Electrochemically induced Favorsky rearrangement: transformations of dialkyl ketones into α,β-unsaturated carboxylic esters

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Electrolysis of dialkyl ketones in MeOH in the presence of the NaI—NaOH mediator system placed in an undivided cell involves a process analogous to the Favorsky rearrangement of α,α-dihalodialkyl ketones giving rise to methyl esters of α,β-unsaturated carboxylic acids in 70—75% substance yields and 60—70% current yields.

Key words: electrolysis, electrochemical oxidation, dialkyl ketones, mediator systems, unsaturated carboxylic esters.

Oxidation of ketones is used in the synthesis of carboxylic acids and their derivatives.[1] The haloform reaction provides the simplest approach to the synthesis of carboxylic acids or their esters from methyl ketones.[2,3] Since the acetyl group is much more readily introduced into the aromatic ring compared to the carboxyl group, this method is of particular importance in the synthesis of aromatic carboxylic acids.[4]

Due to considerable progress made in the electrochemistry of organic compounds in the last decades, the electrosynthesis became a highly competitive method in modern organic chemistry.[5,6] The organic electrosynthesis occupies a special place among methods of organic synthesis because some transformations of organic compounds can be performed exclusively with the use of methods of electroorganic chemistry, whereas methods of classical organic chemistry are unsuitable for this purpose. However, electrochemical oxidation of ketones is selective only in specific cases.

Direct electrochemical oxidation of ketones affords mixtures of carboxylic acids, saturated and unsaturated hydrocarbons, and carbon oxide and dioxide.[7—10]

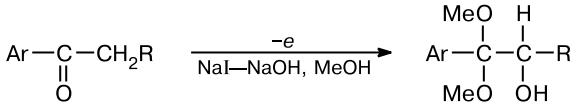
Electrooxidation in MeCN or trifluoroacetic acid leads to the nonselective remote 1,5- and 1,6-functionalization of dialkyl ketones as a result of subsequent transformations of the $R^1R^2C{=}O^{+\bullet}$ radical cations produced at an anode.[11,12]

Some oxidative transformations of ketones performed by methods of classical organic chemistry, such as the haloform reaction, involve preliminary α-halogenation of ketones as the key step.[13] This step plays an important role in the general process of electrochemical oxidation of ketones, if salts of hydrohalic acid are added to the reaction mixture as a mediator. Under these conditions, the electrocatalytic haloform reaction takes place resulting in transformations of alkyl methyl and aryl methyl ketones into carboxylic esters.[14]

Electocatalytic oxidation of cyclohexanone and alkyl aryl ketones to α-hydroxy ketals was carried out with the use of alkali bromides as mediators.[15]

Electrooxidation of cyclic ketones was performed[16,17] also with the use of the two-component NaI—NaOH mediator system. The employment of this system made it possible[18] to substantially improve the selectivity and efficiency of oxidation of alkyl aryl ketones to α-hydroxy ketals (Scheme 1).

Scheme 1



The present study was aimed at using the sodium halide—sodium hydroxide system for electrocatalytic oxidation of dialkyl ketones **1a—e** (Scheme 2, Table 1; for the preliminary communication, see Ref. 19).

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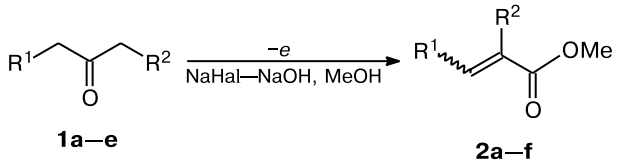
Scheme 2



1a—e **2a—f**

Hal = Br, I

	1a	1b	1c	1d	1e	
R^1	Et	Pr^n	$(CH_2)_4Me$	$(CH_2)_6Me$	Me	
R^2	Et	Pr^n	$(CH_2)_4Me$	$(CH_2)_6Me$	CH(Me)Et	
	2a	**2b**	**2c**	**2d**	**2e**	**2f**
R^1	Et	Pr^n	$(CH_2)_4Me$	$(CH_2)_6Me$	CH(Me)Et	Me
R^2	Et	Pr^n	$(CH_2)_4Me$	$(CH_2)_6Me$	Me	CH(Me)Et

As can be seen from Table 1, the addition of NaOH led to an increase in the current yield of unsaturated carboxylic esters from 30 to 70%. The use of the NaBr—NaOH mediator system instead of the NaI—NaOH system resulted in a decrease in the current yield of esters **2a—f** to 50% and a slight decrease in the substance yield. An increase in the electrolysis temperature to 60 °C had virtually no effect on the results. Under the optimum conditions, esters **2a—f** were synthesized in current and substance yields of 70 and 70—77%, respectively.

