ORGANIC LETTERS

2008
Vol. 10, No. 21
4987−4990

Palladium-Catalyzed Carboxamidation Reaction and Aldol Condensation Reaction Cascade: A Facile Approach to Ring-Fused Isoquinolinones

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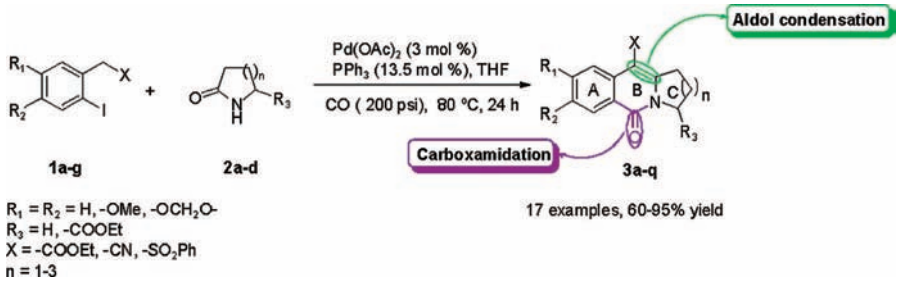
Received September 3, 2008

ABSTRACT



Palladium-catalyzed carboxamidation reaction and aldol condensation reaction cascade are very useful for the synthesis of various ABC ring substituted fused isoquinolinones.

The isoquinolinone moiety is an important class of heterocyclic compounds from both synthetic and biological points of view. It is well-known that many compounds possessing this subunit display biological activities of medicinal interest.[1] Ring-fused isoquinolinone heterocyclic compounds are also valuable as synthetic precursors for the large and diverse family of biologically important alkaloids such as 22-hydroxyacuminatine and rosettacins.[2,3] There are very few synthetic methods found in the literature for ring-fused isoquinolinones based on the use of homophthalic anhydride,[4a] an oxidative radical cyclization process,[4b] or photochemical reactions.[4c] These methods, however, typically provide low to moderate product yields. Very recently, a one-pot domino N-amidoacylation/aldol-type condensation reaction has also been reported for the synthesis of ring-fused isoquinolinones.[4d]

Transition-metal-catalyzed reactions are widely used for the synthesis of various heterocyclic ring systems.[5] Among these, palladium-catalyzed carbonylative-cyclization is a valuable synthetic tool for the formation of a wide variety of oxygen and nitrogen containing heterocyclics.[6] In the course of our studies on the palladium-catalyzed synthesis of heterocyclic compounds, we have recently reported new methods for the preparation of benzoxazinones,[7] quinazolinones,[8] and medium-ring tricyclic lactams.[9] Herein, we now

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10.1021/ol802067y CCC: $40.75
Published on Web 10/11/2008

report a new palladium-catalyzed carboxamidation reaction and aldol condensation reaction cascade of active methylene compouds **1**, lactams **2**, and CO for rapid access to a variety of ring-fused isoquinolinones (Figure 1).[10,11]

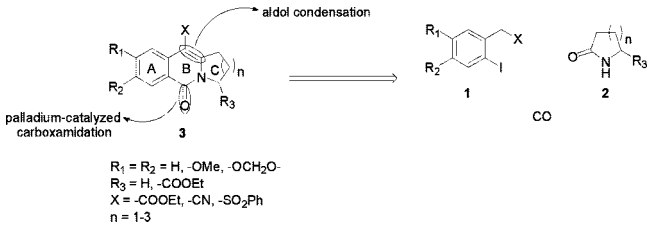
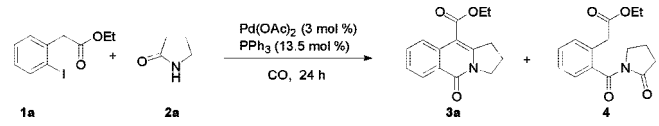


Figure 1. Strategy for the synthesis of ring-fused isoquinolinones.

Initially, we examined the noted strategy by reacting ethyl 2-(2-iodophenyl)acetate **1a** (1 mmol) as an active methylene compound with the five-membered ring lactam 2-pyrrolidone **2a** (1.1 mmol) at 300 psi of carbon monoxide in the presence of $Pd(OAc)_2$ (0.03 mmol), triphenylphosphine (PPh_3) (0.135 mmol), and KO^{t}Bu (3 equiv) in acetonitrile at 110 °C for 24 h. The reaction with KO^{t}Bu afforded 60% yield of the desired fused isoquinolinone (**3a)** with several byproducts (Table 1, entry 1).[12] Thus, a series of bases and solvents were screened at various temperatures to optimize the reaction conditions. When the organic base triethylamine was used with THF at 80 °C, 38% carboxamidation product (**4**) was obtained, while 61% of starting material was left unreacted. It was found that the use of K_2CO_3 as the base and THF as the solvent at 80 °C provides the desired product in 95% yield (Table 1, entry 4).We have also studied other reaction parameters such as lower pressure of carbon monoxide or lower temperature, which resulted in incomplete consumption of starting materials with undesired carboxamidation product **4** (Table 1, entries 5).

