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A One-Pot, Multicomponent Synthesis of 5′-Amino-2,2′-dioxo-spiro[indoline-3,3′-pyrrole]-4′-carbonitriles

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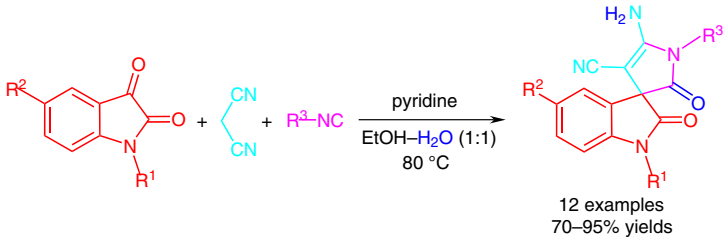

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Abstract A novel, one-pot, multicomponent synthesis of 5′-amino-2,2′-dioxospiro[indoline-3,3′-pyrrole]-4′-carbonitriles is described. The Knoevenagel condensation reaction between isatin derivatives and malononitrile gave the corresponding cyclic arylmethylidenemalononitriles that, on treatment with isocyanides, afforded 2,2′-dioxospiro-bis-γ-lactams in good to excellent yields.

Key words isatins, isocyanides, spiro compounds, lactams, multicomponent reactions

Spiro[indoline-3,3′-pyrrole] motifs are found in many natural products and biologically active synthetic compounds. For example, indole alkaloids strychnofoline, spirotryprostatin A, and spirotryprostatin B have been shown to possess antimitotic properties, so are of interest as anticancer drugs.[1] Rhynchophylline is a noncompetitive NMDA antagonist and calcium channel blocker,[2] and horsfiline presents analgesic effects.[3] Synthetic compound MI-219 is a potent, highly selective, and orally active inhibitor of the MDM2–p53 interaction, which has been studied as a new agent for cancer treatment (Figure 1).[4] A prominent structural feature of all these natural and synthetic products is the presence of a spiro[indoline-3,3′-pyrrole] core. Thus, development of new approaches for the preparation of these spiro compounds have attracted a great deal of attention.[5–11]

In a continuation of our studies on the development of efficient methods for the synthesis of biologically active heterocyclic compounds from readily accessible precursors,[12] we have recently described a one-pot and four-component synthesis of pyrrolo[1,2-*a*]quinoline-3-carbonitriles. The 2-arylmethylidenemalononitriles generated in

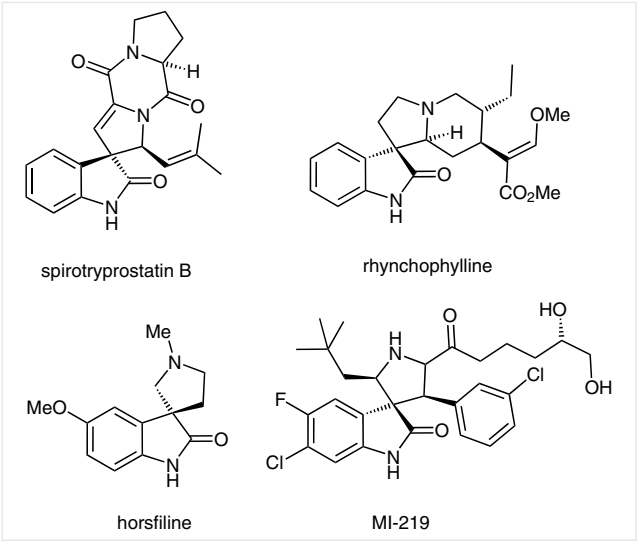
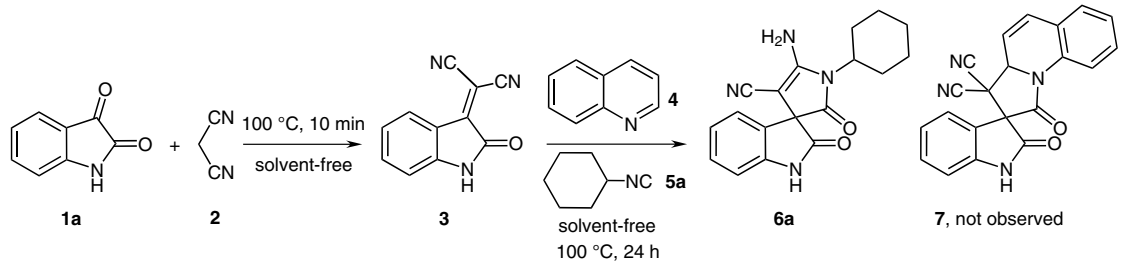


