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[BMIm]BF_4-LiCl as an effective catalytic system for the synthesis of dicoumarols

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Abstract

A homogeneous ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate doped with LiCl ([BMIm]BF_4-LiCl) was found as catalyst solvents for the synthesis of dicoumarols by the condensation of 4-hydroxycoumarin and aldehyde at 80 ˚C. In this field, several types of aromatic aldehyde, containing electron-withdrawing groups as well as electron-donating groups, were rapidly changed to the corresponding derivatives in good to excellent yields. Application of this new homogeneous catalyst system offered the advantages of short reaction times, solvent-free conditions, high yields, and easy work-up procedure compared to the conventional methods of the syntheses. The ionic liquid can be recovered for the subsequent reactions and reused without any loss of efficiency.

Keywords: Homogeneous catalyst; 4-hydroxycoumarin; ionic liquid; dicoumarols.

Introduction

Ionic liquids have been the subject of considerable current interest as benign reaction media in organic synthesis because of their unique properties of non-volatility, nonflammability, recyclability and ability to dissolve a wide range of materials, among others [1]. During the past few years, a variety of ionic liquids have been demonstrated as efficient and practical alternatives to organic solvents for many important organic transformations [2].

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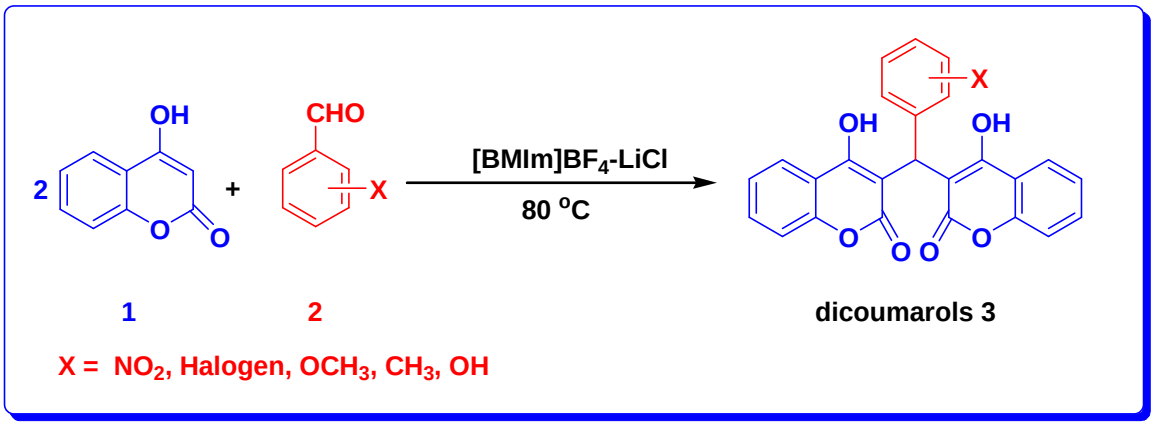
Nevertheless, the ability of ionic liquids to help as catalysts has not been explored to any great extent [3]. Ionic liquids are compounds that are entirely composed of ions and are liquid at or close to room temperature. With the continued efforts of some chemists, ionic liquids have not only become increasingly popular as reaction and extraction media in research and development, they have also widely been promoted as “green solvents”, which are regarded as powerful alternatives to the volatile organic compounds (VOCs) in the field of organic synthesis. Furthermore, the task-specific ionic liquids (TSILs) where a functional group is covalently tethered to the cation or anion (or both) of the ionic liquid, are the latest generation of ionic liquids. The incorporation of this functionality should imbue the ionic liquid with a capacity to behave not only as a reaction medium, but also as a reagent or catalyst in some reactions or processes [4]. Therefore, ionic liquids (IL) presently are the focus of growing attention [5]. Amongst these, metal-containing ionic liquids (MCIL) assure a prominent position because of their particular characteristics which show advantages in catalyst stability and solubility as well as considerable reusability [6]. However the most interesting attribute of this kind of ionic liquids is their potential application towards homogeneous catalysis. Owing to these fascinating features associated with easy phase-separation of reaction mixtures, ionic liquids have achieved an outstanding position as a new generation of solvents in the area of organic synthesis.

