

Three-component synthesis of novel spiro[4*H*-pyran-3,3'-oxindoles] using 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-dione

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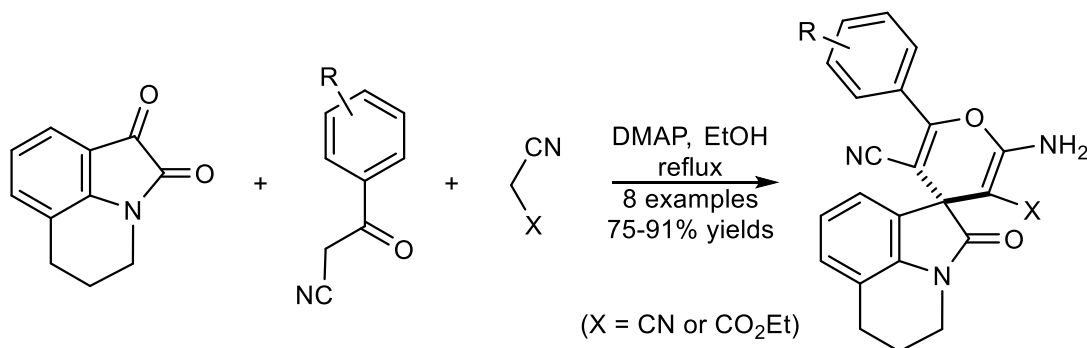
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Abstract

One-pot, three-component reactions of the tricyclic isatin 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-dione with variously substituted aryl cyanomethyl ketones and malononitrile, or ethyl cyanoacetate, generates spiro[4*H*-pyran-3,3'-oxindoles], such as, 2-amino-2'-oxo-6-(phenyl)-5',6'-dihydro-2'*H*,4'*H*-spiro[pyran-4,1'-pyrrolo[3,2,1-*ij*]quinoline]-3,5-dicarbonitrile.



Keywords: Isatins, oxindole, spirocycle, ethyl cyanoacetate, malononitrile

Introduction

Interest in the properties and synthesis of spirooxindoles, general structure **1**, is witnessed by the continuing flow of papers and reviews, important examples of the latter being 'Pyrrolidinyl-spirooxindole natural products as inspirations for the development of potential therapeutic agents',¹ 'Recent progress on routes to spirooxindole systems derived from isatin',² 'Recent advances in the synthesis of biologically active spirooxindoles',³ 'Discovery of orally active anticancer candidate CFI-400945 derived from biologically promising spirooxindoles: success and challenges',⁴ 'Recent applications of isatin in the synthesis of organic compounds',⁵ 'Catalytic asymmetric synthesis of spirooxindoles: recent developments',⁶ and 'Recent advances in spirocyclization of indole derivatives'.⁷

We have been examining the use of 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-dione (**3**), a tricyclic analogue of isatin (**2**), for construction of spiro-3,3'-oxindoles. This paper is the latest in a series in which we have developed a three-component one-pot route to spirooxindoles. The route is applicable to a range of structurally varied starting components, as illustrated in our previous papers; Figure 1 shows a selection of the products from those studies.⁸ Herein, we describe a further extension of this methodology using a new combination of three components.

