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Synthesis of Five-Membered Heterocycles by Indirect Electrochemical Approach in "Green" Media

C. Durães, J. Lombard, S. Pereira, A. P. Esteves, and M. J. Medeiros*,z

Centro de Química, Universidade do Minho, Largo do Paço, 4704-553 Braga, Portugal

Radical cyclization continues to be a central methodology for the preparation of natural products containing heterocyclic rings. Hence, some electrochemical results obtained by cyclic voltammetry and controlled-potential electrolysis in the study of electroreductive intramolecular cyclization of ethyl (2*S*, 3*R*)-2-bromo-3-propargyloxy-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy) propanoate (**1a**), 2-bromo-3-allyloxy-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)propanoate (**1b**), 2-bromo-[1-(prop-2-yn-1-yloxy)propyl]benzene (**1c**) and [1-bromo-2-methoxy-2-(prop-2′-yn-1-yloxy)ethyl]benzene (**1d**) promoted by (1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane)nickel(I), $[Ni(tmc)]^+$, electrogenerated at glassy carbon cathodes in ethanol and ethanol:water mixtures containing tetraalkylammonium salts, are presented. During controlled-potential electrolyses of solutions containing $[Ni(tmc)]^{2+}$ and bromoalkoxylated compounds (**1**) catalytic reduction of the latter proceeds *via* one-electron cleavage of the carbon–bromine bond to form a radical intermediate that undergoes cyclization to afford the substituted tetrahydrofurans.
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Owing to their widespread presence in nature as well as their broad range of biological activity, lignans have attracted considerable attention from organic chemists.[1] Some lignans exhibit anti-tumor activity, whereas others function as diuretic, analgesic, and antirheumatic compounds.[2] A major subgroup of lignans is comprised by tri- and tetra-substituted tetrahydrofurans, which are very useful precursors for the synthesis of a variety of natural products with biological activity.[2]

Although several synthetic approaches have been reported, radical cyclization continues to be a central methodology for the preparation of natural products containing heterocyclic rings.[3] Particularly important are tetrahydrofuran derivatives containing an exocyclic double bond which can be further functionalised as required. Asymmetric induction in free radical reactions is a topic of current interest. Radical reactions have become much more important since the discovery that they can proceed with high stereoselectivity. Several examples have been described in which stereocontrol has been achieved through the use of chiral auxiliaries.[4,5]

A majority of radical cyclizations in heterocyclic chemistry are still accomplished with the aid of tri-*n*-butyltin hydride, Bu_3SnH, as a stoichiometric reagent.[3] However, medicines, drugs and food additives contaminated with tin are unsafe for human consumption. To avoid the use of toxic triorganotin hydrides, which are also troublesome to separate from the desired products, considerable effort has been aimed to the development of more eco-friendly methodologies for the generation of reactive radicals. A convenient alternative to synthetic methods involving organometallic hydrides is the electrochemical nickel−catalyzed radical−type cyclizations for the synthesis of heterocyclic compounds.[6]

Our research group has some experience in the catalytic reductive cyclization of unsaturated halides to produce substituted tri- and tetrahydrofurans, by indirect electroreduction using Ni(II) complexes as the catalysts.[6,7]

In attempting to extend the results of the previous investigations, we undertake further studies on the electrosynthesis of substituted tetrahydrofurans by indirect electrochemical methods using Ni(II) macrocyclic complexes as catalysts in ethanol and ethanol:water mixtures. In view of the stereoselectivity of these cyclization reactions, the acetylated D-glucose was used as chiral auxiliary. The reactivity aspects related to carbon centered radicals were also investigated. Different alpha substituents to carbon radical were considered to understand the effect of the electrophilic radical character in the yields and diastereomeric ratio of the cyclization reaction.

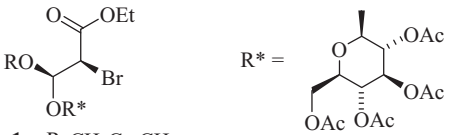
Experimental

Reagents.— Each of the following chemicals was used as received: nickel(II) bromide (Aldrich, 98%), 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane (tetramethylcyclam, tmc, Fluka, 97%). Ethanol (EtOH) from Riedel-de-Häen, Analytical Reagent, was used as received. We purchased tetraethylammonium bromide (Et_4NBr) with a purity of 98% from Fluka; this electrolyte was stored in a vacuum oven at 80°C to remove traces of water. Deaeration procedures were carried out with zero-grade argon (Air Products). Published procedures were employed for the preparation of $[Ni(tmc)]Br_2$,[8] ethyl (2*S*,3*R*)-2-bromo-3-propargyloxy-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)propanoate (**1a**),[9] 2-bromo-3-allyloxy-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosiloxy)propanoate (**1b**),[9] 2-bromo-[1-(prop-2-yn-1-yloxy)propyl]benzene (**1c**)[9] and [1-bromo-2-methoxy-2-(prop-2′-yn-1-yloxy)ethyl]benzene (**1d**).[9]

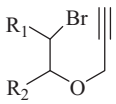
A method described by McCague et al.[10] provided the basis for the syntheses of (2*R**,3*S**)-3-ethoxycarbonyl-4-methylene-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyra-nosyloxy)tetrahydrofuran (**2a**), (2*R**,3S*,4*S**)-3-ethoxycarbonyl-4-methyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)tetrahydrofuran (**2b**), 3-methyl-4-methylene-2-phenyltetrahydrofuran (**2c**) and 2-methoxy-4-methylene-3-phenyltetrahydrofuran (**2d**).

