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Palladium-Catalyzed Sequential Cyanation/N-Addition/N-Arylation in One-Pot: Efficient Synthesis of Luotonin A and Its Derivatives

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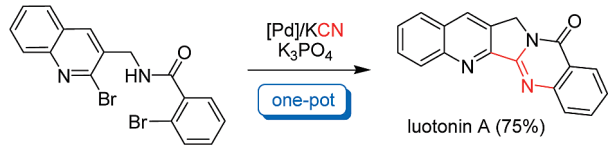
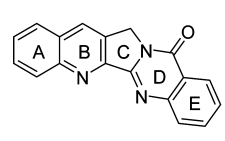
ABSTRACT

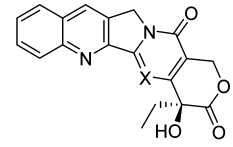


With the catalysis of palladium, a number of 2-bromo-*N*-(2-iodobenzyl)benzamides underwent sequential cyanation/N-addition/N-arylation leading to the efficient construction of isoindolo[1,2-*b*]quinazolin-10(12*H*)-ones in a two-stage, one-pot manner. This method also allowed the convenient synthesis of luotonin A and its derivatives.

A number of alkaloids that incorporate the pyrroloquinazoline chromophore have been isolated from natural sources and display a wide range of biological activities.[1] A typical example is luotonin A (**1**), isolated from a Chinese medicinal plant (*Peganum nigellastrum*) in 1997.[2] Luotonin A is a human DNA topoisomerase I poison and exhibits potent cytotoxicity against P-388 cells.[2,3] These important biological activities have attracted considerable attention on the synthesis of luotonin A and its derivatives.[4,5] Although luotonin A is not potent enough to be a drug candidate for cancer chemotherapy, it serves as a good lead compound, and modifications on the A, B, and E rings of luotonin A have been reported.[5b,6] More recently, Hecht and co-workers have discovered that the water-soluble 14-azacamptothecin (**2a**), a hybrid between luotonin A and the naturally occurring antitumor agent camptothecin (**2b**), is nearly as potent as camptothecin in stabilizing the covalent binary complex formed between human topoisomerase I and DNA.[7]



luotonin A (**1**)



14-azacamptothecin (**2a**, X = N)
camptothecin (**2b**, X = CH)

The anticancer activity of luotonin A and 14-azacamptothecin encourages the further identification of more potent analogues. Hence, methods for the efficient, general, and rapid assembly of the luotonin A skeleton are certainly highly desirable. Curran et al. nicely introduced the synthesis of luotonin A and analogues by cascade radical annulations of

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(1) For a review, see: Mhaske, S. B.; Argade, N. P. *Tetrahedron* **2006**, *62*, 9787.
(2) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1997**, *46*, 541.
(3) Cagir, A.; Jones, S. H.; Gao, R.; Eisenhauer, B. M.; Hecht, S. M. *J. Am. Chem. Soc.* **2003**, *125*, 13628.
(4) For a review on the synthesis of luotonin A, see: Ma, Z.; Hano, Y.; Nomura, T. *Heterocycles* **2005**, *65*, 2203.

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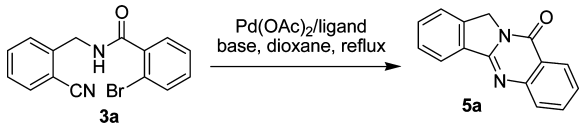
Table 1. Optimization of the Synthesis of **5a** from **3a**



entry[a]	ligand[b]	base	time (h)	yield (%)[c]
1	PPh_3	Cs_2CO_3	24	trace
2	BINAP	Cs_2CO_3	24	4
3	DPEphos	Cs_2CO_3	24	27
4	dppe	Cs_2CO_3	24	6
5	dppp	Cs_2CO_3	24	11
6	dppb	Cs_2CO_3	24	10
7	dppf	Cs_2CO_3	2	76
8	dppf	K_2CO_3	2	91
9	dppf	K_3PO_4	2	94
10[d]	**dppf**	**K_3PO_4**	**2**	**96**
11	dppf	none	24	0
12	none	K_3PO_4	24	0

