Synthesis of Novel Spiro[chromene-4,3'-indolines] and Spiro(indoline-3,4'-pyrano[3,2-*h*]quinolines)

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Abstract—The condensation of 1-alkylisatines with malononitrile and 8-hydroxyquinoline or 5,5-dimethyl-cyclohexane-1,3-dione in the presence of an aqueous solution of trimethylamine proceeds regioselectively as a one-pot three-component domino process to form spiro[chromene-4,3'-indoline] and spiro(indoline-3,4'-pyrano[3,2-*h*]quinoline).

Keywords: 1-alkylisatines, malononitrile, 8-hydroxyquinoline, 5,5-dimethylcyclohexane-1,3-dione, three-component condensation, spiro(indoline-3,4'-pyrano [3,2-*h*]quinoline), spiro[chromene-4,3'-indoline]

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Multicomponent reactions, which involve 1*H*-Indole-2,3-dione (isatin) and occur as one-pot catalytic domino processes, are the most common and efficient methods of synthesis of spiro-fused heterocyclic compounds [1].

The three-component reactions of isatin with malononitrile or cyanoacetic ester, and compounds with an enolic component or its synthetic equivalent in the structure were used to obtain a great number of carbo- and heterocyclic spirooxindoles, which are of interest for medical or combinatorial chemistry [2, 3].

As known, natural or synthetic oxindoles exhibit diverse biological activities, including a wide range of biological activity, including DNA-damaging [4], cyto-toxic [5–7], fungicidal [8], antibacterial [9], and others.

Proceeding with our research into the synthesis of spiro-fused isatins by base-catalyzed three-component reactions [10, 11] and aiming at expanding the combinatorial potential of this synthetic approach, we involved in such reactions 1-substituted isatins, malononitrile, and 5,5-dimethylhexane-1,3-dione (dimedone) or 8-hydroxy-quinoline.

It was shown that the one-pot three-component condensation of the mentioned compounds in ethanol in the presence of an aqueous solution of trimethylamine occurs in a regioselective fashion by a cascade mechanism to form spiro-fused 2-oxindoles: spiro(chromene-4,3'-indoline) derivatives in the case of dimedone and spiro(indoline-3,4'-pyrano[3,2-h]quinoline) derivatives in the case of 8-hydroxyquinoline. The synthesized novel spiro-fused compounds combine two different heterocyclic system comprising a carbocycle and three different heterocycles, which determines the spectrum of their biological activity.

The syntheses realized in the present work are presented in Scheme 1. The suggested mechanism of the reaction is shown in Scheme 2.

The dielectrophile 2-(2-oxoindolin-3-ylidene)malononitrile (7) formed by the condensation of substituted isatin 1 and malononitrile (2) undergoes a regioselective Michael reaction with the participation of both electrophilic centers (the cyano group and the β -position of the activated double bond), leading to pyran ring closure; In both cases, the enolic OH group attacks exclusively the cyano group. The same reaction route was also suggested for similar syntheses of spiro-fused isatin derivatives [2, 10–13].

The IR spectra of the synthesized compounds contain characteristic $v(NH_2)$ bands at 3450–3150 cm⁻¹, v(CN) bands at 2198–2190 cm⁻¹, and v(C=O) bands at 1714–1680 cm⁻¹. The ¹³C NMR spectra of the products containing a dimethylhexanone fragment display signals



1a–1f, **5a–5f**, **6a–6e**, R = H (**a**), CH_3 (**b**), C_2H_5 (**c**), C_3H_8 (**d**), C_4H_9 (**e**), Bn (**f**); **5a–e**, R = H (**a**), CH_3 (**b**), C_2H_5 (**c**), C_3H_7 (**d**), C_4H_9 (**e**), $CH_2C_6H_5$ (**f**); **6a–6e**, $R = CH_3$ (**a**), C_2H_5 (**b**), C_3H_8 (**c**), C_4H_9 (**d**), $CH_2C_6H_5$ (**e**).

at δ_C 31.6, 46.1, and 57.5 ppm assigned to the <u>C</u>(Me₂) carbon, quaternary spiro-oxindole carbon, and carbon atoms linked to the CN group, respectively.

