CHAPTER 5

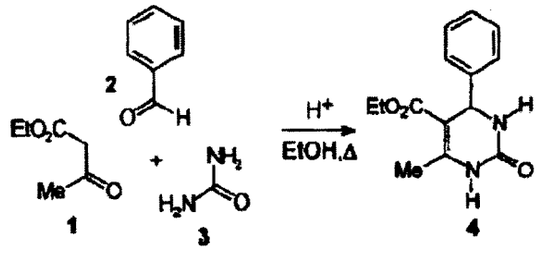
Multi component reactions (MCRs): biginelli 3,4 dihydropyrimidin-2(1H)-ones synthesis catalyzed by 11-molybdo-1-vanadophosphoric acid ($H_4PMo_{11}VO_{40}$)

5.0 Multi Component Reactions (MCRs): Biginelli 3,4-Dihydropyrimidin-2(1*H*)-ones synthesis catalyzed by 11-molybdo-1-vanadophosphoric acid ($H_4PMo_{11}VO_{40}$)

5.1 Introduction

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry [1-5]. In times where a premium is put on speed, diversity, and efficiency in the drug discovery process [6], MCR strategies offer significant advantages over conventional linear-type syntheses [1-5]. In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components [1-5]. In an ideal case, the individual building blocks are commercially available or are easily synthesized and cover a broad range of structural variations. MCRs can provide products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry techniques [2-6]. The search and discovery for new MCRs on one hand [7], and the full exploitation of already known

multicomponent reactions on the other hand, is therefore of considerable current interest. One such MCR that belongs in the latter category is the venerable Biginelli dihydropyrimidine synthesis. In 1893, Italian chemist Pietro Biginelli reported on the acid catalyzed cyclocondensation reaction of ethyl acetoacetate (**1**), benzaldehyde (**2**), and urea (**3**) [8]. The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1*H*)-one **4** (Scheme 1) [8]. Apart from a series of publications by the late Karl Folkers [9] in the mid 1930s, the "Biginelli reaction" or "Biginelli condensation" as it was henceforth called was largely ignored in the early part of the 20th century. The synthetic potential of this new heterocycle synthesis therefore remained unexplored for quite some time. In the 1970s and 1980s, interest slowly increased, and the scope of the original cyclocondensation reaction, shown in Scheme 1, was gradually extended by variation of all three building blocks (Figure 1), allowing access to a large number of multifunctionalized dihydropyrimidines of type **4** [10].



Scheme 1. Biginelli Dihydropyrimidine Synthesis

A comprehensive review article on the Biginelli reaction was published in 1993 [10]. Since this first review article, a tremendous increase in activity has occurred, as evidenced by the growing number of publications and patents on the subject.

This is mainly due to the fact that the multifunctionalized dihydropyrimidine scaffold **4** (DHPMs, "Biginelli compounds") represents a heterocylic system of remarkable pharmacological efficiency. In the past decades, a broad range of biological effects, including antiviral, antitumor, antibacterial, and antiinflammatory activities, has been ascribed to these partly reduced pyrimidine derivatives [10]. More recently, appropriately functionalized DHPMs have emerged as, e.g., orally active antihypertensive agents (**5**, **6**) [12-14] or R1a adrenoceptor-selective antagonists (**7**) [15]. A very recent highlight in this context has been the identification of the structurally rather simple DHPM monastrol (**8**) as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest [16]. Monastrol specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for the development of anticancer drugs [16]. Furthermore, apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have recently been isolated [17]. Most notable among these are the batzelladine alkaloids A and B (e.g., **9**), which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells and, therefore, are potential new leads for AIDS therapy [18].

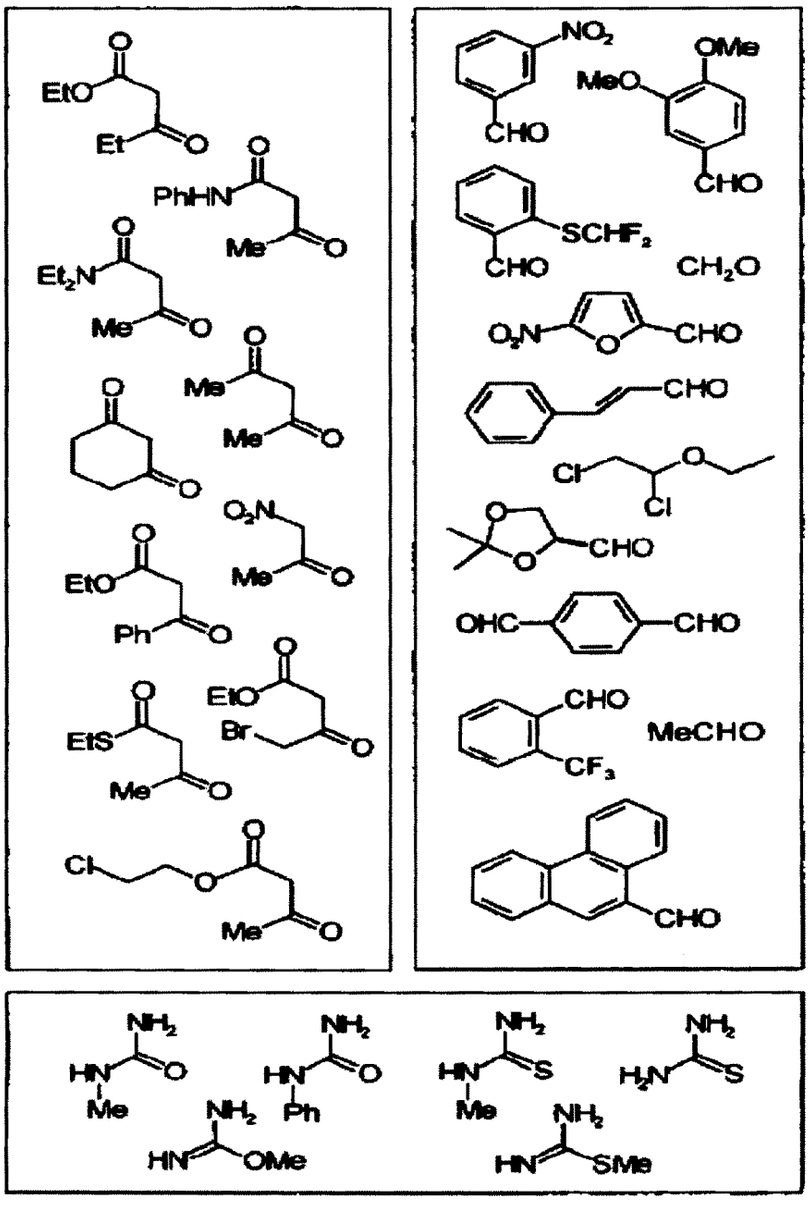


FIGURE 1. Building blocks in Biginelli MCRs.

