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A FACILE APPROACH FOR THE SYNTHESIS OF COUMARINS VIA PECHMANN CONDENSATION USING ACIDIC IONIC LIQUID UNDER SOLVENT FREE CONDITION

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ABSTRACT

An efficient and green method for the synthesis of substituted coumarins by the condensation reaction between phenols and ethyl acetoacetate using acidic ionic liquid [cmmim][BF_4] as a reusable catalyst under solvent free condition has been described. The methodology provides easy access to substituted coumarins with higher yields under mild reaction condition and shorter reaction time as compared to conventional acid catalysts.

Key words: *Acidic ionic liquid, Coumarin, Green chemistry.*

INTRODUCTION

Among the heterocyclic compounds, coumarin derivatives have attracted the attention of organic chemists due to their wide range of applications [1]. Coumarin derivatives have a broad spectrum of biological activities, including antibacterial [2], anticancer [3], inhibitory of platelet aggregation [4], inhibitory of HIV-1 protease [5] and inhibitory of steroid 5α-reductase [6]. These derivatives are also widely used as additives in food and cosmetic industries [7], in perfumeries [8], in agrochemicals [7], as optical brightening agents [9] and as dispersed fluorescent [10]. Coumarins have also been evolved as the intermediate in the synthesis of many important pharmaceutical moieties [11]. Due to such extensive applications, several methodologies have been developed for their synthesis viz. Pechmann[12], Knoevenagel [13], Perkin [14], Wittig [15] and Reformatsky [16] reactions. Pechmann condensation is the most common and easy method for the synthesis of substituted coumarin derivatives as it involves acid catalysed condensation reaction between a phenol and a β-keto ester. Many acid catalysts like H_2SO_4, HCl, H_3PO_4, PPA, P_2O_5, $AlCl_3$, $FeCl_3$, $POCl_3$ and CF_3COOH have been employed for Pechmann condensation [17]. A large variety of heterogeneous catalysts such as functionalized mesoporous Zr-TMS, Amberlyst, Nafion-H, $Sm(NO_3)_3 \cdot 6H_2O$, $Bi(NO_3)_3 \cdot 5H_2O$ and heteropolyacids have also been reported [18]. Use of chloroaluminate ionic liquids [19] and use of microwave irradiation [20] under solvent free condition have also been cited. Nevertheless, most of these methods suffer from limitations such as use of excess amount of catalyst, long reaction times, harsh reaction conditions, generation of side products, corrosion problems and tedious workup procedures.

The fundamental goal of any synthetic organic chemist is to develop sustainable and greener methodologies for the synthesis of targeted organic moieties. As a result, ionic liquid (ILs) received foremost attention due to its unique properties like negligible vapor pressure, broad liquid ranges, reusability and high thermal stability [21]. Especially, inherent Lewis/Brønsted acidity of ionic liquid gained much attention as a suitable reaction media which can accelerate the reaction [22].

Here in, we report condensation reaction between substituted phenols and ethyl acetoacetate for the synthesis of substituted coumarins promoted by acidic 1-carboxymethyl-3-methyl imidazolium tetrafluoroborate [cmmim][BF_4] ionic liquid without any added catalyst. The products have been duly characterized using nuclear magnetic resonance spectroscopy, infra-red spectroscopy and mass spectrometry.

EXPERIMENTAL

All chemicals were of research grade and used as obtained without any further purification. The IL was prepared under ultrasonic irradiation, according to the method reported earlier [23].The melting points were determined in capillary tubes using heavy paraffin liquid in Thiele tube. Melting points are uncorrected and are compared with the reported literature values. The reaction progress and purity of products were determined by TLC silica gel plates (Merck 60 F254). IR Spectra were recorded on a Shimadzu FT-IR-S8401 and FT-IR-8400 spectrophotometer using KBr, mass spectra on AB APPLIED BIOSYSTEMS IMDS SCIEX. API-2000 LC/MS/MS spectrometer. The ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and DEPT-135 spectra were recorded on BRUKER AVANCE 400 MHz instrument using $CDCl_3$ as the solvent.

General procedure for the synthesis of substituted coumarins

In a typical experiment, 10 mmol phenol, 10 mmol ethyl acetoacetate (EAA) and 200 mg IL [cmmim][BF_4] were stirred in preheated oil bath at 120 °C. The reactions were carried out in a 50 mL round bottom flask by suspending it slight below the oil surface. The reaction was typically allowed to proceed for time period as mentioned in Table 2 at 120° C with vigorous stirring. After the completion of the reaction (as determined by TLC), the mixture was

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cooled to room temperature, some ice water was added to reaction mixture and then filtered through a sintered funnel under suction. The crude product was crystallized from hot ethanol to afford pure coumarin. The IL contained in aqueous filtrate was recovered by heating the aqueous filtrate at 80 °C under reduced pressure (10 mm Hg) for 4 h. The recovered ionic liquid was found to be pure enough to be used in next run without any further purification.

