

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

X. Possible Influence of the Halogen in the Grignard Reagent

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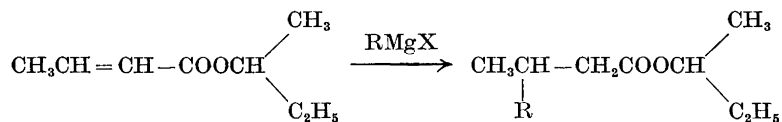
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The yields of simple conjugate addition products from *sec*-butyl crotonate and alkylmagnesium halides decrease in the sequence $\text{Cl} \geq \text{Br} \gg \text{I}$. In the cuprous chloride catalyzed reaction the yields from the three halides are equal and the same as those from the chlorides in the uncatalyzed reaction (about 80–85 %). Improvements of the preparative procedure for 3-methylalkanoic acids have been attained in certain cases. Thus, from *tert*-butylmagnesium chloride a 78 % yield of β,γ,γ -trimethylvaleric ester has been obtained.

In most discussions of reactions involving Grignard reagents the significance of the halogen is largely neglected. The relative reactivities of the different halides ($\text{I} > \text{Br} > \text{Cl}$) in the *preparation* of the Grignard reagents are well-known, and this knowledge suitably coupled with considerations of availability and ease of handling of the halides and of the alkylmagnesium halides is usually decisive for the choice of the Grignard reagent. Thus, in series of Grignard reagents investigated, most halides employed are bromides, but as the methylmagnesium halide the iodide is often used and as the *tert*-butyl- and benzylmagnesium halides the chlorides.

However, it appears to be a widely accepted implicit assumption that the opposite sequence: $\text{Cl} > \text{Br} > \text{I}$ holds true for the reactivities of the Grignard reagents¹.

The present paper describes the results of conjugate additions of some alkylmagnesium halides to *sec*-butyl crotonate under conditions which have previously^{2,3} been found favourable for 1,4-addition of alkylmagnesium bromides;

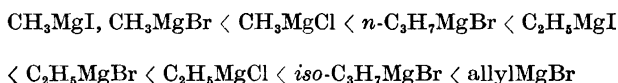


The reactions were carried out by the slow addition of the ester to an excess of cooled Grignard reagent, uncatalyzed² as well as cuprous chloride catalyzed³, the catalyst being applied in small portions throughout the addition of the ester.

It is seen (Tables 1 and 2) that the bromides are quite satisfactory as compared to the other two halides, and, all circumstances considered, probably would be the preferred halides in many cases. Although alkylmagnesium chlorides may give better yields (and cuprous chloride catalysis is rendered unnecessary), the alkyl chlorides are less reactive towards magnesium and the preparation of the Grignard reagents from them is, therefore, somewhat more troublesome. In case of the lower alkyls the alkyl chlorides also have the disadvantage of being very low boiling. The alkylmagnesium chlorides are, furthermore, considerably less soluble in ether, a fact which with *tert*-butyl- and methylmagnesium chlorides causes the reaction mixture to become heterogeneous. The iodides, as represented by *n*-butyl-, *n*-propyl- and methylmagnesium iodides, are definitely inferior to the other two halides.

Naturally, an evaluation of the effect of variations in the halogen moiety on a Grignard reagent is difficult. In the first place the extent to which various competing reactions occur should be estimated, and, in the second place, a large number of factors must be considered in the attempted interpretation, such as electronegativities of organic radicals, steric effects, and solubilities of reactants and products.

One of the few accounts in the literature, known to the present authors, which deal with the relative reactivities of alkylmagnesium chlorides, bromides and iodides*, is a paper by Wotiz, Hollingsworth and Dessy⁶, who have determined the rate of extraction of a proton from an alkyne by means of a series of Grignard reagents. These may be arranged according to increasing reactivity as follows:



This sequence indicates that alkylmagnesium chlorides are more reactive than bromides which are again more reactive than iodides, and the results are thus in accordance with the above-mentioned generally assumed reactivity order¹. It should be noted, however, that the differences due to changes in the halogen moiety are smaller than the differences caused by varying the alkyls of the Grignard reagents. In this reaction with alkynes, coordination of the magnesium atom should be insignificant and the steric requirements on the Grignard reagent should be small. Thus the above results may be considered to give the order of nucleophilic reactivities of the Grignard reagents.

