# Microwave Induced Regioselective Synthesis of Novel Dispiro[acenaphthenone-indanedione]pyrrolizidines



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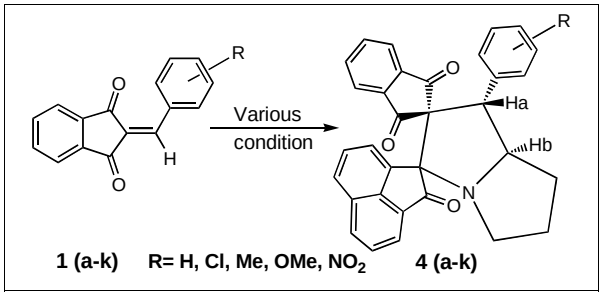


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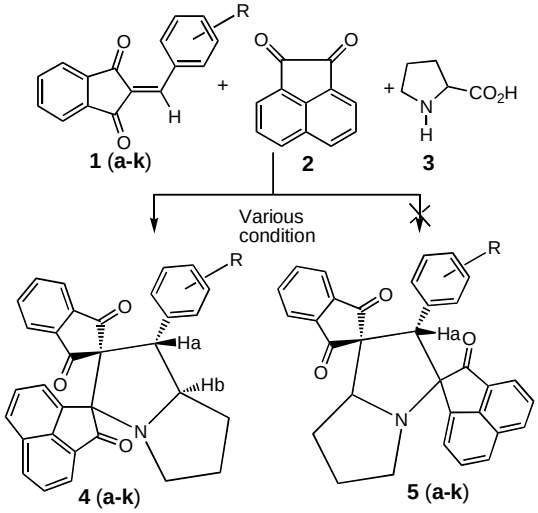
## Introduction.

There has been a gradual change from the linear convergent sequences of reactions for the stepwise construction of the target skeletons to "multi-component synthesis" reactions involving the combination of three or more components in a single synthetic transformation [1]. Multicomponent reaction involving microwave radiation has in some instances replaced conventional reaction conditions [2-5]. The most evident improvements are reduced reaction times and cleaner reaction due to fewer side reactions. Microwave-assisted intermolecular [3+2] cycloaddition reactions of azomethine ylide with alkenes and alkynes [6] represent an efficient and convergent method for the construction of pyrrolizidine units. The ease of generation of 1,3-dipole coupled with the observed highly regio and stereoselective nature of the cycloaddition has led to a number of syntheses, which utilizes such a reaction as the key step [7]. Pyrrolizidine alkaloids have attracted great deal of interest as they are widely distributed in nature and possess various biological activities [8]. 1,3-Indanedione possess significant pharmacological properties such as anti-blood coagulant and anti-inflammatory [9]. Spiro compounds represents an important class of naturally occurring substances characterized by highly pronounced biological properties [10,11]. As a part of our endeavor to synthesize novel dispiroheterocycles through 1,3-dipolar cycloaddition methodology [12-13], herein we report for the first time, the synthesis of a rare class of novel dispiroheterocyclic compounds *via* the 1,3-dipolar cycloaddition of the azomethine ylide derived from acenaphthenequinone **2** and L-proline **3** with 2-arylidene-1,3-indanedione **1** (**a-k**) under various conditions by decarboxylative route [14], for the purpose of designing a new class of complex dispiroheterocycles with potential biological activities. The reaction afforded a series of spiro [2.2'] acenaphthen-1'-one-spiro [3.2"] indane-1", 3"-dione-4-aryl pyrrolizidines **4** (**a-k**) regioselectively. No trace of the other regioisomer **5** (**a-k**) was detected. The structures of compounds **4** (**a-k**) were established by spectroscopic techniques and elemental analysis. Thus the IR spectrum of the cycloadduct **4b** exhibited peaks at 1720 and 1742 $cm^{-1}$ due to acenaphthenone and indanedione ring carbonyl groups.

