Pechmann Reaction in Non-Chloroaluminate Acidic Ionic Liquids under Solvent-Free Conditions

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Abstract: Four non-chloroaluminate acidic ionic liquids have been used as catalysts for Pechmann condensations of phenols under solvent-free conditions. SO_3H-functionalized trifluoromethanesulfonate imidazolium ionic liquid has proved to be the most active catalyst. Ionic liquid loads as low as 5 mol % can be used leading to high yields with activated phenols at an oil bath temperature of 80 °C. The acidities of the four ionic liquids have also been tested using the Hammett method in dichloromethane. The results are consistent with their catalytic activities as observed in the Pechmann reaction of resorcinol. This methodology offers significant improvements for the synthesis of coumarins with regard to yield of products, simplicity in operation, and green aspects by avoiding toxic catalysts and solvents.

Keywords: acid catalysis; coumarins; determination of acidity; ionic liquids; Pechmann condensation

Coumarin and its derivatives have been attracting great interest because of their importance in synthetic organic chemistry. Many products which contain the subunit of coumarin exhibit useful and diverse biological activity.[1] These compounds find application in pharmaceuticals, fragrances, agrochemicals, and insecticides.[2] A very valuable method for the synthesis of coumarins is the Pechmann reaction, which starts from phenols. In the conventional production of coumarins by the Pechmann reaction, concentrated sulfuric acid is used as the catalyst.[3] This process causes formation of by-products, needs long reaction time, and introduces corrosion problems.[4] For these reasons, there have been some attempts to find alternative, environmentally benign synthesis routes. Nafion-H,[5] zeolite H-BEA, Amberlyst 15,[6] montmorillonite clay,[7] and other solid acids[8] have been employed for this purpose in the Pechmann condensation. Some organic acids and metal Lewis acids have also been examined in this transformation.[9] Although these methods are suitable for certain synthetic conditions, sometimes, however, many of these procedures are associated with one or more disadvantages such as expensive reagents, long reaction time, tedious work-up, low selectivity, and large amounts of solid supports which would eventually result in the generation of a large amount of toxic waste.

It is also noteworthy that a majority of existing catalysts used in Pechmann condensation are solid acids. In many cases the key drivers for the use of solid acids are their lack of vapor pressure and their phase heterogeneity, the latter facilitating product isolation. Even so, solid acids are fraught with drawbacks of their own, including heterogeneous kinetics and a susceptibility to ready deactivation. Consequently, a valuable middle ground would be found in chemically functional liquids that, like solids, have no vapor pressure and which can also act as acidic catalysts in catalytic reactions.

The recently emerged chloroaluminate ionic liquids hold great potential in meeting these demands, as evidenced by their increasing popularity as catalysts and reaction media.[10] Pechmann reactions have also been conducted in chloroaluminate ionic liquids.[11] Nevertheless, chloroaluminates are very sensitive to hydrolysis. Traces of water can change the composition of the melt and the concentration of protons. As a result, it is difficult to accurately control the acidity of these ionic liquids. Another disadvantage is that the chloroaluminate ionic liquids, which cannot be stored for a long time, should be prepared at the time of the catalytic reactions. Non-chloroaluminate acidic ionic liquids which are air and moisture stable, have hence been developed and applied for acidic reactions.[12] As a part of our studies to explore the utility of existing ionic liquids in chemical reactions, we have investigated many acid-catalyzed reactions, including alkylation, esterification, Beckmann rearrangement, cyclization of 1-dodecene, acetalization and oligomerization of branched olefins.[13] In continuation of our work in studying acid-catalyzed reactions in ionic liquids, we report in this paper the synthesis of coumarin derivatives by the Pechmann condensation in non-chloroaluminate acidic ionic liquids.

We initial tested the Pechmann condensation between resorcinol and methyl acetoacetate at 80 °C under sol-

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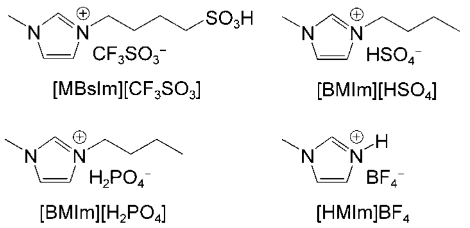


Scheme 1. Four non-chloroaluminate acidic ionic liquids used in Pechmann condensation

