An Alternate Synthesis of *6H*-Indolo[2,3-*b*]quinoline via One-Pot Alkylation–Dehydration–Cyclization–Aromatization Approach

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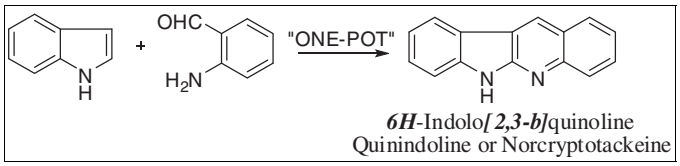

***6H*-Indolo*[2,3-b]*quinoline**
Quinindoline or Norcryptotackeine

A simple, straightforward and efficient synthesis of 6*H*-indolo[2,3-*b*]quinoline, a natural product isolated from leaves of *Justicia betonica*, is achieved through a pivalic acid-assisted one-pot alkylation–dehydration–cyclization–aromatization approach. This synthesis constitutes a formal approach toward a biologically important alkaloid neocryptolepine.

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INTRODUCTION

Indoloquinoline alkaloids are known for their natural occurrence and diverse biological activities [1]. 6*H*-Indolo [2,3-*b*]quinoline **1**, also known as quinindoline or norcryptotackeine, was isolated from the leaves of *Justicia betonica* along with 5*H*-indolo[2,3-*b*]quinolin-11(6*H*)-one **2** [2]. Quinindoline **1** is a recognized precursor of well-known alkaloid 5-methyl-5*H*-indolo[2,3-*b*]quinoline **3** named as neocryptolepine or cryptotackeine isolated from roots of West African plant *Cryptolepis sanguinolenta* [3] (Fig. 1).

Decoction of *C. sanguinolenta* was used in the past for treatment of infectious diseases, fever, and malaria. This made the isolated alkaloids a subject of intense biological screening and as medicinally important compound [4]. Neocryptolepine **3** exhibited *in vitro* and *in vivo* antiplasmodial activity and antibacterial activity and also inhibited the growth of the yeast *Candida albicans*. Antiproliferative study on human hepatocellular carcinoma HepG2 and human breast carcinoma MCF-7 cells revealed methyl substituted 6*H*-indolo[2,3-*b*]quinolines to be most active. Many methyl derivatives of neocryptolepine **3** displayed antibacterial, antimycotic, *in vitro* cytotoxic activity, *in vivo* antitumor properties, and DNA topoisomerase II inhibition. Synthetic derivatives of neocryptolepine **3** displayed *in vitro* inhibition of β-haematin formation in cell-free systems, indicating a potential mechanism for their antiplasmodial activity, and also exhibited antitrypanosomal activity. Amino-substituted neocryptolepine derivatives exhibited schistosomicidal activity.

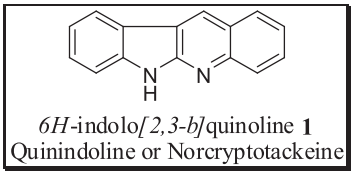
Potential medicinal applications have motivated many synthetic chemists to develop methodologies for its preparations through diverse approaches [5]. One-pot approaches [6] have become widely popular as these methods can be easily utilized by medicinal chemists and other application-oriented researchers to have an easy access to this skeleton. Here are the highlights of such one-pot methodologies.

Our group had developed a one-pot synthesis of indoloquinoline by reaction of indole-3-carboxaldehyde and aryl amines in presence of iodine as a catalyst in refluxing diphenylether [6a]. This process involves iodine-catalyzed sequential imination, nucleophilic addition, and annulation reactions. Thereafter, Vaghei and Malaekehpoor [6b] reported NBS as catalyst instead of iodine for these reactions at room temperature and synthesized various substituted indoloquinolines. A recyclable heterogeneous Ru catalyst is reported by Khorshidi and Tabatabaeian [6c] for these reactions. Seidel's group [7] explored a divergent reaction of indole with *N*-methyl-2-aminobenzaldehyde using p-TSA to obtain neocryptolepine. Similarly, Liang's group [8] exploited a metal-free iodine-mediated selective difunctionalization of N-benzylindoles by Friedel–Craft alkylation with *N*-tosylaminobenzaldehyde to give benzylindoloquinoline. This was then debenzylated to indoloquinoline by $AlCl_3$ and then regioselectively methylated at quinoline *N*-atom with dimethylsulfate to give neocryptolepine. Pumphrey et al. [9] demonstrated a Ru catalyzed C–H bond amination strategy for synthesis of neocryptolepine using aryl azide. Maes's group [10] synthesized chloroneocryptolepine starting from quinolinium triflates and chloroanilines via a one-pot condensation and Pd-catalyzed intramolecular direct arylation strategy.

