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A highly regioselective synthesis of spiro [oxindole-chromanone]pyrrolidines and pyrrolizines through 1,3-dipolarcycloaddition protocol

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ABSTRACT

Intermolecular 1,3-dipolar-cycloaddition reaction of azomethine ylides, generated through decarboxylation route, with (E)-3-arylidene-4- chromanones as dipolarophiles has been investigated. A new class of functionalized spirooxindoles with pyrrolidine and pyrrolizines framework has been synthesized with high regioselectivity. The structures were established by spectroscopic techniques as well as single crystal X-ray analysis.

Keywords: Spiropyrrolidines, Spiropyrrolizines, 1,3-Dipolar addition, Azomethine ylides, Chromanones, Oxindole.

INTRODUCTION

Intermolecular 1,3-dipolar cycloaddition reaction of azomethine ylide with olefins are considered as one of the most useful method for the construction of the pyrrolidine structural unit.[1,2] This method is widely used in the synthesis of natural products such as alkaloids and pharmaceuticals.[3] Spiro-oxindole ring system represents an important class of naturally occurring substances characterized by highly pronounced biological properties.[4-6]Oxindole derivatives are found to be potent aldose reductase inhibitors(ARI) , which help to treat and prevent diabetic complications arising from elevated levels of sorbitol.[7]

Pyrrolidine and oxindole alkaloids[8] constitute another class of compounds with significant biological activities which are normally found in rhyncophylline, corynoxeine, nitraphylline, vincatine, horsifiline etc.[9] As a part of our ongoing research[10] program in the area of cycloaddition reaction of azomethine ylides with 3-arylidene-4-chromanones, we herein report the highly regioselective synthesis of Spiro[oxindole-chromanone] pyrrolidines and pyrrolizines through 1,3 –dipolar cycloaddition protocol. Although highly functionalised and substituted spiropyrrolidines are known, there seems to be no report on the synthesis of dispiroheterocycles using isatin and chromanone moiety. The construction of novel dispiropyrrolidinyl derivatives (**4a-f**) was achieved through the 1,3-dipolar cycloaddition reactions of (E)-3-arylidene-4-chromanones (**3**) with the azomethine ylides generated from isatin (**1**) and sarcosine (**2**) through decarboxylation method.

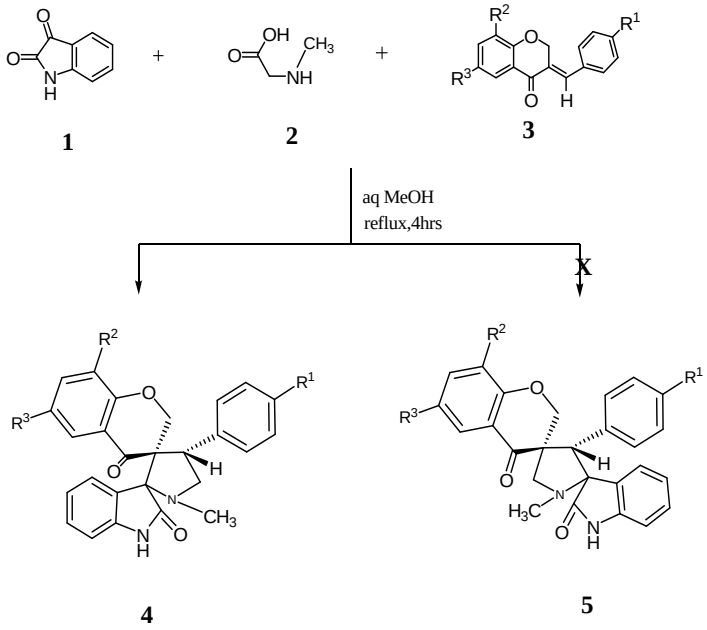
MATERIALS AND METHODS

Refluxing a solution of (E)-3-benzylidenechroman-4-one (**3**) in boiling aqueous methanol with isatin (**1**) and sarcosine (**2**) afforded 1-*N*-methyl-spiro[2.3'] oxindole-Spiro[3.3"](6"-methoxychroman-4"-one)-4-phenyl pyrrolidine (**4**) (Scheme1, Table 1). The reaction gave a single product in all cases as evidenced by thin layer chromatography (TLC). The reaction afforded a series of novel Spiro derivatives (**4a-f**) through regioselective cycloaddition of azomethine ylides with the exocyclic double bond of 3-arylidene-chroman-4-ones (**3**) in all cases. No trace of the other regioisomer (**5a-f**) was detected. The cycloaddition proceeded smoothly to afford the *syn-endo*

cycloadduct. The regio and stereo chemical outcome of the cycloaddition was determined by spectrochemical and single crystal X-ray analysis.

