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## PRACTICAL TOTAL SYNTHESIS OF LUOTONIN A BY INTRAMOLECULAR DOUBLE HETERO DIELS–ALDER REACTION

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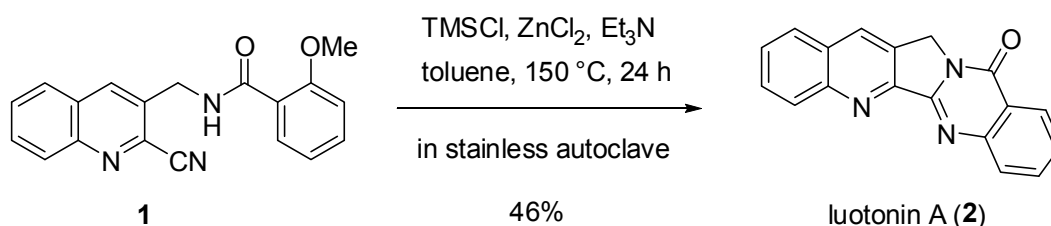
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#Dedicated to Professor Albert Padwa on the occasion of his 75<sup>th</sup> birthday

**Abstract** – An intramolecular double hetero Diels–Alder reaction of *N*-(2-cyanoquinolin-3-ylmethyl)-2-tosyloxybenzamide (**3c**) provided luotonin A (**2**) in 82% yield. Surprisingly, *N*-(2-bromoquinolin-3-ylmethyl)-2-tosyloxybenzamide (**4**) directly provided luotonin A (**2**) in 78% yield in the presence of Pd<sub>2</sub>(dba)<sub>3</sub> (5 mol %), dppf (20 mol %), and K<sub>2</sub>CO<sub>3</sub> (6 eq).

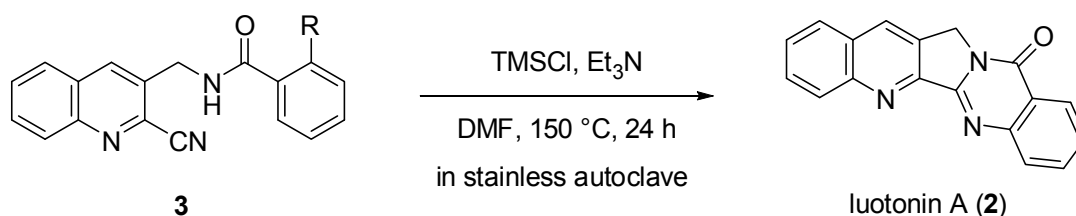
We previously reported a concise total synthesis of luotonin A (**2**), isolated from *Peganum nigellastrum* by Nomura and colleagues in 1997.<sup>1</sup> This synthetic approach employed an intramolecular double hetero Diels–Alder reaction of *N*-(2-cyanoquinolin-3-ylmethyl)-2-methoxybenzamide (**1**).<sup>2</sup> Although the total synthesis required three steps, a yield of only 46% luotonin A (**2**) was afforded (**Scheme 1**).<sup>3</sup>



**Scheme 1.** Previous our synthesis of luotonin A (**2**)

To further improve the yield of the key step, we examined the effects of various benzene ring substituents on the intramolecular double hetero Diels–Alder reaction.<sup>4</sup> In this paper, we report several notable results of the above cycloaddition.

The substrates **3** were prepared as described previously.<sup>2</sup> The products of the cycloaddition reaction are summarized in **Table 1**. Although the chloro-substituted **3a** gave luotonin A (**2**) in only a 26% yield (entry 1), the bromo-substituted **3b** produced **2** in a 73% yield (entry 2). Luotonin A (**2**) was obtained in a 62% yield in the absence of ZnCl<sub>2</sub> (entry 3). This result suggests that a Lewis acid may not necessarily be required for the cycloaddition process. Fortunately, the tosyl-substituted **3c** proved to be a suitable substrate for the intramolecular double hetero Diels–Alder reaction, and luotonin A (**2**) was afforded in 82% yield (entry 4).

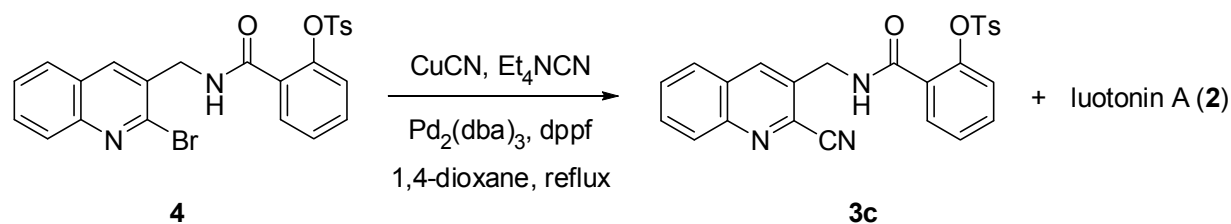


**Table 1.** Intramolecular double hetero Diels–Alder reaction of **3**

entry	substrate	R	additive	yield (%)
1	<b>3a</b>	Cl	ZnCl <sub>2</sub>	26
2	<b>3b</b>	Br	ZnCl <sub>2</sub>	73
3	<b>3b</b>	Br	none	62
4	<b>3c</b>	OTs	none	82