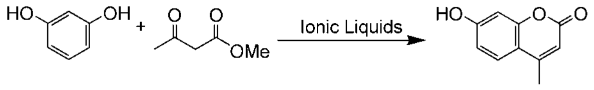
vent-free conditions. Four existing non-chloroaluminate acidic ionic liquids, including [MBsIm][CF_3SO_3], [BMIm][HSO_4], [BMIm][H_2PO_4] and [HMIm]BF_4, have been used (Scheme 1). Table 1 shows the results of the experiments carried out under the same conditions for comparing the catalytic performances of these acidic ionic liquids. In our hands, [MBsIm][CF_3SO_3] proved to be very active, leading to 95% yield of 7-hydroxy-4-methylcoumarin within 15 min (Entry 1) when 10 mol % ionic liquid was used. [BMIm][HSO_4] could also used as catalyst to promote the Pechmann condensation, but its activity seems to be slightly inferior as compared with that of [MBsIm][CF_3SO_3] because the reaction time has to prolonged to 1 hour for the complete conversion of resorcinol (Entries 2 and 3). Attempts to perform the reaction with [BMIm][H_2PO_4] and [HMIm]BF_4 led only to recovery of unreacted starting material even at elevated temperature and prolonged reaction time (Entries 4 and 5). Similarly, no reaction was observed in the absence of ionic liquid (Entry 6). In view of the foregoing, [MBsIm][CF_3SO_3] should be a suitable catalyst for the Pechmann condensation.

We then addressed the question of what would be the smallest amount of [MBsIm][CF_3SO_3] that could be employed in this reaction. Therefore, a study of the Pechmann condensation of resorcinol in the presence of 5 mol % catalyst was undertaken. The result is reported in Table 1. It is shown that with 5 mol % [MBsIm][CF_3SO_3], the reaction went to completion in 1 hour, which is quite remarkable (Entry 7).[4,7b] The resorcinol could not be completely consumed when the [MBsIm][CF_3SO_3] amount was further decreased to 2 mol % even at prolonged reaction time (3 h) (Entry 8). Similarly, a decrease of the reaction temperature seems to be unfavorable because the yield of 7-hydroxy-4-methylcoumarin was only 53% at 50 °C (Entry 9).

The Pechmann reaction proceeds through transesterification and intramolecular hydroxyalkylation, followed by dehydration according to the descriptions in previous reports.[2,6] These three steps are all typical acid-catalyzed reactions. Therefore, the outcome of the Pechmann reaction depends very much on the Brønsted acidity of catalyst.[4] However, acidity determinations based on room temperature ionic liquids is a relatively new subject. The determination of the Brønsted acidity of a non-chloroaluminate ionic liquid has not even been considered yet. A commonly used method to evaluate the acidity of a Brønsted acid in solution is the Hammett method, wherein a basic indicator has been used to trap the dissociative proton. The properties of the protons depend on both the nature of the solvent and the nature and concentration of the chosen acid. The Brønsted acidity was evaluated from the determination of the Hammett acidity functions, using UV-visible spectroscopy. In the present case, this method consists of evaluating the protonation extent of the uncharged indicator bases (named I) in a solution, in terms of the measurable ratio [I]/[IH^+]. In a given solvent (s), assumed as being dissociating, the Hammett function (H_0) is defined as:

$$H_0 = pK(I)_{aq} + \log([I]_s/[IH^+]_s)$$

Table 1. Pechmann condensation between resorcinol and methyl acetoacetate in different ionic liquids.[a]



Entry	Ionic liquids	Ratio of IL/ resorcinol [M/M%]	Time [min]	Temp. [°C]	Yield [%]
1	[MBsIm][CF_3SO_3]	10	15	80	95
2	[BMIm][HSO_4]	10	15	80	35
3	[BMIm][HSO_4]	10	60	80	89
4	[BMIm][H_2PO_4]	10	180	100	0
5	[HMIm]BF_4	10	180	100	0
6	–	–	180	80	0
7	[MBsIm][CF_3SO_3]	5	60	80	95
8	[MBsIm][CF_3SO_3]	2	180	80	77
9	[MBsIm][CF_3SO_3]	5	60	50	53

[a] Reaction conditions: resorcinol, 15 mmol; methyl acetoacetate, 15 mmol.