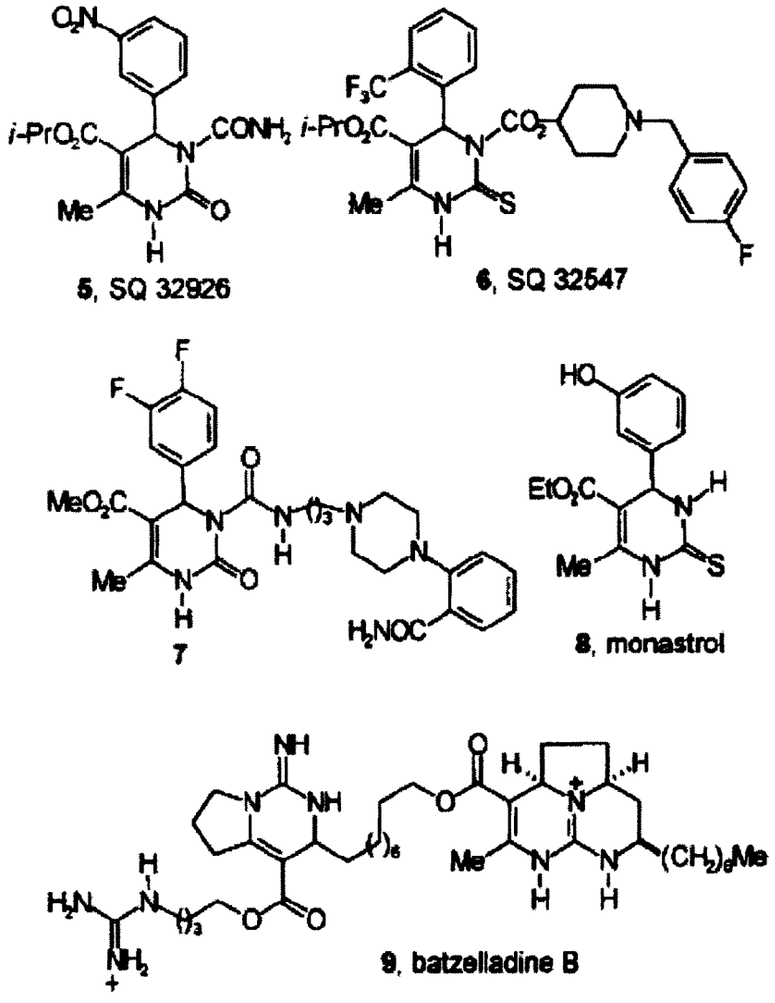
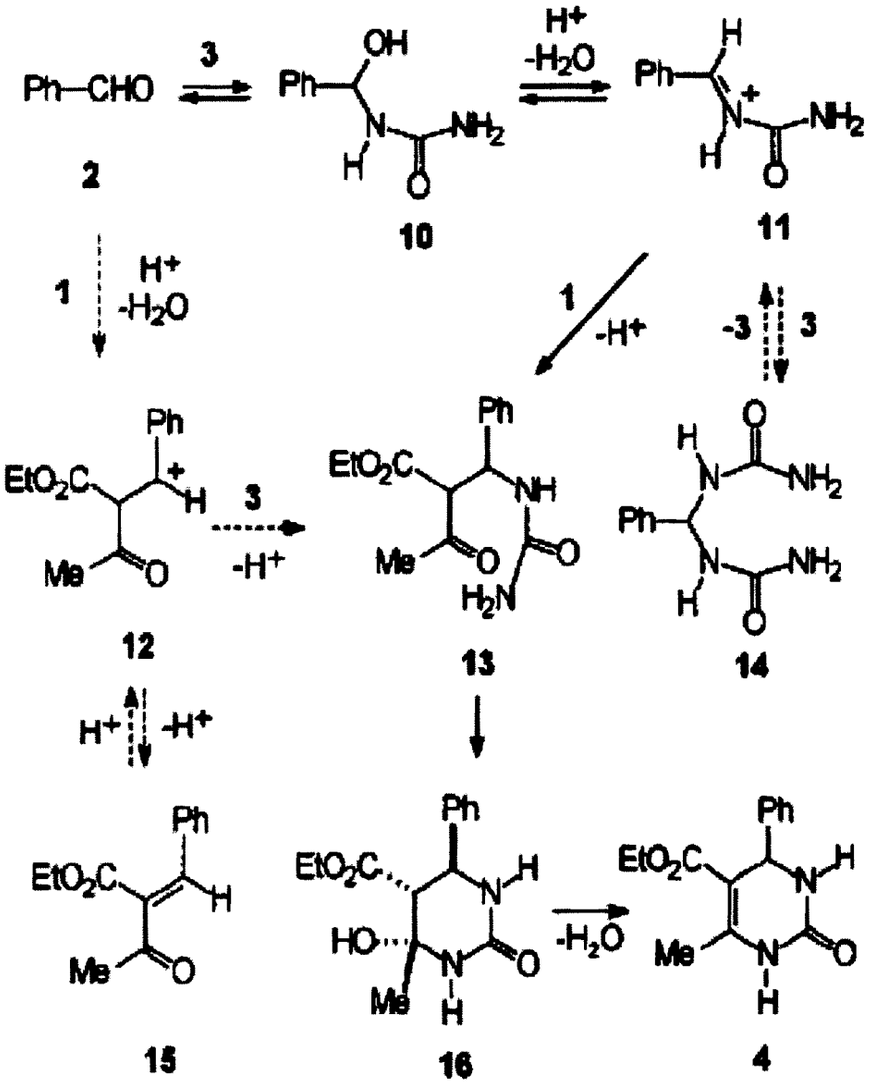


FIGURE 2. Examples of biologically active DHPMs.

Mechanistic Studies and Improved Protocols

The mechanism of the Biginelli reaction has been the subject of some debate over the past decades. Early work by Folkers and Johnson suggested that bisureide **14**, i.e., the primary bimolecular condensation product of benzaldehyde (**2**) and urea (**3**), is the first intermediate in this reaction.[9]. In 1973, Sweet and Fissekis proposed a different pathway and suggested that carbenium ion **12**,

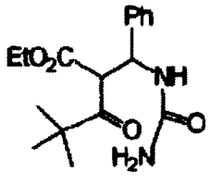
produced by an acid-catalyzed aldol reaction of benzaldehyde (**2**) with ethyl acetoacetate (**1**), is formed in the first and limiting step of the Biginelli condensation (**2→ 12→ 13**) [19]. Kappe reinvestigated the mechanism in 1997, using $^{1}H/^{13}C$ NMR spectroscopy and trapping experiments and had established the key step in this sequence involves the acid-catalyzed formation of an *N*-acyliminium ion intermediate of type **11** from the aldehyde (**2**) and urea (**3**) precursors [20]. Interception of the iminium ion **11** by ethyl acetoacetate (**1**), presumably through its enol tautomer, produces an open-chain ureide **13** which subsequently cyclizes to hexahydropyrimidine **16**. Acid-catalyzed elimination of water from **16** ultimately leads to the final DHPM product **4**. The reaction mechansim can therefore be classified as an R-amidoalkylation, or more specifically as an R-ureidoalkylation [21]. The alternative "carbenium ion mechanism" (**2→ 12→13**) [19] does not constitute a major pathway; however, small amounts of enone **15** are sometimes observed as byproduct [20].



Scheme 2. Mechanism of Biginelli Reaction

Although the highly reactive *N*-acyliminium ion species **11** could not be isolated or directly observed, further evidence for the proposed mechanism was obtained by isolation of intermediates **17** and **18**, employing sterically bulky [22] or electron-deficient acetoacetates [23], respectively. The relative stereochemistry in hexahydropyrimidine **18** was established by an X-ray analysis.23 In fact, a

number of hexahydropyrimidines closely related to **18** could be synthesized by using perfluorinated 1,3-dicarbonyl compounds or â-keto esters as building blocks in the Biginelli condensation [24].



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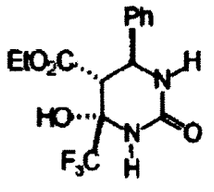

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The elucidation of the mechanism of the Biginelli MCR has prompted a renewed interest in improving the efficiency of this process. One major drawback of the traditional Biginelli protocols is the low yield that is encountered when some of the building blocks shown in Figure 1 are employed.

