ORGANIC LETTERS

2011
Vol. 13, No. 21
5720–5723

First Direct Evidence of Radical Intermediates in Samarium Diiodide Induced Cyclization by ESR Spectra

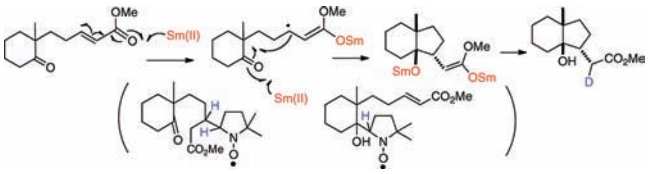
Masakazu Sono,*,[†] Shin-ichi Hanamura,[†] Midori Furumaki,[†] Hisao Murai,*,[‡] and Motoo Tori*,[†]

Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan and Department of Chemistry, Faculty of Science, Shizuoka University, Shizuoka 422-8529, Japan

sono@ph.bunri-u.ac.jp; shmurai@ipc.shizuoka.ac.jp; tori@ph.bunri-u.ac.jp

Received June 8, 2011

ABSTRACT



The mechanism of samarium diiodide (SmI_2)-induced cyclization of α,β-unsaturated esters and ketones to bicyclic compounds was examined using ESR spectroscopy. This is the first report of direct evidence of the radical intermediates in the SmI_2 reaction. The preferential reduction of the α,β-unsaturated carbonyl part in some substrates should be recognized as a main route.

Single-electron reduction by samarium diiodide (SmI_2) is a well-known organic reaction.[1] In the past 30 years, various reviews have been published and this reaction is used in many synthetic works.[2] The reaction mechanism and the effect of cosolvents, additives, or temperature have also been investigated in detail.[3]

Carbonyl-alkene couplings represent one of the widely studied and useful C–C bond forming reactions promoted by SmI_2.[4] This is a highly effective method for the reductive coupling of aldehydes or ketones with alkenes and aromatic systems. Mechanistically, these reactions have been described as a ketyl-alkene coupling, involving single-electron reduction of the carbonyl substrate to give a ketyl radical anion intermediate followed by addition to the unsaturated C–C bond. More recent reports have shown the selective conjugate reduction of the electron-deficient double bond followed by anionic (or possibly radical) addition to the carbonyl group.[5] As with many other SmI_2 mediated transformations, fine-tuning of the reaction using additives such as proton sources or HMPA can have a marked influence on the efficiency and stereochemical outcome of the reaction.[6] The reduction potential of SmI_2 in THF and the effect of varying concentrations of HMPA on the redox potential were determined. The oxidation potential of SmI_2 can be changed from −1.33 V (0 eq of HMPA) to −2.05 V (4 eq of HMPA) vs the Ag/$AgNO_3$ reference electrode.[7] On the other hand, comparison of the half-wave potentials of α,β-unsaturated carbonyls with those of corresponding saturated carbonyl compounds has been extensively studied in electrochemistry.[8] The first waves of carbonyl groups, referred to as SCE, are −2.45 V (cyclohexanone), −2.25 V (methyl ethyl ketone), −1.8 V (propionaldehyde), −1.55 V (cyclohex-2-en-

---

[†] Tokushima Bunri University.

[‡] Shizuoka University.

(1) (a) Namy, J. L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5–7. (b) Girard, P.; Namy, L. J.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693–2698. (c) Kagan, H. B.; Namy, L. J.; Girard, P. *Tetrahedron, suppl. 1* **1981**, *37*, 175–180. (d) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351–10372.

(2) (a) Procter, D. J.; Flowers, R. A., I. I.; Skrydstrup, T. *Organic Synthesis Using Samarium Diiodide: A Practical Guide*; Royal Society of Chemistry Publishing: U.K., 2010. (b) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7140–7165. (c) Berndt, M.; Gross, S.; Hölemann, A.; Reissig, H.-U. *Synlett* **2004**, 422–438. (d) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371–3403. (e) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727–2751. (f) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745–777. (g) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338. (h) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68.

10.1021/ol202403q

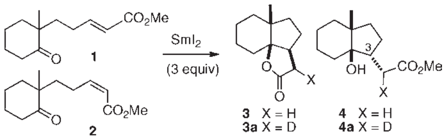
1-one), −1.50 V (acrolein), and −1.42 V (methyl vinyl ketone), respectively.[8] Therefore, the reduction of an α,β-unsaturated carbonyl moiety seems easier than that of the isolated ketone carbonyl group in electrochemical conception. No direct evidence has been provided until now.

