Pergamon

Tetrahedron Letters 41 (2000) 5699–5703

TETRAHEDRON
LETTERS

Exclusive 1,4-aryl migration in a stereoselective cyclization of *N*-benzylalk-4-enylaminyl radicals

Hisanori Senboku,* Hikaru Hasegawa, Kazuhiko Orito and Masao Tokuda*

Division of Molecular Chemistry, Graduate School of Engineering, Hokkaido University, Sapporo 060-8628, Japan

Received 1 May 2000; revised 29 May 2000; accepted 2 June 2000

Abstract

Tandem cyclization of *N*-benzylalk-4-enylaminyl radicals readily occurs to give 1,4-aryl migration pyrrolidines, *trans*-*N*-methyl-2-alkyl-5-(1-phenylalkyl)pyrrolidines, exclusively. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: pyrrolidines/pyrrolidinones; radicals and radical reactions; rearrangement; cyclisation.

Radical cyclization is one of the most attractive methods for the synthesis of cyclic compounds and has been widely used in organic syntheses.[1,2] Carbon radicals are frequently used in the synthesis of carbocycles as well as heterocycles,[1,2] but synthesis of heterocyclic compounds by cyclization of heteroatom-centred radicals has not been well-explored.

In a previous paper[3] we reported a new generation of aminyl radicals from *N*-chloroalk-4-enylamine with Bu_3SnH–AIBN in refluxing benzene and its stereoselective cyclization to give *trans*-2,5-disubstituted pyrrolidines. Recently, we also reported its application to a synthesis of *trans*-*N*-methyl-2-butyl-5-heptylpyrrolidine, an ant venom alkaloid,[4] and to a stereoselective tandem cyclization affording 1,2,5-trisubstituted pyrrolizidines.[5] In the course of our study on a stereoselective synthesis of the *N*–H derivative of *trans*-2,5-disubstituted pyrrolidines, we found that a tandem cyclization of *N*-benzylalk-4-enylaminyl radicals took place efficiently to give the 1,4-phenyl-migrated *N*-methyl-2,5-disubstituted pyrrolidines exclusively.

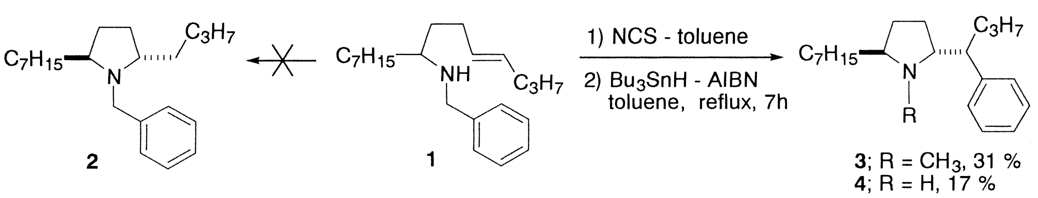
Several reviews[6] and investigations[7] of 1,4-aryl migration (1,4-aryl shift) in radical reactions have been reported. However, there have been only a few reports on an aryl migration after the radical cyclization[7f,8] and, in most cases, yields of the migration products were low. Moreover, they were often obtained as a mixture with other products. In this communication, we report an exclusive 1,4-migration of an aryl group in the stereoselective cyclization of *N*-benzylaminyl radicals.

---

* Corresponding author. Tel: +81 11 706 6599; fax: +81 11 706 6598; e-mail: tokuda@org-mc.eng.hokudai.ac.jp

