One-Pot Synthesis of New Spiro[cyclopropane-1,3′-[3*H*]indol]-2′(1′*H*)-ones from 3-Phenacylideneoxindoles

Masoud Shaabanzadeh[a]* and Faranak Khabari[b]

[a]Chemistry Department, Islamic Azad University, Damghan Branch, Damghan 36716-39998, Iran
[b]Chemistry Department, Member of Young Researchers Club of I. A. U., Islamic Azad University, Saveh Branch, Saveh 39187-366, Iran
*E-mail: masoud.shaabanzadeh@gmail.com

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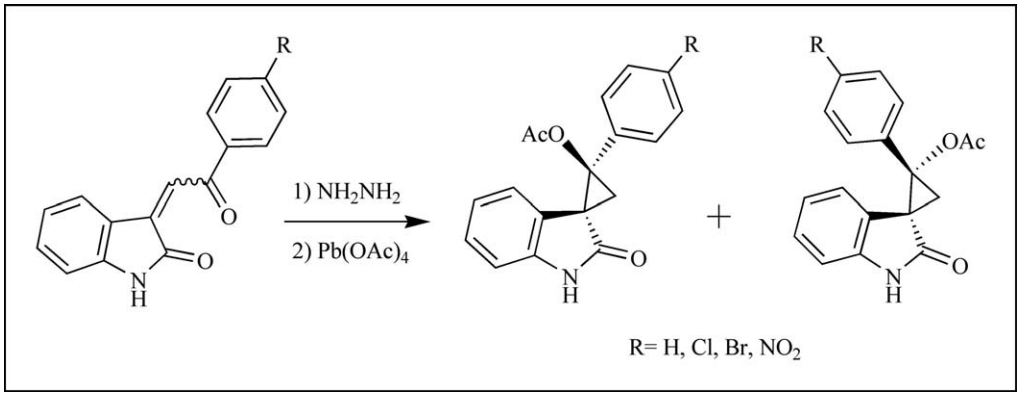

In a one-pot procedure, the 3-phenacylideneoxindoles **1a–d** were reacted with hydrazine and then *in situ* with lead(IV) acetate and new diastereoisomers of spiro[cyclopropane-1,3′-[3*H*]indol]-2′(1′*H*)-ones were prepared. Compounds **1a–d** underwent a highly diastereoselective cyclopropanation leading to diastereoisomers **2a–d**. These new compounds containing both 2-oxindole and cyclopropane moieties may be valuable in medicinal chemistry.

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INTRODUCTION

Isatin or 1*H*-indole-2,3-dione is an indole derivative. This compound was found in many plants. Isatin is an endogenous compound identified in humans that possesses wide range of biological activities. It has anxiogenic, anticonvulsant activity, and acts as a potent antagonist on atrial natriuretic peptide receptors *in vitro* [1]. Isatin Mannich or Schiff bases had antibacterial, antifungal, antiviral, anti HIV, antiprotozoal, anticancer, muscle relaxant, and antiallergic activity [2–5].

The cyclopropane ring is a main structural part in many synthetic and natural compounds that exhibits a wide range of biological activities from enzyme inhibition to antibiotic, herbicidal, antitumor, and antiviral properties [6–18]. Some derivatives of cyclopropane have shown potent HIV antiviral activities as non-nucleoside reverse transcriptase inhibitors [19]. Because of diversity of cyclopropane-containing compounds with biological activity, chemists have tried to find novel and facile methods for synthesis of these compounds [20–24].

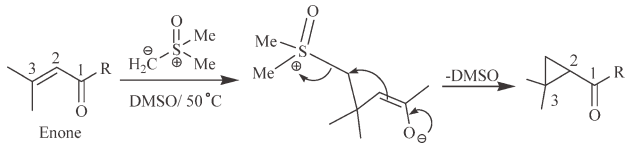
In this study along our pervious works on the synthesis of spiro derivatives of isatins and other biologically active compounds [25,26], we report a simple one-pot procedure for the synthesis of some spiro[cyclopropane-1,3′-[3*H*]indol]-2′(1′*H*)-ones **2a–d** and **3a–d**, which directly prepared from various 3-phenacylideneoxindoles **1a–d** derivatives of isatin. These new compounds containing both active 2-oxindole and cyclopropane moieties may be of value in pharmaceutical and medicinal chemistry.

