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Selective Synthesis of Either Isoindole- or Isoindoline-1-carboxylic Acid Esters by Pd(0)-Catalyzed Enolate Arylation

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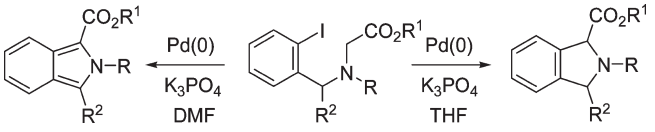

Two efficient palladium-catalyzed intramolecular α-arylation reactions of α-amino acid esters have been developed that allow either 1-isoindolecarboxylic acid esters or the corresponding isoindolines to be selectively synthesized simply by a slight change of reaction conditions.

The isoindole moiety and its reduced counterpart isoindoline (2,3-dihydro-1*H*-isoindole) have become attractive targets in organic and medicinal chemistry. These heterocyclic frameworks are an integral part of the structure of some biologically active compounds[1] and a few naturally occurring products.[2] Moreover, the isoindoles have been widely used for their high level of reactivity in cycloaddition reactions[3] and, more recently, for their fluorescent and electroluminescent properties,[4,5] which make them attractive candidates for organic light-emitting devices (OLEDs).[6]

However, the instability of the isoindole nucleus together with the lack of a general method for the synthesis of substituted derivatives have frequently restricted their use, creating a demand for new and straightforward methodologies to access these substrates. Apart from the aromatization of existing rings, the classical and most generally applicable methods for the synthesis of isoindoles include cyclizative condensations of *o*-disubstituted benzenes, elimination reactions (inter alia from isoindolinium salts, isoindoline *N*-oxides, or 2-substituted isoindolines), retrocycloaddition processes, and nucleophilic addition reactions to phthalamidines.[7] Recent progress in synthetic organic chemistry has led to the development of new methods for the preparation of diversely substituted isoindoles.[8]

Regarding the isoindoline family, the synthesis of 1- and 1,3-substituted derivatives is also clearly underdeveloped,[9] and very few reports about metal- or organocatalyzed syntheses of isoindolines can be found in the literature.[10]

As part of our ongoing program on the synthesis of nitrogen heterocycles,[11] we have recently reported an efficient methodology for the synthesis of indole-3-carboxylic acid derivatives based on the palladium-catalyzed intramolecular α-arylation of *β*-(2-iodoanilino) esters[12a] and amides.[12b] Interestingly, in the ester series, depending on the reaction conditions, the α-arylation reaction gave access to either indoles or indolines (Scheme 1).[12a]

These studies in the indole series and our previous discovery that isoindoles could be directly obtained by sequential palladium-catalyzed arylation/dehydrogenation of α-amino ketones[11c] (Scheme 2) encouraged us to examine the cyclization of α-amino esters to establish a general method for the synthesis of 1-isoindolecarboxylic acid esters.[13]

(1) (a) Bare, T. M.; Draper, C. W.; McLaren, C. D.; Pullan, L. M.; Patel, J.; Patel, J. B. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 55–60. (b) Portevin, B.; Tordjman, C.; Pastoureau, P.; Bonnet, J.; De Nanteuil, G. *J. Med. Chem.* **2000**, *43*, 4582–4593. (c) Kukkola, P. J.; Bilci, N. A.; Ikeler, T. J.; Savage, P.; Shetty, S. S.; DelGrande, D.; Jeng, A. Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1737–1740. (d) Diana, P.; Martorana, A.; Barraja, P.; Lauria, A.; Montalbano, A.; Americo, A.; Dattolo, G.; Cirrincione, G. *Bioorg. Med. Chem.* **2007**, *15*, 343–349. (e) Diana, P.; Martorana, A.; Barraja, P.; Montalbano, A.; Dattolo, G.; Cirrincione, G.; Dall'Acqua, F.; Salvador, A.; Vedaldi, D.; Basso, G.; Viola, G. *J. Med. Chem.* **2008**, *51*, 2387–2399. (f) Van Goethem, S.; Van der Veken, P.; Dubois, V.; Soroka, A.; Lambeir, A.-M.; Chen., X.; Haemers, A.; Scharpé, S.; De Meester, I.; Augustyns, K. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4159–4162.

