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Synthesis of Lactams by Radical Substitution Reaction of α,β-Unsaturated Acyl Radicals at Amine Nitrogen

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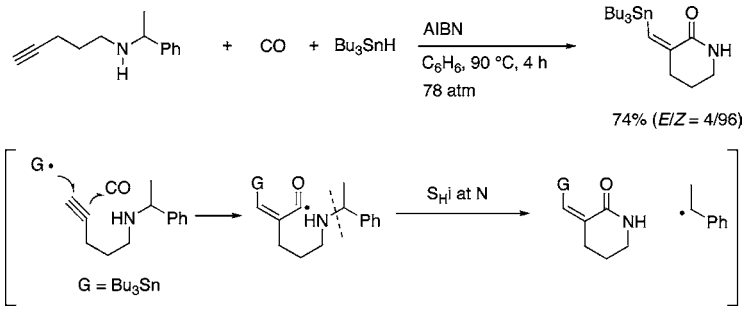
ABSTRACT

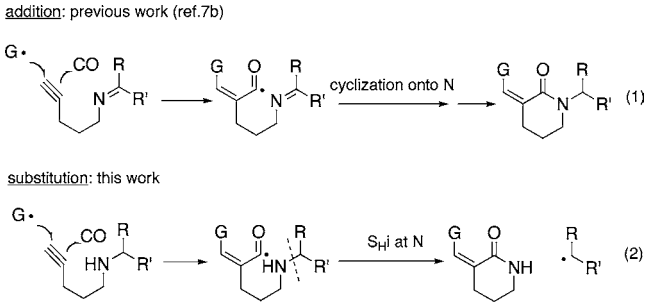


Substitution at nitrogen by α,β-unsaturated acyl radicals took place accompanied by elimination of an α-phenethyl radical. This reaction led to the development of a new carbonylative annulation method for five- to seven-membered ring lactams.

Whereas radical cyclization reactions have become a powerful tool for creating heterocyclic rings,[1,2] the potential of intramolecular homolytic substitution (S_Hi) reactions to create heterocyclic rings has remained underexploited. Examples are restricted to mainly group 14 and 16 elements, such as Si, Ge, Sn, S, Se, and Te,[3,4] whereas S_Hi-type ring formation reactions at nitrogen, an element in group 15, have been scarcely reported.[5] In pursuit of new radical-mediated carbonylation processes,[6] we recently reported that polarity-matched acyl radical cyclization onto the nitrogen of imines is a useful tool for the synthesis of lactams (the first equation of Scheme 1).[7,8] Herein, we report that the substitution reaction of acyl radicals at the nitrogen of amines also provides a useful route for the synthesis of nitrogen-unsubstituted lactams (the second equation of Scheme 1).[9]

We envisioned that if an acyl radical bearing a benzylamine moiety could be generated expulsion of a benzyl

Scheme 1. Two Types of [*n* + 1] Annulation Strategies to Lactam Rings



(1) Renaud, P., Sibi, M. P., Eds. *Radical in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2001; Vols. 1 and 2.

(2) (a) Bowman, W. R.; Fletcher, A. J.; Potts, G. B. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2747. (b) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224.

(3) For reviews, see: (a) Schiesser, C. H.; Wild, L. M. *Tetrahedron* **1996**, *52*, 13265. (b) Walton, J. C. *Acc. Chem. Res.* **1998**, *31*, 99. (c) Beckwith, A. L. J. *Chem. Soc. Rev.* **1993**, 143. (d) Schiesser, C. H. *Chem. Commun.* **2006**, 4055.

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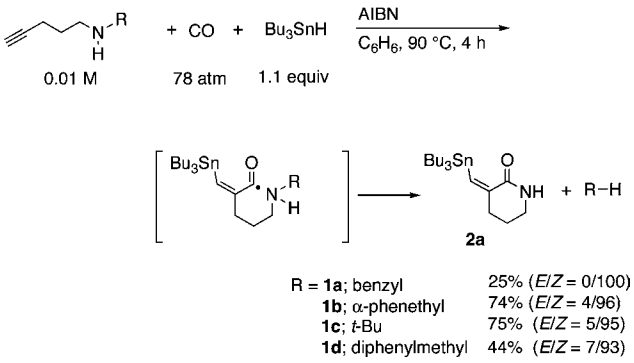
radical in an S_Hi manner would lead to the formation of a lactam ring. When we examined the stannylcarbonylation of (*N*-benzyl)pentynylamine (**1a**) with tributyltin hydride and AIBN under CO pressure, we found that the envisaged six-membered ring lactam **2a**, which does not contain a benzyl group on nitrogen, is formed, albeit in low yield together with lactams containing a benzyl substituent on nitrogen (Scheme 2).

