ORGANIC LETTERS

2005
Vol. 7, No. 15
3295−3298

One-Carbon Homologation of *N*-Sulfonylaziridines to Allylic Amines Using Dimethylsulfonium Methylide

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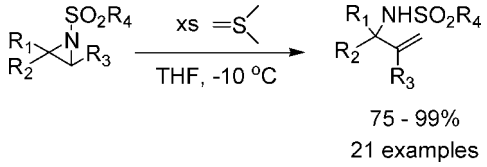
Received May 14, 2005

ABSTRACT

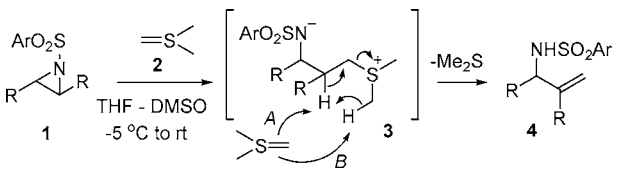


Regio- and stereodefined allylic *N*-sulfonylamines are synthesized in high yields and under experimentally straightforward conditions by reaction of *N*-sulfonylaziridines with excess dimethylsulfonium methylide.

Allylamines (e.g., **4**) are important building blocks in organic chemistry, and therefore methods for their synthesis are of significance.[1] Because of the increasing availability of aziridines (e.g., **1**), typically accessed from alkenes,[2] the eliminative ring-opening of aziridines constitutes an attractive strategy to access allylamines. The latter has been achieved from aziridines by, for example, cobalt(I)-catalyzed[3] or base-induced[4] isomerization or by deoxygenation[5] or deiodination[6] of 2-hydroxymethyl or 2-iodomethyl derivatives, respectively. The alkylative ring-opening of 2-(alkoxymethyl)-aziridines to give 2-substituted 1-amino-2-alkenes has also been recently reported.[7] In seeking a straightforward method to homologate aziridines to allylic amines, we were attracted to a report in 1991 by Nadir and co-workers that focused on the synthesis of azetidines from *N*-arylsulfonylaziridines using dimethyloxosulfonium methylide.[8]

During that study, it was observed that reaction of excess (4 equiv) dimethylsulfonium methylide **2**[9] with *trans*-aziridines **1** (R = Ph; Ar = Ph, *p*-ClC_6H_4) gave allylic amines **4** (Scheme 1); the corresponding *cis*-2,3-diphenyl-substituted and *trans*-2,3-dimethyl-substituted aziridines were found not to be viable substrates, and the process was not examined further. The reaction likely occurs by ring-opening of the

Scheme 1. Homologation of Aziridines to Allylic Amines



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(1) For reviews, see: (a) Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685−700. (b) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708.

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(4) (a) Mordini, A.; Russo, F.; Valacchi, M.; Zani, L.; Degl'Innocenti, A.; Reginato, G. *Tetrahedron* **2002**, *58*, 7153−7163. (b) Müller, P.; Riegert, D.; Bernardinelli, G. *Helv. Chim. Acta* **2004**, *87*, 227−239.

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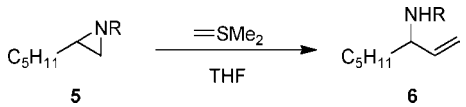
10.1021/ol051124p CCC: $30.25
Published on Web 06/21/2005

aziridine **1** by ylide **2** acting as a nucleophile to give betaine **3**, from which elimination of Me_2S takes place by either (or both) of two pathways (*A* and *B*).[10] In the present paper, we demonstrate that this transformation, in fact, holds considerable promise for the one-carbon homologation of aziridines to allylic amines.

One important requirement for successful homologation of an aziridine by the above process is that the rate of nucleophilic ring-opening of the aziridine is faster than (or competitive with) decomposition[11] of the labile ylide **2**. Therefore, we initially investigated the reaction of dimethylsulfonium methylide **2** with terminal aziridines **5** possessing different protecting groups on nitrogen (Bn, Boc, and Ts, Table 1). An excess (3 equiv) of ylide **2** was generated under standard conditions (Me_3SI, *n*-BuLi, THF, −10 °C),[11] and then the aziridine was added and the reaction allowed to warm slowly to 5 °C over a certain time period. Under these conditions, the benzyl-protected aziridine **5a** proved to be unreactive, while the *N*-Boc-protected aziridine **5b** underwent rapid decomposition, giving no identifiable products (Table 1, entries 1 and 2). The *N*-tosylaziridine **5c** gave, after 3 h, the desired allylic amine **6c** (38% yield; 84% yield based on recovered starting material, entry 3). Extended reaction times did not improve the yield of **6c**, likely due to decomposition of the ylide **2**. However, it was found that maintaining the reaction at −15 °C for 18 h led to an improvement in the yield of **6c** (80%, entry 4), but some starting material was still observed.

