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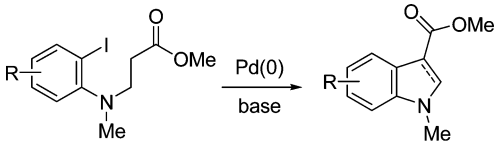
Synthesis of Indole-3-carboxylic Acid Derivatives by Pd(0)-Catalyzed Intramolecular α-Arylation of β-(2-Iodoanilino) Esters

Daniel Solé* and Olga Serrano

Laboratori de Química Orgànica, Facultat de Farmàcia, and Institut de Biomedicina (IBUB), Universitat de Barcelona, 08028-Barcelona, Spain

dsole@ub.edu

Received January 7, 2008



β-(2-Iodoanilino) esters undergo intramolecular α-arylation in the presence of $Pd(PPh_3)_4$ and potassium phenoxide. The reaction is a useful methodology for the preparation of indole-3-carboxylic acid ester derivatives.

The indole nucleus is a ubiquitous motif in bioactive natural products as well as synthetic pharmaceuticals.[1] Accordingly, after 100 years of intensive research, a variety of well-established methods for elaborating and functionalizing indoles are available. In particular, recent advances in the area of palladium-catalyzed transformations have led to the development of several reliable methods for the synthesis of indoles from simple starting materials.[2]

During the last years, the palladium-catalyzed arylation of enolate-type nucleophiles has received a great deal of attention.[3] The intermolecular versions of the reaction have been thoroughly explored, and it is now possible to introduce an aromatic moiety to a broad range of enolate-type nucleophiles.[4−9] In contrast, the intramolecular processes, which offer promising procedures for the construction of complex polycyclic compounds, have remained less explored. Among them, the most extensive study has been done on the intramolecular α-arylation of ketones[10−16] and amides,[17−22] while few examples of the use of dicarbonyl compounds,[23−25] aldehydes and nitro derivatives,[26] or esters[27] have been reported.

As part of our ongoing program on the synthesis of nitrogen heterocycles, we have been studying the palladium-catalyzed intramolecular coupling of amino-tethered vinyl[28] or aryl halides[12] with enolates.[29] During this work, we have also reported the palladium-catalyzed intramolecular acylation of β-(2-iodoanilino) esters to give 2,3-dihydroquinolin-4-ones.[30] This reaction appears to involve the formation of a four-membered azapalladacyclic transient intermediate, which strongly modifies the interaction of the metal center with the carbonyl group forcing the otherwise unfavorable nucleophilic attack. We realized that if we significantly increased the enolization of the ester we could overcome the nucleophilic attack at the alkoxy-

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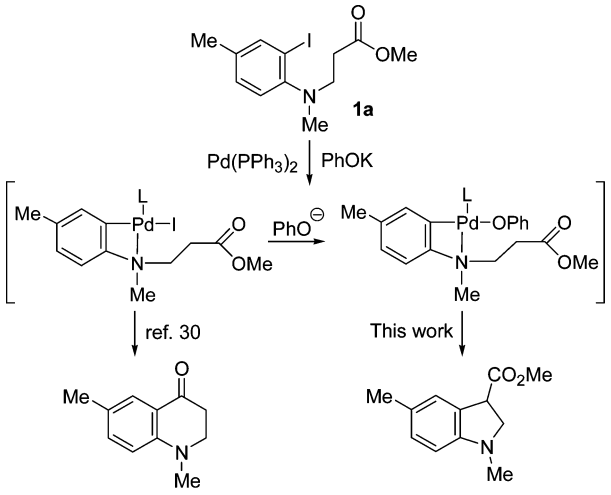
10.1021/jo800034m CCC: $40.75
Published on Web 02/20/2008

SCHEME 1



carbonyl group and favor the α-arylation (Scheme 1). The lower reactivity of esters and the relative instability of the *β*-amino ester moiety under basic conditions would make enolization a more challenging task. However, it should be noted that we have recently reported the Pd(0)-catalyzed intramolecular coupling of amino-tethered vinyl halides with esters using potassium phenoxide as the base.[28c]

We herein report our studies on the Pd(0)-catalyzed intramolecular α-arylation of *β*-(2-haloanilino) esters, which constitutes a useful methodology for the synthesis of functionalized indole-3-carboxylic acid ester derivatives.

