

Synthesis of Dihydrobenzofurans via Palladium-Catalyzed Annulation of 1,3-Dienes by *o*-Iodoaryl Acetates

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The palladium-catalyzed annulation of 1,3-dienes by o-iodoaryl acetates provides an efficient approach to biologically interesting dihydrobenzofurans. The annulation is believed to proceed via (1) oxidative addition of the aryl iodide to Pd(0), (2) *syn*-addition of the resulting arylpalladium complex to the 1,3-diene, (3) intramolecular coordination of the phenolic oxygen to the Pd center, (4) hydrolysis of the acetyl group, and (5) reductive elimination of Pd(0), which regenerates the catalyst. This reaction is quite general, regioselective, and stereoselective, and a wide variety of terminal, cyclic, and internal 1,3-dienes, as well as electron-rich and electron-deficient o-iodoaryl acetates, can be utilized.

The dihydrobenzofuran unit is very common in natural products and biologically significant synthetic compounds.¹ Previously developed methodology for the synthesis of dihydrobenzofurans has utilized the [3+2] cycloaddition of phenols to alkenes,² the intramolecular acid-catalyzed cyclization of allylic phenols³ and quinines,⁴ and the electrophilic cyclization of 2-(2-hydroxyethyl)phenyl diazonium salts,⁵ as well as radical⁶ and transition metal-catalyzed⁷ cyclizations. Unfortunately, these methods are not very general and, in most cases, do not tolerate sensitive functional groups.

Heteroannulation reactions involving π -allylpalladium intermediates are of great utility for the synthesis of

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heterocyclic systems.⁸ Palladium-catalyzed annulations developed in our laboratories⁹ have provided a versatile route for the construction of complex cyclic systems, using 1,3-dienes and *o*-iodoanilines 1,¹⁰ 2-iodo-2-alkenoic acids 2,¹¹ and *o*-iodophenols 3,¹² which allow an elegant approach to the heterocycles 4-6, respectively (eqs 1–3).



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Unfortunately, the latter annulation appears limited to relatively unhindered 1,3-dienes and electron-deficient o-iodophenols and only one example of this process utilizing an electron-rich arene has been previously reported.¹² Thus, the reaction of 3 and 1,3-cyclohexadiene only affords a 44% yield of the corresponding dihydrobenzofuran 6. Annulations with electron-rich 2-iodo-4-methoxyphenol afforded mainly dehalogenated products and only negligible amounts of the desired dihydrobenzofurans.¹³ Our recent success in the synthesis of dihydrofurocoumarins¹⁴ and dihydrofuroflavonoids¹⁵ by the palladium-catalyzed annulation of 1,3dienes using o-iodoacetoxycoumarins and o-iodoacetoxyflavonoids respectively prompted further exploration of the utility of this methodology for the synthesis of dihydrobenzofurans. The major objective of this project was the development of a general annulation methodology, which could be successfully applied not only to a certain specific class of substrates, such as coumarins and flavonoids, but might utilize a broad range of o-iodoaryl acetates. We now wish to report such success.

We have studied the scope and limitations of the palladiumcatalyzed annulation of 1,3-dienes by various o-iodoaryl acetates (eq 4) under our previous reaction conditions and our newly developed reaction conditions (Table 1).^{14,15}



The annulation of 1,3-cyclohexadiene by aryl iodide 7 gave the desired annulation product 8 in a 72% yield under our newly developed reaction conditions (entry 1, see footnote a of Table 1 for the new procedure), compared to the 44% yield achieved previously.¹² The use of 2,3-dimethyl-1,3-butadiene gave an even higher 92% yield of dihydrobenzofuran 9 (Table 1, entry 2). The same annulation carried out with o-iodophenol, instead of o-iodophenyl acetate, gave lower 48% yield. The yield of dihydrobenzofuran 9 obtained with our previously reported reaction conditions for o-iodophenol¹² was only 18% and the dehalogenated phenol was isolated in 70% yield as a major side product. These results clearly demonstrate the superiority of our new "optimal" acetate reaction conditions over our previously reported procedure.

At this point, we examined the necessity of employing an acetyl group and compared our optimal acetate reaction conditions to our previously reported results using o-iodophenol.¹² Employing a methyl, benzyl, pivaloyl, or benzoyl group on the phenolic oxygen of o-iodophenol in the reaction with 2,3-dimethyl-1,3-butadiene did not lead to any significant amount of dihydrobenzofuran 9, presumably due to a slower rate of hydrolysis compared to the acetyl group. The use of o-chloro- and o-bromophenyl acetates, instead of aryl

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iodide 7, led to only a trace amount of the desired annulation product 9 and virtually all starting materials were recovered. This is most likely due to the slower oxidative addition of carbon-chlorine and carbon-bromine bonds to the Pd(0) complex generated in situ.