We have been interested in the utilization of SmI_2 in synthetic works[9] and have published an intramolecular reductive cyclization reaction producing 5/6, 6/6, 5/7, and 6/7 membered bicyclic compounds.[10] During these studies, we became interested in the mechanistic aspects of these reactions. In the presence of the proton source, the product ratio greatly differs from the case without any additive.[10] We have attributed these differences to the preferential reduction of the α,β-unsaturated carbonyl moiety prior to the C−C bond formation.

Here, we offer evidence of this reaction mechanism by measuring the ESR spectrum using the spin trapping reagent 5,5-dimethyl-1-pyrroline *N*-oxide (DMPO).

When **1** was treated with SmI_2, **4** (entries 1−3) or **3** and **4** (entry 4) were isolated (Table 1). Compound **3** was a lactone and its relative configuration was determined by the NOESY spectrum, while **4** was a hydroxyester whose relative configuration was isomeric at the C-3 position of **3**.

Table 1. Reaction of **1** and **2** with SmI_2



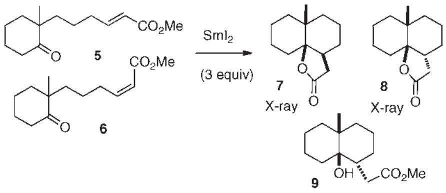
entry	substrate	additives (equiv)	time (h)	yield (%)	
				3	**4**
1	**1**	none	3	-	75
2	**1**	^{t}BuOH (1)	3	-	77
3	**1**	^{t}BuOH (5)	1	-	91
4	**1**	HMPA (12)	1	20	74
5	**2**	none	3	88	9
6	**2**	^{t}BuOH (1)	3	85	12
7	**2**	MeOH (20)	1	67	15
8	**2**	HMPA (12)	1	7	92

Interestingly, **4** always predominated, even in the presence of HMPA (entries 1−4, Table 1). Next, **2** was similarly treated with SmI_2 to afford **3** and **4** (entries 5−8). Except for entry 8, lactone **3** predominated. When the proton source was added to **1** (entries 2, 3), the yield of the product **4** increased. However, in the case of *Z*-isomer **2**, the yield of lactone **3** was not changed very much (entry 6). Interestingly, the mass balance beween **3** and **4** was interchanged in entry 8 when HMPA was added. The mechanism will be discussed later. The ease of cyclizing to a lactone with *cis* substitution is seen in **3**, but in the case of *trans* substitution of the hydroxy and methylene groups, formation of a lactone might be disfavored in the case of a five-membered carbocycle.

When the reaction was quenched with D_2O, the corresponding deuterio compounds, **3a** and **4a**, were obtained. The presence of one deuterium atom was verified by the MS spectra; the position of the deuterium introduction was revealed by NMR. The signals of α-proton to the carbonyl group was greatly decreased in the ^1H NMR spectra of **3a** and **4a** (see Supporting Information).

One-carbon-longer esters **5** and **6** were studied next. These compounds were treated with SmI_2 with or without additives (Table 2). *E*-ester **5** predominantly afforded *trans* fused lactone **8**[11] (entries 1−4), while *Z*-ester **6** mainly gave *cis*-fused lactone **7**[11] (entries

Table 2. Reaction of **5** and **6** with SmI_2



entry	substrate	additives (equiv)	time (h)	yield (%)		
				7	**8**	**9**
1	**5**	none	3	-	72	-
2	**5**	^{t}BuOH (2)	3	-	98	-
3	**5**	^{t}BuOH (10)	1	-	70	13
4	**5**	HMPA (12)	1	-	82	-
5	**6**	none	3	90	-	-
6	**6**	^{t}BuOH (2)	3	74	-	-
7	**6**	^{t}BuOH (10)	1	86	-	-
8	**6**	HMPA (12)	1	75	17	-

