

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Reaction of Certain Nitriles with Grignard Reagents¹BY F. F. BLICKE AND EU-PHANG TSAO^{2,3}

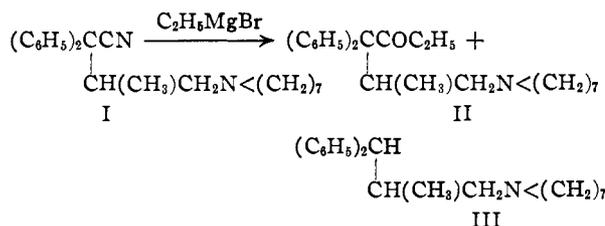
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It was found that diphenylacetonitrile reacted with ethylmagnesium bromide to form 1,1-diphenyl-2-butanone, diphenylmethane and propionitrile which was isolated as propionic acid. When the reaction mixture was carbonated, the reaction products were 1,1-diphenyl-2-butanone, *diphenylmalonic acid* and propionitrile. Other Grignard reagents behaved in a similar manner. Reactions between ethylmagnesium bromide and other nitriles were studied.

In a number of instances it has been found that a nitrile reacted with sodium and an alcohol,⁴⁻⁹ with potassium hydroxide¹⁰ or with sodamide¹¹⁻¹⁸ in such a manner that the cyano group was replaced by hydrogen. A few examples have also been reported in which the same type of cleavage was produced by a Grignard reagent. Thus triphenylacetonitrile reacted with benzylmagnesium chloride to produce triphenylmethane¹⁹; dibenzylmalonitrile and phenylmagnesium bromide yielded dibenzylacetonitrile. Ethylmagnesium bromide reacted with 4-dimethylamino-2,2-diphenyl-3-methylbutanenitrile to form 1-dimethylamino-3,3-diphenyl-2-methylpropane,⁹ with α -phenyl- α -(β -dimethylaminoethyl)-2-pyridylacetonitrile to produce γ -phenyl- γ -(2-pyridyl)-N,N-dimethylpropylamine²⁰ and with 4,5-bis-(dimethylamino)-2,2-diphenylpentanenitrile to yield 3,4-bis-(dimethylamino)-1,1-diphenylbutane.^{21,22}

We found²³ that 2,2-diphenyl-3-methyl-4-(1-

heptamethylenimino)-butyronitrile (I), when treated with excess ethylmagnesium bromide, yielded the expected ketone II in 46% yield and the cleavage product, 1,1-diphenyl-2-methyl-3-(1-heptamethylenimino)-propane (III) in 18.7% yield. The structure of III was established by its synthesis—decyanation of I with sodamide.



In view of this interesting cleavage, it seemed desirable to study the action of several Grignard reagents on nitriles related to I such as diphenyl-, phenyl-, diphenyl- β -dimethylaminoethyl-, phenyl- β -dimethylaminoethyl- and phenyldi-(β -diethylaminoethyl)-acetonitrile.

All of the nitriles employed in this investigation which contained an alpha hydrogen atom reacted with the Grignard reagent with the liberation of a gas. Thus diphenylacetonitrile reacted with ethylmagnesium bromide with the evolution of about one molecular equivalent of a gas which, undoubtedly, was ethane.²⁴ After the reaction mixture had been treated with dilute acid, the reaction products were found to be 1,1-diphenyl-2-butanone (20%) and diphenylmethane (45%). The experiment was repeated and this time the reaction mixture was carbonated. 1,1-Diphenyl-2-butanone²⁵ and *diphenylmalonic acid* (55% yield)²⁶ were isolated as reaction products. The latter compound was contaminated with another solid acid which may have been diphenylacetic acid. The structure of the malonic acid was proved by the neutralization equivalent, by conversion into the known dimethyl ester and by the loss of carbon dioxide with the formation of diphenylacetic acid. Similar results were obtained when ethylmagnesium bromide was replaced by methylmagnesium bromide or phenylmagnesium bromide or by isopropylmagnesium chloride but

(24) The gas did not decolorize bromine.

