ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Direct One-Pot Synthesis of Luotonin F and Analogues via Rational Logical Design

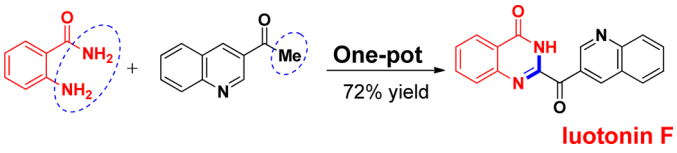
Yan-ping Zhu, Zhuan Fei, Mei-cai Liu, Feng-cheng Jia, and An-xin Wu*

Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Hubei, Wuhan 430079, P. R. China

chwuax@mail.ccnu.edu.cn

Received December 5, 2012

ABSTRACT

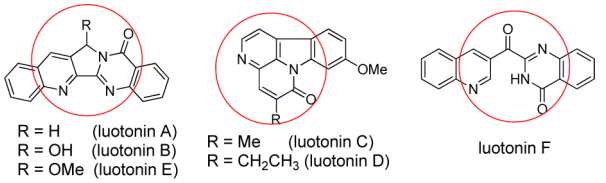


An efficient one-pot synthetic protocol has been proposed for the synthesis of luntonin F from easily available starting materials. Through a rational logical design, multifundamental reactions (iodination, Kornblum oxidation, and annulation) were assembled in one-pot. The developed approach can efficiently synthesize luntonin F and a diversity of analogues.

Maximizing synthetic efficiency while at the same time minimizing unnecessary synthetic steps is a very important but difficult achievement in the total synthesis of natural products.[1] In recent years, the one-pot synthetic strategy has been proposed and employed in the synthesis of natural products.[2] Chu and co-workers previously demonstrated a graceful self-directed one-pot synthesis of luotonin A and analogues.[2a] This approach allowed concomitant construction of multiple rings through a multiple reaction sequence. Liu and co-workers also proposed an elegant one-pot total synthesis of glyantrypine, fumiquinazoline F, and fiscalin B through a microwave-promoted three-component reaction.[2b] Many impressive results have been attained in this area, yet it is clear that a strategy for one-pot synthesis for natural product is still in its infancy.

Luotonins A, B, C, D, E and F are novel alkaloids that have been isolated from the aerial parts of the Peganum nigellastrum Bunge, which has a long history in Chinese medicine for the treatment of rheumatism, inflammation, abscesses, and other maladies.[3] Due to their biological and pharmaceutical activities, extensive synthetic methods have been developed for the synthesis of luotonins (Scheme 1).[4] However, the methodology for the synthesis of luotonin F still remains very limited.

Scheme 1. Structure of Luotonins A–F



In 1999, Nomura and co-workers were the first to achieve the total synthesis of luotonin F by a six-step

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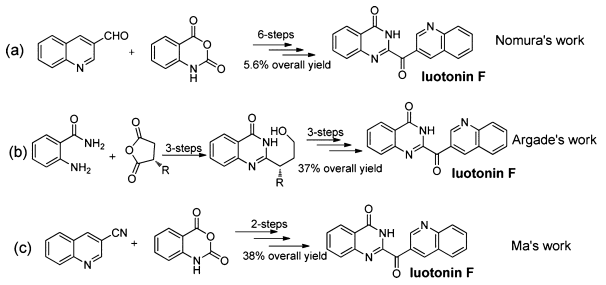
10.1021/ol303331g

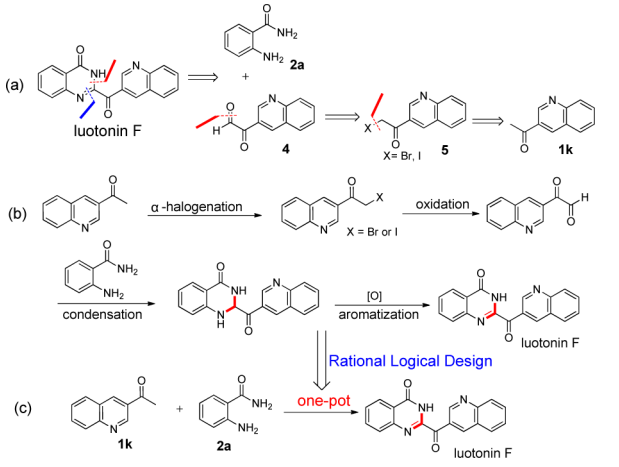
reaction with nearly a 5.6% overall yield from 3-fomylquinoline and isatoic anhydride (Scheme 2a).[5] In 2002, Argade and co-workers described a three-step biogenetic type synthesis of luotonin F with an ensuing overall yield of 38% from the natural product pegamine and 2-aminobenzaldehyde (Scheme 2b).[6] In 2004, Ma and co-workers demonstrated a two-step synthesis of luotonin F from 3-quinolinenitrile isatoic anhydride with 37% overall yield (Scheme 2c).[7] However, all of the above methods still utilized the step-by-step synthetic strategy. Therefore, the development of a practical and efficient, one-pot protocol to access luotonin F is both desirable and valuable; it could also have significance in directing further research for one-pot synthesis of other natural products.