Cells and electrodes.— Cyclic voltammograms were recorded in a three-electrode, two-compartment cell as described in earlier publications.[11] The working electrodes were fabricated from 3-mm-diameter glassy carbon rods (Tokai Electrode Manufacturing Company, Tokyo, Japan, Grade GC-20) press-fitted into Teflon shrouds to provide planar, circular working electrodes with areas of 0.07 cm^2. Before use, the electrodes were cleaned with an aqueous suspension of 0.05-μm alumina (Buehler) on a Master-Tex (Buehler) polishing pad. The counter electrode was a Pt spiral in the same compartment. The experimental reference electrode was a Ag/AgCl/3 M KCl in water, separated from the working electrode by a sinter and Luggin capillary. All solutions were deoxygenated with a fast stream of argon before each experiment. For controlled-potential electrolysis and product analysis, a divided cell with an anodic and a cathodic compartment separated by a glass sinter (as have been described in earlier publications[12]) was used. Working electrodes for controlled-potential electrolyses were disks (0.2 cm in thickness, 2.4 cm in diameter, and approximately 100 cm^2 in total area) sliced from reticulated vitreous carbon logs (RVC 2 × 1-100S, Energy Research and Generation, Oakland, CA) or from carbon felt while a carbon rod was the counter electrode. Procedures for cleaning and handling of these electrodes have been described previously.[13] The catholyte and anolyte compartments were each 15 cm^3 and the reference electrode was again Ag/AgCl/3 M KCl in water mounted in a Luggin capillary. All

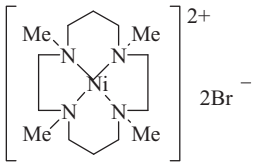
*Electrochemical Society Active Member.
zE-mail: medeiros@quimica.uminho.pt



1a: R=$CH_2C{\equiv}CH$
1b: R=$CH_2CH{=}CH_2$



1c: R_1 = methyl; R_2 = phenyl
1d: R_1 = phenyl; R_2 = methoxy
1e: R_1= ethoxycarbonyl; R_2 = 3,4-dimethoxyphenyl



$Ni(tmc)Br_2$

Scheme 1. Chemical structures of compounds 1a–1e and of $[Ni(tmc)]Br_2$ complex.

preparative electrolyses were carried out in an atmosphere of argon, owing to the extreme sensitivity of Ni(I) complexes to oxygen,[14] and the catholyte solutions were stirred with a magnetic bar.

All potentials are quoted with respect to Ag/AgCl/3 M KCl in water reference electrode (−0.036 vs SCE).

Instrumentation.— Cyclic voltammograms were obtained and controlled-potential electrolyses were carried out with the aid of an AUTOLAB model PGSTAT12 potentiostat–galvanostat. The data from the above experiments were acquired and stored by GPES 4.9 software, which controlled a data acquisition board installed in a personal computer.

Identification and quantification of products.— In order to isolate the products, after electrolysis the EtOH was evaporated under vacuum, the reaction mixture hydrolysed with 0.10 M HCl saturated with NaCl, up to pH 1-2, extracted with CH_2Cl_2 and washed with H_2O. The dried ($MgSO_4$) organic layer was evaporated.

Products were identified by means of GC, GC-MS, FAB, ^{1}H NMR and ^{13}C NMR spectrometry and the compounds characterized and compared with spectra of authentic samples.

^{1}H NMR and ^{13}C NMR data were recorded on a Bruker 300-MHz spectrometer in $CDCl_3$; δ ppm was measured versus residual peak of the solvent. Elemental analyses were performed with a Leco CHNS-932 analyzer. Optical rotation was measured by a micro-polarimeter AA 1000. GC-MS data were recorded on a Hewlett–Packard 5890 Series II gas chromatograph coupled to a Hewlett–Packard 5971 mass-selective detector. FAB mass spectra were recorded with a Kratos Concept spectrometer with a *m*-nitrobenzyl alcohol matrix.

