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A CONVENIENT METHOD FOR THE SYNTHESIS OF β-CHLOROAMINES BY ELECTROPHILIC REDUCTION OF α-CHLOROIMINES

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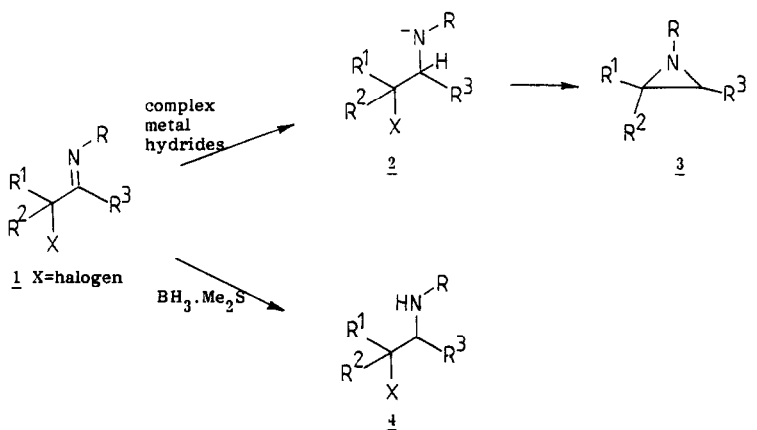
Abstract

α-Chloro-, α,α-dichloro- and α,α,α-trichloroimines were conveniently reduced by borane-methyl sulfide in dichloromethane into the corresponding β-chloroamines. This synthetic procedure was applied to the synthesis of N-(4-methoxyphenyl)-[2,2,2-trichloro-1-(4-methoxyphenyl)]ethylamine, which is a known insecticide.

Introduction

The nucleophilic reduction of α-halogenated imines with complex metal hydrides is a useful synthetic tool for the preparation of aziridines.[1] The reaction proceeds via nucleophilic addition of hydride across the imino bond to form adduct 2, followed by intramolecular nucleophilic substitution. If

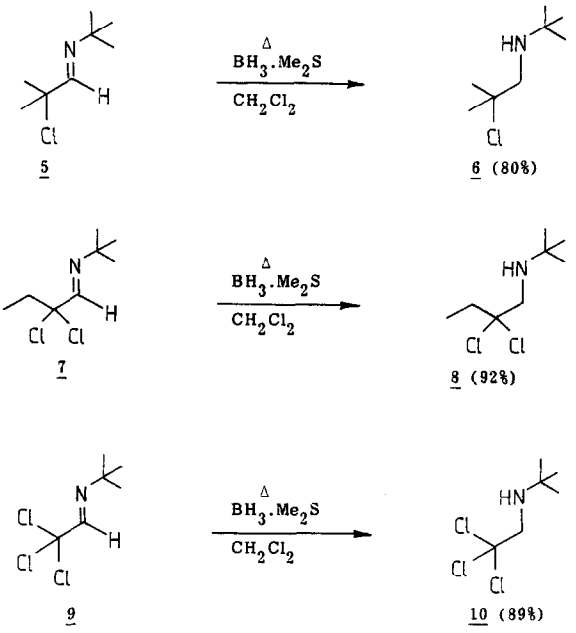


dihalogenated imines were used as starting materials, it was shown that the conversion into aziridines occurred via intermediate azirinium halides.[2]

Starting from α-chloroaldimines,[3,4] α,α-dichloroaldimines,[5,6] α,α-dichloromethylketimines,[7] α,α-dichloroalkyl arylketimines,[2] α-chloroketimines,[8] α,α,α-trichloromethyl aryl ketimines,[9] the reaction with lithium aluminium hydride in ether afforded a great variety of aziridines 3. Only under carefully controlled conditions (low temperature, no excess of hydride source), the intermediate adducts resulting from protonation of 2 could be isolated. Under the usual reaction conditions employed (reflux) the hydride reduction of the imino group is rapidly followed by the intramolecular nucleophilic substitution. Herein we would like to report now on the electrophilic reduction of α-chloroimines leading to β-haloimines, without subsequent intramolecular nucleophilic substitution.