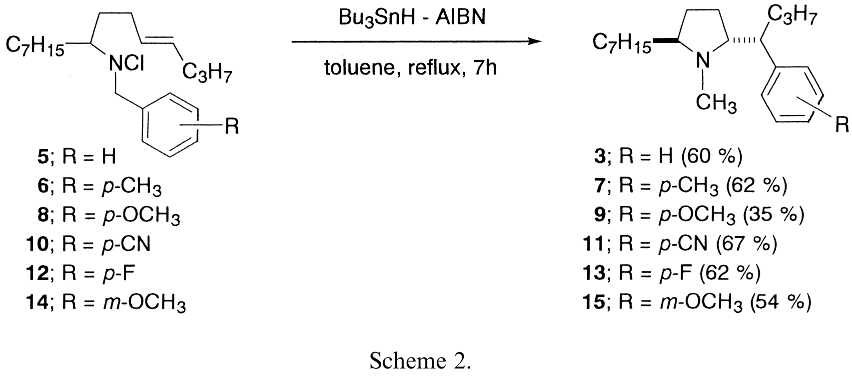
PII: S0040-4039(00)00933-3

Treatment of a toluene solution (0.02 M) of *N*-benzyl-1-heptyloct-4-enylamine (**1**) with NCS (1 equiv.) gave the corresponding *N*-chloroamine in situ, and heating of the mixture under reflux for 7 h in the presence of Bu_3SnH (1 equiv.) and AIBN (0.2 equiv.) gave two kinds of phenyl group-migrated cyclization products, **3** and **4**, in 31 and 17% yields, respectively, together with a small amount of the starting amine **1** (7%) (Scheme 1). Both products **3** and **4** were found to be a single diastereoisomer, respectively, although a stereochemistry of C-1 of 1-phenylbutyl group at the C-2 position of **3** or **4** was not determined yet. These results indicate that a highly stereoselective cyclization of an aminyl radical followed by an efficient migration of a phenyl group occurs in this cyclization.



Scheme 1.

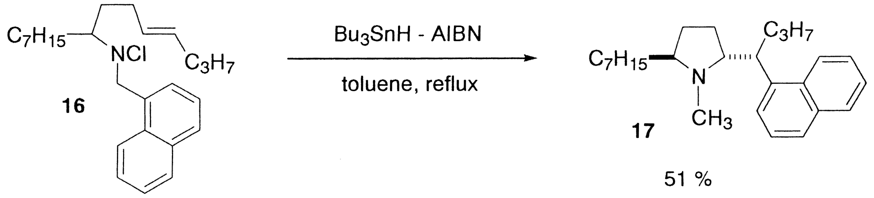
We found that sequential aminyl radical cyclization-1,4-aryl migration readily took place to give the corresponding *N*-methyl derivatives **3**, **7**, **9**, **11**, **13**, and **15** as a single stereoisomer exclusively when isolated *N*-chloro-*N*-benzylalk-4-enylamines were used as the starting substrates. Thus, *N*-chloroamines obtained by treatment of *N*-benzyl-1-heptyloct-4-enylamines with NCS were isolated by TLC (SiO_2), and were reacted with Bu_3SnH (1 equiv.) and AIBN (0.2 equiv.) in toluene (0.02 M) under reflux. Radical reaction of isolated *N*-chloroamine **5** gave *trans*-*N*-methyl-2-heptyl-5-(1-phenylbutyl)pyrrolidine (**3**), exclusively, in 60% yield (Scheme 2). Similar radical reactions of *N*-benzyl-*N*-chloroalk-4-enylamines carrying an electron-donating (**6** or **8**) or electron-withdrawing group (**10** or **12**) at their *para* position of the benzyl group gave the corresponding aryl migration products **7**, **9**, **11**, and **13** in 35–67% yields, as shown in Scheme 2. In all cases the substituents on a phenyl group at its *para* position were retained after the aryl migration, which shows that a 1,4-migration of the aryl group occurs at its *ipso* position. When a



Scheme 2.

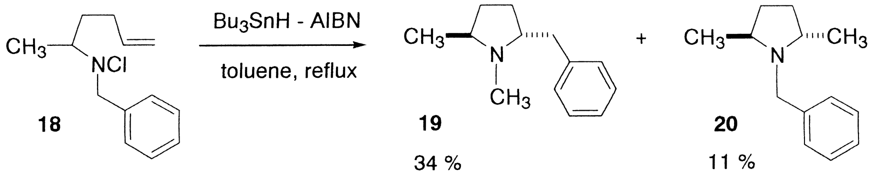
similar radical reaction of a substrate **14** having a *meta*-methoxyphenyl group was carried out, the cyclization-aryl migration also took place efficiently to afford the corresponding pyrrolidine **15** in 54% yield (Scheme 2).

