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THE REACTION OF GRIGNARD REAGENTS WITH THE CYANOBENZOYLDURENES

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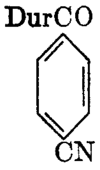
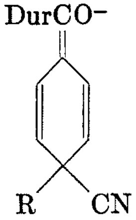
The reaction of Grignard reagents with hindered *o*-methoxy ketones has been observed to involve replacement of the methoxyl group by a hydrocarbon radical (1). Similar replacement of a methoxyl group in a *para* position has been realized only with 3,4-dimethoxy ketones, in which the flanking methoxyl group appears to facilitate the replacement (2).

It has now been found that a cyano group in a *para* position can be replaced. *p*-Cyanobenzoyldurene (I) reacts with methylmagnesium iodide and benzylmagnesium chloride to yield *p*-toluyldurene (III)[3] and *p*-benzylbenzoyldurene (IV), respectively.



I



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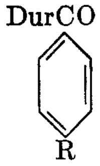
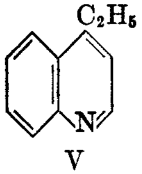
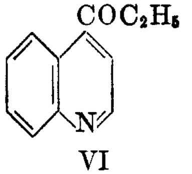


III $R = CH_3$
IV $R = C_6H_5CH_2$

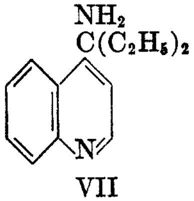
This remarkable reaction shows that the *para* carbon atom is more vulnerable to nucleophilic attack than the carbon atom of the cyano group. The reaction is reminiscent of the behavior of 4-cyanoquinoline with ethylmagnesium bromide, which gives rise to a mixture of 4-ethylquinoline (V), 4-propionylquinoline (VI), and diethyl(4-quinolinyl)methylamine (VII) (3). It should be mentioned that *o*- and *p*-cyanobenzoyldurene are electronically analogous to 4-cyanoquinoline.



V



VI



VII

Furthermore, benzoyl cyanide yields triphenylcarbinol when treated with phenylmagnesium bromide (4). In this case the cyanohydrin, which is probably formed initially, loses the cyanide ion and the resultant ketone reacts with a

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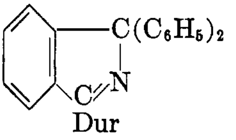
[3] Dur is used to represent duryl.

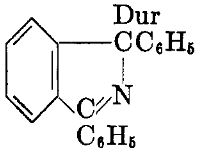
second mole of the Grignard reagent. The adduct (II), presumably formed from the Grignard reagent and *p*-cyanobenzoyldurene, may be regarded as a vinylog of a cyanohydrin, and it is therefore not surprising that it loses the cyanide ion to restore the aromaticity of the ring.

Replacement does not occur, however, with the *ortho* and *meta* isomers. *m*-Cyanobenzoyldurene reacts normally with benzylmagnesium chloride and *sec*-butylmagnesium bromide to give the corresponding diketones in yields of 53% and 31%, respectively.

With *o*-cyanobenzoyldurene the reaction takes a different course to form stable pseudoisoindoles in good yield. One product, obtained in 51% yield by use of the phenyl Grignard reagent, is 1,1-diphenyl-3-durylpseudoisoindole (VIII). Two possible structures may be assigned to the compound on the basis of its analysis. The alternate structure (IX) is rejected, since its formation by action of the Grignard reagent on *o*-cyanobenzoyldurene is highly improbable. Furthermore, the pseudoisoindole is extremely resistant to hydrolysis; prolonged boiling with a mixture of acetic and hydriodic acid does not affect it. Boiling with 85% phosphoric acid produces neither cleavage nor hydrolysis. The alternate isomer (IX) would not be expected to withstand such treatment, since it is an unhindered internal Schiff base. Previously known pseudoisoindoles are very unstable in the free state and extremely sensitive to acids (5). The pseudoisoindole obtained here is stabilized by steric factors and is indeed a compound of remarkable stability. It is undoubtedly formed by addition of the Grignard reagent to the intermediate ketimine. The amine complex then reacts with the hindered carbonyl group to form an internal Schiff base. Formation of the pseudoisoindole thus lends support to the hypothesis that steric hindrance is less effective for an intramolecular than for an intermolecular reaction.



