Regioselective Radical Cyclization by Electrochemical Reduction Using an Arene Mediator. Environmentally Benign Method

Nobuhito Kurono, Eiichi Honda, Fumikazu Komatsu, Kazuhiko Orito, and Masao Tokuda*
Division of Molecular Chemistry, Graduate School of Engineering,
Hokkaido University, Sapporo 060-8628

(Received May 29, 2003; CL-030479)

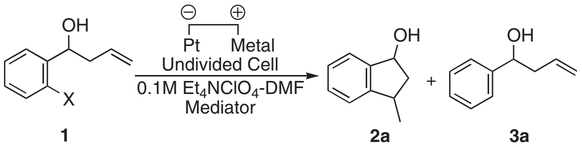
Electrochemical reduction of 2-(but-3-enyl)-1-haloarenes in the presence of phenanthrene as a mediator generated the corresponding aryl radicals and gave cyclized products in good yields. Higher regio- and stereoselectivities than those of usual radical cyclization using AIBN-TBTH were achieved.

Radical cyclization is a useful method for synthesizing cyclic compounds. Carbon radicals are usually generated from the corresponding organic halides by their reaction with AIBN-organotin reagents such as tributyltin hydride (TBTH). However, there are drawbacks in this method, such as toxicity of tin compounds and difficulty in isolating products due to contamination of R_3SnX.

Electrochemical reaction is an environmentally benign method for organic synthesis since it can be carried out under mild conditions by using electrons as clean reagents. Therefore, development of a method for electrochemical generation of carbon radicals from the corresponding organic halides is desirable, but a preferential two-electron reduction usually occurs to give the corresponding carbanions, which finally gives simple reduction products. Only a few methods for electrochemical generation of radicals to give cyclization products have been reported; i.e., direct electrochemical reduction of 2-halo-*N*-arylbenzamide derivatives[1] and arenediazonium salts carrying alk-2-enylamino groups[2] and electrochemical reduction of alkenyl halides using Ni(II) or Co(II) catalyst[3,4] and of *N*-(2-iodophenyl)-*N*-alkylcinnamides using an oxygen mediator.[5]

We intended to develop a method for electrochemical generation of aryl radicals from the corresponding aryl halides by the use of arene as a single electron transfer mediator,[6] since we have found that naphthalene radical anion generated electrochemically worked successfully as a single electron transfer reagent in the preparation of highly reactive zinc.[7] We also intended to develop regio- and stereoselective cyclization reactions by the use of an electrochemical method. Although similar electrochemical cyclization of *N*-allyl-2-chloroacetanilide using (*E*)-stilbene as an electron transfer agent was reported by Grimshaw et al.,[8] only substrates carrying cyano groups at their phenyl rings could be used for the cyclization, and yields of the cyclization products were not satisfactory. Here we wish to report the electrochemical radical cyclization of aryl halides using an arene mediator in which higher regio- and stereoselectivities than those of usual radical cyclizations using AIBN-TBTH were achieved.

Electrochemical radical cyclization of 1-(2-iodophenyl)-1-hydroxy-3-butene (**1a**; X = I) was examined under various conditions to optimize the cyclization reactions (Scheme 1).



Scheme 1.

Electrolysis was carried out at a constant current in an undivided cell equipped with a platinum cathode and a sacrificial anode. An anode material used as a sacrificial anode was the most effective for the reactions. It was found that the use of Mg, Zn, Al, Fe or Ti metal as an anode gave a cyclized product **2a**, whereas the use of Cu, Ni, In, Pb, Sn, or Ag metal as an anode resulted in a preferential formation of **3a**. No reduction of **1a** occurred when a Pt anode was employed. Therefore, a platinum cathode and a magnesium anode were used in the following electrolyses. The effect of current density was also examined, and the electrolysis of **1a** at current densities of 45, 60, 75, and 90 mA/cm^2 gave **2a** in yields of 67, 69, 76, and 58%, respectively. Electricity of 5 F/mol was needed for complete consumption of **1a**.

