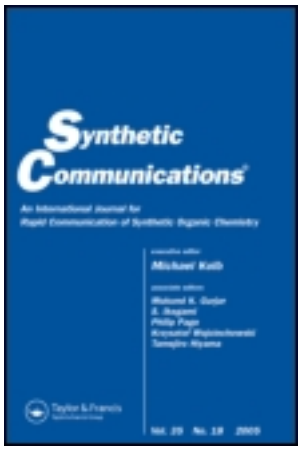

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SOLVENT-FREE ONE-POT SYNTHESIS OF SPIRO[INDOLINE-3,4′(1H′)-PYRANO-[2,3-c]PYRAZOL]-2-ONE DERIVATIVES BY GRINDING

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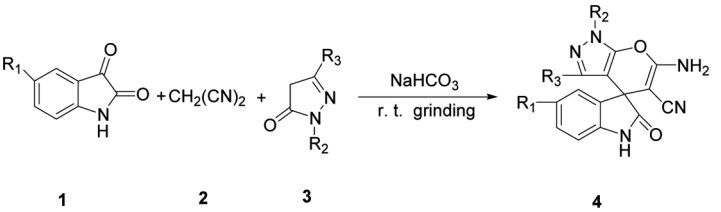
GRAPHICAL ABSTRACT



1 2 3 4

Abstract *The solvent-free one pot synthesis of spiropyranyl-oxindole in the presence of $NaHCO_3$ under grinding has been achieved. This process is simple, fast, efficient and environmentally benign.*

Keywords Isatin; one pot; solvent-free; spiropyranyl-oxindole

INTRODUCTION

The spiro-oxindole framework represents an important structural motif in a number of bioactive natural products and pharmaceuticals.[1] Recently, the synthesis of heterocyclic spiro-oxindole compounds has attracted considerable attention because the spiro-oxindole compounds containing the heterocyclic system showed an increased spectrum of biological activities.[2] Pyran derivatives are known subunits in many natural products and biologically active compounds, as well as important intermediates in organic synthesis.[3] Thus, it is expected that the resulting compounds would show biological activity if the oxindole is joined to the pyran

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system through a spiro carbon atom at C-3. In connection with an ongoing synthesis program, we are interested in the development of new route for the preparation of spiropyranyl-oxindole.

With the present growing concern about controlling environmental pollution, the design of an environmentally friendly chemical processes has attracted considerable interest in organic synthesis. The organic solvents are high in the list of harmful chemicals because they are used in huge amounts and are usually volatile liquids that are difficult to contain. In recent years, the solvent-free reaction under grinding conditions, developed by Tanaka and Toda,[4] has generated great interests. Numerous successful reactions widely used in a variety of organic syntheses have been reported.[5] The advantages of this methodology are high efficiency, mild conditions, operational simplicity, low cost, and environmental acceptability. The one-pot process is one of the most efficient and economical methods for construction of complex molecules from simple and available starting materials without having to spend time and resources on the isolation and purification of intermediates.[6]

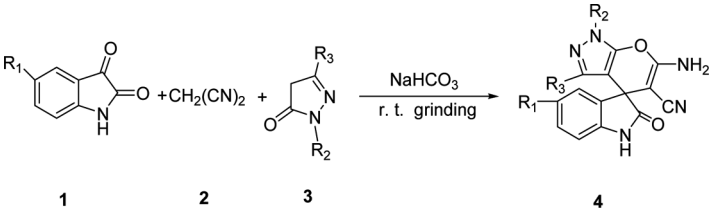
In continuation of our research devoted to organic reactions under solvent-free conditions,[5b] here we report a solvent-free, one-pot procedure for the synthesis of spiropyranyl-oxindoles from isatins, malononitrile, and 2-pyrazolin-5-ones in the presence of $NaHCO_3$ (Scheme 1).

The base plays a crucial role in this reaction because the formation of spiropyranyl-oxindole involves Knoevenagel condensation and Michael addition reaction. First we tested K_2CO_3 as the base. In the initial experiment, the mixture of **1a** (2 mmol), malononitrile **2** (2.2 mmol), **3a** (2.2 mmol), and K_2CO_3 (6 mmol) was ground at room temperature. After the starting materials were consumed, the expected **4a** was obtained in 70% yield after 5 min, but some dark by-products were produced. These by-products reduced the yield and increased the difficulty of separation and purification. We thought that these side reactions resulted from K_2CO_3. When the reaction was carried out with $NaHCO_3$ as the base instead of K_2CO_3 for 7 min under the same conditions, the yield of **4a** was 81%.

To investigate the scope and limitation of this process, various isatins and 2-pyrazolin-5-ones were examined under the same conditions. In all cases, the reaction proceeded smoothly to afford corresponding spiropyranyloxindoles in good to excellent yields. The results are shown in Table 1.

