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A tandem palladium-catalyzed Heck-lactonization through the reaction of *ortho*-iodophenols with β-substituted acrylates: synthesis of 4,6-substituted coumarins

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Abstract

Coumarins were obtained in one pot through a palladium-catalyzed Heck-lactonization reaction involving *ortho*-iodophenols and methyl crotonate or a *Z*-enoate derived from D-mannitol. These reactions were investigated under different conditions and palladium sources. In the more interesting cases, coumarins were prepared in water, using triethylamine as base and 1 mol % of $PdCl_2$ as catalyst.

1. Introduction

The arylation of olefins by ArHgX in the presence of stoichiometric amounts of $PdCl_2$ was discovered by Heck[1] in 1968 and the first catalytic versions of this reaction were reported by Mizoroki, in 1971,[2] and Heck, in 1972,[3] using ArI as a source of ArPdX species. Today the Heck reaction is one of the most industrially important palladium-catalyzed carbon–carbon coupling.[4] The reaction of *ortho*-iodoaniline with β-substituted enoates in the presence of catalytic amounts of $Pd(OAc)_2$ was also firstly reported by Heck[5] and in this case a tandem Heck-lactamization reaction took place, leading to 4-substituted quinolones. Surprisingly, coumarins were not obtained when *ortho*-iodophenol was used as starting material.[5] On the other hand, the $Pd(OAc)_2$ catalyzed reaction of methyl acrylate with *ortho*-iodophenol led to the corresponding cinnamate (Heck adduct, without lactonization).[6]

The oxy-arylation of chromens by *ortho*-iodophenols was reported by Larock[7] and Kiss et al.[8] The oxy-arylation and the aza-arylation of dihydronaphthalene and related olefins by *ortho*-iodoanilin was also reported by the Larock's group.[9]

During the course of our work, Ulgheri et al. reported the first and sole example of a tandem palladium-catalyzed Heck-lactonization through the reaction of methyl cinnamate and *para*-methyl, *ortho*-bromophenol in the presence of catalytic amounts of $Pd(OAc)_2$.[10] This letter prompted us do disclose our own results on this reaction. As part of a program aiming towards the synthesis of new bioactive compounds, we became interested in the preparation of coumarin derivatives.[11,12] Therefore, we decided to reinvestigate[5,10] the reaction between *ortho*-iodophenols (**1a**–**d**) and acrylate derivatives as a strategy to prepare these compounds. Enoates (*Z*)-**2** and (*E*)-**2**,[13] as well as methyl crotonate (**3a**) and methyl cynnamate (**3b**), were used as substrates (Fig. 1).

2. Results

These reactions were firstly studied (Scheme 1, Table 1) under the conditions described by Kiss et al.[8] for the oxy-arylation of chromens by *ortho*-iodophenols (acetone, $Pd(OAc)_2$, Ag_2CO_3, PPh_3).

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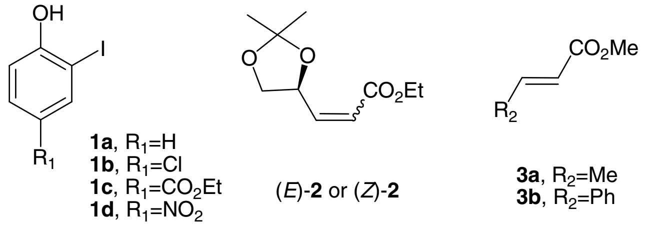
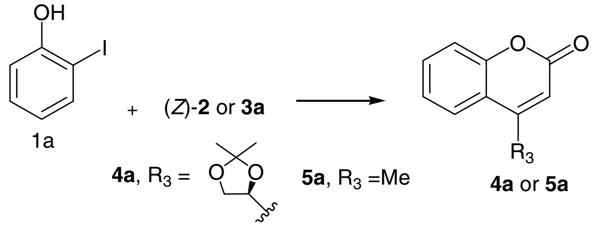


Fig. 1. *ortho*-Iodophenols and olefins used in this work.



