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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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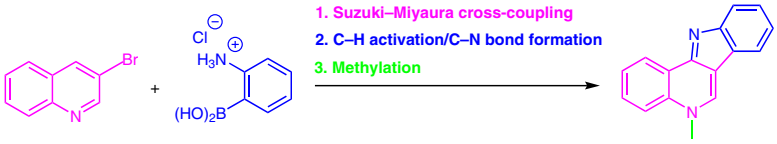


Received: 02.06.2017
Accepted: 06.06.2017
Published online: 27.06.2017
DOI: 10.1055/s-0036-1590807; Art ID: so-2017-d0024-l

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 interest[6] 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 reaction[11] 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.

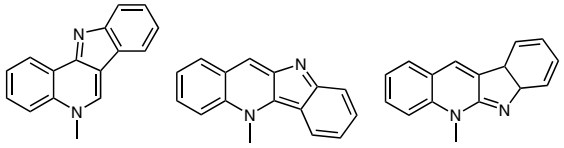
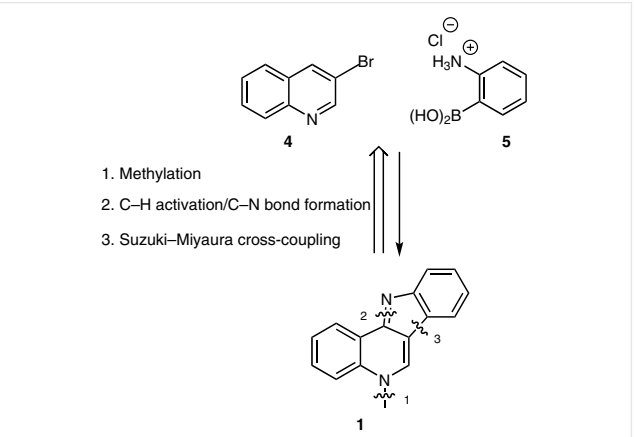


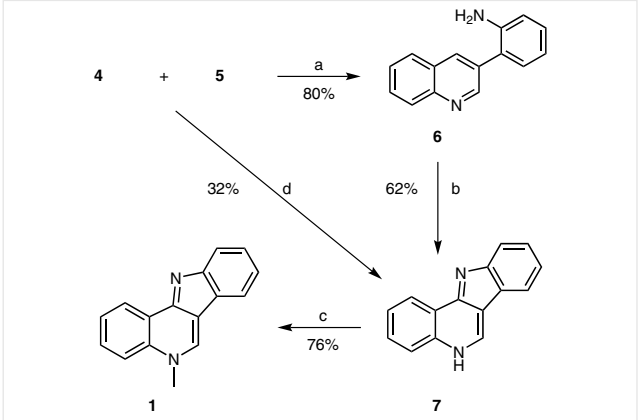
Figure 1 Structure of isocryptolepine (**1**), cryptolepine (**2**) and neocryptolepine (**3**)

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**).



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



Scheme 2 Synthesis of isocryptolepine (**1**). *Reagents and conditions*: (a) $PdCl_2$(dppf), K_2CO_3, EtOH/H_2O (5:1), 60 °C, 24 h; (b) $PdCl_2$(dppf), IMes, H_2O_2, AcOH, MW sealed tube 10 min 118 °C; (c) MeI, toluene, reflux, 3 h; (d) $PdCl_2$(dppf), K_2CO_3, EtOH/H_2O (5:1), MW sealed tube 4 h 60 °C followed by addition of $PdCl_2$(dppf), IMes, H_2O_2, AcOH, MW sealed tube 18 min, 118 °C.

The synthesis commenced with the Suzuki–Miyaura cross-coupling reaction between 3-bromoquinoline (**4**) and 2-aminophenylboronic acid hydrochloride (**5**). Under optimised conditions, using $PdCl_2$(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 $PdCl_2$(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 11*H*-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 $PdCl_2$(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 [$PdCl_2$(dppf)], hydrogen peroxide, and IMes followed by stirring the reaction mixture at 118 °C for 18 min, resulted in the formation of 11*H*-indolo[3,2-*c*]quinolone (**7**) in 32% yield in one pot from 3-bromoquinoline (**4**) and boronic acid (**5**).[24] The ^{1}H and ^{13}C NMR spectra of 11*H*-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 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.

Funding Information

The University of Stavanger Toppforsk program and the research program Bioactive is acknowledged for financial support of the study.

Acknowledgment

Dr. Emil Lindbäck is thanked for valuable help and advice. Thanks are also due to Dr. Bjarte Holmelid, University of Bergen, for recording mass spectra.

