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Electroreductive Coupling of Phthalimides with α,β-Unsaturated Esters: Unusual Rearrangement of Resulting Silyl Ketene Acetals

Naoki Kise,* Shinsaku Isemoto, and Toshihiko Sakurai

Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University, Koyama, Tottori 680-8552, Japan

kise@bio.tottori-u.ac.jp

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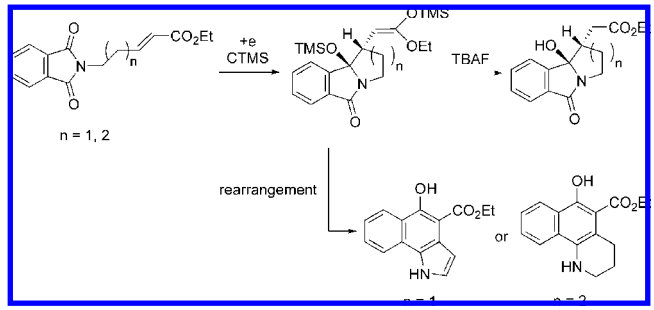
ABSTRACT



The electroreductive intramolecular coupling of phthalimides with α,β-unsaturated esters in the presence of chlorotrimethylsilane and subsequent desilylation of resulting silyl ketene acetals with TBAF gave five- and six-membered *trans*-cyclized products stereospecifically. The silyl ketene acetals were readily rearranged to benzoindole and tetrahydrobenzoquinoline by standing or treatment with a Lewis acid under open-air conditions. The electroreductive intermolecular coupling of *N*-methylphthalimide with methyl acrylate also proceeded.

In 1980, Shono and Ohmizu reported the electroreductive intermolecular cross-coupling of aliphatic ketones and aldehydes with α,β-unsaturated esters in the presence of chlorotrimethylsilane (CTMS).[1] We have also disclosed that electroreduction in the presence of CTMS is an effective tool for the reductive cross-coupling of aromatic imines[2] and ketones[3] and acylimidazoles.[4] To extend this electroreductive method to other reductive cross-couplings, we started investigation into the electroreductive intramolecular coupling of phthalimides with α,β-unsaturated esters in the presence of CTMS using *N*-substituted phthalimides **1** and **4** as substrates. We thereby found that tricyclic compounds **3** and **6** incorporating an isoindolinone ring were obtained stereospecifically after desilylation of initially formed silyl ketene acetals **2** and **5** (Scheme 1). In addition, it is noted that unprecedented rearranged products, benzoindole **7** ($n = 1$) and tetrahydrobenzoquinoline **8** ($n = 2$), were produced from **2** and **5** by standing or treatment with a Lewis acid (Scheme 1). We report herein the electroreductive intra- and intermolecular couplings of phthalimides with α,β-unsaturated esters in the presence of CTMS and

(1) Shono, T.; Ohmizu, H.; Kawakami, S.; Sugiyama, H. *Tetrahedron Lett.* **1980**, *21*, 5029–5032.

(2) (a) Shono, T.; Kise, N.; Kunimi, N.; Nomura, R. *Chem. Lett.* **1991**, 2191. (b) Kise, N.; Ozaki, H.; Moriyama, N.; Kitagishi, Y.; Ueda, N. *J. Am. Chem. Soc.* **2003**, *125*, 11591–11596. (c) Kise, N.; Ohya, K.; Arimoto, K.; Yamashita, Y.; Hirano, Y.; Ono, T.; Ueda, N. *J. Org. Chem.* **2004**, *69*, 7710–7719. (d) Kise, N.; Morimoto, S. *Tetrahedron* **2008**, *64*, 1765–1771.

(3) (a) Kise, N.; Arimoto, K.; Ueda, N. *Tetrahedron Lett.* **2003**, *44*, 6281–6284. (b) Kise, N.; Shiozawa, Y.; Ueda, N. *Tetrahedron Lett.* **2004**, *45*, 7599–7603. (c) Kise, N.; Agui, S.; Morimoto, S.; Ueda, N. *J. Org. Chem.* **2005**, *70*, 9407–9410. (d) Kise, N.; Shiozawa, Y.; Ueda, N. *Tetrahedron* **2007**, *63*, 5415–5426.

