Synthesis of α-Haloadipic Acids from 1,2-Cyclohexanedione

E.K. Starostin, A.A. Mazurchik, A.V. Ignatenko, G.I. Nikishin*

N.D. Zelinsky Institute of Organic Chemistry, USSR Academy of Sciences, 117913, Leninsky Prospekt 47, Moscow, Russia

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A preparative method for the synthesis of α-haloadipic acids **4a–c** by oxidative cleavage of 1,2-cyclohexanedione (**1**) in copper(II) halide/hydrogen peroxide or copper(II) halide (catalyst)/alkali metal halide/hydrogen peroxide system is reported.

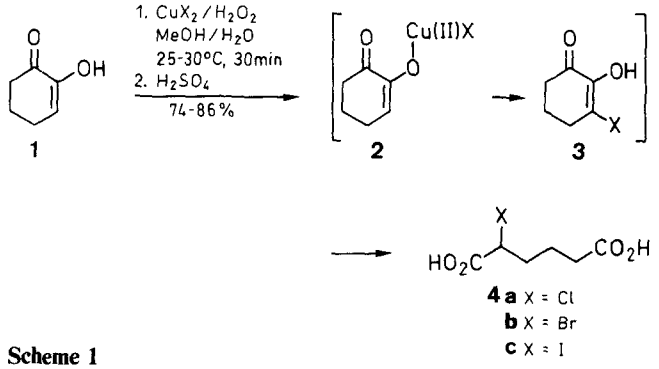
α-Chloro- and α-bromoadipic acids are considered as useful reagents in organic synthesis. The well-known methods of their production include, as the key steps, halogenation of adipic acid halides and esters,[1–3] and oxidation of α-chloro- or α-bromocyclohexanone with nitric acid.[4] However yields of the target products were low.

In this paper we report a new method for the synthesis of α-haloadipic acids based on oxidative cleavage of 1,2-cyclohexanedione (**1**).

The oxidative cleavage of 1,2-diketones by hydrogen peroxide has been investigated in detail.[5] Previously it has been shown that the mechanism of oxidation of **1** and the composition of the products obtained depend on the reaction conditions and the oxidizing system. Thus, by oxidation of **1** with singlet oxygen in the presence of the fluoride ion, mainly 4-formylbutyric acid was formed.[6] 3,5,5-Trimethyl-1,2-cyclohexanedione was oxidized in a weakly alkaline medium to 3,3-dimethyl-5-oxohexanoic acid.[7] Oxidation of alkyl-substituted 1,2-cyclohexanediones with copper(II) chloride/oxygen system led to a mixture of products with oxocarboxylic acids as the major product.[8] As a rule, these reactions are accompanied by evolution of carbon monoxide.

In this study we have found that oxidation of **1** with an aqueous solution of 30% hydrogen peroxide in the presence of copper halides in neutral medium at pH ≃ 7, α-halogenated adipic acids **4** were formed in 74–86% yield. Conversion of **1** was about 95%. The reaction proceeded with both stoichiometric and catalytic amounts of copper halides. With catalytic amounts of copper halides potassium and sodium halides were used as a source of halide ions. In the presence of other copper salts, e.g. sulfate, nitrate, acetate and cyanide, 1,2-cyclohexanedione (**1**) practically does not react with hydrogen peroxide. Apparently the formation of a chelate **2** (Scheme 1) takes place initially with its further transformation into 3-halo-1,2-cyclohexanedione **3**, the latter being oxidized to **4a–c** under the reaction conditions.

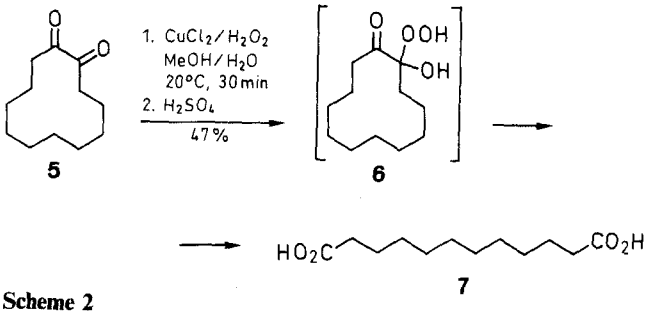
Ketones react easily with copper(II) halides to form the corresponding α-halo ketones.[9,10] Compound **3a** was obtained in 27% yield upon interaction of **1** with an aqueous solution of copper(II) chloride. The control experiment showed that in the absence of copper halides **3a** practically did not react with aqueous hydrogen peroxide. Probably, **1** was oxidized by the copper halide/hydrogen peroxide system into adipic acid with subsequent halogenation to form the product **4**. However under these conditions no reaction of adipic acid was



Scheme 1

observed. Complex **2** was not detected, though the formation of similar chelate α-dicarbonyl complexes with copper(II) chloride was supposed to take place,[8,11] and a corresponding cobalt(II) complex with 1,2-cyclohexanedione was isolated.[12]

Unlike 1,2-cyclohexanedione (**1**), the macrocyclic dione **5** could be oxidized to 1,12-dodecanedioic acid **7** by the copper(II) chloride/hydrogen peroxide system. Such a distinction in reaction products results from the different mechanism of the reactions. In contrast to **1**, **5** is almost not enolized and reacts with hydrogen peroxide yielding α-hydroxy, α-hydroperoxide **6**, which is further decomposed by copper(II) chloride with formation of **7** (Scheme 2).



