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Ultrasound Assisted One-pot Synthesis of Dihydropyrimidinones Using Holmium Chloride As Catalyst

S. Kakaei[1*], H. Sid Kalal[1], and H. Hoveidi[2]

[1] *NFCRS, Nuclear Science and Technology Research Institute, P.O. Box 11365-3486, Tehran, Islamic Republic of Iran*
[2] *Graduate Faculty of Environment, University of Tehran, Tehran, Islamic Republic of Iran*

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Abstract

A simple and green chemical procedure was reported for the synthesis of dihydropyrimidinones from various aldehydes, ethyl acetoacetate and urea or thiourea using holmium chloride as catalyst. The reactions were performed under solvent free conditions with ultrasound irradiation as the energy source. The advantages of this protocol include the excellent yield, operational simplicity, short time and the avoidance of the use of organic solvents and friendly preparation. Products were identified by mp. and IR, NMR and Mass spectroscopies.

Keywords: Biginelli reaction; Solvent-free; Ultrasound-assisted; One-pot; Holmium chloride.

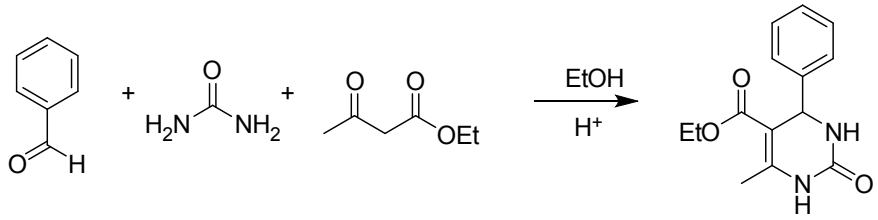
Introduction

P. Biginelli reported the synthesis of functionalized 3,4-dihydropyrimidin-(1*H*)-ones (DHPMs) *via* three component condensation reaction of an aromatic aldehyde, urea, and ethyl acetoacetate [Scheme 1]. In the past decade, this multicomponent reaction has experienced a remarkable revival, mainly due to the interesting pharmacological and therapeutic properties of DHPMs, such as antiviral, antitumour, antibacterial and anti-inflammatory activities [1].

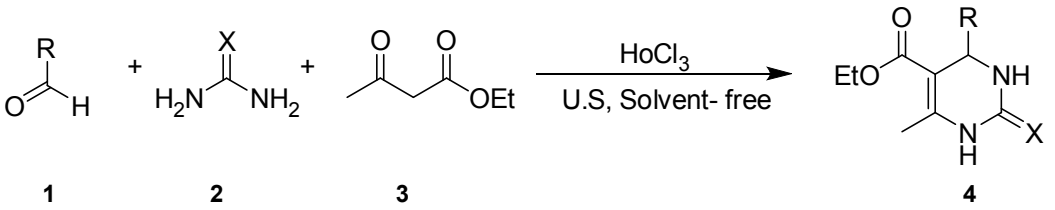
The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated in the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1*H*)-one [2-4]. However, this method suffers from drawbacks such as low yields (20–40%), particularly in case of substituted aldehydes, and loss of acid sensitive functional groups during the reaction. This has led to multi-step synthetic strategies that produce slightly better yields, but lacking the simplicity of the original one-pot Biginelli protocol. [5] The search for more suitable preparation methods of dihydropyrimidinones continues today.

This has led to the disclosure of several methodologies for the synthesis of dihydro-pyrimidinones derivatives by using Lewis acid catalysts as well as protic acids including $FeCl_3{\cdot}6H_2O$, $NiCl_2{\cdot}6H_2O$ [6], lanthanide triflate [7], H_3BO_3 [8], VCl_3 [9], $Sr(OTf)_2$ [10], PPh_3 [11], indium(III) halides [12], LiBr [13], silicasulfuric acid [14], $Mn(OAc)_3{\cdot}2H_2O$ [15], $Y(NO_3)_3{\cdot}6H_2O$ [16]. In $(OTf)_3$ [17], $TaBr_5$ [18],

* Corresponding author: Tel: +982182063617; Fax: +98-2188221116; Email: skakaei@aeoi.org.ir



