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# Double reductive cyclization: a facile synthesis of the indoloquinoline alkaloid cryptotackieine

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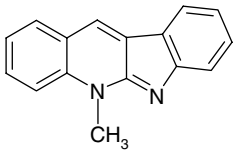
**Abstract**—A new synthesis of the indoloquinoline alkaloid cryptotackieine, isolated from *Cryptolepis sanguinolenta*, is described which involves a Perkin reaction, a tandem double reduction–double cyclization reaction followed by regioselective methylation at the quinoline nitrogen.


Two independent groups reported the isolation of a new indoloquinoline alkaloid in 1996 from the ethanolic extracts of *Cryptolepis sanguinolenta*, a shrub indigenous to tropical West Africa, which was named as cryptotackieine **1** by one group,[1] and neocryptolepine by the other group.[2] Cryptotackieine (neocryptolepine), which displays strong antiplasmodial activity against chloroquine-resistant *Plasmodium falciparum* strains[3] was found to be the N-methyl derivative of the linear indolo[2,3-*b*]quinoline ring system. It has been reported that cryptotackieine (neocryptolepine) and various methyl derivatives of such systems display biological properties such as antimuscarinic, antibacterial, antiviral, antimicotic, antihyperglycemic, and cytotoxic activities in vivo, and significant antitumor properties in vitro.[4]




**1**

The interesting biological activity of **1** has generated an interest in developing a new synthetic pathway to polyheteroatomic ring systems such as 6*H*-indolo[2,3-*b*]-quinoline, the precursor to cryptotakieine (neocryptolepine).[5] In 1997, Alajarin et al.[6] reported the synthesis of cryptotackieine **1** in three steps using an aza-Wittig reaction with an overall yield of 15%.

In the same year, Timari et al. reported a synthesis in five steps with an improved overall yield of 24%. The key reaction of this method was the Suzuki coupling reaction between 3-bromoquinoline and *N*-pivaloylaminophenylboronic acid.[7] In 1999, Molina et al. described an iminophosphorane mediated approach to obtain **1** in 26% overall yield, which involved eight steps.[8] Molina has also prepared **1** in nine steps in 9% overall yield using an intramolecular aza-Wittig reaction[9] as the key step. Wang and co-workers reported the synthesis of **1** in four steps via a biradical pathway[10] with an overall yield of 5%. In 2004, Ila and co-workers reported a five-step synthesis of **1** with an overall yield of 27%, which involved heterocyclization as the key step.[11] More recently, Mohan and co-workers reported the synthesis of **1** via three steps using a photocyclization reaction as the key step with an overall yield of 40%.[12]

In continuation of our interest[13] in domino reactions, we report herein a facile synthesis of 6*H*-indolo[2,3-*b*]-quinoline **3**, the immediate chemical precursor of the alkaloid cryptotackieine (neocryptolepine). Our retrosynthetic analysis of **3** indicated that it should be possible to prepare **3** via a one-pot double reduction, isomerization, and double cyclization (Scheme 1). The

