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Article

Hydroxyalkylation of indole with cyclic carbonates catalyzed by ionic liquids

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ABSTRACT

A simple and eco-friendly procedure has been developed for the synthesis of hydroxyalkyl indoles from indole and cyclic carbonates in the presence of a catalytic amount of imidazolium based ionic liquids under solvent-free conditions. The effects of reaction time, the catalyst amount, temperature, and the ratio of the reactants were investigated to develop the optimum conditions for the transformation. Under the optimized reaction conditions, indole reacted with ethylene carbonate or propylene carbonate to give 1-(2-hydroxyethyl)indole or 1-(2-hydroxypropyl)indole, as well as the corresponding sequential derivatives, in high yields. The catalytic activity of the ionic liquids was affected by the anions of the ionic liquids in the order of $\text{BF}_4^- < \text{Br}^- < \text{Cl}^- < \text{OAc}^-$, which was consistent with the hydrogen bond basicity of the anions of the ionic liquids.

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1. Introduction

Hydroxyalkyl indoles are frequently used in a variety of different areas of research, including medicine [1,2] and organic synthesis [3–5], as well as the development of second-order nonlinear optical materials [6–8]. Hydroxyalkyl indoles are traditionally synthesized from extremely toxic halohydrin compounds in the presence of a stoichiometric amount of a strong base [9,10]. They can also be synthesized from the reaction of indole with ethylene carbonate in the presence a stoichiometric amount of sodium hydride [11]. Although these procedures can provide access to hydroxyalkyl indoles, they are not environmentally benign and are limited by their requirement toxic starting materials and explosive reagents.

Cyclic carbonates are considered to be safe, nontoxic, and eco-friendly reagents [12–14], which can be used as electrophiles for the introduction of hydroxyalkyl moieties to generate

functionalized alcohols [15–17]. Furthermore, ethylene carbonate has a low melting point (35 °C) and a high boiling point (248 °C), whereas propylene carbonate is a liquid at temperatures in the range of –49 to 242 °C. The wide temperature ranges over which these compounds exist as liquids and their high solvency means that these cyclic carbonates can be used as stoichiometric reagents without the need for any other organic solvents.

Ionic liquids have been applied to a wide variety of organic reactions as novel solvents and catalysts [17–24]. For example, ionic liquids have been used as catalysts in the reactions of glycerol and ethylene carbonate to synthesize glycerol carbonate [25], and in the reactions of aniline and ethylene carbonate to synthesize bis-*N*-(2-hydroxyethyl)aniline [17]. As a part of our ongoing research towards the development of green synthetic methodologies involving carbonates that are catalyzed by ionic liquids [26–29], we have previously reported

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that imidazolium-based ionic liquids are excellent catalysts for the reaction of indole and dimethyl carbonate to synthesize N-based heterocycles carbamate [26], as well as the reaction of aniline and ethylene carbonate to synthesize 2-oxazolidinones [27,28]. We have also reported that the acid-base bifunctional ionic liquid [PEmim]PbCl₃ is an efficient catalyst for the reaction of aniline with dimethyl carbonate [29]. Herein, we report a convenient and environmentally benign process for the synthesis of hydroxyalkyl indoles using cyclic carbonates as hydroxyalkylating reagents in the presence of a catalytic amount of an ionic liquid under solvent-free conditions.

2. Experimental

2.1. General

Ethylene carbonate and propylene carbonate were purchased from Alfa Aesar (Tianjin, China). All of the other reagents used in the study were purchased as the analytical reagent grade and used without further purification. The ionic liquids were synthesized according to procedures previously described in the literature with minor modifications [30]. All of the ionic liquids and products were characterized by ¹H NMR spectroscopy. The ¹H NMR spectra were recorded on a 400 MHz Bruker spectrometer (Switzerland) in deuterated solvent with tetramethylsilane as an internal reference.

