

Intramolecular cyclization of propargyl derivatives using environmentally friendly methodologies*

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Abstract: The electrochemical intramolecular cyclization of propargyl derivatives containing a carbon–halogen bond in *N,N'*-dimethylformamide at constant current in a diaphragmless cell has been developed using Ni(II) complexes as electron-transfer mediators.

INTRODUCTION

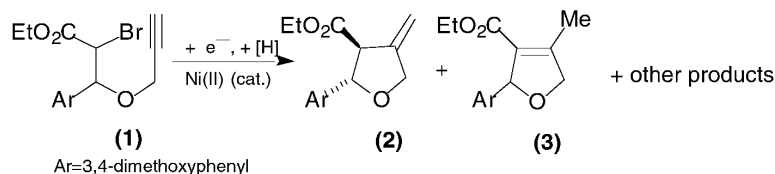
Radical cyclization continues to constitute one of the important methodologies for the synthesis of natural products containing heterocyclic rings. Most radical cyclizations in heterocyclic chemistry are still carried out using Bu₃SnH as a stoichiometric reagent [1]. Particularly, a highly stereocontrolled synthesis of furanolignans, namely, (±)-isogmelinol [2], has been attempted by the tin hydride method. A key step of this synthesis concerns the intramolecular radical cyclization of the propargyl bromoester, **1**, for the formation of the heterocyclic ring precursor of type **2** (Scheme 1).

Important research is being devoted to develop new methodologies for radical generation, avoiding the use of toxic triorganotin compounds, which are also troublesome to separate from reaction products and a number of substitutes for tributyltinhydride are already available, as for example, the work of Chatgililoglu *et al.* [3] on (R₃Si)₃Si, Studer *et al.* [4] on TEMPO, Neumann *et al.* [5] on immobilized R₃SnH, and Stoodley *et al.* [6] on 1-ethylpiperidinium hypophosphite. Moreover, a new method using Ni(II)-catalyzed electroreductions has been studied in reactions involving vinyl or aryl bromides [7,8], bromoacetals [9], or α-bromoamides [10], as well as other unsaturated halides [11–13]. These electrochemical reactions involve the reductive generation of Ni(I) intermediate complexes that induce a radical-type reactivity on the organic halide and constitute a convenient alternative to the tin hydride method. Generally, intramolecular cyclizations involving halogenated substrates with olefins have been studied by this methodology. The present work reports the electrochemical intramolecular cyclization of bromo propargylic ester **1** (Scheme 1) in the presence of a Ni(II) complex, which is reduced in the first step of the electrolysis to a Ni(I) catalyst. This reaction is in competition with the cleavage of the C–O bond, giving compounds **4** and **5**. Results on the Ni(II)-catalyzed electrochemical reduction of **1** and on the influence of some experimental conditions, such as the nature of the sacrificial anode, the nature of the cathode, and the nature of the ligand associated to the nickel complex, are presented.

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Dedicated to the memory of Dr. Ana Freitas.



Scheme 1

RESULTS AND DISCUSSION

Cyclic voltammetric studies of a solution of bromoester **1** in *N,N'*-dimethylformamide (DMF) containing 0.1 M *n*-Bu₄BF₄ at a glassy carbon electrode show three well-defined reduction peaks at potentials -1.65, -1.93, and -2.43 V vs. SCE. We attribute the first reduction peak at -1.65 V to irreversible reductive cleavage of the carbon–bromine bond.

The catalytic electroreduction of the bromoester **1** was performed at constant current, in DMF in a specially designed single-compartment cell, fitted with a consumable sacrificial anode, under an inert gas at room temperature [15]. The results are summarized in Table 1.

