A green efficient synthesis of spiro[indoline-3,4'(1*H*')-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 anti-microbials, 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 $N(CH_2CH_2OH)_3$ 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'(1'*H*)-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 $KF{\cdot}2H_2O$ 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.

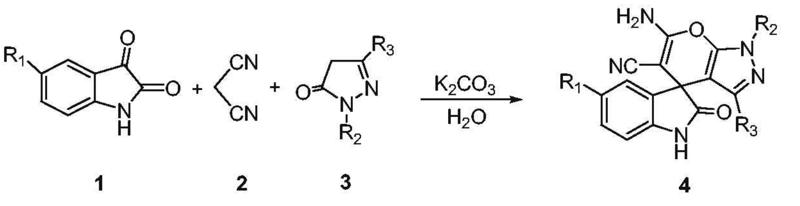
To investigate the scope and limitation of this process, various isatins, bearing electron-donating or electron-withdrawing substituent, and 2-pyrazolin-5-ones were examined under the same condition. In all cases, the reaction proceeded smoothly to afford corresponding spiropyranyloxindoles in high to 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	$KF2H_2O$	240	77.2



4a–4d R_2 = Ph, **4e–4l** R_2 = H

4a–4h R_3 = CH_3, **4i–4l** R_3 = Ph

Scheme 1

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Table 2 Synthesis of spiropyranyloxindoles 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

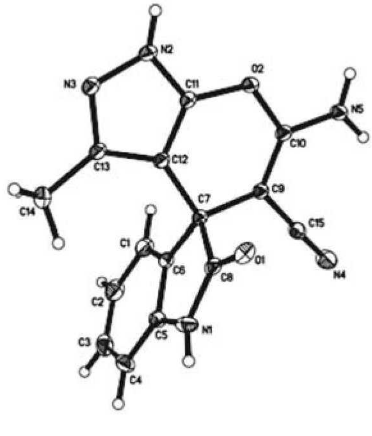


Fig. 1 X-ray structure of compound **4e**.

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 spiropyranyloxindoles 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

