

Synthesis of δ -Carbolines via a Pd-Catalyzed Sequential Reaction from 2-Iodoanilines and *N*-Tosyl-enynamines

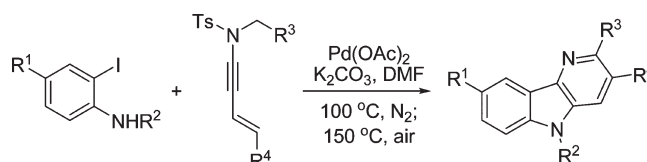
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ABSTRACT



A facile Pd-catalyzed sequential reaction has been developed for the synthesis of δ -carbolines from 2-iodoanilines and *N*-tosyl-enynamines. This protocol involves Larock heteroannulation/elimination/electrocyclization/oxidative aromatization cascade sequences and allows access to multisubstituted δ -carbolines in moderate to good yields.

Pyrido[*x,y-b*]indoles, commonly known as carbolines, are not only the fundamental motif found in various natural alkaloids but also the key structural units for pharmaceutical compounds.¹ Thus the synthesis of carbolines has attracted considerable attention and many methods have been established for their synthesis, such as Pd-catalyzed intramolecular

arylation of arylaminopyridines,² [2 + 2 + 2] cycloaddition of *o,N*-dialkynyl-*N*-tosylanilides and nitriles,³ and photostimulated cyclization of anilinothalopyridines.⁴

Compared with α -, β -, and γ -carbolines, few methods are described for the synthesis of δ -carbolines.⁵ Therefore it is important to develop direct and efficient strategies that afford δ -carboline derivatives.

(1) (a) Takeuchi, T.; Oishi, S.; Watanabe, T.; Ohno, H.; Sawada, J.; Matsuno, K.; Asai, A.; Asada, N.; Kitaura, K.; Fujii, N. *J. Med. Chem.* **2011**, *54*, 4839. (b) Ishiyama, H.; Ohshita, K.; Abe, T.; Nakata, H.; Kobayashi, J. *Bioorg. Med. Chem.* **2008**, *16*, 3825. (c) Mazu, T. K.; Etukala, J. R.; Jacob, M. R.; Khan, S. I.; Walker, L. A.; Ablordepey, S. Y. *Eur. J. Med. Chem.* **2011**, *46*, 2378. (d) Arzel, E.; Rocca, P.; Grellier, P.; Labaëid, M.; Frappier, F.; Guéritte, F.; Gaspard, C.; Marsais, F.; Godard, A.; Quéguiner, G. *J. Med. Chem.* **2001**, *44*, 949.

(2) (a) Sako, K.; Aoyama, H.; Sato, S.; Hashimoto, Y.; Baba, M. *Bioorg. Med. Chem.* **2008**, *16*, 3780. (b) Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1505.

(3) (a) Dassonneville, B.; Witulski, B.; Detert, H. *Eur. J. Org. Chem.* **2011**, 2836. (b) Nissen, F.; Detert, H. *Eur. J. Org. Chem.* **2011**, 2845.

(4) (a) Dhanabal, T.; Sangeetha, R.; Mohan, P. S. *Tetrahedron* **2006**, *62*, 6258. (b) Laha, J. K.; Barolo, S. M.; Rossi, R. A.; Cuny, G. D. *J. Org. Chem.* **2011**, *76*, 6421.

(5) (a) Rocca, P.; Cochenec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1993**, *58*, 7832. (b) Yang, C.; Tai, H.; Sun, P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2843. (c) Peng, H.; Chen, X.; Chen, Y.; He, Q.; Xie, Y.; Yang, C. *Tetrahedron* **2011**, *67*, 5725. (d) Sharma, S. K.; Mandadapu, A. K.; Saifuddin, M.; Gupta, S.; Agarwal, P. K.; Mandwal, A. K.; Gauniyal, H. M.; Kundu, B. *Tetrahedron Lett.* **2010**, *51*, 6022.

(6) (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2001**, *3*, 3297. (c) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 153. (d) Gao, G. L.; Niu, Y. N.; Yan, Z. Y.; Wang, H. L.; Wang, G. W.; Shaikat, A.; Liang, Y. M. *J. Org. Chem.* **2010**, *75*, 1305. (e) Ali, S.; Zhu, H.; Xia, X.; Ji, K.; Yang, Y.; Song, X.; Liang, Y. *Org. Lett.* **2011**, *13*, 2598. (f) Zhou, H.; Xing, Y.; Yao, J.; Chen, J. *Org. Lett.* **2010**, *12*, 3674. (g) Zhou, H.; Xie, Y.; Ren, L.; Su, R. *Org. Lett.* **2010**, *12*, 356.