Our efforts were initially focused on the reaction of esters **1a**,**b**. The most representative results of these studies are summarized in Table 1. We were pleased to find that, in the presence of 5% mol of $Pd(PPh_3)_4$ and 2.25 equiv of PhOK in refluxing THF, aryl iodide **1a** underwent the desired cyclization to give a reaction mixture in which indoline **2** was the only detected product (entry 1). The amount of the catalyst could be reduced to 2.5% mol without any effect on the cyclization reaction (entry 2). However, after column chromatography of the reaction mixtures, considerable amounts of indole **3**, produced by air oxidation of the cyclization product,[28,31] were isolated together with indoline **2**. It should be noted that, in contrast to the synthesis of indoles, the synthesis of indolines has received little attention, and apart from the intensively studied reduction of indoles,[32] only a few efficient methods have been reported.[33]

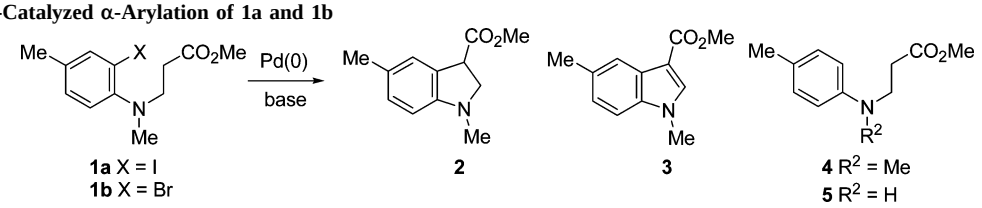
The use of LiO-*t*-Bu, a stronger base than PhOK, in combination with a biaryl-based phosphine[27] resulted in the formation of indole **3** as the main product (entry 3). On the other hand, the use of a weak base such as K_3PO_4 in the presence of a catalytic quantity of phenol[34] resulted in low reaction rates when using either THF (entry 4) or toluene as the solvent (entry 5), while the more polar solvent DMF directly afforded indole **3** (entries 6 and 7). Interestingly, the use of K_3PO_4 in DMF without phenol led to the formation of a complex reaction mixture from which indole **3** was isolated together with major amounts of anilines **4** and **5**[30,35] (entry 8).

Bromide **1b** was less efficient than iodide **1a** in the α-arylation reactions and afforded lower yields of the cyclization products (entries 9 and 10).

The scope of the α-arylation reaction was examined with respect to a range of differently substituted *β*-(2-iodoanilino) esters (Table 2). The results of optimization studies carried out with **1a** led us to use two general procedures for their cyclization reactions: method A, which is based on the use of PhOK (2.25 equiv) as the base, and method B, in which K_3PO_4 is used together with a catalytic amount of phenol.

As shown in Table 2, the reaction is applicable to iodoanilines with different electronic properties on the aromatic ring. It was

