Indirect Electrochemical Radical Cyclization of Bromo Acetals by the Combined Use of Cobaloxime and Sacrificial Electrode

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Synopsis. An improved procedure for the electrochemical radical cyclization of 2-bromoethyl 2-alkynyl ethers has been developed by the combined use of chloro(pyridine)-cobaloxime(III) and a zinc plate as a sacrificial anode in an undivided cell. The reaction is feasible with 5 mol% of the cobalt catalyst and applicable to a variety of bromo acetals under neutral conditions.

The organocobalt complexes are useful as an electron carrier reagent of various transformations including carbon–carbon bond formations,[1—3] rearrangements,[4] olefin syntheses via β-elimination,[3] and others.[5,6] Especially, the cobalt-mediated radical cyclization for the construction of hetero-ring systems has been shown to be a keen tool in the synthesis of biologically significant compounds.[7] The radical cyclization of bromo alkenes and alkynes with electrochemically recyclable cobaloxime(I) (bis[dimethylglyoximato(1-)-*N*,*N*']cobalt) has been achieved in the cathodic chamber of a divided cell by using 50 mol% of cobaloxime(III).[3] In order to improve the turnover of an electron carrier reagent in this conversion, we studied the electrolysis by using a sacrificial anode in an undivided cell.[8]

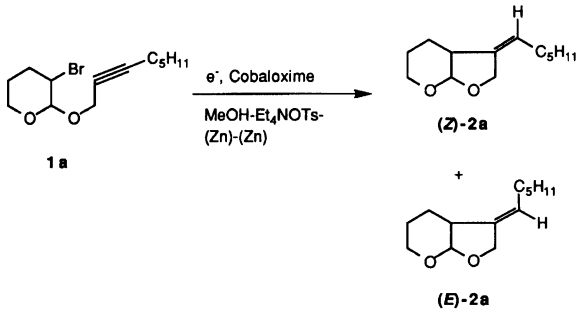
In order to clarify the minimum amount of an electron carrier reagent, the electrolyses of **1a** were carried out in a (Zn)–(Zn) electrode system under varying the amounts of cobaloxime and the results are shown in Table 1 (Scheme 1). Formation of **2a** from **1a** can be attained by using 5 mol% of cobaloxime (Entry 2).[9] No significant change of the yield of **2a** is found even though the amount of cobaloxime is increased to 20 mol% (Entry 4).

The radical reactions mediated by the cobaloxime have usually been carried out in the presence of aqueous alkaline solution. Neutral conditions, however, are needed for base-sensitive compounds such as esters, amides, silylated derivatives, and others. Interestingly, the present cobaloxime-sacrificial electrode system for the radical cyclization of **1a** is operative under neutral conditions, giving **2a** in good yields (Entries 3 and 5). The ratio of the geometric isomers **2a** change slightly by increasing the amount of cobaloxime as a mediator. Formation of (*Z*)-isomer[10] is favored under a neutral condition.[11]

Table 1. Cobaloxime-Mediated Electrocyclization of Bromo Acetal **1a**[a]

Entry	Cobaloxime	40% NaOH	Yield/%[b]	Ratio
	mol%	ml	**2a**	(*Z*)/(*E*)
1	0	0.1	5	1.1/1.0
2	5	0.1	81	1.2/1.0
3	5	0	67	1.5/1.0
4	20	0.1	63	1.2/1.0
5	20	0	77	1.8/1.0

a) Carried out by using **1a** (100 mg, 0.35 mmol) and cobaloxime in a MeOH (5 ml)-Et_4NOTs (300 mg)-(Zn)–(Zn) system. Constant voltage of 10 V was applied at 55—60 °C. b) Yields are based on isolated products.



Scheme 1.

The role of a sacrificial electrode was found to be important in this electroreduction. Electroreduction of **1b** in a (Zn)–(Zn) electrodes system gave **2b** in 70% yield (Table 2), while the electrolysis of **1b** in an (Mg)–(Mg) electrodes system gave **2b** in 53% yield. No satisfactory conversion could be attained in an (Al)–(Al) electrodes system. A combination of a (Pt) cathode and a (Zn) anode was effective, giving **2b** in 69% yield from **1b**. On the other hand, a diverse use of these electrodes, i.e. a (Pt) anode and a (Zn) cathode, was not successful at all.

