

## Reactions between 2-Furaldehyde and Grignard Reagents. II. 1,4- and "Abnormal" Additions of Benzylmagnesium Chloride

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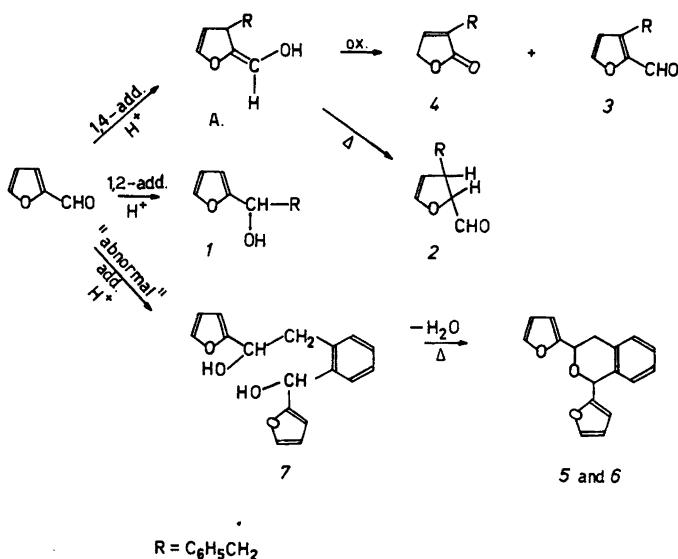
When benzylmagnesium chloride reacts with 2-furaldehyde, 1,2-, 1,4- and "abnormal" additions are the main reactions. 1,4-Addition predominates when the reagent is in great excess. "Abnormal" addition is favoured by a low ratio between reagent and substrate.

Two compounds, 3-benzyl-2-furaldehyde and 3-benzyl-2-(5*H*)-furanone, formed by air or oxygen oxidation of the 1,4-addition product, were also isolated. The formation of the various reaction products is discussed.

In a previous paper, it was shown that *t*-butylmagnesium chloride gives 1,4- and 1,6-additions besides 1,2-addition to 2-furaldehyde.<sup>1</sup> Other investigations have shown that benzylmagnesium halides give considerable amounts of

conjugate addition products in reactions with  $\alpha,\beta$ -unsaturated aldehydes.<sup>2</sup> Further, benzylmagnesium halides seem to have a tendency to add in the conjugated manner to the furan ring of some furan derivatives, such as 2-acetylfuran<sup>3</sup> and diethyl furfurylidene malonate.<sup>4</sup> These facts seemed to justify a study of the reaction between 2-furaldehyde and benzylmagnesium chloride.

Gas chromatographic analyses of the reaction mixtures showed the presence of six substances, 1-(2-furyl)-2-phenylethanol (*1*; 1,2-addition product), 3-benzyl-2,3-dihydro-2-furaldehyde (*2*; 1,4-addition product), 3-benzyl-2-furaldehyde (*3*), 3-benzyl-2-(5*H*)-



Scheme 1. Reaction between Grignard reagent and 2-furaldehyde.

furanone (4) and two stereoisomers of 1,3-bis(2-furyl)isochromane (5 and 6) (Scheme 1). Silylation of the worked-up reaction mixture revealed three new peaks on GLC, while the peaks due to 1, 2, 5 and 6 disappeared. Two of the peaks were due to the trimethylsilyl ethers of compounds 1 and 7, respectively, and the third peak was identified as the trimethylsilyl ether of the enol A. Further, if the worked-up reaction mixture was subjected to air for some time or when oxygen was bubbled through it, the enol was quantitatively transformed to the compounds 3 and 4. If compound 2 would be the primary reaction product, oxidation could not result in the formation of compound 4. However, compound 3 could possibly be formed by oxidation of either the aldehyde 2 or the enol A. These facts indicate that the enol is the true and relatively stable 1,4-addition product which rearranges during the gas chromatographic analysis to the dihydrofuranaldehyde. Compounds 3 and 4 are then apparently oxidation products.

The enol formed in the reaction between *t*-butylmagnesium chloride and 2-furanaldehyde is probably much more unstable and immediately rearranges to the dihydrofurfural during the work-up of the reaction mixture. This is indicated by the facts that no enol could be detected by silylation and that treatment with oxygen did not increase the amounts of the *t*-butyl analogues of compounds 3 and 4.

Silylation of the reaction mixture from the present reaction also revealed that compounds 5 and 6 had formed in the gas chromatograph by dehydration of compound 7, 2-[*o*-(2-furylhydroxymethyl)]phenyl-1-(2-furyl)ethanol. This compound is an analogue to the one isolated by Schmidlin *et al.*<sup>5</sup> from the reaction between benzylmagnesium chloride and benzaldehyde.

