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Synthesis of dihydrofuroflavonoids via palladium-catalyzed annulation of 1,3-dienes

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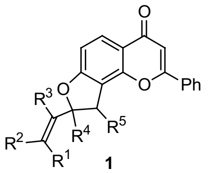
Abstract—The palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxyflavonoids provides an efficient approach to biologically interesting dihydrofuroflavonoids. This reaction is very general, regioselective, and a wide variety of terminal, cyclic, and internal 1,3-dienes can be utilized.

Dihydrofuroflavonoids occur commonly in plants and fruits and are very important because of their pronounced biological properties.[1] According to recent reports, derivatives of dihydrofuroflavones (**1**) have high cytotoxicity against P-388 cells.[2] Derivatives of dihydrofuroflavanones (**2**) are effective inhibitors of protein kinase,[3] aromatase,[4] and larvae growth.[5] Derivatives of dihydrofuroisoflavones (**3**) exhibit high antifungal activity.[6]



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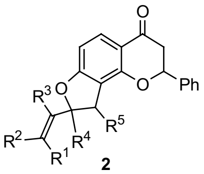

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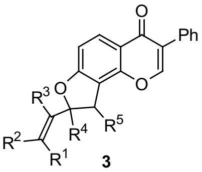
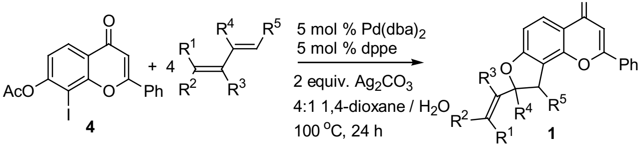


3

Despite significant interest, no efficient, general method for the synthesis of dihydrofuroflavonoids has really been developed. Recently, we reported an efficient method for the synthesis of dihydrofurocoumarins,[7] which looked very promising for the synthesis of dihydrofuroflavonoids.

Herein, we report our results on the palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxyflavonoids that provides a very general and effective route to a wide variety of dihydrofuroflavonoids. Using our previously developed reaction conditions,[8] the scope, and limitations of this annulation (Scheme 1) have been studied using various *o*-iodoacetoxyflavonoids and 1,3-dienes and representative examples are shown in Table 1.

Analogous to the annulation of *o*-iodoacetoxycoumarins,[7] the annulation of various 1,3-dienes by the flavone **4** has given the expected products **5**–**11** in 62–96% yields with excellent regioselectivity (entries 1–7). Running the reaction on a 2.0 mmol scale resulted in an even higher 90% yield (entry 7), indicating the utility of this procedure for practical applications. The annulation of isoprene gave a 3:2 mixture of regioisomers **12a** and **12b** in an 86% yield (entry 8). The analogous annulation of isoprene by *o*-iodophenol has been shown to be mostly governed by steric factors, favoring addition to the less hindered double bond and thus affording a 7:1 ratio of the corresponding annulation products.[9] The poor regioselectivity in entry 8 presumably results from the higher reactivity of the cationic arylpalladium intermediate (see the later mechanistic discussion) toward the more electron-rich disubstituted double bond, leading to a competition between steric and electronic factors,



Scheme 1.

Keywords: Palladium catalyzed; Dihydrofuroflavone; Flavone; Isoflavone; Flavanone; Flavonoid; 1,3-Diene.

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Table 1. Synthesis of dihydrofuroflavonoids by the palladium-catalyzed annulation of 1,3-dienes

