Studies on the Mechanism of the Enolization Reaction of Grignard Reagents with Ketones

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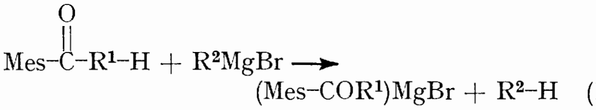
The rates of evolution of alkane from reactions of methyl-, ethyl-, isopropyl-, and t-butyl-magnesium bromides with methyl, ethyl, and isopropyl mesityl ketones in diethyl ether were evaluated on the basis of second-order kinetics for the initial stages of the reactions analogous to addition reactions of Grignard reagents to unhindered ketones. Since the rate changes for the four alkylmagnesium bromides for a specific ketone, enolization cannot be the rate-determining step. The relative order for the Grignard reagents for any ketone, $\mathrm{Et > Pr^i > Me \gg Bu^t}$, is explained in terms of an increasing steric effect in the transition state superimposed on the electronic effect of the Grignard alkyl group. The relative order for the alkyl mesityl ketones, $\mathrm{Me > Et \gg Pr^i}$, is approximately the statistical order with a steric effect occurring in the isopropyl case. Removal of hydrogen from the α-carbon *via* a six-membered ring transition state involving the ketone and Grignard reagent is postulated for the rate-determining step, the initial stage of the reaction being co-ordination of the Grignard magnesium to the ketone oxygen in a fast step.

ALTHOUGH the mechanisms and stereochemistry of addition [1] and reduction [2] reactions of Grignard reagents have been well studied by means of kinetics and are now fairly well understood, to our knowledge no kinetic studies on the enolization reaction have been published. We report our results on reactions of alkyl mesityl ketones with alkylmagnesium bromides.

In connection with our interest [3] in restricted rotation about the ketone carbonyl group, we had occasion to treat isopropyl mesityl ketone with ethylmagnesium bromide as described by Fuson and his co-workers [4] and noted that the reaction proceeded at a rate suitable for kinetic studies. Another attractive feature of this reaction was the report that the reaction of methyl mesityl ketone and methylmagnesium iodide proceeded quantitatively as measured by the evolution of methane gas.[5] One goal of the work was to determine the mechanism of removal of the proton, whether directly from carbon or from an enol form. The proposed study involved reactions of alkyl mesityl ketones with alkylmagnesium bromides according to the general reaction (1).



$$\mathrm{Mes{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}R^1{-}H + R^2MgBr \longrightarrow (Mes{-}COR^1)MgBr + R^2{-}H} \qquad (1)$$

$\mathrm{R^1{-}H = Me, Et, or\ Pr^i;\ R^2 = Me, Et, Pr^i, or\ Bu^t}$

EXPERIMENTAL

Preparation and Purification of Reagents and Solvents.—Diethyl ether was allowed to stand over calcium chloride for several days, filtered, distilled, and redistilled from sodium ribbon until the sodium retained a silver appearance for 24 h. The final distillation was conducted under nitrogen and the purified ether was stored over sodium under nitrogen. Aliquot portions were removed through a serum stopper with syringes equipped with hypodermic needles.

Standard sodium hydroxide and hydrochloric acid solutions were prepared to be *ca.* 0.1N. The base was standardized by titration against potassium acid phthalate. The acid was then standardized by titration against the standard base. These solutions were used to determine the concentrations of Grignard solutions.

Grignard reagents. These were prepared in stock quantities using anhydrous ethyl ether (750 ml), Grignard-grade magnesium turnings (250 mmol), and alkyl bromide (225 mmol). Commercial samples of alkyl bromides were distilled just before using. Grignard reagents were prepared by adding the alkyl bromide dropwise to maintain a gentle reflux of ether. After addition of alkyl bromide was complete, the mixture was refluxed 5—10 min longer and allowed to stand overnight to allow solids to settle. The clear supernatant was decanted into a standard taper (s.t.) round bottomed flask under nitrogen with the aid of apparatus [6] constructed for the purpose; the stock flask was fitted with an s.t. joint which connected it to the dry nitrogen supply.

