Nitrogen-philic Cyclization of Acyl Radicals onto N=C Bond. New Synthesis of 2-Pyrrolidinones by Radical Carbonylation/Annulation Method

Ilhyong Ryu,* Kazutoshi Matsu, Satoshi Minakata, and Mitsuo Komatsu*

Department of Applied Chemistry
Faculty of Engineering, Osaka University
Suita, Osaka 565-0871, Japan

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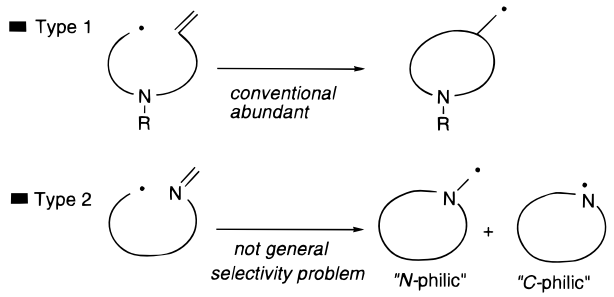
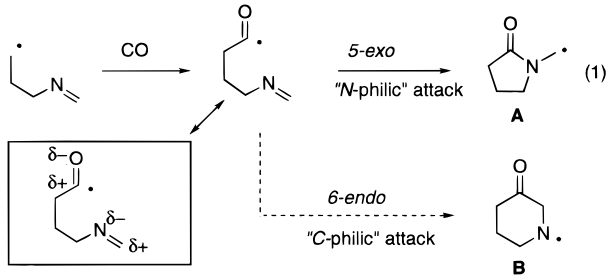
Radical cyclization reactions have become part of the repertoire of the synthetic organic chemist, even for the synthesis of nitrogen-containing heterocycles such as alkaloids.[1,2] As for five-membered ring formation, however, the strategic flexibility of the systems reported thus far is still insufficient, since useful strategies are limited to straightforward extensions of the 5-hexenyl radical cyclization in which a carbon atom at the 2, 3, or 4 position is replaced by a nitrogen atom (type 1, Scheme 1). In pursuit of alternate radical cyclization methodologies for the synthesis of nitrogen heterocycles, radical cyclizations onto N−C double bonds have been examined by Takano,[3] Warkentin,[4] Bowman,[5] and their co-workers (type 2, Scheme 1).[6] Unfortunately, this type of alkyl radical cyclization is often plagued by poor selectivities giving mixtures of nitrogen-containing heterocycles via 5-exo and 6-endo cyclizations. This suggests that the rates of both modes of cyclization are too close to be controlled, limiting the synthetic utility of this otherwise unique strategy.

Scheme 1



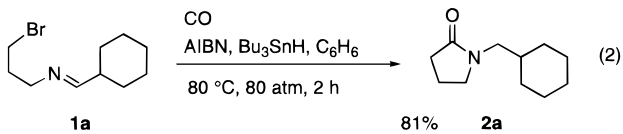
It occurred to us that the introduction of a *polar* component into radical cyclization chemistry would create new selective cyclization systems. The use of an acyl radical which is $\delta+/\delta-$ polarized should increase the selectivity by matching with the $\delta-/\delta+$ character of the N−C acceptor double bond.[7] This would create an "*N*-philic" acyl radical cyclization (eq 1). With this



(1)

working hypothesis in mind, we examined the 5-exo/6-endo cyclization of acyl radicals onto imine N−C bonds and found that indeed the *cyclization proceeds with complete selectivity for the nitrogen-philic mode (5-exo)*. We report herein a novel synthesis of 2-pyrrolidinones using a 4 + 1 type carbonylation/annulation method in which polarity is a key factor in controlling the selectivity of the radical cyclization.

The reaction of 3-bromopropylimine **1a** with carbon monoxide was carried out in the presence of tributyltin hydride and a catalytic amount of AIBN (2,2′-azobisisobutyronitrile) using an autoclave equipped with a glass liner. Under the conditions shown in eq 2, the desired 2-pyrrolidinone **2a** was obtained in 81% yield after isolation by flash chromatography on silica gel.[8]



(2)

Acyl radical cyclization took place at the nitrogen atom selectively. None of the corresponding six-membered ring product resulting from "carbon-attack" was observed.