RESULTS AND DISCUSSION

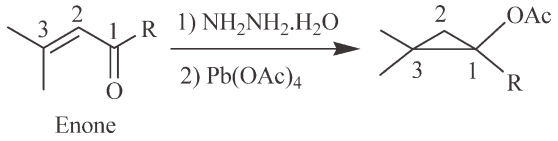
Among the synthetic procedures for preparation of cyclopropane rings, the Michael initiated ring closure reaction [6,14,21,23,24] of α,β-unsaturated carbonyl compounds such as α,β-enones with dimethylsulfoxonium methylides or Corey–Chaykovsky reaction [27,28] is the well-known method. In this reaction, the cyclopropane ring forms between carbon atoms of positions 2 and 3 of enones by addition of a new methylene group (Scheme 1).

The Kishner cyclopropanation reaction is another procedure [29–31]. In the Kishner's method, the cyclopropane derivatives were prepared by thermal decomposition of 2-pyrazolines. The Kishner reaction needs higher

Scheme 1



Scheme 3



temperatures for removing the nitrogen from 2-pyrazoline to afford cyclopropane (Scheme 2).

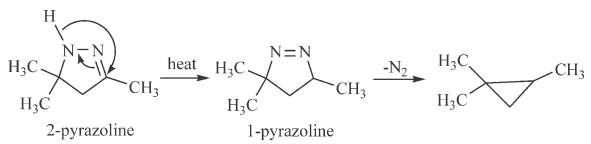
In this work, we report a novel one-pot procedure to synthesis the cyclopropane derivatives with connecting the C-1 and C-3 positions of α,β-enones (Scheme 3). This is a direct and useful method toward preparation of cyclopropanes through the 2-pyrazoline intermediate. Using the lead(IV) acetate renders decomposition of 2-pyrazolines easy [32] and formation of highly substituted cyclopropanes will be possible [33].

For the synthesis of new spiro molecules in this study, we needed the various 3-phenacylideneoxindoles **1a–d**. They have been prepared in our pervious work by the reaction of isatin with acetophenones in a solvent free condition catalyzed first by dimethylamine and then with glacial acetic acid and hydrochloric acid (Scheme 4) [26].

The **1a–d** were reacted with hydrazine hydrate in toluene and then *in situ* with lead(IV) acetate to afford a series of new spiro[cyclopropane-1,3′-[3*H*]indol]-2′(1′*H*)-one derivatives **2a–d** and **3a–d** (Scheme 5).

The reaction intermediate was a spiro[[3*H*]indole-3,3′-[3*H*]pyrazol]-2(1*H*)-one **4** which is the product of hydrazine addition to 3-phenacylideneoxindoles. This reaction is the main method used for preparation of 2-pyrazolines in last century [34–36]. The intermediate **4** was not separated and reacted *in situ* with lead(IV) acetate to form new diastereoisomers **2a–d** and **3a–d**. The reaction of 2-pyrazolines with lead(IV) acetate was performed by Freeman [32] and Kennedy *et al*. [33]. The reaction intermediate is a 1-pyrazoline similar to compound **5**. Particularly, Kennedy's method is a general approach for synthesis of highly substituted cyclopropanes. Bonding of oxidant atom lead(IV) to the nitrogen atom of intermediate **4** increases the polarity of imino group of 2-pyrazoline ring and will facilitate the attack of the acetate anion to the carbon of imino double bond. Therefore, the unstable intermediate **5** forms and readily decomposes to the products by loss of nitrogen. The mechanism of the reaction may be as the Scheme 6.

