



Ionic liquids catalyzed Biginelli reaction under solvent-free conditions

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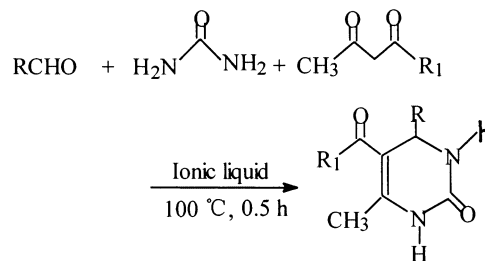
Received 23 April 2001; revised 18 June 2001; accepted 22 June 2001

Abstract—3,4-Dihydropyrimidin-2(1*H*)-ones were synthesised in high yields by one-pot three-component Biginelli condensation in the presence of room temperature ionic liquids such as 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (BMImBF₄) or hexafluorophosphate (BMImPF₆) as catalysts under solvent-free and neutral conditions. © 2001 Elsevier Science Ltd. All rights reserved.

Recently, the interest in synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones (denoted as Biginelli compounds) and their derivatives is increasing tremendously because of their therapeutic and pharmacological properties and also because of interesting biological activities of several marine alkaloids which contain the dihydropyrimidine nucleus.^{1–4} Synthetic strategies for the dihydropyrimidine nucleus involves one-pot to multi-step approaches. The classical Biginelli synthesis is a one-pot condensation using β -dicarbonyl compounds with aldehydes (aromatic and aliphatic aldehydes) and urea or thiourea in ethanol solution containing catalytic amounts of acid.⁵ This method, however, involves long reaction times, harsh reaction conditions and unsatisfactory yields. Improvements in such syntheses have been sought continuously. Recently, it was reported that Lewis acids (such as BF₃·OEt₂) in combination with transition metals and a proper proton source were effective catalysts for this reaction.² Dihydropyrimidines were also synthesized in high yields by one-pot cyclocondensation of aldehydes, acetoacetates and urea using various acid catalysts like Amberlyst-15, Nafion-H, KSF clay and dry acetic acid under microwave irradiation.^{6,7} More recently, lanthanide triflate,¹ lanthanum chloride,⁸ ferric chloride hexahydrate,⁹ and indium chloride¹⁰ as catalysts for the one-pot syntheses of dihydropyrimidinones were also reported.

On the other hand, because of the great potential of room temperature ionic liquids as environmentally benign media for catalytic processes, much attention has currently been focused on organic reactions catalyzed by ionic liquids, several organic reactions catalyzed by ionic liquids have been reported with high performance.^{11–16} This offered some new clues that using ionic liquids as catalysts for those traditionally acid–base synthetic reactions may not only be possible but also practical and even highly efficient.

Our new approach reported herein involves the use of room temperature ionic liquids based on 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (BMImBF₄) or hexafluorophosphate (BMImPF₆)¹⁷ as catalysts for the Biginelli condensation reaction under solvent-free conditions.



R = C₆H₅, 4-(CH₃O)-C₆H₄, 4-(Cl)-C₆H₄,

4-(NO₂)-C₆H₄, C₅H₁₁

R₁ = OEt, CH₃

Keywords: ionic liquid; Biginelli reaction; 3,4-dihydropyrimidin-2(1*H*)-ones; one-pot process.

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1-*n*-Butyl-3-methylimidazolium tetrafluoroborate (BMImBF₄) and hexafluorophosphate (BMImPF₆) ionic liquids were, respectively, synthesized according to the procedures reported in previous literatures.¹⁷

Typical experimental procedures were as follows: Aldehyde (25.0 mmol), β-dicarbonyl compound (25.0 mmol), urea (37.5 mmol) and BMImBF₄ (0.05–0.2 mmol) were successively charged into a 50 ml round-bottomed flask with a magnetic stirring bar. Then the reaction proceeded at 100°C for 30 min during which time a solid product gradually formed. After the reaction, the resulting solid product with pale yellow color was crushed, washed with water, filtered and dried in vacuo to afford the primary product. A pure product was obtained by further recrystallization of the primary product with ethyl acetate. The characterization of the products is well known, therefore only the basic identifications including FT-IR (IFS 120HR, Bruker), ¹H NMR (FT-80A, using TMS as internal standard) and melting points measurements, were conducted.

The results of ionic liquids catalyzed Biginelli reactions are shown in Table 1. Firstly, no desirable product could be detected when a mixture of benzaldehyde, ethyl acetoacetate and urea (mole rate 1:1:1.5) was heated at 100°C for 30 min in the absence of ionic liquids (entry 1), indicating a catalyst must be needed for the Biginelli reaction. Then, the condensation reaction of benzaldehyde, ethyl acetoacetate in stoichiometric ratio and urea in slightly excess amount was tested in the presence of different amounts of BMImBF₄, i.e. 0.2, 0.4 and 0.8 mol% BMImBF₄ relative to the amount of benzaldehyde (entries 2, 3 and 4) at 100°C without any additional solvent. Isolated yields of 85, 92 and 95%, respectively, could be achieved after the reaction had only proceeded for 30 min. This indicates that the conversion was increased with increasing amounts of ionic liquid.

