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One Pot Synthesis of Some New Spiro[3H-Indol-3,5′(4′H)-[1,2,4] Oxadiazol]-2-Ones and Bis[Spiro[3H-Indol-3,5′(4′H)-[1,2,4] Oxadiazol]-2-Ones]

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ONE POT SYNTHESIS OF SOME NEW SPIRO[3*H*-INDOL-3,5´(4´*H*)-[1,2,4] OXADIAZOL]-2-ONES AND BIS[SPIRO[3*H*-INDOL-3,5´(4´*H*)-[1,2,4] OXADIAZOL]-2-ONES]

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Abstract : A facile preparation of the title compound by 1,3-dipolar cycloaddition reaction of benzonitrile oxides with isatin imines or isatin diimines, in excellent yield, are reported.

Systematic investigation of spiro indoles with C-3 as spiro atom is interest due to broad spectrum of biological activities of these compounds. Therefore, it was presumed that these molecules would have enhanced biological activities because they incorporate both indole [1] and oxadiazole moieties.[2,3] Since little attention has been given to the preparation of spiroindoles **4**, we decided to synthesize a series of spiroindole derivatives (**3-5**) and bis spiroindole (**6**) in an one pot procedure.

The spiro skeleton **3** was first reported in 1978 by Franke [4] with no spectroscopic data and characterized only by elemental analyses.

In this work the spiroindoles **3-6** prepared from the reaction of corresponding imines (**1**) or diimines of isatin (**2**) with benzonitrile oxides, [5,6] generated *in situ* from the corresponding oximes, according to the method of the Larsen and torssell.[7] Some of the starting materials have poor solubilities in dichloromethane,

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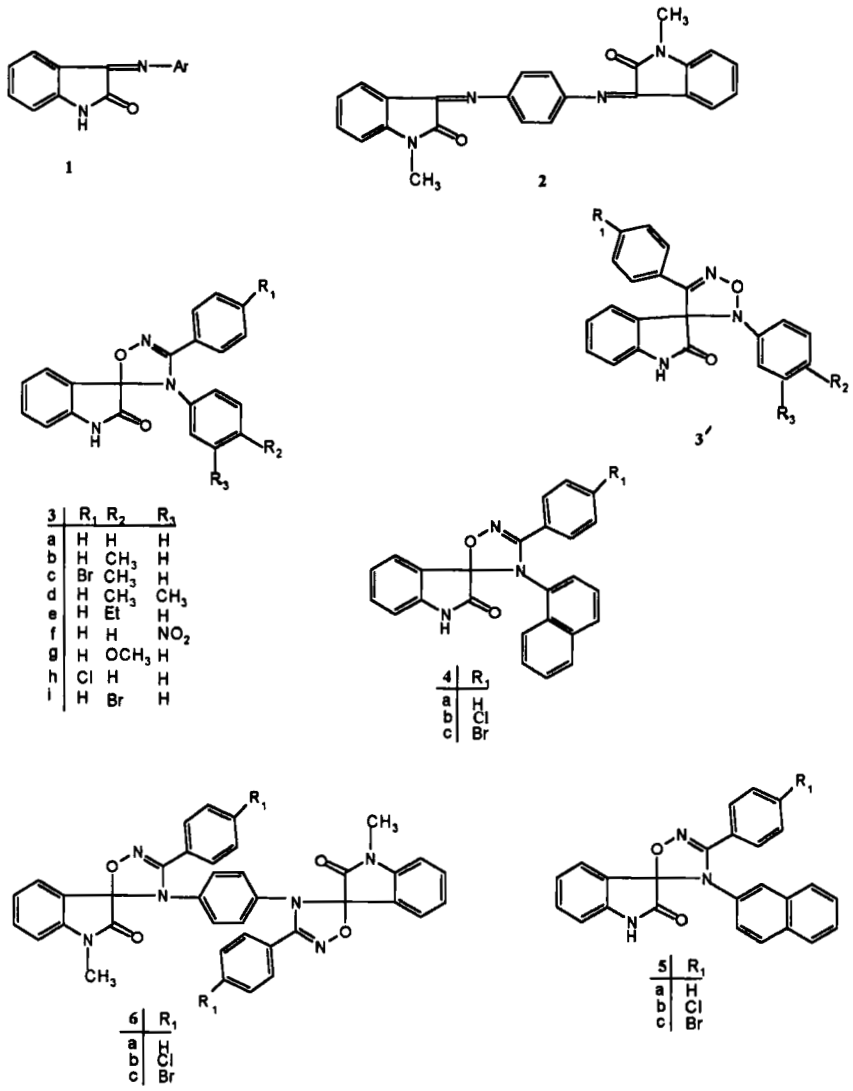

Scheme 1

thus DMSO was used as a co-solvent. The products are obtained in fairly high yields.