Alternative Synthetic Strategies

The first method reported by Bigineli in 1893 was associated with drawbacks of lower yields especially when aliphatic or substituted aromatic aldehydes were used in the synthesis. However, with the realization that Biginelli type possess diverse biological activities, the intrest in their synthesis rejoiced which led to the development of several modified and improved protocols. The main aim behind the development of new protocols was to develop versatile, more practical and environmentally benign alternatives. Especially, in the last decade a huge amount of work has been done and in this chapter we have summarized the work published till July 2005.

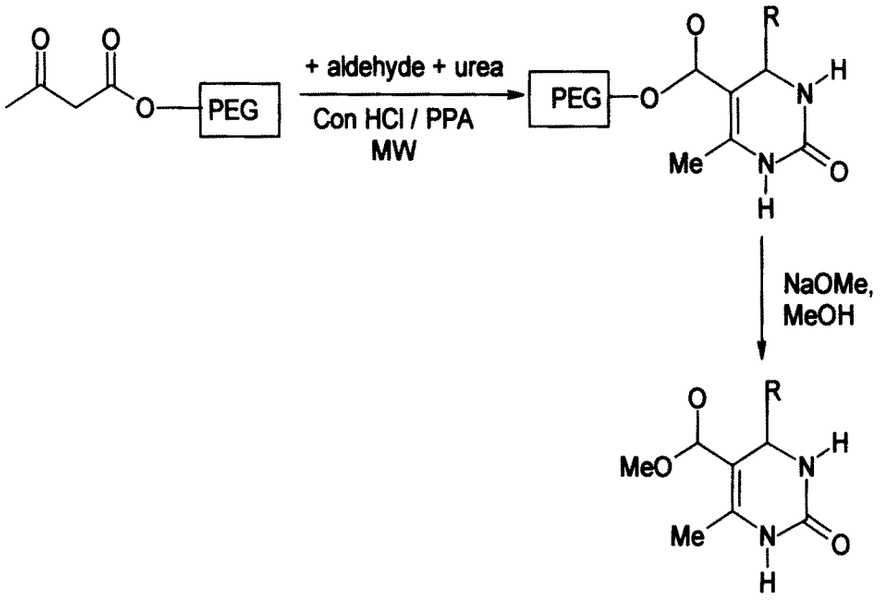
The main aim in various reported protocols has been to use different acid catalysts exceptionally there is only one method in which pyridine is used as a catalyst [25].

Ffurther, the original reaction needed several hours to go to completion hence the other aim of improved protocol has been to reduce the time essential for the reaction. To make the protocol environmentally benign, few attempts under solvent free conditions have also been made. All these methods have been divided into the following groups.

1. Microwave Assisted methods.
2. Solid super acid catalysed methods.
3. Lewis acid catalysed methods.
4. Methods involving polymer supported catalysts.
5. Miscellaneous methods.

1. Microwave Assisted Methods.

The original Biginelli reaction was carried out using concentrated HCl as catalyst and needed several hours (~48 hrs). as the microveve irradiation(MW's) is known to accelerate the rate of reactions considerably, the obvious way to expediate Biginelli reaction is irradiation with MW's. Wang et.al. [26] have reported the MW assisted method for the Bigineli type compounds in presence of both Concentrated. HCl as well as polyphosphoric acid (PPA). The only modification of the original method was, they used polyethylene glycol supported ethyl acetoacetate for the condensation to yield PEG-bound DMPH's which on cleavage with NaOMe gave desired DMPH (Scheme 3).



Scheme 3

Ramalingam et.al [27] have reported the use of dry acetic acid, Nafion-H as well as Amberlite-15 as acid catalyst. The reaction was carried out in CH_3CN/THF solvent system under the influence of MW's.

Recently Mitra and Bannerjee [28] have reported the use of montomorillonite-KSF clay as a solid acid catalyst for the reaction under solvent free conditions. Though they have claimed that KSF clay was used by them for the first time, Bigi et.al [29] had already used the same clay catalyst for Biginelli reaction under the reflux conditions of 130°C for 48 hours. However, use of ferric chloride under non MW conditions was also reported earlier [30]. In all the MW assisted methods undoubtedly rate enhancements are achieved. In a view to investigate the reaction behind the rate enhancements, Kappe et.al [31] carried out an extensive work and concluded that MW's do not have any special effects if solvent is used in the reaction. In all the reported procedure though acid catalyst was used. Kidwai

et.al [32] have proved that without the use of any catalyst, as well as solvent the synthesis of DMPH's is possible under MW irradiation. However, the time required for such reactions is longer.

2. Solid Super Acid Catalysed Methods.

Zeolites due to their acidic and shape selective nature have emerged as alternatives to homogeneous catalysts. A single step liquid phase Biginelli reaction is reported recently by Kulkarni et.al [33] as well as by Choudhary et.al [34]. Using HY-Zeolite and Si-MCM-41 suported $FeCl_3$ as a catalyst. Yadav et.al reported the use of heteropoly acid, $Ag_3PW_{12}O_{40}$ as a heterogeneous catalyst for Biginelli synthesis in water as a solvent [35].

3. Lewis Acid Catalysed Methods.

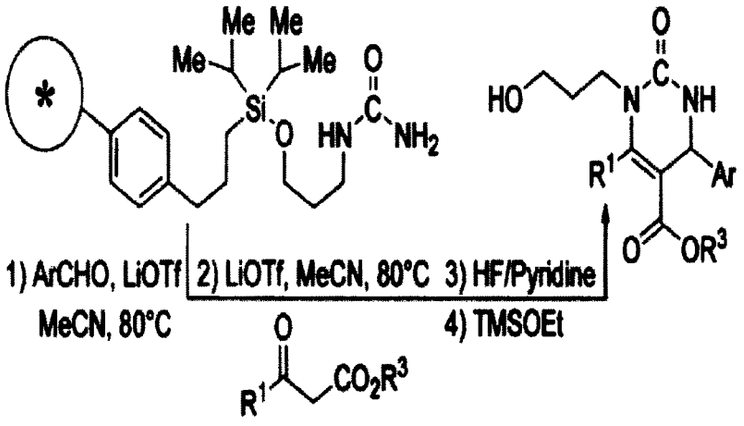
The halides of Ce, Bi, In and La are well known Lewis acids, Bose et.al [36] have reported the use of $CeCl_3$ as a reusable, cost effective and less toxic Lewis acid catalyst for Biginelli reaction in the presence of solvent as well as solvent free conditions. Kaimal et.al [37] reported the use of $BiCl_3$ while Ranu et.al [38] have reported the use of $InCl_3$ as a catalyst for Bigineli reaction and almost simultaneously the use of $InBr_3$ has been reported by Peppe et.al [39] as a reusable catalyst for Biginelli reaction. The Lewis acids such as $NiCl_2 \cdot 6H_2O$ [40] and $LiClO_4$ [41] are also known to catalyze Bigineli reaction.

The salt of lanthanides such as chlorides and triflates have emerged as novel Lewis acid catalysts. Chlorides, though are cheaper, are non reusable while the triflates are reusable but much costlier. Lu et.al [42] have reported the use of $CaCl_3 \cdot 7H_2O$ as a non reusable catalyst. While Wang et.al [43.44] , Adappa et.al [45] and Sudlai et.al [46] have reported the use of triflates of Yb, Bi, and Cu respectively for

Biginelli reaction. Gosh et.al [47] examined the effect of high pressure. Indium triflate catalysed Biginelli reaction. This effect was found to be small when moderately hindered aldehydes or ureas are involved. However, particularly in the case of bulky aldehydes, the sensitivity of the reaction to pressure increases with increasing steric congestion in line with earlier studies described. The results also provide insights into the mechanism. Such a result highlights the synthetic utility of high pressure activation for the preparation of hindered Biginelli products.