Scheme 1. Biginelli Dihydropyrimidine Synthesis



Scheme 2. Optimized Reaction conditions

$Ce(NO_3)_3{\cdot}6H_2O$ [19], silica chloride [20], HCOOH [21], $SrCl_2{\cdot}6H_2O$-HCl [22], $Yb(OTf)_3$ [23], $Bi(NO_3)_3{\cdot}5H_2O$ [24], tungstate sulfuric acid [25], $HClO_4$-SiO_2 [26], $MgBr_2$ [27], $Sr(NO_3)_2$ [28], 12-molybdophosphoric acid [29] and so on. In addition, ionic liquids [30], microwave irradiation [31] and ultrasound irradiation [32] were also utilized as the catalytic condition. However, in spite of their potential utility, many of these methods involve expensive reagents, strong acidic conditions and long reaction times. Furthermore, the scope of the substrates was limited to aromatic aldehydes. Due to increasing environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures that can avoid using harmful organic solvents, or even better, do not need solvents at all. Recently, sonochemistry as a new trend in organic chemistry has offered a versatile and more environmentally friendly conditions for a large variety of syntheses. Thus, a large number of organic reactions can be carried under ultrasonic irradiation in high yields, short reaction times and mild conditions [33-37]. Moreover, solvent-free conditions are especially important for providing an eco-friendly system. Currently, much emphasis have been given to the use of inorganic reagents in organic reactions, as these reactions often provide the milder conditions and easier work up than similar reactions using organic reagents [38].

Following of our interest in green chemistry [28,29], we would like report an environmentally procedure for the synthesis of dihydropyrimidinones 4 under ultrasonic irradiation in the presence of holmium chloride hexahydrate as a catalyst under solvent free condition [Scheme 2].

The reactions were completed in 2- 4 hours with 87–96% yields. All the products were identified by comparing their physical and spectral data with those of authentic compound reported in the literature.

Materials and Methods

All reactants were obtained from commercial sources, and freshly distilled prior to use. Melting points were determined with a TG (Rheometric Scientific STA 1500) apparatus and were not corrected. Ultrasonic irradiation was carried out with a Misoui X3000 (35 KHz, 54w). ^{1}H (300) and ^{13}C (75) NMR (Bruker) spectra were recorded for methanol-d_4 solution with TMS as an internal standard, mass spectra were acquired with the use of MS spectrometer (Trio 1000-Sison instruments), IR spectra were obtained by using an FT-IR (Bruker Victor22) spectrophotometer.

Results and Discussion

To prepare dihydropyrimidinones 4, we first selected the reaction of benzaldehyde, ethyl acetoacetate, and urea under different amounts of holmium chloride as a catalyst to optimize the reaction conditions. The results

Table 1. Effect amount of catalyst on the formation of **4a** (P=35 W), 80°C

Entry	Catalyst (mol %)	Time (h)	Isolated Yields (%)
1	0	5	trace
2	1	1	18
3	2	1	26
4	5	1	67
5	8	1	69
6	10	1	69
7	15	1	69

Table 2. Effects of the ultrasound power and the irradiation time on the formation of **4a**

Entry	Time (h)	Power (W)	Temp. (°C)	Yields (%)[a]
1	1	10	80	25
2	1	25	80	37
3	1	30	80	54
4	1	35	80	69
5	1	40	80	72
6	1	45	80	75
7	1	55	80	70
8	2	45	80	85
9	3	45	80	72

[a] Reaction conditions: benzaldehyde1.0 mmol; ethylacetoacatate 1.0mmol; urea 1.5 mmol; $HoCl_3$ 8 mol%

are presented in Table 1. No desired product 4a was observed after 5 h under ultrasound irradiation and solvent free at 80 °C [Table 1, entry 1]. However, the product (4a) was obtained with 18% yield at same temperature [Table 1, entry 2], and the yield increased to 26%. The yield was improved to 67% by increasing the amount of the catalyst [Table 1, entries 3, 4]. When the loading amount of $HoCl_3$ was increased from 5 to 8 mol%, the yield was further improved remarkably from 67 to 69% [Table 2, entries 4 and 5]. However, further increasing to 15 mol% catalyst did not improve the yield from 69% [Table 2, entries 6, 7]. Thus, the optimal conditions are benzaldehyde, ethyl acetoacetate, and urea in a molar ratio of (1:1:1.5) with addition of $HoCl_3$ (8 mol%) in 80 °C for 1 h [Table 1, entry 5].

