The Reaction of 1,2-Amino Alcohols with Carbon Dioxide in the Presence of 2-Pyrrolidone Electrogenerated Base. New Synthesis of Chiral Oxazolidin-2-ones

M. Antonietta Casadei,[†] Marta Feroci,*[,‡] Achille Inesi,*[,§] Leucio Rossi,[§] and Giovanni Sotgiu[||]

Dip. ICMMPM, Università "La Sapienza", via Castro Laurenziano, 7, I-00161 Roma, Italy, Dip. CICM, Università degli Studi, I-67040, Monteluco di Roio, L'Aquila, Italy, Dip. di SCTSBA, Università "La Sapienza", P.le A. Moro, 5, I-00185 Roma, Italy, and Dip. di Ingegneria Elettronica, Università di Roma Tre, via Vasca Navale, 84, I-00146 Roma, Italy

feroci@uniroma1.it

Received February 22, 2000

The heterocyclic derivatives of 1,2-amino alcohols have often been successfully employed as chiral auxiliaries in asymmetric synthesis.[1] In this context the role played by chiral oxazolidin-2-ones (Evans' chiral auxiliaries)[2] has been particularly significant. These compounds have been used as chiral auxiliaries in a wide range of reactions (aldol, alkylation, Diels−Alder reactions, etc.) directed to the stereoselective synthesis of natural products, antibiotics and pharmaceuticals.[3]

1,2-Amino alcohols (or other amino acid derivatives) and phosgene (or its derivatives) are the starting materials in the classical syntheses of oxazolidin-2-ones.[1] Nowadays, diethyl carbonate is the reagent of choice for the synthesis of these auxiliaries.[4] Considerable efforts have been made in order to find some proper methodologies involving the use of innocuous materials (e.g., carbon dioxide) in the place of such toxic and dangerous reagents as phosgene or its derivatives.

Recently, the possible employment of carbon dioxide, a cheap and abundant raw material, as a source of carbon has been considered. Remarkable results have been obtained in the synthesis of organic compounds containing the −C(O)O− group (acids, esters, carbonates, carbamates and derivatives).[5] Nevertheless, oxazolidinones have been obtained, via direct employment of carbon dioxide, only in a limited number of cases and under drastic conditions of temperature (120−170 °C) and pressure (8−48 bar).[6] In this context, we have found that tetraethylammonium carbonate (TEAC) and tetraethylammonium peroxydicarbonate (TEAPC), electrochemically generated by cathodic reduction of solutions saturated with CO_2 or a mixture of O_2 and CO_2 respectively, react with 1,2-amino alcohols yielding, after addition of TsCl, oxazolidin-2-ones in fair to good yields.[7] However, some problems have been evidenced in the use of TEAC and TEAPC as carboxylating agents.[8a]

As already reported by us,[8] solutions of Et_4NClO_4 (TEAP) in aprotic solvents containing an electrogenerated base (EGB)[9] (as 2-pyrrolidone electrogenerate anion[10]) and saturated with carbon dioxide showed a remarkable carboxylating power toward amines and alcohols. Primary amines and alcohols were converted into carbamates and carbonates in excellent yields, whereas secondary ones were converted in good or moderate yields. Tertiary alcohols and phenols were unreactive.

Since the above-mentioned solutions (a) show a strong carboxylating power toward substrates containing amino or alcoholic groups and (b) are easy to prepare without the employment of toxic or polluting reagents, we thought that a preliminary study of their reactivity toward 1,2-amino alcohols, targeted to the synthesis of chiral oxazolidin-2-ones under mild and safe conditions, could be of interest. (*R*)-(−)-2-amino-2-phenylethanol **1a** was chosen as a reference compound.

Results and Discussion

2-Pyrrolidone was electrolyzed in MeCN−TEAP, in a divided cell (Pt anode and cathode) under galvanostatic control, and then the electrolized solution was added to 1,2-amino alcohol **1a**. Carbon dioxide was bubbled into the solution for 60 min. Last, tosyl chloride was added. The workup of the solutions afforded oxazolidin-2-one **2a** (Scheme 1).

The yield of **2a** was affected by different parameters including the number of Faradays per mole of 2-pyrrolidone supplied to the electrodes (n), the mole ratio 2-pyrrolidone/1,2-amino alcohol (ρ), and the nature of the solvent. The results are reported in Table 1. The best yield of **2a** was obtained with $n = 1$, $\rho = 4$ and using MeCN as solvent.

