Studies on the Mechanism of the Enolization Reaction of Grignard Reagents and Ketones. Part 2.[1] Pseudo-first-order Rate and Deuterium Isotope Effect Studies

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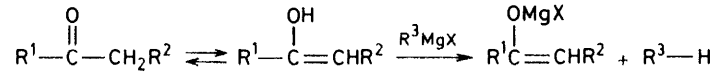
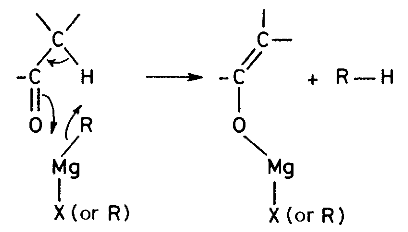
Kinetics of enolization reactions of some alkyl mesityl ketones with alkylmagnesium bromides were studied under pseudo-first-order conditions by measuring formation of gaseous alkane. Using a large fixed excess of isopropyl mesityl ketone, the reaction was first order in ethylmagnesium bromide; with a fixed excess of ethylmagnesium bromide, the reaction was first order in ketone. At high excess variable concentrations of ketone, however, k_2 values decreased with increasing ketone concentration in a good linear relation between the two variables. When both Grignard and ketone concentrations (at 1 : 1 mole ratios) were varied, a nonlinear relationship resulted between concentrations and k_2 values. Rates did not vary significantly between highly pure and reagent grade magnesium. Reactions in tetrahydrofuran at b.p. 67 °C took place at significantly slower rates than reactions in ether at b.p. 36 °C at comparable concentrations whereas reactions in di-n-butyl ether at b.p. 141 °C occurred at a much faster rate at higher concentrations. Reactions of α-deuterio-substituted methyl, ethyl, and isopropyl mesityl ketones with ethylmagnesium bromide showed isotope effects confirming breaking of the C–H bond as the rate-determining step in accord with the proposed mechanism. Values of k_H/k_D = 2.6—3.1 indicate a moderate degree of C–H bond stretching in the transition state. A two-step mechanism is proposed.

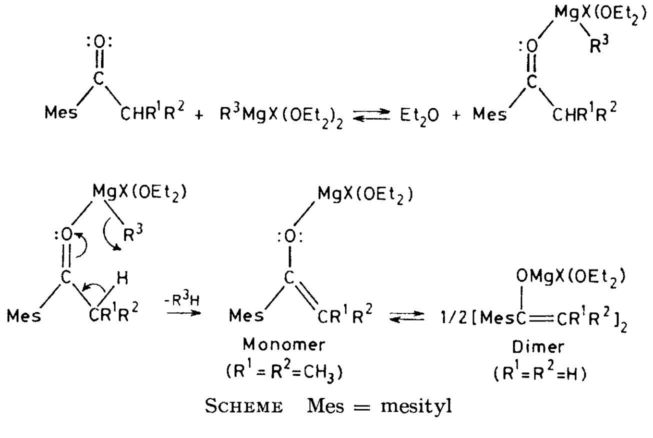
IN reactions of hindered ketones with Grignard reagents to form hydrocarbons and the corresponding magnesium-containing products, Smith and Guss[2] originally suggested that ketones undergo preliminary enolization, with the enol form subsequently reacting with the Grignard reagent [equation (1)]. Lutz and Kibler[3] were apparently the first to propose a mechanism in which ketone and Grignard reagent react *via* a six-membered ring [equation (2)], a mechanism currently accepted[4] although only equilibrium-type studies on the extent of enolization have been carried out.[4,†] More recently, we proposed[1] on the basis of kinetic studies and other evidence a two-step mechanism (Scheme) in which the keto carbonyl group co-ordinates with magnesium in a rapid equilibrium first step; in the second step, breaking of the C–H bond occurs *via* a cyclic transition state. Evidence for the initial rapid equilibrium step was previously obtained[5,6] for the mechanism of the addition reaction of ketones and Grignard reagents. Structures of the final products as magnesium enolates have been established, that from methyl mesityl ketone (1) as a dimer[7] and that from isopropyl mesityl ketone (3)[8] and related mesityl ketones[9] as monomers incorporating three-co-ordinate magnesium. Other possible mechanisms are also discussed in Part 1.[1] Since our previous work was completed prior to most of the elegant work on the mechanism of the addition reaction of Grignard reagents and ketones reviewed by Ashby *et al.*[6] as well as prior to clarification of the structure of Grignard reagents,[6,10,11] the work in the present paper was designed to take advantage of these results in order to test the mechanism



$$R^1\text{—}\overset{\overset{\displaystyle O}{\|}}{C}\text{—}CH_2R^2 \rightleftharpoons R^1\text{—}\overset{\overset{\displaystyle OH}{|}}{C}{=}CHR^2 \xrightarrow{R^3MgX} R^1\overset{\overset{\displaystyle OMgX}{|}}{C}{=}CHR^2 + R^3\text{—}H \quad (1)$$



