Synthesis of Coumarins in a Molten n-Bu$_4$NOAc/n-Bu$_4$NBr Mixture through a Domino Heck Reaction/Cyclization Process

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Abstract: 4-Arylcoumarins can be prepared in good to high yields by reacting readily available methyl or butyl 3-(*o*-hydroxyaryl)acrylates with aryl iodides and bromides in an n-Bu$_4$NOAc/n-Bu$_4$NBr mixture at 100 °C in the presence of Pd(OAc)$_2$.

Keywords: coumarins; cyclization; Heck reaction; ionic liquids; palladium

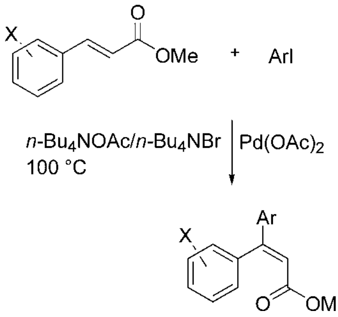
Introduction

During our continuing studies on the Heck reaction of disubstituted alkenes we have found that the presence of acetate anions in the Heck reaction of β-substituted α,β-unsaturated carbonyl compounds may favor the formation of vinylic substitution products with the original β-substituent on the same side of the carbonyl group.[1] Acetate anions might be involved in the irreversible displacement of palladium from σ-alkylpalladium adducts suppressing isomerizations based on the well-known elimination-readdition of hydridopalladium species.[1a]

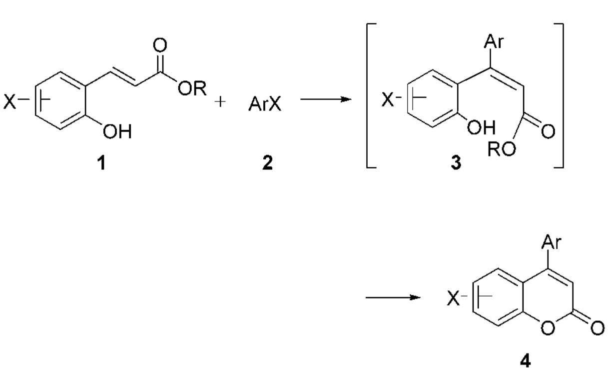
Recently, we have taken advantage of this acetate effect to develop a simple and stereoselective synthesis of β,β-diarylacrylates from cinnamate esters.[2] In particular, aryl iodides were treated with methyl 3-arylacrylates in a molten n-Bu$_4$NOAc/n-Bu$_4$NBr mixture in the presence of Pd(OAc)$_2$ to afford a variety of β,β-diarylacrylates, usually in good to high yields (Scheme 1). Subsequently, the reaction has been extended to aryl bromides.[3]

The reaction (which most probably involves palladium nanoparticles stabilized by quaternary ammonium ions)[4] appeared to us to be particularly promising for the development of domino vinylic substitution/cyclization processes. In fact, because of the *cis* configuration – in the Heck product – of the carbonyl group and the pre-existing β-substituent, a cyclization reaction would be expected to follow the initial vinylic substitution in the presence of *ortho* nucleophiles in the original β-aryl unit. In particular, we envisioned that this domino process could constitute a new approach to coumarins (Scheme 2).

The coumarin motif is abundant in a number of complex natural products exhibiting a broad range of pharmacological activities,[5] including anticancer[6] and anti-HIV[7] activity. Coumarin derivatives have also been used as luminescent probes,[8] photostable laser dyes,[9] and triplet sensitizers.[10] However, the synthesis of this class of compounds currently relies on classical



Scheme 1.



Scheme 2.

