

5-EXO,5-EXO CASCADE CYCLIZATIONS OF HALO-OLEFINS BY ENVIRONMENTALLY FRIENDLY REACTION USING INDIRECT ELECTROLYSIS

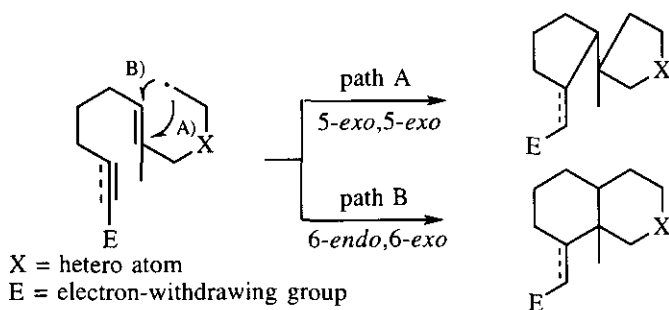
Akira Katsumata, Kiyosei Takasu, and Masataka Ihara*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578, Japan

Abstract – $[\text{Ni}(\text{cyclam})](\text{ClO}_4)_2$ or vitamin $\text{B}_{12\text{a}}$ -mediated electroreduction of the 1-bromo-5-ene-10-yne (**4**) and the 1-bromo-5,10-diene (**6**) gave bicyclic five-membered ring compounds in a highly regioselective manner by 5-*exo*,5-*exo* cascade radical cyclizations.

Recently, radical reactions have emerged as useful tools for carbon-carbon bond formation in organic synthesis.¹ The majority of useful radical-mediated addition reactions has been carried out using organostannane² or organosilane³ radical sources. However, the above methods have some drawbacks that a stoichiometric amount of chemical reagents and high dilution conditions are required, and the separation of the cyclized products from byproducts is sometimes a troublesome task.

Previously, we demonstrated the syntheses of six-membered ring compounds by the environmentally friendly cyclization with Ni(II)-mediated electrolysis.⁴ As an extension, we applied this methodology for the cascade cyclizations of halo-olefins. Although the cascade radical reactions have been widely studied,⁵ most of the cyclizations were performed by treatment with Bu_3SnH . Our previous studies have demonstrated that the substrates having a bromoacetal function as a radical generated group tethered with an electron-withdrawing group as a radical acceptor effectively undergo cyclization under the electrolytic conditions.⁴ Accordingly, we designed the reaction system as shown in **Scheme 1**.

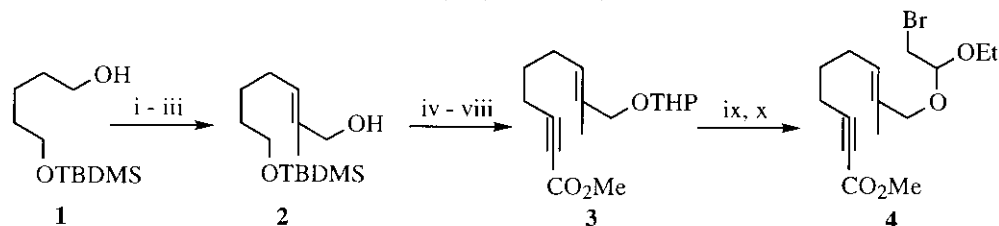


Scheme 1

In this system, we have envisaged the formation of two possible products by competitive cyclization in a 5-*exo*,5-*exo* (path A) and a 6-*endo*,6-*exo* (path B) fashion. Here, we report results of the cascade radical

cyclization by electrolysis.

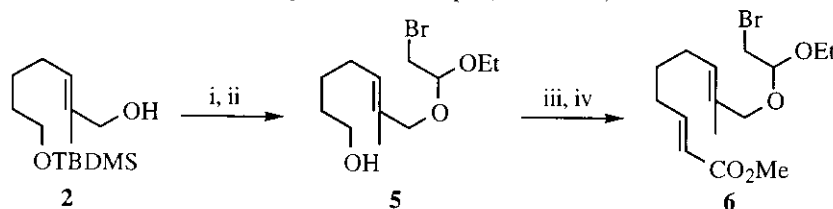
Bromoacetals (**4**) and (**6**) were prepared from 5-(*tert*-butyldimethylsilyloxy)-1-pentanol (**1**)⁶ as follows. The allyl alcohol (**2**), which was derived from **1**, was converted into the acetylenic ester (**3**) in five steps; protection with 3,4-dihydro-2*H*-pyran (DHP), deprotection of the TBDMS group with Bu₄NF (TBAF), oxidation with pyridinium dichromate (PDC), dibromoolefination, and elimination with BuLi followed by methyl chloroformate trap.⁷ After deprotection of THP group, the treatment of allyl alcohol with 1,2-dibromoethyl ethyl ether, prepared from bromine and ethyl vinyl ether, in the presence of *N,N*-dimethylaniline^{2b,8} furnished the bromoacetal (**4**) (Scheme 2).



