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Task-specific ionic liquid-catalyzed efficient couplings of indoles with 1,3-dicarbonyl compounds: an efficient synthesis of 3-alkenylated indoles

Sougata Santra, Adinath Majee *, Alakananda Hajra *

Department of Chemistry, Visva-Bharati University, Santiniketan, Birbhum 731 235, India

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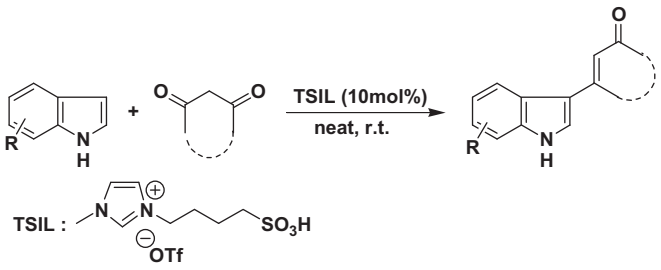
ABSTRACT

Direct alkenylation of indoles at the 3-position with 1,3-dicarbonyl compounds under Brønsted acidic ionic liquid catalysis has been developed. The yields were excellent, and the catalyst can be reused at least six times without noticeable loss of catalytic activity.

Indole derivatives occur in a large number of biologically active natural products, and they have been widely applied in medicinal chemistry.[1] The synthesis of indole derivatives has received much interest over a century, and a variety of methods are available in the literature.[2] 3-Substituted indoles are versatile intermediates and many well-established methods available for the synthesis of 3-alkylated indole derivatives.[3] By contrast, only a few methods are available for direct alkenylation of indoles at the 3-position.[4] So, the development of a simple and efficient method for the synthesis of 3-alkenylated indole derivatives is highly desirable.

The application of Brønsted acidic task-specific ionic liquids (TSILs) as catalytic materials is growing continuously in the field of catalysis. Combining the useful characteristics of solid acids and mineral acids, TSILs have been applied to replace traditional mineral liquid acids, such as hydrochloric acid and sulfuric acid in chemical reactions. The use of Brønsted acidic TSILs to catalyze organic reactions is an area of ongoing activity and has been successfully used as catalyst for various chemical transformations.[5] In continuation of our interest in ionic liquid mediated reactions[6] herein, we wish to report the development of a simple procedure utilizing a functionalized ionic liquid, 1-butane sulfonic acid-3-methylimidazolium triflate, [BSMIM]OTf as a catalyst for direct alkenylation of indoles at the 3-position with 1,3-dicarbonyl compounds (Scheme 1).[7]



Scheme 1. Alkenylation of indole.

To optimize the reaction conditions, first we examined the coupling between acetylacetone and indole in presence of different acid catalysts under solvent-free conditions at room temperature (Table 1). Poor conversions were obtained using 1-butane sulfonic acid-3-methylimidazolium *p*-toluenesulfonate, [BSMIM]OTs and *p*-toluene sulfonic acid (PTSA) as a catalyst (10 mol %). Other acids such as triflic acid produced the coupling product in moderate yield. The best result was obtained (84% yield) when the coupling reaction was carried out in presence of 10 mol % 1-butane sulfonic acid-3-methylimidazolium triflate, [BSMIM]OTf. In absence of catalyst, no formation of desired product was observed. Acid (10 mol %) was required as optimum amount of catalyst and increasing the amount of catalyst did not improve the yields while decreasing the amount of catalyst decreased the yield.

To demonstrate the generality of this method, we examined the scope of this reaction under the optimized reaction conditions and the results are summarized in Table 2. A wide range of structurally

* Corresponding authors. Tel./fax: +91 34632 61526 (A.H.).
E-mail addresses: adinath.majee@visva-bharati.ac.in (A. Majee), ahajra75@yahoo.com, alakananda.hajra@visva-bharati.ac.in (A. Hajra).

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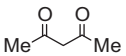
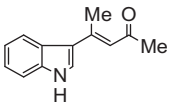
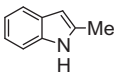
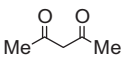
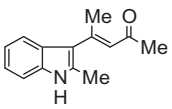
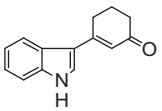
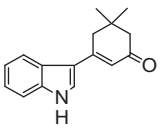
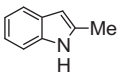
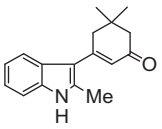
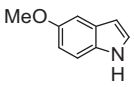
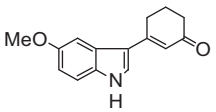
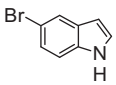
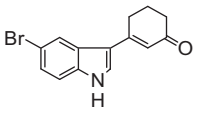
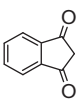
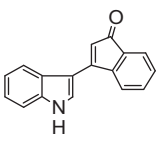
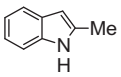
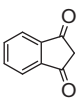
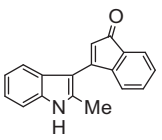
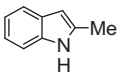
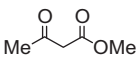
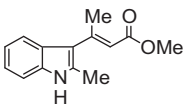
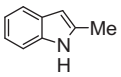
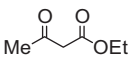
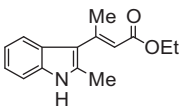
Table 1
Coupling between indole and acetylacetone under different reaction conditions at room temperature