Scheme 1




The $^1$H NMR spectrum of **4b** exhibited several multiplets in the region δ 2.05-2.80 due to pyrrolizidine $-NCH_2$ protons. The pyrrolizidine -NCH-proton ($H_b$) appeared as multiplet in the region δ 4.89-4.95.The benzylic proton ($H_a$) appeared as doublet at δ 4.78 (J = 9.28 Hz). On decoupling the pyrrolizidine $-NCH_2$ protons in the region δ 2.05-2.27, the pyrrolizidine –NCH- proton ($H_b$) in the

region δ 4.89-4.95 appeared as doublet at δ 4.93 (J = 9.28 Hz). The stereochemistry of the protons $H_a$ and $H_b$ was deduced on the basis of their coupling constants and comparison with related systems [15-17]. If the other regioisomer **5** (**a-k**) were formed, one would expect a singlet for the benzylic proton, which was not observed.

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| Entry | R | Product | Method A | | Method B | | Method C | | Method D | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | h | % | Min. | % | Min. | % | Min. | % |
| 1 | H | **4a** | 3.0 | 63 | 4.5 | 69 | 2.5 | 84 | 2.0 | 93 |
| 2 | *p*-C1 | **4b** | 3.2 | 60 | 5.0 | 66 | 3.0 | 81 | 2.3 | 90 |
| 3 | *p*-Me | **4c** | 3.6 | 58 | 5.8 | 62 | 4.0 | 78 | 2.0 | 86 |
| 4 | *p*-OMe | **4d** | 3.8 | 60 | 6.0 | 66 | 3.0 | 80 | 2.0 | 88 |
| 5 | *p*-$NO_2$ | **4e** | 2.5 | 70 | 3.0 | 74 | 2.0 | 90 | 1.0 | 96 |
| 6 | *m*-C1 | **4f** | 3.0 | 63 | 4.2 | 68 | 2.3 | 82 | 1.2 | 90 |
| 7 | *m*-$NO_2$ | **4g** | 2.5 | 68 | 3.1 | 71 | 2.3 | 85 | 1.3 | 92 |
| 8 | *o*-C1 | **4h** | 3.0 | 62 | 4.0 | 65 | 2.4 | 78 | 1.2 | 86 |
| 9 | *o*-$NO_2$ | **4i** | 2.5 | 72 | 3.0 | 75 | 2.2 | 88 | 1.2 | 93 |
| 10 | 3,4-OMe | **4j** | 4.0 | 56 | 6.0 | 60 | 3.3 | 75 | 2.0 | 86 |
| 11 | 3,4,5-OMe | **4k** | 4.2 | 54 | 6.0 | 58 | 3.4 | 73 | 2.8 | 80 |

h= Time in hour; Min. = Time in minutes; %= yield in percentage. Method A: Conventional methanol / reflux; Method B: methanol / MW; Method C: K-10 Montmorillonite; Method D: Neat / MW.

The $^{13}C$ NMR spectrum of **4b** exhibited peaks at δ 78.27 and 80.32 ppm due to the two-spiro carbon atoms. The indanedione ring carbonyls resonated at δ 198.06 and 198.59 ppm while the acenaphthenone ring carbonyl resonated at δ 206.44 ppm. Further the structure of the product was confirmed through mass spectra, which exhibited a molecular ion peak at *m/z* 503.9 ($M^+$).

Identical results were observed for the other derivatives of 2-arylidene-1,3-indanedione, irrespective of the nature of the substituent present in the arylidene moiety of 2-arylidene-1, 3-indanediones.

From Table 1, it is evident that conventional alcohol reflux afforded yields varying from 58-72%. The reaction carried out under microwave irradiation using methanol as solvent, gave improved yield of the products. However, the reaction carried out under solvent-free microwave irradiation condition by gently grinding all the three components with/without K-10 Montmorillonite clay afforded the anticipated cycloadducts in excellent yields with high regio and stereoselectivity and also of sufficient purity.

To the best of our knowledge, to date there has been no report of the cycloaddition reaction of the 1,3-dipole azomethine ylide derived from acenaphthenequinone and L-proline with 2-arylidene-1, 3-indanediones as dipolarophiles.

We have also shown that it is possible to apply the tenets of green chemistry for the generation of a rare class of novel dispiropyrrolizidine heterocycles *via* [3+2] cycloaddition of azomethine ylides.