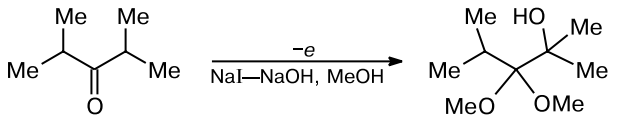
Unlike electrolysis of ketones with normal structures, electrolysis of diisopropyl ketone (**3**) performed in the presence of the NaI—NaOH mediator system by passing the electricity of 2.6 F mol^{-1} afforded 3,3-dimethoxy-2,4-dimethylpentan-2-ol (**4**) in 41% substance yield and 32% current yield (Scheme 3).

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

Ketone	Quantity of electricity /F mol^{-1}	Substance yield (%)[b]	Ratio of E/Z isomers	Current yield (%)
1a[c]	8.0	**2a**, 63	1.1	32
1a[c,d]	8.0	**2a**, 43	1.1	22
1a[e]	4.3	**2a**, 70	1.1	65
1a[f]	4.3	**2a**, 72	1.1	70
1a	4.3	**2a**, 75 (67)	1.1	70
1a[d]	5.8	**2a**, 68	1.1	47
1b	4.3	**2b**, 76 (65)	1.0	71
1b[d]	5.8	**2b**, 66	1.0	46
1c	4.3	**2c**, 77 (69)	0.9	72
1d	4.3	**2d**, 74 (64)	0.9	69
1e	4.3	**2e**, 51; **2f**, 23 (63)[g]	1.8; 1.1	69[g]

[a] Ketone (15 mmol), NaI (10 mmol) as the mediator, NaOH (1 mmol) in MeOH (20 mL), Fe cathode, C anode, undivided cell, 30 °C; the conversions of compounds **1a—e** were 98—100%.
[b] According to the results of NMR spectroscopy and GLC analysis, the yield with respect to the compound isolated is given in parentheses.
[c] Without addition of NaOH.
[d] Sodium bromide was used as the mediator.
[e] In the presence of NaOH (5 mmol).
[f] In the presence of NaOH (2 mmol).
[g] For a mixture of **2e** and **2f**.

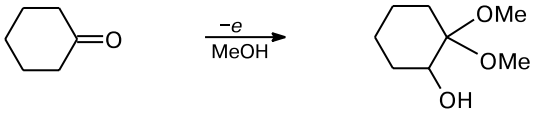
Scheme 3



3 **4**

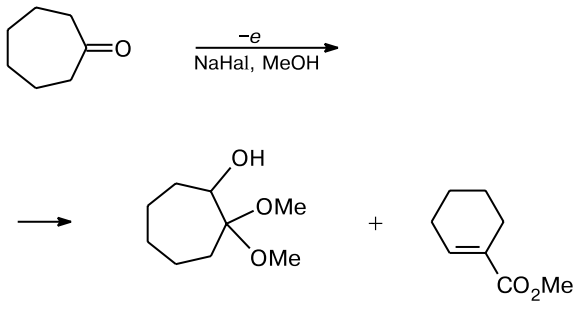
Earlier,[16,17] electrooxidation of cyclohexanone in MeOH in the presence of NaBr, NaI, or the NaBr—MeOH and NaI—MeOH mediator systems produced exclusively 2,2-dimethoxycyclohexanol (Scheme 4).

Scheme 4



Electrolysis of cycloheptanone in MeOH in the presence of NaI or NaBr afforded[17] a mixture of 2,2-dimethoxycycloheptanol and methyl cyclohexene-1-carboxylate (Scheme 5).

