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Green synthesis of 5-benzylidene rhodanine derivatives catalyzed by 1-butyl-3-methyl imidazolium hydroxide in water

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Abstract A basic functionalized ionic liquid, 1-butyl-3-methyl imidazolium hydroxide ([*bmim*][OH]), catalyzed the *Knoevenagel* condensation of rhodanine with aromatic aldehydes. It proceeded smoothly in water to afford the 5-benzylidene rhodamine derivatives in high yields at room temperature. This new method offers several advantages, such as excellent yields, short reaction times, and simple procedure. The catalyst can be reused at least 5 times without significant loss of activity.

Keywords Aromatic aldehyde; Rhodanine; Benzylidenerhodamine; Ionic liquid.

Introduction

Ionic liquids have attracted extensive research interest in recent years as environmental benign solvents due to their favorable properties, like non-inflammability, negligible vapor pressure, reusability, and high thermal stability [1]. They have also been referred to as ''designer solvents'' as their physical and chemical properties could be adjusted by a careful choice of cation and anion. Apart from this they exhibit acidic or basic properties. Combining these unique properties of ionic liquids they are emerging as ''green reaction media''. The use of ionic liquids as reactions medium may offer a convenient solution to both the solvent emission and catalytic recycling problem [2]. Moreover, the low cost of water, along with its non-toxic nature, renders it as attractive medium for chemical synthesis. Reactions in aqueous media offer many advantages, such as simple operation and high efficiency in many organic reactions that involve water soluble substrates and reagents [3]. These advantages become even more attractive if such reactions can be conducted using ionic liquids in aqueous media.

Rhodanine derivatives have shown a wide range of pharmacological activities, which include anticonvulsant, antibacterial, antiviral, and antidiabetic effects [4]. Additionally, rhodanine-based molecules have been popular as small molecule inhibitors of numerous targets such as HCV protease [5], aldose reductase [6], β-lactamase [7], JNK-stimulating phosphatase-1 (JSP-1) [8], *etc*. Rhodanine and some of its derivatives have higher sensitivity and selectivity for the analysis of certain noble metal ions [9]. Thus, the synthesis of rhodanine derivatives currently is of much importance. It is well known that 5-benzylidene rhodanine derivatives are generally prepared by reacting aromatic aldehydes with rhodanine in organic solvents (*i.e.*, ethanol, acetic acid) and in the presence of base (*i.e.*, NaO*Ac*, NH_4O*Ac*) [10]. Conventional approaches for the synthesis of these compounds often involve long reaction times, harsh reaction conditions, unsatisfactory yields, and environmentally unfavorable solvents. Recently, microwave irradiation has been used in this reaction to

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decrease reaction times and increase yields [11]. Thus, the development of a new procedure for the synthesis of 5-benzylidene rhodanine derivatives would be highly desirable. In continuation of our work on development of benign procedures using functionalized ionic liquid [12], we would like to report an efficient method for the synthesis of 5-benzylidene rhodanine derivatives in the presence of basic ionic liquid [*bmim*][OH] as catalyst. To our knowledge, synthesis of 5-benzylidene rhodanine derivatives catalyzed by [*bmim*][OH] have not been reported. Herein, we describe a simple and straightforward procedure for synthesis of 5-benzylidene rhodanine derivatives *via* the condensation of aromatic aldehydes with rhodamine catalyzed by [*bmim*][OH] in aqueous media under mild conditions.

Results and discussion

The *Knoevenagel* condensation of the C-5 active methylene of rhodanine with aromatic aldehydes proceeded smoothly in the presence of 10 mol% of basic ionic liquid [*bmim*][OH] at room temperature and the results are summarized in Table 1. It shows that the aromatic aldehydes having different substituents, such as fluoro, chloro, nitro, methyl, methoxy, methyl, *etc*. were converted to the corresponding products in high yields. However, the aromatic aldehydes with electron-withdrawing groups, such as fluoro, chloro or nitro proceeded at faster rates than those with electron-donating groups, such as methoxy, methyl, *etc*.

The catalyst plays a crucial role in the success of the reaction in terms of the rate and the yields. Taking the benzaldehyde reacted with **2** as an example, the reaction could be carried out in the absence of the catalyst when the mixture was stirred at room temperature for 12 h, but the product was obtained in very poor yield (15%). We have tested some catalysts such as tetramethylammonium hydroxide and tetrabutylammonium hydroxide, the yields of the two basic catalysts were 72% and 75%, respectively, showing that [*bmim*][OH] was the best catalyst for this reaction.

