EFFICIENT AND GREEN MICROWAVE-ASSISTED MULTICOMPONENT BIGINELLI REACTION FOR THE SYNTHESIS OF DIHYDROPYRIMIDINONES CATALYZED BY HETEROPOLYANION-BASED IONIC LIQUIDS UNDER SOLVENT-FREE CONDITIONS

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GRAPHICAL ABSTRACT

Abstract
An efficient and green route for the synthesis of dihydropyrimidinones via microwave-assisted Biginelli reaction catalyzed by 3 mol% of heteropolyanion-based ionic liquids under solvent-free conditions has been reported. The practical reaction was found to be compatible with different structurally diverse substrates. Good to excellent yields, short reaction times, and operational simplicity are the main highlights of this protocol. Moreover, the heteropolyanion-based ionic liquids were easily reusable for this Biginelli reaction.
INTRODUCTION

Multicomponent reactions (MCRs) promote the formation of several bonds in one operation with remarkable advantages, such as simple procedure, multiple-bond-forming efficiency, time and energy savings, easy extraction and purification processes, and minimized waste generation.\(^{[1]}\) From an environmental and economic perspective, MCRs have acted as efficient tools for the construction of chemical libraries of drug-like compounds with structural complexity and diversity.\(^{[2]}\) The Biginelli reaction\(^{[3]}\) is ranked as one of the most powerful MCRs for the synthesis of the dihydropyrimidinone (DHPM) scaffold, which has exhibited a wide range of pharmaceutical and therapeutic properties, such as antiviral, antitumor, antibacterial, and anti-inflammatory activities\(^{[4]}\) and has been suggested as useful building blocks for the synthesis of versatile heterocyclic derivatives.\(^{[5]}\) Classical Biginelli reaction involves one-pot condensation of aldehyde, \(\beta\)-ketoester, and urea under strongly acidic conditions, which suffers from the drawbacks including harsh conditions, long reaction times, and poor yields and purities.\(^{[6]}\) These disadvantages have led to the development of a number of improved catalytic systems that involve Brønsted acids\(^{[7]}\) or bases,\(^{[8]}\) metal Lewis acids,\(^{[9]}\) organocatalysts,\(^{[10]}\) and heterogeneous catalysts.\(^{[11]}\)

However, in spite of their potential utility, many of these methods involve expensive and/or toxic catalysts and reagents, stoichiometric amount of catalyst, strongly acidic conditions, unsatisfactory yields, purification issues, and limited substrate scope, and thus they are not closer to the principles of green chemistry. Hence, the development of clean, high-yielding, and environmentally friendly approaches employing recyclable catalysts in Biginelli synthesis still remains an active area of research.

Over recent decades, ionic liquids (ILs) have attracted much interest as environmentally benign solvent and/or catalysts different from classical conventional ones because of their remarkable properties, such as negligible vapor pressure, low toxicity, low flammability, high thermal and chemical stability, solvent power, reusability, and structural versatility.\(^{[12]}\) Moreover, a variety of organic transformations have been successfully conducted using ILs as environmentally friendly alternatives to traditional organic solvents or catalysts.\(^{[13]}\) In recent years, a variety of ILs have already been employed with success as efficient catalysts for the Biginelli reaction, including cations derived from alkylammonium, dialkylimidazolium, and pyridinium.\(^{[14]}\) Most recently, a series of heteropolyanion-based ILs (HPAILs) have been prepared as hybrid materials by combining Keggin heteropolyanions with task-specific ILs (TSILs) cations.\(^{[15]}\) In view of the advantages of heteropolyanions and TSILs, HPAILs attract great research interest because of their diverse chemical structures and improved catalytic behaviors. HPAILs usually have high melting points and high thermal and chemical stability because of the heteropolyanion existing in the compounds, which is consistent with the requirements of a solid acid catalyst. Moreover, HPAILs have turned out to be environmentally friendly, highly efficient, and reusable catalysts for acid-catalyzed\(^{[16]}\) or oxidative organic transformations\(^{[17]}\) because of advantages such as operational simplicity, no toxicity, low cost, easy isolation, and reusability. To the best of our knowledge, there has been only one report on the
HPAIL-catalyzed Biginelli reaction, by Neto and coworkers.\[14a\] Although excellent yields were obtained, the catalytic system involved 1-n-butyl-3-methylimidazolium bis (trifluoromethanesulfonyl)imide (BMI·NTf$_2$) as reaction solvent/medium at 90°C for 4 h. Thus, it is recognized that the HPAIL-catalyzed Biginelli reaction was not fully explored, especially with regard to solvent-free conditions.