Perkin,[11] Pechmann,[12] or Knoevenagel[13] reactions, which suffer from major drawbacks (drastic conditions, stoichiometric amounts of Lewis or mineral acids, multistep protocols, troublesome work-up procedures). Attempts to expand the synthetic approach to functionalized coumarins by using transition metal-catalyzed procedures have been reported.[14] However, some of them are of limited scope, and most of the palladium-catalyzed procedures rely on the functionalization of a preformed coumarin nucleus[14d–m] or are limited to alkyne-based cyclization reactions.[14n–r]

Herein we report that the reaction of readily available methyl and butyl 3-(*o*-hydroxyaryl)acrylates with aryl iodides and bromides in the presence of $Pd(OAc)_2$ (no phosphine ligands are required) in an n-Bu_4NOAc/n-Bu_4NBr mixture, constitutes an efficient new route to 4-arylcoumarins bearing a variety of functional groups.

Results and Discussion

Cinnamic acid esters **1** were readily prepared in 70–90% yields through the palladium-catalyzed reaction of *o*-iodophenols with methyl or butyl acrylate[15] [1 equiv. of *o*-iodophenol, 1.3 equivs. of acrylate ester, 0.01 equiv. of $Pd(OAc)_2$, 1.3 equivs. of Et_3N, MeCN, 80–100 °C under argon].

Reaction conditions successfully employed by us in the synthesis of β,β-diarylacrylates [1 equiv. of cinnamate, 1.5 equivs. of aryl iodide and 0.05 equivs. of $Pd(OAc)_2$ in an n-Bu_4NOAc/n-Bu_4NBr mixture at 100 °C] were used when the domino process was attempted using *p*-iodoanisole and methyl 3-(*o*-hydroxyphenyl)acrylate as the model system. Pleasingly, the desired coumarin product **4a** was isolated in 82% yield after 8 h.

Control experiments were performed to evaluate the efficiency of this protocol. Some results from this study are summarized in Table 1 and show that the process could be successfully extended to *p*-bromoanisole (Table 1, entry 2). Notably, it could not be driven to completion under conditions using a molecular solvent such as DMF as the reaction medium (Table 2, entries 3 and 4). The use of butyl 3-(*o*-hydroxyphenyl)acrylate gave **4a** in higher yield (Table 1, entry 5). No significant amounts, if any, of the vinylic substitution intermediate were detected when the reaction was monitored by TLC and HPLC analysis (the same trend has been observed with other aryl halides and acrylate esters), both with the methyl and the butyl ester. This suggests that the cyclization of vinylic substitution intermediates to coumarin is the fast step and that displacement of the more basic butoxide anion does not affect the reaction course to a large extent.

Therefore, we focused primarily on the use of the more convenient aryl bromides when the substrate scope of this synthesis was explored. Both butyl and methyl esters were employed. Our preparative results are shown in Table 2.

Butyl esters were usually found to provide better results than methyl esters with electron-rich and slightly electron-poor aryl halides. Similar yields were instead obtained with strongly electron-poor aryl halides. For example, the coumarin derivative was isolated in 35–37% yield with *p*-bromobenzaldehyde both with the methyl acrylate and the butyl acrylate (Table 2, entries 13 and 14).

As to the aryl halide partner, a variety of electron-rich and slightly electron-poor aryl bromides react well in the ionic liquid medium to provide the desired coumarin derivatives usually in good to high yields. Moderate yields were instead obtained with aryl bromides containing strongly electron-withdrawing substituents.

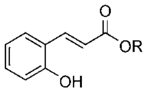
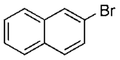
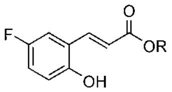
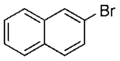
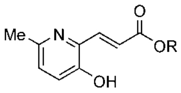
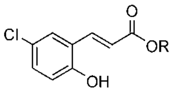
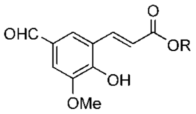
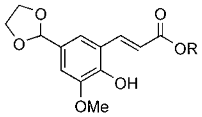
As far as the β-aryl group is concerned, good to excellent results can be obtained when it contains electron-donating and weak electron-withdrawing substituents. Strongly electron-withdrawing substituents *para* to the *o*-hydroxy group appear to hamper the reaction. For example, when **1g** was subjected to our standard conditions, a complex reaction mixture was formed which