4. Methods Involving Polymer Supported Catalysts.

Lanthanide triflates are well proven catalyst for Bigineli reaction. However, for the recovery, as well as reuse of catalyst tedious work up procedure is ssential. As a modification to this, Dondoni and Massi [48] have used Yb(III) supported on Amberlyst-15 as a reusable catalyst. This catalyst avoids the use of aqueous workup procedures. The use of soluble polymer involving PEG supported EAA has already been discussed [49]. Michael J. Lusch et. al [50] reported the Direct Solid-Phase Split-Pool, Lewis acid-catalyzed Biginelli synthesis of 3,4-dihydropyrimidinones performed on high-capacity polystyrene macrobeads with a polymer *O*-silyl-attached *N*-(3-hydroxypropyl)urea. Resin-urea was first reacted separately with either 4-bromo- or 4-chlorobenzaldehyde and LiOTf in MeCN at 80 °C. After washing, the beads were pooled and reacted with ethyl acetoacetate and LiOTf in MeCN at 80 °C. Formation of only *one* kind of Biginelli product per bead demonstrated the feasibility of a solid-phase.



Scheme 4. Direct Solid-Phase Split-Pool, Lewis acid-catalyzed Biginelli synthesis

The Polyaniline-bismoclite complex was used as an efficient catalyst by Palaniappan et.al for the [51]. Biginelli synthesis excellent yields. Furthermore, after completion of reaction the catalyst could be easily recovered and reused without affecting its activity.

6. Miscellaneous Methods.

As an alternative to mineral or Lewis acids Tu et.al [52] have suggested the use of boric acid while Jin et.al [53] have used p-toluene sulfonic acid as a protic acid catalyst. Zolfigol et.al [54] have recently reported the use of silica sulphuric acid as a reusable solid acid catalyst while the use of LiBr is reported almost simultaneously by two different groups [55,56]. Yadav et.al [57] have reported the insitu generated trimethylsilyl iodide as an efficient catalyst so also they have reported the use of vanadium trichloride for the synthesis of DMPH's Libraries [58]. Among these LiBr and vanadium trichloride behave as Lewis acids. Shabbani et.al [59] have reported the use of ammonium chloride as very inexpensive but efficient catalyst for Biginelli reaction.

A sonochemical method for the synthesis of Biginelli compounds was developed. The target products were obtained within 2 to 5 min in 90—95% yields. The classical Biginelli reaction (ethanol, HCl as a catalyst) is accelerated 40 and more times by ultrasound. After the reaction mixture was exposed to ultrasound for 2 to 5 min and the solvent was removed to obtain the target compounds in 90—95% yields, irrespective of the aldehyde nature [60]. Tetrabutylammonium hydrogen sulfate (TBAHS) as a solid protic acid and phase-transfer reagent catalyzed the Biginelli reaction [61] in high yields at 80°C. Recently ,Biginelli compounds have been synthesized in excellent yields in short reaction time at ambient temperature in the absence of any added catalyst in room temperature ionic liquid (IL) under ultrasound irradiation. The evidence for the role of IL in promoting this multicomponent reaction has been given [62]. More recently Ahmad Shaabani et.al utilized ionic liquid 1,1,3,3-tetramethylguanidinium trifluoroacetate as a efficient and environmentally friendly reaction media as well as promoter for the synthesis of Biginelli compounds [63].

5.2 Present Work

In the last three chapters we have efficiently used polyoxometalates as oxidation catalyst. In this chapter we wish to report on the utilization of acidic property of polyoxometalate in organic synthesis. Several features making them economically and environmentally attractive. On the one hand, they are very strong acids, approaching the superacid region; on the other hand, they are efficient oxidants exhibiting fast reversible multielectron redox transformations under rather mild conditions. Their acid-base and redox properties can be varied over a wide range by changing the chemical composition. Solid HPAs possess an ionic structure comprising fairly mobile basic structural units-heteropolyanions and

counter-cations (H^+, H_3O^+, $H_5O_2^+$, etc.) - unlike the network structure of e.g. zeolites and metal oxides. This unique structure manifests itself by an extremely high proton mobility and a 'pseudoliquid phase [64] manifested by the ability of heteropolyanions to stabilize the cationic organic intermediates [65]. Above all, heteropolyoxometalates are very soluble in polar solvents and fairly thermally stable in the solid state. These properties render them potentially promising acid, redox and bifunctional catalysis in homogeneous as well as heterogeneous systems. The advantage of heteropoly acid catalyst compared with the conventional acid catalyst e.g. (H_2SO_4, SiO_2, Al_2O_3) are as follows

- Broad operational choice: Heteropoly acids can b used in homogeneous / heterogenous (gas-liquid, liquid-liquid or biphasic liquid-liquid) systems.
- Being stronger acids heteropoly acids are generally more active catalyst than mineral acids and conventional solid acid catalyst e/g.zeolites as already mentioned.
- They are efficient, operating under mild condition
- They lack side reactions typical of mineral acids such as sulphonation, chlorination, nitration and so on.

As a result, heteropoly acids provide a strong option for more efficient and claner processing compound with conventional acid catalysts.

The intense activity in the field of dihydropyrimidine chemistry during the past decade, from both academic and industrial laboratories, has prompted us to undertake the synthesis of Biginelli compounds. In continuation of our planned work on exporations of polyoxometalates as a catalyst, we ventured to undertake the work on the use of 11-molybdo-1-vanadophosphoric acid [$H_4PMo_{11}VO_{40}$] as a acid catalyst for the synthesis of Biginelli dihydropyrimidones.

5.3 Experimental

Synthesis of H_4 [$PMo_{11}VO_{40}$]. nH_2O

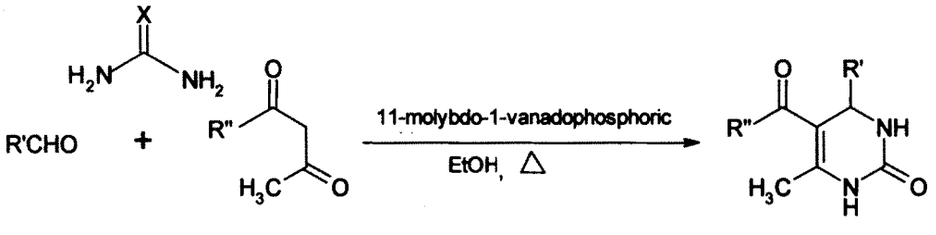
Sodium phosphate dibasic dodecahydrate (1.77 gm, 5 mmol), was dissolved in 25 ml water and mixed with sodium metavanadate (1.52 gm, 12.5 m nol) made soluble in 25 ml boiling water. The mixture was cooled and acidified to red colour with 1.25 ml concentrated sulphuric acid. To this coloured solution was added sodium molybdate dihydrate (33.25 gm, 137.42 mmol) in 50 ml of water. Finally 21.25 ml of concentrated sulphuric acid was added. Colour of the solution turned to light red. After cooling, thesolution was extracted with four fractions each of 25 ml diethyl ether to isolate the heteropolyacid in a separating funnel. In this extraction the heteropoly etherate was present as the middle layer. After separation, a stream of air was passed through the heteropoly etherate layer to free it from ether. The orange solid that separated was dissolved in water, concentrated to the first appearance of crystal in a vacuum desiccator over concentrated sulphuric acid and then allowed to crystallize further. The orange crystals that formed were dried and used for further studies.