RESULTS AND DISCUSSION

The IR spectra of **4** showed two carbonyl peaks at 1687 cm^{-1} and 1715 cm^{-1} which correspond to the chromanone and oxindole ring carbonyls respectively. The ^1H NMR spectrum of the cycloadduct **4** exhibited a singlet at δ 7.80, which corresponds to -CONH proton. A triplet at δ 4.98 corresponds to benzylic proton. The cycloaddition proceeded to afford syn-endo cycloadducts which was very well established from the crystal structure of the compound.[11] Further, the regiochemistry of the cycloadduct **4** was established by the ^1H NMR spectrum where a doublet at δ 4.70 corresponds to aryloxymethyl protons and a doublet at δ 3.42 corresponds to N-CH_2 proton.



1 **2** **3**

4 **5**

Scheme 1

A singlet at δ 3.69 correspond to –OCH_3 protons. ^{13}C NMR spectrum of **4** adds conclusive support for the proposed structure. It exhibits the presence of benzylic carbon at δ 56.93, spiro carbons at δ 65.70 and δ 72.21, N-methyl carbon at δ 34.64, and N-CH_2 carbon at δ 44.01. The signals at δ 192.17 and δ 177.57 indicate the presence of chromanone and oxindole ring carbonyls respectively. These observed chemical shift values confirmed the proposed structure .The mass spectrum of the compound showed a peak at m/z 440.77 (M^+) which corresponds to the molecular weight of the compound. Identical results were obtained with other derivatives and it has been observed that the cycloaddition had taken place regioselectively across the exocyclic double bond of the arylidene chromanone irrespective of the nature of the substituent present in the arylidene moiety.

Table 1. Synthesis of 1-*N*-methyl-spiro[2.3']Oxindole-Spiro [3.3"](6"-methoxychroman-4"-one)-4-phenyl pyrrolidines (4a-f) *via* Scheme 1

Compound	R_1	R_2	R_3
4a	**H**	**H**	**OCH_3**
4b	**H**	**OC_2H_5**	**CH_3**
4c	**OCH_3**	**OCH_3**	**CH=CH (CH_3)**
4d	**CH_3**	**H**	**OCH_3**
4e	**OCH_3**	**OC_2H_5**	**CH_3**
4f	**CH_3**	**OCH_3**	**CH_3**

Spiro-Compound 4a: IR (KBr): 1687, 1715 cm^{-1}; ^1H NMR ($CDCl_3$/400 MHz): δ 2.20 (s, 3H), 3.42 (d, 2H, J=5.2 Hz), 3.69(s, 3H), 4.74 (d, 2H, J=12.4 Hz), 4.98 (t, 1H, J=9.0 Hz), 7.80 (s, 1H), 6.42-7.47 (m,12H); ^{13}C NMR ($CDCl_3$/400 MHz): δ 34.64, 44.01, 55.78, 56.93, 65.70, 72.21, 74.51, 108.80, 117.75, 124.38, 126.93, 127.33, 128.50, 129.06, 129.44, 141.11, 155.91, 177.57, 192.17 ppm; EIMS m/z : 440.77 (M^+) ; CHN Anal. Calcd for $C_{27}H_{24}N_2O_4$: C, 73.62; H, 5.49; N, 6.36; O, 14.53%; found: C, 73.58; H, 5.34; N, 6.57; O, 14.51%.

Spiro-compound 4b: IR (KBr): 1688, 1717 cm^{-1}; ^1H NMR ($CDCl_3$/400 MHz): δ 1.33 (t, 3H, J=5.4 Hz), 2.05 (s, 3H), 2.18 (s, 3H), 3.32 (d, 2H J=4.8 Hz), 3.79 (q, 2H), 4.75 (d, 2H, J=12.4 Hz), 4.93 (t, 1H, J=12.4Hz), 7.80 (s, 1H), 6.46-7.41 (m, 11H); ^{13}C NMR ($CDCl_3$/400 MHz): δ 34.78, 44.55, 55.76, 56.85, 65.02, 72.65, 74.51, 119.27, 120.33, 126.93,127.45,128.50,129.44,129.53,136.50, 141.11, 155.91, 172.68, 198.46 ppm; EIMS m/z : 468.20 (M^+); CHN Anal. Calcd for $C_{29}H_{28}N_2O_4$: C, 74.34; H, 6.02; N, 5.98; O, 13.66%; found: C, 74.32; H, 6.15; N, 5.80; O, 13.55%.

