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Palladium-Catalyzed Carbonylation−Decarboxylation of Diethyl(2-iodoaryl)malonates with Imidoyl Chlorides: An Efficient Route to Substituted Isoquinolin-1(2*H*)-ones

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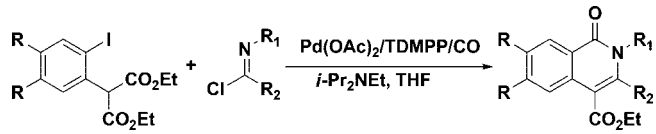
ABSTRACT



A wide variety of substituted isoquinolin-1(2*H*)-ones were synthesized in reasonable to good yields by the palladium-catalyzed cyclization of diethyl(2-iodoaryl)malonates with imidoyl chlorides and carbon monoxide in tetrahydrofuran. A palladium-catalyzed carbonylation−decarboxylation process may be involved in the one-step synthesis of the isoquinolin-1(2*H*)-ones.

Isoquinolin-1(2*H*)-one derivatives are an important class of heterocyclic compounds with substantial biological activities[1] that can be found in naturally occurring products and synthetic pharmaceuticals such as thalifoline,[2] dorianine,[3] narciclasine,[4] pancratistain,[5] and lycoricidine.[5] In addition, isoquinolin-1(2*H*)-ones are versatile building blocks for the total synthesis of natural alkaloids.[6] There are a number of approaches to the synthesis of isoquinolin-1(2*H*)-ones reported in the literature including the rearrangement of 2-(2-benzofuranyl)-benzonitriles,[7] base-promoted condensation reaction of 2-(bromomethyl)-benzonitrile,[8] transformation of isocoumarins or 3-hydroxyphthalides,[9] double metalation of arylbenzamides,[10] the cyclization of 2-chlorobenzonitriles with β-ketoesters,[11] intramolecular Diels−Alder reactions,[12] Wittig reaction,[13] as well as photochemical reactions,[14] etc. Recently, several examples of transition metal-catalyzed routes to isoquinolin-1(2*H*)-ones have appeared in the literature.[3,15]

Although some of the methods are effective for the synthesis of isoquinolones, these usually afford the 2- or

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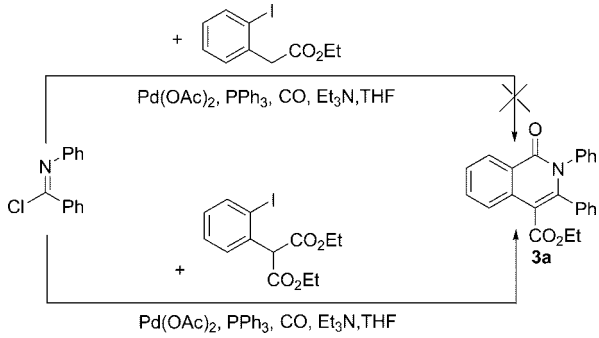
3-substituted target compounds. The introduction of polysubstituents in the isoquinolone ring often requires multistep reactions.

As part of our continuing effort to attain the efficient preparation of different carbonyl-containing heterocycles by palladium-catalyzed cyclocarbonylation, we have synthesized thiochroman-4-ones,[16] lactones,[17] 2(5*H*)-furanones,[18] 1,3-oxazin-4-ones,[19] 1,3-benzothiazin-2-ones,[20] quinazolin-4(3*H*)-ones,[21] and different ring-sized lactams.[22]

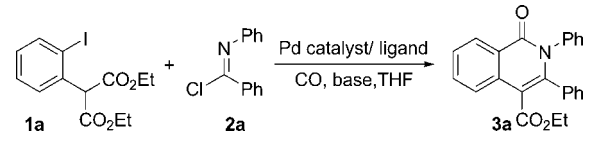
Encouraged by these results, we decided to explore the application of Pd-catalyzed carbonylation to the construction of the isoquinolin-1(2*H*)-one skeleton. Initial studies focused on the Pd-catalyzed cyclocarbonylation of ethyl(2-iodophenyl)acetate and *N*-(phenyl)benzimidoyl chloride using 3 mol % of $Pd(OAc)_2$, 13.5 mol % of PPh_3 as the catalyst, and 3 equiv of Et_3N in 8 mL of THF at 400 psi of pressure of carbon monoxide at 120 °C for 24 h. However, the substrates failed to produce any of the desired isoquinolin-1(2*H*)-one (Scheme 1).