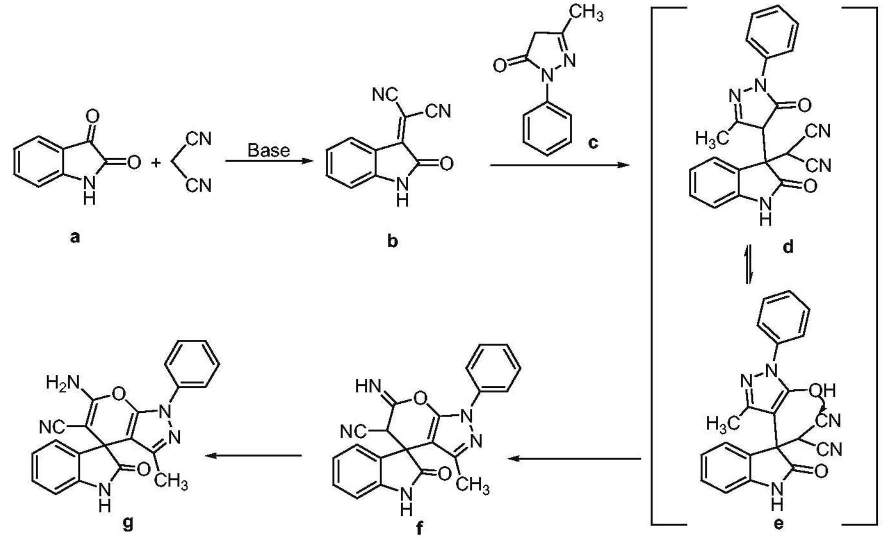
All reagents and solvents were obtained from commercial sources and used without purification. Melting points were determined on WRS-1 digital melting point apparatus made by Shanghai Physical Optical Instrument Factory (SPOIF), China. IR spectra were measured in KBr on a PE-580B spectrometer. ^1H NMR 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'(1H')-pyrano[2,3-c]pyrazol]-2-one (**4a**): M.p. 219–220 °C, lit. m.p. 220 °C.[24] IR (cm^{-1}): 3291 (NH_2), 3173 (NH), 2195 (CN), 1700 (CO). ^1H NMR δ: 1.54 (s, 3H, CH_3), 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, NH_2), 7.79(m, 2H, ArH), 10.75(s, 1H, CONH). Anal. Calcd for $C_{21}H_{15}N_5O_2$: 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'(1H')-pyrano[2,3-c]pyrazol]-2-one (**4b**): M.p. 223–224 °C, lit. m.p. 230–232 °C.[25] IR (cm^{-1}): 3316 (NH_2), 3186 (NH), 2204 (CN), 1706 (CO). ^1H NMR δ: 1.59 (s, 3H, CH_3), 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, NH_2), 7.78 (d, 2H, J = 8 Hz, ArH), 10.90 (s, 1H, CONH). Anal. Calcd for $C_{21}H_{14}ClN_5O_2$: 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 (NH_2), 3187 (NH), 2205 (CN), 1705 (CO). ^1H NMR δ: 1.59 (s, 3H, CH_3), 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, NH_2), 7.78(d, 2H, J = 7.5 Hz, ArH), 10.90 (s, 1H, CONH). Anal. Calcd for $C_{21}H_{14}BrN_5O_2$: 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 (NH_2), 3189 (NH), 2206 (CN), 1711 (CO). ^1H NMR δ: 1.59 (s, 3H, CH_3), 7.17 (d, 1H, J = 8.5 Hz, ArH), 7.36 (m, 1H, ArH), 7.52 (m, 2H, ArH), 7.73 (s, 2H, NH_2), 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 $C_{21}H_{14}N_6O_4$: 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(NH_2), 3175(NH), 2196(CN), 1700(CO). ^1H NMR δ: 1.53 (s, 3H, CH_3), 6.90 (d, 1H, J = 8.5 Hz, ArH), 7.02 (m, 2H, ArH), 7.24 (s, 2H, NH_2), 7.25 (m, 1H, ArH), 10.60 (s, 1H, CONH), 12.29 (s, 1H, N–NH). Anal. Calcd for $C_{15}H_{11}N_5O_2$: 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: C_{15} H_{11} N_5 O_2, Mr = 293.29, Volume = 694.26(14) Å^3, 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), γ 107.3650(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 (NH_2), 3136 (NH), 2182 (CN), 1714 (CO). ^1H NMR δ: 1.58 (s, 3H, CH_3), 6.92 (d, 1H, J = 8 Hz, ArH), 7.14 (d, 1H, J = 2.5 Hz, ArH), 7.29 (s, 2H, NH_2), 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. Calcdd for $C_{15}H_{10}ClN_5O_2$: 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 (NH_2), 3139 (NH), 2182 (CN), 1713 (CO). ^1H NMR δ: 1.58 (s, 3H, CH_3), 6.88 (d, 1H, J = 8 Hz, ArH), 7.24 (d, 1H, J = 2 Hz, ArH), 7.32 (s, 2H, NH_2), 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 $C_{15}H_{10}BrN_5O_2$: 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 (NH_2), 2194 (CN), 1731 (CO). ^1H NMR δ: 1.58 (s, 3H, CH_3), 7.14 (d, 1H, J = 8.5 Hz, ArH), 7.43 (s, 2H, NH_2), 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 $C_{15}H_{10}N_6O_4$: 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 (NH_2), 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, NH_2), 10.49 (s, 1H, CONH), 12.89 (s, 1H, N–NH). Anal. Calcd for $C_{20}H_{13}N_5O_2$: 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 (NH_2), 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, NH_2) 10.66 (s, 1H, CONH), 12.95 (s, 1H, N–NH). Anal. Calcd for $C_{20}H_{12}ClN_5O_2$: 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 (NH_2), 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, NH_2), 10.66 (s, 1H, CONH), 12.95 (s, 1H, N–NH), Anal. Calcd for $C_{20}H_{12}BrN_5O_2$: 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 (NH_2), 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, NH_2), 7.90 (s, 1H, CONH), 8.10 (m, 1H, ArH), 13.00 (s, 1H, N–NH). Anal. Calcd for $C_{20}H_{12}N_6O_4$: C, 60.00; H, 3.02; N, 20.99. Found: C, 60.12; H, 3.08; N, 20.87%.

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