In continuation of our interest in indoloquinoline alkaloids [1,6a,11], we herein report a simple one-pot assembly of indoloquinoline skeleton by pivalic acid-mediated cyclization between indole and *o*-aminobenzaldehyde.

RESULTS AND DISCUSSION

In literature [7,8] as described earlier, *N*-tosyl-*o*-aminobenzaldehyde and *N*-methyl-*o*-aminobenzaldehyde have been reported as substrate for the synthesis of indolo[2,3-*b*]quinoline system. However, direct use of



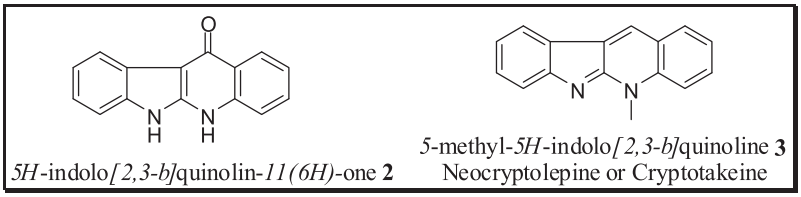


Figure 1. Naturally occurring indolo[2,3-*b*]quinolines.

unsubstituted *o*-aminobenzaldehyde was lacking, maybe because of its propensity for dimerization and polymerization. We thought that directly using *o*-aminobenzaldehyde can give 6*H*-indolo[2,3-*b*]quinoline **1**, and its N-alkylation then can give neocryptolepine **3** and its analogs. Further, as arene being not protected, additional step of removal of the protecting group from nitrogen may not be required. Initially, we tried the reaction using p-TSA and I_2 condition reported for *N*-methylindole without success. Strong acid like TFA is known to give 3-(2-amino-phenyl)quinolines with indole and *o*-aminobenzaldehyde [7].

Scheme 1. One-pot cyclization.

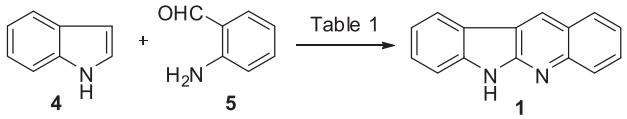


Table 1

Various catalyst and reagents (Scheme 1).

Entry	Reaction condition	% Yield[a]
1	p-TSA, Ph_2O, reflux, 4 h	–
2	I_2, dioxane, reflux, 24 h	–
3	Ph_2O, reflux, 6 h	11
4	MnO_2, dioxane, reflux, 24 h	–
5	Pd/C, dioxane, reflux, 24 h	–
6	DDQ, dioxane, reflux, 24 h	–
7	PivOH (1 eq.), Ph_2O, reflux, 6 h	56
8	PivOH, reflux, 6 h	–

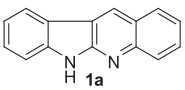
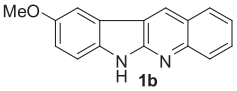
[a]Isolated yield.

We then tried the reaction using indole **4** and freshly prepared *o*-aminobenzaldehyde **5** and heated this mixture in solvent at high temperature; we were delighted to observe product formation after reflux for 6 h, but on purification, product **1** was isolated in just 11% yield (Scheme 1; Table 1). Then, we investigated this reaction by employing various oxidizing reagents that we anticipated may help in final oxidation step. Thus, we tried MnO_2, Pd/C, and DDQ but were unsuccessful to obtain any product formation.

Pivalic acid, being a non-nucleophilic weak acid, binds reversibly to the amino group and activates the carbonyl, thereby increasing the electrophilicity of aldehyde **5**. We tried this for the reaction and observed product **1** formation in moderate yield. Increasing the acid strength did not furnish us any product formation. This one-pot reaction, although average yielding, is very simple and efficient.