IR was recorded as KBr pellet on a Thermo Nicolet spectrometer and reported in cm^{-1}. NMR was recorded on Bruker Avance 300MHz spectrometer, for ^{1}HNMR, chemical shifts (δ) are reported in parts per million relative to tetramethyl silane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

5.4 Results and Discussion

Most of the cases the catalyst, 11-molybdo-1-vanadophosphoric acid [$H_4PMo_{11}VO_{40}$] has been utilized for oxiation of ethane[66], n-butane [67], n-pentane [68] and isobutyricacid [69-73]. In these reactions, the incorporation of vanadium atoms into molybdophosphoric acid has been reported to enhance catalytic performances. Therefore, the states and the role of vanadium in the working state of the heteropolyacid catalysts are of great interest. In aqueous solution, HPAs are completely dissociated at the first three steps, the consecutive dissociation usually being unnoticeable because of leveling effect of the solvent [74,75]. According to the electroconductivity data, $H_4PMo_{11}VO_{40}$ and $H_5PMo_{10}V_2O_{40}$ are strong 1-4 and 1-5 electrolytes, respectively, in aqueous solution [76].

Thus, treatment of benzaldehyde, ethyl acetoacetate and urea in the presence of the 11-molybdo-1-vanadophosphoric acid ($H_4PMo_{11}VO_{40}$) in ethanol at reflux resulted in the formation of 4-phenyl-3,4-dihydropyrimidinone in 92% yield (Scheme 5).

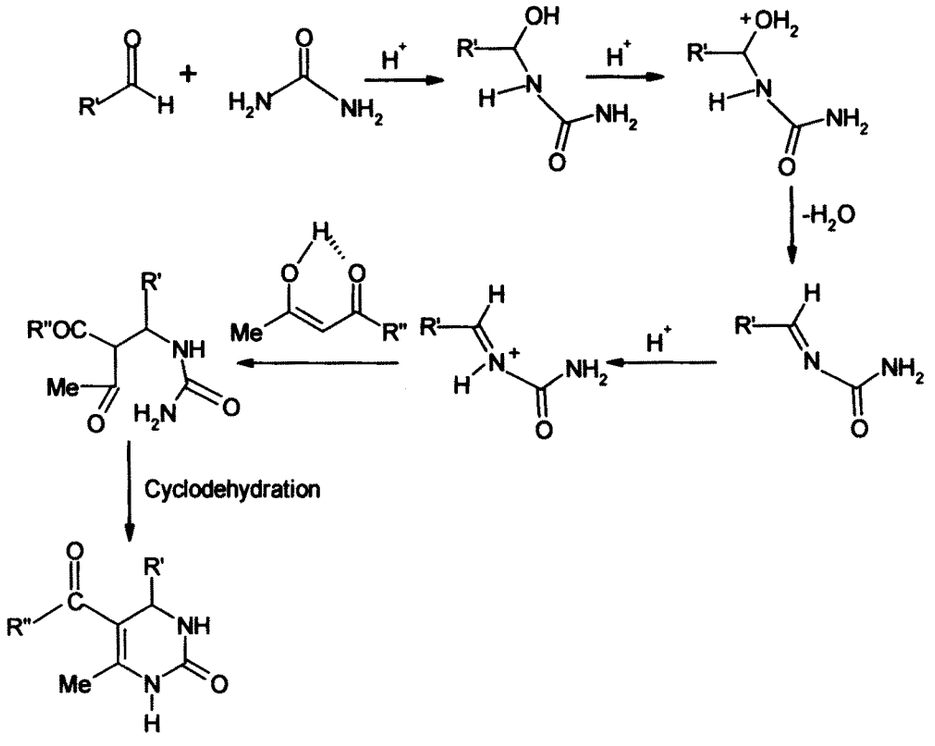


Scheme 5

In a similar fashion, a variety of aromatic and heterocyclic aldehydes underwent three-component condensation smoothly to afford a wide range of suostituted dihydropyrimidinones. Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency by using this procedure (Table 1). Most importantly, aromatic aldehydes carrying either electron-donating or -withdrawing substituents reacted well under the reaction conditions to give the corresponding dihydropyrimidinones in high-to-quantitative yields with high purity. Acid-sensitive furfural also worked well without the formation of any side products (**4h**, Table 1). Another important feature of this method is survival of a variety of functional groups, such as olefin, nitro, halide, ether, and ester groups, under the reaction conditions. Table 1). Unlike most of the reported methods, this procedure does not require any additives or activators. Some other methods require the use of toxic reagents in combination with Bronsted acids, such as hydrochloric acid and acetic acid, as additives [77]. This procedure not only preserves the simplicity of the Biginelli reaction, but also produces excellent yield of the products with high purity. Thiourea has been used with similar success to produce the corresponding thio derivatives of dihydropyrimidinones, which are also of much interest with respect to their biological activities (entries **4u**, **4v**, and **4w**, Table 1) [78]. Decreased reaction times and improved yields are realised as a result of the increased reactivity of the substrates on the surface of heteropolyacid. By using heteropolyacid as catalyst, the yields of the one-pot Biginelli reaction [8] can be increased from 20-60% to 81-96% while the reaction times are shortened from 18 h to 4.5-8.0 h. To optimize the conditions, we carried out the reactions using different quantities of reactants. The best results were obtained using a 0.1:1.0:1.0:2.0 ratio of heteropolyacid, aldehyde,

1,3-dicarbonyl compound, and urea or thiourea. In the absence of the heteropolyacid, the products were obtained in low yields (15-20%) after long reaction times (15-18 h). Thus, this procedure provides easy access to the preparation of substituted pyrimidinones having a wide range of substitution patterns on all three components. The scope and generality of this process is illustrated with respect to the various 1,3-diketones and aldehydes that are tolerated; the results are presented in Table 2.

According to the mechanism suggested by Folkers, Johnson and Kappe, we think the reaction may proceed through imine formation from the aldehyde and urea, which is activated by protonation. Subsequent addition of the carbanion derived from 1,3-diketone or b-keto ester to the imine followed by cyclodehydration afford dihydropyrimidin-2(1*H*)-one (Scheme 6).

