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THE REACTION OF GRIGNARD REAGENTS WITH 1,3-DIOXOLANES. INFLUENCE OF SOLVATION; KINETICS AND MECHANISM

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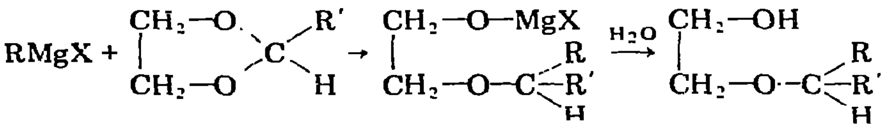
Summary

The reaction of 2-ethyl-1,3-dioxolane (D) with ethylmagnesium bromide, solvated by one equivalent of a basic solvent (E) (diethyl ether, diisopropyl ether and perdeutero-tetrahydrofuran) was studied in benzene at 40.5°. Ring-cleavage of the dioxolane occurs with first-order kinetics in two different coordination complexes, i.e. EtMgBr·E·D and EtMgBr·2D. When the Grignard reagent is in excess, an additional second-order reaction takes place between the complex EtMgBr·E·D and the monosolvated Grignard reagent. The rate constants are related to the basicities of the different ethers, E, used. The results confirm that the reaction proceeds via a transition state with oxocarbonium ion character. In agreement with this concept the reaction rates decrease with increasing basicity of the complexing ethers as the Lewis acidity of the attacking Grignard reagent is lowered.

Introduction

The reaction of Grignard reagents with organic compounds, such as acetals and orthoesters, which contain more than one alkoxy-group has been a subject of study from the very beginning of Grignard chemistry [1-8]. The first report dealing with cyclic acetals was on the reaction of methylmagnesium iodide with isosafrole [9].

In this laboratory it was demonstrated that such reactions proceed smoothly when the Grignard reagents are prepared in an aromatic hydrocarbon in the presence of one equivalent of a 2-alkyl-1,3-dioxolane [10-12]. The only product isolated from the reaction mixture after hydrolysis was the monoether of 1,2-ethanediol (eqn. 1).



(1)

Several authors have studied the reaction or have used it for preparative purposes [13-15] and much work in this field has been published by Atavin et al. [16, 17]; related information came from the experiments of Mousset [18-20]. Nevertheless the mechanism of the reaction is not yet clear. From the available data the conclusion may be drawn that the first step is coordination of the Grignard reagent with the 1,3-dioxolane followed by ring-cleavage in this complex.

Since coordination processes of organomagnesium compounds are reversible it is evident that the solvating properties of dioxolanes and of other basic solvents present in the reaction mixture influence the rate of the ring-cleavage reaction. It is the purpose of the present study to determine this influence.

Results and discussion

In order to study the kinetics of the reaction of ethylmagnesium bromide with 2-ethyl-1,3-dioxolane (D) the Grignard reagent was prepared in benzene in the presence of one equivalent of a basic solvent E; D was added to this solution. It was found earlier that the rate of the reaction depends on the ratio D/EtMgBr[*] [21].

Diisopropyl ether, diethyl ether and perdeutero-tetrahydrofuran[**] were used as the basic solvent, E. The disappearance of one or more characteristic signals in the NMR spectrum of the solution was used to follow the progress of the reaction for about one half-life or more. From the complete disappearance of the signals due to the reactant, which was not present in excess, it was concluded that the yield of the reaction was quantitative (> 95%); this was confirmed for several reactions by analyzing the reaction mixtures after hydrolysis. This is contrary to the results obtained by Atavin and coworkers [16] who reported that maximum yields could only be obtained when the Grignard reagent was present in two-fold excess. It seems likely that their unsatisfactory yields must be attributed among other reasons to the fact that the reactions were incomplete. According to our results the ethereal solvent is not completely removed under their conditions; this is expected to retard the reaction rate (vide infra).

It was found that the reaction is first-order within a run for ratios of D/EtMgBr varying from 10/1 to 1/10, but the value of the rate constant $k_{1\mathrm{exp}}$ varies with the ratio.

