

Synthesis of 2-(1*H*-indol-3-yl)pyridine derivatives through multi-component reaction

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A straightforward and practical approach is established for the synthesis of 2-(1*H*-indol-3-yl)pyridine derivatives achieved through the one-pot three-component reaction of chalcone, 3-(2-cyanoacetyl)-1*H*-indole and ammonium acetate. This method offers several advantages such as short reaction time, high yields, and simple procedure.

Keywords: 2-(1*H*-indol-3-yl)pyridine derivatives, 3-(2-cyanoacetyl)-1*H*-indole, chalcone, multi-component reaction, microwave irradiation

The publication of the Strecker reaction in 1850 is considered as the beginning of the multicomponent reaction (MCR) story.¹ MCR is important in organic and medicinal chemistry^{2–4} due to its diversity, efficiency and rapid access to complex and highly functionalised organic molecules.⁵ Hence, combined with the use of combinatorial chemistry and high throughput parallel synthesis, such reactions have constituted an increasingly valuable approach to drug research.⁶ In the past decade, there have been tremendous developments in three- and four-component reactions and great efforts are being made to find and develop new MCRs.^{7,8}

A large number of substituted pyridines have attracted attention from organic and medicinal chemists due to their useful biological and pharmacological activities,⁹ such as antifungal, antimalarial, antiviral and antiproliferative properties.^{10–12} On the other hand, 3-substituted indole nucleus is prevalent in many natural products and is extremely important in medicinal chemistry.^{13,14} Due to the medicinal potential of pyridine and 3-substituted indole derivatives, various methods have been reported for the synthesis of these compounds through the reaction of aromatic aldehydes and 3-(2-cyanoacetyl)-1*H*-indole.^{15–18} These reactions are based on unsubstituted 3-(2-cyanoacetyl)-1*H*-indole as a reactant. Here we report a facile method for the synthesis of a series of 2-(1*H*-indol-3-yl)pyridine derivatives in the presence of 3-(2-cyanoacetyl)-1*H*-indole, chalcone and ammonium acetate.

The starting compound chalcone **1** was prepared according to the procedure described by Mauricio *et al.*¹⁹ The synthesis of 3-(2-cyanoacetyl)-1*H*-indole (**2a–c**, **2e**, **2f**) have been carried out using a similar method to the literature,²⁰ the preparation of 7-methyl-3-(2-cyanoacetyl)-1*H*-indole (**2d**) and 5-bromo-3-(2-cyanoacetyl)-1*H*-indole (**2f**) used the same

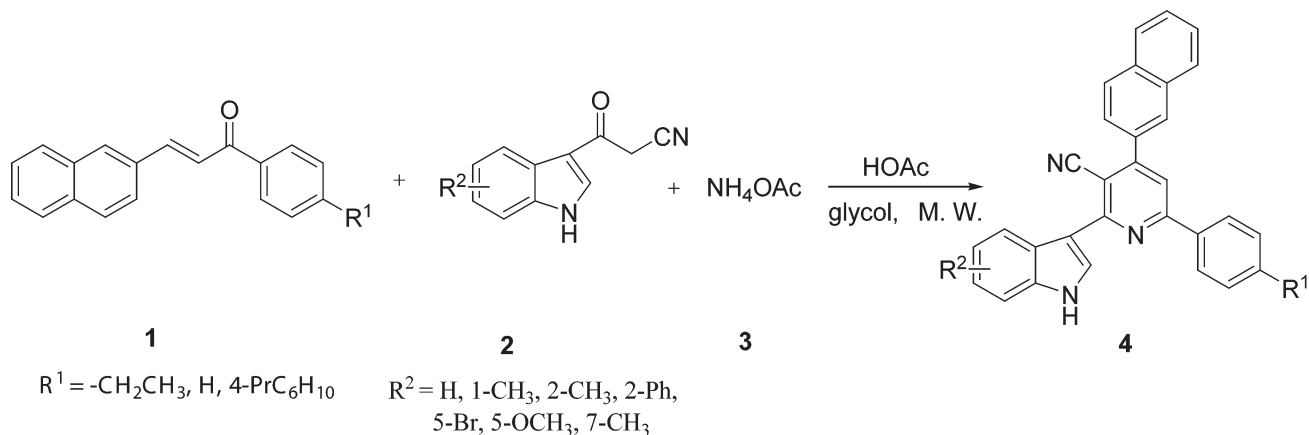
method of preparation as **2a**. However, when 2-nitroindole or 5-nitroindole was used, we failed to get the expected product owing to the lower reactivity of the nitroindoles.

