

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

**The Behavior of Pyrogallol Trimethyl Ether and 3,4,5-Trimethoxybenzotrile toward Grignard Reagents**

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Recently Haller and Schaffer<sup>1</sup> investigated the course of reaction between isobutylmagnesium bromide and 3,4,5-trimethoxybenzotrile at the refluxing temperature of toluene. In addition to the expected 3,4,5-trimethoxyphenyl isobutyl ketone there was obtained a phenolic ketone and a second neutral ketone. On the basis of the reactions of these compounds, analytical data, and the known reactivity of the methoxyl group in the 4-position of trimethylpyrogallol derivatives, it was suggested that they were 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone and a 3,5-dimethoxy-4-butylphenyl isobutyl ketone.

At Dr. Haller's suggestion we continued this problem. We confirmed the observations of Haller and Schaffer and have obtained additional evidence for cleavage of the vicinal ether linkage. By increasing the molar ratio of the Grignard reagent from two and one-half to four-fold excess and the reaction time from three to five hours at a temperature of 110°, the yield of hydrolysis products may be greatly increased at the expense of the trimethoxy ketone. However, at 40° and with the longer reaction period cleavage of the ether linkage does not occur, the only product being the trimethoxy ketone.

The cleavage of ethers by Grignard reagents usually requires a reaction temperature of the order of 200°<sup>2</sup> but with more active linkages as in phenyl allyl ether cleavage occurs at 50 to 75°.<sup>3</sup> In trimethylpyrogallol derivatives the methoxyl group in the 4-position can be replaced with hydrogen<sup>4</sup> or hydrolyzed by sulfuric acid<sup>5,6</sup> to the corresponding dimethoxy phenol. It may be anticipated that at 110° Grignard reagents would cause a cleavage of the activated ether linkage.

The structure of the phenolic product resulting from the action of isobutylmagnesium bromide on 3,4,5-trimethoxybenzotrile was shown to be

(1) Haller and Schaffer, *THIS JOURNAL*, **61**, 2175 (1939).(2) Grignard, *Compt. rend.*, **151**, 322 (1910); Simonis and Remmert, *Ber.*, **47**, 269 (1914); Späth, *ibid.*, **47**, 766 (1914); Späth, *Monatsh.*, **35**, 319 (1914); Hirao, *J. Chem. Soc. Japan*, **54**, 991 (1933), and earlier articles; Grignard and Ritz, *Bull. soc. chim.*, **3**, 1181 (1936); Challenger and Miller, *J. Chem. Soc.*, 894 (1938).(3) Lüttringhaus, Sääf and Hauschild, *Ber.*, **71**, 1673 (1938).

(4) Houben, "Die Methoden der organischen Chemie," pt. 3, 1930, p. 179.

(5) Alimchandani, *J. Chem. Soc.*, **125**, 539 (1924).(6) Asahina and Kusaka, *Ber.*, **69**, 454 (1936).

the suggested 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone by hydrolysis of 3,4,5-trimethoxyphenyl isobutyl ketone with sulfuric acid to yield the same phenol obtained from the Grignard reaction. Oxidation of the phenol with chromic anhydride in glacial acetic acid produced the known 2,6-dimethoxybenzoquinone, showing the location of the phenolic group. Several attempts were made to oxidize the neutral ketone to 3,5-dimethoxyterephthalic acid,<sup>7</sup> but only intractable tars resulted.

The formation of a phenol is the characteristic reaction in the cleavage of an aryl alkyl ether by a Grignard reagent but in the case of trimethylpyrogallol cleavage may occur at the aryl-oxygen linkage, accounting for the formation of the neutral ketone in which a butyl group has apparently replaced the methoxyl group. When pyrogallol trimethyl ether was heated at 110° with methylmagnesium iodide the only product was 2,6-dimethoxyphenol, obtained in 84% yield. Possibly an activating group in the para position is necessary to sufficiently weaken the aryl-oxygen to cause its cleavage.

