

THE RATES OF REACTIONS OF SUBSTITUTED O-METHOXYPHENYL-  
MAGNESIUM BROMIDES WITH DI-t-BUTYL KETONE

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Although great many Grignard reactions have been run, relatively few kinetic studies have been performed because of the rapid reaction rates and lack of techniques detecting such a rapid reaction. Thus the reaction must be run at very low temperature (1) in order to determine the rate by a conventional method, unless a special compound which shows a rather low reactivity is used. Smith and Su (2) were able to determine the rate of ethylmagnesium bromide toward 2,4-dimethyl-4'-(methylthio)benzophenone by quickly scanning at the region of 350  $\mu$ .

Fuson and coworkers (3) found the abnormally high reactivity of 2-methoxyphenylmagnesium halides toward sterically hindered ketones and explained the results in terms of the intramolecular coordination of methoxyl oxygen to magnesium. This suggests the possibility of determining the rate of reaction by the usual technique such as titration, because the reaction will be fairly slow when a sterically hindered ketone is selected as a substrate. Thus the kinetic study of the reaction between 2-methoxyphenylmagnesium bromide and di-t-butyl ketone was undertaken.

The expectation was found to be really the case and it was possible to follow the rate by iodometry after decomposing the unreacted Grignard reagent with the

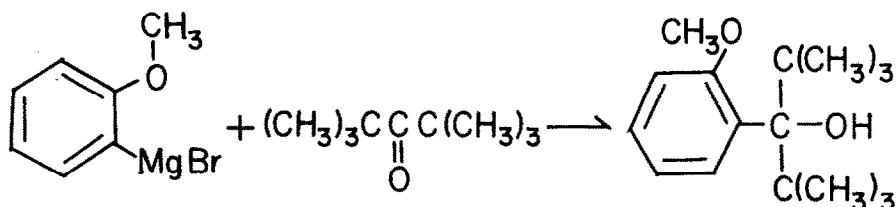
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excess iodine (4). The total magnesium was also checked by chelatometry. The reproducibility was checked and it was found that the results were reproducible only when the reaction was run under highly purified nitrogen. The results are shown in Table 1

Di-t-butyl ketone is known to add methyl and ethyl-magnesium compounds but not the bulkier ones. Since the reaction of phenylmagnesium bromide under these conditions did not proceed to the measurable extent, it is reaffirmed that the methoxyl group at the ortho position is inserting the accelerating influence to the reaction. The reaction rate is second order and is first order each in 2-methoxyphenylmagnesium bromide and in di-t-butyl ketone. The temperature dependence of the reaction rates enabled to estimate the enthalpy and entropy of activation as 9.91 kcal/mol and -40 e. u. (at 60°C), respectively.

The reaction product is 2-methoxyphenyldi-t-butylcarbinol (b. p. 138-139/6 mmHg. Anal. Found: C, 76.64; H, 10.21%. Calcd. for C<sub>16</sub>H<sub>26</sub>O<sub>2</sub>: C, 76.75; H, 10.47%) which is expected when the reaction is normal 1,2-addition.



Considering the anomalous reactivity of 2-methoxyphenylmagnesium bromide, it will be natural to attribute the results to the small bulkiness due to intramolecular coordination of the methoxyl oxygen. Then it follows that if the conformation of the methoxyl group is distorted by a substituent, a situation may occur where intramolecular coordination is prohibited or at least suppressed to cause retardation of the reaction. t-Butyl group is introduced to the 3-position of 2-methoxyphenylmagnesium bromide in this respect, because it is assumed that the conformation favorable for coordination may be disfavored by introducing a substituent at the position. The results are shown in Table 2 together with other substituted ones. As expected, 3-t-butyl-5-methyl-2-methoxymagnesium bromide react more sluggishly

TABLE 1  
Rates of Reaction of Phenyl- and 2-Methoxyphenylmagnesium  
Bromides with Di-*t*-butyl Ketone in Tetrahydrofuran

Run	Organomagnesium Bromide (RMgBr)	Initial Concentration		Reaction Temperature (°C)	Rate Constant $k_2 \times 10^2$ (mol/l min.)
		of RMgBr (mol/l)	of ( <i>t</i> -Bu) <sub>2</sub> CO (mol/l)		
1	Phenyl-	0.0624	0.0812	60	0.00
2	2-Methoxyphenyl*	0.0594	0.0778	60	1.13
3		0.0693	0.0764	45	0.819
4		0.0677	0.0728	30	0.390

\* The reproducibility of the rate was checked at 3 concentrations.

TABLE 2  
Rates of Reactions of Substituted 2-Methoxyphenylmagnesium  
Bromides with Di-*t*-butyl Ketone in Tetrahydrofuran

Run	Organomagnesium Bromide (RMgBr)	Initial Concentration		Reaction Temperature (°C)	Rate Constant $k_2 \times 10^2$ (mol/l min.)
		of RMgBr (mol/l)	of ( <i>t</i> -Bu) <sub>2</sub> CO (mol/l)		
5	3- <i>t</i> -Butyl-5-methyl- 2-methoxyphenyl-	0.0602	0.1009	60	0.535
6		0.0648	0.0748	53	0.356
7	2-Methoxy-1-naphthyl-	0.0623	0.1016	60	0.00
8	2,6-Dimethoxyphenyl-	0.0547	0.0985	60	0.00

with di-*t*-butyl ketone. However the fact that it can react with the ketone indicates that the *t*-butyl group is not inserting sufficient effect to prevent the intramolecular coordination\*\*. The enthalpy and entropy of activation are obtained as 11.6

\*\* The coordination is enhanced when the basicity of oxygen is higher. Thus losing coplanarity of the methoxyl group with the benzene ring will retard the reaction. Separation of the effects by this and by the disturbance of the conformation favorable for coordination is not possible at present.

kcal/mol and -34 e. u. (at 60°C), respectively, from the temperature dependence of the rates.

2,6-Dimethoxyphenylmagnesium bromide and 2-methoxy-1-naphthylmagnesium bromide did not show any measurable rate of reaction with di-*t*-butylketone and no addition product was isolated after 20 hour heating. The results may be attributed to the steric effect of 6-methoxyl group or peri-hydrogen. The step where steric hindrance inserts the true effect, either coordination of oxygen or bond formation of the Grignard reagent with carbonyl carbon, has not been known, but the results obtained here raise no objection against the postulation that exchange of the ligands, from ether to ketone, is the rate determining step (5).

We also have some evidence in favor of the above postulation of the rate determining step by measuring the rates of reaction of 2-methoxyphenylmagnesium bromide with di-*t*-butyl ketone in various solvents but drawing a solid conclusion may have to be waited until extensive survey of the reaction rate is accomplished.

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