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Reactions of 2,2,2-Trichloroethylamines with Grignard Reagents and Alkyllithiums

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2,2,2-Trichloro- and 2,2-dichloroethylamines were found to suffer monoalkylation with Grignard reagents and alkyllithiums giving, in the main, chain-lengthened β,γ- or α,β-unsaturated amines. Which product is formed depends upon the individual structures of the substrates and organometallic compounds.

Keywords—2,2,2-trichloroethylamine; 2,2-dichloroethylamines; β,γ-unsaturated amine; enamine; Grignard reagent; alkyllithium

The chemical properties of 2,2,2-trichloroethylamines with anionic reagents are of interest, as our previous papers[1] on the reactions of the amines with *tert*-butoxide and lithium aluminum hydride have illustrated their versatility and usefulness in organic synthesis. As a part of our continuing studies on the reactivities of chlorine atoms at the 2-position of amines, we wish to report in the present paper the reactions of 2,2,2-trichloro- and 2,2-dichloroethylamines with Grignard reagents and alkyllithiums. These reactions provide useful synthetic procedures to obtain chain-lengthened unsaturated amines.

Several 2,2,2-trichloroethylamines (**1a**—**e**) were allowed to react with Grignard reagents and alkyllithiums in ether, and the results are summarized in Table I.

Ethyl- and butylmagnesium bromide, possessing representative straight chain alkyl moieties, reacted to give β,γ-unsaturated amines (**2a**—**e**), which were proved to be mixtures of *E* and *Z* isomers by gas–liquid chromatographic (GLC) analysis and ^{13}C-nuclear magnetic resonance (CMR) measurements. Since alternative known methods for synthesizing β,γ-unsaturated amines are relatively cumbersome, the reaction should be practically useful.

The corresponding alkyllithiums, ethyl- and butyllithium, showed a somewhat decreased selectivity in the formation of β,γ-unsaturated amines. Ethyllithium gave only β,γ-unsaturated amines, but butyllithium gave α,β- and β,γ-unsaturated amines as inseparable mixtures, as determined from their infrared (IR) and proton nuclear magnetic resonance (PMR) spectra, which exhibit bands and signals corresponding to those of α,β-unsaturated amines in addition to those of β,γ-unsaturated amines. In the cases of *tert*-butyl- and isopropylmagnesium bromide, possessing α-branched alkyl moieties, no alkylation occurred with 2,2-dichloroamines (**3a**, **b** and **4a**, **b**). Reaction with *tert*-butyllithium, however, gave β,γ-unsaturated amines (**5a**—**c**). Phenylmagnesium bromide was inert, whereas phenyllithium gave β,γ-unsaturated amines (**6a**—**c**).

2,2-Dichloroethylamines (**3a**, **b**) were inert to alkylmagnesium bromides, but reacted with butyl, *tert*-butyl and phenyllithium. The results are summarized in Table II. As can be seen, the products of these reactions were identical with those of the reactions of 2,2,2-trichloroethylamines (**3a**, **b**).

The most likely mechanism can be depicted as shown in Chart 1. In the first step, from **1** to **7**, one chlorine of trichloromethyl is metalated by alkyllithium or Grignard reagent, which acts as a base abstracting a chlorine cation (analogous examples[2] have been reported). As shown in Table I, alkyllithiums reacted much faster than Grignard reagents. This appears to be due to the stronger basicity of the former. The next step may be a substitution of one chlorine of **7** by alkyl to give **8**, induced by nucleophilic attack of alkylmetal. In the cases of Grignard reagents possessing α-branched alkyls, *tert*-butyl- and isopropyl, this reaction may

be sterically hindered, so that actually 2,2-dichloroethylamines **3** are obtained as the hydrolysis products of **7**. As proposed in the previous paper,[2b] the alkylated **8** presumably then suffers elimination of metal chloride to form a carbenoid intermediate, followed by isomerization of this intermediate. In the cases of *tert*-butyl- and phenyllithium, β,γ-unsaturated amines **2** may be kinetically more favored than that of α,β-unsaturated amines, **5**. There is a prototropic equilibrium between **2** and **5**, and the latter is considered to be thermodynamically more stable, since isomerization from **2** to **5** is known to occur in the presence of *tert*-butoxide.[3] Therefore, the production of **5** together with **2** only in the case of butyllithium may be interpreted as a result of thermodynamic control, because of the stronger basicity of butyllithium.

