Electronic supplementary materials *Mendeleev Commun.*, 2014, **24**, 260−261

Syntheses of spiroindole melatonin analogues *via* 2-(indolin-3-ylidene)acetonitrile cycloadditions

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The melting points were determined on an Electrothermal 9100 melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded at 400.13 MHz on a Bruker Avance 400 spectrometer. The chemical shifts (δ) are given in ppm using TMS as the internal standard. The coupling constants (*J*) are given in Hz. The IR spectra were measured in Nujol mulls on a Specord UR-20 spectrometer.

The course of the reactions and the purity of the products were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates with EtOAc as the eluent. Liquid chromatography was carried out on Merck silica gel (40/60). The mass spectra (MS) were obtained with a Finnigan MAT INCOSSO spectrometer (EI, 70 eV) and microTOF II (ESI).

Isatins **1a** and **1b** were synthesized according to the literature procedure;[1] isatin **1c** was prepared according to a known procedure.[2] Knoevenagel condensation products **4a-c** were synthesized according to the methods described respectively: **4a**,[3] **4b**,[4] **4c**.[5] Nitriles **2a** and **2b** were prepared according to the literature procedure.[3]

*Synthesis of 2'-oxo-1',2'-dihydrospiro[cyclopropane-1,3'-indole]-2-carbonitrile (**3a**)*

Diazomethane was synthesized starting from *N*-nitrosomethylurea (1.16 g, 0.013 mol) and potassium hydroxide (2.24 g, 0.04 mol) in water (6 ml) and diethyl ether (18 ml). A solution of thus obtained diazomethane was added to **2a** (0.25 g, 0.0015 mol), and the mixture was stirred at room temperature for 5 h, after which the discoloration of the mixture was observed. Then the mixture was concentrated, dissolved in toluene (10 ml), refluxed for 8 h, cooled, concentrated, and washed with diethyl ether. Light-yellow product **3a** was obtained as an isomeric mixture (5 : 2 according to ^{1}H NMR); the yield 0.23 g (90%) mp 156-157 °C.

^{1}H NMR (400.13 MHz, DMSO-d_6): 1.88* (m, 1H), 1.92** (dd, J = 5.0, 9.6, 1H), 2.13* (dd, J = 4.8, 9.4, 1H), 2.19** (dd, J = 5.1, 6.8, 1H), 2.63** (dd, J = 2.0, 7.4, 1H), 2.94* (dd, J = 2.0, 7.8, 1H), 6.94* (d, J = 7.8, 1H), 6.97** (d, J = 7.8, 1H), 7.04** (t, J = 7.6, 1H), 7.10** (d, J = 7.6,

1H), 7.16* (d, J = 7.1, 1H), 7.20-7.24* (m, 2H), 7.28**(t, J = 7.3, 1H), 10.82* (s, 1H), 10.87** (s, 1H). **, major isomer; *, minor isomer.

*Synthesis of 5'-methoxy-2'-oxo-1',2'-dihydrospiro[cyclopropane-1,3'-indole]-2-carbonitrile (**3b**)*

Diazomethane was synthesized starting from N-nitrosomethylurea (1.16 g, 0.013 mol) and potassium hydroxide (2.24 g, 0.04 mol) in water (6 ml) and diethyl ether (18 ml). A solution of diazomethane was added to **2b** (0.25 g. 0.0012 mol), and the mixture was stirred at room temperature for 5 h, after which the discoloration of the mixture was observed. Then the mixture was concentrated, dissolved in toluene (10 ml), refluxed for 8 h, cooled, concentrated, and washed with diethyl ether. White product **3b** was obtained as an isomeric mixture (3 : 1 according to ^{1}H NMR); the yield 0.222 g (83%) mp 181-182 ^{o}C.

^{1}H NMR (400.13 MHz, DMSO-d_6): 1.95* (dd, J = 4.8, 7.6, 1H), 2.00** (dd, J = 4.5, 9.6, 1H), 2.09** (dd, J = 2.0, 4.8, 1H), 2.16* (dd, J = 4.5, 4.8, 1H), 2.51** (dd, J = 2.6, 7.0, 1H), 2.73* (dd, J = 1.8, 9.1, 1H), 3.72* (s, 3H), 3.76**(s, 3H), 6.75* (d, J = 2.5, 1H), 6.80-6.82* (m, 1H), 6.83** (d, J = 2.5, 1H), 6.87** (dd, J = 2.5, 8.3, 1H), 6.95** (d, J = 3.8, 1H), 6.97* (s, 1H), 9.66 (s, 1,1H). **, major isomer; *, minor isomer.

IR (cm^{-1}): 1700 (C(O)NH), 2270 (CN), 3200-3250 (C(O)NH).

