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Three-step synthesis of an annulated β -carboline via palladium catalysis

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Abstract

The synthesis of β -carbolines is a mature field, yet new methods are desirable to introduce new functionality onto the core scaffold. We describe the incorporation of an additional fused ring onto the β -carboline via a novel palladium-catalyzed, one-pot Sonogashira coupling/intramolecular [2+2+2] cyclization. This method generates three rings in one flask and produces an annulated β -carboline in 80% yield. A preliminary mechanistic study into the sequence of events is described, which confirms an unprecedented catalytic role for palladium.

Keywords

β -carboline; cyclotrimerization; Sonogashira coupling; palladium catalysis; heteroannulation

β -Carbolines are a class of indole alkaloids that contain a unique pyrido[3,4-*b*]indole framework with well-documented neuroactivity.¹ Simple β -carbolines like harman (**1**) are produced endogenously in humans but are also found in foods and beverages such as cooked meat and fish, coffee, cigarette smoke, and fermented beverages.² More complex β -carbolines (**2–4**) have been isolated from plants and marine invertebrates as secondary metabolites and are decorated by substituent groups that impart a wide range of biochemical and pharmacological functions.^{1b} For example, eudistomin U (**2**) binds DNA and has been shown to have antibacterial activity.³ (*S*)-Brevicolline (**3**) strengthens labor contractions in pregnant women with abnormally relaxed muscle tissue⁴ while hyrtioerectine A (**4**) and plakortamine D (**5**) are cytotoxic to human cervical and colon cancer cell lines, respectively.⁵

The extensive biological activity of this class of molecules has naturally attracted much attention from the synthetic community. Traditional methods toward β -carbolines involve Pictet-Spengler⁶ or Bischler-Napieralski⁷ condensations of tryptamine or tryptophan, followed by aromatization.⁸ More recent approaches have involved palladium-catalyzed cross-coupling methodologies,⁹ aza-Wittig/electrocyclic ring closures,¹⁰ gold(III)-catalyzed

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Supplementary data

Supplementary data associated with this article, including all experimental details and the full characterization of **8**, **9**, and **10**, can be found in the online version.

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cycloisomerizations,¹¹ inverse electron demand Diels-Alder reactions,¹² and oxidative C-H/C-H couplings.¹³

Recently, an intermolecular [2+2+2] cyclization reaction catalyzed by either Ru(II) or Rh(I) was reported between diynes and nitriles, along with its application in the synthesis of eudistomin U (**2**).¹⁴ Since the nitrile component in these reactions must be electron deficient and in large excess, we hypothesized that synthesis of a 3,4-annulated β -carboline could proceed intramolecularly via [2+2+2] cyclization without any activation of the nitrile. There are very few methods for preparing carbolines bearing an extra fused ring on the pyridyl unit, many of which involve annulation of a preformed pyridine to the indole nitrogen.¹⁵ Development of new methodology that would form the pyridine at a later stage while simultaneously creating a new ring would create a novel heterocyclic scaffold in only a few steps. In this paper, we report the synthesis of a 3,4-dihydropyrrolo- β -carboline via a surprising one-pot palladium-catalyzed Sonogashira/desilylation/[2+2+2]-cyclization reaction. We will further describe our preliminary investigations into its mechanism.

We modeled our synthesis after the highly efficient Rh-catalyzed [2+2+2] cyclotrimerization employed by Witulski et al.¹⁶ in their syntheses of annulated carbazoles. We began by preparing aryl iodide **6** according to a two-step literature procedure. Upon reacting iodide **6** with terminal alkyne **7** under Sonogashira cross coupling conditions,¹⁷ we obtained trimethylsilylalkyne **8** in 44% yield along with the fully cyclized β -carboline **9** as a minor byproduct (15%). This was a largely fortuitous discovery, but suggested to us that the synthesis of complex heterocycle **9** could proceed under mild conditions in as few as three steps.

Given this unexpected observation, we optimized the reaction conditions to maximize the yield of our ultimate target, β -carboline **9**. We first screened a variety of Pd(0) and Pd(II) catalysts under otherwise identical conditions. Table 1 shows that Pd(0) catalysts give a slightly better yield of cyclized product **9** than Pd(II) catalysts (entries 1–5), with the highest combined yield obtained using Pd(PPh₃)₄. Microwave irradiation resulted in complete consumption of starting material **6** but low overall yield of the cyclized product **9** (entry 6, 26%). Optimal conditions were observed when an additional 5% Pd(PPh₃)₄ was added to the reaction mixture after 2 h and stirred overnight (entry 7, 80%). Interestingly, a lower yield was observed under extended heating, suggesting that **8** is thermally unstable (entry 8, 36%). This was confirmed by ¹H NMR experiments in *d*₇-DMF, which showed 78% decomposition of **8** after 21 h at 80 °C.

