JOC Article

Synthesis of β- and γ-Carbolines by the Palladium/Copper-Catalyzed Coupling and Cyclization of Terminal Acetylenes

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A variety of 3-substituted β- and γ-carbolines have been synthesized from *N*-substituted 3-iodoindole-2-carboxaldehydes and 2-bromoindole-3-carboxaldehydes, respectively. The coupling of these aldehydes with various terminal acetylenes with $PdCl_2(PPh_3)_2$/CuI as the catalyst readily affords the corresponding alkynylindole carboxaldehydes, which have subsequently been converted to the corresponding *tert*-butylimines and cyclized to β- and γ-carbolines by either copper-catalyzed or thermal processes.

Introduction

Palladium-catalyzed annulation processes have recently proven to be a powerful method for the construction of a wide variety of hetero- and carbocycles in our own laboratories.[1] In addition, the transition metal-mediated,[2] base-promoted,[3] electrophile-induced,[4] and thermal[5] cyclization of alkynes, which possess a nucleophile in close proximity to the carbon−carbon triple bond, have also been shown to be very effective for the synthesis of a wide variety of hetero- and carbocycles. In our own laboratories, a variety of isoquinolines, pyridines, and naphthyridines have been successfully synthesized by the copper-catalyzed,[6] the palladium-catalyzed,[7] and the electrophile-induced[8] cyclization of alkynes having a *tert*-butylimino group in close proximity to the carbon−carbon triple bond.

Pyrido[3,4-*b*]indoles and pyrido[4,3-*b*]indoles, commonly known as β- and γ-carbolines, respectively, are the key structural units for a variety of biologically important alkaloids.[9] Numerous β- and γ-carbolines have been studied extensively as antitumor agents.[9] The isolation and synthesis of naturally occurring carbolines and the synthesis of β- and γ-carboline derivatives have received considerable attention in the literature[9,10] due to their biological and pharmaceutical importance.

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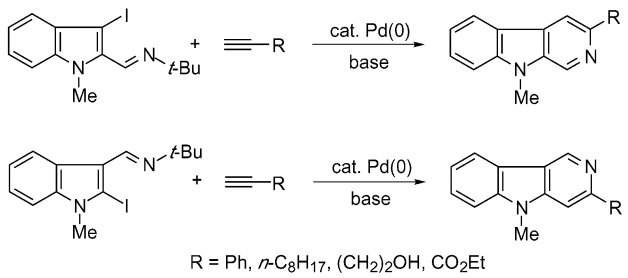
SCHEME 1



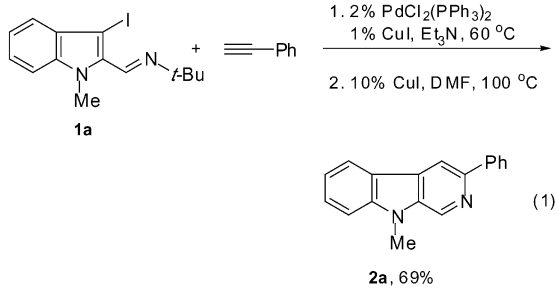
Hibino and Sakamoto have separately reported that substituted β-carbolines and their *N*-oxides can be synthesized readily by heating the corresponding 3-(1-alkynyl)indole-2-carboxaldehydes with NH_3[5a] or NH_2OH.[5b,c] The β-carboline *N*-oxides obtained by this method have been further elaborated by Hibino in the total synthesis of naturally occurring β-carboline alkaloids pyridindolols.[5b,c] Recently, Rossi has improved Sakamoto's carboline synthesis to the synthesis of 1,3-disubstituted β-carbolines by employing 2-acyl-3-(1-alkynyl)-indoles and NH_3.[5d] Similarly, γ-carbolines and their *N*-oxides have also been synthesized by heating the corresponding 2-(1-alkynyl)indole-3-carboxaldehydes with NH_3 or NH_2OH.[5a,g] The reduction of γ-carboline *N*-oxides by PCl_3 readily affords the corresponding γ-carbolines in satisfactory yields.[5g]

Recently, we have developed a general synthesis of 3,4-disubstituted β- and γ-carbolines by the palladium-catalyzed iminoannulation of *internal* acetylenes.[11] We have also developed a general synthesis of isoquinolines and pyridines by the palladium- and copper-catalyzed coupling and cyclization of *terminal* acetylenes.[6] Our interest in the synthesis of carbolines prompted us to examine the synthesis of a variety of 3-substituted β- and γ-carboline derivatives. Our goal during this work was to provide a clean, high-yielding, and general synthesis of functionalized β- and γ-carbolines, which would provide a useful alternative to Sakamoto's carboline synthesis.[5a] Preliminary studies on this project have previously been communicated.[12] Herein, we wish to report the full details of this successful synthesis of various β- and γ-carbolines by the palladium/copper-catalyzed coupling and copper-catalyzed or thermal cyclization of *terminal* acetylenes.

Results and Discussion

During the course of our investigation of the palladium-catalyzed iminoannulation of *internal* alkynes, we also examined the palladium-catalyzed iminoannulation of *terminal* alkynes. Unfortunately, the annulation of terminal alkynes, such as phenylacetylene, 1-decyne, 3-butyn-1-ol, and ethyl propiolate, by the *tert*-butylimine of 3-iodo-1-methylindole-2-carboxaldehyde and 2-iodo-1-methylindole-3-carboxaldehyde (**1a** and **1b**) under our standard conditions[11] for β- and γ-carboline synthesis gave the desired β- and γ-carbolines in relatively low yields in most cases (Scheme 1). Our several attempts to increase the yields of this annulation chemistry failed to give any improved results.

