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Halogen–Metal Interchange Reactions of 3,3,3-Trichloro-1,2-epoxypropane and of Chloral with Organolithium Compounds and Grignard Reagents[1]

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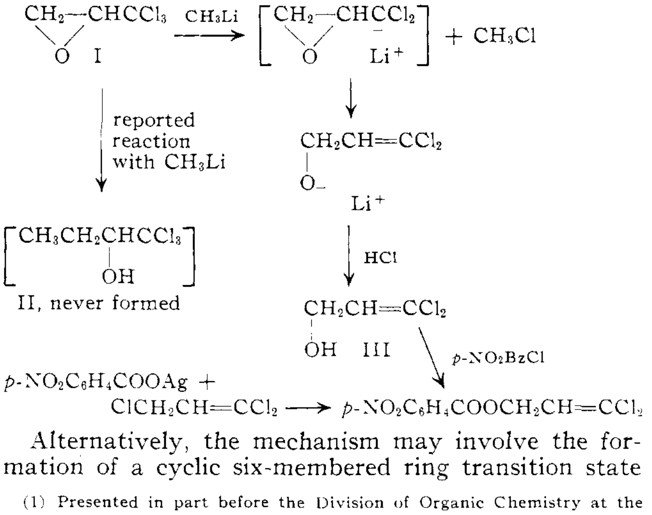
3,3,3-Trichloro-1,2-epoxypropane (I) reacts with methyllithium or phenyllithium to form 3,3-dichloroallyl alcohol (III) and methyl chloride or chlorobenzene. The formation of these products shows that a halogen–metal interchange reaction has occurred. None of the products expected from the opening of the epoxide ring by a carbanion could be detected. Even with *n*-butylmagnesium chloride and with di-*n*-butylmagnesium, a similar halogen–metal interchange reaction occurs. This is believed to be the first case reported in which a Grignard reagent undergoes a halogen–metal interchange reaction rapidly and to the exclusion of the usually observed reaction path. With *n*-butylmagnesium chloride, the epoxide ring is also attacked by chloride ion, but not by the *n*-butyl carbanion, and the chlorohydrin is formed. Phenyllithium also undergoes a halogen–metal interchange reaction with chloral rather than adding to the carbonyl group in the expected manner. The above reactions indicate that the trichloromethyl group is unusually reactive in the halogen–metal interchange reaction.

In connection with a search for new methods of synthesizing alkyltrichloromethylcarbinols, we re-examined the reaction of methyllithium with 3,3,3-trichloro-1,2-epoxypropane (I). This has been reported to yield ethyltrichloromethylcarbinol (II) in 84% yield,[3] but in our hands the only products formed were 3,3-dichloroallyl alcohol (III) in 85% yield and methyl chloride in 70% yield. The reaction was carried out as described in the literature. Under a nitrogen atmosphere, a stoichiometric amount of an approximately 1 *N* ethereal methyllithium solution was slowly added to the epoxide in ether at −75° following which the reaction was allowed to warm to room temperature. The boiling point of the product obtained was in agreement with that reported by Gilman and Abbott,[3] and the product formed a *p*-nitrobenzoyl derivative having the same melting point as they gave. However, on the basis of the data obtained from elemental analysis, the infrared spectrum, and the nuclear magnetic resonance spectrum, the product was shown to be 3,3-dichloroallyl alcohol, a new compound. Furthermore, authentic *p*-nitrobenzoates of 3,3-dichloroallyl alcohol and of ethyltrichloromethylcarbinol were prepared by other syntheses. A comparison of these derivatives with the *p*-nitrobenzoate of the product obtained from the methyllithium reaction again showed the reaction product to be 3,3-dichloroallyl alcohol. The products formed show that a halogen–metal interchange reaction has occurred as shown in the equations.



Alternatively, the mechanism may involve the formation of a cyclic six-membered ring transition state formed after the preliminary coordination of the methyllithium with the epoxide oxygen. This transition state would then break down to form the above lithium salt of the dichloroallyl alcohol and methyl chloride.

Phenyllithium was allowed to react with the epoxide I under the same experimental conditions. Again, 3,3-dichloroallyl alcohol was obtained (81% yield). Chlorobenzene was isolated in 68% yield.