Figure 1 Examples of natural products and synthetic molecules with a spiro[indoline-3,3′-pyrrole] core structure

situ from Knovenagel condensation reaction of malononitrile and aromatic aldehydes were treated with quinoline and cyclohexyl isocyanide under solvent-free conditions to afford the corresponding pyrrolo[1,2-*a*]quinolines.[13] We were prompted to investigate whether isatin derivatives could play the role of the carbonyl component in this multicomponent reaction, which would lead to a new skeleton. Thus, a mixture of isatin **1a** and malononitrile **2** were condensed at 100 °C under solvent-free conditions to give cyclic arylmethylidenemalononitrile **3** within 10 minutes. Quinoline **4** and cyclohexyl isocynide **5a** were then added to the mixture, which was stirred at 100 °C for a further 24 hours. TLC monitoring of the reaction mixture indicated formation of a new product (Table 1, entry 2), which was purified. Identification of its structure by NMR spectrosco-



Scheme 1 Condensation of isatin and malononitrile followed by treatment with quinoline and cyclohexyl isocynide

py revealed that it was 5′-amino-1′-cyclohexyl-2,2′-dioxo-1′,2′-dihydrospiro[indoline-3,3′-pyrrole]-4′-carbonitrile (**6a**), obtained in 20% yield and not the expected spiro[pyrroloquinoline-2,3′-indoline] **7** (Scheme 1). However, further investigations showed that the presence of quinoline in this reaction was crucial; omission of the base led to a very low yield of the product (entry 8). To improve the yield of **6a**, the effects of different bases, reaction temperatures, reaction times and solvents were examined in this model reaction, for which the reaction conditions would be optimized. By varying the parameters, the highest yield was obtained with one equivalent of pyridine as base, EtOH–H_2O (1:1) as the reaction medium, at 80 °C after 20 hours; under these conditions, **6a** was obtained in 85% yield (entry 9).

Table 1 Optimization of the Reaction Conditions for Synthesis of **6a**[a]

Entry	Solvent	Base	*T* (°C)	*t* (h)	Yield of **6a** (%)[b]
1	CH_3CN	quinoline	reflux	24	trace
2	none	quinoline	100	24	20
3	CH_2Cl_2	quinoline	reflux	24	trace
4	toluene	quinoline	60	24	trace
5	toluene	quinoline	reflux	24	trace
6	EtOH–H_2O	quinoline	60	6	70
7	EtOH–H_2O	quinoline	80	20	82
8	EtOH–H_2O	–	80	20	trace
9	EtOH–H_2O	pyridine	80	20	85
10	EtOH–H_2O	DMAP	80	20	50
11	EtOH–H_2O	isoquinoline	80	20	83

[a] Reaction conditions: isatin (1 mmol), malononitrile (1 mmol), cyclohexyl isocynide (1.1 mmol), base (1 mmol).
[b] Isolated yield.

After optimization of the reaction conditions, to explore the generality of the reaction, a series of 5′-amino-2,2′-dioxospiro[indoline-3,3′-pyrrole]-4′-carbonitriles **6** was prepared from isatins **1a**–**f** and isocynides **5a** and **5b** (Figure 2). Thus, a mixture of isatin **1**, malononitrile **2**, isocynide **5**, and pyridine in EtOH–H_2O (1:1) was stirred at 80 °C for 20 or 24 h to afford the corresponding spiro[indoline-3,3′-pyrrole] derivatives **6a**–**l**. TLC and NMR spectroscopic analysis of the reaction mixtures clearly indicated the formation of **6** in good to excellent yields.[14] The results are summarized in Table 2.

