REACTIONS OF DIAZOMETHANES WITH GRIGNARD REAGENTS

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The first recorded preparation of a compound of the diazomethane type was that of diazocamphor. This was prepared by Schiff and Maissen¹, who apparently did not appreciate the significance of the compound. It was not until Curtius² prepared diazoacetic ester that the aliphatic diazo compounds were established as a new class.

Both cyclic and linear formulas have been proposed for diazomethane and supported on the basis of the chemical and physical properties of the compound. In discussing the structure of aliphatic diazo compounds Taylor and Baker³ call special attention to the relatively recent work of Boersche. In a review of the work in this field Boersche⁴ considered the following possibilities for the structure of diazomethane:

He concluded that previously there had not been sufficient physical or chemical evidence to decide between the cyclic and linear formulas. He examined the compound by means of electron diffraction analysis and on the basis of his results proposed that diazomethane be regarded as a resonance-hybrid of structures II and III. Hurd⁵ in an excellent review and discussion of the structure and chemistry of aliphatic diazo compounds favors three linear formulas, one stable and two reactive. Using

¹ SCHIFF AND MAISSEN, Gazz. chim. ital., 11, 171 (1881).

² CURTIUS, Ber., 16, 2230 (1883).

³ TAYLOR AND BAKER, "Sidgwick's Organic Chemistry of Nitrogen." Oxford University Press, Oxford, 1937, p. 362.

⁴ BOERSCHE, Monatsh., 65, 331 (1935).

⁵ GILMAN, "Organic Chemistry," John Wiley & Sons, Inc., New York, 1938, Vol. I, p. 645.

the abridged electronic formulas, structure IV is the stable form and the resonance isomers V and VI the reactive forms.



Reactions with acids, alcohols, aldehydes, ketones, etc. may be represented as occurring with structure V and those with Grignard reagents, phosphines and others with structure VI.

The present research was undertaken for the purpose of gaining additional evidence concerning the intermediate compounds formed in the reactions of aliphatic diazo compounds, particularly with Grignard reagents, and of studying the generality of the reactions of diazomethane and substituted diazomethanes with Grignard reagents.

Zerner⁶ in his study of the reaction of diazoacetic ester and diazomethane with several Grignard reagents found evidence to indicate that hydrazones were formed. The reaction was represented by the following equations:



The similarity of Zerner's formula for the diazo compound to VI is worthy of note.

The final position of the hydrogen which upon hydrolysis replaced the --MgX group is of little value in interpreting the reaction since a hydrogen atom so easily rearranges. The --MgX group can be replaced⁷ by a variety of groups which do not readily rearrange and a part of the work here reported concerns such replacements. While replacement-labeling reactions are generally quite reliable there are some exceptions. Illustrative of this is the recent work of Kohler⁸ and co-workers, involving addition of bromomagnesium enolates to the carbonyl linkage. Therefore, particularly when dealing with ionized compounds as in the present case, conclu-

- ⁷ GILMAN AND SCHULZE, Rec. trav. chim., 47, 752 (1928).
- ⁸ KOHLER, TISHLER, AND POTTER, J. Am. Chem. Soc., 57, 2517 (1935).

⁶ ZERNER, Monatsh., 34, 1609 (1913).

sions concerning the structures of intermediates established by such replacement-labeling reactions are subject to certain limitations.

The diazo compound selected for this part of the study was diphenyldiazomethane. It was chosen because it contains no other reactive group, no easily rearrangeable hydrogen, also because of the relative ease of preparation, and because it has been used in many studies as a typical aliphatic diazo compound.

