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Copper-Catalyzed Synthesis of 2,3-Disubstituted Indoles

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Keywords: Indoles / Copper catalyst / BINOL / Domino reactions / One-pot synthesis

The copper-catalyzed one-step synthesis of 2,3-disubstituted indoles from readily available starting materials, 2-iodoaniline and various β-keto esters was described. The advantage of this method is the use of cheap catalysts and simple experimental procedures under mild reaction conditions. As the substituted indole derivatives are important starting materials for the synthesis of biologically active indole alkaloids and drug candidates, this method would have potential usage for above purpose.

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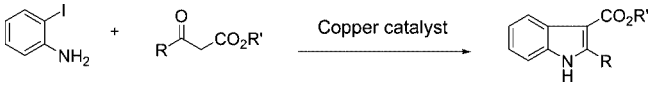
Indole derivatives are widely distributed in nature[1] and are known to be an important structural unit for the development of pharmaceuticals,[2] agrochemicals,[3] material sciences[4] and perfumes.[5] For over a hundred years, the synthesis of indoles has been an important area of focus for organic chemists, and a huge amount of methods for the synthesis of indoles have been demonstrated.[6] However, it was noted that in some cases, specific substitution patterns remain difficult to obtain by standard indole-forming reactions so the search for new methodologies for the synthesis of indole derivatives is still an important task in synthetic organic chemistry.[6] In this paper, we would like to describe the one-step synthesis of 2,3-disubstituted indoles by a copper-catalyzed[7] domino reaction of 2-iodoaniline and β-keto esters (Scheme 1).[8] 2,3-Disubstituted indole substructures are widely distributed in nature as indole alkaloids and drugs, for example, vinblastine, reserpine, okaramines and indomethacin, so that it seems necessary to develop a mild and flexible method for the synthesis of such compounds.[6]



Scheme 1. Copper-catalyzed one-step indole-forming reaction.

Table 1 shows the reaction conditions investigated in the reaction of 2-iodoaniline with methyl acetoacetate as a model case. The reactions of aromatic halides with soft carbon nucleophiles such as malonic acid esters[9] and β-keto esters[10] have been reported and the conditions were helpful for our present investigations. It was found that the choice of additives (Table 1, Entries 1, 2, 5, 6, 8 and 9), base (Table 1, Entries 9, 10 and 11), and solvent (Table 1, Entries 6 and 7) was crucial in this reaction. When the reaction was carried out at 50 °C with the use of 10 mol-% CuI and K_2CO_3 (1 equiv.), indole **3** was produced in 35% yield (Table 1, Entry 1). The yield decreased in the presence of proline as an additive[11a] (Table 1, Entry 2), although it increased when the catalyst loading was increased to 20 mol-% with a longer reaction time (Table 1, Entry 3). Good conversion was achieved with the use of strong base (NaH) and 50 mol-% CuI (Table 1, Entry 4) even at room temperature. When other additives such as ethylenediamine,[11h] *N*-methylglycin[11a] and 2-thenoic acid[11b] were used, moderate-to-good yields (26 to 66%) were observed (Table 1, Entries 5 to 8). As a result, the reaction proceeded smoothly at 50 °C with the use of 10 mol-% CuI and 20 mol-% of BINOL[11d] (racemate) with cesium carbonate (1 equiv.) as the base in DMSO to produce indole **3** in 79% isolated yield (Table 1, Entry 11).[12]

Next, we investigated the reaction using a variety of β-keto esters[13] under the optimized conditions. It was found that β-keto esters including branched and bulky substituents (Table 2, Entries 2 and 3), terminal alkenes (Table 2, Entry 4), long chains (Table 2, Entries 5 and 6), aromatic rings (Table 3, Entries 1 and 2) and heteroaromatic rings (Table 3, Entries 3–5) were feasible for the present reaction to give the corresponding indoles in moderate-to-excellent yields.[14]

In summary, we have developed a cheap and simple way to synthesize 2,3-disubstituted indoles under mild reaction conditions based on a copper-catalyzed Ullmann-type coupling reaction. The mechanistic investigation of this process is now underway.

