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Efficient Synthesis and Molecular Structure of 2-Hydroxyisophthaldehyde

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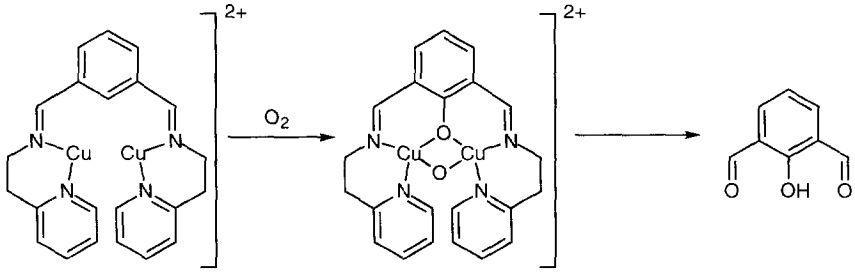
Abstract: A new highly effective procedure has been developed for the preparation of 2-hydroxyisophthaldehyde from 2,6-dimethylphenol. The X-ray crystal structure shows infinite chains of molecules joined by hydrogen bonds. © 1997 Published by Elsevier Science Ltd.

The activation of molecular oxygen by low molecular weight synthetic metal complexes is an area of considerable interest[1]. For instance a number of dinuclear copper complexes have been prepared to mimic proteins such as haemocyanin,[2a] tyrosinase[2b] and dopamine-β-hydroxylase,[2c] whose typical features are binding or activation of molecular oxygen.

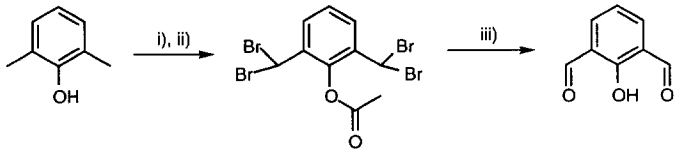
For the construction of biomimetic systems which contain multidentate nitrogen donor ligands, 2-hydroxyisophthaldehyde has been proven to be a very useful building block.[1-3] The synthetic accessability of this dialdehyde, however, is rather limited. Three general routes can be distinguished: (i) The Reimer-Tiemann reaction on phenols has been reported to yield 2-hydroxyisophthaldehyde but only in very low yield, the major product being salicylaldehyde.[4] (ii) A recent methodology is based on a dinuclear copper(I) complex as a tyrosinase mimic prepared by the condensation of isophthaldehyde and two equivalents of 2-aminoethyl-2-pyridine.[5] When this complex is reacted with molecular oxygen in solution, a rapid hydroxylation of the 2-position takes place and after removal of the copper and cleavage of the imine functionality, 2-hydroxyisophthaldehyde is obtained (scheme 1). Drawbacks of this rather lengthy method are the sensitivity of the copper(I) complex to oxygen and water and the usage of the expensive 2-aminoethyl-2-pyridine.



Scheme 1 Synthesis of 2-hydroxyisophthaldehyde via method (ii)

(iii) Previously we have reported a route *via* tetrabromination of 2,6-dimethylphenoxy acetate with bromine followed by acidic hydrolysis.[3] This method however suffers from poor reproducibility, as it is highly dependent on the quality and dryness of the bromine and often gives variable amounts of 5-bromo-2-hydroxyisophthaldehyde as byproduct during the hydrolysis. Here we wish to report a facile three step procedure from 2,6-dimethylphenol with good yields and good reproducibility.

In the first step 2,6-dimethylphenol is acetoxylated using acetylchloride in dichloromethane and triethylamine (Scheme 2). After distillation 2,6-dimethyl acetoxybenzene is obtained in high yield (90%). Bromination with 4 equivalents of N-bromosuccinimide in tetrachloromethane with IR-irradiation[6] overnight gives in 88% yield a yellow solid which is sufficiently pure for the next step. Analytically pure tetrabromide was obtained after one recrystallisation from pentane-dichloromethane.



Scheme 2. i) AcCl, NEt_3, CH_2Cl_2; ii) NBS, CCl_4, IR-irradiation, 6-10 hrs relux. iii) NaOAc, HOAc, 2 days reflux.

Finally, the tetrabromide was hydrolysed to the dialdehyde with simultaneous removal of the acetoxy group by refluxing for two days in acetic acid with excess sodium acetate,[7] which gives the desired product as bundles of long white needles in 72% yield after recrystallisation from water. This procedure was also successfully applied to the synthesis of 5-hydroxyisophthaldehyde from 3,5-dimethylphenol.