To ascertain whether this method for converting 1,2-amino alcohols into oxazolidin-2-ones could be generalized, the reactivity of linear and cyclic 1,2-amino alcohols bearing primary or secondary amine and hydroxy groups

* To whom correspondence should be addressed.
[†] Dip. of ICMMPM.
[§] University of L'Aquila. E-mail: inesi@ing.univaq.it.
[‡] Dip. SCTSBA.
[||] University of Roma Tre.

(1) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835−875.

(2) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129. (b) Evans, D. A. *Aldrichim. Acta* **1982**, *15*, 23−32.

(3) Ager, D. J.; Prakash, I.; Schaad, D. R. *Aldrichim. Acta* **1997**, *30*, 3−12.

(4) (a) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77−80. (b) For other novel and recent syntheses of chiral oxazolidin-2-ones, see: Lewis, N.; McKillop, A.; Taylor, R. J. K.; Watson, T. J. *Synth. Commun.* **1995**, *25*, 561−568; Li, G.; Lenington, R.; Willis, S.; Kim, S. H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1753−1754 and ref. therein and Zhao, H.; Thurkauf, A. *Synlett* **1999**, *8*, 1280−1282 and references therein.

(5) (a) Aresta, M.; Forti, G. *Carbon Dioxide as a Source of Carbon*; Nato Asi Ser. C, Vol. 206; Reidel D.: Dordrecht (NL), 1987. (b) Aresta, M.; Quaranta, M. *Proceedings of the International Conference on Carbon Dioxide Utilization*, Bari, Italy, 1993, p 63−77; *Proceedings of the International Conference on Carbon Dioxide Utilization*, Karlsruhe, Germany, 1999, p 82. (c) Feroci, M.; Inesi, A.; Rossi, L. In *Novel Trends in Electroorganic Synthesis*; Torii, S., Ed.; Springer-Verlag: Tokyo, 1998; pp 193−196.

(6) (a) Lynn, J. W. U. S. Patent 2,975,187, 1961; *Chem. Abstr.* **1961**, *55*, 16568. (b) Steele, A. B. U. S. Patent 2,868,801, 1959; *Chem. Abstr.* **1959**, *53*, 10261.

(7) Feroci, M.; Inesi, A.; Mucciante, V.; Rossi, L. *Tetrahedron Lett.* **1999**, *40*, 6059−6060.

(8) (a) Feroci, M.; Inesi, A.; Rossi, L. *Tetrahedron Lett.* **2000**, *41*, 963−966. (b) Casadei, M. A.; Cesa, S.; Rossi, L. *EurJOC*, in press.

(9) (a) Utley, J. H. P. *Top. Curr. Chem.* **1987**, *142*, 131−165. (b) Utley, J. H. P.; Ling-Chung, S. K.; Smith, C. Z. In *Electroorganic Synthesis*; Little, R. D., Weinberg, N. L., Eds.; Marcel Dekker Inc.: NewYork, 1991; p 377−386. (c) Baizer, M. M. In *Organic Electrochemistry*; Lund, H., Baizer, M. M., Eds.; Marcel Dekker Inc.: New York, 1991; pp 1265−1282.

(10) (a) Bonafoux, D.; Bordeau, M.; Biran, C.; Dunoguès, J. *J. Organomet. Chem.* **1995**, *493*, 27−32. (b) Shono, T.; Ishifune, M.; Okada, T.; Kashimura, S. *J. Org. Chem.* **1991**, *56*, 2−4.

10.1021/jo0002386 CCC: $19.00
Published on Web 07/06/2000

Scheme 1

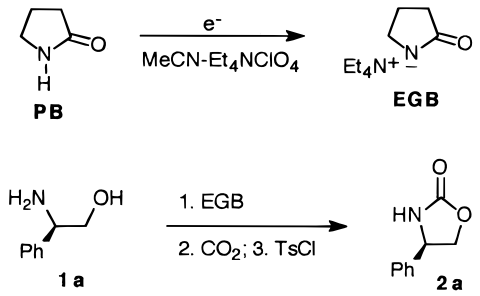


Table 1. Synthesis of Oxazolidin-2-one 2a from Amino Alcohol 1a According to the General Procedure

entry	n[a]	ρ[b]	yield,[c] %	solvent
1	0.5	4	49	MeCN
2	1.0	4	95	MeCN
3	1.5	4	85	MeCN
4	2.0	4	78	MeCN
5	2.5	4	66	MeCN
6	1.0	2	50	MeCN
7	1.0	6	65	MeCN
8	1.0	8	43	MeCN
9	1.0	4	47[d]	DMF
10	1.0	4	76[d]	NMP

[a] *n*: number of Faradays per mole of starting 2-pyrrolidone supplied to the electrode. [b] ρ mole ratio 2-pyrrolidone/**1a**. [c] Isolated yields, based on the starting amino alcohol. [d] HPLC yields.

has been studied (Table 2). This investigation was carried out under optimized reaction conditions, i.e., $n = 1$, $\rho = 4$, MeCN as solvent.

