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# Synthesis of Novel Pyrazole Derivatives by Vilsemeier Haack Reaction

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**ABSTRACT**
*A series of substituted carboxylic acid hydrazides on reaction with substituted acetophenone gave corresponding hydrazones which on Vilsmeier- Haack reaction resulted in corresponding formyl pyrazoles. The structures of the newly synthesized compounds were confirmed on the basis of IR and $^1$H-NMR. And also synthesized compounds were screened for their antibacterial (Staphylococcus aureus, Bacillus subtilis, Escherichia coli and Pseudomonas aeruginosa) and antifungal (Aspergillus niger and Candida albicans) activity. The results revealed that, compounds exhibited significant biological activity against the tested microorganisms.*
**Keywords:** *Vilsmeier-Haack reaction, Hydrazones, N-formyl hydrazones, Biological activity.*

## INTRODUCTION

Pyrazole derivatives have attracted the attention of research scholars on account of their wide range of applications in medicine. Steroids containing pyrazole moiety are of interest as psychopharmacological agents[1]. Pyrimidinopyrazoles are being studied in the fight against cancer [2]. Pyrazole derivatives have been found to have antimalarial activity[3] and antihyperglycemic activity[4]. Some alkyl and aryl substituted pyrazoles have a sharp pronounced sedative action on the central nervous system[5]. Certain alkyl pyrazoles show significant bacteriostatic, bactericidal and fungicidal, analgesic and antipyretic activities[6]. Literature search reveals that formylation of hydrazones yield formyl pyrazoles. The Vilsmeier-Haack reaction is common method for the synthesis of 4-formyl pyrazoles [7]. The Schiff's bases of aldehydes and ketones on treatment with DMF and POCl3 undergo cyclisation reactions forming pyrazole derivatives and undergo formylation on to the pyrazole ring[8]. Hydrazones of aliphatic and aromatic methyl ketones yield pyrazole-4-carboxaldehydes upon diformylation on treatment with Vilsmeier reagent[9]. Such type of cyclisation with formylation using Vilsmeier-Haack reaction is also reported by Selvi S, Perumal PT [10], Sridhar R et al [11], Hemanth Kumar K et al [12], Sing, Karan et al[13] and D. B. Arunkumar et al[14].

By considering the wide range of application of formyl pyrazoles and of our special interest in Vilsmeier-Haack reaction [15-21] we attempted formylation of substituted acetophenone hydrazones using Vilsmeier-Haack reagent. It was planned to synthesize different formylpyrazole derivatives by reacting substituted acetophenone hydrazones with Vilsmeier-Haack reagent DMF/POCl3. With the hope of cyclisation and formylation of acetophenone hydrazones to form formylpyrazole.

In the present work we have developed an efficient and general process involving synthesis of activated aromatic ester followed by reaction with hydrazine for the synthesis of hydrazides which gave desired hydrazides in excellent yield and purity under mild conditions. The starting compounds acid hydrazides required for the