With optimized conditions in hand, we briefly examined the mechanism of this reaction. When trimethylsilylacetylene **8** was heated in the absence of any catalyst (Et₃N:DMF (2:1), 80 °C, 2h), neither desilylation nor [2+2+2] cyclization products were observed by thin-layer chromatography. Identical results were obtained when 10% CuI and 10% PPh₃ were independently added. Upon treatment with Pd(PPh₃)₄, however, complete conversion to the fully cyclized β -carboline **9** was observed in 91% yield (Scheme 2), an unprecedented mechanistic outcome for Pd(0). Cyclotrimerizations involving a nitrile as a π -donor have not been observed previously under palladium catalysis, but this result is not surprising given numerous examples of palladium-catalyzed cyclotrimerizations that yield substituted benzenes.¹⁸ It is interesting to note, however, that Witulski did not report any significant cyclotrimerization under identical conditions for annulated carbazoles.

It is unclear whether desilylation occurs before or after [2+2+2] cyclization. Interestingly, we have never observed terminal alkyne product **10** as an intermediate in these reactions. However, terminal alkyne **10** prepared independently underwent [2+2+2] cyclization to provide β -carboline **9** in very low yield, suggesting a protective role for the TMS group. One

can envision converting terminal alkyne **10** into a variety of internal alkynes prior to [2+2+2] cyclization, similar to methods already reported in the literature.¹⁴

A key difference between the one-pot procedure (**6**→**9**) and the conversion of **8** to **9** directly is the presence of a proton source, an important distinction since both starting substrates yield the same product. While it is reasonable to propose that deprotonation of alkyne **7** with triethylamine could easily serve as a proton shuttle later in the mechanism, no such pathway exists during the conversion of **8** to **9**. When this latter reaction was quenched with DCl during workup, the ¹H NMR showed only a protiated species, indicating that the pyridinyl C–H bond forms earlier in the catalytic cycle. A more thorough understanding of this mechanism is needed to determine the exact sequence of events. Overall though, these results demonstrate that Pd(PPh₃)₄ facilitates two distinct catalytic cycles: Sonogashira cross coupling and [2+2+2] cyclization.

In conclusion, we have described a strategy for the synthesis of new heterocycles bearing an additional fused ring on a β-carboline core. These 3,4-annulated β-carbolines are accessible in as few as three steps using inexpensive substrates. The key transformation in this sequence is a palladium-catalyzed Sonogashira/desilylation/[2+2+2]-cyclization that constructs three rings in one reaction flask. This methodology has enormous potential to generate new heterocyclic scaffolds with diverse skeletal arrangements and opens the door to an unexplored niche in Pd-catalysis. Complete substrate scope and functional group compatibility studies are currently being investigated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Naturally occurring β -carbolines

Scheme 1.
Synthesis of a 3,4-annulated β -carboline

Scheme 2.
Palladium-catalyzed [2+2+2] cyclizations

Table 1

Optimization of the One-Pot Sonogashira/Desilylation/[2+2+2] Cyclization

Entry	Conditions ^a	Isolated yield of 8 (%)	Isolated yield of 9 (%)
1	5% PdCl ₂ (PPh ₃) ₂ , 10 % CuI, 10% PPh ₃	44	15
2	5% PdCl ₂ , 10 % CuI, 10% PPh ₃	48	18
3	5% Pd(OAc) ₂ , 10 % CuI, 10% PPh ₃	53	17
4	5% Pd ₂ (dba) ₃ , 10 % CuI, 10% PPh ₃	44	20
5	5% Pd(PPh ₃) ₄ , 10 % CuI, 10% PPh ₃	58	21
6	5% Pd(PPh ₃) ₄ , 10 % CuI, 10% PPh ₃ , μ -wave, 180 °C, 5 min	0	26
7 ^b	5% Pd(PPh ₃) ₄ , 10 % CuI, 10% PPh ₃	0	80
8	5% Pd(PPh ₃) ₄ , 10 % CuI, 10% PPh ₃ , 24 h	8	36

^a All reactions were performed in a mixture of Et₃N:DMF (2:1) at 80 °C for 2 h unless otherwise noted;

^b An additional 5% Pd(PPh₃)₄ was added after 2 h and stirred at 80 °C for another 17 h.