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Coumarins from Free *ortho*-Hydroxy Cinnamates by Heck-Matsuda Arylations: A Scalable Total Synthesis of (*R*)-Tolterodine

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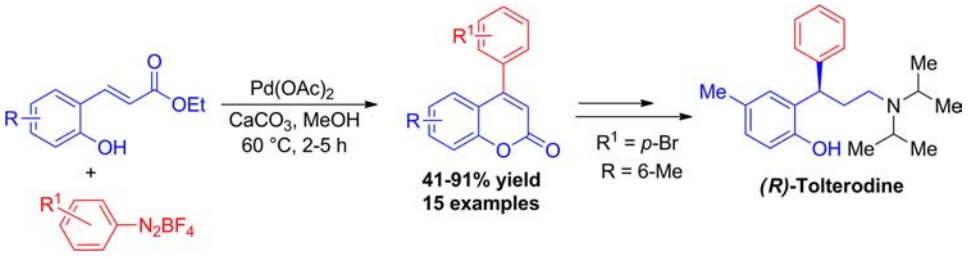
ABSTRACT



Free *ortho*-hydroxy cinnamate ester derivatives are evaluated in the synthesis of structurally diverse 4-aryl-coumarins *via* a tandem Heck-Matsuda cyclization reaction. Free phenolic groups were considered incompatible with such a reaction, which usually provide the corresponding diazo dyes. A concise and scalable route employing a ligand-free, Pd-catalyzed Heck-Matsuda arylation under aerobic conditions for the preparation of (*R*)-Tolterodine in high overall yield and *ee* is also presented.

Arylation methods are among the most important reaction types in organic synthesis. Aryl groups are found in an outstanding number of natural products and pharmaceuticals.[1] In recent years, our group and others have been exploring the palladium-catalyzed coupling of arenediazonium salts to olefins (Heck-Matsuda reaction) as a convenient method to obtain arylated and diarylated compounds of biological and medicinal interest.[2] In this context, coumarins might be considered representative diarylated species of great interest due to their biological properties. Their diverse physiological activity such as disease prevention, growth modulation, antioxidant properties, bacteriostatic and antitumor activity makes these compounds attractive core structures for further derivatization, screening and development as novel therapeutic agents.[3] A simple procedure for the rapid synthesis of a diverse array of 4-aryl-coumarins was reported in 2005 by Tunge and co-workers operating on the basis of a sequential Pd(II)-Fujiwara-cycloisomerization of arylated alkynoates followed by a Pd(0)-catalyzed cross coupling reaction.[4] In that same year, Cacchi reported an efficient route to 4-aryl-coumarins from readily available methyl

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(1) For reviews, see: (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (b) Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.

(2) For reviews, see: (a) Taylor, J. G.; Moro, A. V.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, 1403. (b) Felpin, F.-X.; Nassar-Hardy, L.; Callonnec, F. L.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815. (c) Roglans, A.; Pla-Quintana, A.; Moreno-Manãs, M. *Chem. Rev.* **2006**, *106*, 4622.

(3) (a) Weber, U. S.; Steffen, B.; Siegers, C. P. *Res. Commun. Mol. Pathol. Pharmacol.* **1998**, *99*, 193. (b) Egan, D.; James, P.; Cooke, D.; O'Kennedy, R. *Cancer Lett.* **1997**, *118*, 201. (c) Cooke, D.; O'Kennedy, R. *Anal. Biochem.* **1999**, *274*, 188. (d) Budzisz, E.; Brzezinska, E.; Krajewska, U.; Rozalski, M. *Eur. J. Med. Chem.* **2003**, *38*, 597.

(4) Li, K.; Zeng, Y.; Neuenswander, B.; Tunge, J. A. *J. Org. Chem.* **2005**, *70*, 6515.