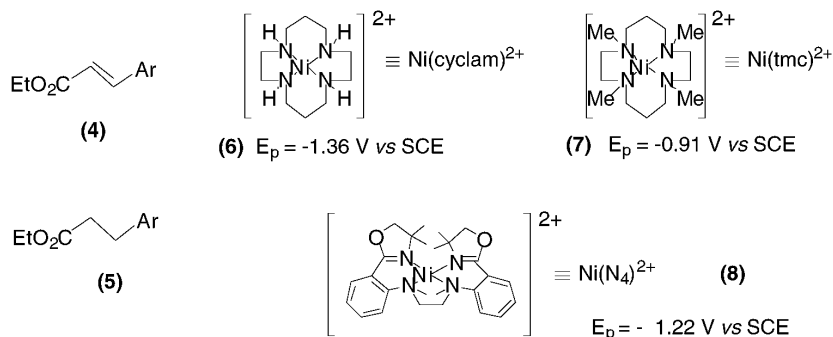
Table 1 Electrochemical intramolecular cyclisation of bromoester **1** catalyzed by an electrogenerated Ni(I) complex (20 mol%) in DMF containing 0.006 mol dm⁻³ tetrabutylammonium tetrafluoroborate.

Entry	Cathode	Anode	Ni ^{II} L	Selectivity of cyclized products ^c	Yield (%)			
					2 + 3	2	3	4
1 ^a	Carbon fiber	Mg	6	41	2	17	4	23
2	Carbon fiber	Mg	6	80	30	33	6	10
3	Stainless steel	Mg	6	22	–	14	7	44
4	Carbon fiber	Zn	6	93	78	–	6	–
5	Carbon fiber	Zn	–	61	46	–	29	–
6	Platinum	Zn	6	53	28	13	30	6
7	Carbon fiber	Zn	7	69	68	–	–	30
8	Carbon fiber	Zn	8	45	45	–	55	–
9	Carbon fiber	Zn	6 ^b	95	95	–	–	–

^a*I* = 60 mA in 0.3 A dm⁻², all other runs *I* = 30 mA in 0.15 A dm⁻²

^b10 mol% of catalyst

^cSelectivity of the intramolecular cyclization (2 + 3) among the other isolated compounds 2–5



The study was initiated by carrying out the electrolysis of **1** in the presence of $[\text{Ni}(\text{cyclam})](\text{ClO}_4)_2$, **6** (20 mol%), using a sacrificial magnesium anode and a carbon fiber cathode. The influence of the current intensity was examined in reactions run at a constant current of 60 mA in 0.3 A dm^{-2} and 30 mA in 0.15 A dm^{-2} . In the first case (entry 1), the reaction proceeded through the cleavage of both carbon–halogen and carbon–(propargyl)oxy bonds to afford the aryl propionic ester **5**, along with the cyclized rearranged ester **3**, as the main products. This result is in agreement with that reported by Duñach *et al.* [16] in the study of intramolecular cyclization of *o*-halogenated aromatic compounds involving triple bonds, in which a moderate yield of the cyclized rearranged 3-methylbenzofuran was isolated. The possibility of electrochemical reductive cleavage of propargyl ethers has been reported [16]. However, in the reaction run at 30 mA the cyclized methylene ester product **2** was formed in 30% yield, together with the cyclized rearranged ester **3** (33%) (entry 2), and for this reason further experiments were conducted at a constant current of 30 mA. At this point, it should be stressed that the comparison of $^1\text{H-NMR}$ data of the residue of the electrolysis with that of an authentic sample of the *trans*-cyclized methylene ester showed that the sole isolated cyclized-2 product was the *trans*-cyclized methylene ester. The authentic samples were prepared by chemical synthesis as described in the experimental section.

In order to get some more insight into the influence of the nature of the electrodes in the reaction selectivity, the nature of the cathode was examined next. Thus, the use of a stainless steel gauze with a magnesium anode led, for the electrolysis of **1**, to the cleaved ester **5** as the major compound, in 44% yield, along with a small amount of the cyclized ester **3** (14%) (entry 3). These results indicate that the radical cyclization of the bromoester **1** is strongly affected by the nature of the cathodic material. Thus, a carbon fiber cathode seems to be much more effective when compared to a stainless steel gauze electrode.

The nature of the anode was also investigated. It was observed that the change of the anode from magnesium to zinc had a major effect on the product yields and distribution (entry 4). Thus, the electrolysis of **1** led to the cyclic product **2** as the main compound in 78% yield and 93% selectivity, with a small amount of the cinnamyl ester, **4** (6%). These results show that the nature of the anodic metal plays also a decisive role on the radical cyclization of the bromoester **1**. Moreover, compound **4** cannot be generated from the corresponding radical $(\text{1-Br})^\bullet$ but from an anion $(\text{1-Br})^-$, which means that the radical derived from **1** must be reduced to the corresponding anion in the electrochemical process to form compound **4**.

