

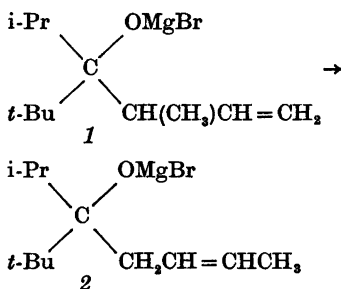
Mechanism of the Grignard Addition Reaction. XII. The Reversibility of the Addition of Allylic Grignard Reagents to Di-*t*-butyl Ketone

TORKIL HOLM

Institute of Organic Chemistry, Technical University of Denmark, DK-2800 Lyngby, Denmark

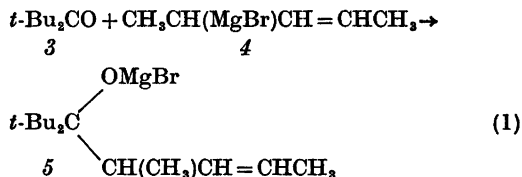
The reaction between di-*t*-butyl ketone with α , γ -dimethylallylmagnesium bromide has been studied by chemical, thermochemical and kinetic methods. Derivatives of both the ketone and the Grignard reagent have been obtained starting with the tertiary alcohol. The enthalpy of activation of the reverse reaction equals the sum of ΔH^\ddagger (forward) and ΔH_r (reverse). The *cis/trans* isomerisation of the tertiary alcohol occurs by retro addition-readdition.

In a recent study by Benkeser and Broxterman¹ on the reaction of *t*-butyl isopropyl ketone with crotylmagnesium bromide the observed slow conversion of the reaction product 1 to a mixture of *cis* and *trans* 2 was interpreted as taking place through a reversal of the Grignard addition reaction.



The theory of a retro Grignard addition was based solely on this observed rearrangement. It would seem, however, that the isomerisation might equally well be explained as, *e.g.*, a 1,3-radical type rearrangement of the allylic system and that more direct evidence was needed to prove, whether the Grignard addition is, in fact, truly reversible.

In the present investigation the most convenient system for the study of the problem was found to be di-*t*-butyl ketone (3) and α , γ -dimethylallylmagnesium bromide (4). Definitive proof of the reversibility of reaction (1)

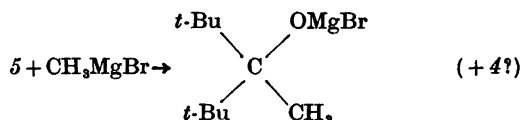


would require the isolation of both starting materials 3 and 4 after thermally induced decomposition of 5. Indirect evidence would be obtained by isolating derivatives of each starting material, *e.g.* by treating 5 with a reagent which might displace the hypothetical equilibrium (1) by scavenging either 3 or 4 as fast as it is formed. The problem in this case would be whether the derivatives were formed after spontaneous dissociation of 5 into 3 and 4 or whether the splitting was induced by attack on 5 of the reagent used for the scavenging.

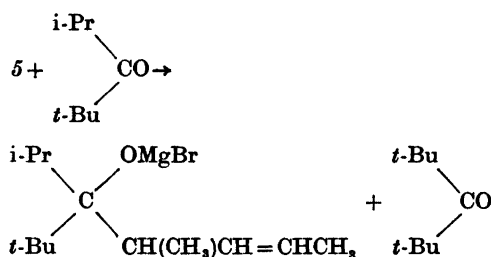
In the present work derivatization of 3 and 4, when starting from 5, has been combined with kinetic and thermochemical investigations of the reactions concerned. The accordance in the observations leaves no doubt that eqn. 1 represents a true equilibrium.

A derivative of 3 was obtained when 5 was heated with an excess of a Grignard reagent, *e.g.* methyl- or allylmagnesium bromide. After work-up a tertiary alcohol was obtained in

which the dimethylallyl radical was displaced by the radical of the "foreign" Grignard reagent:



To get a derivative from 4 the alcoholate 5 was heated with isopropyl-*t*-butyl ketone, and after work-up pentenyl-isopropyl-*t*-butyl carbinol was obtained together with di-*t*-butyl ketone, evidently as the result of reversal of eqn. 1 followed by addition of 4 to the "foreign" ketone:



Heating of 5 alone was found to induce *cis/trans* isomerisation from an initial ratio of *ca.* 1:1 to a thermodynamically determined equilibrium of *ca.* 1:3.

