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Deoligomerization: A New Route to Lactams from Unsaturated Amides via Radical Oligomerization

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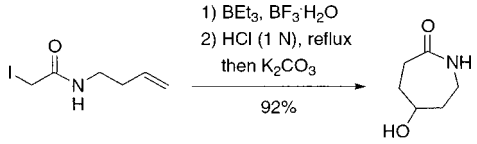
ABSTRACT



Triethylborane-initiated atom transfer radical oligomerization of *N*-allyl or *N*-(3-butenyl)iodoacetamides followed by treatment with hydrochloric acid and subsequent neutralization with K_2CO_3 led to the formation of the corresponding 5-hydroxyl-substituted δ-lactams or caprolactams, respectively. This oligomerization–deoligomerization sequence serves as an alternative to the corresponding intramolecular cyclization reactions.

Lactams are of considerable interest in a number of areas ranging from drug discovery to polymer industry. Synthesis of lactams has been, and continues to be, a subject of significance for organic chemists. Among numerous methods developed, radical strategies,[1] especially intramolecular cyclizations of unsaturated α-carbamoyl radicals,[2,3] have been demonstrated to be a unique tool in the construction of lactam skeletons from β-lactams to medium- or large-sized ones. However, these transformations suffer from the energy barriers of the interconversion between s-trans and s-cis rotamers of α-carbamoyl radicals, while cyclization usually requires the s-cis conformations of higher energy.[4] As a result, intermolecular oligomerizations become predominant in many cases. Many techniques have been developed for radical cyclization, including high dilution,[5] elevated temperature,[4,6] and substrate modifications,[7] all aiming at inhibiting intermolecular oligomerizations. However, encouraged by our recent results in converting radical oligomers to a single product,[8] we report here that radical oligomerization can be utilized in lactam synthesis just as it is in the corresponding radical cyclization.

Our finding originated from our attempt to carry out the triethylborane-initiated atom transfer radical cyclization of *N*-allyl iodoacetamide (**1a**) with the catalysis of Lewis acids.[9]

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(2) For a comprehensive review, see: Srikrishna, A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 2, p 151.

(3) For the latest examples, see: (a) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron* **2000**, *56*, 3941. (b) Penfold, D. J.; Pike, K.; Genge, A.; Anson, M.; Kitteringham, J.; Kilburn, J. D. *Tetrahedron Lett.* **2000**, *41*, 10347. (c) Wakabayashi, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2377. (d) Bryans, J. S.; Chessum, N. E. A.; Parsons, A. F.; Ghelfi, F. *Tetrahedron Lett.* **2001**, *42*, 2901. (e) Clark, A. J.; Battle, G. M.; Bridge, A. *Tetrahedron Lett.* **2001**, *42*, 4409. (f) Ishibashi, H.; Kodama, K.; Higuchi, M.; Muraoka, O.; Tanabe, G.; Takeda, Y. *Tetrahedron* **2001**, *57*, 7629. (g) Nagashima, H.; Isono, Y.; Iwamatsu, S.-i. *J. Org. Chem.* **2001**, *66*, 315. (h) Clark, A. J.; Battle, G. M.; Heming, A. M.; Haddleton, D. M.; Bridge, A. *Tetrahedron Lett.* **2001**, *42*, 2003. (i) Clark, A. J.; Battle, G. M.; Briedge, A. *Tetrahedron Lett.* **2001**, *42*, 1999.

(4) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746.

(5) Barth, F.; O-Yang, C. *Tetrahedron Lett.* **1990**, *31*, 1121.

(6) For an example, see: Nagashima, H.; Wakamatsu, H.; Ozaki, N.; Ishii, T.; Watanabe, M.; Tajima, T.; Itoh, K. *J. Org. Chem.* **1992**, *57*, 1682.

(7) For examples, see: (a) Nagashima, H.; Ozaki, N.; Ishii, M.; Seki, K.; Washiyama, M.; Itoh, K. *J. Org. Chem.* **1993**, *58*, 464. (b) Russell, G. A.; Li, C.; Chen, P. *J. Am. Chem. Soc.* **1995**, *117*, 3645. (c) Russell, G. A.; Li, C.; Chen, P. *J. Am. Chem. Soc.* **1996**, *118*, 9831.

