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Synthesis of Dihydrofurocoumarins via Palladium-Catalyzed Annulation of 1,3-Dienes by *o*-Iodoacetoxycoumarins

Roman V. Rozhkov and Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, Iowa 50010

larock@iastate.edu

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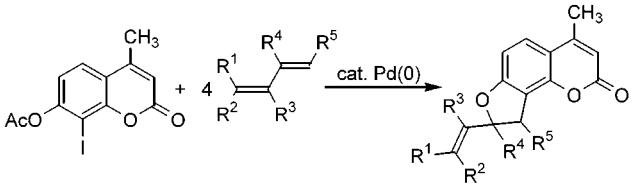
ABSTRACT



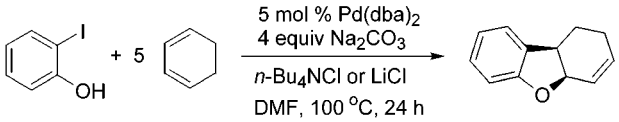
A variety of biologically interesting dihydrofurocoumarins have been synthesized in high yields by the palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxycoumarins. This reaction is very general and regioselective, and a wide variety of terminal, cyclic, and internal 1,3-dienes can be utilized.

Dihydrofurocoumarins occur commonly in plants and fruits and are very important because of their pronounced biological properties.[1] According to recent reports, dihydrofurocoumarins exhibit significant cytotoxicity against KB cells[2] and an ability to inhibit c-AMP[3] synthetase, as well as acetylcholinesterase.[4]

Because of the biological and pharmaceutical importance of dihydrofurocoumarins, numerous methods for their synthesis have been developed during the last 30 years. Earlier methods involved multiple steps and suffered from low (2−20%) overall yields.[5] Recent synthetic approaches based on the Claisen rearrangement[6] and the Sonogashira coupling[7] give 40−60% overall yields, but these methods lack broad-generality and, therefore, cannot be used for the synthesis of large libraries of biologically active dihydrofurocoumarins.

Palladium-catalyzed annulations developed in our laboratories provide a versatile route to the construction of complex cyclic systems.[8] Previously, we reported an efficient method for the synthesis of *cis*-dihydrobenzofurans by the palladium-catalyzed annulation of 1,3-dienes by *o*-iodophenols (Scheme 1).[9] This methodology looked very promising

Scheme 1



for the synthesis of dihydrofurocoumarins. Herein, we report that the palladium-catalyzed annulation of 1,3-dienes by

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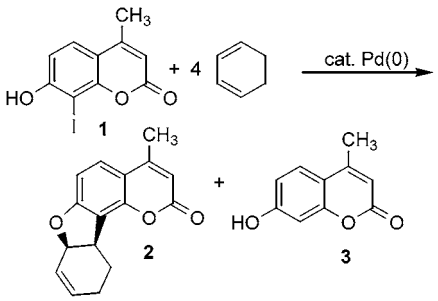
o-iodohydroxycoumarin derivatives provides a very general and effective route to a wide variety of angular and linear dihydrofurocoumarins.

For our initial investigations, the annulation of 1,3-cyclohexadiene by iodocoumarin **1** was selected as a model reaction (Scheme 2). Surprisingly, under the optimal reaction

Scheme 2

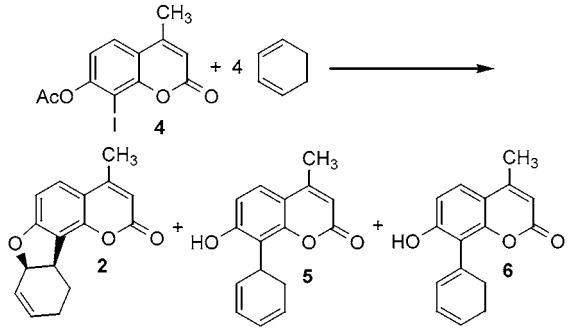


conditions used in the dihydrobenzofuran project,[9] the annulation gave only a 6% yield of the desired *cis*-dihydrofurocoumarin **2**. Instead, the reduced coumarin **3** was isolated in 88% yield. Variation of the bases, phosphine ligands, and solvents used in this reaction had little effect on the outcome of the reaction. The best result was achieved using Ag_2CO_3 as a base, dppe as a ligand, and THF as a solvent at 60 °C. This provided a 17% yield of the desired product **2**, a 15% yield of the reduced coumarin **3**, and 63% of the starting material **1**. The positive effect of Ag_2CO_3 is presumably due to abstraction of a halide from the arylpalladium complex and formation of a cationic arylpalladium intermediate, which is assumed to be more reactive toward addition to the C=C bond.[10]