TABLE I. Reaction[a] of $CCl_3CHN\begin{matrix}R^1\\R^2\end{matrix}$ (**1a—e**)

Subst. No.	$N\begin{matrix}R^1\\R^2\end{matrix}$	R^3	Reagent	React. temp. (°C)	React. time (h)	No.	Product	Yield[b] (%)
1a		H	C_2H_5MgBr	30—32	24	**2a**	$CH_3CH{=}CHCH_2$  $(E+Z)$	42
1a		H	C_2H_5Li	10—15	2	**2a**	$CH_3CH{=}CHCH_2$ $(E+Z)$	31
1a		H	C_4H_9MgBr	30—32	24	**2b**	$C_3H_7CH{=}CHCH_2$  $(E+Z)$	50
1a		H	C_4H_9Li	10—15	2		$C_3H_7CH{=}CHCH_2$ $(E+Z)$ $C_4H_9CH{=}CH$ (E)	48
1a		H	$(CH_3)_2CHMgBr$	30—32	24	**3a**	$CHCl_2CH_2$ 	51
1a		H	$(CH_3)_3CMgBr$	30—32	16	**3a**	$CHCl_2CH_2$ 	61
1a		H	$(CH_3)_3CLi$	10—15	2	**5a**	$(CH_3)_3CCH{=}CHN$  (E)	41
1a		H	C_6H_5Li	10—15	2	**6a**	$C_6H_5CH{=}CHN$ (E)	46
1b		H	C_2H_5MgBr	30—32	16	**2c**	$CH_3CH{=}CHCH_2N$  $(E+Z)$	27
1b		H	C_2H_5Li	10—15	2	**2c**	$CH_3CH{=}CHCH_2N$ $(E+Z)$	32
1b		H	C_4H_9MgBr	30—32	24	**2d**	$C_3H_7CH{=}CHCH_2N$  $(E+Z)$	47
1b		H	C_4H_9Li	10—15	2		$C_3H_7CH{=}CHCH_2N$ $(E+Z)$ $C_4H_9CH{=}CHN$ $(E+Z)$	56
1b		H	$(CH_3)_3CMgBr$	30—32	16	**3b**	$CHCl_2CH_2N$ 	38