Gilbert and co-workers have described a procedure to evaluate the Brønsted acidity of $HNTf_2$ in [BMIm][NTf_2] ionic liquid using the Hammett method.[14] However, the acidity determination of a pure acidic ionic liquid without a solvent should be impossible because the initial absorbance of the total unprotonated form of the indicator (blank value) cannot be obtained. For the comparison purposes, the acidities of these four non-chloroaluminate ionic liquids have been examined using 4-nitroanline (Hammett constant is 0.99) as indicator in dichloromethane and the results are shown in Figure 1. In this experiment, dichloromethane was chosen as test solvent at first glance because it is an aprotic polar solvent, stable under acidic conditions and has considerable solubility for all tested ionic liquids. The maximal absorbance of the unprotonated form of the indicator was observed at 349 nm in CH_2Cl_2. When an acidic ionic liquid was added, the absorbance of the unprotonated form of the indicator decreased. As shown in Figure 1, the absorbance of the unprotonated form of the indicator on four non-chloroaluminate acidic ionic liquids decreased as follows: [BMIm][H_2PO_4] > [HMIm]BF_4 > [BMIm][HSO_4] > [MBsIm][CF_3SO_3]. By taking as the initial reference the total unprotonated form of the indicator (when no acid is added to the CH_2Cl_2 solution, spectrum a), we could determine the [I]/[IH^+] ratio from the measured absorbances after each ionic liquid (spectra b–e), and then the Hammett function (H_0) is calculated (see Table 2).

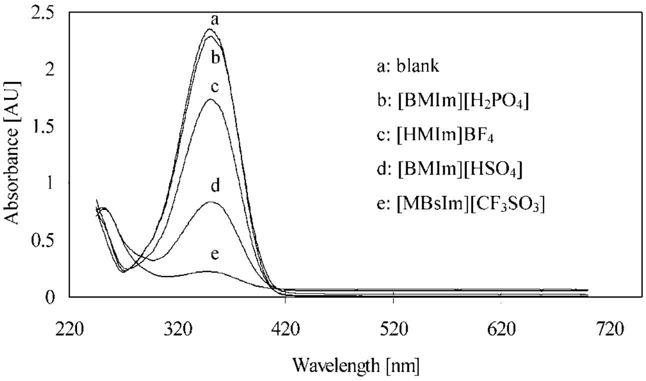


Figure 1. Absorption spectra of 4-nitroaniline for various ionic liquids in dichloromethane.

The smallest H_0 was obtained in a 10 mmol/L CH_2Cl_2 solution of [MBsIm][CF_3SO_3], it indicated that ionic liquid [MBsIm][CF_3SO_3] exhibits a stronger Brønsted acidity than the other three non-chloroaluminate ionic liquids used in this work. The Brønsted acidity of [BMIm][HSO_4] is slightly inferior as compared with [MBsIm][CF_3SO_3], but stronger than those of [HMIm]BF_4 and [BMIm][H_2PO_4]. It should be pointed out that, although this method cannot yet offer an accurate quantitative value for acidic ionic liquids, these results should be applicable for an acidity comparison of existing non-chloroaluminate acidic ionic liquids. This order of ionic liquid acidity is consistent with the sequence of catalytic activity observed in the reaction of resorcinol, indicating the determining role of catalyst acidity on the Pechmann condensation.

Having these results in hand, other phenols have been subjected to the conditions of run 7 in Table 1, and the results are listed in Table 3. The ionic liquid [MBsIm][CF_3SO_3] proved to be active towards all substrates. Many phenols, such as resorcinol, pyrogallol, phloroglucinol, 3-methoxyphenol and 2-methylresorcinol could be converted to corresponding coumarins in excellent yields (Entries 1–5). The reactivities of 3-methylphenol and 1-naphthol seem to be inferior as compared with that of the former; yields of 4,7-dimethylcoumarin and 4-methyl-7,8-benzocoumarin were 76% and 61%, respectively (Entries 6 and 7). One of the main aims of using non-chloroaluminate ionic liquids as catalysts was to study the possibility of their recycle and reuse. Because [MBsIm][CF_3SO_3] is an air and moisture stable ionic liquid, it could be recycled after reaction from the aqueous solution by means of removal of volatile components under vacuum conditions. And it was reused in the Pechmann condensation between resorcinol and methyl acetoacetate. The reaction was carried out three times in consecutive runs with only a slight decrease in isolated yields (Table 3, entry 8). Obviously, the recycling procedure is analogous to that of sulfuric acid system, complex and time and energy consuming. However, in the current context of environmental impact, the sulfuric acid system is not attractive as it requires catalyst in 10–12 equivalent amounts.[15]

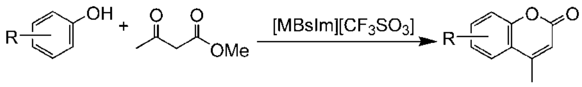
In summary, the use of non-chloroaluminate acidic ionic liquids as catalysts for the Pechmann condensation avoids the use of moisture sensitive reagents or high

