will require further study of **1** and related species. The generality of this reaction is being explored.

Acknowledgment. We thank the National Science Foundation for support for this research. Funds for the purchase of the X-ray equipment were made available from NSF Grant CHE-85-14495.

Supplementary Material Available: ORTEP diagrams and tables of crystal data, positional parameters, bond distances and angles, and thermal parameters for **1** (16 pages); table of observed and calculated structure factor amplitudes for **1** (18 pages). Ordering information is given on any current masthead page.

Novel Radical Cyclization of *N*-Aziridinyl Imines

Sunggak Kim,* In Seo Kee, and Sangphil Lee

Department of Chemistry, Korea Advanced Institute of Science and Technology, Seoul 130-012, Korea

Received August 19, 1991

Despite the synthetic usefulness of radical cyclization reactions,[1] the cyclization pathway is mainly limited to 5-exo closure along with somewhat less efficient 6-exo and 6-endo closure due to stereoelectronic and geometric reasons.[2] A fundamentally new approach for the formation of five- and six-membered-ring radicals from acyclic precursors was sought, and we report here an unprecedented radical cyclization using 2-phenyl-*N*-aziridinyl imines which we believe has considerable synthetic potential for the formation of carbon–carbon bonds. Our approach is outlined in Scheme I and is based on three factors along with the original Eschenmoser reaction.[3] First, alkyl radicals are known to add to oxime ethers.[4] Second, β-fragmentation of three-membered rings is a facile process due to the relief of ring strain.[5] Third, consecutive β-fragmentations via ejection of styrene and nitrogen are expected to be fast processes.[6]

Our initial study focused on the use of the *N*-aziridinyl imines as radical acceptors. *N*-Aziridinyl imines were prepared in 60–80% yield by treatment of aldehydes and ketones in ethanol with a

Scheme I

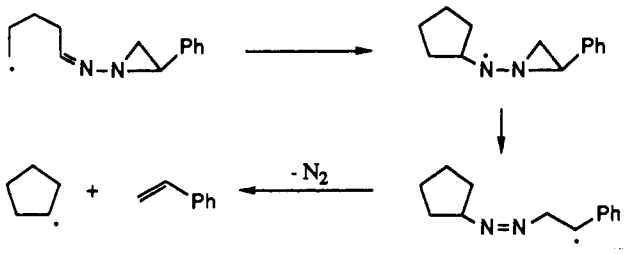
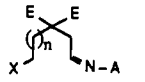
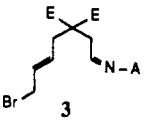
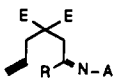
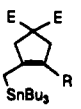
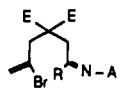
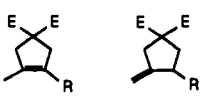


Table I. Radical Cyclization of 2-Phenyl-*N*-aziridinyl Imines

substrate[a]	time, h	product (yield, %)
		
1a: n=1, X=Br	4	**2a** (30)
1b: n=1, X=SePh	2	**2a** (75)[b]
1c: n=2, X=Br	2	**2c** (85)
		
3	4	**4** (89)
		
5a: R=H	3	**6a** (84)
5b: R=CH_3	3	**6b** (96)
		
7a: R=H	4	**8a** (87/13)[c] **9a** (67)
7b: R=CH_3	6	**8b** (94/6)[c] **9b** (92)

[a] E = COOEt, A = 2-phenyl-*N*-aziridinyl group. [b] Nine percent of the reduction product was obtained. [c] The ratio was determined by ^{1}H NMR analysis and refers to **8a/9a** and **8b/9b**, respectively.

