

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

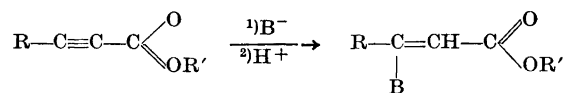
### VII. Additions to Acetylenic Esters

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The reactions of *n*-butylmagnesium bromide with esters of phenylpropionic, tetrolic and acetylenedicarboxylic acids have been investigated. With *sec*-butyl phenylpropiolate and tetrolate conjugate addition takes place if the reaction is catalyzed by cuprous chloride; otherwise tertiary acetylenic alcohols are formed. Diethyl acetylenedicarboxylate gave a small yield of conjugate addition product when the reaction was uncatalyzed and the reaction time very short. The ethyl ester of phenylpropionic acid gave unsatisfactory results. The general reactivity of the triple bond is considered.

Isolated carbon-carbon triple bonds are in general more reactive towards nucleophilic reagents than are double bonds. Thus, alcohols are added, in the presence of the corresponding alkoxides, to alkynes but not to alkenes. Sometimes electrophilic catalysts, such as certain metallic salts, must be present in order to secure addition, *e.g.* the additions of water and hydrogen cyanide to acetylene in the presence of mercuric sulfate and cuprous chloride, respectively. As in the case of the ethylenic bond, a carbonyl group in conjugation with the multiple bond will enhance the reactivity towards nucleophilic reagents and, conversely, reduce the reactivity towards electrophilic reagents. Thus,  $\alpha,\beta$ -acetylenic esters are known to add nucleophilic reagents without the presence of a catalyst:



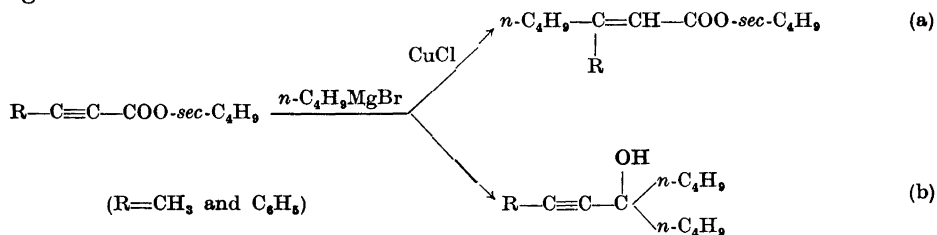
Several Michael-type condensations with malonic and cyanoacetic esters are described in the literature<sup>1</sup> for the cases of phenylpropionic, tetrolic, propionic and acetylenedicarboxylic esters. Other nucleophilic reagents, such as

ammonia <sup>2</sup> and phenylhydrazine <sup>2,3</sup>, have also been added to the triple bond of  $\alpha,\beta$ -acetylenic esters. Recently, the addition of methyl thioglycolate to dimethyl acetylenedicarboxylate has been described <sup>4</sup>. In this, as well as some of the above cases, the primarily formed products undergo further reactions under certain conditions.

Also reactions of Grignard reagents with  $\alpha,\beta$ -acetylenic esters are described in the literature. Wilson and Hyslop <sup>5</sup> found that only normal tertiary alcohols were formed from ethyl phenylpropiolate and methyl- and phenylmagnesium bromides. No yields were reported. Hurd and Cohen <sup>6</sup>, however, were able to obtain the ketone (phenylpropiolophenone) from ethyl phenylpropiolate and phenylmagnesium bromide in 85 % yield. Thus in these as well as in some other cases <sup>7</sup> only 1,2-additions (to the carbonyl group) have been encountered.

With acetylenic ketones Kohler <sup>8</sup> has found that benzoyl-phenylacetylene with phenylmagnesium bromide gives exclusively 1,2-addition under conditions where the corresponding ethylenic compound, benzalacetophenone, gives chiefly 1,4-addition. However, Fuson and Meek <sup>9</sup> have found that with mesityl-phenylacetylene, in which the carbonyl group is sterically hindered, 1,4-addition of methyl- and mesitylmagnesium bromides takes place in good yields, although the yield with phenylmagnesium bromide is only 20 %.

