

5-SUBSTITUTED 2-FURANCARBALDEHYDES AND WATER-SOLUBLE FURAN DERIVATIVES* **

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5-Halo-2-furaldehydes *Ia*, *Ib* react with trimethylamine in aprotic solvents to furnish 5-trimethylammonium salts of 2-furaldehyde *Ila*, *Ilb*. The reactivity of this salt was utilized for a simple preparation of 5-substituted 2-furaldehydes *IV* in water at room temperature. The possibility to synthesize azomethines *V* and ethylenes *VI*, having the trimethylammonium group in position 5 of the furan ring maintained, is discussed.

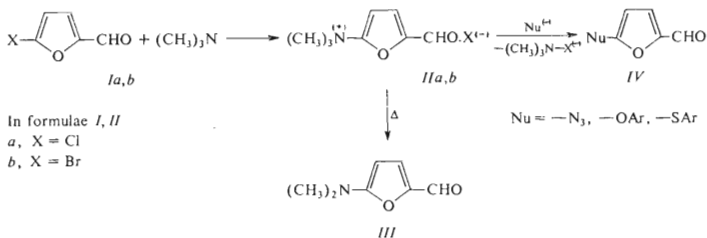
5-Substituted 2-furancarbaldehydes have been prepared by alkylation², cyclization^{3,4}, diazotization^{5,6}, formylation⁷, and reduction methods², and by nucleophilic displacement of the suitably chosen substituents in position 5 of the furan ring, as *e.g.* halogen^{6,8,9}, nitro group^{10,11} *etc.*

The quaternary ammonium group at the sp^2 hybridized carbon atom of aliphatic and aromatic compounds is an excellent leaving group¹²⁻¹⁹ and, since it is responsible for a good solubility of chemicals in water, there is a great chance for utilization in the synthesis. After being successful with substitution of bromine in 5-nitro-2-furylvinyl bromide^{20,21} and in 5-nitro-2-thienylvinyl bromide²² with tertiary amines, we went on with replacement of halogen also at the sp^2 carbon of furan ring applying the Menshutkin reaction²³. This reaction was already found to be appropriate when preparing some heterocyclic trimethyl ammonium salts, particularly nitrogen-containing heterocycles^{14,16,24}. Formation of by-products (tertiary amines) by transalkylation was reported²⁵ in attempting to prepare trimethylammonium salts of thiophene.

Quaternization of 5-halo-2-furancarbaldehydes *Ia*, *b* with trimethylamine in aprotic solvents as *e.g.* benzene, ether, tetrahydrofuran, dimethoxyethane proceeds at room temperature according to Scheme 1. 5-Iodo-2-furancarbaldehyde does not give the trimethylammonium salt at the given conditions, nor at 100 h-reaction. The by-product is the transalkylated tertiary amine *III*; it is the main product, when the reaction was carried out in protic solvents at 50–60°C.

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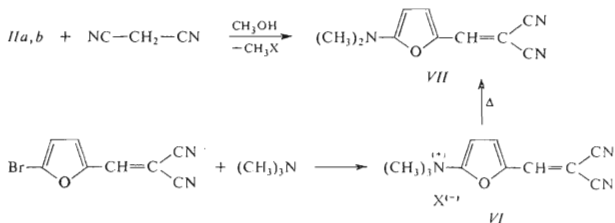


SCHEME 1

Attempts to crystallize compounds *IIa, b* at elevated temperatures in protic solvents resulted in decomposition to substance *III*. The decomposition starting at 50°C was examined by ¹H NMR spectroscopy in the 50–140°C temperature interval.

A relatively good stability of aqueous solutions of *IIa, b* at room temperature allowed to utilize these compounds for the synthesis of 5-substituted furancarbaldehydes *IV*, Nu-C₄H₃O-CH=O. Substances *IIa, b* react with nucleophiles Nu to afford the water sparingly soluble products *IV*, which are purer as those obtained from 5-halo-^{6-8,9} and 5-nitro-2-furaldehydes^{10,11}. The best nucleophiles were found to be the azide anion, alkali metal thiolates and phenolates. The reaction is indicated by the evolution of trimethylamine.