To conclude, we would like to note that we still could not establish the absolute configuration of the synthesized 3-spiroindolines; the same situation was mentioned in some other publications concerning the synthesis of the spiro-fused isatin derivatives [6, 14, 15].

EXPERIMENTAL

Solvents were distilled before use and crystalline substances were recrystallized from appropriate solvents.

The IR spectra were measured on a Thermo Nicolet

Avatar 330 instrument in mineral oil. The ¹H and ¹³C NMR spectra were run on a Varian Mercury-300 VX spectrometer at 300 and 75.46 MHz, in DMSO- d_6 -CCl₄(1:3), internal reference TMS. The elemental analyses were obtained on a Eurovector EA 3000 analyzer. Thin-layer chromatography was performed on Silufol UV-254 plates in ethanol–benzene (2:5), visualization in iodine vapor.

Spiro[chromene-4,3'-indolines] 5a–5e and spiro-(indoline-3,4'-pyrano[3,2-*h*]quinolines 6a–6e (general procedure). A mixture of 20 mmol of isatine 1a–1f, malononitrile (2), 5,5-dimethylcyclohexane-1,3-dione (3) or 8-hydroxyquinoline (4) and 1 mL of aqueous trimethylamine in 80 mL of ethanol was stirred under reflux for



2 h, after which 40 mL of the solution was distilled off, and the remaining solution was left to stand in the cold. The crystals that formed were filtered off and recrystal-lized from ethanol.

2-Amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboni-trile (5a). Yield 5.5 g (82%), mp 280–282°C, R_f 0.24. IR spectrum, v, cm⁻¹: 3368, 3246 (NH' NH₂), 1686 (C=O), 1604-1590 (C=C). ¹H NMR spectrum, δ , ppm: 1.07 s and 1.12 s (6H, Me₂), 2.09 d and 2.19 d [2H, 6,8-H(CH₂), J 15.9 Hz], 2.52 d and 2.61 d [2H, 6,8-H(CH₂), J 17.6 Hz], 6.80–6.94 m (3H) and 7.11 t.d (1H, C₆H₄, J 7.5, 1.5 Hz), 6.84 br.s (2H, NH₂), 10.26 s (1H, NH). Found, %: C 68.02; H 5.15; N 12.53. C₁₉H₁₇N₃O₃. Calculated, %: C 68.05; H 5.11; N 12.53.

2-Amino-2,5'-dioxo-1',7,7-trimethyl-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboni-trile (5b). Yield 4.80 g (70%), mp 273–275°C. R_f 0.64. IR spectrum, v, cm⁻¹: 3284, 3107 (NH₂), 2192 (CN), 1701, 1682, 1666 (C=O), 1602 (C=C). ¹H NMR spectrum, δ , ppm: 1.07 s and 1.12 s (6H, Me₂), 2.08 d and 2.16 d [2H, 6,8-H(CH₂), *J* 16.0 Hz], 2.54 d and 2.61 d [2H, 6,8-H(CH₂), *J* 17.5 Hz], 3.20 s (3H, NCH₃), 6.87–7.01 m (3H, C₆H₄), 6.90 br.s (2H, NH₂), 7.23 d.d.d (1H, C₆H₄, *J* 7.6, 6.9, 2.2 Hz). ¹³C NMR spectrum, δ , ppm: 25.9, 27.2, 27.7, 31.6, 40.1, 46.2, 49.9, 57.2, 107.5, 110.8, 116.5, 121.8, 122.2, 127.8, 133.2, 143.4, 158.5, 163.2, 175.9, 193.4. Found, %: C 68.72; H 5.45; N 12.15. C₂₀H₁₉N₃O₃. Calculated, %: C 68.75; H 5.48; N 12.03.

