One-pot diastereoselective synthesis of new spiro indenoquinoxaline derivatives containing cyclopropane ring

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Abstract
A one-pot procedure was introduced for the synthesis of some new spiro derivatives of indenoquinoxaline containing cyclopropane ring from chalcones. The chalcones **1a-e** were reacted with hydrazine hydrate and then *in situ* with lead(IV) acetate (LTA) and two new diastereomers **2a-e** and **3a-e** were prepared. The compounds **2a-e** diastereoselectively produced in higher yields than **3a-e**.

Keywords: Spiro compounds, chalcones, LTA, indenoquioxalines, cyclopropane, diastereoselective reaction

Introduction

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.[1, 2] Some derivatives of cyclopropane have shown potent HIV antiviral activities as non-nucleoside reverse transcriptase inhibitors.[3] Due to diversity of cyclopropane containing compounds with biological activity, chemists have tried to find novel and facile methods for synthesis of these compounds.[4, 5]

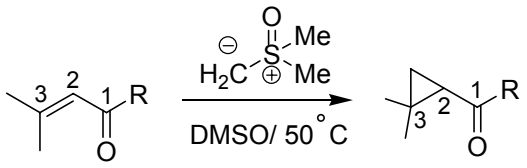
Indenoquinoxaline derivatives are important classes of nitrogen containing heterocycles and they have applications in dyes and are useful intermediates in organic synthesis and have also been used as building blocks for the synthesis of organic semiconductors.[6] More studies have discovered that these compounds exhibit diverse medical functions such as antimetabolism and antitubercular properties.[7]

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).[1, 8] In this study along our pervious works on the synthesis of spiro indenoquinoxalines and other biologically active compounds,[9, 10] we report a novel one-pot facile procedure for the synthesis of some spiro indenoquinoxaline-cyclopropane derivatives which directly prepared from chalcones of indenoquinoxaline.

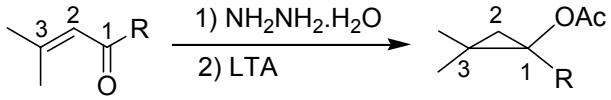
Results and Discussion

Among the synthetic procedures for preparation of cyclopropane rings, the Michael initiated ring closure (MIRC) reaction of α,β-unsaturated carbonyl compounds (like chalcones) with dimethylsulfoxonium methylides or Corey-Chaykovsky reaction is the well-known method.[11,12] In this reaction, the cyclopropane ring forms between C-2 and C-3 carbons of chalcones by addition of a new CH_2 group (Scheme 1).



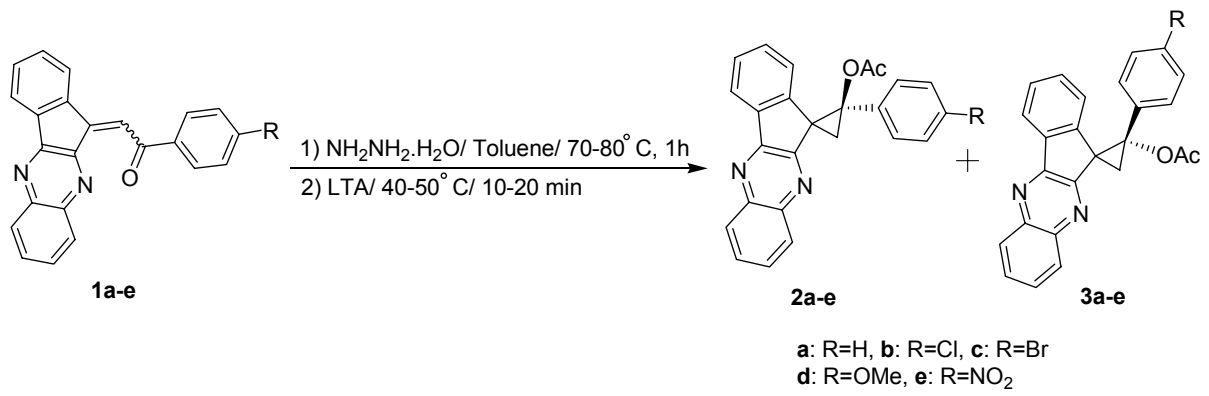
Scheme 1. Corey-Chaykovsky reaction.

In the present work, we wish to report a novel one-pot procedure to synthesis the cyclopropane derivatives with connecting the C-1 and C-3 carbons of chalcones (Scheme 2).



