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Electrochemically induced Favorsky rearrangement of alkyl benzyl ketones

M. N. Elinson,★ S. K. Feducovich, A. S. Dorofeev, A. N. Vereshchagin, and G. I. Nikishin

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,
47 Leninsky prosp., 119991 Moscow, Russian Federation.
Fax: +7 (095) 135 5328. E-mail: elinson@ioc.ac.ru

Electrolysis of alkyl benzyl ketones in MeOH in an undivided electrolyzer in the presence of the NaI—NaOH mediator system induces the process similar to the Favorsky rearrangement to produce arylalkanecarboxylates in 80—90% yield (per substance) and with the 50—55% current efficiency.

Key words: electrolysis, electrochemical oxidation, alkyl benzyl ketones, mediators, mediator systems, arylalkanecarboxylates.

Ketone oxidation reactions are used to obtain carboxylic acids and their derivatives.[1] The haloform reaction is the simplest method for the preparation of carboxylic acids or esters from methyl ketones.[2,3] This method is especially significant in syntheses of aromatic carboxylic acids due to a much greater easiness of introduction of the acetyl group into the aromatic ring compared to the introduction of the carboxylic group.[4]

A sharp increase in studies on the electrochemistry of organic compounds in the last decades allowed electrosynthesis to become a competitive method of the modern organic chemistry.[5,6]

However, the electrochemical oxidation of ketones was highly selective only in particular cases.

The direct oxidation of ketones produces a mixture of saturated and unsaturated hydrocarbons, carbon oxide and dioxide.[7—10]

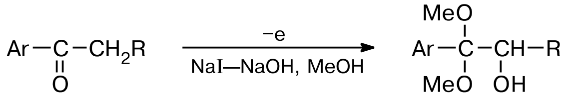
The electrooxidation in MeCN or TFA results in the nonselective remote functionalization of ketones due to the subsequent transformations and decomposition of the primarily formed radical cations $R^1R^2C{=}O^{\bullet +}$.[11,12]

In some oxidative transformations of ketones by methods of the classical organic chemistry, such as the haloform reaction, the preliminary α-halogenation of ketones is the key step.[13]

This step is a part of the overall process of electrochemical ketone oxidation in the presence of halide as a mediator in the system. Under such conditions, the electrocatalytic variant of the haloform reaction occurs: alkyl methyl and aryl methyl ketones are transformed into carboxylates.[14]

Cyclohexanone and alkyl aryl ketones were electrooxidized to the corresponding α-hydroxyketals using bromides as mediators.[15] The electrooxidation of alkyl benzyl ketones in MeOH produced arylalkanecarboxylates. However, the latter reaction was insufficiently selective, and α-hydroxyketals formed in significant amounts along with esters.[15]

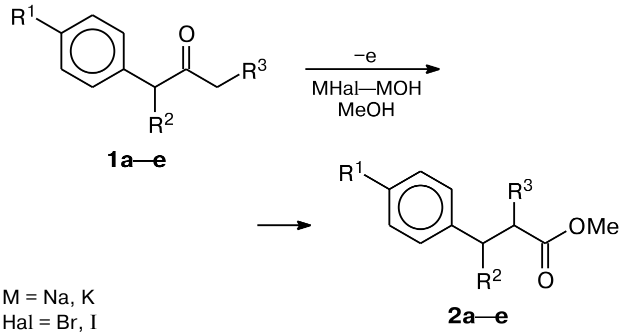
The two-component NaI—NaOH mediator system was also successfully used for the electrooxidation of cyclic ketones.[16,17] The recent use of this system made it possible to substantially improve the electrochemical oxidation of alkyl aryl ketones to the corresponding α-hydroxyketals.[18]



$$\mathrm{Ar{-}\underset{\underset{O}{\|}}{C}{-}CH_2R \xrightarrow[\text{NaI—NaOH, MeOH}]{-e} Ar{-}\underset{MeO}{\overset{MeO}{C}}{-}\underset{OH}{CH}{-}R}$$

The purpose of the present study was to use an alkali metal iodide—metal hydroxide system for the enhancement of the efficiency and selectivity of the electrochemical oxidation of alkyl benzyl ketones **1a—e** to methyl esters **2a—e** (Scheme 1, Table 1).