TABLE 1. Pd(0)-Catalyzed α-Arylation of 1a and 1b



1a X = I
1b X = Br

2

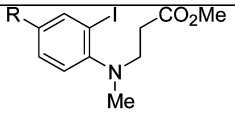
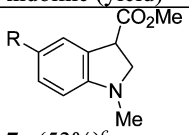
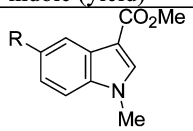
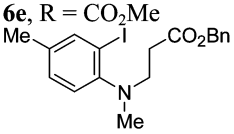
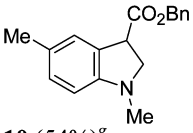
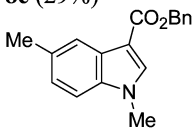
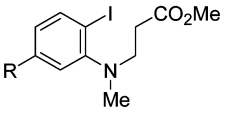
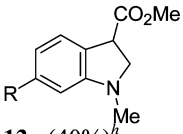
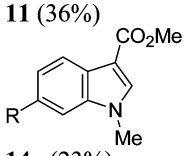
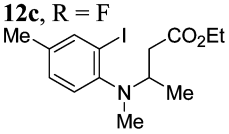
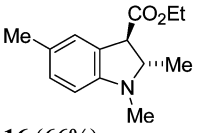
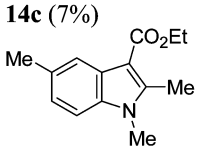
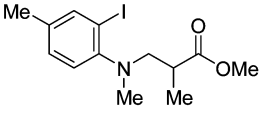
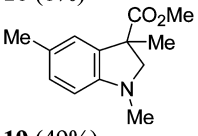
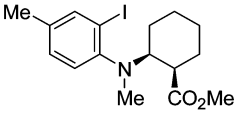
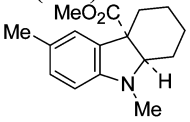
3

4 R^2 = Me
5 R^2 = H

entry	X	catalyst (%)	additives (equiv)	solvent	*T* (°C)/time (h)	NMR yield[a] (%)	isolated yield (%)
1	I	$Pd(PPh_3)_4$ (5)	KO^{t}Bu (2.25) phenol (2.75)	THF	reflux/7.5	**2** (87)	**2** (50), **3** (17)
2	I	$Pd(PPh_3)_4$ (2.5)	KO^{t}Bu (2.25) phenol (2.75)	THF	reflux/7.5	**2** (95)	**2** (56), **3** (5)
3	I	$Pd_2(dba)_3$ (5) L[b] (5.5)	LiO^{t}Bu (2)	dioxane[c]	90 °C/24		**2** (5), **3** (47)[d]
4	I	$Pd(PPh_3)_4$ (10)	K_3PO_4 (3) Phenol (0.3)	THF	reflux/24	**1a** (70), **2** (28)	
5	I	$Pd(PPh_3)_4$ (10)	K_3PO_4 (3) Phenol (0.3)	Toluene[c]	90 °C/48	**1a** (15), **2** (75)	**1a** (14), **2** (38), **3** (14)
6	I	$Pd(PPh_3)_4$ (10)	K_3PO_4 (3) phenol (0.3)	DMF[c]	90 °C/24		**3** (66)
7	I	$Pd(PPh_3)_4$ (5)	K_3PO_4 (3) phenol (0.3)	DMF[c]	90 °C/24		**3** (55)
8	I	$Pd(PPh_3)_4$ (10)	K_3PO_4 (3)	DMF[c]	110 °C/48		**3** (16), **4** (27), **5** (28)
9	Br	$Pd(PPh_3)_4$ (5)	KO^{t}Bu (2.25) phenol (2.75)	THF	reflux/24	**2** (73)	
10	Br	$Pd(PPh_3)_4$ (10)	K_3PO_4 (3) phenol (0.3)	DMF[c]	90 °C/24		**2** (17), **3** (30)

[a] Yield determined by ^{1}H NMR. [b] L: 2-diphenylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl. [c] The reaction was carried out in a sealed tube. [d] *tert*-Butyl 1,5-dimethylindole-3-carboxylate, which could not be separated from **2**, was also produced in 8% yield.

TABLE 2. **Synthesis of Indoles and Indolines by Pd(0)-Catalyzed α-Arylation of *β*-(2-Iodoanilino) Esters**

entry	ester	method[a]	time	indoline (yield)[b]	indole (yield)[b]
					
1	**6a**, R = H	A	8 h	**7a** (53%)[c]	**8a** (20%)
2	**6a**, R = H	B	24 h		**8a** (51%)
3	**6b**, R = OMe	A	8 h	**7b**[d]	**8b** (46%)
4	**6b**, R = OMe	B	48 h		**8b** (67%)
5	**6c**, R = Cl	A	24 h	**7c** (17%)	**8c** (6%)
6	**6c**, R = Cl	B	24 h		**8c** (32%)
7	**6d**, R = F	A	20 h		**8d** (70%)
8	**6d**, R = F	B	24 h		**8d** (60%)
9	**6e**, R = CO_2Me	A[e]	16 h		**8e** (24%)[f]
10	**6e**, R = CO_2Me	B	36 h		**8e** (29%)[f]
					
