

Conjugate Additions of Grignard Reagents to α , β -Unsaturated Esters

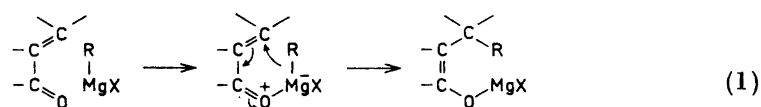
XII. Some Experiments Related to the Mechanism with Reference to the Grignard Reagent Structure *

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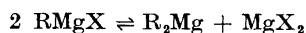
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The presence of an excess of magnesium bromide decreases the yield of simple conjugate addition product from the reaction between *sec*-butyl crotonate and the Grignard reagent from butyl bromide. The use of dibutylmagnesium instead of the Grignard reagent results in an increased yield. These results are in agreement with current views concerning the structure of the Grignard reagent as well as with the cyclic mechanisms generally accepted for the Grignard reactions.

The mechanism for the conjugate addition of Grignard reagents to α , β -unsaturated carbonyl compounds is commonly considered to involve the coordination of the Grignard reagent magnesium with the carbonyl oxygen, followed by a cyclic synchronous electron shift within a six-membered ring transition state ^{1a}:

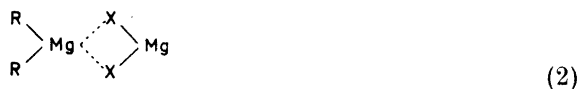


It has, however, become increasingly clear that the formula RMgX cannot correctly represent the Grignard reagent, and even the equilibrium proposed by Schlenk and Schlenk ²:

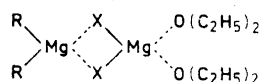


* A preliminary report of this work has been published previously ¹.

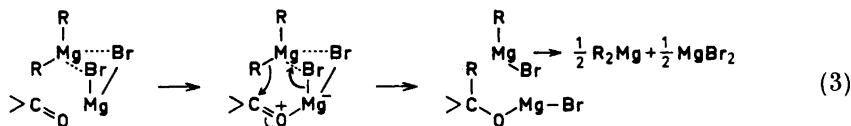
has been made improbable by the conclusive evidence offered by Dessy *et al.*³, that very little, if any, exchange of magnesium takes place in a Grignard reagent prepared from R_2Mg and $^{28}MgBr_2$. On this and other evidence which has recently been reviewed and discussed by Hamelin⁴ and by Mosher *et al.*⁵ the following formulation has been put forward and appears reasonable:



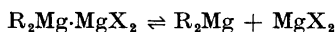
or rather some coordination complex of it with molecules of ether, such as



Such a structure for the Grignard reagent renders possible the following mechanism for the addition to a carbonyl group (Hamelin,⁴ Mosher⁵):

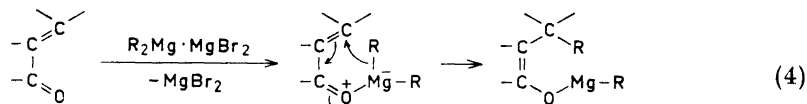


This mechanism appears more satisfactory than the mechanism proposed by Swain^{6,7} involving two molecules of alkylmagnesium halide. Swain and Boyles⁷ demonstrated that the presence of an excess of magnesium bromide favours the addition process in competition with the reduction in cases when the addition process is hindered. This effect of magnesium bromide has been considered as supporting evidence for the Swain mechanism, but it is, in fact, just as satisfactorily explained by the above mechanism (3) (*cf.* Hamelin⁴), provided the Schlenk equilibrium is formulated as suggested by Dessy³:



On the other hand, according to this theory, dialkylmagnesium might be expected to be less reactive in the carbonyl addition than the Grignard reagent, since in this case either a transition state with two molecules of dialkylmagnesium, analogous to that of the Swain mechanism, or a four-membered ring transition state should be involved. Both of these should be less favourable than (3). Furthermore, only one of the two alkyl groups of the dialkylmagnesium could be utilized in the addition, since the other alkyl is "lost" as it remains attached to the magnesium atom in the resulting magnesium alcoholate. Evidence for these ideas have indeed emerged from the extensive work on addition reactions of dialkylmagnesiums to ketones recently reported,^{5,8,9} although the situation here does not appear so clear as in the case of the Swain magnesium bromide effect.

