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Synthesis of substituted [1,2,4]oxadiazino[2,3-*a*]indole-7,8-dicarbonitriles

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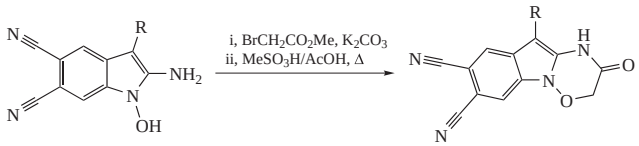
10-Aryl-2-oxo-2,3-dihydro-1*H*-[1,2,4]oxadiazino[2,3-*a*]indole-7,8-dicarbonitriles were obtained in two steps from the corresponding 2-amino-1-hydroxyindoles and methyl bromoacetate.

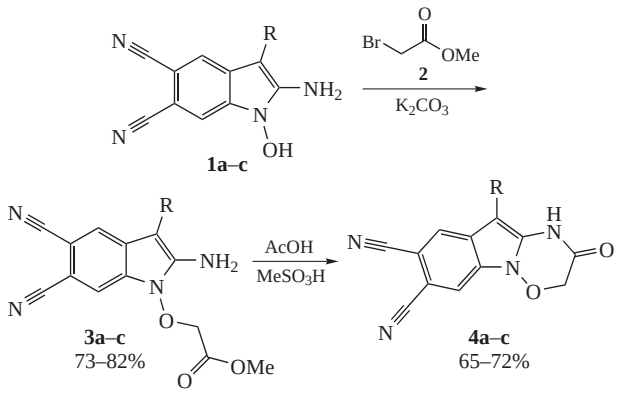


Until now, only several syntheses of 2-amino-1-hydroxyindoles have been reported,[1–4] while the data on the preparation of the fused heterocyclic systems on their basis are absent. Fused indole systems,[5–7] not uncommon in natural products and alkaloids, are among priorities for chemists.[8,9] Obviously, cyclization of 2-amino-1-hydroxyindoles to some other heterocyclic systems by analogy with *o*-aminophenols is of synthetic interest. As substituted 1-hydroxyindole-5,6-dicarbonitriles are known to be inhibitors of mono-aminooxidase at submicromolecular concentrations,[10] we reasoned that 2-amino-1-hydroxyindole-5,6-dicarbonitriles **1a–c**[3] (Scheme 1) can be used as starting materials for novel fused indole systems.

The aim of this work was the synthesis of new substituted [1,2,4]oxadiazino[2,3-*a*]indoles. [1,2,4]Oxadiazines exhibit various biological activities[11,12] and are usually obtained by [3+3] cyclocondensation from amidoxime deivatives[13,14] or from α-bromohydroxamates with isoquinoline *N*-oxides[15] or nitrones.[16]

Herein, we describe the two-step preparation of new substituted 2,3-dihydro-1*H*-[1,2,4]oxadiazino[2,3-*a*]indole-7,8-dicarbonitriles **4a–c** (see Scheme 1).

In the first step, alkylation of 2-amino-1-hydroxyindoles **1a–c** with methyl ester of bromoacetate **2** in the presence of potassium carbonate at 40–50 °C afforded 1-O-derivatives **3a–c** in up to 82% yields.† The chemoselectivity at this step is due to high acidity of hydroxy group in compounds **1** (*cf.* refs. 17, 18). In the second step, the intramolecular amidation of amino esters **3a–c** catalyzed by 20 mol% of $MeSO_3H$ in acetic acid at 100 °C



Scheme 1

† IR spectra were measured on a Perkin-Elmer RX-1 spectrometer in the range of 700–4000 cm^{-1} using suspensions of substances in Vaseline oil. Mass spectra were obtained using a FINNIGAN MAT INCOS 50 mass spectrometer; the ionization energy was 70 eV. NMR spectra were recorded on Bruker DRX-500 and DRX-300 instruments at 30 °C for solutions in DMSO-d_6. Signals of residual protons of the solvent in ^{1}H NMR spectra (δ_H 2.50) or the signal of DMSO-d_6 in ^{13}C spectra (δ_C 39.5) were used as references. Elemental analysis was carried out on a Perkin Elmer 2400 instrument.

Compounds **3a–c** *(general procedure).* Methyl bromoacetate **2** (3 mmol) and K_2CO_3 (4 mmol) were added to a solution of compound **1a–c** (1 mmol) in DMF (5 ml) and the mixture was agitated at 40–50 °C. Then the mixture was cooled, diluted with cold water (5 ml), the crystal sediment of the product **3a–c** was filtered off and dried in air.

