

The Addition of Grignard Reagents to Alkylidenemalonic Esters

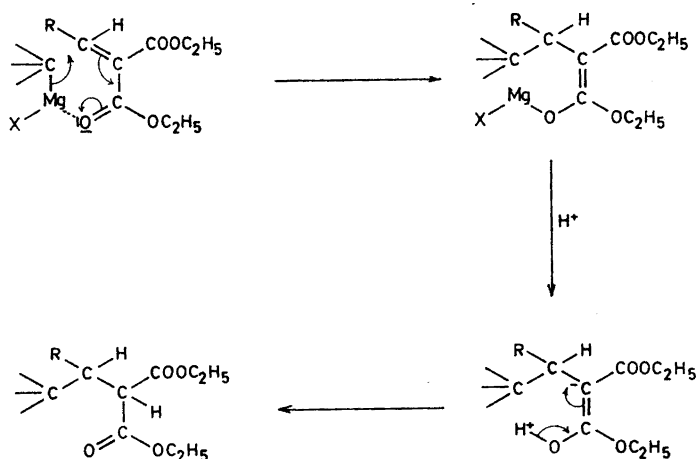
III. The Reactions between Aliphatic Alkylmagnesium Halides and Diethyl and Diisopropyl Isopropylidenemalonates

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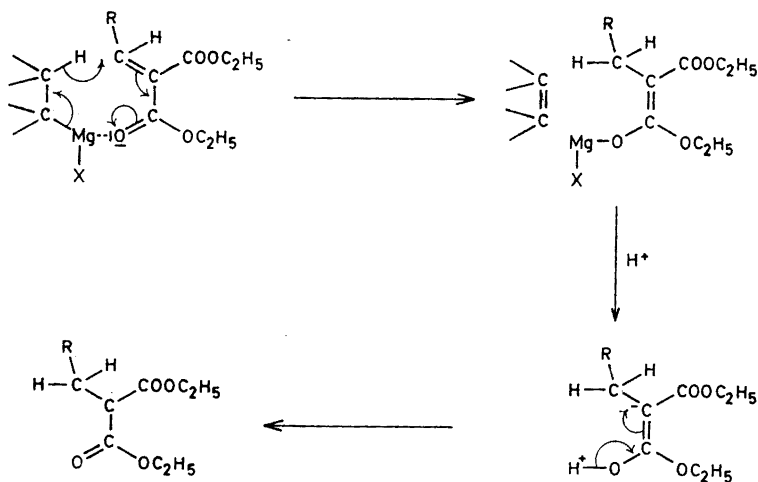
When methylmagnesium iodide reacts with diethyl and diisopropyl isopropylidenemalonates, 1,2-addition and 1,4-addition occur. Ethylmagnesium bromide and isopropylmagnesium bromide react with the same malonates to form both 1,4-addition products and reduction products. When *tert*-butylmagnesium chloride is employed, the esters are quantitatively reduced. In the reactions with methylmagnesium iodide, the diethyl ester gives more 1,2-addition product and less 1,4-addition product than the diisopropyl ester. With the other alkylmagnesium halides, the proportions of 1,4-addition and reduction products do not differ significantly. These results are in satisfactory accordance with the reaction mechanism proposed for the reduction of alkylidenemalonic esters with Grignard reagents.

In a recent study of the reactions between Grignard reagents and alkylidenemalonic esters,¹ it was found that 1,4-addition occurs if the alkyl groups in the Grignard reagent and in the β -position of the malonate are small in size. When the alkyl groups are larger and more branched, higher proportions of the esters are reduced to the corresponding saturated alkylmalonic esters. The courses of the reactions seem to be dependent on steric factors. 1,4-Additions of Grignard reagents to the conjugated double bond system $C=C-C=O$ are generally thought to occur by a cyclic mechanism, the application of which to alkylidenemalonic esters is shown in Scheme 1. With increasing steric hindrance due to large and branched groups in the Grignard reagent and in the β -position of the malonic ester, the alkyl group of the Grignard reagent may, however, orient itself in the way shown in the first formula of Scheme 2. The steric hindrance is then considerably smaller and the reduction can occur by an electron transfer within an eight-membered ring. The reduction may thus be interpreted as a side tracked 1,4-addition.



