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Synthesis of β- and γ-Carbolines by the Palladium-Catalyzed Iminoannulation of Internal Alkynes

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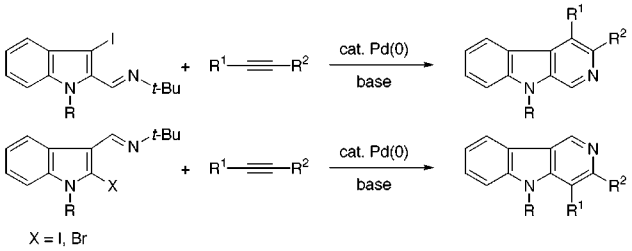
ABSTRACT



A variety of substituted β- and γ-carbolines have been prepared in good to excellent yields by the annulation of internal acetylenes by the *tert*-butylimines of *N*-substituted 3-iodoindole-2-carboxaldehydes and 2-haloindole-3-carboxaldehydes, respectively, in the presence of a palladium catalyst.

Pyrido[3,4-*b*]indoles and pyrido[4,3-*b*]indoles, commonly known as β- and γ-carbolines, respectively, are the structural units for a variety of biologically important alkaloids.[1,2] For example, numerous β-carbolines possess potent and varied CNS and anticancer activity,[1] and γ-carbolines have been studied extensively as antitumor agents.[3] The latter are condensed analogues of the ellipticine/olivacine anticancer agents, and some do indeed display potent activity. The isolation and synthesis of naturally occurring carbolines and the synthesis of β- and γ-carboline derivatives have received considerable attention in the literature[1,2,4] as a result of their biological and pharmaceutical importance.

Annulation processes have proven quite valuble in organic synthesis because of the ease with which a variety of complicated hetero- and carbocycles can be rapidly constructed. In our own laboratories, it has been demonstrated that palladium-catalyzed annulation methodology[5] can be effectively employed for the synthesis of indoles,[6] isoindolo[2,1-*a*]indoles,[7] benzofurans,[8] benzopyrans,[8] isocoumarins,[8,9] α-pyrones,[9,10] indenones,[11] and polycyclic aromatic hydrocarbons.[12]

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(2) γ-Carbolines: (a) Matsukura, N.; Kawachi, T.; Morino, K.; Ohgaki, H.; Sugimura, T.; Takayama, S. *Science* **1981**, *213*, 346. (b) Hibino, S.; Sugino, E.; Ogura, N.; Shintani, Y.; Sato, K. *Heterocycles* **1990**, *30*, 271.

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(5) 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.

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

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

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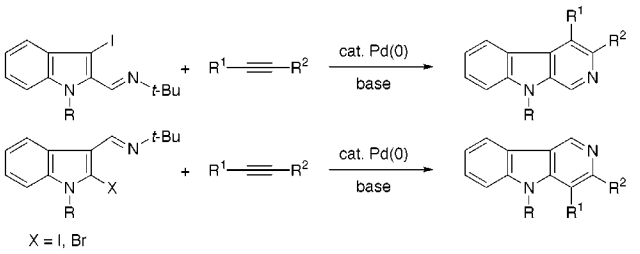
Recently, we have developed a general synthesis of isoquinolines and pyridines by the palladium-catalyzed iminoannulation of internal alkynes.[13] Our interest in extending this type of iminoannulation reaction prompted us to examine the synthesis of a variety of β- and γ-carboline derivatives (Scheme 1). Herein, we wish to report the

Scheme 1



successful application of this palladium-catalyzed annulation chemistry to the synthesis of various β- and γ-carbolines.

Our initial studies focused on the palladium-catalyzed iminoannulation employing the *tert*-butylimine[14] of 1-*H*-3-iodoindole-2-carboxaldehyde (**1**). The reaction of diphenylacetylene and imine **1** was chosen as the model system for optimization of this annulation process. In the early stages of this work, the reaction conditions examined were similar to the conditions employed in our earlier isoquinoline synthesis.[13] For example, the reactions were run with 0.25 mmol of the *tert*-butylimine, 2 equiv of diphenylacetylene, 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, and 1 equiv of Na_2CO_3 as a base in 5 mL of DMF at 100 °C. However, these conditions failed to produce any of the desired β-carboline **2**. Further attempts using several inorganic and pyridine bases also failed to afford **2**. However, when tertiary amines such as NEt_3, *i*-Pr_2NEt, or *n*-Bu_3N were employed, the desired β-carboline **2** was isolated in ca. 50% yield. We have also explored the effect on the reaction yield of other variables, such as the palladium catalyst and the amounts of ligand and base. The optimum reaction conditions thus far developed (conditions A in Table 1) employ 0.25 mmol of imine **1**, 2 equiv of diphenylacetylene, 5 mol % of $Pd(OAc)_2$, 5 mol % of PPh_3, and 1 equiv of *n*-Bu_3N as a base in 5 mL of DMF at 100 °C, which affords a 54% yield of **2** (entry 1, Table 1).

