## Intramolecular Formal [4 + 2] Cycloaddition of Nitriles with Amides Triggered by TMSOTf/Et$_3$N: Highly Efficient Construction of Pyrrolo[1,2-*a*]-pyrimidin-4(6*H*)-ones

Feng Liu and Chaozhong Li*

*Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China*

*clig@mail.sioc.ac.cn*

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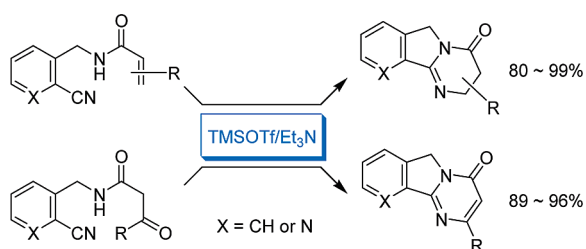
By treatment with TMSOTf/Et$_3$N, *N*-(2-cyanoaryl-methyl)-substituted acrylamides or *β*-ketoamides underwent N-addition cascades under mild conditions to afford the corresponding pyrrolo[1,2-*a*]pyrimidin-4(6*H*)-ones as the formal [4 + 2] cycloaddition products in high yields.

Pyrrolo[1,2-*a*]pyrimidin-4(6*H*)-ones, especially the [7,8]-aryl-fused ones (**1**), are a class of heterocyclic compounds of significant biological interest. A typical example is the naturally occurring luotonin A (**2**) isolated from a Chinese medicinal plant (*Peganum nigellastrum*) in 1997,[1] which is a human DNA topoisomerase I poison[2] and exhibits potent cytotoxicity against P-388 cells. A number of luotonin A analogues have thus been evaluated for their ability to stabilize the covalent binary complex formed between human topoisomerase I and DNA.[3] Among them, the 16,17,18,19-tetrahydroluotonin A (**3**) also showed good concentration-dependent cytotoxicity, indicating an aromatic E-ring is not essential for targeting the topoisomerase I−DNA covalent binary complex.[3c] More importantly, Hecht and co-workers have recently discovered

that the water-soluble 14-azacamptothecin (**4**), a hybrid between luotonin A and the naturally occurring antitumor agent camptothecin, is also a potent DNA topoisomerase I poison.[4]

The synthesis of luotonin A and analogues has thus drawn much attention.[5,6] However, most of the literature works were centered at the construction of the skeleton with an aromatic E-ring, while few methods were known for the synthesis of the analogues with a saturated E-ring (as in **3** and **4**). Hecht et al. reported the preparation of **3** via the condensation of 1,2-dihydropyrrolo[3,4-*b*]quinolin-3-one with a *β*-aminoacrylate.[3c] However, the yield was only 6%. The intramolecular aryl radical addition to the C≡N bond of pyrimidin-4-ones to form the 5-membered pyrrole ring was also found to be of low efficiency.[4b,4c] More recently, Malacria and co-workers reported the one-step construction of the pyrrolopyrimidinone skeleton via a radical cyclization cascade with the acyclic *N*-acyl-*N*-(2-iodobenzyl)cyanamides as the precursors.[6c] Owing to the important biological activity of luotonin A derivatives, it is certainly highly desirable to develop general and efficient methods for their synthesis. Herein, we report that the trimethylsilyl triflate/triethylamine-triggered intramolecular reactions between arylnitriles and acrylamides or *β*-ketoamides via a formal [4+2] cycloaddition manner provide a convenient and efficient entry to the synthesis of pyrrolopyrimidinones.



1 (X = CH or N)    luotonin A (2)

3    14-azacamptothecin (4)
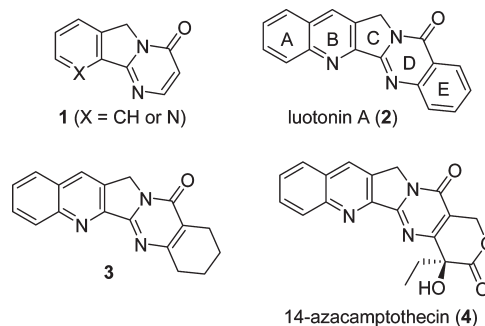
Our initial approach to pyrrolopyrimidinones was to conduct the intramolecular amidyl radical addition to a C≡N bond as part of our systematic study on N-centered radical cyclization reactions.[7] This idea was vigorously tested with *N*-(2-cyanobenzyl)but-2-enamide (**5a**) as the

(1) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1997**, *46*, 541.

