Synthesis of 5- and 6-Oxoalkanoic Acids by Copper(II)-Catalyzed Oxidative Cleavage of Cycloalkanones with Dioxygen

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α-Substituted cycloalkanones are oxidized to oxo acids by the copper(II)/dioxygen/acetic acid/water system. This catalytic procedure compares well with the previously described systems involving vanadium precursors.

The importance of dioxygen as an oxidizing agent for organic compounds has grown considerably over the past several years. Copper complexes have been extensively investigated as promoters for the activation of dioxygen in chemical and biological systems.[1,2]

The oxidative cleavage of ketones by various oxidizing agents, mainly according to stoichiometric procedures, has been reviewed.[3] The use of catalytic systems is a very efficient means of preparing dicarboxylic acids from cyclic ketones or oxo acids (starting from α-substituted cycloalkanones).[3-7] Nitric acid and a catalytic system consisting of vanadium(V) and copper(II) are used on an industrial scale to prepare adipic acid.[4] The available data,[3,4] do not fully explain the key role of copper(II) in the industrial processes involving nitric acid. Promising results have been obtained with dioxygen and iron(III) chloride.[5] More recently, rather unsophisticated catalyst precursors, heteropolyacids $H_{3+n}[PMo_{12-n}V_nO_{40}] \cdot y\, H_2O$[6] and vanadium(V) oxoalkoxides[6,7] have also been used for the preparation of oxo acids under very mild conditions [T = 60 °C, p (dioxygen) = 10^3 mbar]. An example of oxidative cleavage by a "copper(II)/dioxygen" system has been evidenced with benzylic ketones.[8,9] A mechanistic study of the oxidation of deoxybenzoin in the presence of copper(II) reveals that the diketone is not an intermediate in the formation of benzoic acid.[9] Among the effective catalysts are copper(II)/pyridine[10,11] and copper(II)/phenanthroline.[12] Different systems involving cobalt, manganese or copper as efficient catalysts, have been described for the oxidation of isomers of 2-methylcyclohexanone in kinetic studies, by molecular oxygen at 80–100 °C.[13] In this oxidation, the cobalt and manganese complexes appear to be more efficient. The selectivity of this reaction for oxo acids was higher than that of the uncatalyzed oxidation.

We recently designed a novel catalytic system, "ethylammonium nitrate/water/copper(II) chloride dihydrate/ Q^+Cl^- (Q^+Cl^-: phase transfer agent), to prepare α-chloroketones from the parent carbonyl compounds and observed the oxidative cleavage of open-chain ketones as a side reaction.[14] An oxidation carried out under nearly identical experimental conditions (but in the absence of Q^+Cl^-) with "$R^2_{4-n}R^1_n N^+ NO_3^-$/water/copper(II)/dioxygen" (R^1 = H, R^2 = Et, n = 1; R^1 = H or Et, n = 4) transforms benzylic ketones to acids[14] and α-substituted cycloalkanones to the corresponding oxo acids almost quantitatively, e.g. 2-methylcyclohexanone (**1a**) gives 6-oxoheptanoic acid (**2a**) in 96 % yield. The involvement of onium nitrates led us to look for another efficient and less expensive procedure. As the best preliminary results were obtained with copper(II) salts and dioxygen with a mixed solvent system (acetic acid/water), we used this system for the oxidative cleavage of substituted cycloalkanones.

A solvent effect on the oxidation of **1a** with pure dioxygen and copper(II) nitrate was found (Table 1). Thus, in aqueous media, the conversion reaches only 90 % after 24 hours, moreover the selectivity for **2a** is very high (97 %). With pure acetic acid slightly lower values are obtained. The system copper(II)/acetic acid/water is certainly one of the best for the oxidation of **1a** to **2a** (yield > 90 %). 6-Oxoheptanoic acid can be produced in high yield (96 %), in 4 hours. We would like to emphasize that the copper(II) nitrate is catalytically more reactive than the acetate.