As indicated in the footnotes to Tables 1-3 some of the Grignard solutions contained considerable amounts of additional Et_2Mg, which could be observed in the NMR spectra after the reactions had gone to completion. From the remaining amounts of Et_2Mg it was concluded that its reactivity towards D is much lower than that of EtMgBr. Thus the presence of Et_2Mg was neglected in the calculations of the rate constants.

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[*] Throughout this paper EtMgBr represents the total amount of ethylmagnesium bromide in solution, irrespective of its degree of association and the complexing ethers.

[**] Deuterated THF was used because the NMR absorption of THF (vide infra) complicated the rate measurements. The results of preliminary experiments with perdeuterated diethyl ether indicate that the rate of reaction may increase somewhat when substituting hydrogen by deuterium in E.

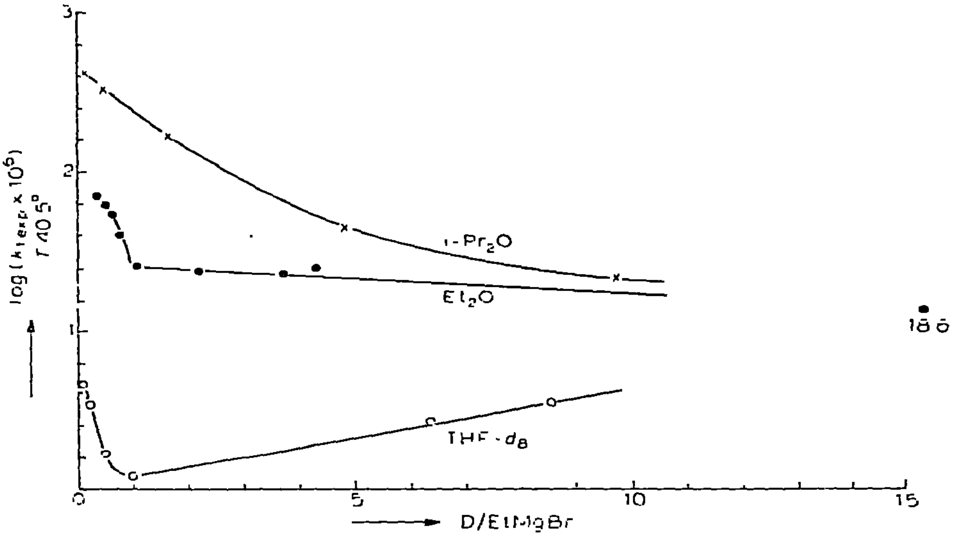


Fig. 1. First order rate constants (s^{-1}) as a function of the ratio D/EtMgBr for different ethers.

The possibility that the Grignard reagent reacted as a mixture of diethylmagnesium and magnesium bromide was excluded on the basis of the following evidence.

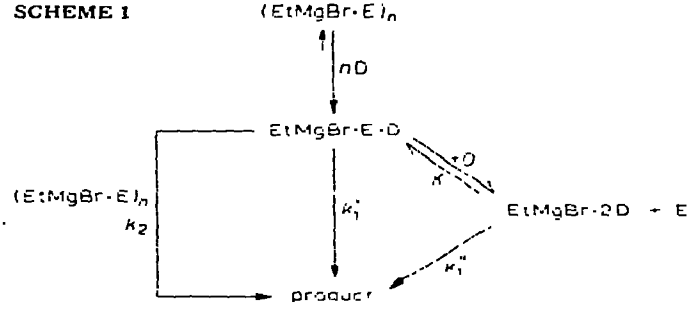
1. $MgBr_2$ is insoluble in benzene and one equivalent of an ether.

2. Neither $(Et_2Mg{\cdot}Et_2O)_x$ nor precipitated $MgBr_2$ in benzene react with D at 40.5°.

3. Simultaneous attack of both species on D cannot give rise to the observed first-order kinetics if the ratio D/Mg > 1.

The results given in Fig. 1 show that k_{1exp} varies with varying ratios D/EtMgBr. This indicates that k_{1exp} cannot be a straightforward first-order rate constant. This can be explained by assuming that the formation of the product occurs via different complexes as indicated in Scheme 1.