Since cycloadducts **6a-c** possess two stereogenic centers, two diasteroisomers are possible, thus two non-separable diastereomers of **6a** were obtained in the

approximate ratio 1:1.5, while products **6b** and **6c** were obtained as a single diastereomer on the basis of ^{1}H NMR and ^{13}C NMR spectroscopic data.

The ir spectra of compounds **3-6** exhibited carbonyl absorption at 1710-1740 cm^{-1} region, a peak at 1675-1690 cm^{-1} which is due to $\nu_{C=N}$ and a band at 3130-3240 cm^{-1} which is assigned to ν_{N-H}.

The carbonyl absorption at about 170-174, imine carbon (C=N) at 155-158 and a signal at 98-99 attributable to the spiro carbon atom in the ^{13}C NMR spectra clearly prove that the adducts (**3-6**) have the proposed structures instead of the other possible structures (**3'**). The ^{1}H NMR and elemental analyses data are in agreement with the proposed structures (see Experimental).

Experimental

Melting points were measured on a Mettler FP5 and are uncorrected. IR spectra were recorded as KBr pellets on a Shimadzu IR-470 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were determined on a Brucker 500 DRX AVANCE instrument at 500 and 125 MHz, respectively. Mass spectra were recorded on a Shimadzu QP 1100 EX equipment. Elemental analyses were performed using a Heraeus CHN-O rapid analyzer.

Imines and diimines of isatin (**1** and **2**) were prepared in quantitative yields according to standard procedures. [8]

General procedure

N-Chlorosuccinimide (NCS, 5 mmol) was stirred in a flask containing dichloromethane (15 ml) and 0.1ml pyridine. The oximes (5 mmol) were added at 20-30 °C in one portion and also after *ca* 10 min, imines (5 mmol) or diimine of isatin (25 mmol, in this case the reaction mixture was heated to *ca* 35 °C) was added similarly. Triethylamine (75 mmol in 5ml CH_2Cl_2) was added dropwise over *ca* 15 min and the temperature raised to 35-40 °C. The reaction mixture was stirred for 15 min and then washed with water (2×20 ml) to remove triethylamine hydrochloride and dried ($CaSO_4$). The red solution was concentrated *in vacuo* and crystals deposited when left in open air. The analytical sample was obtained by recrystallization twice from ethanol/water.

3a:light yellow prisms, Yield 92%, mp 216 °C (lit.,[4] 218-219°C); ν_{max}/cm^{-1} 3200 (N-H), 1720 (C=O), 1690 (C=N); δ_H ($CDCl_3$) 6.7-7.9 (m, 14 H), 8.1 (brs, 1 H, N-H), δ_C ($CDCl_3$) 173.3 (C=O),156.1 (C=N), 111.5-142.0 (18 signals arom), 98.6 (spiro carbon); MS (*m/z*, %) 341 (M^+, 25), 313 (M^+-CO, 50), 195 (M^+-$C_8H_4NO_2$, 100) (Found: C, 73.7; H, 4.5; N, 12.2. $C_{21}H_{15}N_3O_2$ requires C, 73.88; H, 4.43; N, 12.31%)

3b : Yellow prisms, Yield 90%, mp 183 °C; ν_{max}/cm^{-1} 3216 (N-H), 1725 (C=O), 1690 (C=N); δ_H ($CDCl_3$) 2.1 (s, 3 H, CH_3), 6.6-7.5 (m, 13 H), 8.7 (brs, 1 H, N-H), δ_C ($CDCl_3$) 174.0 (C=O), 156.3 (C=N), 111.8-142.2 (18 signals arom), 98.8 (spiro carbon), 21.4 (CH_3); MS (*m/z*, %) 355 (M^+, 10), 327 (M^+-CO, 10), 209 (M^+-$C_8H_4NO_2$, 100) (Found: C, 74.4; H, 4.7; N, 11.9. $C_{22}H_{17}N_3O_2$ requires C, 74.35; H, 4.82; N, 11.82%).

