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An Expeditious I_2-Catalyzed Entry into 6*H*-Indolo[2,3-*b*]quinoline System of Cryptotackieine

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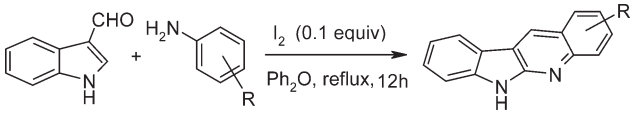


A synthesis of a series of novel 6*H*-indolo[2,3-*b*]-quinolines with different substituents on the quinoline ring is described. The method involves reaction of indole-3-carboxyaldehyde with aryl amines in the presence of a catalytic amount of iodine in refluxing diphenyl ether to yield indolo[2,3-*b*]quinolines in one-pot. The present approach provides a new route for the synthesis of polycyclic structures related to an alkaloid cryptotackieine (neocryptolepine).

In recent years indoloquinoline alkaloids have received considerable interest due to their interesting biological properties.[1] The roots of West African plant *Cryptolepis sanguinolenta*, a rich source of indoloquinoline alkaloids have been traditionally used by the Ghanaian healers to treat a variety of health disorders including malaria. Since 1974, a decoction of this plant has been used in the clinical therapy of rheumatism, urinary tract infections, malaria, and other diseases.[2] Cryptolepine **1**, neocryptolepine (cryptotackieine) **2**, and isocryptolepine (cryptosanguinolentine) **3** (Figure 1) are three major metabolites out of thirteen alkaloids isolated from this plant.[3] Chemically these are isomeric indoloquinolines, but more importantly they inhibit DNA replication and transcription[1a] and also exhibit strong antiplasmodial activity.[4]

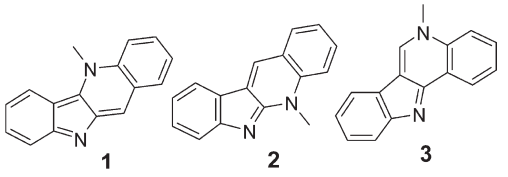
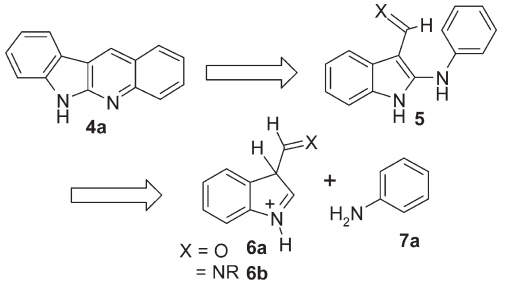


FIGURE 1. Cryptolepine **1**, neocryptolepine (cryptotackieine) **2**, and isocryptolepine (cryptosanguinolentine) **3**.

In continuation of our interest[5] in indoloquinoline alkaloids, we report herein a novel one-pot synthesis of indolo-[2,3-*b*]quinolines using iodine as catalyst. Our retrosynthetic analysis (Scheme 1) indicated that if 3*H*-indolinium cation **6a** or **6b** is generated, it should be possible for nitrogen of aniline **7a** to make a nucleophilic attack followed by annulation and subsequent oxidation should lead to 6*H*-indolo[2,3-*b*]-quinoline **4a**.

SCHEME 1. Retrosynthesis of 6*H*-indolo[2,3-*b*]quinoline 4a



To test this hypothesis, we initially heated indole-3-carboxyaldehyde **8** with excess aniline **7a** in refluxing diphenyl ether in the presence of acetic acid. It was observed that only Schiff's base **9** was formed. Recently the use of iodine has received considerable attention as an inexpensive, environmentally tolerable, and readily available mild Lewis acid for different organic transformations.[6] So, a few crystals of iodine were added to the above reaction mixture containing Schiff's base and the heating was continued for further 10 h. This resulted in the formation of two solid products. The more polar solid was found to be acetanilide **10** while the less polar 6*H*-indolo[2,3-*b*]quinoline **4a** (Scheme 2).

In order to optimize the reaction conditions, the reaction was studied with different concentrations of these reagents (Table 1).

Initially the reactions were carried out with two equivalents of aniline **7a** and varying concentrations of iodine (entries 1−6). In the absence of iodine (entry 1), no formation of product **4a** was observed. The optimum concentration of iodine required was determined to be 0.1 equiv (entry 3).

