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# THREE COMPONENT SYNTHESIS OF SOME γ–SPIROIMINOLACTONES UNDER MICROWAVE-ASSISTED SOLVENT-FREE CONDITIONS

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**Abstract** – Series of some γ-spiroiminolactone derivatives were synthesized through microwave-assisted, three component reaction of isocyanides, dialkyl acetylenedicarboxylates and indenoquinoxalin-11-ones in DMF or in a solvent-less operation on solid support montmorillonite K10.

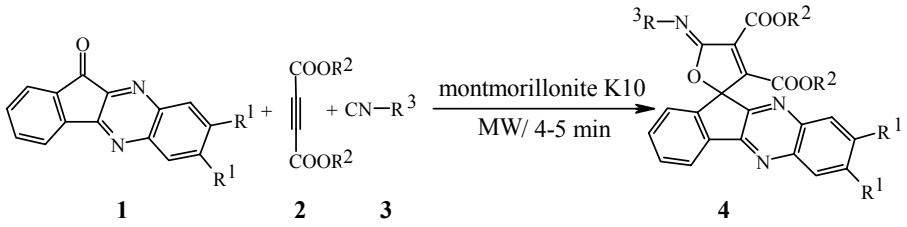
The multiple component condensation (MCC) approach is interesting in view of the fact that products are formed in a single step and the diversity can be conveniently achieved simply by varying the reacting components.[1] The generation of small-molecule libraries requires the development of efficient protocols with special emphasis on the ease of manipulation of reaction.[2] We succeeded in developing such a protocol which is amenable to the generation of a library of some γ-spiroiminolactone derivatives in a three-component condensation reaction under solvent-free conditions or in DMF using MW irradiation.

Microwave-assisted organic synthesis is an increasingly popular field as indicated by numerous publications in the last few years.[3] The combination of solvent-free reactions conditions and microwave irradiation leads to large reductions in reaction times, enhancements in conversions and sometimes, in selectivity with several advantages of the eco-friendly approach, termed green chemistry.[4]

Recently, a new three component reaction was described by Nair *et al.*, which enabled the synthesis of γ-spiroiminolactones.[5] Therefore, in continuation of our previous[6a] work on the synthesis of γ-spiroiminolactones from isatin or tryptanthrine and in the context of our interest in use of microwaves,[6b] we report the facile synthesis of some γ-spiroiminolactones in a three-component condensation of indenoquioxalin-11-ones, dialkyl acetylenedicarboxylates and isocyanides under microwave irradiation.

Recently, γ-spirolactones have been the subject of a consideration because of their effect as aldestrone inhibitors.[7] Quinoxaline derivatives constitute useful intermediates in organic synthesis. The resultant

pharmacological interest in compounds which belong to the quinoxaline and γ-spiroiminolactone family, has led to development of the synthesis of γ-spiroiminolactones from indenoquinoxalin-11-one derivatives.




**1** **2** **3** **4**

**Scheme 1**

In our initial experiment, we worked with indenoquinoxalin-11-ones (**1**), dialkyl acetylenedicarboxylates (**2**) and isocyanides (**3**), on solid support montmorillonite K10 or in DMF as a solvent, wherein the reactions are completed within minutes and in high yields (70-90%, **Scheme 1**, **Table 1**) using an unmodified household MW oven. On the other hand, heating the same reaction mixture in benzene under reflux conditions afforded the products in longer reaction times as shown in **Table 1**. These were characterized on the basis of their elemental analyses and IR, $^{1}$H NMR, $^{13}$C NMR and MS spectral data.

**Table 1.** Synthesis of γ-spiroiminolactone derivatives from indenoquinoxalin-11-ones

| **4** | $R^1$ | $R^2$ | $R^3$ | Reflux | | MW | |
|---|---|---|---|---|---|---|---|
| | | | | time(h) | yield(%) | time(min) | yield(%) |
| **a** | H | Me | cyclohexyl | 4 | 78 | 3 | 85 |
| **b** | H | Me | *t*-Bu | 4 | 85 | 3 | 90 |
| **c** | H | Et | cyclohexyl | 5 | 65 | 4 | 75 |
| **d** | H | Me | 2,6-dimethylphenyl | 5 | 75 | 4 | 80 |
| **e** | Me | Me | cyclohexyl | 5 | 70 | 4 | 76 |
| **f** | Me | Me | 2,6-dimethylphenyl | 5 | 73 | 4 | 80 |