(a) (2*R**,3*S**)-3-ethoxycarbonyl-4-methylene-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopy-ranosyloxy)tetrahydrofuran (**2a**): $[\alpha]_D^{24}$ = + 16.7° (conc. 0.34% em $CHCl_3$); ^{1}H NMR (300MHz, $CDCl_3$) δ: 1.28 (3H, t, *J* = 7.0Hz, OCH_2CH_3), 2.00, 2.03, 2.05 and 2.09 (12H, 4s, 4x$MeCO_2$), 3.60 (1H, broad s, H-3), 3.74 (1H, ddd, *J* = 9.8, 4.8 and 2.4Hz, H-5′), 4.13 (1H, dd, *J* = 12.2 and 2.4 Hz, H_a-6′), 4.17–4.21 (2H, m, OCH_2CH_3), 4.27 (1H, dd, *J* = 12.2 and 4.8Hz, H_b-6′), 4.48 (1H, app dq, *J* = 12.9 and 2.1Hz, H_a-5), 4.59 (1H, app dq, *J* = 12.9 and 2.4/1.5Hz, H_b-5), 4.75 (1H, d, *J* = 8.1Hz, H-1′), 5.00 (1H, dd, *J* = 9.6 and 8.1Hz, H-2′), 5.08 (1H, app t, *J* = 9.9/9.3 Hz, H-4′), 5.16–5.18 (1H, m, C = CHH), 5.32 (1H, app q, *J* = 2.4 Hz, C = CHH), 5.20 (1H app t, *J* = 9.6/9.3Hz, H-3′), 5.64 (1H, broad s, H-2) ppm; *m/z* (FAB) 525 (MNa^+, 85%), 331 ($C_{14}H_{19}O_9^+$, 100), 169 ($C_9H_{13}O_3^+$, 37), 157 (M^+-OR^*, 20), 109 ($C_6H_5O_2^+$, 15); (b) (2*R**,3*S**,4*S**)-3-ethoxycarbonyl-4-methyl-2-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)tetra-hydrofuran (**2b**) (and its diastereomer): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.99 (0.6H, d, *J* = 7.2Hz, Me-4), 1.17 (2.4H, d, *J* = 6.6Hz, Me-4), 1.27 (2.4H, t, *J* = 7.1Hz, OCH_2CH_3), 1.29 (0.6H, t, *J* = 6.9Hz, OCH_2CH_3), 2.01, 2.04, 2.10 and 2.11 (12H, 4s, 4x$MeCO_2$), 2.43–2.54 (1H, m, H-4), 2.68 (0.8H, dd, *J* = 8.8 and 3.0Hz, H-3), 3.11 (0.2H, dd, *J* = 7.8 and 3.0Hz, H-3), 3.65 (1H, dd, *J* = 9.9 and 8.4Hz, H_a-5), 3.73 (1H, ddd, *J* = 9.8, 4.8 and 2.4 Hz, H-5′), 4.05 (1H, app t, *J* = 7.9Hz, H_b-5), 4.11 (1H, dd, *J* = 12.2 and 2.4 Hz, H_a-6′), 4.18 (2H, dq, *J* = 2.0 and 7.0Hz, OCH_2CH_3), 4.30 (1H, dd, *J* = 12.2 and 4.8 Hz, H_b-6′), 4.71 (0.8H, d, *J* = 8.1Hz, H-1′), 4.73 (0.2H, d, *J* = 8.1Hz, H-1′), 5.02 (1H, dd, *J* = 9.6 and 8.1Hz, H-2′), 5.09 (0.2H, app t, *J* = 9.9/9.6 Hz, H-4′), 5.10 (0.8H, app t, *J* = 9.9 /9.3 Hz, H-4′), 5.20 (0.2H, app t, *J* = 9.3, H-3′), 5.21 (0.8H, app t, *J* 9.9/9.3 Hz, H-3′), 5.51 (0.8H, *d*, *J* 3.0Hz, H-2), 5.55 (0.2H, *d*, *J* = 3.0Hz, H-2) ppm; ^{13}C NMR ($CDCl_3$) δ: 14.19, 15.72, 20.54, 20.57, 20.59, 20.66, 20.69, 20.73, 37.96, 58.74, 61.09, 61.92, 68.22, 71.52, 72.16, 72.83, 74.40, 99.55, 107.81; Anal. Calcd for $C_{22}H_{31}O_{13}$ (503.47): C, 52.48; H, 6.21%. Found: C, 52.40; H, 6.68%; *m/z* (FAB) 527 (MNa^+, 80%), 505 (MH^+, 85), 331 ($C_{14}H_{19}O_9^+$, 100), 169 ($C_9H_{13}O_3^+$, 35), 157 (M^+-OR^*, 38), 109 ($C_6H_5O_2^+$, 10); (c) 3-methyl-4-methylene-2-phenyltetrahydrofuran (**2c**) (and its diastereomer): ^{1}H NMR (300MHz, $CDCl_3$) δ: 0.72 (0.6H, d, *J* = 6.9Hz, CH_3), 1.11 (2.4H, d, *J* = 6.6Hz, CH_3); 2.45–2.55 (0.8H, m, H-3); 2.95–3.05 (0.2H, m, H-3); 4.29 (1H, d, *J* = 9.6Hz, H-2); 4.45 (1H, dq, *J* = 13.2 e 2.4Hz, H_a-5); 4.69–4.74 (1H, m, H_b -5); 4.92 (1H, app q, *J* = 2.7Hz, C = CHH); 4.97–5.01 (1H, m, C = CHH); 7.37–7.39 (5H, m, C_6H_5); and (d) 2-methoxy-4-methylene-3-phenyltetrahydrofuran (**2d**): ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.41 (3H, s, OCH_3); 3.81 (1H, broad s, H-3); 4.61 (2H, app q, *J* = 2.0Hz, H_2-5); 4.99 (1H, app q, *J* = 2.0Hz, C = CHH); 5.02 (1H, broad s, H-2); 5.12 (1H, app q, *J* = 2.0Hz, C = CHH); 7.20–7.40 (5H, m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ: 54.78, 56.74, 69.94, 107.38, 110.84, 126.80, 127.61, 128.67, 141.05, 149.83; Anal. Calcd for $C_{12}H_{14}O_2$ (190.24): C, 75.76; H, 7.42%. Found: C, 75.62; H, 7.38%; *m/z* (70 eV) 190, M^+ (0.5); 159, $[M-CH_3O]^+$ (8); 129, $[M-CH_3OCHOH]^+$ (100); 91, $[C_6H_5CH_2]^+$ (32); 77, $[C_6H_5]^+$ (11).

