Control of Addition: Reduction Ratio in the Grignard Reaction with Ketones by a Salt Effect

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Summary The yield of addition of a Grignard reagent to a hindered ketone has been enhanced at the expense of reduction by complexing the Grignard reagent with lithium perchlorate or tetrabutylammonium bromide

ONE mol of di-isopropyl ketone with two mol of Pr^nMgBr (in Et_2O) gave 36% of addition product and nearly 62% of reduction product We have succeeded in increasing the yield of addition product from 36 to 70% by premixing with the Grignard reagent 1·5 mol of $LiClO_4$ or one mol of Bu_4NBr per mol RMgX

Reactions were carried out (Et_2O 20°) by adding, over 60 min , a ketone solution to a 1M-solution of Grignard reagent, pure or mixed with a salt In all the experiments, one molar equivalent of ketone was allowed to react with two molar equivalents of Grignard reagent The reactions were complete and the enolization yield was lower than 2% The addition : reduction ratio was evaluated at different time intervals by g c (Figure)

We have previously attributed[1] the increase in the relative yield of reduction during the reaction, to the ability of the reaction products (alcoholates) to react with the ketone The change in addition : reduction ratio with time and its value at the beginning of the reaction give further helpful information

In the normal reaction (Curve 1), the relative amount of reduction is rather high at the beginning of the reaction, then it increases readily as the reaction proceeds, and finally a high yield of reduction product is obtained In the presence of $LiClO_4$ (Curve 2) or of Bu_4NBr (Curve 3) the relative yield of reduction product, lower at the beginning, increases only slightly during the reaction, to a final value lower than that in the normal reaction

The salt effect might be explained by the formation of a ketone–salt complex, the salt polarizing the carbonyl group more strongly than the Grignard reagent does If this were the case, one might expect that the salt would be most effective when mixed with the ketone prior to reaction with the Grignard reagent Owing to its high solubility in ether, $LiClO_4$ can be mixed either with the ketone or with the Grignard reagent, but we have observed that the yield of addition product is the highest when $LiClO_4$ is premixed with the Grignard reagent

On the other hand, Bu_4NBr is only slightly soluble either in ether or in a solution of ketone in ether, but fairly soluble in the Grignard reagent When a large amount of this salt is added to the Grignard reagent (one mol per mol of RMg-X, as in run 3), the mixture separates in two layers and the lower layer contains most of the salt and of the Grignard reagent Under these conditions, run 3 may be regarded as a reaction between the ketone and a very concentrated Grignard reagent–salt mixture This may explain the higher effect of Bu_4NBr compared to that of $LiClO_4$

Thus we are led to the conclusion that the salt is complexed with the Grignard reagent In this complex, the ionic character of the Grignard reagent must be enhanced. The addition reaction is favoured, since the corresponding transition state must be more polar than the reduction transition state A study is now being made concerning the influence of salts upon the competition between alcoholates and the Grignard reagent, which is illustrated by the difference between the slope of the Curve 1 (normal reaction) and the slopes of the Curves 2 and 3 (with salts) Similar results were obtained in the presence of other salts

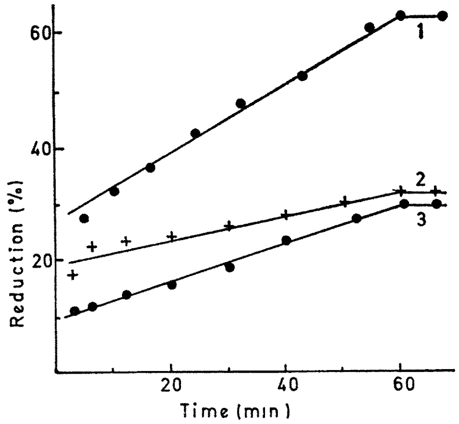

FIGURE *Plot of the relative yield of reduction against time for reactions of one molar equivalent of di-isopropyl ketone with two equivalents of n-propylmagnesium bromide—Curve* 1 *normal reaction, Curve* 2 *with* 1 5 *equivalents of* $LiClO_4$, *Curve* 3 *with one equivalent of* $Bu_4N^+ Br^-$

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[1] M Chastrette and R Amouroux, *Compt rend* 1970, **270C**, 92