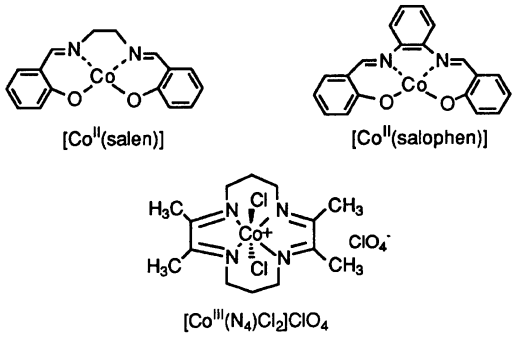
We examined effect of the kind of cobalt complexes on the radical cyclization of 1-bromo-5-alkynes and the results are shown in Table 3. The highest result is obtained with cobaloxime in the electroreduction of **1b** (Entry 2).

In a similar manner as described above, other 1-(2-bromoethoxy)-2-alkynes were submitted to the indirect electrolysis and the results are shown in Table 3. The cyclization of the trimethylsilylated bromo acetal **1e** under neutral conditions gives the corresponding bicyclic ether **2e**, bearing a vinylsilane group (Entry 5), while the electrolysis in the presence of aqueous 40% sodium hydroxide causes the cleavage of a carbon–silicon bond, giving **2c** (Entry 6).

Table 2. Effect of Cobalt-Complexes in the Electroreduction of **1b**[a)]

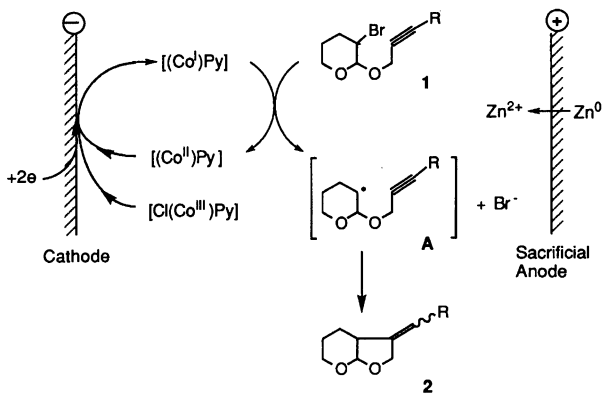
Entry	Cobalt Complex	Yield/% **2b**
1	None	5
2	Cobaloxime(III)	70
3	$[Co^{II}(salen)]$	37
4	$[Co^{II}(salophen)]$	34
5	$[Co^{III}(acac)_3]$	30
6	$[Co^{III}(N_4)Cl_2]ClO_4$[b)]	39

a) Carried out by using **1b** (100 mg, 0.40 mmol) and cobalt complex (5 mol%) in a MeOH (5.0 ml)–Et_4NOTs (300 mg)-(Zn)–(Zn) system. Constant applied voltage of 10 V (100—120 mA) was supplied at 55—60 °C. b) (N_4) is an abbreviation for 2,3,9,10-tetramethyl-1,4,8,11-tetraazacyclotetradeca-1,3,8,10-tetraene.



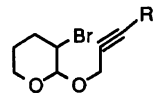
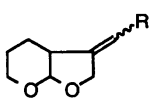
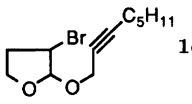
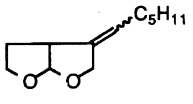
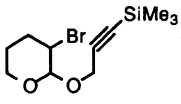
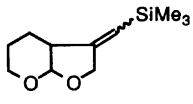
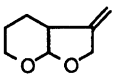
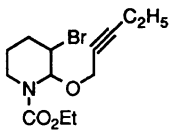
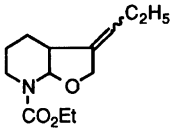
The radical cyclization of bromo alkynes in a combined system of cobaloxime as a mediator with a sacrificial electrode can be understood by taking the reaction path shown in Scheme 2 into the account. Cobaloxime(I) may be electrochemically generated from cobaloxime(III) and induces the reductive cleavage of carbon-bromine bond of 2-bromoethyl-2-alkynyl ethers **1**, producing the radical intermediate **A**. Trapping of a carbon radical with an internal carbon–carbon triple bond could lead to the cyclized **2**, smoothly. The sacrificial anode may be gradually dissolved into the electrolyte solution. The reaction proceeds, and the dissolved metal ion would be neutralized by the liberated anionic species such as bromide ion.

In conclusion, the present cobaloxime-sacrificial anode system was found to be advantageous in terms of the turnover of the catalyst[9)] and convenience of the procedure.



