A facile and efficient one-pot synthesis of dihydropyrimidinones in ionic liquid under solvent-free conditions

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ABSTRACT

Dihydropyrimidinones were synthesized by one-pot three components Biginelli condensations in the presence of room temperature ionic liquid 1-benzyl-3-methylimidazolium dihydrogen phosphate ([bnmim]H₂PO₄) in higher yields under solvent-free conditions in shorter reactions time and green aspect by avoiding toxic catalyst and organic solvents. © 2008 Trade Science Inc. - INDIA

INTRODUCTION

3,4-dihydropyrimidin-2(1H)-ones (DHPMs) named Biginelli compounds are known to exhibit a wide range of biological activities such as antiviral[1], antitumor[2] and antibacterial[3]. Appropriately functionalized dihydropyrimidinones have emerged as potent calcium channel blockers[4], antihypertensive agents[5], and α-1a adrenergic antagonists[6]. Moreover, several marine alkaloids containing the DHPMs core unit have shown interesting biological properties. In particular, batzelladine dione alkaloids have been found to be potent HIV gp-120-CD4 inhibitors[7]. In 1893, Italian chemist Pietro Biginelli reported on the acid-catalyzed cyclocondensation reaction of an aldehyde, a β-ketoester, and urea (or thiourea), a procedure known as the Biginelli reaction is receiving increased attention[8]. However, this reaction suffers from the harsh conditions, high times and frequently low yields.

In recent years, new methods for the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones have been developed by using different groups. In order to improve the efficiency of the Biginelli reaction different Lewis catalysts such as In(III)-halides[9], ZrCl₄[10], LaCl₃[11], Zn(OTf)₂[12], Cu(OTf)₂[13], Yb(OTf)₃[14], chloroacetic acid[15] and ionic liquids such as (EtNH₃)NO₃[16], (bmmim)PF₆ or BF₄[17], (bmmim)Cl2AlCl₃[18], (Hmim)Tf₂[19], have been reported. However, in above some reported methods suffer from one or more drawbacks like high temperature requirement, highly acidic conditions, high reaction times, use of toxic organic solvents and frequently low yields. Therefore, the development of mild, efficient and versatile method is still strongly desirable.

Design of solvent-free reactions and use of ionic liquids[20] in organic synthesis, particularly those based on imidazolium cation[21], have experienced an impetus in recent years. Some of their unique physical and chemical properties such as thermal stability, negligible vapour pressure, recyclability, increasing reaction rate, selectivity and tendency to immobilize starting materials and catalyst make them an attractive substitute to various volatile organic solvents.

The ionic liquid plays the dual role of solvent and Lewis acid catalyst and they were used, for example, in
Friedel-Crafts reactions\(^{[22]}\), Diels–Alder reactions\(^{[23]}\), 1, 3-dipolar cycloadditions reactions\(^{[24]}\), polyhydronolines\(^{[25]}\) and bis(indoly) methanes\(^{[26]}\). Also, ionic liquids with acidic counterions like 1-hexyl-3-methylimidazolium hydrogen sulphate ([hmim][HSO\(_4\)])\(^{[27]}\), 1-butyl-3-methyl-imidazolium dihydrogen phosphate ([bmim][H\(_2\)PO\(_4\)])\(^{[27]}\) and 1-butyl-3-methyl-imidazolium chloroaluminate ([bmim]Cl.2AlCl\(_3\))\(^{[28]}\) can be used as good acid catalysts.

In recent years, ultrasonic acceleration of chemical reactions has become a widely used method all over the world because of advantages it offers in synthetic chemistry, which includes reduction in reaction time and saving energy. A large number of organic reactions can be carried out in higher yields\(^{[29-31]}\). In addition it affords higher yields and purity of product as compared to conventional method. Recently, our laboratory has reported the one-pot synthesis of acylals to give high yield under ultrasound\(^{[32]}\).

In continuation of our ongoing research on Biginelli reaction\(^{[16,33-34]}\), herein, we wish to report a very facile and efficient one-pot method for the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones and -thiones (1-16) without any solvent in the presence of acidic ionic liquid[bmim] H\(_2\)PO\(_4\). (SCHEME 1).

**EXPERIMENTAL**

**Apparatus and reagents**

All products are known compounds and these physical data, IR and \(^1\)H NMR spectra were essentially identical with those of authentic samples. All the reagents and aldehydes were obtained from commercial suppliers and were not purified. Melting points were determined in open capillaries apparatus and were uncorrected. The reactions were monitored by TLC. IR spectra were recorded on Perkin-Elmer FT spectrophotometer in KBr disc. \(^1\)H NMR spectra were recorded on Varian 300 MHz spectrophotometer in DMSO-d\(_6\) as a solvent and TMS as an internal standard.

