Iranian Journal of Catalysis 8(4), 2018, 249-255

IRANIAN JOURNAL OF CATALYSIS

Facile synthesis of dihydropyrimidinone derivatives *via* Biginelli reaction using Brønsted acidic ionic liquid $[H\text{-}NMP]^+[CH_3SO_3]^-$ as an efficient homogeneous catalyst

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Received 7 December 2017; received in revised form 14 March 2018; accepted 13 April 2018

ABSTRACT

In this research, a green, operationally simple, highly efficient and facile cascade Biginelli reaction using various aromatic aldehydes, ethyl acetoacetate, and urea/thiourea has been developed. First, the ionic liquid was prepared from the reaction of 1-methyl-2-pyrolidone with methane sulfonic acid. Then, this ionic liquid was applied as an acidic catalyst in the synthesis of dihydropyrimidinones as a target product under mild conditions. The ionic liquid and resulting products were characterized by physical and spectral data such as melting point, IR, ^{1}HNMR and ^{13}CNMR. The significant advantages of this protocol are short reaction time, excellent yields and easily available starting materials.

***Keywords**: Aldehyde, Thiourea, Dihydropyrimidinone, Ionic liquid, Catalyst.*

1. Introduction

Dihydropyrimidinone (DHPM) derivatives are widely used as integral backbones of some biologically active compounds such as calcium channel modulating [1,2], anti-cancer agents [3] or anti-hypertensive agents [4,5] antibacterial [6] and antiviral properties [7]. The dihydropyrimidinone derivatives can be obtained through the Biginelli reaction, a three-component condensation of a *β*-ketoester, aldehyde, and urea derivative on acid catalyst under thermal conditions [8-13].

Recent research has demonstrated that (R)-mon-97 has much more potent antitumor activity than monastrol [14] and (R)-SQ 32926 is an antihypertensive agent with potent oral activity (Fig. 1) [15]. The great potential of DHPMs in biological and pharmaceutical fields has accordingly triggered growing interest in their synthetic study [16-20].

Nowadays, ionic liquids have appeared as a group of green solvents with incomparable properties such as high thermal stability, partial vapor pressure, immiscibility with a type of organic solvents and recyclability [21].

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Ionic liquids have been extensively applied as a mild and effective catalyst for various reactions [22,23].

Recently, organic reactions in solvent free conditions have vastly been preferred in view of the green methodology. Furthermore, in recent years, there has been an increasing interest in reactions that proceed in the absence of solvents due to their reduced pollution, low costs and simplicity in the process and handling [24-26]. The development of multi-component reactions (MCRs) in the presence of task-specific ionic liquid (IL), used not only as eco-compatible reaction media but also as catalysts, is an approach that meets the requirements of sustainable chemistry [27].

2. Experimental

2.1. Materials

All commercially available reagents were used without further purification and purchased from the Merck Chemical Company in high purity. The solvents were purified by the standard procedure.

2.2. Apparatus

IR spectra were obtained as KBr pellets on a Perkin-Elmer 781 spectrophotometer and on an impact 400 Nicolet FT-IR spectrophotometer.

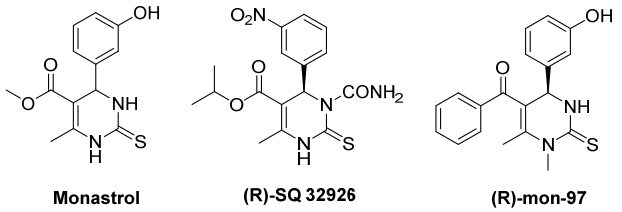


Fig. 1. Pharmacologically active DHPMs.

^{1}HNMR and ^{13}CNMR were recorded in $CDCl_3$ and DMSO-$d_6$solvents on a Bruker DRX-400 spectrometer with tetramethylsilane as an internal reference. Melting points were determined on a Yanagimoto micro melting point apparatus. The purity determination of the substrates and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates (from Merck Company).

2.3. Preparation of [H-NMP]$^+$[CH_3SO_3]$^-$

1-Methyl-2-pyrolidone (0.2 mol) was poured into a 250 mL three-necked flask with a magnetic stirrer. Then, equimolar concentrated methane sulfonic acid (98 wt %) was added dropwise slowly into the flask over approximately 30 min in an ice bath. Stirring of the mixture was continued for another 4 h at room temperature. The mixture was washed with diethyl ether three times to remove non-ionic residues and dried in the vacuum to obtain the [H-NMP]$^+$[CH_3SO_3]$^-$ [25]. The ionic liquid was prepared in quantitative yield and characterized by ^{1}H NMR data before using in the reaction and after the recovery, as follows.

