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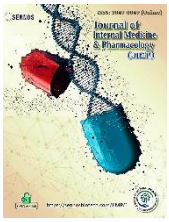

Review Article

Biginelli Reaction- A Green Chemistry Approach for Synthesis of Tetrahydro Pyrimidine Derivatives.

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ARTICLEINFO

ABSTRACT

The Biginelli reaction, involving a three-component reaction of an aromatic aldehyde, urea, and ethyl acetoacetate, has emerged as an extremely useful synthetic tool to organic chemists for the synthesis of tetrahydro pyrimidine derivatives and related heterocyclic compounds. Green chemistry is an eco-friendly synthetic pathway for pollution-free synthesis and manufacturing of the product. The tetrahydro pyrimidine and its derivatives are highly significant because they generally show diverse medicinal properties, such as calcium channel blockers, antihypertensive and anti-inflammatory agents, andα1-a antagonists. The current review focuses on the green synthesis approach for the synthesis of tetrahydro pyrimidine derivatives via the Biginelli reaction. The review also throws light on recent advances in Biginelli's reaction

Keywords: Biginelli Reaction, Green chemistry, Tetrahydro Pyrimidine Derivative, Multicomponent reaction.

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1. Introduction

The development of new efficient methods to synthesize organic heterocycles that are both economical and eco-friendly presents a great challenge for the scientific community. Solvent-free reactions are highly significant from both economical and synthetic points of view. These kinds of reactions ensure an essential facet of green chemistry to reduce the risks to humans and the environment[1]. Green chemistry is a synthetic pathway for pollution prevention, green chemistry is a new way of looking at chemicals and their manufacturing processes to minimize any negative environmental effects. These can be achieved by preventing waste, synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product and the use of auxiliary substances should be made unnecessary whenever possible and innocuous when used[2]. Multicomponent reactions (MCRs) have gained importance because of their efficiency and effectiveness as a method for one-pot synthesis of a wide range of heterocycles. The optimal MCR is sufficiently flexible. Thus, it can be conducted to generate adducts with a variety of functional groups that may then be selectively paired to enable different cyclization manifolds, thereby leading to a diverse collection of products. Among the MCRs, the Biginelli reaction is used for the direct synthesis of tetrahydro pyrimidine derivatives[3]. The Biginelli reaction, which was discovered in the 1890s, is a three-component reaction between urea, an aldehyde, and a β-keto ester resulting in the synthesis of a 4-aryl-3,4- dihydropyrimidine-2(1H)-one (DHP). This reaction is very useful and found applications in the syntheses of biologically active compounds containing a pyrimidine core [4]. In the past years, 3,4-dihydropyridine-2-(1H)-ones and their derivatives attracted a lot of attention due to their interesting pharmacological properties. The tetrahydro pyrimidine and its derivatives are highly significant because they generally show diverse medicinal properties, such as calcium channel blockers, antihypertensive and anti-inflammatory agents, andα1-a antagonists[5]. Furthermore, tetrahydro pyrimidine derivatives have emerged as important target molecules because of their pharmacological and therapeutic properties, such as antimitotic, antiviral, antitumor, anti-carcinogenic, antibacterial, and fungicidal activities[6]. Several improvements were made towards good reaction conditions, and they involved the use of catalysts/reagents, transition metal–based reagents, ionic liquids, polymer-immobilized reagents, microwaves, and ultrasound irradiation; these improvements have been recently reported for the synthesis of the aforementioned compounds[7]. The possibility to vary the starting reagents, catalysts, and solvents, as well as the possibility of introducing substituents that are easily converted into various functional groups. The rapid development of combinatorial chemistry also led to an increased interest in Biginelli reaction. Several reviews are devoted to the reaction.

2. Conditions for Biginelli Reaction

The classic method of carrying out the Biginelli reaction assumes one-pot condensation of ethyl acetoacetate, benzaldehyde, and urea under strongly acidic conditions indicated in (figure.1). The reaction proceeds with low yields and requires a relatively long time (15–20 h)[8]. A significant number of works have been devoted to the

optimization of reaction conditions to increase the yields of target DHPMs. The influence of solvents and catalysts on the yields of the target products obtained in the Biginelli reaction has been recently studied[9]. One approach is an optimization of the solvents (acetic acid, acetonitrile, THF, DMFA, etc.) and the selection of appropriate catalyst systems. To accelerate the reaction, experiments have been performed with microwave irradiation, infrared irradiation, as well as ultrasonication, thereby reducing the reaction time to a few minutes and increasing yields up to 98%[10].