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SCHEME 2. Synthesis of 6*H*-indolo[2,3-*b*]quinoline 4a

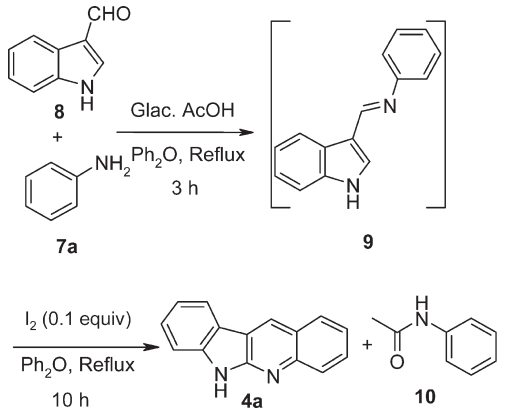
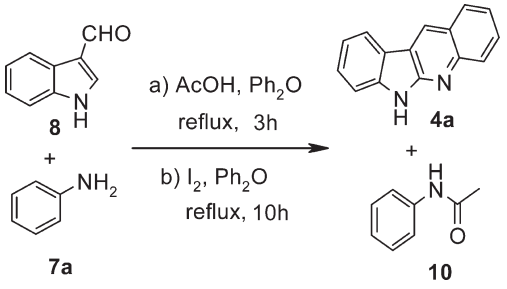


TABLE 1. Reaction of Indole-3-carboxyaldehyde with Aniline



entry	I_2 (equiv)	**7a** (equiv)	yield (%) of **4a**
1	0.0	2	0
2	0.05	2	20
3	0.1	2	23
4	0.2	2	21
5	0.5	2	18
6	1.0	2	12
7	0.1	1	0
8	0.1	1.5	19
9	0.1	3	23
10	0.1	4	23

When the reactions were carried out by varying the amount of aniline **7a** and keeping the concentration of iodine as 0.1 equiv (entries 7−10), it was observed that with one equivalent of aniline **7a**, no product **4a** (entry 7) was forming. The maximum yield of **4a** was obtained when two or more than two equivalents of the aniline (entries 3, 9, and 10) were used.

We initially thought that HI generated in the reaction media may have catalyzed the reaction to give the desired product **4a**. However, when HI was tried directly as a catalyst instead of I_2, no formation of product **4a** was observed (monitored by tlc). On the basis of the above studies, a plausible mechanism for the formation of **4a** is given in Scheme 3.

Thus, initial electrophilic attack of iodine on **9** generates 3-iodo-indolinium cation **11**. Subsequent nucleophilic attack by aniline **7a** on **11** will lead to 2-*N*-phenyl substituted indole **12**. Intramolecular electrophilic substitution leading to annulated structure **14** via **13** followed by expulsion of

SCHEME 3. Proposed Mechanism for the Formation of 4a

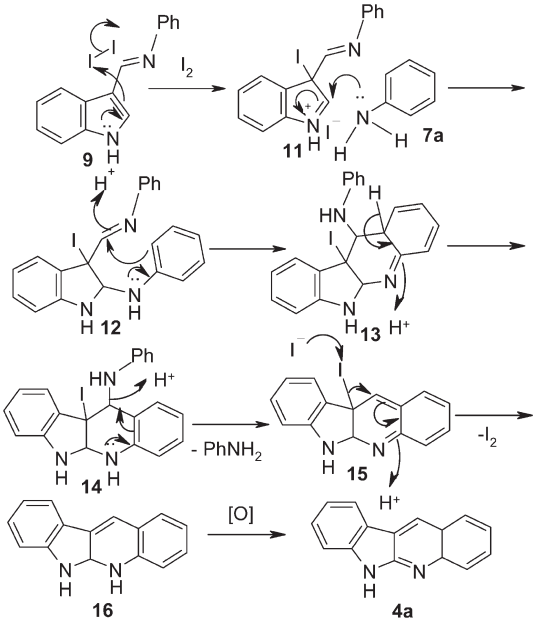
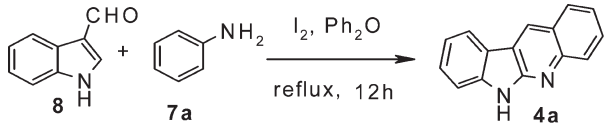


TABLE 2. Reaction of Indole-3-carboxyaldehyde with Aniline in Absence of Acetic Acid



entry	I_2 (equiv)	**7a** (equiv)	yield (%) of **4a**
1	0.1	1	0
2	0.1	1.5	30
3	0.1	2	45
4	0.1	3	45
5	0.05	2	34
6	0.3	2	37

aniline may form **15**. Further, departure of iodine followed by oxidation[7] could lead to aromatized heterocycle **4a**.