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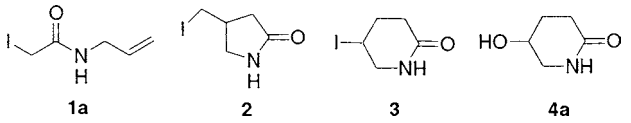
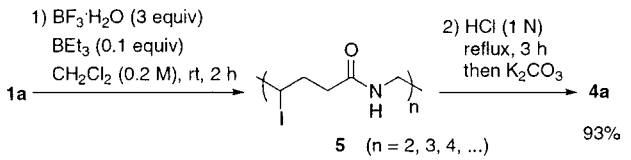
Under various experimental conditions employed, the cyclization of **1a** to γ-lactam **2** in a 5-exo mode or to δ-lactam **3** in a 6-endo mode proved to be unsuccessful. Instead, Lewis acids ($BF_3{\cdot}OEt_2$, $BF_3{\cdot}H_2O$, $Mg(OTf)_2$, etc.) significantly accelerated the radical oligomerization even in very low concentrations. However, when the oligomeric mixture (as a precipitate in CH_2Cl_2 solution) was collected and heated with hydrochloric acid, it quickly dissolved in the aqueous solution. After neutralization with K_2CO_3, a compound of high polarity was isolated and characterized to be 5-hydroxy-2-piperidinone (**4a**),[10] which is structurally similar to the 6-endo cyclization product **3**. The only difference is that the iodine atom in **3** changes to the hydroxy group in **4a**.



This result urged us to optimize the above experimental conditions. Thus, direct oligomerization of **1a** in CH_2Cl_2 with the catalysis of $BF_3{\cdot}H_2O$ (3 equiv) at room temperature (rt) for 2 h gave oligomers **5** (see Supporting Information), which were refluxed with hydrochloric acid (1 N) for 3 h and then treated with K_2CO_3 at room temperature to give product **4a** in 93% yield (equation 1). In the absence of $BF_3{\cdot}H_2O$, the oligomerization was very slow and the radical initiator triethylborane was quickly consumed. With $BF_3{\cdot}OEt_2$ or $Mg(OTf)_2$ as the catalyst, the oligomerization was faster but incomplete, as evidenced by ^1H NMR monitoring. As a result, the yields of **4a** were lowered (~65%).



Thus, various substrates were subjected to the above process (eq 1), and the results are summarized in Table 1.

As shown in Table 1, all the *N*-allyliodoacetamide derivatives **1a**−**d** gave the corresponding δ-lactams, while the *N*-(3-butenyl)iodoacetamide substrates **1e**−**h** led to the formation of caprolactams. These results clearly demonstrate that radical oligomerization can be successfully utilized in lactam synthesis. More importantly, these products look as if they were generated via the corresponding intramolecular cyclization of the unsaturated amides in the 6-endo or 7-endo mode followed by subsequent replacement of the iodine atom by the hydroxy group. While the direct intramolecular 6-endo or 7-endo radical cyclization was unsatisfactory,[2,11] the above oligomerization−deoligomerization process provided a new route to achieving the same goal.

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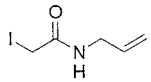
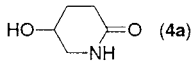
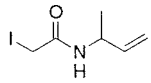
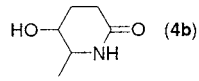
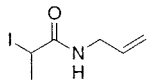
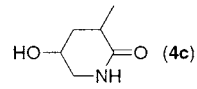
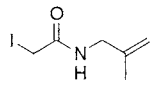
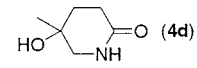
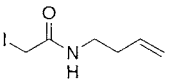
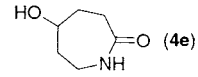
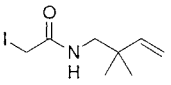
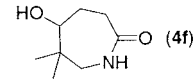
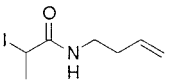
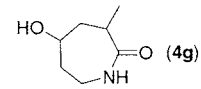
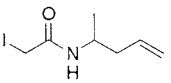
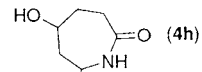
(10) Nielsen, J. T.; Elming, N.; Clauson-Kaas, N. *Acta Chem. Scand.* **1955**, *9*, 30.

