J. Serb. Chem. Soc. 61(11)1033-1037(1996)
JSCS-2323

UDC 547.922/.5:541.138/.2
Original scientific paper

Improved electrochemical epoxidation of cholesterol and avarol dimethyl ether*

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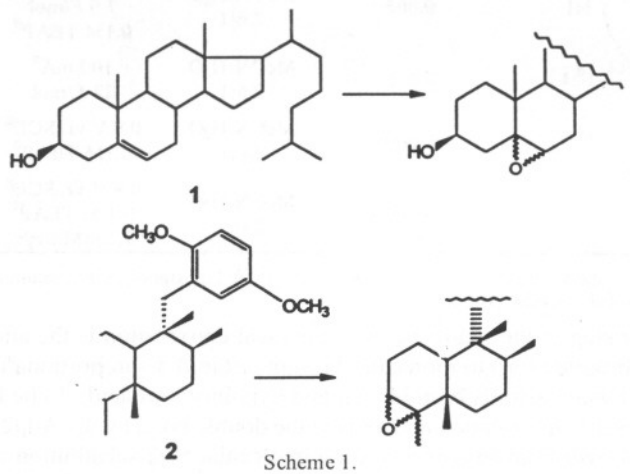
(Received 15 July 1996)

Electrochemical epoxidation of cholesterol and avarol dimethyl ether with bromide as heteromediator was performed, and its mechanism discussed. The influence of the solvent, the mediator concentration, and different electrolytic techniques on yield of the products was examined. Under optimal conditions, the yield of the cholesterol epoxides (5α,6α and 5β, 6β) was 88%, and of the corresponding epoxides of the avarol dimethyl ether 72%.

Key words: electrochemical epoxidation, cholesterol, avarol dimethyl ether.

Epoxides are very useful intermediates for various chemical transformations.[1] They have been widely used in syntheses of natural products as well as in industrial processes, so that numerous methods for their preparation have been developed.

Indirect electrochemical epoxidation of olefins using halogen anions as heteromediators is a well known procedure.[2-9] We wish to report here our complementary study



Scheme 1.

* Dedicated to Professor Dragomir K. Vitorović on the occasion of his 70th birthday.

concerned with the nature and advantages of this relatively simple, cheap and potentially useful process. We outline below examples of the electrochemical epoxidation of two natural products: cholesterol **1** and avarol dimethyl ether **2** (Scheme 1).

RESULTS AND DISCUSSION

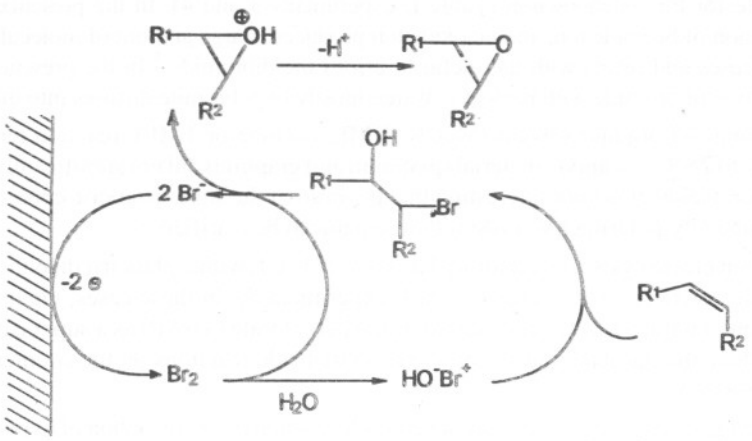
Electrochemical epoxidation of cholesterol was performed in a mixture of an organic solvent and water in the presence of sodium bromide. We investigated the influence of the composition of the mixture, the concentration of the mediator and different electrolytic techniques on the yields and distribution of the products. The results are presented in Table I.