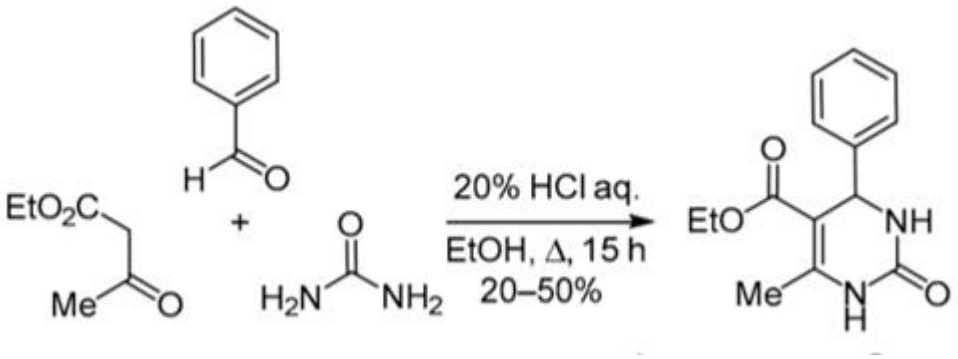


Figure.1. Biginelli reaction.

In particular, recently the synthesis of 3,4-dihydropyrimidine-2(1H)-one derivative have made great advance [2]. More considerably, the asymmetric synthesis of 3,4-dihydropyrimidine-2(1H)- one derivative catalyzed by organ catalysts has particularly stirred up the interest of synthetic organic chemists[11]. In general, there are three plausible accepted mechanisms for the Biginelli reaction (Figure.2). Among them, the most energetically favourable one is the generation of iminium, which resulted from the reaction between benzaldehyde and urea followed by the condensation with ethyl acetoacetate (Figure.2) [12]. It is important to note that urea stabilizes the Lewis acid and also accepts and releases protons in many steps during the reaction. Therefore, it can be assumed that the Biginelli reaction is a urea-catalyzed multicomponent reaction that proceeds through the generation of iminium species[13].

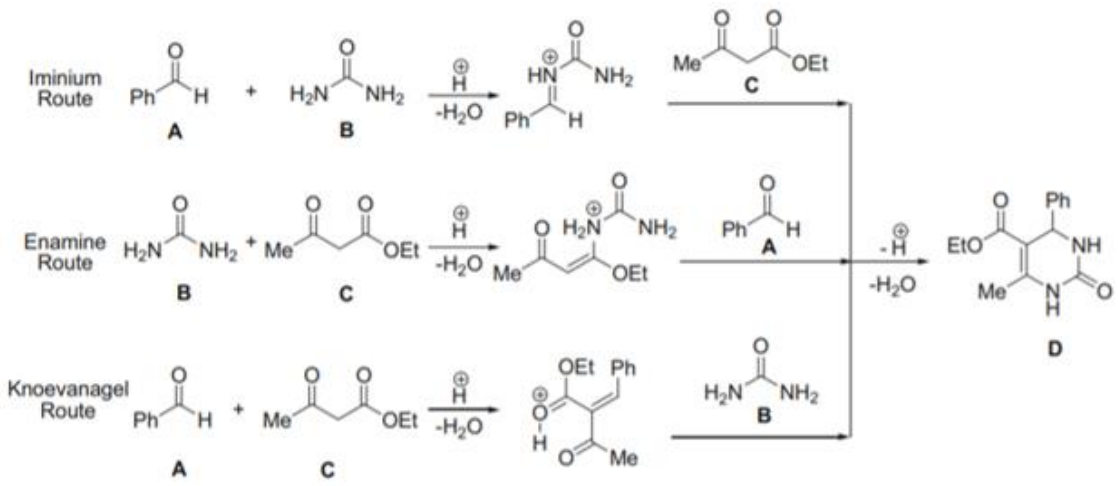
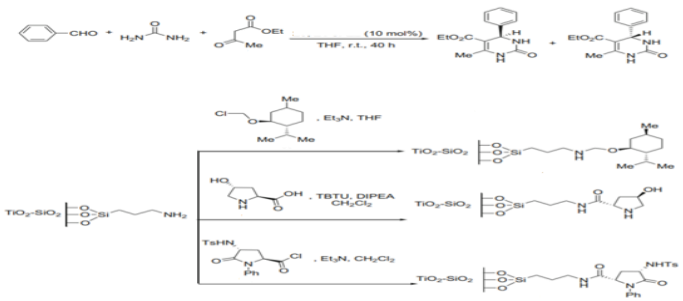