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

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



1 2 3 4

Scheme 1. Preparation of product **4**.

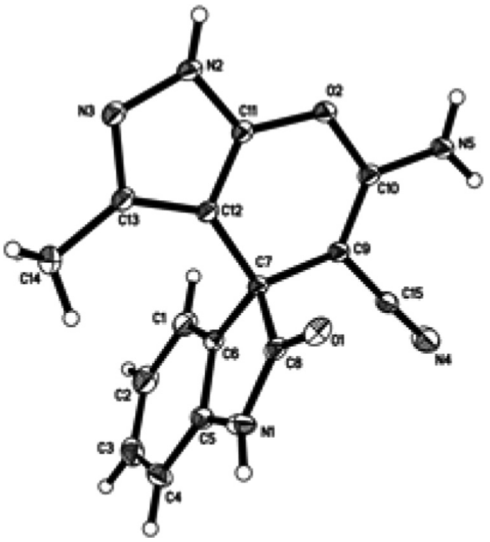


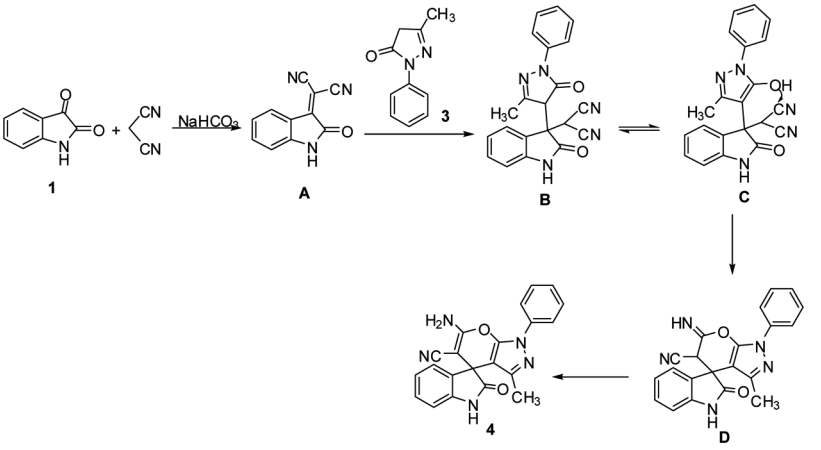
Figure 1. X-ray structure of compound **4e**.

The arylidenemalononitriles **A** is formed via Knoevenagel condensation reaction of isatins with malononitrile using $NaHCO_3$ as the base. Compound **B** is given through Michael addition in which 1-phenyl-3-methyl-5-pyrazolone **3** (employed as nucleophile) attacks arylidenemalononitriles **A**. Then the intramolecular nucleophilic addition reaction, involving the hydroxyl group and the cyano group in compound **C**, takes place, and the imine **D** is generated. The spiro compounds **4** is obtained from imine **D**.

In conclusion, we have developed a solvent-free, one-pot procedure for synthesis of spiro[indoline-3,4′(1′H)-pyrano[2,3-c]pyrazol]-2-one. Its advantages are short reaction times, good yields, operational simplicity, and environmental acceptability.

Table 1. Solvent-free one-pot synthesis of spiropyranyloxindole **4a–k**

Entry	R_1	R_2	R_3	Reaction time (min)	Yield (%)
1	H	Ph	CH_3	7	81 (**4a**)
2	Cl	Ph	CH_3	7	70 (**4b**)
3	NO_2	Ph	CH_3	7	80 (**4c**)
4	H	H	CH_3	7	92 (**4d**)
5	Cl	H	CH_3	7	86 (**4e**)
6	Br	H	CH_3	7	95 (**4f**)
7	NO_2	H	CH_3	7	82 (**4g**)
8	H	H	Ph	7	87 (**4h**)
9	Cl	H	Ph	7	90 (**4i**)
10	Br	H	Ph	7	95 (**4j**)
11	NO_2	H	Ph	7	89 (**4k**)



Scheme 2. Mechanism for the formation of product **4**.

EXPERIMENTAL

All reagents and solvents were obtained from commercial sources and were used without purification. All melting points were uncorrected. Melting points were determined on a WRS-1 digital melting-point apparatus made by Shanghai Physical Instrument Factory (SPOIF), China. Infrared (IR) spectra were measured in KBr on a PE-580B spectrometer. ^{1}H NMR spectra were recorded on a Bruker AM-500, using dimethylsulfoxide (DMSO) as solvent and tetramethylsilane (TMS) as internal reference. Elemental analyses were measured an the Elementar Vario EL III. X-ray crystal data were collected with a Bruker Smart Apex2 CCD.