pentane solution of 1-amino-2-phenylaziridine at 0 °C, and a mixture of syn and anti isomers was used. **CAUTION!** *1-Amino-2-phenylaziridinium acetate is explosive, and proper precautions should be taken whenever it is used.*[7] Treatment of the bromide **1a** (Table I) with *n*-Bu_3SnH (2.0 equiv) and AIBN (0.1 equiv) in benzene (0.01 M in the bromide) at 80 °C for 4 h afforded 30% of **2a** along with 33% of the *N*-aziridinylpiperidine.[8] Under the same conditions, the use of the phenyl selenide **1b** obviated the problem of intramolecular N-alkylation and gave **2a** in 75% yield. **1c** was cleanly cyclized to **2c**, and there was no evidence of the N-alkylated product. As shown in Table I, radical cyclization of **3**, **5a**, and **7a** using structurally different radical precursors proceeded smoothly, yielding the cyclized products in high yields.[9,10] Similarly, the keto hydrazones **5b** and

(1) For recent reviews, see: (a) Hart, D. J. *Science* **1984**, *223*, 883. (b) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: New York, 1986. (c) Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541. (d) Curran, D. P. *Synthesis* **1988**, 417, 489. (e) Laird, E. R.; Jorgensen, W. L. *J. Org. Chem.* **1990**, *55*, 9.

(2) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734. (b) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. *J. Chem. Soc., Chem. Commun.* **1980**, 482. (c) Stork, G. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon Press: New York, 1983; p 359. (d) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

(3) Felix, D.; Muller, R. K.; Horn, U.; Joos, R.; Schreiber, J.; Eschenmoser, A. *Helv. Chim. Acta* **1972**, *55*, 1276.

(4) (a) Corey, E. J.; Pyne, S. G. *Tetrahedron Lett.* **1983**, *24*, 2821. (b) Hart, D. J.; Seely, F. L. *J. Am. Chem. Soc.* **1988**, *110*, 1631. (c) Bartlett, P. A.; McLaren, K. L.; Ting, P. C. *J. Am. Chem. Soc.* **1988**, *110*, 1633. (d) Enholm, E. J.; Burroff, J. A.; Jaramillo, L. M. *Tetrahedron Lett.* **1990**, *31*, 3727.

(5) For recent examples of fragmentation of three-membered rings, see the following. (a) Epoxides: Ayral-Kaloustian, S.; Agosta, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 314. Barton, D. H. R.; Motherwell, R. S. H.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2363. Johns, A.; Murphy, J. A.; Patterson, C. W.; Wooster, N. F. *J. Chem. Soc., Chem. Commun.* **1987**, 1238. Murphy, J. A.; Patterson, C. W.; Wooster, N. F. *J. Chem. Soc., Chem. Commun.* **1988**, 294. Johns, A.; Murphy, J. A. *Tetrahedron Lett.* **1988**, *29*, 837. Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181. Kim, S.; Lee, S.; Koh, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 5106. (b) Cyclopropanes: Ratier, M.; Pereyer, M. *Tetrahedron Lett.* **1976**, 2273. Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5135. Feldman, K. S.; Ruckle, R. E., Jr.; Romanelli, A. L. *Tetrahedron Lett.* **1989**, *30*, 5845. (c) Benzoylaziridine: Padwa, A.; Eisenhardt, W. *J. Am. Chem. Soc.* **1971**, *93*, 1400.

(6) (a) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1979**, *101*, 7129. (b) Evans, D. A.; Nelson, J. V. *J. Am. Chem. Soc.* **1980**, *102*, 774. (c) Mohamadi, F.; Collum, D. B. *Tetrahedron Lett.* **1984**, *25*, 271. (d) Padwa, A.; Gareau, Y.; Xu, S. L. *Tetrahedron Lett.* **1991**, *32*, 983. (e) Leone, C. L.; Chamberlin, A. R. *Tetrahedron Lett.* **1991**, *32*, 1691.

