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Conjugate addition of indoles to α,β-unsaturated ketones using $Cu(OTf)_2$ immobilized in ionic liquids☆

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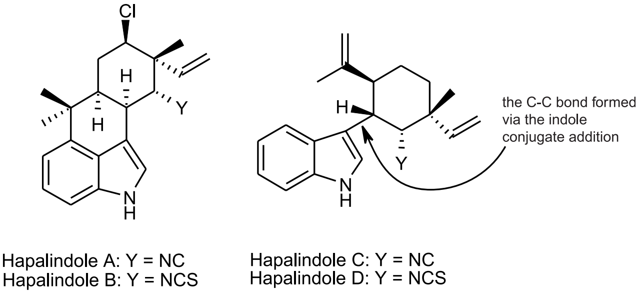
Abstract—Indoles undergo smooth conjugate addition with α,β-unsaturated ketones in the presence of 10 mol% copper(II) triflate immobilized in air and moisture stable [bmim]BF_4 ionic liquid under mild conditions to afford the corresponding conjugate addition products in high to quantitative yields. The recovery of $Cu(OTf)_2$ is facilitated by the ionic liquid. The recovered catalyst was reused four to five times with consistent activity.

1. Introduction

The conjugate addition of indoles to α,β-unsaturated ketones constitutes a key reaction in the total synthesis of complex natural products such as hapalindole.[1,2] The hapalindole alkaloids were isolated from the blue-green algae *Hapalosiphon fontinalis*. They exhibit potent anti-bacterial and antimycotic activity.



Consequently, numerous methods have been reported for the conjugate addition of indoles to electron-deficient olefins through the activation of enones or nitro alkenes by Lewis acids.[2,3] Asymmetric versions of conjugate additions of indoles to α,β-unsaturated ketones have also been reported using chiral Lewis acid catalysts to produce enantiomerically enriched indole derivatives.[4] Typically, conjugate addition reactions are performed under the influence of strong bases such as alkali metal alkoxides or hydroxides.[5] The strong basic conditions often lead to a number of undesirable side reactions such as aldol cyclizations, ester solvolysis, base induced rearrangements such as retro-Claisen or retro-Michael reactions and polymerization reactions. Subsequently, Lewis acids have been found to catalyze conjugate addition reactions under mild conditions.[6,7] However, most of the catalysts cannot be recovered and reused because they decompose under the quenching conditions. Furthermore, many of these methods often involve the use of strong acids, which always demand aqueous work-up for catalyst separation, recycling and disposal. Since indoles and their derivatives have become increasingly useful and important in the field of pharmaceuticals, the development of simple, efficient, and environmentally benign approaches are desirable.

Room temperature ionic liquids (RTLs) have been used as ‘green’ solvents and possess unique properties such as wide temperature liquid range, air and moisture stability, high solubilizing properties, immiscibility with a number of organic solvents, negligible vapour pressure and ease of recyclability.[8] Particularly, 1,3-dialkylimidazolium based ionic liquids are being used as green solvents for the immobilization of transition metal based catalysts, Lewis acids and enzymes.[9] They are referred to as ‘designer solvents’ as their properties such as hydrophilicity, hydrophobicity, Lewis acidity, viscosity and density can be altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion and the length of alkyl chain attached to the imidazole moiety. These structural variations offer flexibility to the chemist to devise

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Keywords: Ionic liquids (ILs); α,β-Unsaturated ketones; $Cu(OTf)_2$; 3-Substituted indole derivatives.

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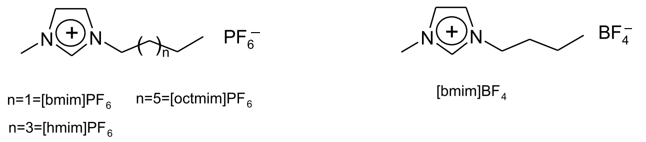


Figure 1.

idealized solvents, catering to the needs of any particular process (Fig. 1).

