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The Effect of α-Alkoxy Group in Radical-Mediated β-Fragmentation Reactions

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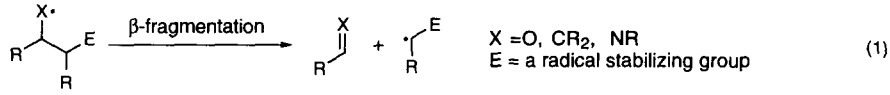
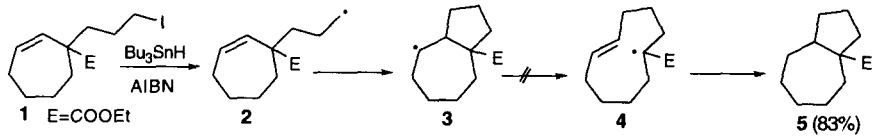
Summary: β-Fragmentation reactions of alkyl and aminyl radicals were greatly facilitated by the presence of α-alkoxy groups. © 1997 Elsevier Science Ltd.

β-Fragmentations in radical reactions are unique and versatile, and they are quite different from β-fragmentations in ionic reactions.[1] The driving forces for β-fragmentations in radical reactions are often (i) relief of ring strain,[2] (ii) cleavage of carbon-heteroatom bonds,[3] (iii) formation of π bonds along with cleavage of C-C bonds (eq 1).[4] Among three different types of driving forces for β-fragmentations, we were interested in type iii, where cycloalkyloxy radicals normally undergo facile β-fragmenations because of strong π-bond energy of C=O bonds. β-Fragmentations of alkyl and aminyl radicals do not normally occur, although their β-fragmentations would produce more stable radicals. Thus, β-fragmentations involving the formation of C=C and C=N bonds are very rare.[5] We wish to report that the presence of α-alkoxy groups facilitated β-fragmentations of alkyl and aminyl radicals significantly.



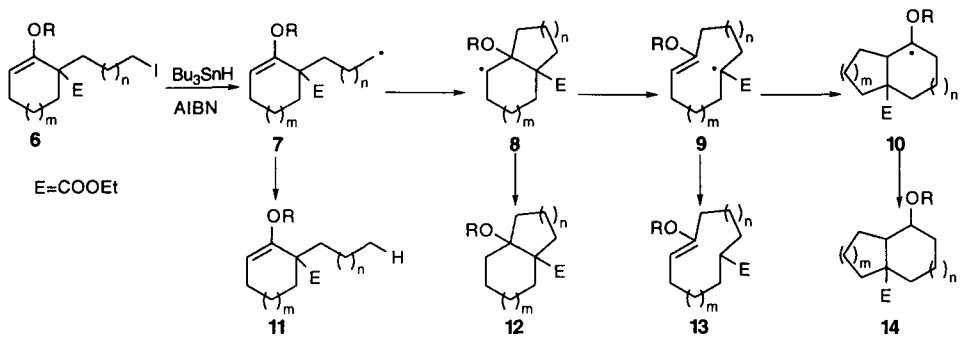
(1)



(2)

We initially examined the possibility of β-fragmentations of alkyl radicals involving the formation of C=C bonds along with the generation of stable radicals (eq 2). The reaction of iodide **1** with Bu_3SnH/AIBN in refluxing benzene under a high dilution for 3 h afforded only **5** in 83% yield. Apparently, β-fragmentation of the alkyl radical **3** into **4** did not take place.

