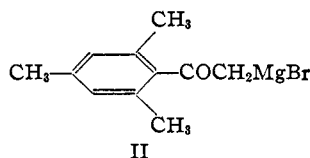
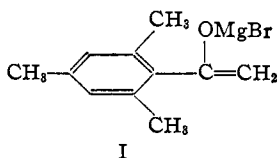


[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Reactions of Bromomagnesium Enolates of Mesityl Ketones. II. Condensation

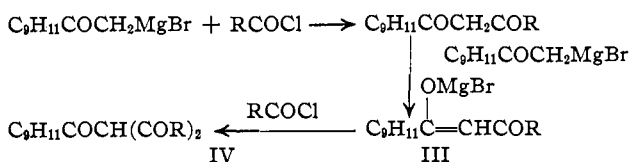
BY REYNOLD C. FUSON, W. O. FUGATE AND C. H. FISHER

The bromomagnesium derivative of acetomesitylene may be formulated as an enolate (I) or as a compound of the RMgBr type (II).



A study of its reactions has revealed the somewhat surprising fact that in all cases it behaves as though it were a true Grignard reagent. This is perhaps most striking in connection with condensation with carbonyl compounds. In the work presently reported condensation has been effected with acid chlorides, esters, carbon dioxide, aldehydes and ketones. The product in each instance is that which is predicated by formula II.

Acid chlorides and *esters* proved to be especially interesting in this connection for they reacted to give carbonyl compounds rather than carbinols. The reason for this interruption was that the newly formed aldehyde or ketone reacted in the enolic form, decomposing the excess of the original bromomagnesium derivative:



Indeed, if the amount of acid chloride present is not controlled carefully the bromomagnesium derivative of the diketone (III) is transformed to a triketone (IV).¹

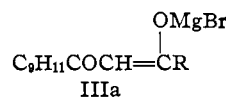
However, acetyl chloride and benzoyl chloride give satisfactory yields of the corresponding diketones when one mole of the chloride is added gradually to two moles of the bromomagnesium compound (II). Similar results were obtained with propiomesitylene and benzoyl chloride.

(1) Kohler and Baltzly, *THIS JOURNAL*, **54**, 4015 (1932).

With hindered acid chlorides such as 2,4,6-trimethylbenzoyl chloride this control was unnecessary; evidently the bromomagnesium derivative of the diketone in these cases had no appreciable tendency to undergo further acylation with the hindered acid chloride.

That esters also yield diketones is explained in a similar manner. The product with ethyl formate-oxyethyleneacetomesitylene showed remarkable stability.

It should be pointed out in passing that formula IIIa is less probable than III for the postulated enolate. It is known that the mesityl radical promotes enolization to a greater degree than do other radicals; this would favor III over IIIa.



Aldehydes and *ketones* condense with the bromomagnesium derivative of acetomesitylene (II) to give carbinols. This seems to be a general property of the bromomagnesium derivatives of hindered ketones for it also has been observed with α -benzohydrilacetomesitylene,² propiomesitylene³ and isobutyromesitylene.³ Actually, in the present work carbinols were isolated only from benzaldehyde and benzophenone. When 2-methoxy-1-naphthaldehyde and acetophenone were used the products were the corresponding substituted vinyl mesityl ketones.

Carbon dioxide reacted with the bromomagnesium derivatives of acetomesitylene, propiomesitylene, isobutyromesitylene and 3,5-dibromoisobutyromesitylene to give the corresponding β -keto acids. While this type of reaction seems to proceed with unusual ease with these highly hindered substances, it is by no means novel.⁴ The acids were identified by decarboxylation to the original ketones.

Coupling was effected by treating the bromomagnesium derivative with anhydrous cupric chlo-

(2) Kohler, Tishler and Potter, *ibid.*, **57**, 2517 (1935).

(3) Fuson, Fisher, Ulliyot and Fugate, *J. Org. Chem.*, **4**, 111 (1939).

(4) (a) Malmgren, *Ber.*, **36**, 2608 (1903); (b) Umnova, *J. Russ. Phys.-Chem. Soc.*, **45**, 881 (1913); (c) Ivanoff and Spossoff, *Bull. soc. chim.*, [4] **49**, 19 (1931); (d) Kohler and Tishler, *THIS JOURNAL*, **54**, 1594 (1932); (e) Ivanoff and Pchenitchny, *Bull. soc. chim.*, [5] **1**, 223 (1934).

ride. However, the yield of the resulting ethane was small. Bromine induced no coupling but led to the formation of α -bromoacetomesitylene.

