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NaH-mediated Iodoaziridination Reaction of *N*-Allylic Tosylamides

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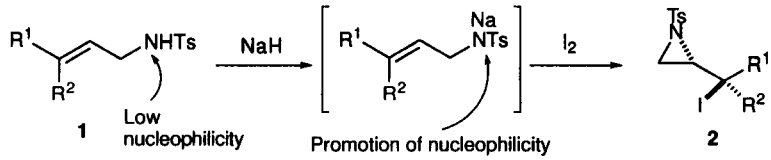
Abstract: In the presence of NaH and I_2, iodocyclization reaction of *N*-allylic tosylamide derivatives proceeds in a highly stereospecific *trans*-addition manner to give good yields of iodoaziridines. © 1997 Elsevier Science Ltd.

In contrast to the preparation of four, five or six-membered heterocyclic compounds through halocyclization reactions, three-membered heterocyclic forming reactions have been so far uncommon.[1] As far as we know, although a few examples of haloepoxidation reactions with allyl alcohol derivatives have been reported, the chemical yields are generally not satisfactory or are not described in the literature.[2,3] In addition, there has been no report on a haloaziridine forming reaction which involves the attack of a nitrogen atom as an intramolecular nucleophile.

In the course of our work on a basic metallic reagent-mediated iodocyclization,[4,5] we recently found that the iodocarbocyclization reaction of allylmalonate derivatives proceeds in the presence of I_2, $Ti(OR)_4$ and CuO or pyridine to give iodomethylcyclopropane derivatives in good yields.[6,7] In this reaction, $Ti(OR)_4$ acts as a basic reagent to promote the nucleophilicity of the malonate moiety through the formation of a titanium enolate, while CuO or pyridine may play a role as a HI scavenger to prevent the decomposition of unstable iodomethylcyclopropanes by HI. These results may indicate that the formation of three-membered ring compounds through halocyclization would be possible by the activation of the nucleophilic center and the prevention of the decomposition of unstable products. On the basis of this consideration, we attempted to prepare three-membered heterocyclic compounds by a basic metallic reagent-mediated halocyclization.

In this paper, we report the result of iodoaziridination reaction of *N*-allylic tosylamide derivatives which proceeds in a highly stereospecific manner through the activation of an amide nucleophile by NaH. The present reaction is the first example of a haloaziridination reaction and should provide a stereoselective synthesis of iodoaziridines with two consecutive chiral centers from simple *N*-allylic amides.[8]

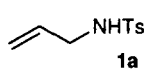
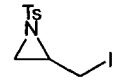
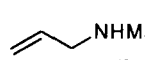
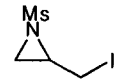
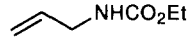
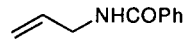
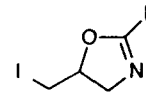


The reaction of *N*-allylic tosylamide **1a** with I_2, NIS, or NBS gave an addition product of I_2 to olefin or resulted in the recovery of **1a** without the formation of haloaziridine because of the low nucleophilicity of tosylamide.[9] After a survey of various basic metallic reagents for the activation of the tosylamide nucleophile, we found that the use of NaH is most effective; that is, the reaction using NaH (1 equiv.) and I_2

(3 equiv.) in Et_2O gave iodoaziridine **2a** in a good yield (Table 1, Entry 1, 81 %).[10, 11] The effect of NaH should be noteworthy, as when other metallic reagents such as *n*-BuLi, LiAl(O*t*-Bu)$_4$ or Ti(O*i*-Pr)$_4$ were used as a base, no iodoaziridine **2a** could be obtained. NaH may act as not only an activating reagent for the enhancement of the nucleophilicity of tosylamide but also a neutralizing reagent for the trapping of HI. Et_2O is the most effective solvent, while the use of toluene, THF or CH_3CN also leads to an addition product of I_2 to olefin to give lower yields of **2a**.

Although the reaction of mesylamide **1b** also proceeded under the same conditions, in comparison with that of **1a**, decrease in the chemical yield of **2b** was observed (Entry 2, 53 %). In contrast to sulfonyl amides **1a** and **1b**, in the reactions of carbamate **1c** and benzamide **1d**, the formation of aziridine was not observed. With **1c**, starting material **1c** was quantitatively recovered (Entry 3), while the reaction of **1d** gave a five-membered ring compound **3d** as a major product through the attack of amide carbonyl oxygen (Entry 4).

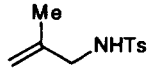
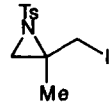
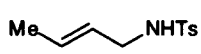
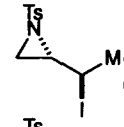
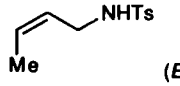
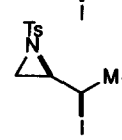
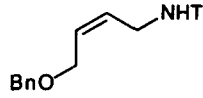
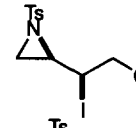
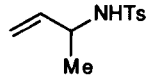
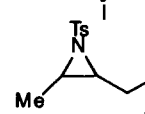
Table 1. Iodocyclization of various *N*-allylic amides[a]

Entry	Amide 1	Time (h)	Product 2 or 3	Yield (%)[b]
1	 **1a**	4	 **2a**	81
2	 **1b**	4	 **2b**	53
3	 **1c**	14	—	0
4	 **1d**	14	 **3d**	34

[a] Iodoaziridination: **1** (1 mmol), NaH (1 mmol), I_2 (3 mmol), Et_2O (5 ml), rt.
[b] Isolated yield.

