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# Facile 5-Endo Amidyl Radical Cyclization Promoted by Vinylic Iodine Substitution

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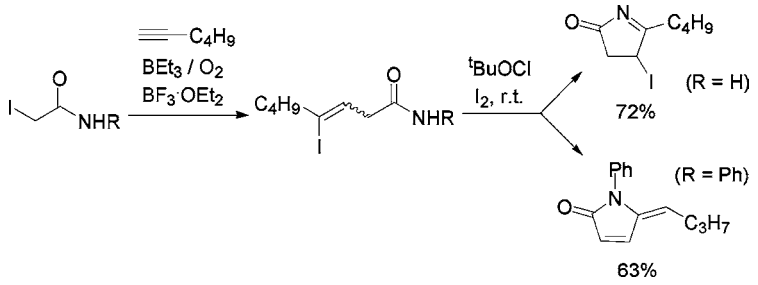
## ABSTRACT




**$BF_3$·$OEt_2$-catalyzed atom-transfer radical addition of iodoacetamides to alkynes yielded the corresponding vinyl iodides, which upon treatment with $^t$BuOCl and $I_2$ afforded $\gamma$-lactam derivatives in moderate to good yield. The mechanism was proposed to be 5-endo amidyl radical cyclization, and vinylic iodine substitution provided the driving force for the cyclization.**

Tremendous progress in free-radical reactions and their applications in organic synthesis have been achieved within the past two decades.[1] Among them, cyclization of amidyl radicals has received considerable attention[2] because it is the direct way to construct a lactam skeleton via C−N bond formations and thus is of great potential in natural product synthesis. The most widely studied mode of amidyl cyclization is 5-exo cyclization.[2,3] Other modes of cyclization such as 6-exo cyclization[4] are rarely seen and remain a challenging task for synthetic organic chemists. We here report the first examples of efficient 5-endo amidyl cyclization reactions leading to the formations of cyclic iminoketones or unsaturated lactams, and our results reveal that the iodine substitution on the C=C bonds plays an important role in the cyclization.

Our finding originated from our investigation on the atom transfer radical addition (ATRA) reactions of iodoacetamides (**1**) with alkynes (**2**). We envisioned that the treatment of the ATRA products **3** with $^t$BuOI[5] would generate the corresponding amidyl radical **4**, which might add to the C=C bond in a 5-endo mode to give the cyclized radical **5**. The radical **5** then underwent $\beta$-elimination to afford the lactam **6**, which might rearrange to the thermodynamically more stable lactam **7** as the final product (Scheme 1). This two-step radical sequence would provide a simple entry to the pyrrolidinones **7**, which are important building blocks in organic synthesis.

(1) For review articles, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon: Oxford, U.K., 1986. (b) Curran, D. P. *Synthesis* **1988**, 417 and 489. (c) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237. (d) Melikyan, G. G. *Synthesis* **1993**, 833. (e) Iqbal, J.; Bhatia, B.; Nayyar, N. K. *Chem. Rev.* **1994**, *94*, 519. (f) Snider, B. B. *Chem. Rev.* **1996**, *96*, 339. (g) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: Weinheim, Germany, 1996. (h) Gansauer, A.; Bluhm, H. *Chem. Rev.* **2000**, *100*, 2771. (i) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001.

(2) For review articles, see: (a) Esker, J.; Newcomb, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1993; Vol. 58, p 1. (b) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (c) Stella, L. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, p 407.

(3) For the latest example, see: Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Barluenga, S.; Hunt, K. W.; Kranich, R.; Vega, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 2233.

(4) Horner, J. H.; Musa, O. M.; Bouvier, A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 7738.

