Precursors to Isobenzofuran. Monoacetals of *o*-Phthalaldehyde

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The preparation of monoacetals of *o*-phthaldehyde is described. Reduction of the monoacetal provides the acetal of *o*-(hydroxymethyl)benzaldehyde. This last compound was used to generate isobenzofuran in the presence of dienophiles such as dimethyl fumarate, dimethyl acetylenedicarboxylate, and *p*-benzoquinone.

Isobenzofuran has been generated recently in a number of ways.[1,2] Our approach[3] has been to prepare and dehydrate 1-hydroxyphthalan or a precursor of this compound. During attempts to selectively reduce *o*-phthalaldehyde to *o*-(hydroxymethyl)benzaldehyde (i.e., 1-hydroxyphthalan) it was observed that the overreduction product *o*-benzenedimethanol formed a monoacetal with *o*-phthalaldehyde.

This observation was pursued and acceptable yields of the monoacetal[4] **1a** were obtained by shaking a methylene chloride solution of the dialdehyde and diol with *freshly prepared* anhydrous copper sulfate. Other diols were investigated and of these 2,2-dimethyl-1,3-propanediol proved the best in terms of yield and ease of purifying the product **1b**. Monoacetals with 2,2-diethyl-1,3-propanediol and *cis*-2-butene-1,4-diol were also prepared but not investigated further after **1b** was obtained.

Reduction of **1a** or **1b** with sodium borohydride produced in good yields the *o*-(hydroxymethyl)benzaldehyde acetals **2a** and **2b** (Scheme I). These, of course, are precursors to *o*-(hydroxymethyl)benzaldehyde (and hence isobenzofuran). Hydrolysis of these acetals in the presence of a suitable dienophile should permit capture of the isobenzofuran generated as the 1-hydroxyphthalan dehydrates.

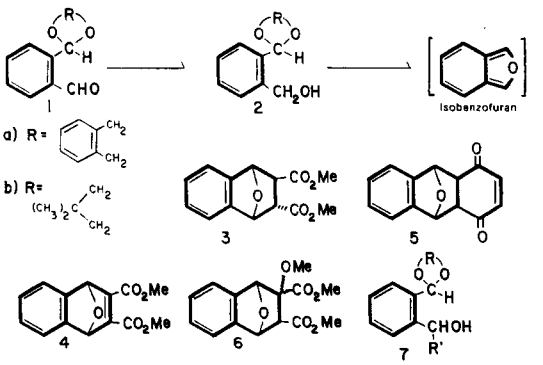
This was tested with **2b** and the dienophiles dimethyl fumarate, dimethyl acetylenedicarboxylate, and *p*-benzoquinone. The liberated diol was a minor complicating feature in the reaction mixture, but it was readily removed by chromatography. Thus the fumarate adduct **3** and the acetylenedicarboxylate adduct **4**[3] were obtained in 65% yield. Spectroscopic properties of **3** are reported here although the compound has been reported elsewhere.[3]

The reaction mixture formed with *p*-benzoquinone was complex (by TLC). However, both *exo*- and *endo*-**5** were isolated and characterized. Unlike 1-alkoxyisobenzofuran where homoquinone products have been reported,[5,6] the Diels–Alder reaction here progressed normally.

Interestingly, the Diels–Alder adduct **4** readily underwent Michael addition of methanol in the presence of sodium bicarbonate producing **6**. The stereochemistry of **6** has yet to be determined.

In conclusion, this paper describes the synthesis of **2a** and **2b**, which can be used for the in situ generation of isobenzofuran. This supplements our earlier procedure[3] and offers the possibility of treating monoacetals **1a** or **1b** with organometallic reagents. Compounds such as **7** can be prepared and used as sources of substituted isobenzofurans.

Scheme I. Transformations of the *o*-Phthalaldehyde Monoacetals



Experimental Section

Melting points were determined in open capillaries with a Mel-Temp apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 983 spectrometer and NMR spectra were determined on a Bruker WP-80 spectrometer with tetramethylsilane (Me_4Si) as the internal standard. Chemical analyses were determined by MHW Laboratories, Phoenix, AZ.

Preparation of the Monoacetal 1a of *o*-Phthalaldehyde with 1,2-Benzenedimethanol. General Procedure. Anhydrous copper sulfate (52 g) in a 250-mL long-neck round-bottom flask held in a horizontal position was heated with constant turning over a flame until the residual water was expelled. After the flask was sealed and cooled, 40 mL of methylene chloride was added followed by 2 g each of *o*-phthalaldehyde (0.015 m) and 1,2-benzenedimethanol (0.015 m). The flask was swept with nitrogen, sealed, and shaken in a cold room (5 °C) for 14 h. TLC (1:10 ethyl acetate–benzene) showed that the reagents were largely consumed.

