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Electro-reductive cyclization of aryl halides promoted by fluorene derivatives

Koichi Mitsudo[a,*], Yumiko Nakagawa[a], Jun-ichi Mizukawa[a], Hideo Tanaka[a], Ryoichi Akaba[b], Takahiro Okada[a], Seiji Suga[a,*]

[a] Graduate School of Natural Science and Technology, Okayama University, 3-1-1 Tsushima-naka, Kita-ku, Okayama 700-8530, Japan
[b] Department of Chemistry, Gunma College of Technology, 580 Toba-machi, Maebashi, Gunma 371-8530, Japan

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ABSTRACT

In the presence of fluorene derivatives, the electro-reduction of aryl chlorides, bromides, and iodides bearing an ethylene moiety proceeded smoothly to afford the corresponding cyclized products. Noteworthy is that aryl chlorides, which have more negative reduction potential than aryl bromides and iodides, exhibited high reactivity in the reaction, and the corresponding five-membered and six-membered cyclized products were obtained in good to high yields. Mechanistic study suggests that the electro-reduction of fluorene derivatives was essential for the reactions, indicating that they work as a mediator.

1. Introduction

Reductive radical cyclization of aryl halides bearing an unsaturated bond has been frequently used to construct fused aromatics in organic syntheses [1–3]. To realize the radical cyclization, it is significant to suppress competing two-electron reduction which gives dehaloprotonated products (Scheme 1). One-electron reduction of an aryl halide would give an anion radical intermediate which would cyclize to afford the cyclized product. On the contrast, two-electron reduction would give anionic species which could not be cyclized and would be protonated during work-up process.

One typical way to realize the radical cyclization of aryl halides is to use of set of tributyltin hydride and azobisisobutyronitrile (AIBN) [4–8]. However, these reactions have problems such as the toxicity of tin compounds and the difficulty of the separation of the product from thus toxic contaminants.

To overcome the problem, several alternative methods have been developed [9–18]. One of the most environmentally benign methods among thus far reported is the electrochemical reduction of aryl halides; however, because two-electron reduction competes with one-electron reduction [19,20], there have been few reports on electro-reductive radical cyclization. Duñach and co-workers reported Ni-catalyzed electro-reductive cyclizations of aryl halides [21–24], and Co-catalyzed electro-reductive cyclization was reported by Torii and co-workers [25]. Recently, Kurono and Tokuda found that phenanthrene worked as a good mediator for electro-reductive cyclization of aryl halides having an olefin moiety [26,27].

While several methods have been reported, the scope of the substrates was often limited to aryl iodides and bromides, and applicable aryl chlorides have been restricted. Therefore, an efficient method for the radical reaction of aryl halides, including aryl chlorides, is still a challenging topic and highly in demand. We have studied synthesis and electro-chemical behavior of fluorene derivatives [28,29]. During the course of our study, we found that the electro-reductive radical cyclization in the presence of fluorene derivatives proceeded smoothly to give the corresponding cyclized products in high yields (Scheme 2). Notably, aryl chlorides were also applicable to the electro-reduction, and the corresponding cyclized products were obtained in high yields. We herein detail the electro-reductive cyclization reaction of aryl iodides, bromides, and chlorides promoted by fluorene derivatives.

2. Experimental

2.1. Apparatus and materials

The reactions were performed in a Schlenk tube fitted with silicon rubber equipped a magnesium sacrificial anode and a platinum cathode (1 cm × 1.5 cm). Unless otherwise noted, all materials were obtained from commercial suppliers and used without further

* Corresponding authors. Tel.: +81 86 251 8081; fax: +81 86 251 8081.
E-mail addresses: mitsudo@cc.okayama-u.ac.jp (K. Mitsudo), suga@cc.okayama-u.ac.jp (S. Suga).

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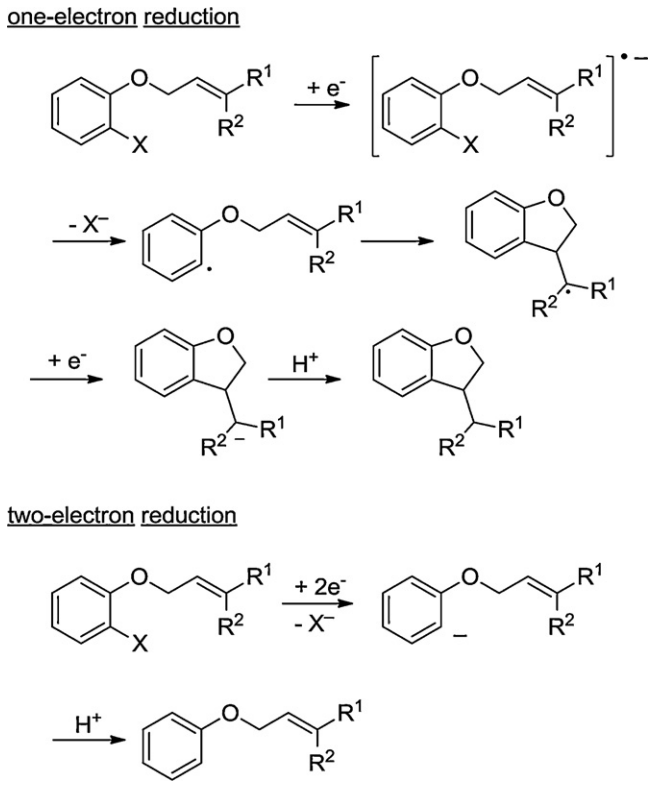


