Phenyl Migration during Preparation of Grignard Reagents

Erling Grovenstein, Jr.,* Auburn B. Cottingham, and Leslie T. Gelbaum

School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332

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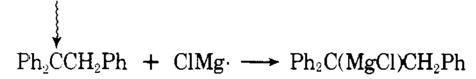
Magnesium reacts in diethyl ether with 5-chloro-4,4-diphenyl-1-pentene, 2-chloro-1,1,1-triphenylethane, and 1-chloro-2,2,3-triphenylpropane to give Grignard reagents in which phenyl groups have undergone an appreciable amount of [1,2]sigmatropic rearrangement. In tetrahydrofuran less rearrangement was observed in the Grignard reagent. These rearrangements are believed to occur in intermediate radicals formed during preparation of the Grignard reagents.

While phenyl and other aryl groups are known to undergo migration[1] during reaction of lithium metal with certain alkyl halides to give rearranged organolithium compounds and while organolithium compounds themselves,[2] somewhat less commonly, undergo migration of aryl groups, aryl migrations during reaction of alkyl halides with magnesium to give rearranged Grignard reagents are unknown or poorly documented although rearranged hydrocarbon by-products have been reported.[3,4] Also Grignard reagents, once formed, evidently do not undergo aryl migration; thus 2,2-diphenylpropylmagnesium chloride has been prepared unrearranged from the corresponding chloride in tetrahydrofuran and did not rearrange in refluxing dioxane or in pyridine.[5]

In some preliminary experiments directed toward another goal[6] it was desired to prepare 3,3-diphenyl-5-hexenoic acid. Since 5-chloro-4,4-diphenyl-1-pentene was available, preparation of the acid by carbonation of the Grignard reagent prepared from the chloride in diethyl ether was attempted. This Grignard product, however, gave rise to a complex mixture of five carboxylic acids of which 2-benzyl-2-phenyl-4-pentenoic acid (product of 1,2 migration of phenyl) was the major component. In contrast the same Grignard preparation in tetrahydrofuran gave, as expected, nearly pure 3,3-diphenyl-5-hexenoic acid.

Since the reaction of 5-chloro-4,4-diphenyl-1-pentene is complicated likely by migration of the allyl group[6] and prototropic migration of the double bond in addition to the phenyl group, reaction of the simpler chloride 2-chloro-1,1,1-triphenylethane with magnesium[7] was studied. The results are summarized in Table I which gives the GLC-volatile products (other than triphenylethylene) from carbonation of reactions run under various conditions. It is obvious that in both diethyl ether and di-*n*-butyl ether the organomagnesium product is extensively rearranged with the quantity of 1,1,2-triphenylethyl Grignard reagent (product of 1,2 migration of phenyl) being comparable to that of the expected 2,2,2-triphenylethylmagnesium halide. In tetrahydrofuran, however, the quantity of rearranged organomagnesium compound is negligible. In general, the quantity of rearranged hydrocarbon 1,1,2-triphenylethane was appreciable in all of the ethereal solvents investigated; however, there are irregularities, possibly due to the adventitious presence of protonating or hydrogen atom-transfer agents.

For each run tested in Table I, within the experimental error, the total percentage of volatile rearranged products was invariable with time. *Hence the organomagnesium product itself does not rearrange at an appreciable rate.* The observed phenyl migration must, therefore, occur *during formation* of the Grignard reagent likely by way of radicals which are, in part, free enough from the surface of the magnesium to permit rearrangement. Similar interpretations have been advanced to explain rearranged hydrocarbon by-products formed[3,4] during preparation of other Grignard reagents and to account for extensive racemization during preparation[8] of optically active Grignard reagents from optically active cyclopropyl halides. The 1,2 shift of aryl groups in free radicals is a well known reaction and occurs with special ease in the case of the 2,2,2-triphenylethyl radical.[9]



$$\begin{tikzcd} Ph_3CCH_2Cl \arrow[r, "Mg"] & Ph_3CCH_2\cdot + ClMg\cdot \arrow[r] \arrow[d, squiggly] & Ph_3CCH_2MgCl \\ & Ph_2CCH_2Ph + ClMg\cdot \arrow[r] & Ph_2C(MgCl)CH_2Ph \end{tikzcd}$$