## EXPERIMENTAL

### General.

All melting points are uncorrected. IR spectra were recorded on a SHIMADZU-FTIR 8300 instrument. Mass spectra were recorded on a JEOL DX 303 HF Spectrometer with MASSPEC System (MSW/9629). $^1H$ and $^{13}C$ NMR were recorded in $CDC1_3$ using TMS as internal standard on a JEOL spectrometer at 400 and 100 MHz respectively. Elemental analyses were carried out on a PERKIN-ELMER 240 B instrument. The starting materials **1** (**a-k**) were prepared as per the literature procedure [18].

### General Procedure for the Cycloaddition Reaction of Azomethine Ylide Generated from Acenaphthenequinone **2** and L-proline **3** with 2-Arylidene-1,3-indanediones **1 (a-k)**.

Method A: A mixture of acenaphthenequinone **2** (1.0 mmol), L-proline **3** (1.0 mmol) and 2-arylidene-1, 3-indanediones **1** (**a-k**) (1.0 mmol) were refluxed in methanol (25 mL) until the completion of the reaction as evidenced by TLC analysis. After the reaction was over, the solvent was removed under reduced pressure and the crude product was chromatographed on silica gel using hexane-ethyl acetate (9:1) as eluent to afford the cycloadducts **4** (**a-k**).

Method B: A mixture of acenaphthenequinone **2** (1.0 mmol), L-proline **3** (1.0 mmol) and 2-arylidene-1, 3-indanediones **1** (**a-k**) (1.0 mmol) in methanol (25 mL) were irradiated under microwave conditions (600 W). After the completion of the reaction as evidenced by TLC analysis, the solvent was removed under reduced pressure and the crude product was chromatographed on silica gel using hexane-ethyl acetate (9:1) as eluent to afford the cycloadducts **4** (**a-k**).

Method C: A mixture of acenaphthenequinone **2** (1.0 mmol), L-proline **3** (1.0 mmol) and 2-arylidene-1, 3-indanediones **1 (a-**

**k)** (1.0 mmol) were ground with K-10 Montmorillonite clay and irradiated under microwave conditions (600 W). After completion of the reaction, the crude product was extracted with dichloromethane, the organic layer dried over $MgSO_4$, the solvent was removed *in vacuo* and the residue was chromatographed on silica gel using hexane-ethyl acetate (9:1) as eluent to afford the cycloadducts **4** (**a-k**).

Method D: A mixture of acenaphthenequinone **2** (1.0 mmol), L-proline **3** (1.0 mmol) and 2-arylidene-1,3-indanediones **1** (**a-k**) (1.0 mmol) were ground and irradiated under microwave conditions (600 W). After completion of the reaction, the crude product was extracted with dichloromethane, the organic layer dried over $MgSO_4$. After the completion of the reaction as evidenced the mixture was allowed to stand at room temperature until it solidified. The crude product was chromatographed on silica gel using hexane-ethyl acetate (9:1) as eluent to afford the cycloadducts **4** (**a-k**).

Spiro[2.2']acenaphthen-1'-one-spiro[3.2"]indane-1",3"-dione-4-phenyl-pyrrolizidine (**4a**).

Yellow solid, mp: 186-187 °C; IR (KBr): 1720, 1740 $cm^{-1}$; $^1H$ NMR: δ 2.07-2.27 (m, 4H), 2.70-2.80 (m, 2H), 4.80 (d, J = 9.28 Hz, 1H, $H_a$), 4.92-4.98 (m, 1H, $H_b$), 7.04-7.95 (m, 15H, ArH); $^{13}C$ NMR: 30.30, 31.27, 47.52, 53.93, 68.82, 78.16, 80.21, 122.84, 123.33, 123.78, 126.21, 128.33, 128.41, 129.41, 130.55, 131.46, 132.81, 134.12, 136.23, 136.71, 137.27, 141.42, 142.54, 198.24, 198.68, 206.57; MS *m/z*: 469.5 ($M^+$).

*Anal.* Calcd. for $C_{32}H_{23}NO_3$: C, 81.85; H, 4.93; N, 2.98. Found: C, 81.88; H, 4.96, N, 3.00.

