

the remaining high boiling fraction resulted in a small amount of benzoic acid.

The products from the benzoyl peroxide-phenol reaction were investigated in a similar manner. The solid acid mixture obtained by bicarbonate extraction, acidification, ether extraction, ether evaporation and drying, melted at 121° and had a neutral equivalent of 121 without recrystallization. No ferric chloride test could be obtained from solutions of the acid.

### Summary

The decomposition of benzoyl peroxide in the presence of ten ethers, five alcohols, five phenols, and four amines has been studied quantitatively. In most of the ethers (anisole and diphenyl ether excepted) the reaction is very rapid. Although of first order, it is strongly inhibited by oxygen and is hence a chain reaction. The same is true of the peroxide decomposition in primary and secondary alcohols, the accelerating effect of *t*-butyl alcohol being less marked.

In the presence of phenols and amines oxygen inhibition is slight or lacking, but the decomposition still is of nearly first order with respect to peroxide.

The increased rate of decomposition of the peroxide in ethers and amines is not accompanied by increased polymerization of vinyl acetate present in the same solutions.

The products of the reaction have been investigated in several cases. Reasons are given for believing that benzoate radicals attack ethers with removal of  $\alpha$ -hydrogen, phenols with removal of hydroxylic hydrogen, secondary amines with removal of hydrogen from nitrogen, tertiary amines with rupture of the carbon-nitrogen bond, and alcohols with rupture of carbon-hydrogen, oxygen-hydrogen, and possibly also carbon-oxygen bonds.

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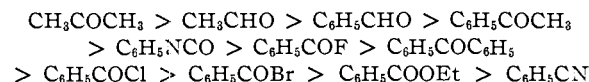
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[CONTRIBUTION NO. 1113 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, AND THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

## The Mechanism of Addition of Grignard Reagents to Nitriles

BY C. GARDNER SWAIN<sup>1</sup>

The addition reactions of Grignard reagents are difficult to study kinetically due to their high speed. It has been demonstrated by competition experiments<sup>2</sup> that the relative reactivity of different addends with phenylmagnesium bromide is



Direct rate measurement is easily possible only with nitriles and esters, since the others react practically completely in a few minutes or less.

None of the studies which are reported in the literature establish the kinetic order of the reaction of any of these addends with a Grignard reagent or other organometallic compound. However, Gilman developed a sensitive color test<sup>3</sup> for the presence of organometallic reagents, and by assuming constant sensitivity for the test and noting the time for disappearance of a positive test on aliquots taken periodically from the reaction mixture, the series of relative reactivity of different nitriles<sup>4</sup> (Table I) and of different reagents<sup>5,6</sup> (Tables II and III) were established.

If there were a sluggish equilibrium between dialkylmagnesium, present in considerable concentration, and alkylmagnesium bromide in an

ordinary Grignard solution, we should expect to find a complicated dependence of rate upon concentration in any kinetic study. Dioxane precipitations do not give a clear picture of the composition of solutions of Grignard reagents, because the composition of the precipitate changes at a rapid rate after the dioxane is added.<sup>7</sup>

With the aid of the color test, Gilman and Brown found that diphenylmagnesium completely free from halide reacts twenty times more slowly than phenylmagnesium bromide with *n*-valeronitrile. However, in the presence of equivalent magnesium iodide or bromide, diphenylmagnesium reacts within a few minutes to give phenylmagnesium iodide or bromide so completely that there is no detectable magnesium iodide or bromide left in the solution.<sup>8</sup> Similar results were obtained by Gilman and Fothergill on aliphatic Grignard reagents.<sup>8</sup> The simplicity of the kinetics which we actually obtained below with the *n*-butyl Grignard reagent support this idea that the equilibrium is either rapid or else well on the side of alkylmagnesium bromide.

