Oxidative Rearrangement of 3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde Acetals†

J. Chem. Research (S), 1998, 470–471†

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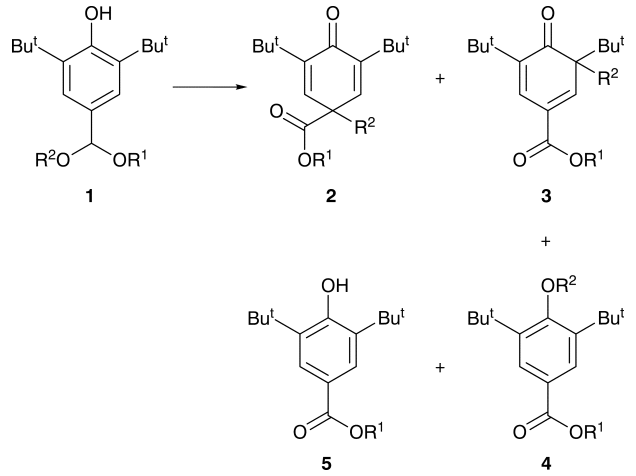
3,5-Di-*tert*-butyl-4-hydroxybenzaldehyde acetals rearrange to various esters when oxidized with potassium ferricyanide in alkaline medium.

During the course of our studies on pharmacologically active 3,5-di-*tert*-butyl-4-hydroxybenzyl ethers we started to investigate the oxidation of both symmetrical and unsymmetrical 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde acetals in order to generate reactive quinone methides.

Here we wish to report a molecular rearrangement of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde acetals **1** by treatment with potassium hexacyanoferrate(III) in benzene–aqueous sodium hydroxide. A common oxidation procedure[1] gave a mixture of products depending on the structure of the acetal **1** (Scheme 1 and Table 1).



Scheme 1 Oxidation of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde acetals; $R^1 = R^2 = CH_2$(3-Py) **a**; R^1 = Me, $R^2 = CH_2$(3-Py) **b**; $R^1 = R^2$ = Me **c**

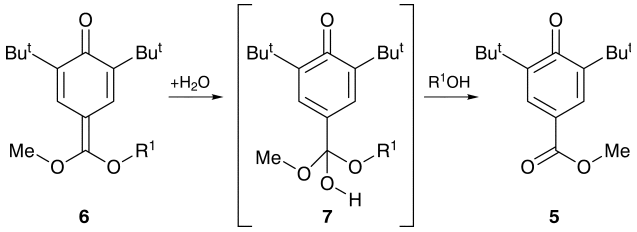
We suggest the formation of quinone methide **6** to be the initial step. Addition of water and subsequent elimination of alcohol[2,3] leads to the formation of the ester **5** (Scheme 2).

Meanwhile quinone methide **6** can undergo Claisen ester enolate[4] like rearrangement of radical reactions to give rearranged products **2**, **3** and **4**. The steric effect of *tert*-butyl groups facilitate the formation of cyclohexadienone **2**

Table 1 Yields of reaction products after oxidation of 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde acetals

		Yield[a] (%)			
R^1	R^2	**2**	**3**	**4**	**5**
CH_2(3-Py)	CH_2(3-Py)	76	2	3	10
Me	CH_2(3-Py)	90	—	—	—
Me	Me	—	—	—	91

[a]Yields refer to isolated products.



Scheme 2 Hydrolysis of quinone methide **6**

type derivatives, while products **3** and **4** are less prominent in the reaction mixture.[5]

Experimental

All ^{1}H NMR spectra were recorded on a 90 MHz Bruker WH-90 instrument. IR spectra were recorded on an Perkin-Elmer apparatus in Nujol. Acetals **1a**–**c** were prepared from 2,6-di-*tert*-butyl-4-[3-(3-pyridyl)-2-oxaprop-1-yl]phenol[6] and 3,5-di-*tert*-butyl-4-hydroxybenzaldehyde correspondingly according to known methods.[3] All oxidations were carried out in an argon atmosphere and solutions were degassed and saturated with argon prior to use. Column chromatography was performed on Kieselgel 60 using hexane–ethyl acetate. The purity of final products was tested by TLC on Kieselgel 60 F_{254} plates (Merck). Eluent: hexane–ethylacetate, visualisation agent: 15 wt.% solution of phosphomolybdic acid in ethanol.

