Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 4285–4288
Tetrahedron Letters

Ring contraction of *N*-chlorolactams, a novel rearrangement

Alexandre Drouin and Jean Lessard*

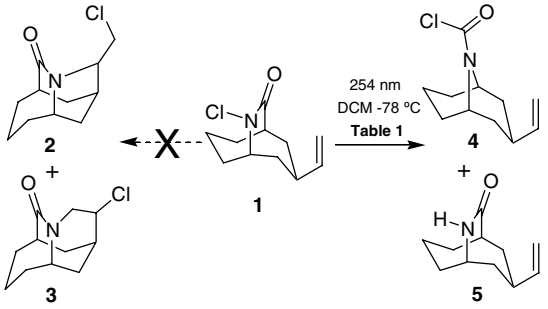
Département de Chimie, Université de Sherbrooke, 2500 Boul. Univsersité, Sherbrooke, Québec, Canada J1K 2X9

Received 21 February 2006; revised 31 March 2006; accepted 5 April 2006
Available online 4 May 2006

Abstract—Upon photolysis in methylene chloride at −78 °C, different *N*-chlorolactams underwent a novel ring contraction to the corresponding carbamoyl chlorides, which were converted to the methyl carbamates. The rearrangement is 100% stereoselective, occurring with retention of configuration at the migrating carbon center. The yields of isolated carbamates ranged from 40% to 57%, the other product being the parent lactam, 18% to 38%.

1. Introduction

Amidyl radicals have been extensively studied over the past years.[1] Back and Brunner[2] and Phan and Shannon[3] photolyzed different *N*-chlorolactams derived from aza-steroids to generate the corresponding *N*-acyl imines. The formation of polymers upon photolysis of *N*-chlorolactams in benzene was also reported.[4] Chow and Perry,[5] Kuehne and Horne,[6] Lessard and collaborators,[7,8] as well as Surzur and collaborators[9] showed that amidyl radicals add to double bonds to generate a carbon–nitrogen bond, both in intramolecular and intermolecular reactions. Other studies were carried out by Neale et al.,[4,10] Johnson and Green,[11] Chow and collaborators,[12] Beckwith and collaborators.[13,14] Those studies demonstrated that amidyl radicals could also abstract a nonactivated hydrogen atom in an intramolecular reaction. In the course of our studies on the reactivity of Π_N amidyl radicals in intramolecular additions to double bonds,[15,16] we had prepared the *N*-chlorolactam **1**,[17] the amidyl radical of which could add to the double bond only via the Π_N configuration.[18] The cyclization would have given rise to a tricyclic core via a *5-exo-trig* or *6-endo-trig* cyclization (see **2** and **3**, respectively, in Scheme 1). However, upon photolysis, no cyclized product was observed, nor any *N*-acyl imines. Instead, *N*-chlorolactam **1** underwent a ring contraction to generate the carbamoyl chloride **4** (Scheme 1). To the best of our knowledge, such ring contraction of a lactam has been observed only once by Edwards and collaborators[19] as a side reaction from the photolysis or thermolysis of *O*-mesylated hydroxamic acids. In this letter, we report the preliminary results on this new rearrangement of *N*-chlorolactams, which is conceptually similar to the Lossen, Curtius, Schmidt or Hofmann rearrangements,[20] except that it can be applied to cyclic systems. This ring contraction opens new possibilities for the synthesis of N-heterocycles bearing one or two chiral centers next to the nitrogen. Applications to the synthesis of complex alkaloids are foreseen.



Scheme 1. Photolysis of *N*-chlorolactam **1**.

