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Highly efficient synthesis of dicoumarols and xanthene derivatives in presence of Brønsted–Lewis acidic ionic liquids catalyst

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Abstract A series of metal chloride-based acidic ionic liquids have been prepared and used as an efficient catalyst in one-pot multicomponent synthesis of biscoumarins and substituted xanthenes derivatives under solvent-free conditions. Among the acidic ionic liquids, N-methylpyrrolidonium zinc chloride (Hnmp/ZnCl₃)-based Brønsted-Lewis acidic ionic liquids were found to be an effective and recyclable catalyst for a one-pot synthesis of biscoumarins through the domino Knoevenagel-Michael reaction of a variety of aldehydes with 4-hydroxycoumarin in short reaction times. The reactions which occur under relatively mild conditions afforded the biscoumarin derivatives employing a very low loading of catalyst in satisfactory isolated yields and high purity after simple work-up. The Brønsted-Lewis acidic ionic liquid catalyst was reused four times without any variation in yield.

Keywords Brønsted–Lewis acidic ionic liquids · Dicoumarols · 4-Hydroxycoumarin

Introduction

Coumarin and its derivatives are widely distributed throughout nature, notably in high concentration in the Tonka bean, woodruff and bison grass [1]. Coumarin derivatives have been extensively investigated with regard to their biological activities, pharmaceutical and therapeutic properties, and in therapeutic application besides their employment as anticoagulant (antivitamin K activity) [2]. Undeniably, they are traditional blue-fluorescent labels, nonlinear optical chromophores and sustaining agents. α, α -(Benzylidene)-bis-(4-hydroxycoumarin), commonly known as biscoumarin, is one of the important coumarin derivatives have shown a remarkably broad spectrum of pharmacological and physiological activities as well as additives in food and cosmetics [3, 4]. Many synthetic approaches to biscoumarins using Pechmann, Perkin, Knoevenagel, Reformatsky, and Wittig reactions have been reported [5]. Among the various approaches, domino Knoevenagel-Michael reactions between carbonyl compound and 4-hydroxycoumarin in the presence of catalyst or promoter are a general strategy and many articles dealing with their synthesis, and reactivity has been published [6–17].

Acidic ionic liquids (ILs) have attracted a lot of attention due to their low vapor pressure, ease of separation from reaction products, excellent thermal stability and high ionic conductivity with broad application such as catalysts, reaction media, gas adsorbents and chromatography stationary phases [18–21]. The introductions of functionalized ionic liquids that are "task specific" [22-24] containing metal chlorides are designed to replace some expensive metal halide catalysts and opened many new possibilities for the application these halides in chemical reactions [25]. Furthermore, acidic ILs possess the advantages of both liquid and solid acid catalysts such as water solubilities, recyclable, high acid density, easy separation and reusability. In this context, acidic ILs are now widely acknowledged as a new class of advanced acidic catalyst for applications in the fields of chemistry and industry [18, 26-29].

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MCl₂= FeCl₃, ZnCl₂, SnCl₂, AlCl₃

Scheme 1 Preparation of acidic ionic liquids





Fig. 1 Structures of eight kinds of acidic ionic liquids

Experimental

General

All starting materials and Brønsted–Lewis acidic ionic liquids components such as aldehydes, dimedone, 4-hydroxycoumarin, ZnCl₂, SnCl₂, AlCl₃ and FeCl₃ were commercially available. Melting point was determined on Buchi 535 melting point apparatus. ¹H and ¹³C NMR spectra were recorded on 500 MHz NMR spectrometer using DMSO-d₆ as solvent. Chemical shifts were expressed in (ppm) downfield from TMS. All the reactions were monitored by thinlayer chromatography (TLC) with UV light as detecting agents.

Acidic ionic liquid preparations

IL5–IL8 was prepared according to our previous paper [30].

