

HETEROCYCLES FROM 2-ALKYL-OR ARYLTHIO-1-CHLOROENAMINES

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2-Alkyl-or arylthio-1-chloroenamines are readily prepared from tertiary amides or from ynamines. The 2-arylthio derivatives are readily cyclized to 3-dialkylaminobenzothio-phenes in the presence of Lewis acids. With sodium azide they give 2-amino-1-azirines bearing a thioether group at position 3. These highly functionalized azirines are potential precursors of the 2-amino-1-azirinyli-cations.

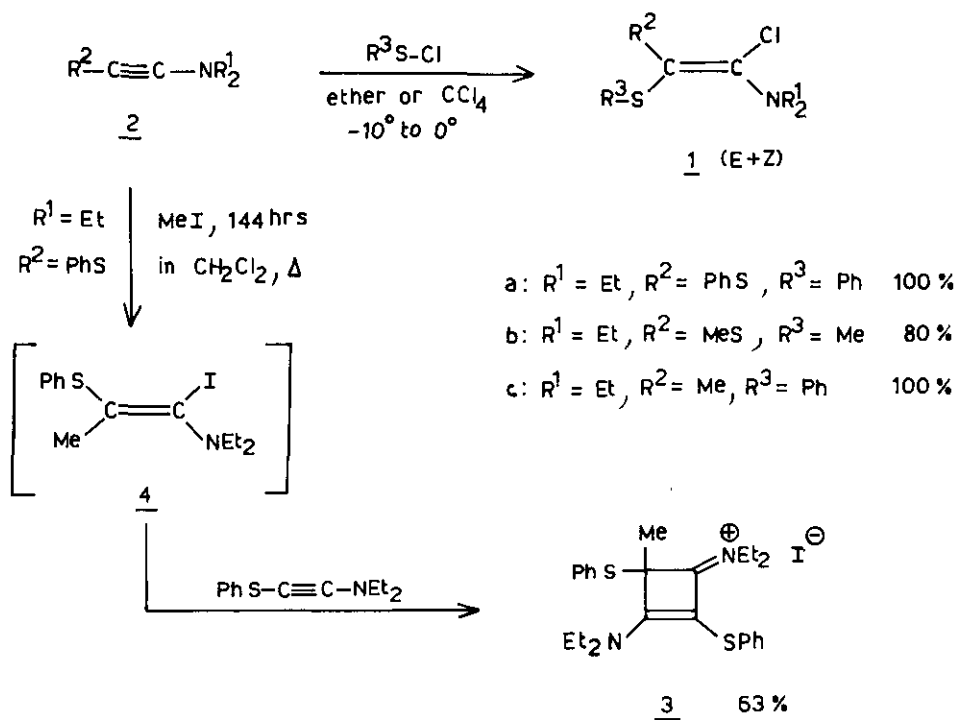
α -Haloenamines are 1,2 ambiphilic reagents¹ which react either as nucleophiles at C-2 or as electrophiles at C-1. This versatile behaviour results from an equilibrium between the covalent enamine structure and the isomeric keteniminium halide. It has been shown that selective control of the nucleophilicity versus the electrophilicity of the reagent can be effected by appropriate choice of the halogen and the amine substituents². The synthetic potential of the simplest representatives of this class has been the subject of earlier reports¹ of our laboratory.

We now describe the synthesis of α -chloroenamines 1 bearing alkyl- or arylthio groups at C-2 and their use for the synthesis of some highly functionalized heterocycles.

