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Metal-Catalyzed Cyclotrimerization Reactions of Cyanamides: Synthesis of 2-Aryl-α-carbolines

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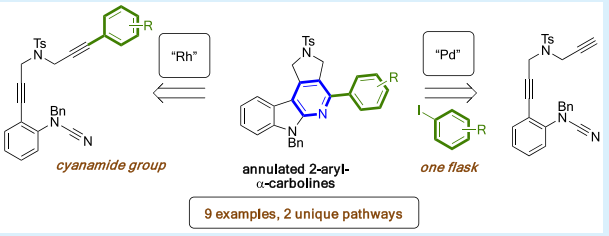
ABSTRACT: The synthesis of annulated 2-aryl-α-carboline heterocycles is described using transition metal catalysis. A linear strategy is described that uses Rh(I) catalysis to form the α-carboline scaffold by [2+2+2] cyclotrimerization. Alternatively, a tandem catalytic approach using a Pd(II) precatalyst afforded the same target molecules by mediating a Sonogashira reaction and a [2+2+2] cyclotrimerization in the same reaction flask. In each case, nine different 2-aryl-α-carbolines have been prepared in high to modest isolated yields.



The challenge of forming multiple bonds or multiple rings in a single reaction flask has attracted the attention of organic chemists because of the advantages such reactions might have in terms of synthetic efficiency and atom economy. Several approaches to solving this problem, including strategic retrosynthetic disconnections, biomimetic synthesis, and cascade or multicomponent reactions, have invariably accelerated complex molecule construction.[1−4] A common feature of many of these methods involves the strategic use of transition metals in the development of new reaction methodologies.[5−9] Our group has been interested in the use of transition metal catalysis for the construction of elaborate pyridine-containing heterocycles, which are often important pharmacophores in drug discovery. In particular, we have disclosed Rh(I)- and Pd(0)-catalyzed methods for the synthesis of β-carboline heterocycles.[10−12] While β-carbolines have attracted interest from both the academic organic chemistry community and the pharmaceutical industry, investigations involving their α-carboline isomer are much rarer. In this Letter, we describe two new methods for the construction of complex α-carbolines using transition metal catalysis.

α-Carbolines are pyrido[2,3-*b*]indoles whose core scaffold is present in several natural products and bioactive pharmaceuticals. For example, mescengricin (**1**) is a neuronal cell-protecting substance,[13] while implitapide (**2**) is a microsomal triglyceride transfer protein inhibitor used to treat atherosclerosis.[14] Other α-carboline structures include the grossularines **3**−**5**, which are cytotoxic against human and mouse tumor cells,[15] and cryptotackieine **6**, which has antiplasmodial activity against chloroquine-resistant strains of *Plasmodium falciparum* (Figure 1).[16] α-Carbolines **3**−**6** are unique in that they contain additional fused rings that pose a higher level of complexity from a synthetic standpoint. In fact, very few structure−activity studies have been performed on annulated α-carbolines due to a lack of reaction methodology to access them. Most current methods, while robust and high-yielding, typically involve the coupling of two smaller fragments to build the α-carboline core that precludes the simultaneous formation of additional ring annulations.[17−20] Thus, we hypothesized that we could adapt our initial work on the synthesis of β-carbolines to the α-isomer to access these structures.

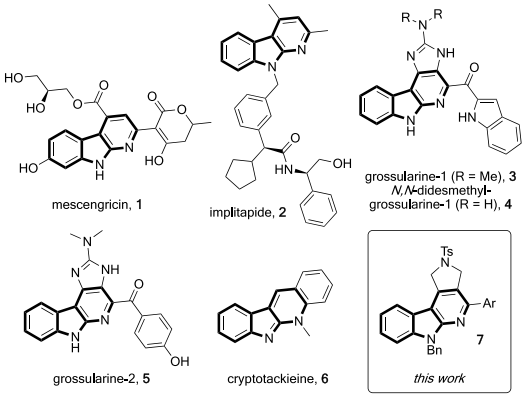


Figure 1. Naturally occurring α-carbolines.