Scheme 2



In comparison with the Kishner reaction, the lead(IV) acetate used here catalyzed the reaction and reacted with intermediate **4** and caused rapid nitrogen extrusion and then the reaction carried out in lower temperatures, whereas the Kishner reaction needs higher temperatures [29–31] for nitrogen loss. This is an advantage of this work. Furthermore, the starting material in the Kishner's method was a 2-pyrazoline derivative, but we used α,β-enones (3-phenacylideneoxindoles) as the starting compounds and then the separation and purification steps for intermediate **4** were omitted. Therefore, the overall yield of the reaction increased.

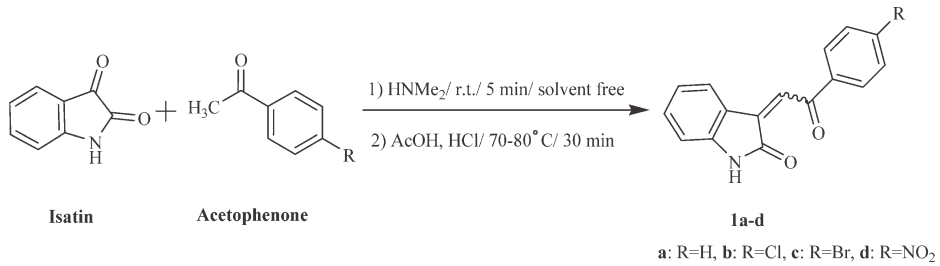
The reaction gave diastereoisomers **2a–d** as major products together with their isomers **3a–d** as minor products. In this case, a high diastereoselectivity was obtained. For instance, the diastereomeric ratios were determined by integration of separated signals in the ^{1}H NMR spectra of the mixture of compounds **2c** and **3c** in the reaction product (Fig. 1). The resulted diastereomeric ratios for products were **2a:3a** = 2.70:1, **2b:3b** = 4.26:1, **2c:3c** = 1.78:1, **2d:3d** = 1.94:1.

All compounds **2a–d** and **3a–d** are new derivatives of spiro[cycloprapane-1,3′-[3*H*]indol]-2′(1′*H*)-ones and have not reported in literature. Their structures were deduced from their IR, ^{1}H, and ^{13}C NMR spectra. Their purity was tested by CHN elemental analysis. The experimentally obtained CHN data have shown good agreements (about ±0.2%) with calculated values.

For example, the ^{1}H NMR spectrum of **2b** indicated two doublets at δ 2.18 and 2.69 ppm (J = 7 Hz), which belong to diastereotopic methylene protons at position 3 of cyclopropane ring and a singlet at δ 2.04 ppm for methyl protons of acetate group. The multiplets at δ 6.85–7.95 ppm showed the aromatic protons. A singlet at δ 8.91 ppm indicates the secondary amino proton. The ^{1}H decoupled ^{13}C NMR spectrum of **2b** exhibited spiro carbon at δ 37.97, C-2 carbon atom of cyclopropane ring at δ 70.84, methyl carbon at δ 21.25, methylene carbon at δ 27.05, carbonyl carbon of acetate group at δ 169.76, and amido carbon of 2-oxindole moiety at δ 175.42 ppm.

In the ^{1}H NMR spectrum of compound **3a**, a doublet was appeared at δ 5.65 ppm (J = 0.02 × 400 = 8 Hz) for the H-4′ hydrogen of 2-oxindole part. This proton

Scheme 4



was shielded by the magnetic anisotropy effect of phenyl ring attached to the position 2 of cyclopropane ring (Fig. 2, the structure was not optimized). Similar doublets were appeared for other synthesized compounds **3b–d**.

CONCLUSION

In summary, some novel spiro[cyclopropane-1,3′-[3*H*]indol]-2′(1′*H*)-ones were synthesized from 3-phenacylideneoxindoles in a one-pot simple and rapid procedure, and the products were obtained in good yields. These compounds may be active biological substances and worthy of attention for the medicinal and pharmaceutical chemists.

