Microwave-assisted synthesis of 3-cyano-2-(1*H*-indol-3-yl)pyridine derivatives by a multicomponent reaction

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Preparation of a series of 3-cyano-2-(1*H*-indol-3-yl)pyridine derivatives through the one-pot multicomponent coupling of aromatic aldehydes, aromatic ketones, 3-(cyanoacetyl)indole and ammonium acetate is studied in the present article. All these compounds were obtained in good yield and their structures were confirmed by ^{1}H NMR, IR and elementary analysis.

Keywords: aromatic aldehydes, aromatic ketones, 3-(cyanoacetyl)indole, 3-cyano-2-(1*H*-indol-3-yl)pyridine derivatives, multi-component reactions

The pyridine substructure is one of the most important heterocycles found in natural products, pharmaceuticals, and functional materials.[1,2] During the last two decades, a large number of substituted pyridines have been shown to have biological activity.[3–5] Pyridine derivatives containing multi-functional groups such as streptonigrin, streptonigrone and lavendamycin are reported as anticancer drugs, and cerivastatin as the enzyme inhibitors.[6] Therefore, it is not surprising that research on the synthesis of polyfunctionalized heterocyclic compounds containing pyridine ring fragments has received significant attention.[7,8]

Multi-component reactions (MCRs), with three or more reactants that combine in a one-pot procedure to give a single product, provide a powerful tool, enabling straightforward access to a large number of structurally related, drug-like compounds.[9–15] Hence, the recent interest in these reactions in organic and medicinal chemistry.[16–19]

Due to our interest in the multicomponent syntheses and in multi-functional pyridine derivatives, we report a simple and suitable protocol for the preparation of a series of 3-cyano-2-(1*H*-indol-3-yl)pyridine derivatives. The target compounds were synthesised by four-component reaction of aldehydes, aromatic ketones, 3-(cyanoacetyl) indoles and ammonium acetate under microwave irradiation condition. The starting compounds, 3-(cyanoacetyl)indoles was prepared according to the procedure described by Slatt *et al.*[20]

In our initial study, various reaction conditions including solvents and microwave power were tested in the one-pot four-component synthesis of target compounds under MW irradiation. We found HOAc/glycol(1/2) and 350W was the optimal experimental conditions. Under these conditions, a series of new 3-cyano-2-(1*H*-indol-3-yl)pyridine derivatives were synthesised in good yields (Scheme 1). The optimised results are summarised in Table 1.

Table 1 Synthesis of compounds **5a–k** under microwave irradiation

Entry	R^1	R^2	Product	Time /min	Yield[a] /%
1	H	H	**5a**	8	85
2	2-OCH_3	H	**5b**	8	84
3	4-CH_3	H	**5c**	8	89
4	3-CH_3	H	**5d**	8	88
5	2,4-Cl_2	H	**5e**	12	72
6	3,4-(CH=CH-CH=CH)	H	**5f**	8	82
7	H	4-Br	**5g**	8	81
8	H	4-CH_3CH_2	**5h**	8	85
9	H	4-(4-PrC_6H_{10})	**5i**	8	86
10	3,4-(CH=CH-CH=CH)	4-CH_3CH_2	**5j**	8	83
11	3,4-(CH=CH-CH=CH)	4-(4-PrC_6H_{10})	**5k**	8	82

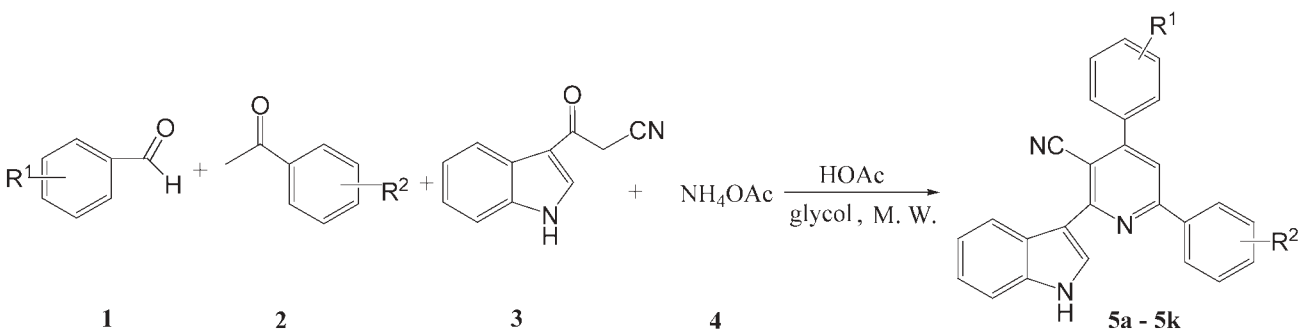
[a]Isolated yield.