The low thermostability of the trimethylammonium group at furan ring allowed to proceed only to those reactions, which can be carried out at ambient temperature. Replacement of the anionoid part of the molecule resulted in a better thermostability of the quaternary ammonium salt to the detriment of the solubility in water. Compounds *IIa, b* gave with 70%-perchloric acid the salt *IIc*, which, according to the



SCHEME 2

^1H NMR experiment, begins to decompose at 90–110 °C. The picrate *IId* decomposes in the 100–130°C interval. Salts *Ila*, *b* react with 2,4-dinitrophenylhydrazine in 70%-perchloric acid to furnish 2,4-dinitrophenylhydrazone *V*.

Attempts to condense compounds *Ila*, *b* with malonodinitrile in methanol resulted in a cleavage of alkylhalide and formation of 5-(*N,N*-dimethylamino)-2-furfurylidenemalonodinitrile³⁰ (*VII*).

5-Bromo-2-furfurylidenemalonodinitrile was quaternized with trimethylamine in non-polar solvents to the salt *VI*. Thermal decomposition of *VI* to *VII* was monitored by ^1H NMR spectrometry in hexadeuteriodimethyl sulfoxide. It has been found that the trimethylammonium derivative *VI* decomposes to *VII* at 80°C within 10 min.

EXPERIMENTAL

Melting points were determined on a Kofler micro hot-stage, the IR and UV spectra were measured with a UR-20 (Zeiss, Jena) and UV VIS (Zeiss, Jena) spectrophotometers, respectively. The ^1H NMR spectra were recorded with a Tesla BS 487 C apparatus operating at 80 MHz with tetramethylsilane as an internal reference.

5-Chloro-2-furaldehyde (m.p. 34–35°C, ref.²⁶) and 5-bromo-2-furaldehyde (m.p. 83–84°C, ref.²⁷) were freed from hydrochloric and hydrobromic acid, respectively by neutralization in an ethereal solution and immediately used after being dried with MgSO_4 .

2-Fural-5-trimethylammonium Chloride (*Ila*)

Trimethylamine (2.5 g) was added to a benzene (50 ml) solution of 5-chloro-2-furaldehyde (4 g) at 5–10°C with stirring. The insoluble product was filtered off after 6 h and washed with ether. Yield 3.6 g (approx. 64%), m.p. 137–145°C (decomp.). The work-up of the filtrate afforded 5-(*N,N*-dimethylamino)-2-furaldehyde²⁸. For $\text{C}_8\text{H}_{12}\text{ClNO}_2$ (189.5) calculated: 18.20% Cl, 7.39% N; found: 18.92% Cl, 7.92% N. ^1H NMR spectrum (ppm, δ , hexadeuteriodimethyl sulfoxide): 3.72 (s, 9 H, CH_3), 7.72 (d, $J = 3.9$ Hz, 1 H, $\text{C}_{(3)}\text{—H}_{\text{fur}}$), 7.26 (d, $J = 3.9$ Hz, 1 H, $\text{C}_{(4)}\text{—H}_{\text{fur}}$), 9.68 (s, 1 H, CHO).

2-Fural-5-trimethylammonium picrate (*IId*) was prepared from *Ila* according to¹²; m.p. 149 to 151°C (decomp.). ^1H NMR spectrum (hexadeuteriodimethyl sulfoxide): 3.75 (s, 9 H, CH_3), 7.70 (d, $J = 3.8$ Hz, 1 H, $\text{C}_{(3)}\text{—H}_{\text{fur}}$), 7.19 (d, $J = 3.8$ Hz, 1 H, $\text{C}_{(4)}\text{—H}_{\text{fur}}$), 9.66 (s, 1 H, CHO), 8.58 (s, 2 H, H_{arom}).

2-Fural-5-trimethylammonium Bromide (*I Ib*)

