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Cyclization of Alkenyl Radicals in 5- and 6-(*π-Exo*)-*exo-dig* Modes: New Entry to *Exo*-cyclic Dienes

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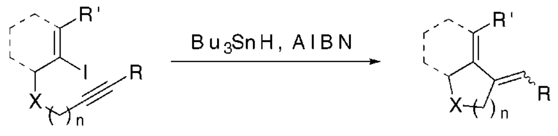
ABSTRACT

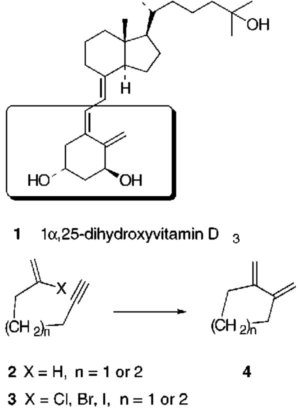


n = 1 or 2

Radical cyclizations of alkenyl iodides in both 5- and 6-(*π-exo*)-*exo-dig* modes were effected by tributyltin hydride and AIBN to give *exo*-cyclic dienes fused to five- and six-membered rings in good yields.

Exo-cyclic dienes are versatile and useful diene components in Diels−Alder reactions.[1] They are also characteristic substructures of vitamin D_3 and its derivatives,[2] e.g., **1**, Scheme 1. Among various methodologies known for synthesis of *exo*-cyclic dienes, the palladium-catalyzed cyclization[3] of enynes **2** to *exo*-cyclic dienes **4** and anionic cyclization[4] of haloenynes **3** to **4** are general and efficient. Alternatively, the radical cyclizations of haloenynes **3** to **4** would be straightforward.[5−7] However according to the previous study, only 5-(*π-exo*)-*exo-dig* radical cyclization was facile. The corresponding 6-(*π-exo*)-*exo-dig* cyclization was reported to be unfavorable.[6] To the best of our knowledge, there are only two cases of 6-(*π-exo*)-*exo-dig* radical cyclization of poor yields reported in the literature.[7] As an extension of our study in radical cyclization reactions,[8] we have also investigated radical cyclizations of alkenyl iodides. Contrary to the previous reports, we found that not only 5-(*π-exo*)-*exo-dig* but also 6-(*π-exo*)-*exo-dig* radical

Scheme 1



1 1α,25-dihydroxyvitamin D_3

2 X = H, n = 1 or 2 **4**

3 X = Cl, Br, I, n = 1 or 2

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[1] Fringuelli, F.; Taticchi, A. *Dienes in the Diels−Alder Reaction*, Wiley: New York, 1990, Chapter 3.

[2] Norman, A. W. *Vitamin D, The Calcium Homeostatic Steroid Hormone*; Academic Press: New York, 1979.

[3] (a) Lautens, M.; Smith, N. D.; Ostrovsky, D. *J. Org. Chem.* **1997**, *62*, 8970−8971. (b) Trost, B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; Macpherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255−4267. (c) Trost, B. M.; Romero, D. L.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268−4278. (d) Meyer, F. E.; Ang, K. H.; Steinig, A. G.; de Meijere, A. *Synlett* **1994**, 191−193.

[4] Bailey, W. F.; Wachter-Jurcsak, N. M.; Pineau, M. R.; Ovaska, T. V.; Warren, R. R.; Lewis, C. E. *J. Org. Chem.* **1996**, *61*, 8216−8228.

[5] (a) Capella, L.; Montevecchi, P. C. *Tetrahedron Lett.* **1994**, *35*, 8445−8448. (b) Journet, M.; Rouillard, A.; Cai, D.; Larsen, R. D. *J. Org. Chem.* **1997**, *62*, 8630−8631.

[6] Crich, D.; Fortt, S. M. *Tetrahedron Lett.* **1987**, *28*, 2895−2898.

[7] (a) Capella, L.; Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem.* **1995**, *60*, 7424−7432. (b) Caddick, S.; Shering, C. L.; Wadman, S. N. *J. Chem. Soc., Chem. Commun.* **1997**, 171−172.

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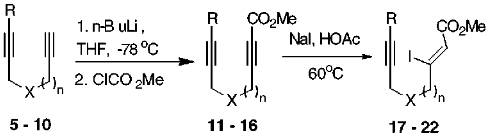
cyclizations proceeded smoothly to give *exo*-cyclic dienes in good yield. Herein we report our preliminary results.

