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Palladium-Catalyzed Cyclocarbonylation-Decarboxylation of Diethyl(2-iodoaryl)malonates with Vinyl Ketones Affording Functionalized Enolic 2-Acyl-3,4-dihydronaphthalenones

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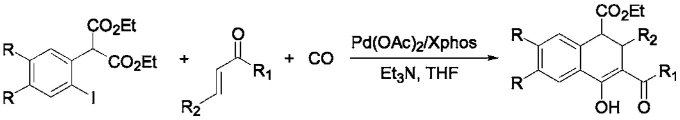
ABSTRACT



A wide variety of enolic tautomers of functionalized 2-acyl-3,4-dihydronaphthalen-1(2*H*)-ones were obtained in moderate to excellent yields by the palladium-catalyzed cyclocarbonylation-decarboxylation of diethyl(2-iodoaryl)malonates with vinyl ketones and carbon monoxide. The reaction may proceed via the formation of a keto-diester, followed by oxidative addition, CO insertion, intramolecular cyclization, and decarboxylation to give the enolic substituted 2-acyldihydronaphthalenones.

3,4-Dihydronaphthalen-1(2*H*)-one, known as α-tetralone, and its derivatives continue to occupy an important place in organic and medicinal chemistry because of the presence of this moiety in a number of natural products[1] and synthetic pharmaceuticals.[2] 2-Acyl-3,4-dihydronaphthalenones are key building blocks for the construction of many bioactive products such as (±)brasiliquinone B[3] and tetrahydronaphthalene.[4] Classical approaches for the synthesis of 2-acyl-3,4-dihydronaphthalenones include the condensation of the corresponding 3,4-dihydronaphthalenone with aldehydes, followed by oxidation of the resultant ketols with Jones reagent.[5] Acylation of α-tetralone using boron trifluoride etherate or diethyl carbonate followed by treatment with sodium acetate in refluxing methanol completes the synthetic process.[3,6] These methods need to start from the corresponding tetralone and require multistep reactions. Routes to highly substituted 2-acyl-3,4-dihydronaphthalenones are more com-

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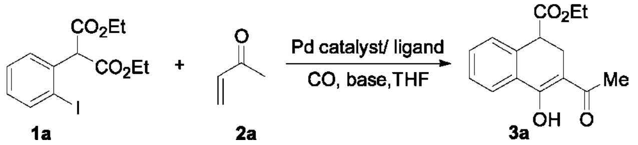
plicated and are accompanied by the formation of byproducts.[7]

Transition-metal-catalyzed reactions are useful for the construction of heterocyclic and carbocyclic systems.[8] The palladium-catalyzed cyclocarbonylation reaction provides efficient access to a wide variety of carbonyl-containing heterocycles.[9] We previously demonstrated that palladium-catalyzed cyclocarbonylation can be used for the synthesis of thiochroman-4-ones,[10] ring-fused isoquinolinones,[11] lactones,[12] 2(5*H*)-furanones,[13] 1,3-oxazin-4-ones,[14] 1,3-benzothiazin-2-ones,[15] quinazolin-4(3*H*)-ones[16] and different ring-sized lactams.[17] Recently, we developed a novel cyclocarbonylation process, followed by decarboxylation, which provides an effective approach for the one-step synthesis of substituted heterocyclic isoquinolin-1(2*H*)-ones.[18] This result prompted us to extend this type of cyclocarbonylation-decarboxylation reaction method to the synthesis of carbocycles. Herein, we report the successful application of this palladium-catalyzed cyclocarbonylation-decarboxylation to the synthesis of variously substituted 2-acyl-4-carboxylic acid ethyl ester-3,4-dihydronaphthalen-1(2*H*)-ones.