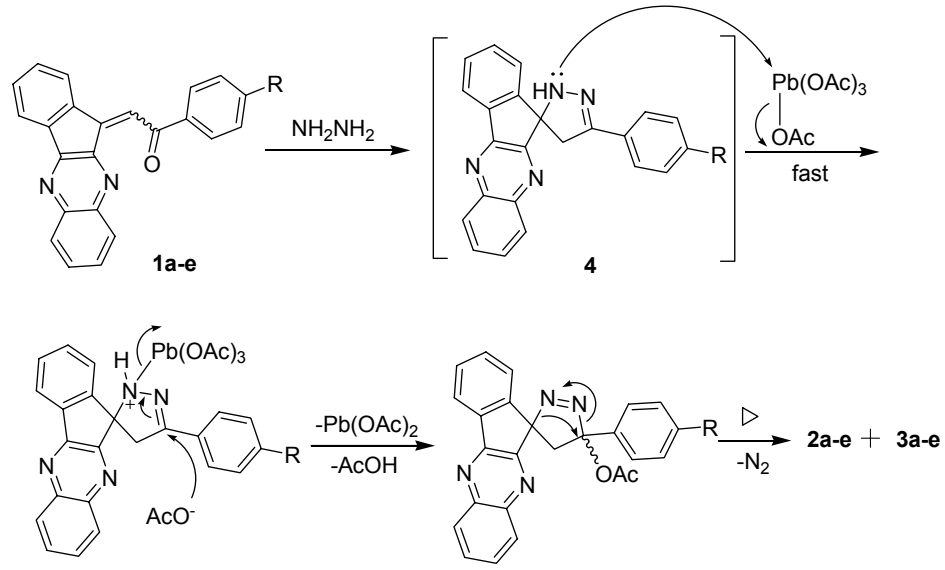
Scheme 2. One-pot procedure for synthesis of cyclopropane from chalcones.

The chalcones **1a-e** were prepared by the reaction of indenoquinoxaline with acetophenones in a solvent free condition catalyzed by dimethylamine and then glacial acetic acid and HCl.[10,14] These chalcones reacted with hydrazine hydrate in toluene and then *in situ* with lead(IV) acetate (LTA or $Pb(OAc)_4$) to afford new spiro indenoquinoxaline-cyclopropane derivatives **2a-e** and **3a-e** (Scheme 3).



Scheme 3. One-pot synthesis of spiro indenoquinoxaline-cyclopropane derivatives.

The intermediate of this reaction is a spiro indenoquinoxaline-pyrazoline **4** which was not separated and reacted *in situ* with LTA to form new diastereomers **2a-e** and **3a-e** and then the overall yield of the reaction increased. A probable mechanism of the one-pot reaction is presented in scheme 4.



Scheme 4. Reaction mechanism for preparation of diastereomers **2a-e** and **3a-e**.

This one-pot reaction was diastereoselective and diastereomers **2a-e** were prepared in higher yields than their **3a-e** 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 (Figure 1). This ratio was **2a**:**3a**=2.85:1. The ratios of other derivatives were **2b:3b**=3:1, **2c:3c**=3.35:1, **2d:3d**=1.04:1, **2e:3e**=3:1.

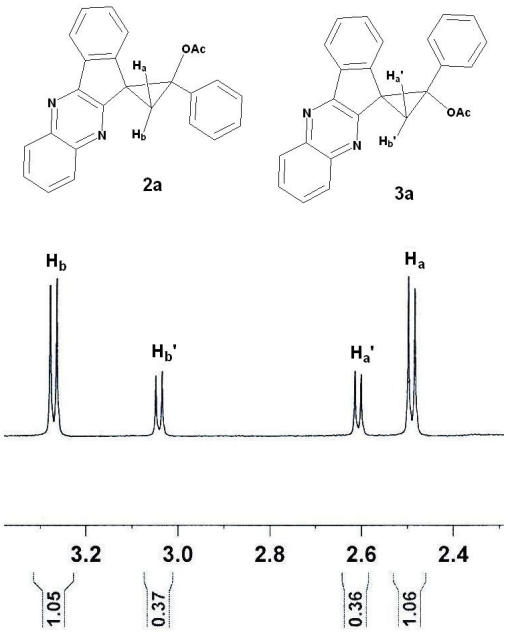


Figure 1. Diastereomeric ratio of **2a** and **3a** determined by ^{1}H NMR signal integrations.