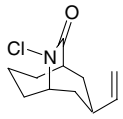
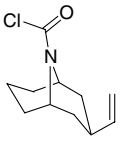
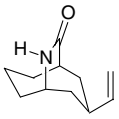
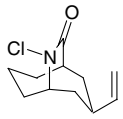
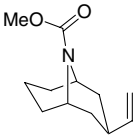
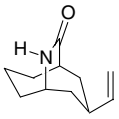
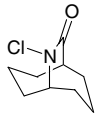
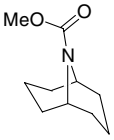
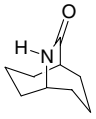
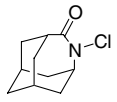
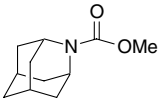
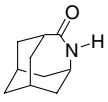
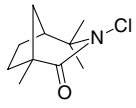
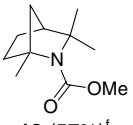
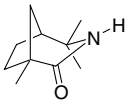
2. Results and discussion

The photolysis of *N*-chlorolactams **1**, **6**, **7**, and **8** was carried out in anhydrous dichloromethane (DCM) at −78 °C in a Rayonnet reactor equipped with 254 nm UV lamps.[16] The results are reported in Table 1. The rearrangement product, isolated as the carbamoyl

Keywords: *N*-Chlorolactams; Nitrogen-heterocycles; Photolysis; Rearrangement; Ring contraction.
* Corresponding author. Tel.: +1 819 821 7091; fax: +1 819 821 8017; e-mail: Jean.Lessard@usherbrooke.ca

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.04.024

Table 1. Results obtained from the photolysis of *N*-chlorolactams **1**, **6**, **7**, and **8**[a]

Entry	*N*-Chlorolactam	Rearranged product (yield)[b]	Parent lactam (yield)[b]
1[c]	 **1**	 **4** (40%)	 **5** (48%)
2[c,d]	 **1**	 **15** (44%)[e,f]	 **5** (34%)[g]
3[d]	 **6**	 **9** (53%)[f]	 **10** (28%)
4[d]	 **7**	 **11** (48%)[f]	 **12** (32%)
5[d]	 **8**	 **13** (57%)[f]	 **14** (18%)

[a] In anhydrous DCM at 254 nm.
[b] Yield of isolated product.
[c] The difference in yields between entries 1 and 2 is due to the variation of the temperature during the photolysis (−78 to 0 °C in entry 1, and −78 to −60 °C in entry 2).
[d] The reaction mixture was poured into methanol containing 2 equiv of triethylamine.
[e] Methyl carbamate **15** isolated in 25% yield and its dichloro-derivative in 19% yield.
[f] The formation of small amounts (5–10%) of C-chlorinated products was evidenced by GC–MS.
[g] Parent lactam **5** isolated in 26% yield and its dichloro-derivative in 8% yield.

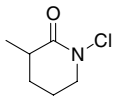
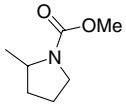
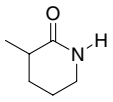
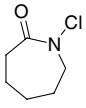
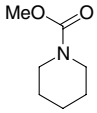
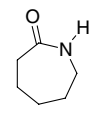
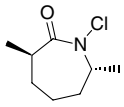
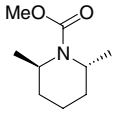
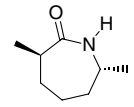
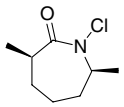
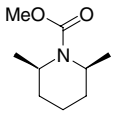
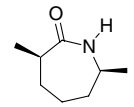
chloride (Scheme 1 and Table 1) or the methylcarbamate (Table 1), and the parent lactam accounted for 75–88% of the isolated products. *N*-Chlorolactam **1** gave 40% of carbamoyl chloride **4** and 48% of parent lactam **5** after chromatographic separation (Table 1, entry 1). As it was more convenient to isolate the product of rearrangement as the methyl carbamate, the crude reaction mixture was treated with methanol and triethylamine to convert the carbamoyl chloride to the methyl carbamate (Table 1, entries 2–5).