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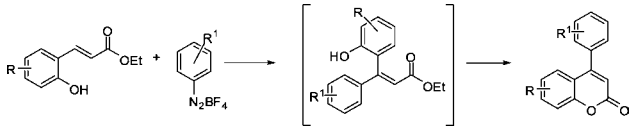
and butyl 3-(*o*-hydroxyaryl)acrylates with aryl iodides and bromides in the presence of $Pd(OAc)_2$.[5] A similar strategy to Cacchi's was applied by Piccolo (2007) in the enantioselective synthesis of a 4-arylcoumarin en route to the asymmetric synthesis of (*S*)-Tolterodine.[6]

Recently, we have demonstrated that various alkyl cinnamates could be efficiently and stereoselectively arylated with arenediazonium salts when using $Pd(OAc)_2$ as catalyst in good to high yields.[7] We envisioned that, if successful, the application of this method to *ortho*-hydroxy-cinnamate esters could lead to the straightforward synthesis of *ortho*-hydroxy-3,3-diaryl-acrylates and their subsequent transformation to 4-aryl-coumarins. In this context, we describe herein a feasible method for the synthesis of 4-aryl-coumarins from free *ortho*-hydroxy-cinnamate ester derivatives via a tandem Heck-Matsuda cyclization procedure (Scheme 1). The generality of the method is demonstrated by a concise and enantioselective total synthesis of (*R*)-tolterodine, an antimuscarinic drug used in the treatment of urinary incontinence[8] (Scheme 5).

Scheme 1. Synthesis of 4-Aryl-coumarins via Tandem Heck Arylation/Cyclization



Cinnamate esters were prepared by either (*E*)-selective one-pot Wittig reaction in aqueous media (**a**)[9] or by Horner-Wadsworth-Emmons reaction (**b**) using commercially available benzaldehydes (Scheme 2). With the desired cinnamates **3a**−**3f** in hand, we started our investigation of the Heck arylation/cyclization with the *ortho*-hydroxy-cinnamate ester **3d** using the same conditions described previously for the arylation of cinnamate ester derivates.[7] This procedure uses methanol as solvent and $Pd(OAc)_2$ as catalyst at 60 °C without an added base. The base-free conditions seemed ideal to avoid the formation of phenolates, which would be highly reactive toward arenediazonium salts. However, under base-free conditions, the 4-aryl-coumarin **6i** was obtained in only 29% yield. In view of these rather disapointing results, we speculated that the basicity of the reaction medium could be an important factor in circumventing more detrimental Brønsted acid promoted side reactions.

(5) Battistuzzi, G.; Cacchi, S.; De Salve, I.; Fabrizi, G.; Parisi, L. M. *Adv. Synth. Catal.* **2005**, *347*, 308.

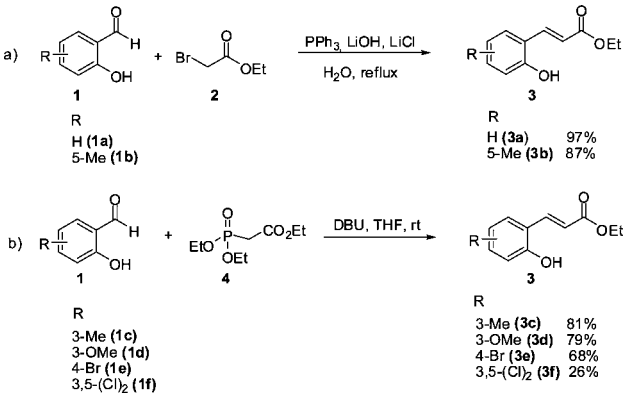
(6) (a) Ulgheri, F.; Marchetti, M.; Piccolo, O. *J. Org. Chem.* **2007**, *72*, 6056. For a recent report on the synthesis of 4-aryl-coumarins using the an oxidative Heck reaction, see: (b) Li, Y.; Qi, Z.; Wang, H.; Fu, X.; Duan, C. *J. Org. Chem.* **2012**, *77*, 2053.