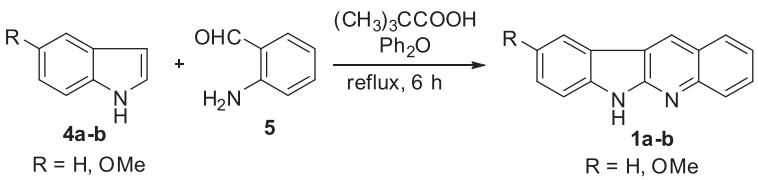
Table 2

Scope of reaction[a] (Scheme 2).

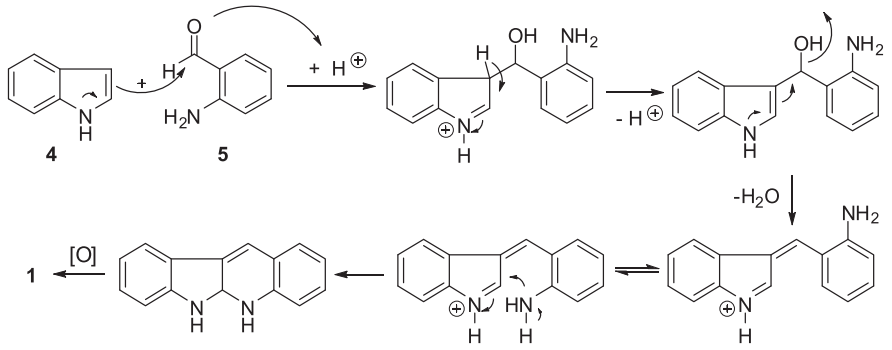
Entry	Indoloquinoline **1a-b**	% Yield[b]
1	 **1a**	56
2	 **1b**	54

[a]**4** (1 mmol), **5** (1.5 mmol), pivalic acid (1 mL), Ph_2O (10 mL) reflux, 6 h.
[b]Isolated yield.

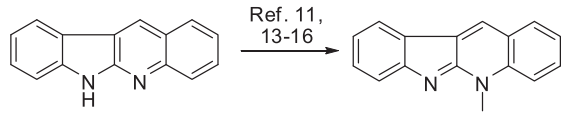
Scheme 2. Substrate study.



Scheme 3. Mechanistic rationale.



Scheme 4. Formal synthesis of neocryptolepine.



6H-indolo*[2,3-b]*quinoline
Quinindoline
Norcryptotackeine **1**

5-methyl-*5H*-indolo*[2,3-b]*quinoline
Neocryptolepine
Cryptotakeine **3**

We extended this methodology for synthesizing a derivative using 5-methoxyindole **4b** and obtained the corresponding product in 54% yield (Scheme 2; Table 2).

Based on the product formation and reaction conditions employed, a probable mechanism is postulated (Scheme 3). First alkylation of indole **4** with *o*-aminobenzaldehyde **5** takes place followed by dehydration, and cyclization furnishes dihydroindoloquinoline, which oxidizes in air to give the final product indoloquinoline **1**.

The transformation of natural product indoloquinoline to neocryptolepine is well known in literature [11,13–16] using MeI or Me_2SO_4 as methylating agents. Thus, this synthesis formulates a formal synthesis of alkaloid neocryptolepine **3** (Scheme 4).

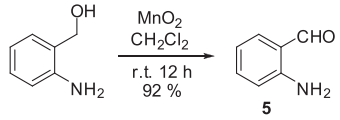
CONCLUSION

6*H*-Indolo[2,3-*b*]quinoline **1** is successfully synthesized in one pot by alkylation–dehydration–cyclization–aromatization approach using pivalic acid with indole and *o*-aminobenzaldehyde. This method provides scope for generating a library of such compounds for various biological applications. The overall yields in this methodology were comparable with the other efficient syntheses known in literature. This synthesis also constitutes the formal synthesis of alkaloid neocryptolepine **3**.

EXPERIMENTAL SECTION

Commercial reagents were purchased from Sigma-Aldrich (Mumbai, India) and used without further purification. Solvents were distilled prior to use. Reactions were monitored by thin layer chromatography with TLC silica gel 60 F254 purchased from Merck (Mumbai, India). Column chromatography was performed on silica gel (60–120 mesh). Flash chromatography was performed on a Combiflash Companion (Teledyne Isco, NE) with silica gel (230–400 mesh). Melting points were recorded in open capillary tubes using Thiele's apparatus and are uncorrected. The IR spectra were recorded on Shimadzu FTIR spectrophotometer (Kyoto, Japan). The ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker AVANCE 400 instrument (Switzerland) using $CDCl_3$ and DMSO-d_6 as solvent. Chemical shifts δ are expressed relative to TMS or residual solvent; the coupling constant *J* is given in hertz. The multiplicities of the carbon signals were obtained from DEPT-135 experiment. The following abbreviations were used: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet, and dd = double doublet.