2.2. Typical procedure for the [Bmim]BF₄ catalyzed reaction of indole and ethylene carbonate

The reaction of indole with ethylene carbonate was conducted in a 5 ml round-bottomed flask equipped with a magnetic stirrer under nitrogen atmosphere. Indole (0.234 g, 2 mmol), ethylene carbonate (0.880 g, 10 mmol), and 1-butyl-3-methyl-imidazolium tetrafluoroborate ([Bmim]BF₄) (0.045 g, 0.2 mmol) were mixed together and heated to the required temperature. Upon completion of the reaction (as determined by TLC), chloroform (10 ml) was added and the organic phase was extracted three times with water to remove the ionic liquid. The organic phase was then analyzed using a Shimadzu GC-14B gas chromatograph (GC; Kyoto, Japan) equipped with a CBP1-M25-025 capillary column (Shimadzu, Kyoto, Japan) using *n*-dodecane as the internal standard. The aqueous phase was evaporated under vacuum, and the ionic

Fig. 1. GC spectrum of the reaction mixture containing **1a**, **2a**, and **3a**.

liquid was recycled for the next reaction. The pure product was obtained by chromatography on silica gel. The structure of the products was characterized by ¹H NMR analysis and mass spectroscopy (MS).

3. Results and discussion

3.1. [Bmim]BF₄ catalyzed reaction of indole and ethylene carbonate

[Bmim]BF₄ is one of the most commonly used ionic liquid, and it has been applied as a catalyst for the reactions of N-based heterocycles with dimethyl carbonate [26], as well as the reaction of aniline and ethylene carbonate [27]. On the basis of these examples, it was envisaged that [Bmim]BF₄ could be used as a potential catalyst for the reactions of indole with different cyclic carbonates. With this in mind, a preliminary experiment was conducted to identify the products from this reaction. The GC spectrum of the products is shown in Fig. 1. Three products were detected in the reaction mixture, including 1-(2-hydroxyethyl)indole (**1a**), 1-(2-(2-hydroxy)ethoxyethyl)indole (**2a**), and 1-(2-(2-(2-hydroxy)ethoxyethyl)oxyethyl)indole (**3a**) (Scheme 1).

To optimize reaction parameters, the effects of the reaction time, catalyst amount, reaction temperature, and molar ratio of reactants on the reaction profile were investigated. The results are shown in Fig 2. As shown in Fig. 2(a), the conversion of the indole reached a plateau at 86% following 9 h of the reaction and remained at this level despite further increases in the reac-

Scheme 1. Reaction of indole with ethylene carbonate.

Fig. 2. Effects of reaction time (a), catalyst amount (b), and reaction temperature (c) on the [Bmim]BF₄ catalyzed reaction of indole and ethylene carbonate. Reaction conditions: indole 2 mmol, ethylene carbonate 10 mmol, 9 h (except (a)), [Bmim]BF₄ 0.2 mmol (except (b)), 140 °C (except (c)).

tion time. The yield of **1a** increased at a similar rate to the yield of **2a** over the first 9 h and then decreased over an extended reaction time. The yield of **3a** was 2% following the first 9 h of the reaction and increased to 4% following a 12 h reaction period.

As shown in Fig. 2(b), the reaction of indole with ethylene carbonate did not proceed in the absence of the catalyst. In the presence of [Bmim]BF₄, the reaction proceeded smoothly. Increasing the amount of ionic liquid led to a gradual increase in the yields of **1a** and **2a**. Any increase in the yield of **3a**, however, was slight. The indole conversion reached its highest level (86%) when a 10% charge of the [Bmim]BF₄ catalyst was used.

The [Bmim]BF₄ catalyzed reaction of indole with ethylene carbonate was investigated in the temperature range of 120–160 °C (Fig. 2(c)). The conversion of indole increased gradually when the temperature was increased from 120 to 160 °C and reached a maximum of 96% at 150 °C. The yield of **1a** increased when the temperature was below 140 °C and was subsequently reduced by approximately 20% when the temperature was further increased from 140 to 160 °C. In contrast, the yield of **2a** increased remarkably when the temperature was increased from 130 to 150 °C, and effectively reached a plateau with further increases in the temperature. The yield of **3a** was found to be in the range of 2%–10% when the temperature was in the range of 140–160 °C. It is noteworthy that the reduction in the yield of **1a** was consistent with an increase in the yields of **2a** and **3a**. These results effectively confirmed that **2a** and **3a** were formed from the reaction of **1a** with ethylene carbonate (Scheme 1).

