Palladium–catalyzed synthesis of 2,3-dihydro-2-substituted-2-vinyl-1,4-benzodioxins

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Dedicated to Professor Marcial Moreno-Mañas on the occasion of his 60th birthday
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Abstract
Various 2,3-dihydro-2-substituted-2-vinyl-1,4-benzodioxins are obtained by alkylation of the methyl carbonate of 2,3-dihydro-1,4-benzodioxin-2-ylideneethanol with various carbon nucleophiles in the presence of a palladium complex. Although the yields in alkylation products are good in the case of a non–bulky nucleophile, formation of the diene was generally observed when a bulky nucleophile was used.

Keywords: Substituted 2-vinyl-benzodioxins, condensation, palladium, alkylation

Introduction
Compounds containing 1,4-benzodioxin and 1,4-benzodioxan structures have attracted considerable interest in recent years. This is mainly due to the interesting properties of these compounds. Some of them act as α- or β-blocking agents and could be used in antidepression or antihypertension therapy. Others have antihyperglycemic properties or act as inhibitors of 5-lipoxygenase. The 1,4-benzodioxan frame is also found in a variety of biological active natural products. It is also to be noticed that these compounds are useful intermediates in a variety of synthetic transformations.

There are many approaches for the synthesis of substituted 1,4-benzodioxins, even in an asymmetric way. We have recently described the preparation of various 2,3-dihydro-2-ylidene-1,4-benzodioxins via a palladium–catalyzed condensation of benzene-1,2-diol with different propargylic carbonates. Among the prepared heterocyclic compounds, we expected that tert-butyldimethyl-[(2,3-dihydro-1,4-benzodioxin-2-ylidene)ethoxy]silane, obtained by palladium condensation of benzene-1,2-diol with propargylic carbonate, could be a valuable
starting material for the preparation of 2,3-dihydro-2-substituted-2-vinyl-1,4-benzodioxins. We described in this paper preliminary results in this field.

**Results and Discussion**

Cyclization of benzene-1,2-diol 1 with carbonate 2\textsuperscript{23} was performed in THF at room temperature in the presence of 2.5 mol% Pd\textsubscript{2}(dba)\textsubscript{3} and 10 mol% dppb or 1,4-bis(diphenylphosphino)butane to afford after column chromatography 2,3-dihydro-1,4-benzodioxin derivative 3 in 67% yield (Scheme 1). Desilylation of compound 3 performed in THF as the solvent in the presence of tetrabutylammonium bromide trihydrate gave 2,3-dihydro-1,4-benzodioxin-2-ylideneethanol 4 in 95% yield after column chromatography. Carbonate 5 was obtained in 95% yield after column chromatography by condensation of this alcohol 4 with methyl chloroformate in CH\textsubscript{2}Cl\textsubscript{2} in the presence of pyridine and dimethylaminopyridine.

![Scheme 1](image-url)

(a) Pd\textsubscript{2}(dba)\textsubscript{3}, THF, 20 h; (b) Bu\textsubscript{4}NBr.3H\textsubscript{2}O, THF; (c) ClCO\textsubscript{2}Me, DMAP, C\textsubscript{6}H\textsubscript{5}N, CH\textsubscript{2}Cl\textsubscript{2}; (d) Pd\textsubscript{2}(dba)\textsubscript{3}, NuH, THF.

**Scheme 1**
The reaction of various nucleophiles with this carbonate 5 was performed in THF at room temperature in the presence of 2.5 mol % Pd$_2$(dba)$_3$ and 10 mol % dppb. The results are summarized in Table 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile NuH</th>
<th>Yield % compound 6</th>
<th>Yield % compound 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_2$(CO$_2$CH$_3$)$_2$</td>
<td>67</td>
<td>11</td>
</tr>
<tr>
<td>2</td>
<td>CH$_2$(COCH$_3$)$_2$</td>
<td>53</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>CH(CH$_3$)(CO$_2$CH$_3$)$_2$</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>CH$_2$(COCH$_3$)(CO$_2$C$_2$H$_5$)</td>
<td>61</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>C(NHCOCH$_3$)(CO$_2$CH$_3$)$_2$</td>
<td>0</td>
<td>24</td>
</tr>
</tbody>
</table>