All compounds **2a-e** and **3a-e** are new derivatives of 11*H*-indeno[1,2-*b*]quinoxalin-11-one containing a spiro cyclopropane ring at C-11 carbon atom of indenoquinoxaline. The prepared compounds have shown an excellent agreement between calculated and experimentally obtained data for CHN elemental analysis. Their structures were deduced from their elemental analyses and their IR, ^{1}H and ^{13}C NMR spectra.

For instant, the ^{1}H NMR spectrum of **2a** indicated two doublets at δ 2.48 and 3.26 ppm (J = 0.014×500= 7 Hz) which belong to diastereotopic CH_2 protons of C-3' position of cyclopropane ring and a singlet at δ 2.10 ppm for hydrogens of CH_3 in acetate group. The multiplets at δ 7.19-8.39 ppm showed the aromatic protons. The ^{1}H decoupled ^{13}C NMR spectrum of **2a** exhibited spiro carbon at δ 38.69, C-2' carbon of cyclopropane ring at δ 72.17, carbon of CH_2 at δ 27.39, carbon of CH_3 at δ 21.29 and carbon of acetate group at δ 170.67 ppm.

In the ^{1}H NMR spectrum of compound **3a** a doublet was appeared at δ 6.07 (J = 0.016×500= 8 Hz) ppm for the H-1 hydrogen atom of indenoquinoxaline ring. This hydrogen was shielded by the magnetic anisotropy effect of the phenyl ring attached to the position 2' of cyclopropane ring (Figure 2).

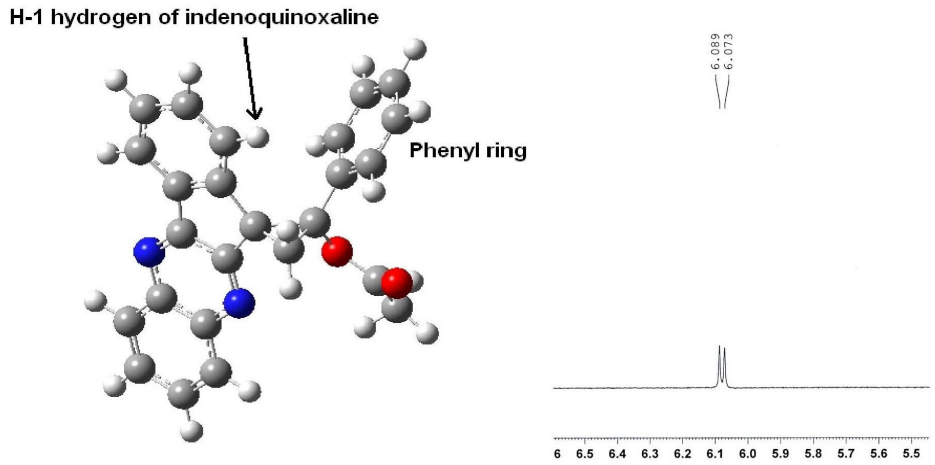


Figure 2. H-1 hydrogen shielded by anisotropic effect of the phenyl ring.

Conclusions

In summary, some novel spiro indenoquinoxalines containing the cyclopropane ring were synthesized from chalcones in a one-pot simple procedure and the products were obtained in good yields. These compounds can be active biological substances and worthy of attention for the medicinal chemists.

Experimental Section

General. The chemicals used in this work are the pure products which were purchased from Merck and Fluka companies. Melting points were measured on a Qallenkamp melting point apparatus in open capillary tubes and are uncorrected. IR spectra were taken from a Bruker Vector 22 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. 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. Indenoquinoxaline were prepared by the procedure described by Ruhemann.[13] The chalcones of indenoquinoxaline were synthesized with method of Lindwall and Mclennan.[14]

General procedure for preparation of chalcones of indenoquinoxaline.
To a solid homogenous mixture of 10 mmol indenoquinoxaline and 10 mmol acetophenones, 10 drops of dimethylamine was added and the mixture stirred for 15-30 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 **1a-e** were produced and washed with water (2×20ml) and then recrystallized from absolute ethanol.[10]

General procedure for preparation of spiro indenoquinoxaline-cyclopropane derivatives 2 and 3.

The chalcones **1a-e** (10 mmol) were dissolved in 20 ml toluene and then 11 mmol hydrazine hydrate was added to this solution and the mixture was stirred and refluxed at 70-80 ºC for one hour. 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-e** and **3a-e** were prepared (Scheme 3). The products were filtered and fractionally crystallized from ethanol/water.

