The Action of Arylmagnesium Bromides on Benzylidenemalonic Esters

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Kohler\(^1\) has shown that ethyl diphenylmethylmalonate is formed when phenylmagnesium bromide is allowed to react with ethyl benzylidene-

malonate (Equation I; \(R = R' = \text{phenyl}\)). Although the reaction formally resembles the reaction between arylmagnesium halides and cinnamic esters, which reaction has recently been investigated by Fuson and Jackson\(^2\) and by Hauser, Yost, and Ringler\(^3\), very little seems to have been done to ascertain its limitations. The author of this paper has previously prepared ethyl phenyl-

\(p\)-tolylmethylmalonate (\(R = p\)-tolyl, \(R' = \text{phenyl}\)), ethyl phenyl-\(p\)-anisylmethyl-

malonate (\(R = p\)-anisyl, \(R' = \text{phenyl}\)), and ethyl phenyl-\(a\)-naphthylmethyl-

malonate (\(R = \text{a-naphtyl}, R' = \text{phenyl}\)) from the corresponding Grignard reagents and ethyl benzylidemalonate\(^4\). However, when an attempt was made to prepare ethyl di-\(o\)-anisylmethylmalonate from \(o\)-anisylmagnesium bromide and ethyl \(o\)-methoxybenzylidenemalonate, an oil was obtained from which different substances were isolated, but not the desired ester.

\[\text{COOC}_4\text{H}_5\]  \[\text{COOC}_4\text{H}_5\]

\[\text{CH} - C\]

\[\text{C-O}_2\text{C}_4\text{H}_5\]

\[\parallel\]

\[O\]

\[\text{H}_2\text{O}\]

\[\text{CH} - \text{CH}\]

\[\text{COOC}_4\text{H}_5\]

\[\text{COOC}_4\text{H}_5\]
As it was of some interest to establish if ethyl phenyl-o-anisylmethylmalonate can be prepared either from ethyl benzylidenemalonate and o-anisylmagnesium bromide or from ethyl o-methoxybenzylidenemalonate and phenylmagnesium bromide, some experiments were performed. The latter substances gave ethyl phenyl-o-anisylmethylmalonate, which by saponification and decarboxylation was transformed into β-phenyl-β-o-anisypropionic acid. The product of the reaction between o-anisylmagnesium bromide and ethyl benzylidenemalonate was, however, an oil from which no pure compound has hitherto been isolated. In order to determine whether ethyl phenyl-o-anisylmethylmalonate had formed, the oil was saponified and the oily acids were heated to 200—210° in order to obtain the more easily crystallizing β-phenyl-β-o-anisypropionic acid, but only oils were formed. Since phenylmagnesium bromide reacts in the normal way with ethyl o-methoxybenzylidenemalonate, but o-anisylmagnesium bromide and ethyl benzylidenemalonate react abnormally, experiments were made to determine how o-tolylmagnesium bromide reacts with ethyl benzylidenemalonate. An oil was obtained and pure diarylmalonate could not be isolated. After saponification and decarboxylation of the oil was, however, β-phenyl-β-o-tolylpropionic acid isolated.

From the fact that ethyl diarylmethylmalonates are not formed when o-anisylmagnesium bromide reacts with ethyl benzylidenemalonate and its o-methoxy derivative and that the corresponding ethyl diarylmethylmalonates are formed when o-tolylmagnesium bromide and phenylmagnesium bromide are allowed to react with ethyl benzylidenemalonate and ethyl o-methoxybenzylidenemalonate, respectively, it was concluded that o-anisylmagnesium bromide reacts abnormally. In order to prove this, carbon dioxide was introduced into an ether solution of o-anisylmagnesium bromide. A small amount of impure o-methoxybenzoic acid was isolated from the reaction mixture, the principal product being di-o-methoxybenzophenone, which substance is probably formed according to Equations II.

