An Easy Palladium-Catalyzed Access to Substituted 3-Methylene-3,4-dihydro-2*H*-1,5-benzodioxepines

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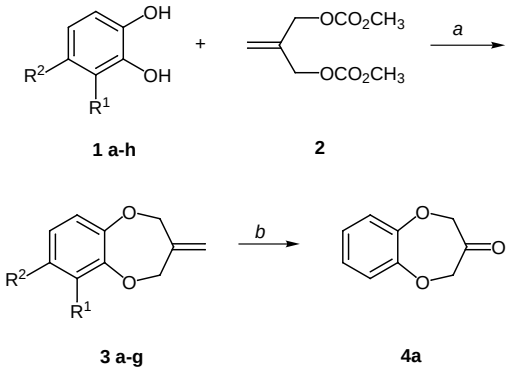
Received 12 March 2001; revised 23 April 2001

Abstract: Palladium-catalyzed condensation of substituted benzene-1,2-diols with the biscarbonate of 2-(hydroxymethyl)allyl alcohol gave the corresponding 3-methylene-3,4-dihydro-2*H*-1,5-benzodioxepines in good yields.

Key words: catalysis, palladium, cyclization, phenols, allyl complexes

2*H*-1,5-Benzodioxepin-3(4*H*)-one (**4a**) is a key intermediate in the synthesis of analogs of 3,4-dihydro-2*H*-1,5-benzodioxepine, which possess interesting biological properties. For example, members of this series constitute a unique class of β-adrenergic stimulants and have also interesting bronchial dilator activity.[1] The antifungal strobilurins I and K are also derivatives of 3,4-dihydro-2*H*-1,5-benzodioxepine.[2] These compounds have been obtained in very low yields by condensation of benzene-1,2-diol (**1a**) and 1,3-dichloro-2-hydroxypropane followed by oxidation with $KMnO_4$[3] or by an allylation-epoxidation-cyclization-oxidation sequence.[2] An alternative synthesis started with the condensation of benzene-1,2-diol (**1a**) with ethyl bromoacetate. Dieckmann cyclization of the obtained diester with sodium *tert*-butoxide yielded 2*H*-1,5-benzodioxepin-3(4*H*)-one (**4a**).[4] In another case, 6-methoxy-3-oxo-2*H*-[1,5]-benzodioxepine was obtained by Thorpe cyclization of 1,2-bis(cyanomethoxy)benzene, affording an enaminonitrile which was easily hydrolyzed to the ketone **4a**.[1]

We have shown that benzene-1,2-diol (**1a**) can act as a bisnucleophile in π-allylpalladium chemistry. The palladium-catalyzed condensation of substituted benzene-1,2-diols with 1,4-bis(methoxycarbonyloxy)but-2-ene gave the corresponding 2,3-dihydro-2-vinylbenzo-1,4-dioxines in good yields,[5] whereas the same condensation performed with substituted 2-aminophenols or substituted 1,2-diaminobenzenes gave the corresponding 2-vinyl-3,4-dihydro-2*H*-1,4-benzoxazines[6] or 2-vinyl-1,2,3,4-tetrahydroquinoxalines,[7] respectively. We expected that this methodology would be suitable for the synthesis of substituted 3-methylene-3,4-dihydro-2*H*-1,5-benzodioxepines **3**, which are valuable precursors of the corresponding 2*H*-1,5-benzodioxepin-3(4*H*)-ones **4** by a simple oxidative cleavage (Scheme 1).



a $R^1 = R^2 = H$; **b** $R^1 = CH_3$, $R^2 = H$; **c** $R^1 = H$, $R^2 = CH_3$;
d $R^1 = OCH_3$, $R^2 = H$; **e** $R^1 = H$, $R^2 = OCH_3$; **f** $R^1 = H$, $R^2 = CHO$;
g $R^1 = CHO$, $R^2 = H$; **h** $R^1 = NO_2$, $R^2 = H$

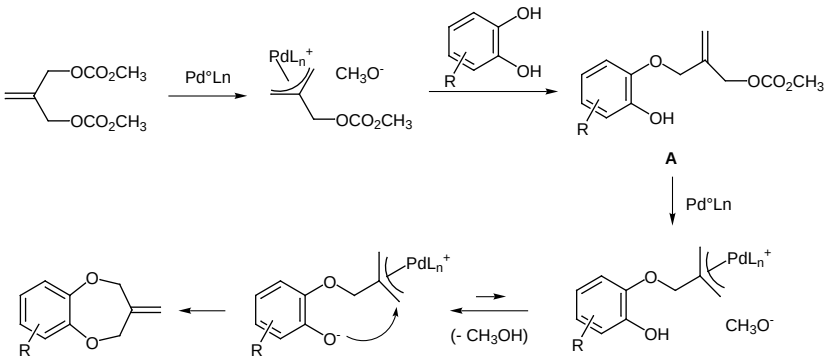
Scheme 1 *Reaction conditions*: a) $Pd_2(dba)_3$, dppb, THF, 25°C, 24 h; b) cat. OsO_4, $NaIO_4$, EtOH–acetone–H_2O, 4 h, then H_2O, 86%

