SYNTHESIS OF BIOLOGICALLY AND PHARMACOLOGICALLY ACTIVE DIHYDROPYRIMIDONES/THIONES: A REVIEW

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ABSTRACT

The dihydropyrimidones/thiones (DHPM’s) and its derivative are an important class of organic as well as heterocyclic compounds. The chemistry of these compounds revised day by day because these are one of the most advantaged medicinal pharmacophore which appears as an important structural part in many naturally occurring and synthetically prepared medicinal drugs and heterocyclic compounds. Literature survey reveals that in the last few years many scientists, chemists and researchers are engaged in the synthesis of various types of dihydropyrimidones/thiones and its derivatives as they having great biological and pharmacological activities. Generally synthesis of dihydropyrimidones/thiones involve one pot multicomponent reaction of various aldehydes, β- ketoester (1,3- dicarbonyl compound) and urea or thiourea.

KEYWORDS: Synthesis of dihydropyrimidones/thiones, Lewis acids, multicomponent reactions.

INTRODUCTION

Multicomponent reactions have manifested as a powerful tool for the rapid introduction of molecular diversity and molecular economy. The ability of building up the pharmaceutical molecules makes multi-component condensation reactions an important tool in the organic synthesis. The design and development of advance multicomponent reactions for the synthesis of various heterocycles receives growing interest from last few decades.

Now a day’s organic chemists have engaged in the development of new and known multicomponent reactions as an encouragement to rapidly intend simple synthesis to large
number of novel compounds. Among them, the esteemed three component Biginelli reaction has recently attracted an improved interest based on the invention of many different catalysts that allow the preparation of the resultant dihydropyrimidones (DHPMs) with excellent results as compare to the limited success encountered in the original reports.

The Italian chemist Pietro Biginelli (1893) for the first time reported the acid-catalysed cyclo-condensation reaction of ethyl acetoacetate, benzaldehyde, and urea.\[1\] The three components reaction mixture in ethanol was simply heated with a catalytic amount of concentrated hydrochloric acid (HCl) at reflux temperature and the product that precipitated on cooling in the reaction mixture was 3,4-dihydropyrimidin-2-1(H)-one as shown in Scheme- 1.

![Scheme- 1: Biginelli reaction.](image)

The Dihydropyrimidinones (DHPMs) are an important class of organic and heterocyclic compounds which have attracted extraordinary attention during the last decade due to their broad biological and pharmaceutical activities. Dihydropyrimidinones and their derivatives can act as calcium and potassium channel blocker\[2\], antihypertensive agents\[3\], α-la-antagonist\[4\], anticancer agents\[5\], antioxidants\[6\] and neuropeptide Y (NPY) antagonists.\[7\] Similarly 3,4-Dihydropyrimidinones and their sulfur analogues were found to exhibit a wide spectrum of biological activities such as antimalarial\[8\], antiviral, antitumor\[9\], antitubercular\[10\], antibacterial\[11\], anti HIV agent\[12\] and anti-inflammatory behavior. The structure of some of them illustrated below.
Potassium Channel Antagonists 1-4 as shown in fig. 1

![Chemical structures 1-4](image1.png)

Figure 1: DHPMs against Potassium Channel Blockers.

Antihypertensive Agents 5-7 as shown in fig. 2

![Chemical structures 5-7](image2.png)

Figure 2: DHPMs against Antihypertensive Agents.
Anti-tubercular Activity 8-9 as shown in fig. 3

![Figure 3: DHPMs against Anti-tubercular Activity.](image)

Anti-Malarial Agents 10-12 as shown in fig. 4

![Figure 4: DHPMs against Anti-Malarial Activity.](image)

Antitumor Activity 13-14 as shown in fig. 5

![Figure 5: DHPMs against Antitumor Activity.](image)
Anti-bacterial Activity 15-16 as shown in fig. 6

![Antibacterial Activity Diagram](image)

Figure 6: DHPMs found against Anti-Bacterial Activity.

Anti-HIV Agents Batzelladine A 17 as shown in fig. 7

![Antiviral Activity Diagram](image)

Figure 7: DHPMs against HIV Activity.