As shown in Table 1, this 2-pyrrolidinone synthesis by a 4 + 1 annulation method is quite general and the yields are good to

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(2) For recent reviews, see: (a) Sibi, M. P.; Ji, J. In *Progress in Heterocyclic Chemistry*; Suschitzky, H., Gribble, G. W., Eds.; Pergamon Press: Oxford, 1996; Vol. 8. (b) Renaud, P.; Giraud, L. *Synthesis* **1996**, 913. (c) Fallis, A. G. Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. For selected recent examples on the synthesis of nitrogen heterocycles using radical cyclizations, see: (d) Parsons, P. J.; Penkett, C. S.; Cramp, M. C.; West, R. I.; Warrington, J.; Saraiva, M. C. *Synlett* **1995**, 507. (e) Curran, D. P.; Josien, H.; Ko, S.-B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2683. (f) Boger, D. L.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 1271. (g) Sato, T.; Kugo, Y.; Nakaumi, E.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1801. (h) Minisci, F.; Fontana, F.; Coppa, F.; Yan, Y. M. *J. Org. Chem.* **1995**, *60*, 5430. (i) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 465. (j) Kizil, M.; Lampard, C.; Murphy, J. A. *Tetrahedron Lett.* **1996**, *37*, 2511. (k) Czernecki, S.; Ayadi, E.; Xie, J. *Tetrahedron Lett.* **1996**, *37*, 9193. (l) Clive, D. L. J.; Coltart, D. M. *Tetrahedron Lett.* **1998**, *39*, 2519. (m) Aurrecoechea, J. M.; Fernandez-Acebes, A. *Synlett* **1996**, 39. (n) Della, E. W.; Knill, A. M. *J. Org. Chem.* **1996**, *61*, 7529. (o) Robertson, J.; Peplow, M. A.; Pillai, J. *Tetrahedron Lett.* **1996**, *37*, 5825. (p) Pandey, G.; Reddy, G. D.; Chakrabarti, D. *J. Chem. Soc., Perkin Trans. 1* **1996**, 219.

(3) (a) Takano, S.; Suzuki, M.; Kijima, A.; Ogasawara, K. *Chem. Lett.* **1990**, 315. (b) Takano, S.; Suzuki, M.; Ogasawara, K. *Heterocycles* **1994**, *37*, 149.

(4) (a) Tomaszewski, M. J.; Warkentin, J. *Tetrahedron Lett.* **1992**, *33*, 2123. (b) Tomaszewski, M. J.; Warkentin, J. *J. Chem. Soc., Chem. Commun.* **1993**, 966. (c) Tomaszewski, M. J.; Warkentin, J.; Werstiuk, N. H. *Aust. J. Chem.* **1995**, *48*, 291.

(5) (a) Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron Lett.* **1994**, *35*, 6369. (b) Bowman, W. R.; Stephenson, P. T.; Terrett, N. K.; Young, A. R. *Tetrahedron* **1995**, *51*, 7959. (c) Bowman, W. R.; Stephenson, P. T.; Young, A. R. *Tetrahedron* **1996**, *52*, 11445.

(6) Nitrogen radical cyclizations constitute the third type of strategy for the synthesis of nitrogen-containing heterocycles, see: (a) Beckwith, A. L. J.; Maxwell, B. J.; Tsanakatsidis, J. *Aust. J. Chem.* **1991**, *44*, 1809. (b) Esker, J. L.; Newcomb, M. *Adv. Heterocycl. Chem.* **1993**, *58*, 1. (c) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1275. (d) Bowman, W. R.; Clark, D. N.; Marmon, R. J. *Tetrahedron* **1994**, *50*, 1295. (e) Bowman, W. R.; Broadhurst, M. J.; Coghlan, D. R.; Lewis, K. A. *Tetrahedron Lett.* **1997**, *38*, 6301. (f) Maxwell, B. J.; Tsanaktsidis, J. *J. Am. Chem. Soc.* **1996**, *118*, 4276. (g) Tokuda, M.; Fujita, H.; Suginome, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 777. (h) Togo, H.; Hoshina, Y.; Yokoyama, M. *Tetrahedron Lett.* **1996**, *37*, 6129. (i) Zard, S. Z. *Synlett* **1996**, 1148. (j) Kaim, L. E.; Meyer, C. *J. Org. Chem.* **1996**, *61*, 1556. Also see a unique strategy based on radical cyclization onto azide functionality: (k) Kim, S.; Joe, G. H.; Do, J. Y. *J. Am. Chem. Soc.* **1994**, *116*, 5521. (l) Kizil, M.; Murphy, J. A. *J. Chem. Soc., Chem. Commun.* **1995**, 1409.