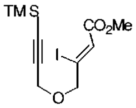
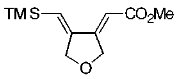
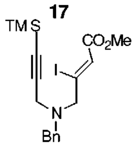
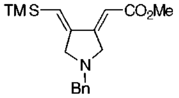
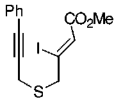
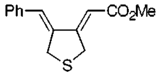
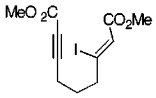
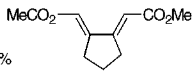
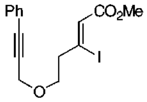
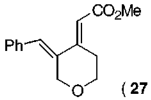
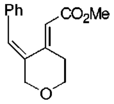
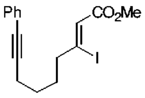
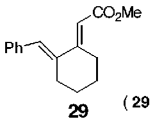
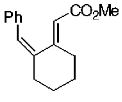
Diynyl esters **11**−**16** were prepared by conventional methods.[9] Reaction of compounds **5**, **6**, **7**, **9**, and **10** with *n*-butyllithium and methyl chloroformate gave acetylenic methyl esters **11**, **12**, **13**, **15**, and **16**. Double deprotonation of **8** with *n*-butyllithium (2.2 equiv) followed by reaction with methyl chloroformate (3 equiv) afforded diester **14**. Treatment of esters **11**−**16** with sodium iodide and acetic acid at 65 °C according to Lu's method[10] gave β-iodo α,β-unsaturated esters **17**−**22,** Scheme 2. Radical cyclizations of β-iodo α,β-unsaturated esters **17**−**20** were effected by the treatment with tributyltin hydride and AIBN to afford *exo*-cyclic dienes **23**−**26** in 58−77% yield.[11] In these 5-(π-*exo*)-*exo-dig* cyclizations, the *exo*-cyclic dienes obtained were all in *E*,*E* configuration, Table 1.

Scheme 2



5, **11**, **17** X = O, R = TMS, n = 1
6, **12**, **18** X = N-Bn, R = TMS, n =1
7, **13**, **19** X = S, R = Ph, n = 1
8, **14**, **20** X = CH_2, R = H (for **8**), CO_2Me (for **14**, **20**), n = 1
9, **15**, **21** X = O, R = Ph, n = 2
10, **16**, **22** X = CH_2, R = Ph, n = 2

Table 1. Radical Cyclization of β-Iodo α,β-Unsaturated Esters

Entry	Iodo Compound	Yield	*Exo*-cyclic Diene	Yield [a]
1	 **17**	86%	 **23**	75% [b]
2	 **18**	86%	 **24**	58% [b]
3	 **19**	75%	 **25**	75% [b]
4	 **20**	34%	 **26**	77% [b]
5	 **21**	81%	 **27**  **28**	68% [b] (**27** : **28** = 5 : 1) [c]
6	 **22**	81%	 **29**  **30**	76% [b] (**29** : **30** = 7 : 1) [c]

[a] Isolated yield. [b] The structures of the *exo*-cyclic dienes were confirmed by NOE experiments. [c] The ratios were determined by ^1H NMR integration.

We then attempted the 6-(π-*exo*)-*exo-dig* radical cyclization with β-iodo α,β-unsaturated esters **21** and **22**. Compounds **21** and **22** were treated with tributyltin hydride and AIBN by slow addition using a syringe pump. Surprisingly, compounds **21** and **22** also underwent radical cyclization

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(8) (a) Sha, C.-K.; Shen, C.-Y.; Jean, T.-S.; Chiu, R.-T.; Tseng, W.-H. *Tetrahedron Lett.* **1993**, *34*, 7641−7644. (b) Sha, C.-K.; Santhosh, K. C.; Lih, S.-H. *J. Org. Chem.* **1998**, *63*, 2699−2704. (c) Sha, C.-K.; Ho, W.-Y. *J. Chem. Soc., Chem. Commun.* **1998**, 2709−2710. (d) Sha, C.-K.; Lee, F.-K.; Chang, C.-J. *J. Am. Chem. Soc.* **1999**, *121*, 9875−9876.