(7) Taylor, J. G.; Correia, C. R. D. *J. Org. Chem.* **2011**, *76*, 857.

(8) (a) Wefer, J.; Truss, M. C.; Jonas, U. *World J. Urol.* **2001**, *19*, 312. (b) Rovner, E. S.; Wein, A. *J. Eur. Urol.* **2002**, *41*, 6.

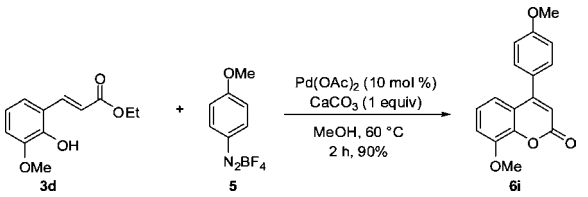
(9) Wu, J.; Yue, C. *Synth. Commun.* **2006**, *36*, 2939.

Scheme 2. Preparation of *o*-Hydroxy-cinnamate Ester Substrates



Therefore, we performed the same reaction in the presence of 1 equiv of $CaCO_3$ as base. To our satisfaction and surprise, the product yield of **6i** was increased to 90% (Scheme 3). Attempts to lower the catalyst loading from 10 to 5 mol % resulted in decreased yields (43%).

Scheme 3. Heck Arylation/Cyclization of *o*-Hydroxy-cinnamate Ester **3d**

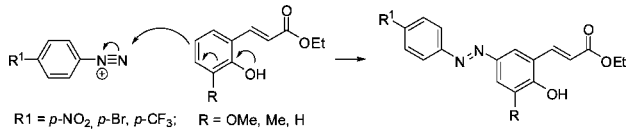


With these encouraging initial results in hand, we decided to evaluate the scope of the arylation/cyclization protocol to other *ortho*-hydroxy-cinnamate esters as well as to investigate the compatibility of the arenediazonium salts toward other functionalized free phenols. The prevalence of the Heck coupling over the well-known diazonium coupling, leading to azo dyes, is striking since the diazonium coupling is a very facile base-catalyzed process (see Scheme 4).[10] In most of the cases examined, the corresponding coumarins were obtained in moderate to good yields for several combinations of aryl diazonium tetrafluoroborates and free phenol cinnamates (Table 1). Many aryl diazonium salts possessing electron-neutral, electron-donating (ED), and electron withdrawing groups (EWG) were well-tolerated under the reaction conditions. Entries 6, 7, 10, and 12 clearly indicate successful Heck arylations involving diazo-coupling prone phenol derivatives and highly electrophilic aryldiazonium salt bearing electron withdrawing groups. However, some limitations were observed. Cinnamates **3a**, **3c** and **3d** failed to provide the corresponding 4-aryl coumarins with aryldiazonium salts bearing strong EWG such as *p*-NO_2, *p*-Br or *p*-CF_3.

(10) Hartwell, J. L.; Fieser, L. F. *Org. Synth.* **1943**, *2*, 145.

For such reactions, we observed complex mixture of colored compounds. We believe that in those cases diazo coupling may be a competitive process with the Heck-Matsuda reaction as illustrated in Scheme 4.

Scheme 4. Possible Diazo Coupling



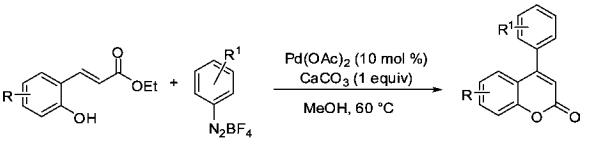
Gratifyingly, cinnamate esters containing electron-donating (**3b**) or electron-withdrawing groups (**3e**, **3f**) at the 5 position of the aromatic ring were reactive with neutral, electron-rich and electron-poor arenediazonium salts providing 4-aryl-coumarins **6d**−**g**, **6j**−**o** in 41−88% isolated yields (Table 1, entries 4−7 and 10−15).