Figure.2: Three mechanisms for the Biginelli reaction.

3. Recent Advances in Biginelli reaction

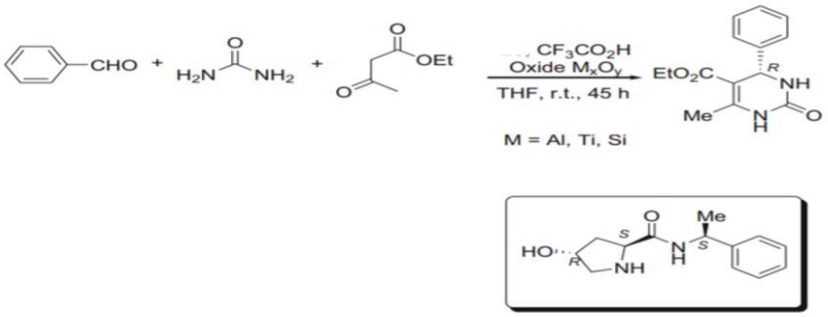
Recent progress in biginelli reaction is discussed in the subsequent section.

The synthesis of 3,4-dihydropyrimidine-2 (1H)-ones was accomplished via asymmetric Biginelli reaction using the type of the chiral catalysts by Titova et al. [14] (Scheme.1) The Biginelli reaction of benzaldehyde, urea, and ethyl acetoacetate in one pot in the presence of a catalytic amount of chirally modified TiO2–SiO2 in tetrahydrofuran at ambient temperature in 40 h furnished the desired products (% ee, 17% yield, catalyst 20), (14% ee, 15% yield, catalyst) (18% ee, 20% yield, catalyst). The catalysts were synthesized from the coupling reaction of (3-aminopropyl) silane-modified TiO2–SiO2 (APS-modified TiO2–SiO2) with chiral molecules[14]. It was indicated that the reaction with catalyst yielded the highest enantiomeric excess. The previous studies presented that the rate of the Biginelli reaction using metal nano oxides reduced in comparison with the classical acid catalyst, although, products in good yield were obtained under increasing reaction time [15].



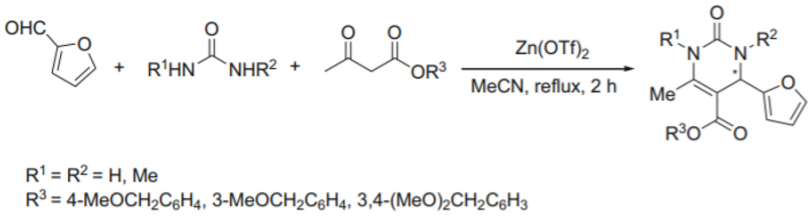
Scheme.1: Asymmetric Biginelli reaction using nanosized catalysts.

heterogeneous catalysts in 2015 by Titova and co-workers (Scheme.2) [16]. The one-pot Biginelli reaction of benzaldehyde, urea, and ethyl acetoacetate using the chiral N-[(2S,4R)-4-hydroxyprolyl] -(S)1-phenylethylamine as catalyst CF3COOH and titanium, silicon, and aluminium oxides (individual and mixed, bulk and nanosized) in THF in 45 h at room temperature obtained the expected molecule[17]. Among bulk oxide catalysts, aluminium and silicon showed the best results which were increased Biginelli reaction yields from 45%, and ee values from to 60% with high chemo- and stereoselectivity. The mixed nano oxides SiO2–TiO2 (1:1), compared with individual nanosized oxides, was performed an obvious advantage in 92% yield with 66% enantiomeric excess. The reason for this change can be elucidated with a significant increase in the strength and concentration of Lewis acid and Bronsted centres on the surface of TiO2–SiO2, which is connected with Ti–O–Si bonds[18].