It has been reported[15] that aryl halides and indole can undergo palladium-catalyzed amination to produce *N*-arylindoles. The low yields of carboline observed under many reaction conditions examined may be a direct result of the *N*-arylation of our N−H containing indole by another molecule of starting aryl iodide, although no evidence to support this supposition has been obtained. The easiest way to solve this problem is to employ the *N*-protected imines. 3-Iodo-1-methylindole-2-methylene-*tert*-butylamine (**3**) has therefore been prepared and allowed to react with diphenylacetylene under our optimum conditions (conditions A) for the annulation of diphenylacetylene by imine **1**. As expected, a substantial 76% yield of the desired β-carboline **4** was observed, along with a significant reduction in reaction time from 10 to 4 h (entry 2).

The annulation of several other internal alkynes with imine **3** under conditions A has afforded the desired disubstituted β-carbolines in good to excellent yields (entries 3−5). For example, 4-octyne affords the desired product **5** in a 72% yield and 2-butyne-1,4-diol affords a 96% yield of β-carboline **6**. However, when an unsymmetrical alkyne is employed, two regioisomers with relatively poor regioselectivity are observed. For example, when imine **3** and ethyl 3-phenylpropiolate are employed, the annulation reaction gives two regioisomers **7** and **8** in 58% and 42% yields, respectively (entry 5). The *N*-methoxymethyl-substituted imine **9** has also been employed in the annulation of diphenylacetylene. The desired β-carboline **10** was produced in an 80% yield (entry 6).

Encouraged by our success on β-carboline synthesis, we have investigated the palladium-catalyzed iminoannulation of internal alkynes using 2-iodoindoleimine **11** in order to synthesize substituted γ-carbolines. Unfortunately, conditions A, which have proven quite successful in our β-carboline synthesis failed to provide any of the desired products from the annulation of diphenylacetylene or 4-octyne by imine **11**. However, when the optimum conditions used in our earlier isoquinoline synthesis (conditions B) were employed in the reaction of imine **11** and 4-octyne, the reaction gave the desired γ-carboline **12** in a 78% yield (entry 7). Interestingly, conditions B generate a single regioisomer **13** bearing the more hindered phenyl group in the 4-position when the unsymmetrical alkyne ethyl 3-phenylpropiolate is employed (entry 8). When several other alkynes, including diphenylacetylene, 1-phenylpropyne, 3-phenyl-2-propyn-1-ol, and diethyl acetylenedicarboxylate were employed in this palladium-catalyzed iminoannulation with imine **11**, messy reactions and low yields have been observed in all cases.

To our pleasant surprise, the reaction of the bromoimine **14** with diphenylacetylene under conditions B afforded a 58% yield of the desired product **15** after 96 h (entry 9). When the temperature was increased to 125 °C, the reaction was complete in a much shorter time (18 h) and a 70% yield of the γ-carboline **15** was observed (entry 10).

The palladium-catalyzed iminoannulation of several other internal alkynes by imine **14** under conditions B at 125 °C

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

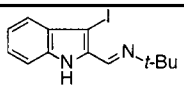
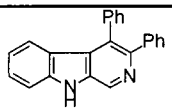
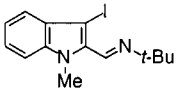
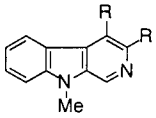
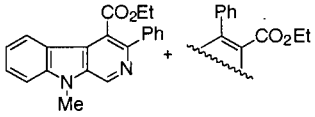
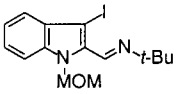
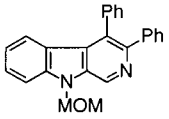
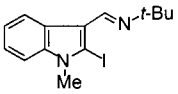
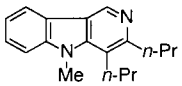
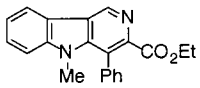
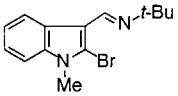
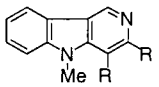
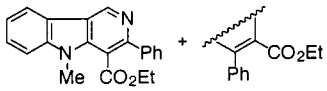
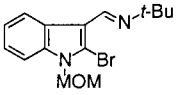
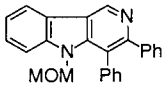
(12) (a) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.

