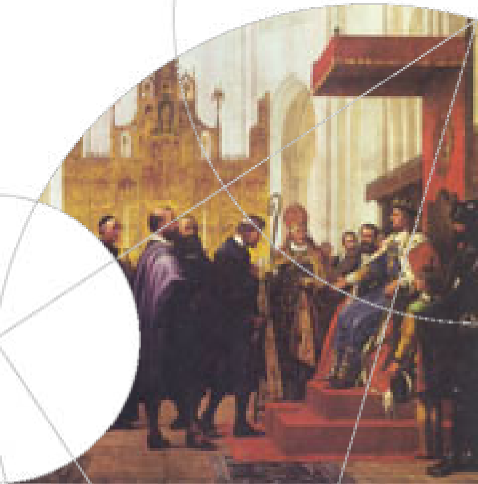
Electrochemical organic synthesis

Ole Hammerich



What is ’organic electrochemistry’

Organic electrochemistry is concerned with the exchange of electrons between a substrate and an electrode and the chemical reactions that result from such electron transfer processes.

Organic electrochemical processes are conceptually related to other organic reactions the mechanisms of which include one or more electron transfer steps, for instance, photoinduced electron transfer.

At the borderline of organic chemistry, electron transfer processes play an important role in many reactions that involve organometallic compounds and in biological processes.

Traditional redox reactions and electrochemical reactions

Equivalents to organic electrochemistry are found in the oxidation and reduction of organic compounds with inorganic reagents where, in the electrochemical process, the oxidation agent is replaced by the anode (+) and the reduction agent by the cathode (-).

$$3\ \mathrm{Ar\text{-}CH_2OH} + 2\ \mathrm{Cr_2O_7}^{2-} + 16\ \mathrm{H}^+ \rightarrow 3\ \mathrm{Ar\text{-}COOH} + 4\ \mathrm{Cr}^{3+} + 11\ \mathrm{H_2O}$$

$$\mathrm{Ar\text{-}CH_2OH} + \mathrm{H_2O} \rightarrow \mathrm{Ar\text{-}COOH} + 4\ e^- + 4\ \mathrm{H}^+$$

$$\mathrm{Ar\text{-}NO_2} + 3\ \mathrm{Sn} + 7\ \mathrm{H}^+ \rightarrow \mathrm{Ar\text{-}NH_3}^+ + 3\ \mathrm{Sn}^{2+} + 2\ \mathrm{H_2O}$$

$$\mathrm{Ar\text{-}NO_2} + 6\ e^- + 7\ \mathrm{H}^+ \rightarrow \mathrm{Ar\text{-}NH_3}^+ + 2\ \mathrm{H_2O}$$

Organic electrochemical synthesis

Pros

1. Replacement of inorganic redox reagents with electrode processes reduces the number of steps in the overall reaction
2. Green technology; no toxic wastes, no fire or explosion hazards, no storage and handling of aggressive reagents, mostly room temperature chemistry
3. Electrode reactions are often selective and present direct routes to products otherwise difficult to make (via electro-chemical ‘umpolung’)
4. Electrons are cheap and are easy to transport around. Electricity can be made from many different natural resources
5. Easily scalable

Cons

1. Electrochemistry is considered a specialists topic
2. Reaction mechanisms are often complex, which leaves the synthetic organic chemist uncomfortable
3. Requires equipment (electrodes, cells, current sources and potentiostats) and chemicals (supporting electrolytes) that are often not available in the traditional laboratory
4. Electron transfer is heterogeneous and electrochemical reactions take time (1 mole of e^- = 1 Faraday = 96485 C = 96485 A·s = 26.8 A·h)

Organic electrochemical synthesis

Pro and Con

The number of experimental parameters that may be manipulated is large including the

- a) electrode potential (the driving force, the rate of the process)
- b) current (conversion/time)
- c) electrode material (control of the overpotential)
- d) solvent and the supporting electrolyte
- e) mass transfer to/from the electrodes (stirring/pumping rate)
- f) cell design

in addition to all the other parameters that may be manipulated in a conventional organic synthetic reaction

Reaction types

Additions:

$R\text{-}CH{=}CH\text{-}R + 2\ Nu^- \rightarrow R\text{-}CHNu\text{-}CHNu\text{-}R + 2e^-$

$R\text{-}CH{=}CH\text{-}R + 2e^- + 2H^+ \rightarrow R\text{-}CH_2\text{-}CH_2\text{-}R$

Substitutions:

$R\text{-}CH_3 + Nu^- \rightarrow R\text{-}CH_2Nu + 2e^- + H^+$

$R\text{-}Cl + CO_2 + 2e^- \rightarrow R\text{-}COO^- + Cl^-$

Eliminations:

$R\text{-}CH_2\text{-}CH_2\text{-}R \rightarrow R\text{-}CH{=}CH\text{-}R + 2e^- + 2H^+$

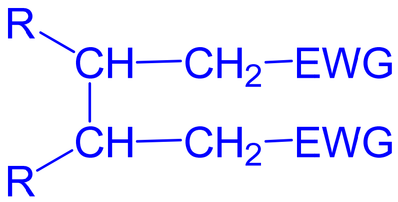
$R\text{-}CHNu\text{-}CHNu\text{-}R + 2e^- \rightarrow R\text{-}CH{=}CH\text{-}R + 2\ Nu^-$

Coupling reactions:

$2\ R\text{-}COO^- \rightarrow R\text{-}R + 2e^- + 2\ CO_2$ (Kolbe reaction)

