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Highly Efficient Intramolecular Addition of Aminyl Radicals to Carbonyl Groups: A New Ring Expansion Reaction Leading to Lactams

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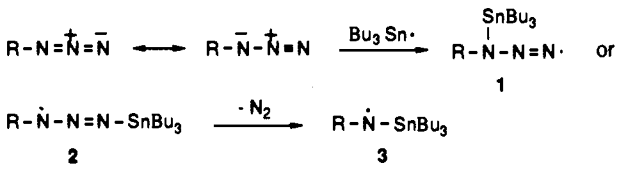
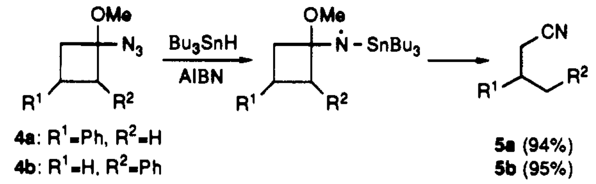
Despite recent interest in C–N bond formation by radical methods,[1] intramolecular C–N bond-forming reactions are less well studied than intramolecular C–C bond-forming reactions.[2] Aminyl radicals are known to be much less efficient in cyclizations than aminium cation radicals,[3a] Lewis acid complexed aminyl radicals,[3b] and amidyl radicals[3c] due to the slow rate of cyclization and the unfavorable equilibrium. In this paper we report (1) the use of azido groups as precursors for aminyl radicals, (2) intramolecular addition of aminyl radicals to carbonyl groups, and (3) its application to lactam formation.

To explore an intriguing possibility of nitrogen-centered radical addition to the carbonyl group, generation of an aminyl radical in the presence of a carbonyl group is requisite. Since previously known methods are not well suited for this purpose,[4] we turn our attention to alkyl azides as a starting point in our approach. We envision that alkyl azides under radical conditions (Bu_3SnH/AIBN) would generate initially **1** or **2**, which would yield the aminyl radical **3** by the loss of N_2 as shown in Scheme I.[5,6] To demonstrate the generation of an aminyl radical from the azido group, we examined the reactions shown in Scheme II.[7] Thus,

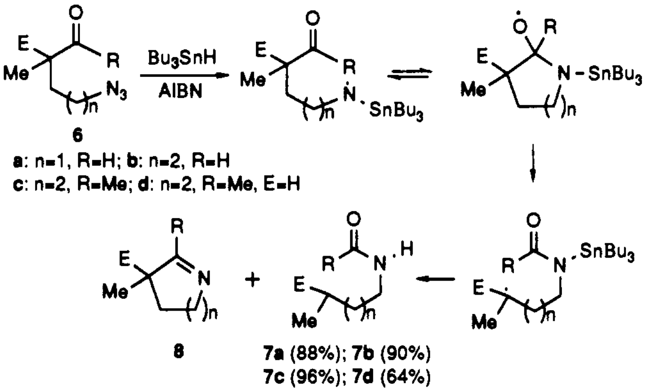
Scheme I



Scheme II



Scheme III [a]



[a] E = COOEt.

treatment of **4a** with Bu_3SnH (1.1 equiv) and AIBN (0.1 equiv) in refluxing benzene (0.05 M) for 4 h gave **5a** in 94% isolated yield. A similar result was obtained with **4b**.

As illustrated in Scheme III, intramolecular addition of an aminyl radical to a carbonyl group would be regarded as an energetically unfavorable and reversible process because it breaks a strong C=O bond, generating an alkoxy radical which is much less stable than the starting aminyl radical.[8] However, we conceive 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. When **6a** was treated with Bu_3SnH/AIBN in refluxing benzene (0.1 M) for 2 h, clean formyl group transfer occurred, yielding **7a** in 85% yield along with a small amount of **8a** (7%).[9] The formation of **8a** could be completely suppressed by conducting the reaction under high dilution conditions. Thus, the following was adopted as our standard procedure. The addition of a 0.05 M benzene solution of Bu_3SnH (1.1 equiv) and AIBN (0.1 equiv) by a syringe pump over 4 h to a 0.05 M refluxing benzene solution

