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Intramolecular Formal [4 + 2] Cycloaddition of Nitriles with Amides Triggered by TMSOTf/Et_3N: Highly Efficient Construction of Pyrrolo[1,2-*a*]-pyrimidin-4(6*H*)-ones

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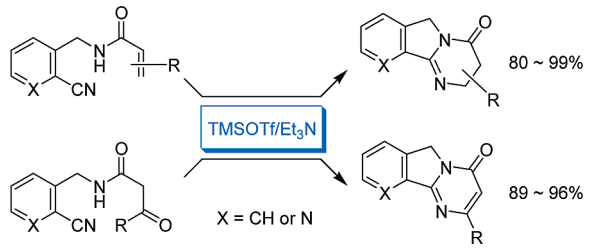
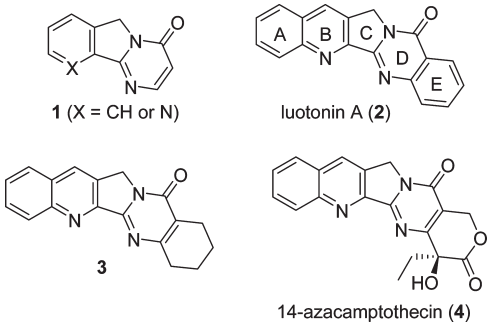
Received May 1, 2009



By treatment with TMSOTf/Et_3N, *N*-(2-cyanoarylmethyl)-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.



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.

DOI: 10.1021/jo900907h Published on Web 06/08/2009

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

entry	conditions	yield[a] (%)
1	TMSCl (1.5 equiv), Et_3N (1.0 equiv), CH_2Cl_2, rt, 17 h	0
2	TMSCl (1.5 equiv), Et_3N (1.0 equiv), $(CH_2Cl)_2$, reflux, 8 h	8
3	TMSOTf (1.5 equiv), Et_3N (1.0 equiv), CH_2Cl_2, rt, 6 h	94
4	TMSOTf (1.5 equiv), Et_3N (2.0 equiv), CH_2Cl_2, rt, 6 h	78
5	TMSOTf (0.8 equiv), Et_3N (0.8 equiv), CH_2Cl_2, rt, 6 h	38
6	TMSOTf (1.5 equiv), CH_2Cl_2, rt, 24 h	0
7	Et_3N (0.5 equiv), CH_2Cl_2, rt, 24 h	0

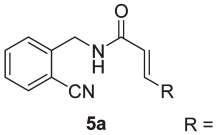
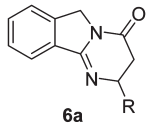
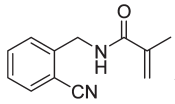
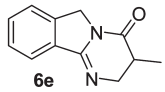
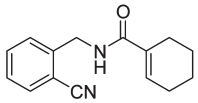
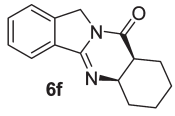
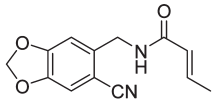
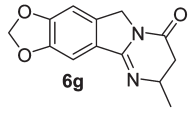
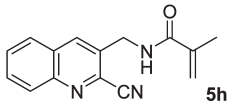
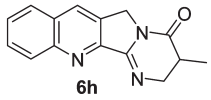
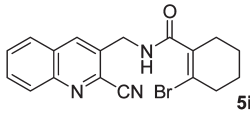
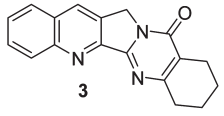
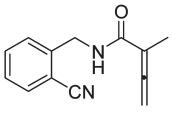
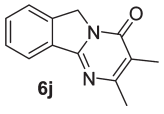
[a] Isolated yield based on **5a**.

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_3N 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, Table 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_3N (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_3N (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_3N (3 equiv) at room temperature allowed

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_2Et	**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_3N (28 μL, 0.2 mmol), CH_2Cl_2 (4 mL), rt, 6 h. [b] Isolated yield based on **5**. [c] Four equivalents of Et_3N was used, and the reaction was performed at refluxing temperature for 10 h.

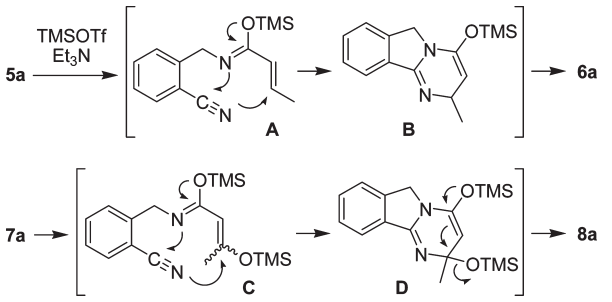
the production of pyrrolopyrimidinone **6j** in 60% yield. When the reaction was carried out in 1,2-dichloroethane at refluxing temperature, **6j** was achieved in 96% yield. A

(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.

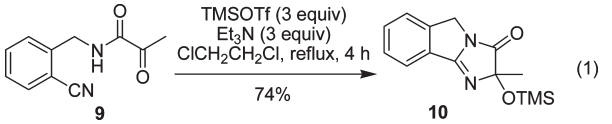
SCHEME 1. Proposed Mechanisms for the Reactions of Nitriles with Amides



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/Et_3N, 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.



(1)

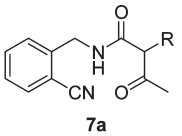
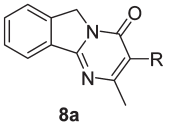
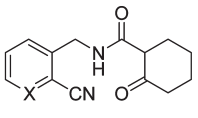
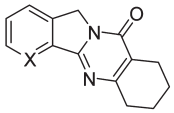
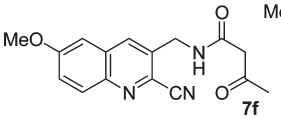
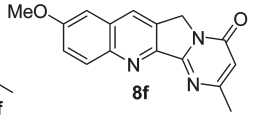
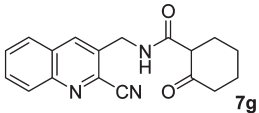
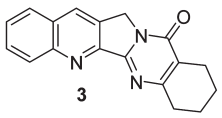
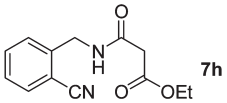
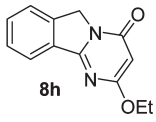
As a summary, the chemistry detailed above has clearly demonstrated that the intramolecular formal [4 + 2] cycloaddition of nitriles with amides serves as a highly efficient and convenient route to pyrrolopyrimidinones. This finding should be of important application in organic synthesis.

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) 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 CH_2Cl_2 (4 mL), and the mixture was stirred at rt for 6 h. Saturated aqueous $NaHCO_3$ solution (5 mL) was then added, and the two layers were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL), and the combined organic phase was dried over anhydrous $MgSO_4$. 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, $CDCl_3$) 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, $CDCl_3$) 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 $C_{12}H_{12}N_2O$: 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,

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), Et_3N (84 μL, 0.6 mmol), $ClCH_2CH_2Cl$ (4 mL), rt, 4 h, then reflux, 4 h. [b] Isolated yield based on **7**.

(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.

$CDCl_3$) δ 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, $CDCl_3$) δ 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) ν (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 $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.53; H, 5.71; N, 13.29.

Acknowledgment. This project was supported by the National NSF of China (Grant Nos. 20672136, 20702060, and 20832006) and by the Shanghai Municipal Committee of Science and Technology (Grant No. 07XD14038).

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