(25) When the reaction mixtures were not carbonated, the yields of the ketone in three experiments were 20, 22 and 20%, respectively. In each of two experiments in which the reaction mixtures were carbonated, the yield of ketone was 5%.

(26) In an independent experiment, diphenylmalonic acid was synthesized, for comparison purposes, by the action of isopropylmagnesium chloride on diphenylacetic acid and carbonation of the Ivanov reagent (the chloromagnesium derivative of the chloromagnesium salt of diphenylacetic acid) produced.

(1) Abstract of Papers, 123rd Meeting of the American Chemical Society, Los Angeles, Calif., March 15-19, 1953, p. 14L.

(2) This paper represents part of a dissertation submitted by Eu-Phang Tsao in partial fulfillment of the requirements for the Ph.D. degree in the University of Michigan, 1952.

(3) Parke, Davis and Company Fellow.

(4) E. Bamberger, *Ber.*, **20**, 1702 (1887).

(5) E. Bamberger and W. Lodter, *ibid.*, **20**, 1703 (1887).

(6) D. Vorländer, *ibid.*, **44**, 2471 (1911).

(7) A. F. Titley, *J. Chem. Soc.*, 509 (1926).

(8) F. Bergel, J. W. Haworth, A. L. Morrison and H. Rinderknecht, *ibid.*, 261 (1944).

(9) J. H. Gardner, N. R. Easton and J. R. Stevens, *THIS JOURNAL*, **70**, 2906 (1948).

(10) E. L. May and E. Mosettig, *J. Org. Chem.*, **13**, 459 (1948).

(11) Report No. PB-981, Office of the Publication Board, Dept. of Commerce, Washington, D. C., p. 91.

(12) M. Bockmühl and G. Ehrhart, *Ann.*, **561**, 60, 65 (1948).

(13) M. M. Klenk, C. M. Suter and S. Archer, *THIS JOURNAL*, **70**, 3846 (1948).

(14) M. Jackman, C. Bolen, F. C. Nachod, B. F. Tullar and S. Archer, *ibid.*, **71**, 2301 (1949).

(15) E. Walton, P. Ofner and R. H. Thorp, *J. Chem. Soc.*, 648 (1949).

(16) M. Jackman, F. C. Nachod and S. Archer, *THIS JOURNAL*, **72**, 716 (1950).

(17) A. W. Ruddy, *ibid.*, **73**, 4096 (1951).

(18) N. Sperber, D. Papa, E. Schwenk, M. Sherlock and R. Fricano, *ibid.*, **73**, 5752 (1951).

(19) Ramart-Lucas and M. F. Salmon-Legagneur, *Bull. soc. chim.*, [4] **43**, 321 (1928).

(20) J. L. E. Erickson and M. M. Bennett, *THIS JOURNAL*, **57**, 560 (1935).

(21) E. M. Schultz, *ibid.*, **74**, 5793 (1952).

(22) Incidentally, it is of interest to note that Grignard reagents have effected the following unusual transformations: conversion of diphenyldimethylaminomethylacetonitrile into diphenylacetonitrile,¹² ethyl diphenyldimethylaminomethylacetate into 1,1-diphenyl-2-butanone¹³ and β,β' -bis-(1-piperidyl)-pivalophenone into 1-(1-piperidyl)-2-methyl-3-phenyl-3-pentanol (J. J. Denton, V. A. Lawson, W. B. Neier and R. J. Turner, *ibid.*, **71**, 2050 (1949)).

(23) This experiment will be described by the authors in a later publication.