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(1) (a) Newcomb, M.; Burchill, M. T.; Deeb, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 6528. (b) Newcomb, M.; Deeb, T. M.; Marquardt, D. J. *Tetrahedron* **1990**, *46*, 2317. (c) Newcomb, M.; Marquardt, D. J.; Deeb, T. M. *Tetrahedron* **1990**, *46*, 2329. (d) Newcomb, M.; Marquardt, D. J.; Kumar, M. U. *Tetrahedron* **1990**, *46*, 2345. (e) Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron Lett.* **1990**, *31*, 85. (f) Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron Lett.* **1990**, *31*, 3545. (g) Boivin, J.; Fouquet, E.; Zard, S. Z. *J. Am. Chem. Soc.* **1991**, *113*, 1055. (h) Boivin, J.; Fouquet, E.; Zard, S. Z. *Tetrahedron Lett.* **1991**, *32*, 4299. (i) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron Lett.* **1992**, *33*, 4993. (j) Barton, D. H. R.; Jaszberenyi, J. C.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1992**, *114*, 5904.

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(9) Thermal reaction of **6a** with Bu_3SnH in refluxing benzene for 15 h gave only **8a** in 90% yield.

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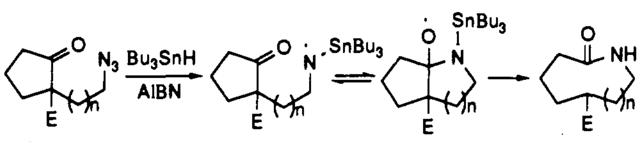
Scheme IV



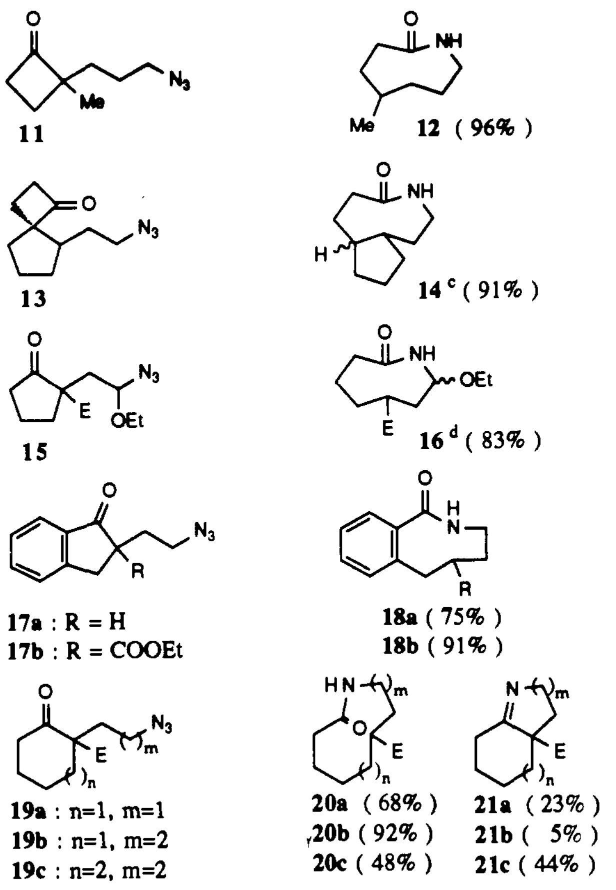
9a: n=1
9b: n=2
10a (93%)
10b (96%)

of **6a** with additional stirring for 1 h afforded **7a** in 88% yield.[10] Similar results were obtained with **6b** and **6c**. It is noteworthy that **6d** undergoes smooth acetyl group transfer from carbon to nitrogen to afford **7d** in 64% yield, demonstrating the great generality of this process.

