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L-Proline as an efficient and reusable promoter for the synthesis of coumarins in ionic liquid

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Abstract: The effect of L-proline as a promoter on the condensation reaction of salicylaldehyde or its derivatives with ethyl acetoacetate in neutral ionic liquid [emim]BF_4 was studied. All reactions were carried out under mild reaction conditions and achieved high yields. Moreover, the ionic liquid containing L-proline could be recycled and reused for several times without noticeably decreasing in productivity. The results show that the L-proline-[emim]BF_4 system has a potential in contribution to the development of environmentally friendly and inexpensive processes in organic syntheses.

Key words: L-Proline, Ionic liquid, Coumarins, Knoevenagel condensation
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INTRODUCTION

The Knoevenagel condensation has often been used to prepare substituted coumarin, one of the most important chemicals in the cosmetics, agricultural, pharmaceutical and material industries for its bioactivity and photodynamic effect (Kostova *et al*., 1993; Palmer and Josephs, 1995; Mitra *et al*., 1998; Wang *et al*., 2002). Highly efficient reactions have been reported, involving the condensation of salicylaldehydes with malonates in the presence of piperidine under microwave conditions (Bogdal, 1998), and the use of montmorillonite KSF (Bigi *et al*., 1999) which requires high temperature and long reaction time (100 °C, 24 h). Solid-phase syntheses of 3-alkoxycarbonylcoumarins (Watson and Christiansen, 1998) and 3-acetylcoumarin utilizing the polymer reagent (vanden Eynde and Rutot, 1999) were also reported; however, they are not so effective in terms of yield and purity of products or recyclability of the polymer reagent. Furthermore, although $P(RNCH_2CH_2)_3N$ as an efficient promoter (Kisanga *et al*., 2002) has been introduced recently, the reaction has to be conducted in benzene or isobutyronitrile, which are not environmentally friendly solvents. Alternatively, coumarins could also be synthesized by other methods including Pechmann (Gu *et al*., 2005; Fang *et al*., 2008), Perkin (Camur and Bulut, 2008), Reformatsky (Chen *et al*., 2005), Wittig (Yavari *et al*., 1998) reactions, and by flash vacuum pyrolysis (Cartwright and McNab, 1997).

Room temperature ionic liquids are emerging as potential green alternatives to volatile organic solvents, and recently have been used as environmentally benign media for several important reactions due to their unique physical and chemical properties. L-Proline in combination with ionic liquids has proved to be an efficient system for Knoevenagel condensation (Wang *et al*., 2006), direct asymmetric aldol reactions (Loh *et al*., 2002; Kotrusz *et al*., 2002; Gruttadauria *et al*., 2004; Salaheldin *et al*., 2004), cross-aldol reactions (Córdova, 2004), Michael additions (Kitazume *et al*., 2003; Hagiwara *et al*., 2004; Kotrusz *et al*., 2004; Rasalkar *et al*., 2005), α-aminations of aldehydes and ketones (Kotrusz *et al*., 2005), Ullmanntype reactions (Wang *et al*., 2005), as

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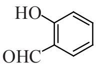
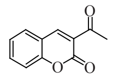
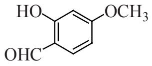
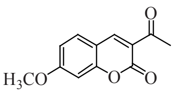
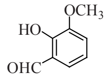
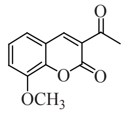
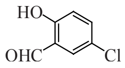
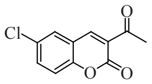
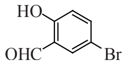
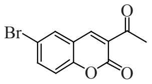
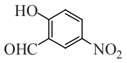
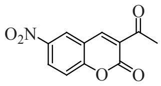
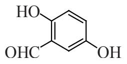
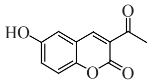
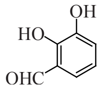
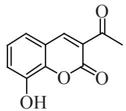
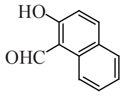
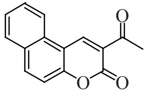
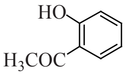
well as Mannich reactions (Chowdari *et al*., 2003). To the best of our knowledge, there is no attempt of the use of L-proline as a promoter in ionic liquid for the synthesis of coumarins. We, therefore, present an efficient and practical synthesis of substituted coumarins from the corresponding salicylaldehyde and ethyl acetoacetate. The method applied here resulted in easier product work-up in this milder condition compared with that reported in the literature, and in high yields (81%~95%). In addition, the ionic liquid containing L-proline could be recycled and reused for several times without noticeably decreasing in productivity in subsequent reactions.

