ORGANIC LETTERS

2006
Vol. 8, No. 7
1323−1325

Electroreductive Intramolecular Coupling of Aromatic Imino Esters: Is Four-Membered Cyclization Much More Favorable than Six-Membered Cyclization?

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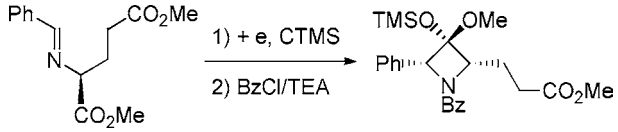
Received December 28, 2005

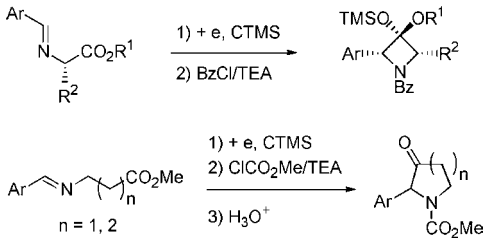
ABSTRACT



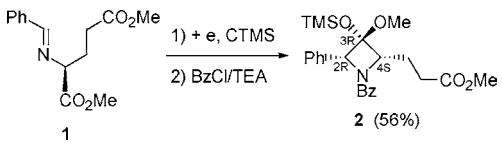
The electroreduction of an aromatic imino ester prepared from (*S*)-glutamic acid in the presence of chlorotrimethylsilane and triethylamine afforded a four-membered cyclized product, a mixed ketal of cis-2,4-disubstituted azetidine-3-one, stereospecifically. Calculations for the transition states by the DFT method support the predominant formation of the azetidine. The electroreduction of an aromatic imino ester prepared from (*S*)-aspartic acid gave almost equal amounts of a diastereomerically pure mixed ketal of cis-2,4-disubstituted azetidine-3-one and a diastereomeric mixture of 2,5-disubstituted pyrollidine-3-one.

Reductive intramolecular coupling of imino esters is a promising method for the construction of cyclic amines. We have recently reported that the reductive intramolecular coupling of aromatic α-, *β*-, and *γ*-imino esters was realized by electroreduction in the presence of chlorotrimethylsilane (CTMS) to give azetidines,[1] pyrrolidines,[2] and piperidines,[2] respectively (Scheme 1). In this context, we attempted the reductive coupling of imino ester **1** prepared from (*S*)-glutamic acid dimethyl ester and benzaldehyde (Scheme 2). Contrary to our expectations, a mixed ketal of cis-2,4-disubstituted azetidine-3-one **2** was obtained stereospecifically as the only cyclized product; no piperidine was

Scheme 1



Scheme 2



1 **2** (56%)

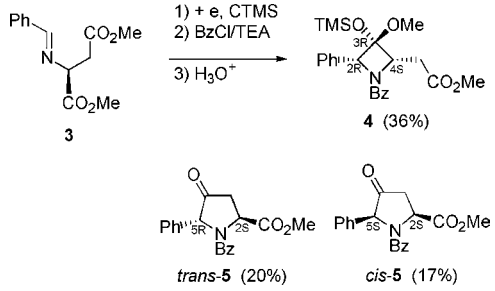
(1) Kise, N.; Ozaki, H.; Moriyama, N.; Kitagishi, Y.; Ueda, N. *J. Am. Chem.* Soc. **2003**, *125*, 11591−11596.

(2) Kise, N.; Ohya, K.; Arimoto, K.; Yamashita, Y.; Hirano, Y.; Ono, T.; Ueda, N. *J. Org. Chem.* **2004**, *69*, 7710−7719.

10.1021/ol053144x CCC: $33.50
Published on Web 02/28/2006

produced. This result shows that four-membered cyclization is much more favorable than six-membered cyclization in the reductive intramolecular coupling of **1**. To the best of our knowledge, this is the first example where four-membered cyclization completely predominates over six-membered cyclization, although a number of four-membered cyclizations have been reported.[3,4] We describe herein the results of experimental and theoretical studies on the electroreductive cyclization of **1**. The transition states of the cyclization were calculated to elucidate the selective formation of **2**. Furthermore, we examined the electroreductive intramolecular coupling of imino ester **3** derived from (*S*)-aspartic acid dimethyl ester and obtained a diastereomerically pure mixed ketal of cis-2,4-disubstituted azetidine-3-one **4** and a mixture of cis- and trans-2,5-disubstituted pyrollidine-3-one **5** (Scheme 3).

