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THREE-STEP TOTAL SYNTHESIS OF PYRROLOQUINAZOLINO-QUINOLINE ALKALOID, LUOTONIN A, BY INTRAMOLECULAR HETERO DIELS-ALDER REACTION[#]

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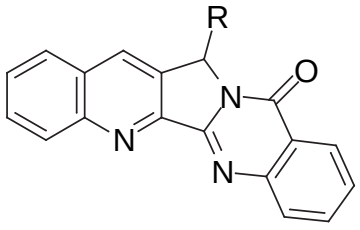
Abstract - Total synthesis of luotonin A (**1**) was accomplished, starting from 3-aminomethyl-2-bromoquinoline (**4**) in three steps *via* intramolecular hetero Diels–Alder reaction.

We have been exploring intramolecular hetero Diels–Alder reactions of 1-azadienynes for the construction of biologically active heterocycles such as nothapodytine B.[1] In order to demonstrate the flexibility of our protocol, we envisioned a novel one-pot generation of quinazolinone ring systems by using cyano group as a Diels-Alder dienophile.[2] Since luotonins A (**1**) and B (**2**) possess quinazolinone framework as their partial structures, luotonin A (**1**) was adopted as our present target molecule. Luotonins A (**1**) and B (**2**) were originally isolated by Nomura and his coworkers in 1997 from the aerial parts of *Peganum nigellastrum* (Figure 1).[3] Because these alkaloids have unique pyrroloquinazolinoquinoline ring system and luotonin A (**1**) shows cytotoxic activity against mouse leukemia P-388 cells, luotonin A (**1**) has attracted significant attention in recent years.[4] In this communication, we report a three-step synthesis of luotonin A (**1**) employing intramolecular hetero Diels–Alder reaction.

Figure 1

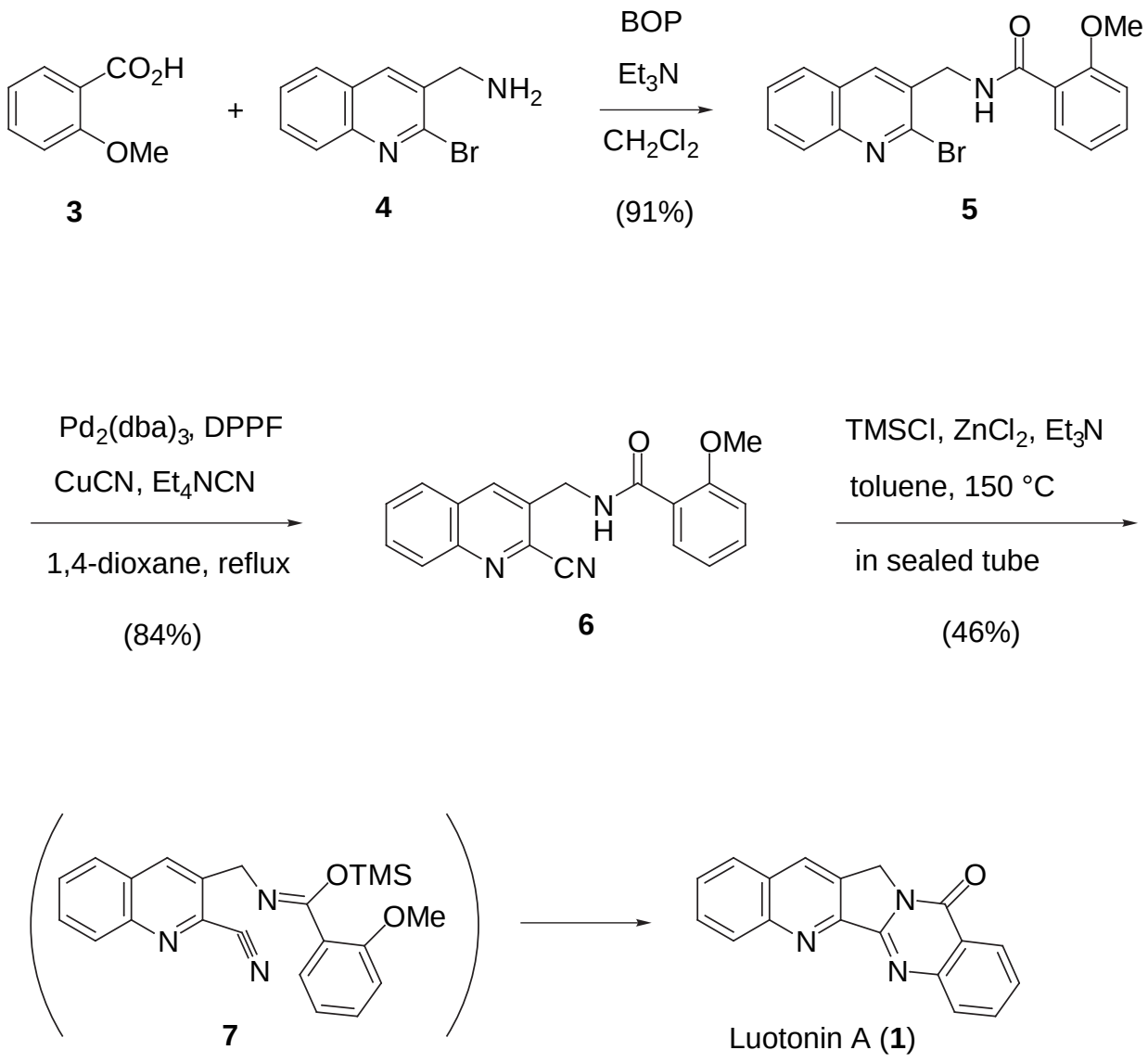


Luotonin A (**1**): R=H
Luotonin B (**2**): R=OH

The requisite substrate (**6**)[5] for the pivotal hetero cycloaddition was easily prepared in two steps as depicted in Scheme 1. Condensation of 2-methoxybenzoic acid (**3**) with 3-aminomethyl-2-bromoquinoline (**4**)[6] in the presence of BOP and Et_3N provided the amide (**5**) in 91% yield. To introduce cyano group into the C-2 position of **5**, palladium-catalyzed coupling reaction of **5** with CuCN was investigated.[7] As a result, the reaction proceeded smoothly in the presence of 4 mol % of $Pd_2(dba)_3$, 16 mol % of DPPF and stoichiometric amounts of Et_4NCN, giving the cyanide (**6**) in 84% yield.

With the efficient synthesis of **6** established, the compound (**6**) was next subjected to intramolecular hetero Diels–Alder reaction. Heating of **6** with TMSCl and Et_3N at 150 ℃ in the presence of $ZnCl_2$ produced luotonin A (**1**) in 46% yield. The synthetic **1** thus obtained was spectroscopically identical with that reported.[3]

Scheme 1



REFERENCES AND NOTES

Dedicated to Professor James P. Kutney on the occasion of his 70th birthday.

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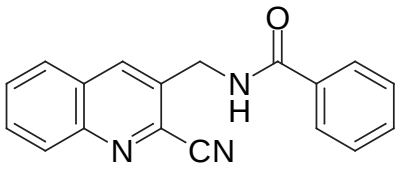
5. The intramolecular hetero Diels–Alder reaction of **8** afforded neither the corresponding cycloadduct nor luotonin A (**1**).



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