[a] Reaction conditions: **3a** (0.2 mmol), $Pd(OAc)_2$ (0.02 mmol), ligand (0.04 mmol), base (0.4 mmol), dioxane (2 mL), reflux. [b] BINAP: 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl. DPEphos: bis[(2-diphenylphosphino)phenyl]ether. dppe: 1,2-bis(diphenylphosphino)ethane. dppp: 1,3-bis(diphenylphosphino)propane. dppb: 1,4-bis(diphenylphosphino)butane. dppf: 1,1′-bis(diphenylphosphino)ferrocene. [c] Isolated yield based on **3a**. [d] 5 mol % of $Pd(OAc)_2$ and 10 mol % of dppf were used.

isonitriles, featuring the one-step construction of the B and C rings.[5b] However, their method required the use of highly toxic bis(trimethyltin) as the initiator. Other methods typically suffered from either the low efficiency or the lack of generality.[4−7] Herein we report that the palladium-catalyzed sequential cyanation/N-addition/N-arylation of *N*-((2-bromoquinolin-3-yl)methyl)-2-bromobenzamides allows the convenient and rapid assembly of the luotonin A skeleton in a one-pot procedure.

We recently reported the TMSOTf/Et_3N-triggered intramolecular formal [4 + 2] cycloaddition of nitriles with α,β-unsaturated amides or β-ketoamides leading to the synthesis of luotonin A derivatives with a saturated E ring.[8] However, analogues with an aromatic E ring cannot be accessed by this method. We envisioned that the intramolecular nucleophilic N-addition of an amide to a C≡N bond would generate the imidamide intermediate, which might

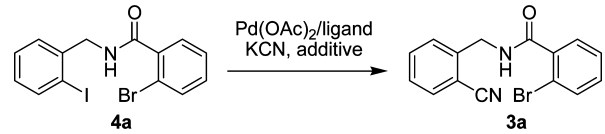
(5) For the latest examples of the synthesis of luotonin A, see: (a) Bowman, W. R.; Cloonan, M. O.; Fletcher, A. J.; Stein, T. *Org. Biomol. Chem.* **2005**, *3*, 1460. (b) Tangirala, R.; Antony, S.; Agama, K.; Pommier, Y.; Curran, D. P. *Synlett* **2005**, 2843. (c) Servais, A.; Azzouz, M.; Lopes, D.; 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.

(6) (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.

(7) (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.

(8) Liu, F.; Li, C. *J. Org. Chem.* **2009**, *74*, ASAP (DOI: 10.1021/jo900907h).

Table 2. $Pd(OAc)_2$-Catalyzed Cyanation of Iodide **4a**



entry[a]	ligand[b]	additive	solvent	yield (%)[c]
1	PPh_3	CuI	THF	0
2	BINAP	CuI	THF	0
3	DPEphos	CuI	THF	0
4	dppf	CuI	THF	0
5	PPh_3	–	THF	trace
6	dppb	–	THF	16
7	dppe	–	THF	24
8	dppf	–	THF	19
9	DPEphos	–	THF	60
10	**DPEphos**	–	**dioxane**	**86**

[a] Reaction conditions: **4a** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), ligand (0.1 mmol), KCN (1.2 mmol), additive (0.1 mmol), solvent (4 mL), reflux, 24 h. [b] See Table 1. [c] Isolated yield based on **4a**.

