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Pushing Radical Cyclization from Regioselective to Regiospecific: Cyclization of Amidyl Radicals Controlled by Vinylic Halogen Substitution

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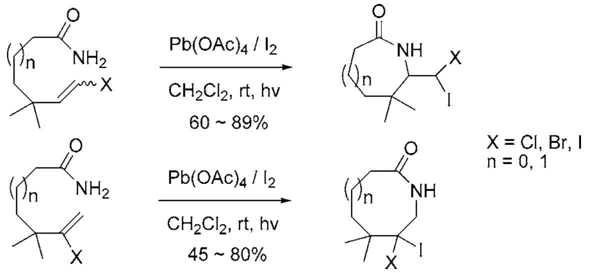
ABSTRACT



Efficient and regiospecific 6-exo, 7-endo, 7-exo, and even 8-endo amidyl radical cyclizations can be accomplished by the direct reactions of unsaturated *N*-H amides if they bear a vinylic halogen (Cl, Br, I) substituent. This remarkable halogen-substitution effect could be rationalized in terms of lone pair–lone pair electron repulsion between the N radical and the vinylic halogen atom, in addition to the well-known steric and radical-stabilizing effect.

Lactams are of considerable interest in a number of areas ranging from drug discovery to polymer industry. Cyclization of amidyl radicals offers a great potential to the synthesis of lactams of various ring sizes and thus has drawn increasing attention in the past few years.[1,2] For example, Nicolaou and co-workers reported the successful *o*-iodoxybenzoic acid (IBX)-mediated 5-exo cyclization of unsaturated *N*-aryl amides.[2a] Studer et al. extended this methodology to the oxidative cyclization of acylated alkoxyamines.[2f] Nevertheless, the exploration of amidyl radical-based synthetic methodologies remains challenging mainly for the following two reasons: (1) Amidyl radicals are highly reactive.[2d,3,4] This makes the control of regioselectivity difficult. For example, the cyclization of 5-hexenamidyl radical afforded the corresponding δ-lactam and caprolactam in 4:1 ratio.[2d] With a terminal methyl substitution, the amidyl radical generated from the treatment of *N*-phenylthio amide **1**[5] with Bu$_3$SnH/AIBN gave the mixture of 6-exo cyclization product **2** and 7-endo cyclization product **3** in 8:1 ratio (see the Supporting Information for details). (2) The generation of

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(1) For reviews, 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.

(2) For recent examples, see: (a) 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. (b) Gagosz, F.; Moutrille, C.; Zard, S. Z. *Org. Lett.* **2002**, *4*, 2707. (c) Tang, Y.; Li, C. *Org. Lett.* **2004**, *6*, 3229. (d) Chen, Q.; Shen, M.; Tang, Y.; Li, C. *Org. Lett.* **2005**, *7*, 1625. (e) Martin, A.; Pérez-Martin, I.; Suárez, E. *Org. Lett.* **2005**, *7*, 2027. (f) Janza, B.; Studer, A. *J. Org. Chem.* **2005**, *70*, 6991. (g) Gaudreault, P.; Drouin, C.; Lessard, J. *Can. J. Chem.* **2005**, *83*, 543.

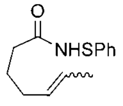
(3) Horner, J. H.; Musa, O. M.; Bouvier, A.; Newcomb, M. *J. Am. Chem. Soc.* **1998**, *120*, 7738.

(4) Daoust, B.; Lessard, J. *Tetrahedron* **1999**, *55*, 3495.

(5) Esker, J. L.; Newcomb, M. *Tetrahedron Lett.* **1993**, *34*, 6877.

10.1021/ol060983q CCC: $33.50

amidyl radicals directly from the parent *N*-H amides, which is of more synthetic value, often suffers from the competing ionic processes.[2f] For example, we screened various experimental conditions by treatment of 5-hexenamide **4** with IBX,[2a] diacetoxyiodobenzene (DIB)/I_2,[6a] ^{t}BuOCl/I_2,[6b] AgOAc/I_2,[6c] $Pb(OAc)_4/I_2$,[6b] or ^{t}BuOK/I_2.[6d] In all cases, no desired lactams could be obtained while in most cases only lactone **5** was isolated as the electrophilic iodolactonization product (see the Supporting Information).