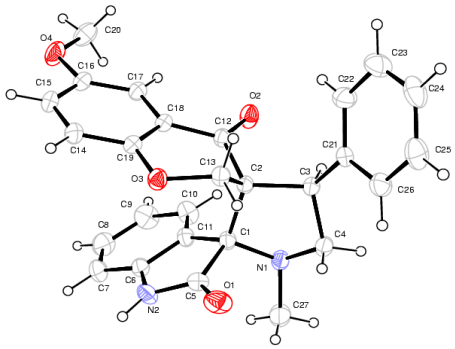
Spiro-compound 4c: IR (KBr): 1690, 1720 cm^{-1}; ^1H NMR ($CDCl_3$/400 MHz): δ 2.27 (s, 3H), 3.67 (s, 3H), 3.70 (s, 3H), 3.73 (d, 3H J=5.4 Hz), 3.93 (d, 2H J=4.9 Hz),4.70 (d, 1H, J=6.2 Hz), 4.75 (d, 2H, J=12.4 Hz), 4.98 (t, 1H, J=8.6Hz), 6.06 (d, 1H, J=7.8 Hz), 6.75-7.54 (m, 10H), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$/400 MHz): δ 33.37, 37.55, 55.32, 65.70, 67.34, 68.36, 72.46, 74.72, 108.77, 114.15, 115.96, 119.03, 124.43, 128.50, 129.44, 129.53, 136.76, 147.44, 155.91, 172.08, 198.44 ppm; EIMS m/z : 510.58 M^+); CHN Anal. Calcd for $C_{31}H_{30}N_2O_5$: C, 72.92; H, 5.92; N, 5.49; O, 15.67%; found: C, 72.59; H, 5.98; N, 5.88; O, 15.55%.

Spiro-compound 4d: IR (KBr): 1687, 1754 cm^{-1}; ^1H NMR ($CDCl_3$/400 MHz): δ 2.20 (s, 3H), 2.30 (s, 3H), 3.69 (s, 3H), 3.72 (d, 2H, J=4.8 Hz), 4.77 (d, 2H, J=12.2 Hz), 4.98 (t, 1H, J=8.8 Hz), 6.48-7.57 (m,11H), 8.00 (s, 1H) ; ^{13}C NMR ($CDCl_3$/400 MHz): δ 24.33, 34.64, 44.01, 56.93, 65.39, 72.21, 74.51, 117.75, 122.14, 124.38, 126.93, 127.33, 128.50, 129.06, 129.44, 136.50, 141.11, 155.91, 172.57, 192.17 ppm; EIMS m/z : 454.19 (M^+) ; CHN Anal. Calcd for $C_{28}H_{26}N_2O_4$: C, 73.99; H, 5.77; N, 6.16; O, 14.08%; found: C, 73.84; H, 5.68; N, 6.38; O, 14.10%.

Spiro-compound 4e: IR (KBr): 1688, 1717 cm^{-1}; ^1H NMR ($CDCl_3$/400 MHz): δ 1.30 (t, 3H, J=5.4 Hz), 2.08 (s, 3H), 2.18 (s, 3H), 3.30 (d, 2H J=4.7 Hz), 3.68 (s, 3H), 3.76 (q, 2H), 4.72 (d, 2H, J=12.4 Hz), 4.83 (t, 1H, J=12.2Hz), 7.90 (s, 1H), 6.56-7.51 (m, 10H); ^{13}C NMR ($CDCl_3$/400 MHz): δ 24.61, 34.75, 44.65, 55.76, 56.85, 65.17, 72.65, 74.51, 119.36, 120.23, 126.87, 127.45, 128.50, 129.38, 129.67, 135.75, 141.11, 156.01, 172.56, 198.34 ppm; EIMS m/z : 498.22 (M^+); CHN Anal. Calcd for $C_{30}H_{30}N_2O_5$: C, 72.22; H, 6.04; N, 5.68; O, 16.06%; found: C, 72.27; H, 6.06; N, 5.62; O, 16.05%.