Spectroscopic data of compounds

7-hydroxy-4-methyl-2H-chromen-2-one (3a)

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.77 (s, 1H), 7.35 (d, 1H, J=8.4 Hz), 6.72 (m, 2H), 5.96 (s, 1H), 2.29 (s, 3H). ^{13}C NMR: δ 18.61, 102.99, 110.76, 112.51, 113.17, 125.70, 153.08, 155.21, 161.30, 161.56. DEPT-135: Up Peaks: δ 18.64, 102.91, 110.71, 113.18, 125.83. IR (KBr): 3166, 2811, 1682, 1602, 1273, 1064 cm^{-1}. LC-MS: 177.0 [M$^+$+1].

5,7-dihydroxy-4-methyl-2H-chromen-2-one (3b)

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (s, 2H), 6.94 (d, 1H, J=8.4 Hz), 6.75 (d, 1H, J=8.4 Hz), 5.96 (s, 1H), 2.30 (s, 3H). ^{13}C NMR: δ 18.78, 110.65, 112.47, 113.17, 115.34, 132.46, 143.59, 149.55, 153.66, 160.76. DEPT-135: Up Peaks: δ 18.80, 110.65, 112.47, 115.34. IR (KBr): 3420, 3224, 1645, 1512, 1230, 1064 cm^{-1}.LC-MS: 193.0 [M$^+$+1]

7-methoxy-4-methyl-2H-chromen-2-one (3c)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, 1H, J=8.8 Hz), 6.84 (m, 2H), 6.14 (s, 1H), 3.86 (s, 3H), 2.39 (s, 3H) ^{13}C NMR: δ 18.90, 55.65, 100.72, 111.56, 112.35, 113.45, 126.32, 154.00, 156.31, 161.45, 163.10 DEPT-135: Up Peaks: δ 18.90, 55.65, 100.71, 111.56, 112.34, 126.32 IR (KBr): 3051, 1690, 1564, 1212, 1078 cm^{-1}.

7-hydroxy-4,8-dimethyl-2H-chromen-2-one (3d)

^{1}H NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 1H), 7.43 (d, 1H, J=8.8 Hz), 6.82 (d, 1H, J=8.8 Hz), 6.12 (s, 1H), 2.35(s, 3H), 2.14 (s, 3H). ^{13}C NMR: δ 7.19, 19.20, 111.24, 111.39, 112.56, 113.71, 124.25, 152.84, 153.12, 159.44, 161.10. DEPT-135: Up Peaks: δ 7.19, 19.20, 111.24, 113.70, 124.25.

7,8-dihydroxy-4-methyl-2H-chromen-2-one (3e)

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 2H), 7.10 (d, 1H, J=8.4 Hz), 6.79 (d, 1H, J=8.4 Hz), 6.13 (s, 1H), 2.39 (s, 3H). ^{13}C NMR: δ 18.45, 110.36, 112.56, 112.81, 115.55, 132.65, 143.58, 149.28, 154.14, 159.98. DEPT-135: Up Peaks: δ 18.45, 110.36, 112.56, 115.54.

4,7-dimethyl-2H-chromen-2-one (3f)

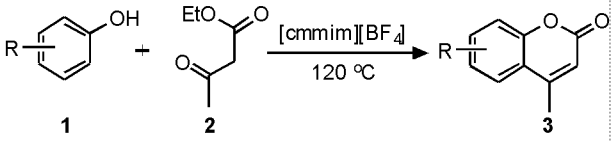
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, 1H, J=8.8 Hz), 6.99-7.04 (m, 2H), 6.15 (s, 1H), 2.38 (s, 3H), 2.36 (s, 3H). ^{13}C NMR: δ 18.54, 21.59, 110.64, 117.38, 117.56, 124.68, 125.76, 143.16, 152.79, 153.81, 161.44. DEPT-135: Up Peaks: δ 18.54, 21.60, 110.65, 117.38, 124.68, 125.75.