Therefore, the synthesis of this heterocyclic core unit is of much recent importance. The Biginelli reaction, a one-pot low yield condensation of β-dicarbonyl compounds with aldehydes and urea or thiourea in the presence of catalytic amount of hydrochloric acid gained intense research interest. Other protic acids such as HCOOH, H₂SO₄, AcOH etc are also known to catalyze Biginelli reaction. Recently several methods have been reported to prepare dihydropyrimidinones using different Lewis acids such as Bi(OTf)₃, Cu(OTf)₂, LiBr, NbCl₅, HClO₄-SiO₂, SnCl₂-CdCl₂, LiClO₄, CAN, BF₃.OEt₂, NiCl₂.6H₂O or FeCl₃.6H₂O, InBr₃, ZnCl₂, RuCl₃, ZrCl₄, CeCl₃.7H₂O, La(OTf)₃, AlCl₃, Sr(OTf)₂, FeCl₃, LaCl₃, In(OTf)₃, H₃BO₃, trimethylsilyl chloride (TMSCl), polyphosphoroteester, Silicasulfuric acid, Y(NO₃)₃.6H₂O, TaBr₃, Ce(NO₃)₃.6H₂O, SrCl₂.6H₂O-HCl, Bi(NO₃)₃.5H₂O, 1,1,3,3-tetramethylguanidinium trifluoroacetate and [bmim] BF₄-immobilized Cu(II) acetylacetonate etc.
Several other catalysts, such as polymer-supported ytterbium(II) reagent, Ag₃PW₁₂O₄₀, ferric chloride/tetraethyl orthosilicate, MgCl₂-6H₂O, iodine-alumina, trimethylchlorosilane, heteropolyacids, Silica gel supported-sodium hydrogen sulfate, natural HEU type zeolite and N-bromosuccinimide can also catalyze the Biginelli reaction.

**Literature Review**

B. P. Bandgar, V. T. Kambale, S. N. Bavikar and Abasaheb Dhavane reported the potentiality of sodium tetrafluoroborate to catalyze organic transformations such as the synthesis of dihydropyrimidinones/thiones which do not require additive or protic/Lewis acid. The synthesis of dihydropyrimidinones/thiones by a three-component one-pot condensation of an aldehyde, β-ketoester and urea using sodium tetrafluoroborate[36] as a commercially available, mild, inexpensive and novel promoter for open chained 1,3-dicarbonyl compounds to afford dihydropyrimidinones as shown in Scheme-2.

In the recent years, the use of lanthanide(III) compounds as catalysts in organic synthesis has attracted great interest from many chemists. Lanthanide additives or complexes can increase the reactivity and selectivity of many types of reaction. Jun Lu et al had developed a simple and efficient method for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones using novel lanthanum chloride heptahydrate as the catalyst[24] in good yields from readily available starting material β-ketoester, aldehyde, and urea or thiourea and refluxing them in ethanol as shown in Scheme-3.
Hemant Hegde, Santosh L. Gaonkar and Nitinkumar S. Shetty has reported Bronsted base catalyzed Biginelli type reactions. A base-catalyzed report of Biginelli reaction utilized t-BuOK as a catalyst for the synthesis of Biginelli type condensation of aldehyde, 2-phenylacetophenone, and urea or thiourea to form 4,5,6-triaryl-3,4-dihydropyrimidin-2(1H)-ones as a predominant product\textsuperscript{[37]} as shown in Scheme- 4.

\[ \text{R} = 4-\text{Cl}, 4-\text{Me}, 4-\text{NO}_2, 4-\text{F}, 4-\text{OMe} \text{ etc.} \]

\textbf{Scheme- 4.}

Seyedeh Hatemeh Hojati et al perform the Biginelli reaction by reacting benzaldehyde, ethyl acetoacetate and urea using 1,3-Dichloro-5,5-dimethylhydantoin (DCDMH) as catalyst to afford 3,4-dihydropyrimidine-2(1H0-ones\textsuperscript{[38]} as shown in Scheme- 5. DCDMH is a stable, inexpensive and commercially available heterocycle which has catalytic application in organic synthesis. The DCDMH catalyst heated at 110$^\circ\text{C}$ for 3 hours then used under the same reaction conditions showed that this reaction was performed successfully without any loss of catalytic activity of DCDMH, which indicates DCDMH is a highly efficient catalyst in the synthesis of dihydropyrimidones.

