# Task-specific ionic-liquid-catalyzed efficient synthesis of indole derivatives under solvent-free conditions

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**Abstract:** A sulfonic-acid-functionalized ionic liquid is used as a Brønsted acid catalyst for the efficient synthesis of indole derivatives in good-to-high yields at room temperature under solvent-free conditions. The catalyst can be reused for ten consecutive runs without significant loss of activity.

Key words: functionalized ionic liquid, indole derivatives, bis(indolyl)methanes, Michael adduct, recycling.

**Résumé :** On a utilisé un liquide ionique à base d'acide sulfonique fonctionnalisé comme catalyseur acide de Brønsted pour développer des synthèses efficaces de dérivés de l'indole obtenus avec des rendements allant de bons à éleves, dans des conditions sans solvant. Le catalyseur peut être réutilisé jusqu'à dix fois sans perte significative de son activité.

Mots-clés : liquide ionique fonctionnalisé, dérivés de l'indole, bis(indolyl)méthanes, adduit de Michael, recyclage.

[Traduit par la Rédaction]

## Introduction

Michael reaction is one of the most important carboncarbon bond-forming reactions.<sup>1</sup> The syntheses and the reactions of indole derivatives have received much interest for over a century because a number of their derivatives occur in nature and show versatile biological activities.<sup>2</sup> Since the 3-position of indole is the preferred site for electrophilic substitution reaction, 3-substituted indoles are versatile intermediates for the synthesis of a wide range of indole compounds.<sup>3</sup> Till date, several catalysts were used to catalyze the Michael addition of indoles to electron-deficient olefins; however, most of them were Lewis acids.<sup>4-20</sup> Many Lewis acids are deactivated or sometimes decomposed by nitrogen-containing reactants. Even when the desired reactions proceed, more than stoichiometric amounts of Lewis acids are required because the acids are deactivated by the nitrogen atom of indoles. However, the acid-catalyzed conjugate addition of indoles requires careful control of acidity to prevent side reactions such as dimerization and polymerization. For this reason, the need of a less expensive catalyst is desirable to secure catalytic activity, low toxicity, moisture, and air tolerance.

The application of Brønsted acidic task-specific ionic liquids (TSILs) as catalytic materials is growing continuously in the field of catalysis. Combining the useful charac-

Received 23 July 2009. Accepted 5 October 2009. Published on the NRC Research Press Web site at canjchem.nrc.ca on 29 January 2010.

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#### Scheme 1.



teristics of solid acids and mineral acids, TSILs have been synthesized to replace traditional mineral liquid acids, such as hydrochloric acid and sulfuric acid, in chemical reactions. In view of green chemistry, the substitution of harmful liquid acids by reusable TSILs is the most promising catalytic system in chemistry.<sup>21–23</sup> Some "greener" halogen-free ionic liquids that involve phosphate or octyl sulfate anions have been reported, and effects of the anion and toxicology have been studied.<sup>24-26</sup> The use of Brønsted acidic TSILs to catalyze organic reactions is an area of ongoing activity and TSILs have been successfully used for various chemical transformations.<sup>27-29</sup> In continuation of our interest in ionicliquid-mediated reactions,<sup>30</sup> we have explored the utility of a functionalized ionic liquid,1-butane sulfonic acid-3-methylimidazolium tosylate, [BSMIM]Ts, as a catalyst for the conjugate addition of indoles with electron-deficient alkenes to produce 3-substituted indole derivatives under solvent-free conditions at room temperature (Scheme 1). To the best of our knowledge, this is the first report of a functionalized ionic liquid catalyzed Michael addition of various indoles to electron-deficient alkenes.

#### **Results and discussion**

The experimental procedure is very simple. In a preliminary experiment, indole (2 mmol) was treated with methyl vinyl ketone (2 mmol) in the presence of TSIL (5 mol%) under solvent-free conditions at room temperature, providing the corresponding Michael adduct, exclusively, within 5 min

| Entry | Nucleophile      | Electrophile                                      | Product  | Time (h) | Yield (%) <sup>a</sup> |
|-------|------------------|---|--|----------|------------------------|
| 1     |                  | Me<br>O   | Me<br>H  | 5 min    | 95                     |
| 2     | N Me             | Me  | Me   | 5 min    | 88                     |
| 3     | Br               | Me  | Br Me  | 10 min   | 85                     |
| 4     | MeO N<br>N<br>H  | Me  | MeO  | 10 min   | 82                     |
| 5     | N Me             | Ph<br>O<br>O                                      | N Me   | 2        | 85                     |
| 6     | MeO              | Ph<br>O<br>O                                      | MeO Ph O<br>N Ph O<br>Ph                                 | 5        | 64                     |
| 7     |                  | Ph<br>O<br>O                                      | Ph O<br>Ph<br>N<br>H Ph O                                | 1.5      | 82                     |
| 8     |                  | Ph<br>O   | Me   | 8        | 50                     |
| 9     | N Me             | Ŭ   |  | 1        | 76                     |
| 10    | N H              | Me<br>Me O  |  | 13       | 70                     |
| 11    | O <sub>2</sub> I | $\sum_{\substack{C=C \\ H \\ CO_2Et}}^{N} CO_2Et$ | $ \begin{array}{c}                                     $ | 10 min   | 82                     |
| 12    |                  | Ph_ <sub>C=C</sub> <sup>CN</sup><br>H CN          | CN<br>N<br>H   | 17       | 40                     |

Table 1. Conjugate addition of indoles with electron-deficient olefins.