4-methyl-2H-benzo[h]chromen-2-one (3g)

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85-7.89 (m, 2H), 7.63-7.69 (m, 4H), 6.32 (s, 1H), 2.46 (s, 3H). ^{13}C NMR: δ 19.21, 114.42, 115.10, 120.43, 122.43, 123.76, 124.53, 127.32, 127.87, 128.64, 135.24, 150.89, 153.64, 161.10. DEPT-135: Up Peaks: δ 19.21, 114.41, 120.43, 122.44, 124.53, 127.32, 127.88, 128.65.

RESULTS AND DISCUSSION

The synthesis of substituted coumarin 3 (Scheme 1) was carried out by one pot condensation reaction between substituted phenols 1 and ethyl acetoacetate 2 in presence of acidic ionic liquid [cmmim][BF_4] under conventional thermal heating at 120° C. The sole ionic liquid was found to be effective as a reaction media as well as promoter for the reaction.



Scheme 1

For the optimization of reaction condition, resorcinol(10 mmol) and ethyl acetoacetate(10 mmol) were employed as the model reactants in presence of 200 mg [cmmim][BF_4] at different temperatures to measure catalytic performance of the ionic liquid. As shown in Table 1, no product was found to be obtained when reaction was carried out at 50 °C (Entry 1). It was observed that reactants remained almost insoluble in reaction media under this condition. Consequently, more reactions with the same substrate were carried out at higher temperatures (Entry 2, 3 and 4). It was observed that increase in reaction temperature boosted the yield with lowering in the reaction time. When the amount of ionic liquid was

Table 1 : Optimization data for the synthesis of coumarins using [cmmim][BF_4] under conventional heating.

Entry	Amount of IL (mg)	Reaction temperature (°C)	Reaction time [a] (h)	% Yield [b]
1	200	50	6.0	0
2	200	70	6.0	Trace
3	200	100	3.0	73
4	200	120	2.5	88
5	100	120	3.0	68
6	200	140	2.5	87

[a]All the reactions were run till completion as indicated by TLC

[b]Isolated yields

Table 2 Characteristic data of the synthesized coumarins from substituted phenols

Compound	R-	Reaction time (h) [a]	% Yield [b]	M.P.(°C)
3a	3-HO-	2.5	88	184-186
3b	3,5-$(HO)_2$-	2.5	86	284-286
3c	3-MeO-	3.0	91	156-158
3d	2-CH_3-3-HO-	3.5	93	262-264
3e	2,3-$(HO)_2$-	2.0	89	240-242
3f	3-CH_3-	4.0	83	130-132
3g	α-naphthyl	6.0	78	154-156

