Choline Hydroxide: An Efficient and Biocompatible Basic Catalyst for the Synthesis of Biscoumarins Under Mild Conditions

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Abstract In this work, choline hydroxide is found to be an efficient and green catalyst for the synthesis of biscoumarins through the Domino Knoevenagel–Michael reaction of a series of aldehydes with 4-hydroxylcoumarin under mild conditions. A series of aldehydes with different substituted functional groups, especially those which are sensitive to acid, have been converted to biscoumarins with good to excellent isolated yields, and the reactions can be easily scaled up to multigrams. The target products can be simply separated by filtration, and the aqueous solution of choline hydroxide (as filtrate) can then be reused for the next run reaction.

Graphical Abstract Choline hydroxide was found to be a green and efficient catalyst for the synthesis of biscoumarins through the Domino Knoevenagel–Michael reactions under mild conditions.



Keywords Basic ionic liquid · Biscoumarins · One-pot reaction · Aldehyde

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1 Introduction

Biscoumarin and its derivatives have received increasing attention due to their wide range of biological activity such as anti-HIV, anti-bacterial, anti-oxidant, anti-cancer, and anti-coagulant activities [1-4]. Biscoumarins are usually synthesized through the Domino Knoevenagel-Michael reactions of aldehydes with two equivalents of 4-hydroxycoumarin in the presence of catalyst. The present catalyst systems such as molecular iodine [5], SO₃Hfunctionalized ionic liquids [6], ionic liquids with both Lewis acid and bronsted acid sites [7], $Zn(Proline)_2$ [8], sodium dodecyl sulfate [9], p-dodecylbenzenesulfonic acid/piperidine [10], sulfated titania [11], heteorpoly acid [12], nano silica chloride [13], propane-1,2,3-triyltris (hydrogen sulfate) [14] and $Ce_2(SO_4) \cdot 4H_2O$ [15], are almost acidic and often suffered from drawbacks like low yield, long reaction time, high reaction temperature, necessity of refluxing in organic solvent and use of expensive, toxic and unreusable catalyst. In the aspect of green chemistry and industrial application, a non-toxic, reusable and efficient catalytic system at reduced temperature for the synthesis of biscoumarins is in great necessary.

As a non-toxic and naturally abundant derivative of choline and a water soluble essential nutrient, choline hydroxide has shown excellent catalysis performance for aldol reaction [16, 17] and transesterification reaction for biodiesel production [18]. This suggests that choline hydroxide is a suitable basic catalyst in organic transformations. However, its utilization in the basic catalyzed Domino reactions has not been reported to our knowledge. As a continuation of our longstanding interest in the development of choline-based ionic liquids in sustainable catalysis [19–23], we describe here a simple and efficient

procedure for the synthesis of biscoumarins under mild conditions through the Domino Knoevenagel–Michael reactions by using aqueous solution of choline hydroxide as a cheap and reusable basic catalyst. This catalyst system benefits from feasible catalyst preparation, simple work-up and separation procedures, high tolerance to various functional groups, and no use of volatile organic solvents. In addition, the catalyst itself is non-toxic and biocompatible, and this catalysis system can be scaled up for multi-gram synthesis with high isolated yield for the target biscoumarin. This suggests that the approach reported here is green and has great promising in industrial application.

2 Results and Discussion

First, the reaction between benzaldehyde and 4-hydroxylcoumarin was used as a model reaction to investigate the catalytic activities of the choline-based ionic liquids for the synthesis of biscoumarin, and the results were collected in Table 1. It was found that aqueous solution of choline hydroxide could promote this reaction at 50 °C to give a 82 % isolated yield for the target product after 3 h, while the other choline-based ionic liquids which have a little weaker basicity such as choline acetate ([choline][Ac]), *N*,*N*-dimethylethanolamine acetate ([DMEA][Ac]) and N,N-dimethylethanolamine lactate ([DMEA][Lac]), had lower catalytic activity. Comparatively, catalytic activity of the choline-based ionic liquids with acidic anions was even much weaker. Considering the fact that almost all of the acidic catalyzed biscoumarins synthesis were performed at the temperature above 90 $^{\circ}$ C, this result suggested that basic catalysts would have better catalysis performance compared with acidic catalysts under reduced temperature.