Experimental

Condensation with Acid Chlorides and Esters.—The same general procedure was employed with slight modifications in all of the reactions studied. For a 0.1 mole run the bromomagnesium derivative was prepared by adding a solution of 0.1 mole of the mesityl ketone in 25 cc. of dry ether during thirty minutes to 100 cc. of an ethereal solution of a slight excess of ethylmagnesium bromide. The bromomagnesium derivative began to precipitate when about half of the ketone had been added. Refluxing was continued for thirty minutes after all of the ketone had been added.

An ether solution of the acylating agent was added to the mixture and, after the reaction was complete, the resulting mixture was decomposed with iced hydrochloric acid. The ether layer was then washed with 10% sodium carbonate solution. The diketone was usually obtained as the copper derivative by shaking the ether solution with a saturated solution of cupric acetate for several minutes and subsequently removing the ether.

The diketones or β -keto aldehydes were obtained easily by shaking an ether suspension of the copper derivative with dilute hydrochloric acid.

2, 4, 6, 2', 4', 6' - Hexamethyldibenzoylmethane.—In a 0.031-mole run equivalent amounts of the reagent and 2,4,6-trimethylbenzoyl chloride were employed. The reaction was complete after five hours of gentle refluxing. Acidification of the sodium carbonate solution gave 1.5 g. of 2,4,6-trimethylbenzoic acid. The yield of copper derivative was 6.5 g. (64%). The dark green copper derivative was recrystallized from benzene.

Anal. of the copper derivative. Calcd. for $C_{22}H_{16}O_4Cu$: C, 74.34; H, 6.84. Found: C, 74.74; H, 7.04.

The diketone, which melted at 96–97°, was identical with that previously reported.⁵

2,4,6 - Trimethyl - 2',4',6' - triethyldibenzoylmethane.—Four hundredths mole of the bromomagnesium derivative of acetomesitylene was treated with an equivalent amount of 2,4,6-triethylbenzoyl chloride and the resulting mixture refluxed overnight. Three grams of the acid was recovered from the sodium carbonate solution. After recrystallization from a mixture of carbon tetrachloride and ligroin, the olive green copper derivative melted at 287°; yield 6.5 g. (49%).

Anal. of the copper derivative. Calcd. for $C_{28}H_{28}O_4Cu$: C, 75.59; H, 7.66. Found: C, 75.72; H, 7.68.

The diketone was a pale yellow oil, b. p. 188–190° (2 mm.), n_D^{20} 1.5697. It gave a red color with ferric chloride.

Anal. Calcd. for $C_{24}H_{20}O_2$: C, 82.28; H, 8.57. Found: C, 82.07; H, 8.75.

In a similar experiment the same copper derivative was prepared by treating 0.1 mole of the bromomagnesium derivative of 2,4,6-triethylacetophenone with an equivalent amount of 2,4,6-trimethylbenzoyl chloride. The yield of the copper derivative was 15 g. (46%).

(5) Fisher, Snyder and Fuson, *THIS JOURNAL*, **54**, 3665 (1932).

α -Benzoylacetomesitylene.—A suspension of 0.1 mole of the bromomagnesium derivative of acetomesitylene was cooled in a salt-ice bath and 0.05 mole of benzoyl chloride added during ten minutes. Stirring was continued at this temperature for ten minutes and the mixture decomposed. Steam distillation of the ether layer gave 8 g. of acetomesitylene. The residue was taken up in ether, the ether solution dried over magnesium sulfate and evaporated to dryness. A small amount of the triketone (IV) crystallized during the evaporation. The residue was recrystallized from petroleum ether; yield 10 g. (75%); m. p. 76–78.5°. The α -benzoylacetomesitylene was identical with that prepared by cleavage of the corresponding enol methyl ether.⁶

α -Benzoylpropioimesitylene.—A solution of 0.025 mole of benzoyl chloride was added to a cold suspension of the bromomagnesium derivative of propioimesitylene and the mixture stirred for two hours at room temperature. The yield of the copper derivative of α -benzoylpropioimesitylene was 5 g. (65%). Distillation of the residue gave 4.4 g. of propioimesitylene. The residue in the distilling flask gave, after recrystallization, 0.7 g. of the enol benzoate of α -benzoylpropioimesitylene. Both the diketone and its enol ester were identified by comparison with the compounds previously reported.⁸