Trimethylamine (4 g) was added to the solution of 5-bromo-2-furaldehyde (8.8 g) in 1,2-dimethoxyethane at 5–10°C; the flask was stoppered and shaken at 10–20°C for 6 h. The insoluble product was filtered off and washed with ether. Yield 6.6 g, m.p. 140–150°C (decomp.). 5-(*N,N*-Dimethylamino)-2-furaldehyde (*III*, 0.4–1 g, 5–15%, ref.²⁸) and 0.8–2 g (10–25%) of 5-bromo-2-furaldehyde were separated from the filtrate. Crystallization from cool methanol and ether afforded preparation of m.p. 145–148°C (decomp.). For $\text{C}_8\text{H}_{12}\text{BrNO}_2$ (234.1) calculated: 34.19% Br, 5.98% N; found: 34.92% Br, 6.33% N. ^1H NMR spectrum (hexadeuteriodimethyl sulfoxide): 3.69 (s, 9 H, CH_3), 7.68 (d, $J = 3.9$ Hz, 1 H, $\text{C}_{(3)}\text{—H}_{\text{fur}}$), 7.28 (d, $J = 3.9$ Hz, 1 H, $\text{C}_{(4)}\text{—H}_{\text{fur}}$), 9.69 (s, 1 H, CHO).

2-Fural-5-trimethylammonium iodide was prepared from *Iib* according to¹²; m.p. 145–150°C (decomp.). ¹H NMR spectrum (hexadeuteriodimethyl sulfoxide): 3.72 (s, 9 H, CH₃), 7.70 (d, *J* = 3.9 Hz, 1 H, C₍₃₎—H_{fur}), 7.27 (d, *J* = 3.9 Hz, 1 H, C₍₄₎—H_{fur}), 9.71 (s, 1 H, CHO).

5-(N,N-Dimethylamino)-2-furaldehyde (*III*)

The trimethylammonium salt *Iia*, or *Iib* (5 g) was suspended in toluene (50 ml), heated to boiling at 26 kPa for 30 min and the solvent distilled off at 2.7 kPa. Yield 2.24 g (80%), m.p. 56–62°C (ref.^{28,29}).

5-Azido-2-furaldehyde

Sodium azide (2.5M, 20 ml) was added to *Iib* (2.34 g) dissolved in water (20 ml). Ether (30 ml) was added after 10 min and the mixture was stirred for 10 min. The organic layer was separated and the aqueous one extracted with ether (4 × 30–50 ml) in 10 min intervals. The combined ethereal extracts were dried with MgSO₄ and the organic solvent was removed. Yield 1 g (74%), m.p. 56–57°C (decomp.) (ref.^{10,28}). IR spectrum (KBr, cm⁻¹): 2 145 (N₃), 1 685 (CHO). ¹H NMR spectrum (CDCl₃): 5.96 (d, *J* = 3.7 Hz, 1 H, C₍₃₎—H_{fur}), 7.22 (d, *J* = 3.7 Hz, 1 H, C₍₄₎—H_{fur}), 9.43 (s, 1 H, CHO).

Substituted Arylthio- and Phenoxy-2-furaldehydes *IV*

Alkali metal arylthiolate or phenolate (70 mmol) in water (100 ml) was added to a solution of the trimethylammonium salt (50 mmol) in water (100 ml) in a separatory funnel. The course of the reaction was indicated by turbidity of the solution possibly accompanied by separation of the aldehydes *IV* and by a strong evolution of trimethylamine. Ether (100 ml), or dichloromethane was added after 10 min in order to extract the aldehyde being formed. Extraction was continued after additional 30 min; the solution was extracted until the organic phase became colourless, or until the evolution of trimethylamine ceased. The combined ethereal extracts were dried with MgSO₄ and the solvent removed.

5-(4-Thiotolyl)-2-furaldehyde was obtained in a 68% yield; m.p. 58–60°C, (58–60°C, ref.⁸). ¹H NMR spectrum (CDCl₃): 7.16 (d, *J* = 3.6 Hz, 1 H, C₍₃₎—H_{fur}), 6.46 (d, *J* = 3.6 Hz, 1 H, C₍₄₎—H_{fur}), 9.52 (s, 1 H, CHO), 7.31 (4 H, H_{arom}), 2.33 (s, 3 H, CH₃).

5-(4-Chlorophenylthio)-2-furaldehyde: yield 65%, m.p. 65–67°C (65–66°C, ref.^{6,8}). ¹H NMR spectrum (CDCl₃): 7.21 (d, *J* = 3.5 Hz, 1 H, C₍₃₎—H_{fur}), 6.62 (d, *J* = 3.5 Hz, 1 H, C₍₄₎—H_{fur}), 9.56 (s, 1 H, CHO), 7.31 (4 H, H_{arom}).