The mixture was filtered through a layer of diatomaceous earth and the solid washed thoroughly with methylene chloride. The filtrate and washings were concentrated to a small volume (ca. 10 mL) and then treated with 30 mL of hexane. The crude product (3.03 g) which precipitated was purified by dissolving in 12 mL of methylene chloride and reprecipitating with 10 mL of hexane. After filtering and drying, 1.87 g (49%) of the monoacetal **1a**, mp 134–136 °C, was obtained. Concentration of the mother liquors provided an additional 0.69 g of **1a** (total yield 67%), mp 132–133.5 °C. An analytical sample was obtained by chromatography of the isolated material on silica gel eluting with pentane–methylene chloride followed by precipitation with pentane:

† We are sorry to report the sudden death of Dr. J. G. Smith on July 31, 1985.

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mp 134–136 °C; NMR ($CDCl_3$) δ 4.93 and 5.16 (AB q, J = 14 Hz, 4 H), 6.52 (s, 1 H), 7.5–8.0 (m, 8 H), 10.40 (s, 1 H); IR (KBr) 2860, 2780, 1690, 1260, 1220, 1210, 1100, 1080, 1020, 930, 750, 735 cm^{-1}. Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.56; H, 5.56. Found: C, 75.62; H, 5.56.

Preparation of the Monacetal 1b of *o*-Phthalaldehyde with 2,2-Dimethylpropane-1,3-diol. The procedure used for the preparation of **1a** was employed except that the crude product was crystallized from methanol–water, giving 64% of **1b**: mp 44–47 °C; NMR ($CDCl_3$) δ 0.83 (s, 3 H), 1.31(s, 3 H), 3.77 (s, 4 H), 6.02(s, 1 H), 7.5–8.1 (m, 4 H), 10.44 (s, 1 H); IR($CDCl_3$) 1690, 1380, 1210, 1110, 1090 cm^{-1}. Anal. Calcd for $C_{13}H_{16}O_3$: C, 70.87; H, 7.34. Found: C, 70.62; H, 7.18.

Reduction of the Monoacetal 1a. General Procedure. Preparation of 2-(2,7-Dioxa-4,5-benzocycloheptyl)benzyl Alcohol (2a). A mixture of 35 mL of *tert*-butyl alcohol, 15 mL of water, 1.0 g (4 mmol) of **1a**, and 0.20 g (5 mmol) of sodium borohydride was shaken for 1.5 h, during which time the mixture became gelatinous. Water (100 mL) was then added, and the solid which precipitated was filtered, washed with water, and dried under vacuum, giving 0.95 g of **2a** (94%), mp 117–118 °C. The analytical sample was obtained by dissolving **2a** in methylene chloride, filtering the solution, and precipitating the compound with pentane: mp 117–118 °C; NMR ($CDCl_3$) δ 2.84 (t, J = 6.6 Hz, 1 H, exchanges with D_2O), 4.73 (d, J = 6.6 Hz, 2 H, s with D_2O), 5.01 (s, 4 H), 6.14 (s, 1 H), 7.2–7.7 (m, 8 H); IR (KBr) 3250, 3210, 1450, 1370, 1260, 1220, 1115, 1100, 1050, 1030, 920, 740 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O_3$: C, 74.97; H, 6.30. Found: C, 74.64; H, 6.37.

The acetate of **2a**, prepared with acetic anhydride and pyridine, had mp 62–63 °C: IR (Nujol) 1740, 1250, 1240, 1225, 1020, 730 cm^{-1}.

Preparation of 2-(2,6-Dioxa-4,4-dimethylcyclohexyl)benzyl Alcohol (2b). The sodium borohydride reduction was performed as described using 3.35 g (0.015 m) of crude **1b**. The product was isolated by diluting with water, removing *tert*-butyl alcohol under vacuum from the aqueous solution, and extracting with hexane. The extract was concentrated and cooled to −5 °C when 3.38 g of **2b** crystallized, mp 74–76 °C. An analytical sample was prepared by chromatography on silica gel (CH_2Cl_2): mp 76–77 °C; NMR ($CDCl_3$) δ 0.82 (s, 3 H), 1.34 (s, 3 H), 3.02 (t, 1 H, J = 6.5 Hz, exchanges with D_2O), 3.85 and 3.69 (AB q, 2 H), 4.76 (d, 2 H, s with D_2O), 5.58 (s, 1 H), 7.3–7.8 (m, 4 H); IR (Nujol) 3414, 1113, 1090, 1010, 766 cm^{-1}. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.23; H, 8.18. Found: C, 70.09; H, 8.33.

