

Facile and Rapid Synthesis of 3,4-Dihydropyrimidin-2-(1H)-ones and Thione Derivatives Through the Biginelli Protocol Using *N*-Methylimidazolium Acetate

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ABSTRACT: Some protic ionic liquids (PILs) were synthesized by the direct neutralization reaction of *N*-methylimidazole and 4-*N,N*-dimethylaminopyridine as nitrogen-containing heterocyclic organic bases with acetic acid and trifluoroacetic acid. The relative acidity of the prepared ionic liquids was evaluated by Hammett acidity function using UV-Vis spectroscopy. The catalytic effects of the obtained ionic liquids were investigated in the synthesis of 3,4-dihydropyrimidin-2-(1H)-ones and thione derivatives through Biginelli reaction. Among *N*-methylimidazolium acetate [MImH][OAc], *N*-methylimidazolium trifluoroacetate [MImH][CF₃CO₂], 4-*N,N*-dimethylaminopyridinium acetate [DMAPH][OAc] and 4-*N,N*-dimethylaminopyridinium trifluoroacetate [DMAPH][CF₃CO₂], [MImH][OAc] provided the best results. Using 5 mol% of [MImH][OAc] as a catalyst, 3,4-dihydropyrimidin-2-(1H)-ones and thione derivatives were obtained in high to excellent yields at 100 °C during 15-50 min.

KEYWORDS: Biginelli reaction; 3,4-Dihydropyrimidin-2-(1H)-one; *N*-Methylimidazolium acetate; Protic ionic liquid.

INTRODUCTION

Multicomponent reactions (MCRs) often termed as ‘cascade’ and ‘domino’ reactions, are one-pot processes which allow the formation of target molecules by treatment of three or more reactants in a single vessel [1]. Besides they serve as versatile tools for the construction of structurally complex molecules in a single step, MCRs often offer the advantage of simplicity, atom economy, and synthetic convergence over conventional chemical reactions, and they may be well classified as sustainable and eco-compatible processes [2-5].

Since the first report on Biginelli reaction in 1893,

this is still nearly the most important multicomponent reaction. This reaction allows direct access to biologically active 3,4-dihydropyrimidin-2(1H)-ones and -thione derivatives through acid-catalyzed three-component condensation reaction of aromatic aldehydes, urea or thiourea and 1,3-dicarbonyl compounds. Because of the significant biological activity [6] and pharmacological efficacy [7-9] of DHPM derivatives, it has received increasing attention in organic and medicinal chemistry.

The first report on the Biginelli reaction was achieved under strongly acidic conditions. Due to the drawbacks

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1021-9986/2021/3/888-897

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which accompanied with the use of the strong acids, Lewis acids such as metal halides [10-15] and metal triflates [16,17] were reported as impressive alternatives to facilitate the Biginelli reaction. In recent decades, ionic liquids have shown as environmentally acceptable reaction medium as well as catalyst in many organic reactions [18]. Ionic liquids with acidic nature have also been introduced to improve the Biginelli reaction [19-22]. In addition, several procedures using catalytic systems such as organocatalysts [23-27], solid materials and supported reagents [28-40] have been applied for this purpose. Protocols employing ultrasound [41] and microwave [42] irradiations as energy sources to facilitate this reaction have also been reported. In spite of their potential efficiency, these protocols may suffer from drawbacks such as the use of large amounts of the expensive catalysts, use of highly toxic organic solvents and tedious workup procedures. Therefore, it has led to renewed exploration of the reaction conditions with a compatible solvent and catalyst to enhance the reaction.

Acidic catalysis has an important role in chemical processes especially in organic syntheses and transformations [43]. Due to the toxic and corrosive nature of conventional mineral and Lewis acids, their application is accompanied with significant risks in handling, containment, disposal and regeneration. On the other hand, protic ionic liquids (PILs) as Brønsted acidic materials show all favorable properties of ionic liquids with the advantage of easier synthesis. They are simply prepared by neutralization reaction between certain Brønsted acids and bases [44]. We have also developed the catalytic applications of some protic ionic liquids in the synthesis of heterocyclic compounds [45-47] and Michael addition reaction [48]. Though numerous catalytic methods have been developed to enhance the yield and scope of the Biginelli reaction, yet there is a room to develop an eco-compatible and cost effective catalyst for this reaction. Herein, the catalytic application of *N*-methylimidazolium acetate as a protic ionic liquid in three component Biginelli reaction for the synthesis of dihydropyrimidin-2-(1H)-ones and thione derivatives is described.