2-Amino-7,7-dimethyl-2,5'-dioxo-1'-ethyl-5,6,7,8tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (5c). Yield 3.62 g (50%), mp 278–280°C, R_f 0.73. IR spectrum, v, cm⁻¹: 3271, 3157 (NH₂), 2198 (CN), 1698, 1680 (C=O), 1634, 1611, 1602 (C=C). ¹H NMR spectrum, δ, ppm: 1.07 s (3H, CH₃), 1.13 s (3H, CH₃), 1.28 t (3H, CH₃, *J* 7.2 Hz), 2.08 d (1H, CH₂, *J* 16.0 Hz) and 2.18 d (1H, CH₂, J 16.0 Hz), 2.53 d (1H, CH₂, J 17.6 Hz) and 2.62 d (1H, CH₂, J 17.6 Hz), 3.74 q (2H, NCH₂, J7.2 Hz), 6.86 br.s (2H, NH₂), 6.88 br.d (1H, C₆H₄, J 7.8 Hz), 6.94 t.d (1H, C₆H₄, J 7.3, 0.9 Hz), 6.98 d.d.d (1H, C₆H₄, J7.3, 1.7, 0.5 Hz), 7.22 d.d.d (1H, C₆H₄, J7.7, 7.3, 1.7 Hz). ¹³C NMR spectrum, δ, ppm: 11.7, 27.1, 27.8, 31.6, 34.1, 40.1, 46.0, 49.8, 57.5, 107.5, 110.8, 116.4, 121.5, 122.4, 127.8, 133.4, 142.3, 158.4, 163.0, 175.3, 193.3. Found, %: C 69.62; H 5.75; N 11.53. C₂₁H₂₁N₃O₃. Calculated, %: C 69.41; H 5.82; N 11.56.

2-Amino-7,7-dimethyl-2,5'-dioxo-1'-propyl-5',6',7',8'-tetrahydrospiro[chromene-4,3'-indoline]- 3-carbonitrile (5d). Yield 5.2 g (69%), mp 248–247°C, $R_{\rm f}$ 0.80. IR spectrum, v, cm⁻¹: 3276, 3162 (NH₂), 2196 (CN), 1698, 1678 (C=O), 1633, 1609 (C=C). ¹H NMR spectrum, δ, ppm: 1.02 t (3H, CH₃, J7.4 Hz), 1.07 s (3H, CH₃), 1.12 s (3H, CH₃), 1.74 sextet (2H, CH₂CH₃, J 7.4 Hz), 2.07 d (1H) and 2.18 d (1H, CH₂, J 16.0 Hz), 2.52 d (1H) and 2.62 d (1H, CH₂, J 17.6 Hz), 3.55-3.73 m (2H, NCH₂), 6.87 br.d (1H, C₆H₄, J7.6), 6.88 br.s (2H, NH₂), 6.93 d.d.d (1H, C₆H₄, J 7.3, 7.3, 1.0 Hz), 6.98 d.d (1H, C₆H₄, J7.3, 1.7 Hz), 7.21 d.d.d (1H, C₆H₄, J 7.6, 7.3, 1.7 Hz). ¹³C NMR spectrum, δ, ppm: 11.1 (CH₃ Pr), 20.0 (CH₂), 27.1 (CH₃), 27.8 (CH₃), 31.6, 40.1 (CH₂), 41.3 (CH₂), 46.1, 49.8 (NCH₂), 57.5 (<u>C</u>CN), 107.6 (CH), 110.8, 116.4 (CN), 121.6 (CH), 122.4 (CH), 127.7 (CH), 133.3, 142.9, 158.4, 163.1, 175.7, 193.3. Found, %: C 70.12; H 5.96; N 11.38. C₂₂H₂₃N₃O₃. Calculated, %: C 70.05; H 6.14; N 11.13.