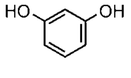
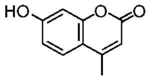
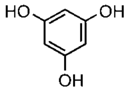
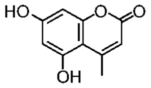
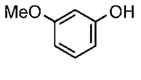
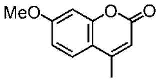
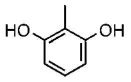
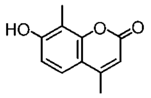
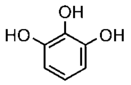
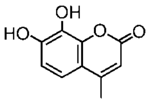
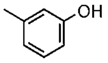
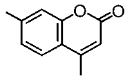
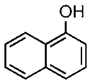
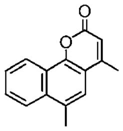
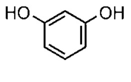
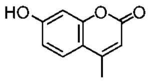
Table 2. H_0 values of various ionic liquids in dichloromethane.[a]

Ionic liquids	Absorbance [AU]	[I] [%]	[HI^+] [%]	H_0
–	2.350	100	0	–
[BMIm][H_2PO_4]	2.286	97.3	2.7	2.55
[HMIm]BF_4	1.734	73.8	26.2	1.44
[BMIm][HSO_4]	0.837	35.6	64.4	0.73
[MBsIm][CF_3SO_3]	0.223	9.5	90.5	0.01

[a] Concentration: 10 mmol/L; indicator: 4-nitroanline.

Table 3. Pechmann reactions between phenols and methyl acetoacetate in ionic liquid [MBsIm][CF_3SO_3].[a]



Entry	Phenols	Products	Time [h]	Yields [%]	mp [°C]
1			1	95	183–186 (185–187[9d])
2			1	90	182–185 (180–185[11a])
3			1	92	161–162 (160–162[9d])
4			1.5	92	137–139 (138–139[9d])
5			0.5	94	236–239 (236–239[9d])
6			4	76	130–132 (131.5–132[7b])
7			6	61	155–156 (154–156[9d])
8[b]			1	89	183–186 (185–187[9d])

[a] Reaction conditions: ionic liquid, 0.75 mmol; phenols, 15 mmol; methyl acetoacetate, 15 mmol; 80 °C.

[b] Reused a third time.

temperature reaction conditions to promote the reaction.[9b,11] Catalyst ([MBsIm][CF_3SO_3]) loads as low as 5 mol % can be used leading to good to high yields with activated phenols at an oil bath temperature of 80 °C. This clearly indicates the efficiency of the ionic liquid [MBsIm][CF_3SO_3] for this transformation. Preliminary acidity determinations of four non-chloroaluminate acidic ionic liquids revealed that the Brønsted acidities of the ionic liquids play a determining role in the rate acceleration of the Pechmann condensation. The ionic liquid [MBsIm][CF_3SO_3] can be recovered conveniently and reused up to three times, although with some loss of activity. Moreover, this methodology offers significant improvements with regard to yield of products, simplicity in operation, and green aspects by avoiding toxic catalysts and solvents. These advantages of this novel catalytic system are expected to contribute to the development of more benign Pechmann condensations of phenols with methyl acetoacetate.

Experimental Section

Preparation of Ionic Liquids

All used ionic liquids were prepared according previous methods.[12g, h,13e, f]

Typical Procedure

In a typical experiment, ionic liquid (0.75 mmol) was dissolved in a mixture of resorcinol (15.0 mmol) and methyl acetoacetate (15.0 mmol) in a 25-mL round-bottom flask equipped with a distillation condenser. The content was stirred vigorously for the desired time at 80 °C. At the end of reaction, the reaction mixture was cooled to room temperature. The liquid mixture should be solidified at ambient temperature. Ethanol (10 mL) was added and heated at 50 °C until complete dissolution of the solid. This ethanol solution was then put into a 100-mL beaker containing a lot of water. Crystalline products were collected by filtration to give 7-hydroxy-4-methylcoumarin in

95% yield; the crude crystals thus obtained were recrystallized from EtOH to give pure 7-hydroxy-4-methylcoumarin as colorless prisms (mp 183–186 °C). The ionic liquid could be recovered from aqueous solution by means of removal of volatile components under vacuum conditions.

UV-VIS Acidity Evaluation

Dichloromethane solutions of ionic liquids were prepared from dried CH_2Cl_2 and ionic liquids that have been treated under vacuum at 80 °C for 2 hours. All the spectra were recorded with an Agilent B453 spectrophotometer.

Acknowledgements

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