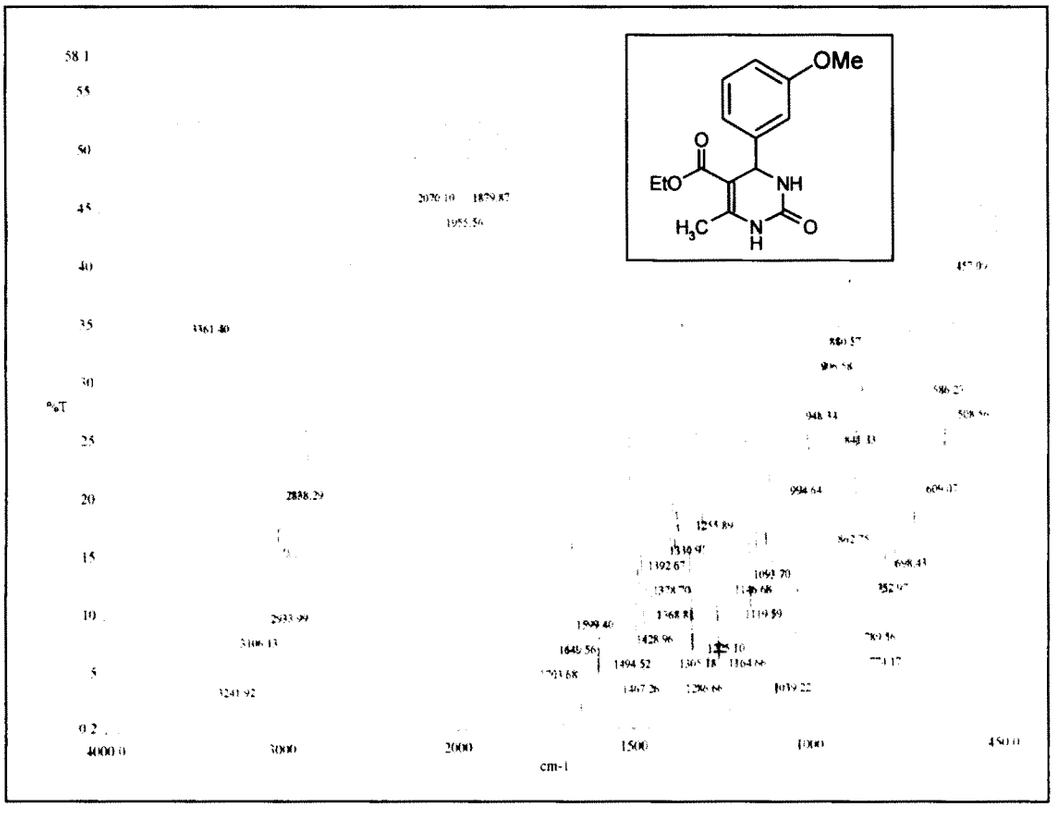


Scheme 6

During the reaction process, the hydrogen ion, H^+, is donated by the heteropolyacid. The hydrogen ion not only help the dehydration but also benefit the enolization of 1,3-diketone or b-keto ester to form the enolate intermediate.

5.5 Spectra

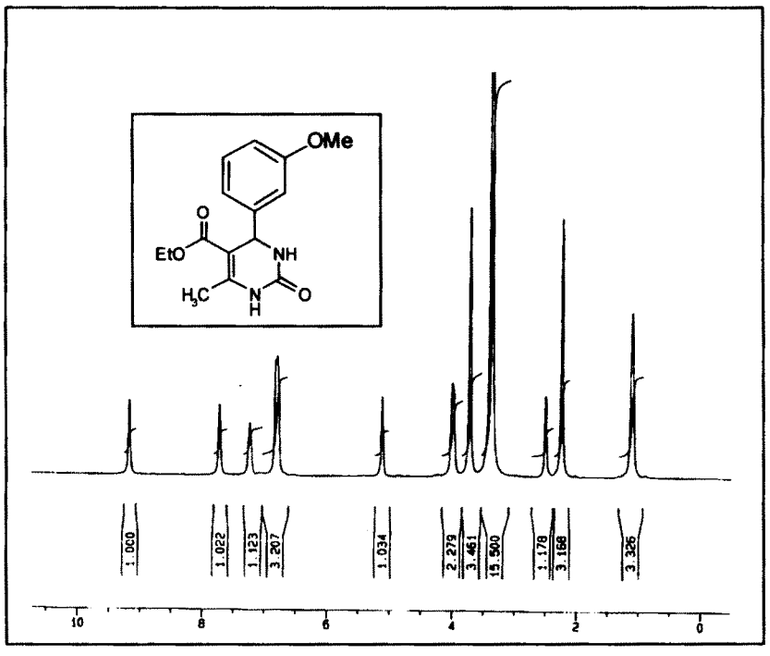
The IR spectrum of the product **4e** exhibited band at 1715 cm^{-1} and 1677 cm^{-1} due to ester carbonyl and amide carbonyl. Where as NH stretching band appeared at 3361 cm^{-1} respectively (Spectrum No.1).



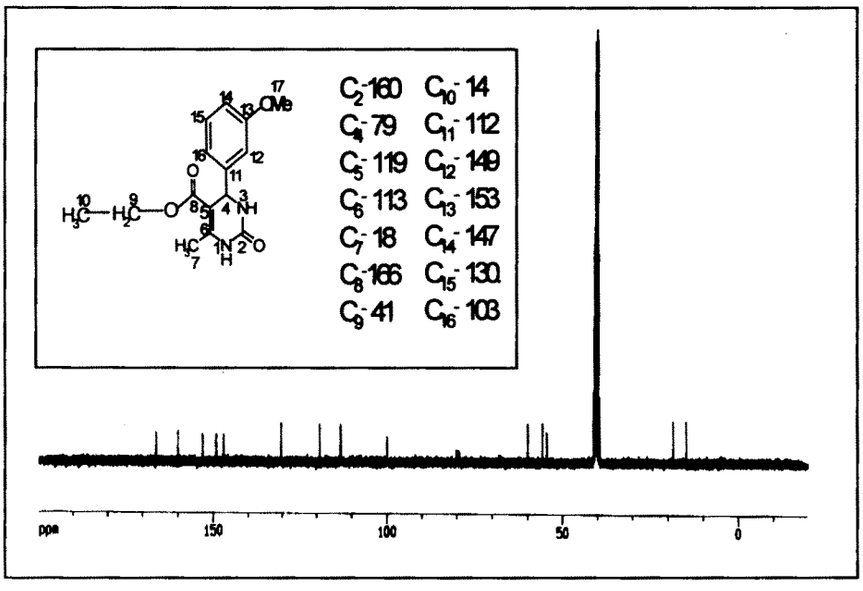
Spectrum No. 1.FTIR Spectrum of the product **4e** recorded as KBr pellet.

The ^{1}HNMR of the above compound (Spectrum No. 2) shows triplet and quadrate at 1.10 and 4.00 ppm due to ester ethyl group and singlet at 3.71 ppm is due to methoxy protons. Whereas the characterstic pyrimidone C_4 proton resonated at 5.12 ppm and two NH protons appeared as broad singlet at 7.23 and 9.17 ppm

which was confirmed by D_2O exchange. Aromatic protons resonated in the range 6.79-7.72 ppm. The ^{13}CNMR of the same compound is in agreement with the structure (Spectrum No.3)

