Letter

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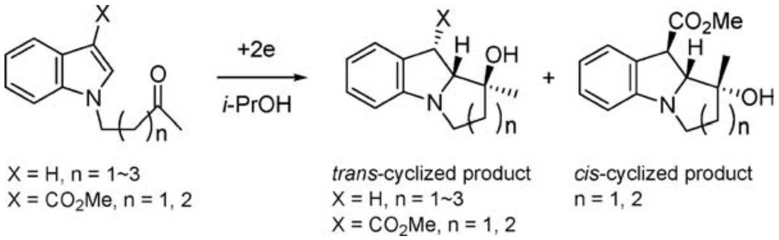

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Electroreductive Intramolecular Coupling of 1-Indolealkanones

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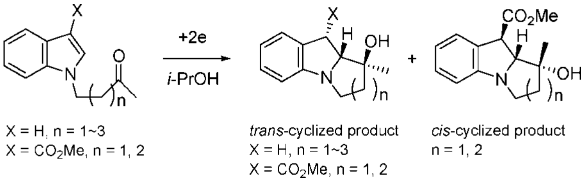
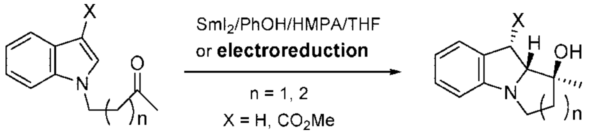
ABSTRACT



The electroreduction of 1-indolealkanones in isopropanol gave five-, six-, and seven-membered *trans*-cyclized products stereospecifically. On the other hand, the electroreduction of 3-methoxycarbonyl-1-indolealkanones afforded mixtures of two diastereomers of the corresponding *trans*- and *cis*-cyclized products. The DFT calculations for the radical anions support that the reductive couplings of 1-indolealkanones and 3-methoxycarbonyl-1-indolealkanones proceed through different reaction mechanisms.

Since SmI_2 (samarium diiodide) is one of the excellent reducing agents to produce ketyl radicals from ketones by one electron transfer, a variety of reductive couplings of ketones with unsaturated groups have been developed with SmI_2.[1] For instance, the reductive coupling of 1-indolealkanones with SmI_2/PhOH/HMPA was demonstrated by Gross and Reissig to produce benzannulated pyrrolizidines and indolizidines (Scheme 1).[2] On the other hand, Shono and co-workers disclosed that electroreduction is a useful method for the reductive couplings of ketones with olefins[3] and acetylenes[4] before the reduction with SmI_2 was developed. After that, we reported electroreductive coupling of ketones with the other unsaturated groups such as aromatic rings,[5] nitriles,[6] and oximes.[7] It should be noted that these electroreductive couplings can be performed without using metal reducing agents in an alcoholic solvent at ambient temperature. We therefore attempted the reductive coupling of 1-indolealkanones by means of electroreduction without using expensive SmI_2 and highly toxic HMPA. We describe herein the results of the electroreductive intramolecular coupling of 1-indolealkanones (Scheme 1). Nonsubstituted 1-indolealkanones (X = H) stereospecifically gave the *trans*-cyclized products the same as those obtained with SmI_2.[2] On the contrary, in the case of 3-methoxycarbonyl-1-

Scheme 1



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[1] Reviews on SmI_2 reduction: (a) Kagan, H. B *Tetrahedron* **2003**, *59*, 10351. (b) Berndt, M.; Gross, S.; Hoelemann, A.; Ressig, H.-U. *Synlett* **2004**, 422. (c) Edmonds, D.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371.

[2] Gross, S.; Ressig, H.-U. *Org. Lett.* **2003**, *5*, 4305.

[3] (a) Shono, T.; Mitani, M. *J. Am. Chem. Soc.* **1971**, *93*, 5284. (b) Shono, T.; Nishiguchi, I.; Ohmizu, H.; Mitani, M. *J. Am. Chem. Soc.* **1978**, *100*, 545.

[4] Shono, T.; Nishiguchi, I.; Ohmizu, H. *Chem. Lett.* **1976**, 1233.

