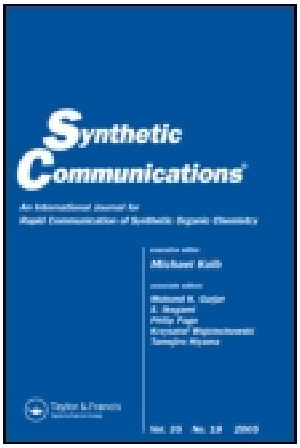

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Acidic Ionic Liquid-Catalyzed Highly Efficient Reaction of Indoles to α,β-Unsaturated Ketones

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Acidic Ionic Liquid–Catalyzed Highly Efficient Reaction of Indoles to α,β-Unsaturated Ketones

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Abstract: A novel method for the Michael reaction of indoles to *α*,*β*-unsaturated ketones catalyzed by acidic ionic liquid is reported. We obtained the corresponding products in excellent yields in the presence of [hmim]HSO_4. Development of this method has resulted in a new protocol for the synthesis of *β*-indolylketones.

Keywords: Acidic ionic liquid, indole, Michael reaction, *α*,*β*-unsaturated ketone

In recent years, room-temperature ionic liquids (RTILs) have generated considerable excitement as potential green-chemistry designer solvents. In view of their special properties (good solvating capability, wide liquid range, negligible vapor pressure, ease of recycling), ionic liquids have found wide application in catalytic and noncatalytic reactions.[1] Lately, the synthesis of task-specific ionic liquids (TSILs), which have a functional group in their frameworks, have been widely reported.[2] In these papers, the use of ionic

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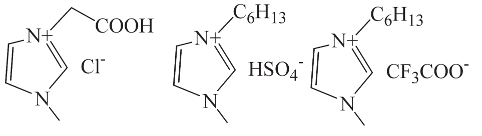
liquids as reaction media and catalyst can offer a solution to solvent emission and catalyst recyclability problems. These new ionic liquids are likely to make synthetic processes less expensive and potentially more efficient and environmentally friendly.

Because β-indolylketones are important building blocks for the synthesis of many natural products such as hapalindole D 1,[3] the Michael reactions of indoles to α,β-unsaturated ketones [Eq. (1)] have attracted tremendous attention for the simplification or improvement of the existing methods.[4] During the past few years, several different Lewis acid catalysts available for the Michael reaction, such as $InBr_3$,[5a] $Yb(OTf)_3$,[6a] $Zr(OTf)_4$,[6a] CAN,[7] I_2,[8] $Bi(OTf)_3$,[9a] $CeCl_3$,[10b] and so on.[11] However, many of these procedures involve strong acidic conditions, expensive reagents, longer reaction time, lower yields of products, complex handling, and difficulty of reuse. Therefore, a green and efficient catalyst is still desirable.



[acmim]Cl **[hmim]HSO_4** **[hmim]Tfa**

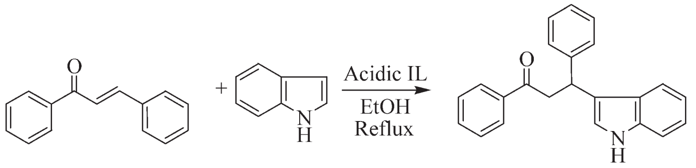
Scheme 1. Structure of acidic ionic liquids.

In continuation of our interest in TSIL-mediated reactions of indoles,[12d,13] we subsequently investigated a novel reaction of indoles and α,β-unsaturated ketones catalyzed by acidic ionic liquids. Herein, three acidic ionic liquids, [acmim]Cl[12a,12b] (ac = acetoxy, m = methyl, im = imidazolium), [hmim] HSO_4[12c–f] (h = n-hexyl, m = methyl, im = imidazolium), and [hmim] Tfa[14] (h = n-hexyl, m = methyl, im = imidazolium), are employed to catalyze the reaction of indoles and α,β-unsaturated ketones. Acidic ionic liquid [hmim]HSO_4 is an effective and reusable catalyst for this reaction.

In our initial research, 1,3-diphenylpropenone as a typical representative of α,β-unsaturated ketones was selected to react with indole using different acidic ionic liquids to optimize the reaction.