The reaction sequence for the synthesis of isoquinolines and pyridines by the palladium- and copper-catalyzed coupling and cyclization of terminal acetylenes[6] was then examined for the synthesis of β-carbolines by employing the *tert*-butylimine of 3-iodo-1-methylindole-2-carboxaldehyde (**1a**) and examining its coupling with several terminal alkynes. In short, the palladium/copper-catalzyed coupling of imine **1a** with a terminal acetylene was complete in a few hours as monitored by TLC analysis. The precipitate and the solvent were subsequently removed by filtration and evaporation. DMF and 10 mol % of CuI were then added to the residue. The resulting mixture was then heated at 100 °C until the cyclization was complete. Unfortunately, only phenylacetylene gave an acceptable yield (69%) of the desired β-carboline **2a** (eq 1). When other acetylenes, such as 1-decyne, 3-butyn-1-ol, and ethyl propiolate, were employed, the reactions afforded low yields of the corresponding β-carbolines in all cases.



Since the same reaction procedure has proven successful for the synthesis of isoquinolines, one wonders why this reaction procedure does not work well in the β-carboline synthesis. The reasons appear complicated. The palladium/copper-catalyzed Sonogashira coupling[13] of ethyl 3-iodo-1*H*-indole-2-carboxylate and ethyl 3-iodo-1-(methanesulfonyl)indole-2-carboxylate with terminal acetylenes has been reported previously to proceed in relatively low yields.[14] As an analogue to the above carboxylates, imine **1a** might also suffer the problem of low yields when it undergoes the coupling reaction with terminal acetylenes. Moreover, the bulky *tert*-butylimine moiety in imine **1a** might also affect the Sonogashira reaction. Furthermore, the Sonogashira coupling might produce byproducts, which cannot be removed in the one-pot process and might interfere with the subsequent copper-catalyzed cyclization.

To investigate the major factors that cause the low yields of β-carboline products, the coupling product of imine **1a** with phenylacetylene was therefore isolated before it was employed in the subsequent copper-catalyzed cyclization. Instead of the *tert*-butylimine, the alkynylindole aldehyde **3a**, which is apparently arising from hydrolysis of the corresponding *tert*-butylimine

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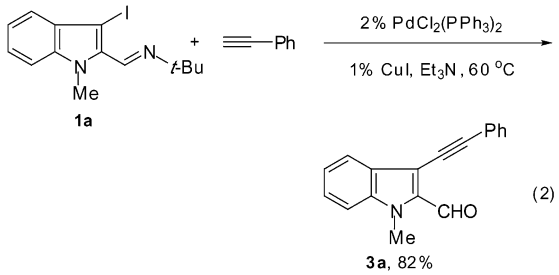
during column chromatography, was isolated in an 82% yield (eq 2). As a control experiment, the coupling of



(2)

3-iodo-1-methylindole-2-carboxaldehyde (**4a**) with phenylacetylene was performed, affording the same alkynylindole aldehyde **3a** in a 100% yield. Aldehyde **3a** was then quantitatively converted to the corresponding *tert*-butylimine, which was subsequently employed in the copper-catalyzed cyclization and smoothly afforded the desired *β*-carboline **2a** in a 90% yield (Scheme 2).

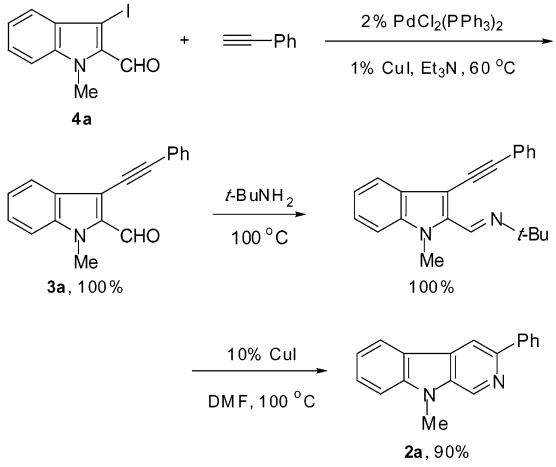
By comparing the results of eqs 1 and 2 with those of Scheme 2, we conclude that the bulky *tert*-butylimine moiety does affect the Sonogashira coupling of imine **1a** with phenylacetylene, and the byproducts generated by the Sonogashira coupling of imine **1a** with phenylacetylene also interfere with the subsequent copper-catalyzed cyclization. These problems might also happen in the *β*-carboline synthesis employing other acetylenes under the standard reaction sequence of our isoquinoline synthesis, which afforded low yields of *β*-carbolines in all cases, as mentioned previously.

As we have seen, the control experiment employing aldehyde **4a** and phenylacetylene gave a higher total yield (90%) of the desired *β*-carboline **2a** (Table 1, entry 1) than the reaction employing the sequence of our earlier isoquinoline synthesis (69%). The transformation of aldehyde to the corresponding *tert*-butylimine is essentially quantitative, as observed in our previous work.[1m,n,6,11] We have thus simply changed the reaction sequence to that of the control experiment, which requires no further purification and characterization of the *tert*-butylimines. This ensures essentially pure starting materials for each step (Scheme 3). The results of this study are summarized in Table 1.

As shown in Table 1, the palladium/copper-catalyzed Sonogashira coupling of 3-iodo-1-methylindole-2-carboxaldehyde (**4a**) with a variety of terminal acetylenes afforded excellent yields of the corresponding 3-alkynyl-1-methylindole-2-carboxaldehydes **3a**−**g**, which were then converted into the correponding *tert*-butylimines which were subsequently subjected to copper-catalyzed cyclization to generate the desired 3-substituted *β*-carbolines **2a**−**g** in excellent yields (entries 1−7). Aryl-, alkenyl-, and alkyl-substituted terminal acetylenes have proven successful in this *β*-carboline synthesis (entries 1−4). Moreover, hydroxy-, ester-, and cyano-substituted terminal alkynes also afforded the coupling products and the corresponding *β*-carbolines in excellent yields (entries 5−7).