Table 1. Aryl halides, solvents and 3-(*o*-hydroxyphenyl)acrylates in the synthesis of **4a**.[a]

Entry	R Acrylate **1**	Aryl Halide **2**	Conditions	Yield of **4a** [%][b]
1	Me	p-MeO-C_6H_4-I	n-Bu_4NOAc (2.1 equivs.), n-Bu_4NBr (1.5 equivs.)	82
2	Me	p-MeO-C_6H_4-Br	n-Bu_4NOAc (2.1 equivs.), n-Bu_4NBr (1.5 equivs.)	78
3	Me	p-MeO-C_6H_4-Br	AcOK (2.5 equivs.), DMF (1.5 mL)	Traces[c]
4	Me	p-MeO-C_6H_4-Br	$NaHCO_3$ (2.5 equivs.), n-Bu_4NCl (1 equiv.), DMF (1.5 equivs.)	22[d]
5	n-Bu	p-MeO-C_6H_4-Br	n-Bu_4NOAc (2.1 equivs.), n-Bu_4NBr (1.5 equivs.)	88[e]

[a] Unless otherwise stated, reactions were run in the presence of 5 mol % of $Pd(OAc)_2$ at 100 °C for 8 h by using 1.5 equivs. of **2** and 1 equiv. of **1**.
[b] Yields are given for isolated products.
[c] The starting acrylate ester was recovered in 78% yield.
[d] The starting acrylate ester was recovered in 56% yield.
[e] 6 h.

Table 2. Synthesis of 4-arylcoumarins **4** from 3-(*o*-hydroxyphenyl)acrylates **1** and aryl iodides and bromides **2**.[a]

Entry	3-(*o*-Hydroxyphenyl)acrylate Ester **1**			Aryl Halide **2**	*t* [h][b]	Yield of **4** [%][c]
1		R = Me	**1a**	*p*-MeO-C_6H_4-Br	8	**4a** 78
2		R = *n*-Bu	**1b**	*p*-MeO-C_6H_4-Br	8	**4a** 88
3		R = Me	**1a**	*m*-MeO-C_6H_4-Br	8	**4b** 75
4		R = *n*-Bu	**1b**	*p*-MeCOO-C_6H_4-Br	2	**4c** 70[d]
5		R = Me	**1a**	*p*-Me_2N-C_6H_4-Br	7	**4d** 74
		R = *n*-Bu	**1b**	*p*-Me_2N-C_6H_4-Br	7	**4d** 98
6		R = Me	**1a**	*p*-Me-C_6H_4-Br	10	**4e** 75
7		R = Me	**1a**	*p*-F-C_6H_4-Br	24	**4f** 75
8		R = Me	**1a**	*m*-F-C_6H_4-Br	31	**4g** 70
9		R = Me	**1a**	*p*-*t*-Bu-C_6H_4-Br	30	**4h** 61
10		R = *n*-Bu	**1b**	*p*-*t*-Bu-C_6H_4-Br	10	**4h** 82
11		R = *n*-Bu	**1b**	*p*-MeCONH-C_6H_4-Br	24	**4i** 77
12		R = *n*-Bu	**1b**	*o*-MeCONH-C_6H_4-Br	24	-[e]
13		R = Me	**1a**	*p*-CHO-C_6H_4-Br	24	**4j** 35
14		R = *n*-Bu	**1b**	*p*-CHO-C_6H_4-Br	24	**4j** 37
15		R = Me	**1a**	*p*-Ph-C_6H_4-Br	8	**4k** 68
16		R = *n*-Bu	**1b**	*p*-Ph-C_6H_4-Br	10	**4k** 83
17		R = Me	**1a**	*m*-CF_3-C_6H_4-Br	31	**4l** 67[f]
18		R = *n*-Bu	**1b**	*p*-Br-C_6H_4-Br	24	**4m** 30[g]
19		R = *n*-Bu	**1b**	*p*-Br-C_6H_4-I	33	**4m** 50[g]
20		R = *n*-Bu	**1b**		24	**4n** 65[h]
21		R = Me	**1c**	*p*-Ph-C_6H_4-Br	48	**4o** 68
22		R = Me	**1c**		24	**4p** 70
23		R = Me	**1c**	*p*-MeO-C_6H_4-I	4.5	**4q** 86
24		R = Me	**1d**	*p*-MeO-C_6H_4-I	26	**4r** 37
25		R = *n*-Bu	**1e**	*p*-MeO-C_6H_4-I	30	**4r** 36
26		R = Me	**1f**	*p*-MeO-C_6H_4-I	5	**4s** 82
27		R = Me	**1g**	*p*-MeO-C_6H_4-Br	5.5	–
28		R = Me	**1h**	*p*-MeO-C_6H_4-Br	5.5	**4t** 70[i]