TABLE I. Influence of the reaction conditions on the yield of products

Experiment	$n_{cholest}$:n_{NaBr}	C_{NaBr} *vs.* w (mol/dm3)	Solvent (v/v)	Conditions	Yield (%)
1	1:1	0.26	MeCN:H_2O 4:1	250 mA[a] 6.1 *F*/mol[b]	12
2	1:1	0.14	MeCN:H_2O 5:1	100 mA[a] 6.9 *F*/mol	23
3	1.2:1	0.058	MeCN:H_2O 2.6:1	100 mA[a] 7.0 *F*/mol	46
4	1.2:1	0.025	MeCN:H_2O 2.6:1	100 mA[a] 6.9 *F*/mol	70
5	1:1	0.025	MeCN:H_2O 2.6:1	100 mA[a] 6.4 *F*/mol	70
6	1:1	0.009	MeCN:H_2O 2.6:1	100 mA[a] 7.9 *F*/mol	80
7	1:1	0.006	MeCN:H_2O 2.6:1	100 mA[a] 7.9 *F*/mol 0.1M TEAP[c]	88
8	1[d]:1	0.025	MeCN:H_2O 2.6:1	100 mA[a] 27 *F*/mol	70[e]
9	1[f]:1	0.009	MeCN:H_2O 2.6:1	0.9 V *vs.* SCE[g] 0.1M TEAP[c]	56
10	1[f]:1	0.009	MeCN:H_2O 2.6:1	0.9 V *vs.* SCE[g] 0.1 M TEAP[c] 7.1 mM Et_3N	72

[a]Electrolysis at constant current; [b]*vs.* NaBr; [c]Divided cell; [d]Cholestanol; [e]Cholestanone; [f]Avarol dimethyl ether; [g]Electrolysis at constant potential

The first step in the indirect electrochemical epoxidation is the anodic oxidation of the mediator (bromide ion) to molecular bromine. Rapid disproportionation of bromine in the presence of water affords bromide ion and hypobromous acid.[10] The latter electophilic species diffuses into the solution and adds to the double bond by the Ad_E2 mechanism. The resulting bromohydrin undergoes a fast intramolecular S_N2 substitution reaction followed by deprotonation of the intermediate oxonium cation[11] (Scheme 2). The majority of our electrochemical epoxidations was performed in the presence of an equimolar amount (or small excess) of the mediator with respect to the olefin. Theoretically, the reaction cycle requires only a catalytic amount of the mediator but a large fraction of bromine is effectively "trapped" in the three consecutive reactions, which are much slower than the electrochemical



Scheme 2.

process; also half of the oxidized bromide, after disproportionation is returned to the anode and some of the hypobromous acid dissociates and thus loses its electrophilic character. A certain amount of the generated hypobromite is oxidized into bromate.

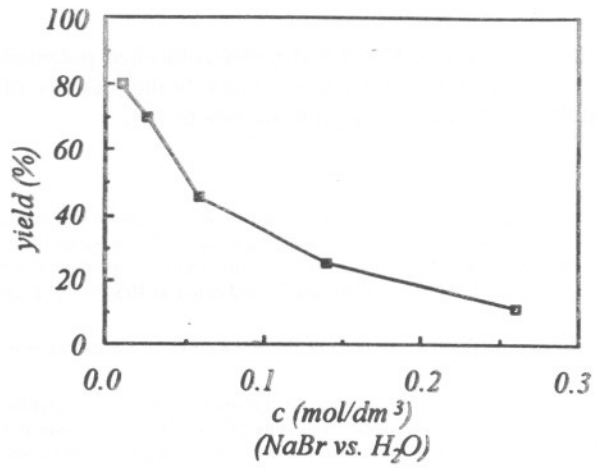


Fig. 1. Influence of the sodium bromide concentration on the yield of the epoxide.

The presence of water in the electrolyte is necessary for the disproportionation of molecular bromine and the generation of the electrophilic agent. In the absence of water only bromination takes place. Too much water results in the substrate being insoluble, and the yields are reduced. Best yields (80%) were obtained in the mixture of acetonitrile and water of the composition 2.6 : 1 (v/v).

The yields of the epoxide strongly depend on the ratio of sodium bromide and water (Fig. 1). The yields of the epoxide varied from 12% ($c_{NaBr\ vs.\ water}$ = 0.26 M) to 80% ($c_{NaBr\ vs.\ water}$ = 0.009 M) under similar reaction conditions. The composition of the solvent mixture is not

responsible for this phenomenon (Table I, experiments 3 and 4). In the presence of a high concentration of bromide ion, anodic oxidation produces a large amount of molecular bromine which diffuses and reacts with the olefin to afford the dibromide.[3] In the presence of a low concentration of bromide with respect to water, mostly hypobromite diffuses into the solution.