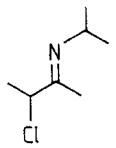
Results and Discussion

The reaction of α-chloroimines with borane-methyl sulfide complex in dichloromethane under reflux afforded β-chloroamines in good to excellent yields. In view of the known tendency of β-haloamines to cyclize in the free base form, it is remarkable that the present β-chloroamines could be isolated free from side products. The purity usually being higher than 96%, these β-chloroamines can be used directly for further elaboration without



additional purification. α-Chloroaldimine 5, α,α-dichloroaldimine 7 and α,α,α-trichloroaldimine 9 upon reaction with excess borane-methyl sulfide

complex in ether were converted into β-chloroamine 6, β,β-dichloroamine 8 and β,β,β-trichloroamine 10, respectively (Table I). This electrophilic reduction is not applicable for aliphatic α-chloroketimines 11 and 12 which gave rise to complex reaction mixtures. However, reduction of aromatic



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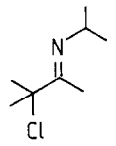

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α-chloroketimines with borane-methyl sulfide complex under reflux provided the corresponding β-chloroamines without any difficulty (Table I). Accordingly, α-chloroketimine 13, N-methyl α,α-dichloroketimine 15 and N-aryl α,α-dichloroketimines 17-19 were transformed into the corresponding β-chloroamines 14, 16, and 20-22, respectively in 90-98% yield.

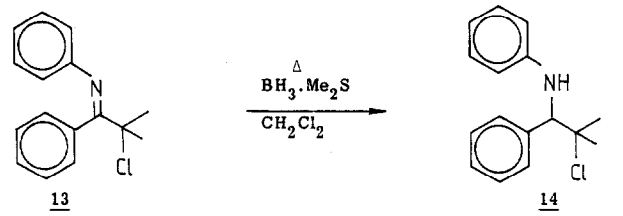
Table I : Electrophilic Reduction of α-Haloimines with Borane-methyl sulfide

Starting α-Haloimine	Molar Equiv. $BH_3.Me_2S$ (1M in CH_2Cl_2)	Reflux Time	Yield[a] of β-chloroamine
5	1	7h	6:80%[b]
7	2	36h	8:92%
9	2	120h	10:89%
13	2	70h	14:98%
15	1.5	18h	16:90%
17	2	18h	20:95%
18	2	23h	21:95%[c]
19	6	48h	22:96%
25	6	16h	26:90%[d]

[a] Yield of the crude compound. These β-chloroamines are usually obtained with sufficient purity (> 95%) for further elaboration. They can be extra purified by passing through a short silicagel column with ether : chloroform (1:1).
[b] Bp. 55-56°C/16 mmHg (61%)
[c] Mp. 85°C (EtOH)
[d] Mp. 90°C.

A number of β,β,β-trichloroamines have been reported to exhibit interesting physiological activity,[10-20,28] e.g. insect sterilant, insecticide, fungicide, bactericide and anti-tumor activity. The synthetic procedure for the preparation of β-haloimines, disclosed in this paper, was utilized for the preparation of such a known insecticidal compound. Condensation of

p-methoxyacetophenone 23 with p-anisidine gave N-[1-(4-methoxyphenyl)-1-ethylidene]-4-methoxyaniline 24, which was trichlorinated in the α-position with N-chlorosuccinimide in carbon tetrachloride to afford α,α,α-trichloro-



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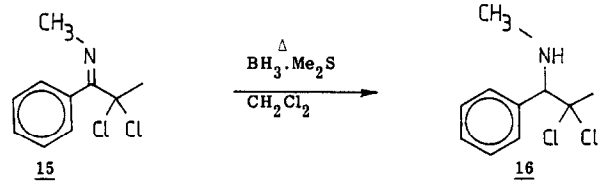