The mechanism of the conjugate addition to an α,β -unsaturated carbonyl compound (*cf.* (1), above) should — in contrast to the "normal" 1,2-addition to a carbonyl group — involve only the dialkylmagnesium moiety of the Grignard reagent:



This implies that the reaction should begin with the displacement of the magnesium halide from the Grignard reagent, the magnesium atom of the dialkylmagnesium this time being the one with which the carbonyl oxygen forms a coordinative bond, since otherwise 1,2-addition would take place. Consequently, one should here expect a "negative Swain effect", *i.e.* the addition of an excess of magnesium bromide should impede the conjugate addition. On the other hand, previous removal of magnesium bromide, *i.e.* the use of dialkylmagnesium instead of Grignard reagent, should favour the conjugate addition.

In the present work both of these predictions have been fulfilled. The presence of excess of magnesium bromide (one equivalent with respect of the Grignard reagent) decreases the yield of simple conjugate addition product

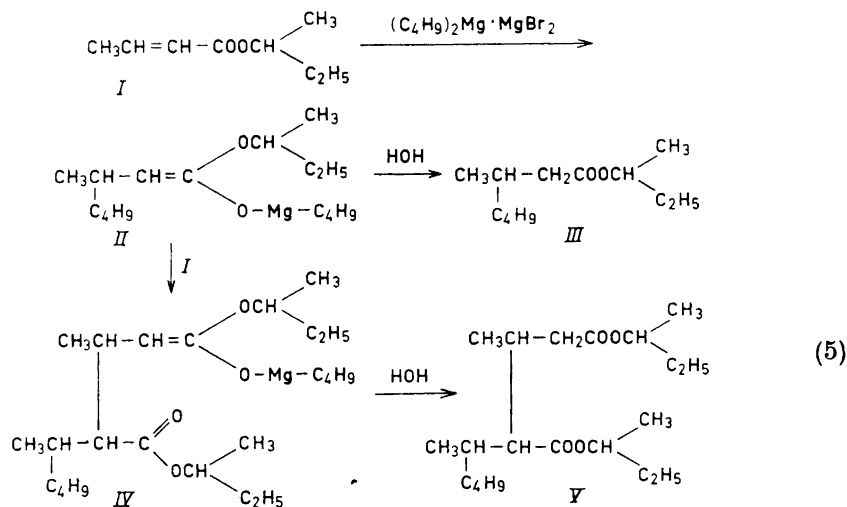
Table 1. Yields of simple conjugate addition product (*sec*-butyl 3-methylheptanoate) from the reactions of *sec*-butyl crotonate with various butylmagnesium compounds.

Butylmagnesium compound R = C ₄ H ₉		Amount of <i>sec</i> -butyl crotonate mole	Moles of butyl- magnesium compound to 1 mole of ester	Yield of <i>sec</i> -butyl 3-methyl- heptanoate %
Type	Quantity mole			
"RMgBr"	1.25	0.2	6.25	75–78
"RMgBr"	0.5	0.2	2.5	75–78
"RMgBr"	0.3	0.2	1.5	30–50
"RMgBr" + MgBr ₂	0.5 + 0.5	0.2	2.5	50
R ₂ Mg	0.44	0.17	2.5	86–88
R ₂ Mg	0.24	0.15	1.6	87
R ₂ Mg	0.225	0.16	1.4	84
R ₂ Mg	0.265	0.21	1.25	72

"RMgBr" means ordinary Grignard reagent from magnesium turnings and butyl bromide.

from 75–78 % to about 50 %, while the yield is increased to 86–88 % if dialkylmagnesium is used instead of the Grignard reagent (Table 1).

We have used the reaction of *sec*-butyl crotonate with the Grignard reagent from butyl bromide as the standard, since this particular process has previously been worked out to a reliable procedure rendering a yield reproducible within a narrow percentage range, when the right conditions are fulfilled^{10,11}. The yield could be taken as a measure of reactivity since it is very sensitive to the competing formation of the by-product (V, below), previously described,¹² which is now believed¹³ to be formed by the Michael addition of the magnesium enolate of the simple conjugate addition product (II, below) to another molecule of crotonic ester (I). This means that the Grignard reagent and the magnesium enolate are competing for the crotonic ester, and any impairment of conditions for the conjugate addition of the Grignard reagent will result in a lowered yield of *sec*-butyl 3-methylheptanoate (III):



The observation previously made,¹⁰ that the maximum yield of simple conjugate addition product (3-methylheptanoic ester, III) is obtained when 2.5 equivalents of Grignard reagent to one equivalent of crotonic ester is employed, is consistent with the above mechanism (4), since — like in the carbonyl addition reaction with dialkylmagnesium, mentioned above — only one of the two alkyl groups of the dialkylmagnesium is utilized for the conjugate addition. The other alkyl group stays with the magnesium atom, participating in the formation of an alkylmagnesium enolate of the ester, and is thereby lost by the subsequent hydrolysis of the reaction mixture.

