# One-Pot, Three-Component Synthesis of Spironaphthopyrano[2,3-*d*]pyrimidine-5,3′-indolines in Water



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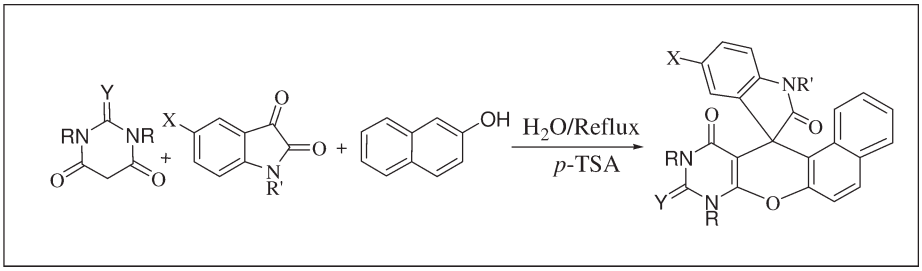


A clean, one-pot and three-component synthesis of new spironaphthopyrano[2,3-*d*]pyrimidine-5,3′-indoline derivatives by cyclo-condensation reaction of isatins, 2-naphthol, and barbituric acids in aqueous media is reported.

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## INTRODUCTION

Multicomponent reactions (MCRs) have been frequently used by synthetic chemists as a facile means to generate molecular diversity from bifunctional substrates that react sequentially in an intramolecular fashion [1,2]. Devising such types of MCRs that achieve the formation of multiple bonds in a single operation is one of the major challenges in modern organic synthesis [3,4]. As such processes avoid time-consuming and costly purification processes, and protection-deprotection steps, they are inherently more environmentally benign and atom economic [5]. They provide a powerful tool toward the one-pot synthesis of diverse and complex compounds and small and drug-like heterocycles [6]. Designing of MCRs in water is another attractive area in green chemistry [7], because water is a cheap, safe, and environmentally benign solvent. There is need for developing MCRs in water with a suitable catalyst and without the use of any harmful organic solvents.

Indole moiety is probably the most well-known heterocycle and a common and important feature of a variety of natural products and medicinal agents [8]. Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiroindoline derivatives highly enhances biological activity [9,10]. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [11–13]. Therefore, a number of methods have been reported for the preparation of spirooxindole fused heterocycles [14–17].

Substituted amino-pyrans take a significant place among the 6-membered oxygen-containing heterocycles. Some of them possess anticancer and antimicrobial activity [18,19]. Serotonin receptor modulators (pteropodine and its stereoisomers) and natural alkaloids, containing both spiro-indole and pyran cycles, were isolated from stem bark of *Uncaria tomentosa* (Fig. 1) [11]. Several spiroheterocycles containing both indole and pyran heterocycles possess anticonvulsant and analgetic [20], herbicidal and antibacterial activities [21].

Pyrimidine and its derivatives have been studied for over a century because of a variety of chemical and biological significance. They have been reported as antibacterial, antiviral, and antitumor agents [22]. A number of heterocyclic compounds fused with pyrimidines are known for their varied biological activities [23–26]. Similarly, naphthopyran derivatives are an important class of compounds with excellent photochromic properties [27–29], some of which are also structural motifs present in many biologically active compounds [30–32]. For example, some naphthopyran derivatives could have potential applications in biochemical research as photoswitch tag compounds [33].

As part of our continuing efforts on the synthesis of biologically active heterocyclic compounds [34–41], we recently described an efficient synthesis of spiropyrimidoquinoline-pyrrolopyrimidines and spiroindoline-pyridodipyrimidines via a condensation reaction between amino-uraciles and isatines [42,43]. We have also

