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Uncommon intramolecular palladium-catalyzed cyclization of indole derivatives

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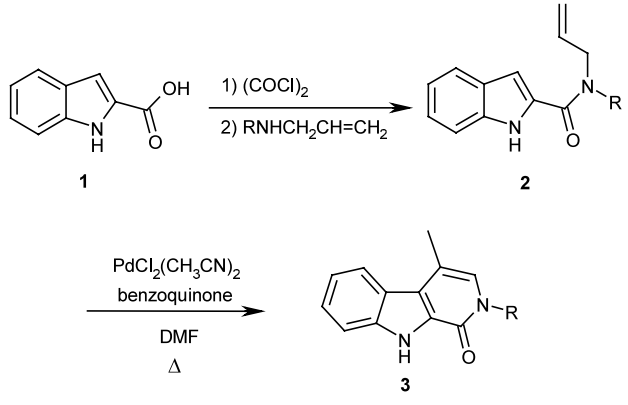
Dedicated to the memory of Professor Alessandro Marchesini

Abstract—A novel synthetic strategy based on the intramolecular palladium-catalyzed oxidative cyclization reaction, allows the formation of C–C bond and the synthesis of β-carbolinones. The reaction has been performed in the presence of catalytic amount of $PdCl_2(CH_3CN)_2$ and benzoquinone as a reoxidant.

The catalytic processes which allow the formation of carbon–carbon bonds based on the oxidative addition of carbon–hydrogen bonds are of considerable interest with respect to the potential use in organic synthesis.[1] The literature data report oxidative inter- or intramolecular coupling like arylation of aromatic heterocycles[2] and alkenylation of arenes[3,4] with olefins with the cleavage of sp^2-C–H bond in the presence of palladium compounds. Cyclization to carbazoles from diphenylamine derivatives[5] and conversion of arylaminoquinones to carbazoloquinones[6] have also been reported as well as cyclization of bisindolyl systems to indolocarbazole derivatives[7] and cyclization leading to the synthesis of indole alkaloids.[8]



Scheme 1.

Most of the applications of palladium described above use a stoichiometric amount of expensive $Pd(OAc)_2$. The oxidative process would be of much greater synthetic utility if one could use only a catalytic amount of palladium. In the catalytic reactions, in situ regeneration of palladium(II) from palladium(0) is the crucial step for catalytic cycle. Progress has been made towards the catalytic oxidative pathway. Several reoxidation reagents have been reported such as copper acetate,[6a,b] *tert*-butyl hydroperoxide,[6c] and more recently oxygen[6d] or a mixture of benzoquinone and *tert*-butyl hydroperoxide.[3]

As a part of our ongoing interest in developing novel synthetic strategies for the construction of condensed aromatic heterocyclic derivatives,[9] we focused our attention on the intramolecular Heck reaction[10] and subsequently on the intramolecular oxidative cyclization reaction.

We report here a very efficient example of an intramolecular palladium-catalyzed oxidative cyclization reaction of an indolic substrate bearing a non-activated double bond in the 2 position. On the contrary, the reported coupling reactions of aromatic compounds with olefins were efficient for the unsaturated systems bearing an electron-withdrawing substituent at the α-carbon. Starting from indole-2-carboxylic acid **1**, the reaction with oxalyl chloride and the suitable allyl-

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amines gave the corresponding indole 2-*N*-allylcarboxamides **2a–d**. The intramolecular oxidative cyclization reaction was performed with $PdCl_2(CH_3CN)_2$ (10% mol) as catalyst and benzoquinone (1 equiv.) as reoxidant in a mixture of DMF–THF at 80°C for 45 min., to give in very good yield β-carbolinones **3a–c**. We have just reported the synthesis of these products by an intramolecular Heck cyclization.[10] Nevertheless in that case the protection of the 1 position of the indolic substrate was necessary to prevent the decomposition of the starting material and the loss of iodine atom. The monosubstituted amide, indole 2-carboxylic acid allylamide **2d**, does not give any cyclization product (Scheme 1 and Table 1). The in situ reoxidation of Pd(0) to Pd(II) leads to the subsequent transformation of benzoquinone to hydroquinone.