Change of organic solvent (MeCN, DME, acetone or TMF), reaction temperatures (from 0 °C to 25 °C), or anode material (platinum and graphite) did not significantly influence the reaction yields. It is very interesting that the ratio of the stereoisomeric epoxides is 1 : 1, as determined by polarimetry, a result that remains to be clarified.

When electrolysis was performed in a divided cell (with a glass frit diaphragm) yields were on the average, 10% higher (Table I, experiment 7). In these cases, the mixture was supplemented with 0.1 M tetraethylammonium perchlorate (TEAP) as a supporting electrolyte to reduce the resistance of the medium, so that side reactions on the counter electrode were minimized.

During the electrolysis there are several side reactions (*e.g.*, oxidation of hypobromites to bromates, oxidation of secondary alcohols *etc.*), so that current efficiency is in the range of 25-33%. We noticed that under higher current densities ($j = 50–100$ mAcm^{-2}) there were smaller amounts of side products generated, because of shorter electrolysis time. However, a higher current density can induce local overheating in the area of the working electrode, and cause both the thermal degradation of the product and the favoring of alternative reaction pathways.[12]

Epoxidation of olefins typically requires 6-7 Fmol^{-1} *vs.* NaBr while for the oxidation of the secondary alcohol cholestanol, 27 Fmol^{-1} were used under identical reaction conditions.[13]

Epoxidation of avarol dimethyl ether **2** was performed under controlled potential conditions (0.9 V *vs.* SCE), in order to prevent possible side reactions. In the presence of triethylamine (1.1 eq) as an external base, the yield increased from 56% to 72%.

EXPERIMENTAL

Avarol dimethyl ether was prepared by the usual procedure.[4] Acetonitrile and triethylamine were purified in the usual way.[15] Tetraethylammonium perchlorate (TEAP) was prepared by dropwise addition of perchloric acid (10% in excess) into the aqueous solution of tetraethylammonium bromide. TEAP separated as a white precipitate. It was recrystallized three times from water, and dried at 105 °C for three hours.

A 200W Voltcraft DIGI40 was used for syntheses at a constant current and a potentiostat/galvanostat EG&G PAR 173 for syntheses at a constant potential.

A platinum cylindrical gauze was used as the working electrode, a platinum gauze as the counter electrode and saturated calomel electrode (SCE) as a reference electrode for the preparative electrolysis at a constant potential. A platinum foil was the working electrode and DSE, the counter electrode for syntheses at a constant current. Diaphragms were soaked in concentrated nitric acid and rinsed in water.

The cells were conical, and their volumes were between 15 to 50 ml.

Polarimetric measurements were performed on a Carl Zeiss Jena Polamat A polarimeter.

General procedure

Cholesterol (0.10 g, 0.26 mmol) and sodium bromide (0.028 g, 0.26 mmol) were added into an acetonitrile: water mixture (2.6 : 1 v/v). Electrolysis was performed in the undivided cell with a platinum anode and graphite as the counter electrode, under constant current conditions ($j = 100$ mAcm^{-2}). The reaction mixture was electrolyzed until TLC indicated the absence of starting material. A saturated aqueous solution of potassium bisulfite was then added and the mixture was extracted with methylene chloride, washed with saturated sodium chloride solution and dried (Na_2SO_4). The organic solvent was evaporated under reduced

pressure and the resulting oily residue was purified by column chromatography (silica-gel, toluene: ethyl acetate, 9 : 1 v/v), followed by crystallization (acetone: water, 88 : 12 v/v) to afford the product as colorless crystals, identified by published data.

Acknowledgement. This work was supported by Ministry of Science and Technology of the Republic of Serbia.

ИЗВОД

ОПТИМИЗОВАНА ЕЛЕКТРОХЕМИЈСКА ЕПОКСИДАЦИЈА ХОЛЕСТЕРОЛА И ДИМЕТИЛ-ЕТРА АВАРОЛА

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Урађена је електрохемијска епоксидација холестерола и диметил-етра аварола са бромидом као хетеромедијатором, и продискутован њен механизам. Испитан је утицај растварача, концентрације медијатора и различитих електролитичких техника на принос производа. Укупни принос оба стереоизомерна епоксида холестерола (5α,6α и 5β,6β) био је 88%, а одговарајућих епоксида диметил-етра аварола 72%.

(Примљено 15. јула 1996)

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