A NOVEL METHOD FOR THE SYNTHESIS OF FORMYL PYRAZOLES USING VILSMEIER-HAACK REACTION

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ABSTRACT
A series of acetophenone substituted phenyl carbonyl hydrazones has been synthesized and their formylation was carried out by using Vilsmeier-Haack reaction. All the hydrazones and their formyl derivatives were screened for antibacterial activities.

Keywords: Vilsmeier-Haack reaction, Formylation, Hydrazones, N-formyl hydrazones.

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 agents1. Pyrimidino pyrazoles are being studied in the fight against cancer2. Pyrazole derivatives have been found to have antimalarial activity3 and antihyperglycemic activity4. Some alky1 and aryl substituted pyrazoles have a sharp pronounced sedative action on the central nervous system5. Certain alky1 pyrazoles show significant bacteriostatic, bactericidal and fungicidal, analgesic and antipyretic activities6.

Literature search reveals that formylation of hydrazones yield formyl pyrazoles7. 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 ring8.

Hydrazones of aliphatic and aromatic methyl ketones yield pyrazole-4-carboxaldehydes upon diformylation on treatment with Vilsmeier-Haack reagent9. Such type of cyclisation with formylation using Vilsmeier-Haack reaction15 -20 we attempted formylation of 4-carboxaldehydes upon diformylation on treatment with Vilsmeier-Haack reagent.

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.

RESULTS AND DISCUSSION

The 1HNMR 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 which was also characterized by elemental analysis.

A possible mechanism for the formylation of 4-formyl pyrazole is out lined in Scheme- III

In the present work we have developed an efficient and general process involving performing activated ester followed by reaction with hydrazine for the preparation of hydrazides which gave desired hydrazides in excellent yield and purity under mild conditions.

The starting compounds acid hydrazides 3a-d required for the preparation of the target compounds were obtained by hydrazinolysis of esters 2a-d which in turn were prepared by refluxing carboxylic acids 1a-d with absolute methanol and conc. H2SO4. Compounds 2a-d on condensation with different acetophenones in methanol containing a catalytic amount of glacial acetic acid gave acetophenone hydrazones 4a-d – 7a-d. The hydrazones 4a-d – 7a-d on treatment with V.H. reagent (DMF/POCl3) yielded formyl pyrazoles. (Scheme-I and Scheme-II)

ABSTRACT
A series of acetophenone substituted phenyl carbonyl hydrazones has been synthesized and their formylation was carried out by using Vilsmeier-Haack reaction. All the hydrazones and their formyl derivatives were screened for antibacterial activities.

Keywords: Vilsmeier-Haack reaction, Formylation, Hydrazones, N-formyl hydrazones.
Scheme-I

\[
\begin{align*}
1a-d & \rightarrow \text{CH}_3\text{OH} \rightarrow \text{CH}_2\text{N-NH}_2\cdot\text{H}_2\text{O} \\
1a-d & \rightarrow \text{R,} \quad a = -4\text{OH} \\
& \quad b = -4\text{Cl} \\
& \quad c = -2\text{Cl} \\
& \quad d = -\text{H} \\
\end{align*}
\]

Scheme-II

\[
\begin{align*}
3a & \rightarrow \text{H}_2\text{C-C-} \rightarrow \text{H}_2\text{C-C-} \\
3a & \rightarrow \text{DMF} \rightarrow \text{POCl}_3 \\
3a & \rightarrow \text{NO}_2 \\
\end{align*}
\]
Cyclisation along with formylation (Scheme-III)
Table I: Antibacterial activity of compounds 4a-d, 6a-d, 7a-d, 8a-d and 11a-d Zone of inhibition (mm) Antibacterial activity of compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>P.vulgaris</th>
<th>S.aureus</th>
<th>S. typhimurium</th>
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<tbody>
<tr>
<td>4a</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4b</td>
<td>04</td>
<td>-</td>
<td>-</td>
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<tr>
<td>4c</td>
<td>12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4d</td>
<td>06</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6a</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6b</td>
<td>05</td>
<td>-</td>
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</tr>
<tr>
<td>6c</td>
<td>10</td>
<td>-</td>
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<tr>
<td>6d</td>
<td>-</td>
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<tr>
<td>7a</td>
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<tr>
<td>7b</td>
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<tr>
<td>7d</td>
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<td>-</td>
</tr>
<tr>
<td>8a</td>
<td>09</td>
<td>12</td>
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</tr>
<tr>
<td>8b</td>
<td>-</td>
<td>-</td>
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<td>8c</td>
<td>08</td>
<td>13</td>
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<tr>
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</tr>
<tr>
<td>10d</td>
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<tr>
<td>11a</td>
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<tr>
<td>11b</td>
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<td>11c</td>
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</tr>
<tr>
<td>11d</td>
<td>12</td>
<td>-</td>
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Table II: Antibacterial activity of compounds 5a-d and 9a-d, D zone of inhibition (mm)

