



Review Paper

Recent Developments in Biginelli Reaction

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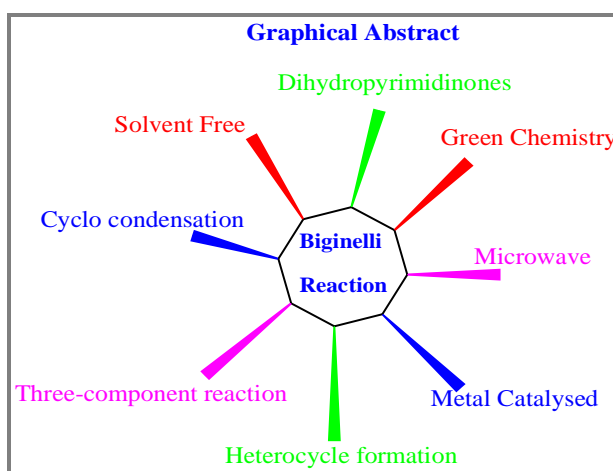
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ABSTRACT

In present review gives idea of an efficient and green methods were reported for the synthesis of an Biginelli product using the various solvent and solvent free medium. The mild reaction conditions, operational simplicity and volatile-solvent free conversion.

Graphical Abstract

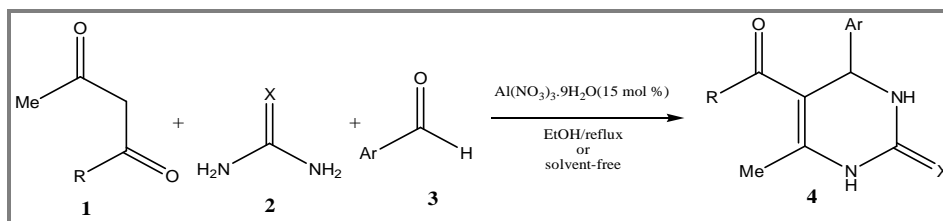


Keywords: Biginelli product, Green Chemistry, Solvent free, Dihydropyrimidinones.

INTRODUCTION

Developments in Biginelli reaction: Pietro Biginelli in 1891 first reported a cyclo condensation reaction between benzaldehyde, ethylacetoacetate and urea which gave a heterocyclic system of 3,4-dihydropyrimidinones (DHPMs), which is known as Biginelli reaction[1]. Dihydropyrimidinones shows an extensive range of biological activities such as antiviral, anti-bacterial, anti-tumor and anti-inflammatory [2]. These compounds also have appeared as calcium channel blockers and antihypertensive [3].

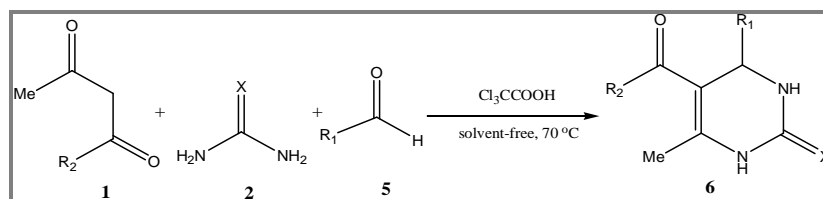
Eskandar Kolvari gave procedure for an efficient and improved modification of the Biginelli reaction which has mild reaction conditions, operational simplicity and easy workup, good to excellent yields, cheap and nontoxic catalyst and short reaction times [4] shown in Scheme 1.



Scheme 1. Aluminum nitrate-catalyzed synthesis of 3,4-dihydropyrimidin-2-ones/thiones

Biginelli reaction is an appropriate three-component reaction which provides a useful route for the manufacture of 3,4-dihydropyrimidin-2(1H)-ones **4** which shows extensive biological applications such as antihypertensive, antibacterial, antitumor, antiviral, α -1a-antagonism, antioxidant and anti-inflammatory actions [5, 6]. Although many catalysts have been developed in accelerating this reaction [7, 8], it is still desirable to develop this reaction using newer reagents with better efficiency, simple working technique, milder reaction conditions and a higher yield of products with potential bioactivity.

