ORGANIC LETTERS

2001
Vol. 3, No. 17
2709−2711

# Radical [3 + 2] Annulation of *N*-Allyl-*N*-chlorotosylamide with Alkenes via Atom-Transfer Process

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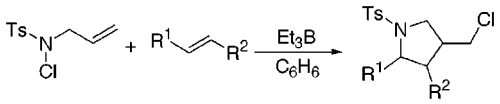
**Received June 20, 2001**

## ABSTRACT

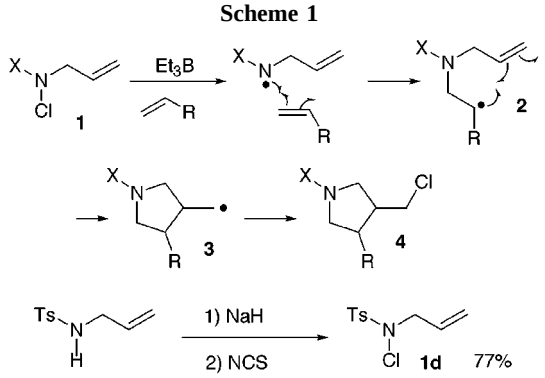



**A radical [3+2] annulation reaction with an N-centered radical has been developed. The reaction of alkenes with *N*-allyl-*N*-chlorotosylamide yields the corresponding pyrrolidine derivatives in good yields in the presence of $Et_3B$ as a radical initiator.**

The use of radical species in organic synthesis has increased dramatically in the past two decades.[1] During those years, inter- and intramolecular radical addition reactions that exploit carbon-centered radical species have found widespread application.[2] Recently, intramolecular cyclization of N-centered radicals has emerged as an efficient method for the construction of nitrogen heterocycles.[3,4] However, only few examples of the intermolecular addition of N-centered radicals have been reported so far.[5] Herein we wish to report the intermolecular radical addition of *N*-allylamidyl radicals toward alkenes to form pyrrolidine derivatives, [3 + 2] annulation products.

In general, annulation is a more convergent strategy than intramolecular cyclization, and hence radical annulation based on an intermolecular addition can be an expeditious strategy for constructing cyclic compounds.[6] Scheme 1 outlines the course of the radical annulation reaction with an N-centered radical via a radical addition−cyclization sequence. The N-centered radical from **1** undergoes the

**Scheme 1**




(1) (a) *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001. (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH Verlagsgesellschaft mbH.: Weinheim, 1996. (c) Giese, B.; Kopping, B.; Göbel, T.; Dickhaut, J.; Thoma, G.; Kulicke, K. J.; Trach, F. *Org. React.* **1996**, *48*, 301. (d) Curran, D. P. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford 1991; Vol. 4, Chapter 4.2, p 779. (e) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224.

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(3) For recent examples, see: (a) Uchiyama, K.; Hayashi, Y.; Narasaka, K. *Tetrahedron* **1999**, *55*, 8915. (b) Uchiyama, K.; Ono, A.; Hayashi, Y.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 8915. (c) Senboku, H.; Hasegawa, H.; Orito, K.; Tokuda, M. *Tetrahedron Lett.* **2000**, *41*, 2945. (d) Senboku, H.; Kajizuka, Y.; Hasegawa, H.; Fujita, H.; Suginome, H.; Orito, K.; Tokuda, M. *Tetrahedron* **1999**, *55*, 6465. (e) Hemmerling, M.; Sjoholm, A.; Somfai, P. *Tetrahedron: Asymmetry* **1999**, *10*, 4091. (f) Liu, J. F.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8263. (g) Cossy, J.; Tresnard, L.; Gomez P. D. *Eur. J. Org. Chem.* **1999**, 1925. (h) Snider, B. B.; Liu, T. *J. Org. Chem.* **1997**, *62*, 5630. (i) Clark, A. J.; Filik, R. P.; Peacock, J. L.; Thomas, G. H. *Synlett* **1999**, 441.

(4) For reviews, see: (a) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543. (b) Neale, R. S. *Synthesis* **1971**, 1. (c) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337. (d) Zard, S. Z. *Synlett* **1996**, 1148. (e) Esker, J. L.; Newcomb, M. *Adv. Heterocycl. Chem.* **1993**, *58*, 1.

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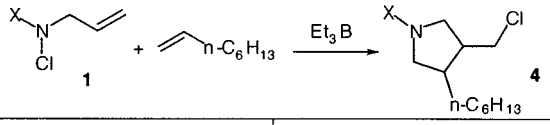
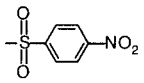
**Published on Web 07/31/2001**

intermolecular addition toward an alkene to form an alkyl radical **2**. The subsequent 5-exo radical cyclization proceeds smoothly to yield the cyclic radical **3**, which eventually abstracts the chlorine atom from the starting material **1** and regenerates the N-centered radical.

