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Synthesis of Annulated γ-Carbolines by Palladium-Catalyzed Intramolecular Iminoannulation

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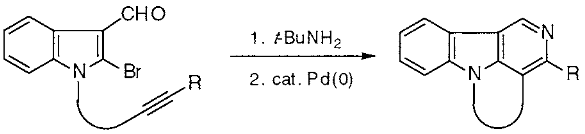
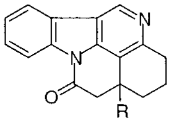
ABSTRACT

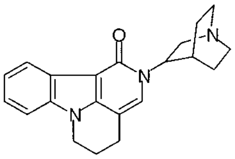


A variety of N-substituted 2-bromo-1*H*-indole-3-carboxaldehydes incorporating an alkyne-containing tether on the indole nitrogen have been converted to the corresponding *tert*-butylimines, which have been subjected to palladium-catalyzed intramolecular iminoannulation, affording various annulated γ-carbolines in excellent yields.

Pyrido[4,3-*b*]-5*H*-indoles, commonly known as γ-carbolines, which are condensed analogues of the ellipticine/olivacine anticancer agents, have been studied extensively because of their potential biological and pharmaceutical importance.[1] However, there are relatively few synthetic studies of γ-carboline derivatives having wide scope and generality,[2] and the synthesis of new alkaloid derivatives of γ-carboline with an additional ring fused across the 4- and 5-positions is rare.[3] Two closely related examples of this type of heteropolycyclic system having interesting biological activity are the pentacyclic γ-carboline **1**, which is a cardiovascular agent,[4] and the indolonaphthyridone **2**, which acts as a conformationally restricted 5-HT$_3$ receptor antagonist.[5]



1 R = Me, Et



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Annulation processes have proven to be very useful in organic synthesis due to the ease with which a wide variety of complicated carbocycles and heterocarbocycles can be rapidly constructed. In our own laboratories, it has been demonstrated that palladium-catalyzed annulation methods[6] can be effectively employed for the synthesis of indoles,[7] isoindolo[2,1-*a*]indoles,[8] benzofurans,[9] benzopyrans,[9] isocoumarins,[9,10] α-pyrones,[10,11] indenones,[12] pyridines,[13] isoquinolines,[13] and polycyclic aromatic hydrocarbons.[14] How-

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[4] Yanagisawa, H.; Shimoji, Y.; Hashimoto, T. Jpn. Kokai Tokkyo Koho JP 05310738, 1993, Heisei; *Chem. Abstr.* **1994**, *120*, 245056.

[5] Clark, R. D.; Miller, A. B.; Berger, J.; Repke, D. B.; Weinhardt, K. K.; Kowalczyk, B. A.; Eglen, R. M.; Bonhaus, D. W.; Lee, C.-H.; Michel, A. D.; Smith, W. L.; Wong, E. H. F. *J. Med. Chem.* **1993**, *36*, 2645.

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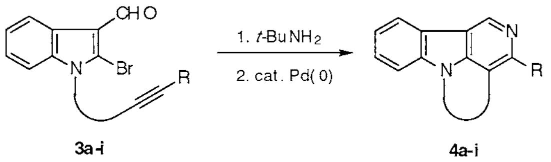
ever, palladium-catalyzed intramolecular annulation has not been well explored mainly because of the difficulty of assembling a halide, a carbon−carbon triple bond, and other necessary elements into the appropriate positions into a single molecule.[15]

Recently, we have developed a general synthesis of 3,4-disubstituted β- and γ-carbolines by the palladium-catalyzed iminoannulation of internal acetylenes.[16] While certain β- and γ-carbolines could be prepared in good to excellent yields, the regioselectivity of the reaction was too sensitive to the nature of the internal acetylenes to be of broad applicability.[16] Alternatively, by readily incorporating an alkyne-containing tether onto the indole nitrogen, subsequent palladium-catalyzed intramolecular iminoannulation should enable regioselective construction of two rings in a single step and provide the well-recognized entropic advantage of promoting stubborn reactions. Our own interest in carboline synthesis therefore prompted us to examine the synthesis of a variety of annulated γ-carbolines. Herein, we report the successful synthesis of various annulated γ-carbolines by palladium-catalyzed intramolecular iminoannulation (Scheme 1).