(2)



SCHEME Mes = mesityl

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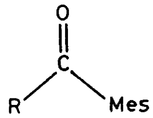
† Professor J. March, Adelphi University, has stated to us that F. C. Whitmore worked on the mechanism of the enolization reaction and that graduate classes at Pennsylvania State University were taught the cyclic mechanism shortly after Whitmore's death in 1947. We thank Professor March for the information and for early references on the mechanism of enolization.

proposed for the enolization reaction of Grignard reagents with ketones and to obtain information on the rate-determining step and the nature of the transition state for the reaction.



(1) R=Me

(2) R=Et

(3) R=Pt^{i}

EXPERIMENTAL

Isopropyl Mesityl Ketone * (3).—Isobutyryl chloride used for the ketone synthesis was prepared by the method of Brown,[12] b.p. 92 °C (lit.,[12] 91.5 °C); yield 80% (lit.,[12] 88%). The ketone was synthesized by a Friedel–Crafts reaction between isobutyryl chloride and mesitylene using anhydrous aluminium chloride and carbon disulphide as solvent; b.p. 108—109 °C at 5 Torr (lit.,[13] 104 °C at 4 Torr); yield 73%.

Ethyl Mesityl Ketone * (2).—This was prepared by a similar procedure to that used for methyl mesityl ketone, b.p. 110—111 °C at 6 Torr (lit.,[14] 125.1 °C at 13 Torr); yield 80% (lit.,[14] 70%).

Methyl Mesityl Ketone * (1).—This was prepared [13,15] by a Friedel–Crafts reaction between acetyl chloride (55 g, 0.70 mol) and mesitylene (79 g, 0.66 mol) in methylene chloride (300 ml) at 0 °C (ice–salt mixture) using aluminium chloride (103 g, 0.77 mol); b.p. 106—107 °C at 10 Torr (lit.,[1] 88—92 °C at 4 Torr); yield 91 g (85%).

Deuteriated ketones were prepared by exchange of methyl (1), ethyl (2), and isopropyl mesityl ketones (3) with deuterium oxide using a modification of the method of McWilliam *et al.*[16] Complete deuteriation was indicated by the absence of absorption for the α-protons in the ^{1}H n.m.r. spectra. I.r. spectra showed weak C–D stretching bands as well as expected changes in bending vibrational bands corresponding to replacements of hydrogen by deuterium.

Alkylmagnesium bromides were prepared by a slight modification of the procedure described by Fieser and Fieser [17] using reagent grade magnesium (Mallinckrodt) or ultra-pure magnesium (Ventron chips) and sodium-dried ether under nitrogen with a few crystals of iodine as initiator. For rate measurements with an excess of Grignard reagent, a highly concentrated solution (1.1M) was prepared and diluted to the concentration desired. For example, ethylmagnesium bromide was prepared as follows. Typically, magnesium chips (9.0 g) were reacted with ethyl bromide (Baker Analyzed; 31.5 g, 0.289 mol) in anhydrous ether (300 ml). The Grignard reagent thus prepared was filtered through glass wool under nitrogen. The clear filtrate was preserved in an Erlenmeyer flask fitted with a rubber septum (Aldrich). Only Grignard solutions less than one week old were used for the kinetic studies.