When a silyl-substituted terminal alkyne, triethylsilylacetylene, was employed, the coupling successfully afforded a 100% yield of the desired alkynylindole **3h** (entry 8). However, the copper-catalyzed cyclization did not afford any of the desired triethylsilyl-substituted *β*-carboline. Instead, a 28% yield of the desilylated *β*-carboline **2h** was isolated by column chromatography, along with a 70% yield of the desilylated intermediate 2-*tert*-butyl-9-methyl-9*H*-pyrido[3,4-*b*]indolium hydroxide, which was confirmed by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The *β*-carbolinium salt thermally eliminates the *tert*-butyl group to form the *β*-carboline **2h** in a 58% yield at 130 °C after 72 h. To avoid the difficulty in isolating the highly polar *β*-carbolinium salt, after the copper-catalyzed cyclization reaction was complete as judged by TLC analysis, the reaction mixture was continuously heated at 130 °C for 72 h. Unfortunately, the *β*-carboline **2h** was isolated in only a 41% yield by this process (entry 8).

SCHEME 2



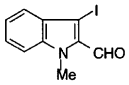
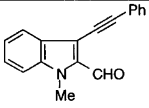
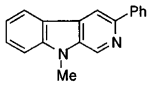
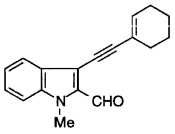
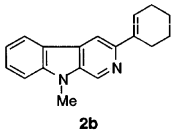
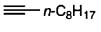
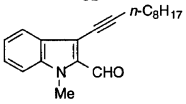
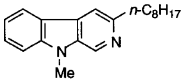
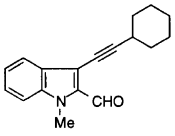
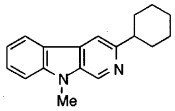
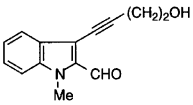
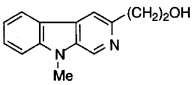
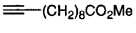
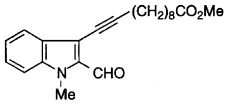
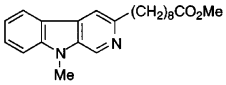
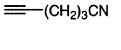
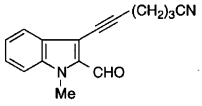
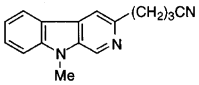
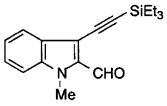
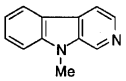
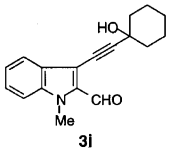
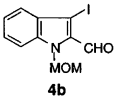
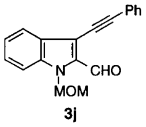
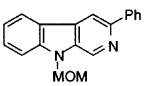
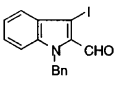
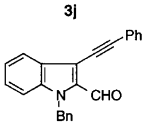
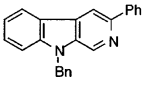
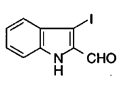
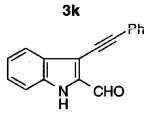
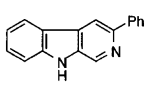
When an acetylene containing a bulky group, namely 1-ethynylcyclohexanol, was employed, the coupling successfully gave the alkynylindole **3i** in a 100% yield (entry 9). Surprisingly, the cyclization did not afford any of the desired product. Instead, the *β*-carboline **2h**, which had lost the cyclohexane ring, and the same *β*-carbolinium salt that was formed in the silyl case were detected by TLC analysis and ^{1}H NMR spectroscopy. To avoid isolation of the extremely polar *β*-carbolinium salt, the reaction mixture was heated at 130 °C for 72 h to eliminate the *tert*-butyl group present in the salt. Unfortunately, only a 35% yield of the *β*-carboline **2h** was isolated (entry 9). Again, loss of the hydroxycyclohexyl group is the predominant reaction.

An electron-deficient terminal acetylene, ethyl propiolate, was also employed in the palladium/copper-catalyzed coupling process. Unfortunately, the reaction did not afford any significant amount of the coupling product. Two electron-rich terminal acetylenes, ethoxyacetylene and 2-ethynylbenzofuran, also failed to produce the coupling products in decent yields. Presumably, these terminal alkynes are too reactive and thus polymerize under the coupling conditions.[15]

Finally, *N*-methoxymethyl- and *N*-benzyl-substituted iodoindoles **4b** and **4c** were employed in the palladium/

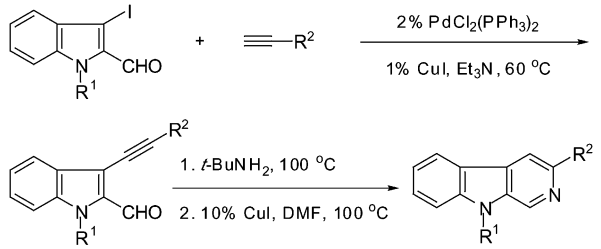
(15) Ethyl propiolate and ethoxyacetylene are prone to polymerization. For examples, see: (a) Gal, Y.-S.; Lee, W.-C.; Choi, S.-K. *Korea Polym. J.* **1997**, *5*, 10. (b) Tabata, M.; Inaba, Y.; Yokota, K.; Nozaki, Y. *J. Macromol. Sci., Pure Appl. Chem.* **1994**, *31*, 465. (c) Jacobs, T. L.; Juster, N. *J. Chem. Eng. Data* **1969**, *14*, 125.