The condensation of substituted benzene-1,2-diols **1** with the allylic biscarbonate **2** was performed at room temperature in THF in the presence of a catalytic amount of palladium acetate and 1,4-bis(diphenylphosphino)butane (dppb). The mechanism of this cyclization is shown in Scheme 2. Reaction of the biscarbonate **2** with palladium(0) gave the corresponding π-allylpalladium complex. The attack of the phenolate obtained by exchange between benzene-1,2-diol and methylate anion afforded the intermediate **A**. Subsequent formation of a new π-allylpalladium complex, followed by the intramolecular attack of the phenolate, gave the substituted 3-methylene-3,4-dihydro-2*H*-1,5-benzodioxepines. The results obtained, using various substituted benzene-1,2-diols, are summarized in the Table.

Condensation of carbonate **2** and benzene-1,2-diol (**1a**) gave the corresponding cyclic compound **3a** in 88% yield after column chromatography (Table, entry 1). 3-/4-Methyl-substituted benzene-1,2-diols **1b** and **1c** afforded 6-methyl-3-methylene-3,4-dihydro-2*H*-1,5-benzodioxepine (**3b**) and 7-methyl-3-methylene-3,4-dihydro-2*H*-1,5-benzodioxepine (**3c**) in 99% and 97% yield, respectively (Table, entries 2 and 3). 3-/4-Methoxybenzene-1,2-diols **1d** and **1e** gave also the corresponding benzodioxepine

Synthesis 2001, No. 10, 30 07 2001. Article Identifier:
1437-210X,E;2001,0,10,1456,1458,ftx,en;T02101SS.pdf.

ISSN 0039-7881



Scheme 2

derivatives **3d** and **3e** in very good yields (99% and 94%, respectively) (Table, entries 4 and 5). The presence of an electron-withdrawing group on benzene-1,2-diol seems detrimental for the cyclization. For example, 3-formylbenzene-1,2-diol (**1f**) gave the cyclized product **3f** in 79% yield (Table, entry 6), whereas 4-formylbenzene-1,2-diol (**1g**) gave the cyclized compound **3g** in only 22% yield, whatever conditions we used (Table, entry 7). More noteworthy, 4-nitrobenzene-1,2-diol (**1h**) underwent no reaction at all, even at higher temperature, the carbonate **2** was recovered. Such a behavior was previously noticed in the palladium-catalyzed alkylation of nitrophenols with various allylic carbonates.[8] This could be due to the fact that the nitrophenoxy group itself in intermediate **A** is a better leaving group than the carbonate, or that the phenoxy anion with an electron-withdrawing group is such a poor nucleophile that it does not react with the π-allylpalladium intermediate.

Oxidation of compound **3a** in a one-pot reaction by addition of OsO_4 and $NaIO_4$ afforded after column chromatography the corresponding 2*H*-1,5-benzodioxepin-3(4*H*)-one (**4a**) in 86% yield.

In conclusion, we have shown that the palladium-catalyzed condensation of various substituted benzene-1,2-diols with the biscarbonate derived from 2-(hydroxymethyl)allyl alcohol allows an easy access to substituted 3-methylene-3,4-dihydro-2*H*-1,5-benzodioxepines, particularly when the substituent is an electron-donating group. These compounds are easily transformed into the corresponding 2*H*-1,5-benzodioxepin-3(4*H*)ones as exemplified for **4a**.

Table Palladium-Catalyzed Cyclization of **1a**–**h** with **2**

Entry	Benzene-1,2-diol	Product	Yield (%)
1	**1a** ($R^1 = R^2 = H$)	**3a**	88
2	**1b** ($R^1 = CH_3$, $R^2 = H$)	**3b**	99
3	**1c** ($R^1 = H$, $R^2 = CH_3$)	**3c**	97
4	**1d** ($R^1 = OCH_3$, $R^2 = H$)	**3d**	99
5	**1e** ($R^1 = H$, $R^2 = OCH_3$)	**3e**	94
6	**1f** ($R^1 = CHO$, $R^2 = H$)	**3f**	79
7	**1g** ($R^1 = H$, $R^2 = CHO$)	**3g**	22
8	**1h** ($R^1 = H$, $R^2 = NO_2$)	**3h**	0

