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Anodic Oxidation of the *N*-Cyanomethyloxazolidine System.

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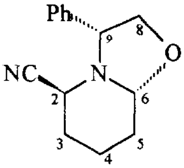
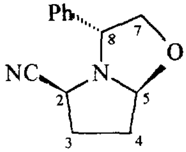
Abstract: The electrochemical oxidation of the *N*-cyanomethyloxazolidine system in acetonitrile at a platinum electrode afforded a radical cation which might follow either one of two pathways, according to the experimental conditions: the first, in the presence of chloride or bromide ions led to halogenated products, the second, in the presence of water, led to lactam / amide formation. The mechanistic pathway of both reactions is discussed.

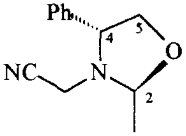
Recently, we have reported that the anodic oxidation of 2-cyano-6-oxazolopiperidine **1a** (and analogs **1b** and **1c**), in the presence of chloride and bromide ions, afforded a regioselective mono- or bis- chlorination α to the *N*, *O*-acetal function[1]. This electrochemical reaction represented a novel addition to the repertoire of transformations that might be performed on the chiral cyano-oxazolo synthons **1**[2-4]. The two potential iminium functions present in **1** were distinguished by this oxidation process and only the α-aminoether function was oxidized. This interesting electrochemical behaviour of **1** permitted regioselective α-substitution of the oxazolidine function while preserving the aminonitrile function.



1a



1b



1c

We have therefore investigated the mechanistic aspect of the electrochemical chlorination of **1**, and have extended the study to the electrosynthesis of some 5-bromo products together with the corresponding lactam / amide derivatives by means of specific experimental conditions.

Cyclic voltammetry (CV) investigations:

Voltammetry of **1a** running in acetonitrile containing lithium perchlorate as supporting electrolyte, on a platinum electrode, exhibited an irreversible one electron step (Epa = 1.80 V s.c.e.) whatever the sweep rate value [Fig.1 →]. The irreversibility of voltammograms is probably due: **(a)** to a low rate of heterogenous charge transfer between the electrode surface and the molecule and (or); **(b)** to the formation of a radical cation which is involved in a chemical step yielding a species no more oxidizable than **1a**. In this latter case, the chemical step can not be a deprotonation. Hence the potential (Epa = 1.80 V s.c.e.) measured for this compound has no direct thermodynamic significance.

The same type of electrochemical behaviour was observed with a solution of **1b** (Epa = 1.95 V s.c.e.) and **1c** (Epa = 1.75 V s.c.e.). Thus, the α-aminonitrile and the α-aminoether moieties act as *N*-deactivating groups. The oxidizability of **1**, reflected in the oxidation peak potential, is in the same range than those reported for the classical *N*-deactivating groups (carbamate, amide)[5].

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Fig 1

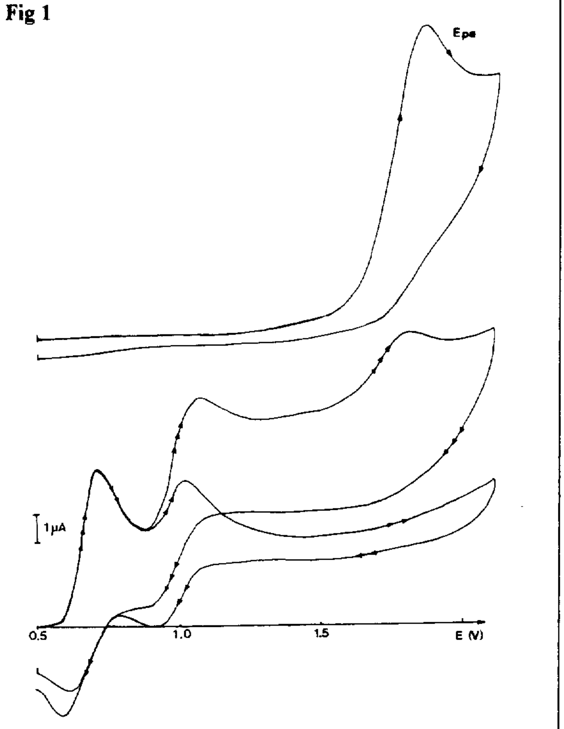


Fig 2

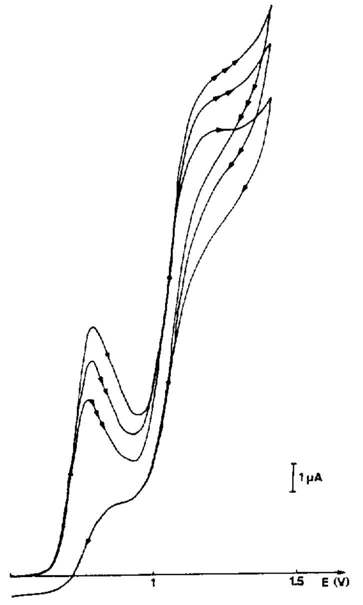
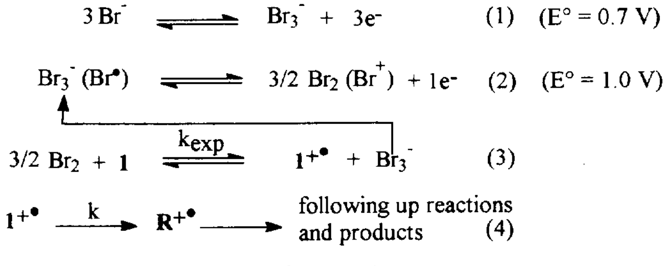