As shown in Table 1, the reaction did not occur in the absence of a catalytic amount of acidic ionic liquids (Table 1, entry 1), and it is more important to notice that [hmim]PF_6 cannot promote this addition (Table 1, entry 2). Interestingly, the use of [acmim]Cl and [n-Bu_4 N]HSO_4 could not promote the reaction (Scheme 1). Because of the acidity of these ionic liquids, the reaction proceed smoothly in the presence of 20 mol% [hmim]HSO_4 and 20 mol% [hmim]Tfa. Then we screened the effect of a variety of solvents on the Michael reaction. Alcohol, especially ethanol, was the best solvent in terms of yield, reaction time, low toxicity (compared with CH_3CN), and economic viability. In addition, we reduced the amount

Table 1. Synthesis of 3-(3-indolyl)-1,3-diphenylpropan-2-one in different solvents using acidic ionic liquids



(1)

Entry	Cat. (mol%)	Solvent	Time (h)	Yield (%)[a]
1	None	EtOH	7	0
2	20% [hmim]PF_6	EtOH	4	0
3	20% [acmim]Cl	EtOH	11	0
4	20% [hmim]Tfa	EtOH	12	73
5	20% [n-Bu4 N]HSO_4	EtOH	4	0
6	20% [hmim]HSO_4	H_2O	6	4
7	20% [hmim]HSO_4	MeOH	3	94
8	20% [hmim]HSO_4	CH_3CN	6	98
9	20% [hmim]HSO_4	CH_2Cl_2	7	9
10	20% [hmim]HSO_4	THF	8	88
11	20% [hmim]HSO_4	EtOAc	6	49
12	20% [hmim]HSO_4	EtOH	2	97
13	10% [hmim]HSO_4	EtOH	3	99
14	5% [hmim]HSO_4	EtOH	5	99

[a] Isolated yields.

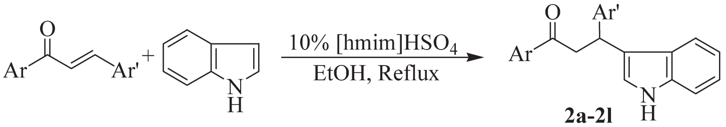
of [hmim]HSO_4 to 5 mol%. The reaction went to completion within 5 h at 80 °C with a yield of 99%.

Using the best conditions mentioned previously, we continued to investigate the reactions of indole to a variety of α,β-unsaturated ketones at 80 °C. The results are listed in Table 2, which indicated that all the aromatic α,β-unsaturated ketones underwent smooth reaction with indole to give the corresponding products with high yields. Unexpectedly, the yield of 4-methylpent-3-en-2-one (Table 2, entry 12) is only 48%. This catalyst system is more efficient for the aromatic α,β-unsaturated ketones.

Next, we studied the Michael reaction of various substituted indoles to 1,3-diphenyl-propenone under identical conditions (Table 1, entry 13). The results were summarized in Table 3.

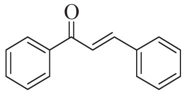
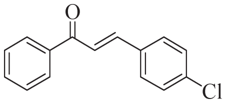
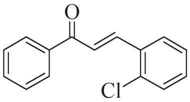
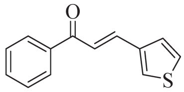
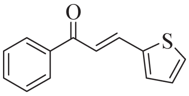
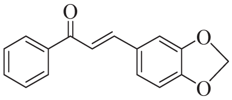
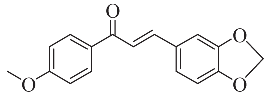
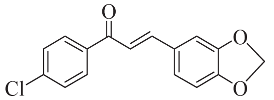
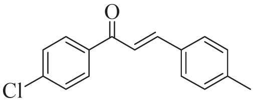
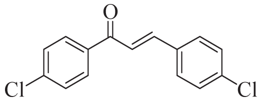
The Michael addition on the indole occurred exclusively at the 3-position. In accordance with this finding, the Michael reaction of 3-methylindole (Table 3, entry 3) did not take place after the mixture was magnetically stirred at an external temperature of 80 °C for 4 h. The reaction of other substituted indoles and 1,3-diphenyl-propenone proceeded smoothly in EtOH in the presence of 10 mol% [hmim]HSO_4 to provide the desired products in high yields.

Table 2. Reaction of indole catalyzed by 10 mol% [hmim]HSO_4 with various α,β-unsaturated ketones in EtOH



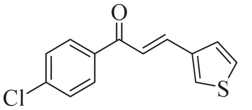
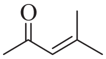
2a-2l

(2)

Entry	α,β-Unsaturated ketones	Product[a]	Time (h)	Yield (%)[b]
1		**2a**	3	99
2		**2b**	4	88
3		**2c**	3.1	98
4		**2d**	3.5	90
5		**2e**	3	81
6		**2f**	4.1	94
7		**2g**	3	99
8		**2h**	4.5	91
9		**2i**	5.5	96
10		**2j**	5.5	96

(*continued*)

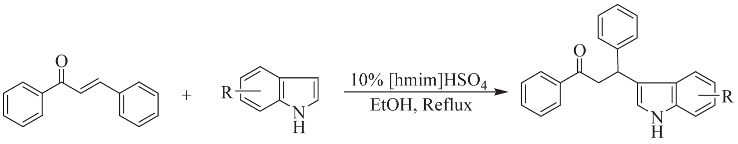
***Table 2*.** Continued

Entry	α,β-Unsaturated ketones	Product[a]	Time (h)	Yield (%)[b]
11		**2k**	5	95
12		**2l**	6	48

[a] All products were characterized by ^{1}H NMR, IR, and HRMS spectroscopy and elemental analysis.

