The Preparation of 2, 5-Thiophenedicarboxaldehyde

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Although thiophenedicarboxaldehydes are of interest as synthetic intermediates, only two of them have appeared in the literature; Steinkopf and Köhler prepared 3, 4-dichloro- and 3, 4-dibromo-2, 5-thiophenedicarboxaldehydes by hydrolyses of the corresponding 3, 4-dihalogeno-2, 5-bis-(dihalogenomethyl) thiophenes.[1]

The present paper will describe the preparation of 2, 5-thiophenedicarboxaldehyde (IV) from 2, 5-bis(chloromethyl) thiophene (I). In general, the procedures used for the preparation of benzene derivatives can not always be applied to the thiophene analogues, and such is also the case in the preparation of IV. In connection with an investigation of the reactions of methoxymethylthiophenes, the present author previously attempted to synthesize IV by treating 2, 5-bis(methoxymethyl) thiophene with bromine in carbon tetrachloride, but instead of the expected dialdehyde a small amount of another material containing bromine was obtained.[2] The method was virtually identical with that described by Markees for preparing terephthaldehyde from *p*-bis(methoxymethyl)-benzene.[3] The cupric nitrate oxidation of I

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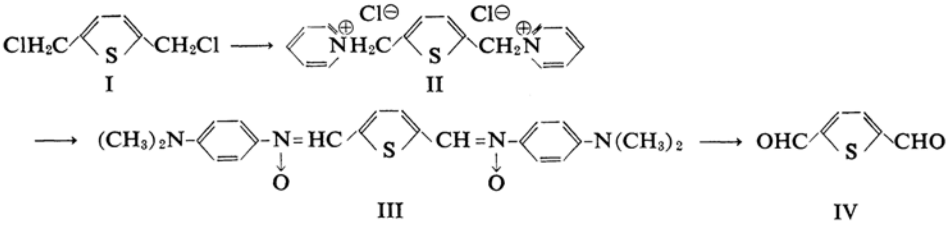
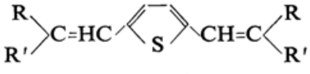
[1] W. Steinkopf and W. Köhler, *Ann.*, 532, 250 (1937).

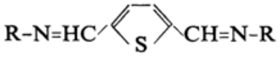
[2] Y. Matsuki and T. Sone, *J. Chem. Soc. Japan, Ind. Chem. Sec.* (*Kogyo Kagaku Zassi*), **62**, 1559 (1959).

[3] D. G. Markees, *J. Org. Chem.*, **23**, 1490 (1958).





Va : R=R′=CN
Vb : R=R′=$COOC_2H_5$
Vc : R=H, R′=COOH



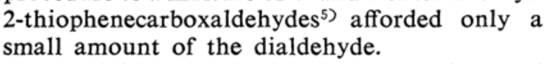
VIa : R=C_6H_5
VIb : R=2-(C_4H_3S)CH_2

or the application of the Sommelet procedure to I was also unsuccessful.

The dialdehyde was easily available by means of Kröhnke's method.[4] The reaction of I with pyridine afforded 1,1′-(2,5-thiophenediyldimethylene)bis[pyridinium chloride] (II) almost quantitatively. The reaction of II with *p*-nitroso-*N*,*N*-dimethylaniline gave α,α′-(2,5-thiophenediyl)bis[*N*-(*p*-dimethylaminophenyl)-nitrone] (III), which was converted into IV by hydrolysis with hydrochloric acid (overall yield, 60%.) The application of the Sommelet procedure to a mixture of 4- and 5-chloromethyl-2-thiophenecarboxaldehydes[5] afforded only a small amount of the dialdehyde.

The dialdehyde IV is highly reactive and reacts with various active methylene compounds and amines to give the corresponding condensation products (V) and the Schiff bases (VI) respectively.