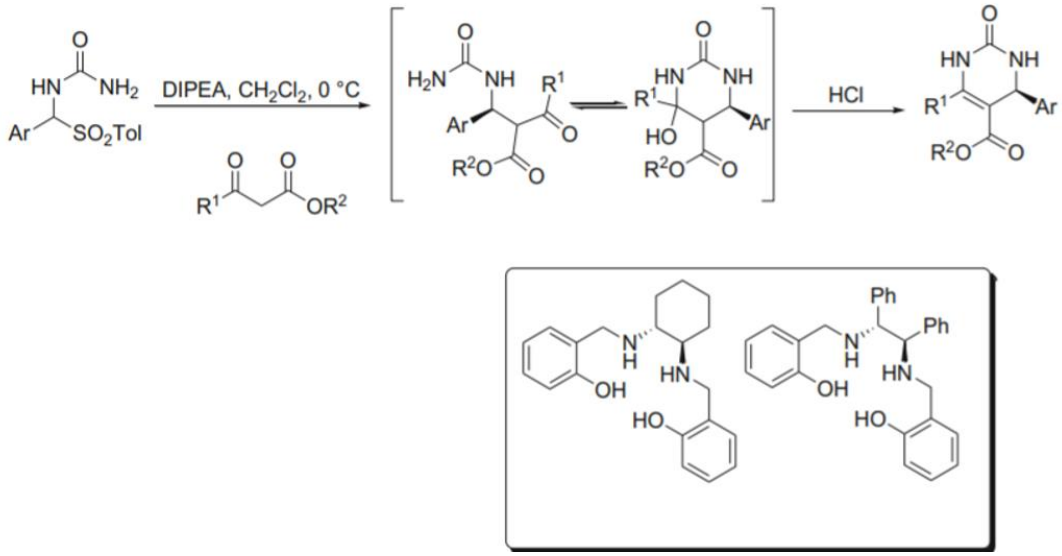
Scheme.2: Using the metal-oxides as heterogeneous catalysts in Biginelli reactions

Ambroise et al. [19] presented the reaction of aldehyde, urea derivatives, and β-keto ester using zinc triflate [Zn(OTf)2] as a catalyst in refluxing MeCN in 2 h to obtain a unique series of dihydropyrimidine-2-ones in 30–73% yield (Scheme .3). In this strategy, the key step is a ring-forming Biginelli reaction. They also evaluated the activity of these products for the inhibition of sodium iodide symporter (NIS) in a rat thyroid cell-based assay. Some newly DHPMs exhibited a most potent activity with a half maximum inhibitory concentration (IC50) value of pM. The biological assay was showed that the maximum activity toward NIS resides in one enantiomer.



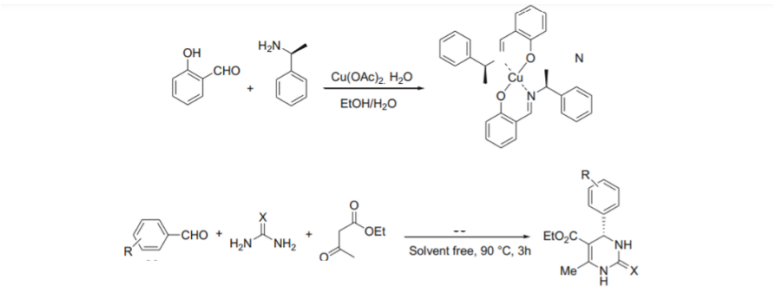
Scheme.3: Synthesis of DHPMs as picomolar sodium iodide symporter inhibitors.

A straight and scalable pathway for the highly enantioselective asymmetric synthesis of enantiopure dihydro pyrimidinones (DHPMs) was reported by Saá and Lillo in 2016. The crucial step in this pathway was the one-pot Biginelli reaction[20]. The reaction of α-ureido sulfones with alkyl β-ketoesters using N, N-diisopropylethylamine (DIPEA) as suitable organic base and salan as a network of cooperative hydrogen bonds (NCHB) organ catalysts in CH2Cl2 at 0 °C present the desired products 5 in moderate to high yields (72–99%) with 64–99% enantiomeric excess (Scheme. 4)[21].