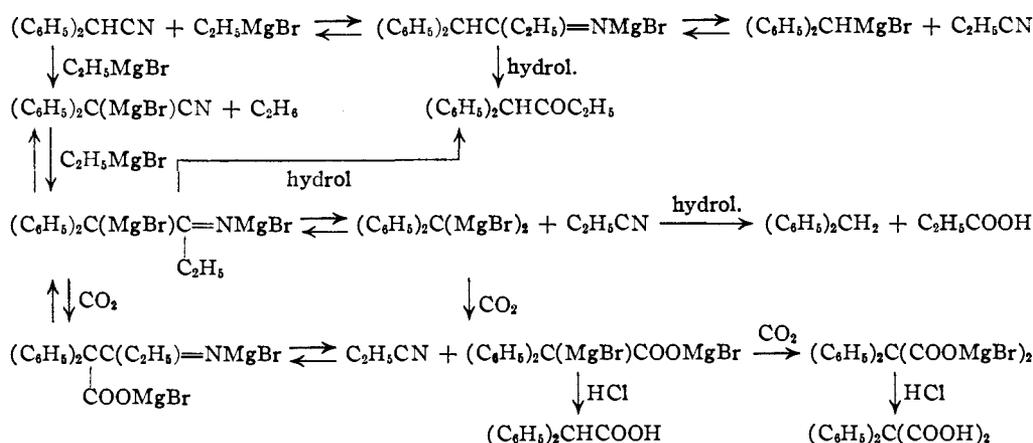
in these instances the yields of diphenylmethane and of diphenylmalonic acid were much lower.

Phenylacetonitrile reacted with excess ethylmagnesium bromide with the evolution of about two molecular equivalents of ethane; after carbonation of the reaction mixture, 1-phenyl-2-butanone and phenylmalonic acid were obtained. The malonic acid was characterized by the melting point, neutralization equivalent, analysis, decarboxylation to phenylacetic acid and by conversion into the known dimethyl ester.²⁷

It has been reported^{28,29} that there was no evidence of ketone formation when phenyl- α -(β -dimethylaminoethyl)-acetonitrile, or the corresponding β -diethylaminoethyl compound, was allowed to react with ethylmagnesium iodide. However, we found that, under conditions which were similar to those employed by other investiga-

present was hydrolyzed. We were able to isolate and identify acetic, propionic and benzoic acid, respectively, in those instances in which ethylmagnesium, ethylmagnesium and phenylmagnesium bromide had been employed. There was no evidence that diphenylcyanoacetic acid, which might have been formed from the bromomagnesium derivative of diphenylacetonitrile, was produced during the carbonation of the reaction mixture.

The indicated steps imply a two-way reversible cleavage of ketiminomagnesium bromides which would ordinarily not be noticed. In the instances at hand, the benzhydryl Grignard reagents produced are derived from particularly stable carbanions and their formation should be favored. The removal of cyano groups described in references 9, 19, 20 and 30 can be understood in terms of this general concept.



tors,^{28,29} the former nitrile reacted with ethylmagnesium bromide to produce 1-dimethylamino-3-phenyl-4-hexanone in 51% yield.

The reaction mixture, obtained after interaction of phenyldi-(β -diethylaminoethyl)-acetonitrile with ethylmagnesium bromide, was carbonated but no carboxylic acid was formed by this process.

The reaction scheme shown below, suggested by Dr. P. A. S. Smith, may explain the formation of the ketone, aliphatic nitrile, diphenylmethane and diphenylmalonic acid in the reactions in which diphenylacetonitrile was employed. In accordance with this mechanism, a nitrile, such as propionitrile³⁰ should be formed in each instance in which diphenylmethane was produced. Since the nitriles would have been difficult to isolate, that part of the reaction product in which the nitriles should be

(27) D. Ivanov and I. Paounov (*Compt. rend.*, **197**, 923 (1933)), stated that 92-95% of the molar amount of propane was evolved when phenylacetonitrile reacted with isopropylmagnesium chloride and that, after carbonation of the reaction mixture, phenylcyanoacetic acid was formed in 40% yield. However, no evidence was reported which showed that the acid obtained actually was phenylcyanoacetic acid. They stated also that the same acid was produced when ethylmagnesium or phenylmagnesium bromide was substituted for isopropylmagnesium chloride.

(28) D. J. Brown, A. H. Cook and I. Heilbron, *J. Chem. Soc.*, S106 (1949).

(29) W. Wilson, *ibid.*, 6 (1952).

(30) According to A. Mavrodin (*Compt. rend.*, **191**, 1064 (1930)), benzonitrile was one of the initial products formed when ethyl diethylcyanoacetate reacted with phenylmagnesium bromide; the nitrile then reacted with the Grignard reagent to form benzophenone.