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(3) For recent examples, see: (a) Chen, Y.-L.; Lee, M.-H.; Wong, W.-Y.; Lee, A. W. M. *Synlett* **2006**, 2510–2512. (b) Chen, Z.; Müller, P.; Swager, T. M. *Org. Lett.* **2006**, *8*, 273–276. (c) Rincón, R.; Plumet, J. *Synlett* **2008**, 911–913.

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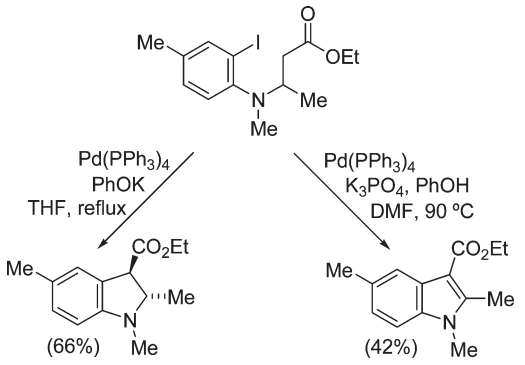
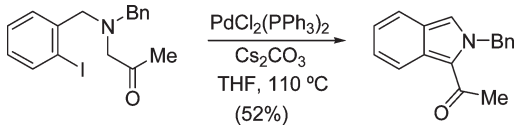
SCHEME 1



SCHEME 2



The ester group appeared to be an attractive substituent not only because it could be elaborated into other frameworks but also because, as part of a conjugated donor−acceptor system with the nitrogen, it would provide the isoindole nucleus with some electronic stabilization.

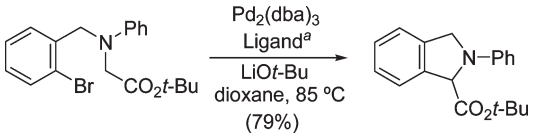
It should be noted that Buchwald has reported the synthesis of dihydroisoindoles by palladium-catalyzed intramolecular α-arylation[14] of *tert*-butyl α-amino esters (Scheme 3).[10a]

Herein, we report the development of palladium-catalyzed intramolecular α-arylation reactions of α-(2-iodobenzylamino) esters for the selective syntheses of either 1-isoindolecarboxylic acid esters or the corresponding isoindolines (Scheme 4).

Our initial investigation was carried out with iodides **1a** and **1d**, bromide **1b**, and triflate **1c**, screening a variety of bases, ligands, and solvents (see more details in the Supporting Information). These optimization studies gave us two different procedures for the cyclization reactions of **1a**. Thus, while the use of $Pd(PPh_3)_4$ (0.1 equiv) in combination with K_3PO_4 (3 equiv) as the base in THF at 110 °C (method A) gave isoindoline **2**, the use of $Pd(PPh_3)_4$ and K_3PO_4 together with a catalytic amount of phenol (0.3 equiv) in DMF at 90 °C (method B) afforded isoindole **3**, which results from the palladium-catalyzed dehydrogenation of the initially formed isoindoline.[15,16]

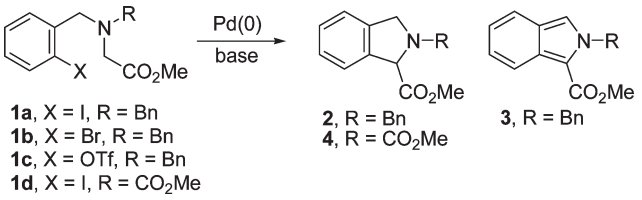
Although the additive phenol seems to play a positive role in the α-arylation reaction,[12a,17,18] it is not necessary for the palladium-catalyzed dehydrogenation process, as evidenced when isoindole **3** was obtained in 78% yield after treating isoindoline **2** with $Pd(PPh_3)_4$ (0.05 equiv) and K_3PO_4 (2 equiv) in DMF at 90 °C.

