

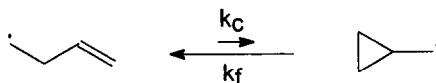
## Free Radical Mediated Construction of Small Ring Compounds: the Double Annulation of Bicyclo[3.1.0]hex-2-enes

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**Abstract:** A free radical approach to fused cyclopropane derivatives is described. Homolytic decomposition of thiohydroxamic esters **4a-e** in the presence of dimethyl acetylenedicarboxylate affords bicyclo[3.1.0]hex-2-enes **6a-e** in moderate yields. © 1997 Elsevier Science Ltd.

Free radical reactions have found widespread application in the synthesis of 5-, 6-membered rings, and macrocycles.<sup>1</sup> However, small ring compounds are not considered as suitable synthetic targets for the application of radical cyclization methodology. The strain associated with cyclopropane ring formation lowers the rate of 3-*exo*-cyclization ( $k_c \sim 10^4 \text{ s}^{-1}$ ),<sup>2</sup> and accelerates 3-*exo*-fragmentation ( $k_f \sim 10^8 \text{ s}^{-1}$ )<sup>3</sup> thus shifting the equilibrium between the reaction intermediates strongly in favour of butenyl radical (Scheme 1). Rare examples of cyclopropane formation by 3-*exo*-cyclization are restricted to geometrically constrained butenyl radicals possessing strongly activated double bonds, and giving rise to highly stabilized cyclic intermediates.<sup>4</sup>

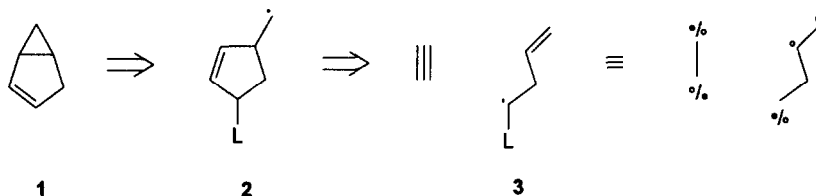


Scheme 1

Some time ago we reported a more general free radical approach to cyclopropanes, relying on the 3-*exo*-cyclization/ $\beta$ -elimination reaction sequence, where the efficient quenching of cyclopropylcarbinyl intermediate was effected by a fast elimination of a suitably positioned radical good leaving group.<sup>5</sup> Recently, a related approach was used in the synthesis of fused cyclopropane derivatives.<sup>6</sup>

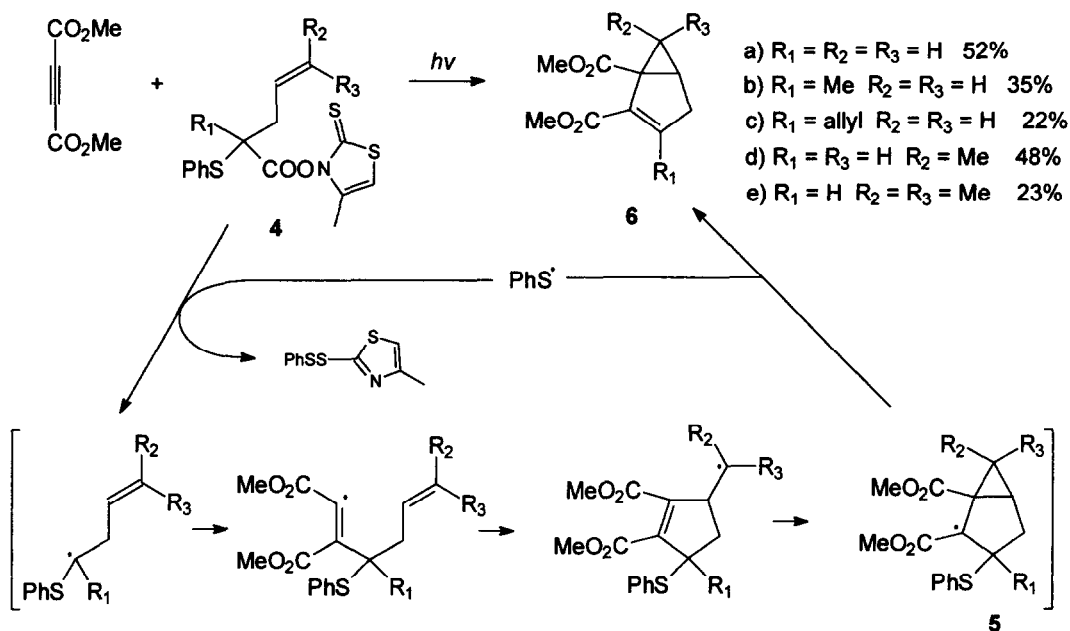
We now wish to report an extension of this method, based on the combination of the aforementioned 3-*exo*-cyclization/ $\beta$ -elimination cascade with free radical annulation procedure,<sup>7</sup> which allows the construction of bicyclo[3.1.0]hex-2-ene derivatives in a single sequential radical reaction, from two acyclic molecules. The

retrosynthetic analysis of the target structure **1**, outlined in Scheme 2, relies on 3-*exo*-cyclization/ $\beta$ -elimination sequential reaction of cyclopentenylmethyl radical **2**, which in turn could be created by an addition/cyclization reaction of a suitably substituted 3-butenyl radical **3** with an acetylene acceptor.