Scheme 1



1a—e

2a—e

M = Na, K
Hal = Br, I

a: $R^1 = R^2 = R^3 = H$; **b:** $R^1 = R^2 = H$, $R^3 = Me$; **c:** $R^1 = R^3 = H$, $R^2 = Me$; **d:** $R^1 = MeO$, $R^2 = R^3 = H$; **e:** $R^1 = Cl$, $R^2 = R^3 = H$

As mentioned above, the electrooxidation of alkyl methyl and aryl methyl ketones in MeOH in the presence

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Table 1. Electrooxidation of alkyl benzyl ketones **1a**—**e**[a]

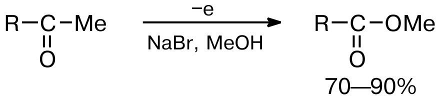
Entry	Ketone	Mediator	Metal hydroxide	Amount of electricity $/F\,\mathrm{mol}^{-1}$	Yield[b] (%)
1	**1a**	NaBr	—	7.0	**2a**, 61 (17)
2	**1a**	NaI	—	6.0	**2a**, 69 (23)
3	**1a**	NaBr	NaOH	4.5	**2a**, 71 (32)
4	**1a**	NaI	NaOH	3.2	**2a**, 88 (55)
5	**1a**	NaI	NaOH[c]	3.2	**2a**, 81 (51)
6	**1a**	KI	KOH	3.2	**2a**, 86 (54)
7	**1b**	NaI	NaOH	3.2	**2b**, 87 (54)
8	**1c**	NaI	NaOH	3.2	**2c**, 85 (53)
9	**1d**	NaI	NaOH	3.2	**2d**, 79 (49)
10	**1e**	NaI	NaOH	3.2	**2e**, 83 (52)

[a] Ketone (15 mmol), mediator (10 mmol), alkali (2 mmol) in MeOH (20 mL), Fe cathode, C anode, undivided electrolyzer, 30 °C; conversion of **1a**—**e** is 98—100%.

[b] The yield per substance according to the ^{1}H NMR spectroscopic data; the current efficiency (%) is given in parentheses.

[c] NaOH (5 mmol).

of alkali metal bromides in an undivided electrolyzer results in the electrocatalytic variant of the haloform reaction producing methyl carboxylates in which the number of carbon atoms in the hydrocarbon chain is by one atom less than that in the starting ketones.[14]



$$\underset{\mathrm{O}}{\overset{}{\mathrm{R{-}\underset{\|}{C}{-}Me}}} \xrightarrow[\text{NaBr, MeOH}]{-e} \mathrm{R{-}\underset{\|}{C}{-}OMe} \quad 70\text{—}90\%$$

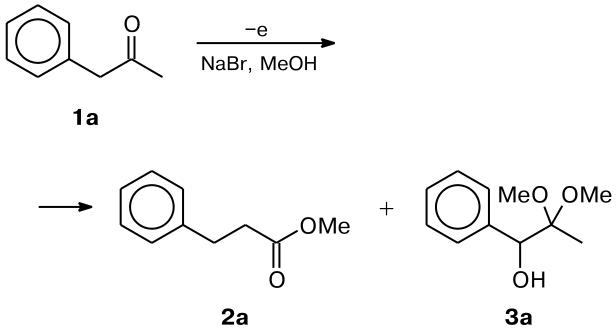
The electrolysis of alkyl benzyl ketone **1a** under similar conditions gave methyl 3-phenylpropionate (**2a**) in 61% yield and with the 17% current efficiency (Table 1, entry 1). Thus, the electrolysis of **1a** in the presence of NaBr also affords methyl carboxylate but the number of carbon atoms in the hydrocarbon chain remains unchanged. This process is analogous to the Favorsky rearrangement with the only difference that ketone instead of haloketone (as in the chemical variant of the Favorsky rearrangement) is used as the initial compound and by-product **3a** forms in 32% yield (Scheme 2).

The use of the NaI mediator increases the yield and efficiency of **2a** to 69 and 23%, respectively. The use of the NaBr—NaOH and NaI—NaOH mediator systems (entries 3 and 4) further enhances the yields of **2a**. Under the optimal conditions using the NaI—NaOH mediator system, ester **2a** was obtained in 88% yield and with the 55% efficiency (entry 4); by-product **3a** formed in ~6% yield.

