Electro-Generated Acids Catalyzed Epoxoyolefin Cyclizations via Cationic Chain Reactions

Kouichi MATSUMOTO,a,* Hiroki SHIMAO,a Yuta FUJIKI,a Norihito KAWASHITA,b and Shigenori KASHIMURAa

a Department of Chemistry, School of Science and Engineering, Kindai University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan
b Department of Life Science, School of Science and Engineering, Kindai University, 3-4-1 Kowakae, Higashi-osaka, Osaka 577-8502, Japan
* Corresponding author: kmatsuno@chem.kindai.ac.jp

ABSTRACT

We show that a catalytic amount of electro-generated acid (EGA) prepared from the oxidation of a Bu4NB(C6F5)4/CH2Cl2 solution catalyzes effectively the tandem cyclization of epoxoyolefins, producing the corresponding polycyclized compounds in 23%–57% yields. The scope and limitations of the substrates are examined, and we compare the stability of the intermediates through theoretical calculations. The success of the current reactions might be due to the high reactivity of EGA, because the counter anion is bulky and stabilized B(C6F5)4− derived from Bu4NB(C6F5)4 as the supporting electrolyte.

Keywords : Epoxoyolefin, Tandem Cyclization, Electro-generated Acid, Cationic Chain Reaction

1. Introduction

Polynes and their related compounds have attracted much attention, because they perform cyclization producing polycyclic molecules.1–3 Various substrates have been tested as starting materials for developing polycyclic molecules, such as polynes, epoxoyolefins, and acetal-olefins.1–3 Among them, the literature by Loh et al.4 introduces that “Corey, van Tamelen and Goldsmith, among others, have exploited the acid-promoted cascade cyclization of epoxy olefins as a very useful strategy for the building of polycyclic terpenoids”.5–7 In this study, we focus on epoxoyolefin as a polyene derivative, because this cyclized compound bears an OH group, which might be used in further transformation. In recent examples of sequential cyclization of epoxoyolefins, a stoichiometric amount of InBr3 in CH2Cl2 was found to be effective in driving cyclization reactions (Scheme 1(a)).4,8 In addition, a catalytic amount of InBr3 was also found to produce the same compound in moderate yields.4 Moreover, the combination of Ph4PBF4 and hexafluoroisopropyl alcohol has been found to drive the cyclization of epoxylenses (Scheme 1(b)).9

The electrochemical method is a suitable procedure in the framework of green chemistry, because electrochemical reactions do not produce waste.10–11 In electrochemistry, the reactive species can be generated on the surface of electrodes. In the past, the reactivity of electro-generated acids has been investigated.14–18 Changing the reactivity of electro-generated acids appeared to be easy, because the supporting electrolyte could serve as the counter-anion of the electro-generated acids. Thus, we hypothesized that an electro-generated acid bearing B(C6F5)4− would be highly reactive in organic transformations.19–21 because B(C6F5)4− is a bulky and stabilized counter-anion by electro-negative fluorine atom, which might increase the reactivity of EGA and the related reaction intermediate. In this work, we found that a catalytic amount of EGA in Bu4NB(C6F5)4/CH2Cl2 can catalyze epoxoyolefin cyclization, giving the corresponding cyclized products in low to moderate yields (Scheme 1(c)). These results show that the reaction is a prominent strategy, considering the current procedure. The electrochemical approach is a simple procedure, and the preparation of the EGA ratio is quite easy, because it depends on the amount of electricity. Herein, we report the details of our work.

2. Experimental

2.1 General remarks

1H and 13C NMR spectra were recorded using a Varian MERCURY 300 (1H, 300 MHz; 13C, 75 MHz) and a JEOL JNM-ECS 400 (1H, 400 MHz; 13C, 100 MHz). CDCl3 was used as the NMR solvent. The chemical shifts of 1H NMR were corrected using 7.26 ppm of the residual CHCl3 or 0.00 ppm of tetramethylsilane as an internal standard. The chemical shifts of 13C NMR were corrected using 77.0 ppm of CDCl3. Merck pre-coated silica gel F254
plates (thickness 0.25 mm) were used for the TLC analysis. A silica-gel column (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40–100 μm) was used for the flash chromatography with an air pump. Preparative GPC separation was carried out with a Japan Analytical Industry LC-9201 or LC-9210 NEXT equipped with JAIGEL-1H and JAIGEL-2H, using CHCl3. All reactions were carried out under a N2 atmosphere, unless mentioned. B3LYP/6-311+g(dp) calculation was used to optimize the intermediates. All the calculations were carried out using Gaussian16 Revision B.01.

2.2 Materials

All materials such as solvents and chemical reagents were purchased from commercial suppliers and used without further purification, unless mentioned. Bu4NB(C6F5)4 was prepared according to the literature. CH2Cl2 as the dry solvent was prepared in purified through a short silica-gel column using Et2O to remove trace amount of MeOH as the stabilizer. Then, CH2Cl2 was distilled again in the presence of P2O5. Finally, CH2Cl2 was distilled in the presence of K2CO3. Activated molecular sieves 4Å were added to CH2Cl2 for storage. Substrates were prepared the polyenes and epoxyolefins following the previously reported procedure. The synthesized substrates were identified through comparison with reported spectral data.

