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[bmim]Br as an Efficient Medium for the Green and Catalyst-Free Synthesis of Biscoumarin Derivatives

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A series of biscoumarin derivatives were synthesized *via* the reaction of 4-hydroxycoumarin and aromatic aldehydes in the presence of ionic liquid, 1-butyl-3-methylimidazolium bromide, [bmim]Br, without the use of any catalyst. This method has the advantages of good yields, milder reaction conditions, easier work up, no catalyst and environmentally benign procedure.

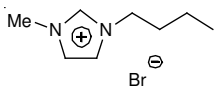
Key Words: Ionic liquid, [bmim]Br, 4-Hydroxycoumarin, Biscoumarins, Catalyst-free.

INTRODUCTION

4-Hydroxycoumarins and its derivatives are known for their various biological activities such as anticoagulant, insecticidal, antihelminthic, hypnotic, antifungal, phytoalexin and HIV protease inhibition[1-3]. Biscoumarins, the bridge substituted dimers of 4-hydroxycoumarin, have enormous potential as anticoagulants[4,5]. A number of biscoumarins have been screened for anticoagulant activity and quite a few of them have also been found to be urease inhibitors[6]. These compounds have generally been synthesized in the presence of several catalysts such as TEBA[7], I_2[8] and TBAB[9], *etc*. The synthesis of biscoumarins have also been reported by microwave irradiation[10,11]. Though the above methodologies are quite useful, most of the methods encounter some limitations, such as requirement of toxic catalysts, long reaction time and harsh reaction conditions. Thus, alternative procedures with more general applicability, considerably faster reaction with high yields and environmentally friendly conditions are still in demand.

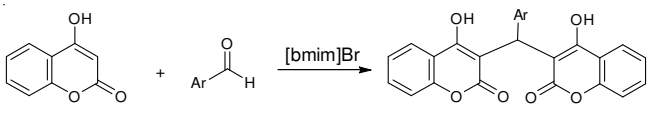
Green/sustainable chemistry (GSC) is, in a word, chemistry and chemical technology for environmentally friendly products and processes. Green chemistry has been defined as a set of principles that reduces or eliminates the use or generation of hazardous substances throughout the entire life of chemical materials[12,13]. If one compares the technology with medical care, green/sustainable chemistry focuses on precaution (or prevention) rather than diagnosis and cure. Here, the idea of placing more stress on the stage of design, as stated in the definition[12,13], is important and useful. From both economical and environmental points of view, the use of non-volatile solvents and nonmetallic catalysts is very promising. In the last few years room temperature ionic liquids (RTILs), especially those based on 1,3-dialkylimidazolium cations[14], have been recognized as a possible environmentally benign alternative to chemical volatile solvents because of their unique properties, such as nonvolatility, nonflammability and high thermal stability[15].

As part of our current studies on the development of new routes for the synthesis of organic compounds in ionic liquids[16-23], herein we wish to report a green and rapid methodology for the synthesis of biscoumarins in ionic liquid, 1-butyl-3-methylimidazolium bromide, [bmim]Br (Fig. 1) as an efficient promoting medium without the use of any catalyst (**Scheme-I**).



[bmim][Br]

Fig. 1. Ionic liquid structure



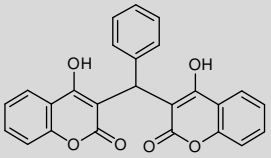
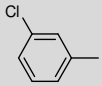
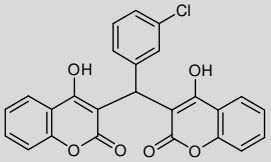
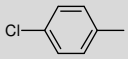
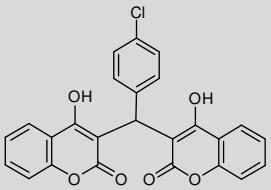
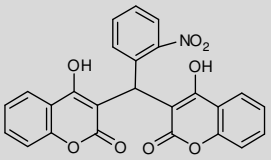
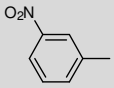
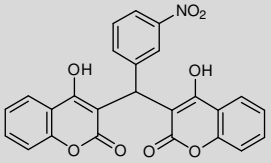
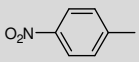
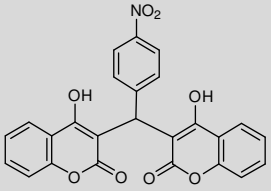
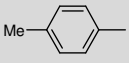
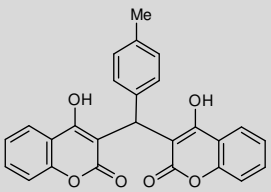
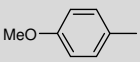
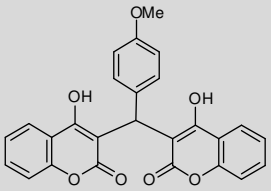
1 2a-h 3a-h

Scheme-I: Synthesis of biscoumarins

EXPERIMENTAL

All compounds were known and their physical and spectroscopic data were compared with those of authentic samples and found to be identical. [bmim]Br was prepared according

TABLE-2
SYNTHESIS OF BISCOUMARINS

Entry	Ar	Products[a]	Time (min)	Yields (%)[a]	Melting point (ºC)	
					Found	Reported [Ref.]
1		 **3a**	20	84	229-231	228–230 [8]
2		 **3b**	22	85	220-223	222-224 [10]
3		 **3c**	24	88	263-265	258–259 [11]
4		 **3d**	20	77	203-205	200–202 [10]
5		 **3e**	25	80	213-215	212–215 [10]
6		 **3f**	18	86	233-235	232–234 [8]
7		 **3g**	30	85	267-268	269–270 [11]
8		 **3h**	40	78	246-248	249–250 [11]

[a]Isolated yields.

to the literature procedure[24]. Melting points were recorded on an electrothermal type 9100 melting point apparatus. The IR spectra were obtained on a 4300 Shimadzu spectrophotometer as KBr disks. The ^{1}H NMR (500 MHz) spectra were recorded on Bruker DRX500 spectrometer.