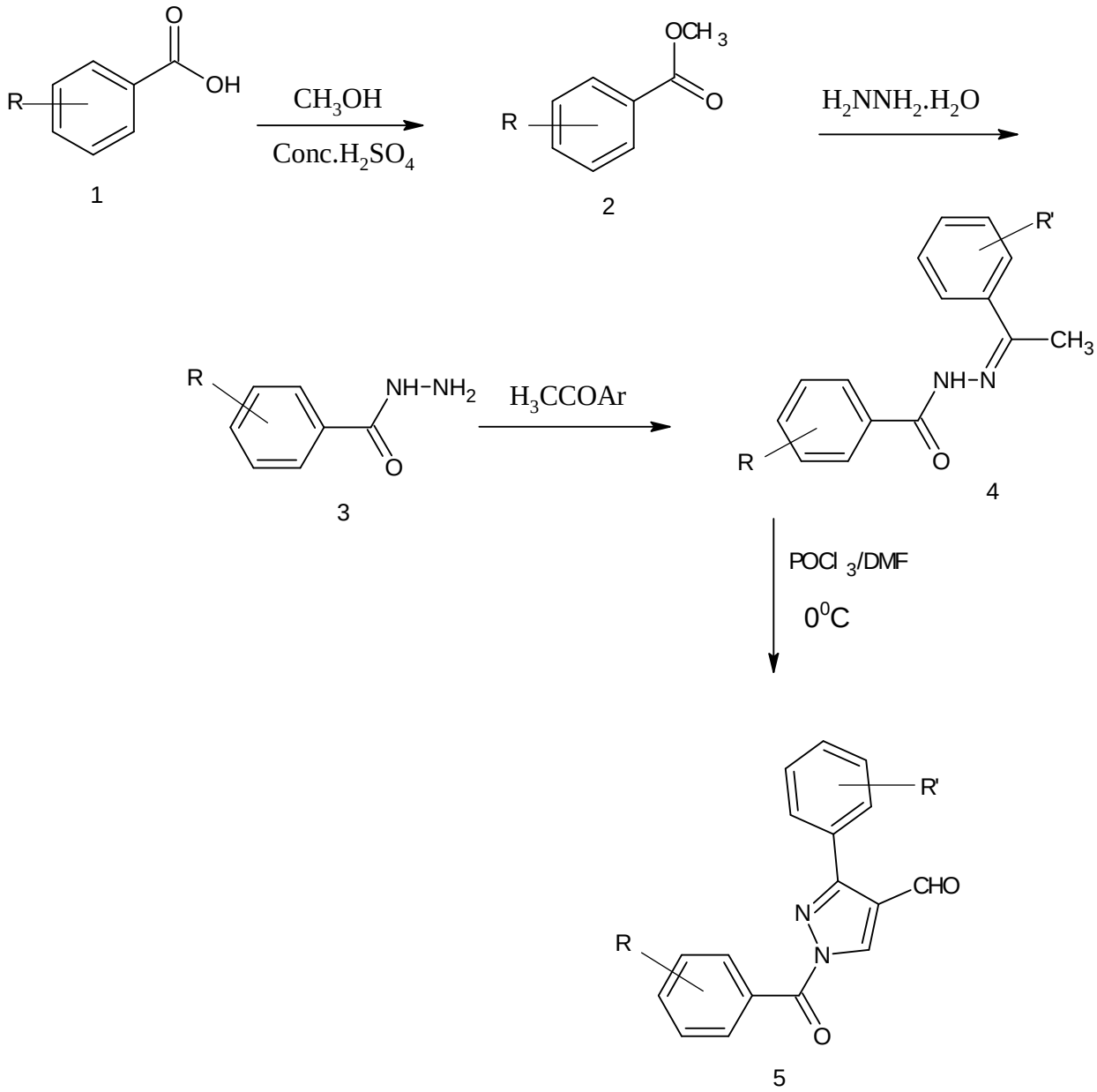
preparation of the target compounds were obtained by hydrazinolysis of esters which in turn were prepared by refluxing carboxylic acids with absolute methanol and conc. $H_2SO_4$. Compounds on condensation with different acetophenones in methanol containing a catalytic amount of glacial acetic acid gave acetophenone hydrazones. The hydrazones on treatment with V.H. reagent ($DMF/POCl_3$) yielded formylpyrazoles.

## MATERIALS AND METHODS

The melting points were recorded in open capillary bath in paraffin bath. IR spectra were recorded on a Bruker IR spectrophotometer (in KBr pellets). $^1H$ NMR spectra are recorded on a Bruker AM 400 instrument using tetramethyl-silane 0 (TMS) as an internal reference and $CDCl_3$ as solvent. Chemical shifts are given in parts per million (ppm). Elemental (CHN) analysis was done by using elemental analyser. The compounds were analysed for carbon, hydrogen and nitrogen and the results obtained are in good agreement with the calculated values.

**Experimental Studies**

**Scheme for the reactions**



**Synthesis of esters of benzoic acid and 4-bromo benzoic acid**

Both the esters were prepared by Fischer's esterification process which includes refluxing the substituted aromatic acids for 30 minutes with methanol by using conc. $H_2SO_4$ as a catalyst.

**Synthesis of benzhydarzide and 4-bromo benzhydrazide from methyl benzoate and 4-bromo methyl benzoate**

Both the esters synthesized are subjected to hydrazinolysis by using hydrazine hydrate in alcohol. It was then refluxed for 2 hours. The solid separated out at the end of refluxing was corresponding hydrazide.

**Synthesis of 4-methoxy acetophenonephenyl-1-carbonyl hydrazone from benzhydrazide**

A mixture of 0.01 mole benzhydrazide and 0.01 mole 4-methoxy acetophenone was refluxed in 30 ml of methanol containing a drop of glacial acetic acid as catalyst for 30minutes. The solid separated at the end of refluxing was corresponding hydrazone.

**Synthesis of 4-methoxy acetophenone-4-bromophenyl-1-carbonyl hydrazone from 4-bromo benzhydrazide**

A mixture of 0.01 mole 4-bromo benzhydrazide and 0.01 mole 4-methoxy acetophenone was refluxed in 30 ml of methanol containing a drop of glacial acetic acid as catalyst for 30minutes. The solid separated at the end of refluxing was corresponding hydrazone.

