

Studies on the Furan Series

Part I. The Acidic Condensation of Aldehydes with Methyl 2-Furoate

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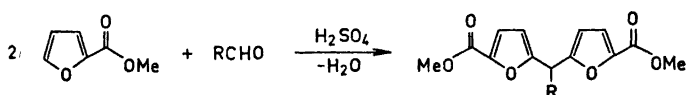
Aldehydes condense with methyl 2-furoate in concentrated sulphuric acid, yielding bis(5-carbomethoxy-2-furyl)methoxy derivatives. The condensation yield of aromatic aldehydes depends on the substituents in the benzene ring.

The 2- and 5-positions of the furan ring are susceptible to electrophilic attack. This is why furan condenses with aldehydes under acidic conditions to form difurylalkyl derivatives. Brown and Sawatsky¹ have studied the condensation of furan and sylvan with aliphatic aldehydes in hydrochloric acid and obtained variable yields of difurylalkanes. Both furan and sylvan are sensitive to acid catalyzed ring opening reactions and resinification. Furan compounds, which have electron withdrawing substituents (*e.g.* furoic acid derivatives), are stable in acidic solutions, and reactions under stronger conditions than in aqueous hydrochloric acid are possible.

Some papers on the condensation of furoic acid esters have been published. Dinelli and Marini,²⁻⁴ and Decsei and Zsador⁵ treated ethyl 2-furoate with trioxane, Shono *et al.*⁶ with paraldehyde, and Willard and Hamilton⁷ methyl 2-furoate with chloral. All the reactions occurred in concentrated sulphuric acid, and the main products were bis(5-carbomethoxy-2-furyl)methoxy derivatives. Both bis(5-carbomethoxy-2-furyl)methane and -ethane have been prepared also by Lapkin and Orlova⁸ using methyl 2-furoate, α -chlorinated ethers and zinc.

In the present investigation methyl 2-furoate was chosen as the furanoid compound. Both aliphatic and aromatic aldehydes were used. All the condensations were carried out in concentrated sulphuric acid.

The main reaction was:



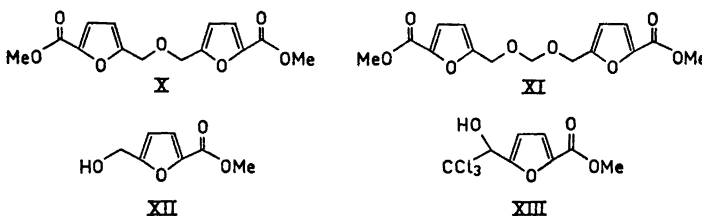
The aldehydes employed, compounds synthesized, reaction times and yields are given in Table 1. Some tarry material was formed in every reaction.

Table 1. Condensation products of aldehydes with methyl 2-furoate.

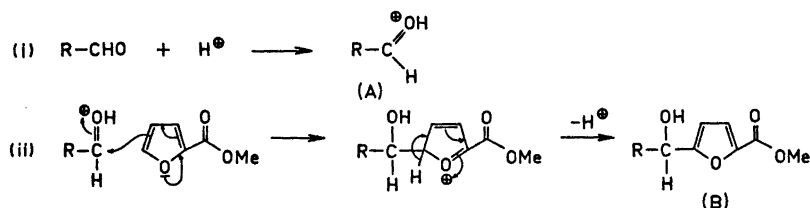
Reactants	Products (R =)	Yield (%)	Reaction time (h)
Formaldehyde	I H-	80	0.5
Acetaldehyde	II CH ₃ -	84	2
Propionaldehyde	III CH ₃ CH ₂ -	63	3
Butyraldehyde	IV CH ₃ (CH ₂) ₂ -	60	16
Chloral	V CCl ₃ -	83	12
Benzaldehyde	VI Phenyl-	6	24
<i>o</i> -Nitrobenzaldehyde	VII <i>o</i> -Nitrophenyl-	22	12
<i>m</i> -Nitrobenzaldehyde	VIII <i>m</i> -Nitrophenyl-	49	12
<i>p</i> -Nitrobenzaldehyde	IX <i>p</i> -Nitrophenyl	67	12
Anisaldehyde	No reaction		120
Veratraldehyde	No reaction		150

