Preliminary communication

The reaction of benzophenone with Grignard reagents: separation of the rate and product determining steps

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The reaction of benzophenones with Grignard reagents may yield a variety of products including reduction products (benzhydrol and benzopinacol) as well as addition products formed by 1,2-addition and/or conjugate 1,4- and 1,6-addition. In 1929 Blicke and Powers suggested[1] that all products originate from reaction between the magnesium ketyl and an alkyl radical, both formed in an initial single electron transfer (SET):

$$(C_6H_5)_2CO + RMgX \rightarrow (C_6H_5)_2\overset{\centerdot}{C}-O-MgX + \overset{\centerdot}{R}$$
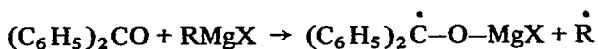
This suggestion later received support from ESR measurements demonstrating the occurrence of benzophenone ketyl during the reactions[2], and from the finding of benzopinacol in significant amounts when neopentylmagnesium chloride is used as the reagent[3]. For t-butylmagnesium chloride, it has recently been shown[4] that the amount of 1,2- and 1,6-addition products may vary from nil to 55%, and to 100% respectively with varying substitution in the benzophenone, even though the over-all rate obeys the Hammett rate law. Clearly, the rate limiting and product determining steps are not the same.

Alkylmagnesium reagent prepared from primary and secondary alkyl halides form varying amounts of benzhydrol as one of the reaction products. In such cases the ratio between benzhydrol and other products changes on exchanging the β-hydrogens for deuterium as shown in Table 1. The decrease in rate of benzhydrol formation is, however, accompanied by an increase in the rate of formation of alternative products so that the over-all rate is only slightly lowered. Hence, separation of the rate limiting and the product determining steps is again indicated.

The reaction of isobutylmagnesium bromide with benzophenone yields exclusively benzhydrol, and it has been shown by Dunn and Warkentin[5] that, in a mixture of β-deuterated and the nondeuterated reagent, deuterium is incorporated into the product with an apparent isotope effect $\dfrac{k_D}{k_H}$ of 2.0—2.1. During the present investigation a value of 2.7 was estimated by mass spectroscopic analysis of the benzhydrols formed in the reaction of a 0.02 M benzophenone/ether solution with a 1/1 mixture of 1.0 M β-deuterioisobutylmagnesium bromide and 1.0 M non-deuterated isobutylmagnesium bromide. Direct rate
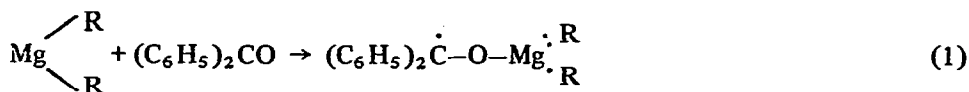
TABLE 1

PSEUDO FIRST ORDER RATE CONSTANTS AND PRODUCT DISTRIBUTIONS FOR THE REACTIONS OF 0.50 M ALKYLMAGNESIUM BROMIDES WITH 0.020 M BENZOPHENONE AT 20° IN DIETHYL ETHER. ALSO GIVEN IS ISOTOPIC PURITY $\frac{D}{H+D}$, AND PERCENTAGE EXCESS OF BROMIDE ION IN THE GRIGNARD REAGENT.
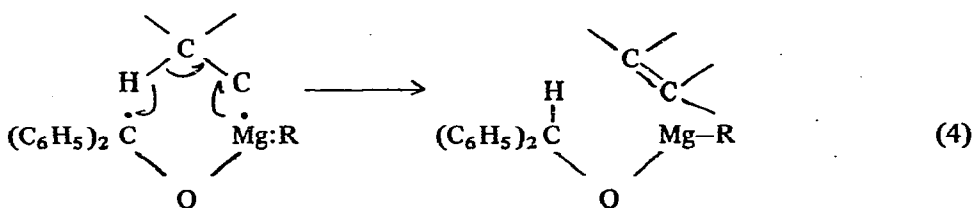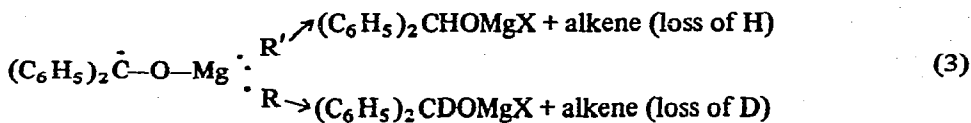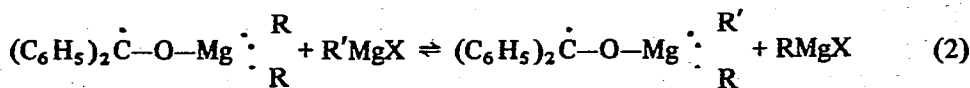
R in RMgBr	k_{tot} (sec^{-1})	$\frac{D}{H+D}$ (%)	Br$^-$ (%)	Reduction (%)	1,2-Addition (%)	1,6-Addition (%)
CH$_3$	0.3		0	0	100	0
CH$_3$CH$_2$	8.1		1.0	6	94	0
CD$_3$CH$_2$	8	95	1.0	2.4	97	0
CH$_3$CH$_2$CH$_2$	4.0		1.5	49	51	0
C$_2$H$_5$CH$_2$CH$_2$	4.0		5.2	55	45	0
C$_2$H$_5$CH$_2$CH$_2$ ^{a}	1.56		5.2	55	45	0
C$_2$H$_5$CD$_2$CH$_2$ ^{a}	1.28	97	6.0	34	66	0
C$_2$H$_5$CD$_2$CH$_2$ ^{a}	1.55	50	5.6	52	48	0
(CH$_3$)$_2$CH	29		12.5	20	41	39
(CD$_3$)$_2$CH	25	92	12.5	13.5	42	45
C$_2$H$_5$(CH$_3$)CH	11.6		19.5	45	25	30
CH$_3$CD$_2$(CD$_3$)CH	11	80	14.0	30	28	42
(CH$_3$)$_2$CHCH$_2$	1.11		7.0	100	0	0
(CH$_3$)$_2$CDCH$_2$	1.08	95	7.0	100	0	0
Cyclopentyl	64		14.2	100	0	0
Cyclohexyl	2.6		24.0	30	27	42

