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Synthesis of α-Carbolines via Pd-Catalyzed Amidation and Vilsmeier−Haack Reaction of 3-Acetyl-2-chloroindoles

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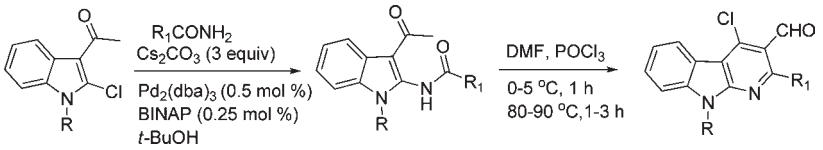
ABSTRACT



A new class of α-carboline derivatives has been synthesized by $Pd_2(dba)_3$/BINAP catalyzed amidation of 3-acetyl-2-chloroindoles followed by a Vilsmeier−Haack reaction and is reported.

Pyrido[2,3-*b*]indoles (α-carbolines) have been focused due to their biological activities which are antiviral and antitumor[1] due to the formation of intercalation complexes with DNA or the inhibition of topoisomerase II.[2] α-Carboline derivatives possess anxiolytic or neuroprotectant, anti-inflammatory activity[3] and are inhibitors of IKK-2. The α-carboline derivatives were also useful for the treatment of cancer and immune-related diseases.[4] The core structure of the pyrido[2,3-*b*]indoles is found in several naturally occurring alkaloids and carcinogenic metabolites (Figure 1).[5] α-Carbolines were also discerned in cigarette smoke and pyrolysis of protein-containing food products.[6]

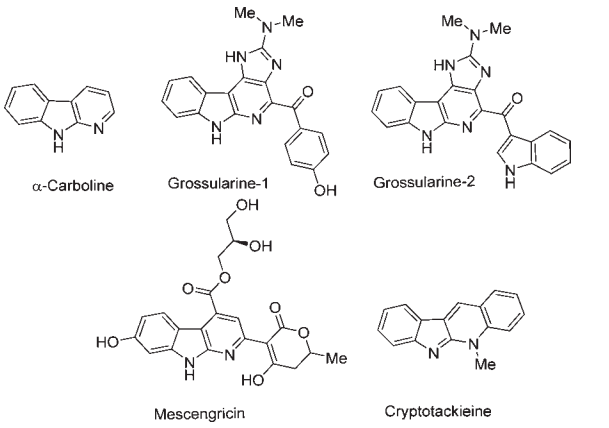


Figure 1. α-Carboline and α-carboline containing natural products.

In recent years Pd catalyzed C−N bond formation reactions have been paid great attention because the resulting molecules have been traditionally valuable in organic synthesis and pharmaceuticals[7] and have important electronic

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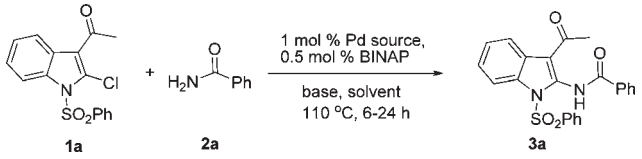
properties.[8] These reactions have been extensively studied by the groups of Buchwald and Hartwig.[9] Over the past decade Pd based catalyst systems using phosphine ligands have been developed,[10] and these systems were very useful in both industrial and academic laboratories[11] on both a minute and very large scale. While Pd catalyzed amidations of bromo and iodo compounds were well established,[12] and the amidation of chloro compounds was not. These results prompted us to explore the Pd catalyzed amidation of 3-acetyl-2-chloroindoles.

The Vilsmeier−Haack reaction is an efficient and economical method for the formylation of reactive aromatic,[13] heteroaromatic,[14] and conjugated carbocyclic systems.[15] This reaction has great importance in various synthetic methodologies,[16] and the results are noteworthy and exalting. In the literature the synthetic methods for the α-carbolines involve annulation of the pyridine ring onto indole derivatives;[17] multistep processes having poor yields and cyclizations of azaindoles[18] have been used. Due to the ubiquity of α-carbolines in many biologically active molecules we are exploring the synthetic methodology for the α-carboline through the Pd catalyzed cross-coupling amidation reactions of 3-acetyl-2-chloroindoles followed by cyclization with the Vilsmeier−Haack reaction.

