

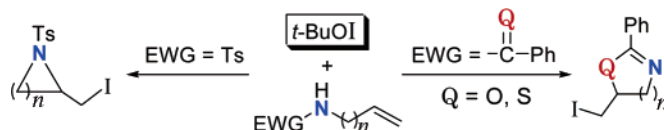
# Practical and Convenient Synthesis of *N*-Heterocycles: Stereoselective Cyclization of *N*-Alkenylamides with *t*-BuOI under Neutral Conditions

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## ABSTRACT



*tert*-Butyl hypoiodite (*t*-BuOI) was found to be a powerful reagent for the cyclization of *N*-alkenylamides leading to a variety of *N*-heterocycles under extremely mild conditions. When *N*-alkenylsulfonamides were employed in the reaction, three- to six-membered saturated *N*-heterocycles were obtained in good to excellent yields with complete stereoselectivity. The method was applicable to the cyclization of alkenylbenzamide derivatives to afford *N*-, *O*- or *N*-, *S*-heterocycles.

Nitrogen-containing heterocycles, including aziridines, azetidines, pyrrolidines, piperidines, and related compounds, are frequently present as substructures in natural products and show potent biological activities.<sup>1</sup> For these reasons, the development of practical and convenient methods for the construction of these heterocycles is highly desirable.<sup>2</sup> Although there are many approaches to the synthesis of heterocycles based on a cyclization mode, for example, hydroamination catalyzed by transition metals<sup>3</sup> or acids<sup>4</sup> and radical cyclization,<sup>5</sup> these procedures have certain disadvantages that

include the need for heavy metals and/or heating conditions and difficulty in controlling the stereochemistry of the products.

We recently reported on the novel ionic iodine atom transfer cyclization by the reaction of 4-pentenyl iodides with Chloramine-T, leading to the formation of iodomethylated pyrrolidines with complete stereoselectivity.<sup>6</sup> In the course of the studies on clarification of the reaction pathway, *N*-chloro-*N*-alkenylsulfonamides were found to be precursors of the desired products, and the subsequent treatment with NaI enabled the cyclization (Scheme 1).

This finding stimulated us to investigate an alternative cyclization of *N*-alkenylamides by exploiting *tert*-butyl hypoiodite. While this reagent, which is generated by reacting *t*-BuOCl with metal iodide salts or iodine,<sup>7</sup> would be

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(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) See, for example: (a) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690–7691. (b) Manzoni, M. R.; Zabawa, T. P.; Kasi, D.; Chemler, S. R. *Organometallics* **2004**, *23*, 5618–5621. (c) Pohlki, A.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104–114. (d) Nobis, M.; Driessen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983–3986. (e) Brunet, J. J.; Neibecker, D. In *Catalytic Heterofunctionalization*; Togni, A.; Grützmacher, H., Eds.; Wiley-VCH: Weinheim, Germany, 2001; pp 91–141. (f) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675–703.

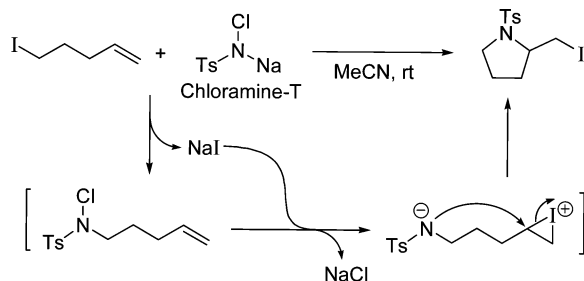
(4) See, for example: (a) Schlummer, B.; Matwig, J. F. *Org. Lett.* **2002**, *4*, 1471–1474. (b) Kumadaki, I.; Jonoshita, S.; Sato, K.; Omote, M.; Ando, A. *Heterocycles* **2001**, *54*, 589–592.

(5) For recent reviews and examples of the cyclization of *N*-centered radicals, see: (a) Esker, J. L.; Newcomb, M. *Adv. Heterocycl. Chem.* **1993**, *58*, 1–45. (b) Zard, S. Z. *Synlett* **1996**, 1148–1154. (c) Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543–17594. (d) Uchiyama, K.; Hayashi, Y.; Narasaka, K. *Tetrahedron* **1999**, *55*, 8915–8930. (e) Senboku, H.; Kajizuka, Y.; Hasegawa, H.; Fujita, H.; Sugimoto, H.; Orito, K.; Tokuda, M. *Tetrahedron* **1999**, *55*, 6465–6474. (f) Liu, J. F.; Heathcock, C. H. *J. Org. Chem.* **1999**, *64*, 8263–8266. (g) Cossy, J.; Tresnard, L.; Gomez, P. D. *Eur. J. Org. Chem.* **1999**, 1925–1933.