\[
\begin{align*}
\text{O-CH}_3\text{O} - \text{C}_6\text{H}_4 \cdot \text{MgBr} + \text{CO}_2 & \quad \rightarrow \quad \text{O-CH}_3\text{O} - \text{C}_6\text{H}_4 \cdot \text{COOMgBr} \\
\text{O-CH}_3\text{O} - \text{C}_6\text{H}_4 \cdot \text{MgBr} + \text{O-CH}_3\text{O} - \text{C}_6\text{H}_4\text{C}=\text{O} & \quad \rightarrow \\
\text{O-CH}_3\text{O} - \text{C}_6\text{H}_4 \cdot \text{OMgBr} & \quad \rightarrow \quad \text{O-CH}_3\text{O} - \text{C}_6\text{H}_4 \cdot \text{OMgBr} \\
\text{O-CH}_3\text{O} - \text{C}_6\text{H}_4 \cdot \text{OMgBr} & \quad \rightarrow \quad \text{O-CH}_3\text{O} - \text{C}_6\text{H}_4
\end{align*}
\]

In connection with the syntheses of different β-aryl-propionic acids from arylmagnesium bromides and succinic anhydride Baddar and El-Assal
observed a similar abnormal reaction of o-anisylmagnesium bromide, although
they did not attribute it to this Grignard reagent, but to the first product
of the reaction, β-o-anisoylpropionic acid.

EXPERIMENTAL

Action of o-anisylmagnesium bromide on ethyl benzylidenemalonate

A Grignard reagent was prepared from 2.4 g of magnesium turnings and 18.7 g of
o-bromoanisol in 50 ml of dry ether. The solution was filtered in an atmosphere of hydro-
gen and the filter was washed with about 30 ml of dry ether. The combined ether solu-
tions were then gradually added to a solution of 18.6 g of ethyl benzylidenemalonate in
500 ml of dry ether. Every drop caused the formation of a yellow precipitate. When the
addition was complete, the mixture was warmed for one hour on the water bath. The
precipitate was filtered off and treated with a mixture containing 80 ml of water, 20 ml
of conc. hydrochloric acid, and 80 ml of ether. The solutions were allowed to separate
and the aqueous layer was discarded. The ether solution was shaken with a dilute solu-
tion of sodium hydroxide in order to remove the small amounts of acids remaining, and
finally with water. After evaporation of the ether, there remained 15.87 g of an oil which
did not crystallize. Attempts were made to purify it by chromatography, but only oily
fractions were obtained, and when these fractions were saponified and heated to 200—
210°, tarry oils remained which did not crystallize.

The ether filtrate from the yellow precipitate was treated in a similar way and an
additional steam distillation was performed in order to remove anisol and unchanged
o-bromoanisol, but also in this case an oil (7.79 g) remained that did not crystallize.
Chromatography gave no purification. When the chromatographical fractions were
saponified and heated to 200—210°, tarry oils formed again.

Action of phenylmagnesium bromide on ethyl o-methoxybenzylidenemalonate

A Grignard reagent was prepared from 2.4 g of magnesium turnings and 15.7 g of
bromobenzene in 50 ml of dry ether. The solution was filtered in an atmosphere of hydro-
gen and the filter was washed with about 30 ml of dry ether. The combined ether solu-
tions were then gradually added to a solution of 20 g of ethyl o-methoxybenzylidenemalonate in
500 ml of dry ether. Also in this case a yellow precipitate formed, and when the
addition was completed, a lump had formed that stopped the stirrer. After the mixture
had been warmed for one hour on the water bath, the ether solution was decanted into a
mixture of 40 ml conc. hydrochloric acid and 200 ml of water. The lump was washed with
dry ether and the washings were combined with the main portion. The mixture was
shaken and the ether layer was isolated. It was washed with water, and after it had
been dried with anhydrous sodium sulfate, the ether was evaporated. The residue, a
yellow oil, was treated with ligroin and after some time 5.86 g of crystals separated. The
substance, ethyl phenyl-o-anisylmethylmalonate, was recrystallized from ethyl alcohol,
after which it melted at 86—87°.

C_{21}H_{24}O_5  Calc.  C  70.76  H  6.79
           Found  C  70.67  H  6.71
Two grams of the recrystallized substance were dissolved in 100 ml of alcohol and a mixture containing 2 g of potassium hydroxide, 2 ml of water, and 25 ml of alcohol was added. The solution was heated for two hours on a boiling water bath. The alcohol was then evaporated and the residue was dissolved by mixing with 100 ml of ether and 100 ml of water. After separation, the ether solution was dried with anhydrous sodium sulfate. After the ether had been evaporated, there remained only a very small amount of an oil (0.01 g). The aqueous solution was acidified and after some time 1.77 g of crystals had formed.