The parent lactams observed in all reactions were formed by intermolecular hydrogen abstraction from the solvent or from the substrate, either by the amidyl radical[21] (Bloomfield type mechanism)[22] or by the chlorine atom (Goldfinger type mechanism).[23]

Photolysis of *N*-chlorolactams **6**, **7**, and **8** gave the rearranged methylcarbamates **9**, **11**, and **13**, respectively, together with the corresponding parent lactams **10**, **12**, and **14** (Table 1, entries 3–5). Comparison of the results obtained with *N*-chlorolactams **1** and **6** (entries 2 and 3) indicates that the vinyl group of **1** had no influence on the course of the reaction. When the photolysis of **1** was repeated on a larger scale, products resulting from the addition of molecular chlorine (generated through the Goldfinger mechanism)[23] to the double bond were obtained in relatively important amounts. Indeed, the dichloro derivative of carbamate **15** was isolated in 19% yield together with 25% of **15** (for a total of 44% of rearranged products). In addition, the dichloro derivative of parent lactam **5** was isolated in 8% yield together with 26% of **5** (34% of unrearranged lactams) (Table 1, entry 2).

We also studied the photolysis of monocyclic *N*-chlorolactams **16** derived from δ-valerolactam and, **17**, **18**, and **19** derived from ε-caprolactam (Table 2). δ-*N*-Chloro-3-methylvalerolactam **16** gave the methyl carbamate **20** and the parent lactam **21** in a 45:55 ratio (entry 1; determined by GC–MS). On the other hand, unsubstituted ε-*N*-chlorocaprolactam **17** gave the methyl carbamate **22** and the parent lactam **23** in a 6:94 ratio (entry 2; determined by GC–MS). In comparison with **17**, ε-*N*-chloro-caprolactams **18** and **19** gave much better yields of rearranged methyl carbamates **24** and **26** (entries 3 and 4). Indeed, 52% of methyl carbamate **24** and 33% of parent lactam **25** were isolated from the photolysis of **18**, and 43% of methyl carbamate **26** and 38% of par-

Table 2. Results obtained from the photolysis of *N*-chlorolactams **16**, **17**, **18**, and **19**

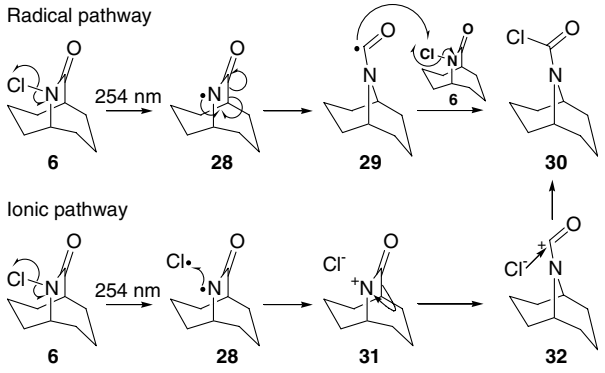
Entry	*N*-Chlorolactam	Rearranged product (yield)	Parent lactam (yield)
1	 **16**	 **20** (45%)[a]	 **21** (55%)[a]
2	 **17**	 **22** (6%)[a]	 **23** (94%)[a]
3	 *rac*-**18**	 **24** (52%)[b]	 *rac*-**25** (33%)[b]
4	 *rac*-**19**	 **26** (43%)[b]	 *rac*-**27** (38%)[b]

[a] Ratios determined by GC–MS.
[b] Yield of isolated products.

ent lactam **27** were isolated from the photolysis of **19**. The difference in the observed ratio of rearranged product to parent lactam in the photolysis of *N*-chlorolactams **17** on one hand, and *N*-chlorolactam **16**, **18**, and **19** on the other hand, could be explained by the migratory aptitude of the carbon, the migration of a secondary carbon being faster than that of a primary carbon.[24] Methyl carbamates **24** and **26** were isolated as single diastereoisomers, as shown, revealing that the rearrangement is 100% stereoselective and that migration occurs with retention of configuration at the migrating carbon (determined by NMR and GC). This result suggests that the migration is a concerted process. It is noteworthy that ring contraction from six- to five-membered ring (entry 5 of Table 1 and entry 1 of Table 2) is as efficient as ring contraction from a seven- to a six-membered ring (entries 2–4 of Table 1 and entries 3 and 4 of Table 2).