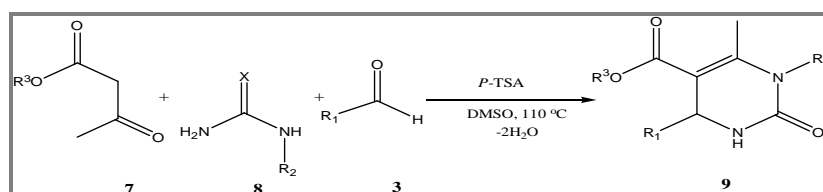
Zahed Karimi-Jaberi and Mohammad Sadegh Moaddeli studied a novel approach to explore the use of trichloroacetic acid for the synthesis of 3,4-dihydropyrimidin-2(1H)-ones **6** and their analogous 2(1H)thione has been designated through the Biginelli reaction at 70 °C under solvent-free reaction conditions [9] (Scheme 2).



Scheme 2: The Biginelli Reaction

Multicomponent reactions (MCRs) are attractive reactions for the preparation of diversely substituted products starting from three or more precursor molecules, forming products containing atoms/moieties of all precursor components. MCRs are often one-pot reactions with high-atom economy, convergence and efficiency. Generally, one-pot procedures have many advantages compared to multiple-step synthesis [10]. The Biginelli reaction was discovered in 1891 by the chemist Pietro Biginelli [11]. Later, Biginelli identified the reaction product as a 3,4-dihydropyrimidin-2(1H)-one (DHMP) **9** [12].

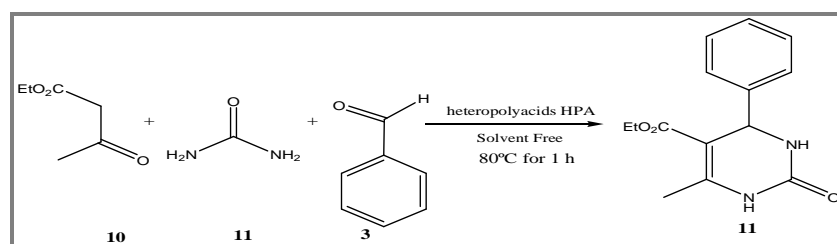
The Biginelli reaction combined with the Passerini reaction for the first time in a sequential multicomponent reaction approach [13] (Scheme 3).



Scheme 3. Biginelli reaction of the preparation of DHMP acid

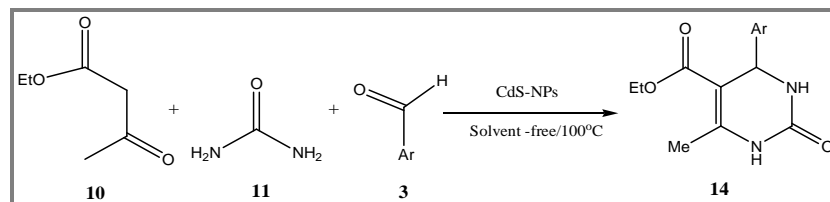
The transition metal plays role in various catalytic activities hence, vanadium integrated molybdophosphoric acid (PMoV) shows unique catalytic nature for oxidations due to its bifunctional property. Vanadium shows redox nature and molybdophosphoric acid has oxidative/acidic in character as catalysts. Substituting Mo atoms with the corresponding V atoms such reactions have studied by various chemists hence, the heteropoly acids HPA bulk used as catalysts.

Oriana Dalessandro elaborated use of V, Bi and Bi-V Keggin structure where Mo is partially replaced by V, Bi and V respectively, in the solvent-free multicomponent synthesis of 3,4-dihydropyrimidin-2-(1H)-ones **11** by the Biginelli method [14] (Scheme 4).



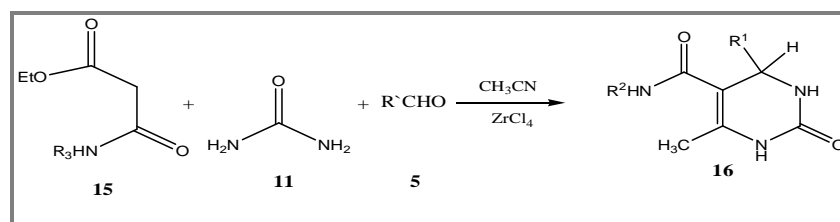
Scheme 4. Multicomponent synthesis of 3,4-dihydropyrimidin-2-(1H)-ones by the Biginelli.

Pourshamsian gave synthesis of 3,4-Dihydropyrimidinones **14** and their derivatives are synthesized via Biginelli routes involving an aromatic aldehydes, ethylacetoacetate and urea in one-pot procedure by using CdS nano-particles as efficient heterogeneous catalyst in solvent-free conditions. Compared with classical Biginelli reaction reported in 1893, this new method offers several advantages such as a simple procedure with an easy work-up, short reaction time and excellent yields. Mild reaction conditions and ecofriendly character of CdS make it a vital alternate route to the classic acid catalyzed Biginelli's reactions shown in scheme 5.



