

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

### XI. The Preparation of Alkylsuccinic Acids from Maleic Esters

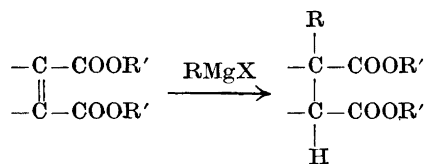
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The addition of various alkylmagnesium halides to maleic esters has been worked out as a practical high-yield route to alkylsuccinic acids, including *tert*-butylsuccinic acid. The reaction of phenylmagnesium bromide to give phenylsuccinic acid failed.

Some general aspects of the reaction are considered.

Several methods for the preparation of substituted succinic acids are described in the literature<sup>1</sup>. One of these, which at first sight should be obviously attractive, is the conjugate addition of an organometallic compound to esters (or other derivatives) of ethylenedicarboxylic acids:



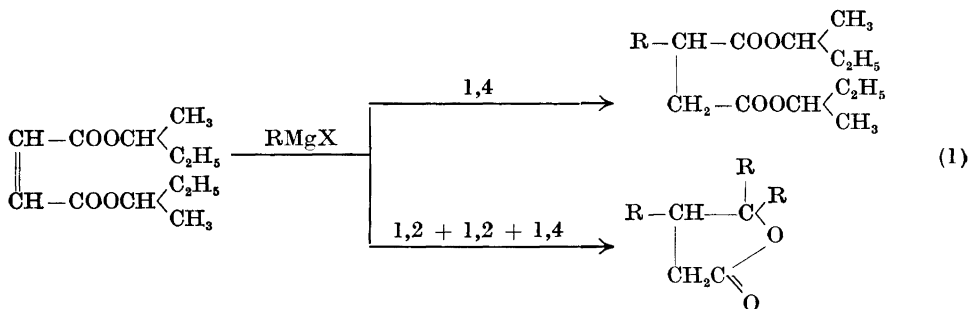
In fact, fair and moderate yields have been reported in many cases from the use of this principle. The results presented in this paper constitute an extension of the work of these earlier investigators. In certain respects substantial improvements have been achieved.

Addition of a Grignard reagent to esters of maleic and fumaric acids has been reported by Marvel *et al.*<sup>2</sup>, who obtained a 30 % yield of isopropylsuccinic ester using isopropylmagnesium bromide. By the use of the cadmium reagent instead of the Grignard reagent a 30 % yield is reported also, but this yield is calculated on the basis of unrecovered maleic ester. Actually, only 19 % of the theoretical amount of isopropylsuccinic ester (based on the amount of starting material used) was obtained. Michael<sup>3</sup> has obtained a 20–25 % yield

of diethyl ethylsuccinate by the action of ethyl iodide and zinc on diethyl fumarate.

On the other hand, Hsing and Li <sup>4</sup>, by using ethylenetetracarboxylic ester, which is readily available <sup>5</sup>, obtained very satisfactory yields of addition products (substituted ethanetetracarboxylic esters) from phenyl-, methyl-, and ethylmagnesium bromides. However, the subsequent transformation of the ethanetetracarboxylic ester into the substituted succinic acid gave only a moderate yield in the case of ethylsuccinic acid, and in the case of methylsuccinic acid the yield was poor. Wideqvist <sup>6</sup> reported the complete failure of the attempted preparation, according to the Hsing and Li procedure <sup>4</sup>, of *tert*-butylsuccinic acid; the only product isolated from the reaction between tetraethyl ethylenetetracarboxylate and *tert*-butylmagnesium bromide was tetraethyl ethanetetracarboxylate, the hydrogenation product of the starting material.

In a previous communication <sup>7</sup> the addition of butylmagnesium bromide to the di-*sec*-butyl esters of maleic and fumaric acids was described. The *sec*-butyl esters were used in order to provide a hindrance to the attack of the Grignard reagent on the ester carbonyl group. Nevertheless considerable amounts of lactone were formed as the results of 1,2-addition as well as 1,4-addition:



This was true in the case of both maleic and fumaric ester, although the yields of both reaction products, and more especially of butylsuccinic ester, were much better from maleic than from fumaric ester. Furthermore, whereas by cuprous chloride catalysis, the yields of this latter product from both the two unsaturated esters were greatly increased, the formation of the lactone was largely suppressed in the case of maleic ester, but not in the case of fumaric ester.

Thus, a satisfactory yield of butylsuccinic ester was indeed obtained from maleic ester, and we have now tried to apply this cuprous chloride catalyzed addition reaction with *sec*-butyl maleate to Grignard reagents other than butylmagnesium bromide. The results are summarized in Tables 1 and 2, which also includes the previously reported <sup>7</sup> result with butylmagnesium bromide.