In the above two cases, the halogen–metal interchange reaction must be much faster than the attack of a strongly nucleophilic ion on the epoxide ring, for in each case a halide ion was present from the preparation of the organolithium reagent—bromide ion from the starting bromobenzene and iodide ion from the starting methyl iodide. In neither case was any of the halohydrin detected. It is unusual to find *methyl*lithium undergoing the halogen–metal interchange reaction so readily; it usually does this only under very exceptional circumstances.[4]

The reaction of the epoxide I with a typical Grignard reagent was also studied under the same conditions since Grignard reagents do not undergo the halogen–metal interchange reaction.[5] The reaction of the epoxide with methylmagnesium iodide had been studied previously.[3] In accordance with the earlier work, we found that the halogen–metal interchange reaction did not occur, but the major reaction was the opening of the epoxide ring by iodide ion to yield the iodohydrin in 69% yield. There was no evidence for an attack of the methyl carbanion on the epoxide ring.

With *n*-butylmagnesium chloride, formation of the halohydrin was slower, occurring in 25% yield, as would be predicted for the change from iodide to chloride ion. However, *the halogen–metal interchange reaction did occur* with the formation of 3,3-dichloroallyl alcohol in 43% yield. The accompanying *n*-butyl chloride was obtained in 25% yield. Again, no attack

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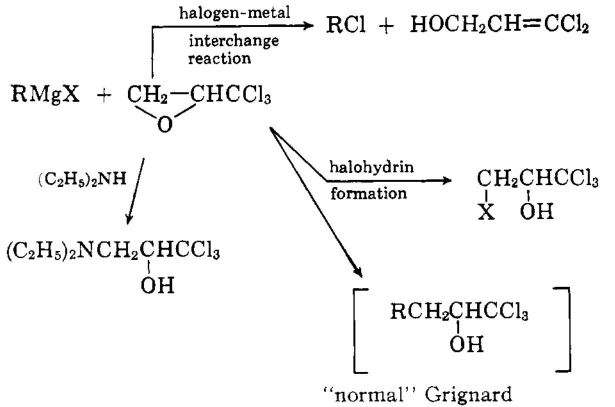
(2) This investigation was supported in part by a Predoctoral Fellowship to L. W. F. from the Division of General Medical Studies, United States Public Health Service.

(3) H. Gilman and R. K. Abbott, Jr., *J. Org. Chem.*, **8**, 224 (1943).

(4) G. E. Coates, "Organometallic Compounds," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1960, p. 5.

(5) Most sources state that Grignard reagents do not undergo the metal–halogen interchange reaction, although the reaction of some sterically hindered α-halogen ketones with Grignard reagents yields a magnesium enolate and an alkyl or aryl halide. The α-halogen ketones that act in this manner appear to be those that have "positive" halogen, *i.e.* they act as halogenating agents in other reactions (C. H. Fisher, H. R. Snyder, and R. C. Fuson, *J. Am. Chem. Soc.*, **54**, 3665 (1932)). Aside from these, we know of only three examples of the halogen–metal interchange reaction in the literature and all involve iodo compounds. A diiodo-N-ethylcarbazole reacted with *n*-butylmagnesium bromide (3.7% yield) after 20 hr. of refluxing (H. Gilman and S. M. Spatz, *ibid.*, **63**, 1553 (1941)). Phenylmagnesium bromide reacted with 1-iodoheptafluoropropane to give the interchange products in 83% yield (O. R. Pierce, A. F. Meiners, and E. T. McBee, *ibid.*, **75**, 2516 (1953)). Likewise, trifluorovinyl iodide reacted readily with phenylmagnesium bromide to give the interchange products in 33% yield (R. N. Sterlin, L. N. Pinkina, I. L. Knunyants, and L. F. Nezgovorov, *Khim. Nauka i Promy.*, **4**, 809 (1959), from *Chem. Abstr.*, **54**, 10837 (1960)).