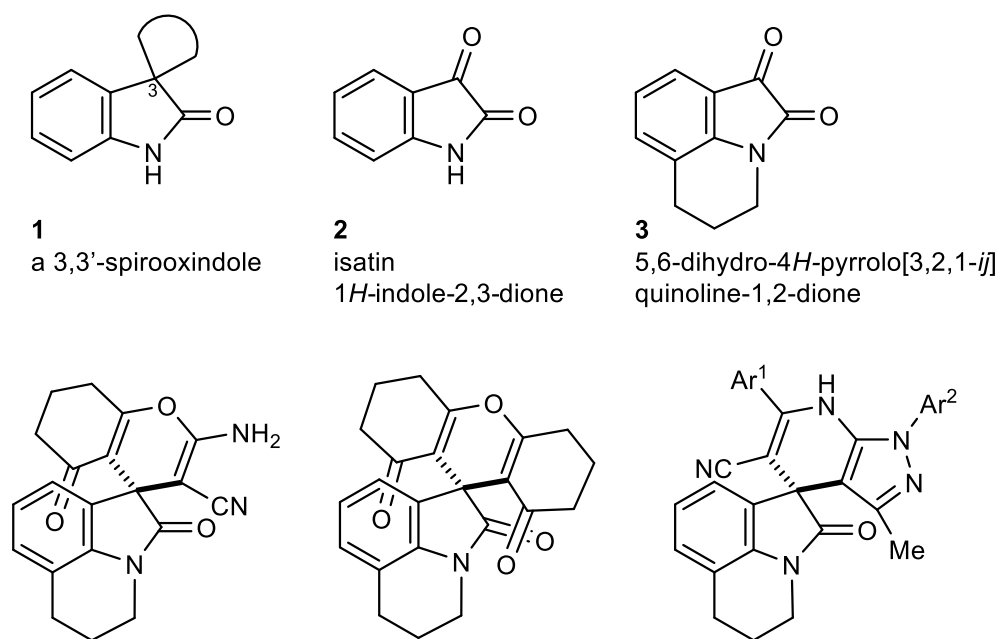
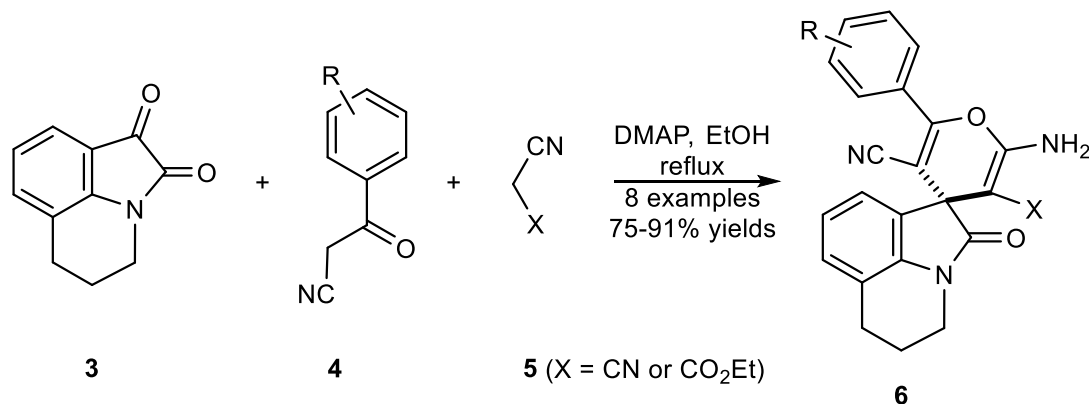


Figure 1. Some previously synthesized spiro-3,3'-oxindoles based on reactions of **3**.⁸

Results and Discussion

5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-dione (**3**) is readily prepared from 1,2,3,4-tetrahydroquinoline by reaction with oxalyl chloride and then Friedel–Crafts ring closure of the resulting amide-acid chloride with aluminium trichloride.⁹ Like simpler isatins, the ketone-carbonyl of the α -keto-amide unit is especially electrophilic and this property is at the basis of the work reported here, and our previous results.⁸ Cyanomethyl aryl ketones **4** were made according to the literature via methyl bromination of acetophenones and then displacement of bromide with cyanide.¹⁰

When the tricyclic isatin **3** is reacted with two other components, both of which can in principle take part in a Knoevenagel condensation, and both of which can provide a nucleophilic enol/enolate, 3,3'-spirocyclic products result.⁸ These must be the result of two steps involving first, a Knoevenagel condensation and then an addition to the conjugated system thus produced and finally cyclisation. Scheme 1 and Table 1 summarize the three-component one-pot syntheses that we report here, involving isatin **3**, a cyanomethyl aryl ketone **4** as the second component and malononitrile **5** (X = CN) or ethyl cyanoacetate **5** (X = CO₂Et), as the third, giving spiro-products **6**. A range of bases were assessed for the process, 4-(*N,N*-dimethylamino)pyridine (DMAP) being by far the best. Acidic conditions led only to decomposition and tars.