Fig 1: Cyclic voltammograms at 0.04 V s^{-1} potential scan rate in acetonitrile (MeCN) containing $LiClO_4$ (5×10^{-2} mol L^{-1}) of ;—▸ a solution of **1a** (2×10^{-3} mol L^{-1}); —▸▸ a solution of tetraethylammonium bromide (1×10^{-3} mol L^{-1}) ;—▸▸▸ a mixture of **1a** (2×10^{-3} mol L^{-1}) and bromide ions (1×10^{-3} mol L^{-1}).

Fig 2: Cyclic voltammograms of a mixture of **1a** (1×10^{-2} mol L^{-1}) and bromide ions (1×10^{-3} mol L^{-1}) at different scan rates:—▸ v = 0.1 V s^{-1} ;—▸▸ v = 0.075 V s^{-1} ;—▸▸▸ v = 0.05 V s^{-1}.

The anodic oxidation of **1a** in the presence of bromide ions (tetraethylammonium bromide) is a catalytic mediated process whereby Br_2 acts as an electron transfer agent[6-9] (mediator) according to scheme 1:



Scheme 1

This was clearly demonstrated by the cyclic voltammograms recorded with a solution of bromide ions in the absence and in the presence of **1a**. The CV of bromide ion showed two successive anodic signals [Fig. 1—▸▸] attributed to the redox systems 3 Br^- / Br_3^- and Br_3^- / 3/2 Br_2 (scheme 1) respectively.[10] When the medium was supplemented by **1a**, the voltammogram exhibited three successive anodic peaks [Fig. 1—▸▸▸].

The first one was unchanged, while the peak current involving Br_2 species formation was increased by a catalytic current, which depended on the **1a** concentration, and the corresponding peak current attributed to the oxidation of **1a** was lowered [Fig.1 —•—•]. The ratio (i_k / i_d) of the catalytic peak current (i_k), with the diffusion controlled peak current (i_d) was measured using various potential scan rates (v) [Fig.2]. The increase of this ratio when the scan rate was decreased [Fig.2], fitted well with the diagnostic criteria for a catalytic process, described by different authors[11,13]. An apparent catalytic rate constant (k_{exp}, scheme 1) was determined to be $k_{exp} = 10 \pm 2\ s^{-1}$ [$2.0 \pm 0.4\ s^{-1}$] (Br^-, $c_{Br^-} = 1 \times 10^{-3}$ mol L^{-1}; **1a** [**1c**] $c_l = 1 \times 10^{-2}$ mol L^{-1}; γ (excess factor) = c_l / c_{Br^-} = 10) using working curves reported in ref. 12 and 14. In addition, the kinetic control ($k >> k_{exp}$, scheme 1) by the redox reaction (scheme 1 eq.(3)) of the catalytic process was illustrated by the increase of the (i_k / $i_d \times \gamma$) ratio (0.65, 0.85 and 0.93) with the increase of bromide concentration ($c_{Br^-} = 1 \times 10^{-3}$, 2×10^{-3} and 4×10^{-3} mol L^{-1} respectively) for given values of excess factor ($\gamma = 2$) and potential scan rate ($v = 0.2\ V\ s^{-1}$), according to ref.12. With **1b**, we could not determine k_{exp}.

Thus, in the presence of the transfer agent Br_2 species, electrogenerated at E° = 1.0 V s.c.e., the oxidation of **1** takes place at a considerably lower potential than determined by CV (Epa = 1.80 V s.c.e.). This catalytic efficiency is probably due to a low rate of heterogenous charge transfer and to the subsequent chemical reactions (4) which force a displacement of redox equilibrium (3) to the right-hand side (scheme 1). The effectiveness of the catalytic process decreases according to the sequence **1a** > **1c** > **1b**.

