

## Novel Radical Cyclizations of Alkyl Azides. A New Route to N-Heterocycles

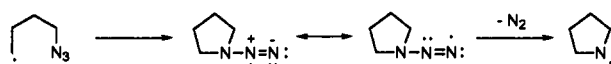
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Received March 14, 1994  
Revised Manuscript Received April 29, 1994

Although the synthetic importance of radical cyclizations in the synthesis of various carbocyclic and heterocyclic systems has been recognized in recent years,<sup>1</sup> radical cyclizations involving direct carbon–nitrogen bond formation by intramolecular addition of alkyl radicals to nitrogen-related radical acceptors have not been reported.<sup>2–4</sup> We now report a reaction of this type which has considerable potential for the synthesis of N-heterocycles. Our approach is outlined in Scheme 1 and relies on intramolecular

### Scheme 1



addition of an alkyl radical to an azido group, followed by the loss of nitrogen to produce an aminyl radical. Furthermore, we report the first demonstration of intramolecular addition of an aminyl radical to an imino group.

Since the azido group is known to be susceptible to  $\text{Bu}_3\text{Sn}$  radicals,<sup>5</sup> the 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. Therefore, we examined the reactions shown in eq 1. Treatment of **1a** with  $\text{Bu}_3\text{SnH}$  (1.0 equiv) and AIBN (0.1 equiv) in refluxing benzene for 4 h afforded only **2** in 91% yield, whereas **1b** gave 54% of **2** and 25% of **3b** (after tosylation) under the same conditions, indicating that only the iodo group can be utilized as a radical precursor.<sup>6</sup> However, it was gratifying to find that azides are relatively inert toward tris(trimethylsilyl)silyl radical,<sup>7</sup>

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(2) For recent reports on intramolecular addition of nitrogen-centered radicals to olefins, see: (a) Newcomb, M.; Deeb, T. M.; Marquardt, D. J. *Tetrahedron* 1990, 46, 2317. (b) Newcomb, M.; Marquardt, D. J.; Deeb, T. M. *Tetrahedron* 1990, 46, 2329. (c) Newcomb, M.; Marquardt, D. J.; Kumar, M. U. *Tetrahedron* 1990, 46, 2345. (d) Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron Lett.* 1990, 31, 85, 3545. (e) Boivin, J.; Fouquet, E.; Zard, S. Z. *J. Am. Chem. Soc.* 1991, 113, 1055. (f) Newcomb, M.; Esker, J. L. *Tetrahedron Lett.* 1991, 32, 1035. (g) Newcomb, M.; Ha, C. *Tetrahedron Lett.* 1991, 32, 6493. (h) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron Lett.* 1992, 33, 4993. (i) Aube, J.; Peng, X.; Wang, Y. *J. Am. Chem. Soc.* 1992, 114, 5466.

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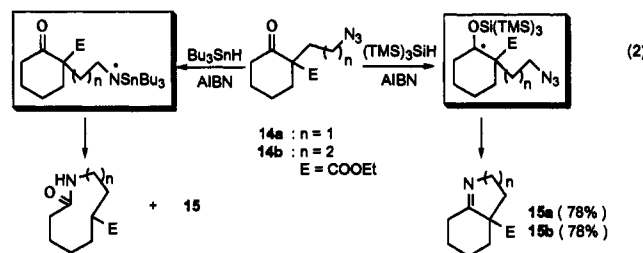
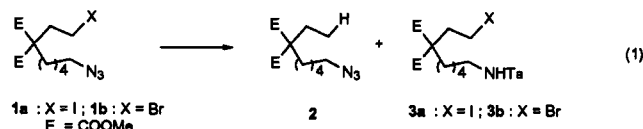
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Table 1. Radical Cyclization of Alkyl Azides<sup>a</sup>

substrate	method <sup>a</sup>	time, h	product(yield, %)
	A	2	<b>5a</b> (88%)
<b>4b</b> : n = 2	B	14	<b>5b</b> (50%)
	A	3	<b>7</b> (78%)
<b>6b</b> : X = Br	B	8	<b>7</b> (76%)
	A	2	<b>9</b> (81%)
<b>8b</b> : n = 1, X = Br	B	8	<b>9</b> (77%)
<b>8c</b> : n = 2, X = Br	B	15	<b>10</b> (56%) <sup>b</sup>
	B	4	<b>12</b> (60%)

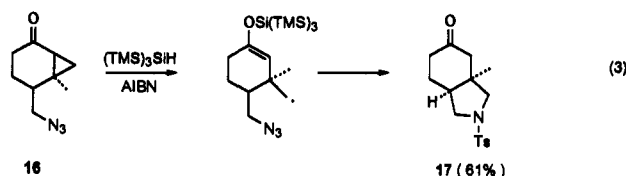
<sup>a</sup> (a) Method A:  $\text{Bu}_3\text{SnH}$ /AIBN. Method B:  $(\text{TMS})_3\text{SiH}$ /AIBN; E = COOMe. (b) The direct reduction product (20%) was isolated.