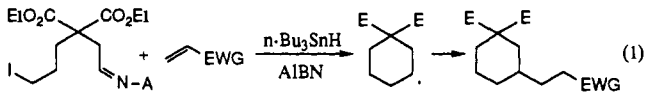
(7) **CAUTION!** After preparation of 1-amino-2-phenylaziridinium acetate (approximately 10-g scale) by the known procedure (Muller, R. K.; Joos, R.; Felix, D.; Schreiber, J.; Wintner, C.; Eschenmoser, A. *Org. Synth.* **1976**, *55*, 114), it exploded during storage at room temperature, causing minor injuries. The cause of the explosion is unclear at present. Thus, it is desirable to use a pentane solution of 1-amino-2-phenylaziridine for the preparation of *N*-aziridinyl imines.

(8) The byproduct was 1-(2′-phenylaziridinyl)-4,4-bis(ethoxycarbonyl)-piperidine. Furthermore, it was obtained in 75% yield without the formation of **2a** when **1a** was treated with *n*-Bu_3SnH in refluxing benzene for 4 h without the addition of AIBN. ^{1}H NMR (300 MHz, $CDCl_3$, −50 °C): δ 1.19 (t, 3 H, J = 7.1 Hz), 1.21 (t, 3 H, J = 7.1 Hz), 1.89 (t, 2 H, J = 11.5 Hz), 2.10 (d, 1 H, J = 4.5 Hz), 2.15 (d, 1 H, J = 7.64 Hz), 2.28–2.51 (m, 4 H), 2.72 (dd, 1 H, J = 4.8, 7.9 Hz), 3.08–3.11 (m, 2 H), 4.12 (q, 2 H, J = 7.1 Hz), 4.16 (q, 2 H, J = 7.1 Hz), 7.16–7.32 (m, 5 H). IR (NaCl): 2952, 1733, 1452, 1367, 1246, 1129 cm^{-1}. HRMS (M^+): calcd for $C_{19}H_{26}O_4N_2$ 346.1892, found 346.1877.

0002-7863/91/1513-9882$02.50/0

7b were cyclized without significant differences in their reactivity. Furthermore, it is noteworthy that no reduction products were observed except for **1b**.

We have briefly examined the feasibility of the cyclization–intermolecular addition sequence[11] because this illustrates a unique feature of the present method, demonstrating the formation of two carbon–carbon bonds in succession at the same carbon (eq 1).[12] The addition of a 0.1 M benzene solution of *n*-Bu_3SnH (2



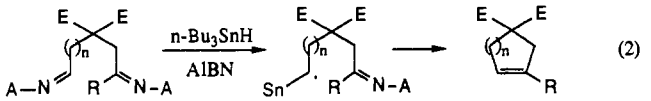
(1)

10

11: EWG = CN (86%)
12: = COOMe (87%)

equiv) and AIBN (0.1 equiv) by a syringe pump over 2 h to a 0.1 M refluxing benzene solution of the iodide **10** and acrylonitrile (10 equiv) with additional stirring for 1 h afforded **11** in 86% yield. A similar result was realized with methyl acrylate.

Our attention was next given to the use of the aziridinyl imines as radical precursors, and our approach relied on intermolecular addition of *n*-Bu_3Sn radical to an aziridinyl imine group to generate the α-*n*-Bu_3Sn-substituted carbon-centered radical, as shown in eq 2. Thus, treatment of **13a** with *n*-Bu_3SnH (0.3 equiv) and

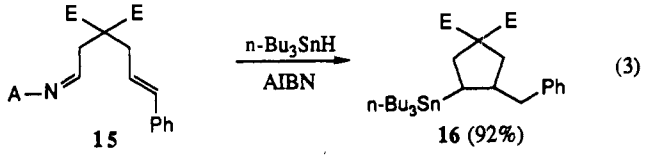


(2)

13a n=1, R=Me
13b n=1, R=H
13c n=2, R=H

8a (82%)
14b (62%)
14c (65%)

AIBN (0.1 equiv) in toluene (0.05 M in the substrate) at 110 °C for 6 h afforded **8a** in 82% yield,[13] demonstrating the efficacy of an aziridinyl imine group as a radical precursor as well as a radical acceptor. This cyclization will be especially valuable in the construction of cyclic systems bearing a carbon–carbon double bond. An additional example using the cinnamyl group as a radical acceptor, in which further functionalization of the *n*-Bu_3Sn group would be possible,[14] is shown in eq 3.[15]



(3)

15

16 (92%)

In conclusion, the radical cyclization of aziridinyl imines provides a reliable method for the formation of five- and six-membered-ring radicals. The ability of aziridinyl imines to function as radical precursors as well as radical acceptors enhances the synthetic utility of the present method. Further studies on radical reactions using aziridinyl imines are now in progress.

