ISSN: 2454 - 4248
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An Efficient Multicomponent One Pot Synthesis of Dihydropyrimidnones by Biginelli Reaction

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***Abstract* : -** In our reaction various aldehydes are use and instead of ethyl acetoacetate used methyl acetoacetate and instead of thiourea used urea in presence of 85% H_3PO_4 and 95% ethanol mainly played a role of dehydrating agent by convection method. as Acid catalyzed condensation of ethyl acetoacetate, aldehyde and urea in ethanol by refluxing the mixture and on cooling he obtained a solid crystalline product 3,4-dihydropyrimidin-2(1H)-one which apparently was a three component reaction, the acid used here was HCL (hydrochloric acid). This reaction is also known as Biginelli condensation or as Biginelli dihydropyrimidine synthesis.

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I. INTRODUCTION

Pyrimidinones or Dihydropyrimidinones (DHPMs) are well known for their wide range of bioactivities and their application in the field of drug research have stimulated the invention of a wide range of synthetic method for their preparations and chemical transformation out of the five major bases in nucleic acid three are Pyrimidine derivatives which comprises of cytosine which is found in DNA and RNA, Uracil in RNA and Thymine DNA because of their environment as bases in DNA and RNA, they have become very important in the world of synthetic organic chemistry Aryl substituted 3,4 dihydropyrimidin-2H thione and Medicinal Chemistry.

In recent years, the growing interest on exploitation of a multicomponent reaction MCR[1-4] for the fat development of library of biologically.The promising greener economy as compared to multicomponent reaction one such MCR is the classical Biginelli[5] their component reaction on which involve catalysed reaction the MCRs reactions have gained importance because of their efficiency and effectiveness as a method for one-pot synthesis of a wide range of hetrocycles[1-6].The optimal MCR is sufficiently flexible. Among the MCRs the Biginelli reaction[7] is used for the direct synthesis of 3,4 dihydropyramidine derivative. The 3, 4 dihydropyramidine and its derivatives are highly significant because they generally, show diverse medical properties such as Calcium channel blockers, antihypertensive and anti-inflammatory agents, and α 1-a antagonist [8-11].

Furthermore 3,4 dihydropyramidine derivatives have emerged as important target molecules because of their Pharmacological and antiviral, antitumor, anticarcinogenic, antibacterial and fungicidal activities [12-19]. In the initial here there was not much synthesis activities in this reaction but during last 100 years or so this reaction received much. Attention and as a result their where nearly 500 research publishing mostly involving catalyst changes. During this year from its Discovery emphasis was on understanding the course of reaction with some emphasis on structural varieties subsequent to this academic development the Biginelli scaffold was shown to be of great value from a pharmaceutical point of view, because of this importance, investigation very fast and virtual every major journal was flooded with papers on the Biginelli reaction [20].

Biginelli dihydropyramidine synthesis has been regularly and continuously subjected to alteration for improvement and simplification. The numbers of improved variants employing new reagent catalysts, methodologies and techniques have emerged. Serval synthetic methods involving solvent-free green reaction have been developed. Likewise, serval chemical transformations have been successfully affected involving.

Dihydropyramidinones particularly at 1 or 3, 2 and 5 positions including acylation [21]. Over the past decade, dihydropyramidine-2(1H)-ones and their derivatives have attracted considerable attention in organic chemistry as the dihydropyramidine scaffold displays a fascinating array of pharmacological and therapeutic properties[22].

In this efficient approach to partly reduce pyrimidines, termed the Biginelli reaction or condensation, was largely ignored in the following years, and therefore also the synthetic potential of these multi functionalized Dihydropyrimidines remained unexplored. In recent year, however, interest in these compounds has an increased rapidly, and the scope of the original cycloaddition reaction has been widely extended by variation of all three components.

The simple MCR for dihydropyrimidinone synthesis and utilisation of these multidisciplined moieties is in Falls swing for the last few decades which is clearly evident from the increasing number of publications and patents. The properties of these compounds can be changed considerably by varying the reactants of the reaction, which is profound interest to contemprory scientific community. The original cyclocondensation reaction has been extended widely to

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include the variations in the all three components. Of these, the aldehyde component has been varied to the largest extent and now includes not only many aromatic [13, 24, 25, 27] but also aliphatic [25-31] and heterocyclic aldehydes [32] of particular interest are reactions where the aldehyde component is derived from a carbohydrate [33]. Another unusual substitute for an aldehyde in the standard Biginelli reaction is α, β dichloro ethyl ethyl ether [34]. The 4-unsubstituted derivatives is prepared by reaction of methylene urea with ethyl acetoacetate [33-35]. In some cases, aldehydes diacetates have been used instead of the unprotected aldehydes [29-32].

