WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 11, 410-427. Review Article ISSN 2277– 7105

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

Pritesh R. Jain and *Ashok A. Patil

P.G. Research Centre, Department of Chemistry, JET's Z.B. Patil College, Dhule- 424002 Maharashtra, India.

Article Received on
10 April 2018,
Revised on 30 April 2018,
Accepted on 20 May 2018
DOI: 10.20959/wjpr201811-12465

***Corresponding Author**
Ashok A. Patil
P.G. Research Centre,
Department of Chemistry,
JET's Z.B. Patil College,
Dhule- 424002 Maharashtra,
India.

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.

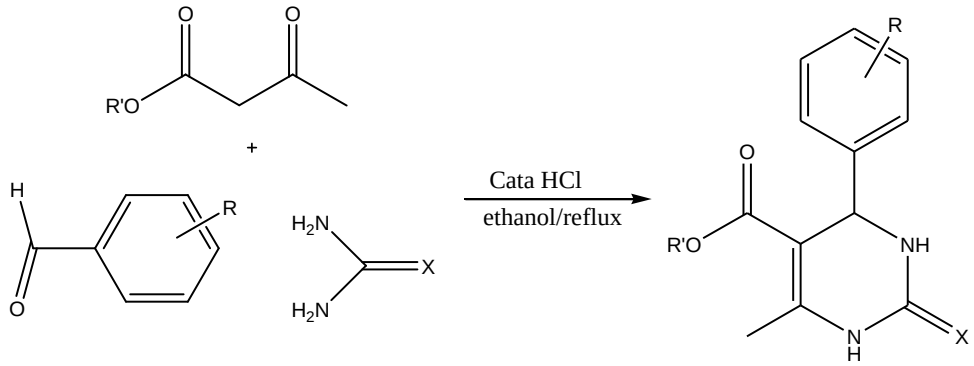
INTRODUCTION

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 multicomonent 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.

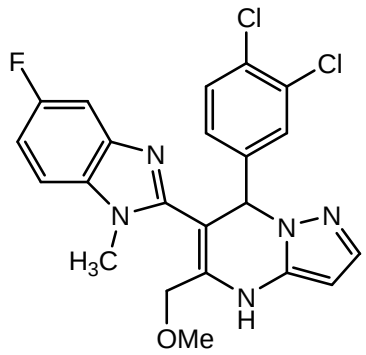
The Italian chemist Pietro Biginelli (1893) for the first time reported the acid- catalysed cyclo-condensation reaction of ethyl acetoacetate, benzaldehyde, and urea.[1] The three components reaction mixture in ethanol was simply heated with a catalytic amount of concentrated hydrochloric acid (HCl) 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.



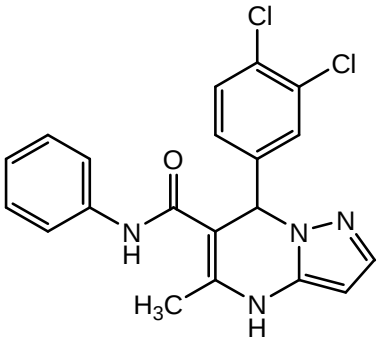
Scheme- 1: Biginelli reaction.

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], anti-tubercular[10], antibacterial[11], anti HIV agent[12] and anti-inflammatory behavior. The structure of some of them illustrated below.

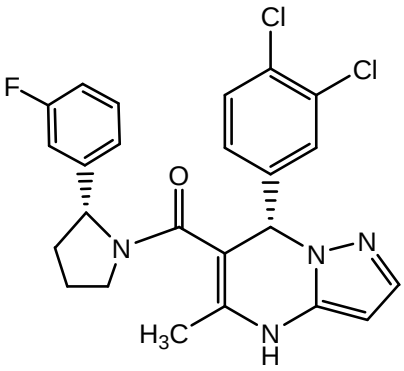
Potassium Channel Antagonists 1-4 as shown in fig. 1



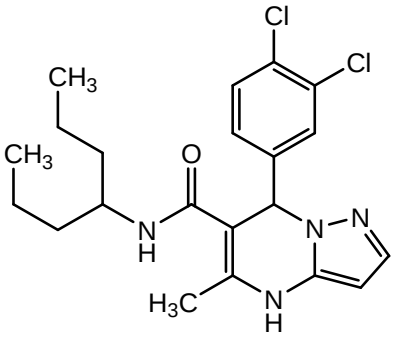
1



2



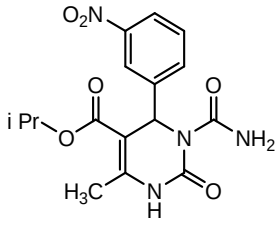
3



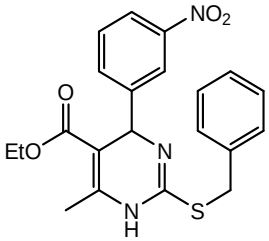
4

Figure 1: DHPMs against Potassium Channel Blockers.

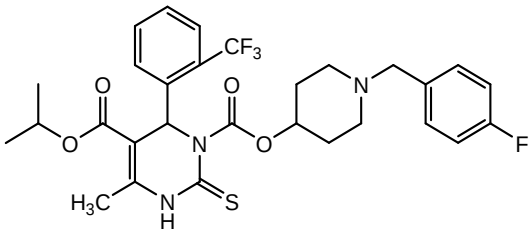
Antihypertensive Agents 5-7 as shown in fig. 2



5



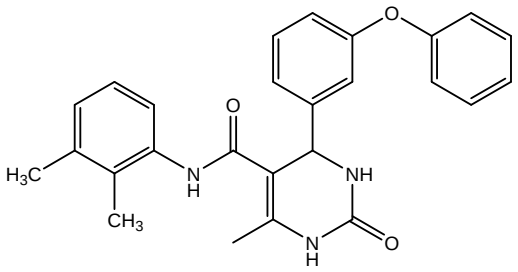
6



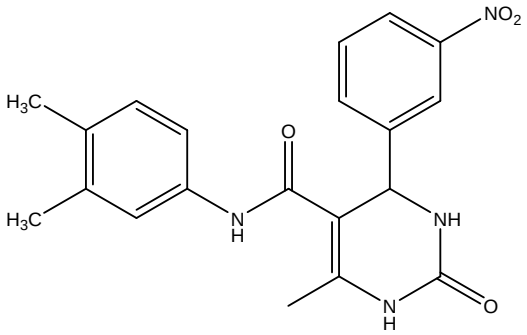
7

Figure 2: DHPMs against Antihypertensive Agents.