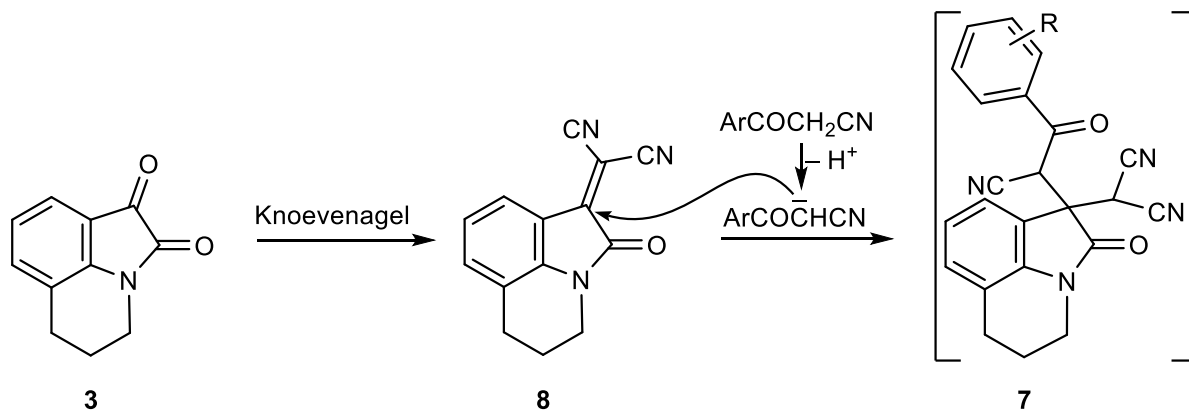
Scheme 1. Three-component one-pot reaction between 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-dione (**3**), a cyanomethyl aryl ketone **4** and malononitrile [**5** (X = CN)] or ethyl cyanoacetate [**5** (X = CO₂Et)] giving spiro-products **6**.

Table 1. Yields and reaction times for synthesis of spiro-products **6**

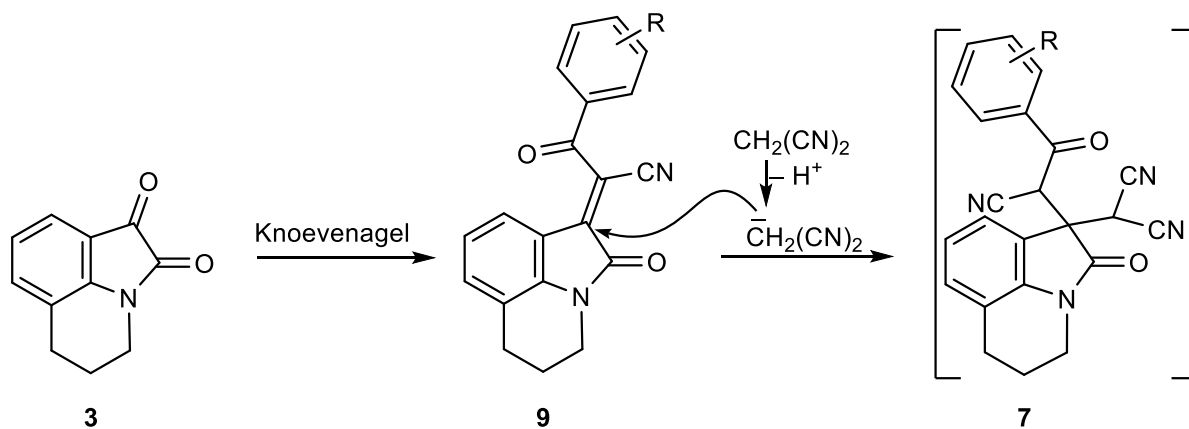
Entry	Product	X	R	Time (h)	Yield (%)
1	6a	CN	H	12	78
2	6b	CN	4-Me	12	83
3	6c	CN	4-Cl	9	91
4	6d	CN	4-Br	9	89
5	6e	CO ₂ Et	H	27	75
6	6f	CO ₂ Et	4-Me	28	79
7	6g	CO ₂ Et	4-Cl	24	83
8	6h	CO ₂ Et	4-Br	25	8

There are two routes by which spirocycles **6** could be reached, each of which leads to a key intermediate **7** prior to formation of the spirocyclic 4*H*-pyran. Thus, illustrating using malononitrile, initial Knoevenagel condensation of isatin **3** with malononitrile could give the ylidene malononitrile **8**, conjugate addition of the enol/enolate of the cyanomethyl ketone **4** would then give intermediate **7** (Scheme 2). Alternatively, initial Knoevenagel condensation of isatin **3** with a cyanomethyl ketone would lead to the ylidene **9**, conjugate addition of malononitrile anion would then lead also to the intermediate **7** (Scheme 3). From compound **7**, enolisation and ring closure with an irreversible prototropy completing the sequence, would provide the isolated spirocycle **6** (Scheme 4).