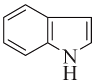
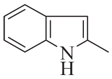
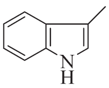
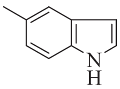
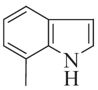
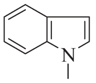
[b] Isolated yields.

Table 3. Reaction of 1,3-diphenyl-propenone catalyzed by 10 mol% [hmim]HSO$_4$ with various substituted indoles in EtOH



3a-3f

(3)

Entry	Indole	Product[a]	Time (h)	Yield (%)[b]
1		**3a**	3	99
2		**3b**	2.5	93
3		**3c**	4	—
4		**3d**	4	92
5		**3e**	3.25	63
6		**3f**	4	46

[a] All products were characterized by ^{1}H NMR, IR, and HRMS spectroscopy and elemental analysis.

[b] Isolated yields.

Table 4. Recyclability of 20 mol% [hmim]HSO_4 in EtOH

Entry	Time (h)	Yield (%)[a]	Mass of the IL and flask before reaction (g)
0	2	97	41.2783
1	2	98	41.2823
2	6	69	41.2859
3	9	56	41.2802

[a] Isolated yields.

With the success of these reactions, we continued our task by studying the reusability of ionic liquid [hmim]HSO_4 in EtOH (Table 4). The catalytic activity of acidic ionic liquids gradually decreased in the second and third cycles (entries 2 and 3). The reason was probably that the a few acidic ionic liquids were lost in the extraction procedure.

In brief, we provide a novel method for the reaction of indole with α,β-unsaturated ketones. Instead of Lewis acids, [hmim]HSO_4/EtOH make this procedure quite simple, more convenient, and environmentally benign. This preliminary work demonstrates the potential application of ionic liquids with acidic counterions as good acid catalysts in the synthesis of 3-(3-indolyl)-1,3-diphenylpropan-2-one and their derivatives of biological importance. Further studies of other ionic liquids with acidic counterions for promoting other acid-catalyzed reactions are under way.

EXPERIMENTAL

Melting points were recorded on an Electrothermal digital melting-point apparatus and are uncorrected. ^1H NMR (400 MHz) spectra were recorded on a Varian Mercury spectrometer in $CDCl_3$. IR spectra were obtained on a Nicolet FT-IR500 spectrophotometer using KBr pellets. Elemental analysis was performed by a Carlo-Erba EA1110 CNNO-S analyzer. High-resolution mass spectra (HRMS) were obtained using a GCT-TOF instrument. Ultrasonication was performed in a KQ-250E ultrasonic cleaner with a frequency of 40 KHz and a normal power of 250 W. The reaction flask was located in the water bath of the ultrasonic cleaner, and the temperature of the water bath was controlled by heating.

Typical Experimental Procedure

A mixture of indoles (0.0702 g, 0.60 mmol), 1,3-diphenylpropenone (0.104 g, 0.50 mmol), and [hmim]HSO_4 (0.0132 g, 0.05 mmol) in EtOH (4.0 mL) was stirred at 80 °C. After completion of the reaction as indicated by thin-layer chromatography (TLC), the mixture was concentrated in vacuo to remove the solvent. The resulting solution was extracted with ether (5 × 10.0 mL). The ether layer was dried (Na_2SO_4), concentrated under vacuum, and purified by column chromatography to afford the pure product. For synthetic procedures of acidic ionic liquids, please see Ref. [12].

Data

3-(3-Indolyl)-1,3-diphenylpropan-2-one (**2a**)

Solid; mp 125–127 °C; IR (KBr): $\nu = 3413$ (NH), 1679 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.67–3.83$ (m, 2H, CH_2), 5.04 (t, $J = 7.2$ Hz, 1H, CH), 6.97–7.53 (m, 13H), 7.91–7.96 (m, 3H). HRMS: m/z calcd. for $C_{23}H_{19}NO$: 325.1467; found: 325.1431. Anal. calcd. for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30. Found: C, 84.74; H, 5.84; N, 4.35.