Scheme 5. Synthesis of 3,4-Dihydropyrimidinones one pot solvent free reaction.

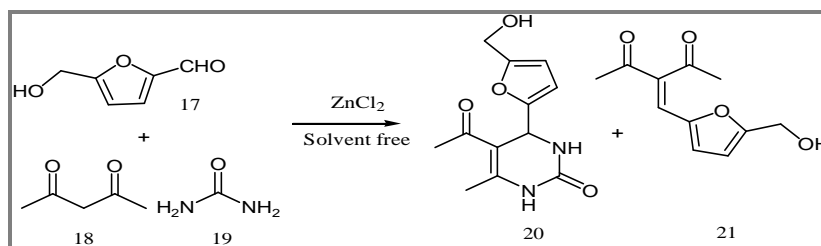
The synthesis of various dihydropyrimidinone derivatives bearing carbonyl moieties in 5-position under reflux conditions and microwave irradiation is described. An efficient three-component Biginelli reaction using catalytic amounts of zirconium(IV) chloride as an efficient catalyst leads to the formation of these compounds **16** [15] shown in scheme 6.



Scheme 6. Biginelli reaction using catalytic amounts of zirconium(IV) chloride.

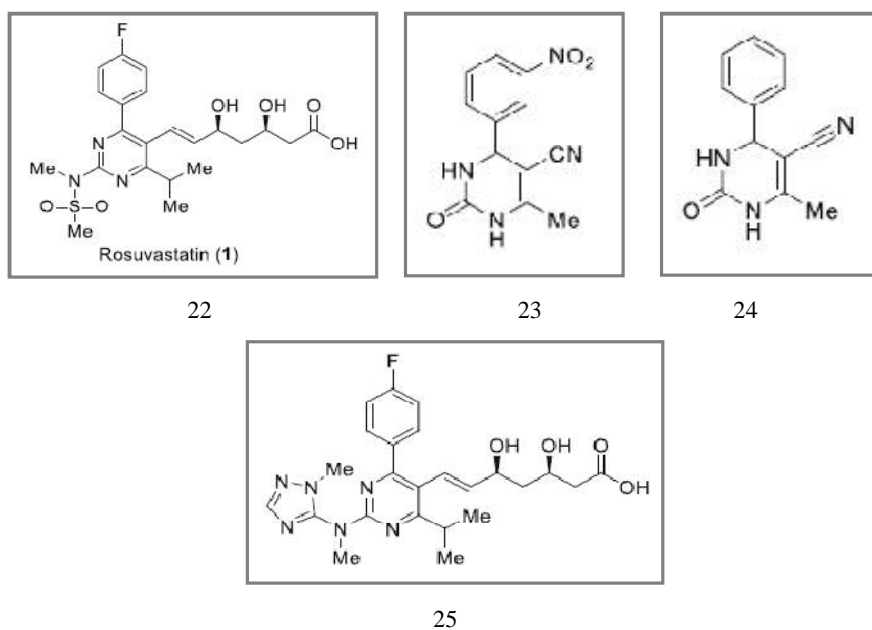
Weigang Fan *et. al.* gave use of the renewable platform molecule 5-hydroxymethylfurfural (HMF) in the multi-component Biginelli reaction has been investigated. Multicomponent reactions (MCR) using HMF offer straightforward access to novel fine chemicals. However, the peculiar

reactivity and lower stability of HMF have limited its use in such strategies. the use of HMF in 3-component Biginelli reactions, leading in one single step to a series of functionalized dihydropyrimidinones obtained in moderate to good yields, with a broad substrate scope of 1,3-dicarbonyl compounds and urea building blocks.



Scheme 7. 5-hydroxymethylfurfural (HMF) in the multi-component Biginelli reaction.

