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Synthesis of β- and γ-carbolines by the palladium/copper-catalyzed coupling and copper-catalyzed or thermal cyclization of terminal acetylenes

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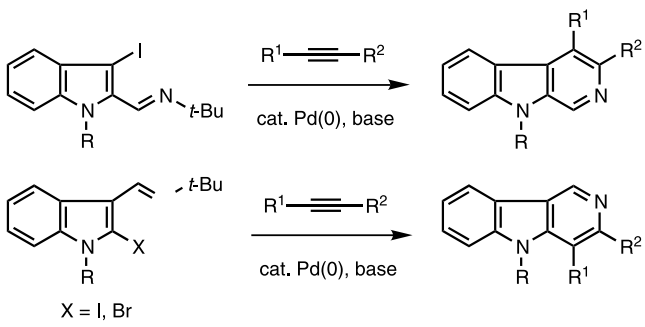
Abstract—A variety of 3-substituted β- and γ-carbolines have been synthesized from *N*-substituted 3-iodoindole-2-carboxaldehydes and 2-bromoindole-3-carboxaldehydes, respectively. The coupling of these aldehydes with various terminal acetylenes using cat. $PdCl_2(PPh_3)_2$/CuI readily affords the corresponding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

The transition metal-mediated,[1] base-promoted,[2] electrophile-induced[3] and thermal cyclization[4] of alkynes which possess a nucleophile in close proximity to the carbon–carbon triple bond have been shown to be very effective for the synthesis of a wide variety of hetero- and carbocycles. In our own laboratory, a variety of isoquinolines, pyridines and naphthyridines have been successfully synthesized by the copper-catalyzed,[5] palladium-catalyzed[6] and electrophile-induced[7] cyclization of alkynes having a *tert*-butylimine group in close proximity to the 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.[8] Numerous β- and γ-carbolines have been studied extensively as antitumor agents.[8] The isolation and synthesis of naturally occurring carbolines and the synthesis of β- and γ-carboline derivatives have received considerable attention in the literature,[8,9] because of their biological and pharmaceutical importance.

Recently, we have developed a general synthesis of 3,4-disubstituted β- and γ-carbolines by the palladium-catalyzed iminoannulation of *internal* alkynes (Scheme 1).[10] Our interest in carboline synthesis has prompted us to examine the synthesis of a variety of 3-substituted β- and γ-carboline derivatives from *terminal* alkynes. Herein, we wish to report the successful synthesis of various β- and γ-carbolines by the palladium/copper-catalyzed coupling and subsequent copper-catalyzed or thermal cyclization of terminal acetylenes.

We have found that the palladium/copper-catalyzed coupling of 3-iodo-1-methylindole-2-carboxaldehyde (**1a**) with phenylacetylene gave a 100% yield of the alkynylindole **2a**, which was then converted to the corresponding *tert*-butylimine in a quantitative yield (Scheme 2 and Table 1). The *tert*-butylimine was then subjected to copper-catalyzed (10 mol% CuI) cyclization, which afforded a 90% yield of the desired β-carboline **3a** after 20 h (Table 1, entry 1). As observed in our previous carboline synthesis,[10] transformation of the aldehyde to the corresponding *tert*-butylimine is essentially quantitative, requiring no further purification or characterization. We thus employed this coupling–imination–cyclization sequence to synthesize a variety of



Scheme 1. Iminoannulation of internal alkynes.

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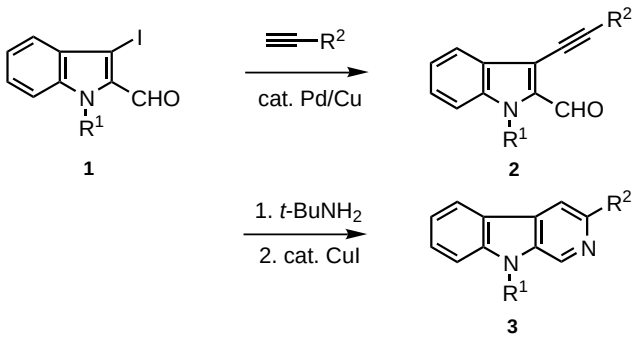


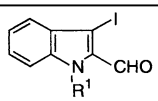
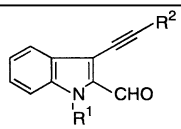
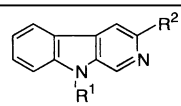
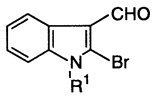
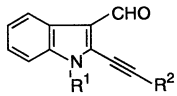
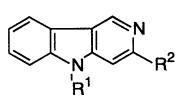
Scheme 2. β-Carboline synthesis.

