Pergamon

Tetrahedron Letters 40 (1999) 7275–7278

TETRAHEDRON LETTERS

A divergent approach to cryptotackieine and cryptosanguinolentine alkaloids

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Received 16 June 1999; accepted 2 August 1999

Abstract

A seven-step synthesis of the 1-methyl-3-(*o*-azidophenyl)quinolin-2-one, a common intermediate for the synthesis of the cryptotackieine and cryptosanguinolentine alkaloids, is described. This intermediate is directly converted into cryptotackieine **1** by an intramolecular aza-Wittig reaction with trimethylphosphine; alternatively heating followed by reduction of the resulting indoloquinoline derivative provided cryptosanguinolentine **2**.

Keywords: alkaloids; aza-Wittig reaction; insertion reaction; microwave heating; nitrogen heterocycles.

Cryptotackieine **1** (also named neocryptolepine) and cryptosanguinolentine **2** (also named isocryptolepine) two structurally and biosynthetically related natural products were isolated a few years ago by two independent groups from *Cryptolepis sanguinolenta*,[1] a shrub indigenous to tropical West Africa, which has been used in folk medicine as an antimalarial agent. Cryptotackieine **1** which displays a strong antiplasmodial activity[2] was found to be a *N*-methyl derivative of the linear indolo[2,3-*b*]quinoline ring system, whereas the cryptosanguinolentine **2**, which differs in the fusion of the indole and quinoline rings, possesses an angular indolo[3,2-*c*]quinoline ring system. It has been reported[3] that some *N*-methyl derivatives of these ring systems display important antimicrobial and cytotoxic activity.

In the course of our studies directed towards the synthesis of azaheterocycles based on heterocyclization reactions of azahexatriene systems,[4] we have reported that arylheterocumulenes containing an unsaturated side-chain at the *ortho*-position undergo thermal cyclization to afford quinoline derivatives.[5]

In conjunction with synthetic efforts[6] on the total synthesis of the target alkaloids **1** and **2**, we have devised and improved a reliable divergent approach which is based on the formation of the key common 1-methyl-3-(*o*-azidophenyl)quinoline-2-one intermediate **11** and its suitable use for the preparation of cryptotackieine **1** and cryptosanguinolentine **2** by a selective indolization process. Consequently, the approach permits preparation of **1** and **2** from a common intermediate (Scheme 1).

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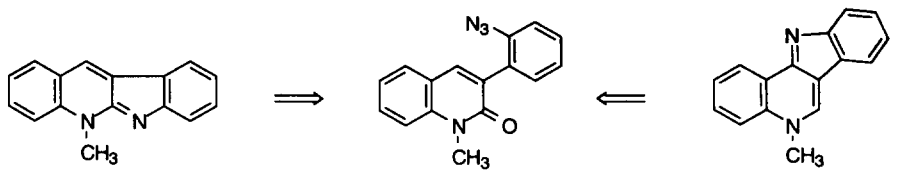
0040-4039/99/$ - see front matter
PII: S0040-4039(99)01477-X