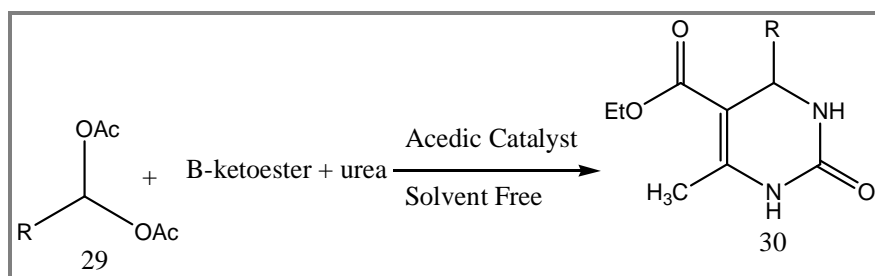
Sharad S Pachore *et. al.*, Studied a Biginelli reaction of β -ketonitriles, aldehydes and urea in principle can yield 5-cyano substituted dihydropyrimidinones. Although potentially very useful, this substituted heterocycle is often difficult to synthesize via the three- component reaction, presumably due to the lack of stability of β -ketonitriles. The present work describes the development of reaction conditions yielding the desired product. Interesting mechanistic observations have also been noted. Thirteen new compounds (derivatives) of 5-cyanodihydropyrimidin were synthesized [17, 18].



Scheme 8. PEG-HClO₄ catalyzed modified Biginelli reaction.

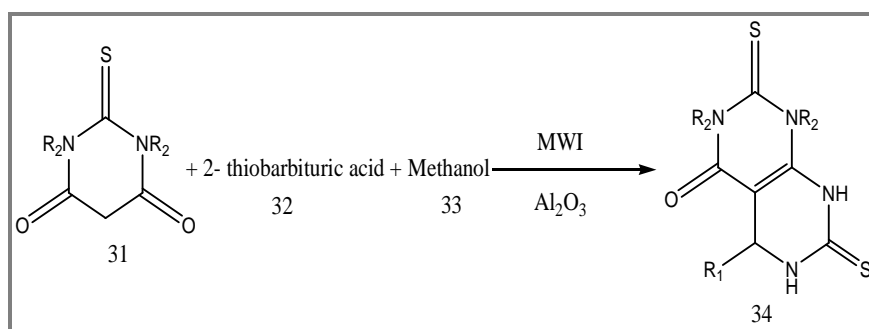
Siddiqui *et al.*, (2014) reported the use of perchloric acid modified PEG-6000 (PEG-HClO₄) as a biodegradable catalyst for substituted DHPMs under solvent free conditions. Terephthalaldehyde/isophthalaldehyde were also used to synthesize bis-DHPMs. A typical procedure involved the homogenization of mixture of substituted benzaldehydes, 1,3- diketones (cyclic and acyclic), urea and PEG-HClO₄ using a mortar and pestle for 1-2 min. The catalyst remains unaffected after nine cycles. The great reduction in time with excellent yields, solvent free reaction and reusability of catalyst were the advantages of PEGHClO₄ catalyst. Comparatively, the methodology was found to be effective and attractive [19] (Scheme 8).

In 2008, Khabazzadeh and coworkers reported for the first time the synthesis of Biginelli products using acylals (1,1-diacetates, 29) with PW, PMo or ZnCl₂ as a catalyst under solvent free conditions (Scheme 9). The solventless reaction mixture containing acylals, β-ketoester, urea or thiourea and the catalyst was heated to afford good yields of DHPMs[20]. Although the protocol found conventional due to elevated temperature, moderate yields but, short reaction time, solvent free condition and use of acylals as substrate highlighted the new valuable modification in the Biginelli reaction.



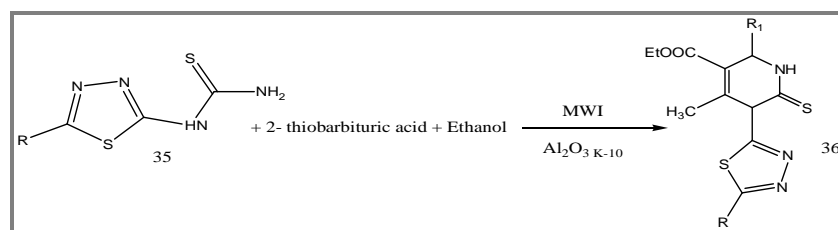
Scheme 9. Synthesis of DHPM's using acylals.

In 2003, Kidwai and coworkers investigated the Biginelli reaction under microwave irradiation using alumina as a catalyst. The β-diketocompound (31) was used 2- thiobarbituric acid (32), the methanolic (34) Biginelli reaction mixture was adsorbed on alumina (Scheme 10). The mixture was stirred well, dried in air, and subjected to MWI (800W) to afford high yields of DHPMs. Results were compared with the yields obtained from classical Biginelli reaction [21]. The protocol showed reduction in reaction time with high yields but seems merely effective.



