# Synthetic Studies Toward 4*H*-1,3-Benzodioxin-2-ones

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Received December 1, 1986

The investigation into the synthesis of 4*H*-1,3-benzodioxin-2-ones, utilizing the corresponding 2-(hydroxymethyl)phenol as the starting diol, is described. The results illustrate that the synthesis of 4*H*-1,3-benzodioxin-2-ones can be achieved utilizing carefully controlled reaction conditions, in a 3-15% yield.

Recently, we desired to synthesize a number of 4*H*-1,3-benzodioxin-2-one derivatives. The literature revealed only a few related examples which were synthesized for proof of structure [1,2]. These seemingly simple derivatives may have received little attention since the formation and stability of six membered cyclic carbonates are known to be varied depending on the particular system under consideration [3-6]. A further complication in the synthesis of 4*H*-1,3-benzodioxin-2-ones results from the self-condensation of the starting diols (*i.e.* 2-(hydroxymethyl)phenol) to yield a complex mixture of products including triol **1** and polymeric material [7-9]. The investigation reported in this paper examines the synthesis of selected 4*H*-1,3-benzodioxin-2-ones.
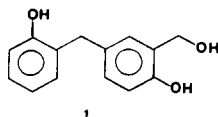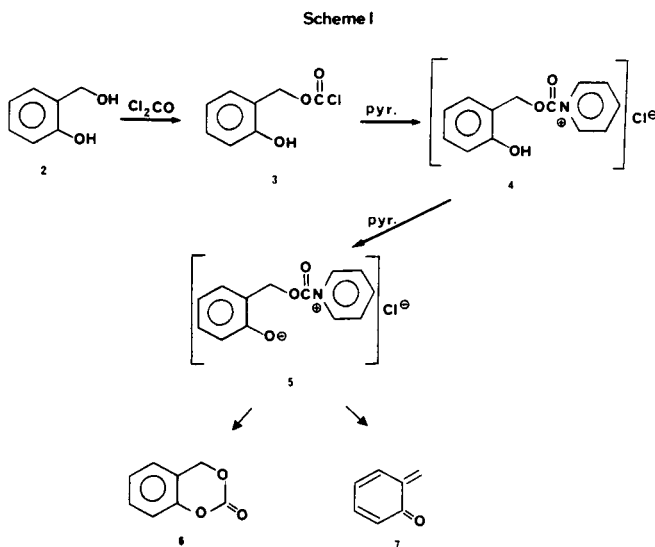


Reaction of 2-(hydroxymethyl)phenol (**2**) in methylene chloride and pyridine (2.8 equivalents) with a solution of phosgene in toluene (1.1 or 2.2 equivalents) resulted in no desired 4*H*-1,3-benzodioxin-2-one (**6**) (Table I). The solid material isolated was a complicated mixture of products which presumably resulted from the self-condensation of 2-(hydroxymethyl)phenol (**2**) [7-9]. A simplified mechanism of the reaction would presumably occur as depicted in Scheme I. The reaction of **2** with phosgene would yield the chloroformate **3** and hydrogen chloride. Reaction with one equivalent of pyridine would generate the pyridine hydrochloride salt while one additional equivalent of pyridine would react with the chloroformate **3** to generate the pyridine-chloroformate complex **4**. Excess pyridine, present in the reaction, would abstract the phenolic proton to yield the intermediate **5**. Intermediate **5** could cyclize to yield the desired 4*H*-1,3-benzodioxin-2-one (**6**) or undergo an elimination reaction yielding a reactive intermediate **7**, which would further react to generate a mixture of products. It should be noted that a base, such as pyridine, is required for a phenol to react with a chloroformate to form a carbonate [10].

Table I

Synthesis of 4*H*-1,3-Benzodioxin-2-ones

| Substrate | Conditions [a] | Yield % [b] |
|---|---|---|
| **2** | A | 0 |
| | B | 15 |
| | C | 0 |
| | D | 0 |
| **8** | A | 0 |
| | B | 3 |
| | C | 0 |
| **10** | C | 6 |
| | D | 6 |

[a] Conditions: (A) pyridine (2.8 equivalents)/phosgene (1.1 equivalents)/dichloromethane; (B) pyridine (1.5 equivalents)/phosgene (1.1 equivalents)/dichloromethane; (C) *n*-butyllithium (2.1 equivalents)/phosgene (1.2 equivalents)/THF; (D) Carbonyl diimidazole/room temperature/toluene. [b] Isolated yield of the corresponding 4*H*-1,3-benzodioxin-2-one product.