Anti-tubercular Activity 8-9 as shown in fig. 3



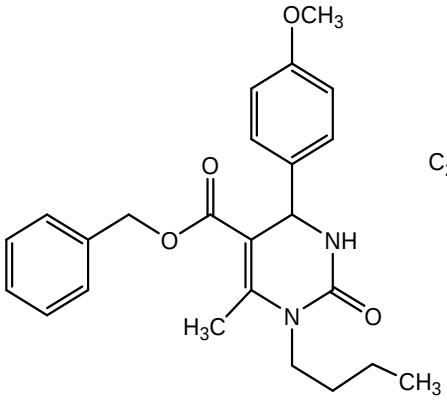
8



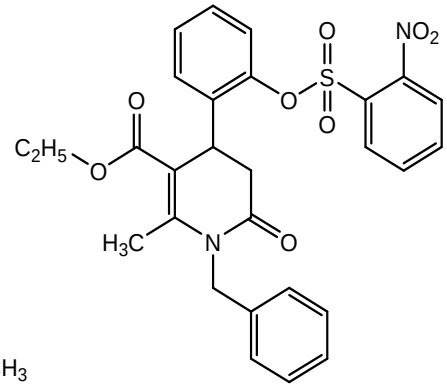
9

Figure 3: DHPMs against Anti-tubercular Activity.

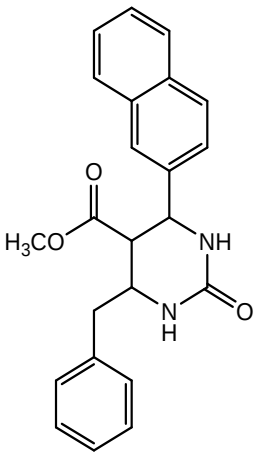
Anti-Malarial Agents 10-12 as shown in fig. 4



10



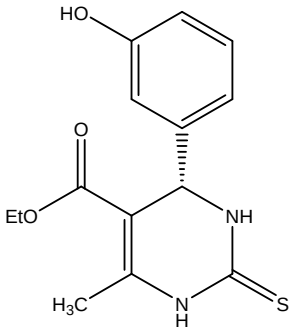
11



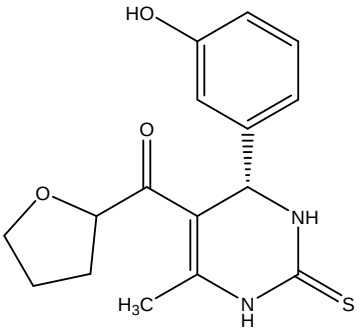
12

Figure 4: DHPMs against Anti-Malarial Activity.

Antitumor Activity 13-14 as shown in fig. 5



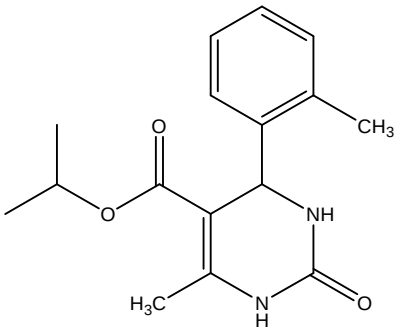
13



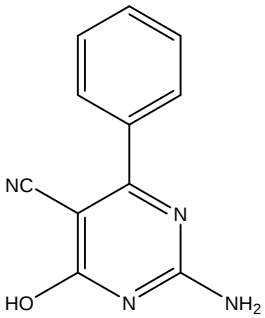
14

Figure 5: DHPMs against Antitumor Activity.

Anti-bacterial Activity 15-16 as shown in fig. 6



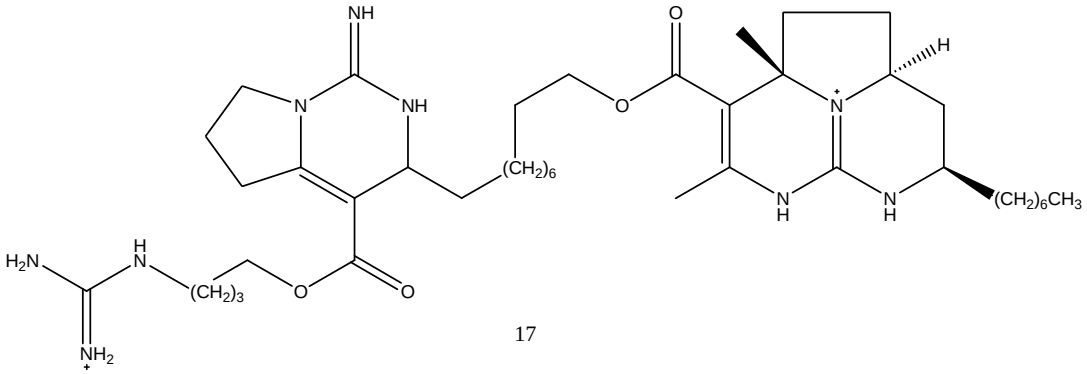
15



16

Figure 6: DHPMs found against Anti-Bacterial Activity.

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



17

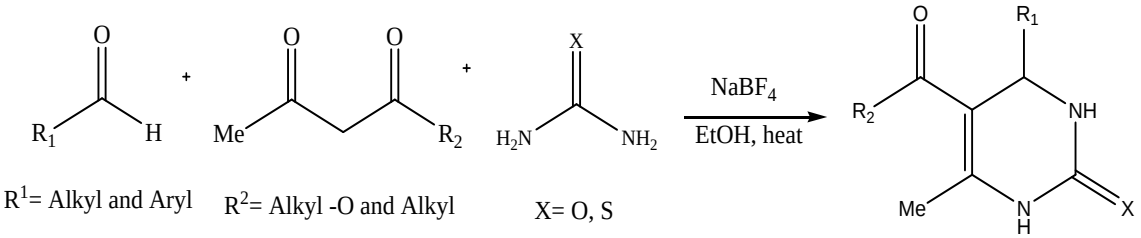
Figure 7: DHPMs against HIV Activity.