3-substituted β-carbolines using *N*-substituted 3-iodoindole-2-carboxaldehydes and other terminal acetylenes (Scheme 2).[11] The results of this study are summarized in Table 1, entries 2–5.

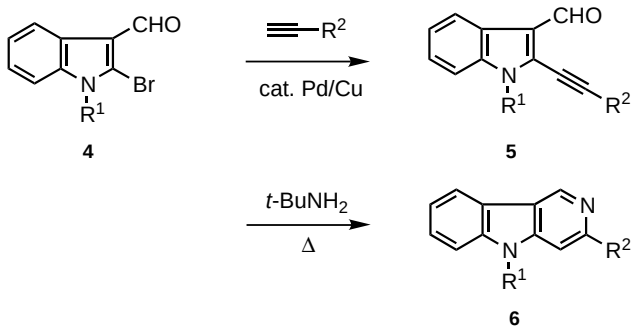
As summarized in Table 1, the palladium/copper-catalyzed Sonogashira coupling[12] of 3-iodo-1-methylindole-2-carboxaldehyde (**1a**) with a variety of terminal acetylenes afforded excellent yields of the corresponding 3-alkynyl-1-methylindole-2-carboxaldehydes, which were then converted to the corresponding *tert*-butylimines. Subsequent copper-catalyzed cyclization was also quite effective, generating the desired 3-substituted β-carbolines in excellent yields (entries 2–4). Alkyl-substituted terminal acetylenes have proven quite successful in this β-carboline synthesis. For example, 1-decyne gave 88 and 93% yields of the coupling product **2b** and β-carboline **3b**, respectively (entry 2). Moreover, hydroxy- and ester-substituted terminal alkynes also afforded Sonogashira coupling products and the corresponding β-carbolines in excellent yields (entries 3 and 4). For example, 4-butyn-1-ol afforded an 87% yield of the coupling product **2c**, which subsequently gave the desired β-carboline **3c** in a 95% yield (entry 3). Methyl 10-undecynoate produced 98 and 95% yields of the coupling and cyclization products **2d** and **3d**, respectively (entry 4). Finally, *N*-methoxymethyl-substituted iodoindole **1b** was employed in the palladium/copper-catalyzed coupling and copper-catalyzed cyclization of phenylacetylene. The coupling afforded the alkynylindole **2e** in a 95% yield, and cyclization generated the desired β-carboline **3e** in a 100% yield (entry 5).

Encouraged by our success with the β-carboline synthesis, we have also investigated the palladium-catalyzed coupling of terminal acetylenes using *N*-substituted 2-bromoindole-3-carboxaldehydes in order to synthesize various 3-substituted γ-carbolines (Scheme 3). The palladium/copper-catalyzed coupling of phenylacetylene and 2-bromo-1-methylindole-3-carboxaldehyde (**4a**)

Table 1. Synthesis of β- and γ-carbolines by the palladium/copper-catalyzed coupling and copper-catalyzed or thermal cyclization of terminal acetylenes[a]

Entry	Aldehyde		Alkyne	Coupling time (h)[b]	Alkynylindole	% Yield[c]	Cyclization time (h)[b]	Carboline	% Yield[c]
									
	R^1		R^2						
1	Me	**1a**	Ph	3	**2a**	100	20	**3a**	90
2	Me	**1a**	n-C_8H_{17}	16	**2b**	88	24	**3b**	93
3	Me	**1a**	$(CH_2)_2OH$	16	**2c**	87	15	**3c**	95
4	Me	**1a**	$(CH_2)_8CO_2Me$	16	**2d**	98	18	**3d**	95
5	MOM	**1b**	Ph	16	**2e**	95	20	**3e**	100
									
	R^1		R^2						
6	Me	**4a**	Ph	24	**5a**	93	20	**6a**	92
7	Me	**4a**	n-C_8H_{17}	20	**5b**	82	24	**6b**	87
8	Me	**4a**	$(CH_2)_9OH$	16	**5c**	61	20	**6c**	72
9	Me	**4a**	$(CH_2)_8CO_2Me$	16	**5d**	86	20	**6d**	88
10	MOM	**4b**	Ph	20	**5e**	97	18	**6e**	80

[a] See references 11 and 13 for representative procedures. [b] 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 entry 1. [c] Isolated yields.



