

The Anomalous Reactivity of *o*-Methoxyphenylmagnesium Bromides

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In the reactions between carbon dioxide and the Grignard reagents prepared from *o*-methoxybenzyl chloride, *o*-bromodimethylaminobenzene, and *o*-bromomethylthiobenzene, both the corresponding acids and the corresponding ketones are formed. The Grignard reagents prepared from β -(*o*-methoxyphenyl)ethyl chloride and γ -methoxypropyl bromide yield only the corresponding acids under the same conditions. The anomalous reactivity leading to ketone formation is associated with the formation of strained planar rings through a complex bond between the magnesium atom and the nitrogen, oxygen, or sulphur atoms. Such rings are not likely to be formed by the molecules of the above-mentioned two Grignard reagents which react normally. Steric hindrances of different kinds seem to be involved in other previously described cases in which the anomalous reactivity is cancelled.

Some time ago, the author showed that in the reaction between *o*-methoxyphenylmagnesium bromide and carbon dioxide 2,2'-dimethoxybenzophenone is formed in addition to *o*-methoxybenzoic acid, and that a similar ketone formation occurs when a methyl or methoxy substituted *o*-methoxyphenylmagnesium bromide reacts with carbon dioxide unless the second substituent is in the ortho position relative to the original methoxy group or to the magnesium atom^{1,2}. It was concluded that the ketone formation is an exceptional reaction of the Grignard reagent.

When the investigations were extended to *o*-methoxybenzylmagnesium chloride and β -(*o*-methoxyphenyl)ethylmagnesium chloride, it was found that the former gave the corresponding ketone (isolated only as its 2,4-dinitrophenylhydrazone) and the corresponding acid, whereas the latter gave β -(*o*-methoxyphenyl)propionic acid as the only product of the reaction. These reaction products seem to indicate that the exceptional reactivity is connected with ring formation in such a way that one of the two "etherate" ether molecules of the Grignard reagent has been displaced by the methoxy group, *i.e.* *o*-methoxybenzylmagnesium chloride and *o*-methoxyphenylmagnesium bromide have the constitutions shown by formulae I and II.

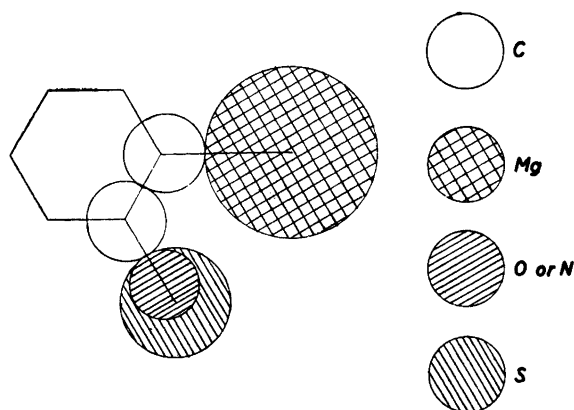
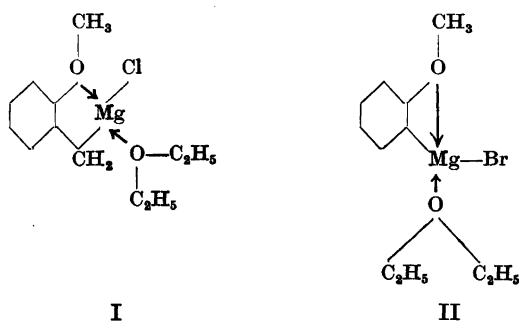


Fig. 1. The theoretical positions of the atoms in *o*-methoxyphenylmagnesium bromide, *o*-dimethylaminophenylmagnesium bromide, and *o*-methylthiophenylmagnesium bromide as based on the assumption that the bond lengths and the valence angles have the usual values and that attractive forces do not exist between the Mg atom on one side and the O, N, and S atoms on the other. The radii of the circles are proportional to the bond lengths of the atoms. Atoms not participating in the reaction have been omitted.



That these ring formations are possible with all atoms in one plane is shown in Figs. 1 and 2. From these figures it will also be seen that the rings must be under strain, at least with respect to the valence angles. In the case of β -(*o*-methoxyphenyl)-ethylmagnesium chloride the ring would contain too many atoms. The intramolecular strained ring may be expected to favour the polarization of the carbon-to-magnesium bond and thus to increase the reactivity of the compound.