---

(3) (a) Flowers, R. A., II. *Synlett* **2008**, 1427–1439. (b) Flowers, R. A., II; Prasad, E. In *Handbook on the Physics and Chemistry of Rare Earths*; Gschneidner, K. A., Jr., Bunzli, J.-C., Pecharsky, V. K., Eds.; Elsevier: 2006; Vol. 36, pp 393−473. (c) Dahlén, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, 3393–3403. (d) Enemaerke, R. J.; Daasbjerg, K.; Skrydstrup, T. *Chem. Commun.* **1999**, 343–344. (e) Enemærke, R. J.; Hertz, T.; Skrydstrup, T.; Daasbjerg, K. *Chem.—Eur. J.* **2000**, *6*, 3747–3754. (f) Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2002**, *124*, 6895–6899. (g) Prasad, E.; Knettle, B. W.; Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2004**, *126*, 6891–6894. (h) Faran, H.; Hoz, S. *Org. Lett.* **2008**, *10*, 865–867. (i) Sadasivam, D. V.; Antharjanam, P. K. S.; Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2008**, *130*, 7228–7229. (j) Choquette, K. A.; Sadasivam, D. V.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2010**, *132*, 17396–17398. (k) Kan, T.; Hosokawa, S.; Nara, S.; Tamiya, H.; Shirahama, H.; Matsuda, F. *J. Org. Chem.* **2004**, *69*, 8956–8958. (l) Dahlén, A.; Hilmersson, G. *Chem.—Eur. J.* **2003**, *9*, 1123–1128. (m) Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* **2001**, *42*, 5565–5569. (n) Chopade, P.; Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2004**, *126*, 44–45. (o) Prasad, E.; Flowers, R. A., II. *J. Am. Chem. Soc.* **2005**, *127*, 18093–18099. (p) Teprovich, J. A., Jr.; Balili, M. N.; Pintauer, T.; Flowers, R. A., II. *Angew. Chem., Int. Ed.* **2007**, *46*, 8160–8163. (q) Farran, H.; Hoz, S. *J. Org. Chem.* **2009**, *74*, 2075–2079. (r) Amiel-Levy, M.; Hoz, S. *J. Am. Chem. Soc.* **2009**, *131*, 8280–8284. (s) Tarnopolsky, A.; Hoz, S. *J. Am. Chem. Soc.* **2007**, *129*, 3402–3407.

(4) (a) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Chem. Commun.* **1986**, 624–625. (b) Fukuzawa, S.; Nakanishi, A.; Fujinami, T.; Sakai, S. *J. Chem. Soc., Perkin. Trans. 1* **1988**, 1669–1675. (c) Otsubo, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 5763–5764.

(5) (a) Hutton, T. K.; Muir, K. W.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811–4814. (b) Johnston, D.; Couché, E.; Edmonds, D. J.; Muir, K. W.; Procter, D. J. *Org. Biomol. Chem.* **2003**, 328–337. (c) Taaning, R. H.; Lindsay, K. B.; Schiøtt, B.; Daasbjerg, K.; Skrydstrup, T. *J. Am. Chem. Soc.* **2009**, *131*, 10253–10262. (d) Hansen, A. M.; Lindsay, K. B.; Antharjanam, P. K. S.; Karaffa, J.; Daasbjerg, K.; Flowers, R. A., II; Skrydstrup, T. *J. Am. Chem. Soc.* **2006**, *128*, 9616–9617.

(6) (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132–3139. (b) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 872–882.

(7) (a) Shabangi, M.; Flowers, R. A., II. *Tetrahedron Lett.* **1997**, *38*, 1137–1140. (b) Shabangi, M.; Sealy, J. M.; Fuchs, J. R.; Flowers, R. A., II. *Tetrahedron Lett.* **1998**, *39*, 4429–4432.

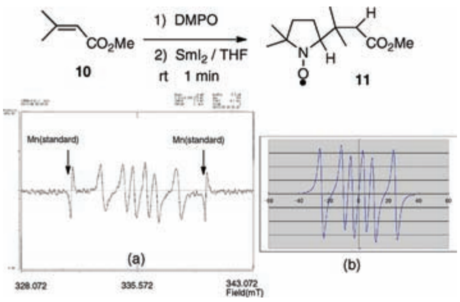


Figure 1. Reaction of methyl 3-methylbut-2-enoate (**10**) with SmI_2 in the presence of DMPO. (a) ESR spectrum of the reaction mixture; (b) simulated spectrum of adduct **11**.

5−8). These structures were solved by X-ray crystallographic analyses.

We wanted to obtain direct evidence to show that the radical intermediate is produced in these reactions. We used a radical trapping reagent to see the ESR spectrum. To confirm the ESR pattern, methyl 3-methyl-2-butenoate (**10**) was allowed to react with SmI_2 in the presence of DMPO and the ESR spectrum of the adduct was measured. The ESR spectrum in Figure 1a was obtained. The simulated spectrum was also shown in Figure 1b. In this case there is no other site of reduction; only adduct **11** was produced. This result shows that single-electron reduction of the α,β-unsaturated ester gives a radical anion intermediate by SmI_2 followed by trapping to a carbon radical at the β-position of the samarium enolate.

