## LETTERS 2000Vol. 2, No. 14 <u>2011–2013</u>

ORGANIC

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

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Received March 9, 2000

ABSTRACT



Radical cyclizations of alkenyl iodides in both 5- and 6-( $\pi$ -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.<sup>1</sup> They are also characteristic substructures of vitamin  $D_3$  and its derivatives,<sup>2</sup> e.g., 1, Scheme 1. Among various methodologies known for synthesis of exo-cyclic dienes, the palladium-catalyzed cyclization<sup>3</sup> of enynes 2 to *exo*-cyclic dienes 4 and anionic cyclization<sup>4</sup> 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-( $\pi$ -exo)-exo-dig radical cyclization

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10.1021/ol005785s CCC: \$19.00 © 2000 American Chemical Society Published on Web 06/16/2000



was facile. The corresponding  $6-(\pi-exo)-exo-dig$  cyclization was reported to be unfavorable.<sup>6</sup> To the best of our knowledge, there are only two cases of  $6-(\pi-exo)-exo-dig$ radical cyclization of poor yields reported in the literature.<sup>7</sup> As an extension of our study in radical cyclization reactions,<sup>8</sup> we have also investigated radical cyclizations of alkenyl iodides. Contrary to the previous reports, we found that not only 5-( $\pi$ -exo)-exo-dig but also 6-( $\pi$ -exo)-exo-dig radical

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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.<sup>9</sup> 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<sup>10</sup> gave  $\beta$ -iodo  $\alpha$ , $\beta$ -unsaturated esters 17–22, Scheme 2. Radical cyclizations



of  $\beta$ -iodo  $\alpha$ , $\beta$ -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.<sup>11</sup> In these 5-( $\pi$ -

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(11) For the first example of the  $\beta$ -iodo  $\alpha,\beta$ -unsaturated ester radical cyclization in 6-( $\pi$ -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<sub>3</sub>SnH (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<sub>2</sub>O (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 NaHCO3 solution and brine and dried (Na<sub>2</sub>SO<sub>4</sub>). Silica gel flash column chromatography (hexane–CH<sub>2</sub>Cl<sub>2</sub>, 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<sub>2</sub>Cl<sub>2</sub>, 1:1). Data for the *E* isomer: colorless crystals from hexane; mp 105–6 °C.; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) 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<sub>3</sub>) 2939, 1606, 1509, 1249, 1101 cm<sup>-1</sup>; MS (EI) m/z 256 (M<sup>+</sup>, 100); HRMS calcd for

*exo*)-*exo*-*dig* cyclizations, the *exo*-cyclic dienes obtained were all in *E*,*E* configuration, Table 1.





<sup>*a*</sup> Isolated yield. <sup>*b*</sup> The structures of the *exo*-cyclic dienes were confirmed by NOE experiments. <sup>*c*</sup> The ratios were determined by <sup>1</sup>H NMR integration.

We then attempted the  $6-(\pi-exo)-exo-dig$  radical cyclization with  $\beta$ -iodo  $\alpha,\beta$ -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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 $<sup>\</sup>rm C_{17}H_{20}O_2$  256.1463, found 256.1453. Data for the Z isomer: pale yellow oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  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); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>3</sub>) 2938, 1607, 1509, 1247, 1094 cm<sup>-1</sup>; MS (EI) m/z 256 (M<sup>+</sup>, 100); HRMS calcd for  $\rm C_{17}H_{20}O_2$  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  $6 - (\pi - exo) - exo - dig$  mode of radical cyclization of **21** and **22**, we then examined more reactions as shown in Table 2. The required radical precur-

Table	2.	6-( <i>π</i> - <i>Exo</i> )- <i>Exo</i> - <i>Di</i>	g Cyclization of	Alkenyl Radical
	Entr	y Alkenyl lodide	Exo-Cyclic Diene	Yield <sup>a</sup>
		O I R	O P R	
	1 2	37 R = H 38 R = Et	44 R=H 45 R=Et	55% 65% ( <i>E</i> : <i>Z</i> = 3 : 1) <sup>b</sup>
	3	39 R = TMS	46 R = TMS	68% ( <i>E</i> : <i>Z</i> =1.8:1) <sup>b</sup>
	4		Jan K	
			47	71% ( E:Z=3:1) <sup>b</sup>
	5	41 R = Ph	<b>48</b> R = Ph	72% ( <i>E</i> : <i>Z</i> = 9:1) <sup>b</sup>
	6	42 R = <i>p</i> -MeO-Ph	<b>49</b> R = <i>p</i> -MeO-Ph	82% ( <i>E</i> : <i>Z</i> = 2.4 : 1) <sup>b</sup>
	7	43 R = 2-thienyl	50 R = 2-thienyl	75% ( <i>E</i> : <i>Z</i> = 1.6 : 1) <sup>b</sup>

<sup>*a*</sup> Isolated yield. <sup>*b*</sup> The structures of the *exo*-cyclic dienes were confirmed by NOE experiments, and the ratios of *E* and *Z* isomers were determined by <sup>1</sup>H NMR integration.

sors 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.

When compounds **37–43** were treated with tributyltin hydride and AIBN, once again we found that  $6(\pi$ -exo)-exodig radical cyclizations were facile, Table 2.<sup>12</sup> 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.<sup>6</sup> 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,<sup>6</sup> we found that  $6-(\pi-exo)-exo-dig$  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).

OL005785S