Apart from common Alkyl acetoacetates which have employed frequently as the β-ketones component other acetoacetate acid esters such as benzyloacetate [28, 36], methyl acetoacetate [36], β-chloroethyl [37], 2-furanylmethyl [38], and ethylthiocetoacetate [38] and benzylacetic have been used successfully in the Biginelli reaction.

Similarly, ethyl trifluoromethylacetocetate [25] afford corresponding 6-functionalist dihydropyrimidinones. Legend [39] use simple Ketones to form DHMPs under a solvent free microwave assisted condition. The diketones are substituted by spirofused hydrocycles [40] and α-substitute ketoacids [41] for the successful formtion of Biginelli in compound. Primary, secondary and tertiary acetoacetamides have been used in place of ester to produce [25, 42, 44]. Substituted ureas and trioureas can replace the urea component. It should be emphasized that monosubstituted ureas or thioureas form exclusively N-1 substituted dihydropyrimidines [43, 45].

The N-3 alkylated products cannot be obtained by the standard Biginelli reaction or by alkylation of unsubstituted derivatives. N, N'- disubstituted ureas do not react at all under these conditions. Nilsson and Overman [46] effectively utilised the guanidine derivatives instead of urea for the formation of biologically active dihydropyrimidinones.

The classical Biginelli condensation was catalyzed by mineral acids. Later the mineral acids have been replaced successfully by various Lewis acids and metallic solid [48], polymer supported reagents [49], ionic liquids [50], non-metallic reagents [51], and solid catalysts such as clay [52], dowex [53], silica [54], etc. These reagents have been used under conventional as well as modern experimental conditions. The modern methodologies used for the Biginelli reaction involves the microwave assisted organic synthesis [48-54], ionic liquid face organic synthesis [55] and sono chemical techniques [56]. Also, combinatorial approaches [57] towards DH PMs has been advanced under solid phase [57 a, b] or fluorous phase [57 c, d] reaction conditions.

Yet another novel approach to DHPMs have been described by Shutalev et al [58 a] and is outlined below. This synthesis is based on the condensation of readily available α-tosyl substituted (thio) urea's with the (in situ prepared) enolates of aceto-acetate or 1, 3 dicarbonly compounds to give hexahydro pyrimidine which is which is then converted directly into DHPMs. This method works particularly well for aliphatic aldehydes and thioureas and produces high overall yields of the desired target molecular or compounds.

Several research groups have investigated the mechanism of the Biginelli reaction. It dependence upon acid catalysis has been experimentally established [59, 60] and a mechanism proposed by folkers and co-workers [61] in 1933 was accepted. The proposed mechanism has the first step believed to be the condensation between the aldehyde and urea with some similarities iminium intermediate generated act as an electrophile for the nucleophilic addition of the ketonester enol, and the ketone carbonyl of the resulting adduct undergoes condensation with the urea-NH2 to give catalyst product.

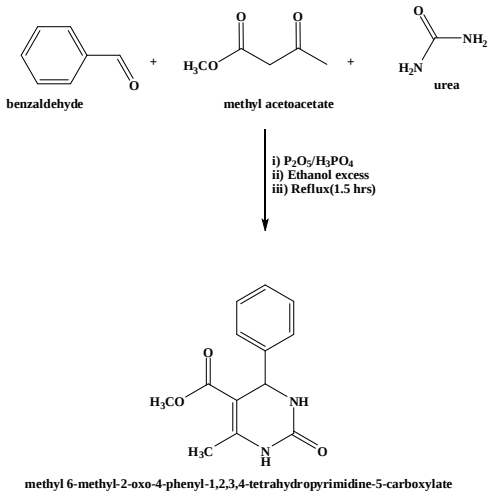
II. EXPERIMENTAL WORK

Scheme-I:-

A mixture of benzaldehyde (0.01 mole) methylacetoacetate MAA (0.01 mole) and urea (0.01 mole) was treated with phosphoric acid and ethanol (0.1 ml 95%), Take this mixture into in a round bottom flask with some porcelain

Now allow to reflux the reaction mixture using condenser and burner. For 1.5 hrs. The reaction mixture then was cooled and progress of reaction was monitored by TLC

Then the product was recrystallized with ethanol. Allow to dry the product. Determine melting point and amount yield of resultant product obtained



Scheme-II:-

A mixture of para methoxy benzaldehyde (0.01 mole) methyl acetoacetate (0.01 mole) and urea (0.01 mole) was treated with phosphoric acid and ethanol (0.1 ml 95%),

Take this mixture into in a round bottom flask with some porcelain

Now allow to reflux the reaction mixture using condenser and burner. For 1.5 hrs the reaction mixture then was cooled and progress of reaction was monitored by TLC

