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One-Pot Synthesis of α-Carbolines via Sequential Palladium-Catalyzed Aryl Amination and Intramolecular Arylation

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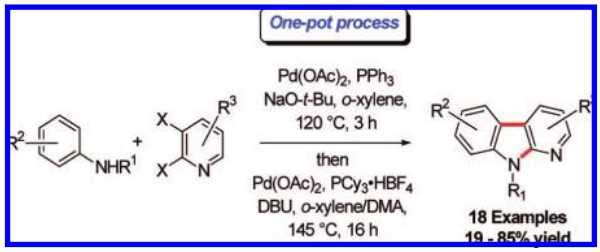

A one-pot synthesis of α-carbolines via a palladium-catalyzed aryl amination followed by intramolecular arylation is described. 2,3-Dichloro- and 2,3-dibromopyridines have been shown to react with readily available anilines to obtain various substituted α-carbolines in moderate to excellent yields.

Several natural products have been isolated that contain a pyrido[2,3-*b*]indole (α-carboline, **1a**) including mescengricin (**2**),[1] an inhibitor of L-glutamate excitotoxicity in neurons, and the marine cytotoxic agents grossularine-1 (**3a**) and grossularine-2 (**3b**) (Figure 1).[2] Interestingly, α-carboline byproduct has also been detected from the combustion of protein-containing foods and tobacco.[3] Furthermore, synthetic α-carbolines have demonstrated an array of biological properties, including anxiolytic, anti-inflammatory, and central nervous system stimulating activities.[4]

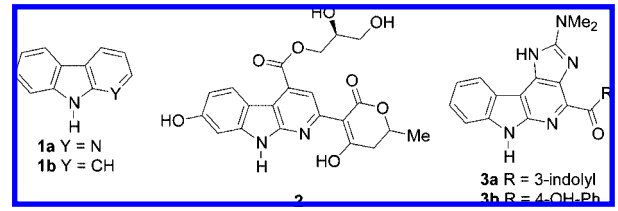

FIGURE 1. Natural products that contain an α-carboline core.

The modified Graebe−Ullmann reaction of triazoles,[5] intramolecular Diels−Alder reactions,[6] and cyclizations of azaindoles[7] have been utilized to synthesize α-carbolines (**1a**). In many cases, these multistep processes result in poor overall yields of the α-carbolines and often suffer from limited accessibility of starting materials. In addition, many of these methods are capable of yielding products with only limited substitution patterns. Other methods that involve either annulation of the pyridine ring onto indole derivatives[8] or by formation of the pyrrole ring via intramolecular cyclization of appropriately substituted *N*-phenyl-2-pyridinamines or 3-phenylpyridines have also been reported.[9]

More recently, palladium-catalyzed one-pot syntheses of N-substituted carbazoles (**1b**) have been described that utilize either a domino Suzuki cross-coupling/S_NAr reaction of aniline-derived boronic esters with electron-deficient 2-fluoro-3-halobenzene[10] or reaction between *N*-phenylanilines and 2,3-dichlorobenzene (Scheme 1, Route A, Y = CH).[11] However, only two examples of N-substituted α-carbolines and no

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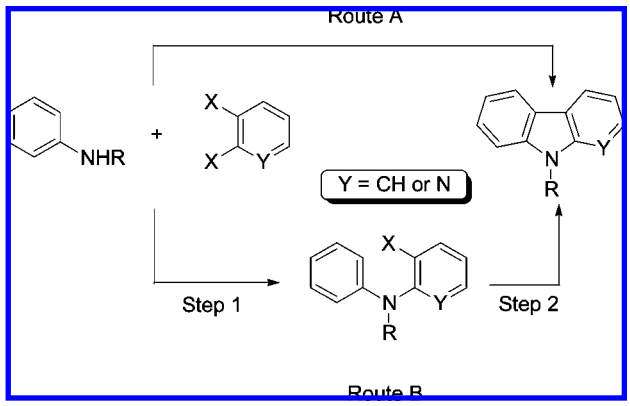
SCHEME 1. One-Pot Domino (Route A) or Sequential (Route B) Reactions To Produce α-Carbolines (1a) and Carbazoles (1b)