(4) Kise, N.; Kaneko, H.; Uemoto, N.; Yoshida, J. *Tetrahedron Lett.* **1995**, *36*, 8839–8842.

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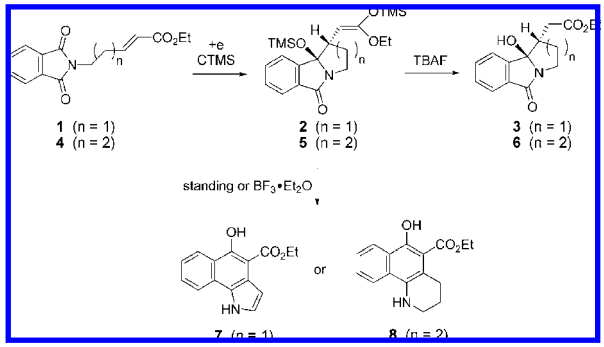
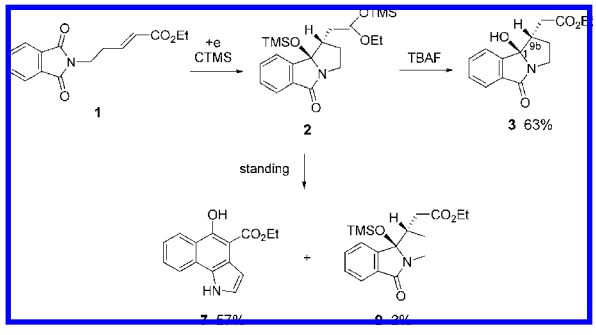
Scheme 1



following usual desilylation and unusual rearrangement of the resulting silyl ketene acetals. Recently, the intra- and intermolecular reductive couplings of phthalimides with α,*β*-unsaturated esters using samarium(II) iodide as a reducing agent have also been reported, although the stereoconfigurations of the intramolecularly coupled products were not determined.[5]

According to the reported procedure,[1−4] the electroreduction of (*E*)-ethyl 5-(1,3-dioxoisoindolin-2-yl)pent-2-enoate (**1**) (1 mmol) was carried out in 0.3 M solution of Et_4NOTs in DMF (15 mL) containing CTMS (5 mmol) at a constant current of 100 mA (300 *C*) employing a divided cell and platinum electrodes. After usual workup, the formation of a silyl ketene acetal **2** was ascertained by ^1H and ^{13}C NMR analyses of the crude product, although **2** could not be isolated because of its instability. When the electroreduction was carried out in the absence of CTMS, only a complex mixture was obtained. This fact shows that the presence of CTMS is essential for the electroreductive cyclization of **1** to **2**, similarly to the previous results.[1−4] The crude ketene acetal **2** was immediately treated with TBAF in THF at 0 °C for 10 min to give a desilylated five-membered cyclized product **3** in 63% yield and >99% stereoselectivity by ^1H NMR analysis (Scheme 2). The 1,9b-*trans* stereochemistry