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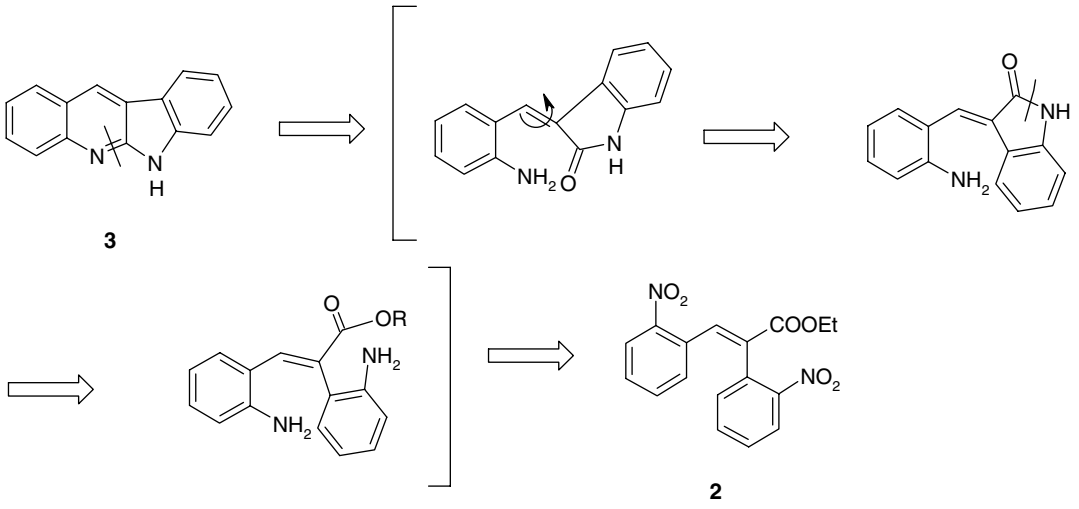
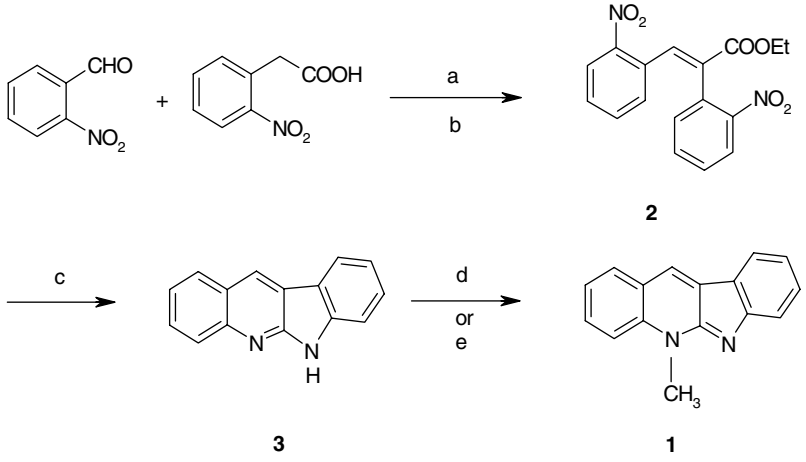



**Scheme 1.**




**Scheme 2.** Reagents and conditions: (a) $Ac_2O$, $Et_3N$, reflux, 5 h; (b) EtOH, $H_2SO_4$, reflux, 24 h, 71%; (c) Fe/AcOH:EtOH:$H_2O$/HCl, 120 °C, 24 h, 74%; (d) MW, $Me_2SO_4$/DMF, 140 °C, 5 min, 75%; (e) $Me_2SO_4$, $CH_3CN$, reflux, 6 h, $K_2CO_3$, 80%.

required unsaturated ester **2** could be easily assembled from commercially available *o*-nitrobenzaldehyde and *o*-nitrophenylacetic acid using the Perkin reaction.

Thus, condensation of *o*-nitrobenzaldehyde and *o*-nitrophenylacetic acid in the presence of $Ac_2O$ and $Et_3N$ yielded the corresponding α,β-unsaturated acid, which on esterification afforded the required ester **2** in 71% yield.[14] Reduction of **2** with Fe/AcOH in presence of HCl provided 6*H*-indolo[2,3-*b*]quinoline **3** in 74% in a single step.[15] In this step, four reactions had taken place in a tandem manner, that is, reduction of both the nitro groups, cyclization, isomerization of the intermediate *E*-amide to the *Z*-amide followed by a second cyclization. In the final step, compound **3** was subjected to regioselective methylation on the quinoline nitrogen as reported[8,12] to give cryptotackieine (neocryptolepine) **1** in 80% yield. The overall yield of **1** was found to be 42% over the three steps and is comparable with those reported (Scheme 2). The spectral data for compound **1** were identical with those reported[1] for the natural product.

In conclusion, we have developed a new and efficient three-step synthesis of the alkaloid cryptotackieine (neocryptolepine) using a Perkin reaction followed by a 'one-pot' double reduction, double cyclization and isomerization in excellent yield. Due to the easy availability of the starting materials and high yields realized in the different steps, this approach represents an efficient synthesis of the title compound.

