ORGANIC LETTERS

2011
Vol. 13, No. 6
1398–1401

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

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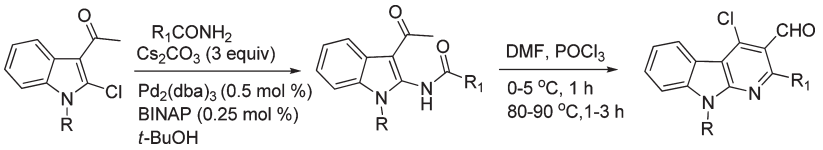
Received January 11, 2011

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]

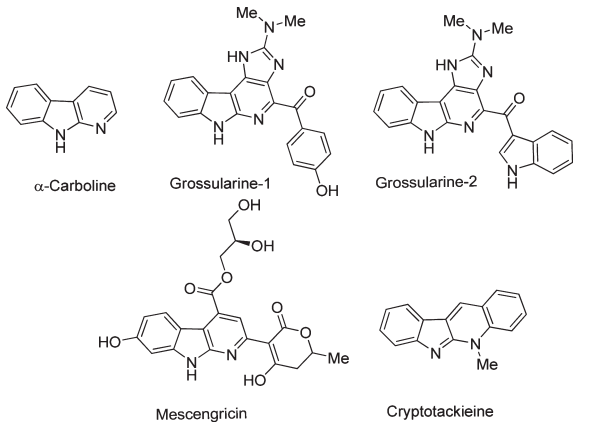


Figure 1. α-Carboline and α-carboline containing natural products.

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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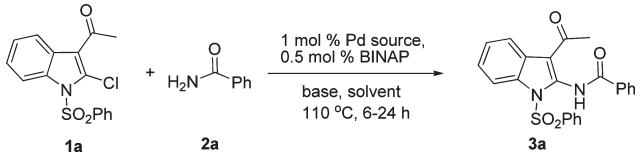
10.1021/ol2000827
Published on Web 02/11/2011

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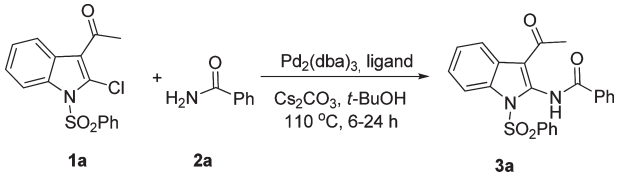
(20) (a) The CCDC deposition number of **3h** is 806183; molecular formula, $C_{14}H_{16}N_2O_2$; chemical formula weight is 244.28; triclinic; unit cell parameters: *a* 7.1902(14) Å, *b* 10.650(2) Å, *c* 10.795(2) Å, α 104.16(3)°, *β* 103.50(3)°, *γ* 96.70(3)°, and space group *P*212121. (b) The CCDC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

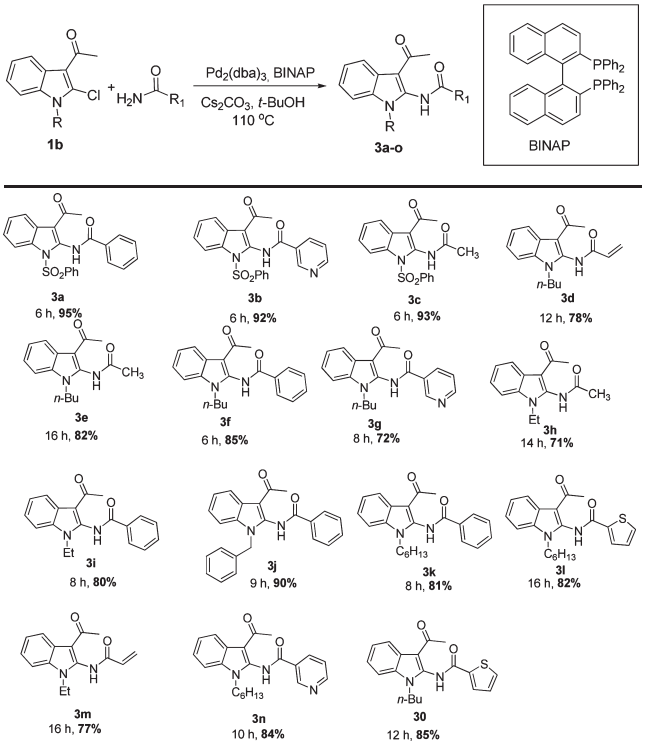


1a 2a 3a

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.