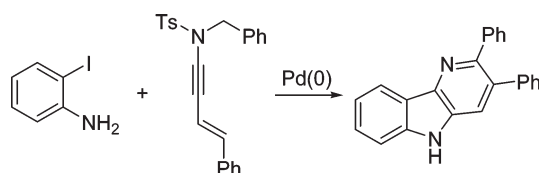
(7) (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840.

(8) (a) Dunetz, J. R.; Danheiser, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 5776. (b) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426. (c) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slater, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047. (d) Yao, P.-Y.; Zhang, Y.; Hsung, R.; Zhao, K. *Org. Lett.* **2008**, *10*, 4275. (e) Dooleweerd, K.; Ruhland, T.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 221. (f) Witulski, B.; Alayrac, C.; Tevzadze-Saefel, L. *Angew. Chem., Int. Ed.* **2003**, *42*, 4257. (g) Kramer, S.; Dooleweerd, K.; Lindhardt, A. T.; Rottländer, M.; Skrydstrup, T. *Org. Lett.* **2009**, *11*, 4208.

Pd-catalyzed sequential reaction of functionalized alkynes represents an elegant and efficient way to construct complex and valuable molecules.⁶ In the past 15 years, ynamides, a special class of functionalized alkynes, have emerged as important synthons in modern organic synthesis.⁷ Many nitrogen heterocycles including natural alkaloids, such as indoles,⁸ pyridines,⁹ lennoxamine,¹⁰ and antiostatins A₁,¹¹ were successfully synthesized from ynamides.

In our continuous efforts to develop novel and efficient methodologies for the synthesis of heterocyclic compounds,¹² we were recently interested in Pd-catalyzed sequential reactions of ynamides. In the course of the study for the synthesis of aminoindoles from 2-iodoanilines and ynamides via Larock reaction,¹³ we found an interesting product δ -carboline (Scheme 1).

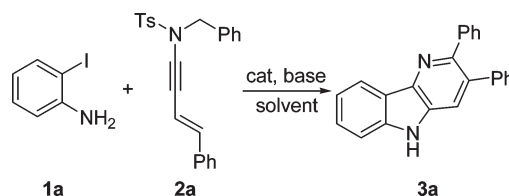
Scheme 1



Considering the formation of the two heterocyclic rings in one step and ready availability of the starting material, we anticipate that this reaction might be an efficient route to construct δ -carboline. Here in we report this novel Pd-catalyzed sequential reaction.

Initial studies focused on the reaction of 2-iodoaniline **1a** with *N*-tosyl-enynamine **2a** under the conditions of a Larock reaction.^{13a} The δ -carboline product **3a** was isolated in 60% yield (Table 1, entry 1). Further studies showed that additive LiCl was not necessary in this reaction (entry 2). Addition of 1.5 equiv of

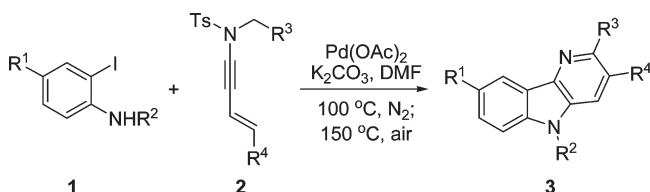
Table 1. Optimization of the Reaction Conditions^a



entry	catalyst	base	solvent	yield of 3a (%)
1 ^b	Pd(OAc) ₂	K ₂ CO ₃	DMF	60
2	Pd(OAc) ₂	K ₂ CO ₃	DMF	74
3 ^c	Pd(OAc) ₂	K ₂ CO ₃	DMF	76
4	PdCl ₂ (PPh ₃) ₂	K ₂ CO ₃	DMF	35
5	PdCl ₂	K ₂ CO ₃	DMF	51
6	Pd(OAc) ₂	CS ₂ CO ₃	DMF	48
7	Pd(OAc) ₂	Na ₂ CO ₃	DMF	27
8	Pd(OAc) ₂	KOAc	DMF	70
9	Pd(OAc) ₂	K ₂ CO ₃	DMA	56
10	Pd(OAc) ₂	K ₂ CO ₃	DMSO	64

^a Unless otherwise specified, the reaction was carried out using **1a** (0.5 mmol), **2a** (0.5 mmol), catalyst (0.025 mmol), and base (2.5 mmol) in solvent (10 mL) at 100 °C under N₂ for 20 h and then 150 °C under air for 6 h. ^b 0.5 mmol of LiCl was added. ^c 0.75 mmol of **2a** was added.

