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Radical cyclizations involving the evolution of nitrogen

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Abstract. The radical cyclizations of N-aziridinyl imines and alkyl azides provided reliable methods for the formation of five- and six-membered carbon-centered and nitrogen-centered radicals from acyclic precursors. N-Aziridinyl imino and azido groups were utilized as radical precursors as well as radical acceptors in radical cyclization. Furthermore, intramolecular addition of aminyl radicals to carbonyl groups proceeded cleanly, yielding 1,5-acyl group transfer from carbon to nitrogen.

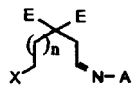
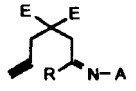
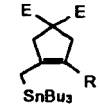
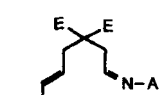
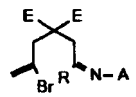
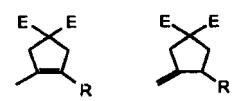
Despite the synthetic usefulness of radical cyclization reactions, the cyclization pathway is mainly limited to 5-exo closure along with somewhat less efficient 6-exo and 6-endo closure due to stereoelectronic and geometric reasons.[1] Fundamentally new approaches for the formation of five- and six-membered ring radicals from acyclic precursors were sought, and the radical cyclizations of 2-phenyl-*N*-aziridinyl imines and alkyl azides provided general solutions to these problems.

Radical cyclization of N-aziridinyl imines. Our approach is outlined in Scheme 1 and is based on three factors along with the original Eschenmoser reaction.[2] First, alkyl radicals are known to add to oxime ethers.[3] Second, β-fragmentation of three-membered rings is a facile process due to the relief of ring strain. Third, consecutive β-fragmentations via ejection of styrene and nitrogen are expected to be fast processes.

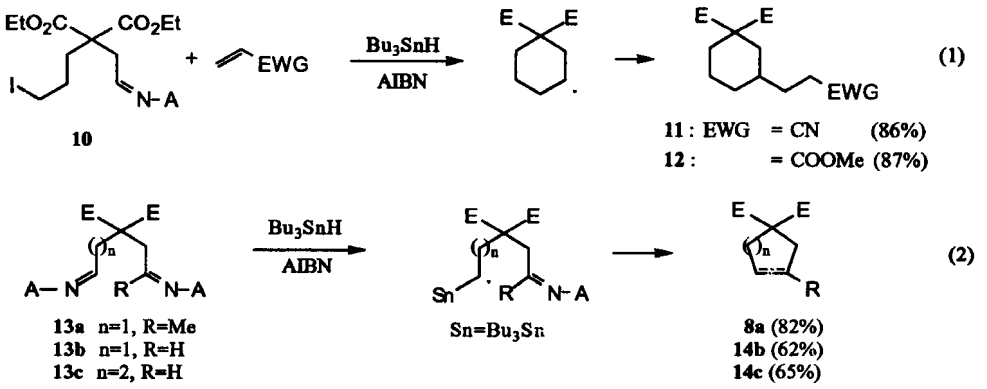
Scheme I

Our initial study focused on the use of the *N*-aziridinyl imines as radical acceptors.[4] Treatment of the bromide **1a** (Table 1) with Bu_3SnH (2.0 equiv) and AIBN (0.1 equiv) in benzene at 80 °C for 4 h afforded 30% of **2a** along with 33% of the *N*-aziridinylpiperidine resulting from intramolecular N-alkylation. Under the same conditions, the use of the phenylselenide **1b** solved the problem of intramolecular N-alkylation and gave **2a** in 75% yield. **1c** was cleanly cyclized to **2c**, and there was no evidence of the N-alkylated product. As shown in Table 1, radical cyclization of **3**, **5a**, and **7a** using structurally different radical precursors proceeded smoothly, yielding the cyclized products in high yields. Similarly, the keto hydrazones **5b** and **7b** were cyclized without significant difference in their reactivity.