^{1}HNMR (D_2O): δ= 3.16–3.13 (t, 2H, *J*= 6.8 Hz), 2.46 (s, 3H), 2.38 (3H), 2.13–2.09 (t, 2H, *J*= 7.2 Hz), 1.68–1.64 ppm (q, 2H, *J*= 7.2 Hz).

2.4. General procedure for the preparation of 3,4-dihydropyrimidin-2-ones/thiones

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea or thiourea (1.5 mmol) and [H-NMP]$^+$[CH_3SO_3]$^-$(20 mol%) was stirred under solvent-free conditions. The reaction mixture was monitored by TLC and after completion of the reaction, it was washed with cool water. Then, the mixture was extracted with (2×10 ml CH_2Cl_2) and [H-NMP]$^+$[CH_3SO_3]$^-$was removed by washing with water as a by-product. The whole mixture was slightly concentrated and ice was added to the mixture. The product was purified by recrystallization from ethanol as an appropriate solvent and confirmed by physical and spectral data compared with those of authentic samples.

3. Results and Discussion

In continuation of our work on the multi-component synthesis of heterocyclic compounds[22,23], we have designed a unique synthetic route to privileged heterocyclic medicinal scaffolds that combine the synthetic efficiency of multi-component protocols with the environmental benefit of using an ionic liquid as a reaction medium.

In the last decade, ionic liquids (ILs) have become powerful alternatives to conventional molecular organic solvents due to their catalysis [28], biocatalysis [29], liquid-liquid separations [30] and extraction [31]. Herein we report the reaction of ethyl acetoacetate, urea/thiourea and aromatic aldehydes catalyzed by [H-NMP]$^+$[CH_3SO_3]$^-$ ionic liquid.

We have carried out a series of experiments to standardize the reaction conditions for the efficient formation of bioactive heterocycles via a one-pot, three-component reaction.

First, the [H-NMP]$^+$[CH_3SO_3]$^-$ as the Brønsted acidic ionic liquid was investigated in the synthesis of dihydropyrimidinones. Then, the reaction parameters such as temperature and the catalyst amount were optimized in the reaction of 4-nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and urea/thiourea (1.5 mmol) in the presence of [H-NMP]$^+$[CH_3SO_3]$^-$ as a model reaction. The condensation of 4-nitrobenzaldehyde, ethyl acetoacetate and urea in the presence of a catalytic amount of [H-NMP]$^+$[CH_3SO_3]$^-$ under solvent-free conditions at 70 to 100 °C was examined. The results are summarized in Table 1. It was concluded that solvent-free condition at 90 °C in the presence of ionic liquid as the catalyst is the optimized condition for this three-component reaction. An increase in the reaction temperature did not improve the yields significantly.

Table 1. Synthesis of dihydropyrimidinone under different temperatures.

Entry	Temp. (°C)	Time (min)	Yield (%)[b]
1	70	25	66
2	80	20	80
3	90	30	96
4	100	30	96

[a]Reaction conditions: 4-Nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.5 mmol).
[b]Isolated yield.

After determination of the convenient temperature, in order to optimize the reaction conditions, the reaction of 4-nitrobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea (1.5 mmol) as a sample reaction was investigated in the presence of various amounts of $[H\text{-}NMP]^+[CH_3SO_3]$- as a homogeneous catalyst under solvent-free conditions at 90 ℃ (Table 2).

In this reaction, the best results were obtained using 20 mol% of catalyst (as can be seen from Table 2, entry 7), while a higher amount of the catalyst did not affect reaction times and yields (Table 2, entry 8).

The effect of different solvents in the condensation of benzaldehyde, ethyl acetoacetate and urea in the presence of $[H\text{-}NMP]^+[CH_3SO_3]^-$ as a model has been studied. As shown in Table 3, among the tested solvents such as ethanol, methanol, CH_3CN, CH_2Cl_2, and a solvent-free system, the best result was obtained after 6 min under solvent-free conditions in excellent yield (92%).

