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Electrochemical Carboxylation of *N*-(2-Bromopropionyl)-4*R*-phenyloxazolidin-2-one: An Efficient Route to Unsymmetrical Methylmalonic Ester Derivatives

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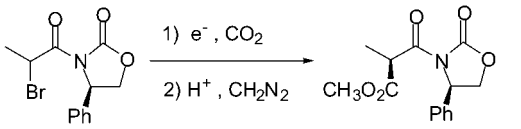
ABSTRACT



major diastereoisomer

Electrochemical carboxylation of *N*-(2-bromopropionyl)-4*R*-phenyloxazolidin-2-one aimed at the synthesis and chiral resolution of unsymmetrical methylmalonic ester derivatives is described. The presence of the Evans' chiral auxiliary permits an easy resolution of the mixture of the two diastereoisomers.

Optically active α-monoalkylmalonic derivatives are valuable building blocks in asymmetric synthesis, providing access to unsymmetrical 2-substituted 1,3-propandiols in an enantiomerically enriched form.[1,2] The common chemical approach to these chiral malonates in enantiopure form consists of the resolution of the diastereoisomeric mixtures by means of a chiral resolving agent (typically an optically active alcohol[1] such as menthol or 8-phenylmenthol). Menthyl and 8-phenylmenthyl half-esters of methylmalonic acid have been obtained in 62 and 60% yields, respectively, and were composed of the two isomers in a ∼3:2 ratio. They could be converted into the corresponding chiral diol derivative by reduction (after activation).[1]

The electrochemical methodology permits the carboxylation[3] in the α-position to carbonyl groups by direct reduction of α-haloketones in the presence of carbon dioxide[4,5] (50−57% yields in α-ketocarboxylic acids) or by direct reduction of vinyl triflates also in the presence of carbon dioxide[6,7] (28−77% yields in cyclic α-ketocarboxylic acids and 33−67% yields in linear ones). To our knowledge, no electro-

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Table 1. Electrolyses[a] of Solutions of **1** under Different Experimental Conditions

				products (yield, %)[b]			
entry	anode/cathode	solvent/electrolyte	T	**3**	**4**	**2a** + **2b**	dr[c]
1	Mg/Pb[d]	MeCN/Et_4NClO_4	rt	33	30	36	57:43
2	Mg/Pb[d]	MeCN/Et_4NClO_4	−10 °C	65	20	15	65:35
3	Mg/Pb[d]	MeCN/Et_4NClO_4	−20 °C	72	22	5	83:17
4	Mg/Pb	THF/Bu_4NBF_4	−20 °C	37		62	63:37[e]
5	Mg/Pb[f]	THF/Bu_4NBF_4	−20 °C	32	5	40	69:31[e]
6	Mg/Pb	THF/Bu_4NBF_4	−40 °C	22		55	59:41[e]
7	Mg/Pt	THF/Bu_4NBF_4	−20 °C			70	60:40[e]
8	Mg/Pt[f]	THF/Bu_4NBF_4	−20 °C	53	10	36	68:32
9	Al/Pt	THF/Bu_4NBF_4	−20 °C	7		78	59:41[e]
10	Al/Pt[f]	THF/Bu_4NBF_4	−20 °C	22		27	52:48[e]

[a] Compound **1** (2 F/mol), undivided cells, galvanostatic conditions (I = 4 mA/cm^2). [b] Yields of isolated products, calculated with respect to the starting oxazolidinone **1**. [c] Diastereoisomeric ratio was determined by ^{1}H NMR. [d] Et_3N was added to the solution prior to electrolysis. These electrolyses were carried out under potentiostatic conditions (E = −1.7 V vs SCE). [e] Starting material was recovered at the end of the electrolysis. [f] Et_3N was added to the solution prior to electrolysis.

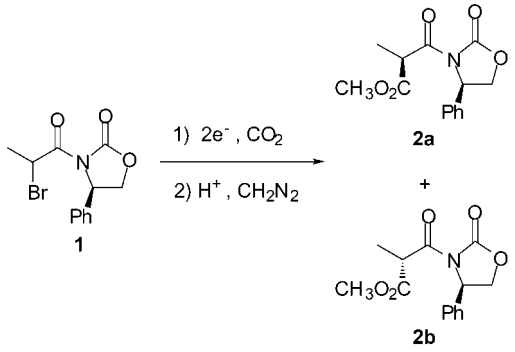
chemical carboxylation of α-haloesters or amides has been reported.