Scheme 1. Carbonylation of *N*-(Phenyl)benzimidoyl Chloride with Ethyl(2-iodophenyl)acetate or Diethyl(2-iodophenyl)malonate



The same reaction using diethyl(2-iodophenyl)malonate instead of ethyl(2-iodophenyl)acetate did produce 2,3,4-trisubstituted isoquinolone **3a** in 21% yield with some recovered starting material and *N*-phenylbenzamide as a byproduct (Scheme 1). The starting materials were consumed completely by extending the reaction time to 48 h, and the yield of **3a** increased to 34% (Table 1, entry 2). An interesting feature of this reaction is that the formation of the isoquinolin-1(2*H*)-one is accompanied by CO insertion and an ethyl carboxylate group leaving in a single operational step.

Table 1. Optimization of the Reaction of Diethyl(2-iodoaryl)malonate with *N*-(Phenyl)benzimidoyl Chloride[a]



entry	catalyst system	base	time(h)	CO (psi)	yield (%)[b]
1	$Pd(OAc)_2/PPh_3$	Et_3N	24	400	21
2	$Pd(OAc)_2/PPh_3$	Et_3N	48	400	34
3	$Pd(OAc)_2$/dppb	Et_3N	48	400	trace
4	$Pd(OAc)_2$/dppp	Et_3N	48	400	trace
5	$Pd(OAc)_2$/dppf	Et_3N	48	400	trace
6	$Pd(OAc)_2/(m\text{-tolyl})_3P$	Et_3N	48	400	33
7	$Pd(OAc)_2/Bu_3P$	Et_3N	48	400	ND[c]
8	$Pd(OAc)_2$/TDMPP	Et_3N	48	400	47
9	$Pd(OAc)_2$/TDMPP	K_2CO3	48	400	41
10	$Pd(OAc)_2$/TDMPP	Cs_2CO_3	48	400	44
11	$Pd(OAc)_2$/TDMPP	$i\text{-}Pr_2NEt$	48	400	53
12	$Pd(OAc)_2$/TDMPP	$i\text{-}Pr_2NEt$	48	200	31
13	$PdCl_2(PPh_3)$/TDMPP	$i\text{-}Pr_2NEt$	48	400	40
14	$Pd_2(dba)_3$/ TDMPP	$i\text{-}Pr_2NEt$	48	400	48

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), Pd cat. (0.03 mmol), phosphine ligand (0.135 or 0.07 mmol), base (3.0 mmol), CO 200 or 400 psi, 120 °C, THF (8.0 mL). [b] Isolated yield. [c] Not determined: a complex mixture of unidentified compounds was obtained.

Optimization of the reaction was effected using different conditions, and the results are summarized in Table 1. Entries 2−8 indicated that the choice of phosphine ligand was important for this transformation. When bidentate phosphine ligands were employed (Table 1, entries 3−5), only trace amounts of the desired isoquinolin-1(2*H*)-ones were detected, while *N*-phenylbenzamide was obtained as a major product in good yields. Use of the tri-*m*-tolylphosphine ($(m\text{-tolyl})_3P$) as ligand afforded **3a** in only 33% yield (Table 1, entry 6), while the trialkylphosphine and tributylphosphine gave a complex mixture of products (Table 1, entry 7). Performing the same reaction using the tri(2,6-dimethoxyphenyl)phosphine (TDMPP) as the ligand increased the yield of **3a** to 47% (Table 1, entry 8).

The yield of isoquinolin-1(2*H*)-one **3a** was also dependent on the nature of the base. The presence of inorganic bases, such as K_2CO_3 and Cs_2CO_3, gave **3a** in 41% and 44% yield, respectively (Table 1, entries 9 and 10). The more hindered amine base *N*,*N*-diisopropylethylamine ($i\text{-}Pr_2NEt$) afforded **3a** in 53% yield with a small amount of *N*-phenylbenzamide

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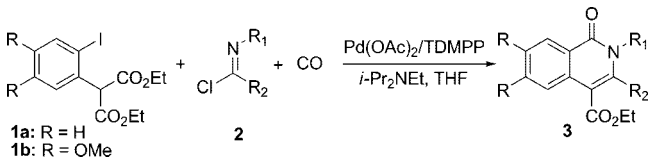
Table 2. One-Step Synthesis of Substituted Isoquinolones from Diethyl(2-iodophenyl)malonates **1** and Imidoyl Chlorides **2**[a]

