COMPARATIVE ASSESSMENT OF CATALYTIC ACTIVITY OF VARIOUS CATALYSTS IN THE SYNTHESIS OF DIHYDROPYRIMIDINONES

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ABSTRACT

An efficient and greener synthesis of series of dihydropyrimidinone (DHPMs) derivative were accomplished via three-component one pot cyclocondensation between substituted aryl aldehydes, diketone/ketoester and urea. This solvent free approach is totally nonpolluting having several advantages such as shorter reaction time, mild reaction conditions, simple workup and reduced the environmental impact.

Keywords: Biginelli, Natural Catalyst, Dihydropyrimidinone (DHPMs), 3, 4-dihydroprimidin-2(1H) ones (DHPM)
INTRODUCTION

The combination of an aldehyde $^1$, β-ketoester $^2$, and urea $^3$ under acid catalyst to give a dihydropyrimidinone$^4$ was first reported by Pietro Biginelli in 1893$^1$ referred to as the Biginelli Reaction. This one-pot condensation reaction generates compounds with pharmacological activity, including calcium channel modulation, mitotic kinesis, enzyme inhibition and anti-viral and anti-bacterial activity. The dihydropyrimidinone also exhibit anti-tumor, and anti-inflammatory properties. Although the original reaction condition suffered from poor yield and limited substrate scope, the recent discovery of dihydropyrimidinone has led to a renewed exploration of the reaction condition, revealing the variety of compatible solvent, acid catalyst and an expanded substrate scope. Most recently, the development of asymmetric method has allowed to generation condition of enantioenriched dihydropyrimidinone. Further the reaction manifold has been extended from its solution phase origins to include microwave assisted, solid phase and fluoro phase reaction.

The gradual development of the Biginelli reaction over the past 115 years, coupled with the biological study of resulting compounds, has provided an entry way into the relatively an explored Dihydropyrimidinone compounds.

Dihydropyrimidinone (DHPMs) are well known for their wide range of bioactivity and their application in the field of practical research. The 1$^{st}$ synthesis of dihydropyrimidinone was reported by Biginelli in 1893$^1$. Later, the multifunctionalised dihydropyrimidinones or Biginelli compound synthesis was drastically increased since its heterocyclic system of remarkable pharmacological efficiency. Since the several review on synthesis and chemical properties of pyrimidones have been published.

In recent years, dihydropyrimidine-2(1H) ones derivatives have gained much interest for their biological and pharmaceuticals properties such as HIV gp-120-CD4 inhibitors, calcium channel blockers, α-adrenergic and neuropeptide Y antagonist dihydropyrimidinones (DHPMs), commonly known as Biginelli compounds, have attained
unprecedented attention due to its greater biological, pharmaceutical and therapeutic properties.

In 1893, Pietro Biginelli reported the first synthesis of 3, 4- dihydropriimidin-2(1H) ones (DHPM) by a very simple one-pot condensation reaction of an aromatic aldehyde, urea and ethyl acetoacetate in ethanolic solution. This efficient approach to partly reduced pyrimidines, termed the biginelli reaction or condensation, was largely ignored in the following years, and therefore, also the synthetic potential of these multi-functionalized dihydropyrimidinones remained unexplored. In recent years, however, interest in these compounds has increased rapidly, and the scope of the original cyclocondensation reaction has been widely extended by variation of all three components. Many dihydropyrimidinones and their derivatives are pharmacologically important as calcium channel blockers, antihypertensive agent and α-1a antagonist. Dihydropyrimidinones, denoted as biginelli, compounds and derivatives are highly important heterocyclic unit in the realm of natural and synthetic organic chemistry that possess diverse therapeutic and pharmacological properties (26).

**General Reaction:**
3. SCHEME

A mixture of aromatic aldehyde (10 mmol.), was ethyl acetoacetate (1.30gm, 10mmol.), urea (15mmol.) and catalyst (10mmol %). was heated with stirring at for appropriate time. The progress of reaction was monitored by TLC, after completion of the reaction, crushed ice was added, the solid product was filtered off, washed with ice cold water, dried and crystallized from ethanol.

Scheme 1. Synthesis of ethyl 6- methyl- 2- oxo- 4 phenyl- 1, 2 , 3 , 4 tetrahydropyrimidine-5- carboxylate.

Scheme 2. Synthesis of ethyl 4- (4- chlorophenyl)- 6-methyl-2- oxo- 1, 2, 3, 4- tetrahydro-3-oxobutanoate p-Chlorobenzaldehyde
Scheme 3. Synthesis of ethyl 4- (4- bromophenyl)- 6- methyl- 2 - oxo- 1, 2, 3, 4 - tetrahydropyrimidine- 5- carboxylate.

4. EXPERIMENTAL SECTION

1. Synthesis of ethyl 6- methyl- 2- oxo- 4- phenyl- 1, 2, 3, 4-tetrahydropyrimidone- 5- carboxylate.

A mixture of benzaldehyde (1.06 gm, 10 mmol.), ethyl acetoacetate (1.30 ml, 10 mmol.), Urea (0.9 gm, 15 mmol.) and Catalyst (10 mmol %), was heated with stirring. The progress of reaction was monitored by TLC. After completion of the reaction crushed ice
was added, the solid product was filtered off, washed with ice cold water, dried and recrystallized from ethanol. M. P. 204°C.

