A Convenient Method for the Synthesis of 2-Arylaziridines from Styrene Derivatives via 2-Arylethenyl(diphenyl)sulfonium Salts

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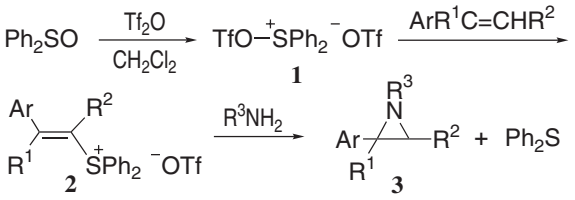
Styrene derivatives reacted with diphenyl(trifluoromethanesulfonyloxy)sulfonium trifluoromethanesulfonate (**1**) at low temperature to afford 2-arylethenyl(diphenyl)sulfonium triflates (**2**). Treatment of **2** with primary amines gave the corresponding 2-arylaziridines in high yields. One-pot synthesis of various aziridines was also successfully carried out without isolation of the intermediate **2**.

Aziridines are the building units useful to organic synthesis and are employed in various reactions,[1] for example, highly regio- and stereoselective ring opening reactions.[2] On the other hand, aziridines that are found in natural products are well-known to have unique biological activities.[3] Therefore, aziridines have been frequently chosen as target compounds by many synthetic chemists.

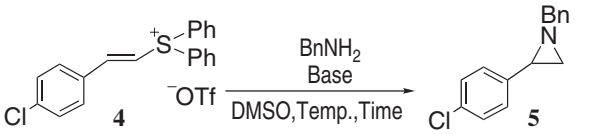
A commonly used method for the synthesis of aziridines from alkenes and primary amines involves the so-called Gabriel–Cromwell reaction of 1-haloethenyl carbonyl compounds[4] or 1-haloethenesulfonic acid derivatives.[5] Johnson et al. reported that (dimethylamino)phenyloxosulfonium salts reacted with primary amines to give aziridines.[6] However, the preparation of the above salts was a tough problem, and only a few examples of aziridination had been reported. In this communication, a convenient synthesis of 2-arylaziridines from styrene derivatives and various primary amines via 2-arylethenyl(diphenyl)sulfonium salts is described. The overall synthetic scheme is illustrated in Scheme 1. The triflate **1**, prepared from diphenyl sulfoxide and triflic anhydride (Tf_2O) at low temperature, reacts with styrenes to form the corresponding 2-arylethenyl(diphenyl)sulfonium triflate **2**,[7] which is in turn treated with primary amines to give aziridines **3** and diphenyl sulfide.



Scheme 1.

In the first place, effects of bases were examined by taking the aziridination of 2-arylethenyl(diphenyl)sulfonium salt **4** with benzylamine in DMSO as a model (Table 1). Aziridination of **4** with 1.1 equiv. of benzylamine resulted in incomplete consumption of **4** in spite of the prolonged reaction time or addition of 1.1 equiv. of Hünig's base (entries 1 and 2). On the other hand, when 2.2 equiv. of benzylamine was used, the aziridination led to completion (entry 3) and the reaction time was shortened by heating the reaction mixture (entry 4) or by adding a base such as Hünig's base (entry 5). More than two equiv. of a primary amine was required to accelerate the reaction. Furthermore, the aziridination reaction was also completed by using a combination of 1.2 equiv. of benzylamine and 3 equiv. of *tert*-butylamine (entry 6). Since *tert*-butylamine was much less reactive than benzylamine, 1-*tert*-butyl-2-(4-chlorophenyl)aziridine was not obtained. The use of *tert*-butylamine as a base simplified the work-up procedures because the excess amount of *tert*-butylamine (bp 46 °C) was removed easily after the completion of aziridination.

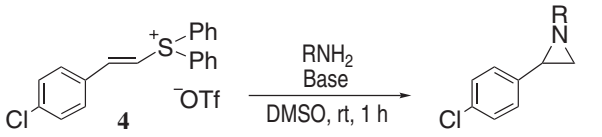
Table 1. Effect of equivalents of benzylamine and bases on the model aziridination of **4**[a]

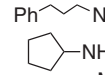


Entry	$BnNH_2$ / equiv.	Base / equiv.	Temp., Time	Yield / %
1	1.1	none	50°C, 6 h	41
2	1.1	*i*-Pr_2NEt / 1.1	50°C, 6 h	65
3	2.2	none	rt, 12 h	98
4	2.2	none	50°C, 3 h	92
5	2.0	*i*-Pr_2NEt / 1.0	rt, 1 h	92
6[b]	1.2	*t*-$BuNH_2$ / 3.0	rt, 1 h	96

[a]Single isomer with *E*-configuration. [b]1-*tert*-Butyl-2-(4-chlorophenyl)aziridine was not obtained.