These results show that benzylmagnesium chloride and 2-furanaldehyde react in three different ways, namely by "normal" 1,2-addition, by 1,4-addition and by an "abnormal" addition. The course of the reaction is, however, highly dependent on the ratio of Grignard reagent to aldehyde (Table 1). The highest proportion of 1,2-addition is obtained when the ratio is 1:1 and when the substrate is in excess. A high ratio favours the 1,4-addition and a small ratio the "abnormal" one. The latter reaction dominates when the ratio is 1:2 and

Table 1. Relative amounts of reaction products formed in the reaction between benzylmagnesium chloride (I) and 2-furanaldehyde (II).

[I]/[II]	1,2-Add.	"Total" 1,4-Add.	"Abnormal" addition
0.5 <sup>a</sup>	22	20	58
0.5	34	48	18
1.0	33	58	9
2.5	20	79	1
5.0	17	83	—
10.0	6	94	—

<sup>a</sup> Inverse addition.

the Grignard reagent is slowly added to the aldehyde. The fact that the 1,4-addition occurs almost quantitatively when the Grignard reagent is present in great excess, might be explained by a double coordination: one reagent molecule to the oxygen atom of the carbonyl group and one molecule to the oxygen atom of the furan nucleus. The latter would enhance the activation of position 3 of the nucleus. This enhanced activation might also explain the fact that the ratio of the 1,4- and 1,2-compounds in the present reaction is far greater than is usually found for reactions with  $\alpha,\beta$ -unsaturated aldehydes. The fact that the "abnormal" addition is favoured by low ratios of reagent to aldehyde is in concordance with the results of Young and Siegel in their investigation of the reaction between citronellal and benzylmagnesium chloride.<sup>6</sup> *Mutatis mutandis* the mechanism proposed by them can, of course, be applied to the present reaction. Small amounts of compounds 3 and 4 were formed in every experiment and they are included in "total" 1,4-addition in Table 1.

The formation of a 1,6-addition product was observed in the reaction between *t*-butylmagnesium chloride and 2-furanaldehyde. However, in the present reaction no 1,6-addition product was detected. This was, as a matter of fact, expected because the central carbon of benzylmagnesium chloride is less crowded than that of *t*-butylmagnesium chloride.

## EXPERIMENTAL

*2-Furanaldehyde.* Commercial 2-furanaldehyde (Riedel-de Haën, BRD) was purified by distillation (b.p. 161–162 °C).

The reactions of 2-furaldehyde with benzylmagnesium chloride were performed in a way previously described.<sup>1</sup> In this case, however, the reagent was 0.5 M and every reaction was performed under N<sub>2</sub> using diethyl ether, distilled from benzophenone ketyl, as solvent. Six experiments with different ratios between reagent and substrate were performed (Table 1). In one of the experiments the reagent was added to the substrate. In all the other experiments the substrate was added to the reagent. The reaction mixtures were worked up in the usual way using NH<sub>4</sub>Cl-solution. GLC analysis (glass column 3 mm × 3 m; 1 % XE-60 on Gas-Chrom Q; N<sub>2</sub> 30 ml/min) gave six peaks, due to the compounds 1, 2, 3, 4, 5 and 6. The proportions of the different reaction products were calculated from the gas chromatograms.

If the reaction mixtures were exposed to air for a longer time or if a stream of oxygen was passed through them, the peaks due to 3 and 4 increased while the peak due to 2 gradually decreased and finally disappeared. Because 2 can hardly be oxidized to 4 by oxygen treatment in solution, the reaction mixture from one experiment was silylated with a mixture of HMDS and TMCS in anhydrous pyridine and analyzed by GLC. The peaks due to 1, 2, 5 and 6 disappeared and three new peaks were observed. Combined GLC-MS analysis (LKB 9000) showed that one of the peaks was due to silylated 1 and one to silylated 7. These facts show that the compounds 5 and 6 had been formed from compound 7 during the gas chromatographic analysis and that 2, which hardly is silylated under the experimental conditions used, is not a primary reaction product. The third peak gave a mass spectrum that corresponds to the expected fragmentation of the silyl derivative of the enol A. Further, because the enol A is expected to be oxidized by oxygen to 3 and 4, the existence of the enol A as a primary 1,4-addition product is rather well-established. The fact that 2 but not A was detected in the gas chromatographic analysis of the unsilylated reaction mixture must be a consequence of a rearrangement that occurred in the column.