2-Methyl-5-thiophenecarboxaldehyde (VII) was easily chloromethylated by the usual chloromethylation procedure to give 2-methyl-3-chloromethyl-5-thiophenecarboxaldehyde (VIII), which was then converted into 2-methyl-3,5-thiophenedicarboxaldehyde (IX) by the Sommelet procedure. Similarly, the chloromethylation of 2-methyl-5-acetylthiophene (X), followed by oxidation, gave 2-methyl-5-acetyl-3-thiophenecarboxaldehyde (XII). 2-Methyl-3,5-thiophenedicarboxylic acid (XIII), which is difficult to obtain by the usual manner, was prepared from IX by silver oxide oxidation.



VII : R=CHO VIII : R=CHO IX : R=CHO
X : R=$COCH_3$ XI : R=$COCH_3$ XII : R=$COCH_3$

Experimental[6]

1,1′-(2,5-Thiophenediyldimethylene)bis[pyridinium chloride] (II).—When a mixture of 2,5-bis-(chloromethyl)thiophene[7] (I, 4.5 g.), pyridine (5.2 g.), and absolute ethanol (5 ml.) was warmed on a water bath, colorless precipitate separated within a few minutes. After the mixture had been warmed for a further 30 min., the precipitate was collected and washed with ether, by which process II was obtained in a nearly quantitative yield. Recrystallization from ethanol afforded colorless hygroscopic crystals (m. p. above 280°C).

Found: N, 7.60. Calcd. for $C_{16}H_{16}Cl_2N_2S$: N, 8.25%.

α,α′-(2,5-Thiophenediyl)bis[*N*-(*p*-dimethylaminophenyl)-nitrone] (III).—Into a mixture of II (9.2 g.), *p*-nitroso-*N*,*N*-dimethylaniline (7.5 g.), and ethanol (150 ml.), a solution of sodium hydroxide (2 g.) in water (50 ml.) was stirred while the mixture was being ice-cooled. After being stirred for 1 hr. under ice cooling and then at room temperature for a further 2 hr., the mixture was diluted with water (100 ml.) and allowed to stand overnight. The brownish red precipitate which deposited was collected and recrystallized from ethanol; m. p. 254~255°C (decomp.). Yield, 8.0 g. (72%).

Found: C, 64.63; H, 5.49; N, 13.36. Calcd. for $C_{22}H_{24}O_2N_4S$: C, 64.68; H, 5.92; N, 13.71%.

2,5-Thiophenedicarboxaldehyde (IV).—III (8.2 g.) was added to ice-cooled 2 N hydrochloric acid (160 ml.), and the resultant brownish red solution was stirred for 30 min. while being cooled with ice, during which time a pale yellow precipitate was formed. The mixture was allowed to stand overnight at room temperature. The precipitate was collected and washed well with cold water to give 2 g. of the crude aldehyde (m. p. 115~116°C). The filtrate was extracted with ether, and the ether was evaporated to give an additional 0.3 g. of the product (m. p. 109~114°C). The total yield was 82.5%. Recrystallization from petroleum ether gave pale yellow leaflets (m. p. 115~116°C).

Found: C, 51.53; H, 2.88. Calcd. for $C_6H_4O_2S$: C, 51.41; H, 2.87%.

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[4] S. J. Angyal, "Organic Reactions," Vol. 8, Ed. by R. Adams, John Wiley & Sons, Inc., New York (1954), p. 203.

[5] T. Sone, unpublished work.

[6] All melting points are uncorrected. The ultraviolet spectra were measured with a Hitachi EPU-2-A-type spectrophotometer, while the infrared spectra were measured with a Hitachi EPI-2A spectrophotometer. Microanalyses were carried out by Misses Yoko Endo and Yukiko Endo of this Institute, to whom the author is indebted.

[7] J. M. Griffing and L. F. Salisbury, *J. Am. Chem. Soc.*, **70**, 3416 (1948).

UV λ_{max}^{MeOH} mμ (log ε) : 290 (4.23), 269 (4.15; shoulder), IR (KBr disk) : ν_{co} 1664 cm^{-1}.

2, 5 - Bis(2, 2 - dicyanovinyl)thiophene (Va). — A mixture of IV (140 mg.), malononitrile (150 mg.), and absolute ethanol (2 ml.) was allowed to stand for a few minutes while occasionally being stirred; by this method yellow crystals precipitated (190 mg.; m. p. 265~266°C (decomp.)). Recrystallization from a mixture of acetone and methanol afforded fine yellow needles (m. p. 265~266°C (decomp.)).

