



An efficient synthesis of indoloquinoline alkaloid—neocryptolepine (cryptotackieine)

Prakash T. Parvatkar, Santosh G. Tilve

Department of Chemistry, Goa University, Taleigao Plateau, Goa 403 206, India

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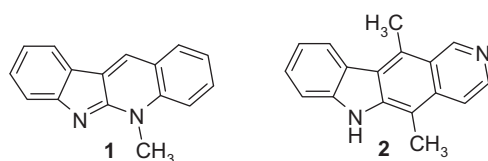
One-pot and Wittig reaction

ABSTRACT

A short and convenient method for the synthesis of neocryptolepine (cryptotackieine) is described using Wittig reaction and one-pot reduction–cyclization–dehydration approach as the key steps.

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Plants are still the important resources for the discovery of new drugs. The roots of the West African plant *Cryptolepis sanguinolenta* have long been used by Ghanaian healers to treat a variety of disorders such as infectious diseases, amebiasis, and fever including malaria^{1–3} and have proved to be a rich source of indoloquinoline alkaloids. Neocryptolepine **1** (also named cryptotackieine) is one of the thirteen characterized alkaloids isolated from *C. sanguinolenta*^{4,5} and has a considerable structural resemblance to the highly potent alkaloid ellipticine **2**.

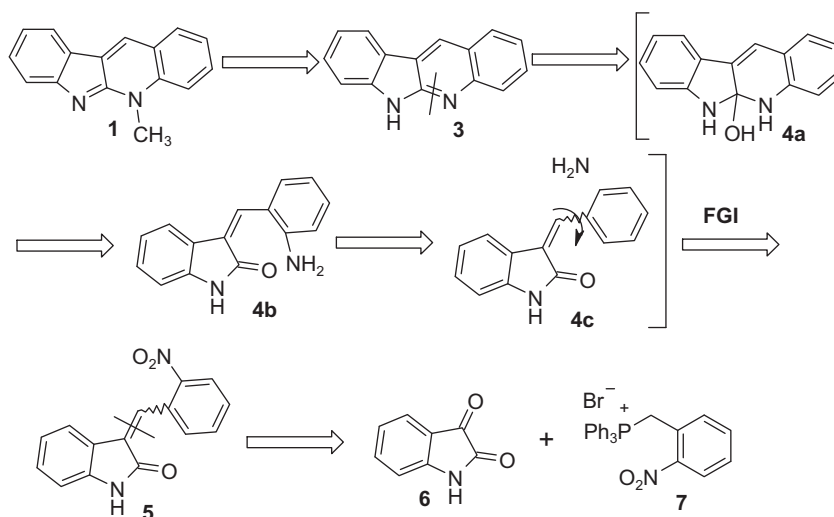


Neocryptolepine **1** is a tetracyclic heteroaromatic alkaloid containing linear indolo[2,3-*b*]quinoline ring system and displays a strong antiplasmodial activity⁶ in addition to antimicrobial and cytotoxic activity.^{7,8} Novel structural features and wide biological activity profile of neocryptolepine attracted both synthetic and medicinal chemists. It was first synthesized in 1994 by Peczyńska-Czoch and co-workers⁷ before its isolation from natural source in four steps with an overall yield of 9% via Graebe–Ullmann reaction. Later on in 1997, Alajarin et al.⁹ reported its formal

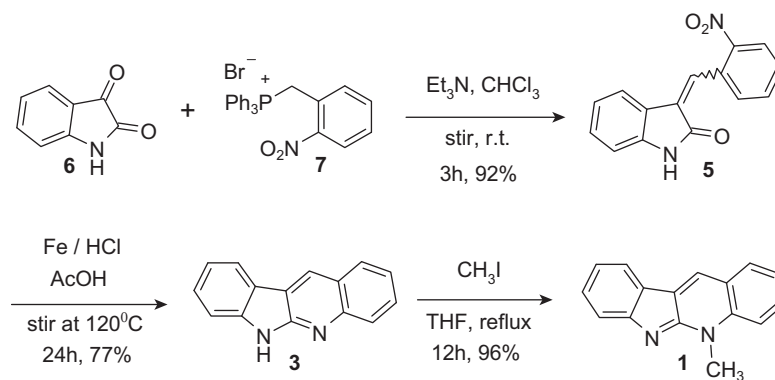
synthesis in two steps with an overall yield of 19% using aza-Wittig reaction. In the same year, Timari et al.¹⁰ reported the total synthesis in five steps with an improved overall yield of 24% using Suzuki coupling as the key step. Molina and co-workers^{11,12} developed two routes using aza-Wittig reaction—one involving eight steps with 26% overall yield (in 1999)¹¹ while the other route involves nine steps with 9% overall yield (in 2001).¹² Wang and co-workers¹³ in 1999 prepared **1** in four steps via biradical pathway with an overall yield of 5%. Pieters and co-workers¹⁴ reported the five step synthesis in 2002 using a diradical cyclization approach. In the same year, Ho and Jou¹⁵ prepared **1** in five steps with an overall yield of 33% using DCC coupling and Favorskii rearrangement as the main steps. In 2004, Ila and co-workers¹⁶ reported its synthesis in five steps with an overall yield of 27% via heterocyclization approach. Mohan and co-workers¹⁷ in 2006 reported the synthesis of **1** via photocyclization reaction with an overall yield of 40% in three steps. In 2007, we prepared neocryptolepine in three steps with an overall yield of 42% using double reduction–double cyclization approach.¹⁸ Sharma and Kundu¹⁹ reported its synthesis in three steps via C–N bond formation using SnCl₂·2H₂O with 24% overall yield (in 2008). We reported the formal synthesis of neocryptolepine in one-pot using iodine as a catalyst in 45% yield (in 2009).²⁰ Recently in 2010, Kraus and Guo²¹ reported the synthesis of **1** in five steps with an overall yield of 24% via intramolecular Wittig reaction. In the same year, Haddadin et al.²² prepared neocryptolepine in three steps using reduction as the key step with 28% overall yield. More recently in 2011, Hostyn et al.²³ reported its synthesis in three steps using Pd-catalyzed intramolecular direct arylation as the key reaction with an overall yield of 88%, which is the highest yield reported so far.