Spiro-compound 4f: IR (KBr): 1687, 1754 cm^{-1}; ^1H NMR ($CDCl_3$/400 MHz): δ 2.27 (s, 3H), 2.30 (s, 3H), 2.35 (s, 3H), 3.73 (s, 3H), 3.72 (d, 2H, J=4.8 Hz), 4.77 (d, 2H, J=12.2 Hz), 4.98 (t, 1H, J=8.8 Hz), 6.51-7.59 (m,10H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$/400MHz): δ 24.33, 24.60, 37.94, 44.01, 56.93, 65.71, 72.21, 74.51, 117.75, 122.14, 124.28, 126.29, 128.23, 128.50, 129.06, 129.44, 136.50, 141.70, 152.71, 172.57, 198.47 ppm; EIMS m/z : 468.19 (M^+) ; CHN Anal. Calcd for $C_{29}H_{28}N_2O_4$: C, 74.34; H, 6.02; N, 5.98; O, 13.66%; found: C, 74.30; H, 5.98; N, 6.08; O, 13.64%.

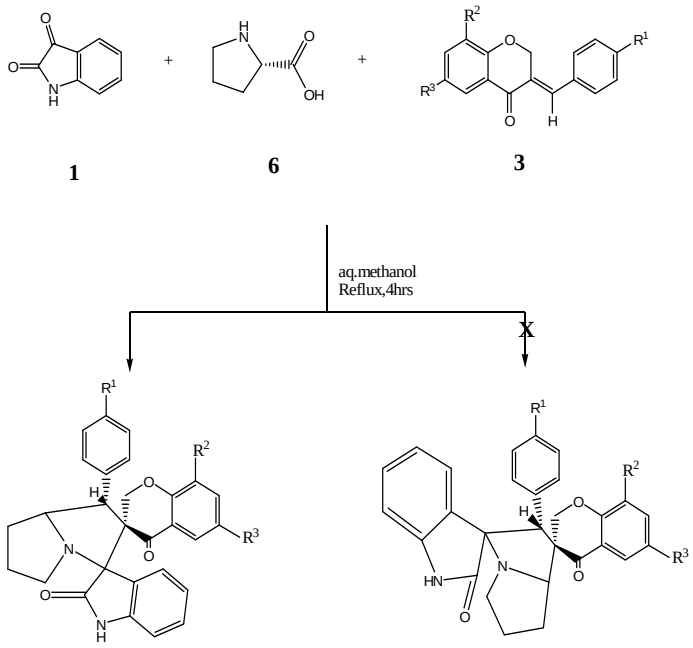
In continuation of our research,[12,13] we synthesized another series of novel oxindole-spiropyrrolizines (**7a-f**) (Scheme 2, Table 2), which are structurally similar to compounds **4a-f** but differ in the *N*-methyl group where a pyrrolizine moiety replaces the *N*-methyl group.



ORTEP diagram of compound 4a[11]

Refluxing a solution of (E)-3-benzylidenechroman-4-one (**3**) in boiling aqueous methanol with isatin (**1**) and *L*-proline (**6**) afforded Spiro [2.3'] oxyindolino-spiro [3.3"]-(6"-methoxychroman-4"-one)-4-phenyl hexahydro pyrrolizine **(7)**. The reaction proceeded via formation of an azomethine ylide which readily undergoes 1,3-dipolar cycloaddition reaction with 3-arylidene -4- chromanones to give a single cycloadduct , in a one pot three component process as evidenced by thin layer chromatography (TLC) and spectral studies. The reaction afforded a series of novel spiro derivatives regioselectively in all cases as no trace of the other regioisomer was detected.