We found that most of the Lewis acids could promote the reaction, but the yields were not so high. In comparison with other catalysts, the use of 8 mol% of HoCl3 could make the yield to reach 69% under the ultrasound power of 35W and the irradiation time of 1 h. It could be seen that 8 mol% amount of HoCl3 gave the best result of this reaction, although other factors could not yet be optimized. Based on the above optimized results, i.e., 8 mol% of HoCl3 as a catalyst, we further examined the effects of the ultrasound power and the irradiation time on the Biginelli reaction, involving benzaldehyde, ethylacetoacetate and urea to afford (4a), as shown in Scheme 2. The results are listed in Table 2. It could be found that with the increase of the ultrasound power from 10W to 45W, the yield of (4a) showed a linear increase from 25% to 75% when the irradiation time was 1 h. However, with the ultrasound power of 45W, when we increased the ultrasound irradiation time to 2 h, the yield of (4a) increased first, then showed a slight decrease when the time was more than 2 h. So, the optimized ultrasound power and the irradiation time were 45W and 2 h, respectively. Holmium chloride could be recovered by filtration and reused with similar reactivity after washing with hot ethanol or methanol and heating at 100 °C for 6 h. The results are in agreement with those of Biginelli reaction. Indeed, holmium chloride seems to be an excellent catalyst for the one-pot, three components Biginelli condensation under solvent free conditions to afford the corresponding 3,4-dihydropyrimidinones in high yields at 80 °C.

The reaction consists in several successive steps with formation of two intermediates: acylimine resulting from reaction of urea with aldehyde, and the enol resulting from enolisation of β- ketoacetate. A condensation between these intermediates produces the cyclic transient intermediate which, by elimination of water, gives the dihydropyrimidinone [39]. The reactivity of aromatic aldehyde in the Biginelli reaction is better than aliphatic aldehydes. Furthermore, aromatic aldehydes, carrying either electron-donating or electron-withdrawing substituents, all reacted very well, giving

Table 3. $HoCl_3$ catalyzed synthesis of DHPMs

Entry	4	R	X	Time (h)	Mp (^oC)	Yield (%)[a]	Lit.
1	4a	Benzaldehyde	O	2	205	85	206 [14]
2	4b	4-Methoxy- Benzaldehyde	O	2.5	202	92	198-200 [27]
3	4c	Furfuraldehyde	O	2	207	97	206-208 [27]
4	4d	Cinnamaldehyde	O	3.5	236	92	240-242 [27]
5	4e	4-Dimethylamino Benzaldehyde	O	3	256	94	256-258 [6]
6	4f	Salicylaldehyde	O	3.5	200	89	201-203 [6]
7	4g	4-Chloro Benzaldehyde	O	2.5	213	93	213-215 [14]
8	4h	3-Hydroxy Benzaldehyde	O	3	165	93	167-170 [14]
9	4i	α-Hexyl Benzaldehyde	O	2	236	87	237-238 [6]
10	4j	Benzaldehyde	S	3	206	94	206-208 [40]
11	4k	4-Methoxy- Benzaldehyde	S	3	154	93	150-152 [40]
12	4l	Furfuraldehyde	S	2	187	95	185 [28]
13	4m	Cinnamaldehyde	S	4	244	91	244-246 [29]
14	4n	4-Dimethylamino Benzaldehyde	S	3	208	95	209-210 [27]
15	4o	Salicylaldehyde	S	3	244	90	240-241 [29]
16	4p	4-Chloro Benzaldehyde	S	2	194	94	190-192 [40]
17	4q	3-Hydroxy Benzaldehyde	S	3	185	91	183-185 [29]

[a] yields refers to pure solid products, properly characterized by m.p. spectral (IR, ^1H NMR and Mass) data.

excellent yields. The electronic effect and nature of the substituent on the aromatic aldehyde did not show any remarkable effect in terms of yields. The results are listed in Table 3. The comparison of reaction time and yield with or without ultrasonic conditions show that the ultrasonic irradiation accelerates the Biginelli reaction. The solvent-free condition facilitated the Biginelli condensation. Under ultrasonication and solvent free condition, dihydropyrimidinone derivatives were obtained similar to or higher yields than those obtained without ultrasonic irradiation. The main advantage of ultrasonic application is the decrease in reaction time.