"normal" Grignard reaction product not obtained with this epoxide

of the alkyl carbanion on the epoxide ring could be detected. With a dioxane–ether solution of di-*n*-butylmagnesium, prepared in the usual way by the addition of dioxane to an ether solution of the Grignard reagent,[6] no halohydrin was detected, and the major products were again the 3,3-dichloroallyl alcohol in 63% yield and *n*-butyl chloride in 22% yield. It is apparent that in these two cases we have examples of Grignard reagents undergoing the halogen–metal interchange reaction to the exclusion of what would be considered a more normal reaction path.

With phenylmagnesium bromide, a 69% yield of the bromohydrin was obtained, and no halogen–metal interchange reaction was detected. This is in accord with the known lower reactivity of phenyl compounds in this reaction.[7]

The formation of the halohydrins in the above reactions shows that the epoxide does undergo nucleophilic substitution reactions. This reaction also is probably facilitated by coordination of the metal ion present with the epoxide oxygen. That the epoxide ring is quite reactive under other conditions was shown by treatment of the epoxide with anhydrous diethylamine and with aqueous methylamine. Each of these amines reacted rapidly to yield products which were assigned the usual amino alcohol structures on the basis of analytical data and infrared spectra.

The results obtained with Grignard and alkyllithium reagents are summarized in Table I.

Table I

Reactions of 3,3,3-Trichloro-1,2-epoxypropane with Grignard and Alkyllithium Reagents

	Yield, %		
Reagent	Trichloromethylcarbinol	Halohydrin	3,3-Dichloroallyl alcohol
CH_3Li	0	0	84
C_6H_5Li	0	0	81
CH_3MgI	0	69	0
n-C_4H_9MgCl	0	25	43
(*n*-$C_4H_9)_2Mg$	0	. .	63
C_6H_5MgBr	0	69	0

Reactions of Chloral with Organometallic Compounds.—The reactions of chloral with Grignard reagents have been studied by several investigators. Ethyl-, *n*-amyl-, cyclohexyl-, β-phenethyl-, γ-phenylpropyl-, and δ-phenylbutylmagnesium bromides yield no carbinols at all, the sole product of each of these reactions being the olefin and 2,2,2-trichloro-1-ethanol.[3,8] On the other hand, methylmagnesium iodide, vinylmagnesium chloride, various arylmagnesium bromides, and benzylmagnesium bromide do give the expected trichloromethylcarbinols in yields ranging from 26 to 75% of the theoretical amount.[3,9,10] It appears that a normal addition reaction to the carbonyl group occurs only when structural features do not allow the oxidation–reduction reaction to take place. The reaction of organolithium reagents with chloral has not been reported. In view of their general use in situations where Grignard reagents fail to add to a carbonyl system in the normal manner, the reaction of chloral with a typical organolithium compound, phenyllithium, was studied. Again, the halogen–metal interchange reaction occurred. Chlorobenzene was obtained in 51% yield. The only other product was a high-boiling unidentified residue which was presumed to be derived from dichloroacetaldehyde. No phenyltrichloromethylcarbinol, the normal addition product, could be detected. This appears to be the only known case in which phenyllithium undergoes a halogen–metal interchange reaction to the exclusion of an addition reaction to an aldehydic carbonyl group.

The reactions of *n*-butylmagnesium chloride and of phenylmagnesium bromide with chloral were reinvestigated to see if any evidence of halogen–metal interchange in these reactions could be detected. The only reactions found to occur were the oxidation–reduction and the normal addition, respectively, in agreement with the reports in the literature.[3,8]

Experimental

All melting and boiling points are corrected. Analyses are by Dr. Franz J. Kasler. The infrared spectra were determined on a Beckman IR-5. Liquids were measured as a film between sodium chloride plates. With solids, melt techniques were used.