Entry	Catalyst (mol %)	Time (h)	Yield[a] (%)
1	—	5	0
2	PTSA (10)	5	<10
3	[BSMIM]OTs (10)	5	<10
4	CF_3SO_3H (10)	5	48
5	CF_3SO_3H (15)	5	57
6	[BSMIM]OTf (10)	1.5	84
7	[BSMIM]OTf (5)	5	68
8	[BSMIM]OTf (15)	1.5	83

[a] Isolated yield.

diverse 1,3-dicarbonyl compounds underwent condensation by this method to produce 3-alkenyaled indoles in high yields with complete *E*-selectivity. Various cyclic 1,3-diones such as 1,3-cyclohexanedione, dimedone, and indane-1,3-dione reacted very well with various indoles under the present reaction conditions. 1,3-Ketoesters such as ethyl acetoacetate and methyl acetoacetate also produced the desired product in high yields. 1*H*-Indole, 5-bromo-1*H*-indole, 5-methoxy-1*H*-indole, and 2-methyl-1*H*-indole were employed as the indole derivatives for this condensation reaction. In general the reactions were clean and no formation of bis-indoles was observed under the present reaction conditions.[3d] Complete *E*-selectivity was observed in all the cases. The catalyst

Table 2
TSIL-catalyzed alkenylation of indoles with 1,3-dicarbonyl compounds

Entry	Indole	1,3-Dicarbonyl compound	Product	Time (h)	Yield[a] (%)
1				1.5	84
2				1.5	87
3				2	86
4				2.5	85
5				2.5	89
6				2	82
7				2	84
8				1.5	81
9				2	83
10				1.5	92
11				2	94

[a] Isolated yield.

was reused for six times without noticeable decrease in catalytic activity (80% for entry 1, Table 2).

In conclusion, a method for direct alkenylation of indoles at the 3-position with 1,3-dicarbonyl compounds under Brønsted acidic ionic liquid catalysis has been developed. The advantages of this procedure are: (a) simple operation; (b) excellent yields; (c) fast reaction; (d) general applicability; (e) reusability of catalyst and (f) above all, metal-free synthesis avoiding toxic reagents and solvents. Further studies to broaden the scope of this methodology toward the synthesis of biologically important compounds are under investigation.

Acknowledgments

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Supplementary data

Supplementary data (spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.05.069.

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7. Synthesis of methyl 3-(2-methyl-1*H*-3-indolyl)-2-butenoate (Table 2, entry 10): A mixture of 2-methylindole (262 mg, 2 mmol) and methyl acetoacetate (237 μL, 2.2 mmol) was stirred in presence of acidic ionic liquid (74 mg, 10 mol %) at room temperature for 1.5 h (TLC). After completion, the reaction mixture was extracted with diethyl ether (10 mL × 3). Evaporation of solvent furnished the crude product which was subjected to column chromatography to obtain the analytically pure product as a brown solid (422 mg, 92%). Mp 132–133 °C. IR (KBr) 3330, 2950, 1677, 1600, 1423 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.17 (br 1H), 7.66 (dd, J = 6.7, 2.7 Hz, 1H), 7.31–7.27 (m, 1H), 7.18–7.14 (m, 2H), 5.98 (d, J = 1.0 Hz, 1H), 3.77 (s, 3H), 2.70 (d, J = 1.0 Hz, 3H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.9, 152.7, 135.2, 133.2, 127.0, 121.8, 120.4, 119.6, 116.7, 116.6, 110.6, 51.0, 20.5, 13.5. Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.21; H, 6.42; N, 6.01%. The catalyst, left in the reaction vessel was dried under vacuum and was reused for subsequent reactions. Small amount of methanol (0.5 mL) was added to the reaction mixture when both indoles and 1,3-dicarbonyl compounds are solids. The spectral and analytical data of another new compound is given below.
Ethyl 3-(2-methyl-1*H*-3-indolyl)-2-butenoate (Table 2, entry 11): Pale yellow solid, mp 114–116 °C. IR (KBr) 3411, 2933, 1718, 1625, 1454 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.27 (br 1H), 7.66 (dd, J = 8.5, 2.5 Hz, 1H), 7.29–7.25 (m, 1H), 7.16–7.12 (m, 2H), 5.96 (d, J = 1.1 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.68 (d, J = 1.1 Hz, 3H), 2.49 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.6, 152.4, 135.3, 133.2, 127.1, 121.8, 120.4, 119.6, 117.1, 116.8, 110.6, 59.7, 20.6, 14.5, 13.6. Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.91; H, 7.01; N, 5.62.