



Coumarin syntheses via Pechmann condensation in Lewis acidic chloroaluminate ionic liquid

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Received 11 September 2001; revised 25 October 2001; accepted 30 October 2001

Abstract—1-Butyl-3-methylimidazolium chloroaluminate, [bmim]Cl·2AlCl₃ ionic liquid is used as an alternative to conventional acid catalysts in the Pechmann condensation of phenols with ethyl acetoacetate leading to the formation of coumarin derivatives. The reaction time is reduced drastically even at ambient conditions. The ionic liquid plays the dual role of solvent and Lewis acid catalyst providing a quick and efficient route to the syntheses of coumarins. © 2001 Elsevier Science Ltd. All rights reserved.

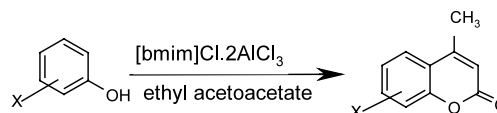
Coumarins occupy an important place in the realm of natural and synthetic organic chemistry. They are used as anticoagulants,¹ additives in food and cosmetics² and in the preparation of insecticides, optical brighteners³ and dispersed fluorescent and laser dyes.⁴ Coumarins have been synthesised by several methods, including Pechmann,^{5a} Perkin,^{5b} Knoevenagel,^{5c,d} Reformatsky^{5e} and Wittig⁶ reactions.

The Pechmann reaction is the most widely applied method for synthesising coumarins as it involves the condensation of phenols with β -keto esters in the presence of a variety of acidic condensing agents and gives good yields of 4-substituted coumarins.^{7,8} Several acid catalysts have been used in the Pechmann reaction including sulfuric acid,^{5a} phosphorus pentoxide,⁹ aluminium chloride,¹⁰ trifluoroacetic acid¹¹ and many more.⁷ However, these catalysts have to be used in excess; for example, sulfuric acid in 10–12 equiv.,⁸ trifluoroacetic acid in three to 4 equiv.,¹¹ and phosphorous pentoxide is required in a five-fold excess. Further, the disposal of acid waste leads to environmental pollution.

With the rapid development in the field of synthetic organic chemistry, researchers from both academia and industry have started giving serious thought to the detrimental effect of non-green processes and chemicals on the environment. They have successfully developed several environmentally benign procedures to avoid, or at least minimise, these effects. Syntheses of coumarins have been carried out successfully using solid acid

catalysts¹² and by combination of solid acid catalysts and microwave irradiation¹³ as an alternative to conventional methods. Ionic liquids have recently gained recognition as possible environmentally benign alternative solvents in various chemical processes. They have attracted the attention of chemists owing to their unique physical and chemical properties.¹⁴ Because of their vanishingly low vapour pressure, ionic species do not contribute to volatile organic compound emission. They have also been referred as ‘designer solvents’,¹⁵ as their properties can be altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion and alkyl chain attached to the organic cation. These structural variations offer flexibility to the chemist to devise the most idealised solvent, catering for the needs of any particular process. Several reactions have been carried out in ionic liquids, such as Diels–Alder^{16a,b} and Wittig reaction,^{16c} benzoin condensations^{16d} and hydrogenation^{16e} reactions and even enzyme catalysed reactions.^{16f,g}

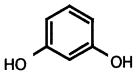
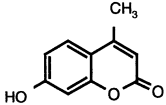
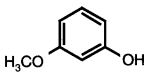
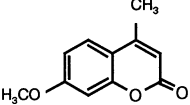
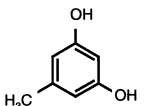
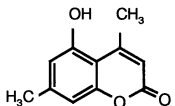
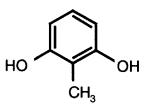
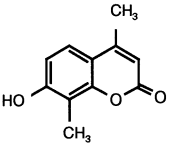
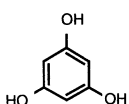
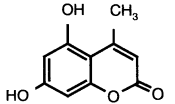
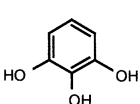
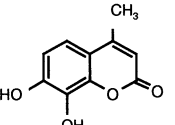
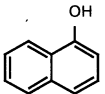
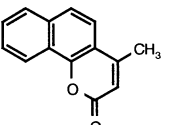

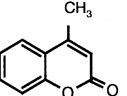
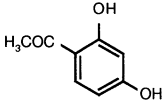
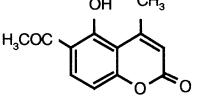
Chloroaluminate ionic liquids have been used in Friedel–Crafts¹⁷ and other reactions in which they play the dual role of Lewis acid catalyst and solvent. In continuation of our efforts to explore new reactions in these liquids, we have carried out the Fries rearrangement in an ionic liquid.¹⁸



Scheme 1. Pechmann condensation in acidic chloroaluminate ionic melt.