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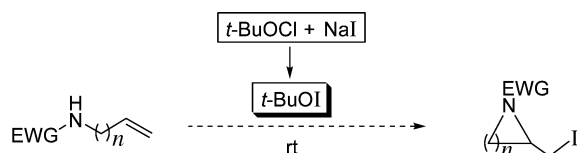
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**Scheme 1.** A Representative Example of Previous Studies on the Synthesis of a Pyrrolidine



expected to be a powerful iodinating agent, there are only a few examples where it is used in organic reactions.<sup>8</sup> Among these, the addition reaction of *t*-BuOI to styrene is known, but the use of UV light or Lewis acid is required for the reaction to proceed.<sup>9</sup> If *t*-BuOI were to be utilized in the reaction with an alkenylamide, the reagent would first induce the iodination of the amide nitrogen and not the addition to the olefin moiety. The resulting *N*-iodinated alkenylamide would cyclize via iodine atom transfer from the amido nitrogen to the olefin, whose phenomenon might be explained by the stability of an iodonium ion. Namely, we anticipated that the reaction of *N*-alkenylamides with *t*-BuOI would directly afford the desired cyclic products under neutral conditions (Scheme 2). Although a similar transformation

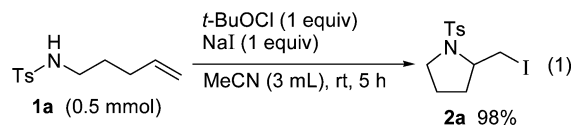
**Scheme 2.** Proposed Cyclization of *N*-Alkenylamides with *t*-BuOI



for construction of aziridines has been studied by Taguchi's group, the method suffers from drawbacks of the requirement for a strong base and difficulty in the complete control of the stereochemistry.<sup>10</sup> In this paper, we report on a practical and convenient synthesis of three- to six-membered *N*-heterocycles from *N*-alkenylamides utilizing *t*-BuOI, in which the cyclization proceeds with complete stereoselectivity under extremely mild conditions.

As mentioned in a previous report,<sup>6</sup> the reaction of *N*-(4-pentenyl)-*p*-toluenesulfonamide (**1a**) with *t*-BuOCl in acetonitrile at room temperature for 24 h gave only an *N*-chlorinated compound in quantitative yield. The simultaneous

addition of *t*-BuOCl and NaI to an acetonitrile solution of the alkenylamide led to the direct cyclization to afford an iodomethylated *N*-tosylpyrrolidine **2a** in 98% yield within only 5 h (eq 1).



To verify the superiority of the system, iodine or IPy<sub>2</sub>-BF<sub>4</sub>, which would be potential reagents, was evaluated for the cyclization of **1a**. Although the reaction proceeded under the same conditions, the efficiencies were rather low to afford **2a** in 61% (by I<sub>2</sub>) and 77% (by IPy<sub>2</sub>BF<sub>4</sub>), respectively. Since the *t*-BuOCl/NaI system was found to be a powerful tool for the construction of an *N*-heterocycle, a variety of alkenylsulfonamides were employed in the cyclization to establish the generality of the reaction (Table 1). Both *trans*-

**Table 1.** Cyclization of a Variety of Alkenylsulfonamides Using the *t*-BuOCl/NaI System<sup>a</sup>

entry	substrate	product	yield (%)
1			93
2			100
3			96
4			94
5			97
6 <sup>b</sup>			97
7 <sup>c</sup>			27
8 <sup>d</sup>			79

<sup>a</sup> Reaction conditions: alkenylsulfonamide (0.17 mol/L), *t*-BuOCl, NaI (1 equiv), MeCN, rt, 5 h. <sup>b</sup> *t*-BuOCl, NaI (1.2 equiv), 24 h. <sup>c</sup> *t*-BuOCl, NaI (1.3 equiv), 24 h. <sup>d</sup> Alkenylsulfonamide (0.09 mol/L), *t*-BuOCl, NaI (1.2 equiv), 24 h.

and *cis*-*N*-(4-hexenyl)-*p*-toluenesulfonamides (**1b** and **1c**) were efficiently converted to the corresponding pyrrolidines

(8) (a) Barton, D. H. R.; Beckwith, A. L. J.; Goosen, A. *J. Chem. Soc.* **1965**, 181–190. (b) Tanner, D. D.; Gidley, G. C. *J. Am. Chem. Soc.* **1968**, 90, 808–809. (c) Kametani, T.; Watt, D. S.; Ji, T.; Fitz, T. *J. Org. Chem.* **1985**, 50, 5384–5387. (d) Montro, R.; Wirth, T. *Org. Lett.* **2003**, 5, 4729–4731.

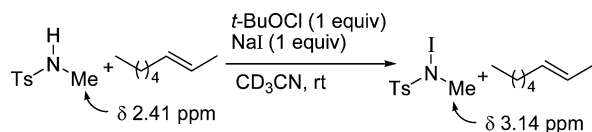
(9) Heasley, V. L.; Berry, B. R.; Holmes, S. L.; Holstein, L. S., III; Milhoan, K. A.; Sauerbrey, A. M.; Teegarden, B. R.; Shellhamer, D. F. *J. Org. Chem.* **1988**, 53, 198–201.

(10) Kitagawa, O.; Taguchi, T. *Synlett* **1999**, 8, 1191–1199.

