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## Electroreductive intramolecular coupling of aromatic δ- and ε-keto esters

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**Abstract**—Electroreduction of aromatic  $\delta$ - and  $\epsilon$ -keto esters in the presence of chlorotrimethylsilane and triethylamine gave fiveand six-membered cyclized products. The products were transformed to the corresponding  $\alpha$ -hydroxy ketones. © 2003 Elsevier Ltd. All rights reserved.

Reductive intramolecular coupling of keto esters is a useful method for the synthesis of cyclic ketones and has been effectively realized by McMurry and Miller with low-valent titanium as a reducing agent.<sup>1</sup> Recently, it has been reported that the reductive coupling of aromatic \delta-keto esters with SmI2 produced cyclic 2hydroxycyclopentanones and 2-cyclopentenones.<sup>2</sup> On the other hand, electroreduction is an effective tool for reductive cross-coupling of ketones with a variety of functional groups. For instance, we have reported the electroreductive intra- and intermolecular couplings of ketones with nitriles,<sup>3</sup> O-methyl oximes,<sup>4</sup> and aromatic rings.<sup>5</sup> We wish to report herein that the electroreduction of aromatic  $\delta$ - and  $\epsilon$ -keto esters in the presence of chlorotrimethylsilane (CTMS) gave five- and six-membered intramolecularly coupled products, respectively (Scheme 1). This reaction provides a new method for the synthesis of  $\alpha$ -hydroxy cyclopentanones and  $\alpha$ hydroxy cyclohexanones.

Conditions for the constant current electroreduction of keto esters were surveyed with methyl 5-keto-5phenylpentanoate 1a using a divided cell, and the results are summarized in Table 1. The cyclized products were obtained as  $\alpha$ -trimethylsiloxy ketal **2a** (about 2:1 mixture of two diastereomers) and  $\alpha$ -trimethylsiloxy ketone 3a together with ketone 4a. In the absence of CTMS, complex mixtures were formed (run 1). The presence of CTMS was crucial for the reductive intramolecular coupling of **1a** (run 2). Furthermore, the addition of triethylamine significantly improved the yields of the cyclized products (run 3).<sup>6</sup> From the results of runs 3-5, THF was the solvent of choice. As a supporting electrolyte, tetrabutylammonium salts were suitable (runs 3, 6–9). Among them, Bu<sub>4</sub>NClO<sub>4</sub>, Bu<sub>4</sub>NBr, Bu<sub>4</sub>NPF<sub>6</sub>, and Bu<sub>4</sub>NCl gave almost the same combined yields of 2a and 3a. The use of LiClO<sub>4</sub>, however, brought about a considerably poor result (run 10). Although Pb seemed to be the best cathode mate-



Scheme 1.

 $<sup>\</sup>label{eq:keywords:electroreduction; reductive coupling; $\delta$-keto esters; $\epsilon$-keto esters; $\alpha$-hydroxy ketones. * Corresponding author. Fax: +81-857-31-5636; e-mail: kise@bio.tottori-u.ac.jp$ 

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Run	Solvent of catholyte <sup>a</sup>	Additive <sup>b</sup>	Cathode material	Yield (%) <sup>c</sup>		
				2a	<b>3</b> a	4a
1	Bu <sub>4</sub> NClO <sub>4</sub> /THF	None	Рb	0	0	0
2	Bu <sub>4</sub> NClO <sub>4</sub> /THF	CTMS	Pb	12	20	16
3	Bu <sub>4</sub> NClO <sub>4</sub> /THF	CTMS/TEA	Pb	32	30	17
4	Bu <sub>4</sub> NClO <sub>4</sub> /DMF	CTMS/TEA	Pb	25	16	0
5	Bu <sub>4</sub> NClO <sub>4</sub> /CH <sub>3</sub> CN	CTMS/TEA	Pb	3	13	0
6	Bu₄NBr/THF	CTMS/TEA	Pb	39	23	20
7	Bu <sub>4</sub> NPF <sub>6</sub> /THF	CTMS/TEA	Pb	32	31	12
8	Bu <sub>4</sub> NCl/THF	CTMS/TEA	Pb	29	38	4
9	$Bu_4NBF_4/THF$	CTMS/TEA	Pb	29	23	9
10	LiClO <sub>4</sub> /THF	CTMS/TEA	Pb	1	8	10
11	Bu <sub>4</sub> NClO <sub>4</sub> /THF	CTMS/TEA	Pt	33	25	10
12	Bu <sub>4</sub> NClO <sub>4</sub> /THF	CTMS/TEA	Ag	34	17	11
13	Bu <sub>4</sub> NClO <sub>4</sub> /THF	CTMS/TEA	Zn	29	21	8
14	Bu <sub>4</sub> NClO <sub>4</sub> /THF	CTMS/TEA	Sn	25	23	16
15	Bu <sub>4</sub> NClO <sub>4</sub> /THF	CTMS/TEA	Cu	20	22	0
16	Bu <sub>4</sub> NClO <sub>4</sub> /THF	CTMS/TEA	Al	17	8	1

<sup>a</sup> 0.3 M Electrolyte in solvent.

<sup>b</sup> 5 mol amount.

