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Selective 6-endo Cyclization of the Acyl Radicals onto the Nitrogen of Imine and Oxazoline C−N Bonds

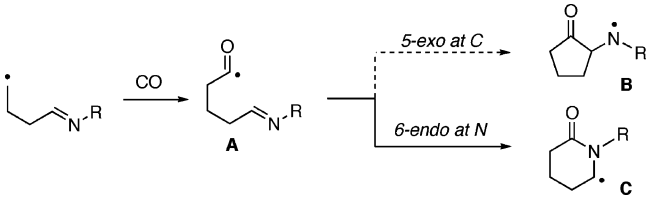
Mami Tojino, Noboru Otsuka, Takahide Fukuyama, Hiroshi Matsubara, and Ilhyong Ryu*

Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan

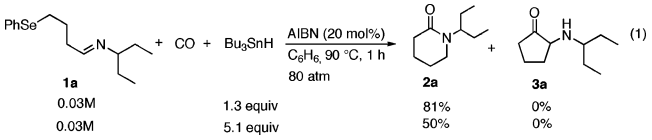
Received April 14, 2006; E-mail: ryu@c.s.osakafu-u.ac.jp

The many remaining challenges in the synthesis of organic compounds have resulted in the generation of ingenious synthetic methods, including many which employ radical chemistry.[1,2] It is generally accepted that 5-exo radical cyclizations are favored relative to 6-endo cyclizations in those cases where the Beckwith−Houk model operates[3] and applications of the 5-exo cyclization for the synthesis of heterocycles are abundant.[4] We previously reported that the introduction of a polar functionality into radical cyclization substrates results in selective 5-exo radical cyclization onto the imine nitrogen,[5,6] leading to lactams with incorporation of carbon monoxide as the carbonyl group. These exo-type radical cyclizations occur with complete *N*-philic regioselectivity, which may be ascribed to the "polarity-matched" combination of an acyl radical and an imine N−C, as predicted by MO calculations.[7] We envisaged that the strength of polarity matching in radical cyclization chemistry might even permit a 6-endo cyclization onto nitrogen, in the presence of an alternative, 5-exo cyclization pathway (Scheme 1). Herein, we report that acyl radicals generated by the addition of alkyl or vinyl radicals to carbon monoxide[9] cyclize onto the C−N bonds of imines and oxazoline with perfect 6-endo selectivity, driven by a preference for attack at nitrogen.

Scheme 1. Two Possible Modes of Acyl Radical Cyclization onto an Imine C−N Bond

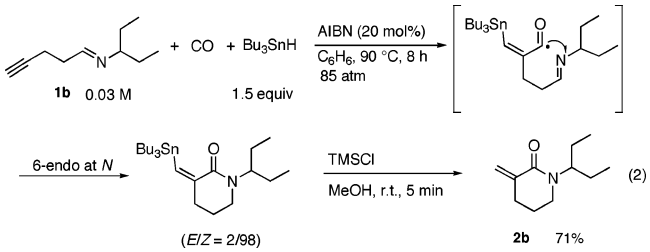


When the reaction of a phenylseleno-substituted imine **1a**, which is prepared from 4-phenylselenobutanal and 3-aminopentane, with carbon monoxide was carried out in the presence of tributyltin hydride and AIBN (2,2′-azobisisobutyronitrile), 2-piperidinone **2a** was obtained in 81% yield after isolation by flash chromatography on silica gel (eq 1). Careful examination of NMR spectra of the



crude reaction mixture failed to detect even trace amounts of the five-membered ring product **3a**. This regiochemical selectivity favoring the 6-endo product **2a** is in a sharp contrast with Fallis' acyl radical cyclization onto the C−N double bond of diphenylhydrazones, which proceeds selectively at carbon via a 5-exo pathway to form the aminyl radical stabilized by the diphenylamino group.[8] Another possible route which would lead to the 6-endo product is via an initial 5-exo cyclization of acyl radical **A** onto the imine carbon to give **B**, followed by isomerization to give the six-membered ring radical **C**. However, an attempt to trap five-membered ring radical **B** using a large excess (5.1 molar equiv) of Bu_3SnH gave only a decreased yield of 6-endo product **2a** (50%) along with the formation of reduction product of **1a** (34%) without even a trace of **3a**.