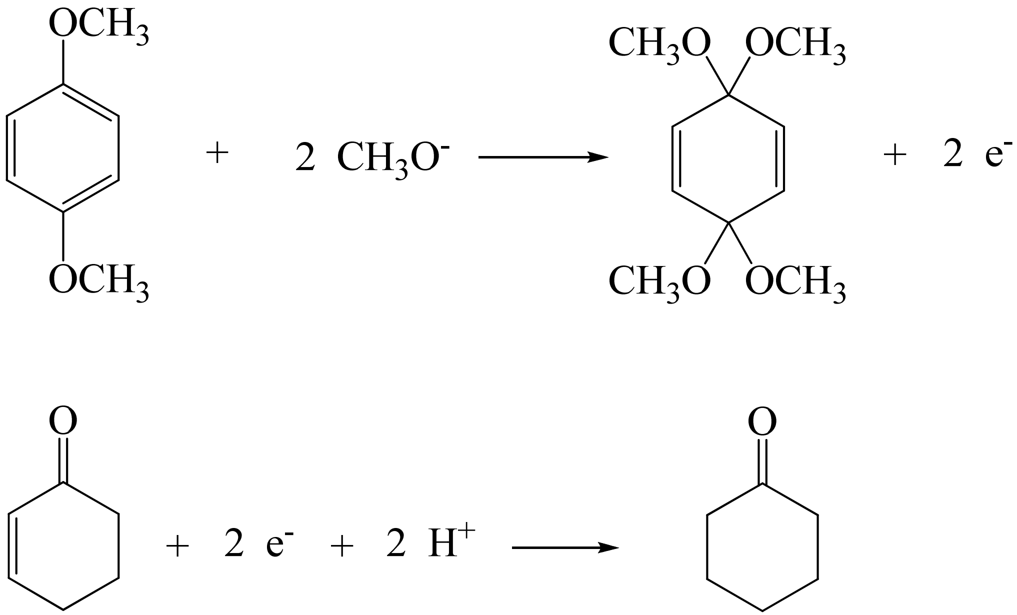
$2\ R\text{-}Cl + 2e^- \rightarrow R\text{-}R + 2\ Cl^-$

$2\ R\text{-}CH{=}CH\text{-}EWG + 2e\text{-} + 2H+ \rightarrow$

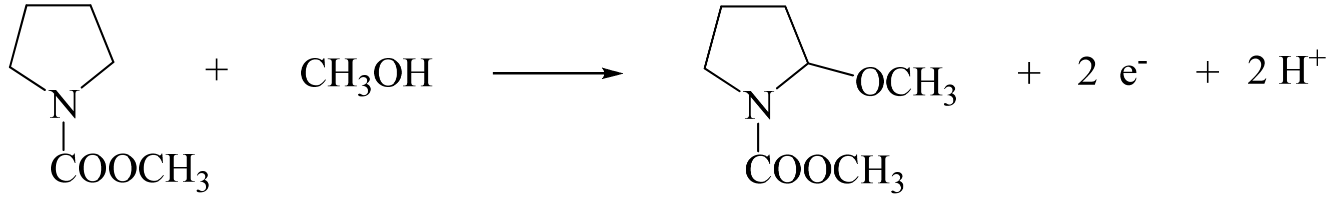


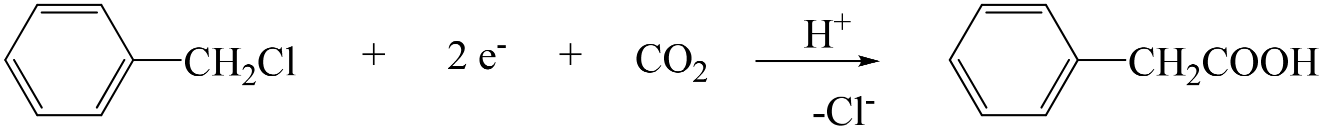
(Hydrodimerization)

Additions

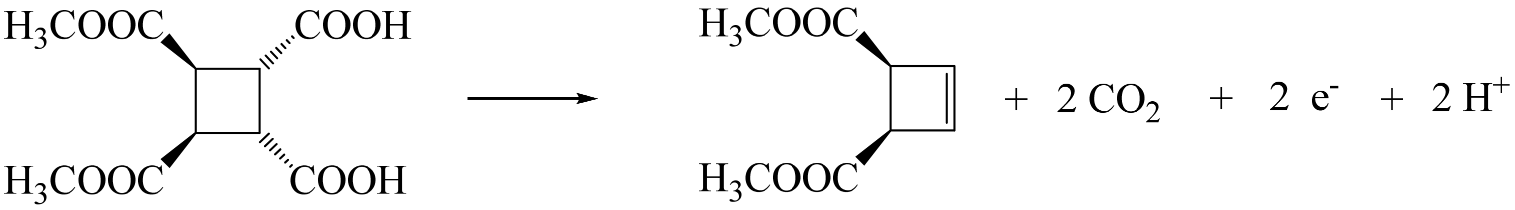


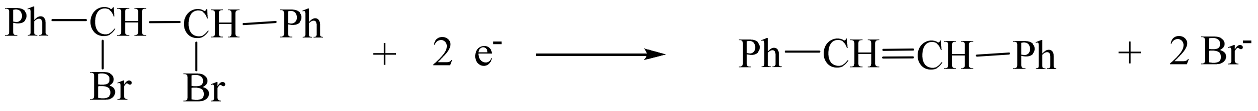
Substitutions





Eliminations



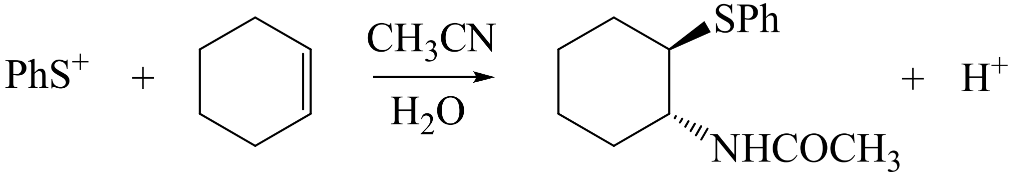


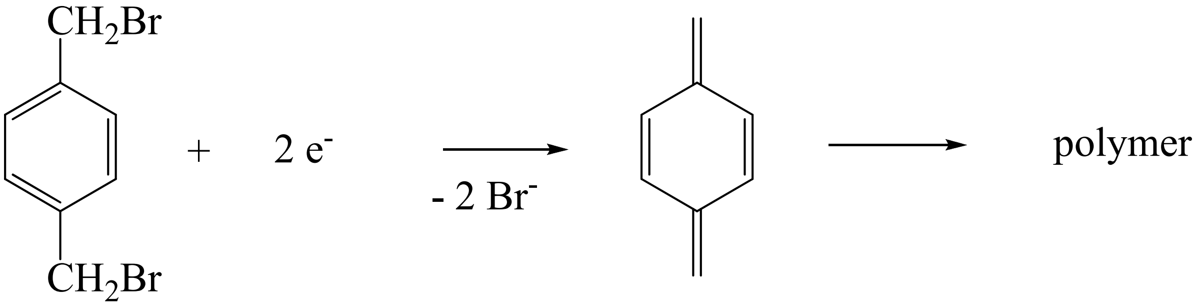
$$\mathrm{Ph{-}CH(Br){-}CH(Br){-}Ph} + 2\ e^- \longrightarrow \mathrm{Ph{-}CH{=}CH{-}Ph} + 2\ \mathrm{Br}^-$$