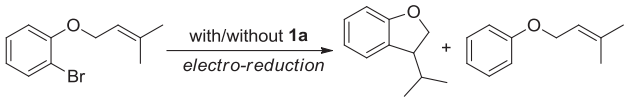
Scheme 1. One-electron reduction *vs.* two-electron reduction.

purification. 9,9-Disubstituted fluorenes were prepared according to the literature [29]. Acetonitrile (CH_3CN) and dimethylformamide (DMF) were dried over CaH_2 prior to use. Tetrahydrofuran (THF) was dried over benzophenone ketyl. All solvents for electro-reduction were degassed by sonication under argon prior to use. All reactions were performed under argon.

2.2. General procedure for electro-reductive cyclization of aryl halides bearing an olefin moiety

To a solution of *o*-chlorophenyl dimethylallyl ether (0.3 mmol) and 9,9-diethylfluorene **1c** (68 mg, 0.3 mmol) in 0.1 M Et_4NClO_4 solution of CH_3CN (6 mL) was passed a constant current (120 mA, 3 F/mol) with magnetic stirring. After the electrolysis, to the reaction mixture was added aq 5% HCl and extracted with Et_2O (3× 10 mL). The combined organic phase was washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

Table 1
Electro-reduction of **2a** with and without **1a**.[a]



2a 3a 4a

Entry	**1a** (equiv.)	**3a**[b]	**4a**[b]	Recov. of **2a**[b]
1	0	25%	42%	15%
2	1	82%	2%	N.D.[c]
3[b]	2	86%	Trace	N.D.

[a] Reaction was performed at 0 °C in an undivided cell (test tube) equipped Mg anode and Pt cathode in the presence of 0.1 M Et_4NClO_4. Constant current (112 mA) was passed (3 F/mol).
[b] Isolated yield.
[c] Not detected.

2.3. Cyclic voltammetry

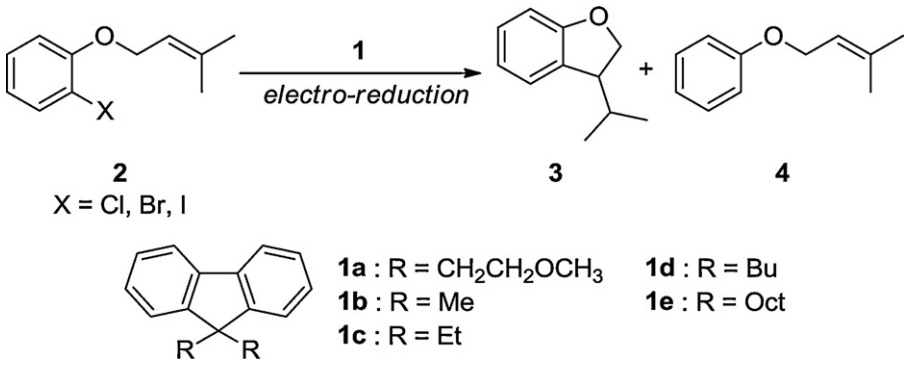
A glassy carbon (surface area: $A = 0.071\ cm^2$, BAS), a Ag/Ag^+ (Ag wire in 0.1 M $AgNO_3/CH_3CN$), and an activated carbon electrode ($A = 1\ cm^2$) were used as working, reference, and counter electrodes, respectively. The working electrode was polished with 5 μm diamond slurry and then with 0.5 μm alumina slurry. After polishing, it was washed with deionized water and acetone, and dried in an oven. An CH_3CN solution including 10 mM of each substrate and 0.1 M of $TEABF_4$ was prepared as an electrochemical oxidation solution. Using the electrodes and the solutions, beaker-typed three-electrode electrochemical cells were constructed, and were connected with the potentiostat (BAS 600BS) to perform cyclic voltammetry (CV). The CV measurement was carried out in an argon atmosphere.

3. Results and discussion

3.1. Electro-reduction of *o*-bromophenyl 3,3-dimethylallyl ether with and without fluorene

We first examined the electro-reduction of *o*-bromophenyl 3,3-dimethylallyl ether (**2a**) with and without **1a** (Table 1). The electrolysis was carried out at 0 °C with 112 mA of current. Without fluorene **1a**, both cyclized product **3a** (25% yield) and reductive dehalogenation product **4a** (42% yield) were obtained (entry 1). The presence of **1a** drastically increased the yield of **3a**, and decreased the amount of **4a** (entries 2 and 3). Fluorene **1a** was stable to the reaction conditions and could be recovered quantitatively after the reaction.

The product selectivity of **3a**/**4a** in the electro-reduction was influenced by the substituents on the fluorene derivative. Several fluorene derivatives **1a**–**e** were used for the reaction (Table 2). When the electro-reduction of **2a** was conducted with **1a** at room



Scheme 2. Electro-reduction of **2** in the presence of fluorene derivatives **1a**–**e**.