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Facile benzene ring contraction to cyclopentene derivatives during the copper promoted oxidation of phenol with dioxygen

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Abstract

The oxidation of phenol with dioxygen in the presence of copper metal, primary alcohols and pyridine, under mild conditions, produces new compounds deriving from the aromatic ring contraction (alkyl 1-hydroxy-2-oxo-4,5,5-trialkoxycyclopent-3-ene-1-carboxylate **2**) which were characterized by ^{1}H and ^{13}C-NMR. In particular an X-ray study of the methyl derivative is reported.

Keywords: Benzene; Copper; Oxidation; Phenol; Ring contraction

1. Introduction

Copper promoted oxidations of organic substrates have been widely investigated owing to copper's crucial role in important redox-active proteins [1]; particular interest has been shown in dioxygen activation towards aliphatic [2] and aromatic hydroxylated compounds [3], as reaction models for enzymatic systems such as tyrosinase and pyrocathechase oxygenases.

It has been reported in recent years that the interaction of molecular oxygen with phenols can be modulated to ring hydroxylation [3,4], carbon–carbon coupling [5], quinone and iminoquinone formation [4,6] by using different experimental conditions and, particularly, by using copper species in different oxidation states.

In the case of the metal copper promoted oxidation of phenol in the presence of methanol and under mild conditions (typically room temperature, dioxygen pressure = 310 KPa, substrate/copper ratio = 4, methanol/pyridine = 2) 4,5-dimethoxyl-1,2-benzoquinone **1a** was produced in high yield while no other reaction products were detected [5]. However, we report now that by increasing the reaction temperature to 70°C a new, unexpected reaction takes place, namely, aromatic ring contraction, leading to the highly substituted cyclopentenone **2a** (Scheme 1). We have extended this reaction to other primary alcohols generalizing this simple synthesis of alkyl 1-hydroxy-2-oxo-4,5,5-trialkoxycyclopent-3-ene-1-carboxylates (**2**) and elucidated some details of the ring contraction using 4-substituted phenols.

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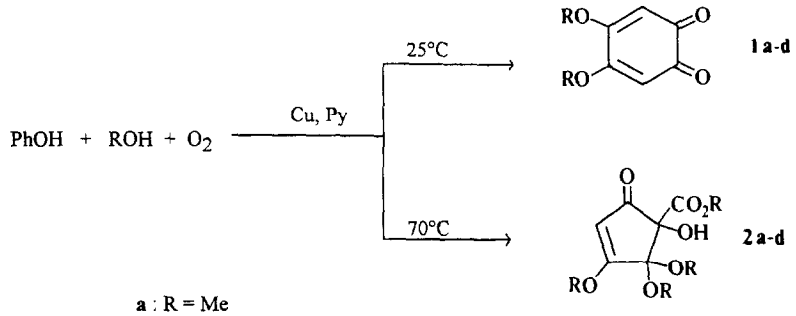


Scheme 1. Oxidation of phenol in the presence of primary alcohols. Reaction conditions: 4 mmol PhOH; 1 mmol Cu powder (200–300 nm); 10 cm^3 ROH–Py 2:1 (v/v); $pO_2 = 310$ kPa.

2. Experimental

2.1. General methods

Phenol, copper derivatives, pyridine and alcohols were of the highest purity grade from Fluka. Gaseous oxygen, from Siad, was 99.99% pure. The copper metal was 99.99% and its particle size 250–310 mesh (about 40–70 μm). ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Bruker 80 MHz spectrometer and ^{13}C-NMR spectra on a Varian 200 MHz spectrometer using spin-echo Fourier transform (SEFT) techniques. MS spectra were recorded on a VG7070-EQ instrument in the electron impact mode (70 eV). Elemental analyses were performed on a Perkin Elmer 2400 analyzer.

2.2. Oxidation procedures

The reactions were carried out in a thermostatted glass reactor (ca. 25 cm^3) provided with an electronically controlled magnetic stirrer connected with a large reservoir (5,000 cm^3) containing oxygen at 310 kPa. Oxygen consumption was measured by a Brooks model 5810 mass-flow meter.

Table 1
Oxidation of phenol in the presence of primary alcohols at 70°C [a]

Entry	Alcohol	Product [b]	Yield (%)
1	MeOH	**2a**	65
2	EtOH	**2b**	62
3	nPrOH	**2c**	58
4	nBuOH	**2d**	57

[a] Reaction conditions: 4 mmol PhOH; 1 mmol Cu powder (200–300 nm); 10 cm^3 ROH–Py 2:1 (v/v); $pO_2 = 310$ kPa.
[b] Satisfactory elemental analyses and ^{1}H-NMR data were obtained.

