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Diastereoselective Cathodic Reduction of Chiral Phenylglyoxylamides[1]

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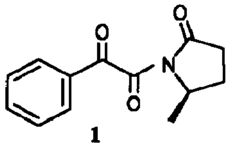
Abstract: The cathodic reduction of (*R*)-5-methyl-2-pyrrolidinone- and (*S*)-4-isopropyl-2-oxazolidinone phenylglyoxylate affords the corresponding mandelic acid derivatives in 82-90% chemical yield and 42-81% *de* depending on electrolyte and temperature.

Reactive intermediates as radical ions, carbocations, carbanions and radicals are frequently used in organic synthesis. They become easily and in a wide variety accessible by electron transfer[2]. For this reason electrolysis is widely employed in CC-bond forming reactions and functional group interconversions[3].

The extent of asymmetric induction achieved in organic electrosynthesis is differently progressed[4] but in general diastereoselectivities and enantioselectivities lack behind those accomplished in chemical synthesis.

In this contribution the diastereoselectivity of the cathodic reduction of the carbonyl group in (*R*)-5-methyl-2-pyrrolidinone phenylglyoxylate (**1**)[5] and in (*S*)-4-isopropyl-2-oxazolidinone phenylglyoxylate (**2**)[5] is studied.



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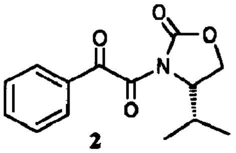

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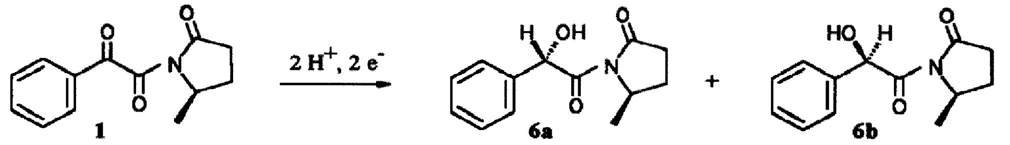
Reasons for the choice of **1** and **2** were: (a) the reduction potential for the keto group is shifted anodically in a favorable range for electrolysis by both the phenyl substituent and the amide carbonyl group, (b) the mechanism of the cathodic reduction of phenylglyoxylic acid (**3**) has been intensively studied[6], (c) the diastereoselectivity of the cathodic reduction of (-)-menthyl phenylglyoxylate has already been reported[7], (d) the chiral auxiliary can be recovered by hydrolysis of the amide, and (e) the chiral auxiliaries (*R*)-5-methyl-2-pyrrolidinone (**4**) and (*S*)-4-isopropyl-2-oxazolidinone (**5**) employed here have induced high facial selectivities in diastereoselective alkylations and additions of the enolates of the corresponding amides[8].

Results: The amides **1** and **2** are reduced to the corresponding mandelic acid derivatives **6a,b** and **7a,b** (eq. 1 and 2) between - 800 mV and -1060 mV vs. Ag/AgCl-reference electrode depending on the electrolyte. In the preparative scale reduction of **1** and **2** four reaction variables were changed in order to study their influence on the diastereoselectivity of the product formation. These were (a) the solvent, (b) the supporting electrolyte, (c) the size of the acid present in the electrolyte, and (d) the temperature. The cathodic reduction of **1** leads to an excess of **6a** (Table 1), this of **2** to an excess of **7a** (Table 2) as determined by hydrolysis of the excess diastereomer to mandelic acid.

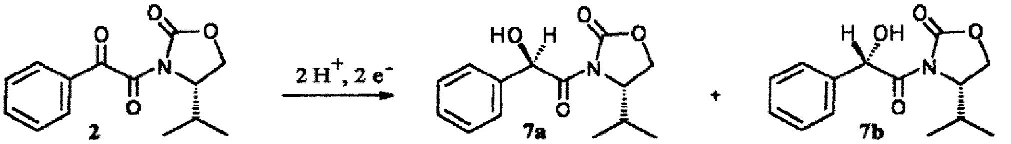


(1)