Then, the effect of the amount of ionic liquid on catalysis performance was investigated using the model reaction at 50 °C, and the results were included in Table 2. It can be seen that the isolated yield of the target compound reached to a maximum within 1 h when the amount of the catalyst was 1.5 equivalent of aldehyde. Further increase of the amount of choline hydroxide resulted in a slight decrease of biscoumarin yield. These results demonstrated that low catalyst amount led to a relatively low reaction rate, while excess catalyst gave rise to side reactions. Therefore, 1.5 equivalent amount of choline hydroxide based on aldehyde was selected as the optimal catalyst amount. Under this optimized condition, the effect of reaction temperature was investigated and the results were given in Table 3. It was shown that 50 °C is the most favorable reaction temperature because of the high reactivity and selectivity for the formation of the target compound.

Next, a series of biscoumarins were synthesized using different aldehydes and 4-hydroxycoumarin under optimized reaction conditions. It can be seen from Table 4 that in almost of the cases, whether the nature of the substitution was electron withdrawing or electron donating, the aromatic aldehydes could be reacted to arrive at excellent isolated yields within 2 h (entries 1–14, Table 4). Similar results were obtained with the heteroaromatic aldehydes (entries 15, 16, Table 4). Interestingly, when piperonyl aldehyde was used as a substrate, the acetal group could be

Table 1 Catalytic performance of different choline-based ionic liquids on the synthesis of biscoumarin



Entry ^a	Catalyst	Reaction time (h)	Yield (%) ^b
1	ChOH (40 %)	2	82
2	[choline][Ac]	2	74
3	[DMEA][Ac]	2	69
4	[DMEA][Lac]	2	60
5	[choline][HSO ₄]	4	47
6	[choline][H ₂ PO ₄]	4	55
7	[DMEA][HSO ₄]	4	40
8	[DMEA][H ₂ PO ₄]	4	54

^a The mole ratio of benzaldehyde: 4-hydroxylcoumarin: ionic liquid = 1:2:0.2

^b Isolated yield

Entry	Catalyst	Ratio ^a	Time (h)	Yield (%) ^b
1	ChOH (40 %)	1:2:0.1	2	81
2	ChOH (40 %)	1:2:0.2	2	82
3	ChOH (40 %)	1:2:0.5	2	90
4	ChOH (40 %)	1:2:1	2	96
5	ChOH (40 %)	1:2:1.5	1	99
6	ChOH (40 %)	1:2:2	1	97

Table 2 Optimization of catalyst amount using the model reaction

The reaction was performed at 50 $^{\circ}\mathrm{C}$

^a Isolated yield

^b The molar ratio of benzaldehyde: 4-hydroxylcoumarin: ionic liquid

Catalyst	Temperature (°C)	Time (h)	Yield (%) ^a
ChOH (40 %)	r.t.	2	80
ChOH (40 %)	35	2	85
ChOH (40 %)	50	1	99
ChOH (40 %)	70	1	98
	Catalyst ChOH (40 %) ChOH (40 %) ChOH (40 %) ChOH (40 %)	Catalyst Temperature (°C) ChOH (40 %) r.t. ChOH (40 %) 35 ChOH (40 %) 50 ChOH (40 %) 70	Catalyst Temperature (°C) Time (h) ChOH (40 %) r.t. 2 ChOH (40 %) 35 2 ChOH (40 %) 50 1 ChOH (40 %) 70 1

The molar ratio of benzaldehyde: 4-hydroxylcoumarin: ionic liquid = 1: 2: 1.5

^a Isolated yield

Table 4 Reaction of aromatic/heteroaromatic aldehydes with 4-hydroxycoumarin catalyzed by choline hydroxide



