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SYNTHESIS OF NEW SPIRO[1,4,2-DIOXAZOLE-5,3′-INDOLIN]-2′-ONE BY 1,3-DIPOLAR CYCLOADDITION

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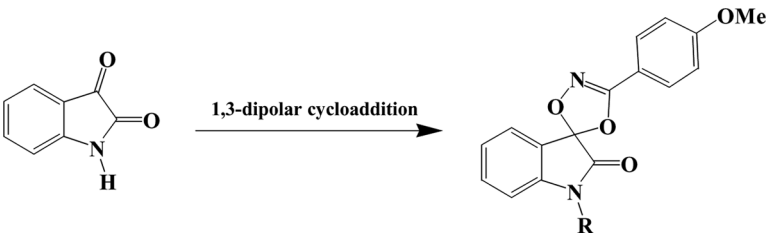
GRAPHICAL ABSTRACT



Abstract *Novel spiro[1,4,2-dioxazole-5,3′-indolin]-2′-one derivatives were synthesized by 1,3-dipolar cycloaddition reactions of the isatin derivative with aryl nitrile oxide. The cycloadducts were characterized by spectral data including ^{1}H NMR, ^{13}C NMR, infrared, mass spectra, and elementary analysis.*

Keywords 1,4,2-Dioxazole; 1,3-dipolar cycloaddition; isatin; isoxazole; isoxazoline

INTRODUCTION

Spiroindoline derivatives are synthetic or natural products[1–4] with various interesting properties. Their biological activities[5] are attributed to their specific structure composed of an indoline core linked to other heterocyclic arrangements such as isoxazoline, triazoline, or dioxazoline systems. For example, the spiro[indole-thiazolidine] compounds are used as pharmacological agents and as mammalian cell cycle inhibitors,[4] and possess anti-inflammatory,[5] antibacterial,[6] and anticonvulsant activities.[7] Spiro[indole-pyrrolidines] (Fig. 1, **I**) exhibit local anesthetic activity[8] and binding affinity to glycine receptors.[9] Spiro[3*H*-indole-3,4′-[4*H*] pyran]-2(1*H*)-ones (Fig. 1, **II**) are used as anti-inflammatory agents and have central nervous system activities.[10] Spiro[3*H*-indole-3,3′-pyrazoline]-2-ones are used as blood platelet aggregations.[11]

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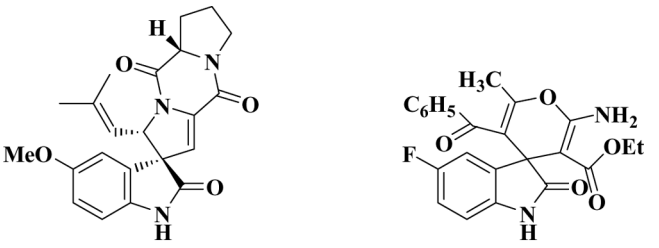


Spirotryprostatin B (I) **(II)**

Figure 1. Examples of indolone spiro-derivatives.

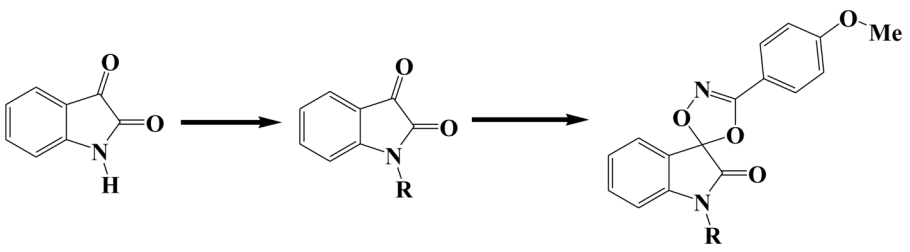
They are also used as precursors in the total synthesis of natural alkaloids.[12,13]

In continuation of our previous synthetic work on isatin and its derivatives,[14,15] we have performed the synthesis of a novel series of compounds corresponding to isatin bearing dioxazolyl and/or oxazolidinyl heterocyclic moieties. Our synthetic strategy for the building of such spirooxindolyl compounds consisted of a 1,3-dipolar cycloaddition reaction on the 3-exocyclic position of the C=O double bond of indoline-2,3-dione derivatives. The synthetic strategy used in this rationale consisted of the pathway described in Scheme 1. To our knowledge, there are only a few published manuscripts in the literature dedicated to the synthesis of such compounds.[16,17]