In the present investigation certain  $\alpha,\beta$ -acetylenic esters have been subjected to the action of *n*-butylmagnesium bromide under conditions which have previously been found favourable for conjugate addition to  $\alpha,\beta$ -ethylenic esters, uncatalyzed <sup>10</sup> as well as catalyzed by cuprous chloride <sup>11</sup>. The results are given in Table 1.



In the uncatalyzed reactions (b) *sec*-butyl tetrolate and phenylpropiolate, in contrast to the corresponding ethylenic compounds, do not give conjugate addition products but carbonyl addition products (*i.e.* tertiary alcohols) \*. These results prove the triple bond of acetylenic esters to be less reactive towards Grignard reagents than the double bond in ethylenic esters.

This is in agreement with other evidence that a triple bond to a much less degree than a double bond is able to participate in conjugation with other multiple bonds <sup>12</sup>. For example, the methyl group of ethyl tetrolate does not

\* The yield of tertiary alcohol from phenylpropionic ester (also the ethyl ester, *cf.* below) is diminished by the formation of varying quantities of a lower boiling (106–107°/5 mm) product with higher refractive index ( $n_D^{25}$  1.5392). This compound, which rather quickly turns into a viscous yellow syrup, may be an elimination product from the tertiary alcohol. It contains oxygen, but shows no infra-red absorption for either carbonyl or hydroxyl groups.

Table 1. Type of products and yields from reactions of  $\alpha,\beta$ -acetylenic esters with *n*-butylmagnesium bromide.

	No catalyst	CuCl-catalyst
<i>sec</i> -Butyl phenylpropiolate	Tertiary alcohol <sup>a</sup> (1,2-addition) 28–47 % <sup>b</sup>	Ethylenic ester <sup>c</sup> (1,4-addition) 55 %
Ethyl phenylpropiolate	Tertiary alcohol <sup>a</sup> (1,2-addition) 21–37 % <sup>b</sup>	High-boiling, non-distillable product
<i>sec</i> -Butyl tetrolate	Tertiary alcohol <sup>d</sup> (1,2-addition) 63 %	Ethylenic ester <sup>e</sup> (1,4-addition) 73 %
Di- <i>sec</i> -butyl acetylenedicarboxylate (crude)		High-boiling, non-distillable product. Tar
Diethyl acetylenedicarboxylate <sup>f</sup>	Diethyl di- <i>n</i> -butylsuccinate <sup>g</sup> 15 % Mostly high-boiling residue	High-boiling, non-distillable product <sup>h</sup>

<sup>a</sup> Phenylethynyl-di-*n*-butylcarbinol, b.p. 131°/0.9 mm,  $n_D^{25}$  1.5213. (Found: C 83.50; H 9.69. Calc. for  $C_{17}H_{24}O$  (244.36): C 83.55; H 9.90). <sup>b</sup> cf. foot-note, page 152. <sup>c</sup> *sec*-Butyl  $\beta$ -*n*-butyleinamate, b.p. 124.5°/0.8 mm,  $n_D^{20}$  1.5072. (Found: C 78.40; H 9.19. Calc. for  $C_{17}H_{24}O_2$  (260.36): C 78.42; H 9.29). <sup>d</sup> 1-Propynyl-di-*n*-butylcarbinol, b.p. 108°/11 mm,  $n_D^{20}$  1.4562. (Found: C 79.15; H 12.07. Calc. for  $C_{13}H_{22}O$  (182.30): C 79.06; H 12.16). <sup>e</sup> *sec*-Butyl 3-methylhept-2-enoate ( $\beta$ -*n*-butylcrotonate), b.p. 104–105°/13 mm,  $n_D^{20}$  1.4478. (Found: C 72.65; H 10.96. Calc. for  $C_{12}H_{22}O_2$  (198.30): C 72.68; H 11.18). <sup>f</sup> Ester added during  $\frac{1}{2}$  h only, and worked up immediately. <sup>g</sup> B.p. 97–102°/0.7 mm,  $n_D^{25}$  1.4379. (Found: C 67.15; H 10.30. Calc. for  $C_{16}H_{30}O_4$  (286.40): C 67.09; H 10.56). <sup>h</sup> This result was obtained also when the addition time for the ester was reduced to  $\frac{1}{2}$  h.