During the past few years, nonclassical methods have been developed in organic synthesis in order to improve yields, selectivity, and experimental conditions.\[18\] Among them, microwave-assisted technology has become an important method because of unique advantages, such as the significant rate enhancements, yield and selectivity improvements, very simplified ease of manipulation and workup, and less environmentally polluting processes.\[19\] Especially the use of microwave-assisted technology in conjunction with solvent-free conditions allows expeditious and efficient procedures in organic synthesis.\[20\] With our continuous investigation on the methodology of green synthesis,\[21\] herein we report an efficient and environmentally benign protocol for the Biginelli reaction successfully accomplished by using HPAILs as catalyst under microwave irradiation (MWI) and solvent-free conditions (Scheme 1).

**RESULTS AND DISCUSSION**

Among the various HPAILs, our study is mainly focused on N-substituted imidazole-, pyridine-, and triethylamine-based HPAILs, which have already been used as catalysts for many different acid-catalyzed transformations by us and others.\[16\] Thus, six structurally related HPAILs (Fig. 1) were prepared according to the procedure described in the literature.\[16a\]

**Figure 1.** N-Substituted imidazole-, pyridine-, and triethylamine-based HPAILs.
Initially, the cyclocondensation of benzaldehyde, ethylacetoacetate, and urea under microwave irradiation (MWI) and solvent-free conditions was considered as a standard model reaction to determine the optimum condition (Table 1). First, when the reaction was carried out in the absence of any catalyst under MWI at 100 °C for 30 min, only 8% yield of desired dihydropyrimidinone was obtained (Table 1, entry 1), whereas the rate and yield of the reaction both increased dramatically in the presence of 2 mol% of [MIMP] _3_ PW _12_ O _40_ (Table 1, entry 2). The results revealed that the catalyst should be absolutely necessary for the Biginelli reaction. At the same time it was shown that the yield of the reaction increased when heating at 120 °C (Table 1, entry 3), but there was not appreciable change at higher temperature (130 °C) (Table 1, entry 4).

In the screening test of optimum catalyst concentration, it was found that using 3 mol% of [MIMP] _3_ PW _12_ O _40_ (Table 1, entry 5) could give the best result and that greater amount of the catalyst did not obviously improve the result (Table 1, entry 6). Thus, catalytic activities of other related catalysts were investigated under the same reaction conditions. From the results, it was noticed that all six HPAILs prepared before could promote the reaction in different degrees. It was shown that the catalytic activities of [MIMP] _3_ PW _12_ O _40_ and [TEAPS] _3_ PW _12_ O _40_ were slightly lower than that of [PyPS] _3_ PW _12_ O _40_ (Table 1, entries 5, 8, and 10). In the cases of catalysts combining with different heteropolyanions, the results demonstrated that PW _12_ O _40_ was more active than PMo _12_ O _40_ HPAILs (Table 1, entries 5 and 7–11). Although pure HPA catalyst H _3_ PW _12_ O _40_ gave a high yield of 90%, its good solubility throughout organic solvents and water made its isolation from the reaction mixture difficult (Table 1, entry 12).

Finally, the optimum result was obtained when the reaction was performed using 3 mol% of [PyPS] _3_ PW _12_ O _40_ under MWI (700 W) and solvent-free condition affording dihydropyrimidinone in 95% yield at 120 °C for 5 min (Table 1, entry 8).

