Simple and Rapid Synthesis of New Spiro Isatin-Cyclopropane Derivatives from 2-Pyrazolines

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Abstract

Introduction: Isatin is a compound which has many biological effects such as antibacterial, antifungal, anti HIV and anticancer activities. The cyclopropane ring is a main structural part in many synthetic and natural compounds that exhibits many biological activities and chemists have tried to synthesis it by novel methods.

Aim: In this study, a rapid and simple procedure was reported for the synthesis of new spiro isatin-cyclopropanes which prepared from 2-pyrazolines. These compounds have both isatin and cyclopropane moieties and may be of value in medicinal and pharmaceutical chemistry.

Materials and Methods: The 2-pyrazolines were dissolved in toluene and then solid lead tetraacetate (LTA) was added to them at 40-50 ºC and the reaction was continued for 10-20 minutes and new spiro isatin-cyclopropane compounds were prepared. The products were purified and their structures were deduced from their spectroscopic analysis.

Results: The Kishner cyclopropanation needs higher temperatures. In this study, reaction was catalyzed with LTA and carried out in lower temperatures. One of the two resulted diastereomers was produced in higher yields than the other. For example, the diastereomeric ratio, **2a**:**3a**=2.7:1, was determined by signal integrations in ^{1}H NMR spectra of the mixture of compounds **2a** and **3a**.

Conclusion: Some spiro isatin-cyclopropanes were synthesized in a rapid and simple procedure.

Keywords: Spiro compounds, isatin, cyclopropane, 2-pyrazoline, lead tetraacetate

ntroduction

Isatin is an endogenous compound identified in humans that possesses wide range of biological activities. Isatin has anxiogenic, anticonvulsant activity and acts as a potent antagonist on atrial natriuretic peptide receptors *in vitro*.[1, 2] Isatin derivatives of Mannich

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bases had antibacterial, antifungal, antiviral, anti HIV, antiprotozoal, anticancer, muscle relaxant and antiallergic activity.[3-5]

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] Due to diversity of cyclopropane containing compounds with biological activity, chemists have tried to find novel and facile methods for synthesis of these compounds.[20, 21]

Many synthetic methods have been reported for the preparation of cyclopropanes such as intramolecular cyclization, addition of carbenes to olefins and Michael initiated ring closure (MIRC).[6, 22, 23] In this study along our pervious works on the synthesis of spiro isatins and other biologically active compounds,[24, 25] we report a rapid and simple procedure for the synthesis of some spiro isatin-cyclopropanes **2a-d** and **3a-d** which directly prepared from various 2-pyrazoline derivatives of isatin **1a-d**. These new compounds have both isatin and cyclopropane moieties and may be of value in medicinal and pharmaceutical chemistry.

Materials and Methods

General Procedures. All chemicals used in this work were purchased from Merck and Fluka companies. Melting points were measured on a Gallenkamp melting point apparatus in open capillary tubes and are uncorrected. IR spectra were taken from a Bruker Vector22 FT-IR spectrometer. ^{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 $CDCl_3$ as the solvent and TMS as the internal standard. All prepared compounds were filtered and recrystallized from ethanol/water. The 2-pyrazoline derivatives of isatin were synthesized with method according to our pervious paper.[25]

General procedure for preparation of spiro isatin-pyrazolines 1a-d. To a solid homogenous mixture of 10 mmol isatin and 10 mmol acetophenones, 10 drops of dimethylamine was added and the mixture stirred for 5 minutes and a colorless solid formed and then 20 ml glacial acetic acid and five drops of concentrated HCl was added to this precipitate and the mixture warmed in 80 ºC for 30 minutes and after dehydration, chalcones were produced. Then, 11 mmol hydrazine hydrate was added to this solution and the mixture was stirred and refluxed at 70-80 ºC for one hour (Scheme3).

General procedure for preparation of spiro isatin-cyclopropane derivatives 2 and 3. The 2-pyrazolines **1a-d** (10 mmol) were dissolved in 20 ml toluene and then 11 mmol of solid LTA was added to the reaction mixture at 40-50 ºC and nitrogen extrusion began. The reaction was continued for 10-20 minutes and the spiro compounds **2a-d** and **3a-d** were prepared (Scheme 4). The products were filtered and recrystallized from ethanol/water.