Fig 3

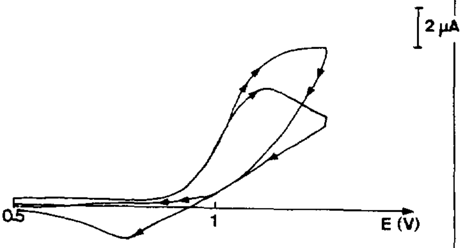


Fig 4

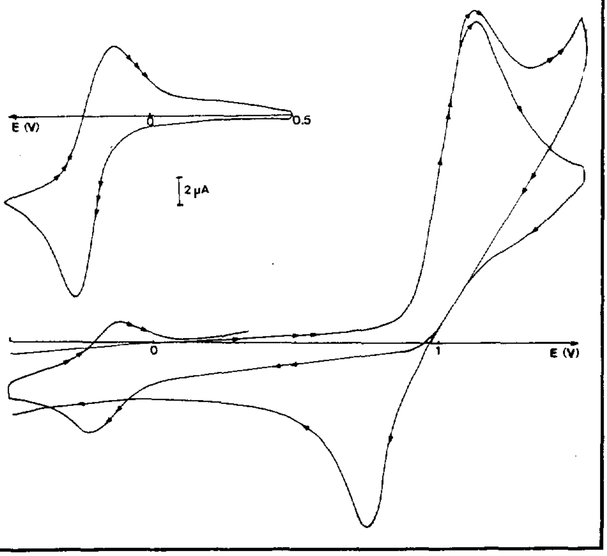


Fig 3: Cyclic voltammograms at 0.04 V s^{-1} potential scan rate in MeCN containing $LiClO_4$ (5×10^{-2} mol L^{-1}) of: —• a solution of tetraethylammonium chloride (1×10^{-3} mol L^{-1}); —•— a mixture of **1a** (5×10^{-3} mol L^{-1}) and chloride ions (1×10^{-3} mol L^{-1}).

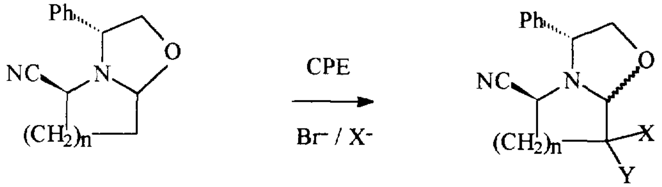
Fig 4: Cyclic voltammograms at 0.09 V s^{-1} potential scan rate in MeCN containing $LiClO_4$ (5×10^{-2} mol L^{-1}) of: —• a solution of chloride ions (2×10^{-3} mol L^{-1}); —•— a mixture of **1a** (2×10^{-3} mol L^{-1}) and chloride ions (2×10^{-3} mol L^{-1}) recorded with a second sweep; —•—•— at 0.18 V s^{-1} potential scan rate of a hydrogen chloride solution ($c = 2 \times 10^{-3}$ mol L^{-1}).

In the same way, the chloride ion (tetraethylammonium chloride) also acts as mediator as shown by CV curves [Fig 3]. Unfortunately, the rate constant of the electron transfer between Cl_3^- ($Cl^•$) species and **1a** was too slow to be determined by CV [Fig 3]. However, during this catalytic process, Cl_3^- species react with radical cations and lead to hydrogen chloride formation, which could be detected by a backward coupled cathodic reversible system at -0.28 V s.c.e. [Fig 4—•—] attributable to hydrogen chloride reduction [Fig 4—••—].

Controlled potential electrolyses (CPE):

halogenation process:

We have already reported the anodic oxidation of **1a** in the presence of Cl^- and Br^- to afford the 5,5'-dichloro product **2a**[1]. In a continuation of our research in this area, we now wish to describe CPE experiments, performed on **1a**, under different conditions (see scheme 2 and table), using chloride, bromide, or fluoride ions as reagents[15,16].



1a (n = 2)
1c (n = 0)

2a (X = Y = Cl, n = 2)
3a (X = Cl, Y = H, n = 2)
4a (X = Y = Br, n = 2)
5c (X = Br, Y = H, n = 0)

Scheme 2

Table: Controlled potential electrolysis[a] of 1a:

REACTANTS (10^{-3} mol)[b]	POTENTIAL V (s.c.e.)	ELECTRICITY (n)[c]	SUBSTITUTED PRODUCTS	YIELDS (%)[d]	EPIMERIC RATIO[e]
Cl^-(1.5) / Br^-(0.15)	1.25	4	2a	95	65:35
Cl^-(1.5) / Br^-(0.15)	1.25	10	3a[f]	70	50:50[g]
Cl^-(1.5)	1.25	5	2a + 3a	35 + 30	65:35 + 50:50[g]
Br^-(2.0)	1.25	5	4a	30	100
Br^-(2.0)	0.7	5	4a	78	100

