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SYNTHESIS OF 1,2,3-TRISUBSTITUTED AND 1,2,2,3-TETRASUBSTITUTED AZIRIDINES FROM α-CHLOROKETIMINES

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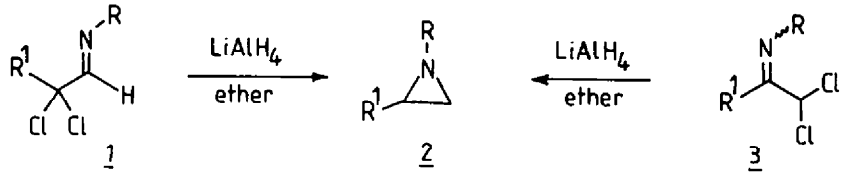
Abstract

Secondary α-chloroketimines react with lithium aluminium hydride in ether to afford mixtures of cis- and trans-1,2,3-trisubstituted aziridines. The reaction products are formed by nucleophilic addition of hydride across the imino bond and subsequent intramolecular nucleophilic substitution. Tertiary α-chloroketimines react similarly with lithium aluminium hydride to yield 1,2,2,3-tetrasubstituted aziridines. α,α-Dichloroketimines react with lithium aluminium hydride in a stereospecific way to afford cis-aziridines, exclusively. These results are interpreted in terms of formation of an intermediate α-chloroaziridine, from which a chloride anion is expelled to afford an intermediate azirinium chloride. The latter strained intermediate undergoes stereospecific addition of hydride to give cis-aziridines.

Introduction

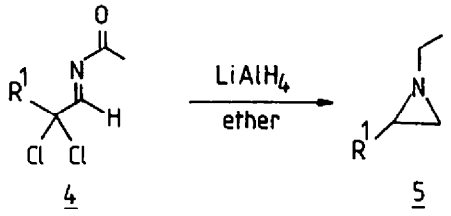
α-Chloroimines have been shown already to be good synthons for the preparation of aziridines. α,α-Dichloroaldimines 1 and α,α-dichloromethylketimines 3 are known to react with lithium aluminium hydride in ether to afford 1,2-disubstituted aziridines 2.[3,4] Also the more activated N-acetyl α,α-dichloroaldimines 4 produced N-ethyl 1,2-disubstituted aziridines 5 on reaction



1 2 3

with lithium aluminium hydride.[5] Secondary α-chloroaldimines 6 and tertiary α-chloroaldimines 7 reacted similarly with lithium aluminium hydride to produce 1,2-disubstituted and 1,2,2-trisubstituted aziridines 2 and 8, respecti-

vely.[6,7] A deeper insight was gained in the mechanism of these reactions of α-haloimines with complex metal hydrides by the stereospecific conversion of α,α-dichloroarylketimines 9 into cis-aziridines 10.[8] The mechanism involved



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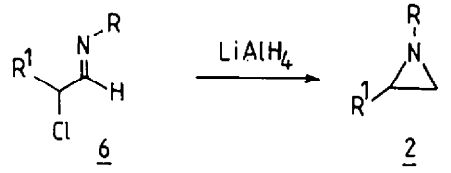

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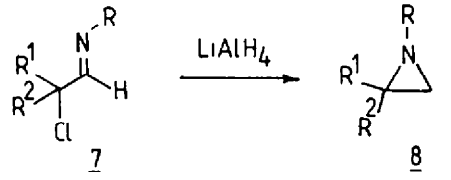
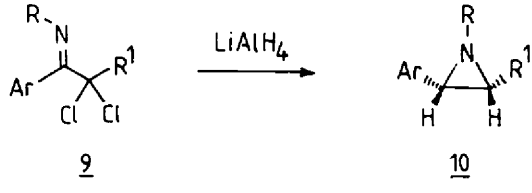
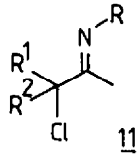


7 8

the intermediacy of α-chloroaziridines and azirinium chlorides.[8,9] In order to complete the study on the scope and limitations of the aziridination of α-chloroimines, we investigated the use of secondary and tertiary α-chloroketimines 11 and 12, respectively, for the preparation of aziridines.



