

Convenient and efficient protocols for coumarin synthesis via Pechmann condensation in neutral ionic liquids

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Abstract

Neutral ionic liquids with catalytic amount of acid have been employed for coumarin synthesis via Pechmann condensation of phenols and ethyl acetoacetate under ambient conditions. The reaction was also successfully carried out at high temperature in 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquid, without the use of any acid catalyst. The possibility of Brønsted acidic ionic liquids catalysing this reaction has also been investigated. Ionic liquids were recycled efficiently.

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1. Introduction

Pechmann condensation of phenols with β -ketonic esters in the presence of various acidic reagents is the most widely employed method for coumarin synthesis [1,2]. Coumarins remain an important class of compounds. Scientists have shown keen interest in synthesizing coumarins in view of their anticoagulant properties [3] as well as their use in the syntheses of insecticides and optical brighteners [4]. Several methods have been employed for the synthesis of coumarins that include the use of solid acid catalysts [5–7], microwave irradiation or a combination of both [8,9]. Recently, sulfamic acid has been employed for the Pechmann condensation [10].

Ionic liquids as new generation solvents have proved their utility in various reactions of synthetic importance [11–13]. Apart from tunable physical and chemical properties of ionic liquids, their immiscibility with various organic solvents enables the biphasic separation of the desired products. We have employed the ionic liquids for useful synthetic transformations and also for enzyme catalysed reactions [14–19]. Pre-

viously, we have reported coumarin synthesis via the Pechmann condensation in Lewis acidic chloroaluminate ionic liquid [15]. In the above protocol, ionic liquid plays the dual role of solvent and Lewis acid catalyst providing a quick and efficient route to the synthesis of coumarins. This route furnishes excellent yields in short time under ambient conditions, as compared to other conventional methods. However, there are some disadvantages associated with the use of chloroaluminate ionic liquids; they are moisture sensitive and cannot be recycled after the reaction. In the present study, we have adopted two different approaches to the Pechmann condensation employing neutral ionic liquids to establish cleaner synthetic methodologies.

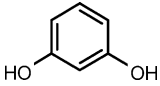
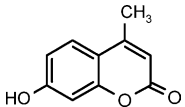
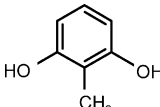
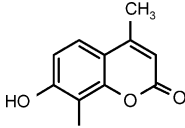
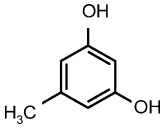
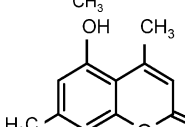
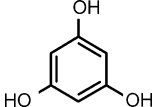
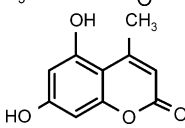
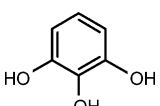
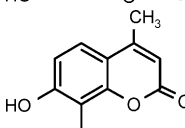
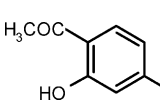
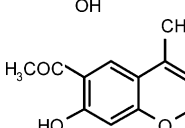
2. Experimental

2.1. Material

Ionic liquids were prepared by the procedures given in the literature and purified by the modifications suggested by Park and Kazlauskas [20]. All other chemicals and reagents were of analytical grade and used as received.

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Table 1
Coumarin synthesis via Pechmann condensation in neutral ionic liquids by two alternate methodologies

Entry	Substrate	Product	Time (min)	Method A		Method B
				Temperature (°C)	Yield ^a (%)	Yield ^a (%)
1.			45	30	95	91
2.			45	30	92	90
3.			45	30	92	92
4.			45	30	94	95
5.			45	30	91	90
6.			60	100	47	–

Method A—by employing neutral ionic liquids [bmim]PF₆ or [bmim]BF₄ with catalytic amount of POCl₃; Method B—by employing [bmim]PF₆ ionic liquid at 100 °C for 45 min without any acid catalyst.

^a Isolated yields.