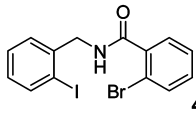
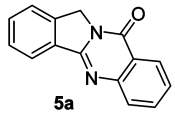
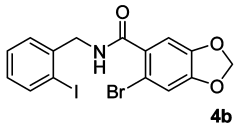
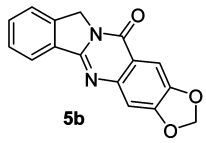
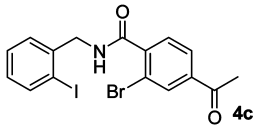
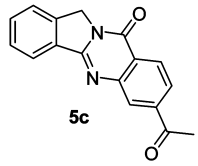
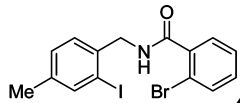
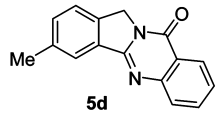
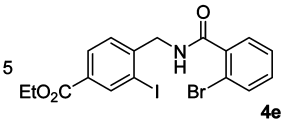
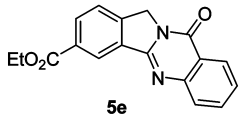
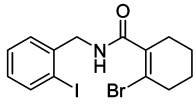
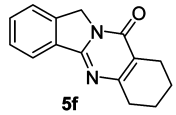
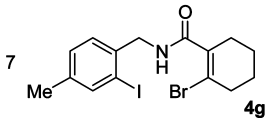
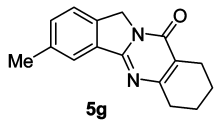
undergo further transition-metal-catalyzed intramolecular N-arylation with an aryl halide to allow the one-step generation of the pyrroloquinazolinone skeleton (the C and D rings of luotonin A). To explore this possibility, 2-bromo-*N*-(2-cyanobenzyl)benzamide (**3a**) was used as the model substrate, which could be synthesized in 55% yield by the cyanation of *N*-(2-iodobenzyl)-2-bromobenzamide (**4a**) with KCN under the catalysis of $Pd(PPh_3)_4$/CuI according to the literature method[9] (also vide infra). A typical experimental procedure[10] for the Sonogashira coupling was initially applied to the cyclization of **3a**: 10 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, and 200 mol % of Cs_2CO_3 in refluxing dioxane. After 24 h, the expected product **5a** was observed in only a trace amount, while most of the starting material remained unchanged (entry 1, Table 1). Switching PPh_3 to a bidentate phosphine ligand resulted in an increased yield of **5a** (entries 2−7, Table 1). To our delight, with the use of 1,1′-bis(diphenylphosphino)ferrocene (dppf) as the ligand, **5a** was obtained in 76% yield within a much shorter period of time (entry 7, Table 1). We next examined the bases. K_2CO_3 or K_3PO_4 showed a better performance than Cs_2CO_3 (entries 7−9, Table 1). Finally, the combination of K_3PO_4 (200 mol %), $Pd(OAc)_2$ (5 mol %), and dppf (10 mol %) allowed the formation of **5a** in almost quantitative yield (entry 10, Table 1). As a comparison, no reaction occurred

(9) Anderson, B. A.; Bell, E. C.; Ginah, F. O.; Harn, N. K.; Pagh, L. M.; Wepsiec, J. P. *J. Org. Chem.* **1998**, *63*, 8224.

(10) Chen, Q.; Li, C. *Organometallics* **2007**, *26*, 223.

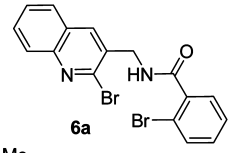
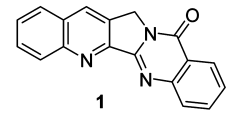
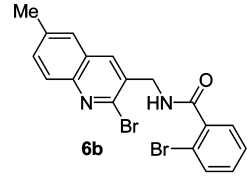
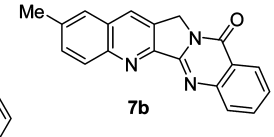
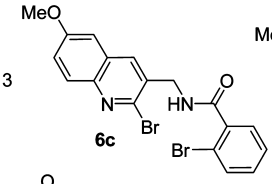
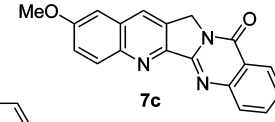
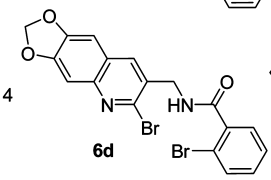
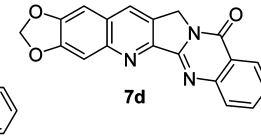
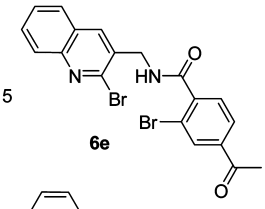
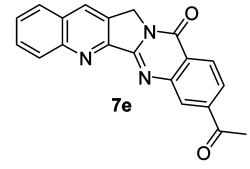
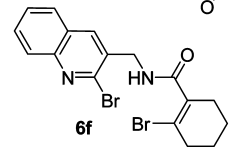
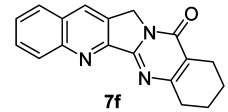
(11) For reviews on palladium-catalyzed N-arylation, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negichi, E.-i., Ed.; Wiley: New York, 2002; Vol. 1, p 1051. (c) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176. (d) Prim, D.; Campagne, J. M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041. (e) Yang, B. Y.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125. (f) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. (g) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (h) Hartwig, J. F. *Acc. Chem. Res.* **1998**, *31*, 852.