### Determination of the Kinetic Order

The reaction between *n*-butylmagnesium bromide and benzonitrile in ether solution was followed by measuring evolution of gas from aliquot samples taken periodically from the reacting solution. It is homogeneous and second order with a rate constant of  $3.7 \pm 0.6 \times 10^{-4}$  l. mole<sup>-1</sup> sec.<sup>-1</sup> at 25°, and  $5.8 \pm 0.9 \times 10^{-5}$  at 0°. This corre-

(7) Noller and White, *THIS JOURNAL*, **59**, 1354 (1937).

(8) Gilman and Brown, *ibid.*, **52**, 1181 (1930); Gilman and Fothergill, *ibid.*, **51**, 3149 (1929).

(1) National Research Fellow, 1945-1946; American Chemical Society Fellow, 1946-1947.

(2) Entemann and Johnson, *THIS JOURNAL*, **55**, 2900 (1933); Kharasch and Cooper, *J. Org. Chem.*, **10**, 46 (1946).

(3) Gilman and Schultze, *THIS JOURNAL*, **47**, 2002 (1925).

(4) Gilman and Lichtenwalter, *Rec. trav. chim.*, **55**, 588 (1936).

(5) Gilman and Young, *J. Org. Chem.*, **1**, 315 (1936).

(6) Gilman, St. John, St. John and Lichtenwalter, *Rec. trav. chim.*, **55**, 577 (1936).

TABLE I  
 ADDITION OF PHENYLMAGNESIUM BROMIDE TO NITRILES<sup>a</sup>

Nitrile	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CN	C <sub>6</sub> H <sub>5</sub> CN	$\left\{ \begin{array}{l} m\text{-CH}_3\text{C}_6\text{H}_4\text{CN} \\ p\text{-CH}_3\text{C}_6\text{H}_4\text{CN} \end{array} \right\}$	<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CN	<i>p</i> -(CH <sub>3</sub> ) <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CN
Time, hr.	0.09	0.31	0.55	1.7	5.1
Ratio	.29	1.00	1.8	5.5	16

 TABLE II  
 ADDITION OF PHENYLACETYLENYLMETALLIC REAGENTS TO BENZONITRILE<sup>b</sup>

Metal	Cs	K	Na	Li	MgBr
Time, hr.	(3.9)	4.4 (5.8)	6.8	60	86
Ratio	1.00	1.5	2.1	18	26

 TABLE III  
 ADDITION OF GRIGNARD REAGENTS TO BENZONITRILE<sup>c</sup>

Radical	Mesityl	Allyl	<i>p</i> -Tolyl	Phenyl	Ethyl	<i>n</i> -Propyl
Time, hr.	0.01	0.05	0.10	0.31	0.85	3.1
Ratio	.03	.16	.32	1.00	2.7	10

Radical	<i>i</i> -Propyl	<i>n</i> -Butyl	<i>s</i> -Butyl	<i>t</i> -Butyl	Phenylethynyl
Time, hr.	3.7	4.2	12	25	77
Ratio	12	14	39	81	250

<sup>a</sup> Conditions: 0.67 *M* RMgBr, 0.8 *M* nitrile, ether solution, 25°. <sup>b</sup> Conditions: 0.4 *M* RM, 0.8 *M* C<sub>6</sub>H<sub>5</sub>CN, ether suspension, 25°, for values in parenthesis; 0.5 *M* RM, 1.0 *M* C<sub>6</sub>H<sub>5</sub>CN for others. <sup>c</sup> Conditions: Same as in (a). The reaction was nearly quantitative addition since benzonitrile has no active hydrogen. A mixture of 0.075 mole of mesitylmagnesium bromide and 0.075 mole of benzonitrile, gave 92% of benzoylmesitylene and 4% of benzophenone after hydrolysis and purification (*cf.* 92%/8% calculated from 30-fold ratio observed in direct rate measurement with color test); a mixture of phenyl and *n*-butylmagnesium bromides gave 70% benzophenone and 9% *n*-valerophenone (*cf.* 86%/14% calculated from 14-fold ratio); and a mixture of *n*-butyl and phenylethynylmagnesium bromides gave 68% *n*-valerophenone (*cf.* 90%/10% calculated from 18-fold ratio). The first two of these competition experiments would not be consistent with relative reactivities differing by more than a factor of about three from those obtained above by direct rate measurements with the color test. Saturation of the solution with magnesium bromide had no effect on the time.<sup>9</sup>

sponds to a half life of 7.6 hours with 0.1 *M* reactants at 25° and to an activation energy of 12.0 ± 1.0 kcal.