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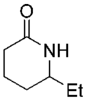

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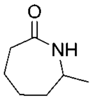

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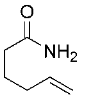

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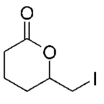

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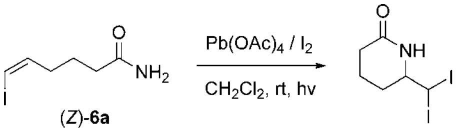
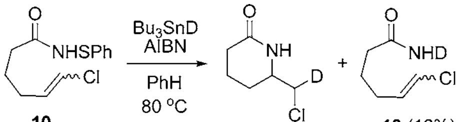
We here report that efficient and regiospecific 6-exo, 7-endo, 7-exo, and even 8-endo amidyl radical cyclizations can be accomplished by the direct reactions of unsaturated *N*-H amides if they bear a vinylic halogen substituent. When (*Z*)-6-iodo-5-hexenamide (**6a**), initially used as the substrate for Ullmann coupling,[7] was treated with $Pb(OAc)_4/I_2$ in CH_2Cl_2 in the dark at room temperature for 4 h, the corresponding 6-exo radical cyclization product **7a** was achieved in 44% yield along with the isolation of *δ*-(diiodomethyl)-*δ*-lactone (37%) as the iodolactonization product. When the reaction was photolyzed with the aid of a 125 W high-pressure mercury lamp, **7a** was achieved exclusively in 85% yield while no lactone could be detected (eq 1). This result is in sharp contrast to that for amide **4**. Thus, a number of amides **6** and **8** with different vinylic halogen substitutions were examined under the optimized conditions in eq 1 and the results are summarized in Table 1.



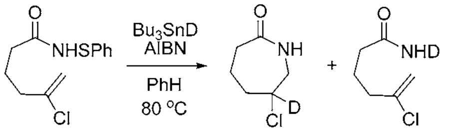
(*Z*)-**6a** **7a** (85%) (1)

As can be seen in Table 1, both (*Z*)- and (*E*)-isomers of **6a** gave the same product **7a**. On the other hand, the reaction of amide **8a** with an internal iodine substitution afforded the 7-endo cyclization product **9a** exclusively. Changing the iodine atom to bromine or chlorine (**6b**,**c** and **8b**,**c**) yielded similar results. Moreover, with various substitution patterns on the chain of the amides (**6d**−**f** and **8d**−**f**) the above reactivity and regiospecificity were nicely reproduced.

To further verify the above regiospecificity, we prepared chloro-substituted *N*-phenylthio amides **10** and **11** and carried out their reactions with Bu_3SnD/AIBN (eqs 2 and 3). Amide **10** with a terminal Cl-substitution afforded the 6-exo cyclization product **12** and the direct reduction product **13** while no 7-endo cyclization or 1,5-H migration product could be detected by ^{1}H NMR and HPLC. Meanwhile, amide **11** with an internal Cl-group gave only the 7-endo cyclization product **14** and the direct reduction product **15**. These two experiments strongly supported the regiospecificity as well

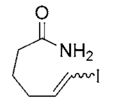
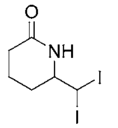
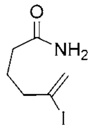
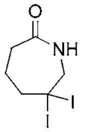
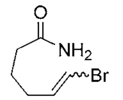
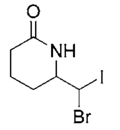
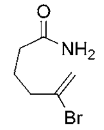
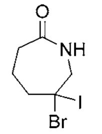
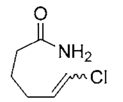
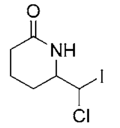
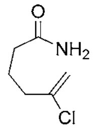
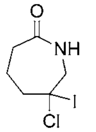
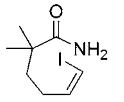
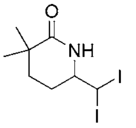
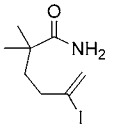
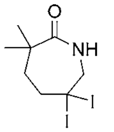
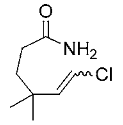
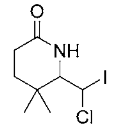
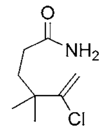
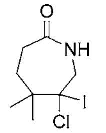
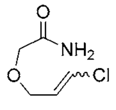
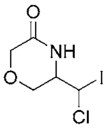
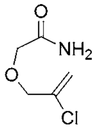
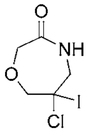


10 **12** (61%) **13** (16%) (2)



11 **14** (52%) **15** (31%) (3)

Table 1. Photolysis of Amides **6** and **8** with $Pb(OAc)_4/I_2$

6-exo		7-endo	
substrate	product (yield)[a]	substrate	product (yield)[a]
 **6a**[b]	 **7a** (84%)	 **8a**	 **9a** (72%)
 **6b**[b]	 **7b**[f] (79%)	 **8b**	 **9b** (89%)
 **6c**[c]	 **7c**[f] (81%)	 **8c**	 **9c** (70%)
 **6d**	 **7d** (81%)	 **8d**	 **9d** (72%)
 **6e**[d]	 **7e**[g] (89%)	 **8e**	 **9e** (77%)
 **6f**[e]	 **7f**[f] (81%)	 **8f**	 **9f** (52%)

[a] Isolated yield based on **6** or **8**. [b] *Z*:*E* = 55:45. [c] *Z*:*E* = 14:86. [d] *Z*:*E* = 30:70. [e] *Z*:*E* = 40:60. [f] Two stereoisomers in ~1:1 ratio. [g] Two stereoisomers in 5:1 ratio.