<sup>c</sup> Isolated yields.

rial (run 3), other cathode materials (Pt, Au, Ag, Zn, Sn, and Cu) except for Al cathode also afforded the cyclized products in moderate to good yields (runs 11-16). The reaction profile of the electroreduction of **1a** (1 mmol scale) under the conditions of run 3 is illustrated in Figure 1. This result showed that **1a** was almost completely consumed at 300C (3.11 F/mol) and product **4a** was formed from **3a** by further reduction. Indeed, the electroreduction of **3a** under the same conditions gave **4a** in a separate experiment.

A typical procedure is as follows (run 6 in Table 1). A 0.3 M solution of Bu<sub>4</sub>NBr in THF (15 mL) was placed in the cathodic chamber of a divided cell (40 mL beaker) equipped with a lead cathode (5×5 cm<sup>2</sup>), a platinum anode  $(2 \times 1 \text{ cm}^2)$ , and a ceramic cylindrical diaphragm. A 0.3 M solution of Bu<sub>4</sub>NClO<sub>4</sub> in DMF (4 mL) was placed in the anodic chamber. Keto ester (1a) (206 mg, 1 mmol), CTMS (0.64 mL, 5 mmol), and triethylamine (0.70 mL, 5 mmol) were added to the cathodic chamber. After 300C of electricity was passed at a constant current of 50 mA at room temperature, the catholyte was evaporated in vacuo. To the residue was added Et<sub>2</sub>O (30 mL) and insoluble Bu<sub>4</sub>NBr was filtered off. After removal of the solvent, the crude mixture was purified by column chromatography on silica gel (hexane:ethyl acetate, 50:1) to 2-4a. Although the products 2a and 3a were isolated as a mixture, these compounds could be separated by preparative TLC (hexane:ethyl acetate, 20:1).<sup>7</sup>

The electroreductions of other  $\delta$ -keto esters (1b and 1c) and  $\epsilon$ -keto esters (5a and 5b) were carried out under the same conditions as run 6 in Table 1, and the results are exhibited in Scheme 2. The reduction of 1b, a *para*methoxylated analog of 1a, gave the corresponding cyclized products 2–4b in yields higher than those obtained with 1a. Cyclic  $\delta$ -keto ester 1c derived from 1-tetralone afforded tricyclic products 2–4c. 5-Keto-5-



Figure 1. Reaction profile of electroreduction of 1a under the conditions of run 3 in Table 1.



## Scheme 3.

Scheme 2.

phenylpentanoate **5a** and its *para*-methoxylated analog **5b** produced six-membered  $\alpha$ -trimethylsiloxy ketals **6** (almost single diastereomers) and  $\alpha$ -trimethylsiloxy ketones **7**. In these cases, no  $\alpha$ -desiloxylated ketone **8** corresponding to **4** was detected and small amounts of simply reduced trimethylsiloxyethers **9** were formed.

The obtained mixtures of  $\alpha$ -trimethylsiloxy ketals 2 (6) and  $\alpha$ -trimethylsiloxy ketones 3 (7) could be easily desilylated by treatment with Bu<sub>4</sub>NF/THF to give the corresponding  $\alpha$ -hydroxy ketones 10 (11) in high yields (Scheme 3).

The reaction mechanism can be speculated to be as shown in Scheme 4. Anion 12 is formed from 1a by

two-electron transfer and subsequent O-silylation. The anion attacks the ester carbonyl group intramolecularly to give 13. While O-silylation of 13 yields ketal 2a, elimination of the methoxy anion leads to ketone 3a. Further reduction of 3a results in  $\alpha$ -desiloxylated ketone 4a through the formation of silyl enol ether 14.

In summary, the reductive intramolecular couplings of aromatic  $\delta$ - and  $\epsilon$ -keto esters were effectively achieved by electroreduction in the presence of chlorotrimethyl-silane and triethylamine to give five- and six-membered cyclized products. Desilylation of the  $\alpha$ -siloxylated products afforded  $\alpha$ -hydroxy cyclopentanones and  $\alpha$ -hydroxy cyclohexanones.



## Scheme 4.

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- 6. Although the role of triethylamine is not clear at present,

it works as a base to neutralize hydrogen chloride generated by the reaction of CTMS with water slightly present.

7. **2a** (2:1 mixture of two diastereomers):  $R_{\rm f}$  0.81 and 0.73 (hexane:ethyl acetate, 5:1); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  -0.20 (s, 6 H), -0.08 (s, 3 H), -0.01 (s, 6 H), 0.21 (s, 3 H), 1.60–2.68 (m, 6 H), 2.93 (s, 1 H), 3.38 (s, 2 H), 7.15–7.55 (m, 5 H). **3a**:  $R_{\rm f}$  0.65 (hexane:ethyl acetate, 5:1); IR (neat) 1751, 1493, 887, 843, 756, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  -0.04 (s, 9 H), 1.71–1.89 (m, 1 H), 1.96–2.11 (m, 1 H), 2.17–2.55 (m, 4 H), 7.25–7.43 (m, 5 H); <sup>13</sup>C NMR (CDCl<sub>3</sub>)  $\delta$  1.73 (q), 17.32 (t), 35.61 (t), 39.29 (t), 82.39 (s), 126.55 (d), 127.77 (d), 128.12 (d), 140.32 (s), 216.08 (s).