Table 2. Aziridines from **4**[a] and various amines or benzenesulfonamide



Entry	RNH_2 / equiv.	Base / equiv.	Yield / %[b]
1	 / 1.2	*t*-$BuNH_2$ / 3.0	96
2	 / 1.2	*t*-$BuNH_2$ / 3.0	97
3	/ 1.2	*t*-$BuNH_2$ / 3.0	94
4[c]	 / 4.0	none	98[d]
5[e]	*t*-$BuNH_2$ / 9.0	none	96[f]
6[g]	NH_3	none	82[f]
7[h]	$PhSO_2NH_2$ / 1.2	NaH / 1.2	97

[a]Single isomer with *E*-configuration. [b]Isolated yields unless otherwise noted. [c]The reaction time was 18 h. [d]Combined yield of the chromatographically separable diastereomers (1.2:1). [e]Without the solvent. [f]Determined by ^1H NMR analysis using an internal standard. [g]An excess amount of NH_3 gas was used. [h]THF was used as the solvent, and the reaction time was 12 h.

Next, aziridination of **4** with various primary amines was tried

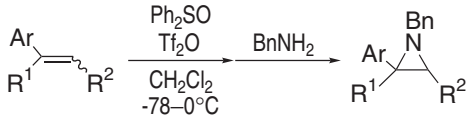
(Table 2, entries 1-5). The reactions proceeded smoothly to produce various *N*-substituted aziridines in high yields. In the case of aziridination with 1-phenylethylamine, a mixture of diastereomeric aziridines was obtained in 98% combined yield without any significant diastereoselectivity (entry 4). The aziridination with *tert*-butylamine proceeded very slowly, and it was carried out without the solvent to afford *N*-*tert*-butylaziridine in 96% yield (entry 5). *N*-nonsubstituted aziridine was synthesized in 82% yield with gaseous ammonia (entry 6). Similar to the primary amines, benzenesulfonamide also reacted with **4** by using sodium hydride as a base to give the corresponding aziridine in 97% yield (entry 7).

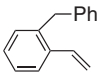
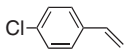
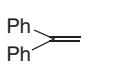
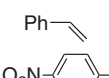
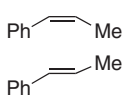
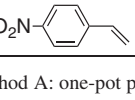
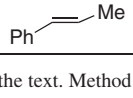
One-pot synthesis of aziridines from the corresponding styrenes and benzylamine without isolating the intermediate, 2-arylethenyl(diphenyl)sulfonium salts, was examined (Table 3). The results of entries 1 and 5 indicated that the one-pot procedure (Method A) was more effective than the stepwise one (Method B) and that it was useful especially when 2-arylethenyl(diphenyl)sulfonium salts were not stable enough for the isolation. In the case of 1,1-diphenylethylene, the aziridination proceeded very slowly compared to the others, which was probably due to its steric effects (entry 6). Aziridination of *trans*- and *cis*-β-methylstyrene with benzylamine gave the two diastereomeric aziridines in almost the same yields and diastereomeric ratios (1:1) (entries 7 and 8). The result suggested that the stereochemistry of aziridines was not influenced by the configurations of olefins.

A proposed reaction mechanism is shown in Scheme 2: a primary amine reacts initially with the 2-arylethenyl(diphenyl)sulfonium salt to form the intermediate **6**,[8] in which internal proton transfer takes place to give **7**. A subsequent intramolecular nucleophilic substitution of an amino group gives aziridinium triflate **8** and diphenyl sulfide. It was considered that the excess amount of a primary amine captured triflic acid from **8**, and the protonation of R^3NH_2 with **8** was suppressed.[9]

