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FREE RADICAL ANNULATION OF CYCLOPENTANE RING

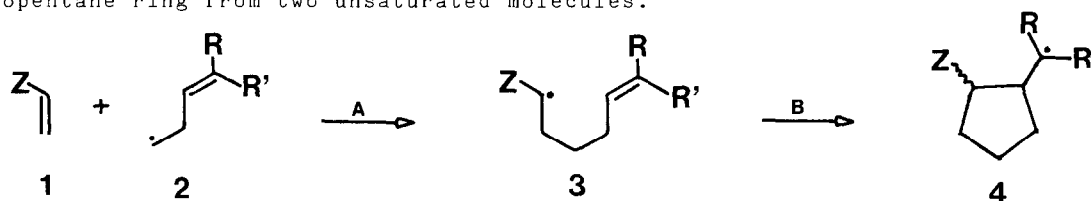
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**Abstract:** Homoallyl radical, e.g. 2, reacts with an electron-deficient olefinic bond 1 with a new C-C bond forming and arising of a 5-hexenyl radical 3 which further undergoes to 5-exo-trigonal cyclization with a cyclopentane ring (4) annulation.

Regioselective intermolecular addition of an alkyl radicals onto the electron-deficient olefinic bond become an useful reaction for carbon-carbon bond formation<sup>1</sup>. This general reaction is independent of the radical precursors and of the Michael acceptors. On the other hand intramolecular cyclization of 5-hexenyl radical to the cyclopentylmethyl radical is well known reaction for the construction of carbocyclic<sup>2-7</sup>, and heterocyclic rings<sup>8-10</sup>. This reaction is stereoelectronically controlled and also proceeds regardless of the alkenyl radical precursors<sup>3,8</sup>. Alkenyl radical cyclization has been systematically investigated and applied in the synthesis of variety cyclic and polycyclic organic molecules<sup>6,7,9</sup> and natural products<sup>10-12</sup>.

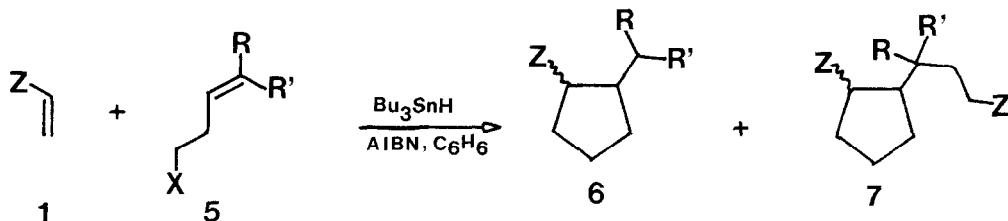
We conceived to connect Giese's intermolecular radical conjugated addition (step A, Scheme 1.) and Walling-Beckwith's intramolecular 5-hexenyl radical cyclization (step B) into one sequence of radical chain reactions, in order to close a cyclopentane ring from two unsaturated molecules.



Scheme 1.

We found that annulation of cyclopentane ring can be achieved by tri-*n*-butyltin hydride reduction of homoallyl halides 5 (X = I or Br) in an excess of electron-deficient olefinic compounds 1 (Z = CN, COOEt, COCH<sub>3</sub>, CHO) (Scheme 2.).

Annulation of cyclopentane ring by addition of homoallyl radical 2, as a three carbon block, onto the conjugated olefinic bond 1, as a radicophilic two carbon block, represent a two C-C bond forming reaction, i.e. 2 + 3 stepwise cycloaddition reaction. Cyclopentane ring annulation was observed in the  $\beta$ -acetylenic radical addition onto the conjugated olefinic bond<sup>13</sup>.



Scheme 2.

The cyclization reactions were generally performed by treating of homoallylic halides 5 (11 mmole) with tri-*n*-butyltin hydride (12 mmole), ten times excess of acrylonitrile or other electron-deficient olefinic compounds (120 mmole) and AIBN as an initiator in benzene or other solvent with refluxing in an inert atmosphere. Products were isolated<sup>14</sup> and separated by column (SiO<sub>2</sub>) or gas chromatography and characterized by ir, H nmr and mass spectra (Table 1).

Table 1. Annulation of cyclopentane ring. Products and their yields (%)

Exp.	Starting compounds				Products <sup>a</sup>		Method	Time hrs
	<u>1</u>	<u>5</u>	<u>5</u>	<u>5</u>	<u>6</u>	<u>7</u>		
	Z	R	R'	X				
i.	CN	Ph	Ph	I	23 <sup>b</sup>	-	c	48
ii.	CN	Ph	Ph	Br	16 (70) <sup>d</sup>	-	e, f	45 (30)
iii.	COOEt	Ph	Ph	I	25 (39) <sup>g</sup>	-	c	48
iv.	COOEt	Ph	Ph	Br	(45) <sup>g</sup>	-	e	48
v.	CN	Me	Ph	I <sup>h</sup>	52 <sup>l</sup> (67)	-	c, j	40 (12) <sup>i</sup>
vi.	CN	Me	Me	I	-	44 <sup>k</sup> (65) <sup>g</sup>	c	4
vii.	COOEt	Me	Me	I	-	38 <sup>l</sup> (75) <sup>g</sup>	f	3
viii.	COCH <sub>3</sub>	Me	Me	I	-	25 <sup>m</sup> (75) <sup>g</sup>	c	4
ix.	CHO	Me	Me	I	-	60 <sup>g, m</sup>	c	1.5
x.	CN	H	H	Br	-	30 (58) <sup>g</sup>	f	5

a. Isolated yields after column chromatograph.