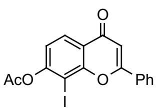
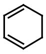
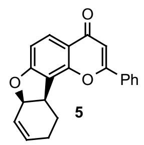
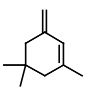
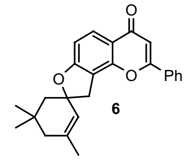
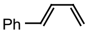
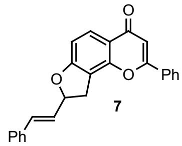
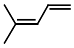
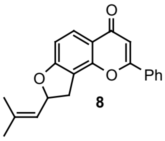
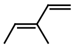
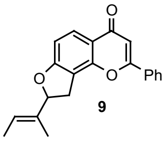
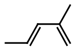
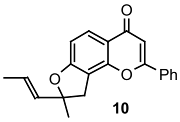
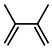
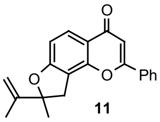
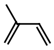
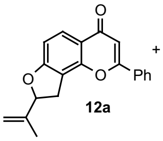
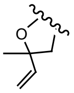
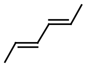
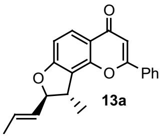
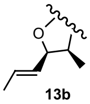
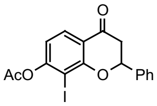
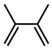
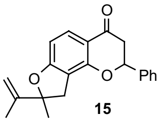
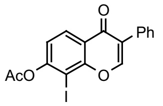
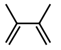
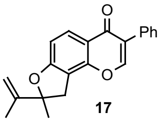
Entry	Flavonoid	1,3-diene	Product(s)	% Yield[a] (ratio of isomers)
1	 **4**		 **5**	62
2			 **6**	75
3			 **7**	80
4			 **8**	82
5			 **9**	76
6			 **10**	96
7			 **11**	77, 90[b]
8			 **12a** +  **12b**	86 (3:2)
9			 **13a** +  **13b**	68 (20:1)[c]
10	 **14**		 **15**	88

Table 1 (*continued*)

Entry	Flavonoid	1,3-diene	Product(s)	% Yield[a] (ratio of isomers)
11	 **16**		 **17**	95

[a] All yields are isolated and based on a single run.

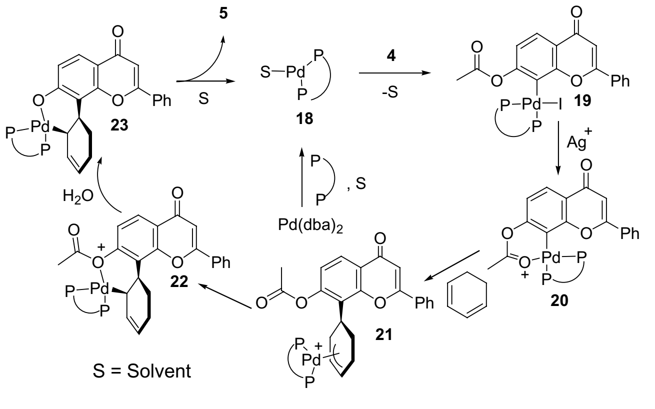
[b] This experiment was performed on a 2.0 mmol scale.

[c] The diene used was 95% *trans*,*trans*.

which produces a mixture of the two isomeric products. The use of *trans*,*trans*-2,4-hexadiene (95% purity) gave a 20:1 ratio of isomers **13a** and **13b** in a 68% yield (entry 9). The exclusive generation of *E*-stereochemistry in the newly formed carbon–carbon double bond in products **7**, **9**, **10**, and **13** is consistent with the intermediacy of *syn*-π-allylpalladium intermediate in these reactions.[10]

In an attempt to broaden the scope of this reaction, similar reactions have been performed on flavonoids **14** and **16**. Flavanone **14** and isoflavone **16** gave the desired annulation products **15** and **17** from 2,3-dimethyl-1,3-butadiene in 88% and 95% yields, respectively (entries 10 and 11).

A proposed mechanism for this annulation process is shown in Scheme 2. Initial oxidative addition of the iodoflavone **4** to palladium intermediate **18** generated in situ forms arylpalladium intermediate **19**. Abstraction of the iodide by silver carbonate leads to a cationic intermediate **20**, presumably stabilized by coordination to the neighboring acetyl group. Next, complex **20** adds to the 1,3-diene in a *cis*-fashion to give π-allylpalladium intermediate **21**. Coordination of the acetoxy oxygen to the palladium atom, leading to the formation of intermediate **22**, restricts rotation of the C–C bonds in the allyl moiety, and is, presumably, responsible for the high stereoselectivity when *trans*,*trans*-2,4-hexadiene is utilized (Table 1, entry 9). Since no hydrolysis of the starting material **4** has been observed under our reaction conditions, the deacylation of intermediate **22** is presumably accelerated by coordination of the acetyl oxygen atom to the cationic palladium center. Finally, complex **23** undergoes reductive elimination to give the final product **5** and regenerates the palladium catalyst **18**.



Scheme 2.

In summary, we have developed an efficient palladium-catalyzed annulation of 1,3-dienes by *o*-iodoacetoxyflavonoids, which affords good yields of dihydrofuroflavonoids. The process is quite general, regio and stereoselective, and a variety of *o*-iodoacetoxyflavonoids, as well as symmetrical and unsymmetrical 1,3-dienes can be utilized.