Diphenyldiazomethane was treated with an equimolecular amount of phenylmagnesium bromide, and hydrolyzed, benzophenone phenylhydrazone being obtained as was expected from the work of Zerner⁶ and Forster and Cardwell.⁹

The reaction was then repeated except that diphenylcarbamyl chloride was added to the reaction mixture of the phenylmagnesium bromide and diphenyldiazomethane before hydrolysis. On hydrolysis in the cold a yellow crystalline compound was formed. It was thought that the reaction might have taken place in the following manner:



If this mechanism is the correct one the intermediate compound, $(C_6H_5)_2C=N-N(MgBr)C_6H_5$, should be the same as that formed when benzophenone phenylhydrazone is treated with phenylmagnesium bromide. This intermediate compound should give the same final product when treated with diphenylcarbamyl chloride. This was found to be the case; the compounds were identical. The assumption that the compound obtained in both reactions was benzophenone 2,4,4-triphenylsemicarbazone was further supported by hydrolysis to benzophenone and a base corresponding in analysis and melting point to 2,4,4-triphenylsemicarbazide. The benzophenone triphenylsemicarbazone was also synthesized in a slightly different manner. Benzophenone phenylhydrazone was treated

⁹ FORSTER AND CARDWELL, J. Chem. Soc., 103, 861 (1912).

with sodium amide forming the sodium derivative and to this was added diphenylcarbamyl chloride. The product was the same as that formed by the other two methods.

Diphenyldiazomethane was next treated with benzylmagnesium chloride. Benzophenone benzylhydrazone was formed. The reaction was repeated except that diphenylcarbamyl chloride was added to the initial reaction product before hydrolysis. A well defined crystalline compound was obtained, presumably benzophenone 2-benzyl-4,4-diphenylsemicarbazone.

The compound was also synthesized from the known benzophenone 4,4-diphenylsemicarbazone¹⁰ by replacing the active hydrogen by —MgX and treating with benzyl bromide. The melting point of a mixture of the two compounds showed them to be the same. Upon hydrolysis benzophenone and a base corresponding in analysis to 2-benzyl-4,4-diphenylsemicarbazide were formed.

In order to carry out the primary reaction with another typical aliphatic Grignard reagent, methylmagnesium iodide was used. Benzophenone methylhydrazone was the product and was identified by hydrolysis to benzophenone and methylhydrazine.

From the reaction of unsubstituted diazomethane with phenylmagnesium bromide, Zerner⁶ isolated benzaldehyde phenylhydrazone which he supposed had been formed by the oxidation of 1-phenyl-2-benzylhydrazine. In the present work when diazomethane was allowed to react with a slight excess of phenylmagnesium bromide it was impossible to isolate any definite compound. However when a large excess of the Grignard reagent was used 1-phenyl-2-benzylhydrazine was formed. The reaction may be represented by the following equations:



¹⁰ TOSCHI AND ANGLIOLANI, Gazz. chim. ital., [1], [45, 205 (1915); [C. A., 9, 2388 (1915)]³.

The hydrazine was identified by oxidation with hydrogen peroxide to benzaldehyde phenylhydrazone.

The reaction of ethylmagnesium bromide with benzaldehyde phenylhydrazone reported by Grammaticakis¹¹ is of interest in this connection. With benzaldehyde phenylhydrazone, $1-\alpha$ -phenyl-*n*-propyl-2-phenylhydrazine was formed. With phenylhydrazones of ketones a similar reaction apparently did not occur.

When benzylmagnesium chloride was used with diazomethane under the same conditions as phenylmagnesium bromide, the product was 1methyl-2-benzylhydrazine rather than the expected l-benzyl-2-phenethylhydrazine. The 1-methyl-2-benzylhydrazine was identified by reduction to benzylamine and methylamine.

 $H_2C = N_2 + C_6H_5CH_2MgCl \rightarrow CH_3NHNHCH_2C_6H_5$

$\mathrm{CH_3NHNHCH_2C_6H_5} + \mathrm{H_2} \rightarrow \mathrm{CH_3NH_2} + \mathrm{C_6H_5CH_2NH_2}$

n-Butylmagnesium bromide with diazomethane formed a compound having the general properties and correct analysis for 1-methyl-2-*n*-butylhydrazine. It was not identified by the reduction method.