The concentration of the stock solution was determined at the beginning of each run by withdrawing a sample by means of a syringe, expelling a known volume into an excess of standard hydrochloric acid and determining the excess of acid by titration with standard sodium hydroxide using phenolphthalein. The Grignard solutions as prepared were *ca.* 0.3N (except for t-butylmagnesium bromide which was >0.1N) and were diluted to 0.10N, the concentration used in the runs.

Ketones. These were prepared according to literature procedures. Acetylmesitylene [7] had b.p. 88—92° at 4 Torr, propionylmesitylene [8] b.p. 150—153° at 19 Torr, and isobutyrylmesitylene [9] b.p. 99—102° at 2 Torr.

Kinetic Runs.—Apparatus.[6] An s.t. Erlenmeyer flask containing a side-arm for a serum stopper was used. The flask was connected to an s.t. cold-finger reflux condenser in turn connected to drying tubes of calcium chloride and phosphorus pentaoxide leading to a water-filled gas burette. A manometer was connected between the drying tubes and the gas burette. The cold-finger condenser was cooled by pumping water from an external ice–water mixture at 75—100 ml $\mathrm{s^{-1}}$, allowing the escape of isobutane in the runs with t-butylmagnesium bromide.

General procedure. Before each run the apparatus was swept with dry nitrogen. For each run, a Grignard solution of the desired normality was prepared in the reaction flask. For diethyl ether, the loss of liquid volume (1.5 ml) resulting from vaporization was taken into account in calculating the amount of diluent required. The Grignard solution was brought to reflux and an equivalent amount of ketone quickly injected. During rapid evolution of gas, the volume was recorded each 10 s; longer intervals were selected for slower reaction rates.

Calculations.—Correction of volumes to standard conditions. Each observed volume ($V_{\mathrm{obs.}}$) was corrected to the volume (V_{stp}) at 0° and 760 Torr using equation (2) where P is the total pressure and $p^t_{H_2O}$ the vapour pressure of water at the temperature of observation; the first factor corrects for the presence of water vapour in the gas in contact with the gas

$$V_{stp} = [(P - p^t_{H_2O})/P](273/T)[(P - p^{0^\circ}_{ether})/760] \quad (2)$$

burette assuming saturation. The third factor corrects the observed volume for the presence of ether vapour assumed to be at 0° as it passes the cold-finger condenser; $p^{0^\circ}_{ether}$ is the vapour pressure of ether at 0°.

Rate equation.[6] Since the volume of hydrocarbon formed in the reaction was measured, it was convenient to derive a pseudoconcentration term by dividing the moles of hydrocarbon H by the volume of solution V. Thus, for the general reaction Grignard (G) + Ketone (K) = Grignard Enolate (E) + Hydrocarbon (H) the rate expression for a second-order reaction is (3). For [G] = [K], [G] = G/V,

$$\mathrm{d}(H/V)/\mathrm{d}t = k[\mathrm{G}][\mathrm{K}] \quad (3)$$

and $G = G_0$ at time zero, leading to equation (4). By

$$V^{-1}\mathrm{d}H/\mathrm{d}t = k[(G_0 - H)/V]^2 \quad (4)$$

integration, equation (5) is obtained. Since the volume of

$$H/(G_0 - H) = [G]_0kt \quad (5)$$

gas is proportional to the number of moles, the left-hand side of the equation may be replaced by $V/(V_\infty - V)$ where V_∞ is the volume of gas at the completion of the reaction of G_0 moles of Grignard. The final equation is (6). Since the

$$V/(V_\infty - V) = [G]_0kt \quad (6)$$

starting Grignard concentrations were 0.10N in all cases, this equation reduces to (7).

$$k = 10[\text{slope of } V(V_\infty - V) \textit{ versus } t] \quad (7)$$

Theoretically, V_∞ should be equal to 22.4 ml after reduction to standard conditions. Some of the plots[6] of $V/(22.4 - V)$ *versus* t were linear as far as the reactions were followed while curves for some were linear for the initial part of the reaction and deviated at the latter stages. The slopes are based on the initial part of the reactions. In studies on the Grignard addition reaction, it was reported[1a] that alkoxide formed at the beginning of the reaction caused complications in the later stages as the concentration of alkoxide increases.