\textbf{Scheme- 5.}

B. R. Chaudhari and Co-workers reported Biginelli’s reaction with new and efficient catalyst aluminium sulphate octadecahydrate (Al$_2$(SO$_4$)$_3$.18H$_2$O) having high catalytic activity which is aluminium (III) salt of sulfuric acid was used as novel catalyst for the synthesis of
dihydropyrimidones[^39] Scheme- 6. The aluminium sulphate is inexpensive, simple, easily available, high yielding catalyst having much less reaction time with lower environmental pollution.

![Scheme-6](image)

As environmental awareness has increased in chemical research and industry, the challenge for a sustainable environment requires clean procedures. In addition, other new methods, including microwave irradiation, ionic liquids and clays, solvent free and catalysts free procedures and synthesis of solid phase had also been used for the synthesis of dihydropyrimidones.

Chen Jiang Liu and Ji De Wang discovered Lewis acid applications for the synthesis of dihydropyrimidinones and ultrasound-assisted synthesis. The preparation of 4-(2-phenyl-1,2,3-triazol-4-yl)- 3,4-dihydropyrimidin-2(1H) thiones[^40] from 1,3-dicarbonyl compounds, 2-phenyl-1,2,3-triazole-4- carbaldehyde and urea or thiourea in the presence of efficient Sm(ClO$_4$)$_3$ catalyst under ultrasound irradiation as shown in Scheme- 7. It requires mild reaction conditions, short reaction times with easy isolation method and good yields.

![Scheme-7](image)

Charansing H. Gill and its Co-worker reported organic transformations in aqueous media without using hazardous reagents or solvents. The use of solid acid catalysts had gained an immense importance in organic synthesis due to their several advantages such as operational simplicity, no toxicity, reusability, low cost, and ease of isolation after completion of the reactions.
reaction. It is well-known that thiamine hydrochloride (VB1) is a cheap and non-toxic reagent; it contains a pyrimidine ring and a thiazole ring linked by a methylene bridge.

![Figure 8: Structure of thiamine hydrochloride (VB1).](image)

The commercially available catalyst thiamine hydrochloride is used as a catalyst for Bigenelli reaction of substituted aldehydes, β-ketoester and urea to afford 3,4-dihydropyrimidin-2-(1H)-ones in aqueous medium using ultrasound irradiation\(^\text{[41]}\) as shown in Scheme- 8. This reaction had advantages of green synthesis with no organic solvents involved in reaction, less reaction time, improved yields and mild reaction conditions.

![Scheme- 8.](image)

Ridha Ben Salem et al synthesized dihydropyrimidones by simple one pot, multicomponent method, Biginelli condensation of an aldehyde, β-ketoester and urea in the absence of solvent using ammonium chloride, Montmorillonite KSF as catalysts under ultrasonic irradiation\(^\text{[42]}\) as shown in Scheme- 9.

![Scheme- 9.](image)

D. Somasundran, S. Elumalai and S. Guhanathan established a useful and more efficient alternative using an inexpensive, non-hazardous and simple eco-friendly reagent pineapple
juice for one-pot synthesis of dihydropyrimidinones/thiones under mild condition\cite{43} as Scheme-10. These types of approaches towards the chemical processes are needed for energy preservation or less hazardous waste production. Due to acidic nature pineapple juice (pH=3.7) as a natural catalyst had been found to be a suitable substitute for various homogeneous acid catalysts.

\[
\text{Ethyl acetoacetate} \quad R_1 \quad O \quad O \quad \text{Et}
\]

\[
\text{Aldehyde} \quad R_2 \quad \text{H} \quad \text{H}_2\text{N} \quad \text{NH}_2 \quad \text{Urea}
\]

\[
\text{Pine apple juice} \quad 3 \text{ hrs stirring}
\]

\[
\text{Scheme-10.}
\]

De Vasconcelos and Co-workers reported an efficient and clean new method to prepare 3,4-dihydropyrimidin-2(1H)ones by a one-pot three-component cyclo-condensation reaction of a 1,3-dicarbonyl compound, aldehyde, and urea using citric acid or tartaric acid as a promoter for the Biginelli reaction in ethanol as solvent\cite{44} as shown in Scheme-11.