Dicoumarol and its derivatives are the parent frameworks found in a large number of naturally occurring as well as synthetic products possessing prominent positions in medicinal chemistry [7-9]. They frequently display a wide range of biological and pharmacological activities, such as antifungal [10], antibacterial [11], antioxidant [11], anti-HIV [12,13], antibiotic [14], antitumor [15], anticoagulant [15], and anti-inflammatory [15]. The coumarin anticoagulants are antagonists of vitamin K. Their target is vitamin K 2,3-epoxide reductase in the liver microsomes. The latter case is an enzyme that is inhibited by therapeutic doses of anticoagulants by reducing the synthesis of anticoagulant factors [16]. Further, lanthanum (III) complexes of dicoumarol are observed to show effective cytotoxic activity [17]. Dicoumarol in combination with Taxol has been reported to show a synergistic inhibition of cell division of sea urchin embryos. This combination drug markedly reduces the high toxicity of Taxol [18].

Dicoumarols are generally synthesized by combination of two equivalents of 4-hydroxycoumarin and different aldehydes. In the recent few years, several methods have been reported for this synthesis which includes the use of different catalysts like molecular iodine [19], DBU [20], piperidine [21], $MnCl_2$ [22], propane-1,2,3-triyl tris(hydrogen sulfate) [23], poly(4-vinylpyridine) and 1,4-butanesultone [24], SO_3H functionalized ionic liquids [25], [BMIm][BF_4] [26], tetrabuthylammonium bromide (TBAB) [27], Zn(Proline)2 [28], sodium dodecyl sulfate (SDS) [29], tetrabutylammonium hexatungstate ([TBA] 2[W_6O_{19}]) [30], sulfated titania (TiO_2/SO_4^{2-}) [31], ruthenium(III) chloride hydrate ($RuCl_3.nH_2O$) [32], n-dodecylbenzene sulfonic acid (DBSA) [33], silica chloride nanoparticles (nano SiO_2Cl) [34], and refluxing in ethanol [8] or acetic acid [9].

However, despite their own merit, in some cases, Lewis acids form stable complexes or even decompose with the ligands present in reaction media, so they may need to be used in excess quantities. Some catalysts are expensive and some others suffer from the formation of by-products, longer reaction time, and corrosion as well as waste acid pollution problems. In continuation of our studies focused on development of ionic liquids as catalysts in the synthesis of organic compounds [35-39], herein we describe the efficiencies of the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate doped with LiCl ([BMIm]BF_4-LiCl) for promoting the synthesis of dicoumarols.



Scheme 1. Synthesis of dicoumarols in the presence of [BMIm]BF_4-LiCl

Experimental

General

All of the solvents and reagents were purchased from Fluka or Merck chemical companies. Melting points were measured with an Electrothermal apparatus and are uncorrected. IR spectra were obtained in KBr discs on a Shimadzu IR-470 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were determined on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively.

Procedure for the preparation of [BMIm]BF_4-LiCl

Ionic liquid [BMIm]BF_4-LiCl was prepared by the reported method [30]. 1-Methylimidazole (5.1 g, 62.1 mmol) was added to 32 mL of 1-chlorobutane. The mixture was heated to reflux for 24 h and then cooled to room temperature, the obtained oily product was separated from reaction mixture by decanting, washed with EtOAc (2 × 20 mL), and the solvent of the collected organic phase was removed under reduced pressure to give 1-butyl-3-methylimidazolium chloride ([BMIm]Cl). In second step, $LiBF_4$ (5 g, 53 mmol) was added to [BMIm]Cl (9.3 g, 53 mmol) dissolved in anhydrous acetone (40 mL). The mixture was then stirred for 48 h at room temperature to get a solution and then stored at 4 ºC over 2 days in refrigerator giving the excess of the dissolved LiCl crystals to precipitate. After separation of the precipitated LiCl crystals (0.87 g, 20.5 mmol), the solvent of the filtered solution was removed under reduced pressure. The ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate doped with 60 mol % of LiCl ([BMIm]BF_4-LiCl) was obtained as a yellow oil.