Supporting Information

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

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(18) **(Quinolin-3-yl)aniline (6):** 3-Bromoquinoline (**4**; 0.39 mL, 2.9 mmol), 2-aminophenylboronic acid hydrochloride (**5**; 500 mg, 2.9 mmol) and potassium carbonate (1.195 g, 8.6 mmol) were dissolved in EtOH–H_2O (5:1, 1.2 mL) under a nitrogen atmosphere. $PdCl_2$(dppf) (105 mg, 0.14 mmol) was added and the reaction mixture was stirred at 60 °C overnight. The reaction mixture was then allowed to cool to ambient temperature and the volatiles were removed under reduced pressure. Purification of the concentrate by silica gel column chromatography (PE–EtOAc, 1:1 v/v) gave compound **6** (R_f = 0.16 (PE–EtOAc 75:25 v/v)) as a pale-yellow solid (507 mg, 80%); mp 130–132 °C (lit. ref. 25 119–120 °C). IR (NaCl): 3438, 3331, 3208, 3061, 1619, 1575, 1497, 1452 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.04 (d, *J* = 2.2 Hz, 1 H,), 8.27 (d, *J* = 2.1 Hz, 1 H), 8.16 (d, *J* = 8.5 Hz, 1 H), 7.86 (d, *J* = 8.1 Hz, 1 H), 7.75 (ddd, *J* = 1.4, 6.9, 8.4 Hz, 1 H), 7.61–7.57 (m, 1 H), 7.26–7.22 (m, 2 H), 6.91 (dt, *J* = 1.0, 7.5 Hz, 1 H), 6.84 (d, *J* = 7.9 Hz, 1 H), 3.79 (br s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.4, 147.1, 143.9, 135.3, 132.3, 130.7, 129.4, 129.3, 129.2, 127.8, 127.7, 126.9.123.6, 119.0, 115.8 (in agreement with NMR data reported in ref. 26). HRMS (ESI): *m*/*z* [M + H^+] calcd. for $C_{15}H_{13}N_2^+$: 221.1079; found: 221.1073.

(19) ***H*-Indolo[3,2-*c*]quinolone (7):** 2-(Quinolin-3-yl)aniline (**6**; 60 mg, 0.27 mmol) was dissolved in acetic acid (1 mL) and added to a premixed solution of $PdCl_2$(dppf) (40 mg, 0.054 mmol), IMes (4.1 mg, 0.013 mmol), H_2O_2 (35 wt%, 0.065 mL, 0.08 mmol) and acetic acid (2 mL). The reaction mixture was introduced into a sealed reactor tube, which was placed in the cavity of a microwave oven for 10 min at 118 °C. The 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 product was then purified by silica gel column chromatography (CH_2Cl_2–EtOAc, 8:2 → 6:4 v/v) to give compound **7** [R_f = 0.25 (CH_2Cl_2–EtOAc, 1:1 v/v)] as an off-white solid (37 mg, 62%) along with recovered starting material **6** (9 mg, 15%).

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(24) ***H*-Indolo[3,2-*c*]quinolone (7) one-pot reaction:**3-Bromoquinoline (**4**; 0.04 mL, 0.28 mmol), 2-aminophenylboronic acid hydrochloride (**5**; 50 mg, 0.28 mmol), potassium carbonate (119 mg, 0.86 mmol) and $PdCl_2$(dppf) (20.4 mg, 0.028 mmol) were dissolved in EtOH–H_2O (5:1, 1.2 mL). The reaction mixture was introduced into in a sealed reactor tube, which was placed in the cavity of a microwave oven for 4 h at 60 °C. Formation of 2-(quinolin-3-yl)aniline (**6**) was monitored by TLC. This was then followed by addition of acetic acid (4 mL), $PdCl_2$(dppf) (20.4 mg, 0.028 mmol), IMes (4.3 mg, 0.014 mmol), and H_2O_2 (35 wt%, 0.065 mL, 0.08 mmol). The reaction mixture was introduced into a sealed reactor tube, which was placed in the cavity of a

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 (CH_2Cl_2–EtOAc 8:2 → 6:4 v/v) to give compound **7** [R_f = 0.25 (CH_2Cl_2–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-d_6): 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). ^{13}C NMR (100 MHz, DMSO-d_6): 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 $C_{15}H_{11}N_2^+$: 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 ($CHCl_3$–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 CH_2Cl_2 (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 CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo to give isocryptolepine (**1**) [R_f = 0.23 (CH_2Cl_2–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-d_6): 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 (ddd, *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 (ddd, *J* = 1.2, 7.1, 8.2 Hz, 1 H), 7.25–7.21 (m, 1 H), 4.26 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.1, 153.1, 138.7, 136.0, 129.7, 126.2, 125.9, 125.6, 124.4, 121.6, 120.2, 120.0, 118.9, 118.0, 116.7, 42.6 (in agreement with NMR data reported in ref. 18). HRMS (ESI): *m*/*z* [M + H^+] calcd. for $C_{16}H_{13}N_2^+$: 233.1079; found: 233.1080.

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