In order to see the effect of α-alkoxy group in β–fragmentation, we prepared substrate **6** by routine operations. As shown in Scheme 1, when **6** is treated with Bu_3SnH/AIBN, four products are expected to be formed, where the latter two products (**13** and **14**) would be produced via β-fragmentation of **8**. Furthermore, the ratio of **13** and **14** would depend on the size of the ring (m,n). As predicted, the radical reaction of **6a** with Bu_3SnH/AIBN in refluxing benzene under a high dilution afforded a mixture of four products roughly in an equal ratio.[6] A much better result was obtained with **6b**, where **14b** was isolated in 80% yield along with **12b** (14%). Since we were unable to observe any β-fragmentation products with **1**, this result clearly

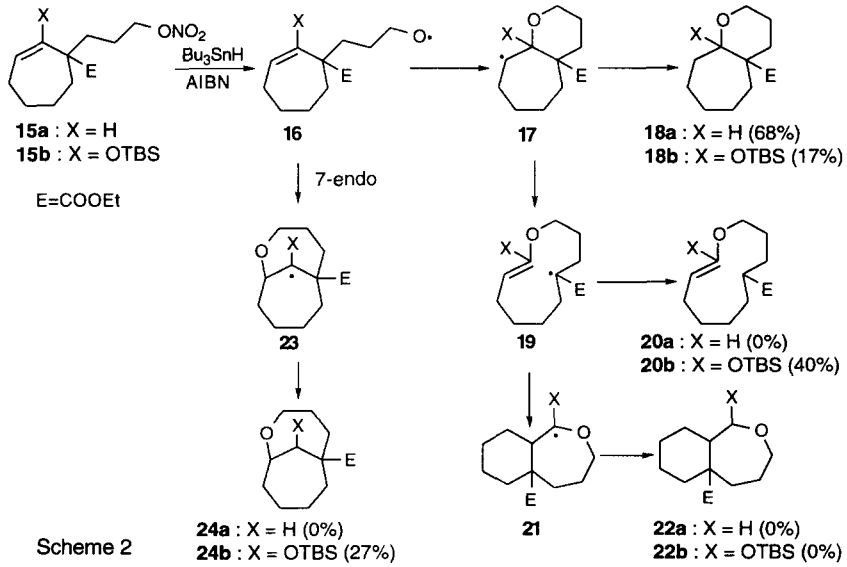


a : R = Me, m = 1, n = 1	**11a** (20)	**12a** (22)	**13a** (22)	**14a** (28)
b : R = TBS, m = 2, n = 1	**11b** (0)	**12b** (14)	**13b** (0)	**14b** (80)
c : R = TBS, m = 1, n = 2	**11c** (81)	**12c** (0)	**13c** (4)	**14c** (0)
d : R = TBS, m = 2, n = 2	**11d** (0)	**12d** (32)	**13d** (49)	**14d** (0)

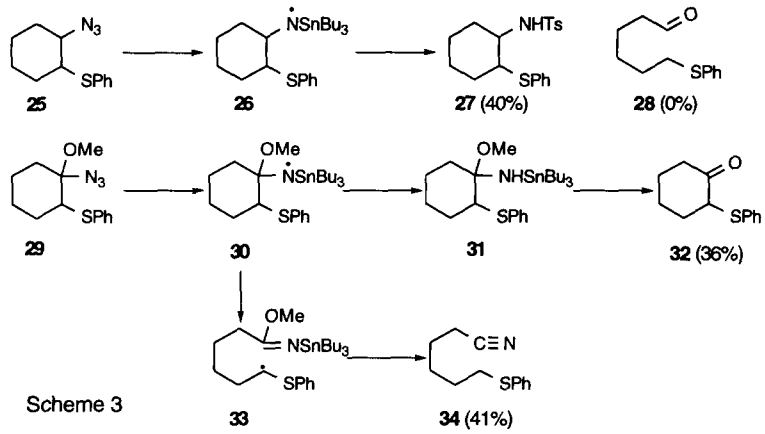
Scheme 1

demonstrates the importance of α-silyloxy group in β-fragmentation of alkyl radical **8b**. In the case of **6c**, the direct reduction product was obtained in 81% yield along with a small amount of β-fragmentation product **13c** (4%). Furthermore, when **6d** was subjected to the similar conditions, the β-fragmentation product **13d** (49%) was favored over the cyclized product **12d** (32%). Although the ratio of β-fragmentation relative to direct quenching and cyclization depends very much on the size of the ring, it is evident that the presence of α-alkoxy group certainly facilitates the β-fragmentation of alkyl radicals.