b. Mixture of cis- and trans-isomers in ratio of 1 : 2.

c. 5 (Exp. i.) / Bu<sub>3</sub>SnH / 1 : 1 / 15 eq., AIBN, C<sub>6</sub>H<sub>6</sub>, reflux.

d. Yield calculated on the converted bromide 5 (Exp. ii.).

e. Toluene was used as a solvent.

f. 5 (Exp. ii.) 1 eq. / Bu<sub>3</sub>SnH 0.25 eq. / NaBH<sub>4</sub> 1.5 eq. / 10 eq. / t-BuOH<sup>12</sup>.

g. Gas chromatography yields.

h. Mixture of Z and E isomers was used.

i. Mixture containing trans-isomer and two cis-enantiomers was separated by gc, (10% OV-275 on Chromosorb) and has a ratio 2.8 : 1 : 1.5.

j. 5 (Exp. v.) / Bu<sub>3</sub>SnH / 1 : 1 / 12 eq., Et<sub>2</sub>O/hν / 25°C<sup>15</sup>.

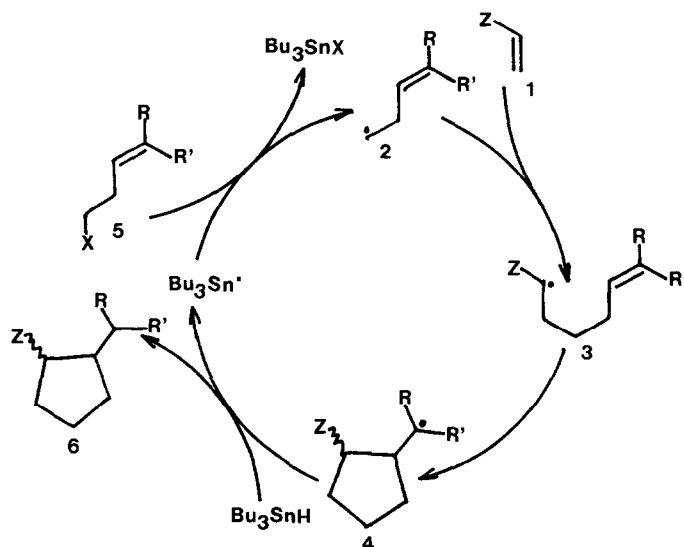
k. Mixture of two isomers in ratio of 2 : 1.

l. Ratio of two isomers is 0.7 : 1.

m. Ratio of isomers is 3 : 1.

For example, reaction of 4-phenyl-3-penten-1-yl iodide 5 (Exp. v.) with tri-*n*-butyltin hydride and acrylonitrile, under above conditions, afforded as a major product the mixture of cis- and trans-2-(1-phenylethyl)-cyclopentyl cyanide 6 (52%), together with the minor product 2-phenyl-2-pentene and starting iodide 5.

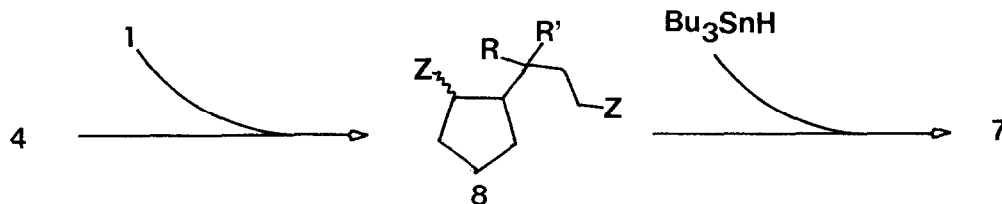
The first step in this chain cycloaddition reaction is production of a tri-*n*-butyltin radical, and in subsequent reaction with alkenyl halides 5 homoallyl radical 2 is generated. Although the homoallyl radical 2 may be in an equilibrium with cyclopropylmethyl radical<sup>16</sup>, intermolecular conjugated addition onto the electron-deficient olefinic bond 1 is predominant reaction when olefinic compounds were used in an excess (Scheme 3.). Only minor amount of buten derivatives (e.g. 5, X = H) as a reduction products (up to 8%), were detected. This C-C bond forming reaction generates an adduct radical 3 which is much less nucleophilic because of the presence of nitrile or other electron-withdrawing group. Possessing an appropriate



Scheme 3.

located olefinic bond (e.g. i  $\delta$ -position) radical 3 rather undergoes to the 5-exo-trigonal intramolecular addition to close a cyclopentane ring 4 than to the 5-endo-cyclization or hydrogen abstraction from organotin hydride, since cyclohexane derivative or unsaturated nitrile have not been detected in the reaction mixtures. The fate of cyclopentylmethyl radical 4 generated after ring closure reaction, i.e. second C-C bond formation, depends of the substituents on the radical centre and reaction conditions. More stable tertiary radicals 4 (R = R' = Ph and R = Ph, R' = Me, Expts. i - v) rather undergo to abstraction of hydrogen from tin hydride thus affording a saturated cyclopentane derivatives 6 than to addition reactions. However, when tertiary radicals are not benzylic, e.g. 4 (R = R' = Me, Expts. vi - ix) or is primary radical, e.g. 4 (R = R' = H, Exp. x) they rather undergo to the intermolecular addition onto the olefinic compounds 1 thus producing a new  $\alpha$ -substituted radical 8 (Scheme 4. Table 1.). Termination reaction for such a radical is hydrogen abstraction thus giving a difunctional cyclopentane derivative of type 7 as a final products of the three C-C bond formation proces<sup>17</sup>.

The other possibilities of free radical two steps cyclopentane ring annulation are in progress.



Scheme 4.

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