When the condensation was effected with trioxane, three byproducts could be separated from the black tar formed. The compounds were isolated by preparative thin layer chromatography and identified by NMR spectroscopy: 4 % of bis(5-carbomethoxyfurfuryl)ether (X), 8 % of bis(5-carbomethoxyfurfuryloxy)methane (XI) and 5 % of methyl 5-hydroxymethyl-2-furoate (XII). All these compounds are known and have been prepared previously by Moldenhauer *et al.*⁹

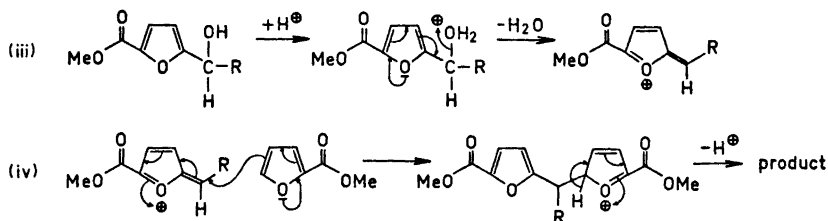
Willard and Hamilton⁷ have mentioned that in the reaction of chloral and furan, it is possible to isolate a byproduct, which is 1-(2-furyl)-2,2,2-trichloroethanol. In our case we found that 7 % of 1-(5-carbomethoxy-2-furyl)-2,2,2-trichloroethanol (XIII) could be separated from the main product V.



The reaction is presumed to be a normal acidic condensation, starting with the protonation of the aldehyde. The nucleophilic attack of the furan ring on the aldehyde carbon can then take place.

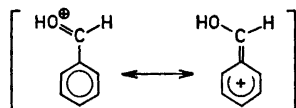


A new protonation occurs and the reaction can continue.



It was possible to isolate the intermediate B as compounds XII and XIII in the condensation of methyl 2-furoate with trioxane and chloral, respectively.

In the aliphatic series the substituents R have a slight influence on the yields, which are about the same order of magnitude. On the other hand, in the aromatic series the yields depend on the nature of R. Benzaldehyde gives only 6 % of the condensation product, because the protonated intermediate A is deactivated through resonance:



Electron donating groups in the benzene ring reduce the positive charge of the aldehyde carbon, and condensation becomes more difficult. If the +I-effect of the substituent is great enough (*e.g.* anis- and veratraldehyde) no reaction will occur. When the effect is -I, the yields will increase (when compared with benzaldehyde), as in the case of *o*-, *m*-, and *p*-nitrobenzaldehyde. The nitro groups in the *o*- and *p*-positions should have a greater influence on the condensation than in the *m*-position. The fact that *o*-nitrobenzaldehyde gave the smallest yield may be due to steric factors.

EXPERIMENTAL

Melting points are uncorrected. Proton NMR spectra were recorded on a Varian A-60 spectrometer in CDCl_3 , and relate to internal tetramethylsilane. The UV spectra were determined with a Beckman DK-2 spectrometer in ethanol (ϵ in parentheses); IR spectra with a Perkin-Elmer 125 spectrometer (using KBr pellet and liquid film techniques), and mass spectra with a Perkin-Elmer 270B mass spectrometer. Elemental analyses were carried out on an F & M 185 CHN-analyzer.

Furoic acid was prepared in accordance with the method of Salchinkin and Lapkova¹⁰ and esterified in boiling methanol to methyl 2-furoate. Other chemicals were of commercial quality.

