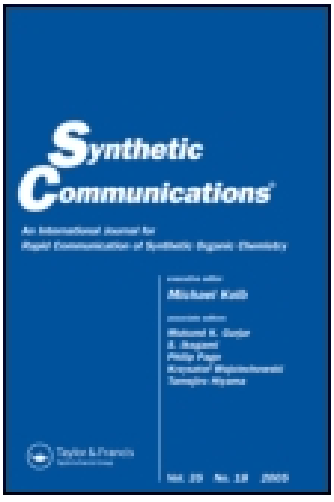

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Copper(II) Bromide-Catalyzed Conjugate Addition of Indoles to α,β-Enones

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Copper(II) Bromide–Catalyzed Conjugate Addition of Indoles to α,β-Enones

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Abstract: Copper(II) bromide was found to be an efficient catalyst for the conjugate addition of indoles to α,β-enones in acetonitrile at room temperature.

Keywords: Conjugate addition, copper(II) bromide, α,β-enone, indole

The simple and direct method for the synthesis of 3-alkyl indoles involves the conjugate addition of indoles to α,β-unsaturated carbonyl compounds in the presence of protic[1] or Lewis acids.[2] However, the acid-catalyzed conjugate addition of indoles requires careful control of acidity to prevent side reactions such as dimerization or polymerization, whereas Lewis acid–catalyzed reactions involve toxic and expensive reagents coupled with long reaction times.[3] We felt a need to develop a mild and cheap catalyst for these reactions. A recent report on the samarium triodide – catalyzed alkylation of indoles[3g] prompted us to report our results on the conjugate addition of indoles to α,β-enones catalyzed by copper(II) bromide to furnish 3-alkylated indole (Scheme 1).

2-Methylindole (**1b**) with benzylideneacetophenone (**2a**) in the presence of 15 mol% of $CuBr_2$ in acetonitrile reacted smoothly within 15 min at ambient temperature to afford 3-(2-methyl-3-indolyl)-1,3-diphenyl-propan-l-one (**3a**) in 83% yield. To test the generality of the protocol, the reactions

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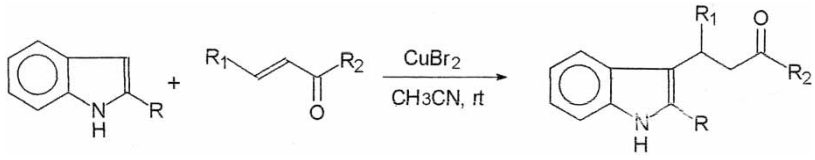


Scheme 1. R = H, Me; R_1 = H, alkyl, aryl; R_2 = alkyl, aryl.

were also carried out using several other α,β-unsaturated carbonyl compounds such as benzylideneacetone (**2a–g**), giving rise to Michael adducts (**3b–j**) in good yields (Table 1). Because of extensive polymerization, however, reactions of **1a** and **1b** with methyl vinyl ketone (**2f**) furnished the corresponding adducts **3g** and **3h** in modest yields (Table 1, entries 7 and 8). Interestingly, reactions of **1a** and **1b** with dibenzylideneacetone (**2h**) (with 2:1 molar ratio) in the presence of 30 mol% $CuBr_2$ gave bis-alkylated products **3k** and **3l** respectively (Table 1, entries 11 and 12). All the compounds were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS data by comparison with the known compounds.

In summary, we have demonstrated that $CuBr_2$ is an efficient and mild Lewis acid catalyst for alkylation of indole/2-methyl indole with α,β-unsaturated carbonyl compounds.

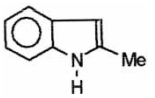
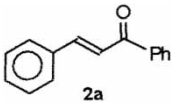
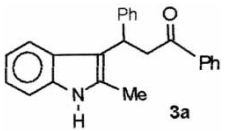
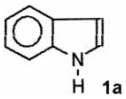
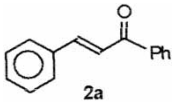
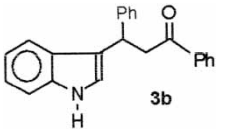
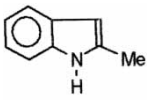
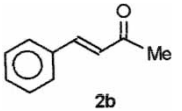
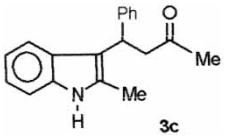
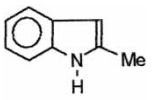
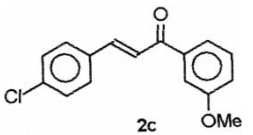
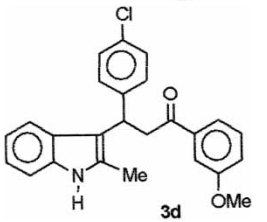
Melting points were taken on a Fisher-Johns melting-point apparatus and are uncorrected. The FT-IR spectra were scanned with a Jasco FT-IR spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AC 200 (200-MHz) spectrometer. Mass spectra were recorded with a Shimadzu GC-MS QP 5050A mass spectrometer. All reactions were carried out under an argon atmosphere Acetonitrile was dried and distilled over P_2O_5. Compounds **2a–d** and **2h** were prepared following the literature procedure.[4] Compounds **1a**, **1b**, **2e–g**, and $CuBr_2$ were used as received from Fluka.