3c : Yellow needles, Yield 85%, mp 105 °C; ν_{max}/cm^{-1} 3205 (N-H), 1725 (C=O), 1685 (C=N); δ_H ($CDCl_3$) 2.2 (s, 3 H, CH_3), 6.7-8.6 (m, 12 H), 11.4 (s, 1 H, N-H), δ_C ($CDCl_3$) 174.0 (C=O),156.2 (C=N), 111.6-143.1 (18 signals arom), 98.6 (spiro carbon), 21.2 (CH_3); MS (*m/z*, %) 433 (M^+, 10),435 (M^++2, 10) 405 (M^+-CO, 10), 287 (M^+-$C_8H_4NO_2$, 10), 209 (M^+-$C_8H_4NO_2Br$, 100) (Found: C, 60.8; H, 3.9; N, 9.7. $C_{21}H_{15}N_3O_2Br$ requires C, 60.84; H, 3.71; N, 9.67%).

3d : light yellow prisms, Yield 90%, mp 155 °C; ν_{max}/cm^{-1} 3248 (N-H), 1715 (C=O), 1680 (C=N); δ_H ($CDCl_3$) 1.9 (s, 3 H, CH_3), 2.1 (s, 3 H, CH_3), 6.4-7.2 (m, 12 H), 8.1 (s, 1 H, N-H), δ_C ($CDCl_3$) 173.9 (C=O), 157.0 (C=N), 112.1-143.1 (18 signals arom), 98.7 (spiro carbon), 21.2 (CH_3), 20.7 (CH_3); MS (*m/z*, %) 369 (M^+, 25), 341 (M^+-CO, 100), 223 (M^+-$C_8H_4NO_2$, 75) (Found: C, 74.8; H, 5.3; N, 11.4. $C_{23}H_{19}N_3O_2$ requires C, 74.78; H, 5.18; N, 11.37%).

3e : light yellow prisms, Yield 87%, mp 75 °C; ν_{max}/cm^{-1} 3242 (N-H), 1720 (C=O), 1690 (C=N); δ_H ($CDCl_3$) 0.99 (t, 3 H, CH_3), 2.4 (q, 2 H, CH_2) 6.6-7.5 (m, 13 H), 8.9 (s, 1 H, N-H), δ_C ($CDCl_3$) 174.2 (C=O), 156.3 (C=N), 112.1-143.4 (18 signals arom), 98.9 (spiro carbon), 28.5 (CH_2), 15.3 (CH_3); MS (*m/z*, %) 369 (M^+, 10), 341 (M^+-CO, 90), 223 (M^+-$C_8H_4NO_2$, 75) (Found: C, 74.7; H, 5.3; N, 11.4. $C_{23}H_{19}N_3O_2$ requires C, 74.78; H, 5.18; N, 11.37%).

3f : light yellow prisms, Yield 90%, mp 170 °C; ν_{max}/cm^{-1} 3150 (N-H), 1730 (C=O), 1690 (C=N); δ_H ($CDCl_3$) 6.6-7.8 (m, 13 H), 8.5 (s, 1 H, N-H), δ_C ($CDCl_3$) 172.9 (C=O), 155.4 (C=N), 112.2-148.7 (18 signals arom), 98.6 (spiro carbon); MS (*m/z*, %) 386 (M^+, 10), 358 (M^+-CO, 60), 240 (M^+-$C_8H_4NO_2$, 40), 195 (M^+-$C_8H_4N_2O_4$, 100) (Found: C, 65.1; H, 3.7; N, 14.4. $C_{21}H_{14}N_4O_4$ requires C, 65.28; H, 3.56; N, 14.50%).

3g : light yellow prisms, Yield 80%, mp 127 °C; ν_{max}/cm^{-1} 3240 (N-H), 1727 (C=O), 1685 (C=N); δ_H ($CDCl_3$) 3.6 (s, 3 H, OCH_3), 6.6-7.8 (m, 13 H), 8.7 (s, 1 H, N-H), δ_C ($CDCl_3$) 174.1 (C=O), 156.2 (C=N), 111.7-144.1 (18 signals arom), 98.6 (spiro carbon), 55.6 (OCH_3); MS (*m/z*,

%) 371 (M^+, 20), 343 (M^+-CO, 100), 225 (M^+-$C_8H_4NO_2$, 95) (Found: C, 71.2; H, 4.7; N, 11.4. $C_{22}H_{17}N_3O_3$ requires C, 71.15; H, 4.61; N, 11.31%).