Results and Discussion

*The electrochemistry of bromoalkoxylated derivatives **1**.*— Cyclic voltammograms were obtained at different scan rates at a vitreous carbon electrode for 1.0 mM solutions of acetylated D-glucose-based of bromoalkoxylated derivatives **1a** and **1b** and of bromoalkoxylate derivatives **1c** and **1d** (Scheme 1) in EtOH containing 0.10 M Et_4NBr. Figures 1 and 2, curve A, show the cyclic voltammograms obtained at 0.10 V s^{-1} at a vitreous carbon electrode for **1a** and **1c**, respectively; only a single, highly irreversible reduction wave is seen at potentials near to −1.50 V vs an aqueous Ag/AgCl/3 M KCl. This peak probably corresponds to the reductive cleavage of the carbon-bromine bond. Similar behavior was observed for **1b** and **1d**. Bromoalkoxylated derivatives **1a** − **1d** were also reduced at potentials below −1.50 V vs Ag/AgCl under the same experimental conditions in cyclic voltammetric studies carried out in EtOH:H_2O containing 0.10 M Et_4NBr and in PrOH containing 0.20 M Et_4NBr.

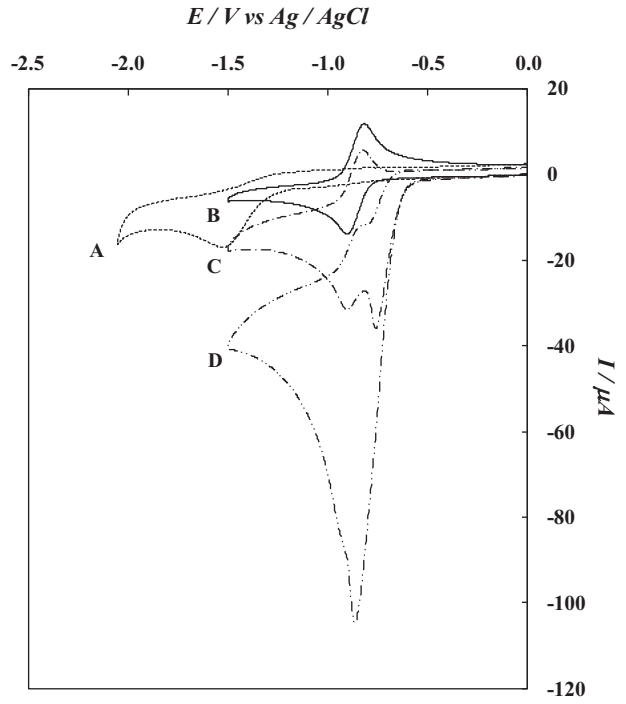


Figure 1. Cyclic voltammograms recorded at a vitreous carbon electrode (area, 0.070 cm^2) at a scan rate of 0.10 Vs^{-1} in EtOH containing 0.10 M Et_4NBr : (A) 1.0 mM **1a**; (B) 1.0 mM $[Ni(tmc)]Br_2$; (C) 1.0 mM $[Ni(tmc)]Br_2$ and 2.0 mM **1a**; (D) 1.0 mM $[Ni(tmc)]Br_2$ and 10.0 mM **1a**.

The reduction of the [Ni(tmc)]Br_2 complex.— A cyclic voltammetric study of solutions of $[Ni(tmc)]Br_2$ complex was carried out in EtOH and in EtOH:H_2O (9:1) containing 0.10 M Et_4NBr. Hence, cyclic voltammograms were recorded at a series of potential scan rates between 0.020 and 0.200 V s^{-1} at a vitreous carbon electrode for solutions of $[Ni(tmc)]Br_2$ complex in EtOH / Et_4NBr (0.10 M) and in Figures 1 and 2, curve B, can be seen a cyclic voltammogram recorded at 0.10 V s^{-1}. The figures show that the complex underwent a reversible one-electron reduction to a stable product and that no further reduction occurred within the potential range of the medium. Similar results have been obtained in cyclic voltammetric studies carried out in EtOH:H_2O containing 0.10 M Et_4NBr and in PrOH / Et_4NBr (0.20 M). Formal electrode potentials are − 0.86 V vs Ag/AgCl/3 M KCl and − 0.87 V vs Ag/AgCl/3 M KCl in EtOH / Et_4NBr (0.10 M) and EtOH:H_2O / Et_4NBr (0.10 M), respectively, and − 0.88 V vs Ag/AgCl/3 M KCl in PrOH / Et_4NBr (0.20 M).

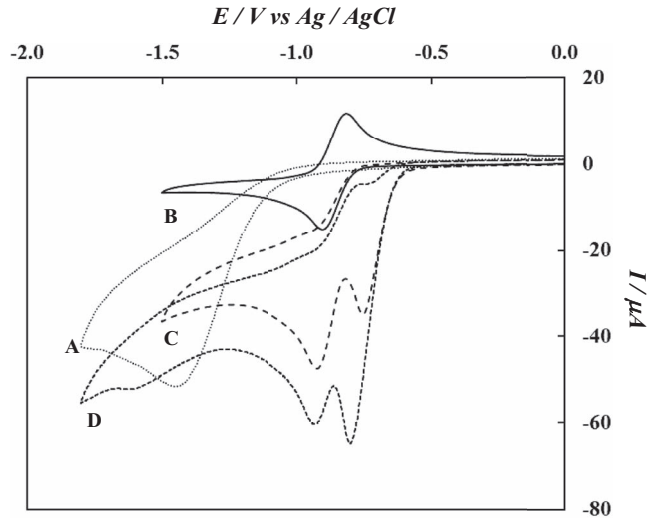


Figure 2. Cyclic voltammograms recorded at a vitreous carbon electrode (area, 0.070 cm^2) at a scan rate of 0.10 Vs^{-1} in EtOH containing 0.10 M Et_4NBr : (A) 5.0 mM **1c**; (B) 1.0 mM $[Ni(tmc)]Br_2$; (C) 1.0 mM $[Ni(tmc)]Br_2$ and 5.0 mM **1c**; (D) 1.0 mM $[Ni(tmc)]Br_2$ and 10.0 mM **1c.**