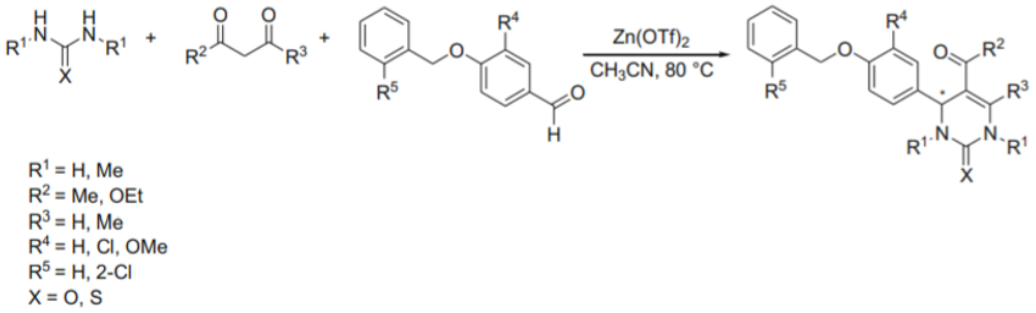
Scheme 4: Preparation of DHPMs from the reaction of an α-ureidosulfone with an alkyl β-ketoester.

In 2015, Kamali performed the asymmetric synthesis of the corresponding chiral 3,4-dihydropyrimidine2-ones (DHPOs) and their sulphur derivatives 3,4- dihydropyrimidine-2-thiones (DHPTs) via a solvent-free Biginelli reaction as a key step in one pot by catalysed chiral Schiff base Cu (II)-complex (BPACu). The copper chiral complex has been synthesized from the reaction of benzaldehyde, (S)-1-phenylethylamine and Cu(OAc)·H2O in a manner reported by Iglesias and Fernández et al.[22] . The synthesis of target products or started with the reaction of benzaldehydes, urea, and ethyl acetoacetate in the presence of the catalytic bis{(S)-(+) (1-phenylethyl)-[(2-oxo-1Hbenzo-1-ylidene) methyl] aminato} copper (II) (BPACu) in 3 h at 90 °C under the solvent-free Biginelli reaction conditions in high yields with good enantioselectivities (up to 79% ee) with (S) configuration. The advantages of this method are short-times reaction, good enantioselectivities, easy work-up, high to excellent yields, and solvent-free conditions (Scheme.5).



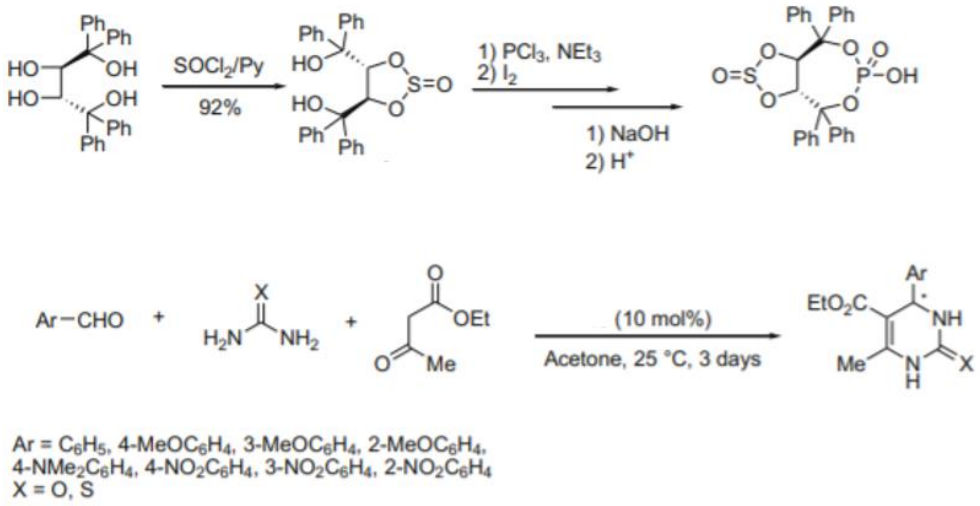
Scheme 5: Biginelli reaction in the presence of BPACu.

