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THE ADDITION OF METHYLMAGNESIUM IODIDE TO BENZOYLDURENE

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In earlier studies embracing benzoylmesitylene (1), benzoylisodurene (1), benzoyldurene (2), the mesitoylnaphthalenes (3), and similar diaryl ketones, it has been demonstrated that addition of Grignard reagents occurs in spite of the excessive crowding about the carbonyl group. The addition may be 1,2, 1,4, or 1,6, depending on the nature of the ketone and of the Grignard reagent which is used. Recently Young and Roberts (4) made the surprising discovery that 1,2 addition occurs when benzyl and s-butenyl Grignard reagents are condensed with acetomesitylene. These and methylmagnesium iodide are the only Grignard reagents which have been found to combine with mesityl ketones in this manner. In most cases addition takes place in the 1,4 manner. There is evidence, however, that even 1,4 addition is limited to reagents having small alkyl or aryl groups. In fact, in two instances 1,6 addition has been observed; benzyl- and t-butylmagnesium chloride react in this manner with benzoyldurene (2).

Thus it appears that in the condensation of Grignard reagents with highly hindered diaryl ketones 1,2, 1,4, and 1,6 addition may be competing reactions. It remained, however, to discover an example in which all three types of addition occurred simultaneously. The present paper deals with such a case—the condensation of methylmagnesium iodide with benzoyldurene (I).



When benzoyldurene was heated at 130° for six hours with three molar equivalents of methylmagnesium iodide in *n*-butyl ether solution, the product consisted of a mixture from which several pure compounds could be isolated. One of these was 1-duryl-1-phenylethylene (II), the olefin which would be formed by dehydration of the carbinol produced by 1,2 addition. This result is similar to those obtained with benzoylmesitylene, benzoylisodurene, and *p*-toluyl-mesitylene (1).

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The 1-duryl-1-phenylethylene (II) was converted by the action of ozone to a mixture of benzoyldurene and durylphenylacetic acid. The formation of the ketone is noteworthy inasmuch as similar hydrocarbons yielded, not the expected ketones, but the corresponding vinyl alcohols (5). The production of substituted acetic acids from olefins having terminal methylene groups has been observed repeatedly in chromic acid oxidations (6). Several examples of this type of change have been observed with ozone (5, 7). The identity of the 1-duryl-1-phenylethylene was confirmed by an independent synthesis; it was formed in low yield by the condensation of durylmagnesium bromide with acetophenone.

In the condensation of benzoyldurene with methylmagnesium iodide, p-toluyldurene (IV) was isolated also, though in small amount, showing that 1,6 addition had occurred. The chief product, however, was that formed by 1,4 addition. It was possible, by suitable procedures, to isolate the 1,4 addition product either in the form of the peroxide (V) of the enol or in the ketonized form, dihydro-o-toluyldurene. Two isomeric dihydro ketones were isolated from the reaction mixture; for convenience they have been designated as A (m.p. 123-124°) and B (m.p. 103-103.5°). The two isomers were never produced together. From the data at hand it is not clear what relationship exists between the method of conducting the condensation and the nature of the dihydro ketone formed. Possibly the acidity of the medium in which the enol is ketonized is the deciding factor. A third dihydro-o-toluyldurene (isomer C) was formed when isomer B was treated with platinum in an atmosphere of nitrogen.

The three isomeric dihydro-o-toluyldurenes gave positive tests for unsaturation and failed to evolve gas when tested for active hydrogen in the Kohler-Richtmyer apparatus (8). Each isomer underwent dehydrogenation when heated with palladium on charcoal, to yield o-toluyldurene (III). Dehydrogenation occurred spontaneously with isomers A and B but not with isomer C.

It is possible to write formulas for six dihydro-o-toluyldurenes which possess no alpha hydrogen atom. By use of the one known dihydro-o-toluic acid it has been possible to synthesize the ketone corresponding to formula VI. 2,3-Dihydro-o-toluic acid (9) was converted to the acid chloride and the latter condensed with durene by the Friedel-Crafts method. The product, obtained in 70% yield, melted at 123° and was identical with isomer A.

Whatever the exact structures of the other two isomers (B and C) may be, it is certain that they, like isomer A, have the skeletal arrangement of o-toluyl-durene and that their formation likewise depends on initial 1,4 addition.

2,3,5,6-Tetramethylbenzohydryl ether (VII) was also isolated. It was probably formed from the durylphenylcarbinol produced by the reduction of benzoyldurene.

