A New Rare Example of Cyclopropanation in Free-Radical Chemistry

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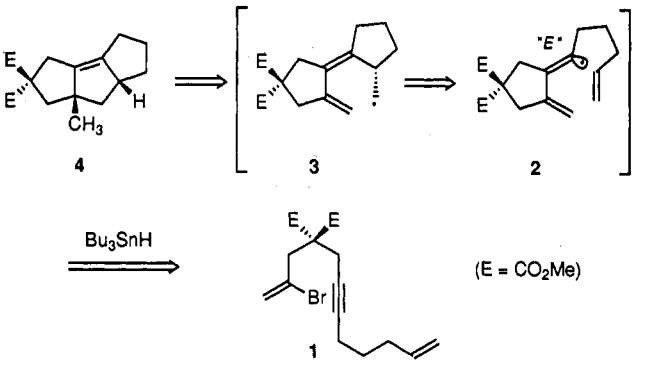
Summary: Cyclic homoallylic radicals add on diene moieties according to a 3-*exo-trig* mode cyclization. The thus-formed radical, existing in two canonical forms, provides bicyclo[3.1.0] and -[4.1.0] skeletons. The formation of the thermodynamically most stable double bond may account for the chemoselectivity of this [2 + 1] cycloaddition reaction.

Over the last 10 years, cascades of radical cyclizations have demonstrated their great efficiency for the construction of complex polycyclic molecules.[1] In connection with our efforts toward the development of methodology which will efficiently build elaborate polycyclic frameworks such as triquinanes, from acyclic polyunsaturated bromomethyl dimethylsilyl propargyl ethers,[2] we investigated a new strategy which could afford such tricyclic compounds from 1.

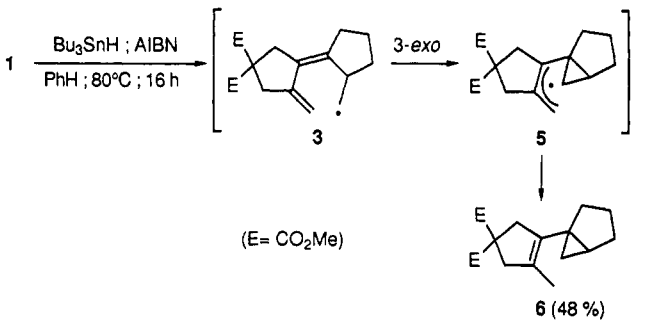
This one is based upon an initial favorable 5-(π-*exo*)-*exo-dig* cyclization[3] that would generate a rapidly inverting trisubstituted-alkyl σ vinyl radical **2** which is expected to react only in the *E* configuration as we have already observed[4] because of the allylic interaction for the *Z* isomer. Finally, the generated homoallylic radical **3** might give a 5-*exo-trig* mode cyclization leading to the linear triquinane framework **4** (Scheme 1). It is noteworthy that palladium-catalyzed polycyclization of similar dienynes has been already achieved.[5]

The acyclic precursor **1** was easily prepared by a convergent synthesis from dimethyl malonate and was treated by tributyltin hydride (1.2 equiv) with 0.1 equiv of AIBN in refluxing benzene (0.02 M) over a period of 16 h. In these conditions, the tricyclic product **6** was isolated in 48% yield (75% based on recovered starting material) and no 5-*exo-trig* radical process occurred. Indeed, the homoallylic radical **3** possesses different sites of attack and gave exclusively a 3-*exo-trig* mode cyclization generating **5** which exists in two canonical forms (Scheme 2). The hydrogen abstraction of the allylic primary radical was faster than the rearrangement[6] or the reduction of the tertiary α-cyclopropyl radical. The rate for the ring

Scheme 1



Scheme 2



opening of cyclopropylcarbinyl radical is well documented,[7] and only a few examples of isolated cyclopropane derivatives in free-radical chemistry have been reported.[2b,8] Very recently, Luh et al. have observed the same chemoselectivity as ours.[9] The formation of the vinylcyclopropane derivatives *versus* rearranged products was due to the hydrogen abstraction of the most stable radical where the presence of a silyl group was indispensable. In our case, whereas a primary radical is less stable than a tertiary one, the driving force for the cyclopropanation was the difference in thermodynamic stability of the disubstituted exocyclic double bond and the tetrasubstituted endocyclic one. This may account for the fact that no rearranged product was observed.