[5] (a) Shono, T.; Kise, N.; Suzumoto, T.; Morimoto, T. *J. Am. Chem. Soc.* **1986**, *108*, 4676. (b) Kise, N.; Suzumoto, T.; Shono, T. *J. Org. Chem.* **1994**, *59*, 1407.

[6] (a) Shono, T.; Kise, N. *Tetrahedron Lett.* **1990**, *31*, 1303. (b) Shono, T.; Kise, N.; Fujimoto, T.; Tominaga, N.; Morita, H. *J. Org. Chem.* **1992**, *57*, 7175.

[7] (a) Shono, T.; Kise, N.; Fujimoto, T. *Tetrahedron Lett.* **1991**, *32*, 525. (b) Shono, T.; Kise, N.; Fujimoto, T.; Yamanami, A.; Nomura, R. *J. Org. Chem.* **1994**, *59*, 1730.

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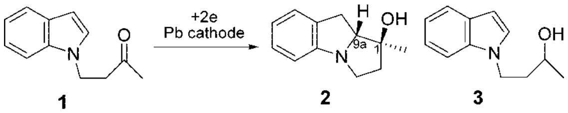
indolealkanones (X = CO_2Me), *cis*-cyclized products were also formed in addition to *trans*-cyclized products. These results indicate that the reaction mechanism of the electroreductive coupling of 3-methoxycarbonyl-1-indolealkanones is different from that of 1-indolealkanones. To elucidate the difference in the reaction mechanisms, the spin and charge densities in intermediate radical anions derived from both types of substrates (X = H and CO_2Me) were calculated by the DFT method.

First, the electroreduction of 4-(1*H*-indol-1-yl)butan-2-one (**1**) was carried out according to our reported method[5] (Scheme 2) using a Pb cathode and a divided cell in isopropanol containing Et_4NOTs as a supporting electrolyte. A five-membered cyclized product **2** was obtained in 61% yield as a single diastereomer together with a simply reduced alcohol **3** (16%). The use of Et_4NBr in place of Et_4NOTs increased the yield of **2** to 66% comparable to that obtained with SmI_2 (70%), while the use of ethanol in lieu of isopropanol as a solvent strongly inhibited the formation of **2** (38%) and promoted the production of **3** (39%). In general, the undivided cell is much more convenient than the divided cell especially for large-scale electrolysis. In this case, however, the product **2** might be oxidized at an anode surface under undivided cell conditions, and then it was predicted that the yield of **2** considerably decreased. Surprisingly, the yield of **2** was not so lowered (56%) using an undivided cell. The ^1H and ^{13}C NMR data of **2** were in agreement with the reported data for **2**.[2] Furthermore, we undoubtedly confirmed the 1,9a-*trans* stereochemistry in **2** by X-ray crystallographic analysis of HCl salt of **2** (Supporting Information).

Scheme 2

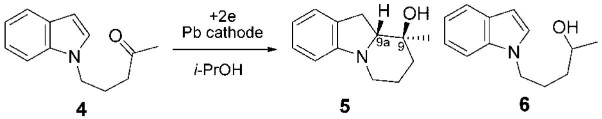


solvent	electrolyte	cell	% yield of 2	3
i-PrOH	Et_4NOTs	Divided	61	16
i-PrOH	Et_4NBr	Divided	66	12
EtOH	Et_4NBr	Divided	38	39
i-PrOH	Et_4NOTs	Undivided	56	23
SmI_2/PhOH/HMPA/THF[a]			70	

[a] Ref 2.

The electroreduction of 5-(1*H*-indol-1-yl)pentan-2-one (**4**) using a divided cell gave a six-membered cyclized product **5** in 68% yield as a single isomer with a small amount of simply reduced alcohol **6** (Scheme 3). The use of an undivided cell provided almost the same result as that of a divided cell. The stereochemistry of the obtained **5** was assigned to be the same as that of the product obtained from **4** with SmI_2 by comparison with the reported NMR data.[2] We also ascertained the 9,9a-*trans* stereochemistry in **5** by X-ray crystallography of **5**•HCl (Supporting Information).