Table 1. Optimization of the Pd-Catalyzed Cross-Coupling of 1-(2-Chloro-1-(phenylsulfonyl)-1*H*-indol-3-yl)ethanone and Benzamide[a]



entry	Pd source	base	solvent	yield(%)[b]
1	$Pd(OAc)_2$	K_2CO_3	toluene	49
2	$PdCl_2$	K_2CO_3	toluene	27
3	$PdCl_2(PPh_3)_2$	Cs_2CO_3	toluene	41
4	$[(allyl)PdCl]_2$	Cs_2CO_3	toluene	56
5	$Pd(OAc)_2/H_2O$ Act	K_2CO_3	dioxane	39
6	$Pd(OAc)_2/H_2O$ Act	K_3PO_4	toluene	43
7	$Pd(OAc)_2/H_2O$ Act	Cs_2CO_3	toluene	41
8	$Pd(OAe)_2/H_2O$ Act	Cs_2CO_3	*t*-BuOH	35
9	$Pd(OAc)_2/H_2O$ Act	Cs_2CO_3	DMSO	20
10	**$Pd_2(dba)_3$**	**Cs_2CO_3**	***t*-BuOH**	**95**
11	$Pd_2(dba)_3$	K_2CO_3	*t*-BuOH	84
12	$Pd_2(dba)_3$	K_3PO_4	*t*-BuOH	76
13	$Pd_2(dba)_3$	*t*-BuOK	*t*-BuOH	62
14	$Pd_2(dba)_3$	Cs_2CO_3	DME	67
15	$Pd_2(dba)_3$	Cs_2CO_3	toluene	45
16	$Pd_2(dba)_3$	Cs_2CO_3	DMSO	21
17	$Pd_2(dba)_3$	K_2CO_3	DMF	10
18	$PdCl_2$	Cs_2CO_3	*t*-BuOH	40
19	$Pd(OAc)_2$	Cs_2CO_3	*t*-BuOH	32
20	$PdCl_2$	K_2CO_3	*t*-BuOH	35

[a] Conditions: 1-(2-chloro-1-(phenylsulfonyl)-1*H*-indol-3-yl)ethanone (1.0 mmol), benzamide (1.2 mmol), Pd (1 mol %), BINAP (0.25 mol %), base (3.0 mmol), solvent (2.0 mL/mmol), 110 °C, 6−24 h. [b] Isolated yields.

3-Acetyl-2-chloroindoles (**1b**) can be easily prepared from the Vilsmeier−Haack reaction of 2-oxindole followed by protection.[19] We initiated probing the conditions under which the coupling reaction of 1-(2-chloro-1-(phenylsulfonyl)-1*H*-indol-3-yl)ethanone and benzamide proceeded efficiently. We screened different catalysts and ligands as depicted in Tables 1 and 2, respectively. We found that the $Pd_2(dba)_3$/BINAP catalyst system is efficient for the cross-coupling of a variety of primary amides with 3-acetyl-2-chloroindoles. Significantly better results were obtained by using this catalyst system as shown in Table 3. For example, the reaction of 1-(2-chloro-1-(phenylsulfonyl)-1*H*-indol-3-yl)ethanone with benzamide using 0.5 mol % of $Pd_2(dba)_3$ and 0.25 mol % of (±)-BINAP afforded the desired product (**3a**) with 95% yield in 6 h as shown in Table 3. The structure of **3h** is also confirmed by the single crystal X-ray crystal structure as shown in Figure 2.[20] Most of the reactions

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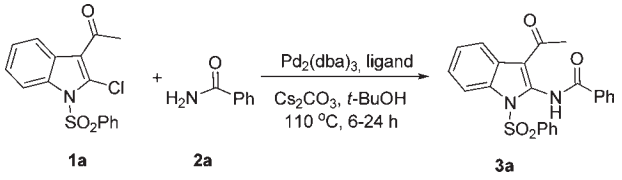
(20) (a) The CCDC deposition number of **3h** is 806183; molecular formula, $C_{14}H_{16}N_2O_2$; chemical formula weight is 244.28; triclinic; unit cell parameters: *a* 7.1902(14) Å, *b* 10.650(2) Å, *c* 10.795(2) Å, α 104.16(3)°, *β* 103.50(3)°, *γ* 96.70(3)°, and space group *P*212121. (b) The CCDC deposition number of **4a** is 806182; molecular formula: $C_{17}H_{17}Cl_1N_2O_1$; chemical formula weight is 300.78; triclinic; unit cell parameters: *a* 7.1902(14) Å, *b* 10.650(2) Å, *c* 10.795(2) Å, α 104.16(3)°, *β* 103.50(3)°, *γ* 96.70(3)°, and space group $P\bar{1}$.