EXPERIMENTAL

All chemicals used in this study were purchased from Merck and Fluka companies. Melting points were measured on a Qallenkamp melting point apparatus in open capillary tubes. The melting point measurement showed that the synthesized compounds decompose before they melt because they have highly crowded structure at cyclopropane ring. The IR spectra were taken from a Bruker Vector 22 FTIR spectrometer, and samples were used as a potassium bromide pellet. ^{1}H NMR was recorded on a Bruker DRX-400 Avance instrument, and ^{13}C NMR (125 MHz) was run on a Bruker DRX-500 Avance instrument using deuteriochloroform as the solvent and tetramethylsilane as the internal standard. The purity of prepared spiro compounds was tested by the elemental analysis of C, H, and N elements using a Heraus CHN rapid analyzer. All prepared compounds were filtered and fractionally crystallized from ethanol/water solution.

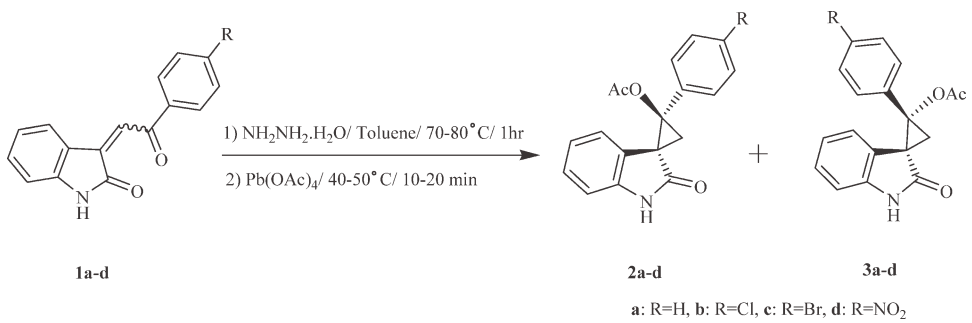
The starting materials, 3-phenacylideneoxindoles **1a–d**, were prepared in this laboratory according to the procedure reported in literature [26].

General procedure for preparation of spiro[cyclopropane-1,3′-[3*H*]indol]-2′(1′*H*)-ones 2a–d and 3a–d. The **1a–d** (10 mmoles) were dissolved in toluene (20 mL) and then hydrazine hydrate (11 mmoles) was added to this solution and the mixture was stirred and refluxed at 70–80°C for 1 h. Then, 11 mmoles of solid lead(IV) acetate was added to the reaction mixture at 40–50°C and nitrogen extrusion began. The reaction was continued for about 10–20 min, and the spiro compounds **2a–d** and **3a–d** were prepared (Scheme 5). The products were filtered and fractionally crystallized from ethanol-water.