1'-Acetoxy-1'-phenylspiro[indol-3,2'-cyclopropane]-2(1*H*)-one (2a). Light yellow solid, yield 73%, decomp.>98 ^{o}C, IR (KBr): 3419 (N-H of isatin), 3058, 3027, 2928, 2884, 1762 (C=O of acetate), 1709 (C=O of isatin), 1621, 1597 cm^{-1}, ^{1}H NMR (400 MHz) 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 (125 MHz) 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-),

1'-Acetoxy-1'-phenylspiro[indol-3,2'-cyclopropane]-2(1*H*)-one (3a). Light yellow solid, yield 27%, decomp.>98 ^{o}C, IR (KBr): 3419 (N-H of isatin), 3056, 3025, 2928, 2884, 1760 (C=O of acetate), 1709 (C=O of isatin), 1620, 1597 cm^{-1}, ^{1}H NMR (400 MHz) 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 isatin), 6.63-7.84 (m, 8H, ArH), 8.45 (s, 1H, NH), ^{13}C NMR (125 MHz) δ: 21.47

(CH_3), 27.94 (CH_2), 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-),

1'-Acetoxy-1'-(4-chlorophenyl)spiro[indol-3,2'-cyclopropane]-2(1*H*)-one (2b). Light yellow solid, yield 81%, decomp.>101 ^oC, IR (KBr): 3417 (N-H of isatin), 3059, 3027, 2927, 2886, 1751 (C=O of acetate), 1703 (C=O of isatin), 1622, 1597 cm^{-1}, ^1H NMR (400 MHz) 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 (125 MHz) 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-),

1'-Acetoxy-1'-(4-chlorophenyl)spiro[indol-3,2'-cyclopropane]-2(1*H*)-one (3b). Light yellow solid, yield 19%, decomp.>101 ^oC, IR (KBr): 3417 (N-H of isatin), 3057, 3026, 2927, 2884, 1751 (C=O of acetate), 1705 (C=O of isatin), 1621, 1597 cm^{-1}, ^1H NMR (400 MHz) 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 isatin), 6.66-7.79 (m, 7H, ArH), 8.83 (s, 1H, NH), ^{13}C NMR (125 MHz) 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-),

1'-Acetoxy-1'-(4-bromophenyl)spiro[indol-3,2'-cyclopropane]-2(1*H*)-one (2c). Light yellow solid, yield 65%, decomp.>110 ^oC, IR (KBr): 3419 (N-H of isatin), 3058, 3029, 2926, 2893, 1715 (broad, C=O of acetate and C=O of isatin overlapped), 1621, 1597 cm^{-1}, ^1H NMR (400 MHz) 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), ^{13}C NMR spectrum was not recorded due to low solubility of **2c** in $CDCl_3$.

1'-Acetoxy-1'-(4-bromophenyl)spiro[indol-3,2'-cyclopropane]-2(1*H*)-one (3c). Light yellow solid, yield 35%, decomp.>110 ^oC, IR (KBr): 3419 (N-H of isatin), 3056, 3028, 2926, 2892, 1715 (broad, C=O of acetate and C=O of isatin overlapped), 1620, 1597 cm^{-1}, ^1H NMR (400 MHz) 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 isatin), 6.73-7.87 (m, 7H, ArH), 8.39 (s, 1H, NH), ^{13}C NMR spectrum was not recorded due to low solubility of **3c** in $CDCl_3$.

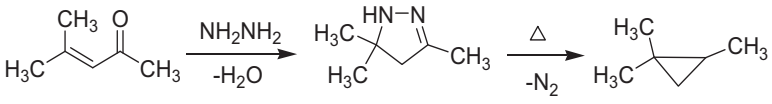
1'-Acetoxy-1'-(4-nitrophenyl)spiro[indol-3,2'-cyclopropane]-2(1*H*)-one (2d). Light yellow solid, yield 66%, decomp.>154 ^oC, IR (KBr): 3420 (N-H of isatin), 3080, 3031, 2925, 2890, 1719 (broad, C=O of acetate and C=O of isatin overlapped), 1624, 1597 cm^{-1}, ^1H NMR (400 MHz) δ: 2.09 (s, 3H, CH_3), 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 (125 MHz) 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-),