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, H_2SO_4, 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, $NbCl_5$, $HClO_4$-SiO_2, $SnCl_2$-$CdCl_2$, $LiClO_4$, CAN, $BF_3.OEt_2$[13], $NiCl_2.6H_2O$ or $FeCl_3.6H_2O$[14], $InBr_3$[15], $ZnCl_2$[16], $RuCl_3$[17], $ZrCl_4$[18], $CeCl_3.7H_2O$[19], $La(OTf)_3$[20], $AlCl_3$[21], $Sr(OTf)_2$[22], $FeCl_3$[23], $LaCl_3$[24], $In(OTf)_3$[25], H_3BO_3[26], trimethylsilyl chloride (TMSCl)[27], polyphosphorateester[28], Silicasulfuric acid[29], $Y(NO_3)_3{\cdot}6H_2O$[30], $TaBr_5$[31], $Ce(NO_3)_3{\cdot}6H_2O$[32], $SrCl_2{\cdot}6H_2O$-HCl, $Bi(NO_3)_3{\cdot}5H_2O$[33], 1,1,3,3-tetramethylguanidinium trifluoroacetate[34] and [bmim] BF_4-immobilized Cu(II) acetylacetonate[35] etc.

Several other catalysts, such as polymer-supported ytterbium(II) reagent, $Ag_3PW_{12}O_{40}$, ferric chloride/tetraethyl orthosilicate, $MgCl_2$-$6H_2O$, 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

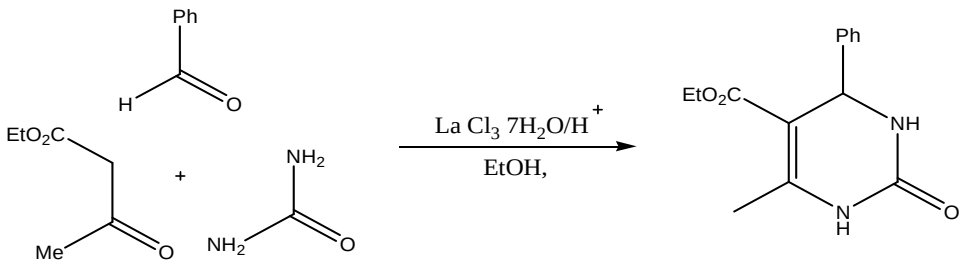
B. P. Bandgar, V. T. Kambale, S. N. Bavikar and Abasaheb Dhavane reported the potentiality of sodium tetrafluoroborate to catalyze organic transformations such as the synthesis of dihydropyrimidinones/ thiones which do not require additive or protic/Lewis acid. The synthesis of dihydropyrimidinones/ 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 dihydropyrimidones as shown in Scheme- 2.



R^1= Alkyl and Aryl R^2= Alkyl -O and Alkyl X= O, S

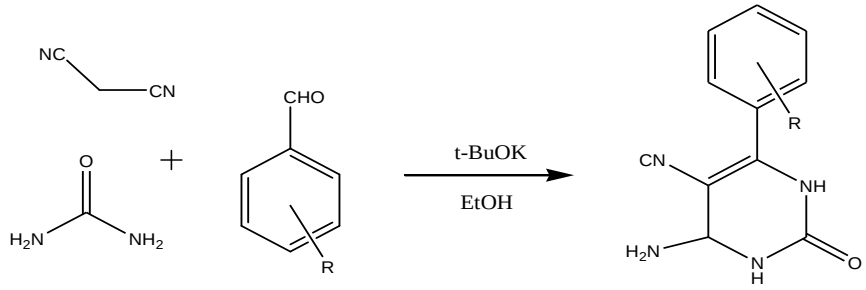
Scheme- 2.

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.



Scheme- 3.

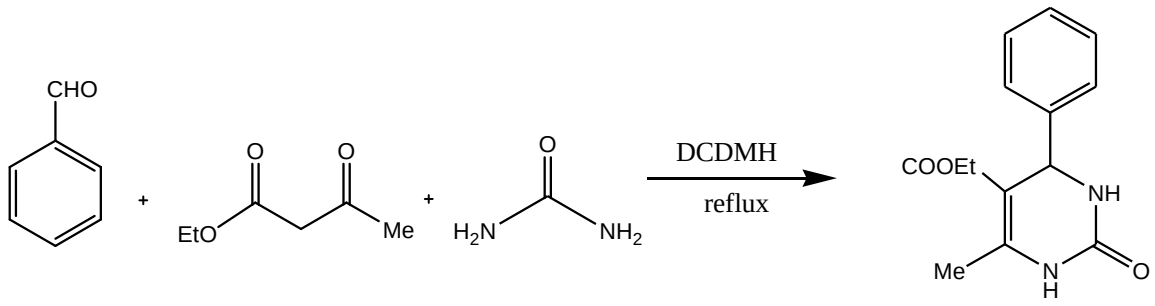
Hemant Hegde, Santosh L. Gaonkar and Nitinkumar S. Shetty has reported Bronsted base catalyzed Biginelli type reactions. A base-catalyzed report of Biginelli reaction utilized t-BuOK as a catalyst for the synthesis of Biginelli type condensation of aldehyde, 2-phenylacetophenone, and urea or thiourea to form 4,5,6-triaryl- 3,4-dihydropyrimidin-2(1H)-ones as a predominant product[37] as shown in Scheme- 4.



R= 4-Cl, 4-Me, 4-NO_2, 4-F, 4-OMe etc.

Scheme- 4.