2.3. Alkyl 1-hydroxy-2-oxo-4,5,5-trialkoxycyclopent-3-ene-1-carboxylates (2)

Phenol (752 mg, 8 mmol) was dissolved in 10 ml of pyridine/alcohol 1:2 (v/v). Copper (127 mg, 2 mmol) was added and the mixture was stirred at 70°C under oxygen (310 kPa) until the gas absorption stopped (ca. 4 h). The solvents were then evaporated in vacuo and the residue was purified by flash chromatography using AcOEt–hexane 7:3 as eluent. Products **2** were obtained in 57–65% yields as reported in Table 1. **2a** (Found: C, 48.81; H, 5.75%; calc. for $C_{10}H_{14}O_7$: C, 48.78; H, 5.73%); ^{1}H-NMR ($CDCl_3/D_2O$) ppm: 3.34(s,3H); 3.38(s,3H); 3.68(s,3H); 3.89(s,3H); 5.49(s,1H). ^{13}C-NMR ($CDCl_3$) ppm: 53.34, 53.73, 54,74, 60.39, 86.56, 103.10, 106.11, 170.50, 183.59, 196.00: IR(KBr) cm^{-1}: 3500(m), 1710(s), 1600(s). m.p. 97°C. **2b** (Found: C, 55.68; H, 7.36; calc. for $C_{14}H_{22}O_7$: C, 55.62; H, 7.34%); ^{1}H-NMR ($CDCl_3/D_2O$) ppm: 1.04–1.55(m,12H); 3.48–3.91(m,4H); 4.01–4.35(m,4H); 5.48(s,1H). ^{13}C-NMR ($CDCl_3$) ppm (selected values): 85.48, 102.03, 107.01, 168.09, 182.02, 194.86. MS (*m/z*) 302, 229,171,143. Oily material. **2c** (Found: C, 60.29;

H, 8.48; calc. for $C_{18}H_{30}O_7$: C, 60.32; H, 8.44%); ^{1}H-NMR ($CDCl_3/D_2O$) ppm: 1.27–1.92(m,20H); 3.68–4.00(m,4H); 4.03–4.50(m,4H); 5.50(s,1H). ^{13}C-NMR ($CDCl_3$) ppm (selected values): 84.72, 100.07, 106.98, 165.89, 181.84, 194.78. Oily material. **2d** (Found: C, 63.69; H, 9.19%; calc. for $C_{22}H_{38}O_7$: C, 63.74; H, 9.24%); ^{1}H-NMR ($CDCl_3/D_2O$) ppm: 0.78–1.27(m,12H); 1.27–2.03(m,16H); 3.70–4.47(m,8H); 5.36(s,1H). ^{13}C-NMR ($CDCl_3$) ppm (selected values): 83.96, 101.94, 105.00, 163.96, 181.86, 195.01. m.p. 108°C.

*2.4. Methyl 1-hydroxy-2-oxo-4,5,5-trimethoxycyclopent-3-ene-1-carboxylate (**2a**) from (**1a**)*

i) 4,5-Dimethoxy-1,2-benzoquinone (672 mg, 4 mmol) was dissolved in 10 ml of pyridine/alcohol 1:2 (v/v). Copper (63 mg, 1 mmol) was added and the mixture was stirred at 25°C under oxygen (310 KPa) until the gas absorption stopped (ca. 4 h). The solvents were then evaporated in vacuo and the residue was purified by flash chromatography using AcOEt–hexane 7:3 as eluent. The product **2a** was isolated in 68% yield.

ii) 4,5-Dimethoxy-1,2-benzoquinone (672 mg, 4 mmol) was dissolved in 10 ml of pyridine/alcohol 1:2 (v/v). Copper(II) chloride dihydrate (170 mg, 1 mmol) was added and the mixture was stirred at 70°C under oxygen (310 kPa) until the gas absorption stopped (ca. 4 h). The solvents were then evaporated in vacuo and the residue was purified by flash chromatography using AcOEt–hexane 7:3 as eluent. The product **2a** was isolated in 65% yield.

*2.5. 5-Methoxy-4-methyl-1,2-benzoquinone (**3a**) and 4,5-dimethoxy-4-methyl-2-hydroxy-2,5-cyclohexadien-1-one (**4a**).*

4-Methylphenol (864 mg, 8 mmol) was dissolved in 10 ml of pyridine/alcohol 1:2 (v/v). Copper (127 mg, 2 mmol) was added and the mixture was stirred at 25°C under oxygen (310 kPa) until the gas absorption stopped (ca. 4 h). The solvents were then evaporated in vacuo and the crude reaction mixture analyzed by ^{1}H-NMR [7]. The **3a**/**4a** ratio was found to be 1:4.