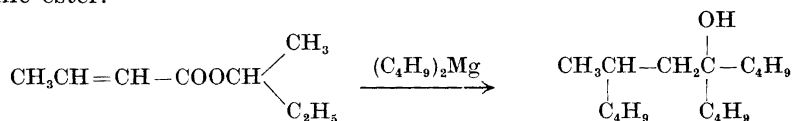
On the other hand, 2.5 equivalents of Grignard reagent corresponds to only 1.25 mole of dialkylmagnesium, and, accordingly, this amount of dialkylmagnesium should be sufficient to secure the maximum yield. We have verified, that whereas only a moderate yield (30–50 %) is obtained when 1.5 equivalent of Grignard reagent is employed, the maximum yield (84 %) is obtained when 1.4 equivalent of dibutylmagnesium is used.

The reason for the decrease in yield (to 72 %, *cf.* Table 1), when 0.125 mole of dibutylmagnesium is used instead of 0.14 mole, is the much larger extent to which the dibutylmagnesium reacts with atmospheric oxygen during the lengthy and laborious preparation of this organometallic reagent as compared to the Grignard reagent. When correction is made for this side-reaction on the basis of the butanol formed, the actual amount of dibutylmagnesium, available for reaction with the crotonic ester, is found to be considerably smaller than that indicated by the titration of the dibutylmagnesium solution.

The apparent necessity of using at least two equivalents of Grignard reagent should probably be considered an essential point in the argument concerning the structure of the Grignard reagent. The magnesium bromide effect alone is no evidence against the structure RMgX . This effect might, in a similar way as the Swain magnesium bromide effect, also be explained simply by the strong coordination of magnesium bromide with carbonyl oxygen, as the coordination of the Grignard reagent RMgX , necessary to the conjugate addition according to the cyclic mechanism, is thereby being hindered.

It should also be noted that the presence of an excess of magnesium bromide does not result in the formation of increased amounts of 1,2-addition products, which might have been expected from the mechanism (3). This fact, however, is not so surprising, since the 1,2-addition never occurs to any appreciable extent with *sec*-butyl crotonate (*cf.* below). The main side-reaction with this ester is the above-mentioned Michael addition (5).

From the reactions with dibutylmagnesium none or only a trace of the Michael addition product V was found. On the other hand, a small yield (5%) of the saturated tertiary alcohol 5-butyl-7-methylundecan-5-ol was obtained. This would be the reaction product from one 1,4- and two 1,2-additions to crotonic ester:



The formation of this compound is rather remarkable, since no *saturated* tertiary alcohol has ever been encountered by us in conjugate additions.* Furthermore, the very fact that *sec*-butyl crotonate does at all undergo 1,2-additions to form a tertiary alcohol has not previously been observed with the butyl Grignard reagent. One might suggest, that the saturated tertiary alcohol is formed from the crotonic ester by a two-step process, both steps being unique for the dibutylmagnesium at variance from the Grignard reagent. The first step is the formation of the unsaturated tertiary alcohol by two 1,2-additions, this reaction type being facilitated by the lower *steric* requirements of the dialkylmagnesium as compared to the Grignard reagent (2). The second step is brought about by the reactivity of dialkylmagnesiums towards unconjugated double bonds, practically unknown for Grignard reagents¹⁴.

* It should be noted, that the formation of a saturated tertiary alcohol during a conjugate addition reaction has recently been reported by Fuson *et al.*^{13a} who, however, offer an alternative explanation for this side-reaction.

EXPERIMENTAL

Fractional distillations were carried out in a simple 45 cm \times 8 mm Podbielniak type column with a tantalum wire spiral, a heated jacket and a partial reflux head.

All products were checked or/and analyzed by gas chromatography in a Perkin-Elmer fractometer No. 116 E. The infra-red spectrophotometer used was the Perkin-Elmer Infracord, model 137.

