

# Reactions between Furfurylidenemalonic Esters and Grignard Reagents. III. Diethyl 5-Methylfurfurylidenemalonate

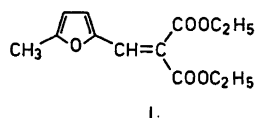
## Isolation of a 1,6-Addition Product

GUST.-AD. HOLMBERG, LARS JALANDER, HÅKAN NORRÅRD and BARBRO PETTERSSON

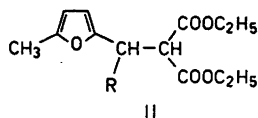
Institutionen för organisk kemi, Åbo Akademi, SF-20500 Åbo 50, Finland

When methylmagnesium iodide and ethylmagnesium bromide react with diethyl 5-methylfurfurylidenemalonate, only 1,4-addition products are formed. Isopropylmagnesium bromide gives a small quantity of reduction product beside the 1,4-addition product. *t*-Butylmagnesium chloride gives reduction product, 1,4-addition product, and two 1,6-addition products. The last-mentioned compounds easily rearrange to diethyl 3-*t*-butyl-5-methylfurfurylmalonate, which was isolated by preparative gas chromatography.

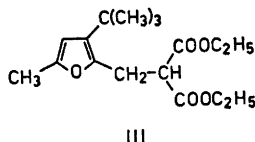
Reactions between diethyl furfurylidenemalonate and different Grignard reagents have previously been studied in this laboratory.<sup>1,2</sup> 1,4-Additions were shown to be the principal reactions. Methylmagnesium iodide and ethylmagnesium bromide did not give any other reactions at all. Isopropylmagnesium bromide caused reduction of a small portion of the unsaturated ester to diethyl furfurylmalonate besides the 1,4-addition. Isobutylmagnesium chloride reacted in the same way but the reduced quantity was larger. *t*-Butylmagnesium chloride gave, in addition to these reactions, also 1,6- and 1,8-additions through extension of the conjugated double bond system to the furan nucleus. Apparently, the product of the last-mentioned reaction immediately rearranged to diethyl 5-*t*-butylfurfurylmalonate when the reaction mixture was brought into contact with water. The two 1,6-addition products were stabler but rearranged prototropically to one and the same product, diethyl 3-*t*-butylfurfurylmalonate, in acid solution.



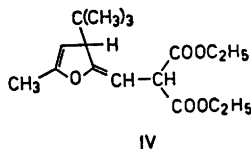
The reaction products could not, however, be isolated in the experiments with *t*-butylmagnesium chloride. The structures of the products were therefore deduced mainly from mass spectra taken with a combined gas chromatograph/mass spectrometer. An introduction of an alkyl group in position 5 of diethyl furfurylidenemalonate was expected to reduce the number of reaction products and in this way to facilitate separation and make ordinary structure determinations possible. *t*-Butylmagnesium chloride was therefore allowed to react with diethyl 5-methylfurfurylidenemalonate (I). A gas chromatographic analysis of the reaction products showed that four compounds were present. A fifth compound, probably a dimer, appeared secondarily after standing for some days. Two of the primary reaction products rearranged in acid solution to a new compound while the other two compounds did not react. After the number of products had been reduced in this way, the compounds were easily separated by preparative gas chromatography. The NMR spectra of the fractions obtained showed that the substances



were diethyl 5-methylfurfurylmalonate (II; R = H), diethyl 2,2-dimethyl-1-(5'-methyl-2'-furyl)-propylmalonate [II; R = (CH<sub>3</sub>)<sub>2</sub>C], and diethyl 3-*t*-butyl-5-methylfurfurylmalonate (III). Because the last-mentioned compound had formed from two primary reaction products by prototropical rearrangement, it is quite clear that these compounds were the *cis* and *trans* isomers of diethyl 3-*t*-butyl-5-methyl-2,3-dihydro-2-furylidenemethylmalonate (IV).



These results show that *t*-butylmagnesium chloride gives reduction and 1,4- and 1,6-additions with diethyl 5-methylfurfurylidenemalonate. The molar ratio of the products of these reactions was 8:58:34 in the present experiments. It is remarkable that the possibilities of the two isomers of diethyl 3-*t*-butyl-5-methyl-2,3-dihydro-2-furylidenemethylmalonate being formed are not equal. The molar ratio of these was 25:9.



A series of experiments was performed with methylmagnesium iodide, ethylmagnesium bromide, and isopropylmagnesium bromide in order to examine whether these Grignard reagents give rise to 1,6-additions beside reduction and 1,4-additions but the results in this respect were as negative as those with diethyl furfurylidenemalonate.<sup>1</sup> The reagents gave reduction and 1,4-addition in the same way as in these experiments. The only difference was that isopropylmagnesium bromide gave a smaller quantity of reduction product and a larger quantity of 1,4-addition product in the experiment with the methyl-substituted ester.