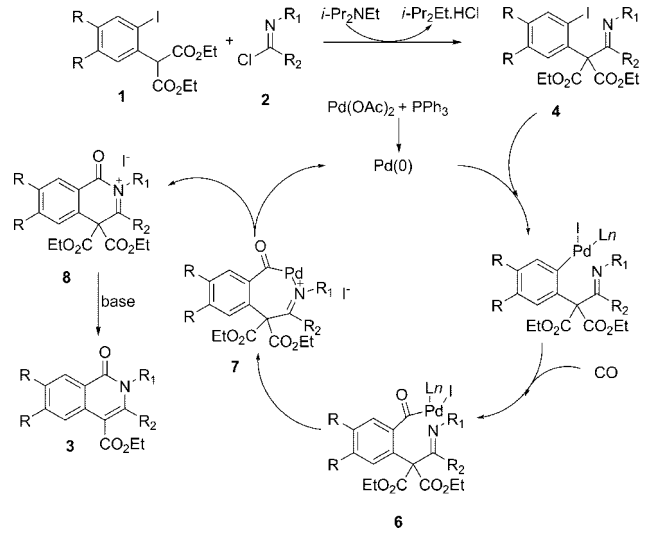


entry	1	2	product 3	yield(%)[b]
1	1a	2a	3a	53
2	1a	2b	3b	63
3	1a	2c	3c	60
4	1a	2d	3d	52
5	1a	2e	3e	48
6	1a	2f	3f	50
7	1a	2g	3g	42
8	1a	2h	3h	33
9	1a	2i	3i	64
10	1a	2j	3j	65
11	1b	2a	3k	65
12	1b	2i	3l	70

[a] Diethyl(2-iodophenyl)malonate **1** (1.0 mmol), imidoyl chloride **2** (1.0 mmol), $Pd(OAc)_2$ (0.03 mmol), TDMPP (0.135 mmol), *i*-Pr_2NEt (3.0 mmol), CO 400 psi, THF (8.0 mL), 120 °C, 48 h. [b] Ioslated yield.

as a byproduct (Table 1, entry 11). While $Pd_2(dba)_3$ or $PdCl_2(PPh)_3$ can be used to catalyze the reaction (Table 1, entries 13 and 14), neither are as effective as $Pd(OAc)_2$.

Scheme 2. Proposed Mechanism for the Pd-Catalyzed Carbonylation Reaction of **1** and **2**



Reducing the pressure of carbon monoxide from 400 to 200 psi resulted in the recovery of some starting material and a lower yield for **3a** (Table 1, entry 12).

On the basis of the above results, reactions were effected using the catalytic system comprised of $Pd(OAC)_2$ and TDMPP, in *i*-Pr_2NEt as the base and CO (400 psi) at 120 °C in THF for 48 h.

The scope of the present synthetic method was extended to a variety of ethyl(2-iodoaryl)malonates and different imidoyl chlorides. The results are summarized in Table 2.

Reaction of **1a** with an imidoyl chloride containing a 4-methoxyl or 4-methyl phenyl group at nitrogen or carbon gave the corresponding 2,3,4-trisubstituted isoquinolin-1(2*H*)-ones **3b**−**e** in 48−63% yields (Table 2, entries 2−5). The reaction tolerates both the electron-donating and -withdrawing substituents. Concerning the latter, the use of imidoyl chlorides having a 4-chlorophenyl group afforded **3f** and **3g** in 50% and 42% yields, respectively (Table 2, entries 6 and 7). The yield of **3h** was only 33% when the imidoyl chloride bearing two 4-chlorophenyl groups was subjected to the normal reaction conditions. An imidoyl chloride bearing an alkyl substituent gave better product yields. Treatment of **1a** with the imidoyl chloride having a *t*-butyl or isopropyl group afforded the expected products, **3i** and **3j**, in 64% and 65% yields (Table 2, entries 9 and 10). The diethyl(2-iodophenyl)malonate derivative having electron-donating dimethoxy substituents **1b** reacted with **2a** to form the corresponding product **3k** in 65% yield (Table 2, entry 11). In a similar manner, **1b** underwent carbonylation with **2i** affording **3l** in 70% yield (Table 2, entry 12).

A possible reaction mechanism for the formation of isoquinolin-1(2*H*)-ones **3** is outlined in Scheme 2. It is conceivable that an imidoyl chloride reacts with diethyl(2-iodoaryl)malonate in the presence of a base to generate intermediate **4**. Oxidative addition of **4** to the in situ

generated palladium(0) species[23] can lead to the arylpalladium complex **5**. Insertion of carbon monoxide into the aryl carbon−palladium bond of **5** would afford the aroylpalladium iodide complex **6**, and the imine nitrogen then attacks the acylpalladium to form a seven-membered palladacyclic ammonium salt **7**.[24] Reductive elimination of **7** may lead to the isoquinolone salt **8** and regenerate the palladium(0) species. The salt **8** subsequently undergoes base-induced decarboalkoxylation to afford isoquinolin-1(2*H*)-one **3**.

In conclusion, we have developed a novel and effective approach for the one-step synthesis of polysubstituted isoquinolin-1(2*H*)-ones. The reaction is compatible with a variety of functional groups and affords the heterocycles in quite good yields. In addition, the present methodology demonstrates the viability of the Pd-catalyzed cyclocarbonylation−decarboxylation pathway.

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Supporting Information Available: Experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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