examples of N-unsubstituted α-carbolines were disclosed in these reports (Scheme 1, Route A, Y = N). Herein, we report methodology for the synthesis of α-carbolines via a one-pot sequential palladium-catalyzed aryl aminations of 2,3-dihalopyridines followed by intramolecular arylations of the 3-halo-*N*-phenyl-2-pyridinamine intermediates (Scheme 1, Route B, Y = N). This methodology allowed direct access to both N-substituted and N-unsubstituted α-carbolines.

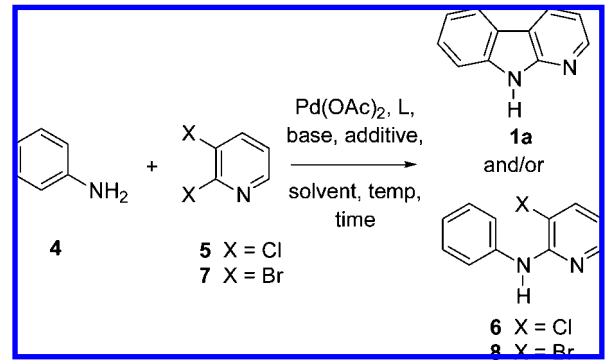
Initial attempts to mediate a domino reaction between aniline (**4**) and 2,3-dichloropyridine (**5**) utilizing reaction conditions similar to those used to prepare a N-substituted α-carboline in a one-pot synthesis by Ackermann and Althammer [5 mol % of $Pd(OAc)_2$ and 10 mol % of $PCy_3 \cdot HBF_4$, K_3PO_4, or NaO-*t*-Bu, NMP,[12] or toluene, 130 or 105 °C] did not yield the desired N-unsubstituted α-carboline **1a** (Table 1, entries 1 and 2).[11] The only product isolated was 3-chloro-*N*-phenyl-2-pyridinamine (**6**)[13] in 20−25% yield, resulting from the initial coupling reaction of aniline to the 2-position of the 2,3-dichloropyridine. Changing the ligand to PPh_3, the solvent to *o*-xylene, and elevating the temperature to 145 °C did provide **1a**, albeit in only 15% yield (entry 3) along with intermediate **6**. Conducting the reaction in the absence of ligand or in the presence of other common phosphine ligands (i.e., DPPF, BINAP, DIPHOS, *t*-Bu_2PMe, DavePhos, or DCHPB) was less effective. Likewise, other bases (i.e., NaOAc, KOAc, Li_2CO_3, Na_2CO_3, K_2CO_3, Cs_2CO_3, or K_3PO_4) or solvents (i.e., *o*-xylene/DMA (2:1), toluene/DMA (2:1), pyridine, DMF, NMP, nitrobenzene, or dioxane) or additives (i.e., LiI, TBAB, AgOAc) offered no improvement in the synthesis of the α-carboline. Conducting the reaction in the presence of PPh_3 and NaO-*t*-Bu in *o*-xylene for 3 h, but lowering the temperature to 120 °C, proved to be excellent conditions for preparing intermediate **6** in 79% isolated yield (entry 4). Similarly, 2,3-dibromopyridine (**7**) under the same reaction conditions generated 3-bromo-*N*-phenyl-2-pyridinamine (**8**)[9c] in 76% isolated yield (entry 5).

The cyclization of **6**, however, did occur in the presence of $PCy_3 \cdot HBF_4$ as ligand, DBU[9d,e] as base and a mixed solvent system [i.e., 10 mol % of $Pd(OAc)_2$, 20 mol % of $PCy_3 \cdot HBF_4$, 200 mol % of DBU, *o*-xylene/DMA (1:1), 145 °C, 16 h] to give α-carboline **1a** in 95% isolated yield. Similarly, **8** under the same reaction conditions provided **1a** in 90% yield.

