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Efficient and Regioselective 9-*Endo* Cyclization of α-Carbamoyl Radicals

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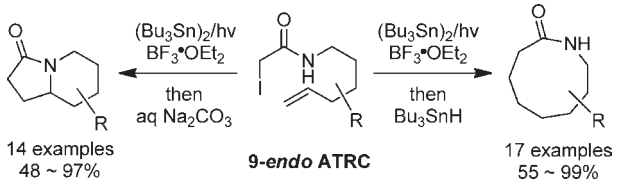
ABSTRACT



With the promotion of Lewis acid BF_3•OEt_2, various *N*-(hex-5-enyl)-2-iodoalkanamides underwent efficient and regioselective 9-*endo* iodine-atom-transfer radical cyclization reactions at room temperature. The cyclized products were readily converted to the corresponding azonan-2-ones by reduction with Bu_3SnH or to hexahydroindolizin-3(5*H*)-ones by treatment with aqueous Na_2CO_3 in a one-pot, two-stage manner.

Azonan-2-ones, along with their reduction product azonanes, are structural motifs in a number of biologically active natural products such as rhazinilam-type indole alkaloids[1] and *Lycopodium* alkaloids.[2] They are also versatile intermediates in organic synthesis. However, the efficient and general synthesis of nine-membered lactams is still a challenging task. They are often prepared by indirect methods such as ring expansion reactions[3] or Claisen rearrangement[4] of heterocyclic enamines. The direct construction of the nine-membered ring via Beckmann rearrangement[5] or the dehydration of ω-amino acids[6] suffers from the low chemoselectivity or limited scope of application. The recently developed ring-closing metathesis[7] requires the use of expensive and air-sensitive metal complexes. Herein we report that the 9-*endo* cyclization of α-carbamoyl radicals provides an efficient and convenient entry to various substituted azonan-2-ones.

Radical cyclizations have gained increasing popularity in organic synthesis in the past decades.[8] However, most studies were centered on the 5-*exo* or 6-*exo* cyclizations, while other types of cyclization[9] such as 9-*endo* cyclization were much less investigated. Nevertheless, scattered examples could be found in the literature on the 9-*endo* cyclizations of aryl,[10] vinyl,[11] alkyl,[12] and α-ester radicals.[13] On the other hand, the 9-*endo* cyclization of α-carbamoyl

(1) For examples, see: (a) Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1783–1789. (b) Kam, T. S.; Subramaniam, G.; Chen, W. *Phytochemistry* **1999**, *51*, 159–169. (c) Kam, T. S.; Subramaniam, G. *Nat. Prod. Lett.* **1998**, *11*, 131–136.

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(6) For examples, see: (a) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004–3007. (b) Pascal, C.; Dubois, J.; Guenard, D.; Gueritte, F. *J. Org. Chem.* **1998**, *63*, 6414–6420.

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(8) For selected reviews, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bond*; Pergamon: Oxford, U. K., 1986. (b) Curran, D. P. *Synthesis* **1988**, 417–439. (c) Curran, D. P. *Synthesis* **1988**, 489–513. (d) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001. (e) Rowlands, G. J. *Tetrahedron* **2009**, *65*, 8603–8655. (f) Rowlands, G. J. *Tetrahedron* **2010**, *66*, 1593–1636.

(9) For reviews, see: (a) Srikrishna, A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, pp 151–187. (b) Yet, L. *Tetrahedron* **1999**, *55*, 9349–9403.

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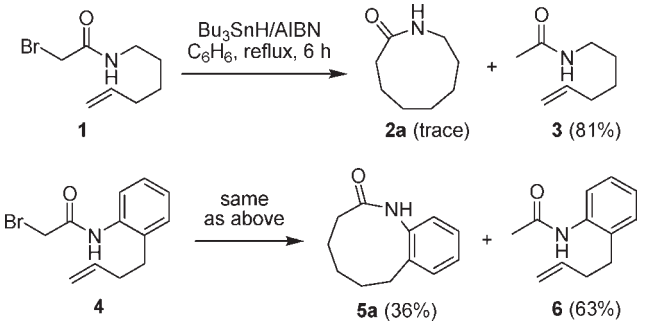
radicals remains unexplored. Owing to our interest in the reactivity of α-carbamoyl radicals,[14] we set out to explore this possibility.