Scheme 3

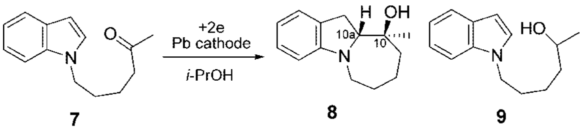


electrolyte	cell	% yield of 5	6
Et_4NBr	Divided	68	>5
Et_4NOTs	Undivided	65	>5
SmI_2/PhOH/HMPA/THF[a]		73	

[a] Ref 2.

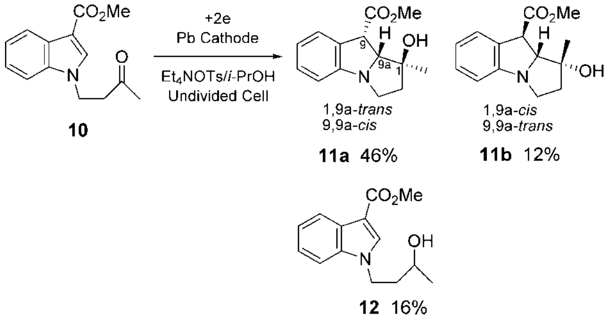
In addition, we tried the electroreduction of an unprecedented substrate, 6-(1*H*-indol-1-yl)hexan-2-one (**7**), to explore the possibility of seven-membered cyclization (Scheme 4). Using a divided cell, the expected cyclized product **8** was formed in 32% yield as a single isomer, although a simply reduced alcohol **9** was a major product (58%). The use of an undivided cell brought about a poor yield of **8** (5%). The 10,10a-*trans* configuration in **8** was determined by NOESY−NMR spectroscopy. Next, methyl 1-(3-oxobutyl)-1*H*-indole-3-carboxylate (**10**) was subjected to the electroreduction. In this case, a complex mixture was obtained using a divided cell. Fortunately, the electroreduction of **10** using an undivided cell gave two five-membered cyclized products **11a** and **11b** in 46% and 12% yields, respectively, with a simply reduced alcohol **12** (Scheme 5). On the other hand, it has been reported that the reduction of **10** with SmI_2/

Scheme 4



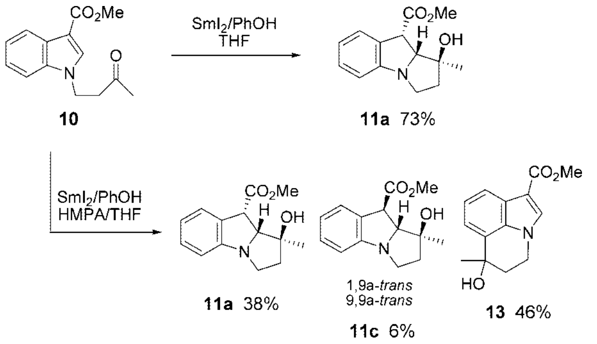
electrolyte	cell	% yield of 8	9
Et_4NBr	Divided	32	58
Et_4NOTs	Undivided	5	67

Scheme 5



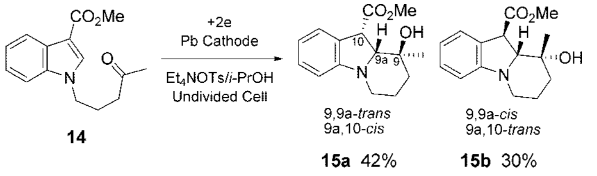
PhOH in THF gave **11a** (1,9a-*trans* and 9,9a-*cis*) as only one product, while that with SmI_2/PhOH/HMPA in THF afforded two five-membered cyclized products **11a** and **11c** (1,9a-*trans* and 9,9a-*trans*) and a six-membered cyclized product **13** (Scheme 6).[2] The major product **11a** in the electroreduction of **10** was confirmed to be 1,9a-*trans* and 9,9a-*cis* by comparison with the reported NMR data.[2] The unknown minor product **11b** was assigned to be 1,9a-*cis* and 9,9a-*trans* by NOE− and NOESY−NMR analyses. This result shows that **11b** was formed by *cis*-cyclization of **10** differently from the stereospecific formation of *trans*-cyclized products from **1**, **4**, and **7** described above.