1'-Acetoxy-1'-(4-nitrophenyl)spiro[indol-3,2'-cyclopropane]-2(1*H*)-one (3d). Light yellow solid, yield 34%, decomp.>154 ^oC, IR (KBr): 3420 (N-H of isatin), 3082, 3031, 2924, 2890, 1719 (C=O of acetate and C=O of isatin overlapped), 1622, 1597 cm^{-1}, ^1H NMR (400 MHz) 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 isatin), 6.66-8.65 (m, 7H, ArH), 9.49 (s, 1H, NH), ^{13}C NMR (125 MHz) 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-),

Results and Discussion

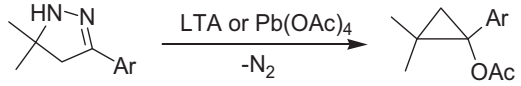
Among the synthetic procedures for preparation of cyclopropane rings, the Michael initiated ring closure reaction of α,β-unsaturated carbonyl compounds with dimethylsulfoxonium methylides or Corey-Chaykovsky reaction is the well-known method.[26,27] The Kishner's cyclopropanation method is another procedure.[28] In the Kishner's method, the cyclopropane

derivatives were prepared by thermal decomposition of 2-pyrazolines which formed by reacting of α,β-unsaturated ketones or aldehydes with hydrazine (Scheme 1).



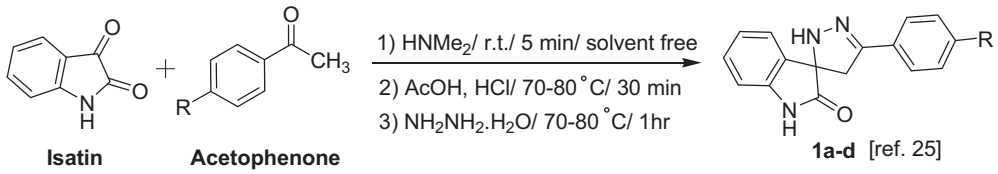
Scheme 1- Kishner cyclopropane synthesis.

In the Kishner's procedure, the reaction needs higher temperatures for removing the nitrogen. In the present study, we wish to report a simple procedure to synthesis the cyclopropane derivatives from the reaction of 2-pyrazolines with lead tetraacetate (LTA or $Pb(OAc)_4$) (Scheme 2). The LTA catalyzed the reaction and reacted with 2-pyrazoline and caused rapid nitrogen extrusion and reaction carried out in lower temperatures.



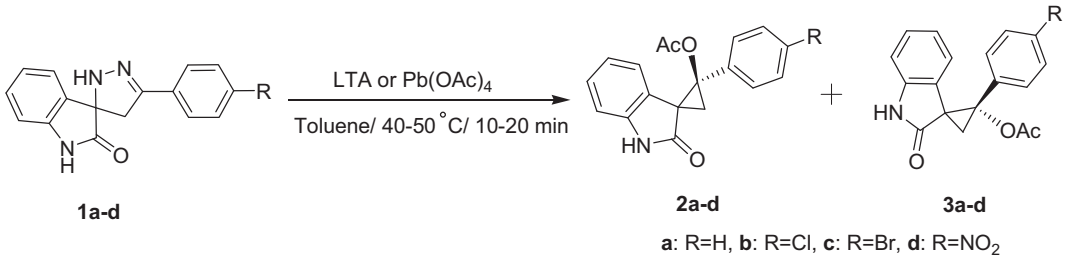
Scheme 2- Method for preparation of cyclopropane from 2-pyrazoline.