General procedure. In all reactions 5.00 g of methyl 2-furoate was dissolved into 50 ml of conc. H_2SO_4 at 0°C , and 1.5–2.0 \times the equivalent amount of an aldehyde was added gradually. During stirring, the temperature of the mixture rose to room temperature. The reaction times are given in Table 1. After stirring the mixture was poured onto ice and shaken twice with 50 ml of ethyl acetate, which was washed with dilute NaHCO_3 , dried with MgSO_4 and evaporated. The chromatography of the viscous residue was performed on a silica gel column (elution with chloroform).

The reported yields are based on the amount of methyl 2-furoate used.

Condensation products

Bis(5-carbomethoxy-2-furyl)methane (I): Yield 4.20 g (80 %); m.p. 121°C (recrystallization from a mixture of petrol ether and chloroform). Decsei and Zsador⁵ give the melting point 120–122°C. ν_{\max} 3120, 2960, 1730 cm^{-1} ; λ_{\max} 264 (44 000) μm ; τ 2.88 (2H d 3.5 cps), 3.80 (2H d 3.5 cps), 5.83 (2H s), 6.12 (6H s). (Found: C 58.96; H 4.51. Calc. for $\text{C}_{13}\text{H}_{12}\text{O}_6$: C 59.09; H 4.58.) Using preparative TLC (elution with CHCl_3 –EtOAc 1 : 1) three by-products were isolated from the residue of I. All these compounds have been synthesized previously Moldenhauer *et al.*⁹

The NMR and IR spectra of the byproducts:

Bis(5-carbomethoxyfurfuryl)ether (X): τ 2.90 (2H d 3.5 cps), 3.56 (2H d 3.5 cps), 5.42 (4H s), 6.18 (6H s).

Bis(5-carbomethoxyfurfuryloxy)methane (XI): τ 2.90 (2H d 3.5 cps), 3.55 (2H d 3.5 cps), 5.22 (2H s), 5.40 (4H s), 6.18 (6H s).

Methyl 5-hydroxymethyl-2-furoate (XII): ν_{\max} 3410, 3120, 2960, 1730 cm^{-1} ; τ 2.99 (1H d 3.5 cps), 3.68 (1H d 3.5 cps), 5.43 (2H s), 6.18 (3H s), 6.40 (1H dis. with D_2O).

1,1-Bis(5-carbomethoxy-2-furyl)ethane (II): Yield 4.60 g (84 %); m.p. 81°C (recryst. from a mixture of water and ethanol); τ 2.93 (2H d 3.5 cps), 3.77 (2H d 3.5 cps), 5.67 (1H q 7 cps), 6.17 (6H s), 8.33 (3H d 7 cps). (Found: C 60.50; H 5.13. Calc. for $\text{C}_{14}\text{H}_{14}\text{O}_6$: C 60.43; H 5.07.)

1,1-Bis(5-carbomethoxy-2-furyl)propane (III): Yield 3.62 g (63 %). The compound was a viscous oil at room temperature. τ 2.92 (2H d 3.5 cps), 3.73 (2H d 3.5 cps), 5.89 (1H t 7 cps), 6.18 (6H s), 7.90 (2H quintet 7 cps), 9.08 (3H t 7 cps). (Found: C 61.49; H 5.15. Calc. for $\text{C}_{15}\text{H}_{16}\text{O}_6$: C 61.64; H 5.52.)

1,1-Bis(5-carbomethoxy-2-furyl)butane (IV): Yield 3.60 g (60 %); m.p. 70°C (recryst. from water-ethanol); τ 2.90 (2H d 3.5 cps), 3.72 (2H d 3.5 cps), 5.76 (1H t 7 cps), 7.80–8.80 (4H m), 9.05 (3H t). (Found: C 63.04; H 5.91. Calc. for $\text{C}_{16}\text{H}_{18}\text{O}_6$: C 62.74; H 5.92.)