<sup>a</sup> Yields refer to those of pure isolated products fully charaterized by spectral and physical data.

in 95% yield. The structure of the product was settled from the spectral data. The crude product obtained after ether extraction was found to be pure, as there was no detectable amount of impurities or starting material in the <sup>1</sup>H NMR of the crude product. We next examined the generality of the present reaction conditions to a series of substituted indoles and electron-deficient alkenes. The results are summarized in Table 1.

Electron-deficient olefins, such as chalcone, benzalacetone, cyclohexenone, and dibenzylidene acetone, afforded the products in good-to-excellent yields. The reaction of dibenzilidene with indole gave mono-addition product in 82% yield. A hindered enone, mesityl oxide, which is difficult for conjugate addition, is also reacted to produce Michael adduct in fairly good yield (Table 1, entry 10). By using substituted indoles, good-to-excellent yields were obtained. The substituents did not affect the reactivity of indoles significantly. The catalytic system also worked well with benzylidene malonate to produce the corresponding product in 82% yield (Table 1, entry 11). For benzylidene malononitrile, the corresponding Michael adduct was obtained in low yield under the same conditions even after a prolonged reaction time (Table 1, entry 12). The present protocol could be used on a 100 mmol scale using 2 mol% of the catalyst, which could be reused several times.

Generally, the reactions are clean, and the products are obtained in high yields without the formation of any side products, such as *N*-alkylation products. However, under the

present reaction conditions,  $\alpha$ , $\beta$ -unsaturated aldehydes and esters did not afford the corresponding Michael addition products. Furthermore, the indole nitrogen did not require prior protection, and the avoidance of strong bases for deprotection permitted compatibility with a wide range of functional groups. The procedure did not require any inert atmospheric condition.

The efficacy and generality of the present protocol can be realized by comparing some of the results presented here with recently reported two ionic-liquid-based methods<sup>31,32</sup> as shown in Table 2, which compares reaction time, yields, and reaction conditions. Thus, it is clear from Table 2 that the present protocol can act as an effective method with respect to reaction times, yields, and reaction conditions.

We extended the utility of catalyst for Michael addition of aniline and benzyl amine to methyl vinyl ketone under the present reaction conditions (Scheme 2). Surprisingly, both reactions proceeded very well in short times (25 min and 8 min, respectively), and the adducts were isolated in excellent yields. The results indicate that the catalyst can catalyze the Micheal addition of both aromatic and aliphatic amines. This is a clear advantage over the recent reported ionicliquid-catalyzed conjugate addition of aliphatic amines to electron-deficient alkenes.<sup>28</sup>

Synthesis of bis(indolyl)methanes is a subject of continuous interest to synthetic organic/medicinal chemists, as indoles and their derivatives have versatile biological activities and are widely present in various biologically active natural products.<sup>33</sup> The catalyst is also effective for the preparation of indole derivatives such as bis(indolyl)methane from benzaldehyde under present reaction conditions (Scheme 3).We found that 10 mg of the catalyst was sufficient to obtain the desired bis(indolyl)methane in 96% yield within 5 min at room temperature in neat conditions. Thus, this acidic ionic liquid is a versatile catalyst for various chemical transformations.

The reusability of the catalyst is an important benefit, especially for commercial applications. Thus, the recovery and reusability of the catalyst were investigated. After completion, the mixture was extracted with ether  $(3 \times 5 \text{ mL})$  to obtain the desired products. The catalyst, left in the reaction vessel, was dried under vacuum and was reused for subsequent reactions. It showed the same activity as a fresh catalyst in term of yields. After ten recycles, the catalyst had a high activity and gave the desired product in fairly good yield (91%; Table 1, entry 1). Thus, this makes the process more cost-effective.

In conclusion, we have developed a mild, simple, environment-friendly, and cost-advantageous procedure for the Michael addition of indoles to electron-deficient alkenes using a recyclable task-specific acidic ionic liquid under solvent-free conditions. We believe that this procedure will provide a better and more practical alternative to the existing methodologies for the synthesis of 3-substituted indole derivatives. The catalyst is also effective for Michael addition of both aromatic and aliphatic amines as well as the synthesis of bis(indolyl)methane derivatives. Further procedures to broaden the scope of this methodology towards pharmaceuticals and biologically active compounds are under investigation.