The structures of the reaction products of *t*-butylmagnesium chloride and diethyl furfurylidenemalonate had been deduced mainly from mass spectra. Consequently, the results might be called in question. However, a comparison

of these spectra and those now obtained from substances whose structures are unquestionable reveals that the conclusions concerning the structures were correct.

## EXPERIMENTAL

*Diethyl 5-methylfurfurylidenemalonate* (I) was prepared from 5-methylfurfural and diethyl malonate according to the general method for the preparation of  $\alpha,\beta$ -unsaturated esters previously used in this laboratory.<sup>1</sup> The ester, b.p. 177–179 °C/12 mmHg, was purified by recrystallisation from ligroin. The yield of pure material, m.p. 56–57 °C, was 62%. (Found: C 62.00; H 6.23. Calc. for C<sub>13</sub>H<sub>16</sub>O<sub>5</sub>: C 61.90; H 6.39.) MS: *m/e*(r.a.) M<sup>+</sup> 252(63), calc. 252; (M+1)<sup>+</sup> (8.9, calc. 8.9); (M+2)<sup>+</sup> (2.0, calc. 1.3); (M-C<sub>2</sub>H<sub>5</sub>)<sup>+</sup> 223(26); (M-OC<sub>2</sub>H<sub>5</sub>)<sup>+</sup> 207(71); (M-COOC<sub>2</sub>H<sub>5</sub>)<sup>+</sup> 179(100); CH<sub>3</sub>-C<sub>4</sub>H<sub>2</sub>O-CH=CH-CO<sup>+</sup> 135(30); unidentified ions at 163(22); 152(15); 110(88). NMR spectrum: the furan proton H-3 at  $\tau$  3.41 coupled to H-4 at  $\tau$  3.98 ( $J=3.0$  Hz); methyl protons at  $\tau$  7.70 long-range coupled to H-4 ( $J=0.9$  Hz); methine proton in position  $\beta$  at  $\tau$  2.78 (singlet); methylene protons (ester) at  $\tau$  5.75 and 5.80 coupled to the methyl protons at  $\tau$  8.67 and 8.70 ( $J=7.1$  Hz).

5-Methylfurfural used in this synthesis was prepared according to Traynelis, Miskel Jr, and Sowa.<sup>2</sup> When a sample of 5-methylfurfural prepared according to Rinke<sup>3</sup> from sugar was used, the ester obtained was not quite pure.

The reactions of diethyl 5-methylfurfurylidenemalonate with methylmagnesium iodide, ethylmagnesium bromide and isopropylmagnesium bromide were performed on semimicro and macro scales according to the method previously described.<sup>1</sup>

Diethyl 1-(5'-methyl-2'-furyl)ethylmalonate (II; R = CH<sub>3</sub>), b.p. 140–142 °C/7 mmHg, was the only product in the experiments with methylmagnesium iodide. It was isolated by distillation under reduced pressure. (Found: C 62.46; H 7.30. Calc. for C<sub>14</sub>H<sub>20</sub>O<sub>5</sub>: C 62.67; H 7.51.) The NMR spectrum of the compound shows a rather complex signal at  $\tau$  6.4–6.80 from the hydrogen atoms at the  $\alpha$  and  $\beta$  carbon atoms. The complexity is a consequence of long-range coupling of the hydrogen atoms of the attached methyl group to the hydrogen of the  $\alpha$  position. An almost identical signal is found in the spectra of the homologue, diethyl 1-(2'-furyl)ethylmalonate,<sup>1</sup> and  $\alpha,\beta$ -dibromobutyric acid,<sup>4</sup> which contains the same structural element, CH<sub>3</sub>-CH-CH-C=O, attached to negative atoms and groups. The present spectrum also shows the appropriate signals from the other hydrogen nuclei of the compound.

Diethyl 1-(5'-methyl-2'-furyl)propylmalonate (II; R = C<sub>2</sub>H<sub>5</sub>), b.p. 144–146 °C/18 mmHg, was the only reaction product in the experiment with ethylmagnesium bromide. It was isolated

by distillation under reduced pressure. (Found: C 63.72; H 7.75. Calc. for  $C_{15}H_{22}O_5$ : C 63.81; H 7.85.) The NMR spectrum shows the presence of an AB spin system with the shifts at  $\tau$  6.55 and 6.80 ( $J = 9.6$  Hz) due to the hydrogen atoms in the  $\alpha$  and  $\beta$  positions. The two signals of the latter atom are split into triplets as a consequence of coupling to the two hydrogen atoms of the attached methylene group. Appropriate signals from the other hydrogen atoms of the compound are found in the spectrum.