SCHEME 3[a]



[a]Ligand: 2-(diphenylphosphino)-2′-(*N*,*N*-dimethylamino)biphenyl.

SCHEME 4



Interestingly, under Buchwald's conditions, which involve the use of a biaryl-based phosphine as the ligand and *t*-BuOLi as the base,[10a] isoindole **3** was obtained in 44% yield. The different behavior of **1a** and the α-amino esters studied by Buchwald under these reaction conditions could be due to the substitution pattern of the substrates. Thus, the combination of the *N*-aryl substituent and the *tert*-butyl ester could have prevented the aromatization process.

Aryl bromide **1b**, triflate **1c**, and carbamate **1d** were less efficient than **1a** in the α-arylation reactions. None of them led to the corresponding isoindole under the reaction conditions optimized with **1a**, **1b** being completely unreactive and **1c** and **1d** decomposing.

The scope of the developed selective α-arylation processes was then examined using a range of diversely substituted α-(2-iodobenzylamino) esters (Tables 1 and 2).

As shown in Table 1, the synthesis of both isoindolines and isoindoles[19] was generally carried out with good yields. It should be noted that although we were able to isolate and characterize the majority of the isoindoles, they are rather unstable compounds with a high tendency to undergo aerial oxidation on standing in solution,[20] which necessitates avoiding any contact with chloroform.

The α-arylation reactions were not restricted to methyl esters. When ethyl and *tert*-butyl esters were used as substrates, both cyclization products were obtained in similar yields (entries 1−4). As previously observed during the optimization studies carried out with **1a**, isoindolines can be prepared using Cs_2CO_3 instead of K_3PO_4 although with lower yields (entries 6 and 11).[21] Under the reaction conditions of method A, the α-arylation of the amino esters bearing aryl substituents at the nitrogen proceeded more slowly than in the case of the *N*-benzyl-substituted substrates. Furthermore, it was not possible to characterize isoindoline **9d**, which was obtained from *p*-phenylendiamine

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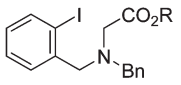
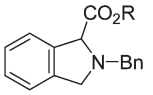
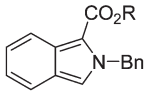
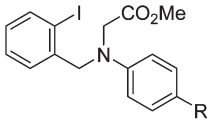
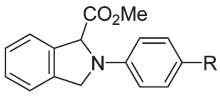
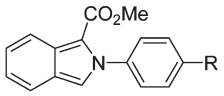
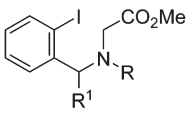
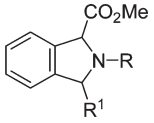
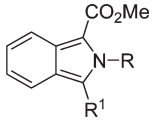
(21) The cyclization reaction of **8b** using Cs_2CO_3 as the base afforded a 4:1 mixture of isoindoline **9b** and the hydrodehalogenation product.

TABLE 1. Synthesis of Dihydroisoindole- and Isoindole-1-carboxylic Acid Esters

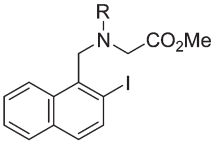
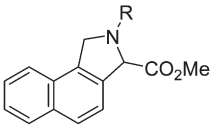
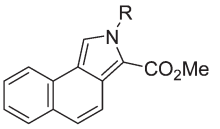
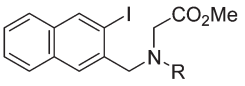
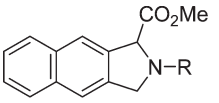
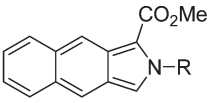
entry	α-amino ester	method[a]	time	isoindoline (yield)[b]	isoindole (yield)[b]
					
1	**5a**, R = Et	A	24 h	**6a** (88%)	
2		B	24 h		**7a** (85%)
3	**5b**, R = *t*-Bu	A	24 h	**6b** (91%)	
4		B	24 h		**7b** (78%)
					