Table 1. Radical Cyclization of 2-Phenyl- *N*-aziridinyl Imines

substrate[a]	time,h	product (yield, %)	substrate[a]	time,h	product (yield, %)
					
1a: n=1, X=Br	4	**2a** (30)	**5a**: R=H	3	**6a** (84)
1b: n=1, X=SePh	2	**2a** (75)[b]	**5b**: R=CH_3	3	**6b** (96)
1c: n=2, X=Br	2	**2c** (85)			
					
3	4	**4** (89)	**7a**: R=H	4	**8a** (87/13) **9a** (67)
			7b: R=CH_3	6	**8b** (94/6) **9b** (92)

[a] E=COOEt, A=2-phenyl-*N*-aziridinyl group [b] Nine percent of the reduction product was obtained.



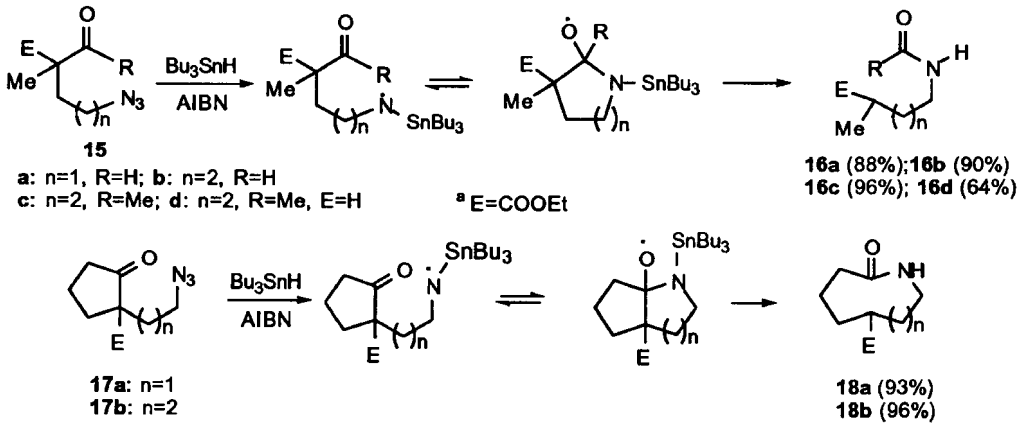
We have briefly examined the feasibility of the cyclization-intermolecular addition sequence because this illustrates a unique feature of the present method, demonstrating the formation of two carbon-carbon bonds in succession at the same carbon.[5] As shown in eq 1, radical reaction of **10** with Bu_3SnH/AIBN in the presence of acrylonitrile and methyl acrylate gave **11** and **12** in 86% and 87%, respectively. The possibility of using the aziridinyl imines as radical precursors was briefly studied, and our approach relies on intermolecular addition of Bu_3Sn radical to an aziridinyl imino group to generate the α-Bu_3Sn-substituted carbon-centered radical, as shown in eq 2. Thus, treatment of **13a** with Bu_3SnH (0.3 equiv) and AIBN in toluene at 110 °C for 6 h afforded **8a** in 82% yield, demonstrating the efficacy of an aziridinyl imino group as a radical precursor as well as a radical acceptor.[6,7] Similar results were also obtained with **13b** and **13c**.

Intramolecular addition of aminyl radicals to carbonyl groups. Aminyl radicals are known to be much less efficient in cyclizations than aminium cation radicals and amidyl radicals due to the slow rate of cyclization and the unfavorable equilibrium.[8] We have studied the use of azido groups as precursors for aminyl radicals and intramolecular addition of aminyl radicals to carbonyl groups.[9]

To explore an intriguing possibility of aminyl radicals to the carbonyl group, generation of an aminyl radical in the presence of a carbonyl group is requisite. For this purpose, we turned our attention to alkyl azides as a starting point in our approach. As shown in Scheme 2, intramolecular addition of an aminyl radical to the carbonyl group would be regarded as an energetically unfavorable process because it breakes a strong C=O bond, generating an alkoxy radical which is much more reactive than the starting aminyl radical. However, we conceived that this might be overcome by β-fragmentation of an alkoxy radical and the driving force would be provided by resonance stabilization of the amide group formed by the β-fragmentation. Gratifyingly, our approach was realized with success and it appeared to be a highly efficient and synthetically useful process.

