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Reactions between Furfurylidenemalonic Esters and Grignard Reagents. IV. Diethyl 3-Methylfurfurylidenemalonate

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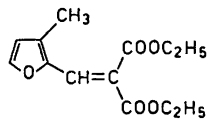
When *t*-butylmagnesium chloride reacts with diethyl 3-methylfurfurylidenemalonate, reduction, 1,4-, 1,6-, and 1,8-addition products are formed. The methyl group in position 3 of the furan nucleus does not have any blocking effect on the 1,6-addition reaction but only one product, the *trans* isomer, is formed. Methylmagnesium iodide, ethylmagnesium bromide, isopropylmagnesium bromide, and isobutylmagnesium chloride react in the same way as with diethyl furfurylidenemalonate and its 5-methyl derivative.

The rearrangements of the 1,6- and 1,8-addition products of *t*-butylmagnesium chloride and furfurylidenemalonic esters are discussed.

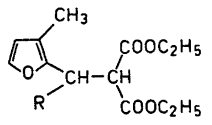
The reactions of Grignard reagents with furfurylidenemalonic ester and its 5-methyl homologue have previously been studied in this laboratory.[1–3] The main reaction in all known cases is a 1,4-addition of the Grignard reagent to the conjugated double bond system C=C–C=O. This reaction is partly suppressed by reduction of the olefinic double bond of the ester if the alkyl group of the Grignard reagent is branched at the α or β carbon atom and there is at least one hydrogen atom on the β carbon atom.[1] Benzylmagnesium chloride gives 1,4- and 1,8-additions with diethyl furfurylidenemalonate.[1] The latter reaction implies an extension of the conjugated double bond system to the furan nucleus. *t*-Butylmagnesium chloride gives 1,6- and 1,8-addition together with 1,4-addition and reduction with diethyl furfurylidenemalonate.[2] If diethyl 5-methylfurfurylidenemalonate is substituted for diethyl furfurylidenemalonate in the reaction with *t*-butylmagnesium chloride, reduction, 1,4- and 1,8-additions are observed.[3] No 1,8-addition occurs because the methyl group in position 5 of the furan nucleus of the ester apparently prevents the *t*-butyl group from entering at this position.

The reduction and 1,4-addition products, furfurylmalonic ester, 5-methylfurfurylmalonic ester, and their homologues alkylated in the β position, are, of course, quite stable while the dihydrofuran derivatives which are formed in the 1,6- and 1,8-addition reactions are unstable and rearrange prototropically in acid solution to furan derivatives. The 1,8-addition products seem to be so unstable that they rearrange immediately after their formation from the primary reaction products, which still contain magnesium.[1,2] Unlike these compounds, the 1,6-addition products are stable enough to allow their detection by combined gas chromatography/mass spectrometry.[2,3] Attempts to isolate them in a pure state have not been successful. The isolation of one rearranged 1,6-addition product, diethyl 3-*t*-butyl-5-methyl-furfurylmalonate, has, however, been achieved.[3]

The observed blocking effect of the methyl group in position 5 of the furan nucleus of diethyl 5-methylfurfurylidenemalonate justified an examination of the reactions between *t*-butylmagnesium chloride and diethyl 3-methylfurfurylidenemalonate (I). A gas chromatographic analysis of the products of this reaction on a column containing OV-17 as the stationary phase showed that four compounds are formed. None of them rearrange in acid solution. The components of the reaction mixture were separated by preparative gas chromatography. The high temperature that had to be used caused pyrolysis to some extent but the fractions were pure enough to allow identification of the sub-



I



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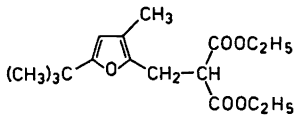

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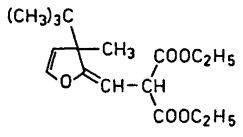


IV

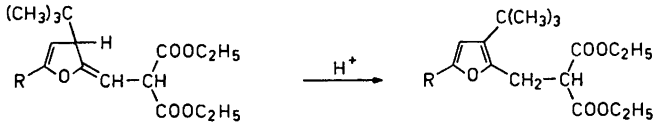
stances. The NMR and mass spectra of the fractions show that diethyl 3-methylfurfurylmalonate (II; R = H), diethyl 2,2-dimethyl-1-(3′-methyl-2′-furyl)propylmalonate [II; R = $(CH_3)_3C$], diethyl 5-*t*-butyl-3-methylfurfurylmalonate (III), and diethyl 3-*t*-butyl-3-methyl-2,3-dihydro-2-furylidenemetylmalonate (IV) are formed in the reaction. The presence of diethyl 3-methylfurfurylmalonate and diethyl 5-*t*-butyl-3-methylfurfurylmalonate was proved by comparison of the spectra with spectra of authentic samples obtained by independent syntheses.