Acknowledgment. We thank Lucky Ltd. and The Organic Chemistry Research Center for financial support of this work. We are also grateful to Drs. Chwang Siek Pak and Sung-Eun Yoo of Korea Research Institute of Chemical Technology for their help.

(9) The structures of **6a** and **6b** were further ascertained by ^1H NMR analysis of the destannylated products after treatment of **6a** and **6b** with DCl, respectively.

(10) Satisfactory spectral data and high-resolution mass spectra were obtained for the reaction products.

(11) (a) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1983**, *105*, 6765. (b) Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303. (c) Stork, G.; Sher, P. M.; Chen, H.-L. *J. Am. Chem. Soc.* **1986**, *108*, 6384.

(12) Nagai, M.; Lazor, J.; Wilcox, C. S. *J. Org. Chem.* **1990**, *55*, 3440.

(13) Additional AIBN (0.1 equiv) was added after 2 h.

(14) Pereyre, M.; Quintard, J.-P.; Rahm, A. *Tin in Organic Synthesis*; Butterworths: 1987 and references cited therein.

(15) Treatment of **15** with *n*-Bu_3SnH (1.1 equiv) and AIBN (0.1 equiv) in benzene (0.01 M) at 80 °C for 4 h afforded **16** in 92% yield. The ratio of cis and trans isomer (**16**) could not be determined by ^1H NMR.

Registry No. 1a, 137435-35-9; **1b**, 137435-36-0; **1c**, 137435-37-1; **2a**, 4167-77-5; **2c**, 1139-13-5; **3**, 137435-38-2; **4**, 137435-39-3; **5a**, 137435-40-6; **5b**, 137435-41-7; **6a**, 137435-42-8; **6b**, 137435-43-9; **7a**, 137435-44-0; **7b**, 137435-45-1; **8a**, 2698-64-8; **8b**, 74160-66-0; **9a**, 137435-46-2; **9b**, 93638-77-8; **10**, 137435-47-3; **11**, 137435-48-4; **12**, 137435-49-5; **13a**, 137435-50-8; **13b**, 137435-51-9; **13c**, 137435-52-0; **14b**, 21622-00-4; **14c**, 38511-09-0; **15**, 137435-53-1; **16**, 137435-54-2; acrylonitrile, 107-13-1; methyl acrylate, 96-33-3; diethyl (2-bromoethyl)(2-oxoethyl)propanedioate, 137435-55-3; diethyl (2-oxoethyl)[2-(phenylseleno)ethyl]-propanedioate, 137435-56-4; diethyl (3-bromopropyl)(2-oxoethyl)-propanedioate, 137435-57-5; diethyl (4-bromo-2-butenyl)(2-oxoethyl)-propanedioate, 137435-58-6; diethyl (2-oxoethyl)-2-propynylpropanedioate, 137435-59-7; diethyl (2-oxopropyl)-2-propynylpropanedioate, 137435-60-0; diethyl (2-bromo-2-propenyl)(2-oxoethyl)propanedioate, 137435-61-1; diethyl (2-bromo-2-propenyl)(2-oxopropyl)propanedioate, 137435-62-2; diethyl (3-iodopropyl)(2-oxoethyl)propanedioate, 137435-63-3; diethyl (2-oxoethyl)(2-oxopropyl)propanedioate, 137435-64-4; diethyl bis(2-oxoethyl)propanedioate, 137435-65-5; diethyl (2-oxoethyl)-(3-oxopropyl)propanedioate, 137435-66-6; diethyl (2-oxoethyl)(3-phenyl-2-propenyl)propanedioate, 137435-67-7; 1-amino-2-phenylaziridine, 19615-20-4; 1-(2'-phenylaziridinyl)-4,4-bis(ethoxycarbonyl)-piperidine, 137435-68-8.

