Electrogenerated Base-Induced N-Acylation of Chiral Oxazolidin-2-ones. 2[1]

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Abstract: An improved and efficient electrochemical N-acylation of chiral oxazolidin-2-ones has been achieved. The generation of the nitrogen anion is obtained under mild conditions and without addition of base or probase, by direct electrolysis of a solution of MeCN−TEAP containing the oxazolidinone. Acylation agents (acid chlorides or anhydrides) were added at the end of the electrolysis. N-Acylated products were isolated in high to excellent yields.

Since the initial papers of Evans,[2] chiral oxazolidin-2-ones have been often used as chiral auxiliaries in asymmetric synthesis.[3] Actually, *N*-acyloxazolidin-2-ones are able to induce a considerable diastereoselectivity in alkylation,[4] acylation,[2] aldol reaction,[5] and enantioselective Diels−Alder reactions.[6]

Recently, a highly enantioselective and diastereoselective Mukaiyama−Michael reaction of enolsilanes and acryloyloxazolidinones has been set up by Evans and co-workers.[7] Studying the addition reactions with chiral Ni(II) complex of glycine, Soloshonok and co-workers[8] have demonstrated that 3-(*trans*-enoyl)oxazolidin-2-ones are synthetically superior Michael acceptors than the corresponding alkyl enolates, allowing for a remarkable improvement in reactivity and diastereoselectivity. Finally, asymmetric aldol additions, carried out using chlorotitanium enolates of *N*-acyloxazolidinone, oxazolidinethione, or thiazolidinethione has been described by Crimmins and co-workers.[9]

Scheme 1

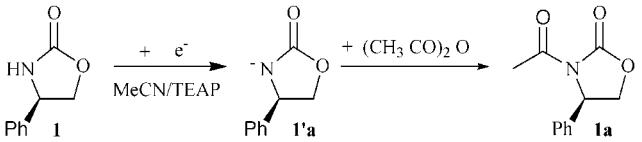

Table 1. Electrolyses, under Different Conditions, of Solutions of Oxazolidin-2-one 1 (MeCN-0.1 mol dm^{-3} TEAP as Solvent) Followed by Addition of Acetic Anhydride 7[a,b] (Scheme 1)

entry	cathode	anode	I/mA cm^{-2}	**1a**, yield (%)[c]	recovered **1** (%)
1	C	Pt[d]	25	63	28
2	Pb	Pt[d]	25	77	3
3	Cu	Pt[d]	25	81	11
4	Pt	Pt[d]	16	96	-
5[e]	Pt	Pt[d]	16	54	28
6	Pt	Mg[f]	16	32	61
7	Pt	Al[f]	16	-	96
8[g]	Pt	Pt[d]	16	10	79
9[h]	Pt	Pt[d]	16	96	2

[a] n = 1.0 (number of Faradays per mol of **1** supplied to the electrodes). [b] ρ = 1.0 (mole ratio **1**/ acetic anhydride). [c] Isolated yields. [d] Divided cell. [e] DMF instead of MeCN as solvent. [f] Undivided cell. [g] $LiClO_4$ instead of TEAP as supporting electrolyte. [h] Oxazolidinone **1** was added at the end of the electrolysis.

The frequent utilization of chiral or nonchiral oxazolidin-2-ones in asymmetric synthesis has spurred many authors to investigate new methodologies of synthesis and acylation of this class of molecules. Traditionally, the methods for N-acylation of chiral oxazolidin-2-ones involve the presence of an acylating agent (acid chlorides, symmetrical or mixed anhydrides) and, in any case, of a base (*n*BuLi or triethylamine and catalytic amounts of 4-(*N*,*N*-dimethylamino)pyridine) strong enough to deprotonate the substrate, yielding the corresponding *N*-anion.[10]

On this subject, the electrochemical methodology is able to suggest effective alternative solutions. In fact, anionic intermediates can be obtained (selectively, in mild conditions and avoiding the use of chemical deprotonating reagents) by cathodic reduction of suitable substrates.