Many of the pharmacologically relevant substitution patterns on the aromatic ring were introduced with high efficiency. Thiourea has been used with similar success to provide the corresponding dihydropyrimidin-2-(1*H*)-thiones with high yields, which are also of much interest with regard to biological activity. Acid sensitive aldehydes (4c) worked well without formation of any side product. Especially noteworthy is the survival of a variety of functional groups, such as hydroxy, halides, amin, double bond, etc., under the reaction conditions.

Compared to the conventional heating method, the achieved yields under ultrasound irradiation increase 6-8% and only one-third of the reaction time need. The scope and efficiency of the current procedure was investigated by the reaction of a series of aromatic aldehydes, ethyl acetoacetate and urea or thiourea in the presence of minimum amount of catalyst [Scheme 2]. Corresponding dihydropyrimidinones were obtained with good to excellent yields in appropriate times according to Table 3.

General procedure for the $HoCl_3$ catalyzed synthesis of Dihydropyrimidinones

A mixture of ethyl acetoacetate (1mmol), benzaldehyde (1mmol), urea (1.5mmol), and the 8mol% of the catalyst was placed in a round bottom flask without any solvent. It was then irradiated in a Misoui X3000 at 45 W (80 $^\circ$C) and the irradiation time of 2 h. After cooling, the reaction mixture was poured on crushed ice (50 g) for 5-10 min. The solid separated was filtered under suction, washed twice with cold water (30mL) and then recrystallized from ethanol to afford the pure products 4. All the products were characterized by Mp, spectral and analytical data.

Entry 1: 5-Ethoxycarbonyl-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-one (4a)

M.P: 205 °C, IR (KBr, cm^{-1}): 3245, 3118, 2978, 2983, 1725, 1701, 1649, and 1595. ^{1}H NMR (Methanol-d_4, 300 MHz) δ = 1.12 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 2.29 (s, 3H, C_6H_5-CH_3), 4.02 (q, *J* = 7.2 Hz, 2H, OCH_2CH_3), 5.19 (s, 1H, CH), 7.27-7.42 (m, 5H, C_6H_4), 7.75 (d, *J* = 7.2 Hz, 1H, NH), 9.21 (s, 1H, NH).

^{13}C NMR (Methanol-d_4, 75 MHz) δ = 13.5, 17, 55.3, 60, 101.1, 126.7, 127.7, 128.6, 144.7, 147.8, 166.5. MS (70 ev) m/z (%): 262 (M^+, 26), 231 (78.4), 187 (73.7), 183 (100), 172 (38.2), 155 (62.8), 137 (48.5), 77 (34.2), 51 (37.2), 42 (71.2).

Entry 2: 5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-one (4b)

Mp: 202 °C, IR (KBr, cm^{-1}): 3251, 3108, 1711 and 1652. ^{1}H NMR (Methanol-d_4, 300 MHz) δ = 1.11 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.19 (s, 3H, C_6H_5-CH_3), 3.72 (q, *J* = 7.2 Hz, 2H, OCH_3), 3.89 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 5.09 (s, 1H, CH), 7.19-6.88 (m, 4H, C_6H_4), 7.72 (s, 1H, NH), 10.01 (s, 1H, NH).

Entry 7: 4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3, 4-dihydropyrimidin-2(1H)-one (4h)

Mp: 213 °C; IR (KBr, cm^{-1}): 3130, 1697, and 1643. ^{1}H NMR (Methanol-d_4, 300 MHz) δ = 1.08 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 2.24 (s, 3H, CH_3), 3.98 (q, *J* = 7.0 Hz, 2H, OCH_2CH_3), 5.14 (s, 1H, CH), 7.36-7.17 (m, 4H, C_6H_4), 7.77 (s, 1H, NH), 9.24 (s, 1H, NH).

Entry 8: 5-Ethoxycarbonyl-4-(3-hydroxyphenyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-one (4i)

Mp: 165 °C, IR (KBr, cm^{-1}): 3252, 3108, 1687 and 1653. ^{1}H NMR (Methanol-d_4, 300 MHz) δ = 1.23 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.22 (s, 3H, CH_3), 3.98 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 5.06 (s, 1H, CH), 7.11-6.62 (m, 4H, C_6H_4), 7.66 (s, 1H, NH), 9.23 (s, 1H, NH), 9.46(s, 1H, OH).