*The electrochemistry of the [Ni(tmc)]Br_2 complex in the presence of bromoalkoxylated derivatives **1**.*— Figure 1 also shows the cyclic voltammograms recorded for solutions of $[Ni(tmc)]Br_2$ in the presence of different concentrations of acetylated D-glucose-based bromopropargyl ester **1a** in EtOH / Et_4NBr (0.10 M). The experiments show that, after addition of D-glucose-based derivative **1a** to the $[Ni(tmc)]Br_2$ complex solution, the cathodic peak potential, associated with the formation of $[Ni(tmc)]^+$, shifts to a less negative value (e.g. –0.75 V) which is due to the rapid reaction of $[Ni(tmc)]^+$ with **1a** and the anodic wave due to oxidation of $[Ni(tmc)]^+$ back to $[Ni(tmc)]^{2+}$ vanishes because of the chemical consumption of $[Ni(tmc)]^+$. A cathodic postwave can also be observed which arises from the formation of $[Ni(tmc)]^+$ complex unable to locate a molecule of **1a** close to the electrode surface due to depletion of **1a** (Figure 1, curve C).

On further addition of **1a**, the cathodic current increased further and the cathodic postwave almost disappeared (Figure 1, curve D). Furthermore, with progressive increases in the concentration of **1a**, the cathodic peak potential shifted toward more negative values.

Figure 2, curves C and D, shows the cyclic voltammograms recorded for the reduction of 1 mM $[Ni(tmc)]Br_2$ in the presence of 5 mM and 10 mM of **1c**, respectively, at a glassy carbon disc in EtOH containing Et_4NBr (0.10 M) as supporting electrolyte. Again, it can be seen that the cathodic peak potential, due to the formation of $[Ni(tmc)]^+$, shifts to a less negative value (e.g. –0.74 V) and the anodic wave due to oxidation of $[Ni(tmc)]^+$ back to $[Ni(tmc)]^{2+}$ vanishes. A cathodic postwave can also be observed which arises from the formation of $[Ni(tmc)]^+$ complex unable to find a molecule of **1c** close to the electrode surface due to depletion of **1c**. When the initial concentration of **1c** is increased from 5 to 10 mM, the cathodic peak current due to the formation of $[Ni(tmc)]^+$, increases significantly with addition of **1c**. Such behavior indicates that the reaction between the electrogenerated $[Ni(tmc)]^+$ and **1c** is fast and the overall sequence regenerates $[Ni(tmc)]^{2+}$.

The cylic voltammetry experiments were also carried out with **1b** and **1d** and essentially similar results were obtained.

The catalytic current observed is due to the following mechanism:

$$[Ni(tmc)]^{2+} + e^- \rightleftharpoons [Ni(tmc)]^+ \quad [1]$$

$$[Ni(tmc)]^+ + RBr \rightarrow [Ni(tmc)]^{2+} + \text{products} \quad [2]$$

The data obtained from these experiments are presented in Table I.

From these data we can observe that the extent of the catalytic reaction increases when raising [RBr], for a given mediator concentration. This is seen by the large cathodic peaks on cyclic voltammograms for solutions containing $[Ni(tmc)]^{2+}$ and an excess of substrate (the increase in peak current for the Ni(II) complex reduction is a measure of the rate at which the complex is regenerated and hence that the complete catalytic cycle is rapid). It leads to the possibility of quick and efficiently synthetic electrolyses with only a catalytic amount of the nickel(II) complex.

*Controlled-potential electrolyses of [Ni(tmc)]Br_2 complex in the presence of bromoalkoxylated derivatives **1**.*— Controlled-potential electrolyses of solutions of $[Ni(tmc)]Br_2$ in the presence of bromoalkoxylated compounds **1** in EtOH, EtOH:H_2O (9:1) and PrOH containing 0.10 M Et_4NBr at reticulated vitreous carbon or carbon felt cathodes were performed. The potential was set at approximately 100 mV negative to the peak potential of the reduction wave of the catalyst in the presence of the bromoalkoxylated derivatives **1**. The data from those experiments are presented in Table II.

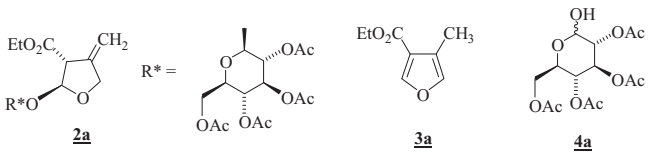
First, the electroreduction of compound **1a** was performed in EtOH containing 0.10 M Et_4NBr. It was found that the electrolysis of **1a** in the presence of $[Ni(tmc)]Br_2$ afforded two major products, ethyl

Table I. Data of the ratio I_c/I_d obtained from the cyclic voltammetry experiments of 1.0 mM [Ni(tmc)]Br_2 complex in the presence of different concentrations of 1 in aqueous media. Potential scan rate 100 mV/s.

Medium	Compound	I_c/I_d[a] $\gamma = 2$[b]	$\gamma = 7$[b]	$\gamma = 10$[b]
EtOH / 0.10 M Et_4NBr	**1a**	2.5	5.6	9.2
EtOH:H_2O (9:1) / 0.10 M Et_4NBr	**1a**	1.8	4.0	9.0
		$\gamma = 2$[b]	$\gamma = 5$[b]	$\gamma = 10$[b]
PrOH / 0.10 M Et_4NBr	**1a**	1.7	4.4	7.7
EtOH / 0.10 M Et_4NBr	**1b**	2.0	3.9	6.1
EtOH / 0.10 M Et_4NBr	**1c**		2.3	4.3
PrOH / 0.20 M Et_4NBr	**1d**	2.3	7.4	
EtOH / 0.10 M Et_4NBr	**1e**[c]	2.2	5.1	9.8

[a] I_c - catalytic peak current intensity of the catalyst in the presence of substrate and I_d - peak current intensity of the catalyst in the absence of substrate.
[b] γ = [RBr] / [Ni (II)].
[c] Data from Ref. 7.