As can be seen from Table 1, the results indicated that this method works with a wide variety of substrates. A series of different position substituted aromatic aldehydes including either electron-withdrawing or electron-donating groups and different substituted acetophenones proceeded smoothly.

The structures of the compounds **5a–k** were fully supported by IR, ^{1}H NMR spectroscopy and elemental analysis.

Based on the above results, a plausible mechanism was proposed (Scheme 2). Aldehyde **1** reacted with aromatic ketones **2** to give chalcone **6** and 3-(cyanoacetyl)indole **3** with ammonium acetate **4** to afford intermediate **7**, chalcone **6** and intermediate **7** further reacted to yield **8**. Michael addition product **8** was then cyclised to afford the Hantzsch dihydropyridine derivative **9** with an elimination of water, finally deprotonation of **9** leaded to formation of highly substituted pyridine derivative **5**.

In summary, our results pointed to a sequential application of multicomponent reaction of aldehydes **1**, aromatic ketones



Scheme 1

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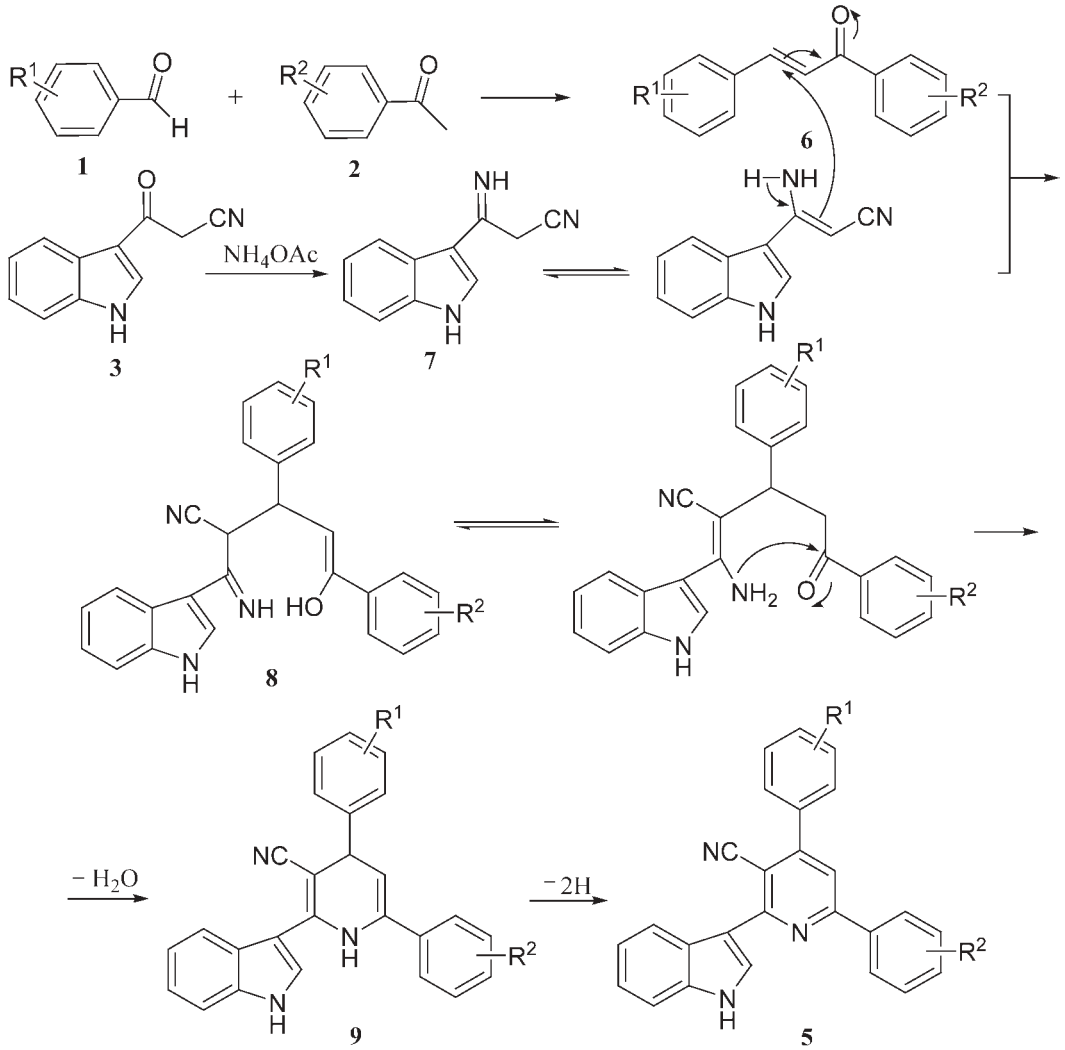

