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Iodine-catalyzed efficient conjugate addition of pyrroles to α,β-unsaturated ketones☆

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Abstract—Iodine was used as a catalyst for the conjugate addition of pyrroles to α,β-unsaturated ketones at room temperature. Mono- and dialkylated products were obtained by using equimolar amounts of the reactants. However, the use of excess enones afforded only dialkylated products.

Pyrrole and C-alkylated pyrroles are among the most important fundamental constituents of biologically and physiologically active molecules, such as chlorophyll, porphyrin, hemoglobin, Vitamin B_{12} and bile pigments.[1] 2-Alkyl- or 2-acyl pyrroles are versatile synthons for the synthesis of a wide range of pyrrole derivatives.[2] There already exist several indirect routes affording *C*-alkyl pyrroles: (i) Wolff–Kischner reduction of 2-formyl or 2-acyl pyrroles,[3] (ii) isomerization of *N*-alkyl pyrroles by thermal rearrangement at high temperature, resulting in 2- and 3-alkyl pyrroles[4] and (iii) preparation of 2- and 3-alkyl pyrroles using a pyrrolylmagnesium halide.[5] However, these indirect methods involve the drawbacks of multistep reactions and of polymerization under many reaction conditions. A direct useful procedure for C-alkylation of pyrroles involves their conjugate addition to α,β-unsaturated ketones. Acid-catalyzed alkylation of pyrroles is limited and requires careful control of the acidity to prevent polymerization.[6] The Lewis acids, $InCl_3$,[7] $Bi(NO_3)_3$[8] and $CuBr_2$,[9] have recently been applied as catalysts for this reaction. A microwave-assisted method was also used for the alkylation of pyrroles.[10]

In recent years, iodine has emerged as a very effective catalyst for various organic transformations.[11] However, to our knowledge, there is no report on the conjugate addition of pyrroles to α,β-unsaturated ketones using iodine as a catalyst. In connection with our ongoing research to develop iodine-catalyzed organic transformations,[12] we herein report a highly convenient conjugate addition of pyrroles to α,β-unsaturated ketones.

Initially, a systematic study was carried out for the catalytic evaluation of iodine in the conjugate addition of pyrrole with methyl vinyl ketone using an equimolar-ratio of reagents (Table 1, entry a). The reaction was complete within 3 min when 5 mol % of iodine was used in CH_3CN at room temperature. 2-Alkyl pyrrole, **3a** and 2,5-dialkyl pyrrole, **4a**, were obtained in a ratio of 1:3 in 95% yield (Scheme 1, Table 1). Increasing the amount of catalyst did not enhance the yield of the products. No products were observed when the reaction was carried out in the absence of iodine, this proved the catalytic role of iodine. Similarly, other α,β-unsaturated ketones (**2b**–**2f**) reacted well with pyrrole at room temperature to give the corresponding 2-alkyl and 2,5-dialkyl pyrroles in 73–95% combined yields, in various ratios (Scheme 1, Table 1). Iodine is inexpensive and readily available.

Alkylation was also carried out[13] with *N*-methyl and *N*-benzoyl pyrroles. *N*-Benzoyl pyrrole afforded only monoalkylated products in somewhat low yields (Table 1, entries m and n). This can be attributed to the lower electron density on the ring carbon due to the electron withdrawing benzoyl group on the ring nitrogen.

Only dialkylated pyrroles were obtained by increasing the molar ratio of alkene to pyrrole. The reaction of

Keywords: Iodine; Pyrrole; α,β-Unsaturated ketone; Conjugate addition.

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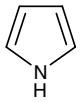
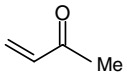
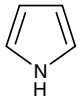
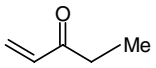
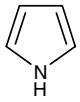
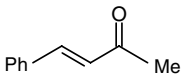
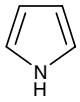
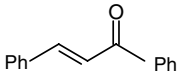
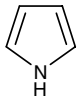
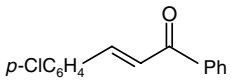
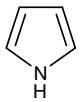
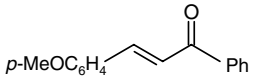
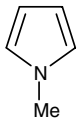
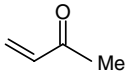
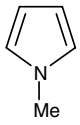
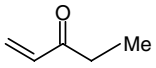
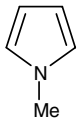
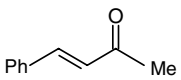
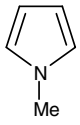
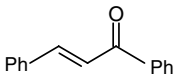
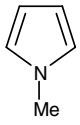
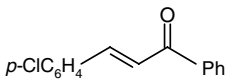
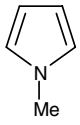
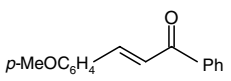
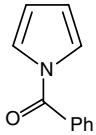
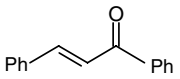
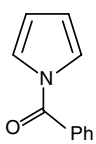
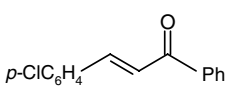
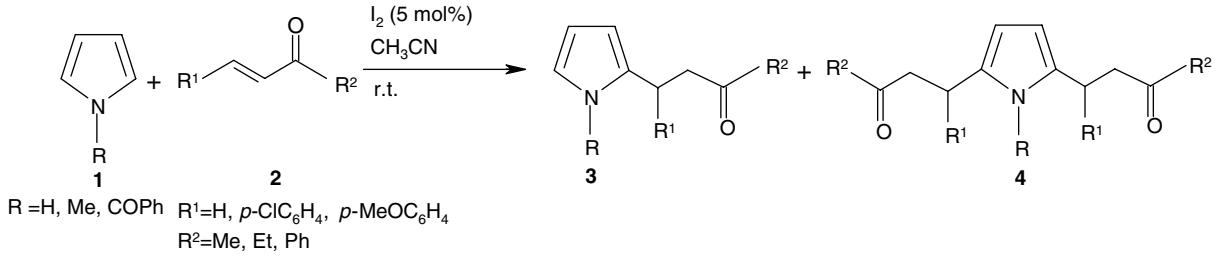
Table 1. I_2-Catalyzed conjugate addition of pyrroles with α,β-unsaturated ketones (1:1) in CH_3CN at room temperature[a]