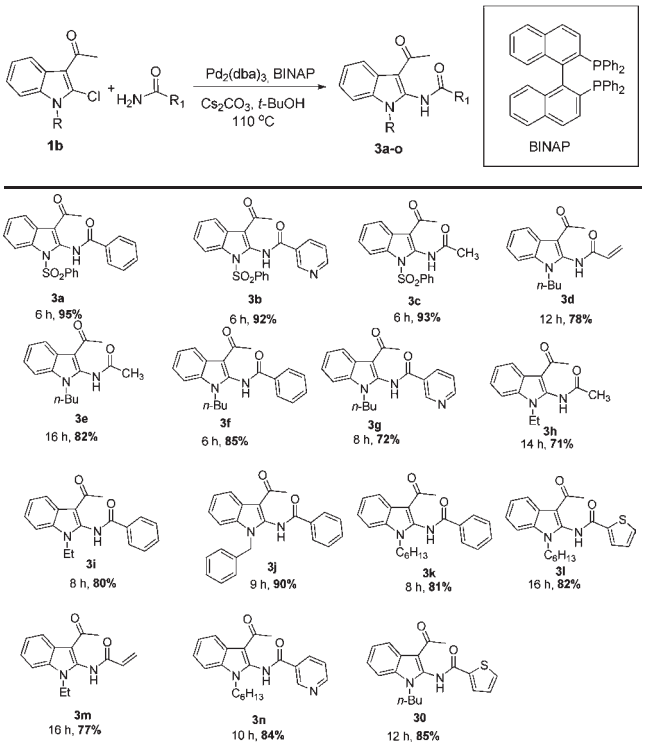
Table 2. Ligands Effect on Amidation of 1-(2-Chloro-1-(phenylsulfonyl)-1*H*-indol-3-yl)ethanone[a]



ligand	% conversion (time (h))	yield (%)[b]
PPh_3	40 (24)	32
PCy_3	65 (24)	57
DPPM	35 (24)	15
DPPE	20 (24)	–
DPPP	>4 (24)	–
Cyclodiphosphazane-[ClPN(*t*-Bu)]$_2$	53 (24)	47
BINAP	100 (6)	95

[a] Conditions: 1-(2-chloro-1-(phenylsulfonyl)-1*H*-indol-3-yl)ethanone (1.0 mmol), benzamide (1.2 mmol), $Pd_2(dba)_3$ (0.5 mol %), ligand (0.25 mol %), Cs_2CO_3 (3.0 mmol), solvent (2.0 mL/mmol), 110 °C, 6−24 h. [b] Isolated yields.

Table 3. Pd-Catalyzed Cross-Coupling of 3-Acetyl-2-chloroindoles and Amides



proceeded to completion in less than 24 h using the $Pd_2(dba)_3$/BINAP system. After completion of amidation reactions of 3-acetyl-2-chloroindoles we concluded that an electron-withdrawing group at the first position of 3-acetyl-2-chloroindoles gave excellent yields compared to an electron-releasing group.

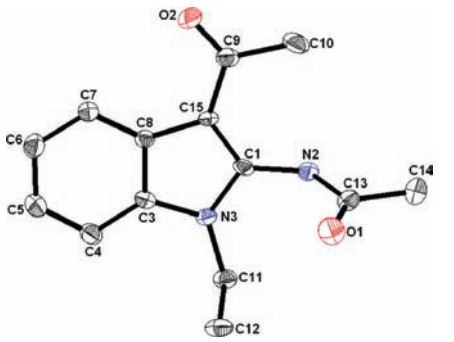
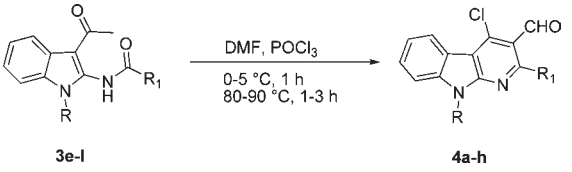
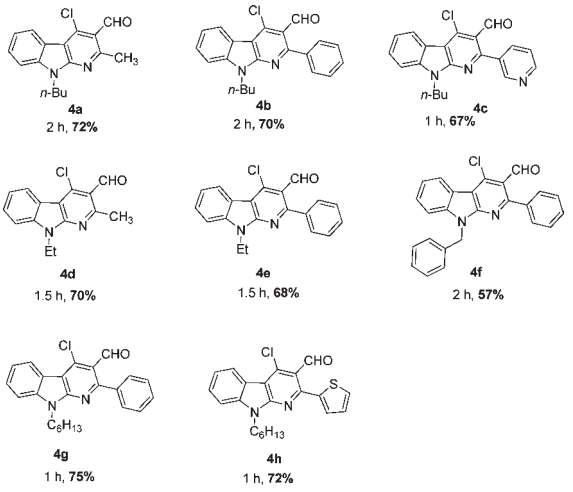


Figure 2. ORTEP diagram of **3h**.