(2) Cagir, A.; Jones, S. H.; Gao, R.; Eisenhauer, B. M.; Hecht, S. M. *J. Am. Chem. Soc.* **2003**, *125*, 13628.

(3) (a) Ma, Z.; Hano, Y.; Nomura, T.; Chen, Y. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1193. (b) Cagir, A.; Jones, S. H.; Eisenhauer, B. M.; Gao, R.; Hecht, S. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2051. (c) Cagir, A.; Eisenhauer, B. M.; Gao, R.; Thomas, S. J.; Hecht, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 6287. (d) Lee, E. S.; Park, J. G.; Kim, S. I.; Jahng, Y. *Heterocycles* **2006**, *68*, 151.

(4) (a) Cheng, K.; Rahier, N. J.; Eisenhauer, B. M.; Thomas, S. J.; Gao, R.; Hecht, S. M. *J. Am. Chem. Soc.* **2005**, *127*, 838. (b) Rahier, N. J.; Cheng, K.; Gao, R.; Eisenhauer, B. M.; Hecht, S. M. *Org. Lett.* **2005**, *7*, 835. (c) Elban, M. A.; Sun, W.; Eisenhauer, B. M.; Gao, R.; Hecht, S. M. *Org. Lett.* **2006**, *8*, 3513.

(5) For a review on the synthesis of luotonin A, see: Ma, Z.; Hano, Y.; Nomura, T. *Heterocycles* **2005**, *65*, 2203.

(6) For the latest examples on the synthesis of luotonin A, see: (a) Bowman, W. R.; Cloonan, M. O.; Fletcher, A. J.; Stein, T. *Org. Biomol. Chem.* **2005**, *3*, 1460. (b) Tangirala, R.; Antony, S.; Agama, K.; Pommier, Y.; Curran, D. P. *Synlett* **2005**, 2843. (c) Servais, A.; Azzouz, M.; Lopes, D.; Courillon, C.; Malacria, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 576. (d) Zhou, H.-B.; Liu, G.-S.; Yao, Z.-J. *J. Org. Chem.* **2007**, *72*, 6270.

(7) (a) Tang, Y.; Li, C. *Org. Lett.* **2004**, *6*, 3229. (b) Chen, Q.; Shen, M.; Tang, Y.; Li, C. *Org. Lett.* **2005**, *7*, 1625. (c) Lu, H.; Li, C. *Tetrahedron Lett.* **2005**, *46*, 3574. (d) Hu, T.; Shen, M.; Chen, Q.; Li, C. *Org. Lett.* **2006**, *8*, 2647. (e) Lu, H.; Chen, Q.; Li, C. *J. Org. Chem.* **2007**, *72*, 2564. (f) Liu, F.; Liu, K.; Yuan, X.; Li, C. *J. Org. Chem.* **2007**, *72*, 10231. (g) Yuan, X.; Liu, K.; Li, C. *J. Org. Chem.* **2008**, *73*, 6166.

**TABLE 1.  Optimization of the Synthesis of 6a from 5a**



| entry | conditions | yield[a] (%) |
|---|---|---|
| 1 | TMSCl (1.5 equiv), Et$_3$N (1.0 equiv), CH$_2$Cl$_2$, rt, 17 h | 0 |
| 2 | TMSCl (1.5 equiv), Et$_3$N (1.0 equiv), (CH$_2$Cl)$_2$, reflux, 8 h | 8 |
| 3 | TMSOTf (1.5 equiv), Et$_3$N (1.0 equiv), CH$_2$Cl$_2$, rt, 6 h | 94 |
| 4 | TMSOTf (1.5 equiv), Et$_3$N (2.0 equiv), CH$_2$Cl$_2$, rt, 6 h | 78 |
| 5 | TMSOTf (0.8 equiv), Et$_3$N (0.8 equiv), CH$_2$Cl$_2$, rt, 6 h | 38 |
| 6 | TMSOTf (1.5 equiv), CH$_2$Cl$_2$, rt, 24 h | 0 |
| 7 | Et$_3$N (0.5 equiv), CH$_2$Cl$_2$, rt, 24 h | 0 |
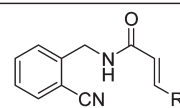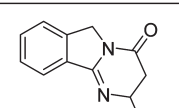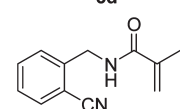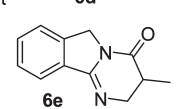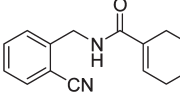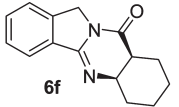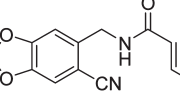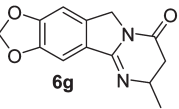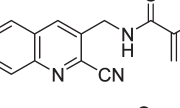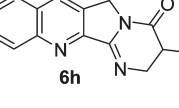
[a] Isolated yield based on **5a**.