Isopropylmagnesium bromide gave diethyl 5-methylfurfurylmalonate (II; R = H; see below) and diethyl 2-methyl-1-(5'-methyl-2'-furyl)propylmalonate (II; R =  $(CH_3)_2CH$ ). The ratio of the reaction products was about 1:100. The latter product was isolated by preparative gas chromatography (column 9 mm  $\times$  4.0 m; stationary phase 25 % SE-30 on Chromosorb W; helium flow 200 ml/min; initial temperature about 250 °C, slow programming to 300 °C; injected quantity 0.1 ml each time). (Found: C 64.64; H 7.99. Calc. for  $C_{16}H_{24}O_5$ : C 64.84; H 8.16.) The NMR spectrum shows the presence of an AB spin system with the shifts at  $\tau$  6.37 and 6.72 ( $J = 11.0$  Hz) due to the hydrogen atoms in the  $\alpha$  and  $\beta$  positions. The two signals from the latter atom are split into doublets as a consequence of coupling to the hydrogen atom of the methine group attached to the  $\beta$  carbon atom. In addition to these signals appropriate signals from the other hydrogen atoms are found in the spectrum.

The reactions of diethyl 5-methylfurfurylidene-malonate with *t*-butylmagnesium chloride were performed according to the method previously described. The reaction products were analysed by gas chromatography (column 3 mm  $\times$  1.5 m; stationary phase 3 % SE-30 on Chromosorb W; nitrogen flow about 28 ml/min; initial temperature 100 °C; temperature programming 10 °C/min). Four peaks with the relative retention times 1.00 (compound A), 1.37 (compound B), 1.68 (compound C), and 1.73 (compound D) were obtained when the analysis was carried out immediately after the experiment. When the analysis was repeated the following day, a fifth peak with the relative retention time 2.07 (compound E) appeared. A sample of the reaction products was dissolved in ethanol and the solution was acidified with a small quantity of sulfuric acid. The acid solution was poured into a sodium hydrogen carbonate solution after two days and the mixture was extracted with ether. The gas chromatogram of this ether solution showed four ordinary and two rather small peaks. The relative retention times of the larger peaks were 1.00 (compound A), 1.37 (compound B), 1.59 (compound F), and 2.05 (compound E) and those of the small peaks 1.76 and 1.93. The compounds in the latter reaction mixture were separated by preparative gas chromatography (*cf.* above).

Compound A was diethyl 5-methylfurfurylmalonate (II; R = H). (Found: C 61.69; H 7.05.

Calc. for  $C_{13}H_{18}O_5$ : C 61.41; H 7.14.) The NMR spectrum shows an  $AB_2$  peak system with the shifts at  $\tau$  5.56 and 6.99 ( $J = 5.8$  Hz) due to the hydrogen atoms at the  $\alpha$  and  $\beta$  carbon atoms. In addition to these signals, the spectrum contains the appropriate signals from the rest of the hydrogen atoms of the compound.

Compound B was identified as diethyl 2,2-dimethyl-1-(5'-methyl-2'-furyl)propylmalonate (II; R =  $(CH_3)_2C$ ). (Found: C 66.04; H 8.35. Calc. for  $C_{17}H_{26}O_5$ : C 65.78; H 8.44.) The NMR spectrum shows a simple AB quartet with the shifts at  $\tau$  6.40 and 6.59 ( $J = 9.1$  Hz) due to the hydrogen atoms in the  $\alpha$  and  $\beta$  positions. The appropriate signals from the remaining hydrogen atoms are found in the spectrum.

Compound F was shown to be diethyl 3-*t*-butyl-5-methylfurfurylmalonate (III). (Found: C 65.54; H 8.24. Calc. for  $C_{17}H_{26}O_5$ : C 65.78; H 8.44.) The NMR spectrum contains an  $AB_2$  peak system with the shifts at  $\tau$  6.41 and 6.86 ( $J = 9.1$  Hz) due to the hydrogen atoms in the  $\alpha$  and  $\beta$  positions. In addition to these signals and in contrast to the other NMR spectra in this paper, the spectrum of compound F contains only one furan signal, a singlet. The shift is at  $\tau$  4.38 and the signal is apparently due to H-4. Appropriate signals from the remaining hydrogen atoms are also found in this case in the spectrum.

The compounds C and D could not be separated by preparative gas chromatography.

Compound E was not isolated in its pure state. Its mass spectrum reveals that it might be a dimer.

The ratio of the peak areas of compounds A, B, C, D, and E is 10:100:42:16:10. The molar ratio of the compounds A, B, C, and D calculated from the above ratio and the structures of the compounds is 8:58:25:9. After treatment with sulfuric acid, the ratio of the compounds, A, B, and F is 8:57:35.