TABLE 1. Synthesis of β-Carbolines by the Palladium/Copper-Catalyzed Coupling and Copper-Catalyzed Cyclization of Terminal Acetylenes

entry	aldehyde	alkyne	alkynylindole	time (h)[a]	% yield[b]	product	time (h)[a]	% yield[b]
1	 **4a**		 **3a**	3	100	 **2a**	20	90
2			 **3b**	18	98	 **2b**	24	93
3			 **3c**	16	88	 **2c**	24	93
4			 **3d**	16	96	 **2d**	40	93
5			 **3e**	16	87	 **2e**	15	95
6			 **3f**	16	98	 **2f**	18	95
7			 **3g**	16	82	 **2g**	20	88
8			 **3h**	16	100	 **2h**	92[c]	41
9			 **3i**	18	100	**2h**	92[c]	35
10	 **4b**		 **3j**	16	95	 **2i**	20	100
11	 **4c**		 **3k**	18	89	 **2j**	18	99
12	 **4d**		 **3l**	4	93	 **2k**	24	trace[d]

[a] The reaction time was not optimized. Some of the coupling reactions in this study might be complete in a much shorter time than listed, as is the case in entries 1 and 12. [b] Isolated yields. [c] The reaction was heated at 100 °C for 20 h and subsequently at 130 °C for 72 h. [d] A 36% yield of **3l** was isolated.

SCHEME 3



copper-catalyzed coupling and copper-catalyzed cyclization of phenylacetylene. The coupling process afforded the alkynylindole aldehydes **3j** and **3k** in 95% and 89% yields, and the cyclization generated the desired β-carbolines **2i** and **2j** in 100% and 99% yields, respectively (entries 10 and 11). The unprotected iodoindole, 3-iodo-1*H*-indole-2-carboxaldehyde (**4d**), undergoes palladium-catalyzed Sonogashira coupling with phenylacetylene, producing the corresponding alkynylaldehyde **3l** in a 92% yield. Unfortunately, the subsequent cyclization only afforded a trace of the desired β-carboline **2k**. A messy reaction was observed and 36% of aldehyde **3l** was recovered (entry 12).

Encouraged by our success with the β-carboline synthesis, we have also investigated the palladium/copper-catalyzed coupling of terminal acetylenes using *N*-substituted 2-bromoindole-3-carboxaldehydes to synthesize various 3-substituted γ-carbolines. The palladium/copper-catalyzed coupling of phenylacetylene and 2-bromo-1-methylindole-3-carboxaldehyde (**5a**) was first examined. The coupling reaction proceeded smoothly, producing the desired alkynylindole **6a** in a 93% yield. Alkynylindole **6a** was then heated with *tert*-butylamine at 100 °C in a sealed tube. To our pleasant surprise, instead of the corresponding *tert*-butylimine, the γ-carboline product **7a** was detected by TLC analysis after 20 h and subsequently isolated in a 92% yield (Table 2, entry 1). This preliminary result prompted us to investigate the scope of this synthesis of 3-substituted γ-carbolines by the palladium/copper-catalyzed coupling and thermal cyclization of terminal acetylenes (Scheme 4). The results of this study are summarized in Table 2.

As shown in Table 2, the palladium/copper-catalyzed Sonogashira coupling of 2-bromo-1-methylindole-3-carboxaldehyde (**5a**) with a variety of terminal acetylenes afforded good to excellent yields of the corresponding 2-alkynyl-1-methylindole-3-carboxaldehydes, which were then converted to the *tert*-butylimines, which subsequently underwent thermal cyclization in situ to generate the desired 3-substituted γ-carbolines in good to excellent yields (entries 1−6). As we expected, aryl-, alkenyl-, alkyl-substituted terminal acetylenes have again proven successful in this γ-carboline synthesis (entries 1−4). Unfortunately, 3-propyn-1-ol, which was quite successful in the β-carboline synthesis, did not give any significant yield of the coupling product. However, another hydroxy-containing acetylene, 10-undecyn-1-ol, afforded Sonogashira coupling product **6e** and the corresponding γ-carboline **7e** in 61% and 72% yields, respectively (entry 5). Methyl 10-undecynoate also underwent coupling and cyclization successfully, affording an 86% yield of coupling product **6f** and an 88% yield of the γ-carboline product **7f** (entry 6). Surprisingly again, 5-cyano-1-pentyne, which proved successful in our β-carboline synthesis, failed to give any decent yield of the Sonogashira coupling product.

Triethylsilylacetylene undergoes the coupling smoothly, generating a 94% yield of alkynylindole aldehyde **6g**. However, the subsequent thermal cyclization afforded none of the desired γ-carboline. Instead, an 86% yield of the desilylated salt, 2-*tert*-butyl-5-methyl-5*H*-pyrido[4,3-*b*]indolium hydroxide, was observed and confirmed by ^{1}H NMR spectroscopy and mass spectrometry. To avoid isolation of the extremely polar γ-carbolinium salt, a process similar to that of the corresponding β-carboline system was carried out. After the cyclization was complete as judged by TLC analysis, the solvent *tert*-butylamine was removed by vacuum and DMF was added to the residue. The mixture was then heated at 130 °C for 72 h. Unfortunately, only a 41% yield of the γ-carboline **7g** was isolated (entry 7).