Found: C, 60.29; H, 1.32; N, 23.47. Calcd. for $C_{12}H_4N_4S$: C, 61.00; H, 1.70; N, 23.71%.

2,5-Bis(2,2-diethoxycarbonylvinyl)thiophene (Vb). —A mixture of IV (140 mg.), ethyl malonate (400 mg.), piperidine (2 drops), and absolute ethanol (2 ml.) was allowed to stand overnight. The mixture was then treated with 2 N hydrochloric acid, and the precipitate thereby formed was collected by filtration and washed with dilute ethanol (200 mg.; m. p. 65~68°C). Recrystallization from petroleum ether afforded pale yellow leaflets (m. p. 68~69°C).

Found: C, 57.06; H, 5.65. Calcd. for $C_{20}H_{24}O_8 \cdot S$: C, 56.59; H, 5.69%.

2, 5-Bis(2-carboxyvinyl)thiophene (Vc).—A mixture of IV (350 mg.), malonic acid (550 mg.), piperidine (3 drops), and pyridine (3 ml.) was heated on a water bath for 3 hr. and then, after 5 min. refluxing, acidified with hydrochloric acid. The precipitate thereby formed was collected (490 mg.; m. p. above 300°C). Recrystallization from ethanol yielded a brownish yellow powder.

Found: C, 53.19; H, 3.89. Calcd. for $C_{10}H_8O_4S$: C, 53.56; H, 3.59%.

2, 5 - Bis[(phenylimino)methyl]thiophene (VIa). —After a mixture of IV (140 mg.), aniline (200 mg.), and ethanol (2 ml.) had been allowed to stand at room temperature, a yellow precipitate began to separate (270 mg.; m. p. 201~202°C). Recrystallization from a mixture of ethanol and benzene afforded pale yellow leaflets (m. p. 202~203°C).

Found: C, 74.79; H, 4.67; N, 9.41. Calcd. for $C_{18}H_{14}N_2S$: C, 74.45; H, 4.85; N, 9.64%.

2, 5-Bis[(2-thenylimino)methyl]thiophene (VIb). — A mixture of IV (140 mg.), 2 - thenylamine (240 mg.), and ethanol (5 ml.) was allowed to stand at room temperature; a precipitate formed within 10 min. (230 mg.; m. p. 133~137°C). Recrystallization from ethanol afforded coloress leaflets (m. p. 146~147°C).

Found: C, 58.19; H, 3.93; N, 8.03. Calcd. for $C_{16}H_{14}N_2S_3$: C, 58.14; H, 4.26; N, 8.47%.

The Chloromethylation of 2-Methyl-5-thiophenecarboxaldehyde (VII).—Into a mixture of VII (12.6 g.), trioxane (5.0 g.), zinc chloride (5.0 g.), and carbon tetrachloride (50 ml.), a stream of dry hydrogen chloride was stirred over a 30 min. period. Then the mixture was gradually warmed to 50°C and stirred for 1 hr. at the same temperature, while a stream of hydrogen chloride continued to pass through. The resultant solution was diluted with water, and then the layers were separated. The organic layer was washed well with water, a dilute sodium carbonate solution, and again with water, and then dried. After the carbon tetrachloride had been removed, the residue was fractionated in vaccuo, yielding 13.8 g. (79%) of crude 2-methyl-3-chloromethyl-5-thiophenecarboxaldehyde (VIII) (b. p. 105 ~ 110°C/2.5 ~ 3 mmHg; m. p. 49~51°C), which was recrystallized from a mixture of ether and petroleum ether to give colorless needles (m. p. 50~51°C).

Found: C, 48.07; H, 4.09. Calcd. for C_7H_7ClOS: C, 48.13; H, 4.03%.

UV λ_{max}^{MeOH} mμ (log ε) : 222 (3.95), 264 (4.03), 299 (4.00). IR (KBr disk) : ν_{co} 1659 cm^{-1}.