Cryptotackieine **1** **11** Cryptosanguinolentine **2**

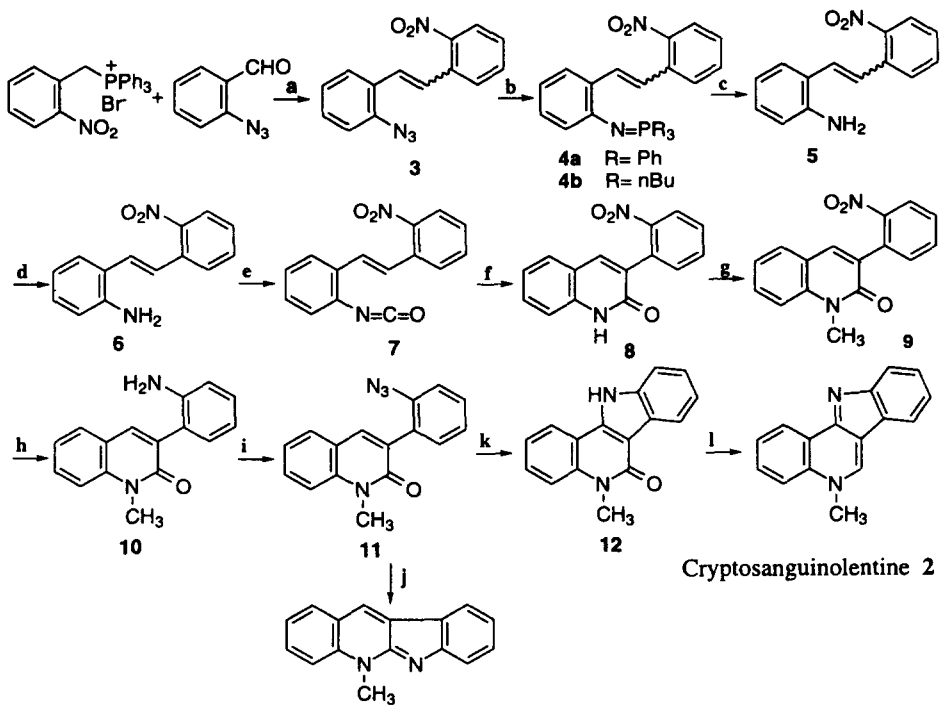
Scheme 1.

Condensation of (2-nitrobenzyl)triphenylphosphonium bromide with *o*-azidobenzaldehyde[7] in the presence of anhydrous potassium carbonate and catalytic amounts of dibenzo-18-crown-6 yielded the stilbene derivative **3** in 85% yield as a 4:1 mixture of *Z:E* isomers (Scheme 2). Staudinger reaction with triphenylphosphine and the azide **3** in dry dichloromethane provided the iminophosphorane **4a** in 92% yield as a 4:1 mixture of *Z:E* isomers. Thiophenol/AIBN-catalyzed isomerization afforded the *E*-iminophosphorane isomer **4a** in 70% yield. Aza-Wittig reaction of the *E*-isomer **4a** with carbon dioxide under a variety of conditions led to a mixture of the isocyanate **7** (minor product) and the corresponding diaryl carbodiimide (major product), that we were not able to separate. However, reaction of **3** with tri-*n*-butylphosphine followed by hydrolysis of the resulting iminophosphorane **4b** gave the stilbene derivative **5** in 84% yield as a 7:1 mixture of *Z:E* isomers, which were separated by column chromatography; *Z*→*E* isomerization led to the (*E*)-2-amino-2′-nitrostilbene **6** in 92% yield. One-flask conversion[8] of compound **6** into the quinolin-2-one derivative **8** was achieved in 80% yield by sequential treatment with bis(trichloromethyl)carbonate (triphosgene) and further microwave-promoted cyclization of the resulting isocyanate **7**. Conversion of the quinoline-2-one **8** into the common intermediate **11** was achieved by the three-step sequence: (a) methylation to give **9** (82%); (b) catalytic hydrogenation in the presence of palladium on charcoal to afford **10** (91%); and (c) diazotization followed by the reaction with sodium azide provided **11** (85%).[9]

Initial attempts to promote cyclization of the intermediate **11** into cryptotackieine **1** by treatment with triphenylphosphine and then thermal cyclization of the resulting iminophosphorane were unsuccessful even after an extended reaction time and high temperature. However, when **11** was treated with the more reactive trimethylphosphine at room temperature, nitrogen evolution was observed and further heating in nitrobenzene at reflux temperature for 24 h of the resulting iminophosphorane provided **1** in a disappointing yield of 13%. Better results and shorter reaction times were obtained when the aza-Wittig reaction was accomplished under microwave irradiation. Thus, when a solution of the iminophosphorane derived from **11** and trimethylphosphine in nitrobenzene was heated under microwave between 150 and 180°C for 30 min, cryptotackieine **1** was obtained in 40% yield.[10] Although, intramolecular aza-Wittig imination reactions involving amide carbonyl groups have been reported,[4] the conversion **11**→**1** represents the first example of an intramolecular aza-Wittig reaction involving a 2-pyridone carbonyl group, to the best of our knowledge.