Cleavage reactions

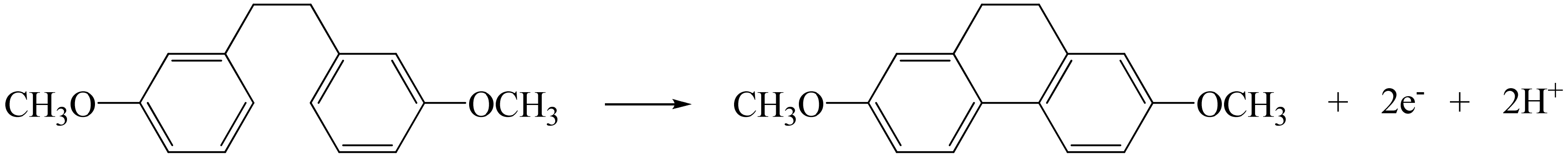
(1) $PhS{-}SPh \longrightarrow 2\,PhS^{+} + 2\,e^{-}$

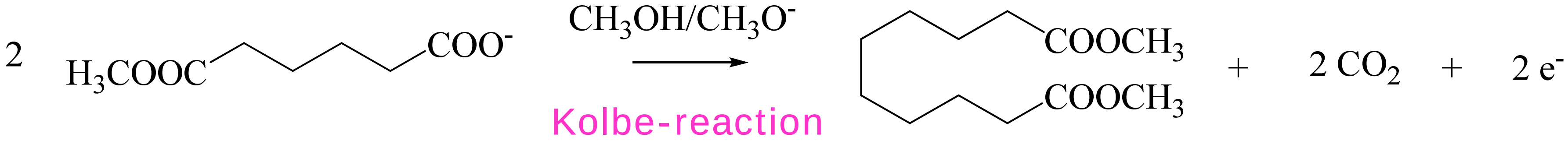
(2)

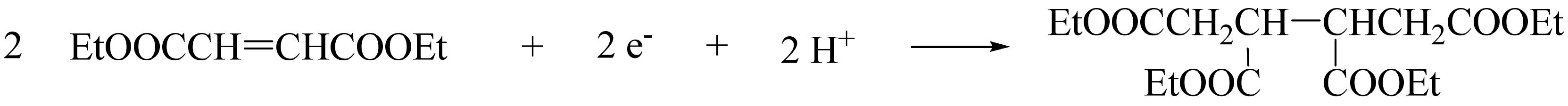




Coupling reactions



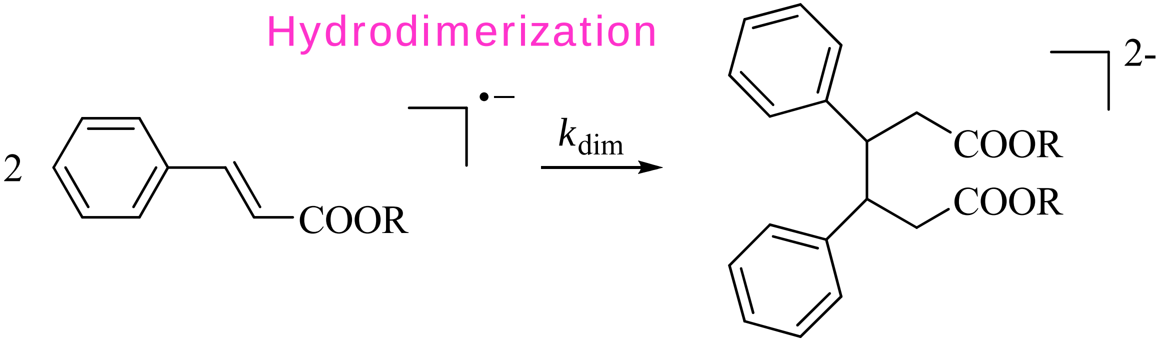




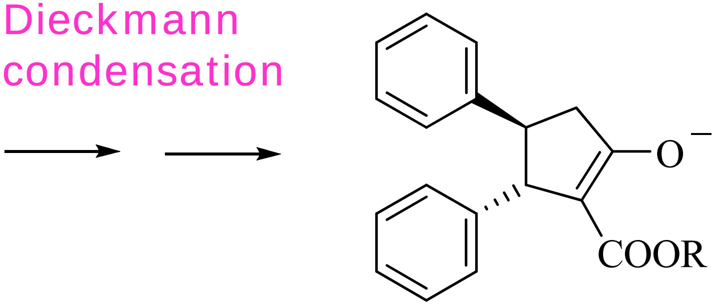
$$2\ \mathrm{EtOOCCH{=}CHCOOEt} + 2\,e^- + 2\,H^+ \longrightarrow \mathrm{EtOOCCH_2}\underset{\mathrm{EtOOC}}{\mathrm{CH}}-\underset{\mathrm{COOEt}}{\mathrm{CH}}\mathrm{CH_2COOEt}$$

