

## An Efficient One-Pot Synthesis of Bis (Indolyl)methanes Catalyzed by Ionic Liquid with Multi-SO<sub>3</sub>H Groups under Ambient Temperature in Water

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**Abstract:** Ionic liquid with multi-SO<sub>3</sub>H groups was employed as a catalyst for facile preparation of bis(indolyl)methanes via the one-pot condensation of indole with aldehydes or ketones. Various aliphatic and aromatic aldehydes or ketones were utilized in the reaction and in all situations the desired product were synthesized successfully. The described novel synthesis method propose several advantages of safety, mild condition, short reaction times, high yields, simplicity and easy workup compared to the traditional method of synthesis.

**Key words:** Ionic liquid with multi-SO<sub>3</sub>H groups • Bis(indolyl)methanes • Indole • Water solvent  
• Chemoselective

### INTRODUCTION

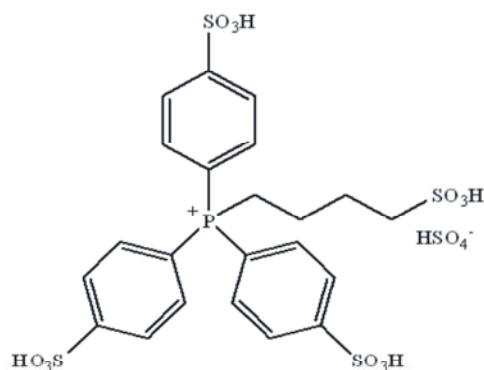
Bis(indolyl)methanes are a biologically valuable group of organic compounds. A large number of these compounds have been isolated from earthly and marine natural sources such as sponges [1]. They are also identified to promote useful estrogen metabolism and are found in cruciferous plants [2]. Bis(indolyl)methanes have many applications in material sciences, agrochemicals and pharmaceuticals [3]. So, in the recent years, there is a great interest in the synthesis of these compounds [4,5].

Many methods are reported to synthesize of bis (indol-3-yl) methanes. The reaction of 1H-indole with aldehydes or ketones produces azafulvenium salts which react further with a second 1H-indole molecule to form bis(indol-3-yl)methanes [6]. Nowadays, synthesis of this category of molecules under mild conditions have been reported in the presence of promoters, such as, ALPW<sub>12</sub>O<sub>40</sub> [7], Dy(OTf)<sub>3</sub>/ionic liquid [8], In (OTf)<sub>3</sub>/ionic liquid [9], MW/Lewis acids (BiCl<sub>3</sub>, FeCl<sub>3</sub>, InCl<sub>3</sub>, CoCl<sub>2</sub>, ZnCl<sub>2</sub>) [10], silica sulfuric acid (SSA) [11], acidic ionic liquid [12], trichloro-1,3,5-triazine [13], H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> [14], ceric ammonium nitrate (CAN) [15], However, some of these reported methods have one or more disadvantages

such as moisture sensitive, or highly toxic in environment and unpleasant experimental procedure and reagents which are expensive. A mild and efficient catalyst for the synthesis of bis(indolyl)methanes is very desirable.

Performing organic reactions in aqueous media has attracted much attention because of wonderful water properties. It would be significantly safe, cheap, non-toxic and environmentally friendly compared to organic solvents [16]. Additionally, the catalyst system can be recycled using the water soluble catalyst and the insoluble products can be separated by simple filtration. So, development of a mild and efficient catalyst system for the synthesis of bis(indolyl)methanes is highly desirable. It should not only be stable in water but also should be completely soluble in it.

In recent years, ionic liquids have attracted much attention as a new class of green solvent and catalyst [17]. These aqueous media is utilized for organic synthesis due to their astonishingly properties, such as wide liquid range, favorable solvating capability, requirement low temperature, tunable polarity, high thermal stability and ease of recyclability [18]. Ionic liquids have also negligible vapor pressure, which facilitates product separation by distillation. Moreover,

Fig. 1: IIs with multi SO<sub>3</sub>H groups

they are cheapest and environmentally friendly solvents, because water exhibits unique reactivity and selectivity, which is different from those in conventional organic solvents. So, the appropriate property of ionic liquids lead to the development and application of so-called “task-specific” ionic liquids to synthesize the desirable products.