Entry 10: 5-Ethoxycarbonyl-6-methyl-4-phenyl-3, 4-dihydropyrimidin-2(1H)-thione (4k)

Mp: 206 °C, IR (KBr, cm^{-1}): 3249, 3121, 1701 and 1541. ^{1}H NMR (Methanol-d_4, 300 MHz) δ = 1.11 (t, *J* = 7.1 Hz, 3H, OCH_2CH_3), 2.16 (s, 3H, CH_3), 4.02 (q, *J* = 7.1 Hz, 2H, OCH_2CH_3), 5.20 (d, *J* = 3.5 Hz, 1H, CH), 7.37-7.21 (m, 5H, C_6H_5), 9.55 (s, 1H, NH), 10.25 (s, 1H, NH).

Entry 11: 5-Ethoxycarbonyl -4-(4-methoxylphenyl)- 6-methyl -3,4-dihydropyrimidin-2(1H)-thione (4l)

Mp 154 °C, IR (KBr, cm^{-1}): 3251, 3119, 1685 and 1543. ^{1}H NMR (Methanol-d_4, 300 MHz) δ= 1.10 (t, *J* = 6.9 Hz, 3H, OCH_2CH_3), 2.27(s, 3H, CH_3), 3.17 (s, 3H, OCH_3), 4.02 (q, *J* = 6.9 Hz, 2H, OCH_2CH_3), 4.98 (s, 1H, CH), 7.16-6.86 (m, 4H, C_6H_4), 9.55 (s, 1H, NH), 10.17 (s, 1H, NH).

Entry 16: 4-(4-Chlorophenyl)- 5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione (4r)

Mp: 194 °C, IR (KBr, cm^{-1}): 3254, 3121, 1665 and 1547. ^{1}H NMR (Methanol-d_4, 300 MHz) δ = 1.12 (t, *J* = 6.5 Hz, 3H, OCH_2CH_3), 2.32 (s, 3H, CH_3), 4.01(q, *J* = 6.5 Hz, 2H, OCH_2CH_3), 5.12 (s, 1H, CH), 7.41-7.17 (m, 4H, C_6H_4), 9.73 (s, 1H, NH), 10.40 (s, 1H, NH).

Conclusion

We have successfully developed a versatile protocol for the synthesis of DHMPs from the reaction of aldehydes, ethyl acetoacetate, urea or thiourea catalyzed by $HoCl_3$ as a heterogeneous catalyst. The protocol offers several advantages such as mild reaction conditions, short reaction times, easy isolation and good yields. It was also revealed that the proposed method is more economic, if the reaction is exposed to ultrasounds instead of using conventional heating methods. Hence, it is an important supplement to the existing methods for the synthesis of dihydroprimidiones and their corresponding thio-derivatives. The process doesn't need any hazardous or harmful solvents, and thus it is a simple, environmentally friendly technique of high atom economy.

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References

1. Kappe C.O. Recent advances in the Biginelli dihydropyrimidine synthesis. New tricks from an old dog. *Acc. Chem. Res.*, **33**: 879-888 (2000).
2. Biginelli P. Aldehyde-urea derivatives of aceto-and oxaloacetic acids, *Gazz. Chim. Ital.,* **23**: 360-413 (1893).
3. Folkers K., Johnson T. B. The Mechanism of Formation of Tetrahydropyrimidines by the Biginelli Reaction1. *J. Am. Chem. Soc.,* **55**: 3781-3791 (1933).
4. Kappe C.O. 100 years of the Biginelli dihydropyrimidine synthesis. *Tetrahedron,* **49**: 6937-6963 (1993).
5. Sabitha G., Reddya B. Ceria/vinylpyridine polymer nanocomposite: an ecofriendly catalyst for the synthesis of 3, 4-dihydropyrimidin-2(1*H*)-ones. *Tetrahedron Lett.* **46** (47): 8221–8224 (2005).
6. Lu J., Bai Y. Catalysis of the Biginelli Reaction by Ferric and Nickel Chloride Hexahydrates. One-Pot Synthesis of 3, 4-Dihydropyrimidin. *Synthesis,* **4**: 466–470 (2002).