Heterogeneous reactions at metallic surfaces via radical intermediates are apt to be rather irreproducible. The total percentage of rearrangement in Table I showed considerable variability from run to run and had no consistent variation with the method of purification of the solvent or the grade of magnesium employed. The amount of rearrangement in tetrahydrofuran evidently increases with the reaction temperature and was almost negligible at 27 °C. For comparisjns at similar temperatures, the smaller amount of rearrangement in THF than in di-*n*-butyl ether parallels results which have been reported[10] for reaction of 6-bromo-1-hexene with magnesium where "rearrangement" corresponds to formation of the cyclopentylmethyl radical. With 2-chloro-1,1,1-triphenylethane, however, diethyl ether and di-*n*-butyl ether gave similar amounts of rearranged products unlike the results reported for 6-bromo-1-hexene. That the rearranged product from 2-chloro-1,1,1-triphenylethane in THF is primarily 1,1,2-triphenylethane rather than rearranged Grignard reagent as in diethyl ether may reflect the higher reactivity of THF than diethyl ether toward radicals.[8b,11]

Finally, in order to test the generality of phenyl migration in reactions of halides with magnesium, the reaction of 1-chloro-2,2,3-triphenylpropane in diethyl ether was studied. Carbonation after 4 h gave 3,3,4-triphenylbutanoic acid containing 28 mol % of 2-benzyl-2,3-diphenylpropanoic acid (product of 1,2 migration of phenyl). Upon storing a portion of this Grignard solution for 23 h at room temperature before carbonation, the proportion of rearranged acid was unchanged, a result which parallels our study upon 2-chloro-1,1,1-triphenylethane. Unlike the reactions of 1-chloro-2,2,3-triphenylpropane with lithium, potassium, and cesium in THF,[12] none of the product 2,2,4-triphenylbutanoic acid (from 1,2 migration of benzyl) was found in the reaction with magnesium.

In conclusion, 1,2 migration of phenyl (and likely other aryl groups) appears to be of rather general occurrence during reactions of β-phenylethyl halides with magnesium, especially for reactions in diethyl ether; rearrangement is likely to be observed not only in the hydrocarbon by-products but also in the Grignard reagent itself. The three chlorides studied in the present work were slow in their reactions with magnesium under all conditions tested. Also the yields of Grignard reagent were poor to moderate; the highest yield reported in Table I is only 48%, with the average yield of diethyl ether being 42%. These results contrast with yields of 96 to 99.7% which have been reported[13] for *n*-alkyl chlorides. It may be argued that in most of the present reactions the alkyl chloride was added

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Table I. Reaction of 2-Chloro-1,1,1-triphenylethane with Magnesium

RCl, mmol	solvent	temp.,[g] °C	reaction time, h	Ph_3CCH_3, mmol	Ph_2CHCH_2Ph, mmol	$Ph_3CCH_2CO_2H$, mmol	$PhCH_2$-CPh_2-CO_2H, mmol	total rearrangement,[h] %
6.8[a]	Et_2O[d]	27	5	1.38	0.15	1.75	0.48	17
6.8[a]	Et_2O[d]	27	7	0.24	0.08	1.77	0.58	25
		25	113	1.95	0.19	0.52	0.38	19
16.6[b]	Et_2O[e]	27	5	2.9	0.14	0.61	1.70	35
		25	96	0.87	0.13	2.5	2.2	41
17.0[c]	Et_2O[e]	27	3	3.5	0.08	2.4	1.68	23
		25	24	2.3	0.00	1.94	1.39	25
6.8[a]	THF[f]	38	23	0.37	0.07	0.026	0.001	15
		25	171	4.4	0.76	0.000	0.000	15
17.1[b]	THF[f]	45	13	5.3	0.99	0.22	0.00	15
17.3[b]	THF[e]	27	3.5	2.2	0.20	3.8	0.0	3
		25	20	2.7	0.16	1.8	0.0	3
13.2[c]	THF[e]	27	4	1.41	0.16	2.1	0.0	4[i]
17.1[a]	n-Bu_2O[j]	27	3	3.4	0.20	1.49	0.95	19
		25	23	2.9	0.48	1.15	0.60	21