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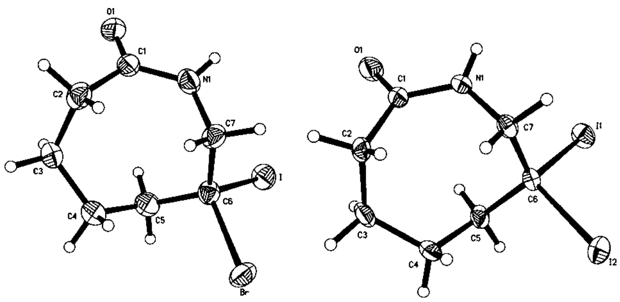
(6) (a) Concepcion, J. I.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1984**, *25*, 1953. (b) Barton, D. H. R.; Beckwith, A. L. J.; Goosen, A. *J. Chem. Soc.* **1965**, 181. (c) Beebe, T. R.; Barnes, B. A.; Bender, K. A.; Halbert, A. D.; Miller, R. D.; Ramsay, M. L.; Ridenour, M. W. *J. Org. Chem.* **1975**, *40*, 1992. (d) Akhtar, M.; Barton, D. H. R. *J. Am. Chem. Soc.* **1964**, *86*, 1528.

(7) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035.

as the radical nature[8] of the photostimulated reactions of **6** and **8** with Pb(OAc)$_4$/I$_2$. Moreover, these experiments also helped to demonstrate the additional advantage of the direct use of parent amides **6** and **8** in that, even if the amidyl radicals were quenched by the direct H-abstraction from the solvent,[2g] they could be regenerated by reaction with Pb(OAc)$_4$/I$_2$ and ultimately led to the clean formation of cyclized products in high yield.

We then extended this methodology to the 7-exo vs 8-endo cyclization system. We were delighted to find that regiospecific 7-exo cyclization reactions of **16a**−**c** proceeded smoothly to afford the caprolactams **17a**−**c** in satisfactory yields (eq 2). Moreover, exclusive eight-membered lactams **19a**−**f** were achieved in the reactions of amides **18a**−**f** bearing an internal vinylic halogen substituent (eq 3 and Figure 1). These are also the first examples of 7-exo and 8-endo cyclizations of amidyl radicals. The only exception was that 1,6-H migration predominated in the reactions of amides **20** leading to the formation of δ-lactones **21** (82%, 69%, and 37% for X = Cl, Br, and I, respectively). Again, without a halogen substitution, amides such as 6-heptenamide gave only the iodolactonization products under the above experimental conditions.



19e **19f**

Figure 1. ORTEP drawings of crystals **19e** and **19f**.

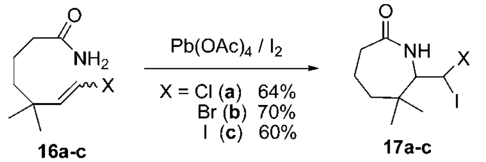
The above halogen-substitution effect is therefore significant not only in that it allows the radical processes to overtake the ionic ones but also in that the regioselectivities can be nicely directed by the vinylic halogen.

To gain more insight into the role of halogen substitution, density functional calculations at the B3LYP/6-31G* level were performed on the cyclization of radicals **22** and **23**. The results are summarized in Table 2 (also see the Supporting Information). With an internal Cl-substituent, the activation energy (E_a) for 6-exo cyclization jumped from 3.7 to 7.4 kcal/mol while the E_a for 7-endo cyclization stays around 4.0 kcal/mol (entries 1 and 2, Table 2). A similar but reversed pattern is computed for the terminal Cl-substituted radical **23** (entry 3, Table 2). In both cases, the activation energy difference is larger than 3 kcal/mol, consistent with the experimental results.[9] As a comparison, the methyl-substituted radicals have lower activation energies presumably because of the increase of electron density of the C=C bond. In the meantime, the energy differences become smaller. The calculated 1.6 kcal/mol difference in activation energies for **23** (R = Me) is also in excellent agreement with the experimental data of **1**.