After some preliminary experimentation, it was found that a mixture of chalcone, 3-(2-cyanoacetyl)-1*H*-indole, and ammonium acetate **3** afforded 3-cyano-2-(1*H*-indol-3-yl)-4-(2-naphthyl)-6-(4-ethylphenyl)pyridine **4a** under microwave irradiation. In order to improve the isolated yield of **4a**, various reaction conditions including solvents and reaction time were tested in the one-pot three-component synthesis of target compound under MW irradiation. Founding HOAc/glycol(1/2) and 120°C was the optimal experimental conditions.

To extend the scope of this procedure for the synthesis of 2-(1*H*-indol-3-yl)pyridine derivatives, a series of reactions were carried out under the optimal conditions. We were pleased to find that the reaction proceeded smoothly and desired products were afforded in excellent yields (Table 1).

As shown in Table 1, the reaction proceeded smoothly with a wide range of functionalised 3-(2-cyanoacetyl)-1*H*-indole, including those containing methyl, bromo, methoxyl and phenyl. The electronic effects of the substitution on the 3-(2-cyanoacetyl)-1*H*-indole have no significant influence on the reaction yield.

In addition, we extended our investigation to the synthesis of **4b** in HOAc/glycol under classical heating conditions. After refluxing for 8 h, the desired product **4b** was obtained in 62% yield, however, the yield of **4b** was up to 82% (Table 1, entry 2) under microwave irradiation condition. Therefore, microwave irradiation had several advantages over the conventional heating by significantly reducing the reaction times and improving the reaction yield, owing to a specific non-thermal microwave effect.



Scheme 1

Table 1 Synthesis of compounds **4a–i** under microwave irradiation at 120 °C

Entry	R ¹	R ²	Product	Time/min	Yield ^a /%	M.p. /°C
1	4-CH ₂ CH ₃	H	4a	8	86	239
2	4-CH ₂ CH ₃	1-CH ₃	4b	8	82	190–191
3	4-CH ₂ CH ₃	2-CH ₃	4c	12	79	201–202
4	4-CH ₂ CH ₃	7-CH ₃	4d	8	85	273–274
5	4-CH ₂ CH ₃	2-C ₆ H ₅	4e	12	74	228–229
6	4-CH ₂ CH ₃	5-Br	4f	8	80	263
7	4-CH ₂ CH ₃	5-OCH ₃	4g	8	83	218–219
8	H	H	4h	8	82	264–265
9	4-(4-PrC ₆ H ₁₀)	H	4i	8	84	237–238

^aIsolated yield.

The structures of compounds **4a–i** were elucidated by IR, ¹H NMR and elementary analysis. The IR spectrum of **4d**, for instance, exhibited the absorption band at 3303 cm⁻¹ due to the presence of NH functional and the band at 2215 cm⁻¹ showed the presence of C≡N. In the ¹H NMR spectrum (DMSO) of **4d**, a sharp singlet at δ 11.83 corresponds to NH proton, methyl protons (N-CH₃) were resonated in the range of δ 2.56.

Based on the above results, a plausible mechanism was proposed (Scheme 2). 3-(2-cyanoacetyl)-1H-indole reacted with ammonia from ammonium acetate to give intermediate **5**, which further reacted with chalcone to yield **6**. Michael addition product **6** was then cyclised to afford the Hantzsch dihydropyridine derivative **7** with elimination of water, finally deprotonation of **7** led to formation of highly substituted pyridine derivative **4**.

