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The Aziridination of *N*-Tosylimines with Amide-Stabilized Sulfonium Ylides: A Simple and Efficient Preparation of Aziridinyl Carboxamides

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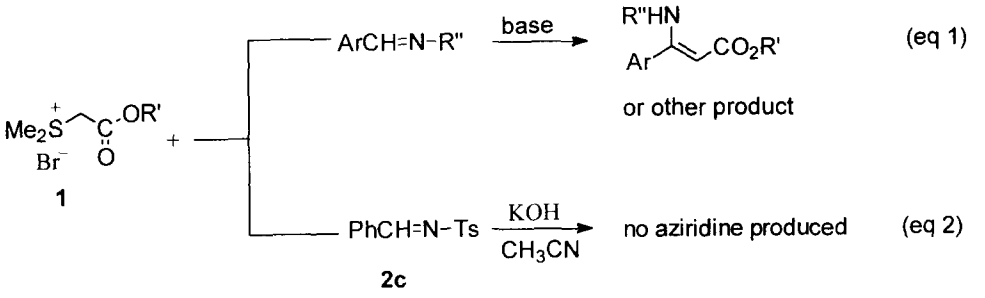
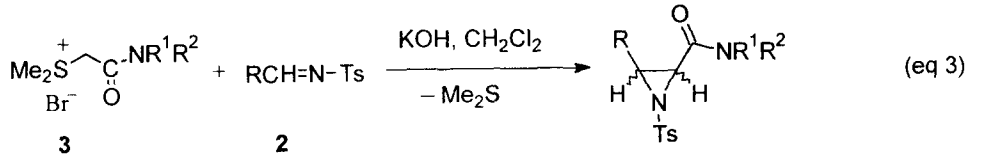
Abstract:: Reaction of *N*-sulfonylimines **2** with *N,N*-dialkylcarbamoylmethyl dimethylsulfonium bromides **3** in the presence of solid KOH gives the aziridinyl carboxamides **4** in good to excellent yields.

With the fair demonstration of the versatility of aziridine carboxylic acid derivatives in the synthesis of amino acids,[1] a variety of synthetic methods for this type of specially important synthetic intermediates have been developed.[1,2] Among them, the direct aziridination of C=C or C=N bonds, includes carbene[3] or nitrene[4] transfer, aza-Darzens reaction,[5] Lewis acid-catalyzed route,[6] etc. Previously, we have succeeded in the preparation of vinylaziridines by the reaction of *N*-tosylimine with allylic sulfonium ylides[7] (semistabilized ylides). However, this reaction failed with a carboxylate-stabilized ylide in preparation of aziridine carboxylate. When an ylide derived from sulfonium salt **1** bearing a carboxylic ester group was reacted with common *N*-alkyl or -arylimines, only enamines (eq 1),[8a,b] cyclopropanes,[8b] or a more complex product[8c] were obtained. Even with the more reactive *N*-tosylimine **2c**, we still failed in obtaining the desired aziridine (eq 2). Fortunately, when we tried to use a carboxamide-bearing ylide derived from sulfonium salt **3** replacing ester sulfonium salt **1** to perform the same reaction, the aziridines **4** were obtained efficiently under very mild conditions (eq 3). Herein, we would like to communicate these results.





3a: R^1, R^2 = Me;
3b: R^1, R^2 = Et;
3c:R^1, R^2 = $(CH_2)_5$.

4 (75-98% yields)

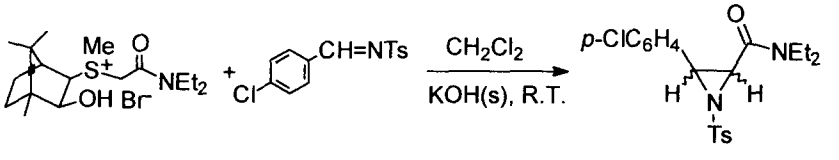
These reactions were carried out simply by mixing three solids of *N*-tosylimines **2**[9] (1.0 equiv.), sulfonium salt **3**[10] (1.2 equiv.), and powdered KOH (1.2 equiv.) in CH_2Cl_2 and by stirring at room temperature for about 1 hour. After the reaction was complete (by TLC), column chromatography gave the pure product. The investigation of the effect of solvent and base on the yields and the *trans/cis* selectivity illustrated that under solid-liquid phase transfer conditions, the variation of these factors could only affect the yield and showed almost no effect on the selectivity. The CH_2Cl_2 / KOH system is the most suitable condition for this reaction. Some results are summarized in Table 1. It is easy to find that the present reaction works well with various *N*-tosylimines,[11] derived from aromatic, heteroaromatic, as well as aliphatic aldehydes. Excellent yields have been achieved in most examples. It should be mentioned that the same ylide (derived from **3**) with the relatively unreactive *N*-alkyl or -arylimines did not produce the desired aziridinyl amide. The aziridinyl carboxamide can also not be prepared by the aza-Darzens reaction using *N*-tosylimines with *N,N*-dimethyl bromoacetic amide under the above-mentioned ylide reaction conditions.