In this work, we have adopted a retrosynthetic strategy that makes use of an intramolecular [2+2+2] cyclotrimerization[21−24] reaction in the last step of the synthesis to form the annulated pyrido[2,3-*b*]indole ring.[25,26] This approach

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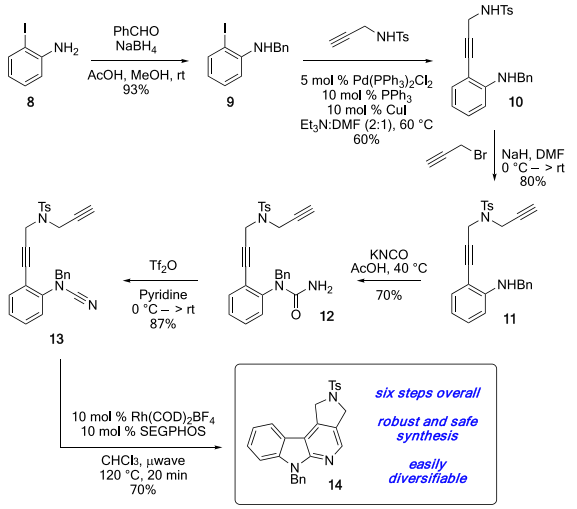
required us to prepare an intermediate that contained two alkyne units and a cyanamide functional group. This follows closely our own precedent for using dialkynyl nitrile intermediates for [2+2+2] cyclotrimerizations,[10−12] but with the added challenge of introducing a highly reactive and hydrolytically unstable cyanamide as a key intermediate. The use of cyanamide intermediates in [2+2+2] cyclotrimerization reactions was recently described for an intermolecular reaction between an alkynyl nitrile and an exogenous alkyne using a nickel(0) catalyst,[27] providing good precedent for our strategy. While this is the only example of a [2+2+2] methodology toward α-carbolines, only a few substrates were reported. By contrast, our approach offers the advantage of rapid synthesis using microwave irradiation that is amenable to further diversification under mild conditions.

The synthesis of the cyanamide intermediate is described in Scheme 1. We began by protecting the commercially available

Scheme 1. Synthesis of the Diynyl Cyanamide Substrate and Rh(I)-Catalyzed [2+2+2] Cyclotrimerization

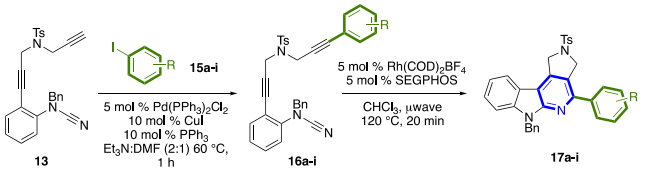


2-iodoaniline with a benzyl group via reductive amination. Installation of the first alkyne unit proceeded smoothly via Sonogashira coupling[28] to afford the internal alkyne **10**.

Remarkably, this reaction could be performed on a gram scale with no interference from the free amino groups. Introduction of a propargyl group, however, proved more challenging. Using propargyl alcohol as a reagent under Mitsunobu conditions[29] gave a complex mixture that was inseparable from impurities via column chromatography. Luckily, selective deprotonation of the sulfonamide N−H followed by alkylation with propargyl bromide afforded the terminal alkyne **11** in good yield. Direct incorporation of the cyanamide functional group by $NCS/Zn(CN)_2$ was unsuccessful and led to modest yields with an appreciable amount of recovered starting material.[30] We did not want to use the highly toxic reagent cyanogen bromide,[31] so we ultimately decided to perform a two-step procedure involving urea formation and dehydration with trifluoromethanesulfonic anhydride.[32] This sequence led to the formation of cyanamide **13** in good overall yield. Cyanamide **13** was stable and could be stored under an inert atmosphere at 4 °C for months without decomposition. With cyanamide intermediate **13** in hand, we used Tanaka's standard conditions[25] to perform the [2+2+2] cyclotrimerization. Under microwave irradiation at 120 °C, annulated α-carboline **14** could be isolated in good yield after just 20 min. A screen of seven different solvents was performed, which identified chloroform as the ideal solvent (see Table S1 for the full details).

