Synthesis of Novel Pyrazole Derivatives by Vilsemeier Haack Reaction

Authors

Jyothi N. Rao*, Pooja, Nithya, Royline

Department of Postgraduate Studies and Research in Chemistry, St Aloysius College (Autonomous), Mangaluru, 575003, India

Email: jyothirao83@yahoo.com

ABSTRACT

A series of substituted carboxylic acid hydrazides on reaction with substituted acetophenone gave corresponding hydrazones which on Vilsmeier-Haack reaction resulted in corresponding formylpyrazoles. The structures of the newly synthesized compounds were confirmed on the basis of IR and 1H-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: Vilmeier-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 Vilmeier-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 under formylation on to the pyrazole ring [8]. Hydrazones of aliphatic and aromatic methyl ketones yield pyrazole-4-carboxaldehydes upon diformylation on treatment with Vilmeier reagent [9]. Such type of cyclisation with formylation using Vilmeier-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 Vilmeier-Haack reaction [15-21] we attempted formylation of substituted acetophenone hydrazones using Vilmeier-Haack reagent. It was planned to synthesize different formylpyrazole derivatives by reacting substituted acetophenone hydrazones with Vilmeier-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$_2$SO$_4$. 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

Experimental Studies

Scheme for the reactions

1. R$_2$COOH + CH$_3$OH + Conc. H$_2$SO$_4$ → R$_2$COOH

2. R$_2$COOH + H$_2$NNH$_2$ → R$_2$CONHNH$_2$

3. R$_2$CONHNH$_2$ + H$_2$COCOAr → R$_2$CONHNHCOAr

4. R$_2$CONHNHCOAr + POCl$_3$/DMF $0^\circ$C → R$_2$CONHNHCHO

5. R$_2$CONHNHCHO
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. H₂SO₄ as a catalyst.

Synthesis of benzhydrazide 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 30 minutes. The solid separated at the end of refluxing was corresponding hydrazone.

Synthesis of 4-methoxy acetophenone-4-bromophenyl-1-carbonyl hydrazone from 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 30 minutes. The solid separated at the end of refluxing was corresponding hydrazone.

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) POCl₃ at 0°C, 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 was re-crystallized with chloroform.

Characterization of synthesized compound
%Yield = 79.21 Melting point = 162°C I.R (KBr): 3218, 2845, 1689, 1588, 1452 cm⁻¹, ¹H-NMR (CDCl₃): δ 7.90 (1H, S, -CHO), 7.59 (1H, S, -CH), 3.8 (3H, S, -OCH₃), 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) POCl₃ at 0°C, 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 was re-crystallized with chloroform.

Characterization of synthesized compounds
%Yield = 66.98 Melting point = 128°C I.R (KBr): 1664, 1590, 1499, 1245, 2915 cm⁻¹, ¹H-NMR (CDCl₃): δ 8.5 (1H, S, -CHO), 7.89 (1H, M, -CH), 3.8 (3H, S, -OCH₃), 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 thurengienses* and Gram negative strains, *Escherichia coli* and *Pseudomonas aeruginosa*. Here chloramphenicol is 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 Ketoconazole is 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 synthesised compounds (250 µg/ml)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Antibacterial activity 250(µg/disc)</th>
<th>Antifungal activity 250(µg/disc)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gram positive</td>
<td>Gram negative</td>
</tr>
<tr>
<td></td>
<td><em>Staphylococcus aureus</em></td>
<td><em>Bacillus thurengiensis</em></td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em></td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td><em>Aspergillus niger</em></td>
<td><em>Candida albicans</em></td>
</tr>
<tr>
<td>1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl) benzene</td>
<td>_</td>
<td>3</td>
</tr>
<tr>
<td>1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl)4-bromobenzene</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
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 $\delta$7.2 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.

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.

ACKNOWLEDGEMENT
The authors are thankful to UGC for providing funds, Jain University, Bengaluru and TIFR, Mumbai for providing spectral analysis facilities.

REFERENCES
6. (b) KS. Raevskii, M. Batulin Yu, Farmakol, I.Toksikol, 1963, 26(5), 551; Chem Abstr 1964, 60, 1256C.
7. (a) E. Hernab, J. Gabliks Cancer Chemotherapy Rept 1964, 14: 85.
9. (c) KT. Potts In Comprehensive Heterocyclic Chemistry, Pergamon Press; Oxford 1986, Vol. 5, part 4A.