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A Simple Catalytic Synthesis of Condensed Pyridones from *o*-Bromoarylcarboxamides Involving *ipso* Substitution via Palladacycles

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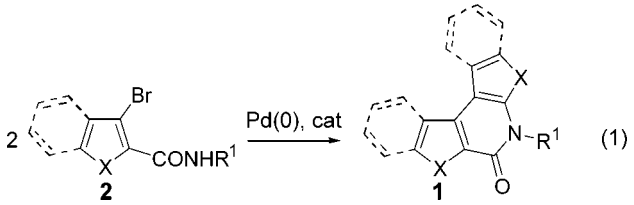
Palladacycles are key intermediates in inter- and intramolecular cross-coupling reactions.[1] We recently described a catalytic procedure involving palladacycles,[2] which has been applied to the synthesis of condensed quinolin-4(5*H*)-ones shown in Scheme 1, starting from *o*-substituted iodoarenes and amides of *o*-bromo arene- and heteroarenecarboxylic acids.[3] The reaction has been carried out in the presence of norbornene, $Pd(OAc)_2$/2-trifurylphosphine (TFP) and K_2CO_3 in DMF.

Surprisingly, in the absence of norbornene, coupling of two molecules of the *o*-bromoaromatic carboxamide followed an unpredictable pathway, which is the subject of this preliminary communication. Symmetrically condensed pyridones **1** were obtained simply starting from **2** (X = HC=CH, S, O, N-Me), in the presence of $Pd(OAc)_2$/TFP as the catalyst, K_2CO_3 as a base in DMF at 105 °C (eq 1). Under these conditions, compounds **1** were isolated in 23−86% yield (Table 1).



(1)

As shown in Table 1, the reaction readily occurs using secondary amides with N-bonded Me, PMB, and Ph, while the primary ones did not give the expected products (e.g., entry 6). In addition to **1a** (23%) and **1b** (30%) the reactions of **2a** and **2b** gave compounds **3** and **4** in 34% and 20% yield, respectively (Figure 1). As we shall see, these compounds derive from the same initial steps as for **1a** and **1b**.

Scheme 2 shows a possible reaction pathway (TFP ligand is omitted). Palladium(0) oxidatively adds to the Br-amide **2** in the first step. At this point, we suggest that complex **5** gives rise to a five-membered palladacycle **6**,[5] in which the $CONHR^1$ group takes part in the construction of a metallacycle. This favors further reaction with a second molecule of **2** possibly through an oxidative addition process involving a palladium(IV) species[6] leading to C−C bond formation in a new palladium complex **7** (Scheme 2). The latter then undergoes intramolecular *ipso* aromatic substitution at the carbon atom bearing the $CONHR^1$ with formation of **1**, amine, and CO_2.[7] Accordingly the reaction of **2c** (R^1 = Ph) gave aniline (^1H NMR of the crude), which was isolated as 1-(PMB)-3-phenylurea (23% yield) after addition of an excess of PMBNCO to the crude. To account for this result we propose that the aminocarbonyl group is attacked by the palladium-bonded bicarbonate anion (formed by exchange of the Pd−Br bond with $KHCO_3$). This would lead to the unstable carbamic carbonic mixed anhydride HOCOOCONHPh, which decomposes to amine and two molecules of CO_2.[8] C−N bond-forming reductive elimination regenerates palladium(0), and the reaction turns out to be catalytic. To our knowledge this process is unprecedented.

The amine R^1NH_2 itself resulting from the *ipso*-substitution process can compete, if sufficiently nucleophilic, with the inorganic

Scheme 1

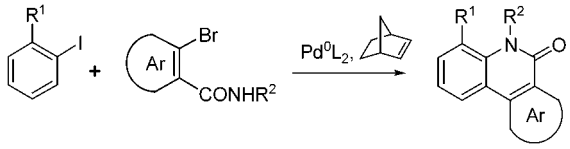
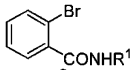
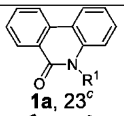
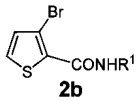
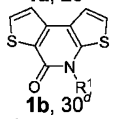
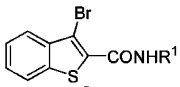
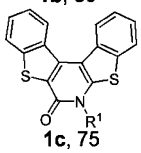
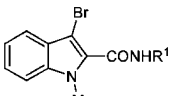
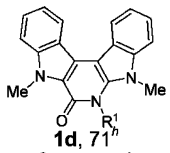
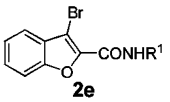
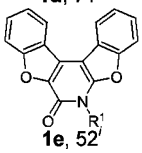


Table 1. Pd-catalyzed Synthesis of **1**[a]

	2	R^1	Time (h)	1 yield (%)[b]
1	 **2a**	Me	20	 **1a**, 23[c]
2	 **2b**	Me	24	 **1b**, 30[d]
3	 **2c**	Me	20	 **1c**, 75
4	**2c**	PMB[e]	48	**1c**, 50 (74)[f]
5	**2c**	Ph	24	**1c**, 86
6	**2c**	H	24	-[g]
7	 **2d**	Me	48	 **1d**, 71[h]
8	 **2e**	Me	20	 **1e**, 52[i]

[a] Reaction conditions: **2** (0.45 mmol, 1 equiv), $Pd(OAc)_2$ (5 mol %), TFP (10 mol %), K_2CO_3 (2 equiv), DMF (10 mL) at 105 °C. Reaction conditions were not optimized. Unless otherwise indicated, conversion of **2** was complete. [b] Isolated yield. [c] 34% yield of **3** (see Figure 1). [d] 20% yield of **4** (see Figure 1). [e] *p*-Methoxybenzyl. [f] In parentheses the yield in the presence of aniline (0.5 equiv).[4] [g] No trace of **1c** was observed; only **2c** and dehalogenated **2c** were isolated in ca. 25 and 9% yield. [h] 90% conversion. [i] 80% conversion.