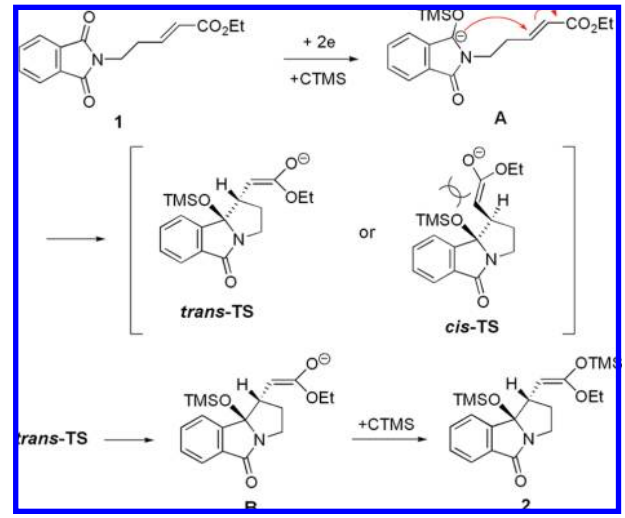
Scheme 2



in **3** was determined beyond doubt by X-ray crystallographic analysis. Alternatively, we found that the unstable silyl ketene acetal **2** was rearranged to 1-hydroxy-2-naphthoate **7** by standing. After the electroreduction of **1**, a THF solution of the crude **2** was allowed to stand under open-air atmosphere at room temperature for 48 h to give 1*H*-benzo[*g*]indole **7** (57% yield) with a small amount (3% yield) of unrearranged silyl ether **9** (Scheme 2). The structure of the unusual rearranged product **7** was assigned by its ^1H and ^{13}C NMR analyses and confirmed by X-ray crystallography of the methyl ester analogue of **7**.

To investigate the initial step of the electroreductive coupling, we measured the cyclic voltammetry of **1**, *N*-methylphthalimide, and methyl acrylate (3 mM) in 0.03 M Bu_4NClO_4/DMF on a platinum cathode. The cyclic voltammograms of **1** and *N*-methylphthalimide showed a first reduction peak at −1.50 and −1.53[6] V vs SCE, respectively, whereas that of methyl acrylate gave no reduction peak from 0 to −2.0 V vs SCE. These observations clearly show that the phthalimide moiety is much more reducible than the α,*β*-unsaturated ester moiety in **1**. Hence, the reaction mechanism of the electroreductive coupling of **1** can be presumed as illustrated in Scheme 3. Anion **A** is formed by a two-electron

Scheme 3



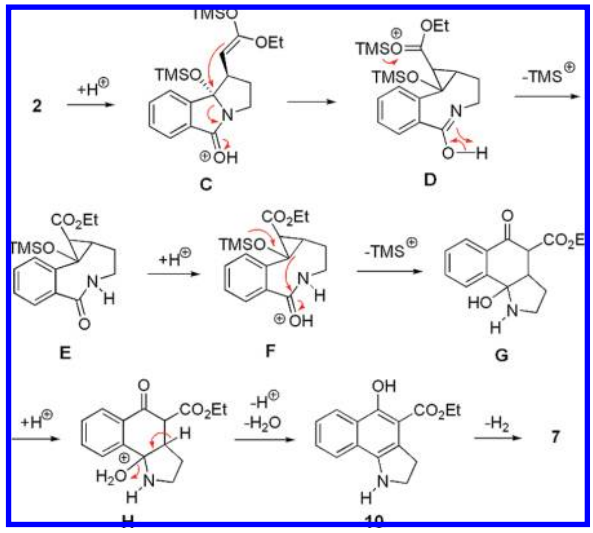
transfer to the phthalimide carbonyl group of **1** and following *O*-silylation. The carbanion in **A** adds to the α,*β*-unsaturated ester moiety intramolecularly through transition state **TS**. Since ***cis*-TS** is more unfavorable than ***trans*-TS** as a result of electronic and steric repulsions between trimethylsilyloxy and ester enolate groups, the *trans*-isomer of silyl ketene acetal **2** is produced predominantly through subsequent *O*-silylation of resultant ester enolate anion **B**.

Next, we presumed the mechanism of the unusual rearrangement of the ketene silyl acetal **2** to benzoindole **7** as exhibited in Scheme 4. The initial step is acid-

(5) Vacas, T.; Álvarez, E.; Chiara, J. L. *Org. Lett.* **2007**, *9*, 5445–5448.

