PYRAZOLINE SYNTHESIS THROUGH A CHALCONE INTERMEDIATE

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RESEARCH ARTICLE

[1]**Md Hedaitullah***,[1]Walia Ramanpreet, [1]Iqbal Khalid, [1]Singh Balwan, [2]Hussain Asif

[1] HIMT College of Pharmacy, Knowledge Park 1, Greater Noida, U.P. India.

[2] Jamia Hamdard, Hamdard Nagar, New Delhi, India.

**Corresponding Author's E-mail: hedaitpharma@gmail.com*

ABSTRACT

Pyrazoline derivatives, being used as potential medicinal agents, possess many important pharmacological activities and therefore they are useful materials in drug research. A series of these derivatives HT- 1 to HT- 6 containing 5-4-(chlorophenyl)-1,3-diphenyl- 4,5-dihydro-1H-pyrazole derivatives were synthesized, structures were confirmed using melting point, IR, NMR and MS and evaluated for their antibacterial activity using disc diffusion method at concentration 2mg/ml. The reference used was Amikacin and mostly, all synthesized compounds exhibited a significant antibacterial activity against *Staphylococcus aureus* (MTCC No. 96) as Gram positive bacteria, *Staphylococcus epidermidis*(MTCC No. 435) as Gram positive and *Escherichia coli* (MTCC No. 739) as Gram negative bacteria. It was observed that HT-1 and HT-2 possess good antibacterial potential against *S. aureus*, HT- 5 against *S.epidermidis* and HT-1 and HT-4against *E. coli*.

Keywords: Pyrazoline, Disc diffusion method, Amikacin.

INTRODUCTION

Pyrazolines are important nitrogen containing five-membered heterocyclic compound whose derivatives possess many important pharmacological activities and therefore they are useful materials in drug research. Pyrazolines are used as antitumour(1), immunosuppressive (2), antibacterial (3) and antitubercular agents. (4) Some of the pyrazoline derivatives are reported to possess anti-inflammatory (5), anticancer (6), and antidiabetic (7) and antidepressant properties. (8) These compounds are also used as dyestuffs, analytical reagents and agrochemicals. (9) In this paper new series of pyrazoline derivatives were synthesized which possessed anti-bacterial activity.

Pyrazoline derivatives differ considerably in their properties from those of pyrazole which are feebly basic and forms salt with acids, owing to their much lower stability. Pyrazole is feebly basic and forms salts with inorganic acids. The imino hydrogen may be replaced by an acyl group. Pyrazole is very resistant to oxidation and reduction, but may be hydrogenated catalytically, first to pyrazoline and then to pyrazolidine (Figure 1)

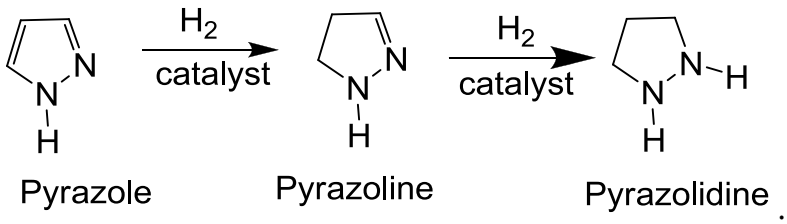


Figure 1: Pyrazole hydrogenated catalytically, to pyrazoline & then to pyrazolidine

Both of these compounds are stronger bases than pyrazole. The pyrazolines give the reactions of aliphatic derivatives, resembling unsaturated compounds in their behavior towards permanganate and nascent hydrogen. They resemble hydrazones in the manner in

which they are hydrolyzed by mineral acids, which on decomposition forms gaseous nitrogen and nitrogen-free substances. Pyrazoline and its homologues are weak bases. In general they only dissolve in concentrated acids, forming unstable salts which dissociate on the addition of water. The parent substance, pyrazoline, an oil of boiling point 114^{o}C, is the most stable of all these compounds.

Pyrazoline are the three partially reduced forms of the pyrazole structure with different positions of the double bonds and exists in equilibrium with one another (Figure-2). 2-pyrazoline exhibits the monoimino character and hence more stable than the rest even though all the three types have been synthesized.