The reaction of indole with ethylene carbonate was performed at different molar ratios of indole to ethylene carbonate, and the results are shown in Table 1. The level of indole conversion increased as the molar ratio of indole to ethylene

Table 1

Effect of indole to ethylene carbonate (EC) molar ratio on reaction of indole with ethylene carbonate.

<i>n</i> (indole)/ <i>n</i> (EC)	Conversion (%)	GC yield (%)		
		1a	2a	3a
1/1	62	30	9	1
1/3	91	35	30	4
1/5	96	41	45	4

Reaction conditions: 150 °C, 9 h, [Bmim]BF₄ = 10 mol% based on indole.

carbonate was reduced. A molar ratio of 1/5 of the indole to the ethylene carbonate gave the highest conversion of 96%.

3.2. Reaction of indole with cyclic carbonates catalyzed by various ionic liquids

To evaluate the effect of different ionic liquids on the reaction, a series of ionic liquids with different anions and cations were investigated for their ability to catalyze the reaction of indole with ethylene carbonate. The results are listed in Table 2. In the presence of imidazolium based ionic liquids, the level of indole conversion was generally very high and in the range of 90%–100% with a variety of different anions. Although the differences were only slight, the conversion of indole followed the order of BF₄[−] < Br[−] < Cl[−] < OAc[−], which was consistent with the hydrogen bond basicities of the anions in the ionic liquids [31,32]. It is noteworthy that the combined yields of **1a**, **2a**, and **3a** decreased as the conversion of indole increased (Table 2, entries 1–4). This reduction in the combined yields was probably caused by the sequential reactions of the hydroxyl group of the product with ethylene carbonate to give indole substituted polyethylene glycols in the presence of the highly active catalysts. In fact, the yield of **3a**, which was considered to be the sequential derivative of **1a** and **2a**, also followed the order of

Table 2

Reaction of indole and ethylene carbonate catalyzed by various ionic liquids.

Entry	Ionic liquid	Conversion (%)	GC yield (%)			Selectivity for 1a + 2a + 3a (%)
			1a	2a	3a	
1	[Bmim]BF ₄	96	41	45	4	94
2	[Bmim]Br	98	27	51	13	93
3	[Bmim]Cl	99	9	43	22	75
4	[Bmim]OAc	100	4	37	28	69
5	[Bmmim]BF ₄	90	36	34	2	80
6	[Bmmim]Br	93	41	30	4	81
7	[Bmmim]Cl	99	18	50	17	85
8	[Bmmim]OAc	100	2	37	26	65
9 ^a	[Bmim]BF ₄	95	41	44	4	94
10 ^b	[Bmim]BF ₄	92	40	42	3	92
11 ^c	[Bmim]BF ₄	80	35	35	3	91

Reaction conditions: indole 2 mmol, ethylene carbonate 10 mmol, ionic liquid 0.2 mmol, 150 °C, 9 h.

^aThe 2nd run. ^bThe 3th run. ^cThe 4th run.

Table 3

Reaction of indole with propylene carbonate catalyzed by ionic liquids.

Entry	Ionic liquid	Temperature (°C)	Conversion (%)	GC yield (%)		
				1b	2b	3b
1	[Bmim]BF ₄	140	48	35	0	0
2	[Bmim]BF ₄	150	87	70	5	0
3	[Bmim]BF ₄	160	85	73	4	0
4 ^a	[Bmim]BF ₄	150	88	73	5	0
5	[Bmim]OAc	140	95	30	29	7

Reaction conditions: indole 2 mmol, propylene carbonate 10 mmol, ionic liquid 0.2 mmol, 9 h (^a 12 h).

BF₄⁻ < Br⁻ < Cl⁻ < OAc⁻. When ionic liquids [Bmmim]BF₄, [Bmmim]Br, [Bmmim]Cl, and [Bmmim]OAc, in which the proton at the 2-position of the imidazolium ring was replaced with a methyl group, were applied to catalyze the reaction, the indole conversion levels were also very high (90%–100%). The indole conversion levels and the yields of **3a** followed the order BF₄⁻ < Br⁻ < Cl⁻ < OAc⁻ (Table 2, entries 5–8). These results revealed that the anions in the ionic liquids with greater levels of hydrogen bond basicity, such as OAc⁻ and Cl⁻, were more active for the reaction of the indole with ethylene carbonate.