From fractional time data.[6] Although $t_{1/2}$ values are usually used, in the present study $t_{1/4}$ values (times in s for evolution of 1/4 of the theoretical volume of 22.4 ml or 5.6 ml of alkane) were also used to calculate rate constants as a check on the values calculated by the method described above. The values for rate constants calculated from $t_{1/4}$ data for the diethyl ether reactions are equal to the values listed in Table 1 within experimental error. Values for the rate constants were obtained from equation (8). For $[G_0] = 0.10$N and $t_{1/4}$ in s: $k = 200/t_{1/4}$.

$$k = 1/3[G_0]t_{1/4} \quad (8)$$

RESULTS AND DISCUSSION

The second-order rate constants are in Table 1. In all cases the relative order of the Grignard reagents found for reaction with any of the ketones was Et > Pr^i > Me ≫ Bu^t. This order appears to be the reflection of an increasing steric effect on the reaction. Wotiz *et al.*[10] reported the order Pr^i > Et > Me for reactions of alkylmagnesium bromides with hex-1-yne where no steric effect would be expected. They attributed the relative order to anionic hyperconjugation. In the present study the same relative order was observed for the first two members of the series, Et > Me. However, apparently the increased steric requirements of the isopropyl group causes a decrease in reaction rate which outweighs the increase in the electronic effect; this results in an overall slower rate for the isopropyl Grignard reagent, *i.e.* Et > Pr^i. This steric effect is especially evident for the t-butyl Grignard reactions which were extremely slow compared to the other Grignards.

Similarities and differences among the four Grignard reagents can be brought out more clearly by placing the results on the same relative scale. Since the largest observed rates appeared in the methyl mesityl ketone series and the ratio is *ca.* 100 : 1, a value of 100 was assigned to the relative reactivity of ethylmagnesium bromide in each ketone series. These values are in Table 2.

On this basis, the methyl and isopropyl ketones have approximately the same relative reactivities towards isopropyl- and methyl-magnesium bromides while the ethyl ketone values are higher toward these two Grignard reagents. For t-butylmagnesium bromide, the relative values for methyl and ethyl ketones are the same while that for the isopropyl ketone is about three times as large.

The differences in relative reactivities between isopropyl mesityl ketone and the methyl and ethyl ketones can be considered here. The relative order of reactivity of the ketones for each of the Grignards is Me > Et > Pr^i. For a comparison from a statistical point of view, Table 3 can be constructed in which a relative reactivity of 3.0 is assigned to the methyl ketone in each Grignard series on the basis of the number of hydrogens α to the carbonyl group. A relative order for the three ketones toward the same Grignard reagent as predicted on statistical grounds would be 3 : 2 : 1 for the methyl,

TABLE 1

Second-order rate constants[a] (l mol^{-1} min^{-1}) for reactions of alkyl mesityl ketones and alkylmagnesium bromides

Alkyl mesityl ketone	Alkylmagnesium bromide			
	Me	Et	Pr^i	Bu^t
Me	2.1	9.6	4.6	0.086
Et	2.0	5.2	3.2	0.052
Pr^i	0.32	1.1	0.55	0.038

[a] Averages for duplicate runs.

TABLE 2

Relative reactivities[a] for reactions of alkyl mesityl ketones and alkylmagnesium bromides

Alkyl mesityl ketone	Alkylmagnesium bromide			
	Et	Pr^i	Me	Bu^t
Me	100	48	22	0.9
Et	100	62	38	1.0
Pr^i	100	50	29	3.5

[a] Rate for ethylmagnesium bromide reaction = 100 for each series.

