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A Fragmentation-Rearrangement Sequence of Cyclobutylcarbinyl Radicals

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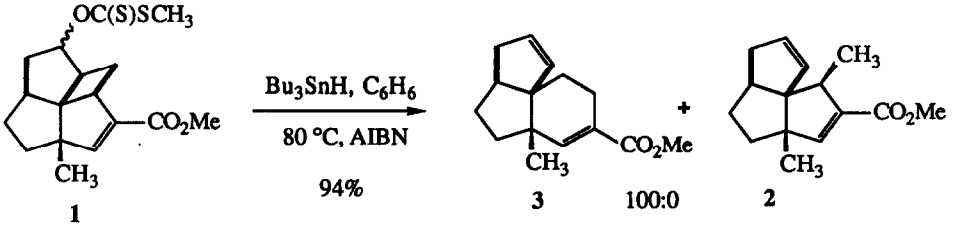
Key Words: Radical fragmentation, radical rearrangement, cyclobutylcarbinyl radical, photocycloaddition, ring expansion.

Abstract: The fragmentation of cyclobutylcarbinyl radicals produces primary radicals which can undergo addition to adjacent pi-bonds resulting in ring expansion reactions. This tandem fragmentation-expansion sequence provides a unique entry into some complex carbon skeleta.

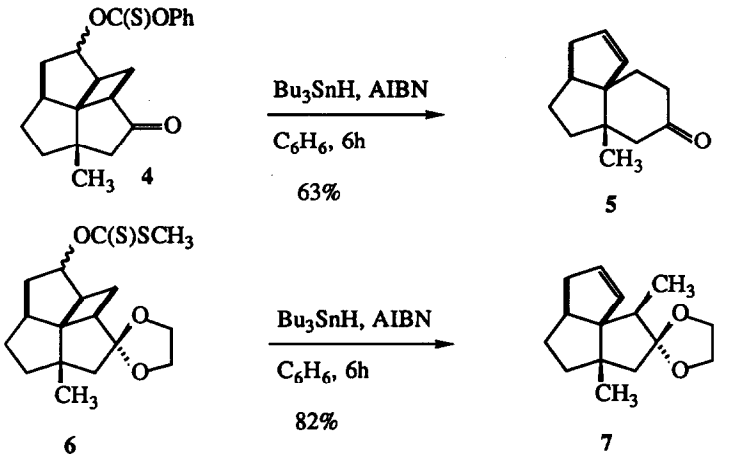
Radical based reactions have been successfully exploited in the development of a wide variety of useful synthetic transformations in recent years.[2] Much of the attention in this area has focused on transformations involving carbon-carbon bond formation by the addition of carbon radical centers to olefins. Considerably less effort has been expended on the development of radical based fragmentation and rearrangement reactions.[3-11] Beckwith[3] has studied the stereoelectronic requirements of the fragmentation of cyclobutylcarbinyl radicals and Beckwith,[4] Dowd[5] and Baldwin[6] have reported on some unusual radical based ring expansion reactions. We had previously disclosed results on an atom transfer fragmentation and reductive fragmentation reaction of a cyclobutylcarbinyl radical during a synthesis of (±)-silphinene.[7] Boger has recently demonstrated that radical rearrangements and cyclizations can be executed in tandem.[8] We report here on a tandem fragmentation-rearrangement reaction of cyclobutylcarbinyl radicals.

During the course of a study directed toward the synthesis of the functionalized triquinane subergorgic acid, the xanthate **1** was exposed to Bu_3SnH and AIBN in benzene (c = 1.5 mMol, syringe pump addition, 4h) at 80°C. The expected product from cyclobutylcarbinyl radical fragmentation, triquinane **2**, was not observed. The ^1H NMR of the product lacked a doublet for the methyl group and the ^{13}C NMR displayed an additional methylene. The product (isolated in 94% yield)[12] was subsequently identified as the ring expanded product **3**. Similarly, the thionocarbonate **4** provided the cyclohexanone **5** in 63% yield. Ketal **6** lacking a π-bond adjacent to the intermediate primary radical undergoes simple fragmentation to produce the triquinane **7** in 82% yield.



