

[Chem. Pharm. Bull.
29(3) 616-622 (1981)]

Reduction of 2,2,2-Trichloroethylamines with Lithium Aluminum Hydride

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(Received July 9, 1980)

It has been found that the lithium aluminum hydride reduction of 2,2,2-trichloroethylamines occurs to give amines with rearranged carbon skeletons or aziridines, depending on the precise substrate structure.

Keywords—2,2,2-trichloroethylamines; lithium aluminum hydride; rearrangement; aziridines; ring expansion

As a part of our continuing interest in the chemistry of 2,2,2-trichloroethylamines,¹⁾ we report in the present paper details of the lithium aluminum hydride reduction of these compounds. The reaction is of interest in that it occurs with rearrangement of the carbon skeleton to give amines with rearranged structures or aziridines.

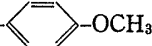
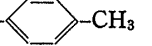
The lithium aluminum hydride reduction was initiated with representative 2-chlorinated amines *i.e.*, 2,2,2-trichloro- (1a), 2,2-dichloro- (2a) and 2-chloro-N,N-dimethyl-1-phenylethylamine (3). Each of the three substrates gave the same product (4a) with rearrangement of the carbon skeleton, as shown in Table I.

TABLE I.

$\text{Ph}-\underset{\text{X}}{\text{CH}}-\text{N}(\text{CH}_3)_2 \xrightarrow[\text{reflux in Et}_2\text{O}]{\text{LiAlH}_4 \text{ (3 molar equiv.)}} \text{Ph}-\text{CH}_2\text{CH}_2-\text{N}(\text{CH}_3)_2$		
1a, 2a, 3		4a
	Reaction time (hr)	Yield (%)
1a X = CCl ₃	30	50
2a X = CHCl ₂	24	59
3 X = CH ₂ Cl	3	83

TABLE II.

$\text{CCl}_3\overset{\text{R}^1}{\underset{\text{R}^2}{\text{C}}}-\text{NR}^3\text{R}^4 \xrightarrow{\text{LiAlH}_4^a)} \text{R}^1\overset{\text{R}^2}{\text{CH}}\text{CH}_2-\text{NR}^3\text{R}^4, \text{CH}_3\overset{\text{R}^1}{\underset{\text{R}^2}{\text{C}}}-\text{NR}^3\text{R}^4, \text{R}^1\overset{\text{R}^2}{\text{C}}-\text{N}-\text{R}^4$					
	1b—q	4b—m	5a—b	6a—d	
Subst.	R ¹	R ²	NR ³ R ⁴	Reaction time (hr)	Product (Yield ^{b)} %)
1b		-(CH ₂) ₄ -		2	4b(75)
1c		-(CH ₂) ₄ -		3	4c(51)
1d	(CH ₃) ₂ CH	H		20	4d(26), 5a(60)
1e	(CH ₃) ₂ CH	H		48	4e(45), 5b(29)
1f	C ₆ H ₅	H		300 ^{c)}	4f(54)
1g	C ₆ H ₅	H		46	4g(63)

Subst.	R ¹	R ²	NR ³ R ⁴	Reaction time (hr)	Product (Yield ^b %)
1h	C ₆ H ₅	H	N< $\begin{smallmatrix} \text{CH}_3 \\ \text{CH}_2\text{C}_6\text{H}_5 \end{smallmatrix}$	150	4h (36)
1i	-(CH ₂) ₅ -		NHCH(CH ₃) ₂	10	6a (65)
1j	-(CH ₂) ₅ -		NH- 	8	6b (67)
1k	(CH ₃) ₂ CH	H	NHCH(CH ₃) ₂	20	6c (71)
1l	(CH ₃) ₂ CH	H	NH- 	20	6d (70)
1m	C ₆ H ₅	H	NHCH(CH ₃) ₂	20	4i (67)
1n	C ₆ H ₅	H	NH- 	30	4j (74)
1o	C ₆ H ₅	H	NHCH ₃	10	4k (71)
1p	C ₆ H ₅	H	NH- 	20	4l (71)
1q	C ₆ H ₅	H	NH- 	20	4m (55)

a) Conditions: reflux in ether. Molar ratio: LiAlH₄/Subst. = 3.

