RADICAL CYCLIZATION REACTIONS. CYCLOPROpane RING FORMATION BY 3-EXO-CYCLIZATION OF 5-PHENYLTHIO-3-PENTENYL RADICALS

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Abstract: Free radical cyclopropane ring closure was accomplished by thermal decomposition of thiohydroxamic esters of 6-phenylthio-4-hexencic acids. When the reaction was performed in the presence of acrylonitrile, an addition/cyclization/elimination process took place and the corresponding cyclopentancarbonitriles were obtained.

Free radical formation of cyclopropane ring was rather considered as a 3-butenyl/cyclopropylcarbinyl radical interconversion than as a method for the construction of a three membered carbocyclic ring. Cyclopropylcarbinyl radicals were observed as intermediates in 1,2-group migration and are usually in equilibrium with 3-butenyl type radicals. Cyclopropane derivatives were only prepared, under homolytic conditions, by a free radical displacement in 3-butenylcobaloximes by halomethyl radicals.

We assumed that 3-exo-cyclization of 3-pentenyl radicals 1 to the cyclopropane derivatives 3 could be achieved by an efficient quenching of the cyclopropylcarbinyl radicals 2. In order to favour 3-exo-cyclization (k_c = 0.8-1.3 x 10^4 sec^-1 at 25°C) and suppress reversible opening of the cyclopropylcarbinyl radical 2 (k_f = 1.3 x 10^8 sec^-1 at 25°C), it was necessary to find a reaction for quenching radicals 2 having a rate constant higher than ring opening (k_q > k_f). Since it was estimated that the rate of elimination of the phenylthio group (k_e) adjacent to a radical center would be higher than > 1.6 x 10^7 sec^-1 at 25°C, we wanted to check if this elimination could be a good propagation step in the radical chain reaction and afford cyclopropane 3 as final reaction product.

Free radical cyclopropane ring formation was accomplished when 3-pentenyl type radicals 2 possessed a phenylthio group, as a good radical lea-
ving group, in the 5-position. Thus, by thermal decomposition of thiohydro-
amic esters of 6-phenylthio-4-hexenoic acids 4, in boiling toluene soluti-
on, 2-vinylcyclopropane derivatives 5 were obtained in 43 -60% yields (Method A, Scheme 1.)\(^\text{13}\). On the other hand, 3-pentenyl type radicals \(^2\) could
be intercepted, before cyclopropane ring closure, by an intermolecular add-
tion to the radicophilic olefins, thus generating 5-heptenyl type radicals.\(^\text{14}\)
By decomposition of esters \(^4\) under the same experimental conditions as in
Method A, but in the presence of a five-fold excess of acrylonitrile, cyclo-
pentaneacetonitriles \(^6\) were obtained in 50 - 65% yields (Method B) (see
Scheme 1. and Table 1.).\(^\text{15}\)

By performing the decomposition of esters \(^4\) without electron deficient
olefins the intermediary 5-phenylthio-3-pentenyl radicals \(^8\) (Scheme 2.) un-
derwent intramolecular 3-exo-cyclization with concomitant expulsion of the

**Table 1. Decomposition of thiohydroxamic esters of 6-phenylthio-4-hexenoic
acids 4.**

<table>
<thead>
<tr>
<th>Starting esters(^a)</th>
<th>R</th>
<th>(R')</th>
<th>Method</th>
<th>Products</th>
<th>Isolated(^b) and GC(^c) yields in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(4a)</td>
<td>PhCH(_2)</td>
<td>H</td>
<td>A</td>
<td>5(a)</td>
<td>32 (47)</td>
</tr>
<tr>
<td>(4a)</td>
<td>PhCH(_2)</td>
<td>H</td>
<td>B</td>
<td>6(a)</td>
<td>33 (50)(^d)</td>
</tr>
<tr>
<td>(4b)</td>
<td>PhCH(_2)</td>
<td>CH(_3)</td>
<td>A</td>
<td>5(b)</td>
<td>25 (43)</td>
</tr>
<tr>
<td>(4b)</td>
<td>PhCH(_2)</td>
<td>CH(_3)</td>
<td>B</td>
<td>6(b)</td>
<td>40 (52)</td>
</tr>
<tr>
<td>(4c)</td>
<td>n-C(_{10})(_21)</td>
<td>H</td>
<td>A</td>
<td>5(c)</td>
<td>30 (60)</td>
</tr>
<tr>
<td>(4c)</td>
<td>n-C(_{10})(_21)</td>
<td>H</td>
<td>B</td>
<td>6(c)</td>
<td>32 (63)</td>
</tr>
</tbody>
</table>