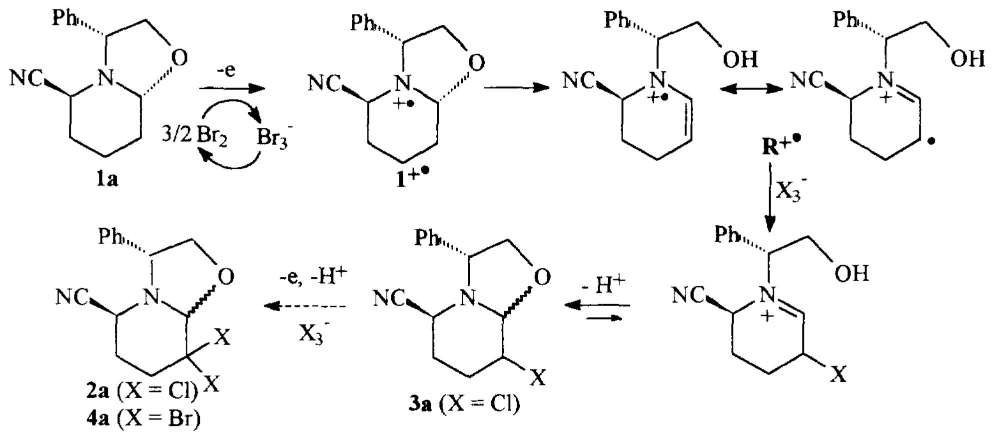
[a] In acetonitrile, at a platinum electrode, with lithium perchlorate as supporting electrolyte, using 0.5×10^{-3} mol of **1a**; [b] amount of tetraethylammonium halogen ion; [c] number of electrons transferred per molecule of **1a**; [d] yields of isolated products; [e] mixture of diastereoisomers, except for **4a**; [f] **3a** constituted the sole compound when tetraethylammonium perchlorate is used instead of lithium perchlorate as supporting electrolyte; [g] **3a** was obtained as a mixture of diastereoisomers, separable by chromatography.

Besides the 5,5'-dichloro product **2a**, CPE produced a separable 1:1 mixture of an epimeric 5-monochloro compound **3a**, if chloride ions were acting as mediator **and** reactant. Interestingly, **3a** constituted the sole compound isolated in 70% yield when tetraethylammonium perchlorate was used instead of lithium perchlorate. The occurrence of HCl formation during these preparative electrolyses might be attested by a CV response, since a reversible reduction peak, assigned to the HCl system, was recorded after exhaustive electrolyses.

Likewise, when chloride ions were replaced by bromide ions, a single isomer of the 5,5'-dibromo compound **4a** was isolated in a 30% yield. The yield of **4a** increased (78%) when the potential of the electrolysis was decreased (E = 0.7 s.c.e. *versus* 1.25 V s.c.e.) From **1c**, the monobromo compound **5c** was produced in 35% yield (E = 0.6 V s.c.e.) Finally, no bromo compound was isolated from **1b**. This failure may be explained by the fact that the optimal electrolysis potential of 0.7 V s.c.e. is not high enough to effect an indirect oxidative bromination. It is noteworthy that, under the optimal conditions, of 0.7 V s.c.e. (or 0.6 V s.c.e.) the bromide ion is principally in an oxidized radical form $Br_3^{\cdot}$.

Finally, the attempted reaction between **1a** and fluoride ions did not afford the corresponding fluorinated compound, whatever the experimental conditions[17]. Similarly, all CPE experiments, using a nucleophile like methylate[18], cyanide, or acetate[19], only gave degradated products. It is clear, therefore, that only oxidizable halogen ions, chloride and bromide, can react in this electrosynthesis.

From all these experiments, two main conclusions can be drawn: **(a)** all the CPEs confirm that chloride and bromide ions are involved in a catalytic process[6-9], but it is clear that bromide ions behave as the better electron transfer agent, since there was a significant increase in the yield of **2a**, (95% *versus* 35%) when the electrolysis mixture was supplemented with bromide ions. Thus, chloride and bromide ions are both mediators and reactants in the course of the reaction; **(b)** formation of the monohalogenated compound requires only two electrons per molecule of **1a**, since the consumption of **4 ± 0.1** electrons was involved in the quantitative dichlorination process (**2a**).



Scheme 3

Scheme 3 shows a postulated mechanism based on all the available experimental evidence for the formation of the halogenated products. The different steps can be detailed as follows:

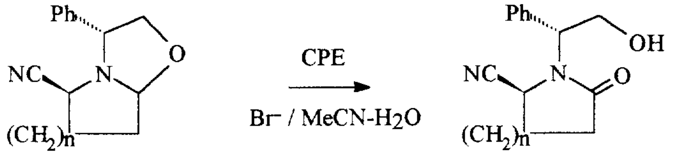
The indirect oxidation of **1a**, involving Br_2 (Br^+) species, initially affords a radical cation which upon rearrangement leads to a second radical cation $\mathbf{R}^{+\bullet}$. A deprotonation of the radical cation could be suggested to take place during the oxidation[20,21]. Two experimental facts, arguing against a deprotonation step following the charge transfer, can be mentioned: **(a)** CV investigations and coulometric values of CPEs corresponded to a monoelectronic oxidation of **1a**; **(b)** a deprotonation would take place α to the CN, since H-2 is the most acidic proton[3]. The acidity of the experimental medium may be related to the effectiveness of the reaction. Thus the failure of CPEs performed with **1a** using methylate (cyanide or acetate) as reagent, may be explained by the base-promoted deprotonation of the radical cation leading to undesired products.