Entry ^a	R	Product	Time (h)	Yield (%)
	СНО			
	B			
1	R = H	3a	1	99
2	R = 4-F	3b	1	99
3	R = 4-Cl	3c	2	99
4	R = 4-Br	3d	2	94
5	R = 4-OH	3e	1	94
6	R = 2-OH	3f	1	99
7	$R = 4-NO_2$	3g	2	89
8	$R = 3-NO_2$	3h	2	93
9	$R = 2-NO_2$	3i	2	75
10	R = 4-CH ₃	3ј	2	94
11	$R = 4-CF_3$	3k	2	96
12	R = 4-OCH ₃	31	1	95
13	$R = 4-(OH)-3-(OCH_3)$	3m	2	93
14	NСНО	3n	2	81

Table 4 continued				
Entry ^a	R	Product	Time (h)	Yield (%)
15	СНО	30	1	98
16	ОСНО	3р	3	95
17 ^b	R = H	3 a	1	Quanti

^a Reaction conditions: the molar ratio of benzyaldehyde: 4-hydroxylcoumarin: choline hydroxide was 1:2:1.5, and the reaction temperature was 50 $^{\circ}$ C

^b The reaction scale was 10 mmol benzaldehyde, 20 mmol 4-hydroxylcoumarin and 15 mmol choline hydroxide

well kept and excellent isolated yield could be obtained for the target compound within 3 h, suggesting that the acidic sensitive groups were well tolerant in this catalytic system. In these reactions, the solid target compounds could be filtered off from the reaction mixture after the completion of the reaction. Simple recrystallization using aqueous ethanol would give pure biscoumarins and no column purification for the products was needed. The filtrate of the aqueous solution of ionic liquid could be directly reused for the next run of catalysis. In addition, the scaled up reaction between benzaldehyde and 4-hydroxylcoumarin was conducted under the optimized reaction condition, the target compound could be obtained with quantitative isolated yields within 1 h (entry 17, Table 4).

The recovered aqueous solution of choline hydroxide was used directly for the next run reaction under the same conditions, and the reutilization results were collected in Fig. 1. It was found that the catalytic activity could be well maintained for at least five cycles without significant decrease.



Fig. 1 The reusability of choline hydroxide

3 Conclusions

In this work, an efficient basic catalyst was developed for the one-pot synthesis of biscoumarins under mild conditions. A series of biscoumarins with different substitute groups could be synthesized with good to excellent isolated yields, and acidic sensitive groups could be well kept in this catalytic system. These reactions could be efficiently scaled up to multigrams, and the target products could be simply separated by filtration. The ionic liquid catalyst, choline hydroxide, is cheap, easy to prepare, highly biocompatible and biodegradable. These benefits plus its excellent catalytic efficiency and reusability make it an ideal green catalyst for the one-pot preparation of biscoumarins.

4 Experimental

4.1 Preparation of Ionic Liquids

Choline hydroxide was prepared as follows: analytical grade choline chloride was recrystallized using aqueous solution of ethanol and then ion exchanged to hydroxide anion using strong basic anion exchange resin until no chloride anion could be detected using aqueous solution of AgNO₃. The concentration of choline hydroxide was determined by acid–base titration. The other ionic liquids were prepared according to the literatures [20, 21].

4.2 Typical Procedure for the Preparation of Biscoumarins

Aldehyde (1 mmol), 4-hydroxylcoumarin (2 mmol) and aqueous solution of 40 wt% choline hydroxide (1.5 mmol) were added to a 10 ml round bottom flask and then the mixture was stirred at 50 °C at desired time, and the reaction was monitored by TLC. When the reaction was completed, the mixture was cooled to room temperature

and filtered to obtain solid target product. The pure product was obtained by washing using 10 % ethanol aqueous solution, and the filtrate containing choline hydroxide can be reused directly for the next cycle.

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