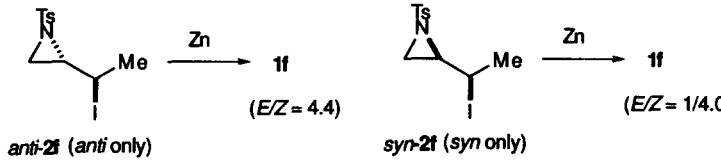
The iodoaziridination reactions of various *N*-allylic tosylamides **1e-1h** were further investigated under the conditions mentioned above (Table 2).[10] Similar to allyl derivative **1a**, the reaction of methallyl derivative **1e** also proceeded in good yield to give iodoaziridine **2e** (Entry 1). In the reactions of crotyl derivatives *E*-**1f** (*E*/*Z*=4) and *Z*-**1f** (*E*/*Z*=1/4.5), diastereomer mixtures of aziridine **2f** were obtained in ratios of *syn*/*anti*=1/3.9 and *syn*/*anti*=4.6, respectively (Entries 2, 3). The relative configurations of *syn*- and *anti*-**2f**, which can be easily separated by column chromatography, were determined by converting to crotyl derivative **1f** from *syn*- and *anti*-**2f** by *trans*-elimination, respectively (Scheme 1).[12] These results indicate that the present reaction proceeds through a stereospecific *trans*-addition of the amide nucleophile and iodine to the olefin (Scheme 2, path a) but not through an addition of iodine to the olefin and the subsequent substitution reaction of the iodide by the amide nucleophile (path b).[8a] In addition to the results of Entries 2 and 3, the reaction of stereochemically pure *Z*-olefin **1g** with an oxygen function was found to give *syn*-**2g** as a single stereoisomer (Entry 4); thus, the iodoaziridination clearly proceeds in almost complete stereospecificity. For the investigation of the diastereoselectivity in the reaction, the iodoaziridination of chiral *N*-allylic tosylamide **1h** was further examined. Although the reaction proceeded in good yield (92 %), selectivity was hardly observed, giving a diastereomer mixture of **2h** in a ratio of *cis*/*trans*=1/1.5 (Entry 5).

Table 2. Iodoaziridination of various *N*-allylic tosylamides[a]

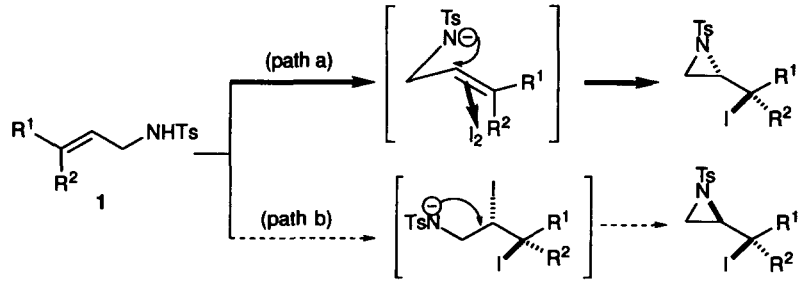
Entry	Amide 1	Product 2	Yield (%)[b]
1	 **1e**	 **2e**	68
2[c]	 *E*-**1f** (E/Z = 4)[d]	 *anti*-**2f** (*syn*/*anti* = 1/3.9)[d]	68
3[c]	 *Z*-**1f** (E/Z = 1/4.5)[d]	 *syn*-**2f** (*syn*/*anti* = 4.6)[d]	64
4	 **1g** (*Z* only)	 **2g** (*syn* only)	69
5	 **1h**	 **2h** (*cis*/*trans* = 1/1.5)[d]	92

[a] Iodoaziridination: **1** (1 mmol), NaH (1 mmol), I_2 (3 mmol), Et_2O (5 ml), rt.
[b] Isolated yield. [c] The chemical structures of major isomers were drawn.
[d] The ratios were determined by 300 MHz ^{1}H-NMR.

Scheme 1



Scheme 2



All reactions shown in Table 2 were carried out within 15 min at rt, while prolonged reaction time led to considerable decrease in the chemical yield.

In conclusion, we have succeeded in the development of the iodoaziridination reaction of *N*-allyltosylamide derivative which proceeds in a highly stereospecific *trans*-addition manner through the activation of the tosylamide nucleophile by NaH.

References and Notes

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10. Typical procedure of iodoaziridination: To tosylamide **1a** (212 mg, 1 mmol) in Et_2O (5 ml) was added NaH (24 mg, 1 mmol) under argon atmosphere at rt. After the mixture was stirred for 20 min, I_2 (762 mg, 3 mmol) was added, and then the reaction mixture was stirred for 4 hr at rt. The mixture was poured into aqueous $Na_2S_2O_3$ solution and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane / AcOEt = 9) gave **2a** (272 mg, 81 %). **2a**: white crystals; mp 35.5 °C; ^{1}H-NMR ($CDCl_3$) δ 2.17 (1H, d, *J* = 3.7 Hz), 2.45 (3H, s), 2.83 (1H, d, *J* = 6.6 Hz), 2.99-3.14 (3H, m), 7.36 (2H, d, *J* = 8.4 Hz), 7.84 (2H, d, *J* = 8.4 Hz); ^{13}C-NMR ($CDCl_3$) δ 2.3, 21.6, 36.1, 41.0, 128.2, 129.7, 134.4, 144.8.
11. Haloaziridine product could not be obtained by the combination of NaH and NBS or NIS.
12. The incomplete stereospecificity observed in the *trans*-elimination of stereochemically pure *syn*- or *anti*-**2f** by Zn may be due to the contribution of radical cleavage mechanism in some extent. Kimpe, N. D.; Jolie, R.; Smaele, D. D. *J. Chem. Soc., Chem. Commun.* **1994**, 1221-1222.

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