**Synthesis of 1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl) benzene**

To the Vilsmeier-Haack reagent prepared from 30 ml of DMF and 3.3 ml (0.036 mole) $POCl_3$ at 0℃, 3.048g (0.012mole) of 4-methoxy acetophenone phenyl-1-carbonyl hydrazonewas added in small aliquots at a time and the reaction mixture was refluxed over a boiling water bath for 10 hours. After refluxion the reaction mixture was poured into ice cold water, the solid separated on neutralization with sodium acetate trihydrate was filtered, washed with water and wasre-crystallized with chloroform.

**Characterization of synthesized compound**

%Yield = 79.21 Melting point = 162℃ I.R (KBr): 3218, 2845, 1689, 1588, 1452 $cm^{-1}$, $^1$H-NMR ($CDCl_3$): δ 7.90 (1H, S, -CHO), 7.59 (1H, S, -CH), 3.8 (3H, S, $-OCH_3$), 7.29 (5H, M, -Ar), 6.98 (4H, M, -Ar)

**Synthesis of 1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl)4-bromobenzene**

To the Vilsmeier-Haack reagent prepared from 30 ml of DMF and 3.3 ml (0.036 mole) $POCl_3$ at 0℃, 3.048g (0.012mole) of 4-methoxy acetophenone-4-bromophenyl-1-carbonyl hydrazone was added in small aliquots at a time and the reaction mixture was refluxed over a boiling water bath for 10 hours. After refluxion the reaction mixture was poured into ice cold water, the solid separated on neutralization with sodium acetate trihydrate was filtered, washed with water and wasre-crystallized with chloroform.

**Characterization of synthesized compounds**

%Yield = 66.98 Melting point = 128℃ IR (KBr): 1664, 1590, 1499, 1245, 2915 $cm^{-1}$, $^1$H-NMR ($CDCl_3$): δ 8.5 (1H, S, -CHO), 7.89 (1H, M, -CH), 3.8 (3H, S, $-OCH_3$), 7.97 (4H, M, -Ar), 7.70 (4H, M, -Ar)

**Biological Activity**

The novel synthesized 1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl) benzene and 1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl)4-bromobenzene were screened for their in vitro antimicrobial activity using agar disc-diffusion method. The synthesized compounds were used at the concentration of 250µg/ml DMF as a solvent.

**Antibacterial Activity**

The antibacterial activity of newly synthesized 1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl) benzene and 1-(3-4-methoxy phenyl-4-

formyl pyrazole-1-carbonyl) 4-bromobenzene were screened against two Gram positive bacterial strains *Staphylococcus aureus* and *Bacillus thurengienesis* and Gram negative strains, *Escherichia coli and Pseudomonas aeruginosa.* Here chloramphenicolis tested as reference drug to compare the activity.

**Antifungal Activity**

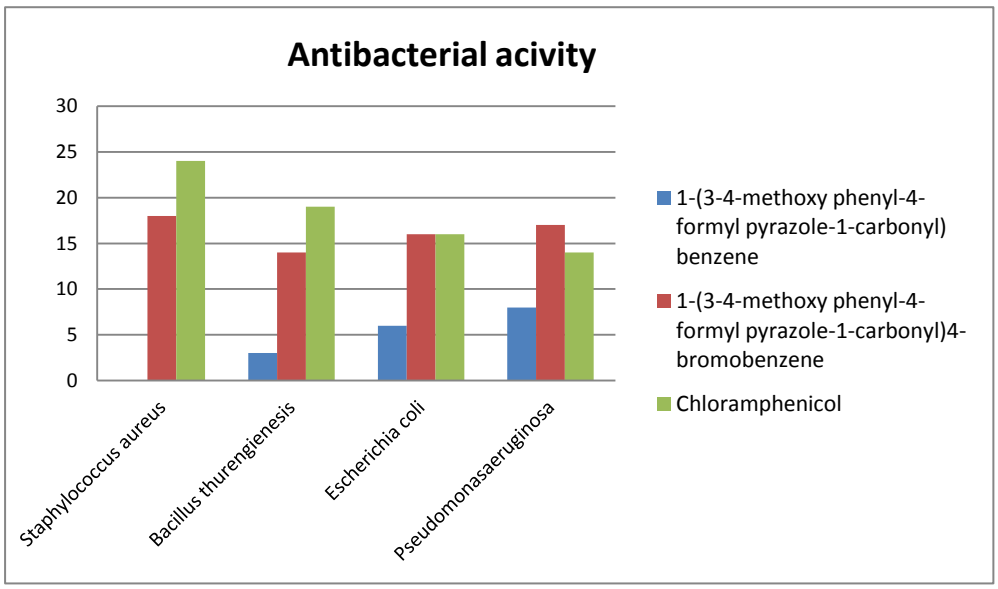
The antifungal activity of newly synthesized 1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl) benzene and 1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl) 4-bromobenzene were screened against the *Aspergillus niger* and *Candida albicans*. Here Ketoconazoleis tested as reference drug to compare the activity.