**Scheme I**



Examination of the proposed reaction mechanism as well as considering the potential for intermediate **4** to cyclize to form **6** or intermediate **3** or **4** to undergo the elimination reaction to yield **7** and the ability of 2-(hy-

droxymethyl)phenol (2) to undergo self-condensation suggests a number of possible reasons for the failure of the reactions to produce 4H-1,3-benzodioxin-2-one (6). These include (i) the reaction conditions cause self-condensation of the starting diol 2, (ii) the expected intermediates 3, 4, or 5 were not formed or were formed only in a low yield, (iii) the intermediates were reluctant to cyclize and form 4H-1,3-benzodioxin-2-one (6), (iv) decomposition of the desired 4H-1,3-benzodioxin-2-one (6) or its intermediates occurred. In any case, the amount of base, pyridine, in the reaction would be expected to have a significant effect on the reaction with regard to the formation of the intermediates and on the basicity of the reaction mixture. Therefore, the reaction was investigated when the amount of pyridine was less than stoichometeric. When 1.1 equivalents of phosgene and 1.5 equivalents of pyridine were utilized in the reaction with 2 a 15% yield of carbonate 6 was formed, while 1.0 equivalent of pyridine resulted in an 8% yield of 6. These results illustrate the importance of pyridine in the reaction, however, the specific interactions occurring with pyridine can only be speculated on.

To investigate this reaction, the synthesis of the intermediates presumably formed in the mechanism, described in Scheme I, were examined. The isolation of chloroformate 3 was attempted by reaction of 2 in methylene chloride with an excess of the phosgene solution. Since phenols are known to be unreactive toward phosgene if a base is not present in the reaction, no reaction should occur at the phenolic hydroxyl site [10]. Attempted isolation of the chloroformate 3 resulted in only a complex mixture of products being obtained. Previous reports on benzyl chloroformate indicate that it is not stable in the neat form above room temperature, but is known to decompose to benzyl chloride and carbon dioxide [11]. A similar decomposition may be occurring in our case, but at a lower temperature allowing the complex mixture of products to be formed.

In an effort to obtain some information about the chloroformate intermediate 3, the reaction was examined utilizing nmr. A solution of 2-(hydroxymethyl)phenol (2) in deuteriochloroform was treated with an excess of a solution of phosgene in toluene. This solution was allowed to stir at room temperature and was periodically monitored by nmr. Examination of the nmr spectra of the reaction after 1.5 hours revealed two benzylic peaks in a ratio of approximately 2/1 and after 3.5 hours only one major benzylic peak was observed. The chemical shift of the benzylic protons of 2-(hydroxymethyl)phenol (2) were dependent on the ratio of toluene to deuteriochloroform. Thus, an assignment of a particular chemical shift to a particular type of benzylic proton could not be made. The only conclusion which can be made is that after approximately 3.5 hours of stirring at room temperature only one major compound existed, as indicated by the one type of benzylic protons observed in the nmr spectrum.

In an attempt to verify that the benzylic peak observed by nmr corresponded to the chloroformate derivative 3, 2-(hydroxymethyl)phenol (2) was reacted with an excess of the phosgene solution and stirred for 3.5 hours at room temperature. From our previous nmr data it would be expected that one major type of compound existed. The excess phosgene was removed by bubbling nitrogen through the solution and 1.4 equivalents of pyridine was added. The solution was stirred for 16 hours at room temperature then subjected to the normal workup procedure to generate 15% of 6. Since the product 6 was formed we can conclude, although not conclusively, that the benzylic peak observed by nmr corresponds to the chloroformate 3 and that the low yield of 6 results due to the reluctance of the intermediates to form the 4H-1,3-benzodioxin-2-one (6) or from decomposition of 6 once it was formed.

The possibility that decomposition of 6 occurred after it was formed was investigated. 4H-1,3-Benzodioxin-2-one (6) was mixed in methylene chloride and toluene and either pyridine or pyridine hydrochloride was added to the solution. 4H-1,3-Benzodioxin-2-one (6) was found to be unchanged by pyridine hydrochloride (acidic reaction conditions) after stirring at room temperature for 24 hours, while the pyridine reaction conditions (basic reaction conditions) decomposed 6 to a complex mixture of products after 30 minutes. These results conclusively demonstrate that excess pyridine used in the reaction will destroy 4H-1,3-benzodioxin-2-one (6), which explains in part why the initial reactions failed to yield any 4H-1,3-benzodioxin-2-one (6). In the reactions where limited amounts of pyridine were used, 4H-1,3-benzodioxin-2-one (6) would be stable and reinforces the idea that the low yield of 6 is due to the reluctance of the intermediates (Scheme I) to form 6.

Since the reluctance to form 4H-1,3-benzodioxin-2-one (6) may be directly related to the intermediate pyridine-chloroformate complex 4, which results as a consequence of the reaction conditions, several alternate standard carbonate forming procedures were investigated. If 2 was reacted with 2.1 equivalents of n-butyllithium followed by 1.2 equivalents of phosgene only an intractable tar was isolated. The reaction of 2 with an excess of carbonyl diimidazole in toluene at room temperature or reflux resulted in only starting material being isolated. These results indicate that 4H-1,3-benzodioxin-2-one (6) formation is extremely sensitive to the reaction conditions.