3,3-Dichloroallyl Alcohol (III) from Methyllithium and 3,3,3-Trichloro-1,2-epoxypropane.—This preparation followed the procedure of Gilman and Abbott.[3] Under a nitrogen atmosphere, an ether solution of methyllithium was prepared from methyl iodide and thinly sliced lithium metal. An acid titration showed the solution to be about 1 *N* in methyllithium. A volume equivalent to 0.26 mole of the methyllithium was added slowly to 0.26 mole of 3,3,3-trichloro-1,2-epoxypropane[11] dissolved in 200 ml. of dry ether. A 1000-ml. three-necked flask, immersed in a Dry Ice–acetone bath and equipped with a Hershberg stirrer, gas inlet tube, and a water-cooled condenser, the top of which was connected to a double Dry Ice–acetone trap to catch the effluent gases, was used for the reaction. The clear yellow solution darkened as it warmed to room temperature. The reaction mixture was decomposed at 0° with 125 ml. of a saturated ammonium chloride solution. Distillation yielded 28 g. (85% yield) of the 3,3-dichloroallyl alcohol, b.p. 78–79° (20 mm.), $n^{25}D$ 1.4939. It reduced a potassium permanganate solution, gave a positive Lucas test, and showed strong infrared absorption in the double bond and hydroxyl region; infrared spectrum, ν_{max}: 3400–3050, 2915, 2850, 1615, 1475–1390, 1360, 1265, 1215, 1100–1065, 1050–1000, 960, 885–855, and 825 cm.$^{-1}$. The n.m.r. spectrum in deuteriochloroform at 60 Mc. on a Varian HR-60 showed peaks at τ 6.27 (singlet due to alcoholic OH); 5.87 and 5.77 (methylene protons); 4.09, 3.99, and 3.89 (CH group). Since the $-CH_2-$ and $-CH-$ are adjacent to each other, there is spin–spin interaction and the coupling constants $J_{1,2}$ and $J_{2,1}$ should be equal. This was found to be the case. The areas under the curves show the protons to be in the relative ratios of 1:2:1 as expected.

Anal. Calcd. for $C_3H_4Cl_2O$: C, 28.37; H, 3.09; Cl, 55.85. Found: C, 28.66; H, 3.35; Cl, 55.60.

When the epoxide was added to the methyllithium solution (reverse of above procedure), the same results were obtained.

The 3,3-dichloroallyl alcohol reacted readily with *p*-nitrobenzoyl chloride to form the ***p*-nitrobenzoyl derivative of 3,3-dichloroallyl alcohol**, m.p. 69–70° after recrystallization from petroleum ether.

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(6) D. L. Cottle and W. C. Hollyday, Jr., *J. Org. Chem.*, **12**, 510 (1947).

(7) R. G. Jones and H. Gilman, *Org. Reactions*, **6**, 342 (1951).

(8) P. M. Dean and W. I. Wolf, *J. Am. Chem. Soc.*, **58**, 332 (1936); V. W. Floutz, *ibid.*, **65**, 2255 (1943); **67**, 1615 (1945).

(9) J. Jocicz, *J. Russ. Phys.-Chem. Soc.*, **34**, 96 (1902), from Beilstein's "Handbuch," 4th Ed., Vol. 6, 1st suppl., F. Richter, Ed., Julius Springer, Berlin, 1931, p. 237; J. Jocicz, *J. Russ. Phys.-Chem. Soc.*, **36**, 8 (1904), from *Bull. soc. chim. France*, **34**, 204 (1905); M. S. Kharasch, S. C. Kleiger, J. A. Martin, and F. R. Mayo, *J. Am. Chem. Soc.*, **63**, 2305 (1941); V. W. Floutz, *ibid.*, **65**, 2255 (1943); **71**, 2859 (1949).

(10) H. Normant and J. Ficini, *Bull. soc. chim. France*, 1441 (1956).

(11) W. Reeve and L. W. Fine, *Can. J. Chem.*, **41**, 2231 (1963).

Anal. Calcd. for $C_{10}H_7Cl_2NO_4$: C, 43.50; H, 2.55; Cl, 25.68. Found: C, 43.73; H, 2.80; Cl, 25.48.

An authentic sample of the *p*-nitrobenzoyl derivative was prepared by refluxing a suspension of 15 g. of silver *p*-nitrobenzoate in 20 ml. of ethanol with 5 g. of 1,1,3-trichloro-1-propene[11] for 3 hr. It melted at 70–71° after recrystallization from petroleum ether. The mixture melting point showed no depression.

Anal. Calcd. for $C_{10}H_7Cl_2NO_4$: C, 43.50; H, 2.55; Cl, 25.68. Found: C, 43.57; H, 2.80; Cl, 25.55.