Dimethyl malonate (Table 1, entry 1) and acetylacetone (Table 1, entry 2) reacted with carbonate 5 to give after column chromatography the alkylated 2,3-dihydro-2-vinyl-benzo-1,4-dioxins 6a and 6b in 67 and 53% yield, respectively. The formation of 2-vinylbenzo-1,4-dioxine 7 was also observed in 11 and 33% yield, respectively. When dimethyl methylmalonate was used as the nucleophile (Table 1, entry 3), the formation of the alkylated compound 6c was observed in quite low yield (6%) together with diene 7 (15%). The use of dimethyl acetamidomalonate as the nucleophile (Table 1, entry 5) afforded only the unsaturated compound 7 in 24% yield, with no trace of the corresponding alkylated compound.

Finally reaction of carbonate 5 with ethyl acetoacetate as the nucleophile gave the alkylated product 6d in 61% yield as a mixture of the two diastereoisomers in a ratio 66:34, together with the diene 7 in 18% yield (Table 1, entry 4).

The formation of compounds 6 and 7 could be explained according to Scheme 2. The first step is the formation of the η$^3$-allyl intermediate A by oxidative addition of the palladium complex on compound 5. One possibility is the generation of the nucleophile by abstraction of a hydrogen from Nu-H by CH$_3$O$^-$. The attack of the nucleophile on the η$^3$-allyl intermediate A occurred not at the less hindered termini, but at the more electrophilic termini of this intermediate affording compound 6 bearing a quaternary carbon center. This regioselectivity is in agreement with previous studies on η$^3$-allyl intermediates bearing an oxygen atom on one of the termini of the η$^3$-allyl system. It is to be noticed that this alkylation reaction is very sensitive to the bulkiness of the nucleophile; the more bulky the nucleophile is (dimethyl methylmalonate, dimethyl acetamidomalonate), the lowest is the chemical yield in the alkylated product.

The formation of the diene 7 could be explained by a β-hydrogen elimination from the intermediate A, leading to compound 7 and the formation of H(CH$_3$O)Pd(dppb), affording Pd(dppb) via a reductive elimination of CH$_3$OH. It seems that there is a competition between these two pathways.
Scheme 2

Mechanism of formation of compounds 6 and 7

Conclusions

In conclusion, we have shown that various 2,3-dihydro-2-substituted-2-vinyl-1,4-benzodioxins 6 bearing a quaternary carbon could be very easily obtained from tert-butyldimethyl-[(2,3-dihydro-1,4-benzodioxin-2-ylidene)ethoxy]silane 4 via a palladium–catalyzed alkylation reaction of the corresponding carbonate with various carbon–nucleophiles. However the chemical yields are strongly dependent on the bulkiness of the nucleophile, with the preferential formation of a diene when this nucleophile is too bulky. Work is actually in progress in our group in order to prepare chiral 2,3-dihydro-2-substituted-2-vinyl-1,4-benzodioxins 6 via the use of chiral ligands.

Experimental Section

**General Procedures.** All manipulations involving palladium catalysis were performed in Schlenk tubes under a nitrogen atmosphere. Unless otherwise stated, the materials were commercial samples; propargylic carbonate 2 was prepared as previously described. All organic solvents were of analytical quality and used as purchased. Solvents mixtures are defined by volume ratios (v/v). Tetrahydrofuran was distilled from sodium/benzophenone. All $^1$H– and $^{13}$C–NMR spectra were recorded on a Brücker AM 300 spectrometers in CDCl$_3$. Chemical shifts are reported on the $\delta$ scale with the reference to tetramethylsilane or CDCl$_3$ as the internal standard and the coupling constants $J$ are given in Hz. The IR–spectra were recorded on a Perkin–Elmer 681 instrument. Tin–layer chromatography was performed using Merck silica gel 60 F$_{254}$ precoated aluminium plates, 0.2 mm thickness. Visualisation was by UV or by spraying
with 10% sulphuric acid and then heating. Column chromatography was carried out using Merck silica gel (Kieselgel 60, 70–230 mesh).

