Facile and Rapid Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-one Derivatives Using $[Et_3NH][HSO_4]$ as Environmentally Benign and Green Catalyst

Pouramiri, Behjat; Fayazi, Raziye; Tavakolinejad Kermani, Esmat*[+]

Department of Chemistry, Shahid Bahonar University of Kerman, Kerman 76169, I.R. IRAN

ABSTRACT: *5-acetyl-6-methyl-4-aryl-3,4-dihydropyrimidin-2(1H)-ones were synthesized in good to excellent by one-pot three-component Biginelli condensation in the presence of ammonium* salt $[Et_3NH][HSO_4]$ *as an inexpensive and green catalyst under solvent-free conditions. High yields, short reaction time, easy work-up, a green environment which requires no toxic organic solvents and reusability of the catalyst are the advantages of this procedure. A broad range of structurally diverse aldehydes (aromatic aldehydes bearing electron withdrawing and electron releasing groups) was applied successfully, and corresponding products were obtained in good to excellent yields without any by-product. In addition, this catalyst was stable during the reaction process and could also be reused several times with consistent activity.*

KEYWORDS: *Biginelli reaction; 3,4-Dihydropyrimidin-2(1H)-one; Triethylammonium hydrogen sulfate; Ionic liquid.*

INTRODUCTION

In recent years, preparation and use of eco-friendly catalysts to improve the efficiency of reactions or provide a higher yield has been the subject of interests especially in the green organic synthesis [1-5]. Ionic Liquids (ILs) play a significant role in green chemistry, especially in organic reactions due to their promising features such as the ability to control product distribution [6], offering enhanced rate [7] and/ or reactivity [8], ease of product recovery [9], catalyst immobilization [10], and recycling [11]. These compounds have also been effectively utilized for the synthesis of novel bioactive compounds [12]. In addition, ILs have very low vapor pressure and are non-explosive and thermally stable in a wide temperature range and can be easily separated from the organic components [13].

3,4-Dihydropyrimidin-2-(1*H*)-ones (DHPMs) and its derivatives have received significant attention in recent years due to their wide range of biological and therapeutic activities such as anti-tumor, anti-bacterial, anti-viral and anti-inflammatory activities [14-17]. Previously different derivatives of 3,4-dihydropyrimidin-2-(1*H*)-ones have exhibited calcium channel modulators, a1a-antagonists and neuropeptide Y (NPY) antagonist [18] The classical Biginelli synthesis is a one-pot condensation

** To whom correspondence should be addressed.*
+ E-mail: etavakoly@yahoo.com
1021-9986/2018/1/159-167 9/$/5.09
DOI:

of aldehydes (aromatic and aliphatic aldehydes), β-ketoester and urea under strongly acidic condition. However, this method involves long reaction times, unsatisfactory yields (20-40%) and harsh reaction conditions [19]. In recent years several methods for the synthesis of DHPMs have been developed to improve and modify this reaction by means of microwave irradiation [20], L-proline [21], $Ce(NO_3)_3$ [22], $Cu(NO_3)_2$ $3H_2O$ [23], Titanium (IV) oxide [24], $Bi(N0_3)_3$ [25], $H_3[PW_{12}O_{40}]$ [26], Fe_3O_4(at)Silica sulfuric acid [27], nanomagnetic-supported sulfonic acid [28], FeCl3-supported nanopore silica [29], metal oxide-MWCNTs [30] and nanosilica-supported tin(II) chloride [31].

However, the combination of solvents, toxic reagents, low yields and long reaction times makes some of these previously reported protocols environmentally hazardous. Because of the importance of these compounds, there has been considerable interest to explore, green, rapid, and higher yielding protocol. In continuation of our research on ionic liquids and their applications as catalyst in organic synthesis [32-34], we decided to investigate triethylammonium hydrogen sulfate ($[Et_3NH][HSO_4]$) as a green catalyst for the practical and environmentally benign one-pot three-component synthesis of 5-acetyl-6-methyl-4-aryl-3,4-dihydropyrimidin-2(1*H*)-ones (entries 2-11) under solvent-free conditions (Scheme 1).

EXPERIMENTAL SECTION

General

Starting materials, solvents, and reagents were either prepared in our laboratories or purchased from Merck, Fluka chemical companies, and used without purification. The products were characterized by their spectral data. IR spectra were recorded by using a BRUKER FT-IR spectrophotometer with KBr plates, ^1H and ^{13}C NMR spectra were recorded on a Bruker 400-MHz spectrometer in chloroform as a solvent and tetramethylsilan (TMS) as an internal standard. Melting points were recorded on an electrothermal apparatus and were uncorrected. $[Et_3NH][HSO_4]$ was prepared according to a literature method [35].

In all cases, the final products were precipitated out from the reaction mixture and purified by recrystallization.