Entry	Nucleophile	α,β-Unsaturated ketone **2**	Time (min)	Total isolated yield (%) of 2-alkyl pyrrole **3** and 2,5-dialkyl pyrrole **4**	**3**:**4**
a			3	95	1:3
b			3	92	1:4
c			5	79	1:2
d			5	77	1:2
e			6	75	1:2
f			6	73	1:2
g			3	96	1:3
h			3	94	1:4
i			5	72	1:1
j			7	71	1:2
k			8	78	1:1
l			8	72	1:1
m			12	54[b]	—
n			12	38[b]	—

[a] The structures of the products were established from their spectral (^1H NMR and MS) data.
[b] Only monoalkylated product was obtained.



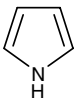
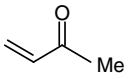
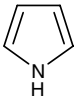
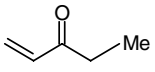
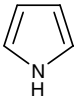
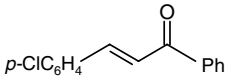
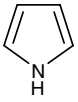
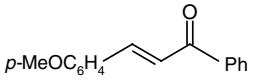
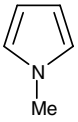
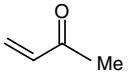
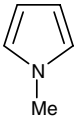
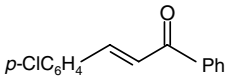
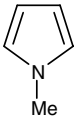
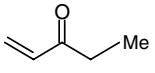
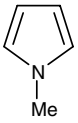
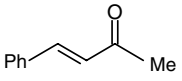
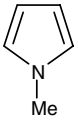
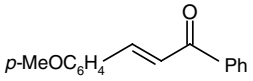
Scheme 1.

pyrroles with α,β-unsaturated ketones (1:3) in the presence of 5 mol % of iodine in CH_3CN afforded 2,5-dialkylated pyrroles in 74–91% yield within a short reaction time at room temperature (Table 2).

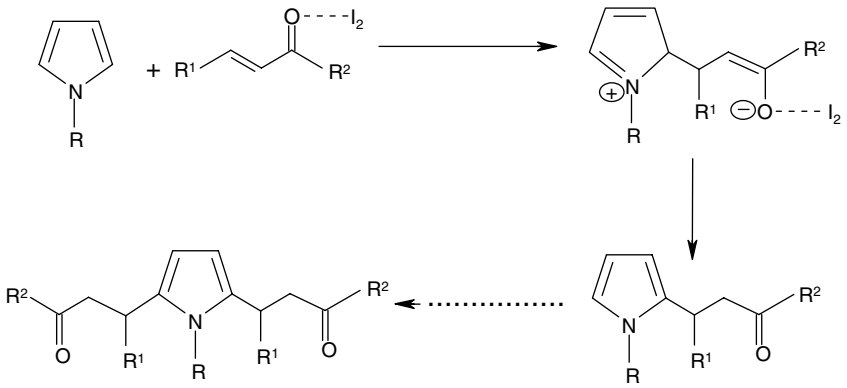
The mechanism of the reaction of indoles with carbonyl compounds in the presence of iodine has already been reported.[14] In agreement with this mechanism, iodine having mild Lewis acidity activates the carbonyl group of the enone and facilitates conjugate addition of pyrrole (Scheme 2). Iodine was removed by washing with sodium thiosulfate solution.