EXPERIMENTAL

Typical Experimental Procedure

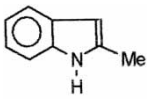
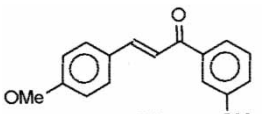
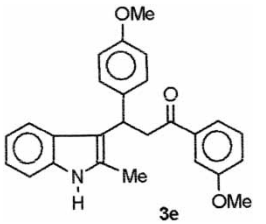
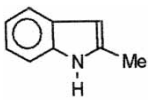
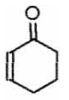
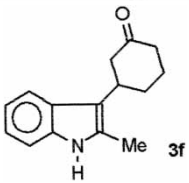
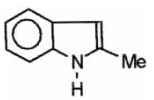
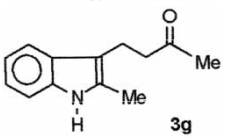
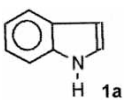
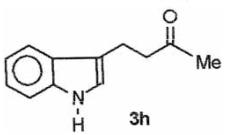
A solution of indole **1** (3.0 mmol), α,β-unsaturated carbonyl compounds **2** (3.0 mmol), and $CuBr_2$ (0.45 mmol, 0.1 g, 15 mol%) in dry acetonitrile (10 ml) was stirred at room temperature for an appropriate time (see Table 1). The mixture was concentrated, diluted with water and ethylacetate, and filtered over Celite. The filtrate was extracted with ethylacetate and dried (Na_2SO_4). Removal of solvent followed by silica-gel chromatography (hexane/ethyl acetate 85:15) afforded **3**.

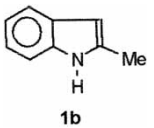
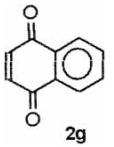
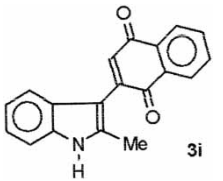
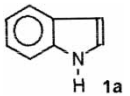
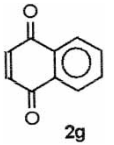
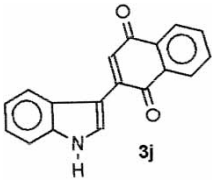
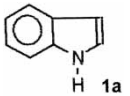
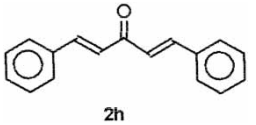
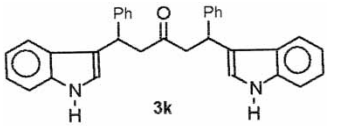
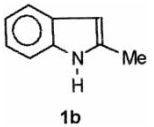
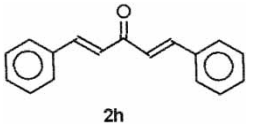
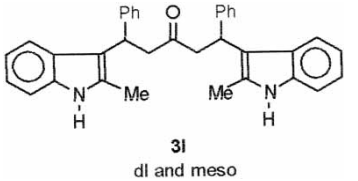
Table 1. $CuBr_2$-catalyzed conjugate addition of indoles to α,β-enones[a,b]

Entry	Nucleophile	Electrophile	Product	Time (h)	Yield (%)[c]
1	 1b	 2a	 3a	0.25	83
2	 1a	 2a	 3b	0.25	72
3	 1b	 2b	 3c	0.33	82
4	 1b	 2c	 3d	0.33	73

(*continued*)

Table 1. Continued

Entry	Nucleophile	Electrophile	Product	Time (h)	Yield (%)[c]
5	 1b	 2d	 3e	0.33	55
6	 1b	 2e	 3f	0.5	54
7	 1b	 2f	 3g	0.25	45
8	 1a	 2f	 3h	0.25	39

9	 1b	 2g	 3i	0.33	90
10	 1a	 2g	 3j	0.33	68
11	 1a	 2h	 3k dl and meso	0.50	65
12	 1b	 2h	 3l dl and meso	0.50	52

[a]Reaction conditions: indole/2-methylindole (3.0 mmol), α,β-enone (3.0 mmol), and $CuBr_2$ (0.45 mmol) in acetonitrile at ambient temperature (entries 1–10).

