HETEROCYCLES, Vol. 80, No. 2, 2010, pp. 879 - 885. © The Japan Institute of Heterocyclic Chemistry
Received, 19th August, 2009, Accepted, 11th September, 2009, Published online, 16th September, 2009
DOI: 10.3987/COM-09-S(S)115

NOVEL RADICAL CYCLIZATION METHOD ACCOMPANIED BY ELIMINATION OF HYDRAZYL RADICAL

Shoji Kobayashi, Hidefumi Hirao, Tatsuro Kawauchi, and Ilhyong Ryu*

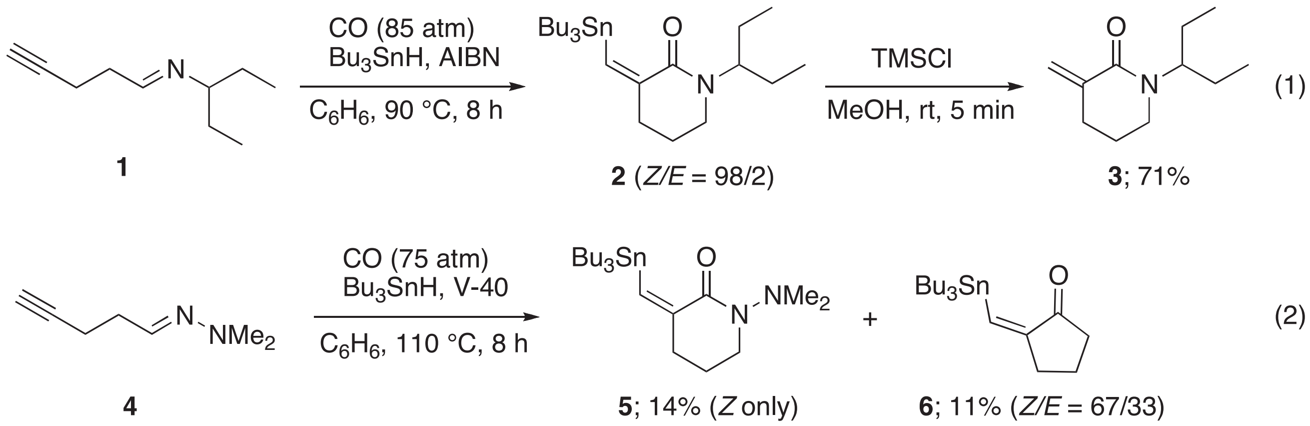
Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, 599-8531, Japan. E-mail: ryu@c.s.osakafu-u.ac.jp

Dedicated to Professor Akira Suzuki on the occasion of his 80th birthday

Abstract – The potential of hydrazine group as the new radical leaving group was studied. Radical cyclization of (*E*)-1,1-dialkyl-2-(1-alkyloct-2-en-7-ynyl)hydrazines with *n*-Bu_3SnH/AIBN, followed by protodestannylation, gave 1-alkenyl-2-methylenecyclopentanes, which arose by 5-exo cyclization and subsequent β-elimination of hydrazyl radical.

