[Contribution from the Noyes Chemical Laboratory, University of Illinois]

REPLACEMENT OF METHOXYL GROUPS IN *p*-METHOXYARYL KETONES BY THE ACTION OF THE GRIGNARD REAGENT

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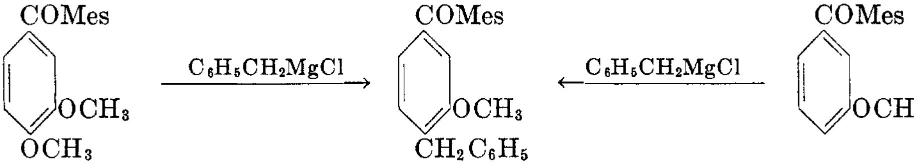
The introduction by means of the Grignard reagents of an alkyl or aryl radical into the *ortho* position of benzoylmesitylene and certain similarly constituted aryl ketones (1) was found to occur more readily with the corresponding *o*-methoxyl ketones (2). It seemed probable that alkylation in the *para* position, observed with benzyl, *t*-butyl (3), and methyl (4) Grignard reagents, would likewise proceed more readily with the corresponding *p*-methoxyaryl ketones. However, early attempts to convert anisyl duryl ketone to *p*-benzylphenyl duryl ketone by the action of benzylmagnesium chloride were not successful. The hope of achieving this type of reaction was revived when it was found that similar replacements of *ortho* alkoxyl groups in the benzonitrile series were made possible by the presence of a second alkoxyl group on the adjoining carbon atom (5).

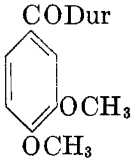
This suggestion has proved fruitful. When 3,4-dimethoxyphenyl mesityl ketone (I) was treated with benzylmagnesium chloride, the methoxyl group in the 4 position was replaced by benzyl. The structure of the product, 3-methoxy-4-benzylphenyl mesityl ketone (II) was established by an independent synthesis. 3-Methoxyphenyl mesityl ketone (III) was found to react with benzylmagnesium chloride to undergo benzylation in the same manner as benzoyldurene (3).



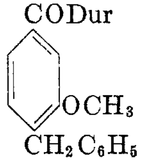
I II III

Phenylmagnesium bromide appeared to act on 3,4-dimethoxyphenyl mesityl ketone in a similar manner, but no proof of structure has been obtained for the product, presumed to be 4-mesitoyl-2-methoxybiphenyl.

Similar results were obtained with 3,4-dimethoxyphenyl duryl ketone (IV), the methoxyl group in the 4 position being replaced by a benzyl group. The product (V) was obtained also by treatment of 3-methoxyphenyl duryl ketone with benzylmagnesium chloride.

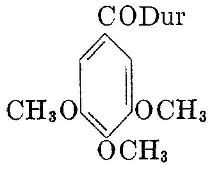


IV

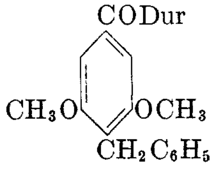


V

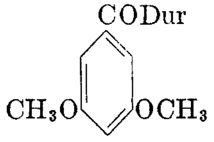
Another interesting example of this replacement was observed when 3,4,5-trimethoxyphenyl duryl ketone (VI) was treated with benzylmagnesium chloride. The product, 3,5-dimethoxy-4-benzylphenyl duryl ketone (VII), was identical with the benzylation product from 3,5-dimethoxyphenyl duryl ketone (VIII). The yield (58%) in the replacement reaction indicates that the promoting effect of the *ortho* methoxyl group is additive.



VI

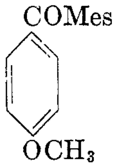


VII

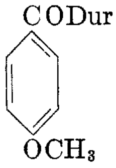


VIII

Renewed attempts to effect replacement of methoxyl groups in anisyl mesityl ketone (IX) and anisyl duryl ketone (X) have been unsuccessful. Rather, the formation of dihydro compounds of unknown structure was observed.

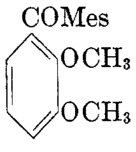


IX

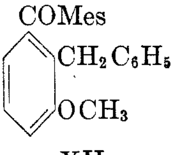


X

The relation of the second methoxyl group to the replacement of a methoxyl *ortho* to a hindered carbonyl group has also been investigated. 2,3-Dimethoxyphenyl mesityl ketone (XI), when treated with benzylmagnesium chloride, yielded 2-benzyl-3-methoxyphenyl mesityl ketone (XII). However, the low yield in this reaction compared to the yields previously reported (2) indicates that the effect of the second methoxyl group is not important in this case.