Concentrations of Grignard reagent solutions were determined by hydrocarbon gas evolution, a modification of the Zerewitinoff method of estimating active hydrogen.[18] A known volume of stock solution was diluted to 30 ml under nitrogen in a 100 ml three-necked flask [1] equipped with efficient condensers through which ice–water was circulated in order to minimize the vapour pressure of ether. The reaction vessel was placed in a thermostat at 40 °C to maintain rapid boiling of the solution. The volume of gaseous hydrocarbon liberated by reaction of n-butanol (0.50 ml, 0.41 g, 0.0055 mol) with the Grignard reagent at the b.p. of ether was measured over mercury in a gas burette. After making a correction for the vapour pressure of ether [19] at 0 °C by subtracting from the barometric pressure and correcting to standard conditions (0 °C; 760 Torr), the concentration of reagent in the reaction flask and hence that of the stock solution was calculated. (The vapour presure of n-butanol at 0 °C is negligible.) In the previous paper [1] concentrations were determined by titration with standard acid. A comparison of rate constants with those previously reported [1] shows reasonable agreement considering the difference in method of Grignard estimation, concentrations of reactants, and methods of measuring volume.

Apparatus and Method.—The same experimental set-up described above for estimation of the Grignard reagent was used. The calculated amount of standard reagent was injected with a syringe through a rubber septum into the flask and diluted to 30 ml with ether. Concentrations of diluted reagent were 0.030—0.035M. After bringing the solution to reflux, the reaction assembly was closed and the initial reading of gas burette was taken after equalizing mercury levels in the gas burette. By means of another syringe (0.5 or 1.0 ml capacity), the calculated quantity of ketone was injected. The volume of evolved hydrocarbon gas was measured at selected intervals of time according to the speed of the reaction. This method of measuring volumes is more convenient than that previously reported [1] in which the gas was collected over water which necessitated corrections of measured volumes for water vapour as well as measures to protect the reaction mixture from water vapour.

Kinetic Studies.—The rate of the reaction between the alkyl mesityl ketones and alkylmagnesium bromides was followed by measuring the volume of alkane liberated at selected intervals of time. The same experimental set-up was used as for estimation purposes. From values of the corrected volume, x in terms of concentration was determined. From the initial concentration a, values of $a - x$ were calculated. Using least square plots of log$(a - x)$ *versus* time, values of k_1 (pseudo-first-order rate constants) were computed with a Fortran computer (Hazeltine 2000) along with intercepts, standard deviations, and correlation coefficients; the latter two sets of data were used in monitoring duplicate experiments for reproducibility.

Kinetics of the reactions between the deuteriated alkyl mesityl ketones and ethylmagnesium bromide were determined by the same procedure as for reactions with non-deuteriated compounds. In the isotope effect studies, the concentration of the reactants was fixed at a 1 : 1 ratio and the volume of hydrocarbon (ethane) liberated at intervals of time was noted. From this volume, values of x, $a - x$, and $x/[a(a - x)]$ were evaluated. A plot of $x/[a(a - x)]$ *versus* time was linear with the slope giving the value of the second-order rate constant. (More detailed derivations are in Part 1.[1])

RESULTS AND DISCUSSION

Pseudo-first-order Kinetic Studies.—In view of the successful results obtained in the studies [6] of the mechanism of the addition reaction of Grignard reagents and ketones in which a large excess of one of the reactants was

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* ^{1}H N.m.r. and i.r. spectral data are in accord with the expected structures for the ketones.

used to establish pseudo-first-order rate dependence, similar techniques were employed in the present study of the mechanism of the enolization reaction. The reaction of isopropyl mesityl ketone and ethylmagnesium bromide was selected as the standard for these studies because this reaction [1] proceeded at a convenient rate for measurement under pseudo-first-order conditions. The reactions were all reasonably linear to 60—70% reaction. After this time the kinetic plots deviated slightly from linearity. The same effect was noted previously [6] for the addition reactions between ketones and Grignard reagents and attributed to reactions with alkoxide species formed in the earlier stages of the reactions.

The kinetics were followed with the purpose of establishing the order with respect to each reactant. Table 1 shows the results for the kinetics followed at excess ketone concentration. The constant values of k_1 and $k_2 = k_1$/[ketone] show that the reaction is first-order with respect to the Grignard reagent.

Table 1

Rates of reactions of fixed excess of isopropyl mesityl ketone [a] and ethylmagnesium bromide: order with respect to Grignard reagent

[Ethylmagnesium bromide]/M	k_1 [b]/s^{-1}	k_2/l mol^{-1} s^{-1}
0.0232	0.003 71	0.0110
0.0340	0.003 60	0.0107
0.0471	0.003 73	0.0111

[a] [Ketone] 0.337M. [b] Each value is an average of two experimental constants; temperature 36 °C (b.p. of diethyl ether).