As acetanilide **10** was forming due to the presence of acetic acid in the reaction medium, the reaction was carried out in absence of it. It took 18 h for the formation of Schiff's base **9** and a further 8 h to complete the reaction giving only one product **4a** and the yield was doubled to 45%.

As acetic acid was used for the formation of Schiff's base, we thought of using iodine itself as an agent for its formation and further transformations.

Thus, the mixture of indole-3-carboxyaldehyde **8**, aniline **7a** and iodine were refluxed in diphenyl ether. To our delight, the reaction was complete in 12 h. The yield of the product **4a** was found to be 45%. Since the yield had increased in the absence of acetic acid, we studied the influence of the amount of iodine and aniline **7a** on the yield (Table 2). However, no further improvement in yields was observed. The modest yield is due to the decomposition of the Schiff's base intermediate under the reaction condition and also some loss during purification by column chromatography owing to its low solubility.

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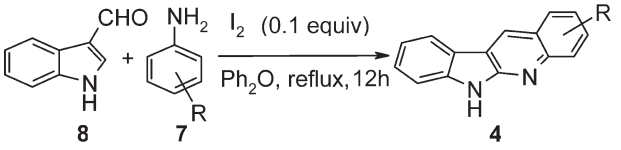
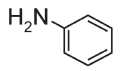
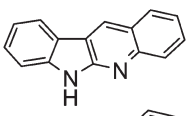
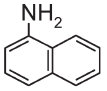
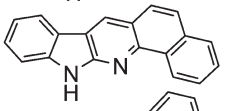
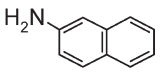
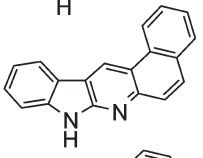
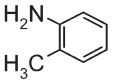
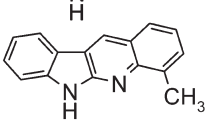
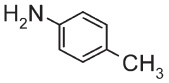
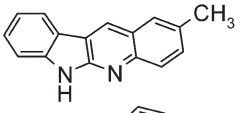
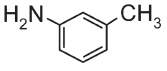
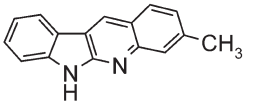
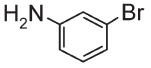
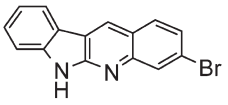
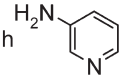
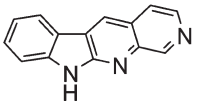
TABLE 3. Synthesis of Different Indoloquinolines Using I_2 as a Catalyst



Entry	Substrate 7	Product 4	Yield[a] (%)
a			45
b			48
c			53
d			41
e			38
f			40
g			44
h			29

[a]Yield of the isolated products.

The potential biological activities of these indoloquinolines prompted us to check the feasibility of making the library of such compounds (Table 3). As methyl-substituted indolo[2,3-*b*]-quinolines have shown promising anticancer activity,[8−10] we prepared 2-, 3-, and 4-methyl substituted indolo[2,3-*b*]-quinolines from corresponding toluidines in 38−41% yield (entries d−f). Next, we tried the reaction with naphthylamines (α and *β*), to get the corresponding annulated pentacyclic benzo-indolo[2,3-*b*]quinolines in 48 and 53% yield (entries b,c). The reaction with *m*-bromo-aniline gave 3-bromo-indolo-[2,3-*b*]quinoline in 44% yield (entry g). The reaction was also studied with amino heterocycle 3-amino pyridine to obtain the corresponding product in 29% yield (entry h).

The common route among the reported[8−19] methods for the synthesis of 6*H*-indolo[2,3-*b*]quinoline involves building of an indole ring on a quinoline precursor, while the present route describes the construction of a quinoline ring on an indole precursor.