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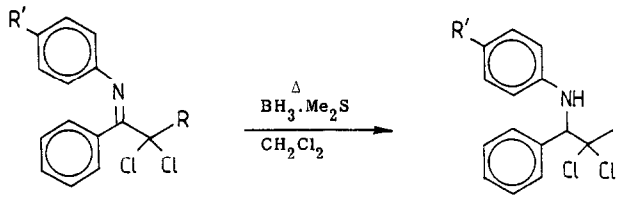
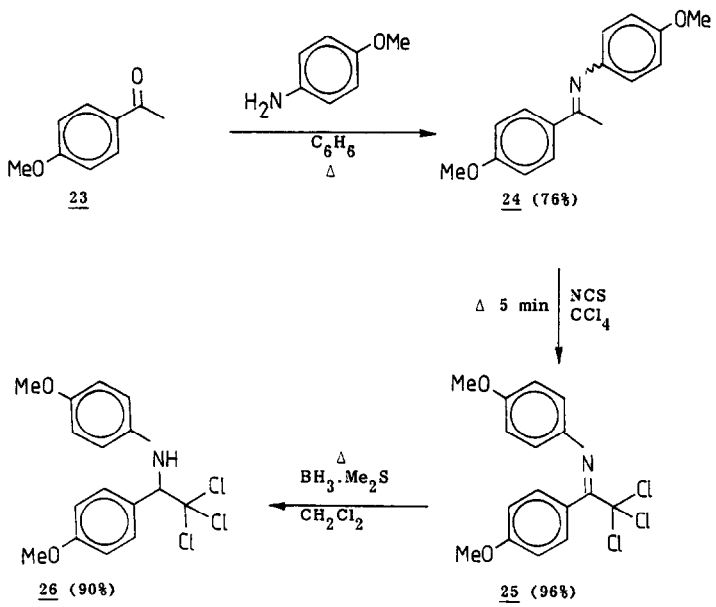


17 R=Me; R'=H
18 R=R'=Me
19 R=Et; R'=H

20 R=Me; R'=H
21 R=R'=Me
22 R=Et; R'=H

ketimine 25. Electrophilic reduction of this α,α,α-trichloroketimine 25 with borane-methyl sulfide complex in dichloromethane under reflux gave N-(4-methoxyphenyl)-N-[2,2,2-trichloro-1-(4-methoxyphenyl]ethylamine 26. This β,β,β-trichloroamine 26 displays insecticidal properties, comparable to DDT,[17,18] towards the housefly and mosquito larvae but the biodegradability is much higher.[21]

The present method for the synthesis of β-chloroamines from α-haloimines comprises an easy procedure. The electrophilic reduction most probably entails initial complexation of borane at the imino nitrogen, followed by a hydride shift from boron to the imino carbon. The resulting amine-boron complex is finally decomposed by aqueous sodium hydroxide during the workup procedure.



Experimental Part

Infrared spectra were recorded with a Perkin Elmer model 1310 spectrophotometer. 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 Matt 112 mass spectrometer (70 eV) using a direct inlet system or by using a GC-MS coupling (capillary column). Preparative GC was performed with stainless steel or glas columns (3m, SE 30) or a Varian 1700 gas chromatograph. α-Halogenated aldimines 5,[22] 7[23] and 9[24] were prepared as described previously. α-Chloroketimine 13 was prepared (quantitative yield) by chlorination with N-chlorosuccinimide in carbon tetrachloride in similar way as previously described for the α,α-dichlorination of alkyl aryl ketimines.[25] α-Chloroketimine 13 (purity >97%) was used directly in the next reduction step.

N-(2-chloro-2-methyl-1-phenyl-1-propylidene)aniline 13 :
^1H NMR (CCl_4) : 1.83 (6H,s,Me_2); 6.3-7.1 (5H,m,NC_6H_5); 7.10 (5H,s,$C_6H_5C{=}N$). IR (NaCl) : 1638 cm^{-1} ($\nu_{C=N}$). Mass spectrum m/z (%) : 257/9 (M^+; 2); 221(4); 222(4); 180(100); 77(66); 51(20).