Scheme 1



The *tert*-butylimine of indole **3a** was first prepared and employed in the palladium-catalyzed intramolecular iminoannulation under the reaction conditions used in our earlier intermolecular γ-carboline synthesis.[16] Considering that an intramolecular reaction might provide an entropic advantage, we decreased the reaction temperature from 125 to 100 °C. We were excited to see that under these reaction conditions, the palladium-catalyzed intramolecular iminoannulation produced a 93% yield of the desired γ-carboline **4a** in only 10 h (Table 1, entry 1). It is noteworthy that transformation of the aldehydes to the corresponding *tert*-butylimines is essentially quantitative, requiring no further purification and characterization of the starting imines used for the subsequent palladium-catalyzed annulation, as we have observed in our previous work.[16,17] Thus, by employing a one-pot protocol, namely imine formation, followed by a palladium-catalyzed intramolecular iminoannulation, we have been able to synthesize a variety of annulated γ-carbolines (Scheme 1). The results of this investigation are summarized in Table 1.

As seen in Table 1, by employing 2-bromo-1*H*-indole-3-carboxaldehydes with a trimethylene tether from the indole nitrogen to the carbon−carbon triple bond, the parent isocanthine skeleton[3a,b] can be readily constructed (entries 1−5). This route allows easy access to a variety of substituted isocanthine derivatives and tolerates various functional groups. For example, tethered indoles **3a**−**e** containing aryl, alkyl, hydroxy, ether, ester, and pyrimidyl functionalities all afforded the desired annulation products **4a**−**e** in excellent yields (entries 1−5).

Interestingly, by employing indole **3f** with a tetramethylene tether, we have been able to isolate an annulated γ-carboline **4f** with a seven-membered ring fused to the 4- and 5-positions in a 90% yield (entry 6). We have also been able to obtain an annulated γ-carboline **4g** with a five-membered ring in a 91% yield, by employing indole **3g** with a dimethylene tether (entry 7). It is worth noting that ring systems similar to carbolines **4f** and **4g** have never been efficiently prepared by either an intramolecular Diels−Alder reaction[18] or electrocyclization of a 1-azatriene,[3c] since those reactions require significant straining of the tether to achieve the necessary transition-state geometry, especially in the case of a five−five ring juncture.

Furthermore, other types of tethers have also proven to be successful in this intramolecular annulation chemistry. For example, both indole **3h** with a tether containing an aryl moiety and indole **3i** with a tether incorporating a cyclopentenyl group afforded the desired annulated γ-carbolines **4h** and **4i** in 88 and 94% yields, respectively (entries 8 and 9).

Unfortunately, all efforts to prepare N-substituted 2-bromo-1*H*-indole-3-carboxaldehydes with an amide linkage have been unsuccessful so far. Therefore, annulated γ-carbolines bearing an amide linkage have yet to be prepared by this protocol.

Interestingly, the palladium-catalyzed intramolecular annulation of aldehyde **3f** itself under the conditions of our earlier indenone synthesis[12] has generated a 48% yield of heterocycle **5a**, which apparently arises from tautomerization of the anticipated less stable heterocycle **5b** (Scheme 2). Similar tautomerization has also been observed in our intermolecular indenone synthesis.[12] Unfortunately, the pal-

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(9) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.

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(14) (a) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.

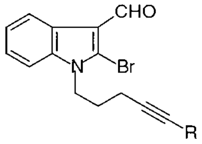
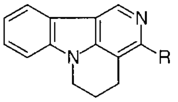
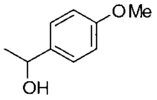
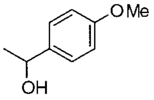
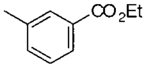
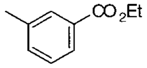
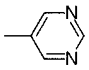
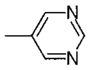
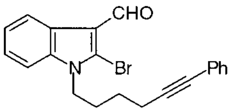
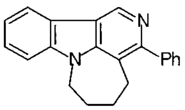
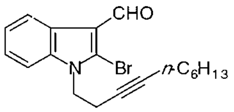
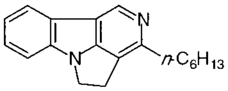
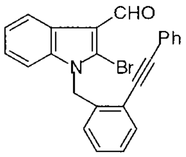
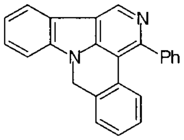
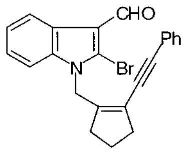
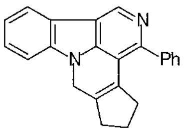
(15) To the best of our knowledge, this is the first example of palladium-catalyzed intramolecular annulation involving a halide, a carbon−carbon triple bond, and a nucleophile in the same molecule. For palladium-catalyzed intramolecular benzoannulations, see: (a) Kawasaki, T.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 2653. (b) Weibel, D.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 1217. (c) Saito, S.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 5042. For other palladium-catalyzed intramolecular annulations, see: (d) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387. (e) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454.