5	**8a**, R = H	A	60 h	**9a** (86%)	
6		A[c]	72 h	**9a** (69%)	
7		B	24 h		**10a** (61%)
8	**8b**, R = F	A	50 h	**9b** (82%)	
9		B	24 h		**10b** (81%)
10	**8c**, R = OMe	A	40 h	**9c** (94%)	
11		A[c]	53 h	**9c** (90%)	
12		B	24 h		**10c** (78%)
13	**8d**, R = N(Me)CH_2CO_2Me	A	96 h	**9d**[d]	**10d** (35%)
14		B	24 h		**10d** (67%)
15	**8e**, R = CO_2Me	A	70 h	**9e** (65%)	
16		B	24 h		**10e**[e]
					
17	**11a**, R^1 = Me, R = Bn	A	24 h	**12a** (85%)[f]	
18		B	24 h		**13a** (65%)
19	**11b**, R^1 = Pr, R = Bn	A	24 h	**12b** (73%)[f]	
20		B	36 h		**13b** (45%)
21	**11c**, R^1 = Ph, R = Bn	A	24 h	**12c** (65%)[g]	
22		B	36 h		**13c** (66%)
23	**14**, R^1 = Me, R = *p*-$MeOC_6H_4$	A	48 h	**15** (98%)[h]	
24		B	24 h		**16** (40%)

[a]Method A: 10 mol % of $Pd(PPh_3)_4$ and K_3PO_4 (3 equiv) in THF at 110 °C in a sealed tube. Method B: 10 mol % of $Pd(PPh_3)_4$, K_3PO_4 (3 equiv), and phenol (0.3 equiv) in DMF at 90 °C. [b]Unless otherwise indicated, yields refer to pure products isolated by flash chromatography. [c]5 mol % of $Pd(PPh_3)_4$ and Cs_2CO_3 (3 equiv) were used. [d]^{1}H NMR analysis of the crude reaction mixture gave a 1:1 mixture of **8d** and isoindoline **9d**. [e]^{1}H NMR analysis of the crude reaction mixture gave isoindole **10e** as the only reaction product. The reaction of crude **10e** with DMAD afforded the corresponding Diels−Alder adduct in 46% overall yield for the α-arylation/Diels−Alder sequence. See ref 19. [f]1.2:1 mixture of isomers. [g]4:1 mixture of isomers. [h]3.5:1 mixture of isomers.

8d as a 1:1 mixture with the starting material, after 4 days under the reaction conditions of method A. Unfortunately, **9d** oxidized during the purification process to give isoindoline **10d** (entry 13).

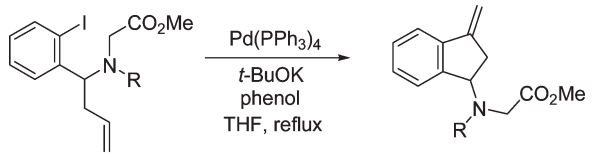
Both cyclization methods were successfully applied to the preparation of 1,3-disubstituted substrates (entries 17−24). However, the palladium-catalyzed dehydrogenation of the initially formed isoindolines proceeded somewhat slowly in the substrates with the bulky propyl and phenyl groups at the benzylic position (entries 20 and 22). For these substrates, short reaction times resulted in the isolation of significant amounts of the corresponding isoindolines together with the isoindoles. α-Amino esters **17a** and **17b**, which have an allyl substituent at the benzylic position, failed to undergo the α-arylation reactions and only afforded the Heck cyclization products. Interestingly, the best results were obtained when

TABLE 2. Synthesis of Benzoisoindolecarboxylic Acid Esters

entry	α-amino ester	method[a]	time	benzoisoindoline (yield)[b]	benzoisoindole (yield)[b]
					
1	**19a**, R = Bn	A	24 h	**20a** (55%)	
2		B	24 h		**21a** (40%)
3	**19b**, R = Ph	A	24 h	**20b** (98%)	
4		B	24 h		**21b** (84%)
					