5-(2-Chlorophenoxy)-2-furaldehyde: yield 65%, m.p. 73–75°C. For C₁₁H₇ClO₃ (222.6) calculated: 59.35% C, 3.17% H, 15.92% Cl; found: 59.25% C, 3.02% H, 15.70% Cl. ¹H NMR spectrum (CDCl₃): 7.21 (d, *J* = 3.8 Hz, 1 H, C₍₃₎—H_{fur}), 5.51 (d, *J* = 3.8 Hz, 1 H, C₍₄₎—H_{fur}), 9.40 (s, 1 H, CHO), 7.25 (4 H, H_{arom}).

5-(4-Chlorophenoxy)-2-furaldehyde: yield 60%, m.p. 50–52°C (ref.⁶). ¹H NMR spectrum (CDCl₃): 7.21 (d, *J* = 3.8 Hz, 1 H, C₍₃₎—H_{fur}), 5.60 (d, *J* = 3.8 Hz, 1 H, C₍₄₎—H_{fur}), 9.41 (s, 1 H, CHO), 7.10, 7.32 (4 H, H_{arom}).

Reaction of *Iia* with 2,4-Dinitrophenylhydrazine

Compound *Iia* (0.2 g) dissolved in a mixture of water (5 ml) and ethanol (20 ml) was added to a stirred solution of 2,4-dinitrophenylhydrazine (0.24 g) in perchloric acid (10%, 30 ml). The sepa-

rated substance was filtered off and washed with cold water. Yield 0.37 g of an orange coloured substance; m.p. 277–282°C (decomp.). ^1H NMR spectrum (hexadeuteriodimethyl sulfoxide): 6.95 (d, $J = 3.7$ Hz, 1 H, $\text{C}_{(3)}\text{—H}_{\text{fur}}$), 7.17 (d, $J = 3.7$ Hz, 1 H, $\text{C}_{(4)}\text{—H}_{\text{fur}}$), 8.55 (s, 1 H, $\text{CH}=\text{N}$), 3.75 (s, 9 H, CH_3).

5-N,N-Dimethylamino-2-furfurylidenemalonodinitrile (VII)

a) Aldehyde *Iib* (2.34 g) in methanol (50 ml) was added to malonodinitrile (0.7 g) in methanol (10 ml) at room temperature and stirred for 5 h. The solvent was removed under diminished pressure; yield 1.5 g (80%), m.p. 181–183°C (ref.³⁰). UV spectrum methanol, λ_{max} , (log ϵ): 465 (4.67). ^1H NMR spectrum (hexadeuteriodimethyl sulfoxide, 80°C): 7.45 (d, $J = 4.7$ Hz, 1 H, $\text{C}_{(3)}\text{—H}_{\text{fur}}$), 5.91 (d, $J = 4.7$ Hz, 1 H, $\text{C}_{(4)}\text{—H}_{\text{fur}}$), 7.13 (s, 1 H, $\text{CH}=\text{N}$), 3.17 (s, 6 H, CH_3). b) Compound *VI* (0.56 g) in methanol (20 ml) was refluxed with Na_2CO_3 (0.2 g) for 2 h and the solvent was distilled off. Yield 0.35 g (95%), m.p. 191–193°C (ref.³⁰).

N-[5-(2,2-Dicyanovinyl)-2-furyl]trimethylammonium bromide (VI)

Trimethylamine (1 g) in benzene (20 ml) was added to 5-bromo-2-furfurylidenemalonodinitrile³⁰ (2.32 g) in benzene (50 ml) at 5–10°C. The salt separated during 1 h was filtered off and washed with ether. Yield 2.1 g (75%), m.p. 180–183°C (decomp.). For $\text{C}_{11}\text{H}_{12}\text{BrN}_3\text{O}$ (282.1) calculated: 14.89% N, 28.35% Br; found: 15.11% N, 28.77% Br. ^1H NMR spectrum (hexadeuteriodimethyl sulfoxide): 7.32 (d, $J = 4$ Hz, 1 H, $\text{C}_{(3)}\text{—H}_{\text{fur}}$), 7.60 (d, $J = 4$ Hz, 1 H, $\text{C}_{(4)}\text{—H}_{\text{fur}}$), 8.45 (s, 1 H, $\text{CH}=\text{N}$), 3.75 (s, 9 H, CH_3).

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