Recently, Jianguo *et al.* [19] introduced a new ionic liquid with multi-SO<sub>3</sub>H groups (Figure 1) which have much higher activity than other reported catalysts with the additional advantage of reusability.

In continuation of our investigations on the development of new synthetic methodologies [20], we herein report a new, convenient, mild and efficient procedure for the synthesis of bis(indolyl)methanes from one-pot condensation of various aldehydes or ketones with indole using this non-volatile ionic liquid with multi-SO<sub>3</sub>H groups under ambient temperature.

## Experimental

**General Procedure for the Synthesis of Bis (indolyl) Methanes:** A mixture of indole (2.0 mmol), aldehyde or ketone (1.0 mmol) and ionic liquids (1 mol%) in water (2 mL) was stirred at room temperature for an appropriate time. The progress of the reaction was monitored by TLC (n-hexane/ethyl acetate 4:1). After completion of the reaction, the resulting solid (crude product) was filtered and then recrystallized from ethanol-water to obtain pure product. The physical data (mp, NMR, IR) of these known compounds were found to be identical with those reported in the literature.

**Bis-(4-Nitrophenylmethylene)-Bis-(1H-indole) (Table 3, Entry 5):** yellow solid; mp 220-222 °C (lit. 217-220 °C); IR (KBr): 3455, 3424, 3385, 1590, 1517, 1456, 1341, 745 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 5.92 (s, 1H), 6.63 (d, J = 2.3 Hz, 2H), 6.94 (t, J = 7.9 Hz, 2H), 7.10-7.31 (m, 6H), 7.43 (d, J =

8.6 Hz, 2H), 7.96 (brs, 2H, NH), 8.16 (d, J = 8.8 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 40.3, 111.3, 118.1, 119.4, 119.6, 122.5, 123.6, 126.5, 129.7, 136.7, 151.8.

### Bis-(4-tolylmethylene)-bis-(1H-indole) (Table 3, Entry 6):

Pale red solid; mp 92-94 °C (lit. 93-94 °C); IR (KBr): 3420, 3385, 3056, 2923, 1515, 1457, 1340, 1225, 1095, 998, 779, 742 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.34 (s, 3H), 5.85 (s, 1H), 6.66 (s, 2H), 7.01 (t, J = 7.1 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 7.13 (dd, J = 7.7 Hz, 2H), 7.27 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.44 (d, J = 8.1 Hz, 2H), 7.84 (br s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 21.4, 40.1, 111.3, 119.2, 119.5, 120.1, 122.3, 123.5, 127.2, 128.8, 129.4, 136.6, 136.9, 141.6.

### 3,3'-(Biphenyl-4-ylmethylene)-bis-(1H-indole) (Table 3, Entry 13):

Pink solid; mp 246-248 °C; IR (KBr): 3413, 2360, 1448, 1363, 1216, 1079, 788, 744 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 5.95 (s, 1H), 6.74 (d, J = 2.3 Hz, 2H), 7.06 (t, J = 7.8 Hz, 2H), 7.22 (t, J = 7.9 Hz, 2H), 7.35 (t, J = 7.8 Hz, 1H), 7.40 (d, J = 8.5 Hz, 2H), 7.42-7.46 (m, 6H), 7.55 (d, J = 8.6 Hz, 2H), 7.62 (d, J = 8.8 Hz, 2H), 7.97 (brs, 2H, NH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 39.8, 111.1, 119.2, 119.6, 119.9, 121.9, 123.6, 126.9, 127.0, 127.1, 128.6, 129.1, 136.7, 138.8, 141.1, 143.1.

