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Oxidative Cleavage of 2-Substituted Cycloalkane-1,3-diones and of Cyclic β-Ketoesters by Copper Perchlorate / Oxygen.

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Key Words: *2-Substituted cycloalkane-1,3-dione, cyclic β-ketoester, copper perchlorate hexahydrate, oxygen, oxidative cleavage, (ω-1), ω-dioxocarboxylic acids, (ω-1)-oxoalkanedioic acids monoesters.*

Abstract: *A preparative method for the synthesis of (ω-1), ω-dioxocarboxylic acids and (ω-1)-oxoalkanedioic acids monoesters by respective oxidative cleavage of 2-substituted cycloalkane-1,3-diones and cyclic β-ketoesters, by copper perchlorate in acetonitrile in an oxygen atmosphere, is reported.*

The oxidative cleavage of ketones by various oxidizing agents, mainly according to stoichiometric procedures has been reviewed [1]. Catalytic oxidation of ketones have also been realized. In the case of cyclic ketones, the catalytic oxidative cleavage furnished an efficient method of preparing dicarboxylic acids or oxoacids. For example, cyclohexanone was oxidized to adipaldehydic acid with air or oxygen in an aqueous solution containing a copper halide and an acid or a base as a catalyst [2]. Oxoacids were obtained when α-alkyl substituted cyclohexanones were treated with molecular oxygen in the presence of Cu (II) and Cu (I) stearates [3] or copper salts of saturated carboxylic acids [4] or, more recently by the copper (II)/ dioxygen/ acetic acid/ water system [5]. Furthermore, different systems involving Co [3], Mn [3], Fe [6], V [7], Mo [8] as efficient catalysts have been described for the oxidation of methylcyclohexanones with molecular oxygen. In the case of 1,2-diketones, it has been shown that the mechanism as well as the composition of the products obtained depended on the reaction conditions. For instance when singlet oxygen is used in the presence of fluoride anion, 4-oxopentanoic acid was the main product of oxidation [9]. Similarly 3,3-dimethyl-5-oxohexanoic acid was formed from 3,5,5-trimethylcyclohexane-1,2-dione using an excess of hydrogen peroxide in an alkaline medium [10]. More generally oxocarboxylic acids can be obtained as major products when alkyl substituted cyclohexane-1,2-diones were treated by copper (II) chloride and oxygen [11].

With the intention of obtaining (ω-1), ω-dioxocarboxylic acids, 2-alkyl cyclohexane-1,3-diones were treated by copper salts such as $CuCl_2$, 2 H_2O, $CuSO_4$, 5 H_2O, $Cu(OAc)_2$, H_2O or $Cu(ClO_4)_2$, 6 H_2O in the presence of oxygen in acetonitrile. The best yields in (ω-1), ω-dioxocarboxylic acids were obtained when $Cu(ClO_4)_2$, 6 H_2O was used [12]. Furthermore, the treatment of cyclic β-ketoesters by using the system $CuClO_4$, 6 H_2O / O_2 led to the formation of the corresponding (ω-1)-oxoalkanedioic acids monoesters in good yields. The results are reported in the Table.

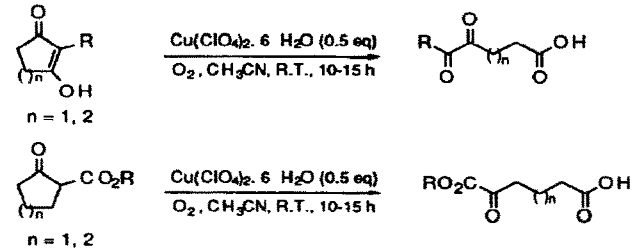
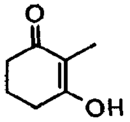
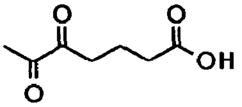
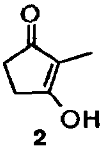
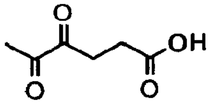
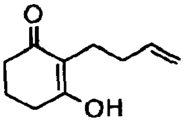
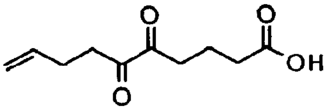
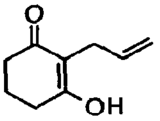
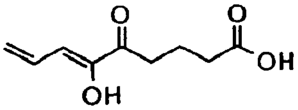
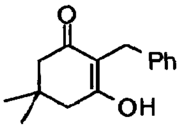
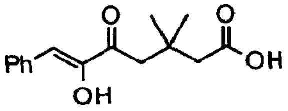
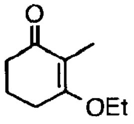
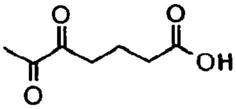
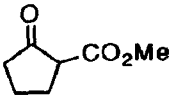
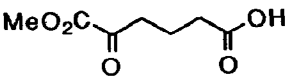
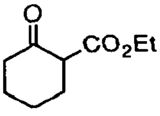
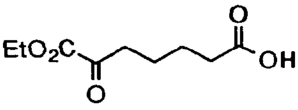
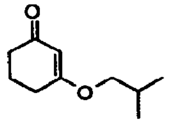