***o*-Aminobenzaldehyde (5).**

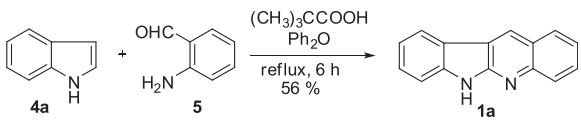


A mixture of *o*-aminobenzyl alcohol (0.615 g, 5 mmol) and MnO_2 (2.0 g) was stirred in CH_2Cl_2 at room temperature. This was filtered after 12 h, and removing solvent under vacuum gave product **5** in 92% (0.557 g) yield.

Orange oil [12].

^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.05 (br s, 2 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 6.66 (t, *J* = 7.6 Hz, 1 H), 7.23 (t, *J* = 7.2 Hz, 1 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 9.78 (s, 1 H) ppm.

6*H*-Indolo[2,3-*b*]quinoline (1a).



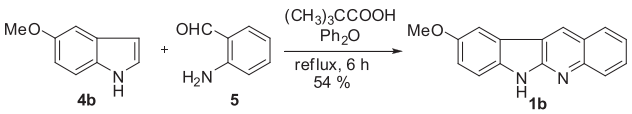
A mixture of indole **4a** (0.117 g, 1 mmol), freshly prepared *o*-aminobenzaldehyde (0.182 g, 1.5 mmol), and pivalic acid (1 mL) was refluxed in Ph_2O (10 mL) for 6 h (TLC; 10% EtOAc/hexanes). After cooling, the mixture was chromatographed (silica gel), Ph_2O was removed eluting with hexanes, and further elution with 20% EtOAc/hexanes afforded the product **1a** as yellow solid in 56% (0.122 g) yield.

mp > 300°C (Lit. mp: 342–346 °C) [6a,11]

IR (KBr): 3143, 3055, 1612, 1580 cm^{-1}.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 7.27 (t, *J* = 8.0 Hz, 1 H), 7.46–7.53 (m, 3 H), 7.72 (t, *J* = 7.2 Hz, 1 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 8.10 (d, *J* = 8.0 Hz, 1 H), 8.25 (d, *J* = 8.0 Hz, 1 H), 9.05 (s, 1 H), 11.69 (s, 1 H) ppm.

9-Methoxy-6*H*-indolo[2,3-*b*]quinoline (1b).



Similar procedure as described above was followed with 5-methoxyindole **4b** (0.147 g, 1 mmol) and freshly prepared *o*-aminobenzaldehyde (0.182 g, 1.5 mmol) for 6 h, and the corresponding indoloquinoline **1b** was obtained as light-green solid in 54% (0.134 g) yield.

mp: 286°C (Lit. mp: 284–286°C) [11a]

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 3.87 (s 3 H), 7.14 (dd, *J* = 8.4, 2.8 Hz, 1 H), 7.39 (d, *J* = 8.8 Hz, 1 H), 7.46 (t, *J* = 7.2 Hz, 1 H), 7.70 (t, *J* = 8.4 Hz, 1 H), 7.88 (d, *J* = 2.4 Hz, 1 H), 7.94 (d, *J* = 8.8 Hz, 1 H), 8.07 (d, *J* = 8.0 Hz, 1 H), 9.04 (s, 1 H), 11.49 (s, 1 H) ppm.

^{13}C-NMR (100 MHz, DMSO-d_6): δ = 55.64 (CH_3), 105.38 (CH), 111.60 (CH), 116.55 (CH), 118.08 (Cq), 121.23 (Cq), 122.50 (CH), 123.37 (Cq), 126.90 (CH), 127.64 (CH), 128.63 (2X CH), 135.82 (Cq), 146.33 (Cq), 153.26 (Cq), 153.57 (Cq) ppm.

Liquid chromatography mass spectrometry (LCMS): *m/z* $[M + H]^+$ 249.

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