General Procedure for Preparing Spiro[indoline-3,4′(1′ H)-pyrano[2,3-c]pyrazol]-2-one Derivatives

A mixture of isatin **1** (2 mmol), malononitrile **2** (145 mg, 2.2 mmol), 2-pyrazolin-5-one **3** (2.2 mmol), and $NaHCO_3$ (504 mg, 6 mmol) was ground at room temperature with a glass mortar and pestle. The reaction was monitored by thin-layer chromatography (TLC). The precipitate is collected by suction filtration and washed with water. The product **4** was recrystallized from ethanol and dried under room temperature.

Selected Data

6′-Amino-5′-cyano-3′-methyl-1′-phenylspiro[indoline-3,4′(1′H)-pyrano-[2,3-C]pyrazole]-2-one (4a). Mp 219–220 °C, lit. mp 220 °C.[7] ^{1}H NMR (500 MHz, DMSO) δ 1.54 (s, 3H, CH_3), 6.93–6.95 (m, 1H, Ar-H), 7.01–7.04 (m, 1H, Ar-H), 7.17–7.19 (m, 1H, Ar-H), 7.27–7.30 (m, 1H, Ar-H), ′7.33–7.37 (m, 1H, Ar-H), 7.50–7.54 (m, 2H, Ar-H), 7.59 (s, 2H, NH_2), 7.78–7.80 (m, 2H, Ar-H), 10.75 (s, 1H, NH). IR (potassium bromide) 3460, 3174, 2195, 1700, 1653 cm^{-1}.

6′-Amino-5′-cyano-3′-methyl-1′-phenylspiro[5-choro-indoline-3,4′(1′H)-pyrano[2,3-C]pyrazole]-2-one (4b). Mp 223–224 °C, lit. mp 230–232 °C.[8] ^{1}H NMR (500 MHz, DMSO) δ 1.59 (s, 3H, CH_3), 6.95–6.97 (m, 1H, Ar-H), 7.33–7.37 (m, 3H, Ar-H), 7.51–7.54 (m, 2H, Ar-H), 7.65 (s, 2H, NH_2), 7.77–7.79 (m, 2H, Ar-H), 10.90 (s, 1H, NH). IR (potassium bromide) 3367, 3186, 2204, 1706, 1658 cm^{-1}.

6′-Amino-5′-cyano-3′-methyl-1′-phenylspiro[5-nitro-indoline-3,4′(1′H)-pyrano[2,3-C]pyrazole]-2-one (4c). Mp 219–220 °C, lit. mp 226–228 °C.[8] ^{1}H NMR (500 MHz, DMSO) δ 1.59 (s, 3H, CH_3), 7.17–7.18 (m, 1H, Ar-H), 7.35–7.38 (m, 1H, Ar-H), 7.51–7.54 (m, 2H, Ar-H), 7.73 (s, 2H, NH_2), 7.79–7.81 (m, 2H, Ar-H), 8.22–8.28 (m, 2H, Ar-H), 11.48 (s, 1H, NH). IR (potassium bromide) 3377, 3189, 2206, 1711, 1658 cm^{-1}.

6′-Amino-5′-cyano-3′-methylspiro[indoline-3,4′(1′H)-pyrano[2,3-C]-pyrazole]-2-one (4). Mp 279–280 °C, lit. mp 275 °C.[7] ^{1}H NMR (500 MHz, DMSO) δ 1.53 (s, 3H, CH_3), 6.89–6.91 (m, 1H, Ar-H), 6.98–7.04 (m, 2H, Ar-H), 7.23–7.26 (m, 3H, Ar-H, NH_2), 10.60 (s, 1H, NH), 12.29 (s, 1H, NH). IR (potassium bromide) 3459, 3175, 2195, 1700, 1654 cm^{-1}.

6′-Amino-5′-cyano-3′-methylspiro[5-choro-indoline-3,4′(1′H)-pyrano-[2,3-C]pyrazole]-2-one (4e). Mp 239–240 °C, lit. mp 230–232 °C.[8] ^{1}H NMR (500 MHz, DMSO) δ 1.58 (s, 3H, CH_3), 6.92–6.93 (m, 1H, Ar-H), 7.13–7.14 (m, 1H, Ar-H), 7.29–7.31 (m, 3H, Ar-H, NH_2), 10.76 (s, 1H, NH), 12.35 (s, 1H, NH). IR (potassium bromide) 3346, 3136, 2182, 1714, 1644 cm^{-1}.

6′-Amino-5′-cyano-3′-methylspiro[5-bromo-indoline-3,4′(1′H)-pyrano-[2,3-C]pyrazole]-2-one (4f). Mp 282–283 °C. ^{1}H NMR (500 MHz, DMSO) δ 1.58 (s, 3H, CH_3), 6.87–6.89 (m, 1H, Ar-H), 7.23–7.24 (m, 1H, Ar-H), 7.32 (s, 2H, NH_2), 7.42–7.44 (m, 1H, Ar-H), 10.78 (s, 1H, NH), 12.35 (s, 1H, NH). IR (potassium bromide) 3391, 3138, 2181, 1713, 1642 cm^{-1}. Anal. calcd. for $C_{15}H_{10}BrN_5O_2$: C, 48.41; H, 2.71; N, 18.82. Found: C, 48.71; H, 2.81; N, 18.45.