The catalyst is reusable, due to its insolubility in organic solvents and it displayed high activity which afforded the corresponding products in excellent yield.

General procedure for the synthesis of triethylammonium hydrogen sulfate $[Et_3NH][HSO_4]$

In a 500 ml round-bottomed flask, sulfuric acid (98 g, 1.0 mol) 98% solution in water was dropped into the triethylamine (101 g, 1.0 mol) at 60 ^oC in 1 hour. After the addition, the reaction mixture was stirred for an additional period of 1 hour at 70 ^oC to ensure the reaction had proceeded to completion. Then the traces of water was removed by heating the residue at 80 ^oC in high vacuum (5 mm Hg) until the weight of the residue remained constant.

General procedure for the synthesis of 3,4-dihydropyrimidinones

General procedure: A mixture of aldehyde (1 mmol), acetylacetone (1 mmol), urea (1.2 mmol) and $[Et_3NH][HSO_4]$ (0.5 mmol) under solvent-free conditions was heated to 80 ^oC for the required time which was monitored by TLC. After completion of the reaction, water (5 mL) was added to the mixture and stirred for 5 min. The solid was filtered for separation of the crude product. The $[Et_3NH][HSO_4]$ was dissolved in water. The separated product was washed twice with water (2×5 mL) and purified by recrystallization in ethanol (96 %). All of the synthesis compounds were characterized by spectral data and comparison of their physical data with the literature. For recycling the catalyst, after washing solid products with water completely, the water containing IL (IL is soluble in water) was evaporated under reduced pressure and IL was recovered and reused.

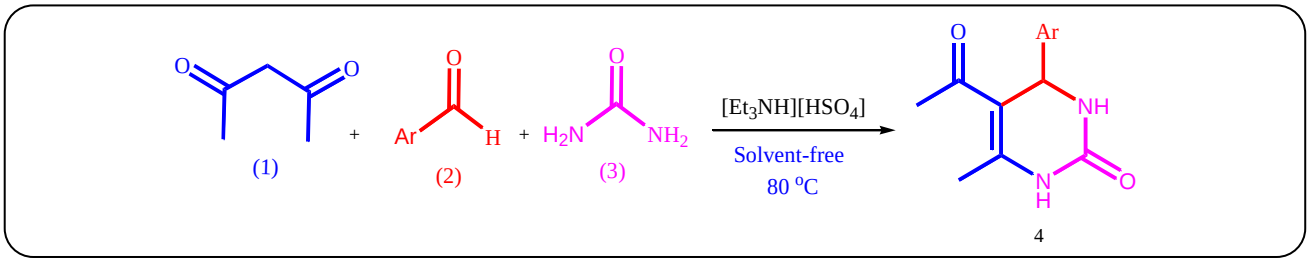
Some selected data are as follows

5-Acetyl-6-methyl-4-phenyl-3,4-dihydro-1H-pyrimidin-2-one (entry 1)

IR (KBr): ν= 3257 (NH), 2923 (CH aliph), 1701 (C=O), 1674 (C=O), 1598 (C=C arom), 1238cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ= 2.15 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 5.47 (d, 1H, CH, *J*=2.8 Hz), 5.67 (s, 1H, NH), 7.31-7.39 (m, 5H, CH arom), 7.54 (s, 1H, NH), ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 19.7, 30.4, 55.9, 110.5, 126.6, 128.3, 129.1, 142.7, 145.9, 153.1, 195.2.

5-Acetyl-4-(2-methoxy-phenyl)-6-methyl-3,4-dihydro-1H-pyrimidin-2-one (entry 2)

IR (KBr): ν= 3264 (NH), 3104 (CH arom), 2945 (CH aliph), 1701 (C=O), 1681 (C=O), 1598 (C=C), 1241 (C-O)cm^{-1}.



Scheme 1: Solvent-free three-component synthesis of 3,4-dihydropyrimidinones using triethylammonium hydrogen sulfate ([Et$_3$NH][HSO$_4$]).

^{1}H NMR(400 MHz, $CDCl_3$) δ= 2.02 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 5.57 (s, 1H, CH), 6.89 (t, 1H, *J*=7.6 Hz), 7.01-7.05 (m, 2H), 7.24-7.28 (m, 1H), 7.34 (s, 1H, NH), 9.12 (s, 1H, NH), ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 18.5, 29.6, 48.5, 55.3, 107.7, 111.1, 120.3, 126.7, 128.9, 130.8, 148.0, 152.0, 156.2, 194.5.