[b]Reaction conditions: indole/2-methylindole (2.0 mmol), α,β-enone (1.0 mmol), and $CuBr_2$ (0.3 mmol) acetonitrile at ambient temperature (entries 11 and 12).

[c]Isolated and unoptimized yields.

Data

3-(2-Methyl-3-indolyl)-1,3-diphenyl-propan-1-one (**3a**)[3c]

Solid, mp 179–180°C; IR (KBr): 3367, 3024, 1684, 1618, 1460, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.89$ (d, 2 H, $J = 7.8$ Hz), 7.51 (br s, 1 H, NH), 7.00–7.48 (m, 12 H), 5.11 (t, 1 H, $J = 7.0$ Hz), 3.94 (dd, 2 H, $J = 2.7$, 7.3 Hz), 2.39 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 199.3$, 144.1, 137.0, 135.4, 132.8, 131.7, 128.4, 128.2, 127.9, 127.4, 127.3, 125.8, 120.5, 118.9, 113.2, 110.5, 43.5, 36.7, 11.9.; EIMS: m/z = 339 (M^+), 234, 221, 220, 216, 146, 128.

3-(3-Indolyl)-1,3-diphenyl-propan-l-one (**3b**)[3c]

Solid, mp 130–132°C; IR (KBr): 3399, 3019, 1676, 1457, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.92$–7.95 (m, 3 H), 7.00–7.54 (m, 13 H), 5.07 (t, 1 H, $J = 7.2$ Hz), 3.77 (m, 2 H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 198.6$, 144.2, 137.0, 136.6, 133.0, 128.5, 128.4, 128.0, 127.8, 126.6, 126.3, 122.0, 121.4, 119.5, 119.3, 119.1, 111.1, 45.2, 38.2; EIMS: m/z = 325 (M^+), 246, 220, 206.

4-(2-Methyl-3-indolyl)-4-phenyl-butan-2-one (**3c**)[3c]

Solid, mp 108–109°C; IR (KBr): 3400, 3010, 1712, 1620, 1461, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.79$ (br s, 1 H, NH), 6.96–7.47 (m, 9 H), 4.86 (t, 1 H, $J = 6.7$ Hz), 3.38 (dq, 2 H, $J = 8.3$, 16.2 Hz), 2.42 (s, 3 H), 2.01 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 208.3$, 143.9, 135.4, 135.8, 128.2, 127.3, 125.8, 120.6, 118.9, 112.8, 110.5, 48.2, 36.7, 30.7, 11.9; EIMS: m/z = 277 (M^+), 234, 217, 143, 129, 102.

3-(2-Methyl-3-indolyl)-1-(3-methoxyphenyl)-3-(4-chlorophenyl)-propan-1-one (**3d**)

Thick oil; IR (KBr): 3369, 3015, 1682, 1598, 1461 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.81$ (br s, 1 H, NH), 7.03–7.49 (m, 12 H), 5.05 (t, 1 H, $J = 7.0$ Hz), 3.94–3.77 (m, 2 H), 3.73 (s, 3 H), 2.39 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 198.9$, 159.5, 142.5, 138.1, 135.3, 131.7, 131.3, 129.4, 128.7, 128.1, 126.9, 120.6, 120.6, 119.5, 119.0, 118.6, 112.7, 111.9, 110.5, 55.0, 43.2, 36.2, 11.7; EIMS: m/z = 404 (M^+), 254, 216, 135, 82. Anal. calcd. for $C_{25}H_{22}ClNO_2$:C, 74.34; H, 5.49; N, 3.47. Found: C, 74.45; H, 5.58; N, 3.56.

3-(2-methyl-3-indolyl)-1-(3-methoxyphenyl)-3-(4-methoxyhenyl)-propan-1-one (**3e**)

Thick oil; IR (KBr): 3377, 3008, 1682, 1598, 1461, 1035 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.38$ (br s, 1 H, NH), 6.78–7.50 (m, 12 H), 5.04 (t, 1 H, $J = 7.0$ Hz), 3.39–4.01 (m, 2 H), 3.75 (s, 3 H), 3.72 (s, 3 H), 2.37 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 199.3$, 159.6, 157.5, 138.5, 136.2, 135.4, 131.6, 129.4, 128.4, 127.3, 120.5, 119.5, 118.9, 113.5, 111.9, 110.4, 55.1, 55.0, 43.7, 36.1, 11.7; EIMS: m/z = 399 ($M^+ - 1$), 369, 277, 235, 217, 204, 191. Anal. calcd. for $C_{26}H_{25}CNO_3$: C, 78.17; H, 6.31; N, 3.51. Found: C, 78.26; H, 6.21; N, 3.59.