When diazomethane was treated with ethylmagnesium iodide, methylmagnesium iodide, and methylmagnesium bromide, respectively, decomposition occurred during the reaction and it was not possible to isolate definite compounds from the reaction mixtures.¹²

In the reactions of diazomethane with the benzyl and n-butyl Grignard reagents in which hydrazines were formed it is evident that a reaction equivalent to reduction must be involved.

Many studies have been made of the reducing action of Grignard reagents. Of these that by Kharasch and Weinhouse¹³ may be mentioned, and the reduction of nitrogen compounds by Gilman¹⁴ and coworkers, by Rheinboldt and Kirberg¹⁵, and by Franzen and Deibel.¹⁶ The reduction of nitrogen compounds by Grignard reagents is particularly significant with respect to the present work.

The only other known case in which a Grignard reagent apparently adds to a terminal atom is with isocyanides. The reaction does not go particu-

¹¹ GRAMMATICAKIS, Compt. rend., 202, 1289 (1936); 204, 502 (1937).

¹² MERLIN J. MAURY (State University of Iowa) has shown that phenyldiazomethane reacts with phenylmagnesium bromide and benzylmagnesium chloride to form benzaldehyde phenylhydrazone and benzaldehyde benzylhydrazone, respectively, in good yields.

¹³ KHARASCH AND WEINHOUSE, J. Org. Chem., 1, 209 (1936).

¹⁴ GILMAN AND COWORKERS, J. Am. Chem. Soc., 47, 2406 (1925); 48, 2004 (1926); Rec. trav. chim., 49, 212 (1930); 50, 522 (1931); J. ORG. CHEM., 2, 84 (1937).

¹⁵ RHEINBOLDT AND KIRBERG, J. prakt. Chem., **118**, 1 (1928).

¹⁰ FRANZEN AND DEIBEL, Ber., 38, 2716 (1905).

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larly well. Perhaps the most complete recent account of it was given several years ago.¹⁷

Attention may be called to an apparent lack of correlation between aliphatic diazo compounds and compounds like ketenes, isocyanates, and isothiocyanates. With these latter classes containing terminal cumulated unsaturated linkages Grignard reagents add to the terminal unsaturated linkage,

$$\begin{array}{c} \text{RN=C=O} + \text{RMgX} \rightarrow \text{RN=C-O-MgX} \\ \downarrow \\ \text{R} \end{array}$$

while with aliphatic diazo compounds the addition is apparently to the terminal atom. A reasonable conclusion is that the reactive form of the aliphatic diazo compounds with which Grignard reagents react does not have a terminal cumulated unsaturated linkage.

EXPERIMENTAL

Diphenyldiazomethane.—The method of preparation was a modification of that used by Staudinger.¹⁸ Mechanical stirring instead of shaking during the oxidation of the benzophenone hydrazone was found to be more convenient. Low-boiling (30-40°) petroleum ether was used. The yields obtained were a little lower (75-85%) than those recorded by Staudinger (85-98%) but the reaction time was shorter. With shaking, the time for complete oxidation was six to nine hours. With efficient stirring three to four hours was found to be sufficient.

Grignard reagents.—A standard solution of phenylmagnesium bromide (about 2 moles per liter) was prepared,¹⁹ and the desired amount was pipetted out for each experiment. This was found to be as accurate as individual preparations of phenylmagnesium bromide for each experiment, provided the bottle was kept tightly stoppered when not in use. The other Grignard reagents described were prepared just previous to their use.

The Grignard reagents were added slowly with stirring to ethereal solutions of diphenyldiazomethane by means of a dropping funnel. The reaction flask was kept at 0° to -5° to avoid decomposition of the diazo compound due to the heat of reaction.

Phenylmagnesium bromide with diphenyldiazomethane.—Twenty-eight grams (.14 mole) of diphenyldiazomethane was treated with 25.5 g. (.14 mole) of phenylmagnesium bromide. After addition of the Grignard reagent, the stirring was continued for one-half hour, and the reaction mixture was then hydrolyzed with ammoniacal ammonium chloride solution. A yellow crystalline solid insoluble in ether and water was formed. This was filtered off, dried, and weighed. It melted at $134-136^\circ$,* and a mixture with benzophenone phenylhydrazone showed no depression in melting point.