Analyses, found (%): C 67.35, H 4.82, N 13.15, calculated for $C_{12}H_{10}N_2O_2$ (%): C 67.28, H 4.71, N 13.08.

Diels-Alder synthesis of **5** *and* **9**

General procedure

Method A. A solution of dienophile **4** in an appropriate solvent and 5 equivalents of diene were refluxed for 2 h. Then the mixture was concentrated, and the product was recrystallized from isopropanol.

Method B. A mixture of dienophile **4** in anhydrous acetonitrile, 5 equivalents of diene, and 0.1 equivalent of ZnI_2 were refluxed for 2 h. Then the precipitate was filtered off, washed with water, and recrystallized from isopropanol.

*3-Cyano-2'-oxo-1',2'-dihydrospiro{bicyclo[2.2.1]hept-5-ene-2,3'-indole}-3-carboxylic acid (**5a**).*

Method A. The reaction of **4a** (3 g, 0.014 mol), cyclopentadiene (5 ml, 0.06 mol), and ZnI_2 (0.3 g) in acetonitrile (20 ml) gave a white product as an isomeric mixture (10 : 1 according to ^{1}H NMR); the yield 3.25 g (83%).

^{1}H NMR (400.13 MHz, DMSO-d_6, major isomer): 1.86 (d, J = 9.1, 1H); 2.54 (d, J = 9.4, 1H); 3.02 (s, 1H); 3.74 (s, 1H); 6.44 (m, 1H); 6.68 (m, 1H); 7.13 (d, J = 7.3, 1H); 7.27 (t, J = 7.3, 1 H); 7.52 (t, J = 7.6, 1H); 7.77 (d, J = 7.3, 1H); 10.84 (s, 1H).

^{13}C NMR (400.13 MHz, DMSO-d_6, major isomer): 46.85, 52.43, 54.79, 59.86, 60.24, 109.91, 120.29, 121.73, 125.84, 129.41, 129.94, 135.66, 136.64, 142.46, 167.07, 175.72.

IR (cm^{-1}): 1680 (NHC(O)), 1740 (C(O)OH), 2250 (CN), 3370 (NH).

Analyses, found (%): C 68.29; H 4.39; N 9.98; calculated for $C_{16}H_{12}N_2O_3$ (%): C 68.56; H 4.32; N 9.99.

*3-Cyano-5'-nitro-2'-oxo-1',2'-dihydrospiro{bicyclo[2.2.1]-hept-5-ene-2,3'-indole}-3-carboxylic acid (**5c**)*

Method A. The reaction of **4c** (2 g, 7.72 mmol) and cyclopentadiene (3.4 ml, 0.04 mol) in ethanol (20 ml) gave dark-orange product **5c**; the yield 1.5 g (61%).

Method B. The reaction of **4c** (3 g, 0.012 mol), cyclopentadiene (5.1 ml, 0.06 mol), and ZnI_2 (0.3 g) in acetonitrile (20 ml) gave dark-orange product **5c**; the yield 2.5 g (67%).

^{1}H NMR (400.13 MHz, DMSO-d_6): 1.83 (d, J = 9.7, 1H); 2.92 (d, J = 9.4, 1H); 3.37 (s, 1H); 3.83 (s, 1H); 6.67 (dd, J = 3.1, 4.8, 1H); 7.12 (dd, J = 3.0, 4.8, 1H), 7.30 (d, J= 8.6, 1H), 7.89 (d, J= 2.1 H), 8.44 (dd, J = 2.0, 8.8, 1H), 11.79 (s, 1H).

^{13}C NMR (400.13 MHz, DMSO-d_6): 39.84, 40.05, 46.85, 52.43, 54.80, 109.91, 120.27, 121.73, 125.84, 129.41, 129.93, 135.65, 136.64, 142.46, 167.08, 175.72.

IR (cm^{-1}): 1340, 1520 (NO_2), 1640 (NHC(O)), 1720 (C(O)OH), 2250 (CN), 3270 (NH).

ESI HRMS: 326.0764 (M+H, δ=0.21 p.m., calculated 326.0771), 348.0605 (M+Na, δ=0,4 p.m., calculated 348.0591).

*Synthesis of 2-Cyano-4,5-dimethyl-2'-oxo-1',2'-dihydrospiro[cyclohex-4-ene-1,3'-indole]-2-carboxylic acid (**8a**).*

Method A. The reaction of **4a** (3 g, 0.014 mol), 2,3-dimethylbutadiene (4.8 g, 0.06 mol), and ethanol (20 ml) gave light-beige product **8a**; the yield 3.1 g (75%).

