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An Efficient One Pot Synthesis and Biological Screening of Some Pyrazole Based Heterocycles

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Abstract

Present work deals with the preparation of some Pyrazole derivative salts which was prepared by using different kinds of aldehydes and hydrazine derivatives by using alkoxide as a base and using the 1,3- dicarbonyl compound like ethyl acetoacetate at room temperature. The reaction mixture was stirred on magnetic stirrer for about 10 to 20 minutes till colour change is observed and then product is separated by using organic solvent. The product obtained was converted to sodium salt of Pyrazole derivative by base hydrolysis. The entire synthesized compound was tested for their antibacterial activity against the Gram-positive and Gram-negative strains of bacteria. The investigation of antibacterial screening data revealed that most of the tested compounds showed moderate to good antibacterial activity.

Keywords: Antibacterial; Hydrazine hydrate/Phenyl hydrazine hydrochloride; Alkoxide

Introduction

Pyrazole is amongst the most important privileged scaffolds found in synthetic and natural products of medicinal interest.Pyrazole containing molecules possess a wide range of biological activities such asantibacterial, antifungal, antiviral, anticancer, antidiabetic, anti-inflammatory, etc.Considering the valuable potential of pyrazoles, numerous synthetic methods were developed over the past decades.There are two classical methods for the synthesis of pyrazoles first is 1,3-dipolar cycloaddition reaction of diazo-compounds with alkynes and second one condensation reaction of 1,3-dicarbonyls with hydrazine's. Although these methods provide pyrazoles in acceptable yields, they suffer from their own limitations such as the use of hazardous transition metals and limited substrate scope, poor regioselectivity and time consuming.Therefore Pyrazole synthesis was investigated extensively and several improved synthetic routes were developed [1-5]. In recent years one pot three component synthesis has been taken a greater importance as it synthesize the most important pyrazole and its different kinds of derivative in just a single step. In our experiment we have tried to decrease the reaction time required to complete the reaction for that purpose we had successfully driven our reaction, by Biginilli type of condensation in basic medium and those synthesized compounds were subjected to antibacterial activity to compare their potentials.

Materials and Methods

All the chemicals and solvents were obtained from E-Merck, and SD fine chemicals L.T.D. India (AR, LR grade) Melting points were determined in open capillaries in liquid paraffin bath and are uncorrected [6-10]. Purity of the compound was routinely checked on silica gel TLC plates using $CHCl_3$ as solvent. ^1H NMR spectra were recorded on Bruker AV, 200 MHz spectrometers in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts was shown in δ scale. Multiplicities of ^1H NMR signals are designated as s (singlet), d (doublet), dd (doublet of doublet), dt (doublet of triplet), t (triplet), quin (quintet), m (multiplet) etc. IR data were recorded an Alpha-T ATR-FTIR.

General procedure for preparation of pyrazole derivative

In present work we prepared pyrazole salt by using different kinds of aldehyde and hydrazine derivatives by using alkoxide as a base. In this one pot condensation 0.01mol of an aldehyde, (0.01) mol of hydrazine derivative and (0.01) mol of 1,3-dicarbonyl compound was taken in RB flask and reaction mix was stirred on magnetic stirrer for 10-15 min till color change is observed [11-15].

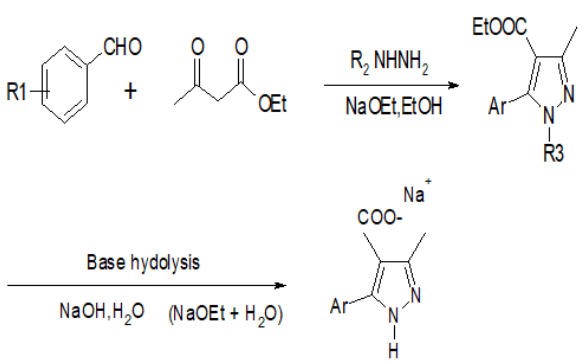

Figure 1: Scheme of the synthesis.

S. No.	R1	R2/ R3	Ar	Time (min.)	M.P. (°C)	Yield (%)
A*1	4-NO_2	H	4 - NO_2 Ph	1	154	75
2	3,4-OMe	H	3,4-O MePh	7	174	72
3	3-NO_2	H	3- NO_2 Ph	1	140	78
4	H	H	Ph	10	120	68
B*1	4-NO_2	Ph	4 - NO_2 Ph	15	170	63
2	3,4-OMe	Ph	3,4-O MePh	15	186	72
3	3-NO_2	Ph	3- NO_2 Ph	15	152	66
4	H	Ph	Ph	15	132	58

Table 1: Experimental data.