SCHEME 1



(E i-Pr_2O, Et_2O, THF-d_8,
D 2-ethyl-1,3-dioxolane,
k_1' and k_1'' first-order rate constants,
k_2 second-order rate constant,
K equilibrium constant)

The complex EtMgBr·E cannot be monomeric since the coordination number of magnesium is four. The exact value of n is not yet known.

TABLE 1

FIRST-ORDER RATE CONSTANTS OF THE REACTION OF EtMgBr·i-Pr$_2$O [a] WITH D IN BENZENE AT 40.5° AT VARYING RATIOS OF D/EtMgBr

Ratio D/EtMgBr	$(k_{1\,\mathrm{exp}} \pm \sigma) \times 10^4$ [b] (s^{-1})	Correlation coefficient
9.63	0.229 ± 0.012	0.991
4.84	0.436 ± 0.034	0.979
1.68	1.62 ± 0.13	0.981
0.45	3.42 ± 0.61	0.928
0.17	4.30 ± 0.42	0.982

[a] The ratio EtMgBr/i-Pr$_2$O was 1/1.32. An excess of Et$_2$Mg of 4% was present in solution. *See also* footnote to Scheme 1. [b] σ = standard deviation of the mean.

TABLE 2

FIRST-ORDER RATE CONSTANTS OF THE REACTION OF EtMgBr Et$_2$O [a] WITH D IN BENZENE AT 40.5° AT VARYING RATIOS D/EtMgBr

Ratio D/EtMgBr	$(k_{1\,\mathrm{exp}} \pm \sigma) \times 10^5$ [b] (s^{-1})	Correlation coefficient
18.6	1.50 ± 0.16	0.968
4.26	2.55 ± 0.29	0.975
3.71	2.49 ± 0.20	0.977
2.19	2.49 ± 0.20	0.970
1.10	2.55 ± 0.14	0.990
0.79	4.07 ± 0.20	0.994
0.65	5.37 ± 0.19	0.994
0.53	6.34 ± 0.70	0.970
0.34	7.31 ± 0.46	0.983

[a] The ratio EtMgBr/Et$_2$O was 1.0/1.0. No excess of MgBr$_2$ or Et$_2$Mg was present. See also footnote to Scheme 1. [b] σ = standard deviation of the mean.

TABLE 3

FIRST-ORDER RATE CONSTANTS OF THE REACTION OF EtMgBr·THF-d_8 [a] WITH D IN BENZENE AT 40.5° AT VARYING RATIOS D/EtMgBr

Ratio D/EtMgBr	$(k_{1\,\mathrm{exp}} \pm \sigma) \times 10^6$ [b] (s^{-1})	Correlation coefficient
8.5	3.64 ± 0.25	0.982
6.3	2.61 ± 0.28	0.978
1.0	1.17 ± 0.12	0.958
0.50	1.77 ± 0.20	0.963
0.20	3.52 ± 0.27	0.980
0.10	4.31 ± 0.64	0.968

[a] The ratio of (EtMgBr + Et$_2$Mg)/THF-d_8 was 1.0/1.0. The solution contained Et$_2$Mg in addition to EtMgBr; the ratio of these two organomagnesium compounds was 1.0/1.3. See also footnote to Scheme 1. [b] σ = standard deviation of the mean.

The addition of D to the Grignard complex causes coordination of D with magnesium with the formation of two different complexes: if a large excess of D is used EtMgBr·2D is formed independent of the nature of E. It is seen from the results that when D is in excess the values for $k_{1\,exp}$ converge to the value of k_1''. If smaller amounts of D are added two complexes are present in solution: EtMgBr·E·D and EtMgBr·2D. Each of these complexes gives rise to the same product but with different first-order rate constants.