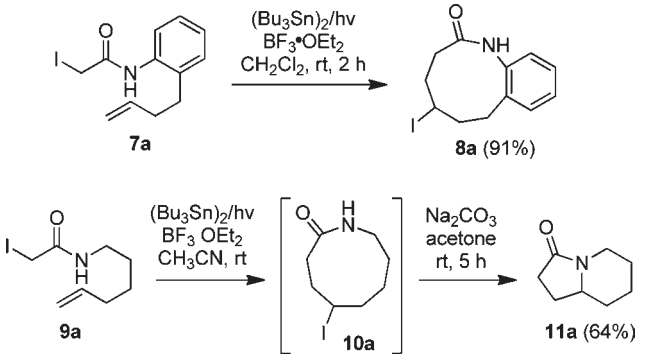
Scheme 1. Reactions of Bromoacetamides with Bu_3SnH/AIBN



2-Bromo-*N*-(hex-5-enyl)acetamide (**1**) was initially used as the substrate. The slow addition (with the aid of a syringe pump) of the benzene solution of Bu_3SnH and AIBN into **1** in benzene (0.03 M) at reflux yielded only a trace amount of the expected cyclization−reduction product **2a**, the major product being the direct reduction product **3** (Scheme 1). Similarly, the reaction of benzo-fused amide **4** with Bu_3SnH/AIBN gave the cyclized product **5** in only 36% yield while the direct reduction product **6** was obtained in 63% yield.

We then turned to examine the corresponding iodine-atom-transfer cyclization reactions.[15,16] Iodoacetamides

Scheme 2. Iodine-Atom-Transfer Reactions of Iodoacetamides



7a and **9a** were employed for this purpose. The direct cyclization of **7a** under the catalysis of BEt_3/O_2 or $(Bu_3Sn)_2/h\nu$ proceeded sluggishly. However, we were delighted to find that the cyclization was significantly accelerated by Lewis acid BF_3•OEt_2.[17,18] When substrate **7a** was treated with $(Bu_3Sn)_2$ (30 mol %) and BF_3•OEt_2 (300 mol %) in CH_2Cl_2 at rt under sunlamp irradiation, the expected azonanone **8a** was obtained in 91% yield (Scheme 2). No products derived from the 8-*exo* cyclization could be detected. The reaction was very clean except that a slow decomposition of **8a** was observed during the workup procedure. Substrate **9a** also underwent cyclization smoothly under the above conditions. However, the cyclized product **10a** was very unstable. It underwent fast decomposition during the purification step, and hexahydroindolizinone **11a** was detected, which could be generated via intramolecular nucleophilic substitution. Indeed, when the crude product **10a**, without purification, was directly treated with an aqueous Na_2CO_3 solution, the bicyclic product **11a** was isolated in 46% yield based on the substrate **9a**. To improve the yield of **11a**, we switched the solvent from CH_2Cl_2 to CH_3CN. The radical cyclization in CH_3CN proceeded nicely as well under the promotion of BF_3•OEt_2. After the same workup with Na_2CO_3, **11a** was secured in 64% yield. Presumably the intermediate **10a** was more stable in CH_3CN than in CH_2Cl_2.

Thus, a number of iodoamide substrates were subjected to the above radical cyclization conditions in either CH_2Cl_2 or CH_3CN followed by workup with aqueous Na_2CO_3. The results are listed in Table 1. In all cases the expected indolizinones were obtained in good to excellent yields. With benzo-fused substrates **7b**−**7g**, the corresponding tricyclic products **12b**−**12g** were obtained as mixtures of two stereoisomers. The configurations of the two stereoisomers of **12b** were unambiguously determined by the coupling constants of related protons and by 2D NOESY experiments (see the Supporting Information).

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(15) For a review, see: Byers, J. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, pp 72−89.

(16) For a seminal example of iodine-transfer radical cyclization reactions, see: Curran, D. P.; Chen, M.-H.; Kim, D. *J. Am. Chem. Soc.* **1986**, *108*, 2489–2490.

(17) For a review on the effect of Lewis acids in radical reactions, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562–2579.

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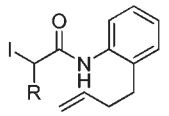
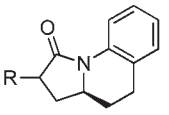
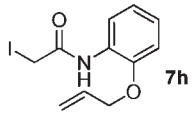
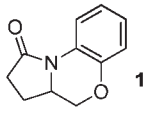
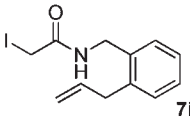
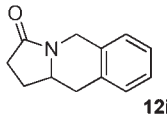
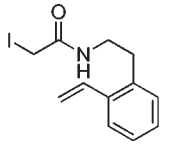
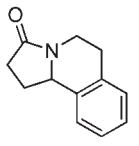
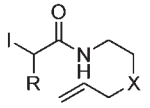
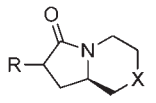
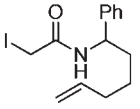
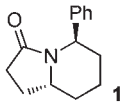
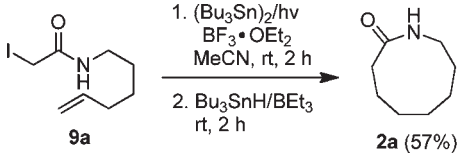
Table 1. Synthesis of Indolizinones

entry[a]	substrate		product	yield (%)[b]	*trans* :*cis*[c]
					
