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Stereoselective electrochemical transformation of 4-substituted cyclohexanones into *cis*-5-substituted-2,2-dimethoxycyclohexanols

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Abstract—Electrolysis of 4-substituted cyclohexanones in methanol in the presence of sodium halides in an undivided cell results in the stereoselective formation of *cis*-5-substituted-2,2-dimethoxycyclohexanols in 70–80% yield.

The oxidation of ketones is a method for preparing carboxylic acids, α-hydroxyketones, diketones and other useful intermediates in organic synthesis.[1] The formation of adipic acid from cyclohexanone is an important industrial process. α-Hydroxyketones are significant 'building blocks' in the construction of natural products and fine chemicals.[2–5]

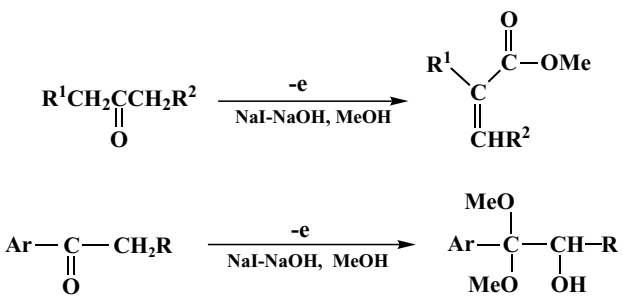
The advance of electrooxidation in recent years has provided organic chemists with a new versatile synthetic device of great promise.[6] Despite the long history of the electroorganic chemistry, most of the electroorganic reactions that could provide product selectivity have been developed only within the last 20 years. However, in the case of the electrochemical oxidation of ketones, only rare examples of the procedures, which could ensure product selectivity, are known. Moreover, little, if any, is known about the stereoselective electrochemical oxidation of ketones.

The direct electrochemical oxidation of ketones led to the formation of a mixture of acids, saturated and unsaturated hydrocarbons, carbon monoxide and dioxide.[7–10] Remote non-selective oxidative functionalization of aliphatic ketones was observed when electrooxidation was carried out in acetonitrile or trifluoroacetic acid as a result of the subsequent transformation of the initially produced cation radical $R^1R^2C{=}O^{\bullet+}$.[11,12]

In some oxidative transformations of ketones, such as in the haloform reaction, the α-halogenation of ketones is the key step.[13] So for certain cases, the selective indirect electrooxidation of ketones with electrochemically generated halides is possible. Thus, the electrocatalytic variant of the haloform reaction, a procedure to prepare carboxylic acid esters by the electrooxidation of methyl alkyl and methyl aryl ketones in methanol in the presence of alkali metal bromides, is well known.[14]

The use of the mediatory system NaI–NaOH for the indirect electrooxidation of carbonyl compounds is also known. It was employed for the electrooxidation of aldehydes[15] and cyclic ketones.[15,16]

Continuing our studies on the electrooxidation of ketones,[17–19] we have recently accomplished the indirect electrochemical oxidation of aliphatic ketones into unsaturated conjugated esters[20] and aryl alkyl ketones[21] into α-hydroxyketals in the presence of the NaI–NaOH system (Scheme 1).



Scheme 1.

Keywords: electrochemical reactions; stereoselectivity; cyclohexanones.

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Now we report our results on the new stereoselective indirect electrochemical transformation of 4-substituted cyclohexanones **1a–d** into *cis*-α-hydroxyketals **2a–d**, in methanol, in an undivided cell in the presence of sodium halides as mediators (Table 1).

The reactions on electrodes, which take place during the process, are usual for the mediatory system NaI–NaOH in methanol and lead to the formation of iodine or bromine at the anode and methoxide anions at the cathode.[20,21]

Then α-monohalogenation of the enol form of the ketone takes place in the solution in the same manner as it has previously been established for cyclic[16] and aliphatic ketones (Scheme 2).[20]

In the presence of methoxide anions there is an equilibrium between the two possible isomers of α-halogenoketone **3** possessing either an axial or an equatorial halogen.

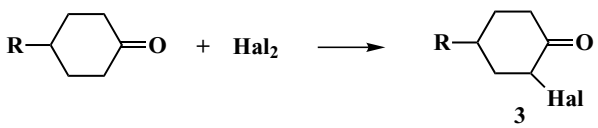
α-Halogenoketone **3** thus formed, undergoes reversible methoxy anion attack on the carbonyl group with a further intramolecular nucleophilic substitution of the halogen and subsequent cyclization to form epoxide **4** (Scheme 3).[16,22]

It should be mentioned that the substituent R in all possible isomers of anion **A** presumably exists in the equatorial position. It has been established earlier that the isomer with both an axial halogen and a hydroxy anion substituent undergoes faster cyclization into the *cis*-epoxide **4**.[23,24] *cis*-Epoxide **4** exists in the form of a distorted chair with axial and equatorial epoxide C–O bonds.[25,26] Thus, in the resulting *cis*-epoxide **4** both R and MeO substituents are equatorial, the O–C(OMe) bond is axial and the O–C(H) bond is equatorial.[25,27]

The following attack on *cis*-epoxide **4** by the second methoxide anion resulted in the formation of ketal **2** with both the R and OH substituents equatorially orientated, i.e. leads to *cis*-5-substituted-2,2-dimethoxycyclohexanols **2** (Scheme 3).[27,28] Thus, kinetic and thermodynamic products coincide in the reaction studied.