[a]All the reactions were run till the completion as indicated by TLC

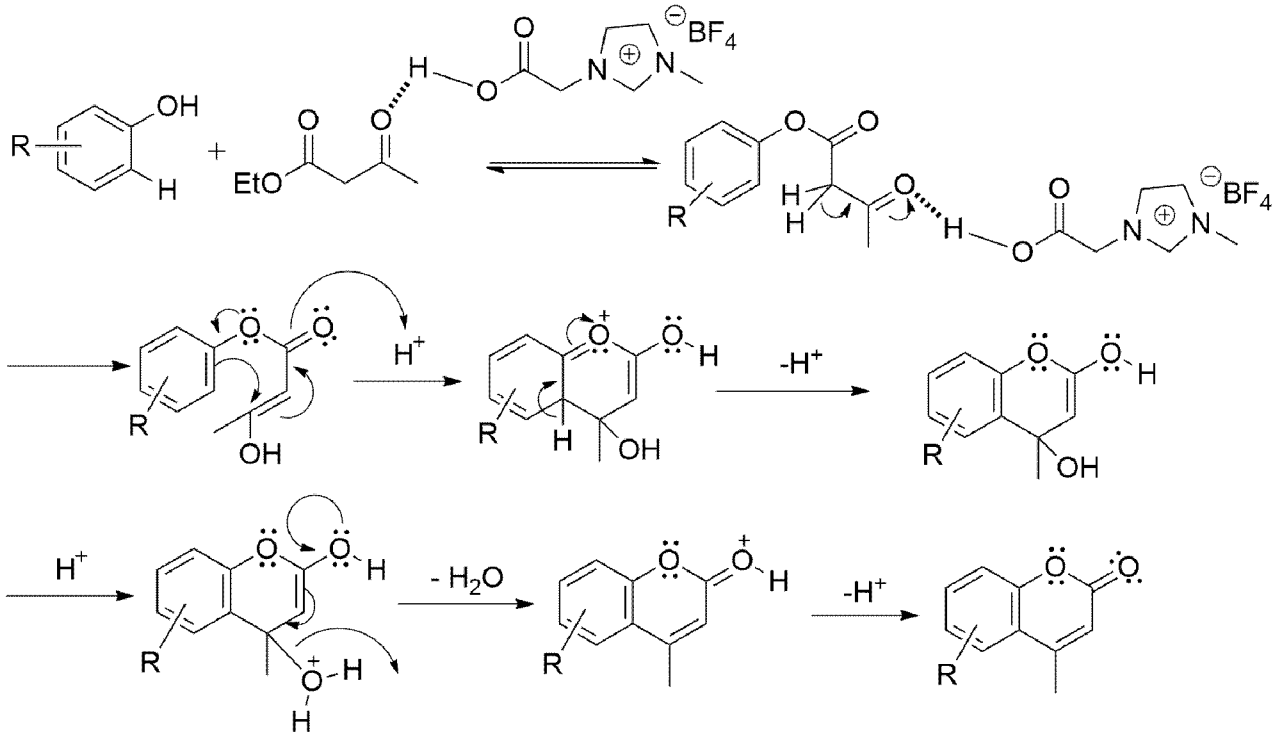
[b]yield after crystallization

reduced from 200mg, significant decrease in yield was observed (Entry 5), which indicates that the amount of ionic liquid also plays a key role in acceleration of reaction with higher yield. The temperature higher than 120°C did not improve the result to greater extent (Entry 6). From these experiments, the most optimum reaction condition was observed to be 120°C reaction temperature in the presence of 200 mg of ionic liquid.

The Pechmann condensation reaction of other phenols and ethyl acetoacetate in the presence of [cmmim][BF_4] was accomplished under the optimized reaction conditions derived from above study and the results are presented in Table 2.

It can easily be concluded that all the reactions proceeded smoothly in ionic liquid and gave good to excellent isolated yields. All the reactions were monitored by TLC and were taken to the completion. The synthesized coumarins were homogeneous on TLC and can be used without any purification for all further practical purpose. However, all the synthesized compounds were crystallized by using ethanol as the solvent. The yields were calculated after crystallization. All the compounds were characterized by melting point, ^{1}H NMR, ^{13}C NMR and DEPT-135 spectral techniques. Additional confirmation for the structures is also obtained by IR and mass spectrometric studies for representative samples from the series. All the data were in agreement with the cited literature.

The IL [cmmim][BF_4] promoted the reaction due to its inherent Brønsted acidity. The -COOH proton of [cmmim][BF_4] is capable of bonding with the carbonyl oxygen of ethyl acetoacetate. The capacity of IL to form H-bond with the substrate may have pushed the reaction in to the forward direction. Based on this the mechanistic pathway for the reaction is given as under (Scheme 2).



Scheme 2

To check activity of the recovered ionic liquid, it was again employed for the same reaction by charging the same substrates. The recovered ionic liquid was found to be equally effective for at least three runs. The effectiveness of the recovered ionic liquid in terms of yield is shown in stick plot (Figure 1).

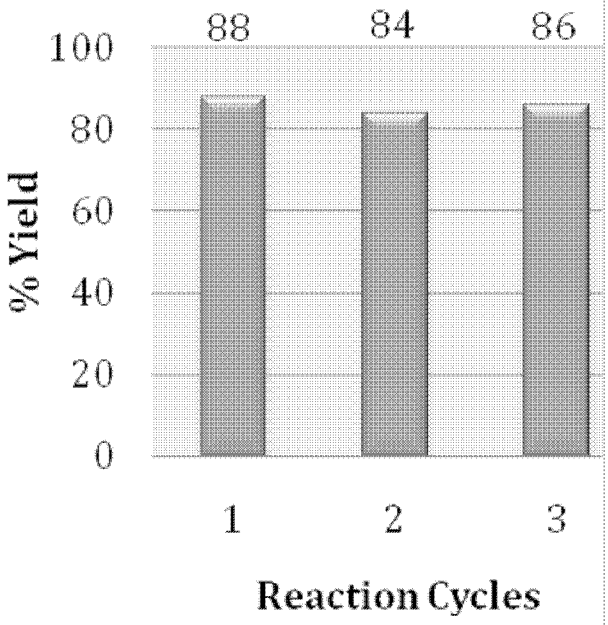


Figure 1 Recyclibility of [cmmim][BF_4] in model reaction of resorcinol and ethyl acetoacetate.

CONCLUSION

The process describes a novel and efficient method for the synthesis of substituted coumarins in presence of acidic ionic liquid [cmmim][BF_4]. The procedure combines the advantages of avoiding hazardous catalysts and solvents. The method gives an imperative alternative to the conventional acid and chloroaluminate based ionic liquid catalyzed procedures leading to coumarin derivatives.

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