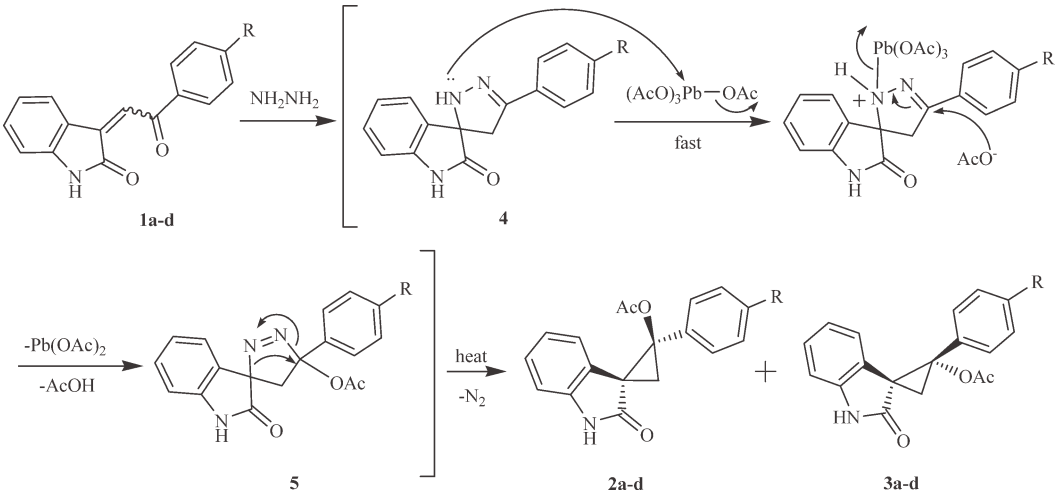
rel-(1R,2R)-2-Acetyloxy-2-phenylspiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (2a). Light yellow solid (1.96 g), yield 67%, decomp.>98°C; IR (potassium bromide): 3419 (N—H), 3058, 3027, 2928, 2884, 1762 (C=O of acetate), 1709 (C=O of oxindole), 1621, 1597 cm^{-1}; ^{1}H NMR: δ 2.04 (s, 3H, CH_3), 2.19 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 2.77 (d, 1H, J = 7 Hz, C**H**$_{2b}$), 6.93–8.06 (m, 9H, ArH), 8.40 (s, 1H, NH); ^{13}C NMR: δ 21.30 (CH_3), 27.05 (CH_2), 37.98 (spiro carbon), 71.70 (Ph—**C**—OAc), 110.52, 122.17, 122.46, 128.36, 128.70, 129.21, 129.75, 130.47, 134.27, 141.86, 169.77 (—**C**OO—), 175.57 (—**C**ONH—); Anal. Calcd. for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.67; H, 5.14; N, 4.75%.

rel-(1R,2S)-2-Acetyloxy-2-phenylspiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (3a). Light yellow solid (0.64 g), yield 22%, decomp.>98°C; IR (potassium bromide): 3419 (N—H), 3056, 3025, 2928, 2884, 1760 (C=O of acetate), 1709 (C=O of oxindole), 1620, 1597 cm^{-1}; ^{1}H NMR: δ 2.03 (s, 3H, CH_3), 2.26 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 2.52 (d, 1H, J = 7 Hz, C**H**$_{2b}$), 5.65 (d, 1H, J = 8 Hz, H-4′ of oxindole), 6.63–7.84 (m, 8H, ArH), 8.45 (s, 1H, NH); ^{13}C NMR: δ 21.47 (CH_3), 27.94 (CH_2),

Scheme 5



Scheme 6



37.47 (spiro carbon), 71.08 (Ph—**C**—OAc), 110.02, 121.69, 122.77, 127.93, 128.65, 129.16, 129.80, 131.90, 134.20, 141.35, 170.85 (—**C**OO—), 175.96 (—**C**ONH—); Anal. Calcd. for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.58; H, 5.05; N, 4.61%.

rel-(1R,2R)-2-Acetyloxy-2-(4-chlorophenyl)spiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (2b). Light yellow solid (2.41 g), yield 74%, decomp.>101°C; IR (potassium bromide): 3417 (N—H), 3059, 3027, 2927, 2886, 1751 (C=O of acetate), 1703 (C=O of oxindole), 1622, 1597 cm^{-1}; ^1H NMR: δ 2.04 (s, 3H, CH_3), 2.18 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 2.69 (d, 1H, J = 7 Hz, C**H**$_{2b}$), 6.85–7.95 (m, 8H, ArH), 8.91 (s, 1H, NH); ^{13}C NMR: δ 21.25 (CH_3), 27.05 (CH_2), 37.97 (spiro carbon), 70.84 (ClC_6H_4—**C**—OAc), 110.61, 122.31, 122.46, 127.13, 128.65, 128.99, 129.41, 131.89, 135.09, 141.80, 169.76 (—**C**OO—), 175.42 (—**C**ONH—); Anal. Calcd. for $C_{18}H_{14}ClNO_3$: C, 65.96; H, 4.31; N, 4.27. Found: C, 65.89; H, 4.31; N, 4.25%.