EXPERIMENTAL

Materials and apparatus

Chemicals were either prepared in our laboratory or were purchased from Merck and Aldrich chemical

companies. The progress of the reactions was followed by thin-layer chromatography (TLC) using silica gel GF₂₅₄ plates. IR spectra were recorded on a JASCO FT-IR 4600 spectrophotometer. ¹H and ¹³C NMR spectra were recorded on Bruker Avance DPX 500 MHz spectrometers using TMS as internal standard. Melting points were measured with a Cole-Parmer Electrothermal IA9200 melting point apparatus and are uncorrected. The relative acidity of the protic ionic liquids was evaluated using a SPEKOL 2000 UV-Vis spectrophotometer with 4-nitroaniline as the indicator according to the reported procedure [49].

Synthesis of the protic ionic liquids

The employed protic ionic liquids were synthesized according to the procedure previously reported in the literature [45], which equimolar ratio of an acid was added dropwise slowly to a stirring solution of an amine in CH₂Cl₂ in an ice bath. Then, it was allowed to attain room temperature and stir for 3 hours. Next, the solvent was evaporated and corresponding protic ionic liquid was obtained in a quantitative yield which was further characterized by ¹H and ¹³C NMR spectroscopy analysis. The relative acidity of the protic ionic liquids was evaluated using a UV-Vis spectrophotometer with 4-nitroaniline as the indicator according to the reported procedure [49]. In a typical experiment an ethanolic solution of 4-nitroaniline (0.1 mM) was added to a solution of the corresponding PIL (10 mM) and the mixture was stirred overnight. Then, the absorbance was measured and compared with reference solution absorbance. The absorbance difference was correlated to the Brønsted acidity through the Hammett acidity function $H_0 = pK_a(\text{In}) + \log[\text{In}]/[\text{InH}^+]$, which $pK_a(\text{In})$ is the pK_a value of indicator aqueous solution and equals to 0.99; $[\text{In}]$ and $[\text{InH}^+]$ are the molar concentrations of the unprotonated and protonated forms of the indicator.

Synthesis and characterization of *N*-methylimidazolium acetate

To a round bottomed flask containing CH₂Cl₂ (10 mL), *N*-methylimidazole (1.59 mL, 20 mmol) was added. While the reaction mixture was stirring in an ice bath, acetic acid (1.14 mL, 20 mmol) was added dropwise slowly during 10 min. Then, it was allowed to reach at room temperature and it was stirred for 3 hours. Next, the solvent was evaporated

and *N*-methylimidazolium acetate was obtained as a colorless liquid in 2.73 g, quantitative yield. IR (neat, cm^{-1}): 3444 (NH), 3121 (CH arom), 1640 (COO), 1565 (COO); ^1H NMR (500 MHz, CDCl_3) δ (ppm): 1.92 (s, 3H, CH_3CO), 3.59 (s, 3H, CH_3N), 6.80 (s, 1H, CH sp^2), 6.94 (s, 1H, CH sp^2), 7.56 (s, 1H, NCHN), 12.16 (s, 1H, NH^+).

General procedure for the preparation of 3,4-dihydropyrimidin-2-(1H)-ones/thiones

A mixture of aldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea or thiourea (1.0 mmol) and $[\text{MImH}][\text{OAc}]$ (5 mol%) was heated with stirring at 100 °C. The progress of the reaction was monitored by TLC. After completion of reaction, twice cool water was added to the reaction mixture and decanted to remove the ionic liquid. Then, the crude product was dissolved in hot ethanol and the product recrystallized from ethanol. Various aromatic aldehyde derivatives were put under the same condition and melting point of the obtained products were determined by the open capillary tube method in electrothermal melting point apparatus (Table 4). The obtained Biginelli products (DHPMs) were also confirmed by spectroscopy analysis.