Scheme 2. Methods for the Synthesis of Luotonin F



Retrosynthetically (Scheme 3a), it was envisioned that luotonin F could be obtained from 2-oxo-2-(quinolin-3-yl)-acetaldehyde **4** and 2-aminobenzamide **2a** through an intermolecular condensation and aromatization process,[8] while **4** could be furnished from the α-haloge ketone **5** through Kornblum oxidation.[9] It was also thought that **5** could easily be prepared from 3-acetylquinoline **1k** through a halogenation process.[10] The synthetic process is depicted in Scheme 3b. It is thought to consist of a α-halogenation, Kornblum oxidation, intermolecular condensation, and aromatization reaction sequence. Based on the draft (Scheme 3a–b), we wanted to test whether it would be possible to develop a one-pot protocol for the synthesis of luotonin F from 3-acetylquinoline **1k** and 2-aminobenzamide **2a** via a rational logical design, in which multiple reactions would self-sequentially take place in one-pot (Scheme 3c).

Scheme 3. Retrosynthetic Analysis and the Protocols for One-Pot Synthesis of Luotonin F



With this idea in mind, we optimized the reaction conditions using acetophenone **1a** and 2-aminobenzamide **2a** as model substrates (Table 1). Initially, the reaction was carried out with I_2 (1.1 equiv) in DMSO at 110 °C (entry 1). This afforded a 73% combined yield of **3aa** and **3af** (with a ratio of 1.2:1). To improve the chemoselectivity of the products, various catalysts, additives, and oxidants were investigated in further detail in DMSO. First, a series of Brønsted acids, such as HCl, HOAc, $MeSO_3H$, CF_3SO_3H, and L-proline, were screened for the reaction. However, the products **3aa** and **3af** were still only produced with a ratio of 1:1 (entries 2–6). Even when various metal salts and bases, such as CuO, CuBr, NaOH, PPh_3, pyridine, DABCO, DBU, and K_3PO_4–H_2O were added, the reaction efficiency was still showed no improvement (entries 7–14). Moreover, neither additives (NIS and TBAI) nor oxidant (TBHP) led to any further improvement in the reaction efficiency (entries 15–18). However, to our delight, the reaction efficiency was greatly improved when 2-aminobenzamide **2a** in 2 mL DMSO was added dropwise to a mixture of acetophenone **1a** (1.0 mmol) and I_2 (1.1 mmol) in 3 mL DMSO at 110 °C (entry 19). The desired product **3aa** was obtained in 75% yield; while the product **3af** was hardly observed at all. Subsequent increases and decreases in the temperature did not enhance the reaction yield any further (entries 20–23).

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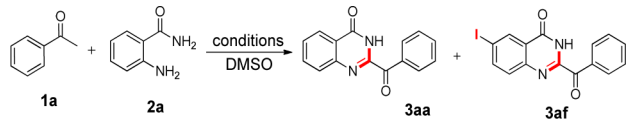
Table 1. Optimization Studies[a]

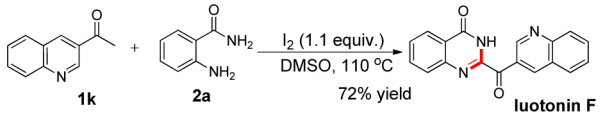


entry	additive (mol %)	cat.	oxidate	temp. (°C)	yield **3aa/3af** (%)[b]
1	I_2 (110)			110	40/33
2	I_2 (110)	HCl		110	35/27
3	I_2 (110)	HOAc		110	30/25
4	I_2 (110)	CF_3SO_3H		110	20/30
5	I_2 (110)	CH_3SO_3H		110	25/30
6	I_2 (110)	L-proline		110	38/28
7	I_2 (110)	CuO		110	30/23
8	I_2 (110)	CuBr		110	36/25
9	I_2 (110)	NaOH		110	37/27
10	I_2 (110)	PPh_3		110	35/20
11	I_2 (110)	Pyridine		110	33/26
12	I_2 (110)	DABCO		110	28/38
13	I_2 (110)	DBU		110	28/39
14	I_2 (110)	$K_3PO_43H_2O$		110	26/38
15	I_2 (80)		TBHP	110	35/15
16	I_2 (50)		TBHP	110	33/13
17	NIS (50)		TBHP	110	35/13
18	TBAI (50)		TBHP	110	0/0
19[c]	**I_2 (110)**			**110**	**75/<5**
20[c]	I_2 (110)			90	40/<10
21[c]	I_2 (110)			100	62/<10
22[c]	I_2 (110)			120	73/<5
23[c]	I_2 (110)			130	70/<5