Nine tenths of a gram of this substance were heated in the oil bath to 200—210°, during which carbon dioxide was evolved. When the melted substance had cooled, it was crystallized from benzene. The melting point of the substance, β-phenyl-β-o-anisyl-propionic acid, was 133—134°.

\[ \text{C}_{16}\text{H}_{16}\text{O}_{3} \]
Calc. C 74.98 H 6.29
Found » 74.79 » 6.29

The lump that had formed when the phenylmagnesium bromide was added to the solution of ethyl o-methoxybenzylidenemalonate was treated with a mixture of ether, water, and conc. hydrochloric acid, but no pure substance could be isolated.

**Action of o-tolylmagnesium bromide on ethyl benzylidene-malonate**

A Grignard reagent was prepared from 2.8 g of magnesium turnings and 20.5 g of o-bromotoluene in 50 ml of dry ether. To the solution 500 ml of dry ether were added and to this dilute mixture 24.8 g of ethyl benzylidenemalonate dissolved in 100 ml of dry ether were slowly added. During this addition two layers formed. The upper one was an ether solution, but the lower one was a rather thick oil. After the mixture had been warmed for one hour on the water bath, the two layers were treated separately by pouring into mixtures of ether and dilute hydrochloric acid.

No pure substance could be isolated from the ether layer, but when 2.01 g of the oil that remained when the ether had been distilled off were saponified with an alcoholic solution containing 4 g of potassium hydroxide in the way described in connection with the saponification of ethyl phenyl-o-anisylmethyalmalonate, 1.46 g of an acid were obtained. This acid was heated without further purification in the oil bath to 200—210°, during which carbon dioxide was evolved. When the melted substance had cooled, it was dissolved in a small quantity of benzene, and after some time β-phenyl-β-o-tolyl-propionic acid, m.p. 131—132°, precipitated.

\[ \text{C}_{16}\text{H}_{16}\text{O}_{3} \]
Calc. C 79.97 H 6.71
Found » 79.92 » 6.68

When the oily layer was treated in the same manner a small quantity of the same acid was isolated, but only after the oil had been chromatographically purified.

Another experiment was performed without the addition of 500 ml of dry ether. The results were similar, but the yield of β-phenyl-β-o-tolylpropionic acid from the oily layer was somewhat larger.

**The reaction between o-anisylmagnesium bromide and carbon dioxide**

A Grignard reagent was prepared from 0.96 g of magnesium turnings and 5 g o-bromoanisol in 20 ml of dry ether. Carbon dioxide was then conducted into the solution during two hours. The reaction mixture was poured into dilute hydrochloric acid to which ice
had been added. More ether was added, the mixture was shaken and the ether solution was separated. Acids and phenols were removed by extraction with a dilute solution of sodium hydroxide. The ether layer was removed, and after drying with anhydrous sodium sulfate, the ether was evaporated. The residue (1.80 g) crystallized after a few hours and was then treated with a small quantity of ether. Crystals (1.04 g) of di-o-methoxybenzophenone (m.p. 98—100°) were filtered off. From the filtrate a small amount (0.09 g) of the same substance was isolated.

The alkaline water solution was acidified and the oil that separated was dissolved in ether. Organic acids were removed from the ether solution by shaking with a solution of sodium carbonate, and from this solution, a small quantity (0.20 g) of impure o-methoxybenzoic acid was isolated. The ether solution was shaken with a dilute solution of sodium hydroxide, from which 0.31 g of an oil separated after addition of hydrochloric acid. The oil smelled of guaiacol, but this substance could not be isolated.

This experiment was performed with o-bromoanisol prepared from o-anisidine. The results were exactly similar when the experiment was repeated with o-bromoanisol prepared from o-bromoanisol.

SUMMARY

1. Ethyl phenyl-o-anisylmethylmalonate is formed when phenylmagnesium bromide is allowed to react with ethyl o-methoxybenzylidenemalonate, but not when o-anisylmagnesium bromide reacts with ethyl benzylidenemalonate.

2. It was established that ethyl phenyl-o-tolylmethylmalonate is formed in the reaction between o-tolylmagnesium bromide and ethyl benzylidenemalonate by isolating β-phenyl-β-o-tolylpropionic acid from the reaction product after saponification and decarboxylation.

3. When carbon dioxide is introduced into a solution of o-anisylmagnesium bromide, di-o-methoxybenzophenone is formed as the main product. Only a small amount of impure o-methoxybenzoic acid was isolated.

REFERENCES


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