A Concise Synthesis of Isocryptolepine by C–C Cross-Coupling Followed by a Tandem C–H Activation and C–N Bond Formation

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Abstract Isocryptolepine (1), a potent antimalarial natural product, was prepared in three steps from 3-bromoquinoline and 2-aminophenylboronic acid hydrochloride. The key transformations were a Suzuki–Miyaura cross-coupling reaction followed by a palladium-initiated intramolecular C–H activation/C–N bond formation between an unprotected amine and an aromatic C–H group. The two key reactions can also be performed in one pot.

Key words C–H activation, C–N bond formation, isocryptolepine, one-pot reaction, Suzuki–Miyaura cross-coupling

Isocryptolepine (1, Figure 1), a naturally occurring quinoline alkaloid isolated from the West African plant Cryptolepis sanguinolentain,1 has been shown to display potent antimalarial activity against the virulent and increasingly resistant strain of Plasmodium falciparum.2 Malaria is a serious health concern that is responsible for the loss of millions of lives every year. The World Health Organization estimated that, during 2015 alone, there were as many as 214 million new cases of malaria and 438,000 deaths.3 The disease is caused by one of four protozoan parasite strains, Plasmodium vivax, P. falciparum, P. ovale, and P. malariae. Resistance towards antimalarial drugs available today is a major concern and the need to develop new antimalarial drugs represents a common interest globally.4,5 Isocryptolepine (1) belongs to the indoloquinoline family, which also includes cryptolepine (2) and neocryptolepine (3), and all are characterised by a quinoline and indole fused ring system. While both cryptolepine and neocryptolepine are tetracyclic heteroaromatic linearly fused alkaloids, isocryptolepine is a tetracyclic heteroaromatic angularly fused alkaloid.

Development of efficient synthesis of these quinoline alkaloids has recently been of high interest6 as a potential scaffold for future medical chemistry. Generally, the reported syntheses of isocryptolepine utilise the following key synthetic strategies: palladium-catalysed coupling reactions,7 Fischer indole cyclisation,8 photochemical cyclisation,9 Pictet–Spengler cyclisation,10 aza-Wittig reaction11 and a recently reported one-pot approach.12 Herein, we present an efficient and convenient synthesis of isocryptolepine from readily available starting materials and show that the two key steps in the synthesis can also be performed in one pot.

Our retrosynthetic analysis of isocryptolepine (1), which is shown in Scheme 1, was inspired by the seminal work of Buchwald and co-workers,13 and by a recent publication by Bjørsvik and Elumalai, who reported a protocol that gave access to carbazole frameworks upon intramolecular C–N bond formation via C–H activation.14 Interestingly, this method,14 together with another iridium-catalysed method,15 in contrast to many earlier methods,16 involved tandem C–H activation and C–N bond formation, which allowed the C–N formation to take place between an unprotected amine and an aromatic C–H. We envisaged that the intramolecular palladium-catalysed tandem C–H activation and C–N bond formation of a 2-aminobiaryl intermediate 6, which could be obtained from bromide 4 and boronic acid 5.
by a Suzuki–Miyaura cross-coupling,17 would be the key step in our synthesis. Finally, a selective N-methylation would provide isocryptolepine (1).

The synthesis commenced with the Suzuki–Miyaura cross-coupling reaction between 3-bromoquinoline (4) and 2-aminophenylboronic acid hydrochloride (5). Under optimised conditions, using PdCl2(dppf) as catalyst and potassium carbonate as base in EtOH/water (5:1), the coupling product 6 was formed in 80% yield (Scheme 2).18 2-Aminobiaryl 6 was then subjected to a tandem C–H activation and C–N bond formation utilising the conditions reported by Bjørsvik and Elumalai,14 which involved treating compound 6 with PdCl2(dppf), 1,3-bis(2,4,6-trimethylphenyl)imidazole-2-ylidene (IMes), and hydrogen peroxide in acetic acid for 10 min at 118 °C in a microwave (MW). Gratifyingly this resulted in the formation of 11H-indolo[3,2-c]quinolone (7) in 62% yield after column chromatography along with unreacted starting material (15%).19 Attempts to prolong the reaction time to force the reaction to completion only resulted in a reduced yield of the desired product 7. Compound 7 was then subjected to a regioselective methylation using a previously reported method.20 By such means, the desired natural product isocryptolepine (1) was formed in 76% yield. All spectroscopic data for compound 1 were in full agreement with the reported data.20,21

We have previously reported on our one-pot chemistry in which a Suzuki–Miyaura cross-coupling reaction is followed by reductive amination,22 and demonstrated the advantages of combining several steps into one pot.23 With that in mind, and with the successful synthesis of isocryptolepine (1) in hand, we attempted to combine the two palladium-catalysed steps in one pot. Conducting the Suzuki–Miyaura cross-coupling reaction first, utilising PdCl2(dppf) as precatalyst, followed by changing the reaction medium from basic to acidic by addition of acetic acid when the Suzuki–Miyaura cross-coupling reaction had reached completion (as judged by TLC analysis) in addition to adding more catalyst [PdCl2(dppf)], hydrogen peroxide, and IMes followed by stirring the reaction mixture at 118 °C for 18 min, resulted in the formation of 11H-indolo[3,2-c]quinolone (7) in 32% yield in one pot from 3-bromoquinoline (4) and boronic acid (5).24 The 1H and 13C NMR spectra of 11H-indolo[3,2-c]quinolone (7), obtained from the two described synthetic routes were compared and found to match. Finally, selective N-methylation of 7 utilising a previously described method,20 gave isocryptolepine (1) (76% yield),25 resulting in an overall yield of 19% over the two steps.