With 0.4 mol% of BMImBF₄ as catalyst, aromatic aldehydes with either electron-donating or electron-withdrawing substituents (entries 5, 6 and 7) were also used as one of the substrates. It can be seen that all reacted very well and the yields achieved from the aromatic aldehydes with electron-donating substituents were slightly higher than aromatic aldehydes with electron withdrawing substituents.

Under the same reaction conditions and substrates as entries 3, 5, 6 and 7, BMImPF₆ as catalyst was also examined (entries 8, 9, 10 and 11). Even higher yields, i.e. 94, 98, 98 and 92%, respectively, were obtained in comparison with BMImBF₄ as catalyst, indicating that the BF₄⁻ and PF₆⁻ anions have some impact on the catalytic performance, and the PF₆⁻ anion is more favorable for such reactions.

Under the same reaction conditions as entry 3, *n*-hexyl aldehyde, which replaced the aromatic aldehyde as one of the substrates, was tested and 4-*n*-pentyl-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one was produced in 93% yield (entry 12). This shows that aliphatic aldehydes exhibit analogous behavior to that of aromatic aldehydes, and this characteristic was similar to that of lanthanide triflate as catalyst.¹ Furthermore, the experimental results showed that besides ethyl acetoacetate, acetylacetone can also be used as one of the substrates. The highest yield was obtained for the benzaldehyde, acetylacetone and urea three-component Biginelli condensation (entry 13), and the corresponding yield was also improved for the 4-nitrobenzaldehyde, acetylacetone and urea three-component Biginelli condensation (entry 14), in comparison with the result of entry 7. For the purpose of comparison, toluene (10 ml, entry 15) was added into the reaction system, which was employed in entry 14, and the possible influence of solvent was examined. The reaction was refluxed at 100°C for 2 h, and the yield was

Table 1. Ionic liquids catalyzed Biginelli reactions under solvent-free conditions^a

Entry	Ionic liquid (mmol)	Amount of ionic liquid (mol%)	R	R ₁	Isolation yield (%)
1	None	0	C ₆ H ₅	OC ₂ H ₅	0
2	BMImBF ₄ (0.05)	0.2	C ₆ H ₅	OC ₂ H ₅	85
3	BMImBF ₄ (0.1)	0.4	C ₆ H ₅	OC ₂ H ₅	92
4	BMImBF ₄ (0.2)	0.8	C ₆ H ₅	OC ₂ H ₅	95
5	BMImBF ₄ (0.1)	0.4	4-(CH ₃ O)-C ₆ H ₄	OC ₂ H ₅	95
6	BMImBF ₄ (0.1)	0.4	4-(Cl)-C ₆ H ₄	OC ₂ H ₅	96
7	BMImBF ₄ (0.1)	0.4	4-(NO ₂)-C ₆ H ₄	OC ₂ H ₅	90
8	BMImPF ₆ (0.1)	0.4	C ₆ H ₅	OC ₂ H ₅	94
9	BMImPF ₆ (0.1)	0.4	4-(CH ₃ O)-C ₆ H ₄	OC ₂ H ₅	98
10	BMImPF ₆ (0.1)	0.4	4-(Cl)-C ₆ H ₄	OC ₂ H ₅	98
11	BMImPF ₆ (0.1)	0.4	4-(NO ₂)-C ₆ H ₄	OC ₂ H ₅	92
12	BMImBF ₄ (0.1)	0.4	<i>n</i> -Pentyl	OC ₂ H ₅	93
13	BMImBF ₄ (0.1)	0.4	C ₆ H ₅	CH ₃	99
14	BMImBF ₄ (0.1)	0.4	4-(NO ₂)-C ₆ H ₄	CH ₃	92
15 ^b	BMImBF ₄ (0.1)	0.4	4-(NO ₂)-C ₆ H ₄	CH ₃	77
16	BMImCl (0.1)	0.4	C ₆ H ₅	OC ₂ H ₅	56
17	<i>n</i> -Bu ₄ NCl (0.1)	0.4	C ₆ H ₅	OC ₂ H ₅	0

Reaction conditions: RCHO 25.0 mmol, CH₃COCH₂COR₁ 25.0 mmol, urea 37.5 mmol, 100°C, 0.5 h.

^a All products were characterized by FT-IR, ¹H NMR and their melting points in comparison with that of previous literatures.

^b Refluxed in toluene (10 ml) in the presence of BMImBF₄ (0.1 mmol) for 2 h.

lower than that obtained in entry 14. Finally, the catalytic performances of two kinds of quaternary ammonium salts used as catalyst were also tested (entries 16 and 17). Low reaction yield was obtained, and the reaction of Biginelli condensation could almost not be observed when the BMImCl (1-*n*-butyl-3-methylimidazolium chloride) and *n*-Bu₄NCl was used as catalyst, respectively. This indicated that both cation and anion in the ionic liquids played an important role as the catalyst towards the Biginelli condensation.

In summary, a novel method for the synthesis of dihydropyrimidinones by three-component Biginelli condensations of aldehydes with β -dicarbonyl compounds and urea using room temperature ionic liquids as catalyst under solvent-free and neutral conditions was developed on high yield for the first time. The main advantages of this methodology are: (1) relatively simple catalyst system; (2) shorter reaction times; (3) higher yields; (4) free of organic solvent, and (5) easy synthetic procedure. Further investigations of the scope and mechanism of this reaction are under way.

Acknowledgements

This work was financially supported by Science Foundation of the Personal Ministry of China.

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