General procedure for the synthesis of dicoumarol derivatives

1 mL of [BMIm]BF_4-LiCl was added to a mixture of 4-hydroxycoumarin (2 mmol) and an aromatic aldehyde (1 mmol) in a round bottom Flask. The mixture was heated at 80 ˚C and the reaction monitored by TLC using silica gel coated on aluminum sheets and ethyl acetate-petroleum ether as eluent. After completion of the reaction, water (8 mL) was added to the mixture and filtered. The solid residue was recrystallized from ethanol 95.5%.

The selected spectral data

4-hydroxy-3-((4-hydroxy-2-oxo-2*H*-chromen-3-yl)(phenyl)methyl)-2*H*-chromen-2-one (**3a**): White crystalline solid; Yield 98%; mp 228-230 ˚C; IR 3034, 1659, 1602, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$; 300 MHz): δ 6.1 (1H, s, CH) and 7.2-8.4 (13H, m, 13CH). ^{13}C NMR ($CDCl_3$; 75.47 MHz): *δ* 37.4, 94.5,

114.5, 116.7, 123.2, 123.8, 125.4, 126.5, 128.0, 132.2, 138.0, 152.1, 154.1, 164.0.

4-hydroxy-3-((4-hydroxy-2-oxo-2*H*-chromen-3-yl)(4-chlorobenzaldehyde) methyl)-2*H*-chromen-2-one (**3c**): Yellow crystalline solid; Yield 96%; mp 259-261 ˚C; IR 3035, 1662, 1615, 1526, 1345, 759; ^{1}H NMR ($CDCl_3$; 300 MHz): δ 6.6 (1H, s, CH) 7.3-8.3 (12H, m, 12CH). ^{13}C NMR ($CDCl_3$; 75.47 MHz): δ 42.92, 115.87, 118.09, 123.45, 123.83, 125.94, 129.32, 131.24, 131.66, 135.90, 152.27, 163.33, 165.92, 196.16.

4-hydroxy-3-((4-hydroxy-2-oxo-2*H*-chromen-3-yl)(4-methoxybenzaldehyde) methyl)-2*H*-chromen-2-one (**3i**): Yellow crystalline solid; Yield 96%; mp 243-245 ˚C; IR 3300, 3076, 2978, 1684, 1650, 1620, 1601, 1571, 1263; ^{1}H NMR ($CDCl_3$; 300 MHz): δ 3.7 (3H, s, OCH_3), 6.4 (1H, s, CH) and 7.1-8.1 (12H, m, 12×CH). ^{13}C NMR ($CDCl_3$; 75.47 MHz): δ 42.62, 55.46, 113.88, 115.67, 116.48, 116.68, 124.57, 124.94, 128.30, 130.48, 133.08, 152.40, 163.55, 165.22, 193.13.

Results and discussion

In continuation of our ongoing program in developing methods for the synthesis of heterocyclic compounds and identifying new catalysts [35-39], we herein report a novel and efficient protocol for the synthesis of dicoumarols under [BMIm]BF_4-LiCl ionic liquid as catalyst solvents (Scheme 1). We first considered a reaction between 4-hydroxycoumarin and 4-chlorobenzaldehyde by screening the reaction conditions. To determine the optimum conditions, we examined the influence of the reaction temperature, and the type of IL (Table 1). Initially, the reaction, in the absence of catalyst, was performed for a period of 7-8 h at room temperature and at 80 ^{o}C. The desired dicoumarol **3a** were not obtained (Table 1, Entries 9 and 10). This reaction was performed using [BMIm]Cl, [BMIm]Br, [BMIm]OH and [BMIm]HSO_3 ionic liquids. But it requires slightly longer reaction time and its low yield (Table 1, Entries 11-14). It could be seen that the best result was obtained with 1 mL of [BMIm]BF_4-LiCl at 80 ˚C (Table 1, Entry 17). After optimizing the conditions, we next examined the generality of these conditions to other substrates using several aromatic aldehydes bearing electron-withdrawing and electron-donating groups (Scheme 1). The results, summarized in Table 2, delineate the efficiencies of the method in terms of fairly high yields of the products and short reaction times. *Ortho* substituted aldehydes finished desired product with longer reaction time and