α,α-Dichloroketimines 15, 17, 18 and 19 were synthesized by chlorination of the corresponding alkyl aryl ketimines with N-chlorosuccinimide in carbon tetrachloride,[25] or by condensation of the corresponding α,α-dichloroketone with the appropriate primary amine in the presence of titanium(IV) chloride.[24]

General Procedure for the Electrophilic Reduction of α-Chloroimines

A solution of 0.05 mol of the appropriate α-chloroimine in 100 ml of dichloromethane, containing 0.05-0.3 mol of borane-methyl sulfide complex (1M solution), was refluxed for the time indicated in Table I. After cooling, the reaction mixture was stirred with 100 ml of 2N aqueous sodium hydroxide at room temperature for 30 minutes. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated in vacuo to leave the corresponding β-chloroamines in good yields (purity >96%). Most β-chloroamines are very viscous oils except 21 and 26 which are solid compounds. Because of the thermal lability of β-chloroamines, most of these compounds were not distilled as they were sufficiently pure (>96%) for further elaboration. They can be additionally purified by passing them over a short silica gel column using ether : chloroform (1:1) as eluent.

N-t-Butyl-N-(2-chloro-2-methyl)-1-propylamine 6 :
^1H NMR (CCl_4) δ 1.06 (9H,s,t-Bu); 0.95 (1H,s,br,NH); 1.55 (6H,s,Me_2); 2.66 (2H,s,CH_2). IR (NaCl) : no ν_{NH} visible. Mass spectrum m/e (%) 163/5 (M^+; 1); 148/50(8); 128(1); 127(1); 112(16); 86(33); 72(16); 70(4); 58(13); 57(22); 56(5); 55(13); 41(11), 30 (100; $CH_2=\overset{+}{N}H_2$). ^{13}C NMR ($CDCl_3$) : 29.22 (q,Me_3); 30.50 (q,Me_2); 49.93 (s,$\underline{C}Me_3$); 55.53 (t,$\underline{C}_2N$); 71.55 (s,$\underline{C}$-Cl).
Found : Cl, 21.5; N, 8.5. $C_8H_{18}ClN$ requires Cl, 21.7; N, 8.6%.

N-t-Butyl-N-(2,2-dichloro)-1-butylamine 8 :
^1H NMR (CCl_4) δ 1.12 (9H,s,t-Bu); 1.1 (3H,covered by t-Bu signal,Me); 2.28 (2H,q,J=7Hz,$C\underline{H}_2$Me); 3.12 (2H,s,broadened,CH_2N); NH invisible. IR (NaCl) : no ν_{NH} visible. Mass spectrum m/z (%) : no M^+; 182/4/6(4); 146/8(5); 106/8(5); 86 (32; $CH_2=\overset{+}{N}H$-t-Bu); 70(4); 58(20); 57(24); 56(4); 55(4); 42(10); 41(16); 30 (100; $CH_2=\overset{+}{N}H_2$).
Found : Cl, 35.6; N, 7.0. $C_8H_{17}Cl_2N$ requires Cl, 35.8; N, 7.1%.

N-t-Butyl-N-(2,2,2-trichloro)ethylamine 10 :
^1H NMR (CCl_4) δ 1.13 (9H,s,t-Bu); 1.4 (1H,s,broad,NH); 3.41 (2H,s,NCH_2). IR (NaCl) : 3340 cm^{-1} (ν_{NH}). Mass spectrum m/z (%) : no M^+; 188/90/92/94 (15); 152/54/56(14); 117/19(7); 112/14/16(16); 86 (34; $CH_2=\overset{+}{N}H$-t-Bu); 77(12); 57(69); 56(20); 42(27); 41(61); 36(39); 30 (100; $CH_2=\overset{+}{N}H_2$).
Found : Cl, 52.1; N, 6.9. $C_6H_{12}Cl_3N$ requires Cl, 52.0; N, 6.85%.

N-Phenyl-N-(2-chloro-2-methyl-1-phenyl)-1-propylamine 14

^{1}H NMR ($CDCl_3$) δ 1.46 and 1.75 (each 3H,each s,Me_2); 4.33 (1H,s,broadened, CH-N); 4.6 (1H,s,broad,NH); 6.4-7.5 (10H,m,2xC_6H_5). IR (NaCl) : 3400 cm^{-1} (ν_{NH}). Mass spectrum m/z (%) : 259/61 (M^+; 0.2); 223(3); 222(1); 182(100); 167(3); 132(1); 131(2); 120(1); 119(1); 118(1); 117(1); 116(1); 115(1); 105(3); 103(77); 91(5); 77(84); 51(3).