## **Experimental**

The synthesis of the ionic liquid was carried out using a method similar to the reported.<sup>34</sup>

## Typical procedure for the synthesis of 4-(1*H*-indol-3-yl)butan-2-one (Table 1, entry 1)

A mixture of indole (234 mg, 2 mmol) and MVK (162 µL, 2 mmol) was stirred in presence of acidic ionic liquid (39 mg, 5 mol%) at room temperature for 5 min (TLC). After completion, the reaction mixture was extracted with diethyl ether (3  $\times$  10 mL). Evaporation of solvent furnished the addition product as a solid (355 mg, 95%) whose spectroscopic data (IR and <sup>1</sup>H NMR) are in good agreement with those reported.<sup>5</sup> The catalyst left in the reaction vessel was dried under vacuum and was reused for the subsequent reaction. This procedure was followed for the synthesis of 3substituted indoles listed in Table 1. Small amount of ethanol (0.5 mL) was added to the reaction mixture when both indoles and alkenes are solids. Analytically pure compound was obtained by silica gel chromatography using *n*-hexane/ EtOAc as eluent. The spectral and elemental analyses of the compound, which are not readily available, are provided here.

The typical procedure for entry 1 (Table 1) was followed for 100 mmol scale reaction, taking a mixture of indole (11.7 g), MVK (8.1 mL), and acidic ionic liquid (780 mg). The pure product was obtained in 96% yield (17.90 g).

# **3-(5-Methoxy-1***H***-indol-3-yl)-1,3-diphenylpropan-1-one** (Table 1, entry 6)

Solid; mp 150–151 °C. IR (cm<sup>-1</sup>) v: 3367, 1677, 1589, 1483, 1215. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.95 (d, J = 0.7 Hz, 2H), 7.93 (d, J = 1.4 Hz, 1H), 7.55–7.17 (m, 10H), 6.97 (d, J = 2.3 Hz, 1H), 6.85–6.80 (m, 1H), 5.03 (t, J = 2.3 Hz, 1H), 6.85–6.80 (m, 2000) (t, J = 2.3 Hz, 1H), 6.85–6.80 (m, 2000) (t, J = 2.3 Hz, 2000) (t,

Table 2. Comparison of the present protocol with ionic-liquid-based reported methods.

| Entry | Product           | Present method |                        | Reported method <sup>31</sup> |                        | Reported method <sup>32</sup> |                        |
|-------|-------------------|----------------|------------------------|-------------------------------|------------------------|-------------------------------|------------------------|
| Linuy | Tioddol           | Time           | Yield (%) <sup>a</sup> | Time (h)                      | Yield (%) <sup>b</sup> | Time (h)                      | Yield (%) <sup>c</sup> |
| 1     | Me<br>N<br>H<br>O | 5 min          | 95                     | 24                            | 96                     | 3.5                           | 90                     |
| 2     | Me<br>N Me        | 5 min          | 88                     | 16                            | 88                     | 3                             | 93                     |
| 3     | Br Me             | 10 min         | 85                     | 12                            | 95                     | _                             | _                      |
| 4     | MeO H Me          | 10 min         | 82                     | 12                            | 92                     | _                             | _                      |
| 5     | N Me              | 1 h            | 76                     | 20                            | 70                     | 4.5                           | 87                     |
| 6     | Me                | 13 h           | 70                     | _                             | —                      | _                             | _                      |

<sup>a</sup> Present reaction conditions: acidic ionic liquid (5 mol%), RT, solvent-free (2 mmol scale).

<sup>b</sup> Reported reaction conditions: silica-supported sodium sulfonate with ionic liquid [DMIm]SbF<sub>6</sub> (11 – 14 mol%) in water, 30 °C (10 mmol scale).

<sup>c</sup> Reported reaction conditions: Cu(OTf)<sub>2</sub> (10 mol%) immobilized in ionic liquid [bmim]BF<sub>4</sub> (3 mL), RT (1 mmol scale).

7.1 Hz, 1H), 3.84–3.80 (m, 1H), 3.78 (s, 3H), 3.75–3.69 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>2</sub>) & 198.5, 153.8, 144.1, 137.1, 132.9, 131.7, 128.5, 128.4 (2C), 128.1 (2C), 127.8 (2C), 127.0 (2C), 126.3, 122.1, 119.1, 112.2, 111.7, 101.5, 55.8, 45.1, 38.1. Anal. calcd. (%) for C<sub>24</sub>H<sub>21</sub>NO<sub>2</sub> (355.4): C 81.10, H 5.96, N 3.94; found: C 80.95, H 5.81, N 3.76.

#### Acknowledgements

A. H. is pleased to acknowledge the financial support from the Department of Science and Technology (Grant No. SR/FTP/CS-107/2006). A. M. is pleased to acknowledge the financial support from the Council of Scientific and Industrial Research (CSIR) (Grant No. 01(2251)/08/EMR-II). D. K. thanks CSIR and M. R. thanks Visva-Bharati for their fellowships.

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