Scheme 3



The electroreduction of **1** and subsequent benzoylation of the resulting mixture were carried out according to our reported method (Scheme 2).[1,5] An *N*-benzoyl mixed ketal of cis-2,4-disubstituted azetidine-3-one **2** was isolated in 56% yield and 92% ee (by ^{1}H NMR with Eu(hfc)$_3$) as a single stereoisomer together with N-α-trimethylsilylated amine **6** (20% yield). Surprisingly, the corresponding six-membered cyclized product, *N*-benzoyl piperidine **7**, could not be detected. Fortunately, racemic **2** derived from *dl*-glutamic acid crystallized and the stereostructure of **2** could be determined to be 2*R*,3*R*,4*S* by X-ray crystallography (Figure 1), although optically active **2** obtained from (*S*)-glutamic acid had a pastelike composition.

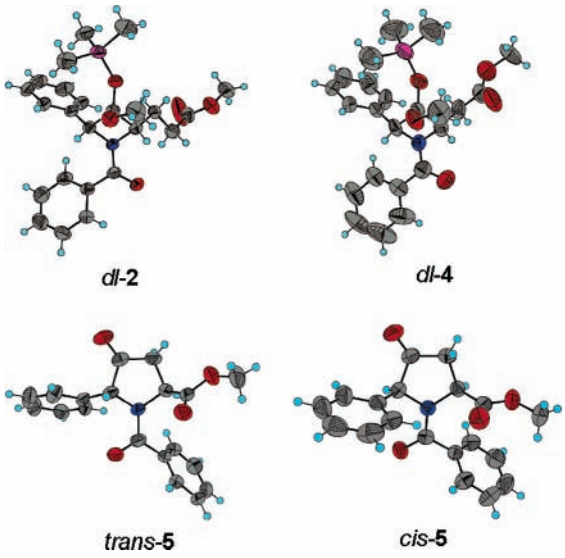
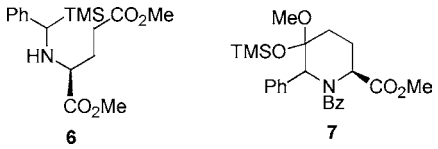
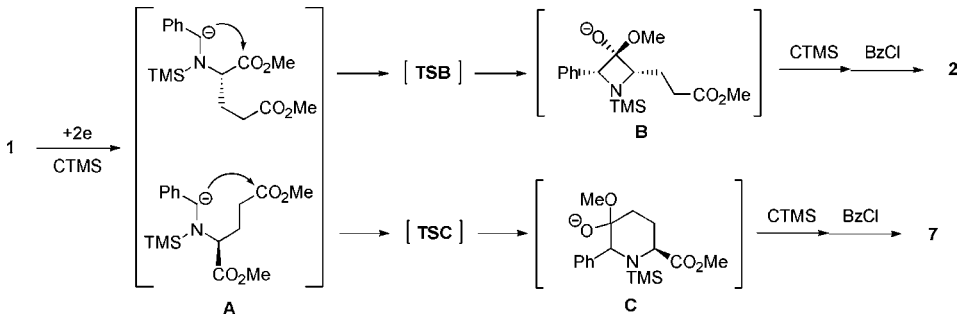


Figure 1. X-ray crystal structures of *dl*-**2**, *dl*-**4**, *trans*-**5**, and *cis*-**5**.



According to our previous reports,[1,2] the reaction mechanism of the reductive intramolecular coupling of **1** can be presumed as depicted in Scheme 4. Two-electron transfer and N-silylation to **1** afford anion **A**. The four- and six-membered cyclized products **B** and **C** are formed by the intramolecular attack of the carbanion in **A** to the α- and *ω*-methoxycarbonyl groups, respectively. The experimental result shows that the four-membered cyclization of **A** is much faster than the corresponding six-membered cyclization. Therefore, we calculated the transition states for the cyclization of **A** by the DFT method at the B3LYP/6-31+G** level.[6] Four diastereomeric transition states **TSB** and **TSC** were obtained for each of the four- and six-membered