(13) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306.

(14) All of the *tert*-butylimines were prepared by heating a mixture of the corresponding aldehyde and *tert*-butylamine. A representive procedure for preparation of the imines follows. To 3-iodo-1*H*-indole-2-carboxaldehyde (0.81 g, 3.0 mmol) was added *tert*-butylamine (6 mL, 2 mL/mmol). The mixture was flushed with Ar, and the vial was carefully sealed. The reaction mixture was stirred at 100 °C for 24 h, diluted with ether, and dried over anhydrous Na_2SO_4. Removal of the solvent afforded 0.98 g (100%) of the imine as a yellow solid.

(15) (a) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827. (b) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403. (c) Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, *41*, 481.

Table 1. Synthesis of β- and γ-Carbolines by the Palladium-Catalyzed Annulation of Internal Alkynes[a]

entry	imine		alkyne	cond., time (h)	product(s)		% yield
1		**1**	Ph—≡—Ph	A, 10		**2**	54
		**3**	R—≡—R				
2			Ph—≡—Ph	A, 4		**4**	76
3			*n*-Pr—≡—*n*-Pr	A, 2		**5**	72
4			$HOCH_2$—≡—CH_2OH	A, 2		**6**	96
5			Ph—≡—CO_2Et	A, 5		**7+8**	58+42
6		**9**	Ph—≡—Ph	A, 3		**10**	80
7		**11**	*n*-Pr—≡—*n*-Pr	B, 50		**12**	78
8			Ph—≡—CO_2Et	B, 28		**13**	72
		**14**	R—≡—R				
9			Ph—≡—Ph	B, 96		**15**	58
10			Ph—≡—Ph	B[b], 18		**15**	70
11			*n*-Pr—≡—*n*-Pr	B[b], 16		**12**	67
12			$HOCH_2$—≡—CH_2OH	B[b], 20		**16**	65
13			Ph—≡—CO_2Et	B[b], 20		**17+13**	37+63
14		**18**	Ph—≡—Ph	B[b], 72		**19**	70

[a] Representative procedures. Conditions A: 5 mol % $Pd(OAc)_2$, 5 mol % PPh_3, *n*-Bu_3N (0.25 mmol), the acetylene (0.50 mmol), the imine (0.25 mmol), and DMF (5 mL) were placed in a 4-dram vial, and the mixture was heated at 100 °C for the indicated time. Conditions B: 10 mol % PPh_3, Na_2CO_3 as the base (0.25 mmol), all else the same as for conditions A. [b] The reaction was run at 125 °C.

was then examined. Symmetrical alkynes such as 4-octyne and 2-butyne-1,4-diol afforded the desired γ-carbolines in good yields (entries 11 and 12). The unsymmetrical alkyne ethyl 3-phenylpropiolate produced two regioisomers, with the isomer bearing the more hindered phenyl group in the 4-position as the major product (entry 13). Finally, when the *N*-methoxymethyl bromoimine **18** was employed in the annulation of diphenylacetylene, the reaction gave a 70% yield of the desired product **19** (entry 14).

We propose a mechanism for this palladium-catalyzed iminoannulation chemistry, which is similar to our isoquinoline synthesis.[13] Specifically, oxidative addition of the indole halide to Pd(0) produces an organopalladium intermediate, which then inserts the acetylene, producing a vinylic palladium intermediate, which then reacts with the neighboring imine substituent to form a seven-membered palladacyclic ammonium salt. Subsequent reductive elimination produces a *tert*-butylcarbolinium salt and regenerates Pd(0). As previously suggested by Heck,[16] the *tert*-butyl group apparently fragments to relieve the strain resulting from the

(16) (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.

interaction with the substituent present on the neighboring carbon.

In conclusion, an efficient, palladium-catalyzed synthesis of substituted β- and γ-carbolines has been developed. A variety of aryl-, alkyl-, ester-, and hydroxymethyl-substituted acetylenes undergo this process in moderate to excellent yields. When unsymmetrical alkynes are employed, mixtures of regioisomers are observed in most cases. Further investigation into the scope and limitations of this palladium-catalyzed iminoannulation of internal alkynes is under way.

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Supporting Information Available: General experimental procedures and spectral data for 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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