2-Amino-1'-butyl-7,7-dimethyl-2,5'-dioxo-5,6,7,8tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (5e). Yield 5.7 g (73%), mp 247–248°C, R_f 0.80. IR spectrum, v, cm⁻¹: 3360, 3288, 3149 (NH₂), 2193 (CN), 1702, 1684, 1668 (C=O), 1603 (C=C). ¹H NMR spectrum, δ, ppm: 1.00 t (3H, CH₃, J7.3 Hz); 1.07 s (3H, CH₃), 1.13 s (3H, CH₃), 1.41–1.53 m (2H, CH₂CH₃), 1.64–1.75 m (2H, CH₂C₂H₅), 2.08 d (1H, CH₂, J15.9 Hz), 2.19 d (1H, CH₂, J15.9 Hz), 2.52 d (1H, CH₂, J17.6 Hz), 2.62 d (1H, CH₂, J17.6 Hz), 3.58–3.76 m (2H, NCH₂), 6.85 br.s (2H, NH_2), 6.85–7.00 m (3H, C₆H₄), 7.21 t.d (1H, C₆H₄, J7.5, 1.7 Hz). ¹³C NMR spectrum, δ, ppm: 13.4 (CH₃), 19.5 (CH₃), 27.2 (CH₃), 27.8 (CH₃), 28.7 (CH₂), 31.6 (CMe₂), 39.3 (CH₂), 40.1 (CH₂), 46.1 (C_{spiro}), 49.9 (CH₂), 57.6 (<u>CCN</u>), 107.6 (CH), 110.8, 116.4, 121.5 (CH), 122.4 (CH), 127.7 (CH), 133.4, 142.8, 158.4, 163.1, 175.6, 193.3. Found, %: C 70.33; H 6.28; N 10.95. C₂₃H₂₅N₃O₃. Calculated, %: C 70.57; H 6.44; N 10.73.

2-Amino-1'-benzyl-7,7-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (5f). Yield 5.4 g (64%), mp 248–247°C, R_f 0.80. IR spectrum, v, cm⁻¹: 3380, 3320, 3206 (NH₂), 2197 (CN), 1714, 1680, 1660 (C=O), 1601 (C=C). ¹H NMR spectrum, δ , ppm: 1.10 s (3H, CH₃), 1.15 s (3H, CH₃), 2.14 d (1H, CH₂, *J* 15.9 Hz), 2.24 d (1H, CH₂, *J* 15.9 Hz), 2.57 d (1H, CH₂, *J* 17.5 Hz), 2.66 d (1H, CH₂, *J* 17.5 Hz), 4.90 d (1H, NCH₂, *J* 16.2 Hz), 4.97 d (1H, NCH₂, *J* 16.2 Hz), 6.59 d (1H_{arom}, *J* 7.7 Hz), 6.91–7.12 m (3H_{arom}), 6.96 br.s (2H, NH₂), 7.20–7.34 m (3H_{arom}), 7.44–7.49 m (2H_{arom}). ¹³C NMR spectrum, δ , ppm: 27.2 (CH₃), 27.8 (CH₃), 31.6 (<u>C</u>Me₂), 40.1 (CH₂), 43.4 (CH₂),

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46.3 (C_{spiro}), 49.8 (CH₂), 57.4 (<u>C</u>CN), 108.5 (CH), 110.8, 116.8, 121.9 (CH), 122.3 (CH), 126.5 (CH), 126.6 (2CH), 127.6 (CH), 127.9 (2CH), 133.2, 135.6, 142.4, 158.5, 163.4, 176.1, 193.6. Found, %: C 73.44; H 5.41; N 9.84. C₂₆H₂₃N₃O₃. Calculated, %: C 73.39; H 5.45; N 9.88.