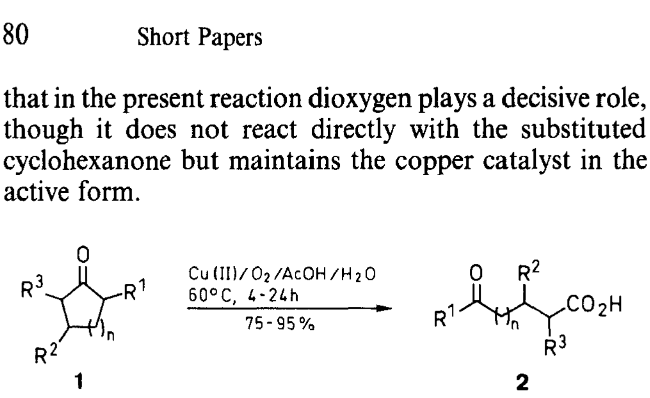
The use of this catalytic system, copper/dioxygen/acetic acid/water was extended to other substituted cycloalkanones with one or two alkyl radicals or a phenyl group (Table 2). Treatment of 2,4-dimethylcyclopentanone (**1b**) gives 3-methyl-5-oxohexanoic acid (**2b**) in high yield. 2-Phenylcyclohexanone (**1c**) produces mainly 5-benzoylvaleric acid (**2c**). Among the byproducts are benzoic acid (5 %) and the 5-benzoylpentanal (6 %).

Other cyclohexanones are also converted in good to fair yields under mild conditions, e.g. 2,6-dimethylcyclohexanone (**1d**) gives 2-methyl-6-oxoheptanoic acid (**2d**) which is the only product of the direct oxidative cleavage of the substrate. (−)-2-Isopropyl-5-methylcyclohexanone, [(−)-menthone, **1e**] reacts similarly, oxidative cleavage proceeding to the extent of 90 %. The yield of (+)-3,7-dimethyl-6-oxooctanoic acid [(+)-6,7-dihydro-6-oxocitronellic acid] (**2e**) is 85 % (Scheme). This synthesis gives a novel possibility of preparing a chiral synthon from a natural product. 6-Oxo-3,7-dimethyloctanal (2 %) is the only byproduct identified.

This result compares well with literature data, e.g the oxidation of (−)-menthone (**1e**) which was reported by Beckmann using chromium(VI) precursors[15] and a vanadium peroxidic complex generated with aqueous hydrogen peroxide.[16] While similar results were obtained with these stoichiometric [chromium(VI)] or catalytic [vanadium(V)/hydrogen peroxide] processes, the copper(II)/dioxygen/acetic acid/water system is a catalytic one using dioxygen.

Usually, the ratio of oxygen uptake to substrate of about 1 (0.90–1) (Table 2) is in favour of a single oxidative cleavage process; subsequent cleavage of the resulting oxo acids does not occur under these conditions.

It has to be emphasized that under identical conditions but in nitrogen the starting ketone is recovered even with a large excess of copper(II) nitrate trihydrate. This means that in the present reaction dioxygen plays a decisive role, though it does not react directly with the substituted cyclohexanone but maintains the copper catalyst in the active form.



1–2	n	R^1	R^2	R^3
a	2	Me	H	H
b	1	Me	Me	H
c	2	Ph	H	H
d	2	Me	H	Me
e	2	*i*-Pr	Me	H

Scheme

This catalytic process is the first example of the selective oxidation of α-substituted cycloalkanones by dioxygen in the presence of a homogeneous copper(II) catalyst, under acidic conditions to afford linear oxo acids. Some of these products have been utilized in the synthesis of macrocyclic lactones.[17-19]

Table 1. Oxidative cleavage of 2-methylcyclohexanone **1a** to **2a** by $Cu(NO_3)_2 \cdot 3H_2O/O_2/AcOH/H_2O$ system at 60°C.[a]

Solvent (mL)	Time (h)	Conversion[b] (%)	Yield[b,c] (%)
H_2O (1.2)	24	90	87
$AcOH/H_2O$ (4 : 1)	24	98	91
$AcOH/H_2O$ (4.5 : 0.5)	4	98	96 (70)[d]
$AcOH/H_2O$ (4.75 : 0.25)	8	97	93
AcOH (4.5)	24	80	76
$AcOH/H_2O$ (4.5 : 0.5)	24	75[e,f]	60

[a] The reaction was carried out in an all glass reactor vessel equipped with a gas burette system.

[b] Conversion and yield [based on **1a** (17.6 mmol)] are determined by GC.

[c] Product was analysed by GC/MS, ^1H and ^{13}C NMR spectroscopy.

[d] The yield given in parenthesis refers to pure isolated product [the reaction was carried out in a 2-necked flask equipped with a gas inlet for O_2 (14 L/h)].

[e] $Cu(OAc)_2 \cdot H_2O$ was used as the catalyst precursor.

[f] The conversion was not improved by increasing the temperature to 80°C.