Under the conditions that prevail in the reductions of unsaturated malonic esters with Grignard reagents, monocarboxylic esters are not reduced. This fact is explained by the absence of a second carboxy group. In the malonates, this highly electronegative group in the α -position activates the ethylenic double bond and reduces the electron density at the carbon atom in the β -position in such a degree that the reduction can occur.

In the above mechanism (Scheme 1) an eight-membered ring is involved. At the moment of reaction, the atoms of this ring should be in a plane. This reduces the plausibility of the mechanism. On the other hand, it should



also be remembered that the valence of the hydrogen atom has no fixed direction. Thus, the angle formed by the hydrogen atom and the two neighbouring carbon atoms of the ring may vary within very wide limits. This circumstance facilitates the intermediate ring formation.

The reports from this laboratory have until now dealt with unsaturated malonates that have only *one* substituent in the β -position. Although 1,4-addition of Grignard reagents to diethyl isopropylidenemalonate has been used to prepare different *tert*-alkylmalonates,²⁻⁴ no other reaction products

Table 1. Retention times and constitution of the reaction products.

Grignard reagent	Retention times ^a	Diethyl series Products	Retention times ^a	Diisopropyl series Products
CH ₃ Mg I	0.597	$\begin{array}{c} \text{CH}_3 \\ \\ \text{C}=\text{C} \\ \quad \\ \text{CH}_3 \quad \text{C}=\text{CH}_2 \\ \quad \quad \\ \quad \quad \text{COOC}_2\text{H}_5 \end{array}$	0.683	$\begin{array}{c} \text{CH}_3 \\ \\ \text{C}=\text{C} \\ \quad \\ \text{CH}_3 \quad \text{C}=\text{CH}_2 \\ \quad \quad \\ \quad \quad \text{COOCH}(\text{CH}_3)_2 \end{array}$
	1.09	$\begin{array}{c} \text{CH}_3 \\ \\ \text{C}-\text{CH} \\ \quad \\ \text{CH}_3 \quad \text{COOC}_2\text{H}_5 \\ \quad \quad \\ \quad \quad \text{COOC}_2\text{H}_5 \end{array}$	1.47	$\begin{array}{c} \text{CH}_3 \\ \\ \text{C}-\text{CH} \\ \quad \\ \text{CH}_3 \quad \text{COOCH}(\text{CH}_3)_2 \\ \quad \quad \\ \quad \quad \text{COOCH}(\text{CH}_3)_2 \end{array}$
C ₂ H ₅ Mg Br	1.00	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{CH} \\ \quad \\ \text{CH}_3 \quad \text{COOC}_2\text{H}_5 \\ \quad \quad \\ \quad \quad \text{COOC}_2\text{H}_5 \end{array}$	1.23	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{CH} \\ \quad \\ \text{CH}_3 \quad \text{COOCH}(\text{CH}_3)_2 \\ \quad \quad \\ \quad \quad \text{COOCH}(\text{CH}_3)_2 \end{array}$
	1.92	$\begin{array}{c} \text{CH}_3 \\ \\ \text{C}-\text{CH} \\ \quad \\ \text{C}_2\text{H}_5 \quad \text{COOC}_2\text{H}_5 \\ \quad \quad \\ \quad \quad \text{COOC}_2\text{H}_5 \end{array}$	2.33	$\begin{array}{c} \text{CH}_3 \\ \\ \text{C}-\text{CH} \\ \quad \\ \text{C}_2\text{H}_5 \quad \text{COOCH}(\text{CH}_3)_2 \\ \quad \quad \\ \quad \quad \text{COOCH}(\text{CH}_3)_2 \end{array}$
$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{Mg Br} \\ \\ \text{CH}_3 \end{array}$	1.00	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{CH} \\ \quad \\ \text{CH}_3 \quad \text{COOC}_2\text{H}_5 \\ \quad \quad \\ \quad \quad \text{COOC}_2\text{H}_5 \end{array}$	1.24	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{CH} \\ \quad \\ \text{CH}_3 \quad \text{COOCH}(\text{CH}_3)_2 \\ \quad \quad \\ \quad \quad \text{COOCH}(\text{CH}_3)_2 \end{array}$
	2.81	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{C}-\text{CH} \\ \quad \quad \\ \text{CH}_3 \quad \text{CH}_3 \quad \text{COOC}_2\text{H}_5 \\ \quad \quad \quad \\ \quad \quad \quad \text{COOC}_2\text{H}_5 \end{array}$	3.37	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{C}-\text{CH} \\ \quad \quad \\ \text{CH}_3 \quad \text{CH}_3 \quad \text{COOCH}(\text{CH}_3)_2 \\ \quad \quad \quad \\ \quad \quad \quad \text{COOCH}(\text{CH}_3)_2 \end{array}$
$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{C}-\text{Mg Cl} \\ \\ \text{CH}_3 \end{array}$	1.00	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{CH} \\ \quad \\ \text{CH}_3 \quad \text{COOC}_2\text{H}_5 \\ \quad \quad \\ \quad \quad \text{COOC}_2\text{H}_5 \end{array}$	1.23	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}-\text{CH} \\ \quad \\ \text{CH}_3 \quad \text{COOCH}(\text{CH}_3)_2 \\ \quad \quad \\ \quad \quad \text{COOCH}(\text{CH}_3)_2 \end{array}$

