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A ONE-POT SYNTHESIS OF PHAITANTHRIN E THROUGH INTERMOLECULAR CONDENSATION/INTRAMOLECULAR ARYL C-H AMINATION CASCADE

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Abstract – A one-pot synthesis of phaitanthrin E starting from methyl indole-3-carboxylate and isatoic anhydride through intermolecular condensation/intramolecular aryl C-H amination cascade was developed.

Alkaloids with an indolo[2,1-*b*]quinazoline core, represented by tryptanthrin (**1**), have attracted considerable biological and synthetic interest because of their intriguing structural features and wide range of promising biological activities.¹ Many structural analogues of these alkaloids have been synthesized and some compounds have shown notable activity.² In 2008, five new alkaloids, phaitanthrins A (**2**), B (**3**), C (**4**), D (**5**), and E (**6**), were isolated from *Phaius mishmensis* (Orchidaceae), and compound **2** showed moderate cytotoxicity against three human cancer cell lines.³ Total syntheses of **2**, **3**, and **4** were reported separately by two groups in 2013.^{4,5} In 2015, the first total synthesis of **5** and **6** was accomplished through a biogenetic pathway starting from anthranilic acid, *o*-aminophenylacetic acid, and glycolic acid, involving a one-pot transformation of a diamide intermediate through intramolecular dehydrative cyclization.⁶ We previously reported a one-pot synthesis of tryptanthrin (**1**) and candidine (**7**) by oxidative dimerization of indole-3-carboxaldehyde involving further conversion of **1** to **2** and **3**, and we found that oxidative coupling of indole-3-carboxaldehyde with isatoic anhydride also produced **1** and **4**.⁷ Moreover, **1** was synthesized through oxidative dimerization of skatole in a one-pot reaction.⁸ In continuing our studies, we envisioned that methyl indole-3-carboxylate (**8**) bearing the CO₂Me group could serve as a useful building block for **6**. In this paper, we describe one-pot access to **6** starting from methyl indole-3-carboxylate (**8**) and isatoic anhydride (**9**) through an intermolecular condensation/intramolecular aryl C-H amination cascade.

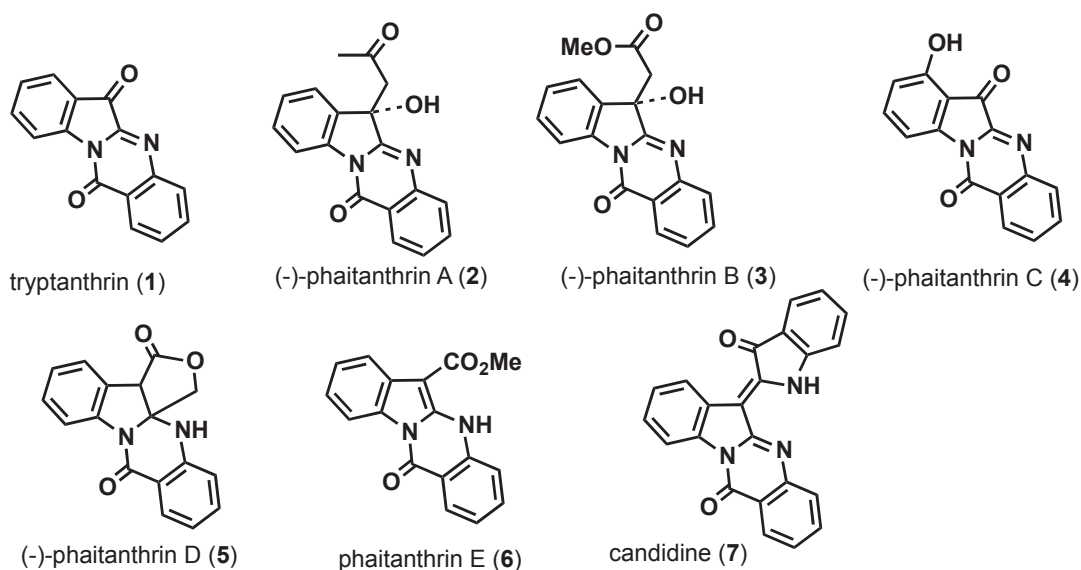
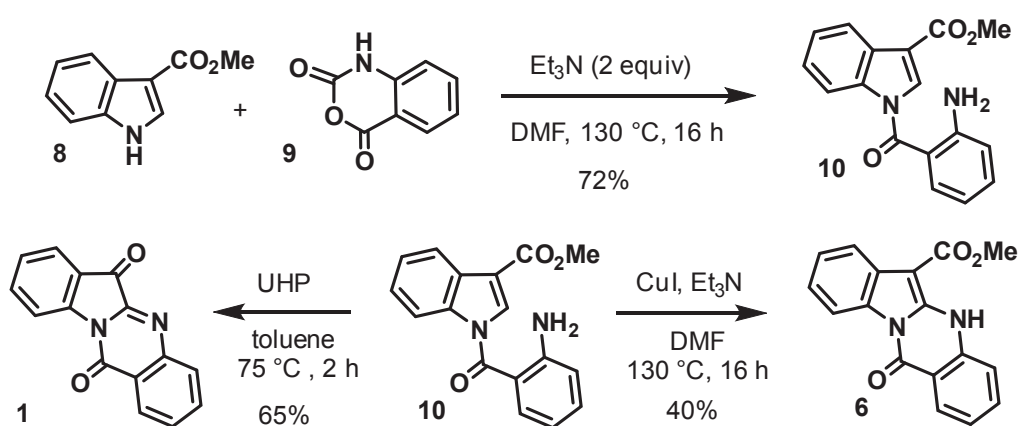
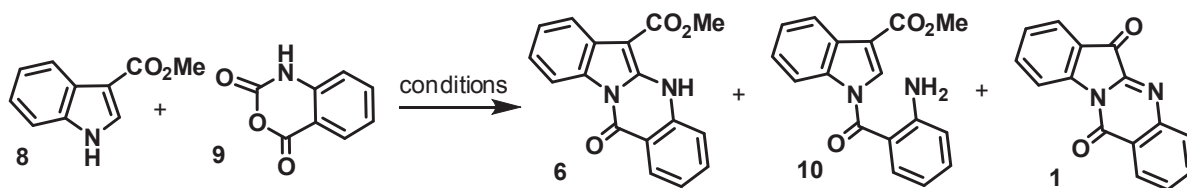


