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The Reaction of 1-Alkynes with Organometallic Compounds. IV.[1] Reactions in the Presence of Dioxane

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Halogen-free diethylmagnesium reacts with hexyne-1 three times as fast as ethylmagnesium bromide. The relative reactivity of hexyne with the reaction mixture produced by the addition of dioxane to ethylmagnesium bromide is a function of the quantity of dioxane and agitation time. Whereas the carbonation of hexynylmagnesium bromide does not yield 2-heptynoic acid, this acid was produced in 73% yield by the carbonation of dihexynylmagnesium. The reaction mixtures of ethylmagnesium bromide, hexyne and dioxane also yield this acid when carbonated. The reactivity of such mixtures toward other functional groups is also described. Such mixtures are useful synthetic reagents.

In the determination of relative rates of evolution of the hydrocarbon, R–H, in the reaction

$$\text{R—Mg—X} + \text{C}_4\text{H}_9\text{C}{\equiv}\text{C—H} \longrightarrow \text{R—H} + \text{C}_4\text{H}_9\text{C}{\equiv}\text{C—MgX} \quad (1)$$

the value of 100 (based on half-lives) was assigned to the reaction of the ethyl Grignard reagent ($R = C_2H_5$, $X = Br$) when the reaction contained equimolar quantities in one normal ether solution and proceeded at the reflux temperature of the mixture.[3] In this paper we are reporting the results of experiments conducted in the presence of dioxane. They were performed in order to ascertain certain facts which will eventually be helpful in the understanding of the mechanism of such reactions.

Ether solutions of Grignard reagents are complex mixtures of compounds and ions.[4] The equilibrium reaction postulated by Schlenk[5] is a useful, although oversimplified, representation of such mixtures.

$$2\text{RMgX} \rightleftharpoons \text{R}_2\text{Mg} + \text{MgX}_2 \qquad (2)$$

Since one of the components was thought to be dialkylmagnesium, we determined the relative reactivity of diethylmagnesium (0.25 mole) with hexyne-1 (0.5 mole) in a one normal ether solution. The reaction was about three times as fast as the comparable one using "ethylmagnesium bromide." The relative reactivity of 300 was established on the basis of the half-life, the evolution of 0.25 mole of ethane.[6] This information is of great interest since the literature contains no comparisons of reactivities of organomagnesium compounds in reactions yielding a hydrocarbon. The diethylmagnesium was prepared by the method[7] of Noller in which dioxane was added to "ethylmagnesium bromide" and the precipitate removed by centrifugation. The supernatant solution was evaporated to dryness.[8] The gray solid residue containing less than 0.4% of bromine was redissolved in ether. The solid could have contained traces of strongly associated molecules of dioxane. However, its possible presence is of no significance. This became apparent when the relative reactivity of a solution of 1 mole of diethylmagnesium and half a mole of dioxane in ether (1 normal solution) was found to be 299. Thus, the presence of dioxane solvent can be compared to tetrahydrofuran which was also found to be without effect on the rate of such reactions.

Since such a preparation of "halogen free" diethylmagnesium is lengthy and hazardous, we also established the relative reactivity of hexyne-1 with the heterogeneous mixture produced by the addition of dioxane to "ethylmagnesium bromide." The results, plotted in Fig. 1, show that dioxane shifts the position of equilibrium of equation 2 toward the right. The increase in the reactivity, which we interpret as the result of an increase in the amount of diethylmagnesium present, is a function of the amount of dioxane added (up to one equivalent quantity per RMgX) and the time interval between the addition of dioxane to RMgX and the addition of hexyne-1 (reflux time in Fig. 1). The presence of an excess of one equivalent of dioxane (for example 1.75 equiv., and 30 min. of reflux time) did not change the reactivity within the limits of our experimental error.