Experimental Part

Reaction of Diphenylacetonitrile with Ethylmagnesium Bromide. (A).—Diphenylacetonitrile (19.3 g., 0.1 mole), dissolved in 60 cc. of toluene, was added to a stirred solution of ethylmagnesium bromide which had been prepared from 7.3 g. (0.3 mole) of magnesium, 32.7 g. (0.3 mole) of ethyl bromide and 100 cc. of ether. After the ether had been removed by distillation, the mixture was refluxed for 6 hours. A soda-lime tube attached to the condenser prevented the entrance of carbon dioxide into the reaction mixture.

The cooled mixture was stirred for 1 hour with 160 cc. of 3 N sulfuric acid, the layers were separated and the aqueous layer was extracted with ether. The solvents were removed from the combined ether and toluene solutions and the residue was distilled. The material (19.1 g.) (a mixture of diphenylmethane, diphenylacetonitrile, propionitrile and 1,1-diphenyl-2-butanone) which boiled at 69-137° (1.5 mm.) was refluxed with a mixture of 16 g. of potassium hydroxide, 50 cc. of isobutyl alcohol and 10 cc. of water for 68 hours. The aqueous layer was separated and the alcoholic layer was evaporated to dryness. Ether and water were added to dissolve the residue, and the two layers were then separated. The aqueous solution was added to the aqueous layer mentioned above, and the solution was acidified with dilute sulfuric acid. The crystalline precipitate, which weighed 4 g. and proved to be diphenylacetic acid (m.p. and mixed m.p. 145-147°) was filtered and the aqueous filtrate was distilled. The acidic distillate required 0.046 mole of sodium hydroxide for neutralization. After removal of the water, the residue was heated at 110° for 3 hours; the sodium propionate weighed 4.3 g. The *p*-bromophenacyl ester melted at 59.5-60.5°; mixed m.p. 59-60°.

The solvent was removed from the ether solution and the residue distilled. The portion which boiled at 95-98° (2 mm.) was diphenylmethane; m.p. 25-26°; ultraviolet spectrum λ_{max} 2620 Å. The 1,1-diphenyl-2-butanone (4.5

g.) obtained boiled at 135–141° (2 mm.); oxime, m.p. 118.5–120°³¹; semicarbazone, m.p. 194–195°.³²

Anal. Calcd. for C₁₄H₁₂: C, 92.81; H, 7.19. Found: C, 92.86; H, 7.28.

(B).—In this instance the reaction mixture, obtained in the manner described above, was stirred, cooled to 0° and carbonated with Dry Ice. After 1 hour the cooled mixture was treated with 120 cc. of 3 *N* hydrochloric acid and stirred for 1 hour. The aqueous layer was extracted with ether and the extract was combined with the organic layer. The solution was extracted with sodium carbonate solution and the extract was acidified. The precipitated, crude diphenylmalonic acid (14.0 g.) began to melt at 130° with the evolution of carbon dioxide. Since this acid has been reported^{33–35} to be very unstable,³⁶ the crude acid was used for the preparation of the dimethyl ester which was obtained in 77% yield by the use of diazomethane; m.p. 93.5–94.5°.³⁷

*Anal.*³⁴ Calcd. for C₁₇H₁₆O₄: C, 71.87; H, 5.68. Found: C, 71.48; H, 5.87.

The solvents were removed from the organic layer which contained diphenylacetonitrile, propionitrile and 1,1-diphenyl-2-butanone, and the residue was distilled; b.p. 85–134° (1.5 mm.). A part of the diphenylacetonitrile (1.5 g.) crystallized in the distillate and it was removed by filtration; mixed m.p. 74–75.5°.³⁸ The filtrate was refluxed with a mixture of 5 g. of potassium hydroxide, 16 cc. of isobutyl alcohol and 4 cc. of water for 68 hours. Diphenylacetic acid (1.4 g.), 1,1-diphenyl-2-butanone (1.2 g.) and propionic acid (2.9 g., determined by titration) were obtained.

In each of the following experiments, unless otherwise noted, the general procedure was the same as that described above.

