# The Effect of Different Alkoxy Groups on the Anomalous Reactivity of o-Alkoxyphenylmagnesium Bromides

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The reactions between carbon dioxide and 2-alkoxy-5-methyl-phenylmagnesium bromides containing ethoxy, n-propoxy, n-butoxy, isopropoxy, and isobutoxy groups as alkoxy groups have been studied. As in the case of the methoxy homologue both the corresponding acids and the corresponding ketones are formed in these reactions, the yield of ketone being the lowest in the case of 2-isopropoxy-5-methyl-phenylmagnesium bromide. This fact is associated with steric effects that probably cancel the anomalous reactivity of o-methoxyphenyl-magnesium bromides with a methyl group, methoxy group or a condensed benzene ring in the ortho position relative to the original methoxy group.
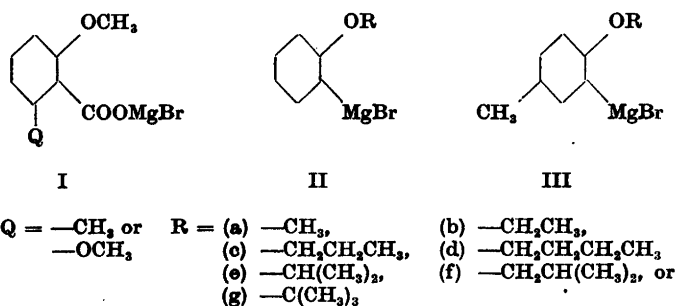
Some time ago the author proposed a reaction mechanism to explain the anomalous reactivity of o-methoxyphenylmagnesium bromides [1]. The mechanism in question involves an intramolecular ring formation by replacement of one of the two "etherate" ether molecules of the Grignard reagent by the methoxy group. The strained rings were expected to favour the polarization of the carbon-to-magnesium bonds:
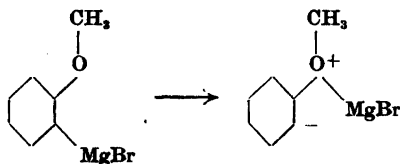
The anomalous reactivity of the o-methoxyphenylmagnesium bromides is cancelled by a methyl or methoxy group in the ortho position relative to the magnesium or oxygen atom [2,3]. The same rule is also valid in the naphthalene series if the condensed ring is considered to be a substituent [4]. In the former case, *i. e.* when the substituent is in the ortho position relative to the magnesium atom, it is believed that the first reaction product (I) is sterically hindered in the same way as certain mesityl derivatives. A molecular study of the

latter case (the substituent and the oxygen atom in the ortho position relative each other) shows that the methoxy group is unable to rotate freely. It may thus be prevented from occupying the proper position for ring formation. If this is right, it may be expected that the anomalous reactivity would even be cancelled when the steric effect is produced in another way.

A substance with the required properties is 2-*tert.*-butoxyphenylmagnesium bromide (IIg). Unfortunately, 2-*tert.*-butoxybromobenzene, which is needed for its preparation, is very difficult to synthesize. For this reason other substances had to be used although they were not as well adapted. In 2-*iso*-propoxyphenylmagnesium bromide (IIe) the rotation of the alkoxy group is not quite prevented, but is nevertheless obstructed to some extent. In this case a decrease in the yield of the corresponding ketone may be expected.

I II III

Q = —CH$_3$ or   R = (a) —CH$_3$,   (b) —CH$_2$CH$_3$,
    —OCH$_3$ (c) —CH$_2$CH$_2$CH$_3$,   (d) —CH$_2$CH$_2$CH$_2$CH$_3$
                  (e) —CH(CH$_3$)$_2$,   (f) —CH$_2$CH(CH$_3$)$_2$, or
                  (g) —C(CH$_3$)$_3$

o-Alkoxyphenylmagnesium bromides with a primary carbon atom attached to the oxygen ought to possess an anomalous reactivity of about the same order as that of the methoxy homologue, although substances in which the β carbon atom in the alkoxy group is secondary as in 2-*iso*butoxyphenylmagnesium bromide (IIf) should perhaps give a somewhat lower yield of the corresponding ketone.

For the preparation of the 2-alkoxyphenylmagnesium bromides the corresponding 2-alkoxybromobenzenes are required. These substances are most conveniently obtained through alkylation of o-bromophenol, which, however, is very difficult to purify. Consequently 3-bromo-4-hydroxytoluene was chosen as the starting material, because it is easily prepared and purified [5], and because the methyl group, at least in the methoxy derivative (IIIa) did not cancel the anomalous reactivity. The bromocresol was alkylated to give the ethoxy, n-propoxy, n-butoxy, *iso*propoxy, and *iso*butoxy derivatives (IIIb, c, d, e, and f). From the latter the corresponding Grignard reagents were then prepared and reacted with carbon dioxide.

The formation of an acid in the reaction between a Grignard reagent and carbon dioxide is considered to be the normal reaction. In the formation of one molecule of the corresponding ketone, one molecule of the Grignard reagent reacts normally to form a derivative of an acid (I or its homologue). Another molecule of the Grignard reagent then reacts with this first reaction product. This latter reaction is considered a consequence of the anomalous reactivity of the Grignard reagent. According to this the number of moles of the Grignard reagent, which react normally, is equal to the sum of the moles of acid and

ketone which have been formed during the reaction. The number of moles which react anomalously is equal to those of the ketone. In order to obtain comparable values, the ratios

$$\frac{\text{moles of ketone}}{\text{moles of ketone} + \text{moles of acid}}$$

have been calculated and used as a measure of the anomalous reactivity. From Table 1 in which these values have been collected it is to be seen that the anomalous reactivity of the *iso*propoxy homologue is considerably, and that of the *iso*butoxy derivative slightly lower than those of the other Grignard reagents. Also in the series methoxy, ethoxy, *n*-propoxy, and *n*-butoxy a slight decrease of the anomalous reactivity can be observed.