Coupling/condensation reactions

Hydrodimerization

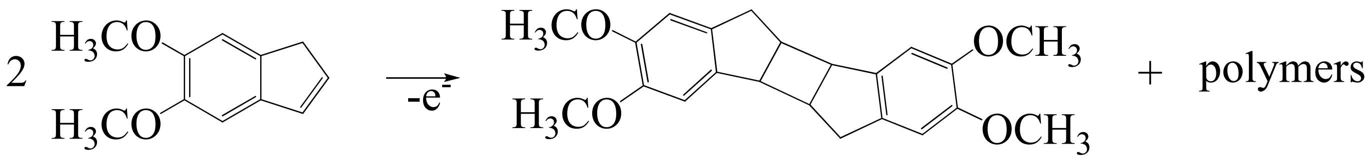


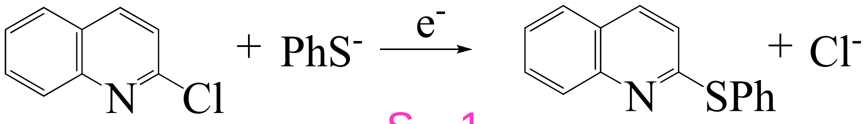
Dieckmann condensation



Electron transfer induced chain reactions

[2+2] cycloaddition





$S_{RN}1$

Conventional organic chemistry is ’2-electron chemistry’

In general organic compounds have an even number of electrons

G.N. Lewis (1916): A covalent bond is the result of two atoms or groups sharing en electron-pair

Therefore, organic redox reactions are mostly ’2-electron reactions’

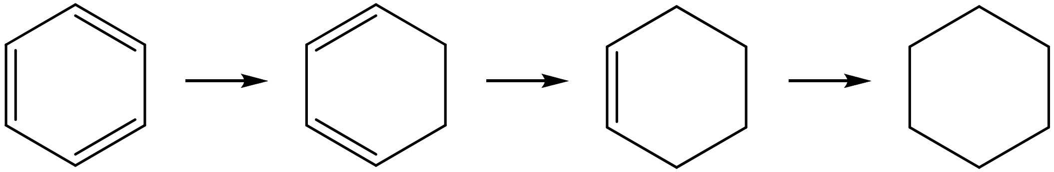
Examples:

$Ar\text{-}NO_2 \rightarrow Ar\text{-}NO \rightarrow Ar\text{-}NHOH \rightarrow Ar\text{-}NH_2$

$R\text{-}COOH \rightarrow R\text{-}CHO \rightarrow R\text{-}CH_2OH \rightarrow R\text{-}CH_3$

$R\text{-}SO_2\text{-}R \rightarrow R\text{-}SO\text{-}R \rightarrow R\text{-}S\text{-}R$

$R\text{-}C{\equiv}N \rightarrow R\text{-}CH{=}NH \rightarrow R\text{-}CH_2NH_2$



Organic electrochemistry is ’1-electron chemistry’

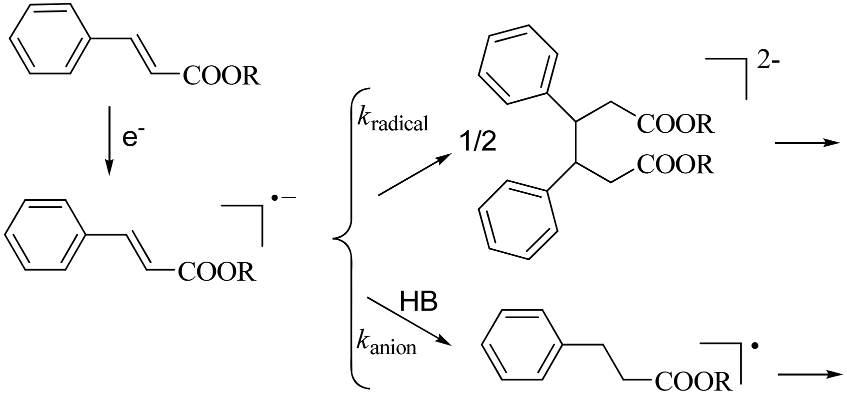
Reaction mechanisms are often complex, which leaves the synthetic organic chemist uncomfortable

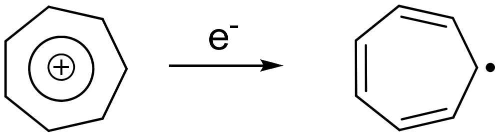
Electrochemistry is ’electron transfer chemistry’ and electrons are transferred one by one driven by the electrode potential

π-systems

For neutral π-systems the primary intermediates are radical cations and radical anions, that is, the intermediates are radicals and ions at the same time and it is not easy to predict whether the radical character or the ion character predominates for a given radical ion.

For charged π-systems the primary intermediates are radicals that may dimerize





Organic electrochemistry is ’1-electron chemistry’

Reaction mechanisms are often complex, which leaves the synthetic organic chemist uncomfortable

Electrochemistry is ’electron transfer chemistry’ and electrons are transferred one by one driven by the electrode potential

σ-systems

For neutral σ-systems electron transfer is dissociative resulting in radicals and cations or anions

For charged σ-systems dissociative electron transfer results in neutral fragments and radicals

$$R{-}Cl \xrightarrow{e^-} R^\bullet + Cl^-$$

$$R_4N^+ \xrightarrow{e^-} R_3N + R^\bullet$$

Organic electrochemistry is ’1-electron chemistry’

Electrochemistry is ’electron transfer chemistry’ and electrons are transferred one by one