Scheme 1. Palladium-catalyzed reaction between *ortho*-iodophenol **1a** and olefins *(Z)*-**2** and **3**. Synthesis of coumarins **4a** and **5a**.

Table 1
Reaction between *ortho*-iodophenol (**1a**) and olefins **2** and **3** Synthesis of coumarins **4a** and **5a**

Entry	Olefin	Base	Catalyst	Product	Yield (%)
1	*E*-**2**	Ag_2CO_3	$Pd(OAc)_2$	—	SM
2	*Z*-**2**	Ag_2CO_3	$Pd(OAc)_2$	**4a**	68
3[a]	*Z*-**2**	Ag_2CO_3	$Pd(OAc)_2$	**4a**	66
4[b]	*Z*-**2**	Ag_2CO_3	$Pd(OAc)_2$	**4a**	53
5[c]	*Z*-**2**	Ag_2CO_3	$Pd(OAc)_2$	**4a**	50
6[d]	*Z*-**2**	Ag_2CO_3	$Pd(OAc)_2$	**4a**	SM
7	*Z*-**2**	Et_3N	$Pd(OAc)_2$	**4a**	41
8[c]	*Z*-**2**	Et_3N	$Pd(OAc)_2$	**4a**	39
9[c]	*Z*-**2**	K_2CO_3	$Pd(OAc)_2$	—	SM
10[e]	*Z*-**2**	$NaHCO_3$	$Pd(OAc)_2$	**4a**	44
11	*Z*-**2**	Ag_2CO_3	$PdCl_2$	**4a**	7
12	*Z*-**2**	Ag_2CO_3	$Pd(PPh_3)_4$	**4a**	50
13	**3a**	Ag_2CO_3	$Pd(OAc)_2$	**5a**	63
14	**3b**	Ag_2CO_3	$Pd(OAc)_2$	—	SM

Reaction mixtures were heated to 80 °C for 40 h in the presence of 10 mol % of catalyst, 0.2 equiv of PPh_3, and 3 equiv of base in acetone at 70 °C.

[a] 2 equiv of Ag_2CO_3 was used in this reaction.

[b] 1 equiv of Ag_2CO_3.

[c] DMF was used as a solvent instead of acetone.

[d] MeCN was used as a solvent.

[e] Tetrabutylammonium chloride was used as an additive.

Only unreacted enoate was isolated from the reaction between **1a** and *E*-**2** in this condition (entry 1). In contrast, a tandem Heck-lactonization took place when *Z*-**2** was used as starting material, resulting in the preparation of coumarin **4a** in 68% (entry 2). The yield was almost the same in the presence of 2 instead of 3 equiv of Ag_2CO_3 (entry 3) but dropped off to 53% when 1 equiv was used (entry 4). A yield of 50% of **4a** was obtained when DMF instead of acetone was used (entry 5) and no reaction was observed in MeCN (entry 6). Ag_2CO_3 could be replaced by Et_3N, but the yield decreased to 41% in acetone (entry 7) and 39% in DMF (entry 8). No reaction occurred when K_2CO_3 was used as base in DMF (entry 9), but the use of $NaHCO_3$ in the presence of tetrabutylammonium chloride led to **4a** in 44% (entry 10). When $PdCl_2$ was used as a source of Pd[0] instead of $Pd(OAc)_2$, the yield of **4a** decreased to 7% (entry 11) while the use of $Pd(PPh_3)_4$ led to this product in 50% yield (entry 12). Finally the use of **3a** as substrate using $Pd(OAc)_2$ as catalyst led to **5a** in 63% yield, but no reaction was observed for **3b** (entries 13 and 14). All attempts to reduce the amount of $Pd(OAc)_2$ under these conditions were unfruitful.