These results show that *t*-butylmagnesium chloride gives reduction, 1,4-, 1,6-, and 1,8-additions with diethyl 3-methylfurfurylidenemalonate. The molar ratio of the products was 7:40:19:34 in the present experiments. No blocking effect of the methyl group in position 3 was observed.

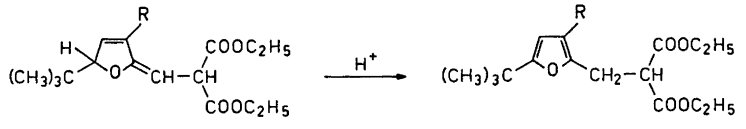
Both diethyl furfurylidenemalonate and its 5-methyl homologue give two 1,6-addition products, which are *cis* and *trans* isomers.[2,3] Diethyl 3-methylfurfurylidenemalonate gives only one 1,6-addition product. For sterical reasons, it is clear that the product is the *trans* isomer.

The structures of the 1,6-addition products (V; R = H or CH_3) of *t*-butylmagnesium chloride with diethyl furfurylidenemalonate and its 5-methyl homologue which rearrange prototropically in acid solution to 3-*t*-butylfuran derivatives (VI) have up till now been proved only by deductions based on mass spectra and the structure of one rearranged product.[2,3] Consequently, the results might have been called in question. The isolation of diethyl 3-*t*-butyl-3-methyl-2,3-dihydro-2-furylidenemethylmalonate (IV), which cannot rearrange prototropically, strongly supports the proposed structures. This fact again shows the practicability of mass spectrometry for determining structures.

A series of experiments were performed with methylmagnesium iodide, ethylmagnesium bromide, isopropylmagnesium bromide, and isobutylmagnesium chloride in order to examine whether these Grignard reagents give rise to 1,6- and 1,8-additions as well as the 1,4-addition but the results were as negative as those with diethyl furfurylidenemalonate and its 5-methyl homologue.[1,3] The reagents give reduction and 1,4-addition with diethyl 3-methylfurfurylidene-



V VI



VII VIII

malonate in the same way as in the previously reported experiments.

The unrearranged 1,8-addition products (VII; R = H or CH_3) of *t*-butylmagnesium chloride with diethyl furfurylidenemalonate and its 3-methyl homologue have not been detected directly in any of the examined cases. Their intermediate presence in the reaction mixtures has been deduced by analogy with the 1,6-addition products and from the structures of the rearranged compounds (VIII). Any plausible explanation as to why the 1,8-addition products are less stable than the 1,6-addition products has not been given.

The unrearranged addition products (V and VII; R = H or CH_3) can be considered to be vinyl ethers, the resonance energies of which are relatively low (14.1 kJ/mol in divinyl ether and 14.9 kJ/mol in ethyl vinyl ether).[4] The rearrangements imply formation of furan derivatives (VI and VIII) with high resonance energies (72 kJ/mol in unsubstituted furan [4]). Therefore, the total rate of the rearrangements ought to be high. This would explain why the primary 1,8-addition products (VII) have not been directly detected but it does not answer the question why the rearrangements of the 1,6-addition products (V) are so much slower. The reason for this retardation seems to be the steric strain in the rearranged products (VI) produced by the bulky groups in positions 2 and 3 of the furan nucleus.

A rough estimation of the steric strain in the rearranged 1,6-addition products (VI) can be performed in the following way. *cis*-Isobutyl-*t*-butylethylene can *mutatis mutandis* be compared with the compounds in question. Unfortunately, no determination of the steric strain in this hydrocarbon can be found in the literature. However, the steric strain in *cis*-*t*-butylmethylethylene (*Z*-4,4-dimethyl-2-pentene) and *cis*-di-*t*-butylethylene (*Z*-2,2,5,5-tetramethyl-3-hexene) has been calculated from the heats of hydrogenation of the *cis* and *trans* isomers. Turner, Nettleton, and Perelman obtained values in kcal/mol that on conversion give 17.9 and 39.2 kJ/mol, respectively,[5] while the values obtained by Rockenfeller and Rossini give 16.4 and 44.0 kJ/mol.[6] The steric strain of *cis*-isobutyl-*t*-butylethylene must be between these extremes and it can be concluded that the steric strain in the rearranged 1,6-addition products (VI) is large enough to explain why the rates of the rearrangements of the 1,6-addition products are retarded.