When 1-ethynylcyclohexanol was employed, the coupling was successful, producing an 87% yield of alkynylindole **6h**, which was then heated with *tert*-butylimine. Surprisingly, neither the desired γ-carboline nor the γ-carboline minus the hydroxycyclohexyl group or the γ-carbolinum salt were observed. Instead, the corresponding *tert*-butylimine was detected after 24 h by TLC analysis, which was further confirmed by ^{1}H NMR spectroscopy, and the imine was isolated in a 100% yield after removal of the solvent *tert*-butylamine by vacuum. CuI (10 mol %) and DMF were then added to the *tert*-butylimine to facilitate the cyclization, as was done in the β-carboline synthesis. Interestingly, the *tert*-butylimine completely disappeared and the γ-carbolinium salt minus the hydroxycyclohexyl group, the same salt as we obtained earlier in the silyl case, was observed after only 2 h by TLC analysis and ^{1}H NMR spectroscopy. Apparently, CuI accelerates the fragmentation process.[16] The reaction mixture was then heated at 130 °C for 72 h, and a 40% yield of the γ-carboline **7g** was isolated (entry 8).

Similar to our observations in the β-carboline synthesis, the electron-deficient alkyne ethyl propiolate and the electron-rich alkyne ethoxyacetylene failed to afford significant amounts of the coupling products. Interestingly, another electron-rich terminal alkyne, 2-ethynylbenzofuran, produced the coupling product in a 67% yield, along with a 33% yield of the starting bromide as an unseparable mixture. This mixture was employed in another Sonogashira coupling under our standard conditions, affording cleanly the alkynylindole **6i** in a 78% total yield. Surprisingly, if the amount of 2-ethynylbenzofuran was increased from 1.2 to 3 equiv, the coupling gave a messier reaction and a lower yield (56%) of the alkynylindole **6i**. The resulting alkynylindole **6i** was subjected to the subsequent thermal cyclization, which produced a 95% yield of the desired γ-carboline **7h** (entry 9).

Finally, *N*-methoxymethyl- and *N*-benzyl-substituted bromoindoles **5b** and **5c** were employed in the palladium/

(16) The base-promoted deacetonation of α,β-acetylenic carbinols has been well-studied. For representative examples, see: (a) Veliev, M. G.; Shatirova, M. I.; Chalabiev, C. A.; Mamedov, I. M.; Mustafaev, A. M. *Russ. J. Org. Chem.* **1995**, *31*, 52. (b) Havens, S. J.; Hergenrother, P. M. *J. Org. Chem.* **1985**, *50*, 1763. (c) Fowler, J. S. *J. Org. Chem.* **1977**, *42*, 2637. The base-promoted fragmentation of a 1-hydroxycyclohexyl-substituted acetylene is also known. See: (d) Henbest, H. B.; Jones, E. R. H.; Walls, I. M. S. *J. Chem. Soc.* **1949**, 2696.

TABLE 2. Synthesis of γ-Carbolines by the Palladium/Copper-Catalyzed Coupling and Thermal Cyclization of Terminal Acetylenes

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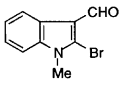
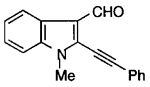
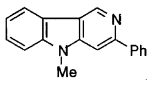
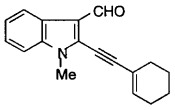
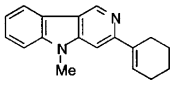
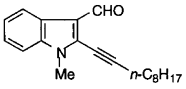
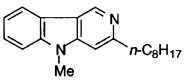
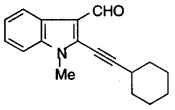
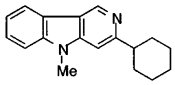
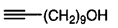
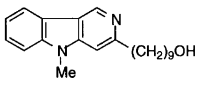
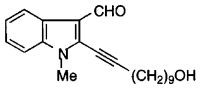
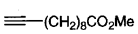
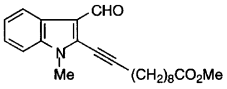
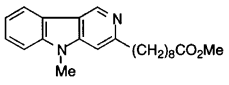
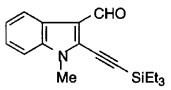
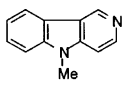
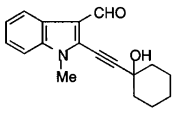
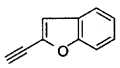
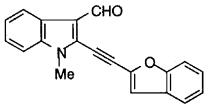
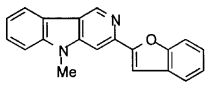
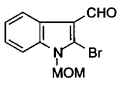
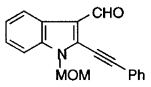
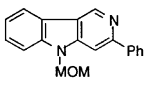
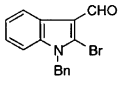
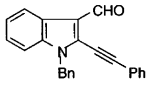
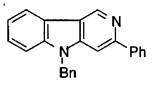
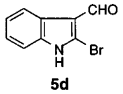
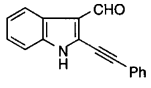
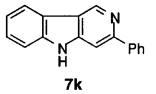
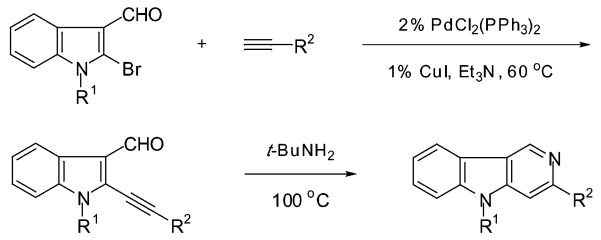
1	 **5a**		 **6a**	24	93	 **7a**	20	92
2			 **6b**	20	98	 **7b**	40	93
3			 **6c**	20	82	 **7c**	24	87
4			 **6d**	4	89	 **7d**	40	83
5			 **6e**	16	61	 **7e**	20	72
6			 **6f**	16	86	 **7f**	20	88
7			 **6g**	16	94	 **7g**	92[c]	41
8			 **6h**	18	87	**7g**	92[c]	40
9			 **6i**	6[d]	78[d]	 **7h**	40	95
10	 **5b**		 **6j**	20	97	 **7i**	18	80
11	 **5c**		 **6k**	18	73	 **7j**	22	90
12	 **5d**		 **6l**	14	64	 **7k**	20	49