Compare with traditional solvents, ionic liquids are easily reused, which is superior to the conventional solvents and catalysts. Hence, we decided to study the catalytic activity of the recycled reaction system of [*bmim*][OH]/H_2O in the synthesis of **3a**. After the separation of products, the catalyst-containing aqueous medium was reused in the next run without further purification. As shown in Table 2, the reaction medium can be recycled at least five times without significant decrease of the yields, the yields ranged from 86% to 81%.

In conclusion, we have developed a simple and effective method for the synthesis of 5-benzylidene rhodamine derivatives by the *Knoevenagel* condensation of various aromatic aldehydes with rhodanine in the presence of [*bmim*][OH] at room temperature. The catalyst can be reused at least five times without significant loss of activity. Furthermore, water was chosen as the solvent, which is cheap and benign.

Table 1 Synthesis of 5-benzylidene rhodanine derivatives[a]

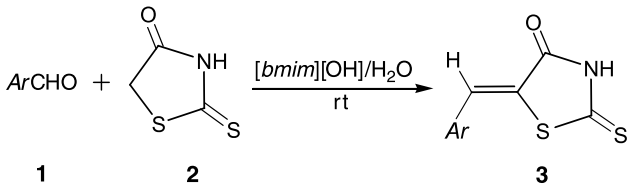
Entry	*Ar*	Time/min	Comp.	Yield/%[b]	mp/°C	mp/°C [Ref.]
1	H	60	**3a**	86	203–204	205 [4c]
2	2-Cl	30	**3b**	91	180–181	181–182 [13]
3	4-Cl	30	**3c**	95	230–231	229–230 [13]
4	2,4-Cl_2	30	**3d**	92	232–233	233–234 [13]
5	4-F	30	**3e**	96	221–222	219 [4c]
6	4-Br	30	**3f**	90	230–231	230 [4c]
7	3-NO_2	20	**3g**	96	263–264	263–265 [13]
8	4-NO_2	10	**3h**	98	255–256	255–256 [11]
9	4-CH_3	90	**3i**	80	224–225	221–223 [13]
10	4-CH_3O	90	**3j**	87	250–251	249–250 [13]
11	4-OH	90	**3k**	81	185–186	184–185 [11]
12	4-$(CH_3)_2N$	90	**3l**	88	273–274	170–271 [13]
13	2-fruyl	30	**3m**	91	230–231	228–229 [13]

[a] Reaction conditions: aldehyde (5 mmol), rhodanine (5 mmol), [*bmim*][OH] (0.5 mmol), H_2O (2 cm^3) as solvent, rt
[b] Isolated yield

Table 2 Reusing of the ionic liquid [*bmim*][OH]/H_2O for synthesis of **3a**[a]

Entry	Run	Yield/%[b]
1	fresh	86
2	1	87
3	2	84
4	3	82
5	4	83
6	5	81

[a] Reaction conditions: benzaldehyde (5 mmol), rhodanine (5 mmol), [*bmim*][OH] (0.5 mmol), H_2O (2 cm^3) as solvent, rt, reaction time, 60 min
[b] Isolated yield



Scheme 1

Experimental

Melting points were determined in open capillaries and corrected. ^1H NMR spectra were obtained from solution in *DMSO*-d_6 with *TMS* as internal standard using a Bruker DRX 300 (300 MHz) spectrometer. IR spectra were recorded on a Nicolete spectrometer (KBr).

The synthesis of this task-specific ionic liquid [*bmim*][OH] has been carried out according to Ref. [14]. The ionic liquid was formed quantitatively and in high purity as assessed by ^1H NMR. All other chemicals and reagents were of analytical grade and used as obtained.

General procedure for the preparation of 5-benzylidene rhodanine derivatives

A mixture of 5 mmol of the aromatic aldehyde, 5 mmol rhodanine, 0.5 mmol [*bmim*][OH] and 2 cm^3 H_2O in a flask was stirred at room temperature for the appropriate time (reaction were monitored by TLC). The reaction mixtures were filtered to get the crude products, which were purified by recrystallization from ethanol. The ionic liquid remained in the aqueous phase and reused in subsequent reaction without further purification. All products are known compounds, which were characterized by IR and ^1H NMR spectral data and their mps compared with literature reports.

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