**2b** and **2c** in excellent yields (entries 1 and 2). It is noteworthy that complete stereoselectivity as well as stereospecificity was observed in the reaction when geometric isomers were used. The *cis*-fused bicyclic pyrrolidines **2d–f** were readily synthesized from alkenylsulfonamides having five- to seven-membered cycloalkenes **1d–f** in extremely high yields with complete stereoselectivity (entries 3–5). The present method was applicable to the efficient synthesis of iodomethylated aziridine **2g** under neutral conditions in contrast to the case with Taguchi's method (entry 6). The formation of azetidines by electrophilic cyclization appears to be a difficult process, and only a limited number of successes have been reported.<sup>11</sup> Essentially all the reactions were achieved by the introduction of some substituents to homoallylamine derivatives (a phenyl group on the carbon of the olefin and/or alkyl groups on the carbon  $\alpha$  to the nitrogen). However, the method enabled an unfunctionalized homoallyl sulfonamide to cyclize to azetidine **2h** (entry 7). A six-membered ring, piperidine **2i**, was also obtained in good yield by this procedure (entry 8).

To clarify which moiety, the sulfonamide nitrogen or the C–C double bond, was first iodinated by *t*-BuOI, the active species, the following experiment was carried out (Scheme 3).<sup>12</sup> When a mixture of *N*-methyl-*p*-toluenesulfonamide

**Scheme 3.** Iodination Reaction: Sulfonamide versus Olefin

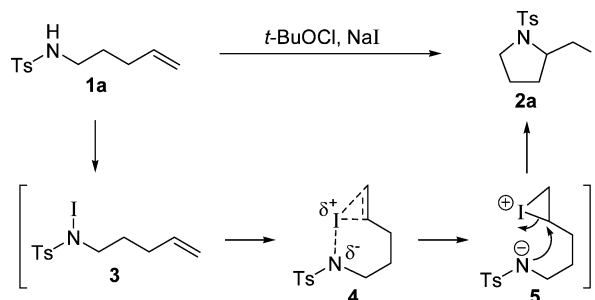


(methyl;  $\delta$  2.41 ppm) and *trans*-2-octene in  $\text{CD}_3\text{CN}$  was treated with *t*-BuOCl and NaI, the  $^1\text{H}$  NMR spectra showed that the *trans*-2-octene signals remained unchanged, but a new methyl singlet at  $\delta$  3.14 ppm appeared. The chemical shift of the singlet was identified by comparison with that of an authentic sample prepared by reacting *N*-methyl-*p*-toluenesulfonamide and *N*-iodosuccinimide in  $\text{CD}_3\text{CN}$ . This result indicates that *t*-BuOI first iodinates the nitrogen of the sulfonamide.

Thus, the most likely pathway for the present cyclization is proposed to be as follows (Scheme 4). *t*-BuOI is generated in situ by the reaction of *t*-BuOCl and NaI.<sup>7</sup> The active species iodinates the sulfonamide nitrogen, followed by intramolecular iodonium ion transfer to the olefin moiety leading to the three-membered iodonium ion **5**, and the cyclization of **5** then proceeds smoothly to afford the product. The formation of the iodonium ion is supported by the stereospecific and diastereoselective cyclizations shown in Table 1.

The present method was successfully applicable to the synthesis of other heterocycles from alkenylbenzamides or alkenylbenzthioamides (Table 2). When *N*-(2-propenyl)-

**Scheme 4.** Plausible Reaction Pathway Leading to a Pyrrolidine



**Table 2.** Cyclization of Alkenylbenzamides Using the *t*-BuOCl/NaI System

n	Q	<i>t</i> -BuOCl (equiv)	NaI (equiv)	time (h)	yield (%)
1	O ( <b>6a</b> )	1.1	1.1	5	95 ( <b>7a</b> )
2	O ( <b>6b</b> )	1.1	1.1	24	82 ( <b>7b</b> )
1	S ( <b>6c</b> )	1	1	5	77 ( <b>7c</b> )
2	S ( <b>6d</b> )	1.1	1.1	24	47 ( <b>7d</b> )

benzamide (**6a**) was treated with *t*-BuOCl and NaI in acetonitrile at room temperature, cyclization proceeded smoothly to afford an iodomethylated oxazoline **7a** in 95% yield, in which no detectable *N*-benzoylaziridine was produced. A six-membered ring, an oxazine derivative **7b**, was readily obtained from a benzamide having a homoallyl group **6b** using the procedure. Thioamide derivatives were also converted to the corresponding *N*-, *S*-heterocycles.

In summary, an efficient, simple, and practical method for the synthesis of a variety of *N*-heterocycles from *N*-alkenylamides by utilizing *t*-BuOI under neutral and very mild conditions has been developed. Since the cyclization pathway involved a cyclic iodonium ion, the stereochemistry could be controlled completely. The application of the potential reagent, *t*-BuOI, to other organic reactions is currently in progress.

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**Supporting Information Available:** Experimental details and spectral data for the major products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(12) See Supporting Information.