Scheme 3. γ-Carboline synthesis.

was first examined. The coupling reaction proceeded smoothly, producing the desired alkynylindole **5a** in a 93% yield (Table 1, entry 6). The alkynylindole **5a** was then heated with *tert*-butylamine at 100°C, with the expectation of forming the corresponding *tert*-butylimine. To our pleasant surprise, instead of the *tert*-butylimine, the γ-carboline product **6a** was detected by TLC analysis after 20 h and subsequently isolated in a 92% yield. This preliminary result prompted us to investigate the synthesis of 3-substituted γ-carbolines by the palladium/copper-catalyzed coupling and thermal cyclization of other terminal acetylenes.[13] The results of this study are summarized in Table 1, entries 7–10.

As shown in Table 1, the palladium-catalyzed Sonogashira coupling of 2-bromo-1-methylindole-3-carboxaldehyde (**4a**) with a variety of terminal acetylenes afforded good to excellent yields of the corresponding 2-alkynyl-1-methylindole-3-carboxaldehydes. The *tert*-butylimines, generated in situ by heating the corresponding aldehydes with *tert*-butylamine, underwent spontaneous thermal cyclization to produce the desired 3-substituted γ-carbolines in good to excellent yields. As we expected, alkyl-substituted terminal acetylenes have again proven successful in this γ-carboline synthesis. For example, 1-decyne gave 82 and 87% yields of the coupling product **5b** and γ-carboline **6b**, respectively (entry 7). Unfortunately, 3-butyn-1-ol, which is 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 the coupling product **5c** and the corresponding γ-carboline **6c** in 61 and 72% yields, respectively (entry 8). Moreover, methyl 10-undecynoate also underwent coupling and cyclization successfully, affording an 86% yield of the coupling product **5d** and an 88% yield of the γ-carboline **6d** (entry 9). Finally, the *N*-methoxymethyl-substituted bromoindole **4b** was employed in the palladium-catalyzed coupling and thermal cyclization of phenylacetylene. The coupling afforded the alkynylindole **5e** in a 97% yield, and the cyclization generated the desired γ-carboline **6e** in an 80% yield (entry 10).

Mechanistically, it is believed that the carbon–carbon triple bond of the alkynyl *tert*-butylimine is nucleophilically attacked by the nitrogen of the imine moiety due to its close proximity. The cyclization, either catalyzed by CuI (β-carboline synthesis) or promoted by heat (γ-carboline synthesis), forms an aromatic carbolinium salt with a *tert*-butyl group on the nitrogen. As previously suggested by Heck,[14] the *tert*-butyl group apparently fragments to isobutene, relieving the strain resulting from interaction with the substituent present on the neighboring carbon.

In conclusion, an efficient synthesis of β- and γ-carbolines by the palladium/copper-catalyzed coupling and copper-catalyzed or thermal cyclization of terminal acetylenes has been developed. A variety of functionalized terminal acetylenes participate in this process to afford the desired nitrogen heterocycles in good to excellent yields. Further investigation into the scope and limitations of this β- and γ-carboline synthesis is under way.

Acknowledgements

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11. A representative procedure for the β-carboline synthesis follows: CuI (1 mg, 1 mol%), $PdCl_2(PPh_3)_2$ (7 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 then 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. The precipitates and solvent were then removed by filtration and evaporation, and the coupling product was isolated by column chromatography. 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 heated at 100°C for 24 h and then cooled, diluted with ether, dried (Na_2SO_4), and filtered. The solvent was evaporated, affording the corresponding *tert*-butylimine, which was then 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. The solvent was removed under reduced pressure and the β-carboline was isolated by column chromatography.
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13. A representative procedure for the γ-carboline synthesis follows: DMF (0.4 mL) was added in the coupling reactions to increase the solubility of the *N*-substituted 2-bromoindole-3-carboxaldehydes. The rest of the procedure is similar to that used in the β-carboline synthesis. The coupling product was transferred to a 2-dram vial and *tert*-butylamine (5 mL/mmol) was added. The mixture was flushed with Ar and heated at 100°C for the indicated period of time. The solvent was evaporated and the residue was purified by column chromatography.
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