precursor, which could be readily prepared from the condensation of 2-cyanobenzylamine with crotonoyl chloride. To our disappointment, no desired cyclization product such as **6a** could be observed under various conditions for the oxidative generation of amidyl radicals.[7] However, in an attempt to generate the amidyl radicals by conversion of **5a** to the corresponding silyl imidate ester[8] with TMSCl/Et$_3$N followed by oxidation with cerium ammonium nitrate (CAN),[9,10] we were surprised to find that, without the addition of CAN, the cyclized product **6a** was obtained in a low yield (entries 1 and 2, T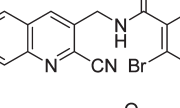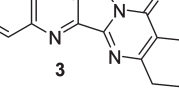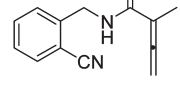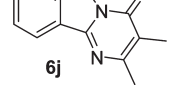able 1). Switching TMSCl to the more reactive TMSOTf led to the formation of **6a** in almost quantitative yield (entry 3, Table 1). Lowering the amount of TMSOTf resulted in a decrease of product yield, indicating that a slight excess of TMSOTf was necessary for the completion of the reaction (entry 5, Table 1). As a comparison, no reaction was observed with the only use of either TMSOTf or Et$_3$N (entries 6 and 7, Table 1).

The above method was then extended to a number of unsaturated amides, and the results are summarized in Table 2. Substrates **5a−h** with various substitution patterns all afforded the expected 2,3-dihydropyrrolopyrimidinone products in high yields. In the case of **5f**, an excellent *cis*-stereoselectivity was observed (entry 6, Table 2). The allene **5j** furnished the pyrrolopyrimidinone **6j** in 85% yield as the isomerization product (entry 10, Table 2). The reaction of bromide **5i** under the optimized conditions proceeded sluggishly. However, when the reaction was performed at refluxing temperature with an increased amount of Et$_3$N (4 equiv), the 16,17,18,19-tetrahydroluotonin A **3** was directly achieved in 80% yield (entry 9, Table 2).

The successful formation of the luotonin A derivative **3** from the bromide **5i** prompted us to extend the above method to the reactions of β-ketoamides. Thus, β-ketoamide **7b** was chosen as the model substrate for the optimization of reaction conditions. After the screening of a few combinations, we were pleased to find that the use of TMSOTf (3 equiv) and Et$_3$N (3 equiv) at room temperature allowed

(8) Mekouar, K.; Genisson, Y.; Leue, S.; Greene, A. E. *J. Org. Chem.* **2000**, *65*, 5212.

(9) For the generation of amidyl radicals from imidate esters, see: (a) Newcomb, M.; Esker, J. L. *Tetrahedron Lett.* **1991**, *32*, 1035. (b) Esker, J. L.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4933.

(10) For the generation of carbon-centered radicals by oxidation of silyl ethers with CAN, see: (a) Sinder, B. B.; Kwon, T. *J. Org. Chem.* **1990**, *55*, 4786. (b) Paolobelli, A. B.; Ruzziconi, R. *J. Org. Chem.* **1996**, *61*, 6434.