To examine the substrate scope of this catalyzed Biginelli reaction, a variety of aromatic, heterocyclic, and aliphatic aldehydes were subjected to react with 1,3-dicarbonyl compounds and urea/thiourea under these optimized reaction conditions. The results are summarized in Table 2. In all cases, the reaction proceeded smoothly

| Entry | Catalyst | Temp. (°C) | Time (min) | Yield (%)³ |
|-------|----------|------------|------------|------------|
| 1     | No catalyst | 100        | 30         | 8          |
| 2     | [MIMP] _3_ PW _12_ O _40_, 2 mol% | 100        | 10         | 83         |
| 3     | [MIMP] _3_ PW _12_ O _40_, 2 mol% | 120        | 5          | 91         |
| 4     | [MIMP] _3_ PW _12_ O _40_, 2 mol% | 130        | 5          | 91         |
| 5     | [MIMP] _3_ PW _12_ O _40_, 3 mol% | 120        | 5          | 93         |
| 6     | [MIMP] _3_ PW _12_ O _40_, 4 mol% | 120        | 5          | 93         |
| 7     | [MIMP] _3_ PMo _12_ O _40_, 3 mol% | 120        | 5          | 86         |
| 8     | [PyPS] _3_ PW _12_ O _40_, 3 mol% | 120        | 5          | 95         |
| 9     | [PyPS] _3_ PMo _12_ O _40_, 3 mol% | 120        | 5          | 89         |
| 10    | [TEAPS] _3_ PW _12_ O _40_, 3 mol% | 120        | 5          | 84         |
| 11    | [TEAPS] _3_ PMo _12_ O _40_, 3 mol% | 120        | 5          | 78         |
| 12    | H _3_ PW _12_ O _40_, 3 mol%    | 120        | 5          | 90         |

³Reaction conditions: benzaldehyde (3.0 mmol), ethylacetoacetate (3.0 mmol), urea (4.5 mmol), related catalyst, MWI (700 W).

Isolated yields.
to afford the corresponding DHPMs and -thiones within short reaction time (5–10 min) in good to excellent yields (83–96%). A wide range of aromatic aldehydes bearing either electron-donating or electron-withdrawing substituents at different positions afforded good yields of DHPMs in high purity (Table 2, entries 1–7 and 11–28). Meanwhile, the HPAIL-catalyzed condensation was compatible with a variety of functional groups including methoxy, methyl, chloro, nitro, and hydroxyl. Besides the β-ketoester, β-diketone (Table 2, entries 23–28) could also be employed with similar success to provide the corresponding products. In addition, both urea and thiourea were suitable substrates as demonstrated from the yields of the

Table 2. Scope of microwave-assisted Biginelli reaction catalyzed by HPAILs under solvent-free conditions

| Entry | R¹   | R²    | X     | Time (min) | Yield (%) |
|-------|------|-------|-------|------------|-----------|
| 1     | C₆H₅ | OEt   | O     | 5          | 95        |
| 2     | 4-MeO-C₆H₄ | OEt   | O     | 5          | 96        |
| 3     | 4-Me-C₆H₄  | OEt   | O     | 5          | 95        |
| 4     | 4-Cl-C₆H₄  | OEt   | O     | 5          | 92        |
| 5     | 4-NO₂-C₆H₄ | OEt   | O     | 5          | 93        |
| 6     | 4-OH-C₆H₄  | OEt   | O     | 5          | 91        |
| 7     | 2-OH-C₆H₄  | OEt   | O     | 8          | 90        |
| 8     | 2-Furyl    | OEt   | O     | 8          | 88        |
| 9     | n-C₆H₁₃    | OEt   | O     | 8          | 85        |
| 10    | i-Pr       | OEt   | O     | 8          | 83        |
| 11    | C₆H₅       | OEt   | S     | 10         | 93        |
| 12    | 4-Me-C₆H₄  | OEt   | S     | 10         | 91        |
| 13    | 4-Cl-C₆H₄  | OEt   | S     | 10         | 92        |
| 14    | 4-NO₂-C₆H₄ | OEt   | S     | 10         | 90        |
| 15    | C₆H₅       | OMe   | O     | 5          | 94        |
| 16    | 4-MeO-C₆H₄ | OMe   | O     | 5          | 95        |
| 17    | 4-Me-C₆H₄  | OMe   | O     | 5          | 93        |
| 18    | 4-Cl-C₆H₄  | OMe   | O     | 5          | 92        |
| 19    | 4-NO₂-C₆H₄ | OMe   | O     | 8          | 90        |
| 20    | C₆H₅       | OMe   | S     | 10         | 94        |
| 21    | 4-Me-C₆H₄  | OMe   | S     | 10         | 91        |
| 22    | 4-NO₂-C₆H₄ | OMe   | S     | 10         | 92        |
| 23    | C₆H₅       | Me    | O     | 5          | 94        |
| 24    | 4-Me-C₆H₄  | Me    | O     | 5          | 93        |
| 25    | 4-NO₂-C₆H₄ | Me    | O     | 5          | 92        |
| 26    | C₆H₅       | Me    | S     | 5          | 92        |
| 27    | 4-Me-C₆H₄  | Me    | S     | 5          | 91        |
| 28    | 4-NO₂-C₆H₄ | Me    | S     | 5          | 85        |