In order to examine the scope and limitations of the effect of α-alkoxy groups, we studied the radical reaction of **15a**,[7] in which the alkoxy group was generated by intramolecular addition of an alkoxy radical to an alkenyl group. Although an α-alkoxy group was available, β-fragmentation in **17a** (X=H) did



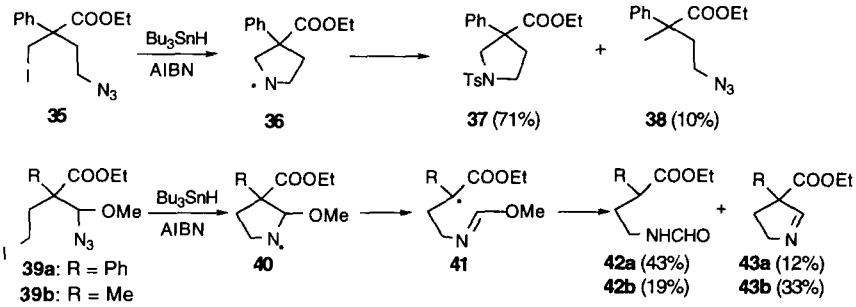
Scheme 2



Scheme 3

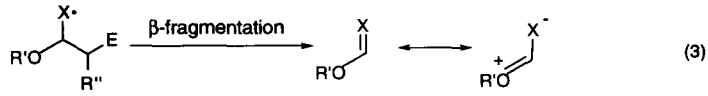
not occur, yielding only cyclized product **18a** in 68% yield. However, the presence of another α-alkoxy group facilitated the β-fragmentation of an alkyl radical. Thus, when **15b** was subjected to the similar conditions,[6] β-fragementation product **20b** was obtained in 40% yield along with **18b** (17%). In addition, somewhat surprisingly, 7-*endo* addition product **24b** was also isolated in 27% yield.[8]

Our attention was next turned to the question of whether α–alkoxy groups would also facilitate β-fragmentations involving the formation of C=N bonds. As shown in Scheme 3, azido groups were utilized to generate aminyl radicals.[9] Radical reaction of **25** with Bu_3SnH/AIBN in refluxing benzene[6] afforded direct reduction product **27** (40%) after tosylation along with diphenyl disulfide (50%). There was no indication of the presence of β-fragmentation product **28**. However, when the reaction was carried out with **29** bearing an α-methoxy group under the similar conditions, a mixture of **32** and **34** was isolated in 36% and 41% yield, respectively. Apparently, **34** was produced via β-fragmenation of aminyl radical **30** and subsequent thermal elimination of tributyltin methoxide.



Scheme 4

We next examined the effect of α-alkoxy group in the cyclic aminyl radicals as shown in Scheme 4. As we previously reported the radical cyclization of alkyl azides,[9b] when azide **35** was treated with Bu_3SnH/AIBN under a high dilution, the cyclized product **37** was isolated in 71% yield along with direct reduction product **38** (10%). However, in **40** bearing α-alkoxy group, β-fragmenation occurred to some extent, depending on the stability of the resulting radicals. When **39a** was treated with Bu_3SnH/AIBN,[6] β-fragmenation product **42a** was obtained in 43% yield along with quenching product **43a** (12%) after thermal elimination of methanol, indicative of the importance of α-alkoxy group in the β-fragmentations



(3)

X = CR_2, NR
E = a radical stabilizing group

involving the formation of C=N bonds. A similar result was also obtained with **39b**, although a less amount of β-fragmentation product **42b** was isolated.

The experimental results obtained in this study clearly indicate that the β-fragmentations of alkyl and aminyl radicals are greatly facilitated in the presence of α-alkoxy groups. The reason for this observation is not clear at the present. We assume that the resonance stablization of β-fragmentation products due to the presence of α-alkoxy group would facilitate the β-fragmentaions of alkyl and aminyl radicals (eq 3).

Acknowledgement. This work was financially supported by the Organic Chemistry Research Center (OCRC) and KAIST.

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