ORGANIC LETTERS

2002
Vol. 4, No. 12
2097−2099

Unique Ionic Iodine Atom Transfer Cyclization: A New Route to Iodomethylated Pyrrolidine Derivatives from γ-Iodoolefin and Chloramine-T

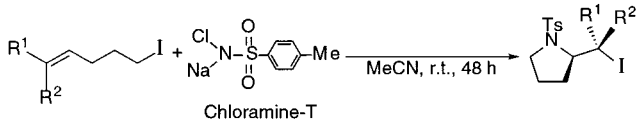
Satoshi Minakata, Daisuke Kano, Yoji Oderaotoshi, and Mitsuo Komatsu*

Department of Applied Chemistry, Graduate School of Engineering, Osaka University, Yamadaoka 2-1, Suita, Osaka 565-0871, Japan

komatsu@ap.chem.eng.osaka-u.ac.jp

Received April 16, 2002

ABSTRACT



Pyrrolidines and bicyclic pyrrolidine derivatives can effectively be synthesized from γ-iodoolefins using commercially available chloramine-T (CT) as a nitrogen source. The cyclization proceeds with high stereoselectivity via a cyclic iodonium intermediate.

Saturated nitrogen-containing heterocycles, including pyrrolidines, piperidines, and related compounds, are often present as substructures of natural products and frequently show potent and diverse biological activities.[1] Thus, their syntheses have attracted considerable attention over the years.[2] Chloramine-T (CT) is a well-known commercially available oxidizing reagent and also serves as a source of chloronium cation and/or nitrogen anion.[3] The most impressive synthetic methodology using CT as a nitrogen source to date has been reported by Sharpless and co-workers. Their procedure involves the catalytic aminohydroxylation of olefins with CT, and the method has been elegantly extended to an asymmetric version.[4] Recently, we and other groups have reported that CT is a good source of nitrogen for use in the catalytic aziridination of olefins.[5] With the intention of developing the utility of CT as an N1 unit, the potent reagent was applied to the synthesis of five-membered nitrogen heterocycles. In this paper, we report on a novel and convenient synthesis of pyrrolidine derivatives from γ-iodoolefins using CT as a nitrogen source, in which an iodo substituent of the substrates plays a key role in successfully achieving the cyclization and a high degree of stereoselectivity.

In a preliminary experiment, the iodo group of 1-iodooctane was smoothly substituted by CT in MeCN at room temperature to give octylsulfonamide, with no need for treatment with a reagent such as Na_2SO_3 to reduce the initial substitution product ($TsSO_2NClR$). Considering our previous

(1) See, for example: O'Hagen, D. *Nat. Prod. Rep.* **2000**, *17*, 435−446.

(2) For recent reviews, see: (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Bird, C. W., Ed.; Pergamon: Oxford, 1996; Vol. 2, pp 119−206. (b) Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3493−3513. (c) Nadin, A.; Mitchinson, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2553−2581. (d) Nadin, A.; Mitchinson, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862−2892. (e) Gribble, G. W.; Gilchrist, T. L. *Progress in Heterocyclic Chemistry*; Pergamon: Oxford, 2001; Vol. 13.

(3) (a) Campbell, M. M.; Johnson, G. *Chem. Rev.* **1976**, *78*, 65−79. (b) Bremner, D. H. In *Synthetic Reagents*; Pizey, J. S., Ed.; Wiley: New York, 1985; Vol. 6, pp 9−59. (c) Agarwal, M. C.; Upadhyay, S. K. *J. Sci. Ind. Res.* **1990**, *49*, 13−32.

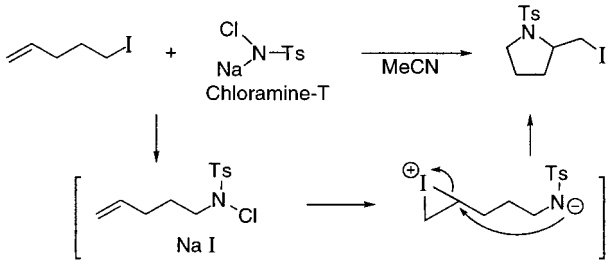
(4) (a) Sharpless, K. B.; Chong, A. O.; Oshima, K. *J. Org. Chem.* **1976**, *41*, 177−179. (b) Herranz, E.; Sharpless, K. B. *J. Org. Chem.* **1978**, *43*, 2544−2548. (c) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451−454. (d) Rubin, A. E.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2637−2640.

