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Ionic liquid promoted an improved synthesis of 3,4-dihydropyrimidinones using [bmim]BF_4 immobilized Cu (II) acetylacetonate as recyclable catalytic system

Suman L. Jain, Jomy K. Joseph, and Bir Sain*

Chemical and Biotechnology Division, Indian Institute of Petroleum, Dehradun 248005, India

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An improved method for the synthesis of 3,4-dihydropyrimidinones by one pot cyclocondensation of aldehyde, *β*-dicarbonyl compound and urea with significant enhancement in reaction rates using room temperature ionic liquid [bmim] BF_4 immobilized $Cu(acac)_2$ as recyclable catalytic system is described.

KEY WORDS: Biginelli reaction; ionic liquid; copper acetylacetonate; recyclable system.

1. Introduction

In the recent years, evolution of chemical reactions involving less hazardous, environmentally acceptable and recyclable catalytic systems is gaining considerable attention both in industrial and academia research [1]. However, most of the existing processes in organic synthesis involving toxic and volatile organic solvents as reaction media, which are environmentally unacceptable from green chemistry, view points. Replacement of these conventional solvents with their green alternatives such as room temperature ionic liquids, water and supercritical fluids is become a fast developing area in present day organic synthesis [2–3]. Room temperature ionic liquids (RTLs), possess several unique properties such as nonvolatile nature, good solvating ability, high thermal stability, tunable melting points, negligible vapor pressure, recyclability and also lead to the significant improvements in reaction rates and yields of the desired products [4–8]. Because of their green credentials and potential to enhance catalytic efficiency/life time by recycling of catalyst, room temperature ionic liquids are finding increasing applications as reaction media for organic reactions as well as for immobilization of transition metal catalysts [9]. 3,4-Dihydropyrimidinones denoted as Biginelli compounds, and their derivatives are highly important heterocyclic units in the realm of natural and synthetic organic chemistry that possess diverse therapeutic and pharmacological properties including antiviral, antitumor, antibacterial and anti-inflammatory activities [10–13]. Furthermore, these compounds have emerged as calcium channel blockers, antihypertensive agents and α-1a-adrenergic antagonists. Owing to the wide range of pharmacological and biological activities, the synthesis of these compounds has become an important target in current years. Biginelli reaction first reported in 1893, [14] involving acid catalyzed one-pot cyclocondensation of aldehyde, dicarbonyl compound and urea is a simple and direct approach for their synthesis. However limitations associated with this method are poor yields particularly in case of substituted aldehydes and use of strong acidic conditions. Subsequently, several improved protocols using lewis acids [15–18] such as $BF_3{\cdot}OEt_2$, $CdCl_2$, $NiCl_2$, $FeCl_3$, triflates, solid acid catalysts [19–20], microwave assisted [21–23], ultasound irradiated [24–25] have been reported in the literature. Recently Peng and Deng [26] reported the Biginelli condensation employing [bmim]BF_4 and [bmim}PF_6 as catalysts under solvent free conditions. Herein, we wish to report an efficient, simple and recyclable protocol with the significant enhancements in reaction rates for the synthesis of 3,4-dihydropyrimidinones using [bmim]BF_4-immobilized copper(II)acetylacetonate as recyclable catalytic system under mild reaction conditions.

2. Results and discussion

Initially, we studied the cyclocondensation of benzaldehyde, urea and ethyl acetoacetate in the presence of 5 mol% $Cu(acaca)_2$ immobilized in [bmim]BF_4 (1 mL) at 50 °C. The reaction was completed within 15 min and desired dihydropyrimidinone was obtained in 98 % isolated yield. This remarkable activation in reaction rate, prompted us to explore the potential of this protocol for the synthesis of a variety of 3,4-dihydropyri-