Compounds 1, 2, 3 and 4 were separated and purified by preparative GLC (Varian Aerograph A-700; column 9.5 mm × 6.1 m; 30 % SE-30 on Chromosorb W; He 200 ml/min). Compounds 5 and 6 were isolated and purified in a way described below. <sup>1</sup>H NMR spectra were taken of all isolated compounds (Perkin-Elmer R 12 and JEOL FX-60).

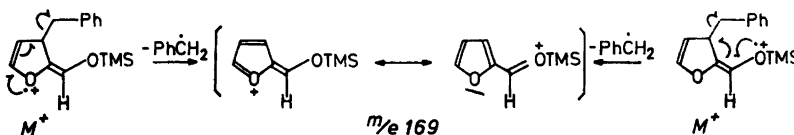
3-Benzyl-2,3-dihydro-2-furaldehyde (2). The structure of this compound was determined by comparing its <sup>1</sup>H NMR spectrum with that of the corresponding *t*-butyl compound. The magnitude of the coupling constant between H-2 and H-3 also in this case indicated the presence of the *trans* isomer. The signals of the benzyl methylene group and the H-3 proton form an A<sub>2</sub>B system in which the signal of H-3, forming the B part, is also coupled to those of H-2, H-4 and H-5. This made the B part of the A<sub>2</sub>B system too complicated to be completely resolved at 60 MHz. Therefore no exact analysis was performed. The A<sub>2</sub> part of the system, however, made it possible to determine the shift of the ArCH<sub>2</sub> protons. <sup>1</sup>H NMR (60 MHz, CCl<sub>4</sub>): δ 4.3 (H-2, dd, *J* 4.1 and 1.1 Hz), 2.9–3.4 (H-3, m, *J* 4.2, 2.5 and 1.7 Hz), 4.8 (H-4, dd, *J* 2.7 and 2.5 Hz), 6.3 (H-5, dd, 2.7 and 1.7 Hz), 9.4 CHO, d, *J* 1.1 Hz), 2.7 (ArCH<sub>2</sub>) 7.0 (ArH, broad "singlet"). MS [IP 70 eV; *m/e* (% rel. int.)]: 188 (1.4, M), 159 (44.8, M – CHO), 128 (4.0), 97 (8.7, M – ArCH<sub>2</sub>), 91 (96.0, ArCH<sub>2</sub>), 69 (100).

1-(2-Furyl)-2-phenylethanol (1). In the <sup>1</sup>H NMR spectrum the furyl protons gave an ABX system which was not completely analyzed and the shifts and couplings are not given here. <sup>1</sup>H NMR (60 MHz, CCl<sub>4</sub>): δ 4.7 (FurCH, B part of A<sub>2</sub>B system, *J* 6.7 Hz), 3.0 (ArCH<sub>2</sub>, A part of A<sub>2</sub>B system, *J* 6.7 Hz), 7.1 (ArH, broad "singlet"), 1.7 (OH, s). MS [IP 70 eV; *m/e* (% rel. int.)]: 188 (1.7, M), 170 (100, M – H<sub>2</sub>O), 141 (76.0, M – H<sub>2</sub>O – CHO), 115 (39.3), 97 (30, M – ArCH<sub>2</sub>), 91 (10.6, ArCH<sub>2</sub>).

Trimethylsilyl ether of 3-benzyl-2,3-dihydro-2-furylidene methanol (TMS ether of A). The MS of this compound is characterized by the base peak at *m/e* 169. The loss of a benzyl radical from the parent ion is highly favoured by the fact that two ways of allylic cleavage are possible. Further, the resulting fragment is stabilized by resonance (Scheme 2). MS [IP 70 eV; *m/e* (% rel. int.)]: 260 (0.5, M), 245 (3.1, M – CH<sub>3</sub>), 169 (100, M – ArCH<sub>2</sub>), 91 (5.7, ArCH<sub>2</sub>), 73 (69.9, TMS).

Trimethylsilyl ether of 1. MS [IP 70 eV; *m/e* (% rel. int.)]: 260 (0.1, M), 245 (23.3, M – CH<sub>3</sub>), 169 (17.7, M – ArCH<sub>2</sub>), 91 (5.9, ArCH<sub>2</sub>), 73 (100, TMS).

3-Benzyl-2-furaldehyde (3). The <sup>1</sup>H NMR spectrum shows, by the positions of the two furan proton signals, that this is a 3-substituted 2-furaldehyde. <sup>1</sup>H NMR (60 MHz, CCl<sub>4</sub>): δ 6.2 (H-4, d, *J* 1.6 Hz), 7.4 (H-5, dd, *J* 1.6 and 0.6 Hz), 9.7 (CHO, d, *J* 0.6 Hz), 4.1 (ArCH<sub>2</sub>, s),



Scheme 2. The MS fragmentation of the TMS ether of A.