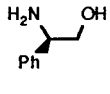
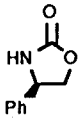
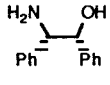
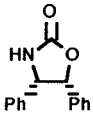
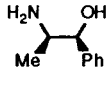
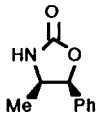
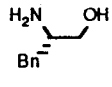
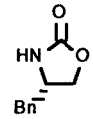
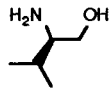
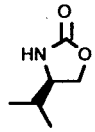
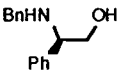
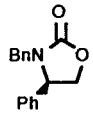
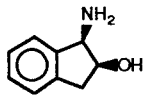
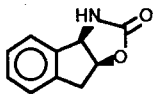
1,2-Amino alcohols whose amino group is a primary one were converted into the corresponding oxazolidinones in higher yields with respect to those in which a secondary amino group is present (Table 2, entries 1 and 6). Conversely, the different substitution on the carbon atom bearing the hydroxy function did not seem to affect the reaction yield (Table 2, entries 1 and 2). The nature of the substituents (alkyl or aryl groups) on the carbon atom in the α position to the nitrogen may affect the yields in oxazolidin-2-ones (Table 2, entries 1,4,5; 2,3).

As previously stated, amines as well as alcohols undergo the carboxylation process and the respective yields are affected by the nature (primary or secondary) of the reactive group. Therefore, amino alcohols could be carboxylated either at the amine or at the hydroxy group or even at both. Nevertheless, it is only the nature of the amine group that affects the yields of oxazolidinone, while that of the hydroxy group has no influence. This result suggests that, in the formation of the heterocyclic ring, the initial carboxylation of the hydroxy group might not be involved. To confirm this assertion, this procedure was applied to the amino alcohol **1a** with the addition of EtI instead of TsCl. From the reaction mixture it was possible to isolate **2a** (8%), **3a** (63%), and **3b** (12%). In addition, no product derived from the selective carboxylation of the hydroxy group could be isolated (Scheme 2).

Last, in the conversion of chiral 1,2-amino alcohols into chiral oxazolidin-2-ones, according to the present methodology, the absolute configuration of all chiral atoms is retained. This result allows to exclude the tosylation of the hydroxy group (Scheme 3).[14]

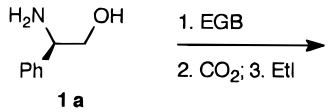
(11) Ishikawa, A.; Katuki, T. *Tetrahedron Lett.* **1991**, 3547−3550.
(12) Berry, M. B.; Craig, D. *Synlett* **1992**, *1*, 41−44.
(13) Ghosh, A. K.; Onishi, M. *J. Am. Chem. Soc.* **1996**, *118*, 2527−2528.

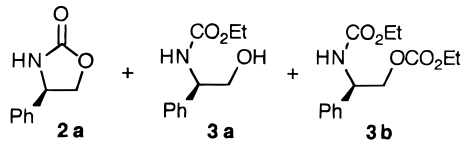
Table 2. Reactions of 1,2-amino Alcohols with 2-pyrrolidone EGB, CO_2, and TsCl in MeCN−TEAP[a]

Entry	Substrate	Product[b]	Yield, %[c]
1			95
2			89
3			79 [d,11]
4			71[d,12]
5			81[d,12]
6			64
7			66 [d,13]

[a] According to the general procedure under optimized conditions of synthesis. [b] All compounds were compared with commercially available samples. [c] Isolated yields, based on the starting amino alcohol. [d] *N*-Tosylamino alcohol (yields 5−9%) was recovered at the end of the reaction (see the references for spectral data).

Scheme 2



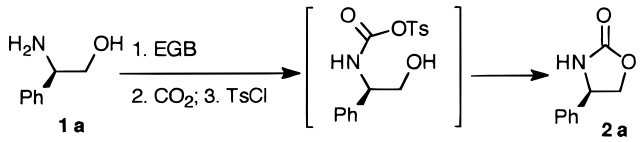


Conclusions

The study of the reactivity of 1,2-amino alcohols toward carbon dioxide in the presence of 2-pyrrolidone electrogenerated base allowed to establish a new methodology for the synthesis of oxazolidin-2-ones. Chiral oxazolidin-2-ones (Evans' chiral auxiliaries) were obtained in good to high yields avoiding the use of toxic, polluting or

(14) Probably the carbamate anion reacts with TsCl to form a mixed anhydride, that is a highly reactive acylating agent. The literature (Brewster, J. H.; Ciotti, C. J., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 6214−6215) reports the formation of such anhydride from a carboxylic acid and TsCl even in the presence of alcoholic hydroxy groups.