Ketones **1b**—**e** were transformed into esters **2b**—**e** in 79—88% yields and with the ~50% efficiency under the conditions optimal for the transformation of ketone **1a** into ester **2a**.

Based on the obtained results and taking into account the previously considered mechanisms of electrochemical oxidation of cyclohexanone[16,17] and alkyl aryl ketones[18] in the presence of halides as mediators, we proposed the mechanism of electrochemical rearrangement of alkyl benzyl ketones **1a**—**e** to arylalkylcarboxylates **2a**—**e**.

Scheme 2



The reactions on electrodes, which occur during the electrochemical transformation of **1a**—**e** into arylalkylcarboxylates **2a**—**e**, are usual for the mediator system used and involve the formation of halogen on the anode and hydrogen release on the cathode with the generation of the methoxide ions

Anode: $2\,\mathrm{Hal}^- - 2\,e \longrightarrow \mathrm{Hal}_2$,

Cathode: $2\,\mathrm{MeOH} + 2\,e \longrightarrow 2\,\mathrm{MeO}^- + \mathrm{H}_2$,

Hal = I, Br.

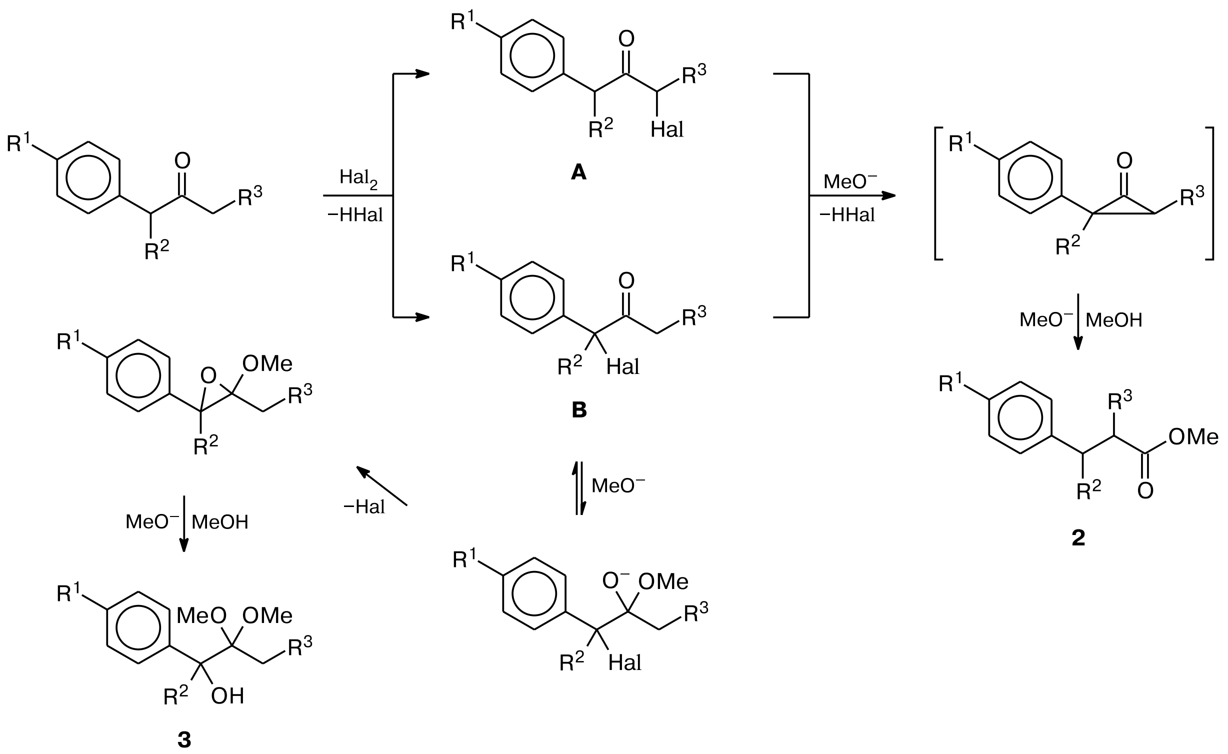
Then the α-halogenation of ketones **1a**—**e** occurs in a solution, as it has previously been established for alkyl aryl ketones, to form intermediate α-haloketones of two types: **A** and **B** (Scheme 3).