In order to examine the influence of the catalyst, the electrolysis of the bromoester **1** was carried out in the absence of the $[\text{Ni}(\text{cyclam})](\text{ClO}_4)_2$, with a Zn/C couple of electrodes. A nonselective reaction occurred, and a mixture of cyclic compound **2**, along with the cinnamyl ester **4**, was obtained in 46 and 29% yields, respectively (entry 5). These results indicate that the presence of the nickel complex was an important factor to determine the reaction selectivity. Similar results have been reported by Torii *et al.* [17] in the study of indirect electrochemical radical cyclization of 2-bromoethyl 2-alkynyl ethers by the combine use of chloro(pyridine)-cobaloxime(III) and a zinc plate as a sacrificial anode in an undivided cell. The reaction was feasible with 5 mol% of the cobalt catalyst and applicable to a variety of bromo acetals under neutral conditions, giving the corresponding cyclized products in good yields. Further work is needed, however, to elucidate in what manner the zinc ions influence the yield of the cyclized ester **2**.

The influence of the nature of the cathode was also examined using a zinc anode. The use of a platinum cathode led, for the electrolysis of **1**, to the formation of both cyclic compounds **2** and **3**, in 28 and 13% yields, respectively, together with the cinnamyl ester **4** (30%) (entry 6). Here again, the nature of the cathodic material influenced the results, as reported above in the presence of a magnesium anode.

The influence of the nature of the ligand on the reaction selectivity was also investigated in reactions using a Zn/C couple of electrodes in DMF. Hence, when $[\text{Ni}(\text{tmc})]\text{Br}_2$, **7**, (tmc = 1,4,8,11-tetramethylcyclam) was used as the catalyst, the electrolysis of bromoester **1** afforded the cyclized product

2 in 68% yield, together with the cleavage compound **5** (30%) (entry 7). These results demonstrate that the [Ni(tmc)]Br₂ system efficiently catalyzes the cyclization of **1** but also to some extent, the cleavage of the carbon–(propargyl)oxygen bond. Duñach *et al.* [16] also observed that changes on the ligand's nature influence the reaction selectivity. Hence, when [Ni(tmc)]²⁺ was used as the catalyst in the intramolecular cyclization of *o*-halogenated aromatic compounds, the cyclized compound was obtained in 40% yield while with [Ni(cyclam)]²⁺ was produced in 86% yield.

The electroreduction of **1** was also performed in the presence of [Ni(N₄)](BF₄)₂, **8** as the catalytic system. As well as the [Ni(tmc)]Br₂ system, the [Ni(N₄)](BF₄)₂ catalyst also gave rise to the formation of both the cyclic compound **2** and the cleavage product **4**, in 45% and 55% yields, respectively (entry 8).

In sharp contrast, when [Ni(cyclam)](ClO₄)₂ was used as the catalyst precursor in the electrolysis of **1**, the process involved a more selective radical-type reactivity of the reduced carbon–halogen bond of the substrate, and enabled the preferential formation of 5-membered heterocyclic ring. Ozaki *et al.* [9], in the study of indirect electrochemical radical cyclization of halogeno ethers using nickel (II) complexes as electron-transfer catalysts, showed that various halides cyclized preferentially via the 5-*exo*-trig mode in good yields to the corresponding tetrahydrofuran derivatives as sole products. These results and yields are similar to those obtained in the present work in the best conditions.

Finally, the reaction was performed under the same experimental conditions but in the presence of 10 mol% of catalyst **6** based on the concentration of the bromoester **1**. The cyclized compound **2** was obtained in 95% yield as the only product of the reaction (entry 9). This result is in agreement with that presented above (entry 4) and shows that the ratio [RBr]/[Ni(II)] does not interfere on the reaction mechanism.

In conclusion, an extension of the work done on the nickel-catalyzed electrochemical reaction has been developed. The electrochemical reactivity of a substrate such as **1** provided an example of the feasibility of the electrochemical radical-type cyclization involving propargyl derivatives. Good yields were attained by a careful control of the reactivity, by varying the ligand environment in the catalytic system and the nature of the electrodes. Moreover, this method is practical in that radical reactions can be conducted by the use of a catalytic amount of an appropriate metal complex at ambient temperature and in an environmentally friendly procedure. In an effort to extend the scope of these investigations, other alternative strategies are being explored.