In summary, we have demonstrated an efficient synthesis of 3-cyano-2-(1H-indol-3-yl)-4-(2-naphthyl)pyridine derivatives involving three-component condensation of chalcone, 3-(2-cyanoacetyl)-1H-indole and ammonium acetate under microwave irradiation in a simple one-pot procedure. High efficiency and short reaction time were the advantages of this protocol.

Experimental

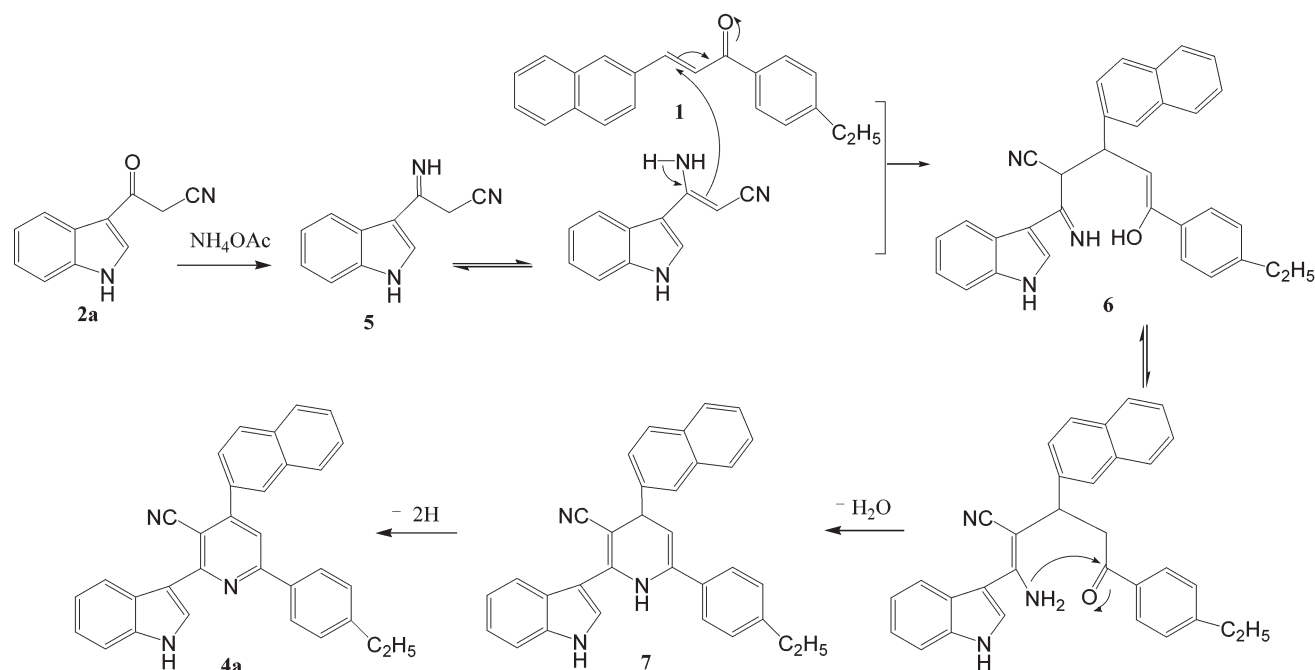
Melting points were determined on an electrothermal digital melting point apparatus and uncorrected. ¹H NMR spectra were obtained on a Varian VXP-500s spectrometer using DMSO-*d*₆ as solvent and tetramethylsilane (TMS) as internal reference. IR Spectra was determined on a Nicolet 6700 spectrophotometer using KBr pellets. Elementary

analyses were performed by a Heraeus CHN-O-RAPID analyser. Microwave reactions were carried out in a Xianghu XH-100B microwave oven (450W). TLC analysis was performed on 0.25mm silica gel GF254 plates. All chemicals were purchased and used without further purification.