[a] Magnesium turning for Grignard reaction from Fisher Scientific Co. [b] Doubly sublimed magnesium, freshly milled. [c] Magnesium rod from Fisher Scientific Co., freshly milled. [d] The solvent was freshly distilled from $LiAlH_4$. [e] The solvent was freshly distilled from benzophenone sodium ketyl. [f] The solvent was freshly distilled from $NaAlH_4$. [g] For the double entry the reaction was stirred for the number of hours indicated at the first temperature, a portion of the mixture was carbonated, and the remainder of the mixture was stored at room temperature for the indicated additional time before carbonation. [h] Expressed as mole percent of volatile products reported in the table. [i] Some 43% of the alkyl chloride remained unreacted. [j] The n-butyl ether was freshly distilled from molten sodium.

all at once rather than by the more orthodox procedure of adding the halide gradually; however, tests upon simple *chlorides* have shown that such differences in procedure make little or no significant difference in yields of organomagnesium chlorides.[13]

The chlorides studied here are part of a group which were designed to demonstrate the occurrence of 1,2-aryl migration in carbanions.[14] Simple molecular orbital calculations predict[15] that, other factors being equal, [1,2]sigmatropic rearrangements should occur with greater ease in free radicals than carbanions. While the lifetime or freeness of radicals being formed at a metal surface are poorly understood, the present results with magnesium were perhaps to be anticipated.

Experimental Section

All Grignard reactions were carried out, unless otherwise specified, in Morton flasks under a nitrogen atmosphere with high-speed stirring.[16] Magnesium was placed in the flask and the flask was flame dried while prepurified nitrogen was passed through the flask. Analyses by gas chromatography (GLC) were performed on instruments equipped with hydrogen-flame ionization detectors; qualitative GLC analyses are reported as "area percent" of total volatile constituents whereas "quantitative" GLC analyses were calculated with calibration factors and utilized known samples and internal standards. The 1,1,1-triphenyl-2-chloroethane,[2] 1-chloro-2,2,3-triphenylpropane,[17] 5-chloro-4,4-diphenyl-1-pentene,[6] and hydrocarbons and acids which were derived therefrom were prepared by methods which have already been given under the corresponding chloride. The reference sample of 2-benzyl-2,3-diphenylpropanoic acid was prepared essentially by the procedure of Hauser and co-workers.[18,19]

Reaction of 5-Chloro-4,4-diphenyl-1-pentene with Magnesium. A. In Diethyl Ether. To 3.4 g (0.14 g-atom) of magnesium in 85 mL of anhydrous ether was added 10 drops of methyl iodide and then the mixture was stirred with a magnetic stirrer at reflux for 30 min before addition of 14.9 g (0.058 mol) of 5-chloro-4,4-diphenyl-1-pentene in 15 mL of anhydrous ether. After 6 h at reflux temperature the reaction mixture was carbonated by addition of dry ice. The usual workup gave 3.1 g (20% yield for $C_{18}H_{18}O_2$) of acids. A GLC analysis of the acids as methyl esters on a 20 ft × 1/8 in. column packed with 15% Apiezon H on 60/80 mesh Chromosorb W at 203 °C gave products listed as area percent (relative retention time, identify): 12% (1.24, 2,2-diphenyl-4-hexenoic acid?), 57% (1.49, 2-benzyl-2-phenyl-4-pentenoic acid), 12% (1.54, 3,3-diphenyl-5-hexenoic acid?), 7% (1.71), and 11% (1.87). The identity of the major product 2-benzyl-2-phenyl-4-pentenoic acid was confirmed by NMR spectral comparisons of the methyl ester with an authentic sample;[6] the NMR spectrum of the mixture suggested that, in part, the allyl group of the reactant had been isomerized to a propenyl group in the products.