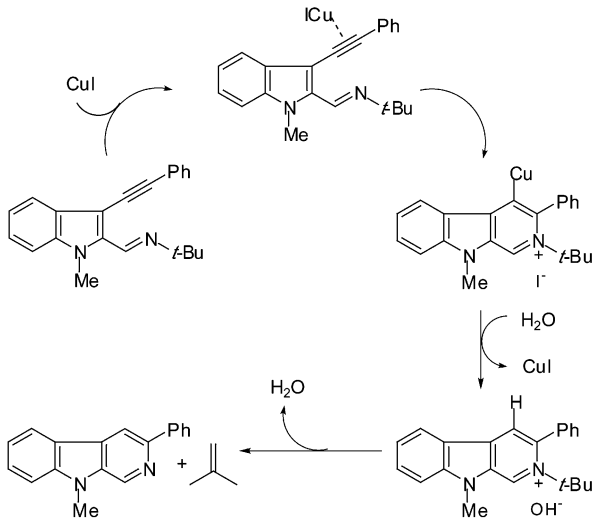
[a] The reaction time was not optimized. Some of the coupling reactions might be complete in a much shorter time, as is the case in entries 4 and 9. [b] Isolated yields. [c] The reaction was heated at 100 °C for 22 h and subsequently at 130 °C for 72 h. [d] An unseparable mixture of 67% of **6i** and 33% of **5a** was isolated after 3 h, which was subjected to another Sonogashira coupling for 3 h.

copper-catalyzed coupling and thermal cyclization of phenylacetylene. The coupling afforded the alkynylindole aldehydes **6j** and **6k** in 97% and 73% yields, and the cyclization generated the desired γ-carbolines **7i** and **7j**

SCHEME 4



SCHEME 5

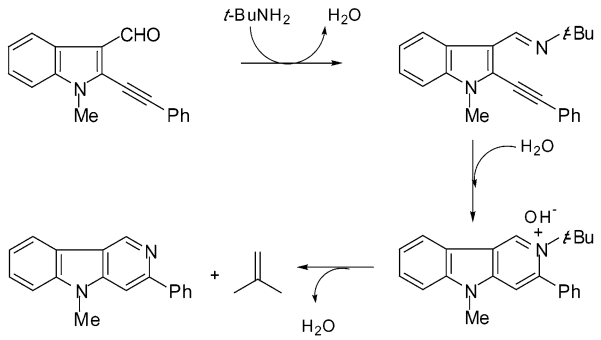


in 80% and 90% yields, respectively (entries 10 and 11). The unprotected indolealdehyde, 2-bromo-1*H*-indole-3-carboxaldehyde (**5d**), underwent palladium-catalyzed Sonogashira coupling with phenylacetylene, producing the corresponding alkynylaldehyde **6l** in a 64% yield. Unfortunately, the subsequent thermal cyclization only afforded a 49% yield of the desired γ-carboline **7k** (entry 12).

We believe that a reasonable mechanism for the synthesis of β-carbolines by the palladium/copper-catalyzed coupling and copper-catalyzed cyclization of terminal acetylenes involves CuI coordinating to the carbon−carbon triple bond of the *tert*-butylimine, followed by intramolecular nucleophilic attack of the nitrogen of the imine moiety on the carbon−carbon triple bond forming a β-carbolinium intermediate. This copper intermediate is presumably protonated by spurious amounts of water present in the system, regenerating CuI and producing a carbolinium salt, which then relieves the strain resulting from the interaction with the substituent present on the neighboring carbon by fragmentation of the *tert*-butyl group,[17] producing the β-carboline (Scheme 5).

We also propose a mechanism for the synthesis of γ-carbolines by the palladium/copper-catalyzed coupling and thermal cyclization of terminal acetylenes (Scheme 6). Specifically, the nitrogen of the imine moiety nucleophilically attacks the carbon−carbon triple bond of the *tert*-butylimine, capturing a proton from water to form the γ-carbolinium salt. The *tert*-butyl group in the γ-carbolinium salt apparently fragments to relieve the

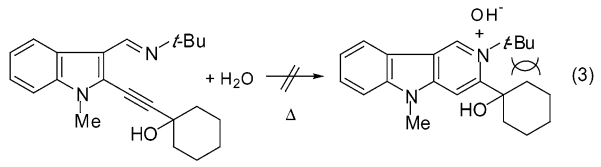
SCHEME 6



strain resulting from the interaction with the substituent present in the 3-position.

It is now easy to understand why the copper-catalyzed cyclization of the *tert*-butylimine of the silyl-substituted alkynylindole **3h** and the thermal cyclization of the *tert*-butylimine of the silyl-substituted alkynylindole **6g** both afforded the corresponding desilylated carbolinium salts.[18] In these two cases, the triethylsilyl group undergoes protodesilylation under the reaction conditions. Due to the lack of strain between the *tert*-butyl group and the hydrogen in the 3-position, the *tert*-butyl group either fragments incompletely (β-carboline synthesis) or survives without fragmentation (γ-carboline synthesis) under the standard reaction conditions. However, a higher temperature (130 °C) promotes thermal fragmentation of the *tert*-butyl group, as discussed previously.