^{a} Grignard reagent concentration 0.200 M.

measurements, however, showed that the deuterated reagent is virtually as reactive as the non-deuterated, indicating the existence of a rate determining SET step different from the product determining hydrogen/deuterium transfer step. The experiment also indicates that the first and the second step may involve two different alkyl groups, and the mechanism outlined below is an attempt to rationalize this finding.

It is well known that an exceedingly rapid exchange of alkyl groups takes place in a Grignard reagent[6]. It is also known that, when the alkyl is primary, any dialkylmagnesium present in the Schlenk equilibrium is so reactive that most of the reaction occurs via this species[7]. One may now assume that the bonds between the primary alkyl groups and magnesium are retained in the radical intermediate as two resonance stabilized "three quarter" bonds: [R·Mg:R]$^+$ ↔ [R:Mg·R]$^+$. Compensation for the electron deficiency may be provided by coordination with the solvent. The life time of the dialkylmagnesium radical is assumed to be long enough for alkyl exchange to take place at magnesium. It seems reasonable to formulate the biradical shown as the actual intermediate. In the collapse of the biradical a choice is possible between addition and reduction, and for the reduction process between hydrogen and deuterium, which accounts for the observed isotope effect.

$$\text{Mg}\overset{R}{\underset{R}{\diagup\!\!\diagdown}} + (C_6H_5)_2CO \rightarrow (C_6H_5)_2\overset{\cdot}{C}-O-\text{Mg}\overset{\cdot R}{\underset{\cdot R}{}} \tag{1}$$

$$(C_6H_5)_2\overset{\bullet}{C}\text{--O--Mg} \overset{\bullet}{\underset{R}{\overset{R}{\cdot\cdot}}} + R'MgX \;\rightleftharpoons\; (C_6H_5)_2\overset{\bullet}{C}\text{--O--Mg} \overset{\bullet}{\underset{R}{\overset{R'}{\cdot\cdot}}} + RMgX \qquad (2)$$

$$(C_6H_5)_2\overset{\bullet}{C}\text{--O--Mg} \overset{\nearrow^{R'}(C_6H_5)_2CHOMgX + \text{alkene (loss of H)}}{\underset{R\rightarrow(C_6H_5)_2CDOMgX + \text{alkene (loss of D)}}{\cdot\cdot}} \qquad (3)$$

$$\qquad (4)$$

The rapid exchange (2) is considered essential in order to explain why the apparent isotope effect exceeds a value of about 2.2. One might assume that collapse of the biradical occurred fast enough to exclude exchange. Because of the statistical distribution of hydrogen and deuterium containing isobutyl groups, 25% of the diisobutylmagnesium would contain only deuterium and 25% only protium, while 50% would contain both protium and deuterium. Assuming no exchange, 25% D-benzhydrol and 25% H-benzhydrol would be secured beforehand. Even with an 8 to 1 preference of protium over deuterium in the collapse of the mixed biradical, the product distribution would be $25 + \dfrac{7}{8} \cdot 50 = 68.75\%$ of H-benzhydrol, and $25 + \dfrac{1}{8} \cdot 50 = 31.25\%$ of D-benzhydrol, corresponding to an apparent isotope effect of 2.20, in contrast to the experimental value of 2.7.

      The collapse of the biradical to benzhydrol and olefin is of course superficially reminiscent of the cyclic reduction mechanism introduced by Whitmore (cf. Mosher and LaCombe[8]) but differs from the latter in being stepwise. The asymmetric induction observed in the reduction by certain dissymmetric Grignard reagents can probably be rationalized equally well on the basis of the stepwise mechanism.

      For secondary and tertiary alkylmagnesium reagents the formation of 1,4- and 1,6-addition products indicates the participation of a less complex radical species than the dialkylmagnesium "semiradicals" described above. Since a 1,6-attack takes place far from the site of the initial electron transfer, separation of the radical from the magnesium is conceivable.

EXPERIMENTAL

Materials

      Grignard reagents were prepared in evacuated systems using sublimed magnesium and ether distilled from lithium aluminium hydride. Deuterated alkyl halides were prepared as described in ref. 5. The degree of deuterium exchange in the β-positions was estimated by

NMR. Product distributions were determined by a combination of GLC and NMR (Varian A60). Mass spectroscopic analysis of benzhydrol and of deuteriobenzhydrol (M 184 and M 185) was performed on a Perkin–Elmer 270 instrument equipped with GLC inlet. Since some separation of the deuterated and non-deuterated products occurred on the column, multiple scans were taken covering the total chromatographic peak. The contributions from all scans were considered in the calculations.

Kinetics

Rate measurements were performed using pseudo first order conditions for benzophenone by means of the thermographic method described in ref. 4. Standard concentrations were: for the Grignard reagents 0.50 M, and for benzophenone 0.020 M.

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