The standard conjugate addition reaction using the Grignard reagent was carried out (uncatalyzed) as previously described,¹⁰ *sec*-butyl crotonate (0.2 mole), dissolved in 200 ml of ether, being added, over a period of 90 min, to the ice-cooled Grignard reagent from 0.52 g-atoms of magnesium turnings and 0.65 mole of butyl bromide.

Magnesium bromide was prepared in ether solution, essentially as described by Rowley.¹⁵ To 12.5 g (0.52 g-atoms) of magnesium turnings suspended in 200 ml of ether was added dropwise during 1 h, with cooling in ice-water, 80 g (0.5 mole) of bromine. Reflux of the ether took place, and after the addition was complete the solution was boiled under reflux for another 2 h. To this solution, cooled to room temperature, was added 0.2 mole of *sec*-butyl crotonate, the mixture stirred for 15 min, and the resulting solution (instead of a solution of ester in pure ether) was used as the ester solution in the addition reactions, which — except for the excess of magnesium bromide — were carried out exactly as in the standard addition procedure mentioned above.¹⁰

Dibutylmagnesium was obtained as an ether solution in the following way, essentially as described by Wotiz *et al.*¹⁶ Dioxane was dried, either with butyl Grignard reagent until no further reaction with water took place or by reflux over sodium metal for 24 h; the dioxane was subsequently distilled directly from the drying agent. The Grignard reagent (1.0 mole) was prepared from magnesium turnings (26.4 g, 1.1 g-atom) in ether (30 ml) to which was added butyl bromide (137 g, 1.0 mole) dissolved in ether (300 ml). The resulting Grignard reagent solution was cooled for 15 min in ice-water. Then a mixture of dry dioxane (117 g, 1.3 mole) and ether (100 ml) was added, during 1 h, with stirring. A thick slurry of magnesium bromide was precipitated. The mixture was stirred overnight at room temperature. The pasty mixture was centrifuged for 7 h at 2700 rpm., a clear supernatant solution being produced. The yield, determined by titration with hydrochloric acid was about 0.22 mole of dibutylmagnesium (44 %) dissolved in about 0.5 l of solvent (mainly ether). This solution was concentrated by distillation to about 125 ml, and to two or one such portion of dibutylmagnesium solution the ester solution was added in exactly the same way as in the standard addition procedure with the Grignard reagent, mentioned above.¹⁰ The results are summarized in Table I.

The simple conjugate addition product was of the same purity in all three cases. It contained about 97–98 % *sec*-3-methylheptanoate, and 2–3 % 7-methylundecan-5-one,¹⁷ (formed by one 1,2-addition followed by 1,4-addition to the resulting α,β -unsaturated ketone). The higher-boiling product from the normal Grignard addition consists essentially of the above-mentioned Michael addition product V.

From the magnesium bromide reaction a much larger amount of high-boiling product was obtained. Most of this (about 3/4) was the Michael addition product V, but, besides, appreciable amounts of other, mostly unknown, compounds were detected; these are only present as traces in the product from the normal Grignard addition. The most predominant of these other by-products is di-*sec*-butyl α -ethyl- β -methylglutarate,¹⁸ presumably formed by the Michael addition of *sec*-butyl butyrate to *sec*-butyl crotonate, the former ester being the hydrogenation product of the latter. This reduction process has previously been encountered in the Grignard reaction with esters of certain dibasic unsaturated esters,¹⁹ and recently also with crotonic ester under certain special conditions.¹⁸

The small quantity of high-boiling product from the dibutylmagnesium reaction was almost entirely one single substance, b.p. 90–92.5/0.3 mm, n_D^{25} 1.4471 (Found: C 78.80; H 13.60). This compound was identified by comparison of infra-red spectra and by gas chromatography to be 5-butyl-7-methylundecan-5-ol, *i.e.* the tertiary alcohol 2-methylhexyldibutylcarbinol. This alcohol was synthesized in 73 % yield by the reaction between methyl 3-methylheptanoate²⁰ and butyl Grignard reagent, essentially as described for methylphenylcarbinol in *Organic Syntheses*²¹. The product had the b.p. 91°/0.3 mm, n_D^{20} 1.4492 (Found: C 79.30; H 13.85. Calc. for C₁₈H₃₄O (242.43): C 79.26; H 14.14).

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