[a] Reaction conditions: a mixture of acetophenone **1a** (1.0 mmol), 2-aminobenzamide **2a** (1.0 mmol), I_2 (1.1 mmol), catalyst (50 mol %), oxidant (1.0 mmol), were heated in DMSO (3 mL). [b] Ratio of products was determined by ^{1}H NMR. [c] 2-Aminobenzamide **2a** (1.0 mmol in 2 mL DMSO) was added dropwise to a mixture of acetophenone **1a** (1.0 mmol) and I_2 (1.1 mmol) in DMSO (3 mL) upon stirred at 110 °C for 2 h.

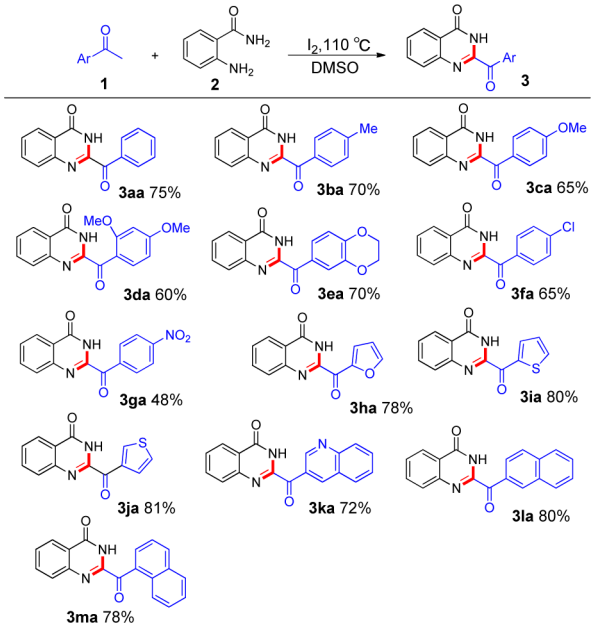
With the optimal conditions established, we applied them to synthesize luotonin F in one-pot. To our delight, the reaction of 3-acetylquinoline **1k** with 2-aminobenzamide **2a** occurred smoothly to afford the desired luotonin F in 72% yield in the presence of I_2 in DMSO at 110 °C for 1 h (Scheme 4). Compared with the previous reports, this method not only provided high yields, but also provided an efficient method achieved in just one step.

Scheme 4. One-Pot Synthesis of Luotonin F



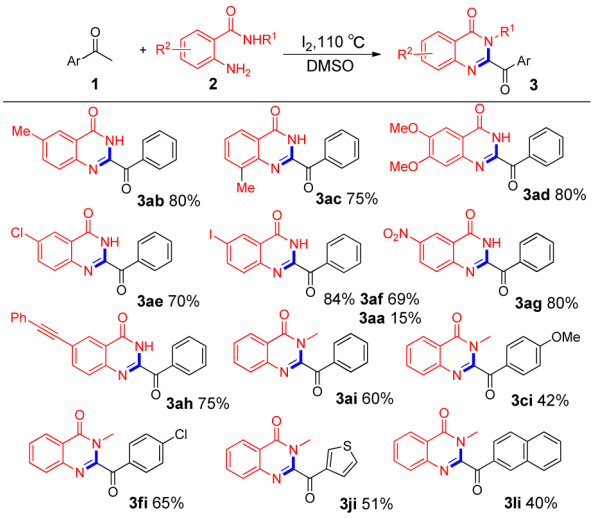
Inspired by the above results, the scope of aromatic ketones was further investigated and the results are subsequently listed in Scheme 5. A wide array of aromatic ketones were examined in the reaction with 2-aminobenzamide **2a**; moderate to good yields were achieved in the corresponding products (Scheme 5). The substrates with electron-donating groups and halogen on aryl ring, such as 4-Me, 4-OMe, 3,4-OCH_2CH_2O, and 4-Cl, exhibited good reactivity (**3ba**−**3fa**). However, when the strong electron-withdrawing group NO_2 was situated in the para position, the aromatic ketone **1g** was converted into the desired product **3ga** with a yield of just 48%. It is notable that heterocycles, such as 2-acetylfuran **1h**, 2-acetylthiophen **1i**, 3-acetylthiophen **1j**, and 3-acetylquinoline **1k**, were also found to be suitable for the reaction and gave the corresponding products **3ha**−**3ka** in good yields (72−81%). In addition, the sterically hindered 2-acetylnaphthalene **1l** and 1-acetylnaphthalene **1m** also furnished the desired products **3la** and **3ma** smoothly in 80 and 78% yields, respectively.