(9) (a) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: New York, 1988; pp 97−100 and 247−288. (b) Geiger, R. E.; Lalonde, M.; Stoller, H.; Schleich, K. *Helv. Chim. Acta* **1984**, *67*, 1274−1282. (c) Cao, X.-P.; Chan, T.-L.; Chow, H.-F. *Tetrahedron Lett.* **1996**, *37*, 1049−1052.

(10) (a) Lu, X.; Ma, S. *J. Chem. Soc., Chem. Commun.* **1990**, 1643−1644. (b) Lu, X.; Ma, S. *Tetrahedron Lett.* **1990**, *31*, 7653−7656. (c) Marek, I.; Alexakis, A.; Normant, J.-F. *Tetrahedron Lett.* **1991**, *32*, 5329−5332. (d) Lu, X.; Ma, S. *J. Org. Chem.* **1992**, *57*, 709−713. (e) Piers, E.; Wong, T.; Coish, P. D.; Rogers, C. *Can. J. Chem.* **1994**, *72*, 1816−1819. (f) Luo, F.-T.; Hsieh, L.-C. *J. Chin. Chem. Soc.* **1994**, *41*, 871−873.

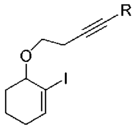
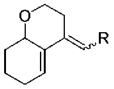
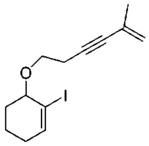
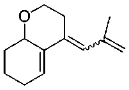
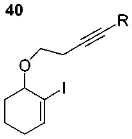
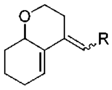
(11) For the first example of the β-iodo α,β-unsaturated ester radical cyclization in 6-(π-*exo*)-*endo-trig* mode, see: Thomas, E. J.; Munt, S. P.; Maguire, R. J. *J. Chem. Soc., Perkin. Trans. 1* **1998**, 2853−2863.

(12) Satisfactory spectral and analytical data were obtained for all new compounds. A typical experimental procedure for the radical cyclization of **42** is as follows: To a solution of the **42** (100 mg, 0.26 mmol) in dry benzene (20 mL) under reflux were added Bu_3SnH (83 mg, 0.29 mmol) and AIBN (5 mg) in dry benzene (6 mL) slowly with a syringe pump (4 h). The reaction mixture was then refluxed for 2 h. After cooling to room temperature, the solvent was removed on a rotary evaporator. The crude product was dissolved in Et_2O (20 mL). A saturated solution of KF (10 mL) in water was added, and the mixture was stirred at room temperature for 2 h. The organic layer was then washed with saturated $NaHCO_3$ solution and brine and dried (Na_2SO_4). Silica gel flash column chromatography (hexane−CH_2Cl_2, 1:1) gave compound **49** as a mixture of *E* and *Z* isomers. (55 mg, 82%). *E* and *Z* isomers were separated by silica gel preparative TLC (hexane−CH_2Cl_2, 1:1). Data for the *E* isomer: colorless crystals from hexane; mp 105−6 °C.; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, $J = 8.7$ Hz, 2 H), 6.85 (d, $J = 8.7$ Hz, 2 H), 6.48 (d, $J = 2.1$ Hz, 1 H), 5.85 (dd, appears as t, $J = 3.6$ Hz, 3.6 Hz, 1 H), 4.03−3.97 (m, 2 H), 3.78 (s, 3 H), 3.53−3.43 (m, 1 H), 2.75−2.69 (m, 1 H), 2.62−2.50 (m, 1 H), 2.28−2.13 (m, 1 H), 2.11−1.99 (m, 2 H), 1.84−1.71 (m, 1 H), 1.63−1.49 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 26.2, 29.9, 30.9, 55.3, 66.8, 75.6, 113.6, 123.0, 123.1, 130.2, 130.5, 136.5, 139.3, 158.3; IR ($CHCl_3$) 2939, 1606, 1509, 1249, 1101 cm^{-1}; MS (EI) *m*/*z* 256 (M^+, 100); HRMS calcd for $C_{17}H_{20}O_2$ 256.1463, found 256.1453. Data for the *Z* isomer: pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, $J = 8.7$ Hz, 2 H), 6.75 (d, $J = 8.7$ Hz, 2 H), 6.12 (d, $J = 2.0$ Hz, 1 H), 5.59 (dd, appears as t, $J = 3.6$ Hz, 3.6 Hz, 1 H), 4.15−3.97 (m, 2 H), 3.77 (s, 3 H), 3.68−3.58 (m, 1 H), 2.61−2.49 (m, 1 H), 2.25−2.17 (m, 1 H), 2.12−1.50 (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.0, 25.6, 30.0, 38.7, 55.2, 68.4, 75.3, 113.4, 123.5, 127.4, 130.0, 130.3, 134.8, 137.0, 157.8; IR ($CHCl_3$) 2938, 1607, 1509, 1247, 1094 cm^{-1}; MS (EI) *m*/*z* 256 (M^+, 100); HRMS calcd for $C_{17}H_{20}O_2$ 256.1463, found 256.1464.

