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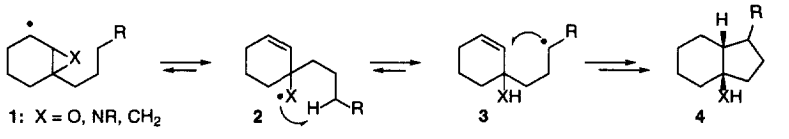
Radical Induced Cyclopropane Fragmentation—H-Abstraction—Cyclization Cascade: Synthesis of Carbocyclic Systems Containing Bridgehead Methyl Groups

Gilles Chambournier, Venkat Krishnamurthy, Viresh H. Rawal*[1]
Department of Chemistry, The Ohio State University, Columbus, OH 43210

Abstract: The intramolecular hydrogen abstraction by an alkyl radical has been exploited for the first time in a synthetically useful tandem sequence that gives rise to cis-fused bicyclic systems carrying bridgehead methyl groups, a structural feature found in numerous natural products. © 1997 Elsevier Science Ltd.

The various reactions of organic radicals when properly choreographed allow the development of useful methods for the synthesis of complex molecules.[2,3] For example, we have harnessed the exceptionally fast rearrangement of oxiranylcarbinyl radicals by incorporating this process in systems that allow a cascade of other radical reactions to follow (Scheme 1, X=O).[4] The success of this methodology with epoxides prompted us to investigate analogous fragmentation–H-abstraction–cyclization sequences of aziridines and cyclopropanes. The latter process was especially of interest as it would yield a cis-fused carbocycle containing an angular methyl group, a structural motif found frequently in biologically important natural products. We report here the first tandem sequence involving a radical-induced cyclopropane fragmentation followed by a 1,5-hydrogen transfer and cyclization.

Scheme 1

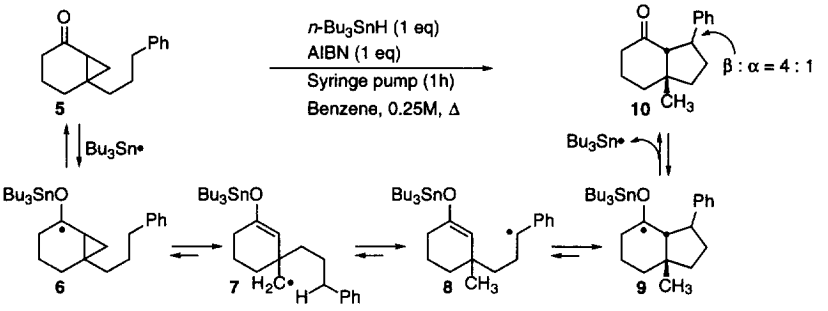


The main challenge in realizing this strategy using the cyclopropylcarbinyl radical rearrangement was the efficient promotion of the intramolecular 1,5-hydrogen translocation step (**2**→**3**, X=CH_2). While the reduction or cyclization of a carbon-centered radical generated by the fragmentation of a cyclopropane is well precedented,[2,3,5] there appear to be no reports where this radical has abstracted a hydrogen in an intramolecular fashion. The vast majority of 1,5-hydrogen transfers are to either oxygen or nitrogen radicals, frequently as part of the Barton or Hofmann-Loffler-Freytag reactions, respectively. Among carbon-centered radicals, hydrogen abstractions from aliphatic positions are generally by vinyl or aryl radicals,[6] processes that are strongly exothermic. Hydrogen abstractions by alkyl radicals, on the other hand, are weakly exothermic and hence are too slow to be synthetically useful.[7,8] Literature precedents suggested that intermolecular hydrogen abstraction from a hydrogen source such as tin hydride would be a serious competing reaction to the 1,5-hydrogen transfer.

Of the several possible options for triggering the cyclopropylcarbinyl radical rearrangement,[4] we chose the reversible addition of Bu_3Sn• radicals to a cyclopropyl ketone (Scheme 2).[4e,5] The initial studies were conducted on the readily available cyclopropyl ketone **5**, in which the 1,5-hydrogen transfer (**7**→**8**) was expected to be facilitated by the presence of the phenyl ring. Upon exposure to a source of Bu_3Sn•, ketone **5**

underwent the expected rearrangement to yield the desired bicyclic system (**10**) along with a substantial amount of unreacted starting material. A low concentration of tin hydride was maintained so as to minimize the intermolecular reduction of the methylene radical (**7**). The mechanism indicated for this process suggests that the transformation could be performed using a catalytic amount of $Bu_3Sn\bullet$. In practice, the reaction progressed sluggishly with truly catalytic amounts of tin. The transformation was best accomplished with full equivalents of the Bu_3SnH and AIBN, both added slowly via separate syringes to a 0.25M solution of the cyclopropyl ketone in refluxing benzene. Under these conditions bicycle **10** was obtained in 26% yield (42% based on recovered starting material).

