Conjugate Additions of Grignard Reagents to alpha,beta-Unsaturated Esters
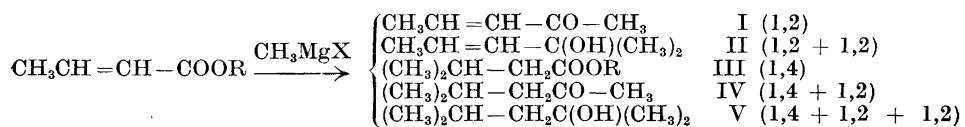
III. Additions of Methylmagnesium Bromide

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The cuprous chloride catalyzed additions of methylmagnesium bromide to *sec*-butyl and ethyl esters of crotonic, tiglic and cinnamic acids and to *sec*-butyl β,β-dimethylacrylate are described. The crotonic esters give simple 1,4-addition products (*iso*valeric esters), whereas the other esters form saturated methyl ketones, resulting from both 1,4-addition and one 1,2-addition. The general features of additions of Grignard reagents to α,β-unsaturated esters are considered.

In principle, addition of a Grignard reagent to an α,β-unsaturated ester may lead to five different products, as the result of one 1,4- and one or two 1,2-additions. From crotonic ester and a methylmagnesium halide the following compounds could thus be formed:
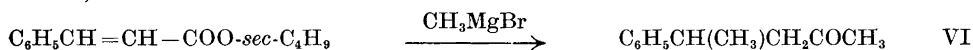
$$CH_3CH=CH-COOR \xrightarrow{\text{CH}_3\text{MgX}} \begin{cases} CH_3CH=CH-CO-CH_3 & \text{I (1,2)} \\ CH_3CH=CH-C(OH)(CH_3)_2 & \text{II (1,2 + 1,2)} \\ (CH_3)_2CH-CH_2COOR & \text{III (1,4)} \\ (CH_3)_2CH-CH_2CO-CH_3 & \text{IV (1,4 + 1,2)} \\ (CH_3)_2CH-CH_2C(OH)(CH_3)_2 & \text{V (1,4 + 1,2 + 1,2)} \end{cases}$$

Methylmagnesium halides are, according to literature, usually added mainly to the carbonyl group of α,β-unsaturated carbonyl compounds, tertiary alcohols (type II) being produced [1-5], although the formation of small amounts of compounds resulting from 1,4-addition has also been reported, *e.g.* ethyl *iso*valerate (type III) (besides crotyldimethylcarbinol) from ethyl crotonate [4] and 3-methylpentanone-2 (type IV) (besides *iso*propenyldimethylcarbinol) from ethyl methacrylate [5].

In 1941, Kharasch and Tawney [6] demonstrated, that, in the case of the α,β-unsaturated cyclic ketone *iso*phorone, they were able to change the direction of addition of methylmagnesium bromide drastically from predominantly 1,2- to almost exclusively 1,4-addition by adding a catalytic amount of cup-

rous chloride. Such an effect of cuprous chloride has more recently been verified by other workers (for further references, see Ref.[3]).

As described in the first paper in this series [3], it was found that when cuprous chloride was present, *sec*-butyl *iso*valerate (III) was formed in 45 % yield by the conjugate addition of methylmagnesium bromide to *sec*-butyl crotonate, and with *sec*-butyl cinnamate this Grignard reagent gave a 40 % yield of 4-phenylpentanone-2 (VI) as a result of both 1,4- and 1,2-addition (*cf*. IV, above). In the second paper [7], however, in which the uncatalyzed 1,4-additions of higher Grignard reagents to *sec*-butyl crotonate and tiglate are described, it was stated that methylmagnesium bromide gives mixtures of compounds which are of little preparative value.

The present paper reports a number of addition reactions of methylmagnesium bromide with some α,β-unsaturated esters. It has been established that a catalyst, such as cuprous chloride must be present in order to secure any great degree of conjugate addition. When *sec*-butyl crotonate or cinnamate react with methylmagnesium bromide under conditions [7] which in the case of higher Grignard reagents lead to good yields of simple 1,4-addition compounds, well-defined substances can not be easily isolated by fractional distillation. The reaction products are mixtures, probably of several of the compounds corresponding to types I—V, as well as the below-mentioned high-boiling condensation-addition compounds and non-distillable polymerisation products from the unsaturated esters. When, however, the addition reactions are carried out in the presence of catalytic amounts of cuprous chloride under cooling in an ice-salt freezing mixture, there are obtained fair to good yields of products (Table 1), which in the case of crotonic ester is the simple 1,4-addition product (III, *iso*valeric ester), but in the case of cinnamic ester, is the above-mentioned saturated methyl ketone (VI), resulting from both 1,4- and 1,2-addition:

$$C_6H_5CH = CH - COO\text{-}\textit{sec}\text{-}C_4H_9 \quad \xrightarrow{\quad CH_3MgBr \quad} \quad C_6H_5CH(CH_3)CH_2COCH_3 \qquad VI$$

Similarly, *sec*-butyl tiglate and *sec*-butyl β,β-dimethylacrylate give the saturated methyl ketones, 3,4-dimethylpentanone-2 (VII) and 4,4-dimethylpentanone-2 (methyl *neo*pentyl ketone, VIII), respectively.