*Methyl [(2-amino-5,6-dicyano-3-phenyl-1*H*-indol-1-yl)oxy]acetate* **3a**. Yield 263 mg (76%), mp 192–194 °C. IR (ν/cm^{-1}): 3320, 1637 (NH_2), 2221 (CN), 1731 (C=O), 1610, 1510 (Ar), 1225, 1043 (C–O). ^{1}H NMR (DMSO-d_6) δ: 3.77 (s, 3H, OMe), 5.11 (s, 2H, CH_2), 7.02 (s, 2H, NH_2), 7.28 (t, 1H, H-4′, *J* 7.7 Hz), 7.46 (t, 2H, H-3′, H-5′, *J* 7.7 Hz), 7.55 (d, 2H, H-2′, H-6′, *J* 7.7 Hz), 7.86 (s, 1H, H-4), 8.07 (s, 1H, H-7). ^{13}C NMR (DMSO-d_6) δ: 52.1, 74.0, 90.5, 105.9, 112.4, 117.6, 119.4, 120.2, 125.6, 126.0, 127.3, 127.6 (2C), 128.86, 128.9 (2C), 132.3, 145.7, 168.3. MS, *m*/*z* (%): 346 $[M]^+$ (8), 273 (13), 258 (100), 230 (25), 202 (11), 176 (12). Found (%): C, 65.62; H, 4.05; N, 16.15. Calc. for $C_{19}H_{14}N_4O_3$ (%): C, 65.89; H, 4.07; N, 16.18.

*Methyl {[2-amino-5,6-dicyano-3-(4-methylphenyl)-1*H*-indol-1-yl]oxy}-acetate* **3b**. Yield 295 mg (82%), mp 200–201 °C. IR (ν/cm^{-1}): 3355, 1638 (NH_2), 2217 (CN), 1742 (C=O), 1610 (Ar), 1216, 1040 (C–O). ^{1}H NMR (DMSO-d_6) δ: 2.34 (s, 3H, Me), 3.77 (s, 3H, OMe), 5.10 (s, 2H, CH_2), 6.94 (s, 2H, NH_2), 7.26 (d, 2H, H-3′, H-5′, *J* 7.9 Hz), 7.40 (d, 2H, H-2′, H-6′, *J* 7.9 Hz), 7.82 (s, 1H, H-4), 8.05 (s, 1H, H-7). MS, *m*/*z* (%): 360 $[M]^+$ (3), 287 (25), 272 (100), 256 (17). Found (%): C, 66.39; H, 4.47; N, 15.52. Calc. for $C_{20}H_{16}N_4O_3$ (%): C, 66.66; H, 4.48; N, 15.55.

*Methyl {[2-amino-3-(4-chlorophenyl)-5,6-dicyano-1*H*-indol-1-yl]oxy}-acetate* **3c**. Yield 278 mg (73 %), mp 207–209 °C. IR (ν/cm^{-1}): 3347, 1639 (NH_2), 2226 (CN), 1745 (C=O), 1611, 1513 (Ar), 1220, 1037 (C–O). ^{1}H NMR (DMSO-d_6) δ: 3.77 (s, 3H, OMe), 5.10 (s, 2H, CH_2), 7.08 (s, 2H, NH_2), 7.48 (d, 2H, H-3′, H-5′, *J* 8.3 Hz), 7.53 (d, 2H, H-2′, H-6′, *J* 8.3 Hz), 7.88 (s, 1H, H-4), 8.07 (s, 1H, H-7). MS, *m*/*z* (%): 382 $[M]^+$ (4), 380 $[M]^+$ (12), 366 (10), 307 (20), 294 (33), 292 (100), 256 (54). Found (%): C, 59.68; H, 3.43; N, 14.69. Calc. for $C_{19}H_{13}ClN_4O_3$ (%): C, 59.93; H, 3.44; N, 14.71.

for 0.5 – 1 h brought about the target heterocyclic compounds **4a**–**c** in up to 72% yields.‡ The choice of $MeSO_3H$ as the catalyst was traditional as it is often used for the preparation of fused systems.[19,20]

The structures of compounds **3a**–**c** and **4a**–**c** were determined by NMR spectroscopy and mass spectrometry data. The mass spectra contain molecular ions, and their further fragmentation is in accordance with the structures. In the ^{1}H NMR spectra, signals of methylene group at 5.10–5.11 ppm for esters **3a**–**c** and 5.15–5.16 ppm for final products **4a**–**c** are observed. Compounds **4a**–**c** manifest characteristic signals of amide proton at 12.04–12.13 ppm and closely located singlets of H-6 and H-9 protons (8.15–8.24 ppm), and their ^{13}C NMR spectra contain signals of carbonyl (164–168 ppm) and methylene (72–74 ppm) groups. The HMBC data of compound **4a** corroborate its structure.

In summary, by the example of obtaining 2,3-dihydro-1*H*-[1,2,4]oxadiazino[2,3-*a*]indole-7,8-dicarbonitriles we have demonstrated that 2-amino-1-hydroxyindoles can be good candidates to access a variety of fused heterocyclic systems.