2'-Acetoxy-2'-phenylspiro[indeno[1,2-*b*]quinoxalin-11,1'-cyclopropane] (2a). Light yellow solid, yield 74%, decomp.>110 ^{o}C; IR (KBr): 3052, 2920, 2851, 1752, 1606, 1569 cm^{-1}; ^{1}H NMR (500 MHz) δ: 2.10 (s, 3H, CH_3), 2.48 (d, 1H, J = 7 Hz, C**H$_{2a}$**), 3.26 (d, 1H, J = 7 Hz, C**H$_{2b}$**), 7.19-8.39 (m,13H, ArH); ^{13}C NMR (125 MHz) δ: 21.29 (CH_3), 27.39 (CH_2), 38.69 (spiro carbon), 72.17 (Ph-**C**-OAc), 122.58, 123.15, 127.98, 128.75, 129.14, 129.25, 129.55, 129.63, 129.76, 130.90, 131.94, 134.89, 137.40, 141.60, 142.45, 145.51, 154.40, 159.63, 170.67 (**C**=O); Anal. Calcd. for $C_{25}H_{18}N_2O_2$ (378.4): C, 79.35; H, 4.79; N, 7.40; Found: C, 79.27; H, 4.69; N, 7.38%.

2'-Acetoxy-2'-phenylspiro[indeno[1,2-*b*]quinoxalin-11,1'-cyclopropane] (3a). Light yellow solid, yield 26%, decomp.>110 ^{o}C; IR (KBr): 3053, 2920, 2850, 1750, 1608, 1567 cm^{-1}; ^{1}H NMR (500 MHz) δ: 2.01 (s, 3H, CH_3), 2.60 (d, 1H, J = 7 Hz, C**H$_{2a}$**), 3.03 (d, 1H, J = 7 Hz, C**H$_{2b}$**), 6.07 (d, 1H, J = 8 Hz, H-1 Indqn.), 7.12-8.34 (m,12H, ArH); ^{13}C NMR (125 MHz) δ: 21.44 (CH_3), 26.59 (CH_2), 38.37 (spiro carbon), 72.13 (Ph-**C**-OAc), 123.01, 123.39, 128.10, 128.75, 128.86, 129.36, 129.61, 129.76, 130.64, 131.05, 131.94, 134.81, 137.94, 141.24, 142.12, 145.07, 154.09, 158.8, 170.2 (**C**=O); Anal. Calcd. for $C_{25}H_{18}N_2O_2$ (378.4): C, 79.35; H, 4.79; N, 7.40; Found: C, 79.39; H, 4.61; N, 7.30%.

2'-Acetoxy-2'-(4-chlorophenyl)spiro[indeno[1,2-*b*]quinoxalin-11,1'-cyclopropane] (2b). Light yellow solid, yield 75%, decomp.>107 ^{o}C; IR (KBr): 3060, 2924, 2851, 1756, 1610, 1588 cm^{-1}; ^{1}H NMR (400 MHz) δ: 2.09 (s, 3H, CH_3), 2.46 (d, 1H, J = 7 Hz, C**H$_{2a}$**), 3.19 (d, 1H, J = 7 Hz, C**H$_{2b}$**), 7.16-8.33 (m, 12H, ArH); ^{13}C NMR (125 MHz) δ: 21.38 (CH_3), 26.60 (CH_2), 38.34 (spiro carbon), 71.24 (Ar-**C**-OAc), 123.07, 123.36, 128.21, 128.26, 129.03, 129.07, 129.32, 129.40, 129.64, 131.11, 132.28, 133.50, 137.97, 141.19, 142.10, 144.73, 154.07, 158.45, 170.02 (**C**=O); Anal. Calcd. for $C_{25}H_{17}ClN_2O_2$ (412.9): C, 72.73; H, 4.15; N, 6.79; Found: C, 72.65; H, 4.03; N, 6.77%.