EXPERIMENTAL

3-Methylfurfural. Vilsmeyer formulation of 3-methylfuran [7] according to Kutney, Hanssen, and Nair [8] gave an oil, b.p. 69 – 71 °C/2.4 kPa. It was used in the synthesis of diethyl 3-methylfurfurylidenemalonate without removal of the small quantity of 4-methylfurfural.

5-t-Butyl-3-methylfurfural was prepared from 2-*t*-butyl-4-methylfuran [9] in the same way as 3-methylfurfural. The yield was 87 % of material boiling at 94 – 95 °C/1.05 kPa. NMR spectrum: 4 singlets; aldehyde proton at δ 9.54; H-4 proton at δ 5.92; methyl protons at δ 2.26; *t*-butyl protons at δ 1.30.

Diethyl 3-methylfurfurylidenemalonate (I) was prepared from 3-methylfurfural and diethyl malonate by the method previously used in this laboratory.[1,3] The ester, b.p. 197 °C/2.95 kPa, was purified by recrystallisation from ligroin. The yield of pure material, m.p. 70.5 – 71.5 °C, was 64 %. (Found: C 62.09; H 6.30. Calc. for $C_{13}H_{16}O_5$: C 61.90; H 6.39.) NMR spectrum and MS confirm the structure.

Diethyl-5-t-butyl-3-methylfurfurylidenemalonate was prepared from 5-*t*-butyl-3-methylfurfural and diethyl malonate by the same method. The pure ester melted at 67 – 68 °C after distillation under reduced pressure (b.p. 175 – 180 °C/2.0 kPa) and recrystallisation from ligroin. (Found: C 66.38; H 7.80. Calc. for $C_{17}H_{24}O_5$: C 66.21; H 7.85.) NMR spectrum and MS confirm the structure.

Diethyl 3-methylfurfurylmalonate (II; R = H). Diethyl 3-methylfurfurylidenemalonate (10 g) was dissolved in ethanol (150 ml) and hydrogenated at room temperature and atmospheric pressure in the presence of freshly prepared and thoroughly washed Raney nickel [10] (from 2.0 g of nickel alloy). The catalyst was filtered off and diethyl 3-methylfurfurylmalonate, b.p. 154 – 155 °C/1.9 kPa, was distilled. (Found: C 61.19; H 7.04. Calc. for $C_{13}H_{18}O_5$: C 61.41; H 7.14.) NMR spectrum and MS confirm the structure.

Diethyl-5-t-butyl-3-methylfurfurylmalonate (III) was prepared from diethyl 5-*t*-butyl-3-methylfurfurylidenemalonate in the same way as the preceding ester. The pure compound boiled at 166 °C/1.3 kPa. (Found: C 65.58; H 8.33. Calc. for $C_{17}H_{26}O_5$: C 65.78; H 8.44.) NMR spectrum and MS confirm the structure.

The reactions of diethyl 3-methylfurfurylidenemalonate with methylmagnesium iodide, ethylmagnesium bromide, isopropylmagnesium bromide and isobutylmagnesium chloride were performed on the semimicro and macro scales exactly using the previously described method.[1] The results were analogous to those obtained with diethyl furfurylidenemalonate and its 5-

methyl homologue.[1,3] Methylmagnesium iodide gave diethyl 1-(3′-methyl-2′-furyl)ethylmalonate (II; R = CH_3) and ethylmagnesium bromide diethyl 1-(3′-methyl-2′-furyl)propylmalonate (II; R = C_2H_5). Diethyl 3-methylfurfurylmalonate (II; R = H) and diethyl 2-methyl-1-(3′-methyl-2′-furyl)propylmalonate [II; R = $(CH_3)_2CH$] were formed in the experiments with isopropylmagnesium bromide. The molar ratio was 17:83. Isobutylmagnesium chloride gave diethyl 3-methylfurfurylmalonate (II; R = H) and diethyl 3-methyl-1-(3′-methyl-2′-furyl)butylmalonate [II; R = $(CH_3)_2CH-CH_2$] in the molar ratio of 22:78. Elemental analyses, NMR spectra, and MS confirm the structures.