It is proposed that the intermediate $\mathbf{R}^{+\bullet}$ will undergo a radical coupling at the C-5 position with a X_3^- ($X^\bullet$) species. The occurrence of a radical coupling, in the mechanistic pathway, is consistent with the optimal value of the electrolysis potential in order to produce an X_3^- species (0.7 V s.c.e. for Br_3^- and 1.25 V s.c.e. for Cl_3^-). In addition, the redox behaviour of halogen species in this reaction fulfills a requirement for a radical coupling process, namely by permitting the oxidation of both **1** and X^-.

Finally, the resulting halogenated iminium ion, may be converted into the monohalogenated compound by intramolecular oxazolidine ring closure and proton loss. The fixation of the second halogen atom may proceed through an analogous mechanistic sequence.

Lactam / amide synthesis:

In order to illustrate, with an other example, the anodic behaviour of **1**, we further report the electrosynthesis of the lactam / amide **6**[22] (Scheme 4).



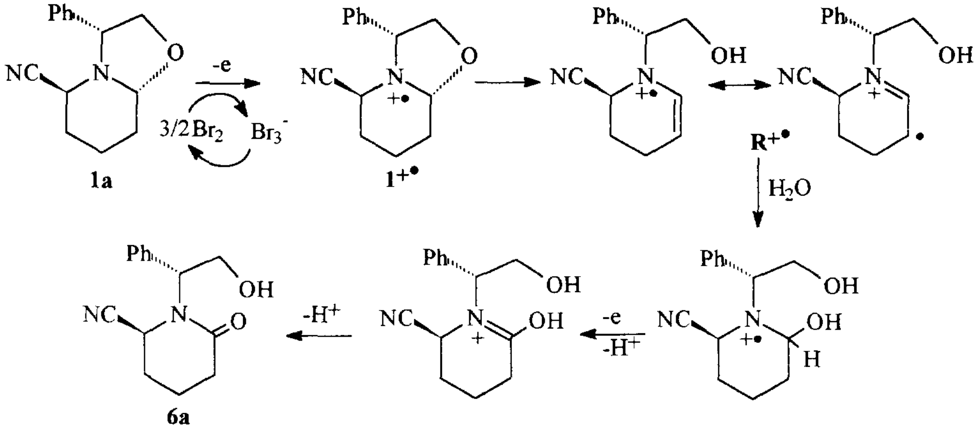
1a (n = 2)
1b (n = 1)
1c (n = 0)

6a (n = 2), ρ = 85%
6b (n = 1), ρ = 50%
6c (n = 0), ρ = 73%

Scheme 4

CPE of **1a** at E = 1.1V s.c.e., on a platinum electrode, in a 2:1 acetonitrile-water mixture, using bromide ions (excess of potassium bromide) as mediator and lithium perchlorate as supporting electrolyte, led to the lactam **6a**, as a single isomer, in high yield (85%). Under the same experimental conditions, **1b** and **1c** furnished the corresponding lactam **6b** and amide **6c** in a 50% and 23% yield respectively. During the course of these electrolyses, we observed the acidification of the reaction solution attributable to HBr formation. From a synthetic point of view, it is noteworthy that when the CPE of **1c** was carried out at 1.25V s.c.e., in acetonitrile, using residual water as reactant and tetraethylammonium bromide as mediator, the yield of **6c** was significantly higher (73%).

6a, **6b** and **6c** have not been cited to the best of our knowledge. Nevertheless, it has been reported that 2-alkylated-2-cyano-6-oxazolopiperidines can be chemically oxidized using bromine, to give the corresponding lactam[23]. Interestingly, using this chemical process, compound **1a**, which is not alkylated at the C-2 position, affords only degradated products. In contrast, the present electrochemical method prevents overoxidation and leads to a clean and high yielding reaction.



Scheme 5

Moreover, several points should be worthnoting in the electrosynthesis of the the lactam / amide compounds: **(a)** although there is a clear similarity in reaction conditions to form the brominated products, especially for **1c**, no bromo compound was isolated -an observation that agrees with the hypothesis of a common intermediate in the two mechanistic pathways; **(b)** Br_2 (Br^+) species is still involved as a mediator; **(c)** the lactam / amide formation occurs selectively from the oxazolidine functionality, although unlike halogenation, this electrosynthesis affords introduction of a substituent α to the nitrogen atom; **(d)** a coulometric value of **3.0 ± 0.1** after exhaustive electrolysis suggests that **2.0 ± 0.1** electrons are involved for lactam / amide formation and **1.0 ± 0.1** for the oxidation of any excess bromide anions.

Thus, it seems reasonable to suggest that the indirect electrochemical oxidation of **1** occurs only at the *N,O*-acetal function, leading to the same radical cation **$R^{+•}$** as postulated in the halogenation process (*cf.* schemes 3 and 5). In turn, this species will be able to couple with a molecule of water, to form a new radical cation, which upon further oxidation will afford the lactam compound **6a**.