Figure 1. Indoloquinazoline alkaloids

Initially, according to a previously reported protocol,⁷ the oxidative coupling reaction of **8** with **9** (1.5 equiv) using urea-hydrogen peroxide (UHP) (5 equiv) in toluene at 75 °C in air for 12 h was performed. This resulted in recovery of **8** (80%) along with trace amounts of amide **10** (8%). Ester **8** withstood the oxidative conditions for long reaction time, in contrast to the formation of **1** by the reaction of indole-3-carboxaldehyde with **9**. Amide **10** was obtained in 72% yield by heating **8** with **9** in the presence of Et₃N (2 equiv) in DMF at 130 °C for 16 h (Scheme 1).



Scheme 1

Table 1. Cu-Mediated coupling reaction of methyl indole-3-carboxylate (**7**) with isatoic anhydride (**8**)^a

Entry	CuX	Amine	Solv.	Temp.	Time	Yield (%) ^b		
						6	10	1
1	CuI (1.5 equiv)	-----	DMF	130 °C	16 h	---	12	35
2	CuI (1.5 equiv)	Et ₃ N (2 equiv)	DMF	130 °C	16 h	62	10	---
3	CuBr (1.5 equiv)	Et ₃ N (2 equiv)	DMF	130 °C	16 h	10	---	---
4	CuI (1.0 equiv),	Et ₃ N (2 equiv)	DMF	130 °C	16 h	47	28	---
5	CuI (0.5 equiv),	Et ₃ N (2 equiv)	DMF	130 °C	16 h	23	16	---
6	CuI (3 equiv)	Et ₃ N (2 equiv)	DMF	130 °C	16 h	60	5	---
7	CuI (1.5 equiv)	pyridine (2 equiv)	DMF	130 °C	16 h	---	---	---
8	CuI (1.5 equiv)	<i>i</i> -Pr ₂ NEt (2 equiv)	DMF	130 °C	16 h	51	---	---
9	CuI (1.5 equiv)	DABCO (2 equiv)	DMF	130 °C	16 h	20	---	33

^a **8** and **9** (1.5 equiv) were heated in air. ^b Isolated yield.

We expected that intramolecular C-H amination of **10** would produce the indoloquinazoline core. Initially, **10** was oxidized with UHP (5 equiv) in toluene at 75 °C for 2 h, producing **1** in 65% yield. Considerable efforts have been made to develop metal-mediated C-H amination;⁹ therefore, we investigated whether a copper-mediated intramolecular aryl C-H amination in **10** would lead to **6**. Heating **10** with CuI (1.5 equiv) in DMF at 130 °C for 16 h provided no products. However, to our surprise, we found that the addition of Et₃N (2 equiv) promoted the reaction to produce **6** in 40% yield.

Therefore, we envisioned that coupling **8** with **9** in the presence of a copper complex could allow the one-pot formation of **6** involving the formation of amide **10** and intramolecular amination steps (Table 1). Although heating **8** and **9** with CuI (1.5 equiv) in DMF at 130 °C provided **10** (12%) and **1** (35%) without **6**, performing the reaction in the presence of Et₃N (2 equiv) produced **6** in 62% yield along with trace amounts of **10** (10%) (entries 1 and 2). The NMR data for **6** agreed well with the literature data.⁶ Hence, in a search for optimized conditions, other copper complexes were screened initially. However, the reaction did not occur with CuOAc, Cu(OAc)₂, CuCl, CuCl₂, and CuBr₂, and only trace amounts of **6** was obtained with CuBr (entry 3). Reducing the amount of CuI resulted in a considerable decrease in the yield of **6** (entries 4 and 5), and increasing the amount to 3 equiv did not improve the yield (entry 6). Pyridine, *i*-Pr₂NEt, and DABCO were less effective than Et₃N (entries 7–9).