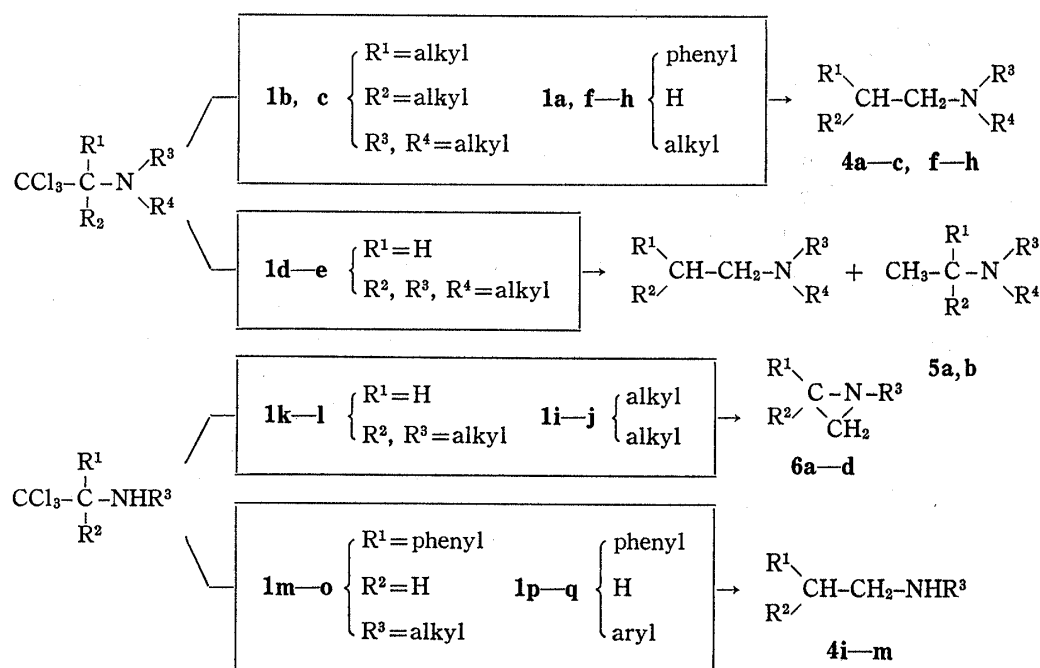
b) Based on the product actually isolated.

c) In this run 6 molar equivalents of LiAlH₄ was used.

Compound **1a** was prepared by the reaction between N,N,N',N'-tetramethylbenzylidenediamine and trichloroacetic acid, and **2a** was prepared by the reaction of **1a** with lithium aluminum hydride reduction, as described later. A preparation of **3** has been reported,²⁾ but it is rather laborious.

The lithium aluminum hydride reduction of 2,2,2-trichloroethylamines is of great potential interest, because many types of compounds are readily obtainable by the reactions of enamines, N,N'-alkylidenediamines and Schiff bases with trichloroacetic acid.

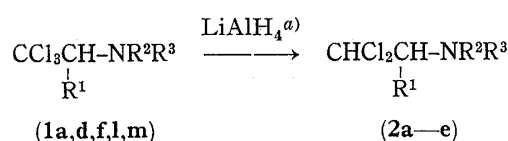
The lithium aluminum hydride reduction of 2,2,2-trichloroethylamines, **1b—q**, of various structures was examined under reflux in ether, with the results shown in Table II. Three classes of reactions occurred to give amines of rearranged (**4a—m**) and non-rearranged (**5a, b**) structures and aziridines (**6a—c**). The following general sequences can be written. The method is certainly useful for syntheses of these amines, the nature of the product being controlled by the nature of R¹, R², R³ and R⁴ of the amine substrates.



The rearranged and non-rearranged amines, **4a—m** and **5a, b**, were identified by ^1H -nuclear magnetic resonance (NMR) spectroscopy (see Table IV). The aziridines, **6a—d**, were identified by ^{13}C -NMR spectroscopy (see Table V); the chemical shifts of C^2 and C^3 at high magnetic field provided strong evidence for the aziridine structures.

In the experiments in Table II, the NMR spectra of the materials produced at earlier reaction times were checked by NMR measurement. 2,2-Dichloroethylamines were detected as intermediates in the runs with the substrates **1a** and **1d—o** (the methine proton of the dichloromethyl moiety appeared as a doublet in the cases of $\text{R}^1=\text{H}$ or as a singlet in the cases of $\text{R}^1, \text{R}^2=\text{alkyl}$ at 5.8—6.2 ppm in the NMR spectra). Actually, the reactions of **1a, 1d, 1f, 11** and **1m** for shorter times, with less lithium aluminum hydride, gave the corresponding 2,2-dichloroethylamines in considerable yields (see Table III). Data for the assignment of these products are listed in Table VI.