Biomimetic Synthesis of Enantiomerically Pure D-*myo*-Inositol Derivatives

Steven L. Bender* and Richard J. Budhu

Department of Chemistry
University of California at Irvine
Irvine, California 92717

Received August 28, 1991

Since D-*myo*-inositol 1,4,5-trisphosphate (D-1,4,5-IP_3) was identified as the second messenger in a vast number of important signal transduction processes,[1] numerous syntheses of 1,4,5-IP_3 and other inositol phosphates have been reported.[2,3] These studies have established effective methodology for the polyphosphorylation of partially protected *myo*-inositol derivatives, but no *generalizable* synthesis of enantiomerically pure inositol derivatives has been reported whereby the protection pattern and functionality may be controlled in a versatile manner. Our approach to this problem was inspired by biosynthetic considerations. The enzyme *myo*-inositol-3-phosphate synthase (EC 5.5.1.4) converts glucose-6-phosphate to D-*myo*-inositol 3-phosphate by an interesting sequence of chemical transformations (Scheme I), including a stereospecific intramolecular aldol reaction (i.e., **1** → **2** → **3**).[4] Herein we report our initial studies on a biomimetic conversion of glucopyranoside derivatives to enantiomerically pure *myo*-inositol derivatives.[5]

Our approach relies on the Ferrier reaction to generate a "mercury enolate" **8** that, as a functional equivalent of **2**, undergoes the desired carbocyclization process to provide the inosose **7** (Scheme II). Although the Ferrier reaction is well-established for the stereoselective conversion of unsubstituted enol ethers **4**

(1) Berridge, M. J.; Irvine, R. F. *Nature (London)* **1984**, *312*, 315-321.

(2) *Inositol Phosphates and Derivatives: Synthesis, Biochemistry, and Therapeutic Potential*; Reitz, A. B., Ed.; ACS Symposium Series 463; American Chemical Society: Washington, DC, 1991.

(3) For recent reviews, see: (a) Potter, B. V. L. *Nat. Prod. Rep.* **1990**, 1-24. (b) Billington, D. C. *Chem. Soc. Rev.* **1989**, *18*, 83-122.

(4) (a) Wong, Y.-H. H.; Sherman, W. R. *J. Biol. Chem.* **1985**, *261*, 11083. (b) Donahue, T. F.; Henry, S. A. *J. Biol. Chem.* **1981**, *256*, 7077. (c) Maeda, T.; Eisenberg, F., Jr. *J. Biol. Chem.* **1980**, *255*, 8458. (d) Eisenberg, F., Jr.; Maeda, T. In *Inositol and Phosphoinositides*; Bleasdale, J. E., Eichberg, J., Hauser, G., Eds.; Humana: New Jersey, 1985; p 3. (e) Frey, P. A. In *Pyridine Nucleotide Coenzymes: Chemical, Biochemical, and Medical Aspects*; Dolphin, D., Avramovic, O., Poulson, R., Eds.; Wiley: New York, 1987; Vol. 2, pp 461-511.

(5) For previous nonstereoselective, alkali-promoted cyclizations of hexos-5-ulose derivatives, see: (a) Kiely, D. E.; Fletcher, H. G., Jr. *J. Am. Chem. Soc.* **1968**, *90*, 3289-3290. (b) Kiely, D. E.; Fletcher, H. G., Jr. *J. Org. Chem.* **1969**, *34*, 1386-1390. (c) Kiely, D. E.; Sherman, W. R. *J. Am. Chem. Soc.* **1975**, *97*, 6810-6814.

0002-7863/91/1513-9883$02.50/0