After optimization of the reaction conditions, a highly efficient one-pot three-component synthesis of dihydropyrimidinone derivatives has also been developed applying the same methodology (Table 4). To ascertain limitation of the reaction, the reaction of ethyl acetoacetate with various aromatic aldehydes was carried out according to the general optimized experimental procedure. The corresponding products are summarized in this Table. The yields of most products are higher than 90%. Thus, the aldehydes bearing electron withdrawing group gave the corresponding products and also electron-donating substituents with ethyl acetoacetate and urea/thiourea under the optimized conditions (Table 4). As shown in this Table, in the presence of ionic liquid as a catalyst, excellent product yields were achieved in shorter reaction time under solvent-free conditions.

Table 2. The reaction in the presence of various catalyst amounts.

Entry	Time (min)	Catalyst loading (mol %)	Yield (%)
1	100	0	0
2	30	10	60
3	30	15	80
4	30	20	96
5	20	20	96
6	10	20	96
7	5	20	96
8	20	25	96

Table 3. The reaction in the presence of various solvents.

Entry	Solvent	Time (min)	Yield (%)
1	EtOH	55	45
2	MeOH	65	35
3	CH_2Cl_2	70	50
4	CH_3CN	75	55
5	None	6	92

It is valuable mentioning that, although a small amount of catalyst was utilized, it could be simply recovered by filtration and reused. To reuse the catalyst, after the separation of **4c** as solid product by filtration, the water containing Brønsted acidic ionic liquids was evaporated under vacuum and the recovered catalyst was recycled for several times without any decrease in catalytic activity, the reaction yields were ranged from 97% to 88 %.

Several various proposed reaction mechanisms [30-32] for the Biginelli reaction were reported. Among these pathways, the Knoevenagel-based mechanism is proposed as a possible reaction route for this reaction as shown in Scheme 1.

The efficiency of $[H\text{-}NMP]^+[CH_3SO_3]^-$ as the homogeneous catalyst in comparison with previously reported catalysts was shown in Table 5. The ionic liquid was found to be the most efficient catalyst among all of the tested catalysts in terms of reaction time, yield, temperature and solvent.

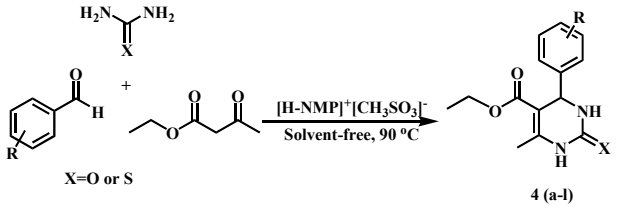
4. Conclusions

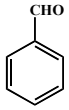
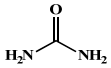
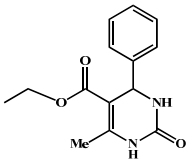
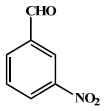
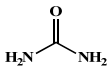
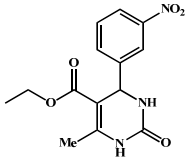
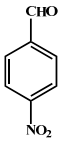
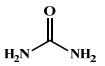
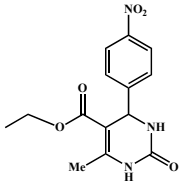
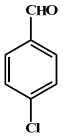
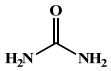
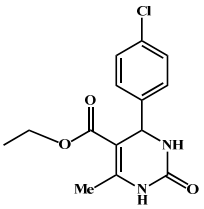
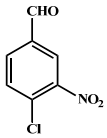
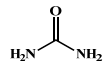
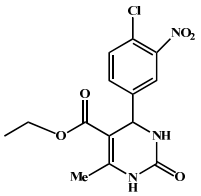
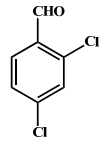
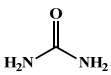
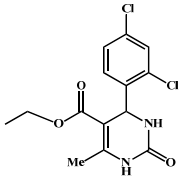
As illustrated in the study reported in this manuscript, the synergistic use of MCRs and IL allows the development of new methodologies for the efficient synthesis of dihydropyrimidinones. These processes offer several advantages such as high yields, shorter reaction times, environmentally benign and milder reaction condition, and safe operations. Furthermore, combining MCRs with ILs opens an interesting eco-compatible alternative to more conventional approaches in the field of heterocyclic chemistry and should have an important impact on modern organic synthesis.

Acknowledgements

The authors are grateful to University of Kashan for supporting this work by Grant No. 159148/35.

Table 4. Synthesis of dihydropyrimidinones in the presence of $[H\text{-}NMP]^+[CH_3SO_3]^-$ under solvent-free conditions at 90 °C.



