

Conjugate Additions of Grignard Reagents to alpha, beta-Unsaturated Esters

VIII. Further Studies on the Effect of Cuprous Chloride

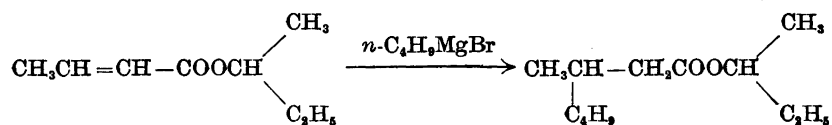
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The yields of 1,4-addition products from *sec*-butyl crotonate and Grignard reagents are improved by cuprous chloride catalysis provided that the catalyst is added to the Grignard reagent in small portions concurrently with the addition of the ester solution, whereas the catalyst has little effect when added in one portion before the ester addition starts (except in the case of methylmagnesium bromide). This and other evidence for a limited life time of cuprous chloride in the Grignard reagent solution is presented.

Certain problems relating to the reactivities of crotonic, tiglic and cinnamic esters are considered.

In previous communications the effect of cuprous chloride in promoting 1,4-addition of Grignard reagents to α,β -unsaturated esters has been discussed, *e.g.* the reaction of *n*-butylmagnesium bromide with *sec*-butyl crotonate:



It was first thought¹ that this catalyst was essential to secure any reasonable yield of conjugate addition product, even with *sec*-butyl esters, the use of which effectively prevents addition to the carbonyl group. Later it was found that the results of the first paper could not be reproduced in all cases, and a reinvestigation² led to a somewhat different procedure according to which the use of cuprous chloride was abandoned. The use of *sec*-butyl esters and a somewhat larger excess of Grignard reagent were proved to be sufficient conditions for a generally applicable procedure, although the yield of *sec*-butyl 3-methylheptanoate from *sec*-butyl crotonate and *n*-butylmagnesium bromide by the new procedure (70–75 %) was not quite so high as that originally obtained by the cuprous chloride method. The reason for the non-reproducibility of the original procedure was not found.

In later work again, cuprous chloride has been found to exert a strong influence in certain other cases. Thus, the reaction of methylmagnesium bromide resulted in 1,4-addition only when cuprous chloride had been added to the Grignard reagent prior to the ester³, and it was found that even ethyl⁴ and methyl¹ crotonate with *n*-butylmagnesium bromide in the presence of cuprous chloride gave 1,4-addition products in good yields, although in the latter case a secondary acetoacetic ester condensation took place. In the case of acetylenic esters cuprous chloride is able to bring about a complete change in orientation from 1,2- to 1,4-addition⁵.

Recently cuprous chloride was found to catalyze reduction of the double bonds of citraconic and mesaconic esters in competition with conjugate addition of *n*-butylmagnesium bromide⁶. A suggestion concerning the possible mode of action of cuprous chloride was advanced, the essentials of which were a) the formation of a cuprous alkyl from cuprous chloride and the Grignard reagent according to Gilman⁷:



and b) the coordination of the cuprous ion from the cuprous alkyl with the ethylenic α -carbon atom of the α,β -unsaturated ester, combined with the concept of a cyclic electron shift operating within a six-membered ring. These ideas, which appear to be quite useful in explaining the effects of cuprous chloride in the work of this series, will be further set out in a forthcoming publication⁸ (p. 282–283).

The purpose of this communication is to report some experiments which have been carried out as a consequence of the above-mentioned considerations.

It has long since been realized that when cuprous chloride is added to the Grignard reagent (*e.g.*, *n*-butylmagnesium bromide) in ether solution at 0°, a black precipitate appears, generally after 10–15 min. Presumably copper is formed according to the following equation⁷:



In order to test this assumption an experiment was carried out, in which an excessively large amount of cuprous chloride was used.

In a run with 0.4 mole (56.8 g) of *sec*-butyl crotonate the Grignard reagent was prepared from 1.25 g-atom of magnesium and 1.56 mole of *n*-butyl bromide (as compared with 1.0 g-atom and 1.3 mole, resp. in the usual runs².) The Grignard solution was cooled in an ice-salt bath for 15 min. Cuprous chloride was added gradually in small portions from a small flask, connected with one of the side-necks of the reaction vessel. A total of 36.4 g (0.36 mole, 25 mole per cent with respect to the Grignard reagent) was added during about 30 min. After approximately one fourth of the amount of cuprous chloride had been added a vigorous reaction set in with evolution of enough heat to cause the ether to boil violently, mercury thereby being blown out of the mercury seal. Immediately the reaction mixture acquired a shiny red colour and a black precipitate formed. The rest of the cuprous chloride could now be added without any further vigorous reaction. The ester was then added during 3 h as previously described, but the yield of 1,4-addition product was only 28 %

The black precipitate, which was filtered from the reaction mixture before this was worked up, was almost certainly copper, since it became warm on exposure to the air and gained in weight. It dissolved in nitric but not in hydrochloric acid. When boiled with the latter acid the precipitate turned red.