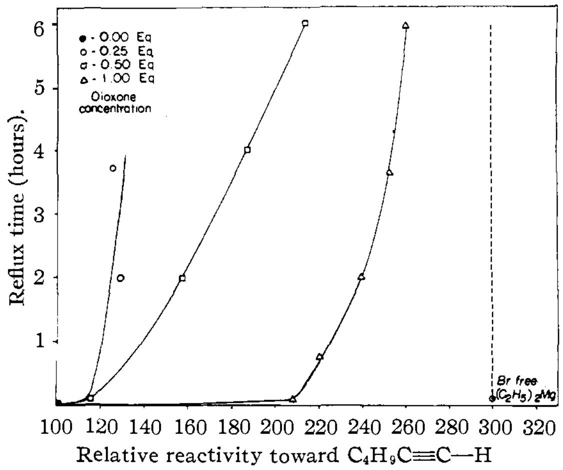

Fig. 1.—"Schlenk equilibrium" $2C_2H_5MgBr \rightleftharpoons (C_2H_5)_2Mg + MgBr_2$.

The relationship between the amount of dialkylmagnesium produced by the addition of dioxane and agitation time was previously recognized.[7,9] The present method of analysis is somewhat shorter, possibly more reliable and in good agreement with

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[1] Part III, *J. Org. Chem.*, **20**, 1545 (1955).

[2] National Science Foundation Predoctoral Fellow.

[3] J. H. Wotiz, C. A. Hollingsworth and R. Dessy, THIS JOURNAL, **77**, 103 (1955).

[4] For a comprehensive review see M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Inc., New York, N. Y., 1954, pp. 104–115, and references therein.

[5] W. Schlenk and W. Schlenk, *Ber.*, **62B**, 920 (1929).

[6] Between the $^1/_2$-life and the $^3/_4$-life the reaction of Et_2Mg with hexyne was twice as fast as the reaction of EtMgBr.

[7] C. Noller and W. White, THIS JOURNAL, **59**, 1354 (1937).

[8] G. Coleman and R. Blomquist, *ibid.*, **63**, 1693 (1941).

[9] R. Kullman, *Compt. rend.*, **231**, 866 (1950).

the ones listed. The experimental points listed in Fig. 1 are reproducible with an accuracy of ±2.5%. The plots indicate that the reactivity of halogen-free diethylmagnesium is not reached when one equivalent of dioxane is present. Even when reflux time was extended to 12 hours the reactivity was again 261. This experimental point does not appear in Fig. 1.

The results described above suggested the need for comparison of reactivities of Grignard reagents with dialkylmagnesium compounds (halogen-free or in the mixture produced by the addition of dioxane to a Grignard reagent) toward other functional groups. Gilman[10] concluded that phenylmagnesium bromide is more reactive than diphenylmagnesium toward valeronitrile and Cope[11] found a similar relationship toward dimethyl sulfate. Other workers[5,12] considered RMgX and R_2Mg as being equally reactive. Aston,[13] however, found that methylmagnesium iodide in butyl ether reacts one-fiftieth as rapidly with acetone than with dimethylmagnesium. Wright[14] showed that in a reaction with benzoin, dimethylmagnesium shows a preferential reaction with the hydroxyl group. With enolizable ketones, dimethylmagnesium[14] is less reactive toward the carbonyl group than is methylmagnesium iodide.

In this paper is also reported a comparison of the nature and yield of products in reactions of other functional groups toward some Grignard reagents and Grignard reagent–dioxane mixtures. The selected reactions were the ones where Grignard reagents are known to form a single product in very low yield or the reactions where more than one product is formed. Differences were anticipated because of possible changes in the reactivity of RMgX and R_2Mg as a result of electronic and steric factors. Since 1-alkynylmagnesium halides are of low reactivity,[15] carbonation by pouring onto Dry Ice[16] yields less than 5% of acidic product. However, 2-heptynoic acid, $C_4H_9C\equiv C—CO_2H$, was prepared in 73% yield when dihexynylmagnesium in ether (prepared from "halogen-free" diethylmagnesium and hexyne-1) was poured onto Dry Ice, thus showing the enhanced reactivity of dihexynylmagnesium, $(C_4H_9C\equiv C)_2Mg$, over hexynylmagnesium bromide toward solid carbon dioxide.

The position of the equilibrium of reaction 2 (R = $C_4H_9C\equiv C—$) can also be shifted toward the right by the addition of dioxane. This was demonstrated by adding dioxane to an ether solution of hexynylmagnesium bromide (prepared from "ethyl Grignard" and hexyne-1) refluxing the heterogeneous mixture for two hours; carbonation by pouring onto Dry Ice produced 2-heptynoic acid in a 38% yield. The reverse addition of reagents produced the acid in 60% yield upon carbonation.

