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A direct synthesis of neocryptolepine and isocryptolepine

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ABSTRACT

A formal synthesis of indolequinoline alkaloid neocryptolepine and isocryptolepine is described which employed a common intermediate and used an intramolecular Wittig reaction followed by regioselective methylation in excellent yield.

1. Introduction

More than 2.5 million people die annually from malaria, one of the most serious parasitic diseases in developing and industrialized nations.[1,2] The root of the west African plant *Cryptolepis sanguinlenta* has been traditionally used to treat a variety of health disorders, including malaria, rheumatism, urinary tract infections, and other diseases.[3,4] The linear indolequinoline alkaloids cryptolepine **1**, neocryptolepine **2** (also called cryptotackieine), and isocryptolepine **3** (also called cryptosanguinolentine) were isolated from *C. sanguinlenta* in 1996 by two groups (Fig. 1).[5] All of these compounds can function as DNA-intercalating agents, inhibiting DNA replication and transcription. These compounds also exhibit potent antiplasmodial activity. However, compound **1** has a 10-fold higher affinity for DNA than the other alkaloids and also shows stronger inhibition of human topoisomerase II.[6] Consequently, compounds **2** and **3** are more promising leads for new anti-malarial agents.

In the past decade, the significant biological activity and challenging structure of this class of natural products have drawn synthetic chemists' attention. Several syntheses for compounds **2**[7–10] and **3**[11–19] have been reported.

In 1997, Alajarin reported a formal synthetic route to compound **2** using an aza-Wittig-type reaction in three steps with an overall yield of 15%.[7] In 2001, Molina reported a total synthesis of compound **2** in 10 steps in 9% yield and compound **3** in 11 steps in 17% yield, which used an intramolecular aza-Wittig reaction under microwave-assisted conditions as the key reaction.[8] Pieters and co-workers reported a total synthesis of compound **2** in five steps in 2002 using a diradical cyclization as the key step.[9] More recently, Tilve and co-workers have reported a direct synthesis of compound **2** via double reductive cyclization. The overall yield for this synthesis is 42% over four steps, which is the highest yield reported so far.[10] In 2006, Mohan and co-workers reported a three-step synthesis of isocryptolepine **3** in 28% overall yield involving an indole synthesis as the key step.[12] We recently reported a synthesis of **3** from 2-(2-nitrophenyl)indole which was prepared using our recently reported indole synthesis.[20]

2. Results and discussion

The most common approach involves organometallic coupling of substituted quinolines. We report herein a direct and distinctly different strategy. Our retrosynthetic analysis of intermediate **4** showed that it could be prepared in one pot by intermediate **5** by an intramolecular Wittig reaction. Keto amide **5** could be made by a coupling reaction using commercially available Wittig salt **6** (Scheme 1). The target molecules neocryptolepine **2** and isocryptolepine **3** could be prepared via the same intermediate **4**.

In our initial approach, the reaction of isatin with ethyl chloroformate in THF with triethyl amine, followed by sodium carbonate, gave the acid **7** in 95% yield (Scheme 2). With acid **7**, Steglich–Hasser esterification with commercially available phosphonium salt **6**, followed by an intramolecular Wittig reaction in the presence of potassium *tert*-butoxide, gave a very complex reaction. We also tried to prepare the acid chloride in situ first and then couple it with phosphonium salt **6**, followed the same intramolecular Wittig reaction. This also failed. After careful study, we found that the intermediate **8** did not form under these conditions. Instead of using the unstable intermediate **8**, we decided to introduce an azide as the nitrogen source in the *o*-position because azides are generally stable groups under acid or base conditions. The new

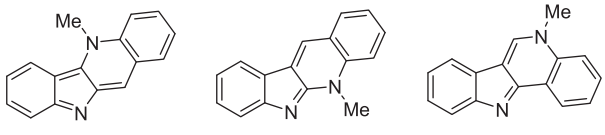

Figure 1.