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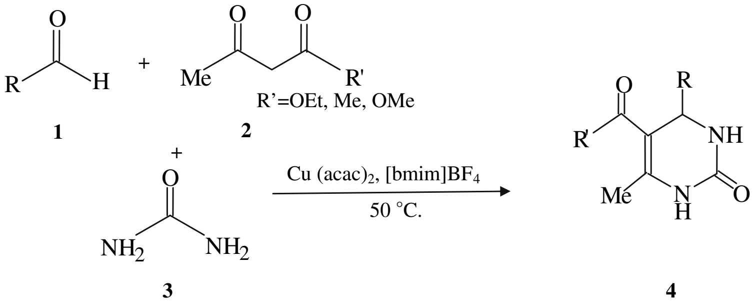
*To whom correspondence should be addressed.
E-mail: birsain@iip.res.in



Scheme 1.

midinones. A variety of aliphatic, heterocyclic and aromatic aldehydes were subjected to react with urea and β-dicarbonyl compound in the presence of 5 mol % Cu(acaca)$_2$ immobilized in [bmim]BF$_4$ under similar reaction conditions. All the aldehydes studied were smoothly converted to the corresponding 3,4-dihydropyrimidinones in excellent yields, which were identified by comparing their physical (mps) and spectral data (1H NMR and IR) with those of authentic samples. The use of both β-ketoesters and 1,3-dicarbonyl compound (acetylacetone) reacted smoothly under described reaction conditions and afforded better yields of the corresponding 3,4-dihydropyrimidinones. To evaluate the effect of copper acetylacetonate, we studied the condensation of benzaldehyde, urea and ethylacetoacetate using [bmim]BF$_4$ (1 mL) alone without adding copper acetylacetonate at 50 °C under the described reaction conditions. In the absence of catalyst, reaction was found to be slow and required longer reaction time (1h), indicating that copper acetylacetonate to be a promoter for this reaction in ionic liquid.

To investigate the reusability of the catalyst we performed the cyclocondensation of benzaldehyde, urea and ethyl acetoacetate under similar reaction conditions. After completion, product was separated by extraction with diethyl ether and ionic liquid layer containing Cu(acac)$_2$ was reused as such for subsequent experiments for 3 runs without aid of further catalyst under these reaction conditions. The reaction was found to proceed smoothly, afforded comparable isolated yields of the product as 98, 97, and 97 % respectively, indicating the recyclability and reusability of the catalyst and ionic liquid both. Further in the fourth run it was found to be slight decrease in the isolated yield of the desired 3,4-dihydropyrimidinone (94%). To compare the efficiency of this method, we carried out the cyclocondensation of benzaldehyde, urea and ethyl acetoacetate in various organic solvents such as acetonitrile, ethanol, dichloroethane and THF (1 mL) in place of ionic liquid using 5 mL % Cu(acac)$_2$ as catalyst under similar reaction conditions. These results are presented in the Table 2. In general, the reaction was found to be very slow in organic solvents and afforded poor yields of the desired product. Use of 5 mol% Cu(acac)$_2$ immobilized in [bmim]BF$_4$ (1 mL) was found to be optimum for maximum yield and reaction time points of view.

In the present system, the use of ionic liquid as reaction medium makes it possible to recycle the homogeneous catalyst there by making the process more environmental friendly. Also the use of copper acetylacetonate in conjunction with [bmim]BF$_4$ showed rate enhancements, high yields and short reaction times in this transformation.

3. Experimental

All the solvents and aldehydes were commercially available and purified before use. Room temperature ionic liquid [bmim]BF$_4$ and copper acetylacetonate were purchased from Aldrich and used as such.

3.1. *Typical experimental procedure*

To a stirred solution of benzaldehyde (5 mmol, 535 mg), urea (5 mmol, 300 mg) and ethylacetoacetate (5 mmol, 650 mg) in ionic liquid [bmim]BF$_4$ (1 mL) was added copper(II) acetylacetonate (5 mol%) and the mixture was heated at 50 °C for 15 min. The progress of reaction progress was monitored by TLC (SiO$_2$) using ethyl acetate/ hexane (4:6) as eluent. After completion the reaction, the product was separated by extraction with diethyl ether, ionic liquid layer was further washed with diethyl ether for two times. The combined ether layer was dried over anhydrous MgSO4 and evaporated the solvent to afford pure 5- ethoxycarbony-6-methyl-4-phenyl-3,4-dihydropyrimidin-2-one in 98 % yield, mp. 201 °C (202 °C).[27]. Similarly other aldehydes were reacted with urea and β-dicarbonyl compound and their reaction times and yields are presented in Table 1.