2.2. General experimental procedure for the POCl₃ catalysed Pechmann condensation in neutral ionic liquids

To a homogeneous mixture of ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF₆) (4 ml), phenol (10 mmol) and ethyl acetoacetate (10 mmol), POCl₃ (3 mmol) was added and the reaction mixture was stirred for the time and temperature as shown in Table 1. The reaction was quenched by addition of 10% aqueous NaOH solution. Coumarins can then be separated from the aqueous layer by neutralization with 6 N HCl.

2.3. General experimental procedure for the Pechmann condensation in [bmim]PF₆ ionic liquid without any acid catalyst

The reaction was performed by using 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF₆) ionic liquid, and following similar procedure as mentioned above except that neither POCl₃ nor any other acid catalyst was used in the reaction. The reaction was carried out at 100 °C. The reaction was quenched by addition of

10% aqueous NaOH solution. Coumarins can then be separated from the aqueous layer by neutralization with 6 N HCl.

2.4. General experimental procedure for the recycling of ionic liquids

The ionic liquid that settled down, after quenching the reaction mixture with 10% aqueous NaOH solution, was extracted with dichloromethane. The dichloromethane layer was stirred vigorously with 10% aqueous NaOH in order to remove coumarin and acid traces. Further, dichloromethane layer was washed with water. The solvent was then evaporated and resultant ionic liquid was subjected to consecutive extractions with diethyl ether to remove organic impurities present. The resultant ionic liquid was then dried under vacuum at 60 °C and reused for subsequent reactions.

2.5. General work up procedure and recyclability of [bmim]BF₄ ionic liquid

When 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄) ionic liquid, was used for the reaction, the

reactions were quenched by addition of water. The coumarin derivative separated as a solid was isolated by filtration. The ionic liquid was recovered by evaporation of water on a rotary evaporator. The ionic liquid was further purified as per the procedure used for the purification of [bmim]PF₆ ionic liquid.

3. Results and discussions

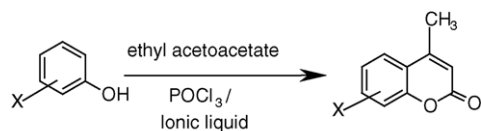
Because of their negligible vapour pressure, thermal stability and easy recyclability, neutral ionic liquids have been referred to as environmentally benign solvents. These ionic liquids have been employed as excellent and recyclable medium for a wide array of reactions; e.g., Heck reaction [21], Bischler–Napierlaski cyclisation [22], Beckmann rearrangement [23] addition of thiols to unsaturated ketones [24] and L-proline catalysed aldol reaction [25].

We thought it would be advantageous to employ these neutral ionic liquids for Pechmann condensation and also emphasized the recyclability of the medium. We have carried out the Pechmann condensation of phenols and ethyl acetoacetate catalysed by POCl₃ in 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF₆) and 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄) ionic liquids for the first time (Scheme 1).

Phenols bearing electron-donating groups show excellent reactivity and furnish almost quantitative yields at room temperature as shown in Table 1. We examined several acid catalysts for the reaction such as phosphorus pentoxide, phosphorus oxychloride, trifluoroacetic acid and 4-toluene sulphonic acid. The reaction proceeded smoothly at room temperature by using phosphorus oxychloride (POCl₃) giving high yield of coumarins.

To study the extent of percent conversion as a function of time, we chose resorcinol as a model substrate and its reaction with ethyl acetoacetate in [bmim]PF₆ or [bmim]BF₄ was studied under similar experimental conditions for different times. Both the ionic liquids gave almost similar results; Fig. 1 demonstrates high initial rates of the reaction. The maximum yield was obtained in 45 min and no significant change in yield was observed thereafter, even if the reaction continued up to 2 h.

[bmim]PF₆ ionic liquid is known to release hydrofluoric acid (HF), when it comes in contact with moisture. This prompted us to investigate the possibility of HF acting as a catalyst in the Pechmann condensation. Conse-



Scheme 1. Pechmann condensation of phenols and ethyl acetoacetate in neutral ionic liquids catalysed by POCl₃.