---and so are protons and so are ----

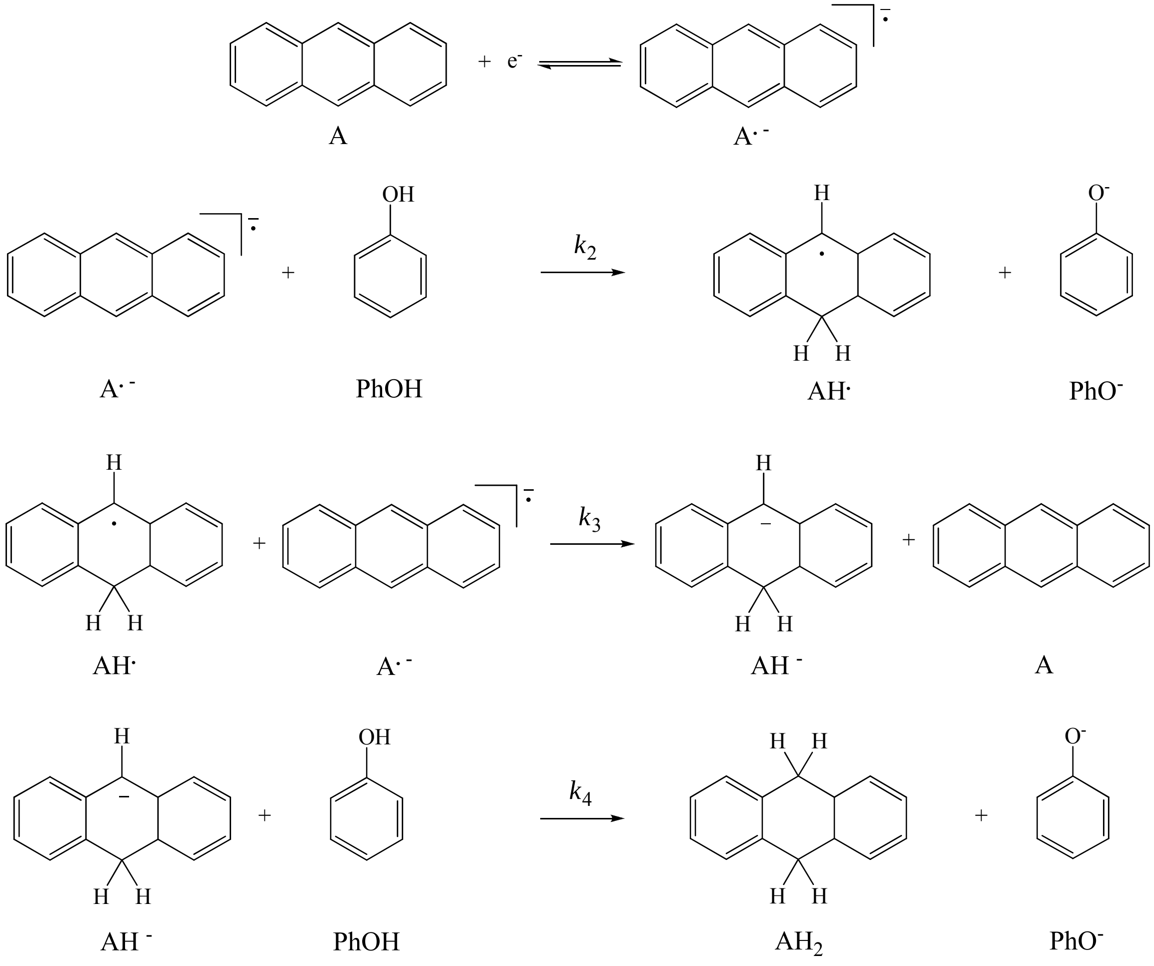
The electrochemical reduction of a –CH=CH- system, for instance,

$$R\text{-}CH{=}CH\text{-}R + 2e^{-} + 2H^{+} \rightarrow R\text{-}CH_2\text{-}CH_2\text{-}R$$

therefore is a four-step process including the transfer of
2 electrons and 2 protons

The order of the four steps depends on the substrate and the conditions

The mechanism of electrochemical hydrogenation of anthracene



Stoichiometry: $A + 2e^- + 2\ PhOH \longrightarrow AH_2 + 2\ PhO^-$

Practical aspects

Remember:

The number of experimental parameters that may be manipulated is large including the

- a) electrode potential
- b) current
- c) electrode material
- d) solvent and the supporting electrolyte
- e) mass transfer to/from the electrodes
- f) cell design

in addition to all the other parameters that may be manipulated in a conventional organic synthetic reaction

Any of these parameters may affect the products and/or yields

Take-home-message: Do as told in the recipe !

The electrode potential – driving force

- The Nernst equation
- The standard potential, E^o and the formal potential, $E^{o'}$
- The heterogenous electron transfer rate constants, k_s^{red} and k_s^{ox}

$$O + ne \underset{k_s^{ox}}{\overset{k_s^{red}}{\rightleftarrows}} R$$

$$\boxed{E = E^o + \frac{RT}{nF}\ln\frac{(O)}{(R)}} = E^o + \frac{RT}{nF}\ln\frac{f_O[O]}{f_R[R]}$$

$$\boxed{E = E^{o'} + \frac{RT}{nF}\ln\frac{[O]}{[R]}} \qquad E^{o'} = E^o + \frac{RT}{nF}\ln\frac{f_O}{f_R}$$

n is the number of electrons (for organic compounds, typically, *n* = 1)
R is the gas constant
T is the absolute temperature
F is the Faraday constant
Parentheses, (), are used for activities and brackets, [], for concentrations
f_O and f_R are the activity coefficients of O and R, respectively.

Most organic compounds are oxidized or reduced in the potential range +3 to -3 V

Voltage difference vs. potential difference

Two-electrode system for electrochemical synthesis

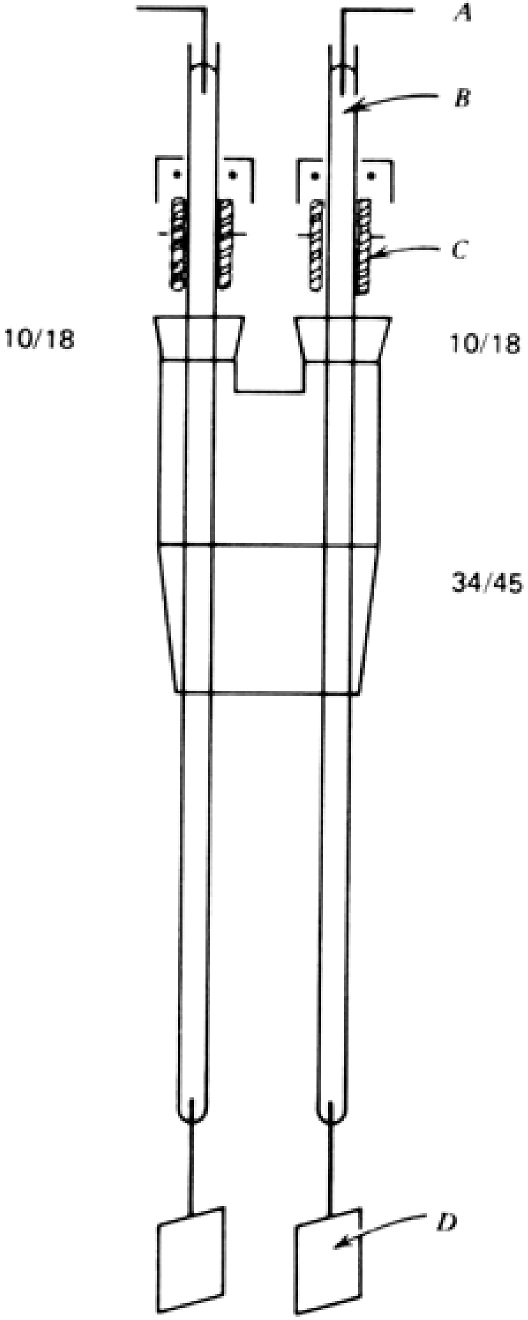
The *voltage* difference, ΔV, between the two electrodes is NOT the same as the *potential* difference, ΔE