We recognized that cyanamide **13** was a privileged intermediate that could be further functionalized at the terminal alkyne position via Sonogashira coupling. The resulting internal alkynes **16a−i** that would result could then undergo [2+2+2] cyclotrimerization to yield a diverse collection of 2-aryl-substituted annulated α-carbolines **17a−i**. Table 1 summarizes this strategy using nine different

Table 1. Two-Step Synthesis of 2-Aryl-α-carbolines via Sequential Palladium and Rhodium Catalysis



entry	iodoarene **15a-i**	yield of **16a-i** (%)[a]	yield of **17a-i** (%)[b]
a		88	96
b		94	90
c		95	87
d		89	91
e		88	69
f		92	66
g		79	88
h		97	96
i		96	98

[a]Standard conditions: 1.0 equiv of **13**, 1.1 equiv of **15a−i**, 5 mol % $Pd(PPh_3)_2Cl_2$, 10 mol % CuI, 10 mol % PPh_3, 2:1 Et_3N/DMF (0.04 M), 60 °C, 1 h. [b]Standard conditions: 1.0 equiv of **16a−i**, 5 mol % $Rh(COD)_2BF_4$, 5 mol % SEGPHOS, $CHCl_3$ (0.01 M), microwave irradiation, 120 °C, 300 W, 20 min.

commercially available iodoarenes. The Sonogashira reaction proceeds smoothly in all cases to afford the internal alkyne as an isolable intermediate, as long as the reaction is monitored closely by TLC (*vide infra*). Employing the standard cyclotrimerization conditions resulted in the 2-aryl-substituted annulated α-carbolines in excellent yields. The yields of this strategy are generally high across a range of functional groups. Especially notable is the benzonitrile substituent (entry b), which did not interfere in the [2+2+2] cyclotrimerization.

During this proof-of-principle study, we noticed the tendency for the Sonogashira couplings to give mixed results depending on the length of the reaction. We ultimately discovered that leaving the reaction mixture to stir for longer periods of time at high temperatures led to the formation of α-carbolines **17a−i**, which reduced the overall yield of the Sonogashira product but conveniently gave the ultimate target. This was not surprising to us, because we also observed this tandem catalysis in the preparation of β-carbolines. Because this unexpected side reaction offered us an opportunity to

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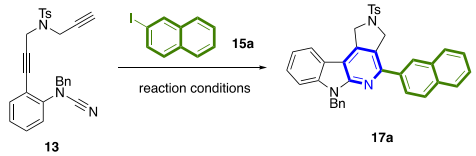
further shorten the synthesis of these substrates, we wanted to determine whether such tandem palladium catalysis could be used in the construction of the same set of α-carbolines in Table 1. Such a strategy is novel because the product will result only if a single catalyst can perform more than one unique chemical reaction.

We chose 2-iodonaphthalene as a model substrate for identifying reaction conditions suitable for this transformation, which are summarized in Table 2. Conventional heating of

Table 2. Optimization of the Reaction of the Tandem Pd-Catalyzed [2+2+2] Cyclotrimerization[a]