\[
\text{Thiourea or urea} \quad \text{Cittric acid or tartaric acid}
\]

\[
X=S,O
\]

\[
\text{Scheme-11.}
\]

In the recent days, magnetic nanoparticles as magnetic catalysts had been extensively investigated as inorganic core for the synthesis of organic shell/inorganic core composite particles due to their imminent applications in lots of fields. The use of magnetic nanoparticle catalysts can deal with the isolation and recycling problem encountered in many catalytic reactions.
In the development of efficient and environmental friendly magnetic nanoparticle catalyst, Fazad Zamani and Elham Izadi developed novel and efficient sulfonated-phenylaceticacid coated Fe$_3$O$_4$ nanocomposite (Fe$_3$O$_4$/ PAA-SO$_3$H) heterogeneous catalyst, used in one-pot synthesis of different 3,4-dihydropyrimidin-2(1H)-ones via multicomponent reaction as shown in Scheme- 12. This catalyst shows high catalytic activity, high degree of chemical stability and do not swell up in organic solvents. It can easily recover with an external magnetic field and its catalytic efficiency remains after many repeated reactions.

![Scheme- 12.](image)

V. Mirkhani et al. introduced highly sulfonated carbon material as catalyst by simultaneous sulfonation, dehydration and carbonization of sucrose C$_{12}$H$_{22}$O$_{11}$ in one step. The obtained catalyst is a highly sulfonated carbon solid acid (CH$_{0.45}$O$_{0.65}$S$_{0.22}$) fig. 9 with an amorphous structure used as a promising alternate solid acid catalyst for preparation of dihydropyrimidinones in the Biginelli reactions in one pot condensation of ethyl acetoacetate, benzaldehyde and urea under solvent free reactions as shown in Scheme- 13.

![Figure 9: Synthesis of highly sulfonated carbon catalyst.](image)
M. Kucukislamoglu and Co-workers developed novel synthetic methodology in heterogenous catalyst system. The synthesis of a variety of 3,4-dihydropyrimidin-2(1H)-ones using Alumina sulfuric acid (ASA) as an acid catalyst in the condensation reaction of various aromatic aldehydes and β-ketoester with urea or thiourea without using solvent at room temperature\(^\text{[47]}\) as shown in Scheme- 14. ASA possesses high activity, stable in presence of water and recoverable by simple filtration method.

Farhad Hatamjafari reported new route in heterocyclic synthesis for the synthesis of DHPM’s. They used the SiO\(_2\)-CaCl\(_2\) as a catalyst in a one pot, three component Biginelli reaction in solvent-free conditions between various aromatic aldehydes, ethylacetoacetate and urea or thiourea to afford dihydropyrimidones\(^\text{[48]}\) as shown in Scheme- 15. The use of this catalyst in the reaction reduces generation of hazardous chemical materials.
Vijay V. Dabholkar, Keshav S. Badhe and Swapnil K. Shinde gave a new method for the synthesis of dihydropyrimidones/thiones using calcined Mg/Fe hydrotalcite catalyst. In this method various aldehyde, ethyl acetoacetate and urea under solvent free condition in the presence of calcined Mg/Fe hydrotalcite as a heterogeneous base catalyst to form dihydropyrimidone-2(1H)-ones\(^ {49}\) as shown in Scheme 16. It was simple, environmentally friendly, convenient, highly efficient and green synthetic method.

**CONCLUSION**

In summary, we enlist the simple, efficient, one-pot and green methods for the synthesis of various dihydropyrimidones/thiones and its derivatives using small organic molecules as a Lewis acids, Bronsted bases, natural protic acids and nanoparticles as a catalyst. In last few years literature survey showed that fast growing importance towards synthesis of dihydropyrimidones/thiones due to its ability to show important biological and pharmacological activities. These methods offers an advantage of less reaction time, solvent free, mild reaction conditions, recyclable catalyst, economical, use of inexpensive starting material and simple workup and gives good to excellent yields of product.
ACKNOWLEDGEMENT

We greatly acknowledge Chairman, All the managing Directors and Principal JET’s Z. B. Patil College, Dhule for providing lab facilities, constant encouragement and useful suggestions.

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