2'-Acetoxy-2'-(4-chlorophenyl)spiro[indeno[1,2-*b*]quinoxalin-11,1'-cyclopropane] (3b). Light yellow solid, yield 25%, decomp.>107 ^{o}C; IR (KBr): 3062, 2925, 2854, 1757, 1613, 1584 cm^{-1}; ^{1}H NMR (400 MHz) δ: 1.99 (s, 3H, CH_3), 2.52 (d, 1H, J = 7 Hz, C**H$_{2a}$**), 3.01 (d, 1H, J = 7 Hz, C**H$_{2b}$**), 6.10 (d, 1H, J = 8 Hz, H-1 Indqn.), 7.14-8.27 (m, 11H, ArH); ^{13}C NMR (125 MHz) δ:

21.21 (CH_3), 27.26 (CH_2), 38.64 (spiro carbon), 71.24 (Ar-**C**-OAc), 122.74, 125.72, 127.98, 128.65, 129.24, 129.36, 129.46, 129.53, 129.78, 130.80, 132.28, 133.38, 137.49, 141.56, 142.48, 145.11, 154.33, 159.34, 170.69 (**C**=O); Anal. Calcd. for $C_{25}H_{17}ClN_2O_2$ (412.9): C, 72.73; H, 4.15; N, 6.79; Found: C, 72.59; H, 4.11; N, 6.64%.

2'-Acetoxy-2'-(4-bromophenyl)spiro[indeno[1,2-*b*]quinoxalin-11,1'-cyclopropane] (2c). Light yellow solid, yield 77%, decomp.>150 ^oC; IR (KBr): 3060, 2928, 2849, 1751, 1612, 1550 cm^{-1}; ^1H NMR (400 MHz) δ: 2.09 (s, 3H, CH_3), 2.45 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 3.18 (d, 1H, J = 7 Hz, C**H**$_{2b}$), 7.24-8.33 (m, 12H, ArH); ^{13}C NMR (125 MHz) δ: 21.37 (CH_3), 26.55 (CH_2), 38.30 (spiro carbon), 71.28 (Ar-**C**-OAc), 123.07, 123.37, 128.27, 129.09, 129.33, 129.40, 129.65, 129.72, 131.17, 132.00, 132.56, 133.71, 137.98, 141.19, 142.10, 144.70, 154.06, 158.42, 170.01 (**C**=O); Anal. Calcd. for $C_{25}H_{17}BrN_2O_2$ (457.3): C, 65.66; H, 3.75; N, 6.13; Found: C, 65.48; H, 3.66; N, 6.07%.

2'-Acetoxy-2'-(4-bromophenyl)spiro[indeno[1,2-*b*]quinoxalin-11,1'-cyclopropane] (3c). Light yellow solid, yield 23%, decomp.>150 ^oC; IR (KBr): 3059, 2925, 2851, 1751, 1611, 1553 cm^{-1}; ^1H NMR (400 MHz) δ: 1.99 (s, 3H, CH_3), 2.51 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 3.00 (d, 1H, J = 7 Hz, C**H**$_{2b}$), 6.12 (d, 1H, J = 8 Hz, H-1 Indqn.), 7.19-8.27 (m, 11H, ArH); ^{13}C NMR (125 MHz) δ: 21.20 (CH_3), 27.20 (CH_2), 38.45 (spiro carbon), 71.29 (Ar-**C**-OAc), 122.74, 122.89, 127.98, 129.23, 129.35, 129.47, 129.52, 129.78, 130.82, 132.29, 132.56, 133.90, 137.50, 141.70, 142.60, 145.08, 154.45, 159.32, 170.55 (**C**=O); Anal. Calcd. for $C_{25}H_{17}BrN_2O_2$ (457.3): C, 65.66; H, 3.75; N, 6.13; Found: C, 65.59; H, 3.71; N, 6.02%.

2'-Acetoxy-2'-(4-methoxyphenyl)spiro[indeno[1,2-*b*]quinoxalin-11,1'-cyclopropane] (2d). Light yellow solid, yield 51%, decomp.>132 ^oC; IR (KBr): 3060, 2957, 2930, 2836, 1753, 1612, 1575 cm^{-1}; ^1H NMR (400 MHz) δ: 2.08 (s, 3H, CH_3), 2.46 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 3.18 (d, 1H, J = 7 Hz, C**H**$_{2b}$), 3.81 (s, 3H, OCH_3), 6.80 (d, 2H, J = 8 Hz, ArH), 7.22-8.27 (m, 10H, ArH); ^{13}C NMR (125 MHz) δ: 21.31 (CH_3), 26.92 (CH_2), 38.53 (spiro carbon), 55.63 (O**C**H$_3$), 71.98 (Ar-**C**-OAc), 113.35, 123.00, 123.27, 128.02, 128.84, 129.10, 129.36, 129.74, 130.68, 132.38, 133.42, 137.88, 141.28, 142.04, 145.25, 154.13, 158.94, 159.89, 170.73 (**C**=O); Anal. Calcd. for $C_{26}H_{20}N_2O_3$ (408.4): C, 76.45; H, 4.94; N, 6.86; Found: C, 76.34; H, 4.93; N, 6.83%.