Effects of various mediators and their amounts on the cyclization of **1a** were also examined, and the results are summarized in Table 1. Use of 6 equiv. of naphthalene gave **2a** in 76% yield (Entry 1). When phenanthrene was used as a mediator, **2a** was obtained in 73% yield even when 2 equivalents of phenanthrene was used (Entry 4). When 9,10-diphenylanthracene, 9-phenylanthracene or 9-cyanophenanthrene was used, the cyclized product was obtained in low to moderate yields (Entries 7-9).

The present electrochemical method for radical cyclization has several advantages, such as cleanness, feasibility, regioselectivity and stereoselectivity, compared with the usual radical cyclization using AIBN-TBTH. Aryl iodide (**1a**), bromide (**1b**), or chloride (**1c**) can be used as a radical precursor in this electrochemical cyclization method. Electrolysis of **1a**, **1b** or **1c** in the presence of 2.0 or 4.0 equiv. of phenanthrene gave the cyclization product **2a** in yields of 62-80% (Table 2, Entries 1-6), although conventional radical cyclization of **1c** using AIBN-TBTH gave no **2a** and the starting **1c** was recovered unreacted (Table 2, Entry 8). A higher diastereomeric ratio of *syn*- and *anti*-**2a**[9] was obtained in the electrochemical cyclization of **1a** (Table 2, Entries 1 and 2), although a similar cyclization using AIBN-TBTH gave a 1.4:1 ratio of *syn*- and *anti*-**2a** (Entry 7).

Regioselectivity of the present electrochemical cyclization is interesting from a synthetic viewpoint. In usual cyclization of carbon radicals, 6-*endo* cyclization preferentially occurs to give a six-membered ring in the case of a 5-hexenyl radical car-

Table 1. Effects of various polyaromatic compounds on electrochemical radical cyclization

$$\mathbf{1a} \xrightarrow[\text{0.1M Et}_4\text{NClO}_4\text{-DMF, 0 °C, 5 F/mol, 75 mA/cm}^2]{\ominus\ \oplus\ \text{Pt Mg, Undivided Cell}} \mathbf{2a} + \mathbf{3a}$$

Entry	Mediator (Red. Potential (V vs Ag/Ag$^+$))	Equiv.[a]	Yield[b] / % 2a	3a	recov.**1a**
1	Naphthalene (-2.94)	6.0	76	14	0
2	Naphthalene	2.0	59	8	18
3	Phenanthrene (-2.87)	4.0	80	14	0
4	Phenanthrene	2.0	73	12	0
5	Phenanthrene	1.0	58	4	22
6	Phenanthrene	0.5	36	3	44
7	9,10-Diphenylanthracene (-2.27)	2.0	48	8	23
8	9-Phenylanthracene (-2.31)	2.0	30	15	21
9	9-Cyanophenanthrene (-2.22)	2.0	47	4	22

[a] Equivalents of mediator to **1a**.
[b] Isolated yields.

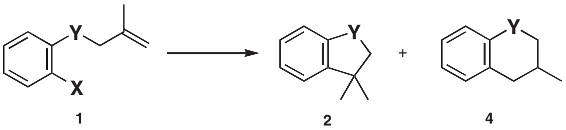
Table 2. Electrochemical radical cyclization of various aryl halides and conventional reaction using AIBN-TBTH

$$\mathbf{1} \xrightarrow[\text{0.1M Et}_4\text{NClO}_4\text{-DMF, 0 °C, Phenanthrene}]{\ominus\ \oplus\ \text{Pt Mg, Undivided Cell}} \mathbf{2a} + \mathbf{3a}$$

Entry	Substrate X	Equiv.[a]	Yield[b] / % 2a (*syn* : *anti*)	3a
1	I **(1a)**	2.0	64 (2.3 : 1)	11
2	I **(1a)**	4.0	80 (2.3 : 1)	14
3	Br **(1b)**	2.0	64 (2.4 : 1)	11
4	Br **(1b)**	4.0	73 (2.4 : 1)	10
5	Cl **(1c)**	2.0	62 (2.1 : 1)	10
6	Cl **(1c)**	4.0	69 (2.5 : 1)	8
7	I **(1a)**	AIBN-TBTH[c]	86 (1.4:1)	
8	Cl **(1c)**	AIBN-TBTH[c]	No Reaction	

