synthesized from 3-methyl-1-R pyrazol-5-one[10]. However , pyrazolone chloro derivatives were not reported so far, hence the present study is devoted to synthesize some pyrazolone chloro derivatives and to explore their possible biological activities.

EXPERIMENTAL

Melting points were determined by open capillary tube in paraffin melting point bath and therefore the values reported are uncorrected .The purity of the compounds was checked by TLC was run on silica gel 60 F_{254} aluminium sheet using chloroform, ethyl acetate , hexane, toluene , methanol, as developing solvent . IR spectra were recorded on Shimadzu 1700.The IR spectra of the compounds were recorded in the region, 4000 - 400 cm^{-1} using Shimadzu FTIR 840 OS.

A-1 Preparation of 3-Methyl-5-chloro-1-phenylpyrazol

Mixture of 3-methyl-1-phenylpyrazol-5-one(one mole), phosphorous oxytrichloride (2 mole)and N-N di methyl aniline (1 mole) used as catalyst was heated at 125°c to 130°c till the reaction completed, to check the progress TLC was checked every two hours. After the completion, reaction mixture was cooled to room temperature gradually then dumps in to ice, solid not obtained. Chloroform was added in it for extraction and organic layer separated. This organic layer washed with saturated sodium bi carbonate solution till neutral pH obtained of the product. From this organic layer chloroform was distilled out and liquid product obtained.

A-9 Preparation of 3-methyl-5-chloro-1-(4 tolyl)-phenylpyrazol

Mixture of 3-methyl-1(4-tolyl)phenyl-5-pyrazolone (one mole), phosphorous oxytrichloride (2 mole)and N-N di methyl aniline (1 mole) used as catalyst was heated at 125°c to 130°c till the reaction completed, to check the progress TLC was checked every two hours. After the completion, reaction mixture was cooled to room temperature gradually then dumps in to ice, solid not obtained. Chloroform was added in it for extraction and organic layer separated. This organic layer washed with saturated sodium bi carbonate solution till neutral pH obtained of the product. From this organic layer chloroform was distilled out and liquid product obtained.

A-11 Preparation of 3-methyl-5-methoxy-1-phenylpyrazol

Mixture of 3-methyl-5-chloro-1-phenylpyrazol (1 mole), NaOH flakes (1 mole), methanol used as reactant and as solvent. This mixture heated up to reflux till the reaction completed, to check the progress TLC was checked every two hours. After the completion, reaction mixture dump into water than extracted with chloroform then the layer separated. This chloroform layer evaporated to and liquid ethereal product was obtained.

A-12 Preparation of 3-methyl-5-ethoxy-1-phenylpyrazol

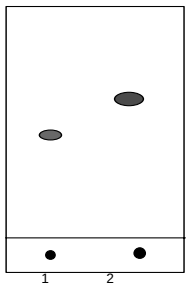
Mixture of 3-methyl-5-chloro-1-phenylpyrazol (1 mole), NaOH flakes(1 mole), ethanol use as reactant and as solvent. This mixture heated up to reflux till the reaction completed, to check the progress TLC was checked every two hours. After the completion, reaction mixture dump into water than extracted with chloroform then the layer separated. This chloroform layer evaporated to and liquid ethereal product was obtained

Preparation of antibacterial and antifungal activity

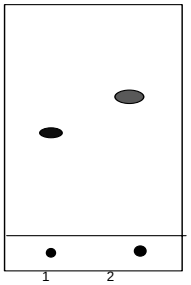
In the agar diffusion method different concentrations are incorporated in to an agar medium. A replicator device may be used to inoculate multiple specimens on to a series of plates with varying concentration of antibiotic. In current study, the antimicrobial activity was carried out by the agar diffussion method. Here responses of organism to the synthesized compounds were measured and compared with the response of the standard reference drug. The standard reference drugs used in the present work were Ampicillin (antibacterial) and Amphoterecin-B (antifungal). The plates were incubated at room temperature for 1

TLC observations:

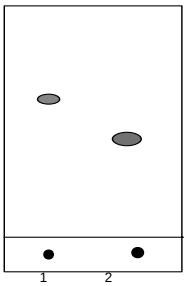
A-1



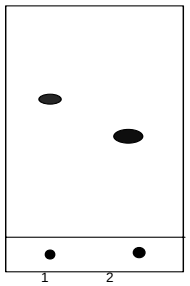
No:- 1 Starting material
No:- 2 Reaction mass



No:- 1 Starting material
No:- 2 Reaction mass



No:- 1 Starting material
No:- 2 Reaction mass



No:- 1 Starting material
No:- 2 Reaction mass

hour and then in bacteriological incubators at 37°c for 24 hrs for bacterial and in BOD incubator at 22°c for 24 to 48 hours for fungal, after addition of drugs in the well, which was prepared by sterile cork borer. After incubation the zones were measured with the help of digital zone reader and were compared with standard drugs.

RESULTS AND DISCUSSION

Spectral studies

IR spectra

The characterization absorption peaks were observed for all relevant groups. The absorption peaks around 721 cm^{-1} indicated the formation of chloro, aromatic methyl indicated at 1377 cm^{-1}, methylene indicated at 1462 cm^{-1}, aromatic alkenes indicated at 1530 cm^{-1}.