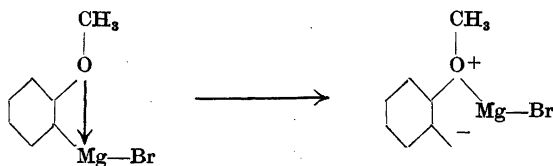
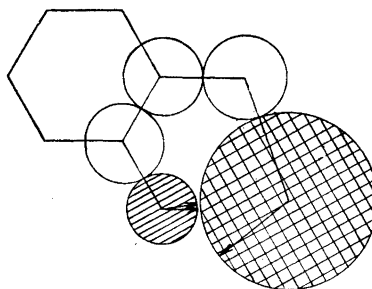
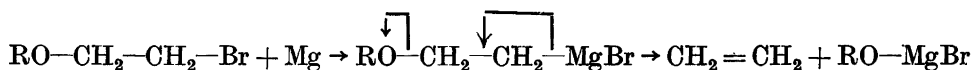


Fig. 2. The theoretical positions of the atoms in *o*-methoxybenzylmagnesium chloride when the distance between Mg and O atoms is a minimum as based on the assumptions stated in Fig. 1. The arrows indicate possible directions of the complex bonds.

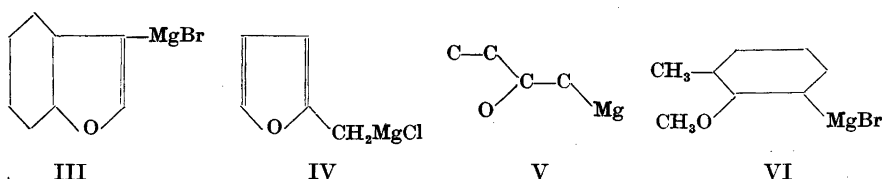


If this hypothesis is correct, one may expect that β -methoxyethylmagnesium bromide and other non-aromatic Grignard reagents with an alkoxy group in the β position relative to the magnesium atom would possess an exceptional reactivity of the type in question, provided that the magnesium atom and the ether group are in the "cis" position relative each other. Unfortunately such Grignard reagents cannot be prepared since any attempt in this direction leads to the formation of unsaturated compounds³⁻⁵. Mann and Steward⁶ have recently discussed reactions of this type and proposed the following mechanism for β -alkoxyethylmagnesium bromide:



The hypothesis proposed above for the exceptional reactivity of *o*-methoxyphenylmagnesium bromide and related compounds requires that β ether Grignard reagents with the oxygen atom and the magnesium atom in the "trans" position relative to each other should give acids but no ketones in the reaction with carbon dioxide. Compounds of this kind are not generally stable but decompose according to the mechanism of Mann and Steward. The only Grignard reagent of this type that appears to have been synthesized (although in poor yield) is 3-bromobenzofurylmagnesium bromide (III). Reichstein and Baud⁷ isolated from the products of the reaction between this Grignard reagent and carbon dioxide chiefly *o*-hydroxyphenylacetylene (formed according to the mechanism of Mann and Steward) and a small amount of 3-benzofuroic acid. No ketone seems to have been formed, which supports the above hypothesis.

The fact that aromatic Grignard reagents do not decompose according to the mechanism of Mann and Steward is, of course, due to the stabilization of



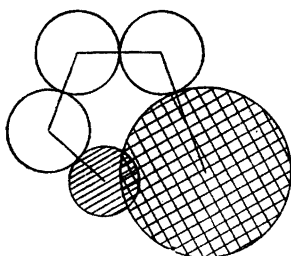
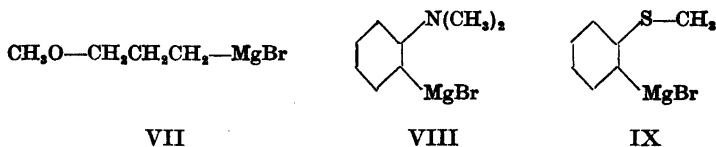


Fig. 3. The structure of an alkoxyethylmagnesium halide computed as for the Grignard reagents in Fig. 1 and 2.

the bonds in the aromatic nucleus. A similar stabilization might be expected in furfurylmagnesium chloride (IV). This compound is not, however, well adapted for an investigation of the present type, because a Wurtz' type of reaction seems to predominate in the reaction between magnesium and furfuryl chloride⁸. Further, even if the corresponding ketone would not be formed in the reaction between this Grignard reagent and carbon dioxide, this could be explained by noting that the compound in question has a constitution that in certain respects resembles that of 3-methyl-2-methoxyphenylmagnesium bromide (VI), which does not give the corresponding ketone in the reaction with carbon dioxide. An examination of the constitutions of the two substances (IV and VI) and formula V, which gives the part that is common to both, shows that the carbon atom in position 4 of the furyl derivative corresponds to the carbon atom in the methyl group of the benzene derivative. Introduction of this latter methyl group cancelled the anomalous reactivity of *o*-methoxyphenylmagnesium bromide, and one might expect that the carbon atom in position 4 would also cancel a potential anomalous reactivity of the furan derivative.