Biginelli reaction: a typical procedure

A mixture of 4-chlorobenzaldehyde (0.140 g, 1.0 mmol), urea (0.060 g, 1.0 mmol), ethyl acetoacetate (0.126 mL, 1.0 mmol) and $[\text{MImH}][\text{OAc}]$ (0.007 g, 5 mol%) was stirred in an oil bath at 100 °C. The progress of the reaction was monitored by TLC (EtOAc : Petroleum ether 3 : 1). After 15 min, the reaction was completed and cool water was added and decanted. Washing the reaction mixture was repeated twice to remove *N*-methylimidazolium acetate. Then, the residue was dissolved in hot ethanol and recrystallization in EtOH provided the corresponding product as a white solid in 0.255 g, 91% isolated yield (Table 4, entry 4).

5-Ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (4d)

mp 205-206 °C (Lit [34], 204-206 °C); IR (KBr, cm^{-1}) 3243 (NH), 3116 (CH arom), 2980 (CH aliph), 1705 (C=O), 1648 (C=O); ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ (ppm): 0.92 (t, $J = 7.0$ Hz, 3H, OCH_2CH_3), 2.1 (s, 3H, CH_3), 3.82 (q, $J = 7.0$ Hz, 2H, OCH_2CH_3), 5.0 (s, 1H, CH), 7.09 (d, $J = 8.5$ Hz, 2H, AA'), 7.22 (d, $J = 8.5$ Hz, 2H, BB'), 7.63 (s,

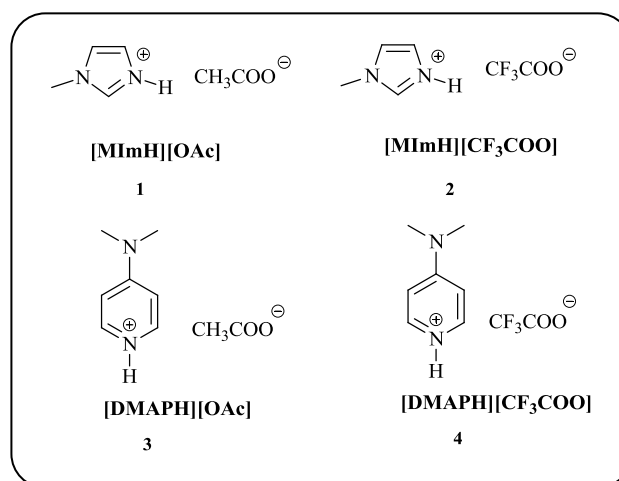


Fig. 1: Overview of the synthesized protic ionic liquids.

1H, NH), 9.11 (s, 1H, NH); ^{13}C NMR (125 MHz, $\text{DMSO}-d_6$) δ (ppm): 14.49, 18.26, 53.92, 59.70, 99.33, 128.65, 128.83, 132.28, 144.24, 149.15, 152.47, 165.65.

RESULTS AND DISCUSSION

Four different protic ionic liquids were prepared by neutralization reaction of nitrogen heterocyclic compounds including *N*-methylimidazole and *N,N*-dimethylaminopyridine with acetic acid and trifluoroacetic acid (Fig. 1).

In order to validate the acidic properties of the prepared protic ionic liquids, their Hammett acidity function were calculated. The Hammett method consists of the determination of acidity functions using UV-Vis spectroscopy, where a basic indicator is used to trap the dissociated proton. Herein, 4-nitroaniline was selected as an indicator and ethanol was used as a solvent. A maximum absorbance (A_{max}) of 1.56 was observed for the unprotonated form of 4-nitroaniline at $\lambda_{\text{max}} = 374$ nm in ethanol. The Hammett acidity function (H_0) was calculated from the ratio of the measured absorbances of the unprotonated and protonated forms of 4-nitroaniline (Table 1). The Hammett acidity functions (H_0) of the examined *N*-methylimidazolium acetate was found 2.03. In contrast, *N*-methylimidazolium trifluoroacetate revealed an H_0 of 3.38 with an A_{max} value of 1.564. It was very close to the absorbance measured for the indicator 4-nitroaniline alone (1.569). This showed that the latter possessed very poor acidity. There is a strong correlation between proton transfer from acid to the base and the pK_a difference between the acid and base precursors [44].