$\Delta V = \Delta E + iR_s$

R_s: the solution resistance

iR_s: the so-called ohmic drop

R_s may amount to several hundred ohms



The current – conversion/time

The heterogenous electron transfer rate constants

$k_s^{red} = k^o \exp[-\alpha nF (E - E^o) / (RT)]$
$k_s^{ox} = k^o \exp[(1 - \alpha)nF (E - E^o) / (RT)]$

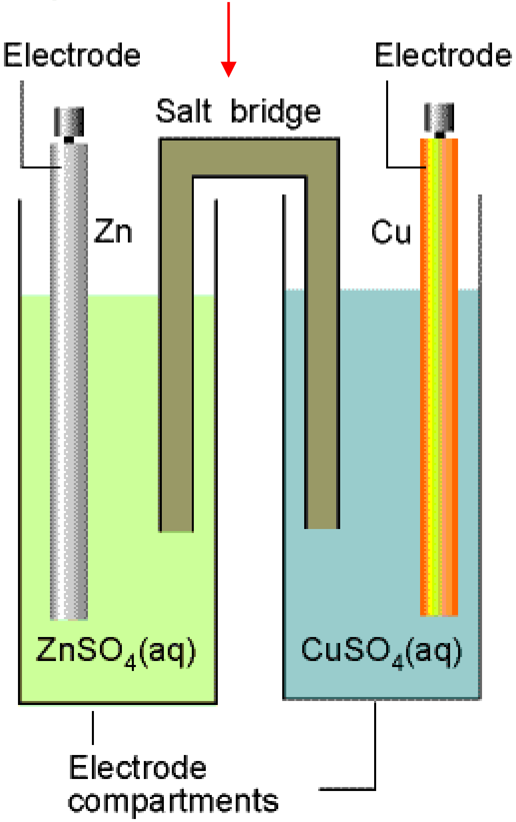
The Butler-Volmer equation
$i = nFA(k_s^{red}[O]_{x=0} - k_s^{ox}[R]_{x=0})$
$= nFAk^o \{[O]_{x=0} \exp[-\alpha nF (E - E^o) / (RT)] - [R]_{x=0} \exp[(1 - \alpha)nF (E - E^o) / (RT)]\}$

k^o is the standard heterogeneous electron transfer rate constant
α is the electrochemical transfer coefficient
(corresponds in electrochemistry to the Brønsted coefficient in organic chemistry)
A is the electrode area
$[O]_{x=0}$ and $[R]_{x=0}$ are the *surface concentrations* of O and R, respectively
(the Nernst equation)

Mass transport (stirring, pumping) is important

The current flow through the system

is caused by the transport of ions



A high concentration of the supporting electrolyte is important

The electrode material

The potential limiting processes (in aqueous solution or water containing organic solvents)

$2\ H_2O + 2e^- \rightarrow H_2 + 2\ OH^-$
$2\ H_2O \rightarrow O_2 + 4\ H^+ + 4e^-$

Overpotential for hydrogen evolution
Pd < Au < Fe < Pt < Ag < Ni < Cu < Cd < Sn < Pb < Zn < Hg

Overpotential for oxygen evolution
Ni < Fe < Pb < Ag < Cd < Pt < Au

Special electrode materials
Glassy carbon, carbon rods, Boron-doped diamond (BDD),
Dimensionally stable anodes (Ti covered with metal oxides) ---

Solvent and supporting electrolyte

The Solvent:

In addition to the usual solvent properties:

Applicable in the potential range +3V to -3V

Medium to high dielectric constants

The supporting electrolyte

Applicable in the potential range +3V to -3V

Well dissociated

Both:

Easy to remove during work-up

Preferably non-toxic

Aprotic

Non-nucleophilic and/or non-electrophilic

Recyclable

Solvents for oxidation:

MeCN, CH_2Cl_2, MeOH

Solvents for reduction:

MeCN, DMF, DMSO, THF

Supporting electrolytes for aprotic conditions:

R_4NBF_4, R_4NPF_6

typically Bu_4NPF_6

substitutions/additions:

MNu or R_4NNu

Alkoxylations: KOH

Components of a simple, undivided cell

Undivided and divided cells

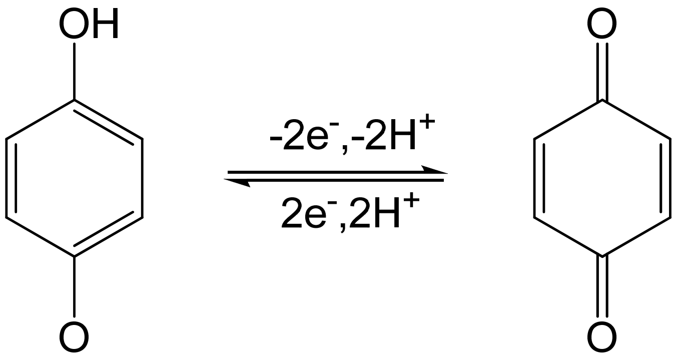
Two processes are going on in the electrochemical cell, always !