Here we report our preliminary results for the electrochemical carboxylation of *N*-(2-bromopropionyl)-4*R*-phenyloxazolidin-2-one aimed at the synthesis and chiral resolution of unsymmetrical methylmalonic ester derivatives. The subsequent selective reduction of the amidic function in the presence of the methyl ester group, to yield the corresponding chiral alcohol, is well described in the literature.[8]

The advantage of this kind of approach is that the resolving agent is present in the molecule prior to the introduction of the second carbonyl group by carboxylation, so it allows the transformation of this second function in an acid or ester in an easy way without the side reaction of diester formation.

The starting material was *N*-(2-bromopropionyl)-4*R*-phenyloxazolidin-2-one **1** (Scheme 1), both as an epimeric mixture and as pure diastereoisomers, and the outcome of the reaction was the same in all cases (no memory of chirality was evidenced).

Scheme 1



The electrolyses[9] were carried out on solutions (solvent-supporting electrolyte) containing **1** in which carbon dioxide was continuously bubbling. Various experimental conditions have been considered, and the results are reported in Table 1. All the electrolysis products are described in Figure 1.

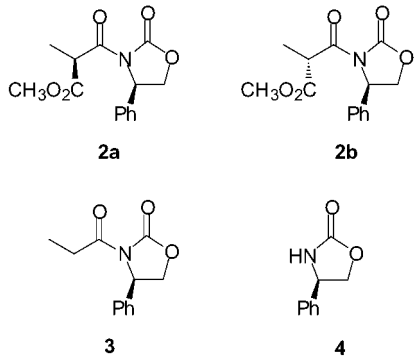


Figure 1

The two diastereoisomers **2a** and **2b** could be easily separated by column chromatography.

The yields in carboxylated products are influenced by various factors: electrolysis temperature (Table 1, entries 1−4 and 6), solvent system (Table 1, entries 3 and 5), and electrode material (cathode, Table 1, entries 4 and 7; anode, Table 1, entries 7 and 9). The higher yields in **2a** + **2b** (78%, Table 1, entry 9) were obtained using aluminum as a sacrificial anode and platinum as a cathode, in THF/Bu_4NBF_4 as a solvent−electrolyte system, at −20 °C under galvanostatic conditions. In this case, the diastereoisomeric ratio between the two carboxylated products was ∼3:2. If the reaction was carried out in MeCN−Et_4NClO_4,[10] the yields were lower (Table 1, entries 1−3), while the dr increased slightly with decreasing the temperature. MeCN probably

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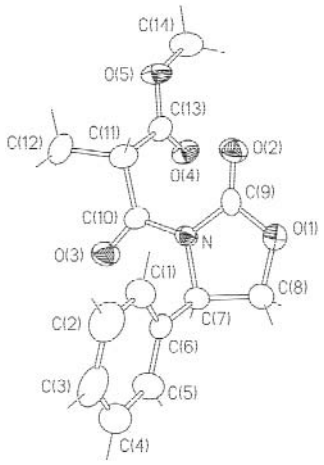

Figure 2

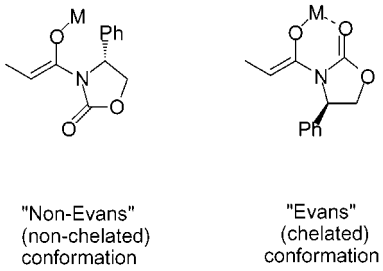

Figure 3

acts as a proton donor; in fact, when this solvent was used, the yields in reduced product **3** were very high to the detriment of those of the carboxylated products.

The role of Et_3N in this reaction is not so clear: Evans[11] reported that Et_3N forms a kind of aggregated complex with the enolate that derives from the reduction of the C−Br bond, so it should enhance the diastereoselectivity of the carboxylation reaction; on the other hand, the yields in **2a** + **2b** are considerably lowered by the presence of the amine. The presence of **4** among the electrolysis products is probably due to the decomposition of the enolate ion via a ketene pathway.[12]

When the ammonium salt was replaced by $LiClO_4$, no carboxylated product could be isolated from the electrolyzed solution. Only 6% in **2a** + **2b** was obtained working with divided cells in the same experimental conditions as those of entry 9 (Table 1).