**TABLE 2.  Intramolecular Reactions of Nitriles with Unsaturated Amides**



| entry[a] | substrate | | product | yield (%)[b] |
|---|---|---|---|---|
| 1 | **5a** | R = Me | **6a** | 94 |
| 2 | **5b** | R = H | **6b** | 89 |
| 3 | **5c** | R = Ph | **6c** | 92 |
| 4 | **5d** | R = CO$_2$Et | **6d** | 99 |
| 5 | **5e** | | **6e** | 95 |
| 6 | **5f** | | **6f** | 99 |
| 7 | **5g** | | **6g** | 94 |
| 8 | **5h** | | **6h** | 89 |
| 9[c] | **5i** | | **3** | 80 |
| 10 | **5j** | | **6j** | 85 |

[a] Reaction conditions: **5** (0.2 mmol), TMSOTf (55 μL, 0.3 mmol), Et$_3$N (28 μL, 0.2 mmol), CH$_2$Cl$_2$ (4 mL), rt, 6 h. [b] Isolated yield based on **5**. [c] Four equivalents of Et$_3$N was used, and the reaction was performed at refluxing temperature for 10 h.

the production of pyrrolopyrimidinone **6j** in 60% yield. When the reaction was carried out in 1,2-dichloroethane at refluxing temperature, **6j** was achieved in 96% yield. A

## SCHEME 1. Proposed Mechanisms for the Reactions of Nitriles with Amides
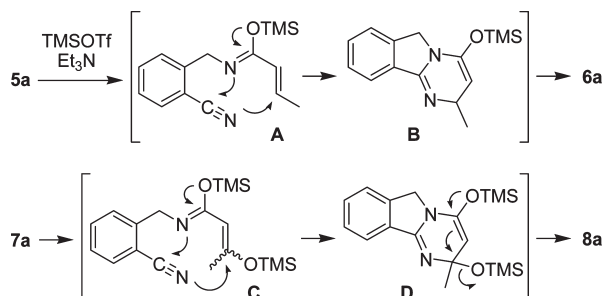


number of β-ketoamides were then examined under the optimized conditions (Table 3). In all cases, clean reactions were observed, and the expected products were isolated in excellent yields (entries 1−7, Table 3). Interestingly, this method was also applicable to malonates such as **7h**, albeit in a lower efficiency (entry 8, Table 3). Thus, the novel [4 + 2] cycloaddition between amides and nitriles allows the highly efficient, one-step construction of the pyrrolopyrimidinone skeleton under mild conditions.

On the basis of the above results, a plausible mechanism could be drawn as outlined in Scheme 1. The amide **5a** was first converted to the silyl imidate ester **A** on reaction with TMSOTf/Et₃N, which then underwent tandem conjugate nucleophilic N-addition to give the cyclized intermediate **B**. The treatment of **B** with water afforded the product **6a**. In the case of β-ketoamide **7a**, the di-*O*-silylation intermediate **C** was formed first, which accounts for the use of excess TMSOTf (3 equiv). The tandem N-addition then took place to give the intermediate **D**, which underwent further β-elimination of TMSOH to furnish **8a**. An alternative mechanism is the Diels−Alder cycloaddition. However, this seems unlikely in our cases because activated nitriles or elevated temperatures are typically required for the Diels−Alder reactions with nitriles as the dienophiles.[11]

To provide further evidence on the proposed mechanism, the α-ketoamide **9** was prepared and subjected to the above optimized conditions in Table 3. The cyclized silyl ester product **10** was isolated in 74% yield (eq 1). This strongly implies that the reactions between nitriles and amides proceed via the nucleophilic N-addition cascade.
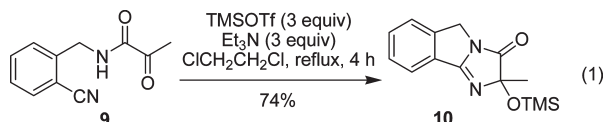


As a summary, the chemistry detailed above has clearly demonstrated that the intramolecular formal [4 + 2] cycloaddition of nitriles with amides serves as a highly efficient and convenient route to pyrrolopyrimidinones. This finding should be of important application in organic synthesis.

## Experimental Section

**2-Methyl-2,3-dihydropyrimido[2,1-*a*]isoindol-4(6*H*)-one (6a). Typical Procedure.** Trimethylsilyl triflate (55 μL, 0.3 mmol)

## TABLE 3. Intramolecular Reactions of Nitriles with β-Ketoamides or α-Ethoxycarbonylamide

| entry[a] | substrate | | product | yield (%)[b] |
|---|---|---|---|---|
| 1 | **7a** | R = H | **8a** | 90 |
| 2 | **7b** | R = Me | **6j** | 96 |
| 3 | **7c** | R = allyl | **8c** | 95 |
| 4 | **7d** | X = CH | **8d** | 92 |
| 5 | **7e** | X = N | **8e** | 89 |
| 6 | **7f** | | **8f** | 96 |
| 7 | **7g** | | **3** | 91 |
| 8 | **7h** | | **8h** | 43 |



