

Coumarin synthesis via Knoevenagel condensation in moisture stable room temperature ionic liquids[†]

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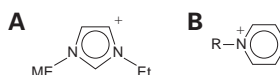
Several coumarins have been synthesised by Knoevenagel condensation in the piperidine/HOAc/moisture stable room temperature ionic liquid ([Emim]⁺BF₄⁻ referring to structure) system at room temperature; the yield of the reaction is good and the reaction medium can be recycled.

Keywords: coumarins, Knoevenagel condensation, ionic liquids

2-Oxo-2H-chromenes (coumarins) constitute an important class of naturally occurring oxygen ring compounds and act as a structural subunit of more complex natural products.¹⁻⁵ They have been widely used as flash pumpable laser dyes, fragrances, pharmaceuticals, optical brightening agents and agrochemicals.⁶⁻⁸ It is important that the synthesis of coumarin and its derivatives can be achieved by a simple and effective method. There are several methods of synthesis, such as the Knoevenagel condensation, Perkin reaction, Pechmann reaction and Claisen rearrangement.⁹ Also there are some reports concerning improvements of these methods.¹⁰⁻¹⁵ However, these methods take place under harsh conditions and/or require some expensive catalysts.^{10,14-15}

One of the prime concerns of industry and academia is the search for replacements to the environmentally damaging solvents used on a large scale, especially those which are volatile and difficult to contain. In recent years, considerable attention has been focused on the use of ionic liquids, particularly the moisture stable room temperature ionic liquids, as environmentally benign solvents for organic and organometallic reactions. Examples are Friedel–Crafts reactions,^{16,17} Diels–Alder reactions,¹⁸⁻²⁰ Heck reactions^{21,22} and Bechmann condensations,^{23,24} refer to structures A and B.

Recently, synthesis of coumarins via Pechmann condensation²⁵ and Knoevenagel condensation²⁶ in [Emim]⁺AlCl₄⁻(A)



or [Rpy]⁺AlCl₄⁻(B) has been reported. However, [Emim]AlCl₄⁻ and [Rpy]AlCl₄⁻ are moisture sensitive and both of these reactions were carried out in a glove box under inert atmosphere, and hydrochloric acid was needed in the work-up, which means the ionic liquids can not be reused easily. We have now examined the synthesis of coumarins via Knoevenagel condensation in [Emim]BF₄⁻, which is ideal for general use in organic synthesis.²⁷ Comparing with the conventional solvents, our reaction takes place smoothly at room temperature and produces coumarins in one pot with good yields.¹¹⁻¹³ Furthermore, the reaction medium can be recovered almost quantitatively and thus be recycled (Table 1).

Firstly, we added salicylaldehyde (1a) and diethyl malonate (2a) (1:1mol) to the piperidine/HOAc/[Emim]BF₄⁻ system (IL.). With no special precautions, the Knoevenagel condensation of the above substrates occurred smoothly not only at r.t. but also at around 50°C (Scheme 1), and the yields of the reaction were satisfactory (Table 1, Compd. 3a–3a^c). With 2,2-dimethyl-1,3-dioxane-4,6-dione (2b) as a substrate, we also obtained the coumarin (as a acid) both at r.t. and around 50°C (Table 1, Compd. 3b–3b^c). With ethyl acetoacetate (2c) as a substrate the

Table 1 The products and the yields

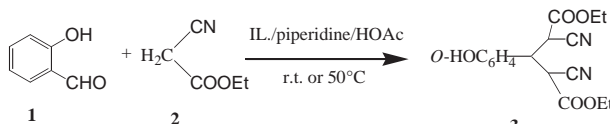
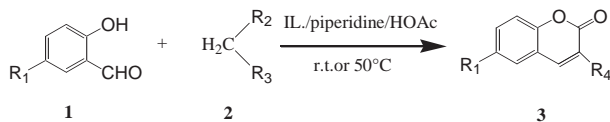
Compound	R ¹	R ²	R ³	R ⁴	Experimental		Literature	
					Yield ^b /%	M.p. ^e /°C	Yield ^b /%	M.p. ^e /°C
3a	H	CO ₂ Et	CO ₂ Et	CO ₂ Et	87	90–92	86 ^{f,26}	91–92 ²⁸
3a ^c	H	CO ₂ Et	CO ₂ Et	CO ₂ Et	80	90–92	86 ^{f,26}	91–92 ²⁸
3b	H	CH ₂ (CO ₂)	C(CH ₃) ₂	COOH	79	186–188	75 ^{g,13}	187 ¹³
3b ^c	H	CH ₂ (CO ₂)	C(CH ₃) ₂	COOH	70	186–188	75 ^{g,13}	187 ¹³
3c	H	CO ₂ Et	COCH ₃	COCH ₃	90	122–123	70 ^{g,13}	123 ¹³
3c ^c	H	CO ₂ Et	COCH ₃	COCH ₃	20	122–123	–	123 ¹³
3d	Cl	CO ₂ Et	CO ₂ Et	CO ₂ Et	86	147–148	92 ^{f,26}	145–147 ¹¹
3e	Cl	CH ₂ (CO ₂)	C(CH ₃) ₂	COOH	78	198–200	68 ^{g,13}	198–200 ¹³
3f	Cl	CO ₂ Et	COCH ₃	COCH ₃	91	148–149	72 ^{g,13}	148–150 ¹³
3g	Br	CO ₂ Et	CO ₂ Et	CO ₂ Et	88	163–164	73 ^{h,11}	162–164 ¹¹
3h	Br	CH ₂ (CO ₂)	C(CH ₃) ₂	COOH	75	199–200	99 ^{h,11}	200–202 ¹¹
3i	Br	CO ₂ Et	COCH ₃	COCH ₃	90	216–217	–	217 ²⁹
3j	OCH ₃	CO ₂ Et	CO ₂ Et	CO ₂ Et	85	141–142	94 ^{i,30}	140–141 ³⁰
3k	OCH ₃	CO ₂ Et	COCH ₃	COCH ₃	88	181–183	83 ^{j,31}	182–183 ³¹
3l ^d	H	CO ₂ Et	CN	COCH ₃	80	138–139	–	138–140 ³²