^{1}H-NMR ($CDCl_3$) ppm: **(3a)** 2.14(d,3H,J=1.6 Hz); 3.88(s,3H); 5.74(s,1H); 6.24(q,1H,J=1.6 Hz); **(4a)** 1.51(s,3H); 3.10(s,3H); 3.86(s,3H); 5.67(s,1H); 5.73(s,1H); 6.62(bs,1H,D_2Oexch.)

*2.6. Methyl 1-hydroxy-2-oxo-4,5-dimethoxy-4-methyl-cyclopent-3-ene-1-carboxylate (**5a**)*

The crude mixture of **3a**/**4a** (ca. 1.5 g) was dissolved in 10 ml of pyridine/alcohol 1:2 (v/v). Copper (127 mg, 2 mmol) was added and the mixture was stirred at 25°C under oxygen (310 KPa) until the gas absorption stopped (ca. 4 h). The solvents were then evaporated in vacuo and the residue was purified by flash chromatography using AcOEt–hexane 6:4 as eluent. The product **5a** was isolated in poor yield (8%) as oily material.

^{1}H-NMR ($CDCl_3$) ppm: 1.23(s,3H); 3.14(s,3H); 3.61(s,3H); 3.82(s,3H); 4.00(bs,1H,D_2Oexch.); 5.48(s,1H). ^{13}C-NMR ($CDCl_3$) ppm: 16.74, 53.09, 53.40, 59.08, 81.05, 83.66, 105.05, 170.73, 195.87, 197.70.

*2.7. 4-tert-Butyl-5-methoxy-1,2-benzoquinone (**3b**)*

4-*tert*-Butylphenol (1.2 g, 8 mmol) was dissolved in 10 ml of pyridine/alcohol 1:2 (v/v). Copper (127 mg, 2 mmol) was added and the mixture was stirred at 25°C under oxygen (310 KPa) until the gas absorption stopped (ca. 4 h). The solvents were then evaporated in vacuo and the residue was purified by flash chromatography using AcOEt–hexane 6:4 as eluent. The product **3b** was isolated in 66% yield.

^{1}H-NMR ($CDCl_3$) ppm: 1.13(s,9H); 3.89(s,3H); 5.77(s,1H); 6.29(s,1H).

2.8. 4,5-Dimethoxy-4-tert-butyl-2-hydroxy-2,5-cyclohexadien-1-one (4b)

i) 4-*tert*-Butylphenol (1.2 g, 8 mmol) was dissolved in 10 ml of pyridine/alcohol 1:2 (v/v). Copper (127 mg, 2 mmol) was added and the mixture was stirred at 70°C under oxygen (310 kPa) until the gas absorption stopped (ca. 4 h). The solvents were then evaporated in vacuo and the residue was purified by flash chromatography using AcOEt–hexane 1:1 as eluent. The product **4b** was collected in 69% yield.

ii) 4-*tert*-Butyl-5-methoxy-1,2-benzoquinone **3b** (776 mg, 4 mmol) was dissolved in 10 ml of pyridine/alcohol 1:2 (v/v). Copper (63 mg, 1 mmol) was added and the mixture was stirred at 25°C under oxygen (310 kPa) until the gas absorption stopped (ca. 4 h). The solvents were then evaporated in vacuo and the residue was purified by flash chromatography using AcOEt–hexane 1:1 as eluent. The product **4b** was obtained in 70% yield and it was characterized by ^{1}H-NMR and ^{13}C-NMR.

^{1}H-NMR ($CDCl_3$) ppm: 0.97(s,9H); 3.09(s,3H); 3.79(s,3H); 5.70(s,1H); 5.77(s,1H); 6.53(bs,1H,D_2Oexch.). ^{13}C-NMR ($CDCl_3$) ppm: 27.30, 41.84, 4.09, 56.91, 84.88, 103.53, 114.30, 148.28, 180.09, 183.97.

3. Results and discussion

Phenol reacts smoothly with dioxygen at 70°C in the presence of methanol/pyridine, and the purification of the reaction product by flash chromatography allowed us to obtain pure methyl 1-hydroxy-2-oxo-4,5,5-trimethoxycyclopent-3-ene-1-carboxylate **2a** in 65% yield. By using other primary alcohols such as ethanol, n-propanol and n-butanol, analogous behaviour has been observed and the isolated products, after chromatographic separation, were collected in 57–62% yield (Table 1).