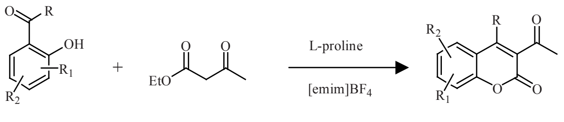
RESULTS AND DISCUSSION

To a dry round bottom flask charged with 2 mmol substrate and 2.1 mmol ethyl acetoacetate, was added the ionic liquid [emim]BF_4 (1 ml), followed by 40 mol% L-proline, and the reaction mixture was stirred at room temperature. At the end of the reaction, water was added with continuous stirring, and then the solid material was filtered off to give high purity products without further purification of column chromatography. The achieved results are summarized in Table 1. The reaction worked well with aromatic salicylaldehydes containing electrondonating

Table 1 Preparation of coumarins via Knoevenagel reaction in ionic liquid [emim]BF_4[a]

Entry	Substrate	Product	Temperature	Time (h)	Yield (%)[b]
1			rt	6	95
2			rt	6	86
3			rt	6	81
4			rt	6	90
5			rt	4	95
6			rt	6	90
7			rt	6	92
8			rt	6	87
9			rt	6	88[c]
10		–	60 °C	24	–

[a]The reaction was conducted with 40 mol% L-proline, 2 mmol salicylaldehyde or its derivatives and 2.1 mmol ethyl acetoacetate in 1 ml ionic liquid [emim]BF_4 at room temperature (rt):



where R=H or CH_3; R_1, R_2=substitute groups. [b]Isolated yields; [c] Washed with CH_3OH

and electron-withdrawing substituents present in the aromatic rings. Compared with salicylaldehyde, the yield of the reaction of 2-hydroxy-1-naphthaldehyde (Table 1, entry 9) with ethyl acetoacetate was a bit low maybe due to hindrance effect, and this was also reflected by the higher yields in entries 2 and 7 compared respectively with entries 3 and 8 in Table 1. However, the reaction between 2-hydroxyacetophenone and ethyl acetoacetate produced no product in this system even when it was stirred at 60 °C for 24 h (Table 1, entry 10), indicating that the presence of methyl prevented the reaction from continuing.

Our efforts began with salicylaldehyde and ethyl acetoacetate in ionic liquid [emim]BF_4 at room temperature without L-proline (Table 2). The catalytic activity of L-proline for these reactions was investigated, and no reaction took place in ionic liquid in 24 h in the absence of L-proline (Table 2, entry 1). When 5 mol% L-proline was added, the reaction yield was 85% (Table 2, entry 2), and when 40 mol% L-proline was added, the reaction yield increased to 95% (Table 2, entry 5). However, using 50 mol% L-proline resulted in lower yield (Table 2, entry 6). The amount of ionic liquid used in the reaction was also optimized, and the results show that the yield increased as the amount of ionic liquid increased from 0.5 ml (Table 2, entry 8) to 1 ml (Table 2, entry 5); however, the yield began to decrease as IL increased to 1.5 ml (Table 2, entry 9). Therefore, the best result was observed when 40 mol% L-proline was used as a promoter in 1 ml ionic liquid. The reaction gave almost no products of CH_3CN, tetrahydrofuran (THF), and CH_2Cl_2, and yielded a low level of dimethyl sulfoxide (DMSO) in the presence of L-proline when the reaction time was prolonged to 48 h. In summary, both L-proline and [emim]BF_4 had an important effect to the reaction: without one of the two, the reaction would not take place.