5-Acetyl-4-(4-hydroxy-phenyl)-6-methyl-3,4-dihydro-1H-pyrimidin-2-one (entry 3)

IR (KBr): ν= 3264 (NH), 3266 (OH), 3103 (NH), 2956 (CH arom), 2817 (CH aliph), 1697 (C=O), 1648 (C=O), 1566 (C=C), 1230 (C=O)cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ= 2.06 (s, 3H, CH3), 2.26 (s, 3H, CH3), 5.14 (s, 1H, CH), 6.70 (d, 2H, *J*=8 Hz), 7.04 (d, 2H, *J*=8Hz), 7.51 (s. 1H, NH), 9.10 (s, 1H, NH), ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 18.6, 30.0, 53.3, 109.5, 115.0, 127.6, 134.6, 147.4, 151.9, 156.4, 194.5.

5-Acetyl-4- (4-chloro-phenyl)-6-methyl -3,4-dihydro-1H-pyrimidin-2-one (entry 5):

IR (KBr): ν= 3287 (NH), 2930 (C-H), 1679 (C=O), 1598 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ= 2.13 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 5.26 (s, 1H, CH), 7.25 (d, 2H, *J*=8 Hz), 7.39 (d, 2H, *J*=8 Hz), 7.96 (s, 1H, NH), 9.23 (s, 1H, NH), ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 18.8, 30.3, 52.8, 109.4, 128.2, 128.4, 131.8, 143.0, 148.3, 151.9, 194.1.

5-Acetyl-4-(4-methoxy-phenyl)-6-methyl-3,4-dihydro-1H-pyrimidin-2-one (entry 6)

IR (KBr):ν= 3229 (NH), 3122 (CH arom), 2943 (CH aliph), 1700 (C=O), 1636 (C=O) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ= 2.07 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.72 (s, 3H,CH_3), 5.20 (s, 1H, CH), 6.88 (d, 2H, *J*=8 Hz), 7.16 (d, 2H, *J*=8 Hz), 7.74 (s, 1H, NH), 9.14 (s, 1H, NH), ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 18.7, 30.1, 53.1, 55.0, 109.5, 113.8, 127.6, 136.2, 147.6, 151.9, 158.4, 194.4.

RESULTS AND DISCUSSION

Herein, we describe the utility of [Et$_3$NH][HSO$_4$] as an efficient catalyst in solvent-free conditions for the Biginelli reaction (scheme 1)

To achieve optimum reaction conditions, we initially investigated the one-pot, three-component reaction of acetylacetone, benzaldehyde, and urea as the model reaction under various conditions. This reaction was tested in different protic and aprotic organic solvents, and in the presence of various amount of [Et$_3$NH][HSO$_4$].

The results are presented in Table 1.

These results showed that solvent-free condition at 80°C provided the product in 92% yield after 17 min. (Table 1, entry 12).

Without using the catalyst, the condensation reaction did not proceed until 4 h reflux (Table 1, entry 1).

In the following study on the model reactions, the reactions were examined at various temperatures in the presence of different amounts of [Et$_3$NH][HSO$_4$] in the various solvents (Table 1, entries 2-6) and under solvent-free conditions (Table 1, entries7-14). This observation revealed that the maximum yield of the product in the shortest reaction time was obtained at 80 °C under solvent-free condition.

In order to study the generality of the procedure, a series of DHPMs having different steric and electronic properties were synthesized using the optimized conditions. In all cases, the corresponding 3,4-dihydropyrimidin-2(1*H*)-one derivatives were obtained in good to excellent yields. The results are presented in Table 2.

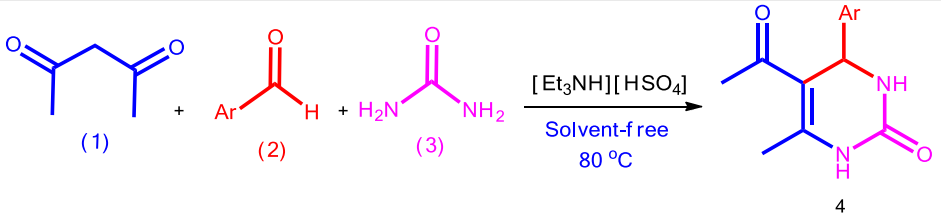
In order to show the merit of the present work, we compared the results of the synthesis of 5-acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (Entry 1 in Table 1) with some previously reported catalysts. The yield of the product in the presence of [Et$_3$NH][HSO$_4$] is comparable to reported catalysts. However, the reaction

Table 1: Optimization of temperature and amounts of [Et₃NH][HSO₄].

Entry	Catalyst Amount (mol%)	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	None	EtOH	reflux	4	0
2	$[Et_3NH][HSO_4]$ (30)	CH_3CN	reflux	2	35
3	$[Et_3NH][HSO_4]$ (40)	$CHCl_3$	reflux	4	30
4	$[Et_3NH][HSO_4]$ (50)	EtOH	r.t	2	40
5	$[Et_3NH][HSO_4]$ (50)	EtOH	reflux	1	60
6	$[Et_3NH][HSO_4]$ (50)	THF	reflux	5	35
7	$[Et_3NH][HSO_4]$ (50)	None	r.t	1	65
8	$[Et_3NH][HSO_4]$ (50)	None	30	55 min	70
9	$[Et_3NH][HSO_4]$ (30)	None	70	30 min	82
10	$[Et_3NH][HSO_4]$ (45)	None	80	23 min	85
11	$[Et_3NH][HSO_4]$ (40)	None	80	27 min	88
12	$[Et_3NH][HSO_4]$ (50)	None	80	17 min	92
13	$[Et_3NH][HSO_4]$ (60)	None	80	17 min	92
14	$[Et_3NH][HSO_4]$ (50)	None	100	17 min	92

a) Isolated yields.