3-(2-Methyl-3-indolyl)cyclohexan-l-one (**3f**)[3c]

Solid, mp 91–92°C; IR (KBr): 3380, 3014, 2939, 1703, 1619; 1459 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.83$ (br s, 1 H, NH), 7.65–7.68 (m, 1 H), 7.03–7.30 (m, 3 H), 2.92–3.28 (m, 2 H), 1.65–2.52 (m, 7 H), 2.33 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 212.2$, 135.3, 130.2, 126.7, 120.6, 118.8, 113.4, 110.6, 48.1, 41.3, 37.2, 31.3, 25.9, 11.8; EIMS: m/z = 227 (M^+), 184, 170, 107, 83, 69.

4-(2-Methyl-3-indolyl)-butan-2-one (**3g**)[3b]

Thick oil; IR (KBr): 3478, 3018, 1713, 1456, 1216 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.80$ (br s, 1 H, NH), 7.07–7.44 (m, 4 H), 2.96 (t, 2 H, $J = 7.1$ Hz), 2.76 (t, 2 H, $J = 7.2$ Hz), 2.38 (s, 3 H), 2.10 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 209.2$, 135.2, 131.2, 128.1, 120.8, 118.9, 117.6, 112.6, 110.3, 110.1, 44.1, 30.1, 18.3, 11.4; EIMS: m/z = 201 (M^+), 143, 135, 121, 110, 97, 70.

4-(3-Indolyl)-butan-2-one (**3h**)[3b]

Solid, mp 70–71°C; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.95$ (br s, 1 H, NH), 7.78 (d, 1 H, $J = 7.5$ Hz), 6.99–7.38 (m, 4 H), 3.09 (t, 2 H, $J = 7.4$ Hz), 2.85 (t, 2 H, $J = 7.3$ Hz), 2.14 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 211.1, 209.1, 136.2, 127.0, 121.8, 121.5, 119.1, 118.5, 114.8, 111.2, 43.9, 29.9, 19.2; EIMS: m/z = 187 (M^+), 149, 135, 110, 97, 82, 69.

2-(2-Methyl-3-indolyl)-1,4-naphthaquinone (**3i**)[3f]

Solid, mp 182–184°C; IR (KBr): 3328, 3018, 1667, 1593, 1454 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.51$ (br s, 1 H, NH), 8.12–8.21 (m, 2 H), 7.47–7.78 (m, 2H), 7.51–7.53 (m, 1 H), 7.09–7.25 (m, 4 H), 2.41 (s, 3 H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 185.3$, 184.8, 144.4, 137.2, 135.4, 134.5,

133.7, 133.5, 132.7 132.2, 127.6, 126.9, 125.9, 122.1, 120.8, 110.7, 107.1, 13.7; EIMS: m/z = 287 (M^+), 286, 270, 269.

2-(3-Indolyl)-1,4-naphthaquinone (**3j**)[3f]

Solid, mp 178–179°C; IR (KBr): 3328, 3018, 1667, 1593, 1454 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 8.75$ (br s, 1 H, NH), 8.10–8.30 (m, 4 H), 7.71–7.76 (m, 2 H), 7.25–7.41 (m, 4 H).

1,5-Bis(3-indolyl)-1,5-diphenyl-pentan-3-one (**3k**)[3a]

Solid, inseparable mixture of *dl* and *meso* isomers; IR (KBr): 3402, 3018, 1707, 1618, 1455, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.82$ (br s, 2 H, NH), 6.97–7.37 (m, 18 H), 6.67–6.73 (m, 2 H), 4.78 (t, 2 H, $J = 7.5$ Hz), 3.07–3.20 (m, 4 H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 208.6$, 208.5, 143.9, 143.8, 136.3, 128.3, 127.5, 126.2, 121.7, 119.2, 118.0, 111.2, 49.6, 49.6, 37.9.

1,5-Bis(2-methyl-3-indolyl)-1,5-diphenyl-pentan-3-one (**3l**)

Brown solid, inseparable mixture of *dl* and *meso* isomers; IR (KBr): 3422, 3027, 1709, 1618, 1418, 1217, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): $\delta = 7.66$ (br s, 2 H, NH), 6.97–7.34 (m, 18 H), 4.76 (t, 2 H, $J = 7.0$ Hz), 3.04–3.43 (m, 4 H), 2.21 (s, 2 H), 2.10 (s, 4 H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 211.2$, 209.2, 143.9, 143.8, 135.3, 131.8, 128.1, 127.3, 119.2, 119.0, 112.9, 112.6, 110.4, 48.2, 47.9, 36.6, 11.8, 11.6.

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