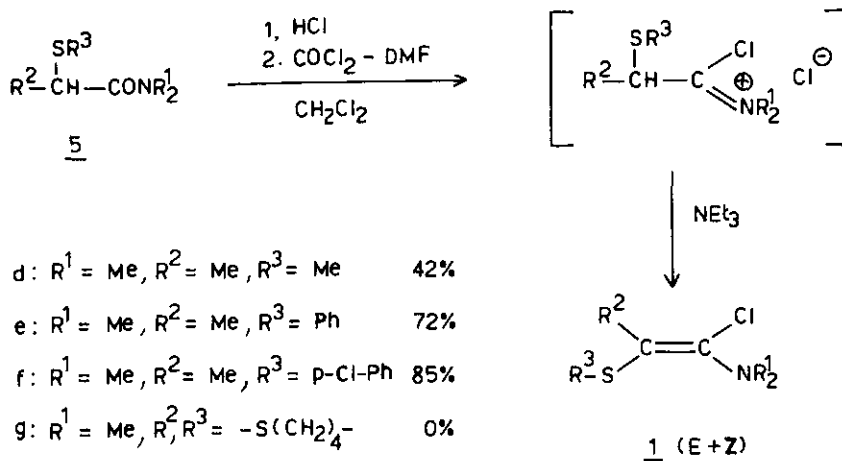
SYNTHESIS

The first method involves the addition of sulphenylchlorides to ynamines 2. Reports by Senning^{3a} and Schindler^{3b} had shown that trichloromethylsulphenylchloride readily added across the triple bond of N,N-diethylaminopropyne. We have applied successfully this mild reaction to the synthesis of several α -chloroenamines 1 (Scheme 1). An alternative route involving the alkylation of an ynamine⁴ already bearing a thioether group was unsuccessful: the reaction of methyl iodide with 2a yielded a cyclobutenecyanine 3 arising from a cycloaddition between 2a and the highly electrophilic α -iodoenamine 4.

The practical method⁵ of conversion of tertiary amides 5 into α -chloroenamines could also be applied to the synthesis of 1 (Scheme 2). The following conditions gave the best results: a solution of 0,1 mole of α -phenylthio-N,N-dimethylpropionamide and 0,01 mole of DMF in 200 ml of dichloromethane was saturated with HCl gas. The mixture was then treated with 0,2 mole of COCl₂ for 40 hrs at room temperature. Evaporation of the solvent left a residue which was dissolved in 50 ml of dry chloroform. Triethylamine (0,3 mole in 25 ml of CHCl₃) was added dropwise (~2hrs) to the solution at -10°C. Addition of petroleum ether (b.p. 60°-80°) filtration and distillation gave 1d (75%, E+Z). The method was also applied



SCHEME 1



SCHEME 2

successfully to the preparation of 1e and 1f. However poor results were obtained in the case of the phosgenation of 5g. The spectral properties of the new α -chloroenamines 1 are shown in Table 1.

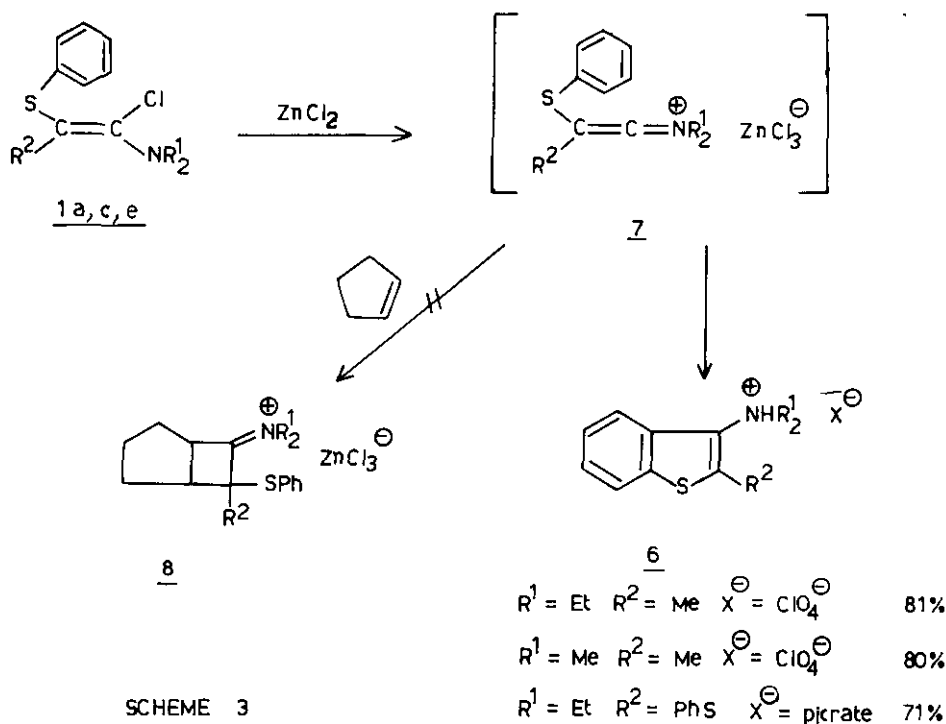
Table 1 : Spectral data of the α -chloroenamines 1