We then examined the carbonylation of alkynyl imine **1b** using tributyltin hydride and AIBN. After the reaction was complete, the reaction mixture was treated with TMSCl and MeOH to remove the tributyltin group. Again, the reaction gave the 6-endo product, α-methylene lactam **2b**, selectively in 71% yield (eq 2).



To explore the generality of the 6-endo radical ring formation reaction, a variety of substituted alkynyl imines were examined, and the results are summarized in Table 1. Good yields of six-membered α-methylene lactams are obtained for reactions of both aldimines and ketimines. Although diastereoselection was minimal for ketimines **1f** and **1g** (entries 5 and 6), a substrate with a bulkier substituent, such as ketimine **1h** derived from 2,2-dimethyl-1-methylpropylamine, reacted with higher diastereoselectivity 77/23 (entry 7). Given that the endo cyclization generates a radical inside the ring, we also attempted a tandem radical reaction to synthesize a fused bicyclic lactam. The reaction of **1i** gave bicyclic lactam **2i** in 64% yield, which was obtained via 6-endo/5-exo tandem cyclization (entry 8). α,β-Unsaturated lactam **2j**, having an endo unsaturation, was obtained when the reaction of vinyl iodide **1j** containing an imine moiety was carried out (entry 9). We also examined oxazoline derivatives to determine whether a similar 6-endo cyclization takes place with these substrates. Alkynyl oxazoline **1k** in fact did undergo selective 6-endo cyclization to provide bicyclic lactam **2k** in 71% yield after protodestannylation (entry 10). An optically active oxazoline derivative **1l** was also examined, which gave **2l** after protodestannylation in good yield (entry 11).[10]

All these results demonstrate that polar interactions between generated α,β-unsaturated acyl radical and imine and oxazoline C═N bonds provide a general platform for selective 6-endo cyclizations. In support of this, DFT calculation predicts that the 6-endo cyclization of 2-methylene-6-aza-5-hexenoyl radical is kinetically favored: the energy barrier for the 6-endo cyclization is 13.8 kJ/mol, whereas that for the 5-exo mode is 46.2 kJ/mol (BHandHLYP/aug-cc-pVDZ//BHandHLYP/cc-pVDZ).[11]

With the generality of the reaction established, we then examined its application in the synthesis of natural products, specifically in the preparation of (*R*)-(−)-coniine (eq 3). Thus treatment of oxazoline derivative **1m**, which was prepared from 4-phenylselenobutyric acid and (*R*)-2-phenylglycinol, with carbon monoxide in the

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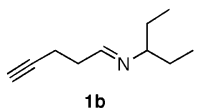
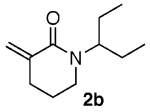
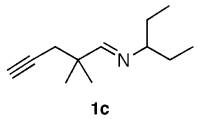
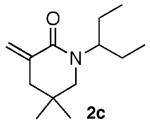
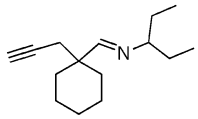
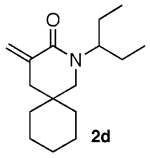
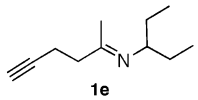
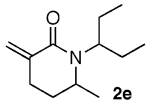
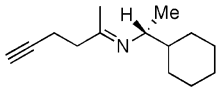
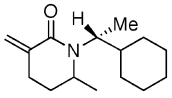
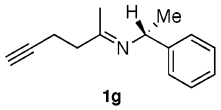
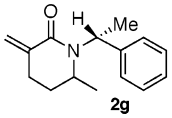
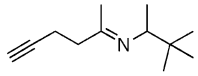
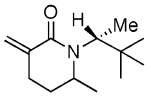
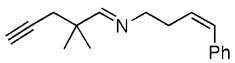
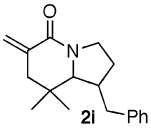
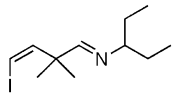
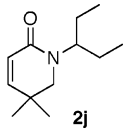
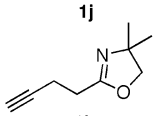
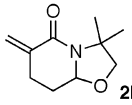
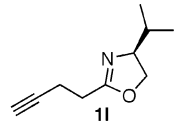
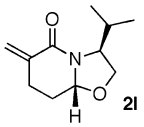
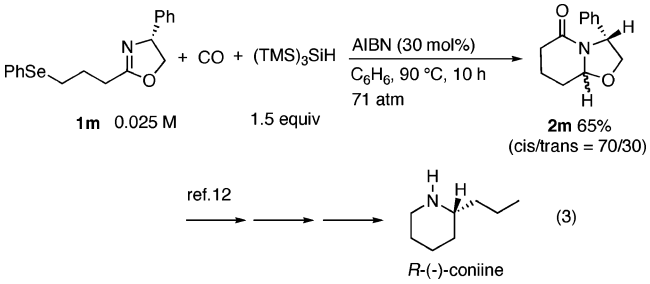
Table 1. 6-endo Cyclization of Acyl Radicals onto the Nitrogen of C−N Double Bonds[a]

