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Synthesis of chiral oxazolidin-2-ones by 1,2-amino alcohols, carbon dioxide and electrogenerated acetonitrile anion

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Abstract—An improved electrochemical synthesis of chiral oxazolidin-2-ones from chiral 1,2-amino alcohols is obtained by direct electrolysis of solutions of MeCN–TEAP containing the amino alcohol, with subsequent CO_2 bubbling and addition of TsCl. This synthesis avoids any addition of bases or probases and yields oxazolidinones in high yields. © 2002 Elsevier Science Ltd. All rights reserved.

In the last 20 years chiral oxazolidin-2-ones (Evans' chiral auxiliaries)[1–3] have been often employed in a wide range of reactions directed towards the stereoselective synthesis of natural products, antibiotics and pharmaceuticals.[4]

Classical syntheses of chiral oxazolidin-2-ones, using chiral 1,2-amino alcohols or their derivatives as starting materials, require toxic and hazardous reagents (phosgene or its derivatives) and/or drastic conditions (strong base or very high temperature and pressure).[1,5–8]

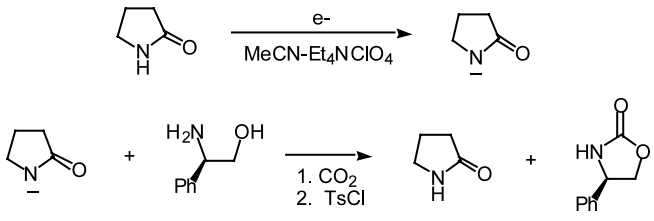
Consequently, many attempts have been made in order to set up the synthesis of chiral oxazolidin-2-ones in mild conditions and to avoid the use of hazardous chemicals.[9–17]

Recently, syntheses of chiral oxazolidin-2-ones by carboxylation of chiral amino alcohols via CO_2 and 2-pyrrolidone electrogenerated base, EGB (mole ratio EGB/substrate: 4) has been reported.[12] Therefore, an initial step for the electrochemical reduction of the probase (PB) 2-pyrrolidone to the electrogenerated base 2-pyrrolidone anion is required (Scheme 1).

According to these methodologies, the synthesis of oxazolidin-2-ones involves the initial carboxylation and deprotonation of the amino group. Consequently, the presence of a base strong enough for the deprotonation of the N–H group (i.e. the generation of a *N*-anion) is required. It follows that a large excess (4 mole ratio) of a by-product (2-pyrrolidone) is obtained, that complicates the work-up for the isolation of the main product.

Nevertheless, many electrochemical methods for generating organic anions avoiding any addition of bases, by cathodic cleavage of X–H bond (X: O, N, C) during the electrolysis of solutions containing weak organic acids (-OH, -NH, -CH acids), have been reviewed by Petrosyan.[18] Organic syntheses based on the generation of *N*-anions via electrochemical deprotonation of -NH acids have been described.[18,19]

Herein we report a simple and soft methodology for the direct synthesis of chiral oxazolidin-2-ones from chiral amino alcohols and carbon dioxide, thus avoiding any peculiar addition of bases or probases and the presence of the by-product (the conjugate acid of the EGB).



Scheme 1.

Keywords: electrochemistry; oxazolidin-2-ones; carbon dioxide.

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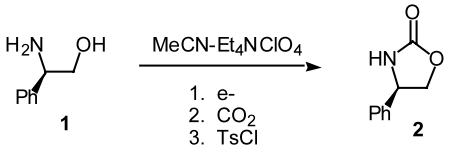
The synthesis is carried out by electrolysis, under galvanostatic control, of solutions of a chiral amino alcohol (MeCN–TEAP[20] as solvent-supporting electrolyte system, divided cell) followed by bubbling of CO_2 and addition of TsCl (Scheme 2).

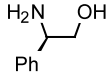
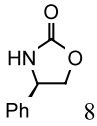
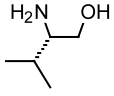
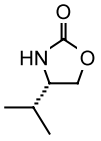
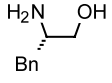
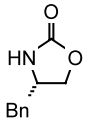
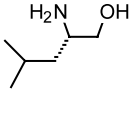
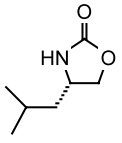
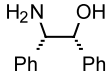
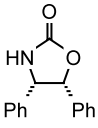
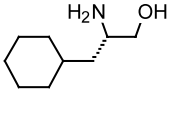
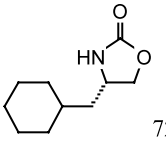
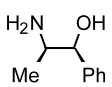
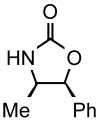
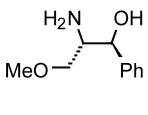
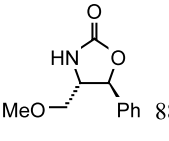
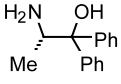
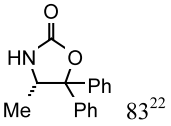
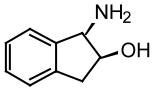
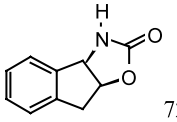
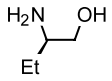
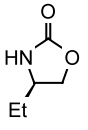
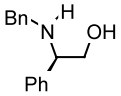
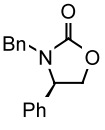
The yields of oxazolidinones are greatly affected by the number (n) of Faradays per mole of amino alcohol supplied to the electrodes. In fact, taking **1** as model compound, the yield of isolated **2** increases (29, 55, 67, 74, 88%) by increasing the value of n (1.0, 2.0, 3.0, 3.5, 4.0, respectively).