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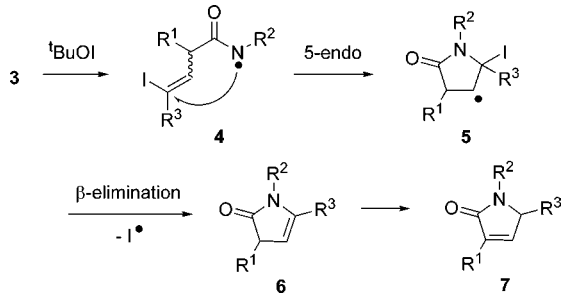
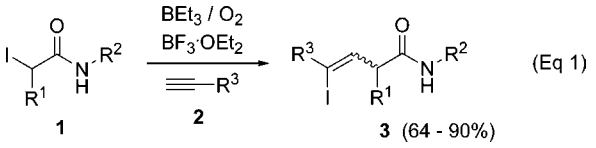
**Scheme 1**

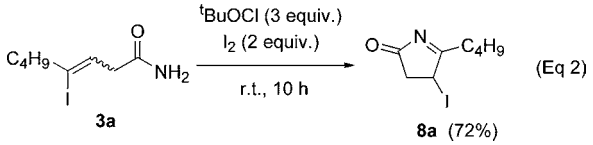



The ATRA reactions of iodoacetates or iodoacetonitriles with terminal alkynes with bis(tributyltin) as the initiator were well studied by Curran et al.[6] However, the corresponding ATRA reactions of iodoacetamides have not been explored. As a model example, we carried the reaction of *N*-phenyliodoacetamide with 1-hexyne at room temperature with triethylborane or bis(tributyltin) as the initiator. The reaction was very slow, and more than 50% of the starting amide remained unchanged after 24 h. The expected product *N*-phenyl-4-iodo-3-octenoamide (**3e**) was isolated as a mixture of two stereoisomers (*Z*/*E* = 3:1) in less than 30% yield. To achieve higher yield, we tried the catalysis of Lewis acids[7] in the above reaction. Among the Lewis acids screened ($BF_3$·$OEt_2$, $BCl_3$, $MgBr_2$·$OEt_2$, $Mg(OTf)_2$, $Yb(OTf)_3$, $ZnCl_2$), boron trifluoride etherate[8] showed the best result. When the above reaction with $BEt_3$ as the initiator was carried out in the presence of $BF_3$·$OEt_2$ (2 equiv) at room temperature for 20 h, **3e** was achieved in 78% yield with a slightly higher stereoselectivity (*Z*/*E* = 5:1). Thus, a number of iodoacetamides **1** and alkynes **2** were employed and satisfactory yields (64−90%) of the corresponding condensation products **3a**−**g** were achieved in this manner (eq 1). The ratios of stereoisomers were in the range of 2.5:1 to 10:1 with the (*Z*)-isomers preferred (see the Supporting Information for details).




(Eq 1)

The next step was to generate the amidyl radical. It was well documented that treatment of an amide with $^t$BuOI could generate the corresponding *N*-iodoamide, which upon heating or photolysis would produce the amidyl radical via the homocleavage of the weak N−I bond.[5] Thus, the two isomers of 4-iodo-3-octenoamide **3a**, without separation, were subjected to the reaction with $^t$BuOCl and $I_2$ in $CH_2Cl_2$ in the dark at room temperature. The reaction was complete within 10 h, and the product was isolated in 72% yield and characterized to be the cyclic iminoketone **8a** rather than the expected lactam **6** or **7** (eq 2).

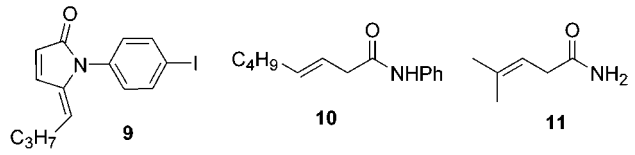



(Eq 2)

While there are other ways to prepare $^t$BuOI in situ ($AgOAc/I_2$/$^t$BuOH,[9] $PhI(OAc)_2/I_2$/$^t$BuOH,[10] $^t$BuOCl/$I_2$,[5] $^t$BuOK/$I_2$[11]), we observed that $^t$BuOCl/$I_2$ gave a higher yield of the cyclization product. The reason for the differences is still unclear.[12] It should be mentioned that the direct treatment of **3a** with $I_2$ at room temperature did not give **8a** at all while **3a** remained unchanged.