entry	substrate **1**	lactam **2**	yield[b]
1	 **1b**	 **2b**	71%
2	 **1c**	 **2c**	60%
3	 **1d**	 **2d**	77%
4	 **1e**	 **2e**	80%
5[d]	 **1f**	 **2f**	77% (52/48)[c]
6[e]	 **1g**	 **2g**	77% (57/43)[c]
7	 **1h**	 **2h**	73% (77/23)[c]
8	 **1i**	 **2i**	64% (66/34)[c]
9	 **1j**	 **2j**	65%
10	 **1k**	 **2k**	71%
11	 **1l**	 **2l**	67% (4/96)[c]

[a] Conditions: **1** (0.5 mmol), Bu_3SnH (0.75 mmol), AIBN (0.2 equiv), benzene, CO (80−85 atm), 90 °C, 8 h. For a typical procedure, see the Supporting Information. [b] Isolated yields by chromatography on silica gel. [c] Determined by ^1H NMR. [d] V-40 (1,1′-azobis(cyclohexane-1-carbonitrile)), 100 °C, 12 h. [e] V-65 (2,2′-azobis(2,4′-dimethylvaleronitrile)), 70 °C, 12 h.

presence of tris(trimethylsilyl)silane and AIBN provided bicyclic lactam **2m** in 65% yield as 7:3 cis:trans mixture. Since Amat and coworkers used **2m** as key substrate for their (*R*)-(−)-coniine synthesis,[12] we have achieved the formal synthesis of (*R*)-(−)-coniine.

In conclusion, we have developed a new method for the synthesis of 2-piperidinones based on the free-radical-mediated carbonylation



and 6-endo cyclization of the resultant acyl radicals onto the imine and oxazoline nitrogen. We do believe that polar interactions will be an important concept to expand the scope of radical cyclization methodologies into new areas.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the MEXT, Japan. We thank Professors C. H. Schiesser and C. Crudden for helpful discussions. We acknowledge Library & Science Information Center, Osaka Prefecture University, for the computational study.

Supporting Information Available: Experimental procedures, compound characterization data, and details of computational studies on the reaction profile of cyclization of the 2-methylene-6-aza-5-hexenoyl radical. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The diastereoselectivity of initially formed stannylmethylene lactam, which was measured by ^1H NMR, was cis/trans = 42/58. Epimerization of cis-isomer to trans-isomer took place during the acidic protodestannylation procedure. For acidic epimerization of a related compound, see: Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molis, E.; Miravitlles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074.
(11) The 6-endo cyclization is thermodynamically favored: $\Delta E = -144.1$ kJ/mol for 6-endo, $\Delta E = -52.4$ kJ/mol for 5-exo. One reviewer mentioned a possibility that the interaction of *N* lone pair of imine with an α-ketenyl radical (α,β-unsaturated acyl radical) is stronger than that with an acyl radical. Our computational work is getting such a trend, and we will provide a full discussion in the full paper.
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