However, the general statement that the sequence of the reactivities of the Grignard reagents is the reverse of the sequence of the reactivities of the corresponding halides towards magnesium¹ is apparently not in accordance

* Gilman⁵ also reports decreasing reactivities for the *n*-butylmagnesium halides: Cl > Br > I in the reduction of azobenzene.

with Wotiz' above-mentioned results, this divergence being especially evident in the case of allylmagnesium bromide (*cf.* also below).

In contrast to the above-mentioned reaction of Grignard reagents with alkynes⁷, the addition of Grignard reagents to α,β -unsaturated carbonyl compounds is generally believed to take place according to a mechanism⁸ which involves the primary coordination of magnesium with carbonyl oxygen, followed by a cyclic synchronous electron shift within a six-membered ring, resulting in the transfer of the alkyl group to the β -carbon atom. Therefore, although here again the nucleophilic reactivity of the alkyl group should be of importance, also the electrophilic reactivity of the magnesium atom as well as the spatial properties of the Grignard reagents as a whole may play a significant role. Furthermore, the situation is in this case still more complex. A variety of competing reactions may take place besides the 1,4-addition, *e.g.* 1,2-additions⁹, condensation reactions⁴ and reductions¹⁰, and it is hard to say how the probability of the occurrence of these processes is influenced by the different factors. Again the case of allylmagnesium bromide is illustrative. As mentioned above, its nucleophilic reactivity is found to be exceptionally high. In the reaction with α,β -unsaturated esters, this Grignard reagent gives, exclusively and in high yields, 1,2-addition products under conditions which in the case of other Grignard reagents lead to 1,4-addition only¹¹. Furthermore, addition to the carbonyl group of the so-called "butenyl" Grignard reagent [is taking place with sterically hindered ketones which are reduced by other Grignard reagents¹². The peculiar reactivity of the allylic Grignard reagents is presumably caused by a special mechanism operating^{12,11}.

Also, as mentioned above, the solubilities of the alkylmagnesium halides differ considerably, and this fact may strongly affect the results. Thus methyl-, ethyl- and *tert*-butylmagnesium chlorides are slurries of greyish-white precipitates in ether. Wotiz, Hollingsworth and Dessy⁶ state that such precipitates consist of magnesium chloride. This being true would — according to the Schlenk equilibrium — mean that the metalloorganic compounds in these cases to a much larger extent are dialkylmagnesiums than alkylmagnesium halides (or a complex between dialkylmagnesium and magnesium halide, as recently suggested by Dessy¹³). The former are believed to be less reactive than the latter as regards coordination of magnesium with the carbonyl oxygen¹⁴. Since the above-mentioned mechanism³ involves such a complex formation and since, furthermore, a large excess of Grignard reagent is essential for obtaining high yields of simple 1,4-addition products from α,β -unsaturated esters and Grignard reagents², the relatively lower yields from *tert*-butyl- and methylmagnesium chloride may in part be accounted for on the basis of the low solubility of these Grignard reagents. Especially the strongly improved yield from the soluble *tert*-butylmagnesium bromide indicates that the solubility may be important. Also the significant rise in the yield obtained from the chloride when a greater amount of Grignard reagent is used (see experimental part) could be taken as an evidence that the low solubility causes the excess of Grignard reagent to be too small in the usual procedure to provide favourable conditions for the 1,4-addition. It is consistent with these interpretations that at 0° (*cf.* below), the yield from the soluble *tert*-butylmagnesium bromide is unaffected by such an increase in the quantity of the

Table 1. Additions of Grignard reagents (RMgX) to *sec*-butyl crotonate; % 1,4-addition.