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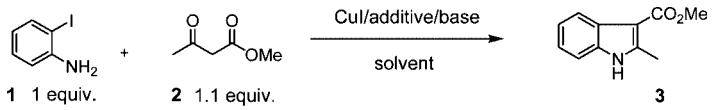
Table 1. Reaction of 2-iodoaniline with methyl acetoacetate.

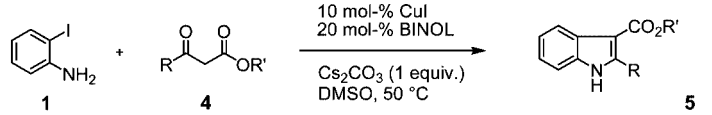


1 1 equiv. **2** 1.1 equiv. **3**

Entry	CuI [mol-%]	Additive [mol-%]	Base (equiv.)	Solvent	Temp [°C]	Time [h]	Yield[a] [%]
1	10	none	K_2CO_3 (1)	DMSO	50	4	35 (66)[b]
2	10	L-proline (20)	K_2CO_3 (1)	DMSO	50	4	26
3	20	L-proline (40)	K_2CO_3 (4)	DMSO	r.t.	48	46 (71)[b]
4	50	L-proline (100)	NaH (1)	DMSO	r.t.	15	77
5	10	H_2N NH_2 (20)	K_2CO_3 (1)	DMSO	50	4	36
6	20	MeHN COOH (40)	K_2CO_3 (1)	DMSO	50	4	66 (82)[b]
7	10	MeHN COOH (20)	K_2CO_3 (1)	DMF	50	4	26 (32)[b]
8	10	S COOH (20)	K_2CO_3 (1)	DMSO	50	4	38 (75)[b]
9	10	BINOL (20)	K_2CO_3 (1)	DMSO	50	4	61 (99)[b]
10	10	BINOL (20)	K_3PO_4 (1)	DMSO	50	4	48 (98)[b]
11	10	BINOL (20)	Cs_2CO_3 (1)	DMSO	50	4	79 (99)[b]

[a] Isolated yield. [b] Isolated yield based on 2-iodoaniline (**1**) consumed.

Table 2. Synthesis of 2-alkyl-3-methoxycarbonylindole derivatives.



1 **4** **5**

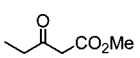
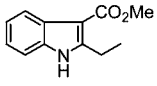
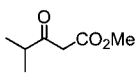
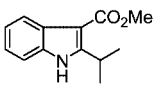
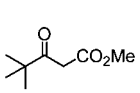
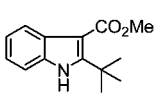
Entry	β-Keto ester	Product	Isolated yield [%]
1		 **5a**	60 (98)[a]
2		 **5b**	62 (98)[a]
3		 **5c**	68[b]

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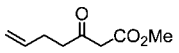
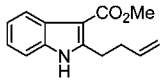
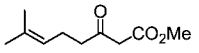
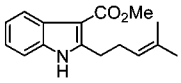
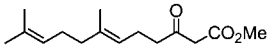
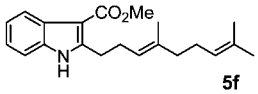
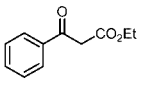
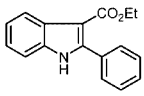
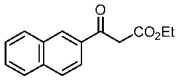
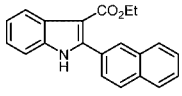
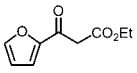
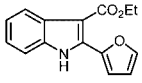
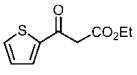
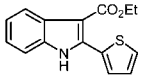
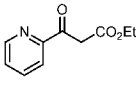
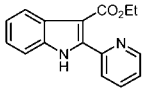
Table 2. *(continued)*

Entry	β-Keto ester	Product	Isolated yield [%]
4		 **5d**	56 (69)[a]
5		 **5e**	72[b]
6		 **5f**	69

[a] Isolated yield based on 2-iodoaniline (**1**) consumed. [b] 2 equiv. of β-keto ester **4** was used.

Table 3. Synthesis of 2-aryl/heteroaryl-3-methoxycarbonylindole derivatives.