We next turned our attention to the synthetic application of this new Heck protocol. Our initial target was a concise total synthesis of (*R*)-tolterodine. Different approaches have been reported for the racemic and asymmetric synthesis of tolterodine over the last decades.[6a]

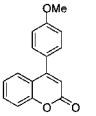
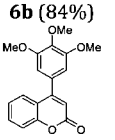
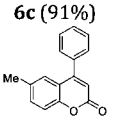
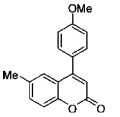
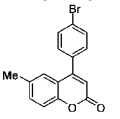
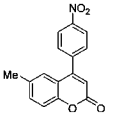
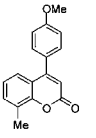
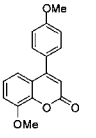
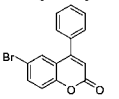
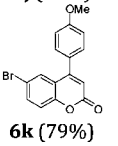
We envisioned a concise synthesis of tolterodine through a Heck-Matsuda reaction between *ortho*-hydroxy-cinnamate ester **3b** (generated from commercially available 2-hydroxy-5-methyl-benzaldehyde) and the arenediazonium salt **5d** to provided coumarin **6d,** a known intermediate in a previously reported total synthesis of tolterodine.[6a] The Heck-Matsuda arylation/cyclization was performed on 1.4 g of the *ortho*-hydroxy-cinnamate ester **3b** with 4-bromobenzenediazonium tetrafluoroborate under our optimized conditions to furnish 6-methyl-4-phenyl-coumarin **6d** in 63% isolated yield over two steps (Scheme 5).[12] As expected, the C−Br bond underwent smooth debromination *in situ* to afford the 4-aryl-coumarin **6d** in good yield.[13]

Conjugate reduction mediated by a phosphine ligated CuH species is known to be a powerful method for the induction of chirality β to a carbonyl.[14] Therefore, asymmetric reduction of coumarin **6d** was carried out using similar conditions to those described by Lipshutz in which $Cu(OAc)_2$ (10 mol %), (*R*)-JOSIPHOS (10 mol %) as ligand and excess DEMS (diethoxymethylsilane) are employed.[15] The resulting lactol **7** was isolated in 74% yield. Reducing the amounts of copper and ligand from

Table 1. Heck Arylation of *o*-Hydroxy-cinnamate Esters **3** with Diazonium Salts **5**[a]



3a-f 5 6a-o

entry	R	R¹	time (h)	product yield (%)[b]
1	H	H	5	 **6a** (68%)
2	H	4-OMe	3	 **6b** (84%)
3	H	3,4,5-OMe	2	 **6c** (91%)
4	5-Me	H	4	 **6d** (41%)
5	5-Me	4-OMe	2	 **6e** (88%)
6	5-Me	4-Br	4	 **6f** (83%)
7	5-Me	4-NO_2	3	 **6g** (49%)
8	3-Me	4-OMe	3	 **6h** (77%)
9	3-OMe	4-OMe	2	 **6i** (90%)
10	5-Br	H	4	 **6j** (70%)
11	5-Br	4-OMe	2	 **6k** (79%)

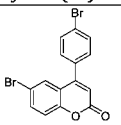
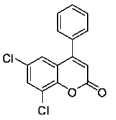
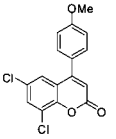
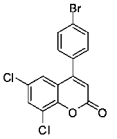
(11) (a) Andersson, P. G.; Schink, H. E.; Österlund, K. *J. Org. Chem.* **1998**, *63*, 8067. (b) De Castro, K. A.; Ko, J.; Park, D.; Park, S.; Rhee, H. *Org. Process Res. Dev.* **2007**, *11*, 918. (c) De Castro, K. A.; Rhee, H. *Synthesis* **2008**, 1841. (d) Yoo, K.; Kim, H.; Yun, J. *J. Org. Chem.* **2009**, *74*, 4232. (e) Gallagher, B. D.; Taft, B. R.; Lipshutz, B. H. *Org. Lett.* **2009**, *11*, 5374.