In summary, we have developed a one-pot synthesis of phaitanthrin E (**6**) using methyl indole-3-carboxylate (**8**) and isatoic anhydride (**9**) in the presence of CuI. The one-pot reaction proceeded through in situ generation of amide **10**, followed by Cu-mediated intramolecular aryl C-H amination.

EXPERIMENTAL

Melting points were recorded with a Yamato MP21 and were uncorrected. High-resolution MS spectra were recorded with a JEOL JMS-T100LP mass spectrometer. IR spectra were measured with a Shimadzu IRAffinity-1 spectrometer. The NMR experiments were performed with a JEOL JNM-ECA500 (500 MHz) spectrometer, and chemical shifts are expressed in ppm (δ).

Methyl 1-[(2-aminophenyl)carbonyl]-1H-indole-3-carboxylate (10**):** Et₃N (4 mmol) was added to a solution of **8** (355 mg, 2 mmol) and **9** (490 mg, 3 mmol) in DMF (20 mL), and the mixture was stirred at 130 °C for 16 h. After cooling to room temperature, the mixture was added to 10% aq. HCl, extracted with AcOEt (100 mL), washed with brine, and dried over MgSO₄. The solvent was removed, and the residue was purified by silica gel column chromatography with CH₂Cl₂/AcOEt (50:1) to give **10** (431 mg, 73%) as a colorless solid. Mp 158–159 °C (CH₂Cl₂/hexane). IR (CHCl₃): 3343, 1694, 1660 cm⁻¹.

¹H-NMR (CDCl₃) δ : 3.91 (s, 3H), 5.27 (br s, 2H), 6.74 (td, $J = 1.2, 6.9$ Hz, 1H), 6.80 (d, $J = 8.1$ Hz, 1H), 7.33–7.37 (m, 2H), 7.38–7.42 (m, 2H), 8.05 (s, 1H), 8.19–8.21 (m, 2H). ¹³C-NMR (CDCl₃) δ : 51.6, 112.5, 114.2, 115.8, 116.9, 117.3, 121.7, 124.7, 125.3, 127.7, 131.7, 134.0, 134.4, 136.5, 150.1, 164.7, 169.3.

HR-MS (ESI) m/z : Calcd for C₁₇H₁₄N₂NaO₃ [(M + Na)⁺]: 317.0902. Found 317.0877.

Dakin oxidation of **10 using UHP:** UHP (941 mg, 10 mmol) was added to a solution of **10** (588 mg, 2 mmol) in toluene (30 mL) at room temperature, and the mixture was heated at 75 °C. After 16 h, the mixture was gradually cooled to room temperature, 10% NaOH solution (4 mL) was added to the mixture, and stirred for 0.5 h. The mixture was diluted with AcOEt (100 mL) and washed with brine, and dried over MgSO₄. The solvent was removed, and the residue was separated by silica gel column chromatography with CH₂Cl₂/AcOEt (50:1) to give **1**⁷ (322 mg, 65%).

Phaitanthrin E (6**):** After a mixture of CuI (1.05 g, 6 mmol) and Et₃N (1.3 g, 8 mmol) in DMF (50 mL) was stirred at room temperature for 0.5 h, methyl indole-3-carboxylate (**8**) (701 mg, 4 mmol) and isatoic anhydride (**9**) (979 mg, 6 mmol) were added to the mixture and the mixture was stirred at 130 °C for 16 h. After cooling, 10% aq. HCl solution was added to the mixture, and the mixture was extracted with AcOEt (100 mL). The organic layer was washed with brine and dried over MgSO₄. The solvent was removed, and the residue was separated by silica gel column chromatography with CH₂Cl₂ to give **6** (725 mg, 62%) as amorphous powder and **10** (10%). IR (CHCl₃): 3329, 3020, 1697, 1665, 1626, 1579 cm⁻¹. ¹H-NMR (CDCl₃) δ : 4.01 (s, 3H), 7.28 (d, $J = 8.6$ Hz, 1H), 7.30–7.34 (m, 2H), 7.43 (td, $J = 1.2, 8.0$ Hz, 1H), 7.71 (td, $J = 1.7, 7.7$ Hz, 1H), 7.94 (d, $J = 8.0$ Hz, 1H), 8.39 (d, $J = 8.0$ Hz, 1H), 8.70 (d, $J = 8.0$ Hz, 1H),

10.29 (br s 1H). ^{13}C -NMR (CDCl_3) δ : 51.4, 86.7, 114.4, 115.7, 116.3, 119.4, 122.4, 123.2, 125.7, 126.3, 128.7, 130.4, 135.3, 138.2, 144.1, 158.5, 167.3. HR-MS (ESI) m/z : Calcd for $\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}_3$ [(M + H) $^+$] 293.0926. Found 293.0926.

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