The mass spectra of the reaction products are collected in Table 1. No greater differences are observed between the spectra of the compounds of type II and those of the corresponding compounds without the methyl group in position 5.<sup>1,2</sup> Two fragmentation reactions dominate when R is hydrogen or a small alkyl group: (1) the cleavage of the bond between the  $\alpha$  and  $\beta$  carbon atoms which gives rise to the ions  $(M-159)^+$  and (2) the loss of a carbethoxy group and a hydrogen atom at the  $\beta$  carbon which results in the ions  $(M-74)^+$ . These ions finally lose an ethoxy radical,  $\cdot OC_2H_5$ , and are transformed into the ions  $(M-119)^+$ . With increasing size and degree of branching of group R, these reactions are suppressed by a third reaction: loss of a carbethoxy group and group R which results in the formation of the ions at  $m/e$  180. Even these ions lose an ethoxy radical and are converted into the ions at  $m/e$  135,  $CH_3-C_4H_7O-CH=CH-CO^+$ .

The spectra of the compounds C and D are

Table 1. Abundances of important ions in the mass spectra of the reaction products.

Mass of ion	R in formula II					Compound		F
	H	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	i-C <sub>3</sub> H <sub>7</sub>	t-C <sub>4</sub> H <sub>7</sub>	C	D	
M	19	6	9	14	8	3	4	18
M-45	8	1	2	39	4	—	—	—
M-74	40	17	21	13	—	—	—	27
M-89	—	—	—	—	—	—	—	10
M-102	19	6	<sup>a</sup>	—	2	4	7	3
M-119	27	13	11	6	—	—	—	3
M-146	18	10	7	3	2	—	—	4
M-159	100	100	100	100	35	7	3	100
254	<sup>b</sup>	—	—	—	25	27	27	—
253	—	—	3	3	29	25	40	—
180	<sup>c</sup>	—	38	44	43	50	42	4
135	<sup>d</sup>	6	18	98	100	100	100	42
122	—	<sup>e</sup>	7	7	—	2	2	3
95	<sup>f</sup>	—	9	22	26	23	19	7

<sup>a</sup> cf. *m/e* 180. <sup>b</sup> cf. M. <sup>c</sup> cf. M-74. <sup>d</sup> cf. M-119. <sup>e</sup> cf. M-146. <sup>f</sup> cf. M-159.

of the same type as those of the two isomers of diethyl 3-*t*-butyl-2,3-dihydro-2-furylidene-methylmalonate,<sup>2</sup> *i.e.* high abundances of the ions at *m/e* 135, CH<sub>3</sub>-C<sub>4</sub>H<sub>9</sub>O-CH=CH-CO<sup>+</sup>, and *m/e* 254, (M-C<sub>4</sub>H<sub>9</sub>)<sup>+</sup>, and low abundances of the ions (M-159)<sup>+</sup>. This fact and the rearrangement of the compounds into diethyl 3-*t*-butyl-5-methylfurfurylmalonate show that compounds C and D are the *cis* and *trans* isomers of diethyl 3-*t*-butyl-5-methyl-2,3-dihydro-2-furylidene-methylmalonate.

The spectrum of compound F, diethyl 3-*t*-butyl-5-methylfurfurylmalonate agrees well with that of its homologue without the methyl group in position 5.<sup>2</sup> The abundance of the ion (M-159)<sup>+</sup> is high and those of the ions (M-74)<sup>+</sup> and (M-89)<sup>+</sup> are higher than most of the other ions. The relatively high abundance of the ion at *m/e* 135, CH<sub>3</sub>-C<sub>4</sub>H<sub>9</sub>O-CH=CH-CO<sup>+</sup>, is as difficult to explain as the corresponding ion at *m/e* 121 in the mass spectrum of diethyl 3-*t*-butylfurfurylmalonate.

The elemental analyses were carried out by Mr. F. Sels, Janssen Pharmaceutica, Beerse, Belgium.

## REFERENCES

- Holmberg, G. A., Karlsson, M., Ulfstedt, O. and Olli, M. *Acta Chem. Scand.* 26 (1972) 3483.
- Holmberg, G. A., Olli, M., Strand, U. and Jalonen, H. *Acta Chem. Scand.* 27 (1973) 1219.
- Traynelis, J. V., Miskel, Jr., J. J. and Sowa, J. R. *J. Org. Chem.* 22 (1957) 1269.

4. Rinke, I. J. *Org. Syn. Coll. Vol. 2* (1950) 293.

5. *High resolution NMR spectra catalog*, Varian Associates, 1962 and 1963, Spectrum 403.

Received April 13, 1974.