Table 2: Synthesis of 3,4-dihydropyrimidin-2(1H)-ones.



4

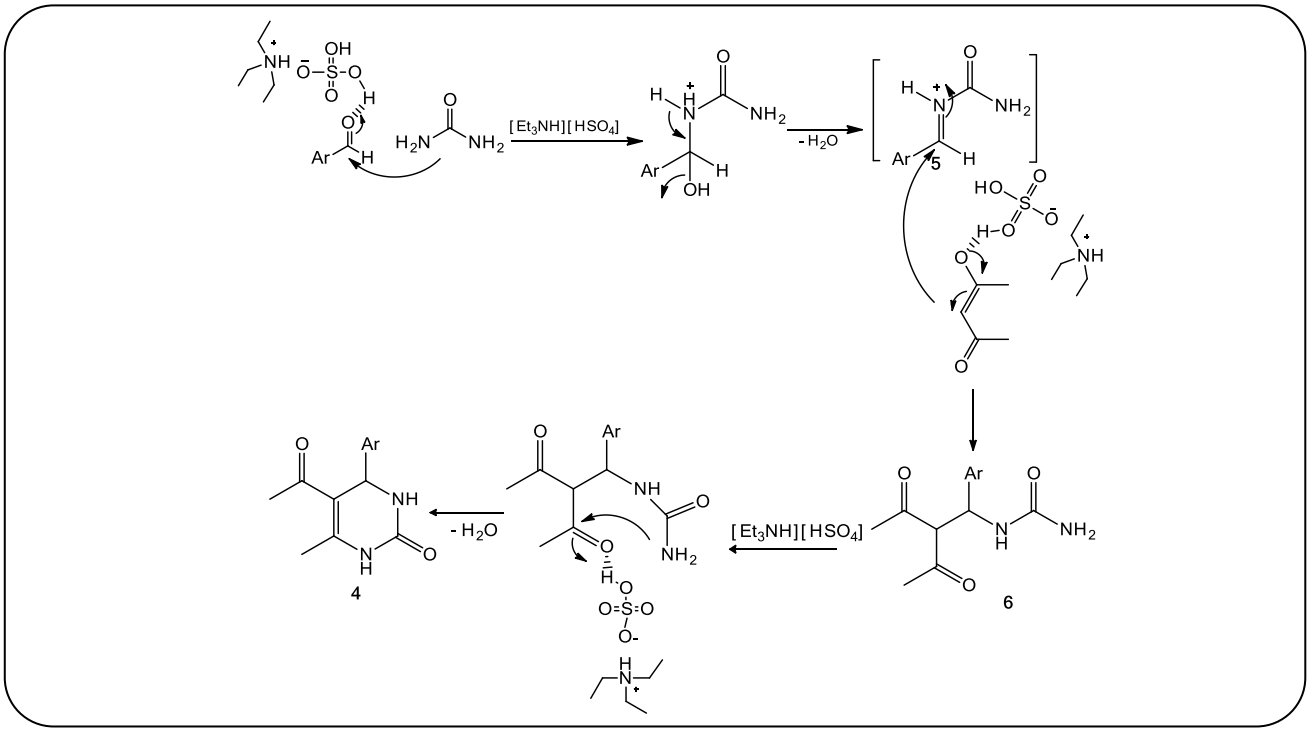
Entry	Aldehyde	Times (min)	Yield[a] (%)	M.p. (°C)	
				Found	Reported
1	PhCHO	۱۷	92	235-236	234-236 [36]
2	2-$OMeC_6H_4CHO$	20	89	250-251	250-251[38]
3	4-OHC_6H_4CHO	15	91	238-240	238-239[23]
4	4-MeC_6H_4CHO	18	89	228-229	228-230[39]
5	4-ClC_6H_4CHO	۱۵	92	210-211	210-211[40]
6	4-$MeOC_6H_4CHO$	16	90	181-182	180-182[41]
7	2,4-Cl,ClC_6H_3CHO	22	98	197-200	198-200[23]
8	4-$BrNC_6H_4CHO$	15	93	239-240	238-240 [42]
9	2-$O_2NC_6H_4CHO$	۲۱	95	228-230	229-230[25]
10	3-$O_2NC_6H_4CHO$	13	94	288-289	287-289[23]
11	4-$O_2NC_6H_4CHO$	15	93	232-235	233-235 [36]

a) Isolated yields.