low yields compared to their *meta* and *para* counterparts, this might be due to steric hindrance. We also studied the reactions with different aliphatic aldehydes such as propanal, and butanal, but unfortunately we failed to get the desired products. The results represented that the reactions were performed within 10-30 min of heating, and the favorable products were provided in good yields (Table 2). The ionic liquid [BMIm]BF_4-LiCl plays the role of catalyst as well as solvent for the synthesis of dicoumarols. Certainly, the catalysis activity is attributed to the dissolved Lewis acidic Li^+ ions in [BMIm]BF_4 ionic liquid as a solvent. Another advantage of the present method may be requiring no metal catalysts or additional solvent, whilst proceeding with an appropriate rate in comparison with other methods that give similar skeletons.

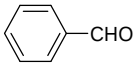
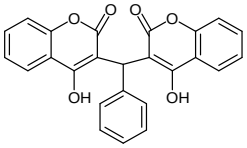
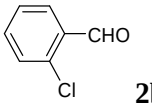
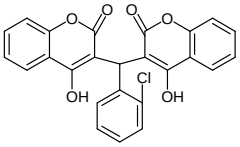
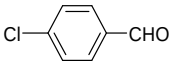
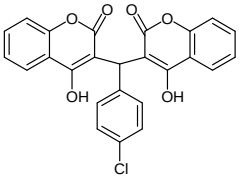
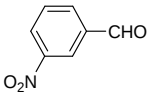
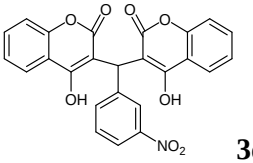
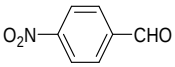
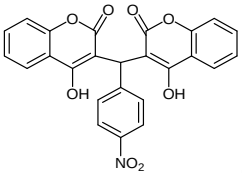
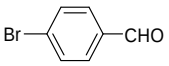
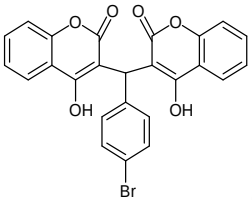
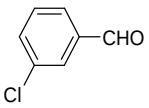
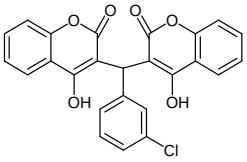
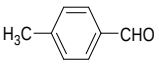
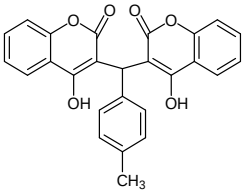
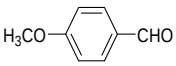
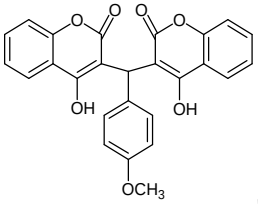
The work-up procedure is so simple for all the syntheses and includes the addition of water at the end of the reaction, filtration, and finally recrystallization of the products from ethanol. The ionic liquid was removed simply by dissolution in water added to the reaction mixture and then recovered by evaporation of water at 80 ˚C under reduced pressure. The catalytic activity of the ionic liquid system remained evidently unaltered even after five successive retrieval and when reused in the same synthesis.