Reaction of Diphenylacetonitrile with Methylmagnesium Bromide. (A).—Diphenylacetonitrile (19.3 g.), dissolved in 60 cc. of toluene, was added to methylmagnesium bromide prepared from 28.5 g. of methyl bromide, 7.3 g. of magnesium and 100 cc. of ether. After removal of the ether, the mixture was refluxed for 15 hours. In this instance, the crude, initial product was not distilled. There were isolated diphenylacetic acid (15.2 g., m.p. 144–146°), sodium acetate (1.3 g., *p*-bromophenyl ester, m.p. and mixed m.p. 84.5–85.5°) and a very small amount (0.3 g.) of a product, m.p. about 40°, which we thought might be 1,1-diphenylacetone³⁹ but some of the data obtained do not support this opinion.

Anal. Calcd. for C₁₈H₁₄O (diphenylacetone): C, 85.66; H, 6.71. Found: C, 85.41; H, 7.33.

After reaction of the product with hydroxylamine, a substance was obtained which melted at 150–151°.⁴⁰

Anal. Calcd. for C₁₆H₁₆ON (oxime): C, 79.96; H, 6.71; N, 6.22. Found: C, 80.22; H, 7.42; N, 5.51.

(B).—After the addition of 100 cc. of toluene, the original reaction mixture was carbonated with gaseous carbon dioxide below 0°. The products were diphenylmalonic acid (3.5 g., m.p. 144–145°; neut. equiv., calcd. 128.1; found 131.1), diphenylacetic acid (13.8 g.) and 1,1-diphenylacetone (0.4 g.).

Reaction of Diphenylacetonitrile with Isopropylmagnesium Chloride. (A).—To the Grignard reagent, prepared from 23.7 g. of isopropyl chloride, 7.3 g. of magnesium and 100 cc. of ether, there was added 19.3 g. of diphenylacetonitrile dissolved in 100 cc. of toluene. After the ether had been removed, the mixture was refluxed for 5 hours and then

treated as described in the first experiment. After the distillate (16.6 g.), which boiled at 123–131° (1.5 mm.), was hydrolyzed there were obtained 14.3 g. of diphenylacetic acid, an acid distillate which required 0.002 mole of sodium hydroxide for neutralization, 0.6 g. of diphenylmethane and 2.7 g. of benzhydryl isopropyl ketone which melted at 73.5–75°,⁴¹ after recrystallization from petroleum ether (40–60°); semicarbazone, m.p. 166–167.5°.⁴²

(B).—In this experiment, 50 cc. of toluene was added before carbonation which was carried out below 0° with a stream of carbon dioxide. The products isolated were diphenylmalonic acid (2.0 g., m.p. 138–141°), 13.8 g. of diphenylacetonitrile, 1.8 g. of diphenylacetic acid (after hydrolysis) and 1.3 g. of benzhydryl isopropyl ketone.

Diphenylmalonic Acid.—A solution of 21.2 g. (0.1 mole) of diphenylacetic acid in 150 cc. of ether was added, dropwise, to a stirred solution of isopropylmagnesium chloride which had been prepared from 31.4 g. of isopropyl chloride (0.4 mole), 9.8 g. (0.4 mole) of magnesium and 100 cc. of ether. After the addition of 150 cc. of toluene the ether was removed by distillation and the toluene solution was refluxed for 6 hours. It was then cooled in a Dry Ice–acetone bath, stirred and carbon dioxide was passed into the solution for several hours. The mixture was cooled in an ice-bath, acidified with dilute hydrochloric acid, the aqueous layer was extracted with ether and the ether extract added to the toluene solution. The combined solutions were extracted with sodium bicarbonate solution and the latter acidified with dilute hydrochloric acid. The precipitated acid (22.8 g.) began to melt, with the evolution of a gas at 143°.⁴³ The neutralization equivalent (146.6) indicated that the acid was a mixture of diphenylacetic and diphenylmalonic acid in a molar ratio of 38:62 (34% of diphenylacetic and 66% of diphenylmalonic acid).