Table 3. Synthesis of Isoindolo[1,2-*b*]quinazolin-10(12*H*)-ones

entry	substrate	product	yield (%)[a] (method)[b]
1	 **4a**	 **5a**	91 (A)
2	 **4b**	 **5b**	45 (A) 71 (B)
3	 **4c**	 **5c**	78 (A)
4	 **4d**	 **5d**	90 (A)
5	 **4e**	 **5e**	71 (A)
6	 **4f**	 **5f**	87 (A)
7	 **4g**	 **5g**	55 (A)

[a] Isolated yield based on **4**. [b] See text.

Table 4. Synthesis of Luotonin A and Its Derivatives

entry	substrate	product	yield (%)[a] (method)[b]
1	 **6a**	 **1**	75 (A)
2	 **6b**	 **7b**	79 (A)
3	 **6c**	 **7c**	trace (A) 75 (B)
4	 **6d**	 **7d**	trace (A) 61 (B)
5	 **6e**	 **7e**	64 (A)
6	 **6f**	 **7f**	88 (A)

[a] Isolated yield based on **6**. [b] See text.

without the ligand dppf or the base (entries 11 and 12, Table 1). To the best of our knowledge, this is the first example of N-arylation of imidamides under palladium catalysis.[11,12]

As can be seen above, both the cyanation of aryl iodide **4a** and the intramolecular N-arylation of bromide **3a** were carried out under palladium catalysis. It would be ideal that these two steps could be operated in a one-pot procedure. To achieve this goal, the cyanation step had to be performed in a higher efficiency under the catalysis of $Pd(OAc)_2$.[13,14] Thus, iodide **4a** was chosen as the model for the optimization of reaction conditions (Table 2). Initially we switched the $Pd(PPh_3)_4$/CuI catalyst system to the $Pd(OAc)_2/PPh_3$/CuI combination. However, no reaction occurred (entry 1, Table 2). Changing PPh_3 to a diphosphine ligand did not help (entries 2−4, Table 2). On the other hand, when the cocatalyst CuI was removed out of the catalyst system, the formation of the product **3a** could be observed in variable amounts, depending on the types of ligands used (entries 5−9, Table 2). Among the diphosphine ligands screened, bis[(2-diphenylphosphino)phenyl]ether (DPEphos) offered the best result (entry 9, Table 2). When the reaction of **4a**

(12) For Pd- or Cu-catalyzed N-arylation of amidines, see: (a) Brain, C. T.; Brunton, S. A. *Tetrahedron Lett.* **2002**, *43*, 1893. (b) Brain, C. T.; Steer, J. T. *J. Org. Chem.* **2003**, *68*, 6814. (c) Brasche, G.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1932. (d) Liu, X.; Fu, H.; Jiang, Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 348. (e) Deng, X.; McAllister, H.; Mani, N. S. *J. Org. Chem.* **2009**, *74*, ASAP (DOI: 10.1021/jo900912h).

(13) For reviews on the cyanation of aryl halides, see: (a) Ellis, G. P.; Romney-Alexander, T. M. *Chem. Rev.* **1987**, *87*, 779. (b) Sundermeier, M.; Zapf, A.; Beller, M. *Eur. J. Inorg. Chem.* **2003**, 3513.