Antibacterial screening

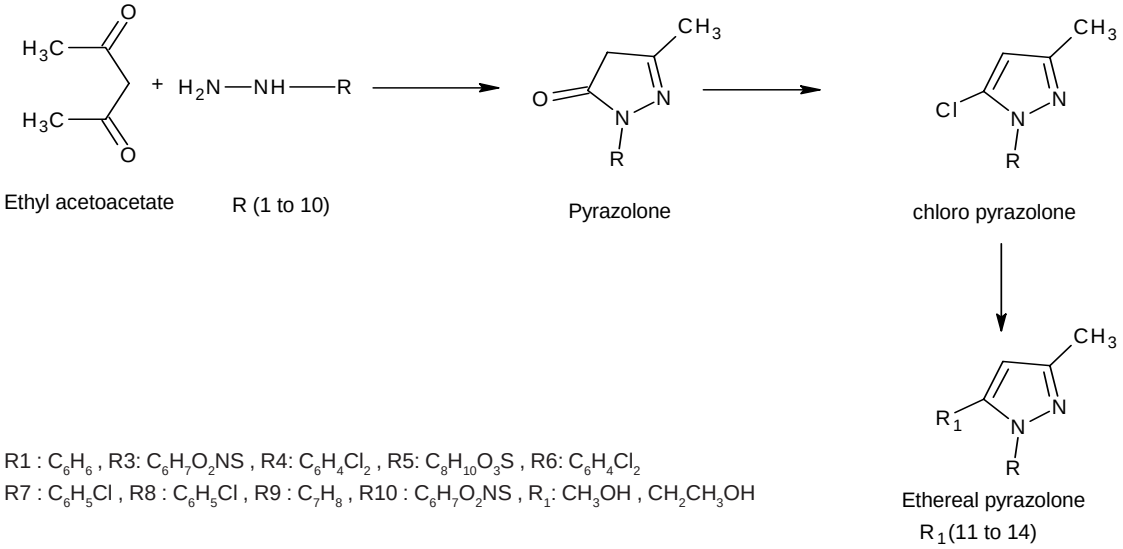
All synthesized compound were evaluated for in vitro antibacterial activity against four pathogenic bacterial by standard agar diffusion method. The zone of inhibition was determined using Ampicillin as reference standard. All chloro pyrazolone derivatives showed significant antibacterial activity against tested pathogens. However none of the synthesized compounds were

Table 1: Physical data of the synthesised compound

S. No.	Compound Code	Time Hr's	% Yield	Mol Formula	% Calculated M.Wt	C	H	N	CL
1	A1	4	93	$C_{10}H_9N_2CL$	192.5	62.33	4.67	14.54	18.44
2	A2	4	92	$C_4H_5N_2CL$	116.5	41.2	4.29	24.03	30.47
3	A3	4	91	$C_{10}H_{10}O_2N_3CLS$	271.5	44.19	3.68	15.46	13.07
4	A4	4	92	$C_{10}H_7N_2CL_3$	261.5	45.88	3.82	10.7	40.72
5	A5	4	93	$C_{12}H_{13}O_3N_2CLS$	300.5	39.93	4.32	9.31	11.81
6	A6	4	94	$C_{10}H_7N_2CL_3$	261.5	45.88	3.82	10.7	40.72
7	A7	4	96	$C_{10}H_8N_2CL_3$	227	52.86	3.52	12.33	31.27
8	A8	4	93	$C_{10}H_8N_2CL_3$	227	52.86	3.52	12.33	31.27
9	A9	4	92	$C_{11}H_{11}N_2CL$	206.5	63.92	5.32	13.55	17.19
10	A10	4	92	$C_{10}H_{10}O_2N_3CLS$	271.5	44.19	3.68	15.48	13.07
11	A11	4	65	$C_{11}H_{12}ON_2$	188	70.12	6.38	14.89	
12	A12	4	62	$C_{12}H_{14}ON_2$	202	71.12	6.93	13.86	
13	A13	4	68	$C_{12}H_{14}ON_2$	202	71.12	6.93	13.86	
14	A14	4	69	$C_{13}H_{16}ON_2$	216	72.22	7.4	12.96	

Tabel 2: Antimicrobial screeining-zone of inhibition (MM)

Microorganism (Bacteria)	A-1	A-9	A-11	A-12	A-13	A-14	Standard Ampicillin
S. aureus (mm)	-	15.0	-	12.0	10.0	11.5	19.2
B. pumillus (mm)	-	11.0	10.0	14.5	12.0	10.0	18.5
E-coli (mm)	-	14.0	11.0	11.5	12.0	12.0	17.3
Ps. Aeruginosa (mm)	-	-	-	17.0	-	-	13.7
Microorganism (fungal)	A-1	A-9	A-11	A-12	A-13	A-14	Standard Amphoterecin- B
C.albicans	-	-	-	-	-	-	16.1
S.cervisiae	-	14.0	-	-	-	17.5	15.4



Scheme 1.

superior to the standard Ampicillin. The compound A-1 was not active against tested pathogens.

Antifungal screening :- All synthesized compounds were evaluated for in vitro antifungal activity again two pathogenic fungi by standard agar diffusion method. The zone of inhibition was determined using Amphoterecin-B as reference standard. All pyrazolone derivatives showed significant antibacterial activity against tested pathogens. All the compounds were not active against C.albicans.

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