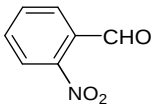
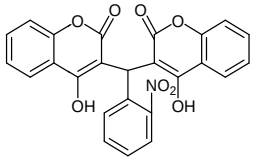
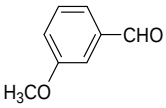
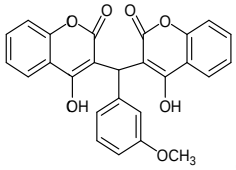
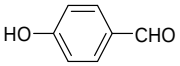
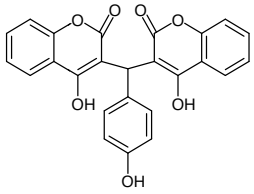
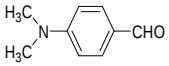
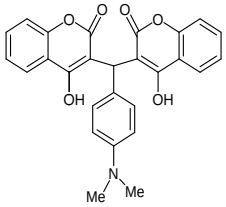
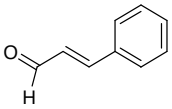
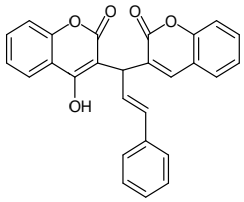
Table 1. Optimization of reaction conditions for the model reactants, 4-hydroxycoumarin **1** and 4-chlorobenzaldehyde **2c**

Entry	Catalyst/ Solvent/ Conditions	Time (min)	Yield(%) [a]
1	-/ rt	480	-
2	-/ 80 °C	420	Trace
3	[BMIm]Cl/ 80 °C	420	46
4	[BMIm]Br/ 80 °C	360	54
5	[BMIm]OH/ 80 °C	540	68
6	[BMIm]HSO_3/ 80 °C	300	78
7	[BMIm]BF_4-LiCl/ rt	120	65
8	[BMIm]BF_4-LiCl/ 70 °C	30	89
9	-/ rt	480	-
10	-/ 80 °C	420	Trace
11	[BMIm]Cl/ 80 °C	420	46
12	[BMIm]Br/ 80 °C	360	54
13	[BMIm]OH/ 80 °C	540	68
14	[BMIm]HSO_3/ 80 °C	300	78
15	[BMIm]BF_4-LiCl/ rt	120	65
16	[BMIm]BF_4-LiCl/ 70 °C	30	89
17	[BMIm]BF_4-LiCl/ 80 °C	10	96

[a]Isolated yield

Table 2. Synthesis of dicoumarols by the reaction of 4-hydroxycoumarin and aromatic aldehydes in [BMIm]BF_4-LiCl at 80 ˚C

Entry	Ar	Product[a]	Time (min)	Yield (%)[b]	Mp (°C) (Found)	Mp (°C) (Reported)
1	 **2a**	 **3a**	10	98	228-230	229-230 [9,18]
2	 **2b**	 **3b**	15	84	237-239	239 [21]
3	 **2c**	 **3c**	10	96	259-261	260-262 [9]
4	 **2d**	 **3d**	15	88	219-223	220-224 [19]
5	 **2e**	 **3e**	25	86	232-234	232-234 [19]
6	 **2f**	 **3f**	30	92	265-267	266-268 [21]
7	 **2g**	 **3g**	15	94	228-230	228-230 [29]
8	 **2h**	 **3h**	25	88	265-267	266-268 [29]
9	 **2i**	 **3i**	15	89	243-245	242-244 [19]

10	 **2j**	 **3j**	30	85	202-204	204 [18]
11	 **2k**	 **3k**	30	97	236-238	238 [21]
12	 **2l**	 **3l**	30	85	191-192	193 [21]
13	 **2m**	 **3m**	25	87	221-223	222-224 [29]
14	 **2n**	 **3n**	30	92	194-195	196 [21]

[a] All the products were characterized by comparison of their spectroscopic and physical data with those reported in literature.
[b] Isolated yield