^{1}H NMR (400.13 MHz, DMSO-d_6): 1.64 (s, 3H); 1.72 (s, 3H); 2.12 (d, J = 17.1, 1H,); 2.38 (d, J = 17.7, 1H); 2.58 (d, J = 16.9, 1H); 3.36 (d, J = 16.9, 1H); 6.77 (d, J = 7.5, 1H); 6.91 (t, J = 7.3, 1H); 7.14 (t, J = 7.6, 1H); 7.51 (d, J = 7.6, 1H); 10.28 (s, 1 H).

^{13}C NMR (400.13 MHz, DMSO-d_6): 18.79 (2 CH_3); 36.72; 39.18; 47.30; 50.08; 109.83; 111.19; 119.47; 121.96; 123.50; 129.39; 130.59; 135.79; 142.56; 168.42; 176.71.

IR (cm^{-1}): 1740 (C(O)NH), 1760 (C(O)OH), 2290 (CN).

*2-Cyano-5'-methoxy-4,5-dimethyl-2'-oxo-1',2'-dihydrospiro[cyclohex-4-ene-1,3'-indole]-2-carboxylic acid (**8b**)*

Method A. The reaction of **4b** (1 g, 4.1 mmol) and 2,3-dimethylbutadiene (1.6 g, 0.02 mol) in ethanol (10 ml) gave beige product **8b**; the yield 0.19 g (14%).

Method B. The reaction of **4b** (3.0 g, 0.0123 mol), ZnI_2 (0.3 g), and 2,3-dimethylbutadiene (4.8 g, 0.06 mol) in acetonitrile (10 ml) gave beige product **8b**; the yield 1.8 g (45%).

Analyses, found (%): C 65.11; H 5.64; N 8.39; calculated for $C_{18}H_{18}N_2O_4$* ¼ H_2O (%): C 65.34; H 5.64; N 8.47.

^{1}H NMR (400.13 MHz, DMSO-d_6): 1.63 (s, 3H); 1.71 (s, 3H); 2.13 (d, J = 18.2, 1H,); 2.42 (d, J = 16.6, 1H); 2.52 (d, J = 18.5, 1H); 3.31 (d, J = 16.4, 1H); 3.70 (s, 3H); 6.74 (d, J = 8.3, 1H); 6.82 (dd, J = 2.1, 8.6, 1H), 7.09 (d, J = 2.1, 1H), 10.3 (s, 1 H).

^{13}C NMR (400.13 MHz, acethone-d_6): 18.80 ($2CH_3$); 37.94; 40.29; 48.64; 50.59; 56.03; 110.79; 111.83; 114.17; 119.59; 123.23; 123.53; 132.73; 136.27; 156.44; 168.48; 177.43.

IR (cm^{-1}): 1680 (NHC(O)), 1720 (C(O)OH), 2250 (CN), 3370 (NH).

*2-Cyano-4,5-dimethyl-5'-nitro-2'-oxo-1',2'-dihydrospiro[cyclohex-4-ene-1,3'-indole]-2-carboxylic acid (**8c**).*

Method B. The reaction of **4c** (3 g, 0.012 mol), 2,3-dimethylbuthadiene (4.8 g, 0.06 mol), and ZnI_2 (0.3 g) in acetonitrile (20 ml) gave a light-brown product; the yield 2.0 g (53%). The product was obtained as an isomeric mixture (10 : 1 according to ^{1}H NMR).

^{1}H NMR (400.13 MHz, DMSO-d_6, major isomer): 1.68 (s, 3H); 1.84 (s, 3H); 2.0 (d, J = 17.7, 1H,); 2.74 (d, J = 17.0, 1H); 2.80 (d, J = 18.0, 1H); 2.96 (d, J = 18.2, 1H); 7.05 (d, J = 8.6, 1H); 7.67 (d, J = 2.2, 1H); 8.20 (dd, J = 2.3, 8.8, 1H); 11.42 (s, 1 H).

^{13}C NMR (400.13 MHz, DMSO-d_6, main isomer): 18.27, 18.85, 38.47, 39.20, 48.56, 109.96, 118.23, 119.86, 122.63, 124.23, 126.28, 130.52, 142.17, 149.12, 166.94, 177.95.

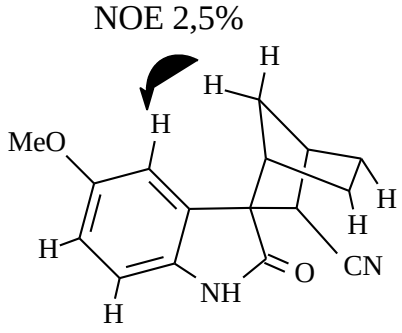

Figure S1 The NOE data for compound **7b.**

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