α -Acetylacetomesitylene.—(a) One-tenth mole of the enolate was cooled in an ice-salt bath and a solution of 0.05 mole of acetyl chloride added during five minutes. Stirring and cooling were continued for one hour. After decomposition the ether layer was dried, the ether removed and the residue distilled. Eight grams of acetomesitylene was recovered and 7 g. (69%) of the diketone boiling at 143–146° (8 mm.) obtained. After recrystallization from methanol the diketone melted at 45–46°. It was identified by a mixed melting point with an authentic specimen.⁷

(b) A solution of 0.1 mole of ethyl acetate in 25 cc. of ether was added during two and one-half hours to a suspension of 0.1 mole of the bromomagnesium derivative of acetomesitylene. The mixture was then refluxed overnight.

The diketone was isolated in the manner described above. Ten and five-tenths grams of acetomesitylene was recovered and 5.5 g. (26%) of the acetyl derivative was obtained.

Hydroxymethyleneacetomesitylene.—To a suspension of 0.1 mole of the bromomagnesium derivative of acetomesitylene, 7.4 g. (0.1 mole) of ethyl formate in 25 cc. of ether was added during the course of one hour. The enolate dissolved during this time and refluxing was continued for several hours. The copper derivative of the aldehyde was recrystallized from a mixture of carbon tetrachloride and ligroin; yield, 7.2 g. (33%). Nine grams of acetomesitylene was recovered from the filtrate.

Anal. of the copper derivative. Calcd. for $C_{24}H_{26}O_4Cu$: C, 65.22; H, 5.88. Found: C, 64.86; H, 6.05.

The hydroxymethylene compound was a colorless oil, b. p. 108–110° (3 mm.); n_D^{20} 1.5641. It gave a blood red color with ferric chloride and dissolved slowly in 10% sodium hydroxide solution.

(6) Kohler and Barnes, *ibid.*, **55**, 690 (1933).

(7) Woodward and Fuson, *ibid.*, **55**, 3472 (1933).

Formula	M. p., °C.	C	Calcd. H	Analysis, %		Found H	Br
				Br	C		
$C_9H_{11}COCH_2COOH^a$	104–105	69.90	6.79		69.6	6.8	
$C_9H_{11}COCH(CH_3)COOH^a$	111.5–112.5	70.91	7.27		71.17	7.29	
$C_9H_{11}COC(CH_3)_2COOH^a$	86–87	71.79	7.69		72.16	8.07	
$C_9H_9Br_2COC(CH_3)_2COOH^b$	108–110	42.86	4.08	40.82	42.81	4.37	40.2

^a These acids were identified by thermal decomposition to give the corresponding ketones. The ketones were identified as the 3,5-dinitro derivatives. ^b Decomposition of α -3,5-dibromo-2,4,6-trimethylbenzoylisobutyric acid gave 3,5-dibromoisobutyromesitylene; m. p. 69.5–70.5°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.79; H, 7.37. Found: C, 75.81; H, 7.74.

Preparation of the β -Keto Acids.—The procedure used in the preparation of α -2,4,6-trimethylbenzoylisobutyric acid is typical. A solution of 19 g. of isobutyromesitylene in 25 cc. of ether was added during thirty minutes to 100 cc. of a solution containing a slight excess of ethylmagnesium bromide. The resulting mixture was then refluxed for thirty minutes and transferred to a catalytic reduction⁸ machine whose tank contained carbon dioxide which passed into the mixture under pressure. During the first forty-five minutes the mixture was shaken by hand and cooled in a freezing mixture. The pressure dropped from 38 to 24 lb. (2.5 to 1.7 atm.). Mechanical shaking was then commenced and the mixture shaken at room temperature for twelve hours.

The mixture was then chilled in an ice-bath and poured very slowly into iced hydrochloric acid. The ether layer was extracted with cold sodium carbonate solution and the sodium carbonate extract acidified carefully with iced hydrochloric acid. The yield of α -2,4,6-trimethylbenzoylisobutyric acid was 18 g. (77.4%). The acid was recrystallized by dissolving it at room temperature in ether, adding a small amount of petroleum ether and then removing the solvent slowly under reduced pressure; m. p. 86–87° with decomposition. The original mesityl ketone was obtained when the acid was heated on a steam-cone for two hours.