VIII



IX

It is known that Grignard reagents react with aldimines to form amines although in low yield (6). An interesting example of amine formation occurs with benzoylacetonitrile and the allyl Grignard reagent (7). The reaction with the allyl Grignard reagent yields amines with many nitriles.

It has also been shown that the cyano group of *p*-cyanobenzoyldurene is reduced to the amine by the Stephen reduction. This would seem to indicate that the intermediate aldimine is abnormally reactive. Similarly the ketimine formed from *o*-cyanobenzoyldurene is apparently reactive enough to condense with the Grignard reagent in good yield. The differences in behavior of *o*- and *p*-cyanobenzoyldurene toward the Grignard reagent are probably due to steric factors which may hinder *ortho* replacement and alkylation.

Pseudoisoindole formation was also carried out with *p*-tolylmagnesium bromide and *p*-anisylmagnesium bromide, the products being obtained in yields of 31% and 36%, respectively. The aliphatic Grignard reagents, methylmagnesium iodide and allylmagnesium bromide, also gave pseudoisoindoles in yields of 83% and 76%, respectively. The pseudoisoindoles formed from aliphatic Grignard reagents were sufficiently basic to yield stable salts with mineral acids. Those derived from aromatic Grignard reagents did not form salts under comparable conditions. Benzylmagnesium chloride and *sec*-butylmagnesium bromide gave intractable oils with *o*-cyanobenzoyldurene. With α-naphthylmagnesium bromide the reaction did not proceed beyond the first stage, and the salt of the imine was obtained. This fact suggests that steric factors may be important in reactions of this type. Hydrolysis of this salt gave the expected diketone.

EXPERIMENTAL

p-Cyanobenzoyldurene. *p*-Cyanobenzoyl chloride was prepared in 80% yield by the action of crude thionyl chloride on *p*-cyanobenzoic acid; b.p. 150–151° (25 mm.); m.p. 69–70° [Reported (8) m.p. 65°]. To a solution made up of 24.6 g. of *p*-cyanobenzoyl chloride, 22 g. of durene, and 300 ml. of carbon disulfide was added 49 g. of aluminum chloride. The mixture, after being heated for 8 hours under reflux, was decomposed with dilute hydrochloric acid. The *p*-cyanobenzoyldurene melted at 208.5–210°; 80% yield. After recrystallization from ethanol it melted at 210–211°.

Anal.[4] Calc'd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51.
Found: C, 82.17; H, 6.69.

p-(2,3,5,6-Tetramethylbenzoyl)benzylamine. Dry hydrogen chloride was passed into a suspension of 38 g. of anhydrous stannous chloride in 300 ml. of dry ether until the salt dissolved, with the formation of a viscous lower layer. The introduction of the gas was accompanied with stirring, the reaction mixture being cooled in an ice-bath. To the mixture was added over a period of 10 minutes, a solution of 18 g. of *p*-cyanobenzoyldurene in 150 ml. of chloroform. The clear reaction mixture was stirred overnight at room temperature; a white precipitate began to form after the first hour. The precipitate was warmed with 100 ml. of water containing 5 ml. of concentrated hydrochloric acid and the *hydrochloride of p-(2,3,5,6-tetramethylbenzoyl)benzylamine* was obtained; yield 25 g. The crude salt was recrystallized five times from water; m.p. 252–254°; yield 87%.

Anal. Calc'd for $C_{18}H_{22}ClNO$: C, 71.15; H, 7.30.
Found: C, 71.19; H, 7.33.