In conclusion, we have employed molecular iodine as an effective catalyst for the alkylation of pyrrole with α,β-unsaturated ketones. The procedure has the advantages

Table 2. Synthesis of 2,5-dialkylated pyrroles catalyzed by I_2 using pyrroles and α,β-unsaturated ketones (1:3) in CH_3CN at room temperature[a]

Entry	Nucleophile	α,β-Unsaturated ketone **2**	Time (min)	Isolated yield (%) of 2,5-dialkylated pyrrole **4**
1			10	91
2			10	89
3			15	82
4			15	81
5			10	92
6			15	78
7			10	90
8			10	79
9			15	74

[a] The structures of the products were established from their spectral (^{1}H NMR and MS) data.



Scheme 2.

of short reaction times, high yields, mildness and operational simplicity, which make it a useful and attractive process for the synthesis of C-alkylated pyrroles.

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References and notes

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13. *General experimental procedure for the alkylation of pyrrole*: A solution of pyrrole (1 mmol), α,β-unsaturated ketone (1 or 3 mmol) and I_2 (5 mol %) in dry CH_3CN (5 mL) was stirred at room temperature for the appropriate time (Tables 1 and 2). After completion (TLC), the mixture was concentrated and diluted with water (10 mL), and ethyl acetate (10 mL) and washed with aqueous sodium thiosulfate solution (3 × 10 mL). The organic layer was evaporated under reduced pressure. Pure products were obtained by column chromatography of the residue on silica gel using hexane–ethyl acetate (1:9).
The spectral (^{1}H NMR and MS) and analytical data of some representative products are given below.
Product **3e**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.32 (1H, br s), 7.94 (2H, d, $J = 8.0$ Hz), 7.52 (1H, t, $J = 8.0$ Hz), 7.43 (2H, t, $J = 8.0$ Hz), 7.31–7.14 (4H, m), 6.50 (1H, m), 5.99 (1H, m), 5.72 (1H, m), 4.72 (1H, dd, $J = 5.0$, 3.0 Hz), 3.76 (1H, dd, $J = 12.0$, 5.0 Hz), 3.52 (1H, dd, $J = 12.0$, 3.0 Hz); FABMS: *m/z* 310 (^{35}Cl), 312 (^{37}Cl) $[M^{\cdot}+H]^+$ Anal. Calcd for $C_{19}H_{16}ClNO$: C, 73.67; H, 5.17; N, 4.52. Found: C, 73.73; H, 5.13; N, 4.59.
Product **3k**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.92 (2H, d, $J = 8.0$ Hz), 7.50 (1H, t, $J = 8.0$ Hz), 7.44 (2H, t, $J = 8.0$ Hz), 7.23–7.08 (4H, m), 6.46 (1H, m), 6.04–5.96 (2H, m), 4.77 (1H, dd, $J = 5.0$, 4.0 Hz), 3.70 (1H, dd, $J = 12.0$, 4.0 Hz), 3.42 (1H, dd, $J = 12.0$, 5.0 Hz), 3.32 (3H, s); FABMS: *m/z* 324 (^{35}Cl), 326 (^{37}Cl) $[M^{\cdot}+H]^+$ Anal. Calcd for $C_{20}H_{18}ClNO$: C, 74.19; H, 5.56; N, 4.33. Found: C, 74.16; H, 5.43; N, 4.42.
Product **4e**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 8.21 (1H, br s), 7.87 (4H, d, $J = 8.0$ Hz), 7.52 (2H, t, $J = 8.0$ Hz), 7.41 (4H, t, $J = 8.0$ Hz), 7.22–7.14 (8H, m), 5.52 (2H, s), 4.61 (2H, dd, $J = 5.0$, 3.0 Hz), 3.65 (2H, dd, $J = 12.0$, 5.0 Hz), 3.41 (2H, dd, $J = 12.0$, 3.0 Hz); FABMS: *m/z* 552 ($2 \times {}^{35}$Cl), 554 (^{35}Cl, ^{37}Cl), 556 ($2 \times {}^{37}$Cl) $[M^{\cdot}+H]^+$ Anal. Calcd for $C_{34}H_{27}Cl_2NO_2$: C, 73.91; H, 4.89; N, 2.54. Found: C, 73.98; H, 4.82; N, 2.45.
Product **4k**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.90 (4H, d, $J = 8.0$ Hz), 7.51 (2H, t, $J = 8.0$ Hz), 7.41 (4H, t, $J = 8.0$ Hz), 7.17–7.02 (8H, m), 5.94 (2H, s), 4.73 (2H, dd, $J = 5.0$, 4.0 Hz), 3.65 (2H, dd, $J = 12.0$, 4.0 Hz), 3.35 (2H, dd, $J = 12.0$, 5.0 Hz), 3.06 (3H, s); FABMS: *m/z* 566 ($2 \times {}^{35}$Cl), 568 (^{35}Cl, ^{37}Cl), 570 ($2 \times {}^{37}$Cl) $[M^{\cdot}+H]^+$ Anal. Calcd for $C_{35}H_{29}Cl_2NO_2$: C, 74.20; H, 5.12; N, 2.47. Found: C, 74.16; H, 5.19; N, 2.42.
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