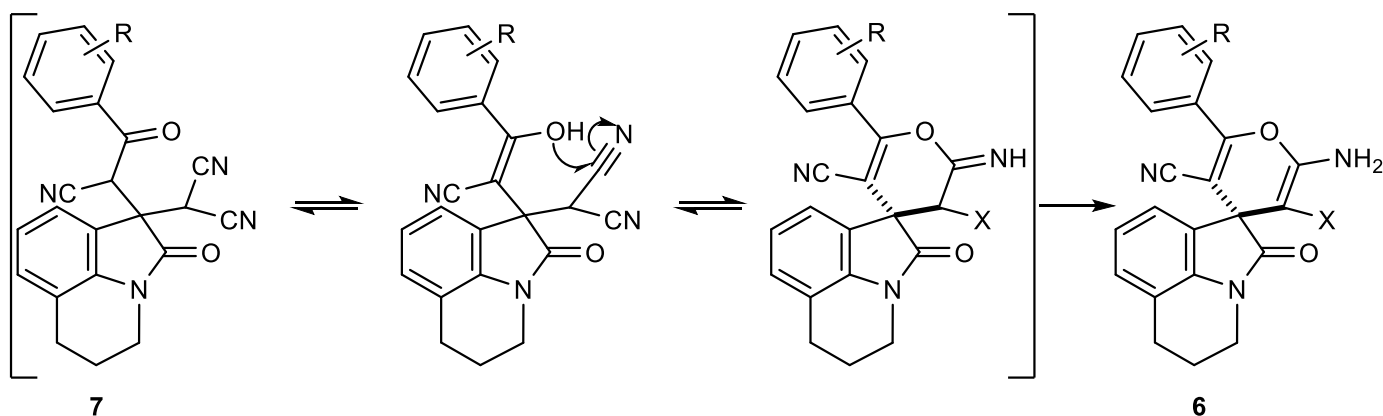
To test these two interpretations, we synthesized the ylidene malononitrile **8** by condensation of isatin **3** with malononitrile and DMAP in ethanol at room temperature (98%, 6 min). The ylidene **9** (R = H) had been prepared previously¹¹ by the reaction of isatin **3** with cyanomethyl phenyl ketone (**4**, R = H) in ethanol heated at reflux with *p*-toluenesulfonic acid as catalyst (78% yield).



Scheme 2. Reaction of compound **3** with malononitrile.



Scheme 3. Reaction of compound **3** with a cyanomethyl aryl ketone.



Scheme 4. Ring closure to form the spiro system.

With the two possible intermediates in hand, we were able to verify that they do indeed react with the third component in the predicted way. Thus, reaction of the ylidene malononitrile **8** with the ketone **4** (R = H) or of the ylidene **9** (R = H) with malononitrile gave the tetracyclic spirocycle **6a** in high yields.

Conclusions

Reaction of the tricyclic isatin **3** with a mixture of a cyanomethyl aryl ketone **4** and malononitrile or ethyl cyanoacetate with DMAP as catalyst produces tetracyclic spirocycles **6**. The three-component reaction tentatively involves an initial Knoevenagel condensation with either malononitrile or the cyanomethyl aryl ketone.

Experimental Section

General. Melting points were recorded on an Electrothermal Engineering LTD 16218 (Bibby Scientific Limited, Staffordshire, UK). ^1H and ^{13}C NMR spectra were recorded on an Avance AQS 300 MHz spectrometer (Bruker, Karlsruhe, Germany) at 300 and 75 MHz, respectively. Chemical shifts δ are in parts per million (ppm) measured in $\text{DMSO-}d_6$ as solvent and relative to TMS as the internal standard. Infrared spectra were recorded on a Nexus 670 FT-IR instrument (Thermo Nicolet, USA). Microanalyses were performed on a Leco Analyzer 932 (Leco, USA). For thin layer chromatography, silica-coated aluminum plates (Merck Kieselgel F₂₅₄) were used.