Conclusion

The study dealing with the electrochemical behaviour of the *N*-cyanomethyloxazolidine system has led to the conclusion that: **(a)** the monoelectronic oxidation of **1** specifically activates the α-aminoether function to give access to the corresponding iminium salt while conserving the α-aminonitrile function. Thus, the oxidation of **1**, reverses the reactivity of the two masked iminium functions and allows a regioselective substitution at the oxazolidine side; **(b)** these electrochemical reactions share a common intermediate, the radical cation **$R^{+•}$**, that can then follow either one of two pathways, in the presence of water, to lactam / amide formation and in the presence of X_3^-, to halogenated products.

The halogenated compounds, which are novel compounds, can be prepared on a large scale galvanostatically, and should be of interest as synthetic intermediates [24,25]. A further synthetic application of the electrogenerated radical cation **$R^{+•}$** to the coupling with vinyl ether derivative is currently under investigation.

EXPERIMENTAL

Apparatus, cells and electrodes.

The ^{1}H NMR and ^{13}C NMR spectra were recorded on a BrukerWM-300 spectrometer operating at 300 MHz. The NMR abbreviations used are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; J, coupling constant; ax, axial position; eq, equatorial position. The proton type was determined by ^{1}H-^{1}H and ^{13}C-^{1}H correlations and the carbon type (methyl, methylene, methine or quaternary) was determined by DEPT experiments. Mass spectra were recorded on a Nermag R 10-10 spectrometer equipped with desorption chemical ionisation mode using ammonia as the reagent gas. Melting points were determined on a Kofler apparatus and were not corrected. Elemental analyses were carried out at Institut de Chimie des Substances Naturelles, Gif-sur-Yvette.

Electrochemical measurements were made with a Tacussel PRG-5 multipurpose polarograph which was used simply as a rapid response potentiostat. For cyclic voltammetry, triangular waveforms were supplied by a Tacussel GSTP-3 function generator. Current-potential curves were recorded on a Sefram SI 8312 instrument. The cell was a Tacussel water-jacketted cell, whose temperature is 25°C. The reference electrode was a saturated calomel electrode (s.c.e.) to which all potentials have been referred. The counter electrode was a platinum Tacussel Pt 11. The working electrode was a platinum disc (effective area 0.040 cm^2) of a Tacussel EDI rotating electrode and was used without a particular pre-treatement. CPEs were carried out using a three-compartment water-jacketted cell, whose counter and reference electrodes were filled with the background solution. A Tacussel PJT 120-1 potentiostat and a Tacussel IG5-N electronic integrator were included in the circuit. The counter electrode was a platinum foil. The solid working electrode was a platinum grid (6 cm diameter).

Materials.

The solvents used for extractions and chromatography were obtained from SDS. Acetonitrile (MeCN) was distilled over calcium hydride and used immediately for CV and CPE experiments. Tetraethylammonium chloride, bromide, perchlorate and lithium perchlorate were all obtained from Fluka.

8-chloro-3-phenyl-hexahydro-oxazolo-[3,2-a]-pyridine-5-carbonitrile (3a):

2-cyano-6-oxazolopiperidine **1a**^{2} (0.114 g; 5×10^{-4} mol) was dissolved in dry acetonitrile (200 mL) containing tetraethylammonium perchlorate (2.30 g; 1×10^{-2} mol) as supporting electrolyte. Tetraethylammonium chloride (0.25g; 1.5×10^{-3} mol) and tetraethylammonium bromide (0.035g; 1.5×10^{-4} mol) were added and the resulting solution was oxidized at a platinum electrode (E = 1.25 V s.c.e.) at 5°C under nitrogen. After exhaustive electrolysis, MeCN was distilled off and the residue was extracted with dichloromethane (100 mL) after the addition of water (100 mL). The organic layer was dried over sodium sulfate and evaporated. Preparative column chromatography (toluene: ethylamin,100 / 0.2) afforded **3a** as two separated epimers **3a'** and **3a''** (0.092 g; 70% combined yield).

3a' white crystals m.p. 96°C; MS (DCI) m/z: 263-265 (MH$^+$); ^{1}H NMR (C_6D_6, 300 MHz) δ (ppm): 1.0 (m, 2H, H-3), 1.7 (m, 2H, H-4), 2.95 (m, 1H, H-2$_{(eq)}$), 3.45 (dd, 1H, J = 7.5, 7.6 Hz, H-8,), 3.55 (ddd, 1H, J = 8, 8.2, 8.3 Hz, H-5$_{(ax)}$), 3.65 (dd, 1H, J = 7.8, 7.9Hz, H-9$_{(ax)}$), 3.8 (dd, 1H, J = 7.7, 7.6 Hz, H-8), 4.2 (d, 1H, J = 8,3 Hz , H-6$_{(ax)}$), 7.4 (m, 5H, Ar); ^{13}C NMR (C_6D_6, 300 MHz) δ (ppm): 29.0 ($\underline{C}H_2$-3), 32.0 ($\underline{C}H_2$-4), 47.0 ($\underline{C}$H-2), 58.0 ($\underline{C}$H-5), 65.0 ($\underline{C}$H-9), 73.0 ($\underline{C}H_2$-8), 94.0 ($\underline{C}$H-6), 115.0 ($\underline{C}$N), 127.0-129.0 ($\underline{C}$H-Ar),135.0 ($\underline{Cq}$-Ar).