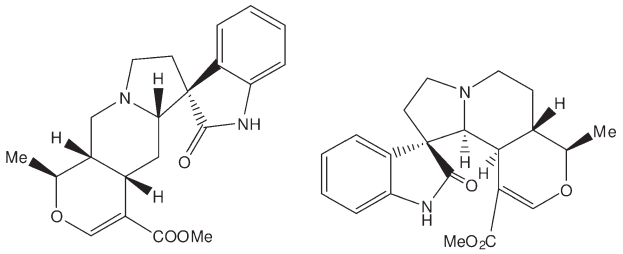



**Figure 1.** Spirooxindole natural alkaloids.

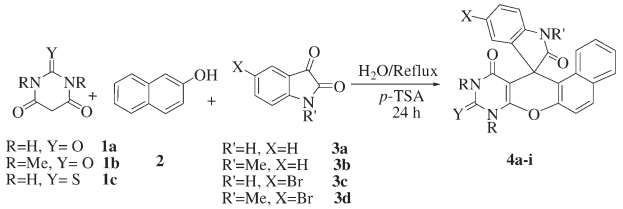
developed an efficient synthesis of spiro[dibenzo[*b*,*i*]-xanthene-13,3′-indoline]-pentaones via a reaction of isatins and 2-hydroxy-naphthoquinone in water [44].

Considering the important biological properties of spirooxindole-fused heterocycles, we report herein a one-pot, three-component and clean synthesis of spironaphthopyrano[2,3-*d*]pyrimidine-5,3′-indolines 4 through a one-pot, three-component condensation reaction of barbituric acids **1a–c**, 2-naphthol **2**, and isatins **3a–d** in water (Scheme 1).

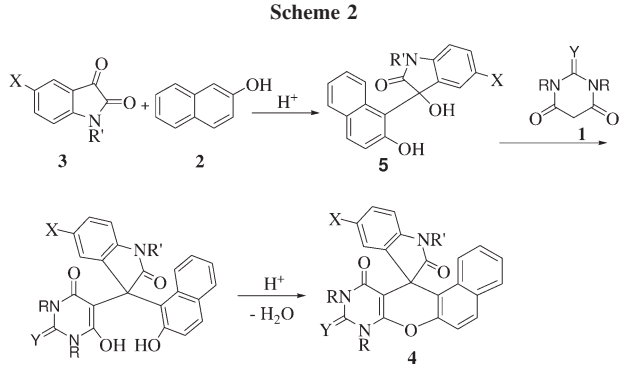
## RESULTS AND DISCUSSION

In a pilot experiment, a mixture of barbituric acid **1a**, 2-naphthol **2**, and isatin **3a** at refluxing water was stirred in the presence of catalytic *p*-toluenesulfonic acid (*p*-TSA) as an inexpensive and available catalyst to afford the spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2,2′,4(1*H*,3*H*)-trione **4a** in 85% for 24 h. Then, to delineate this approach, particularly in regard to library construction, this methodology was evaluated using three commercially available barbituric acids **1a–c**, 2-naphthol **2**, and four substituted isatins **2a–d**, and the corresponding spironaphthopyrano[2,3-*d*]pyrimidine-5,3′-indoline derivatives **4a–i** were synthesized by the one-pot, three-component condensation reaction for good yields under similar conditions (Table 1). $^{1}$H- and $^{13}$C-NMR spectra of the crude products clearly indicated the formation of spirooxindol-fused naphthopyranopyrimidine **4**. The nature of these compounds as 1:1:1 adducts was apparent from their mass spectra, which displayed, in each case, the molecular ion peak at appropriate *m*/*z* values. Compounds **4a–i** are stable solids whose structures were established by IR, $^{1}$H- and $^{13}$C-NMR spectroscopy and elemental analysis.

**Scheme 1**




**Scheme 2**




The results were good in terms of yields and product purity in the presence of *p*-TSA, whereas without *p*-TSA the yields of products were trace even after 48 h.

To the best of our knowledge, this new procedure provides the first example of an efficient and three-component method for the synthesis of spironaphthopyrano[2,3-*d*]pyrimidine-5,3′-indoline derivatives. This method, based on three-component *p*-TSA-catalyzed reaction in water, is the most simple and convenient and would be applicable for the synthesis of different types of spironaphthopyranopyrimidine-indolines.

We have not established an exact mechanism for the formation of spironaphthopyranopyrimidine-indolines **4**; however, the formation of products **4** can be rationalized via initial formation of intermediate **5** by condensation of 2-naphthol **2** and isatin **3** [45]. Subsequent addition of barbituric acids **1** to the intermediate **5**, followed by cyclization afforded the **4** and water (Scheme 2).