Entry	Aldehydes	Urea/Thiourea	Product	Time (min)	Yields (%)[a]
1				6	92
2				7	95
3				4	97
4				8	95
5				4	96
6				5	93

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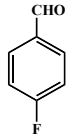
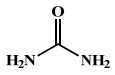
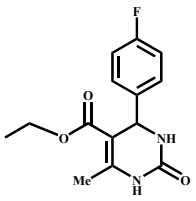
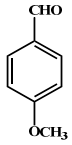
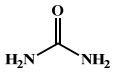
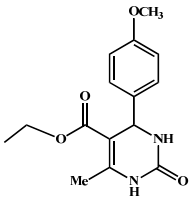
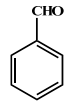
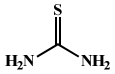
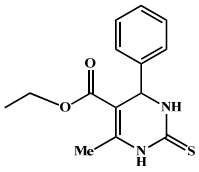
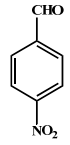
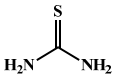
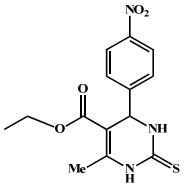
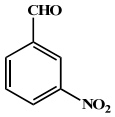
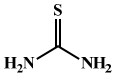
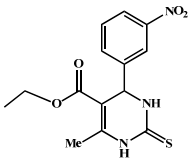
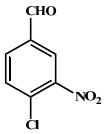
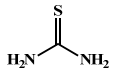
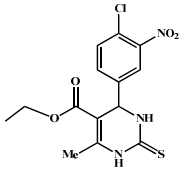
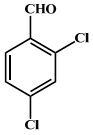
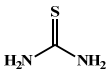
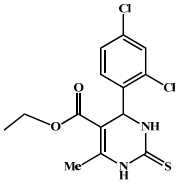
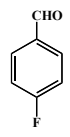
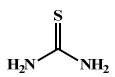
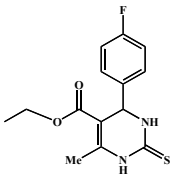
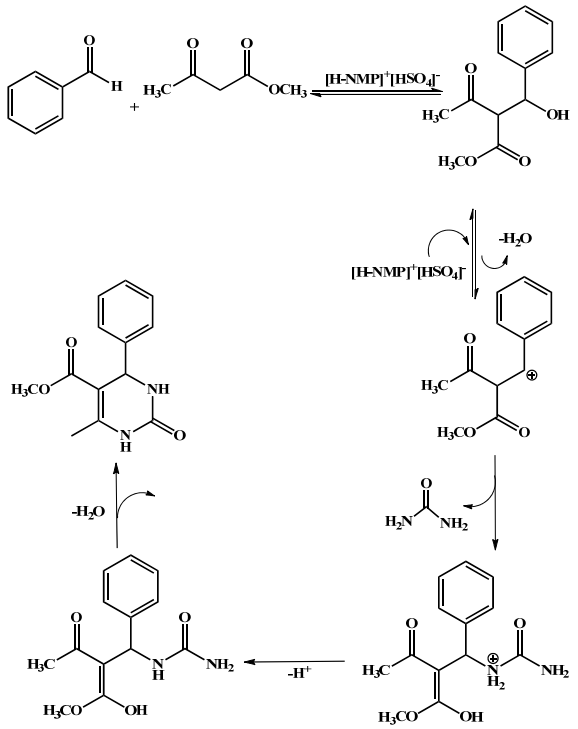
7				5	94
8				12	92
9				9	90
10				8	94
11				11	93
12				**7**	95
13				10	93
14				8	90

[a]Isolated yields.



Scheme 1. The proposed Knoevenagel reaction mechanisms for synthesis of dihydropyrimidinones.

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Table 5. The synthesis of 4c using different catalysts.

Entry	Catalyst	Time (min)	Yield (%)	Ref.
1	Cu@PMO-IL, 60 °C, solvent-free	120	80	[32]
2	TSILs, 100 °C, solvent-free	10	88	[33]
3	[Cbmim] Cl, Reflux, MeCN	90	69	[34]
4	ZnO, 80 °C, BMI·BF4	12 h	67	[35]
5	MWCNTs-OSO_3H, 120 °C, solvent-free	20	94	[11]
6	Al-MCM-41, 80 °C, solvent-free	15	84	[12]
7	$H_6GeW_{10}V_2O_{40}.22H_2O$, 80 °C, solvent-free	3 h	91	[13]
8	$[H\text{-}NMP]^+[CH_3SO_3]^-$, 90 °C, solvent-free	4	97	This work

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