Reactions involving palladium catalysis were performed in Schlenk tubes under N_2. THF was purified by distillation in the presence of sodium and benzophenone. TLC was performed on precoated sheets $60F_{254}$, and silica gel chromatography was done using Merck silica gel (Gerudan SI 60, 0.040–0.063 mm). Melting points are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz, and ^{13}C NMR spectra at 75 MHz; NMR chemical shifts are reported in ppm downfield from TMS, and *J* values are given in Hertz. $Pd_2(dba)_3$, bis-1,4-(diphenylphosphino)butane (dppb), starting benzene-1,2-diols **1a–d,f,g** and 2-(hydroxymethyl)allyl alcohol were purchased from a commercial source. 4-Methoxybenzene-1,2-diol (**1e**) was prepared according to the literature.[9] Petroleum ether used refers to the fraction boiling at 40–65°C.

2-{[(Methoxycarbonyl)oxy]methyl}allyl Methyl Carbonate (2)
Methyl chloroformate (3.9 mL, 45.4 mmol) was added at 0°C to a solution of 2-(hydroxymethyl)allyl alcohol (1 g, 11.4 mmol), DMAP (0.56 mg, 4.6 mmol), and pyridine (3.9 mL, 45.4 mmol) in CH_2Cl_2 (40 mL). After stirring for 24 h at r.t., the mixture was hydrolyzed with sat. aq solution of $CuSO_4$ (20 mL) and extracted with Et_2O (3 × 50 mL). Evaporation of the solvent followed by flash-chromatography on silica gel using a 5:1 mixture of petroleum ether–EtOAc as the eluent afforded 2.19 g of the biscarbonate **2** (94%); R_f 0.38 (petroleum ether–EtOAc, 5:1).

^{1}H NMR ($CDCl_3$): δ = 3.70 (s, 6 H, CH_3), 4.60 (s, 4 H, OCH_2), 5.25 (s, 2 H, $=CH_2$). ^{13}C NMR ($CDCl_3$): δ = 54.8, 67.6, 117.9, 137.7, 155.4.

These analytical data are in agreement with the literature.[10]

3-Methylene-3,4-dihydro-2*H*-1,5-benzodioxepines 3a–h; General Procedure
The palladium catalyst was prepared by stirring a solution of $Pd_2(dba)_3$ (20.8 mg, 0.023 mmol) and dppb (41.4 mg, 0.09 mmol) in THF (7 mL) under argon for 0.5 h. This solution was added under argon at r.t. to a solution of benzene-1,2-diol **1** (0.91 mmol) and biscarbonate **2** (222.6 mg, 1.1 mmol) in THF (7 mL). After stirring for 24 h, the solvent was evaporated and the residue was purified by flash-chromatography on silica gel to afford the cyclized product **3**.

3-Methylene-3,4-dihydro-2*H*-1,5-benzodioxepine (3a)
Oil; R_f 0.60 (petroleum ether–EtOAc, 20:1).

^{1}H NMR ($CDCl_3$): δ = 4.83 (s, 4 H, OCH_2), 5.08 (s, 2 H, $=CH_2$), 6.87–7.00 (m, 4 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 73.9, 112.1, 121.1, 123.2, 144.1, 149.7.

These analytical data are in agreement with the literature.[11]

6-Methyl-3-methylene-3,4-dihydro-2*H*-1,5-benzodioxepine (3b)
Oil; R_f 0.31 (petroleum ether–EtOAc, 50:1).

^{1}H NMR ($CDCl_3$): δ = 2.25 (s, 3 H, CH_3), 4.77 (s, 2 H, OCH_2), 4.79 (s, 2 H, OCH_2), 5.09 (br s, 2 H, $=CH_2$), 6.80 (br s, 3 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 16.3, 73.7, 73.9, 111.9, 118.8, 122.4, 124.7, 130.3, 144.4, 148.2, 149.8.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.50; H, 6.83.

7-Methyl-3-methylene-3,4-dihydro-2*H*-1,5-benzodioxepine (3c)
Oil; R_f 0.38 (petroleum ether–EtOAc, 50:1).

^{1}H NMR ($CDCl_3$): δ = 2.25 (s, 3 H, CH_3), 4.73 (s, 2 H, OCH_2), 4.75 (s, 2 H, OCH_2), 5.08 (br s, 2 H, $=CH_2$), 6.69–6.88 (m, 3 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 20.6, 73.8, 74.1, 112.2, 120.8, 121.4, 123.6, 133.0, 144.2, 147.4, 149.3.

Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.18; H, 7.04.