We examined the reaction of several *N*-allyl-*N*-chloroamine derivatives **1** with alkenes in the presence of $Et_3B$ as a radical initiator (Table 1). The initial trial was disappointing. The reaction of *N*-allyl-*N*-benzyl-*N*-chloroamine (**1a**) with 9.0 equiv of 1-octene yielded only the reduction product, allylbenzylamine, by the action of $Et_3B$ (0.1 equiv). This result indicates that the aminyl radical derived from *N*-chloroamine would abstract the allylic hydrogen atom of the alkene rapidly. The use of *N*-benzoyl derivative **1b** also provided no detectable amount of the desired pyrrolidine **4**. We were pleased to find that *N*-allyl-*N*-chlorosulfonamides underwent the smooth radical [3 + 2] annulation reaction with a catalytic amount of $Et_3B$. *N*-Allyl-*N*-chlorosulfonamide **1d** was easily prepared via chlorination of sodium salt of sulfonamides with *N*-chlorosuccinimide (Scheme 1).[7]

**Table 1.** Effect of the Substituent on Nitrogen[a]

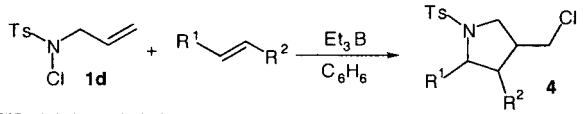


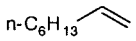
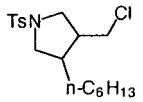
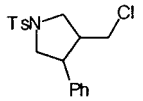
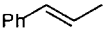
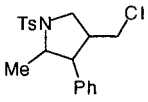
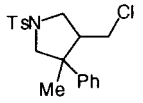
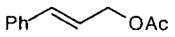
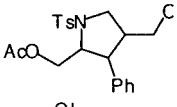
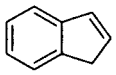
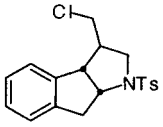
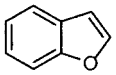
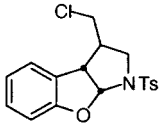
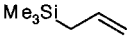
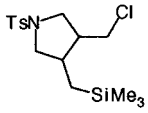
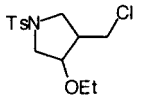
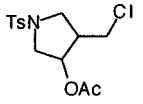

| X | yield (%) | X | yield (%) |
|---|---|---|---|
| $CH_2Ph$ **1a** | 0 | Ts **1d** | 60 |
| COPh **1b** | 0 |  **1e** | 65 |
| Ms **1c** | 40 | | |

[a] Reactions were carried out with **1** (0.5 mmol) and 1-octene (4.5 mmol) in benzene (1.5 mL) in the presence of triethylborane (0.05 mmol).

We then investigated the radical annulation reaction of *N*-allyl-*N*-chlorosulfonamide with various alkenes in benzene (Table 2).[8] Among alkenes we employed, allyltrimethylsilane and styrene derivatives are particularly good partners in this annulation protocol.[9] Whereas radical annulation often requires a large excess amount of alkenes,[10] this reaction yields the corresponding pyrrolidine derivatives in good to excellent yields with 2.0 equiv of alkenes. Although the hydrogen abstraction with N-centered radicals can be problematic, the intermolecular addition and the subsequent

**Table 2.** Radical [3 + 2] Annulation Reaction with *N*-Allyl-*N*-chlorosulfonamide[a]




| entry | alkene | product | yield (%) | selectivity |
|---|---|---|---|---|
| 1[b] |  |  | 60 | 63/37 |
| 2 |  |  | 96 | N. D.[c] |
| 3 |  |  | 79 | 62/38 |
| 4 |  |  | 96 | 78/22 |
| 5 |  |  | 52 | 56/44 |
| 6 |  |  | 83 | 57/43 |
| 7 |  |  | 82 | 83/17[d,f] |
| 8 |  |  | 80 | 69/31[e,f] |
| 9 |  |  | 28 | 68/32 |
| 10 |  |  | 57 | 71/29[e,f] |

[a] Reactions employed **1d** (0.5 mmol) and alkene (1.0 mmol) in benzene (1.5 mL) in the presence of $Et_3B$ (0.05 mmol) unless otherwise noted. The reaction mixture was stirred for 3 h at room temperature. [b] Octene (9.0 equiv) was employed. [c] The stereoselectivity could not be determined. [d] *endo*/*exo*. [e] *cis*/*trans*. [f] The stereochemistry was assigned on the basis of NOE difference experiments.