Scheme 4



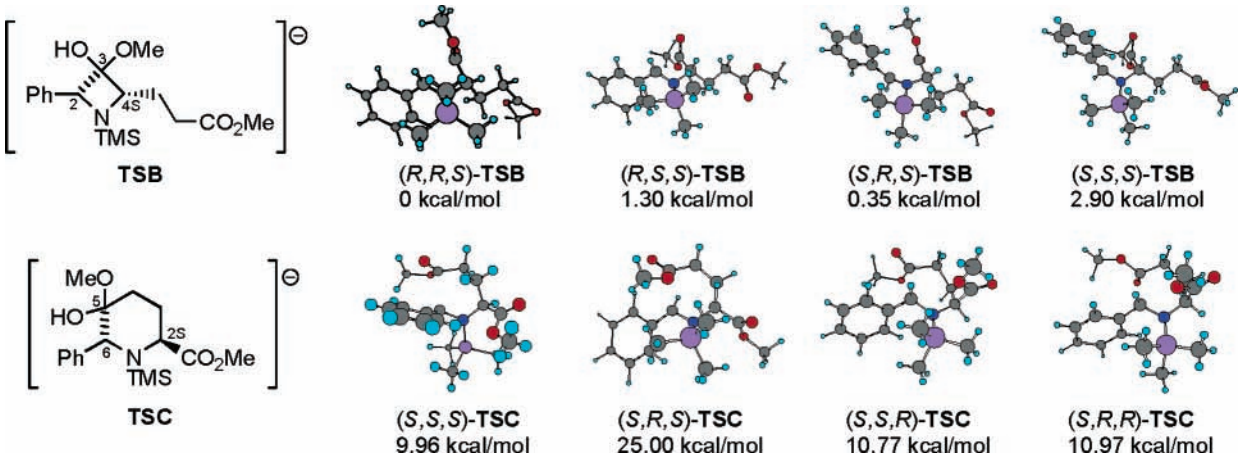


Figure 2. Optimized structures (B3LYP/6-31+G**) and relative energies of transition states for the four- (TSB) and six-memberd cyclization (TSC) of the anion A.

cyclizations, respectively. The optimized structures and their relative energies of the transition states are exhibited in Figure 2.[7] The results of calculations bring the following findings: (1) the transition states for the four-membered cyclization **TSB** are much lower in energy (~10 kcal/mol) than those for the six-membered cyclization **TSC**; (2) the transition state (*R*,*R*,*S*)-**TSB** is the most favorable of the four transition states giving four possible stereoisomers of four-membered cyclized products. These computational outcomes agree well with the stereospecific formation of 2*R*,3*R*,4*S*-**2**.

Next, the electroreduction of **3** and the following benzoylation were carried out under the same conditions as above (Scheme 3). Because the products could not be separated, the mixture was treated with 1 M HCl for 30 min to give three products: *N*-benzoyl-mixed ketal of cis-2,4-disubstituted azetidine-3-one **4** (36% yield, 34% ee), *N*-benzoyl trans-2,5-disubstituted pyrrolidine-3-one, *trans*-**5** (20% yield), and its cis isomer *cis*-**5** (17% yield). The stereostructures of these products were confirmed by X-ray crystallographic analysis (Figure 1). These results suggest that four-membered cyclization is comparable to five-membered cyclization in the reductive intramolecular coupling of **3**.

In conclusion, the electroreduction of aromatic imino ester **1** derived from (*S*)-glutamic acid dimethyl ester in the presence of CTMS gave azetidine **2** stereospecifically. The overwhelming preference of four-membered cyclization to six-membered cyclization in the reductive intramolecular coupling of **1** is well explained by the DFT calculations for the transition states. On the other hand, the electroreduction of imino ester **3** prepared from (*S*)-aspartic acid dimethyl ester produced almost equal amounts of four- and five-membered cyclized products, **4** and **5**.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research (C) (No. 16550097) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: A PDF file of experimental procedures, ^{1}H and ^{13}C NMR spectra of **2**, **4**, *trans*-**5**, and *cis*-**5**, and the results of calculations for the transition states. Crystallographic CIF files for *dl*-**2**, *dl*-**4**, *trans*-**5**, and *cis*-**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL053144X

(3) For recent reviews, see the following. (a) Formation of four-membered heterocycles through electrophilic heteroatom cyclization: Robin, S.; Rousseau, G. *Eur. J. Org. Chem.* **2002**, 3099−3114. (b) Formation of four-membered carbocycles: Hartley, R. C.; Caldwell, S. T. *Perkin 1* **2000**, 477−501.

(4) For recent reports for the asymmetric synthesis of multisubstituted azetidines, see: (a) Burtoloso, A. C. B.; Correia, C. R. D. *J. Organomet. Chem.* **2005**, *690*, 5636. (b) De Talancé, V. L.; Banide, E.; Bertin, B.; Comesse, S.; Kadouri-Puchot, C. *Tetrahedron Lett.* **2005**, *46*, 8023. (c) Bräuner-Osborne, H.; Bunch, L.; Chopin, N.; Couty, F.; Evano, G.; Jensen, A. A.; Kusk, M.; Nielsen, B.; Rabasso, N. *Org. Biomol. Chem.* **2005**, *3*, 3926. (d) Mendler, B.; Kazmaier, U.; Huch, V.; Veith, M. *Org. Lett.* **2005**, *7*, 2643. (e) Couty, F.; Evano, G.; Vargas-Sanchez, M.; Bouzas, G. *J. Org. Chem.* **2005**, *70*, 9028.

(5) Similarly to our previous report,[1] a complex mixture was formed in the absence of CTMS.

(6) The calculations were carried out using the Gaussian 03W program: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; 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.; Bakken, V.; 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 B.02; Gaussian, Inc.: Pittsburgh, PA, 2003.

(7) It was confirmed that the optimized structures had only one imaginary frequency according to the vibration analysis. The imaginary frequency was verified to be consistent with the intramolecular coupling by displaying the vibrational mode using the Gauss View program.