Table 3: Comparison of the results of the synthesis of 5-acetyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one with different reported catalysts.

Entry	Catalyst (mol %)	Temperature	Time	Yield[a] % [ref]
	Ph_3P (10%)	100 °C	10h	62[43]
1	L-proline (10%)	r.t	2h	91[44]
2	P_2O_5 (10%)	reflux	1.2h	91[45]
3	H_2SO_4, silica gel (30 %)	60 °C	2h	89[46]
4	$MgBr_2$ (10%)	100 °C	1h	88[47]
5	B_2O_3/Al_2O_3 (15%)	75 °C	6h	87[48]
6	$[(CH_2)_2COOHHmim][HSO_4]$ (1.5%)	75 °C	1h	85[49]
7	$H_4SiW_{12}O_{40}*xH_2O$ (2 %)	reflux	6h	84[50]
8	$ClCH_2COOH$ (10 %)	90 °C	3h	88[51]
9	$[Et_3NH][HSO_4]$ (50%)	80 °C	17 min	92(This work)

a) Isolated yields.



Scheme 2: The proposed mechanism for the synthesis of dihydropyrimidinones using [Et₃NH][HSO₄].

in the presence of these catalysts required longer reaction times than this work (Table 3).

The proposed mechanism for the synthesis of 3,4-Dihydropyrimidin-2(1*H*)-one Derivatives using $[Et_3NH][HSO_4]$ is shown in scheme 2. Firstly, we assumed that the reaction of the aldehydes and urea generates an acylimine intermediate (5). Interception of this iminium ion intermediate by activated 1,3-dicarbonyl compound produces an open-chain ureide (6) which subsequently undergoes cyclization and dehydration to afford the corresponding dihydropyrimidinone (4).

Finally, we investigated the possibility of recycling of $[Et_3NH][HSO_4]$ using the model reaction forming 5-acetyl-6-methyl-4-phenyl-3,4-dihydro-1H-pyrimidin-2-*one*. After reaction completion, water (5 mL) was added to the mixture, stirred for 5 min and the solid was filtered.

Table 4: Recycling yields[a].

No of Cycles[a]	Fresh	Run 1	Run 2	Run 3
Yield[b]	92	89	87	86
Time (min)	17	16	15	15

a) Reaction condition: benzaldehyde (1 mmol), acetylacetone (1 mmol), urea (1.2 mmol) and $[Et_3NH][HSO_4]$ (0.5 mmol).
b) Yields refer to pure isolated yields.

After washing solid product with water (2×3 mL) completely, the aqueous layer containing the catalyst ($[Et_3NH][HSO_4]$ is soluble in water) was evaporated under reduced pressure and catalyst was recovered and reused for subsequent reactions. The recovered catalysts were reused three runs with only moderate (about 10%) loss in their activity (Table 4).

CONCLUSIONS

In summary, a simple, efficient and practical approach for the synthesis of dihydropyrimidinone derivatives by the three-component Biginelli condensation reaction of aldehydes with acetylacetone and urea in the presence of $[Et_3NH][HSO_4]$ as an eco-friendly catalyst under solvent-free conditions was reported. The catalyst is recyclable (up to three times) without significant loss of activity. The main advantages of this methodology are: shorter reaction times; higher yields; free of organic solvent, and easy synthetic procedure.

Acknowledgments

The authors express appreciation to Shahid Bahonar University of Kerman, Faculty Research Fund for its support of this investigation.

Received: Mar. 26, 2016; Accepted: Jun. 19, 2017

REFERENCES

[1] Clark J.H., Solid Acids for Green Chemistry, *Accounts of Chemical Research*, **35**(9):791-797 (2002).

[2] Saeedi M., Jeiroudi M., Ma'mani L., Mahdavi M, Alipour S., Shafiee A., Foroumadi A.R., Brønsted Acidic Phosphonium Based Ionic Liquid Functionalized SBA-15 [HO_3S-PhospIL@SBA-15]: Green, Recyclable, and Efficient Catalyst for the Synthesis of Pyrano[3,2-c]Chromenone Derivatives, *Iran. J. Chem. Chem. Eng. (IJCCE)*, **34**(4):39-45 (2015).

[3] Martins M.A.P., Teixeira M.V.M., Cunico W., Scapin E., Mayer R., Pereira C. M.P., Zanatta N., Bonacorso H.G., Peppe C., Yuan Y.F., Indium(III) Bromide Catalyzed One-Pot Synthesis of Trichloromethylated Tetrahydropyrimidinones, *Tetrahedron Letters*, **45**(49):8991-8994 (2004).