The thermochemistry and kinetics of reaction (1) and related reactions were investigated

by means of the flow stream thermographic procedure² or, for slow reactions, by the use of a steady state heat flow calorimeter.³

From the measurements shown in Table 1 it is seen that the enthalpy of reaction of allylic Grignard reagents with ketones is numerically low compared with values obtained with methylmagnesium bromide. Furthermore the enthalpy of reaction of allylic reagents with the highly hindered di-*t*-butyl ketone is very much less negative than the values obtained with acetone. The reaction of 3 and 4 in (1) then shows only an enthalpy of reaction of -106 kJ/mol which is little more than half the value obtained with acetone and methylmagnesium bromide.

The reaction rates between allylic Grignard reagents and various substrates are given in Table 2. With an unhindered ketone like acetone the rates are exceedingly high even with highly hindered reagents, and with an unhindered reagent like allylmagnesium bromide even di-*t*-butyl ketone reacts momentarily. Hindrance in both ketone and the reagent, however, leads to measurable rates, and the rate of 3 reacting with 4 for example is remarkably low.

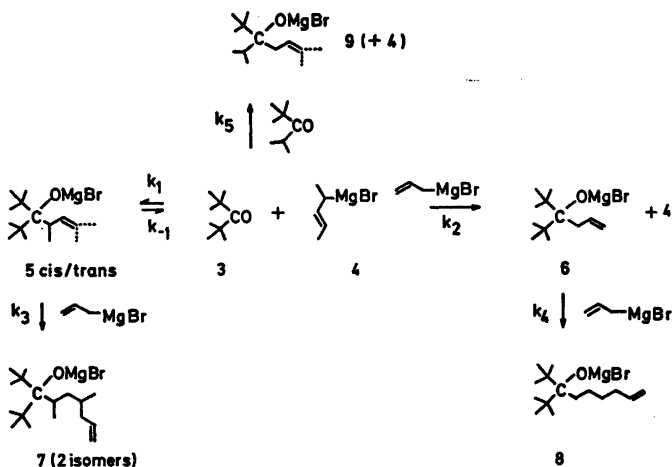
For a reversible reaction the enthalpy of reaction should equal the difference between the enthalpies of activation for the forward and the reverse reaction (eqn. (2)).

Table 1. Enthalpy of reaction in kJ/mol of ketones reacting with Grignard reagents in diethyl ether.

	Me ₂ CO	i-PrCO- <i>t</i> -Bu	<i>t</i> -Bu ₂ CO	Ph ₂ CO
CH ₂ =CHCH ₂ MgBr	-178		-108	-157
CH ₃ CH=CHCH ₂ MgBr		-105		
CH ₃ CH=CHCH(MgBr)CH ₃			-106	
CH ₃ MgBr	-204		-150	-171

Table 2. Pseudo first order rate constants in s⁻¹ for the reaction of 0.05 M ketone in diethyl ether at 20 °C with allylic Grignard reagents at the concentrations stated. Rates of addition to azobenzene showed for comparison.

	Me ₂ CO	i-PrCO- <i>t</i> -Bu	<i>t</i> -Bu ₂ CO	PhN=NPh
CH ₂ =CHCH ₂ MgBr 0.35 M	>10 ⁴	>10 ⁴	>10 ⁴	120
CH ₃ CH=CHCH ₂ MgBr 0.22 M	>10 ⁴	64	19	13
CH ₃ CH=CHCH(MgBr)CH ₃ 0.21 M	>10 ⁴	100	2.3	50



Scheme 1.

$$\Delta H_{\ddagger}(1) + \Delta H^{\ddagger}(\text{forward}) = \Delta H^{\ddagger}(\text{reverse}) \quad (2)$$

The enthalpy of activation for reaction (1) was determined on the basis of rate measurements at 20 and 40 °C and was found to be 31 kJ/mol. For the less hindered reactants isopropyl-*t*-butyl ketone and crotylmagnesium bromide the value was 27 kJ/mol.

In order to obtain the kinetics of the reverse reaction it was necessary to use a scavenging agent which was much more reactive toward 3 than is 4. This condition is fulfilled by allylmagnesium bromide (see Table 2). A problem using this reagent is that it adds to the double bond of the magnesium salt of the allyl carbinol, a reaction analogous to the addition of allylmagnesium bromide to the magnesium salt of 4,4-diphenylbut-3-en-1-ol. This means that two reactions are competing in a mixture of 5 and allylmagnesium bromide leading to a reaction mixture (Scheme 1) containing the products 7 and 8. Since the product 6 was never observed it was concluded that k_4 was large.

The occurrence of the side reaction was a complication in determining the enthalpy

of activation for the reverse reaction (1). The procedure adopted was to run the reaction between 5 and a large excess allylmagnesium bromide at various temperatures and to find the time necessary to obtain, after work up, equal heights in the gas chromatogram of the peaks corresponding to 5 and 7. Over the temperature range 52 °C to 109 °C the reaction varied from *ca.* 4000 to *ca.* 5 min, Table 3. The ratio of 7/8 in the reaction mixture decreased over the temperature range by approximately a factor of 2, and 7 was not considered in the calculations.