4-methylfuran-3-carboxylate (**3a**) and tetraacetylglucose (**4a**) in 71% total yield (in 50:50 ratio based on ^{1}H-NMR spectrum) (Table II, entry 1).



2a **3a** **4a**

The influence of the water in the reaction selectivity was also investigated in EtOH:H_2O mixtures (9:1) as the solvent. Thus, the electrolysis of **1a** afforded the cyclised product **3a** together with **4a** in quantitative yield (in 43:57 ratio based on ^{1}H-NMR spectrum) (Table II, entry 2). It can be observed that the presence of water did not strongly interfere with the overall product distribution and also with the selectivity of the reaction.

The electroreduction of **1a** was also explored in the presence of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a proton donor. It was seen that the cyclised compound **2a** was only formed in the presence of a proton donor and the yield seems to depend on the concentration of HFIP (Table II, entries 3–6).

The influence of the nature of the solvent was also studied in propan-1-ol / 0.10 M Et_4NBr. It was observed that the electroreduction of **1a** gave rise to the cyclic compound **2a** in a yield of 70% along with **3a** and **4a** in 30% total yield (in 47:53 ratio based on ^{1}H-NMR spectrum) (Table II, entry 7).

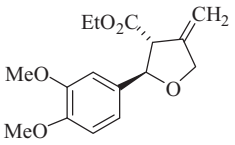
The formation of the cyclic compound **2a** is in good agreement with the Baldwin's rules[15] that predict the formation of a five-membered ring. However, the substituent group on the α-carbon of the starting halide display an important role in the formation of a secondary product. In fact, the hydrogen atom adjacent to the carboxylic ester function of **2a** is strongly acidic. Hence, compounds **3a** and **4a** were formed *via* a based-catalyzed elimination of the leaving group from compound **2a**. This latter process is the so-called E1cB mechanism. These results are corroborated by our previous investigation on electroreductive intramolecular cyclization of bromoalkoxylated derivative **1e**.[7] In this case, the cyclic compound **2e** can be deprotonated owing to the acidity of the hydrogen atom adjacent to the carboxyl moiety, giving rise to the corresponding stabilized carbanion. Then, if the rearranged carbanion is protonated, formation of **2e′** ensues due to

Table II. Coulometric Data and Product Distributions for Catalytic Reduction of 1 by [Ni(tmc)]$^+$ Electrogenerated at Reticulated Vitreous Carbon or Carbon Felt Cathodes in EtOH or PrOH Containing 0.10 M Et_4NBr. T = 20°C

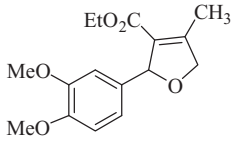
Entry	Solvent	Substrate	[Ni(tmc)]$^{2+}$, mmol	[1], mmol	[HFIP], mM[a]	n[b]	Product distribution,%[c]		
RBr = Ethyl (2*S*, 3*R*)-2-bromo-3-propargyloxy-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)propanoate (**1a**)							**2a**	**3a**	**4a**
1	EtOH	**1a**	0.014	0.075	—	1.2	—	36	36
2	EtOH:H_2O (9:1)	**1a**	0.014	0.029	—	1.5	—	43	57
3	EtOH	**1a**	0.014	0.075	9	1.0	—	40	60
4	EtOH	**1a**	0.014	0.075	19	1.0	100	—	—
5	EtOH	**1a**	0.014	0.075	28	1.0	100	—	—
6	EtOH	**1a**	0.014	0.075	47	1.0	52	traces	18
7	1-PrOH	**1a**	0.014	0.072	-	1.0	70	14	16
2-bromo-3-allyloxy-3-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-glucopyranosyloxy)propanoate (**1b**)								**2b**	
8	EtOH	**1b**	0.94	5.0	—	1.0	61 (80:20)[d]		
RBr = 2-bromo-[1-(prop-2-ynyloxy)propyl]benzene (**1c**)								**2c**	
9	EtOH	**1c**	0.015	0.072	—	1.1		88 (80:20)[d]	
10	EtOH	**1c**[e]	0.015	0.072	—	1.0		84 (80:20)[d]	
11	EtOH	**1c**[e]	0.015	0.072	—	2.2		46 (80:20)[d]	
RBr = [1-bromo-2-methoxy-2-(prop-2′-yn-1-yloxy)ethyl]benzene (**1d**)								**2d**	
12	PrOH	**1d**	0.014	0.072	—	1.1		89	
13	PrOH	**1d**[e]	0.008	0.069	—	1.1		99	
14	PrOH:H_2O (9:1)	**1d**[e]	0.010	0.065	—	1.1		86	
RBr = ethyl 2-bromo-3-(3′,4′-dimethoxyphenyl)-3-propargyloxypropanoate (**1e**)							**2e**	**2e′**	
15	EtOH	**1e**[f]	0.006	0.030	—	1.1	86	14	

[a] HFIP = 1,1,1,3,3,3-hexafluoropropan-2-ol.
[b] Number of electrons per molecule of starting material.
[c] % = yield expressed as the percentage of **1** incorporated into each product.
[d] Diastereomeric ratio.
[e] Electrolyses carried out in a specially designed single-compartment cell using a sacrificial Mg anode.
[f] Data from Ref. 7.

the isomerization of **2e** promoted by electrogenerated base[7] (Table II, entry 15).