It has further been found that, in this reaction, the ethyl esters give the same products in the same yields as do the *sec*-butyl esters (in the case of crotonic ester, of course, ethyl *iso*-valerate instead of the *sec*-butyl ester is formed).

As mentioned above, the reaction leading to products of type IV consists of one 1,4- and one 1,2-addition, and the question could be asked, as to which one of the two additions takes place first [5,2]. No answer, however, could be given on the basis of the experiments here described, since, in each case, only one of the possible products has been obtained. Probably this sequence differs from case to case, depending on the structure of the ester (and of the Grignard reagent), and the whole problem is thus intimately connected with the influence of the structure on the course of the addition. Investigations of this relationship are in progress.

Table 1. Additions of methylmagnesium bromide to α,β-unsaturated esters in the presence of cuprous chloride.

Ester	Product	Yield %	b. p., °C found	b. p., °C lit.	n_D^{25} found	n_D^{25} lit.
sec-butyl crotonate	sec-butyl isovalerate [a]	51	57/15 mm	100/98 mm [3]	1.4043	1.4075 [3]
ethyl crotonate	ethyl isovalerate	54	134	133.8 [8]	1.3967	1.3975 [8]
sec-butyl tiglate	3,4-dimethyl-pentanone-2, VII [b,g]	63	133−134	136−138 [9]	1.4088 n_D^{14}	1.4129 [9]
ethyl tiglate	3,4-dimethyl-pentanone-2, VII	64				
sec-butyl β,β-dimethyl acrylate	4,4-dimethyl-pentanone-2, VIII [c,g]	33 [d]	124	124−125 [10]	1.4037	1.4018 [10]
sec-butyl cinnamate [3]	4-phenyl-pentanone-2, VI	40 [e]	88.5/1.7 mm		1.5102	
ethyl cinnamate	4-phenyl-pentanone-2, VI [f,g]	77	69/0.8 mm		1.5071	

[a] III (R = sec-butyl); calc. for $C_9H_{18}O_2$ (158.23): sap.equiv. 158.2. Found: 158.1. [b] Calc. for $C_7H_{14}O$ (114.18): C 73.63; H 12.36. Found: C 73.75; H 12.48. [c] Calc. for $C_7H_{14}O$ (114.18): C 73.63; H 12.36. Found: C 73.40; H 12.32. [d] This yield could probably be increased by leaving the reaction mixture over-night in stead of for only 1—2 h, since a large amount (30 %) of unreacted ester was recovered in spite of a great excess of Grignard reagent. [e] This yield could probably be increased, since actually too little Grignard reagent (1.5 equiv.) was used, and a considerable amount (20 %) of unreacted ester was recovered (se Ref. [3]). [f] Calcd. for $C_{11}H_{14}O$ (162.22): C 81.44; H 8.70. Found: C 81.30; H 8.63. [g] Infra-red spectrum shows the presence of a ketone group, and the absence of hydroxyl groups and double bonds.
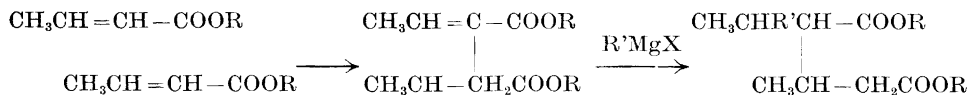
The experimental facts here described, together with the previously reported [3,7] results, seem to indicate the following general picture of the addition of Grignard reagents to α,β-unsaturated esters:

a. Adding ethyl esters to Grignard reagents without special precautions (as Grignard reactions are ordinarily carried out) results mainly in 1,2-additions (to the carbonyl group), tertiary alcohols (of type II) being formed *.

b. By the use of esters with large alcohol moieties, such as sec-butyl esters [3], instead of ethyl esters, 1,2-addition is largely prevented (except with certain Grignard reagents, e.g. methylmagnesium halides). Instead, 1,4-addition takes place, but if special conditions (*c*, below) are not fulfilled, the ester first, to a large extent, dimerizes by a Michael-type condensation to an α-alkylidene-