Scheme 2.

Table 3. Electroreductive Cyclization of Bromo Acetals with Cobaloxime as a Mediator and Zinc Foil as a Sacrificial Anode[a)]

Entry	Substrate	Product	Yield/%[b)]
1	 R;C_5H_{11} **1a**	 **2a**	77[c)]
2	R;C_2H_5 **1b**	**2b**	70
3	R;H **1c**	**2c**	54
4	 **1d**	 **2d**	80
5	 **1e**	 **2e**	70
6	**1e**	 **2c**	77[d)]
7	 **1f**	 **2f**	71

a) Unless otherwise noted, the electrolyses were carried out by using cobaloxime (5 mol%) under neutral conditions. b) Yields are based on isolated products. c) The amount of cobaloxime was increased to 20 mol%. d) Carried out in a MeOH (5 ml)–40% NaOH (0.1 ml)–Et_4NOTs (300 mg)-(Zn)–(Zn) system.

Experimental

Apparatus and Procedures. Starting bromo acetals were prepared by bromoalkoxylation of 3,4-dihydro-2*H*-pyran derivatives with 2-alkyn-1-ols in the presence of *N*-bromosuccinimide. IR spectra were recorded on a JASCO FT-5000 spectrometer. ^1H NMR spectra were taken in $CDCl_3$ (Me_4Si or $CHCl_3$ as an internal standard). Column chromatography was carried out by using a Merck Kieselgel 60, Art. 7734 (silica gel) with hexane–AcOEt as an eluent. An undivided cell (2.0 cm diameter and 10 cm height, and 30 ml volume) fitted with a gas inlet pipe, a stirring bar, and a thermometer was used. Two metal foil electrodes ($1.0\times1.5\times0.1$ cm^3) were placed parallel to each other 10 mm apart. The vessel was immersed in a water bath maintained at 55—60 °C on a hot plate.

Indirect Electroreductive Cyclization of Bromo Acetals in a Cobaloxime and Sacrificial Anode System. A Typical Procedure. Preparation of 7-(Hexylidene)-2,9-dioxabicyclo[4.3.0]nonane (2a). To the electrolysis cell were placed the bromo acetal **1a** (100 mg, 0.35 mmol), chloro(pyridine)cobaloxime(III) (7 mg, 0.02 mmol), and Et_4NOTs (300 mg, 1.0 mmol). The mixture were dissolved in MeOH (5 ml) and aqueous 40% NaOH (0.1 ml). Into the solution were immersed two zinc foils

($1.0\times1.5\times0.1$ cm^3) as a cathode and an anode, and the entire mixture was electrolyzed under a constant applied voltage of 10 V (current: 60—120 mA). During the electrolysis, the mixture was heated at 55—60 °C. The reaction was monitored by TLC and the electrolysis was continued until almost all of the starting material had been consumed (the electrolysis period was 2 h and the electricity passed amounted to 13—26 $F\,mol^{-1}$). The mixture was filtered through a celite pad and into the filtrate was added aqueous saturated NH_4Cl (5 ml). The resulting solution was concentrated on a rotary evaporator. The products were taken up in AcOEt and the extracts were washed with brine, dried (Na_2SO_4), and concentrated under vacuum. The crude products were purified by column chromatography on SiO_2 (hexane–AcOEt=5 : 1) to yield **2a** (58.9 mg, 81%) as a mixture of two separable stereoisomers (less polar component/polar component=1/1.2) along with the starting **1a** (6.8 mg, 7%).

(*E*)-2a (less polar component): IR (neat) 2858, 1742, 1657, 1439, 1400, 1379, 1311, 1278, 1245, 1207, 1149, 1077, 1025, 959, 897, 870, 822, 733 cm^{-1}; ^1H NMR (200 MHz) δ=0.89 (t, J=6.8 Hz, 3H, CH_3), 1.29 (m, 6H, CH_2), 1.48—1.63 (m, 4H, CH_2), 1.96—2.09 (m, 2H, CH_2), 2.57—2.69 (m, 1H, CHC=C), 3.62—3.92 (m, 2H, CH_2–O), 4.23 (dd, J=12.3, 1.5 Hz, 1H, OCH_2C=C), 4.54 (dt, J=12.3, 1.7 Hz, 1H, OCH_2C=C), 5.14—5.26 (m, 1H, CH=C), 5.19 (d, J=3.9 Hz, 1H, CH–O).