A series of 4-(4-(benzyloxy) phenyl)-5-carbonyl-2-oxo1,2,3,4-tetrahydro pyrimidine derivatives were synthesized through the one-pot multicomponent Biginelli reaction in 2013 by Walczak et al. (Scheme 6). The desired products were prepared by reaction of appropriate (thio)ureas, 4-benzyloxybenzaldehydes, and compounds under Biginelli reaction conditions (Zn (OTf)2, MeCN, 80 °C) in one pot. According to the docking study, the compounds will present novel synthetic probes useful for clarification of complex RORα physiopathology.



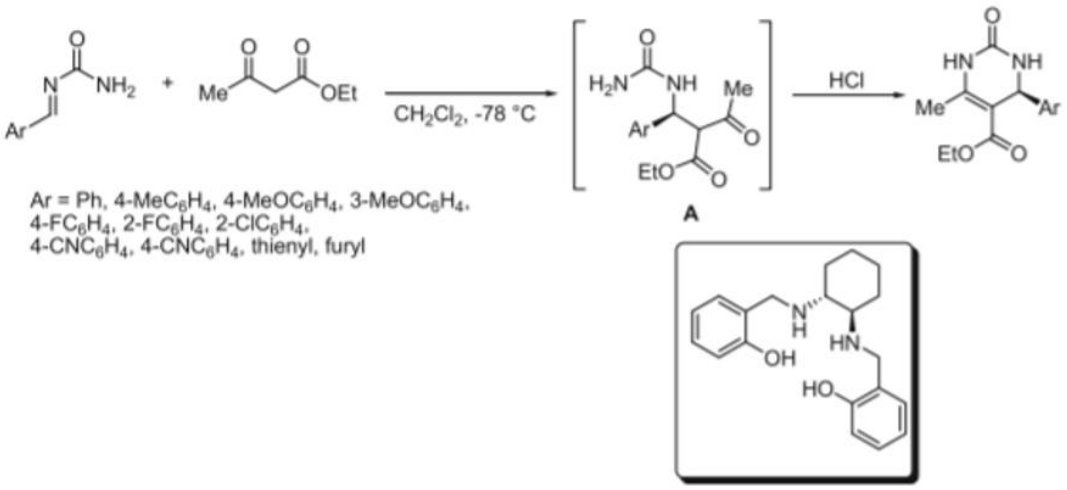
Scheme 6: Synthesis of tetrahydro pyrimidine derivatives in the presence of Zn.

The dihydro pyrimidinone derivatives or dihydro pyrimidine thiones were obtained from the asymmetric Biginelli reaction of benzaldehyde, urea or thiourea or and ethyl acetoacetate in the presence of an unusual sterically hindered chiral cyclic phosphoric acid derived from l-tartaric acid (synthesized based on regioselective cyclo sulfidation reaction of (2R,3R)-1,1,4,4-tetraphenylbutanetetraol with thionyl chloride in acetone at ambient temperature in 3 days[23]. In 2016 by Hu and Shan et al. It was found that the electron-rich groups such as 3- or 4-OMe and 4-NMe2 on the aromatic ring were well tolerated to give the expected target molecules, except for 2-$MeOC_6H_4CHO$[24]. The enantioselectivities and yields for the asymmetric Biginelli reaction were reduced in the presence of electron-withdrawing groups on the aromatic ring, whereas the reaction with the presence of m-ntirobenzaldehyde resulted in enantioselectivity (Scheme 7).



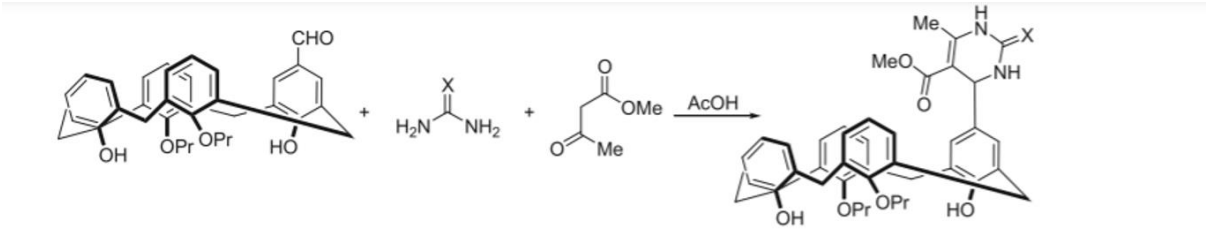
Scheme 7: Application of chiral cyclic phosphoric acid in a Biginelli reaction.