A portion of the hydrochloride was added to 100 ml. of 10% sodium carbonate and the mixture boiled for 10 minutes. The free amine was removed, washed with water, and recrystallized from ligroin; m.p. 133–135°.

Anal. Calc'd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92.
Found: C, 80.84; H, 8.15.

A small amount of the amine was dissolved in acetic anhydride and the solution allowed to stand at room temperature for 4 hours. After two recrystallizations from a mixture of benzene and ligroin the *p-acetamidomethylbenzoyldurene* melted at 152.5–153°.

Anal. Calc'd for $C_{20}H_{23}NO_2$: C, 77.63; H, 7.49.
Found: C, 77.74; H, 7.64.

The *benzylidene derivative* was prepared by heating a solution of 0.9 g. of the amine, 0.5 g. of benzaldehyde, and 15 ml. of absolute ethanol under reflux for 2 hours. The yield was nearly quantitative. After recrystallization from ethanol the compound melted at 157–159°.

Anal. Calc'd for $C_{25}H_{25}NO$: C, 84.47; H, 7.09.
Found: C, 84.45; H, 7.23.

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[4] The microanalyses were carried out by Miss Emily Davis and Miss Rachel Kopel.

m-Cyanobenzoyldurene. *m*-Cyanobenzoic acid was prepared from *m*-aminobenzoic acid by a procedure patterned after that employed by Valby and Lucas for the *para* isomer (9). The product recrystallized from water melted at 218–219°; yield 42% [Reported (10) m.p. 220–221°].

m-Cyanobenzoyl chloride was made in 87% yield by heating a mixture of the acid (18 g.), thionyl chloride (30 ml.), and benzene (30 ml.) under reflux (11). The acid chloride distilled at 140–142° (15 mm.) and crystallized in the receiver.

To 16 g. of durene and 30 g. of aluminum chloride in 200 ml. of carbon disulfide was added over a 30-minute period 17.5 g. of *m*-cyanobenzoyl chloride in 100 ml. of carbon disulfide. The mixture was heated under reflux, with stirring, for 12 hours. The product was poured on a mixture of dilute hydrochloric acid and ice. The carbon disulfide layer was removed and washed twice with 5% sodium carbonate solution and then with water. The carbon disulfide was distilled on the water-bath and the residue recrystallized from methanol; yield 18.1 g. (64%); m.p. 157.5–159°.

Anal. Calc'd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51.

Found: C, 82.10; H, 6.64.

o-Cyanobenzoyldurene. This nitrile was prepared by heating a mixture of 24 g. of *o*-bromobenzoyldurene, 7.7 g. of cuprous cyanide, and 7.7 ml. of pyridine at 200° for 2 hours under reflux in an oil-bath. While hot, the black product was poured into a mortar, where it was allowed to cool and solidify. The solid so obtained was broken up and ground to a fine powder and extracted with three 400-ml. portions of boiling methanol, the material being filtered in each case to remove solids. The alcohol solutions were combined and concentrated to 500 ml. The crystals which appeared when the solution was cooled were separated and the filtrate was concentrated to 100 ml. and a second crop taken. The nitrile was warmed with dilute ammonia solution to remove traces of cupric salts and then was recrystallized from methanol; yield 13.3 g. (67%); m.p. 191–192°.

Anal. Calc'd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51.

Found: C, 82.10; H, 6.40.

Reaction of p-cyanobenzoyldurene with Grignard reagents. Methylmagnesium iodide. A suspension of 2.6 g. of *p*-cyanobenzoyldurene in 150 ml. of ether was poured into a Grignard reagent prepared from 7.1 g. of methyl iodide, 1.2 g. of magnesium, and 35 ml. of ether. The mixture was heated under reflux for 12 hours, and the ether layer decanted into a beaker containing dilute hydrochloric acid. The ether solution was washed with water, dried over sodium sulfate, and evaporated to dryness. The solid residue was recrystallized from methanol; m.p. 142–144°; yield 14%. After two recrystallizations from methanol, the product melted at 143.5–144.5°. A mixture melting point with an authentic specimen of *p*-toluyldurene showed no depression. About half of the *p*-cyanobenzoyldurene was recovered unchanged.