Compd.	IR max cm^{-1} (CCl_4)	$^1\text{H-NMR}$ (CCl_4) δ
a	1562	1.11 (6H, t, J=7Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 2.81 (4H, q, J=7Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 6.93 (10H, s, $\text{S-C}_6\text{H}_5$)
b	1560 and 1565	1.06 (6H, t, J=7Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 2.33 (6H, s, S-CH_3), 2.8 (4H, q, J=7Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$)
c	1622	1.12* and 1.05 (6H, 2t, J=7.5Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 1.87 and 1.25* (3H, 2s, CH_3), 2.75* and 2.73 (4H, 2q, J=7.5Hz, $\text{N}(\text{CH}_2\text{CH}_3)_2$), 7.4 (5H, m, $\text{S-C}_6\text{H}_5$)
d	1634	1.97* and 2.06 (3H, 2s, CH_3), 2.22 (3H, s, S-CH_3), 2.41 (6H, s, $\text{N}(\text{CH}_3)_2$)
e	1632	1.80* and 1.87 (3H, 2s, CH_3), 2.5 and 2.52* (6H, 2s, $\text{N}(\text{CH}_3)_2$), 7.28 (5H, m, $\text{S-C}_6\text{H}_5$)
f	1632	1.8* and 1.87 (3H, 2s, CH_3), 2.51 (6H, s, $\text{N}(\text{CH}_3)_2$), 7.16 (4H, m, $\text{S-C}_6\text{H}_4\text{-pCl}$)