The electrochemical methods for generating organic anions either by two-electron cleavage of a σ bond or by direct cathodic deprotonation of relatively weak organic acids have been reviewed by V. A. Petrosyan.[11] Organic syntheses founded on the electrochemical deprotonation of N−H acids have been reported by several authors.[11,12] Recently, nitrogen anions have been obtained via electrochemical reduction of oxazolidin-2-ones.[13] In a previous paper[1] we have described the N-acylation of chiral

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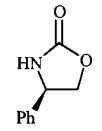
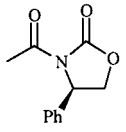
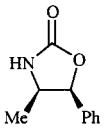
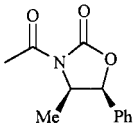
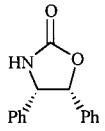
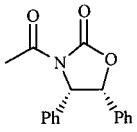
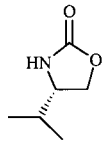
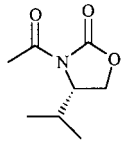
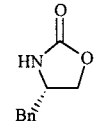
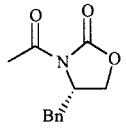
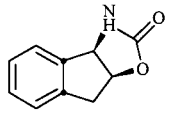
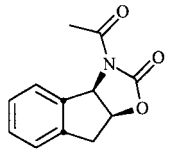
Table 2. Synthesis of *N*-Acetyloxazolidin-2-ones 1a−6a by Electrochemical Deprotonation of Oxazolidin-2-ones 1-6 Followed by Addition of Acetic Ahydride 7[a,b]

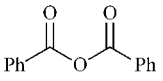
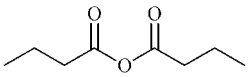
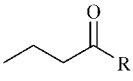
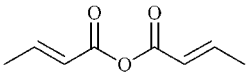
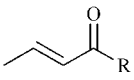
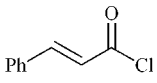
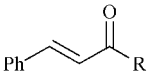
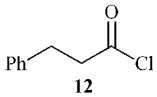
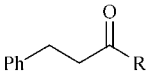
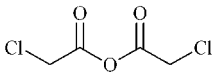
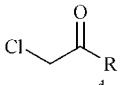
Entry	Oxazolidin-2-one	*N*-Acetyloxazolidin-2-one (yield, %)[c]
1	 **1**	 **1a** (96)
2	 **2**	 **2a** (93)
3	 **3**	 **3a** (89)
4	 **4**	 **4a** (93)
5	 **5**	 **5a** (94)
6	 **6**	 **6a** (97)

[a] n = 1.0 (number of Faradays per mol of **1** supplied to the electrodes). [b] ρ = 1.0 (mole ratio **1**/acetic anhydride **7**). Pt cathode and anode. Divided cell. I = 16 mA cm^{-2}. [c] Isolated yields.

oxazolidin-2-ones via deprotonation of these substrates using electrogenerated bases (EGBs) such as the anion of 2-pyrrolidone. Here below we wish to report a new method without the use of such EGBs. In fact, N-acylation of chiral oxazolidin-2-ones **1**−**6** has been obtained by electrochemical deprotonation of these substrates avoiding any addition of probases (PBs: i.e., extra compounds precursors of EGBs). Acid chlorides, bromides, and anhydrides **7**−**13** have been used as acylating agents (Scheme 1).

Solutions of MeCN/TEAP containing **1** (taken as model compound) were electrolyzed at room temperature under galvanostatic conditions in a divided cell (C, Pb, Cu, or Pt cathode and Pt anode) or in an undivided cell (Pt cathode and Mg or Al sacrificial anode). After the consumption of 1.0 F mol^{-1} of oxazolidin-2-one, the current was switched off, and acetic anhydride **7** was added to the cathodic solutions. The workup of these

Table 3. Synthesis of *N*-Acyloxazolidin-2-ones 1b−g by Electrochemical Deprotonation of Oxazolidin-2-one 1 Followed by Addition of Acylating Agents 8-13[a,b]

Entry	Acylating agent	*N*-Acyloxazolidin-2-one (yield, %)[c]
1	 **8**	 **1b** (96)
2	 **9**	 **1c** (89)
3	 **10**	 **1d** (86)
4	 **11**	 **1e** (89)
5	 **12**	 **1f** (97)
6	 **13**	 **1g** (98)[d]