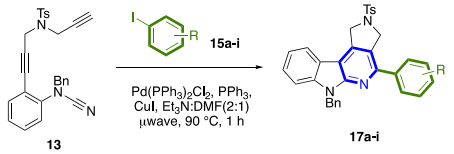
entry	catalyst (5 mol %)	solvent	yield of **17a** (%)
1	$PdCl_2(PPh_3)_2$	$CHCl_3$	19
2	$PdCl_2(PPh_3)_2$	MeCN	19
3	$PdCl_2(PPh_3)_2$	DMF	30
4	$PdCl_2(PPh_3)_2$	$PhCH_3$	11
5	$PdCl_2(PPh_3)_2$	dioxane	31
6	$PdCl_2(PPh_3)_2$	pyridine	10
7	$PdCl_2(PPh_3)_2$	Et_3N/DMF (2:1)	24
8[b]	$Pd(dba)_2$	Et_3N/DMF (2:1)	26
9[b]	$Pd(PPh_3)_4$	Et_3N/DMF (2:1)	21
10[b]	$PdCl_2$	Et_3N/DMF (2:1)	29
11[b]	$Pd_2(dba)_3$	Et_3N/DMF (2:1)	30
12[b]	$Pd(OAc)_2$	Et_3N/DMF (2:1)	16
13[b]	$PdCl_2(MeCN)_2$	Et_3N/DMF (2:1)	8
14[b]	Xphos Pd G2	Et_3N/DMF (2:1)	21
15[b]	$PdCl_2(PPh_3)_2$	Et_3N/DMF (2:1)	46
16[b,c]	$PdCl_2(PPh_3)_2$	Et_3N/DMF (2:1)	36
17[b–d]	$PdCl_2(PPh_3)_2$	Et_3N/DMF (2:1)	73
18[e]	$PdCl_2(PPh_3)_2$	Et_3N/DMF (2:1)	decomposition

[a]All reactions were performed for 30 min under microwave irradiation at 80 °C and 300 W (0.015 M). [b]With 10 mol % PPh_3. [c]At 90 °C. [d]For 60 min. [e]Conventional heating to 80 °C.

these reaction mixtures resulted in decomposition of the starting material, so we focused on reducing the reaction time using microwave irradiation. Reaction solvents other than a 2:1 Et_3N/DMF mixture resulted in poor isolated yields. In addition, Pd(0) precatalysts resulted in yields that were lower than those with Pd(II) precursors. Finally, the addition of 10 mol % PPh_3 resulted in an increase in the yield of **16a**, with the optimal condition found after heating for 60 min (entry 17). Optimization of the reaction time provided a balance among complete consumption of the starting material, formation of the cyclized product from the Sonogashira intermediate, and prevention of decomposition. Interestingly, when substrate **13** was subjected to the microwave irradiation at 90 °C for 30 min without the addition of an exogenous aryl iodide, α-carboline **14** was formed in only 34% yield, suggesting that terminal alkynes are poor substrates for the [2+2+2] cyclotrimerization reaction.

Using the optimized conditions, we subjected cyanamide precursor **13** to tandem catalysis with each of the iodoarene substrates **15a–i** in a multicomponent reaction. These results are summarized in Table 3. Low yields were obtained with a few substituents, in particular the benzonitrile (**17b**) and

Table 3. Substrate Scope of the Tandem Pd-Catalyzed [2+2+2] Cyclotrimerization



entry	iodoarene	yield of **17a-i** (%)[a]
a		73
b		11
c		41
d		30
e		34
f		47
g		20
h		62
i		36

[a]Standard conditions: 1.0 equiv of **13**, 1.1 equiv of **15a–i**, 5 mol % $Pd(PPh_3)_2Cl_2$, 10 mol % CuI, 10 mol % PPh_3, 2:1 Et_3N/DMF (0.015 M), 60 °C, microwave irradiation for 1 h, 90 °C, 300 W, 1 h.

anisole (**17g**) derivatives. Modest to good yields were obtained for the other substrates, which include both electron-donating and electron-withdrawing substituents. These results indicate that, while tandem palladium catalysis is an attractive route to some substrates, the isolated yields are more variable than those of the analogous Rh(I)-catalyzed pathway.

In summary, we have developed two new routes to 2-aryl-substituted annulated α-carbolines using transition metal catalysis. These methods demonstrate that Rh(I) and Pd(II) precursor complexes can mediate reactions that lead to elaborate pyridine-containing heterocycles via [2+2+2] cyclotrimerization reactions. The functional group tolerance of these pathways is better for the stepwise sequence under Rh(I) catalysis than the Pd(II)-catalyzed one-pot procedure. However, the tandem catalytic pathway provides a short alternative route to these densely functionalized heterocycles. Research efforts in this area will continue with an increase in the functional group and architectural diversity of the target molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00891.

Experimental procedures and accompanying analytical data (^1H and ^{13}C NMR, IR, and MS) for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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