The alkyl 1-hydroxy-2-oxo-4,5,5-trialkoxycyclopent-3-ene-1-carboxylates (**2**) represent new compounds which were characterized by ^{1}H and ^{13}C-NMR spectroscopy and, in particular, the methyl derivative (**2a**) was fully elucidated by the X-ray diffraction study.

Crystal data for **2a**: $C_{10}H_{14}O_7$, $M=246.22$, monoclinic, space group $P2_1c$, $a=12.567(5)$, $b=7.336(3)$, $c=13.453(5)$ Å, $\beta=111.30(2)°$, $U=1155.5(8)$ Å^3, $Z=4$, $D_c=1.415$ g cm^{-3}, $F(000)=520$, nickel-filtered Cu-Kα radiation, $\lambda=1.541838$ Å, $\mu=10.51$ cm^{-1}.

The intensity data were collected on a Siemens AED diffractometer, using the θ–2θ scan technique at room temperature. 2188 unique reflections were measured with θ in the range 3–70°; 1930, having $I>2\sigma(I)$, were used in the refinement. The structure was solved by Patterson and Fourier methods and refined by full-matrix least-squares procedures, with anisotropic thermal parameters in the last cycles of refinement for all non-hydrogen atoms. All hydrogen atoms were clearly localized in the final ΔF map and refined isotropically. The R and R_w values were 0.0646 and 0.0886. Atomic coordinates, thermal parameters and a complete list of bond distances and angles have been deposited at Cambridge Crystallographic Data Centre. See Notice Authors, Issue No. 1.

The molecular structure of **2a** is shown in Fig. 1, together with the atom-numbering scheme and the most significant bond distances and

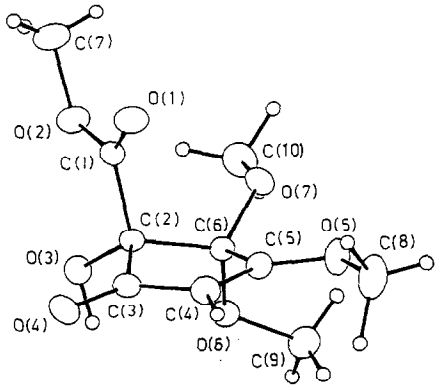
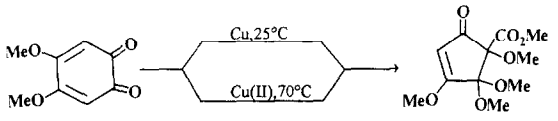


Fig. 1. View of the molecular structure of 2. Selected bond distances (Å) and angles (°): C(2)–C(3) 1.555(2), C(3)–C(4) 1.439(2), C(4)–C(5) 1.349(2), C(5)–C(6) 1.527(2), C(2)–C(6) 1.567(2), C(3)C(2)C(6) 102.2(1), C(2)C(3)C(4) 108.9(1), C(3)C(4)C(5) 109.1(1), C(4)C(5)C(6) 113.4(1), C(5)C(6)C(2) 101.7(1).



1a 2a

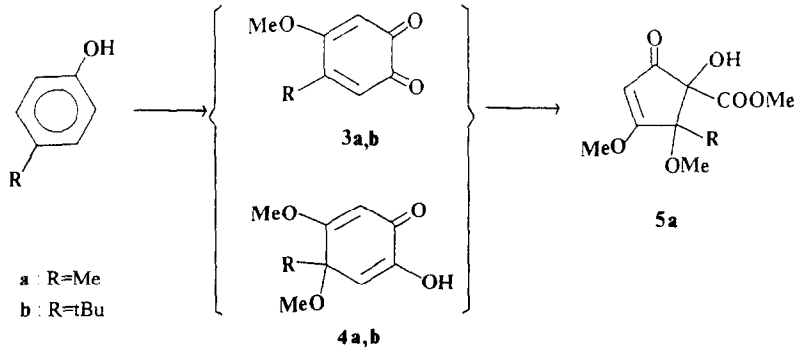
Scheme 2. Oxidation of 4,5-dimethoxy-*o*-quinone **1a** to **2a**. Reaction conditions: 4 mmol of **1a**; 1 mmol of copper species; 10 cm^3 MeOH/Py 1:1 (v/v); $pO_2 = 310$ kPa; reaction time 4 h; yield of isolated product 65–68%.

angles. The cyclopentene ring adopts an envelope conformation with the four C(3)C(4)C(5)C(6) atoms coplanar to within 0.032(1) Å while C(2) is 0.348(1) Å out of this plane. The molecule shows a chiral centre at C(2) and in the crystals both enantiomers are present. Bond distances and angles do not present unusual values. The hydroxyl group exchanges a bifurcated hydrogen bond towards O(6) (intramolecular) and towards a O(4) atom of an adjacent molecule, so forming dimeric units.

