Indirect Electroreductive Radical Cyclization of Halogeno Ethers using Nickel(ii) Complexes as Electron-transfer Catalysts

Shigeko Ozaki,* Hidenori Matsushita and Hidenobu Ohmori

Faculty of Pharmaceutical Sciences, Osaka University, 1-6, Yamadaoka, Suita, Osaku-fu, 565 Japan

Indirect electrochemical radical cyclization of halogeno ethers is achieved under mild conditions using nickel(ii) complexes as electron-transfer catalysts.

Radical cyclization is rapidly becoming an important method for the formation of cyclic systems, especially for the construction of *cis*-fused bicyclic systems.[1] Until recently the majority of synthetically useful radical-mediated carbon–carbon bond forming reactions have been carried out using organostananne[2] or organomercury[3] radical initiators. Organotin hydrides have proved particularly useful for C–C bond formation in radical-chain reactions.[2] The trialkyl- and triphenyl-tin hydrides methods, however, require stoichiometric amount of reagents in high dilution (<0.02 mol dm^{-3}) in order to minimize quenching of the initial radical centres by hydrogen radical abstraction from tributyltin hydride.

We have previously performed electroreductive synthesis of bicyclic ketones by intramolecular 1,4-addition of alkyl bromides using cobalt or nickel complexes as a mediator and have shown that the method is a convenient alternative to the use of organometallic reagents such as organocuprates.[4]

In this paper, we report electroreductive cyclization of halogeno ethers and a halogeno ester using nickel(ii) complexes[5] having various redox potentials ranging from -0.95 to -1.38 V vs. standard calomel electrode (SCE) (measured by cyclic voltammetry, Scheme 1) as electron-transfer catalysts, where the reaction possibly proceeds according to Scheme 1.
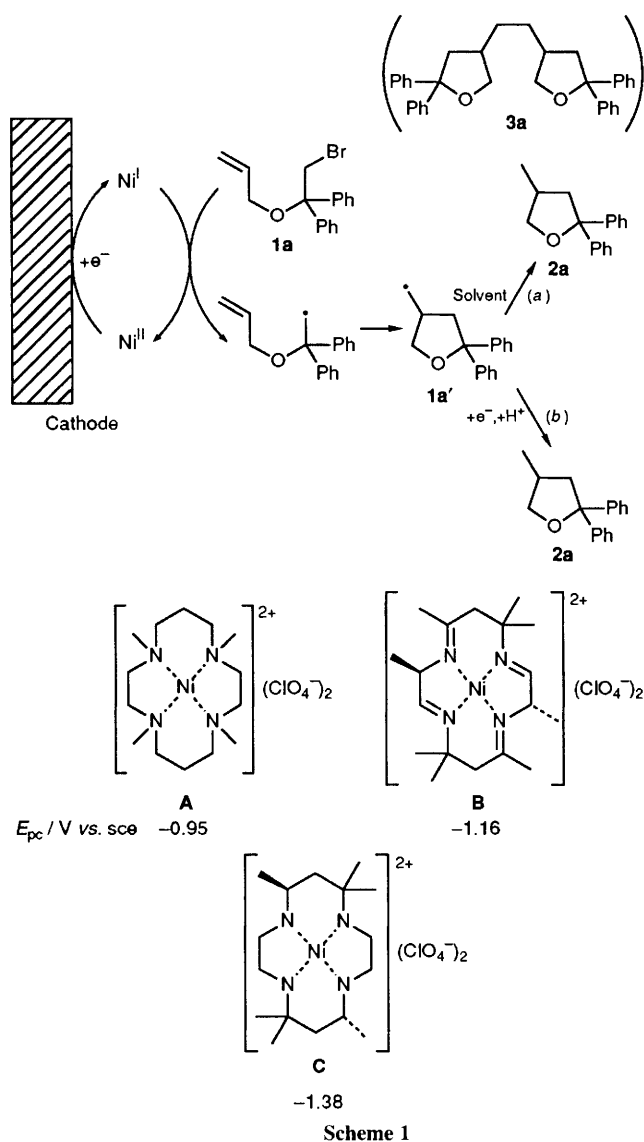
The radical cyclization of the halogeno ethers[6] and halogeno ester[6] by electroreductively generated nickel(i) species was carried out in dimethylformamide (DMF) (10 ml) containing supporting electrolyte (Et$_4$NClO$_4$; 0.1 mol dm^{-3}),

halide (0.5 mmol), proton source (NH$_4$ClO$_4$; 2 equiv. based on the halide), and a catalytic amount of the nickel(ii) complex (0.2 equiv. based on the halide) potentiostatically at the reductive peak potential of the nickel(ii) complex using a graphite electrode as the cathode in an H-shaped divided cell under an inert gas with mechanical stirring.

Electrolysis of the halides at -1.30 V vs. SCE without the nickel(ii) complex did not proceed at all. After all the halide had been consumed by electrolysis for ca. 5 h, the catholyte was subjected to the usual extractive work-up followed by purification on silica gel column chromatography to give the cyclized products.†

As shown in Table 1, various halides cyclized via the 5-*exo-trig* mode in good yields to the corresponding tetrahydrofuran derivatives as sole products except for **1a** which gave the dimerized product **3a** along with **2a**.