The effects of the byproduct NaX (X = Cl or Br) and *t*-BuOH, which forms in the aryl amination step, on the intramolecular arylation step were examined. Repeating the cyclization reactions of **6** or **8** in the presence of 1 equiv of NaCl or NaBr and *t*-BuOH reduced the yield of **1a** to 72 and 75%, respectively, along with minor amounts (<10%) of the dehalogenated derivative.[14] These results demonstrate that the byproduct from the aryl amination step only minimally affects the cyclization step during the attempted domino reaction.

Given that optimized reaction conditions were identified for each the aryl amination and intramolecular arylation steps, attempts were next made to allow for the conversion of **4** and

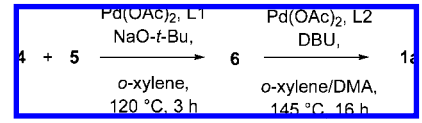
TABLE 1. Attempted One-Pot Domino Synthesis of N-Unsubstituted α-Carboline 1a from the Reaction of 4 with 5 or 7



entry	ligand	base	solvent	temp (°C), time (h)	yield (%) 1a	yield (%) 6 or 8
1	PCy_3[a]	K_3PO_4	NMP	130, 18	0	**6** (20)[b]
2	PCy_3[a]	NaO-*t*-Bu	tol[c]	105, 18	0	**6** (25)[b]
3	PPh_3	NaO-*t*-Bu	*o*-xyl[d]	145, 40	15	**6** (48)
4	PPh_3	NaO-*t*-Bu	*o*-xyl[d]	120, 3	0	**6** (79)
5	PPh_3	NaO-*t*-Bu	*o*-xyl[d]	120, 3	0	**8** (76)

[a] $PCy_3 \cdot HBF_4$ was used. [b] Remainder was unreactive starting materials. [c] Toluene. [d] *o*-Xylene.

TABLE 2. Optimization of the One-Pot Sequential Synthesis of N-Unsubstituted α-Carboline 1a from 4 and 5[a]



entry	L1	L2	solvent ratio[b]	yield **1a** (%)
1	PPh_3		1:1	<5
2	PCy_3[c]		1:1	<5
3	PPh_3	PCy_3[c]	1:1	60
4	PPh_3	PCy_3[c]	1:2	15
5	PPh_3	PCy_3[c]	2:1	40
6	PPh_3	PCy_3[c,d]	1:1	28

[a] Reaction conditions: 5 mol % of $Pd(OAc)_2$, 10 mol % of L1, 120 mol % of NaO-*t*-Bu, *o*-xylene (0.4 M), 120 °C, 3 h followed by addition of 5 mol % of $Pd(OAc)_2$, 10 mol % of L2, 200 mol % of DBU, *o*-xylene/DMA, 145 °C, 16 h. [b] *o*-Xylene/DMA. [c] $PCy_3 \cdot HBF_4$ was used. [d] No additional $Pd(OAc)_2$ was added for the second reaction.

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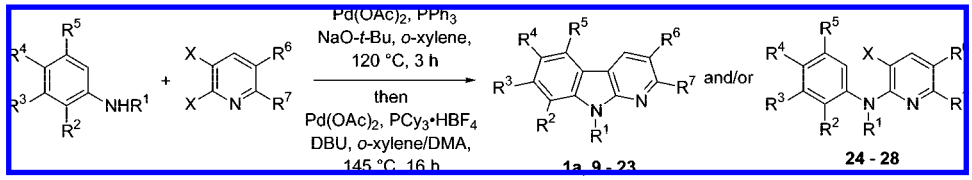
TABLE 3. Synthesis of Various Substituted α-Carbolines[a]