The possibility of recycling the [Bmim]BF₄ catalyst was also investigated under the optimal reaction conditions. The indole conversion and yield are listed in Table 2 (entries 9–11). The results revealed that the [Bmim]BF₄ catalyst could be recycled four times with only a slight reduction in the conversion of indole and similar selectivity for **1a**, **2a**, and **3a** in the range of 91%–94%.

When propylene carbonate was used as the hydroxyalkylating reagent, the ionic liquid [Bmim]BF₄ gave 1-(2-hydroxypropyl)indole (**1b**) as the sole product in a yield of 35% at 140 °C (Table 3, entry 1). This increase in the selectivity of the reaction may have occurred because of the steric hindrance afforded by the methyl group of the propylene carbonate, which could suppress the tendency towards the sequential hydroxyalkylation of the indole derivatives. Increasing the temperature to 150 °C led to a significant increase in the yield of **1b** (Table 3, entry 2). Further extending the time to 12 h or more, however, as well as increasing the temperature to 160 °C did not lead to any remarkably improvement in the yield of **1b** (Table 3, entries 3 and 4). The ionic liquid [Bmim]OAc was also investigated as a catalyst for the reaction of indole with propylene carbonate, and the yields of **1b**, 1-(2-(2-hydroxy)propoxypropyl)indole (**2b**) and 1-(2-(2-(2-hydroxy)propoxypropyl)oxypropyl)indole (**3b**) were found to be 30%, 29%, and 7%, respectively (Table 3, entry 5). Compared with [Bmim]BF₄, [Bmim]OAc gave higher conversion of indole and higher yields of **2b** and **3b**. These results further confirmed that the basicity of the anions was favorable for the reaction of indole with propylene carbonate. It is assumed that the reaction probably starts via the activation of indole through a hydrogen bonding interaction between the anions of the ionic liquids and the hydrogen atom of indole (N–H···A_{anion}⁻), with the activated indole subsequently undergoing nucleophilic attack on the methylene group of the propylene carbonate to form sequential hydroxyalkylation products with the release of carbon dioxide [33].

4. Conclusions

We have developed a simple and eco-friendly procedure for the synthesis of hydroxyalkyl indoles from indole and cyclic carbonates catalyzed by ionic liquids under solvent-free conditions. The ionic liquids show high activity for the reaction of indole with ethylene carbonate or propylene carbonate to give 1-(2-hydroxyethyl)indole (**1a**) and 1-(2-hydroxypropyl)indole (**1b**), respectively, together with their sequential derivatives in high yields. The indole conversion levels and the yields of **3a** were affected by the anions of the ionic liquids and followed the order of BF₄⁻ < Br⁻ < Cl⁻ < OAc⁻, which was consistent with the hydrogen bond basicity of the anions in the ionic liquids.

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Graphical Abstract

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Hydroxyalkylation of indole with cyclic carbonates catalyzed by ionic liquids

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An eco-friendly procedure is presented for the synthesis of hydroxyalkyl indoles from indole and cyclic carbonates in the presence of a catalytic amount of imidazolium based ionic liquids under solvent-free conditions.

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离子液体催化吲哚羟烷基化反应

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摘要: 报道了咪唑类离子液体催化吲哚和环状碳酸酯反应合成羟烷基吲哚, 系统考察了反应时间、催化剂用量、反应温度和反应物比例对离子液体催化反应性能的影响. 在优化的反应条件下, 吲哚与碳酸乙烯酯或碳酸丙烯酯反应可高效地生成1-(2-羟乙基)吲哚、1-(2-羟丙基)吲哚及其相应的衍生物. 离子液体的催化活性与离子液体中的阴离子有关, 其催化活性顺序为 $\text{BF}_4^- < \text{Br}^- < \text{Cl}^- < \text{OAc}^-$, 与阴离子的碱度顺序一致.

关键词: 离子液体; 吲哚; 环状碳酸酯; 羟烷基化

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