*Reaction conditions: aldehyde (3.0 mmol), 1,3-dicarbonyl compound (3.0 mmol), urea/thiourea (4.5 mmol), [PyPS]₃PW₁₂O₄₀ (3 mol%), MWI (700 W), 120 °C.

*Isolated yields.
corresponding Biginelli adducts (Table 2, entries 11–14, 20–22, 26–28). However, it was observed that the reaction of aromatic aldehydes with urea is fast as compared to thiourea. Another important feature of this procedure is that good yields were achieved (83–88% yield) in the cases of heterocyclic and aliphatic aldehydes (Table 2, entries 8–10), which normally were less reactive or completely inert to the Biginelli reaction.

The outstanding feature of the HPAILs as catalysts over conventional ones is their excellent solubility in water or strong polar solvents but nonmiscibility with apolar esters, that would lie in the feasibility of their recovery. Hence, the recycling of [PyPS]$_3$PW$_{12}$O$_{40}$ in the multicomponent Biginelli reaction was investigated (Table 3). In each case, after completion of the reaction (monitored by thin-layer chromatography, TLC), [PyPS]$_3$PW$_{12}$O$_{40}$ was removed from the reaction mixture by simple filtration after vigorous stirring with hot EtOAc. After removal of the solvent, the almost pure product was obtained and recrystallization could be used for further purification. The catalyst could be reused five times for the synthesis of dihydropyrimidinone with a little loss of activity (Table 3). It was proved that HPAIL is easily reusable for this multicomponent Biginelli reaction.

According to the mechanism suggested by Folkers, Johnson, and Kappe, the reaction may proceed through imine formation from the aldehyde and urea, subsequent addition of the carbanion derived from 1,3-dicarbonyl compounds to the imine, followed by cyclodehydration to afford DHPMs. In our cases, HPAIL promotes the reactions because of its inherent Brønsted acidity. Hydrogen bonding is formed between HPAIL and carbonyl oxygen of aldehyde as well as ethyl acetoacetate during the reaction. The formation of hydrogen bond between IL and substrate leads them to the activation. The hydrogen ion, donated by HPAIL, not only helps the dehydration but also benefits the enolization of 1,3-dicarbonyl compounds to form enolate intermediate. Based on this, a plausible mechanistic pathway for this reaction is suggested.

In conclusion, we have successfully developed a microwave-assisted HPAIL-catalyzed approach for the synthesis of bioactive dihydropyrimidinones under solvent-free conditions. The developed method not only preserved the operational simplicity of Biginelli’s one-pot condensation but also provided compatibility with various functional groups and good to excellent yields of dihydropyrimidinones within short reaction times. Moreover, the HPAILs are recyclable and reused for more than five cycles without showing any significant loss in its catalytic activity. This strategy complements the existing reports on the synthesis of dihydropyrimidinones.

Table 3. Reusability studies of catalyst for the synthesis of DHPMs$^a$

| Number of cycles | 1  | 2  | 3  | 4  | 5  |
|------------------|----|----|----|----|----|
| Yield (%)$^b$    | 95 | 93 | 91 | 90 | 90 |

$^a$Reaction conditions: benzaldehyde (3.0 mmol), ethylacetoacetate (3.0 mmol), urea (4.5 mmol), [PyPS]$_3$PW$_{12}$O$_{40}$ (3 mol%), MWI (700 W), 120 °C.