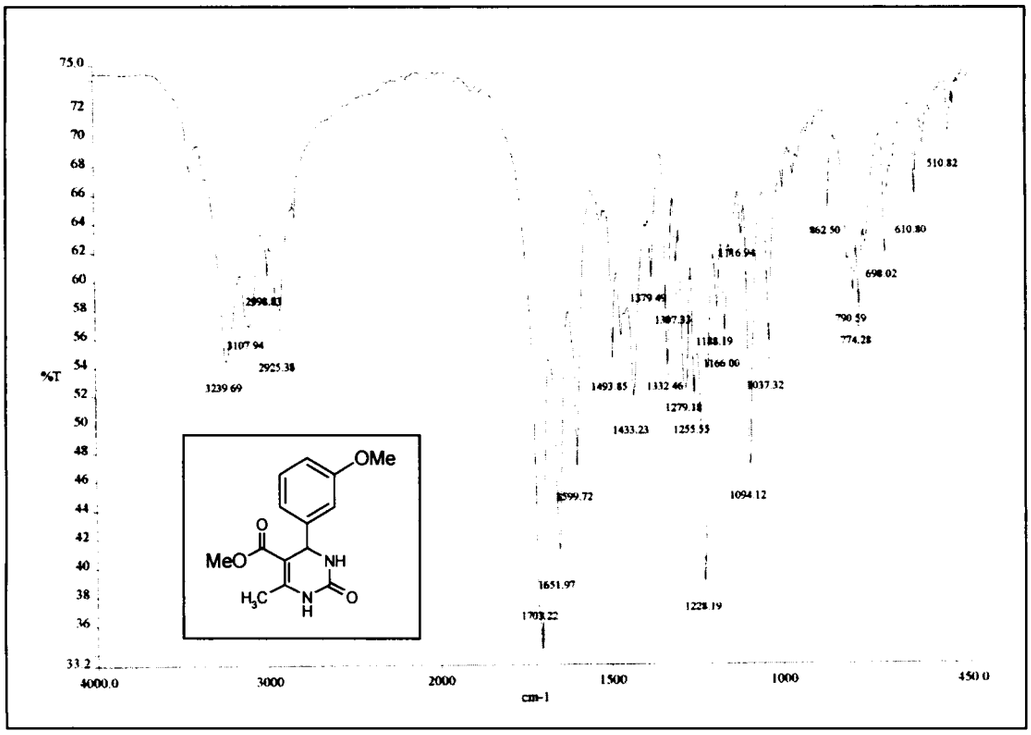


Spectrum No. 2.^{1}HNMR Spectrum of the product **4e in** $CDCl_3$- d_6-DMSO



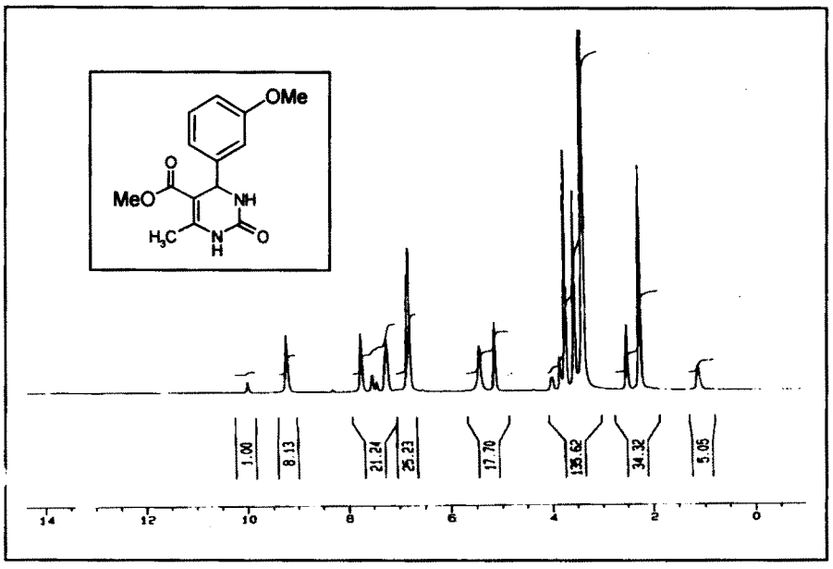
Spectrum No. 3.^{1}HNMR Spectrum of the product **4e in** $CDCl_3$- d_6-DMSO

In the IR spectrum of the product **4m** exhibits (Spectrum No.4) two carbonyl stretching bands at 1703 and 1651 cm^{-1} due to ester carbonyl and amide carbonyl and a band around 3300 cm^{-1} is due to NH stretching.



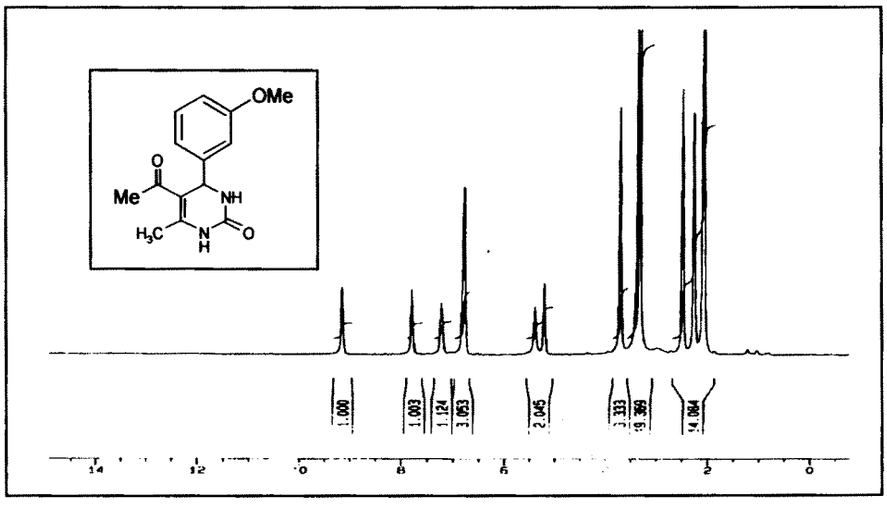
Spectrum No.4. FTIR Spectrum of the product **4m** recorded as KBr pellet.

In ^{1}HNMR spectrum, the above compound (Spectrum No.5) resonated two singlets at 3.72 and 3.83 ppm due to methoxy and ester methyl protons and singlet at 5.41 ppm is due to C_4-H of the pyrimidone. Where as NH protons resonated at 7.23 and 9.20 ppm as a broad singlet. Aromatic protons resonated in the range of 6.78-7.72 ppm respectively.



Spectrum No. 5. ^{1}HNMR Spectrum of the product **4e in** $CDCl_3$- d_6-DMSO

The ^{1}HNMR of the product **4s** (spectrum No.6) shows three singlets at 2.08, 2.50 and 3.72 ppm are due to CH_3CO-, -CH_3 and -OCH_3 and the characterstic CH of the pyrimidone appeared as a singlet at 5.22 ppm. Where as two NH peaks appeared as a broad singlet at 7.24 and 9.18 ppm which was ccnfirmed by D_2O exchange and aromatic protons resonated in the range of 6.80-7.81 ppm and rest of the results aresummarised in the Table.



Spectrum No. 6. ^{1}HNMR Spectrum of the product **4s in** $CDCl_3$- d_6-DMSO

The ^{1}HNMR results of the products are summarised in Table 1.

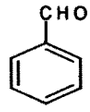
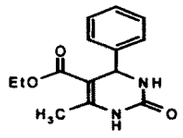
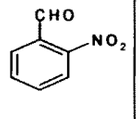
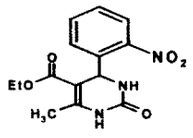
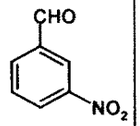
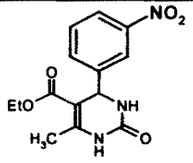
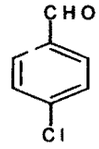
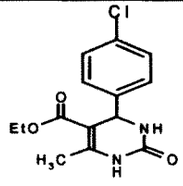
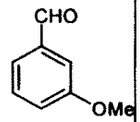
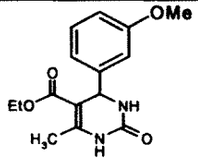
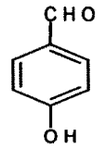
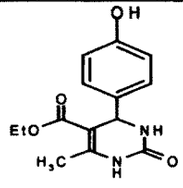
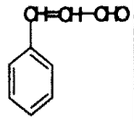
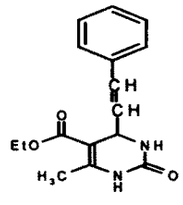
Table 1