A mixture of chalcone **1** (2 mmol), 3-(2-cyanoacetyl)-1H-indole **2** (2 mmol) and ammonium acetate **3** (0.62 g, 8 mmol) in HOAc 2 mL and glycol 4 mL were irradiated for the given time at 120 °C. After the completion of the reaction (the reaction was followed by TLC), the mixture was allowed to cool to room temperature and extracted with dichloromethane, washed with H₂O (3×10 mL) and the organic layer dried over MgSO₄ and concentrated under vacuum. The crude product was chromatographed on silica gel (200–300 mesh) using a mixture of petroleum ether and dichloromethane as eluent to afford the pure product **4**.

3-Cyano-2-(1H-indol-3-yl)-4-(2-naphthyl)-6-(4-ethylphenyl)pyridine (4a): Pale yellow powder. IR (KBr) ν 3440, 3049, 2961, 2930, 2216, 1599, 1536, 1457, 1437, 1422 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ 11.85 (s, 1H), 8.45 (d, *J* = 8.0 Hz, 1H), 8.42 (d, *J* = 2.5 Hz, 1H), 8.39 (d, *J* = 1.0 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 2H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.09–8.04 (m, 3H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.67–7.64 (m, 2H), 7.57 (d, *J* = 7.0 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.26–7.24 (m, 2H), 2.72–2.71 (m, 2H), 1.25 (t, *J* = 7.5 Hz, 3H). Anal. Calcd for C₃₂H₂₃N₃: C, 85.50; H, 5.16; N, 9.35. Found: C, 85.60; H, 5.25; N, 9.23%.

3-Cyano-2-(N-methylindol-3-yl)-4-(2-naphthyl)-6-(4-ethylphenyl)pyridine (4b): Pale yellow powder. IR (KBr) ν 3054, 2961, 2360, 2213, 1566, 1520, 1460, 1359 cm⁻¹. ¹H NMR (500 MHz, DMSO-*d*₆): δ 8.44 (d, *J* = 7.5 Hz, 1H), 8.39 (d, *J* = 4.5 Hz, 2H), 8.29 (d, *J* = 8.0 Hz, 2H), 8.15 (d, *J* = 8.5 Hz, 1H), 8.09–8.05 (m, 3H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.67–7.65 (m, 2H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.35–7.28 (m, 2H), 4.00 (s, 3H), 2.74–2.69 (m, 2H), 1.25

**Scheme 2**

(t, $J = 7.5$ Hz, 3H). Anal. Calcd for $C_{33}H_{25}N_3$: C, 85.50; H, 5.44; N, 9.06. Found: C, 85.40; H, 5.52; N, 9.12%.

3-Cyano-2-(2-methyl-1H-indol-3-yl)-4-(2-naphthyl)-6-(4-ethylphenyl)pyridine (4c): Pale yellow powder. IR (KBr) ν 3393, 3054, 2963, 2361, 2217, 1568, 1522, 1459 cm^{-1} . 1H NMR (500 MHz, DMSO- d_6): δ 11.63 (s, 1H), 8.43 (s, 1H), 8.26 (d, $J = 8.0$ Hz, 2H), 8.18 (s, 1H), 8.16 (d, $J = 8.5$ Hz, 1H), 8.12–8.06 (m, 2H), 7.98–7.96 (m, 1H), 7.72 (d, $J = 8.0$ Hz, 1H), 7.66–7.65 (m, 2H), 7.42 (t, $J = 8.0$ Hz, 3H), 7.17–7.10 (m, 2H), 2.71–2.69 (m, 2H), 2.64 (s, 3H), 1.24 (t, $J = 7.5$ Hz, 3H). Anal. Calcd for $C_{33}H_{25}N_3$: C, 85.50; H, 5.44; N, 9.06. Found: C, 85.59; H, 5.38; N, 9.10%.