‡ *[1,2,4]Oxadiazino[2,3-*a*]indole-7,8-dicarbonitriles* **4a**–**c** *(general procedure)*. Methanesulfonic acid (0.2 mmol) was added to a solution of ester **3a**–**c** (1 mmol) in acetic acid (3 ml), and the mixture was agitated at 100 °C for 0.5–1 h. Then the mixture was cooled, the crystal sediment was filtered off, thoroughly washed with water, and dried in air.

*2-Oxo-10-phenyl-2,3-dihydro-1*H*-[1,2,4]oxadiazino[2,3-*a*]indole-7,8-dicarbonitrile* **4a**. Yield 226 mg (72%), mp 239–240 °C. IR (ν/cm^{-1}): 3176 (NH), 2218 (CN), 1709 (C=O), 1568 (Ar), 1227 (C–O). ^{1}H NMR (DMSO-d_6) δ: 5.16 (s, 2H, CH_2), 7.39 (t, 1H, H-4′, J 7.5 Hz), 7.51 (t, 2H, H-3′, H-5′, J 7.5 Hz), 7.56 (d, 2H, H-2′, H-6′, J 7.5 Hz), 8.19 (s, 1H, H-4), 8.24 (s, 1H, H-7), 12.10 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 72.4 (3), 96.3 (C-10), 104.4 (C-7), 105.6 (C-8), 114.2 (C-6), 117.5 (CN), 117.6 (CN), 124.8 (C-5a), 125.0 (C-9), 127.5 (C-4′), 128.3 (C-9a), 129.3 (C-2′, C-3′, C-5′, C-6′), 129.9 (C-1′), 134.3 (C-11), 164.5 (C=O). MS, *m*/*z* (%): 314 $[M]^+$ (100), 284 (41), 271 (18), 256 (41), 230 (18), 201 (20). Found (%): C, 68.52; H, 3.19; N, 17.79. Calc. for $C_{18}H_{10}N_4O_2$ (%): C, 68.79; H, 3.21; N, 17.83.

*2-Oxo-10-*p*-tolyl-2,3-dihydro-1*H*-[1,2,4]oxadiazino[2,3-*a*]indole-7,8-dicarbonitrile* **4b**. Yield 226 mg (69%), mp 249–250 °C. IR (ν/cm^{-1}): 3172 (NH), 2230 (CN), 1709 (C=O), 1580 (Ar), 1221 (C–O). ^{1}H NMR (DMSO-d_6) δ: 2.38 (s, 3H, Me), 5.15 (s, 2H, CH_2), 7.32 (d, 2H, H-3′, H-5′, J 7.8 Hz), 7.44 (d, 2H, H-2′, H-6′, J 7.8 Hz), 8.15 (s, 1H, H-4), 8.22 (s, 1H, H-7), 12.04 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 20.8, 72.4, 96.3, 104.3, 105.4, 114.1, 117.1, 117.2, 124.4, 124.5, 126.4, 127.8, 128.8 (2C), 129.5 (2C), 133.7, 136.4, 164.0. MS, *m*/*z* (%): 328 $[M]^+$ (100), 298 (29), 271 (14), 269 (18), 255 (18). Found (%): C, 69.21; H, 3.66; N, 17.04. Calc. for $C_{19}H_{12}N_4O_2$ (%): C, 69.51; H, 3.68; N, 17.06.

*10-(4-Chlorophenyl)-2-oxo-2,3-dihydro-1*H*-[1,2,4]oxadiazino[2,3-*a*]indole-7,8-dicarbonitrile* **4c**. Yield 226 mg (65%), mp 253–254 °C. IR (ν/cm^{-1}): 3167 (NH), 2233 (CN), 1704 (C=O), 1578 (Ar), 1222 (C–O). ^{1}H NMR (DMSO-d_6) δ: 5.16 (s, 2H, CH_2), 7.53 (d, 2H, H-3′, H-5′, J 8.7 Hz), 7.57 (d, 2H, H-2′, H-6′, J 8.7 Hz), 8.19 (s, 1H, H-4), 8.22 (s, 1H, H-7), 12.13 (br. s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 72.3, 95.0, 104.5, 105.6, 114.1, 117.0, 117.1, 124.1, 124.4, 127.7, 128.3, 128.8 (2C), 130.7 (2C), 131.6, 134.0, 163.9. MS, *m*/*z* (%): 350 $[M]^+$ (11), 348 $[M]^+$ (27), 283 (29), 252 (100), 201 (32), 111 (16), 75 (23). Found (%): C, 61.76; H, 2.58; N, 16.04. Calc. for $C_{18}H_9ClN_4O_2$ (%): C, 61.99; H, 2.60; N, 16.07.

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