The IR spectral analysis of **7** showed two carbonyl peaks at 1675 cm^{-1} and 1745 cm^{-1} which correspond to the chromanone and oxindole ring carbonyls. The ^1H NMR spectrum of the cycloadduct **7** exhibited a singlet at δ 3.56 for three methoxy protons. A doublet at δ 4.54 indicates the presence of aryloxy methyl proton. A doublet at δ 4.93 corresponds to the benzylic proton. Doublets at δ 3.77 and δ 3.34 correspond to N-CH and N-CH_2 proton. ^{13}C NMR spectrum of **7** adds conclusive support for the proposed structure. ^{13}C NMR spectra of **7** exhibits the presence of two Spiro carbons at δ 66.69 and δ 72.81. Chromanone and oxindole ring carbonyls at δ 193.25 and δ 206.45. The signals at δ 56.43 and δ 48.17 indicate the presence of benzylic and N-CH_2 carbon. The mass spectrum of the compound showed a peak at m/z 466.62 (M^+) which corresponds to the molecular weight of the compound. Identical results were observed for the other derivatives irrespective of the nature of the substituent present in the arylidene ring.



Scheme 2

Table 2. Synthesis of Spiro[2.3']Oxyindolino-spiro[3.3"]-(6"-methoxy chroman-4"-one)-4-phenylhexahydro pyrrolizine (7a-f) *via* Scheme 2

Compound	R_1	R_2	R_3
7a	**H**	**H**	**OCH_3**
7b	**OCH_3**	**OC_2H_5**	**OCH_3**
7c	**H**	**OCH_3**	**$CH=CH(CH_3)$**
7d	**CH_3**	**H**	**OCH_3**
7e	**OCH_3**	**OCH_3**	**CH_3**
7f	**CH_3**	**OCH_3**	**CH_3**

Spiro-compound 7a: IR (KBr): 1685, 1715 cm^{-1}; ^1H NMR ($CDCl_3$/400 MHz): δ 2.13 (m, 4H), 3.34 (d, 2H, J=12.4 Hz), 3.56(s, 3H), 3.77 (d, 1H, J=14.4Hz) 4.54 (d, 2H, J=12.4 Hz), 4.93 (d, 1H, J= 11.3 Hz), 6.06-7.91δ (m, 12H) 7.82 (s, 1H,) ; ^{13}C NMR ($CDCl_3$/400 MHz): δ 24.45, 28.05, 48.17, 51.25, 56.43, 66.69, 72.81, 72.96, 109.72, 121.36, 123.61, 125.28, 127.81, 128.32, 129.27, 130.40, 131.47, 137.23, 141.67, 162.94, 172.45, 193.25 ppm; EIMS m/z: 466.62 (M^+); CHN Anal. Calcd for $C_{29}H_{26}N_2O_4$: C, 74.66; H, 5.62; N, 6.00; O, 13.72%; found: C, 74.45; H, 5.68; N, 5.97; O, 13.35%.

Spiro-compound 7b: IR (KBr): 1672, 1718 cm^{-1}; ^1H NMR ($CDCl_3$/400 MHz): δ 1.52 (t, 3H, J=5.4Hz), 2.18 (m, 4H), 3.34 (d, 2H, J=12.2 Hz) , 3.56 (s, 3H), 3.61 (s, 3H) , 3.62 (d,1H, J=14.2Hz), 4.15 (q, 2H), 4.58 (d, 2H, J=12.2Hz) , 4.93 (d, 1H, J=11.4 Hz), 6.36-7.85 (m, 10H), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$/400 MHz): δ 24.40, 28.24, 48.29, 51.48, 56.55, 66.60, 72.48, 109.86, 121.48, 123.55, 125.15, 127.24, 128.36, 129.31, 129.27, 130.40, 131.47, 137.28, 141.56, 162.55, 172.21, 192.98 ppm; EIMS m/z : 524.61 (M^+); CHN Anal. Calcd for $C_{32}H_{32}N_2O_5$: C, 73.26; H, 6.15; N, 5.34; O, 15.25%; found: C, 73.20; H, 6.21; N, 5.25; O, 15.34%.

Spiro-compound 7c: IR (KBr): 1685, 1712 cm^{-1}; ^1H NMR ($CDCl_3$/400 MHz): δ 2.16 (m, 4H) , 3.38 (d, 2H , J= 12.2 Hz) , 3.50 (d, 1H, J= 14.2 Hz), 3.63 (d, 3H, J=5.4 Hz), 3.68 (s, 3H) , 3.98 (d, 1H, J=6.2 Hz), 4.58 (d, 2H,

J=12.2 Hz), 4.98 (d, 1H, J= 6.4 Hz), 5.88 (s, 1H) , 6.05 (s, 1H) , 6.59-7.62 (m, 11H), 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$/ 400 MHz): δ 24.46, 28.00, 48.17, 51.25, 56.43, 66.69, 72.81, 72.96, 109.72, 121.33, 123.61, 125.43, 127.85, 128.32, 129.32, 129.27, 131.96, 132.28, 137.24, 141.63, 147.65, 150.08, 162.94, 172.41, 193.25 ppm; EIMS m/z: 506.59 (M^+); CHN Anal. Calcd for $C_{32}H_{30}N_2O_4$: C, 75.87; H, 5.97; N, 5.53; O, 12.63%; found: C, 75.90; H, 6.00; N, 5.50; O, 12.60%.