Benzylmagnesium chloride. A warm solution of 1.3 g. of *p*-cyanobenzoyldurene in 100 ml. of dry benzene was added to a Grignard reagent prepared from 3.2 g. of benzyl chloride, 0.6 g. of magnesium, and 50 ml. of dry ether. The mixture was stirred during the addition, which required 10 minutes. It was heated under reflux for 8 hours, with stirring, and decomposed with an ice-cold solution of ammonium chloride. The ether layer was extracted twice with ice-cold hydrochloric acid (1:1), washed with water, and dried over sodium sulfate. Evaporation of the solvent left an oil which crystallized from methanol; m.p. 122–126°; yield 44%. After two recrystallizations from alcohol the product melted at 129–129.5°. A mixture melting point with an authentic specimen of *p*-benzylbenzoyldurene showed no depression.

Reaction of Grignard reagents with m-cyanobenzoyldurene. Benzylmagnesium chloride. A Grignard reagent was prepared from 3.2 g. of benzyl chloride, 0.6 g. of magnesium, and 50 ml. of ether. To this solution was added 1.3 g. of *m*-cyanobenzoyldurene in 50 ml. of warm, dry benzene. Addition required 10 minutes, and the mixture was then heated under reflux for 4 hours, with stirring. When the ketone was added a bright red color developed. Addition of dilute hydrochloric acid to the solution produced a precipitate. The diketone so obtained was recrystallized from methanol (Darco); yield 0.95 g. (53%); m.p. 136.5–137.5°.

Anal. Calc'd for $C_{25}H_{24}O_2$: C, 84.25; H, 6.79.
Found: C, 83.96; H, 7.02.

The *phenylhydrazone* was prepared by dissolving 0.3 g. of the diketone in warm ethanol and adding 0.3 g. of phenylhydrazine with a drop of acetic acid. When the solution was allowed to stand overnight, the derivative separated. The product, recrystallized from ethanol, formed yellow prisms; m.p. 173–174°.

Anal. Calc'd for $C_{31}H_{30}N_2O$: C, 83.37; H, 6.77.
Found: C, 83.29; H, 6.85.

sec-Butylmagnesium bromide. sec-Butylmagnesium bromide was prepared in 50 ml. of ether from 0.6 g. of magnesium and 3.4 g. of *sec*-butyl bromide. To this solution under reflux was added 1.3 g. of *m*-cyanobenzoyldurene in 50 ml. of warm benzene over a period of 15 minutes. The solution turned deep red and, after 12 hours, was decomposed with dilute hydrochloric acid. The ether-benzene layer was washed twice with 5% sodium carbonate solution and then with water. Removal of the solvent on the steam-bath gave an oil which crystallized from methanol. After three recrystallizations from this solvent (Darco) a colorless product was obtained; yield 0.5 g. (31%); m.p. 139.5–140.5°.

Anal. Calc'd for $C_{22}H_{26}O_2$: C, 81.95; H, 8.13.
Found: C, 81.98; H, 7.94.

An attempt to prepare the phenylhydrazone of this compound was unsuccessful.

Reaction of Grignard reagents with o-cyanobenzoyldurene. Phenylmagnesium bromide. Phenylmagnesium bromide was prepared from 15.7 g. of bromobenzene and 2.4 g. of magnesium in 60 ml. of ether. To this solution was added dropwise over a period of 1 hour a solution of 2.6 g. of *o*-cyanobenzoyldurene in 60 ml. of benzene. The solution turned green when the ketone was added, and after an 18-hour reflux period, had become dark red. When the mixture was decomposed with dilute hydrochloric acid, a gray solid precipitated. This material was recrystallized from ethanol (Norit). It formed colorless prisms; yield 1.8 g.; m.p. 222.5–223.5°. The ether-benzene layer was washed with water, and the volatile solvent removed. The resulting oil was subjected to steam-distillation to remove biphenyl and then crystallized from ethanol; yield 0.3 g.; m.p. 222.5–223.5°. A mixture melting point showed no depression indicating that the two solids were identical. The total yield of 1,1-diphenyl-3-durylpseudoisoindole amounted to 2.1 g. (51%).