An attempt was made to follow the reaction between phenyllithium and benzonitrile by a technique involving the taking of aliquots. However, the reaction was at the very least two thousand times as fast as the reaction between *n*-butylmagnesium bromide and benzonitrile, or over one hundred times as fast as that between phenylmagnesium bromide and benzonitrile (Table III), and could not be followed.

### Discussion

The second order kinetics of the reaction between *n*-butylmagnesium bromide and benzonitrile eliminates from consideration a mechanism involving a unimolecular or solvolytic ionization of the organometallic reagent to a carbanion as the rate determining step.

Formation of a complex between reagent and

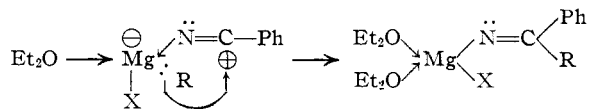
(9) Gilman and St. John, *THIS JOURNAL*, **49**, 222 (1930).

addend seems to be eliminated as the rate determining step by the whole series of relative reactivity of different nitriles obtained by Gilman (Table I). For example, benzonitrile reacts faster with phenylmagnesium bromide than does *p*-tolunitrile, although the latter would be expected to be more nucleophilic and to form a stronger complex from a consideration of inductive effects.

A rate-determining reaction of a complex with a second molecule of Grignard reagent is eliminated because it would require the kinetics to be second order in the reagent alone and third order over-all.

Direct reaction of Grignard reagent with nitrile is unlikely, because then we should expect the aliphatic reagents to react faster than phenyl Grignard. Ethylsodium will react with benzene to give phenylsodium and ethane,<sup>10</sup> demonstrating that the "salts" of ethane (considered as a very weak acid) are less stable at equilibrium than the "salts" of benzene. In many reactions, including metalation, cleavage of ether and reaction with benzophenone (*vide infra*), it is furthermore found that ethylmagnesium or *n*-butylmagnesium bromide reacts faster than phenylmagnesium bromide. However here, in the nitrile reaction, we have the opposite series of reactivity of different Grignard reagents (Table III).

The following mechanism, on the other hand, is consistent with the kinetic order and all reported series of relative reactivity. A complex between reagent and addend is formed rapidly and reversibly, though very possibly in low concentration at equilibrium relative to the total concentration of Grignard reagent. The rate-determining step consists of an *intramolecular* rearrangement of the complex, in which the radical attached to the metal migrates, with its pair of electrons, to the nitrile carbon. The rearrangement may be pictured as follows<sup>11</sup>

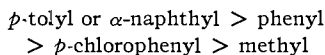


There is evidence for this mechanism in the fact that the series of decreasing relative reactivities with benzonitrile of Grignard reagents with different organic radicals is the same, as far as the data overlaps, as the series of decreasing migration aptitudes of these same radicals in the pinacol re-

(10) Schorigin, *Ber.*, **41**, 2723 (1908).