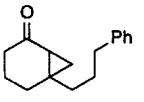
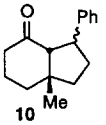
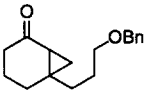
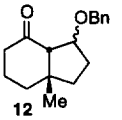
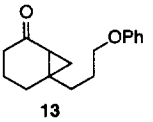
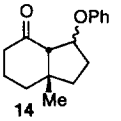
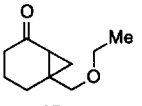
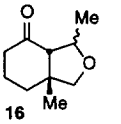
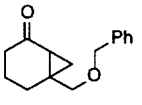
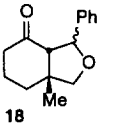
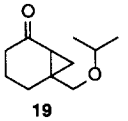
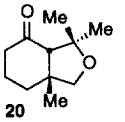
Scheme 2



The low yield for the above example may be a consequence of competing reduction resulting from slow hydrogen abstraction (**7**→**8**) and/or slow cyclization of the benzylic radical (**8**→**9**). The two issues are intimately related, so that improvement in one aspect was expected to adversely affect the other. The hydrogen abstraction step could be speeded up using side-chains that are better hydrogen donors (i.e., have weaker C-H bonds), such as those having a heteroatom attached to the hydrogen donating carbon. Previous work from this and other labs had suggested that the intermediate heteroatom-substituted radicals would undergo the cyclization step.[2b,10] In order to address this issue, we prepared several substrates having an oxygen atom attached to the radical bearing carbon and examined their reactivity in the tandem sequence.

Some interesting observations can be made from the efficiency of the fragmentation-cyclization of different oxygen substituted substrates (Table 1).[9] Substitution of the phenyl group with an OR group had no noticeable effect on the yield of the tandem sequence (entries 2 and 3). As with the phenyl group, the oxygen substituent is expected to weaken the C-H bond and promote the hydrogen abstraction. However, stabilization of the resulting radical through conjugation with the oxygen lone pairs is expected to slow the rate of the cyclization step. Note that for substrates in which the oxygen substituent was endocyclic to the five-membered ring (entries 4-6) the yield of the cyclized product was measurably higher than when the oxygen was exocyclic (entries 2 and 3). Assuming the rate of the hydrogen abstraction is comparable for similar oxygen substituted substrates (*Cf.* entries 2 and 4), then the difference in yields may reflect a difference in the efficiency of the cyclization step. The radical intermediates from substrates **15**, **17**, and **19**, which can be considered 2-oxahex-5-enyl radicals, are expected to benefit from (a) the smaller C–O–C bond angle (106.8° vs. 109.5° for C–C–C), a lone-pair version of the gem-dimethyl effect, and (b) the shorter C–O bond length (1.41 Å vs. 1.52 Å for C–C).[10,11] Substrate **19** gave the highest yield of the cyclized product, despite having only one abstractable hydrogen available for a 1,5-hydrogen transfer. The main side-product in all of these reactions was the cyclopropane-fragmented starting material, arising from reduction of intermediates such as **7** or **8**.

Table I. Cyclopropane Fragmentation – H-Transfer – Cyclization Reactions

Entry[a]	Substrate	Product	% Yield[b]	Ratio (β:α)
1	 5	 10	26 (42)[c]	4 : 1
2	 11	 12	26 (44)[c]	1 : 1
3	 13	 14	26 (56)[c]	3 : 1
4	 15	 16	46 (68)[c]	1 : 8
5	 17	 18	73	1 : 1
6	 19	 20	83	

[a]General reaction conditions: A solution of the cyclopropane in benzene at reflux was treated with Bu_3SnH and AIBN (0.1 M each in benzene), added via syringe pump over 6-10h. [b]Ratios and stereochemical assignments determined by ^1H NMR. [c]Yield based on recovered starting material.

The tandem fragmentation–H-translocation–cyclization sequence described here constitutes the first synthetic methodology utilizing the intramolecular hydrogen abstraction by an alkyl radical as a key step. These studies demonstrate that 1,5-hydrogen abstraction by an aliphatic radical can be successfully incorporated into a reaction's design, provided a good hydrogen donor site is available.

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9. The structure assigned to all new compounds is consistent with spectroscopic data (200, 250, or 300 MHz ^{1}H NMR, ^{13}C, IR, HRMS). Data from a representative entry is shown. ^{1}H NMR ($CDCl_3$, 250 MHz) δ (multiplicity, hydrogens) **11**: 7.3 (m, 5H), 4.45 (s, 2H), 3.42 (t, *J* = 6 Hz, 2H), 2.25 (bd, *J* = 18 Hz, 1H), 2.05-1.4 (m, 10H), 1.32 (dd, *J* = 5.6, 4.7 Hz, 1H), 0.9 (dd, *J* = 10, 4.7 Hz, 1H); **12**: 7.3 (m ,5H), 4.51 (d, *J* = 12 Hz, 0.5 H), 4.48 (d, *J* = 12 Hz, 0.5 H,) 4.46 (d, *J* = 12 Hz, 0.5H), 4.4 (m, 0.5H), 4.33 (d, *J* = 12 Hz, 0.5 H), 4.26 (m, 0.5H), 2.5-1.4 (m, 8H), 1.2 (s, 1.5 H), 1.1 (s, 1.5 H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (multiplicity) **11**: 208.9 (s), 138.4 (s), 128.3 (d), 127.6 (d), 127.5 (d), 72.9 (t), 69.9 (t), 36.1 (t), 35.5 (t), 33.6 (d), 27.8 (s), 26.6 (t), 25.5 (t), 18.3 (t), 17.1 (t); **12**: 213.6 (s), 213.2 (s), 138.5 (s), 128.3 (d), 128.2 (d), 127.5 (d), 127.4 (d), 127.3 (d), 127.2 (d), 84.3 (d), 82.3 (d), 71.3 (t), 71.0 (t), 66.8 (d), 64.5 (d), 46.6 (s), 43.6 (s), 41.8 (t), 39.8 (t), 39.2 (t), 37.8 (t), 34.9 (t), 34.4 (t), 30.9 (t), 30.8 (t), 27.9 (q), 27.2 (q), 22.2 (t), 21.1 (t).
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