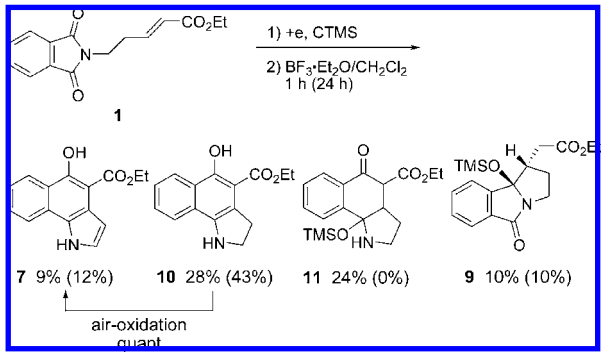
(6) The reduction peak of *N*-methylphthalimide was reported to be −1.47 V vs SCE in Bu_4NPF_6/acetonitrile on a glassy carbon cathode: Warzecha, K.-D.; Gorner, H.; Griesbeck, A. G. *J. Phys. Chem. A.* **2006**, *110*, 3356–3363.

Scheme 4



catalyzed electrophilic addition of *N*,*O*-acetal moiety to ketene silyl acetal moiety in **C** and subsequent desilylation of resulting **D** leads to **E**. In Scheme 4, proton derived from residual water is assumed to be an acid catalysis. The unstable bicyclo[6,1,0] intermediate **E** undergoes acid-catalyzed rearrangement to give bicyclo[4,3,0]*N*,*O*-acetal **G** through **F**. Acid-catalyzed dehydration of **G** to dihydroindole **10** through **H** and following air-oxidation of **10** finally produce the benzoindole **7**. As just described, the formation of **7** from **2** is assumed to be catalyzed by a weak acid, such as residual water in the crude **2**. Therefore, to accelerate the rearrangement of **2**, the crude **2** was treated with a catalytic amount of BF_3·Et_2O in CH_2Cl_2 at room temperature for 1 h under nitrogen atmosphere. As shown in Scheme 5, rearranged products

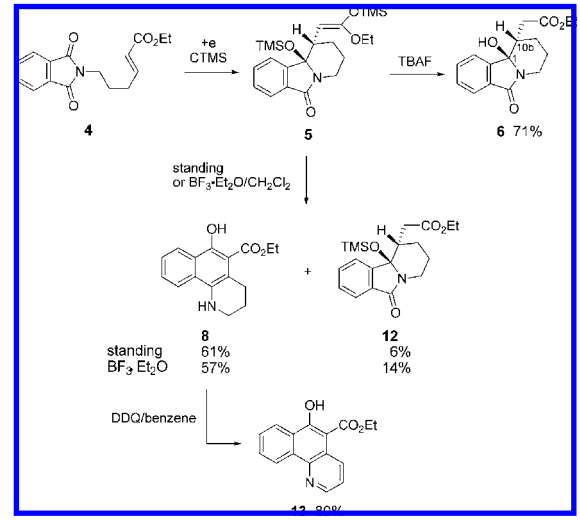
Scheme 5



7, **10**, and **11** (9%, 28%, and 24% yields, respectively) were obtained together with unrearranged silyl ether **9** (10% yield). When the reaction time was prolonged for 24 h, the yields of **7** and **10** were increased (12% and 43% yields, respectively) and the silyl ether **11** disappeared. The production of **10** and **11**, which is a silyl ether of **G**, suggests the intermediacy of **10** and **G** in the formation of **7** from **2.** The indole **7** was formed from **10** by air-oxidation during isolation. Indeed, the dihydroindole **10** could be quantitatively oxidized to the indole **7** in THF solution by exposure to air at room temperature for 24 h.

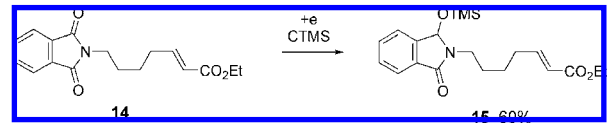
This electroreductive intramolecular coupling is also effective for six-membered ring formation. The electroreduction of (*E*)-ethyl 6-(1,3-dioxoisoindolin-2-yl)hex-2-enoate (**4**) and subsequent desilylation of resultant silyl ketene acetal **5** under the same conditions as above gave a six-membered cyclized product **6** in 71% yield as a single diastereomer (>99% selectivity by ^{1}H NMR analysis) as shown in Scheme 6. The stereostructure of **6** was unambiguously assigned to