This comparative study of the reactions taking place in benzene under reflux conditions revealed a substantial rate enhancement for reactions conducted under MW irradiation conditions, presumably due to the increase in polarity after change of solvent from the benzene to DMF and also because of selective absorption of microwave energy by polar molecules specially by zwitterionic intermediates. Montmorillonite K10 is one of the solids most efficiently heated by microwaves and is also known for its adsorbing properties of organic molecules. We showed that irradiation of the mixture of starting material, adsorbed on montmorillonite K10, led to the expected iminolactone (**4**) in a higher yield (80-90%) than for the purely irradiation procedure (40-50%). This indicates in the absence of DMF as a solvent, montmorillonite K10 may be needed for this reaction.

For the sake of comparison, the reactions were also performed with conventional heating (Δ) using an oil bath under the same conditions (time and solvent). We obtained the corresponding iminolactones, in 15-20% yield, using boiling DMF as a solvent after 5 minutes as shown in **Table 2**.

These results showed the utility of the microwave irradiation in organic synthesis and its advantages in comparison with classical heating.

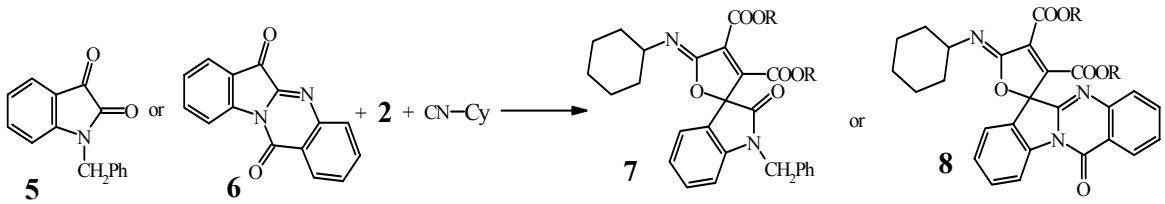
To extend the scope of the reaction, we wanted to check the performance of the MW irradiation for the

preparation of γ-spiroiminolactone derivatives from 1-benzylisatin and tryptanthrine (**Scheme 2**).

**Table 2.** Comparison of reflux with MW in DMF

| 4 | Reflux (DMF) | | MW (DMF) | |
|---|---|---|---|---|
| | time | yield(%) | time | yield(%) |
| **a** | 5 min | 18 | 5 min | 85 |
| **b** | 5 min | 20 | 5 min | 90 |
| **c** | 5 min | 15 | 5 min | 75 |
| **d** | 5 min | 15 | 5 min | 80 |
| **e** | 5 min | 15 | 5 min | 76 |
| **f** | 5 min | 17 | 5 min | 80 |

Thus we carried out this reaction under MW conditions and we isolated resonable yields of iminolactones as shown in **Table 3**. The structure elucidation of these compounds was reported.[6a]




**Scheme 2**

**Table 3**. Synthesis of γ-spiroiminolactone derivatives from **5** and **6**

| 5/6 | $R^2$ | Reflux | | MW | | 7/8[b] |
|---|---|---|---|---|---|---|
| | | time | yield(%)[a] | time | yield(%) | |
| **5** | Me | 4 h | 78 | 4 min | 80 | **7a** |
| **5** | Et | 4 h | 76 | 4 min | 78 | **7b** |
| **5** | *t*-Bu | 4 h | 65 | 4 min | 70 | **7c** |
| **6** | Et | 4 h | 64 | 4 min | 68 | **8a** |
| **6** | *t*-Bu | 4 h | 55 | 4 min | 62 | **8b** |

[a]isolated yield. [b]reference (6a)

In conclusion, we have demonstrated that microwave irradiation can facilitate the three-component condensation reaction of isocyanides, dialkyl acetylenedicarboxylates with indenoquinoxalin-11-ones or 1-benzylisatin or tryptanthrine that effects an easy and effective one-pot synthesis of iminolactones.[8]

## EXPERIMENTAL

IR spectra were measured on a Shimadzu IR-470 Spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were determined on a Bruker 500 DRX AVNCE instrument at 500 and 125 MHz, respectively. MS spectra were recorded on a Shimadzu QP 1100EX mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses were performed using a Heracus CHN-O-Rapid analyzer. Microwave irradiation were carried out in a National oven, model 5250, at 2450 MHz.