Alternatively, when compound **11** was exposed to heat in *o*-xylene at reflux temperature indolization took place by a nitrene insertion process across the 4-position of the pyridone ring to give **12** in 82% yield, thus completing the assembly of the framework of the cryptosanguinolentine. The final step was to effect the reduction of the carbonyl group of the 2-pyridone ring. After several trials, the best results were obtained by using Red-Al as reducing agent. Thus, reaction of **12** with Red-Al in toluene at reflux temperature and then treatment of the crude product with anhydrous $MgSO_4$ provided cryptosanguinolentine **2** in 90% yield.[11]

In conclusion, we have developed a new and divergent approach to the alkaloid cryptotackieine **1** (eight steps) and cryptosanguinolentine **2** (nine steps) through a common azido-quinolin-2-one derivative



Scheme 2. Reactions and conditions. (a) K_2CO_3/dibenzo-18-crown-6/CH_2Cl_2, rt 85%; (b) i: Ph_3P, CH_2Cl_2, rt, ii: PhSH/AIBN/benzene, reflux, *E*-**4a** 70%; (c) from **4b**, THF/H_2O, rt 84%; (d) PhSH/AIBN/benzene, reflux, 92%; (e) triphosgene, CH_2Cl_2, 0°C→rt; (f) MW, nitrobenzene, 80%; (g) CH_3I, DMF, 60°C, 82%; (h) H_2, Pd/C, EtOH, rt 91%; (i) $NaNO_2/H_2SO_4$, H_2O–NaN_3, 85%; (j) MW, Me_3P, nitrobenzene, 180°C, 40%; (k) *o*-xylene, 150°C, 82%; (l) Red-Al, toluene, reflux, 90%

intermediate able to undergo a selective indolization process either by intramolecular aza-Wittig reaction to give directly **1** or by nitrene insertion process followed by reduction to give **2**.[12]

Acknowledgements

We gratefully acknowledge the financial support of the Dirección General de Investigación Científica y Técnica (PB95-1019). S.D. thanks the Fundación Séneca for a studentship.