- | | |
|--|--|
| i. PDC, 4Å molecular sieves, CH ₂ Cl ₂ | vi. PDC, 4Å molecular sieves, CH ₂ Cl ₂ |
| ii. NaH, (EtO) ₂ P(O)CH(Me)CO ₂ Me, DME
(65% for 2 steps) | vii. CBr ₄ , Ph ₃ P, Zn, CH ₂ Cl ₂ (63% for 2 steps) |
| iii. DIBAL-H, CH ₂ Cl ₂ (91%) | viii. BuLi, THF then ClCO ₂ Me (85%) |
| iv. DHP, PPTS, CH ₂ Cl ₂ (92%) | ix. PPTS, EtOH (85%) |
| v. TBAF, THF (93%) | x. 1,2-dibromoethyl ethyl ether,
<i>N,N</i> -dimethylaniline, CH ₂ Cl ₂ (96%) |

Scheme 2

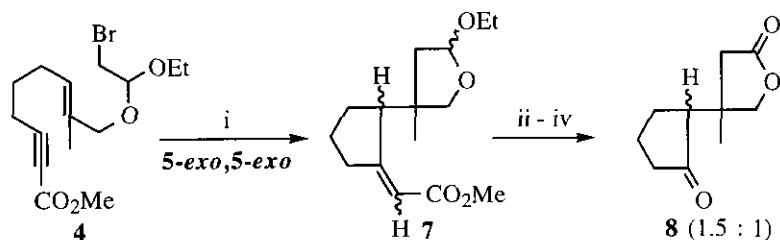
Furthermore, the allyl alcohol (**2**) was transformed into the bromoacetal (**6**) possessing an α,β -unsaturated ester group as a radical acceptor in four steps (Scheme 3).



- | |
|---|
| i. 1,2-dibromoethyl ethyl ether, <i>N,N</i> -dimethylaniline, CH ₂ Cl ₂ |
| ii. TBAF, THF (93% for 2 steps) |
| iii. Dess-Martin periodinane, Py, CH ₂ Cl ₂ |
| iv. NaH, (MeO) ₂ P(O)CH ₂ CO ₂ Me, DME (61% for 2 steps) |

Scheme 3

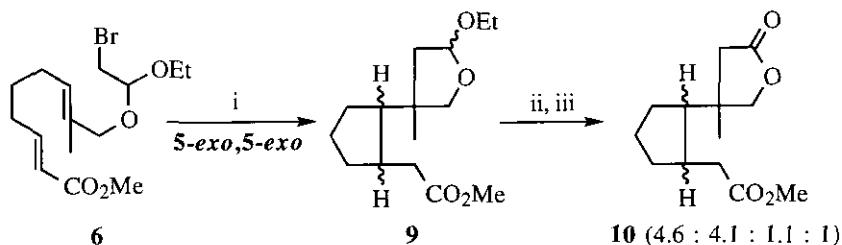
The bromoacetal (**4**) having an acetylenic ester group produced bicyclic five-membered ring compounds (**7**) in a highly regioselective manner by the Ni(II)-mediated electrolysis.⁹ However, the reaction did not proceed, when vitamin B_{12a} was used as the mediator. Structures of bicyclic compounds (**7**) were determined after their conversion into keto lactones (**8**) in three steps, whose IR and ¹³C-NMR spectral data indicated the five-membered ring structure.¹⁰ Two stereoisomers of keto lactones (**8**) were obtained in a ratio of 1.5 : 1 (Scheme 4).



- i. [Ni(cyclam)](ClO₄)₂, NH₄ClO₄, Et₄NClO₄-DMF, -1.5 V (35%)
 ii. 10% HClO₄, THF
 iii. Ag₂CO₃-Celite, benzene (64% for 2 steps)
 iv. O₃, CH₂Cl₂ then Me₂S (47%)

Scheme 4

The bromoacetal (**6**) possessing an α,β -unsaturated ester group gave a stereoisomeric mixture of five-membered ring compounds (**9**) in good yields by Ni(II) or Co(III)-mediated electrolysis. Structures of **9** were proved by their transformation into **10** (Scheme 5).^{11,12}



- i. a) [Ni(cyclam)](ClO₄)₂, NH₄ClO₄, Et₄NClO₄-DMF, -1.5 V (72%)
 b) vitamin B_{12a}, NH₄Cl, LiClO₄-DMF, -1.5 V (65%)
 ii. 10% HClO₄, THF
 iii. Ag₂CO₃-Celite, benzene (86% for 2 steps)

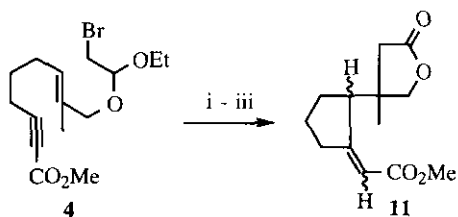
Scheme 5

In conclusion, we have demonstrated the usefulness of radical cyclizations under electrolytic conditions mediated by [Ni(cyclam)](ClO₄)₂ or vitamin B_{12a} for effecting the cascade reactions of halo-olefins. Substrates having a bromoacetal unit as a radical generated group and an acetylenic or α,β -unsaturated ester function as a terminal radical acceptor afforded bicyclic five-membered ring compounds according to Baldwin's rule. Thus, the present procedure provides a useful method for a convenient and clean radical cyclization.