(7) The polar nature of acyl radical is acknowledged in the slow rate of decarbonylation in polar solvents, see: (a) Tsentalovic, Y. P.; Fischer, H. *J. Chem. Soc., Perkin Trans. 2* **1994**, 729. (b) Linazzi, L.; Ingold, K. U.; Scaiano, J. C. *J. Phys. Chem.* **1983**, *87*, 529. (c) Turro, N. J.; Gould, I. R.; Baretz, B. H. *J. Phys. Chem.* **1983**, *87*, 531.

(8) For typical experimental procedure, see the Supporting Information.

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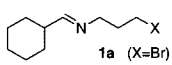
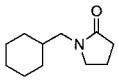
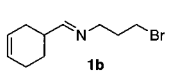
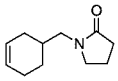
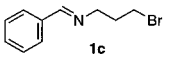
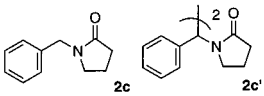
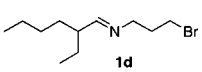
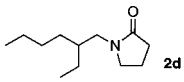
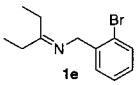
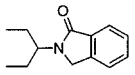
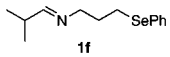
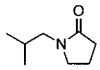
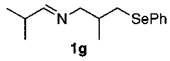
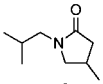
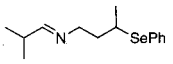
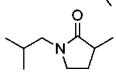
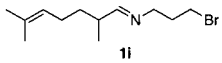
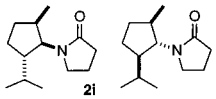
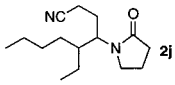
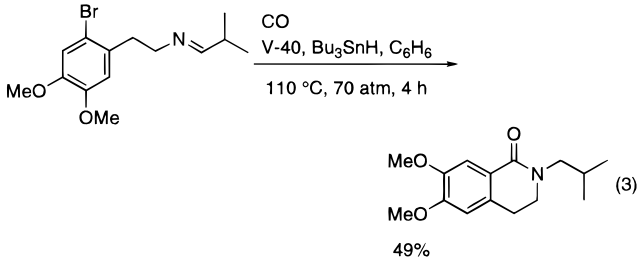
Table 1. Synthesis of 2-Pyrrolidinones by 4 + 1 Type Carbonylation/Annulation[a]

run	substrate **1**	product **2**	yield[b]
1	 **1a** (X=Br)	 **2a**	81%
2	**1a'** (X=Cl)		61%
3	 **1b**	 **2b**	75%
4	 **1c**	 **2c** **2c'**	16, 35% (65/35)[c]
5	 **1d**	 **2d**	71%
6	 **1e**	 **2e**	76%
7	 **1f**	 **2f**	71%
8	 **1g**	 **2g**	70%
9	 **1h**	 **2h**	65%
10	 **1i**	 **2i**	79% (78/22)[c]
11	**1d**,  (4 equiv)	 **2j**	56%[d]

[a] Reaction conditions: For runs 1−5, 10, and 11, [RX] = 0.015−0.020 M, AIBN, CO (78−90 atm), Bu_3SnH, C_6H_6, 80 °C, 2−3 h; for runs 6−9, [RX] = 0.017−0.022 M, V-40 (1,1′-azobis(cyclohexane-1-carbonitrile)), CO (70−90 atm), Bu_3SnH, C_6H_6, 110 °C, 3−5 h. [b] Isolated yields by flash chromatography on silica gel. [c] By NMR. [d] Obtained as a 53:47 mixture of diastereomers (by GC).

high. In every case, only one carbonylation product was observed and neither the six-membered product[9] nor the uncyclized carbonylation/reduction product (aldehyde) was formed. The absence of aldehydes suggests that the present *N*-philic acyl radical/imine cyclization should be very rapid. Both aldimines and ketimines can be used for this reaction, but the benzaldehyde imine cyclization is complicated by the formation of the homo-coupling dimers at the benzylic position, which causes chain cleavage (run 4).[10] This is presumably due to the very slow hydrogen abstraction of the cyclized α-amido benzyl radical, which is expected to be very stable. On the other hand, systems containing aryl radicals do not tolerate aldiminyl C−H bonds because of an undesirable radical translocation,[11] but the use of a ketimine-type substrate gives an excellent yield of 3,4-benzo-2-pyrrolidinone (run 6). The aminoalkyl radical resulting from *N*-philic cyclization can be designed such that it will participate in a second cyclization or an intermolecular C−C bond forming reaction (runs 10, 11). The *N*-philic acyl radical cyclization can be extended to the synthesis of 2-piperidinone by a 5 + 1 type annulation method, and eq 3 demonstrates such an example.