Found : Cl, 13.7; N, 5.5. $C_{16}H_{18}ClN$ requires Cl, 13.65; N, 5.4%.

N-Methyl N-(2,2-dichloro-1-phenyl)-1-propylamine 16

^{1}H NMR (CCl_4) δ 2.01 (3H,s,$MeCCl_2$); 2.26 (3H,s,NMe); 3.90 (1H,s,CH-N); 7.1-7.6 (5H,m,C_6H_5); NH invisible. Mass spectrum m/z (%) : no M^+; 120 (100; $PhCH=\overset{+}{N}HMe$); 91(1); 77(1); 56(6); 51(1); 42(7); 36(2).

Found : Cl, 32.6; N, 6.3. $C_{10}H_{13}Cl_2N$ requires Cl, 32.5; N, 6.4%.

N-Phenyl-N-(2,2-dichloro-1-phenyl)-1-propylamine 20

This compound was described in a previous communication.[26]

N-(4-methylphenyl)-N-(2,2-dichloro-1-phenyl)-1-propylamine 21

^{1}H NMR ($CDCl_3$) δ 2.13 and 2.20 (each 3H,each s,$MeCCl_2$ and p-CH_3); 4.71 (2H, s,broad,NH-CH); 6.54 (2H,d,J=8.5Hz,ortho protons with respect to N); 6.93 (2H,d,J=8.5Hz,meta protons with respect to N). IR (NaCl) : 3385 cm^{-1} (ν_{NH}). Mass spectrum m/z (%) : 293/5/7 (M^+; 3); 196 (100; $Ph-CH=\overset{+}{N}H$-p-tolyl); 194(4); 152(2); 132(5); 118(4); 117(4); 116(3); 115(8); 106(4); 105(2); 104(2); 103(3); 91(37); 89(5); 77(10); 65(18); 63(4); 51(6); 43(12); 41(7); 40(10); 39(10).

Found : Cl, 24.2; N, 4.9. $C_{16}H_{17}Cl_2N$ requires Cl, 24.1; N, 4.8%.

N-Phenyl-N-(2,2-dichloro-1-phenyl)-1-butylamine 22

^{1}H NMR ($CDCl_3$) δ 1.23 (3H,t,J=6.5Hz,CH_3); 2.2 (2H,m,CH_2); 4.80 (2H,s,broad, NH-CH); 6.5-7.6 (10H,m,2xPh). IR (NaCl) : 3400 cm^{-1} (ν_{NH}). Mass spectrum m/z (%) : 293/5/7 (M^+; 1); 222(1); 221(3); 206(3); 182 (100; $Ph-CH=\overset{+}{N}HPh$); 180(5); 176(3); 132(6); 131(6); 129(6); 128(6); 115(10); 104(26); 93(5); 91(13); 77(59); 65(6); 51(16). ^{13}C NMR ($CDCl_3$) δ 9.43 (q,Me); 38.86 (t,CH_2); 68.75 (d,CHN); 98.58 (s,CCl_2); 113.85 (d); 118.34 (d); 127.96 (d); 128.26 (d); 129.12 (d); 129.20 (d); 137.48 (s); 146.30 (s).

Found : Cl, 24.2; N, 4.9. $C_{16}H_{17}Cl_2N$ requires Cl, 24.1; N, 4.8%.