Since the reaction of hexynylmagnesium bromide with acetonitrile does not yield an acetylenic ketone on hydrolysis,[17] we tried to produce the ketone by allowing acetonitrile to react with the mixture produced by the addition of dioxane to ethylmagnesium bromide followed, after five hours, with hexyne. This also failed to produce the ketone. These experiments indicate that although we have increased the reactivity of the organometallic species (as seen in the reaction with CO_2), the other reactant must also be sufficiently reactive. The relative reactivity of nitriles,[18] α-acetylenic nitriles in particular, toward Grignard reagents was found to be of the lowest order among the functional groups reacting with phenylmagnesium bromide.

The carbonation of the Grignard reagent from 1-bromoheptyne-2, $C_4H_9—C\equiv C—CH_2Br$, is known to yield a mixture of 3-octynoic acid, $C_4H_9C\equiv C—CH_2CO_2H$, and butylbutadienoic acid, $C_4H_9C(CO_2H)=C=CH_2$.[19] The addition of an equimolar quantity of dioxane to this Grignard reagent changed the yield of the mixture of acids from 36% to only 5%. However, there was a change in the composition of the produced mixture of acetylenic and allenic acid. There was more (84% as compared to 68%) allenic acid in the mixture formed in the presence of dioxane. In coupling reactions of 1-bromoheptyne-2 with ethylmagnesium bromide, dioxane did not change the nature of product. In both cases 3-ethylheptadiene-1,2 was the only product; however, the yield decreased from 49 to 38% when dioxane was present.

When ethylmagnesium bromide (0.55 mole) reacted with butyryl chloride (0.55 mole) in ether at room temperature, there was obtained 29 g. of product boiling from 110 to 136°; only 16.4 g. of product resulted if the reaction was carried out in the presence of dioxane. These fractions contained hexanone-3 in 21 and 11% yields, respectively. There was no change in yield or composition of products when the reactions were cooled to −78°.

Experimental

Ethylmagnesium bromide and **hexyne-1** were the same reagents described in reference 1.

Dioxane.—1,4-Dioxane was purified by adding ethylmagnesium bromide until any vigorous reaction ceased and distilling the resulting suspension; b.p. 99°, $n^{26}D$ 1.4199.

Diethylmagnesium.—To ethylmagnesium bromide prepared in the usual manner[3] was added slowly 1.33 equivalents of purified dioxane.[7] The temperature of the mixture was kept at 0°. After complete addition the thick white suspension was permitted to come to room temperature and was agitated for nine hours on a wrist action shaker. The mixture was then subjected to centrifugation until a clear supernatant liquid was obtained. This was transferred under a dry nitrogen atmosphere to a flask attached to a vacuum line and the ether–dioxane mixture removed at room temperature, leaving a grayish-white solid. The vacuum was broken with dry nitrogen and the solid redissolved in dry ether. The resulting solution was transferred to permanent storage vessels by means of a glass tube containing a fritted glass filter to remove any suspended material. An aliquot of diethylmagnesium solution was hydrolyzed, and the basic magnesium was determined by titration using the technique suggested by Gilman for assay of Grignard reagents. The total halide content was determined using a potentiometric titration with silver nitrate.

Determination of Rates.—All determinations except those involving diethylmagnesium[19a] were made using 0.02-mole

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(10) H. Gilman and R. Brown, This Journal, **52**, 1181 (1930).

(11) A. Cope, *ibid.*, **56**, 1578 (1934).

(12) P. Bartlett and C. Berry, *ibid.*, **56**, 2683 (1934).

(13) J. Aston and S. Bernhard, *Nature*, **165**, 485 (1950).

(14) G. Wright, This Journal, **61**, 1152 (1939).

(15) H. Gilman, E. St. John, N. St. John and M. Lichtenwalter, *Rec. trav. chim.*, **55**, 577 (1936).

(16) J. H. Wotiz and E. Hudak, *J. Org. Chem.*, **19**, 1580 (1954).

(17) J. Kroeger and J. Nieuwland, This Journal, **58**, 1861 (1936).

(18) C. Enteman and J. Johnson, *ibid.*, **55**, 2900 (1933).

(19) J. Wotiz, *ibid.*, **72**, 1639 (1950).