The ether layer was washed with water, dried over anhydrous sodium sulfate, and evaporated until nearly all of the ether was driven off. On cooling more benzo-

¹⁷ GILMAN AND HECKERT, Bull. soc. chim., 43, 224 (1928).

¹⁸ STAUDINGER, ANTHES, AND PFENNINGER, Ber., 49, 1928 (1916).

¹⁹ GILMAN AND MEYERS, Ind. Eng. Chem., **15**, 61 (1923); GILMAN, WILKINSON, FISHEL, AND MEYERS, J. Am. Chem. Soc., **45**, 150 (1923).

^{*} All melting points are uncorrected.

phenone phenylhydrazone separated. The mother liquor was not further investigated. The total yield of benzophenone phenylhydrazone was 27 g. (70%).

Diphenylcarbamyl chloride with the addition product of diphenyldiazomethane and phenylmagnesium bromide.—Thirteen grams (.07 mole) of diphenyldiazomethane in 50 cc. of dry ether was treated with 12 g. (.07 mole) of phenylmagnesium bromide. Stirring was continued for one-half hour after addition, and then 16 g. (.07 mole) of diphenylcarbamyl chloride in 75 cc. of ether was slowly added. The reaction mixture was allowed to stand at room temperature for two hours, and was then hydrolyzed with dilute hydrochloric acid in the cold. A yellow solid, benzophenone 2,4,4-triphenylsemicarbazone, precipitated. It was filtered, dried and weighed; weight 13 g. After two recrystallizations from alcohol the compound melted at $160-161^{\circ}$.

Anal. Calc'd for C₃₂H₂₅N₃O: N, 8.99. Found: N, 9.40.

Benzophenone 2,4,4-triphenylsemicarbazone from benzophenone phenylhydrazone. To 5 g. (.018 mole) of benzophenone phenylhydrazone in ether was added 3.4 g. (.018 mole) of phenylmagnesium bromide to replace the hydrogen by the -MgBrgroup. To this was added an ether solution of 4.2 g. (.018 mole) of diphenylcarbamyl chloride. The reaction mixture was hydrolyzed with dilute hydrochloric acid, leaving a light yellow precipitate which on recrystallization from alcohol melted at 160°, and by the melting point of a mixture proved to be identical with the benzophenone 2,4,4-triphenylsemicarbazone obtained in the previous experiment. The yield was 4 g. (47%).

Benzophenone 2,4,4-triphenylsemicarbazone from the sodium derivative of benzophenone phenylhydrazone.-Fifteen grams (.055 mole) of benzophenone phenylhydrazone and 3 g. (.07 mole) of sodium amide were intimately mixed by grinding quickly in a mortar. The mixture was transferred to a distilling flask and heated gently in a stream of dry hydrogen. On cooling, the sodiumbenzophenone phenylhydrazone solidified. The flask was broken under dry ether in a mortar; the contents were ground up quickly, and transferred to a three-necked flask with about 140 cc. of ether. To this mixture under vigorous stirring, was added 15 g. (.064 mole) of diphenylcarbamyl chloride in small portions. The reaction mixture was stirred for one-half hour after the addition was completed, and then 100 cc. of water added to dissolve the sodium chloride. The yellow solid which had formed was filtered off and recrystallized from alcohol; weight 8 g. The melting point was 156-158°, and the melting point of a mixture with the benzophenone 2,4,4-triphenylsemicarbazone obtained in the two previous experiments showed it to be the same compound. Two grams more of the compound was obtained from the ether layer. The total yield was 10 g. (39%).