Table 1: Hammett acidity functions (H_0) of the PILs^a

Entry	PIL	Absorbance	[In]%	[InH ⁺]%	H_0
1	-	1.569	100	0	-
2	[NMIImH][OAc]	1.439	91.7	8.3	2.033
3	[NMIImH][CF ₃ CO ₂]	1.564	99.6	0.4	3.38
4	[DMAPH][OAc]	1.715	-	-	-
5	[DMAPH][CF ₃ CO ₂]	1.770	-	-	-

^a $H_0 = p K[In]aq + \log([In]s/[InH^+]s)$. 4-Nitroaniline and the PILs were dissolved in ethanol with 0.1 mM and 10 mM concentrations, respectively.

Table 2: The effect of protic ionic liquids on a Biginelli model reaction^a.

Entry	PIL	Time (min)	Yield %
1	[MImH][OAc]	10	83
2	[MImH][CF ₃ CO ₂]	20	52
3	[DMAPH][CF ₃ CO ₂]	20	46
4	[DMAPH][OAc]	60	40

^a The model reaction was performed with the equimolar ratios of the substrates.

The lower proton activity of PILs which are prepared from acid and base precursors with large pK_a differences is attributed to the stabilization of the PIL cation toward the conjugate base of the acid. Following, the absorbance value measured for 4-*N,N*-dimethylaminopyridinium acetate and 4-*N,N*-dimethylaminopyridinium trifluoroacetate was higher than indicator alone (1.569), which is due to the structural similarity of 4-*N,N*-dimethylaminopyridine and 4-nitroaniline. This reveals that both compounds have nearly the same chromophore.

Subsequently, the efficiency of the prepared ionic compounds on Biginelli dihydropyrimidinone synthesis was evaluated. In a model reaction, equimolar ratios of 4-chlorobenzaldehyde, urea and ethyl acetoacetate were treated. The reaction was investigated in the presence of PILs (10 mol%) at 100 °C (Table 2). *N*-Methylimidazolium acetate provided the best result (Table 2, entry 1). As later it can be seen in the proposed mechanism, the first step of the reaction which is the formation of the *N*-acyliminium ion as the key intermediate and enolization step both requires the acid catalyst. Therefore, according to the higher

Hammett acidity function of *N*-methylimidazolium acetate, the obtained observation would be reasonable.

Next, the reaction was studied employing *N*-methylimidazolium acetate as a catalyst. The effects of the reactants molar ratios, catalyst amount and temperature were examined (Table 3). The best result was obtained using equimolar ratios of the reactants and 5 mol% of *N*-methylimidazolium acetate at 100 °C (Table 3, entry 2). Performing the reaction using 1 mol% of the catalyst or lower temperatures resulted in a noticeable decrease in the yield of the product (Table 3, entries 3-6). In addition, either the reaction time or the yield of the product was not improved using excess amounts of the starting materials (Table 3, entries 7-9). Even, using excess amounts of the urea, the yield of the product was decreased (Table 3, entries 7,9). This may be due to the solid nature of urea that inhibited the treatment of some starting materials that would be remained unreacted in the bulk mixture.

Afterwards, the scope and generality of the reaction was investigated. Treatment of different aldehydes, urea (thiourea) and ethyl acetoacetate were evaluated under

Table 3: Optimization of *N*-methylimidazolium acetate catalyzed Biginelli reaction through synthesis of 5-ethoxycarbonyl-6-methyl-4-(4-chlorophenyl)-3,4-dihydropyrimidine-2(1*H*)-one.

Ar = *p*-Cl-C₆H₄

Entry	Molar ratios of the reactants ^a	Cat. (mol%)	Temp. (°C)	Time (min)	Yield %
1	1: 1: 1	10	100	10	83
2 ^b	1: 1: 1	5	100	15	91
3	1: 1: 1	1	100	15	59
4	1: 1: 1	5	r.t.	24 h	10
5	1: 1: 1	5	50	2 h	25
6	1: 1: 1	5	75	15	58
7	1: 1.5: 1	5	100	15	85
8	1: 1: 1.5	5	100	15	90
9	1: 1.5: 1.5	5	100	15	70

^a Molar ratios of the reactants corresponding respectively to 4-chlorobenzaldehyde, urea and ethyl acetoacetate.

^b The best molar ratios of the reactants and the optimized reaction conditions have been shown in bold.

optimized conditions (Table 4). Reaction of aromatic aldehydes containing both electron donating and electron withdrawing groups with urea afforded the desired products in high yields (Table 4, entries 1-5). This reaction condition was mild enough to tolerate sensitive functionalities such as NO₂ and OMe. However, the reaction with thiourea provided the corresponding dihydropyrimidine-2(1*H*)-thiones in lower yields (Table 4, entries 6-10).

