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Microwave-assisted rapid synthesis of the cytotoxic alkaloid luotonin A

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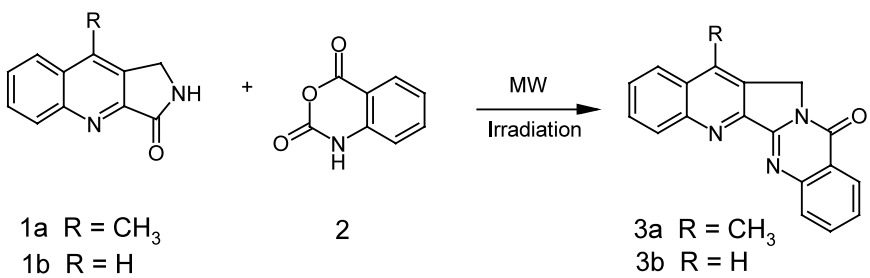
Abstract—The total synthesis of the cytotoxic alkaloid luotonin A has been achieved for the first time in high yields by the cyclocondensation of 3-oxo-1*H*-pyrrolo[3,4-*b*]quinoline with isatoic anhydride in solvent-free conditions under microwave irradiation.

The pyrroloquinazolinoquinoline alkaloids, luotonin A and B were recently isolated from the aerial parts of *Peganum nigellastrum*.[1] The plant (Chinese name Luo-Tuo-Hao) has a history of use in Chinese traditional medicine[2] for treatment of rheumatism, abscesses and inflammation. The alkaloid luotonin A is cytotoxic against the murine leukemia P-388 cell line. Furthermore, deoxyvasicinone was also isolated from the same plant, which is known to possess antitumor activity. The pentacyclic ring system of luotonin A and B is strikingly reminiscent of camptothecin, an inhibitor of topoisomerase I, derivatives of which are clinically useful anticancer agents.[3] Ganesan et al., have reported an efficient approach[4] for the total synthesis of luotonin A. Subsequent reports[5] on the total synthesis of luotonin A involve complex multi-step procedures, harsh reaction conditions, longer reaction times, expensive reagents, anhydrous solvents and cumbersome experimental/work-up procedures. An improved modification of the Ganesan approach has been developed by us for the synthesis of luotonin A using simple, commercially available isatoic anhydride and microwave irradiation. Microwave-assisted reactions have attracted much interest because of the simplicity in operation, greater selectivity and rapid synthesis of a variety of organic compounds.[6] The notable features of the microwave approach are enhanced reaction rates, formation of pure products in high yields and the ease of manipulation. In recent years, solvent-free microwave assisted reactions have gained greater popularity as they provide an opportunity to work with open vessels. This avoids the risk of the development of high pressure and provides a possibility of scaling up the reaction and helps the induction of the reaction under dry conditions. Thus, microwave irradiation has become a powerful tool for the rapid synthesis of a variety of bioactive molecules under solvent-free conditions.

In continuation of our interest in the total synthesis of biologically active molecules,[7] we herein report a novel and efficient synthesis of luotonin A involving the two component condensation of 3-oxo-1*H*-pyrrolo[3,4-



Scheme 1.

Keywords: deoxyvasinone; antitumor; quinazolines; microwave irradiation.

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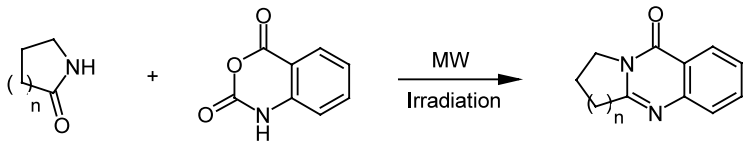
b]quinoline and isatoic anhydride under microwave irradiation under solvent-free conditions (Scheme 1).

The condensation proceeded rapidly in high yields with high selectivity. The intermediate, 3-oxo-1*H*-pyrrolo[3,4-*b*]quinoline was prepared in three steps by known methods.[8] Luotonin A **3b** was isolated in 85% yield within 6 min when an equimolar mixture of lactam, i.e. 3-oxo-1*H*-pyrrolo[3,4-*b*]quinoline **1b** and isatoic anhydride **2** was subjected to microwave irradiation at 450 watts (BPL, BMO-700T, microwave oven) under solvent-free conditions. Similarly, methyl substituted luotonin A **3a** was also synthesized in good yield (87%) under the present reaction conditions. Other lactams such as 2-pyrrolidinone, δ-valerolactam and ε-caprolactam, were also coupled with isatoic anhydride under microwave irradiation to afford the corresponding quinazoline derivatives in high yields[9] (Scheme 2, Table 1).