Scheme 3



dangerous reagents. This methodology represents a further example of the direct employment of carbon dioxide as a source of carbon in organic synthesis.

Experimental Section

General Methods. The electrochemical apparatus, the cell, and the reference electrode as well as the NMR and HPLC instruments were described elsewhere.[15] HPLC analyses were carried out using an RP-18 column and a MeCN−H_2O mixture in a linear gradient from 10:90 to absolute MeCN in 20 min. The flow rate was 1 mL min^{-1}. Acetonitrile (MeCN), *N*,*N*-dimethylformamide (DMF), *N*-methyl-2-pyrrolidone (NMP), and tetraethylammonium perchlorate (TEAP) were purified as already described.[16]

Reagents. Amino alcohols, ethyl iodide (EtI), tosyl chloride (TsCl), as well as 2-pyrrolidone (PB) were commercially available.

Electrochemistry. General Procedure. The electrolyses were carried out under galvanostatic control ($I = 25$ mA cm^{-2}), in a divided cell (platinum gauze cathode and anode), at 0 °C on solutions of 2-pyrrolidone (2.0 mmol, unless otherwise stated) in MeCN−0.1 mol dm^{-3} TEAP (30 mL) (except in the cases in which the solvent was DMF or NMP) in which N_2 was continuously bubbling. After the consumption of 2.0 mF (unless otherwise stated), the current was switched off, the amino alcohol (0.5 mmol) was added to the solution (at room temperature) and the bubbling of CO_2 (instead of N_2) was started and kept for 1 h. Then TsCl (1.0 mmol) was added to the mixture, the solution was stirred overnight at room temperature, and then analyzed. The solvent was removed from the solution under reduced pressure and a flash column chromatography of the residue (using as eluent a mixture light petroleum/ethyl acetate 6:4 or 7:3 in the case of (*R*)−(−)-*N*-benzyl-2-phenylglycinol) allowed the separation of the products, whose identity was established by comparison with commercial standard or by comparison of their spectral (^1H, ^{13}C, and $[\alpha]_D$) data with those reported in the literature. The isolated products and yields are reported in Table 2.

Reduction of 2-Pyrrolidone at Different F/mol. The electrolyses were carried out as previously described, but the current was switched off after the consumption of different amounts of electricity. The yields of isolated **2a** as well as the number of F mol^{-1} of pyrrolidone used in each experiment are reported in Table 1, entries 1−5.

Reaction of Electrochemically Reduced 2-Pyrrolidone in Different Mole Ratios with Amino Alcohol 1a. The electrolyses were carried out as described in the general procedure, but different amounts of 2-pyrrolidone (1.0−4.0 mmol) were used. The current was switched off after the consumption of different amounts of electricity according to the constant value of $n = 1$. The yields of isolated **2a** as well as the mole ratio between 2-pyrrolidone and **1a** are reported in Table 1, entries 2 and 6−8.

Reduction of 2-Pyrrolidone in Different Solvents. The electrolyses were carried out as described in the general procedure, but using DMF or NMP as solvents. The products and yields are reported in Table 1, entries 9 and 10.

Reaction of Electrochemically Reduced 2-Pyrrolidone with 1a, CO_2, and EtI. The electrolysis was carried out as described in the section "Electrochemistry", but EtI (in 5-fold molar excess with respect to the amino alcohol) was added to the solution instead of TsCl. From the solution, **2a** (8%), **3a**[17] (63%) and **3b**[17] (12%) were isolated.

Acknowledgment. The authors wish to thank Mr. M. Di Pilato for his contribution to the experimental part of this work. This work was supported by research grants from MURST (1998, 40%) and CNR, Roma Italy.

JO0002386

(15) Casadei, M. A.; Cesa, S.; Feroci, M.; Inesi, A. *New J. Chem.* **1999**, *4*, 433−436.

(16) Casadei, M. A.; Cesa, S.; Feroci, M.; Inesi, A.; Rossi, L.; Micheletti Moracci, F. *Tetrahedron* **1997**, *53*, 167−176.

(17) Casadei, M. A.; Micheletti Moracci, F.; Zappia, G.; Inesi, A.; Rossi, L. *J. Org. Chem.* **1997**, *62*, 6754−6759.