Because a 17% yield of luotonin A (**2**) formed during the transformation of the bromide **4** into the cyanide **3c** (entry 1), we searched for conditions that provided an additive effect, as shown in **Table 2**.<sup>3b</sup> When the coupling reaction was conducted in the presence of one equivalent of K<sub>2</sub>CO<sub>3</sub>, the yield of luotonin A (**2**) increased slightly (entry 2). Surprisingly, luotonin A (**2**) was provided in 78% yield when this reaction was performed in the presence of six equivalents of K<sub>2</sub>CO<sub>3</sub> (entry 3). Investigations into the role of K<sub>2</sub>CO<sub>3</sub> and the reaction mechanism underlying these reaction conditions are underway.

In conclusion, the intramolecular double hetero Diels–Alder reaction of *N*-(2-cyanoquinolin-3-ylmethyl)-2-tosyloxybenzamide (**3c**) gave luotonin A (**2**) in 82% yield. Additionally, luotonin A (**2**) was obtained directly from *N*-(2-bromoquinolin-3-ylmethyl)-2-tosyloxybenzamide (**4**) under the coupling conditions.



**Table 2.** Luotonin A (**2**) formation during the course of transformation of bromide **4** into cyanide **3c**

entry	additive	time (h)	yield (%)	
			<b>3c</b>	luotonin A ( <b>2</b> )
1	none	4	60	17
2	K <sub>2</sub> CO <sub>3</sub> (1 eq.)	3	73	23
3	K <sub>2</sub> CO <sub>3</sub> (6 eq.)	3	0	78

## EXPERIMENTAL

IR spectra were measured on a SHIMADZU FT-IR 8300 spectrophotometer. <sup>1</sup>H NMR spectra were recorded on JEOL JX-500 (500 MHz) spectrometers with CHCl<sub>3</sub> (δ 7.26) as an internal standard. <sup>13</sup>C NMR spectra were recorded on JEOL JX-500 (125 MHz) spectrometer with CHCl<sub>3</sub> (δ 77.16) as an internal standard. All compounds purified by chromatography were sufficiently pure (> 95% by <sup>1</sup>H NMR analysis) for use in subsequent reactions.

**Luotonin A (2).** (**Method A**) A mixture of tosylate **3c** (10.0 mg, 0.02 mmol), ZnCl<sub>2</sub> (5.7 mg, 0.04 mmol), TMSCl (0.06 mL, 0.44 mmol) and Et<sub>3</sub>N (0.06 mL, 0.44 mmol) in DMF (5.0 mL) was heated at 150 °C in a stainless autoclave for 24 h. After removal of the solvent, saturated aqueous NH<sub>4</sub>Cl solution was added. The resulting mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over MgSO<sub>4</sub>, and evaporated. Purification of the crude product by flash chromatography (Hexane:EtOAc=1:1) afforded luotonin A (**2**) (5.1 mg, 82%) as a pale yellow needle, mp 280-283 °C (lit.<sup>5</sup> 281-283 °C).

Data for luotonin A (**2**): <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 5.34 (s, 2H), 7.58 (ddd, *J* = 0.8, 7.2 and 7.2 Hz, 1H), 7.67 (ddd, *J* = 0.8, 7.2 and 7.2 Hz, 1H), 7.88 (ddd, *J* = 7.2, 7.2 and 1.2 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 8.45 (dd, *J* = 8.0 and 1.2 Hz, 1H) and 8.41-8.47 (m, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 160.8, 152.7, 151.3, 149.6, 149.5, 134.7, 131.7, 130.9, 130.8, 129.6, 129.0, 128.7, 128.7, 128.1, 127.6, 126.6, 121.5, and 47.5.

**Luotonin A (2). (Method B)** A mixture of bromide **4** (11.2 mg, 0.02 mmol), CuCN (7.9 mg, 0.09 mmol), Pd<sub>2</sub>(dba)<sub>3</sub> (1.0 mg, 0.001 mmol), DPPF (2.5 mg, 0.004 mmol) and Et<sub>4</sub>NCN (5.2 mg, 0.03 mmol) in 1,4-dioxane (10 mL) was heated at 130 °C in a stainless autoclave for 4 h. The resulting mixture was diluted with EtOAc, and the precipitates were filtered off through Celite. The filtrate was washed with saturated aqueous NaHCO<sub>3</sub> solution, saturated aqueous NaCl solution, dried over MgSO<sub>4</sub>, and evaporated. Purification of the crude product by flash chromatography (Hexane:EtOAc=1:1) afforded luotonin A (**2**) (4.9 mg, 78%) as a pale yellow needle.

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