Under the action of the methoxide ion, haloketone **A** undergoes intramolecular cyclization to intermediate cyclopropanone, whose opening produces ester **2** according to the Favorsky rearrangement mechanism. The fact that only one transformation route occurs for haloketone **A** is most probably caused by the presence of an acidic benzyl proton in this ketone. Haloketone **B** is characterized by two reaction routes. One of them is similar to the transformation of haloketone **A** and also results in the formation of ester **2**. However, since the benzyl proton is absent, haloketone **B** is capable of the second reaction route: addition of the methoxide ion to the carbonyl group followed by intramolecular cyclization to intermediate epoxide and its opening, under the electrolysis conditions, to form α-hydroxyketal **3**.

Similar transformations affording α-hydroxyketals have previously been observed in the electrolysis of cyclohexanone[16,17] and alkyl aryl ketones[18] in the presence of halides.

The addition of NaOH has a substantial effect on the process. First, its overall efficiency enhances because the complete conversion of the initial ketone is achieved when a smaller amount of electricity is passed. A similar result

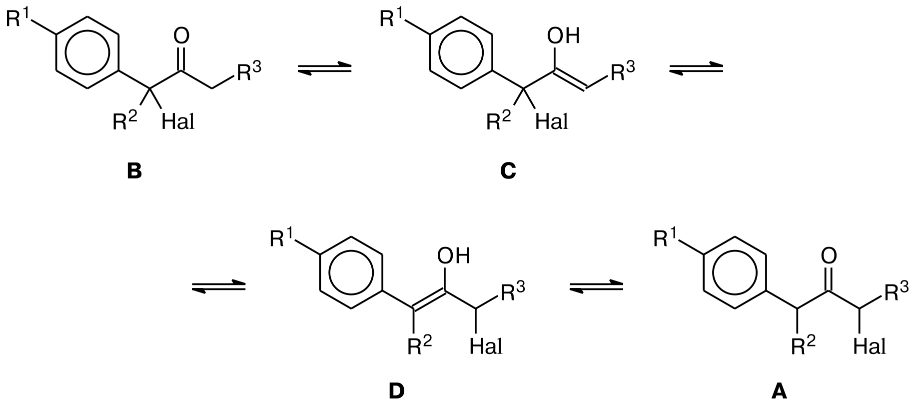
Scheme 3



has earlier[18] been observed for the electrochemical oxidation of alkyl aryl ketones to the corresponding α-hydroxyketals and is probably caused by two factors: (1) introduction of NaOH increases the concentration of the methoxide ions in the solution and, thus, all processes involving the methoxide ions are accelerated and (2) introduction of NaOH increases the current concentration of the enolic form of ketone, thus accelerating the halogenation of the initial ketone. The combined effect of these two factors enhances the overall efficiency of electrooxidation of initial ketones **1a—e**. Second, the introduction of NaOH changes the ratio of ester **2** to α-hydroxyketal **3** toward an increase in the amount of ester **2**. The latter is most likely due to the fact that the most part of haloketone **B** is transformed into ester **2** in the presence of NaOH. We cannot exclude the influence of the NaOH additive on the ratio of haloketones formed in the halogenation step and the mutual transformation of haloketones **A** and **B** in the presence of NaOH (Scheme 4).

Halogen 1,3-migration in haloenol **C** occurs, most likely, according to the principles characteristic of the known fast allyl rearrangement.[19] (Halogen 1,3-migration has previously been mentioned in the rearrangement of α,α-dibromoketones to α,α′-dibromoketones.[20])

Scheme 4



Thus, the process similar to the Favorsky rearrangement was carried out in an undivided electrolyzer during the electrolysis of methanolic solutions of alkyl benzyl ketones **1a—e** in the presence of the mediator.

This process is a convenient and economic method for the direct transformation of alkyl benzyl ketones into the corresponding esters of arylalkanoic acids in the presence of the NaI—NaOH mediator system. The process uses standard and readily available reagents, inexpensive equipment, and an undivided electrolyzer. The procedures of electrolysis and isolation of final compounds are simple and convenient to use in both laboratory setups and larger (pilot or industrial) installations.

Experimental

^{1}H NMR spectra were recorded on Bruker WM-250 and Bruker AM-300 instruments with working frequencies of 250 and 300 MHz, respectively, in $CDCl_3$. Chemical shifts in the NMR spectra were presented in the δ scale relatively to Me_4Si.