3.2. *Spectral data of selected compounds*

5-(ethoxycarbony)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (Table 1, entry 4a): mp 201 °C (202 °C)[27]; IR (KBr): 3240, 1725, 1635 cm-1; ^{1}H

Table 1
Synthesis of 3,4-dihydropyrimidinones by $Cu(acac)_2$-immobilized in $[bmim]BF_4$[a]

Entry	Product	R	R’	Reaction time/min	Yield[a] (%)[b]
1	4a	C_6H_5	OEt	60	85[c]
2	4a	C_6H_5	OEt	15	98
3	4b	$4\text{-}CH_3C_6H_4$	OEt	30	96
4	4c	$4\text{-}CH_3OC_6H_4$	OEt	30	95
5	4d	$4\text{-}NO_2C_6H_4$	OEt	25	94
6	4e	$4\text{-}ClC_6H_4$	OEt	25	92
7	4f	$2\text{-}ClC_6H_4$	OEt	30	90
8	4g	$4\text{-}(CH_3)_2NC_6H_4$	OEt	25	86
9	4h	$2,6\text{-}Cl_2C_6H_3$	OEt	35	89
10	4i	2-pyridyl	OEt	50	87
11	4j	2-Furyl	OEt	50	82
12	4k	$n\text{-}CH_3CH_2CH_2$	OEt	20	92
13	4l	$(CH_3)_2CH$	OEt	15	90
14	4m	$n\text{-}CH_3(CH_2)_2CH_2$	OEt	20	92
15	4o	C_6H_5	CH_3	15	96
16	4p	$4\text{-}NO_2C_6H_4$	CH_3	25	93
17	4q	$4\text{-}CH_3OC_6H_4$	CH_3	20	92
18	4s	C_6H_5	OMe	20	96
19	4t	$4\text{-}NO_2C_6H_4$	OMe	25	94

[a] *Reaction conditions:*aldehyde (5 mmol), urea (5 mmol), β-dicarbonyl compound (5 mmol), $Cu(acac)_2$ (5 mol%) and $[bmim]BF_4$ (1 mL) at 50 °C.

[b] *Isolated yields.*

[c] Experiment carried out in the absence of copper acetylacetonate.

NMR: δ = 9.20 (s, 1H, NH), 7.75 (s, 1H, NH), 7.10–7.28 (m, 5H, arom CH), 5.14 (s, 1H, CH), 3.97 (q, 2H, OCH_2), 2.25 (s, 3H, CH_3), 1.09 (t, 3H, OCH_2CH_3).

5-(Ethoxycarbonyl)-6-methyl-4-(4-methylphenyl)-3, 4-dihydropyrimidin-2(1H)-one (Table 2, entry 4b): mp 214–15°C (215°C) [27]; IR (KBr): 3242, 1715, 1633 cm-1; ^{1}H NMR: δ = 9.16 (s, 1H, NH), 7.80 (s, 1H, NH), 7.16–7.12 (m, 4H, arom CH), 5.09 (s, 1H, CH), 3.96 (q, 2H, OCH2CH3), 2.27 (s, 3H, C6H4-CH3), 2.21 (s, 3H, CH3), 1.08 (t, 3H, OCH2CH3).

5-(Ethoxycarbonyl)-6-methyl-4-(4-nitrophenyl)-3, 4-dihydropyrimidin-2(1H)-one (Table 2, entry 4d): mp 207–08°C(210 °C) [27]; IR (KBr): 3239, 1724, 1645, cm-1; ^{1}H NMR: δ = 9.27 (s, 1H, NH), 8.20 (d, 2H, arom CH), 7.91 (s, 1H, NH), 7.50 (d, 2H, arom CH), 5.18 (d, 1H, CH), 3.79 (q, 2H, OCH_2), 2.25 (s, 3H, OCH2CH_3), 1.10 (t, 3H, CH_3).