The interest in this catalysis oxidation takes advantage of the remarkable ability of copper(II) to react in a low Brönsted acidic medium, especially in an inexpensive solvent. This catalytic procedure compares well with the previously described systems involving vanadium catalysts.[6,7]

Further studies on other substrates and complexes are in progress. Attempts to understand the mechanism of catalytic oxidation of cycloalkanones with dioxygen are also under way. The possibilities are a radical chain process[1] and/or the formation of peroxy intermediates.

The reaction mixtures were analysed by GC (Girdel 30 and Girdel 330 FID apparatus). The columns were 3 % OV-17 on Chromosorb Q (3 m) and OV-1701 (capillary column 50 m), with N_2 or He as carrier gas. The main parameters for the GC analysis are: initial temperature 70°C; final temperature 210°C; carrier 20 mL/min; injector temperature 150°C; detector temperature 220°C. Peaks were identified by comparison of retention times with authentic samples and by GC/MS analysis. Mass spectra were obtained at 70 eV using a Kratos MS 50 spectrometer with a DS 55 data system. ^1H NMR and ^{13}C NMR spectra were recorded on a Fourier transform apparatus (Bruker) at 200 MHz with $CDCl_3$ as solvent.

$Cu(NO_3)_2 \cdot 3H_2O$ (Prolab), $Cu(OAc)_2 \cdot H_2O$ and AcOH (SDS) were used as received. 2-Methylcyclohexanone (**1a**), 2,4-dimethylcyclopentanone (**1b**), 2-phenylcyclohexanone (**1c**), 2,6-dimethylcyclohexanone (**1d**) and 2-isopropyl-5-methylcyclohexanone (**1e**) were obtained from Aldrich.

The typical experiment was performed in an all glass reactor vessel (40 mL) which was attached to a vacuum line with a manometer and a gas inlet. The reaction vessel was charged at atmospheric pressure and heated in an oil bath (50–80 ± 0.5°C). O_2 uptake can be determined using a gas burette system. The reaction mixture (dark blue solution) was analysed by GC using an internal standard (300 μL of heptanoic acid).

Oxidation of Cycloalkanones to Oxo Acids; General Procedure:
A 2-necked flask equipped with a Teflon-coated magnetic bar stirrer was charged with $Cu(NO_3)_2 \cdot 3H_2O$ (314 mg, 1.2 mmol) and $AcOH/H_2O$ (10 mL, 9: 1) and the mixture was stirred under O_2 at 20°C for 5 min. The appropriate cycloalkanone **1** (16–20 mmol) was added and pure O_2 (14 L/h) was then introduced through a gas inlet. The flask was immersed in a bath preheated to 60°C, and the resultant homogeneous blue mixture was vigorously stirred at this temperature for the prescribed time (see Tables 1 and 2) in the presence of pure O_2. After evaporation of $AcOH/H_2O$ mixture, Et_2O (30 mL) was added to the oily residue. The solution thus obtained was extracted with aq sodium bicarbonate (10%) (2 × 20 mL). The sodium salt of the oxo acid passed into the aqueous

Table 2. Catalytic Oxidation of **1** to **2** by $Cu(II)/O_2/AcOH/H_2O$ System[a]

Cycloalkanone	Time (h)	mmol of O_2 absorbed/ mmol of substrate	Conversion[b] (%)	Product[c]	Yield[d] (%)	mp (°C) or bp (°C)/Torr	
						found	reported
1a	4	0.90	98	**2a**	96 (70)	160–162/2	34–35[23]
1b	6	0.72	95	**2b**	91 (65)	114/0.5	114/5[20]
1c	4	0.90	92	**2c**	80 (60)	77–78	77–78[21]
1d	24	0.98	80	**2d**	77 (60)	139–141/2	130/1[24]
1e	24	1	90	**2e**	85 (62)	174–176/2	–[e]

[a-d] see Table 1.

[e] $[\alpha]_D^{25}$ + 10° (c = 0.05, $CHCl_3$) {Lit.[22] $[\alpha]_D^{20}$ + 11.3° (neat)}.

layer which was washed with Et_2O (2 × 10 mL) and then acidified to pH 1 with HCl (12.5 N). NaCl was added to the resultant mixture until saturation. The combined aqueous solution was extracted with Et_2O (2 × 30 mL) and the ethereal layer was concentrated to afford *the oxo acid after distillation.*

(1) Capdevielle, P.; Maumy, M. *l'Actualité Chimique*, April **1986**, 5.

(2) Sigel, H. *Metal Ions in Biological Systems*; Marcel Dekker: New York, 1989; Vol. 12.