The reaction of diethyl(2-iodoaryl)malonate (**1a**) with methyl vinyl ketone (**2a**) was chosen as a model system for the optimization of the reaction conditions (Table 1). Initially, diethyl(2-iodoaryl)malonate **1a** (1.0 mmol) and methyl vinyl ketone **2a** (1.2 mmol) were treated under a pressure of 400 psi carbon monoxide in the presence of 0.03 mmol of Pd(OAc)$_2$, 0.135 mmol of tri(2,6-dimethoxyphenyl)phosphine (TDMPP) and 3.0 mmol of Et$_3$N in 8.0 mL of THF at 120 °C for 24 h. These conditions mirror those used for the synthesis of isoquinolin-1(2*H*)-ones.[18] The desired dihydronaphthalenone **3a** was obtained in 47% yield (Table 1, entry 1). The use of triphenylphosphine (PPh$_3$) and tri*m*-tolylphosphine ((*m*-toly)$_3$P) as ligands afforded **3a** in 74% and 70% yield, respectively (Table 1, entries 2 and 3), while tricyclohexylphosphine (PCy$_3$) afforded **3a** in only 26% yield (Table 1, entry 4). Performing the same reaction using bidentate phosphine ligands resulted in the isolation of **3a** in 59% and 37% yield (Table 1, entries 5 and 6). When employing the bulky and electron-rich monophosphine, Xphos (2-dicyclohexyl-phosphino-2′,4′,6′-triisopropylbiphenyl) and Davephos (2-dicyclohexylphosphine-2′-(*N*,*N*-dimethylamino)biphenyl), the product yields for **3a** increased to 82% and 85% yield, respectively (Table 1, entries 7 and 8). These results show that the ligand employed plays an important role in this transformation.

Table 1. Optimization of the Reaction Conditions for the Reaction of Diethyl(2-iodoaryl)malonate with Methyl Vinyl Ketone[a]



entry	catalyst system	base	temp (°C)	CO (psi)	yield (%)[b]
1	Pd(OAc)$_2$/TDMPP	Et$_3$N	120	400	47
2	Pd(OAc)$_2$/PPh$_3$	Et$_3$N	120	400	74
3	Pd(OAc)$_2$/(*m*-toly)$_3$P	Et$_3$N	120	400	70
4	Pd(OAc)$_2$/PCy$_3$	Et$_3$N	120	400	26
5	Pd(OAc)$_2$/dppb	Et$_3$N	120	400	59
6	Pd(OAc)$_2$/dppp	Et$_3$N	120	400	37
7	Pd(OAc)$_2$/Dave phos	Et$_3$N	120	400	82
8	Pd(OAc)$_2$/X-phos	Et$_3$N	120	400	85
9	Pd(OAc)$_2$/X-phos	K$_2$CO3	120	400	trace
10	Pd(OAc)$_2$/X-phos	CsCO$_3$	120	400	18
11	Pd(OAc)$_2$/X-phos	*i*-Pr$_2$NEt	120	400	62
12	Pd(OAc)$_2$/X-phos	Et$_3$N	120	200	87
13	Pd(OAc)$_2$/X-phos	Et$_3$N	120	100	80
14	Pd(OAc)$_2$/X-phos	Et$_3$N	100	200	81

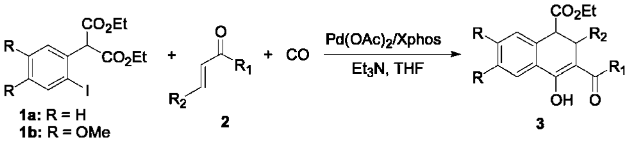
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.2 mmol), Pd cat. (0.03 mmol), phosphine ligand (0.135 or 0.07 mmol), base (3.0 mmol), CO 100, 200, or 400 psi, 120 or 100 °C, THF (8.0 mL). [b] Isolated yield.

