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# Electrogenerated nickel(I) complexes as catalysts for the intramolecular radical cyclisation of unsaturated α-bromoesters

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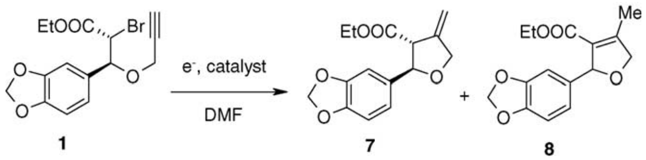
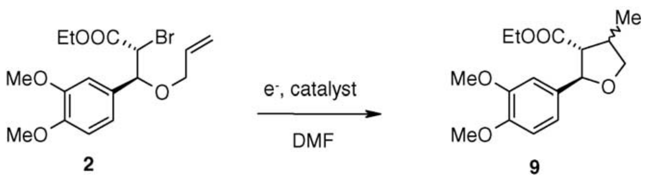
**Abstract**—The indirect electroreduction of unsaturated α-bromoesters using Ni(II) complexes as electron-transfer mediators is achieved in *N*,*N*′-dimethylformamide by constant current electrolysis between a cathode and a sacrificial anode in a diaphragmless cell. Cyclic compounds are obtained in moderate to good yields in conditions that avoid the usual preparation using organotin reagents.

Radical cyclisation is emerging as one of the leading methods for the construction of cyclic systems.[1] While organotin reagents have dominated synthetic procedures involving radical chemistry over the last decade,[1] problems associated with product purification, price and toxicity have stimulated interest in development of more user and environmentally friendly reagents. A new method using Ni(II)-catalysed electroreductions has been studied in reactions involving vinyl or aryl bromides,[2,3] halogeno ethers and halogen esters[4] or bromoacetals[5], as well as other unsaturated halides.[6–10] 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. In order to get more insight on the reaction mechanism of formation of substituted tetrahydrofurans by electrochemical cyclisation of unsaturated halides, we have investigated the cyclisation reaction of ethyl 2-bromo-3-(3′,4′-methylenedioxophenyl)-3-propargyloxy-propanoate **1**[11] (Eq. 1) and ethyl 2-bromo-3-(3′,4′-dimethoxyphenyl)-3-allyloxy-propanoate **2**[11] (Eq. 2) using macrocyclic Ni(II) complexes **3**–**5** and Co(II) complex **6** (Scheme 1).



(1)



(2)

Cyclic voltammetric studies established that electrochemical reduction of Ni(II) complexes and further electron-transfer from electrogenerated Ni(I) complexes to unsaturated halides occurs[6] according to Eqs. (1) and (2). None of the halides was reduced at potentials below −1.50 V.

The electrolyses were conducted in *N*,*N*′-dimethylformamide (DMF) in a single-compartment cell,[12] fitted with a consumable sacrificial anode, under constant current (30 mA in 0.15 A dm$^{-2}$) and at room temperature. A

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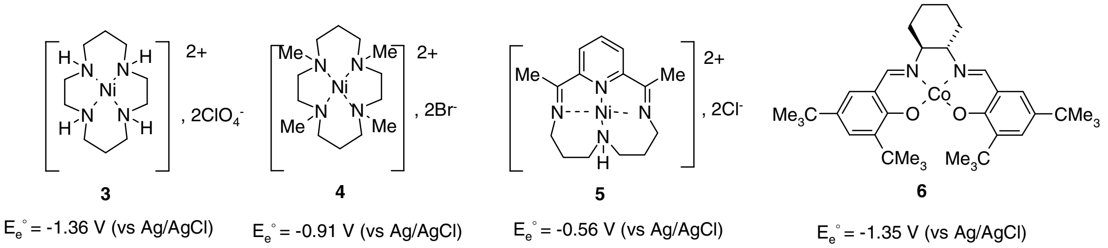