An Arrhenius treatment of the data yielded an enthalpy of activation of *ca.* 125 kJ/mol for the formation of 7 from 5 and since k_{-1} is assumed to be rate limiting this represents $\Delta H^{\ddagger}(\text{reverse})$. Calculation of $\Delta H^{\ddagger}(\text{reverse})$ from eqn. (2) leads to $105 + 31 = 136$ kJ/mol. The apparent discrepancy between the two values probably does not exceed the experimental uncertainty. If the difference was significant it would suggest that the retro addition is not following exactly the same path as the addition, but that a short-cut allows formation

Table 3. Reaction time for approximately 30 % conversion of di-*t*-butyl-2-pent-3-enyl carbinol (5) (*ca.* 0.1 M) in 0.7 M allylmagnesium bromide (54 % excess Br⁺) in diethyl ether at various temperatures.

Temperature, °C	51.7	70.5	82.3	100	109
Time, min	3930	360	77	16	5
Ratio 7/8	1.3	1.3	2.0	3.3	3.0

Table 4. Time for 80 % conversion of ca. 0.1 M bromomagnesium di-*t*-butyl-2-pent-3-enyl carbinolate (5) in diethyl ether in the reaction with isopropyl *t*-butyl ketone ca. 0.2 M.

Temperature, °C	55.5	80.1	100
Time, min	1122	37	3

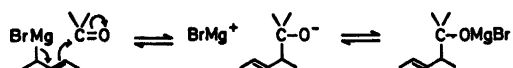
of 6 without the intermediacy of entirely free ketone.

Derivatives of the Grignard reagent 4 were obtained by heating the alcoholate 5 with an excess of a "foreign" ketone. Since isopropyl-*t*-butyl ketone is a much more reactive reagent toward α,γ -dimethylallylmagnesium bromide than is di-*t*-butyl ketone the conversion of 5 into 9 (see Scheme 1) should have the rate limiting step in common with the above mentioned conversion of 5 into 8. This step in both cases should be the thermal dissociation of the alcoholate into ketone and Grignard reagent with the rate constant k_{-1} .

The rate of formation of 9 was followed at various temperatures and determination of the enthalpy of activation was attempted. The rate was found to be 8–10 times faster than the rates observed for formation of 8 (see Table 4). The enthalpy of activation was approximately 130 kJ/mol, not inconsistent with the value obtained by "Grignard exchange". That the "ketone exchange" rate is higher may be a solvent effect, since it may be concluded from Benkeser and Broxtermans work that the exchange of ether by THF is also causing a rate increase. This effect of the better ionizing solvents may indicate that the first step in the retro addition is ionization of the alcoholate. In accordance with this assumption is the observation that the presence of a proton donor like *t*-butyl alcohol is prohibitive for the fission of the alcoholate 5 since no ketone was formed even after prolonged heating at 100 °C. Treatment of the potassium salt of 5 with *t*-butyl alcohol in ether produced the ketone in a smooth reaction at 100 °C.

The values calculated for the entropy of activation for the retro Grignard addition are approximately 25 J/°C when Grignard reagent is in excess and 42 J/°C when ketone is in excess. For the forward reaction the value is -146 J/°C. The six-centered cyclic transition state, which was proposed by Benkeser *et al.* for both reac-

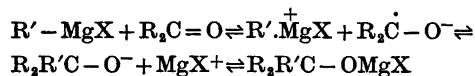
tions is not consistent with these values, which indicate an associative addition mechanism and a dissociative retro addition. It has been shown by Felkin *et al.*⁵ that addition of allylic Grignard reagents are S_E2' and not S_Ei' and the mechanism shown in Scheme 2 is therefore indicated.



Scheme 2.

The suggested mechanism is purely ionic. The relative reactivities of Grignard reagents seem to be easier to explain if the first step is divided into a rate limiting transfer of a single electron (SET) and a fast combination of radical ions. That methylmagnesium bromide has much less reactivity than either benzyl- or ethylmagnesium bromide is not consistent with a purely ionic mechanism since the effect of substitution with the electronegative phenyl should be opposite the effect of the electropositive methyl.^{6,7} The relative reactivities would, however, be reasonably well explained by the operation of SET. The intense yellow colour which appears during the reaction of 3 and 4 might also indicate the formation of coloured ion radicals by SET.

With inclusion of SET the complete mechanism for the Grignard addition and for the reverse reaction would have three steps:



Felkin *et al.* have published observation of the *cis/trans* ratios obtained in reactions of α,γ -dimethylallylmagnesium bromide with various electrophilic substrates.⁸ They obtained ratios near 6 with strongly electrophilic substrates like CO₂ and with electrophiles with decreasing strengths the ratios decreased, reaching with the weakest electrophiles a minimum of 0.3.