show any reactivity towards carbonyl groups in condensation processes of the aldol or Claisen types as compared with ethyl crotonate, which is the vinylog of ethyl acetate <sup>13</sup>. Furthermore, it has been found by G. Østrup of this department <sup>14</sup> that, in the preparation of tetrolyl chloride from the acid and thionyl chloride, addition of hydrogen chloride to the multiple bond takes place to a considerable degree, whereas this is not the case in the analogous preparation of crotonyl chloride, in which the reactivity of the double bond towards electrophilic reagents is strongly reduced by conjugation with the carbonyl group.

The mechanism which has been proposed for conjugate addition of Grignard reagents to  $\alpha,\beta$ -ethylenic systems <sup>15</sup> involves a cyclic synchronous electron

shift within a six-membered ephemeral ring, the energy of activation thereby being especially low. In the corresponding reaction with acetylenic esters, however, the conditions for such a mechanism is much less favourable, since the linearity of the triple bond prevents the formation of a regular hexagon.

The presence of cuprous chloride (*a*, above) has the drastic effect of changing completely the direction of addition from 1,2- to 1,4-addition, the sole products now being the *sec*-butyl esters of  $\beta$ -*n*-butyl- $\alpha,\beta$ -ethylenic acids. This is in agreement with the above-mentioned catalytic effect of metallic salts on additions to the triple bond, and also with the previously described general effect of cuprous chloride that the presence of this compound promotes conjugate additions of Grignard reagents to  $\alpha,\beta$ -unsaturated esters in competition with carbonyl addition reactions<sup>11</sup>.

Diethyl acetylenedicarboxylate was used besides the *sec*-butyl ester, since the latter proved to be difficult to obtain in a pure state, probably due to elimination and decarboxylation during the distillation. Both esters were found to give only tarry or high-boiling products when the standard cuprous chloride catalyzed procedure was followed. A similar result has apparently been obtained by Gilman and Robinson<sup>16</sup> in the uncatalyzed reaction of diethyl acetylenedicarboxylate and phenylmagnesium bromide. On the other hand, Michael<sup>17</sup> has reported the formation in 20–25 % yield of diethyl ethylfumarate by treating diethyl acetylenedicarboxylate for a long period with ethyl iodide in the presence of zinc. No details are given.

We have found that when the addition of *n*-butylmagnesium bromide was uncatalyzed and performed quickly a small yield of a well-defined product could be obtained. This proved to be a di-*n*-butylsuccinic ester, which was presumably formed by two 1,4-additions to the triple bond. For sterical reasons one would expect the product to be an  $\alpha,\alpha'$ -isomer, but previous investigations of conjugate additions to citraconic and mesaconic esters<sup>18</sup> have shown that in such cases mixtures of isomers may be formed. No attempts were made during the present work to determine the structure of the dibutylsuccinic ester.

In the above-mentioned addition of methyl thioglycolate to dimethyl acetylenedicarboxylate<sup>4</sup>, the use of piperidine as a catalyst likewise resulted in two 1,4-additions, the  $\alpha,\alpha'$ -product presumably being formed.

Apparently acetylenedicarboxylic esters are far more reactive than the mono-carboxylic esters, and in the presence of cuprous chloride polymerisation takes place. This was also the case with ethyl phenylpropiolate, when cuprous chloride was present, whereas the *sec*-butyl ester under these conditions did give the 1,4-addition product. The uncatalyzed reaction with ethyl phenylpropiolate gives the same products as does the *sec*-butyl ester.

## EXPERIMENTAL

Microanalyses 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.