2-(2,4,6-Trimethylbenzoyl)-1-phenylethanol.⁹—To a suspension of 0.2 mole of the bromomagnesium derivative of acetomesitylene in approximately 275 cc. of ether, 22 g. of freshly distilled benzaldehyde in 100 cc. of dry ether was added over a period of one hour. During this time the enolate gradually disappeared. Refluxing was continued for three hours.

The mixture was poured into iced hydrochloric acid, the ether layer separated and the aqueous layer extracted twice with ether. The combined ether solution was dried over sodium sulfate. Evaporation of the ether left a reddish-brown oil which deposited crystals of the carbinol on addition of a few cubic centimeters of ligroin. The yield of 2-(2,4,6-trimethylbenzoyl)-1-phenylethanol was 25 g. (47%). Recrystallization from petroleum ether gave 22 g. of the pure material, m. p. 77–77.5°.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.59; H, 7.46. Found: C, 80.13; H, 7.42.

Distillation of the residual oil gave small amounts of benzaldehyde and acetomesitylene and 13 g. (26%) of benzalacetomesitylene, b. p. 215–221° (16 mm.).

(8) Adams and Voorhees, *Org. Syntheses*, **8**, 10 (1928).

(9) This synthesis was carried out by Mr. R. V. Lindsey, Jr.

β -(2-Methoxy-1-naphthyl)-vinyl Mesityl Ketone.—A solution of 9.5 g. of 2-methoxy-1-naphthaldehyde in a mixture of 25 cc. of dry ether and 75 cc. of benzene was added dropwise during three hours to a suspension of 0.05 mole of the bromomagnesium derivative of acetomesitylene. During the addition, the enolate was converted to a chrome yellow solid. To ensure complete reaction, the mixture was then refluxed gently for three hours. The complex was decomposed with iced hydrochloric acid, the ether-benzene layer washed once with water and dried. After removal of the solvent by distillation, an oil remained which solidified when its solution in hot methyl alcohol was allowed to cool slowly, yield 13.5 g. (82%) of β -(2-methoxy-1-naphthyl)-vinyl mesityl ketone melting at 100–103°. After two recrystallizations from methanol the product melted at 107–108°. It reacted slowly with bromine in carbon tetrachloride.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.64; H, 6.67. Found: C, 83.43; H, 7.07.

α,β -Dibromo- β -(2-methoxy-1-naphthyl)-propio-mesitylene.—To an ice-cold solution of 1.5 g. of β -(2-methoxy-1-naphthyl)-vinyl mesityl ketone in 3 cc. of carbon tetrachloride a solution of bromine in carbon tetrachloride was added in small portions until the red color of the bromine solution persisted. Crystallization began before the bromination was complete. After all the bromine was added, 1.5 g. of α,β -dibromo- β -(2-methoxy-1-naphthyl)-propioimesitylene melting at 145–147° with decomposition was collected on a filter. The product was recrystallized by dissolving in the minimum of hot carbon tetrachloride and adding ligroin; m. p. 148–149°.

Anal. Calcd. for $C_{23}H_{22}O_2Br_2$: C, 56.33; H, 4.49; Br, 32.65. Found: C, 56.17; H, 4.80; Br, 32.75.

β -Methylbenzalacetomesitylene.—During a period of one and one-half hours, 96 g. (0.8 mole) of acetophenone in 100 cc. of ether was added to a suspension of 0.7 mole of the bromomagnesium derivative of acetomesitylene in 400 cc. of ether. During this time the enolate was converted to a thick gum. Refluxing was continued for six hours.

The mixture was decomposed by pouring it into 1 kg. of cracked ice and 200 cc. of concentrated hydrochloric acid, the ether layer washed with water and dried over magnesium sulfate. After removal of the ether, no product could be induced to crystallize. However, when distillation was attempted a solid began to form and, on addition of a small amount of petroleum ether, β -methylbenzalacetomesitylene, a pale yellow solid melting at 79–82°, began to crystallize. Sixty-three grams of the solid was collected on a filter. Distillation of the mother liquor gave 38 g. of acetophenone, 20 g. of acetomesitylene, and an additional 35 g. of the α,β -unsaturated ketone. After

three recrystallizations from alcohol the compound melted at 85.5–87°. Kohler and Barnes⁶ reported the melting point as 84°. The yield of β -methylbenzalacetomesitylene was 98 g. (69%).