Concerning the mechanistic aspect of the reaction, we know from literature precedents that photolysis of *N*-chlorolactams gives rise to homolytic cleavage of the N–Cl bond.[16] One possible mechanism for the rearrangement could thus involve radical species (Scheme 2, radical pathway). Homolytic cleavage of the N–Cl bond would be followed by a 1,2-rearrangement of the amidyl radical **28** to a more stable formyl radical **29**, and then, reaction of **29** with the parent *N*-chlorolactam **6** to form the carbamoyl chloride **30** would regenerate the amidyl radical **28**. However, this mechanism is difficult to reconcile with the observation that the rearrangement is 100% stereoselective. We therefore propose a mechanism implying ionic species (Scheme 2, ionic pathway). The first step would also be the homolytic clevage of the N–Cl bond, followed by electron transfer from the nitrogen atom to the chlorine atom[19,25] to generate the acylnitrenium ion **31** and chloride ion. Concerted and rapid [1,2]-migration of the carbon α to the carbonyl onto nitrogen would give the corresponding *N*-acylium ion **32**. The close-by chloride ion (solvent cage) would then react with **32** to generate the corresponding carbamoyl chloride **30**.

Finally, a series of experiments were carried out to determine if the rearrangement could be induced thermally. The results are shown in Table 3. First, *N*-chlorolactam **7** was dissolved in dichloromethane and silver tetrafluoroborate was added. The mixture was refluxed for 16 h, then treated with methanol. The sole compound recovered was the starting *N*-chlorolactam **7**. The same result was obtained when using aluminum trichloride. A similar experiment was realized in trifluoroacetic acid with silver tetrafluoroborate, and again, the only compound recovered was **7**.

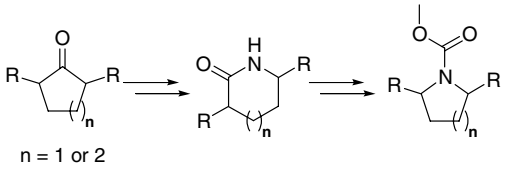


Scheme 2. Proposed mechanisms for the rearrangement with ring contraction of *N*-chlorolactams.

Table 3. Results obtained from thermal treatment of *N*-chlorolactam **7**

Entry	Conditions	Products observed
1	**7**, DCM, $AgBF_4$, reflux 16 h	**7**
2	**7**, TFA, $AgBF_4$, reflux 16 h	**7**
3	**7**, 200 °C, 1 h[a]	**12** and decomposition
4	**7**, Toluene, 200 °C, 1 h[a]	**12** and decomposition

[a] Reaction carried out in a sealed tube.



Scheme 3. Conversion of ketones and ring contraction of lactam to the corresponding N-heterocycle.

N-Chlorolactam **7** was also heated, in a sealed tube, to 200 °C for 1 h as a neat liquid and also in solution in toluene. After treatment with methanol, no trace of the rearranged compound **11** was observed. The parent lactam **12** was the main product of this reaction together with various compounds arising from the decomposition of *N*-chlorolactam **7**.

3. Conclusion

In conclusion we have discovered a novel ring contraction of *N*-chlorolactams, which opens new perspectives for the synthesis of nitrogen heterocycles. It allows, in principle, the conversion of a cyclic ketone to the corresponding nitrogen heterocycle of the same ring size (replacement of the carbonyl group by a nitrogen atom) via a sequence initiated with a Beckmann ring enlargement followed by our novel ring contraction rearrangement (Scheme 3). Further studies currently underway in our laboratory are aimed at optimizing the ring contraction as well as determining its mechanism and scope.

Acknowledgments

We thank Dr. Claude Spino for fruitful discussion and Dr. Daniel Fortin for the X-ray structure determination. This work was supported by a research grant form the Natural Sciences and Engineering Council of Canada (NSERC).

Supplementary data

Complete procedure and characterization of all compounds can be found in the supplementary data.

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.04.024.