[a] Equivalents of mediator to substrate.
[b] Isolated yields.
[c] Reaction of **1a** or **1c** (0.5 mmol) was carried out in toluene (25 mL) under reflux by using 0.2 equiv. of AIBN and 1.1 equiv. of tributyltin hydride.

rying any substituent at the C-5 position.[10] Actually, in the cyclization of **1e**, a 6-*endo* cyclization product (**4**) and 5-*exo* product (**2**) were obtained in 39% and 32% yields, respectively, when the reaction was carried out in toluene under reflux by using an AIBN-TBTH system (Scheme 2). However, similar cyclization of **1e** using the electrochemical method preferentially gave 5-*exo* cyclization product **2**. Electrochemical cyclization of 2-methallyloxyphenyl iodide (**1f**) and 2-iodo-*N*-methallyl-*N*-methylaniline (**1g**) gave exclusively 5-*exo* cyclization product **2** (Scheme 2). These higher regio- and stereoselectivities are probably due to a lower reaction temperature of the present electrochemical radical cyclizations, although a higher temperature is required to initiate a radical reaction when the AIBN-TBTH method is used.



			2	4
X= Br, Y= CH(OH)	**(1e)**	Electrolysis at 0 °C	53%	15%
X= Br, Y= CH(OH)	**(1e)**	AIBN/TBTH toluene, reflux	32%	39%
X= I, Y= O	**(1f)**	Electrolysis at 0 °C	79%	nd
X= I, Y= NMe	**(1g)**	Electrolysis at 0 °C	51%	nd

Scheme 2.

In conclusion, electrochemical reduction of haloarenes in the presence of phenanthrene mediator generated the corresponding aryl radicals efficiently and gave cyclized products in higher regio- and stereoselectivies than those of usual radical cyclizations using AIBN-TBTH.

References

1 J. Grimshaw and J. Trocha-Grimshaw, *Tetrahedron Lett.*, **12**, 993 (1974).
2 F. LeStrat, J. A. Murphy, and M. Hughes, *Org. Lett.*, **4**, 2735 (2002).
3 S. Ozaki, H. Matsushita, and H. Ohmori, *J. Chem. Soc., Chem. Commun.*, **1992**, 1120.
4 S. Torii, T. Inokuchi, and T. Yukawa, *J. Org. Chem.*, **50**, 5875 (1985).
5 R. Munusamy, K. S. Dhathathreyan, K. K. Balasubramanian, and C. H. Venkatachalam, *J. Chem. Soc., Perkin Trans. 2*, **2001**, 1154.
6 D. G. Peters, in "Organic Electrochemistry," ed. by H. Lund and M. M. Baizer, Marcel Dekker, Inc., New York (1991), Chap. VIII, p 390.
7 A. A. Jalil, N. Kurono, and M. Tokuda, *Synlett*, **2001**, 1944; A. A. Jalil, N. Kurono, and M. Tokuda, *Tetrahedron*, **58**, 7477 (2002); A. A. Jalil, N. Kurono, and M. Tokuda, *Synthesis*, **2002**, 2681.
8 M. Dias, M. Gibson, J. Grimshaw, I. Hill, J. Trocha-Grimshaw, and O. Hammerich, *Acta Chem. Scand.*, **52**, 549 (1998).
9 A. Clerici, N. Pastori, and O. Porta, *Eur. J. Org. Chem.*, **2001**, 2235.
10 A. L. J. Beckwith and C. H. Schiesser, *Tetrahedron*, **41**, 3925 (1985); P. Rigollier, J. R. Young, L. A. Fowley, and J. R. Still, *J. Am. Chem. Soc.*, **112**, 9441 (1990); K. Miura, Y. Ichinose, K. Nozaki, K. Fugami, K. Oshima, and K. Utimoto, *Bull. Chem. Soc. Jpn.*, **62**, 143 (1989).

Published on the web (Advance View) July 14, 2003; DOI 10.1246/cl.2003.720