^a Diethyl isopropylmalonate is taken as the standard.

have been observed. It was hence of interest to study the reactions between some aliphatic Grignard reagents and the diethyl and diisopropyl esters of isopropylidenemalonic acid by the technique developed in Part II of this series.¹

The Grignard reagents chosen were methylmagnesium iodide, ethylmagnesium bromide, isopropylmagnesium bromide, and *tert*-butylmagnesium chloride. Each of these was allowed to react with diethyl isopropylidenemalonate and diisopropyl isopropylidenemalonate. In order to ensure complete reaction, large excesses of the Grignard reagents were used (molar ratio of ester to magnesium compound about 1:5). After a short time (15 min) at the reaction temperature (about 0°), the reaction mixtures were treated with dilute hydrochloric acid and the products were examined by gas chromatography. Except for some substances that were formed in only small or negligible quantities, the reaction products were identified and quantitatively determined. The results of these analyses are collected in Tables 1 and 2.

The results for the reactions between the two malonates and ethylmagnesium bromide, and *tert*-butylmagnesium chloride show that the isopropylidenemalonates react in the same way as the previously examined alkylidene-

Table 2. Contributions of concurrent reactions as revealed by quantitative evaluation of gas chromatograms.

Alkyl group in Grignard reagent	Alkyl group in dialkyl isopropylidene-malonate	1,2-Addition %	1,4-Addition %	Reduction %
Methyl (I)	Ethyl (1)	35.7	64.3	
Methyl (I)	Isopropyl (2)	17.6	82.4	
Ethyl (II)	Ethyl (1)		92.9	7.1
Ethyl (II)	Isopropyl (2)		92.9	7.1
Isopropyl (III)	Ethyl (1)		39.4	60.6
Isopropyl (III)	Isopropyl (2)		41.0	59.0
<i>tert</i> -Butyl (IV)	Ethyl (1)			100.0
<i>tert</i> -Butyl (IV)	Isopropyl (2)			100.0

malonates, *i.e.* the larger and the more branched the alkyl group of the Grignard reagent, the greater is the proportion of the malonate that is reduced to the corresponding saturated malonic ester.

When the yields of the reactions between the malonates with one of the mentioned Grignard reagents are compared, it is observed that the ratios of the yields of the 1,4-addition product and the reduction product are not significantly different. The alkyl group in the carbalkoxy group of the ester seems thus not to have any greater influence on the reactions in these cases.

The most striking feature in the tables is, however, that besides 1,4-addition, methylmagnesium iodide undergoes 1,2-addition. The second methyl group in the β -position apparently opposes the 1,4-addition. The same effect of a second alkyl group in the β -position has previously been

observed by Colonge⁵ in the reactions between Grignard reagents and α , β -unsaturated ketones.

The amount of 1,2-addition product formed is greater in the case of the diethyl ester than in the case of diisopropyl ester. This fact shows that 1,2-addition is favoured even in the unsaturated malonic esters if the esters are derivatives of alcohols with small alkyl groups. A corresponding observation concerning alkyl cinnamates was made by Kohler and Heritage.⁶

All these observations support the interpretation of the reduction as a side-tracked 1,4-addition and do not contradict the proposed reaction mechanism.