**General procedures:** Typical experimental procedure **A**: To a mixture of indenoquinoxalin-11-one (**1a**) (0.232 g, 1 mmol) and dimethyl acetylenedicarboxylate (0.148 mL, 1.2 mmol) and cyclohexyl isocyanide (0.147 mL, 1.2 mmol) in dichloromethane (3 mL) was added montmorillonite K10 clay (3 g), mixed

thoroughly and dried. The contents were taken in a Pyrex test tube, placed in an alumina bath inside the microwave oven and irradiated for 4-5 min with a power of 600w. After cooling, product was extracted with dichloromethane and the extract was dried under reduced pressure to leave the crude product which was recrystallised from ethanol to obtaine an analytical sample. Typical experimental procedure **B**: To a mixture of indenoquinoxalin-11-one (**1a**) (0.232 g, 1 mmol) and dimethyl acetylenedicarboxylate (0.148 mL, 1.2 mmol) in DMF (3-5 mL) in a 10 mL glass beaker, cyclohexyl isocyanide (0.147 mL, 1.2 mmol) was added *via* a syrring and irradiated for 3-4 min in the microwave oven with a power of 600w. After cooling, water added to the mixture and the separated solid was filtered off and recrystallised in ethanol to give a white crystalline solid. Typical experimental procedure **C**: To a mixture of indenoquinoxalin-11-one (**1a**) (0.232 g, 1 mmol) and dimethyl acetylenedicarboxylate (0.148 mL, 1.2 mmol) in dry benzen or toluene (30 mL), cyclohexyl isocyanide (0.147 mL, 1.2 mmol) was added *via* a syringe and refluxing was continued for a further 4 h. The solvent was removed under vacuum and the product was crystallised out from ethanol and filtered to give a white crystalline solid.

**Spectral data for products:**

**4a:** mp 230 ˚C, IR (KBr) ($\nu_{max}$, $cm^{-1}$): 2920, 1750, 1727, 1673, 1648; $^1$H NMR ($CDCl_3$) $\delta_H$: 1.15-1.70 (10H, m, -Cy), 3.47(3H, s, OMe), 3.95 (3H, s, OMe), 7.57-8.29 (8H, m, Arom.); $^{13}$C NMR ($CDCl_3$) $\delta_C$: 25.01, 25.01, 26.10, 33.52, 33.63, 53.50, 53.60, 57.07, 90.60, 123.25, 124.95, 129.54, 129.75, 130.35, 130.95, 131.82, 132.68, 138.42, 139.33, 142.05, 142.14, 143.25, 143.36, 154.42, 155.20, 157.55, 159.92, 162.20; MS (m/z, %): 483 ($M^+$, 35), 385 (45). Anal. Calcd for $C_{28}H_{25}N_3O_5$: C, 69.55; H, 5.21; N, 8.69. Found: C, 69.46; H, 5.30; N, 8.80.

**4b:** mp 235 ˚C, IR (KBr) ($\nu_{max}$, $cm^{-1}$): 2950, 1754, 1725, 1676, 1654; $^1$H NMR($CDCl_3$) $\delta_H$: 1.29 (9H, s, t-Bu), 3.46 (3H, s, OMe), 4.03 (3H, s, OMe), 7.28-8.24 (8H, m, Arom.); $^{13}$C NMR ($CDCl_3$) $\delta_C$: 29.95, 53.15, 53.64, 55.68, 90.76, 123.24, 124.72, 129.66, 129.78, 130.47, 130.96, 131.86, 132.62, 138.30, 140.60, 141.02, 142.17, 143.29, 143.44, 153.06, 154.37, 157.58, 160.48, 162.86,; MS (m/z, %): 458 ($M^+$, 35), 442 (100), 410 (20), 368 (30), 342 (30), 310 (20), 241(20), 84 (20), 57(40). Anal. Calcd for $C_{26}H_{23}N_3O_5$: C, 68.26; H, 5.07; N, 9.19. Found: C, 68.15; H, 5.09; N, 9.21.