Table 1. Cathodic Reduction of **1** under Different Electrolysis Conditions[a)]

entry	solvent	acid	supporting electrolyte	reduction potential (mV)[b)]	temperature (°C)	pH	yield (%)[c)]	*de* (%)[d)]	current consumption (F/mol)
1	CH_3OH	HCl/citric acid	NaOH	- 800	20	2.2	82	42	1.3
2	CH_3OH	HCl/citric acid	LiOH	- 800	20	2.2	84	43	1.4
3	CH_3OH	CH_3COOH	NaOAc	- 890	20	5.4	89	52	1.5
4	CH_3CN	CH_3COOH	NaOAc	- 1050	20	4.2	88	62	1.5
5	CH_3CN	$(CH_3)_3CCOOH$	$LiClO_4$	- 910	20	2.7	90	68	1.5

a) Divided double walled beaker glass cell, mercury pool cathode (19.6 cm^2), platinum anode (4 cm^2), glass diaphragm, substrate concentration in catholyte: 0.032 $mol \cdot l^{-1}$, concentration of supporting electrolyte: 0.2 $mol \cdot l^{-1}$. b) At amalgamated gold wire vs. Ag/AgCl-reference electrode. These potentials were chosen as working potentials in the preparative scale electrolysis. c) Isolated yield. d) Excess of **6a**.



(2)

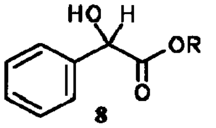
Table 2. Cathodic Reduction of **2** under Different Electrolysis Conditions[a)]

entry	solvent	acid	supporting electrolyte	reduction potential (mV)[b)]	temperature (°C)	pH	yield (%)[c)]	*de* (%)[d)]	current consumption (F/mol)
1	CH_3OH	HCl/citric acid	NaOH	- 870	20	2.2	87	43	1.6
2	CH_3OH	HCl/citric acid	LiOH	- 870	20	2.2	89	45	1.6
3	CH_3CN	CH_3COOH	NaOAc	- 1050	20	3.4	86	59	1.5
4	CH_3CN	$(CH_3)_3CCOOH$	$LiClO_4$	- 1060	20	2.7	87	72	1.7
5	CH_3CN	$(CH_3)_3CCOOH$	$LiClO_4$	- 1060	-20	2.7	83	81	1.5

a) - c) as in Table 1. d) Excess of **7a**.

The structures of **6** and **7** were clearly established by their IR-, NMR- and mass spectra. The diastereomeric excesses of **6** and **7** were determined by glc and by isolation of both diastereomers[9]. The results obtained by both methods were in good agreement. **1** was partially electrolysed as racemic material. The diastereomeric excesses that resulted from *rac*-**1** corresponded well to those from (*R*)-**1**. The electrolyses of **2** were always carried out with enantiomerically pure substance.

The hydrolysis of **6** and **7** to mandelic acid (**8a**) was achieved without racemisation at the stereogenic center of **8a** with a mixture of lithium hydroxide (1.6 equiv.) and hydrogen peroxide (5 equiv.) in tetrahydrofuran/water (4:1, v/v)[10]. Afterwards **8a** was converted to methyl mandelate **8b** with diazomethane. From the pure excess diastereomer of **6** besides recovered **4** and (*S*)-methyl mandelate ((*S*)-**8b**), 30-40% methyl benzoate was isolated. The formation of methyl benzoate could not be suppressed so far, it is formed probably by oxidative cleavage of **6** with hydrogen peroxide. Similarly the hydrolysis of the pure excess diastereomer **7** afforded **5**, (*R*)-methyl mandelate ((*R*)-**8b**) and 30-40% methyl benzoate. The enantiomeric purity of the (*S*)- and (*R*)-methyl mandelates was checked by glc on a heptakis-(2,3,6-tri-*O*-methyl)-*β*-cyclodextrine capillary column. The configuration of the mandelates was determined on the same column in comparison with authentic (*S*)- and (*R*)-**8b**.



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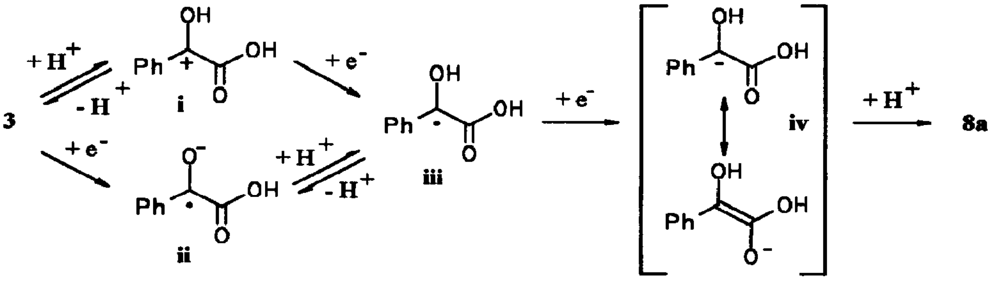
	R
8a	H
8b	CH_3

The mechanism of the cathodic reduction of phenylglyoxylic acid (**3**) has been investigated by *M.B. Fleury* and *J.C. Dufresne*[6]. According to this mechanism **3** is reduced in a CEEC- and/or an ECEC-mechanism to mandelic acid (**8a**) (C = chemical step, E = electron transfer step) (Scheme 1).