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8. Typical procedure. To a solution of bis(trichloromethyl)carbonate (triphosgene) (0.45 g, 1.53 mmol) in dry dichloromethane (20 ml) was added dropwise over a period of 15 min a mixture of 2-amino-2′-nitrostilbene **6** (1 g, 4.17 mmol), triethylamine (0.47 g, 4.59 mmol) and dry dichloromethane (25 ml) at 0°C under N_2. Then, the resulting mixture was allowed to warm to room temperature and stirred for 1 h. The solvent was removed under reduced pressure and the crude isocyanate **7** was dissolved in nitrobenzene (15 ml), in a glass tube which was placed in a Synthewave 402 reactor and irradiated for 12 min at 150°C. After cooling, the precipited solid was separated by filtration, washed with water (2×15 ml), diethyl ether (2×15 ml) and air-dried, to give **8** (0.89 g, 80%); m.p. 318°C (yellow prisms from tetrahydrofuran/diethyl ether). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.25 (t, 1H, J=7.8 Hz, H-6), 7.36 (d, 1H, J=8.1 Hz, H-8), 7.56 (t, 1H, J=8.1 Hz, H-7), 7.65 (d, 1H, J=7.8 Hz, H-5), 7.67 (t, 1H, J=7.8 Hz, H-4′), 7.78 (d, 1H, J=7.8 Hz, H-6′), 7.83 (t, 1H, J=7.8 Hz, H-5′), 8.06 (d, 1H, J=7.8 Hz, H-3′), 8.17 (s, 1H, H-4), 12.00 (s, 1H, NH). ^{13}C NMR (50 MHz, DMSO-d_6) δ 115.0 (C-8), 119.3 (C-4a), 122.1 (C-6), 123.9 (C-3′), 128.2 (C-6′), 129.4 (C-4′), 130.6 (C-7), 130.9 and 131.0 (C-1′ or C-3), 132.2 (C-5), 133.6 (C-5′), 137.5 (C-4), 138.5 (C-8a), 148.9 (C-2′), 160.0 (C-2). IR (nujol) ν 1662 (s), 1531 (s), 1365 (m) cm^{-1}. MS: *m/z* (%) (EI positive) 267 (M+1, 3), 266 (M, 18), 234 (14), 220 (100), 190 (13), 165 (20).
9. M.p. 167°C (d) (brown prisms from dichloromethane/hexane). ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.68 (s, 3H, CH_3N), 7.25 (td, 1H, J=7.7, 1.3 Hz) and 7.30 (td, 1H, J=7.6, 0.9 Hz) (H-5′ or H-6), 7.34–7.38 (m, 2H, H-3′+H-6′), 7.49 (ddd, 1H, J=9.0, 7.3, 1.7 Hz) and 7.65 (ddd, 1H, J=8.6, 7.3, 1.7 Hz) (H-4′ or H-7), 7.56 (d, 1H, J=9.0 Hz, H-8), 7.75 (dd, 1H, J=7.7, 1.3 Hz, H-5), 7.91 (s, 1H, H-4). ^{13}C NMR (75 MHz, DMSO-d_6) δ 29.7 (CH_3N), 114.6 (C-8), 119.0 (C-3′), 119.7 (C-4a), 122.2 and 124.9 (C-5′ or C-6), 129.9 (C-5), 129.2 and 129.5 (C-1′ or C-3), 129.7 and 131.0 (C-4′ or C-7), 131.6 (C-6′), 138.0 (C-2′), 138.6 (C-4), 139.6 (C-8a), 160.1 (C-2). IR (nujol) ν 2123 (s), 2086 (s), 1652 (m) cm^{-1}. MS: *m/z* (%) (EI positive) 277 (M+1, 5), 276 (M, 8), 248 (M–N_2, 100), 234 (28), 219 (67).
10. To a solution of azide **11** (80 mg, 0.29 mmol) in freshly distilled nitrobenzene (3.5 ml) placed in a glass tube, trimethyphosphine (0.29 ml of a 1 M toluene solution) was added dropwise under N_2. The reaction mixture was stirred at room temperature for 45 min (until N_2 evolution had ceased). The tube was placed in a Synthewave 402 reactor and irradiated in following sequence: 5 min at 150°C, 5 min at 165°C and 20 min at 180°C. After cooling the precipitated solid was collected and chromatographed on a silica gel column using acetone as eluent to give **1** in 40% yield.
11. To a suspension of indoloquinolone **12** (50 mg, 0.2 mmol) in dry toluene (15 ml), sodium *bis*(2-methoxyethoxy)aluminium hydride (Red-Al) (0.42 ml of a 65% toluene solution) was added dropwise under N_2. The mixture was refluxed for 32 h. After cooling, the solution was poured into 20% aqueous NaOH solution (50 ml) and then stirred for 30 min. The mixture was extracted with diethyl ether (3×50 ml) and dissolved in dichloromethane (30 ml), anhydrous $MgSO_4$ was added and the mixture was stirred for 2 h. The solvent was removed under reduced pressure and the solid was washed with dichloromethane (3×20 ml). The remaining solid was dissolved in H_2O (75 ml) and the resultant solution was extracted with dichloromethane (2×20 ml). The combined organic layers were concentrated to dryness and the solid residue was chromatographed on a silica gel column using toluene:acetone:NH_4OH 25:25:1 as eluent to give cryptosanguinolentine **2** (42 mg, 90% yield).
12. Spectroscopic data for the compounds **1** and **2** were identical with those reported[1] for the natural products.