In all cases, the more abundant diastereoisomer[13] is **2a**, as demonstrated by the X-ray analysis (Figure 2). This is probably due to the preferential "non-Evans" conformation[14] (that is, the nonchelated one) of the enolate ion during the carboxylation (Figure 3). In fact, in our experimental conditions, the concentration of the metallic ion, which derives from the consumption of the sacrificial anode and could chelate both oxygen atoms, is probably too low with respect to the concentration of the supporting electrolyte cation R_4N^+, which can coordinate but not chelate both carbonyl oxygen atoms. It is also possible that in a solvent such as THF, the metallic cation is not free but ion-paired with the bromide released during the electrolysis.

When the two diastereoisomeric esters (**2a** and **2b**) were allowed to epimerize separately (by reaction with Et_3N in CD_3CN), the equilibrium ratio of **2a**:**2b** was 2:3 in both cases, so we can deduce that in our experimental conditions the reaction is partially controlled by kinetic factors.

Any attempt to carboxylate by electrochemical means (using electrogenerated bases) the starting material not containing the bromine atom (i.e., *N*-propionyl-4*R*-phenyl-oxazolidin-2-one) failed, so the use of a halogenated derivative seems necessary.[15]

(9) **General Procedure.** A solution of 3-(2-bromopropionyl)-4*R*-phenyl-2-oxazolidinone[16] **1** in 30 mL of THF−0.2 mol/L Bu_4NBF_4 was electrolyzed (undivided cells, Pt or Pb cathode, Al or Mg anode, at −20 °C) under galvanostatic conditions ($I = 4$ mA/cm^2) in the presence of carbon dioxide ($p = 1$ atm). After the consumption of 2 Faradays per mol of **1**, the current flow was stopped, the solvent evaporated under reduced pressure, and the residue poured into water. This aqueous phase was extracted with diethyl ether (3 × 30 mL), and this organic solution was worked up as usual, giving the starting material **1**, (*R*)-(−)-4-phenyl-3-propionyl-2-oxazolidinone **3**,[17] and (*R*)-(−)-4-phenyl-2-oxazolidinone **4**, if any. The aqueous solution was then acidified (pH ≈ 3) with dilute HCl and extracted again with ether. This second ethereal phase was cooled at 0 °C and treated with ethereal CH_2N_2.[18] (CAUTION! Diazomethane is toxic and prone to cause development of specific sensitivity; in addition, it is potentially explosive). The usual workup gave the mixture of **2a** and **2b**, whose ratio was calculated by ^{1}H NMR. The two pure isomers were obtained after column chromatography (8:2 *n*-hexanes−ethyl acetate as the eluent). **3-(2-Methoxycarbonylpropionyl)-4*S*-phenyl-2-oxazolidinone (Less Polar Isomer) 2a.** ^{1}H NMR δ ($CDCl_3$): 7.40−7.25 (m, 5H, ar), 5.46 (dd, 1H, $J = 8.9$ Hz, $J = 3.7$ Hz, OC*H*H), 4.70 (t, 1H, $J = 8.9$ Hz, N.−C*H*), 4.53 (q, 1H, $J = 7.2$ Hz, C*H*CO_2CH_3), 4.29 (dd, 1H, $J = 8.9$ Hz, $J = 3.7$ Hz, OC*H*H), 3.71 (s, 3H, CO_2CH_3), 1.40 (d, 3H, $J = 7.2$ Hz, $CH_3CHCO_2CH_3$). ^{13}C NMR δ ($CDCl_3$): 170.81, 169.08, 153.69, 138.80, 129.25, 128.85, 125.94, 70.19, 57.79, 52.53, 45.66, 13.19. GC-MS *m*/*z*: 277 ($M^{+\cdot}$, 3%), 218 ($M^+ - CO_2CH_3$, 3%), 162 (73%), 104 (85%), 77 (79%), 59 (100%). $[\alpha]_D^{20}$ −96.9 (*c* 0.96, AcOEt). **3-(2-Methoxycarbonylpropionyl)-4*R*-phenyl-2-oxazolidinone (More Polar Isomer) 2b.** ^{1}H NMR δ ($CDCl_3$): 7.40−7.31 (m, 5H, ar), 5.44 (dd, 1H, $J = 9.0$ Hz, $J = 3.9$ Hz, OC*H*H), 4.71 (t, 1H, $J = 9.0$ Hz, N.−C*H*), 4.49 (q, 1H, $J = 7.2$ Hz, C*H*CO_2CH_3), 4.25 (dd, 1H, $J = 9.0$ Hz, $J = 3.9$ Hz, OC*H*H), 3.67 (s, 3H, CO_2CH_3), 1.39 (d, 3H, $J = 7.2$ Hz, $CH_3CHCO_2CH_3$). ^{13}C NMR δ ($CDCl_3$): 170.67, 168.81, 153.68, 138.39, 129.08, 128.70, 125.82, 70.30, 57.88, 52.36, 45.55, 12.95. GC-MS *m*/*z*: 277 ($M^{+\cdot}$, 3%), 218 ($M^+ - CO_2CH_3$, 3%), 162 (73%), 104 (85%), 77 (79%), 59 (100%). $[\alpha]_D^{20}$ −44.6 (*c* 0.87, AcOEt).