Table 1. Addition of Ylide **2** to Various N-Protected Terminal Aziridines **5**[a]



5 **6**

entry	R		=SMe_2 (equiv)	temp (°C)	time (h)		yield (%)[b]
1	Bn	**5a**	5	−10 to 5	3	**6a**	0 (99)
2	Boc	**5b**	3	−10	1	**6b**	0
3	Ts	**5c**	3	−10 to 5	3	**6c**	38 (55)
4	Ts	**5c**	3	−15	18	**6c**	80 (15)
5	Ts	**5c**	5	−10 to 5	3	**6c**	91
6[c]	Ts	**5c**	3	−10 to 5	3	**6c**	31
7[d]	Ts	**5c**	3	−10 to 5	3	**6c**	28
8[c,e]	Ts	**5c**	3	−10 to 5	3	**6c**	0
9[f]	Ts	**5c**	3	20	5	**6c**	40
10	Ns	**5d**	5	−10 to 5	3	**6d**	15
11	Ns	**5d**	3	−15	18	**6d**	45
12	Bus	**5e**	3	−10 to 5	3	**6e**	99
13	Bus	**5e**	2.1	−10 to 5	3	**6e**	63 (35)
14	Bus	**5e**	1.1	−10 to 5	3	**6e**	40 (56)
15	Bus	**5e**	2.1	−15	18	**6e**	78 (20)

[a] Ylide **2** generated from Me_3SI and *n*-BuLi unless indicated otherwise. [b] Recovered **5** (%) in parentheses. [c] Et_2O as solvent. [d] *t*-BuOMe as solvent. [e] BuMgCl used as base. [f] NaH used as base and DMSO as solvent.

Increasing the amount of ylide **2** to 5 equiv and carrying out the reaction from −10 to 5 °C over 3 h improved the yield of **6c** to 91% (entry 5). At this point, we investigated whether alternative ways of generating the ylide **2** (3 equiv, using BuMgCl or NaH as the base), changing the solvent (Et_2O, *t*-BuOMe, or DMSO), or maintaining the reaction at lower temperatures would improve the yield of allylic amine **6c**; however, all these changes were detrimental (entries 6−9). Given the initial success of the *N*-tosylaziridine **5c**, other sulfonyl protecting groups were investigated. *N*-Nosylaziridines are reported to be comparatively more susceptible to ring-opening by nucleophiles.[12] However, in the present chemistry, only 15% yield of the corresponding allylic amine **6d** (entry 10) was obtained using the best reaction conditions we had identified for **5c**. The yield of **6d** could be improved to 45% by maintaining the reaction temperature at −15 °C (entry 11). An *N*-Bus (Bus = *tert*-butylsulfonyl)-protected aziridine **5e**[13] was next examined. Pleasingly, this gave allylic amine **6e** in excellent yield (99%) using 3 equiv of ylide **2** (entry 12). Reducing the quantity of ylide used gave a lower yield of **6e** together with unreacted aziridine **5e** (entries 13 and 14), supporting the idea that the excess of ylide **2** acts as the base [rather than the sulfonamido nitrogen in the putative intermediate betaine (cf. **3**, Scheme 1)] to eliminate Me_2S. Lowering the temperature and increasing the reaction time in an attempt to maintain high yields, while reducing the amount of ylide used, was unsuccessful (entry 15).

The methodology developed above was applied to a range of *N*-Bus-protected aziridines **7** (Table 2).[14]

The aziridine **7a**, which is readily available in enantiopure form from (*R*)-tritylglycidyl ether, gave allylic amine **8a** in 90% yield and >99% ee (entry 1).[15] This example illustrates that the homologation process occurs with no loss of stereochemical integrity. Terminal alkene, (unprotected) terminal alkyne, and primary chloride functionalities were tolerated in the reaction (Table 2, entries 2−4). Interestingly,

(7) (a) Hodgson, D. M.; Stefane, B.; Miles, T. J.; Witherington, J. *Chem. Comm.* **2004**, 2234−2235. (b) Rosser, C. M.; Coote, S. C.; Kirby, J. P.; O'Brien, P.; Caine, D. *Org. Lett.* **2004**, *6*, 4817−4819.

(8) Nadir, U. K.; Sharma, R. L.; Koul, V. K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2015−2019.