(*Z*)-2a (polar component): IR (neat) 2942, 2860, 1454, 1400, 1367, 1325, 1301, 1265, 1220, 1149, 1127, 1114, 1093, 1069, 1035, 1006, 973, 953, 932, 899, 870, 733 cm^{-1}; ^1H NMR (200 MHz) δ=0.88 (t, J=6.8 Hz, 3H, CH_3), 1.19—1.73 (m, 8H, CH_2), 1.77—2.08 (m, 4H, CH_2), 2.60 (brs, 1H, CHC=C), 3.43 (td, J=11.5, 2.3 Hz, 1H, CH_2–O), 3.79—3.91 (m, 1H, CH_2–O), 4.43 (d, J=12.9 Hz, 1H, OCH_2C=C), 4.60 (d, J=12.9 Hz, 1H, OCH_2C=C), 5.12 (d, J=3.8 Hz, 1H, CH–O), 5.16—5.28 (m, 1H, CH=C); ^{13}C NMR (50 MHz) δ=14.0, 20.0, 22.0, 22.5, 29.0, 29.5, 31.7, 41.5, 64.5, 69.3, 101.2, 119.8, 136.8.

Spectral data of the compounds listed in Table 2 are as follows.

7-(Propylidene)-2,9-dioxabicyclo[4.3.0]nonane (*E*)-(2b) (less polar component): IR (neat) 3324, 2942, 2876, 1736, 1686, 1454, 1402, 1377, 1299, 1280, 1247, 1210, 1183, 1151, 1104, 1075, 1019, 955, 911, 893, 870, 847, 787, 716 cm^{-1}; ^1H NMR (500 MHz) δ=0.95 (t, J=7.5 Hz, 3H, CH_3), 1.49—1.85 (m, 4H, CH_2), 2.00—2.07 (m, 2H, CH_2), 2.58—2.65 (m, 1H, CHC=C), 3.66—3.68 (m, 1H, CH_2–O), 3.80—3.86 (m, 1H, CH_2–O), 4.20 (dd, J=12.4, 1.5 Hz, 1H, OCH_2=C), 4.51 (dt, J=12.4, 1.7 Hz, 1H, OCH_2C=C), 5.17—5.20 (m, 1H, CH=C), 5.18 (d, J=3.9 Hz, 1H, CH–O); ^{13}C NMR (50 MHz) δ=14.52, 22.32, 22.68, 24.34, 37.42, 61.33, 68.38, 100.92, 122.79, 138.98.

(*Z*)-2b (polar component): IR (neat) 2936, 2870, 1454, 1354, 1301, 1265, 1197, 1127, 1093, 1067, 1036, 973, 955, 897, 870 cm^{-1}; ^1H NMR (500 MHz) δ=0.96 (t, J=7.5 Hz, 3H, CH_3), 1.23—1.29, 1.53—1.64, 1.80—2.00 (m, 6H, CH_2), 2.58 (brs, 1H, CHC=C), 3.41 (td, J=11.4, 2.3 Hz, 1H, CH_2–O), 3.80—3.85 (m, 1H, CH_2–O), 4.42 (d, J=12.9 Hz, 1H, OCH_2C=C), 4.57 (d, J=12.9 Hz, 1H, OCH_2C=C), 5.10 (d, J=3.8 Hz, 1H, CH–O), 5.15—5.22 (m, 1H, CH=C); ^{13}C NMR (50 MHz) δ=13.91, 20.38, 22.57, 22.67, 41.72, 64.53, 69.01, 101.49, 121.56, 136.17.

7-Methylene-2,9-dioxabicyclo[4.3.0]nonane (2c): IR (neat) 2932, 1688, 1452, 1437, 1290, 1205, 1075, 1031, 967, 888, 872, 791 cm^{-1}; ^1H NMR (200 MHz) δ=1.20—1.37 (m, 2H, CH_2), 1.50—1.75 (m, 2H, CH_2), 2.65 (brs, 1H, CHC=C), 3.44 (td, J=11.5, 2.5 Hz, 1H, CH_2–O), 3.80—3.92 (m, 1H, CH_2–O), 4.43—4.65 (m, 2H, OCH_2C=C), 4.97 (q, J=2.5 Hz, 1H, CH=C), 5.03—5.09 (m, 1H, CH=C), 5.15 (d, J=3.8 Hz, 1H, CH–O).