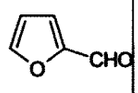
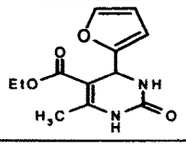
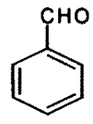
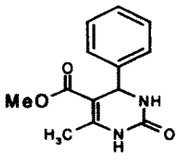
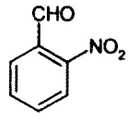
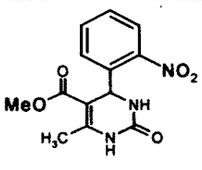
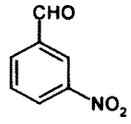
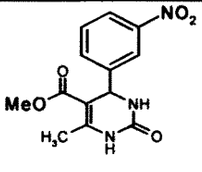
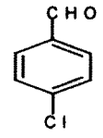
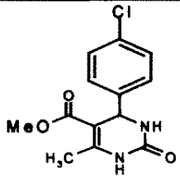
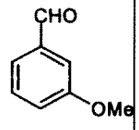
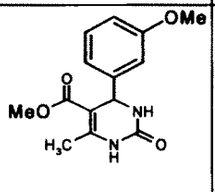
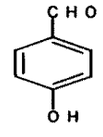
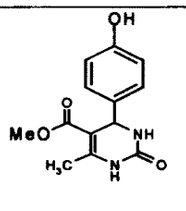
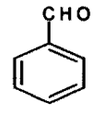
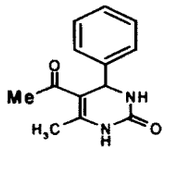
Product	^{1}HNMR Results
4a	1.15(t,3H, -CH_2CH_3), 2.32(s, 3H, CH_3), 4.06(q, 2H, -CH_2CH_3), 5.35(s, 1H, CH), 6.82(s, 1H, NH), 7.36(s, 5H, Ar-H), 8.78(s, 1H, NH).
4b	1.37(t, 3H, -CH_2CH_3), 2.48(s, 3H, CH_3), 4.35(q, 2H, -CH_2CH_3), 5.77(s, 1H, CH), 5.90(s, 1H, NH), 7.47-8.24(m, 5H, Ar-H and NH).
4c	1.22(t, 3H, -CH_2CH_3), 2.36(s, 3H, CH_3), 4.10(q, 2H, -CH_2CH_3), 5.53(s, 1H, CH), 5.62(s, 1H, NH), 7.12-8.20(m, 5H, Ar-H and NH).
4d	1.17(t, 3H, -CH_2CH_3), 2.33(s, 3H, CH_3), 4.07(q, 2H, -CH_2CH_3), 5.36(s, 1H, CH), 6.00(s, 1H, NH), 7.17-7.29(m, 4H, Ar-H), 8.27(s, 1H, NH).
4f	1.26(t, 3H, -CH_2CH_3), 2.31(s, 3H, CH_3), 4.03(q, 2H, -CH_2CH_3), 5.25(s, 1H, CH), 4.84(s, 1H, NH), 6.63-7.14(m, 4H, Ar-H), 8.61(s, 1H, NH),9.82(s, 1H, OH)
4g	1.28(t, 3H, -CH_2CH_3), 2.29(s, 3H, CH_3), 4.14(q, 2H, -CH_2CH_3), 6.17(d, 1H, CH), 6.24(d, 1H,CH=CH),6.49(t, 1H, CH=CH), 4.95(s, 1H, NH), 7.18-7.43(m, 5H, Ar-H), 8.64(s, 1H, NH).
4i	2.39(s, 3H, CH_3), 3.62(s, 3H, $COOCH_3$), 5.39(s, 1H, CH), 5.82(s,1H, NH),7.24-7.34(s, 5H, Ar-H), 8.20(s, 1H, NH)
4o	2.10(s, 3H, $COCH_3$), 2.35(s, 3H, CH_3), 5.36(s, 1H, CH), 7.22-7.65(m, 6H, Ar-H and NH), 8.97(s, 1H, NH).
4p	2.23(s, 3H, $COCH_3$), 2.39(s, 3H, CH_3), 5.54(s, 1H, CH), 5.38(br,1H, NH),7.30-8.20(m, 4H, Ar-H), 8.89(s, 1H, NH)
4t	1.78(s, 3H, $COCH_3$), 2.35(s, 3H, CH_3), 4.64(s, 1H, CH), 5.52(br,1H, NH),6.55-7.54(m, 6H, Ar-H, NH and OH),

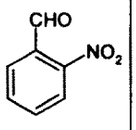
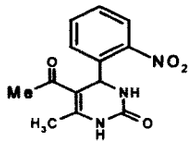
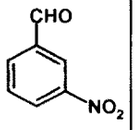
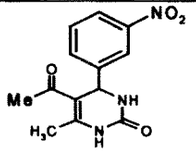
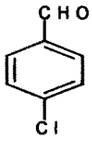
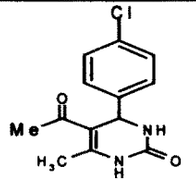
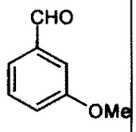
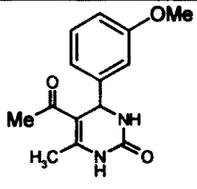
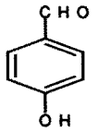
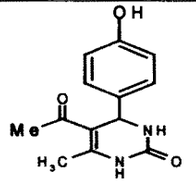
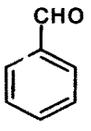
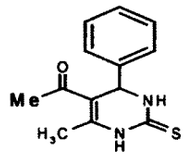
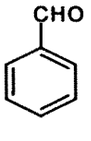
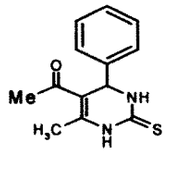
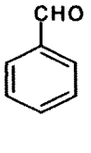
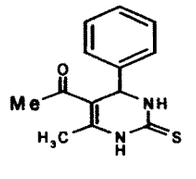
5.6 Conclusions

In summary, we have found that heteropolyacid 11-molybdo-1-vanadophosphoric acid ($H_4PMo_{11}VO_{40}$) is extremely useful and highly efficient homogeneous acid catalyst for the synthesis of biologically potent aryl 3,4-dihydropyrimidinones by means of MCRs three-component condensations of an aldehyde, 1,3-dicarbonyl compound, and urea or thiourea in a one-pot operation. This method is applicable to a wide range of substrates, including aromatic, aliphatic, α,β- unsaturated, and heterocyclic aldehydes, and provides a variety of biologically relevant dihydropyrimidinones in high to-quantitative yields in short reaction times

Table 2. 11-molybdo-1-vanadophosphoric acid catalysed synthesis of Biginelli 3,4-dihydropyriminones (DMPH)

Aldehyde (R')	β-keto ester (R'')	X	Time (h)	Product	DMPH	Yield (%)[b]	MP(°C)
	OEt	O	6		**4a**	94	203-205
	OEt	O	6.5		**4b**	85	208-210
	OEt	O	6		**4c**	90	211-214
	OEt	O	6		**4d**	95	213-215
	OEt	O	6		**4e**	86	213-215
	OEt	O	6.5		**4f**	90	198-201
	OEt	O	6		**4g**	91	232-235

	OEt	O	6		**4h**	86	209-211
	OMe	O	6		**4i**	93	210-213
	OMe	O	8		**4j**	81	279-282
	OMe	O	6		**4k**	83	279-280
	OMe	O	4.5		**4l**	91	206-208
	OMe	O	5		**4m**	95	192-195
	OMe	O	8		**4n**	89	207-209
	Me	O	6.5		**4o**	93	233-235

	Me	O	7.5		**4p**	83	239-242
	Me	O	6		**4q**	91	268-270
	Me	O	6		**4r**	90	209-211
	Me	O	5.5		**4s**	96	229-233
	Me	O	8		**4t**	89	198-201
	OEt	S	5		**4u**	93	192-195
	OMe	S	6		**4v**	90	197-200
	Me	S	6		**4w**	93	220-222

[a] All the products were characterized by ^{1}HNMR spectroscopy.
[b] Yield refers to the isolated pure products after recrystallization.

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