**Scheme 1.**

**Table 1.** Electrochemical intramolecular cyclisation of **1** and **2** catalysed by complexes **3**–**6** (20 mol%)[a]

| Entry | Substrate | Catalyst | Anode | Products (ratio) | Yield of cyclised products/% |
|---|---|---|---|---|---|
| 1 | **1** | **3** | Mg | **8** | 66 |
| 2 | **1** | **3** | Zn | **7**, **8**<br>(45:55) | 71 |
| 3 | **1** | **4** | Zn | **7**, **8**<br>(80:20) | 76 |
| 4 | **1** | **4** | Al | **7**, **8**<br>(73:27) | 74 |
| 5 | **2** | **4** | Mg | **9**<br>(dr[b] = 91:9) | 38 |
| 6 | **2** | **4** | Zn | **9**<br>(dr = 91:9) | 77 |
| 7 | **2** | **4** | Al | **9**<br>(dr = 89:11) | 70 |
| 8 | **2** | **5** | Al | **9**<br>(dr = 91:9) | 60 |
| 9 | **2** | **6** | Al | **9**<br>(dr = 86:14) | 70 |

[a] Typical electrolysis procedure: In a single-compartment cell,[12] with a metal rod (Mg, Al or Zn) as the sacrificial anode (diameter 1 cm) and a carbon fibre cathode (apparent surface, 20 cm$^2$) were introduced freshly distilled DMF (50 cm$^3$), $n$-$Bu_4NBF_4$ ($6 \times 10^{-3}$ M), [Ni(cyclam)]$(ClO_4)_2$, ($2.4 \times 10^{-4}$M) and bromoester **1** or **2** ($1.2 \times 10^{-3}$ M). The solution was stirred and electrolysed at room temperature, at a constant current of 30 mA in 0.15 A dm$^{-2}$ (3–6 V between the electrodes) until disappearance of the substrate (according to GC analysis, 2–3 h). The DMF solvent was then evaporated under vacuum and the reaction mixture was hydrolysed with 0.1 M HCl (50 cm$^3$), extracted with $CH_2Cl_2$ and washed with $H_2O$. The dried ($MgSO_4$) organic layer was evaporated and the residue analysed by GC, GC–MS and 1H NMR, in comparison with those of authentic samples.[13]

[b] dr: diastereoisomeric ratio.

20 mol% of the catalyst with respect to the substrate was used. The results are presented in Table 1.

In order to clarify the influence of the nature of the sacrificial anode, the electrolysis of **1** was carried out in the presence of [Ni(cyclam)]$(ClO_4)_2$ **3** using a sacrificial magnesium anode and a carbon fibre cathode and the results were compared when zinc was used as a sacrificial anode. In the first case (entry 1) the reaction mainly proceeded through the cleavage of carbon–bromine bond to afford 2-(3′,4′-methylenedioxophenyl)-3-(ethoxycarbonyl)-4-methyl-2,5- dihydrofuran **8** in 66% yield, as the main product. When this reaction was performed using the same experimental conditions but in the presence of a sacrificial zinc anode, 2-(3′,4′-methylenedioxophenyl)-3-(ethoxycarbonyl)-4-methylene-tetrahydrofuran **7** was formed in 32% yield, together with the cyclised rearranged ester **8** (39%) (entry 2). These results show that the selectivity of the radical cyclisation of **1** is affected by the nature of the anode material and it is enhanced in favour of cyclised rearranged product **8** when Mg anode is employed.

The influence of the nature of the ligand of the catalyst on the reaction selectivity was next explored. Thus, the electrolysis of **1** in the presence of [Ni(tmc)]$Br_2$ **4** using Zn/C couple of electrodes afforded the cyclised product **7** in 61% yield together with the cyclised rearranged ester **8** (15%) (entry 3). These results demonstrate that the [Ni(tmc)]$Br_2$ system efficiently catalyses the cleavage of the halide bond leading to the formation of the cyclised products. In these experimental conditions, the influence of the nature of the anode in the reaction was also investigated and it was observed that the change of anode from zinc to aluminium had a minor effect on product yields (entry 4). These results are in agreement with that found in our previous study of intramolecular cyclisation of a propargyl derivative[10], in which the cyclised rearranged 3-methylbenzofuran was isolated.

In a similar manner as described above, the intramolecular cyclisation involving a double bond was examined in the case of bromo allyloxy ester **2**. The results are shown in Table 1.

The role of the sacrificial anode was found to be important in this electroreduction like in the previous case. Hence, the electrolysis of bromo allyloxy ester **2** in the presence of [Ni(tmc)]$Br_2$ **4** using a Mg anode and a C cathode gave the 2-(3′,4′-dimethoxyphenyl)-3-(ethoxycarbonyl)-4-methyltetrahydrofuran **9** in 38% yield (entry 5), while the electrolysis of **2** in a Zn/C couple of electrodes system gave the cyclised methylbenzofuran **9** in 77% yield (entry 6). A combination of an Al anode and a C cathode was also effective, giving **9** in 70% yield from **2** (entry 7).