(12) The same reaction when carried out on a smaller scale (0.3−0.5 mmol) gave the Heck product **6d** in 92% yield (average of 3 experiments).

(13) Lower yields of the Heck product were obtained with benzenediazonium salt (entry 4, Table 1).

(14) For reviews, see: (a) Deutsch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916. (b) Llamas, T.; Arrayás, R. G.; Carretero, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 3329. (c) Desrosiers, J.-N.; Charette, A. B. *Angew. Chem., Int. Ed.* **2007**, *46*, 5955.

Table 1. continued

entry	R	R^1	time (h)	product yield (%)[b]
12	5-Br	4-Br	3	 **6l** (58%)
13	3,5-$(Cl)_2$	H	3	 **6m** (77%)
14	3,5-$(Cl)_2$	4-OMe	2	 **6n** (73%)
15	3,5-$(Cl)_2$	4-Br	3	 **6o** (60%)

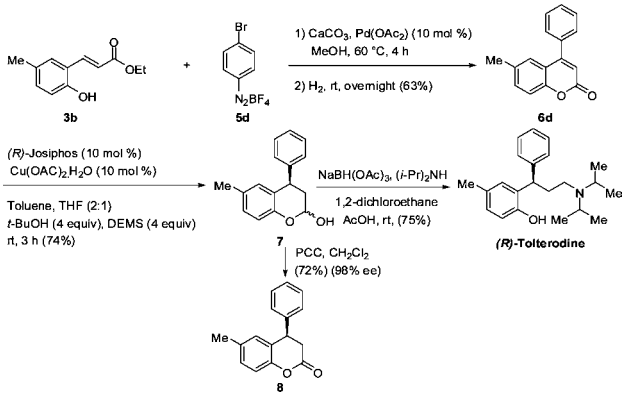
[a] Reactions performed in the presence of *o*-hydroxy-cinnamate ester **3** (0.3 mmol), arenediazonium salt **5** (0.6 mmol), $Pd(OAc)_2$ (10 mol %), $CaCO_3$ (0.3 mmol), MeOH (1.8 mL) at 60 °C. [b] Yields of **6a**–**o** are given for isolated products.

10 to 5 mol % provided a significant lower 57% yield of the desired lactol **7**. In order to evaluate the enantioselectivity of the Cu–H reduction step, lactol **7** was oxidized with PCC to the corresponding lactone (72% yield). Chiral CG analysis indicated a 98% ee for lactone **8**.

Finally, aiming at synthesizing (*R*)-tolterodine, we carried out the reductive amination reaction of lactol **7**. Stirring lactol **7** in the presence of diisopropylamine (DIPA), AcOH and $NaHB(OAc)_3$ at room temperature provided (*R*)-tolterodine in 75% yield in only four steps from cinnamate **3b** in an overall yield of 30%.

(15) Similar results were obtained with (*S*)-JOSIPHOS, which was employed in the synthesis of the enantiomeric lactol **7** (**7b**), lactone **8** (**8b**), and (*S*)-tolterodine. For procedures and spectral data for these compounds see the Supporting Information.

Scheme 5. Synthesis of (*R*)-Tolterodine



In summary, we have described an efficient, mild and operationally simple method for the synthesis of 4-aryl-coumarins from free *ortho*-hydroxy-cinnamate ester derivatives via a tandem Heck arylation/cyclization procedure employing arenediazonium salts under palladium catalysis. The Heck-Matsuda reaction proceeds under aerobic conditions requiring only a few hours to go to completion to afford the corresponding 4-aryl-coumarin derivatives in moderate to good yields. Furthermore, the 6-methyl-4-phenyl-coumarin obtained in the current protocol was used as an intermediate for a concise (4 steps) asymmetric total synthesis of (*R*)-tolterodine in 30% overall yield and 98% ee.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.