[4] Hajipour A., Mohammadsaleh F., A Simple and Effective Protocol for One-Pot Diazotization-Iodination of Aromatic Amines by Acidic Ionic Liquid [H-NMP]HSO_4 at Room Temperature, *Iran. J. Chem. Chem. Eng. (IJCCE)*, **30**(4):23-28 (2011).

[5] Shaabani, A., Farhangi, E., Shaabani, S., A Rapid Combinatorial Library Synthesis of Benzazolo[2,1-b]quinazolinones and Triazolo[2,1-b]quinazolinones, *Iran. J. Chem. Chem. Eng. (IJCCE)*, **32**(1):3-6 (2013).

[6] Earle M.J., Katdare S.P., Seddon K.R., Paradigm Confirmed: the First Use of Ionic Liquids to Dramatically Influence the Outcome of Chemical Reactions, *Org. Lett.*, **6**(5):707-710 (2004).

[7] Earle M.J., McCormac P.B., Seddon K.R. Diels–Alder Reactions in Ionic Liquids. A Safe Recyclable Alternative to Lithium Perchlorate–Diethyl Ether Mixtures, *Green. Chem.*, **1**(1):23-25 (1999)

[8] Chauvin Y., Mussmann L., Olivier H., A Novel Class of Versatile Solvents for Two-phase Catalysis: Hydrogenation, Isomerization, and Hydroformylation of Alkenes Catalyzed by Rhodium Complexes in Liquid 1, 3-Dialkylimidazolium Salts, *Angew. Chem., Int. Ed. Engl.*, **34**(23-24):2698- 2700 (1995).

[9] Klingshirn M.A., Rogers, R.S., Shaughnessy, K.H., Palladium-Catalyzed Hydroesterification of Styrene Derivatives in the Presence of Ionic Liquids, *J. Organomet. Chem.*, **690**(15):3620- 3626 (2005).

[10] Yadav J.S., Reddy B.V.S., Baishya G., Reddy K.V., Narsaiah A.V., Conjugate Addition of Indoles to α, β-Unsaturated Ketones Using Cu $(OTf)_2$ Immobilized in Ionic Liquids, *Tetrahedron*, **61**(40):9541-9544 (2005).

[11] Picquet M., Stutzmann S., Tkatchenko I., Tommasi I., Zimmermann J., Wasserscheid P., Selective Palladium-Catalysed Dimerisation of Methyl Acrylate in Ionic Liquids: Towards a Continuous Process, *Green. Chem.*, **5**(2):153-162 (2003).

[12] Wilkes J.S., A Short History of Ionic Liquids from Molten Salts to Neoteric Solvents, *Green. Chem.*, **4**(2):73-80(2002).

[13] Sheldon R., Green Solvents for Sustainable Organic Synthesis: State of the Art, *Green Chem.*, **7**(5):267-278 (2005).

[14] 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**(12):3864-3868 (2000).

[15] Hu E.H., Sidler D.R., Dolling U.H., Unprecedented Catalytic Three Component One-Pot Condensation Reaction: an Efficient Synthesis of 5-Alkoxycarbonyl-4-aryl-3, 4-dihydropyrimidin-2 (1H)-ones, *J. Org. Chem.*, **63**(10):3454-3457 (1998).

[16] Snider B.B., Shi Z., Biomimetic Synthesis of (+)-Crambines A, B, C1, and C2. Revision of the Structure of Crambines B and C1, *J. Org. Chem.*, **58**(15):3828-3839 (1993).

[17] Fabian WMF, Semones, M A., Conformational Analysis of 4-aryl-dihydropyrimidine Calcium Channel Modulators, A comparison of ab Initio, Semiempirical and X-Ray Crystallographic Studies, *Tetrahedron*, **53**(8):2803-2816(1997).

[18] Atwal K.S., Swanson B.N., Unger S.E., Floyd D.M., Mereland S., Hedberg A., O'Reilly B.C., Dihydropyrimidine Calcium Channel Blockers. 3. 3-Carbamoyl-4-aryl-1, 2, 3, 4-tetrahydro-6-methyl-5-Pyrimidinecarboxylic Acid Esters as Orally Effective Antihypertensive Agents, *J. Med. Chem.*, **34**(2): 806-811 (1991).

[19] Bigi F., Carloni S., Frullanti B., Maggi R., Sartori G., A Revision of the Biginelli Reaction under Solid Acid Catalysis. Solvent-Free Synthesis of Dihydropyrimidines over Montmorillonite KSF, *Tetrahedron Lett.*, **40**(17):3465-3468(1999).

[20] Kapoor K.K., Ganai B.A., Kumar S., Andotra C.S., Antimony(III) Chloride Impregnated on Alumina An Efficient and Economical Lewis Acid Catalyst for One-Pot Synthesis of Dihydropyrimidinones under Solvent-Free Conditions, *Can. J. Chem.*, **84**(3):433-437 (2006).

