A Convenient One-Pot Synthesis of 2,3-Disubstituted Indoles

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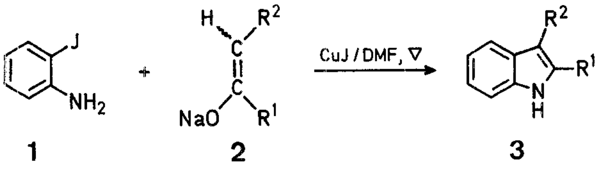
Recently, considerable attention has been directed toward the development of new synthetic methods for the construction of indole nucleus, particularly under non-acidic conditions. Among these, we can cite those involving the use of photostimulated $S_{RN}1$ conditions[1], transition metal catalysts[2], intramolecular aryne reactions[3], intramolecular cyclization of 2-lithiomethylphenyl isocyanide[4], intramolecular Wittig reactions[5] and *ortho*-alkylation of aromatic amines with keto sulfides[6]. However, these methods often suffer from disadvantages such as expensive or less easily available starting materials, or laborious manipulation.

This communication describes the development of a convenient one-pot procedure for the synthesis of 2,3-disubstituted indoles **3** based on copper(I) iodide promoted arylation of stable enolates **2** with 2-iodoaniline (**1**). Several α-aryl carbonyl compounds have been prepared via copper(I) salts-promoted aromatic nucleophilic substitution reactions, but these reactions have not been successfully applied to the synthesis of indoles so far[7,8].



1 **2** **3**

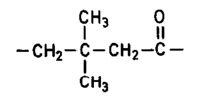
We have now found that stable enolates **2** derived from β-dicarbonyl and related compounds react with 2-iodoaniline (**1**) in the presence of copper(I) iodide in dimethylformamide, giving 2,3-disubstituted indoles **3** in moderate yields. A variety of stable enolates can be employed in this reaction. Generally 1.5 equivalents of enolates are sufficient for the smooth completion of the reaction. In the reaction of sodioacetylacetone with **1**, use of 3 equivalents of the enolate results in a good yield of the product. It has been reported earlier that the reaction of iodobenzene with ethyl sodioacetoacetate in the presence of copper(I) iodide in hexamethylphosphoric triamide brings about carbon-carbon bond formation with cleavage of the keto moiety, leading to the isolation of ethyl phenylacetate as the exclusive product[7]. However, in the present case the *ortho*-amino function reacts with the keto group, preventing any cleavage, and thus furnishing a facile construction of the indole nucleus. The product indoles **3** are useful synthetic intermediates, since the ester or keto group at 3-position of **3** can be easily converted into a variety of functional groups.

Because of the simple one-pot procedure, mild conditions, and easy availability of the starting materials, the method provides a convenient access to the 2,3-disubstituted indoles.

The structures of all new compounds were established by analytical data and ¹H-N.M.R. and I.R. spectra. All melting points were uncorrected. 2-Iodoaniline (**1**)[9] and ethyl propioacetate[10] were prepared by the reported methods.

3-Ethoxycarbonyl-2-methylindole (3a); Typical Procedure:
Sodium hydride (60% in oil, 0.080 g, 2 mmol) is washed with dry hexane under nitrogen in the normal way to remove the oil. The gray solid is then covered with dimethylformamide (1 ml) and ethyl acetoacetate (0.195 g, 1.5 mmol) is added dropwise with stirring.

Table. 2,3-Disubstituted Indoles **3** prepared

Product No.	R^1	R^2	Yield[a] [%]	m.p. [°C]	Molecular formula[b] or Lit. m.p. [°C]	I.R. (KBr) ν [cm^{-1}]	^{1}H-N.M.R. (CDCl$_3$/TMS) δ [ppm]
3a	CH_3	$COOC_2H_5$	60	133°	134–135°[11]	3300, 1640, 1445, 1380, 1360, 1300, 1200, 1180, 1100, 1080, 780, 740, 730	1.41 (t, 3H, J = 7 Hz); 2.65 (s, 3H); 4.42 (q, 2H, J = 7 Hz); 7.1–7.3 (m, 3H); 7.9–8.2 (m, 1H); 8.6–8.8 (br. s, 1H, NH)
3b	C_2H_5	$COOC_2H_5$	65	103°	$C_{13}H_{15}O_2N$ (217.3)	3225, 1640, 1460, 1380, 1340, 1320, 1240, 1200, 1110, 1090, 1060, 780, 720	1.32 (t, 3H, J = 7 Hz); 1.45 (t, 3H, J = 7 Hz); 3.2 (q, 2H, J = 7 Hz); 4.45 (q, 2H, J = 7 Hz); 7.0–7.3 (m, 3H); 8.0–8.2 (m, 1H); 8.5–8.7 (br. s, 1H, NH)
3c	$CH_2-COOC_2H_5$	$COOC_2H_5$	68	116–118°	$C_{15}H_{17}O_4N$ (275.3)	3300, 1660, 1480, 1390, 1310, 1280, 1220, 1110, 800, 775, 700	1.17 (t, 3H, J = 7 Hz); 1.4 (t, 3H, J = 7 Hz); 2.65 (s, 2H); 4.2 (q, 2H, J = 7 Hz); 4.31 (q, 2H, J = 7 Hz); 7.0–7.2 (m, 3H); 7.9–8.1 (m, 1H); 8.5–8.8 (br. s, 1H, NH)
3d	CH_3	$CO-CH_3$	80	195°	196°[12]	3200, 1600, 1570, 1480, 1400, 1360, 1180, 1100, 1060, 1000, 900, 740	2.62 (s, 3H); 2.73 (s, 3H); 7.1–7.3 (m, 3H); 8.0–8.1 (m, 1H); 8.6–8.7 (br. s, 1H, NH)
3e	CH_3	$CO-C_6H_5$	75	182–183°	181°[12]	3400, 1580, 1540, 1500, 1440, 1350, 1300, 1280, 1020, 1000, 760, 700	2.15 (s, 3H); 7.1–7.5 (m, 4H); 7.6–7.9 (m, 4H); 8.1–8.3 (m, 1H); 8.6–8.8 (br. s, 1H, NH)
3f	 $-CH_2-C(CH_3)_2-CH_2-C(=O)-$		78	210°	209–211°[13]	3200, 1620, 1600, 1580, 1480, 1400, 1240, 1140, 1060, 920	1.13 (s, 6H); 2.45 (s, 2H); 2.8 (s, 2H); 7.1–7.3 (m, 4H); 8.2 (s, 1H, NH)

[a] Isolated yield based on 2-iodoaniline (**1**) consumed.
[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.27, N ±0.25.

After several min, when the evolution of hydrogen has ceased, copper(I) iodide (0.286 g, 1.5 mmol) is added to the resultant yellow solution. The color of the solution changes to orange and later to brown when 2-iodoaniline (**1**; 0.219 g, 1 mmol) is added, and the mixture is heated to 120–130 °C. The color further darkens as the temperature increases. The progress of the reaction is monitored by T.L.C. After 6–7 h, when the reaction is over, the mixture is allowed to come to room temperature, poured into water (10 ml), acidified to pH 5–6, and extracted with ether (2 × 15 ml). The ether extract is repeatedly washed with water (2 × 10 ml), dried with sodium sulfate and evaporated to give crystals of 3-ethoxycarbonyl-2-methylindole (**3a**) which is further purified by column chromotography on silica gel followed by recrystallization from benzene/hexane to give yellowish white crystals of the product; yield: 0.120 g (60%); m.p. 133–134 °C; (Lit.[11], m.p. 134–135 °C).

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