Scheme 1. Reduction mechanism of phenylglyoxylic acid (**3**)

In strongly acidic medium **3** is protonated first and the resulting cation **i** is reduced via the radical **iii** to the enolate **iv**, that is subsequently protonated to **8a**. In less acidic medium **3** is reduced to the radical anion **ii**, that is protonated to **iii**, which is subsequently reduced and protonated to **8a**. The reduction mechanism of **3** in acidic medium (pH < 7) should also be valid for the reduction of **1** and **2** in an acidic electrolyte.

The diastereomeric excesses are significantly influenced by the solvent, the size of the acid and the temperature as shown in Tables 1 and 2. The change of the supporting electrolyte and of the chiral auxiliary exerts only a minor influence on the diastereoselectivity. According to the mechanism in Scheme 1 the diastereoselectivity in the reduction of **1** to **6** arises from the protonation of the enolate for which the structures **9** - **12** can be discussed (Figure 1). The final proton transfer can occur from either the *si*- or the *re*-side. The excess diastereomer **6a** is formed by *re*-side protonation, which is favored in the enolates **9** and **12**. According to semi-empirical calculations[11] **9** is the most stable of the four enolates (Figure 1).

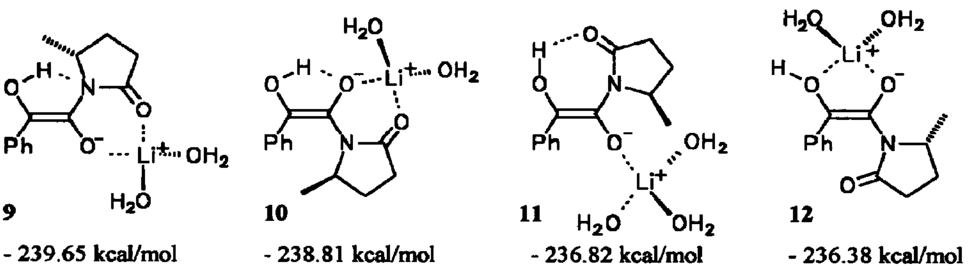


Figure 1. Structures and calculated energies of the possible *E*- and *Z*- enolate intermediates in the cathodic reduction of **1**.

The discrimination between protonation from *re*- and *si*-side should increase with the size of the acid as has been found (Table 1,2). According to this mechanism the amide **2** with the opposite configuration at the stereogenic center in the auxiliary should lead to a preferred *si*-protonation in the enolate, which is indeed the case. However, in spite of the bulkier isopropyl group in **2** as compared to the methyl group in **1** the diastereoselectivity for the reduction of **2** does not exceed this of **1**.

The results show that with the variation of the chiral auxiliary from (-)-menthol[7] to **4** or **5** the diastereomeric excess of the phenylglyoxylate reduction can be increased from 24% to 81%. Compared to the chemical catalytic hydrogenation of (*S*)-5-isobutyl-2,2,3-trimethyl-4-imidazolidinone phenylglyoxylate, which occurs with 96% *de*[12] the electrochemically achieved diastereomeric excess is still low. But compared to diastereoselective protonations[13], which are mechanistically similar to the last step of this electrochemical reduction, the achieved diastereoselectivity is quite good.

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5. For the preparation of amide **1** phenylglyoxylic acid **3** was activated by conversion into its mixed anhydride by reaction with pivaloyl chloride. Without isolation this anhydride was then treated with **4** in the presence of dimethylaminopyridine to afford amide **1** in 70% yield. **2** was obtained in 66% yield using phenylglyoxylic chloride, which was prepared from **3** and oxalyl chloride, and treating this with the lithium salt of **5**, obtained from **5** and butyl lithium.
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9. **6a**: $[\alpha]_D^{20} = -2.7$ ($c = 1$ in ethanol)
   7a: $[\alpha]_D^{20} = -23.4$ ($c = 1$ in ethanol)
10. J.R. Gage, D.A. Evans, *Org. Synth.* **1989**, *68*, 83-91.
11. Optimizations of the geometry were carried out using the PM3 method in the MOPAC 7.0 program with the keywords PRECISE and GNORM = 0.1. Dr. J.J.P. Stewart, MOPAC 7.0, F.J. Seiler Research Laboratory, U.S. Airforce Academy, Colorado Springs.
    We thank T. Löhl, Organisch-Chemisches Institut der Universität Münster, for the PM3 calculations.
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