



# Novel multiple-acidic ionic liquids: Green and efficient catalysts for the synthesis of bis-indolylmethanes under solvent-free conditions



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## ABSTRACT

Four novel multiple-acidic ionic liquids based on triethanolamine (TEA) were prepared and used as efficient catalysts to synthesize bis-indolylmethanes at room temperature without any organic solvent. [TEOA][HSO<sub>4</sub>] showed the best catalytic performance. The optimal amount of catalyst was 10 mol%. Various aldehydes/ketones reacted with indole/substituted indole smoothly and afforded to corresponding products in 70–99% yields within minutes. Additionally, the ionic liquid could be reused up to five times with only a slight decrease in catalytic activity. Finally, a possible reaction mechanism was given. Techniques of acidity test and NMR were introduced to verify the proposed mechanism.

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## Introduction

The bis-indolylmethanes (BIMs) are a valuable class of compounds, which have versatile biological activities and are widely present in various biologically active natural products [1–3]. Studies have shown that the BIMs can promote beneficial estrogen metabolism and induce apoptosis in human cancer cell [4,5]. In view of their significant position in medicinal chemistry, the preparation of BIMs has always been hot in pharmaceutical and organic synthesis [6]. In general, the BIMs are prepared by the condensation of carbonyl compounds with indoles in the presence of catalysts. So far, many catalysts have been reported, such as ABS [7], Fe<sup>III</sup> [8], NaHSO<sub>4</sub>/SiO<sub>2</sub> [9], LiClO<sub>4</sub> [10], HPA/TPI-Fe<sub>3</sub>O<sub>4</sub> [11], ZrOCl<sub>2</sub>·8H<sub>2</sub>O–silica gel [12], *p*-toluenesulfonic acid [13], palladium nanoparticles (PdNPs) [14] and so on. Although these catalysts have achieved a lot of success, most of the reported procedures suffer from some disadvantages such as tedious work-up procedure, long reaction time, use of a larger stoichiometric amount of catalyst and hazardous solvents which is not suited for practical use and incompatible with “green chemistry”. With the rapid development in the field of catalytic and synthetic chemistry,

developing a more practical, green and efficient catalytic system for the synthesis of BIMs is, therefore, highly desirable.

Ionic liquids (ILs) are low melting salts that have attracted steady attention [15]. Compared with traditional organic solvents, ILs present many advantages including low vapor pressure, excellent solvation ability, good thermal stability and recyclability. Furthermore, the properties of ILs can be changed by appropriate modification of their cation or anion, which has earned them the sobriquet of “designer solvents” [16,17]. Thus, ILs have been successfully used as green solvents, as well as catalysts or promoters in Mannich reaction [18], Friedel–Crafts reaction [19], Michael addition [20], Knoevenagel condensation [21] and so on. Without exception, ILs also have been used in the synthesis of BIMs [22–24]. In recent years, it was reported that the strongly acidic SO<sub>3</sub>H-functionalized ILs have been developed as efficient catalysts for many organic reactions affording outstanding performances [25,26]. Owing to the existence of SO<sub>3</sub>H functional groups, it is very likely to be used for the synthesis of BIMs. However, what we have learned is that this is rarely reported.

Triethanolamine (TEA) is an amino alcohol that mostly used in cosmetic formulations such as emulsifiers, wetting agents, thickeners, detergents and alkalinizing agents [27]. Both the properties of amines and alcohols, TEA is also used in chemical field. Recently, our group prepared a series of functionalized ionic liquids based on 2-aminoethanol and successfully used as catalysts for the Henry reaction [28]. Encouraged by the exciting

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performances, herein we report the development of a series of novel multiple-acidic SO<sub>3</sub>H-functionalized ionic liquids based on TEA and their use as catalysts for the synthesis of BIMs.

## Experimental

**General.** All the materials in reactions were commercially available and were used without further purification. <sup>1</sup>HNMR spectra was acquired at 400 MHz, and <sup>13</sup>CNMR was acquired at 100 MHz on a Bruker Avance DPX 400 spectrometer in CDCl<sub>3</sub>, D<sub>2</sub>O or DMSO. Chemical shifts were reported in parts per million (δ), relative to the internal standard of tetramethylsilane (TMS). All reactions were monitored by thin layer chromatography (TLC) performed on 0.25 mm silica gel 60-F plates. Flash chromatography separation was performed on silica gel (100–200 mesh).

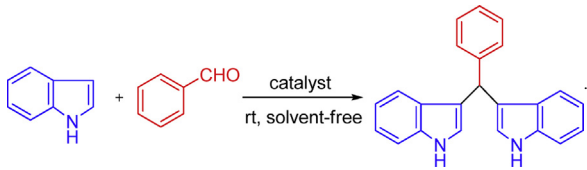
**Preparation of the catalysts [TEOA][X].** Triethanolamine (TEA) (0.1 mol) and dichloromethane (DCM; 30 mL) were added into a 100 mL three-neck flask and cooled in an ice bath. Then, with an intensive mixing, chlorosulfonic acid (0.3 mol) was added dropwise at a temperature of not higher than 5 °C. After addition, the reaction mixture was removed from the ice bath and stirred for 3 h at room temperature. Upon completion of the reaction, the reaction solution was filtered. The resulting solid cake was washed with DCM, and dried for 3 h. The resulting solid was dissolved in 50 mL of water and different acids were added dropwise with vigorous stirring. The reaction mixture was heated at 60 °C for 5 h. The water was evaporated at vacuum distillation and the product was then dried under vacuum at 70 °C for another 8 h to afford the desired ILs.