It is seen that, in the case of alkylmagnesium halides, the reaction provides a satisfactory, general, practical route to alkylsuccinic esters. Of particular interest is the preparation of *tert*-butylsuccinic esters, since the corresponding acid has previously been prepared only by a five-step synthesis from ethyl

cianoacetate, giving an overall yield of 15 % (Wideqvist<sup>6</sup>). We have (from diethyl maleate) obtained a 70 % yield of diethyl *tert*-butylsuccinate, from which the acid was obtained in 91 % yield, giving *tert*-butylsuccinic acid in an overall yield of 64 %. The di-*sec*-butyl ester of *tert*-butylsuccinic acid was obtained in even higher yield, but the isolation of the free acid was in this case troublesome, due to the extremely slow hydrolysis of the ester.

On the other hand, the preparation of phenylsuccinic acid by the addition of phenylmagnesium bromide, which was so successful in the Hsing and Li reaction with ethylenetetracarboxylic ester<sup>4</sup>, failed completely for us, both with di-*sec*-butyl and diethyl maleate. This result will be the subject of further studies.

The formation of lactones appears to be suppressed in the case of the branched-chain Grignard reagents (*tert*-butyl and isopropyl). In these cases, analytically pure alkylsuccinic esters are obtained in high yields, without any indication of a lactone product being formed. On the other hand, with ethyl-, propyl-, and butylmagnesium bromides the yields of alkylsuccinic esters are lower, and some lactone is always formed, even in the presence of cuprous chloride. As indicated by the analyses, the resulting alkylsuccinic esters are, in these cases, actually contaminated with some lactone. The lactones formed from ethyl- and propylmagnesium bromide are lower-boiling than the alkylsuccinic ester, that from butylmagnesium bromide higher-boiling.

These results appear to reveal a general feature of the reaction between Grignard reagents and  $\alpha,\beta$ -unsaturated esters. The following two reactions (illustrated for simplicity with crotonic ester as the example) are both competing with the simple conjugate addition reaction:

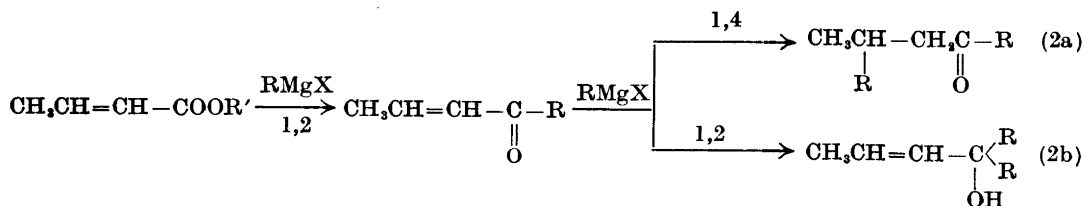
Table 1. Yields of alkylsuccinic esters from the reaction between maleic esters and alkylmagnesium halides.

Maleic ester	Temp. °C	Alkylmagnesium halide					
		ethyl	propyl	isopropyl	butyl	<i>tert</i> -butyl	phenyl
<i>sec</i> -Butyl	0	43 <sup>a,b</sup>		81	67 <sup>e</sup>	78 <sup>f</sup>	0
	-10	57 <sup>c,b</sup>	63 <sup>d</sup>		57 <sup>e</sup>	74 <sup>g</sup>	0
Ethyl	-10			82.5		70 <sup>g</sup>	0

In all cases some non-distillable polymerization product was obtained.

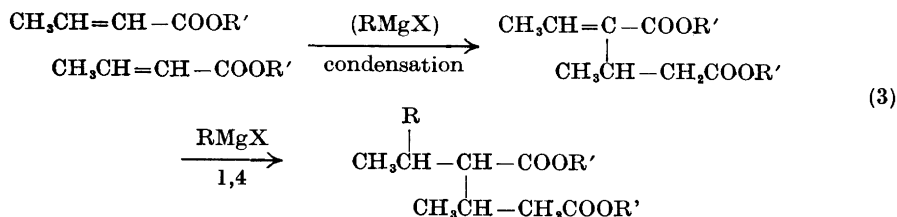
<sup>a</sup> About 25 % lower-boiling lactone was obtained. <sup>b</sup> The lactone was not obtained analytically pure. The first fraction (about one fifth) of the ethylsuccinic ester is probably contaminated with a little lactone. <sup>c</sup> About 10 % lower-boiling lactone was obtained. <sup>d</sup> No lactone was isolated, but the propylsuccinic ester was not entirely pure; cf. Table 2. <sup>e</sup> Very little (6 % or less) higher-boiling lactone was obtained. <sup>f</sup> *tert*-Butylmagnesium bromide (2.5 equiv.) was used. <sup>g</sup> *tert*-Butylmagnesium chloride (0.4 equiv.) was used.

A. A 1,2-addition followed either by a 1,4-addition or by another 1,2-addition:



The lactone formation encountered in the case of maleic esters is the result of reaction (2b) above, followed by the addition of the Grignard reagent to the double bond, which is, in this particular case, conjugated to the second ester group (or lactone carbonyl group), *cf.* eqn. (1).