Scheme 5

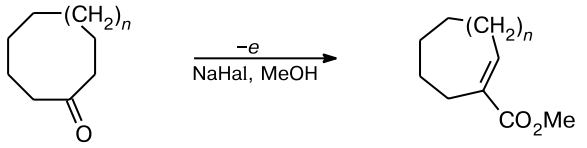


Hal = Br, I

Under analogous conditions, cyclooctanone and cyclododecanone were oxidized[17] to form methyl esters of unsaturated cyclic carboxylic acids accompanied by the ring contraction (Scheme 6).

Based on the results of our study and taking into account the data on the mechanisms of electrochemical oxidation of cyclic ketones[17] and alkyl aryl ketones[18] in the presence of mediators, *viz.*, salts of hydrohalic acids, we propose the mechanism of electrochemical transfor-

Scheme 6

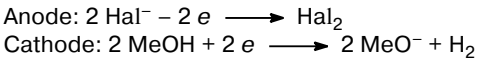


n = 1, 5; Hal = Br, I

mation of dialkyl ketones **1a—e** into methyl esters of unsaturated carboxylic acids **2a—f**.

The reactions at electrodes, which take place in the course of electrochemical transformations of dialkyl ketones **1a—e** into esters **2a—f**, are typical of the mediator systems used (metal halide—metal hydroxide) and involve the formation of halogen at an anode and elimination of hydrogen at a cathode accompanied by the generation of methoxide ions (Scheme 7).

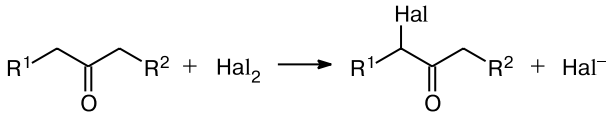
Scheme 7



Hal = Br, I

Then dialkyl ketones **1a—e** in solutions undergo α-halogenation to give α-halodialkyl ketones (Scheme 8).

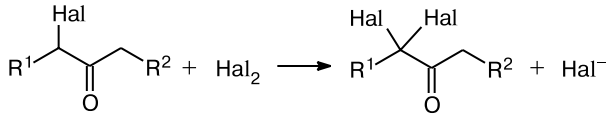
Scheme 8



1a—e

α-Halodialkyl ketones are subjected to further halogenation yielding α,α-dihalodialkyl ketones (Scheme 9).

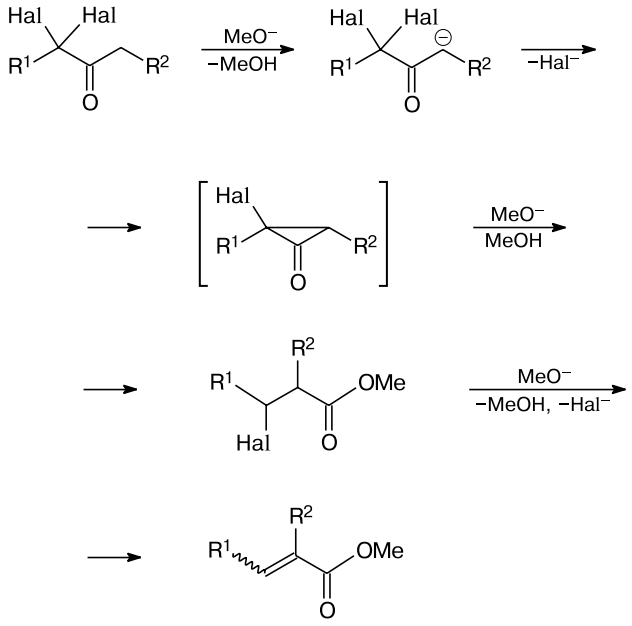
Scheme 9



The subsequent reactions of α,α-dihalodialkyl ketones with methoxide anions generated at a cathode involve the Favorsky rearrangement with the result that α,α-dihalodialkyl ketones are transformed into methyl esters of unsaturated carboxylic acids (Scheme 10).