Table 1. Synthesis of Lactams **4**

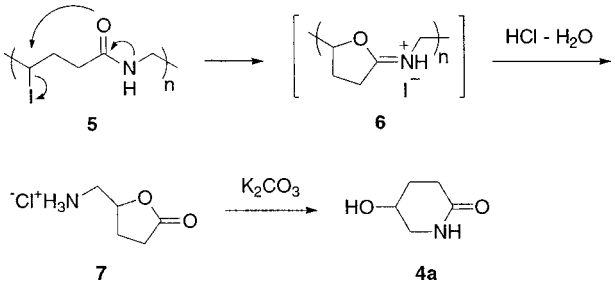
substrate	product	yield (%)[a]
 (**1a**)	 (**4a**)	93
 (**1b**)	 (**4b**)	86[b]
 (**1c**)	 (**4c**)	63[b]
 (**1d**)	 (**4d**)	34
 (**1e**)	 (**4e**)	92
 (**1f**)	 (**4f**)	73
 (**1g**)	 (**4g**)	63[c]
 (**1h**)	 (**4h**)	60[d]

[a] Isolated yield based on **1**. [b] Two stereoisomers in a ca. 1:1 ratio determined by ^1H NMR. [c] Two isomers in a 1:1.6 ratio. [d] Two isomers in a 1:10 ratio.

A plausible mechanism could be drawn as in Scheme 1. Oligomers **5** underwent intramolecular nucleophilic substitution to give intermediates **6**.[12] Further cleavage of the C=N bonds in acid solution generated the lactone **7**.[13] With the addition of K_2CO_3, **7** isomerized to the lactam product **4a**.[13] In fact, **7** could be isolated in high yield (85%) prior to the addition of K_2CO_3.

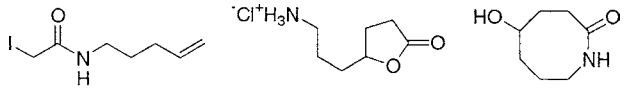
Because the oligomers of different sizes are composed of the same unit, the same product can be achieved regardless of the degree of oligomerization. Therefore, the yields of

Scheme 1. Proposed Mechanism



product lactams depend strongly on the *completeness* of oligomerization rather than the *degree* of oligomerization. The results in Table 1 support our analysis. For example, the relatively low yield of **4d** resulted from the incomplete oligomerization as indicated by ^{1}H NMR monitoring, presumably because of the steric hindrance. Similarly, substrates with internal C═C bonds such as *N*-(2-butenyl)iodoacetamide gave a low yield (~20%) of the corresponding *δ*-lactams also because of the poor oligomerization. Furthermore, two samples of the oligomeric mixture **5** of different molecular weights (MW = 2 210/PDI = 1.28 and MW = 5 060/PDI = 1.14, see Supporting Information) were subjected to the above deoligomerization process, respectively. About equal efficiency was observed in producing product **4a** (94%).

The extension of the above process to iodoamide **8** showed that, after oligomerization and subsequent deoligomerization, the corresponding lactone **9** was obtained in about 60% yield. However, further treatment of **9** with K_2CO_3 failed to give the expected lactam **10** and the reason is still unclear. A possible explanation is that, in this particular case, the lactone form is thermodynamically more stable in the lactone−lactam isomerization. Detailed investigation on the scope and limitation of this oligomerization−deoligomerization process is currently in progress.



8 9 **10**

In conclusion, we have demonstrated that atom transfer radical oligomerization of unsaturated iodoamides followed by deoligomerization and subsequent rearrangement serves as an alternative to the corresponding intramolecular cyclization in the synthesis of lactams. This oligomerization−deoligomerization sequence follows the endocyclization-like mode leading to the formations of hydroxy-substituted lactams, which are important intermediates in organic synthesis.[13,14] *While intramolecular radical cyclization is intrinsically vulnerable to conformational restrictions, it seems that the above oligomerization−deoligomerization process is not.*

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Supporting Information Available: Typical procedure for the synthesis of **4a**−**h** and **9** and characterization of **1**, **4**, **5**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) For 6-exo/7-endo and 7-exo/8-endo amide cyclization reactions, see: (a) Bachi, M. D.; Frolow, F.; Hoornaert, C. *J. Org. Chem.* **1983**, *48*, 1841. (b) Sato, T.; Ishida, S.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 353. (c) Gill, G. B.; Pattenden, G.; Reynolds, S. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 369. (d) Naito, T.; Honda, Y.; Miyata, O.; Ninomiya, I. *J. Chem. Soc., Perkin Trans. 1* **1995**, 19. (e) Blake, A. J.; Hollingworth, G. J.; Pattenden, G. *Synlett.* **1996**, 643. (f) Clark, A. J.; De Campo, F.; Deeth, R. J.; Filik, R. P.; Gatard, S.; Hunt, N. A.; Lastecoueres, D.; Thomas, G. H.; Verlhac, J.-B.; Wongtap, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 671.

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