Spiro[2.2']acenaphthen-1'-one-spiro[3.2"]indane-1",3"-dione-4-(4-chlorophenyl)-pyrrolizidine (**4b**).

Yellow solid, mp: 179-180 °C; IR (KBr): 1720, 1742 $cm^{-1}$; $^1H$ NMR: δ 2.05-2.27 (m, 4H), 2.65-2.80 (m, 2H), 4.78 (d, J = 9.28 Hz, 1H, $H_a$), 4.89-4.95 (m, 1H, $H_b$), 7.04-7.95 (m, 14H, ArH); $^{13}C$ NMR: 31.09, 32.07, 47.70, 53.67, 69.73, 78.27, 80.32, 121.73, 123.22, 123.64, 126.04, 129.11, 129.21, 129.35, 131.08, 131.31, 132.23, 132.63, 133.98, 134.99, 136.10, 136.60,137.04, 141.79, 142.11, 143.49, 198.06, 198.56, 206.44; MS *m/z*: 503.9 ($M^+$).

*Anal.* Calcd. for $C_{32}H_{22}NO_3Cl$: C, 76.26; H, 4.39; N, 2.77. Found: C, 76.30; H, 4.42, N, 2.80.

Spiro[2.2']acenaphthen-1'-one-spiro[3.2"]indane-1",3"-dione-4-(4-methylphenyl)-pyrrolizidine (**4c**).

Yellow solid, mp: 190-191 °C; IR (KBr): 1720, 1740 $cm^{-1}$; $^1H$ NMR: δ 2.02-2.27 (m, 4H), 2.22 (s, 3H), 2.70-2.81 (m, 2H), 4.77 (d, J = 9.28 Hz, 1H, $H_a$), 4.93-4.99 (m, 1H, $H_b$), 6.95-7.95 (m, 14H, ArH); $^{13}C$ NMR: 25.27, 30.28, 31.22, 47.30, 53.57, 69.01, 78.08, 80.06, 121.03, 122.86, 123.33, 125.29, 128.32, 128.52, 129.13, 129.75, 131.44, 131.89, 132.76, 134.57, 135.16, 135.39, 135.64, 141.08, 142.79, 147.26, 198.13, 198.64, 206.32; MS *m/z*: 559.6 ($M^+$).

*Anal.* Calcd. for $C_{33}H_{25}NO_3$: C, 81.96; H, 5.21; N, 2.89. Found: C, 82.00; H, 5.23, N, 2.90.

Spiro[2.2']acenaphthen-1'-one-spiro[3.2"]indane-1",3"-dione-4-(4-methoxyphenyl)-pyrrolizidine (**4d**).

Yellow solid, mp: 183-184 °C; IR (KBr): 1718, 1738 $cm^{-1}$; $^1H$ NMR: δ 2.02-2.28 (m, 4H), 2.68-2.76 (m, 2H), 3.76 (s, 3H), 4.79 (d, J = 9.28 Hz, 1H, $H_a$), 4.91-4.98 (m, 1H, $H_b$), 7.02-7.94 (m, 14H, ArH); $^{13}C$ NMR: 30.21, 31.19, 46.88, 53.49, 53.17, 68.96, 77.87, 79.87, 120.94, 122.81, 123.29, 125.23, 128.48, 128.69, 129.08, 129.70, 130.48, 131.85, 132.70, 134.51, 135.16, 135.07, 135.41, 141.04, 141.37, 147.18, 197.96, 198.47, 206.30; MS *m/z*: 499.5 ($M^+$).

*Anal.* Calcd. for $C_{33}H_{25}NO_4$: C, 79.34; H, 5.04; N, 2.80. Found: C, 79.40; H, 5.08, N, 2.78.

Spiro[2.2']acenaphthen-1'-one-spiro[3.2"]indane-1",3"-dione-4-(4-nitrophenyl)-pyrrolizidine (**4e**).