Table 2

Rates of reactions of isopropyl mesityl ketone and fixed excess of ethylmagnesium bromide: [a] order with respect to ketone

[Ketone]/M	k_1 [b]/s^{-1}	k_2 [c]/l mol^{-1} s^{-1}
0.0300	0.004 59	0.0127
0.0371	0.004 31	0.0119
0.0438	0.004 29	0.0119
0.0505	0.004 77	0.0132

[a] [Ethylmagnesium bromide] 0.362M. [b] Each value is an average of two experimental constants; temperature 36 °C (b.p. of diethyl ether). [c] $k_2 = k_1$/[EtMgBr].

Table 2 shows the results for the kinetics followed at excess Grignard concentration. It can be noted that the values of k_1 and k_2 are reasonably constant. Although Tables 1 and 2 show approximately the same values for the second-order rate constant (average values 0.0109 and 0.0124 l mol^{-1} s^{-1}, respectively), the k_2 values differ significantly from that obtained with the kinetics were followed at a 1 : 1 ratio of reactants (0.0368M) *viz.* k_2 0.0318 l mol^{-1} s^{-1} (average of three experimental constants). This value can also be compared with the value of 0.018 reported previously [1] which was measured at a higher concentration (0.10M) and using a different experimental set-up. (See below for explanation of differences in the values on the basis of differences in concentrations.) Similar results as those in Tables 1 and 2 were also obtained for reactions of (1) ethylmagnesium bromide with methyl mesityl ketone and (2) isopropylmagnesium bromide with isopropyl mesityl ketone.

Table 3

Rates of reactions of isopropyl mesityl ketone and ethylmagnesium bromide: variation of ketone concentration at fixed low concentration of Grignard reagent [a]

[Ketone]/M	k_1/s^{-1}	k_2 [b]/l mol^{-1} s^{-1}
0.185	0.002 33	0.0126
0.204	0.002 30	0.0113
0.306	0.002 95	0.009 65
0.408	0.002 82	0.006 92
0.505	0.003 00	0.005 94
0.607	0.003 17	0.005 22

[a] [Ethylmagnesium bromide] 0.0324M; temperature 36 °C (b.p. of diethyl ether). [b] $k_2 = k_1$/[ketone].

A series of experiments was also carried out with varying excess ketone concentrations at a fixed low concentration of ethylmagnesium bromide. Surprisingly, the k_2 values were found to decrease slightly with increasing ketone concentrations (Table 3). However, when the k_2 values were plotted against the ketone concentrations, a good linear relationship* resulted from which a value of 0.0151 extrapolated to zero concentration of ketone was obtained for k_2. This value is in accord with the average values for k_2 from Tables 1 and 2 which would be increased slightly if also extrapolated to infinite dilution. A tentative explanation of the results is that at higher ketone concentrations, interactions between unreacted ketone molecules and the transition state raise its energy, resulting in a slower rate at higher ketone concentrations.

Several unsuccessful attempts were made to carry out studies at a fixed concentration of ketone and varying high concentrations of Grignard reagents. As emphasized by Ashby *et al.*[6] in order to avoid serious complications in kinetic studies with Grignard reagents, concentrations should be below 0.1M because Grignard reagents are associated above that concentration. The varying degree of association is probably the cause of the erratic results in this case. It can be noted, however, that when a constant high concentration (0.362M) of Grignard reagent was used (Table 2), reproducible data were obtained.

Effect of Concentration on Rate of Reaction at 1 : 1 *Ratio of Reactants*.—The effect of concentration on the rate of the 1 : 1 ratio reaction was also determined for reactions of isopropyl mesityl ketone with isopropylmagnesium bromide and with ethylmagnesium bromide. The rate constants k_2 are listed in Table 4.

The relationship of rate to concentration at the 1 : 1 reactant ratio is non-linear for both Grignards. The rate decreases rapidly with increasing concentration and levels off at the higher concentrations studied. The results show that in addition to the effect of ketone concentration on the rate, there is also a dependence on Grignard concentration.

Thus the k_2 values (l mol^{-1} s^{-1}) for reactions of ethylmagnesium bromide with three alkyl mesityl ketones can be compared at different concentrations (0.033 and 0.10M): methyl mesityl, 0.21, 0.16; ethyl mesityl, 0.11,

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* Slope −0.0176; correlation coefficient −0.974; standard deviation 0.003 04.