**4c:** mp 220 ˚C, IR (KBr) ($\nu_{max}$, $cm^{-1}$): 2940, 1743, 1720, 1685, 1651; $^1$H NMR ($CDCl_3$) $\delta_H$: 0.84 (3H, m, Me), 1.45 (3H, m, Me), 1.20-1.82 (10H, m, -Cy), 3.61(1H, m, CH-N), 3.85 (2H, dq, $^2J$=15.7 Hz, $^3J$=6.5 Hz, $OCH_2$), 4.51(2H, m, $OCH_2$), 7.28-8.23 (8H, m, Arom.); $^{13}$C NMR ($CDCl_3$) $\delta_C$: 13.78, 14.53, 25.07, 25.16, 2609, 33.58, 33.63, 57.14, 62.08, 62.95, 90.26, 123.15, 124.91, 129.65, 129.80, 130.45, 130.96, 131.86, 132.62, 138.36, 139.27, 142.12, 142.14, 143.36, 143.42, 154.46, 155.14, 157.68, 159.88, 162.16; MS (m/z, %): 512 ($M^+$, 35), 438 (30), 414 (100), 341 (30), 268(10), 232 (60), 204 (40), 76 (40), 50 (30). Anal. Calcd for $C_{30}H_{29}N_3O_5$: C, 70.43; H, 5.71; N, 8.21. Found: C, 70.33; H, 5.68; N, 8.15.

**4d:** mp 270 ˚C, IR (KBr) ($\nu_{max}$, $cm^{-1}$): 1751, 1729, 1684, 1648; $^1H$ NMR ($CDCl_3$) $\delta_H$: 2.23 (6H, s, 2Me), 3.51 (3H, s, OMe), 4.12 (3H, s, OMe), 6.84-8.17 (11H, m, Arom.); $^{13}C$ NMR ($CDCl_3$) $\delta_C$: 18.53, 53.42, 53.97, 91.23, 123.37, 124.28, 124.82, 127.80, 127.93, 129.71, 129.94, 130.38, 131.14, 132.22, 132.55, 137.71, 138.61, 142.09, 142.11, 143.47, 144.01, 144.16, 154.28, 155.34, 156.81, 160.13, 162.17; MS (m/z, %): 505 ($M^+$, 35), 475 (60), 388 (100), 232 (25), 59 (70). Anal. Calcd for $C_{30}H_{23}N_3O_5$: C, 71.28; H, 4.59; N, 8.31. Found: C, 71.30; H, 4.55; N, 8.28.

**4e:** mp 241 ˚C, IR (KBr) ($\nu_{max}$, $cm^{-1}$): 1752, 1729, 1675, 1646 ; $^1H$ NMR ($CDCl_3$) $\delta_H$: 1.18-1.84 (10H, m, -Cy), 2.51 (3H, s, Me), 2.53 (3H, s, Me), 3.44 (3H, s, OMe), 3.59 (1H, m, CH-N), 4.03 (3H, s, OMe), 7.49-8.20 (6H, m, Arom.); $^{13}C$ NMR ($CDCl_3$) $\delta_C$: 20.65, 20.84, 25.12, 25.21, 26.06, 33.57, 33.64, 53.11, 53.70, 57.24, 90.78, 122.96, 124.74, 128.95, 129.66, 131.84, 132.18, 138.65, 139.13, 140.35, 140.98, 141.56, 142.24, 142.33, 142.86, 153.51, 156.40, 160.45, 162.65; MS (m/z, %): 512 ($M^+$, 15), 414 (100), 269 (25), 41 (24). Anal. Calcd for $C_{30}H_{29}N_3O_5$: C, 70.43; H, 5.71; N, 8.21. Found: C, 70.56; H, 5.69; N, 8.19.

**4f:** mp 264 ˚C, IR (KBr) ($\nu_{max}$, $cm^{-1}$): 1753, 1730, 1686, 1647; $^1H$ NMR ($CDCl_3$) $\delta_H$: 2.02(3H, s, Me), 2.23 (3H, s, Me), 2.52 (6H, s, 2Me), 3.48 (3H, s, OMe), 4.10 (3H, s, OMe), 6.82-8.13 (9H, m, Arom.); $^{13}C$ NMR ($CDCl_3$) $\delta_C$: 18.57, 20.67, 20.84, 53.34, 53.93, 91.40, 123.03, 124.24, 124.73, 127.80, 127.98, 128.97, 129.57, 132.06, 132.09, 137.60, 138.94, 140.47, 140.97, 141.71, 141.85, 142.23, 144.25, 144.32, 153.42, 155.47, 155.73, 160.16, 162.24; MS (m/z, %): 533 ($M^+$, 100), 501 (45), 414 (65), 269 (20), 59 (70). Anal. Calcd for $C_{32}H_{27}N_3O_5$: C, 72.03; H, 5.10; N, 7.88. Found: C, 72.12; H, 5.05; N, 7.80.

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