General procedure for the synthesis of spirooxindoles **6.** To a stirred mixture of 5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-dione (**3**) (187 mg, 1 mmol), a cyanomethyl substituted-aryl ketone **4** (1 mmol) and malononitrile [**5** (R = CN)] (66.0 mg, 1 mmol) or ethyl cyanoacetate [**5** (R = CO₂Et)] (113 mg, 1 mmol) in EtOH (10 mL), was added DMAP (12.0 mg, 0.1 mmol). The reaction mixture was heated with stirring at reflux for the indicated time (Table 2) and the progress of the reaction was monitored by thin-layer chromatography (silica, EtOAc/hexane, 25:75). After completion of the reaction, the mixture was cooled, concentrated and then diluted with cold H₂O (10 mL). The resulting precipitate was filtered off after 6 h, dried in air, and recrystallized from EtOH, to give products **6**.

2-Amino-2'-oxo-6-phenyl-5',6'-dihydro-2'H,4'H-spiro[pyran-4,1'-pyrrolo[3,2,1-*ij*]quinoline]-3,5-dicarbonitrile (6a**).** Colorless needles (295 mg, 78%); mp 198-200 °C (EtOH); FT-IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$ 3346, 3150, 2937, 2611, 2493, 2205 (C≡N), 1711 (C=O), 1613, 1473, 1363, 1174, 1030, 764; ^1H NMR ($\text{DMSO-}d_6$) δ 1.82-1.98 (m, 2H, CH₂), 2.74-2.85 (m, 2H, CH₂), 3.62-3.81 (m, 2H, CH₂), 7.05 (t, *J* 7.5 Hz, 1H, Ar-H), 7.19 (d, *J* 7.2 Hz, 1H, Ar-H), 7.31 (d, *J* 7.2 Hz, 1H, Ar-H), 7.52-7.61 (m, 3H, Ar-H), 7.69 (bs, 2H, NH₂), 7.79 (d, *J* 6.9 Hz, 2H, Ar-H); ^{13}C NMR ($\text{DMSO-}d_6$) δ 21.3, 24.1, 51.4, 54.0, 87.9, 115.8, 117.5, 121.3, 123.1, 123.5, 128.4, 129.3, 129.5, 130.0, 132.7, 139.1, 160.2, 173.9; Found: C, 72.89; H, 4.36; N, 14.95. C₂₃H₁₆N₄O₂ requires C, 72.62; H, 4.24; N, 14.73%.

2-Amino-2'-oxo-6-(*p*-tolyl)-5',6'-dihydro-2'H,4'H-spiro[pyran-4,1'-pyrrolo[3,2,1-*ij*]quinoline]-3,5-dicarbonitrile (6b**).** Colorless needles (327 mg, 83%), mp 187-189 °C (EtOH); FT-IR (KBr) $\nu_{\text{max}}/\text{cm}^{-1}$: 3422, 3321, 3209, 2933, 2206 (C≡N), 1710 (C=O), 1629, 1478, 1358, 1246, 1169, 755; ^1H NMR ($\text{DMSO-}d_6$): δ 1.81-2.06 (m, 2H, CH₂), 2.37 (s, 3H, CH₃), 2.72-2.86 (m, 2H, CH₂), 3.58-3.76 (m, 2H, CH₂), 6.91-7.12 (m, 1H, Ar-H), 7.19 (d, *J* 7.2 Hz, 1H, Ar-H), 7.28 (d, *J* 6.9 Hz, 1H, Ar-H), 7.38 (d, *J* 7.2 Hz, 2H, Ar-H), 7.64 (bs, NH₂, 2H), 7.70 (d, *J* 7.2 Hz, 2H, Ar-H); ^{13}C NMR ($\text{DMSO-}d_6$): δ 21.3, 21.5, 24.1, 51.4, 54.0, 79.1, 87.1, 115.9, 117.4, 121.3, 123.0, 123.4, 127.2,

128.3, 129.4, 129.5, 129.8, 139.1, 143.0, 160.2, 162.3, 174.1; Found: C, 73.34; H, 4.48; N, 14.35. C₂₄H₁₈N₄O₂ requires C, 73.08; H, 4.60; N, 14.20%.