**Experimental**

Trimethoxygallic acid was prepared in 91% yield by methylation of alkaline sodium gallate with methyl sulfate.<sup>8</sup> The acid chloride was prepared readily with phosphorus pentachloride by heating equimolar amounts of the two reagents for fifteen minutes at 100°, whereas attempts to bring about this conversion with thionyl chloride gave far less satisfactory yields. In the former case, phosphorus oxychloride and unused pentachloride were distilled off at 18 mm. and an excess of concentrated ammonium hydroxide was added to the residue. The amide, m. p. 177°, was prepared in 81% yield. It was converted in 93% yield to 3,4,5-trimethoxybenzotrile, m. p. 86-89°, by heating in benzene solution with phosphorus pentachloride. Neither vacuum distillation nor crystallization from aqueous alcohol was effective in raising the melting point of this material, but isopropyl ether proved to be an efficient solvent. After one crystallization from it, the material melted at 90-92° (literature, 93°).

**Reaction of 3,4,5-Trimethoxybenzotrile with Isobutylmagnesium Bromide**

**First Experiment.**—Haller and Schaffer's<sup>1</sup> conditions were duplicated, starting with 19.3 g. of the nitrile (0.1

(7) Brunner, *Monatsh.*, **50**, 224 (1928).

(8) "Organic Syntheses," Vol. VI, 1926, p. 96.

mole) and 0.25 mole of isobutylmagnesium bromide. Refluxing in toluene solution, after displacement of the ether as solvent, was for three hours. The yield of 3,4,5-trimethoxyphenyl isobutyl ketone, b. p. 164–166° at 6 mm., was 3.8 g. Haller and Schaffer reported its b. p. as 147–150° (1 mm.) and did not observe its solidification. On standing, our product crystallized spontaneously. These crystals melted at 37–39°. The yield of phenolic product, 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone, m. p. 93–93.5°, was 4.5 g.

**Second Experiment.**—The points of difference in procedure were a greater excess of Grignard reagent and a longer period of refluxing. The mixture of 19.3 g. of nitrile and 0.4 mole of Grignard reagent (from 55 g. of isobutyl bromide) was made in ether as before, then the solvent ether was replaced by toluene, and the mixture refluxed for five hours. Only 1.50 g. of 3,4,5-trimethoxyphenyl isobutyl ketone was isolated, but 10.0 g. of 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone was formed. From the toluene solution there was obtained 6.18 g. of oil boiling at 163–167° (5 mm.) and 1.58 g. boiling at 167–177° (5 mm.). This is presumably 3,5-dimethoxy-4-isobutylphenyl isobutyl ketone. Its semicarbazone melted at 183–184°.<sup>1</sup>

**Third Experiment.**—By carrying out the reaction at 40° only the trimethoxy ketone was obtained. To the Grignard reagent prepared from 17.1 g. (0.125 mole) of isobutyl bromide in 65 cc. of ether and 3.04 g. (0.125 mole) of magnesium in 100 cc. of ether was added 19.3 g. (0.100 mole) of the nitrile dissolved in 200 cc. of dry toluene. The mixture was maintained at 40° for five hours. It was then poured onto ice containing 30 cc. of concentrated hydrochloric acid. The organic layer was separated, washed with water, and dried over sodium sulfate. Evaporation of the solvents gave 9.26 g. of the unreacted nitrile. The water layer was refluxed for two hours, cooled, and then the resulting oil extracted with ether. The extract was washed with 5% sodium hydroxide, with water, and dried over sodium sulfate. After removal of the solvent the residue boiled at 163–168° (7 mm.) and solidified at room temperature. The yield was 10.7 g. The sodium hydroxide extract contained no alkali-soluble material; hence, hydrolysis to 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone had not taken place during the reaction.