XI



XII

EXPERIMENTAL[1]

3,4-Dimethoxyphenyl mesityl ketone. A solution of 16 g. of veratroyl chloride (6) in 80 ml. of carbon disulfide was added with mechanical stirring to a mixture of 9.9 g. of mesitylene, 11.4 g. of anhydrous aluminum chloride, and 40 ml. of the solvent over a period of 45 minutes and stirring continued for a like period. The mixture was decomposed with cold dilute hydrochloric acid, and the solvent layer was washed with water and 10% sodium hydroxide solution. The solvent was removed by distillation; there was obtained, after recrystalliza-

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[1] Microanalyses were by Misses Theta Spoor, Betty Snyder, and Jane Wood and the Clark Microanalytical Laboratories, Urbana, Illinois. Melting points are corrected.

tion of the residue from ethanol, 14 g. (62% yield) of the ketone; m.p. 100–102°. It separated from high-boiling petroleum ether in white needles; m.p. 105–105.5°.

Anal. Calc'd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09.
Found: C, 76.23; H, 7.23.

Reaction of 3,4-dimethoxyphenyl mesityl ketone with Grignard reagents. A. *Benzylmagnesium chloride.* To a Grignard reagent prepared from 8.9 g. of benzyl chloride and 1.7 g. of magnesium turnings in 50 ml. of dry ether was added over a period of an hour a solution of 8 g. of the ketone in 65 ml. of ether and 10 ml. of benzene. Addition was accompanied by the formation of a red coloration changing to brown, a slight warming, and finally the separation of a tan precipitate. After being stirred for another hour, the reaction mixture was decomposed with cold dilute hydrochloric acid. Usual procedures yielded 11.4 g. of a light yellow gum; it was dissolved in methanol and the solution deposited 2.1 g. (22% yield) of yellow crystals; m.p. 90.5–92.5°. 3-Methoxy-4-benzylphenyl mesityl ketone separated from methanol in fine white needles; m.p. 93.5–94.5°; b.p. 205–210° (1 mm.).

Anal. Calc'd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02.
Found: C, 83.70; H, 7.25.

B. *Phenylmagnesium bromide.* Treatment of 12 g. of the ketone with this Grignard reagent as described above yielded 14 g. of a dark red gum. Distillation of this material *in vacuo* gave 10.2 g. of a light yellow gum; b.p. 200–210° (1 mm.). It could not be induced to crystallize, but three redistillations gave a light yellow gum which had the composition of 4-mesitoyl-2-methoxybiphenyl. The yield was 15% based on the yield of the bromination product described below.

Anal. Calc'd for $C_{22}H_{22}O_2$: C, 83.60; H, 6.71.
Found: C, 83.36; H, 6.93.

When 2 g. of this gum was treated with 1.08 g. of bromine in 20 ml. of carbon tetrachloride for 4 hours, there was isolated 0.5 g. of a solid which was recrystallized from methanol. White crystals having the composition of a monobromo derivative were obtained; m.p. 110.5–112°.

Anal. Calc'd for $C_{23}H_{21}BrO_2$: C, 67.48; H, 5.17.
Found: C, 67.49; H, 5.08.

Independent synthesis of 3-methoxy-4-benzylphenyl mesityl ketone. *m*-Methoxyphenyl mesityl ketone (5 g.) (2) was treated with benzylmagnesium chloride and the mixture heated under reflux for 2 hours. The resulting 7.7 g. of yellow oil was dissolved in methanol; the solution deposited 0.6 g. (9% yield) of clumped needles; m.p. 92.5–93.5° after recrystallization from methanol. The melting point was not depressed when this material was mixed with that previously isolated from the reaction of 3,4-dimethoxyphenyl mesityl ketone with benzylmagnesium chloride.

3,4-Dimethoxyphenyl duryl ketone. This ketone was prepared in 29% yield by a procedure similar to that described for 3,4-dimethoxyphenyl mesityl ketone. The ketone formed fine white needles after repeated recrystallization from a mixture of ethanol and benzene; m.p. 157.5–159°.

Anal. Calc'd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43.
Found: C, 76.40; H, 7.45.

Reaction of 3,4-dimethoxyphenyl duryl ketone and benzylmagnesium chloride. Treatment of 3.9 g. of the ketone with this Grignard reagent yielded 6.6 g. of a residual oil, which deposited 2 g. (42% yield) of yellow sandlike crystals from methanol. On being recrystallized repeatedly from ethanol-benzene, 3-methoxy-4-benzylphenyl duryl ketone formed white crystals; m.p. 187–188.5°.

Anal. Calc'd for $C_{25}H_{26}O_2$: C, 83.76; H, 7.31.
Found: C, 83.77, 84.01; H, 7.16, 6.87.

Independent synthesis of 3-methoxy-4-benzylphenyl duryl ketone. m-Methoxyphenyl duryl ketone. This ketone was prepared in 87% yield from *m*-methoxybenzoyl chloride (7) and durene by the Friedel-Crafts method. It boiled at 182–184° (3 mm.) and separated from methanol in fine white needles; m.p. 127–127.5°.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51.
Found: C, 80.62; H, 7.51.