From our preliminary results, it appeared that electron-rich aryl iodides have a great propensity to undergo the undesired reduction.[11] The introduction of an electron-withdrawing acetyl group on the phenolic oxygen would be expected to decrease the electron density on the aromatic ring and might, therefore, be expected to improve the yield of the desired coumarin **2** if there were some way to remove the acetyl group during the annulation process. Acylated phenols are sufficiently stable in the pH range from 5 to 8 and, therefore, would be expected to tolerate our reaction conditions.[11]

Using the annulation of 1,3-cyclohexadiene by acetoxy-iodocoumarin **4** as a model system, we have examined the effect of various reaction parameters such as solvent, palladium catalyst, silver salt, phosphine ligand, and reaction temperature on the yield of the desired coumarin **2** (Scheme 3). Although the annulation of coumarin **4** under our best previous reaction conditions obtained for coumarin **1** did not show very promising results, the addition of water raised

Scheme 3



the yield of coumarin **2** to 21%. In sharp contrast to the annulation of coumarin **1**, acetoxy derivative **4** did not give any of the reduced coumarin **3** or its acetoxy analogue. Besides that, the recovery of 78% of the starting material **4** indicated that the undesired reduction is completely inhibited under these reaction conditions.

Great improvements were subsequently achieved using a 4:1 1,4-dioxane/water mixture as the solvent at higher temperatures. Increasing the reaction temperature to 80 and 100 °C improved the yield of the desired product **2** to 44 and 64%, respectively. Besides the desired product, significant amounts of Heck-type products **5** and **6** were isolated. Further optimizations, which utilized $Pd(OAc)_2$ as the catalyst; dppp, dppb, BINAP, and PPh_3 as the phosphine ligand; and AgOAc, Ag_3PO_4, and Ag_2CO_3 as the silver salt, only resulted in a lower yield of the annulated product **2**. We have thus used the following "optimal" procedure for all subsequent annulations: the iodoacetoxycoumarin (0.25 mmol), $Pd(dba)_2$ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag_2CO_3 (0.5 mmol), 1,3-diene (1.0 mmol), and 5 mL of a 4:1 1,4-dioxane/water mixture were stirred at 100 °C for 24 h.

Next, the scope and limitations of this annulation were studied using various 1,3-dienes, and representative examples are shown in Table 1. Most terminal 1,3-dienes gave the expected annulation products in 60 to 80% yields with excellent regioselectivity (entries 2−5). Running the reaction on a 2.0 mmol scale resulted in an even higher 91% yield (entry 5), indicating the utility of this procedure for practical applications. The regioselectivity in these experiments can be explained by a greater affinity of the arylpalladium intermediate for the less hindered terminal C=C double bond over an internal double bond. The annulation of isoprene gave a 3:2 mixture of regioisomers in 73% yield (entry 6). Supposedly, the poor regioselectivity in the annulation of isoprene results from the negligible steric difference between the two terminal double bonds.

Surprisingly, 2,4-hexadiene (3:2 mixture of trans−trans and cis−trans stereoisomers),[12] which has generally been unreactive and afforded dismal yields in most of our previous palladium annulation chemistry, gave a 3:2 ratio of trans

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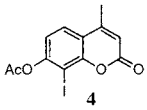
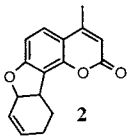
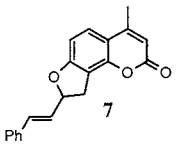
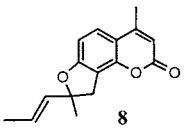
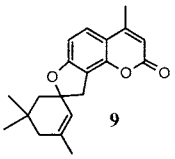
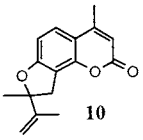
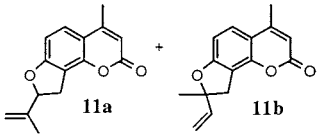
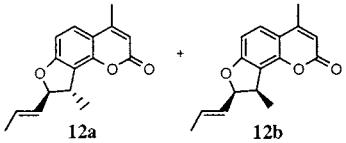
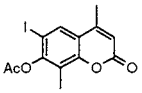
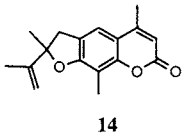
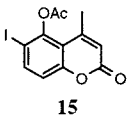
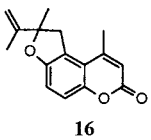
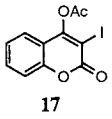
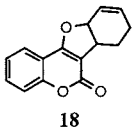
(11) Greene T. W. *Protective Groups in Organic Synthesis*; Wiley and Sons: New York, 1981; p 308.

(12) Ratio of trans−trans and cis−trans isomers was determined by gas chromatography.