### 3,3'-(Naphthalen-1-ylmethylene)-bis-(1H-indole) (Table 3, Entry 17):

Pale pink solid; mp 252-254 °C (lit. 252-253 °C); IR (KBr): 3425, 3055, 2925, 2846, 1593, 1456, 1345, 1090, 743 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.56 (s, 1H), 6.67 (s, 1H), 6.97 (t, J = 7.3 Hz, 2H), 7.20 (t, J = 7.8 Hz, 2H), 7.23-7.46 (m, 9H), 7.55 (s, 1H), 7.71 (d, J = 7.6 Hz, 1H), 7.94 (brs, 2H, NH), 8.17 (d, J = 8.4 Hz, 1H); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 36.3, 111.4, 119.5, 119.6, 120.1, 122.3, 124.6, 125.6, 125.8, 126.4, 127.3, 127.6, 128.7, 134.1, 137.2.

### 3,3'-(Propane-2,2-diyl)-bis-(1H-indole) (Table 3, Entry 24):

pale red solid; mp 163-165 °C (lit. 165-167 °C); IR (KBr): 3425, 2961, 1623, 1456, 1335, 1099, 745 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 1.87 (s, 6H), 6.85 (t, J = 7.3 Hz, 2H), 6.96 (d, J = 2.3 Hz, 2H), 7.17 (d, J = 7.1, 7.9 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 8.03 Hz, 2H), 7.79 (brs, 2H, NH); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 30.3, 34.8, 111.4, 118.7, 120.6, 121.2, 121.3, 125.5, 126.3, 137.3.

### 3,3'-(1-Phenylethane-1,1-diyl)-bis-(1H-indole) (Table 3, entry 26):

Auburn solid; mp 189-191 °C (lit. 189-190 °C); IR (KBr): 3421, 3057, 2974, 1456, 1335, 1217, 1099, 745 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 2.44 (s, 3H), 6.62 (d, J = 2.4 Hz, 2H), 6.94 (t, J = 7.5 Hz, 2H), 7.08-7.55 (m, 11H), 8.15 (brs, 2H, NH); <sup>13</sup>C NMR (400 MHz, CDCl<sub>3</sub>): δ 28.7, 65.5, 111.4, 119.1, 121.4, 122.3, 123.3, 124.5, 125.7, 126.4, 127.8, 128.3, 138.4.

## RESULTS AND DISCUSSION

First, we studied the reaction of benzaldehyde with indole (1) (1:2 molar ratios) to optimize the reaction conditions with respect to temperature, time, solvent, molar ratio of catalyst to the substrate and reusability of catalyst. It was found that 1 mol% of catalyst was sufficient to obtain the desired bis(indolyl)methane (3) in 94% yield within 6 min at room temperature in water using benzaldehyde, (Figure 2).

The effect of solvent on the yield of 3 is given in Table 1. The reaction of 1 with benzaldehyde was chosen as a model reaction for investigating the effect of solvent. Among the solvents examined, water was found to be the most effective.

In order to show the merit of ILs in comparison with the other catalysts used for the similar reaction, some of the results are tabulated in Table 2. According to Table 2, the required ratio for the most catalysts used for this purpose is >1 mol% and also the required reaction times are much longer (1-12 h).

After finding the optimized reaction conditions, the investigation was preceded by performing the reaction between a series of aldehydes and ketones (2) with indole. To show the general applicability of this method, various aldehydes and ketones were efficiently reacted with two equivalents of indole in the same conditions. These results encouraged us to investigate the scope and the generality of this new protocol for various aldehydes and ketones under optimized conditions. As shown in Table 3, a series of aromatic, aliphatic and heterocyclic aldehydes and ketones underwent electrophilic

substitution reaction with indole to afford a wide range of substituted bis(indolyl)methanes in good to excellent yields. The nature and electronic properties of the substituents on the aromatic ring effect the conversion rate and aromatic aldehydes having electron-withdrawing groups on the aromatic ring (Table 3, entries 4, 5, 10) react faster than electron-donating groups (Table 3, entries 6, 7, 9). Ketones (Table 3, entries 24-29) required longer reaction times, which is most probably due to the electron donating and steric effects of the methyl group.

Surprisingly, when terephthalaldehyde (4) was used, *p*-bisindolylmethane benzaldehyde [23], (5) was produced in excellent yield. When we used 4 molar equivalents of indole, *p*-di(bis-indolylmethane)benzene [23], (6) was obtained in excellent yield (Figure 3).