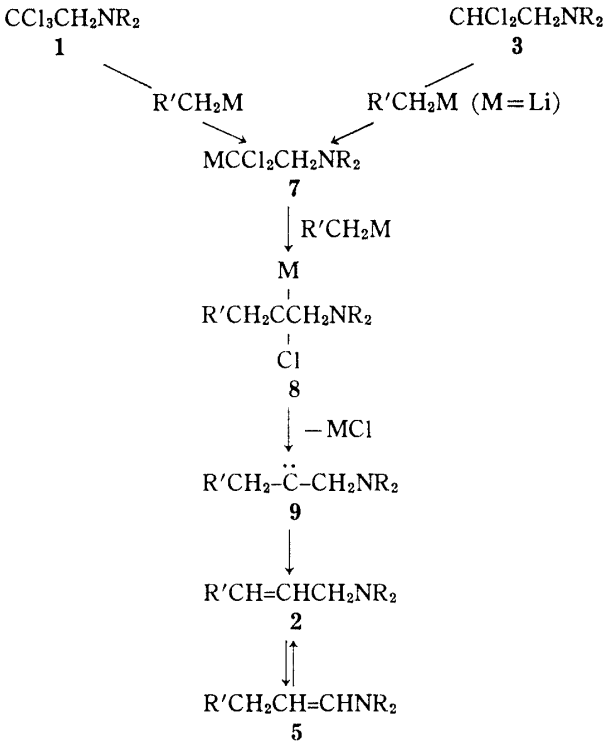
Subst. No.	$N<^{R^1}_{R^2}$	R^3	Reagent	React. temp. (°C)	React. time (h)	No.	Product	Yield[b] (%)
1b		H	$(CH_3)_3CLi$	10—15	2	**5b**	$(CH_3)_3CCH{=}CH$  (*E*)	59
1b		H	C_6H_5Li	10—15	2	**6b**	$C_6H_5CH{=}CH$  (*E*)	42
1c	$N<^{CH_3}_{CH_2C_6H_5}$	H	C_4H_9MgBr	30—32	24	**2e**	$C_3H_7CH{=}CHCH_2N<^{CH_3}_{CH_2C_6H_5}$ (*E*+*Z*)	52
1c	$N<^{CH_3}_{CH_2C_6H_5}$	H	C_4H_9Li	10—15	2		$C_3H_7CH{=}CHCH_2N<^{CH_3}_{CH_2C_6H_5}$ (*E*+*Z*) $C_4H_9CH{=}CHN<^{CH_3}_{CH_2C_6H_5}$ (*E*)	61
1c	$N<^{CH_3}_{CH_2C_6H_5}$	H	$(CH_3)_3CLi$	10—15	2	**5c**	$(CH_3)_3CCH{=}CHN<^{CH_3}_{CH_5C_6H_5}$ (*E*)	59
1c	$N<^{CH_3}_{CH_2C_6H_5}$	H	C_6H_5Li	10—15	2	**6c**	$C_6H_5CH{=}CHN<^{CH_3}_{CH_2C_6H_5}$ (*E*)	55
1d		C_6H_5	$(CH_3)_3CMgBr$	30—32	72	**4a**	$CHCl_2CH$  (C_6H_5)	62
1e	$N(CH_3)_2$	C_6H_5	$(CH_3)_3CMgBr$	30—32	1.5	**4b**	$CHCl_2CHN(CH_3)_2$ C_6H_5	46

a) Molar ratio of RMgBr or RLi/subst. =3, solvent=Et_2O.
b) Based on the product isolated.

TABLE II. Reaction [a] of $CHCl_2CH_2N<^{R^1}_{R^2}$ (**3a, b**)

Subst. No.	$N<^{R^1}_{R^2}$	Reagent	No.	Product[b]	Yield (%)
3a		C_4H_9Li		$C_3H_7CH{=}CHCH_2N$  (*Z*+*E*) $C_4H_9CH{=}CHN$  (*E*)	69
3b		C_4H_9Li		$C_3H_7CH{=}CHCH_2N$  (*Z*+*E*) $C_4H_9CH{=}CHN$  (*E*)	51
3a		$(CH_3)_3CLi$	**5a**	$(CH_3)_3CCH{=}CHN$  (*E*)	51
3b		$(CH_3)_3CLi$	**5b**	$(CH_3)_3CCH{=}CHN$  (*E*)	61
3a		C_6H_5Li	**6a**	$C_6H_5CH{=}CHN$  (*E*)	31
3b		C_6H_5Li	**6b**	$C_6H_5CH{=}CHN$  (*E*)	38

a) Molar ratio of RLi/subst.=3, solvent=ether–hexane, reaction temperature=10—15°C, reaction time=2 h.
b) Based on the product isolated.



M=Li or MgBr, R'=CH_3 or $CH_3(CH_2)_2$

Chart 1. Plausible Mechanistic Paths for the Reactions with $R'CH_2Li$ and $R'CH_2MgBr$

Experimental

All boiling and melting points are uncorrected. IR spectra were taken on a Hitachi EPI-G2 spectrophotometer. PMR spectra were recorded on a Hitachi R-24 spectrometer and chemical shifts are given in ppm downfield from TMS. GLC analysis was carried out with a Hitachi 163 gas chromatograph using a column (3 mm × 1 m) packed with 10% SE-30 on Chromosorb W (80—100 mesh) and a flow rate of carrier gas (N_2) of 30 ml/min.