Having optimized the reaction conditions, the scope of this cascade reaction was further explored by treating different active methylene compounds with a variety of lactams. The results are summarized in Table 2.

Table 1. Optimization of the Reaction Conditions for the Reaction of Ethyl 2-(2-Iodophenyl)acetate with 2-Pyrrolidone[a]



entry	base	solvent	T (°C)	**3a**[b] (%)	**4**[b] (%)
1	^{t}BuOK	CH_3CN	110	60[c]	
2	TEA	THF	80	trace	38[d,e]
3	K_2CO_3	CH_3CN	110	68[e]	
4	K_2CO_3	THF	80	95[e]	
5	K_2CO_3	THF	50	24[f]	40

[a] Reaction conditions: ethyl 2-(2-iodophenyl)acetate **1a** (1 mmol), 2-pyrrolidone **2a** (1.1 mmol), $Pd(OAc)_2$ (0.03 mmol), triphenylphosphine (0.135 mmol), base (3 equiv), solvent (5 mL). [b] Determined by ^{1}H NMR and GC. [c] Using 300 psi CO pressure. [d] 61% **1a** was left unreacted. [e] Using 200 psi CO pressure. [f] Using 100 psi CO pressure, 36% **1a** was left unreacted.

The reaction of ethyl 2-(2-iodophenyl)acetate (**1a**) with five-membered ring lactams 2-pyrrolidone (**2a**) and ethyl pyroglutamate (**2b**)[13] gave the corresponding ring-fused isoquinolinone **3a** and **3b** in excellent yield (Table 2, entries 1 and 2). Even the reaction with six- and seven-membered ring lactams 2-piperidone (**2c**) and caprolactam (**2d**) also provided good yields of fused isoquinolinones (**3c** and **3d**) (Table 2, entries 3 and 4).

The Pd-catalyzed carboxamidation reaction and aldol condensation reaction cascade could be extended to the electron-rich substrate ethyl 2-(2-iodo-4,5-dimethoxyphenyl)acetate (**1b**) and to ethyl 3,4-methylenedioxy-6-iodophenylacetate (**1c**). It was noteworthy that, under the optimized reaction conditions, the expected fused isoquinolinone (**3e**) was not observed upon reacting the electron-rich substrate **1b** with lactam 2-pyrrolidone (**2a**), and only the carboxamidation product was obtained.

A beneficial effect of using the stronger base Cs_2CO_3 on this reaction was observed,[14] and the desired fused isoquinolinone product (**3e**) was isolated in 90% yield (Table 2, entry 5). Furthermore, reaction of substrate **1b** with ethyl pyroglutamate (**2b**) also provided isoquinolinone **3f** in good yield (Table 2, entry 6); however, the yield was moderate using the lactam 2-piperidone (**2c**) (Table 2, entry 7).

The reaction also occurred with the ethyl 3,4-methylenedioxy-6-iodophenylacetate (**1c**) affording 90% and 95% yields of the desired isoquinolinone products, **3h** and **3i**, respectively, upon reaction with the lactams **2a** and **2b** (Table 2, entries 8 and 9).

Apart from ethyl 2-iodophenylacetate, 2-iodophenylacetonitriles (**1d**−**f**) and 2-iodobenzyl phenyl sulfone (**1g**) were also examined for this Pd-catalyzed carboxamidation reaction and aldol condensation reaction cascade, and the results are listed

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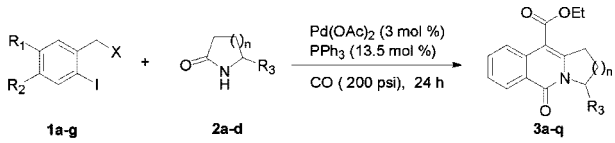
Table 2. Palladium-Catalyzed Carboxamidation Reaction and Aldol Condensation Reaction Cascade of Active Methylene Compounds **1** with Lactams **2**[a]



1a-g **2a-d** **3a-q**

1a: $R_1 = R_2$ = H, X = -COOEt
1b: $R_1 = R_2$ = -OMe, X = -COOEt
1c: $R_1 = R_2$ =-OCH_2O-, X = -COOEt
1d: $R_1 = R_2$ = H, X = -CN
1e: $R_1 = R_2$ = -OMe, X = -CN
1f: $R_1 = R_2$ =-OCH_2O-, X = -CN
1g: $R_1 = R_2$ = H, X = -SO_2Ph
R_3 = H, -COOEt