4-(Hexylidene)-2,8-dioxabicyclo[3.3.0]octane (2d) (a mixture of stereoisomers): IR (neat) 2932, 2860, 1450, 1365, 1253, 1096, 1013, 951, 893 cm^{-1}; ^1H NMR (200 MHz) δ=0.87, 0.88 (t, J=6.7 Hz, 3H, CH_3), 1.20—1.46 (m, 6H, CH_2), 1.80—2.27 (m, 4H, CH_2), 3.20—3.38 (m, 1H, CHC=C), 3.69—4.00 (m, 2H, CH_2–O), 4.24—4.50 (m, 2H, OCH_2C=C), 5.24—5.42 (m, 1H, CH=C), 5.76, 5.79 (d, J=5.0 Hz, 1H, CH–O); ^{13}C NMR (50 MHz) δ=14.00, 22.47+22.52, 28.94+29.04, 29.28+29.54, 31.34+31.51, 33.30+34.84, 44.23+47.20, 67.43+68.11, 69.63+72.23, 109.35+109.75, 121.66+122.62, 140.35+140.52.

7-(Trimethylsilylmethylene)-2,9-dioxabicyclo-[4.3.0]nonane (*E*)-(2e) (less polar component): IR (neat) 2956, 1738, 1642, 1439, 1404, 1280, 1249, 1205, 1152, 1073, 1033, 957, 841, 770 cm^{-1}; ^1H NMR (200 MHz) δ=0.12 (s, 9H, CH_3), 1.45—1.87 (m, 4H, CH_2), 2.45—2.61 (m, 1H, CHC=C), 3.62—3.74 (m, 1H, CH_2–O), 3.79—3.94 (m, 1H, CH_2–O), 4.20 (dd, J=13.4, 1.8 Hz, 1H, OCH_2C=C), 4.58 (dt, J=13.4, 1.6 Hz, 1H, OCH_2C=C), 5.24 (d, J=3.8 Hz, 1H, CH–O), 5.29 (d, J=1.6 Hz, 1H, CH=C); ^{13}C NMR (50 MHz) δ=0.04, 22.84, 25.24, 39.88, 61.03, 70.57, 101.09, 119.15, 157.81.

(*Z*)-(2e) (polar component): IR (neat) 2954, 1638, 1452, 1367, 1249, 1216, 1133, 1116, 1089, 1067, 1035, 1004, 959, 934, 899, 841, 801, 760 cm^{-1}; ^1H NMR (200 MHz) δ=0.09 (s, 9H, CH_3), 1.20—1.66 (m, 2H, CH_2), 1.77—2.10 (m, 2H, CH_2), 2.60 (brs, 1H, CHC=C), 3.43 (td, J=11.4, 2.5 Hz, 1H, CH_2–O), 3.79—3.90 (m, 1H, CH_2–O), 4.44—4.65 (m, 2H, OCH_2C=C), 5.16 (d, J=3.9 Hz, 1H, CH–O), 5.42 (q, J=2.5 Hz, 1H, CH=C); ^{13}C NMR (50 MHz) δ=−0.63, 20.42, 22.50, 44.49, 64.59, 70.53, 101.02, 116.93, 155.03.

2-Ethoxycarbonyl-7-propylidene-9-oxa-2-azabicyclo[4.3.0]nonane (2f) (a mixture of (*Z*)- and (*E*)-isomers): IR (neat) 2940, 2874, 1715, 1429, 1379, 1342, 1301, 1251, 1170, 1133, 1100, 1019, 973, 911, 890, 774 cm^{-1}; ^1H NMR (200 MHz) δ=0.93, 0.95 (t, J=7.5 Hz, 3H, CH_3), 1.24 (t, J=7.1 Hz, 3H, CH_3), 1.31—1.47 (m, 2H, CH_2), 1.60—2.13 (m, 4H, CH_2), 2.93 (m, 1H, CHC=C), 3.82—3.97 (m, 2H, CH_2–N), 4.14—4.16 (q, J=7.1 Hz, 2H, CH_2), 4.20—4.50 (m, 2H, OCH_2C=C), 5.16, 5.28 (m, 1H, CH=C), 5.64 (m, 1H, CH–O).

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9) The turn number of cobaloxime as a catalyst is estimated to be about 50.

10) The stereochemistry of (*Z*)- and (*E*)-isomers were elucidated by the NOE experiments.

11) The electrolysis of **1b** by using 50 mol% of cobaloxime with a platinum cathode in the divided cell produced **2b** in a (*Z*)/(*E*) ratio of 1.2/1.0.