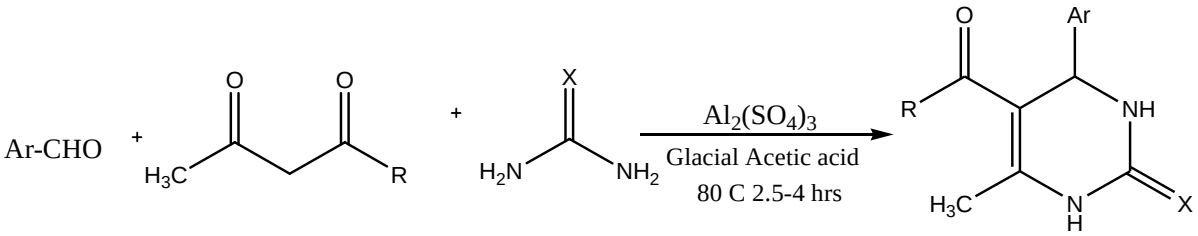
Seyedeh Hatemeh Hojati et al perform the Biginelli reaction by reacting benzaldehyde, ethyl acetoacetate and urea using 1,3-Dichloro-5,5-dimethylhydantoin (DCDMH) as catalyst to afford 3,4-dihydropyrimidine-2(1H0-ones[38] as shown in Scheme- 5. DCDMH is a stable, inexpensive and commercially available heterocycle which has catalytic application in organic synthesis. The DCDMH catalyst heated at 110^{o}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.



Scheme- 5.

B. R. Chaudhari and Co-workers reported Biginelli's reaction with new and efficient catalyst aluminium sulphate octadecahydrate ($Al_2(SO_4)_3.18H_2O$) having high catalytic activity which is aluminium (III) salt of sulfuric acid was used as novel catalyst for the synthesis of

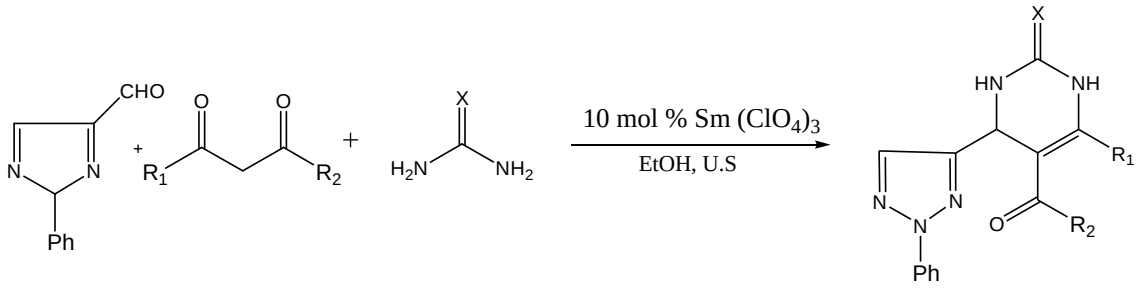
dihydropyrimidones[39] Scheme- 6. The aluminium sulphate is inexpensive, simple, easily available, high yielding catalyst having much less reaction time with lower environmental pollution.



Scheme- 6.

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.

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

reaction. It is well-known that thiamine hydrochloride (VB1) fig. 8 is a cheap and non-toxic reagent; it contains a pyrimidine ring and a thiazole ring linked by a methylene bridge.

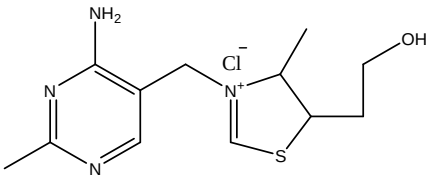
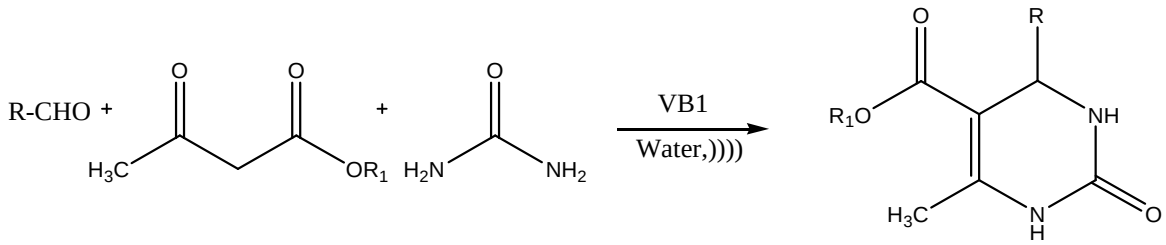


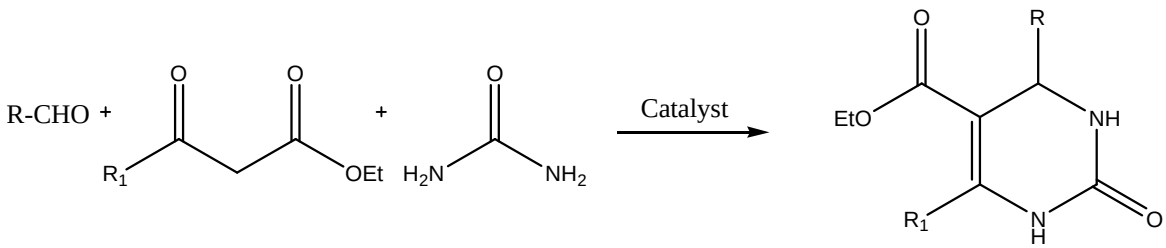
Figure 8: Structure of thiamine hydrochloride (VB1).

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[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.

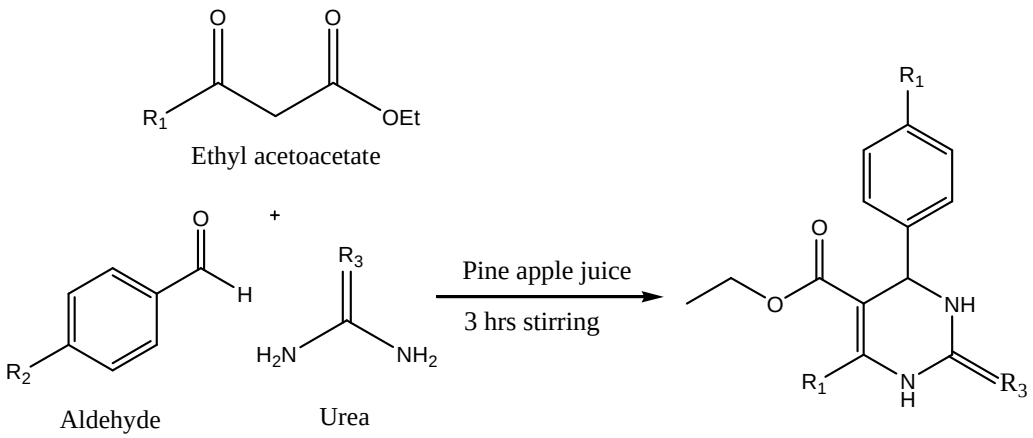
Ridha Ben Salem et al synthesized dihydropyrimidones by simple one pot, multicomponent method, Biginelli condensation of an aldehyde, β-ketoester and urea in the absence of solvent using ammonium chloride, Montmorilonite KSF as catalysts under ultrasonic irradiation[42] as shown in Scheme- 9.