TABLE 4

Effect of concentration on rate of reaction of isopropyl mesityl ketone with isopropylmagnesium bromide and ethylmagnesium bromide at equal concentrations [a]

Isopropylmagnesium bromide		Ethylmagnesium bromide	
Conc. (10^2M)	10^2k_2 [b]/ l mol^{-1} s^{-1}	Conc. (10^2M)	10^2k_2 [c]/ l mol^{-1} s^{-1}
1.90	5.03	1.81	4.91
2.14	4.35	3.54	3.47
2.37	3.83	5.32	2.64
2.54	3.42	5.41	2.55
4.15	2.76	7.46	2.03
4.45	2.54	9.42	1.83
4.54	2.30		
5.87	2.07		
5.93	1.98		
6.70	1.85		
7.04	1.83		

[a] Temperature 36 °C (b.p. of diethyl ether). [b] Range of correlation coefficients 0.9888—0.9989. [c] Range of correlation coefficients 0.9973—0.9995.

0.087; isopropyl mesityl, 0.032, 0.018. These values are also in accord with the above results where the concentration of ketone was varied and the rates determined at the higher concentrations were less than those at lower concentrations. It can be noted that the kinetic plots in the present study where concentrations of *ca.* 0.03M were used, were linear to 60—70% reaction whereas linearity below 50% was obtained for the previous study where concentrations of 0.10M were used.

Solvent Effects.—It was desirable to extend the studies in diethyl ether to other solvents. Earlier studies [20] in di-n-butyl ether were complicated by the high b.p. of the solvent (141 °C) in that the increase in rate observed could be the result of the increase in temperature over that of diethyl ether and/or a solvent effect. Tetrahydrofuran was selected because of its lower b.p. (67 °C) compared with di-n-butyl ether as well as for favourable solubility characteristics. The rate data for the 1 : 1 ratio reaction of methyl, ethyl, and isopropyl mesityl ketones with ethylmagnesium bromide are in Table 5 along with data for comparison with studies in diethyl and di-n-butyl ether.

TABLE 5

Comparison of rates of 1 : 1 ratio reactions of alkyl mesityl ketones with ethylmagnesium bromide in tetrahydrofuran and di-n-butyl ether [a] with reactions in diethyl ether at the solvent boiling point [b]

Alkyl mesityl ketone	Conc. (M)	k_2 [c]/ l mol^{-1} s^{-1}	Solvent
Methyl	0.0300	0.208	Et_2O
	0.10	0.16	Et_2O
	0.0342	0.120	THF
	0.10	13.5	$Bu^n{}_2O$
Ethyl	0.030	0.11	Et_2O
	0.10	0.087	Et_2O
	0.31	0.051	THF
	0.035	0.099	THF
	0.10	12.9	$Bu^n{}_2O$
Isopropyl	0.10	0.18	Et_2O
	0.10	2.45	$Bu^n{}_2O$
	0.20	1.45	$Bu^n{}_2O$

[a] A. G. Pinkus and W. C. Servoss, unpublished results. [b] B.p.s of solvents: Et_2O, 36 °C; THF, 67 °C; $Bu^n{}_2O$, 141—142 °C. [c] The values for THF and $Bu^n{}_2O$ are of lower reproducibility than those in Et_2O probably because of more difficulty in maintaining constant b.p.s at the higher temperatures.

Although the reproducibility of the reactions in tetrahydrofuran (and di-n-butyl ether) is not as good as for those in diethyl ether, a number of significant conclusions can be deduced from the data. Although the b.p. of tetrahydrofuran (67 °C) is higher than that of diethyl ether (36 °C), the reactions at comparable concentrations in tetrahydrofuran are significantly slower (by *ca.* 50%) for both methyl and ethyl ketones. In di-n-butyl ether, however, the reactions take place at a much higher rate than in diethyl ether, and this increase must be due to the much higher temperature (141 °C).

In a comparison of the reaction rates in di-n-butyl ether with those in diethyl ether for the three ketones, the ratio of these rate constants ($k_{Bu^n{}_2O}/k_{Et_2O}$) is 84, 150, and 14 for methyl, ethyl, and isopropyl mesityl ketones, respectively. Although the ratio is nearly doubled on going from methyl to ethyl, the ratio shows a large decrease for the isopropyl ketone. Since the isopropyl ketone is the most hindered of the three ketones and the two n-butyl groups of the solvent ether would also have larger steric requirements compared with ethyl groups, the decrease might be attributed to a steric solvation effect increasing the energy of the transition state.