3a'' white crystals m.p. 98°C; MS (DCI) m/z: 263-265 (MH$^+$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.8 (d, 1H, J = 8 Hz, H-3$_{(eq)}$), 1.4 (m, 2H, H-4), 1.6 (m, 1H, H-3$_{(ax)}$), 3.0 (d,1H, J = 1.5 Hz, H-2$_{(eq)}$), 3.6 (m, 2H, H-8$_{(eq)}$

and H-9$_{(ax)}$), 3.8 (dd, 1H, J = 8.0, 8.0 Hz, H-8$_{(ax)}$), 3.9 (m, 1H, H-5$_{(eq)}$), 4.0 (d, 1H, J = 1 Hz ,H-6$_{(eq)}$), 7.0 (m, 5H, Ar); ^{13}C NMR (CDCl$_3$ 300 MHz) δ (ppm): 23.0 (CH$_2$-3), 29.0 (CH$_2$-4), 48.0 (CH-2), 57.0 (CH-5), 64.0 (CH-9), 74.0 (CH$_2$-8), 90.0 (CH-6), 115.0 (CN), 127.0-129.0 (CH-Ar). 137.0 (Cq-Ar); analysis for $C_{14}H_{15}ClN_2O$, 0.4 H_2O calculated (C, 62.29; H, 5.90; N, 10.38%), found (C, 62.17; H, 5.91; N, 10.29%).

8,8-dibromo-3-phenyl-hexahydro-oxazolo-[3,2-a]-pyridine-5-carbonitrile (4a):
1a (0.114 g; 5×10^{-4} mol) was dissolved in dry acetonitrile (200 mL) containing lithium perchlorate (1.06 g; 1×10^{-2} mol) as supporting electrolyte. Tetraethylammonium bromide (0.42g; 2×10^{-3} mol) was added and the resulting solution was oxidized at a platinum electrode (E = 0.7 V s.c.e.) at 5° C under nitrogen. After exhaustive electrolysis, the above mentioned procedure afforded **4a** as a colorless oil (0.15 g; 78% yield). MS (DCI) m/z: 385-387-389 (MH$^+$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 1.8 (m, 1H, H-3$_{(eq)}$), 2.35 (m, 1H, H-3$_{(ax)}$), 2.7 (m, 1H, H-4$_{(ax)}$), 2.8 (m, H-4$_{(eq)}$), 3.85 (d, 1H, J = 1.5 Hz, H-2$_{(eq)}$), 3.9 (dd, 1H, J = 8.0, 9.0 Hz, H-8), 4.15 (dd, 1H, J = 9.0, 7.0 Hz, H-9), 4.2 (s, 1H, H-6), 4.4 (dd, 1H, J = 8.0, 7.0 Hz, H-8), 7.40 (m, 5H, Ar); ^{13}C NMR (CDCl$_3$, 300 MHz) δ (ppm): 27.0 (CH$_2$-3), 42.0 (CH$_2$-4), 46.0 (CH-2), 63.0 (CH-9), 65.0 (Cq-5), 73.7 (CH$_2$-8), 94.4 (CH-6), 115.0 (CN), 127.0-129.0 (CH-Ar), 135.0 (Cq-Ar); analysis for $C_{14}H_{14}Br_2N_2O$ calculated (C, 43.55; H, 3.65; N, 7.25%), found (C, 43.46; H, 3.81; N, 7.17%).

[2-bromomethyl-4-phenyl-oxazolidin-3-yl]-acetonitrile (5c):
With **1c**[26] (0.101 g; 5×10^{-4} mol) the above mentioned method gave **5c** as a colorless oil (0.05 g; 35% yield). MS (DCI) m/z: 283 (MH$^+$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm):3.60 (m, 1H, CH-CN), 3.85 (d, 2H, J = 4.0 Hz, CH$_2$-Br), 4.3 (m, 3H), 4.8 (t, 1H, J = 4.0 Hz, H-2), 7.4 (m, 5H, Ar); ^{13}C NMR (CDCl$_3$, 300 MHz) δ (ppm): 33.7 (CH$_2$-CN), 37.3 (CH$_2$-Br), 66.3 (CH-4), 73.4 (CH$_2$-5), 91.4 (CH-2), 114.3. (CN), 127.0-129.0 (CH-Ar). 135.0 (Cq-Ar).