GLC analysis was carried out on an LKhM-80 chromatograph with a flame-ionization detector using nitrogen as carrier gas with a rate of 30 mL min^{-1} (column (glass) 2500×3 mm with 5% SE-Superphase on Super Inerton (0.16—0.20 mm)) to monitor the conversion of initial ketones **1a**—**e**.

The initial ketones were commercial reagents (Reakhim and Aldrich). 4-Chlorophenylacetone was synthesized using a known procedure.[21]

Electrolysis (general procedure). A solution of ketone (15 mmol), mediator (10 mmol), and alkali (2 mmol) in MeOH (20 mL) was electrolyzed in an undivided cell equipped with a C anode and a Fe cathode (surface area of the electrodes was 5 cm^2) at 30 °C and a constant current density of 100 mA cm^{-2} passing a specified amount of electricity through the solution (see Table 1). The reaction mixture was neutralized with dilute HCl, and the solvent was evaporated. The mixture was extracted with Et_2O. The extract was washed with an aqueous solution of $Na_2S_2O_3$ and water and dried over Na_2SO_4. The ether was distilled off, and the residue was analyzed by ^{1}H NMR spectroscopy. Esters **2a**—**e** were isolated by distillation.

Methyl 3-phenylpropionate (2a), 79% yield, b.p. 122—124 °C (14 Torr) (*cf.* Ref. 22: b.p. 68—70 °C (2 Torr)). ^{1}H NMR, δ: 2.67 (t, 2 H, CH_2, J = 7 Hz); 2.99 (t, 2 H, CH_2, J = 7 Hz); 3.70 (s, 3 H, OMe); 7.28 (m, 5 H, C_6H_5).

Methyl 2-methyl-3-phenylpropionate (2b), 78% yield, b.p. 59—60 °C (0.7 Torr) (*cf.* Ref. 23: b.p. 90—93 °C (1 Torr)). ^{1}H NMR, δ: 1.15 (d, 3 H, Me, J = 7 Hz); 2.66 (m, 2 H, CH_2); 2.99 (m, 1 H, CH); 3.63 (s, 3 H, OMe); 7.28 (m, 5 H, Ar).

Methyl 3-phenylbutanoate (2c), 76% yield, b.p. 130—132 °C (45 Torr) (*cf.* Ref. 24: b.p. 74—78 °C (0.5 Torr)). ^{1}H NMR, δ: 1.32 (d, 3 H, Me, J = 7 Hz); 2.62 (m, 2 H, CH_2); 3.31 (m, 1 H, CH); 3.67 (s, 3H, OMe); 7.28 (m, 5 H, C_6H_5).

Methyl 3-(4-methoxyphenyl)propionate (2d), 71% yield, b.p. 148—150 °C (14 Torr), m.p. 36—37 °C (petroleum ether) (*cf.* Ref. 22: b.p. 35—36 °C). ^{1}H NMR, δ: 2.66 (t, 2 H, CH_2, J = 7 Hz); 2.93 (t, 2 H, CH_2, J = 7 Hz); 3.68 (s, 3 H, OMe); 3.81 (s, 3 H, OMe); 7.02 (d, 2 H, Ar, J = 8 Hz); 7.14 (d, 2 H, Ar, J = 8 Hz).

Methyl 3-(4-chlorophenyl)propionate (2e), 72% yield, b.p. 136—138 °C (14 Torr) (*cf.* Ref. 22: b.p. 85—86 °C (2 Torr)). ^{1}H NMR, δ: 2.68 (t, 2 H, CH_2, J = 7 Hz); 2.98 (t, 2 H, CH_2, J = 7 Hz); 3.70 (s, 3 H, OMe); 7.31 (m, 4 H, Ar).

2,2-Dimethoxy-1-phenylpropan-1-ol (3) was isolated by crystallization from the reaction mixture (see Table 1, entry 1, ether—hexane, 1 : 1) in 21% yield, m.p. 59—61 °C (*cf.* Ref. 25: m.p. 63—65 °C). ^{1}H NMR, δ: 1.05 (s, 3 H, Me); 2.73 (s, 1 H, OH); 3.24 (s, 3 H, OMe); 3.33 (s, 3 H, OMe); 4.80 (s, 1 H, CH); 7.10—7.55 (m, 5 H, Ar).

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