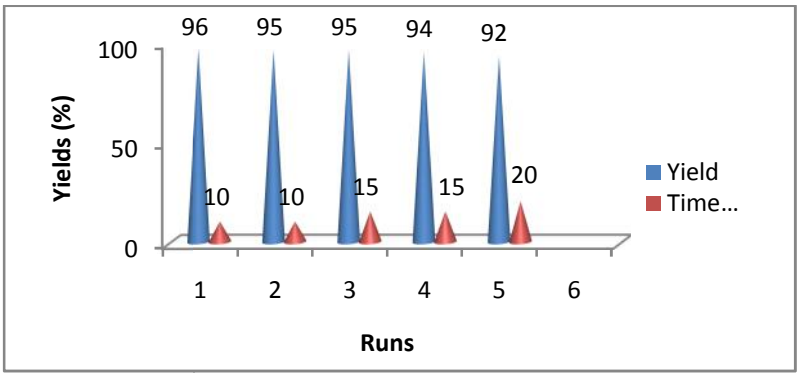
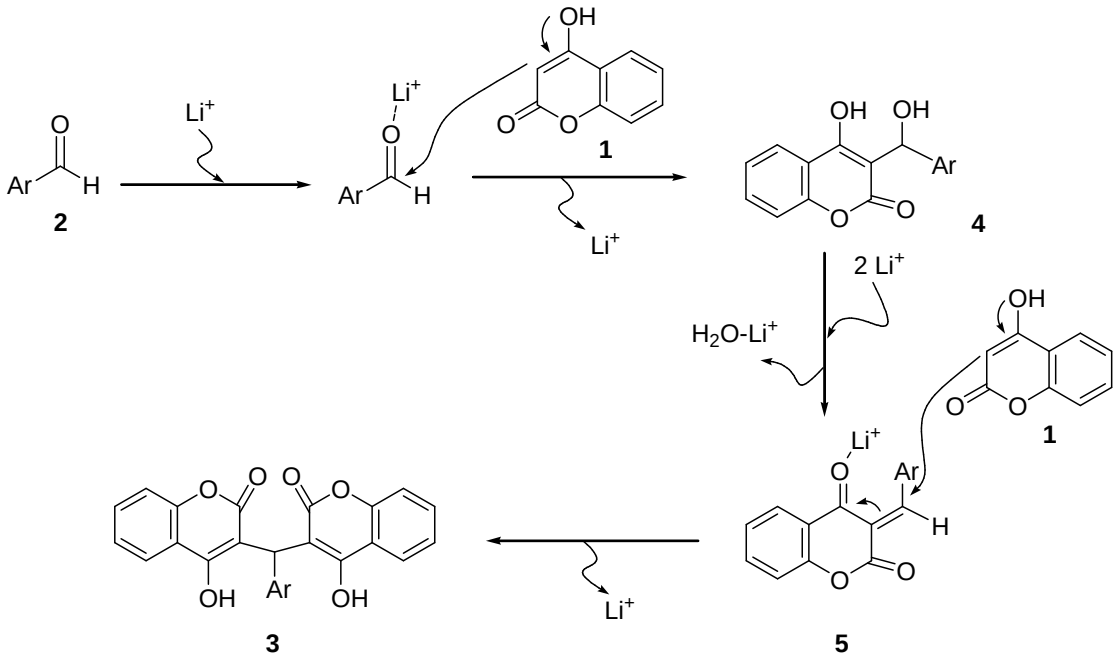


Figure 1. Reusability of the catalyst in product **3c**

The possible mechanism for the reaction is given in Scheme 2. The dicoumarol synthesis presumably initiates by the nuleophilic addition of the substrate 4-hydroxycoumarin **1** on the reactant aldehyde activated by Lithium cation. The resulting

adduct **4** undergoes dehydration to give the key enone intermediate **5** which is likely activated by Lithium cation to follow a Michael type addition onto the second molecule of **1**. The later reaction would produce dicoumarol **3**.



Scheme 2. A plausible mechanism for the synthesis of dicoumarols 3a-n in the presence of [BMIm]BF$_4$-LiCl

Conclusion

In conclusion, we have described an expedient and new method for the synthesis of dicoumarols. The ionic liquid system has the advantages of being inexpensive, easily available, and reusable. Application of this catalyst offered a simple, clean, and cost effective method for the synthesis of the title compounds.

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