1[d]	**7a**	R = H	**12a**	96	–
2[d]	**7b**	R = Me	**12b**	95	3:1
3[d]	**7c**	R = Et	**12c**	95	4:1
4[d]	**7d**	R = *n*-Bu	**12d**	96	5:1
5[d]	**7e**	R = *i*-Pr	**12e**	96	~ 9:1
6[d]	**7f**	R = cyclohexyl	**12f**	93	> 10:1
7[d]	**7g**	R = *t*-Bu	**12g**	97	> 10:1
8[e]	 **7h**		 **12h**	71	–
9[e]	 **7i**		 **12i**	91	–
10[e]	 **7j**		 **12j**	48	–
					
11[e]	**9a**	R = H, X = CH_2	**11a**	64	–
12[e]	**9b**	R = Me, X = CH_2	**11b**	57	1:1
13[e]	**9c**	R = H, X = O	**11c**	70	–
14[e]	 **9d**		 **11d**	65	> 10:1

[a] Reaction conditions: (1) iodoamide (0.3 mmol), $(Bu_3Sn)_2$ (0.09 mmol), BF_3•OEt_2 (0.9 mmol), solvent (10 mL), rt, *hv*, 2 h, then (2) saturated aqueous Na_2CO_3 (10 mL), rt, 5 h. [b] Isolated yield based on the corresponding iodoamide. [c] Determined by ^{1}H NMR (400 MHz). [d] Solvent: CH_2Cl_2. [e] Solvent: CH_3CN.

Interestingly, the substituents R α to the carbonyl group showed a remarkable influence on the product stereoselectivity. The ratio of *trans* to *cis* isomers increases when the size of R increases. These ratios might reflect the stereoselectivity of 9-*endo* radical cyclization if we assume that the intramolecular nucleophilic substitution is an S_N2 process. Indeed, prior to the basic workup, the reaction of **7b** afforded the iodo-substituted azonanone (analogous to **8a**) as the mixture of two stereoisomers in a 3:1 ratio determined by the crude ^{1}H NMR, consistent with the *trans*/*cis* ratio of **12b** (entry 2, Table 1). Note that the ratio did not change with reaction time, implying that no equilibrium between the two stereoisomers occurred under the reaction conditions. For substrates **9a**–**9d** without a benzo-fused substituent, the product yields were lower presumably due to the partial decomposition of the azonanone intermediates. While substrate **9b** with an α-carbonyl substituent gave the mixture of two stereoisomers in 1:1 ratio, substrate **9d** having a phenyl group α to the nitrogen afforded the product **11d** with a high stereoselectivity. The reason for this difference is not clear at this moment.

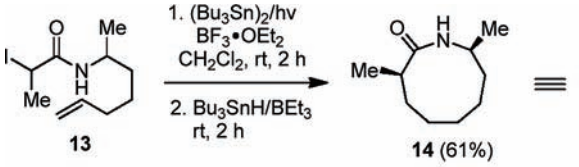
In light of the above results and in order to obtain stable azonanone products, we designed the following experiment (eq 1). After the BF_3•OEt_2-promoted cyclization of **9a** was complete (as indicated by TLC), Bu_3SnH (2 equiv) and BEt_3 (0.5 equiv) were added into the reaction mixture to reduce the iodo-containing intermediate **10a**. Azonanone **2a** was thus obtained in 57% yield in a one-pot, two-stage manner. It is worth mentioning that the direct treatment of **9a** with Bu_3SnH/AIBN in benzene at reflux yielded the direct reduction product **3** only.

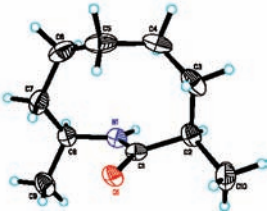


(1)

The above cyclization–reduction sequence was thus applied to a number of unsaturated iodoamides, and the results are summarized in Table 2. The reactions were highly regioselective, and no products derived from 8-*exo* cyclization could be detected. These results parallel closely with those in Table 1.

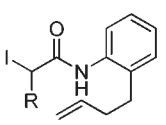
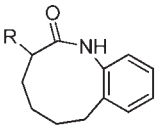
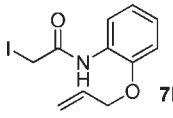
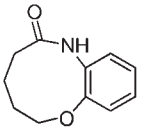
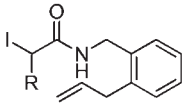
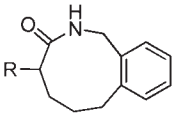
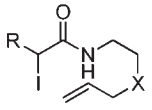
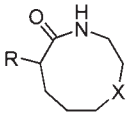
Scheme 3. Stereoselective 9-*Endo* Cyclization





Encouraged by the above excellent regioselectivity of cyclization, we moved one step further to study the reaction of iodoamide **13** with two methyl substituents, one α to the amide carbonyl and the other α to the nitrogen (Scheme 3). The cyclization was carried out in CH_2Cl_2. After the reduction with Bu_3SnH, the product **14** was isolated in 61% yield as a single isomer, whose configuration was finally determined to be 3,9-*cis* by the X-ray diffraction experiment. This example indicates that the 9-*endo* cyclization can be highly stereoselective.

