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CONCOMITANT [2,3]-SIGMATROPIC REARRANGEMENT OF ALLYLIC SULFILIMINES AND INTRAMOLECULAR N-ALKYLATION. SYNTHESIS OF 2-VINYL SUBSTITUTED CYCLIC AMINES

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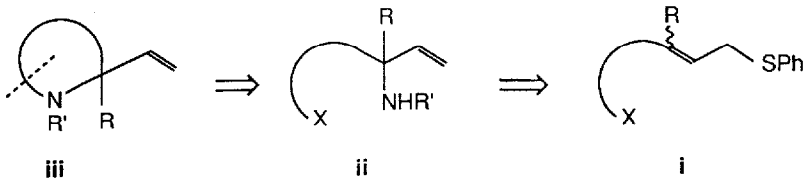
Summary: Allylic phenyl and methyl sulfides bearing a strategically positioned electrophilic center have been shown to undergo concomitant [2,3]-sigmatropic rearrangement and intramolecular N-alkylation upon oxidative conversion to allylic sulfilimines and treatment with aqueous base. This one-pot transformation leads to the title class of compounds in good yield.

The development of synthetic methodology permitting the regio- and stereocontrolled construction of 2-substituted and 2,2-disubstituted cyclic amines remains an active area of research[2] and in this Letter we communicate a novel stratagem for preparing 2-functionalized nitrogen heterocycles. It was conceived that an allylic phenyl sulfide **i** possessing an appropriately appended leaving group X would undergo, upon oxidative amination at sulfur, a [2,3]-sigmatropic rearrangement[3] to give an allylic amine **ii** (Scheme I). Subsequent intramolecular N-alkylation (i.e., cyclization; **ii**→**iii**) would then give rise to a 2-vinyl substituted nitrogen ring system **iii**. To test this hypothesis, the allylic phenyl sulfide **1** was constructed and its one-pot conversion to N-(p-toluenesulfonyl)-2-vinylpyrolidine **2** investigated (Scheme II).

Scheme I

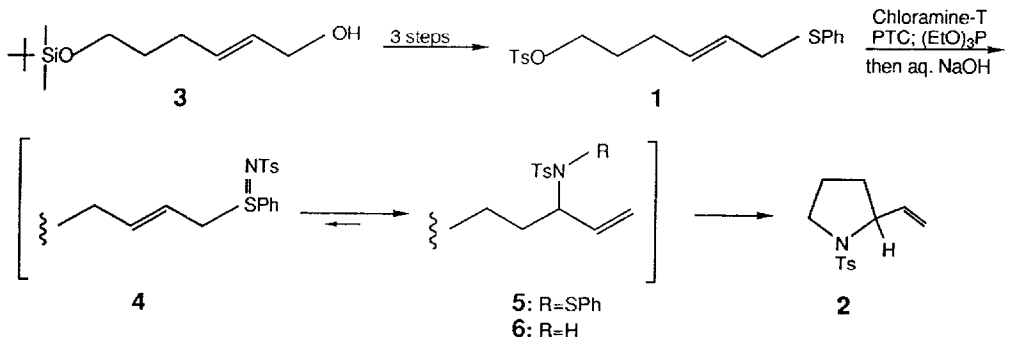


iii **ii** **i**

Sulfide **1** was prepared in three steps from the known allylic alcohol **3**[4a] (Scheme II). Treating **3** with tributylphosphine and N-(phenylthio)succinimide[4b] (1.1 equiv. each) in toluene (1 h, 25 °C) and sequential desilylation and tosylation (standard conditions)

gave **1** in 90% overall yield.[5] Optimal conditions to carry out the key transformation **1→2** were identified after some experimentation. Thus chloramine-T[6a] (1.1 equiv.) was added to a solution of **1** in CH_2Cl_2 (0.2 M) containing hexadecyltributylphosphonium bromide[3f] (0.04 equiv.) and after 30 min at 25 °C, triethylphosphite (1.5 equiv.) was added. The reaction mixture was stirred (10 min) followed by the addition of 1 N aqueous NaOH (3.0 equiv.) and stirring continued (30 min; 25 °C). Extractive work-up and chromatographic purification yielded sulfonamide **2** (85%).[6b]