[21] Yadav J.S., Praveen Kumar S., Kondaji G., Srinivasa Rao R., Nagaiah K., A Novel L-Proline Catalyzed Biginelli Reaction: One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones under Solvent-Free Conditions, *Chem. Lett.*, **33**(9):1168-1169 (2004).

[22] Adib M., Ghanbary K., Mostofi M., Ganjali, M.R., Efficient Ce $(NO_3)_3 \cdot 6H_2O$-Catalyzed Solvent-Free Synthesis of 3, 4-dihydropyrimidin-2(1H)-ones, *Molecules*, **11**(8):649-654 (2006).

[23] Wang D.C., Guo H.M., Qu, G.R., Efficient, Green, Solvent-Free Synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones via Biginelli Reaction Catalyzed by $Cu(NO_3)_2 \cdot 3H_2O$, *Synth. Commun.*, **40**(8): 1115-1122 (2010).

[24] Kassaee, M.Z., Masrouri, H., Movahedi F., Mohammadi R., TiO_2 as a Reusable Catalyst for the One-Pot Synthesis of 3, 4-Dihydropyrimidin-2 (1H)-ones under Solvent-Free Conditions, *Helv. Chim. Acta.*, **93**(2):261-264(2010).

[25] 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 $Bi(NO_3)_3 \cdot 5H_2O$, *Synth. Commun.*, **34**(9):1551-1557 (2004).

[26] Rafiee E., Jafari H., A Practical and Green Approach Towards Synthesis of Dihydropyrimidinones: Using Heteropoly Acids as Efficient Catalysts, *Bioorg. Med. Chem. Lett.*, **16**(9):2463-2466 (2006).

[27] Kiasat, A.R., Davarpanah, J., Fe_3O_4@ Silica Sulfuric Acid Core–Shell Composite as a Novel Nanomagnetic Solid Acid: Synthesis, Characterization and Application as an Efficient and Reusable Catalyst for One-Pot Synthesis of 3, 4-dihydropyrimidinones/ Thiones under Solvent-Free Conditions, *Res. Chem. Intermed.*, **41**(5):2991-3001 (2015).

[28] Kolvari, E.; Koukabi, N.; Armandpour, O. A Simple and Efficient Synthesis of 3,4-dihydropyrimidin-2-(1H)-Ones via Biginelli Reaction Catalyzed by Nanomagnetic-Supported Sulfonic Acid, *Tetrahedron*, **70** (6): 1383-1386 (2014).

[29] Ahn B.J., Gang M.S., Chae K., Oh Y., Shin, J., Chang W., A Microwave-Assisted Synthesis of 3,4-Dihydro-pyrimidin-2-(1H)-ones Catalyzed by $FeCl_3$-Supported Nanopore Silica under Solvent-Free Conditions, *J. Ind. Eng. Chem.*, **14** (3): 401-405 (2008).

[30] Safari J., Gandomi-Ravandi S., A Novel Protocol for Solvent-Free Synthesis of 4,6-Diaryl-3,4-Dihydropyrimidine-2(1H)-ones Catalyzed by Metal Oxide—MWCNTs Nanocomposites, *J. Mol. Struct.*, **1047**: 71-78(2014).

[31] Ghomi J.S., Teymuri R., Ziarati A., A Green Synthesis of 3,4-dihydropyrimidine-2(1H)-One/Thione Derivatives Using Nanosilica-Supported Tin(II) Chloride as a Heterogeneous Nanocatalyst, *Monatsh. Chem.*, **144** (12): 1865-1870 (2013).

[32] Pouramiri B., Tavakolinejad Kermani E., Solvent-Free, Four-Component Synthesis of 3, 4, 7, 8-tetrahydro-3, 3-dimethyl-11-aryl-2H-pyridazino [1, 2-a] Indazole-1, 6, 9 (11H)-triones; Using 1-butyl-3-Methylimidazolium Hydroxide ([bmim] OH) as a Green and Reusable Catalyst, *J. Iran. Chem. Soc.*, **13** (6): 1011-1017(2016).

[33] Khabazzadeh H., Tavakolinejad Kermani E., Jazinizadeh T., An Efficient Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones Catalyzed by Molten [Et_3NH][HSO_4], *Arab. J. Chem.*, **5**(4):485-488 (2012).

[34] Pouramiri B., Tavakolinejad Kermani E., One-Pot, Four-Component Synthesis of New 3,4,7,8-Tetrahydro-3,3-dimethyl-11-aryl-2H-pyridazino [1,2-a]indazole-1,6,9(11H)-triones and 2H-indazolo[2,1-b]phthalazine-1,6,11(13H)-triones Using an Acidic Ionic Liquid N,N- diethyl-N-sulfoethanammonium Chloride ([Et_3N–SO_3H]Cl) as a Highly Efficient and Recyclable Catalyst, *Tetrahedron. Lett.*, **57**(8): 1006-1010 (2016).