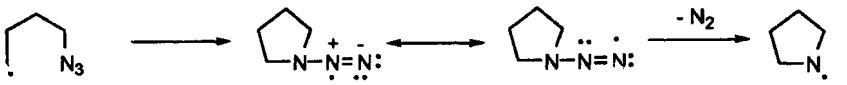
As shown in Scheme 2, when **15a** was treated with Bu_3SnH/AIBN in refluxing benzene under a high dilution condition, clean formyl group transfer occurred, yielding **16a** in 88% yield. Similar results were obtained with **15b** and **15c**. Also, it is noteworthy that **15d** underwent smooth acyl group transfer to afford **16d** in 64% yield, demonstrating the generality of this process. The synthetic utility of this process was further extended to achieve ring expansion to afford medium-sized lactams . For example, when **17a** and **17b** were subjected to our standard condition, smooth ring expansion occurred to yield **18a** and **18b** in 93% and 96% yield, respectively.

Scheme 2 [a]



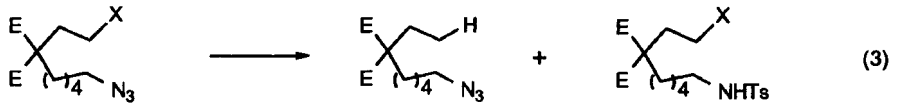
Radical cyclization of alkyl azides. Radical cyclizations involving direct carbon-nitrogen bond formation by intramolecular addition of alkyl radicals to nitrogen-related radical acceptors have not been reported, although intramolecular addition of aryl radicals, generated from aryldiazonium salts and sodium iodide, to the azido group has been previously known.[10] We have developed a new reaction of this type which has considerable potential for the synthesis of N-heterocycles. Our approach is outlined in Scheme 3 and relies on intramolecular addition of an alkyl radical to an azido group, followed by the evolution of nitrogen to produce a five-membered nitrogen-centered radical.

Scheme 3



Since the azido group is known to be susceptible to Bu_3Sn radical,[11] generation of an alkyl radical in the presence of an azido group is essential for the use of the azido group as a radical acceptor. Thus, we examined the reactions shown in eq 3. Treatment of **19a** with Bu_3SnH(1.0 equiv) and AIBN(0.1 equiv) in refluxing benzene for 4h afforded only **20** in 91% yield, whereas **19b** gave 54% of **20** and 25% of **21b** under the same condition, indicating that only the iodo group can be utilized as a radical precursor. However, it is gratifying to find that azides are relatively inert toward tris(trimethylsilyl)silyl radical,[12] extending the synthetic usefulness of azido groups as radical acceptors. Thus, treatment of **19a** and **19b** with $(TMS)_3SiH$/AIBN afforded only **20** in 88% and 84% isolated yield, respectively. The radical cyclization of the iodo azide was carried out with Bu_3SnH/AIBN in refluxing benzene (method A) and gave N-heterocycles in good yields as shown in Table 2.

The synthetic usefulness of this radical cyclization using $(TMS)_3SiH$/AIBN in refluxing benzene (method B) was explored and the iodo, the bromo, and the thionocarbonate group could be utilized as radical precursors as shown in Table 2.[13] Furthermore, a striking difference between method A and B was realized with the keto azides. Using method A, the azido group was a radical precursor for an aminyl radical in the presence of the keto group. Thus, intramolecular addition of an aminyl radical to the carbonyl group occurred, yielding a 10-membered lactam along with a small amount of **31**. However, with method B, the keto group became a radical precursor along with the azido group as a radical acceptor . As shown in eq 4, the reaction of **30** with $(TMS)_3SiH$/AIBN in refluxing benzene afforded **31** in 78% yield.