Anal. Calcd. for $C_{18}H_{20}O$: C, 86.36; H, 7.55. Found: C, 86.15; H, 7.51.

The identification was completed by conversion to β , β -dimethyl- β -phenylpropionemesitylene by the method of Kohler and Barnes.⁶

1,1-Diphenyl-2-(2,4,6-trimethylbenzoyl)-ethanol.—To a suspension of 0.05 mole of the bromomagnesium derivative of acetomesitylene in 120 cc. of ether, 10 g. of benzophenone in 60 cc. of ether was added during the course of two hours. The enolate dissolved completely as the last of the ketone was added. The mixture was then refluxed gently overnight.

The ether solution was poured slowly with stirring into iced hydrochloric acid, the ether layer separated, dried and the ether allowed to evaporate spontaneously. The nearly colorless residual oil was taken up in warm methyl alcohol. When the solution was allowed to cool 13.2 g. (76.5%) of 1,1-diphenyl-2-(2,4,6-trimethylbenzoyl)-ethanol was obtained, m. p. 70–72°. After recrystallization from methanol, the product melted at 74–75°. A mixture with an authentic sample prepared by the method of Kohler and Barnes⁶ showed no depression in melting point.

α -Bromoacetomesitylene.—Three and three-tenths grams of acetomesitylene was converted to the bromomagnesium derivative, the mixture cooled in a salt-ice bath and a slight excess of bromine in 15 cc. of ether added dropwise. The reaction was complete in twenty minutes.

The reaction mixture was treated with dilute hydrochloric acid, the ether layer separated, dried over magnesium sulfate, and the ether removed. After recrystallization from petroleum ether, 2.7 g. (56%) of α -bromoacetomesitylene was obtained, m. p. 52–55°. After purification the product melted at 55–56°, and was identified by a mixed melting point with an authentic sample.

1,2-Di(2,4,6-trimethylbenzoyl)-ethane.—Seven and five-tenths grams of anhydrous cupric chloride was added in

small portions to an ether suspension of 0.05 mole of the bromomagnesium enolate of acetomesitylene in 125 cc. of dry ether and the mixture refluxed gently for twenty hours. During this time a crimson solid appeared in the reaction flask. The mixture was cooled in an ice-bath, decomposed by slowly adding iced hydrochloric acid, the ether layer dried over anhydrous magnesium sulfate and the ether removed by distillation. When the resulting liquid was distilled, 6.1 g. (75.4%) of acetomesitylene was recovered.

The residual oil was left standing for several days during which a solid began to form. The solid, after two recrystallizations from alcohol melted at 137–139°, the melting point of the ethane reported by Kohler and Baltzly¹ and by Conant and Lutz.¹⁰

1,3-Di-(2,4,6-trimethylbenzoyl)-propane.—Three and two-tenths grams of acetomesitylene was converted to the bromomagnesium enolate. To the resulting vigorously stirred suspension of the enolate in about 40 cc. of ether, a solution of 3.5 g. of vinyl mesityl ketone¹¹ in 20 cc. of dry ether was added during a period of thirty minutes. The resulting clear solution was refluxed gently for one hour. After the complex was decomposed with iced hydrochloric acid, the ether layer was separated and dried. When the ether was evaporated, there remained 5.5 g. (82%) of 1,3-di-(2,4,6-trimethylbenzoyl)-propane. After recrystallization from methanol the diketone melted at 131–132°. It was identical with the product previously reported.¹²

Summary

The bromomagnesium derivative of acetomesitylene reacts as a true Grignard reagent. This behavior has been observed in the condensations of this derivative with acid chlorides, esters, carbon dioxide, aldehydes and ketones.

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RECEIVED JUNE 26, 1939

(10) Conant and Lutz, *THIS JOURNAL*, **45**, 1303 (1923).

(11) This compound was supplied by Mr. C. H. McKeever; it will be described in a forthcoming communication.

(12) Fuson, Ross and McKeever, *THIS JOURNAL*, **61**, 414 (1939).