**(Z)-tert-Butyldimethyl-[2,3-dihydro-1,4-benzodioxin-2-ylidene)ethoxy]silane (3).** A mixture of Pd2(dba)3 (20.8 mg, 2.2 x 10^{-2} mmol), in THF (7 mL), was stirred under a nitrogen atmosphere at room temperature for 30 min. This catalyst solution was added to a mixture of benzene-1,2-diol 1 (100 mg, 0.9 mmol) and carbonate 2 (284 mg, 1.1 mmol). The resulting solution was stirred at room temperature for 24 h. The solvent was evaporated and the residue chromatographed over silica (R_f = 0.24, petroleum ether/EtOAc 100:1) to give 196 mg of 3 as an oil (yield 67%);^1^H–NMR δ 7.10–6.80 (4H, m, H_arom), 4.91 (1H, t, J = 6.3, =CH-CH2), 4.47 (2H, s, 3–H), 4.47 (2H, d, J = 6.3, =CH-CH2), 0.88 (9H, s, CH3);^13^C–NMR δ 144.0 (2–C), 143.2 (C_arom), 142.6 (C_arom), 122.3 (C_arom), 122.2 (C_arom), 117.4 (C_arom), 116.6 (C_arom), 107.7 (=CH-CH2), 65.1 (3–C), 56.6 (CH2OSi), 26.1 (CMe3), 18.4 (CMe3), –5.1 (SiMe); IR ν 3060, 3040, 2950, 2920, 2880, 2850 cm^{-1}. Anal. Calcd for C16H24O3Si: C, 65.72; H, 8.28. Found: C, 65.39; H, 8.61.

**(Z)-2,3-Dihydro-1,4-benzodioxin-2-ylideneethanol (4).** A solution of compound 3 (2.57 g, 9 mmol) and Bu4NBr.3H2O (4.60 g, 18 mmol) in tetrahydrofuran (80 mL) was stirred at 25 °C for 1 h. After evaporation of the solvent, the residue was diluted with diethyl ether (100 mL), and the ethereal solution was washed three times with a saturated aqueous solution of sodium chloride (3x40 mL), and dried over sodium sulfate. Chromatography (R_f = 0.24, petroleum ether/EtOAc 4:3) of the residue obtained after evaporation of the solvent gave 1.49 g of compound 4 (yield 95%); oil; ^1^H–NMR δ 7.10–6.80 (4H, m, H_arom), 4.93 (1H, t, J = 7.0, =CH-CH2), 4.44 (2H, s, 3–H), 4.38 (2H, d, J = 7.0, =CH-CH2), 2.65 (1H, bs, OH); ^13^C–NMR δ 144.5 (2–C), 143.9 (C_arom), 142.4 (C_arom), 122.5 (C_arom), 122.4 (C_arom), 117.4 (C_arom), 116.6 (C_arom), 106.7 (=CH-CH2), 65.9 (3–C), 56.8 (CH2OH); IR ν 3350, 3060, 3040, 2950, 2920, 2880, 2850, 1690, 1590, 1480, 1460, 1250 cm^{-1}. These values are in agreement with the literature.\(^{28}\) Carbonic acid (Z)-(2-benzo[1,4]dioxin-2-ylidenemethyl) ester methyl ester (5). To a stirred solution of the alcohol 4 (360 mg, 2 mmol), dimethylaminopyridine (50 mg, 0.4 mmol), and pyridine (632 mg, 8 mmol), in CH2Cl2 (10 mL) at 0 °C under argon was slowly added methyl chloroformiate (756 g, 8 mmol). After being stirred for 24 h at room temperature, the solution was hydrolyzed with a saturated aqueous solution of copper sulfate (10 mL), and extracted three times with diethyl ether (3x20 mL). The ethereal solution was washed with a saturated aqueous solution of copper sulfate (10 mL), and dried over sodium sulfate. Evaporation of the solvent followed by column chromatography (R_f = 0.66, petroleum ether/EtOAc 4:1) of the residue gave 448 mg of compound 5 as an oil (yield 95%); ^1^H–NMR δ 7.10–6.80 (4H, m, H_arom), 5.00–4.87 (3H, m, =CH-CH2, =CH-), 4.45 (2H, s, 3–H), 3.80 (3H, s, CH3); ^13^C–NMR δ 155.8 (CO), 147.0 (2–C), 143.9 (C_arom), 142.2 (C_arom), 122.7 (C_arom), 122.4 (C_arom), 117.4 (C_arom), 116.7 (C_arom), 100.7 (=CH-CH2), 64.8 (3–C), 61.0 (=CH2CH2O), 54.8 (CH3); IR ν 3060, 3040, 3020, 2990, 2950, 2890, 2850, 1750, 1690, 1590, 1490, 1450, 1250 cm^{-1}. Anal. Calcd for C12H12O5: C, 60.00; H, 5.12. Found: C, 60.63; H, 5.16.
Alkylation of carbonic acid (Z)-(2-benzo[1,4]dioxin-2-yldienethyl) ester methyl ester. To a stirred solution of carbonate 5 (104 g, 0.44 mmol) and nucleophile (0.53 mmol) in THF (7 mL) at 25 °C under argon was added the catalyst solution obtained by stirring under argon for 0.5 h \( \text{Pd}_2(\text{dba})_3 \) (10.4 mg, 1.1 × 10⁻² mmol) and dppb (19.4 mg, 4.6 × 10⁻² mmol) in THF (7 mL). After being stirred for 24 h at room temperature, the solvent was evaporated and the residue purified by column chromatography to give the alkylated compound 6.