From the foregoing facts it is clear that the mode of addition of methylmagnesium iodide to benzoyldurene is chiefly 1,4 and that 1,2 and 1,6 addition also occur, though to a less extent.

EXPERIMENTAL

Condensation of methylmagnesium iodide with benzoyldurene. Experiment 1. To the Grignard reagent, prepared in ethyl ether from 34 g. of magnesium and 198 g. of methyl

iodide, was added 100 g. of solid benzoyldurene and 500 ml. of *n*-butyl ether. The flask was placed in an oil-bath and the temperature was gradually raised so that the ethyl ether was slowly distilled. Butyl ether was added from time to time to maintain the original volume. When the removal of the ethyl ether was almost complete, nitrogen was passed in and the temperature was raised to 130°. The reaction mixture was maintained at this temperature for six hours, with constant stirring. The reaction mixture was cooled to 0° and decomposed with ice and sulfuric acid. The organic layer was separated, washed twice with ice-water, and then shaken with 300 ml. of 2 N hydrochloric acid for eighteen hours to ketonize the enol. The organic layer was separated, extracted with 5% sodium carbonate, and washed with water. The solution was dried over magnesium sulfate and the butyl ether was distilled at the water-pump. The residual yellow oil was distilled at reduced pressure to separate the addition products from the polymeric material which was present. The residue in the flask weighed 25 g. Careful refractionation of the distillate yielded four fractions. The first consisted of 10 mg. of a solid with a phenolic odor which sublimed before the distillation started.

The second fraction, collected at $130-140^{\circ}$ (2 mm.), weighed 22 g. Three distillations of this fraction yielded 15 g. of *1-duryl-1-phenylethylene* as a viscous oil which was induced to crystallize from absolute ethanol. It formed large prisms which, after three recrystallizations from this solvent, melted at 71-72°; yield 10 g.

Anal. Calc'd for C₁₈H₂₀: C, 91.47; H, 8.53.

Found: C, 91.32; H, 8.50.

The third fraction consisted of 50 g. of an oily solid distilling at 140–150° (2 mm.). After six recrystallizations from ethanol, 34 g. of the *dihydro-o-toluyldurene* (A), melting at 123–124°, was obtained.

Anal. Calc'd for C₁₈H₂₂O: C, 84.99; H, 8.72.

Found: C, 84.82; H, 8.67.

The fourth fraction, collected at $150-165^{\circ}$ (4 mm.), weighed 3 g. By fractional crystallization of this material from ethanol, it was possible to separate a compound, m.p. 114-128°, from the dihydro-o-toluyldurene (A), m.p. 123-124°. After three recrystallizations the new product melted at 144-145°. It was shown by the method of mixture melting points to be *p*-toluyldurene; yield 0.5 g.

The residue, weighing 5 g., was recrystallized from ether, from absolute ethanol, and from butyl ether. Three grams of 2,3,5,6-tetramethylbenzohydryl ether, m.p. $174-175^{\circ}$, was obtained.

Anal. Calc'd for C34H38O: C, 88.26; H, 8.28.

Found: C, 88.08; H, 8.09.

Experiment 2. The condensation was run in the usual manner; 20 g. of benzoyldurene, 6.8 g. of magnesium, and 39.6 g. of methyl iodide were used. The reaction was effected in *n*-butyl ether by heating at 130° for six hours. The reaction mixture was cooled to 0° in an ice-salt bath and maintained at this temperature while a saturated solution of ammonium chloride was added slowly, with stirring. After the Grignard complex had been decomposed, the ether solution was decanted from the inorganic paste, and the latter washed with 100 ml. of cold ether. The combined extracts were washed three times with ice-water and dried with anhydrous magnesium sulfate. After the butyl ether had been distilled at the water-pump, the residue was fractionated at reduced pressure. Ten grams of distillate was obtained and approximately 10 g. of non-volatile material remained in the flask. Redistillation yielded 3 g. of crude 1-duryl-1-phenylethylene and 6 g. of a dihydroo-tolyl duryl ketone (B) boiling at 136-145° (2 mm.). After three recrystallizations from ethanol 4 g. of white platelets, m.p. 103-103.5°, was obtained. This ketone underwent dehydrogenation so readily that it was impossible to obtain a satisfactory analysis.