N-(1-Naphthyl)methyl derivative **16** was also found to be effective for this sequential cyclization–migration reaction. Thus, a similar radical reaction of **16** also gave an aryl-migrated pyrrolidine **17**, exclusively, in 51% yield, which shows that migration of the naphthyl group also proceeds at its *ipso* position in this case (Scheme 3).



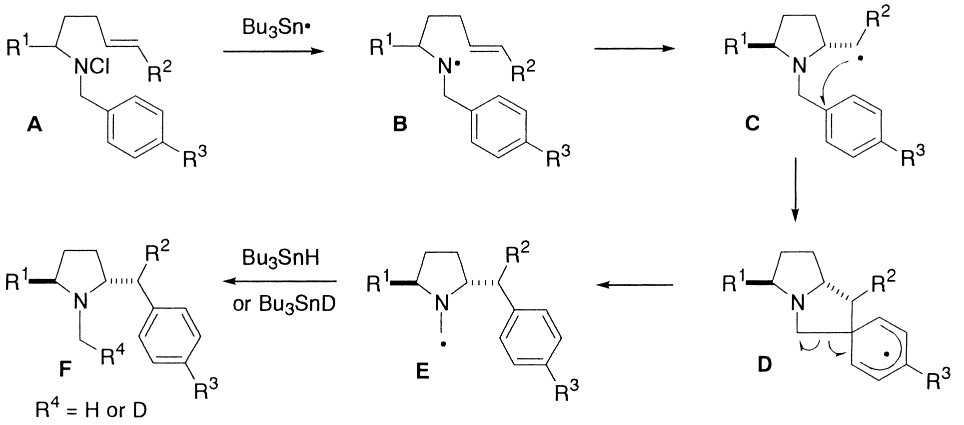
Scheme 3.

The effects of the substituents at a terminal carbon of the double bond in the starting alkenylamines were also examined. When *N*-benzylalk-4-enylamines carrying a phenyl group or dimethyl substituents at the terminal carbon were subjected to this radical reaction, a cyclization of aminyl radical took place stereoselectively to give the corresponding *trans*-*N*-benzylpyrrolidines in good yields, but no phenyl migration occurred.[3] A similar radical reaction of *N*-chloro-*N*-benzyl-1-methylpent-4-enylamine (**18**), carrying no substituents at the terminal carbon, gave phenyl-migrated pyrrolidine **19** and *N*-benzyl-2,5-dimethylpyrrolidine (**20**) in 34% and 11% yields, respectively (Scheme 4).



Scheme 4.

The exclusive formation of aryl group-migrated pyrrolidines is thought to result from an aminyl radical cyclization-1,4-aryl migration sequence. The proposed reaction pathways are shown in Scheme 5. Stereoselective 5-*exo* cyclization of aminyl radical **B**, generated from *N*-chloroamine **A**, affords the intermediate radical **C** having a *trans*-2,5-disubstituted pyrrolidine skeleton. Attack of the resulting secondary alkyl radical **C** on an *ipso* position of the phenyl ring of an *N*-benzyl group gives cyclohexadienyl radical **D**. Rearomatization by a β-scission would result in 1,4-aryl migration to give radical **E**, stabilized by a neighbouring nitrogen atom. Hydrogen abstraction of **E** from Bu_3SnH gives product **F**. The final step was confirmed from the result that when this reaction was carried out by using Bu_3SnD, *N*-monodeuteriomethylpyrrolidine was the only product obtained.



Scheme 5.

Acknowledgements

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No.706: Dynamic Control of Stereochemistry) from the Ministry of Education, Science, Sports and Culture, Japan.

