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 β-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. 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 carboxylic acid 2-7, and heterocyclic rings 8-10. This reaction is stereoelectronically controlled and also proceeds regardless of the alkenyl radical precursors 3, 8. Alkenyl radical cyclization has been systematically investigated and applied in the synthesis of variety cyclic and polycyclic organic molecules 6, 7, 9 and natural products 10-12.

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, COCH3, 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 β-acetylenic radical addition onto the conjugated olefinic bond 13.
Scheme 2.

The cyclization reactions were generally performed by treating of homochiral 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$^1$ and separated by column ($SiO_2$) or gas chromatography and characterized by IR, H NMR and mass spectra (Table 1).

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

<table>
<thead>
<tr>
<th>Exp.</th>
<th>Z</th>
<th>R</th>
<th>R'</th>
<th>X</th>
<th>Method</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.</td>
<td>CN</td>
<td>Ph</td>
<td>Ph</td>
<td>I</td>
<td></td>
<td>23$^b$</td>
</tr>
<tr>
<td>ii.</td>
<td>CN</td>
<td>Ph</td>
<td>Ph</td>
<td>Br</td>
<td></td>
<td>16 (70)$^d$</td>
</tr>
<tr>
<td>iii.</td>
<td>COOEt</td>
<td>Ph</td>
<td>Ph</td>
<td>I</td>
<td></td>
<td>25 (39)$^g$</td>
</tr>
<tr>
<td>iv.</td>
<td>COOEt</td>
<td>Ph</td>
<td>Ph</td>
<td>Br</td>
<td></td>
<td>(45)$^g$</td>
</tr>
<tr>
<td>v.</td>
<td>CN</td>
<td>Me</td>
<td>Ph</td>
<td>I</td>
<td></td>
<td>52$^h$ (67)</td>
</tr>
<tr>
<td>vi.</td>
<td>CN</td>
<td>Me</td>
<td>Me</td>
<td>I</td>
<td></td>
<td>44$^k$ (65)$^g$</td>
</tr>
<tr>
<td>vii.</td>
<td>COOEt</td>
<td>Me</td>
<td>Me</td>
<td>I</td>
<td></td>
<td>38$^l$ (75)$^k$</td>
</tr>
<tr>
<td>viii.</td>
<td>COCH$_3$</td>
<td>Me</td>
<td>Me</td>
<td>I</td>
<td></td>
<td>25$^m$ (75)$^g$</td>
</tr>
<tr>
<td>ix.</td>
<td>CHO</td>
<td>Me</td>
<td>Me</td>
<td>I</td>
<td></td>
<td>6$^{m', m}$</td>
</tr>
<tr>
<td>x.</td>
<td>CN</td>
<td>K</td>
<td>H</td>
<td>Br</td>
<td></td>
<td>30 (58)$^g$</td>
</tr>
</tbody>
</table>

a. Isolated yields after column chromatograph.
b. Mixture of cis- and trans-isomers in ratio of 1 : 2.
c. 5 (Exp. i.)/Bu$_3$SnH/1 /171/15 eq., AIBN, C$_6$H$_6$, 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$_3$SnH 0.25 eq./NaBH$_4$ 1.5 eq./1 10 eq./t-BuOH$^{12}$.
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.$^{15}$
j. 5 (Exp. v.)/Bu$_3$SnH/1 /1/12 eq., Et$_2$O/hv /25$^o$C$^16$.
k. Mixture of two isomers in ratio of 2 : 1.
I. 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 acrylonitrile 6 (52%), together with the minor by 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 a homoallyl radical is generated. Although the homoallyl radical may be in an equilibrium with cyclopropylmethyl radical, intermolecular conjugated addition onto the electron-deficient olefinic bond is predominant reaction when olefinic compounds were used in an excess (Scheme 3). Only minor amount of buten derivatives (e.g. X = H) as a reduction products (up to 8%), were detected. This C-C bond forming reaction generates an adduct radical which is much less nucleophilic because of the presence of nitrile or other electron-withdrawing group. Possessing an appropriate located olefinic bond (e.g. i-5-position) radical rather undergoes to the 5-exo-trigonal intramolecular addition to close a cyclopentane ring 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 cyclopropylmethyl radical generated after ring closure reaction, i.e. second C-C bond formation, depends on the substituents on the radical centre and reaction conditions. More stable tertiary radicals (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 than to addition reactions. However, when tertiary radicals are not benzylic, e.g. (R = R' = Me, Expts. vi - ix) or is primary radical, e.g. (R = H, R' = H, Exp. x) they rather undergo to the intermolecular addition onto the olefinic compounds thus producing a new α-substituted radical (Scheme 4, Table 1). Termination reaction for such a radical is hydrogen abstraction thus giving a difunctional cyclopentane derivative of type as a final products of the three C-C bond formation processes.

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


14 Tri-n-butyltin halides were separated from the reaction mixture by washing of an ethereal solution of reaction products with 10% aqueous potassium fluoride. Precipitated organotin fluoride was filtered off and organic layer worked up on the usual manner. J. E. Lettner and J. Jacobus, J. Org. Chem., 44, 449 (1979).


17. Radical 8 (R = R' = H) undergoes to further addition reaction onto 1 and several telomorphic compounds were detected.

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