A chelate formation of the type in question is not likely in γ -methoxypropylmagnesium bromide (VII; cf. Fig. 3). It may thus be expected that this Grignard reagent will give only the corresponding acid in the reaction with carbon dioxide. This prediction was experimentally confirmed.

Finally, if the hypothesis proposed above is correct the exceptional reactivity of the type in question should be possible also in cases in which the methoxy



group is replaced by other groups with unshared electrons on the central atom, which are able to form a complex bond with the magnesium atom similar to that formed between magnesium and the oxygen in the methoxy group. Compounds of this type, *o*-dimethylaminophenylmagnesium bromide (VIII) and *o*-methylthiophenylmagnesium bromide (IX) were studied. Both gave the corresponding acids and the corresponding ketones in accordance with the hypothesis.

On the basis of the above it seems justified to suppose that the ring formation is the explanation for the exceptional reactivity of *o*-methoxyphenylmagnesium bromide and other Grignard reagents with unshared electron pairs which are able to form a bond with magnesium, which leads to the formation of a strained planar ring.

As mentioned above, *o*-methoxyphenylmagnesium bromides do not give the corresponding ketones in the reaction with carbon dioxide if there is a methyl or methoxy group in the *ortho* position relative to the methoxy group or to the magnesium atom. A molecular model study shows that in the first case the methoxy group is not able to rotate freely. In the second case, a steric hindrance similar to that existing in mesityl compounds is probable.

EXPERIMENTAL

o-Methoxybenzyl chloride was obtained from *o*-methoxybenzyl alcohol which was prepared from ethyl *o*-methoxybenzoate.

Lithium aluminium hydride (7.5 g; technical grade) and dry ether (500 ml) were placed in a flask (1 l), which was equipped with a mercury-sealed stirrer, a reflux condenser, and a dropping funnel. The stirrer was started and after five hours a solution of ethyl *o*-methoxybenzoate* (57.8 g) in dry ether (200 ml) was added through the dropping funnel at such a rate that the ether refluxed gently. When the addition was complete, the reaction mixture was warmed on a water bath for three quarters of an hour. The excess of lithium aluminium hydride was destroyed by adding ethyl acetate and the reaction products were hydrolyzed by adding water. The reaction mixture was then poured into a solution of concentrated hydrochloric acid (100 ml) in water (1 l) in order to dissolve the precipitated aluminium hydroxide. The ether phase was removed and the aqueous phase was extracted with a second portion of ether. The ether solutions were combined and dried with anhydrous sodium sulphate. When the solvent had been evaporated, *o*-methoxybenzyl alcohol, b. p. 126–127°/15 mm, was obtained by distillation. The yield was 77.5 % (34.5 g).

A small amount of this alcohol was converted into the corresponding *p*-nitrobenzoate. The melting point of the ester was 81–82°, as reported by Mozingo and Folkers¹⁰.

o-Methoxybenzyl alcohol (33.2 g) was dissolved in chloroform (50 ml) and added to a flask (250 ml) equipped with a reflux condenser and a dropping funnel, through which a solution of thionyl chloride (30 g) in chloroform (50 ml) was gradually added. When addition was complete, the reaction mixture was heated to boiling until evolution of gas ceased. The solvent was distilled off under normal pressure and the residue under reduced pressure. The yield of *o*-methoxybenzyl chloride, b. p. 108–109°/15 mm, was 35.5 % (13.7 g).

β -(*o*-Methoxyphenyl)ethyl chloride was prepared according to Hill, Short, and Stromberg¹¹ from β -(*o*-methoxyphenyl)ethyl alcohol, which was obtained from *o*-methoxyphenylmagnesium bromide and ethylene oxide according to Bogert and Hamann¹².

A small amount of the alcohol was converted into the corresponding *p*-nitrobenzoate. This latter substance melted at 58–59°. (Found: N 4.77. Calc. for C₁₆H₁₅O₅N: N 4.65).