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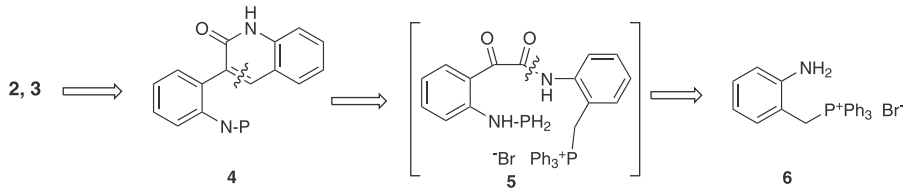
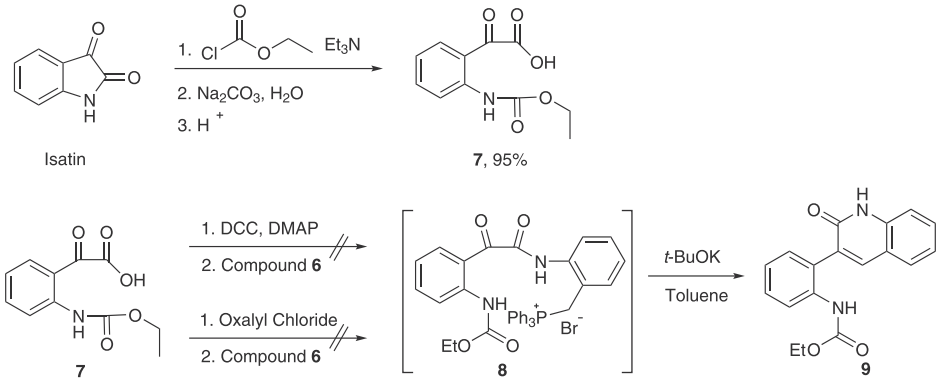
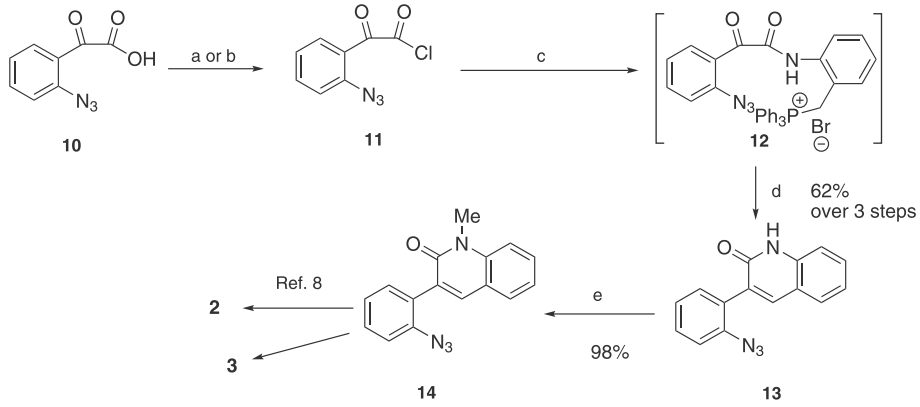


Scheme 1. Retrosynthetic analysis.



Scheme 2. Unsuccessful approach to **9**.



Scheme 3. Reagent and conditions: (a) $SOCl_2$, benzene, reflux, 1 h; (b) $(COCl)_2$, CH_2Cl_2, rt, 3 h; (c) compound **6**, CH_2Cl_2, rt, 12 h; (d) *t*-BuOK, THF, rt, 5 h, 62% from compound **10**; (e) MeI, K_2CO_3, DMF, 60 °C, 8 h, 98%.

approach started from the known acid **10**, which can easily be made from isatin in one step in 92% yield (Scheme 3).[21] The acid chloride **11** was prepared from compound **10** by two different methods, one using oxalyl chloride in methylene chloride solution and the other using thionyl chloride. The resultant solid was directly used for the next step without further purification. Condensation of (2-aminobenzyl) triphenylphosphonium bromide with compound **11** in methylene chloride, followed by intramolecular Wittig reaction with potassium *tert*-butoxide at room temperature, led to lactam **13** in 62% yield in three steps and one pot from compound **10**.[22] Methylation of **13** with methyl iodide in the presence of potassium carbonate in DMF gave the known intermediate **14** in 98% yield.[23] The overall yield of **14** was 60% over 4 steps in two pots compared to the 22% yield over 9 steps according to the literature.[8] Neocryptolepine **2** can be made in one step from **14** using an intramolecular aza-Wittig reaction under microwave-assisted conditions and isocryptolepine **3** can be made in two steps via nitrene insertion, followed by Red-Al reduction.[8]

In conclusion, we have established a new, efficient, and straightforward formal total synthesis of neocryptolepine **2** and isocryptolepine **3**, employing a common intermediate **14**, and using an intramolecular Wittig reaction, followed by regioselective methylation in excellent yield.