Table 2
Yields of **4a** and **5a** in water and Et_3N (3 equiv) as base

Entry	Olefin	Product	Catalyst	Yield (%)
1	*Z*-**2**	**4a**	$Pd(OAc)_2$	71
2[a]	*Z*-**2**	**4a**	$Pd(OAc)_2$	71
3	*Z*-**2**	**4a**	$Pd(PPh_3)_4$	48
4[b]	*Z*-**2**	**4a**	$Pd(OAc)_2$	73
5	**3a**	**5a**	$Pd(OAc)_2$	44

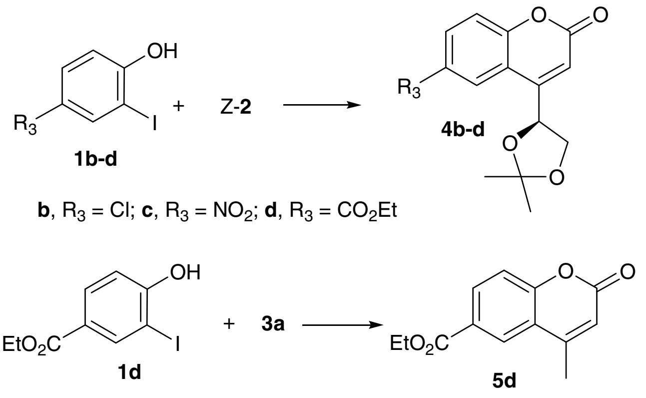
Reaction mixtures were heated to 80 °C for 40 h in the presence of 10 mol % of catalyst, 3 equiv of Et_3N, and water.

[a] 1 equiv of tetrabutylammonium bromide was added in this reaction.

[b] 1 mol % of catalyst was used.

The data in Table 1 suggest that the reaction is favored by a cationic mechanism as better yields were obtained with silver salts.[4] Therefore, we decided to investigate alternative protocols for accomplishing these reactions via a cationic mechanism with the objective of avoiding the use of the toxic reagents Ag_2CO_3 and PPh_3.[14] It has been suggested that reaction in water goes through a cationic mechanism[4] and for this reason the reaction of **1a** with *Z*-**2** and **3a** in water was studied, using Et_3N as base (Table 2).[15]

Coumarin **4a** was obtained in good yield (71%) under the conditions used in Table 2 (entry 1). The same yield was obtained when tetrabutylammonium bromide was used as an additive (entry 2), but decreased to 48% when $Pd(PPh_3)_4$ was employed as the source of Pd[0] (entry 3). The amount of catalyst could be reduced, and 73% yield of **4a** was obtained when 1 mol % of $Pd(OAc)_2$ was used as catalyst (entry 4). Under these conditions, **3a** led to coumarin **5a** in 44% yield (entry 5).



Scheme 2. Reaction between **1b–d** with *Z*-**2** and **3a**.

Table 3
Yields of **4a–d** and **5d** in acetone/Ag_2CO_3 and water/Et_3N in the presence of of $Pd(OAc)_2$

Entry	Olefin	Product	Solvent	Base	Yield (%)
1	*Z*-**2**	**4b**	Acetone[a]	Ag_2CO_3	23
2	*Z*-**2**	**4c**	Acetone	Ag_2CO_3	68
3	*Z*-**2**	**4d**	Acetone	Ag_2CO_3	52
4	**3a**	**5d**	Acetone	Ag_2CO_3	39
5	*Z*-**2**	**4b**	H_2O[b]	Et_3N	78
6	*Z*-**2**	**4c**	H_2O	Et_3N	59
7	*Z*-**2**	**4d**	H_2O	Et_3N	50

Reaction mixtures were heated to 70 °C or 80 °C for 40 h in the presence of 10 mol % of $Pd(OAc)_2$, 3 equiv of base and the solvent.

[a] Reactions in acetone were accomplished in the presence of 0.2 equiv of PPh_3.

[b] Reactions in H_2O were accomplished in the absence of PPh_3.