Recyclability of the catalyst was also investigated through the treatment of 4-chlorobenzaldehyde, urea and ethyl acetoacetate under the optimized conditions. Consequently, after 15 min (the time which is required for the first use), *N*-methylimidazolium acetate was simply separated by washing the mixture with cool water (twice). Then, water was evaporated under reduced pressure and *N*-methylimidazolium acetate was recovered and dried in oven and reused for a similar reaction. For the first run, either the reaction time or yield was unchanged. However, for further runs, the reaction time was increased and after four consecutive runs, the catalytic activity was considerably decreased (Table 5).

The efficiency of [MImH][OAc] as a protic ionic catalyst in comparison with the previously reported

catalysts was shown in Table 6. It was found that [MImH][OAc] is more efficient than many catalytic systems in the case of reaction time and yield. In addition, [MImH][OAc] is more cost effective than most other promoters listed in Table 6 which is also easily prepared through a simple neutralization reaction. However, the results of the recyclability of the catalyst is not efficient as those reported in the literature

Kappe reexamined the proposed mechanisms of the Biginelli dihydropyrimidine synthesis. His investigations confirmed that the reaction supported by an *N*-acyliminium ion as the key intermediate [50]. Interception of this iminium ion by the enol form of ethyl acetoacetate produces open-chain ureides which subsequently cyclize to the Biginelli dihydropyrimidines. Therefore, due to the Bronsted acidic nature of *N*-methylimidazolium acetate, the following mechanism would be reasonable (Scheme 1). As it can be seen in the proposed mechanism, *N*-methylimidazolium acetate has an essential role in the protonation of aldehyde, addition of urea to the protonated aldehyde and dehydration, enolization of ethyl acetoacetate and addition to *N*-acyliminium ion intermediate and finally formation of the cyclization Biginelli product.

Table 4: Synthesis of 3,4-dihydropyrimidin-2-(1H)-ones and thione derivatives through the Biginelli reaction using *N*-methylimidazolium acetate as a catalyst at 100 °C.

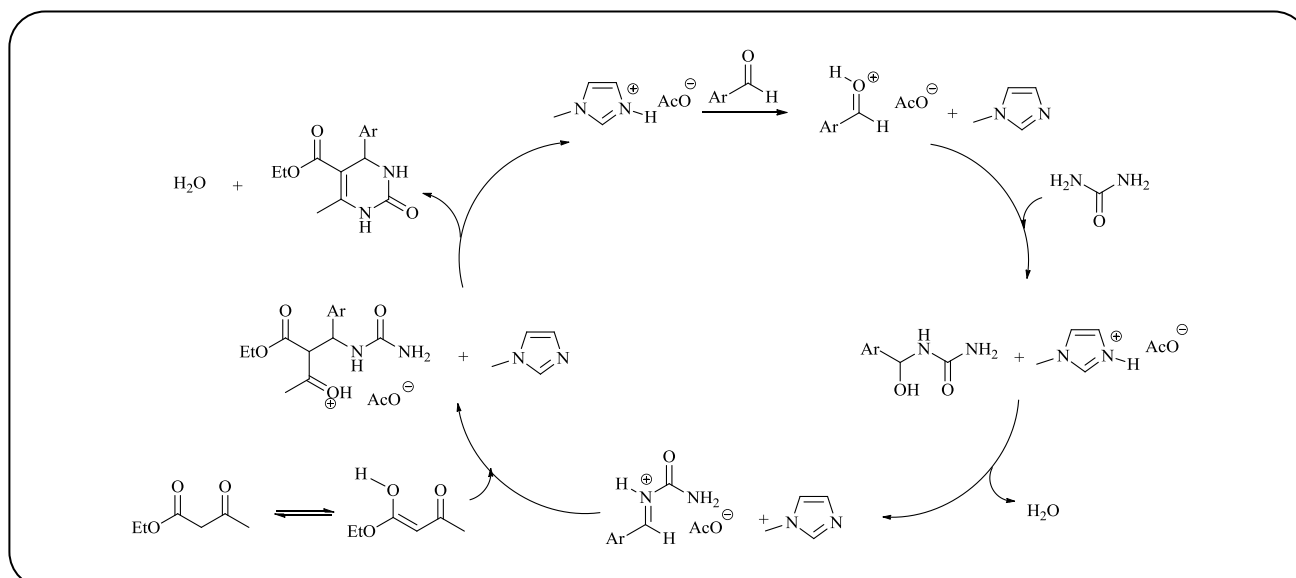
Entry	R	X	Product	Time (min)	Isolated yield %	M. P. °C (reported) ^{Ref.}
1	H	O	4a	45	87	198-199 (198-200) ^[21]
2	CH ₃	O	4b	50	85	216-217 (212-215) ^[21]
3	OCH ₃	O	4c	45	79	206-208 (205-207) ^[21]
4	Cl	O	4d	15	91	205-206 (204-206) ^[34]
5	NO ₂	O	4e	15	87	211-212 (204-206) ^[21]
6	H	S	4f	35	67	205-207 (210-212) ^[21]
7	CH ₃	S	4g	15	69	194-195 (191-193) ^[29]
8	OCH ₃	S	4h	30	71	156-157 (151-153) ^[21]
9	Cl	S	4i	40	74	182-183 (179-180) ^[29]
10	NO ₂	S	4j	45	79	207-208 (206-208) ^[21]