Scheme 6

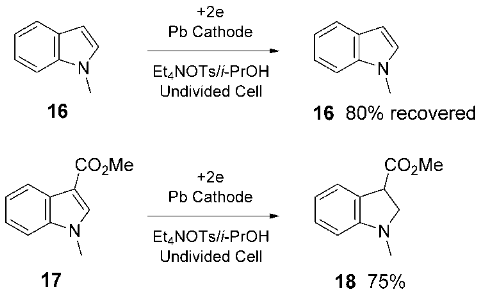


The electroreduction of methyl 1-(4-oxopentyl)-1*H*-indole-3-carboxylate (**14**) using an undivided cell gave two six-membered cyclized products **15a** (9,9a-*trans* and 9a-10-*cis*) and **15b** (9,9a-*cis* and 9a,10-*trans*) in 42% and 30% yields, respectively (Scheme 7). Whereas the reduction of **14** with SmI_2/PhOH/HMPA in THF produced the *trans*-cyclized isomer **15a** in 83% yield as only one product,[2] a significant amount of *cis*-cyclized isomer **15b** was formed in the electroreduction of **14**.

Scheme 7



Scheme 8



The reaction mechanism of the electroreductive coupling of 1-indolealkanones was supposed to be initiated by the formation of ketyl radicals generated by one electron transfer to the substrates, similarly to the already reported electroreductive coupling of ketones with unsaturated groups.[3−7] To ascertain whether indoles are electrochemically reduced or not, we attempted the electroreduction of *N*-methylindoles **16** and **17** (Scheme 8). Under the conditions using an undivided cell, 1-methyl-1*H*-indole (**16**) was recovered,[8] and methyl 1-methyl-1*H*-indole-3-carboxylate (**17**) was reduced to a 2,3-hydrogenated product **18**. These results show that *N*-methylindole **16** is not reduced at all under the present conditions, while 3-methoxycarbonyl substituted *N*-methylindole **17** is reduced. We therefore measured the cyclic voltammetry of **1**, **10**, and **17** under the same conditions as the electrolysis; however, clear and reproducible reduction peaks could not be observed. Consequently, we measured the cyclic voltammetry in 0.03 M Bu_4NClO_4/DMF on a Pb cathode: the cyclic voltammograms of **10** and **17** (1 mM) showed a reduction peak at −2.74 and −2.78 V vs SCE, respectively, whereas that of **1** gave no reduction peak from 0 to −3.0 V vs SCE. These results suggest that the 3-methoxycarbonylindole moiety is more reducible than the carbonyl group of the alkanones. Furthermore, spin and charge densities in radical anions of **1** and **10** (**RA-1** and **RA-10**) were calculated by the DFT method at the B3LYP/6-31+G(d,p) level, and the results were exhibited in Table 1.[9] Since the C2 (carbonyl) carbon in **RA-1** possesses the highest spin density and strong negative charge, **RA-1** has apparently the nature of a ketyl radical. In contrast, the highest spin density exists at the C5 carbon in **RA-10**, hence **RA-10** has the character of a radical anion produced by one-electron transfer to the 3-methoxycarbonylindole moiety in **10**. From these results, it is presumed that the electroreductive coupling of **1** proceeds through a ketyl radical (**RA-1**), while that of **10** is promoted by a radical anion of 3-methoxycarbonylindole (**RA-10**) as illustrated in Scheme 9. The stereospecific formation of the *trans*-cyclized products in the

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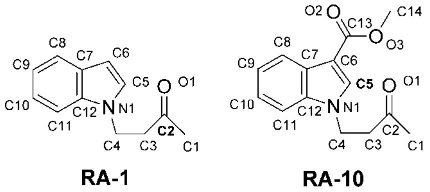
(8) **16** was also recovered by using a divided cell.

(9) The calculations were carried out using the Gaussian 03 program: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C. 02; Gaussian, Inc.: Wallingford, CT, 2004.

