ORGANIC LETTERS

2002
Vol. 4, No. 18
3035−3038

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

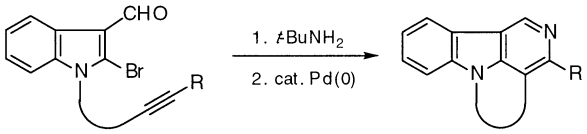
Haiming Zhang and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50011

larock@iastate.edu

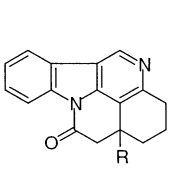
Received May 29, 2002

ABSTRACT

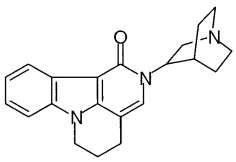


A variety of N-substituted 2-bromo-1*H*-indole-3-carboxaldehydes incorporating an alkyne-containing tether on the indole nitrogen have been converted to the corresponding *tert*-butylimines, which have been subjected to palladium-catalyzed intramolecular iminoannulation, affording various annulated γ-carbolines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



2

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-

(1) (a) Saxton, J. E. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. D., Ed.; Wiley-Interscience: New York, 1994; Vol. 25. (b) Gribble, G. W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 39, Chapter 7. (c) Tan, G. T.; Pezzuto, J. M. In *Chemistry and Toxicology of Diverse Classes of Alkaloids*; Blum, M. S., Ed.; Alaken, Inc.: Fort Collins, CO, 1996; pp 1−119.

(2) (a) Engler, T. A.; Wanner, J. *J. Org. Chem.* **2000**, *65*, 2444. (b) Sakamoto, T.; Numata, A.; Saitoh, H.; Kondo, Y. *Chem. Pharm. Bull.* **1999**, *47*, 1740. (c) Molina, A.; Vaquero, J. J.; Garcia-Navio, J. L.; Alvarez-Builla, J.; de Pascual-Teresa, B.; Gago, F.; Rodrigo, M. M.; Ballesteros, M. *J. Org. Chem.* **1996**, *61*, 5587. (d) Hibino, S.; Sugino, E.; Kuwada, T.; Ogura, N.; Sato, K.; Choshi, T. *J. Org. Chem.* **1992**, *57*, 5917. (e) Hibino, S.; Kano, S.; Mochizuki, N.; Sugino, E. *J. Org. Chem.* **1984**, *49*, 5006. (f) Prikhod'ko, T. A.; Vasilevskii, S. F.; Shvartsberg, M. S. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1984**, *33*, 2383.

(3) (a) Snyder, S. A.; Vosburg, D. A.; Jarvis, M. G.; Markgraf, J. H. *Tetrahedron* **2000**, *56*, 5329. (b) Markgraf, J. H.; Snyder, S. A.; Vosburg, D. A. *Tetrahedron Lett.* **1998**, *39*, 1111. (c) Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447. (d) Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Heterocycles* **1994**, *37*, 697. (e) Shimoji, Y.; Hashimoto, T.; Furukawa, Y.; Yanagisawa, H. *Heterocycles* **1993**, *36*, 123.

(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.

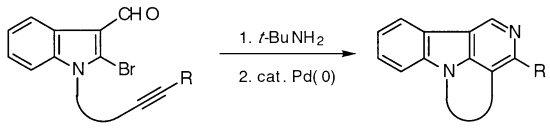
(6) For reviews, see: (a) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111. (b) Larock, R. C. Palladium-Catalyzed Annulation. In *Perspectives in Organopalladium Chemistry for the XXI Century*; Tsuji, J., Ed.; Elsevier Press: Lausanne, Switzerland, 1999; pp 111−124. (c) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435.

10.1021/ol026255u CCC: $22.00
Published on Web 08/15/2002

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



3a-i 4a-i

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-

(7) (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.

(8) (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551. (b) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412.

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

(10) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.

(11) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713.

(12) Larock, R. C.; Doty, M. J.; Cacchi, S. J. *J. Org. Chem.* **1993**, *58*, 4579.

(13) (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (b) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042.

(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.

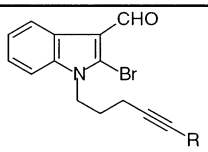
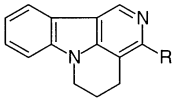
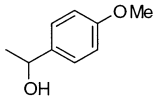
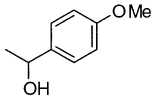
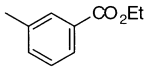
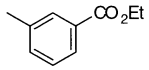
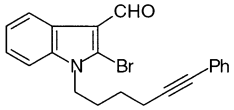
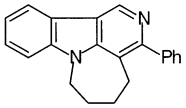
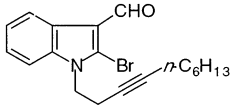
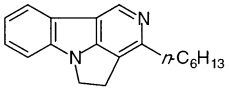
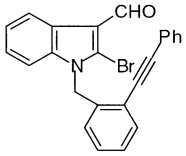
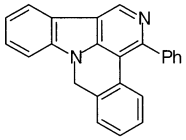
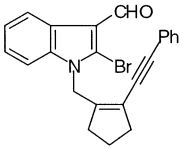
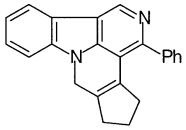
(15) To the best of our knowledge, this is the first example of palladium-catalyzed intramolecular annulation involving a halide, a carbon−carbon triple bond, and a nucleophile in the same molecule. For palladium-catalyzed intramolecular benzoannulations, see: (a) Kawasaki, T.; Saito, S.; Yamamoto, Y. *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.

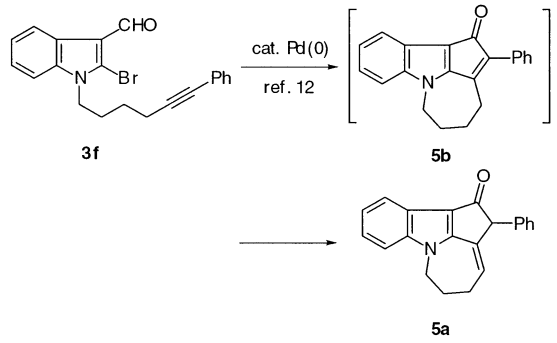
ladium-catalyzed intramolecular annulation of aldehyde **3f** under the conditions of Yamamoto's indenol synthesis[19] did not afford any significant yield of the desired alcohol or the tautomeric ketone.

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.

(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.

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Ltd., for donations of palladium acetate.

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.

OL026255U