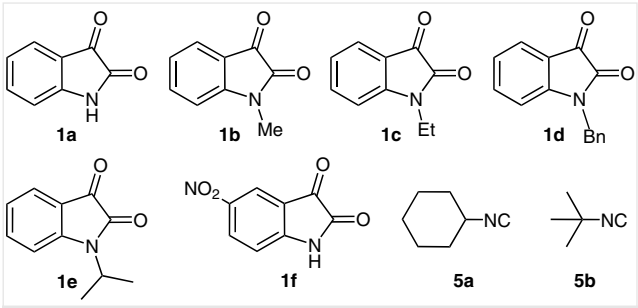
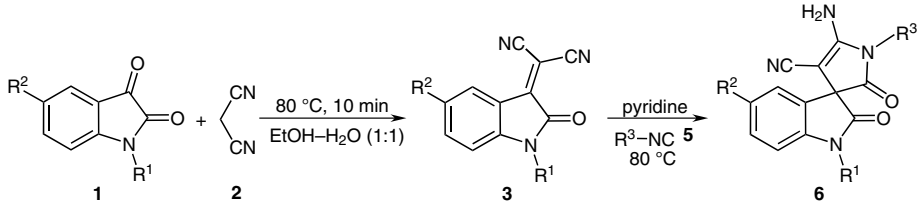


Figure 2 Starting materials for the multicomponent reaction

The structures of the isolated products were deduced on the basis of IR, ^1H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The IR spectrum of **6e** showed the stretching bands for N–H bonds at 3343, 3265, and 3191, nitrile bond at 2187, and C=O bonds at 1739 and 1667 cm^{-1}. The mass spectrum of **6e** displayed the molecular ion [M^+] peak at *m*/*z* 364, which was consistent with the 1:1:1 adduct of *N*-isopropylisatin (**1e**), malononitrile (**2**), and cyclohexyl isocynide (**5a**). Fragment ions such as 321 [$M^+ - C_3H_7$], 282 [$M^+ - C_6H_{10}$], 239 [$M^+ - (C_6H_{11} + C_3H_6)$], $M^+ - (C_6H_{10} + C_3H_7)$, or $M^+ - (NH_2C{=}NCy)$], 212 [$M^+ - (NHC{=}NCy{-}CO)$], 197 [$M^+ - (CyN{=}C{=}O + C_3H_6)$ or $M^+ - (Me_2CHN{=}C{=}O + C_6H_{12})$] were consistent with the structure of **6e**. The ^1H NMR spectrum of **6e** exhibited characteristic multiplets at δ = 1.02–2.10 and 3.78–3.90 ppm for the cyclohexyl moiety along with a doublet at δ = 1.39 ppm and a septet at δ = 4.49 ppm (*J* = 6.9 Hz) for the isopropyl group. Characteristic signals were seen at δ = 7.02–7.35 ppm for the four protons of the phenylene moiety of the oxindole ring, as well as a fairly sharp singlet at δ = 7.79 ppm for the NH_2 group. The ^1H-decoupled ^{13}C NMR spectrum of **6e** showed characteristic signals at δ = 19.4, 19.5, 25.0, 25.7, 29.0, 29.2, 44.6, and 53.0 ppm for the cyclohexyl and isopropyl substituents. Distinguishing signals were observed at δ = 53.6 ppm for the spiro-carbon atom, δ = 117.9 ppm for the nitrile group, and δ = 171.9 and 172.1 ppm due to the two amide carbon-

Table 2 Synthesis of 5′-Amino-2,2′-dioxo-1′,2′-dihydrospiro[indoline-3,3′-pyrrole]-4′-carbonitriles **6a–l**