It should be noted once again that electrolysis of alkyl aryl ketones and cyclohexanone performed under analo-

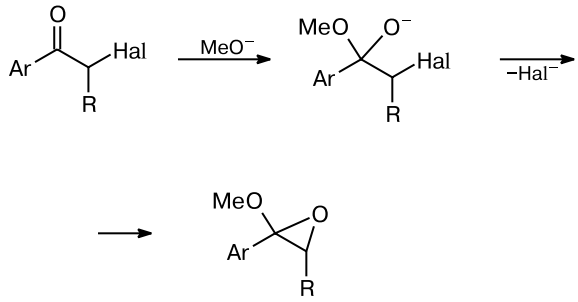
Scheme 10



gous conditions affords the corresponding α-hydroxy ketals.

This difference in the behavior of ketones is determined by a number of factors. For alkyl aryl ketones, the attack of the methoxide ion on the carbonyl group proceeds more readily compared to that in cyclic ketones and dialkyl ketones because of the steric factors and due to a high reactivity of the carbonyl group attributed to conjugation with the aromatic ring. As a result, α-halogenation is succeeded by the attack of the methoxide ion on the carbonyl group of α-halo ketone followed by cyclization to yield intermediate epoxide (Scheme 11).

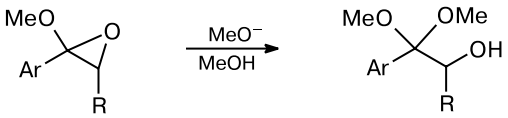
Scheme 11



The reaction of epoxide with the second methoxide ion affords the corresponding α-hydroxy ketal as the final reaction product (Scheme 12).

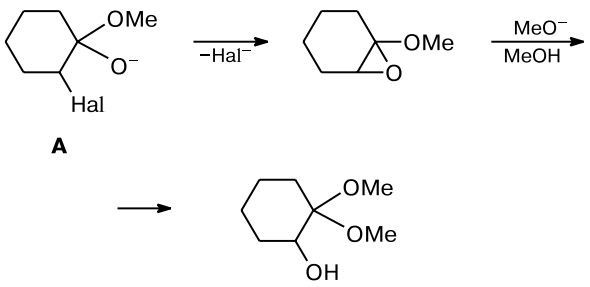
In the case of cyclohexanone, the addition of anions at the carbonyl group leads to the removal of steric hin-

Scheme 12



drance typical of the six-membered ring containing the sp^2-hybridized C atom.[20] This fact improves the stability of formation of intermediate anion **A**, which further reacts through a pathway giving rise to α-hydroxy ketal (Scheme 13).

Scheme 13



Cycloheptanone is intermediate in the reactivity exhibited in the reactions under study between cyclohexanone and higher cyclic ketones. The reactions of cycloheptanone follow both routes.

For higher cyclic ketones and dialkyl ketones, the attack of the methoxide ion on the carbonyl group accompanied by a change in the hybridization of the C atom is generally reversible and does not change the influence of the steric factor.[20] As a result, rapid repeated halogenation of α-halo ketone takes place to form α,α-dihalo ketones, which react further with the methoxide ion according to the mechanism of the Favorsky rearrangement.

The addition of NaOH improves the efficiency of the process. In this case, the initial ketone is completely converted upon passing of a smaller quantity of electricity. An analogous result has been observed earlier upon electrochemical oxidation of alkyl aryl ketones[18] and it is, most likely, associated with the influence of two factors: 1) the addition of NaOH leads to an increase in the concentration of methoxide ions in solutions thus accelerating all processes involving methoxide ions, 2) the addition of NaOH leads to an increase in the running concentration of the enol form of ketone thus accelerating halogenation of the starting ketone. The combined effect of these two factors leads to an increase in the total efficiency of electrooxidation of the starting dialkyl ketones **1a—e**.

Therefore, under the conditions of electrolysis in an undivided cell in the presence of a mediator, dialkyl ketones **1a—e** were involved in a process analogous to the Favorsky rearrangement. It should be noted that the classical version of this rearrangement is carried out with α,α-dihalo ketones as the starting reagents, whose synthesis from dialkyl ketones requires an additional step with the use of a stoichiometric amount of bromine.

The electrochemical approach is a convenient and labor-consuming procedure for the direct transformation of dialkyl ketones into α,β-unsaturated carboxylic esters in the presence of the NaI—NaOH mediator system. This method requires common and readily accessible reagents, inexpensive apparatus, and an undivided cell. The procedures for electrolysis and isolation of the reaction products are simple and convenient for performing both under laboratory conditions and on pilot-scale apparatus.