In the case of DMPO and **1**, the ESR spectrum in Figure 2a was obtained. From the splitting pattern, the radical species was calculated and two patterns were simulated. Both simulation patterns are presented in Figure 2b, c. The *hfc* values for the species **12** were $a(\mathrm{N}) = 1.40$ and $a(\mathrm{H}) = 2.19$ mT, while those for the species **13** were $a(\mathrm{N}) = \sim 1.47$ and $a(\mathrm{H}) = \sim 2.49$ mT in spectra (b) and (c), respectively. When the contribution of both species was 1:1, the simulated spectrum was quite different from spectrum (a). The contribution of spectrum (c) seems to be quite small, and thus, spectrum (b) and 12% of spectrum (c) were combined to afford the simulated spectrum (d). The real one (a) and the simulated one (d) are very similar to each other, showing that the predominant mechanism should be route a (**1**→**14**→**12**) and hence route b (**1**→**16**→**13**) is minor (Figure 3).

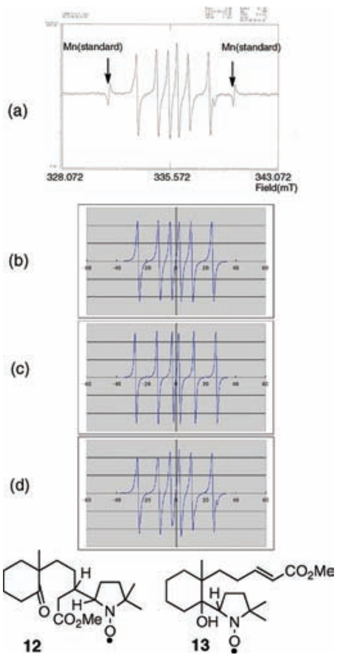


Figure 2. (a) ESR spectrum of the reaction of **1** with SmI_2 in the presence of DMPO (rt, 1 min); (b) simulated spectrum of **12**; (c) simulated spectrum of **13**; (d) sum of **12** and **13** (100:12).

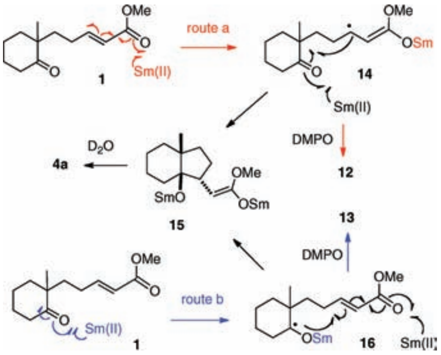


Figure 3. Mechanism for reductive cyclization of **1** and cyclization to **15**.

Because the enone moiety is easily reduced, Sm(II) first reduces the ester carbonyl group to afford a radical anion **14**. Another SmI_2 further reduces the ketone group to provide dianion **15** with the formation of a C−C single bond. When D_2O was added, both anions took deuterium atoms producing **4a** (Figure 3).

Contrary to the results shown in Figure 2, the spin trapping experiment using **2** and DMPO provided a different spectrum as shown in Figure 4a. The simulated spectrum of the sum of **12** and **13** in 1:1 ratio (Figure 4b) is

---

(8) Wagenknecht, J. H.; Eberson, L.; Utley, J. H. P. In *Organic Electrochemistry*, 3rd ed.; Lund, H., Baizer, M. M., Eds.; Marcel Dekker, Inc.: New York, 1991; pp 453−470.

(9) (a) Sono, M.; Hashimoto, A.; Nakashima, K.; Tori, M. *Tetrahedron Lett.* **2000**, *41*, 5115–5118. (b) Sono, M.; Nakashiba, Y.; Nakashima, K.; Tori, M. *J. Org. Chem.* **2000**, *65*, 3099–3106. (c) Sono, M.; Hanaoka, M.; Hashimoto, T.; Asakawa, Y.; Tori, M. *Synlett* **2009**, 469–471.

(10) (a) Sono, M.; Onishi, S.; Tori, M. *Tetrahedron* **2003**, *59*, 3385–3395. (b) Sono, M.; Mizutani, T.; Nozaki, M.; Takaoka, S.; Tori, M. *Heterocycles* **2008**, *76*, 851–860. (c) Sono, M.; Tatara, H.; Ise, N.; Takaoka, S.; Tori, M. *Tetrahedron* **2008**, *64*, 11096–11104.

(11) Crystallographic data for **7** and **8** have been deposited at the Cambridge Crystallographic Data Center as Supplementary Publication Nos. CCDC 817957 and 817958, respectively. Copies of the data can be obtained, free of charge, *via* www.ccdc.cam.ac.uk/data_request/cif, or by mailing to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: data_request@ccdc.cam.ac.uk].