In conclusion, we have developed a short synthesis of isocryptolepine (1). The key step is the selective tandem C–H activation and C–N bond formation between the unprotected amino group and the aromatic C–H. To our knowledge, the synthesis reported herein represents the first example in which a Suzuki–Miyaura cross-coupling is combined with a tandem C–H activation and C–N bond formation in a one-pot reaction. Further work is now focusing on using the developed synthetic strategy for the synthesis of analogues of isocryptolepine (1) with the aim of enhancing the antimalarial activity.

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**Scheme 1** Retrosynthetic analysis of isocryptolepine (1)

**Scheme 2** Synthesis of isocryptolepine (1). Reagents and conditions:
(a) PdCl2(dppf), K2CO3, EtOH/H2O (5:1), 60 °C, 24 h; (b) PdCl2(dppf), IMes, H2O2, AcOH, MW sealed tube 10 min 118 °C; (c) MeI, toluene, reflux, 3 h; (d) PdCl2(dppf), K2CO3, EtOH/H2O (5:1), MW sealed tube 4 h 60 °C followed by addition of PdCl2(dppf), IMes, H2O2, AcOH, MW sealed tube 18 min, 118 °C.
Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590807.

References and Notes


(4) Drug resistance in malaria, report 2001, Bioland P B, World Health Organization; Malaria Epidemiology Branch, Centre for Disease Control and Prevention Chamblee, GA, USA.


microwave oven for 18 min at 118 °C. The crude reaction mixture was then transferred to a 25 mL round-bottom flask with the aid of EtOAc and the volatiles were removed under reduced pressure. The resulting crude mixture was purified by silica gel column chromatography (CH₂Cl₂–EtOAc 8:2 → 6:4 v/v) to give compound 7 (Rf = 0.25 (CH₂Cl₂–EtOAc, 1:1 v/v)) as an off-white solid (19 mg, 32%) along with compound 6 (30 mg, 48%). Mp 340–341 °C (lit. ref. 20 333–334 °C). IR (NaCl): 3060, 2958, 2854, 1682, 1582, 1515, 1493 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): δ = 12.71 (br s, 1 H), 9.59 (s, 1 H), 8.52 (dd, J = 1.1, 7.9 Hz, 1 H), 8.32 (d, J = 7.9 Hz, 1 H), 8.13 (dd, J = 1.1, 8.0 Hz, 1 H), 7.77–7.67 (m, 3 H), 7.52–7.48 (m, 1 H), 7.36–7.33 (m, 1 H). ¹³C NMR (100 MHz, DMSO-d₆): δ = 145.4, 144.8, 139.7, 138.7, 129.4, 128.0, 125.7, 125.5, 122.1, 121.8, 120.6, 120.1, 117.1, 114.3, 111.8 (in agreement with NMR data reported in ref. 10a). HRMS (ESI): m/z [M + H⁺] calcd. for C₁₅H₁₁N₂⁺: 219.0922; found: 219.0925.

(25) Isocryptolepine (1): Compound 7 (70 mg, 0.32 mmol) was treated with methyl iodide (4.0 mL, 0.064 mol) in refluxing toluene (8 mL) for 3 h (see ref. 20). The volatiles were then removed under reduced pressure and the concentrate was purified by silica column chromatography (CHCl₃–MeOH, 19:1 → 18:2 v/v) to give the hydroiodide salt of isocryptolepine. To obtain isocryptolepine as the free base, its hydroiodide salt was dissolved in CH₂Cl₂ (30 mL), aqueous ammonia (25%, 20 mL) was added, and the reaction mixture was stirred at ambient temperature for 10 min. The organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (2 × 10 mL). The combined organic layers were washed with brine, dried (MgSO₄), filtered and concentrated in vacuo to give isocryptolepine (1) (Rf = 0.23 (CH₂Cl₂–MeOH, 90:10 v/v)) as a yellow solid (56 mg, 76%); mp 185–187 °C (lit. ref. 18 191–193 °C). IR (NaCl): 3047, 2922, 2852, 1637, 1596, 1486, 1451 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆): δ = 9.40 (s, 1 H), 8.77 (dd, J = 1.4, 8.1 Hz, 1 H), 8.13–8.11 (m, 1 H), 8.04 (d, J = 8.5 Hz, 1 H), 7.83 (dd, J = 1.6, 7.1, 8.7 Hz, 1 H), 7.80–7.78 (m, 1 H), 7.72–7.68 (m, 1 H), 7.42 (dd, J = 1.2, 7.1, 8.2 Hz, 1 H), 7.25–7.21 (m, 1 H), 4.26 (s, 3 H). ¹³C NMR (100 MHz, DMSO-d₆): δ = 155.1, 153.1, 138.7, 136.0, 129.7, 126.2, 125.9, 125.6, 124.4, 121.6, 120.2, 118.0, 118.9, 116.7, 42.6 (in agreement with NMR data reported in ref. 18). HRMS [ESI]: m/z [M + H⁺] calcd. for C₁₆H₁₃N₂⁺: 233.1079; found: 233.1080.