<table>
<thead>
<tr>
<th>Compound</th>
<th>E. coli</th>
<th>S. aureus</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5b</td>
<td>-</td>
<td>08</td>
</tr>
<tr>
<td>5c</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>5d</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>9a</td>
<td>12</td>
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<tr>
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<td>9c</td>
<td>10</td>
<td>07</td>
</tr>
<tr>
<td>9d</td>
<td>-</td>
<td>05</td>
</tr>
</tbody>
</table>

Experimental section

Preparation of acetophenone-4-hydroxyphenyl-1-carbonyl hydrazone (4a)

A mixture of 4-hydroxybenzhydrazide (0.01 mole) and acetophenone (0.01 mole) in methanol (30 ml) containing a drop of glacial acetic acid was refluxed for 30 minutes. The separated colorless solid was filtered and crystallized from ethanol.

Yield (57.08%), m.p. 240-241°C. m.f. C15H14O2N2

I.R. (KBr): 1670, 1535, 3174, 3375 cm⁻¹

Preparation of 4-hydroxy acetophenone-4-hydroxyphenyl-1-carbonyl hydrazone (4b)

Yield (61.11%), m.p. 274-276°C. m.f. C15H15O2N2

I.R. (KBr): 1608, 1553, 3174, 3375 cm⁻¹

Preparation of 4-hydroxy acetophenone-4-hydroxyphenyl-1-carbonyl hydrazone (4c)

Yield (51.92%), m.p. 212-213°C. m.f. C16H16O3N2

I.R. (KBr): 1649, 1591, 1249, 3149 and 3269 cm⁻¹

Preparation of 4-hydroxy acetophenone-4-hydroxyphenyl-1-carbonyl hydrazone (4d)

Yield (51.57%), m.p. 220-221°C. m.f. C15H13O4N3

I.R. (KBr): 1650, 1514, 1346, 3100 and 3300 cm⁻¹

Preparation of acetophenone-4-hydroxyphenyl-1-carbonyl hydrazone (5a)

A mixture of 4-hydroxybenzhydrazide (0.01 mole) and acetophenone (0.01 mole) in methanol (30 ml) containing a drop of glacial acetic acid was refluxed for 30 minutes. The separated solid was filtered and crystallized from ethanol.

Yield (85.15%), m.p. 175-176°C. m.f. C15H15O2N2Cl

I.R. (KBr): 1660, 1589, 3060 cm⁻¹

Preparation of 4-methoxy acetophenone-4-chlorophenyl-1-carbonyl hydrazone (5b)

Yield (85.80%), m.p. 170-171°C. m.f. C15H15O2N2Cl

I.R. (KBr): 1637, 1506, 3006, and 3181 cm⁻¹

Preparation of 4-nitro acetophenone-4-chlorophenyl-1-carbonyl hydrazone (5c)

Yield (87.61%), m.p. 225-226°C. m.f. C15H12O2N3Cl

I.R. (KBr): 1596, 1720, and 3050 cm⁻¹

Preparation of acetophenone-2-chlorophenyl-1-carbonyl hydrazone (6a)

A mixture of 2-chlorobenzhydrazide (0.01 mole) and acetophenone (0.01 mole) in methanol (30 ml) containing a drop of glacial acetic acid was refluxed for 30 minutes. The separated solid was filtered and crystallized from ethanol.

Yield (49.68%), m.p. 124-125°C. m.f. C15H14O2N2Cl

I.R. (KBr): 1666, 1545, 3200 cm⁻¹
4-hydroxy acetophenone-2-chlorophenyl-1-carbonyl hydrazone (6b)
Yield (90.0%), m.p. 150 °C. m.f. C15H13O2N2Cl
I.R. (KBr): 1630, 1513, 3100, and 3250 cm⁻¹

4-methoxy acetophenone-2-chlorophenyl-1-carbonyl hydrazone (6c)
Yield (90.0%), m.p. 152-153 °C. m.f. C16H15O2N2Cl
I.R. (KBr): 1670, 1601, 1520, and 3206 cm⁻¹

4-nitro acetophenone-2-chlorophenyl-1-carbonyl hydrazone (6d)
Yield (88.0%), m.p. 146-147 °C. m.f. C15H12O2N3Cl
I.R. (KBr): 1664, 1580, 1348, and 3230 cm⁻¹

Preparation of acetophenone phenyl-1-carbonyl hydrazone (7a)
A mixture of benzhydrazide (0.01 mole) and acetophenone (0.01 mole) in methanol (30 ml) containing a drop of glacial acetic acid was refluxed for 30 minutes. The separated solid was filtered and crystallized from ethanol.
Yield (88.0%), m.p. 150-151 °C.
I.R. (KBr): 1645, 1584, 3200

4-hydroxy acetophenone phenyl-1-carbonyl hydrazone (7b)
Yield (78.74%), m.p. 228-229 °C.
I.R. (KBr): 1635, 1540, 3100, 3250

4-methoxy acetophenone phenyl-1-carbonyl hydrazone (7c)
Yield (88.0%), m.p. 158-159 °C.
I.R. (KBr): 1660, 1565, 3206

4-nitro acetophenone phenyl-1-carbonyl hydrazone (7d)
Yield (94.0%), m.p. 180-187 °C.