(5) (a) Newcomb, M.; Kumar, M. U. *Tetrahedron Lett.* **1990**, *31*, 1675. (b) Nagao, Y.; Katagiri, S. *Chem. Lett.* **1992**, 2379. (c) Goosen, A.; McCleland, C. W.; Merrifield, A. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 627.

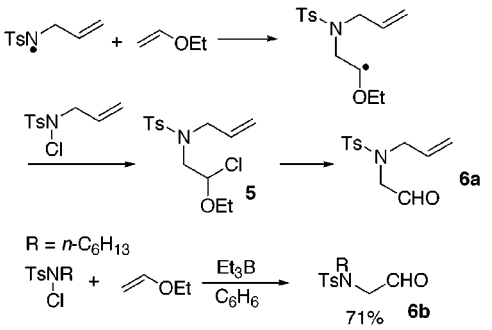
(6) Radical annulation is defined as a radical addition−cyclization sequence initiated by an intermolecular radical addition reaction. For examples of radical annulation with carbon-centered radicals, see: (a) Cekovic, Z.; Saicis, R. *Tetrahedron Lett.* **1986**, *27*, 5893. (b) Barton, D. H. R.; Zard, S. Z.; deSilva, E. *J. Chem. Soc., Chem. Commun.* **1988**, 285. (c) Curran, D. P.; Chen, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 6558. (d) Curran, D. P.; Chen, M.-H.; Spletzer, E.; Seong, C. M.; Chang, C.-T. *J. Am. Chem. Soc.* **1987**, *111*, 8872. (e) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. (f) Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5135. (g) Curran, D. P.; van Elburg, P. A. *Tetrahedron Lett.* **1989**, *30*, 2501.

(7) For preparation of *N*-chlorotosylamide, see: (a) Challis, B. C.; Iley, J. N. *J. Chem. Soc., Perkin Trans. 2* **1985**, 699. (b) Johnson, M. D.; Lampman, G. M.; Koops, R. W.; Gupta, B. D. *J. Organomet. Chem.* **1987**, *326*, 281.

(8) The use of THF or ether as a reaction solvent decreased the yields of the cyclization products. The reaction in water provided only the reduction product (*N*-allyltosylamide).

cyclization are much faster than those side reactions. It is striking that the annulation with indane provided the corresponding tricyclic compound in excellent yield despite the fact that indane is a good hydrogen donor toward radical species (entry 6). In the reaction with cinnamyl acetate, however, the abstraction reaction occurred significantly to give the simple reduction product, *N*-allyltosylamide, in 17% yield (entry 5). The reaction with ethyl vinyl ether afforded α-amino aldehyde **6a** as the major product. In this case, the cyclization of the resultant radical might be relatively slow and the radical would abstract chlorine of chlorosulfonamide (Scheme 2). Aqueous workup would hydrolyze α-chloro ether **5** to the corresponding aldehyde. The use of *N*-hexyl-*N*-chlorotosylamide instead of allyltosylamide provided α-amino aldehyde **6b** in 71% yield. This result indicates that the 1,5-hydrogen abstraction from the hexyl group with the tosylamidyl radical is not so rapid. The use of vinyl acetate instead of ethyl vinyl ether improved the yield up to 57% (entry 10). Aliphatic internal alkenes such as cyclohexene or 5-dodecene afforded unsatisfactory results.[11] Stereoselectivities of this process are not so high and vary with the substrate. The stereochemical outcome is in good agreement with the general trend of stereoselectivity in radical cyclizations of 1-substituted hexenyl radicals.[1b]

**Scheme 2**




In conclusion, we have developed an efficient radical [3 + 2] annulation reaction with *N*-allyl-*N*-chlorotosylamide, yielding pyrrolidine derivatives in good to excellent yields. This facile protocol provides an easy access to nitrogen heterocycles from alkenes. Further effort to expand limitation and improve the stereoselectivity is currently under way in our laboratory.

**Acknowledgment.** This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (No. 412: Exploitation of Multi-Element Cyclic Molecules) from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

OL016310J

(9) **General Procedure.** A solution of triethylborane (0.05 mL, 1.0 M hexane solution, 0.05 mmol) was added dropwise to a solution of chlorotosylamide **1d** (123 mg, 0.5 mmol) and styrene (0.11 mL, 1.0 mmol) in benzene (1.5 mL) at room temperature. After the mixture was stirred for 3 h, solvent was removed under reduced pressure. Purification of the residual oil by chromatography afforded 3-chloromethyl-4-phenyl-1-tosylpyrrolidine (168 mg, 0.48 mmol) in 96% yield.

(10) Typically, 10−20 equiv of alkenyl partners were employed.

(11) The reaction of **1d** with cyclohexene or 5-dodecene afforded *N*-allyltosylamide in quantitative yield. The rate of the radical addition to internal alkenes should be slow, and the abstraction of allylic hydrogen would be predominant.