Reactions of 2,2,2-Trichloroethylamines (1a—c) with Butylmagnesium Bromide or Ethylmagnesium Bromide——General Procedure: A solution of Grignard reagent (freshly prepared from 0.1 mol of alkyl bromide and 0.1 g atom of magnesium in 70 ml of dry ether) was added dropwise to a cooled solution of 0.033 mol of 2,2,2-trichloroethylamine in 40 ml of dry ether with stirring. After completion of the addition, the reaction mixture was heated at 30—32°C with stirring. An aqueous solution of NaCl was added to the mixture. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined ethereal solution was dried over $MgSO_4$. After removal of ether, the resulting residue was distilled under reduced pressure to afford β,γ-unsaturated amine (**2a—e**). Physical and spectral data for the products are listed in Table III.

Reactions of 2,2,2-Trichloroethylamines (1a,b,d,e) with *tert*-Butylmagnesium Bromide or Isopropylmagnesium Bromide——General Procedure: A solution of Grignard reagent (freshly prepared from 0.1 mol of alkyl bromide and 0.11 g atom of magnesium in 70 ml of dry ether) was added dropwise to a cooled solution of 0.033 mol of 2,2,2-trichloroethylamine in 40 ml of dry ether with stirring. After completion of the addition, the mixture was heated at 30—32°C with stirring. The reaction mixture was worked up in the manner described for the above experiment. The products, **3a** and **3b**, were obtained by distillation under reduced pressure, and **4a** and **4b** were obtained by recrystallization of the crystalline residue.

The products **4a** and **4b** were identified as 2,2-dichloroethylamines from the good correspondence of their IR and NMR spectra with those of specimens prepared by the previously reported method.[1b] **3a**: bp 107—108°C (18 mmHg), PMR δ (in $CDCl_3$): 5.69 (1H, t, J=6.0 Hz, $CHCl_2$), 3.81—3.59 [4H, m, $O(CH_2)_2$], 2.97 (2H, d, J=6.0 Hz, $CHCl_2C\underline{H}_2$), 2.75—2.48 [4H, m, $N(CH_2)_2$]. *Anal.* Calcd for $C_6H_{11}Cl_2NO$: C, 39.15; H, 6.02; N, 7.61. Found: C, 38.95; H, 6.03; N, 7.61. **3b**: bp 96—97°C (25 mmHg), PMR δ (in $CDCl_3$): 5.68 (1H, t, J=6.0 Hz, $CHCl_2$), 2.99 (2H, d, J=6.0 Hz, $CHCl_2C\underline{H}_2$), 2.74—2.45 [4H, m, $N(CH_2)_2$], 1.08—1.34 (6H, m, $CH_2CH_2CH_2$). *Anal.* Calcd for $C_7H_{13}Cl_2N$: C, 46.17; H, 7.20; N, 7.69. Found: C, 46.08; H, 7.02; N, 7.54.

Table III. β,γ-Unsaturated Amines (**2a—e**)[a]