2'-Amino-1-methyl-2-oxospiro(indoline-3,4'pyrano[3,2-*h***]quinoline)-3'-carbonitrile (6a).** Yield 4.6 g (65%), mp 355–357°C, R_f 0.64. IR spectrum, v, cm⁻¹: 3416, 3301 (NH₂), 2192 (CN), 1720, 1660 (C=O), 1600 (C=C). ¹H NMR spectrum, δ , ppm: 3.30 s (3H, NCH₃), 6.59 d (1H, C₆H₂, *J* 8.6 Hz), 7.05–7.15 m (3H, C₆H₄), 7.20 br.s (2H, NH₂), 7.38 t.d (1H, C₆H₄, *J* 7.6, 1.6 Hz), 7.48 d (1H, C₆H₂, *J* 8.7 Hz), 7.54 d.d (1H, 8'-H_{quinoline}, *J* 8.3, 4.2 Hz), 8.22 d.d (1H, 7'-H_{quinoline}, *J* 8.3,1.6 Hz), 8.95 d.d (1H, 9'-H_{quinoline}, *J* 4.2, 1.6 Hz). Found, %: C 71.21; H 3.87; N 15.65. C₂₁ H₁₄N₄O₂. Calculated, %: C 71.18; H 3.98; N 15.81.

2'-Amino-1-ethyl-2-oxospiro(indoline-3,4'pyrano[3,2-*h***]quinoline)-3'-carbonitrile (6b).** Yield 4.5 g (61%), mp 318–321°C, $R_{\rm f}$ 0.61. IR spectrum, v, cm⁻¹: 3408, 3122 (NH₂), 2192 (CN), 1699, 1652 (C=O), 1620 (C=C). ¹H NMR spectrum, δ , ppm: 1.30 t (3H, CH₃, *J* 7.1 Hz), 3.76–3.89 m (2H, CH₂), 6.57 d (1H_{arom}, *J* 8.7 Hz), 7.04–7.15 m (3H_{arom}), 7.27 br.s (2H, NH₂), 7.37 t.d (1H, C₆H₄, *J* 7.6, 1.4 Hz), 7.52 d (1H_{arom}, *J* 8.7 Hz), 7.58 d.d (1H_{quinoline}, *J* 8.3, 4.2 Hz), 8.26 d.d (1H_{quinoline}, *J* 8.3, 1.6 Hz), 8.97 d.d (1H_{quinoline}, *J* 4.2, 1.6 Hz). Found, %: C 71.61; H 4.16; N 15.05. C₂₂H₁₆N₄O₂. Calculated, %: C 71.73; H 4.38; N 15.21.

2'-Amino-1-propyl-2-oxospiro(indoline-3,4'pyrano[3,2-h]quinoline)-3'-carbonitrile (6c). Yield 4.9 g (64%), mp 316-318°C, R_f 0.68. IR spectrum, v, cm⁻¹: 3321, 3194 (NH₂), 2192 (CN), 1716, 1660 (C=O), 1608 (C=C). ¹H NMR spectrum, δ, ppm: 1.00 t (3H, CH₃, J7.4 Hz), 1.71–1.84 m (2H, CH₂CH₃), 3.66–3.83 m (2H, NCH₂), 6.58 d (1H, 5'-H_{quinoline}, J 8.6 Hz), 7.03-7.16 m (3H_{arom}), 7.19 br.s (2H, NH₂), 7.35 t.d (1H, C₆H₄, J 7.6, 1.5 Hz), 7.48 d (1H, 6'-H_{quinoline}, J 8.6 Hz), 7.54 d.d (1H, 8'-H_{auinoline}, J 8.2, 4.2 Hz), 8.21 d.d (1H, 7'-H_{auinoline}, J 8.2, 1.5 Hz), 8.95 d.d (1H, 9'-H_{quinoline}, J 4.2, 1.5 Hz). ¹³C NMR spectrum, δ, ppm: 10.9, 20,2, 41.2, 50.4, 54.3, 108.5, 117.6, 118.5, 121.9, 122.7, 123.4, 123.6, 124.7, 128.1, 128.9, 133.7, 135.5, 137.6, 142.5, 144.2, 149.7, 161.0, 176.5. Found, %: C 72.16; H 4.65; N 14.40. C₂₃H₁₈N₄O₂. Calculated, %: C 72.24; H 4.74; N 14.65.