(19a) Note added in proof.—The reactions of diethylmagnesium have been duplicated in the semimicro apparatus.

quantities and were measured in the gasometric apparatus previously described.[1] The Grignard reagent and the proper amount of dry ether were added and the reaction mixture brought to reflux. The dioxane was then added as rapidly as possible, avoiding excessive spattering. In order to keep the concentrations approximately one normal throughout the study, a volume of ether, equivalent to that of the dioxane to be added, was withheld at the beginning of the run. Possible volume changes in replacing ether with the dioxane were neglected.

The addition of dioxane to the refluxing ether solution of the Grignard reagent resulted immediately in a bulky white precipitate. The amount of precipitate was a function of the amount of dioxane used. The solution became very viscous. As the suspension was stirred, however, the viscosity of the mixture decreased and at the end of an hour it was quite fluid. Care was taken to avoid bumping during the reflux period and to avoid splashing the solid on the side of the reaction vessel. The washing action of the refluxing ether usually kept such misplacement of the reactants to a minimum.

The addition of hexyne-1 to the suspension resulted in the immediate release of ethane, and the rate of evolution was measured. The rate of reaction of diethylmagnesium with hexyne-1 was measured using 0.25-mole quantities and employing apparatus described in reference 3.

Preparation of 2-Heptynoic Acid.—(a) Dihexynylmagnesium (0.25 mole) was poured onto a mixture of Dry Ice and dry ether and stirred intermittently over a one-hour period. The mixture was hydrolyzed with saturated ammonium chloride solution, and a small amount of dilute hydrochloric acid was added to make the solution acid. The ether layer was extracted with sodium carbonate solution and the aqueous phase combined. This was acidified with cold dilute hydrochloric acid (1:1) and extracted with ether. After washing and drying over magnesium sulfate, distillation gave 45.5 g., 73% yield,[20] of 2-heptynoic acid, b.p. 108–110° at 5.5 mm., $n^{26}\text{D}$ 1.4600; reported b.p. 122° at 10 mm., $n^{20}\text{D}$ 1.4619.

(b) Into a refluxing solution of 0.275 mole of ethylmagnesium bromide (1 *M*) was added 0.275 mole of purified dioxane. The resulting suspension was stirred vigorously and kept at reflux for five hours. Then 0.25 mole of hexyne-1 was added and the mixture stirred for one hour. The entire slurry was carbonated in the same manner as described above and worked up. Distillation gave 19.0 g., 60%, of 2-heptynoic acid.

(c) Into a refluxing solution of 0.275 mole of ethylmagnesium bromide (1 *M*) was added 0.25 mole of hexyne-1. The solution was stirred at reflux for 1.5 hours and 0.275 mole of purified dioxane added. Stirring and reflux were continued for two hours, and the suspension was carbonated as described above. Upon working up in the usual manner, a 38% yield of heptynoic acid was obtained.

Dihexynylmagnesium with Acetonitrile.[21]—Into a refluxing solution of 0.275 mole of ethylmagnesium bromide (1 *M*) was added 0.275 mole of purified dioxane. The mixture was refluxed for five hours, and 0.25 mole of hexyne-1 was added. This suspension was stirred for one hour, and 0.25 mole of redistilled acetonitrile was added. The reaction mixture was stirred at reflux for five hours and then allowed to stand overnight. It was quenched with saturated ammonium chloride and poured onto a 2:1 mixture of ice–hydrochloric acid; the ether layer separated, and the water layer boiled vigorously for one hour. The water layer was then extracted with ether, and all ether fractions were combined. No ketone was isolated.

3-Octynoic Acid and Butylbutadienoic Acid.—1-Bromoheptyne-2 (70 g., 0.4 mole) was converted into the Grignard reagent using the previously described high dilution technique.[19] The ether solution (600 ml.) was divided in half. (a) One half was carbonated by pouring onto a Dry Ice and ether mixture.[22] The acidic product weighed 10 g. (36% yield). Infrared spectroscopic analysis[23] showed it to contain 68% of allenic component. The yield of butylbutadienoic acid was therefore 6.8 g. or 24.5% of theory. (b) To the second half was added 17.6 g. (0.2 *M*) of dry dioxane. An exothermic reaction and the formation of a white suspended solid was noted. The mixture was stirred and refluxed for four hours. The carbonation was as described in part a. The mixture of acids weighed 1.4 g. (5% yield). Spectroscopic analysis showed that 84% was the allenic acid. The yield of butylbutadienoic acid was therefore 1.2 g. (4.0%).

