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Ethoxycarbonyl Acceleration of Cyclopropylcarbinyl Radical Ring Opening

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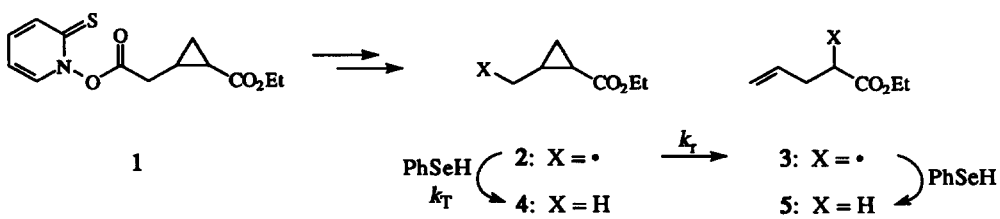
Abstract: Rate constants for ring opening of the [*trans*-(2-ethoxycarbonyl)cyclopropyl]methyl radical were determined by competition kinetics employing benzeneselenol trapping.

Mechanistic studies aimed at uncovering a radical intermediate in a reaction sequence often employ mechanistic probes, substrates that can give a radical that suffers a characteristic skeletal rearrangement. In cases where a putative radical intermediate could be trapped in a first order process such as in oxidation reactions catalyzed by enzymes, very fast radical rearrangements are required for such studies. The cyclopropylcarbinyl radical ring opening is the archetypal fast radical rearrangement with a rate constant[1,2] at 25 °C of 1×10^8 s^{-1}. Polymethyl-substituted cyclopropylcarbinyl radicals rearrange faster than this,[1,3] and rearrangements of phenyl-substituted cyclopropylcarbinyl radicals are accelerated by more than three orders of magnitude over that of the parent system.[1,4] Beckwith and Bowry reported that, as expected, ethoxycarbonyl substitution also accelerated the cyclopropylcarbinyl radical ring opening (i.e. **2** → **3**), but only a limit of $k > 5 \times 10^{10}$ s^{-1} at 60 °C for ring opening was available from their competitive nitroxyl radical coupling studies.[5] We now report rate constants for ring opening of *trans*-**2** determined by competitive trapping with benzeneselenol.

Scheme 1



The method involved a kinetic adaptation[1,2,4] of Barton's PTOC ester chemistry[6] (Scheme 1). Precursor 1[7a] was prepared[6] from the corresponding carboxylic acid;[5] from NMR spectroscopy, precursor 1 was a 33:67 mixture of *cis* and *trans* isomers. Reaction of 1 in radical chain reactions conducted in the presence of PhSeH gave mainly ethyl 4-pentenoate[7] (**5**) and traces of ethyl *trans*-2-methylcyclopropanecarboxylate[7] (*trans*-**4**). No ethyl *cis*-2-methylcyclopropanecarboxylate (*cis*-**4**) was detected by GC although incomplete GC resolution of *cis*- and *trans*-**4** would have precluded detection of *cis*-**4** at levels 10-20% those of *trans*-**4**.

Reactions of **1** were conducted at 25 °C (5 runs), –23 °C (2 runs) and –42 °C (5 runs) in THF with PhSeH concentrations ranging from 0.2 to 1.7 M.[8] These gave a relative Arrhenius function for rearrangement of *trans*-**2** of $\log (k_r/k_T \times M) = 2.8(3) - 1.7(3)/2.3RT$ where the errors in parentheses are 2σ for the last significant figure. If one assumes that the rate constants for PhSeH trapping of *trans*-**2** and of the cyclopropylcarbinyl radical are equal,[4] then addition of the appropriate Arrhenius function for k_T in THF[4b] to the relative Arrhenius function gives $\log (k_r \times s) = 13.8 - 4.0/2.3RT$. The log *A* term is somewhat larger than the expected[3] value of 12.8 for cyclopropylcarbinyl radical openings, but it is similar to those found for ring openings of (2-phenylcyclopropyl)methyl radicals.[4c] The rate constant for ring opening of *trans*-**2** at 25 °C is 8×10^{10} s^{-1} which is nearly as great as that of the phenyl analog; (*trans*-2-phenylcyclopropyl)methyl radical has a rate constant for ring opening at 25 °C of 3×10^{11} s^{-1}.[4c]

The calculated rate constant for ring opening of *trans*-**2** at 60 °C is 1.6×10^{11} s^{-1}, about three times greater than the lower limit set by Beckwith and Bowry,[5] and the rate constant for ring opening of *cis*-**2** will be greater than this. Thus, it is not surprising that only ring opened products were observed[5] in trapping studies employing the nitroxyl radical 2,2,5,5-tetramethylisoindole-*N*-oxyl (TMIO). From the rate constants for TMIO trapping of alkyl radicals,[1,5] one calculates that only about 1% of radical **2** would be trapped at a TMIO concentration of 1 M. Because the products of TMIO trapping were analyzed by HPLC with UV detection, the low yield of trapped product might easily be undetectable.

The Beckwith and Bowry study demonstrated that radical **2** opened rapidly and was potentially useful for mechanistic probe studies. The calibration of the ring opening now available will permit the use of this reaction as a radical clock in studies of very fast radical trapping reactions such as those involving oxidations by iron-containing enzymes.

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References and Notes

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7. (a) Characterized by ^1H NMR spectroscopy. (b) Identified by GC and GC-mass spectral comparison to an authentic sample.
8. The method has been described.[1,2,4] Crude product mixtures were analyzed by GC using predetermined response factors. The yields of (**4** + **5**) were 75-88%. Ratios of **5** (from *trans*-**2**) to *trans*-**4** were 9:1 to 91:1.

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