RESULTS AND DISCUSSIONS

The initial step (Fig. 2) consisted of an alkylation of the 2,3-indolinedione **1**, conducted at room temperature under phase-transfer-catalysis (PTC) conditions, with the individual benzyl chloride, allyl bromide, or propargyl bromide in the presence of dry K_2CO_3. Dimethylformamid was used as solvent, and tetra-*n*-butylammonium bromide (TBAB) was the catalyst. One resulting product (**2–4**) was formed for each individual *N*-alkylation in a good yield. The structural assignment of products **2–4** was straightforward and relied upon the elemental analysis and spectral data, including Fourier transform–Infrared (FT-IR), ^{1}H NMR, ^{13}C NMR, and mass spectrometry.

The 1,3-dipolar cycloaddition reaction of isatin derivatives **2–4** with the nitrile oxide product generated in situ from 4-methoxybenzaldoxime **5** and sodium



Scheme 1. Synthetic pathway followed for the synthesis of isatin derivatives.

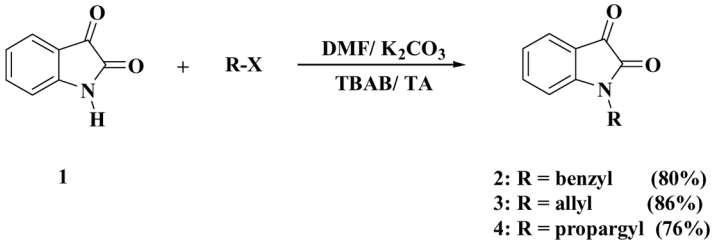


Figure 2. *N*-Alkylation of isatin in phase-transfer–catalysis conditions.

hypochloride was studied (Fig. 3). It was found that beside the C=O participating in the formation of the 1,4,2-dioxazole ring, the C-C alkene (allyl) or alkyne (propargyl) bond also experienced a 1,3-dipolar cycloaddition reaction with the nitrile oxide to form the isoxazole or isoxazoline rings linked to the indole ring via a methylene group.

The structures of the synthesized spiro[indole-dioxazoline] compounds, containing the various substituted isatin rings, were confirmed as follows. The FT-IR spectrum of **6–10** showed peaks around 1610 cm^{-1} for the amide carbonyl, improving the presence of the oxindole moitey. The ^{1}H NMR spectrum of **7** showed the methoxy protons as a singulet at 3.86 ppm, the methylene protons as a singulet at 4.89 ppm, and the aromatic protons as multiplet at 6.74–7.82 ppm. The ^{13}C NMR spectrum exhibited the following signals attributed respectively to: methylene benzylic at 44.0 ppm, methoxy group at 55.4 ppm, C-3 spiro carbon at 105.2 ppm, and isatin carbonyl at 169.3 ppm. Identical results were observed for the other derivatives irrespective of the nature of the substituent present in the N1 of the isatin moiety. The disappearance of the signal at 183 ppm due to the ketonic carbonyl confirmed the involvement of the carbonyl group in 1,3-dipolar cycloaddition.

The respective obtainment of compounds **9** and **11** from the cycloaddition of nitrile oxide to *N*-allylisatin and *N*-propargylisatin can be explained by the involvement of the subsequent reaction of the dipole with the allylic and propargylic groups. The structural elucidation of the novel series of spiro[1,4,2-dioxazole-5,3′-indolin]-2′-one derivatives was accomplished as in the following section. The proton spectrum of **11** showed two singlets at 3.87 and 3.88 ppm, which were assigned to the protons of

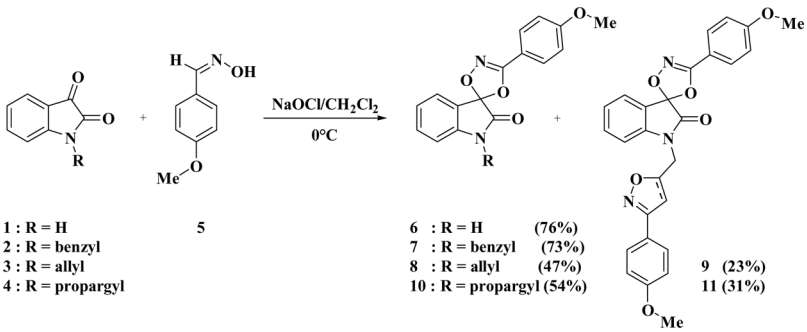


Figure 3. 1,3-Dipolar cycloaddition reaction on N-alkylisatin.