The Dry Ice–acetone traps, catching the effluent gases from the reaction of methyllithium and the epoxide, contained a liquid shown by v.p.c. analysis to consist of ether and another component. Qualitative test showed the presence of chlorine and the absence of iodine. The second component was shown to be **methyl chloride** by reaction with silver *p*-nitrobenzoate in a sealed tube at 150° for 10 hr. The methyl *p*-nitrobenzoate melted at 93–94° after recrystallization from petroleum ether and then ethanol, and the mixture melting point with an authentic sample gave no depression.

Reaction of Epoxide I with Phenyllithium.—This was carried out in the same way as the methyllithium experiment. The phenyllithium was prepared from bromobenzene and lithium with ether as solvent. The phenyllithium solution (0.17 mole, by titration with acid) was added to 28 g. (0.17 mole) of the epoxide dissolved in 50 ml. of dry ether over a 45-min. period at −75°. The red color of the organolithium solution promptly disappeared. The reaction was allowed to warm to room temperature and decomposed with 2 *N* hydrochloric acid solution. Distillation yielded 7.5 g. (68% yield) of chlorobenzene, b.p. 34–37° (25 mm.), and 11 g. (81% yield) of 3,3-dichloroallyl alcohol, b.p. 80–84° (25 mm.). The products were identified by comparison of their vapor phase retention times and infrared spectra with those of authentic samples.

Reaction of Epoxide I with *n*-Butylmagnesium Chloride.—The *n*-butylmagnesium chloride was prepared from 4.8 g. of magnesium and 19 g. of *n*-butyl chloride. The *n*-butylmagnesium chloride (0.17 mole by titration with acid) was added to 28 g. (0.17 mole) of the epoxide dissolved in 150 ml. of dry ether over a 30-min. period at −75° and then allowed to warm to room temperature. The reaction mixture was decomposed with cold 2 *N* hydrochloric acid. Distillation gave 3 g. (25%) of *n*-butyl chloride, b.p. 75–79° (760 mm.); 9.5 g. (43%) of 3,3-dichloroallyl alcohol, b.p. 76–77° (17 mm.); 8.5 g. (25%) of 1,1,1,3-tetrachloro-2-propanol, b.p. 98–100° (17 (mm.); and 1 g. of residue. The products were identified by comparison of their vapor phase retention times and infrared spectra with those of authentic samples. Data on 1,1,1,3-tetrachloro-2 propanol are in ref. 11.

Reaction of Epoxide I with Di-*n*-butylmagnesium.—The reagent was prepared by a modification of the method of Cottle and Hollyday.[6] To an approximately 1.5 *M* ether solution of *n*-butylmagnesium bromide, prepared in the usual way, was added one-quarter of its volume of sodium-dried and distilled dioxane over a 2-hr. period near reflux temperature with efficient stirring. The flask was then kept in the dark at 0° for 3 days. A 150-ml. sample of the clear supernatant solution was found to contain 0.1 mole of the di-*n*-butylmagnesium by titrating an aliquot with acid. Bromide ion was demonstrated to be absent by a silver nitrate test. To the 0.1 mole of di-*n*-butylmagnesium was added 16.2 g. (0.1 mole) of the epoxide in 100 ml. of ether over a period of 1 hr. at 0°. Stirring was continued for 3 hr. and the reaction mixture then allowed to warm to room temperature overnight. It was decomposed at 0° with distilled water. Distillation yielded 2 g. (22% yield) of *n*-butyl chloride, b.p. 75–78° (760 mm.); 8 g. (63% yield) of 3,3-dichloroallyl alcohol, b.p. 75–77° (17 mm.); and 3 g. of an unidentified, chlorine-free, higher boiling fraction, b.p. 110–114° (17 mm.).

Reaction of Epoxide I with Amines.—In a 50-ml. erlenmeyer flask, 16 g. of the epoxide (0.1 mole) was treated with 10 ml. (0.08 mole) of a 25% aqueous methylamine solution. The flask was corked, shaken thoroughly for 10 min., and allowed to stand for 8 hr. with occasional shaking. The organic layer became first viscous, then gummy, and finally solid. It was separated from the aqueous layer, washed, and the 9 g. (59% yield) of product, presumably the **1,1,1-trichloro-3-(methylamino)-2-propanol**, was recrystallized from ethanol–water and then from petroleum ether. It melted at 72–73°.

