

A green efficient synthesis of spiro[indoline-3,4'(1H)-pyrano[2,3-c]pyrazol]-2-one derivatives

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A highly efficient and green method has been described for the synthesis of spiropyranopyrazole-oxindole in water. The reaction was carried out at ambient temperature and the products were obtained in excellent isolated yields. The structure of the product (**4e**) was confirmed by X-ray diffraction analysis.

Keywords: spiropyranyl-oxindole, isatin, water

Indole framework is common in a wide variety of pharmacologically and biologically active compounds.^{1–5} The spiro-oxindole system is the core structure of some pharmacological agents and natural alkaloids. Derivatives of spiro-oxindole are widely used for biologicals, such as antimicrobials, anti-inflammatory, anti-tumourals, antibiotic agents and inhibitors of human NK-1 receptors. They are also found to be parts of aldose reductase inhibitors (ARIs) which can help treat and prevent diabetic complications from arising elevated levels of sorbitol.^{6–16} Pyran derivatives are known subunits in many natural products and biologically active compounds, as well as important intermediates in organic synthesis.^{17–20} Thus, it is expected that the resulting compounds would show biological activity if the oxindole is joined to the pyran system through a spiro carbon atom at C-3.

Due to the synthetic importance of spiropyranyl-oxindole, much effort has been put towards the synthesis of such compounds. As reported previously, the synthesis of pyrano[2,3-c]pyrazole systems using neutral alumina in microwave irradiation.²¹ In 2007, Redkin reported enthol ethanol and $\text{N}(\text{CH}_2\text{CH}_2\text{OH})_3$ were used to produce them.²² In the same year, Shanthi *et al.* developed a new method of indium(III) chloride-catalysed.²³ Because of the present growing concern about controlling environmentally pollution, the design of environmentally friendly chemical processes has attracted considerable interest in organic synthesis. In recent years, the organic reactions in aqueous media have attracted much attention in synthetic organic chemistry, not only because water is one of the most cheapest and environmentally friendly solvent but also water exhibits unique reactivity and selectivity, which are different from those obtained in conventional organic solvents. In continuation of our research devoted to the development of green organic chemistry by performing organic reaction in aqueous media, here we report

a one-pot approach for the synthesis of spiropyranopyrazole oxindoles in the presence of K_2CO_3 in water. (Scheme 1)

Base plays a crucial role in this reaction which involves Knoevenagel condensation and Michael addition reaction. First we tested K_2CO_3 used as base. In the initial experiment, isatin **1a** (1 mmol), malononitrile **2** (1.2 mmol), 1-phenyl-3-methyl-5-pyrazolone **3a** (1.2 mmol), and K_2CO_3 (3 mmol) mixed in water at room temperature. The starting materials were soon consumed, 6'-amino-5'-cyano-3'-methyl-1'-phenylspiro[indoline-3,4'(1H)-pyrano[2,3-c]pyrazol]-2-one **4a** was obtained in 79.5% yield, and the product can easily be separated and purified.

When the reaction was carried out with NaHCO_3 or $\text{KF} \cdot 2\text{H}_2\text{O}$ as base instead of K_2CO_3 under the same conditions, the yields of **4a** were 75.8% (entry 2, Table 1) and 77.2% (entry 3, Table 1). Compared with the yield and reaction time, K_2CO_3 is a more efficient base than others.

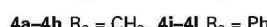
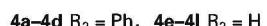
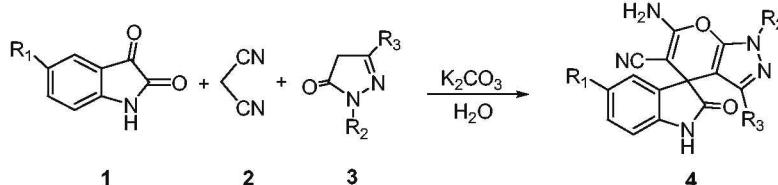
To investigate the scope and limitation of this process, various isatins, bearing electron-donating or electron-withdrawing substituent, and 2-pyrazolin-5-ones were examined under the same condition. In all cases, the reaction proceeded smoothly to afford corresponding spiropyranyloxindoles in high to excellent yields. The results are shown in Table 2.

The structures of compounds **4a–l** were confirmed by ^1H NMR, IR, elementary analysis and X-ray (**4e**).