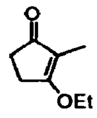
Table: Oxidation of 2-substituted cycloalkane-1,3-diones and of cyclic β-ketoesters

Starting Material	Isolated Product (Yield %)
 **1**	 **9** (96%)
 **2**	 **10** (92%)
 **3**	 **11** (95%)
 **4**	 **12** (50%)
 **5**	 **13** (47%)
 **6**	 **9** (45%)
 **7**	 **14** (95%)
 **8**	 **15** (90%)

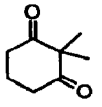
When 2-methylcyclohexane-1,3-dione **1** was treated with O_2 in the presence of $Cu(ClO_4)_2$, $6 H_2O$ in acetonitrile at room temperature overnight, **9** was isolated with a yield of 96 %. In contrast cyclohexane-1,3-dione led to a mixture of unidentified products under the same conditions. The reaction was general as **2** - **5** were transformed to **10** - **13** respectively. Treatment of **6** under the same conditions furnished compound **9** in 45 % yield. In contrast, the vinylethers **16** and **17** as well as the 2,2-dimethylcyclohexane-1,3-dione **18** stayed unchanged under the above conditions.



16



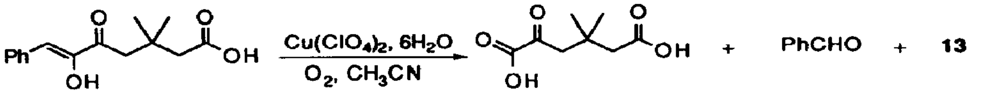
17



18

These results indicate that only **enolized 1,3-diones** could be oxidized to the corresponding ketoacids. Unlike 3-ethoxycyclohex-2-en-1-one **6**, 3-isobutoxycyclohex-2-en-1-one **16** and 3-ethoxycyclopent-2-en-1-one **17** are stable synthons which can not be easily hydrolyzed [13] to the corresponding 1,3-diones and therefore could not be oxidized.

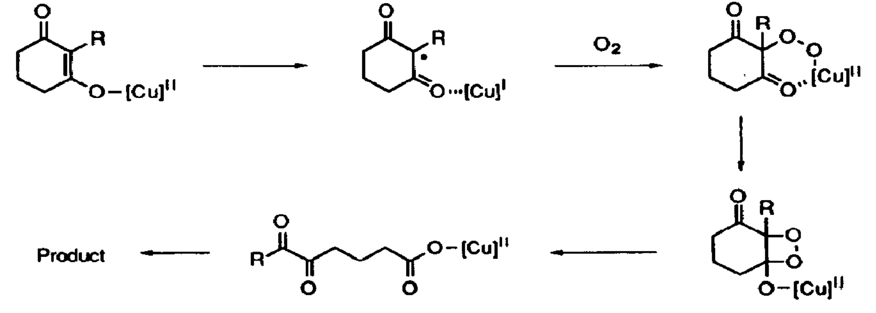
We have to point out that the low yield in compounds **12** and **13** is due to their subsequent enolization. For example treatment of **13** by oxygen in the presence of $Cu(ClO_4)_2$, $6 H_2O$ led to the formation of the corresponding diacid **19** and to the formation of benzaldehyde **20**.



13 **19** (21%) **20** (20%) (55%)

The reaction could be extended to 1,3-dicarbonyl compounds such as β-ketoesters. When **7** and **8** were treated with O_2 in the presence of $Cu(ClO_4)_2$, $6 H_2O$ products **14** and **15** were respectively obtained in good yield. These results could be explained by the fact that the β-ketoesters were slightly enolized.

A possible mechanism for the oxidative cleavage of the 2-substituted cycloalkane-1,3-diones is shown in the scheme which is inspired from that proposed by Brackman and Volger for the oxidation of aldehydes with O_2 [14]. The first step involves a Lewis coordination of the enol with Cu(II). The reaction with oxygen generates a peroxide which undergoes cyclization to a dioxetane. This intermediate undergoes a [2 + 2] cycloreversion with formation of the corresponding (ω-1), ω-dioxocarboxylic acid. This mechanism can also be applied to enolized β-ketoesters.



We have shown that 2-substituted cycloalkane-1,3-diones can be transformed easily to the corresponding (ω-1), ω-dioxocarboxylic acid. Similarly cyclic β-ketoesters can be cleaved oxidatively into (ω-1)-oxoalkanedioic acids monoesters in high yields in the presence of oxygen and copper perchlorate hexahydrate.

General procedure

To a stirred solution of β-diketone (β-ketoester) (4 mmol, 1eq) in acetonitrile (20 mL) saturated with O_2 was added $Cu(ClO_4)_2$, 6 H_2O (0.74 g, 2mmol, 0.5 eq). After 12 h under an O_2 atmosphere at room temperature, the solvent was evaporated. An aqueous saturated solution of NH_4Cl (30 mL) was added to the residue. The resulting aqueous solution was extracted with ethyl acetate (5 x 20 mL) and the organic phases were dried ($MgSO_4$), filtered and evaporated. CH_2Cl_2 was added to the crude material. The solution was filtered on Celite and evaporated. The product can be purified by flash chromatography if necessary.

Acknowledgement

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a) ERASMUS student from Universitá Statale di Milano.

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