Preparation of formyl pyrazoles
1-(3-phenyl-4-formyl pyrazole-1-carbonyl) 4-hydroxybenzene (8a)
To the Vilsmeier-Haack reagent prepared from DMF (10 ml) and POCl₃ (1.1 ml, 0.012 mole) at 0 °C, hydrazone 4a (1.016 gm, 0.004 mole) was added in small aliquots at a time and the reaction mixture was stirred at 60-65 °C for 4 hrs and poured into ice cold water. The solid separated on neutralization with NaHCO₃ was filtered, washed with water and crystallized from aq. Methanol which formed 8a.
Yield 1.016 gm (45.33%), m.p. 99-100 °C,
I.R (KBr): 3235, 2854, 1685, 1607, 1465 cm⁻¹.


Elemental analysis calculated for C₁₇H₁₂N₂O₂, C 73.91, H 4.34, N 10.14, found C 73.80, H 3.62, N 13.10%

Other compounds 8a - e - 11 a - e were prepared according to above mentioned method.

1 H-NMR (DMSO-d₆): δ 8.76 (1H, S, -CHO), 3.8 (3H, S, -OCH₃), 7.2 (1H, S, -CH), 9.32 (1H, S, -OH), 6.87-6.77 (4H, M, -Ar), 6.76-6.72 (4H, M, -Ar)

Elemental analysis calculated for C₁₈H₁₄N₂O₂, C 67.02, H 4.34, N 8.69, found C 66.92, H 4.34, N 8.57%

1-(3-4-methoxyphenyl-4-formyl pyrazole -1-carbonyl) 4-hydroxybenzene (8d)
Yield 1.196 gm (44.51%), m.p. 110-112 °C,
I.R (KBr): 3200, 2855, 1665, 1607, 1461, 1253 cm⁻¹.


Elemental analysis calculated for C₁₈H₁₄N₂O₂, C 67.02, H 4.34, N 8.69, found C 66.92, H 4.34, N 8.57%

1-(3-4-hydroxyphenyl-4-formyl pyrazole -1-carbonyl) 4-hydroxybenzene (8c)
Yield 1.06 gm (65.38%), m.p. 120-121 °C,
I.R (KBr): 3018.78, 2925, 1629.57, 1461.81, 1515.60, 1345.59 cm⁻¹.

1 H-NMR (DMSO-d₆): δ 7.76 (1H, S, -CHO), 7.12 (1H, S, -CH), 9.4 (1H, S, -OH), 6.87-6.77 (4H, M, -Ar), 6.68-6.64 (4H, M, -Ar)

Elemental analysis calculated for C₁₈H₁₂O₂N₃, C 64.46, H 4.34, N 10.14, found C 64.32, H 4.34, N 10.14%

1-(3-4-nitrophenyl-4-formyl pyrazole -1-carbonyl) 4-hydroxybenzene (8d)
Yield 1.196 gm (44.51%), m.p. 110-112 °C,
I.R (KBr): 3238.81, 2855.07, 1629.57, 1607.12, 1461.81, 1515.60, 1345.59 cm⁻¹.

1 H-NMR (DMSO-d₆): δ 8.9 (1H, S, -CHO), 7.6 (1H, S, -CH), 9.2 (1H, S, -OH), 7.44-7.38 (4H, M, -Ar), 6.99-6.80 (4H, M, -Ar)

Elemental analysis calculated for C₁₈H₁₂N₂O₂, C 73.91, H 4.34, N 10.14, found C 73.80, H 3.62, N 13.10%
1-(3, 4-methoxyphenyl-4-formyl pyrazole-1-carbonyl) benzene (11b)
Yield 30%, m.p. 98-100 °C,
LR (KBr): 2840, 1668, 1615, 1515 cm⁻¹

1-(3, 4-hydroxyphenyl-4-formyl pyrazole-1-carbonyl) benzene (11c)
Yield 36%, m.p. 96-97 °C,
LR (KBr): 2856, 1662, 1610, 1517, 1261 cm⁻¹

1-(3, 4-nitrophenyl-4-formyl pyrazole-1-carbonyl) benzene (11d)
Yield 42.05%, m.p. 82-83 °C,
LR (KBr): 2848, 1691, 1612, 1456, 1554, 1349 cm⁻¹

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