methoxy group and a signal at 5.08 ppm due to the methylene protons. A singlet at 6.67 ppm was also observed, corresponding to the isoxazolic proton, while its ^{13}C NMR spectrum contains two signals at 102.7 and 105.2 ppm, which can be respectively assigned to C-3 spiro and CH isoxazolic, as with those corresponding to methylene, methyl, and aromatic carbons. Mass spectrometric analysis was performed by electron impact (EI) with the presence of a molecular ion M^{+} ($m/z = 483$), proving that two molecules of the nitrile oxide were involved in the reaction process.

The formation of the spirodioxazole-oxindole structure in all reactions showed that the cycloaddition proceeded with high chemoselectivity when using the nitrile oxide, which prefers to react with C-3 carbonyl ketone, and with a high regioselectivity as the oxygen of the nitrile oxide adds exclusively to either the substitued carbon of double or to the triple bonds of **3** and **4** respectively

The formation of spirodioxazole-oxindole in all reactions shows that the cycloaddition proceeds chemoselectively, with the nitrile oxide preferring to react with C3 carbonyl ketone and regioselectively with the oxygen of the nitrile oxide adding to the substituent carbon of double and triple bonds of **3** and **4** respectively.

CONCLUSION

1,3-dipolar cycloaddition reaction of isatin derivatives **1–4** with nitrile oxide was studied. It was found that beside its C=O (ketone) participating in formation of 1,4,2-dioxazole ring and C-C (allyl or propargyl), it also underwent a 1,3-dipolar cycloaddition reaction with nitrile oxide to afford isoxazole or isoxazoline rings linked by methylene group to indole ring. The construction of spiro[indole-dioxazole] molecules is essential to explore new medicines and agrochemical compounds.

We evaluate the ability of these new potentially active molecules to cross the blood brain barrier by testing them in vitro.[18] They will also be tested in the near future for their anti-inflammatory and antitumoral properties.

EXPERIMENTAL

Melting points were determined using a capillary melting-point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution with tetramethylsilane (TMS) as an internal reference using a Bruker Avance 300 instrument; chemical shifts are given in δ ppm downfield from tetramethylsilane (TMS). Multiplicities of ^{13}C NMR resources were assigned by distortionless enhancement by polarization transfer (DEPT) experiments. Mass spectra (MS) were recorded in a Varian MAT 311A spectrometer. Elemental analyses were performed by the IUT de Béthune, Département de Chimie (Béthune, France), and infrared spectroscopy was performed using a FT-IR Bruker Vector 22 apparatus equipped with a diamond reflection accessory.

Alkylation Reaction

General procedure. K_2CO_3 (0.02 mol, 2.76 g), 22 mmol alkyl halides, and tetra-n-butylammonium bromide TBAB (0.001 mol, 0.321 g) was added to a solution

of indoline-2,3-dione **1** (20 mmol, 2.92 g) in dimethylformamid 40 mL. The mixture was stirred at room temperature for 24 h. The solution was filtered, and the solvent was removed under reduced pressure. The residue was recrystallized from ethanol to afford **2–4**.

N-Benzylindoline-2,3-dione 2. The compound was obtained as orange crystals in 80% yield, mp = 133–135 °C (ethanol); IR: ν_{max} 1737, 1605 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.86 (s, 2H, NCH_2), 6.70–7.56 (m, 9H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ 44.0 (NCH_2); 111.1, 123.9, 125.4, 127.8, 128.1, 129.1, 138.4 (CH_{Ar}); 117.6, 134.5, 150.7 (Cq); 158.3 ($C{=}O_{amide}$); 183.3 ($C{=}O_{ketone}$). IE-MS: $M^{+\cdot}$ (m/z) = 237.