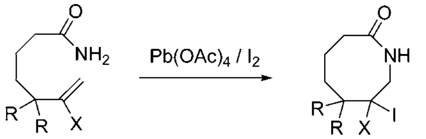
Table 2. Calculated (B3LYP/6-31G*) Activation Energies

entry	radical	E_a(6-exo)[b]	E_a(7-endo)[b]
1	**22/23** (R = H)[a]	3.7	4.1
2	**22** (R = Cl)	7.4	4.0
3	**23** (R = Cl)	3.0	6.2
4	**22** (R = Me)	5.0	2.2
5	**23** (R = Me)	2.3	3.9

[a] Reference 2d. [b] In kcal/mol.

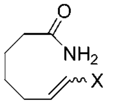


16a-c **17a-c** (4)



18a-f **19a-f** (5)

R = Me, X = Cl (**a**) 80%, Br (**b**) 72%, I (**c**) 45%
H (**d**) 80%, (**e**) 85%, (**f**) 79%



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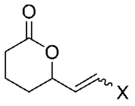

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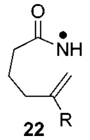

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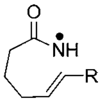

23

It should be noted that in the few separated examples of carbon-centered radicals in the literature the halogen-substitution effect appears to be much less satisfactory.[10] Then what accounts for this remarkable halogen-substitution effect for amidyl radicals? The steric effect and the radical-stabilizing effect of halogen atoms should play an important role in controlling the regioselectivity. However, these are not enough to explain the above results, as Br is of similar size to Me while the radical stabilization energy of a Br atom is even lower than that of a Me moiety.[11] We believe that the lone pair−lone pair electron repulsion between the N

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[8] The electrophilic iodocyclization product of **8c** (with NaHCO$_3$/I$_2$, rt) was identified to be 6-iodomethyl-2,3,4,5-tetrahydropyridine-2-one in 37% yield via a six-membered-ring closure, which in turn indicated that the formation of **9** was not an ionic process.

[9] The activation energies for 1,5-H migration of radicals **22** (R = Cl) and **23** (R = Cl) were also computed (B3LYP/6-31G*) to be 9.1 and 7.5 kcal/mol, respectively, much higher than the activation energies for the preferred cyclization, in excellent agreement with the experimental results in eqs 2 and 3.

[10] (a) Knapp, S.; Gibson, F. S.; Choe, Y. H. *Tetrahedron Lett.* **1990**, *31*, 5397. (b) Ishibashi, H.; Kobayashi, T.; Nakashima, S.; Tamura, O. *J. Org. Chem.* **2000**, *65*, 9022. (c) Cassayre, J.; Gagosz, F.; Zard, S. Z. *Angew. Chem., Int. Ed.* **2002**, *41*, 1783. (d) Kamimura, A.; Taguchi, Y. *Tetrahedron Lett.* **2004**, *45*, 2335. (e) Padwa, A.; Rashatasakhon, P.; Ozdemir, A. D.; Willis, J. *J. Org. Chem.* **2005**, *70*, 519. (f) Sharp, L. A.; Zard, S. Z. *Org. Lett.* **2006**, *8*, 831.

[11] Henry, D. J.; Parkinson, C. J.; Mayer, P. M.; Radom, L. *J. Phys. Chem. A* **2001**, *105*, 6750.

radical and the vinylic halogen, which is much greater than the repulsion between a lone pair and a bonded pair,[1c] adds an additional weight to the regioselectivity. For radical **22** (R = Cl), the computed N−Cl distance is 3.11 Å in the 6-exo transition structure but 3.92 Å in the 7-endo case. Therefore, the extent of lone pair electron repulsion between N and Cl atoms is much greater for 6-exo cyclization than for 7-endo cyclization.[12] A similar picture in favor of 6-exo cyclization can be drawn for **23** (R = Cl). Meanwhile, it is possible that the retardation of the competing iodolactonization also resulted from the lone pair−lone pair repulsion between the vinylic halogen and the I_2 species. The above results and discussion imply that (1) the amidyl radical cyclizations might also be well controlled by other vinylic heteroatom substitutions and (2) the halogen-substitution effect might also find important applications in other types of heteroatom-centered radicals. These are actively pursued in our laboratory.

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Supporting Information Available: Typical procedures for the amidyl radical cyclization reactions, characterizations of compounds **1**−**21**, and computational results on radicals **22** and **23** (PDF), as well as crystal structures of **19e** and **19f** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For a similar discussion, see: Howard, S. T.; Platts, J. A. *J. Org. Chem.* **1998**, *63*, 3568.