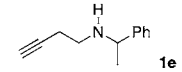
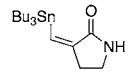
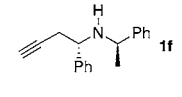
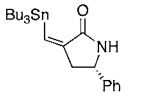
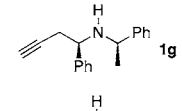
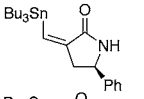
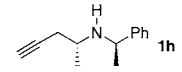
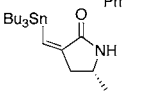
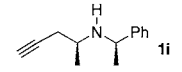
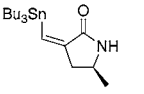
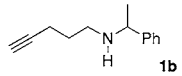
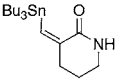
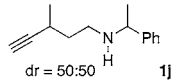
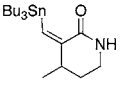
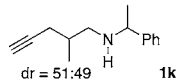
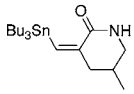
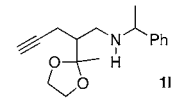
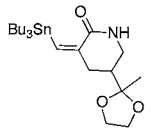
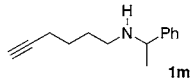
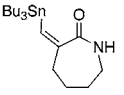
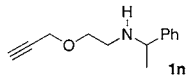
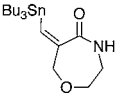
Scheme 2. Effect of the Substituent at Amine Nitrogen for Radical Substitution Reaction



This prompted us to examine several substituents at amine nitrogen, including α-phenethyl, diphenylmethyl, and *t*-butyl. To our delight, we found that **1b**, which has an α-phenethyl group, resulted in the formation of **2a** in 74% yield after isolation by silica gel chromatography. The diphenylmethyl group gives excellent selectivity for the desired product **2a**; however, the yield of **2a** was modest due to poor chain propagation. In this case, tetraphenylethane was detected in the crude reaction mixture, which suggests that the expelled diphenylmethyl radical is too stable to abstract hydrogen smoothly from tributyltin hydride and instead permits dimerization. *N*-*t*-Butylhexynylamine also gave the desired product in good yield.[10]

We examined the generality of the lactam ring formation using a variety of substituted *N*-α-phenethyl alkynylamines, as summarized in Table 1. For example, *N*-unsubstituted

Table 1. Carbonylative S_Hi-Type Reaction Leading to Nitrogen-Unsubstituted Lactams[a]

entry	alkynylamines **1**	products	yield[b]
1	 **1e**		**2e** 84% (*E*/*Z* = 17/83)
2	 **1f**		**2f** 69% (*E*/*Z* = 20/80)
3	 **1g**		**2g** 73% (*E*/*Z* = 14/86)
4	 **1h**		**2h** 62% (*E*/*Z* = 13/87)
5	 **1i**		**2i** 68% (*E*/*Z* = 16/84)
6	 **1b**		**2a** 74% (*E*/*Z* = 4/96)
7	 dr = 50:50 **1j**		**2j** 77% (*E*/*Z* = <<99)
8	 dr = 51:49 **1k**		**2k** 70% (*E*/*Z* = 4<96)
9	 **1l**		**2l** 47% (*E*/*Z* = 5/95)
10	 **1m**		**2m** 71% (*E*/*Z* = 10/90)
11	 **1n**		**2n** 64% (*E*/*Z* = 9/91)

[a] Reaction conditions: for entries 1−9, [RX] = 0.01 M, AIBN (19−20 mol %), CO (74−90 atm), Bu_3SnH (1.3−1.5 equiv), C_6H_6 (50 mL), 90 °C, 4 h; for entries 10 and 11, [RX] = 0.01 M, V-40 (1,1′-azobis(cyclohexane-1-carbonitrile)) (20 mol %), CO (90 atm), Bu_3SnH (1.3 equiv), C_6H_6 (50 mL), 110 °C, 4 h. [b] Isolated yields by flash chromatography on silica gel.