TABLE III.



Subst.	R^1	NR^2R^3	Molar ratio ($\text{LiAlH}_4/\text{Subst.}$)	Reaction time (hr)	Product (Yield ^b) %
1d	$(\text{CH}_3)_2\text{CH}$		1.5	6	2b (46)
1a	C_6H_5	$\text{N}(\text{CH}_3)_2$	3	4	2a (58)
1f	C_6H_5		3	3.5	2c (54)
11	$(\text{CH}_3)_2\text{CH}$	$\text{NH}-\langle\text{cyclohexyl}\rangle$	1.5	1.5	2d (41)
1m	C_6H_5	$\text{NHCH}(\text{CH}_3)_2$	3	1	2e (56)

^a) Conditions: reflux in ether.

^b) Based on the product actually isolated.

The mechanism of the lithium aluminum hydride reduction may be as shown in Chart 1 and 2. The rearrangements of the substrates, **1m—q**, possessing secondary amine moieties may involve aziridine intermediates (Chart 1), and those of **1a—h**, possessing tertiary amine moieties, may involve aziridinium salt intermediates (Chart 2). This view is strengthened by the actual formation of aziridines from **1i—l**. The aziridines or aziridinium may undergo attack of hydride with ring opening to give the amine products. The attack of hydride is selective toward C^2 or C^3 of the aziridine rings, whichever is more electron-deficient. When C^2 is attacked by hydride, nonrearranged products are formed (see Chart 2), as illustrated by some of the products from **1d** and **1e**. A 1-phenyl-substituent renders C^3 electron-deficient. A 2-chloro-substituent makes C^2 electron-deficient, but the effect of the degree of hydrogen substitution of the original 2-chloro-substituents on the attack of hydride is obscure, and may depend upon the substrate structure.

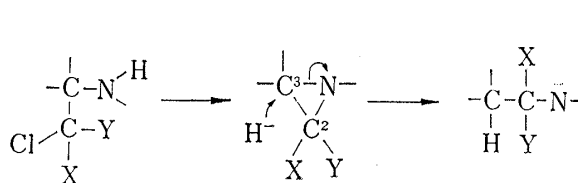


Chart 1

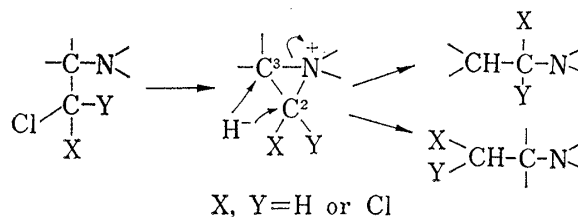
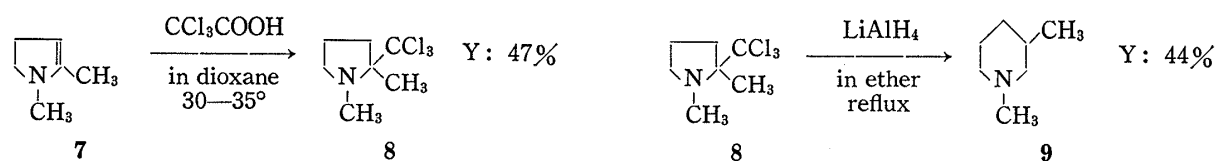


Chart 2

In view of the synthetic significance of the reductive rearrangement, the ring expansion of a pyrroline derivative was examined as a potentially interesting application.



The reaction of 1,2-dimethyl-4,5-dihydropyrrole (7) with trichloroacetic acid gave 1,2-dimethyl-2-trichloromethylpyrrolidine (8), which underwent reductive rearrangement upon treatment with lithium aluminum hydride to give a six-membered 1,3-dimethylpiperidine (9). Further examples of the ring expansion are under investigation.

Experimental

The reaction periods and yields in the lithium aluminum hydride reduction are recorded in Tables I, II and III. Physical, spectral and analytical data for the reaction products are recorded in Tables IV, V and VI.