γ -Methoxypropyl bromide. γ -Methoxypropyl alcohol was prepared from trimethylene glycol and methyl iodide according to Smith and Sprung¹³. The alcohol was then converted into the chloride according to Pummerer and Schönamsgruber¹⁴.

o-Bromodimethylaniline was prepared according to Gilman and Banner¹⁵ from *o*-bromoaniline in 78.2 % yield. *o*-Bromoaniline was obtained by the reduction of *o*-bromonitrobenzene with stannous chloride in the way previously described for 5-amino-3-bromoveratrole³. After distillation under reduced pressure, the yield of *o*-bromoaniline, b. p. 98°/11 mm, was 78.2 %.

o-Bromomethylthiobenzene. *o*-Bromothiophenol (48 g), prepared according to Schwarzenbach and Egli¹⁶ from *o*-bromoaniline, was dissolved in an aqueous solution (100 ml) of sodium hydroxide (10.5 g) and the mixture was shaken with dimethyl sulphate (32 g). When the mixture had cooled, dimethyl sulphate (16 g) and a dilute solution of sodium

hydroxide (5.3 g) in water (50 ml) were added and shaking was continued until the mixture had cooled again. A solution of sodium hydroxide (12 g) in water (50 ml) was now added and the mixture was heated for half an hour on the boiling water bath. After cooling, the oil was taken up into ether and the water solution was extracted once more with ether. The combined ether solutions were dried with anhydrous sodium sulphate and gave after distillation under reduced pressure a 88.5 % yield (48 g) of pure *o*-bromomethylthiobenzene, b. p. 145–146°/27 mm.

The reactions between Grignard reagents and carbon dioxide were examined as has been described previously¹. The results are given below.

o-Methoxybenzylmagnesium chloride (prepared from 5 g of the corresponding halide) gave 0.91 g of *o*-methoxyphenylacetic acid, m. p. 124–125°, and 2.19 g of neutral substances. When the latter were treated with alcohol, 0.80 g of 2,2'-dimethoxydibenzyl (m. p. after recrystallization from alcohol 85–86°) were obtained. The filtrate was evaporated to dryness and the residue (1.20 g) treated with 2,4-dinitrophenylhydrazine. From the mixture the hydrazone (1.02 g) of 1,3-di-*o*-methoxyphenylacetone was isolated. After recrystallization from alcohol, the substance melted at 157.5–158°. (Found: N 12.32. Calc. for C₂₂H₂₂O₆N₄: N 12.44.)

A small amount of the *o*-methoxyphenylacetic acid was converted into its *p*-nitrobenzyl ester. This substance melted at 64.5–65°. (Found: N 4.51. Calc. for C₁₈H₁₅O₅N: N 4.65.)

β -*o*-Methoxyphenylethylmagnesium chloride (prepared from 5 g of the corresponding halide) gave 1.55 g of β -*o*-methoxyphenyl-propionic acid, m. p. 88–89°. The *p*-nitrobenzyl ester of the latter melted at 45–46°. (Found: N 4.41. Calc. for C₁₇H₁₇ON: N 4.44.) No ketone could be isolated.

γ -Methoxypropylmagnesium bromide (prepared from 5 g of the corresponding halide) gave 0.89 g of γ -methoxybutyric acid. Its *p*-phenylphenacyl ester melted at 79–81°, in agreement with the value found by Owen and Sultanbawa¹⁷. No ketone was detected.

o-Dimethylaminophenylmagnesium bromide (prepared from 5 g of the corresponding halide) was treated with carbon dioxide in the usual manner. The reaction mixture was treated with dilute hydrochloric acid and the ether was separated (residue of neutral substances 0.04 g). The aqueous layer was made alkaline with aqueous ammonia, ether was added, and the mixture was filtered. The layers in the filtrate were separated. When the solvent had been evaporated from the ether phase, 1.94 g of 2,2'-di-(dimethylamino)benzophenone were isolated. After recrystallization from ligroin, it melted at 120–121°. With picric acid it formed an addition compound that melted at 150–151°. The aqueous solution was acidified with acetic acid and extracted with ether in an extractor for several hours. When the residue from the ether solution was treated with ether 0.70 g of dimethylanthranilic acid was obtained.

o-Methylthiophenylmagnesium bromide (prepared from 5 g of the corresponding halide) gave 1.10 g of *o*-methylthiobenzoic acid, m. p. 168–169°, and 1.43 g of neutral substances. When the latter were treated with benzene 2,2'-dimethylthiobenzophenone separated. After recrystallization from ethyl alcohol, the latter melted at 105–106°. (Found: S 23.55. Calc. for C₁₅H₁₄OS₂: S 23.37.) The same substance was obtained by hydrolyzing the reaction product from the reaction between *o*-methylthiophenylmagnesium bromide and *o*-methylthiobenzonitrile but not by decomposing *o*-methylthiophenylmagnesium bromide with water.

A small amount of the *o*-methylthiobenzoic acid was converted into its *p*-nitrobenzyl ester. The melting point of this ester was 122–123°. (Found: N 4.71. Calc. for C₁₆H₁₃O₄NS: N 4.62.)

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