EXPERIMENTAL

¹H-NMR spectra were recorded on a Varian Unity Plus (300 MHz) spectrometer in CDCl₃ using the solvent peak as an internal standard. Preparative column chromatography separations were performed on Merck silica gel 60 (230–400 mesh).

Chemical cyclization of the propargyl derivative 1 [6]: A stirred solution of **1** (0.500 g; 1.347 mmol), 1-ethylpiperidinium hypophosphite (1.210 g; 6.375 mmol), and AIBN (0.044 g; 0.2694 mmol) in toluene (50 cm³) was heated at 80 °C for 4 h. The resulting mixture was concentrated, and the residue was dissolved in CH₂Cl₂. The solution was filtered through a pad of Celite, and the filtrate was washed with water (2 × 25 cm³), brine (30 cm³), and water (25 cm³). Evaporation of the dried (MgSO₄) organic phase afforded a transparent greenish liquid that was largely a mixture of **2** and **3**. Flash-column chromatography on silica using diethyl ether-light petroleum 40–60° (2:1) afforded two main fractions. The first eluted material was a yellow liquid (40%), identified as **2** by ¹H-NMR spectroscopy, and the second eluted material was also a yellow liquid (25%) identified as **3** by ¹H-NMR spectroscopy.

Compound 2: 1.28 (3H, t, J 7.0 Hz), 3.49 (1H, apparent ddd, J 8.7, 2.4 and 2.4 Hz), 3.88 (3H, s), 3.90 (3H, s), 4.22 (2H, qABq, J 7.0 and 18.0 Hz), 4.5 (1H, apparent dq, J 13.2 and 2.4 Hz), 4.65 (1H, broad apparent d, J 13.2 Hz), 5.11 (1H, apparent q, J 2.4 Hz), 5.19 (1H, d, J 8.7 Hz), 5.20 (1H, apparent q, J 2.4 Hz), 6.84 (1H, d, J 8.7 Hz), 6.91–6.96 (2H, m) ppm.

Compound 3: 1.15 (3H, t, J 7.0 Hz), 2.19 (3H, d, J 1.2 Hz), 3.87 (3H, s), 3.88 (3H, s), 4.08 (2H, qABq, J 7.0 and 11.0 Hz), 4.72 (1H, apparent ddd, J 1.2, 3.6 and 15.0 Hz), 4.89 (1H, apparent ddd J 0.9, 5.7 and 15.0 Hz), 5.90 (1H, m), 6.83 (1H, d, J 8.1 Hz), 6.84 (1H, broad s), 6.88 (1H, dd, J 8.1 and 1.8 Hz) ppm.

Typical electrolysis procedure

In a single-compartment cell (capacity 50 cm³), such as described in ref. 15, with a Mg or Zn rod as the sacrificial anode (diameter 1 cm) and a carbon fiber cathode (apparent surface, 20 cm²) were introduced freshly distilled DMF (50 cm³), *n*-Bu₄N⁺BF₄⁻ (6 × 10⁻³ mol dm⁻³), [Ni (cyclam)](ClO₄)₂ (2 × 10⁻³ mol dm⁻³), and bromoester **1** (1.0 × 10⁻² mol dm⁻³). The solution was stirred and electrolyzed at room temperature, at a constant current of 30 mA until disappearance of **1** (checked by GLC analysis of aliquots). The DMF solvent was then removed by distillation, and the reaction mixture was hydrolyzed with 0.1 M HCl saturated with NaCl, up to pH 1–2 and extracted with CH₂Cl₂ and washed with H₂O. The dried (MgSO₄) organic layer was evaporated, and the residue analyzed by GC, GC-MS, and ¹H-NMR. The crude residue was submitted to flash chromatography over silica gel using diethyl ether-light petroleum 40–60° (2:1) as eluent. The ¹H-NMR spectra of different fractions collected were compared, when available, to those of authentic samples. Spectral data of electrolysis products **2** and **3** are identical to those described above.

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