The reactions of other substrates **3b**−**g** with $^t$BuOCl/$I_2$ were then carried out in the same fashion (eq 2), and the results are summarized in Table 1.

As can be seen in Table 1, with *N*-unsubstituted substrates **3a**−**d**, the cyclic iminoketones **8a**−**d** were obtained as the cyclization products in good yield. On the other hand, the reactions of *N*-phenyl substrates **3e**,**f** led to the formation of the dienes **8e**,**f** with excellent stereoselectivity. Compound **8e** could be further converted to its *p*-iodo-substituted derivative **9** if the reaction of **3e** was allowed to run for a much longer time. The structure of **9** was unambiguously characterized by its X-ray diffraction analysis (see the Supporting Information). With *N*-methyl-substituted substrate **3g**, the corresponding diene **8g** was also formed. However, the yield was low and the stereoselectivity was poor.




As a comparison, we used compounds **10** and **11** as the substrates. Their reactions with $^t$BuOCl/$I_2$ under the above same experimental conditions were complicated, and no meaningful products could be isolated. These results indicated that, rather than simply acting as a substituent, the iodine atom in **3** played a crucial role in the above cycliza-

(5) Barton, D. H. R.; Beckwith, A. L. J.; Goosen, A. *J. Chem. Soc.* **1965**, 181.

(6) (a) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738. (b) Curran, D. P.; Kim, D. *Tetrahedron* **1991**, *47*, 6189.

(7) For reviews, see: (a) Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2562. (b) Guerin, B.; Ogilvie, W. W.; Guindon, Y. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M, P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, p 441.

(8) For our recent examples using $BF_3$·$OEt_2$ to promote radical reactions, see: (a) Wang, J.; Li, C. *J. Org. Chem.* **2002**, *67*, 1271. (b) Yu, H.; Wu, T.; Li, C. *J. Am. Chem. Soc.* **2002**, *124*, 10302. (c) Fang, X.; Xia, H.; Yu, H.; Dong, X.; Chen, M.; Wang, Q.; Tao, F.; Li, C. *J. Org. Chem.* **2002**, *67*, 8481. (d) Liu, L.; Wang, X.; Li, C. *Org. Lett.* **2003**, *5*, 361. (e) Yu, H.; Li, C. *J. Org. Chem.* **2004**, *69*, 142.

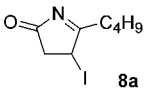
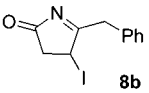
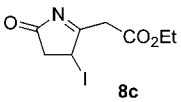
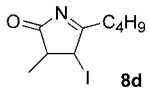
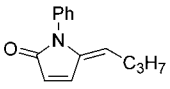
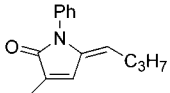
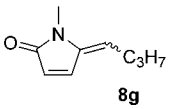
(9) Beebe, T. R.; Barnes, B. A.; Bender, K. A.; Halbert, A. D.; Miller, R. D.; Ramsay, M. L.; Ridenour, M. W. *J. Org. Chem.* **1975**, *40*, 1992.

(10) Concepcion, J. I.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1984**, *25*, 1953.

(11) Akhtar, M.; Barton, D. H. R. *J. Am. Chem. Soc.* **1964**, *86*, 1528.

(12) For discussions on *tert*-butyl hypoiodite, see: (a) Tanner, D. D.; Gidley, G. C.; Das, N.; Rowe, J. E.; Potter, A. *J. Am. Chem. Soc.* **1984**, *106*, 5261. (b) Montoro, R.; Wirth, T. *Org. Lett.* **2003**, *5*, 4729.