γ-lactam **2e** can be prepared from *N*-phenethyl homopropargylamine **1e** in 84% yield (entry 1). The reaction of substituted alkynylamines **1j**−**l** also proceeded smoothly to

(4) For recent examples, see: (a) Studer, A.; Amrein, S.; Matsubara, H.; Schiesser, C. H.; Doi, T.; Kawamura, T.; Fukuyama, T.; Ryu, I. *Chem. Commun*. **2003**, 1190. (b) Ryu, I.; Okuda, T.; Nagahara, K.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1997**, *62*, 7550. (c) Crich, D.; Hutton, T. K.; Ranganathan, K. *J. Org. Chem.* **2005**, *70*, 7672. (d) Carland, M. W.; Martin, R. L.; Schiesser, C. H. *Org. Biomol. Chem.* **2004**, *2*, 2612. (e) Malmström, J.; Jonsson, M.; Cotgreave, I. A.; Hammarström, L.; Sjödin, M.; Engman, L. *J. Am. Chem. Soc.* **2001**, *123*, 3434. (f) Coulomb, J.; Certal, V.; Fensterbank, L.; Lacôte, E.; Malacria, M. *Angew. Chem., Int. Ed*. **2006**, *45*, 633 and references therein.

(5) (a) Depature, M.; Siri, D.; Grimaldi, J.; Hatem, J.; Faure, R. *Tetrahedron Lett.* **1999**, *40*, 4547. (b) Zhang, L. M.; Koreeda, M. *J. Am. Chem. Soc.* **2004**, *126*, 13190.

(6) For reviews on radical carbonylations, see: (a) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050. (b) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177. (c) Ryu, I. *Chem. Soc. Rev.* **2001**, *30*, 16. Also see a review on acyl radicals: (d) Chatgilialoglu, C.; Crich, D.; Komatsu, M.; Ryu, I. *Chem. Rev.* **1999**, *99*, 1991.

(7) (a) Ryu, I.; Matsu, K.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **1998**, *120*, 5838. (b) Ryu, I.; Miyazato, H.; Kuriyama, K.; Matsu, K.; Tojino, M.; Fukuyama, T.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2003**, *125*, 5632. (c) Tojino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Schiesser, C. H.; Kuriyama, H.; Miyazato, H.; Minakata, S.; Komatsu, M.; Ryu, I. *Org. Biomol. Chem.* **2003**, *1*, 4262. (d) Tojino, M.; Otsuka, N.; Fukuyama, T.; Matsubara, H.; Ryu, I. *J. Am. Chem. Soc.* **2006**, *128*, 7712.

(8) For theoretical work, see: (a) Falzon, C. T.; Ryu, I.; Schiesser, C. H. *Chem. Commun*. **2002**, 2338. (b) Matsubara, H.; Falzon, C. T.; Ryu, I.; Schiesser, C. H. *Org. Biomol. Chem.* **2006**, *4*, 1920.

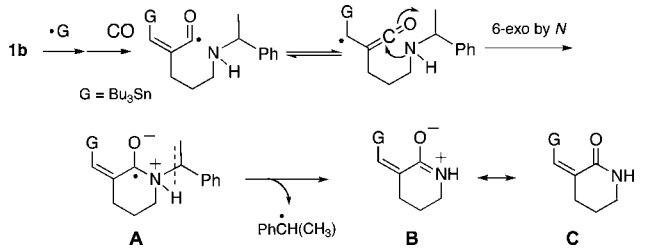
(9) (a) Georg, G. I.; He, P.; Kant, J.; Wu, Z. J. *J. Org. Chem.* **1993**, *58*, 5571. (b) Casadei, M. A.; Gessner, A.; Inesi, A.; Jugelt, W.; Moracci, F. M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2001.