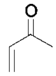
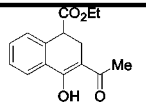
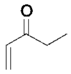
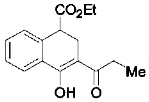
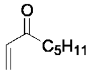
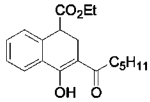
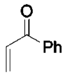
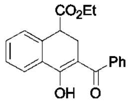
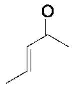
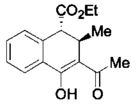
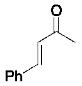
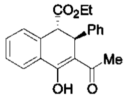
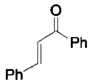
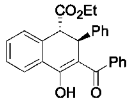
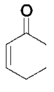
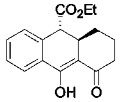
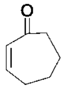
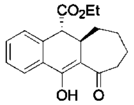
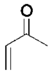
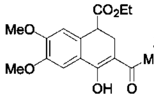
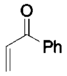
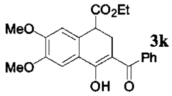
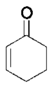
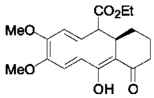
The yield of dihydronaphthalen-1(2*H*)-ones **3a** was also dependent on the nature of the base. The presence of an inorganic base, such as K$_2$CO$_3$ and Cs$_2$CO$_3$, only afforded trace amounts of **3a** (Table 1, entries 9 and 10). The more hindered amine base *N*,*N*-diisopropylethylamine is less effective than triethylamine since it gave **3a** in 62% yield (Table 1, entry 11). A further increase in the yield was achieved by reducing the pressure of carbon monoxide from 400 to 200 psi. (Table 1, entry 12). Lower temperatures resulted in incomplete consumption of the starting materials (Table 1, entry 14). On the basis of the above studies, the reaction conditions using Pd(OAc)$_2$ and Xphos in the presence of Et$_3$N at 120 °C in THF for 24 h, under a pressure of 200 psi CO, were employed as the standard reaction conditions for other substrates.

A wide variety of vinyl ketones react with various diethyl(2-iodoaryl)malonates under the optimized reaction conditions to give the cyclocarbonylation products stereoselectively (Table 2). The stereochemistry of the products was determined by NOE experiments.

Diethyl(2-iodophenyl)malonate **1a** reacted with ethyl vinyl ketone **2b** and amyl vinyl ketone **2c** to give **3b** and **3c** in 85% and 81% yield, respectively (Table 2, entries 2 and 3). Phenyl vinyl ketone **2d** also reacted well with **1a** to afford the corresponding **3d** in 93% yield (Table 2, entry 4). Similarly, 4-substituted vinyl ketone also underwent the cyclocarbonylation reaction. Benzalacetone **2f** reacted with **1a** under the standard conditions to give **3f** in 77% yield (Table 2, entry 6). Chalcone **2g** afforded the corresponding product **3g** in 67% yield (Table 2, entry 7). It is noteworthy here that **3f** and **3g** were obtained as a single diastereomer. However, when methyl propenyl ketone **2e** was employed as the reactant, a mixture of diastereomers of dihydronaphthalene-1(2*H*)-one was obtained in 68% yield. The reaction of **1a** with cyclic ketones, such as cyclohexenone **2h** and cycloheptanone **2i,** also occurred in a highly stereoselective fashion to give the corresponding ring-fused dihydronaphthalene-1(2*H*)-ones **3h** and **3i** in 70% and 74% yield, respectively (Table 2, entries 8 and 9). Performing the same

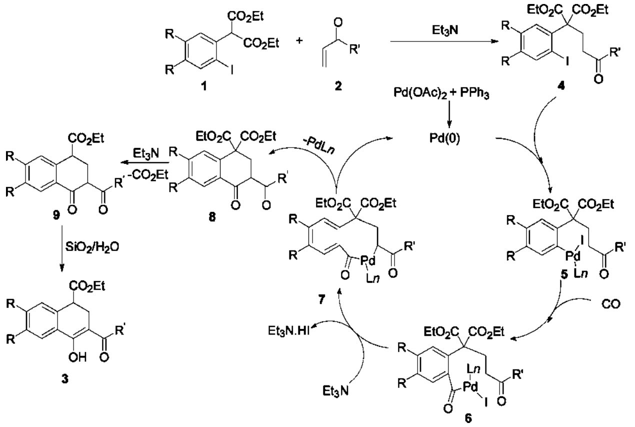
Table 2. Cyclocarbonylation-Decarboxylation of Diethyl(2-iodophenyl)malonates **1** and Vinyl Ketones **2**[a]