Anal. Calc'd for $C_{30}H_{27}N$: C, 89.73; H, 6.78; N, 3.49.
Found: C, 89.44; H, 6.72; N, 3.59.

Attempted hydrolysis of 1,1-diphenyl-3-durylpseudoisoindole. The pseudoisoindole (0.2 g.) was boiled 18 hours with a mixture of 4 ml. of glacial acetic acid and 1 ml. of 48% hydriodic acid. The mixture was poured into 50 ml. of water and the starting material quantitatively recovered.

One gram of the pseudoisoindole was heated under reflux for 48 hours with 40 ml. of 85% phosphoric acid. The acid solution was neutralized to *p*H 7 with 20% sodium hydroxide and then steam-distilled. No durene was obtained. After the mixture had cooled it was filtered, and the gray precipitate so obtained washed with water. The solid, recrystallized from ethanol, proved to be starting material; recovery 0.6 g. A mixture melting point with the starting material showed no depression.

p-Tolylmagnesium bromide. A Grignard reagent was prepared from 17 g. of *p*-bromotoluene, 2.4 g. of magnesium, and 60 ml. of ether. To this solution was added dropwise over a 20-minute period a solution of 5.2 g. of *o*-cyanobenzoyldurene in 60 ml. of benzene. After 24 hours at reflux temperature the solution had turned dark red. Decomposition was carried out with dilute hydrochloric acid, and the ether-benzene layer was washed with water and steam-distilled to remove impurities. The resultant red oil crystallized on cooling and was recrystallized from ethanol or ethyl acetate; yield 2.6 g. (31%). The 1,1-di-(*p*-tolyl)-3-durylpseudoisoindole melted at 225.5–226°.

Anal. Calc'd for $C_{32}H_{31}N$: C, 89.46; H, 7.26; N, 3.26.
Found: C, 89.31; H, 7.18; N, 3.07.

p-Anisylmagnesium bromide. A Grignard reagent was prepared from 28 g. of *p*-methoxybromobenzene, 3.6 g. of magnesium, and 60 ml. of ether. To this solution was added dropwise over a 30-minute period a solution of 7.9 g. of *o*-cyanobenzoyldurene in 100 ml. of benzene. A green color immediately developed. After 12 hours at reflux temperature the solution was decomposed with dilute hydrochloric acid. The ether-benzene layer was washed with water, and the volatile solvent distilled. The residual oil was steam-distilled to remove impurities. The product, which crystallized when cool, was boiled with 150 ml. of ethanol and collected on a filter. The nearly colorless, insoluble material was recrystallized from ethyl acetate; yield 5.0 g. (36%); m.p. 217–218°.

Anal. Calc'd for $C_{32}H_{31}NO_2$: C, 83.26; H, 6.77; N, 3.04.
Found: C, 83.05; H, 6.94; N, 3.11.

α-Naphthylmagnesium bromide. A Grignard reagent was prepared from 20.7 g. of α-bromonaphthalene, 2.4 g. of magnesium, and 80 ml. of ether. To this solution was added 7.9 g. of *o*-cyanobenzoyldurene in 100 ml. of benzene over a period of 20 minutes. The solution turned green immediately and after a reflux period of 14 hours had become dark red. Decomposition was effected by dilute hydrobromic acid, and a precipitate appeared. The mixture was cooled in an ice-bath and filtered; yield of imine salt 9.3 g. (65%). The imine salt was recrystallized from a solvent consisting of one part of alcohol to two parts of ethyl acetate; m.p. 257–273°, with decomposition.