The effect of the nature of the ligand in the reaction selectivity was also examined. Thus, the electrolysis of **2** in the presence of Ni(CR)$Cl_2$ **5** using the Al/C couple of electrodes afforded the cyclised product **9** in 60% (entry 8). The Ni(CR)$Cl_2$ complex system is also able to efficiently catalyse the cleavage of the carbon–halide bond leading to the formation of the cyclised product. Using the same experimental conditions, the electroreduction of **2** was also performed in the presence of Co(salen)-type complex **6** as the catalytic system. Data on product yields show that complex **6** led also to the formation of the cyclised product **9** in 70% yield (entry 9).

It should be noted that the initial *trans* ester to aryl group stereochemistry of compounds **1** and **2** was kept in the cyclised products **7**–**9**. As a new stereocentre was formed by cyclisation of compound **2**, a diastereoisomeric mixture was obtained in each case (Table 1, entries 5–9). NOED experiments showed that in the major stereoisomer, the ester and methyl groups are in a *cis* relationship.

In conclusion, the above study illustrates the preparative interest of the electroreductive catalytic cyclisation of unsaturated halides using consumable anodes and $M^{II}(L)$ ($M = Ni$, Co) complexes. 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, the electrochemical method enables the reactions to be catalytic in nickel complex and the use of mild experimental conditions operating at room temperature.

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13. Products were identified by means of $^1H$ NMR spectrometry with a Varian Unity Plus 300-MHz instrument ($CDCl_3$): (a) for **7**, $\delta$ 1.28 (3H, t *J* 7.2, $OCH_2CH_3$), 3.42–3.47 (1H, m, 3-H), 4.21 (2H, qABq *J* 7.2 and 11.0, $OCH_2CH_3$), 4.49 (1H, apparent dq *J* 13.0 and 2.4, 5-H), 4.63 (1H, br apparent d *J* 13.0, 5-H), 5.10 (1H, apparent q *J* 2.4, =C*H*), 5.15 (1H, d *J* 8.7, 2-H), 5.18 (1H, apparent q *J* 2.4, =C*H*), 5.96 (2H, s, $OCH_2O$), 6.77 (1H, d *J* 8.0, 5′-H), 6.88 (1H, dd *J* 8.0 and 1.8, 6′-H), 6.90 (1H, d *J* 1.8, 2′-H); (b) for **8**, $\delta$ 1.16 (3H, t *J* 7.2, $OCH_2CH_3$), 2.18 (3H, apparent d *J* 1.2, 4-$CH_3$), 4.09 (2H, qABq *J* 7.2 and 10.8, $OCH_2CH_3$), 4.71 (1H, apparent ddd, *J* 15.0, 3.5 and 1.0, 5-H), 4.87 (1H, apparent ddd, *J* 15.0, 5.0 and 1.0, 5-H), 5.83–5.87 (1H, m, 2-H), 5.94 (2H, s, $OCH_2O$), 6.76 (1H, d *J* 8.0, 5′-H), 6.77 (1H, d *J* 1.8, 2′-H), 6.82 (1H, dd *J* 8.0 and 1.8, 6′-H); (c) for **9,** $\delta$ 1.07 (2.55 H, d *J* 6.9, 4-Me), 1.18 (0.45 H, d *J* 6.6, 4-Me), 1.25 (0.45 H, t *J* 7.0, $OCH_2CH_3$), 1.28 (2.55 H, t *J* 7.2, $OCH_2CH_3$), 2.55 (0.15 H, apparent t, *J* 9.0 and 8.7, 3-H), 2.70–2.85 (1H, m, 4-H), 3.00 (0.85, apparent dd *J* 9.0 and 7.8, 3-H), 3.66 (1H, apparent dd, *J* 8.7 and 6.6, 5-$H_a$), 3.87 (3H, s, OMe), 3.89 (3H, s, OMe), 4.12–4.24 (2H, m, $OCH_2CH_3$), 4.28 (1H, dd, *J* 8.4 and 6.6, 5-$H_b$), 5.05 (0.15 H, d, *J* 9.0, 2-H), 5.19 (0.85 H, d, *J* 7.8, 2-H), 6.83 (1H, d *J* 9.0, 5′-H), 6.88–6.92 (2H, m, 2′-H and 6′-H).