The reactions of diethyl 3-methylfurfurylidenemalonate with t-butylmagnesium chloride. The experiments were performed using the method previously described. The reaction products were analysed by gas chromatography (column 3 mm × 1.5 m, stationary phase 1 % OV-17, nitrogen flow 28 ml/min, temperature of the oven 185 °C). Four peaks with relative retention times of 1.00 (compound A), 1.20 (compound B), 1.35 (compound C), and 1.59 (compound D) were obtained.

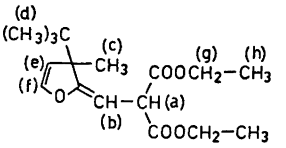
Compound A was shown to be diethyl 3-methylfurfurylmalonate (II; R = H) by comparing retention times and mass spectra (taken on a GC/MS combination instrument.

Compound B was isolated by preparative gas chromatography. Its NMR spectrum shows a simple AB quartet with the shifts at δ 3.69 and 3.48 (J = 9.0 Hz) and an AX quartet with the shifts at δ 7.02 and 5.95 (J = 1.8 Hz) as well as signals from two ester ethyl groups, one methyl, and one *t*-butyl group. These data reveal that substance B is diethyl 2-2,dimethyl-1-(3′-methyl-2′-furyl)propylmalonate [II; R = $(CH_3)_3C$]. (Found: C 65.58; H 8.24. Calc. for $C_{17}H_{26}O_5$: C 65.78; H 8.44). The MS of the substance confirms the structure.

Compounds C and D were not obtained in the pure state by preparative gas chromatography. The identity of compound C and diethyl 5-*t*-butyl-3-methylfurfurylmalonate (III) was therefore established by comparing their retention times and mass spectra.

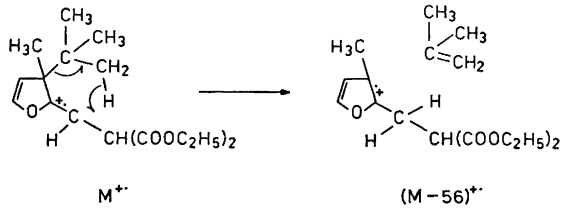
The purest sample of compound D, obtained by preparative gas chromatography, contained small quantities of compound C and diethyl 3-methylfurfurylmalonate. The latter compound is apparently a pyrolysis product of compound D. However, a rather good NMR spectrum of diethyl 3-*t*-butyl-3-methyl-2,3-dihydro-2-furylidenemethylmalonate (IV; *cf.* Table 1) is obtained if the relatively small signals in the NMR spectrum of the obtained sample arising from the impurities mentioned above are disregarded. The doublets of the protons *e* and *f* correspond to the furan protons H-4 and H-5. The fact that the signals are situated at higher field shows that the furan nucleus has reacted to form a dihydrofuran derivative. On the other hand, the chemical shifts of the protons *a* and *b* have moved to lower field as a consequence of the double bond between the β carbon atom and the dihydrofuran group.

Table 1. Chemical shift (δ) and coupling constants (J) in the NMR spectrum of compound D (diethyl 3-*t*-butyl-3-methyl-2,3-dihydro-2-furylidenemethylmalonate).



Proton	δ	Spin system	J in Hz
a	4.25	AB	9.2
b	4.68		
c	1.19		
d	0.90		
e	5.06	AB	2.9
f	6.33		
g	4.06, 4.05	A_2X_5	7.0
h	1.24, 1.22		

The mass spectrum of compound D is quite different in appearence to the spectra of the other compounds in this paper. The most important ions with high masses are found at *m/e* 310 (M^+), 254 (r.a. 11), 253 (5), 181 (35), 180 (71), and 135 (100). The formation of the ion at *m/e* 254 (=M − 56) is explained by the mechanism in Scheme 1. The ion at *m/e* 253 (=M − 57) is simply formed from the molecular



Scheme 1.

ion by splitting of the *t*-butyl group. The formation of the ion at *m/e* 181 is best explained by loss of an ethoxycarbonyl group from the ion at *m/e* 254. The type of reaction that leads to the formation of the ion at *m/e* 180 ($=M-COOC_2H_5-C_4H_9$) has previously been discussed.[2] The ion at *m/e* 135 ($= CH_3\text{-}C_4H_2O\text{-}CH{=}CH\text{-}CO^+$) seems to be a result of a stripping process: $M^+ \rightarrow$ the ion at *m/e* 180 $\rightarrow$ the ion at *m/e* $135 + \cdot OC_2H_5$.

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