Preparations of  $\alpha,\beta$ -acetylenic acids

*Phenylpropionic acid*<sup>19</sup> and *acetylenedicarboxylic acid*<sup>20</sup> were obtained according to the directions in *Organic Syntheses*.

*Tetrolic acid*. But-2-yn-1-ol was prepared as described in *Organic Syntheses*<sup>21</sup>; 1,3-dichlorobut-2-ene (Eastman, technical) \* was hydrolyzed to 3-chlorobut-2-en-1-ol and from this hydrogen chloride was eliminated by means of sodium amide in liquid ammonia. The butynol, dissolved in acetone, was oxidized with chromic anhydride in sulfuric acid as described for the preparation of propionic<sup>22</sup> and  $\gamma$ -chlorotetrolic<sup>23</sup> acids. The yield of tetrolic acid, b. p. 93–98°/15 mm, m. p. 72–73° (from ligroin) was 40 %. The overall yield from 1,3-dichlorobut-2-ene was about 20 %, but could probably be improved.

Preparations of  $\alpha,\beta$ -acetylenic esters

*sec-Butyl esters* were prepared by esterification of the acids as previously described<sup>24</sup>: *sec-Butyl phenylpropionate*, b. p. 112–113°/1 mm,  $n_D^{20}$  1.5368, yield 58 %. (Found: C 77.10; H 6.80. Calc. for  $C_{13}H_{14}O_2$  (202.34): C 77.20; H 6.98.) *sec-Butyl tetrolate*, b. p. 72–73°/12 mm,  $n_D^{25}$  1.4392, yield 59 %. (Found: C 68.70; H 8.66. Calc. for  $C_8H_{12}O_2$  (140.18): C 68.54; H 8.63.) *Di-sec-butyl acetylenedicarboxylate*; by the distillation gas-evolution took place, and the pressure and boiling point were fluctuating. The main fraction passed over at 110–113°/1.4–1.8 mm,  $n_D^{20}$  1.4479; the yield was only about 20 % and the analysis was slightly incorrect (about 1 % in carbon).

*Diethyl acetylenedicarboxylate* was prepared by an esterification procedure similar to that described in *Organic Syntheses* for the dimethyl ester<sup>25</sup>; b. p. 63–64°/1 mm,  $n_D^{25}$  1.4418. (Found: C 56.50; H 5.92. Calc. for  $C_8H_{10}O_4$  (170.16): C 56.46; H 5.92.)

*Ethyl phenylpropionate* was obtained by sulfuric acid catalyzed esterification of the acid with excess of ethanol under reflux for 8 h; b. p. 87–89°/0.8 mm (rep.<sup>5</sup> 104°/1.5 mm),  $n_D^{20}$  1.5534, yield 76 %. (Found: C 75.90; H 5.86. Calc. for  $C_{11}H_{10}O_2$  (174.19): C 75.84; H 5.79).

## Addition reactions

These were carried out as previously described<sup>10,11</sup>, except in one case with diethyl acetylenedicarboxylate (see Table 1).

The identity of the reaction products were further checked by *infra-red spectroscopy*. The spectra were measured with a Beckman IR2 spectrophotometer with sodium chloride prisms, using 5 % solutions in carbon tetrachloride. The alcohols were identified by their hydroxyl band in the 3  $\mu$  region and by the absence of a carbonyl absorption. The spectra of the esters showed an absorption at 1 715  $cm^{-1}$  within the carbonyl region for  $\alpha,\beta$ -unsaturated esters, as well as a somewhat weaker band around 1 650  $cm^{-1}$  (C=C stretching vibration). Furthermore, the *sec*-butyl esters also showed the group of absorption bands around 1 111  $cm^{-1}$ , which has previously been found in the spectra of other *sec*-butyl carboxylates<sup>18</sup>. The diethyl di-*n*-butylsuccinate (from diethyl acetylenedicarboxylate) showed the normal carbonyl band for saturated ester at 1 730  $cm^{-1}$ , but no absorption for conjugated C=O, C=C or OH.

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