The synthetic utility of this aminyl radical addition to the carbonyl group was further extended to achieve ring expansion leading to lactams (Scheme IV).[11] When the azido ketones **9a** and **9b** were treated with Bu$_3$SnH/AIBN using our standard procedure, smooth ring expansion occurred to yield **10a** and **10b** in 93% and 96% yield, respectively. **10b** was obtained as an equilibrium mixture of cis and trans isomers in a ratio of 4:1.[12] Further examples are shown in Table I. Ring expansions of azidocyclobutanones **11** and **13** and azidocyclopentanones **15** and **17b** proceeded cleanly, and there was no evidence of the condensed products except for **17a**.[13] However, when the azido group was connected to cyclohexanones and cycloheptanones, we observed a significant amount of the condensed product in addition to the ring expansion product.[14] When **19a** was treated with Bu$_3$SnD/AIBN, no indication of 1,5-hydrogen atom transfer was observed. Thus, further mechanistic studies are needed to clarify whether the condensed product resulted from the direct reduction of an aminyl radical or the interception of an intermediate alkoxy radical by Bu$_3$SnH.

In conclusion, we have demonstrated the first intramolecular addition of aminyl radicals to carbonyl groups, which appears to be a synthetically useful process, providing a ready access to otherwise inaccessible medium-sized lactams. Further studies to determine the full scope of aminyl radical addition to the carbonyl group are under way.

Table I. Ring Expansion Reactions of Azido Ketones to Lactams[a,b]



11
12 (96%)
13
14[c] (91%)
15
16[d] (83%)
17a : R = H
17b : R = COOEt
18a (75%)
18b (91%)
19a : n=1, m=1
19b : n=1, m=2
19c : n=2, m=2
20a (68%)
20b (92%)
20c (48%)
21a (23%)
21b (5%)
21c (44%)

[a] E = COOEt. [b] The yield refers to the isolated yield. All new products had satisfactory ^{1}H NMR, ^{13}C NMR, IR, and HRMS data. [c] A major isomer was trans according to ^{13}C NMR. [d] A 55:45 mixture of diastereomers.

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Supplementary Material Available: Experimental procedures for the preparation of **5a**, **7a**, and **10a** as well as spectral data (^{1}H NMR, ^{13}C NMR, IR, and HRMS) for the reaction products (5 pages). Ordering information is given on any current masthead page.

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(10) **7a** and **7b** exist as an equilibrium mixture of cis and trans isomers in approximate ratio of 1:4 in CDCl$_3$ according to ^{1}H NMR analysis.

(11) For ring expansion to macrocyclic lactams by nonradical methods, see: (a) Walchli, R.; Hess, M. *Helv. Chim. Acta.* **1982**, *65*, 2299. (b) Walchli, R.; Guggisberg, A.; Hesse, M. *Tetrahedron Lett.* **1984**, *25*, 2205. (c) Bienz, S.; Guggisberg, A.; Hesse, M. *Helv. Chim. Acta.* **1988**, *71*, 1708.

(12) The ratio is tentatively assigned on the basis of previously reported data and ^{1}H NMR analysis. Similarly, **18b** and **20a** exist as a 4:1 equilibrium mixture of cis and trans isomers in CDCl$_3$. Furthermore, 10- and 11-membered lactam (**20b** and **20c**) were obtained as one isomer. Huisgen, R.; Brade, H.; Walz, H.; Glogger, I. *Chem. Ber.* **1957**, *90*, 1437. Moriarty, R. M. *J. Org. Chem.* **1964**, *29*, 2748. Moriarty, R. M.; Kliegman, J. M. *J. Org. Chem.* **1966**, *31*, 3007. Stewart, W. E.; Siddall, T. H. *Chem. Rev.* **1970**, *70*, 517. Dunitz, J. D.; Winkler, F. K. *Acta. Crystallogr.* **1975**, *B31*, 251.

(13) A small amount of a byproduct, which was unstable on silica gel, was observed, and the same product was obtained by treatment of **17a** with Bu$_3$SnH.

(14) The condensed products (**21**) were obtained in high yield by treatment of the azido ketones (**19**) with Bu$_3$SnH in refluxing benzene for 15 h.