(5) (a) Ando, T.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 309−312. (b) Ando, T.; Kano, D.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* **1998**, *54*, 13485−13494. (c) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844−6845. (d) Albone, D. P.; Aujla, P. S.; Taylor, P. C.; Challenger, S.; Derrick, A. M. *J. Org. Chem.* **1998**, *63*, 9569−9571. (e) Ali, S. L.; Nikalje, M. D.; Sudalai, A. *Org. Lett.* **1999**, *1*, 705−707. (f) Simkhovich, L.; Gross, Z. *Tetrahedron Lett.* **2001**, *42*, 8089−8092. (g) Kano, D.; Minakata, S.; Komatsu, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3186−3188.

10.1021/ol026020i CCC: $22.00 © 2002 American Chemical Society
Published on Web 05/14/2002

work,[5b] NaI generated by the substitution might be expected to act as a reducing agent for the N−Cl bond. This result prompted us to propose the following unique reaction (Scheme 1). Namely, if γ-iodoolefin, in place of iodoalkane,

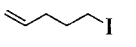
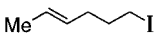
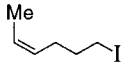
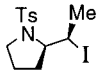
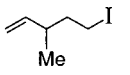
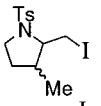
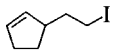
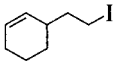
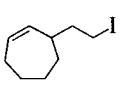
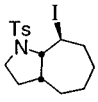
Scheme 1. Proposed Pathway Leading to a Pyrrolidine



is employed in the reaction with CT, iodine atom transfer cyclization would occur via a cyclic iodonium intermediate to afford an iodomethylated pyrrolidine derivative.

In fact, when 5-iodo-1-pentene (**1a**) was treated with 2 equiv of CT in MeCN at room temperature for 48 h, the predicted iodomethylated pyrrolidine derivative **2a** was obtained in 91% yield (Table 1). This simple method could

Table 1. Synthesis of Various Pyrrolidines from γ-Iodoolefins and CT[a]

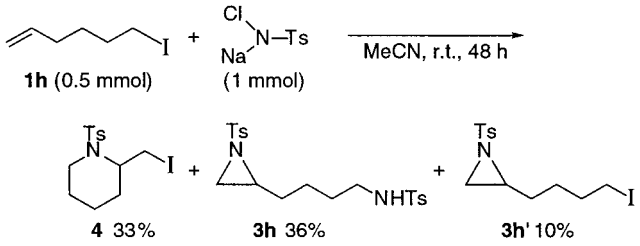
γ-iodoolefin		product		yield (%)
	**1a**		**2a**	91
	**1b**		**2b**	75
	**1c**		**2c**	81
	**1d**		**2d**	77[b]
	**1e**		**2e**	50[c]
	**1f**		**2f**	83[c]
	**1g**		**2g**	64[c]

[a] Reaction conditions: iodoolefin (0.5 mmol), CT (1 mmol), MeCN (3 mL), rt, 48 h. [b] *cis*:*trans* = 69:31. [c] Anhydrous CT and 12 mL of MeCN were used.

be applied to the synthesis of a variety of pyrrolidines from γ-iodoolefins. Both *trans*- and *cis*-6-iodo-2-hexene were effectively converted to the corresponding pyrrolidines in good yields. It is noteworthy that a high degree of stereospecificity was observed in the reactions of geometric isomers of 6-iodo-2-hexene. Bicyclic pyrrolidines were stereoselectively obtained from cyclic olefins of several ring sizes having an iodo substituent at the γ-position in good yields. The stereochemistry of products **2e**−**g** was determined by NOE measurement, and that of **2g** was confirmed by X-ray crystallographic analysis. These highly stereospecific and stereoselective cyclizations are consistent with a reaction pathway involving an ionic intermediate (a cyclic iodonium cation).

As shown in Scheme 2, the present reaction was applicable

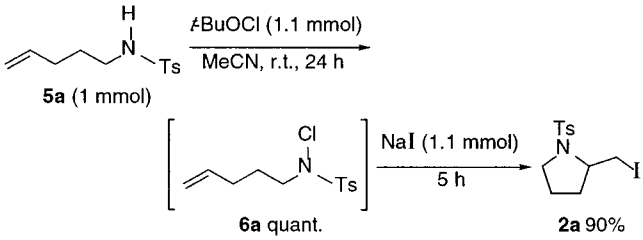
Scheme 2. Piperidine Synthesis from δ-Iodoolefin and CT



to the synthesis of a piperidine from δ-iodoolefin **1h** with CT. The desired piperidine derivative **4** was obtained in 33% yield along with aziridine derivatives **3h** and **3h′**. The latter products, aziridines, presented us with important information in terms of understanding the reaction pathway (vide infra).