entry	X	R^1	R^2	R^3	R^4	R^5	R^6	R^7	yield **1a**, **9**−**23** (%)[b]	yield **24**−**28** (%)
1	Cl	H	H	H	H	H	H	H	**1a** (60)	---
2	Br	H	H	H	H	H	H	H	**1a** (61)	---
3	Cl	H	H	H	OMe	H	H	H	**9** (38)	**24** (40)
4[c]	Cl	H	H	H	OMe	H	H	H	**9** (71)	---
5	Cl	H	H	H	F	H	H	H	**10** (70)	---
6	Cl	H	H	H	C(O)Me	H	H	H	**11** (68)	---
7	Br	H	H	H	CO_2-*t*-Bu	H	H	H	**12** (37)	**25** (38)
8[d]	Cl	H	OMe	H	H	H	H	H	**13** (68)	---
9	Cl	H	F	H	H	H	H	H	**14** (72)	---
10	Cl	H	Me	H	H	Me	H	H	**15** (25)	**26** (28)
11	Cl	H	F	H	H	F	H	H	**16** (63)	---
12	Cl	H	H	OMe	H	OMe	H	H	**---**	**27** (66)
13[d]	Cl	H	H	OMe	H	H	H	H	**17a** (65)	**---**
		H	H	H	H	OMe	H	H	**17b** (8)	
14	Cl	H	H	OCH_2O		H	H	**18a** (59)	---	
		H	H	H	OCH_2O		H	**18b** (19)		
15	Br	H	H	OBn	H	H	H	H	**19a** (53)	---
		H	H	H	H	OBn	H	H	**19b** (5)	
16	Cl	H	H	F	H	H	H	H	**20a20b** (85)[e]	---
		H	H	H	H	F	H	H		
17	Cl	Ph	H	H	H	H	CF_3	H	**21** (52)[f]	---
18	Cl	Me	H	H	H	H	CF_3	H	**22** (74)	---
19	Br	H	H	H	H	H	H	OEt	**23** (19)	**28** (61)

[a] Reaction conditions: 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, 120 mol % of NaO-*t*-Bu, *o*-xylene (0.4 M), 120 °C, 3 h followed by addition of 5 mol % of $Pd(OAc)_2$, 10 mol % of $PCy_3 \cdot HBF_4$, 200 mol % of DBU, *o*-xylene/DMA (1:1), 145 °C, 16 h. [b] Unless otherwise noted, the intermediate *N*-phenyl-2-pyridinamine was not observed. [c] Reaction time extended from 16 to 36 h. [d] 10 mol % Pd catalyst and 20 mol % ligand were used in each step. [e] Combined yield of **20a** and **20b** (1:2). [f] Approximately 22% of the starting material remained as determined by HPCL analysis. Increasing the reaction time of the first step from 3 to 20 h did not change the yield.

5 to **1a** in a one-pot sequential reaction. When either PPh_3 or $PCy_3 \cdot HBF_4$ was utilized as the ligand for both reaction steps, very low yields of **1a** were obtained (Table 2, entries 1 and 2). However, when the first reaction was conducted using PPh_3 as ligand and then the subsequent reaction conducted in the presence of $PCy_3 \cdot HBF_4$, **1a** was obtained in 60% isolated yield (entry 3). It is noteworthy that the addition of DMA as solvent and DBU as base in the second step was necessary. In addition, the presence of the solvent and base from the initial reaction (i.e., *o*-xylene and NaO-*t*-Bu) did not prevent the second reaction from proceeding. Variation of the solvent ratios indicated that a 1:1 mixture in the second reaction step of the sequence gave the highest yield of α-carboline (entries 3−5). Finally, additional $Pd(OAc)_2$ was required in the second step (entry 6). When the $PCy_3 \cdot HBF_4$ was added for the second reaction without an additional 5 mol % of $Pd(OAc)_2$, **1a** was obtained in significantly lower yield.