References and notes

1. For review articles about chemistry of amidyls radical 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. Back, T. G.; Brunner, K. *J. Org. Chem.* **1989**, *54*, 1904.
3. Phan, X. T.; Shannon, P. J. *J. Org. Chem.* **1983**, *48*, 5164.
4. Neale, R. S.; Marcus, N. L.; Schepers, R. G. *J. Am. Chem. Soc.* **1966**, *88*, 3051.
5. Chow, Y. L.; Perry, R. A. *Tetrahedron Lett.* **1972**, *13*, 531.
6. Kuehne, M. E.; Horne, D. A. *J. Org. Chem.* **1975**, *40*, 1287.
7. Intramolecular radical additions: Mackiewicz, P.; Furstoss, R.; Waegell, B.; Côté, R.; Lessard, J. *J. Org. Chem.* **1978**, *43*, 3746–3750; Lessard, J.; Côté, R.; Mackiewicz, P.; Furtoss, R.; Waegell, B. *J. Org. Chem.* **1978**, *43*, 3750–3756.
8. Intermolecular additions: Touchard, D.; Lessard, J. *Tetrahedron Lett.* **1971**, *12*, 4425; Touchard, D.; Lessard, J. *Tetrahedron Lett.* **1973**, *14*, 3827; Driguez, H.; Paton, J. M.; Lessard, J. *Can. J. Chem.* **1977**, *55*, 700; Driguez, H.; Lessard, J. *Can. J. Chem.* **1977**, *55*, 720; Driguez, H.; Lessard, J. *Can. J. Chem.* **1978**, *56*, 119.
9. Flesia, E.; Croatto, A.; Tordo, P.; Surzur, J. M. *Tetrahedron Lett.* **1972**, 535.
10. Neale, R. S. *Synthesis* **1971**, 1, and references cited therein.
11. Johnson, R. A.; Greene, F. D. *J. Org. Chem.* **1975**, *40*, 2186.
12. Joseph, T. C.; Tam, J. N. S.; Kitadani, M.; Chow, Y. L. *Can. J. Chem.* **1976**, *54*, 3517.
13. Barton, D. H. R.; Beckwith, A. L. J.; Goosen, A. *J. Chem. Soc.* **1965**, 181.
14. Beckwith, A. L. J.; Goodrich, J. E. *Aust. J. Chem.* **1965**, *18*, 747.
15. The ground state of the amidyl radical is Π_N: (a) Lessard, J.; Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 3262–3264; (b) Sutcliffe, R.; Griller, D.; Lessard, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1981**, *103*, 624–628; (c) Sutcliffe, R.; Ingold, K. U.; Lessard, J. *J. Am. Chem. Soc.* **1981**, *103*, 7685–7686.
16. Daoust, B.; Lessard, J. *Tetrahedron* **1999**, *55*, 3495–3514.
17. All *N*-chlorolactams were prepared from their corresponding lactams, see Supplementary data for procedure.
18. To the best of our knowledge, no unequivocal addition of the Π_N state of an amidyl radical with an olefin has been reported in the literature to date.
19. Edwards, O. E.; Grue-Sorensen, G.; Blackwell, B. A. *Can. J. Chem.* **1997**, *75*, 857–872.
20. Smith, M. B.; March, J. In *Advanced Organic Chemistry*, 5th ed.; Wiley Interscience, 2001; pp 1411–1415.
21. Johnson, R. A.; Greene, F. D. *J. Org. Chem.* **1975**, *40*, 2192–2196.
22. Bloomfield, G. F. *J. Chem. Soc.* **1944**, 114.
23. Adam, J.; Gosselain, P. A.; Goldfinger, P. *Nature (London)* **1953**, *171*, 704–705.
24. This is well known in ionic rearrangements but no example of a radical migration of an alkyl group has been reported according to our knowledge. See: Smith, M. B.; March, J. In *Advanced Organic Chemistry*, 5th ed.; Wiley Interscience, 2001; pp 1384–1386.
25. For a discussion of similar electron transfers see: Kropp, P. J. *Acc. Chem. Res.* **1984**, *17*, 131; Ho, P.-T. *Can. J. Chem.* **1979**, *56*, 733; Zimmerman, H. E. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 1; Pincock, J. A. *Acc. Chem. Res.* **1997**, *30*, 43; However, see: Vancik, H.; Gabelica, V.; Rogan, V.; Sunko, D. E. *J. Chem. Res. (S)* **1990**, 92.