Then work up of the reaction is carried out and product separated by using organic solvent. Product was dried, yield, M.P. and spectral analysis was carried out. The Scheme of the synthesis was shown in Figure 1. Results were shown in Table 1 and respective image was shown in Figure 2.

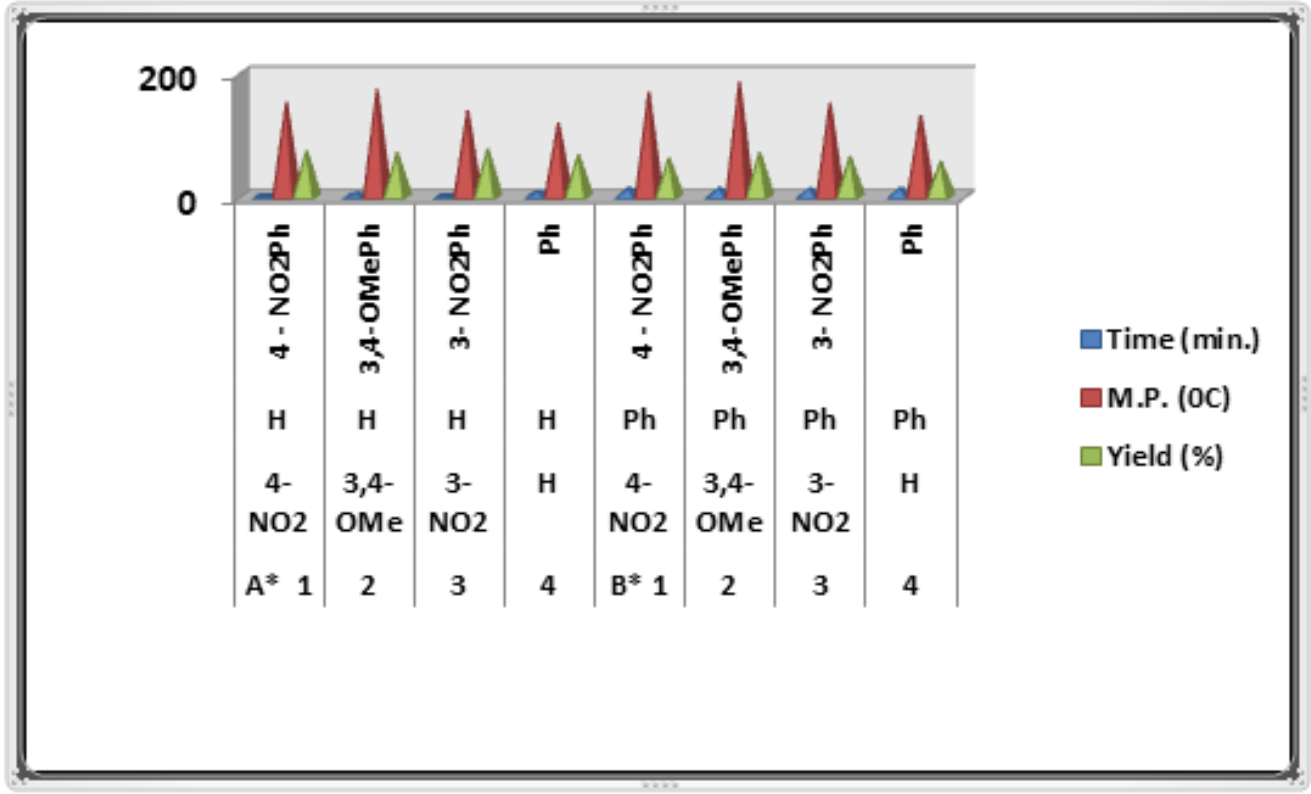

Figure 2: Graphical representation of results.

Antibacterial activity

The plates were inoculated by specific microorganism by spread plate technique; bores were made in the solidified agar plate by using a sterile borer [16-20]. The test solution of specified concentration was added in the bore by using sterile pipette and the plates were kept in freeze for 1hour for diffusion and then incubated at 37°C for 24 hours. After 24 hours the plates were examined and zone of inhibition were recorded. All the synthesized compounds were screened for antibacterial activity against both gram positive *S. aureus* and *Bascillus*

substilis and gram negative *E. coli* and *Proteus vulgaris* bacteria at a concentration of 100 µg/ml, 200 µg/ml, 400 µg/ml, 800 µg/ml [21-25]. Azithromycin is used as standard for comparison of anti-bacterial activity. In presence of base such as NaOH and ethanol was used as a solvent. The results of screening are given in Tables 2 and 3 and respective graphical representation was shown in Figures 3 and 4.