Another significant finding is the effect of concentration on the rate. In the case of the reaction with isopropyl mesityl ketone in di-n-butyl ether, the reaction is slower at the higher concentration of 0.20M compared with that at 0.10M [k(0.10M)/k(0.20M) 1.7]. This effect [20] of concentration on the rate is confirmed by the observations discussed above for the reactions in diethyl ether.

Effect of Purity of Magnesium.—Addition reactions of methylmagnesium halides were reported [21] to be affected by the purity of the magnesium used in their preparation. In addition, Kharasch and Reinmuth [4] indicated that metallic impurities in magnesium of a Grignard reagent might have an effect on the amount of enolization. Therefore, it was thought necessary to investigate any possible effect of magnesium purity on the rate of enolization in the present studies. In a comparison of the 1 : 1 ratio (0.035M) reaction of ethylmagnesium bromide and isopropyl mesityl ketone using ultrapure (Ventron) magnesium *versus* reagent grade (Mallinckrodt), a value for the second-order rate constant k_2 of 0.034 l mol^{-1} s^{-1} was obtained for the ultrapure reagent which can be compared with a value of 0.031 for the reagent grade magnesium. Since these values are equal within experimental error, there does not appear to be any significant effect on the rate of the enolization reaction by using reagent grade magnesium instead of the purer grade.

Kinetic Isotope Effects in Reactions of Ethylmagnesium Bromide with Alkyl Mesityl Ketones and α-Deuterio-substituted Derivatives.—The kinetics of reactions between ethylmagnesium bromide and alkyl mesityl ketones deuteriated in the α-position were studied at a 1 : 1 concentration ratio of reactants. The experimental

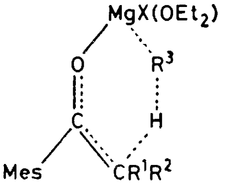
TABLE 6

Second-order rate constants for reactions[a] of ethylmagnesium bromide with deuteriated and non-deuteriated alkyl mesityl ketones

Compound	k_2/l mol^{-1} s^{-1}	k_H/k_D
Methyl mesityl ketone (1)	0.21	3.1
α-Deuteriated (1)	0.068	
Ethyl mesityl ketone (2)	0.11	2.6
α-Deuteriated (2)	0.043	
Isopropyl mesityl ketone (3)	0.032	2.7
α-Deuteriated (3)	0.012	

[a] Concentrations (10^2M) = 3.24, 3.40, and 3.39 for deuteriated methyl, ethyl, and isoropyl mesityl ketones, respectively; reactions of undeuteriated ketones carried out at comparable concentration range. [b] Range of correlation coefficients for deuteriated compounds 0.9972—0.9997.

conditions were the same as in reactions involving non-deuteriated compounds. A comparison of second-order rate constants for the reactions of deuteriated and non-deuteriated ketones shows isotope ratios (k_H/k_D) in the range 2.6—3.1 (Table 6). In comparison with a maximum theoretically calculated possible value [22] of 7 for C–H and C–D bonds, these values indicate that C–H bond breaking is involved in the transition state (4) to a moderate degree.[22]



(4)

Although an α-secondary isotope effect can be considered to be included in the k_H/k_D ratios for methyl and ethyl mesityl ketones since only one of the three and two C–D bonds, respectively, is broken this is generally of small magnitude (*ca.* 0.96—1.2) [22] so that major contribution in the present case is from the primary isotope effect of C–H(C–D) bond breaking.

Conclusions.—The studies under pseudo-first-order conditions show that the enolization reaction of alkyl mesityl ketones with alkylmagnesium bromides is first order in each reagent for the initial 60—70% of the reaction. The isotope effect observed with three α-deuterio-substituted ketones shows that breaking of the C–H bond is involved in the rate-determining step. These results further support the two-step mechanism previously proposed for the reaction: (1) co-ordination of magnesium of the Grignard reagent to carbonyl oxygen in a rapid equilibrium step; (2) rate-determining abstraction of α-hydrogen *via* a cyclic transition stage (4) incorporating a moderate degree of C–H stretching.

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