The high chemoselectivity of this method had also been demonstrated by a competitive reaction between a benzaldehyde and acetophenone with indole, as depicted in Figure 4. The result showed that the chemoselectivity of aldehyde group in the presence of a ketone can also be achieved by using the catalyst in good yield under identical conditions because of the reactivity difference between aldehyde and ketone.

The reusability of the catalysts was checked using 4-nitrobenzaldehyde as a model substrate. At the end of the reaction,  $\text{CH}_2\text{Cl}_2$  was added to the mixture. The aqueous layer was separated and used without further purification. In this media, as shown in (Figure 5), the recovered catalyst can be reused at least six additional times in subsequent reactions without appreciable loss in the catalytic activity.

Table 1: Solvent effect on the reaction between indole and benzaldehyde<sup>a</sup>

Entry	Solvent	Reaction time/min	Yield <sup>b</sup> /%
1	H <sub>2</sub> O	6	94
2	C <sub>2</sub> H <sub>5</sub> OH	8	92
3	CHCl <sub>3</sub>	15	85
4	CH <sub>2</sub> Cl <sub>2</sub>	21	82
5	CH <sub>3</sub> CN	7	92
6	CH <sub>3</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	11	88

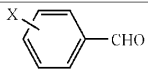
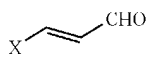
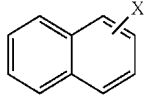
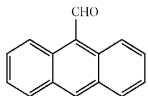
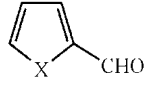
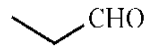
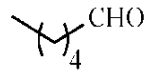
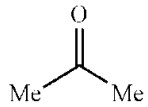
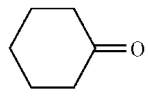
<sup>a</sup> Reaction condition: indole (2 mmol); PhCHO (1 mmol); catalyst (1 mol%); solvent (2 mL);

<sup>b</sup> Isolated yield.

Table 2: Reaction of indole with benzaldehyde in the presence of different catalysts

Entry	Catalyst/mol%	Solvent	Time/min	Yield/%	Ref.
1	IL with multi SO <sub>3</sub> H-groups/1	H <sub>2</sub> O	6	94	This work
2	Ln(OTf) <sub>3</sub> /10	EtOH.H <sub>2</sub> O	720	95	[21a]
3	Al(HSO <sub>4</sub> ) <sub>3</sub> /100	EtOH	60	92	[21b]
4	Dy(OTf) <sub>3</sub> /2	Ionic liquid	60	98	[7]
5	La(PFO) <sub>3</sub> /5	EtOH	30	90	[21c]
6	In(OTf) <sub>3</sub> /5	CH <sub>3</sub> CN	25	71	[21d]
7	Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> /5	MeOH	75	96	[21e]
8	HY-zeolite/0.2 gr	CH <sub>2</sub> Cl <sub>2</sub>	60	85	[5]

Table 3: Reaction of indole with carbonyl compounds employing of 1 mol% catalyst (IL)

Entry	Carbonyl compound	Time/min	Yield/%	Mp/°C Ref.
				
1	X=H	6	94	146-148 <sup>22a</sup>
2	X=4-Cl	5	95	77-79 <sup>22a</sup>
3	X=2,4-Cl <sub>2</sub>	5	95	141-143 <sup>22b</sup>
4	X=2-NO <sub>2</sub>	3	97	141-143 <sup>22c</sup>
5	X=4-NO <sub>2</sub>	1	98	220-222 <sup>22a</sup>
6	X=4-Me	5	96	92-94 <sup>22a</sup>
7	X=2,4-Me <sub>2</sub>	5	95	183-185
8	X=4-OH	9	91	210-212 <sup>9</sup>
9	X=4-OMe	11	91	186-188 <sup>22a</sup>
10	X=4-CN	3	97	210-212 <sup>22d</sup>
11	X=4-F	5	93	72-74 <sup>21c</sup>
12	X=4-Br	5	93	110-112 <sup>22c</sup>
13	X=4-Ph	3	97	246-248
14	X=3-OPh	9	92	85-87 <sup>22f</sup>
				