2-Methyl-3,5-thiophenedicarboxaldehyde (IX).— A mixture of VIII (7.0 g.), hexamethylenetetramine (5.6 g.), and chloroform (20 ml.) was heated on a water bath for 30 min. and then cooled, after which the resulted salt was filtered off. The salt was dissolved in a mixture of water (30 ml.) and acetic acid (30 ml.) and boiled for 30 min. The solution was cooled and extracted with chloroform. The extract was dried, and the chloroform was evaporated to give 3.5 g. the crude aldehyde (m. p. 102~104°C, 57%). Recrystallization from boiling water afforded colorless needles (m. p. 106~107°C).

Found: C, 54.56; H, 4.14. Calcd. for $C_7H_6O_2S$: C, 54.52; H, 3.92%.

UV λ_{max}^{MeOH} mμ (log ε) : 246 (4.49), 290 (3.99). IR (KBr disk) : ν_{co} 1690, 1665 cm^{-1}.

The Chloromethylation of 2 - Methyl - 5-acetylthiophene (X).—Paraformaldehyde (4.5 g.), X (14.0 g.), zinc chloride (5 g.), and carbon tetrachloride (50 ml.) were used; the procedure was the same as described previously for VII. Crude 2-methyl-3-chloromethyl-5-acetylthiophene (XI, 14.0 g. (74%) b. p. 130~135°C/3~3.5 mmHg; m. p. 69.5~71.5°C) was recrystallized from petroleum ether to yield colorless leaflets (m. p. 72~73°C).

Found: C, 50.70; H, 5.07. Calcd. for C_8H_9ClOS: C, 50.92; H, 4.80%.

UV λ_{max}^{MeOH} mμ (log ε) : 223 (4.00), 264 (4.03), 297 (4.02). IR (KBr disk) : ν_{co} 1654 cm^{-1}.

2-Methyl - 5 - acetyl - 3 - thiophenecarboxaldehyde (XII).—This aldehyde (m. p. 110~111°C, 330 mg.) was obtained from XI (2.0 g.), hexamethylenetetramine (1.8 g.), and chloroform (8 ml.) by the method used with IX. Recrystallization from ligroin gave colorless needles, but it did not alter the melting point.

Found: C, 57.26; H, 4.92. Calcd. for $C_8H_8O_2S$: C, 57.12; H, 4.80%.

VU λ_{max}^{MeOH} mμ (log ε) : 246 (4.65), 283 (4.10). IR (KBr disk) : ν_{co} 1659, 1680 cm^{-1}.

2-Methyl-3, 5-thiophenedicarboxylic Acid (XIII). —Into a mixture of silver oxide (0.4 g.) and an aqueous sodium hydroxide solution (10%, 8 ml.), 0.2 g. of IX was swirled. After the reaction mixture had been allowed to stand overnight, the black silver was filtered off. The filtrate was acidified with hydrochloric acid, and the precipitate which separated thereby was collected (180 mg., m. p. 258~260°C (decomp.)). Sublimation under reduced pressure raised the melting point to 275~276°C (decomp.) (lit.[8] m. p. above 250°C (decomp.)).

Found: C, 44.99; H, 3.55. Calcd. for $C_7H_6O_4S$: C, 45.16; H, 3.24%.

UV λ_{max}^{MeOH} mμ (log ε) : 222 (4.36), 259 (3.92). IR (KBr disk) : ν_{co} 1680 cm^{-1}.

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[8] M. Janda, *Collection Czechoslov. Commun.*, **26**, 1889 (1961).

Summary

The application of Kröhnke's method to 2, 5-bis(chloromethyl)thiophene has afforded 2, 5-thiophenedicarboxaldehyde, from which some condensation products with amines and active methylene compounds have then been derived. 2-Methyl-5-acetyl-3-thiophenecarboxaldehyde and 2-methyl-3, 5-thiophenedicarboxaldehyde have also been prepared, from 2-methyl-3-chloromethyl-5-acetylthiophene and 2-methyl-3-chloromethyl-5-thiophenecarboxaldehyde respectively, by the Sommelet procedure.

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