Table 4
Yields of **4a–c** using $PdCl_2$ as catalyst in water

Entry	Olefin	Product	Catalyst	Yield (%)
1	*Z*-**2**	**4a**	$PdCl_2$	81
2[a]	*Z*-**2**	**4a**	$PdCl_2$	84
3[a]	*Z*-**2**	**4b**	$PdCl_2$	90
4[a]	*Z*-**2**	**4c**	$PdCl_2$	51

Reaction mixtures were heated to 80 °C for 40 h in the presence of 10 mol % of catalyst, 3 equiv of Et_3N and water.

[a] 1 mol % of catalyst was used.

In order to expand the scope of this reaction, *ortho*-iodophenols **1b–d** were also used as substrates (Scheme 2, Table 3).

The yields obtained under the conditions described by Kiss ($Pd(OAc)_2$, Ag_2CO_3, PPh_3, and acetone) are compared in Table 3 with those obtained in the presence of $Pd(OAc)_2$ in Et_3N and H_2O. Coumarin **4b** was formed in 23% in the first condition (entry 1), and the yield was improved to 78% for the reaction in water (entry 5). For coumarins **4c** (entries 2 and 6) and **4d** (entries 3 and 7) the yields were slightly lower in water. Coumarin **5d** was obtained in 39% from enoate **3a** (entry 4).

We also tried to find a better catalyst for the reaction in water and the yield was improved using $PdCl_2$ instead $Pd(OAc)_2$ in H_2O and Et_3N (Table 4). Coumarin **4a** was obtained in 81% and 84% yields when, respectively, 10 and 1 mol % of $PdCl_2$ were employed (entries 1 and 2). The yield of coumarin **4b** was also enhanced when 1 mol % of $PdCl_2$ was used (entry 3). For coumarin **4c**, essentially the same yield was obtained (entry 4).

Work is now in progress to prepare new coumarins from other enoates and *ortho*-iodophenols and use new catalyst. The mechanism of this reaction is also under evaluation.

3. Coumarins 4 and 5[16–21]

3.1. General procedure in organic solvents

A mixture of *ortho*-iodophenol (**1a**, 55 mg, 0.25 mmol), enoate (*Z*-**2**, 150 mg, 0.75 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), PPh_3 (13.1 mg, 0.05 mmol), Ag_2CO_3 (207 mg, 0.75 mmol), and acetone (15 mL) was stirred at 70 °C for 40 h under inert atmosphere. It was cooled, filtered through diatomaceous earth and washed with ethyl acetate. The organic phase was washed with brine, dried over Na_2SO_4 and filtered. The solvent was removed in vacuum and the residual mass was purified by column chromatography (hexane–EtOAc, 9:1) to give **4a** (68%).

3.2. General procedure in water

A mixture of $PdCl_2$ (0.9 mg, 0.005 mmol), enoate (*Z*-**2**, 300 mg, 1.5 mmol), *ortho*-iodophenol (**1a**, 110 mg, 0.5 mmol) and Et_3N (0.208 mL, 1.5 mmol) in H_2O (15 mL) was stirred at 80 °C for 40 h under N_2 atmosphere. The mixture was allowed to cool, H_2O (10 mL) was added, and it was extracted with EtOAc (4 × 40 mL). The organic phase was washed with brine, dried over Na_2SO_4, and filtered through diatomaceous earth. The solvent was removed in vacuum and the residual mass was purified by column chromatography (hexane–EtOAc, 9:1) to give **4a** (84%).

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Supplementary data

^1H NMR and ^{13}C NMR of compounds **4a–d**, **5a** and **5d**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.037.