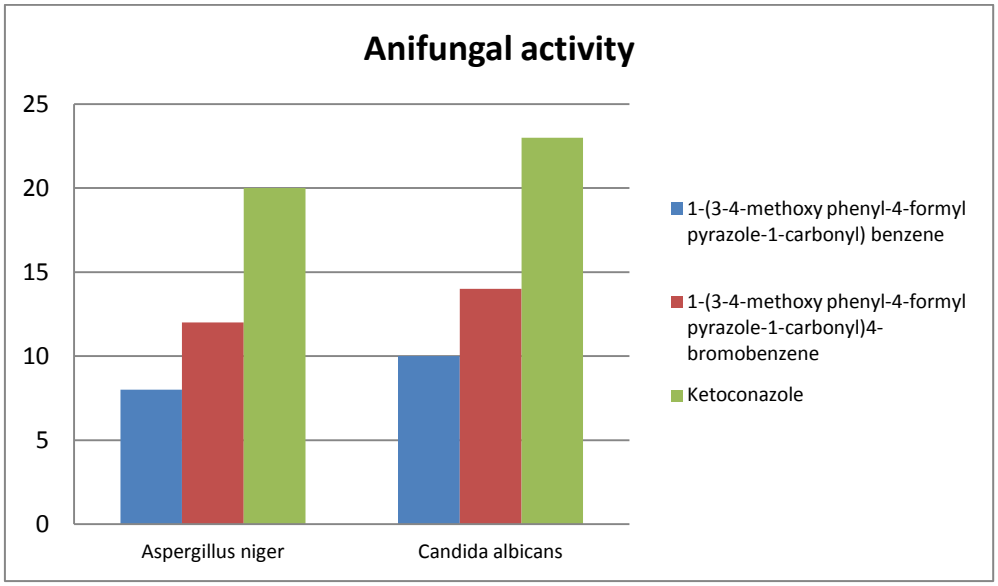
The results were recorded for each tested compound as the average diameter zone of inhibition of bacterial or fungal growth around the disks in mm.

The antibacterial and anti-fungal activity was shown in the Table 1 and depicted in Figure

**Table 1.**Antibacterial and anti-fungal activity (Diameter zone of Inhibition in mm) of newly syntesised compounds (250 µg/ml)

| Compounds | Zone of inhibition(mm) | | | | | |
|---|---|---|---|---|---|---|
| | Antibacterial activity 250(µg/disc) | | | | Antifungal activity 250(µg/disc) | |
| | Gram positive | | Gram negative | | *Aspergillus niger* | *Candida albicans* |
| | *Staphylococcus aureus* | *Bacillus thurengienesis* | *Escherichia coli* | *Pseudomonasae rugi--nosa* | | |
| 1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl) benzene | _ | 3 | 6 | 8 | 18 | 22 |
| 1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl)4-bromobenzene | 18 | 14 | 16 | 17 | 12 | 14 |
| Chloramphenicol | 19 | 14 | 24 | 20 | - | - |
| Ketoconazole | - | - | - | - | 20 | 22 |






## RESULTS AND DISCUSSION

The $^{1}$HNMR spectrum of the recrystallized samples showed the disappearance of the methylene proton signal and N-N-H signal. The proton signal for the newly formed pyrazole appears at δ7.2 ppm leaving the other proton signals almost unchanged. This confirmed the formation of the target molecules.

The IR spectrum of the recrystallised sample also validates the formation of the targeted molecule by showing characteristic stretching vibrations of carbonyl group.

The antibacterial activity of both compounds summarised in the Table 1 and their comparative study has done. Data revealed that the 1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl) benzene showed moderate antibacterial activity against Gram positive and Gram negative bacteria and also for antifungal activity. But these compound showed equal zone of inhibition against both fungus compared with the reference drug ketoconazole.

1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl) 4-bromobenzene showed good activity against all tested microorganisms. These compound has equal zone of inhibition against both the Gram positive bacteria compared with the reference drug chloramphenicol.

## CONCLUSIONS

The novel pyrazole derivatives by Vilsmeier Haack reaction were successfully synthesized in good yields. Their purity and confirmation was checked by physical, analytical, and spectral data. These newly synthesized compounds have been shown to have both antibacterial and antifungal activity and may serve as pharmacological agents.

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