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† *Spectral data*: **2a**: m.p. 47–48 °C; ^{1}H NMR (270 MHz; CDCl$_3$) δ 1.35 (3H, d, C*H*$_3$CH), 2.11 (1H, dd, C*H*HCPh$_2$), 2.35 (1H, m, CH$_3$C*H*), 2.84 (1H, dd, CH*H*CPh$_2$), 3.57 (1H, dd, C*H*HO), 4.19 (1H, dd, CH*H*O) and 7.15–7.44 (10H, m, Ph); **3a**: m.p. 150–151 °C, m/z 474 (M$^+$), 397 (M$^+$ − 77) and 237 (M$^+$ − 237); ^{1}H NMR (270 MHz; CDCl$_3$) δ 1.36 (4H, m, CH$_2$CH$_2$), 2.05 (2H, dd, 2 × C*H*HCPh$_2$), 2.17 (2H, m, 2 × CH$_2$C*H*), 2.82 (2H, dd, 2 × CH*H*CPh$_2$), 3.58 (2H, dd, 2 × C*H*HO), 4.13 (2H, dd, 2 × CH*H*O) and 7.15–7.42 (20H, m, 4Ph); ^{1}H NMR spectra of **2b** (**2e**), **2c** and **2d**, coincide with those in refs. 6(a), 6(b) and 6(c), respectively.

Scheme 1

Table 1 Radical cyclization of halogeno ethers (and halogeno ester) with electrogenerated Ni[I] complexes[a]

Substrate 1	Ni complex	Electricity[b] (F mol⁻¹)	Product 2	Yield[c] (%)
1a	A	1.2	2a	53
	B	2.1		58
	C	1.6		44[d]
1b	A	1.3	2b	85
	B	2.2		84
	C	2.5		85
1c	A	1.3	2c[e]	86
	B	2.2		78
	C	1.9		85
1d	C	2.2	2d	75[f]
1e	B	2.0	2e	10[g]

[a] Electrolysed as described in the text. [b] Electricity consumed for complete conversion of substrate 1. [c] Isolated yield based on substrate 1. [d] Accompanied by 3a (35%). [e] Stereochemistry not determined. [f] Determined by GLC. [g] Sole isolated product accompanied by miscellaneous unidentified products.

Table 2. Radical cyclization of 1b to 2b by Ni[I] complexes generated by reduction with metals[a]

Ni complex	Metal	Time/h	Yield of 2b (%)[b]
A	Zn	1	87
B	Zn	1.5	81
C	Zn	5.5	82
A	Mn	2.5	84
B	Mn	20	79
C	Mn	20	Trace[c]

[a] Reaction with 0.5 mmol of substrate, 0.1 mmol of Ni complex, and 1 mmol of Zn or Mn dust in 10 ml of DMF at 60 °C under inert gas. [b] Isolated yield based on 1b. [c] >90% of 1b was recovered.

Since the cyclized radicals from **1b** and **1c** corresponding to **1a′** (Scheme 1) are vinyl radicals, and are less stable than the methyl radical **1a′**,[7] the rates of hydrogen abstraction from a hydrogen radical donor, possibly solvent, by the radicals **1b′** and **1c′** would be higher than that by **1a′**, resulting in the observed higher yields of **2b** and **2c** than **2a**. The formation of the by-product **3a**, probably caused by dimerization of the cyclized radical **1a′** may also be attributed to the relative stability of the methyl radical **1a′** compared with vinyl radicals.

Electrolysis of **1e**, carried out in order to deduce the stereochemistry of the cyclized product, by comparison of ¹H NMR data with literature data,[8] showed that sole isolated product was the cis-fused α-methylene-γ-butyrolactone **2e**. The amount of electricity consumed (F mol⁻¹) is larger in electrolyses with complexes **B** or **C** than with complex **A**, possibly because the amounts of products formed through route (b) (Scheme 1) and extra electrolysis of reducible substances in the system increase with increasing applied potential.

The present method affords markedly different products from those formed by radical cyclization caused by cobalt(I) species derived from cobaloxime(III) or [Co[III] (salen)] [H₂salen = bis(salicylidene)ethylenediamine] in that Co[I] catalysed radical cyclization is accompanied by the formation of the adduct containing a double bond at the cyclized radical

site by the 1,2-elimination of H–Co from unstable alkyl–cobalt(III) species.[10]

The use of electrochemical reduction for generation of the active Ni[I] species from an Ni[II] complex seems to have the advantage over the use of a metal as a reductant, in that an active Ni[I] species can be generated by applying the reductive potential of the Ni[II] complex regardless of its redox potential. When zinc or manganese dust was used for reduction of the Ni[II] complexes at 60 °C, the time required for about 80% production of **2b** from **1b** increased with increasing redox potential of the Ni complex used. When zinc dust was used, **2b** was obtained in every reaction carried out with complex **A**, **B** or **C**. In the case of manganese, the times needed for about 80% production of **2b** from **1b** are 2.5 h with complex **A** and 20 h with complex **B**, respectively, and the reaction with complex **C** did not proceed.

Radical cyclizations by organotin hydrides usually require reflux in benzene with use of a stoichiometric amount of the hydride, whereas the present method affords products under ambient temperature using a catalytic amount of the nickel reagents. Thus, the present Ni^I catalysed radical cyclization should provide a convenient alternative to the organotin hydride method.

Received, 6th May 1992; Com. 2/02339C

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