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AN UNUSUAL SYNTHESIS OF PHTHALALDEHYDE[#]

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Abstract: A variety of oxidizing agents convert 5-hydroxy-4,5-dihydroisobenzofuran into phthalaldehyde. Other oxidizing agents produce both phthalaldehyde and its 4-hydroxy derivative.

5-Hydroxy-4,5-dihydroisobenzofuran **1** is a bicyclic furan alcohol, easily prepared from furfuryl alcohol by conversion into its propargyl ether followed by a Kanematsu reaction.[1] In connection with a natural product synthesis project ketone **2** was needed as starting material. Hence alcohol **1** was subjected to oxidation.

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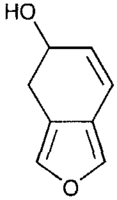

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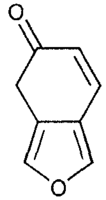

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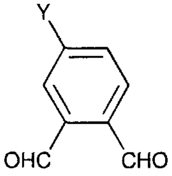

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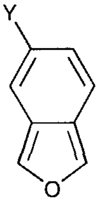
b Y = OH



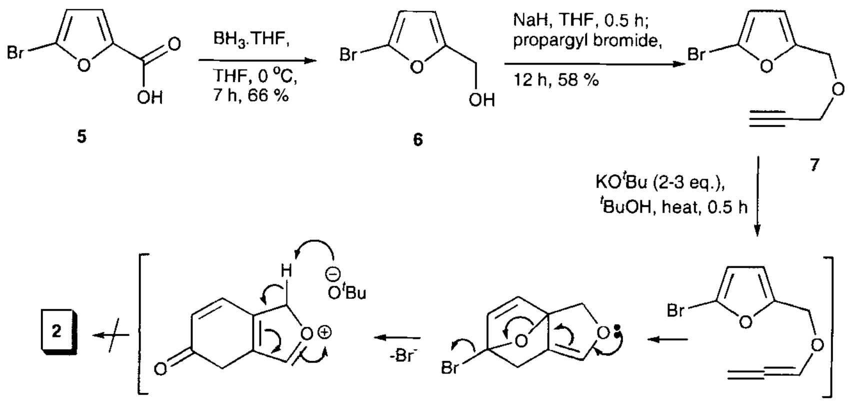
4a Y = H
b Y = OH

Despite the use of a variety of oxidizing agents (i: CAN/H_2O/2 h; ii: *t*-BuOCl/py/CCl_4/4 h; iii: DMSO/$(COCl)_2$-Et_3N/CH_2Cl_2; iv: *m*-$ClC_6H_4CO_3H$/ CH_2Cl_2/1 h; v: *t*-BuOOH/$VO(acac)_2$/C_6H_6/3 h) none of the reactions (at ambient temperature) led to the desired ketone **2**, but, instead, produced phthalaldehyde **3a** in 37-50% yields. Oxidation in a refluxing aqueous SeO_2 suspension for 10 min furnished **3a** in 64% yield.

The above results indicate that no oxidation had taken place at the site of the hydroxy group of alcohol **1**. Instead, the latter had undergone dehydration induced by either Lewis acid catalysis of the oxidizing agent or by solvolysis of an intermediate ester of an inorganic acid. The resultant metastable isobenzofuran[1] **4a** would be expected to suffer oxidation at its furan α-position, affording phthalaldehyde **3a** as product. Had the desired oxidation ocurred, ketone **2** might not have survived, since its enol is metastable 5-hydroxyisobenzofuran **4b**, vulnerable at its furan α-site and en route to 4-hydroxyphthaldehyde **3b**. This scenario actually could be observed, when four more oxidizing systems were studied.

Manganese dioxide oxidation in refluxing dioxane (18 h) yielded a 1:2 **3a-3b** mixture, while PCC in CH_2Cl_2 (-78 °C, 9 h; then 22 °C, 18 h) gave a 1:1 **3a-3b** mixture. Treatment of alcohol **1** with PDC in CH_2Cl_2 as under the PCC oxidation conditions afforded a 1:2 product mixture, though the reaction at 22 °C (18 h) furnished the aldehydes in 4:1 ratio. Oxidation with DDQ in dioxane at 22 °C led to a 1:1 product ratio, whereas in refluxing dioxane (18 h) aldehydes **3a** and **3b**[2] were produced in a 2:1 combination, respectively. Since the dialdehyde yields were in the 51-78% range, the oxidations of alcohol **1** represent a reasonable method of synthesis of phthalaldehyde **3a** and/or its 4-hydroxy derivative **3b**.

Scheme: Furan ring transfer (FRT) study



In the absence of success of the **1**→**2** conversion a Kanematsu reaction sequence was investigated, which was expected to yield ketone **2** without recourse to an oxidation (**Scheme**). 5-Bromofuroic acid **5** was reduced with borane and the resultant 5-bromofurfuryl alcohol **6** was alkylated immediately with propargyl bromide. Exposure of 5-bromofurfuryl propargyl ether **7** to Kanematsu reaction conditions unfortunately yielded only intractable material.

Experimental:

General. M.p.: Reichert micro hotstage; uncorrected. IR spectra (cm^{-1}): IBM 9000 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$ solutions): *General Electric QE-300* spectrometer. MS spectra: Hewlett-Packard 5890 GC-MS spectrometer. TLC: *EM Laboratories* precoated silica gel *60F-25* on 0.2 mm plates; column: *EM Laboratories 60-200* mesh silica gel (elution with EtOAc/hexane mixtures); MPLC: *Merck Laboratory* (A, B, C) silica gel columns, *Fluid metering, Inc.* pump.

Phthalaldehyde (3a): A mixture of alcohol **1** (115 mg, 0.845 mmol) and SeO_2 (47 mg, 0.423 mmol) in H_2O (5 ml) was refluxed for 10 min. The cooled mixture was filtered through a SiO_2 pad and the latter washed with ether. The aqueous solution was extracted with ether and the combined ether solutions were washed with brine and dried (Na_2SO_4). Evaporation of the extract under vacuum furnished phthalaldehyde **3a** (73 mg, 64%). Mp 55-57 °C (lit. Mp 54-55 °C).[3] ^{1}H-NMR ($CDCl_3$): δ 7.77 (*dd*, 2H, *J* = 3.3, 5.5 Hz, H-C(4), H-C(5)); 7.95 (*dd*, 2H, *J* = 3.3, 5.5 Hz, H-C(3), H-C(6)); 10.49 (*s*, 2H, CHO). ^{13}C-NMR ($CDCl_3$): δ 130.7 (C(3), C(6)); 133.5 (C(4), C(5)); 136.0 (C(1), C(2)); 192.2 (CO).

References and Note:

1. K. Hayakawa, Y. Yamaguchi and K. Kanematsu, *Tetrahedron Lett.*, 1985, **26**, 2689.

2. **4-Hydroxyphthalaldehyde (3b):** ^{1}H-NMR ($CDCl_3$): δ 2.00 (br. s, 1H), 7.20 (dd, 1H, *J* = 2.4, 8.4 Hz), 7.43 (d, 1H, *J* = 2.4 Hz), 7.87 (d, 1H, *J* = 8.4 Hz), 10.28 (s, 1H), 10.59 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 117.0, 120.0, 128.6, 134.9, 138.6, 161.9, 191.4, 192.6.

3. C. V. Greco and F. C. Pellegrini, *Synth. Commun.*, 1971, **1**, 307.

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