2-Amino-6-(4-chlorophenyl)-2'-oxo-5',6'-dihydro-2'H,4'H-spiro[pyran-4,1'-pyrrolo[3,2,1-ij]quinoline]-3,5-dicarbonitrile (6c). Colorless needles (377 mg, 91%), mp 237-238 °C (EtOH); FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3341, 3262, 3109, 2952, 2854, 2208 (C≡N), 1687 (C=O), 1636, 1534, 1483, 1357, 1291, 1099, 830, 757, 522; ¹H NMR (DMSO-*d*₆) δ 1.81-2.03 (m, 2H, CH₂), 2.72-2.83 (m, 2H, CH₂), 3.61-3.72 (m, 2H, CH₂), 7.01-7.12 (m, 1H, Ar-H), 7.20 (d, *J* 7.8 Hz, 1H, Ar-H), 7.31 (d, *J* 7.2 Hz, 1H, Ar-H), 7.58-7.41 (m, 2H, Ar-H), 7.68 (bs, 2H, NH₂), 7.83 (d, *J* 8.4 Hz, Ar-H); ¹³C NMR (DMSO-*d*₆): δ 20.3, 32.0, 48.0, 51.5, 78.3, 87.4, 113.7, 122.7, 126.0, 126.1, 128.2, 128.3, 128.9, 134.1, 134.2, 140.6, 160.9, 162.7, 176.8; Found: C, 66.83; H, 3.75; N, 13.42. C₂₃H₁₅ClN₄O₂ requires C, 66.59; H, 3.64; N, 13.51%.

2-Amino-6-(4-bromophenyl)-2'-oxo-5',6'-dihydro-2'H,4'H-spiro[pyran-4,1'-pyrrolo[3,2,1-ij]quinoline]-3,5-dicarbonitrile (6d). Grey needles (407 mg, 89%), mp 211-213 °C (EtOH); FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3363, 3262, 2941, 2202 (C≡N), 1708 (C=O), 1687, 1659, 1595, 1484, 1312, 1159, 1011, 830, 758; ¹H NMR (DMSO-*d*₆) δ 1.83-1.98 (m, 2H, CH₂), 2.69-2.81 (m, 2H, CH₂), 3.60-3.71 (m, 2H, CH₂), 7.05 (t, *J* 7.5 Hz, 1H, Ar-H), 7.19 (d, *J* 7.5 Hz, 1H, Ar-H), 7.31 (d, *J* 7.5 Hz, 1H, Ar-H), 7.69 (bs, 2H, NH₂), 7.74 (d, *J* 8.7 Hz, 2H, Ar-H), 7.81 (d, *J* 8.7 Hz, 2H, Ar-H); ¹³C NMR (DMSO-*d*₆) δ 21.3, 24.1, 51.4, 54.0, 69.1, 88.3, 115.6, 117.4, 121.3, 123.2, 126.3, 129.2, 129.5, 130.4, 132.4, 139.1, 159.4, 160.1, 160.2, 162.3, 173.8; Found: C, 60.39; H, 3.40; N, 12.37. C₂₃H₁₅BrN₄O₂ requires C, 60.15; H, 3.29; N, 12.20%.

Ethyl 2-amino-5-cyano-2'-oxo-6-phenyl-5',6'-dihydro-2'H,4'H-spiro[pyran-4,1'-pyrrolo[3,2,1-ij]quinoline]-3-carboxylate (6e). Colorless needles (320 mg, 75%), mp 201-203 °C (EtOH); FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3426, 3296, 2944, 2216 (C≡N), 1703 (C=O), 1618, 1476, 1306, 1100, 1036, 797; ¹H NMR (DMSO-*d*₆) δ 0.74 (t, *J* 6.6 Hz, 3H, CH₃), 1.83-1.98 (m, 2H, CH₂), 2.70-2.79 (m, 2H, CH₂), 3.49-3.56 (m, 1H, CH₂), 3.68-3.78 (m, 3H, CH₂, CH), 6.93 (t, 1H, *J* 7.5 Hz, Ar-H), 6.98-7.22 (m, 2H, Ar-H), 7.50-7.63 (m, 3H, Ar-H), 7.78 (d, *J* 8.1 Hz, 2H, Ar-H), 8.07 (bs, 2H, NH₂); ¹³C NMR (DMSO-*d*₆) δ 14.2, 21.3, 24.3, 50.9, 59.4, 72.6, 90.1, 115.9, 120.2, 121.6, 122.7, 128.1, 128.4, 129.3, 130.2, 132.4, 132.6, 139.5, 158.6, 160.0, 167.2, 175.7; Found: C, 70.11; H, 5.08; N, 9.98. C₂₅H₂₁N₃O₄ requires C, 70.25; H, 4.95; N, 9.83%.