General procedure for the synthesis of biscoumarins: A mixture of 4-hydroxycoumarin (2 mmol), aromatic aldehyde (1 mmol) and [bmim]Br (1 mmol) was heated in the oil bath at 60 °C for the appropriate time. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature and cold ethanol was added. The precipitate was filtered off and recrystallized from ethanol to give compounds **3a-h** in good yields.

Recycling of the ionic liquid: Due to the fact that the ionic liquid, [bmim]Br, is soluble in cold ethanol, it could therefore be recycled of the filtrate. [bmim][Br] was recovered by evaporation of the ethanol, washed with diethyl ether and dried at 50 ºC under under vacuum for 1 h and reused in another reaction. It could be used at least three times without significant loss of activity.

RESULTS AND DISCUSSION

From the beginning of this study, 4-hydroxycoumarin and benzaldehyde were employed as the model reactants to optimize the reaction conditions. At first, the reaction was carried out by heating a mixture of 4-hydroxycoumarin (2 mmol) and benzaldehyde (1 mmol) under solvent-free conditions without the use of any catalyst in order to synthesis of compound **3a** (Table-1). As shown in Table-1, no product was obtained under solvent-free conditions at 100 ºC even after 2 h (entry 1). Furthermore, the reaction was carried out in different solvents (entries 2-8). As shown, in comparison to conventional solvents, the yield of the reaction in [bmim]Br is higher and the reaction time is shorter. Therefore, it can be suggested that the ionic liquid plays a role as promotor besides the role of the media. The good result was obtained when [bmim]Br was used at 60 ºC for 20 min. Increasing the reaction time or temperature did not improve the yield.

TABLE-1
RESULTS OF THE SYNTHESIS OF COMPOUND **3a** IN DIFFERENT SOLVENTS WITHOUT ANY CATALYSTS[a]

Entry	Solvent	Temp. (°C)	Time (min)	Yield (%)[b]
1	Solvent-Free	100	120	None
2	EtOH	Reflux	100	20
3	$CHCl_3$	Reflux	100	Trace
4	H_2O	Reflux	100	Trace
5	CH_3CN	Reflux	100	Trace
6	[bmim][Br]	60	20	84
7	[bmim][Br]	80	20	84
8	[bmim][Br]	100	50	85

[a]2 mmol 4-hydroxycoumarin and 1 mmol benzaldehyde.
[b]Isolated yields.

Using these optimized reaction conditions, the scope and efficiency of this approach was explored for the synthesis of a wide variety of substituted biscoumarins and the obtained results are summarized in Table-2. All the reactions, delivered good product yields and accommodated a wide range of aromatic aldehydes bearing both electron-donating and electron-withdrawing substituents. In all cases, the obtained product was isolated by a simple work-up.

Reusability of [bmim]Br was also investigated. For this purpose, the same model reaction was again studied under optimized conditions. After the completion of the reaction, the reaction mixture was cooled to room temperature, cold ethanol was added and the product was filtered off. The [bmim]Br was recovered of the filtrate by evaporation of the ethanol, washed with diethyl ether and dried at 50 ºC under vacuum for 1 h and reused for a similar reaction. As shown in Fig. 2, the [bmim]Br could be used at least three times without significant loss of its activity as promoting medium.

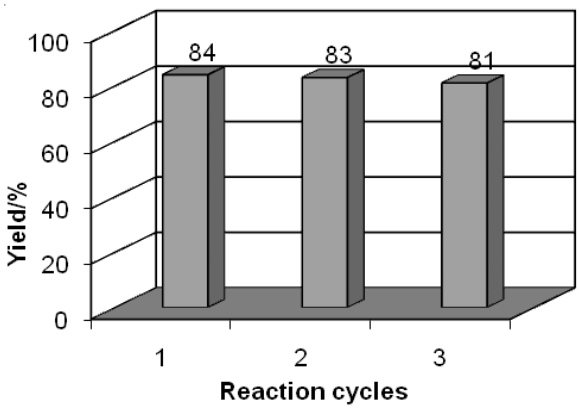


Fig. 2. Reusability of [bmim]Br for model reaction

Conclusion

A simple and efficient method is developed for the synthesis of biscoumarins by the reaction of 4-hydroxycoumarin and aromatic aldehydes in the presence of ionic liquid, [bmim]Br, as an efficient promoting medium without the use of any catalyst. The [bmim]Br can be recycled after a simple work-up and used at least three times without substantial reduction in its activity. Good yields, relatively short reaction times, easy work-up and the absence of catalyst and volatile organic solvents are just a few of the advantages of this procedure.

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