(14) For examples of the $Pd(OAc)_2$-catalyzed cyanation of aryl halides, see: (a) Schareina, T.; Zapf, A.; Magerlein, W.; Muller, N.; Beller, M. *Tetrahedron Lett.* **2007**, *48*, 1087. (b) Weissman, S. A.; Zewge, D.; Chen, C. *J. Org. Chem.* **2005**, *70*, 1508. (c) Schareina, T.; Zapf, A.; Beller, M. *J. Organomet. Chem.* **2004**, *689*, 4576. (d) Schareina, T.; Zapf, A.; Beller, M. *Chem. Commun.* **2004**, 1388. (e) Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 1661. (f) Sundermeier, M.; Zapf, A.; Mutyala, S.; Baumann, W.; Sans, J.; Weiss, S.; Beller, M. *Chem.−Eur. J.* **2003**, *9*, 1828. (g) Sundermeier, M.; Zapf, A.; Beller, M.; Sans, J. *Tetrahedron Lett.* **2001**, *42*, 6707.

with DPEphos as the ligand was performed at a higher temperature (dioxane, reflux), **3a** was achieved in 86% isolated yield (entry 10, Table 2).

We next tried to operate the two reactions in a two-stage, one-pot manner. The following two methods were designed for this purpose. In Method A, the cyanation of the iodide substrate was performed first under the optimized conditions (5 mol % of $Pd(OAc)_2$, 10 mol % of DPEphos, dioxane, reflux, 24 h). The second ligand dppf (10 mol %) and the base K_2CO_3 (200 mol %) were then directly added into the resulting mixture, and the solution was refluxed for another 2 h. In Method B, the same procedure as Method A was followed except that, in the second stage, a second portion of 5 mol % of $Pd(OAc)_2$ was introduced into the reaction mixture along with the addition of dppf and K_2CO_3. To our satisfaction, the final product **5a** was obtained in 91% isolated yield via Method A. Apparently, the presence of DPEphos did not show a significant influence on the N-arylation in the second step.

We then set out to explore the scope and limitation of the above two methods. As can be seen in Table 3, the expected cyclization products **5** were achieved in good to excellent yields directly from the iodides **4**. Functional groups such as −OR, −COMe, and $-CO_2Et$ were well tolerated (entries 2, 3, and 5, Table 3). The sequential cyanation/N-addition/N-alkenylation also proceeded smoothly as evidenced by the reactions of **4f** and **4g**. With the use of Method A, satisfactory results could be obtained in most cases, indicating the high efficiency of the Pd-based catalyst system. The only exception was observed in the reaction of **4b** with a 1,3-dioxolane moiety, in which the product **5b** was isolated in only 45% yield via Method A due to the incomplete N-arylation. However, when Method B was applied, **5b** was obtained in 71% yield.

The above methods were then applied to the synthesis of luotonin A and its derivatives (Table 4). Instead of the use of aryl iodides in **4**, 2-bromoquinolines **6**, which were easily accessible via conventional methods,[7b,c] were now used as the substrates. We were pleased to find that the desired cyanation occurred chemoselectively in all the cases screened. Further N-addition/N-arylation also proceeded smoothly, furnishing the cyclized products in a one-pot procedure. Luotonin A was thus achieved in 75% yield via Method A. The luotonin A derivatives **7b**−**7e** bearing a substituent in either the A or E ring were also synthesized in satisfactory yields from the corresponding dibromides via Method A or B. Again the N-alkenylation was also successful as shown in the reaction of **6f**.

In conclusion, we have successfully developed a novel strategy for the convenient and efficient preparation of pyrroloquinazolinones via palladium-catalyzed sequential cyanation/intramolecular N-addition/intramolecular N-arylation processes in a one-pot, two-stage manner. This method has then been applied to the synthesis of luotonin A starting from the simple amide **6a**, featuring the one-step construction of the C and D rings. Furthermore, the modifications of both the A and E rings of luotonin A are made easy by this strategy in view of the ready access to the corresponding substituted 2-bromobenzoic acids and (2-bromoquinolin-3-yl)methanamines as well as their fast assembly into the amide substrates. This chemistry should find important application in the further identification of luotonin A analogues with more potent anticancer activity.

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Supporting Information Available: Experimental procedures for the synthesis of **1**, **5**, and **7** and characterizations of **1** and **3**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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