(10) In this case, the lactam having *t*-butyl on nitrogen of the lactam **2a** and the *N*-*t*-butyl-α-methylene lactam were also obtained in 6% and 12% yields, respectively. See: Tojino, M.; Uenoyama, Y.; Fukuyama, T.; Ryu, I. *Chem. Commun*. **2004**, 2484.

give the corresponding δ-lactams **2j**−**l** in good yields (entries 7−9). In a similar way, seven-membered ring lactams **2m** and **2n** were synthesized from **1m** and **1n**, respectively (entries 10 and 11). The preparation of chiral γ-lactams was also examined. A diastereomeric mixture of alkynylamines **1f** and **1g** was obtained by the condensation of α-phenethylamine having an (*R*)-configuration with benzaldehyde, followed by reaction with propargyl bromide in the presence of zinc. This gave a mixture of diastereomers **1f** and **1g**, which were separated by recrystallization of the HCl salt. The resulting chiral alkynylamines **1f** and **1g** were subjected to the standard reaction conditions, which gave the chiral γ-substituted α-methylene-γ-butyrolactams **2f** and **2g**, respectively (entries 2 and 3). In a similar way, chiral γ-methyl-substituted γ-lactams **2h** and **2i** were prepared from the corresponding alkynylamines **1h** and **1i** in good yields (entries 4 and 5).

For the present homolytic substitution reaction at N by α,β-unsaturated acyl radicals, we propose a pathway which involves the nucleophilic trap of α-ketenyl radicals, forming intermediate **A** as the first event (Scheme 3). Thus formed

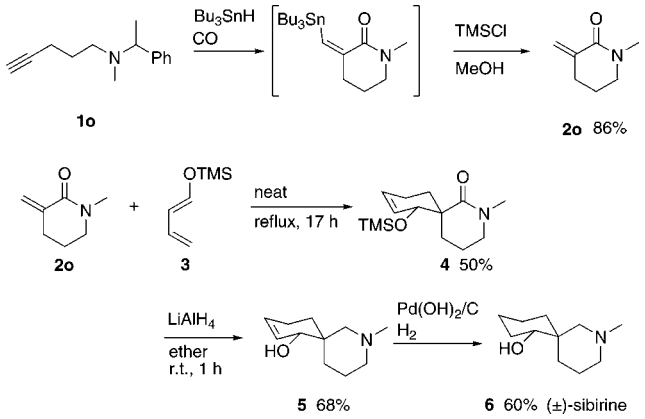
Scheme 3. Proposed Reaction Pathway



A would then undergo β-fission expelling the α-phenethyl radical and yielding **B**, which is a canonical form of the product **C**.[11,12]

Although the present method is useful for the synthesis of lactams unsubstituted at nitrogen, interestingly, the S_Hi-type reaction at nitrogen is possible even in the case of a tertiary amine. The carbonylative S_Hi-type reaction of **1o**, coupled with the subsequent protodestannylation procedure, gave the corresponding *N*-methyl-substituted lactam **2o** in 86% yield (Scheme 4). Thus prepared **2o** was subjected to a Diels−Alder reaction with siloxydiene **3**, resulting in spirocycle **4** in 50% yield. The lithium aluminum hydride reduction of **4** and subsequent hydrogenation using $Pd(OH)_2$ catalyst gave the alkaloid sibirine (**6**).[13]

Scheme 4. Carbonylative S_Hi-Type Reaction of a Tertiary Alkynylamine **1o** and Its Application to the Synthesis of (±)-Sibirine



In conclusion, we have demonstrated that α,β-unsaturated acyl radicals, generated by radical carbonylation of N-substituted alkynylamines in the presence of tributyltin hydride, undergo unusual substitution at the nitrogen atom. According to the protocol, five- to seven-membered ring lactams were prepared in good yields. Thus, in addition to radical addition to imine N−C bonds, homolytic substitution of acyl radicals at nitrogen is a useful tool for lactam ring formation with incorporation of CO.

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Note Added after ASAP Publication. The stereochemistry of structures **4**−**6** in Scheme 4 and the Supporting Information was incorrect in the version published ASAP January 30, 2007; the revised version was published ASAP February 5, 2007.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Interestingly, the 6-aza-7-phenyloctanoyl radical did not undergo a S_Hi-type reaction. This may suggest the importance of the ketenyl radical structure.

(12) A preliminary MO calculation on the BHandHLYP/6-31+G*//BHandHLYP/6-31G* predicted that this two-step pathway is possible.

(13) (a) Wanner, M. J.; Koomen, G. J. *Tetrahedron Lett.* **1989**, *30*, 2301. (b) Deyine, A.; Poirier, J. M.; Duhamel, L.; Duhamel, P. *Tetrahedron Lett.* **2005**, *46*, 2491. (c) Koreeda, M.; Wang, Y.; Zhang, L. *Org. Lett.* **2002**, *4*, 3329.