* One exception is the reaction between ethyl cinnamate and phenylmagnesium bromide, giving predominantly 1,4-addition (β,β-diphenylpropionic ester) [1].

glutaric ester. The Grignard reagent then adds to the α,β-carbon-carbon double bond of this latter ester, so that a high-boiling saturated, substituted glutaric ester is produced:

$$CH_3CH = CH - COOR \qquad CH_3CH = C - COOR \qquad\qquad CH_3CHR'CH - COOR$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad | \qquad\qquad\quad R'MgX$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\longrightarrow$$
$$CH_3CH = CH - COOR \qquad CH_3CH - CH_2COOR \qquad\qquad CH_3CH - CH_2COOR$$

Only minor amounts of the simple conjugate addition product (type III) are formed.

c. The formation of the high-boiling condensation-addition product is suppressed by 1) cooling the Grignard solution during the addition of the ester, 2) diluting the ester solution (with ether) and 3) adding the ester solution slowly. Ordinary Grignard reagents, with the exception af methylmagnesium halides, may in this way give good yields of simple 1,4-addition products (saturated esters of type III)[7]. The reaction thus provides a practical route to 3-methyl-, 2,3-dimethyl- and 3-phenyl-substituted alkanoic acids.

d. The precautions mentioned under c do not prevent 1,2-addition in those cases where such addition takes place in spite of the use of sec-butyl esters, e.g. the Grignard reagent being a methylmagnesium halide.

e. Cuprous chloride has a definitely established effect in promoting 1,4-addition in favor of 1,2-addition.

f. Cuprous chloride has little, if any, effect in preventing the formation of the high-boiling condensation-addition compound [7].

The mode of action of cuprous chloride is still obscure, although it appears likely that some kind of Lewis-acid effect could operate, activating the carbon-carbon double bond [3].

The above-mentioned points c and e suggest that the combination of the conditions mentioned under c with the presence of cuprous chloride should make possible the use of ethyl esters in stead of sec-butyl esters in the simple 1,4-addition process. Preliminary experiments have shown, that n-butylmagnesium bromide with ethyl crotonate in the presence of cuprous chloride gives the 1,4-addition product ethyl 3-methylheptanoate in the same yield (about 70 %) as is obtained with sec-butyl crotonate without catalyst. With ethyl tiglate and cinnamate, however, much lower yields have been obtained. The results of this investigation will be published in a forthcoming paper.

EXPERIMENTAL

Microanalyses are by Mr. Preben Hansen, Microanalytical Division, The Chemical Laboratory, University of Copenhagen. Infra-red spectra were recorded in this laboratory by Mrs. Susanne Refn, M. Sc. Fractional distillations were through a simple 45 cm × 8 mm Podbielniak-type column with a tantalum wire spiral, heated jacket and partial reflux head.

sec-Butyl esters were prepared as previously described [3]. Ethyl crotonate and tiglate were prepared in 80 % yield by the conventional esterification procedure: boiling the acid with excess of ethanol in the presence of concentrated sulfuric acid. Ethyl cinnamate was obtained by the condensation of benzaldehyde with ethyl acetate.

Methyl bromide was either a commercial c. p. product (Fluka, purum) or a technical product (from a steel cylinder), which was purified by passing the gas through sodium hydroxide solution and concentrated sulfuric acid, followed by liquefaction. For weighing it was dissolved in ice-cold ether.

The cuprous chloride catalyzed additions of methylmagnesium bromide were carried out as previously described [3], except that a greater excess of Grignard reagent and a longer addition time for the ester were used. Effective stirring was applied throughout. The methylmagnesium bromide was usually prepared from 6.3 g (0.26 g-atom) of magnesium turnings and 28 to 32 g (about 0.3 mole) of methyl bromide in about 160 ml of ether. The clear solution, after being heated under reflux for 15 min, was cooled in ice-salt for 15 min; 0.25 g of cuprous chloride was added in one portion, and then 0.1 mole of the ester, dissolved in 100 ml of ether, was added dropwise from a graduated dropping funnel during about 1.5 h. During this period the temperature of cooling bath usually rose from about $-18°$ to about $-5°$. Stirring was continued for an additional $10-15$ min at this temperature, then at room temperature for 1 to 2 h. (In the case of tiglic ester this period at room temperature was prolonged overnight, and this should probably also be done with β,β-dimethylacrylic ester in order to obtain maximum yield, *cf.* note[d], Table 1). The reaction mixture was finally poured onto ice and hydrochloric acid and worked up in the conventional way [3].

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