Table 4. Vilsmeier−Haack Reaction of Amide Derivatives





Having developed a successful method for the synthesis of *N*-(3-acetyl-1-(substituted)-1*H*-indol-2-yl)amides, we focused on the synthesis of α-carbolines through a Vilsmeier−Haack reaction. The optimal reaction conditions for the Vilsmeier−Haack reaction were found to involve the use of 3.0 equiv of $POCl_3$ in DMF at 80−90 °C to give 2-substituted-α-carbolines **4a**−**h**. The conditions proved to be generally applicable to a wide range of *N*-(3-acetyl-1-(substituted)-1*H*-indol-2-yl)amides **3e**−**l** providing the appropriate 2-substituted-α-carbolines **4a**−**h** with good yields as shown in Table 4. The structure of 9-butyl-4-chloro-2-methyl-9*H*-pyrido[2,3-*b*]indol-3-carbaldehyde **4a** is also confirmed by single crystal X-ray analysis as shown in Figure 3.[20] This cyclization method is effective for the synthesis of 9-butyl-4-chloro-9*H*-pyrido[2,3-*b*]-indol-3-carbaldehyde **6a** with the use of excess (5 equiv)

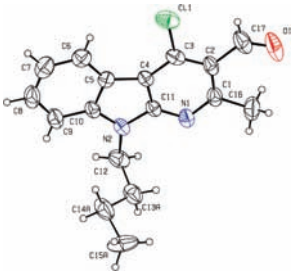
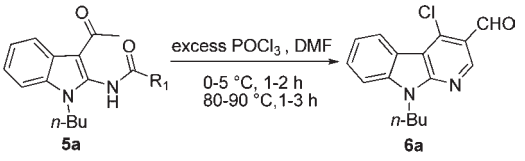


Figure 3. ORTEP diagram of **4a**.

Table 5. Vilsmeier−Haack Reaction of Amide Derivatives



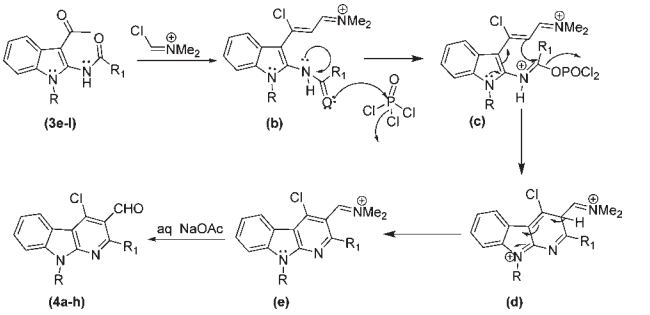
R_1	
= Methyl	1 h, **68%**
= Phenyl	3 h, **74%**
= Pyridyl	2 h, **72%**
= Thiophenyl	1 h, **78%**

$POCl_3$ as depicted in Table 5. 9-Butyl-4-chloro-9*H*-pyrido-[2,3-*b*]indol-3-carbaldehyde (**6a**) yields are increased when R_1 varies from methyl to thiophenyl.

Possible mechanisms for **4a**−**h** and **6a** are depicted in Schemes 1 and 2 (Supporting Information) respectively. In Scheme 1, chloromethyleneiminium salt formed from the DMF and $POCl_3$ reacts with **3e**−**l** and yielded the mono-chloromethyleneiminium salt (**b**) which reacts with $POCl_3$ to give (**c**) which is further involved in electrocyclization followed by hydrolysis in the presence of aqueous NaOAc to give **4a**−**h**. In Scheme 2 (Supporting Information),[21] (**a**) reacts with two molecules of chloromethyleneiminium salt

(21) See the Supporting Information.

Scheme 1. Possible Mechanism for **4a**−**h**



which is formed from the excess of $POCl_3$ and DMF yielded (**g**) which is involved in cyclization; elimination reactions followed by hydrolysis in presence of aqueous NaOAc gave **6a**.

In summary, we described a useful method for the synthesis of an array of α-carboline derivatives in good yields through Pd catalyzed amidation and a Vilsmeier−Haack reaction. This methodology provided the synthesis of additional α-carboline derivatives that can be useful for the various applications involving screening of biological activities. The biological studies of these α-carboline derivatives is currently underway in our laboratory.

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Supporting Information Available. Experimental procedures, Scheme 2, spectroscopic data, LC-MS and elemental analysis for all new compounds, and ORTEP diagram of **4a** (disordered butyl side chain). This material is available free of charge via the Internet at http://pubs.acs.org.