^a Reaction conditions: salicylaldehyde or its derivative (2mmol), derivative of ethyl acetate (2mmol) in piperidine (0.4mmol) / HOAc (2–3 drops) / [Emim] BF₄⁻ (10mL), r.t.. ^b Isolated yields based on salicylaldehyde or its derivative. ^c At 50°C. ^d The product of Michael addition (Scheme 2). ^e All melting points are uncorrected. ^f In an inert atmosphere, the Lewis acidic [bmim]Cl·AlCl₃ was added. The reaction was quenched with 6M HCl after a few minutes. ^g In THF solution refluxed with stirring for 28–40h, the SmI₂ catalyst was added. ^h In ethanol solution refluxed with stirring for 24h. ⁱ In chlorobenzene solution refluxed with stirring for 4h. ^j Without solvent heated on the steam bath for 10min.

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[†] This is a Short Paper, there is therefore no corresponding material in *J. Chem. Research (M)*.

reaction gave a good yield of coumarin at r.t., but a low yield was obtained at 50°C (Table 1, Compd. **3c–3e**).



When ethyl cyanoacetate (**2d**) was used as the substrate, however, the main product was the Michael addition product both at r.t. and around 50°C (Scheme 2, Table 1, Compd. **3l**). It seems that the formation of coumarin and Michael addition product is competitive, and higher acidity of the CH₂ group and higher temperature are favorable to the Michael addition.

The presence of an electron-withdrawing or electron-donating group on the 4-position of the benzene ring appears to have little effect on the rate or yield of the reaction (Table 1, Compd. **3d–3k**). Both piperidine and HOAc are necessary to the reaction. When the reaction was conducted in piperidine/[Emim]BF₄⁻ system, both the rate of the reaction and the yield was low (30% for 24h reaction time). In the absence of acid, perhaps the elimination of water is difficult. If piperidine and HOAc both were not added, no reaction took place at all. The result clearly showed that the [Emim]BF₄⁻ is not a strong enough Lewis acid in this reaction (Table 2).

To evaluate the possibility of recycling the ionic liquid used for the reaction, salicylaldehyde, diethyl malonate, piperidine and HOAc in [Emim]BF₄⁻ were allowed to react in the ionic solvent for 4h and then the products were extracted with ethyl ether. After the recovered ionic liquids were concentrated *in vacuo* (5.0 torr for 6 h at room temperature), a second amount of reactants and piperidine/HOAc were added and the process was repeated up to 4 times. It seems that there is little effect on the rate or yield of the reaction during each cycle (Table 3).

Table 2 The effect of piperidine and HOAc

Piperidine/%mol	HOAc(drop)	Time/h	Yield/% ^b
0	0	24	0
20	0	24	30
20	2-3	3	87

^aReaction conditions: salicylaldehyde (2mmol), CH₂(CO₂Et)₂ (2mmol) in [Emim]BF₄⁻ (10ml), r.t.

^bIsolated yields based on salicylaldehyde.

Table 3 Reused of the ionic liquids [Emim]BF₄⁻

Cycle	Yield/% ^b	Cycle	Yield/%
1	87	3	82
2	85	4	86

^aCycles conditions: salicylaldehyde (2mmol), diethyl malonate (2mmol) in piperidine (0.4mmol) / HOAc (2-3 drops) / [Emim]BF₄⁻ (10ml), r.t.

^bIsolated yields based on salicylaldehyde.

In summary, the moisture stable room temperature ionic liquid, [Emim]BF₄⁻, is an excellent medium for the synthesis of coumarins by Knoevenagel condensation. It takes advantage of mild reaction temperature and gives good yields. Another merit of this reaction lies in the simple separation of the reaction product. The ionic liquids could be recovered almost quantitatively and thus be recycled. Further studies of possible applications of moisture stable room temperature ionic liquids in the base promoted organic reactions are being actively pursued.

Experimental

Reactions were carried out in a 25ml flask equipped with a magnetic stir bar with no special precaution. All the compounds were characterized by NMR, MS and physical constants and gave satisfactory results in comparison with authentic samples. Melting points are in good agreement with literature data (Table 1).

General procedure: To salicylaldehyde (2mmol), diethyl malonate (2mmol), piperidine (0.4mmol) and [Emim]BF₄⁻ (10ml) mixture, HOAc (2–3 drops) were added to a 25ml flask equipped with a magnetic stir bar. With no special precaution, the mixture was stirred at room temperature for 4h. The resultant product was extracted by ether (3×10ml) (To **3b**, 10ml 1N HCl was needed). The product was further purified by column chromatography (4:1, petroleum ether/ethyl acetate), yield: 87%.

Representative data: Product **3a**²⁸: M.p.: 90–92°C, ¹H NMR (CDCl₃/TMS): δ_H 1.40–1.43 (t, *J*=7.14 Hz, 3H), 4.39–4.44 (q, 7.12Hz, 2H), 7.32–7.68 (m, 4H), 8.54 (s, 1H). MS (EI, ab.): 218 (M⁺) (32.89), 190 (3.69), 173 (71.96), 146 (100).

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