Acknowledgment

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22. *Experimental procedure for the preparation of 3-(2-Azidophenyl)quinolin-2-one* **13**: Method A: To a suspension of acid **10** (1.0 g, 5.4 mmol) in 10 mL of benzene was added thionyl chloride (3.86 g, 32.4 mmol). The mixture was boiled with stirring for 1 h and was concentrated under reduced pressure. The residue was recrystallized from benzene to give acid chloride **11** as a brown solid. Method B: oxalyl chloride (0.41 g, 3.24 mmol) was slowly added under an inert atmosphere to an ice-cold solution of compound **10** (0.5 g, 2.7 mmol) in 5 mL of dry CH_2Cl_2. The resulting mixture was treated with a catalytic amount of DMF and allowed to react at rt for 3 h. The solvent and excess reagent were evaporated. The resultant brown solid was directly used in the next step without any purification. The acid chloride **11** (0.1 g, 0.48 mmol) was redissolved in 5 mL of CH_2Cl_2 and phosphonium salt **6** (0.214 g, 0.48 mmol) was added. The resulting mixture was stirred at rt for 12 h. The solvent was removed under vacuum. THF (5 mL) was added to the resultant orange solid, followed slowly by 0.57 mL of a *t*-BuOK (1 M, 0.57 mmol) solution in THF at rt. After 5 h at rt, the reaction was quenched by the addition of an aqueous NH_4Cl solution. The product was extracted twice with ethyl acetate and the combined organic layers were washed with brine. Evaporation of the solvent, followed by column chromatography gave compound **13** (75 mg, 62% for three steps) as yellow powder; mp = 201–202 °C; ^{1}H NMR (400 MHz, DMSO-d_6) 11.94 (s, 1H), 7.91 (s, 1H), 7.68–7.70 (d, *J* = 7.6 Hz, 1H), 7.47–7.54 (m, 2H), 7.33–7.39 (m, 3H), 7.24–7.28 (m, 1H), 7.18–7.22 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) 161.1, 140.0, 139.2, 138.4, 132.1, 130.9, 130.7, 130.0, 129.3, 128.6, 125.3, 122.4, 119.54, 119.49, 115.3; HRMS electrospray (*m*/*z*) calcd for $C_{15}H_{10}N_4O$, 262.0855; found, 262.0858.
23. *Experimental procedure for the preparation of 3-(2-Azidophenyl)-1-methylquinolin-2(1H)-one* **14**: To a mixture of compound **13** (60 mg, 0.23 mmol) in 4 mL of dry DMF and anhydrous K_2CO_3 (191 mg, 1.38 mmol), methyl iodide (49 mg, 0.345 mmol) was added dropwise under argon. The resultant mixture was stirred at 60 °C for 8 h. The reaction was quenched by the addition of 10 mL of water. The product was extracted twice with ethyl acetate and the combined organic layers were washed with brine. Evaporation of the solvent, followed by column chromatography, gave compound **14** (62 mg, 98%) as yellow solid; mp = 168–170 °C (lit. mp = 169 °C)[8]; ^{1}H NMR (400 MHz, $CDCl_3$) 7.67 (s, 1H), 7.54–7.58 (m, 2H), 7.34–7.42 (m, 3H), 7.16–7.25 (m, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 161.1, 140.0, 138.8, 138.6, 131.6, 130.7, 130.3, 129.6, 129.0, 124.7, 122.3, 120.3, 118.6, 114.2, 30.0; HRMS electrospray (*m*/*z*) calcd for $C_{16}H_{12}N_4O$, 276.1011; found, 276.1017.