9 10

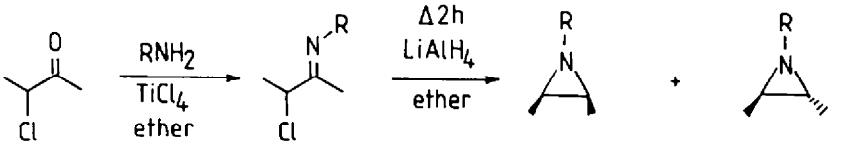


11 $R^2 = H$

12 $R^2 \neq H$

Results and Discussion

α-Chloroketimines 14, 15 (R=t-Bu, i-Pr) and α-chloroketimine 21 were easily prepared from the corresponding α-chloroketones 13 and 20, respectively, by condensation with the appropriate primary amine in the presence of titanium(IV) chloride.[10]



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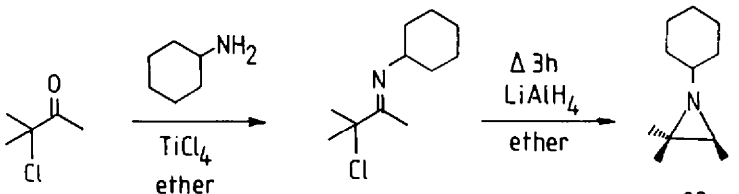
14 R = t-Bu
15 R = i-Pr

16 R = t-Bu
18 R = i-Pr

17 R = t-Bu
19 R = i-Pr



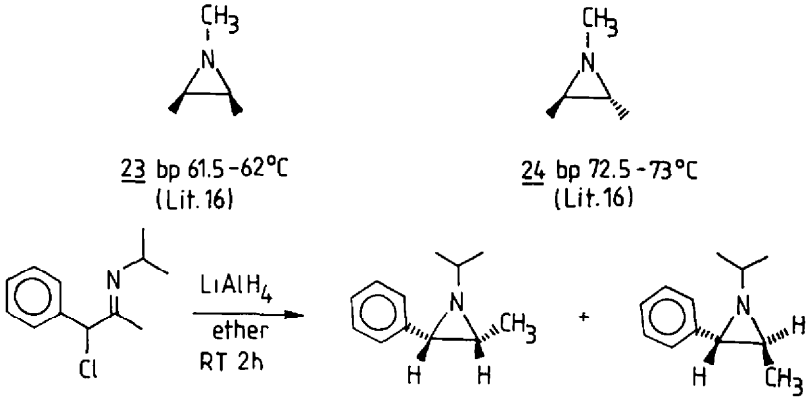
20 21 22

Reaction of N-(3-chloro-2-butylidene)t-butylamine 14 and N-(3-chloro-2-butylidene)isopropylamine 15 with an equimolecular amount of lithium aluminium hydride in ether under reflux for two hours afforded a mixture of cis- and trans-1-alkyl-2,3-dimethylaziridines 16, 17 and 18, 19 in 60-71% yield after distillation (the cis/trans ratio ranged from 1:1 to 2:3 depending upon the scale of the experiment, the rate of addition of the reagents, the initial temperature of the reaction mixture, etc...). Special care has to be taken to the isolation of these aziridines 16-19 because of their high volatility, which certainly reduced the yields, which have not been optimized.

In similar way, the reaction of N-(3-chloro-3-methyl-2-butylidene)cyclohexylamine 21 with one molar equivalent of lithium aluminium hydride in ether under reflux for three hours afforded 1-cyclohexyl-2,2,3-trimethylaziridine 22 in 86% yield after distillation.

The determination of the stereochemistry of the 1,2,3-trisubstituted aziridines 16-19 is a difficult problem in view of the inversion at the nitrogen atom, which complicates the NMR spectral analysis. Due to the N-inversion, these aziridines occur as a rapidly interconverting mixture of conformers.[11,12] For trans-aziridines the N-inversion happens slow enough in order both forms to be distinguished by NMR spectrometry. A general feature of aziridines is that the N-substituent has the tendency to select the preferential conformation in which the N-substituent occupies the trans position

with respect to the ring substituents. This is easily accomplished in cis-2,3-dialkylaziridines. On the other hand, trans-2,3-dialkylaziridines usually will show an equilibrium of invertomers in which the N-substituent will be preferentially located at the least hindered side.[12,13] It may be pointed out that the same phenomenon is applicable to N-unsubstituted aziridines, in which the N-H moiety is preferentially positioned at the least hindered side.[14,15] An important aid in the determination of the stereochemistry of 1,2,3-trisubstituted aziridines is the fact that cis-aziridines display a considerable lower boiling point than the corresponding trans-derivatives (see 23 and 24).[16,17] The attribution of the stereochemical configuration of