TABLE 3

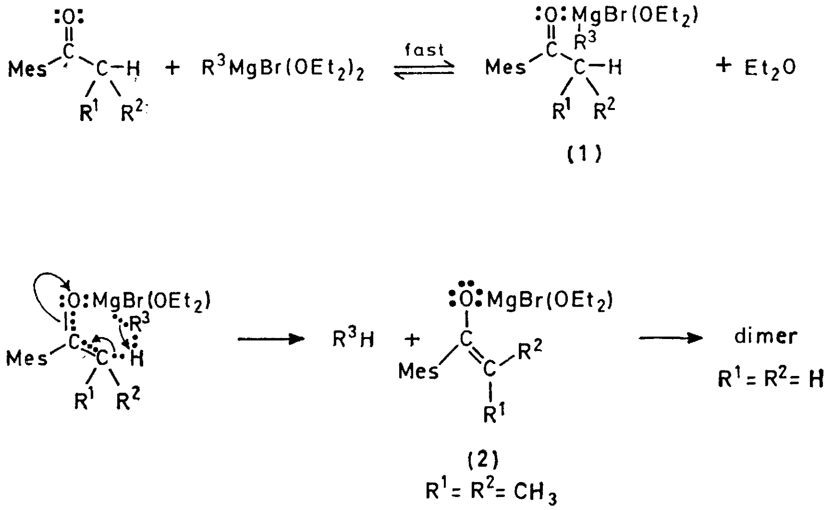
Relative reactivities for reactions of alkyl mesityl ketones and alkylmagnesium bromides based on statistical consideration of number of α-hydrogens in ketone

Alkyl mesityl ketone	Alkylmagnesium bromide			
	Me	Et	Pr^i	Bu^t
Me	3.0	3.0	3.0	3.0
Et	2.9	1.6	2.1	1.8
Pr^i	0.46	0.34	0.36	1.3

ethyl, and isopropyl mesityl ketones, respectively. Reactions of t-butylmagnesium bromide with the three ketones approached the statistical ratio. For the other Grignards (with the exception of methyl) the relative values were *ca.* 3 : 2 : 0.4.

Reaction Mechanism.—In many reactions of ketones involving substitution in the α-position (such as halogenation or deuterium exchange), the rate of the reaction depends on the rate of conversion of keto to enol form which then reacts. The present results in combination with results from extensive studies [1a,11] on the addition reactions of Grignard reagents to ketones appear to rule out enolization as the rate-controlling step on the basis of the following considerations. (1) If enolization were rate controlling, then the rates for each ketone with various Grignard reagents would be expected to be the same whereas in fact the rates of reaction for each ketone are different depending on the particular Grignard reagent used (Table 1). (2) Furthermore, in studies on the addition reaction, evidence from u.v. and i.r. spectroscopic studies [1a,11] shows that the Grignard reagent co-ordinates at the carbonyl oxygen of ketones in a fast equilibrium preceding the addition step. Although analogous spectroscopic studies have not yet been carried out with the mesityl ketones, it was noted in the present study that colours were formed immediately on the addition of the ethyl- and isopropyl-magnesium bromides to the ketones; the colours faded during the course of the reaction. A yellow colour was also observed when magnesium bromide was shaken with isobutyrylmesitylene. Holm [11] also noted the initial formation of colours when Grignard reagents and certain ketones were mixed. By analogy, a co-ordination of the Grignard magnesium with the mesityl ketone oxygen is proposed in the present case.

Tentatively, the mechanism in the Scheme is postulated. The first step is a rapid reversible formation of a complex (1) between the ketone and the Grignard reagent involving replacement of an ether molecule co-ordinated to magnesium with the keto oxygen. The second, rate-determining step postulated is the removal of hydrogen from the α-carbon *via* a six-membered ring transition state to form the alkane and enolate (2). The enolate can dimerize as demonstrated [12] previously in the case of acetylmesitylene, or exist as a monomer having three-co-ordinate magnesium [13] when dimer formation is sterically inhibited as with isopropyl mesityl ketone. Since an enolate has been shown [12,13] to be formed with magnesium co-ordinated to oxygen, this fact would also tend to preclude direct rate-determining attack of Grignard on the α-proton. The latter case would result in a C–Mg bond; a fast rearrangement to the enolate would then be necessary.



SCHEME

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