IL1–IL4

Acidic ionic liquids (IL1–IL4) were prepared by known methods reported on the literature [31, 32] (Scheme 1). The obtained acidic ILs were characterized by ¹H NMR and

 Table 1
 Optimization of acidic ionic liquids for the synthesis of biscoumarin

	ОН	ŎН	Ph OH
PhCHO + [(20 mg) 40 min	
1	2		3
Entry	IL	Temp. (°C)	Yields (%) ^a
1	IL1	100	97
2	IL2	100	80
3	IL3	100	90
4	IL4	100	92
5	IL5	100	78
6	IL6	100	65
7	IL7	100	72
8	IL8	100	78
9	IL1	25	18
10	IL1	40	25
11	IL1	60	65
12	IL1	80	86

^a Isolated yields. Reaction condition: 4-hydroxycoumarin (1 mmol), benzaldehyde (0.5 mmol), catalyst (20 mg), stirred for 40 min

FTIR spectrum; the results were compared with the literature data. A 250-mL three-necked flask with a magnetic stirrer under argon was vacuum-dried and cooled by an Table 2Condensation reactionof various aldehydes and4-hydroxycoumarin

	ŎН		ŎН	Ar OH		
ArCHO	+	IL1 (20 mg) → 30-50 min, 100°C				
1	2			3		
Entry	Ar	Products (3)	Time (min)	Yield (%)	m.p. (°C)	
					Found	Reported [refs.]
1	ОН	ОН ОН	40	97	208–211	208–209 [40]
2	O ₂ N H		30	86	236–238	232–233 [12]
3	ОН		30	81	236–238	231–233 [12]
4			35	90	257–259	248–250 [12]
5	ОН		35	86	229–231	225–227 [16]
6	H ₃ CO	OCH3 OH OH	40	93	269–271	248–250 [12]
7	OCH3		45	90	254–257	232–234 [12]
8	H ₃ C H		45	88	269–271	266–268 [41]

Table 2 continued



ice-water bath and charged with 1-methyl-2-pyrrolidinone NMP (7.43 g, 75 mmol), and HCl (75 mmol, aqueous solution, 32 wt%) was added dropwise for 45 min under stirring. The crude reaction mixture was allowed to warm to 45 °C and continued for 24 h at this temperature. The water was removed by rotary evaporation under reduced pressure at 60 °C, and the crude solid was washed with ethyl acetate to remove any unreacted starting materials. After vacuum drying, [Hnmp]Cl as white solid was obtained. In the next step, [Hnmp] Cl and MCl (ZnCl₂, FeCl₃, AlCl₃ and SnCl₂) in the ratio 1:1 were mixed and stirred under heating at 100 °C for 24 h in N₂ atmosphere to form the pure honey like viscous ionic liquid (Scheme 1).

Typical experimental procedure

With a mixture of aldehyde (0.5 mmol) and 4-hydroxycoumarin (1 mmol) or dimedone (1 mmol) was added acidic ionic liquid (20 mg), and the reaction mixture were heated at the 100 °C with vigorously stirring for 30–50 min. After completion of the reaction, the reaction mixture was allowed to cool to room temperature and was extracted with hot ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was recrystallized from ethanol to afford the pure product which required no further purification. All compounds were characterized as the basis of their spectroscopic data (NMR) and melting point by comparison with those reported on the literature.

Results and discussion

As part of our continued work about the application of green chemistry for organic transformation [33–35] herein, we report the synthesis of a *N*-methylpyrrolidonium metal chloride-based Brønsted–Lewis acidic ionic liquids, which was applied as the highly efficient catalyst for one-pot synthesis of biscoumarins through the domino Knoevenagel–Michael reaction of a variety of aldehydes with 4-hydroxy-coumarin under solvent-free conditions.

First, a series of *N*-methylpyrrolidonium and choline metal chloride-based Brønsted–Lewis acidic ionic liquids were synthesized following the procedure outlined in the literature (Fig. 1).

After preparation of acidic ionic liquids, in order to optimize the reaction condition, benzaldehyde and 4-hydroxycoumarin, as a model reaction under solvent-free conditions to investigate the catalytic performance of acidic ionic liquids. The results are summarized in Table 1. At room temperature, in the presence of acidic ionic liquid, the condensation reaction was negligible. Attempts to improve the Table 3Synthesis of various
xanthenes derivatives in
Brønsted–Lewis acidic ionic
liquids

ArCHO +		1 (20 mg) 50 min., 100 °C	° –		
Entry	4 ArCHO	Product	Yield (%) ^a	m.p (°C)	
ý				Found	Reported
1	O H		95	204–205	202–203 [37]
2	H ₃ CO		80	240–242	242–243 [37]
3	CI		82	230–232	226–228 [37]
4	H ₃ C H		90	214–215	215–216 [37]
5	Br H	Br	80	230–232	238–239 [37]