3-(4-Chlorophenyl)-3-(1*H*-indol-3-yl)-1-phenylpropan-1-one (**2b**)

Please see Ref. 8(a).

3-(2-Chlorophenyl)-3-(1*H*-indol-3-yl)-1-phenylpropan-1-one (**2c**)

Please see Ref. 12(e).

3-(1*H*-Indol-3-yl)-1-phenyl-3-(thiophen-3-yl)propan-1-one (**2d**)

Solid; mp 129–130 °C; IR (KBr): $\nu = 3395$ (NH), 1681 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.77$ (d, $J = 6.4$ Hz, 2H, CH_2), 5.16 (s, 1H, CH), 7.01–7.54 (m, 11H), 7.92–7.96 (m, 3H). HRMS: m/z calcd. for $C_{21}H_{17}NOS$: 331.1031; found: 331.1037. Anal. calcd. for $C_{21}H_{17}NOS$: C, 76.10; H, 5.17; N, 4.23. Found: C, 76.16; H, 5.21; N, 4.25.

3-(1*H*-Indol-3-yl)-1-phenyl-3-(thiophen-2-yl)propan-1-one (**2e**)

Please see Ref. 8(a).

3-(Benzo[d][1,3]dioxol-6-yl)-3-(1*H*-indol-3-yl)-1-phenylpropan-1-one (**2f**)

Solid; mp 115–116 °C; IR (KBr): $\nu = 3370$ (NH), 1675 (CO) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=3.64–3.80 (m, 2H, CH_2), 4.99 (t, $J = 7.0$ Hz, 1H, CH), 5.81–5.91 (m, 2H, OCH_2O), 6.69–7.56 (m, 11H), 7.93–7.97 (m, 3H). HRMS: m/z calcd. for $C_{24}H_{19}NO_3$: 369.1365; found: 369.1362. Anal. calcd. for $C_{24}H_{19}NO_3$: C, 78.03; H, 5.18; N, 3.79. Found: C, 78.10; H, 5.20; N, 3.84.

3-(Benzo[d][1,3]dioxol-6-yl)-3-(1*H*-indol-3-yl)-1-(4-methoxyphenyl)propan-1-one (**2g**)

Solid; mp 72–74 °C; IR (KBr): $\nu = 3405$ (NH), 1666 (CO) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.58$–3.89 (m, 2H, CH_2), 4.11 (s, 3H, OCH_3), 4.98 (t, $J = 7.2$ Hz, 1H, CH), 5.81–6.03 (m, 2H, OCH_2O), 6.64–7.75 (m, 10H), 7.91–8.04 (m, 3H). HRMS: m/z calcd. for $C_{25}H_{21}NO_4$: 399.1471; found: 399.1461. Anal. calcd. for $C_{25}H_{21}NO_4$: C, 75.17; H, 5.30; N, 3.51. Found: C, 75.16; H, 5.24; N, 3.53.

3-(Benzo[d][1,3]dioxol-6-yl)-1-(4-chlorophenyl)-3-(1*H*-indol-3-yl)propan-1-one (**2h**)

Solid; mp 68–70 °C; IR (KBr): $\nu = 3411$ (NH), 1660 (CO) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.67$–3.83 (m, 2H, CH_2), 4.95 (t, $J = 7.4$ Hz, 1H, CH), 5.86–6.68 (m, 2H, OCH_2O), 6.70–7.45 (m, 11H), 7.85–7.98 (m, 3H). HRMS: m/z calcd. for $C_{24}H_{18}ClNO_3$: 403.0957; found: 403.0958. Anal. calcd. for $C_{24}H_{18}ClNO_3$: C, 71.38; H, 4.49; N, 3.47. Found: C, 71.34; H, 5.52; N, 3.47.

1-(4-Chlorophenyl)-3-(1*H*-indol-3-yl)-3-p-tolylpropan-1-one (**2i**)

Solid; mp 84–85 °C; IR (KBr): $\nu = 3420$ (NH), 1674 (CO) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.32$ (s, 3H, CH_3), 3.63–3.79 (m, 2H, CH_2), 4.99 (t, $J = 7.2$ Hz, 1H, CH), 6.97–7.44 (m, 11H), 7.84–7.97 (m, 3H). HRMS: m/z calcd. for $C_{24}H_{20}ClNO$: 373.1233; found: 373.1227. Anal. calcd. for $C_{24}H_{20}ClNO$: C, 77.10; H, 5.39; N, 3.75. Found: C, 77.06; H, 5.44; N, 3.72.