Table 5: Recyclability of *N*-methylimidazolium acetate on a typical Biginelli reaction.

Run	1 st	2 nd	3 rd	4 th
Yield %	91	79	68	53

Table 6: Comparison of some different methods for the synthesis of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one through Biginelli reaction.

Entry	Cat.	Condition	Time	Yield %	Recyclability, yield%	Ref.
1	SbCl ₃ (20 mol%)	CH ₃ CN, Reflux	22 h	75	not reported	[13]
2	[bmim][MeSO ₄] (1 mol%)	Neat, 100 °C	0.5 h	90	4 th , 82	[20]
3	Trichloroisocyanuric acid (15 mol%)	EtOH, Reflux	12 h	94	not reported	[23]
4	Oxalic acid (20 mol%)	Neat, 90 °C	35 min	80	not reported	[25]
5	Al-M41 (50 mg)	Octane, 118 °C	10 h	94	4 th , 88	[28]
6	Fe ₃ O ₄ @mesoporous SBA-15 (50 mg)	EtOH, Reflux	6 h	85	4 th , 85	[30]
7	H ₅ PW ₁₀ V ₂ O ₄₀ /Pip-SBA-15 (2 mol%)	Neat, 100 °C	0.33 h	90	4 th , 90	[31]
8	NanoZnO (5 mol%)	Neat, 60 °C	10 h	95	3 rd , 95	[32]
9	MAI-Fe ₂ Cl ₇ (5 mol%)	[BMIm][BF ₄] (1 mL), 80 °C	2 h	99	4 th , 99	[33]
10	Ompg-C ₃ N ₄ -SO ₃ H (20 mg)	EtOH, Reflux	20 min	98	4 th , 92	[40]
11	[NMImH][OAc] (5 mol%)	Neat, 100 °C	45 min	87	4 th , 53	This work



Scheme 1: A plausible mechanism for the Biginelli reaction using *N*-methylimidazolium acetate as a catalyst.

CONCLUSIONS

In conclusion, we have developed a facile procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones and -thione derivatives using *N*-methylimidazolium acetate as a catalyst. *N*-Methylimidazolium acetate is a liquid that is simply prepared by a neutralization reaction and was characterized by FT-IR and ¹H NMR spectra analysis. The acidity of the catalyst was also determined by Hammett's acidity function. Some other ionic liquids were also prepared and their catalytic activity on a typical Biginelli reaction was investigated. *N*-Methylimidazolium acetate as a catalyst was more effective than the other ionic liquids. The efficiency of *N*-methylimidazolium acetate was examined for the synthesis of different 3,4-dihydropyrimidin-2(1*H*)-ones and -thione derivatives and the desired products were obtained in high to excellent isolated yields. The present protocol offers the advantage of easy operation, short reaction times, and a simple workup procedure. The catalyst is also more cost-effective than many catalytic systems reported in the literature earlier.

Acknowledgments

We are grateful for the financial support from the Research Council of the Behbahan Khatam Alanbia University of Technology.

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Received : Sept. 16, 2019 ; Accepted : Jan. 13, 2020

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