[a] Unless otherwise stated, reactions were run in the presence of 5mol % of $Pd(OAc)_2$ at 100 °C by using 1.5 equivs. of **2** and 1 equiv. of **1**. [b] Reaction times were not optimized. [c] Yields are given for isolated products. [d] Isolated as 4-(*p*-hydroxyphenyl) derivative. [e] The starting aryl bromide was recovered in 63% yield. [f] In the presence of 2.5 equivs. of aryl halide. With 1.5 equivs. of aryl halide, **4l** was isolated in 53% yield. [g] With 3 equivs. of aryl halide. [h] Compound **1b** was recovered in 15% yield. [I] Isolated as the formyl derivative, after acid work-up

we have not further investigated (Table 2, entry 27). However, an appropriately protected aldehydic acrylate (Table 2, entry 28) gave the desired product in 70% yield. Moderate yields were obtained with heterocyclic analogues of 3-(*o*-hydroxyphenyl)acrylates (Table 2, entries 24 and 25).

Interestingly, reactions did not have to be carried out under an argon atmosphere. It appears that the catalytic activity is maintained for a relatively long time even in the presence of oxygen.

Conclusion

In conclusion, we have developed a convenient straightforward route for the construction of the functionalized lactone ring incorporated into the coumarin system from readily available starting materials that may represent a useful alternative to classical methods and compares well with known palladium-based procedures. Work along this line is in progress.

Experimental Section

Typical Procedure for the Preparation of 4-Aryl Coumarins (4) from 3-(*o*-Hydroxyphenyl)acrylate Esters (1) and Aryl Iodides and Bromides (2)

To a stirred solution of **1b** (0.109 g, 0.50 mmol), *p*-bromoanisole (0.093 mL, 0.75 mmol), *n*-BuN$_4$OAc (0.312 g, 1.05 mmol) and *n*-BuN$_4$Br (0.239 g, 0.75 mmol) at 100 °C, Pd(OAc)$_2$ (0.006 g, 0.025 mmol) was added. The mixture was stirred for 8 h at 100 °C. Then, it was diluted with ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (axially compressed column packed with SiO_2, 35 g, 25–40 μm, connected to a Gilson solvent delivery system and to a Gilson refractive index detector) eluting with a 75/25 v/v *n*-hexane/AcOEt mixture) to give **4a**; yield: 0.110 g (88%); mp: 119–120 °C; IR (KBr): $\nu = 1729$, 1605 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.58–7.55$ (m, 2H), 7.43–7.39 (m, 3H), 7.25 (t, $J = 7.5$ Hz, 1H), 7.07–7.04 (m, 2H), 6.36 (s, 1H), 3.90 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 160.7$, 155.3, 154.1, 142.6, 139.9, 133.9, 131.9, 128.9, 128.9, 127.9, 127.5, 127.1, 126.9, 124.1, 118.9, 117.3, 115.0.

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