2.3 Typical procedure for cyclization of epoxyolefin using electro-generated acid (Table 1)

An H-type divided cell (4G glass filter) was used for the electrochemical reaction. We used a carbon felt in the anode and a platinum plate (20 mm × 20 mm) in the cathode. In the anodic and cathodic chambers, 0.1 M Bu4NB(C6F5)4/CH2Cl2 (8 mL × 2) was added under a N2 atmosphere. The electricity (8 mA) passed, until 0.15 F/mol based on 0.5 mmol was consumed at room temperature. At this stage, it was assumed that ca. 0.075 mmol (ca. 15 mol%) of EGA was accumulated in the anodic chamber. After stopping the current, the substrate (1, 0.5 mmol) was added to the anodic chamber and stirred for 1 h. Et3N (1 mL × 2) was added to the anodic and cathodic chambers to quench the reactions. The solution was removed using an evaporator, and the residue was filtered through a short silica-gel column using Et2O to remove Bu4NB(C6F5)4. Then, the solution was removed again, and the obtained crude material was purified via flash chromatography (hexane/AcOEt) and the preparative GPC separation to give the desired product 2.

Products 2a, 2b, 2c, 2d, and 2e, which were known compounds,

and byproducts 3e, 4e, 5e, and 6e were identified through comparison with reported spectral data.

3. Results and Discussion

First, we examined the reactivity of the electro-generated acid using (E)-2,2-dimethyl-3-(3-methyl-6-[(p-tolyl)hex-3-en-1-yl])-oxirane (1a) as the substrate. The typical procedure was as follows. The electrochemical oxidation of the 0.1 M Bu4NB(C6F5)4/CH2Cl2 (8 mL) solution was carried out at room temperature. The electricity amount of 0.15 F/mol based on 0.5 mmol at 8 mA was passed through the solution, and the electro-generated acid (ca. 0.075 mmol) was generated and accumulated in the anodic chamber. Then, 1 (0.5 mmol) was added to the anodic chamber, and stirred for 1 h at the temperature to give the corresponding product 2a in 38% yield (Table 1, entry 1). As for the effect of the temperature, the electrolysis and the subsequent cyclization were carried out at 0°C, −50°C, and −78°C, respectively. The products were obtained in around 50% yields (entries 2–5). Thus, these results suggested that a catalytic amount of EGA could serve as an initiator, and that other substrates bearing various substituents should be tested next. In order to be able to compare the reactivity of EGA with Loh’s condition, we decided to carry out our reactions at room temperature in the following experiments.

For example, the substrate (E)-3-(6-[(p-methoxyphenyl)-3-methyloxepoxyhex-3-en-1-yl])-2,2-dimethylxirane (1b) formed the corresponding product 2b in 32% yield (entry 6). In contrast, (E)-3-(6-(m-methoxyphenyl)-3-methylhex-3-en-1-yl))-2,2-dimethylxirane (1c) gave the product 2e in 57% yield, which contained two regioisomers (entry 7). The reaction of a catalytic amount of EGA with (E)-2,2-dimethyl-3-(3-methyl-6-(m-tolyl)hex-3-en-1-yl)oxirane (1d) and (E)-2,2-dimethyl-3-(3-methyl-6-phenylhex-3-en-1-yl)oxirane (1e) took place to produce 2d in 23% yield and 2e in 35% yield, respectively (entries 8–9). An increased amount of EGA (ca. 30 mol%) and a longer reaction time of 1e did not affect the reaction yields (entries 10–11), which might indicate that the a catalytic cycle involving H+ took place quickly in the solution phase.

In order to obtain a deeper insight in the reaction mechanism, the byproducts from the reaction of 1e with EGA were analyzed by 1H NMR. The presence of various byproducts 3e, 4e, 5e, and 6e together with the desired product 2e was confirmed, as shown in Scheme 2, which indicated that the current reaction involves the cationic intermediate.

Regarding the reaction mechanism, we assumed the following cationic chain reaction, which was initiated by a catalytic amount of electro-generated acid (Scheme 3). In the initiation step, the electrochemical oxidation of the Bu4NB(C6F5)4/CH2Cl2 solution generated EGA, which seemed to be H+ equivalent. EGA reacted...
with 1a to give intermediate Int-1a. The intramolecular cyclization of Int-1a produced Int-2a, which went through the intramolecular Friedel-Crafts reaction to give Int-3a as the arenium ion intermediate. When the energy of the intermediates (Int-1a, Int-2a, and Int-3a) predicted from the reaction mechanism was compared by DFT calculation, the energy decreased from Int-1a to Int-3a (Scheme 3). We considered that the reaction from Int-1a to Int-2a was stabilized at 16.94 kcal/mol via the ring opening reaction from the ring strain of the epoxide. In addition, the reaction from Int-2a to Int-3a was stabilized at 2.51 kcal/mol through delocalization by the formed cation due to the conjugated double bonds, although the dearomatization of the benzene ring occurred.