Method A: Thermal decomposition of \(4\) in refluxing toluene.
Method B: Thermal decomposition of \(4\) in refluxing toluene in the presence of excess of
acrylonitrile.
\(a\) Prepared according to the Barton procedure (ref. 16).
\(b\) Reaction products were isolated on silica gel column, using petroleumether/acetone
99 : 1 as eluent and characterized by IR, NMR and mass spectra.
\(c\) Yields of reaction products were also determined by GC.
\(d\) Taken from reference 17.
phenylthio radical, thus forming a cyclopropane ring 5. The yields of cyclo-
propane derivatives 5 did not change appreciably whether primary, secondary
or tertiary 5-phenylthio-3-pentenyl radicals 8 were involved as intermedia-
tes, thus indicating that the intramolecular reaction leading to the cyclo-
propane ring does not depend on the nucleophilicity of the radical species,
but depends on the appropriate conformation of the intermediary radicals 8,
and is supported by the presence of the phenylthio group in the allylic po-

cification (Scheme 2).

Since the rate of 3-exo-cyclization (k_c) of 3-pentenyl type radi-
cals 8 is much lower than the rate of ring opening (k_f) of the cyclicpropyl-
carbiny1 radicals 9, we believe that the competing reversible reaction could
take place before expulsion of the phenylthio radical, and that for this
reasons the yields of cyclopropane derivatives 5 were not high. Newcomb's
results on the 4-exo-cyclizations of 2,2-dimethyl-5-cyano-4-pentenyl radi-
cals, which appeared during the preparation of the present paper, support
our findings concerning the 3-exo-cyclizations. 18

In addition to the radical 3-exo-cyclizations, 2-vinylcyclopropane de-
rivatives were obtained from similar precursors, involving an intramolecu-
lar addition of carbanion intermediates and concerted elimination of a lea-
ving group. 19

However, the intramolecular addition reaction of radicals 8, leading to
the vinylcyclopropanes 5, was completely suppressed when the reactions were
performed in the presence of excess of acrylonitrile (Method B). By using a
five-fold of excess of the radiophile olefins, the rate of intermolecular
addition of 5-phenylthio-3-pentenyl radicals 8 to these olefins was higher
than the rate of 3-exo-cyclization, and therefore the formation of 5-hepten-
yl type radicals 10 by intermolecular addition to the radiophile olefins
and their subsequent cyclization to 2-vinylcyclopentanecarbonitriles 6 was described in our previous paper. By decomposition of esters 4, according to Method B, in addition to vinylcyclopentanecarbonitrile 6a, 2-vinylcyclopropane derivatives 5a were obtained in 3% yield.

REFERENCES

13. Typical experimental procedure. Method A. Thiohydroxamic esters 4 were prepared in situ without isolation (ref. 16.). To the mixture of 0.87 g (5.9 mM) of N-hydroxy-4-methylthiazole-2(3H)-thione, 0.062 g (0.3 mM) of dimethylaminopyridine and 0.47 g (6 mM) of pyridine in ether (30 ml), a solution of acyl chloride (5.7 mM) was slowly added. When the reaction was completed (1 h), the solvent was removed and the esters were used without purification. The oily residue containing ester 4 (about 5.6 mM) was dissolved in toluene (20 ml) and added dropwise to stirred refluxing toluene (30 ml), in an inert atmosphere. After the addition was completed, the reaction mixture was heated to reflux for 45 min. The solvent was then removed under reduced pressure and the crude reaction products were purified by chromatography on silica gel column (petroleumether/acetone 99 : 1). 2-Benzylvinylcyclopropane 5a was isolated (0.29 g, 32% yield) as a colorless oil. IR (neat): 3060, 1306, 2920, 2840, 1640, 1605, 1495, 1480, 1465, 1400, 1430, 740, 700 cm⁻¹. ¹H-NMR (氘): 0.50-0.70 (m, 2H), 0.75-1.50 (m, 2H), 2.50-2.65 (m, 2H), 4.70-5.60 (m, 3H), 7.20 (s, 5H). MS: 158 (M⁺) 143, 129, 115, 104, 91 (100%), 79, 65, 51.

Method B. Reaction of thiohydroxamic esters 4 with a five molar excess of acrylonitrile in toluene solution, were performed under the same experimental conditions as applied in Method A. See also references 14 and 17.


(Received in UK 29 August 1990)