(10) CAUTION! Although in more than 100 experiments no particular safety problem has been encountered, the use of perchlorates in organic solvent must be considered as potentially dangerous (explosive). Take adequate precautions.

(11) Evans, D. A.; Rieger, D. L.; Bilodeau, M. T.; Urpì, F. *J. Am. Chem. Soc*. **1991**, *113*, 1047−1049.

(12) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc*. **1982**, *104*, 1737−1739.

(13) This kind of molecule exhibits a quite low kinetic acidity; they are, in fact, quite stable to silica gel chromatography and can be isolated in pure enantiomeric form. See: Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc*. **1984**, *106*, 1154−1156.

(14) Yan, T.-H.; Tan, C.-W.; Lee, H.-C.; Lo, H.-C.; Huang, T.-Y. *J. Am. Chem. Soc*. **1993**, *115*, 2613−2621.

(15) Any attempt to obtain **2a** + **2b** by metalation and carboxylation (using Mg or Zn under classical reaction conditions, followed by the addition of CO_2) failed.

(16) Ito, Y.; Sasaki, A.; Tamoto, K.; Sunagawa, M.; Terashima, S. *Tetrahedron* **1991**, *47*, 2801−2820.

(17) Ager, D. J.; Allen, D. R.; Schaad, D. R. *Synthesis* **1996**, 1283−1285.

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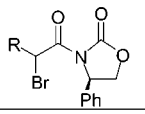
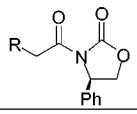
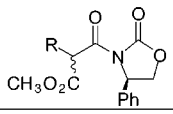
Table 2. Electrochemical Carboxylation of *N*-(α-Bromoacyl)-4*R*-phenyloxazolidin-2-ones[a]

entry	starting bromide: 	products: 				recovered starting material (%)
		(yield, %)[b]	(yield, %)[b]	*(d.r.)*[c]	*δ (Me)*[d]	
1[e]	R: Me	7	78	*(59:41)*	3.71-3.67	14
2	R: Et	8	67	*(53:47)*	3.64-3.70	22
3	R: *i*-Pr	2	64	*(56:44)*	3.64-3.71	30
4[f]	R: Ph	98	-			

[a] Starting bromide (2 F/mol). Electrolysis conditions: entry 9, Table 1. [b] Yields of isolated products, calculated with respect to the starting bromide. [c] Diastereoisomeric ratio was determined by ^{1}H NMR. [d] Chemical shifts of the hydrogen atoms of the methoxycarbonyl group (^{1}H NMR, ppm with respect to tetramethylsilane) of the major and minor diastereoisomers, respectively. [e] This electrolysis is reported in Table 1 (entry 9), and cited here for comparison. [f] Starting material was a chloride (instead of a bromide), and the electrolysis was stopped after 3 F/mol.

To test the applicability of this electrochemical carboxylation, the investigation was extended to *N*-(α-bromoacyl)-4*R*-phenyloxazolidin-2-ones other than the title one (see Table 2). As expected, when the alkyl group is replaced by a phenyl one, the electrochemical carboxylation does not take place and only the reduction product can be detected. Further investigations are necessary to improve these results.

In conclusion, the electrochemical methodology permits the synthesis in good yields and the easy resolution of methylmalonic ester derivatives by reduction and carboxylation of (4*R*)-3-(2-bromopropionyl)-4-phenyl-2-oxazolidinone.

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Supporting Information Available: Characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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