Reaction of m-methoxyphenyl duryl ketone and benzylmagnesium chloride. Ten grams of the ketone was treated with the Grignard reagent, the reaction mixture changing from purple to brown during the course of the addition and a 2-hour reflux period. There was obtained 4.6 g. (34% yield) of 3-methoxy-4-benzylphenyl duryl ketone by dissolving the resulting oil in methanol. One recrystallization from ethanol-benzene gave crystals melting at 185.5–187° and a mixture with the product obtained from 3,4-dimethoxyphenyl duryl ketone melted at 186.5–188°.

3,4,5,-Trimethoxyphenyl duryl ketone. A solution of 29 g. of 3,4,5-trimethoxybenzoyl chloride (8) in 100 ml. of benzene was added over a period of 30 minutes to a reagent prepared from 27.7 g. of bromodurene, 3 ml. of ethyl bromide, and 3.25 g. of magnesium in 150 ml. of ether. After being stirred for an additional 15 minutes, the reaction yielded 6.8 g. (16%) of white crystals from methanol; m.p. 135–139°. The ketone was recrystallized from ethanol; m.p. 141.5–142°.

Anal. Calc'd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37.
Found: C, 73.41; H, 7.33.

Reaction of 3,4,5-trimethoxyphenyl duryl ketone and benzylmagnesium chloride. Addition of a solution of 6 g. of the ketone to the Grignard reagent caused formation of a green color, and finally a light colored solid separated. After stirring the reaction mixture for 45 minutes and decomposing, there was obtained from methanol solution 4.1 g. (58% yield) of crystals; m.p. 125–128°. 3,5-Dimethoxy-4-benzylphenyl duryl ketone separated from ethanol in long, colorless needles; m.p. 139–139.5°.

Anal. Calc'd for $C_{26}H_{28}O_3$: C, 80.38; H, 7.26.
Found: C, 80.29, 80.43; H, 7.29, 7.39.

Independent synthesis of 3,5-dimethoxy-4-benzylphenyl duryl ketone. 3,5-Dimethoxyphenyl duryl ketone. This compound was prepared in 21% yield by the Friedel-Crafts method employing 3,5-dimethoxybenzoyl chloride (9). The ketone separated from methanol in light yellow plates; m.p. 101.5–102°.

Anal. Calc'd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43.
Found: C, 76.58; H, 7.54.

Reaction of 3,5-dimethoxyphenyl duryl ketone and benzylmagnesium chloride. The ketone (2.4 g.) was treated with the benzyl Grignard reagent, giving a brown solution which precipitated a solid when heated under reflux for 90 minutes. From methanol there was obtained 0.74 g. (24% yield) of white crystals; m.p. 124–133°. The compound separated from ethanol in needles; m.p. 138–139°. The mixture melting point with the product obtained from 3,4,5-trimethoxyphenyl duryl ketone showed no depression.

Anisyl mesityl ketone.[2] A solution of *p*-methoxyphenylmagnesium bromide, prepared from 13 g. of magnesium, 72 g. of *p*-bromoanisole, and 200 ml. of dry ether, was added slowly, with stirring, to a solution of 59 g. of mesitoyl chloride in 200 ml. of dry ether. The mixture was decomposed with hydrochloric acid and the ether layer was washed with dilute sodium hydroxide solution. Evaporation of the solvent left the anisyl mesityl ketone as a solid. It was recrystallized from ethanol; m.p. 78°; yield 28 g.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.29; H, 7.10.
Found: C, 80.37; H, 7.31.

Reaction of anisyl mesityl ketone and benzylmagnesium chloride. The ketone (10 g.), when treated with this Grignard reagent, turned red-brown and yielded 16.2 g. of a light yellow gum which was dissolved in methanol. The solution deposited 2.7 g. (20% yield) of bright yellow crystals which were decolorized by distillation at reduced pressure; b.p. 194–200°

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[2] This experiment was carried out by Dr. S. B. Speck.

(1 mm.). The compound, presumably 2-benzyl-4-methoxy-1,2-dihydrophenyl mesityl ketone, separated from methanol in flat white needles; m.p. 119.5–120.5°.

Anal. Calc'd for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56.

Found: C, 83.48, 83.38; H, 7.68, 7.45.

The compound decolorized a solution of bromine in carbon tetrachloride, evolving hydrogen bromide, and reacted with a 0.5% solution of potassium permanganate in water and acetone. An attempted dehydrogenation over palladium on charcoal catalyst gave no crystalline substance.