EXPERIMENTAL

Diisopropyl malonate was prepared by the method used by Bakker and Lolkema⁷ for the preparation of di-*sec*-butyl malonate. A solution of malonic acid (52 g) in isopropyl alcohol (175 g) was saturated with gaseous hydrogen chloride and kept for one week at room temperature. Water and ether were added and the ether phase was washed with water and dilute sodium carbonate solution and dried with sodium sulphate. After the solvent had been evaporated, pure diisopropyl malonate distilled at 105–106°/22 mm Hg. The yield was 68 % (64.14 g).

Diethyl isopropylidenemalonate was prepared as described by Meyenberg⁸ from diethyl malonate, acetone, acetic anhydride, and zinc chloride. The ester was purified in a preparative gas chromatograph.

Diisopropyl isopropylidenemalonate was prepared in the same way as the diethyl ester using diisopropyl malonate instead of diethyl malonate. The ester was purified in a preparative gas chromatograph and finally distilled under reduced pressure. The boiling point of the pure ester was 114°/8 mm Hg. (Found: C 62.94; H 8.91. Calc. for $C_{12}H_{20}O_4$: C 63.13; H 8.83).

The reactions between the Grignard reagents and the two dialkyl isopropylidenemalonates. Two small flasks were carefully dried, provided with plastic caps, and placed in an ice bath. A definite quantity of one of the two malonates was added to one of the flasks and a similar quantity (0.20–0.25 g) of the other malonate to the other flask. A fivefold of recently prepared and analysed Grignard reagent was added with a 10 ml hypodermic syringe to both flasks. The flasks were shaken at short intervals during 15 min. Each reaction mixture was then poured into a mixture of ether, dilute hydrochloric acid, and ice. The layers were separated and the aqueous phases were extracted with small portions of ether. These ether layers were combined with the main ether phases. The ether solutions were then shaken first with 5 % potassium hydrogen carbonate solution and finally with water. After the ether phases had been dried with sodium sulphate, the solvent was evaporated and each residue was dissolved in dry ethyl alcohol (20 ml). The experiment was repeated with the other Grignard reagents. The complete series thus comprised eight reaction mixtures. The alcohol solutions were used for qualitative and quantitative analyses.

A second series of experiments was performed with about fourfold quantities. This series was used for analyses, partly for hydrolysis and methylation for the identification of the reaction products.

The reaction mixtures were qualitatively analysed with a gas chromatograph provided with a hydrogen flame ionization detector. The best separation and the most symmetric peaks were obtained with a 2 m column (1/8") filled with Apiezon L on Chromosorb P (20:80 w/w). Nitrogen was used as carrier gas (25 ml/min). The injector block was held at 320°, the column at 220°, and the detector at 300°. The results are collected in Table 3. The numbers of peaks were confirmed with another column (1.5 m, 1/8") filled with 5 % SE silicon gum on Chromosorb W.

Reference compounds. Diethyl *tert*-butylmalonate was prepared according to Wideqvist² and diethyl (1,1-dimethylpropyl)-malonate and diethyl (1,1,2-trimethylpropyl)-malonate according to Golmov and Malevannaya.⁴ Diethyl isopropylmalonate was prepared by isopropylation of diethyl malonate by the method developed by Adams and

Kamm⁹ for the preparation of diethyl butylmalonate. All reaction products of diethyl isopropylidenemalonate except one with retention time 0.486 (I 1) were identified directly (cf. Table 1). This last substance was isolated and identified as ethyl 2,4-dimethyl-1,3-pentadiene-3-carboxylate in the following way.

Diethyl isopropylidenemalonate (10 g) dissolved in dry ether (40 ml) was gradually added to a Grignard reagent prepared from methyl iodide (35.5 g), magnesium (6.00 g), and dry ether (50 ml) that was cooled in an ice bath. After the addition, the reaction mixture was allowed to stand for 15 min and then poured into a mixture of water, hydrochloric acid, and ice. The ether phase was separated, washed with water and potassium hydrogen carbonate solution, and dried with sodium sulphate. After evaporating the solvent, the components in the remaining oil were separated in a preparative gas chromatograph provided with a 20' 30% SE-30 silicon gum column. The temperatures of

Table 3. Qualitative gas chromatography analyses.

