The Michael Addition of Indole to α,β-Unsaturated Ketones Catalyzed by Iodine at Room Temperature

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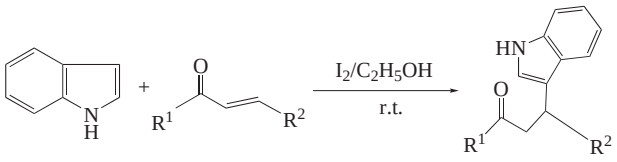
Abstract: Indole undergoes conjugate addition with α,β-unsaturated ketones by means of alkylation of indole in the presence of a catalytic amount of molecular I_2 at room temperature to afford the corresponding adduct in excellent yields (up to 96%). The substitution on the indole nucleus occurred exclusively at the 3-position. *N*-alkylation products have not been observed.

Key words: molecular iodine, indoles, Michael reaction



1 **2** **3**

Scheme 1

The investigation of the chemistry of indoles has been, and continues to be, one of the most active areas of heterocyclic chemistry.[1] Among the derivatives of indoles, β-indolylketones are important building blocks for the synthesis of many natural products such as hapalindole D 1.[2] Therefore, many methods have been developed for the synthesis of this class of compounds. In the last few years, several Lewis acid-mediated Friedel–Crafts-type additions of indoles to α,β-unsaturated ketones exclusively at the 3-position, have been reported.[2–4] However, many of these procedures involved strong acidic conditions, expensive reagents, longer reaction times, low yields of products and complex handling. More recently, we have reported that ceric ammonium nitrate (CAN) efficiently catalyzes the Michael addition of indole to α,β-unsaturated carbonyl ketones under sonic waves.[5] In continuation of our ongoing interest in green chemistry, we are interested in using I_2, which has received considerable attention as an inexpensive and easily available catalyst for efficient various organic transformations,[6,7] to catalyze this reaction.

The I_2–EtOH system offers some advantages over existing methods with $InCl_3$,[8] $CeCl_3 \cdot 7H_2O$–NaI.[4a] As shown in Table 1 (entries 1–4), it is found that this system is more desirable than CAN–MeOH system under ultrasonic irradiation in terms of yields and reaction times using different solvents. Herein, we describe a remarkable catalytic activity of I_2 in conjugate addition of indole **1** with α,β-unsaturated carbonyl compounds **2** which provide an efficient route to the synthesis of β-indolyketones (Scheme 1).

First we carried out the reaction of indole (**1**) with **2a** in the presence of I_2 at room temperature using different solvents. The results are listed in Table 1. The reaction of indole (**1**) with **2a** in the presence of I_2 (10 mmol) and anhydrous EtOH (2 mL) proceeded smoothly at room temperature, giving the 3-oxoalkylation adduct **3a** in 86% yield, while 90% yield was found in anhydrous MeOH (2 mL) (Table 1, entries 1 and 2). Especially noteworthy is that this reaction can also work in aqueous media (entry 4). However, increasing the amount of water resulted in a decrease in yield (entries 5 and 6) under identical conditions, even in the presence of PTC. Considering the toxic nature of the MeOH, study continued to be done using I_2–EtOH system.

Table 1 The Solvent Effect of Michael Addition of Indole **1** with α,β-Unsaturated Compounds **2a**[a]

Entry	Solvent	Time/h.	Yield (%)[b]
1	anhyd EtOH	4 (3)[d]	86 (70)
2	anhyd MeOH	3 (3)	90 (81)
3	CH_3CN	8 (3)	75 (31)
4	C_2H_5OH–H_2O = 95:5	8	80
5	C_2H_5OH–H_2O = 1:1	12	50
6	H_2O (PTC[c])	12	0

[a] All reaction were carried out using cat. amount of I_2 (10% mol) at ambient temperature.
[b] Isolated yields.
[c] Bu_4NBr (10% mol).
[d] The results in parentheses have been reported using cat. amount of CAN (10% mol) under ultrasonic irradiation.[5]