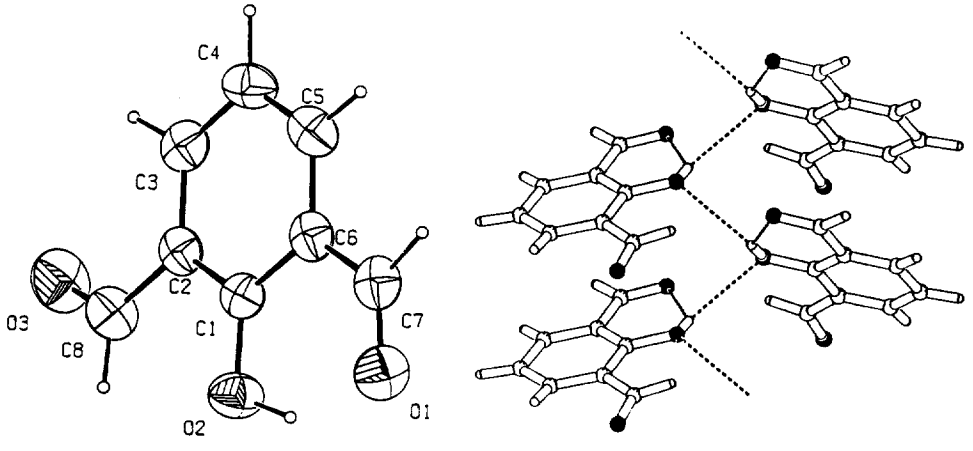


Figure 1a (ORTEP plot of 2-hydroxyisophthaldehyde) and **1b** (crystal packing of 2-hydroxyisophthaldehyde). Selected bond lenghts [Å]: O2-H2 0.94(5), O2-C1 1.345(4), O3-C8 1.203(5), C7-H7 1.05(4), C8-H8 1.02(4); selected bond angles [°]: C1-O2-H2 110(3), O1-C7-C6 124.2(3), O3-C8-C2 124.4(3); selected dihedral angles [°]: H2-O2-C1-C2 168(4), C1-C6-C7-O1 3.2(6), C3-C2-C8-O3 4.2(6).

An X-ray crystal structure analysis of 2-hydroxyisophthaldehyde revealed some interesting features (fig. 1a). Strong intramolecular hydrogen bonding of phenolic H2 with O1 (O1-O2=2.626(4) Å) is observed. An intermolecular hydrogen bond O2-H2...O2 [1/2+x, 1/2-y, -z] joins the molecules into a cooperative linear chain parallel to the z-axis as shown in figure 1b. In conclusion, we have demonstrated a simple, selective and reproducible three-step procedure for the synthesis of the valuable 2-hydroxyisophthaldehyde from 2,6-dimethylphenol with 57% overall yield. Furthermore, this procedure is readily applicable to other dimethyl substituted phenols.

EXPERIMENTAL

2,6-dimethylphenoxy acetate: This compound was prepared from 2,6-dimethyl phenol as described previously.[3]

2,6-(α,α,α',α'tetrabromo)dimethylacetoxybenzene: 3.91 g (0.024 mol) 2,6-dimethylacetoxybenzene and 17 g (0.096 mol) N-bromosuccinimide were refluxed in 100 mL tetrachloromethane under continuous irradiation with an IR lamp until all of the white solids floated on the solution (generally 6-10 h). After hot filtration and evaporation of the volatiles, 10.1 g (0.021 mol, 88%) of the tetrabromo compound was obtained. An analytically pure sample was obtained by crystallisation from CH_2Cl_2/pentane to give cubic white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.51 (s, 3H); 6.63 (s, 2H); 7.44 (t, 1H, J = 8.0 Hz); 7.93 (d, 2H, J = 8.0 Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 20.8; 32.8; 127.7; 131.8; 134.3; 139.8; 167.8. Anal. found (calc.) for $C_{10}H_8O_2Br_4$: C 25.38 (25.03); H 1.72 (1.68); Br 66.02 (66.62). MS (EI): 476 (M^+), HRMS calc 475.726, found 475.726.

2-hydroxyisophthaldehyde: 10.1 g tetrabromide (21.1 mmol) and 21 g sodium acetate were suspended in 100 mL acetic acid and the suspension was heated to reflux for two days. After evaporation of the volatiles, 75 mL H_2O was added followed by extraction with three portions of 100 mL diethylether. The combined water layers were extracted with chloroform. After drying the organic layers on $MgSO_4$, the volatiles were removed and the residue crystallised from H_2O to give 2.26 g (15.1 mmol, 72%) of slightly hygroscopic long white crystals. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (t, 1H, J = 7.6 Hz); 7.98 (d, 2H, J = 7.6 Hz); 10.26 (s, 2H); 11.68 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 119.8; 123.2; 137.4; 163.5; 191.8. Anal. found (calc.) for $C_8H_6O_3$: C 63.59 (64.00); H 4.15 (4.00). MS (EI): 150 (M^+), HRMS calc 150.032, found 150.032.

Crystal data for 2-hydroxyisophthaldehyde. $C_8H_6O_3$ M_r = 150.13, yellow, plateshaped crystal (0.05 × 0.15 × 0.60 mm), orthorhombic, space group $P2_12_12_1$ (no. 19) with a = 3.9416(5), b = 7.5591(9), c = 22.616(3) Å, V = 673.84(5) Å^3, Z = 4, D_x = 1.4499(3) g cm^{-3}, F(000) = 312, μ(Cu Kα) = 9.7 cm^{-1}. 761 Reflections measured, 741 independent, (1.96° < θ < 68.5°, ω/2θ scan, T = 295 K, Cu Kα radiation, Ni filter, l = 1.54184 Å) on an Enraf-Nonius CAD4-F diffractometer on sealed tube. Data were corrected for Lp effects and for a linear decay of 8% of three reference reflections but not for absorption. The structure was solved by automated direct methods (SHELXS96). Refinement on F^2 was carried out by full-matrix least-squares techniques (SHELXL-96); no observance criterion was applied during refinement. Hydrogen atoms were located on a

difference Fourier map and subsequently included in the refinement. Refinement converged at a final *wR*2 value of 0.1341, R1 = 0.0489 (for 617 reflections with $I > 2\sigma(I)$), S = 1.101, for 118 parameters. A final difference Fourier showed no residual density outside -0.23 and 0.25 e $Å^{-3}$. Further details of the crystal structure investigation may be obtained from the Director of the Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB2 1EZ (UK) on quoting the full journal citation.

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