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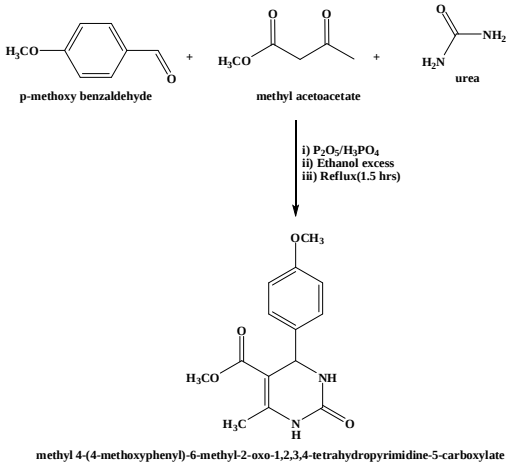


methyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate

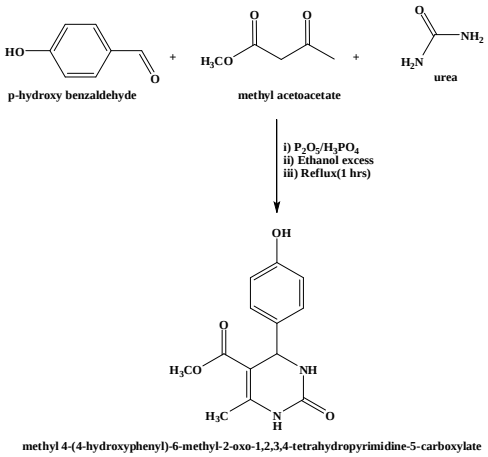
Scheme-III:-

A mixture of para hydroxy benzaldehyde (0.01 mole),methyl acetoacetate (0.01 mole) and urea (0.01 mole) was treated with phosphoric acid and (0.1 ml 95%) ethanol,

Take this mixture into in a round bottom flask with some porcelain

Now allow to reflux the reaction mixture using condenser and burner. For 1.5 hrs The reaction mixture then was cooled and progress of reaction was monitored by TLC

Then the product was recrystallized with ethanol. Allow to dry the product. Determine melting point and amount yield of resultant product obtained



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

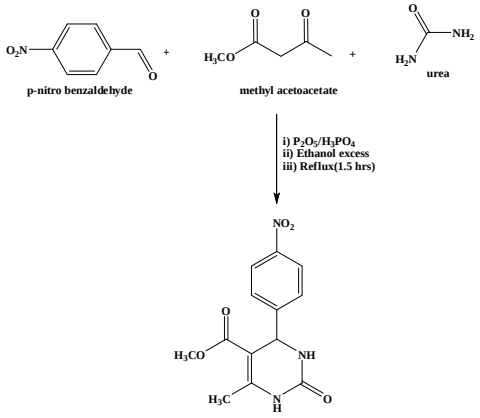
Scheme-IV:-

A mixture of para nitro benzaldehyde (0.01 mole), methylacetocetate (0.01 mole) and urea (0.01 mole) was treated with phosphoric acid and (0.1 ml 95%) ethanol,

Take this mixture into in a round bottom flask with some porcelain

Now allow to reflux the reaction mixture using condenser and burner. For 1.5 hrs The reaction mixture then was cooled and progress of reaction was monitored by TLC

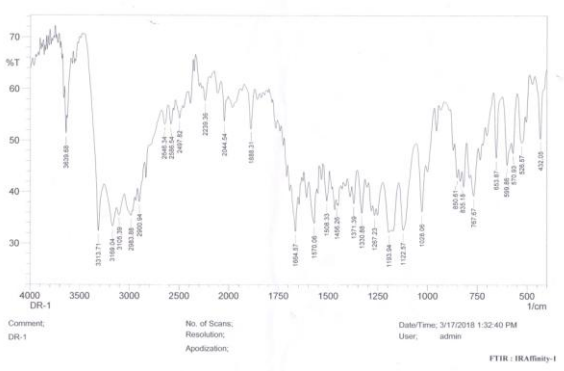
Then the product was recrystallized with ethanol. Allow to dry the product. Determine melting point and amount yield of resultant product obtained



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

III. RESULT AND DISCUSION

A) methyl 6–methyl- 2 –oxo - 4 –phenyl - 1,2,3,4,-tetrahydropyrimidine - 5- carboxylate



Sr. No.	IR SPECTRA		
	Literature frequence Cm^{-1}	*Observed fergunce* Cm^{-}	*Streching*
1	3240.68	3313.71	N-H stretching
2	3112.59	3169.04	Aromatic C-H
3	1727.34	1664.57	C=O

B) methyl4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4tetrahydropyrimidin-5-yl)-2-oxoacteta