2-(2,3-Dihydro-1,4-benzodioxin-2-yl)malonic acid dimethyl ester (6a). Oil; yield 69%; \( R_f = 0.20 \) (petroleum ether/AcOEt 15:1); ¹H–NMR δ 7.00–6.80 (4H, m, H arom), 6.26 (1H, dd, \( J = 17.3, 11.0, -\text{CH}<= \)), 5.49 (1H, dd, \( J = 17.3, 0.7, =\text{CH}_2 \)), 5.38 (1H, dd, \( J = 11.0, 0.7, =\text{CH}_2 \)), 4.56 (1H, d, \( J = 11.4, 3–\text{H} \)), 4.15 (1H, dd, \( J = 11.4, 3–\text{H} \)), 4.01 (1H, s, -CH<), 3.76 (3H, s, CH₃), 3.72 (3H, s, CH₃); ¹³C–NMR δ 166.9 (CO), 166.5 (CO), 142.5 (C arom), 141.7 (C arom), 133.6 (-CH=), 122.2 (C arom), 121.8 (C arom), 118.9 (=CH₂), 117.2 (C arom), 76.1 (2–C), 68.1 (3–C), 55.5 (-CH<), 52.8 (CH₃), 52.6 (CH₃); IR ν 3080, 3040, 3020, 2950, 2920, 2870, 2840, 1750, 1645, 1595, 1490, 1430, 1255 cm⁻¹. Anal. Calcd for C₁₅H₁₆O₆: C, 61.62; H, 5.52. Found: C, 61.89; H, 5.55.

3-(2,3-Dihydro-2-vinyl-1,4-benzodioxin-2-yl)pentane-2,4-dione (6b). Oil; yield 53%; \( R_f = 0.24 \) (petroleum ether/AcOEt 10:1); ¹H–NMR δ 7.00–6.80 (4H, m, H arom), 6.25 (1H, dd, \( J = 17.3, 11.0, -\text{CH}<= \)), 5.51 (1H, d, \( J = 17.3, 1.1, =\text{CH}_2 \)), 5.35 (1H, dd, \( J = 11.0, 1.1, =\text{CH}_2 \)), 4.36 (1H, d, \( J = 11.6, 3–\text{H} \)), 4.30 (1H, s, -CH<), 3.95 (1H, d, \( J = 11.6, 3–\text{H} \)), 2.29 (3H, s, CH₃), 2.21 (3H, s, CH₃); ¹³C–NMR δ 202.9 (CO), 202.7 (CO), 143.0 (C arom), 141.6 (C arom), 133.8 (-CH=), 122.8 (C arom), 122.4 (C arom), 118.0 (=CH₂), 118.0 (C arom), 117.8 (C arom), 77.5 (2–C), 69.2 (3–C), 68.0 (-CH<), 32.8 (CH₃), 32.5 (CH₃); IR ν 3080, 3030, 2990, 2950, 2910, 2870, 1720, 1640, 1590, 1490, 1460, 1250 cm⁻¹. Anal. Calcd for C₁₅H₁₆O₄: C, 69.20; H, 6.20. Found: C, 69.43; H, 6.22.