In a typical experiment, a solution of amino alcohol (1.0 mmol) in MeCN–0.1 mol dm^{-3} Et_4NClO_4 (30 cm^3) was electrolyzed under N_2, at room temperature (Pt cathode and anode, galvanostatic control, $I=16$ mA cm^{-2}); after the consumption of 4.0 mF, the current was switched off and the cathodic solution was stirred under CO_2 for 1 h. Finally, TsCl (1.0 mmol) was added to the mixture, which was stirred overnight at room temperature.



Scheme 2.

Table 1. Synthesis of chiral oxazolidin-2-ones by bubbling CO_2, followed by addition of TsCl, into electrolyzed solutions (MeCN–TEAP) of chiral amino alcohols[a]

Entry	Amino alcohol	Oxazolidin-2-one,[b] yield (%)[c]	Entry	Amino alcohol	Oxazolidin-2-one,[b] yield (%)[c]
1		 88, 74[d]	7		 88
2		 70	8		 71[23]
3		 87	9		 72[24]
4		 85	10		 88[25]
5		 83[22]	11		 72
6		 72[22]	12		 66[12]

[a] According to the general procedure under optimised conditions of synthesis.

[b] All compounds were compared with commercially available samples or with literature data.

[c] Isolated yields, based on the starting amino alcohol. *N*-tosylamino alcohol was recovered at the end of the reaction as spontaneous product between TsCl and amino alcohol (entry 1 and 3: 11%; 2 and 9: 18%; 4: 14%; 5: 8%; 6: 26%; 7: 12%; 8: 7%; 10: 9%; 11: 27%; 12: 24%).[12]

[d] The amino alcohol has been added to the solution at the end of the electrolysis.

The usual work up[12] gave the corresponding chiral oxazolidin-2-one **2** (88% of isolated product, Table 1, entry 1).

To test the efficiency and generality of this electrochemical procedure for the synthesis of chiral oxazolidin-2-ones, the investigation was extended to linear and cyclic amino alcohols bearing primary and secondary amine and hydroxy groups.

In any case chiral oxazolidin-2-ones have been isolated in good to excellent yields. The nature of the amino group (primary or secondary; Table 1, entry 1 versus 12, and of the substituents on the carbon atom in the α-position to the nitrogen atom (Table 1) may affect the yields of oxazolidinones. Besides, *N*-tosylamino alcohols were isolated as by-products from the reaction mixture (Table 1, note c).

Finally, it is quite interesting to observe that **2** has been obtained in good yields (76%; Table 1, note d) even if the amino alcohol **1** has been added to the cathodic solution at the end of the electrolysis carried out in MeCN–TEAP.

As regards this point, we have also to remark that anion $^{-}CH_2CN$ may be produced during electrolyses of MeCN–TEAP solutions.[21] Therefore, the generation of *N*-anions (in the overall process of carboxylation of the amino alcohols, see above) could be related to the deprotonation of the substrate via the base $^{-}CH_2CN$ as well as to the cathodic cleavage of a N–H bond.

In conclusion, a new electrochemical synthesis of chiral oxazolidin-2-ones from chiral amino alcohols and carbon dioxide has been proposed. Oxazolidin-2-ones have been obtained in good to excellent yields under mild conditions, avoiding the use of toxic, polluting or hazardous chemicals and without any addition of bases or probases.

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20. **CAUTION**! Anhydrous tetraethylammonium perchlorate–TEAP is potentially explosive. Therefore, we have considered the use of different solvent-supporting electrolyte systems: MeCN–TEAOTs (tetraethylammonium tosylate) and MeCN–TEATFB (tetraethylammonium tetrafluoroborate). Unfortunately, the use of these systems causes a sensible decrease in the yields (70 and 61% yields, respectively) of the isolated oxazolidin-2-one **2**.
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