Finally, when the Grignard reagent is in excess, it is evident that another type of reaction takes place since there is a sharp increase in the rate of the reaction for D/EtMgBr $<$ 1 (see Fig. 1). The following three considerations have to be made.

1. A first-order mechanism could exist in which a complex consisting of one molecule of dioxolane and two or more EtMgBr·E entities is formed. Such a mechanism can be excluded, however, since it would imply that for D/EtMgBr $\leqslant$ 1 the value for $k_{1\,exp}$ should become constant, and this has not been observed.
2. If a complex such as is described under 1 was present in low concentrations as part of a pre-transition state equilibrium the reaction would follow second-order kinetics.
3. A bimolecular mechanism in which excess $(\text{EtMgBr·E})_n$ reacts with EtMgBr·E·D with rate constant k_2 is kinetically indistinguishable from possibility 2.

Therefore the fast reaction with excess Grignard reagent will be discussed in terms of second-order kinetics. These considerations lead to eqn. 2 for the overall rate of reaction.

$$v = k_1'[\text{EtMgBr·E·D}] + k_1''[\text{EtMgBr·2D}] + k_2[\text{EtMgBr·E·D}][(\text{EtMgBr·E})_n] \quad (2)$$

For $[\text{D}] \gg [\text{EtMgBr}]$ $([\text{EtMgBr·E·D}] \approx 0)$ one obtains eqn. 3.

$$v = \frac{-\text{d}[\text{EtMgBr}]}{\text{d}t} = k_{1\,exp}[\text{EtMgBr}] = k_1''[\text{EtMgBr·2D}] \quad (3)$$

thus $k_1'' = k_{1\,exp}$.

For $[\text{D}] \geqslant [\text{EtMgBr}]$ $([\text{EtMgBr·E}]_n \approx 0)$ eqn. 4 describes the rate equation.

$$v = \frac{-\text{d}[\text{EtMgBr}]}{\text{d}t} = k_{1\,exp}[\text{EtMgBr}] = k_1''[\text{EtMgBr·2D}] + k_1'[\text{EtMgBr·E·D}] \quad (4)$$

Obviously this is not a first-order rate equation unless the ratio [EtMgBr·2D]/[EtMgBr·E·D] is approximately constant. This occurs when (a) $k_1' = k_1''$ (which is the case for E = Et_2O, see Table 4), or (b) only initial rates are measured.

With an excess of Grignard compound $([\text{EtMgBr·2D}] \approx 0)$ eqn. 5 or 6 will represent the rate equation.

$$v = \frac{-\text{d}[\text{EtMgBr·E·D}]}{\text{d}t} = k_1'[\text{EtMgBr·E·D}] + k_2[\text{EtMgBr·E·D}][(\text{EtMgBr·E})_n] \quad (5)$$

or

$$v = \left\{k_1' + k_2[(\text{EtMgBr·E})_n]\right\}[\text{EtMgBr·E·D}] \quad (6)$$

In each experiment the excess of Grignard compound is constant because only one equivalent is consumed in the reaction with the dioxolane; eqn. 6 can therefore be rewritten as eqn. 7.

$$v = \frac{-\mathrm{d}[\mathrm{EtMgBr{\cdot}E{\cdot}D}]}{\mathrm{d}t} = k_{1\,\mathrm{exp}}[\mathrm{EtMgBr{\cdot}E{\cdot}D}] \tag{7}$$

where

$$k_{1\,\mathrm{exp}} = k'_1 + k_2[(\mathrm{EtMgBr{\cdot}E})_n] \tag{8}$$

As already mentioned (eqn. 3) the value for k''_1 can be derived from the $k_{1\,\mathrm{exp}}$ values obtained when large excesses of D are used. This leads to $k''_1 = 20 \times 10^{-6}$ s^{-1} at 40.5°. It seems reasonable to assume that on addition of one equivalent of D to $(\mathrm{EtMgBr{\cdot}E})_n$ the species EtMgBr·E·D is formed quantitatively. Thus for $[\mathrm{D}]/[\mathrm{EtMgBr}] = 1$, $k_{1\,\mathrm{exp}}$ will be k'_1 (EtMgBr·2D being approximately zero, eqn. 4).