B. A dimerizing Michael condensation (or even poly-condensation), followed by 1,4-addition of the Grignard reagent to the resulting alkylidene-glutaric ester<sup>8</sup>:



The simple conjugate addition process is, by the presence of cuprous chloride, favoured over both of these two competing reactions. The 1,2-addition (2) is — in contrast to the dimerization-addition reaction (3) — in most cases largely prevented by the use of *sec*-butyl esters, because the carbonyl group then is sterically protected. A similar steric effect should be expected if bulky Grignard reagents are used in the reaction, although in such a case some steric hindrance to the simple conjugate addition might also be anticipated. In fact, previous<sup>8,9</sup> results with different Grignard reagents<sup>8,9</sup> indicate this to be true, since, under conditions which had been found favourable for the simple conjugate addition of *prim*-alkylmagnesium bromides, the yields from isopropyl- and especially *tert*-butylmagnesium halides were low\*, and the dimerization-addition reaction takes place to a much larger extent. On the other hand, in the present reaction and under the conditions chosen, the 1,2-addition (the lactone formation) is the important competing side-reaction. This fact is presumably due partly to the subsequent, energetically favourable cyclisation to a five-membered ring, and partly to the sluggishness with which maleic esters apparently undergo the dimerization reaction. Accordingly, with the *prim*-alkylmagnesium halides the yield of conjugate addition product is decreased because of the 1,2-addition, which takes place to a considerable degree, whereas, in the case of the bulky isopropyl- and *tert*-butylmagnesium halides no trace of lactone was formed, the yields of conjugate addition pro-

\* This difficulty was overcome later by suitable modifications in the procedure, and high yields have been obtained also in these cases<sup>10,11</sup>.



The preparation of di-*sec*-butyl maleate is previously described<sup>7</sup>. The ethyl ester was a commercial product.

The additions were carried out as previously described<sup>7</sup>, except that the cuprous chloride catalyst was added in small portions to the reaction mixture concurrently with the addition of the ester solution<sup>10</sup>. In certain cases cooling in ice-salt has been applied (cf. Table 1).

*The preparation of free alkylsuccinic acids.* The saponification of di-*sec*-butyl butylsuccinate (as well as of the *sec*-butyl esters of the methyl-butylsuccinic acids<sup>7</sup>) has been accomplished previously, using the standard saponification procedure described<sup>8</sup>, involving the boiling of the ester under reflux for 6–8 h with three equivalents of potassium hydroxide in ethanol. Butylsuccinic acid, m.p. 81°, was thus obtained in almost quantitative yield. The saponification of di-*sec*-butyl *tert*-butylsuccinate proved to be considerably more difficult to deal with. After 6–8 h of reflux, the mono-*sec*-butyl ester of *tert*-butylsuccinic acid (being insoluble in water) was obtained in almost quantitative yield. It was an oil which gradually crystallized completely, was washed with water and dried, m.p. 57–58°. The infra-red spectrum indicated the presence of a carbonyl group and a *sec*-butyl ester group<sup>7</sup>. (Found: C 62.75; H 9.89. Calc. for C<sub>12</sub>H<sub>22</sub>O<sub>4</sub> (230.30): C 62.58; H 9.63). On further attempted saponification of the monoester (this time in aqueous solution) slow hydrolysis took place. Even after 12 h still most of the mono-ester was recovered. After another 24 h of saponification only about 20 % of insoluble mono-ester was recovered, and from the filtrate *tert*-butylsuccinic acid, m.p. 128° (cf. below) was obtained in an amount corresponding to almost quantitative yield, continuous extraction with ether for 20 h being applied.

Due to these difficulties encountered in the saponification of the di-*sec*-butyl ester, and to the reactivity considerations discussed above, the additions of isopropylmagnesium bromide and *tert*-butylmagnesium chloride to the diethyl ester of maleic acid were tried, and indeed found successful (Table 1).

Diethyl isopropylsuccinate, b.p. 71°/0.6 mm,  $n_D^{25}$  1.4280 (rep.<sup>2</sup>: b.p. 65°/0.5 mm or 82°/1 mm,  $n_D^{20}$  1.4261; 123–125°/20 mm,  $n_D^{20}$  1.4284; 118–126°/20 mm,  $n_D^{20}$  1.4311).

Diethyl *tert*-butylsuccinate, b.p. 75.5–76.0/0.5 mm,  $n_D^{25}$  1.4321 (Found: C 62.65; H 9.64. Calc. for C<sub>11</sub>H<sub>22</sub>O<sub>4</sub> (230.30): C 62.58; H 9.63).

The saponification of diethyl *tert*-butylsuccinate was carried out without difficulty in the usual way (see above). *tert*-Butylsuccinic acid, which is readily soluble in water, was obtained in 91 % yield by continuous extraction with ether overnight, distillation of the solvent, and recrystallization from water, m.p. 128° (rep.<sup>6</sup> 132°). (Found: C 55.20; H 8.02. Calc. for C<sub>8</sub>H<sub>14</sub>O<sub>4</sub> (174.19): C 55.16; H 8.10).

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