15	X=Me	11	91	124-126 <sup>22g</sup>
16	X=Ph	9	91	99-101 <sup>22g</sup>
				
17	X=1-CHO	3	97	252-254 <sup>22h</sup>
18	X=2-CHO	5	97	227-229 <sup>22i</sup>
19		5	95	243-245 <sup>22i</sup>
				
20	X=O	10	94	324-326 <sup>22j</sup>
21	X=S	13	91	152-154 <sup>22j</sup>
22		15	91	89-90 <sup>22d</sup>
23		17	91	68-69 <sup>22k</sup>
24		27	86	163-165 <sup>22l</sup>
25		23	88	119-121 <sup>22a</sup>
26	X=H	24	85	189-191 <sup>22a</sup>
27	X=3-NO <sub>2</sub>	19	91	258-260 <sup>22c</sup>
28	X=4-NO <sub>2</sub>	17	92	237-238 <sup>22m</sup>
29	X=4-Cl	22	88	110-112 <sup>22c</sup>

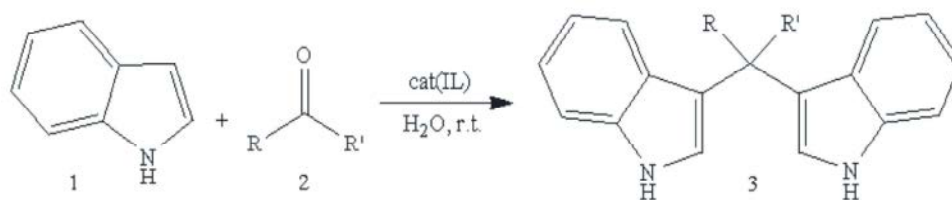


Fig. 2: Synthesis of bis (indolyl) methanes

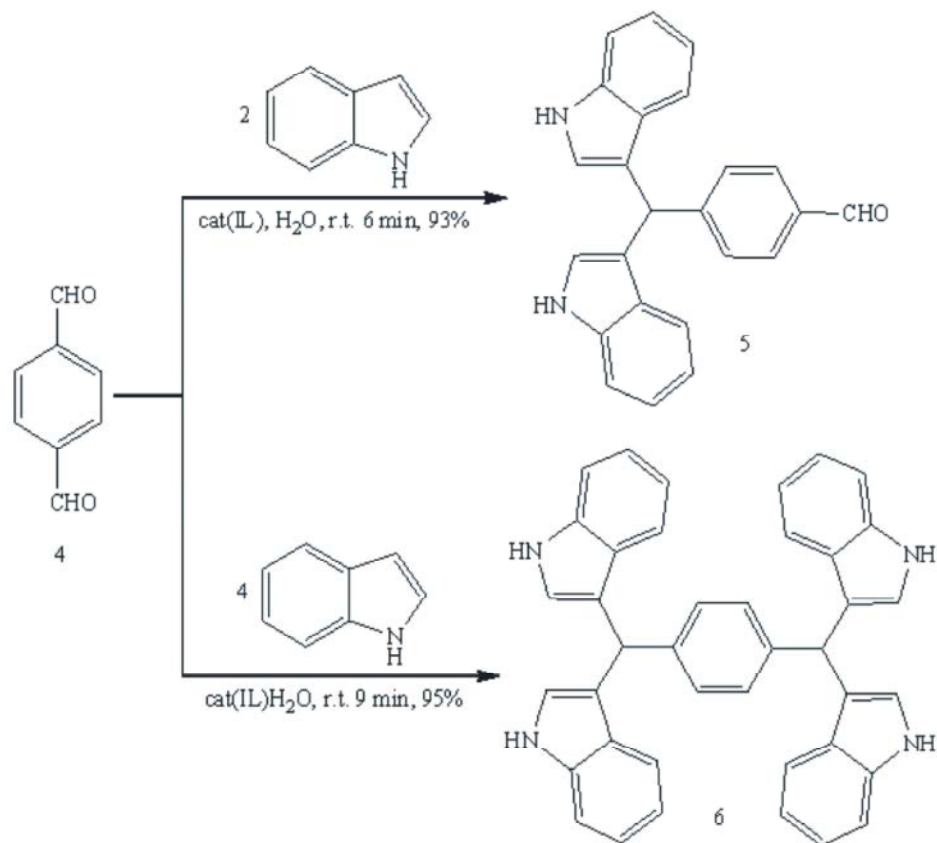


Fig. 3: Synthesis of *p*-bis (indolyl) methanebenzaldehyde and *p*- di(dis-indolylmethane) benzene