REFERENCES AND NOTES

- (a) B. Giese, *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Oxford, 1986. (b) D. P. Curran, in *Comprehensive Organic Synthesis*, ed. by B. M. Trost, I. Fleming, and M. F. Semmelhack, Pergamon, Oxford, 1991, Vol. 4, p. 715. (c) A. L. J. Beckwith, *Chem. Soc. Rev.*, 1993, 143. (d) G. Stork and N. H. Baine, *J. Am. Chem. Soc.*, 1982, **104**, 2321. (e) P. A. Baguley and J. C. Walton, *Angew. Chem., Int. Ed. Engl.*, 1998, **37**, 3072.

2. (a) G. Buchi and H. Wuest, *J. Org. Chem.*, 1979, **44**, 546. (b) G. Stork and R. Mook, Jr., *J. Am. Chem. Soc.*, 1983, **105**, 3720.
3. (a) J. M. Kanabus-Kaminska, J. A. Hawari, D. Griller, and C. Chatgililoglu, *J. Am. Chem. Soc.*, 1987, **109**, 5267. (b) B. Giese and B. Kopping, *Tetrahedron Lett.*, 1989, **30**, 681.
4. M. Ihara, A. Katsumata, F. Setsu, Y. Tokunaga, and K. Fukumoto, *J. Org. Chem.*, 1996, **61**, 677.
5. (a) A. Batsanov, L. Chen, G. B. Gill, and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1996, 45 and references cited therein. (b) G. Pattenden, L. Roberts, and A. J. Blake, *J. Chem. Soc., Perkin Trans. 1*, 1998, 863. (c) D. L. Boger and R. J. Mathvink, *J. Am. Chem. Soc.*, 1990, **112**, 4003. (d) D. L. Boger and R. J. Mathvink, *J. Org. Chem.*, 1990, **55**, 5442. (e) D. L. Boger and R. J. Mathvink, *J. Org. Chem.*, 1992, **57**, 1429.
6. J. A. Marshall, B. G. Shearer, and S. L. Crooks, *J. Org. Chem.*, 1987, **52**, 1236.
7. E. J. Corey and P. L. Fuchs, *Tetrahedron Lett.*, 1972, 3769.
8. D. C. Rowlands, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Org. Chem.*, 1952, **17**, 807.
9. General Procedure for Indirect Electrolysis: The electrolysis was carried out in dry DMF (about 15 mL) containing a supporting electrolyte (0.1 M), the substrate, a proton source (200 mol%), and mediator (10 mol%), potentiostatically at -1.5 V (vs Ag/AgCl) using carbon graphite felt ($0.5 \times 0.5 \times 0.5$ cm³) as the working electrode, under N₂ bubbling using an H-type divided cell separated by a cationic exchange membrane (Nafion® 117) at rt. The reaction was monitored by TLC. After the reaction, the mixture was diluted with H₂O and then thoroughly extracted with Et₂O. The combined extracts were washed with brine, dried (MgSO₄), and evaporated. The product was purified with column chromatography on silica gel.
10. Compound (**8**): **8** in a ratio of 1.5 : 1 (stereoisomers) as a colorless oil; IR (neat, cm⁻¹) 1770, 1730; ¹H-NMR (300 MHz, CDCl₃) δ 3.94-4.39 (m, 2H), 2.02-2.73 (m, 7H), 1.64-1.92 (m, 2H), 1.15 (s, 1.2H), 1.13 (s, 1.8H); ¹³C-NMR (75 MHz, CDCl₃) δ 218.8, 218.2, 177.0, 176.3, 56.0, 55.0, 41.3, 40.9, 40.7, 40.5, 39.2, 39.1, 26.0, 25.8, 20.9, 20.5, 20.3, 20.2; HRMS calcd for C₁₀H₁₄O₃ (M⁺) 182.0942, found 182.0934. In general, 1770 cm⁻¹ of IR data supports γ -lactone structure, and 218 ppm of ¹³C-NMR data suggests cyclopentanone unit.
11. Compound (**10**): **10** in a ratio of 4.6 : 4.1 : 1.1 : 1 (stereoisomers) as a colorless oil; IR (neat, cm⁻¹) 1775, 1730; ¹H-NMR (300 MHz, CDCl₃) δ 3.94-4.18 (m, 2H), 3.69 (s, 2.41H), 3.68 (s, 0.59H), 1.29-2.58 (m, 12H), 1.27 (s, 1.27H), 1.26 (s, 1.14H), 1.16 (s, 0.31H), 1.15 (s, 0.28H); HRMS calcd for C₁₂H₁₇O₃ (M⁺-OMe) 209.1178, found 209.1212.
12. Lactones (**11**) were obtained from **4** in 55% yield for 3 steps by cyclization using Bu₃SnH, and **10** were produced from **6** in 56% yield for 3 steps by the same procedure.



- i. Bu₃SnH, AIBN, benzene, reflux
- ii. 10% HClO₄, THF
- iii. Ag₂CO₃-Celite, benzene (55% for 3 steps)