The high-melting dihydro-o-toluyldurene (A). This compound instantaneously decolorized a solution of bromine in carbon tetrachloride. It reacted with a 2% permanganate solution, and a Zerewitinoff determination showed the absence of active hydrogen. It was not isomerized by acid or alkali at room temperature. Pentabromo derivative. To a solution of 2 g. of the dihydro compound (A) in carbon tetrachloride was added 8.5 g. of bromine in 20 ml. of carbon tetrachloride. The mixture was stirred at room temperature for three hours, at the end of which period it was washed once with a dilute aqueous solution of sodium bisulfite and once with water. The carbon tetrachloride was distilled and the residue was recrystallized several times from benzene. The pentabromo compound was a white crystalline solid; m.p. 195-196°; yield 4 g.

Anal. Calc'd for C₁₈H₂₁Br₅O: C, 33.09; H, 3.22; Br, 61.23.

Found: C, 32.66; H, 3.34; Br, 62.54.

Dehydrogenation. In a large test tube equipped with a cold-finger were mixed 1.5 g. of isomer A and 0.1 g. of 10% palladium-charcoal catalyst. The mixture was heated for thirty minutes at 350° in a metal-bath. It was then cooled, taken up in ethanol, and filtered to remove the catalyst. The brown filtrate was treated with Norit and cooled; 0.7 g. of white crystals, m.p. $100-107^{\circ}$, separated. Recrystallization of the compound from ethanol raised the melting point to $112-112.5^{\circ}$. A mixture melting point determination with an authentic sample of o-toluyldurene showed no depression.

The low-melting dihydro-o-toluyldurene (B). The compound instantaneously decolorized a solution of bromine in carbon tetrachloride and reacted with a 2% potassium permanganate solution.

Isomerization. In an attempted hydrogenation, 2 g. of the dihydro compound (B) was dissolved in 100 ml. of alcohol containing 0.2 g. of platinum oxide and the solution was shaken under 3 atm. of hydrogen at room temperature. The amount of hydrogen taken up was negligible. After the reaction mixture had been shaken for six hours it was filtered, and the alcohol was removed by evaporation. The residue was recrystallized from 95% ethanol. The product was a new form of dihydrotoluyldurene (Isomer C). It was a white crystalline solid melting at $117-118^{\circ}$; yield 1.5 g. This compound instantaneously decolorized a solution of bromine in carbon tetrachloride. It reacted with a 2% permanganate solution, and a Zerewitinoff determination showed the absence of active hydrogen. It was not isomerized by acid or alkali at room temperature. It had been isolated previously from the combined mother liquors of several runs of the reaction of methylmagnesium iodide with benzoyldurene.

Anal. Calc'd for C₁₈H₂₂O: C, 84.99; H, 8.72.

Found: C, 85.28; H, 8.63.

Similar results were obtained when the isomer (B) was shaken with platinum in an atmosphere of nitrogen.

The low-melting dihydro compound was not isomerized by 2N hydrochloric acid at room temperature. Treatment with alkali caused dehydrogenation.

Dehydrogenation was carried out by the procedure that was employed in the dehydrogenation of isomer A; o-toluyldurene, m.p. 112-112.5°, was obtained.

Preparation of the peroxide of the enol. The condensation described in Experiment 2 was repeated but at the end of the six-hour period of heating 70 ml. of the reaction mixture was removed with a pipet, and cooled in an ice-salt bath. After decomposition of the solution with a saturated solution of ammonium chloride, the ether layer was removed and washed four times with ice-water. The solution was divided into two parts, one of which was allowed to stand for several hours. The ether was distilled and the product crystal-lized from ethanol; m.p. 102-103°. A mixture melting point determination showed it to be isomer B. Oxygen was bubbled for twelve hours through the remaining portion of the solution, which was kept in an ice-bath. The butyl ether was then evaporated in a stream of air and the residue was triturated with 100 ml. of low-boiling petroleum ether. The amorphous, white solid which would not dissolve in the petroleum ether was collected on a filter and recrystallized twice from a mixture of high- and low-boiling petroleum ether. The yellow, crystalline peroxide melted, with decomposition, at 126-128°; yield 3 g.

Anal. Calc'd for C₁₈H₂₂O₃: C, 75.49; H, 7.75.

Found: C, 75.28; H, 7.81.