Scheme II

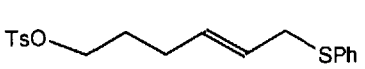
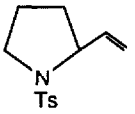
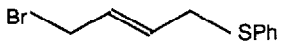
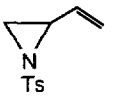
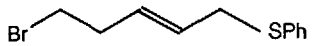
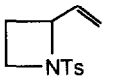
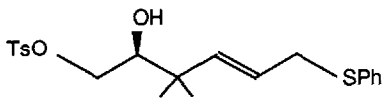
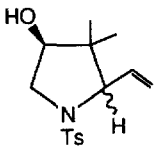
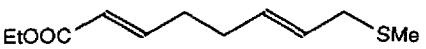
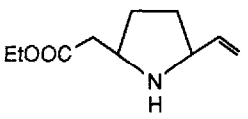
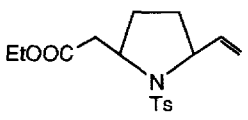
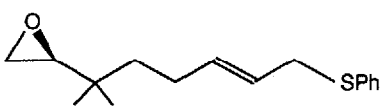
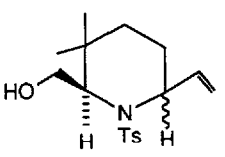
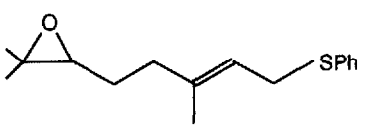
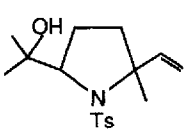
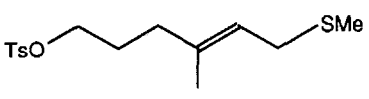
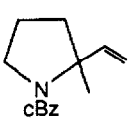
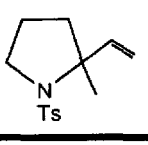


3 **1** **4** **5**: R=SPh **6**: R=H **2**

In situ amination of the phenylthio- moiety in **1** by chloramine-T institutes an allylic sulfilimine **4**/sulfenamide **5** equilibrium (Scheme II). Although the equilibrium **4** ⇄ **5** lies on the side of the sulfenamide **5**,[7] S-N solvolysis is slow under these reaction conditions and triethylphosphite is required to accelerate **5→6** conversion. Addition of aqueous NaOH (in the presence of the phase transfer catalyst) instigates intramolecular cyclization to **2**.

A variety of allylic phenyl and methyl sulfides[8] engage in the [2,3]-sigmatropic rearrangement/intramolecular cyclization process furnishing cyclic N-p-tolylsulfonamides in good yield (Table). 2-Vinyl- aziridine, (entry 2), azetidine (entry 3), pyrolidine (e.g., entries 1,4,5) and piperidine (entry 7) ring systems have been generated using this methodology. O-Mesitylenesulfonylhydroxylamine[6,9] was readily substituted for chloramine-T in these reactions permitting isolation of free amines (entry 5) or N-derivatization with other flexible protecting groups (entry 9). Noteworthy is the range of electrophiles - alkyl halides, tosylates, Michael acceptors, epoxides - which are compatable with chloramine-T and O-mesitylenesulfonylhydroxylamine promoted sulfide amination. Finally, attention is drawn to the facile allylic sulfilimine rearrangement/cyclization promoting formation of 2,2-disubstituted cyclic amines, where the nitrogen atom is attached to a quaternary center (entries 8,9,10).[10]

Table. Conversion of Allylic Phenyl and Methyl Sulfides to 2-Vinyl Cyclic Amines and N-Derivatives

Entry	Sulfide	Aminating Reagent [a]	Product	Isolated Yield (%)
1		CAT		85
2		CAT		60
3		CAT		30
4		CAT		52 [b]
5		MSH		70 [c]
6	"	CAT		87 [d]
7		CAT		40 [b,e]
8		CAT		80 [f]
9		MSH		43 [g]
10	"	CAT		80

a) CAT = Chloramine-T; MSH = *O*-mesitylenesulfonylhydroxylamine. b) Optically active sulfide derived from (R)-pantolactone. c) 1:1 cis/trans. d) 10:1 cis/trans. e) Intermediate allylic sulfonamide isolated (90%) and cyclized with $BF_3{\cdot}Et_2O$. f) Racemic sulfide derived from geraniol. g) Isolated as the N-benzyl carbamate upon reaction with $PhCH_2OC(O)Cl$, $NaHCO_3$.