I_2 was found to be an efficient catalyst in terms of price, handling, temperature, yields and reaction times in comparison to the reported methods. This is because of the mild Lewis acidity of I_2 and a small quantity of the solvent needed. As shown in Table 2, this method works with a

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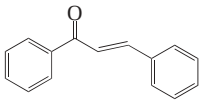
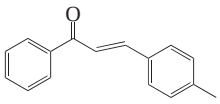
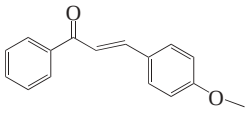
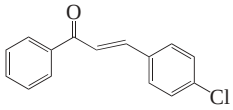
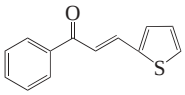
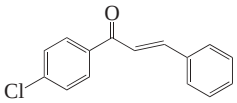
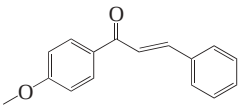
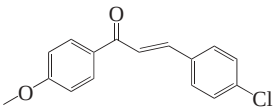
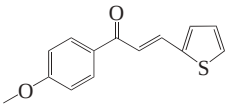
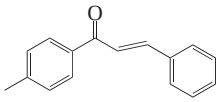
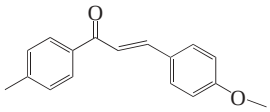
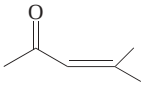
Table 2 Michael Addition of Indole **1** with α,β-Unsaturated Compounds **2a–l**[a,11,12,]

Entry	Chalone		Product	Time (h)	Yield (%)[b]
1	**2a**		**3a**	4	86[3b] (85)[c]
2	**2b**		**3b**	5	86
3	**2c**		**3c**	5	96[9]
4	**2d**		**3d**	5	92
5	**2e**		**3e**	5	86
6	**2f**		**3f**	5	96
7	**2g**		**3g**	5	92[10]
8	**2h**		**3h**	8	60
9	**2i**		**3i**	5	90
10	**2j**		**3j**	5	96[10]
11	**2k**		**3k**	10	92[9]
12	**2l**		**3l**	12	70[3b]

[a] All reactions were carried out in anhyd EtOH at r.t., employing 10 mol% I_2.
[b] All products are determined by IR, ^{1}H NMR, HRMS and mp etc. The superscripts are the citation for the known compounds.
[c] The result for large-scale synthesis (50 mmol level) under identical condition is listed in parentheses.

wide variety of substrates. In most cases, the reactions proceeded smoothly to produce the corresponding 3-(3-oxoalkyl)indole **3** in good yields. The treatment of indole **1** with **2c** afforded **3c** in 96% yield under identical condition. Michael acceptors such as **2l** also reacted well under our condition. The reactions were clean and the products were obtained in excellent yields without the formation of any side products such as N-alkylation products. And these reactions work with an open vessel with stirring, which makes the upscaling of the reactions to larger scale possible without decreasing yields (Table 2, entry 1, footnote c). The I_2–EtOH reaction system is easier to handle and is easy for large-scale reaction as compared to the reaction using CAN under sonication.

In conclusion, we have developed a simple, convenient and efficient protocol for **3** using catalytic amount of I_2 under mild conditions at room temperature. The ability for this reaction to work in protic solvents (e.g. alcohol, water, etc) make this method one of the most efficient methods for the synthesis of this class of compounds. In addition, the mechanism is still ongoing in our laboratory.