Reaction mixture ^a	Number of peaks	Relative retention times ^b of reaction products				
		Directly	After hydrolysis and methylation			
I 1	2	0.597	1.09	0.394	0.753	
I 2	2	0.683	1.47	0.394	0.753	
II 1	2		1.00	1.92	0.650	1.27
II 2	2		1.23	2.33	0.650	1.27
III 1	2		1.00	2.81	0.650	1.89
III 2	2		1.24	3.37	0.650	1.90
IV 1	1		1.00		0.650	
IV 2	1		1.00		0.650	

^a I = Methylmagnesium iodide, II = ethylmagnesium bromide, III = isopropylmagnesium bromide, IV = *tert*-butylmagnesium chloride, 1 = diethyl isopropylidenemalonate, 2 = diisopropyl isopropylidenemalonate.

^b Relative to the single peak in the gas chromatogram of reaction mixture IV 1, the absolute retention time of which was 112 sec.

^c See Table 3.

the injector block, the column, and the heat conductivity detector were 275°, 200°, and 270°, respectively. Each time 0.1 ml of the reaction mixture was injected. The compound with the shorter retention time was identified as ethyl 2,4-dimethyl-1,3-pentadiene-3-carboxylate. (Found: C 71.20; H 9.58. Calc. for C₁₀H₁₆O₂: C 71.39; H 9.58).

Identification of the reaction products of diisopropyl isopropylidenemalonate. Small amounts (about 0.65 g) of the reaction mixtures from the second series of experiments were separately dissolved in solutions of potassium hydroxide (about 1.3 g) in water (about 1.3 ml) and ethyl alcohol (20 ml) and the mixtures were heated for 5–6 h on a boiling water bath. The solvent was evaporated from each solution and the residues were dissolved in water. The resulting solutions were acidified with hydrochloric acid and repeatedly extracted with ether. The ether solutions were then treated with small excesses of diazomethane and reaction products were qualitatively examined by gas chromatography. The results, which are collected in the fourth column of Table 3, show that the pairs of methyl esters are identical. This means that the reaction products of diethyl isopropylidenemalonate and diisopropyl isopropylidenemalonate are ethyl and isopropyl esters of the same acids. The reaction products were thus identified (cf. Table 1).

Quantitative analyses. The gas chromatogram of each reaction mixture contained one or two peaks. When only one peak was present, no difficulties were, of course, ex-

Table 4. Quantitative gas chromatographic analyses.

Reaction mixture		1,2-Addition product		1,4-Addition product		Reduction product	
		% by peak area	% by weight	% by peak area	% by weight	% by peak area	% by weight
I	1	33.5	30.1	66.5	69.9		
I	2	15.3	13.7	84.7	86.3		
II	1			94.0	93.7	6.0	6.3
II	2			93.9	93.7	6.1	6.3
III	1			45.8	44.0	54.2	56.00
III	2			46.5	45.1	53.5	54.9
IV	1					100.0	100.0
IV	2					100.0	100.0

perenced in the evaluation of the result. In the remaining cases, the method of evaluation by peak area measurements using specific calibration factors¹⁰ was employed. As a hydrogen flame ionization detector was used, the measured areas had to be corrected for the carbon contents of the compounds in question. The results of these evaluations are collected in Table 4.

The percentages by weight were converted to mole percentages before they were entered in Table 2.

REFERENCES

- Holmberg, G. A. and Lundell, R. *Acta Acad. Aboensis, Math. et Phys.* **26** (1967) No. 12.
- Wideqvist, S. *Arkiv Kemi, Mineral. Geol.* **B 23** (1946) No. 4.
- Prout, F. S., Huang, E. P.-Y., Hartman, R. J. and Korpics, C. J. *J. Am. Chem. Soc.* **76** (1964) 1911.
- Golmov, V. P. and Malevannaya, Z. P. *Zh. Obshch. Khim.* **28** (1958) 3075; *Chem. Abstr* **53** (1959) 9045.
- Colonge, J. *Bull. Soc. Chim. France* [5] **2** (1935) 754.
- Kohler, E. P. and Heritage, G. *Am. Chem. J.* **33** (1905) 21.
- Bakker, H. J. and Lolkema, J. *Rec. Trav. Chim.* **57** (1938) 1234.
- Meyenberg, A. *Ber.* **28** (1895) 785.
- Adams, R. and Kamm, R. M. *Org. Syn., Coll. Vol. 1* (1941) 1944.
- Kaiser, R. *Gas Phase Chromatography*, Butterworths, London 1963, Vol. III, p. 99.

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