Scheme- 9.

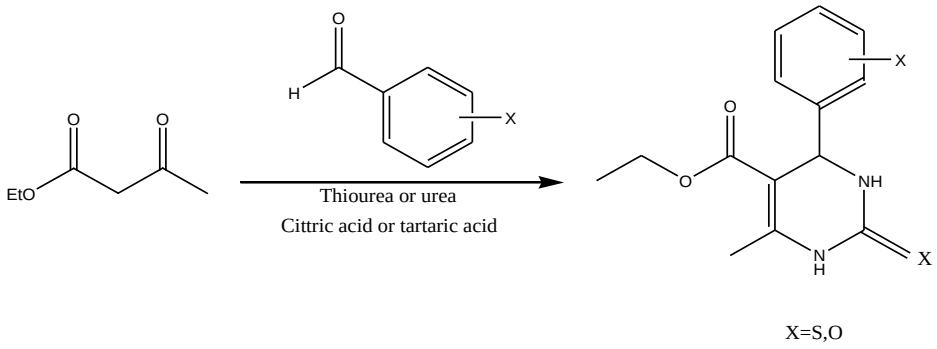
D. Somasundran, S. Elumalai and S. Guhanathan established a useful and more efficient alternative using an inexpensive, non-hazardous and simple eco-friendly reagent pineapple

juice for one-pot synthesis of dihydropyrimidinones/ thiones under mild condition[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.



Scheme- 10.

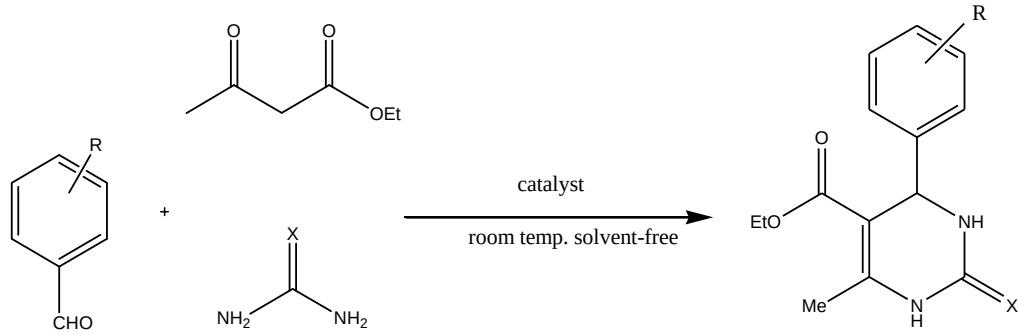
De Vasconcelos and Co-workers reported an efficient and clean new method to prepare 3,4-dihydropyrimidin-2(1H)ones by a one pot three-component cyclo-condensation reaction of a 1,3-dicarbonyl compound, aldehyde, and urea using citric acid or tartaric acid as a promoter for the Biginelli reaction in ethanol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



Scheme- 11.

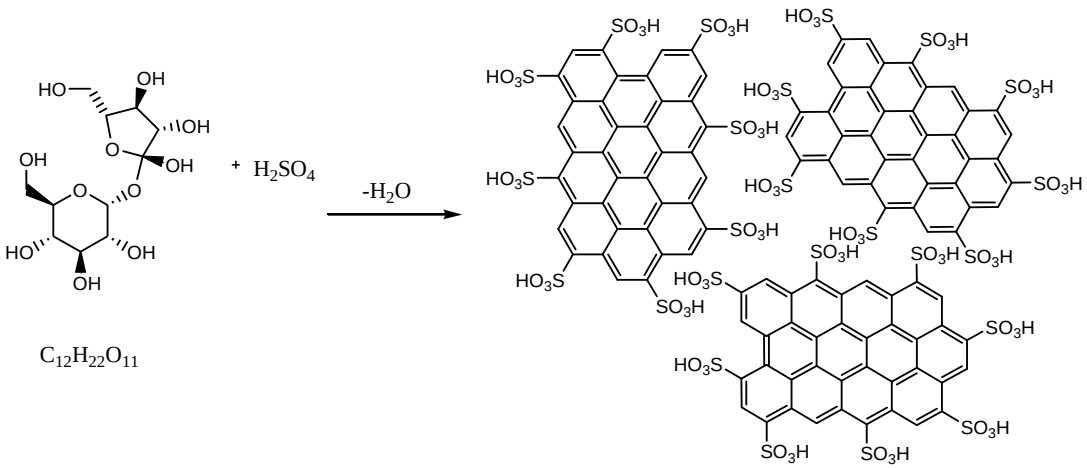
In the recent days, magnetic nanoparticles as magnetic catalysts had been extensively investigated as inorganic core for the synthesis of organic shell/inorganic core composite particles due to their imminent applications in lots of fields. The use of magnetic nanoparticle catalysts can deal with the 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_3O_4 nanocomposite (Fe_3O_4/ PAA-SO_3H) heterogeneous catalyst, used in one-pot synthesis of different 3,4-dihydropyrimidin-2(1H)-ones via multicomponent reaction[45] 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.



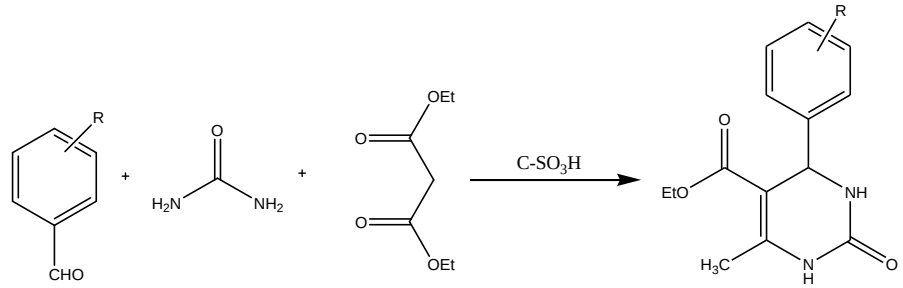
Scheme- 12.