Ethyl 2-amino-5-cyano-2'-oxo-6-(*p*-tolyl)-5',6'-dihydro-2'H,4'H-spiro[pyran-4,1'-pyrrolo[3,2,1-ij]quinoline]-3-carboxylate (6f). Colorless needles (348 mg, 79%), mp 196-197 °C (EtOH); FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3408, 3291, 2933, 2204 (C≡N), 1701 (C=O), 1638, 1482, 1357, 1252, 797; ¹H NMR (DMSO-*d*₆) δ 0.71 (t, *J* 6.9 Hz, 3H, CH₃), 1.83-2.03 (m, 2H, CH₂), 2.37 (s, 3H, CH₃), 2.70-2.81 (m, 2H, CH₂), 3.50-3.66 (m, 1H, CH₂), 3.69-3.77 (m, 3H, CH₂, CH), 6.92 (t, *J* 7.5 Hz, 1H, Ar-H), 7.01-7.12 (m, 2H, Ar-H), 7.36 (d, *J* 8.1 Hz, 2H, Ar-H), 7.68 (d, *J* 8.1 Hz, 2H, Ar-H), 8.04 (bs, 2H, NH₂); ¹³C NMR (DMSO-*d*₆) δ 14.2, 21.3, 21.5, 24.3, 50.9, 59.4, 72.6, 89.4, 116.1, 120.2, 121.5, 122.7, 127.3, 128.0, 128.2, 129.8, 132.6, 139.5, 142.6, 158.6, 160.0, 167.2, 175.8; Found: C, 70.96; H, 5.34; N, 9.64. C₂₆H₂₃N₃O₄ requires C, 70.73; H, 5.25; N, 9.52%.

Ethyl 2-amino-6-(4-chlorophenyl)-5-cyano-2'-oxo-5',6'-dihydro-2'H,4'H-spiro[pyran-4,1'-pyrrolo[3,2,1-ij]quinoline]-3-carboxylate (6g). Colorless needles (382 mg, 83%), mp 215-217 °C (EtOH); FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3421, 3376, 3272, 2931, 2213 (C≡N), 1694 (C=O), 1649, 1527, 1450, 1289, 1104, 748; ¹H NMR (DMSO-*d*₆) δ 0.69-0.76 (m, 3H, CH₃), 1.83-2.05 (m, 2H, CH₂), 2.72-2.86 (m, 2H, CH₂), 3.48-3.59 (m, 1H, CH₂), 3.69-3.77 (m, 3H, CH₂, CH), 6.88-6.99 (m, 1H, Ar-H), 7.05-7.13 (m, 2H, Ar-H), 7.65 (d, *J* 8.4 Hz, 2H, Ar-H), 7.81 (d, *J* 8.4 Hz, 2H, Ar-H), 8.05 (bs, 2H, NH₂); ¹³C NMR (DMSO-*d*₆) δ 15.0, 24.3, 29.3, 51.0, 57.5, 59.4, 72.6, 90.5, 115.8, 121.7, 122.8, 128.4, 129.0, 129.2, 130.6, 131.3, 132.5, 137.1, 139.5, 159.8, 167.1, 175.6; Found: C, 64.76; H, 4.23; N, 8.92. C₂₅H₂₀ClN₃O₄ requires C, 65.01; H, 4.36; N, 9.10%.