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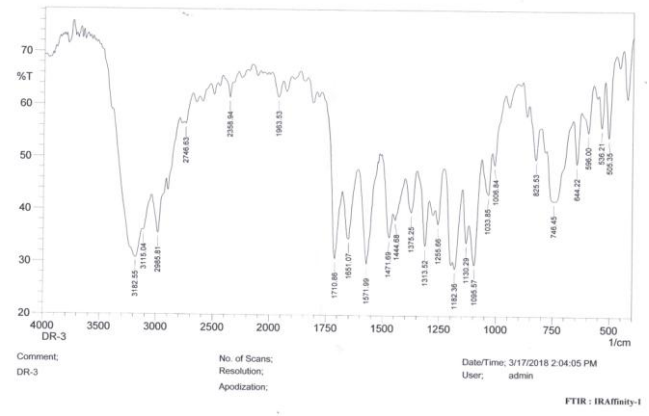
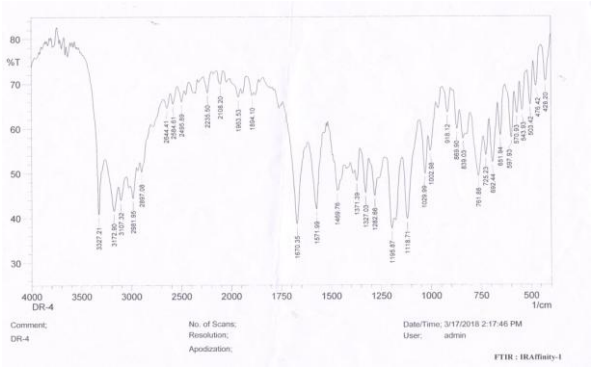


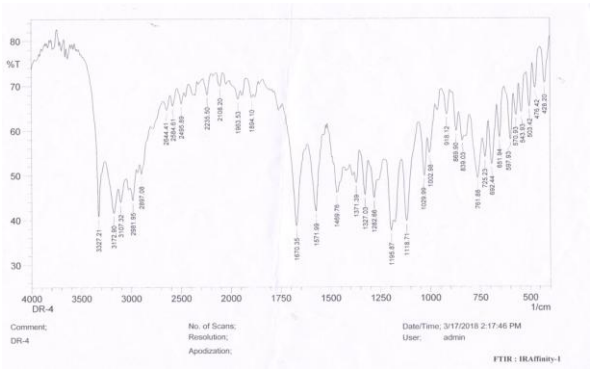
Sr. No.	IR SPECTRA		
	Literature frequence Cm^{-1}	***Observed fergunce Cm***	***Streching***
1	3182.55 - 3115.04	3319.49 – 3172.90	N-H stretching
2	3174.54	3103.46	Aromatic C-H
3	1697.42	1676.14	C=O

C) methyl4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4tetrahydropyrimidin-5-carboxylate



Sr. No.	IR SPECTRA		
	Literature frequence Cm^{-1}	***Observed fergunce Cm***	***Streching***
1	3353.04 - 32285.55	3182.55 – 3115.04	N-H stretching
2	3113.46	2985.81	Aromatic C-H
3	1702.46	1710.86	C=O

D) methyl 6-methyl-4-nitrophenyl-2-oxo-1,2,3,4tetrahydropyrimidin-5-carboxylate



Sr. No.	IR SPECTRA		
	Literature frequence Cm^{-1}	***Observed fergunce Cm***	***Streching***
1	3243.96	3327.21	N-H stretching
2	3116.42	3172.21	Aromatic C-H
3	1725.42	1670.35	C=O

Reactant (I)	Reactant (II)	Reactant (III)	Time (hrs)	M.P. o_C
Methylaceto -acetate	Urea	Benzaldehyde	1.5	202 -203 ^oC
Methylaceto-acetate	Urea	Para methoxy benzaldehyde	1.5	180-181 ^oC
Methylaceto-acetate	Urea	Para hyoxy benzaldehyde	1.5	233-234 ^oC
Methylaceto-acetate	Urea	Para nitro benzaldehyde	1.5	209-210^oC

IV. CONCLUSION

One pot synthesis of 6-methyl-5-ethoxy 4 substituted phenyl 1,2 Diydropyrimidin-2-thiones under Biginelli reaction was reported.

1. Relatively simple catalyst system
2. Higher yield
3. free waste/by product formation
4. Easy synthetic procedure

The application of these method provides a simple powerful tool for the synthesis of large number of ring fused pyrimidine derivatives. The catalyst used in this sentence is an inexpensive chemical that is commonly found are available in most of the organic Laboratories. Another useful aspect is that this procedure is energy efficient. This creation can be adopted for use as an interesting experiment in an organic chemistry teaching laboratory.

V. ACKNOWLEDGEMENT

Author P.K.Mahalle is very much thankful to Head, Department of Chemistry, G.S.College, Khamgaon

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For providing the necessary facilities for this work.

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