Compound	Zone of inhibition (mm)							
	Staphylococcus aureus				*Bacillus subtilis*			
	100 µg	200 µg	400 µg	800 µg	100 µg	200 µg	400 µg	800 µg
A* 1	10	12	13	17	12	14	15	17
2	10	12	12	15	12	15	15	17
3	7	8	11	15	8	10	12	15
4	10	12	13	15	09	11	13	16
B* 1	11	13	14	15	11	12	14	15
2	12	14	16	18	12	14	18	20
3	7	9	14	18	7	10	13	15
4	12	13	16	17	10	12	14	17
Azithromycin	13	14	17	19	15	17	18	21

Table 2: Zone of inhibition for gram positive bacteria graphical representation.

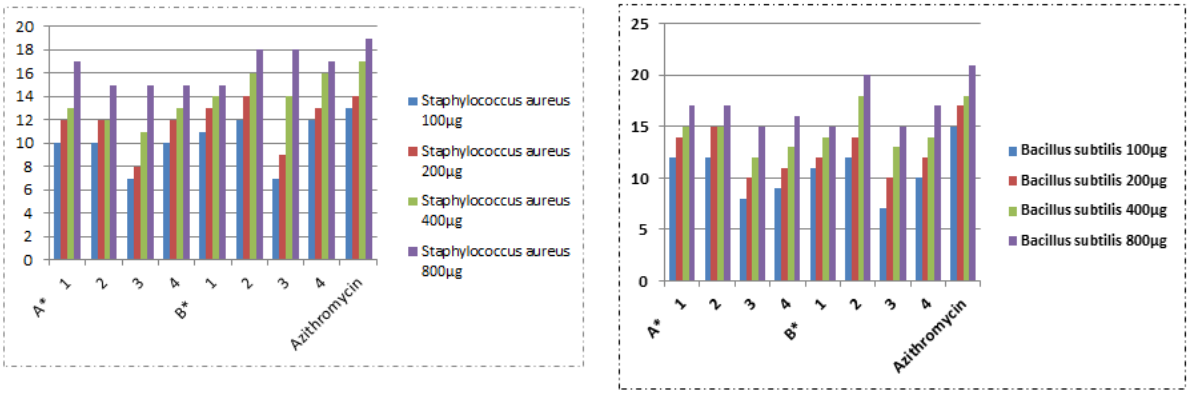

Figure 3: Graphical representation of results.

Compound	Zone of inhibition (mm)							
	Escherichia coli				*Proteus vulgaris*			
	100 µg	200 µg	400 µg	800 µg	100 µg	200 µg	400 µg	800 µg
A* 1	9	11	12	14	9	11	12	14
2	10	11	13	14	10	11	14	15
3	10	12	14	16	10	12	14	16
4	8	10	12	14	7	8	10	12
B* 1	9	11	12	15	8	10	12	12

2	9	11	13	15	11	12	13	14
3	11	12	14	15	9	11	14	15
4	8	10	11	13	8	8	11	12
Azithromycin	14	15	16	18	12	14	16	17

Table 3: Zone of inhibition for gram negative bacteria graphical representation.