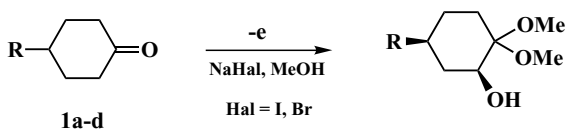
The structures of **2a–d** were established by NMR spectroscopy data using COSY experiments and the CALM program[29] for further analysis of the spin system. Geometry calculations for isomeric structures of **2a–d** were performed in the force field MM2.[30,31] Comparison of the calculated and experimental spectra of **2a–d** established the equatorial position of the R group and hydroxy substituent in all of the compounds studied, i.e. a *cis* (ee) configuration for **2a–d**.

Typical procedure: A solution of 4-substituted cyclohexanone (20 mmol) and the sodium halide (10 mmol) in methanol was electrolyzed in an undivided cylindrical cell with external cooling equipped with a graphite anode and an iron cathode at 30°C under constant current density 100 mA/cm^2 until the quantity of the electricity indicated in Table 1 was passed. The solvent was then removed, and the reaction mixture was extracted with chloroform. Evaporation of chloroform afforded crude **2a–d**, which were purified by distillation.[32]



Scheme 2.

Table 1. Stereoselective electrooxidation of 4-substituted cyclohexanones **1a–d**[a]

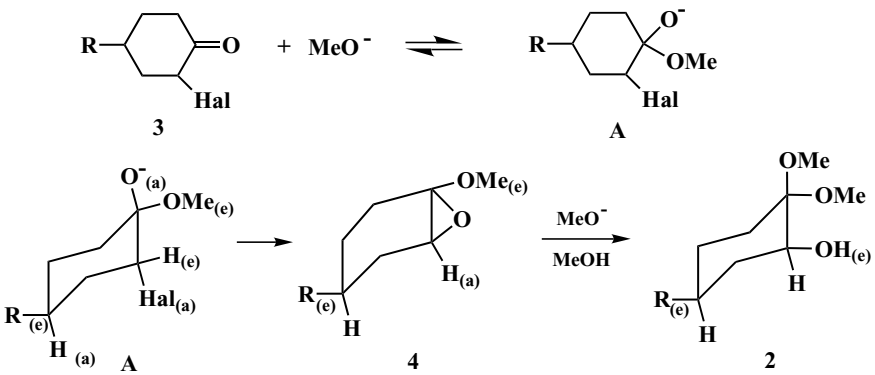


1a-d **2a-d**

Ketone	R	Mediator	Additive	Electricity passed (F/mol)	Product, yield (%)[b]
1a	Me	NaBr	–	2.9	**2a**, 73
1a	Me	NaI	–	2.9	**2a**, 79 (68)
1a	Me	NaI	NaOH	2.9	**2a**, 77
1b	Et	NaBr	–	3.0	**2b**, 71
1b	Et	NaI	–	3.0	**2b**, 78 (65)
1b	Et	NaI	NaOH	3.0	**2b**, 74
1c	*t*-Bu	NaI	–	3.1	**2c**, 73 (61)
1d	Ph	NaBr	–	3.3	**2d**, 65
1d	Ph	NaI	–	3.3	**2d**, 69 (58)
1d	Ph	NaI	NaOH	3.3	**2d**, 64

[a] 20 mmol of ketone, 10 mmol of mediator (1 mmol of NaOH) in 20 ml MeOH, iron cathode, graphite anode, undivided cell, 30°C; 98–100% conversion of **1a–d**.

[b] Determined by GLC and NMR spectroscopy; isolated yields are given in parentheses.



Scheme 3.

Acknowledgements

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32. All new compounds (**2a**–**d**) gave expected NMR spectra, elemental analyses or exact mass measurements.
    Compound **2a**: bp 67–69° (0.5 torr); ^{13}C NMR ($CDCl_3$): δ 99.36, 74.80, 50.37, 48.70, 40.53, 30.67, 30.51, 30.50, 21.52; MS (70 eV): m/z (relative intensity %): 174 (M^+, 10), 143 (18), 142 (5), 102 (9), 101 (100), 88 (21), 57 (22).
    Compound **2b**: bp 77–79° (0.5 torr); ^{13}C NMR ($CDCl_3$): δ 99.54, 74.94, 50.29, 48.66, 38.13, 37.37, 30.49, 28.77, 28.04, 11.59; MS (70 eV): m/z (relative intensity %): 188 (M^+, 6), 157 (9), 129 (3), 101 (100), 88 (25), 57 (22).
    Compound **2c**: bp 89–91° (0.2 torr); ^{13}C NMR ($CDCl_3$): δ 99.21, 75.93, 50.55, 48.73, 46.18, 33.74, 32.09, 31.16, 27.52, 23.05; MS (70 eV): m/z (relative intensity %): 216 (M^+, 1), 185 (3), 159 (2), 129 (20), 101 (100), 88 (27), 69 (31), 67 (36).
    Compound **2d**: bp 101–103° (0.05 torr); ^{13}C NMR ($CDCl_3$): δ 145.28, 128.35, 126.72, 126.19, 99.01, 75.37, 50.64, 48.87, 42.12, 39.62, 31.26, 29.90; MS (70 eV): m/z (relative intensity %): 236 (M^+, 1), 205 (2), 187 (3), 159 (2), 145 (7), 129 (10), 101 (100), 91 (46), 77 (24), 88 (68).