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COMPARATIVE ASSESMENT 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)

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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 in1893[1] referred to as the Biginelli Reaction. Thisone-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 renew 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 Year, 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 1st synthesis ofdihydropyrimidinone wasreported by Biginelli in 1893[1]. Later, themultifunctionlised dihydropyrimidinones or Biginelli compound synthesis was drastically increased since its heterocyclic system of remarkable pharmacological efficiency. Since the several review on synthesis and chemical propertiesof pyrimidoneshave 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

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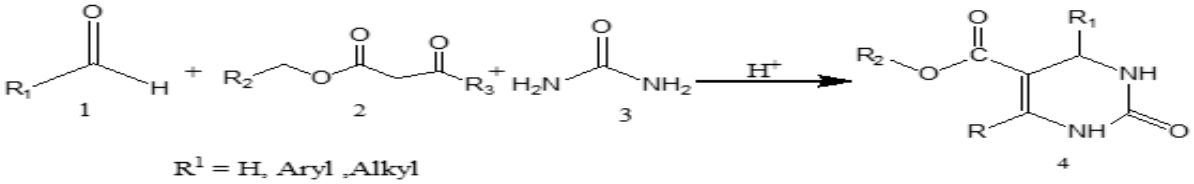
unprecedented attention due to its greater biological, pharmaceutical and therapeutic properties.

In 1893, PietroBiginelli reported the first synthesis of 3, 4- dihydroprimidin-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 componentsmany 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).

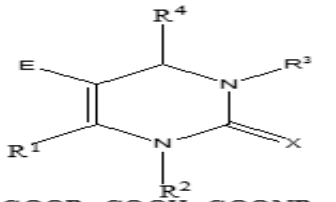
General Reaction:



R^1 = H, Aryl ,Alkyl

R^2= H, Alkyl

R^3= H, Alkyl



E = -COOR,-COOH,-COONR,-CN

X = O,S

R^1= R^2= R^3= H,Alkyl

R^4= H,Alkyl,Aryl Heterocycle

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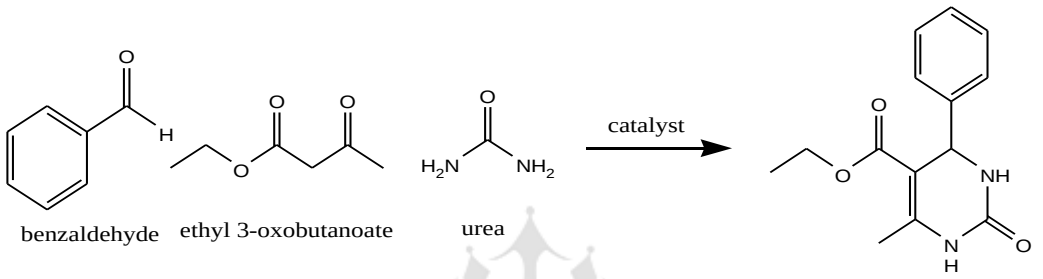
3. SCHEME

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.

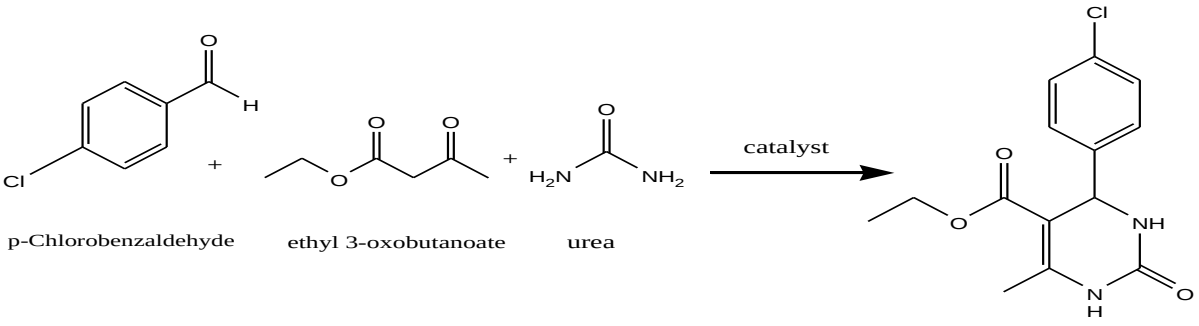
Scheme 1. Synthesis of ethyl 6- methyl- 2- oxo- 4 phenyl- 1, 2 , 3 , 4 tetrahydropyrimidine-5- carboxylate.



benzaldehyde ethyl 3-oxobutanoate urea

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- tetrahydropyrimidine- 5- carboxylate .



p-Chlorobenzaldehyde ethyl 3-oxobutanoate urea

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

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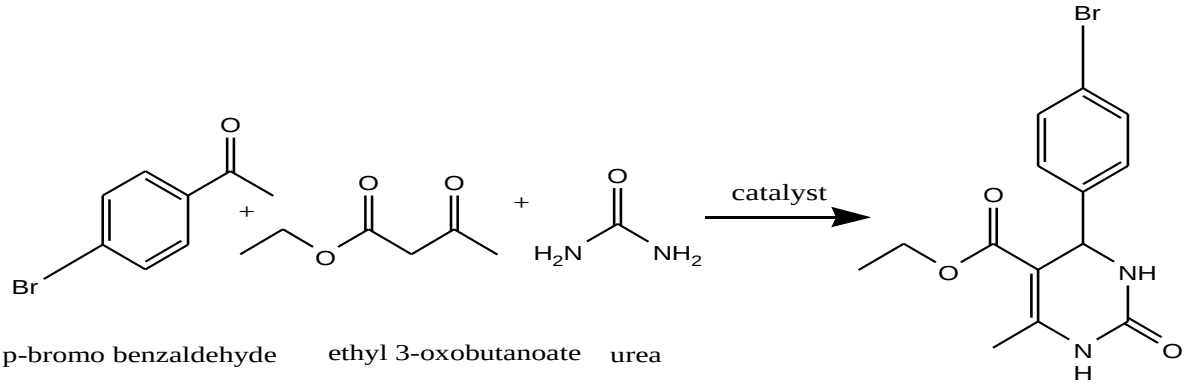
Scheme3. Synthesis of ethyl 4- (4- bromophenyl)- 6- methyl- 2 - oxo- 1, 2, 3, 4 - tetrahydropyrimidine- 5- carboxylate.