Yellow solid, mp: 194-195 °C; IR (KBr): 1344, 1518, 1718, 1742 $cm^{-1}$; $^1H$ NMR: δ 2.08-2.28 (m, 4H), 2.69-2.80 (m, 2H), 4.89 (d, J = 9.28 Hz, 1H, $H_a$), 4.94-5.01 (m, 1H, $H_b$), 7.24-7.92 (m, 14H, ArH); $^{13}C$ NMR: 30.20, 31.26, 46.97, 52.22, 68.87, 77.79, 79.87, 120.91, 122.50, 123.89, 125.36, 128.33, 128.41, 129.36, 129.62, 130.42, 131.35, 132.81, 132.66, 134.46, 135.10, 135.96, 141.09, 142.67, 148.11, 198.31, 198.76, 206.61; MS *m/z*: 514.5 ($M^+$).

*Anal.* Calcd. for $C_{32}H_{22}N_2O_5$: C, 74.67; H, 4.31; N, 5.44. Found: C, 74.67; H, 4.36, N, 5.43.

Spiro[2.2']acenaphthen-1'-one-spiro[3.2"]indane-1",3"-dione-4-(3-chlorophenyl)-pyrrolizidine (**4f**).

Yellow solid, mp: 182-183 °C; IR (KBr): 1718, 1740 $cm^{-1}$; $^1H$ NMR: δ 2.08-2.28 (m, 4H), 2.69-2.80 (m, 2H), 4.77 (d, J = 9.28 Hz, 1H, $H_a$), 4.89-4.95 (m, 1H, $H_b$), 6.98-7.94 (m, 14H, ArH); $^{13}C$ NMR: 30.25, 31.23, 46.98, 53.05, 69.21, 78.09, 80.17, 120.98, 121.84, 122.95, 123.29, 123.71, 126.10, 129.03, 129.10,130.53, 131.42, 132.18, 132.57, 133.90, 134.89, 136.51, 136.94, 141.68, 143.38, 197.98, 198.48, 206.32; MS *m/z*: 503.9 ($M^+$).

*Anal.* Calcd. for $C_{32}H_{22}NO_3Cl$: C, 76.26; H, 4.39; N, 2.77. Found: C, 76.25; H, 4.44, N, 2.83.

Spiro[2.2']acenaphthen-1'-one-spiro[3.2"]indane-1",3"-dione-4-(3-nitrophenyl)-pyrrolizidine (**4g**).

Yellow solid, mp: 178-179 °C; IR (KBr): 1346, 1520, 1720, 1740 $cm^{-1}$; $^1H$ NMR: δ 2.09-2.29 (m, 4H), 2.70-2.81 (m, 2H), 4.90 (d, J = 9.28 Hz, 1H, $H_a$), 4.98-5.04 (m, 1H, $H_b$), 7.24-7.94 (m, 14H, ArH); $^{13}C$ NMR: 30.28, 31.32, 47.08, 52.29, 68.92, 77.84, 79.83, 120.98, 122.58, 123.79, 123.95, 125.42, 128.39, 129.45, 130.53, 131.42, 131.87, 132.71,132.92, 134.43, 135.17, 135.43, 136.07, 138.21, 139.03, 141.18, 142.72, 148.20, 198.38, 198.87, 206.59; MS *m/z*: 514.5 ($M^+$).

*Anal.* Calcd. for $C_{32}H_{22}N_2O_5$: C, 74.67; H, 4.31; N, 5.44. Found: C, 74.71; H, 4.34, N, 5.46.

Spiro[2.2']acenaphthen-1'-one-spiro[3.2"]indane-1",3"-dione-4-(2-chlorophenyl)-pyrrolizidine (**4h**).

Yellow solid, mp: 188-189 °C; IR (KBr): 1720, 1742 $cm^{-1}$; $^1H$ NMR: δ 1.98-2.27 (m, 4H), 2.73-2.81 (m, 2H), 4.81 (d, J = 9.28 Hz, 1H, $H_a$), 5.01-5.07(m, 1H, $H_b$), 6.89-8.03 (m, 14H, ArH); $^{13}C$ NMR: 30.09, 31.11, 47.66, 53.48, 69.54, 78.06, 80.14, 121.56, 123.01, 123.48, 125.93, 128.96, 129.01, 129.27, 130.92, 131.28, 132.48, 133.86, 133.86, 134.81, 135.39, 135.58, 141.42, 141.50, 142.45, 197.97, 198.41, 206.26; MS *m/z*: 503.9 ($M^+$).