Experimental

The ^{1}H NMR spectra were recorded on Bruker WM-250 and Bruker AM-300 instruments at 250 and 300 MHz, respectively, for solutions in $CDCl_3$. The ^{1}H NMR spectra of a mixture of **2e** and **2f** were measured on a Varian 500-PLUS instrument (500 MHz). The chemical shifts are given in the δ scale with respect to Me_4Si.

The mass spectra were obtained on a Hewlett—Packard 5988A spectrometer (EI, 70 eV).

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

The starting ketones were purchased from Reakhim and Aldrich.

Electrolysis (general procedure). A solution of ketone (15 mmol), a mediator (10 mmol), and NaOH (1 mmol) in MeOH (20 mL) was subjected to electrolysis in an undivided cell equipped with a C anode and a Fe cathode (electrode surface was 5 cm^2) at 30 °C and the constant current density of 100 mA cm^{-2}. The quantity of electricity passed is given in Table 1. The reaction mixture was neutralized with dilute HCl and then the solvent was evaporated. The reaction mixture was extracted with Et_2O, 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—f** were isolated by distillation.

Methyl 2-ethylpent-2-enoate (2a).[21,22] B.p. 74—79 °C (25 Torr). ^{1}H NMR, δ: 1.02—1.12 (m, 6 H, CH_3); 2.11—2.42 (m, 4 H, CH_2); 3.72 (s, 3 H, OCH_3); 5.85 (t, (*Z*)-(1 H, CH=), *J* = 7 Hz); 6.74 (t, (*E*)-(1 H, CH=), *J* = 8 Hz).

Methyl 2-propylhex-2-enoate (2b).[23,24] B.p. 91—94 °C (10 Torr). ^{1}H NMR, δ: 0.95—1.07 (m, 6 H, CH_3); 1.38—1.63 and 2.12—2.43 (both m, 4 H each, CH_2); 3.72 (s, 3 H, OCH_3); 5.84 (t, (*Z*)-(1 H, CH=), *J* = 7 Hz); 6.73 (t, (*E*)-(1 H, CH=), *J* = 8 Hz).

Methyl 2-pentyloct-2-enoate (2c). B.p. 128—132 °C (8 Torr). Found (%): C, 74.29; H, 11.58. $C_{14}H_{26}O_2$. Calculated (%): C, 74.18; H, 11.51. ^{1}H NMR, δ: 0.75—0.95 (m, 6 H, CH_3); 1.20—1.48 (m, 12 H, CH_2); 2.10—2.43 (m, 4 H, CH_2); 3.71 (s, 3 H, OCH_3); 5.83 (t, (*Z*)-(1 H, CH=), *J* = 7 Hz); 6.72

(t, (*E*)-(1 H, CH=), *J* = 8 Hz). Compound (*E*)-**2c**. MS, *m/z* (I_{rel} (%)): 226 $[M]^+$ (26), 195 (12), 183 (43), 169 (41), 155 (32), 109 (100), 81 (54), 87 (34), 69 (37), 55 (76). Compound (*Z*)-**2c**. MS, *m/z* (I_{rel} (%)): 226 [M[$^+$ (25), 195 (18), 183 (21), 169 (35), 155 (100), 109 (67), 87 (31), 81 (49), 69 (21), 55 (32).

Methyl 2-heptyldec-2-enoate (2d). B.p. 192—195 °C (10 Torr). Found (%): C, 76.54; H, 12.13. $C_{18}H_{34}O_2$. Calculated (%): C, 76.33; H, 12.05. ^{1}H NMR, δ: 0.75—0.95 (m, 6 H, CH_3); 1.18—1.48 (m, 20 H, CH_2); 2.09—2.44 (m, 4 H, CH_2); 3.71 (s, 3 H, OCH_3); 5.83 (t, (*Z*)-(1 H, CH=), *J* = 7 Hz); 6.72 (t, (*E*)-(1 H, CH=), *J* = 8 Hz). Compound (*E*)-**2d**. MS, *m/z* (I_{rel} (%)): 282 $[M]^+$ (31), 251 (11), 211 (52), 197 (44), 183 (54), 137 (63), 109 (42), 95 (89), 87 (67), 81 (100). Compound (*Z*)-**2d**. MS, *m/z* (I_{rel}(%)): 282 $[M]^+$ (7), 251 (6), 211 (11), 197 (19), 183 (100), 137 (22), 109 (21), 95 (39), 87 (31), 81 (44).