(3) Sheldon, R.A.; Kochi, J.K. *Metal – Catalyzed Oxidations of Organic Compounds;* Academic: New York, 1981, p 345, 363.
Hudlicky, M. *Oxidations in Organic Chemistry*; ACS Monograph 186: Washington, 1990, p 186.
Mijs, W.J.; De Jonge, C.R.H.I. *Organic Synthesis by Oxidation with Metal Compounds*; Plenum: New York and London, 1986, p 1.

(4) Danly, D.E.; Campbell, C.R. *Kirk–Othmer Encyclopedia of Chemical Technology*; Grayson, M., Ed.; Wiley: New York, 1978, Vol. 1, p 510.

(5) Ito, S.; Matsumoto, M. *J. Org. Chem.* **1983**, *48*, 1135.

(6) Brégeault, J.-M.; El Ali, B.; Mercier, J.; Martin, J.; Martin, C. *C.R. Acad. Sci. Paris*, série II, **1988**, *307*, 2011.
El Ali, B.; Brégeault, J.-M.; Mercier, J.; Martin, J.; Martin, C.; Convert, O. *J. Chem. Soc., Chem. Commun.* **1989**, 825.

(7) Hirao, T.; Mori, M.; Ohshiro, Y. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2399.

(8) Jallabert, C.; Lapinte, C.; Rivière, H. *J. Mol. Cat.* **1982**, *14*, 75.

(9) Sayre, L.M.; Jin, S-J. *J. Org. Chem.* **1984**, *49*, 3498.

(10) Saitova, M.A.; Komissarov, V.D. *Kinet. Catal.* **1972**, *13*, 496.

(11) Charman, H.B. *Brit. Patent* 1114885 (1968); *Chem. Abstr.* **1968**, *69*, 51616.

(12) Sakharov, A.M.; Skibida, I.P. *Bull. Acad. Sci. USSR, Div. Chim. Sci.* **1980**, *29*, 344; *Chem. Abstr.* **1980**, *93*, 70561.

(13) Serov, V.V.; Syroezhko, A.M.; Proskuryakov, V.A.; Potekhin, V.M. *Zh. Prikl. Khim.* **1975**, *48*, 252; *Chem. Abstr.* **1975**, *82*, 155220.
Serov, V.V.; Syroezhko, A.M.; Potekhin, V.M.; Proskuryakov, V.A. *Zh. Prikl. Khim.* **1976**, *49*, 855; *Chem. Abstr.* **1976**, *85*, 62428.
Serov, V.V.; Syroezhko, A.M.; Proskuryakov, V.A.; Potekhin, V.M. USSR Patent 487062 (1975); *Chem. Abstr.* **1976**, *84*, 4677.

(14) Atlamsani, A.; Brégeault, J.-M. *New J. Chem.* **1991**, *15*, 671.
Atlamsani, A.; Brégeault, J.-M., results to be published; Atlamsani, A. *Doctoral Thesis*, Université P. et M. Curie, Paris, 1991.

(15) Beckmann, E. *Liebigs Ann. Chem.* **1889**, *250*, 329.

(16) Treibs, W. *Ber. Dtsch. Chem. Ges.* **1932**, *72*, 1194.

(17) Stille, J.K.; Tanaka, M. *J. Am. Chem. Soc.* **1987**, *109*, 3785.

(18) Carvalho, C.; Cullen, W.R.; Fryzuk, M.D.; Jacobs, H.; James, B.R.; Kutney, J.P.; Piotrowska, K.; Singh, V.K. *Helv. Chim. Acta* **1989**, *72*, 205.

(19) Ngooi, T.K.; Scilimati, A.; Guo, Z-W.; Charles, J.S. *J. Org. Chem.* **1989**, *54*, 911.

(20) Carroll, F.I.; Mitchell, G.N.; Blackwell, J.T.; Sobti, A.; Meck, R. *J. Org. Chem.* **1974**, *39*, 3890.

(21) Fieşer, L.F.; Szmuszkovicz, J. *J. Am. Chem. Soc.* **1948**, *70*, 3352.

(22) Klein, E.; Rojahn, W. *Dragoco Rep. (Ger. Ed.)* 1977, *24*, 55; *Chem. Abstr.* **1977**, *87*, 23525.

(23) Dictionary of Organic Compounds; Chapman & Hall: London, Vol. 4, 1982.

(24) Fujisawa, T.; Sato, T.; Kawara, T.; Noda, A. *Tetrahedron Lett.* **1982**, *31*, 3193.