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(11) **Typical Experimental Procedure**: A mixture of indole (0.117 g, 1 mmol), **2c** (0.355 g, 1 mmol), I_2 (0.025 g, 0.1 mmol) and anhyd EtOH (2 mL) was stirred in an open vessel at r.t. until the disappearance of the starting indole (5 h, checked by TLC). After standing for 2 h, the reaction mixture was washed by cold water (2 ´ 25 mL) and cold EtOH (2 ´ 0.5 mL). The crude mixture recrystallized from hot EtOH to afford the pure product **3c** (0.453 g, yield: 96%). 3-(1*H*-Indol-3-yl)-3-(4-methoxy-phenyl)-1-phenyl-propan-1-one (**3c**): solid; mp 161–162 °C (Lit.[9] 162 °C). IR (KBr): 1669 (CO), 3420 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.69–3.83 (m, 5 H, CH_2, CH_3), 5.02 (t, *J* = 7.2 Hz, 1 H, CH), 6.79–7.63 (m, 12 H), 7.98–8.03 (m, 3 H). HRMS: *m*/*z* [M] calcd for $C_{24}H_{21}NO_2$: 355.1572; found: 355.1555 [M^+].
(12) **Selected Characterization Data of New Compounds**. 3-(1*H*-Indol-3-yl)-1-phenyl-3-*p*-tolyl-propan-1-one (**3b**): solid; mp 140 °C. IR (KBr): 1672 (CO), 3428 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.28 (s, 3 H, CH_3), 3.68–3.84 (m, 2 H, CH_2), 5.04 (t, *J* = 7.2 Hz, 1 H, CH), 6.97–7.53 (m, 12 H), 7.91–7.96 (m, 3 H). HRMS: *m*/*z* [M] calcd for $C_{24}H_{21}NO$: 339.1623; found: 339.1634 [M^+].
3-(4-Chloro-phenyl)-3-(1*H*-indol-3-yl)-1-phenyl-propan-1-one (**3d**): solid; mp 127–129 °C. IR (KBr): 1677 (CO), 3401 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.66–3.83 (m, 2 H, CH_2), 5.04 (t, *J* = 7.2 Hz, 1 H, CH), 6.70–7.60 (m, 12 H), 7.92–8.00(m, 3 H). HRMS: *m*/*z* [M] calcd for $C_{23}H_{18}ClNO$: 359.0891; found: 359.0855 [M^+].
3-(1*H*-Indol-3-yl)-1-phenyl-3-thiophen-2-yl-propan-1-one (**3e**): solid; mp 151–153 °C. IR (KBr): 1683 (CO), 3401(NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.83 (d, *J* = 7.2 Hz, 2 H, CH_2), 5.36 (t, *J* = 7.2 Hz, 1 H, CH), 6.87–7.55 (m, 12 H), 7.92–8.00 (m, 3 H). HRMS: *m*/*z* [M] calcd for $C_{21}H_{17}NOS$: 331.1031; found: 331.0977 [M^+].
1-(4-Chloro-phenyl)-3-(1*H*-indol-3-yl)-3-phenyl-propan-1-one (**3f**): solid; mp 158–160 °C. IR (KBr): 1680 (CO), 3445 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.65–3.80 (m, 2 H, CH_2), 5.03 (t, *J* = 7.2 Hz, 1 H, CH), 6.99–7.43 (m, 12 H), 7.84–7.98 (m, 3 H). HRMS: *m*/*z* [M] calcd for $C_{23}H_{18}ClNO$: 359.0891; found: 359.0891 [M^+].
3-(4-Chloro-phenyl)-3-(1*H*-indol-3-yl)-1-(4-methoxy-phenyl)-propan-1-one (**3h**): solid; mp 123–125 °C. IR (KBr): 1658 (CO), 3461(NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$):
δ = 3.22–3.35 (m, 2 H, CH_2), 3.89 (s, 3 H, CH_3), 5.30 (t, *J* = 7.2 Hz, 1 H, CH), 6.93–7.60 (m, 11 H), 7.74–7.95(m, 3 H). HRMS: *m*/*z* [M] calcd for $C_{24}H_{20}ClNO_2$: 389.1183; found: 389.1194 [M^+].
3-(1*H*-Indol-3-yl)-1-(4-methoxy-phenyl)-3-thiophen-2-yl-propan-1-one (**3i**): solid; mp 149–151 °C. IR (KBr): 1670 (CO), 3430 (NH) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.78 (d, *J* = 7.2 Hz, 2 H, CH_2), 3.86 (s, 3 H, CH_3), 5.37 (t, *J* = 7.2 Hz, 1 H, CH), 6.87–7.56 (m, 10 H), 7.92–8.00 (m, 3 H). HRMS: *m*/*z* [M] calcd for $C_{22}H_{19}NO_2S$: 361.1136; found: 361.1066 [M^+].