1,1-Bis(5-carbomethoxy-2-furyl)-2,2,2-trichloroethane (V): Yield 6.40 g (83 %); m.p. 104°C (recryst. from water-ethanol). Willard and Hamilton⁷ give the melting point as 103–104°C. λ_{\max} 264 (28 700), 252 sh (23 600) μm ; ν_{\max} 3140, 2960, 1720 cm^{-1} ; τ 2.84 (2H d 3.5 cps), 3.18 (2H d 3.5 cps), 4.57 (1H s), 6.10 (6H s); m/e 344 (81 %), 313 (38 %), 310 (50 %), 262 (50 %), 257 (50 %), 255 (100 %), 220 (44 %). (Found: C 43.91; H 3.07. Calc. for $\text{C}_{14}\text{H}_{11}\text{Cl}_3\text{O}_6$: C 44.05; H 2.88.) Besides V, a second compound was isolated using column chromatography. It was identified as *1-(5-carbomethoxy-2-furyl)-2,2,2-trichloroethanol (XIII)*. Yield 0.55 g (7 %); m.p. 88°C; ν_{\max} 3400, 1710 cm^{-1} ; τ 2.83 (1H d 3.5 cps), 3.20 (1H d 3.5 cps), 4.58 (1H broad s), 5.30 (1H broad, dis. with D_2O), 6.18 (3H s). (Found: C 41.72; H 2.02. Calc. for $\text{C}_9\text{H}_7\text{Cl}_3\text{O}_4$: C 41.91; H 2.29.) NMR of the tetramethylsilyl derivative: τ 2.83 (1H d 3.5 cps), 3.20 (1H d 3.5 cps), 4.63 (1H s), 6.18 (3H s), 9.85–9.95 (9H broad).

1,1-Bis(5-carbomethoxy-2-furyl)phenylmethane (VI): Yield 0.40 g (6 %); m.p. 22°C (recryst. water-ethanol); τ 2.73 (5H s), 2.96 (2H d 3.5 cps), 3.79 (2H d 3.5 cps), 4.50 (1H s), 6.21 (6H s). (Found: C 66.89; H 4.38. Calc. for $\text{C}_{19}\text{H}_{16}\text{O}_6$: C 67.05; H 4.75.)

1,1-Bis(5-carbomethoxy-2-furyl)-o-nitrophenylmethane (VII): Yield 1.70 g (22 %); m.p. 99°C (recryst. from water-ethanol) ν_{\max} : 3120, 2960, 1720, 1520, 1510 cm^{-1} ; τ 1.90–2.80 (4H m), 2.89 (2H d 3.5 cps), 3.75 (2H d 3.5 cps), 3.50 (1H s), 6.17 (6H s). (Found: C 59.70; H 4.00; N 3.41. Calc. for $\text{C}_{19}\text{H}_{15}\text{NO}_6$: C 59.22; H 3.92; N 3.64.)

1,1-Bis(5-carbomethoxy-2-furyl)-m-nitrophenylmethane (VIII): Yield 3.80 g (49 %); viscous oil at room temperature; τ 1.80–2.60 (4H m), 2.87 (2H d 3.5 cps), 3.73 (2H d 3.5 cps), 4.27 (1H s), 6.15 (6H s). (Found: C 58.94; H 3.77; N 3.54. Calc. for $\text{C}_{19}\text{H}_{15}\text{NO}_6$: C 59.22; H 3.93; N 3.64.)

1,1-Bis(5-carbomethoxy-2-furyl)-p-nitrophenylmethane (IX): Yield 5.10 g (67 %); m.p. 145°C (recryst. from water-ethanol); ν_{\max} 3120, 2960, 1730, 1530, 1510 cm^{-1} ; τ 1.82 (2H d 3 cps), 2.56 (2H d 8 cps), 2.80 (2H d 3.5 cps), 3.72 (2H d 3.5 cps), 4.29 (1H s), 6.15 (6H s). (Found: C 58.84; H 3.54; N 3.54. Calc. for $\text{C}_{19}\text{H}_{15}\text{NO}_6$: C 59.22; H 3.92; N 3.64.)

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