References

1. Recent reviews: (a) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1–14. (b) Banik, B. K. *Cur. Org. Chem.* **1999**, *3*, 469–496. (c) Yet, L. *Tetrahedron* **1999**, *55*, 9349–9403. (d) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543–17594. (e) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. In *Organic Reactions;* Paquette, L. A., Ed. John Wiley & Sons: New York, 1996; *48*, pp. 301–856. (f) Sibi, M. P.; Ji, J. In *Progress in Heterocyclic Chemistry;* Suschitzky, H.; Gribble, G. W., Eds. Pergamon Press: Oxford, 1996; Vol. 8, pp. 14–43. (g) Renaud, P.; Giraud, L. *Synthesis* **1996**, 913–926. (h) Esker, J. L.; Newcomb, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed. Academic Press: New York, 1993; *58*, pp.1–45.
2. Recent communications on radical cyclization: (a) Contelles, J.-M.; Fernández, R.-M. *Tetrahedron Lett.* **2000**, *41*, 381–384. (b) Ishibashi, H.; Inomata, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.* **1999**, *40*, 1149–1152. (c) Ryu, I.; Ogura, S.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1999**, *40*, 1515–1518. (d) Miyabe, H.; Tanaka, H.; Naito, T. *Tetrahedron Lett.* **1999**, *40*, 8387–8390. (e) Matos, M. R. P. N.; Afonso, C. A. M.; McGarvey, T.; Lee, P.; Batey, R. A. *Tetrahedron Lett.* **1999**, *40*, 9189–9193. (f) Ishibashi, H.; Kobayashi, T.; Takamasu, D. *Synlett* **1999**, 1286–1288. (g) Lee, E.; Choi, S. J. *Org. Lett.* **1999**, *1*, 1127–1128.
3. Tokuda, M.; Fujita, H.; Suginome, H. *J. Chem. Soc., Perkin Trans. 1* **1994**, 777–778.
4. Senboku, H.; Hasegawa, H.; Orito, K.; Tokuda, M. *Heterocycles* **1999**, *50*, 333–340.
5. Senboku, H.; Kajizuka, Y.; Hasegawa, H.; Fujita, H.; Suginome, H.; Orito, K.; Tokuda, M. *Tetrahedron* **1999**, *55*, 6465–6474.
6. (a) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed. Free-radical Rearrangements. Academic Press: New York, 1980; pp. 161–310. (b) Wilt, J. W. In *Free Radicals;* Kochi, J. K., Ed. Free Radical Rearrangements. John Wiley & Sons: New York, 1973; Vol. 1, pp. 333–501, and references cited therein.

7. Recent reports on 1,4-aryl migration: (a) Amii, H.; Kondo, S.; Uneyama, K. *Chem. Commun.* **1998**, 1845–1846. (b) Montevecchi, P. C.; Navacchia, M. L. *J. Org. Chem.* **1998**, *63*, 537–542. (c) da Mata, M. L. E. N.; Motherwell, W. B.; Ujjainwalla, F. *Tetrahedron Lett.* **1997**, *38*, 137–140, 141–144. (d) Giraud, L.; Lacôte, E.; Renaud, P. *Helv. Chim. Acta* **1997**, *80*, 2148–2156. (e) Lee, E.; Whang, H. S.; Chung, C. K. *Tetrahedron Lett.* **1995**, *36*, 913–914. (f) Aubé, J.; Peng, X.; Wang, Y.; Takusagawa, F. *J. Am. Chem. Soc.* **1992**, *114*, 5466–5467, and references cited therein.
8. An example of 1,2-aryl migration after radical cyclization: Ishibashi, H.; So, T. S.; Okochi, K.; Sato, T.; Nakamura, N.; Nakatani, H.; Ikeda, M. *J. Org. Chem.* **1991**, *56*, 95–102. An example of 1,4-aryl migration after radical cyclization: Clive, D. L. J.; Boivin, T. L. B. *J. Org. Chem.* **1989**, *54*, 1997–2003.