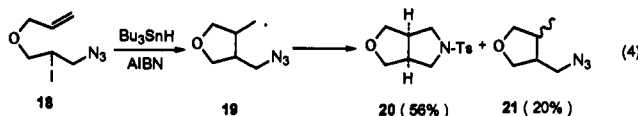
extending the synthetic usefulness of the azido group as a radical acceptor. Thus, treatment of **1a** and **1b** with  $(\text{TMS})_3\text{SiH}$ /AIBN afforded only **2** in 88% and 84% isolated yields, respectively. The radical cyclization of the iodo azide was carried out with  $\text{Bu}_3\text{SnH}$ /AIBN in refluxing benzene (method A). Treatment of **4a** with  $\text{Bu}_3\text{SnH}$ /AIBN in refluxing benzene for 2 h afforded **5a** in 88% yield after tosylation. Similar results were obtained with **6a** and **8a**. The synthetic usefulness of this radical cyclization using  $(\text{TMS})_3\text{SiH}$ /AIBN in refluxing benzene (method B) was explored as summarized in Table 1. The iodo, bromo, and thionocarbonate groups were utilized as radical precursors. Furthermore, a striking difference between methods A and B was realized with the keto

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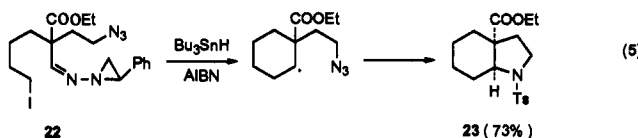
azide **14** as shown in eq 2. Previously, we reported highly efficient



intramolecular addition of aminyl radicals to keto groups using method A, in which azido groups were utilized as radical precursors for aminyl radicals in the presence of keto groups.<sup>8</sup> With method B, the keto group became the radical precursor and the azido group a radical acceptor. Similarly, the reaction of **16** with  $(\text{TMS})_3\text{SiH}/\text{AIBN}$  in refluxing benzene for 1 h generated the carbon-centered radical via  $\beta$ -fragmentation of the cyclopropyl ring, which underwent an intramolecular addition to the azido group to afford **17** in 61% yield after tosylation (eq 3).



Tandem radical cyclization using the azido group as a radical acceptor was examined (eqs 4 and 5). Reaction of **18** with  $\text{Bu}_3\text{SnH}/\text{AIBN}$  in refluxing benzene for 1 h gave initially **19**, in which only the cis isomer cyclized to yield **20**.<sup>9</sup> Azide **21** consisted

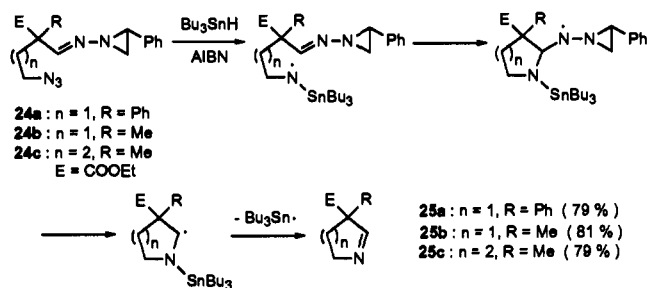


of a 3:2 mixture of trans and cis isomers. The second example utilizes our previously reported radical cyclization of the *N*-aziridinyl imine to generate the cyclohexyl radical,<sup>10</sup> which

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## Scheme 2



undergoes intramolecular addition to the azido group. Thus, treatment of **22** with  $\text{Bu}_3\text{SnH}/\text{AIBN}$  in refluxing benzene for 1 h afforded the cis-fused **23** in 73% yield.

We have briefly studied intramolecular addition of aminyl radicals to imino groups. The *N*-aziridinyl imino group was chosen as the radical acceptor because intramolecular addition of an aminyl radical to an imino group would be irreversible due to fast  $\beta$ -fragmentation of the aziridine ring.<sup>11</sup> As shown in Scheme 2, treatment of **24a** with  $\text{Bu}_3\text{SnH}$  (0.3 equiv) and AIBN (0.05 equiv) in refluxing benzene for 2 h afforded **25a** in 79% yield. Similar results were obtained with **24b** and **24c**.

In conclusion, we have demonstrated highly efficient intramolecular additions of (i) alkyl radicals to azido groups and (ii) aminyl radicals to imino groups. The dual ability of azido groups to serve as radical acceptors as well as radical precursors should enhance the synthetic usefulness of the present methods.

**Acknowledgment.** We thank The Organic Chemistry Research Center and the Korea Science and Engineering Foundation for financial support of our research program. We thank Professor Sung Soo Kim of Inha University for his helpful comments.

**Supplementary Material Available:** Experimental procedures for the preparation of **7** as well as spectral data (<sup>1</sup>H NMR, <sup>13</sup>C NMR, IR, HRMS) for the reaction products (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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