**General procedure for the synthesis of dihydropyrimidinones (1-16)**

1. **By ultrasonic irradiation**

   In a round bottom flask a mixture of urea or thiourea (1.5 mmol), an appropriate \(\beta\)-ketoester (1 mmol) and an aldehyde (1 mmol) was mixed with[bmim] H\(_2\)PO\(_4\) (2 mmol) was irradiated under ultrasonic waves at room temperature for an appropriate time (TABLE 1). Progress of reaction was monitored on TLC, the reaction mixture was cooled to room temperature and the cool mixture was extracted with ethyl acetate (2×20ml). The organic layer was washed with water and dried over anhydrous Na\(_2\)SO\(_4\). Organic solvent was evaporated under reduced pressure and solid compound was crystallized from absolute alcohol to afford the pure corresponding dihydropyrimidinones derivative (1-16) in high yield and high purity. Further, the aqueous layer was distilled at 80\(^0\)C under vacuum to remove water, leaving behind the IL (about 85%), which was reused four times and gave 98%, 96%, 94%, 95% yields (1). The products (1-16) were confirmed by comparisons with authentic samples, IR, \(^1\)H NMR, mass and melting points.

2. **By conventional method**

   A mixture of urea or thiourea (1.5 mmol), an appropriate \(\beta\)-ketoester (1 mmol) and an aldehyde (1 mmol) was mixed with[bmim]H\(_2\)PO\(_4\) (2 mmol) in a round bottom flask equipped with a magnetic stirrer. Then the reaction mixture was stirred for an appropriate time at room temperature (TABLE 1), worked up and purified as above (method-i) to get the desired product.

**RESULT AND DISCUSSION**

To optimize the reaction conditions, the reaction of benzaldehyde, ethyl acetocetate and urea was selected as model to investigate the effects of the ionic liquid at...
different amounts of ionic liquid on the yield and time. The best result was obtained by carrying out the reaction with 1:1:1.5 mol ratios of benzaldehyde, ethyl acetocetate, urea respectively and the 2 mol of ionic liquid \(\text{bnmim}H_2\text{PO}_4\) was irradiated under ultrasonic waves at room temperature for 20 min (yield=98%, product 1) and under vigorously stirring at room temperature for 55 min (yield=95%, product 1). We were encouraged by the results obtained with benzaldehyde. In a similar fashion, a variety of aromatic and heterocyclic aldehydes underwent three-component condensation smoothly to afford a wide range of substituted DHPMs (TABLE 1). Most importantly, aromatic aldehydes carrying either electron donating or electron-withdrawing substituents reacted well under the reaction conditions to give the corresponding DHPMs in high to quantitative yields. This method is even effective with \(\alpha-\beta\)-unsaturated aldehydes, which normally show extremely low conversions in the Biginelli reaction (TABLE 1, product 7). Thiourea has been used with similar success to produce the corresponding thio-derivatives of DHPMs, which are also of much interest with respect to their biological activities\[35\]. Decreased reaction times and didn’t required temperature, joining with improving the yields are among other advantages of this method. The acidic ionic liquid \(\text{bnmim}H_2\text{PO}_4\) was prepared according to literature Fraga-Dabreuil et al.\[36\].

### CONCLUSION

The present method is very simple, mild and efficient for the synthesis of 3, 4-dihydropyrimidin-2(1H)-ones and -thiones. In addition, this protocol has advantages in term of (1) short reaction times; (2) solvent-free reaction; (3) high yields; (4) easy work-up; (5) recyclability of ionic liquid; and (6) avoidance of rigorous reaction conditions. The ionic liquid exhibited high catalytic activities in this reaction. The most important feature of this reaction is that, the reactions were carried out comparatively by ultrasonic irradiation as well as conventional method. Products are obtained in shorter reaction times and greater yields as compared to conventional method (TABLE 1).

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### REFERENCES


### TABLE 1: Synthesis of 3, 4-dihydropyrimidin-2(1H)-ones and -thiones (1-16) using ionic liquid \(\text{bnmim}H_2\text{PO}_4\)

<table>
<thead>
<tr>
<th>Product(^a)</th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>(X)</th>
<th>Time(min)</th>
<th>Yield(%)(^b)</th>
<th>Time(min)</th>
<th>Yield(%)(^b)</th>
<th>Mp ((^\circ)C)</th>
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<td>(\text{C}_6\text{H}_5)</td>
<td>Et</td>
<td>O</td>
<td>55</td>
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<td>20</td>
<td>98</td>
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<td>Et</td>
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<td>50</td>
<td>95</td>
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