A plausible mechanism for this process may probably involve following key steps (Scheme 2).

Table 1 The results of the optimisation of bases

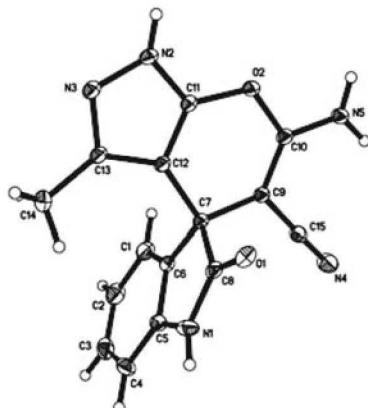
Entry	Condition	Base	t/min	Yield/%
1	Water	K_2CO_3	10	79.5
2	Water	NaHCO_3	75	75.8
3	Water	$\text{KF} \cdot 2\text{H}_2\text{O}$	240	77.2



Scheme 1

Table 2 Synthesis of spiropyranoxindoles in the presence of K_2CO_3 in water

Entry	R ₁	R ₂	R ₃	t/min	Yield/%	Entry	R ₁	R ₂	R ₃	t/min	Yield/%
4a	H	Ph	CH ₃	10	79.5	4g	Br	H	CH ₃	5	79.7
4b	Cl	Ph	CH ₃	15	77.8	4h	NO ₂	H	CH ₃	11	74.6
4c	Br	Ph	CH ₃	20	78.4	4i	H	H	Ph	25	88.6
4d	NO ₂	Ph	CH ₃	22	58.9	4j	Cl	H	Ph	18	89.1
4e	H	H	CH ₃	6	82.5	4k	Br	H	Ph	23	92.9
4f	Cl	H	CH ₃	10	87.3	4l	NO ₂	H	Ph	7	75.7

**Fig. 1** X-ray structure of compound 4e.

The arylidenemalononitriles **b** is formed via Knoevenagel condensation reaction of isatins and malononitrile with K_2CO_3 used as base. The compound **d** is given through Michael addition in which 1-phenyl-3-methyl-5-pyrazolone(**c**) employed as nucleophile attacks on arylidenemalononitriles **b**. Then the intramolecular nucleophilic addition reaction, involving the hydroxyl group and the cyano group in compound **e**, takes place and the imine **f** generated. The spiro compounds **g** is tautomerisation of imine **f**.

In conclusion, we have developed a simple, high efficiency, and green protocol for the synthesis of spiropyranoxindoles derivatives in water at ambient temperature. Furthermore, the procedure offers several advantages including high yields, simple experimental procedure, clean reactions, and low

cost, which make it a useful and attractive strategy in view of economic and environmental advantages.

Experimental

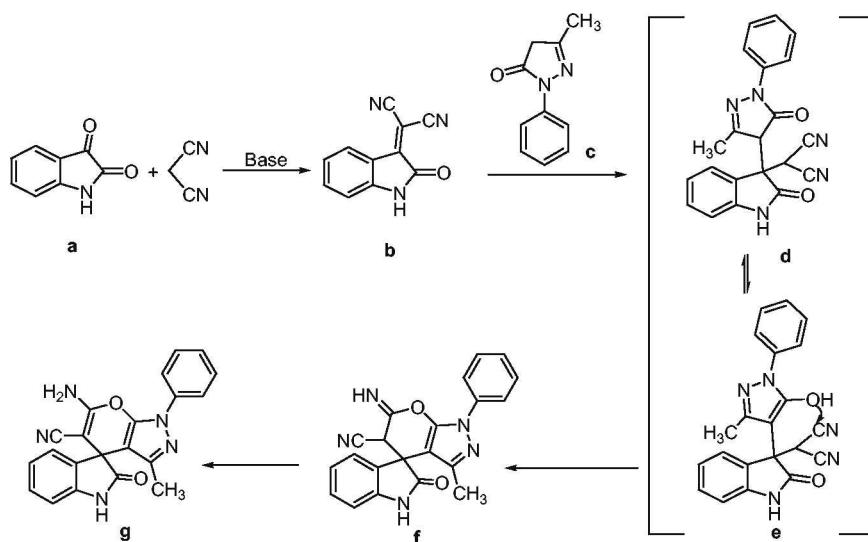
All reagents and solvents were obtained from commercial sources and used without purification. Melting points were determined on WRS-1 digital melting point apparatus made by Shanghai Physical Optical Instrument Factory (SPOIF), China. IR spectra were measured in KBr on a PE-580B spectrometer. ¹H NMR spectra were recorded at a Bruker AM-500, using DMSO-*d*₆ as solvent and TMS as internal reference. Elemental analyses were measured on the elementar vario EL III. X-Ray crystal data were collected with Bruker Smart Apex2 CCD.