2'-Acetoxy-2'-(4-methoxyphenyl)spiro[indeno[1,2-*b*]quinoxalin-11,1'-cyclopropane] (3d). Light yellow solid, yield 49%, decomp.>132 ^oC; IR (KBr): 3061, 2958, 2930, 2834, 1752, 1610, 1572 cm^{-1}; ^1H NMR (400 MHz) δ: 1.98 (s, 3H, CH_3), 2.52 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 2.99 (d, 1H, J = 7 Hz, C**H**$_{2b}$), 3.73 (s, 3H, OCH_3), 6.11 (d, 1H, J = 8 Hz, H-1 Indqn.), 6.70 (d, 2H, J = 8 Hz, ArH), 7.12-8.33 (m, 9H, ArH); ^{13}C NMR (125 MHz) δ: 21.47 (CH_3), 27.77 (CH_2), 38.83 (spiro carbon), 55.69 (O**C**H$_3$), 71.87 (Ar-**C**-OAc), 113.99, 121.39, 123.30, 127.70, 128.65, 129.19, 129.46, 129.74, 131.03, 131.76, 132.01, 137.38, 141.59, 142.41, 145.69, 154.42, 159.8, 160.44, 170.07 (**C**=O); Anal. Calcd. for $C_{26}H_{20}N_2O_3$ (408.4): C, 76.45; H, 4.94; N, 6.86; Found: C, 76.41; H, 4.87; N, 6.78%.

2'-Acetoxy-2'-(4-nitrophenyl)spiro[indeno[1,2-*b*]quinoxalin-11,1'-cyclopropane] (2e). Light yellow solid, yield 75%, decomp.>119 ^oC; IR (KBr): 3060, 2923, 2851, 1755, 1604, 1522 cm^{-1}; ^1H NMR (400 MHz) δ: 2.14 (s, 3H, CH_3), 2.50 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 3.28 (d, 1H, J = 7 Hz,

C**H**$_{2b}$), 7.14-8.32 (m, 12H, ArH); ^{13}C NMR (125 MHz) δ: 21.27 (CH_3), 26.45 (CH_2), 38.48 (spiro carbon), 70.43 (Ar-**C**-OAc), 123.22, 123.54, 124.00, 128.59, 129.33, 129.46, 129.48, 129.66, 131.23, 131.57, 133.02, 138.13, 141.01, 142.17, 144.04, 147.92, 153.99, 157.79, 170.03 (**C**=O); Anal. Calcd. for $C_{25}H_{17}N_3O_4$ (423.4): C, 70.91; H, 4.05; N, 9.92; Found: C, 70.86; H, 3.97; N, 9.96%.

2'-Acetoxy-2'-(4-nitrophenyl)spiro[indeno[1,2-*b*]quinoxalin-11,1'-cyclopropane] (3e). Light yellow solid, yield 25%, decomp.>119 ^{o}C; IR (KBr): 3060, 2922, 2851, 1757, 1605, 1524 cm^{-1}; ^{1}H NMR (400 MHz) δ: 2.01 (s, 3H, CH_3), 2.59 (d, 1H, J = 7 Hz, C**H**$_{2a}$), 3.07 (d, 1H, J = 7 Hz, C**H**$_{2b}$), 6.05 (d, 1H, J = 8 Hz, H-1 Indqn.), 7.15-8.40 (m, 11H, ArH); ^{13}C NMR (125 MHz) δ: 21.10 (CH_3), 26.77 (CH_2), 38.66 (spiro carbon), 70.60 (Ar-**C**-OAc), 123.18, 123.82, 125.81, 128.56, 129.42, 129.58, 129.84, 129.93, 130.89, 131.44, 132.90, 138.25, 141.54, 141.66, 144.39, 148, 155.12, 158.20, 170.00 (**C**=O); Anal. Calcd. for $C_{25}H_{17}N_3O_4$ (423.4): C, 70.91; H, 4.05; N, 9.92; Found: C, 70.93; H, 4.05; N, 9.90%.

Acknowledgements

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