Table 1. Synthesis of Dihydrofurocoumarins by the Annulation of 1,3-Dienes[a]

entry	coumarin	1,3-diene	product(s)	% yield[b] (isomer ratio)
1	 **4**		 **2**	63
2			 **7**	80
3			 **8**	78
4			 **9**	61
5			 **10**	75,91[c]
6			 **11a** **11b**	73 (3:2)
7			 **12a** **12b**	60 (3:2)
8	 **13**		 **14**	70
9	 **15**		 **16**	55
10[d]	 **17**		 **18**	48

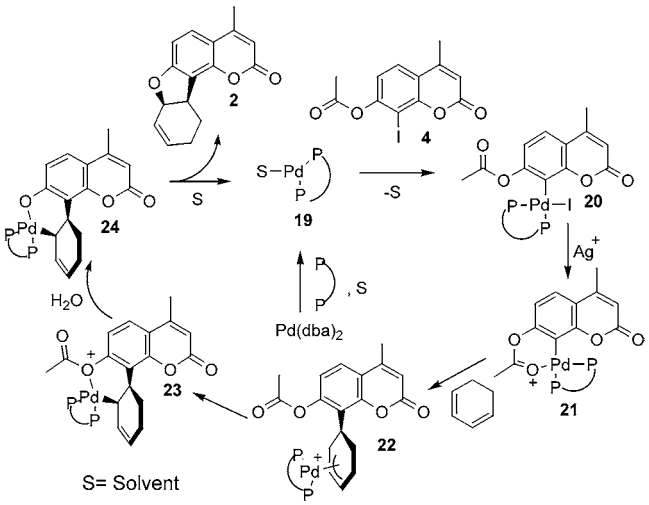
[a] See text for the experimental procedure. [b] All yields are isolated and based on a single run. [c] This experiment was performed on a 2.0 mmol scale. [d] No water was employed in the solvent.

and cis stereoisomers **12a** and **12b** in a 60% overall yield (entry 7). Remarkably, in all of our previous annulation chemistry, relatively hindered 1,3-dienes, like those employed in entries 4, 5, and 7, were completely unreactive and only 1,3-dienes bearing monosubstituted terminal double bonds gave satisfactory results. The exclusive generation of trans stereochemistry in the newly formed double bond in products **7**, **8**, and **12** is consistent with the intermediacy of a *syn*-π-allylpalladium intermediate in these reactions.[13]

In an attempt to broaden the scope of this reaction, similar reactions were performed on other substituted coumarins. Coumarins **13** and **15** gave the expected products in good yields even when using the relatively hindered 2,3-dimethyl-1,3-butadiene (entries 8 and 9). Annulation of coumarin **17** under our "optimal" reaction conditions resulted in hydrolysis of the acetyl group. The likely reason for the fast hydrolysis is the higher acidity of 4-hydroxycoumarin than that of 7-hydroxycoumarin.[14] The same reaction without the addition of water gave a 48% yield of dihydrofurocoumarin **18** (entry 10). In this experiment, the acetyl group is hydrolyzed by trace amounts of water present in commercially available 1,4-dioxane.

The proposed mechanism for this annulation process is shown in Scheme 4. Initial oxidative addition of iodocoumarin **4** to palladium intermediate **19** generated in situ forms arylpalladium intermediate **20**. Abstraction of the iodide by silver carbonate leads to cationic intermediate **21** presumably stabilized by the neighboring acetyl group. According to our results, the presence of the acetyl group completely inhibits formation of the undesired reduced product **3** and dramatically improves the yield of the desired product **2**. This may be due to the lower propensity of complex **21**, compared to its phenol analog**,** to undergo thermal decomposition. Next, complex **21** adds to the 1,3-diene to give the π-allylpalladium intermediate **22**. Coordination of the acetoxy oxygen to the palladium atom gives intermediate **23**, which is rapidly hydrolyzed by water to form intermediate **24**. Since no hydrolysis of starting material **4** was observed under our reaction conditions, the deacylation of intermediate **23** is presumably accelerated by coordination of the acetyl oxygen atom to the cationic palladium center. Finally, complex **24** undergoes reductive elimination to give the final product **2** and the palladium intermediate **19**.

Scheme 4



In conclusion, we have developed an efficient palladium-catalyzed annulation of 1,3-dienes by acetoxyiodocoumarins that affords good yields of dihydrofurocoumarins. The process is quite general, regioselective, and stereoselective, and a variety of *o*-iodoacetoxycoumarins, as well as symmetrical and unsymmetrical 1,3-dienes, can be utilized. Further investigation into the mechanism and the scope of this process is under way.

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Supporting Information Available: General experimental procedures and spectral data for the compounds listed in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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