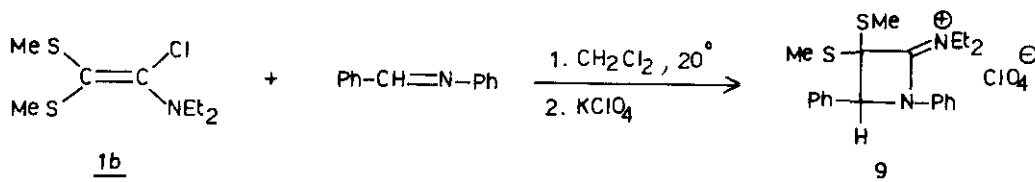
* predominant isomer

HETEROCYCLIZATIONS

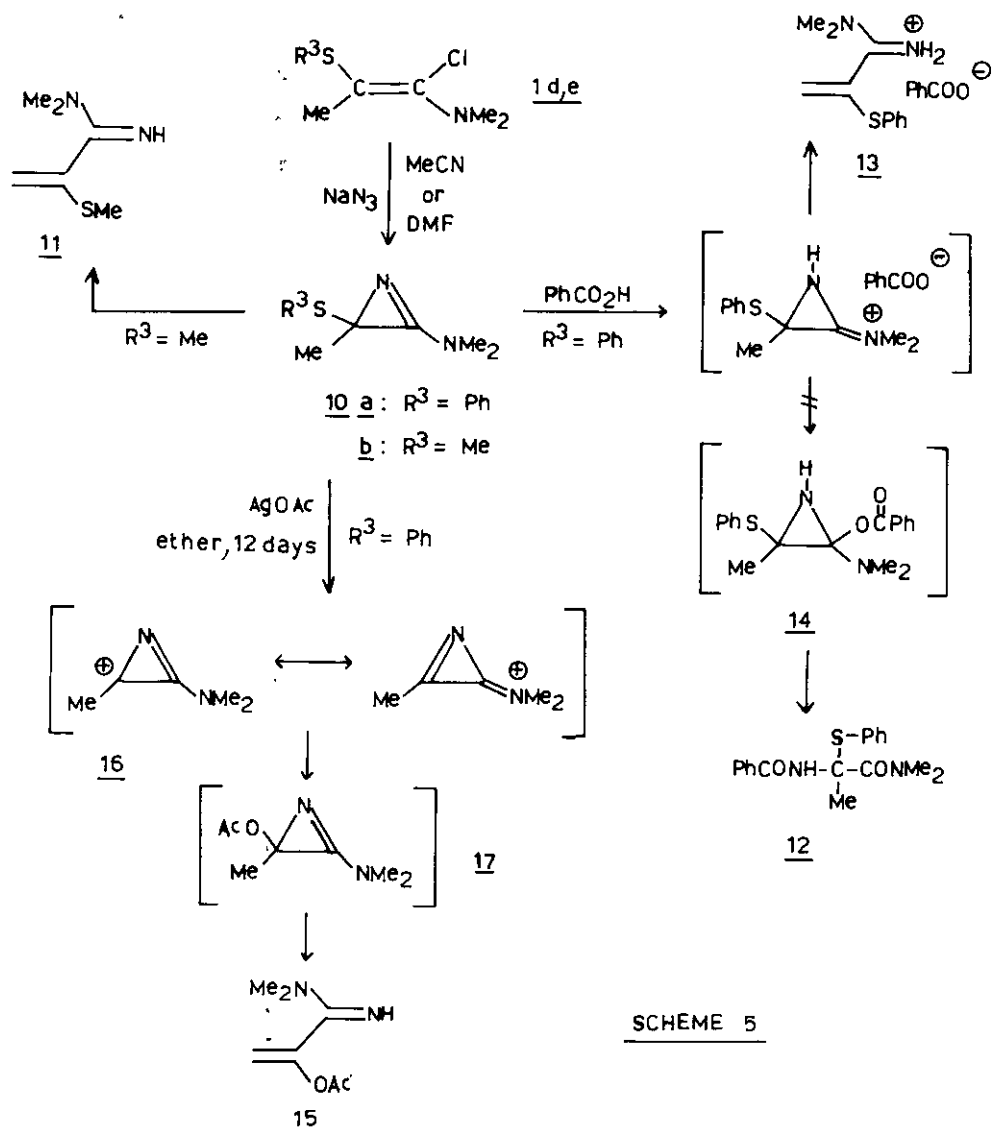
2-Arylthio-1-chloroenamines 1a, 1c and 1e are readily cyclized to 3-dialkylaminobenzothiophenes 6 in the presence of Lewis acids such as silver tetrafluoroborate or zinc chloride (Scheme 3). The key step is obviously the formation of a keteniminium salt 7 which attacks the activated phenyl ring. The products were identified by their spectral properties. Addition of cyclopentene to a mixture of 1e and zinc chloride failed to give the corresponding (2+2) cycloadduct 8. Only the intermolecular cyclization took place.



However the expected (2+2) adduct 9 was obtained when 1b was reacted with benzalazine in dichloromethane at room temperature (Scheme 4). The adduct 9 was identified by elemental analysis and spectral data: IR(KBr): 1687 and 1087 cm^{-1} ; $^1\text{H-NMR}(\text{CDCl}_3)$: δ 1.46(t, 3H, J=7Hz), δ 1.56(s, 3H), δ 2.61(s, 3H), δ 3.13-4.28(m, 4H), δ 5.9(s, 1H), δ 7.1-7.75(m, 10H).