An oxidation at the anode

A reduction at the cathode

Potential problem:

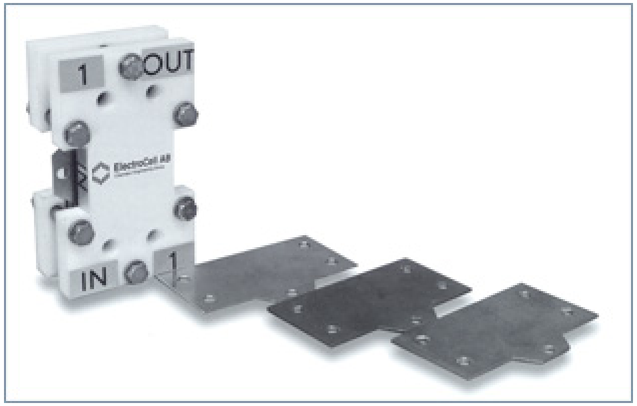
The product formed by oxidation at the anode may undergo reduction (back to the starting material) at the cathode

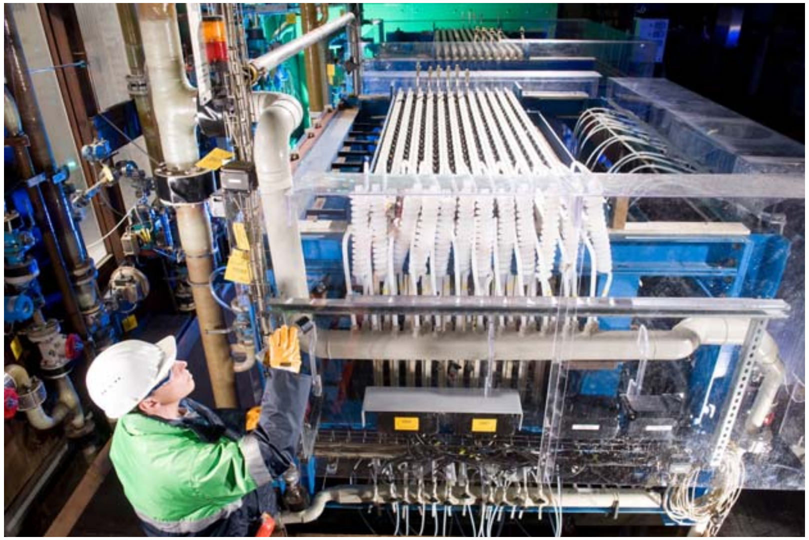


In such cases a divided cell is needed

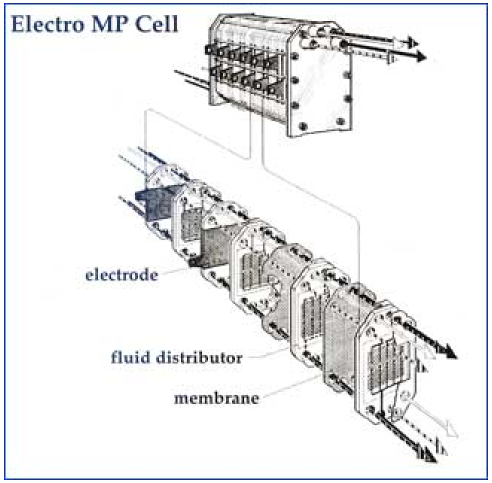
The classical, divided laboratory cell (H-cell)

Small, large and very large (divided) flow cells





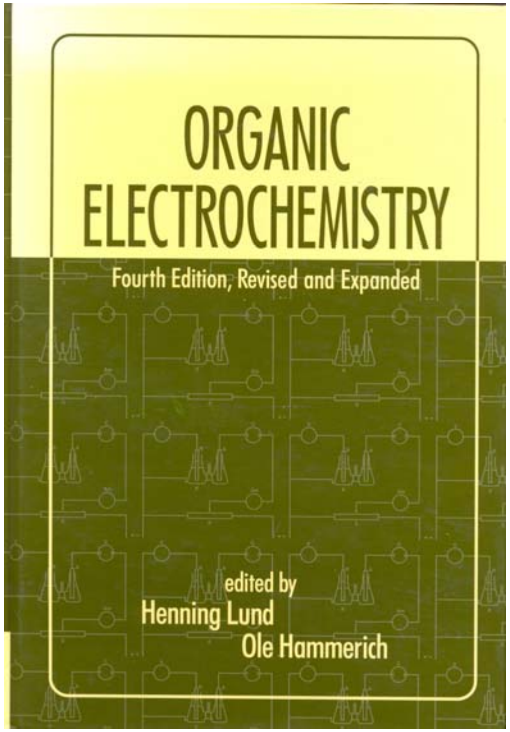
Electro MP Cell



Commercial processes

Product	Starting material	Company
Acetoin	Butanone	BASF
Acetylenedicarboxylic Acid	1,4-Butynediol	BASF
Adipoin Dimethyl Acetal	Cyclohexanone	BASF
Adiponitrile (> 100.000 tons/year)	**Acrylonitrile**	**Monsanto (Solutia), BASF, Asahi Chemical**
4-Aminomethylpyridine	4-Cyanopyridine	Reilly Tar
Anthraquinone	Anthracene	L. B. Holliday, ECRC
Azobenzene	Nitrobenzene	?
Calcium Gluconate	Glucose	Sandoz, India
L-Cysteine	L-Cystine	Several
Diacetone-2-ketogulonic Acid	Diacetone-L-sorbose	Hoffman-LaRoche
1,4-Dihydronaphthalene	Naphthalene	Hoechst
2,5-Dimethoxy-2,5-dihydrofuran	Furan	BASF
Dimethylsebacate	Monomethyladipate	Asahi Chemical
Gluconic Acid	Glucose	Sandoz, India
Hexafluoropropyleneoxide	Hexafluoropropylene	Hoechst
m-Hydroxybenzyl Alcohol	m-Hydroxybenzoic Acid	Otsuka
Mucic Acid	Galacturonic Acid	EDF
Perfluorinated hydrocarbons	Alkyl substrates	3M, Bayer, Hoechst
p-Methoxybenzaldehyde	p-Methoxytoluene	BASF
p-t-Butylbenzaldehyde	p-t-Butyltoluene	BASF, Givaudan
Salicylic Aldeyde	o-Hydroxybenzoic Acid	India
Succinic Acid	Maleic Acid	CERCI, India
3,4,5-Trimethoxybenzaldehyde	3,4,5-Trimethoxytoluene	Otsuka Chemical