Hydrolysis of benzophenone 2,4,4-triphenylsemicarbazone.—Two and five-tenths grams (.005 mole) of benzophenone triphenylsemicarbazone was refluxed with stirring in 85 g. of 20% hydrochloric acid for one-half hour. The solution was cooled, extracted with ether, and the dried ether layer was evaporated to an oil on a steam bath. When seeded with a crystal of benzophenone it solidified to a crystalline mass, which was shown to be benzophenone by comparison with an authentic sample; weight 0.8 g. (88%).

The acid water layer was made alkaline with sodium hydroxide, and extracted with ether; the dried ether layer was evaporated and 10 cc. of alcohol was added. On cooling, the white crystalline 2,4,4-triphenylsemicarbazide separated. The crystals after washing three times with small portions of alcohol melted at 124-125°. Rupe²⁰ records 128° as the melting point of 2,4,4-triphenylsemicarbazide.

²⁰ RUPE, Ber., 33, 247 (1900).

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Anal. Calc'd for C₁₉H₁₇N₈O: N, 13.86. Found: N, 14.27.

Diphenyldiazomethane with benzylmagnesium chloride.—Sixteen grams (.082 mole) of diphenyldiazomethane was treated in the usual way with a slight excess of benzylmagnesium chloride and the reaction mixture hydrolyzed. The crude product weighed 18.2 g. After recrystallization from alcohol it melted at 80.8-81.2°.

Diphenylcarbamyl chloride on the addition product of benzylmagnesium chloride and diphenyldiazomethane.—Eight grams (.041 mole) of diphenyldiazomethane was treated with 6.4 g. (.042 mole) of benzylmagnesium chloride. To the reaction mixture was added 8.8 g. (.04 mole) of diphenylcarbamyl chloride. The reaction mixture was hydrolyzed with ammonium chloride solution, and the yellow benzophenone 2-benzyl-4,4-diphenylsemicarbazone filtered off, dried, and weighed; weight 8 g. The melting point was 118-125°. After two recrystallizations from alcohol it melted at 137-139°.

Anal. Cale'd for C33H27N3O: N, 8.75. Found: N, 9.07.

Benzophenone 2-benzyl-4,4-diphenylsemicarbazone from benzophenone 4,4-diphenylsemicarbazone.—Four grams (.01 mole) of benzophenone 4,4-diphenylsemicarbazone, prepared according to the method given by Toschi and Angliolani¹⁰ was treated with 3.4 g. (.018 mole) of phenylmagnesium bromide in 25 cc. of dry ether to replace the active hydrogen with -MgBr. To the resulting reaction mixture was added 6 g. (.047 mole) of benzyl chloride and 25 cc. of dry benzene. The ether was then distilled off. The solution was refluxed for one hour, cooled, and hydrolyzed with dilute hydrochloric acid. The benzene layer was washed with water, dried over anhydrous sodium sulfate, and evaporated to a small volume. Absolute alcohol was added, and the solution was evaporated again to remove the remaining benzene. On standing in the cold a small crop of crystals formed; m.p. 125-130°. After two recrystallizations from alcohol they melted at 136-137°. The melting point of a mixture with the benzophenone 2-benzyl-4,4-diphenylsemicarbazone obtained in the preceding experiment showed them to be identical. The yield was 0.5 g. (10%).

Hydrolysis of benzophenone 2-benzyl-4,4-diphenylsemicarbazone.—Five grams (.01 mole) of benzophenone 2-benzyl-4,4-diphenylsemicarbazone was refluxed for one hour with 80 g. of 20% hydrochloric acid. The cold solution was extracted with ether, and the washed and dried ether solution was evaporated to an oil, which on standing solidified to crystalline benzophenone. The acid water layer was made alkaline and extracted with ether. The washed and dried ether solution was evaporated until nearly all of the ether had been driven off; 10 cc. of alcohol was added and the solution cooled. The crystals which formed melted at 109–110° after being washed twice with small portions of alcohol. The yield was 1.5 g. (50%). The compound is slightly soluble in ether and cold alcohol, and more soluble in hot alcohol.