(11) It is also possible to picture the complex as merely an association of two dipoles, or a resonance hybrid intermediate between this structure and the structure drawn, but such a formulation does not emphasize clearly the way in which this mechanism differs from one involving direct reaction without the intervention of a complex.

arrangement,<sup>12</sup> which is believed to proceed by intramolecular shift of the radical with its electron pair



These reactivities both fall off, except for the position of the phenylethynyl reagent, in approximately the same manner as the series of decreasing electronegativity determined by Kharasch from the acid cleavage of unsymmetrical dialkylmercury compounds.<sup>13</sup>

The series of reactivity of different Grignard reagents with benzophenone as determined by competition experiments by Kharasch and Weinhouse<sup>14</sup> was *t*-butyl > methyl > phenyl >  $\alpha$ -naphthyl. The products isolated, and their yields, indicated nearly quantitative addition in each of these four cases. This is the opposite series of reactivity to that which holds with benzonitrile. This fact may be connected with a different type of complex formation in the two cases. It has been found<sup>15</sup> that benzophenone rapidly forms a precipitate with just equivalent or less than equivalent phenylmagnesium bromide.<sup>16</sup> Benzophenone can be recovered by adding water to the precipitate. However, with an excess of Grignard reagent the precipitate rapidly redissolves to give complete reaction.<sup>17</sup> Certainly in this case we have *excess*, uncomplexed Grignard reagent reacting directly with benzophenone already polarized by complex formation. Since the complex is stable toward internal reaction (by reason of its being a precipitate) direct attack by a second molecule of Grignard reagent is required. Such a mechanism, if it held for the reaction of benzophenone with all Grignard reagents, would explain the reactivity series observed.

The much greater reactivity of phenyllithium than of phenylmagnesium bromide with benzonitrile indicates a considerable difference in ease of cleavage of ordinary carbon-lithium and carbon-magnesium bonds. The phenylethynyl reagents which exhibited very nearly the same reactivity (Table II) may be unique in being predominantly ionic rather than covalent compounds. The high acidity of acetylenes relative to that of the hydrocarbons derived from the other Grignard reagents commonly studied is in accord with the hypothesis of an unusually stable anion. This would indicate a large spread in reactivity for different carbanions, since cesium phenide would, by any mechanism, be more reactive than phenyllithium, which

(12) Ann. Repts. Chem. Soc. (London), **27**, 118 (1930); Neff, Thesis, University of Chicago, 1927 (C. A., **22**, 3639 (1928)).

(13) Kharasch and Flenner, THIS JOURNAL, **54**, 674 (1932).

(14) Kharasch and Weinhouse, J. Org. Chem., **1**, 209 (1936).

(15) Gilman and Jones, THIS JOURNAL, **62**, 1243 (1940).

(16) Dr. Linus Pauling has suggested that since both the carbonyl oxygen and the magnesium atom can have bivalent coordination, it is possible that chain polymers with a 1:1 ratio of carbonyl groups to Grignard reagent are formed.

(17) This does not cause trouble in synthetic work because the normal direction of addition is ketone to Grignard reagent, where the reaction progresses continuously from the start of the addition.

in turn is already over one thousand times as reactive with benzonitrile as cesium phenylethynide.

## Experimental

### A. Reagents

***n*-Butylmagnesium Bromide.**—One hundred and fifty grams (1.1 moles) of redistilled Eastman Kodak no. 51 *n*-butyl bromide, b. p. 101–102°, mixed with 300 cc. of reagent ether dried over sodium wire was added over a period of three hours to 29 g. (1.2 moles) of fresh magnesium turnings in 400 cc. of dry ether. Stirring was continued two hours more. After settling overnight the clear supernatant liquid was siphoned into 100-cc. narrow-mouth screw-cap bottles under a nitrogen atmosphere. The bottles were kept in a desiccator at 4° and the solution showed no detectable decomposition over a period of two months. Analysis was by gas evolution (*vide infra*). Acid titration gave the same analysis (1.44 *M*), showing no decomposition by air or water, but titration for bromide ion (1.54 *M*) showed 3.5 mole per cent. magnesium bromide from coupling and disproportionation.