[a] Reaction conditions: **7** (0.2 mmol), TMSOTf (110 μL, 0.6 mmol), Et₃N (84 μL, 0.6 mmol), ClCH₂CH₂Cl (4 mL), rt, 4 h, then reflux, 4 h. [b] Isolated yield based on **7**.

was added into the solution of (*E*)-*N*-(2-cyanobenzyl)but-2-enamide (**5a**) (40 mg, 0.2 mmol) and triethylamine (28 μL, 0.2 mmol) in CH₂Cl₂ (4 mL), and the mixture was stirred at rt for 6 h. Saturated aqueous NaHCO₃ solution (5 mL) was then added, and the two layers were separated. The aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL), and the combined organic phase was dried over anhydrous MgSO₄. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel with hexane−ethyl acetate (2:1, v/v) as the eluent to give pure **6a** as a white solid: yield 37.5 mg (94%); mp 154−155 °C (hexane/ethyl acetate); $^1$H NMR (300 MHz, CDCl₃) δ 1.43 (3H, d, *J* = 6.6 Hz), 2.33 (1H, dd, *J* = 10.6, 16.9 Hz), 2.67 (1H, dd, *J* = 5.7, 16.9 Hz), 3.95−4.08 (1H, m), 4.84 (2H, AB, *J* = 16.8 Hz), 7.44−7.49 (2H, m), 7.53−7.59 (1H, m), 7.91 (1H, d, *J* = 8.4 Hz); $^{13}$C NMR (75 MHz, CDCl₃) δ 21.9, 36.9, 48.2, 51.3, 123.2, 123.3, 128.4, 132.0, 132.1, 139.8, 154.2, 168.5; IR (KBr) ν (cm$^{-1}$) 2966, 1697, 1680, 1365, 780, 729; EIMS *m/z* (rel intensity) 200 (M⁺, 24), 185 (100), 157 (25), 131 (15), 116 (24), 89 (18), 77 (5), 63 (7). Anal. Calcd for C₁₂H₁₂N₂O: C, 71.98; H, 6.04; N, 13.99. Found: C, 71.70; H, 5.91; N, 14.15.

**2,3-Dimethylpyrimido[2,1-*a*]isoindol-4(6*H*)-one (6j). Typical Procedure.** Trimethylsilyl triflate (110 μL, 0.6 mmol) was added into the solution of *N*-(2-cyanobenzyl)-2-methyl-3-oxobutanamide (**7b**) (46 mg, 0.2 mmol) and triethylamine (84 μL, 0.6 mmol) in 1,2-dichloroethane (4 mL) at rt, and the mixture was refluxed for 4 h. The resulting solution was cooled to rt, and the same workup procedure outlined in the synthesis of **6a** was followed to give the pure **6j** as a white solid: yield 41 mg (96%); mp 236−237 °C (hexane/ethyl acetate); $^1$H NMR (300 MHz,

(11) (a) Dai, W.; Petersen, J. L.; Wang, K. K. *Org. Lett.* **2006**, *8*, 4665. (b) McClure, C. K.; Link, J. S. *J. Org. Chem.* **2003**, *68*, 8256. (c) Toyota, M.; Komori, C.; Ihara, M. *Heterocycles* **2002**, *56*, 101. (d) Li, W.-T.; Lai, F.-C.; Lee, G.-H.; Peng, S.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **1998**, *120*, 4520.

CDCl$_3$) $\delta$ 2.18 (3H, s), 2.45 (3H, s), 5.05 (2H, s), 7.53−7.63 (3H, m), 8.08 (1H, d, $J$ = 7.2 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 11.3, 22.1, 50.1, 117.6, 123.0, 123.4, 128.7, 131.8, 132.7, 139.4, 155.5, 160.2, 161.4; IR (KBr) $\nu$ (cm$^{-1}$) 2941, 1664, 1655, 1603, 1542, 767; EIMS $m/z$ (rel intensity) 212 (M$^+$, 100), 197 (4), 183 (45), 169 (11), 143 (10), 116 (22), 89 (15), 53 (12). Anal. Calcd for C$_{13}$H$_{12}$N$_2$O: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.53; H, 5.71; N, 13.29.

**Supporting Information Available:** Characterization of **3** and **5−10**. This material is available free of charge via the Internet at http://pubs.acs.org.