After subjection to the following process, the material was obtained in a form which consisted of 94% of the malonic acid. Since the apparent molecular weight of the mixture of acids was 240, 16.2 cc. of 1 *N* sodium hydroxide solution was added to 2.4 g. of the mixture. Upon the addition of 10.2 cc. of *N* hydrochloric acid to the clear solution, 0.8 g. of diphenylacetic acid precipitated; neut. equiv. calcd. 212.1; found 212.2. After the addition of about 8 cc. of 1 *N* hydrochloric acid, 1.5 g. of diphenylmalonic acid precipitated; neut. equiv. calcd. 128.1; found 130.6; m.p. 143–143.5° (dec.). When the malonic acid was heated, it was converted into diphenylacetic acid; mixed m.p. 145–146°; the carbon dioxide evolved was 94% of the calculated amount.

Phenylmalonic Acid.—This acid was prepared in the manner described above by carbonation of the Ivanov reagent obtained from 43.6 g. of ethyl bromide, 9.8 g. of magnesium, 100 cc. of ether and 13.6 g. of phenylacetic acid. The phenylmalonic acid weighed 7.2 g. (40%); m.p. 152–153°; m.p. dimethyl ester, 50–51°.

Reaction of Diphenylacetonitrile with Phenylmagnesium Bromide.—Diphenylacetonitrile (19.3 g.), dissolved in 60 cc. of toluene, was added to phenylmagnesium bromide prepared from 47.1 g. of bromobenzene, 7.3 g. of magnesium and 100 cc. of ether. After removal of the ether, the mixture was refluxed for 10 hours and then acidified with dilute hydrochloric acid. The following reaction products were obtained: benzhydryl phenyl ketone (triphenylvinyl alcohol) (4.0 g.), m.p. 135–136.5°⁴⁴ after recrystallization from ethanol; benzoyl derivative, m.p. 152–153°⁴⁴; benzoic acid (1.7 g.), m.p. 121–122°; diphenylacetic acid (12.0 g.), m.p. 142–145°; crude diphenylmethane (6.5 g.), b.p. 85–96° (1 mm.), m.p. 16–20°, which yielded 3.9 g. of benzophenone when oxidized with chromic acid.

Reaction of Phenylacetonitrile with Ethylmagnesium Bromide.—The ether was removed from a mixture of 11.7 g. of phenylacetonitrile, which had been dissolved in 60 cc. of toluene, and ethylmagnesium bromide, which had been prepared from 43.6 g. of ethyl bromide, 9.8 g. of magnesium and 100 cc. of ether, and the mixture was then refluxed for 7 hours. After carbonation with gaseous carbon dioxide, the

(31) Reference 15, m.p. 119°.

(32) Reference 15, m.p. 195–196°.

(33) H. Staudinger, O. Göhring and M. Schöller, *Ber.*, **47**, 43 (1914).

(34) H. J. Morsman, *Helv. Chim. Acta*, **18**, 1466 (1935).

(35) H. Raffelson, Dissertation, University of Michigan, 1951, p. 67.

(36) Subsequently it was found that the melting point of the crude acid obtained in another experiment could be raised from 138° to 144–145° by solution of the acid in ether and precipitation by benzene, a procedure described by Morsman (ref. 34).

(37) Reference 34, m.p. 93–93.5°.

(38) R. Stollé and F. Schmidt, *Ber.*, **45**, 3113 (1912), reported 74°.

(39) According to S. Stoermer (*Ber.*, **39**, 2288 (1906)), one form of this compound melts at 46°, the other at 61°.

(40) A. McKenzie and R. Roger, *J. Chem. Soc.*, **125**, 844 (1924), stated that the oxime melts at 164–165°.

(41) J. Levy, *Bull. soc. chim.*, [4] **39**, 67 (1936), found 76–77°.

(42) R. Lagrave, *Ann. chim.*, [10] **8**, 397 (1927), found 165°.

(43) Morsman (ref. 34) stated that the melting point of diphenylmalonic acid is about the same as that of diphenylacetic acid and that the malonic acid melts with the evolution of a gas. The melting points reported in "Beilstein" for diphenylacetic acid range from 144–149°.

(44) R. S. Yost and C. R. Hauser, *This Journal*, **69**, 2325 (1947), found 135.5–136.5°; benzoyl derivative, m.p. 152–153°.