It is also understandable that when the bulky 1-hydroxycyclohexyl-substituted alkynylindole **6h** was subjected to thermal cyclization under the standard conditions, which are successful for the less bulky substituted alkynylindoles **6a**−**f**, the reaction produced none of the desired γ-carboline, but afforded the corresponding *tert*-butylimine instead. Apparently, the steric interaction between two neighboring bulky groups disfavors formation of the γ-carbolinium salt intermediate (eq 3). The



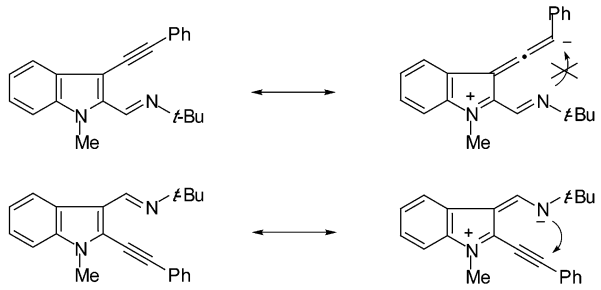
presence of a catalytic amount of CuI apparently accelerates loss of the hydroxycyclohexyl group,[16] as we observed disappearance of the *tert*-butylimine of alkynylindole **6h** and formation of the fragmented γ-carbolinium salt in only 2 h. As discussed previously, the fragmentation process also occurs during the corresponding β-carboline synthesis, which might also be catalyzed by the presence of CuI.

It is worth noting that the nitrogen of the indole moiety of the *tert*-butylimine of the alkynylindoles **3** can donate electrons through resonance to increase the electron density on the carbon−carbon triple bond. Therefore, the carbon−carbon triple bond is less electrophilic, and thus

(17) (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.

(18) The thermal reaction of 1-benzenesulfonyl-3-(trimethylsilylethynyl)indole-2-carboxaldehyde with NH_3 also afforded the corresponding desilylated β-carboline in a low yield (37%). See ref 5a for details.

SCHEME 7



requires CuI coordination to decrease the electron density. On the contrary, the nitrogen of the indole moiety of the *tert*-butylimine of the alkynylindoles **5** donates electrons through resonance to the nitrogen of the imine moiety, which consequently becomes a better nucleophile. As a result, in situ nucleophilic attack of the imino-nitrogen on the carbon−carbon triple bond proceeds smoothly under the thermal conditions used to produce the imine (Scheme 7).

Conclusions

In conclusion, an efficient palladium/copper-catalyzed coupling and copper-catalyzed or thermal-promoted synthesis of β- and γ-carbolines has been developed. A wide variety of functionalized terminal acetylenes participate in this process to afford the desired nitrogen heterocycles in good to excellent yields. However, triethylsilyl- and 1-hydroxycyclohexyl-substituted acetylenes generate the desilylated and fragmented carbolines in moderate yields at an elevated temperature.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz, respectively. Thin-layer chromatography was performed with use of commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short-wavelength UV light (254 nm). All melting points are uncorrected. High-resolution mass spectra were recorded on a Kratos MS50TC double-focusing magnetic sector mass spectrometer with EI at 70 eV. All reagents were used directly as obtained commercially. 3-Iodo-1-(methoxymethyl)indole-2-carboxaldehyde[19] (**4b**), 3-iodo-1*H*-indole-2-carboxaldehyde[19] (**4d**), 2-bromo-1*H*-indole-3-carboxaldehyde[20] (**5d**), and methyl 1-undecynoate[21] were prepared according to previous literature procedures. 3-Iodo-1-methylindole-2-carboxaldehyde (**4a**), 2-bromo-1-methylindole-3-carboxaldehyde (**5a**), 2-bromo-1-(methoxymethyl)indole-3-carboxaldehyde (**5b**), 3-iodo-1-methylindole-2-methylene-*tert*-butylamine, and 2-iodo-1-methylindole-3-methylene-*tert*-butylamine have been reported previously.[11] The preparation of the starting materials 2-ethynylbenzofuran, 1-benzyl-3-iodoindole-2-carboxaldehyde (**4c**), and 1-benzyl-2-bromoindole-3-carboxaldehyde (**5c**) can be found in the Supporting Information.

General Procedure for the Synthesis of β-Carbolines by the Palladium/Copper-Catalyzed Coupling and Copper-Catalyzed Cyclization of Terminal Acetylenes. CuI (1.0 mg, 1 mol %), $PdCl_2(PPh_3)_2$ (7.0 mg, 2 mol %), the *N*-substituted 3-iodoindole-2-carboxaldehyde (0.50 mmol), and Et_3N (4 mL) were placed in a 2-dram vial. The contents were stirred for 1 min and the appropriate acetylene (0.60 mmol) was added. The vial was flushed with Ar and heated in an oil bath at 60 °C for the indicated period of time. Completion of the reactions was established by TLC analysis. The precipitate was removed by filtration. The solvent was evaporated under reduced pressure and the coupling product was isolated by chromatography on a silica gel column. A small amount of the coupling product was used for characterization. The remaining material was transferred to another 2-dram vial, and *tert*-butylamine (5 mL/mmol) was added. The mixture was flushed with Ar and the vial was carefully sealed. The mixture was heated at 100 °C for 24 h and then cooled, diluted with ether, dried over Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure, giving the corresponding *tert*-butylimine. The *tert*-butylimine was transferred to a 2-dram vial and CuI (10 mol %) and DMF (10 mL/mmol) were added. The mixture was flushed with Ar and heated at 100 °C for the indicated period of time. Completion of the reactions was established by TLC analysis. DMF was removed under reduced pressure by rotary evaporation and the β-carboline was isolated by column chromatography.