Table 1. The anomalous reactivity of 2-alkoxy-5-methylphenylmagnesium bromides.

Alkoxy group	Moles of ketone / Moles of ketone + moles of acid
Methoxy	0.46 [a]
Ethoxy	0.47
n-Propoxy	0.44
n-Butoxy	0.41
*Iso*propoxy	0.07
*Iso*butoxy	0.32

[a] According to previously published results [2]

The results show that the anomalous reactivity of *o*-alkoxyphenylmagnesium bromides is influenced by steric effects which prevent or restrict the free rotation of the alkoxy group, *i. e.* which prevent the alkoxy group from occupying the proper position for the formation of a complex bond between the oxygen and magnesium atoms.

EXPERIMENTAL

3-Bromo-4-ethoxytoluene was prepared by alkylation of 3-bromo-4-hydroxytoluene with ethyl *p*-toluenesulphonate in the following way. Sodium (3.85 g) was dissolved in absolute ethyl alcohol (77 ml) and to this solution 3-bromo-4-hydroxy-toluene (31.33 g) was added. After cooling, a solution of ethyl *p*-toluenesulphonate (33.50 g) in ethyl alcohol (30 ml) was gradually added. When the addition was complete, the mixture was heated on a boiling water bath for 1 hour. The solvent was then evaporated under reduced pressure and the residue was treated with a mixture of water and ether. The ether phase was separated and washed with a dilute solution of sodium hydroxide and finally with water. After drying with anhydrous sodium sulphate, the solvent was evaporated and the residue was distilled under reduced pressure. The yield of 3-bromo-4-ethoxytoluene, b. p. 117—118.5°/11 mm, was 87.8 % (31.62 g). Found: Br 37.10; Calc. for $C_9H_{11}OBr$: Br 37.15).

Table 2. Yields, boiling points, and analyses of 3-bromo-4-alkoxytoluenes.

Alkoxy group	Yield, %	B. p.	Br Found	Br Calc.
n-Propoxy	82.4	121.5 — 122.0°/11 mm	34.80	34.88
n-Butoxy	63.7	139.0 — 140.0°/12 mm	32.70	32.87
Isopropoxy	62.8	108.0 — 109.0°/ 8 mm	34.81	34.88

Table 3. Reactions between carbon dioxide and 2-alkoxy-5-methylphenylmagnesium bromides.

Alkoxy group	Acid, isolated g	Acid M. p. °C	M. p. of p-nitro-benzyl ester	Ketone, isolated g	Ketone M. p. °C	M. p. of 2,4-dinitro-phenyl-hydrazone, °C
Ethoxy	1.01	44 — 45	104 — 105	1.51	78 — 79	165 — 166
n-Propoxy	1.26	21 — 22	63 — 64	1.68	46 — 47	*
n-Butoxy	1.35	54 — 55	59 — 60	1.63	71.5 — 72.5	124.5 — 125.5
Isopropoxy	2.48	Oil	52 — 53	0.31	62 — 63	175 — 176
Isobutoxy	1.81	Oil	46 — 47	1.31	59 — 60	121 — 122

* Melted after a rapid heating at 131—132°, and after a slow heating at 151—152°. On the "Kofler Heizbank" the substance melted at 131—132°. On further heating it solidified and melted again at 151—152°.

Table 4. Analyses of prepared substances.

Alkoxy group	2-Alkoxy-5-methylbenzoic acid Found C	Found H	Calc. C	Calc. H	p-Nitro-benzyl ester N Found	p-Nitro-benzyl ester N Calc.	2,2'-Dialkoxy-5,5'-dimethylbenzo-phenone Found C	Found H	Calc. C	Calc. H	2,4-Dinitro-phenylhydrazone N Found	N Calc.
Ethoxy	66.75	6.78	66.65	6.71	4.53	4.44	76.60	7.50	76.48	7.43	11.66	11.71
n-Propoxy	68.18	7.35	68.02	7.27	4.32	4.25	77.41	8.13	77.27	8.03	11.12	11.06
n-Butoxy	69.35	7.85	69.21	7.74	4.20	4.08	78.05	8.62	77.93	8.53	10.58	10.48
Isopropoxy	a				4.31	4.25	77.45	8.20	77.27	8.03	11.11	11.06
Isobutoxy	a				4.22	4.08	78.05	8.65	77.93	8.53	10.57	10.48

a Not sufficiently pure.

3-Bromo-4-isobutoxytoluene was prepared in the same way using isobutyl bromide as alkylating agent except that the reaction mixture was heated 4.5 hours on the boiling water bath. The yield of pure 3-bromo-4-isobutoxytoluene, b. p. 124.5 — 125.5°/8 mm, was 48.9 %. (Found: Br 32.81; Calc. for $C_{11}H_{15}OBr$: Br 32.87).

3-Bromo-4-n-*propoxytoluene,   3-bromo-4-*iso*propoxytoluene,* and *3-bromo-4*-n-*butoxy-toluene* were prepared in the same way using the corresponding bromides as alkylating agents. In these cases the reaction mixture was heated in an autoclave to $120-130°$ for one hour. The yields, boiling points, and analyses are collected in Table 2.

The Grignard reagents were prepared from 0.02 equivalents of magnesium and 3-bromo-2-alkoxytolene in dry ether (30 ml).

The reaction between Grignard reagents and carbon dioxide were examined as previously described [3]. The results are collected in Tables 3 and 4.

REFERENCES

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