In the final step, Int-3a gave 2a, regenerating H⁺, which caused the next cycles to take place (Scheme 3). Thus, the current reaction was explained reasonably well by the cationic chain reaction.

4. Conclusions

We have demonstrated that a catalytic amount of EGA prepared from a Bu₄NB(C₆F₅)₄/CH₂Cl₂ solution in divided cell is effective for the cyclization of epoxides. Substrates bearing various substituents at the benzene ring were tested for the current reactions, and the corresponding products were obtained in 23%–57% yields. The cationic chain mechanism was indicated. DFT calculation cleared the stability of the intermediates. The high reactivity of EGA due to the bulky and stabilized counter-anion B(C₆F₅)₄⁻ might be important for the current reactions. Further synthetic application using EGA is being examined by our laboratory.

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References

1. Some selected reviews of polyene cyclizations. See Refs. 1 to 3. B. Maji, Adv. Synth. Catal., 361, 3453 (2019).
2. A. G. M. Barrett, T. Ma, and T. Mies, Synthesis, 51, 67 (2019).
3. A. C. A. D’Hollander, L. Peilleron, T. D. Grayfer, and K. Carrio, Synthesis, 51, 1753 (2019).
4. J. Zhao, Y. Zhao, and T. Lob, Chem. Commun., 1353 (2008), and references therein.
5. Some recent and selected examples of Corey’s reports for polyene cyclizations. See Refs. 5 to 7. G. Rajendar and E. J. Corey, J. Am. Chem. Soc., 137, 5837 (2015).
6. R. A. Sherer and E. J. Corey, Org. Lett., 12, 3548 (2010).
7. K. J. Suresh and E. J. Corey, J. Am. Chem. Soc., 131, 13928 (2009).
8. See also, Y. Zhao, L. S. Tan, B. Li, S. Li, and T. Loh, Chem. Commun., 3738 (2009).
9. Y. Tian, X. Xu, L. Zhang, and J. Qu, Org. Lett., 18, 268 (2016).
10. Some recent reviews of electro-organic synthesis. See Refs. 10 to 13. L. Schulz and S. R. Waldegger, Synlett, 30, 275 (2019).
11. K.-J. Jiao, Y.-K. Xing, Q.-L. Yang, H. Qiu, and T.-S. Mei, Acc. Chem. Res., 53, 300 (2020).
12. M. C. Leech and K. Lam, Acc. Chem. Res., 53, 121 (2020).
13. Some reports of electro-generated acids. See Refs. 14 to 18. K. Matsumoto, H. Shimazaki, T. Sanada, K. Shimada, S. Hagiwara, S. Suga, S. Kashimura, and J. Yoshida, Chem. Lett., 42, 843 (2013).
14. K. Kawa, T. Saitoh, E. Kaji, and S. Nishiyama, Org. Lett., 15, 5484 (2013).
15. K. Uneyama, A. Isimura, and S. Torii, Bull. Chem. Soc. Jpn., 58, 1859 (1985).
16. K. Uneyama, Top. Curr. Chem., 142, 167 (1987).
17. M. F. Nielsen, Encyclopedia of Electrochemistry (Ed. H. J. Shäfer), Wiley-VCH, Weinheim, Vol. 8, pp. 451–488 (2004).
18. Examples of the use of B(C₆F₅)₄⁻ as the counter anion. See Refs. 19 to 21. K. Matsumoto, S. Fujie, K. Ueoka, S. Suga, and J. Yoshida, Angew. Chem., Int. Ed., 47, 2506 (2008).
19. K. Matsumoto, S. Fujie, S. Suga, T. Nakami, and J. Yoshida, Chem. Commun., 5448 (2009).
20. K. Matsumoto, T. Sanada, H. Shimazaki, K. Shimada, S. Hagiwara, S. Fujie, Y. Ashikita, S. Suga, S. Kashimura, and J. Yoshida, Adv. Synth. Catal., 351, 325 (2013).
21. F. Liu, B. Vijayakrishnan, A. Faridmoayer, T. A. Taylor, T. B. Parsons, G. J. L. Bernardes, M. Kowarik, and B. G. Davis, J. Am. Chem. Soc., 136, 566 (2014).
22. E. Gómez-Bengoa, J. M. García, S. Jiménez, I. Lapuerta, A. Mielgo, J. M. Odriozola, I. Otazo, J. Razkin, I. Urruzuno, S. Vera, M. Oiarbide, and C. Palomo, Chem. Sci., 4, 3198 (2013).
23. In order to avoid the direct oxidation of aromatic rings in the substrates or the generation of benzylic carbonations, we adopted the separated procedure, in which EGA was once generated and accumulated, followed by the addition of substrates after stopping the current.
24. An example of a reactivity of carbocations. H. Mayr and A. R. Oflial, Angew. Chem., Int. Ed., 45, 1844 (2006).