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

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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

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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 fourmembered cyclization completely predominates over sixmembered 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).



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 ¹H 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



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

acid had a pastelike composition.



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





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.

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

(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.

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.

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Supporting Information Available: A PDF file of experimental procedures, ¹H and ¹³C 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.

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