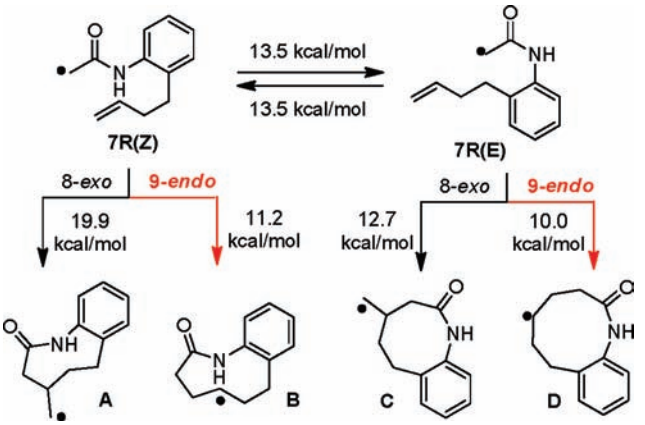
Table 2. Synthesis of Azonan-2-ones

entry[a]	substrate		product	yield (%)[b]
				
1[c]	**7a**	R = H	**5a**	99
2[c]	**7b**	R = Me	**5b**	99
3[c]	**7c**	R = Et	**5c**	99
4[c]	**7d**	R = *n*-Bu	**5d**	99
5[c]	**7e**	R = *i*-Pr	**5e**	99
6[c]	**7f**	R = cyclohexyl	**5f**	99
7[c]	**7g**	R = *t*-Bu	**5g**	99
8[d]	 **7h**		 **5h**	67
				
9[d]	**7i**	R = H	**5i**	92
10[c]	**7k**	R = Me	**5k**	91
11[c]	**7l**	R = Et	**5l**	90
12[c]	**7m**	R = *i*-Pr	**5m**	88
13[c]	**7n**	R = *t*-Bu	**5n**	89
				
14[d]	**9a**	R = H, X = CH_2	**2a**	57
15[d]	**9b**	R = Me, X = CH_2	**2b**	55
16[d]	**9c**	R = H, X = O	**2c**	64

[a] Reaction conditions: (1) iodoamide (0.3 mmol), $(Bu_3Sn)_2$ (0.09 mmol), BF_3•OEt_2 (0.9 mmol), solvent (10 mL), rt, hv, 2 h, then (2) Bu_3SnH (0.6 mmol), BEt_3 (0.15 mmol), rt, dark, 2 h. [b] Isolated yields based on the corresponding iodoamides. [c] Solvent: CH_2Cl_2. [d] Solvent: CH_3CN.

To gain further insight into the reactivity of α-carbamoyl radicals in 9-*endo* cyclization, we performed the density functional calculations on radical **7R** derived from substrate **7a**. The activation free energies calculated at the B3LYP/6-31G* level are listed in Scheme 4. The cyclization may proceed via two possible pathways, the *E*-conformational transition states (TSs) or the *Z*-conformational TSs. In both cases the activation energy for 9-*endo* cyclization is

Scheme 4. Calculated (B3LYP/6-31G*) Activation Free Energies



lower than that for the corresponding 8-*exo* cyclization, consistent with the experimental observations. Moreover, the activation energy for 9-*endo* cyclization via the *Z*-conformational TS (11.2 kcal/mol) is lower than the energy barrier (13.5 kcal/mol) for the *Z* to *E* interconversion of the substrate radical. The activation energy for cyclization is expected to be further lowered in the presence of Lewis acid BF_3•OEt_2.[14a] Therefore, it is more likely that the 9-*endo* cyclization proceeds via the *Z*-conformational TS.

In conclusion, the above experiments in combination with theoretical calculations have clearly demonstrated that the 9-*endo* cyclization of α-carbamoyl radicals is an efficient and highly regioselective process. The cyclization can be significantly promoted by BF_3•OEt_2. The iodine-atom-transfer cyclization followed by reduction with Bu_3SnH allows the convenient generation of various substituted nine-membered lactams. Furthermore, the 9-*endo* iodine-atom-transfer cyclization products can be effectively converted to the corresponding bicyclic indolizinones by the simple workup with Na_2CO_3, which should be an important application in organic synthesis.

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Supporting Information Available. Full experimental procedures, compound characterizations, copies of ^1H and ^{13}C NMR spectra, DFT calculation results, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.