Ozonization of 1-duryl-1-phenylethylene. One gram of the ethylene was dissolved in 100

ml. of glacial acetic acid and a stream of 2.5% ozone was bubbled through the solution at the rate of 50 ml. per minute for three hours. The solution turned green. The ozonide was heated under reflux for one hour with 400 ml. of water. The mixture was cooled and extracted with ether. The ether solution was extracted several times with 5% sodium hydroxide, washed with water, and dried over anhydrous magnesium sulfate. Removal of the ether left the benzoyldurene as a light brown oil. It was crystallized from absolute ethanol; m.p. 117-119°; yield 20 mg. A mixture melting point with a sample of benzoyldurene showed no depression.

The sodium hydroxide solution was acidified, extracted with ether, and washed repeatedly with water. The ether was evaporated, and the brown solid which remained was recrystallized several times from 95% ethanol. Needle-like crystals of an acid were obtained, which melted at $232-234^{\circ}$. This compound was identified as durylphenylacetic acid by comparison with an authentic specimen (10).

Preparation of 1-duryl-1-phenylethylene by the reaction of durylmagnesium bromide with acetophenone. The calculated amount of magnesium was added to a solution of 50 g. of bromodurene in 1 liter of anhydrous ether. The mixture was stirred for forty-eight hours under nitrogen, at the end of which time there was a copious precipitate of durylmagnesium bromide. A 20-ml. portion of the reaction mixture was removed with a pipet and poured on solid carbon dioxide. The amount of 2,3,5,6-tetramethylbenzoic acid formed indicated that 55% of the bromodurene had reacted with the magnesium.

Forty-two grams of acetophenone, dissolved in 200 ml. of anhydrous ether, was added slowly with vigorous stirring to the durylmagnesium bromide prepared as described above. Gentle refluxing occurred and a gummy precipitate formed which eventually prevented stirring of the reaction mixture. When the addition of acetophenone was completed, the Grignard complex was decomposed with saturated ammonium chloride solution and the product was isolated in the usual manner. It was a viscous yellow oil, fractional distillation of which yielded acetophenone, durene, bromodurene, and 1-duryl-1-phenylethylene. The amount of durene isolated indicated that 80% of the acetophenone had enolized. The olefin was obtained from the high-boiling fraction as a light yellow oil; yield 5 g. The oil was crystallized repeatedly from absolute ethanol; yield 3.5 g.; m.p. $71-72^{\circ}$.

Synthesis of 2,3-dihydro-o-toluyldurene. 2,3-Dihydro-o-toluic acid (9) was converted to the acid chloride by treatment with thionyl chloride. Eight and one-half grams of anhydrous aluminum chloride was added over a period of thirty minutes to a mixture of 8.5 g. of durene, 10 g. of the acid chloride, and 200 ml. of carbon disulfide. The mixture was stirred during the addition and for two hours afterward, then poured into a mixture of ice and hydrochloric acid. The 2,3-dihydro-o-toluyldurene, isolated by conventional procedures, was recrystallized from ethanol; m.p. 123-124°; yield 51%. A mixture with the compound obtained by treating benzoyldurene with methylmagnesium iodide showed no lowering of the melting point.

Preparation of the diaryl ketones. The ketones listed in Table I were prepared as reference compounds in connection with the identification of the various condensation products. They were all made by the same general procedure. One-tenth mole of anhydrous aluminum chloride was added in small portions over a period of one and one-half hours to a mixture of 1 mole of the aromatic compound (durene, bromodurene, or pentamethylbenzene), 1 mole of the acid chloride, and 200 ml. of carbon disulfide. The mixture was stirred during the addition and for three hours longer. After decomposition of the mixture, the organic layer was removed and the carbon disulfide was distilled. To the residue was added 200 ml. of 10% sodium carbonate solution and the mixture was steam distilled to remove the unchanged hydrocarbon. The contents of the flask were cooled and filtered. The solid ketone was dried and recrystallized from ethanol. In certain cases the product had a wide melting point range and a preliminary recrystallization from butyl ether was found to be helpful.

As indicated in the Table, several of the duryl ketones were also prepared by the reaction of durylmagnesium bromide with the appropriate acid chloride. The following procedure was used. To a solution of the acid chloride in ether was added, dropwise, the equivalent amount of an ether suspension of durylmagnesium bromide. The solution was stirred for three hours after the addition and then was decomposed with ice and hydrochloric acid. The organic layer was removed and the ether was distilled. The product was freed from durene and bromodurene by steam distillation of the mixture formed by adding 200 ml. of a 10% sodium carbonate solution to the residue. The flask was then cooled and the solid ketone removed by filtration and recrystallized from ethanol.