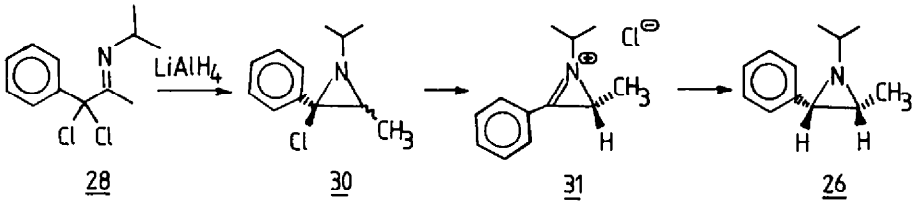


25 26 27

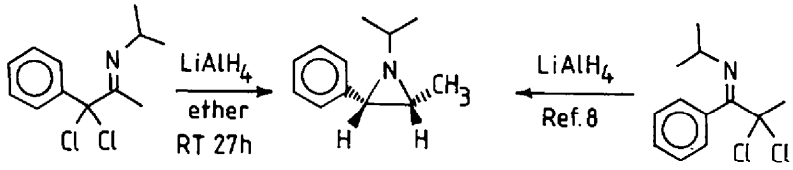
aziridines 16-19 was guided by this difference in boiling points but also on the basis of the related retention times of the gas chromatographic analysis. Injection of a cis-trans mixture of aziridines 16, 17 or 18, 19 on a methyl-silicon (DC 200) column (chromosorb W, 60-80 mesh, 3 m, 10%) gave rise to two peaks, the first one being the cis-isomer and the second one being the trans-isomer. A similar separation by means of gas chromatography was reported already in the literature.[18] The chemical shift (^{1}H NMR, 60 MHz) of the ring protons of N-t-butyl cis- and trans-aziridines 16, 17 differs little and, therefore, the influence of the N-alkyl group is not clearly visible. This effect is slightly visible for the N-isopropyl derivatives 18 and 19 whereby the ring protons, which are located cis with respect to the N-alkyl group, are more shielded than the ring protons in the trans position.[13] Accordingly, it can be concluded that the N-alkyl group of cis derivatives 16 and 18 is preferably positioned trans with respect to the two methyl groups.

The α-phenylsubstituted α-chloroketimines 25 reacted with lithium aluminium hydride in ether at room temperature (2h) to afford a quantitative yield of 1-isopropyl-2-methyl-3-phenylaziridine as a mixture of cis/trans isomers 26 and 27 in a 3:2 ratio, as determined by ^{1}H NMR. On the other hand, the

α-phenyl-α,α-dichloroketimine 28 with lithium aluminium hydride in ether at room temperature (27h) gave rise to cis-1-isopropyl-2-methyl-3-phenylaziridine 26 in 71% yield (after distillation). This result clearly established the reaction mechanism of the aziridination of α-chloroketimines as occurring via intermediate α-chloroaziridines (e.g. 30) and azirinium chlorides (e.g. 31), the latter being attacked by hydride from the side most remote from the alkyl group at the 3-position (i.e. the 3-methyl group in 31).



28 30 31 26



28 26 29

The stereospecific conversion of α-phenyl α,α-dichloroketimine 28 into cis-aziridine 26 underlines the synthetic potential of the aziridination reaction of α-chloroimines because also the isomeric aromatic α,α-dichloroketimines 29 is known to give rise to cis-aziridine 26 in a stereospecific manner.[8]

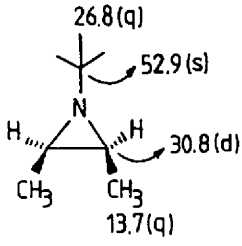
Table I : Synthesis of 1,2,3-Trisubstituted and 1,2,2,3-Tetrasubstituted Aziridines from α-Chloroketimines

Starting α-Chloroketimine	Reaction conditions[a]	Aziridine	Yield	B.p. °C/mmHg
14	Δ 2h	16, 17	71%[b]	109-115/760
15	Δ 2h	18, 19	60%[b]	75-91/760[e]
21	Δ 3h	22	86%	82-84/17
25	RT 2h	26, 27	99%[b,c]	105-110/12
28	RT 27h	26	71%[d]	105-107/12

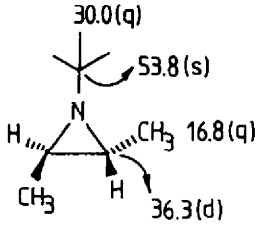
[a] Reaction of α-chloroketimines with one molar equivalent of lithium aluminium hydride in ether; Δ = reflux; RT = room temperature; [b]Mixture of cis- and trans-aziridines; [c]Yield before distillation; [d] Cis-aziridine exclusively; [e] Lit. bp. 102-102.5°C.[28]

The mechanism for the synthesis of aziridines from α-monochloroketimines occurs also by nucleophilic addition of hydride across the imino bond followed by intramolecular nucleophilic substitution, the aziridine being the final reaction product.[19]