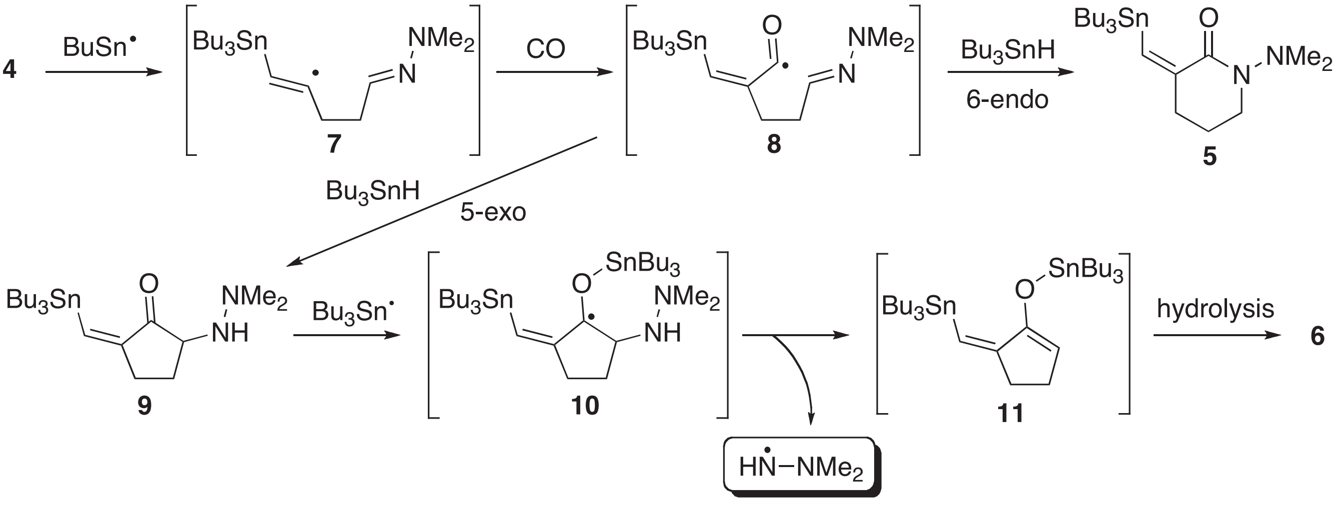
Radical cyclization is a powerful method for the synthesis of cyclic molecules including natural products, bioactive agents, and various functional molecules.[1] A wide variety of leaving groups such as halogens, selenides, sulfides, sulfoxides, sulfones, stannanes, and xanthates are generally used, if addition/elimination sequence is involved in the process.[2] These functional groups, however, sometimes cause problems, especially in the stage of their introduction, owing to insufficient functional group compatibility, inherent toxicity of reactants, or other unforeseen difficulties encountered.

In the meantime, during the course of our studies to develop new radical carbonylation reactions for lactam ring synthesis,[3,4] we discovered that cyclization of the acyl radicals proceeded regioselectively onto the nitrogen of imines (and oxazoline) C–N bonds, providing the 6-endo cyclization products (Scheme 1, Eq. 1).[4f] To expand this methodology, we have examined carbonylative radical cyclization of alkynyl hydrazone **4** in the presence of Bu_3SnH and V-40 as a radical initiator (Scheme 1, Eq. 2). In contrast with 6-endo cyclization onto imine nitrogen, 6-endo cyclization onto hydrazone nitrogen was not smooth, giving **5** in low yield, together with a small amount of 2-((tributylstannyl)methylene)cyclopentanone **6**, which does not contain a hydrazine unit.[5]



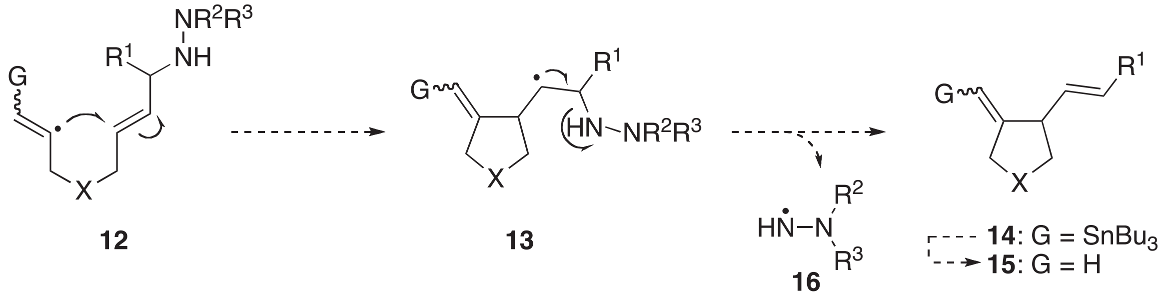
Scheme 1. Carbonylative Radical Cyclization of Alkynyl Imine (**1**) and Alkynyl Hydrazone (**4**)

It can be rationalized that δ-lactam **5** was generated by 6-endo cyclization of α,β-unsaturated acyl radical **8** (Scheme 2).[6] On the other hand, it was supposed that cyclopentanone **6** was generated through hydrazine **9**, which was initially produced by 5-exo cyclization of **8**, by expelling the hydrazyl radical from cyclopentane ring with the aid of tributyltin radical addition to carbonyl oxygen. To the best of our knowledge, there are no published studies demonstrating that such a hydrazine moiety acts as a radical leaving group. Moreover, only a few examples have been reported for the cleavage of N-C bond to generate the nitrogen-centered radicals.[7,8] We therefore considered that evaluating the potential of hydrazine functionality as the radical leaving group would provide not only a conceptually new method for radical reactions, but a new entry into the generation of nitrogen-centered radical for further usage. Herein, we wish to report a novel radical cyclization method involving elimination of the hydrazyl radical, which used vinyl radical cyclization as a model.