Scheme 2

2, 3-(cyanoacetyl)indole **3**, and ammonium acetate **4** for the synthesis of multi-functional 3-cyano-2-(1*H*-indol-3-yl) pyridine derivatives under microwave irradiation. The experimental simplicity, compatibility with various functional groups, short reaction times, the easy workup procedure, and efficient yields, maked this procedure attractive to synthesise a variety of these derivatives.

Experimental

Melting points were recorded on an electrothermal digital melting point apparatus and uncorrected. ^{1}H NMR spectra were determined on a Varian VXP-500s spectrometer using DMSO-d_6 as solvent and tetramethylsilane (TMS) as internal reference. The IR spectra was obtained on a Nicolet 6700 spectrophotometer using KBr pellets. Elementary analyses were performed by a Heraeus CHN-O-RAPID analyzer. Microwave reactions were carried out in a xianghu XH-100B microwave oven.

Experimental procedure

A mixture of aldehyde **1** (2 mmol), aromatic ketone **2** (2 mmol), 3-(cyanoacetyl)indole **3** (2 mmol), and ammonium acetate **4** (8 mmol) in HOAc 2 mL and glycol 4 mL were irradiated at 350 W and 110–130 °C. After completion of the reaction (the reaction was followed by TLC), the mixture was allowed to cool to room temperature and collected by filtration, washed with cool water (3 × 5 mL). The crude product was separated by column chromatography on silica (200–300 mesh), eluted with a mixture of petroleum ether and dichloromethane to afford the pure product (**5a–k**):

3-Cyano-2-(1H-indol-3-yl)-4,6-diphenylpyridine (**5a**): White power; m.p. 248–249 °C. IR (KBr) ν 3314 (NH), 3062, 2219 (CN), 1583, 1572, 1537, 1437 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.84 (s, 1H), 8.40–8.39 (m, 2H), 8.35 (d, J = 8.5 Hz, 2H), 7.97 (s, 1H), 7.82 (m, 2H), 7.62–7.55 (m, 7H), 7.25–7.23 (m, 2H). Anal. Calcd for $C_{26}H_{17}N_3$: C, 84.07; H, 4.61; N, 11.31. Found: C, 84.14; H, 4.58; N, 11.45%.