Scheme 2

For the generation of radicals we chose the Barton method. From the known parent acid,<sup>8</sup> the thiohydroxamic ester **4a** was prepared *via* the corresponding acid chloride. When **4a** was submitted to the photolytic conditions in the presence of 10-fold excess of dimethyl acetylenedicarboxylate, the expected bicyclic compound **6a** was obtained in 52% isolated yield (Scheme 3). Substituted precursors **4b-e** behaved similarly, affording in all cases cyclopropane derivatives **6b-e**.<sup>9</sup>



Scheme 3

The reaction proceeds through bicyclic intermediate **5**, which was earlier indicated as a reactive species that might be responsible for cyclohexene formation in alkenylvinyl radical cyclization.<sup>10</sup> While the intermediacy of a fused bicyclic intermediate in the cyclization of related 1,6-heptadien-2-yl radical was well established on the basis of kinetic data,<sup>10</sup> the mechanism of cyclohexene formation (6-*endo*-cyclization vs. cyclopropylcarbinyl rearrangement) in 1,5-hexadien-1-yl radical cyclization remained uncertain.<sup>10a</sup> Our findings provide the first direct experimental evidence for the intermediacy of *endo* bicyclic cyclopropylcarbinyl radicals of type **5**, by their efficient quenching to the corresponding unsaturated products.

Schematic representation of the reactants (Scheme 2),<sup>11</sup> reveals that 5 of 6 carbon atoms that form the skeleton of the target structure are involved in the reaction as temporary reactive centers, 3 of them having a "double role", *i.e.* acting as radical donors, and acceptors as well, depending on the step of the propagation sequence.<sup>12</sup> This allows for a relatively complex structural transformation to be accomplished starting from simple precursors with a small number of carbon atoms, and more generally, illustrates the potential of free radical reactions as *mechanistic transforms*, according to the recently established terminology.<sup>13</sup>

*Acknowledgements:* The authors acknowledge the contribution of Saša Stanković, who performed the first experiment in the series.

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- Yields given in Scheme 3 are the unoptimized yields of isolated products. Spectral data (<sup>1</sup>H, <sup>13</sup>C, IR and MS) for compounds **6a-e** are fully consistent with proposed structures. Compound **6d** was obtained as a 1 : 3.25 mixture of *cis/trans* isomers. A typical experimental procedure is as follows: The solution of **4a** (134 mg; 0.4 mmol), and *freshly distilled* dimethyl acetylenedicarboxylate (570 mg; 4 mmol) in

benzene (80 ml) was irradiated for 10 min. with a 250 W high pressure mercury lamp, while a stream of argon was continuously bubbled through the solution. Evaporation of the solvent *in vacuo* followed by column chromatography (SiO<sub>2</sub>, 2.5% ethyl acetate in benzene) afforded 41 mg (52%) of **6a** as a colourless oil.

<sup>1</sup>H NMR (δ in ppm): 6.448-6.417 (*m*, 1H); 3.773 (*s*, 3H); 3.691 (*s*, 3H); 2.863 (*ddd*, 1H, J<sub>1</sub> = 2.2 Hz, J<sub>2</sub> = 6.77 Hz, J<sub>3</sub> = 19.59 Hz); 2.497 (*dd*, 1H, J<sub>1</sub> = 2.1 Hz, J<sub>2</sub> = 19.59 Hz); 2.122-2.227 (*m*, 1H); 1.942 (*dd*, 1H, J<sub>1</sub> = 4.21 Hz, J<sub>2</sub> = 8.42 Hz); 0.704 (*app.t*, 1H J = 4.76 Hz)

<sup>13</sup>C: 171.896, 164.452, 141.459 (CH), 138.160 (C), 51.939 (CH<sub>3</sub>), 51.640 (CH<sub>3</sub>), 36.314 (C), 35.217 (CH<sub>2</sub>), 28.583 (CH), 22.860 (CH<sub>2</sub>)

IR<sub>film</sub> (ν<sub>max</sub>): 3059, 2952, 2854, 1739, 1667, 1395, 1336, 1201, 1166 cm<sup>-1</sup>.

MS: 196 (M<sup>+</sup>), 165, 164, 137, 105

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