Literature



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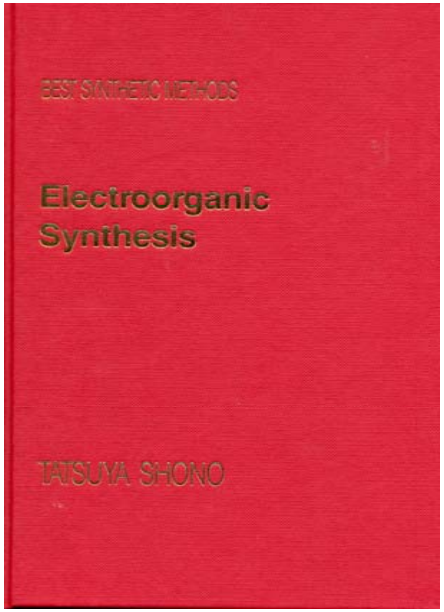

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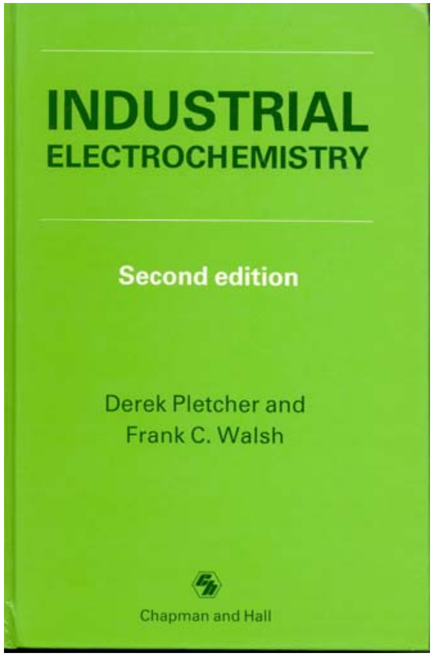

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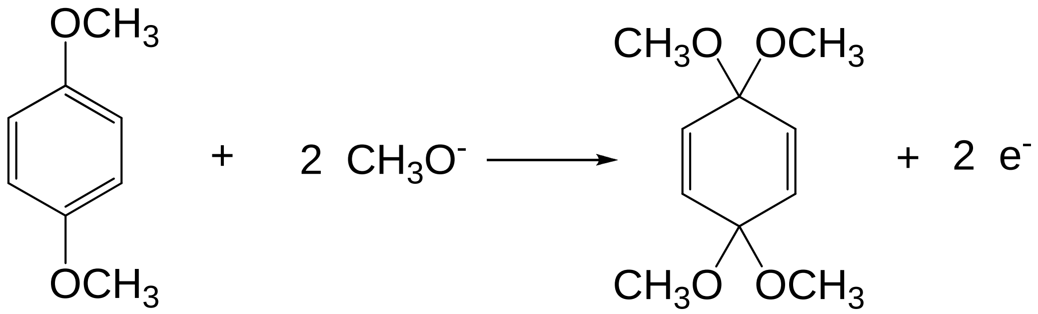
The undivided cell put together

The power supply

Recipe no 1

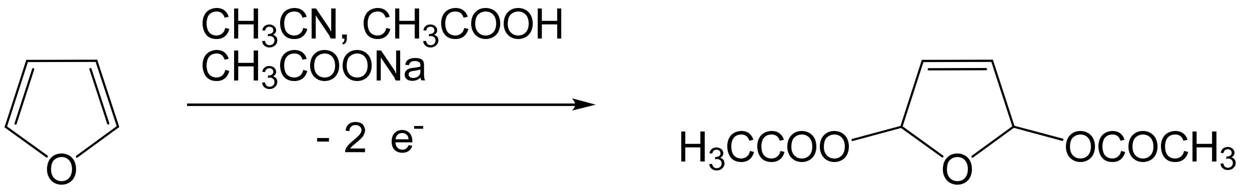


To a magnetically stirred solution of 1 g of KOH in 150 mL of methanol at ~0°C is added 4.6 g (0.033 mol) of 1,4-dimethoxybenzene.

The solution is electrolyzed at 1 A for 2 h in an undivided cell using a Pt gauze anode and a C cathode.

After oxidation the solution is concentrated under reduced pressure. To the residue is added 100 mL of water, which is extracted with three 50 mL portions of ether. After removal of solvent, the residue is recrystallized from light petroleum to give ~5 g of the product (m.p. 40-41°C).

Recipe no 2

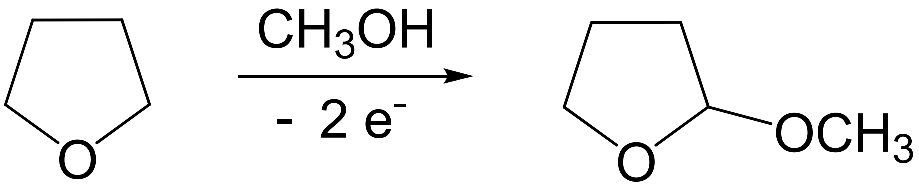


Into a cell equipped with a Pt anode and a C cathode is added a solution of furan (2 g) in a mixture of AcOH (120 mL) and MeCN (30 mL) containing AcONa (6 g).

The mixture is cooled to 3 ~ 7°C during the oxidation.

After 2.5 F (~1 A for 2h) of charge has passed, the reaction mixture is poured into water and extracted with CH_2Cl_2. The extracts are dried with $MgSO_4$ and distilled to give the product.

Recipe no 3



A solution of tetrahydrofuran (7.4 mmol = 0.53 g) and Et_4NOTs (2 mmol = 0.6 g) in a mixed solvent of acetic acid (10 mL) and methanol (120 mL) is put into an undivided cell equipped with a platinum anode and a graphite rod cathode.

After 10 F (~1A for 4 h) of charge is passed, the product is obtained by distillation.