The synthesis of several 4-substituted 4H-1,3-benzodioxin-2-ones was investigated (Scheme II). 2-(1-Hydroxyethyl)phenol (8) was prepared by reacting 2-hydroxy-

benzaldehyde with 3.5 equivalents of methyllithium in ether [12]. Diol **8** was reacted with 1.1 equivalents phosgene and 2.8 equivalents pyridine in methylene chloride resulting in a 0% yield of 4-methyl-4H-1,3-benzodioxin-2-one (**9**). When the reaction was repeated utilizing 1.5 equivalents of pyridine a 3% yield of **9** was isolated. Alternatively, diol **8** was reacted with 2.1 equivalents of n-butyllithium in tetrahydrofuran, followed by 1.2 equivalents of phosgene to yield no desired carbonate **9**.

<div align="center">Scheme II</div>
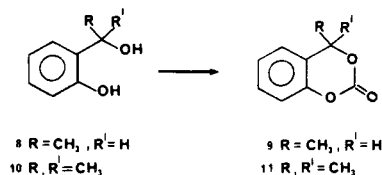


The synthesis of 2-(1-hydroxy-1-methylethyl)phenol (**10**) was conducted by the reaction of 2-hydroxyacetophenone with 2.5 equivalents methyllithium in ether [13]. Diol **10** was reacted with 2.1 equivalents n-butyllithium in tetrahydrofuran, followed by 1.2 equivalents phosgene to yield 6% of 4,4-dimethyl-4H-1,3-benzodioxin-2-one (**11**). Alternatively, the reaction of diol **10** with carbonyl diimidazole in toluene at room temperature yielded 6% of **11**. The reaction of **10** utilizing the pyridine procedures was not attempted since tertiary alcohols are known to be reluctant to react with phosgene even when the base pyridine is present [10].

From the limited number of examples studied, the different behavior of diol **10** as compared to diols **2** and **8** utilizing the conditions of Method C are readily apparent (Table I). This difference in behavior may result from the stability of the products to basic conditions. In the case of 4,4-dimethyl-4H-1,3-benzodioxin-2-one (**11**), the absence of benzylic protons may enable carbonate **11** to be stable to basic reaction conditions. To verify this assumption and for direct comparison to the stability of carbonate **6**, the stability of carbonate **11** was investigated under similar conditions previously described for carbonate **6**. 4,4-Dimethyl-4H-1,3-benzodioxin-2-one (**11**) was mixed in methylene chloride and toluene and pyridine was added to the solution. Carbonate **11** was found to be unchanged after stirring for 24 hours at room temperature. Under these conditions, 4H-1,3-benzodioxin-2-one (**6**) decomposed after 30 minutes. These results indicate that 4,4-dimethyl-4H-1,3-benzodioxin-2-one (**11**) is stable to basic reaction conditions and suggests that the low yield of carbonate **11** obtained results due to the reluctance to form carbonate **11**.

From this investigation it is apparent that the 4H-1,3-benzodioxin-2-one derivatives can be synthesized utilizing carefully controlled reaction conditions. Though

the yield of the derivatives are low, 3-15%, the starting materials are readily available and consequently a significant amount of material is readily synthesized. Once isolated the carbonates have been found to be stable on storage, over an extended period of time. However, it is clear from this study that proof of structure determinations utilizing 4H-1,3-benzodioxin-2-one type of derivatives is not conclusive.

<div align="center">EXPERIMENTAL</div>

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Infrared spectra were recorded on a Perkin-Elmer 1320 spectrophotometer. The chemical shifts and coupling constants (J) are reported in $\delta$ and Hertz respectively, using a Varian XL-300 spectrometer, with TMS as the internal standard. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Radial chromatography was conducted with a Harrison Research Model 7924 chromatotron utilizing a 4 mm plate with silica gel 60 GF 254 (EM Labs) as the adsorbent. Isocratic, normal phase high pressure liquid chromatography (hlpc) was conducted with a Waters Associates Liquid Chromatograph (pump, 6000A; injector, UK6; UV detector, 481 at 254 nm) equipped with a Partisil M20 10/15 column, solvent compositions are indicated for each application.

Synthesis of 4H-1,3-Benzodioxin-2-ones.

Method A.

A solution of phosgene in toluene (44.0 mmoles) was added dropwise to a solution of the diol (40.0 mmoles) in pyridine (112.0 mmoles) and 100 ml of methylene chloride at 0°. The solution was stirred for 30 minutes at 0°, then 15-22 hours at room temperature. Nitrogen was bubbled through the reaction mixture for 30 minutes. Evaporation of the solvent under reduced pressure yielded an oil. The oil was purified according to the procedure indicated for each compound.