N-Allylindoline-2,3-dione 3. The compound was obtained as red crystals in 86% yield, mp = 89–91 °C (ethanol); IR: ν_{max} 1734, 1606 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.24 (dd, 2H, NCH_2, ^3J = 2.4 Hz, ^4J = 0.7 Hz), 5.19 (m, 2H, $=CH_2$, ^3J = 2.4 Hz, ^3J = 1.5 Hz), 5.70 (m, 1H, =CH, ^3J = 1.5 Hz, ^4J = 0.7 Hz); 6.81–7.46 (m, 4H, CH_{Ar}); ^{13}C NMR ($CDCl_3$): δ 42.4 (NCH_2); 118.5 ($=CH_2$); 130.2 (= CH); 110.9, 123.8, 125.2, 138.4 (CH_{Ar}); 117.4, 156.7 (Cq); 157.9 ($C{=}O_{amide}$); 183.2 ($C{=}O_{ketone}$). IE-MS: $M^{+\cdot}$ (m/z) = 187.

N-Propargylindoline-2,3-dione 4. The compound was obtained as orange crystals in 76% yield, mp = 156–158 °C (ethanol); IR: ν_{max} 1738, 1605 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.35 (t, 1H, ≡CH, ^4J = 2.4 Hz), 4.52 (d, 2H, NCH_2, ^4J = 2.4 Hz), 7.22–7.63 (m, 4H, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 36.8 (NCH_2); 73.9 (≡CH); 111.7, 125.2, 126.2, 139.3 (CH_{Ar}); 117.4, 149.4 (Cq); 158.6 ($C{=}O_{amide}$); 182.7 ($C{=}O_{ketone}$). IE-MS: $M^{+\cdot}$ (m/z) = 185.

1,3-Dipolar Cycloaddition

General procedure. Isatin **1** (*N*-alkylisatin **2–4**) (6.8 mmol) was dissolved in 20 mL of dichloromethane. *p*-Methoxybenzaldoxime **5** (10.2 mmol) was added to this solution, and the mixture stirred at 0 °C. Sodium hypochlorite (10 mL, 24%) was added dropwise to the mixture, and stirring continued for 6 h. The organic phase was separated off and dried with Na_2SO_4; and the solvent was evaporated in vacuo. The residue was purified by column chromatography on silica gel using a 8:2 mixture of hexane and ethyl acetate as eluent.

3-(4-Methoxyphenyl)spiro[1,4,2-dioxazoline-5,3′-indoline]-7-one 6. The compound was obtained in 66% yield, mp = 176–178 °C (hexane–ethyl acetate); IR: ν_{max} 3194, 1605 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.72 (s, 3H, OCH_3); 6.92–7.84 (m, 8H, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 54.8 (OCH_3); 101.1 (C_{spiro}); 114.5, 131.6, 112.7, 113.8, 120.7, 123.2, 125.1, 137.9 (CH_{Ar}); 141.3, 160.4, 164.7, 168.5 Cq; IE-MS: m/z (%): 296 [$M^{+\cdot}$], 268 (100), 264 (30), 136 (25), 32 (22). Anal. calcd. for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found: C, 64.94; H, 3.98; N, 9.51%.

3-(4-Methoxyphenyl)-6-benzylspiro[1,4,2-dioxazoline-5,3′-indoline]-7-one 7. The compound was obtained in 73% yield, mp = 144–146 °C (hexane–ethyl acetate). IR: ν_{max} 1610 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.86 (s, OCH_3); 4.89 (s, NCH_2); 6.74–7.82 (m, 13H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 55.4 (OCH_3); 44.0 (NCH_2); 105.2 (C_{spiro}); 110.2, 114.3, 123.8, 125.8, 127.4, 127.9, 128.9, 129.0, 132.9 (CH_{Ar});

114.4, 121.6, 134.7, 143.9, 159.5, 162.5, 169.3 (Cq). IE-MS: m/z (%): 386 [M^+], 358 (100), 354 (43), 296 (34), 253 (24), 91 (38). Anal. calcd. for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25. Found: C, 71.54; H, 4.63; N, 7.31%.

3-(4-Methoxyphenyl)-6-prop-2-enylspiro[1,4,2-dioxazoline-5,3′-indoline] -7-one 8. The compound was obtained in 47% yield, mp = 131–133 °C (hexane–ethyl acetate). IR: ν_{max} 1604 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.32 (s, 3H, OCH_3), 4.22 (m, 2H, NCH_2), 5.67 (m, 1H, =CH), 5.18 (m, 2H, $=CH_2$), 7.01–7.76 (m, 8H, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 54.9 (OCH_3); 43.1 (NCH_2); 119.7 ($=CH_2$); 131.6 (=CH); 104.2 (C_{spiro}); 112.1, 115.5, 124.3, 125.5, 129.5, 137.2 (CH_{Ar}); 114.0, 121.2, 145.1, 161.5, 164.9, 169.9 (Cq). IE-MS: m/z (%): 336 [M^+], 308 (100), 304 (35), 296 (44), 203 (25). Anal. calcd. for $C_{19}H_{16}N_2O_4$: C, 67.85; H, 4.79; N, 8.33. Found: C, 67.77; H, 4.86; N, 8.35%.