In 2016, Saá et al. presented a simple strategy for the produce of enantiomerically enriched dihydropyrimidinone derivatives by carrying out a one-pot Biginelli reaction using a chiral catalyst[25] (Scheme .8). The hetero arylideneureas were reacted with ethyl 3-oxobutanoate via Biginelli reaction using the chiral [(R, R)-N, N'-bis(salicyl)cyclohexane-1,2-diamine] catalyst and HCl in CH_2Cl_2 as the solvent at −78 °C to yield the desired dihydropyrimidinones with high enantioselectivity. The phenol groups in the structure of the catalyst are played a key and significant role in co-ordinately basifying the OH oxygen atoms and acidifying the N–H bonds for an ideal host-guest interaction. The removal of OH groups or its replacement with F atom resulted in no or poor enantioselectivity[26].



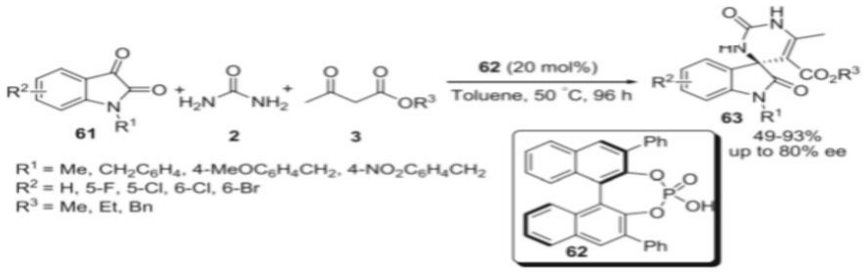
Scheme 8: Use of noncovalent organocatalytic in a Biginelli reaction.

Kal'chenko et al. in 2014 used the Biginelli reaction as a vital step for the synthesis of tetrahydro pyrimidines and tetrahydro pyrimidinediones[27]. The reaction was started with Biginelli reaction of cone-shaped propoxycali arenes, urea or thiourea, and methyl acetoacetate in boiling acetic acid to furnish the desired products and (Scheme.9).



Scheme 9: Synthesis of tetrahydro pyrimidines and tetrahydro pyrimidine thiones.

In 2016, Silvani and co-workers reported the synthesis of chiral enantioenriched spiro(indoline-pyrimidine) diones through condensation of the N-substituted satins as carbonyl substrates, urea and alkyl acetoacetates as further components under asymmetric one-pot Biginelli-like reaction conditions using the BINOL-derived phosphoric acid catalysts[28]. In toluene as the solvent at 50 °C in 96 h with good yields and enantioselectivity (Scheme.11). According to the quantum mechanical methods and NMR spectroscopy on Di stereoisomeric derivatives, it was determined that the absolute configuration at the oxindole quaternary stereo enter has been S for the major enantiomer[29].



Scheme 10: Synthesis of spiro(indoline-pyrimidine)-diones.

He et al. in 2014 presented the use of the crude earthworm extract as a natural catalyst in Biginelli reactions for the synthesis of the desired products (Scheme. 11). The reaction was started with the reaction of various substituted aromatic aldehydes, urea, and acetoacetate in the presence of the crude earthworm extract in mixtures of n-butyl acetate and H_2O in 69–169 h at 45 °C to furnish the desired products in yields of 14–76% with enantioselectivities of 0–57% ee [30]

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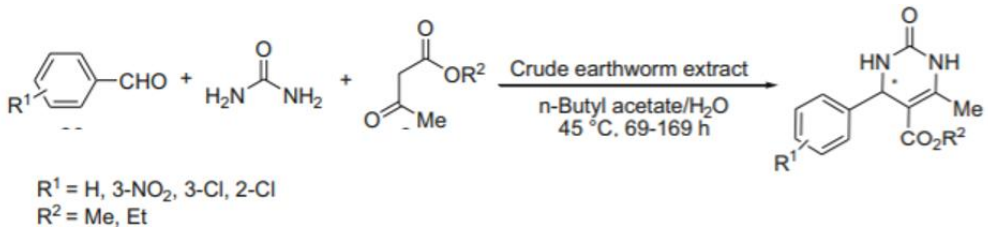

Scheme 11: Crude earthworm extract used as a biocatalyst for Biginelli reactions.