[a] n = 1.0 (number of Faradays per mol of **1** supplied to the electrodes). [b] ρ = 1.0 (mole ratio **1**/acylating agent). Pt cathode and anode. Divided cell; I = 16 mA cm^{-2}. [c] Isolated yields; R = **1**. [d] Mole ratio acylating agent/**1** = 2.0.

solutions afforded *N*-acetyloxazolidinone **1a** and residual unreacted substrate **1** (Table 1). The yield of **1a** is greatly affected by the nature of the electrode material and of the solvent-supporting electrolyte system. The almost quantitative yield, obtained using a Pt cathode (MeCN/TEAP, divided cell, Pt anode; Table 1, entry 4) involves a very high current yield as well as a remarkable reactivity of the oxazolidinone anion **1′a** in MeCN/TEAP solution. Conversely, a drastic decrease in the yield of **1a**, or its total absence, has been obtained using Mg or Al as sacrificial anode (MeCN−TEAP; undivided cell; Pt cathode; Table 1, entries 6, 7) or DMF−TEAP and MeCN−$LiClO_4$ as solvent-supporting electrolyte systems (divided cell, Pt cathode and anode; Table 1, entries 5 and 8). If we consider that electrolysis in MeCN may produce the anion $^{-}CH_2CN$,[14] the formation of **1′a** could be related to the deprotonation of oxazolidin-2-one **1** via the electrogenerated base $^{-}CH_2CN$ as well as to the monoelectronic cathodic cleavage of the N−H bond. To check this statement, a MeCN−TEAP solution was electrolyzed in the absence of oxazolidinone (Table 1, entry 9). The workup of the cathodic solution, after addition of **1** and **7**, afforded **1a** in 96% yield.

To ascertain whether the electrochemical method for acylation of oxazolidin-2-ones avoiding any addition of bases could be generalized, the investigation was extended to chiral oxazolidin-2-ones **2**−**6**. In any case, high to excellent yields of *N*-acetyloxazolidin-2-ones **2a**−**6a**

(14) Lund H. In *Organic Electrochemistry*; Lund, H., Hammerich, O., Eds.; Marcel Dekker Inc., New York, 2001; p 264 and references therein.

were obtained, irrespective of the nature of the substituents of the carbon atom in 4- or 5-position (Table 2).

In addition, if the acylation of oxazolidinone **1** was carried out in the presence of various acylating agents (saturated and unsaturated anhydrides and acid chlorides **8**−**13**), again, the corresponding *N*-acyloxazolidin-2-ones **1b**−**g** were isolated in high to excellent yields (Table 3).

Last, it may be noteworthy that, in all cases examined, the acylation reaction occurs with total retention of the absolute configuration of all the chiral carbon atoms, and any possible epimerization has been avoided.

In conclusion, the acylation of chiral oxazolidin-2-ones (Evans's chiral auxiliaries) has been carried out in high to excellent yields and avoiding any addition of bases or probases by electrochemical deprotonation of the substrates followed by addition of an acylating agent.

Experimental Section

General. The electrochemical apparatus, the cell, and the reference electrode as well as the NMR instrument, polarimeter, and melting point apparatus were described elsewhere.[15a] Acetonitrile (MeCN), *N*,*N*-dimethylformamide (DMF), and tetraethylammonium perchlorate (TEAP) were purified as already described.[15b]

Reagents. All reagents were commercially available and used as received. The ee for the chiral ones was ≥98% (as reported by the supplier).

General Procedure. The electrolysis was carried out under galvanostatic conditions (I = 16 mA cm^{-2}) at Pt cathode and anode (divided cell), at r.t., in MeCN−TEAP (20 mL, 0.1 mol dm^{-3}) containing 0.5 mmol of oxazolidinone with continuous N_2 bubbling. At the end of the electrolysis (1 Fmol^{-1} of oxazolidinone), 0.5 mmol of acylating agent was added to the solution, and the mixture was stirred at r.t. for 3 h. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography affording the *N*-acylated product.

Isolated Products. All the isolated products gave spectral data in accordance with that reported in the literature.[1] The ee (always ≥98%) of the isolated products was in accordance with the ee of the starting materials, as confirmed by NMR spectra and $[\alpha]_D$ values compared with those reported in the literature.

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