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16. *(S)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2H-chromen-2-one* (**4a**): White solid; mp 132–135 °C. IR (KBr): 1721 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.53$ (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.80 (dd, $J = 6.9$, 8.3 Hz, 1H, CH_2), 4.59 (dd, $J = 7.2$, 8.3 Hz, 1H, CH_2), 5.39 (dt, $J = 1.2$, 7.0 Hz, 1H, CH), 6.72 (d, $J = 1.2$ Hz, 1H, =CH), 7.34 (m, 3H, ArH), 7.55 (m, 1H, ArH). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 25.1$, 25.9, 69.3, 73.0, 110.4, 111.5, 117.0, 117.3, 123.1, 124.2, 131.7, 153.3, 153.5, 160.5. MS: $m/z = 246$ [M^+].
17. *6-Chloro-4-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2H-chromen-2-one* (**4b**): White solid; mp 129–130 °C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.53$ (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.81 (dd, $J = 6.7$, 8.4 Hz, 1H, CH_2), 4.59 (dd, $J = 7.2$, 8.4 Hz, 1H, CH_2), 5.31 (dt, $J = 1.2$, 6.9 Hz, 1H, CH), 6.73 (d, $J = 1.2$ Hz, 1H, =CH), 7.32 (d, $J = 8.8$ Hz, 1H, ArH), 7.38 (d, $J = 2.3$ Hz, 1H, ArH), 7.50 (dd, $J = 2.3$, 8.8 Hz, 1H, ArH). ^{13}C NMR (200 MHz, $CDCl_3$): $\delta = 25.1$, 26.0, 69.2, 72.9, 110.7, 112.8, 118.3, 118.8, 122.9, 129.7, 131.7, 152.0, 152.3, 159.9. MS: $m/z = 280$, 282 [M^+].
18. *4-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-nitro-2H-chromen-2-one* (**4c**): White solid; mp: 153–157 °C. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.56$ (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 3.88 (m, 1H, CH_2), 4.65 (m, 1H, CH_2), 5.41 (t, $J = 6.8$ Hz, 1H, CH), 6.82 (s, 1H, =CH), 7.52 (d, $J = 9.2$ Hz, 1H, ArH), 8.41 (m, 2H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 24.9$, 25.9, 69.0, 73.0, 111.1, 113.9, 117.3, 118.5, 119.8, 126.5, 143.7, 152.5, 157.2, 158.8. MS: $m/z = 291$ [M^+].
19. *Methyl 4-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-oxo-2H-chromene-6-carboxylate* (**4d**): Yellow solid. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 1.55$ (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 3.82 (m, 1H, CH_2), 3.97 (s, 3H, OCH_3), 4.65 (m, 1H, CH_2), 5.42 (t, $J = 7.0$ Hz, 1H, CH), 6.76 (s, 1H, =CH), 7.42 (d, $J = 8.4$ Hz, 1H, ArH), 8.13 (s, 1H, ArH), 8.21 (dd, $J = 8.8$, 1.8 Hz, 1H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 25.2$, 25.9, 52.5, 69.3, 73.0, 110.7, 112.4, 117.0, 117.6, 125.4, 126.2, 132.7, 153.2, 156.4, 159.8, 165.4. MS: $m/z = 304$ [M^+].
20. *4-Methyl-2H-chromen-2-one* (**5a**): ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.45$ (s, 3H, CH_3), 6.31 (s, 1H, =CH), 7.33 (m, 2H, ArH), 7.52 (d, $J = 7.1$ Hz, 1H, ArH), 7.61 (d, $J = 7.9$ Hz, 1H, ArH).
21. *Methyl 4-methyl-2-oxo-2H-chromene-6-carboxylate* (**5d**): ^{1}H NMR (200 MHz, $CDCl_3$): 2.51 (d, $J = 1.3$ Hz, 3H, CH_3), 3.97 (s, 3H, OCH_3), 6.36 (d, $J = 1.2$ Hz, 1H, =CH), 7.38 (d, $J = 8.6$ Hz, 1H, ArH), 8.20 (dd, $J = 8.6$, 2 Hz, 1H, ArH), 8.32 (d, $J = 2$ Hz, 1H, ArH).