The high polarity and ability to solubilize both organic and inorganic compounds of ionic liquids can result in enhanced rates of chemical processes and can provide higher selectivities compared to conventional solvents. As a result of their green credentials and potential to enhance rates and selectivities, ionic liquids are finding increasing applications in organic synthesis.[10]

2. Results and discussion

As part of our ongoing programme in developing new synthetic methodologies[11] and in view of the emerging importance of ionic liquids as green solvents in organic reactions, we report herein the use of ionic liquids as recyclable solvents for the conjugate addition of indoles to α,β-unsaturated ketones to produce 3-substituted indole derivatives in high to quantitative yields under mild conditions (Scheme 1).

Accordingly, treatment of indole with methyl vinyl ketone in the presence of 10 mo1% copper(II) triflate immobilized in [bmim]BF$_4$ resulted in the formation of 4-(3-indolyl)-2-butanone **3a** in 90% yield. The reaction proceeded efficiently at room temperature with high 1,4-selectivity and complete conversion of the reaction takes place in a short period of time (3.5 h). The product obtained was isolated by simple extraction with diethyl ether. The ionic liquid was further washed with ether and reused several times without further purification. Encouraged by the results obtained with indole and methyl vinyl ketone, we turned our attention to various substituted indoles and electron-deficient alkenes. Interestingly, numerous cyclic enones and chalcones underwent 1,4-addition with a range of indoles under the reaction conditions to afford the corresponding 3-alkylated indoles. The yields are generally high to quantitative in a few hours. In a similar way to enones, other electron-deficient alkenes such as *trans*-β-nitrostyrene also afforded the conjugate addition product in excellent yield (Table 1, entry: **o**). In the absence of catalyst, the reactions did not proceed after a long reaction time (10–15 h). Interestingly, no by-products arising from 1,2-addition or bis-addition were observed. Compared to conventional solvents, enhanced reaction rates and improved yields are notable features observed using the Cu(OTf)$_2$–[bmim]BF$_4$ catalytic system. The reactivity of copper(II) triflate in various solvents has been studied in the reaction of 2-methylindole and cyclopentenone and the results are summarized in Table 2.

In further experiments, the reactivity of various indoles and enones were studied in both hydrophobic [bmim]PF$_6$ and hydrophilic [bmim]BF$_4$ ionic liquids. Among them, [bmim] BF$_4$ was found to be superior in terms of conversion and reaction rates (Table 2, runs **1** and **2**). The recovered ionic liquid containing copper(II) triflate was reused five times without loss of activity, and even after the fourth cycle, the product **3e** was obtained with similar yield and purity as that obtained in the first cycle. Commercially available ionic liquids were used in this study. The purity of [bmim]BF$_4$ ionic liquid is >97.0% (NMR). The use of ionic liquids as the reaction medium for this transformation helps to recycle the catalyst thereby making the process quite simple, more convenient and environmentally friendly.

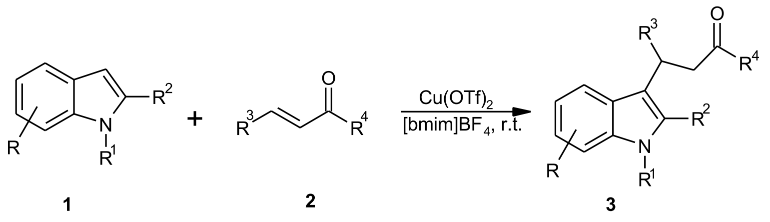
3. Conclusion

In summary, we describe a mild, clean and efficient protocol for the conjugate addition of indoles to α,β-unsaturated ketones using Cu(OTf)$_2$–[bmim]BF$_4$ as a novel and recyclable catalytic system. The enones show enhanced reactivity in ionic liquids thereby reducing the reaction times and improving the yield significantly. The simple experimental procedure combined with ease of recovery and reuse of this novel reaction medium is expected to contribute to the development of a green strategy for the conjugate addition reaction.