Reaction of anisyl duryl ketone and benzylmagnesium chloride. On treatment of 10 g. of the ketone (4) with the benzyl Grignard reagent, warming occurred with the formation of a purple color turning to brown. Stirring was continued for an hour at room temperature. An amber gum (14.1 g.) was isolated and dissolved in methanol, the solution depositing 0.28 g. of a deep yellow powder; m.p. 222–226°. It was insoluble in the usual solvents and was recrystallized from diphenyl ether; m.p. 234.5–237°. The compound had the composition of 2-benzyl-4-methoxy-1,2-dihydrophenyl duryl ketone and reacted with a solution of potassium permanganate in acetone and water.

Anal. Calc'd for $C_{25}H_{28}O_2$: C, 83.29; H, 7.83.

Found: C, 83.01; H, 7.19.

2,3-Dimethoxyphenyl mesityl ketone. This ketone was prepared in 26% yield by the Friedel-Crafts method from *o*-veratroyl chloride (10). It was obtained in light yellow needles from methanol; m.p. 121.5-122°.

Anal. Calc'd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09.

Found: C, 75.69; H, 6.99.

Reaction of 2,3-dimethoxyphenyl mesityl ketone and benzylmagnesium chloride. The ketone (4.5 g.) in ethereal solution was added to the Grignard reagent, causing moderate warming and a red coloration. After stirring the reaction mixture at room temperature for 90 minutes, a light-colored precipitate had formed. A yellow oil (7.6 g.) was isolated and distilled at reduced pressure giving 3.3 g. of a light yellow gum; b.p. 150–190° (1 mm.). From methanol solution it deposited 0.38 g. (7% yield) of sandlike crystals; m.p. 102–106°. Repeated recrystallization of the compound, presumably 2-benzyl-3-methoxyphenyl mesityl ketone, from methanol gave white crystals; m.p. 111.5–112°.

Anal. Calc'd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02.

Found: C, 83.91, 83.85; H, 7.37, 7.12.

Condensation of 2,3,5,6-tetramethylbenzoyl chloride with o-methoxyphenylmagnesium bromide.[3] A filtered solution of the Grignard reagent prepared from 26 g. of *o*-bromoanisole was added dropwise to a solution of 30 g. of 2,3,5,6-tetramethylbenzoyl chloride in 350 ml. of dry ether. The mixture was stirred at room temperature for one hour and decomposed with dilute hydrochloric acid. The ether layer was washed with 5% potassium carbonate solution and with water. Sodium 2,3,5,6-tetramethylbenzoate is insoluble in water. Acidification of the potassium carbonate solution yielded 7.0 g. of 2,3,5,6-tetramethylbenzoic acid. The solvent was distilled from the organic layer and ethanol added to the oily residue. The 2′-(*o*-methoxyphenyl)-2,3,5,6-tetramethylbenzophenone weighed 10.4 g. and, after recrystallization from a mixture of benzene and ethanol, melted at 153–154°.

Anal. Calc'd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02; mol. wt., 344.

Found: C, 83.90; H, 7.13; mol. wt. (ebullioscopic in chloroform), 320, 308.

From the original ethanol filtrate was obtained 16 g. of a solid which, after repeated recrystallization from ethanol, melted at 110–120°. It was probably impure *o*-methoxyphenyl duryl ketone.

4′-Benzyl-2′-(o-methoxyphenyl)-2,3,5,6-tetramethylbenzophenone.[3] A Grignard reagent was prepared from 13 g. of benzyl chloride and 2.5 g. of magnesium, and to it was added 4.2 g. of 2′-(*o*-methoxyphenyl)-2,3,5,6-tetramethylbenzophenone. The deep red solution was heated under reflux for 11 hours and decomposed in the usual way. Distillation of the

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[3] This experiment was carried out by Dr. B. C. McKusick.

product yielded an oil and a tarry residue. Treatment of the tar with ether left 0.20 g. of needles which, after recrystallization from a mixture of ethanol and benzene, melted at 165.5–166.5°.

Anal. Calc'd for $C_{31}H_{30}O_2$: C, 85.68; H, 6.96.
Found: C, 85.97; H, 7.29.

SUMMARY

Replacement of a methoxyl group *para* to a hindered carbonyl group by the radical of a Grignard reagent has been achieved in three instances in which the *para* methoxyl group was flanked by one or more other methoxyl groups. Thus 3,4-dimethoxyphenyl mesityl ketone, 3,4-dimethoxyphenyl duryl ketone, and 3,4,5-trimethoxyphenyl duryl ketone, when treated with benzylmagnesium chloride, yielded respectively 3-methoxy-4-benzylphenyl mesityl ketone, 3-methoxy-4-benzylphenyl duryl ketone, and 3,5-dimethoxy-4-benzylphenyl duryl ketone.

Replacement of the methoxyl group in anisyl mesityl ketone and anisyl duryl ketone in a similar manner has not been realized.

URBANA, ILL.

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