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An easy palladium-catalyzed access to 2-alkylidene-1,4-benzodioxanes

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Abstract

Palladium-catalyzed cyclization of benzene-1,2-diol with various propargylic carbonates led to 2-alkylidene-1,4-benzodioxanes in excellent chemical yields. Diphosphines such as dppb, dpppe or dpph, and monophosphines are the best ligands.

Keywords: cyclization reaction; palladium; propargylic carbonate; benzene-1,2-diol; 2-alkylidene-1,4-benzodioxanes.

During the last years, 1,4-benzodioxins and 1,4-benzodioxanes have attracted considerable interest, mainly due to their very interesting biological activities. Some of them act as α- or β-blocking reagents and could be used in antidepression or antihypertension therapy.[1] Others exhibit antihyperglycemic properties,[2] or could act as inhibitors of 5-lipoxygenase.[3] Moreover, these compounds could also be used for useful synthetic transformations.[4] While there are many synthetic methods for the synthesis of 1,4-benzodioxins,[5] the synthetic routes to 2-alkylidene-1,4-benzodioxanes are less common and often need a multi-step sequence.[6]

Recently Tsuji et al. have shown that propargylic carbonates react with soft carbon nucleophiles and oxo nucleophiles.[7] In the case of soft carbon nucleophiles such as alkyl acetoacetate or acetylacetone, formation of furans was observed via a double alkylation process.[8] In continuation of our recent studies on the synthesis of benzodioxan structures via organometallic catalysis,[5i,j] we felt that benzene-1,2-diol would react with propargyl carbonates under palladium catalysis to give the expected 2-alkylidene-1,4-benzodioxanes (Scheme 1). Herein we wish to report our preliminary results using this methodology.

Reaction of benzene-1,2-diol with allylic carbonate **1a** at room temperature in tetrahydrofuran in the presence of a palladium complex generated in situ by mixing $Pd_2(dba)_3$ with dppb [1,4-bis(diphenylphosphino)butane] gave 2-methylene-1,4-benzodioxane **2a** in 81% yield (Table 1, entry 1). When the reaction was performed with carbonates **1b** or **1c** as the propargylic substrates, the same product, namely 3-methyl-2-vinylidene-1,4-benzodioxane, was obtained in 99% yield (Table 1, entries

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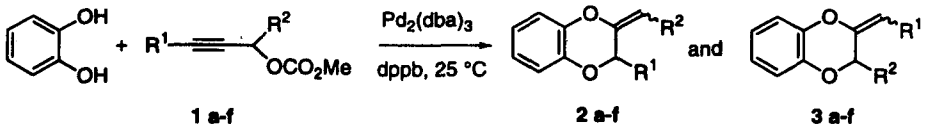


1 a-f 2 a-f 3 a-f

Scheme 1.

Table 1
Synthesis of 2-alkylidene-1,4-benzodioxanes[a]

Entry	Carbonate	R^1	R^2	Products(s)[b]	Yield (%)[c]
1	**1a**	H	H	**2a**	81
2	**1b**	CH_3	H	**2b** (97%) + **3b** (3 %)	99
3	**1c**	H	CH_3	**2c** (4 %) + **3c** (96 %)	99
4	**1d**	H	C_6H_5	(*Z*)-**2d** (40 %) + **3d** (60 %) (100 % *Z*)	99
5	**1e**	n-C_5H_{11}	C_6H_5	(*Z*)-**2e** (78 %) + (*Z*)-**3e** (22 %)	98
6	**1f**	$CH_2OTBDMS$	H	**2f** (31 %) + **3f** (69 %) (*Z*/*E* = 90/10)	97

[a] Typical experiment: a solution of the benzene-1,2-diol (100 mg, 0.9 mmol) and the carbonate **1** (1.1 mmol) in THF (7 mL) is added to the palladium solution obtained by mixing $Pd_2(dba)_3$ (20.8 mg, 2.2×10^{-2} mmol) and the ligand dppb (38.8 mg, 9.1×10^{-2} mmol) in THF (7 mL). After being stirred for 24 h at room temperature, the solvent was evaporated and the product(s) purified by chromatography using petroleum ether/ ethyl acetate as the eluent.
[b] Determined by gas chromatography using an OV1 column (25 m) and by NMR.
[c] Yield of purified product.

2 and 3); only a trace of the regioisomer 3-methylidene-1,4-benzodioxane could be detected by gas chromatography.