Spiro-compound 7d: IR (KBr): 1687, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$/400 MHz): δ 2.14 (m, 4H) , 2.78 (s, 3H), 3.36 (d, 2H, J=12.4 Hz), 3.60 (d, 1H, J=14.4), 3.67 (s, 3H), 4.68 (d, 2H, J=12.4 Hz), 4.90 (d, 1H, J=6.2 Hz), 6.35-7.88 (m, 11H), 7.98 (s, 1H); ^{13}C NMR ($CDCl_3$/400 MHz): δ 24.45, 28.05, 39.37, 48.29, 51.48, 56.23, 66.65, 72.46, 109.76, 121.36, 123.54, 125.28, 127.81, 128.32, 129.27, 129.27, 130.40, 131.47, 137.23, 141.67, 162.94, 172.38, 193.54 ppm; EIMS m/z: 480.55 (M^+); CHN Anal. Calcd for $C_{30}H_{28}N_2O_4$: C, 74.98; H, 5.87; N, 5.83; O, 13.32%; found: C, 74.90; H, 5.80; N, 5.91; O, 13.39%.

Spiro-compound 7e: IR (KBr): 1680, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$/400 MHz): δ 2.17 (m, 4H) ,2.78 (s, 3H), 3.66 (s, 3H), 3.71 (s, 3H) , 3.62 (d,1H, J=14.2Hz), 4.68 (d, 2H, J=12.2Hz) , 4.93 (d, 1H, J=11.4 Hz), 6.51-7.59 (m, 10H), 8.01 (s, 1H); ^{13}C NMR ($CDCl_3$/400 MHz): δ 23.60, 24.62, 29.21,50.26, 55.48, 56.55, 66.50, 72.48, 109.86, 121.36, 123.55, 125.15, 126.24, 128.40, 129.22, 129.27, 130.98, 131.47, 139.72, 141.56, 162.55, 172.38, 192.98 ppm; EIMS m/z : 510.22 (M^+); CHN Anal. Calcd for $C_{31}H_{30}N_2O_5$: C, 72.92; H, 5.92; N, 5.49; O, 15.67%; found: C, 72.88; H, 5.88; N, 5.55; O, 15.69%.

Spiro-compound 7f : IR (KBr): 1674, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$/400 MHz): δ 2.14 (m, 4H) ,2.35 (s, 3H), 2.36 (s, 3H), 3.73 (s, 3H) , 3.68 (d,1H, J=14.2Hz), 4.18 (d, 2H, J=12.2Hz) , 4.87 (d, 1H, J=11.4 Hz), 6.52-7.56 (m, 10H), 8.00 (s, 1H); ^{13}C NMR ($CDCl_3$/400 MHz): δ 23.60, 24.30, 24.62, 29.21,50.21, 56.24, 56.55, 66.84, 72.24, 109.86, 121.36, 123.55, 125.15, 126.24, 128.54, 129.21, 129.45, 130.92, 131.47, 139.63, 141.56, 162.55, 172.08, 192.45 ppm; EIMS m/z : 494.22 (M^+); CHN Anal. Calcd for $C_{31}H_{30}N_2O_4$: C, 75.28; H, 6.11; N, 5.66; O, 12.94%; found: C, 75.33; H, 6.08; N, 5.69; O, 12.90%.

In conclusion, we synthesized a new class of Spiro- oxindole [pyrrolidines/pyrrolizines] through cycloaddition of azomethine ylides generated from isatin, sarcosine and L-proline with 3-arylidene-4-chromanones. In both cases, the azomethine ylide was generated through decarboxylative route and the cycloadditions are highly regioselective, giving good yields of novel dispiroheterocycles. The reaction in particular is of interest since it paves the way for the synthesis of a variety of biologically significant Spiro-oxindole derivatives using easily available starting materials.

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