1,3-Bis(4-chlorophenyl)-3-(1*H*-indol-3-yl)propan-1-one (**2j**)

Solid; mp 136–138 °C; IR (KBr): $\nu = 3395$ (NH), 1669 (CO) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.67$–3.76 (m, 2H, CH_2), 5.02 (m, 1H, CH), 6.98–7.42 (m, 11H), 7.85–8.00 (m, 3H). HRMS: m/z calcd. for $C_{23}H_{17}Cl_2NO$: 393.0687; found: 393.0680. Anal. calcd. for $C_{23}H_{17}Cl_2NO$: C, 70.06; H, 4.35; N, 3.55. Found: C, 70.14; H, 4.34; N, 3.47.

1-(4-Chlorophenyl)-3-(1*H*-indol-3-yl)-3-(thiophen-2-yl)propan-1-one (**2k**)

Solid; mp 116–117 °C; IR (KBr): $\nu = 3417$ (NH), 1671 (CO) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.78$–3.80 (m, 2H, CH_2), 5.34 (t, $J = 6.2$ Hz, 1H, CH), 6.85–7.55 (m, 10H), 7.85–8.00 (m, 3H). HRMS: m/z calcd. for $C_{21}H_{16}ClNOS$: 365.0641; found: 365.0640. Anal. calcd. for $C_{21}H_{16}ClNOS$: C, 68.94; H, 4.41; N, 3.83. Found: C, 69.01; H, 4.47; N, 3.90.

4-(1*H*-Indol-3-yl)-4-methylpentan-2-one (**2l**)

Please see Ref. 8(a).

3-(2-Methyl-1*H*-indol-3-yl)-1,3-diphenyl-propan-1-one (**3b**)

Solid; mp 115–116 °C. IR (KBr): $\nu = 3409$ (NH), 1673 (CO), 1596, 1488, 1457 (ArH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.43$ (s, 3H, CH_3), 3.91–3.95 (m, 2H, CH_2), 5.09 (s, 1H, CH), 6.69–7.50 (m, 12H), 7.73–7.89 (m, 3H). HRMS: m/z calcd. for $C_{24}H_{21}NO$: 339.1623; found: 339.1621. Anal. calcd. for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.13. Found: C, 85.01; H, 6.31; N, 4.05.

3-(5-Methyl-1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (**3d**)

Solid; mp 167–168 °C. IR (KBr): $\nu = 3434$ (NH), 1675 (CO), 1593, 1480, 1447 (ArH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.36$ (s, 3H CH_3), 3.73–3.78 (m, 2H, CH_2), 5.02 (s, 1H, CH), 6.94–7.53 (m, 12H), 7.86–7.94 (m, 3H). HRMS: m/z calcd. for $C_{24}H_{21}NO$: 339.1623; found: 339.1613. Anal. calcd. for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.13. Found: C, 84.90; H, 6.31; N, 4.21.

3-(7-Methyl-1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (**3e**)

Solid; mp 104–105 °C. IR (KBr): $\nu = 3276$ (NH), 1656 (CO), 1596, 1491, 1447 (ArH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.44$ (s, 3H, CH_3), 3.73–3.80 (m, 2H, CH_2), 5.05 (t, $J = 6.8$ Hz, 1H, CH), 6.94–7.54 (m, 12H), 7.88–7.93 (m, 3H). HRMS: m/z calcd. for $C_{24}H_{21}NO$: 339.1623; found: 339.1621. Anal. calcd. for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.13. Found: C, 84.96; H, 6.19; N, 3.94.

3-(1-Methyl-1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (**3f**)

Solid; mp 127–129 °C. IR (KBr): $\nu = 3401$ (NH), 1673 (CO), 1581, 1481, 1450 (ArH) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.70$–3.84 (m, 2H, CH_2), 5.07 (s, 1H, CH), 6.83–7.53 (m, 15H), 7.92–7.96 (m, 3H). HRMS: m/z calcd. for $C_{24}H_{21}NO$: 339.1623; found: 339.1613. Anal. calcd. for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.13. Found: C, 84.79; H, 6.26; N, 4.21.

Recycling the Acidic Ionic Liquid

A mixture of indoles (0.0702 g, 0.60 mmol), 1,3-diphenylpropenone (0.104 g, 0.50 mmol), and [hmim]HSO_4 (0.0264 g, 0.10 mmol) in EtOH (4.0 mL) was stirred at 80 °C. After completion of the reaction as indicated by TLC, the mixture was concentrated in vacuo to remove the solvent. The resulting solution was extracted with ether (5 × 10.0 mL). The ether layer was dried (Na_2SO_4), concentrated under vacuum, and purified by column chromatography to afford the pure product. The insoluble [hmim]HSO_4 could be directly recycled in subsequent runs.

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