Compd. No.	bp (°C) (mmHg)	NMR[b] ($CDCl_3$) δ(ppm)	Formula	Analysis (%) Calcd (Found) C	H	N
2a	72—73 (17)	5.99—5.12 (2H, m, CH=CH), 3.83—3.56 (4H, m, CH_2OCH_2), 3.16—2.61 (2H, m, $CHC\underline{H}_2N$), 2.59—2.26 (4H, m, CH_2NCH_2), 1.79—1.53 (3H, m, CH_3)	$C_8H_{15}NO$	68.04 (67.74)	10.71 (11.09)	9.92 (9.68)
2b	92—93 (7)	5.65—5.35 (2H, m, CH=CH), 3.82—3.60 (4H, m, CH_2OCH_2), 3.11—2.85 (2H, m, $CHC\underline{H}_2N$), 2.56—2.34 (4H, m, CH_2NCH_2), 2.16—1.81 (2H, m, $C\underline{H}_2$-C=C), 1.39 (2H, se, J=6.0, $CHC\underline{H}_2N$), 0.92 (3H, t, J=6.0, CH_3)	$C_{10}H_{19}NO$	70.96 (71.08)	11.31 (11.27)	8.27 (8.32)
2c	64—65 (10)	5.75—5.35 (2H, m, CH=CH), 3.1—2.80 (4H, m, $CHC\underline{H}_2N$), 2.60—2.25 (4H, m, CH_2NCH_2), 1.80—1.30 (9H, $CH_2CH_2CH_2$ and CH_3)	$C_9H_{17}N$	77.63 (77.82)	10.06 (9.86)	12.31 (12.24)
2d	93—95 (23)	5.62—5.39 (2H, m, CH=CH), 3.05—2.81 (2H, m, $CHC\underline{H}_2N$), 2.51—2.20 (4H, m, CH_2NCH_2), 2.20—1.79 (2H, m, CH_2C=C), 1.71—1.09 (8H, m, CH_2-CH_2CH_2 and $CH_3C\underline{H}_2$), 0.89 (3H, t, J=6.0, CH_3)	$C_{11}H_{21}N$	78.97 (78.95)	12.65 (12.66)	8.37 (8.43)
2e	85—86 (0.04)	7.23 (5H, s, C_6H_5), 5.63—5.40 (2H, m, CH=CH), 3.46 (2H, s, $C\underline{H}_2C_6H_5$), 3.10—2.87 (2H, m, CH-CH_2N), 2.18 (3H, s, NCH_3), 2.25—1.73 (2H, m, $C\underline{H}_2$C=C), 1.37 (2H, se, J=6.0, $C\underline{H}_2CH_3$), 0.88 (3H, t, J=6.0, $CH_2C\underline{H}_3$)	$C_{14}H_{21}N$	82.70 (82.72)	10.41 (10.43)	6.89 (6.91)

a) GLC analysis and CMR measurements indicate that each product is a mixture of geometric isomers,
b) s=singlet, d=doublet, t=triplet, m=multiplet, se=sextet, J=Hz.

Reactions of 2,2,2-Trichloroethylamines (1a, b) with Ethyllithium——General Procedure: A solution of ethyllithium (freshly prepared from 0.1 mol of ethyl bromide and 0.1 g atom of lithium in 60 ml of dry ether) was added dropwise to a cooled solution of 0.033 mol of 2,2,2-trichloroethylamine in 40 ml of dry ether with stirring. After completion of the addition, the mixture was stirred at 10—15°C. An aqueous solution of NaCl was added to the reaction mixture. The ethereal layer was separated and the aqueous layer was extracted with ether. The combined ethereal solution was dried over $MgSO_4$. After removal of ether, the residue was distilled under reduced pressure to give β,γ-unsaturated amine (**2a, b**). The IR and PMR spectra of the products showed good correspondence with those of the specimens obtained in the above experiment.

Reactions of 2,2,2-Trichloroethylamines (1a—c) with Butyllithium——General Procedure: The procedure described above was repeated using a solution of 0.1 mol of butyllithium in hexane and 0.033 mol of 2,2,2-trichloroethylamine to afford a mixture of α,β-unsaturated amine and β,γ-unsaturated amine.

IR and PMR spectra of the products are composed of the patterns of the corresponding β,γ-unsaturated amine, obtained in the above experiment, and those of another product. The IR spectrum exhibits a strong absorption band at *ca.* 1650 cm^{-1} which may be due to the carbon-carbon double bond of the α,β-unsaturated amine. A typical identification was made as follows. The other component, with **2b**, of the mixture obtained in the reaction of **1a** with butyllithium was identified as 1-pentene-1-morpholine from the good correspondence of its IR and PMR spectra with those of 1-pentene-1-morpholine prepared by another route.

Reactions of 2,2,2-Trichloroethylamines (1a—c) with Phenyllithium and *tert*-Butyllithium——General Procedure: The procedure described above was repeated using phenyllithium (freshly prepared from 0.1 mol of bromobenzene and 0.1 g atom of lithium), or 58.8 ml of a 1.7 M solution of *tert*-butyllithium in heptane, and 0.033 mol of 2,2,2-trichloroethylamine to afford α,β-unsaturated amine (**5a—c, 6a—c**). The products **5a—c** were purified by distillation under reduced pressure and the products **6a—c** by recrystallization from petr. ether. Physical and spectral data for the products are listed in Table IV.