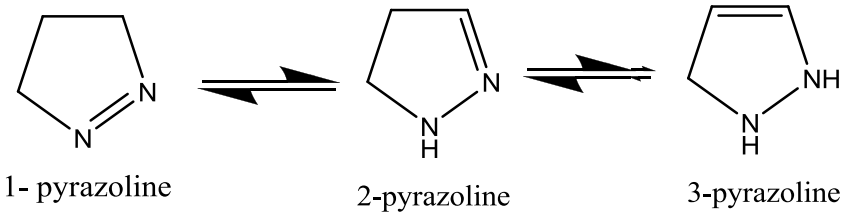


Figure 2: All the three partially reduced forms of pyrazoline

Aldol condensation between acetophenone and substituted benzaldehyde yields chaconne derivative, a condensation product. These chalcone derivatives were reacted with phenyl hydrazine to form 5-4-(chlorophenyl)-1,3-diphenyl- 4,5-dihydro-1H-pyrazole derivatives. The characterization of various synthesized compounds was done by TLC, melting point, IR, NMR & MS.

EXPERIMENTAL

Materials & Method

Materials used in synthesis of compounds HT1 - HT 6 includes benzaldehyde, p-methoxy benzaldehyde, p-chloro benzaldehyde, p-hydroxy benzaldehyde, p- bromo benzaldehyde, p-nitro benzaldehyde , acetophenone, potassium hydroxide pellets, phenyl hydrazine, glacial acetic acid, sulphuric acid and ethanol.

Synthesis

General procedure for synthesis of chalcone [H-1 and H-6]

Trituration was done on adding potassium hydroxide pellets (0.094mol) to the mixture of acetophenone (0.094mol) and benzaldehyde (0.094mol) at room temperature for 1h. The solid product chalcone i.e. 1,3-diphenyl-2-propen-1-one (H-1) (Figure 3) obtained, was washed with water many times to remove excess of potassium hydroxide and then dried under UV light.

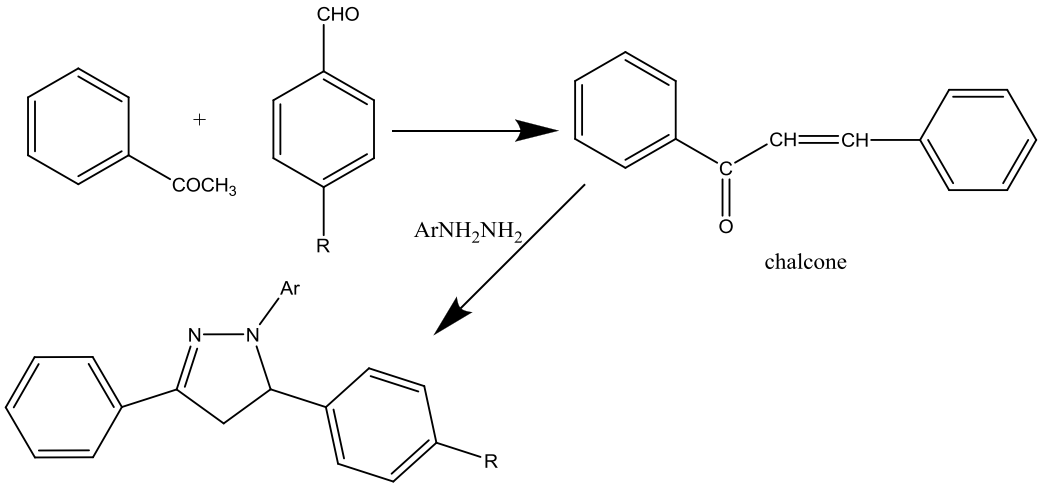


Figure 3: General procedure for synthesis of chalcone

Synthesis of H-2:- A mixture of acetophenone (0.072mol) and *p*-methoxy benzaldehyde (0.072mol) was triturated with potassium hydroxide pellets (0.072mol) at room temperature for 1hr. The solid product 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one i.e. methoxy substituted chalcone, the product was washed with water to remove excess of potassium hydroxide and then dried.

Synthesis of H-3 Potassium hydroxide pellets (0.071mol) were triturated by mixture of acetophenone (0.071mol) and *p*-chloro benzaldehyde (0.071mol) at room temperature for 1hr. The solid product which is a chloro substituted chalcone 3 -(4-chlorophenyl)-1-phenylprop-2-en-1-one synthesized was washed with water to remove excess of potassium hydroxide and then dried.