smoothly to give products **27**/**28** and **29**/**30** in 68% and 76% yields, respectively, Table 1.

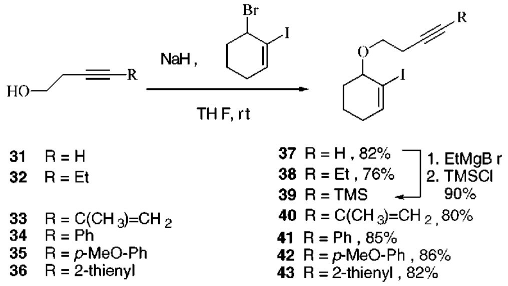
Encouraged by our success on *6-(π-exo)-exo-dig* mode of radical cyclization of **21** and **22**, we then examined more reactions as shown in Table 2. The required radical precursors were procured as outlined in Scheme 3. Treatment of acetylenic alcohols **31**−**36** with NaH in THF followed by reaction with 3-bromo-2-iodocyclohex-1-ene gave compounds **37**, **38**, **40**−**43** in 76−86% yield. Reaction of **37** with EtMgBr and TMSCl gave compound **39** in 90% yield.

Table 2. 6-(*π-Exo*)-*Exo-Dig* Cyclization of Alkenyl Radicals

Entry	Alkenyl Iodide	*Exo*-Cyclic Diene	Yield [a]
			
1	**37** R = H	**44** R = H	55%
2	**38** R = Et	**45** R = Et	65% (E : Z = 3 : 1) [b]
3	**39** R = TMS	**46** R = TMS	68% (E : Z = 1.8 : 1) [b]
4	 **40**	 **47**	71% (E : Z = 3 : 1) [b]
			
5	**41** R = Ph	**48** R = Ph	72% (E : Z = 9 : 1) [b]
6	**42** R = *p*-MeO-Ph	**49** R = *p*-MeO-Ph	82% (E : Z = 2.4 : 1) [b]
7	**43** R = 2-thienyl	**50** R = 2-thienyl	75% (E : Z = 1.6 : 1) [b]

[a] Isolated yield. [b] The structures of the *exo*-cyclic dienes were confirmed by NOE experiments, and the ratios of *E* and *Z* isomers were determined by ^{1}H NMR integration.

Scheme 3



When compounds **37**−**43** were treated with tributyltin hydride and AIBN, once again we found that *6-(π-exo)-exo-dig* radical cyclizations were facile, Table 2.[12] In entries 1−3, compounds **37**, **38**, and **39** underwent cyclization smoothly to give *exo*-cyclic dienes **44**, **45**, and **46** in good yield. It is noteworthy to mention that a similar cyclization in the case of acyclic substrate was reported as totally unsuccessful by Crich et al.[6] When the triple bond was substituted with a isopropenyl group or aromatic rings, entries 4−7, the yields of the *exo*-cyclic dienes **47**−**50** were improved, Table 2.

In conclusion, we have developed a new alkenyl radical cyclization methodology for the construction of *exo*-cyclic dienes fused to five- and six-membered rings. Contrary to the previous report,[6] we found that 6-(*π-exo*)-*exo-dig* cyclizations of alkenyl radicals are highly efficient. We believe that this methodology is potentially useful in the total synthesis of natural products.

Acknowledgment. We thank the National Science Council of the Republic of China for financial support (NSC88-2113-m-007-025).

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