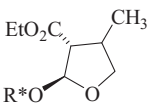


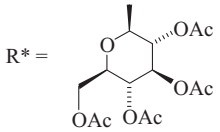
2e



2e'

The same procedure was also applied to the study of compound **1b**. The expected cyclised product **2b** was found to be a mixture of two diastereomers in a ratio of 80:20 with 61% yield (Table II, entry 8).

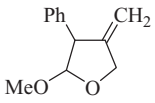




2b

This study was also extended to bromoalkoxylated compounds **1c** and **1d** in order to study the influence of the substituents at the α-carbon on the selectivity of the reaction.

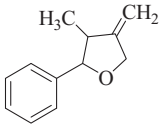
The electroreduction of compound **1d**, where the substituent on the α-carbon is a phenyl group (a moderate electron-withdrawing group), was carried out in PrOH containing 0.20 M Et_4NBr (entries 12). Only the expected cyclic compound **2d** was obtained in 89% yield. These results contrast with those obtained with **1a**.



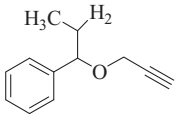
2d

The influence of the nature of the anode was also studied. When the electroreduction of **1d** was performed in the presence of $[Ni(tmc)]Br_2$ using a sacrificial magnesium anode and a carbon felt cathode resulted in the formation of **2d** in yields from 86 to 99% (Table II, entries 13 and 14).

The electroreduction of **1c** was performed in the presence of $[Ni(tmc)]Br_2$ in EtOH and the reaction proceeded to give the cyclic compound **2c** (as a diastereomeric mixture in a 80:20 ratio) in 88% yield (Table II, entry 9) together with a small amount of **3c**.



2c



3c

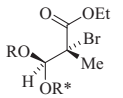
The influence of the nature of the anode was also explored. When the electroreduction of **1c** was carried out in the presence of $[Ni(tmc)]Br_2$ using a sacrificial magnesium anode and a reticulated vitreous carbon cathode resulted in the formation of **2c** (as a diastereomeric mixture in a 80:20 ratio) in 84% yield (Table II, entry 10).

However, during the electrolysis, the anodic metal becomes a stoichiometric reagent rather than simply an electrode. Hence, in a perspective aimed at cleaner and catalytic electrosyntheses, we have explored the electroreduction of **1c** in the absence of sacrificial anode. Then, when the electroreduction of **1c** was performed with graphite anode and a reticulated vitreous carbon cathode, it was observed that the reaction led to the formation of **2c** (as a diastereomeric mixture in 80:20 ratio) in 46% yield along with the dehalogenation product **3c** in 15% yield (Table II, entry 11). It may be concluded that the change of anode from the sacrificial magnesium to graphite had a major effect on product yields and on the selectivity of the reaction, although the reasons are not clear. The same phenomenon was also observed in a previous investigation in the study of the intramolecular cyclisation of a similar bromopropargyl derivative, 1-[2-bromo-2-phenyl-1-(prop-2-ynyloxy)ethyl]-4-methoxybenzene, by electrogenerated nickel(I) complexes using graphite anode instead of magnesium anode.[16] Probably, the presence of Mg^{2+} ions accelerates the decomposition of the alkyl-nickel intermediate formed during the reaction and makes the recycling of the $[Ni(tmc)]^{2+}$ complex more efficient. In the future, we hope to perform independent studies that can explain the phenomenon.

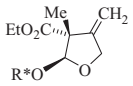
It should be noted that the initial *threo* stereochemistry of compounds **1a**, **1b** and **1d** was corroborated by ^1H NMR data for compounds **2a**, **2b** and **2d**, due to the *trans*-selectivity of these final compounds. According Esteves et. al.[17] the *trans*-selectivity observed in the cyclization reactions can be explained within the stereoinduction Beckwith-Houk model[18] by way of the resonance stabilised radical in which the hydrogen atom, geminal with the carboxyl group, is *syn* to the olefinic bond of the delocalised radical. Moreover, a review chapter by Renaud[18] discusses the factors that govern the stereochemistry of radical cyclization reactions.

However, as revealed in Table II, the electroreductive ring closure of **1c** to **2c** affords a diastereomeric mixture involving the phenyl and the methyl groups (Table II, entries 9–11) according with ^1H NMR data. These results confirm that the *trans*-selectivity in the cyclization reactions, explained within the stereoinduction Beckwith-Houk model[19] as referred above, can only be kept in substrates in which the hydrogen atom is geminal with an electron-withdrawing group and is *syn* to the olefinic bond of the delocalised radical.

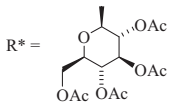
It is interesting to compare our findings with those obtained in earlier investigations of the intramolecular cyclization of bromoesters derivatives of type **1f** in the presence of either *n*-Bu_3SnH and AIBN[10] or ethylpiperidine hypophosphite (EPHP) and AIBN[10] as the radical initiator.