rel-(1R,2S)-2-Acetyloxy-2-(4-chlorophenyl)spiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (3b). Light yellow solid (0.58 g), yield 18%, decomp.>101°C; IR (potassium bromide): 3417 (N—H), 3057, 3026, 2927, 2884, 1751 (C=O of acetate), 1705 (C=O of oxindole), 1621, 1597 cm^{-1}; ^1H NMR: δ 2.02 (s, 3H, CH_3), 2.21 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 2.50 (d, 1H, J = 7 Hz, C**H**$_{2b}$), 5.69 (d, 1H, J = 8 Hz, H-4′ of oxindole), 6.66–7.79 (m, 7H, ArH), 8.83 (s, 1H, NH); ^{13}C NMR: δ 21.39 (CH_3), 27.79 (CH_2), 37.40 (spiro carbon), 70.10 (ClC_6H_4—**C**—OAc), 110.14, 121.89, 122.81, 127.80, 128.14, 128.58, 129.46, 133.42, 135.77, 141.33, 170.88 (—**C**OO—), 175.8 (—**C**ONH—); Anal. Calcd. for $C_{18}H_{14}ClNO_3$: C, 65.96; H, 4.31; N, 4.27. Found: C, 65.81; H, 4.26; N, 4.19%.

rel-(1R,2R)-2-Acetyloxy-2-(4-bromophenyl)spiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (2c). Light yellow solid (2.22 g), yield 60%, decomp.>110°C; IR (potassium bromide): 3419 (N—H), 3058, 3029, 2926, 2893, 1715 (broad, C=O of

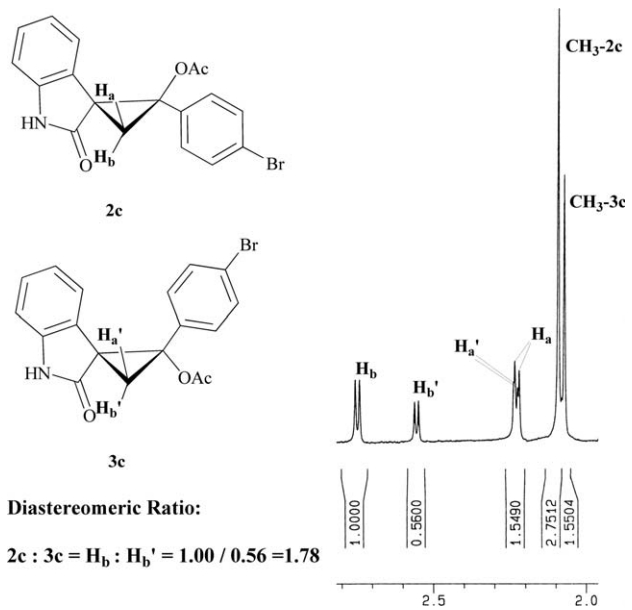


Figure 1. ^1H NMR signal integrations used for determination of diastereomeric ratio.

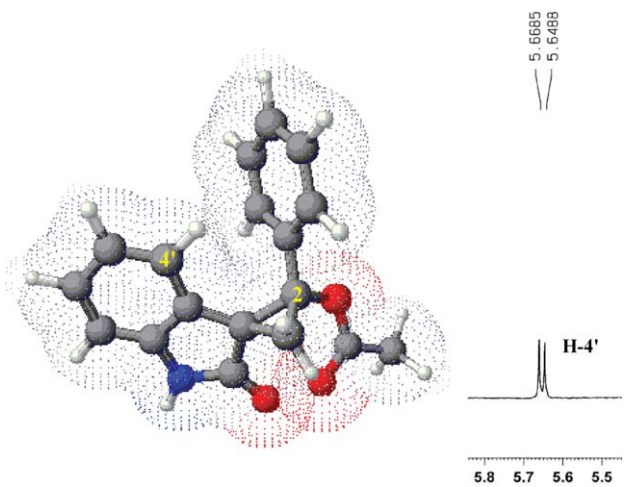


Figure 2. Shielding of H-4′ proton by anisotropic effect of phenyl ring. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