Reactions of 2,2-Dichloroethylamines (3a, b) with Butyllithium——General Procedure: A cooled solution of 0.033 mol of 2,2-dichloroethylamine in 40 ml of dry ether was treated with a solution of 0.1 mol of butyllithium in hexane. After work-up by the procedure described for the above experiment, a mixture of α,β-unsaturated amine and β,γ-unsaturated amine was obtained. The products showed the same IR and PMR spectra as the products obtained by the reaction of 2,2,2-trichloroethylamine with butyllithium.

Reactions of 2,2-Dichloroethylamines (3a, b) with Phenyllithium or *tert*-Butyllithium——The procedure described above was repeated using 2,2-dichloroethylamine and phenyllithium or *tert*-butyllithium to afford α,β-unsaturated amine (**5a, b, 6a, b**). The IR and PMR spectra of the products were consistent with those

TABLE IV. α,β-Unsaturated Amines (**5a**—**c** and **6a**—**c**)

Compd. No.	bp (°C) (mmHg) or mp (°C)	IR $\nu_{max}^{neat\ or\ KBr}$ cm^{-1} (C=C)	NMR[a] ($CDCl_3$) δ (ppm)	Formula	Analysis (%) Calcd (Found) C	H	N
5a	98—99 (20)	1655	5.73 (1H, d, J=14.0, CHN), 4.50 (1H, d, J=14.0, C<u>H</u>=CHN), 3.83—3.59 (4H, m, CH_2OCH_2), 2.08—2.64 (4H, m, CH_2NCH_2), 1.05 (9H, s, $3CH_3$)	$C_{10}H_{19}NO$	70.96 (70.74)	11.31 (11.21)	8.27 (8.19)
6a	73—75	1640	7.14 (5H, s, C_6H_5), 6.54 (1H, d, J=14.0, CHN), 5.36 (1H, d, J=14.0, C<u>H</u>C_6H_5), 3.89—3.62 (4H, m, CH_2OCH_2), 3.14—2.85 (4H, m, CH_2NCH_2)	$C_{12}H_{15}NO$	76.16 (76.01)	7.99 (7.94)	7.40 (7.43)
5b	85—86 (22)	1653	5.75 (1H, d, J=14.0, CHN), 4.47 (1H, d, J=14.0, C<u>H</u>=CHN), 2.88—2.50 (4H, m, CH_2NCH_2), 1.73—1.38 (6H, m, $CH_2CH_2CH_2$), 1.01 (9H, s, $3CH_3$)	$C_{11}H_{21}N$	78.97 (79.00)	12.65 (12.74)	8.37 (8.36)
6b	27—28	1640	7.09 (5H, s, C_6H_5), 6.58 (1H, d, J=14.0, CHN), 5.29 (1H, d, J=14.0, C<u>H</u>C_6H_5), 3.15—2.82 (4H, m, CH_2NCH_2), 1.77—1.38 (6H, m, $CH_2CH_2CH_2$)	$C_{13}H_{17}N$	83.37 (82.82)	9.15 (9.05)	7.48 (7.13)
5c	82—83 (2)	1650	7.23 (5H, s, C_6H_5), 6.03 (1H, d, J=14.0, C<u>H</u>=CHN), 4.32 (1H, d, J=14.0, CHN), 4.00 (2H, s, CH_2), 2.45 (3H, s, CH_3), 1.06 (9H, s, $3CH_3$)	$C_{14}H_{21}N$	82.70 (81.98)	10.41 (10.45)	6.89 (7.03)
6c	30—31	1642	7.31—6.90 (10H, m, C_6H_5), 6.88 (1H, d, J=14.0, CHN), 5.20 (1H, d, J=14.0, C<u>H</u>C_6H_5), 4.21 (2H, s, CH_2), 2.69 (3H, s, CH_3)	$C_{16}H_{17}N$	86.05 (86.41)	7.67 (7.71)	6.27 (6.31)

a) s=singlet, d=doublet, m=multiplet, J=Hz.

of the corresponding products obtained by the reaction of 2,2,2-trichloroethylamine with phenyllithium or *tert*-butyllithium.

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