In conclusion, we have demonstrated an efficient, a clean, and a simple method for the preparation spironaphthopyranopyrimidine-indolines using readily available starting materials. Prominent among the advantages of this new method are novelty, operational simplicity, good yields, and easy work-up procedures used. Moreover, it is worth noting that two C—C and one C—O bonds were formed with concomitant creation of a spirooxindol-fused naphthopyranopyrimidine in this one-pot, three-component process.

## EXPERIMENTAL

Melting points were measured on an Elecrtothermal 9100 apparatus. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. $^{1}$H- and $^{13}$C-NMR spectra were recorded on a BRUKER DRX-300 AVANCE spectrometer at 300.13 and 75.47 MHz, respectively. IR spectra were recorded using a Shimadzu IR-470 apparatus. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer.

**Table 1**

Synthesis of spironaphthopyranopyrimidine-indolines **4**.

| Product **4** | R | R′ | X | Y | Yield (%) |
|---|---|---|---|---|---|
| **a** | H | H | H | O | 85 |
| **b** | H | Me | H | O | 83 |
| **c** | H | H | Br | O | 80 |
| **d** | H | Me | Br | O | 82 |
| **e** | Me | H | H | O | 79 |
| **f** | Me | Me | H | O | 77 |
| **g** | H | H | H | S | 81 |
| **h** | H | H | Br | S | 82 |
| **i** | H | Me | Br | S | 80 |

**Typical procedure for the preparation of spiro[naphtho [1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2,2′,4(1*H*,3*H*)-trione (4a).** A mixture of barbituric acid **1a** (0.13 g, 1 mmol), 2-naphthol **2** (0.14 g, 1 mmol), isatin **3a** (0.15 g, 1 mmol), and *p*-TSA (0.1 g) in refluxing water (5 mL) was stirred for 24 h (the progress of the reaction was monitored by TLC). After completion, the reaction mixture was filtered and the precipitate washed with water (10 mL) and recrystallized by EtOH to afford the pure product **4a** as with powder (85%); m.p > 300°C (dec). IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3265, 3013, 1723, 1645, 1627. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 6.62–8.01 (m, 10H, ArH), 9.67 (s, 1H, NH), 10.79 (s, 1H, NH), 10.87 (s, 1H, NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta_C$ 50.36, 83.2, 111.9, 117.5, 120.4, 121.4, 124.5, 124.9, 127.1, 127.5, 128.2, 129.6, 130.1, 130.6, 131.4, 135.1, 146.5, 149.7, 150.3, 162.4, 178.7. MS(EI, 70 eV) *m*/*z*: 383 ($M^+$). Anal. Calcd for $C_{22}H_{13}N_3O_4$: C, 68.93; H, 3.42; N, 10.96. Found: C, 68.79; H, 3.39; N, 10.90.

**1′-Methyl-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2,2′,4(1*H*, 3*H*)-trione (4b).** Gray powder (83%); m.p > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3324, 2921, 1720, 1680, 1600. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 3.34 (3H, s, $CH_3$), 6.85–8.03 (10H, m, H-Ar), 10.98 (1H, s, NH), 12.25 (1H, s, NH). MS(EI, 70 eV) *m*/*z*: 397 ($M^+$). Anal. Calcd for $C_{23}H_{15}N_3O_4$: C, 69.52; H, 3.80; N, 10.57. Found: C, 69.57; H, 3.76; N, 10.50.

Because of very low solubility of the product **4b**, we cannot report the $^{13}$C-NMR data for this product.

**5′-Bromo-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2,2′,4(1*H*, 3*H*)-trione (4c).** Light brown powder (80%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3316, 3065, 1781, 1712, 1651. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 6.68–8.03 (9H, m, H-Ar), 9.88 (1H, s, NH), 10.85 (1H, s, NH), 11.05 (1H, s, NH). $^{13}$C-NMR (75 MHz, DMSO-$d_6$): $\delta_C$ 50.3, 83.2, 112.1, 115.5, 120.5, 121.3, 122.6, 125.1, 126.5, 128.1, 128.5, 129.4, 130.3, 131.1, 131.5, 132.6, 135, 146.4, 149.7, 162.4, 178.3. MS(EI, 70 eV) *m*/*z*: 463 ($M^+$), 461 ($M^+$). Anal. Calcd for $C_{22}H_{12}BrN_3O_4$: C, 57.16; H, 2.62; N, 9.09. Found: C, 57.20; H, 2.67; N, 9.14.