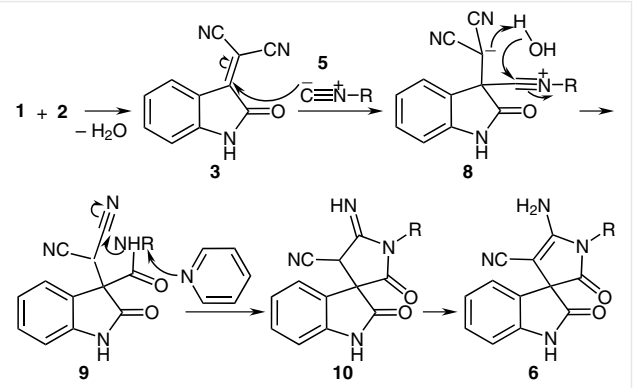


Entry	R^1	R^2	R^3	**6**	*t* (h)	Yield of **6** (%)[a]
1	H	H	Cy	**6a**	20	85
2	Me	H	Cy	**6b**	20	95
3	Et	H	Cy	**6c**	20	85
4	Bn	H	Cy	**6d**	20	85
5	*i*-Pr	H	Cy	**6e**	20	89
6	H	NO_2	Cy	**6f**	24	85
7	H	H	*t*-Bu	**6g**	24	90
8	Me	H	*t*-Bu	**6h**	24	85
9	Et	H	*t*-Bu	**6i**	24	72
10	Bn	H	*t*-Bu	**6j**	24	82
11	*i*-Pr	H	*t*-Bu	**6k**	24	70
12	H	NO_2	*t*-Bu	**6l**	24	87

[a] Isolated yield.

yls of the two fused rings. Two other carbon atoms of the pyrroline ring appeared as a shielded signal at δ = 61.6 ppm and a deshielded signal at δ = 160.4 ppm (due to the $C{=}CN_2$ carbon atoms, respectively), as well as six other distinct resonances (4 × CH and 2 × C) arising from the phenylene moiety of the oxindole ring, in agreement with the proposed structure.[14]

A reasonable mechanistic rationalization for the formation of the spiro-bis-γ-lactams is provided in Scheme 2. First, Knoevenagel reaction of isatin **1** and malononitrile **2** gives the condensation product **3**. Next, the α,β-unsaturated system may undergo nucleophilic addition of the isocyanide **5** followed by protonation to form the positively charged isonitrilium intermediate **8**. The isonitrilium moiety may undergo hydrolysis to produce amide intermediate **9**. One of the nitrile groups of **9** can then undergo nucleophilic addition of the adjacent amide functionality, which is facilitated by the added base, to give the imino amide intermediate **10**. This imino amide can then tautomerize under the reaction conditions to afford 5′-amino-2,2′-dioxospiro[indoline-3,3′-pyrrole]-4′-carbonitriles **6**.



Scheme 2 Proposed mechanism for the formation of 5′-amino-2,2′-dioxospiro[indoline-3,3′-pyrrole]-4′-carbonitriles **6**

In conclusion, we have developed a novel, one-pot and multicomponent approach for the preparation of spiro[indoline-3,3′-pyrrole] derivatives. To our knowledge, this is the first report of the synthesis of 2,2′-dioxospiro[indoline-3,3′-pyrrole] derivatives with the two carbonyl functions located next to the spiro-carbon atom.[15] The mild conditions and good to excellent yields of the products are the main advantages of this reaction. In view of the general biological activities of oxindoles and 2-pyrrolinones, combination of these structures in a single entity might lead to enhanced properties.

Acknowledgment

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(14) **Preparation of Spiro[indoline-3,3′-pyrrole] Derivatives 6a–l; Typical Procedure for 6a:** A mixture of isatin (1 mmol) and malononitrile (1 mmol) in H_2O–EtOH (1:1, 4 mL) was stirred at 80 °C for 10 min. Cyclohexyl isocyanide (1.1 mmol) and pyridine (1 mmol) were added to the mixture, which was then stirred at 80 °C for 20 h. Upon completion of the reaction, as indicated by TLC, the mixture was cooled to room temperature, brine (5 mL) was added, and the mixture was stirred for 5 min. The product was extracted into EtOAc (3 × 5 mL), followed by drying over Na_2SO_4. After filtration, the solvent was removed under the reduced pressure and the residue was crystallized from EtOAc–*n*-hexane (1:1) to afford **6a** as colorless crystals. Compounds **6e** and **6k** were purified accordingly. Other products were purified by column chromatography (EtOAc–*n*-hexane, 1:4).