3-Cyano-2-(2-methyl-1H-indol-3-yl)-4-(2-naphthyl)-6-(4-ethylphenyl)pyridine (4d): Pale yellow powder. IR (KBr) ν 3303, 3056, 2965, 2362, 2215, 1565, 1548, 1503, 1440 cm^{-1} . 1H NMR (500 MHz, DMSO- d_6): δ 11.83 (s, 1H), 8.39 (d, $J = 3.0$ Hz, 2H), 8.30 (d, $J = 8.5$ Hz, 2H), 8.26 (d, $J = 8.0$ Hz, 1H), 8.15 (d, $J = 8.5$ Hz, 1H), 8.10–8.06 (m, 2H), 8.05 (s, 1H), 7.94 (dd, $J = 8.5$ Hz and $J = 1.5$ Hz, 1H), 7.68–7.64 (m, 2H), 7.45 (d, $J = 8.0$ Hz, 2H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.06 (d, $J = 7.0$ Hz, 1H), 2.72–2.71 (m, 2H), 2.56 (m, 3H), 1.25 (t, $J = 7.5$ Hz, 3H). Anal. Calcd for $C_{33}H_{25}N_3$: C, 85.50; H, 5.44; N, 9.06. Found: C, 85.38; H, 5.46; N, 9.15%.

3-Cyano-2-(2-phenyl-1H-indol-3-yl)-4-(2-naphthyl)-6-(4-ethylphenyl)pyridine (4e): Pale yellow powder. IR (KBr) ν 3348, 3057, 2964, 2362, 2336, 2214, 1562, 1535, 1501, 1455 cm^{-1} . 1H NMR (500 MHz, DMSO- d_6): δ 12.01 (s, 1H), 8.24 (s, 1H), 8.21 (s, 1H), 8.14 (d, $J = 8.5$ Hz, 2H), 8.09 (d, $J = 8.0$ Hz, 1H), 8.02 (t, $J = 7.5$ Hz, 2H), 7.74 (d, $J = 8.5$ Hz, 2H), 7.65–7.62 (m, 2H), 7.55–7.42 (m, 6H), 7.36 (d, $J = 8.5$ Hz, 2H), 7.26 (t, $J = 7.5$ Hz, 1H), 7.17 (t, $J = 7.0$ Hz, 1H), 2.71–2.68 (m, 2H), 1.22 (t, $J = 7.5$ Hz, 3H). Anal. Calcd for $C_{38}H_{27}N_3$: C, 86.83; H, 5.18; N, 7.99. Found: C, 86.91; H, 5.12; N, 7.92%.

3-Cyano-2-(5-bromo-1H-indol-3-yl)-4-(2-naphthyl)-6-(4-ethylphenyl)pyridine (4f): Pale yellow powder. IR (KBr) ν 3335, 2970, 2919, 2360, 2215, 1576, 1566, 1532, 1508, 1441 cm^{-1} . 1H NMR (500 MHz, DMSO- d_6): δ 12.04 (s, 1H), 8.68 (d, $J = 2.0$ Hz, 1H), 8.50 (d, $J = 3.0$ Hz, 1H), 8.39 (d, $J = 2.5$ Hz, 1H), 8.29 (d, $J = 8.0$ Hz, 2H), 8.15 (d, $J = 9.0$ Hz, 1H), 8.10–8.06 (m, 3H), 7.93 (dd, $J = 8.5$ Hz and $J = 2.0$ Hz, 1H), 7.67–7.65 (m, 2H), 7.55 (d, $J = 9.0$ Hz, 1H), 7.45 (d, $J = 8.5$ Hz, 2H), 7.40 (dd, $J = 8.5$ Hz and $J = 2.0$ Hz, 1H), 2.74–2.71 (m, 2H), 1.25 (t, $J = 7.5$ Hz, 3H). Anal. Calcd for $C_{32}H_{22}N_3Br$: C, 72.73; H, 4.20; N, 7.95. Found: C, 72.80; H, 4.18; N, 7.83%.