Table 1. Yields of conjugate addition products from Grignard reagents and *sec*-butyl esters of α,β -unsaturated esters. Unless otherwise indicated, product data are published previously ¹⁻³.

| α,β -Unsaturated <i>sec</i> -butyl ester | Grignard reagent RMgBr R | Product: <i>sec</i> -butyl ester | Temp. °C | Yield % | | |
|---|---|---------------------------------------|----------|-------------|------------------|-----------------------|
| | | | | no catalyst | CuCl one portion | CuCl small portions |
| Crotonic | $n\text{-C}_4\text{H}_9$ | 3-methylheptanoic | 0 | 70-75 | 70-75 | 80-85 |
| » | C_2H_5 | 3-methylvaleric | 0 -10 | 78 | 56 ^a | 79 |
| » | $n\text{-C}_3\text{H}_7$ | 3-methylhexanoic ^b | 0 -10 | 60-66 | 56-59 65 | 69-74 88 |
| » | <i>iso</i> - C_3H_7 | 3,4-dimethylvaleric | 0 -10 | 51-57 | 58 71 | 64-71 80 |
| » | <i>tert</i> - C_4H_9 ^c | 3,4,4-trimethylvaleric | 0 -10 | 14 | 14 15 | 27 48 ^d |
| » | CH_3 | <i>iso</i> valeric | -10 | 0 | 51-59 | 61-65 |
| Tiglic | $n\text{-C}_4\text{H}_9$ | 2,3-dimethylheptanoic | 0 | 70 | 50 ^e | 55 |
| » | CH_3 | 3,4-dimethylpentan-2-one ^f | -10 | 0 | 63 | 65 ^g |
| Cinnamic | $n\text{-C}_4\text{H}_9$ | 3-phenylheptanoic | 0 | 36 | 42 | 50 |
| » | CH_3 | 4-phenylpentan-2-one ^f | -10 | 0 | 51 | 49 |
| Sorbic ^h | $n\text{-C}_4\text{H}_9$ | <i>n</i> -butylhexenoic ^h | 0 | 30-40 | 30-58 | 72 |

^aRef.¹; the excess of Grignard reagent was 25 % only. ^bThe data for this ester are given in Ref.¹¹ (p. 298). ^c*tert*-Butylmagnesium chloride was used. ^dThis yield has been further improved by using a larger excess of Grignard reagent ¹¹. ^eThe previously reported ¹ complete failure of this conjugate addition has been found erroneous. ^f1,2 + 1,4-addition product = saturated ketone. ^gYield corrected for 19 % recovered unreacted *sec*-butyl tiglate. The reaction mixture was stirred for 2.5 h at room temperature, while in the one-portion reaction it was left over-night ³. ^hMixture of isomers ³.

This experiment lends support to the idea that cuprous chloride as such has a limited life time in the Grignard reagent solution. Previously it has been found ¹ that this "coupling" reaction takes place much more readily with the

lower Grignard reagents such as methyl- and ethylmagnesium bromide than with *n*-butylmagnesium bromide, and in order to secure a catalytic effect of cuprous chloride towards these two Grignard reagents it is, therefore, necessary to cool the reaction mixture in ice-salt (-8 to -15°). It has now been found (*cf.* Table 1) that strong cooling also is favourable in the cases of *n*-propyl- and *isopropylmagnesium bromides* as well as *tert*-butylmagnesium chloride. With *n*-butylmagnesium bromide (and higher alkylmagnesium bromides), on the other hand, the coupling reaction takes place instantaneously at room temperature, but at 0° it is sufficiently delayed to render a catalytic effect possible. These observations are in accordance with the findings of Gilman ⁷ that cuprous-organic compounds are formed according to (1) and will decompose according to (2), and that the lower cuprous alkyls are very unstable; no comparison between the stabilities of lower and higher cuprous alkyls was, however, reported.

An investigation has now been carried out to see whether the catalytic effect of cuprous chloride (with respect to 1,4-addition) was improved by adding it in small portions at regular intervals during the addition of the ester to the Grignard reagent rather than adding it in one portion before the ester.

In the case of *sec*-butyl crotonate this was indeed the case (Table 1).

As in the standard procedure² the Grignard reagent was prepared from 25 g (1.04 g-atom) of magnesium and 178 g (1.30 mole) of *n*-butyl bromide in 300 ml of ether. Likewise the ester (0.4 mole) dissolved in 400 ml of ether was then added over 3 h to the cooled (*cf.* Table 1) Grignard reagent. Cuprous chloride was used in the following way: 1.4 g of cuprous chloride (1.4 mole per cent with respect to the Grignard reagent) was added, concurrently with the ester, in 0.2 g portions at half-hourly intervals, the first portion being added just before ester addition and the last one just after. Commercial cuprous chloride (E. Merck, Darmstadt, Germany, *p.a.*) was used without previous reduction or drying.

The yield, which is around 70–75 % in the uncatalyzed reaction and is unaffected by cuprous chloride added all at once ², is, by portion-wise addition of cuprous chloride, increased by at least 10 % to 80–85 %.

Under these conditions the yield with ethyl crotonate was only 70 %, being the same as when cuprous chloride was added in one portion ⁴.