General procedure for preparation of 4a–l

A mixture of isatin **1** (1 mmol), malononitrile **2** (1.2 mmol), 2-pyrazolin-5-one **3** (1.2 mmol), and K_2CO_3 (3 mmol) in water (5 ml) was stirred for the time shown in Table 2 (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and the precipitate obtained was washed with dichloromethane and water, and recrystallised from absolute ethanol to afford pure **4**.

*6'-Amino-5'-cyano-3'-methyl-1'-phenylspiro[indoline-3,4'-(1*H*)-pyrano[2,3-*c*]pyrazol]-2-one (4a):* M.p. 219–220°C, lit. m.p. 220°C.²⁴ IR (cm⁻¹): 3291 (NH), 3173 (NH), 2195 (CN), 1700 (CO). ¹H NMR δ: 1.54 (s, 3H, CH₃), 6.94 (d, 1H, *J* = 8 Hz, ArH), 7.02 (m, 1H, ArH), 7.18 (d, 1H, *J* = 7 Hz, ArH), 7.26–7.31 (m, 2H, ArH), 7.52 (m, 2H, ArH), 7.59 (s, 2H, NH₂), 7.79 (m, 2H, ArH), 10.75 (s, 1H, CONH). Anal. Calcd for C₂₁H₁₅N₂O₂: C, 68.28; H, 4.09; N, 18.96. Found: C, 68.25; H, 4.11; N, 18.95%.

*6'-Amino-5-chloro-5'-cyano-3'-methyl-1'-phenylspiro[indoline-3,4'-(1*H*)-pyrano[2,3-*c*]pyrazol]-2-one (4b):* M.p. 223–224°C, lit. m.p. 230–232°C.²⁵ IR (cm⁻¹): 3316 (NH₂), 3186 (NH), 2204 (CN), 1706 (CO). ¹H NMR δ: 1.59 (s, 3H, CH₃), 6.96 (d, 1H, *J* = 8.5 Hz, ArH), 7.34 (m, 3H, ArH), 7.52 (t, 2H, *J* = 8.5 Hz, ArH), 7.64 (s, 2H, NH₂), 7.78 (d, 2H, *J* = 8 Hz, ArH), 10.90 (s, 1H, CONH). Anal. Calcd for C₂₁H₁₄ClN₂O₂: C, 62.46; H, 3.49; N, 17.34. Found: C, 62.45; H, 3.47; N, 17.36%.

**Scheme 2**

6'-Amino-5'-bromo-5'-cyano-3'-methyl-1'-phenylspiro[indoline-3,4'(1H')-pyrano[2,3-c]pyrazol]-2-one (4c): M.p. 198°C IR (cm⁻¹): 3370 (NH₂), 3187 (NH), 2205 (CN), 1705 (CO). ¹H NMR δ: 1.59 (s, 3H, CH₃), 6.91 (d, 1H, *J* = 8 Hz, ArH), 7.35 (t, 1H, *J* = 7 Hz, ArH), 7.46 (m, 2H, ArH), 7.52 (m, 2H, ArH), 7.64 (s, 2H, NH₂), 7.78 (d, 2H, *J* = 7.5 Hz, ArH), 10.90 (s, 1H, CONH). Anal. Calcd for C₂₁H₁₄BrN₅O₂: C, 56.27; H, 3.15; N, 15.62. Found: C, 56.07; H, 3.21; N, 15.55%.