(9) For a recent review of dimethylsulfonium methylide **2**, see: Li, J. J. In *Name Reactions in Heterocyclic Chemistry*; Li, J. J., Ed.; John Wiley & Sons: Hoboken, 2005; pp 2−14.

(10) For related studies with epoxides, see: (a) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D.-S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449−5452. (b) Alcaraz, L.; Cridland, A.; Kinchin, E. *Org. Lett.* **2001**, *3*, 4051−4053. (c) Alcaraz, L.; Cox, K.; Cridland, A. P.; Kinchin, E.; Morris, J.; Thompson, S. P. *Org. Lett.* **2005**, *7*, 1399−1401.

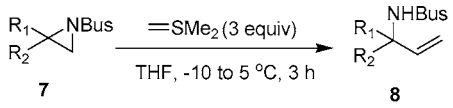
(11) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, 87, 1353−1364.

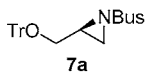
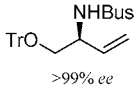
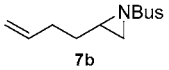
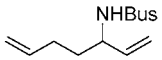
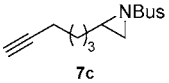
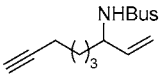
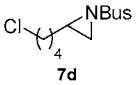
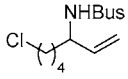
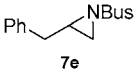
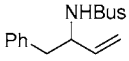
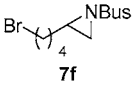
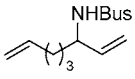
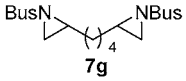
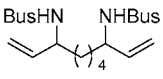
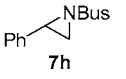
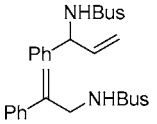
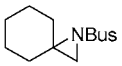
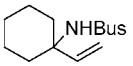
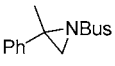
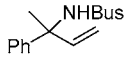
(12) Maligres, P. E.; See, M. M.; Askin, D.; Reider, P. J. *Tetrahedron Lett.* **1997**, *38*, 5253−5256.

(13) (a) Sun, P.; Weinreb, S. M.; Shang, M. *J. Org. Chem.* **1997**, *62*, 8604−8608. (b) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2005**, *7*, 1153−1156.

(14) **Representative Procedure.** *n*-BuLi (1.6 M in hexanes, 0.64 mL, 1.02 mmol) was added dropwise to a stirred suspension of trimethylsulfonium iodide (208 mg, 1.02 mmol) in THF (3 mL) at −10 °C and left stirring for 15 min. Aziridine **5e** (80 mg, 0.34 mmol) in THF (0.5 mL) was added dropwise, and the reaction was allowed to warm to 5 °C over 3 h. After quenching with brine solution, the layers were separated. The aqueous layer was extracted with Et_2O; the combined organic layers were dried ($MgSO_4$), and solvent was evaporated in vacuo. The residue was purified by column chromatography (SiO_2, 30% Et_2O in petroleum ether) to give allylic sulfonamide **6e** (83 mg, 99%) as a colorless oil.

Table 2. Allylic *N*-Bus-Amines **8** from Terminal and 2,2-Disubstituted *N*-Bus-Aziridines **7**



entry	aziridine **7**	allylic *N*-Bus amine **8**		yield (%)
1	 **7a**	 >99% *ee*	**8a**	90
2	 **7b**		**8b**	99
3	 **7c**		**8c**	94
4	 **7d**		**8d**	98
5	 **7e**		**8e**	99
6[a]	 **7f**		**8f**	85
7[b]	 **7g**		**8g**	99
8	 **7h**		**8h**	95[c]
9[a]	 **7i**		**8i**	97
10[a]	 **7j**		**8j**	93

[a] Performed with 5 equiv of =SMe$_2$. [b] Performed with 6 equiv of =SMe$_2$. [c] Ratio 82:18.

primary alkyl bromide-containing aziridine **7f** and bisaziridine **7g** underwent clean double homologations to give dienes **8f**[16] and **8g** (entries 6 and 7). The styrene-derived aziridine **7h** gave a regioisomeric mixture of allylic amines (95% combined yield, 82:18 in favor of initial attack at the terminal position, entry 8). The chemistry was also successfully extended to 2,2-disubstituted aziridines to give the corresponding tertiary allylic amines **8i**,**j** in excellent yields (entries 9 and 10). In these latter cases 5 equiv of ylide **2** was found to be required for the reactions to go to completion.

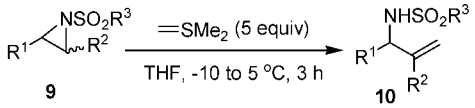
(15) See Supporting Information for details.