Acknowledgements

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References and notes

1. (a) Bohm, B. A. *Introduction to Flavonoids*; Gordon and Breach: Amsterdam, Netherlands, 1998; (b) Rice-Evans, C. A.; Packer, L. *Flavonoids in Health and Disease*; M. Dekker: NY, 1998; (c) Harborn, J. B.; Baxter, H. *The Handbook of Natural Flavonoids*; John Wiley and Sons: NY, 1999; (d) Li, W.; Xiao, P.; Zhang, R. *Phytochemistry* **1995**, *38*, 807; (e) Ngadjui, B. T.; Dongo, E.; Tamboue, H.; Fogue, K.; Abegaz, B. M.. *Phytochemistry* **1999**, *50*, 1401; (f) Ngadjui, B. T.; Kouam, S. F.; Dongo, E.; Kapche, G. M. F.; Abegaz, B. M.. *Phytochemistry* **2000**, *55*, 915.
2. Syah, Y. M.; Achmad, S. A.; Ghisalberti, E. L.; Hakim, E. H.; Makmur, L.; Mujahidin, D. *Fitoterapia* **2001**, *72*, 765.
3. Takashima, J.; Asano, S.; Ohsaki, A. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **2000**, *42*, 487, *Chem. Abstr.* **2000**, *135*, 104986.
4. Lee, D.; Bhat, K. P. L.; Fong, H. H. S.; Farnsworth, N. R.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2001**, *64*, 1286.

5. Machocho, A. K.; Lwande, W.; Jondiko, J. I.; Moreka, L. V. C.; Hassahali, A. *Int. J. Pharmacog.* **1995**, *33*, 222.
6. Maximo, P.; Lourenco, A.; Feilo, S. S.; Roseiro, J. K. *J. Nat. Prod.* **2002**, *65*, 175.
7. Rozhkov, R. V.; Larock, R. C. *Org. Lett.* **2003**, *5*, 797.
8. General procedure: The *o*-iodoacetoxyflavonoid (0.25 mmol), Pd(dba)$_2$ (5 mol%, 0.0125 mmol), dppe (5 mol%, 0.0125 mmol), Ag_2CO_3 (0.5 mmol), and 1,4-dioxane (4 mL) were stirred in a capped vial for 5 min, and then water (1 mL) and the 1,3-diene (1.0 mmol) were added. The resulting reaction mixture was stirred at 100 °C for 24 h, cooled to room temperature, filtered, and the filtrate was concentrated to give a yellow residue. The resulting residue was purified by column chromatography using silica gel as a solid phase and 4:1 hexanes/ethyl acetate as the eluent to afford after solvent removal the final product. Solid products were then recrystallized from 1:1 ethanol/water. **7a**,**10**,**11**,**11a**-Tetrahydro-2-phenylbenzo[*b*]-4*H*-furo[2,3-*h*]-1-benzopyran-4-one (**5**): Obtained in a 62% yield, white solid, mp 122–124 °C; ^{1}H NMR ($CDCl_3$) δ 1.63–1.76 (m, 1H), 2.05–2.33 (m, 3H), 3.81 (ddd, $J = 11.9$, 8.0, 4.9 Hz, 1H), 5.18 (dt, $J = 8.0$, 1.7 Hz, 1H), 6.08 (dm, $J = 10.2$, 2.0 Hz, 1H), 6.27 (dd, $J = 10.2$, 4.9 Hz, 1H), 6.75 (s, 1H), 6.88 (d, $J = 8.6$ Hz, 1H), 7.52–7.57 (m, 3H), 7.84–7.90 (m, 2H), 8.07 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.3, 24.8, 38.7, 80.7, 107.7, 109.5, 115.6 (solvent impurity), 118.2, 118.5, 123.7, 126.2, 127.5, 129.4, 131.6, 132.3, 134.4, 154.2, 162.6, 164.6, 178.1; IR (neat) 1645, 1604 cm^{-1}; HRMS m/z 316.1104 (calcd for $C_{21}H_{16}O_3$, 316.1099).
9. Larock, R. C.; Berrios-Peña, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447.
10. Maitlis, P. M.; Espinet, P.; Russell, M. J. H. *Compr. Organomet. Chem.* **1982**, *6*, 385.