2,2,2-Trichloroethylamines (1a—q)—The materials used for the lithium aluminum hydride reduction were prepared by the reactions of Schiff bases, N,N'-alkyldenediamines and enamines with trichloroacetic acid according to the reported procedures.^{1,3-7} Only 1i has not been described previously, and its physical and analytical data are described below. N-Isopropyl-1-trichloromethylcyclohexylamine Hydrochloride (1i): mp 109—111°. *Anal.* Calcd for C₁₀H₁₉Cl₃N: C, 40.70; H, 6.49; N, 4.75. Found: C, 40.67; H, 6.38; N, 4.86.

Reactions of 1a—q Leading to 4a—m, 5a—b and 6a—d (see Table II)—General Procedure: A cooled solution of 0.033 mol of a 2,2,2-trichloroethylamine (1a—q) in 70 ml of dry ether was treated with 0.1 mol (3.8 g) of LiAlH₄ in small portions with stirring. After the addition, the reaction mixture was refluxed with stirring. Aqueous NaCl was then added to the mixture to decompose excess reagent. The separated ethereal solution was dried over MgSO₄ and the solvent was removed by evaporation. In the runs with 1a—c and 1f—q, the products, 4a—c and 4f—m, were obtained by distillation of the resulting oily residue. In the runs with 1d and 1e, the resulting residue was chromatographed through Al₂O₃ with benzene as an eluent to give the products, 4d—e and 5a—b.

Reactions of 2a and 3 Leading to 4a (see Table I)—The reaction mixture were worked up by the procedures described for the above experiments with 1a—q.

Reactions of 1a, 1d, 1f and 1l—m Leading to 2a—e (see Table III)—General Procedure: A cooled solution of 0.033 mol of a 2,2,2-trichloroethylamine (1a, 1d, 1f and 1l—m) in 70 ml of dry ether was treated with LiAlH₄ (the amount of which is listed in Table III) in small portions with stirring. The reaction mixture was then refluxed with stirring. The reaction mixture was worked up by the procedure described for the experiments with 1a—q. In the runs with 1a and 1f, the products, 2a and 2c, were obtained by recrystallization of the resulting solid residues. In the runs with 1d, 1l and 1m, the products, 2b, 2d and 2e, were obtained by distillation of the resulting residues under reduced pressure. Compounds 2b and 2c were also identified as their HClO₄ salts.

1,2-Dimethyl-2-trichloromethylpyrrolidine (8)—A solution of 11.7 g (0.072 mol) of CCl₃COOH in 20 ml of dry dioxane was added dropwise to a solution of 5.8 g (0.06 mol) of 1,2-dimethyl-4,5-dihydropyrrole (7) in 40 ml of dry dioxane with stirring at 30—35°. After the addition, the reaction mixture was heated at 30—35° with stirring for 3.5 hr until evolution of CO₂ ceased. The solvent was removed by evaporation under reduced pressure and the residue was dissolved in benzene. The benzene solution was washed with aqueous KHCO₃ and dried over MgSO₄. Removal of the benzene gave an oily residue which was distilled under reduced pressure to give the product (8); yield 6.1 g (47%), bp 80—82°/10 mmHg, mp 55—57°. NMR ppm (CDCl₃): 3.50 (2H, m, >NCH₂—), 2.56 (3H, s, NCH₃), 2.38—1.98 (2H, m, —CH₂CH₂N<), 1.96—1.59 (2H, m, —CH₂—CCH₃), 1.50 (3H, s, >CCH₃). *Anal.* Calcd for C₇H₁₂Cl₃N: C, 38.83; H, 5.59; N, 6.47. Found: C, 38.84; H, 5.54; N, 6.40.

1,3-Dimethylpiperidine (9)—A cooled solution of 5.7 g (0.026 mol) of 8 in 60 ml of dry ether was treated with 3.0 g (0.08 mol) of LiAlH₄ in small portions with stirring. After the addition, the reaction mixture was refluxed with stirring for a further 5 hr. Aqueous NaCl was then added to the mixture to decompose excess reagent. The separated ethereal solution was dried over MgSO₄ and the solvent was removed by evaporation. The resulting residue was distilled to give 9; yield 1.3 g (44%). This product was identified as 1,3-dimethylpiperidine, bp 123—125°, by comparison of its infrared (IR) and NMR spectra with those of an authentic specimen prepared by another route.

Acknowledgement The authors are grateful to Prof. Yasuaki Okumura, Faculty of Science, Shizuoka University, for ^{13}C -NMR spectral measurement. Thanks are also due to Dr. M. Uchida and Mrs. K. Kitamura of the Analysis Center of this college for mass spectral measurements and elemental analyses.

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