7. 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.,* **65**: 3864–3868 (2000).
8. Tu S.J., Fang F., Miao C.B., Jiang H., Shi D.Q., Wang X.S. One-pot synthesis of 3,4-dihydropyrimidin-2(1H)-ones using boric acid as catalyst. *Tetrahedron Lett.,* **44**:6153–6155 (2003).
9. Sabitha G., Reddy G.S.K.K., Reddy K.B., Yadav J.S. Vanadium(III) chloride catalyzed Biginelli condensation: solution phase library generation of dihydropyrimidin-(2*H*)-ones *Tetrahedron Lett.,* **44**: 6497–6499 (2003).
10. Su W.K., Li J.J., Zheng Z.G., Shen Y.C. One-pot synthesis of dihydropyrimidiones catalyzed by strontium(II) triflate under solvent-free conditions. *Tetrahedron Lett.,* **46**: 6037–6040 (2005).
11. Debache A., Amimour M., Belfaitah A., Rhouati S., Carboni B. A one-pot Biginelli synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones catalyzed by triphenylphosphine as Lewis base. *Tetrahedron Lett.,* **49**: 6119–6121 (2008).
12. Fu N.Y., Yuan Y.F., Pang M.L., Wang J.T., Peppe C. Indium (III) halides-catalyzed preparation of ferrocene-dihydropyrimidinones. *J. Organomet. Chem.,* 672: 52–57 (2003).
13. Maiti G., Kundu P., Guin C. One-pot synthesis of dihydropyrimidinones catalysed by lithium bromide: an improved procedure for the Biginelli reaction. *Tetrahedron Lett.,* **44**: 2757–2758 (2003).
14. Salehi P., Dabiri M., Zolfigol M.A., Fard M.A.B. Silica sulfuric acid: an efficient and reusable catalyst for the one-pot synthesis of 3, 4-dihydropyrimidin-2(1H)-ones. *Tetrahedron Lett.,* **44**;2889–2891 (2003).
15. Kumar K.A., Kasthuraiah M., Reddy C.S., Reddy C.D. $Mn(OAc)_3 \cdot 2H2O$-mediated three-component, one-pot, condensation reaction: an efficient synthesis of 4-aryl-substituted 3,4-dihydropyrimidin-2-ones. *Tetrahedron Lett.,* **42**:7873–7875 (2001).
16. Nandurkar N.S., Bhanushali M.J., Bhor M.D., Bhanage B.M. $Y(NO_3)_3 \cdot 6H_2O$: 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.,* **27**: 14–17 (2007).
17. Ghosh R., Maiti S., Chakraborty A. $In(OTf)_3$-catalysed one-pot synthesis of 3,4-dihydropyrimidin-2(lH)-ones. *J. Mol. Catal. A Chem*., **217**: 47–50 (2004).
18. Ahmed N., Lier J.E.V. $TaBr_5$-catalyzed Biginelli reaction: one-pot synthesis of 3,4-dihydropyrimidin-2-(1H)-ones/thiones under solvent-free conditions. *Tetrahedron Lett.,* **48**: 5407–5409 (2007).
19. Adib M., Ghanbary K., Mostofi M., Ganjali M.R. Efficient Ce $(NO_3)_3 6H_2O$-catalyzed solvent-free synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones. *Molecules,* **11**:649–654 (2006).
20. Karade H.N., Sathe M., Kaushik M.P. Synthesis of 4-aryl substituted 3, 4-dihydropyrimidinones using silica-chloride under solvent free conditions. *Molecules,* **12**: 1341–1351 (2007).
21. Cheng J., Qi D.Y. An efficient and solvent-free one-pot synthesis of dihydropyrimidinones under microwave irradiation. *Chin. Chem. Lett.,* **18**: 647–650 (2007).
22. Nasr-Esfahani M., Khosropour A.R. An Efficient and Clean One-Pot Synthesis of 3, 4-Dihydropyrimidine-2-(1H)-ones Catalyzed by $SrCl_2$ $6H_2O$-HCl in Solvent or Solvent-Free Conditions. *Bull. Korean Chem. Soc*., **26**:1331–1332 (2005).
23. Huang Y., Yang F., Zhu C. Highly enantioseletive biginelli reaction using a new chiral ytterbium catalyst: Asymmetric synthesis of dihydropyrimidines. *J. Am. Chem. Soc.,* **127**: 16386–16387 (2005).