Then, we investigated this reaction with compound **7** where the introduction of a carbonyl group was necessary to avoid an eventual but probable 1,5-hydrogen atom transfer from the trisubstituted vinyl radical.[10] Contrary to Luh, who did not observe the formation of the bicyclo-[4.1.0] skeleton, the cyclization of **7** (under the same

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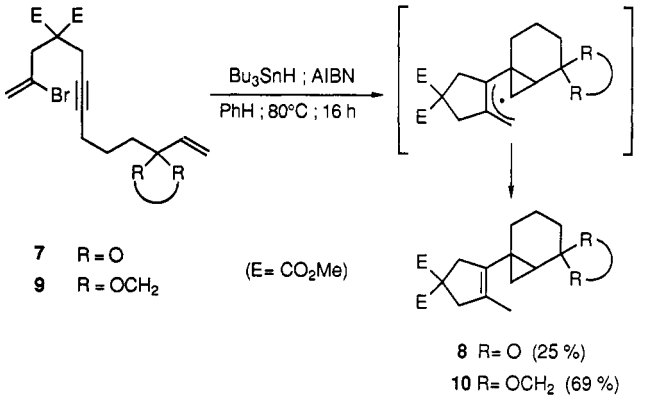
Scheme 3

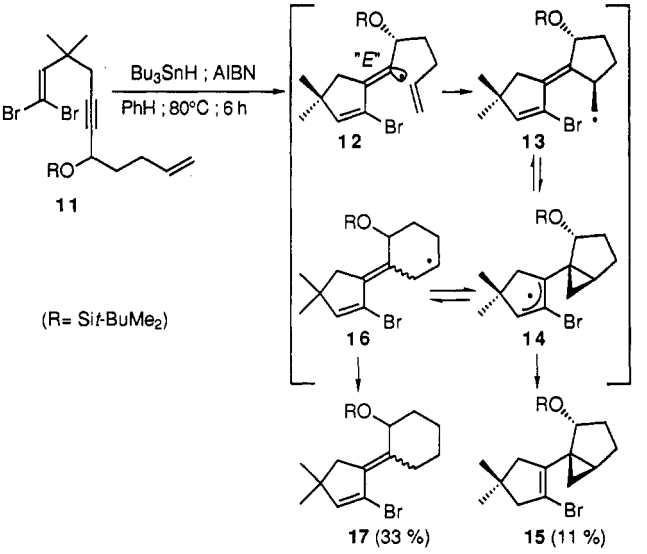


conditions as described before) afforded the vinylcyclopropane derivative **8** in 25% isolated yield with total regio- and chemoselectivity. The modest yield was due to a competing addition of the stannyl radical on the very reactive enone.

In order to suppress this intermolecular addition, **7** was ketalized. In these conditions, the radical cyclization of **9** proceeded very cleanly to furnish **10** in 69% overall isolated yield (92% based on recovered starting material) with the same regio- and chemoselectivity (Scheme 3). Therefore, the structural rigidity of the five-membered ring **3** does not seem to be the determining factor for the [2 + 1] cycloaddition reaction.

Finally, in order to confirm that the cyclopropanation was depending on the thermodynamic stability of the resulting double bond, we cyclized[11] the dibromoolefin **11**. Indeed, the difference between the two canonical forms **14** is a tri- and a tetrasubstituted endocyclic double bond (Scheme 4).

Scheme 4



Thus, the rearrangement of the tertiary α-cyclopropyl radical became the major process (33%) and the diene derivative **17** was isolated in a 7:3 mixture of *E* and *Z* stereoisomers. The difference of stability between a tri- and a tetrasubstituted double bond was not sufficient to provide exclusively a [2 + 1] cycloaddition reaction as observed before. Therefore, the vinylcyclopropane derivative **15** was isolated only in 11% yield as a single diastereoisomer.[12]

In conclusion, these preliminary results may well lead to a general method for cyclopropanation in free-radical chemistry. Depending on the degree of substitution on the diene moiety, we believe that acyclic homoallylic radicals, having the *E* configuration, might lead to various vinylcyclopropane derivatives. Further investigations are under progress in our laboratory.

Supplementary Material Available: ^{1}H and ^{13}C-NMR spectra for **1**, **6–11**, **15**, and **17** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(11) The cyclization of **11** was performed under the same conditions as described for compound **1**. In a typical procedure, a solution of **11** (1.0 mmol) containing Bu_3SnH (1.2 mmol) and AIBN (10 mol %) was refluxed in benzene (50 mL) over a period of 6 h. The solution was evaporated in vacuo to give a yellow oil which was chromatographed on silica (pentane as eluent). The same results were observed when Bu_3SnH was added slowly with a syringe pump. It is noteworthy that the dibromoolefin **11** seems to be very reactive with Bu_3SnH because compounds **15** and **17** were not debrominated in these conditions.

(12) The cyclization of the trisubstituted vinyl radical **12** was totally diastereoselective to give the *anti* isomer **13** because of a 1,3-diaxial interaction for the *syn* isomer. The same stereoselectivity was observed by Luh (ref 9).