**General procedure for the synthesis of Bis-indolylmethanes.** In a typical experiment, a mixture of aldehydes/ketones (1.0 mmol), indole/substituted indole compounds (2.0 mmol) and catalyst (10 mol%) was stirred at room temperature for the appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. The solvent was purified by silica gel column chromatography to afford the corresponding products. The products were characterized by <sup>1</sup>HNMR and <sup>13</sup>CNMR. The residue ionic liquid was dried at 80 °C under vacuum for 6 h and reused several times without further purification.

## Results and discussion

Four kinds of TEA based ionic liquids were synthesized (Scheme 1) and used to the reaction of aldehydes/ketones and indole/substituted indole. At the beginning, the reaction of benzaldehyde and indole was selected as a model reaction to explore the optimal conditions. Moreover, two kinds of conventional ionic liquids [BmIm][BF<sub>4</sub>] and [BmIm][PF<sub>6</sub>] were also tested. The results are shown in Table 1. Notably, the reaction could not proceed at all in the absence of any catalyst (Table 1, Entry 1). Unfortunately, as shown, [BmIm][BF<sub>4</sub>] and [BmIm][PF<sub>6</sub>] also had no catalytic effect even when the time was prolonged to 60 min (Table 1, Entries 2,3). To our delight, the four TEA based ionic liquids showed very good catalytic performances (Table 1,

**Table 1**  
Effect of ionic liquids on the reaction of benzaldehyde and indole<sup>a</sup>



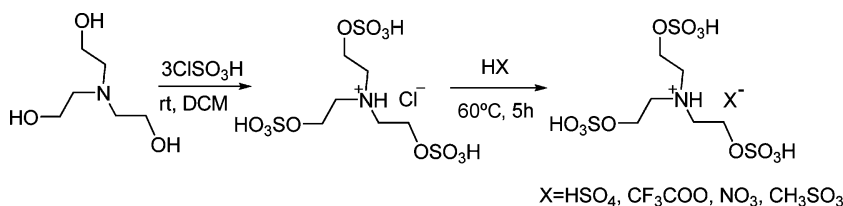
Entry	Catalyst (mol%)	Time (min)	Yield (%) <sup>b</sup>
1	Blank	60	Trace
2	[BmIm][BF <sub>4</sub> ] (30)	60	Trace
3	[BmIm][PF <sub>6</sub> ] (30)	60	Trace
4	[TEOA][NO <sub>3</sub> ] (20)	20	82
5	[TEOA][CF <sub>3</sub> COO] (20)	20	86
6	[TEOA][CH <sub>3</sub> SO <sub>3</sub> ] (20)	15	88
7	[TEOA][HSO <sub>4</sub> ] (20)	10	90
8	[TEOA][HSO <sub>4</sub> ] (5)	25	85
9	[TEOA][HSO <sub>4</sub> ] (10)	10	92
10	[TEOA][HSO <sub>4</sub> ] (15)	10	89

<sup>a</sup> Reaction conditions: benzaldehyde (1.0 mmol), indole (2.0 mmol), room temperature, solvent-free.

<sup>b</sup> Isolated yield.

Entries 4–7). In view of the reaction time and yield, the catalytic effect order was as follows: [TEOA][HSO<sub>4</sub>] > [TEOA][CH<sub>3</sub>SO<sub>3</sub>] > [TEOA][CF<sub>3</sub>COO] > [TEOA][NO<sub>3</sub>]. The [TEOA][HSO<sub>4</sub>] catalyzed the reaction successfully and the yield was up to 90%. With the best catalyst in hand, we carried out the reaction in the presence of 5, 10, 15 and 20 mol% [TEOA][HSO<sub>4</sub>] to optimize the amount of catalyst (Table 1, Entries 7–10). From Table 1, it was found that when the amount of [TEOA][HSO<sub>4</sub>] increases to 10 mol%, the best performance was obtained. Whereas, with continued increase in the amount of catalyst, the yield of reaction would decrease slightly. Thus, the 10 mol% [TEOA][HSO<sub>4</sub>] was the optimal amount of catalyst and was subjected to further examination.

With the optimal conditions in hand, we extended our studies to the reaction of indole with a variety of aldehydes/ketones to evaluate the scope and limitations of this methodology and the results were presented in Table 2. It was apparent that, all reactions proceeded smoothly with functionality-substituted aromatic aldehydes to afford the corresponding BIMs in good to excellent yields. Among these cases, electronic effects had some influence on the reaction course that aromatic aldehydes bearing electron-withdrawing groups (CF<sub>3</sub> and F) reacted generally faster than aldehydes bearing electron-donating (CH<sub>3</sub> and OCH<sub>3</sub>) substituents and obtained higher yields (Table 2, Entries 2–6). The reactions of indole and aromatic aldehydes bearing electron-withdrawing groups (CF<sub>3</sub> and F) were almost quantitative transformation and the yields were up to 98% and 99% (Table 2, Entries 5, 6). Some hetero aromatic aldehydes (thiophene-2-carbaldehyde, furan-2-carbaldehyde) were also employed in this reaction and the reaction time was relatively longer with a lower yield (Table 2, Entries 9, 10). Unfortunately, 3-pyridinecarboxaldehyde that could not react well with indole, only achieved a trace yield (Table 2, Entry 11). Aliphatic aldehydes were also efficient substrates in this reaction



**Scheme 1.** Synthesis of the [TEOA][X] ionic liquids.

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