Method B.

This method is identical to Method A however utilizing 60.0 mmoles pyridine and 44.0 mmoles of phosgene.

Method C.

A solution of n-butyllithium (2.5M in hexane, 27.7 mmoles) was added to a solution of the diol (13.2 mmoles) in 100 ml of tetrahydrofuran at 0°. The solution was stirred for 5 minutes at 0° followed by the addition of a solution of phosgene in toluene (15.8 mmoles) at 0°. The solution was stirred at 0° for 1 hour then at room temperature for 5 hours. Nitrogen was then bubbled through the solution to yield a residue to which ether was added. The resulting mixture was filtered and the filtrate was evaporated under reduced pressure to yield a residue which was purified according to the procedure indicated for each compound.

Method D.

Carbonyl diimidazole (2.5 mmoles) was added to a solution of the diol (2.2 mmoles) in 50 ml of toluene at room temperature. The mixture was stirred at room temperature for 18 hours. Methylene chloride was added and the mixture was washed with water. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to yield a residue which was purified according to the procedure indicated for each compound.

4H-1,3-Benzodioxin-2-one (**6**).

Method B.

The synthesis of **6** was conducted on a 40.0 mmole scale using the conditions described in Method B. The product was purified by flash chromatography on silica gel (methylene chloride) to yield 860 mg (15%) of **6**, mp 72-73°; ir (film): 1770 cm$^{-1}$; $^1$H nmr (deuteriochloroform): $\delta$

7.40-7.07 (m, 4H, aromatic protons), 5.41 (s, 2H, CH$_2$); $^{13}$C nmr (deuterio-chloroform): δ 148.9 (C-2), 146.8 (C-9), 129.7 (C-5, C-7), 125.1 (C-10), 124.0 (C-6), 115.9 (C-8), 68.3 (C-4).

*Anal.* Calcd. for C$_8$H$_6$O$_3$: C, 64.00; H, 4.03. Found: C, 63.99; H, 4.12.

4-Methyl-4$H$-1,3-benzodioxin-2-one (**9**).

### Method B.

The synthesis of **9** was conducted on a 13.0 mmole scale using the conditions described in Method B. The product was purified by radial chromatography (methylene chloride) followed by hplc (20% ethyl acetate/hexane) yielding 62 mg (3%) of **9** as an oil; ir (film): 1770 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 7.40-7.10 (m, 4H, aromatic protons), 5.61 (q, J = 6.6 Hz, 1H, CH), 1.74 (d, J = 6.7 Hz, 3H, CH$_3$); $^{13}$C nmr (deuteriochloroform): δ 148.5 (C-2), 146.7 (C-9), 129.7 (C-5, C-7), 125.1 (C-10), 123.6 (C-6), 116.0 (C-8), 76.0 (C-4), 29.7 (CH$_3$).

*Anal.* Calcd. for C$_9$H$_8$O$_3$: C, 65.85; H, 4.91. Found: C, 65.54; H, 5.00.

4,4-Dimethyl-4$H$-1,3-benzodioxin-2-one (**11**).

### Method C.

The synthesis of **11** was conducted on a 13.0 mmole scale using the conditions described in Method C. The product was purified by radial chromatography (5% ethyl acetate/hexane) followed by hplc (10% ethyl acetate/hexane) yielding 138 mg (6%) of **11** as an oil; ir (film): 1770 cm$^{-1}$; $^1$H nmr (deuteriochloroform): δ 7.38-7.10 (m, 4H, aromatic protons), 1.76 (s, 6H, 2CH$_3$); $^{13}$C nmr (deuteriochloroform): δ 147.6 (C-2), 146.7 (C-9), 129.5 (C-5, C-7), 125.2 (C-10), 123.0 (C-6), 116.1 (C-8), 83.8 (C-4), 28.4 (2CH$_3$).

*Anal.* Calcd. for C$_{10}$H$_{10}$O$_3$: C, 67.41; H, 5.66. Found: C, 67.38; H, 5.56.

### Method D.

The synthesis of **11** was conducted on a 2.0 mmole scale using the conditions decribed in Method D. The product was purified by radial chromatography (10% ethyl acetate/hexane) followed by hplc (10% ethyl acetate/hexane) yielding 30 mg (6%) of **11**, identical to **11** prepared by Method C.

### Stability of 6 and 11.

To a solution of 4$H$-1,3-benzodioxin-2-one **6** or **11** (0.81 mmole),

methylene chloride (2 ml), and toluene (0.25 ml) was added pyridine (1.21 mmoles) or pyridine hydrochloride (1.21 mmoles) at room temperature. The reaction was monitored by thin layer chromatography on silica gel eluted with methylene chloride. The results are described in the text.

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