4. Experimental

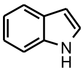
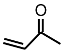
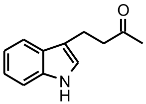
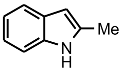
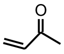
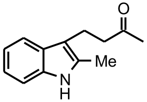
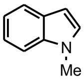
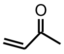
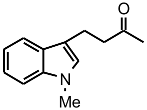
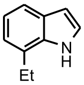
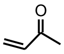
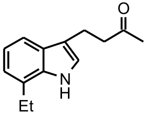
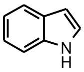
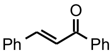
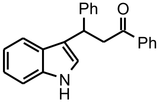
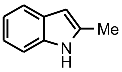
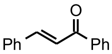
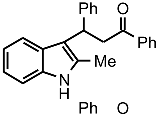
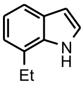
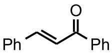
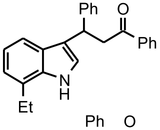
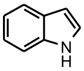
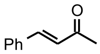
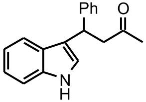
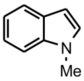
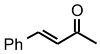
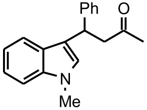
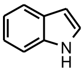
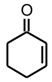
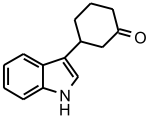
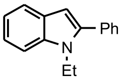
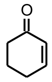
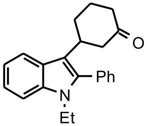
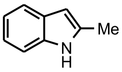
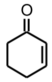
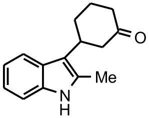
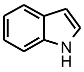
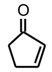
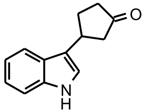
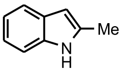
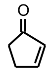
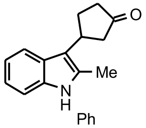
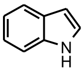
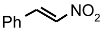
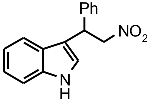
4.1. General methods

Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-C spectro-photometer using KBr optics. ^{1}H NMR and ^{13}C NMR spectra were recorded on Gemini 200 and Bruker Avance 300 MHz spectrometers in CDCl$_3$ using TMS as internal standard, with chemical shifts being given in ppm with respect to internal TMS and J values quoted in Hz. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. All commercial reagents were used without purification. All reaction mixtures were stirred magnetically and were monitored by TLC using 0.25 mm E-Merck silica gel 60 F$_{254}$ pre-coated glass plates, which were visualized with UV



Scheme 1.

Table 1. $Cu(OTf)_2$-catalysed conjugate addition of indoles to enones using $[bmim]BF_4$

Entry	Indole	Enone	Product[a]	Time (h)	Yield (%)[b]
a				3.5	90
b				3.0	93
c				4.0	91
d				3.5	90
e				4.5	85
f				2.0	95
g				4.0	87
h				4.0	89
i				5.0	86
j				6.0	82
k				4.0	88
l				4.5	87
m				5.0	85
n				4.5	89
o				4.0	90

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[a] All the products were characterized by ^1H NMR, IR, mass spectra.

[b] Isolated and unoptimized yields.

Table 2. Reactivity of 10 mol% $Cu(OTf)_2$ in various solvents for the condensation of 2-methylindole with cyclopentenone[a]

Run	Reaction medium	Time (h)	Yield (%)
1	$[bmim]BF_4$	4.5	89
2	$[bmim]PF_6$	5.0	83
3	CH_3CN	8.5	68
4	CH_3OH	7.0	71
5	CH_2Cl_2	8.5	65

[a] Reactions were carried out in 1 mmol scale.

light and then developed by using iodine mixed with silica gel 60–120 mesh.

4.2. General procedure for the conjugate addition of indoles to α,β-unsaturated compounds

A mixture of α,β-unsaturated compound (1 mmol), indole (1 mmol) and 10 mol% $Cu(OTf)_2$ in 1-butyl-3-methyl imidazolium tetrafluoroborate (3 mL) was stirred at ambient temperature for the appropriate time (as shown in the Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether (3×10 mL). The combined ether layers were concentrated in vacuo and the resulting product was directly charged on a small silica gel column and eluted with a mixture of ethyl acetate and *n*-hexane to afford the pure 1,4-adduct. All known compounds were characterized by ^{1}H NMR, IR, mass spectra and their spectroscopic data identical to that reported in the literature.[2,3] The new compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, mass spectra and HRMS.