3-Cyano-2-(1H-indol-3-yl)-4-(2-methoxyphenyl)-6-phenylpyridine (**5b**): White power; m.p. 213–214 °C. IR (KBr) ν 3302 (NH), 3056, 2957, 2212 (CN), 1603, 1583, 1538, 1456, 1434 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.81 (s, 1H), 8.42 (d, J = 7.0 Hz, 1H), 8.33 (d, J = 2.5 Hz, 1H), 8.31 (d, J = 7.0 Hz, 2H), 7.88 (s, 1H), 7.61–7.53 (m, 5H), 7.50 (dd, J = 7.5 Hz and J = 2.0 Hz, 1H), 7.26–7.23 (m, 3H), 7.16 (t, J = 8.0 Hz, 1H), 3.85 (s, 3H). Anal. Calcd for $C_{27}H_{19}N_3O$: C, 80.78; H, 4.77; N, 10.47. Found: C, 80.71; H, 4.88; N, 10.45%.

3-Cyano-2-(1H-indol-3-yl)-4-(4-methylphenyl)-6-phenylpyridine (**5c**): Pale yellow power; m.p. 268 °C. IR (KBr) ν 3314 (NH), 3055, 2927, 2219 (CN), 1581, 1570, 1536, 1492, 1438 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.84 (s, 1H), 8.40–8.36 (m, 4H), 7.93 (s, 1H), 7.73 (d, J = 8.5 Hz, 2H), 7.62–7.55 (m, 4H), 7.43 (d, J = 8.0 Hz, 2H), 7.27–7.21 (m, 2H), 2.44 (s, 3H). Anal. Calcd for $C_{27}H_{19}N_3$: C, 84.13; H, 4.97; N, 10.90. Found: C, 84.25; H, 4.92; N, 10.99%.

3-Cyano-2-(1H-indol-3-yl)-4-(3-methylphenyl)-6-phenylpyridine (**5d**): Pale yellow power; m.p. 211–212 °C. IR (KBr) ν 3309 (NH), 3060, 2922, 2219 (CN), 1584, 1570, 1539, 1485, 1441 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.85 (s, 1H), 8.42–8.34 (m, 4H), 7.95 (s, 1H), 7.63–7.55 (m, 6H), 7.50 (t, J = 7.5 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.28–7.22 (m, 2H), 2.45 (s, 3H). Anal. Calcd for $C_{27}H_{19}N_3$: C, 84.13; H, 4.97; N, 10.90. Found: C, 84.22; H, 5.06; N, 10.97%.

3-Cyano-2-(1*H*-indol-3-yl)-4-(2,4-dichlorophenyl)-6-phenylpyridine (**5e**): Pale yellow power; m.p. 276 °C. IR (KBr) ν 3321 (NH), 3056, 2220 (CN), 1571, 1554, 1535, 1494 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.89 (s, 1H), 8.45 (d, J = 8.5 Hz, 1H), 8.37 (d,

J = 3.0 Hz, 1H), 8.33 (d, *J* = 8.5 Hz, 2H), 7.98 (s, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.73–7.68 (m, 2H), 7.61–7.56 (m, 4H), 7.28–7.25 (m, 2H). Anal. Calcd for $C_{26}H_{15}Cl_2N_3$: C, 70.92; H, 3.43; N, 9.54. Found: C, 70.83; H, 3.49; N, 9.60%.

3-Cyano-2-(1*H*-indol-3-yl)-4-naphthyl-6-phenylpyridine (**5f**): Pale yellow power; m.p. 264–265 °C. IR (KBr) ν 3438 (NH), 3058, 2919, 2217 (CN), 1599, 1533, 1456, 1436, 1424 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 11.86 (s, 1H), 8.46–8.43 (m, 2H), 8.41–8.38 (m, 3H), 8.16 (d, *J* = 8.5 Hz, 1H), 8.10–8.06 (m, 3H), 7.95 (dd, *J* = 8.5 Hz and *J* = 1.5 Hz, 1H), 7.67–7.56 (m, 6H), 7.29–7.24 (m, 2H). Anal. Calcd for $C_{30}H_{19}N_3$: C, 85.49; H, 4.54; N, 9.97. Found: C, 85.61; H, 4.48; N, 10.06%.