In conclusion, we have developed a new one-pot method for the assembly of substituted indoloquinolines by sequential imination, nucleophilic addition, and annulation catalyzed by iodine. Though the yields are moderate, this method is easy and short, which makes it attractive.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in DMSO-d_6. TMS was used as an internal reference. Chromatographic purification was conducted by column chromatography using neutral alumina.

General Procedure for the Synthesis of Different Indoloquinolines. Indole-3-carboxyaldehyde (**8**) (3.46 mmol), aryl amines (**7a**−**h**) (6.92 mmol) and iodine (0.35 mmol) was refluxed in diphenyl ether (20 mL) for 12 h. After cooling, the reaction mixture was chromatographed on alumina and diphenyl ether was removed using hexanes as an eluent. Excess aryl amines (except 3-amino-pyridine) were eluted using 5% ethyl acetate in hexanes. Further elution with 20% ethyl acetate in hexanes afforded the indoloquinolines (**4a**−**h**).

6*H*-Indolo[2,3-*b*]quinoline (4a). Yield 45% (0.3394 g); yellow solid; mp >300 °C; Lit.[15] 342−346 °C. Spectral data are identical with those reported.[5,14,15]

8*H*-Indolo[2,3-*b*]benzo[*h*]quinoline (4b). Yield 48% (0.4450 g); gray solid; mp 264−268 °C. IR (KBr) 3348, 3053, 1609, 1491, 1462, 1385, 1364, 1258, 1234, 1147, 1105, 1018, 899, 812, 797, 746, 685 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.31 (m, 1H), 7.57 (m, 2H), 7.74 (m, 2H), 7.81 (d, 1H, J = 9 Hz), 8.02 (m, 2H), 8.31 (d, 1H, J = 7.5 Hz), 9.11 (s, 1H), 9.26 (d, 1H, J = 9.0 Hz), 12.01 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 111.6, 117.4, 120.2, 120.8, 121.2, 122.1, 123.9, 124.4, 126.7, 127.2, 128.2 (3 × C), 128.4, 131.0, 133.7, 141.2, 144.4, 152.4; HRMS m/z $[M + H]^+$ 269.1070 (calcd for $C_{19}H_{13}N_2$, 269.1079).

8*H*-Indolo[2,3-*b*]benzo[*f*]quinoline (4c). Yield 53% (0.4914 g); gray solid; mp >300 °C. IR (KBr) 3400, 3152, 1614, 1519, 1445, 1398, 815, 740 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32 (m, 1H), 7.57 (s, 2H), 7.64 (m, 1H), 7.78 (dd, 1H, J = 6.9 Hz, 7.5 Hz), 7.94 (d, 1H, J = 9 Hz), 8.06 (dd, 2H, J = 8.4 Hz, 9 Hz), 8.43 (d, 1H, J = 7.2 Hz), 9.03 (d, 1H, J = 8.4 Hz), 10.03 (s, 1H), 11.87 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 111.6, 117.2, 119.9, 120.2, 121.1, 122.3, 123.0, 123.8, 126.4, 127.5, 127.8, 128.2, 129.0, 130.3, 130.4, 131.0, 141.3, 146.4, 152.8; HRMS m/z $[M + H]^+$ 269.1070 (calcd for $C_{19}H_{13}N_2$, 269.1079).

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4-Methyl-6*H*-Indolo[2,3-*b*]quinoline (4d). Yield 41% (0.3291 g); yellow solid; mp 230−232 °C. IR (KBr) 3142, 3090, 1614, 1580, 1460, 1408, 1329, 1230, 1126, 908, 820, 787, 737, 696 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.77 (s, 3H), 7.26 (dd, 1H, J = 6.9, 7.2 Hz), 7.37 (dd, 1H, J = 7.2, 7.5 Hz), 7.46−7.52 (m, 2H), 7.59 (d, 1H, J = 6.9 Hz), 7.95 (d, 1H, J = 7.8 Hz), 8.25 (d, 1H, J = 7.5 Hz), 9.01 (s, 1H), 11.80 (s, 1H, −NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 18.9, 111.3, 118.0, 120.0, 120.7, 122.2, 122.8, 123.9, 127.1, 128.4, 128.5, 129.2, 134.6, 141.9, 145.8, 152.8; HRMS m/z $[M + H]^+$ 233.1076 (calcd for $C_{16}H_{13}N_2$, 233.1078).