Anal. Calc'd for C₂₀H₁₉N₈O: N, 13.7. Found: N, 14.00.

Diphenyldiazomethane with methylmagnesium iodide.—Using 13.2 g. of diphenyldiazomethane and a slight excess of methylmagnesium iodide, the reaction was carried out and the product isolated as previously described for the reaction with benzylmagnesium chloride. The crude product weighed 12 g. After recrystallization from alcohol it melted at $42-43^{\circ}$ in a capillary tube. On a copper bar the melting point was $46-47^{\circ}$. The product was hydrolyzed by refluxing for ten hours with dilute sulfuric acid (6N). Benzophenone and methylhydrazine sulfate were obtained. After recrystallization both were identified by melting points.

Diazomethane.-This compound was prepared by the method of Arndt.²¹

²¹ Organic Syntheses, John Wiley & Sons, N. Y., 1935, Vol. 15, p. 3.

Diazomethane with phenylmagnesium bromide.—To a solution of phenylmagnesium bromide containing approximately 0.20 mole was added dropwise with stirring 0.05 mole of diazomethane dissolved in anhydrous ether. The reaction was carried out in an atmosphere of nitrogen and at room temperature or a few degrees below. The mixture was stirred for several hours and then hydrolyzed with ammonium chloride solution. The ethereal layer was dried and a solution of hydrogen chloride in anhydrous ether added until precipitation was complete. The weight of the hydrochloride was 5.6 gr. (48% yield). It was purified by preparing the free base in ether and again adding ethereal hydrochloric acid.

Anal. Calc'd for C13H15ClN2: Cl, 15.38. Found: Cl, 15.30.

The oxalate was prepared by adding an alcoholic solution of oxalic acid to an ethereal solution of the free base. The melting point of the oxalate was 187-188°. The melting point of the oxalate of 1-phenyl-2-benzylhydrazine recorded in the literature is 190°. The compound was further identified by oxidation to benzalde-hyde phenylhydrazone with hydrogen peroxide according to the method of Thiele.²² The product was identified by comparison with an authentic sample of benzaldehyde phenylhydrazone.

Diazomethane with benzylmagnesium chloride.—Using 0.05 mole of diazomethane the reaction was carried out as described with phenylmagnesium bromide. The 1-methyl-2-benzylhydrazine hydrochloride weighed 3.5 g. (41% yield). It melted at 139-140°.

Anal. Calc'd for C₈H₁₃ClN₂: Cl, 20.6. Found: Cl, 20.3.

The product was reduced to benzylamine and methylamine by sodium amalgam by the method of Schlenk.²³ The amines were separated by fractional distillation of an ethereal solution and converted to the substituted benzamides which were identified by comparison with authentic samples.

Diazomethane with n-butylmagnesium bromide.—The usual procedure was followed except that the temperature of reaction was about 5°. From 5.1 g. of diazomethane, 9 g. of the hydrochloride of methyl-2-n-butylhydrazine was obtained (53% yield). The melting point was 114–115°.

Anal. Calc'd for C₅H₁₅ClN₂: Cl, 25.6. Found: Cl, 25.4.

Diazomethane with ethylmagnesium iodide, methylmagnesium iodide, and methylmagnesium bromide.—Reactions were carried out with the three reagents in the usual way. However, in each case as the diazomethane came in contact with the Grignard reagent there was an evolution of gas. No hydrazine hydrochloride was isolated.

SUMMARY

1. Evidence is presented concerning the apparent structure of the intermediate compounds formed in the addition of Grignard reagents to diphenyldiazomethane.

2. Diazomethane reacts with phenylmagnesium bromide to form 1phenyl-2-benzylhydrazine, with benzylmagnesium chloride to form 1methyl-2-benzylhydrazine, and with *n*-butylmagnesium bromide to form 1-methyl-2-*n*-butylhydrazine.

²² THIELE, Ann., 376, 267 (1910).
²³ SCHLENK, J. prakt. Chem., 78, 52 (1908).