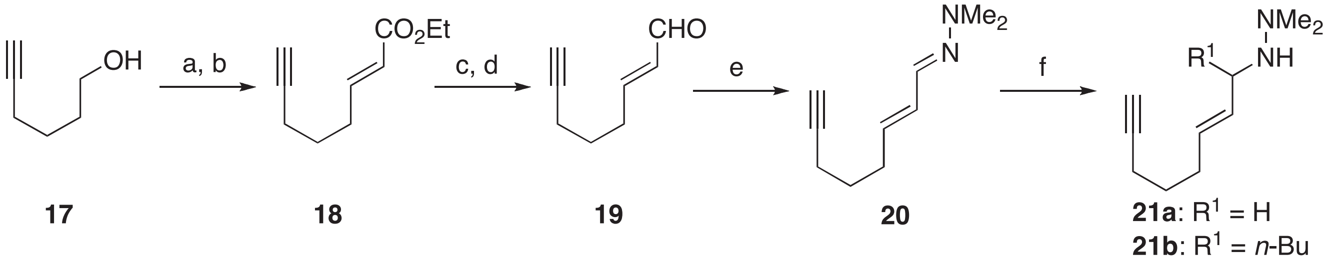
Scheme 2. Proposed Mechanism for the Formation of Lactam (**5**) and Ketone (**6**)

We have designed a reaction system consisting of 5-exo cyclization of vinyl radical **12** due to exceedingly facile cyclization mode.[7a,9] Incorporation of carbon or heteroatom as X into the backbone would produce the corresponding 1,4-diene with carbocycle or heterocycles. The fragmentation of intermediate alkyl radical **13** to afford diene **14** and hydrazyl radical **16** would be the key to the success of this approach. Since the nitrogen-carbon bond is generally strong, it seems of importance to investigate the substituents (R^2 and R^3) that can stabilize the *N*-centered radical as much as possible to facilitate β-scission.[10]



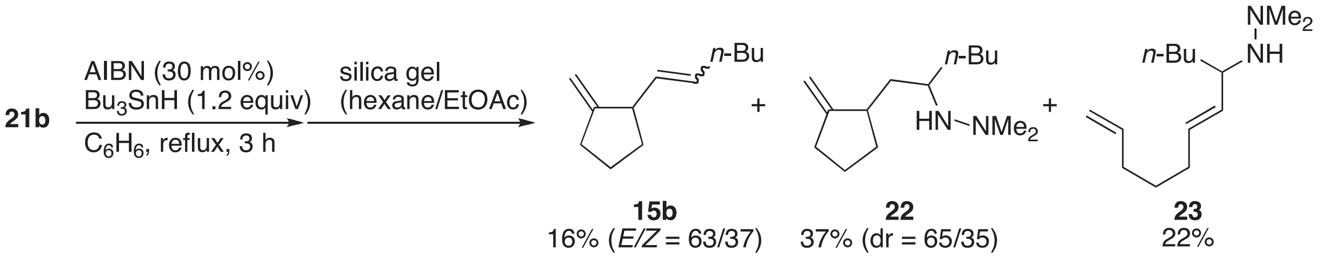
Scheme 3. New Concept of Radical Cyclization Involving Elimination of Hydrazyl Radical.