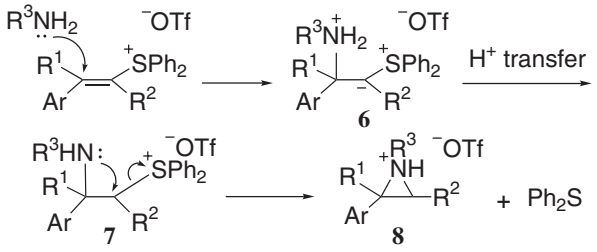
Typical experimental procedure for the one-pot synthesis of aziridines is as follows (Table 3, entry 1, Method A): triflic anhydride (0.082 mL, 0.50 mmol) was added to a solution of diphenyl sulfoxide (101 mg, 0.50 mmol) in dichloromethane (2 mL) under an argon atmosphere at $-78\,^{\circ}C$, and then a solution of 2-benzylstyrene (97 mg, 0.50 mmol) in dichloromethane (1.5 mL)

Table 3. One-pot synthesis of aziridines from styrenes and benzylamine



Entry	Styrene	Method[a]	Y. / %[b]	Entry	Styrene	Method[a]	Y. / %[b]
1		A B	99 73	5		A B	89 78
2[c]		A	71	6		C	66
3		A	94	7		A	39[d]
4		A	95	8		A	39[d]

[a]Method A: one-pot procedure described in the text. Method B: benzylamine (1.2 equiv.) and *tert*-butylamine (3 equiv.) were added to the isolated sulfonium salt in DMSO at rt, and the reaction mixture was stirred at rt for 1 h. Method C: a mixture of benzylamine (9 equiv.) and the isolated sulfonium salt was stirred at rt for 1 day. [b]Isolated yields of aziridines from styrene unless otherwise noted. [c]The reaction time for the second step was 12 h. [d]Combined yield of the chromatographically separable diastereomers (1:1).



Scheme 2.

was added dropwise at $-78\,^{\circ}C$. After the reaction mixture was stirred and warmed up to $0\,^{\circ}C$, a solution of benzylamine (268 mg, 2.50 mmol) in dichloromethane (1.5 mL) was added, and the mixture was stirred at room temperature for additional 2 h. The reaction was quenched with 0.1 M (1 M = mol dm^{-3}) aqueous sodium hydroxide, and the mixture was extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate. After filtration and evaporation, the crude product was purified by preparative TLC to give 1-benzyl-2-(2-benzylphenyl) aziridine (149 mg, 99%).

Thus, an effective and convenient method for the synthesis of aziridines from styrene derivatives and primary amines was established according to the following two-step reaction: preparation of 2-arylethenyl(diphenyl)sulfonium salts from styrenes and subsequent treatment of thus formed salts with primary amines.[10]

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References and Notes

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8 The use of 2-arylethenyl(dimethyl)sulfonium salts instead of 2-arylethenyl(diphenyl)sulfonium salts resulted in *N*-methylation of primary amines to afford 2-arylethenyl methyl sulfides.
9 This consideration is based on the data that pK_a's of conjugate acids of aziridines are usually in the range of 8-9.5, whereas they are ca. 10 for primary amines. See: P. E. Fanta, in "Heterocyclic Compounds with Three- and Four-Membered Rings," ed. by A. Weissberger, John Wiley and Sons, New York (1964), Part 1, p 527.
10 Cyclopropanation was also carried out successfully according to the similar two-step sequence involving preparation of 2-arylethenylsulfonium salts from styrenes, followed by treatment with sodium salts of active methylene compounds. For example, dimethyl[(*E*)-2-phenylethenyl]sulfonium triflate, prepared from styrene, dimethyl sulfoxide, and Tf_2O, was added to a solution of the sodium salt of diethyl malonate (1.2 equiv.) or ethyl cyanoacetate (1.2 equiv.) in THF. The reaction mixture was stirred at rt for 2 h, and diethyl 2-phenyl-1,1-cyclopropanedicarboxylate (77%) or ethyl 1-cyano-2-phenylcyclopropanecarboxylate (76%) was obtained respectively. Similarly, diphenyl[(*E*)-2-phenylethenyl]sulfonium triflate also reacted with the sodium salt of diethyl malonate to give diethyl 2-phenyl-1,1-cyclopropanedicarboxylate (76%, 2 steps from styrene). Preparation of cyclopropanes via sulfonium salts had already been reported, see: a) J. Gosselck, L. Béress, and H. Schenk, *Angew. Chem.*, **78**, 606 (1966). b) J. Gosselck, H. Ahlbrecht, F. Dost, H. Schenk, and G. Schmidt, *Tetrahedron Lett.*, **9**, 995 (1968).