2-Methyl-6*H*-Indolo[2,3-*b*]quinoline (4e). Yield 38% (0.3050 g); yellow solid; mp > 300 °C. IR (KBr) 3400, 3121, 1614, 1519, 1471, 1404, 1232, 848, 740 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.50 (s, 3H), 7.25 (m, 1H), 7.49 (m, 2H), 7.56 (d, 1H, J = 8.7 Hz), 7.86 (s, 1H), 7.88 (d, 1H, J = 8.7 Hz), 8.24 (d, 1H, J = 7.8 Hz), 8.93 (s, 1H), 11.59 (s, 1H, −NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 21.4, 111.3, 118.3, 120.0, 120.7, 122.2, 124.1, 127.2 (two carbons), 127.7, 128.5, 131.4, 132.2, 141.8, 145.2, 152.9; HRMS m/z $[M + H]^+$ 233.1087 (calcd for $C_{16}H_{13}N_2$, 233.1078).

3-Methyl-6*H*-Indolo[2,3-*b*]quinoline (4f). Yield 40% (0.3210 g); yellow solid; mp 228−230 °C. IR (KBr) 3402, 3138, 1614, 1497, 1462, 1232, 908, 798, 740 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 2.55 (s, 3H), 7.26 (m, 1H), 7.32 (d, 1H, J = 7.8 Hz), 7.48 (m, 2H), 7.76 (s, 1H), 7.99 (d, 1H, J = 8.1 Hz), 8.22 (d, 1H, J = 7.5 Hz), 8.97 (s, 1H), 11.63 (s, 1H, −NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.0, 111.3, 117.6, 120.0, 120.9, 122.0, 122.2, 125.4, 126.4, 127.7, 128.3, 128.8, 138.9, 141.7, 147.0, 153.4; HRMS m/z $[M + H]^+$ 233.1078 (calcd for $C_{16}H_{13}N_2$, 233.1078).

3-Bromo-6*H*-Indolo[2,3-*b*]quinoline (4g). Yield 44% (0.4506 g); brown solid; mp 260−264 °C. IR (KBr) 3375, 3132, 1614, 1508, 1472, 1358, 1242, 939, 798, 740 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.30 (dd, 1H, J = 6.9, 7.2 Hz), 7.52 − 7.62 (m, 2H), 7.65 (d, 1H, J = 8.1 Hz), 7.84 (d, 1H, J = 7.5 Hz), 8.02 (d, 1H, J = 8.7 Hz), 8.44 (d, 1H, J = 7.5 Hz), 9.22 (s, 1H), 11.90 (s, 1H, −NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 111.6, 119.6, 120.4, 120.5, 122.3 (2 × C), 122.9, 126.7, 127.2, 127.8, 129.3 (2 × C), 129.5, 142.2, 153.5; HRMS m/z $[M + H]^+$ 297.0037 (calcd for $C_{15}H_{10}N_2Br$, 296.0027).

6*H*-Indolo[2,3-*b*][1,7]naphthyridine (4h). Yield 29% (0.2213 g); brown solid; mp > 300 °C. IR (KBr) 3302, 3130, 1508, 1357, 1226, 935, 815, 738 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.37 (m, 1H), 7.53 (t, 1H, J = 7.2 Hz), 7.73 (d, 1H, J = 8.1 Hz), 7.80 (m, 1H), 8.37 (d, 1H, J = 7.8 Hz), 8.53 (d, 1H, J = 8.4 Hz), 9.01 (s, 1H), 9.68 (s, 1H), 13.0 (s, 1H, −NH); ^{13}C NMR (75 MHz, DMSO-d_6) δ 112.5, 117.4, 120.5, 120.9, 121.7, 123.5, 126.2, 134.1, 137.1, 139.3, 139.6, 140.5, 145.7, 148.9; HRMS m/z $[M + H]^+$ 220.0864 (calcd for $C_{14}H_{10}N_3$, 220.0874).

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Supporting Information Available: Copies of ^1H, ^{13}C NMR, and HRMS of all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.