We initially envisaged the use of inexpensive *N*,*N*-dimethylhydrazine as the leaving group and decided to study the behavior of (*E*)-1,1-dimethyl-2-(oct-2-en-7-ynyl)hydrazine **21a** as a model (Scheme 4). To prepare this compound, we embarked on the sequence shown in Scheme 4. Thus, commercially available 5-hexyn-1-ol **17** was converted to aldehyde **19** in a conventional manner. Condensation of **19** with *N*,*N*-dimethylhydrazine in the presence of molecular sieves 3Å proceeded smoothly at 80 °C to give the conjugated hydrazone **20**. However, we were unable to obtain allylhydrazine **21a** by reduction of **20** with $LiAlH_4$. The parallel study indicated that allylhydrazine lacking α-substituent was unstable and it was immediately auto-oxidized to the corresponding hydrazone during isolation. Therefore, *n*-butyl group was introduced through 1,2-addition to suppress undesirable auto-oxidation, thereby affording the chemically stable hydrazine **21b** in 94% isolated yield.



Scheme 4. *Reagents and conditions*: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to rt; (b) Ph_3PCHCO_2Et, CH_2Cl_2, rt, 63% (2 steps); (c) DIBAL, CH_2Cl_2, –78 °C, 93%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C to rt, 100%; (e) Me_2NNH_2, MS3Å, toluene, 80 °C, 91%; (f) *n*-BuLi, Et_2O, 0 °C to rt, 94% (for **21b**).

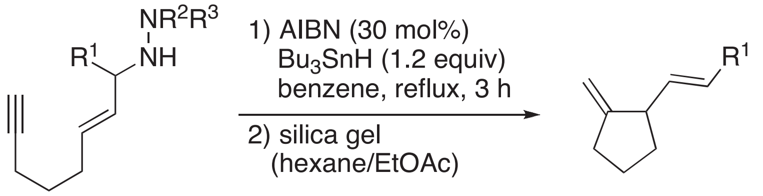
With allylhydrazine **21b** in hand, we then examined the radical cyclization under thermal conditions (Scheme 5). A mixture of **21b** (0.05 M), AIBN (30 mol%), and Bu_3SnH (1.2 equiv) in benzene was refluxed for 3 h. After usual work-up, the crude product was purified by silica gel column chromatography. As expected, cyclic diene **15b** which does not contain the hydrazine moiety was obtained in 16% yield, along with cyclic hydrazine **22** (37%) and acyclic hydrazine **23** (22%).[11] This result suggests that dimethylhydrazine can serve as a leaving group in the tin radical-promoted 5-exo cyclization, albeit with low efficiency. We suspected that competitive hydrogen abstraction of the intermediate radical (cf. **12** and **13**) from Bu_3SnH leading to **23** and **22** would be reduced by decreasing the concentration of the reaction system. Indeed, the proportion of cyclic diene **15b** was marginally increased (**15b**:**22**:**23** = 30:45:25) when the reaction was carried out at a concentration of 0.015 M of **21b**.[12] However, the influence of concentration on the product selectivity was less than we expected.[13]



Scheme 5. Radical Cyclization of *N*,*N*-Dimethylhydrazine (**21b**)

Next, we explored the effect of substituents (R^2 and R^3) on the hydrazine moiety (Table 1). Each substrate was readily prepared from the common intermediate **19** in a similar manner to that described in Scheme 4. When one of the substituents on the nitrogen was replaced by *m*-tolyl group, the yield of **15b** was increased up to 31% (entry 2). Much improvement was realized by introducing two phenyl groups on the hydrazine moiety (entry 4). In contrast, benzyl substituents showed negative effects and no cyclic diene **15b** was obtained, while cyclic hydrazine akin to **22** was formed in a small amount (entry 3).[14] Encouraged by the positive results achieved by introducing the aromatic hydrazines, we then explored the substituents at α-position (R^1). The radical cyclization of methyl-substituted allylhydrazine **21f** provided diene **15c** in 22% yield along with the cyclic hydrazine akin to **22** in 61% yield (entry 5). It is likely that the reduced steric hindrance at the position α to radical provokes smooth hydrogen abstraction from tin hydride, thereby decreasing the yield of **15c**. In contrast, the reaction with phenyl-substituted hydrazine **21g** gave rise to the desired diene **15d** in 60% yield with an excellent *E*/*Z* ratio (entry 6).[15]