Entry	β-Keto ester	Product	Isolated yield [%]
1		 **5g**	55
2		 **5h**	80 (99)[a]
3		 **5i**	95 (97)[a]
4		 **5j**	46[b]
5		 **5k**	59 (91)[c]

[a] Isolated yield based on 2-iodoaniline (**1**) consumed. [b] Yield not optimized. [c] 2 equiv. of β-keto ester **4** was used.

[1] W. Gul, M. T. Hamann, *Life Sci.* **2005**, *78*, 442–453.
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[12] Experimental procedure for the synthesis of **3**: A mixture of 2-iodoaniline (0.1 g, 0.46 mmol), ethyl acetoacetate (66 mg, 0.51 mmol), CuI (8.4 mg, 0.046 mmol), BINOL (17.5 mmol,

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0.092 mmol) and Cs_2CO_3 (0.15 g, 0.46 mmol) in DMSO (1 mL) was stirred at room temp. for 4 h under an atmosphere of nitrogen. The mixture was partitioned between ethyl acetate and saturated NH_4Cl, the organic layer was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was purified by preparative TLC (hexane/EtOAc, 3:1) to provide indole **3** (74 mg, 79%) as a solid. R_f = 0.30 (hexane/EtOAc, 3:1). M.p. 153.9 °C (decomp.). IR (NaCl): $\tilde{\nu}$ = 3016, 1687, 1453, 1208, 1091 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.72 (s, 3 H), 3.93 (s, 3 H), 7.16–7.30 (m, 3 H), 8.08 (d, J = 7.6 Hz, 1 H), 8.67 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 50.8, 104.3, 110.5, 121.2, 121.7, 122.3, 127.1, 134.5, 144.2, 166.6 ppm. HRMS (FAB): calcd. for $C_{11}H_{11}NO_2$ $[M]^+$ 189.0790; found 189.0726.

[13] The β-keto esters used in the reaction were purchased from commercial sources (R = Et, *i*Pr, *t*Bu, Ph), or prepared from methyl acetoacetate by the alkylation of the dianion (R = allyl, prenyl, and geranyl, see: M. P. Moyer, P. L. Feldman, H. Rapoport, *J. Org. Chem.* **1985**, *50*, 5223–5230) and from the corresponding methyl ketone by carboethoxylation (R = 2-naphthyl, 2-furyl, 2-thienyl, and 2-pyridyl, see M. J. Alves, A. G. Fortes, A. Lemos, C. Martins, *Synthesis* **2005**, 555–558).

[14] Selected data for new indole derivatives. **5c**: ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9 H), 3.72 (s, 3 H), 7.09 (dt, J = 1.2, 7.6 Hz, 1 H), 7.20 (dd, J = 1.2, 7.6 Hz, 1 H), 7.30 (dt, J = 1.5, 8.0 Hz, 1 H), 7.83 (d, J = 7.6 Hz, 1 H), 8.84 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5 ($3 \times CH_3$), 38.5, 52.5, 115.0, 125.0, 125.1, 125.7, 128.2, 129.1, 130.6, 136.8, 173.0 ppm. **5e**: IR: $\tilde{\nu}$ = 3305, 2925, 1669, 1457, 1201, 1084, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.55 (s, 3 H), 1.61 (s, 3 H), 2.42 (q, J = 7.3 Hz, 2 H), 3.18 (t, J = 7.3 Hz, 2 H), 3.93 (s, 3 H), 5.16–5.22 (m, 1 H), 7.16–7.25 (m, 2 H), 7.28–7.32 (m, 1 H), 8.10–8.14 (m, 1 H), 8.69 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6, 25.7, 27.5, 28.0, 50.7, 103.8, 110.6, 121.3, 121.6, 122.3, 122.9, 127.1, 133.5, 134.5, 148.2, 166.4 ppm. FAB-MS: *m*/*z* (%) = 258 (72) $[M + H]^+$, 227 (30) $[M – OMe]^+$, 188 (100) $[M – C_5H_9]^+$. HRMS (FAB): calcd. for $C_{16}H_{20}NO_2$ $[M + H]^+$ 258.1494; found 258.1438.

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