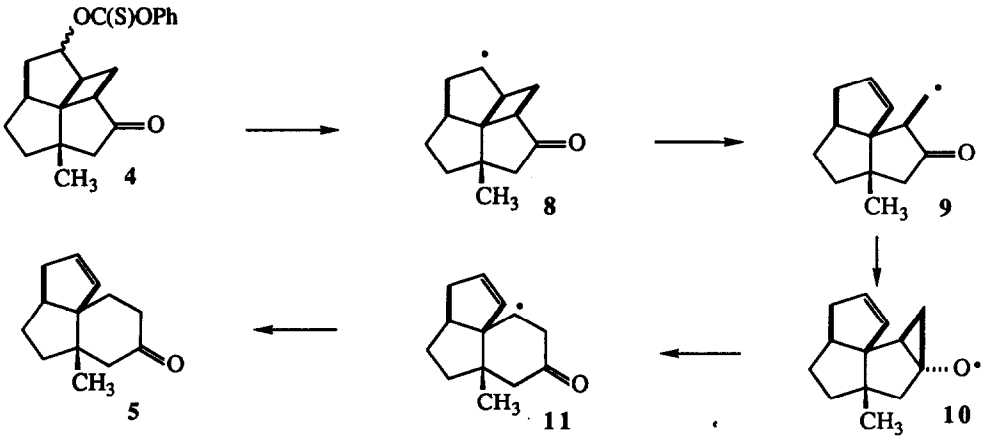
1 **3** 100:0 **2**

The tentative mechanism for this reaction is shown in Scheme 1. The cyclobutylcarbinyl radical **8** fragments to produce the primary radical **9** which undergoes addition to the carbonyl (or C—C π-bond in **1**) to produce the cyclopropyl alkoxy radical **10.** Radical **10** fragments to the more stable secondary radical **11** which is reduced by tributyltin hydride. This sequence is similar to the radical based ring expansions of Dowd,[5] Baldwin[6] and Beckwith[4] who have proposed a cyclopropyl alkoxy radical similar to **10.**

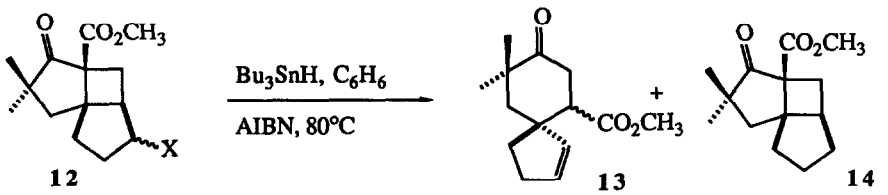


The generality of this process was evaluated by preparing **12a** and **12b** and exposing them to Bu_3SnH in benzene at 80°C. Again, the major product **13** resulted from fragmentation followed by ring expansion. While direct reduction to produce **14** is a minor process with the iodide **12a**, a higher proportion of direct reduction is observed with the xanthate **12b**. This is consistent with previous observations by Porter[13] and Dowd.[5]

Scheme 1



It has been suggested that the presence of an ester group at the α-carbon is essential for the success of the ring expansion in simple cycloalkanone systems.[4,5] While the presence of an α-carboalkoxy group must clearly lower the transition state energy for the final cyclopropane cleavage in the ring expansion, the successful ring expansion of radical **9** suggests that the ester group might not be essential if additional strain is present in the molecule. This prompted the investigation of the fragmentation-rearrangement of iodides **15** and **16**. Surprisingly, the only products obtained from the reaction of these halides with Bu_3SnH were **17** and **18** which result from cleavage of the internal cyclobutane bond. These results are in direct contrast to the proposed stereoelectronic requirements for this cleavage.[2] Interestingly, **19** fragments readily to produce the expected product **20**. Beckwith's seminal study on the rates of cleavage of cyclobutylcarbinyl radicals indicate that the steric environment on the cyclobutane can significantly impact the rates of cyclobutylcarbinyl radical cleavages.[2] Additionally, MM2 calculations indicate that there is slightly better overlap between the SOMO and the exocyclic cyclobutane bond in the minimum energy conformations of compounds such as **12** and **19** than in **15** and **16**. The exact reasons for this alternate mode of cleavage remain unclear. Further studies are in progress to clarify this anomalous behavior.

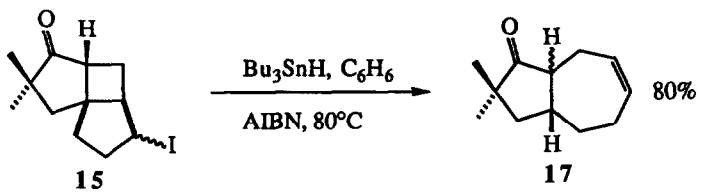


12

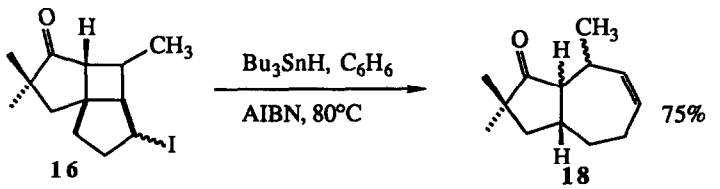
a, X = I
b, X = OC(S)SCH$_3$

13 75% (47%)

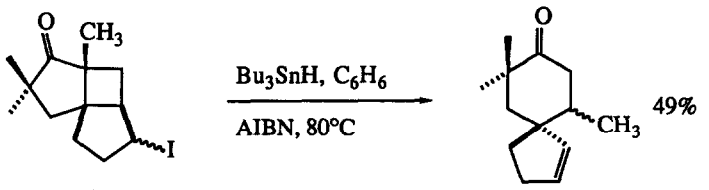
14 12% (30%)



15 → **17** 80%



16 → **18** 75%



19 → **20** 49%

In conclusion, a radical generated by a cyclobutylcarbinyl radical fragmentation can interact with an adjacent π-bond to generate ring expanded products. Precursors for this unusual fragmentation-rearrangement sequence can be readily accessed through [2+2] photocycloadditions. The application of this sequence to the synthesis of complex carbon skeleta is in progress.

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