Table 2 Effect of L-proline and ionic liquid loading on the reaction yield in the Knoevenagel condensation of salicylaldehyde with ethyl acetoacetate[a]

Entry	L-proline (mol%)	Ionic liquid (ml)	Yield (%)[b]
1	0	1	0
2	5	1	85
3	10	1	92
4	30	1	90
5	40	1	95
6	50	1	86
7	40	0	0
8	40	0.5	76
9	40	1.5	80

[a]The reaction was conducted with 2 mmol salicylaldehyde and 2.1 mmol ethyl acetoacetate in the presence of L-proline and/or [emim]BF_4 at room temperature; [b] Isolated yield

Since the L-proline and ionic liquid [emim]BF_4 are soluble in water, they were extracted with water and the solid material was filtered off to give high purity products. The water solution containing L-proline was distilled under a reduced pressure, and the remaining ionic liquid containing L-proline was recycled and reused at least five times without noticeably decreasing the productivity (Table 3). Compared with conventional methods, the L-proline-[emim]BF_4 system offers a clean, efficient, eco-friendly protocol for the synthesis of coumarins, with a high yield and a simple work-up procedure, and also a recyclable reaction medium.

Table 3 Studies on L-proline and ionic liquid recycling in the Knoevenagel condensation of 2-hydroxybenzaldehyde with ethyl acetoacetate[a]

Run	Yield (%)[b]	Run	Yield (%)[b]
1	95	4	94
2	95	5	93
3	93		

[a]The reaction was conducted with 40 mol% L-proline, 2 mmol 2-hydroxybenzaldehyde and 2.1 mmol ethyl acetoacetate in 1 ml ionic liquid [emim]BF_4 at room temperature; [b]Isolated yields

EXPERIMENTAL SECTION

Melting points (mp) were obtained on WRS-1A apparatus and are uncorrected, infrared radiation (IR) spectra were recorded on an NEXUS 470 FT-IR spectrophotometer using KBr optics, and ^1H NMR data were recorded at Advance DMX 500 MHz in $CDCl_3$ or DMSO-d_6 using tetramethylsilane (TMS) as internal standard.

Materials

Ionic liquids were prepared by the procedures given in the literature (Joseph *et al*., 2005). All other chemicals and reagents were commercial materials of analytical grade.

General experimental procedures for the L-proline catalyzed Knoevenagel condensation reaction in neutral ionic liquid

In a typical experiment, 2 mmol of salicylaldehyde or its derivatives and 2.1 mmol of ethyl acetoacetate were added into a 25 ml round bottom flask and stirred with a magnetic stir bar. To this, 1 ml ionic liquid and 40 mol% L-proline were added. Afterwards, the reaction mixture was stirred at room temperature until TLC (thin-layer chromatography) shows the complete disappearance of salicylaldehyde or its derivatives. Then 10 ml water was added and stirred for 5 min, the resulting mixture was filtered, and the solid residue was dried under infrared lamp to give the products in high purity without being further purified by column chromatography.

General experimental procedures for the recycling of L-proline and ionic liquid

After the reaction was completed, the solid material was filtered off. The water solution containing L-proline was distilled under a reduced pressure, and then dried in vacuum to completely remove the water, avoiding the use of toxic and volatile extractants. The L-proline-[emim]BF_4 system was recharged with a new batch of substrates. Table 3 illustrates that the ionic liquid [emim]BF_4 containing L-proline can be reused for at least five times without sacrificing the yields.

Spectral data of some products (Table 1)

1. 3-Acetylcoumarin (entry 1)

Yield: 95%; mp: 118 °C [mp 119~220 °C in (Hirai and Togo, 2005)]; IR (KBr): 1732, 1677, 1613, 1557, 1455, 1233, 1210, 979, 756 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=2.73 (s, 3H, CH_3), 7.33~7.39 (m, 2H, Ar-H), 7.64~7.67 (m, 2H, Ar-H), 8.51 (s, 1H, CH).

2. 3-Acetyl-7-methoxycoumarin (entry 2)

Yield: 86%; mp: 170 °C [mp 171~172 °C in (Fry *et al*., 2004)]; IR (KBr): 1736, 1672, 1616, 1504, 1366, 1210, 989, 837, 767 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=2.71 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 6.84 (d, *J*=2.30 Hz, 1H, Ar-H), 6.91 (q, *J*=3.70 Hz, 1H, Ar-H), 7.55 (d, *J*=8.70 Hz, 1H, Ar-H), 8.50 (s, 1H, CH).

3. 3-Acetyl-8-methoxycoumarin (entry 3)

Yield: 81%; mp: 172 °C [mp 174 °C in (Mogilaiah *et al*., 2003)]; IR (KBr):1735, 1686, 1602, 1568, 1282, 1201, 950, 801, 766 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=2.73 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 7.18~7.29 (m, 3H, Ar-H), 8.48 (s, 1H, CH).