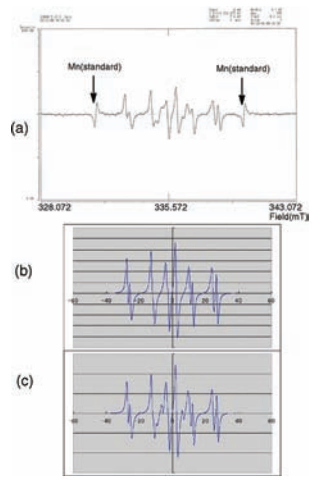


Figure 4. (a) ESR spectrum of the reaction of **2** with SmI_2 in the presence of DMPO (rt, 1 min); (b) simulated spectrum of the sum of **12** + **13** (1:1); (c) simulated spectrum of the sum of (b) + unknown species (see Supporting Information).

slightly different from (a). This is presumably due to contamination by an unknown species or impurities. After several trials, we found that the addition of the unknown species for simulation afforded the spectrum in Figure 4c, which is very similar to (a).

It is thus clear that the α,β-unsaturated carbonyl group is easily reduced by one-electron transfer processes initiated by Sm(II) to produce a radical anion like **14**. This radical can form a C−C bond between the carbonyl carbon synchronized with reduction by another Sm(II) producing a dianion like **15**. Of course these processes compete with the direct reduction of the carbonyl group generating the radical **16**. These results indicate that at least **1** is preferentially reduced at the α,β-unsaturated ester moiety and provide direct evidence that both radicals **14** and **16** are formed by reduction of Sm(II).

The stereochemistries of the products were controlled by the steric repulsion between the carbonyl group and the α,β-unsaturated ester moiety as shown in Figure 5. The *E*-ester **1** proceeds with the cheletion mechanism, while the *Z*-ester **2** proceeeds with the nonchelation control. In the case of **1**, the α,β-unsaturated moiety is preferentially reduced to afford the radical species **14** (A in Figure 5), which is in equilibrium with (B). Because the methyl group at the bridge head position has steric repulsion between the ester moiety (conformation B), the cyclized product has the stereochemistry depicted in **4**. **2** is rapidly reduced at the ketone carbonyl group as shown by the ESR trapping experiments, providing species such as (C) and (D) in Figure 5. Apparently conformation (D) is more stable, because the α,β-unsaturated moiety has steric repulsion between the cyclohexane part in the case of (C). Therefore, **3** is produced as a main product (Table 1). Both conformations (E) and (F) have steric repulsion between the methyl group and the ester part. This is why *trans*-fused products were not formed. These results are in marked contrast to those by Shirahama et al.,[12] because their compounds have hydroxy groups in the side chain to control the stereochemistry by chelation with Sm.

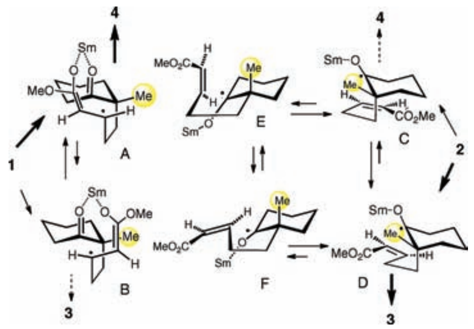


Figure 5. Mechanism for the formation of **3** and **4**.

When HMPA was added (Table 1, entry 8), the ratio was reversed, as in the case of *cis* ester **2**. Addition of HMPA resulted in formation of the bulky surroundings around the Sm atom and the α,β-unsaturated ester part has a steric repulsion, pushing away close to conformation (C), to afford **4**. Thus, the stereochemistry obeys the preferred conformation as shown in Figure 5.

In conclusion, we have observed the formation of two kinds of radicals, **14** and **16**, by radical trapping with DMPO and ESR spectra. This is, to the best of our knowledge, the first report on the detection of radical formation in the SmI_2 reduction. The precise mechanism for a given reductive carbonyl-alkene coupling will depend on the specific combination of reactants and the respective redox potential and rates of reduction of each component by the lanthanide reagent. Spin trap experiments using ESR is useful for the clarification of selectivity and the mechanism of the radical reaction initiated by SmI_2.

Acknowledgment. We thank Dr. Yasuko Okamoto and Mr. Shigeru Takaoka, Tokushima Bunri University, for measuring the MS spectra and X-ray analysis, respectively.

Supporting Information Available. Experimental procedures (besides ESR simulation) and spectroscopic data for **1**−**9** and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(12) Kito, M.; Sakai, T.; Yamada, K.; Matsuda, F.; Shirahama, H. *Synlett* **1993**, 158–162.