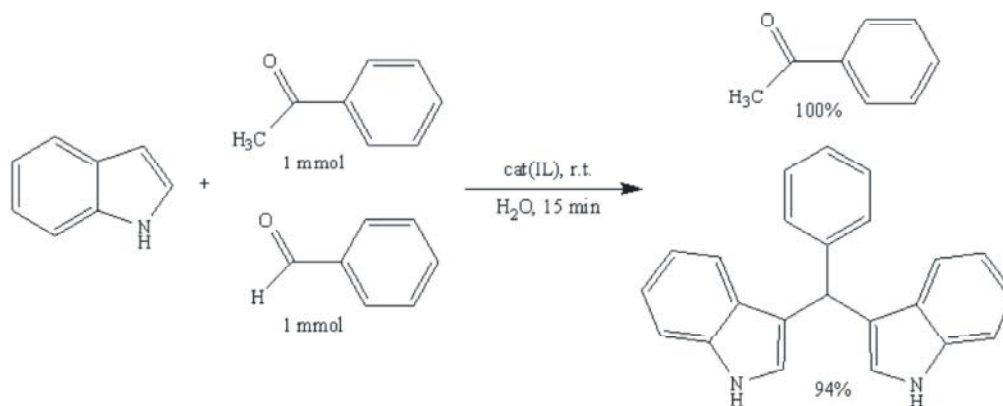


Fig. 4: Chemoselectivity of indole in reaction with benzaldehy in presence of acetophenone

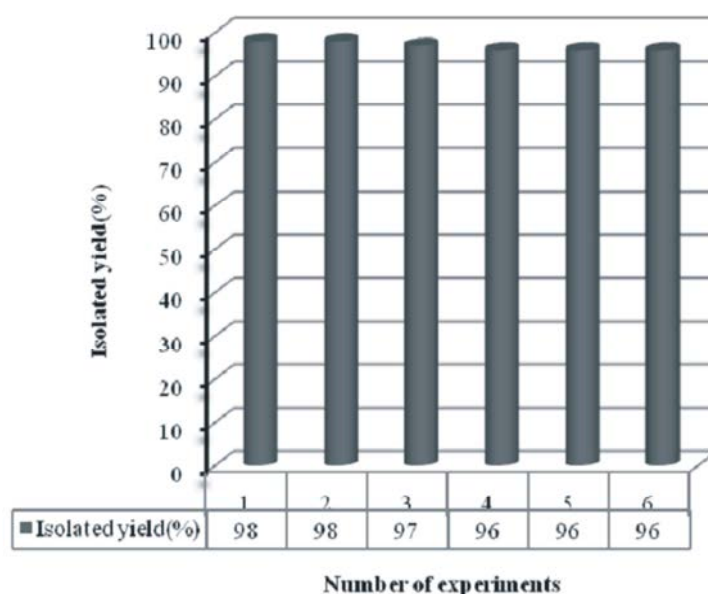


Fig. 5: Reusability studies of catalyst for synthesis of bis-(4-nitrophenyl-1H-indolyl)-methane (Table 3, entry 5)

## CONCLUSIONS

The objective of this paper is to describe green, simple and efficient ionic liquid with multi-SO<sub>3</sub>H groups to catalyze one-pot method for the synthesis of bis (indolyl) methanes derivatives. The experimental procedure for this reaction is remarkably facile and requires no toxic organic solvents. The catalyst offers several advantages including mild reaction conditions, cleaner reactions, shorter reaction times, high yield of the products, lower catalytic loading as well as simple experimental and isolation procedures. Also, the catalysts were able to be reused easily for six-time experiments with a small decrease in the catalytic activity of the recovered catalyst.

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