4.3. Physical and spectroscopic data for all the new compounds

4.3.1. Compound 3d. Pale yellow solid, mp 94–96 °C; IR (KBr): ν 3344, 3051, 2922, 2853, 1706, 1638, 1443, 1322, 1206, 1098, 923, 857, 737, 648 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (t, 3H, $J=7.0$ Hz), 2.10 (s, 3H), 2.78–2.90 (m, 4H), 3.05 (t, 2H, $J=7.0$ Hz), 6.93–7.18 (m, 3H), 7.40 (d, 1H, $J=7.5$ Hz), 7.92 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8, 19.4, 23.9, 29.9, 44.0, 115.5, 116.3, 119.5, 120.5, 121.0, 126.5, 126.8, 135.0, 208.9; EIMS *m/z* (%): 215 (M^+29), 187 (26), 158 (93), 130 (100), 103 (20), 89 (14), 77 (18), 63 (12), 51 (28), 43 (31); HRMS: calcd for $C_{14}H_{18}NO$ ($M+H^+$) 216.1388, found 216.1384.

4.3.2. Compound 3g. White solid, mp 125–126 °C; IR (KBr): ν 3367, 3057, 2964, 2847, 1665, 1593, 1491, 1443, 1356, 1277, 1098, 745, 692 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30 (t, 3H, $J=6.0$ Hz), 2.78 (q, 2H, $J=7.0$ Hz), 3.65–3.86 (m, 2H), 5.05 (t, 1H, $J=7.0$ Hz), 6.80 (s, 1H), 6.90 (d, 2H, $J=4.2$ Hz), 7.10–7.55 (m, 9H), 7.92 (d, 3H, $J=8.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7, 23.8, 38.3, 45.1, 117.2, 119.6, 120.5, 121.3, 126.2, 126.4, 126.7, 127.8 (2C), 128.0 (2C), 128.3 (2C), 128.5 (2C), 128.9, 133.0, 135.4, 137.0, 144.2, 198.6; FABMS *m/z* (%): 353 (M^+12), 234 (100), 219 (12), 204 (15), 154 (10), 145 (12), 130 (10), 121 (10), 109 (10), 109 (18), 105 (57), 95 (38), 83 (41), 69 (60), 55 (35); HRMS: calcd for $C_{25}H_{23}NONa$ ($M+Na^+$) 376.1677, found 376.1678.

4.3.3. Compound 3k. White solid, mp 142–143 °C; IR (KBr): ν 3387, 3041, 2931, 2861, 1698, 1458, 1339, 1222, 1064, 937, 964, 746, 701 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.25 (t, 3H, $J=7.5$ Hz), 1.60–1.80 (m, 1H), 1.98–2.20 (m, 3H), 2.30–2.50 (m, 3H), 2.95– 3.08 (m, 2H), 4.00 (q, 2H, $J=7.5$ Hz), 7.08–7.23 (m, 2H), 7.38 (d, 3H, $J=8.0$, Hz), 7.48 (dd, 3H, $J=8.0$, 2.0 Hz), 7.78 (1H, $J=8.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.3, 25.8, 32.0, 37.4, 38.4, 41.3, 48.4, 109.9, 115.3, 119.0, 119.7, 121.4, 126.0, 128.5 (3C), 130.6 (2C), 132.1, 136.0, 136.9, 211.3; FABMS *m/z* (%): 317 (M^+100), 274 (10), 260 (27), 246 (12), 234 (10), 217 (15), 204 (11), 154 (10), 136 (12), 107 (15), 95 (10), 69 (18), 55 (20); HRMS: calcd for $C_{22}H_{24}NO$ ($M+H^+$) 318.1857, found 318.1846.

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