11	**9**	A	8 h	**10** (54%)[g]	**11** (7%)
12	**9**	B	48 h		**11** (36%)
					
13	**12a**, R = Me	A	8 h	**13a** (40%)[h]	**14a** (23%)
14	**12a**, R = Me	B	24 h	**13a** (24%)	**14a** (42%)
15	**12b**, R = Cl	A	24 h		**14b** (20%)
16	**12b**, R = Cl	B	24 h		**14b** (30%)
17	**12c**, R = F	A	24 h	**13c** (30%)	**14c** (20%)
18	**12c**, R = F	B	24 h		**14c** (7%)
					
19	**15**	A	8 h	**16** (66%)	
20	**15**	B	70 h	**16** (8%)	**17** (42%)[i]
					
21	**18**	A	24 h	**19** (49%)	
22	**18**	B	24 h	**19** (30%)[j]	
					
23	**20**	A	24 h	**21** (71%)	
24	**20**	B[k]	48 h	**21** (78%)	

[a] Method A: 5% mol of $Pd(PPh_3)_4$, phenol (2.75 equiv), and KO-*t*-Bu (2.25 equiv) in THF at reflux. Method B: 10% mol of $Pd(PPh_3)_4$, K_3PO_4 (3 equiv), and phenol (0.3 equiv) in DMF at 90 °C in a sealed tube. [b] Yields refer to pure products isolated by flash chromatography. [c] ^1H NMR analysis of the crude reaction mixture gave 72% yield of **7a** and 13% yield of **8a**. [d] ^1H NMR analysis of the crude reaction mixture gave 80% yield of **7b**. [e] 10% mol of $Pd(PPh_3)_4$. [f] Methyl 4-(methylamino)benzoate was also isolated. [g] ^1H NMR analysis of the crude reaction mixture gave 83% yield of **10**. [h] ^1H NMR analysis of the crude reaction mixture gave 80% yield of **13a** and 15% yield of **14a**. [i] *N*-methyl-*p*-toluidine was also isolated (6%). [j] Methyl 2-methyl-3-[*N*-methyl-*N*-(4-methylphenyl)amino]propionate was also isolated (11%). [k] 20% mol of $Pd(PPh_3)_4$.

found, however, that substrates with electron-withdrawing groups (Cl, F, and CO_2Me) at the arene ring underwent the α-arylation reaction in lower yields than those obtained from iodoanilines with electron-neutral (H and Me) or electron-donating groups (OMe). The low yields of the arylation reactions

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of **6c** are due in part to the formation of dechlorinated products. In general, the indolines could not be obtained in the 3-monosubstituted series, the corresponding indoles being formed directly. In the few cases in which the indolines were formed, their rapid oxidation to the indoles was again observed. On the contrary, the reaction could be successfully applied to the preparation of 2,3- and 3,3-disubstituted and 2,3,3-trisubstituted indolines (entries 19−24). Benzyl and ethyl esters can also be used as substrates in this reaction.

The effectiveness of PhOK in the aforementioned Pd(0)-catalyzed intramolecular arylation reactions is somewhat surprising since the pK_a of phenol is considerably lower than that of esters.[36] It should be noted that no competition was observed between the desired α-arylation and the nucleophilic attack at the alkoxycarbonyl group in any of the cyclization reactions reported in this work. Interestingly, although we previously reported that treatment of **1a** with $Pd(PPh_3)_4$ and K_3PO_4 in either THF or toluene resulted in a nucleophilic attack at the carbonyl,[30] the addition of a catalytic amount of phenol to the same reaction conditions promoted the α-arylation (Table 1, entries 4 and 5). In these reactions, the phenoxide anion might be playing an additional role to that of the base; it could also be acting as a ligand by displacing the iodide at the metal center. Thus, the formation of a transient palladium phenoxide complex would stabilize the otherwise unstable palladium intermediate, preventing the nucleophilic attack at the carbonyl. Moreover, the intramolecular reaction of the phenoxide ligand with the coordinated carbonyl group would facilitate the enolization.[34]

In summary, we have developed a new methodology for the synthesis of indole-3-carboxylic acid esters based on the Pd(0)-catalyzed intramolecular α-arylation of *β*-(2-iodoanilino) esters. Further studies to expand the methodology and provide deeper insight into the role of phenoxide in these processes are underway and will be published in due course.