7.1 (ArH, broad "singlet"). MS [IP 70 eV;  $m/e$  (% rel. int.)]: 186 (100, M), 185 (48.2, M-H), 169 (17.7), 168 (13.8), 157 (33.5, M-CHO), 141 (28.4), 128 (41.0), 91 (12.6, ArCH<sub>2</sub>).

3-Benzyl-2-(5 H)-furanone(4) <sup>1</sup>H NMR (60 MHz, CCl<sub>4</sub>):  $\delta$  6.7 (H-4, tt,  $J$  1.8 and 1.8 Hz), 4.6 (H-5, dt,  $J$  1.8 and 1.8 Hz), 3.5 (ArCH<sub>2</sub>, dt,  $J$  1.8 and 1.8 Hz), 7.1 (ArH, broad "singlet"). MS [IP 70 eV;  $m/e$  (% rel. int.)]: 174 (13.8, M), 130 (13.8, M-CO<sub>2</sub>), 129 (100, M-COOH), 117 (4.4), 115 (16.9), 91 (11.4, ArCH<sub>2</sub>).

2-[o-(2-Furylhydroxymethyl)]phenyl-1-(2-furyl)-ethanol (7). The structure of this compound was determined from a mass spectrum of the silylated compound and from the structures of the dehydration products 5 and 6. MS (of the bis-trimethylsilyl derivative) [IP 70 eV;  $m/e$  (% rel. int.)]: 428 (0.4, M) 413 (0.5, M-CH<sub>3</sub>), 360 (0.6), 339 (0.8, M-TMSO), 338 (1.9, M-TMSOH), 270 (0.4), 249 (1.0, 338-TMSO), 169 (50.1), 141 (11.8), 115 (5.7), 73 (100, TMSO).

1,3-Bis(2-furyl)isochromane (5 and 6). The reaction mixture which contained the largest amount of compound 7 was steam distilled for several hours. The residue contained an almost pure mixture of compounds 5 and 6. The mixture was dissolved in warm ethanol. On cooling, compound 6 precipitated as white crystals, which were purified by repeated recrystallizations from ethanol (m.p. 110–111 °C). The filtrate was treated with light petroleum. This resulted in the precipitation of compound 5. The crystals were recrystallized from a mixture of ethanol and light petroleum (m.p. 73–74 °C). The <sup>1</sup>H NMR and mass spectra show that compounds 5 and 6 are isomers of 1,3-bis(2-furyl)isochromane. Both compounds show in their <sup>1</sup>H NMR spectra an ABX system arising from the protons at carbons 3 and 4. The signals from the aromatic and heteroaromatic protons are overlapping and their shifts are given as intervals. The isomerism between these compounds is certainly due to the presence of two asymmetric carbon atoms in the molecule. One of the isomers is thus a mixture of two enantiomers where the furan rings both are on the same side of the plane of the dihydropyran ring (*cis* configuration). The other isomer consists of a mixture of two enantiomers where the furan rings are on different sides of the plane of the dihydropyran ring (*trans* configuration). The two isomers are then diastereomers of each other.

Compound 5. <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>):  $\delta$  3.0 and 3.3 (H-4 and H-4', AB part of ABX system,  $J_{AB}$  16.5,  $J_{AX}$  11.1 and  $J_{BX}$  3.7 Hz), 4.9 (H-3, X part of ABX system), 6.0 (H-1, s), 5.9–7.4 (ArH, FurH). MS [IP 70 eV;  $m/e$  (% rel. int.)]: 266 (8.0, M), 198 (100.0), 170 (56.0), 169 (32.5), 141 (86.0), 128 (12.0), 115 (26.0).

Compound 6. <sup>1</sup>H NMR (60 MHz, CDCl<sub>3</sub>):  $\delta$  3.5 and 3.0 (H-4 and H-4', AB part of ABX system,  $J_{AB}$  16.0,  $J_{AX}$  11.7 and  $J_{BX}$  2.3 Hz), 5.0 (H-3, X part of ABX system), 6.0 (H-1, s),

6.1–7.4 (ArH, FurH). MS [IP 70 eV;  $m/e$  (% rel. int.)]: 266 (17.6, M), 198 (2.2), 170 (100.0), 169 (22.4), 141 (75.0), 128 (9.5), 115 (21.0).

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