2-(2,3-Dihydro-2-vinyl-1,4-benzodioxin-2-yl)-2methylmalonic acid dimethyl ester (6c). Oil; yield 6%; \( R_f = 0.30 \) (petroleum ether/AcOEt 15:1); ¹H–NMR δ 7.30–6.80 (4H, m, H arom), 6.07 (1H, dd, \( J = 17.1, 10.9, -\text{CH}<= \)), 5.29 (1H, dd, \( J = 10.9, 1.0, =\text{CH}_2 \)), 5.20 (1H, dd, \( J = 17.1, 1.0, =\text{CH}_2 \)), 4.80 (1H, d, \( J = 11.2, 3–\text{H} \)), 4.32 (1H, d, \( J = 11.2, 3–\text{H} \)), 3.73 (3H, s, CH₃), 3.71 (3H, s, CH₃), 3.09 (3H, s, CH₃); IR ν 3040, 2950, 2880, 1750, 1645, 1595, 1490, 1460, 1250 cm⁻¹. Anal. Calcd for C₁₅H₁₆O₄: C, 69.20; H, 6.20. Found: C, 69.43; H, 6.22.

2-(2,3-Dihydro-2-vinyl-1,4-benzodioxin-2-yl)-3-oxobutyric acid methyl ester (6d). As an oily mixture of two diastereoisomers 66:34; yield 61%; \( R_f = 0.30 \) (petroleum ether/AcOEt 15:1); ¹H–NMR δ 6.96–6.86 (4H, m, H arom), 6.07 (1H, dd, \( J = 17.2, 11.0, -\text{CH}<= \)), 5.20 (1H, dd, \( J = 17.1, 0.3, =\text{CH}_2 \)), 5.18 (1H, dd, \( J = 17.1, 0.3, =\text{CH}_2 \)), 4.80 (1H, d, \( J = 11.2, 3–\text{H} \)), 4.32 (1H, d, \( J = 11.2, 3–\text{H} \)), 3.73 (3H, s, CH₃), 3.71 (3H, s, CH₃), 3.09 (3H, s, CH₃); IR ν 3040, 2950, 2880, 1750, 1645, 1590, 1450, 1430, 1255 cm⁻¹. Anal. Calcd for C₁₅H₁₆O₄: C, 69.20; H, 6.20. Found: C, 69.43; H, 6.22.
OCH$_2$CH$_3$), 62.0 (0.66 OCH$_2$CH$_3$), 63.2 (0.34 –CH<), 61.4 (0.66 –CH<), 32.3 (0.66 CH$_3$), 32.2 (0.34 CH$_3$), 14.4 (CH$_3$); IR ν 3080, 3040, 2980, 2930, 2880, 1745, 1715, 1595, 1490, 1255 cm$^{-1}$.

Anal. Calcd for C$_{16}$H$_{18}$O$_5$: C, 66.18; H, 6.25. Found: C, 66.01; H, 6.32.

2-Vinyl-1,4-benzodioxin (7). $R_f = 0.85$ (petroleum ether/AcOEt 15:1); $^1$H–NMR δ 6.90–6.30 (4H, m, H$_{arom}$), 5.95 (1H, bs, 3–H), 5.90 (1H, dd, $J = 17.0$, 11.0, -CH=), 5.42 (1H, dd, $J = 17.0$, 0.8, =CH$_2$), 5.02 (1H, dd, $J = 11.0$, 0.8, =CH$_2$); IR ν 3040, 2950, 2880, 1750, 1645, 1600, 1490, 1430, 1255 cm$^{-1}$. These values are in agreement with those published in the litterature.$^{12}$

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References