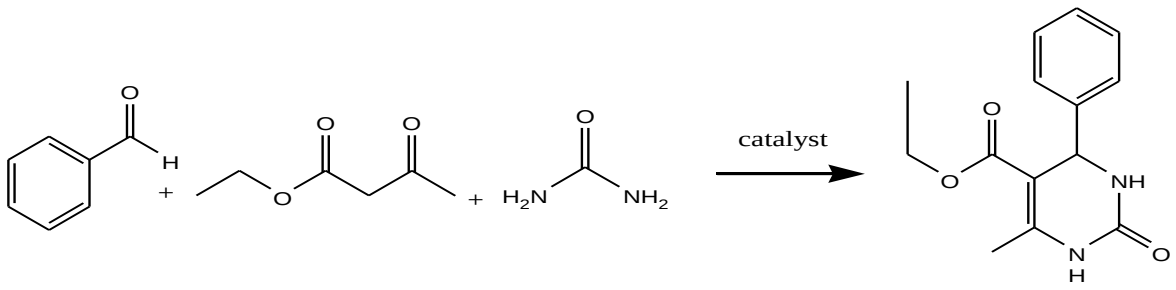


p-bromo benzaldehyde ethyl 3-oxobutanoate urea

ethyl4- (4- bromophenyl)- 6- methyl- 2-oxo- 1, 2 ,3, 4- tetrahydropyrimidi ne- 5-carboxylate

4. EXPERIMENTAL SECTION

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



Benzaldehyde ethyl 3-oxobutanoate urea

ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate

A mixture ofbenzaldehyde (1.06 gm, 10mmol.), 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

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was added, the solid product was filtered off, washed with ice cold water, dried and recrystallized from ethanol. M. P. 204^{0}C,

^{1}HNMR - (300 MHz, $CDCl_3$) δ = 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^{0}C. (Ethyl Acetate+ n- Hexane: 1/9), Rf= 0.59.

Catalyst	PPA	H_3BO_3	$CuCl_2.2H_2O$-HCl	NH_4Cl	$AlCl_3$	$ZnCl_2$	CAN
Temperature	120^{0}C	105^{0}C	100^{0}C	110^{0}C	95^{0}C	75^{0}C	80^{0}C
Time	125 min.	110min	110 min.	90 min.	120min	150 min.	60min.
Yield (%)	65%	62%	55%	50%	68%	58%	72%

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 ^{0}C

^{1}HNMR- (300 MHz, $CDCl_3$) δ = 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 ^{0}C. R_f= 0.68, (n-Hexane).

Catalyst	PPA	H_3BO_3	$CuCl_2.2H_2O$-HCl	NH_4Cl	$AlCl_3$	$ZnCl_2$	CAN
Temperature	120^{0}C	105^{0}C	120^{0}C	100^{0}C	90^{0}C	85^{0}C	80^{0}C
Time	130 min.	110min	95 min.	90 min.	120 min.	95 min.	70min.
Yield (%)	62%	53%	50%	68%	55%	72%	65%

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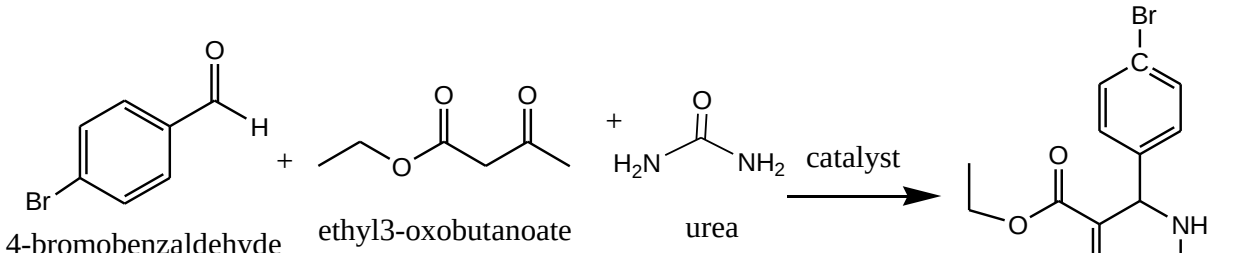
3. Synthesis of ethyl 4- (4- bromophenyl)- 6- methyl- 2- oxo- 1, 2, 3, 4- tetrahydropyrimidine- 5- carboxylate.



4-bromobenzaldehyde ethyl3-oxobutanoate urea

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, 15mmol.) and Catalyst (10 mmol %), was heated with stirring. The progress ofreaction was monitoredby 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) δ = 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).

Catalyst	PPA	H_3BO_3	$CuCl_2.2H_2O$-HCl	NH_4Cl	$AlCl_3$	$ZnCl_2$	CAN
Temperature	100^0C	115^0C	100^0C	120^0C	90^0C	85^0C	80^0C
Time	120min.	100 min.	130 min.	125min.	100min.	90min.	80 min.
Yield(%)	58%	50%	63%	67%	53%	69%	75%

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CONCLUSION

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

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