After k'_1 is known values for k_2 can be calculated from the experimental results obtained in the reactions with D/EtMgBr < 1 (eqn. 8). Table 4 represents the values of k'_1, k''_1 and k_2 obtained for the three different ethers. The rate of the reactions of complexes EtMgBr·E·D depends on the basicity of E; k'_1 is smaller for the stronger base THF-d_8, and greater for the weaker base diisopropyl ether. For E = diethyl ether k'_1 is almost equal to k''_1 which indicates that the basicities of diethyl ether and D are about equal. The following rationalisation can be made regarding the reaction in the complex EtMgBr·E·D: in the case where E is a weak base towards EtMgBr, complexation with the magnesium atom is also weak and renders the Grignard reagent a stronger Lewis acid. The stronger Lewis acid gives a faster reaction with D which is in agreement with the observation that $\mathrm{Et_2Mg}$ shows only strongly reduced reactivity towards D as compared with EtMgBr.

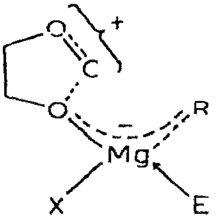
The dependence of the reactivity of the organomagnesium reagent on its Lewis acidity indicates the occurrence of an activated complex A in which charge separation takes place, as was proposed earlier [10]. Confirmation of such an activated complex is found in the observation that stabilisation of the positive charge by alkyl-substitution at the 2-position in the dioxolane considerably accelerates the reaction. Under the experimental conditions we used, no reaction occurs with unsubstituted 1,3-dioxolane, whereas 2-phenyl-1,3-dioxolane reacts too fast with EtMgBr to allow measurements by the present NMR

TABLE 4

VALUES OF k'_1, k''_1 AND k_2 [a] OF THE REACTION OF EtMgBr·E WITH D IN BENZENE AT 40.5°

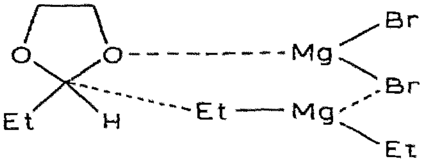
E	$k'_1 \times 10^6$ (s^{-1})	$k''_1 \times 10^6$ (s^{-1})	$k_2 \times 10^5$ ($\mathrm{l\ mol^{-1}\ s^{-1}}$)
i-$\mathrm{Pr_2O}$	240	20	108 × n
$\mathrm{Et_2O}$	25.5	20	81 × n
THF-d_8	1.17	20	3 1 × n

[a] The values of k_2 depend on the constitution of $(\mathrm{EtMgBr{\cdot}E})_n$.



(A)