N-(4-Methoxyphenyl)-N-[2,2,2-trichloro-1-(4-methoxyphenyl)]-ethylamine 26

^{1}H NMR ($CDCl_3$) δ 3.67 and 3.74 (each 3H,each s,2xOMe); 4.95 (1H,s,broad,CH-N); 4.4 (1H,s,broad,NH); 6.62 and 6.75 (each 2H,AB,J=9Hz,N-anisyl); 7.50 and 6.85 (each 2H,AB,J=8.5Hz,C-anisyl). Mass spectrum m/z (%) : no M^+; 270(7);

242(11); 240(8); 135(26); 121(11); 40(100). ^{13}C NMR ($CDCl_3$) δ 55.12 (q,OMe); 55.53 (q,OMe); 74.02 (d,CH-N); 102.88 (s,CCl_3); 113.49 (d); 114.77 (d); 115.84 (d); 128.04 (s,Cl_3C-CH-C=); 130.66 (d); 139.82 (s,N-C=); 153.14 (s,O-C=); 159.98 (s,O-C=).

Found : Cl, 29.4; N, 3.8. $C_{16}H_{16}Cl_3NO_2$ requires Cl, 29.5; N, 3.9%.

Synthesis of N-[1-(4-methoxyphenyl)-1-ethylidene]-p-anisidine 24

p-Methoxyacetophenone 23 (0.1 mol) was condensed with p-anisidine (0.3 mol) in the presence of titanium (IV) tetrachloride (0.055 mol) in benzene under reflux (2h) according to the method of H. Weingarten.[27] The ketimine 24 was obtained in 78% yield, bp. 177-185°C/0.01 mmHg, mp. 126°C. ^1H NMR ($CDCl_3$) δ 2.18 (3H,s,CH_3); 3.76 (3H,s,OMe); 3.80 (3H,s,OMe); 6.5-7 (4H,m,p-anisyl protons); 6.88 (2H,d,J=8.5Hz,meta protons with respect to C=N); 7.88 (2H,d, J=8.5Hz,ortho protons with respect to C=N). IR (NaCl/$CHCl_3$) : 1625 cm^{-1} ($\nu_{C=N}$). Mass spectrum m/z : 255 (M^+, 61); 240(100); 230(7); 107(10); 92(14); 77(20); 64(11).

Found : N, 5.4. $C_{16}H_{17}NO_2$ requires N, 5.5%.

Synthesis of N-[2,2,2-trichloro-1-(4-methoxyphenyl)-1-ethylidene]-p-anisidine 25

A solution of 1.53 g (0.006 mol) of ketimine 24 in 20 ml carbon tetrachloride was treated with 2.64 g of N-chlorosuccinimide (0.0198 mol). The mixture was refluxed for five minutes and further stirred at room temperature for one hour. Filtration of the precipitated succinimide and evaporation of the solvent gave 2.05 g (96%) of the α,α,α-trichloroketimine 25, which solidified upon standing. Recrystallization was performed in ether-pentane (1:1) at -20°C to give the pure compound, mp. 75°C.

^1H NMR (CCl_4) : 3.73 (3H,s,OMe); 3.81 (3H,s,OMe); 6.70 (4H,s,NC_6H_4); 6.82 (2H,d,AB,J=8.5Hz,meta protons with respect to C=N); 7.30 (2H,d,AB,J=8.5Hz, ortho protons with respect to C=N). IR (NaCl/CCl_4) : 1645 cm^{-1} ($\nu_{C=N}$). ^{13}C NMR ($CDCl_3$) δ 55.17 (q,OMe); 55.08 (q,OMe); 99.16 (s,CCl_3); 162.39 (s,C=N); 124.18 (s,=C-C=N); 131.44 (d); 113.58 (d); 113.81 (d); 157.26 (s,MeO-C=); 160.14 (s,MeO-C=); 122.96 (d); 140.37 (s,C=N-C=). Mass spectrum m/z (%) : 357/59/61/63 (M^+; 2); 223/25/27(2); 240(100); 225(6); 197(6); 135(12); 120(6); 107(3); 99(3); 92(14); 77(19); 64(12); 63(7).

Found : Cl, 29.8; N, 4.0. $C_{16}H_{14}Cl_3NO_2$ requires Cl, 29.7; N, 3.9%.

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* N. De Kimpe : "Onderzoeksdirecteur" (Research Director) of the Belgian "Nationaal Fonds voor Wetenschappelijk Onderzoek" (National Fund for Scientific Research).

£ C. Stevens : "Aspirant" of the organization mentioned above.
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