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

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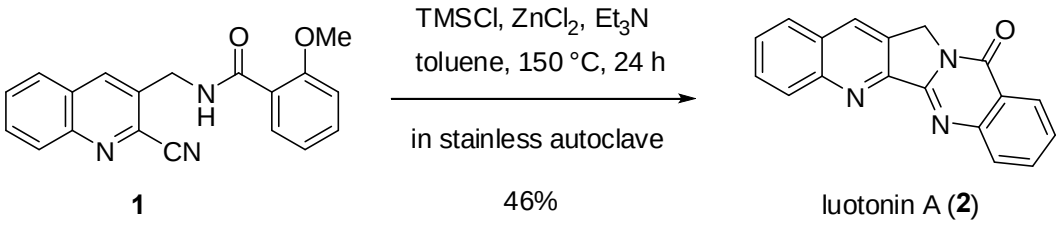
#Dedicated to Professor Albert Padwa on the occasion of his 75th birthday

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 $Pd_2(dba)_3$ (5 mol %), dppf (20 mol %), and K_2CO_3 (6 eq).

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

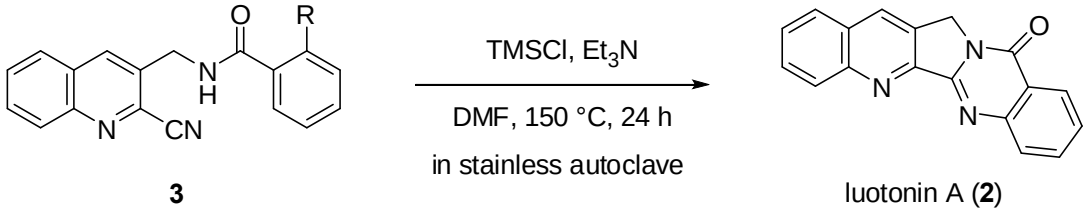


1 luotonin A (**2**)

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.[4] In this paper, we report several notable results of the above cycloaddition.

The substrates **3** were prepared as described previously.[2] The products of the cycloaddition reaction are summarized in **Table 1**. Although the chloro-substituted **3a** gave luotonine 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 $ZnCl_2$ (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).



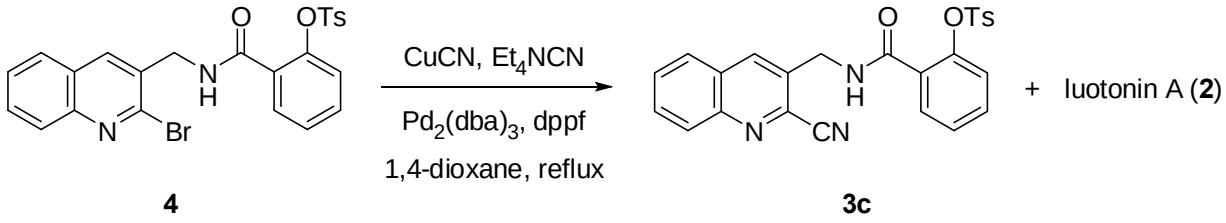
3 luotonin A (**2**)

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

entry	substrate	R	additive	yield (%)
1	**3a**	Cl	$ZnCl_2$	26
2	**3b**	Br	$ZnCl_2$	73
3	**3b**	Br	none	62
4	**3c**	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**.[3b] When the coupling reaction was conducted in the presence of one equivalent of K_2CO_3, 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_2CO_3 (entry 3). Investigations into the role of K_2CO_3 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.



4 **3c**

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

entry	additive	time (h)	yield (%)	
			3c	luotonin A (**2**)
1	none	4	60	17
2	K_2CO_3 (1 eq.)	3	73	23
3	K_2CO_3 (6 eq.)	3	0	78

EXPERIMENTAL

IR spectra were measured on a SHIMADZU FT-IR 8300 spectrophotometer. ^{1}H NMR spectra were recorded on JEOL JX-500 (500 MHz) spectrometers with $CHCl_3$ (δ 7.26) as an internal standard. ^{13}C NMR spectra were recorded on JEOL JX-500 (125 MHz) spectrometer with $CHCl_3$ (δ 77.16) as an internal standard. All compounds purified by chromatography were sufficiently pure (> 95% by ^{1}H NMR analysis) for use in subsequent reactions.

Luotonin A (2). (Method A) A mixture of tosylate **3c** (10.0 mg, 0.02 mmol), $ZnCl_2$ (5.7 mg, 0.04 mmol), TMSCl (0.06 mL, 0.44 mmol) and Et_3N (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_4Cl solution was added. The resulting mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl solution, dried over $MgSO_4$, 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.[5] 281-283 °C).

Data for luotonin A (**2**): ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125 MHz, $CDCl_3$) 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), $Pd_2(dba)_3$ (1.0 mg, 0.001 mmol), DPPF (2.5 mg, 0.004 mmol) and Et_4NCN (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 $NaHCO_3$ solution, saturated aqueous NaCl solution, dried over $MgSO_4$, 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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