Ethyl 2-amino-5-cyano-6-(4-bromophenyl)-2'-oxo-5',6'-dihydro-2'H,4'H-spiro[pyran-4,1'-pyrrolo[3,2,1-ij]quinoline]-3-carboxylate (6h). Colorless needles (414 mg, 82%), mp 195-197 °C (EtOH); FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$

3409, 3303, 2930, 2218 (C≡N), 1698 (C=O), 1621, 1526, 1281, 1099, 757; ¹H NMR (DMSO-*d*₆) δ 0.71 (t, *J* 6.9 Hz, 3H, CH₃), 1.81-2.11 (m, 2H, CH₂), 2.73-2.87 (m, 2H, CH₂), 3.48-3.56 (m, 1H, CH₂), 3.66-3.77 (m, 3H, CH₂, CH), 6.92 (t, *J* 6.9 Hz, 1H, Ar-H), 7.02-7.15 (m, 2H, Ar-H), 7.73 (d, *J* 8.4 Hz, 2H, Ar-H), 7.78 (d, *J* 8.4 Hz, 2H, Ar-H), 8.05 (bs, 2H, NH₂); ¹³C NMR (DMSO-*d*₆) δ 14.2, 21.3, 24.3, 50.9, 59.4, 72.6, 90.5, 115.8, 120.2, 121.7, 122.7, 126.1, 129.3, 130.3, 132.4, 132.5, 139.5, 157.6, 159.8, 167.1, 175.6; Found: C, 59.49; H, 4.11; N, 8.53. C₂₅H₂₀BrN₃O₄ requires C, 59.30; H, 3.98; N, 8.30%.

Condensation of 3 with malononitrile; Synthesis of 2-(2-oxo-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-1(2*H*)-ylidene)malononitrile (8). 5,6-Dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinoline-1,2-dione (**3**) (187 mg, 1 mmol) and an equivalent of malononitrile (66.0 mg, 1 mmol) were dissolved in EtOH and DMAP (12.0 mg, 0.1 mmol) was added. After 6 min at rt, the volatiles were removed and recrystallization of the residue gave the *title compound 8* as purple needles (213 mg, 91%) mp 159 °C (EtOH); FT-IR (KBr) $\nu_{\max}/\text{cm}^{-1}$ 3093, 2939, 2874, 2211 (C≡N), 1672 (C=O), 1589, 1474, 1264, 1088; ¹H NMR (CDCl₃) δ 2.01-2.10 (m, 2H, CH₂), 2.75-2.83 (m, 2H, CH₂), 3.35-3.43 (m, 2H, CH₂), 6.60-6.73 (m, 2H, Ar-H), 7.71 (d, *J* 8.1 Hz, 1H, Ar-H); ¹³C NMR (CDCl₃) δ 21.4, 24.5, 39.23, 82.3, 98.6, 117.8, 122.9, 123.2, 127.8, 128.3, 129.1, 138.5, 150.5, 175.1; Found: C, 74.83; H, 5.41; N, 12.37. C₁₄H₉N₃O₁ requires C, 74.98; H, 5.39; N, 12.50%.

Synthesis of 6a from intermediate 8

Compound **8** (235 mg, 1 mmol) was heated with an equivalent of cyanomethyl phenyl ketone **4** (R = H) (145 mg, 1 mmol) in EtOH with DMAP (12.0 mg, 0.1 mmol) for 7 h. Evaporation and work-up in the usual way gave 2-amino-2'-oxo-6-phenyl-5',6'-dihydro-2'*H*,4'*H*-spiro[pyran-4,1'-pyrrolo[3,2,1-*ij*]quinoline]-3,5-dicarbonitrile (**6a**) (326 mg, 86%), identical to material obtained from the three-component condensation of diketone **3** with ketone **4** (R = H) and malononitrile.

Synthesis of 6a from intermediate 9

Compound **9** (287 mg, 1 mmol), malononitrile (66.0 mg, 1 mmol) and DMAP (12.0 mg, 0.1 mmol) were dissolved in CH₂Cl₂/MeCN (50:50, 5 mL) and the mixture stirred at rt for 15 min. Completion of the reaction was marked by a change in color from blood red to light yellow. The reaction mixture was concentrated in vacuum at rt, and H₂O (20 mL) was added. The resulting precipitate was filtered off and washed with cold EtOH (2 × 1 mL), and the pure product (306 mg, 81%) was obtained by recrystallization from Me₂CO/H₂O, and proved to be identical with compound **6a** obtained from the three-component condensation of diketone **3** with ketone **4** (R = H) and malononitrile.

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Supplementary Material

Copies of ¹H and ¹³C NMR spectra of compounds **6a-i** are given in the Supplementary Material file associated with this manuscript.

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