General procedure for the oxidation of 3,5-*di*-tert-*butyl*-4-*hydroxybenzaldehyde acetals*.—Acetal **1** (0.50 mmol) was dissolved in benzene (5 ml) and under vigorous stirring added in one portion to a pre-cooled (+6 °C) solution of potassium hexacyanoferrate(III) (500 mg, 1.52 mmol) and sodium hydroxide (300 mg, 7.5 mmol) in 5 ml of water. The reaction mixture turned green, stirring was continued for 30–60 min until the green color faded and TLC on Kieselgel 60 showed the disappearance of the starting material.

The organic layer was separated, the aqueous phase washed with 2×3 ml of benzene and extracts washed with brine until neutral pH. The solution was dried over sodium sulfate, evaporated *in vacuo*, and products were separated on a 1.5×15 cm column.

Methyl 3,5-*di*-tert-*butyl*-4-*hydroxybenzoate* (**5c**).—^{1}H NMR ($CDCl_3$ TMS): δ 1.47 (s, 18H, Bu^t), 3.88 (s, 3H, OCH_3), 5.66 (s, 1H, OH), 7.89 (s, 2H, C_6H_2). IR: 1650, 3620 cm^{-1}.

3-*Pyridylmethyl*-3,5-*di*-tert-*butyl*-4-*hydroxybenzoate* (**5a**).—^{1}H NMR ($CDCl_3$ TMS): δ 1.47 (s, 18H, Bu^t), 5.36 (s, 2H, CH_2Py), 5.69 (s, 1H, OH), 7.18–7.40 (m, 1H, Py-5H), 7.62–7.82 (m, 1H, Py-4H), 7.88 (s, 2H, C_6H_2), 8.56 (m, 1H, Py-6H), 8.71 (m, 1H, Py-2H). IR: 1645, 3630 cm^{-1}.

3-*Pyridylmethyl*-3,5-*di*-tert-*butyl*-4-(3-*pyridylmethoxy*)*benzoate* (**4a**).—^{1}H NMR ($CDCl_3$ TMS): δ 1.28 (s, 9H, Bu^t), 1.41 (s, 9H, Bu^t), 4.88 (s, 2 H, OCH_2Py), 5.38 (s, 2H, CO_2CH_2Py), 7.11–7.44 (m, 2H, Py-5H), 7.62–7.87 (m, 2H, Py-4H), 7.99 (s, 2H, C_6H_2), 8.49–8.78 (m, 4H, Py-2H and Py-6H).

2,6-*Di*-tert-*butyl*-4-(3-*pyridylmethyl*)*oxycarbonyl*-4-(3-*pyridylmethyl*)-*cyclohexa*-2,5-*dien*-1-*one* (**2a**).—^{1}H NMR ($CDCl_3$ TMS): δ 1.11 (s, 18H, Bu^t), 3.18 (s, 2H, CH_2Py), 5.19 (s, 2H, CO_2CH_2Py), 6.67 (s, 2H, C_6H_2), 6.89–7.69 (m, 4H, Py-5H and Py-4H), 8.18–8.64 (m, 4H, Py-2H and Py-6H). IR: 1235, 1647, 1665, 1732 cm^{-1}.

2,6-*Di*-tert-*butyl*-4-*methyloxycarbonyl*-4-(3-*pyridylmethyl*)*cyclohexa*-2,5-*dien*-1-*one* (**2b**).—^{1}H NMR ($CDCl_3$ TMS): δ 1.16 (s, 18H, Bu^t), 3.21 (s, 2H, CH_2Py), 3.79 (s, 3H, OCH_3), 6.74 (s, 2H, C_6H_2), 6.96–7.56 (m, 2H, Py-5H and Py-4H), 8.27 (d, $J = 1.5$ Hz, 1H,

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†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Py-2H), 8.41 (dd, $J_1 = 5.0$, $J_2 = 1.5$ Hz, 1H, Py-6H). IR: 1240, 1640, 1665, 1730 cm^{-1}.

2,6-*Di*-tert-*butyl*-4-(3-*pyridylmethyl*)*oxycarbonyl*-6-(3-*pyridylmethyl*)-*cyclohexa*-2,4-*dien*-1-*one* (**3a**).—^{1}H NMR ($CDCl_3$ TMS): δ 0.98 (s, 9H, Bu^t), 1.09 (s, 9H, Bu^t), 2.71 (d, $J = 12.0$ Hz, 1H, CHPy), 3.53 (d, $J = 12.0$ Hz, 1H, CHPy), 5.04–5.38 (m, 2H, CO_2CH_2Py), 7.78–7.76 (m, 6H, 2 × Py-4H, 2 × Py-5H, 2 × C═CH), 8.07–8.67 (m, 4H, 2 × Py-2H, 2 × Py-6H).

Received, 16th January 1998; Accepted, 8th May 1998
Paper E/8/00450A

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