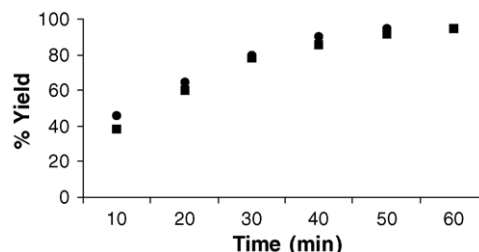


Fig. 1. Correlation between time and percent yield of the reaction between resorcinol and ethyl acetoacetate catalysed by POCl₃ in ionic liquid, [bmim]BF₄ (■) and [bmim]PF₆ (●), at room temperature.

quently, three reactions of resorcinol and ethyl acetoacetate at room temperature were designed for this particular study. First two reactions were carried out using POCl₃ as a catalyst in ionic liquid. In one of those reactions, ionic liquid prepared by reported routine procedure was used. On the other hand, for the second reaction, the ionic liquid was pretreated as per the method suggested by Park and Kazlauskas [20] (the method ensures the removal of known impurities of ionic liquid along with the acidic impurities, if any) and the reaction was carried out under inert atmosphere. The third reaction was carried out in ionic liquid without adding POCl₃. The observed results are presented in Table 2.

The results led us to conclude that HF is not participating in the reaction since no reaction was observed in the third experiment wherein POCl₃ was not used and amongst first two reactions, which were carried out using catalyst, no change in percent yield was observed.

A noteworthy feature of ionic liquid is their recyclability. In the present study, we investigated that ionic liquid, which was used in combination with POCl₃, can be recycled. Ionic liquids have been reused for consecutive four cycles without loss in their efficiency.

[bmim]PF₆ liberates traces of HF when it comes in contact with moisture or heated at high temperature. We thought it would be worthwhile to take advantage of this fact and decided to carry out the Pechmann condensation at high temperature in this ionic liquid.

We studied the reaction of different activated phenols such as resorcinol, pyrogallol and phloroglucinol, etc., with ethyl acetoacetate at high temperature (100 °C) in [bmim]PF₆

Table 2
Comparison of yields for reaction of resorcinol and ethyl acetoacetate carried out at room temperature under different conditions

Reaction	Percent yield
1 ^a	95
2 ^b	92
3 ^c	No reaction

^a Ionic liquid prepared by routine procedure and POCl₃.

^b Ionic liquid pretreated as per the procedure given in ref. [20] and POCl₃.

^c Ionic liquid without POCl₃.

Table 3

Recyclability of [bmim]PF₆ ionic liquid in Pechmann condensation performed at 100 °C

Run no.	Percent yield
1	95
2	92
3	94

without addition of any acid catalyst. The reactions proceeded smoothly offering excellent yields of coumarins. The yields of the reactions at high temperature were comparable to those obtained by employing chloroaluminate ionic liquids or neutral ionic liquids with catalytic amount of acid at room temperature. Interestingly, [bmim]PF₆ ionic liquid can be recycled efficiently and it was used consecutively for three runs without any considerable loss in its activity as shown in Table 3.

Further, we thought of using Brønsted acidic ionic liquids [26] in place of chloroaluminate ionic liquids for Pechmann condensation. Two ionic liquids namely, 1-methylimidazolium *p*-toluenesulfonic acid ([Hmim]Tsa) and 1-methylimidazolium trifluoroacetic acid ([Hmim]Tfa) have been employed, since these ionic liquids proved to be very efficient media for Mannich reaction [27]. We observed that neither of the ionic liquids mentioned above gave us the required conversion at room temperature as well as at high temperature.

4. Conclusion

To conclude, we have demonstrated the use of neutral ionic liquids, 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF₄) and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF₆) for Pechmann condensation as a recyclable media. [bmim]PF₆ ionic liquid, in particular has been employed at high temperature without any acid catalyst providing cleaner and economically viable protocol for Pechmann condensation. Further investigations regarding mechanism of the reaction in this novel medium and use of this recyclable medium for Fisher indole synthesis are in progress.

Acknowledgements

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