Utilizing the optimized protocol for the one-pot sequential synthesis of α-carbolines [5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3, 120 mol % of NaO-*t*-Bu, *o*-xylene (0.4 M), 120 °C, 3 h followed by addition of 5 mol % of $Pd(OAc)_2$, 10 mol % of $PCy_3 \cdot HBF_4$, 200 mol % of DBU, *o*-xylene/DMA (1:1), 145 °C, 16 h], the scope of the reaction was examined. The reaction of 2,3-dicholoropyridine (**5**) or 2,3-dibromopyridine (**7**) with aniline (**4**) resulted in similar yields of **1a** (Table 3, entries 1 and 2). The reaction of 4-anisidine with **5** gave a lower yield of α-carboline **9** (entry 3). However, when the second step of the reaction sequence was prolonged to 36 h, the yield was increased to 71% (entry 4). Anilines containing electron-withdrawing substituents at the 4-position proved to be good substrates (entries 5 and 6). Although ethyl 4-aminobenzoate did not provide the desired α-carboline, presumably due to the instability of the ethyl ester under the basic reaction conditions, the *tert*-butyl ester did give the desired α-carboline **12** in moderate yield (entry 7). Substrates with an electron-donating (i.e., OMe) or -withdrawing (i.e., F) group at the 2-position of the aniline also resulted in good yields of α-carbolines (entries 8 and 9). However, introduction of an additional substituent at the 5-position of the aniline was tolerated, but in the case of an electron-donating group, it resulted in lower yield (entries 10 and 11). When electron-donating groups were in both the 3- and 5-positions of the aniline, no α-carboline was obtained. However, the *N*-phenyl-2-pyridinamine intermediate **27** was isolated in 66% yield (entry 12). Anilines containing substituents in the 3- or 3,4-positions resulted in a mixture of regioisomeric α-carbolines. The major isomers resulted from C−C bond formation *para* to the electron-donating groups (entries 13−15). However, for an electron-withdrawing substituent (i.e., F), C−C bond formation was predominantly at the *ortho*-position, which is in agreement with observations reported for other palladium-catalyzed intramolecular arylations (entry 16).[15] *N*-Phenyl- and *N*-methylanilines coupled with 2,3-dichloro-5-trifluoropyridine resulted in good yields of **21**[11] and **22**, respectively (entries 17 and 18). Finally, the reaction of 2,3-dibromo-6-ethoxypyridine with aniline gave α-carboline **23**, albeit in low yield (19%).

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The *N*-phenyl-2-pyridinamine intermediate **28** was also isolated in 61% yield (entry 19).

In conclusion, a sequential one-pot synthesis of α-carbolines from readily available starting materials via palladium-catalyzed aryl amination followed by an intramolecular arylation has been developed. This methodology provided an array of α-carbolines in moderate to excellent yields and will facilitate the synthesis of additional derivatives that can be used for various applications, including screening for biological activities. Efforts to identify a single phosphine ligand, base, and solvent system that would allow for a domino reaction to produce α-carbolines from various anilines and 2,3-dihalopyridines are also continuing.

Experimental Section

General Procedure for the Synthesis of α-Carbolines. A mixture of 2,3-dihalopyridine (1 mmol), aniline (1.1 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), PPh_3 (26 mg, 0.1 mmol), and NaO-*t*-Bu (115 mg, 1.2 mmol) in *o*-xylene (2.5 mL) was sparged with argon for about 5 min, placed under an argon atmosphere, and heated at 120 °C for 3 h in a screw-capped sample vial. The reaction mixture was allowed to cool to room temperature and then $Pd(OAc)_2$ (11 mg, 0.05 mmol), $PCy_3 \cdot HBF_4$ (37 mg, 0.1 mmol), DBU (305 mg, 2 mmol), and DMA (2.5 mL) were added to the reaction vessel. The reaction mixture was again sparged for about 5 min, placed under an argon atmosphere, and heated at 145 °C for about 16 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (60 mL) with heating at 40−50 °C. The mixture was washed several times with water and then brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent to give the α-carbolines.

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Supporting Information Available: Characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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