2'-Amino-1-butyl-2-oxospiro(indoline-3,4'pyrano[3,2-*h*]quinoline)-3'-carbonitrile \cdot C₂H₅OH (6d). Yield 6.2 g (70%), mp 316–318°C, $R_{\rm f}$ 0.72. IR spectrum, v, cm⁻¹: 3360 (EtOH), 3288, 3149 (NH₂), 2193 (CN), 1702, 1684, 1668 (C=O), 1603 (C=C). ¹H NMR spectrum, δ, ppm: 0.99 t (3H, CH₃, J7.3 Hz), 1.10 t (3H, CH₃, J7.0 Hz), 1.38–1.50 m (2H, CH₂CH₃), 1.65–1.78 m (2H, CH₂C₂H₅), 3.41–3.51 m (2H), 3.68–3.89 m (3H, NCH₂, OCH₂, OH), 6.57 d (1H_{arom}, J 8.7 Hz), 7.03-7.16 m (3H, C₆H₄), 7.16 br.s (2H, NH₂), 7.35 t.d (1H, C₆H₄, J 7.6, 1.2 Hz), 7.47 d (1H_{arom}, J 8.7 Hz), 7.53 d.d (1H, 8'-H_{auinoline}, J 8.3, 4.2 Hz), 8.20 d.d (1H, 7'-H_{auinoline}, J 8.3, 1.6 Hz), 8.95 d.d (1H, 9'-H_{auinoline}, J 4.2, 1.6 Hz). ¹³C NMR spectrum, δ, ppm: 13.3, 18.1, 19.4, 28.9, 39.3, 50.3, 54.3, 56.0, 108.3, 117.5, 118.4, 121.8, 122.6, 123.3, 123.5, 124.7, 128.0, 128.8, 133.8, 135.3, 135.4, 137.7, 142.5, 144.2, 149.6, 161.0, 176.3. Found, %: C 72.58; H 5.31; N 14.29. C₂₄H₂₀N₄O₂. Calculated, %: C 72.71; H 5.08; N14.13.

2'-Amino-1-benzyl-2-oxospiro(indoline-3,4'pyrano[3,2-*h***]quinoline)-3'-carbonitrile (6e).** Yield 5.5 g (69%), mp 333–335°C, R_f 0.66. IR spectrum, v, cm⁻¹: 3321, 3178 (NH₂), 2192 (CN), 1696, 1656 (C=O), 1608 (C=C). ¹H NMR spectrum, δ , ppm: 4.95 and 5.04 d (1H and 1H, CH₂, *J* 15.7 Hz), 6.59 d (1H, 5'/6'-H_{quinoline}, *J* 8.6 Hz), 6.93 br.d (1H, 7-H_{isatine}, *J* 7.8 Hz), 7.05 d.d.d (1H, 5-H_{isatine}, *J* 7.8, 7.4, 0.7 Hz), 7.16 d.d (1H, 4-H_{isatine}, *J* 7.4, 1.2 Hz), 7.22–7.41 m (8H, H_{arom}, NH₂, C₆H₅), 7.49 d (1H, 5'/6'-H_{quinoline}, *J* 8.6 Hz), 7.55 d.d (1H, 8'-H_{quinoline}, *J* 8.3, 4.2 Hz), 8.23 d.d (1H, 7'-H_{quinoline}, *J* 8.3,1.7 Hz), 8.97 d.d (1H, 9'-H_{quinoline}, *J* 4.2, 1.7 Hz). Found, %: C 75.50; H 4.13; N 13.34. C₂₇H₁₈N₄O₂. Calculated, %: C 75.34; H 4.21; N 13.02.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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