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 ($CH_{0.43}O_{0.65}S_{0.22}$) 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[46] as shown in Scheme- 13.



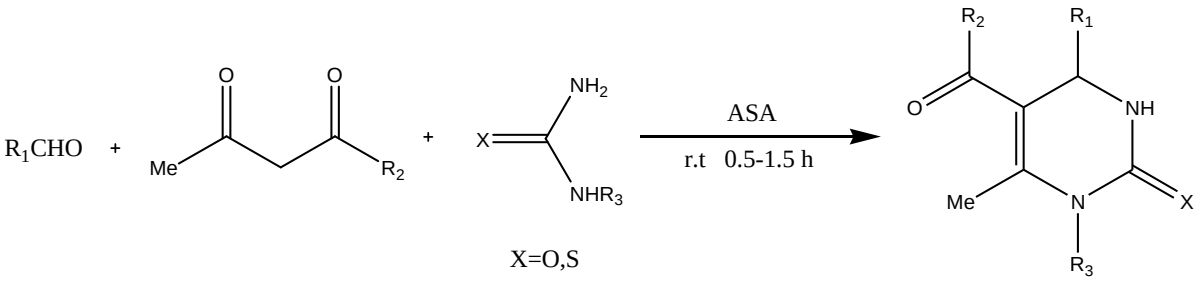
$C_{12}H_{22}O_{11}$

Figure 9: Synthesis of highly sulfonated carbon catalyst.



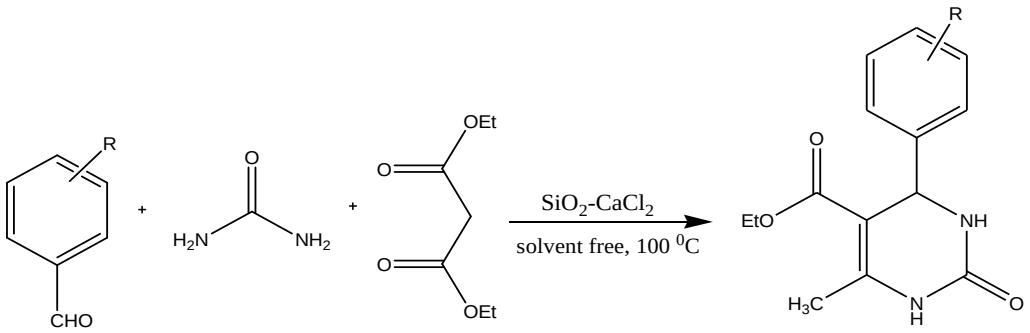
Scheme- 13.

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[47] as shown in Scheme- 14. ASA possesses high activity, stable in presence of water and recoverable by simple filtration method.



Scheme- 14.

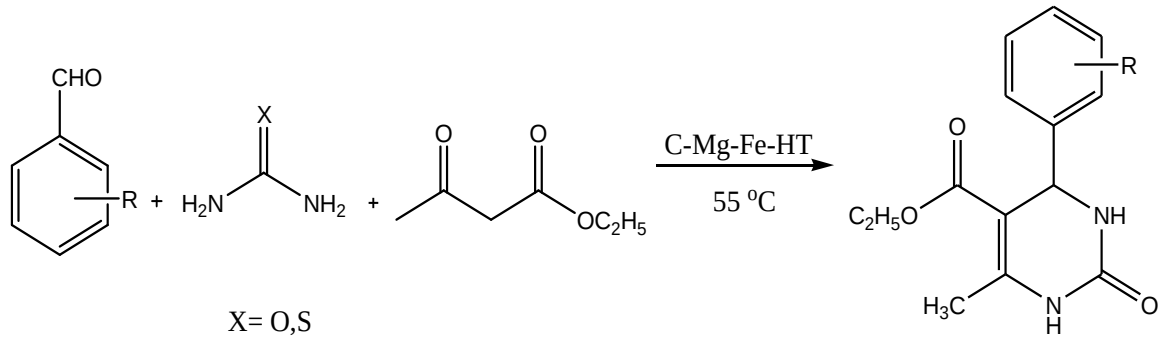
Farhad Hatamjafari reported new route in heterocyclic synthesis for the synthesis of DHPM's. They used the SiO_2-$CaCl_2$ as a catalyst in a one pot, three component Biginelli reaction in solvent-free conditions between various aromatic aldehydes, ethylacetoacetate and urea or thiourea to afford dihydropyrimidones[48] as shown in Scheme- 15. The use of this catalyst in the reaction reduces generation of hazardous chemical materials.



R=H,4-F, 4-CH_3, 4-NO_2, 4-Cl, X=O
R= 4-F, 4-CH_3, 4-NO_2, 4-Cl, X=S

Scheme- 15.

Vijay V. Dabholkar, Keshav S. Badhe and Swapnil K. Shinde gave a new method for the synthesis of dihydropyrimidones/thiones usin 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.



X= O,S

Scheme- 16: Synthesis of Dihydropyrimidones/thiones using c-Mg-Fe-HT.