Table 1. Spin Densities in **RA-1** and **RA-10** Calculated by the B3LYP/6-31+G(d,p) Method[a]

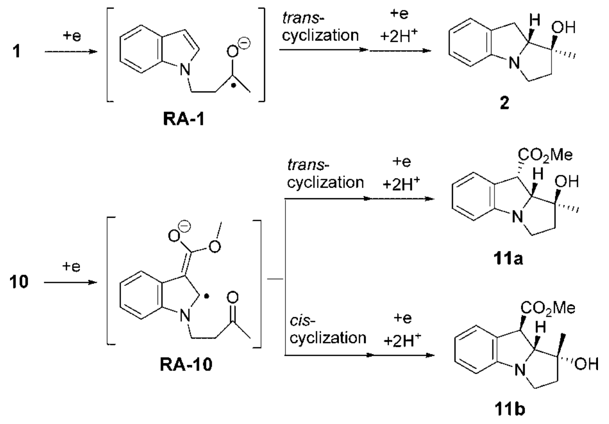


	RA-1		RA-10	
	spin densities[b]	charges[c]	spin densities[b]	charges[c]
C1	−0.165	0.072	0.017	−0.186
C2	**0.535**	−0.538	0.285	0.176
C3	−0.038	0.332	−0.159	0.410
C4	0.108	−0.215	0.167	−0.205
C5	0.200	−0.042	**0.490**	−0.266
C6	−0.033	0.159	−0.121	−0.111
C7	0.038	0.285	0.050	0.970
C8	0.118	−0.613	0.033	−0.692
C9	−0.047	−0.244	0.010	−0.015
C10	0.096	−0.132	−0.037	−0.284
C11	0.057	−0.318	0.117	0.257
C12	−0.046	0.239	−0.082	−0.499
C13	–	–	0.083	0.585
C14	–	–	−0.002	0.216
O1	0.156	−0.384	0.099	−0.521
O2	–	–	0.060	−0.624
O3	–	–	0.001	−0.316
N1	−0.034	0.399	−0.037	0.102

[a] Calculated by the Mulliken population analysis. [b] The highest values in each radical anion are in bold face. [c] Atomic charges with hydrogens summed into heavy atoms.

electroreduction of 1-indolealkanones **1**, **4**, and **7** is in accordance with the reported results of the electroreductive coupling of arylalkanones.[5] The formation of *cis*-cyclized products in the electroreduction of 3-methoxycarbonyl-1-indolealkanones may be attributable to the reaction mechanism different from the mechanism which proceeds through a ketyl radical. The stereoselectivity in the electroreductive intramolecular coupling of alkenones and arylalkanones has been well explained by the calculations of the transition states for the cyclization of the intermediate ketyl radicals.[10] The stereoselectivity in the electroreductive coupling of 1-indolealkanones also may be elucidated by the calculations of the transition states, and now the computational experiments are in progress.

Scheme 9



In conclusion, the electroreduction of 1-indolealkanones **1**, **4**, and **7** in isopropanol using a divided cell stereospecifically gave five-, six-, and seven-membered *trans*-cyclized products **2**, **5**, and **8**, respectively. The yields of **2** and **5** were comparable to those obtained by the reduction with SmI_2/PhOH/HMPA in THF. The electroreduction also could be carried out employing an undivided cell. The electroreduction of 3-methoxycarbonyl-1-indolealkanones **10** and **14** using an undivided cell produced mixtures of *trans*-cyclized products, **11a** and **15a**, and *cis*-cyclized products, **11b** and **15b**. The DFT calculations for the radical anions of **1** and **10** suggest that the reaction mechanism of the electroreductive coupling of **10** is different from the mechanism of the cyclization of **1**.

Supporting Information Available: A PDF file of experimental procedures, X-ray crystallographic data of **2**•HCl and **5**•HCl, ^{1}H and ^{13}C NMR spectra of **8**, **11b**, and **15b**, and the results of calculations for the radical anions **RA-1** and **RA-10**. Crystallographic CIF files for **2**•HCl and **5**•HCl. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Kise, N. *J. Org. Chem.* **2004**, *69*, 2147.