Carbonate **1d** reacted with benzene-1,2-diol to give a 40:60 mixture of 1,4-benzodioxanes **2d**, as the (*Z*) isomer,[6f] and **3d** in 99% yield (Table 1, entry 4). Carbonate **1e** led to the formation of the two cyclized products **2e** and **3e**, in a 78:22 ratio, in 98% yield, the two compounds having the (*Z*) configuration (Table 1, entry 5).

Finally the carbonate **1f**, derived from butynediol, gave compounds **2f** and **3f** in 97% yield as a 31:69 mixture, 1,4-benzodioxane **3f** being a mixture of *Z*:*E* isomers (90:10). In this case we studied the influence of phosphines on the isomer ratio (Table 2). We noticed that diphosphines such as dppb (Table 2, entry 3), dpppe [1,5-bis(diphenylphosphino)pentane] (Table 2, entry 4), or dpph [1,6-bis(diphenylphosphino)hexane] (Table 2, entry 5), gave the cyclized products in quite good yields and almost the same selectivity. Conversely dppe [1,2-bis(diphenylphosphino)ethane] (Table 2, entry 1) and dppp [1,3-bis(diphenylphosphino)propane] (Table 2, entry 2) gave very low yields. Monophosphines gave also quite good yields, except P(*o*-MeO-C_6H_4)$_3$ which gave no reaction at all; it is to be noticed that P(*o*-Me-C_6H_4)$_3$ and P(2-furyl)$_3$ led to the formation of **3f** as the major regioisomer. These results are in marked contrast with those of Tsuji et al.,[8] who found that reaction of soft carbon nucleophiles or oxo nucleophiles with propargylic carbonates occurred only in the presence of dppe as the ligand.

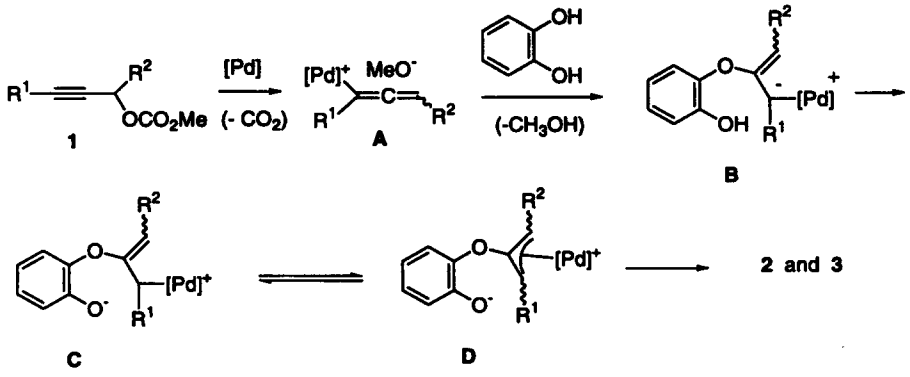
The mechanism of the formation of compounds **2** and **3** is depicted in Scheme 2. Propargylic carbonate **1** reacts with PdL_4 to generate an allenylpalladium intermediate **A**; attack of the benzene-1,4-diol on the central *sp* carbon of this intermediate **A** gives a palladium carbene complex **B**. Abstraction of the proton from the secondary hydroxyl function forms a σ-alkyl complex **C** leading to the π-allyl complex **D**.

Table 2
Palladium-cyclization of benzene-1,4-diol with carbonate **1f**

Entry	Phosphine	Yield (%)[a]	% 2f[b]	% 3f (Z/E)[b]
1	dppe	15	41	59 (93/7)
2	dppp	11	22	78 (92/8)
3	dppb	97	31	69 (89/11)
4	dpppe	60	48	52 (88/12)
5	dpph	98	42	58 (93/7)
6	PPh_3	86	52	48 (88/12)
7	P(*o*-CH_3-C_6H_4)$_3$	88	17	83 (94/6)
8	P(2-furyl)$_3$	74	21	79 (93/7)
9	P(*o*-MeO-C_6H_4)$_3$	0	-	-

[a] Yield of purified product.
[b] Determined by gas chromatography using an OV1 column (25 m) and by NMR.

Attack of the oxo nucleophile on one of the two termini of this π-allyl complex **D** gives the two cyclized compounds **2** and **3**.



Scheme 2.

In conclusion, the palladium-catalyzed reaction of benzene-1,4-diol with propargylic carbonates is a very easy and efficient route to 2-alkylidene-1,4-benzodioxanes. Work is in progress to explain the regioselectivity observed and to extend this reaction to functionalized propargylic carbonates.

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