R	Temp. °C	X					
		Cl		Br		I	
		uncat.	CuCl	uncat.	CuCl	uncat.	CuCl
<i>n</i> -C ₄ H ₉	0	85	85	70–75	82–85	45	86
<i>n</i> -C ₃ H ₇	0 –10	86	89	60–66	69–74 88	43	84
<i>iso</i> -C ₃ H ₇ ^a	0 –10	78–82	82–85	51–57	64–71 80		
<i>tert</i> -C ₄ H ₉ ^{a,b}	0	14 (22)	27 (60–78)	50	52 (49)		
	–10		48 (65)	39	62 (78)		
CH ₃	–10	0	55–65	0	61–65	0	27–29

^a *Isopropyl*- and *tert*-butylmagnesium iodides were not included since the yields of Grignard reagents in these cases were so low due to side-reactions that the results of the addition reactions would be of no significance (cf. Ref.¹, p. 32; Tschelinzew, W. *Zhur. Russ. Fiz. Khim. Obshchestva* 36 (1903) 549 [*Chem. Zentr.* 1904 II, 183]). ^b The percentages given in parentheses are the yields obtained by using a greater excess of Grignard reagent (see experimental part).

Grignard reagent used. In the case of *n*-butylmagnesium chloride the reaction mixture remained homogeneous, and because of the greater nucleophilic reactivity of the chloride the yield is somewhat higher (in the uncatalyzed reaction) than when the bromide is used.

In the case of the methylmagnesium halides the insoluble chloride gives the *same* yield of simple 1,4-addition product as does the bromide. The relative solubilities may, as with the *tert*-butylmagnesium halides, be the reason why the chloride does not give *higher* yield than the bromide.

An indication of a steric effect could perhaps be found in the relative amounts of 1,2-addition products in the cases of methylmagnesium chloride and bromide (Table 2). Whereas considerable amounts of 1,2-addition products are formed from the chloride, 1,2-addition takes place only to a negligible degree when the bromide is used. Instead the amounts of polymerization products is correspondingly increased. In the case of the iodide (cf. below) the smaller nucleophilic reactivity seems to influence the 1,4-addition principally, resulting in enhanced polymerization as well as some increase in 1,2-addition.

Table 2. Additions of methylmagnesium halides to *sec*-butyl crotonate at -10° ; yields (%) of 1,2 + 1,4-addition product (methyl *isobutyl* ketone), 1,4-addition product (*sec*-butyl isovalerate) and higher-boiling residue.

Product	CH ₃ MgCl	CH ₃ MgBr	CH ₃ MgI
1,2 + 1,4	11–16	0–5	17–18
1,4	55–65	61–65	29–27
residue	18–20	25–27	48

As to the iodides (*cf.* note^a, Table 1), they are probably less reactive as nucleophilic reagents, and furthermore, the iodine atom may constitute a steric hindrance to 1,4-addition as well as to 1,2-addition. Whereas the catalytic effect of cuprous chloride is strong enough to overcome the decreased reactivity in the cases of *n*-butyl- and *n*-propylmagnesium iodides (*cf.* Table 1), the corresponding methyl reagent is too unreactive, even in the presence of cuprous chloride, to enable the 1,4-addition to compete successfully with the polymerization. A similar result appears to have been found by Hauser *et al.*¹⁵ from the reaction between *tert*-butyl cinnamate and methylmagnesium iodide in refluxing ether. Thus, although these authors were unable to realize appreciable 1,4-addition (in contrast to what was the case in the reaction with phenylmagnesium bromide), they apparently also obtained very low yield of 1,2-addition products; these were not isolated and the yields are not given. Probably mostly polymerization took place*. When, in the present investigation, the reaction between *sec*-butyl crotonate and methylmagnesium iodide** was carried out uncatalyzed (at 0° as well as at -10°) no 1,4-addition product was found, less polymerization took place (16 %), much unreacted ester was recovered (about 20 %), and a mixture of low-boiling compounds was obtained, probably the 1,2-addition products: methyl *isobutyl* ketone and propenyl-dimethylcarbinol, as evidenced by boiling points and refractive indices. The presence of the latter compound was further indicated by the production of water during the distillation.