Deoxyvascinone **4e**, was obtained in 92% yield within 4 min under microwave irradiation. The quinazolines **4c**, **4d** and **4e** are important precursors for the synthesis of various biologically active molecules. However, the reaction took longer (5–8 h) to afford moderate yields (60–75%) of quinazoline derivatives when the reaction was carried out in an oil bath at 120°C (the highest observed temperature during microwave irradiation) under thermal conditions. Conventional heating at 120°C and longer reaction times required for the condensation of lactams with isatoic anhydride are totally avoided using microwave irradiation, which is becoming an alternative and substitute heating source. The procedure offers several advantages including short



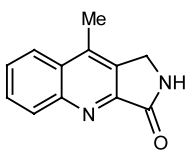
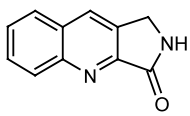
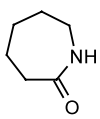
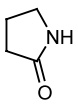
1c n = 3
1d n = 2
1e n = 1

2

4c n = 3
4d n = 2
4e n = 1

Scheme 2.

Table 1. Microwave-assisted synthesis of quinazolines

Entry	Lactam	Product[a]	Irradiation time[b] (min)	Yield[c] (%)
a		3a	6	87
b		3b	7	85
c		4c	8	89
d		4d	7	90
e		4e	6	92

a: All products were characterized by ^{1}H NMR, IR and mass spectroscopy
b: Pulsed irradiation (1min with 20 sec intervals)
c : Isolated and unoptimized

reaction times, cleaner reaction profiles, inexpensive reagents and simple experimental/product isolation procedures.

In conclusion, this paper describes a new and efficient approach for the synthesis of luotonin A through the cyclocondensation of 3-oxo-1*H*-pyrrolo[3,4-*b*]quinoline with isatoic anhydride under solvent-free conditions with microwave irradiation. The process is simple, rapid and higher yielding than the reported methods for the synthesis of luotonin A.