Table 1. Radical Cyclization with Various Hydrazines



21b-g

15b: R^1 = *n*-Bu
15c: R^1 = Me
15d: R^1 = Ph

entry	**21**	R^1	R^2	R^3	yield of **15**^{a} (%)	E/Z^b
1	**21b**	*n*-Bu	Me	Me	16	63:37
2	**21c**	*n*-Bu	Me	*m*-tolyl	31	76:24
3	**21d**	*n*-Bu	Bn	Bn	0	-
4	**21e**	*n*-Bu	Ph	Ph	37	79:21
5	**21f**	Me	Ph	Ph	22	68:32
6	**21g**	Ph	Ph	Ph	60	96:4

^{a} Isolated yield. ^{b} Determined by ^{1}H NMR analysis.

In summary, we have developed a new radical cyclization method employing hydrazine as the leaving group. The fragmentation of intermediate alkyl radical **13** proceeds efficiently to give 1,4-diene **14** even though it involves scission of a rather strong carbon-nitrogen bond. Among the substrates tested, diphenylhydrazine gave the best result. From a synthetic standpoint, a variety of hydrazines are readily accessible from aldehydes or ketones by simple operations. These preliminary investigations represent an important guideline for developing a new type of radical cyclization with nitrogen-based leaving groups, which could be useful for the construction of both carbocycles and heterocycles. Further investigations to improve the leaving-group ability, as well as the use of other starting radicals are currently underway.[16]

ACKNOWLEDGEMENTS

This work was supported by a Grant-in-Aid for Scientific Research from MEXT and JSPS, Japan.

REFERENCES AND NOTES

1. For reviews on free radical reaction used in the synthesis of natural products and related molecules, see: (a) C. P. Jasperse, D. P. Curran, and T. L. Fevig, *Chem. Rev.*, 1991, **91**, 1237; (b) P. J. Parsons, C. S. Penkett, and A. J. Shell, *Chem. Rev.*, 1996, **96**, 195; (c) M. Malacria, *Chem. Rev.*, 1996, **96**, 289; (d) T. Naito, *Heterocycles*, 1999, **50**, 505; (e) H. Ishibashi, T. Sato, and M. Ikeda, *Synthesis*, 2002, 695; (f) W. R. Bowman, A. J. Fletcher, and G. B. S. Potts, *J. Chem. Soc., Perkin Trans. 1*,

2002, 2747.