Table 2
Effect of various solvents[a]

Entry	Solvent	Reaction times (min)	Yields (%)[b]
1	Acetonitrile	60	70
2	Ethanol	50	80
3	Dichloroethane	60	45
4	$[bmim]BF_4$	15	98
5	THF	60	40

[a] *Reaction Conditions:*Benzaldehyde (5 mmol), ethylacetoacetate (5 mmol), urea(5 mmol), solvent (1 mL), $Cu(acac)_2$ (5 mol%) at 50 °C.

[b] *Isolated yields.*

4-(p-Chlorophenyl)-5-(ethoxycarbonyl)-6-methyl-3, 4-dihydropyrimidin-2(1H)-one (Table 2, entry 4e): mp 210–12 °C (212–13 °C) [27]; IR (KBr): 3240, 1723, 1643 cm-1; ^{1}H NMR: δ = 9.26 (s, 1, NH), 7.79 (s, 1H, NH), 7.40–7.30 (m, 4H, arom CH), 5.14 (s, 1H, CH), 3.99 (q, 2H, OCH_2), 2.25 (s, 3H, CH_3), 1.09 (t, 3H, OCH_2CH_3).

5-(Ethoxycarbonyl)-4-(2-furyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 4j): mp 202–04 °C (204.5–05°C) [27]; IR (KBr): 3239, 1705, 1644 cm-1; ^{1}H NMR: δ = 9.22 (s, 1H, NH), 7.74 (s, 1H, NH), 7.53 (d, 1H, furyl CH), 6.30–6.08 (d, 2H, furyl-CH), 5.20 (s, 1H, CH), 4.02 (q, 2H, C$H_2$$CH_3$), 2.22 (s, 3H, C$H_3$), 1.12 (t, 3H, OCH_2CH_3).

4-n-Butyl-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 4m): mp 157 °C (157–58°C) [27]; IR (KBr): 3242, 1715, 1647 cm-1; ^{1}H NMR: δ = 9.02 (s, 1H, NH), 7.59 (s, 1H, NH), 4.65 (t, 1H, CH), 4.05 (m, 2H, OCH_2), 2.16 (s, 3H, CH_3), 1.40–1.15 (m, 6H, –(CH_2)$_3$–), 1.05 (t, 3H, CH_3), 0.85 (t, 3H, CH_3).

5-(Ethoxycarbonyl)-6-methyl-4-styryl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 4n): mp 233–34°C (232–35°C) [27]; IR (KBr): 3246, 1704, 1650 cm-1; ^{1}H NMR: δ = 9.12 (s, 1H, NH), 7.79 (s, 1H, NH), 7.42–7.25 (m, 5H, arom CH), 6.33 (d, 1H, HC = CH), 6.20 (dd, 1H, CH = CH), 4.74 (d, 1H, CH), 4.09 (q, 2H, OCH_2), 2.20 (s, 3H, CH_3), 1.10 (t, 3H, OCH_2CH_3).

5-Aceto-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 4o): mp 233–34 °C (236°C) [27]; IR (KBr): 3241, 1715, 1643 cm-1; ^{1}H NMR: δ = 9.20 (s, 1H, NH), 7.76 (s, 1H, NH), 7.35–7.25 (m, 5H, arom CH), 5.25 (s, 1H, CH), 2.24 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3).

5-(Methoxycarbonyl)-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (Table 2, entry 4s): mp 207–08°C IR (KBr): 3231, 1700, 1641 cm-1; ^{1}H NMR: δ = 9.23 (s, 1H, NH), 7.77 (s, 1H, NH), 7.35–7.25 (m, 5H, arom CH), 5.15 (d, 1H, CH), 3.53 (s, 3H, OCH_3), 2.20 (s, 3H, CH_3).

4. Conclusion

In summary, we have described the use of ionic liquid $[bmim]BF_4$ as green and recyclable reaction media as well as promoter for the Biginelli condensation of various aldehydes, urea and β-dicarbonyl compounds to afford corresponding 3,4-dihydropyrimidinones using catalytic amount of copper acetylacetonate in excellent yields and very short reaction times. The considerable enhancement in reaction rates, recyclability of the reaction medium without loss in activity, high yields, shorter reaction times as compared to those obtained using $[bmim]BF_4$ as catalyst, make this procedure useful and environementally benign tool for the synthesi of 3,4-dihydropyrimidones.

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