The presence of thioether groups at C-2 reduces the electrophilic reactivity of an α -chloroamine. Thus, whereas tetramethyl- α -chloroamine readily reacts with a suspension of sodium azide in ether⁸, no reaction took place when 1d-1e were exposed to the same conditions. However, when the reactions were run in acetonitrile or DMF, both 1d and 1e were smoothly converted into 2-amino-1-azirines 10a and 10b (Scheme 5): 10a, IR 1786 cm^{-1} , $^1\text{H-NMR}(\text{CCl}_4)$ δ 1.68(s, 3H), 2.71(s, 6H), 7.08-7.61(m, 5H), $^{13}\text{C-NMR}(\text{CDCl}_3)$ δ 51.6 (C-3), 162.6 (C-2); 10b, IR 1775 cm^{-1} , $^1\text{H-NMR}(\text{CCl}_4)$ δ 1.56(s, 3H), 1.83(s, 3H), 3.08(s, 6H).



SCHEME 5

Compound 10b rearranged slowly at room temperature to yield quantitatively the vinylamidine 11: IR 1585 cm^{-1} , $^1\text{H-NMR}(\text{CCl}_4)$ $\delta 2.2(\text{s}, 3\text{H})$, $\delta 2.9(\text{s}, 6\text{H})$, $\delta 4.95$ and $5.16(2\text{s}, 2\text{H})$, $\delta 6.06(\text{broad } 1\text{H})$. This result may be accounted for by an initial N_1-C_3 bond cleavage facilitated by the neighbouring methylthio group. This observation was rather surprising: 3-alkyl or aryl substituted 2-amino-1-azirines rearranged only when subjected to pyrolysis in a flow system at above 350°C ⁹. Furthermore, these rearrangements took place with initial cleavage of the C-C bond. It cannot yet be decided whether the differences between the thermal behaviour of 10b and that of 3-alkyl or aryl substituted 2-amino-1-azirines is solely due to

the substitution at C-3 or to experimental conditions used for the rearrangements (condensed phase for 10b, flow system in other cases). As expected, compound 10a showed a higher thermal stability and could be heated for two hours in toluene without decomposition.

It has been shown earlier that 2-amino-1-azirines reacted readily with carboxylic acids to yield α -acylamino-carboxamides¹⁰. This reaction involves a N_1-C_2 bond cleavage. Interestingly the reaction of 10a with benzoic acid did not give the expected product 12 but yielded the unsaturated amidinium salt 13 : IR : 1690-1630-1600-1585 cm^{-1} ; 1H -NMR($CDCl_3$) : δ 2.93(s,6H), δ 5.2 and 5.56(2s,2H). Thus it appears that, instead of adding a carboxylate anion to yield 14, protonated 10a undergoes a very rapid rearrangement involving the cleavage of the N_1-C_3 bond. Such a rearrangement obviously benefits from the electron-donating capacity of the phenylthio group.

We were also intrigued by the possibility of generating the interesting 2-amino-1-azirinylium cation¹¹ from the reaction of 10a with Lewis acids. A slow reaction took place between 10a and a suspension of silver acetate in ether. After 12 days at room temperature, a vinylamidinium 15 was isolated in 77% yield : IR: 3400, 1690, 1640 and 1530 cm^{-1} , 1H -NMR($CDCl_3$) : δ 2.03(s,3H), δ 3.03(s,6H), δ 4.7 and 5.66(2s,2H), δ 8.26(broad 1H). In our opinion this result is best rationalized on the basis of the intermediate formation of 16. Addition of an acetate ion would lead to the new aminoazirine 17 which like 10b, should easily rearrange to give the observed product 15. If this mechanistic hypothesis represents reality, we would have an easy access to this new class of cation which should lead to interesting synthetic possibilities. We are now exploring this new area of heterocyclic synthesis.

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