B. In Tetrahydrofuran. To 2.00 g (0.082 g-atom) of magnesium and 25 mL of THF in the usual Morton apparatus was added 1.1 g (0.008 mol) of methyl iodide. After 10 min, an additional 225 mL of THF was added and then 10.6 g (0.041 mol) of 5-chloro-4,4-diphenyl-1-pentene along with 0.6 g (0.004 mol) of methyl iodide in 10 ml of THF was added over a period of 10 min at room temperature with high-speed stirring. Since the reaction was only about half complete after 5 h of stirring at room temperature, the mixture was heated at reflux for 120 h before being cooled to 25 °C and forced onto solid carbon dioxide. The usual workup gave neutral material (chiefly 4,4-diphenyl-1-pentene by GLC analysis) and 4.8 g (43% yield) of acid which by qualitative GLC analysis as methyl esters on a 6 ft 1/8 in. column packed with Apiezon L on 80/100 mesh Varaport at 175 °C contained products, listed as previously: 93% (1.55, 3,3-diphenyl-5-hexenoic acid), 4% (1.82, unknown), and traces of two more volatile products which evidently arose from impurities in the starting chloride. Recrystallization of the acid from pentane gave a product of mp 105–106 °C which was identical in the NMR spectrum and gave no mixture melting point depression with an authentic sample[6] of 3,3-diphenyl-5-hexenoic acid (mp 106.0–106.5 °C).

Reaction of 2-Chloro-1,1,1-triphenylethane with Magnesium. These reactions were run under the general conditions and with the results summarized in Table I. For reactions with 7 mmol of 2-chloro-1,1,1-triphenylethane, 0.100 g-atom of magnesium was employed, while with 17 mmol of the chloride, 0.21 g-atom of magnesium was used. The solvent (200 mL) was freshly distilled into the reaction flask from the reagent indicated in the table. All of the reactions were initiated by addition of 2.0 mL (32 mmols) of methyl iodide. The reaction mixture was then stirred vigorously for 20 to 30 min at the reaction temperature to consume all of the methyl iodide (in a reaction, not recorded in the table, in which the methyl iodide was not all reacted with the magnesium before addition of the chloride, the rearranged Grignard reagent was found to have reacted preferentially with the methyl iodide to give 1,2,2-triphenylpropane). The 2-chloro-1,1,1-triphenylethane was then added in one portion as a solid by rotation of the goose-necked vial attached to a side arm of the Morton flask by a Ŧ24–40 joint. The reaction mixture was stirred vigorously with the high-speed stirrer at the initial reaction temperature and for the time indicated in Table I before carbonation. In many of the runs about half of the reaction solution was transferred before carbonation through a glass transfer tube (which extended to the bottom of the reaction flask) to a glass storage vessel, all under an atmosphere of nitrogen. The transfer tube contained a Kontes high-vacuum Teflon valve which, when open, permitted transfer of the reaction solution under a slight pressure of nitrogen. The portion of the solution in the storage vessel was kept at room temperature for the time indicated in the table before carbonation. For carbonation the reaction solutions were cooled to near 0 °C and then gaseous carbon dioxide was bubbled through the solution in the storage vessel or over the solution in the Morton flask with stirring. Carbon dioxide was passed slowly through or over the solutions overnight to ensure completion of carbonation. The reaction mixtures were then decomposed with excess dilute hydrochloric acid and extracted thoroughly with diethyl ether. The combined ethereal extracts were extracted with three 50-mL portions of 10% aqueous sodium hydroxide. The ether layer, after drying over anhydrous $MgSO_4$ and removal of ether, yielded the neutral products. The combined sodium hydroxide extracts were acidified with sulfuric acid and extracted thoroughly with diethyl ether; this ethereal extract, after drying over anhydrous $MgSO_4$ and removal of solvent, yielded the acidic products.