General Procedure for the Synthesis of γ-Carbolines by the Palladium/Copper-Catalyzed Coupling and Thermal Cyclization of Terminal Acetylenes. The *N*-substituted 2-bromoindole-3-carboxaldehyde (0.50 mmol), Et_3N (4 mL), and DMF (0.4 mL, to increase the solubility of the aldehyde) were used. The rest of the procedure is identical with that used for the coupling reactions in the β-carboline synthesis. A small amount of the coupling product was used for characterization. The remaining material was transferred to a 2-dram vial and *tert*-butylamine (5 mL/mmol) was added. The mixture was flushed with Ar and the vial was carefully sealed. The mixture was heated at 100 °C for the indicated period of time. Completion of the reactions was established by TLC analysis. The solvent was evaporated under reduced pressure and the γ-carboline was isolated by column chromatography.

Alkynylindoles Prepared: 1-Methyl-3-(phenylethynyl)-indole-2-carboxaldehyde (3a). The reaction mixture was chromatographed with 10:1 hexanes/EtOAc to afford 130 mg (100%) of the indicated compound as a yellow solid: mp 87−89 °C; ^{1}H NMR ($CDCl_3$) δ 4.07 (s, 3H), 7.25 (m, 1H), 7.37 (m, 4H), 7.45 (t, J = 8.0 Hz, 1H), 7.59 (m, 2H), 7.89 (d, J = 8.0 Hz, 1H), 10.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 31.9, 80.4, 97.0, 110.6, 111.9, 121.7, 122.3, 123.1, 127.7, 127.8, 128.5, 128.6, 131.6, 135.5, 139.6, 182.3; IR (neat, cm^{-1}) 2207, 1669; HRMS calcd for $C_{18}H_{13}NO$ 259.0997, found 259.1001.

2-(1-Cyclohexenylethynyl)-1-methylindole-3-carboxaldehyde (6b). The reaction mixture was chromatographed with 6:1 hexanes/EtOAc to afford 130 mg (98%) of the indicated compound as a yellow solid: mp 84−85 °C; ^{1}H NMR ($CDCl_3$) δ 1.60−1.75 (m, 4H), 2.18−2.25 (m, 2H), 2.26−2.33 (m, 2H), 3.81 (s, 3H), 6.43 (m, 1H), 7.27−7.37 (m, 3H), 8.29 (d, J = 8.0 Hz, 1H), 10.15 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 22.1, 26.0, 28.8, 31.1, 75.1, 103.4, 109.6, 119.3, 119.7, 122.1, 123.4, 124.5, 124.8, 133.0, 137.4, 138.9, 185.3; IR (neat, cm^{-1}) 3016, 2935, 2197, 1659; HRMS calcd for $C_{18}H_{17}NO$ 263.1310, found 263.1314.

Characterization of all other alkynylindoles prepared in this study can be found in the Supporting Information.

Carbolines Prepared: 9-Methyl-3-phenyl-9*H*-pyrido-[3,4-*b*]indole (2a). The reaction mixture was chromatographed with 2:1 hexanes/EtOAc to afford a 90% yield of the indicated compound as a yellow solid: mp 135−136 °C; ^{1}H NMR (acetone-d_6) δ 3.99 (s, 3H), 7.27−7.38 (m, 2H), 7.45−7.51 (m, 2H), 7.58−7.63 (m, 2H), 8.24 (m, 2H), 8.31 (dt, J = 7.8, 0.9 Hz, 1H), 8.64 (d, J = 0.9 Hz, 1H), 9.01 (d, J = 0.9 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 29.0, 109.9, 110.8, 119.7, 121.5, 122.0, 126.6, 127.6, 128.5, 128.7, 129.2, 132.0, 136.7, 140.9,

(19) Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C.; Sugino, E.; Hibino, S. *J. Org. Chem.* **1997**, *62*, 2535.

(20) Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447. We used ethyl acetate instead of diethyl ether as the extraction solvent, and were able to isolate 2-bromo-1*H*-indole-3-carboxaldehyde in a 55% yield.

(21) Ranganathan, S.; Maniktala, V.; Kumar, R.; Singh, G. P. *Indian J. Chem. Sect. B* **1984**, *23*, 1197.

142.5, 146.9; IR (neat, cm^{-1}) 3057, 2934; HRMS calcd for $C_{18}H_{14}N_2$ 258.1157, found 258.1161.

3-(1-Cyclohexenyl)-5-methyl-5*H*-pyrido[4,3-*b*]indole (7b). The reaction mixture was chromatographed with 3:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a pale yellow solid: mp 99−100 °C; ^{1}H NMR ($CDCl_3$) δ 1.72 (m, 2H), 1.85 (m, 2H), 2.32 (m, 2H), 2.63 (m, 2H), 3.78 (s, 3H), 6.85 (m, 1H), 7.25−7.30 (m, 2H), 7.36 (d, J = 8.0 Hz, 1H), 7.48 (dt, J = 8.0, 0.9 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 9.20 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3, 23.1, 26.1, 26.6, 29.0, 98.8, 108.8, 118.1, 120.4, 120.5, 121.6, 126.3, 128.0, 137.1, 141.4, 141.6, 146.0, 155.4; IR (neat, cm^{-1}) 3050, 2928; HRMS calcd for $C_{18}H_{18}N_2$ 262.1470, found 262.1475.

Characterization of all other carbolines prepared in this study can be found in the Supporting Information.

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 salts.

Supporting Information Available: Preparation of starting materials, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for compounds **2b**−**j**, **3a**−**l**, **6a-l**, and **7a**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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