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Table 1. Syntheses of coumarins via Pechmann condensations of phenols with ethyl acetoacetate in [bmim]Cl·2AlCl₃

Entry	Substrate	Product	Time (min.)	Temperature (°C)	Yield (%) ^a
1.			10	30	95
2.			10	30	92
3.			10	30	91
4.			10	30	89
5.			10	30	90
6.			10	30	89
7.			30	60	86
8.			120	120	40
9.			45	60	42

^a isolated yields

The versatility of chloroaluminate ionic liquids encouraged us to carry out the Pechmann condensation in this novel reaction medium. We report herein for the first time, the syntheses of coumarins via Pechmann condensations of phenols with ethyl acetoacetate in the Lewis acidic [bmim]Cl·2AlCl₃ ionic liquid (Scheme 1).

The composition of ionic liquids is expressed as the apparent AlCl₃ mole fraction, *N*. Accordingly,

they are classified as basic, neutral or acidic liquids where *N* is 0–0.5, 0.5 and 0.5–0.67, respectively. The Pechmann condensation of phenols with ethyl acetoacetate was carried out in *N*=0.33, 0.5 and 0.67 liquids. Positive results were obtained only in the case of an acidic ionic liquid as expected. The liquid corresponding to *N*=0.67 gave a maximum yield in minimum time and hence was utilised for all the reactions.¹⁹

To study substituent effects on the reactivity of the phenol, the reactions were performed on a variety of phenols. The reactions worked well and the results are illustrated in Table 1. For most of the substrates, the reaction time is reduced drastically even at ambient conditions in contrast to reported procedures,^{7,8} with an excellent yield of coumarins. Substrates (entries 1–6) having electron-donating groups in *para* to the site of electrophilic substitution gave maximum yields at room temperature in the minimum time. 3-Methoxyphenol (entry 2) showed no detectable demethylation under the given conditions. However, control experiments²⁰ by conventional method using AlCl₃ in nitrobenzene showed significant demethylation at high temperature which is necessary to drive the reaction to completion. 1-Naphthol (entry 7) requires a slightly higher temperature and longer reaction time, due to the presence of another phenyl ring. Similarly, phenol (entry 8) required a higher reaction temperature and longer reaction duration, as no electron-donating group is present. A literature survey revealed that, resacetophenone (entry 9) failed to react to give a coumarin derivative in the presence of sulfuric acid as the catalyst. However, the reaction was observed under aluminium chloride catalysis,¹⁰ but required a temperature of 130°C in nitrobenzene as the solvent. In contrast, the ionic liquid furnished comparable yields of the product at 60°C. Furthermore, the method succeeds in exploiting this novel system as a Lewis acid catalyst and solvent which is needed in the reactions in only stoichiometric amounts.

To conclude, we have successfully achieved the syntheses of coumarins using phenols and ethyl acetoacetate via Pechmann condensations in acidic chloroaluminate ionic liquid. Further investigations on the syntheses of coumarins via Knoevenagel condensations of *o*-hydroxy arylaldehydes and the active methylene compounds in these liquids are currently in progress.

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- Typical experimental procedure: To the weighed quantity of phenol (10 mmol) and ethyl acetoacetate (11 mmol), the ionic liquid [bmim]Cl-2AlCl₃ (11 mmol) was added and the reaction mixture was stirred at the desired time and temperature. All additions were carried out in an inert atmosphere. The reaction was quenched by adding 6 M HCl in cold conditions. The resultant product was filtered. The products were further purified by column chromatography and characterised by IR, NMR and physical constants.
- The reaction was carried out using 3-methoxyphenol (10 mmol), ethyl acetoacetate (11 mmol) and AlCl₃ (20 mmol). A poor yield (15%) of the coumarin derivative was obtained at room temperature for 20 min along with 2% of the demethylated product. In another experiment, the reaction was carried out at 125°C for 1 h by using exactly the same quantities as mentioned above. In this case, the overall yield of coumarin derivative was 65%, of which 32% was demethylated product.