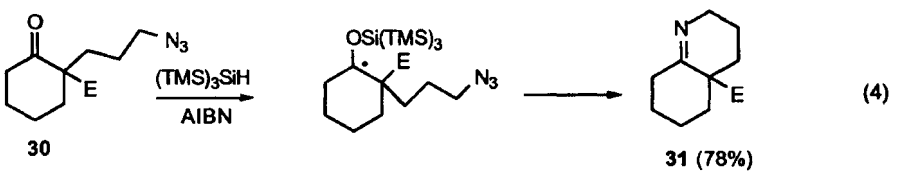
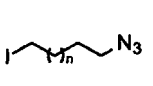
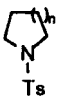
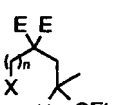
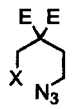
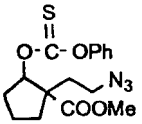
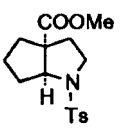
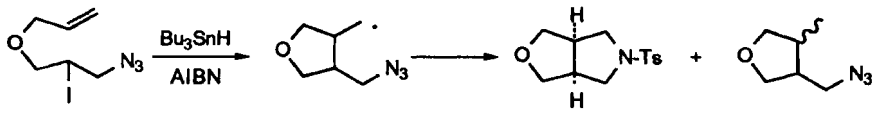


Table 2. Radical Cyclization of Alkyl Azides

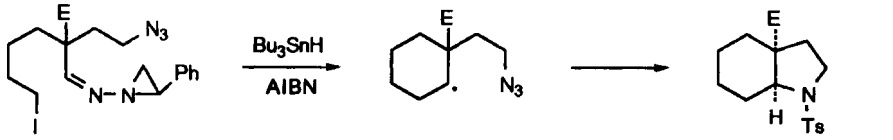
substrate	method[a]	product(yield, %)	substrate	method[a]	product(yield, %)
					
22a : n = 1	A	**23a** (88%)	**26a** : n = 1, X = I	A	**27a** (81%)
22b : n = 2	B	**23b** (50%)	**26b** : n = 1, X = Br	B	**27a** (77%)
			26c : n = 2, X = Br	B	**27c** (56%)
				B	
24a : X = I	A	**25** (78%)	**28**		**29** (60%)
24b : X = Br	B	**25** (76%)			

[a] method A : Bu_3SnH/AIBN; method B : $(TMS)_3SiH$/AIBN; E = COOMe

Tandem radical cyclizations using the azido groups as radical acceptors were examined (eq 5 and 6). Reaction of **32** with Bu_3SnH/AIBN would give initially **33**, in which only a *cis* -isomer cyclized to yield **34**. Thus, **35** consisted of mainly a *trans*-isomer along with a small amount of a *cis*-isomer. The second example utilized our radical cyclization of N-aziridinyl imino group to generate the 6-membered ring radical which underwent radical cyclization to yield **37** in 73% yield.



32 **33** **34**(56%) **35** (20%)



36 **37** (73%)

In conclusion, we have demonstrated that the radical cyclizations of aziridinyl imines and alkyl azides provide reliable methods for the formation of five- and six-membered carbon-centered and nitrogen-centered radicals. The dual ability of the aziridinyl imino group and the azido group to serve as radical precursors as well as radical acceptors would enhance the synthetic usefulness of the present methods. Also, we have shown the first intramolecular addition of aminyl radicals to carbonyl groups, which appeared to be a synthetically useful process, providing a ready access to otherwise readily inaccessible medium-sized lactams.

Acknowledgments. I wish to thank my coworkers, whose names appear in the cited references. Our research has been financially supported by the Organic Chemistry Research Center, the Korea Science and Engineering Foundation and Korea Advanced Institute of Science and Technology.

References and Notes

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