3-(4-Methoxyphenyl)-6-{[3-(4-methoxyphenyl)(4,5-dihydroisoxazol-5-yl)] methyl}spiro[1,4,2-dioxazoline-5,3′-indoline]-7-one 9. The compound was obtained in 23 % yield, mp = 157–159 °C (hexane–ethyl acetate). IR: ν_{max} 1609 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.42–3.55 (s, 3H, OCH_3); 4.12 (m, 2H, NCH_2); 5.17 (m, 1H, CH); 3.01 (m, 2H, CH_2); 6.89–7.81 (m, 12H, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 55.1–55.7 (OCH_3); 44.4 (NCH_2); 77.8 CH; 50.6 (CH_2); 103.2 (C_{spiro}); 111.8, 115.2, 122.9, 125.3, 131.4, 138.2 (CH_{Ar}); 113.9, 120.5, 143.6, 161.4, 167.1, 171.1 (Cq). IE-MS: (m/z, %): 485 [M^+], 457 (100), 453 (34), 352 (28), 296 (37), 189 (30). Anal. calcd. for $C_{27}H_{23}N_3O_6$: C, 66.80; H, 4.78; N, 8.66. Found: C, 66.74; H, 4.90; N, 8.60%.

3-(4-Methoxyphenyl)-6-prop-2-ynylspiro[1,4,2-dioxazoline-5,3′-indoline]-7-one 10. The compound was obtained in 54% yield, mp = 136–138 °C (hexane–ethyl acetate). IR: ν_{max} 1603 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.49 (t, 1H, ≡CH, ^4J = 2.4 Hz); 3.40 (s, 3H, OCH_3); 3.84 (d, 2H, NCH_2, ^4J = 2.4 Hz); 6.74–7.78 (m, 8H, H_{Ar}). ^{13}C NMR ($CDCl_3$): δ 42.1 (NCH_2); 55.3 (OCH_3); 69.6 (CH); 102.4 (C_{spiro}); 112.5, 115.3, 125.1, 129.0, 129.6, 131.3 (CH_{Ar}); 106.4, 116.9, 121.2, 142.8, 162.1, 166.4, 170.0 (Cq). IE-MS: (m/z, %): 334 [M^+], 304 (100), 302 (45), 296 (34), 201 (27). Anal. calcd. for $C_{19}H_{14}N_2O_4$: C, 68.26; H, 4.22; N, 8.38. Found: C, 68.23; H, 4.15; N, 8.44%.

3-(4-Methoxyphenyl)-6-{[3-(4-methoxyphenyl)isoxazol-5-yl]methyl} spiro[1,4,2-dioxazoline-5,3′-indoline]-7-one 11. The compound was obtained in 31% yield, mp = 170–172 °C (hexane–ethyl acetate). IR: ν_{max} 1606 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.87–3.88 (s, 3H, OCH_3), 5.08 (s, 2H, NCH_2), 6.67 (s, 1H, $H_{isoxazole}$), 6.98–7.81 (m, 12H, H_{Ar}); ^{13}C NMR ($CDCl_3$): δ 36.1 (NCH_2); 55.8–55.9 (OCH_3); 102.7 (C_{spiro}); 105.2 ($CH_{isoxazole}$); 110.6, 114.9, 115.1, 125.5, 126.7, 127.7, 129.1, 134.1 (CH_{Ar}); 102.4, 114.0, 121.1, 130.1, 144.0, 159.7, 161.7, 162.0, 162.6, 164.9, 169.0 (Cq). IE-MS: (m/z, %): 483 [M^+], 455 (100), 451 (43), 350 (33), 296 (30), 149 (21). Anal. calcd. for $C_{27}H_{21}N_3O_6$: C, 67.07; H, 4.38; N, 8.69. Found: C, 67.15; H, 4.30; N, 8.64%.

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