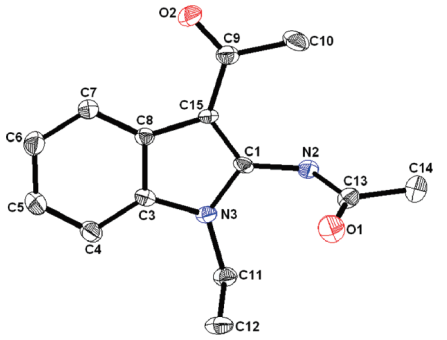
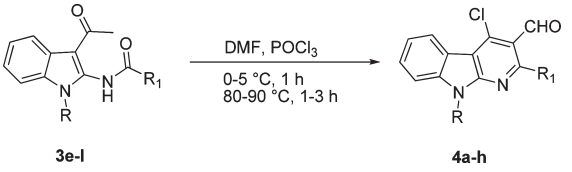
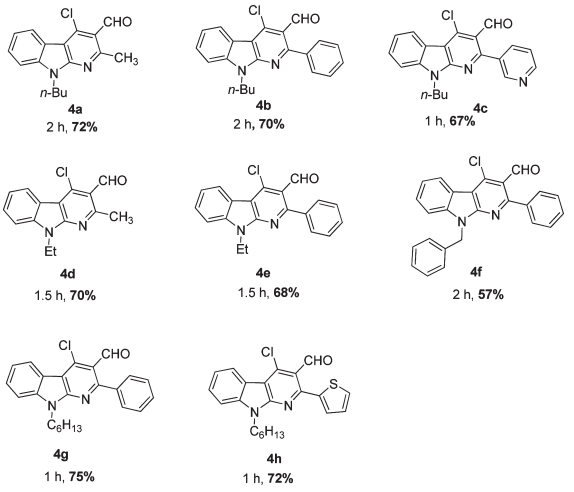


Figure 2. ORTEP diagram of **3h**.

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)

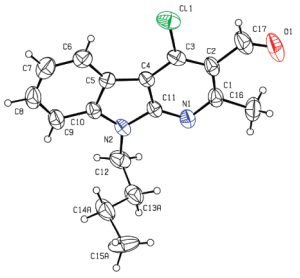
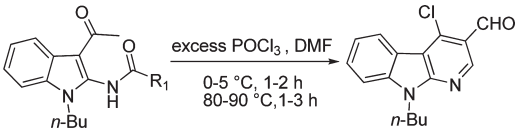


Figure 3. ORTEP diagram of **4a**.

Table 5. Vilsmeier−Haack Reaction of Amide Derivatives



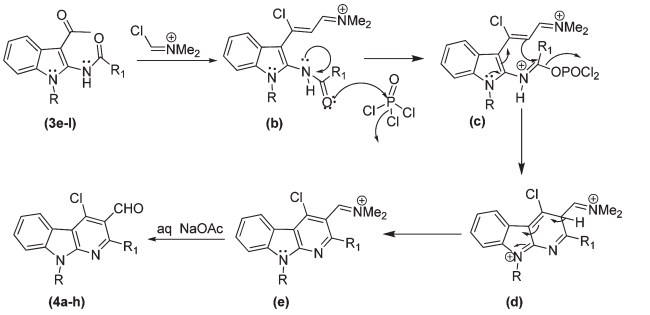
R_1	
= Methyl	1 h, **68%**
= Phenyl	3 h, **74%**
= Pyridyl	2 h, **72%**
= Thiophenyl	1 h, **78%**

$POCl_3$ 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.

Acknowledgment. We thank DST for financial support and for the single-crystal X-ray diffractometer facility in our school. A.S.K. thanks UGC for a senior research fellowship. A.S.K. also thanks Rambabu, Kishore, Bharat, Tanmay, Saikat Sen, Srinu, Anand, and Venu Srinivas for helping in crystal studies.

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.