Methyl 2,4-dimethylhex-2-enoate (2e) and **methyl 2-ethylidene-3-methylpentanoate (2f)** were isolated as a mixture of isomers, b.p. 71—75 °C (18 Torr). Found (%): C, 69.20; H, 10.21. $C_9H_{16}O_2$. Calculated (%): C, 68.97; H, 10.13. Compound (*E*)-**2e**. ^{1}H NMR, δ: 0.82 (t, 3 H, CH_3, *J* = 7 Hz); 0.97 (d, 3 H, CH_3, *J* = 7 Hz); 1.20—1.35 (m, 2 H, CH_2); 1.82 (s, 3 H, CH_3); 2.38 (m, 1 H, CH); 3.71 (s, 3 H, OCH_3); 6.51 (d, 1 H, CH=, *J* = 7 Hz). MS, *m/z* (I_{rel} (%)): 156 $[M]^+$ (16), 141 (5), 127 (15), 95 (35), 88 (29), 81 (25), 69 (75), 67 (31), 59 (100), 55 (83). Compound (*Z*)-**2e**. ^{1}H NMR, δ: 0.84 (t, 3 H, CH_3, *J* = 7 Hz); 1.10 (d, 3 H, CH_3, *J* = 7 Hz); 1.20—1.35 (m, 2 H, CH_2); 1.87 (s, 3 H, CH_3); 2.88 (m, 1 H, CH); 3.69 (s, 3 H, OCH_3); 5.64 (d, 1 H, CH=, *J* = 8 Hz). MS, *m/z* (I_{rel} (%)): 156 $[M]^+$ (8), 141 (5), 127 (10), 95 (27), 81 (17), 79 (25), 69 (23), 67 (28), 59 (100), 55 (34). Compound (*E*)-**2f**. ^{1}H NMR, δ: 0.81 (t, 3 H, CH_3, *J* = 7 Hz); 0.93 (d, 3 H, CH_3, *J* = 7 Hz); 1.20—1.35 (m, 2 H, CH_2); 1.77 (d, 3 H, CH_3); 2.61 (m, 1 H, CH); 3.72 (s, 3 H, OCH_3); 6.72 (q, 1 H, CH=, *J* = 8 Hz). MS, *m/z* (I_{rel} (%)): 156 $[M]^+$ (6), 141 (3), 127 (9), 101 (28), 88 (45), 87 (27), 69 (33), 67 (31), 59 (100), 55 (74). Compound (*Z*)-**2f**. ^{1}H NMR, δ: 0.83 (t, 3 H, CH_3, *J* = 7 Hz); 1.02 (d, 3 H, CH_3, *J* = 7 Hz); 1.20—1.35 (m, 2 H, CH_2); 1.85 (d, 3 H, CH_3); 2.81 (m, 1 H, CH); 3.70 (s, 3 H, OCH_3); 5.79 (q, 1 H, CH=, *J* = 7 Hz). MS, *m/z* (I_{rel} (%)): 156 $[M]^+$ (4), 141 (2), 127 (7), 95 (21), 88 (25), 81 (19), 69 (25), 67 (29), 59 (100), 55 (61).

3,3-Dimethoxy-2,4-dimethylpentan-2-ol (4). B.p. 116—119 °C (10 Torr). ^{1}H NMR, δ: 1.01 (d, 6 H, CH_3, *J* = 7 Hz); 1.03 (s, 6 H, CH_3); 2.05 (m, 1 H, CH); 2.19 (s, 1 H, OH); 3.23 (s, 6 H, OCH_3). ^{13}C NMR, δ: 19.7 and 26.1 (both CH_3); 33.9 (CH); 51.0 (OCH_3); 79.8 (C); 112.8 (O—C—O).

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