The reported literature data show for these reactions an oxidative coupling process that presumably commences with the direct palladation of the aromatic C–H bond forming σ-aryl palladium(II) complex. Subsequently, in a manner akin to an intramolecular Heck reaction, the intermediate undergoes olefin addition and β-hydride elimination and then results in the coupling product.[11] However at present we can not exclude an alternative pathway for this reaction, based on the nucleophilic attack of the electron-rich indole ring on a palladium activated double bond.[12]

In conclusion, the palladium-catalyzed coupling described here offers an easy and highly efficient route to fused aromatic heterocyclic systems. The reaction utilizes readily available starting materials and is conducted under mild conditions. These facts suggest that the catalytic method has potential for even a wider application than that described in the present communication and further studies are in progress.

General procedure for the synthesis of 1H-indole-2-carboxylic acid allylamides **2a–d**: To a solution of indole-2-carboxylic acid **1** (1 mmol) in CH_2Cl_2 (20 ml) oxalyl chloride (0.3 ml, 3 mmol) and DMF (0.05 ml) were added. The reaction was heated to reflux for 1 h then the solvent evaporated to dryness in vacuo. The residue was taken up with CH_2Cl_2 (20 ml) and the suitable allylamine (3 mmol) added at 0°C. After 1 h at rt the mixture was washed with 1N HCl. The organic layer was dried (Na_2SO_4), filtered and evaporated and the residue purified by silica gel column chromatography. Yields are reported in Table 1. All new compounds gave satisfactory analytical and spectroscopic data.

Table 1. Yields (%) of compounds **2** and **3**

Entry	R	**2**	**3**
a	Me	99	97
b	Allyl	95	91
c	Phenyl	86	80
d	H	87	–

Selected spectroscopic data: **2a,** mp 101°C; IR: 3230, 1605, 1459 cm^{-1}; ^1H NMR ($CDCl_3$): 3.29 (3H, s), 4.34 (2H, br s), 5.32 (2H, m), 5.97 (1H, m), 6.89 (1H, s), 7.15 (1H, dt, $J=1.1$, 8.1 Hz), 7.29 (1H, dt, $J=1.1$, 8.1 Hz), 7.46 (1H, dd, $J=1.1$, 8.1 Hz), 7.68 (1H, d, $J=8.1$ Hz), 9.48 (1H, br s, exch. with D_2O); ^{13}C NMR ($CDCl_3$): 36.5 (CH_3), 53.5 (CH_2), 105.5 (CH=), 117.6 (CH_2=), 112.0, 120.4, 122.0, 124.4, 132.8 (CHAr), 127.8, 129.5, 135.9, 164.0 (C).

General procedure for the synthesis of β-carbolinones **3a–c**: to a solution of 1*H*-indole-2-carboxylic acid allylamide **2** (1 mmol) in a mixture of DMF (6 ml) and THF (12 ml) $PdCl_2(CH_3CN)_2$ (26 mg, 10 mol%) and benzoquinone (108 mg, 1 mmol) were added. The mixture was stirred under N_2 for 45 min. at 80°C, then concentrated in vacuo and the residue poured into brine to give the β-carbolinone **3** as a solid. The filtrate was extracted with Et_2O (2×20 ml) and the extracted evaporated to give a residue which was chromatographed on silica gel eluent Et_2O to give an additional amount of compound **3**.

Selected spectroscopic data: **3a** total yield 98%, mp 295°C dec. (from CH_2Cl_2); IR: 3150, 1651, 1589 cm^{-1}; ^1H NMR (C_3D_6O): 2.60 (3H, d, $J=0.7$ Hz), 3.66 (3H, s), 7.08 (1H, d, $J=0.7$ Hz), 7.24 (1H, dt, $J=1.1$, 7.3 Hz), 7.46 (1H, t, $J=7.3$ Hz), 7.71 (1H, d, $J=8.0$ Hz), 8.13 (1H, d, $J=8.0$ Hz), 11.18 (1H, bs, exch. with D_2O); ^{13}C NMR (DMSO): 16.9, 36.4 (CH_3), 113.3, 120.4, 123.0, 126.5, 127.6 (CHAr), 111.4, 123.2, 124.1, 128.1, 140.0, 155.4 (C).

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