entry	1	2	product 3	yield(%)[b]
1	**1a**	 **2a**	 **3a**	87
2	**1a**	 **2b**	 **3b**	85
3	**1a**	 **2c**	 **3c**	81
4	**1a**	 **2d**	 **3d**	93
5	**1a**	 **2e**	 **3e**	55 (7:1)[c]
6	**1a**	 **2f**	 **3f**	77
7	**1a**	 **2g**	 **3g**	67
8	**1a**	 **2h**	 **3h**	70 57[d]
9	**1a**	 **2i**	 **3i**	74
10	**1a**	 **2a**	 **3j**	96
11	**1b**	 **2d**	 **3k**	84
12	**1b**	 **2h**	 **3l**	81

[a] Diethyl(2-iodophenyl)malonates **1** (1.0 mmol), vinyl ketones **2** (1.2 mmol), Pd(OAc)$_2$ (0.03 mmol), Xphos (0.135 mmol), Et$_3$N (3.0 mmol), CO 200 psi, THF (8.0 mL), 120 °C, 24 h. [b] Isolated yield. [c] structures of major isomer are represented. [d] PPh$_3$ as ligand.

Scheme 1. Proposed Reaction Mechanism



reaction using PPh$_3$ instead of Xphos as the ligand resulted in the isolation of **3h** in 57% yield. The palladium-catalyzed cyclocarbonylation-decarboxylation was also successfully extended to the reaction of a diethyl(2-iodophenyl) malonate derivative having electron-donating dimethoxy substituents **1b** with **2a** to form the corresponding product **3j** in 96% yield (Table 2, entry 10). In a similar manner, **1b** underwent carbonylation with **2d** and **2h** afford **3k** and **3l** in 84% and 81% yield, respectively (Table 2, entries 11 and 12).

The NMR spectra of **3** shows that they exist in the keto form before work-up, but they isomerize to the enol form on passing through a silica gel column for purification. The ^{13}C NMR spectrum of crude **3a** displays two carbonyl carbon at δ 206.1 and 198.7, but the ^{13}C NMR spectrum of purified **3a** shows only a carbonyl carbon at δ 196.5, and the ^{1}H NMR spectrum has a hydroxyl singlet at δ 16.24. Similar enolic tautomerism of 2-acyl-1-tetralones has been reported in the literature.[19]

A possible reaction mechanism for the formation of 2-acyl-3,4-dihydronaphthalen-1(2*H*)-ones **3** is outlined in Scheme

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1. It is conceivable that the reaction starts by Michael addition of the vinyl ketone with diethyl(2-iodoaryl)malonate in the presence of a base giving a keto-diester intermediate **4**,[20] which then undergoes oxidative addition to provide in situ generated palladium (0),[21] leading to the arylpalladium complex **5**. Insertion of carbon monoxide into the aryl carbon−palladium bond of **5** could afford the aroylpalladium iodide complex **6**, and subsequent intramolecular attack of the enolate carbon on the palladium atom in **6** may afford a seven-membered palladacycle **7**.[22] Reductive elimination of **7** may lead to the substituted diester 2-acetylcyclohexanone compound **8** and regenerate the palladium(0) species. Compound **8** may subsequently undergo base-induced decarboalkoxylation[18] to afford the dihydronaphthalen-1(2*H*)-ones **9**, which isomerizes to give the enolic tautomer **3** on silica gel.

In conclusion, we have developed an effective one-pot three-component reaction for the synthesis of functionalized enolic 2-acyl-3,4-dihydronaphthalen-1(2*H*)-ones. The reaction tolerates a variety of substitutions and affords 2-acyl-1-tetralones in moderate to excellent yields. In addition, the present method demonstrates that the Pd-catalyzed cyclocarbonylation-decarboxylation can also been extended to the construction of carbocycles.

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

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