**5′-Bromo-1′-methyl-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*] pyrimidine-5,3′-indoline]2,2′,4(1*H*,3*H*)-trione (4d).** Gray powder (82%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3178, 3055, 1719, 1663, 1601. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 3.31(3H, s, $CH_3$), 6.79–8.05 (9H, m, H-Ar), 11.03 (1H, s, NH), 12.29 (1H, s, NH). MS(EI, 70 eV) *m*/*z*: 477 ($M^+$), 475 ($M^+$). Anal. Calcd for $C_{23}H_{14}BrN_3O_4$: C, 58.00; H, 2.96; N, 8.82. Found: C, 57.94; H, 2.91; N, 8.90.

Because of very low solubility of the products **4d–i**, we cannot report the $^{13}$C-NMR data for these products.

**1,3-Dimethyl-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2,2′,4(1*H*,3*H*)-trione (4e).** Gray powder (79%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3296, 1710, 1607, 1528. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 2.97 (3H, s, $CH_3$), 3.62 (3H, s, $CH_3$), 6.61–7.98 (10H, m, H-Ar), 9.83 (1H, s, NH). MS(EI, 70 eV) *m*/*z*: 411 ($M^+$). Anal. Calcd for $C_{24}H_{17}N_3O_4$: C, 70.07; H, 4.16; N, 10.21. Found: C, 70.02; H, 4.20; N, 10.26.

**1′,1,3-Trimethyl-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2,2′,4(1*H*,3*H*)-trione (4f).** Gray powder (77%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3034, 17129, 1667, 1632. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 3.02 (3H, s, $CH_3$), 3.34 (3H, s, $CH_3$), 3.53 (3H, s, $CH_3$), 6.85–8.05 (10H, m, H-Ar). MS(EI, 70 eV) *m*/*z*: 425 ($M^+$). Anal. Calcd for $C_{25}H_{19}N_3O_4$: C, 70.58; H, 4.50; N, 9.88. Found: C, 70.52; H, 4.45; N, 9.81.

**2-Thioxo-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*]pyrimidine-5,3′-indoline]2′,4(1*H*,3*H*)-dione (4g).** Gray powder (81%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3334, 2921, 1771, 1613, 1570. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 6.63-8.01 (11H, m, NH and H-Ar), 9.41 (1H, s, NH), 12.26 (1H, s, NH). MS(EI, 70 eV) *m*/*z*: 399 ($M^+$). Anal. Calcd for $C_{22}H_{13}N_3O_3S$: C, 66.15; H, 3.28; N, 10.52. Found: C, 66.21; H, 3.32; N, 10.61.

**5′-Bromo-2-Thioxo-spiro[naphtho[1′,2′:5,6]pyrano[2,3-*d*] pyrimidine-5,3′-indoline]2′,4(1*H*,3*H*)-dione (4h).** Gray powder (82%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3311, 2921, 1771, 1647, 1559. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 6.70–8.04 (10H, m, NH and H-Ar), 9.56 (1H, s, NH), 12.29 (1H, s, NH). MS (EI, 70 eV) *m*/*z* (%): 479 ($M^+$), 477 ($M^+$). Anal. Calcd for $C_{22}H_{12}BrN_3O_3S$: C, 55.24; H, 2.53; N, 8.78. Found: C, 55.20; H, 2.50; N, 8.73.

**5′-Bromo-1′-methyl-2-hioxo-spiro[naphtho[1′,2′:5,6]pyrano [2,3-*d*]pyrimidine-5,3′-indoline]2′,4(1*H*,3*H*)-dione (4i).** Gray powder (80%); mp > 300°C; IR (KBr) ($\nu_{max}$/cm$^{-1}$): 3311, 2921, 1767, 1647, 1559. $^1$H-NMR (300 MHz, DMSO-$d_6$): $\delta_H$ 3.22 (3H, s, $CH_3$), 715–8.37 (9H, m, H-Ar), 9.60 (1H, s, NH), 12.43 (1H, s, NH). MS(EI, 70 eV) *m*/*z*: 493 ($M^+$), 491 ($M^+$). Anal. Calcd for $C_{23}H_{14}BrN_3O_3S$: C, 55.11; H, 2.87; N, 8.53. Found: C, 55.17; H, 2.93; N, 8.45.

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