**Phenyllithium.**—One hundred and fifty grams (0.95 mole) of redistilled Eastman no. 43 bromobenzene, b. p. 153.5–154°, was added over a period of two hours to 2.0 moles of 3-mm. lithium wire,<sup>18</sup> cut in 1-cm. lengths, in 900 cc. of dry ether. The solution was stored as above. Acid titration gave 1.05 *M*. Analysis by reaction with Michler ketone to give malachite green (*vide infra*) gave 0.82 *M*, showing 22% decomposition by air, at the time the solution was used. The solution was extremely sensitive to atmospheric oxygen, but appeared not to cleave ether because freshly opened bottles gave similar analyses over a period of a month after the preparation.

**Benzonitrile.**—A 1.71 *M* solution of redistilled Eastman no. 487 benzonitrile, b. p. 94–95° at 37 mm., was prepared in reagent ether which had been dried over sodium.

**Michler Ketone.**—Nineteen grams of Eastman no. 243 Michler ketone was crystallized from 75 cc. of benzene, collected under a dry nitrogen atmosphere, washed with dry 28–38° petroleum ether, and dried in a vacuum desiccator; yield, 16 g. of needles, with a pale greenish-yellow tinge.

### B. Apparatus and Procedure

**The Nitrile Reaction.**—The reaction vessel was a 125-cc. filter flask fitted with a rubber stopper carrying a 10-mm. glass tube with its own stopper which could be removed to allow addition of reactants or removal of aliquots with a pipet. This equipment was dried in a vacuum desiccator after previous heating of all glassware in an oven at 120°. The flask was clamped in the thermostat and a slight static pressure of nitrogen applied through the side tube. The nitrogen was burned with 2% hydrogen over copper at 675°, dried over potassium hydroxide, and saturated with ether at 25°. Reaction was initiated by adding a pipetted sample of Grignard solution to an ether solution of benzonitrile in the flask. The resulting volume of the solution was 50 cc. There was no visible precipitate at the start, but a white precipitate formed as the reaction progressed. The solution was swirled before taking samples for analysis.

**Analysis for *n*-Butylmagnesium Bromide.**—The apparatus of Gilman, *et al.*,<sup>19</sup> was found to give 3% accuracy for 1.44 *M* solutions and better than 10% accuracy for solutions as dilute as 0.05 *M* after some modification. A 200-cc. gas buret and a gas-washing bubbler holding 80 cc. of concentrated sulfuric acid and graduated to read the volume to 0.5 cc. were used. T-type stopcocks were inserted between buret and trap and between trap and reactor to permit equilibration with atmospheric pressure. The total volume between the trap and the top mark in the reactor was less than 2 cc. A special three-way stopcock

(18) Fieser and Hershberg, THIS JOURNAL, **59**, 396 (1937).

(19) Gilman, Wilkinson, Fishel and Meyers, *ibid.*, **45**, 150 (1923).

TABLE IV

Run	1			2			3			4				
Temp., °C.	25			25			25			0				
C <sub>6</sub> H <sub>5</sub> CN, <i>M</i>	0.340			0.684			0.676			0.684				
<i>n</i> -C <sub>4</sub> H <sub>9</sub> MgBr, <i>M</i>	0.288			0.288			0.540			0.245				
Ratio	1.18			2.37			1.25			2.79				
<i>t</i> (min.)	67	220	463	16	39	93	191	14	35	72	166	145	280	420
<i>n</i> -C <sub>4</sub> H <sub>9</sub> MgBr, <i>M</i>	0.187	0.094	0.059	0.222	0.159	0.101	0.042	0.436	0.350	0.252	0.150	0.179	0.132	0.101
<i>z</i> (fraction reacted)	0.351	0.673	0.798	0.229	0.448	0.650	0.855	0.193	0.352	0.534	0.723	0.269	0.462	0.588
10 <sup>4</sup> <i>k</i> <sub>2</sub> (1 liter mole sec. <sup>-1</sup> )	3.7	4.0	3.3	4.2	4.2	3.3	3.3	4.1	3.6	3.6	3.1	0.55	0.59	0.59
Average <i>k</i> <sub>2</sub>	3.7 × 10 <sup>-4</sup>			3.7 × 10 <sup>-4</sup>				3.6 × 10 <sup>-4</sup>				5.8 × 10 <sup>-5</sup>		
Half life (min.) calcd. from <i>k</i> <sub>2</sub>	120			53				63				330		