We also used camphor-derived chiral sulfonium salt to proceed this reaction (eq. 4) instead of **3**. The ratio of *trans* / *cis* is 51 / 49, the ee value of the *trans* product is 70.1% by chiral HPLC (determined by chiral HPLC Chiralcel OD), of *cis* is 9.0%.[12]

Table 1. Preparation of aziridine amides 4 by the reaction of *N*-sulfonylimines 2 and sulfonium salts 3 under solid-liquid phase transfer conditions.[a]

Entry	Sulfonium salt	R	Yield,[b] %	*trans* / *cis* [c]
1	**3a**	*p*-MeC_6H_4 (**2a**)	91% (**4aa**)	75 / 25
2	**3a**	*p*-ClC_6H_4 (**2b**)	87% (**4ab**)	21 / 79
3	**3c**	*p*-ClC_6H_4 (**2b**)	96% (**4cb**)	42 / 58
4	**3b**	*p*-ClC_6H_4 (**2b**)	98% (**4bb**)	73 / 27
5	**3a**	C_6H_5 (**2c**)	88% (**4ac**)	72 / 28
6	**3a**	*p*-$CF_3C_6H_4$ (**2d**)	81% (**4ad**)	47 / 53
7	**3a**	3-pyridyl (**2e**)	85% (**4ae**)	59 / 41
8	**3a**	*p*-$O_2NC_6H_4$ (**2f**)	83% (**4af**)	33 / 67
9	**3a**	cyclohexyl (**2g**)	80% (**4ag**)	79 / 21
10	**3a**	*tert*-butyl (**2h**)	75% (**4ah**)	66 / 34

[a] All reactions were carried out under phase transfer conditions at room temperature in a ratio of imines/sulfonium salt/KOH(s) = 1/1.2/1.2 at a 0.5 mmol scale in dichloromethane. [b] Isolated yields based on the imine. [c] Determined by 300 MHz ^{1}H NMR analysis.



(eq. 4)

Yield: 88 %, *trans* / *cis* = 51 / 49
ee: 70.1 % (*trans*), 9.0% (*cis*)

The compatibility of a wide range of substrates, very mild reaction condition and simple manipulations, excellent yields, and the potential use of the products may make the present reaction an efficient entry to a type of very important functionalized aziridines.

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11. Selected characterisation data for compound **4aa**: *trans*: ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3 H), 2.40 (s, 3 H), 3.04 (s, 3 H), 3.24 (s, 3 H), 3.58 (d, J = 4.3 Hz, 1 H), 4.41 (d, J = 4.2 Hz, 1 H), 7.10 (m, 4 H), 7.24 (d, J = 8.2 Hz, 2 H), 7.80 (d, J = 8.2 Hz, 2 H); MS *m/z* 359 (M^++1, 0.64), 203 (100), 158 (18.7), 91 (22.3), 72 (79); Anal. Cacld for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.82. Found: C, 63.44; H, 6.18; N, 7.57. *cis*: δ 2.28 (s, 3 H), 2.41 (s, 3 H), 2.72 (s, 3 H), 2.91 (s, 3 H), 3.76 (d, J = 7.5 Hz, 1 H), 4.09 (d, J = 7.6 Hz, 1 H), 7.10 (m, 4 H), 7.33 (d, J = 8.0 Hz, 2 H), 7.95 (d, J = 8.2 Hz, 2 H).
12. The ratio of *trans / cis* was determined by ^{1}H-NMR and HPLC; the ee values of *trans* and *cis* compounds were determined by HPLC using chiral column (Chiralcel OD), we did not survey the specific rotation data and assign the absolute configuration because the products **4** cannot be separated by flash chromatography.

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