REFERENCES AND NOTES

1. Smith Kline & French Postdoctoral Fellow, 1988-1989.

2. Knouzi, N.; Vaultier, M.; Toupet, L.; Carrie, R. Tetrahedron Lett. **1987**, 28, 1757 and references therein.

3. A) Ash, A.S.F.; Challenger, F.; Greenwood, D. J. Chem. Soc. **1951**, 1877. b) Ash, A.S.F.; Challenger, F. J. Chem. Soc. **1952**, 2792. c) Briscoe, P.A.; Challenger, F.; Duckworth, P.S. J. Chem. Soc. **1956**, 1755. d) Tamura Y.; Sumoto, K.; Minamikawa, J.; Ikeda, M. Tetrahedron Lett. **1972**, 13, 4137. e) Tamura, Y.; Matsushima, H.; Minamikawa, J.; Ikeda, M. Tetrahedron, **1975**, 31, 3035. f) Johnson, C.R.; Mori, K.; Nakanishi, A. J. Org. Chem. **1979**, 44, 2065.

4. a) Marshall, J.A.; DeHoff, B.S. J. Org. Chem. **1986**, 51, 863. b) Walker, K.A.M. Tetrahedron Lett. 1977, 18, 4475.

5. All new compounds exhibited physical and spectroscopic properties consistant with their structure.

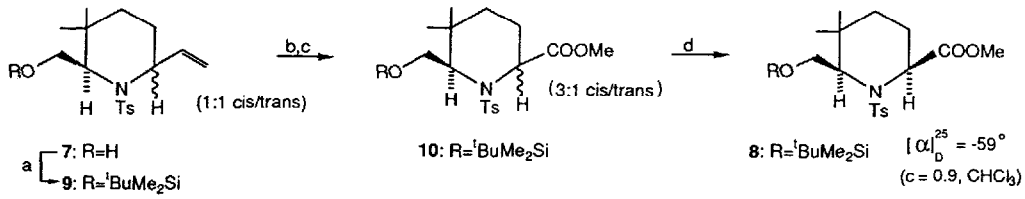
6. a) Chloramine-T hydrate was used as purchased (Aldrich). O-Mesitylenesulfonyl-hydroxylamine (MSH) was prepared as previously described: Tamura, Y.; Minamikawa, J.; Somoto, K.; Fujii, S.; Ikeda, M. J. Org. Chem. **1973**, 38, 1239. b) This represents a general procedure employing chloramine-T as the aminating reagent. The following is a general procedure employing MSH as the aminating reagent: A CH_2Cl_2 solution of 1 (0.2 M) was treated with MSH (1.1 equiv.) at 0 °C. The solution was stirred (30 min), then Et_3N (3.0 equiv.) and $(EtO)_3P$ (1.5 equiv.) were added and the solution was refluxed. Conventional work-up and purification gave the cyclic amine.

7. a) Natsugari, H.; Whittle, R.R.; Weinreb, S.M. J. Am. Chem. Soc. **1984**, 106, 7867. b) Sharpless, K.B.; Hori, T. J. Org. Chem. **1976**, 41, 176.

8. The requisite sulfides (Table) were typically derived from allylic alcohols via initial conversion to phenyl sulfides (with NPTS[4b]) or methyl sulfides (modified Mitsunobu with thioacetic acid (Volante, R.P. Tetrahedron Lett. **1981**, 22, 3119) and then saponification with K_2CO_3/MeOH in the presence of MeI) and subsequent unmasking/generation of the electrophile.

9. Use of MSH led to analogous results in most cases; however, N-chlorobenzyl- and N-chloro-t-butylcarbamate were ineffective. In our hands, allylic N-cBz and N-BOC protected amines were not produced upon treatment of the allylic phenyl or methyl sulfides with these N-chlorocarbamates. This observation is in contrast to the reactivity of allylic phenyl selenides: Shea, R.G.; Fitzner, J.N.; Fankhauser, J.E.; Hopkins, P.B. J. Org. Chem. **1984**, 49, 3647.

10. Oxidation of the vinyl appendage affords N-protected amino acid esters as exemplified by the conversion of 7 (entry 7) to 8. Thus a) t-$BuMe_2SiCl$, imid., DMF; b) O_3, Sudan red 7B, CH_2Cl_2, -78 °C then Ph_3P, 25 °C; c) $NaClO_2$, NaH_2PO_4, t-BuOH, $(CH_3)_2C{=}CHCH_3$, H_2O (Bal, B.S.; Childers, W.E., Jr.; Pinnick, H.W. Tetrahedron, **1981**, 37, 2091) then CH_2N_2; and d) chromatographic isolation of the major isomer 8 (ca. 25% overall yield, structure 8 confirmed by ^1H NMR). Epimerization occurred during isolation/oxidation of the intermediate aldehyde.



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