$^b$Isolated yields.
**EXPERIMENTAL**

**Synthetic Procedure for HPAILs**

Methylimidazole (0.11 mol) and 1,3-propane sulfone (0.10 mol) were dissolved in toluene (30 mL) and stirred for 24 h at 50 °C under a nitrogen atmosphere. A white precipitate (MIMPS) formed, which was filtered, washed with diethyl ether three times, and then dried in a vacuum. MIMPS (0.09 mol) was added to an aqueous solution of H$_3$PW$_{12}$O$_{40}$ (0.03 mol), and then the mixture was stirred at room temperature for 24 h. Water was removed in vacuum to give the product [MIMPS]$_3$PW$_{12}$O$_{40}$ as a solid. Thus [MIMPS]$_3$PMo$_{12}$O$_{40}$, [PyPS]$_3$PW$_{12}$O$_{40}$, [PyPS]$_3$PMo$_{12}$O$_{40}$, [TEAPS]$_3$PW$_{12}$O$_{40}$, and [TEAPS]$_3$PMo$_{12}$O$_{40}$ were prepared using according starting materials (Fig. 1).

**Synthetic Procedure for Dihydropyrimidinones**

[PyPS]$_3$PW$_{12}$O$_{40}$ (314 mg, 0.09 mmol) was added to a mixture of aldehyde (3 mmol), 1,3-dicarbonyl compound (3.0 mmol), and urea/thiourea (4.5 mmol) in a 10-mL, round-bottomed flask. The reaction mixture was stirred at 120 °C under MWI (700 W). The progress of the reaction was monitored by TLC. On completion, the mixture was diluted with hot ethyl acetate (20 mL) with stirring for 30 min. The insoluble catalyst was recovered by filtration. The filtrate was evaporated and the residue was in almost pure form. Recrystallization or column chromatography could be used for further purification.

**5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 1)**

White solid. Mp: 201.1–203.6 °C; IR (KBr): 3244, 3109, 2933, 1710, 1650, 1222, 1089 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.20 (s, 1H), 7.74 (s, 1H), 7.35–7.30 (m, 2H), 7.25–7.21 (m, 3H), 5.15 (d, $J = 3.0$ Hz, 1H), 3.98 (q, $J = 7.0$ Hz, 2H), 2.25
(s, 3H), 1.09 (t, J = 7.0 Hz, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 165.4, 152.2, 148.4, 144.9, 128.4, 127.3, 126.3, 99.3, 59.2, 54.0, 17.8, 14.1. HRMS calcd. for C$_{14}$H$_{17}$N$_2$O$_3$ (M + H$^+$): 261.1234; found: 261.1238.

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione (Table 2, entry 11)

Yellow solid. Mp: 200.4–202.5 ºC; IR (KBr): 3322, 3466, 3176, 3111, 1670, 1575, 1470, 1277, 1197, 1105, 696 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 10.34 (s, 1H), 9.65 (s, 1H), 7.37–7.21 (m, 5H), 5.18 (d, J = 3.6 Hz, 1H), 4.01 (q, J = 6.9 Hz, 2H), 2.29 (s, 3H), 1.10 (t, J = 6.9 Hz, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 174.2, 165.1, 145.0, 143.5, 128.6, 127.7, 126.4, 100.7, 59.6, 54.1, 17.2, 14.0. HRMS calcd. for C$_{14}$H$_{17}$N$_2$O$_2$S (M + H$^+$): 277.1005; found: 277.1006.

5-Methoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 15)

Yellow solid. Mp 211.3–213.7 ºC; IR (KBr): 3238, 3117, 2933, 1719, 1645, 1222, 1092 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 9.23 (s, 1H), 7.77 (s, 1H), 7.35–7.30 (m, 2H), 7.26–7.21 (m, 3H), 5.15 (d, J = 3.3 Hz, 1H), 3.53 (s, 3H), 2.26 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 165.9, 152.2, 148.7, 144.7, 128.5, 127.4, 126.2, 99.1, 53.9, 50.9, 17.9. HRMS calcd. for C$_{13}$H$_{15}$N$_2$O$_3$ (M + H$^+$): 247.1077; found: 247.1079.

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SUPPORTING INFORMATION

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