*Anal.* Calcd. for $C_{32}H_{22}NO_3Cl$: C, 76.26; H, 4.39; N, 2.77. Found: C, 76.23; H, 4.41, N, 2.76.

Spiro[2.2']acenaphthen-1'-one-spiro[3.2"]indane-1",3"-dione-4-(2-nitrophenyl)-pyrrolizidine (**4i**).

Yellow solid, mp: 192-193 °C; IR (KBr): 1346.3, 1520.5, 1718.5, 1742 $cm^{-1}$; $^1H$ NMR: δ 2.10-2.30 (m, 4H), 2.72-2.83 (m,

2H), 4.92 (d, J = 9.28 Hz, 1H, $H_a$), 5.01-5.07 (m, 1H, $H_b$), 7.26-8.06 (m, 14H, ArH); $^{13}$C NMR: 30.32, 31.39, 47.01, 52.34, 69.02, 77.92, 79.94, 120.96, 122.61, 123.11, 124.03, 125.49, 128.41, 128.51, 128.53, 129.36, 129.50, 129.62, 130.48, 130.61, 131.35, 131.81,132.66, 134.46, 135.10, 135.96, 141.09, 142.67, 148.11, 198.48, 198.92, 206.56; MS *m/z*: 514.5 ($M^+$).

*Anal.* Calcd. for $C_{32}$ $H_{22}N_2O_5$: C, 74.67; H, 4.31; N, 5.44. Found: C, 74.63; H, 4.33, N, 5.45.

Spiro[2.2']acenaphthen-1'-one-spiro[3.2"]indane-1",3"-dione-4-(3,4-dimethoxyphenyl)-pyrrolizidine (4j).

Yellow solid, mp: 192-193 °C; IR (KBr): 1718, 1738 $cm^{-1}$; $^1$H NMR: δ 2.08-2.28 (m, 4H), 2.70-2.81 (m, 2H), 3.66 (s, 3H), 3.69 (s, 3H), 4.70 (d, J = 9.28 Hz, 1H, $H_a$), 4.82-4.88 (m, 1H, $H_b$), 7.24-7.98 (m, 13H, ArH); $^{13}$C NMR: 30.28, 31.38, 47.08, 53.38, 60.52, 60.78, 68.97, 77.86, 79.84, 120.96, 122.81, 123.22, 125.18, 125.92, 127.42, 128.30, 129.47, 130.63, 131.47, 132.68, 134.93, 137.03, 138.98, 140.66, 141.23, 142.83, 147.62, 198.08, 198.57, 206.34; MS *m/z*: 529.5 ($M^+$).

*Anal.* Calcd. for $C_{34}$ $H_{27}NO_5$: C, 77.11; H, 5.13; N, 2.64. Found: C, 77.16; H, 5.15, N, 2.62.

Spiro[2.2']acenaphthen-1'-one-spiro[3.2"]indane-1",3"-dione-4-(3,4,5-trimethoxyphenyl)-pyrrolizidine (**4k**).

Yellow solid, mp: 188-189 °C; IR (KBr): 1718, 1738 $cm^{-1}$; $^1$H NMR: δ 2.08-2.28 (m, 4H), 2.69-2.80 (m, 2H), 3.63 (s, 3H), 3.67 (s, 3H), 3.70 (s, 3H), 4.72 (d, J = 9.28 Hz, 1H, $H_a$), 4.84-4.90 (m, 1H, $H_b$), 7.25-7.97 (m, 12H, ArH); $^{13}$C NMR: 30.31, 31.32, 47.12, 53.42, 60.49, 60.72, 61.21, 69.05, 77.94, 79.96, 120.91, 122.74, 123.26, 125.31, 127.56, 128.33, 130.56, 131.52, 132.73, 135.54, 136.95, 139.97, 141.12, 142.79, 147.49, 198.12, 198.64, 206.48; MS *m/z*: 559.6 ($M^+$).

*Anal.* Calcd. for $C_{35}$ $H_{29}NO_6$: C, 75.12; H, 5.22; N, 2.50. Found: C, 75.18; H, 5.24, N, 2.55.

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