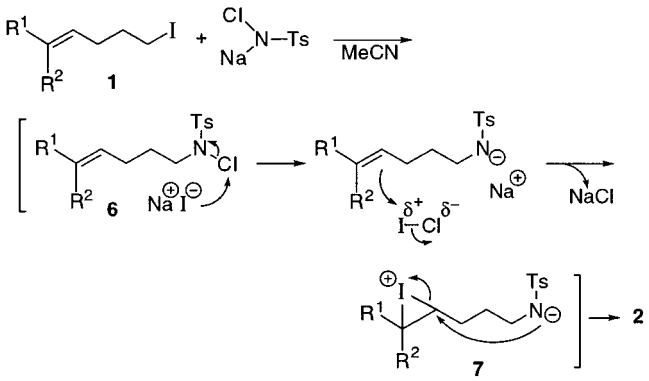
To clarify the most likely pathway for the reaction, the following experiment was carried out. The predicted intermediate **6** was prepared in situ by the chlorination of an authentic sample **5a** with *t*-BuOCl.[6] The reaction was followed by measurement of ^{1}H NMR in CD_3CN, and the yield of **6a** was determined. The subsequent addition of NaI to the reaction mixture afforded pyrrolidine **2a** in 90% yield from **5a** (Scheme 3).

Scheme 3. Experiment To Clarify the Intermediacy of *N*-Chloro Derivative **6a** in the Route to Pyrrolidine **2a**



This result supports the view that the formation of pyrrolidines proceeds via the following pathway (Scheme 4). The iodo group of **1** is substituted by CT to give the *N*-chlorinated alkenylsulfonamide **6**. The liberated I^- reacts with the Cl group of **6**, permitting the interconversion of I^-

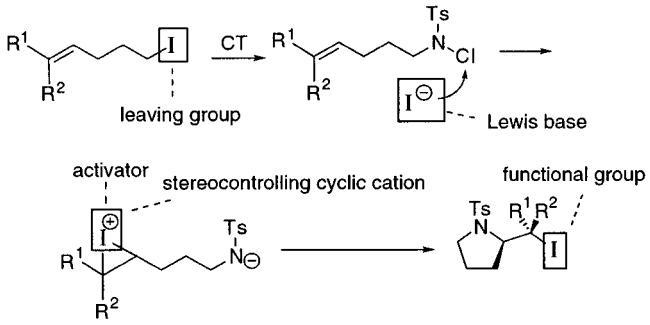
Scheme 4. Plausible Reaction Pathway Leading to Pyrrolidines



to I^+, thus generating cyclic iodonium cation **7**. The intramolecular cyclization of **7** proceeds smoothly to afford **2**. The formation of **7** is supported by the stereospecific and diastereoselective cyclizations shown in Table 1. The results described in Scheme 2 also support the proposed pathway, namely, the reaction of the iodonium intermediate derived from **1h** with remaining CT might give aziridine **3h**,[5b] because of the slower rate of the 6-*exo* cyclization compared to that of the 5-*exo* one. Despite the absence of an I_2 catalyst, aziridines **3h** and **3h′** were obtained by the reaction of **1h** with CT, suggesting the generation of ICl[7,8] in situ by the reaction of **6** with NaI.

In conclusion, this report is the first description of the synthesis of pyrrolidine derivatives from γ-iodoolefin using CT. The iodo group of the substrate has multiple roles as (1) a leaving group for substitution with CT, (2) a Lewis base for the abstraction of the Cl atom, (3) an activator of the olefin moiety, (4) a stereocontrolling cyclic cation, and (5) a functional group on the product.

Scheme 5. Multiple Functions of the Iodo Group



Because the present cyclization is a unique example of an ionic iodine atom transfer reaction,[9] the application of the system to the synthesis of other functional nitrogen-containing heterocycles is now in progress.

Acknowledgment. This work was supported, in part, by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan. K.D. acknowledges the Sasakawa Scientific Research Grant from The Japan Science Society. S.M. thanks Shorai Foundation for Science and Technology and The Naito Foundation. We also wish to acknowledge the Instrumental Analysis Center, Faculty of Engineering, Osaka University.

Supporting Information Available: Experimental procedures and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

OL026020I

(6) (a) Zimmer, H.; Audrieth, L. F. *J. Am. Chem. Soc.* **1954**, *76*, 3856−3857. (b) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2810−2813. (c) Li, G.; Angert, H. H.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2813−2817. (d) Goossen, L. J.; Liu, H.; Dress, K. R.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1080−1083.

(7) In the presence of a catalytic amount of ICl, aziridinations smoothly proceed by the reaction of olefins with CT; see ref 5b.

(8) ICl would also generate in situ by the reaction of remaining CT with NaI. See, for example: Kabalka, G. W.; Gooch, E. E. *J. Org. Chem.* **1981**, *46*, 2582−2584.

(9) Recently, the synthetic route to pyrrolidines via radical [3 + 2] annulation reaction of *N*-allyl-*N*-chlorotosylamides with alkenes was reported by Oshima: Tsuritani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2001**, *3*, 2709−2711.