Table 2. Synthesis of δ -Carbolines **3**^a



entry	substrate						yield of 3 (%)
	1	R ¹	R ²	2	R ³	R ⁴	
1	1a	H	H	2a	Ph	Ph	74 (3a)
2	1b	H	Me	2a	Ph	Ph	66 (3b)
3	1c	H	Bn	2a	Ph	Ph	70 (3c)
4	1d	Me	Bn	2a	Ph	Ph	72 (3d)
5	1e	Cl	Bn	2a	Ph	Ph	43 (3e)
6	1c	H	Bn	2b	4-MeC ₆ H ₄	Ph	69 (3f)
7	1c	H	Bn	2c	4-MeOC ₆ H ₄	Ph	76 (3g)
8	1c	H	Bn	2d	4-FC ₆ H ₄	Ph	60 (3h)
9 ^b	1a	H	H	2e	Et	Ph	29 (3i)
10	1c	H	Bn	2f	Ph	4-MeC ₆ H ₄	65 (3j)
11	1c	H	Bn	2g	Ph	3-ClC ₆ H ₄	58 (3k)

^a Unless otherwise specified, the reaction was carried out using **1** (0.5 mmol), **2** (0.5 mmol), Pd(OAc)₂ (0.025 mmol), and K₂CO₃ (2.5 mmol) in DMF (10 mL) at 100 °C under N₂ and then 150 °C under air. ^b The reaction was carried out at 100 °C.

ynamide **2a** gave no significant improvement in the yield (entry 3). Pd(OAc)₂ proved to be the most suitable

(9) (a) Movassaghi, M.; Hill, M. D.; Ahmad, O. *J. Am. Chem. Soc.* **2007**, *129*, 10096. (b) Garcia, P.; Moulin, S.; Miclo, Y.; Leboeuf, D.; Gandon, V.; Aubert, C.; Malacria, M. *Chem.—Eur. J.* **2009**, *15*, 2129. (c) Tanaka, R.; Yuza, A.; Watai, Y.; Suzuki, D.; Takayama, Y.; Sato, F.; Urabe, H. *J. Am. Chem. Soc.* **2005**, *127*, 7774. (d) Garcia, P.; Evanno, Y.; George, P.; Sevrin, M.; Ricci, G.; Malacria, M.; Aubert, C.; Gandon, V. *Org. Lett.* **2011**, *13*, 2030.

(10) (a) Couty, S.; Liegault, B.; Meyer, C.; Cossy, J. *Tetrahedron* **2006**, *62*, 3882. (b) Couty, S.; Meyer, C.; Cossy, J. *Tetrahedron Lett.* **2006**, *47*, 767.

(11) Alayrac, C.; Schollmeyer, D.; Witulski, B. *Chem. Commun.* **2009**, 1464.

(12) (a) Cao, J.; Yang, X.; Hua, X.; Deng, Y.; Lai, G. *Org. Lett.* **2011**, *13*, 478. (b) Cao, J.; Huang, X.; Wu, L. *J. Org. Chem.* **2011**, *76*, 1440. (c) Cao, J.; Huang, X. *Org. Lett.* **2010**, *12*, 5048. (d) Cao, J.; Huang, X. *J. Comb. Chem.* **2008**, *10*, 526. (e) Cao, J.; Huang, X. *J. Comb. Chem.* **2010**, *12*, 1.

(13) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

(14) *N*-Tosyl-enynamines were easily prepared according to Evano's method: Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381.

catalyst (entries 2, 4–5) while K_2CO_3 was the best base (entries 2, 6–8) for this reaction. Other common solvents such as DMA and DMSO were effective as well, although lower yields were obtained (entries 2, 9–10). Thus the following reaction conditions were chosen as optimum for all subsequent reactions: 0.5 mmol of **1**, 0.5 mmol of **2**, 0.025 mmol of $\text{Pd}(\text{OAc})_2$, and 2.5 mmol of K_2CO_3 in DMF were stirred at 100 °C under N_2 and then 150 °C under air.

Under the optimized conditions, the scope of this Pd-catalyzed sequential reaction was further investigated, as shown in Table 2. The reaction was successful for various 2-iodoanilines (Table 2, entries 1–5). R^3 and R^4 groups of ynamides **2** can be a substituted phenyl group with either an electron-donating or -withdrawing group (entries 5–8, 10–11). Furthermore, the reaction was also successful when R^3 was alkyl, although the yield was lower (entry 9). However the reaction failed to give the desired product when R^4 was alkyl. The structures of these products were confirmed with the help of spectral data. In addition, we were able to obtain single crystals of **3a**, which unambiguously confirmed the proposed structure via X-ray diffraction study¹⁵ (Figure 1).