Ethylmagnesium Bromide and 1-Bromoheptyne-2.—(a) To ethylmagnesium bromide (0.38 mole) in 180 ml. of ether solution was added 52.5 g. (0.3 mole) of 1-bromoheptyne-2 in 60 ml. of ether at a rate to maintain refluxing (20 min.). Two layers appeared. After stirring and refluxing for 15 minutes, concd. ammonium chloride was added. Distillation of the organic portion yielded 18 g. (49% yield) of material which boiled from 125 to 147°. The range of the index of refraction of this mixture at 25° was from 1.4290 to 1.4356. Most of the material boiled at 146 to 147°, $n^{25}\text{D}$ 1.4356. Its infrared spectrum[23] showed a sharp single band at 5.2 μ (1930 cm.$^{-1}$) characteristic of allenes[24] and the absence of bands attributed to acetylenic linkages.[25] Since nonyne-4 was reported[26] to boil at 150–154° at 750 mm., $n^{25}\text{D}$ 1.4296, it is concluded that the product was 3-ethylheptadiene-1,2 free from nonyne-4. The material boiling higher than 147° was the unreacted halide (12 g.). (b) To 0.38 mole of ethylmagnesium bromide in 180 ml. of ether solution was added 31 g. (0.35 mole) of dioxane and the mixture was refluxed and stirred for four hours; 1-bromoheptyne-2 (52.5 g., 0.3 mole) in 60 ml. of ether was added at a rate to maintain refluxing (15 min.). The reaction was worked up as described in part a. There were 14 g. (38% yield) of the allenic hydrocarbon boiling from 105 to 145° (mainly at 145°), showing $n^{25}\text{D}$ 1.4235 to 1.4347 (mainly 1.4347). The higher boiling unreacted halide weighed 17 g.

Ethylmagnesium Bromide and Butyryl Chloride.—(a) To 0.55 mole of ethylmagnesium bromide in 550 ml. of ether solution was added 48.4 g. (0.55 mole) of dry dioxane. The mixture was stirred and refluxed for five hours and added to 58 g. (0.55 mole) of freshly redistilled butyryl chloride dissolved in 100 ml. of dry ether at a rate to maintain refluxing. The product was stirred and refluxed for 20 min. and then hydrolyzed with a concentrated solution of ammonium chloride. The ether layer was dried and distilled, yielding 16.4 g. of a fraction boiling from 110 to 136°. This fraction was assayed for hexanone-3 using the hydroxylamine titration method.[27] Blanks were also determined to correct for any hydrochloric acid originating from any hydrolyzed unreacted butyryl chloride found in the analyzed fraction. The hexanone-3 content was 5.5 g. (10.5% yield). (b) An identical reaction which omitted the dioxane produced 29 g. of liquid which contained 10.7 g. (21% yield) of hexanone-3. (c) An identical reaction as in part a which was cooled in a Dry Ice–acetone slurry during the addition to butyryl chloride produced 17.5 g. of liquid which contained 6.4 g. (13% yield) of hexanone-3. (d) The reaction at −78° without dioxane gave 29 g. of liquid which contained 11 g. (22% yield) of hexanone-3.

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(20) The dihexynylmagnesium used had been stored for six months without elaborate precautions. Some decomposition could have occurred, and the actual yield of acid may be higher.

(21) We have attempted as far as is possible to duplicate the experimental conditions of Kroeger and Nieuwland, reference 16.

(22) J. Wotiz and J. Matthews, *J. Org. Chem.*, **20**, 155 (1955); footnote 4.

(23) Dr. F. A. Miller and co-workers, Mellon Institute, Pittsburgh, Pa.

(24) J. Wotiz and W. Celmer, THIS JOURNAL, **74**, 1860 (1952).

(25) J. Wotiz and F. Miller, *ibid.*, **71**, 3441 (1949).

(26) T. Vaughn, G. Hennion, R. Vogt and J. Nieuwland *J. Org. Chem.*, **2**, 1 (1937).

(27) S. Siggia, "Quantitative Organic Analysis *via* Functional Groups," 2nd Edition, John Wiley and Sons, Inc., New York, N. Y., 1954, p. 27.