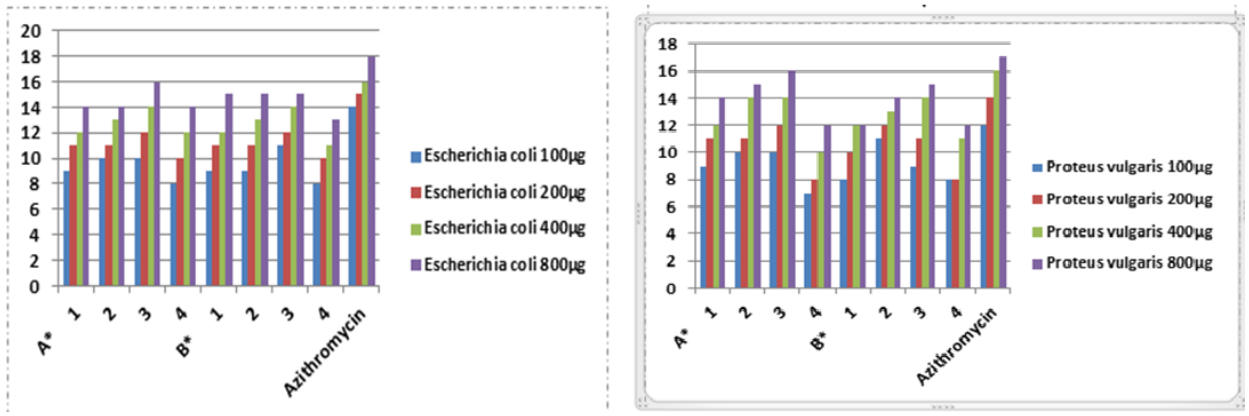

Figure 4: Graphical representation of results.

Amongst all synthesized compounds sodium 3- (3,4-dimethoxyphenyl) -5-methyl-1-phenyl-1H-pyrazole-4-carboxylate were found to be more potent as antibacterial *Staphylococcus aureus* and *Bacillus subtilis* agents. Whereas compound sodium 5-methyl-3-(3-nitrophenyl) -1H-pyrazole-4-carboxylate was more active against antibacterial *Escherichia coli* and *Proteus vulgaris as* antibacterial [26-30]. The zone of inhibition of synthesized compounds was compared with the standard drug Azithromycin at four different concentrations [31-36].

Spectral data

Spectral analysis of given Pyrazole can carried out by NMR spectra & IR spectroscopy:

- Yield 72% mp, 174°C.

IR (KBr) 3300-3500 cm^{-1} (Ar-N-H), 1680-1600 cm^{-1} (C=C), 1550 cm^{-1} (C=N), 1350-1000 cm^{-1}, (C-N), 1400 cm^{-1} (-COO– Na +), 900-690 cm^{-1} (Ar-CH3 out of plane) .

1H-NMR (DMSO) 8.61 δ (s, ^{1}H, Ar-NH), 3.98 δ (s, 3H, p-OCH_3), 3.94 δ (s, 3H, m-OCH_3), 6.91 δ (d, ^{1}H,Ar-H), 7.25 δ (dd,^{1}H,Ar-H), 7.24 δ (d, ^{1}H,Ar-H) .

- Yield 63% mp, 170°C.

IR (KBr) 1390-1300 cm^{-1} (p- NO2), 1500 cm^{-1} (C=N), 1600 cm^{-1} (C=C), 1400 cm-1 (-COO– Na +), 3000 cm^{-1} (=C-H) i.e., (sp2) (C-H), 900-690 cm^{-1} (Ar-CH3 out of plane).

1H-NMR (DMSO) 7.3 δ (m, 5H,Ar-H), 8.2 δ (d, 2equ.H ^{3}J = 7Hz, Ar-H), 7.7 δ (d, 2 equ.H ^{3}J = 7 Hz, Ar-H)

- Yield 68% mp, 120°C.

IR (KBr) 3300-3500 cm^{-1} (Ar-N-H), 1680-1600 cm^{-1} (C=C), 1550 cm^{-1} (C=N), 1300cm^{-1} (C-N), 1400 cm^{-1} (-COO– Na +), 900-690 cm^{-1} (Ar-CH3 out of plane)

1H-NMR (DMSO) 8.61 δ (s, ^{1}H, Ar-NH), 7.84 δ (s, 2H,Ar-H), 7.48 δ (s, 2H,Ar-H), 7.46 δ (s, ^{1}H,Ar-H)

- Yield 78% mp, 140°C.

IR (KBr) 3300-3500 cm^{-1} (Ar-N-H), 1500 cm^{-1} (C=N),1600 cm^{-1} (C=C), 1400 cm^{-1} (-COO– Na +), 1390-1300 cm^{-1} (m- NO2), 900-690 cm^{-1} (Ar-CH3 out of plane)

^{1}H-NMR (DMSO) 8.29 δ (s, ^{1}H, Ar-NH), 7.73 δ (td, ^{1}H,Ar-H), 8.19 δ (d, ^{1}H,Ar-H), 8.17δ (dd, ^{1}H,Ar-H), 7.59 δ (dd, ^{1}H,Ar-H)

Conclusion

The main target of our reaction is to reduce the reaction time and efficiency of the product. Here, we have presented an operationally simple, suitable, fast, efficient method for the preparation of Pyrazole derivative. The main focus of this research work was to synthesize, purify, characterize and evaluate antibacterial activities of the synthesized compounds &which shows good antibacterial activity.

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