The stereochemistry of the phenylsubstituted aziridines 26 and 27 is easily determined via ^1H NMR spectrometry by means of the coupling constant of the vicinal hydrogens of the aziridine ring. The typical coupling constant for the ring hydrogens of cis-aziridines (e.g. 26) is about 6 Hz while the value for the trans hydrogens is much smaller (about 2.5-3.5 Hz).[13,20,21] It should be noted here that the 60 MHz ^1H NMR spectra easily allow distinction between cis- and trans isomers of C-phenylsubstituted aziridines, but this technique is not applicable for aliphatic 1,2,3-trisubstituted aziridines due to the complexity of the ^1H NMR spectra. However, ^{13}C NMR spectra (20 MHz) of such stereoisomeric aziridines are much easier to interpret, as exemplified for the ^{13}C NMR data of cis- and trans-1-t-butyl-2,3-dimethylaziridine 16 and 17 (δ, $CDCl_3$) :



16



17

Aziridines are well-studied azaheterocycles from the viewpoint of fundamental studies as well as from the viewpoint of applied research.[22,23] 1,2,3-Trisubstituted aziridines have been previously synthesized by the Wenker procedure, involving ring closure of β-aminoalcohols[12,17,24] or β-chloroamines.[25] Another synthesis involves the addition of iodine azide across olefins followed by reaction of the resulting β-iodoazides with alkyl- or arylboranes and subsequent base induced ring closure.[26] Tri- and tetrasubstituted aziridines are alsc accessible via N-alkylation of N-unsubstituted aziridines under phase-transfer catalytic conditions[27], but this method has limited generality. Various other methods for the synthesis of such aziridines have been compiled in reviews.[22,23]

The reactivity of α-chloroketimines towards complex metal hydrides differs markedly from the reactivity of the corresponding α-haloketones. While α-haloimines generally give rise to aziridines, α-haloketones with nucleophilic hydrides afford β-haloalcohols and alcohols.[19]

Table II : Spectrometric Data of Tri- and Tetrasubstituted Aziridines

Compound[a]	^{1}H NMR (δ; CCl_4; 60 MHz)	^{13}C NMR (δ, $CDCl_3$, 20 MHz)	Mass Spectra m/e (%)
16	0.86 (9H,s,t-Bu); 0.9 (6H, m,broad,Me_2); ∿ 1.5 (2H,m, 2CH)	13.71 (q,Me); 26.83 (q,t-Bu); 30.82 (d,CH); 52.89 (s,NC)	127 (M^+; 4), 112(9), 71(16), 70(100), 58(5), 57(9), 56 (16), 55(10), 44(2), 43(5), 42(15), 41(12), 40(2), 39(4)
17	1.05 (9H,s,t-Bu); 1.5 (2H, m,2CH); 1.15 (6H,m,broad, Me_2)	16.83 (q,Me); 29.96 (q,t-Bu); 36.32 (d,CH); 53.77 (s,NC)	127 (M^+; 5), 112(8), 71(15), 70(100), 58(6), 57(10), 56 (18), 55(13), 44(5), 43(5), 42(18), 41(15), 40(2), 39(5)
18	0.9-1.2 (12H,m,4Me); 1.2-1.7 (3H,m,NCH and 2CH)	13.37 (q,Me); 21.97 (q, $NCHMe_2$); 38.03 (d,CH); 61.45 (d,$NCHMe_2$)	113 (M^+; 7), 98(5), 85(2), 84(2), 71(11), 70(100), 56 (13), 55(8), 44(4), 43(8), 42(18), 41(10), 40(3), 39 (4)
19	1.01 and 1.05 (2x3H,2xd, J=6.5Hz,$NCHMe_2$); 1.22 (2x3H,broad d,2xMe); 1.6 (2H,m,2CH); 2.14 (1H, septet,J=6.5Hz,NCH)	10.98 and 18.71 (q,2Me); 39.22 and 39.98 (d,2CH); 51.21 (d,NCH); 22.96 and 23.09 (q,$NCHMe_2$)	113 (M^+, 9), 98(5), 85(2), 84(2), 71(11), 70(100), 56 (14), 55(9), 44(4), 43(8), 42(22), 41(11)

Table II : (Continued)