References

1. Ma, Z. Z.; Hano, Y.; Nomura, T.; Chen, J. J. *Heterocycles* **1997**, *46*, 541.
2. Xiao, X.-H.; Qou, G.-L.; Wang, H.-L.; Lui, L.-S.; Zheng, Y.-L.; Jia, Z.-J.; Deng, Z.-B. *Chin. J. Pharmacol. Toxicol.* **1988**, 232.
3. Slichenmyer, W. J.; Rowinsky, E. K.; Donehower, R. C.; Kaufmann, S. H. *J. Nat. Cancer. Inst.* **1993**, *85*, 271.
4. Wang, H.; Ganesan, A. *Tetrahedron Lett.* **1998**, *39*, 9097.
5. (a) Kelly, T. R.; Chamberland, S.; Silva, R. A. *Tetrahedron Lett.* **1999**, *40*, 2723; (b) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1999**, *51*, 1593.
6. (a) Loupy, A.; Petit, A.; Hamelin, J.; Texier-Boullet, F.; Jacquault, P.; Mathe, D. *Synthesis* **1998**, 1213; (b) Caddick, S. *Tetrahedron* **1995**, *51*, 10403; (c) Varma, R. S. *Green Chem.* **1999**, 43.
7. (a) Yadav, J. S.; Sarkar, S.; Chandrasekhar, S. *Tetrahedron* **1999**, *55*, 5449; (b) Rao, A. V. R.; Yadav, J. S.; Valluri, M. *Tetrahedron Lett.* **1994**, *35*, 3613.
8. (a) Madav, R.; Southwick, P. L. *J. Heterocycl. Chem.* **1972**, *9*, 443; (b) Southwick, P. L.; Crouch, R. T. *J. Am. Chem. Soc.* **1953**, *75*, 3413.
9. Experimental procedure: 3-Oxo-1*H*-pyrrolo[3,4-*b*]-quinoline (3 mmol) and isatoic anhydride (3 mmol) were mixed in a Pyrex test tube and subjected to microwave irradiation at 450 watts for an appropriate time (Table 1). After complete conversion, as indicated by TLC, the reaction mixture was extracted with ethyl acetate (2×10 mL). The combined organic layers were washed with water, dried over anhydrous Na_2SO_4, concentrated in vacuo and purified by column chromotography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 3:7) to afford pure product. Spectral data for product **3a**: Solid, mp 258–260 (dec), ^{1}H NMR (DMSO-d_6, 200 MHz): δ 2.90 (s, 3H), 5.40 (s, 2H), 7.60 (dt, 1H, $J=1.5$ and 8.0 Hz), 7.75 (dt, 1H, $J=1.5$ and 8.5 Hz), 7.84 (dt, 1H, $J=1.5$ and 8.5 Hz), 7.86 (dt, 1H, $J=1.5$ and 8.0 Hz), 7.95 (dd, 1H, $J=1.5$ and 8.5 Hz), 8.05 (dd, 1H, $J=1.5$ and 8.0 Hz), 8.25 (dd, 1H, $J=1.5$ and 8.0 Hz), 8.45 (dd, 1H, $J=1.5$ and 8.5 Hz). IR (KBr) ν: 3057, 2928, 2858, 1685, 1608, 1470, 1100, 1035, 769, 690. EIMS: m/z: 299 M^+, 284, 270, 150. ^{13}C NMR ($CDCl_3$, proton decoupled): δ 21.53, 26.67, 29.71, 45.40, 47.83, 49.30, 68.16, 94.56, 96.17, 126.94, 127.09, 127.50, 127.60, 127.82, 128.61, 128.89, 129.40, 137.96, 143.02. Compound **3b**: Solid, mp 250–252 (dec), ^{1}H NMR (DMSO-d_6, 200 MHz): δ 5.45 (s, 2H), 7.50 (dt, 1H, $J=1.5$ and 8.0 Hz), 7.65 (dt, 1H, $J=1.5$ and 8.5 Hz), 7.84 (dt, 1H, $J=1.5$ and 8.5 Hz), 7.86 (dt, 1H, $J=1.5$ and 8.0 Hz), 7.95 (dd, 1H, $J=1.5$ and 8.5 Hz), 8.15 (dd, 1H, $J=1.5$ and 8.0 Hz), 8.40 (dd, 1H, $J=1.5$ and 8.0 Hz), 8.44 (s, 1H), 8.47 (dd, 1H, $J=1.5$ and 8.5 Hz). IR (KBr) ν: 3055, 2925, 2856, 1680, 1630, 1607, 1468, 1098, 1033, 768, 693. EIMS: m/z: 285 M^+, 257, 185, 149. ^{13}C NMR ($CDCl_3$, proton decoupled): δ 26.67, 29.71, 45.40, 47.83, 49.30, 68.16, 94.56, 96.17, 126.94, 127.09, 127.50, 127.60, 127.82, 128.61, 128.89, 129.40, 137.96, 143.02. Compound **4c**: Solid, mp 98–99°C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.83–1.89 (m, 6H), 3.05 (t, 2H, $J=6.7$ Hz), 4.40 (t, 2H, $J=6.7$ Hz), 7.45 (t, 1H, $J=7.8$ Hz), 7.60 (d, 1H, $J=8.0$ Hz), 7.75 (t, 1H, $J=7.8$ Hz), 8.25 (d, 1H, $J=8.0$). IR (KBr) ν: 3065, 2955, 1685, 1570, 1450, 1225. EIMS: m/z: 214 M^+, 200, 185, 160, 119, 76. Compound **4d**: Solid, mp 96–97°C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.09–2.05 (m, 4H), 3.0 (t, 2H, $J=6.5$ Hz), 4.40 (t, 2H, $J=6.5$ Hz), 7.40 (t, 1H, $J=7.5$ Hz), 7.60 (d, 1H, $J=8.0$ Hz), 7.75 (t, 1H, $J=7.5$ Hz), 8.20 (d, 1H, $J=8.0$ Hz). IR (KBr) ν: 3063, 2950, 1680, 1574, 1450, 1228. EIMS: m/z: 200 M^+, 185, 173, 144, 199, 76. Compound **4e**: Solid, mp 105–106°C, ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.28–2.30 (m, 2H), 3.20 (t, 2H, $J=7.5$ Hz), 4.25 (t, 2H, $J=7.5$ Hz), 7.45 (t, 1H, $J=7.8$ Hz), 7.60–7.69 (m, 2H), 8.25 (d, 1H, $J=8.0$ Hz). IR (KBr) ν: 3055, 2948, 1670, 1598, 1430, 1250. EIMS: m/z: 186 M^+, 130, 102, 76.