Table 5. The *cis/trans* ratio of di-*t*-butyl-2-pent-3-enyl carbinol determined by GLC after heating at 100 °C as a 0.2 M solution of the bromomagnesium salt in diethyl ether in the presence of 0.2 M di-*t*-butyl ketone. Also shown is the ratio of di-*t*-butyl carbinol/pentenyl-di-*t*-butyl carbinol in the reaction mixture.

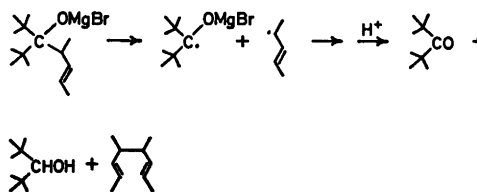
100 °C	Start	1 min	3 min	6 min	12 min
<i>cis/trans</i> carbinol %	1.0	0.76	0.57	0.46	0.42
<i>sec/tert</i> carbinol %	3.3	4.2	6.1	9.2	14.6
54.4 °C	Start	1600 min			
<i>cis/trans</i> carbinol %	1.0	0.46			
<i>sec/tert</i> carbinol %	3.3	4.6			

The results were explained by assuming transition states with varying degree of anionic character.

Assuming the stepwise mechanism outlined above the results of Felkin *et al.* might be interpreted by the difference in life time of different ion radical pairs, since the radical ion formed by SET might be "born" in the *cis* configuration, but would tend to isomerise during its life as radical.

When the alcoholate **5** was heated the initial *cis/trans* ratio of 1:1 changed to the equilibrium value *ca.* 1:3. It seemed a possibility that the isomerisation could take place in an intermediate ion pair and that the rate and activation energy for the isomerisation reaction might therefore be different from the parameters for the retro addition. Determination of the rate of isomerisation at 50 and at 100 °C, however, revealed (see Table 5) that the activation energy for the process was *ca.* 120 kJ/mol which indicates that the isomerisation occurs by retro addition-readdition and that the life time of an eventual radical ion pair is at least not long enough to allow rotation from *cis* to *trans* configuration.

The gas chromatograms revealed that during the heating of the alcoholate **5** increasing amounts of di-*t*-butyl carbinol were produced. The most reasonable explanation for this is that a homolytic cleavage (2) of the carbon-carbon bond is competing with the heterolytic (1) as shown in Scheme 3. A lower temperature coefficient for the homolytic cleavage seems to indicate a lower activation enthalpy.



Scheme 3.

EXPERIMENTAL

Materials. Ketones were prepared by alkylation of diisopropyl ketone⁹ and were purified to 99 % (GLC) by fractional distillation. Allylic bromides were prepared from the alcohols by addition of gaseous hydrogen bromide. The allylic Grignard reagents were prepared by extremely slow addition of the bromide to excess sublimed magnesium (Specpure, Johnson, Matthey Chemicals) in diethyl ether distilled from lithium aluminum hydride with stirring using evacuated equipment. From allylic Grignard reagents and hindered ketones were obtained tertiary alcohols as reported.¹⁰ The products **5 cis**, **5 trans**, **7**, **8**, and **9** were not isolated, but were identified by the combination of gas chromatography and mass spectroscopy, in which the tertiary alcohols produced strong peaks corresponding to the various oxonium ions arising by the loss of either a *t*-butyl or an alkenyl group from the molecular ions, which were not visible.

Kinetics. Reaction mixtures were prepared at room temperature and distributed in sealed ampoules. The ampoules were heated in a thermostated oil bath for the specified time. The reaction mixtures were treated with saturated ammonium chloride, washed with water and base and dried with potassium carbonate. The product distributions were evaluated by GLC.

Fast reactions were measured in a flow stream reactor by thermography² using a liquid speed in the reaction tube of 300 cm/s.

Thermochemistry. Enthalpies of reaction of fast reactions were obtained from the thermographic data. The reaction between methyl magnesium bromide and di-*t*-butyl ketone is slow and the enthalpy of reaction was obtained by the use of the steady state heat flow calorimeter² adding the ketone at a constant rate to an excess of the Grignard reagent over a period of 1–2 h.

Because of the low reactivity of methylmagnesium bromide compared with allylic reagents its reaction as a 1 M ethereal solution with *5* (0.1 M) required several hours at 124 °C. The yield of methyl di-*t*-butyl carbinol increased with time since α,γ -dimethylallylmagnesium bromide was slowly removed from the equilibrium by thermal decomposition. After 48 h the conversion was quantitative as determined by GLC.

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Received June 1, 1976.