Anal. Calcd. for $C_4H_8Cl_3NO$: C, 24.90; H, 4.18. Found: C, 24.70; H, 3.96.

Under the same conditions, 15 g. of diethylamine reacted immediately with 16 g. of the epoxide. The heat of the reaction caused the diethylamine to boil gently, and the reaction was complete within 10 min. The product, presumably the **1,1,1-trichloro-3-(diethylamino)-2-propanol**, weighed 18 g. after recrystallization from ethanol and melted at 67.5–68.5°; infrared spectrum, $\nu_{\max}$: 3225–2610, 1475, 1450, 1390, 1325, 1300–1270, 1190, 1165, 1110, 1085, 1070, 1050, 1000, 925, 892, 835–780, and 755 cm.$^{-1}$.

Anal. Calcd. for $C_7H_{14}Cl_3NO$: C, 35.84; H, 6.06; N, 6.02; Cl, 45.35. Found: C, 35.99; H, 6.04; N, 5.78; Cl, 45.10.

Reaction of Chloral with Phenyllithium.—The phenyllithium solution, prepared from lithium metal and bromobenzene in ether, was added over a 1-hr. period to an equivalent amount of anhydrous chloral in ether at −40 to −30°. The reaction mixture was allowed to warm to 0°, then packed in ice and allowed to warm to room temperature over a 2-hr. period. It was decomposed with 2 *N* hydrochloric acid. From 26 g. (0.17 mole) of chloral, there was obtained 10 g. (51% yield) of chlorobenzene, b.p. 129–130°, and 15 g. of an unidentified high boiling residue. The chlorobenzene was identified by comparison of its vapor phase retention time and infrared spectrum with those of an authentic sample.

1,1,1-Trichloro-2-butanol (II).—1,1,1-Trichloro-3-buten-2-ol was prepared by adding 132 g. (0.9 mole) of anhydrous chloral in ether at 0° to vinylmagnesium chloride[12] (0.9 mole) in tetrahydrofuran according to the procedure of Normant and Ficini.[10] The reaction mixture was stirred and maintained at 0° for 1 hr. after the addition was complete. It was allowed to warm to room temperature overnight and then decomposed with 2 *N* hydrochloric acid. On distillation, 40 g. (26% yield) of **1,1,1-trichloro-3-buten-2-ol**, b.p. 73–75° (23 mm.), was obtained. Its infrared spectrum showed absorption bands at (in cm.$^{-1}$) 3500–3250 (OH) and 1885 (vinyl overtone).

The 1,1,1-trichloro-3-buten-2-ol was dissolved in 2.5 times its weight of ethanol and hydrogenated over 5% its weight of 5% palladium-on-carbon catalyst at 25° and 3 atm. hydrogen pressure. The reaction was complete in 3 hr. From 40 g., there was obtained 36 g. of **1,1,1-trichloro-2-butanol**, b.p. 74–75° (17 mm.), n^{26}D 1.4828. The literature[10] values are b.p. 63–64° (12 mm.) and n^{20}D 1.4831; infrared spectrum, $\nu_{\max}$: 3570–3250, 2950, 2860, 1460, 1410–1375, 1315–1285, 1230, 1130–1085, 1065, 1010, 990, 890, and 835–760 cm.$^{-1}$.

Anal. Calcd. for $C_4H_7Cl_3O$: C, 27.07; H, 3.97; Cl, 59.94. Found: C, 26.87; H, 3.86; Cl, 59.70.

The material reacted readily with *p*-nitrobenzoyl chloride to form a ***p*-nitrobenzoyl derivative**, m.p. 80–80.5° after recrystallization from petroleum ether.

Anal. Calcd. for $C_{11}H_{10}Cl_3NO_4$: C, 40.45; H, 3.08; Cl, 32.57. Found: C, 40.67; H, 3.26; Cl, 32.52.

The mixture melting point with the *p*-nitrobenzoate of the 3,3-dichloroallyl alcohol, m.p. 70°, was 54–56°.

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