6'-Amino-5'-cyano-3'-methyl-5-nitro-1'-phenylspiro[indoline-3,4'(1H')-pyrano[2,3-c]pyrazol]-2-one (4d): M.p. 219–220°C, lit. m.p. 226–228°C,²⁵ IR (cm⁻¹): 3377 (NH₂), 3189 (NH), 2206 (CN), 1711 (CO). ¹H NMR δ: 1.59 (s, 3H, CH₃), 7.17 (d, 1H, *J* = 8.5 Hz, ArH), 7.36 (m, 1H, ArH), 7.52 (m, 2H, ArH), 7.73 (s, 2H, NH₂), 7.79 (m, 2H, ArH), 8.22 (d, 1H, *J* = 2.5 Hz, ArH), 8.28 (dd, 1H, *J*₁: 1.7, *J*₂: 8.5 Hz, ArH), 11.48 (s, 1H, CONH). Anal. Calcd for C₂₁H₁₄N₆O₄: C, 60.87; H, 3.41; N, 20.28. Found: C, 60.74; H, 3.50; N, 20.27%.

6'-Amino-5'-cyano-3'-methylspiro[indoline-3,4'(1H')-pyrano[2,3-c]pyrazol]-2-one(4e): M.p. 279–280°C, lit. m.p. 275°C,²⁴ IR (cm⁻¹): 3293(NH₂), 3175(NH), 2196(CN), 1700(CO). ¹H NMR δ: 1.53 (s, 3H, CH₃), 6.90 (d, 1H, *J* = 8.5 Hz, ArH), 7.02 (m, 2H, ArH), 7.24 (s, 2H, NH₂), 7.25 (m, 1H, ArH), 10.60 (s, 1H, CONH), 12.29 (s, 1H, N–NH). Anal. Calcd for C₁₅H₁₁N₅O₂: C, 61.43; H, 3.78; N, 23.88. Found: C, 61.33; H, 3.75; N, 23.90%. X-ray: CCDC No. 716904. Formula: C₁₅H₁₁N₅O₂, Mr = 293.29, Volume = 694.26(14) Å³, Z = 2, Wavelength = 0.71073 Å, *u* = 0.099 mm⁻¹. Unit cell parameters: *a* = 7.5256(9); *b*, 9.3635(11); *c*, 10.8897(13) α = 94.7820(10), β = 105.5700(10). Space group: P-1.

6'-Amino-5'-chloro-5'-cyano-3'-methylspiro[indoline-3,4'(1H')-pyrano[2,3-c]pyrazol]-2-one (4f): M.p. 239–240°C, lit. m.p. 230–232°C,²⁵ IR (cm⁻¹): 3346 (NH₂), 3136 (NH), 2182 (CN), 1714 (CO). ¹H NMR δ: 1.58 (s, 3H, CH₃), 6.92 (d, 1H, *J* = 8 Hz, ArH), 7.14 (d, 1H, *J* = 2.5 Hz, ArH), 7.29 (s, 2H, NH₂), 7.30 (dd, 1H, *J*₁: 2.5, *J*₂: 8 Hz, ArH), 10.76 (s, 1H, CONH), 12.35 (s, 1H, N–NH). Anal. Calcd for C₁₅H₁₀ClN₅O₂: C, 54.97; H, 3.08; N, 21.37. Found: C, 54.96; H, 3.10; N, 21.34%.

6'-Amino-5'-bromo-5'-cyano-3'-methylspiro[indoline-3,4'(1H')-pyrano[2,3-c]pyrazol]-2-one (4g): M.p. 282–283°C. IR (cm⁻¹): 3347 (NH₂), 3139 (NH), 2182 (CN), 1713 (CO). ¹H NMR δ: 1.58 (s, 3H, CH₃), 6.88 (d, 1H, *J* = 8 Hz, ArH), 7.24 (d, 1H, *J* = 2 Hz, ArH), 7.32 (s, 2H, NH₂), 7.43 (dd, 1H, *J*₁: 2, *J*₂: 8 Hz, ArH), 10.77 (s, 1H, CONH), 12.35 (s, 1H, N–NH). Anal. Calcd for C₁₅H₁₀BrN₅O₂: C, 48.41; H, 2.71; N, 18.82. Found: C, 48.40; H, 2.80; N, 18.66%.

6'-Amino-5'-cyano-3'-methyl-5-nitrospiro[indoline-3,4'(1H')-pyrano[2,3-c]pyrazol]-2-one (4h): M.p. 270–271°C IR (cm⁻¹): 3323 (NH₂), 2194 (CN), 1731 (CO). ¹H NMR δ: 1.58 (s, 3H, CH₃), 7.14 (d, 1H, *J* = 8.5 Hz, ArH), 7.43 (s, 2H, NH₂), 7.92 (d, 1H, *J* = 2 Hz, ArH), 8.23 (dd, 1H, *J*₁: 2, *J*₂: 8.5 Hz, ArH), 11.37 (s, 1H, CONH), 12.41 (s, 1H, N–NH). Anal. Calcd for C₁₅H₁₀N₆O₄: C, 53.26; H, 2.98; N, 24.84. Found: C, 53.02; H, 2.79; N, 24.88%.