Green chemistry

A new, powerful trend in the field of organic chemistry in recent years is the application of "green chemistry", which often envisions the synthesis of complex molecules without solvents or by using water as a solvent shown (figure.3)[31]. A simple and efficient method for the synthesis of DHPMs was reported by Priyadarshini and Chitra.13 They suggested Sn (IV) oxide as a catalyst that was highly active, inexpensive, environmentally friendly, convenient in handling, and nontoxic[6]. Selective synthesis of DHPM derivatives was recently illustrated by Hajipour and co-workers by a reaction of aromatic aldehydes with cyclopentanone and urea (thiourea) in the presence of N, N, N-triethyl-4-sulfobutan1-aminium hydrogen sulphate as a Bronsted acidic ionic liquid and effective catalyst[32]. Previously described CAN-catalysed Biginelli reaction by El-Saghier et al. can be viewed as the green method. The application of polyphosphoric acid on silica gel allowed to carry out the reaction under mild conditions gave high yields, and the catalyst could be easily recovered. A significant number of works have been devoted to the application of environmentally friendly natural clays and silica gel as catalysts[13].

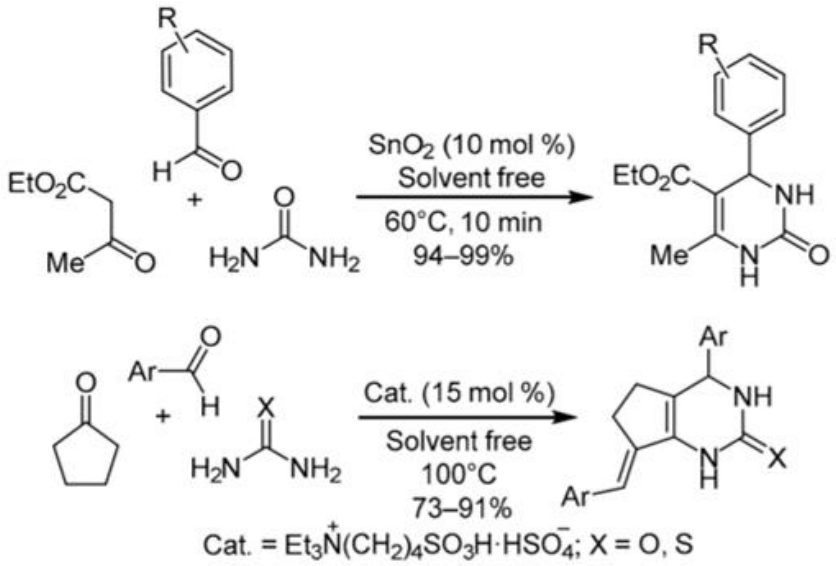

Figure.3 Biginelli reactions by green synthesis.

Conclusion

The Biginelli reaction has been achieved under different catalytic systems under green, unconventional heating, and synthetic technologies. In terms of the pharmaceutical and biological value of tetrahydro pyrimidine derivatives, they are known to act as antiviral, antitumor, anti-hypertensive, antibacterial, antimalarial, and antitubercular. This reaction has great potential for the construction of new heterocyclic systems in addition to biologically active compounds. It can also be used for the synthesis of unique materials such as chiroptical materials, responsive gels, multi-addressable optical switches. It is clear that among the different methodologies for asymmetric Biginelli reactions, the organocatalytic enantioselective Biginelli reaction is a more successful and fruitful approach. Despite the fast developments in this area, the design and discovery of a novel and effective strategy for the synthesis of optically active DHPMs are still in high demand.

Conflict of Interest

The authors declare no competing interests.

Funding

No funding received.

Data Availability

The authors confirm that the data supporting the findings of this study are available within the article

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