Anal. Calc'd for $C_{28}H_{26}BrNO$: C, 71.18; H, 5.55; N, 2.97.
Found: C, 70.99; H, 5.93; N, 3.10.

One gram of the imine salt was heated under reflux for 2 hours with a solution consisting of 4 g. of sodium hydroxide in 50 ml. of ethanol. The solution was then poured into water and the product separated. The yield of crude ketone was nearly quantitative; it was recrystallized from ethanol, m.p. 182–183°.

Anal. Calc'd for $C_{28}H_{24}O_2$: C, 85.68; H, 6.16.
Found: C, 85.94; H, 6.39.

The *phenylhydrazone* of the ketone was prepared in the usual manner; m.p. 196.5–197.5°.

Anal. Calc'd for $C_{34}H_{30}N_2O$: N, 5.81. Found: N, 6.01.

Methylmagnesium iodide. A Grignard reagent was prepared from 7.1 g. of methyl iodide, 1.2 g. of magnesium, and 50 ml. of ether. To this solution was added dropwise over a 10-minute period a solution of 2.6 g. of *o*-cyanobenzoyldurene in 50 ml. of benzene. The solution turned green and after 12 hours at reflux temperature had changed to red. The mixture was then decomposed with excess dilute hydrochloric acid and cooled in an ice-bath. The pseudoisoindole salt was isolated and recrystalllzed from a solvent consisting of two parts of ethyl acetate to one part of ethanol; yield 2.6 g. (83%). One gram of the salt was heated under reflux with 1 g. of sodium hydroxide in 50 ml. of ethanol for 30 minutes. The mixture was poured into water and the 1,1-dimethyl-3-durylpseudoisoindole recrystallized from aqueous ethanol; m.p. 170.5–171.0°.

Anal. Calc'd for $C_{20}H_{23}N$: C, 86.59; H, 8.36; N, 5.05.
Found: C, 86.33; H, 8.65; N, 4.90.

Allylmagnesium bromide. Allylmagnesium bromide was prepared in a cyclic Grignard apparatus (12) and a 0.15-mole aliquot in 100 ml. of ether was introduced into the reaction flask. To this solution was added a suspension of 7.9 g. of *o*-cyanobenzoyldurene in 200 ml. of ether. The solution turned red and was stirred under reflux for three hours. It was then decomposed with excess ammonium chloride solution. The ether layer was washed with water and dried with sodium sulfate. After evaporation of the ether a brown oil was obtained which could not be induced to crystallize. The oil was distilled and the fraction boiling at 175–178° (0.4 mm.) collected. The product crystallized on cooling; yield 7.5 g. (76%). It was purified by a short path distillation carried out in a sublimation apparatus at 100° (0.2 mm.); m.p. 77–79°.

Anal. Calc'd for $C_{24}H_{27}N$: C, 87.48; H, 8.26; N, 4.25.
Found: C, 87.12; H, 8.48; N, 4.48.

SUMMARY

Grignard reagents have been found to react with *p*-cyanobenzoyldurene in such a way as to replace the cyano group by a hydrocarbon radical.

Condensation of *m*-cyanobenzoyldurene with benzylmagnesium chloride and *sec*-butylmagnesium bromide yielded the expected ketones.

o-Cyanobenzoyldurene gave pseudoisoindoles in good yield with both aromatic and aliphatic Grignard reagents. Thus with phenylmagnesium bromide 1,1-diphenyl-3-durylpseudoisoindole was obtained. This product presumably originates by addition of the Grignard reagent to the intermediate ketimine. The amine so formed apparently undergoes intramolecular dehydration between the amino group and the hindered carbonyl function to give the pseudoisoindole or internal Schiff base, which is greatly stabilized by steric factors. Thus with the isomeric cyanobenzoyldurenes it is possible to realize three different types of reaction between the nitrile group and Grignard reagents: replacement of the cyano group of the *para* isomer, ketone formation with the *meta* isomer, and amine formation followed by dehydration with the *ortho* isomer.

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