3h: light yellow needles, Yield 90%, mp 274 °C; ν_{max}/cm^{-1} 3205 (N-H), 1729 (C=O), 1685 (C=N); δ_H ($CDCl_3$) 6.5-7.9 (m, 13 H), 10.6 (s, 1 H, N-H), δ_C ($CDCl_3$) 174.1(C=O), 156.4(C=N), 111.2-144.3 (18 signals arom), 98.7 (spiro carbon); MS (*m/z*, %) 375 (M^+, 25), 377 (M^++2, 8), 347 (M+-CO, 90), 229 (M^+-$C_8H_4NO_2$, 10), 195 (M^+-$C_8H_4NO_2Cl$, 100) (Found: C, 67.3; H, 3.8; N, 11.2. $C_{21}H_{14}N_3O_2Cl$ requires C, 67.12; H, 3.75; N, 11.18%).

3i: light yellow needles, Yield 92%, mp 242 °C; ν_{max}/cm^{-1} 3245 (N-H), 1737 (C=O), 1680 (C=N); δ_H ($CDCl_3$) 6.5-7.7 (m, 13 H), 10.5 (s, 1 H, N-H), δ_C ($CDCl_3$) 174.1(C=O), 156.7 (C=N), 111.4-142.9 (18 signals arom), 98.4 (spiro carbon); MS (*m/z*, %) 419 (M^+, 10), 421 (M^++2, 10), 391 (M^+-CO, 25), 273 (M^+-$C_8H_4NO_2$, 80), 195 (M^+-$C_8H_4NO_2Br$, 100) (Found: C, 59.9; H, 3.3; N, 10.1. $C_{21}H_{14}N_3O_2Br$ requires C, 60.02; H, 3.36; N, 10.00%).

4a: White powder, Yield 92%, mp 257 °C; ν_{max}/cm^{-1} 3135 (N-H), 1730 (C=O), 1690 (C=N); δ_H ([$^2H_6$]DMSO) 6.6-8.1 (m, 16 H), 8.3 (s, 1 H, N-H), δ_C ([$^2H_6$]DMSO) 173.3 (C=O), 157.2 (C=N), 111.3-142.1 (22 signals arom), 98.1 (spiro carbon); MS (*m/z*, %) 391 (M^+, 10), 363 (M^+-CO, 55), 245 (M^+-$C_8H_4NO_2$, 100) (Found: C, 76.7; H, 4.3; N, 10.8. $C_{25}H_{17}N_3O_2$ requires C, 76.71; H, 4.38; N, 10.74%).

4b: light yellow powder, Yield 85%, mp 210 °C; ν_{max}/cm^{-1} 3180 (N-H), 1735 (C=O), 1680 (C=N); δ_H ($CDCl_3$) 6.6-8.1 (m, 15 H), 8.3 (s, 1 H, N-H), δ_C ($CDCl_3$) 174.5 (C=O), 157.1 (C=N), 111.4-142.2 (22 signals arom), 98.1 (spiro carbon); MS (*m/z*, %) 425 (M^+, 10), 427 (M^++2, 3),397 (M^+-CO, 25), 244 (M^+-$C_8H_4NO_2Cl$, 100) (Found: C, 70.6; H, 3.8; N, 9.9. $C_{25}H_{16}N_3O_2Cl$ requires C, 70.51; H, 3.79; N, 9.89%).

4c: light yellow powder, Yield 85%, mp 221 °C; ν_{max}/cm^{-1} 3142 (N-H), 1730 (C=O), 1685 (C=N); δ_H ($CDCl_3$) 6.6-8.1 (m, 15 H), 8.1 (s, 1 H, N-H), δ_C ($CDCl_3$) 174.3 (C=O), 157.1 (C=N), 111.3-142.2 (22 signals arom), 98.0 (spiro carbon); MS (*m/z*, %) 469 (M^+, 10), 471 (M^++2, 10), 441 (M^+-CO, 50), 323 (M^+-$C_8H_4NO_2$, 40), 244 (M^+-$C_8H_4NO_2Br$, 100) (Found: C, 63.8; H, 3.4; N, 8.9. $C_{25}H_{16}N_3O_2Br$ requires C, 63.84; H, 3.43; N, 8.93%).

5a: light yellow powder, Yield 858%, mp 222 °C; ν_{max}/cm^{-1} 3140 (N-H), 1728 (C=O), 1690 (C=N); δ_H ($CDCl_3$) 6.6-8.3 (m, 16 H), 8.3 (s, 1 H, N-H), δ_C ($CDCl_3$) 174.4 (C=O), 157.3 (C=N), 111.3-142.3 (22 signals arom), 98.1 (spiro carbon); MS (*m/z*, %) 391 (M^+, 10), 363 (M^+-CO, 60), 245 (M+-$C_8H_4NO_2$, 100) (Found: C, 76.7; H, 4.3; N, 10.8. $C_{25}H_{17}N_3O_2$ requires C, 76.71; H, 4.39; N, 10.74%).