**Oxidation of 3,5-Dimethoxy-4-hydroxyphenyl Isobutyl Ketone to 2,6-Dimethoxybenzoquinone.**—To 0.5 g. of the phenol dissolved in 20 cc. of glacial acetic acid was gradually added 1.25 g. of chromic anhydride. After the reaction had subsided, the solution was heated on the water-bath for fifteen minutes, cooled, and 35 cc. of water was added. The resulting solution was extracted three times with chloroform and the extract dried over sodium sulfate. After removal of the solvent, the oil was treated with a small quantity of ether and the insoluble material removed by filtration. The precipitate was recrystallized from glacial acetic acid; m. p. 253–254°. When mixed with an authentic sample of 2,6-dimethoxybenzoquinone<sup>10</sup> there was no depression of the melting point.

**3,5-Dimethoxy-4-hydroxyphenyl Isobutyl Ketone from 3,4,5-Trimethoxyphenyl Isobutyl Ketone.**—One gram of

the trimethoxyphenyl isobutyl ketone was dissolved in 4 cc. of concentrated sulfuric acid. The solution was maintained at 35–40° for twenty hours and then poured onto ice. The resulting mixture was extracted with ether and the extract washed with 5% sodium hydroxide. The alkaline solution was acidified, then extracted with ether and the ether solution dried over sodium sulfate. Evaporation of the ether gave 0.80 g. of the phenol. After one recrystallization from 50% ethanol, it melted at 93°. A mixed melting point with the phenol obtained from the Grignard reaction on the nitrile showed no depression.

**Reaction of Pyrogallol Trimethyl Ether with Methylmagnesium Iodide.**—To the Grignard reagent prepared from 85.2 g. (0.60 mole) of methyl iodide in 110 cc. of ether and 14.6 g. (0.60 mole) of magnesium in 175 cc. of ether was added 25.2 g. (0.15 mole) of pyrogallol trimethyl ether dissolved in 200 cc. of dry toluene. The reaction mixture was then heated in an oil-bath and the ether removed by distillation, toluene being added gradually to maintain the original volume. After all of the ether had been replaced with toluene, the mixture was refluxed for ten hours with constant stirring. The reaction mixture was then poured on ice containing 80 cc. of concentrated hydrochloric acid. The organic layer was separated, the water saturated with sodium chloride and extracted with ether. The combined organic solution was extracted with 5% sodium hydroxide and dried over sodium sulfate. Evaporation of the solvents left no residue. The alkaline extract was acidified, the water saturated with sodium chloride and extracted with ether. After drying over sodium sulfate, removal of the ether gave 19.4 g. of 2,6-dimethoxyphenol, b. p. 106–108° (4 mm.). When recrystallized from butyl ether the melting point was 55–56°. When treated with benzoyl chloride in pyridine the phenol gave a benzoate<sup>10</sup> melting at 116–117° and with picric acid formed a picrate<sup>11</sup> melting at 61°.

### Summary

In the reaction of isobutylmagnesium bromide and 3,4,5-dimethoxybenzonitrile, the yield of abnormal products (3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone and 3,5-dimethoxy-4-isobutylphenyl isobutyl ketone) is favored by a 4:1 excess of Grignard reagent and by a prolonged reaction time at 110°. At 40°, only the normal product (3,4,5-trimethoxyphenyl isobutyl ketone) was obtained.

The structure of 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone was established by oxidizing it to 2,6-dimethoxybenzoquinone.

Conversion of 3,4,5-dimethoxyphenyl isobutyl ketone into 3,5-dimethoxy-4-hydroxyphenyl isobutyl ketone was effected by the action of sulfuric acid.

Methylmagnesium iodide reacted with pyrogallol trimethyl ether at 110°, to yield 2,6-dimethoxyphenol.

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(10) Hahn and Wasmuth, *Ber.*, **67**, 701 (1934).

(11) Graebe and Haas, *Aur.*, **340**, 236 (1915).

(9) Graebe and Martz, *Lieb.*, **340**, 221 (1905).