4. 3-Acetyl-6-chlorocoumarin (entry 4)

Yield: 90%; mp: 204 °C [mp 206 °C in (Czerney and Hartmann, 1982)]; IR (KBr): 1739, 1677, 1611, 1553, 1359, 1234, 1205, 983, 973, 837 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=2.73 (s, 3H, CH_3), 7.33 (d, *J*=8.80 Hz, 1H, Ar-H), 7.60 (q, *J*=3.77 Hz, 1H, Ar-H), 7.63 (d, *J*=2.35 Hz, 1H, Ar-H), 8.41 (s, 1H, CH).

5. 3-Acetyl-6-bromocoumarin (entry 5)

Yield: 95%; mp: 231~233 °C [mp 220~221 °C in (Hirai and Togo, 2005)]; IR (KBr): 1736, 1676, 1608, 1551, 1357, 1234, 1206, 983, 970, 835 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=2.73 (s, 3H, CH_3), 7.27 (d, *J*=7.57 Hz, 1H, Ar-H), 7.73 (q, *J*=3.61 Hz, 1H, Ar-H), 7.78 (d, *J*=2.01 Hz, 1H, Ar-H), 8.41 (s, 1H, CH).

6. 3-Acetyl-6-nitrocoumarin (entry 6)

Yield: 90%; mp: 178~179 °C [mp 192 °C in (Mogilaiah *et al*., 2003)]; IR (KBr): 1752, 1680, 1607, 1536, 1346, 1239, 1213, 960, 851, 821, 768, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=2.74 (s, 3H, CH_3), 7.52 (d, *J*=9.15 Hz, 1H, Ar-H), 8.50 (q, *J*=2.20 Hz, 1H, Ar-H), 8.55 (s, 1H, CH), 8.59 (d, *J*=2.45 Hz, 1H, Ar-H).

7. 3-Acetyl-6-hydroxycoumarin (entry 7)

Yield: 92%; mp: 220 °C; IR (KBr): 3178, 1742, 1645, 1569, 1281, 1244, 930, 830, 716 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ=2.57 (s, 3H, CH_3), 7.16 (t, *J*=4.38 Hz, 1H, Ar-H), 7.23 (s, 1H, Ar-H), 7.30 (d, *J*=8.87 Hz, 1H, Ar-H), 8.55 (s, 1H, CH), 9.90 (s, 1H, OH).

8. 3-Acetyl-8-hydroxycoumarin (entry 8)

Yield: 87%; mp: 253 °C; IR (KBr): 3227, 1697, 1602, 1566, 1297, 1227, 1205, 797, 772, 740 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ=2.59 (s, 3H, CH_3), 7.21 (t, *J*=2.62 Hz, 2H, Ar-H), 7.36 (q, *J*=3.0 Hz, 1H, Ar-H), 8.59 (s, 1H, CH), 10.38 (s, 1H, OH).

9. 3-Acetylbenzo cumarin (entry 9)

Yield: 88%; mp: 189~190 °C [mp 190 °C in (Czerney and Hartmann, 1982)]; IR (KBr): 1732, 1676, 1557, 1246, 1218, 976, 825, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ=2.79 (s, 3H, CH_3), 7.48 (d, *J*=9.0 Hz, 1H, Ar-H), 7.62 (t, *J*=7.57 Hz, 1H, Ar-H), 7.74~7.77 (m, 1H, Ar-H), 7.93 (d, *J*=8.05 Hz, 1H, Ar-H), 8.11 (d, *J*=9.05 Hz, 1H, Ar-H), 8.37 (d, *J*=8.40 Hz, 1H, Ar-H), 9.32 (s, 1H, CH).

CONCLUSION

In conclusion, we have demonstrated that the L-proline-[emim]BF_4 system was an efficient alternative for the synthesis of substituted coumarins under very mild conditions. The room temperature ionic liquid played an important role as a solvent, thereby avoiding the use of environmentally unfavourable organic solvents. The L-proline immobilized in ionic liquid could be reused for at least five times, and the product yields remained at a comparable level. The simple experiment and product isolation procedures, ease of recovery, and reuse of the L-proline-[emim]BF_4 system are expected to contribute to the development of environmentally friendly and inexpensive processes in other organic syntheses.

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