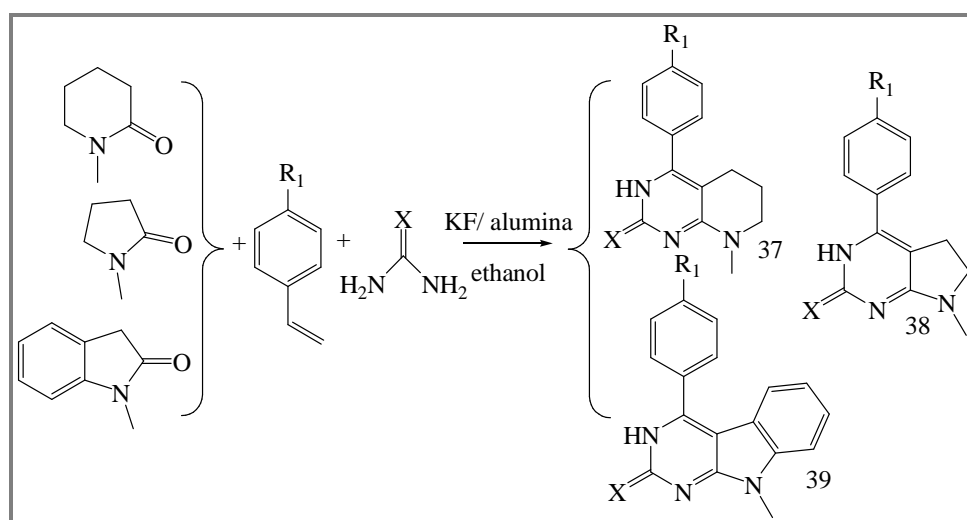
Scheme 10. Alumina catalyzed modified Biginelli Reaction.

In 2004, same research group have reported the microwave assisted Biginelli reaction using alumina or montmorillonite K-10 clay as a catalyst (Scheme 11). Thiadiazol thiourea as (35) were used for reaction. The ethanolic Biginelli reaction mixture was adsorbed on acidic alumina montmorillonite K-10 clay. After drying, the reaction mixture was subjected to microwave irradiation for 7-8 min. Using previously reported work up, high yields of the Biginelli scaffolds were isolated. The solvent free reaction and shorter reaction time makes the protocol an efficient.



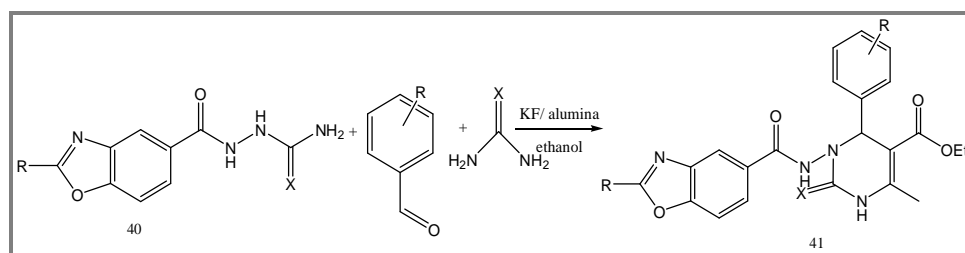
Scheme 11. Alumina catalyzed synthesis of DHPMs using thiazolothioureas.

In 2008, Mizar *et al.*, reported potassium fluoride coated with alumina (KF-alumina,) as a catalyst for the Biginelli like condensation (Scheme 12). The ethanolic mixture containing aldehyde, urea, 1-methylpyrrolidin-2-one and KF-alumina catalyst was refluxed; afforded good amounts of products. 160 Three-component synthesis of 5:6 and 6:6 fused pyrimidines was achieved using KF-alumina as a catalyst from 1-methylpiperidin-2-one, 1-methylindolin-2-one respectively. Although the protocol showed moderate yields with slight reduction in reaction time, the modification in the Biginelli reaction was noticeable.



Scheme 12. Synthesis of fused Biginelli like products.