**Table 1.** 5-Endo Cyclization of **3a**−**g**

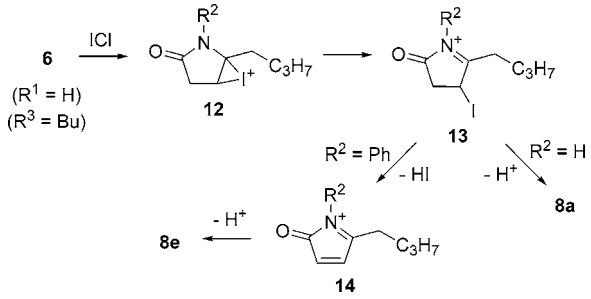
| substrate | $R^1$ | $R^2$ | $R^3$ | product | yield (%)[a] |
|---|---|---|---|---|---|
| **3a** | H | H | $C_4H_9$ |  **8a** | 72 |
| **3b** | H | H | Bn |  **8b** | 73 |
| **3c** | H | H | $CH_2CO_2Et$ |  **8c** | 72 |
| **3d** | Me | H | $C_4H_9$ |  **8d** | 79[b] |
| **3e** | H | Ph | $C_4H_9$ |  **8e** | 63 |
| **3f** | Me | Ph | $C_4H_9$ |  **8f** | 52 |
| **3g** | H | Me | $C_4H_9$ |  **8g** | 37[c] |

[a] Isolated yield based on **3**. [b] Trans/cis = 6:1. [c] *Z*/*E* = 1:1.

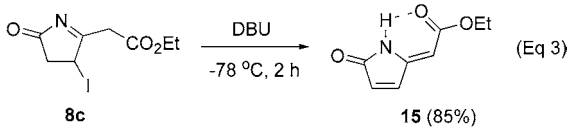
tion reactions presumably by offering the driving force for the 5-endo cyclization via $\beta$-elimination of the iodine radical (**5** → **6**).

On the basis of the above results, a plausible mechanism could be drawn as follows: First, efficient 5-endo amidyl cyclization occurred to give lactam **6** as depicted in Scheme 1. With the presence of the excess amount of $I_2$ or ICl (formed by reaction of $^t$BuOCl and $I_2$),[5] **6** underwent iodination (to give **12)** rather than rearrangement (to give **7**). The intermediate **12** then rearranged to **13**. When $R^2$ is H, the corresponding iminoketone was formed as the product. If $R^2$ is an alkyl or aryl group, dehydroiodination occurred to give the intermediate **14**, which furnished the unsaturated lactam via the loss of a proton (Scheme 2). Our attempt to obtain the intermediate **6** by stopping the reaction of **3a** halfway was unsuccessful presumably because the iodination of **6** was fast.

**Scheme 2**




Cyclic iminoketones are unique building blocks in the synthesis of some natural products.[13] They are also important precursors to lactams.[14] As a typical example, treatment of compound **8c** with DBU (1.5 equiv) in $CH_2Cl_2$ at −78 °C for 2 h afforded the lactam **15** in 85% yield with high stereoselectivity (eq 3). The configuration of **15** was determined by the characteristic chemical shift of the NH proton ($\delta$ 11.6 ppm) resulting from the intramolecular hydrogen bonding.




**8c** **15** (85%)

In conclusion, the intermolecular α-carbamoyl radical addition to an alkyne followed by the intramolecular 5-endo amidyl radical cyclization provides a convenient route to the synthesis of cyclized iminoketones or unsaturated $\gamma$-lactams. Detailed investigation on the general picture of 5-endo amidyl cyclization is currently in progress in our laboratory.

**Acknowledgment.** This project was supported by the National Natural Science Foundation of China and by the Shanghai Municipal Scientific Committee (04QMH1418).

**Supporting Information Available:** Synthesis and characterization of **3a**−**g**, **8a**−**g**, **9**, and **15** and CIF data of crystal **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) For an example, see: Minehan, T. G.; Kishi, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 923.

(14) For an example, see: Hassner, A.; Miller, A. S.; Haddadin, M. J. *Tetrahedron Lett.* **1972**, 1353.