6-(4-Bromphenyl)3-cyano-2-(1H-indol-3-yl)-4-phenylpyridine (**5g**): Yellow power; m.p. 228–229 °C. IR (KBr) ν 3340 (NH), 3057, 2216 (CN), 1589, 1581, 1529, 1457cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 11.84 (s, 1H), 8.39 (d, *J* = 3.0 Hz, 1H), 8.36 (d, *J* = 7.5 Hz, 1H), 8.30 (d, *J* = 8.5 Hz, 2H), 7.98 (s, 1H), 7.82–7.80 (m, 3H), 7.78 (s, 1H), 7.62–7.60 (m, 3H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.26–7.22 (m, 2H). Anal. Calcd for $C_{26}H_{16}N_3Br$: C, 69.34; H, 3.58; N, 9.33. Found: C, 69.49; H, 3.54; N, 9.27%.

3-Cyano-2-(1H-indol-3-yl)-4-phenyl-6-(4-ethylphenyl)pyridine (**5h**): White power; m.p. 225–226 °C. IR (KBr) ν 3369 (NH), 3057, 2968, 2218 (CN), 1568, 1532, 1493, 1447cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 11.83 (s, 1H), 8.41 (d, *J* = 7.5 Hz, 1H), 8.38 (d, *J* = 2.5 Hz, 1H), 8.27 (d, *J* = 8.5 Hz, 2H), 7.92 (s, 1H), 7.82–7.80 (m, 2H), 7.62–7.59 (m, 3H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.26–7.23 (m, 2H), 2.72–2.70 (m, 2H), 1.25 (t, *J* = 7.5 Hz, 3H). Anal. Calcd for $C_{28}H_{21}N_3$: C, 84.18; H, 5.30; N, 10.52. Found: C, 84.23; H, 5.42; N, 10.41%.

3-Cyano-6-[4-(4-propylcyclohexyl)phenyl]2-(1H-indol-3-yl)-4-phenylpyridine (**5i**): White power; m.p. 239 °C. IR (KBr) ν 3428 (NH), 2956, 2919, 2846, 2214 (CN), 1569, 1530, 1492, 1446cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ 11.82 (s, 1H), 8.41 (d, *J* = 7.0 Hz, 1H), 8.38 (d, *J* = 3.0 Hz, 1H), 8.25 (d, *J* = 8.5 Hz, 2H), 7.90 (s, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.61–7.59 (m, 3H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.26–7.22 (m, 2H), 2.50 (t, *J* = 2.0 Hz, 1H), 1.84 (t, *J* = 9.0 Hz, 4H), 1.51–1.48 (m, 2H), 1.35–1.31 (m, 3H), 1.22–1.19 (m, 2H), 1.06–1.03 (m, 2H), 0.90 (t, *J* = 7.0 Hz, 3H). Calcd for $C_{35}H_{33}N_3$: C, 84.81; H, 6.71; N, 8.48. Found: C, 84.73; H, 6.65; N, 8.58%.

3-Cyano-6-(4-ethylphenyl)2-(1H-indol-3-yl)-4-naphthylpyridine (**5j**): Pale yellow power; m.p. 239 °C. IR (KBr) ν 3440 (NH), 3049, 2961, 2216 (CN), 1599, 1536, 1456, 1437 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), 8.15 (d, *J* = 8.5 Hz, 1H), 8.09–8.05 (m, 3H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.67–7.65 (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 $C_{32}H_{23}N_3$: C, 85.50; H, 5.16; N, 9.35. Found: C, 85.61; H, 5.20; N, 9.29%.

3-Cyano-2-(1H-indol-3-yl)-4-naphthyl-6-[4-(4-propylcyclohexyl)phenyl]pyridine (**5k**): Pale yellow power; m.p. 237–238 °C. IR (KBr) ν 3329 (NH), 3056, 2948, 2917, 2215 (CN), 1570, 1532, 1457, 1438 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), 7.67–7.64 (m, 2H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 8.5 Hz, 2H), 7.27–7.23 (m, 2H), 2.60–2.53 (m, 1H), 1.85 (t, *J* = 10.0 Hz, 4H), 1.51–1.49 (m, 2H), 1.34–1.31 (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, 85.72; H, 6.55; N, 7.78%.

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