^a Isolated yield



Fig. 2 Mechanistic assumption for the acidic ionic liquid catalyzed reaction



Fig. 3 Recyclability of acidic ionic liquid

yields by raising the reaction temperature led to improve the yields at 100 °C and reduced the time of reaction to 40 min. Screening different acidic ionic liquids revealed that IL1 emerged as the best catalyst for the synthesis of biscoumarins in quantitative yields (Table 1, entry 1).

With these optimistic results in hand, a variety of heteroaryl as well as aryl and alkyl aldehyde were evaluated in terms of both scope and reaction efficiency, and the results are summarized in Table 2. Aldehyde substrates with electron neutral and electron donating as well as electron withdrawing at the ortho-, meta-, and para-substituents were converted to the biscoumarin derivatives with good to excellent yields. Functional groups such as carboxyl, halogen, methoxy, alkyl and hydroxyl groups were also tolerated.

We next applied this fast reaction rate procedure to another active methylene compound such as dimedone (4) which gives highly functionalized biologically important heterocyclic compounds [36-39] (Table 3). Interestingly, the three-component reaction of a series of aromatic aldehydes with dimedone 4 when carried out under solventfree condition using IL1 furnished the corresponding substituted xanthenes derivatives 5 in good to excellent yields. The reaction proceeded well with no remarkable difference in yields and reaction time between aromatic aldehydes with neither electron-donating groups and nor electron-withdrawing groups. A mechanism is proposed based on experimental data, which suggests that in the initial step, acidic ionic liquids behave as a Brønsted–Lewis acid catalyst and activate carbonyl group of aldehyde (Fig. 2). The nucle-ophilic addition of 4-hydroxycoumarin to activated aldehydes (I), after H_2O removal to give Michael acceptor II. Michael addition of another molecule of 4-hydroxycoumarin to activate intermediate II to give biscoumarin products.

The recovery and reuse of the reaction system were highly preferable in terms of industrial application and green chemistry. To test the catalyst reusability, 4-hydroxycoumarin (6 mmol), benzaldehyde (3 mmol) and IL1 (60 mg) were heated at 100 °C under solventfree condition for 40 min. After completion of the reaction, the crude product was extracted with ethyl acetate and was filtered to separate the IL1. The IL1 was washed with ethyl acetate (10 mL) and dried in vacuum and used for the next run over five cycles without any variation in product yield and reaction rate (Fig. 3). The spent catalyst was characterized by EDAX and ICP. The catalyst leaching was investigated for the model reaction, and the zinc amount was determined by EDAX and ICP-AES in the ethyl acetate solution. The amount of leached Zn in the recovered samples is negligible.

Finally, comparison of the acidic ionic liquid catalyzed preparation of biscoumarins under solvent-free conditions with a range of other methodologies demonstrated the high yields, short reaction times, low loading of catalyst and eco-friendly nature of the protocol (Table 4).

Conclusion

In summary, different metal chloride-based acidic ionic liquids were synthesized and used as operationally simple and clean catalyst for the preparation of a wide variety of biscoumarin and xanthene derivatives. The proposed method is reliable, effective and greener and can replace maybe

Table 4 Comparison of acidicionic liquid with previousprocedure

Entry	Solvent	Catalyst	Temp.	Time (min)	Yield (%)	References
1	-	ChOH (40 mol%)	50	60	99	[6]
2	-	[[PSebim][OTf] (10 mol%))	70	120	95	[8]
3	Water	BiVO4-NPs (30 mg)	80	25	90	[12]
4	Water	Phosphotungstic acid (15 mol%)	80	20	93	[15]
5	Water	P ₄ VPy–CuO-NPs (20 mg)	Reflux	20	90	[16]
6	Ethanol/water	SBA-Pr-SO ₃ H (40 mg)	Reflux	25	97	[41]
7	Water	SBA-Pr-SO ₃ H (40 mg)	80	15	90	[42]
8	_	IL1 (20 mg)	100	40	97	This work

more promising candidates as recyclable ionic catalysts for organic transformation.

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