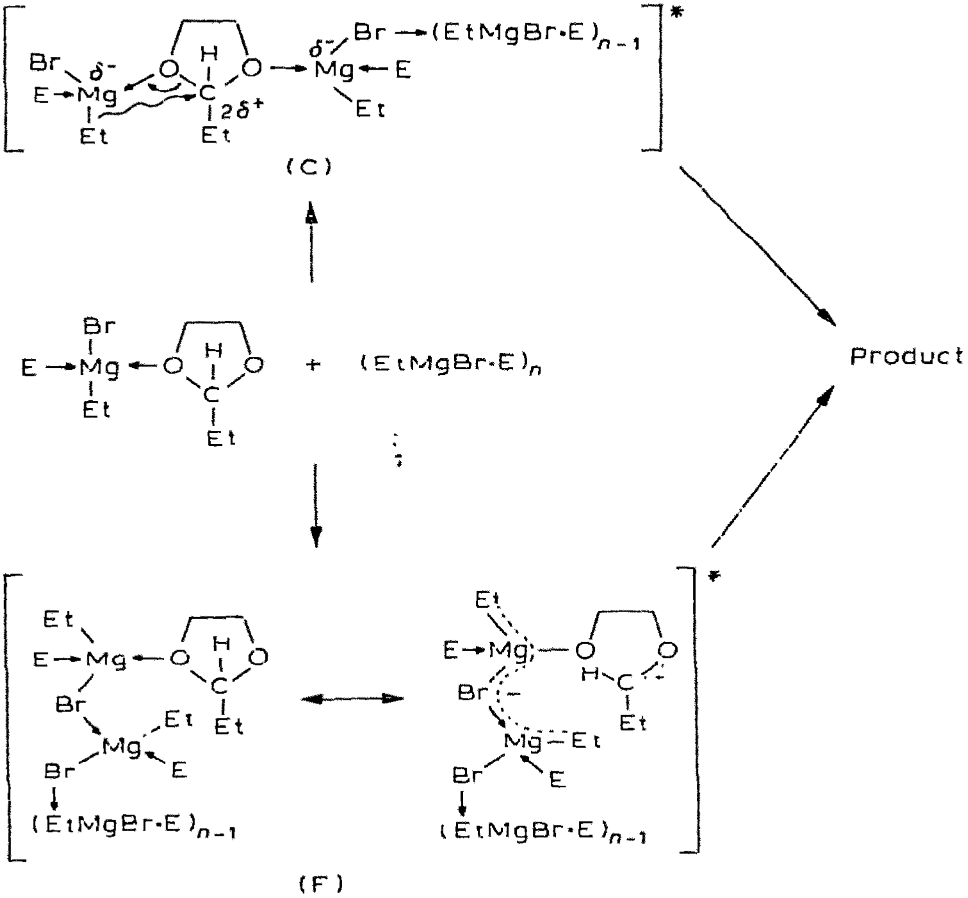
methods. Thus for D/EtMgBr > 1 our evidence is not in agreement with the mechanism proposed by Atavin et al. [16], in which complex B is assumed to participate. When the Grignard reagent is in excess, the activated complex



(B)

must contain at least two EtMgBr entities for each dioxolane. Such an activated complex results from attack of $(EtMgBr{\cdot}E)_n$ on $EtMgBr{\cdot}E{\cdot}D$ which can take place by two possible reaction routes (Scheme 2). Both routes can account for the increased reactivity over that which would be expected for reaction via A.

SCHEME 2



In the reaction via C, the C-2 of the dioxolane ring would acquire a considerable positive charge because the dioxolane is complexed with two Grignard entities; a nucleophilic substitution of Et^- on the positively charged C-2 would then be possible. The route via F should be fast because (a) a polymeric Grignard reagent is a stronger Lewis acid and (b) the negative charge which is formed upon breaking of the C—O bond can be distributed over more centres in the Grignard entities (as can be seen for $n = 1$, F resembles the complex B proposed by Atavin et al. [16]). No definite choice can be made between these two routes at present.

Experimental

All experiments were performed using closed glass apparatus, as described previously [22].

Grignard solutions (EtMgBr·E) of 0.1-0.4 *M* were prepared by adding equivalent amounts of EtBr, Mg and the ether E to benzene. All the reagents were previously extensively dried. After the spontaneous reaction had stopped, interaction was completed by stirring at 50° overnight. The precipitate was allowed to settle (some $MgBr_2$ was always formed) and the clear solution decanted.

In the case of EtMgBr·i-Pr_2O, the Grignard reagent was first prepared in i-Pr_2O and was crystallized by cooling. The crystals were dissolved in benzene after the i-Pr_2O had been decanted. The rates of reaction were measured in sealed NMR tubes by following the decrease of the peak heights (relative to an internal standard which was either E or toluene) with a Varian A-60 NMR spectrometer. Depending on the composition of the reaction mixture, different peaks were used: (a) of the methylene protons of EtMgBr at about 0.17 ppm, (b) of the C-2 proton of D at about 4.90 ppm and (c) of the C-4/C-5 methylene protons of D at about 3.50 ppm [*].

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[*] On mixing the Grignard reagent with the dioxolane, the multiplet for the C-4 and C-5 methylene protons of the dioxolane coalesces instantaneously. This phenomenon is under further investigation.

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