Experimental Section

Representative Procedure for the Pd(0)-Catalyzed α-Arylation Using PhOK as the Base (Table 1, Entry 2). To a solution of ester **1a** (75 mg, 0.23 mmol) in THF (5 mL) were added under argon phenol (59 mg, 0.63 mmol), KO-*t*-Bu (0.5 mmol, 0.5 mL of 1 M solution in *tert*-butyl alcohol), and $Pd(PPh_3)_4$ (7 mg, 0.006 mmol). The solution was heated at reflux for 7.5 h. After being cooled at room temperature, the mixture was diluted with CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ and 1 N aqueous NaOH. The organic layer was dried and concentrated. The residue was purified by flash chromatography (Al_2O_3, from hexanes to hexanes−EtOAc 6%) to give indoline **2** (27 mg, 56%) and indole **3** (3 mg, 5%).

Representative Procedure for the Pd(0)-Catalyzed α-Arylation Using K_3PO_4 as the Base (Table 1, Entry 6). A mixture of ester **1a** (75 mg, 0.23 mmol), K_3PO_4 (143 mg, 0.68 mmol), phenol (6 mg, 0.068 mmol), and $Pd(PPh_3)_4$ (26 mg, 0.022 mmol) in DMF (3 mL) was stirred at 90 °C in a sealed tube for 48 h. The reaction mixture was poured into water and extracted with Et_2O. The organic extracts were washed with brine and with 1 N NaOH solution, dried, and concentrated. The residue was purified by flash chromatography (SiO_2, from hexanes to hexanes−EtOAc 10%) to give indole **3** (31 mg, 66%).

Methyl 1,5-dimethyl-2,3-dihydro-1*H*-indole-3-carboxylate (2): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 2.76 (s, 3H), 3.49 (t, J = 9 Hz, 1H), 3.61 (dd, J = 9 and 7.8 Hz, 1H), 3.77 (s, 3H), 4.08 (broad t, J = 8.4 Hz, 1H), 6.45 (d, J = 8.1 Hz, 1H), 6.96 (dm, J = 8.1 Hz, 1H), 7.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 20.7 (CH_3), 36.6 (CH_3), 46.0 (CH), 52.3 (CH_3), 58.1 (CH_2), 107.9 (CH), 125.5 (CH), 126.9 (C), 127.5 (C), 129.1 (CH), 150.7 (C), 172.5 (C). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.79; H, 7.37; N, 6.57.

Methyl 1,5-dimethylindole-3-carboxylate (3): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.49 (s, 3H), 3.80 (s, 3H), 3.90 (s, 3H), 7.12 (dd, J = 8.4 and 1.5 Hz, 1H), 7.23 (d, J = 8.4 Hz, 1H), 7.73 (s, 1H), 7.96 (m, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 21.5 (CH_3), 33.4 (CH_3), 50.9 (CH_3), 106.3 (C), 109.4 (CH), 121.2 (CH), 124.3 (CH), 126.8 (C), 131.4 (C), 135.1 (CH), 135.5 (C), 165.5 (C). Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 71.02; H, 6.43; N, 6.72.

Acknowledgment. This research was supported by MEC (Spain)-FEDER (Project No. CTQ2007-60573/BQU) and DURSI-Catalonia (Grant No. 2005SGR-00442). D.S. thanks the DURSI for "Distinció per a la promoció de la Recerca Universitària".

Supporting Information Available: Characterization data for all new compounds and experimental procedures for preparation of starting materials. ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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