3-Cyano-2-(5-methoxy-1H-indol-3-yl)-4-(2-naphthyl)-6-(4-ethylphenyl)pyridine (4g): Pale yellow powder. IR (KBr) ν 3295, 2964, 2361, 2216, 1565, 1506, 1535, 1437 cm^{-1} . 1H NMR (500 MHz, DMSO- d_6): δ 11.74 (s, 1H), 8.43 (d, $J = 3.0$ Hz, 1H), 8.37 (s, 1H), 8.36 (s, 1H), 8.35 (s, 1H), 8.16 (s, 1H), 8.14–8.13 (t, $J = 2.5$ Hz, 1H), 8.10–8.06 (m, 2H), 8.03 (s, 1H), 7.92 (dd, $J = 6.5$ Hz and $J = 2.0$ Hz, 1H), 7.67–7.65 (m, 2H), 7.47–7.43 (m, 3H), 6.91 (dd, $J = 8.5$ Hz and $J = 2.5$ Hz, 1H), 3.85 (s, 3H), 2.72–2.71 (m, 2H), 1.25 (t, $J = 7.5$ Hz, 3H). Anal. Calcd for $C_{33}H_{25}N_3O$: C, 82.65; H, 5.25; N, 8.76. Found: C, 82.55; H, 5.28; N, 8.82%.

3-Cyano-2-(1H-indol-3-yl)-4-(2-naphthyl)-6-phenylpyridine (4h): Pale yellow powder. IR (KBr) ν 3438, 3058, 2920, 2217, 1599, 1534, 1456, 1436, 1425 cm^{-1} . 1H NMR (500 MHz, DMSO- d_6): δ 11.86 (s, 1H), 8.47–8.43 (m, 2H), 8.41–8.38 (m, 3H), 8.16 (d, $J = 8.5$ Hz, 1H), 8.10–8.05 (m, 3H), 7.95 (dd, $J = 8.5$ Hz and $J = 1.5$ Hz, 1H), 7.67–7.56 (m, 6H), 7.30–7.24 (m, 2H). Anal. Calcd for $C_{30}H_{19}N_3$: C, 85.49; H, 4.54; N, 9.97. Found: C, 85.58; H, 4.60; N, 10.09%.

3-Cyano-2-(1H-indol-3-yl)-4-(2-naphthyl)-6-[4-(4-propylcyclohexanyl)phenyl]pyridine (4i): Pale yellow powder. IR (KBr) ν 3329, 3057, 2948, 2917, 2215, 1560, 1532, 1457, 1439 cm^{-1} . 1H NMR (500 MHz, DMSO- d_6): δ 11.84 (s, 1H), 8.44 (d, $J = 7.0$ Hz, 1H), 8.41 (d, $J = 3.0$ Hz, 1H), 8.39 (s, 1H), 8.28 (d, $J = 8.0$ Hz, 2H), 8.15 (d, $J = 8.5$ Hz, 1H), 8.10–8.05 (m, 2H), 8.03 (s, 1H), 7.93 (dd, $J = 8.5$ Hz and $J = 2.0$ Hz, 1H), 7.67–7.63 (m, 2H), 7.56 (d, $J = 7.5$ Hz, 1H), 7.45 (d, $J = 8.5$ Hz, 2H), 7.27–7.22 (m, 2H), 2.60–2.53 (m, 1H), 1.85 (t, $J = 10.0$ Hz, 4H), 1.51–1.49 (m, 2H), 1.34–1.30 (m, 3H), 1.22–1.19 (m, 2H), 1.07–1.05 (m, 2H), 0.88 (t, $J = 7.0$ Hz, 3H). Anal. Calcd for $C_{39}H_{35}N_3$: C, 85.84; H, 6.46; N, 7.70. Found: C, 85.76; H, 6.37; N, 7.82%.

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