Reaction with Dimethyl Acetylenedicarboxylate. Preparation of 2,3-Dicarbomethoxy-1,4-epoxy-1,4-dihydronaphthalene (4). A mixture of 0.40 g (1.8 mmol) of **2b**, 0.64 g (5.0 mmol) of dimethyl acetylenedicarboxylate (DMAD), and 9 mg of *p*-toluenesulfonic acid in 80 mL of toluene was heated under nitrogen to 95 °C for 0.5 h. The cooled reaction solution was diluted with 40 mL of hexane and passed through a column of silica gel to adsorb the products. The column was then eluted with toluene to remove the DMAD and then with methylene chloride to remove the product **4**. The crude **4** was heated with a small amount of pentane and left at 0 °C. The supernatant liquid was removed and the oily **4** dried under vacuum, giving 0.31 g (66%), pure by TLC. Spectroscopic properties were identical with those described.[3]

Reaction with Dimethyl Fumarate. Preparation of *trans*-2,3-Dicarbomethoxy-1,4-epoxy-1,2,3,4-tetrahydronaphthalene (3). A mixture of dimethyl fumarate (0.4 g, 2.78 mmol), **2b** (0.4 g, 1.80 mmol), *p*-toluenesulfonic acid (8 mg), and 80 mL of toluene was heated at 95 °C under nitrogen for 0.5 h. The cooled solution was passed through a column of silica gel to adsorb the products and the column then eluted with methylene chloride. Dimethyl fumarate eluted first followed by a series of fractions containing the product **2b**. The combined fractions were treated with heptane when **2b** crystallized (0.29 g, 62%): mp 65–66 °C;[7] NMR ($CDCl_3$) δ 3.05 (d, J = 4 Hz, 1 H), 3.55 (s, 3 H), 3.80 (s) and 3.8–3.96 (m) (4 H), 5.63 (d, J = 5.5 Hz, 1 H), 5.68 (s, 1 H), 7.2–7.4 (m, 4 H); IR (Nujol) 1740, 1310, 1210, 1180 cm^{-1}. Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.39, Found: C, 63.87; H, 5.46.

Reaction with *p*-Benzoquinone. Isolation of *exo*- and *endo*-5. A solution of 0.25 g (1.12 mmol) of **2b**, 0.25 g, (2.58, mmol) of *p*-benzoquinone, and 5 mg of *p*-toluenesulfonic acid in 50 mL of toluene was heated at 75 °C for 2.5 h. The solution was cooled, the diol which crystallized filtered off, and the filtrate chromatographed on silica gel. Benzoquinone eluted first followed by an "exo-rich" fraction and then an "endo-rich" fraction.

The exo-rich fraction (100 mg) was dissolved in methylene chloride and precipitated with pentane. The precipitate, enriched in exo, was chromatographed on silica gel GF plates with ethyl acetate–benzene (1:10). The *exo*-**5** band was removed and recovered by using ethyl acetate to give 20 mg of *exo*-**5**, mp 149–153 °C. An analytical sample was obtained by recrystallization from methylene chloride–hexane: mp 153–155 °C; NMR ($CDCl_3$) δ 2.92 (s, 2 H), 5.72 (s, 2 H), 6.87 (s, 2 H), 7.25 (s, 4 H); IR (KBr) 1665, 1300, 1285, 1155, 878, 772, 661 cm^{-1}. Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.23; H, 4.49.

The endo-rich fraction (100 mg) was precipitated from methylene chloride with hexane and the precipitate chromatographed on silica gel eluting with 1:4 methylene chloride–hexane to give 70 mg of crude *endo*-**5**, mp 146–150 °C. Recrystallization from methylene chloride–hexane gave an analytical sample: mp 151–152 °C; NMR ($CDCl_3$) δ 3.56–3.63 (m, 2 H), 5.74–5.81 (m, 2 H), 6.01 (s, 2 H), 7.16 (s, 4 H); IR (KBr) 1700, 1670, 1200, 880, 760 cm^{-1}. Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.20; H, 4.71.

Preparation of 1,2-Dicarbomethoxy-1,4-epoxy-2-methoxy-1,2,3,4-tetrahydronaphthalene (6). A solution of 91 mg (0.35 mmol) of **4** in 1 mL of methanol was treated with 0.27 mL of an aqueous saturated sodium bicarbonate solution. The resulting mixture was stirred for 2 days at 20 °C, then diluted with water, and extracted with methylene chloride. Concentration of the extract gave 64.6 mg (64%) of crude **6**, mp 153–155 °C. An analytical sample was obtained by recrystallization from methylene chloride–hexane: mp 158–160 °C; NMR ($CDCl_3$) δ 3.45 (d, J = 4.5 Hz, 1 H), 3.46 (s, 3 H), 3.52 (s, 3 H), 3.58 (s, 3 H), 5.32 (s, 1 H), 5.55 (d, J = 4.5 Hz, 1 H), 7.2–7.6 (m, 4 H); IR (KBr) 1750, 1720, 1215, 1090, 651 cm^{-1}. Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.63; H, 5.53. Found: C, 61.48; H, 5.63.

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