Duryl-o-tolylmethane. Ten grams of o-toluyldurene was dissolved in absolute ethanol and 15 g. of sodium was added, in small amounts, at a rate sufficient to keep the mixture boiling vigorously. The reaction mixture was then poured into 400 ml. of water, and the

COMPOUND ^a	ACID CHLORIDE	% атата	м.р. °С	ANALYSIS
o-Toluyldureneð	o-Toluyl	76	112-112.5	Calc'd: C, 85.67; H, 7.99 Found: C, 85.59; H, 8.13
<i>m</i> -Toluyldurene	<i>m-</i> Toluyl	78	111-112	Calc'd: C, 85.67; H, 7.99 Found: C, 85.87; H, 7.93
p-Toluyldurene ^b	<i>p</i> -Toluyl	80	144-145	Calc'd: C, 85.67; H, 7.99 Found: C, 85.58; H, 8.15
p-Anisoyldurene	p-Anisoyl		143.4-144.5	Calc'd: C, 80.56; H, 7.51 Found: C, 80.88; H, 7.77
Benzoylpentamethyl- benzene	Benzoyl	63	135136	Calc'd: C, 85.67; H, 7.99 Found: C, 85.99; H, 7.97
<i>m</i> -Toluylbromo- durene	<i>p-</i> Toluyl	61	131–132	Calc'd: C, 65.42; H, 5.76 Found: C, 65.63; H, 5.99
Duryl <i>trans-</i> 2- methylcyclohexyl ketone	trans-2-Methylcy- clohexanecar- boxylic acid	78	132–134	Cale'd: C, 83.67; H, 10.14 Found: C, 83.70; H, 10.32

TABLE I Diaryl Ketones

^a All the ketones listed in this table were prepared by the Friedel-Crafts method.

 $^{\mathfrak{d}}$ This compound was made by the Friedel-Crafts method and also by the Grignard method.

yellow-white solid which precipitated was collected on a filter and recrystallized from ethanol. The duryl-o-tolylmethane formed needle-like crystals melting at 94.5-95°; yield 4 g.

Anal. Calc'd for C₁₈H₂₂: C, 90.70; H, 9.30.

Found: C, 90.51; H, 9.57.

Durylphenylcarbinol. At one stage in the investigation it seemed possible that durylphenylcarbinol might be among the products formed by the action of the Grignard mixture on benzoyldurene. This carbinol was therefore made for reference. Benzoyldurene was reduced by the general method of Bachmann (11). To an amalgam prepared from 4.5 ml. of mercury and 1.2 g. of sodium were added 25 ml. of benzene, 25 ml. of dry ether, 2.5 ml. of absolute ethanol, and 4.76 g. of benzoyldurene. The container was stoppered and shaken for twenty minutes. In the beginning the reaction mixture developed a deep, opaque red color which, at the end of the reaction, had given way to a pale, transparent green color. The mixture was poured into water contained in a separatory funnel, the mercury drawn off, and the organic layer washed with water and dried. The oil left after distillation of the solvent was distilled under diminished pressure, whereupon it crystallized; b.p. $185-186^{\circ}$ (6 mm.); m.p. $66-69^{\circ}$.

Although the carbinol was not thought to be sufficiently pure for analysis, it formed an α -naphthylurethan, which served to identify it. The urethan was recrystallized from high-boiling petroleum ether; m.p. 177.5–178.5°.

Anal. Calc'd for C₂₈H₂₇NO₂: C, 81.92; H, 6.87.

Found: C, 82.23; H, 6.88.

Oxidation with chromic anhydride in glacial acetic acid converted the carbinol to benzoyldurene in 42% yield.

The gummy residue from the distillation of durylphenylcarbinol crystallized when allowed to stand overnight in contact with ether. Recrystallization from a mixture of benzene and chloroform yielded 650 mg. of 2,3,5,6-tetramethylbenzohydrylether, m.p. 174-175°.

SUMMARY

By treatment of benzoyldurene with methylmagnesium iodide under "forcing" conditions 1-duryl-1-phenylethylene, dihydro-o-toluyldurene, o-toluyldurene, and p-toluyldurene have been produced. These products demonstrate that 1,2, 1,4, and 1,6 addition of the Grignard reagent to the ketone take place concurrently.

The dihydro-o-toluyldurene was obtained from the reaction mixture in two isomeric forms, one of which was shown by an independent synthesis to be 2,3dihydro-o-toluyldurene. The other isomer rearranged to a third isomer when treated with platinum in an atmosphere of nitrogen.

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