The effect of cuprous chloride. *n*-Alkylmagnesium chlorides (as well as isopropylmagnesium chloride) give, even in the absence of this catalyst, the maximum yields, whereas these yields are obtained from the corresponding bromides and iodides only when cuprous chloride is present.

With the *n*-propylmagnesium halides, however, it was found that, whereas the cuprous chloride exerts its full effect at 0° towards *n*-propylmagnesium

* In contrast, Kohler¹⁶ reports the formation of considerable amounts of 1,2-addition product (tertiary alcohol) from methyl cinnamate and methylmagnesium iodide, although the yield is not given in this case either.

** Very similar results were encountered with methylmagnesium chloride and bromide.

iodide, this is not the case towards *n*-propylmagnesium bromide unless the reaction mixture is more strongly cooled (to about -10°)³, *cf.* Table 1. This observation is subject to further studies.

The reaction at 0° with *tert*-butylmagnesium chloride is catalyzed by cuprous chloride, whereas the reaction with *tert*-butylmagnesium bromide is not. Also here there is a significant effect of stronger cooling. At the very low temperature also *tert*-butylmagnesium bromide is somewhat insoluble in ether, and positive effects of cuprous chloride as well as of a larger excess of Grignard reagent are indeed observed (*cf.* Table 1).

The methylmagnesium halides give simple conjugate addition products only when the reactions are cuprous chloride catalyzed and carried out at -10° ⁹.

EXPERIMENTAL

Analyses are by Mr. Preben Hansen, Microanalytical Division, The Chemical Laboratory, The University of Copenhagen. Fractional distillations were through a simple 45 cm \times 8 mm Podbielniak type column with a tantalum wire spiral, a heated jacket and a partial reflux head.

Alkyl halides were either commercial products or they were prepared and/or purified according to conventional methods. *tert*-Butyl bromide, b.p. $71-74^{\circ}$, was obtained in 57 % yield according to Norris¹⁷ by distillation of a mixture of *tert*-butyl alcohol and hydrobromic acid.

Grignard reagents. Alkyl bromides and iodides reacted spontaneously with magnesium when the reaction flask, containing the magnesium, had been flushed with dry nitrogen at about 100° for 10 min and during the subsequent cooling to $35-40^{\circ}$. By the preparation of the alkylmagnesium chlorides a small amount of the corresponding alkyl bromide or iodide was sometimes used as an initiator for the reaction.

The conjugate addition reactions were carried out as previously described^{2,3}, generally with 0.2 mole of ester.

The addition of *n*-propylmagnesium halides to *sec*-butyl crotonate has not been described previously. The product is *sec*-butyl 3-methylhexanoate, b.p. $87^{\circ}/12$ mm, n_D^{25} 1.4164. (Found: C 71.00; H 11.94. Calc. for $C_{11}H_{22}O_2$ (186.29): C 70.91; H 11.91.)

The addition reactions with *tert*-butylmagnesium halides were carried out also (*cf.* Table 1) with a much larger excess of Grignard reagent, but otherwise according to the general procedure, except that the magnesium turnings were those from May and Baker (Dagenham, England). These turnings are much more finely cut than those ordinarily used for Grignard reactions, and they have been found especially suited for the preparation of Grignard reagents from very reactive halides (*cf.* Ref.¹¹), in the case of which there is a considerable risk for reaction between the Grignard reagent and unreacted halide. The Grignard reagent for 0.2 mole of ester was prepared by the slow addition of 0.8 mole of the *tert*-butyl halide (dissolved in 400 ml of ether) to 2 g-atoms of magnesium (suspended in 100 ml of ether) under vigorous stirring (*cf.* Ref.¹⁸). The product, *sec*-butyl 3,4,4-trimethylvalerate, b.p. $97-99^{\circ}/14$ mm, n_D^{25} 1.4248 (rep.⁴ b.p. $95^{\circ}/12$ mm, n_D^{25} 1.4231) was obtained in 60-78 % yield, from *tert*-butyl chloride or bromide.

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