entry	substrate 1	lactam 2	base	product 3	yield (%)[a]
1	**1a**	**2a**	K_2CO_3	**3a**	95
2	**1a**	**2b**	K_2CO_3	**3b**	92
3	**1a**	**2c**	K_2CO_3	**3c**	75
4	**1a**	**2d**	K_2CO_3	**3d**	65
5	**1b**	**2a**	Cs_2CO_3	**3e**	90
6	**1b**	**2b**	Cs_2CO_3	**3f**	85
7	**1b**	**2c**	Cs_2CO_3	**3g**	60
8	**1c**	**2a**	Cs_2CO_3	**3h**	95
9	**1c**	**2b**	Cs_2CO_3	**3i**	90
10	**1d**	**2a**	K_2CO_3	**3j**	95
11	**1d**	**2b**	K_2CO_3	**3k**	93
12	**1d**	**2c**	K_2CO_3	**3l**	85
13	**1e**	**2a**	Cs_2CO_3	**3m**	65[c]
14	**1f**	**2a**	Cs_2CO_3	**3n**	63[c]
15	**1f**	**2b**	Cs_2CO_3	**3o**	80
16	**1g**	**2a**	K_2CO_3	**3p**	90
17	**1g**	**2b**	K_2CO_3	**3q**	85

[a] Reaction conditions: **1** (1 mmol), **2a** (1.1 mmol), $Pd(OAc)_2$ (0.03 mmol), triphenylphosphine (0.135 mmol), base (3 equiv), THF (5 mL), 80 °C, 24 h. [b] Isolated yield. [c] Recrystallization yield.

in Table 2. 2-Iodophenylacetonitrile (**1d**) was effectively converted to isoquinolinones **3j** and **3k** under optimized cascade reaction conditions with the 2-pyrrolidone (**2a**) and ethyl pyroglutamate (**2b**) (Table 2, entries 10 and 11), respectively, whereas reaction with the six-membered ring lactam 2-piperidone (**2c**) provided the corresponding isoquinolinone (**3l**) in 85% yield. Electron-rich 2-iodophenylacetonitriles (**1e** and **1f**) required the use of a strong base Cs_2CO_3 to convert them to the corresponding fused isoquinolinones (**3m**−**o**) in 63−80% yields (Table 2, entries 13−15).

The reaction was also successfully extended to 2-iodobenzyl phenyl sulfone (**1g**) which on treatment with lactams **2a** and **2b** affords **3p** and **3q** in 90% and 85% yield, respectively (Table2, entries 16 and 17).

A possible reaction mechanism for the formation of fused isoquinolinones **3** is depicted in Figure 2. Oxidative addition

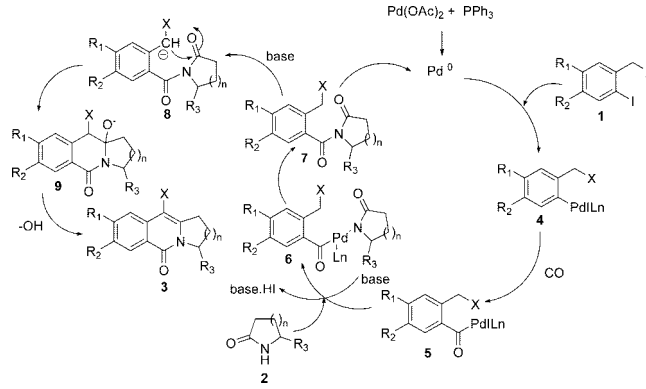


Figure 2. Proposed reaction mechanism.

of **1** to the in situ generated palladium(0) species[15] leads to a palladium complex **4**. Carbon monoxide insertion into the aryl carbon−palladium bond of **4** affords **5** and nucleophilic attack of the lactam on a aroylpalladium complex gives intermediate **6** which undergoes reductive elimination affording carboxamide **7** with regeneration of palladium(0). The intramolecular condensation of the lactam carbonyl group with benzylic anion **8** (generated by treatment with base) gives intermediate **9** which on dehydration ultimately afford the ring-fused isoquinolinone **3**.

In summary, we have developed an efficient and simple synthetic method for the synthesis of biologically and medicinally important ring-fused isoquinolinones by utilizing a palladium-catalyzed carboxamidation reaction and aldol condensation reaction cascade protocol. The products of this cascade reaction can be transferred to other functionality and hence provides further scope for molecular manipulation. Moreover, the method gives easy access to a variety of ABC ring substituted fused isoquinolinones and thus could be very useful to generate a diverse array of ring-fused substituted isoquinolinones for assessing their pharmaceutical and medicinal

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research activities. We are presently exploring the applicability of this cascade protocol to the synthesis of related biologically important heterocycles.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council of Canada for financial support of this research.

Supporting Information Available: Experimental procedures, characterization data for all new compounds, and copies of ^{1}H NMR and ^{13}C NMR spectra for substrates **1a**−**c**,**e**−**g** and products **3a**−**q**.This material is available free of charge via the Internet at http://pubs.acs.org.

OL802067Y