6′-Amino-5′-cyano-3′-methylspiro[5-niro-indoline-3,4′(1′H)-pyrano[2,3-C]pyrazole]-2-one (4g). Mp 270–271 °C; ^{1}H NMR (500 MHz, DMSO) δ 1.58 (s, 3H, CH_3), 7.13–7.15 (m, 1H, Ar-H), 7.43 (s, 2H, NH_2), 7.91–7.92 (m, 1H, Ar-H), 8.23–8.25 (m, 1H), 11.37 (s, 1H, NH), 12.41 (s, 1H, NH); IR (potassium bromide) 3450, 3322, 2193, 1731, 1644 cm^{-1}. Anal. calcd. for $C_{15}H_{10}N_6O_4$: C, 53.26; H, 2.98; N, 24.84. Found: C, 53.36; H, 3.01; N, 24.49.

6′-Amino-5′-cyano-3′-phenylspiro[indoline-3,4′(1′H)-pyrano[2,3-C]-pyrazole]-2-one (4h). Mp 219–220 °C. ^{1}H NMR (500 MHz, DMSO) δ 6.73–6.75 (m, 1H, Ar-H), 6.79–6.81 (m, 2H, Ar-H), 6.89–6.92 (m, 1H, Ar-H), 7.03–7.05 (m, 1H, Ar-H), 7.14–7.18 (m, 3H, Ar-H), 7.24–7.27 (m, 3H, Ar-H, NH_2), 10.49 (s, 1H, NH), 12.89 (s, 1H, NH). IR (potassium bromide) 3384, 3239, 2186, 1705, 1651 cm^{-1}. Anal. calcd. for $C_{20}H_{13}N_5O_2$: C, 67.60; H, 3.69; N, 19.71. Found: C, 67.31; H, 3.74; N, 19.95.

6′-Amino-5′-cyano-3′-phenylspiro[5-choro-indoline-3,4′(1′H)-pyrano[2,3-C]pyrazole]-2-one (4i). Mp 247–249 °C. ^{1}H NMR (500 MHz, DMSO) δ 6.73–6.75

(m,1H, Ar-H), 6.85–6.87 (m, 2H, Ar-H), 7.13–7.14 (m, 1H, Ar-H), 7.19–7.22 (m, 3H, Ar-H), 7.27–7.29 (m, 1H, Ar-H), ′7.35 (s, 2H, NH_2), 10.66 (s, 1H, NH), 12.94 (s, 1H, NH). IR (potassium bromide) 3400, 3229, 2186, 1712, 1643 cm^{-1}. Anal. calcd. for $C_{20}H_{12}ClN_5O_2$: C, 61.63; H, 3.10; N, 17.97. Found: C, 61.51; H, 3.11; N, 18.10.

6′-Amino-5′-cyano-3′-phenylspiro[5-bromo-indoline-3,4′(1′H)-pyrano-[2,3-C]pyrazole]-2-one (4j). Mp 258–259 °C. ^1H NMR (500 MHz, DMSO) δ 6.69–6.71 (m,1H, Ar-H), 6.85–6.86 (m, 2H, Ar-H), 7.19–7.34 (m, 7H, Ar-H, NH_2), 10.66 (s, 1H, NH), 12.95 (s, 1H, NH). IR (potassium bromide) 3398, 3143, 2188, 1714, 1639 cm^{-1}. Anal. calcd. for $C_{20}H_{12}BrN_5O_2$: C, 55.32; H, 2.79; N, 16.13. Found: C, 54.95; H, 2.85; N, 16.31.

6′-Amino-5′-cyano-3′-phenylspiro[5-niro-indoline-3,4′(1′H)-pyrano[2,3-C]pyrazole]-2-one (4k). Mp 212–213 °C. ^1H NMR (500 MHz, DMSO) δ 6.84–6.85 (m, 2H, Ar-H), 6.90–6.92 (m, 1H, Ar-H), 7.18–7.21 (m, 2H, Ar-H), 7.26–7.29 (m, 1H, Ar-H), 7.27–7.29 (m, 1H, Ar-H), 7.46 (s, 2H, NH_2), 7.90 (s, 1H), 8.10 (s, 1H, NH), 13.00 (s, 1H, NH). IR (potassium bromide) 3225, 2194, 1726, 1631 cm^{-1}. Anal. calcd. for $C_{20}H_{12}N_6O_4$: C, 60.00; H, 3.02; N, 20.99. Found: C, 59.69; H, 3.10; N, 20.61.

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