5	**22a**, R = Bn	A	24 h	**23a** (60%)	
6		B	24 h		**24a** (52%)
7	**22b**, R = Ph	A	40 h	**23b** (68%)	
8	**22c**, R = *p*-MeOC$_6$H$_4$	A	24 h	**23c** (86%)	

[a]Method A: 10 mol % of $Pd(PPh_3)_4$ and K_3PO_4 (3 equiv) in THF at 110 °C in a sealed tube. Method B: 10 mol % of $Pd(PPh_3)_4$, K_3PO_4 (3 equiv), and phenol (0.3 equiv) in DMF at 90 °C. [b]Unless otherwise indicated, yields refer to pure products isolated by flash chromatography.

SCHEME 5



17a, R = Bn
17b, R = Ph

18a, R = Bn (60%)
18b, R = Ph (63%)

t-BuOK/phenol were used as additives in these palladium-catalyzed reactions (Scheme 5).[22] The use of other bases resulted in the formation of significant amounts of double-bond isomerization products.

The palladium-catalyzed cyclizations were also extended to the preparation of benzo-fused derivatives (Table 2).[23,24] While the isoindolines were generally obtained in good yields, the formation of isoindoles seems to be highly substrate dependent. Thus, in the benzo[*f*]-fused series, only **24a** could be obtained, the *N*-aryl derivatives being too unstable to be isolated and characterized.[25]

In summary, we have developed two palladium-catalyzed intramolecular α-arylation reactions that allow the selective synthesis of either 1-isoindolecarboxylic acid esters or the corresponding isoindolines. The synthesis of isoindoles takes place through a palladium-catalyzed cascade involving an enolate arylation and the dehydrogenation of the initially formed isoindoline. Besides the potential synthetic application of the above methodologies, the reactions described in this paper are of interest because they illustrate how small changes in the reaction conditions can be used to increase the diversity of palladium-catalyzed processes.

Experimental Section

Representative Procedure for the Synthesis of Isoindolines. A mixture of ester **1a** (100 mg, 0.25 mmol), K_3PO_4 (159 mg, 0.75 mmol), and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) in THF (8 mL) was stirred at 110 °C in a sealed tube for 24 h. The reaction mixture was poured into water and extracted with Et_2O. The organic extracts were washed with brine, dried, and concentrated. The residue was purified by flash chromatography (SiO_2, from CH_2Cl_2 to CH_2Cl_2−MeOH 1%) to give methyl 2-benzylisoindoline-1-carboxylate (**2**, 56 mg, 84%).

Representative Procedure for the Synthesis of Isoindoles. A mixture of ester **1a** (100 mg, 0.25 mmol), K_3PO_4 (159 mg, 0.75 mmol), phenol (7 mg, 0.075 mmol), and $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) in DMF (3 mL) was stirred at 90 °C for 24 h. The reaction mixture was poured into water and extracted with Et_2O. The organic extracts were washed with brine and 1 N NaOH solution, dried, and concentrated. The residue was purified by chromatography (SiO_2, CH_2Cl_2) to give methyl 2-benzylisoindole-1-carboxylate (**3**, 50 mg, 76%).

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

(22) The positive role of phenol as a catalytic additive in the Heck reaction has been previously observed; see: Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Synlett* **2008**, 667–670.

(23) Naphtho-fused heterocycles have been recently identified as good candidates for light-harvesting dyes in solar cells; see: Paci, I.; Johnson, J. C.; Chen., X.; Rana, G.; Popovic, D.; David, D. E.; Nozik, A. J.; Ratner, M. A.; Michl, J. *J. Am. Chem. Soc.* **2006**, *128*, 16546–16553.

(24) Hsu, D.-T.; Lin, C.-H. *J. Org. Chem.* **2009**, *74*, 9180–9187.

(25) Under the reaction conditions of method B, **22b** afforded 2-phenyl-2,3-dihydrobenzo[*f*]isoindol-1-one in 35% yield.