[35] Wang C., Guo L., Li H., Wang Y., Weng J., Wu L., Preparation of Simple Ammonium Ionic Liquids and Their Application in the Cracking of Dialkoxypropanes, *Green Chem.*, **8**(7):603-607(2006).

[36] Romanelli P.G., Sathicq, G.A., Solvent-Free Approach to 3, 4-Dihydropyrimidin-2 (1 H)-(thio) ones: Biginelli Reaction Catalyzed by a Wells–Dawson Reusable Heteropolyacid, *Synth. Commun.*, **37**(22): 3907-3916(2007).

[37] Kumar D., Mishra B.G., Rao V.S., An Environmentally Benign Protocol for the Synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones Using Solid Acid Catalysts under Solvent-Free Conditions, *Indian J. Chem.*, **45** B:2325-2329(2006).

[38] Ramalingan C., Kwak Y-W., Tetrachlorosilane Catalyzed Multicomponent One-Step Fusion of Biopertinent Pyrimidine Heterocycles, *Tetrahedron*, **64**(22): 5023-5031(2008).

[39] Nazari S., Saadat Sh, Kazemian Fard P., Gorjizadeh M., Rezaee Nezhad E., Afshari M., Imidazole Functionalized Magnetic Fe_3O_4 Nanoparticles as a Novel Heterogeneous and Efficient Catalyst for Synthesis of Dihydropyrimidinones by Biginelli Reaction, *Monatsh. Chem.*, **144**(12):1877-1882 (2013).

[40] Mirjalili F.B., Bamoniri A., Akbari A., One-Pot Synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones (thiones) Promoted by Nano-BF_3. SiO_2, *J. Iran. Chem. Soc.*, **8**(1):135-140 (2011).

[41] Rezaei R., Mohammadi M. K,, Khaledi A., Microwave Assisted Solvent-Free One Pot Biginelli Synthesis of Dihydropyrimidinone Compounds on Melamine-Formaldehyde as a Solid Support, *Asian. J. Chem.*, **25**(2): 4588- 4590 (2013).

[42] Shirini F., Abedini M., Pourhasan-Kisomi R., N-Sulfonic Acid Poly (4-vinylpyridinium) Chloride as a Highly Efficient and Reusable Catalyst for the Biginelli Reaction, *Chin. Chem. Lett.*, **25**(1): 111-114, (2014)

[43] 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**(42):6119-6121(2008).

[44] Yadav J.S., Kumar S.P., Kondaji G., Rao R.S., Nagaiah K., A Novel L-Proline Catalyzed Biginelli Reaction: One-Pot Synthesis of 3, 4-Dihydropyrimidin-2 (1H)-ones under Solvent-Free Conditions, *Chem. Lett.*, **33**(9):1168-1169 (2004).

[45] Deshmukh M.B., Anbhule P.V., Jadhav S.D., Mali A.R., Jagtap S.S., Deshmukh S.A., An Efficient, Simple, One Pot Synthesis of Dihydropyrimidine-2 (1H) Ones Using Phosphorus Pentoxide, *Indi. J. Chem. Sec. B*, **46**(9):1545-1548 (2007).

[46] Salehi P., Dabiri M., Zolfigol M.A., Bodaghi Fard M.A., Efficient Synthesis of 3, 4-dihydropyrimidin-2 (1H)-Ones Over Silica Sulfuric Acid as a Reusable Catalyst under Solvent-Free Conditions, *Heterocycles*, **60**(11):2435-2440 (2003).

[47] 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**(1):171-179 (2004).

[48] Zhou X., Cheng T., Zheng X., Ke Q., Wang X., Boron Trioxide–Alumina as a Heterogeneous Catalyst in a Facile Solvent Free One-Pot Synthesis of 3, 4-Dihydropyrimidin-2 (1H)-ones, *J. Chem. Res.*, **36**(4):213-215 (2012)

[49] Gui J., Liu D., Wang C., Lu F., Lian J., Jiang H., Sun Z., One-Pot Synthesis of 3, 4-dihydropyrimidin-2 (1H)-ones Catalyzed by Acidic Ionic Liquids under Solvent-Free Conditions, *Synth. Commun.*, **39**(19):3436-3443(2009).

[50] Niknam K., Daneshvar N., $H_4SiW_{12}O_{40}\cdot xH_2O$ as a New Catalyst for the Synthesis of 3,4-Dihydropyrimidin-2(1H)-one, Heterocycles, **71**(2): 373-378(2007).

[51] Yu Y., Liu D., Liu C., Luo G., One-Pot Synthesis of 3,4-dihydropyrimidin-2(1H)-ones Using Chloroacetic Acid as Catalyst, *Bioorg. Med. Chem. Lett.*, **17**(12):3508-3510 (2007).