Scheme 2

Table. Synthesis of α-Haloadipic Acids

Product	Method	Yield (%)	mp (°C)	Molecular Formula or mp (°C)
4a	A	85	101–103	104–105[15]
	B	80		
4b	A	77	124–125	125–127[2]
	B	74		
4c	A[a]	86	131–133	$C_6H_9IO_4$[c] (272.0)
	B[b]	78		

[a] $CuSO_4 \cdot 5H_2O$ (10 mmol) and NaI (10 mmol) were used.
[b] $CuSO_4 \cdot 5H_2O$ (1 mmol) and NaI (10 mmol) were used.
[c] calc. C 26.49 H 3.33 I 46.65
found 26.31 3.29 46.82.
^1H NMR (CD_3OD): δ = 1.5–2.1 (m, 4 H, CH_2CH_2), 2.35 (t, 2 H, J = 7 Hz, CH_2CO_2H), 4.5 (dd, 1 H, J = 7, 3 Hz, CHI), 9.0 (s, 1 H, CO_2H).

The formation of **6** as a result of interaction of **5** with hydrogen peroxide in the absence of copper(II) halide, was proved by ^1H and ^{13}C NMR spectroscopy. Earlier, it has been shown that decomposition of α-hydroperoxy-, α-hydroxycycloalkanes proceeded smoothly in the presence of copper halides.[13,14]

^1H and ^{13}C NMR spectra were recorded with a Bruker AC-200. 1,2-Cyclohexanedione (**1**) used is a commercial reagent. 1,2-Cyclododecanedione (**5**) was obtained according to the previously described procedure.[16]

α-Chloroadipic Acid (4a); Typical Procedures:
Method A: 1,2-Cyclohexanedione (**1**; 5.6 g, 50 mmol), MeOH (10 mL), H_2O (40 mL) and $CuCl_2 \cdot 2H_2O$ (17.1 g, 100 mmol) were placed into a round-bottom flask equipped with mechanical stirrer, dropping funnel and a thermometer. Under intensive stirring H_2O_2 (30%, 25 mL) was added, keeping the temperature at 25–35 °C by cooling in a water-bath. When the addition was complete, the solution was acidified with 2N H_2SO_4 (2 mL) to pH ≃ 2 and extracted with Et_2O (5 × 70 mL). The Et_2O solution was treated with a sat. solution of $NaHCO_3$ (50 mL). The Et_2O layer was separated, dried ($MgSO_4$). Evaporation of Et_2O gave the unreacted 1,2-cyclohexanedione. The aqueous layer was acidified with 2 N H_2SO_4 (50 mL) to (pH ≃ 2) and extracted with Et_2O (5 × 70 mL). The Et_2O layer was separated and dried ($MgSO_4$). The solvent was evaporated, and the isolated product recrystallized from benzene/EtOH mixture (6:1).

Method B: 1,2-Cyclohexanedione (**1**; 5.6 g, 50 mmol), MeOH (10 mL), H_2O (40 mL), $CuCl_2 \cdot 2H_2O$ (1.71 g, 10 mmol) and NaCl (5.85 g, 100 mmol) were placed into a round-bottom flask equipped with mechanical stirrer, dropping funnel and a thermometer. Under intensive stirring H_2O_2 (30%, 25 mL) was added. The workup procedure was similar to that described above.

3-Chloro-1,2-cyclohexandione (3a):
1,2-Cyclohexanedione (**1**; 5.6 g, 50 mmol) was added to a solution of $CuCl_2 \cdot 2H_2O$ (17.1 g, 100 mmol) in H_2O (50 mL) and stirred for 4 h at 35 °C. The mixture was extracted with Et_2O (5 × 70 mL). The extract was dried ($MgSO_4$) and the solvent evaporated. The product was chromatographed on silica gel (eluent: hexane/EtOH, 3:1) to give the product **3a**; yield 2.2 g (27%); mp 119–120 °C (Lit.[9] mp 118–119 °C).

1,12-Dodecandioic Acid (7):
H_2O_2 (6.0 mL, 30%) was added to a stirred solution of 1,2-cyclododecanedione (**5**; 0.6 g, 3.06 mmol), $CuCl_2 \cdot 2H_2O$ (1.2 g, 6.8 mmol) in H_2O (2.0 mL) and MeOH (10 mL) at r.t. The mixture was stirred for 2 h and acidified with 2N H_2SO_4 (pH ≃ 2) and extracted with Et_2O (4 × 50 mL). The Et_2O solution was washed with sat $NaHCO_3$ solution, the solvent evaporated to recover the unreacted 1,2-cyclododecanedione (**5**) (0.26 g, 1.3 mmol). The aqueous layer was acidified with 2N H_2SO_4 (pH ≃ 2) and extracted with Et_2O (4 × 50 mL). Et_2O was evaporated to afford 1,12-dodecanedioic acid (**7**); yield: 0.33 g (47%); mp 125 °C (Lit.[17] mp 125–126.5 °C).

2-Hydroperoxy-2-hydroxycyclododecanone (6):
H_2O_2 (1.0 mL, 4% solution in Et_2O, 1.0 mmol) was added to 1,2-cyclododecanedione (**5**; 0.19 g, 1.0 mmol), and the mixture was kept for 8 h at r.t. Et_2O was evaporated to furnish the product **6**; yield: 0.2 g (87%). This peroxide is stable against mechanical friction.

^1H NMR (CD_3OD): δ = 1.1–1.7 (m, 16H), 2.22 (t, 2H, J = 7.5 Hz), 2.43 (t, 2H, J = 7.6 Hz).

^{13}C NMR ($CDCl_3$): δ = 21–26 [8 t, $(CH_2)_8$], 29.0 (t, CCOH), 30.6 (t, CC=O), 105.4 (s, COH), 208.83 (s, C=O).

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