was used between the 5-cc. sample buret and 51-cc. reaction bulb. The plug was bored to connect just any two of its three tubes. Sample was admitted through 2-mm. capillary tubing from below into the stopcock and thence either horizontally through a tube flaring into the side of the reaction bulb at its midpoint or else up to a drain outlet. This construction was necessary to prevent plugging of the stopcock in use. It was found necessary to ring seal a "hot finger" into the reaction bulb into which steam could be passed to heat the contents of the bulb to 100° and vaporize the ether. In operation the bulb was swept with a stream of air to remove all ether vapor; dilute 1:20 sulfuric acid was run in up to the lower mark; the trap and gas buret were connected; the leveling bulb was lowered to draw air through the trap to equilibrium; then the gas buret was read, and the leveling bulb again lowered. More dilute acid was next run in to fill the bulb one-quarter full. One to five cc. of sample was run in slowly on top of the acid; 20 cc. more acid was added; then steam was passed into the "hot finger" to boil the ether and drive out dissolved butane. More acid was added up to the upper mark and the gas buret again read. From the difference in reading was subtracted the 51-cc. bulb volume between marks plus the increase in volume of the sulfuric acid in the trap plus 0.10 cc. per per-cent. increase in sulfuric acid over the original 65 cc. volume.

**Analysis for Phenyllithium or its Reaction Product with Michler Ketone.**—To standardize the method 10 cc. of standard solution of Michler ketone in toluene was allowed to react with excess phenyllithium. Five cc. of methanol and then 10 cc. of water was added to the resulting mixture and it was evaporated to 10 cc. on the hot plate to eliminate the toluene. The contents were added to a 50 cc. volumetric flask, washing the last in with 5 cc. of methanol. Two cc. of a 1.0 *M*, pH 5.2, acetate buffer was added and water to the mark. The intensity measured after five minutes in 1 cm. diameter tubes in a Klett colorimeter was 100 = 3 units per micromole assuming quantitative reaction.

Next, by using this color factor, the method was applied to analyzing phenyllithium solutions by adding measured amounts of the latter to a suspension of excess Michler ketone in dry toluene. It was found that volumetric dilutions of phenyllithium down to 0.01 *M*

could not be made in ordinary volumetric glassware. A special cell which allowed nitrogen saturated with ether to be bubbled through the ether contents or passed over the surface was finally used for preparing solutions in an inert atmosphere.

### C. Data

**The Nitrile Reaction.**—The data of typical runs are summarized in Table IV.

The reaction between benzonitrile and phenyllithium was too fast to follow. Even with solution as dilute as 0.034 *M* in benzonitrile and 0.016 *M* in phenyllithium the concentration of phenyllithium was below 0.002 in half a minute, corresponding to a rate constant in excess of 1 liter mole<sup>-1</sup> sec.<sup>-1</sup>. The analytical method was based on reaction of aliquots with excess Michler ketone in dry toluene. Check analyses were run on the phenyllithium solution just before and after use, and also on control solutions in which the phenyllithium was added to dry ether alone rather than to the solution of benzonitrile in dry ether.

### Summary

The reaction between *n*-butylmagnesium bromide and benzonitrile has been followed kinetically in ether solution, and found to be homogeneous and second order, with a rate constant of 3.7 × 10<sup>-4</sup> liter/mole sec. at 25°. The activation energy is 12 kcal.

The observed kinetic order is consistent with a suggested mechanism involving as its rate determining step the intramolecular rearrangement of a complex, present in a low concentration in rapid equilibrium with organometallic reagent and addend.

Phenyllithium and phenylmagnesium bromide show at least a hundredfold difference in reactivity with benzonitrile.

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