For quantitative analysis of the neutral products in Table I diphenylmethane was added as an internal standard; GLC analyses were done at 215 °C on a 6 ft × $^1/_8$ in. column packed with 10% Carbowax 20-M on 100–120 mesh Chromosorb Q. Typical retention times in minutes for the neutral products were Ph_2CH_2, 1.2; Ph_3CCH_3, 9.4; Ph_2CHCH_2Ph, 11.4; and Ph_3CCH_2Cl and $Ph_2C{=}CHPh$, 14.0. Unfortunately since the starting chloride decomposes to triphenylethylene under GLC conditions no analysis for triphenylethylene was possible; the combined yield of triphenylethylene and 2-chloro-1,1,1-triphenylethane for the runs of Table I varied from 4 to 16% save for the one run indicated which evidently contained much unreacted chloride.

For quantitative analysis of the acidic products in Table I diphenylacetic acid was added as an internal standard and then the acids were esterified with diazomethane. The methyl esters were subjected to GLC analysis at 200 °C on a 6 ft × $^1/_8$ in. column packed with 5% SE-30 on 80–100 mesh Varaport. Typical retention times in minutes for the methyl esters of the acids were Ph_2CHCO_2H, 1.6; $Ph_2C(CO_2H)CH_2Ph$, 9.2; and $Ph_3CCH_2CO_2H$, 11.2.

Reaction of 1-Chloro-2,2,3-triphenylpropane with Magnesium. Magnesium (5.0 g, 0.20 g-atom) which was freshly milled from magnesium rod (Fisher Scientific Co.) was allowed to react with 1-chloro-2,2,3-triphenylpropane (5.00 g, 16.3 mmol) in 200 mL of diethyl ether (freshly distilled from benzophenonesodium ketyl) under the same general conditions as described for 2-chloro-1,1,1-triphenylethane. About half of the solution was carbonated after 4.0 h of stirring at 27 °C and the remainder after standing at 25 °C for 23 h. The acids as methyl esters were quantitatively analyzed by GLC at 230 °C on a 6 ft × $^1/_8$ in. column packed with 3.5% OV-17 on 100–200 mesh Chromosorb W (AW DMCS). The 4.0-h fraction contained acids listed as mmoles (retention time in min, identity): 0.77 (12.1, $PhCH_2CPh_2CH_2CO_2H$), 0.30 (13.0, $(PhCH_2)_2CPhCO_2H$), 0.00 (14.6, $PhCH_2CH_2CPh_2CO_2H$). Likewise the 23-h fraction contained 2.5 mmol of $PhCH_2CPh_2CH_2CO_2H$, 1.00 mmol of $(PhCH_2)_2CPhCO_2H$, and no $PhCH_2CH_2CPh_2CO_2H$. In addition in both fractions there was a small amount of an unknown acid of retention time 4.8 min. The neutral products from the carbonation were analyzed by GLC on both OV-17 and Carbowax 20-M columns and were found[20] to contain primarily 1,2,2-triphenylpropane and no 1,1,3-triphenylpropane; however, separation of 1,2,2-triphenylpropane from 1,2,3-triphenylpropane proved to be difficult, such that the amount of 1,2,3-triphenylpropane, if any, can only be judged to be small.

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Registry No.—Magnesium, 7439-95-4; 5-chloro-4,4-diphenyl-1-pentene, 61323-44-2; 2-benzyl-2-phenyl-4-pentenoic acid, 62901-80-8; 3,3-diphenyl-5-hexenoic acid, 62901-81-9; 2-chloro-1,1,1-triphenylethane, 33885-01-7; 1-chloro-2,2,3-triphenylpropane, 16536-64-4.

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