(16) Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083.

(17) Zhang, H.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 1359.

(18) Benson, S. C.; Li, J.-H.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5285.

Table 1. Synthesis of Annulated γ-Carbolines by Palladium-Catalyzed Intramolecular Iminoannulation[a]

entry	aldehyde		annulation time (h)	product		% yield
						
	R			R		
1	Ph	**3a**	10	Ph	**4a**	93
2	n-C_6H_{13}	**3b**	24	n-C_6H_{13}	**4b**	95
3		**3c**	18		**4c**	95
4		**3d**	12		**4d**	93
5		**3e**	40		**4e**	99
6		**3f**	10		**4f**	90
7		**3g**	12		**4g**	91
8		**3h**	24		**4h**	88
9		**3i**	14		**4i**	94

[a] Representative procedure: the aldehyde (0.25 mmol) and *tert*-butylamine (1 mL) were placed in a 2 dram vial. The vial was flushed with Ar and carefully sealed, and the mixture was heated at 100 °C for 8 h. The mixture was cooled, diluted with ether, and dried over anhydrous Na_2SO_4, and the solvent was evaporated. The residue was dissolved in 5 mL of DMF and transferred to a 4 dram vial containing 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, and Na_2CO_3 (0.25 mmol). The mixture was then flushed with Ar and heated at 100 °C for the indicated time.

ladium-catalyzed intramolecular annulation of aldehyde **3f** under the conditions of Yamamoto's indenol synthesis[19] did not afford any significant yield of the desired alcohol or the tautomeric ketone.

We proposed a mechanism for this palladium-catalyzed intramolecular iminoannulation chemistry that is similar to that of our earlier intermolecular iminoannulations.[13,16] Specifically, oxidative addition of the indole bromide to Pd(0) produces an organopalladium intermediate, which then intramolecularly adds across the tethered carbon−carbon triple bond by an exo-dig addition, producing a vinylic palladium intermediate, which then reacts with the neighboring imine substituent to form a seven-membered palladacyclic immonium ion salt. Subsequent reductive elimination produces a *tert*-butylcarbolinium salt and regenerates Pd(0). As previously suggested by Heck,[20] the *tert*-butyl group apparently fragments to relieve the strain resulting from interaction with the substituent present on the neighboring carbon.

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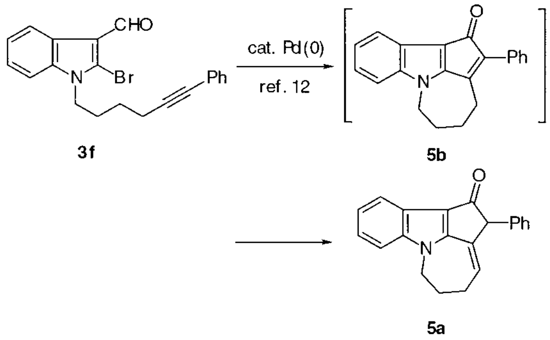
[19] Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089.

[20] (a) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (b) Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3238.

Scheme 2



In conclusion, an efficient synthesis of various annulated γ-carbolines by palladium-catalyzed intramolecular iminoannulation has been developed. A wide variety of functionalized 2-bromo-1*H*-indole-3-carboxaldehydes participate in this process to afford the desired γ-carbolines in excellent yields. This chemistry has also been extended to palladium-catalyzed intramolecular carboannulation, which produces the desired heterocycle in a moderate yield. Further investigation into the scope and limitations of this palladium-catalyzed intramolecular iminoannulation and extensions to other intramolecular annulation chemistry are under way.

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Supporting Information Available: General experimental procedures and spectral data for ketone **5a** and the compounds listed in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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