2. 'Radicals in Organic Synthesis,' Vol. 1 and Vol. 2, ed. by P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001.
3. For reviews on radical carbonylations, see: (a) I. Ryu and N. Sonoda, *Angew. Chem., Int. Ed. Engl.,* 1996, **35**, 1051; (b) I. Ryu, N. Sonoda, and D. P. Curran, *Chem. Rev*., 1996, **96**, 177; (c) C. Chatgilialoglu, D. Crich, M. Komatsu, and I. Ryu, *Chem. Rev*., 1999, **99**, 1991; (d) I. Ryu, *Chem. Soc. Rev*., 2001, **30**, 16.
4. For our recent work, see: (a) I. Ryu, K. Matsu, S. Minakata, and M. Komatsu, *J. Am. Chem. Soc.,* 1998, **120**, 5838; (b) T. Fukuyama, Y. Uenoyama, S. Oguri, N. Otsuka, and I. Ryu, *Chem. Lett.,* 2004, **33**, 854; (c) M. Tojino, Y. Uenoyama, T. Fukuyama, and I. Ryu, *Chem. Commun*., 2004, 2482; (d) Y. Uenoyama, T. Fukuyama, O. Nobuta, H. Matsubara, and I. Ryu, *Angew. Chem. Int. Ed*., 2005, **44**, 1075; (e) I. Ryu, Y. Uenoyama, and H. Matsubara, *Bull. Chem. Soc. Jpn*., 2006, **79**, 1476; (f) M. Tojino, N. Otsuka, T. Fukuyama, H. Matsubara, and I. Ryu, *J. Am. Chem. Soc*., 2006, **128**, 7712; (g) Y. Uenoyama, T. Fukuyama, and I. Ryu, *Org. Lett*., 2007, **9**, 935.
5. For acyl radical cyclization onto hydrazone carbon, see: I. M. Brinza and A. G. Fallis, *J. Org. Chem*., 1996, **61**, 3580.
6. We have not precluded fully an alternative mechanism that includes 5-exo cyclization of acyl radical **8** followed by aziridination to produce azabicyclo[3.1.0]hexane ring that rearranges to δ-lactam to release its strain. For computational studies, see: (a) H. Matsubara, C. T. Falzon, I. Ryu, and C. H. Schiesser, *Org. Biomol. Chem.,* 2006, **4**, 1920; (b) C. H. Schiesser, U. Wille, H. Matsubara, and I. Ryu, *Acc. Chem. Res.,* 2007, **40**, 303.
7. For reviews on the generation and use of nitrogen-centered radicals: (a) A. G. Fallis and I. M. Brinza, *Tetrahedron,* 1997, **53**, 17543; (b) L. Stella, 'Radicals in Organic Synthesis,' Vol. 2, ed. by P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001, pp. 407-426; (c) S. Z. Zard, *Chem. Soc. Rev*., 2008, **37**, 1603.
8. (a) O. Kitagawa, S. Miyaji, Y. Yamada, H. Fujiwara, and T. Taguchi, *J. Org. Chem*., 2003, **68**, 3184; (b) J. Kemper and A. Studer, *Angew. Chem. Int. Ed*., 2005, **44**, 4914; (c) J. Guin, S. Mück-Lichtenfeld, S. Grimme, and A. Studer, *J. Am. Chem. Soc*., 2007, **129**, 4498.
9. M. Newcomb, 'Radicals in Organic Synthesis,' Vol. 1, ed. by P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001, pp. 318-336.
10. For investigation of substituent effects on the stability of *N*-centered radicals of aniline derivatives, see: Z. Li and J.-P. Cheng, *J. Org. Chem*., 2003, **68**, 7350.
11. The crude ^{1}H NMR spectroscopy indicated that the Bu$_3$Sn group on exomethylene was present after the reaction, but was removed during silica gel column chromatography.

12. In this case, decrease of reaction rate and incomplete conversion of starting material were observed.
13. It is assumed that 1,5-hydrogen shift in alkyl radical **13** may be a competitive reaction course, thereby unavoidably affording **22** even under the diluted conditions.
14. This observation supports the possibility of the intermediate alkyl radical undergoing 1,5-hydrogen shift to provide the stable benzyl radical (see, footnote 13).
15. **Typical procedure**: A magnetic stirring bar, **21g** (70.1 mg, 0.191 mmol), AIBN (15.2 mg, 0.0926 mmol), Bu_3SnH (62.0 μL, 0.230 mmol) and benzene (4.5 mL) were placed in a 20 mL 2-neck round-bottomed flask and the mixture was brought to reflux for 3 h under argon. The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane) to give **15d** (21.1 mg, 0.115 mmol, 60%). Compound **15d**: ^{1}H-NMR (500 MHz, $CDCl_3$) δ 1.50-1.66 (m, 2H), 1.78-1.82 (m, 1H), 1.98-2.03 (m, 1H), 2.33-2.40 (m, 1H), 2.43-2.48 (m, 1H), 3.13 (q, 1H, J = 8.3 Hz), 4.82 (s, 1H), 4.95 (s, 1H), 6.09 (dd, 1H, J = 15.6, 8.3 Hz), 6.40 (d, 1H, J = 16.0 Hz), 7.20 (t, 1H, J = 7.4 Hz), 7.30 (t, 2H, J = 7.8 Hz), 7.37 (d, 2H, J = 7.4 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 24.63, 32.68, 34.26, 48.75, 106.57, 126.04, 126.89, 128.46, 130.00, 133.04, 137.67, 155.24. ; IR (neat) ν 3060, 3026, 2954, 2867, 1651, 1495, 1448 cm^{-1}; HRMS (EI): m/z $[M]^+$ calcd for $C_{14}H_{16}$: 184.1252, found 184.1228.
16. Recently substituted allyldiphenylphosphine oxides were developed as radical allylating agents with group 15 elements, see: G. Ouvry, B. Quiclet-Sire, and S. Z. Zard, *Angew. Chem. Int. Ed.*, 2006, **45**, 5002.