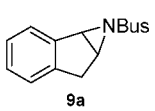
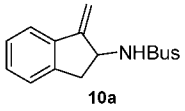
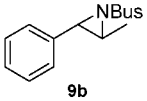
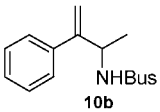
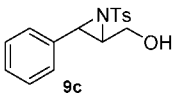
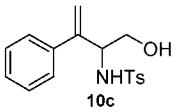
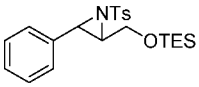
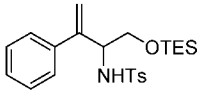
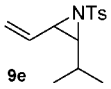
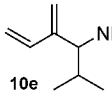
(16) Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D. S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5453−5456. In our system, it was not necessary to add LiI to avoid substantial competing E2 elimination of the bromide.

We next examined whether the chemistry could be broadened to 2,3-disubstituted aziridines other than *trans*-2,3-diphenyl-substituted *N*-arylsulfonylaziridines.[8]

A range of unsymmetrical aziridines **9** possessing unsaturation adjacent to the three-membered ring were found to undergo homologation with complete (Table 3, entries 1, 3−5) or high (entry 2) selectivity for initial reaction at the benzylic (or allylic) positions. The synthesis of diene **10e** (75% yield, entry 5) from vinyl aziridine **9e** illustrates a way to access potentially useful substrates for cycloaddition chemistry.

Table 3. Allylic *N*-Sulfonylamines **10** from Benzylic or Allylic *N*-Sulfonylaziridines **9**

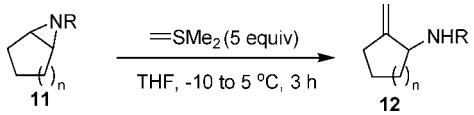


entry	aziridine **9**	allylic *N*-sulfonyl amine **10**	yield (%)
1	 **9a**	 **10a**	95
2[a]	 **9b**	 **10b**	81
3[b]	 **9c**	 **10c**	85
4	 **9d**	 **10d**	79
5	 **9e**	 **10e**	75

[a] Regioisomeric allylic amine also isolated (12%).[15] [b] Performed with 6 equiv of =SMe$_2$.

Both *N*-Bus and *N*-Ts cyclopentyl- and cyclohexyl-fused aziridines gave the corresponding allylic amines in good yields (Table 4).

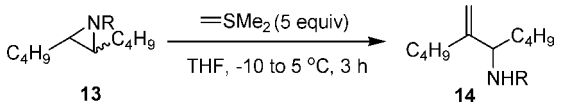
Table 4. Allylic *N*-Sulfonylamines **12** from Cyclopentyl- and Cyclohexyl-Fused *N*-Sulfonylaziridines **11**



entry		R	*n*		yield (%)
1	**11a**	Ts	1	**12a**	82
2	**11b**	Bus	1	**12b**	92
3	**11c**	Ts	2	**12c**	86
4	**11d**	Bus	2	**12d**	94

These latter results demonstrate that unsaturation adjacent to the three-membered ring is not a requirement for effective homologation at substituted positions. However, the chemistry could not be usefully extended to aziridines bearing acyclic alkyl substituents (Table 5). Both cis and trans aziridines **13a** and **13b** gave either poor or no yield of the desired allylic amine with either high or quantitative recovery of starting material. Lowering the reaction temperature and increasing the reaction time did not have a beneficial effect.

Table 5. Attempted Homologation of 2,3-Dialkyl-Substituted *N*-Sulfonylaziridines **13**



13 **14**

entry		R		yield (%)
1	*trans*-**13a**	Ts	**14a**	5
2	*trans*-**13b**	Bus	**14b**	0
3	*cis*-**13a**	Ts	**14a**	31
4	*cis*-**13b**	Bus	**14b**	0

In summary, we have established a process of useful generality for the conversion of *N*-sulfonylaziridines to regiodefined one-carbon-homologated allylic *N*-sulfonylamines. The method uses readily available reagents and occurs under experimentally straightforward conditions. Additional studies in the area of aziridines and sulfonium ylides are currently underway.

Acknowledgment. We thank the EPSRC and GlaxoSmithKline for a CASE award and the EPSRC National Mass Spectrometry Service Centre for mass spectra.

Supporting Information Available: Experimental procedures and characterization data for all new aziridines and allylic amines and ^{1}H and ^{13}C NMR spectra for all allylic amines. This material is available free of charge via the Internet at http://pubs.acs.org.

OL051124P