6-Methoxy-3-methylene-3,4-hihydro-2*H*-1,5-benzodioxepine (3d)
Oil; R_f 0.10 (petroleum ether–EtOAc, 50:1).

^{1}H NMR ($CDCl_3$): δ = 3.81 (s, 3 H, CH_3), 4.75 (s, 2 H, OCH_2), 4.82 (s, 2 H, OCH_2), 5.05 (br s, 2 H, $=CH_2$), 6.55 (d, 1 H_{arom}, J = 8.3 Hz), 6.59 (d, 1 H_{arom}, J = 8.3 Hz), 6.84 (t, 1 H_{arom}, J = 8.3 Hz).

^{13}C NMR ($CDCl_3$): δ= 56.3, 73.9, 74.4, 106.1, 112.2, 113.5, 122.1, 139.5, 143.9, 150.6, 151.6.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 69.14; H, 6.35.

7-Methoxy-3-methylene 3,4-dihydro-2*H*-1,5-benzodioxepine (3e)
Oil; R_f 0.12 (petroleum ether–EtOAc, 50:1).

^{1}H NMR ($CDCl_3$): δ = 3.71 (s, 3 H, CH_3), 4.68 (s, 2 H, OCH_2), 4.75 (s, 2 H, OCH_2), 5.05 (br s, 1 H, $=CH_2$), 5.10 (br s, 1 H, $=CH_2$), 6.45 (dd, 1 H_{arom}, J = 8.8, 2.9 Hz), 6.49 (d, 1 H_{arom}, J = 2.9 Hz), 6.87 (d, 1 H_{arom}, J = 8.8 Hz).

^{13}C NMR ($CDCl_3$): δ = 55.7, 73.7, 74.5, 106.0, 108.5, 112.8, 121.6, 143.5, 144.1, 150.3, 155.7.

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 69.07; H, 6.24.

3-Methylene-3,4-dihydro-2*H*-1,5-benzodioxepine-6-carbaldehyde (3f)
Oil; R_f 0.32 (petroleum ether–EtOAc, 20:1).

^{1}H NMR ($CDCl_3$): δ = 4.78 (s, 2 H, OCH_2), 4.90 (s, 2 H, OCH_2), 5.10 (br s, 1 H, $=CH_2$), 5.14 (br s, 1 H, $=CH_2$), 6.93 (t, 1 H_{arom}, J = 7.8 Hz), 7.15 (dd, 1 H_{arom}, J = 7.8, 1.6 Hz), 7.47 (dd, 1 H_{arom}, J = 7.8, 1.6 Hz), 10.4 (s, 1 H, CHO).

^{13}C NMR ($CDCl_3$): δ = 74.1, 74.3, 113.2, 122.2, 122.7, 127.4, 128.2, 142.8, 150.0, 152.7, 189.7.

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.29; H, 5.31.

3-Methylene-3,4-dihydro-2*H*-1,5-benzodioxepine-7-carbaldehyde (3g)
Oil; R_f 0.25 (petroleum ether–EtOAc, 50:1).

^{1}H NMR ($CDCl_3$): δ = 4.75 (s, 2 H, OCH_2), 4.82 (s, 2 H, OCH_2), 5.05 (br s, 1 H, $=CH_2$), 5.09 (br s, 1 H, $=CH_2$), 7.25–7.45 (m, 3 H_{arom}), 9.81 (s, 1 H, CHO).

^{13}C NMR ($CDCl_3$): δ = 73.5, 74.3, 112.8, 121.9, 122.9, 125.6, 131.8, 139.8, 143.5, 149.5, 190.4.

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.47; H, 5.30.

2*H*-1,5-Benzodioxepin-3(4*H*)-one (4a)
A 2.5% ethanolic solution of OsO_4 (0.12 mL, 0.01 mg, 0.01 mmol), followed by $NaIO_4$ (330 mg, 1.5 mmol) was added to a solution of **3a** (82.3 mg, 0.5 mmol) in a 3:1 mixture of acetone–H_2O (6 mL) cooled to 0 °C. After stirring for 4 h at r.t., the mixture was diluted with H_2O (40 mL) and extracted with EtOAc (3 × 20 mL). Evaporation of the solvent followed by flash-chromatography on silica gel using a 5:1 mixture of petroleum ether–EtOAc as the eluent afforded 70.8 mg of **4a** as a white solid (86% yield).

R_f 0.51 (petroleum ether–EtOAc, 5:1); mp 33–35 °C (Lit.[3] mp 40–42 °C).

^{1}H NMR ($CDCl_3$): δ = 4.68 (s, 4 H, OCH_2), 6.94–7.05 (m, 4 H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 75.7, 121.0, 133.9, 148.4, 204.6.

These analytical data are in agreement with the literature.[3]

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