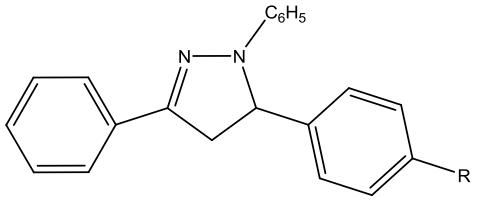
Synthesis of H-4 Potassium hydroxide pellets (0.065mol) were triturated on addition of mixture of acetophenone (0.065mol) and *p*-hydroxy benzaldehyde (0.065mol) at room temperature for 1hr. The solid product is a hydroxy substituted chalcone 3-(4-hydroxy phenyl)-1-phenylprop-2-en-1-one synthesized which was washed with water to remove excess of potassium hydroxide and then dried.

Synthesis of H-5 Potassium hydroxide pellets (0.11mol) were triturated was done on adding with the mixture of acetophenone (0.11mol) and *p*-bromo benzaldehyde (0.11mol) at room temperature for 1h. The product is Bromo substituted 3-(4-bromophenyl)-1-phenylprop-2-en-1-one synthesized was washed with water to remove excess of potassium hydroxide and then dried.

Synthesis of H-6 Potassium hydroxide pellets (0.046mol) were triturated on adding mixture of acetophenone (0.046mol) and *p*-nitro benzaldehyde (0.046mol) at room temperature for 1h. The product is nitro substituted 3-(4-nitrophenyl)-1-phenylprop-2-en-1-one synthesized was washed with water to remove excess of alkali and then dried.

General procedure for synthesis of Pyrazoline derivatives (HT-1 to HT-6) from Chalcone and its derivatives

To chalcone (0.01mol) derivatives (H-1 to H-6) 20ml of 1,4-dioxane and phenyl hydrazine (0.024mol) was added in separate round bottom flasks. To these mixtures 2-3 drops of sulphuric acid was added and the contents were allowed to reflux for 4h. Then 5ml glacial acetic acid was added to all the flasks and the mixtures were again refluxed for next 2h. On cooling to room temperature the contents were poured on crushed ice. As a result the solid products resulted in pyrazoline derivatives (HT-1-HT-6) which were benzaldehyde, methoxy, chloro, hydroxy, bromo and nitro derivatives respectively which were recrystallized using ethanol. The data of synthesized compounds mentioned in the table 1.



1,3,5-triphenyl-4,5-dihydro-1H-pyrazole

Table 1:Data of Synthesized compounds

R	Compound	Melting Point C°	% yield
H	HT-1	52-54	65
OCH_3	HT-2	55-57	42
Cl	HT-3	135-136	55
OH	HT-4	58-60	52
Br	HT-5	72-74	45
NO_2	HT-6	62-63	70

Antibacterial activity

The newly synthesized pyrazoline compounds were screened for antibacterial activity against *Staphylococcus aureus* (MTCC No. 96), *Escherichia coli* (MTCC No. 739) and *Staphylococcus epidermidis* (MTCC No.435) by disc diffusion method. (10,11) Discs measuring 10.0 mm in diameter were punched from Whatman no.1 filter paper. Discs were sterilized by dry heat at 50°C for 3 hrs. Each disc containing concentration (2mg/ml) were prepared using dimethylformamide (DMSO).

The discs of each compounds was placed individually on nutrient agar medium seeded with fresh bacteria respectively using Amikacin

as the positive control. The nutrient agar plates were incubated at 37°C for 30 min before the discs were applied aseptically. The treated plates were incubated at 37°C for 48h. Minimum Inhibitory Concentrations (MIC) were noted and compared with positive control Amikacin, the results of antibacterial studies are as mentioned in Table 2. The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition action.

Table 2: Microbiological results of Pyrazoline compounds

Compound	MIC (mg/ml)	% Inhibition		
		S.aureus	*E.coli*	*S.epidermidis*
HT-1	2	59	55	50
HT-2	2	62	--	43
HT-3	2	--	47	47
HT-4	2	45	53	44
HT-5	2	--	51	45
HT-6	2	50	51	57

(-) Indicates bacteria are resistant to the compounds at concentration 2mg/ml, MIC - minimum inhibitory concentration, i.e., lowest concentration to completely inhibit bacterial growth.

CONCLUSION

We have synthesized a series of 1,3,5-triphenyl-4,5-dihydro-1H-pyrazole derivatives. The synthesized compound HT-1 and HT-2 shows significant antibacterial activity against *S. aureus*, HT-1 and HT-4 against *E. coli* and HT-6 against *S. epidermidis.* Also HT-3 compound shows adequate activity against *E. coli* and *S. epidermidis.* Hence, it is concluded that there is ample scope for further study in developing these as good lead compounds.

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CONFLICT OF INTEREST

Author declares that there are no conflicts of interest.

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