The 2-pyrazolines **1a-d** were prepared in a one-pot procedure. For this purpose, isatin was reacted with acetophenones in a solvent free condition catalyzed by dimethylamine and then completed with glacial acetic acid and HCl. The reaction was continued *in situ* with addition of hydrazine hydrate (Scheme 3).[25]



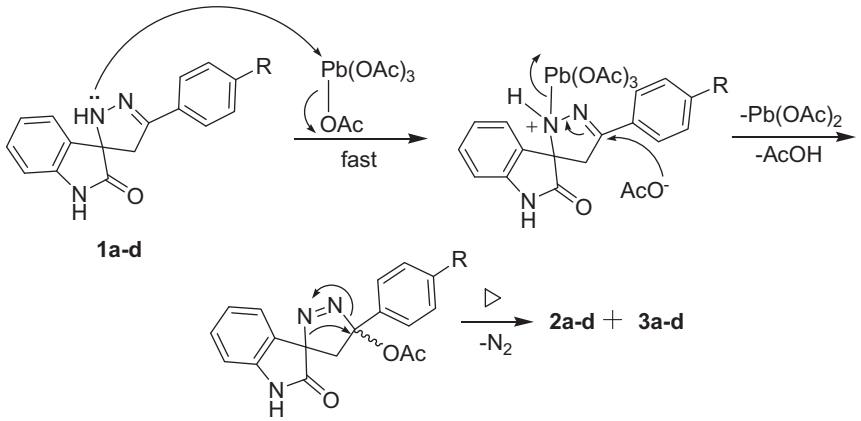
Scheme 3- One-pot preparation of 2-pyrazolines from isatin, acetophenones and hydrazine.

These 2-pyrazolines were reacted with LTA in toluene to afford new spiro isatin-cyclopropane derivatives **2a-d** and **3a-d** (Scheme 4).



Scheme 4- Synthesis of new spiro isatin-cyclopropane derivatives.

A probable mechanism for the reaction is presented in scheme 5.



Scheme 5- Reaction pathway for preparation of diastereomers 2a-d and 3a-d.

The diastereomers **2a-d** were prepared in higher yields than their **3a-d** isomers. For example, the diastereomeric ratios were determined by integration of separated signals in the ^{1}H NMR spectra of the mixture of compounds **2a** and **3a** in the reaction product. This ratio was **2a:3a**=2.7:1. The ratios for other derivatives were **2b:3b**=4.26:1, **2c:3c**=1.85:1, **2d:3d**=1.94:1.

All compounds **2a-d** and **3a-d** are new derivatives of isatin containing a spiro cyclopropane ring at C-3 position of isatin and were not reported in papers. Their structures were deduced from their IR, ^{1}H and ^{13}C NMR spectra.

The ^{1}H NMR spectrum of **2a** indicated two doublets at δ 2.19 and 2.77 ppm (J = 0.0175×400= 7 Hz) which belong to diastereotopic CH_2 protons of 3' position of cyclopropane ring and a singlet at δ 2.04 ppm for hydrogens of CH_3 in acetate group. The multiplets at δ 6.93-8.06 ppm showed the aromatic protons. A singlet at δ 8.40 ppm indicates the hydrogen of NH group. The ^{1}H decoupled ^{13}C NMR spectrum of **2a** exhibited spiro carbon at δ 37.98, 1' carbon of cyclopropane ring at δ 71.70, carbon of CH_3 at δ 21.30, carbon of CH_2 at δ 27.05, carbon of acetate group at δ 169.77 and carbon of amide in isatin moiety at δ 175.57 ppm.

In the ^{1}H NMR spectrum of compound **3a** a doublet was appeared at δ 5.65 (J = 0.02×400= 8 Hz) ppm for the H-4 hydrogen atom of isatin rings (Figure 1). This hydrogen was shielded by the anisotropic effect of the phenyl ring attached to the position 1' of cyclopropane ring.

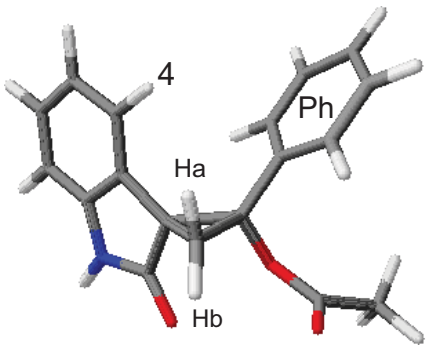


Figure 1- Shielding of H-4 by phenyl ring.

Conclusions

In summary, some novel spiro isatins containing the cyclopropane ring were synthesized from corresponding 2-pyrazolines in a rapid and simple procedure and the products were obtained in good yields. These compounds may be active biological substances and worthy of attention for the medicinal chemists.

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