24. Khodaei M.M., Khosropour A.R., Beygzadeh M. An Efficient and Environmentally Friendly Method for Synthesis of 3, 4-Dihydropyrimidin-2 (1H)-ones Catalyzed by Bi $(NO_3)_3 5H_2O$. *Synth. Commun.,* **34**: 1551–1557 (2004).
25. Nasr-Esfahani M., Karami B., Montazerozohori M., Abdi K. An efficient and clean one-pot synthesis of 3,4-dihydropyrimidine-2(1*H*)-ones catalyzed by tungstate sulfuric acid in solvent-free conditions. *J. Heterocycl. Chem.*, **45**: 1183–1185 (2008).
26. Maheswara M., Oh S.H., Kim K., Do J.Y. Synthesis of 3,4-Dihydropyrimidin-2(*1H*)-ones Using $HClO_4$-SiO_2 as a Heterogeneous and Recyclable Catalyst. *Bull. Korean Chem. Soc.,* **29**: 1752–1754 (2008).
27. Salehi H., Guo Q.-X. A facile and efficient one-pot synthesis of dihydropyrimidinones catalyzed by magnesium bromide under solvent-free conditions. *Synth Commun.,* **34**: 171–179 (2004).
28. Kakaei, S., Salehi H., Ahmadi S.J., Firooz M. A. Microwave Irradiation-Assisted one-Pot Synthesis of 3, 4 Dihydropyrimidinones Using Strontium Nitrate as a Catalyst. *J. Appl. Chem. Res.,* **4**: 34-39 (2008).
29. Kakaei S., Salehi H., Ahmadi S.J., Firooz M. A. Green procedure for synthesis of 3, 4 dihydropyrimidinones using 12-molybdophosphoric acid, as a catalyst and solvent free condition under microwave. *J. Appl. Chem. Res.,* **4**: 5-11 (2010).
30. Peng J.J., Deng Y.Q. Ionic liquids catalyzed Biginelli reaction under solvent-free conditions. *Tetrahedron Lett.,* **42**: 5917–5919 (2001).
31. Banik B.K., Reddy A.T., Datta A., Mukhopadhyay C. Microwave-induced bismuth nitrate-catalyzed synthesis of dihydropyrimidones via Biginelli condensation under solventless conditions. *Tetrahedron Lett.,* **48**: 7392–7394 (2007).
32. Li J.T., Han J.F., Yang J.H., Li T.S. An efficient synthesis of 3,4-dihydropyrimidin-2-ones catalyzed by NH_2SO_3H under ultrasound irradiation. *Ultrason. Sonochem.,* **10**: 119–122 (2003).
33. Mason T.J. Sonochemistry and the environment–Providing a "green" link between chemistry, physics and engineering. *Ultrason. Sonochem.,* **14**: 476-483 (2007).
34. Ruiz E., Rodriguez H., Coro J., Salfran E., Suarez M., Martin N. Ultrasound-assisted one-pot, four component synthesis of 4-aryl 3,4-dihydropyridone derivatives. *Ultrason. Sonochem.,* **18**: 32-36 (2011).
35. Abd EL-Rahman N.M., Saleh T.S., Mady M.F. Ultrasound assisted synthesis of some new 1, 3, 4-thiadiazole and bi (1, 3, 4-thiadiazole) derivatives incorporating pyrazolone moiety. *Ultrason. Sonochem.,* **16**: 70-74 (2009).
36. Moslemin M.H., Nateghi M.R. Rapid and efficient synthesis of fused heterocyclic pyrimidines under

ultrasonic irradiation. *Ultrason. Sonochem.,* **17**: 162-167 (2010).
37. Saïd Y., Moussaoui M., Kammoun R., Ben Salem. Ultrasonic activation of Heck type reactions in the presence of Aliquat-336. *Ultrason. Sonochem.,* **18**: 23-27 (2011).
38. Varma R.S. Solvent-free organic syntheses. using supported reagents and microwave irradiation. *Green Chem.*, **1**: 43-55 (1999).
39. Kappe C.O. A Reexamination of the Mechanism of the Biginelli Dihydropyrimidine Synthesis. Support for an N-Acyliminium Ion Intermediate1. *J. Org. Chem.,* **62**: 7201–7204 (1997).
40. Salehi H., Guo Q.-X. Efficient Magnesium Bromide-Catalyzed One-pot Synthesis of Substituted 1,2,3,4-Tetrahydropyrimidin-2-ones Under Solvent-free Conditions. *Chin. j. Chem.,* **2:** 1, 91-97 (2005).