The use of o-iodophenyl acetate and trans, trans-2, 4-hexadiene gives exclusively the trans-dihydrobenzofuran 10 in 75% yield (Table 1, entry 3). The stereospecificity of this annulation is presumably due to coordination of the phenolic oxygen to the palladium center in the π -allylpalladium intermediate (see the later mechanistic discussion).

Next, a wide variety of electron-rich and electron-deficient aryl iodides were studied. Annulation with terminal, internal, and cyclic dienes and the electron-deficient substrate 11 gave the desired annulation products 12-15in excellent yields (Table 1, entries 4-7). We have also compared our optimized acetate reaction conditions here with those for aryl iodide 11 and the procedure used in our earlier research employing o-iodophenols (Table 1, entry 4).¹² Annulation of 2,3-dimethyl-1,3-butadiene by methyl 4-hydroxy-3-iodobenzoate under our recently developed and previously reported reaction conditions afforded 70% and 52% yields of the desired product 12, respectively. Although the difference in yields is less dramatic compared to that of the electron-rich substrate 7 (Table 1, entry 2), our "optimal" reaction conditions have provided a quantitative yield of the annulation product 12. The annulations of 2,3-dimethyl-1,3-butadiene by the electron-deficient substrates 16 and 18 have also given the desired dihydrobenzofrans 17 and 19 in 88% and 98% yields, respectively (Table 1, entries 8 and 9). Although the acetate of the nitrosubstituted aryl halide 20 could not be prepared due to its high propensity to hydrolyze, the annulation of 2,3-dimethyl-1,3-butadiene by the corresponding phenol gave the desired dihydrobenzofuran 21 in 72% yield (Table 1, entry 10). Thus, one can employ the phenol itself and get good yields of the corresponding dihydrobenzofuran if there is a strong electron-withdrawing group present on the phenol ring.

Since electron-rich aryl iodides failed to undergo annula-tion in our previous studies,^{12,13} we examined the effectiveness of our new methodology on substrates 22, 25, 27, and 29. The annulation of 2,3-dimethyl-1,3-butadiene by aryl iodide 22 gave the desired annulation product 23 in 58% yield (Table 1, entry 11). Surprisingly, employing 1-phenyl-1,3butadiene led to formation of the Heck product 24 in a 64% yield (Table 1, entry 12). When using aryl iodide 22, the 1,3dienes 1,3-cyclohexadiene and trans, trans-2,4-hexadiene gave inseparable, complex mixtures of what appeared to be Heck-type products. This could be due to slower hydrolysis of the acetyl group in the case of electron-rich phenols, leading to β -hydride elimination of the π -allylpalladium intermediate instead of cyclization.

The increased steric hindrance in substrate 25 seems to have little effect on the yield of dihydrobenzofuran 26 (Table 1, entry 13). Remarkably, the remote acetyl group in the bis-acylated 4-iodoresorcinol 27 was not cleaved during the course of the reaction with 2,3-dimethyl-1,3butadiene, giving annulated product 28 in a 40% yield (Table 1, entry 14). The annulation of the sterically hindered naphthalene 29 gave the desired product 30 in a 48% yield (Table 1, entry 15).

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TABLE 1. Synthesis of Dihydrobenzofurans by Palladium-Catalyzed Annulation (eq 4)^a

entry	aryl iodide	pKa of corresponding phenol ^b	1,3-diene	product(s)	% yield ^c
1		8.52			72, 44 ^e
2			\succ	e	92, 48, ^d 18 ^e
3					75
4	MeO 11 MeO MeO MeO MeO MeO MeO MeO MeO	6.91	\succ	MeO Line of the second	100, 70, ^d 52 ^e
5			Ph	MeO H C Ph	96
6					77
7					60
8	Me CAc	6.72	\succ		88
9		6.32			98
10	0 ₂ N	5.45			72
11	MeO 22 OAc	9.00		MeO Contraction 23	58
12			Ph	MeO OAc 24	64
13	OMe OAc 25	8.95	\succ		67
14	AcO 27 OAc	8.76	\succ	Aco 28	40
15	OAc 29	7.63	\succ		48