The origin of the unusual selectivity of the acyl radical cyclization, contrasted with that of the corresponding alkyl radical cyclizations,[5] brings up intriguing mechanistic issues. It is well-known that acyl radicals are considered to be nucleophilic in the context of additions to C−C double bonds having electron-withdrawing groups.[12] In this regard, the present results seem to be contradictory, since the only products observed come from attack of the acyl radical at the nucleophilic nitrogen of the N−C double bond. One rationale for this may be that the carbon-philic attack (6-endo) is the kinetic process and it is followed by subsequent isomerization to the thermodynamically more favorable α-amido radical (5-exo).[13] However, the reaction of **1f** performed at a high tin hydride concentration (0.1 M) gave only the product of 5-exo cyclization (**2f**), together with a comparable amount of the uncyclized reduction product, suggesting that the 5-exo radical might be kinetically formed. A possible explanation for the selective *N*-philic cyclization may involve nucleophilic attack of nitrogen on the carbonyl group, which would give the 5-exo radical via a resonance organization. The role of nitrogen lone pair on the selectivity should be evaluated properly, and we are now addressing the mechanistic issues surrounding this new type of cyclization.

In summary, we have demonstrated the first intramolecular addition of acyl radicals onto N−C double bonds which occurs with complete selectivity for *N*-philic cyclization. The products of this cyclization, 2-pyrrolidinones, are capable of further transformations, and this new reaction provides a basis for the synthesis of five-membered nitrogen-containing heterocycles with incorporation of carbon monoxide in the heterocyclic rings. We believe that "polarity governed" radical reactions such as that reported in this study will be a key feature in the design of selective radical cyclization systems.

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Supporting Information Available: Experimental procedures and spectral data for compounds **2a**−**j** (33 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(9) This selective cyclization to form five-membered rings is generally not observed in related acyl radical cyclizations onto C=C bonds. For leading references on the kinetic and mechanistic studies, see: (a) Chatgilialoglu, C.; Ferreri, C.; Lucarini, M.; Venturini, A.; Zavitsas, A. *Chem. Eur. J.* **1997**, *3*, 376. (b) Ryu, I.; Fukushima, H.; Okuda, T.; Matsu, K.; Kambe, N., Sonoda, N.; Komatsu, M. *Synlett* **1997**, 1265. For selective cyclization onto C=N, see: (c) Brinza, I. M.; Fallis, A. G. *J. Org. Chem.* **1996**, *61*, 3580.

(10) The corresponding cyclization of all carbon systems onto styryl double bonds does not suffer from this type of radical/radical coupling, see: (a) Schwartz, C. E.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 9272. (b) Ryu, I.; Kusano, K.; Hasegawa, M.; Kambe, N.; Sonoda, N. *J. Chem. Soc., Chem. Commun.* **1991**, 1018. (c) Nagahara, K.; Ryu, I.; Kambe, N.; Komatsu, M.; Sonoda, N. *J. Org. Chem.* **1995**, *60*, 7384.

(11) For similar observation, see ref 4b.

(12) For reviews involving acyl radicals, see: (a) Brown, C. E.; Neville, A. G.; Rayner, D. M.; Ingold, K. U.; Lusztyk, J. *Aust. J. Chem.* **1995**, *48*, 363. (b) Ryu, I.; Sonoda, N. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1050. (c) Crich, D.; Yuan, H. In *Advances in Free Radical Chemistry*; Rawal, V. H., Ed.; JAI Press: Greenwich, CT, 1998; Vol. 2, in press. (d) Ryu, I.; Sonoda, N.; Curran, D. P. *Chem. Rev.* **1996**, *96*, 177.

(13) Preliminary ab initio MO calculations at UHF 3-21G level suggested that 5-exo radical **A** is 17.2 kcal/mol more stable than the corresponding 6-endo radical **B** (eq 1).