5b: Yellow powder, Yield 75%, mp 146 °C; $\nu_{max/cm^{-1}}$ 3175 (N-H), 1730 (C=O), 1680 (C=N); δ_H ($CDCl_3$) 6.6-8.1 (m, 15 H), 8.2 (s, 1 H, N-H), δc ($CDCl_3$) 174.5 (C=O), 157.1 (C=N), 111.3-142.2 (22 signals arom), 98.1 (spiro carbon); MS (*m/z*, %) 425 (M^+, 25), 427 (M^++2, 8),397 (M^+-CO, 60),279 (M^+-$C_8H_4NO_2$, 10) 244 (M^+-$C_8H_4NO_2Cl$, 75) (Found: C, 70.5; H, 3.7; N, 9.9. $C_{25}H_{16}N_3O_2Cl$ requires C, 70.51; H, 3.79; N, 9.87%).

5c: Yellow powder, Yield 80%, mp 127 °C; $\nu_{max/cm^{-1}}$ 3145 (N-H), 1725 (C=O), 1685 (C=N); δ_H ($CDCl_3$) 6.6-8.3 (m, 15 H), 8.4 (s, 1 H, N-H), δc ($CDCl_3$) 174.3 (C=O), 157.2 (C=N), 111.4-142.2 (22 signals arom), 98.0 (spiro carbon); MS (*m/z*, %) 469 (M^+, 10), 471 (M^++2, 10), 441 (M^+-CO, 40), 323 (M^+-$C_8H_4NO_2$, 35) (Found: C, 63.9; H, 3.5; N, 8.8. $C_{25}H_{16}N_3O_2Br$ requires C, 63.84; H, 3.43; N, 8.93%).

6a : White prisms, Yield 80%, mp 272 °C; $\nu_{max/cm^{-1}}$ 1725 (C=O), 1690 (C=N); δ_H ($CDCl_3$) 2.92,2.94 (s, s, 6 H, CH_3, ratio 1:1.5), 6.3-7.3 (m, 24 H); δc ($CDCl_3$) 171.3, 170.9 (C=O), 155.49, 155.46 (C=N), 109.3-144.7 (30 signals arom), 98.26, 98.24 (spiro carbon), 26.51, 26.48 (CH_3); MS (*m/z*, %) 633 (M^+, 10), 605 (M^+-CO, 5), 577 (M^+-2CO, 10), 487 (M^+-$C_8H_4NO_2$, 10) (Found: C, 71.9; H, 4.7; N, 13.3. $C_{38}H_{30}N_6O_4$ requires C, 71.91; H, 4.76; N, 13.24%).

6b : White prisms, Yield 85%, mp 265 °C; $\nu_{max/cm^{-1}}$ 1728 (C=O), 1690 (C=N); δ_H ($CDCl_3$) 2.9 (s, 6 H, CH_3), 6.3-7.5 (m, 22 H), δc ($CDCl_3$) 171.0 (C=O), 155.2 (C=N), 111.2-144.6 (15 signals arom), 98.1 (spiro carbon), 26.5 (CH_3); MS (*m/z*, %) 701 (M^+, 10), 703 (M^++2, 10), 673 (M^+-CO, 5), 645 (M^+-2CO, 10), 520 (M^+-$C_8H_4NO_2Cl$, 30) (Found: C, 64.8; H, 3.9; N, 12.0. $C_{38}H_{28}N_6O_4Cl2$ requires C, 64.87; H, 4.01; N, 11.94%).

6c : White prisms, Yield 85%, mp 258 °C; $\nu_{max/cm^{-1}}$ 1729 (C=O), 1685 (C=N); δ_H ($CDCl_3$) 2.9 (s, 6 H, CH_3), 6.3-7.5 (m, 22 H), δc ($CDCl_3$) 171.0 (C=O), 154.6 (C=N), 109.4-144.8 (15 signals arom), 98.3 (spiro carbon), 26.6 (CH_3); MS (*m/z*, %) 791 (M^+, 5), 793 (M^++2, 10), 763 (M^+-CO, 5), 735 (M^+-2CO, 10), 566 (M^+-$C_8H_4NO_2Br$, 10) (Found: C, 57.5; H, 3.6; N, 10.5. $C_{38}H_{28}N_6O_4Br$ requires C, 57.59; H, 3.56; N, 10.60%).

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