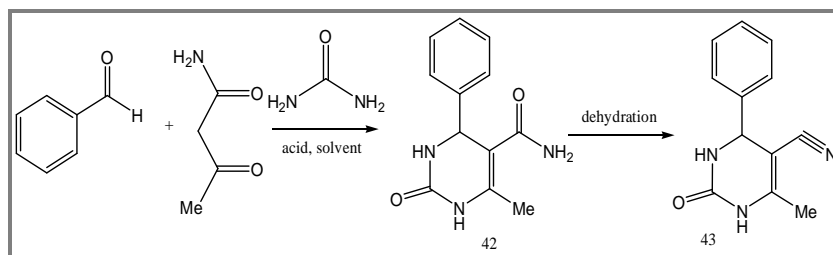
In 2009, Arjun and coworkers performed the solvent free synthesis of benzoxazole substituted DHPMs (41) using alumina supported trifluoro methane sulfonic acid ($F_3C.SO_3H - Al_2O_3$, as a catalyst (Scheme 13).



Scheme 13. Synthesis of benzoxazole-substituted DHPMs.

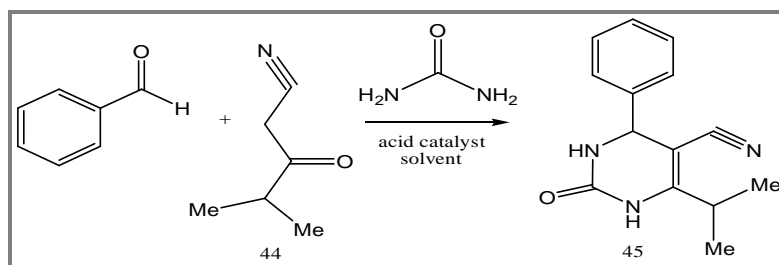
A Biginelli reaction of β -ketonitriles, aldehydes and urea in principle can yield 5-cyano substituted dihydropyrimidinones. Although potentially very useful, this substituted heterocycle is often difficult to synthesize via the three-component reaction, presumably due to the lack of stability of β -ketonitriles. The present work describes the development of reaction conditions yielding the

desired product. Interesting mechanistic observations have also been noted. Thirteen new compounds (derivatives) of 5-cyanodihydro pyrimidin were synthesized [22] (Scheme 14).



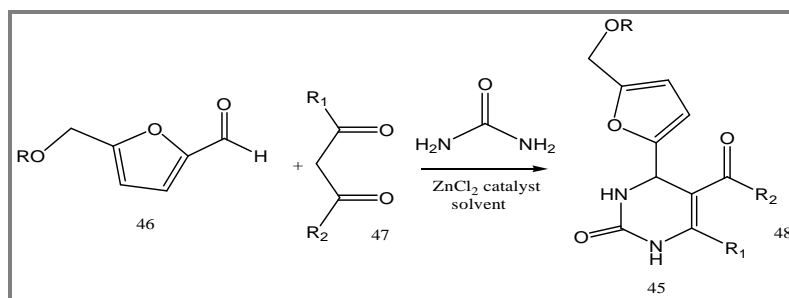
Scheme 14. Synthesis of 5-Cyanodihydropyrimidine via a two step approach.

β -Ketonitrile (44) was selected as model substrate for further exploration (Scheme 15). Preliminary experimentation on the Biginelli reaction began on the basis of reaction conditions reported in the literature. β -Ketonitrile (44) was selected as model substrate for further exploration. Preliminary experimentation on the Biginelli reaction began on the basis of reaction conditions reported in the literature [23].



Scheme 15. Cyano substituted dihydropyrimidone synthesis by catalytic.

Weigang Fan *et al.*, reported our results on the use of HMF in the 3-component Biginelli reactions, leading in one single step to a series of functionalized dihydropyrimidinones obtained in moderate to good yield, with a broad substrate scope of 1,3-dicarbonyl compounds and urea building blocks. This is the first report of the use of HMF in this reaction. The CH_2OH motif found in HMF provides useful functionalization in the target molecules, which cannot be offered by simpler aldehydes such as furfural [24] (Scheme 16).



Scheme 16. The Biginelli reaction of 5-HMF with 1,3-dicarbonyl.

APPLICATION

Biginelli product have wide importance regarding its uses and various application such as 1)Green Chemistry 2)Solvent free reactions 3)Metal Catalysis 4) Heterocycle compounds formation 5) Multi-component reaction 6)Cyclo condensations.

CONCLUSION

We have reviewed here was an efficient and green methods for the synthesis of an Biginelli product using the various solvent and solvent free medium. The mild reaction conditions, operational simplicity and volatile-solvent free conversion, high yields and rapid formation of the products are the notable advantages of the revived methods.

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