Scheme 5. Scope of Aromatic Ketones



We went on to further expand the scope of 2-aminobenzamides **2**. The results are subsequently displayed in Scheme 6. Various substituted 2-aminobenzamides **2** were found to be tolerant in the reaction. For example, 2-aminobenzamides bearing electron-rich (**2b**−**2d**) and electron-deficient (**2e**−**2g**) substituents on aryl ring underwent the reaction smoothly to afford the corresponding products in good yields. When 2-amino-5-iodobenzamide **2f** was used as a substrate, the reaction afforded an 84% combined yield of **3af** and **3aa** (with a ratio of 4.6:1). More importantly, the phenylethynyl group attached to the phenyl ring of 2-aminobenzamides did not affect the overall reaction efficiency and the corresponding product **3ah** was still furnished in 75% yield. Meanwhile, 2-amino-N-methylbenzamide **2i** was also found to react efficiently with a variety of aromatic ketones to provide the corresponding products in 40−65% yields (**3ai**−**3li**). Furthermore, the target compound **3ca** was further determined by X-ray crystallographic analysis (Figure S1).

Scheme 6. Scope of 2-Aminobenzamides



To elucidate the mechanism, some control experiments were performed. Under an argon atmosphere, the reaction of α-iodo ketone **1aa** with 2-aminobenzamide **2a** performed very well to give the product **3aa** in good yield both with I_2 (50 mol %) and without I_2 (Scheme 7a). The reaction between phenylglyoxal (**1ab**) and 2-aminobenzamide **2a** was also investigated under an argon atmosphere. In the presence of I_2 (50 mol %) the product **3aa** was obtained in excellent yield in 30 min (Scheme 7b). However, **3aa** was not observed in 30 min without I_2. When the reaction time was extended to 12 h, the product **3aa** was afforded in 73% yield (Scheme 7c). The results shown in Scheme 7b–c suggest that I_2 was very important in the conversion of **1ab** with **2a** into **3aa**. These results clearly confirm the intermediacy of phenacyl iodine **1aa** and phenylglyoxal **1ab** in the transformation.

In accordance with the results, a possible mechanism for the present reaction is depicted in Scheme 8. It is suggested that acetophenone **1a** with I_2 initially undertook a halogenation reaction to afford the intermediate α-iodo ketone **1aa**, which further transformed into phenylglyoxal (**1ab**) via Kornblum oxidation.[11] This step was likely followed by condensation and addition with 2-aminobenzamide **2a** to yield intermediate **B**. Finally, it is proposed that

(11) Halogenation reaction and Kornblum oxidation processes are well investigated in our previous studies. See refs 9b–9e and 10a–10c.

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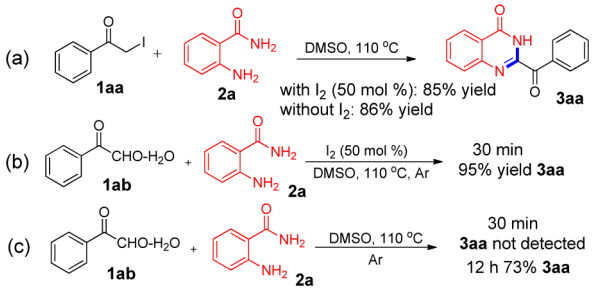
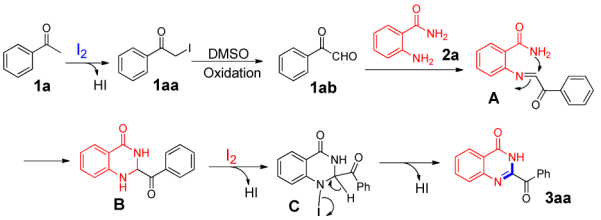
Scheme 7. Control Experiments



Scheme 8. Proposed Mechanism



intermediate **B** underwent oxidation and aromatization to provide the desired product **3aa** in the presence of I_2.[12]

In conclusion, we have developed an efficient one-pot protocol for the synthesis of the natural product luotonin F and derivatives from simple and readily available aromatic ketones and 2-aminobenzamides. Through a rational logical design, multiple fundamental reactions (iodination, Kornblum oxidation, condensation, addition, and aromatization) were self-sequentially assembled in a single reactor. This efficient strategy could have significance for directing further research into one-pot synthesis of many natural products. Further studies on the applications of this strategy will be reported in due course.

Acknowledgment. This work was supported by the National Natural Science Foundation of China (Grant 21032001 and 21272085) and PCSIRT (No. IRT0953). We would also like to thank Dr. Chuanqi Zhou, Hebei University, for analytical support.

Supporting Information Available. Spectrascopic data and general procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.