1-[2-hydroxy-1-phenyl-ethyl]-6-oxo-piperidine-carbonitrile (6a):
1a (0.114 g; 5×10^{-4} mol) was dissolved in an acetonitrile-water mixture (MeCN: H_2O, 2 / 1, 200 mL) containing lithium perchlorate (1.06 g; 1×10^{-2} mol) as supporting electrolyte. Potassium bromide (0.16 g, 1.3×10^{-3} mol) was added and the resulting solution was oxidized at a platinum electrode (E = 1.05 V s.c.e.) at 5°C under nitrogen. After exhaustive electrolysis, using the above mentioned procedure, **6a** was isolated after chromatography (ethyl acetate: methanol, 98 / 2) as a white crystals (0.10 g; 85% yield): m.p.110-112°C, MS (DCI) m/z: 245 (MH$^+$); ^{1}H NMR (CD$_3$OD, 300 MHz) δ (ppm): 2.2 (m, 4H, H-3 and H-4), 2.7 (m, 2H, H-5), 4.2 (m, 2H, CH$_2$-OH), 4.85 (bs, 2H, H-2 and OH), 5.8 (t, 1H, J = 4 Hz, N-CH-Ar), 7.4 (m, 5H, Ar); ^{13}C NMR (CD$_3$OD, 300 MHz) δ (ppm): 19.0 (CH$_2$-4), 29.0 (CH$_2$-3), 32.0 (CH$_2$-5), 47.0 (CH-2), 61.0 (N-CH-Ar), 62.0 (CH$_2$-OH), 118.0 (CN), 127.0-129.0 (CH-Ar), 136.0 (Cq-Ar), 175.0 (C=O); analysis for $C_{14}H_{16}N_2O_2$ calculated (C, 68.83; H, 6.60; N, 11.47%), found (C, 68.57; H, 6.66; N, 11.31%).

1-[2-hydroxy-1-phenyl-ethyl]-5-oxo-pyrrolidine-carbonitrile (6b):
Using the above mentioned method with **1b**[27] (0.107 g; 5×10^{-4} mol) the electrolysis gave **6b** as a colorless oil in 50% yield (0,057 g): MS (DCI) m/z: 231 (MH$^+$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ (ppm): 2.1-2.8 (m, 4H, H-3, H-4), 4.2 (m, 1H, H-2), 4.3 (dd, 1H, J = 5, 13 Hz, CH$_{(eq)}$-OH), 4.4 (dd,1H, J = 9, 13 Hz, CH$_{(ax)}$-OH), 5.35 (dd,1H, J = 9, 5 Hz, N-CH-Ar), 7.4 (m, 5H, Ar); ^{13}C NMR (CDCl$_3$, 300 MHz) δ (ppm): 24.8 (CH$_2$-3), 29.5 (CH$_2$-4), 46.3 (CH-2), 47.0 (CH-2), 58.2 (N-CH-Ar), 61.3 (CH$_2$-OH), 119.0 (CN), 127-129.0 (CH-Ar), 136.0 (Cq-Ar), 175.0 (C=O).

***N*-cyanomethyl-*N*-[2-hydroxy-1-phenyl-ethyl]-acetamide (6c):**

Using the above mentioned method with **1c** (0.101 g; 5×10^{-4} mol) the electrolysis gave **6c** as a colorless oil in 23% yield (0,025 g). In an alternative procedure, **1c** (0.101 g; 5×10^{-4} mol) was dissolved in MeCN (200 mL) containing lithium perchlorate (1.06 g; 1×10^{-2} mol) as supporting electrolyte. Tetraethylammonium bromide (0.1250g; 0.6×10^{-3} mol) was added and the resulting solution was oxidized at a platinum electrode (E = 1.25 V s.c.e.) at 5°C under nitrogen. After exhaustive electrolysis, **6c** was isolated after chromatography (ethyl acetate: cyclohexane, 40 / 60) as a colorless oil (0.08 g; 73% yield). MS (DCI) m/z: 219 (MH^+); ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.1 (s, 3H, $C\underline{H}_3$), 3.25 (d, 1H, J = 18.0 Hz, $C\underline{H}$-CN), 3.65 (d, 1H, J = 18.0 Hz, $C\underline{H}$-CN), 4.05 (dd, 1H, J = 13.0, 9.0 Hz, $C\underline{H}_{(ax)}$-OH), 4.2 (dd, 1H, J = 9.0, 4.0 Hz, N-$C\underline{H}$-Ar), 4.3 (dd, 1H, J = 13.0, 4.0 Hz, $C\underline{H}_{(eq)}$-OH), 7.4 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$, 300 MHz) δ (ppm): 20.0 ($\underline{C}H_3$), 34.6 ($\underline{C}H_2$-CN), 60.3 (N-$\underline{C}$H-Ar), 68.0 ($\underline{C}H_2$-OH), 117.4 ($\underline{C}$N), 127.0-129.0 ($\underline{C}$H-Ar);135.0 ($\underline{C}$q-Ar). 170.0 ($\underline{C}$=O).

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