

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

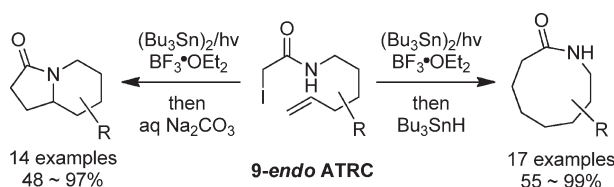
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ABSTRACT



With the promotion of Lewis acid $\text{BF}_3 \cdot \text{OEt}_2$, 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 alkaloids¹ 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 reactions³ or Claisen rearrangement⁴ of heterocyclic enamines. The

direct construction of the nine-membered ring via Beckmann rearrangement⁵ or the dehydration of ω -amino acids⁶ suffers from the low chemoselectivity or limited scope of application. The recently developed ring-closing metathesis⁷ 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 cyclization⁹ 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

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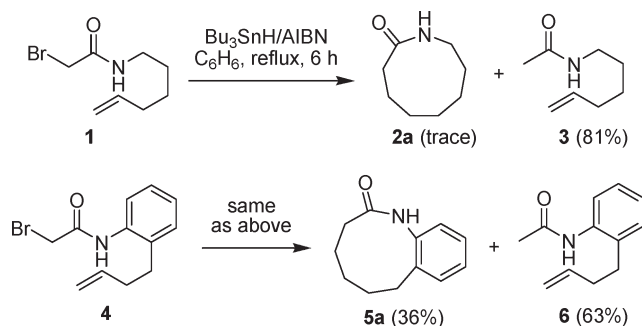
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radicals remains unexplored. Owing to our interest in the reactivity of α -carbamoyl radicals,¹⁴ we set out to explore this possibility.

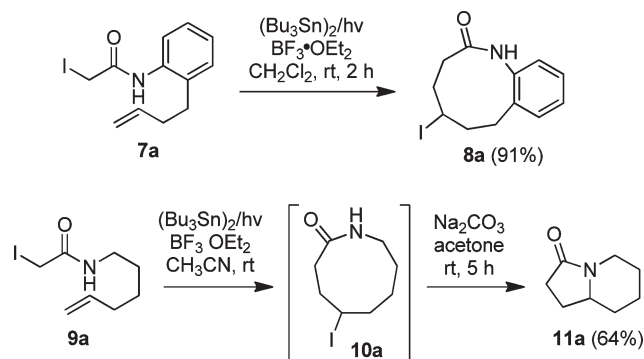
Scheme 1. Reactions of Bromoacetamides with Bu_3SnH /AIBN



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 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 BF_3/O_2 or $(\text{Bu}_3\text{Sn})_2/h\nu$ proceeded sluggishly. However, we were delighted to find that the cyclization was significantly accelerated by Lewis acid $\text{BF}_3\cdot\text{OEt}_2$.^{17,18} When substrate **7a** was treated with $(\text{Bu}_3\text{Sn})_2$ (30 mol %) and $\text{BF}_3\cdot\text{OEt}_2$ (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 $\text{BF}_3\cdot\text{OEt}_2$. 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.

Table 1. Synthesis of Indolizinones

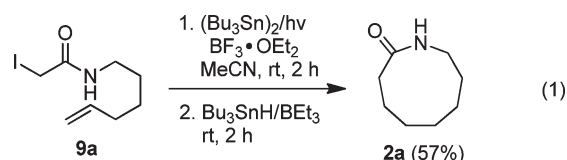
entry ^a	substrate	product	yield (%) ^b	<i>trans</i> : <i>cis</i> ^c
1 ^d	7a R = H	12a	96	—
2 ^d	7b R = Me	12b	95	3:1
3 ^d	7c R = Et	12c	95	4:1
4 ^d	7d R = <i>n</i> -Bu	12d	96	5:1
5 ^d	7e R = <i>i</i> -Pr	12e	96	~ 9:1
6 ^d	7f R = cyclohexyl	12f	93	> 10:1
7 ^d	7g R = <i>t</i> -Bu	12g	97	> 10:1
8 ^e			71	—
9 ^e			91	—
10 ^e			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			65	> 10:1

^a Reaction conditions: (1) iodoamide (0.3 mmol), (Bu₃Sn)₂ (0.09 mmol), BF₃•OEt₂ (0.9 mmol), solvent (10 mL), rt, *hν*, 2 h, then (2) saturated aqueous Na₂CO₃ (10 mL), rt, 5 h. ^b Isolated yield based on the corresponding iodoamide. ^c Determined by ¹H NMR (400 MHz). ^d Solvent: CH₂Cl₂. ^e Solvent: CH₃CN.