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

REFERENCES

1. Biginelli P, Gazz P, Synthesis of 3,4-Dihydropyrimidin-2(1H)-Ones, Chim Ital, 1893; 23: 360-416.
2. Rovnyak GC Atwal KS, Hedberg A, Kimball SD, Moreland S and Gougoutas JZ, Dihydropyrimidine calcium channel blockers for basic 3-substituted-4-aryl-1,4-dihydropyrimidine -5-carboxylic acid esters. Potent antihypertensive agents, J. Med. Chem., 1992; 35: 3254-3263.
3. Zorkun IS, Sarac S, Celebib S, Erolb K, Synthesis of 4-aryl-3,4-Dihydropyrimidin-2(1H)-Thione Derivatives as Potential Calcium Channel Blockers, Bioorg. Med. Chem., 2006; 14: 8582-8589.
4. Kappe CO, Fabian WMF, Semones MA, Conformational analysis of 4-aryl-dihydropyrimidine calcium channel modulators. A comparison of ab initio, semiempirical and X-ray crystallographic studies, Tetrahedron, 1997; 53(8): 2803-2816.
5. Russowsky D, Canto RFS, Sanches SAA, D'Oca MGM, Fatima A, Pilli RA, Kohn LK, Antonio MA, Carvalho JE, Synthesis and differential antiproliferative activity of Biginelli compounds against cancer cell lines: monastrol, oxo-monastrol and oxygenated analogues, Bioorg. Chem., 2006; 34: 173-182.
6. Stefani H, Oliveir C, Almeida R, Pereira CMP, Braga RC, Cella R, Borges VC, Savegnago L, Nogueira CW, Dihydropyrimidin-(2H)-ones obtained by ultrasound irradiation: a new class of potential antioxidant agents, Eur J Med Chem., 2006; 41: 513-518.
7. Atwal KS, Swanson BN, Unger SE, Floyd DM, Moreland S, Hodberg A, O'Reilly BC, J. Med. Chem., 1991; 34(2): 806-811.
8. Chiang AN, Valderramos J-C, Balachandran R, Chovatiya RJ, Mead BP, Schneider C, Bell SL, Klein MG, Huryn DM, Chen XS, Day BW, Fidock DA, Wipf P, Brodsky JL, Select Pyrimidinones Inhibit the Propagation of the Malaria Parasite, Plasmodium Falciparum, Bioorg. Med. Chem., 2009; 17: 1527-1533.

9. Agbaje OC, Fadeyi OO, Fadeyi SA, Myles LE, Okoro CO, Synthesis and in Vitro Cytotoxicity Evaluation of Some Fluorinated Hexahydropyrimidine Derivatives, Bioorg. Med.Chem. Lett., 2011; 21: 989-992.
10. Trivedi AR, Bhuva VR, Dholariya BH, Dodiya DK, Kataria VB, Shah VH, Novel Dihydropyrimidines as a Potential New Class of Antitubercular Agents, Bioorg. Med. Chem. Lett., 2010; 20: 6100-6102.
11. Chitra S, Devanathan D, Pandiarajan K, Synthesis and Antioxidant Activity Evaluation of New Hexahydropyrimido[5,4-C] Quinoline-2,5-Diones and 2-Thioxohexahydropyrimido[5,4-C]Quinoline-5-Ones obtained by Biginelli Reaction in Two Steps, Eur. J. Med. Chem., 2010; 45: 367-371.
12. Snider BB and Chen J, Synthesis of Batzelladine E and its E isomer, Tetrahedron Lett., 1998; 39: 5697-5700.
13. Hu EH, Sidler DR, Dolling U, Unprecedented Catalytic Three Component One-Pot Condensation Reaction: An Efficient Synthesis of 5-Alkoxycarbonyl- 4-aryl-3,4-dihydropyrimidin-2(1H)-ones, J, Org. Chem., 1998; 63(10): 3454-3457.
14. Lu J, Bai Y, Catalysis of the Biginelli Reaction by Ferric and Nickel Chloride Hexahydrates One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones, Synthesis, 2002; 466-470.
15. Fu N-Y, Yuan Y-F, Cao Z, Wang SW, Peppe C, Indium(III) bromide-catalyzed preparation of dihydropyrimidinones: improved protocol conditions for the Biginelli reaction, Tetrahedron, 2002; 58(24): 4801-4807.
16. Sun Q, Wang YQ, Ge ZM, Cheng TM and Li RT, A highly efficient solvent-free synthesis of dihydropyrimidinones catalyzed by zinc chloride, Synthesis, 2004; 7: 1047-1051.
17. De SK, Gibbs RA, Ruthenium(III) Chloride-Catalyzed One-Pot Synthesis of 3,4-Dihydropyrimidin-2-(1H)-ones under Solvent-Free Conditions, Synthesis, 2005; 1748-1750.
18. Reddy CV, Mahesh M, Raju PVK, Ramesh Babu T, Narayana Reddy VV, Zirconium(IV) chloride catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones, Tetrahedron Lett., 2002; 43: 2657-2659.
19. Bose DS, Fatima L, Mereyala HB, Green Chemistry Approaches to the Synthesis of 5-Alkoxycarbonyl-4-aryl-3,4- dihydropyrimidin-2(1H)-ones by a Three-Component Coupling of One-Pot Condensation Reaction: Comparison of Ethanol, Water, and Solvent-free Conditions, J. Org. Chem., 2003; 68(2): 587-590.

20. Ma Y, Qian C, Wang L, Yang M, Lanthanide Triflate Catalyzed Biginelli Reaction. One-Pot Synthesis of Dihydropyrimidinones under Solvent-Free Conditions, J. Org. Chem., 2000; 65(12): 3864-3868.
21. Saini A, Kumar S, Sandhu S, Jagir S, Aluminium(III) halides mediated synthesis of 5-unsustituted 3,4-dihydropyrimidin-2(1H)-ones via three component Biginelli-like reaction, Indian Journal of Chemistry, 2007; 46B(10): 1690-1694.
22. Su W, Li J, Zheng Z, Shen Y, One-pot synthesis of dihydropyrimidiones catalyzed by strontium(II) triflate under solvent-free conditions, Tetrahedron Lett., 2005; 46(36): 6037-6040.
23. Choudhary VR, Tillu VH, Narkhede VS, Borate HB, Wakharkar RD. Microwave assisted solvent-free synthesis of dihydropyrimidinones by Biginelli reaction over Si-MCM-41 supported $FeCl_3$ catalyst, Catal. Commun., 2003; 4: 449–453.
24. Lu J, Bai Y, Wang Z, Yang B, Ma H, One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones using lanthanum chloride as a catalyst, Tetrahedron Lett., 2000; 41: 9075-9078.
25. Ghosh R, Maiti S, Chakraborty A, $In(OTf)_3$- catalyzed one-pot synthesis of 3,4-dihydropyrimidin-2(lH)-ones, J Mol. Catal. A Chem., 2004; 217: 47-50.
26. Tu S, Fang F, Miao C, Jiang H, Feng Y, Shi D, Wang X, Onepot synthesis of 3,4-dihydropyrimidin-2(1H)-ones using boric acid as catalyst, Tetrahedron Lett., 2003; 44: 6153-6155.
27. Pisani L, Prokopcova H, Kremsner JM, Kappe CO, 5-Aroyl-3,4-dihydropyrimidin-2-one library generation via automated sequential and parallel microwave assisted synthesis techniques, J. Comb. Chem., 2007; 9: 415-421.
28. Kappe CO, Falsone SF, Synthesis and reactions of Biginelli compounds Part 12: Polyphosphate ester mediated synthesis of dihydropyrimidines: Improved conditions for the Biginelli reaction, Synlett, 1998; 7: 718-720.
29. Salehi P, Dabiri M, Zolfigol MA, Fard MAB, Silica sulfuric acid: An efficient and reusable catalyst for the one-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones, Tetrahedron Lett., 2003; 44: 2889-2891.
30. Nandurkar NS, Bhanushali MJ, Bhor MD, Bhanage BM, $Y(NO_3)_3{\cdot}6H_2O$: A novel and reusable catalyst for one pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones under solvent-free conditions, J. Mol. Catal. A Chem., 2007; 271: 14-17.
31. Ahmed N, Lier JEV, $TaBr_5$-catalyzed Biginelli Reaction: One-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones under solvent-free conditions, Tetrahedron Lett., 2007; 48: 5407-5409.