6'-Amino-5'-cyano-3'-phenylspiro[indoline-3,4'(1H')-pyrano[2,3-c]pyrazol]-2-one (4i): M.p. 219–220°C. IR (cm⁻¹): 3308 (NH₂), 3120 (NH), 2186 (CN), 1705 (CO). ¹H NMR δ: 6.74 (d, 1H, *J* = 3 Hz, ArH), 6.80 (d, 2H, *J* = 8.5 Hz, ArH), 6.89 (m, 1H, ArH), 7.03 (m, 1H, ArH), 7.16 (m, 3H, ArH), 7.23 (m, 1H, ArH), 7.26 (s, 2H, NH₂), 10.49 (s, 1H, CONH), 12.89 (s, 1H, N–NH). Anal. Calcd for C₂₀H₁₃N₅O₂: C, 67.60; H, 3.69; N, 19.71. Found: C, 67.55; H, 3.63; N, 19.77%.

6'-Amino-5'-chloro-5'-cyano-3'-phenylspiro[indoline-3,4'(1H')-pyrano[2,3-c]pyrazol]-2-one (4j): M.p. 247–249°C. IR (cm⁻¹): 3295 (NH₂), 3126 (NH), 2187 (CN), 1713 (CO). ¹H NMR δ: 6.74 (d, 1H, *J* = 8.5 Hz, ArH), 6.85 (m, 2H, ArH), 7.13 (d, 1H, *J* = 2.5 Hz, ArH), 7.20 (m, 3H, ArH), 7.27 (m, 1H, ArH), 7.35 (s, 2H, NH₂), 10.66 (s, 1H, CONH), 12.95 (s, 1H, N–NH). Anal. Calcd for C₂₀H₁₂ClN₅O₂: C, 61.63; H, 3.10; N, 17.97. Found: C, 61.61; H, 3.08; N, 17.88%.

6'-Amino-5'-bromo-5'-cyano-3'-phenylspiro[indoline-3,4'(1H')-pyrano[2,3-c]pyrazol]-2-one (4k): M.p. 258–259°C. IR (cm⁻¹): 3397 (NH₂), 3142 (NH), 2188 (CN), 1714 (CO). ¹H NMR δ: 6.70 (d, 1H, *J* = 8.5 Hz, ArH), 6.85 (m, 2H, ArH), 7.18–7.35 (m, 7H, ArH, NH₂), 10.66 (s, 1H, CONH), 12.95 (s, 1H, N–NH). Anal. Calcd for C₂₀H₁₂BrN₅O₂: C, 55.32; H, 2.79; N, 16.13. Found: C, 55.21; H, 2.66; N, 16.20%.

6'-Amino-5'-cyano-5'-nitro-3'-phenylspiro[indoline-3,4'(1H')-pyrano[2,3-c]pyrazol]-2-one (4l): M.p. 212–213°C. IR (cm⁻¹): 3325 (NH₂), 2194 (CN), 1726 (CO). ¹H NMR δ: 6.84 (d, 2H, *J* = 7.5 Hz, ArH), 6.91 (d, 1H, *J* = 7.5 Hz, ArH), 7.19 (m, 2H, ArH), 7.27 (m, 2H, ArH), 7.46 (s, 2H, NH₂), 7.90 (s, 1H, CONH), 8.10 (m, 1H, ArH), 13.00 (s, 1H, N–NH). Anal. Calcd for C₂₀H₁₂N₆O₄: C, 60.00; H, 3.02; N, 20.99. Found: C, 60.12; H, 3.08; N, 20.87%.

Thanks are due to the National Natural Science Foundation of China (No. 20872088) and the Foundations of Educations Commission of Shanghai Municipality (Nos. J50102 and 08ZZ44) for financial support.

Received 13 December 2008; accepted 6 January 2009

Paper 08/0336 doi: 10.3184/030823409X416875

Published online: 6 April 2009

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