It should be mentioned that the so-called "inverse" addition of the Grignard reagent to the ester solution containing the cuprous chloride (*cf.* Ref.⁶) results in the formation of a non-distillable oil and only 2–3 % of 1,4-addition product. A similar result was previously obtained with citraconic ester ⁶, and it appears as if the "inverse" addition procedure is of value only in the case of alkylidene-cyanoacetic and -malonic esters ^{6,8}.

In the case of *sec*-butyl tiglate, however, no increase in the yield of 1,4-addition product with *n*-butylmagnesium bromide has been obtained. On the contrary, some drop in yield as compared with the uncatalyzed reaction was encountered. The reason for the inhibitory effect of cuprous chloride in this case is not clear, and since the by-products actually produced have not, so far, been investigated, any comment on this point would be of little value.

In the uncatalyzed reaction of *sec*-butyl cinnamate with *n*-butylmagnesium bromide we have been unable to reproduce the previously reported ³ yield (52 %). The reason

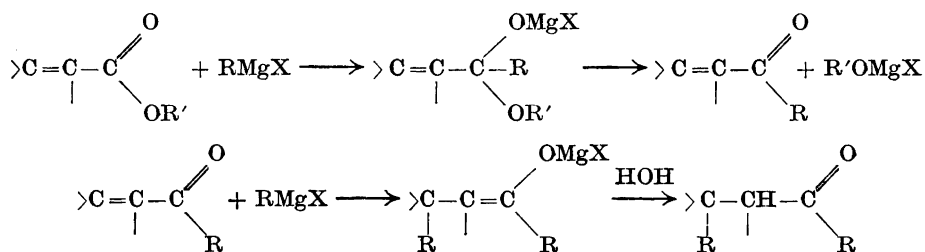
for this has not yet been found. The favourable effect of cuprous chloride on the yield in this case appears, however, to be established. Considerable amounts of the condensation-addition product, analogous to that described from the reaction with crotonic ester¹ were obtained in all reactions with cinnamic ester, but when cuprous chloride was added in small portions the yield of simple 1,4-addition product was 50 % as compared to 36 % in the uncatalyzed reaction.

The results with *sec*-butyl sorbate, which support the views here presented, are described in the following paper of this series⁸ (p. 277).

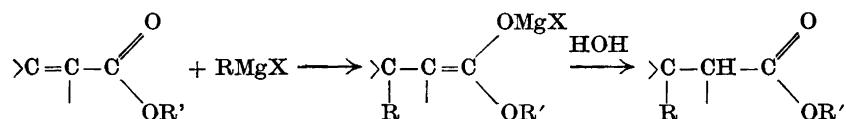
Reactions involving methylmagnesium bromide lead to conjugate addition, only when cuprous chloride is present and the reaction mixture is cooled in ice-salt during the addition of the ester³; otherwise 1,2-addition takes place and no conjugate addition products are formed. With tiglic and cinnamic esters, however, the cuprous chloride catalyzed conjugate addition does not, as with crotonic ester, result in *simple* 1,4-addition; 1,2-addition occurs as well, and the products are saturated ketones³. In these reactions of methylmagnesium bromide the step-wise addition of cuprous chloride hardly offers any advantage over the one-portion addition method.

In the addition of ethylmagnesium bromide to *sec*-butyl crotonate the uncatalyzed reaction (at 0°) gives as high a yield (78 %) as does the cuprous chloride catalyzed reaction (cooled in ice-salt). Apparently, here the 1,2-addition is no serious side-reaction, and the low stability of the cuprous alkyl in this case prevents its catalytic effect to improve the yield of simple 1,4-addition product over that obtained in the uncatalyzed reaction.

The reactions with methylmagnesium bromide are of interest in other respects. The results with tiglic and cinnamic esters raise the question as to which one of the two addition types (1,2 or 1,4) takes place first. Most likely the saturated ketone is the result of a primary 1,2-addition followed by a subsequent 1,4-addition to the α,β -unsaturated ketone¹⁰:



The two addition reactions may thus both occur in the ethereal reaction mixture, whereas the reverse order of addition: a primary 1,4-addition followed by a 1,2-addition to the carbonyl group of the saturated ester could hardly be visualized as taking place:



since the primary addition product must be hydrolyzed before being able to undergo 1,2-addition.

This implies that tiglic and cinnamic esters are less reactive than crotonic ester towards 1,4-addition, since this addition occurs in good yield in the latter case, but does not take place in the former case unless the α,β -unsaturated ester is first transformed into the more reactive α,β -unsaturated ketone. Since none of this ketone has ever been obtained, the 1,4-addition to the ketone must be rapid compared to the primary 1,2-addition to the ester.

Further evidence for these ideas is found in the fact that *sec*-butyl tiglate, in contrast to both *sec*-butyl crotonate and ethyl tiglate, did not give complete reaction by stirring for two hours at room temperature after the addition of the ester, but had to stand overnight; otherwise unreacted ester was recovered.

The authors are indebted to *Otto Mønstedts Fond* for financial support.

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Received September 27, 1960.