* Corresponding authors.

E-mail addresses: pparvatkar@yahoo.com (P.T. Parvatkar), stilve@unigoa.ac.in (S.G. Tilve).



Scheme 1. Retrosynthetic analysis of neocryptolepine 1.



Scheme 2. Synthesis of neocryptolepine 1.

In continuation of our interest^{18,20,24} in indoloquinoline alkaloids, we herein report a new synthesis of neocryptolepine. Our retro-synthetic analysis of 6*H*-indolo[2,3-*b*]quinoline **3** (precursor to neocryptolepine) showed that it could be prepared in one-pot from intermediate **5** via reduction–cyclization–dehydration approach. The intermediate **5** in turn could be obtained by Wittig reaction from easily available starting materials (Scheme 1).

Thus, condensation of (2-nitrobenzyl)triphenylphosphonium bromide **7** with isatin **6** in the presence of triethyl amine yielded the corresponding Wittig product **5** in 92% yield.²⁵ Reduction of **5** with Fe/AcOH in the presence of a catalytic amount of HCl afforded 6*H*-indolo[2,3-*b*]quinoline **3** in 77% yield.²⁶ In this step, reduction of nitro group, isomerization of C–C double bond, cyclization, and then dehydration took place in one-pot to give the aromatized product **3** via intermediate **4c–a**. Finally, the compound **3** is converted to neocryptolepine **1** via regiospecific methylation¹⁵ (Scheme 2). The overall yield of **1** in this three step sequence is 68%.

In conclusion, we have developed a short, simple, and high yielding method for the synthesis of neocryptolepine. The new protocol has advantage in terms of number of steps, overall yield, and efficiency over most of the other reported methods. We are currently evaluating the possibility to extend the range of compounds to be prepared with the synthetic pathway presented in this Letter. These results will be presented in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2011.09.135](https://doi.org/10.1016/j.tetlet.2011.09.135).

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25. **Experimental procedure for the preparation of 5:** To a mixture of isatin **6** (0.30 g, 2.04 mmol) and 2-nitrobenzyl triphenylphosphonium bromide **7** (1.17 g, 2.45 mmol) in CHCl_3 (10 mL) was added Et_3N (0.5 mL) and stirred at room temp for 3 h. The solid which comes out was filtered and dried to give the product **5** (0.50 g, 92%) as a bright red solid. Mp = 228–232 °C; IR (KBr): ν_{max} = 3175 (–NH), 1705 (–C=O), 1616, 1522, 1340, 1232, 866, 735 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$, 400 MHz): (geometrical isomers in 2:1 ratio) δ 10.69 [10.52]^a (s, 1H, –NH), 8.31 [8.29]^a (d, J = 7.6 Hz, 1H), 7.83 [8.16]^a (s, 1H), 7.64–7.89 (m, 4H), 6.72–7.25 (m, 4H).
^aValues in the square brackets are for the minor isomer.
 ^{13}C NMR ($\text{DMSO}-d_6$, 75 MHz):
 δ 111.2 (110.6), 121.4 (121.7), 122.2 (122.3), 123.3 (124.1), 125.2 (126.1), 128.8 (129.4), 129.6 (129.8), 130.7 (130.9), 130.9 (131.4), 131.6 (131.9), 132.4 (132.3), 135.5 (134.2), 143.9 (142.5), 148.4 (147.9), 168.9 (167.6).
Values in the brackets are for the minor isomer.
HRMS: m/z [$\text{M}+\text{Na}$]⁺ calcd for $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_3$, 289.0589; found, 289.0589.
26. **Experimental procedure for the preparation of 3:** Fe powder (3.01 g) was added over a period of 30 min to a stirred solution of compound **5** (0.3574 g, 1.34 mmol) in AcOH (30 mL). To this mixture 5 drops of concd HCl were added and the suspension was stirred at 120 °C for 24 h. 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 (4 × 25 mL). The combined organic extract was washed with 10% aqueous NaHCO_3 (25 mL) and H_2O (3 × 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 6H-indolo[2,3-*b*]quinoline **3** (0.23 g, 77%) as a yellow solid. Mp >300 °C; Lit.⁹ 346 °C.
Spectral data (IR, ^1H and ^{13}C NMR) were identical to those reported^{18,20} for the 6H-indolo[2,3-*b*]quinoline.