Compound[a]	^{1}H NMR (δ; CCl_4; 60 MHz)	^{13}C NMR (δ, $CDCl_3$, 20 MHz)	Mass Spectra m/e (%)
22	1-1.25 (3x3H,overlap,3xMe); 1.2-2.5 (12H,m,($C\underline{H}_2$)$_5$,C$\underline{H}$ and NC$\underline{H}$)	14.93 (q,Me); 18.14 (q,Me); 22.61 (q,Me); 24.96 (t,CH_2); 25.34 (t,CH_2); 26.24 (t,CH_2); 33.13 (t,CH_2); 34.28 (t,CH_2); 39.53 (s,$\underline{C}Me_2$); 43.56 (∿d,$\underline{C}$HMe); 61.41 (∿d,N$\underline{C}$H)	167 (M^+; 3), 152(2), 138(1), 126(2), 124(4), 110(3), 98 (1), 96(1), 86(7), 85(26), 84(100), 83(13), 70(32), 69 (7), 68(5), 67(3), 58(2), 57 (3), 56(9), 55(22), 54(5), 53(4), 44(13), 43(6), 42 (21), 41(34), 40(7), 39(9)
26[b]	0.85 (3H,d,J=5.4Hz,CH_3C); 1.11 and 1.15 (2x3H,2xd, J=5.6Hz,Me_2); 1.4-1.9 (2H, overlap,NC$\underline{H}$ and C$\underline{H}$Me); 2.35 (1H,d,J=6.3Hz,C$\underline{H}$Ph); 7.16 (5H,s,Ph)	13.69 (q,Me); 40.65 (d, $\underline{C}$HMe); 45.93 (d,N$\underline{C}$H); 21.96 and 22.12 (q,Me_2); 61.44 (d,N$\underline{C}$H); 126.44 (d,=$\underline{C}$H para); 127.89 and 128.04 (each d,=$\underline{C}$H ortho and meta); 138.27 (s,$C_{quat.}$)	175 (M^+, 18), 174 (16), 132 (100), 117(6), 105(19), 91 (7), 90(3), 89(3), 79(2), 77 (4), 62(2), 63(1), 54(1), 51 (1), 43(11), 42(2), 41(2), 39(2)
27	1.08 (6H,d,J=6Hz,Me_2); 1.33 (3H,d,J=5.5Hz); 1.7-2.8 (3H, m,C$\underline{H}$-C$\underline{H}$ and NC$\underline{H}$); 7.12 (5H, s,C_6H_5)	20.84, 23.00 and 23.84 (each q,3Me); 44.03 (d,$\underline{C}$HMe); 45.53 (d,$\underline{C}$HPh); 51.53 (d, N$\underline{C}$H); 139.73 (s,$C_{quat.}$); 128.32 and 129.36 (d,=$\underline{C}$H ortho and meta); 126.09 (d, =$\underline{C}$H para)	-[c]

[a] IR spectra revealed no characteristic absorptions (NaCl); [b] ^{1}H NMR and mass spectral data appeared already in one of our previous papers.[8]; [c] Identical to the mass spectrum of compound 26.

Experimental Section

Infrared spectra were recorded with a Perkin Elmer model 1310 spectrophotometer. ^{1}H NMR spectra were measured with a Varian T-60 NMR spectrometer while ^{13}C NMR spectra were recorded with a Varian FT-80 NMR spectrometer (20 MHz). Mass spectra were obtained with a Varian-MAT 112 mass spectrometer (70 eV) using a direct inlet system or by using a GC-MS coupling (capillary column).

α-Chloroketimines 14, 15, 21, 25 and 28 were prepared by condensation of an appropriate α-chloroketone with an appropriate primary amine in the presence of titanium(IV) chloride.[10]

Reaction of α-Chloroketimines with Lithium Aluminium Hydride : General Procedure

This procedure is exemplified by the conversion of N-(3-chloro-2-butylidene)-isopropylamine 15 into aziridines 18 and 19. To a stirred suspention of 3.8 g (0.1 mol) of lithium aluminium hydride in 100 ml dry ether was added dropwise over five minutes a solution of 14.75 g α-chloroketimine 15 in 20 ml of dry ether. The stirred mixture is brought to reflux for 2 hours. After cooling, the reaction mixture is cautiously and portionwise added to ice water. The ether layer was isolated and the aqueous layer was extracted twice with ether. The combined organic extracts were dried (K_2CO_3) and, after filtration, the ether was removed by slow distillation over a short vigreux column. After removal of the solvent, distillation is continued to afford 6.8 g (60%) of a mixture of aziridines 18 and 19. Bp. 77-91°C/760 mmHg. Both isomers were separated by preparative gas chromatography as described in the discussion of the results. CAUTION : aziridines are known to be carcinogenous compounds. Accordingly, care should be taken when handling these volatile aziridines. The reaction conditions for the synthesis of all other aziridines from α-chloroketimines are described in Table I, while the spectral data of these aziridines are compiled in Table II.

Elemental analysis. Compounds 16, 17 : 11.00% N calculated, 10.81% N found. Compound 22 : 8.37% N calculated; 8.24% N found.

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