1f: R=$CH_2C{\equiv}CH$

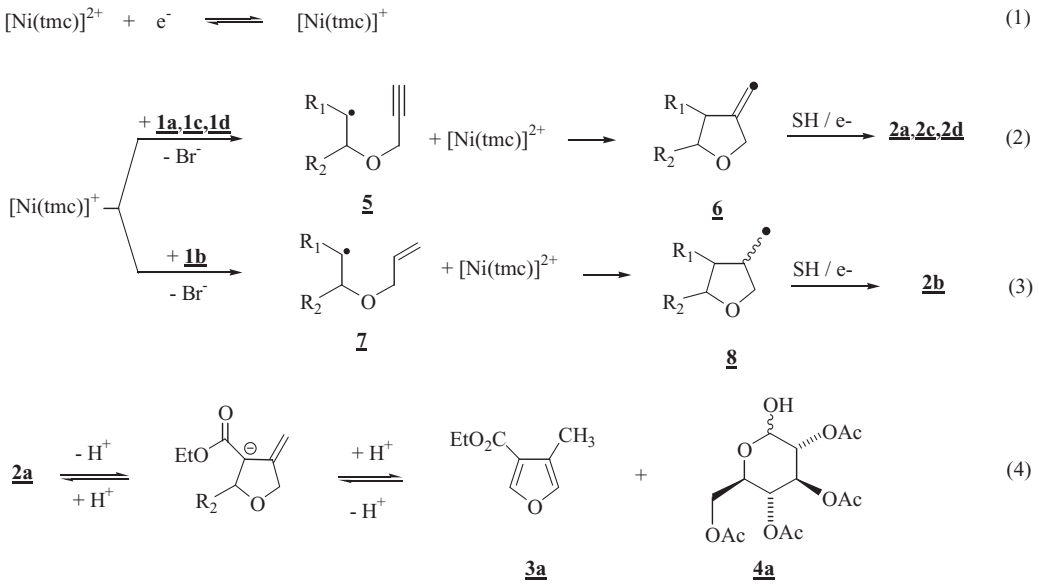


2f



McCague et al.[10] have shown that the intramolecular radical cyclization of bromoester **1f** was achieved with *n*-Bu_3SnH and AIBN in dry toluene to afford the corresponding tetrahydrofuran derivative in 35% yield after chromatography and crystallization; it was concluded that the reaction proceeds through a closure in the *exo* mode to a five-membered ring only. Subsequently, McCague et al.[10] have attempted to improve the efficiency of the transformation and to avoid the use of toxic tin-based reagents. They reported that the best result was achieved when bromoester derivative **1f** was treated with EPHP and AIBN in toluene; the corresponding tri-substituted tetrahydrofuran was obtained in a yield higher than 65%. The cyclization reaction afforded an excellent *trans* selectivity which could be explained by an extension of a stereoinduction model proposed by Giese[20] as it was proposed for **1a**. Based on these results they concluded that the stereochemical outcome of the reaction was determined solely by the acetal configuration and that the D-glucose acetylated auxiliary played no role in the stereoinduction process.

Indeed, the procedures presented using EPHP[10] as hydrogen donor provide efficient methods for the syntheses of highly functionalized tetrahydrofurans in similar yields of those obtained by electrochemical methodologies. However, the simplicity and ease of application of the electrochemical method in environmental friendly media at room temperature makes it a valuable synthetic tool and an



1a: R_1= ethoxycarbonyl; R_2 = tetraacetylglucose
1b: R_1= ethoxycarbonyl; R_2 = tetraacetylglucose
1c: R_1 = methyl; R_2 = phenyl
1d: R_1 = phenyl; R_2 = methoxy

Scheme 2. Proposed reaction mechanism for the indirect electroreductive cyclization of bromoalkoxylated derivatives 1 catalyzed by [Ni(tmc)]Br_2 complex.

interesting alternative to the stoichiometric use of hydrogen donor reagents in radical chemistry.

Discussion.— On the basis of the data obtained in the present study, we propose the mechanism shown in Scheme 2. The product distribution will depend on the relative rates of the several competing reactions.

After the reversible one-electron reduction of $[Ni(tmc)]^{2+}$ takes place (reaction 1), the resulting $[Ni(tmc)]^{+}$ transfers an electron to **1**, cleaving the carbon–bromine bond, to give a radical intermediate **5** [reaction 2] and **7** [reaction (3)]. According to Halcrow and Christou,[21], the nickel(I) species can transfer one electron to an alkyl halide *via* an inner-sphere mechanism, and an alkyl-nickel intermediate might be formed, the subsequent decomposition of which could generate alkyl radicals. Once produced, the radicals **5** and **7** would be expected to undergo rapid intramolecular cyclization to yield carbocyclic radicals, **6** and **8**, respectively. These two radicals can after be reduced or to abstract a hydrogen radical atom from a hydrogen radical atom donor in the medium, to afford **2a, 2c** and **2d** [reaction 2] and **2b** [reaction (3)], respectively.

Alternatively, the heterocyclic compound **2a** can be deprotonated by a base in the medium due to the acidity of the geminal proton to the carboxyl group, giving rise to the corresponding carbanion (reaction (4)). Hence, as soon as the carbanion is formed, it could eliminate the leaving group, leading to the substituted furan **3a** and tetraacetylglucose **4a**. This latter process is commonly encountered as part of the so-called E1cB mechanism, where a carbanion (resulting from deprotonation) is stabilized by resonance and possesses a poor leaving group.[22]

Conclusions

The experimental results presented suggest that the catalytic electroreductive cyclization of the bromoester **1** catalyzed by [Ni(tmc)]Br_2 complex in EtOH and PrOH afford cyclic compounds in high stereoselectivity and the yields are good enough to make this procedure an alternative to other synthetic methods. An advantage of this method is that the radical reactions can be carried out using a catalytic amount of a complex of an appropriate metal, at room temperature, in an environmentally friendly medium.

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