10.1021/ja0566127 CCC: $33.50

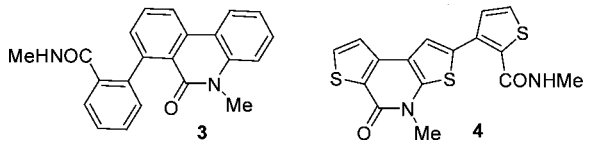
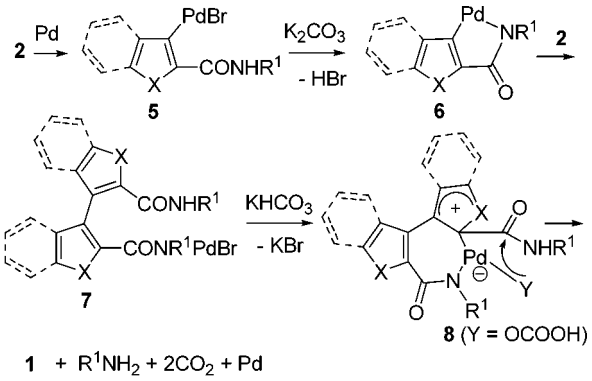
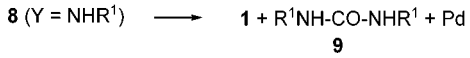


Figure 1. Other products of reaction 1.

Scheme 2



Scheme 3



base for the attack on the aminocarbonyl group leading to **1** and the symmetrically substituted urea **9** (Scheme 3).[9]

Since a possible alternative to the pathway shown in Scheme 3 could involve elimination of R^1NCO, followed by the reaction with a molecule of R^1NH_2, we performed the reaction of **2c** (R^1 = PMB) (2 equiv) in the presence of aniline (1 equiv) to eventually trap the isocyanate. Under these conditions, no trace of the expected urea PhNH−CO−NHPMB was observed, whereas **9** was isolated in 50% yield.[10]

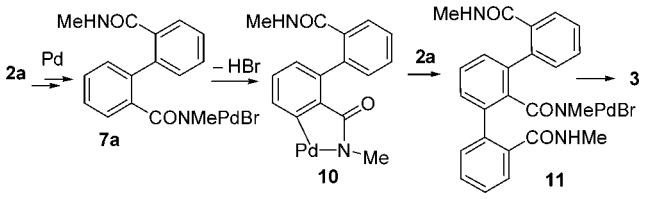
The absence of the mixed urea in this experiment also suggests that a scarcely nucleophilic amine such as aniline, is less prone to react with the $CONHR^1$ group. In fact, we were not able to get any evidence for *N*,*N*-diphenylurea formation in the reaction of **2c** (R^1 = Ph).

Further support to the proposed reaction course comes from the following observations: (a) bis-amides corresponding to hydrogenolysis of complex **7** were found as byproducts (ca. 10%) in reactions of **2c** and **2d**. They turned out to be stable under basic conditions in the absence of palladium (Cs_2CO_3, DMF, 105 °C), suggesting that the presence of the metal is needed for *ipso* substitution according to the mechanism of Scheme 2; (b) we prepared the hydrogenolysis product of complex **7a** (R^1 = Ph) and caused it to react with $PdCl_2(MeCN)_2$ to form **1a** (R^1 = Ph) via the palladium chloride complex corresponding to **7a** (R^1 = Me) (Scheme 2). A small but significant amount of **1a** was obtained (ca. 5% yield after 2 h at 105 °C) with palladium black separation and almost complete recovery of the starting compound; (c) the formation of compound **3**, which is the main product in the reaction of **2a** (R^1 = Me) (Figure 1, Table 1), implies the intermediacy of **7a** to give palladacycle **10** (Scheme 4).[1b,11] The latter will allow the reaction of another molecule of **2a** to form **11** and finally **3** through *ipso* substitution, which is preferred to attack on one of the two aromatic C−H available.[11a]

A different pathway leads to product **4** (Figure 1), the formation of which must be interpreted as deriving from further attack of **2b** to the thienopyridone **1b**.[7,12]

Noteworthy, the selectivity of the reactions with benzocondensed *o*-bromo-heterocyclic amides **2c**−**e** increased, C−H activating arylation being not feasible (entries 3−8).

Scheme 4



In summary, a catalytic multistep process based on a novel reaction sequence combining the palladacyle-catalyzed homocoupling of **2** with intramolecular aromatic *ipso* substitution leads to **1** under mild conditions. They belong to the class of 6-phenanthridinones and their heterocyclic analogues, which show promising biological activity.[13] We believe that the present work opens up the access to important classes of compounds through one-pot procedures much simpler than the conventional ones.[3,13]

Acknowledgment. We thank Consiglio Nazionale delle Ricerche (CNR) and Ministero dell'Università e della Ricerca Scientifica e Tecnologica (PRIN Project 200303977774).

Supporting Information Available: Experimental procedures and characterization for compounds **1**−**4** and hydrogenolysis product from **7c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Urea **9** was detected (^{1}H NMR analysis) in the crude of the reaction of **2c** (R^1 = PMB).

(10) The reaction of **2c** (R^1 = PMB) (2 equiv) in the presence of PhNCO (1 equiv) leads to a 1/1 mixture of PhNH−CO−NHPMB and **9** which quantitatively accounts for the amine eliminated in the course of the reaction.

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