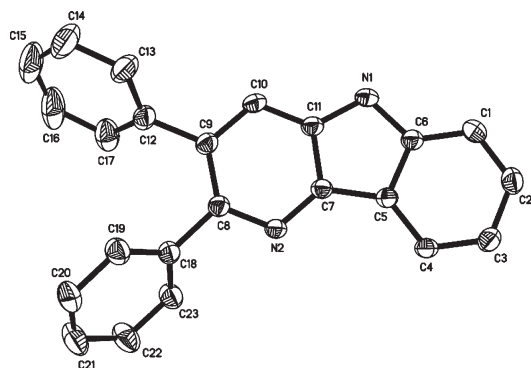
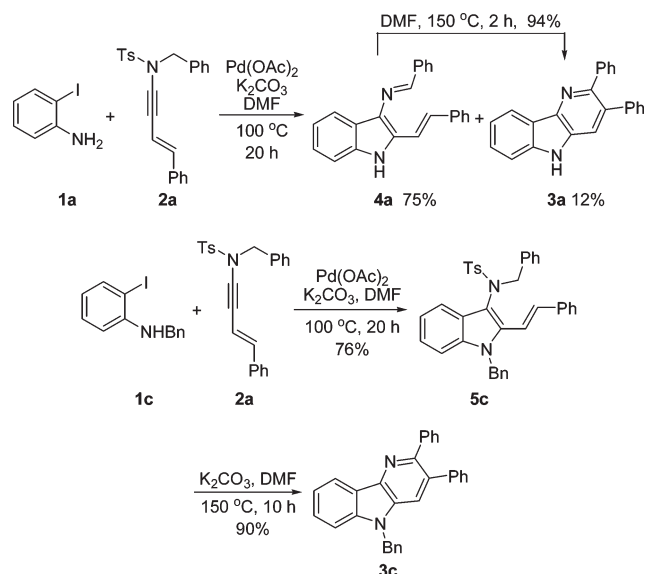


Figure 1. ORTEP representation of **3a**.

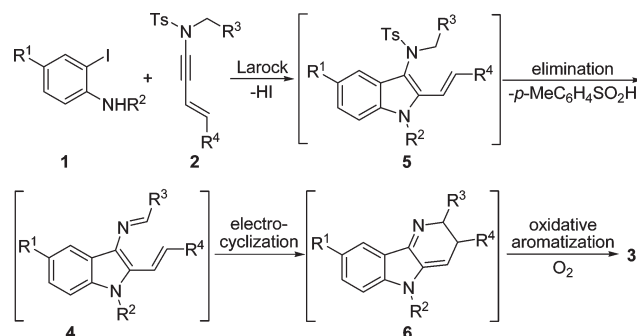
To have more insight into the reaction mechanism, we conducted several control experiments (Scheme 2). The reaction of **1a** and **2a** under the standard conditions was stopped at 20 h, and imine **4a** and δ -carboline **3a** were isolated in 75% and 12% yields, respectively. Further investigation demonstrated that the conversion from **4a** to **3a** only required simply heating at higher temperature. Interestingly, the reaction of *N*-benzyl-2-iodoaniline **1c** and **2a** under the same conditions only gave sulfonamide **5c** as the sole product. However in the presence of K_2CO_3 , **5c** was smoothly converted to the corresponding δ -carboline **3c** at 150 °C in high yield.

Scheme 2



Since the above intermediates were isolated, the following plausible mechanism was proposed for this reaction as shown in Scheme 3: (i) the Larock heteroannulation reaction of 2-iodoaniline **1** and *N*-tosyl-ynamine **2** affords the intermediate sulfonamide **5**; (ii) subsequently, elimination of a molecule of 4-methylbenzenesulfonic acid gives the imine **4**; (iii) that reaction is followed by an electrocyclization reaction to form tricyclic intermediate **6**; (iv) finally, oxidative aromatization by air gives the final product δ -carboline **3**.

Scheme 3



In summary, we have described an interesting Pd-catalyzed sequential reaction for the synthesis of δ -carboline derivatives from 2-iodoanilines and *N*-tosyl-ynamines. The control experiments demonstrate that the protocol consists of Larock heteroannulation, elimination, electrocyclization, and oxidative aromatization, leading to an efficient method to construct δ -carboline derivatives.

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Supporting Information Available. Spectroscopic data for all new compounds. X-ray crystal data for **3a**. Detailed experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.