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14. *Experimental procedure for the preparation of* α,β-*unsaturated ester derivative* **2**: A mixture of *o*-nitrobenzaldehyde (1.06 g, 7.01 mmol), *o*-nitrophenylacetic acid (1.27 g, 7.01 mmol), $Et_3N$ (1.1 mL), and $Ac_2O$ (15 mL) were heated at reflux for 5 h. The mixture was allowed to cool and poured into water (50 mL). This was then extracted with $CHCl_3$ ($3 \times 15$ mL) and the combined organic extracts were washed with aqueous satd $Na_2CO_3$ solution ($3 \times 15$ mL). The combined $Na_2CO_3$ washings were acidified with 6 N HCl. The resulting solid was filtered, dried, redissolved in EtOH (15 mL), $H_2SO_4$ (five drops) were added, and refluxed for 24 h. The reaction mixture was cooled to room temp and after 6 h, the α,β-unsaturated ester **2** (1.71 g, 71%) precipitated as a crystalline white solid and was isolated by filtration. IR (KBr, $cm^{-1}$): *v* 1524, 1570, 1611, 1701; $^1H$ NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.28 (t, 3H, $J = 7.2$ Hz, $-OCH_2CH_3$), 4.29 (q, 2H, $J = 7.2$ Hz, $-OCH_2CH_3$), 7.02–7.08 (m, 2H, Ar-H), 7.28–7.41 (m, 3H, Ar-H), 8.12–8.16 (m, 3H, Ar-H), 8.22 (s, 1H, =CH); $^{13}C$ NMR ($CDCl_3$, 75 MHz) δ (ppm): 13.99, 61.84, 76.60, 77.03, 77.45, 124.56, 124.66, 129.26, 129.37, 131.00, 131.58, 131.68, 133.01, 133.10, 133.55, 133.58, 137.25; HRMS *m*/*z*: $[M+Na]^+$ calcd for $C_{17}H_{14}N_2O_6$, 365.0750; found, 365.0746.
15. *Experimental procedure for the preparation of* 6*H*-indolo[2,3-*b*]*quinoline* **3**: Ester derivative **2** (0.55 g, 1.61 mmol) and Fe powder (3.6 g) were added to a mixture of EtOH (10 mL), acetic acid (10 mL), and $H_2O$ (5 mL). To this mixture five drops of concd HCl were added and the suspension was heated at 120 °C while stirring for 24h. The mixture was allowed to cool to room temp and then filtered through Celite. The filtrate was diluted with water (50 mL) and then extracted with $CHCl_3$ ($3 \times 15$ mL). The combined organic extract was washed with 10% aqueous $NaHCO_3$ (25 mL) and $H_2O$ ($3 \times 15$ mL), dried over anhydrous $Na_2SO_4$, and concentrated to dryness to give a yellow solid. The solid was washed with $Et_2O$ and air dried to give 6*H*-indolo[2,3-*b*]quinoline **3** (0.26 g, 74%). Mp > 300 °C (Lit.[16] mp: 346 °C); IR (KBr, $cm^{-1}$): *v* 1231, 1406, 1460, 1614, 3144; $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ (ppm): 7.27 (tm, 1H, H-9), 7.46–7.57 (m, 3H, H-2, H-7, H-8), 7.72 (ddd, 1H, $J = 8.1$, 7.2, 0.9 Hz, H-3), 7.98 (d, 1H, $J = 8.4$ Hz, H-9), 8.11 (d, 1H, $J = 8.1$ Hz, H-1), 8.27 (d, 1H, $J = 7.8$ Hz, H-10), 9.05 (s, 1H, H-11), 11.70 (s, 1H, NH); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) δ (ppm): 111.39 (C-7), 118.37 (C-10b), 120.14 (C-9), 120.76 (C-11a), 122.29 (C-10), 123.20 (C-2), 124.15 (C-10a), 127.45 (C-1), 128.01 (C-11), 128.67 (C-4), 129.13 (C-8 + C-3), 141.93 (C-6a), 146.79 (C-4a), 153.36 (C-5a).
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