32. Adib M, Ghanbary K, Mostofi M, Ganjali MR, Efficient $Ce(NO_3)_3 \cdot 6H_2O$-Catalyzed solvent free synthesis of 3,4-dihydropyrimidin-2(1H)-ones, Molecules, 2006; 11: 649-654.
33. Khodaei MM, Khosropour AR, Beygzadeh M, An efficient and environmentally friendly method for synthesis of 3,4-dihydropyrimidin-2(1H)-ones catalyzed by $Bi(NO_3)_3 \cdot 5H_2O$. Synth. Commun., 2004; 34: 1551-1557.
34. Shaabani A, Rahmati A, Ionic liquid promoted efficient synthesis of 3,4-dihydropyrimidin-2-(1H)-ones, Catal. Lett., 2005; 100: 177-179.
35. Jain SL, Joseph JK, Sain B, Ionic liquid promoted an improved synthesis of 3,4-dihydropyrimidinones using [bmim]BF4 immobilized Cu (II) acetylacetonate as recyclable catalytic system, Catal. Lett., 2007; 115: 52-55.
36. Bandgar BP, Kamble VT, Bavikar SN and Dhavane A, Sodium Tetrafluoroborate as a New and Highly Efficient Catalyst for One-pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones and Thiones, J. Chin. Chem. Soc., 2007; 54(2): 1-4.
37. Hegde H, Gaonkar SL and Shetty NS, Bronsted base catalysed efficient one pot three component synthesis of dihydropyrimidinone derivatives, JOCPR, 2015; 7(9): 526-531.
38. Hojati SF, Mostafa G, Haghdoust M and Bull SF, 1,3-Dichloro-5,5-dimethylhydantoin as a Novel and Efficient Homogeneous Catalyst in Biginelli Reaction, Korean Chem. Soc., 2010; 31(11): 3238-3240.
39. Khairnar BJ, Kapade RJ, Borse KM and Chaudhari BR, One pot synthesis of 3, 4-dihydropyrimidin -2(1H) - ones catalyzed by aluminium sulphate: An improved procedure for the Biginelli reaction, Oriental Journal of Chemistry, 2010; 26(2): 655-660.
40. Liu C-J and Wang J-D, Ultrasound-Assisted Synthesis of Novel 4-(2-Phenyl-1,2,3-Triazol-4-yl)-3,4-Dihydropyrimidin-2(1H)-(Thio)ones Catalyzed by $Sm(ClO_4)_3$, Molecules, 2010; 15: 2087-2095.
41. Mandhane PG, Joshi RS, Nagargoje DR, Gill CH, An efficient synthesis of 3,4-dihydropyrimidin-2(1H)-ones catalyzed by thiamine hydrochloride in water under ultrasound irradiation, Tetrahedron Letters, 2010; 51: 3138-3140.
42. Slimi H, Moussaoui Y, Salem RB, Synthesis of 3,4-Dihydropyrimidones Catalyzed By Ammonium Chloride or Montmorillonite KSF Without Solvent Under Ultrasonic Irradiation, Journal de la Societe de Tunisie, 2012; 14: 1-5.
43. Somasundaran D, Elumalai S and Guhanathan S, A Greener Way of Citrus Fruit Mediated Synthesis of Dihydropyrimidinones under Solvent Free Conditions Int. J. of Frontiers in Sci. and Tech., 2014; 2(1): 82-92.

44. Vasconcelos A, Oliveira PS, Ritter M, Freitag RA, Romano RL, Quina FH, Pizzuti L, Pereira CMP, Stefanello FM and Barschak AG, Antioxidant Capacity and Environmentally Friendly Synthesis of Dihydropyrimidin-(2H)-ones Promoted by Naturally Occurring Organic Acids, J Biochem Molecular Toxicology, 2012; 24(4): 155-161.
45. Zamani F, Izadi E, Synthesis and characterization of sulfonated-phenylacetic acid coated Fe_3O_4 nanoparticles as a novel acid magnetic catalyst for Biginelli reaction, Catal. Comm., 2013; 42: 104-108.
46. Mirkhani V, Moghadam M, Tangestaninejad S, Mohammadpoor-Baltork I and Mahdavi M, Synthesis, Characterization and Investigation of Catalytiv Activity of a Highly Sulfonated Carbon Solid Acid in the Synthesis of Dihydropyrimidones under Solvent-free Conditions, J. Iran. Chem. Soc., 2011; 8(3): 608-615.
47. Besoluka S, Kucukislamoglub M, Nebioglub M, Zenginb M and Arslanb M, Solvent-Free Synthesis of Dihydropyrimidinones Catalyzed by Alumina Sulfuric Acid at Room Temperature, J. Iran. Chem. Soc., 2008; 5(1): 62-66.
48. Hatamjafari F, Biological Activity and Efficient Synthesis of 3, 4-Dihydropyrimidin-2-(1H)-one/thione Derivatives, Journal of Chemical Health Risks, 2014; 4(4): 55-61.
49. Dabholkar VV, Badhe KS and Kurade SK, One-pot Solvent free synthesis of dihydropyrimidones using calcined Mg/Fe hydrotalcite catalyst, Current Chemistry Letters, 2017; 6: 77-89.