acetate and C=O of oxindole overlapped), 1621, 1597 cm^{-1}; ^1H NMR: δ 2.09 (s, 3H, CH_3), 2.21 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 2.74 (d, 1H, J = 7 Hz, C**H**$_{2b}$), 6.99–7.98 (m, 8H, ArH), 8.48 (s, 1H, NH); Anal. Calcd. for $C_{18}H_{14}BrNO_3$: C, 58.08; H, 3.79; N, 3.76. Found: C, 57.98; H, 3.73; N, 3.75%.

rel-(1R,2S)-2-Acetyloxy-2-(4-bromophenyl)spiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (3c). Light yellow solid (1.15 g), yield 31%, decomp.>110°C; IR (potassium bromide): 3419 (N—H), 3056, 3028, 2926, 2892, 1715 (broad, C=O of acetate and C=O of oxindole overlapped), 1620, 1597 cm^{-1}; ^1H NMR: δ 2.07 (s, 3H, CH_3), 2.22 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 2.55 (d, 1H, J = 7 Hz, C**H**$_{2b}$), 5.76 (d, 1H, J = 8 Hz, H-4′ of oxindole), 6.73–7.87 (m, 7H, ArH), 8.39 (s, 1H, NH); Anal. Calcd. for $C_{18}H_{14}BrNO_3$: C, 58.08; H, 3.79; N, 3.76. Found: C, 57.93; H, 3.65; N, 3.69%.

rel-(1R,2R)-2-Acetyloxy-2-(4-nitrophenyl)spiro[cyclopropane-1,3′-[3H]indol]-2′(1′)-one (2d). Light yellow solid (2.09 g), yield 62%, decomp.>154°C; IR (potassium bromide): 3420 (N—H), 3080, 3031, 2925, 2890, 1719 (broad, C=O of acetate and C=O of oxindole overlapped), 1624, 1597 cm^{-1}; ^1H NMR: δ 2.09 (s, 3H, CH_3), 2.24 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 2.80 (d, 1H, J = 7 Hz, C**H**$_{2b}$), 6.96–8.35 (m, 8H, ArH), 9.59 (s, 1H, NH); ^{13}C NMR: δ 21.13 (CH_3), 26.87 (CH_2), 38.23 (spiro carbon), 70.9 ($NO_2C_6H_4$—**C**—OAc), 110.58, 122.56, 122.72, 123.60, 123.95, 126.52, 128.48, 131.23, 141.27, 141.70, 169.82 (—**C**OO—), 175.54 (—**C**ONH—); Anal. Calcd. for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.91; H, 4.11; N, 8.26%.

rel-(1R,2S)-2-Acetyloxy-2-(4-nitrophenyl)spiro[cyclopropane-1,3′-[3H]indol]-2′(1′H)-one (3d). Light yellow solid (0.94 g), yield 28%, decomp.>154°C; IR (potassium bromide): 3420 (N—H), 3082, 3031, 2924, 2890, 1719 (C=O of acetate and C=O of oxindole overlapped), 1622, 1597 cm^{-1}; ^1H NMR: δ 2.04 (s, 3H, CH_3), 2.26 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 2.59 (d, 1H, J = 7 Hz, C**H**$_{2b}$), 5.8 (d, 1H, J = 8 Hz, H-4′ of oxindole), 6.66–8.65 (m, 7H, ArH), 9.49 (s, 1H, NH); ^{13}C NMR: δ 21.39 (CH_3), 27.15 (CH_2), 38.59 (spiro carbon), 71.11 ($NO_2C_6H_4$—**C**—OAc), 110.22, 122.15, 122.76, 122.90, 123.77, 126.89, 128.25, 131.08, 141.16, 141.60, 170.87 (—**C**OO—), 175.94 (—**C**ONH—); Anal. Calcd. for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.78; H, 4.09; N, 8.20%.

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