5′-Amino-1′-cyclohexyl-1-ethyl-2,2′-dioxo-1′,2′-dihydrospiro[indoline-3,3′-pyrrole]-4′-carbonitrile (6c): Yield: 0.298 g (85%); white crystals; mp 200–202 °C. IR (KBr): 3335, 3297 and 3185 (NH), 2191 (CN), 1735 and 1664 (C=O), 1600, 1453, 1353, 1089, 999, 941, 832, 750, 680, 626 cm^{-1}. ^1H NMR (300.1 MHz, DMSO-d_6): δ = 1.05–2.10 [t, *J* = 7.1 Hz, 3 H, CH_3; m, 10 H, $CH(CH_2)_5$], 3.20–3.90 [q, *J* = 7.1 Hz, 2 H, CH_2; m, 1 H, $CH(CH_2)_5$], 7.05–7.20 (m, 3 H, 3 × CH), 7.36 (t, *J* = 7.1 Hz, 1 H, CH), 7.80–7.89 (br. s, 2 H, NH_2). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 13.0 (CH_3), 25.0 (CH_2), 25.6 (2 × CH_2), 28.9 and 29.1 (2 × CH_2), 35.1 (CH_2), 53.0 [$CH(CH_2)_5$], 53.3 (C–C=O), 61.6 (N_2C=C), 109.8 (CH), 117.9 (CN), 123.3 and 123.9 (2 × CH), 127.5 (C), 130.0 (CH), 143.9 (C–N), 160.4 (N_2C=C), 171.8 and 172.0 (2 × C=O). MS: *m*/*z* (%) = 350 (42) [M^+], 281 (48), 268 (100), 239 (42), 225 (34), 212 (20), 198 (44), 183 (39), 160 (33), 128 (19), 97 (18), 83 (28), 69 (34), 55 (80), 41 (80). Anal. Calcd for $C_{20}H_{22}N_4O_2$ (350.41): C, 68.55; H, 6.33; N, 15.99. Found: C, 68.49; H, 6.37; N, 15.86.

5′-Amino-1′-cyclohexyl-1-isopropyl-2,2′-dioxo-1′,2′-dihydrospiro[indoline-3,3′-pyrrole]-4′-carbonitrile (6e): Yield: 0.324 g (89%); white crystals; mp 196 °C. IR (KBr): 3343, 3265 and 3191 (NH), 2187 (CN), 1739 and 1667 (C=O), 1598, 1450, 1306, 1230, 1171, 1092, 1001, 937, 808, 743, 677 cm^{-1}. ^1H NMR (300.1 MHz, DMSO-d_6): δ = 1.02–2.10 [d (1.39), *J* = 6.9 Hz, 6 H, $C(CH_3)_2$; m, 10 H, $CH(CH_2)_5$], 3.78–3.90 [m, 1 H, $CH(CH_2)_5$], 4.49 (sept, *J* = 6.9 Hz, 1 H, CH), 7.02–7.13 (m, 2 H, 2 × CH), 7.25 (d, *J* = 6.9 Hz, 1 H, CH), 7.35 (t, *J* = 6.9 Hz, 1 H, CH), 7.79 (s, 2 H, NH_2). ^{13}C NMR (75.5 MHz, DMSO-d_6): δ = 19.4 and 19.5 [$C(CH_3)_2$], 25.0 (CH_2), 25.7 (2 × CH_2), 29.0 and 29.2 (2 × CH_2), 44.6 [$C(CH_3)_2$], 53.0 [$CH(CH_2)_5$], 53.6 (C–C=O), 61.6 (N_2C=C), 110.9 (CH), 117.9 (CN), 123.0 and 124.1 (2 × CH), 127.8 (C), 129.9 (CH), 143.7 (C–N), 160.4 (N_2C=C), 171.9 and 172.1 (2 × C=O). MS: *m*/*z* (%) = 364 (33) [M^+], 321 (15), 282 (100), 239 (47), 212 (41), 197 (30), 170 (35), 143 (19), 128 (14), 116 (19), 105 (22), 81 (19), 67 (27), 55 (47), 41 (52). Anal. Calcd for $C_{21}H_{24}N_4O_2$ (364.44): C, 69.21; H, 6.64; N, 15.37. Found: C, 69.18; H, 6.71; N, 15.30.

(15) To our knowledge, there are two reports concerning the synthesis of 2-oxo-2′-thioxospiro[indoline-3,3′-pyrrole] derivatives with carbonyl and thiocarbonyl functions located next to the spiro-carbon atom; see ref. 11.