Scheme 6



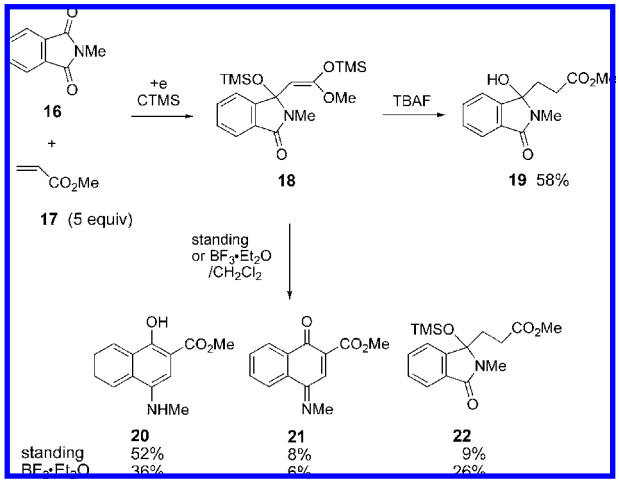
be 1,10b-*trans* by X-ray crystallography. A THF solution of the crude **5** was allowed to stand at room temperature for 24 h to give rearranged product 1,2,3,4-tetrahydrobenzo[*h*]quinoline **8** (61% yield) and unrearranged silyl ether **12** (6% yield) as shown in Scheme 6. On the other hand, treatment of the crude **5** with a catalytic amount of BF_3·Et_2O in CH_2Cl_2 at room temperature for 12 h afforded **8** and **12** (57% and 14% yields, respectively). The tetrahydrobenzoquinoline **8** was readily oxidized to benzoquinoline **13** (80% yield) by treatment with 2 equiv of DDQ in benzene. Unfortunately, this electroreductive method did not work for seven-membered cyclization. The electroreduction of (*E*)-ethyl 7-(1,3-dioxoisoindolin-2-yl)hept-2-enoate (**14**) gave simply reduced trimethylsilyl ether **15** as the sole product (Scheme 7).

Scheme 7



In addition, the intermolecular coupling of *N*-methylphthalimide (**16**) with methyl acrylate (**17**) (5 equiv) was realized by electroreduction under the same conditions; the corresponding coupled product **19**[5] was afforded in 58% yield after desilylation of resultant silyl ketene acetal **18** (Scheme 8). Keeping of the crude **18** at room temperature for 24 h gave rearranged methyl 1-hydroxy-4-(methylamino)-2-naphthoate **20** (52% yield) and its oxidized product **21** (8% yield) together with unrearranged silyl ether **22** (9% yield). However, treatment of the crude **18** with catalytic amount of BF_3•Et_2O in CH_2Cl_2 at room temperature for 12 h decreased the yield of **20** and increased the yield of **22** (Scheme 8).

Scheme 8



In conclusion, the electroreduction of ω-(1,3-dioxoisoindolin-2-yl)-α,β-unsaturated esters **1** and **4** in the presence of CTMS initially gave silyl ketene acetals as intramolecularly coupled products. Subsequent desilylation of the resulting silyl ketene acetals **2** and **5** brought about five- and six-membered *trans*-cyclized products **3** and **6** stereospecifically. The crude silyl ketene acetals **2** and **5** were rearranged to benzoindole **7** and tetrahydrobenzoquinoline **8**, respectively, by standing or by treatment with BF_3•Et_2O. Electroreduction of *N*-methylphthalimide with methyl acrylate also gave intermolecularly coupled silyl ketene acetal **18**, which was transformed to unrearranged isoindoline **19** or rearranged methyl 2-naphthoates **20** and **21** selectively by choosing the conditions of the subsequent treatment.

Supporting Information Available: Experimental procedures and characterization data, X-ray crystallographic data, ^1H and ^{13}C NMR spectra; crystallographic files for **3**, **6**, methyl ester analogue of **7**, and **20** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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