$^1$HNMR - (300 MHz, CDCl$_3$) $\delta$ = 1.18 (t, 3H, J= 7Hz), 2.34 (s, 3H, J= 7Hz), 4.08 (q, 2H), 5.40 (s, 1H), 7.32 (d, 4H), 7.99(s, 1H). M.P. 204°C. (Ethyl Acetate+ n- Hexane: 1/9), Rf= 0.59.

<table>
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<tr>
<th>Catalyst</th>
<th>PPA</th>
<th>H$_3$BO$_3$</th>
<th>CuCl$_2$.2H$_2$O-HCl</th>
<th>NH$_4$Cl</th>
<th>AlCl$_3$</th>
<th>ZnCl$_2$</th>
<th>CAN</th>
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<tbody>
<tr>
<td>Temperature</td>
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<td>105°C</td>
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<td>110°C</td>
<td>95°C</td>
<td>75°C</td>
<td>80°C</td>
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<tr>
<td>Time</td>
<td>125 min.</td>
<td>110 min.</td>
<td>110 min.</td>
<td>90 min.</td>
<td>120 min.</td>
<td>150 min.</td>
<td>60 min.</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>65%</td>
<td>62%</td>
<td>55%</td>
<td>50%</td>
<td>68%</td>
<td>58%</td>
<td>72%</td>
</tr>
</tbody>
</table>

2. Synthesis of ethyl 4- (4- chlorophenyl)- 6- methyl- 2- oxo- 1, 2, 3, 4- tetrahydropyrimidine- 5- carboxylate.

A mixture of p- chlorobenzaldehyde (1.40 gm, 10 mmol.), ethyl acetoacetate (1.30 gm, 10 mmol.) urea (0.9 gm, 15 mmol.) and Catalyst (10 mmol %), was heated with Stirring. The progress of reaction was monitored by TLC. After completion of the reaction, crushed ice was added, the solid product was filtered off, washed with ice cold water, dried and recrystallized from ethanol. M. P. 206°C

$^1$HNMR- (300 MHz, CDCl$_3$) $\delta$ = 1.19 ( t, 3H, J= 7 Hz ), 2.33(s, 3H, J=7Hz ), 4.11(q , 2H), 5.37 (s, 1H ), 6.04( s , 1H), 7.27(d , 2H, J=8Hz), 7.29( d, 2 H, J=8Hz), 8.3( s, 1H). M. P. 206°C. R$_f$= 0.68, (n-Hexane).
3. Synthesis of ethyl 4- (4- bromophenyl)- 6- methyl- 2- oxo- 1, 2, 3, 4- tetrahydropyrimidine- 5- carboxylate.

A mixture of P-bromobenzaldehyde (0.30 gm, 10 mmol.), ethyl acetoacetate (1.30 ml, 10 mmol.), Urea (0.9 gm, 15 mmol.) and Catalyst (10 mmol %), was heated with stirring. The progress of reaction was monitored by TLC. After completion of the reaction, crushed ice was added, the solid product was filtered off, washed with ice cold water, dried and recrystallized from ethanol. M.P. 212\(^0\)C

\(^1\)H NMR - (300 MHz, DMSO) \(\delta = 1.11 (t, J= 7Hz , 3H )\), 2.24 (s, 3H ), 4.01 (q, 2 H, J = 7Hz ), 5.12 (s, 1H ), 7.19 (d, J= 8Hz, 2 H), 7.54 (d, 2 H, J=8 Hz ), 7.77 (s, 1H), 9.24 (s, 1H)

M.P. 212\(^0\)C. \(R_f= 0.75\) (EA/ n-Hexane: 2/10).

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>PPA</th>
<th>(\text{H}_3\text{BO}_3)</th>
<th>(\text{CuCl}_2\cdot2\text{H}_2\text{O-HCl})</th>
<th>(\text{NH}_4\text{Cl})</th>
<th>(\text{AlCl}_3)</th>
<th>(\text{ZnCl}_2)</th>
<th>CAN</th>
</tr>
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<tbody>
<tr>
<td>Temperature</td>
<td>100(^0)C</td>
<td>115(^0)C</td>
<td>100(^0)C</td>
<td>120(^0)C</td>
<td>90(^0)C</td>
<td>85(^0)C</td>
<td>80(^0)C</td>
</tr>
<tr>
<td>Time</td>
<td>120 min.</td>
<td>100 min.</td>
<td>130 min.</td>
<td>125 min.</td>
<td>100 min.</td>
<td>90 min.</td>
<td>80 min.</td>
</tr>
<tr>
<td>Yield(%)</td>
<td>58%</td>
<td>50%</td>
<td>63%</td>
<td>67%</td>
<td>53%</td>
<td>69%</td>
<td>75%</td>
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</table>
CONCLUSION

1. We have assessed various catalysts for the synthesis of variety of Dihydropyrimidinones.
2. We found some catalysts has good activity and gives higheryield of product.
3. CAN is founda nontoxic catalysts.

REFERENCES