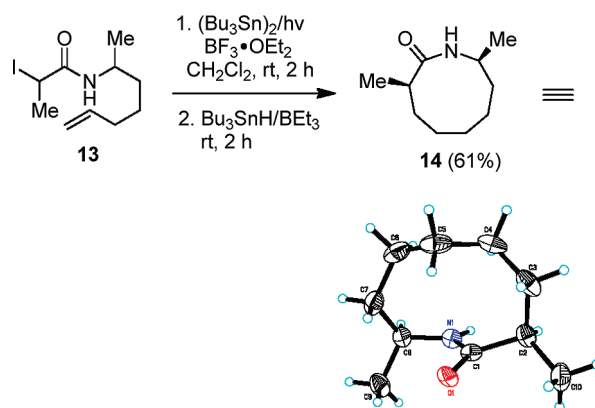
Interestingly, the substituents R α to the carbonyl group showed a remarkable influence on the product stereoselectivity. The ratio of *trans* to *cis* isomers increases when the size of R increases. These ratios might reflect the stereoselectivity of 9-*endo* radical cyclization if we assume that the 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 ¹H 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 BF₃•OEt₂-promoted cyclization of **9a** was complete (as indicated by TLC), Bu₃SnH (2 equiv) and BEt₃ (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 Bu₃SnH/AIBN in benzene at reflux yielded the direct reduction product **3** only.



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

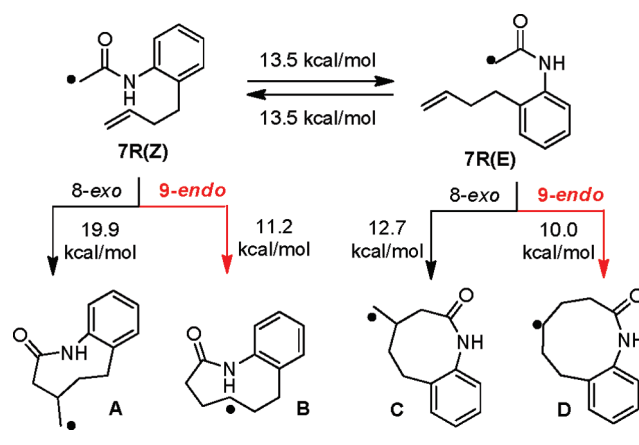
Encouraged by the above excellent regioselectivity of cyclization, we moved one step further to study the reaction of iodoamide **13** with two methyl substituents, one α to the amide carbonyl and the other α to the nitrogen (Scheme 3). The cyclization was carried out in CH₂Cl₂. After the reduction with Bu₃SnH, 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 = <i>n</i> -Bu	5d	99
5 ^c	7e R = <i>i</i> -Pr	5e	99
6 ^c	7f R = cyclohexyl	5f	99
7 ^c	7g R = <i>t</i> -Bu	5g	99
8 ^d			67
9 ^d			92
10 ^c	7k R = Me	5k	91
11 ^c	7l R = Et	5l	90
12 ^c	7m R = <i>i</i> -Pr	5m	88
13 ^c	7n R = <i>t</i> -Bu	5n	89
14 ^d			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), (Bu₃Sn)₂ (0.09 mmol), BF₃•OEt₂ (0.9 mmol), solvent (10 mL), rt, hv, 2 h, then (2) Bu₃SnH (0.6 mmol), BEt₃ (0.15 mmol), rt, dark, 2 h. ^b Isolated yields based on the corresponding iodoamides. ^c Solvent: CH₂Cl₂. ^d Solvent: CH₃CN.

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 BF₃•OEt₂.^{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 BF₃•OEt₂. The iodine-atom-transfer cyclization followed by reduction with Bu₃SnH 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 indolizones by the simple workup with Na₂CO₃, 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 ¹³C 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>.