^{*a*}The *o*-iodoaryl acetate (0.25 mmol), Pd(dba)₂ (5 mol %, 0.0125 mmol), dppe (5 mol %, 0.0125 mmol), Ag₂CO₃ (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. ^{*b*}Sci-Finder compound database. ^{*c*}All yields are isolated and based on a single run. ^{*a*}The *o*-iodophenol was used as the starting material. ^{*c*}The *o*-iodophenol (0.25 mmol), Pd(OAc)₂ (5 mol %, 0.0125 mmol), diene (1.75 mmol), Na₂CO₃ (0.5 mmol), LiCl (0.5 mmol), and DMF (5 mL) were heated at 100 °C for 72 h.

SCHEME 1



A possible mechanism for this annulation process is shown in Scheme 1. Initial oxidative addition of the iodoarene 7 to palladium(0) intermediate **31** generated in situ forms aryl-palladium intermediate **32**.¹⁶ Abstraction of the iodide by Ag₂CO₃ leads to a cationic intermediate **33**,¹⁷ presumably stabilized by coordination to the neighboring acetyl group. The higher reactivity of these cationic arylpalladium complexes toward alkenes, compared to the neutral arylpalladium complexes, is presumably responsible for the excellent yields in our annulations.^{16b} Complex 33 adds to the 1,3diene in a syn-fashion to give initially a σ -allylpalladium complex and then π -allylpalladium intermediate 34.¹² Coordination of the acetoxy oxygen to the palladium atom, leading to the formation of intermediate 35, restricts rotation of the C-C bonds in the allyl moiety, and is presumably responsible for the high stereoselectivity observed when trans, trans-2, 4-hexadiene is utilized (Table 1, entries 3 and 6). Since no hydrolysis of the acetate group in the starting material 7 or the acetoxy group in the product 28 has been observed under our reaction conditions, the deacylation of intermediate 35 is presumably accelerated by coordination of the acylated oxygen atom to the cationic palladium center. The high correlation between the acidity (pK_a) of the phenolic precursors of our *o*-iodoaryl acetates and the annulation yields further supports this deacylation step (Table 1). Finally, complex 36 undergoes reductive elimination to give

the final product **37** with simultaneous regeneration of the palladium catalyst **31**.

Conclusions

In summary, we have developed an efficient palladiumcatalyzed annulation of 1,3-dienes by *o*-iodophenyl acetates, which affords good yields of dihydrobenzofurans. The process is quite general and regio- and stereoselective, and a wide range of electron-deficient and electron-rich *o*-iodoaryl acetates, as well as cyclic, terminal, and internal 1,3-dienes, can be utilized. The presence of the acetyl group greatly improves the yields in this process, particularly with aryl iodides containing electron-donating substituents. However, highly electron-rich *o*-iodoaryl acetates do tend to give somewhat lower yields than electron-deficient aryl iodides and, in the case of internal or aryl-substituted 1,3-dienes, Heck-type products are sometimes observed.

Experimental Section

General Procedure for the Synthesis of Dihydrobenzofurans. The *o*-iodoaryl acetate (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, and filtered, then the filtrate was concentrated to give a yellow residue. The resulting residue was purified by column chromatography with silica gel as a solid phase and 4:1 hexanes/ethyl acetate as the eluent to afford after solvent removal the final product. The following new compound was prepared with this procedure.

Methyl 2-methyl-2-(1-methylethenyl)-2,3-dihydrobenzofuran-5-carboxylate (12): obtained in a 100% yield as a colorless oil; ¹H NMR (CDCl₃) δ 1.55 (s, 3H), 1.80 (dd, J = 1.2, 0.8 Hz, 3H), 3.02 (d, J = 16.0 Hz, 1H), 3.24 (d, J = 16.0 Hz, 1H), 3.85 (s, 3H), 4.84 (q, J = 1.2 Hz, 1H), 5.06 (q, J = 0.8 Hz, 1H), 6.78 (d, J =8.4 Hz, 1H), 7.82 (d, J = 0.8 Hz, 1H), 7.86 (dd, J = 8.4, 0.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 18.9, 26.3, 40.9, 52.1, 91.8, 109.4, 110.6, 122.6, 127.1, 127.2, 131.4, 147.3, 163.2, 167.3; IR (neat) 1714, 1612 ⁻¹; m/z 232.1102 (calcd for C₁₄H₁₆O₃, 232.1099).

The product characterization data for all other dihydrobenzofurans prepared appear in the Supporting Information.

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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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