It is generally accepted that the oxidative ring cleavage of phenol and catechol leading to *cis,cis*-muconic acid derivatives occurs via *o*-benzoquinone formation [3,8]. By assuming that this step precedes the carbon–carbon bond formation leading to the cyclopentene ring, it is consistent to assume that 4,5-dimethoxy-1,2-benzoquinone **1a** is an intermediate from phenol to **2a**. In fact, by reacting **1a** with dioxygen in methanol/pyridine solution in the presence of either Cu metal or Cu(II) salts we were able to prepare compound **2a** in good yield. However, as shown in Scheme 2, metallic copper promotes the formation of compound **2a** at 25°C whereas $CuCl_2$ does it only at higher temperature (70°C). The observation that **2a** is directly obtainable from phenol in the presence of copper metal at 70°C but not at 25°C (limited time explored 24 h) agrees with the hypothesis that copper in the presence of phenol and dioxygen is rapidly converted to Cu(II) catecholate [9]. This latter compound behaves as an active catalyst for the oxidation of phenol to **1a** at 25°C, but like $CuCl_2$, it is less active than metallic copper for the further transformation of **1a** to **2a**.

In order to elucidate the stereochemistry of the ring contraction, we used substituted phenols as reagents and, in particular, 4-methyl-and 4-*tert*-butyl-phenol.

By reacting 4-methylphenol and methanol under dioxygen at 70°C, we failed to obtain structural information because 4,5-dimethoxy-1,2-benzoquinone **1a** and its cyclopentene derivative **2a** were formed owing to the occurrence of an oxidative displacement of the methyl group. The facile oxidative demethylation of hydroxylated benzenes has been already documented as in the case of 4-methylcatechol with PbO_2 as an oxidant [7]. By decreasing the temperature at 20°C we were able to isolate, after 4 h reaction, a mixture of 5-methoxy-4-methyl-1,2-benzoquinone **3a** and 4,5-dimethoxy-4-methyl-2-hydroxy-2,5-cyclohexadien-1-one **4a** [7] in a 1:4 ratio. When the mixture of these two products is allowed to further react with dioxygen in the presence of copper,



Scheme 3. Stepwise oxidation of 4-methylphenol in the presence of MeOH at 20°C. i) 4 mmol of 4-alkylphenol; 1 mmol of metal copper; 10 cm^3 MeOH/Py 1:1 (v/v); $pO_2 = 310$ kPa; reaction time 4 h; reaction temperature 20°C. ii) The reaction mixture (i) was evaporated under vacuum. The residue was dissolved in 10 cm^3 MeOH/Py 1:1 (v/v) and 1 mmol of copper powder (200–300 nm) was added; $pO_2 = 310$ kPa; reaction time 4 h; reaction temperature 20°C; yield of isolated product **5a** (based on 4-methylphenol) 8%.

methanol and pyridine at 20°C, the expected ring contraction leading to **5a** was observed (even if in low yield) (Scheme 3). From the latter experiment we can derive that most probably **4a** is a reaction intermediate between **3a** and **5a**.

This assumption, related to the ring contraction of the *ortho*-quinone **3a**, agrees with the observation that the ring contraction reported for *para*-quinones and producing similar derivatives requires the presence of an hydroxy group in 2-position [10–12].

Otherwise, by reacting 4-*tert*-butylphenol in pyridine/methanol at 70°C with dioxygen in the presence of metal copper, we obtained 4,5-dimethoxy-4-*tert*-butyl-2-hydroxy-2,5-cyclohexadien-1-one **4b** [13] as a very stable compound which did not undergo a further oxidative transformation into its cyclopentene derivative under our experimental conditions. The same product **4b** was obtained from 4-*tert*-butyl-5-methoxy-1,2-benzoquinone **3b** at 20°C in the presence of metal copper and dioxygen in pyridine/methanol.

From a synthetic point of view, we can outline that the new, facile synthesis of cyclopentenone derivatives **2** from the simple reagent phenol is of relevance due to its possible use as a starting material for the preparation of more complex molecules, particularly those belonging to the prostaglandin family.

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