[CONTRIBUTION NO. 177 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, FORDHAM UNIVERSITY]

STUDIES IN THE THIOPHENE SERIES. V. WOLFF-KISHNER REDUCTIONS[1, 2]

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Received February 24, 1949

The reduction of thienyl ketones to the corresponding alkyl thiophenes is usually carried out by means of the Clemmensen reduction (1). This method has the disadvantage, in many cases, of giving low yields, since excessive decomposition of the thiophene nucleus occurs. Although the yields can be improved by applying low temperatures, such a procedure proves time-consuming, sometimes requiring as much as fifty hours (2).

The Wolff-Kishner reaction has been utilized occasionally in the thiophene series, but without particular success. Steinkopf, *et al.* (3) prepared 2-ethylthiophene by first isolating the hydrazone of 2-acetylthiophene and then decomposing it by autoclaving for ten hours with sodium ethoxide. In this procedure they obtained an over-all yield of about 40%. Shepard (4) prepared 2-methyl-5-ethylthiophene in 40% yield by forming the semicarbazone of 2-methyl-5-acetylthiophene and heating it with potassium hydroxide. There appears to be no mention in the literature of the reduction of thiophene aldehydes to methylthiophenes. In view of the rather low yields obtained by the above methods and to avoid the application of autoclave equipment, it was decided to attempt the reduction at atmospheric pressure using ethylene glycol as a solvent (5).

It has now been found that various thiophene aldehydes and ketones can easily be reduced, without isolating the intermediate compound, *via* a simplified Wolff-Kishner reduction to give the corresponding alkyl compound in yields of 70–91%. The procedure consists essentially of mixing the carbonyl compound with an excess of 85% hydrazine hydrate in ethylene glycol solution and removing water and the remaining hydrazine hydrate by heating. The addition of potassium hydroxide and further heating leads to the formation of the reduced product. Unlike the benzene series, in which refluxing for at least three to four hours at temperatures above 170° is required, the hydrazones of the various thiophene compounds decompose vigorously between 90–140° and the reaction is usually completed in fifteen minutes. This method has been applied to nine thiophene aldehydes and two thiophene ketones. The collected data on the compounds prepared are summarized in Table I.

The acylation studies of Hartough and Kosak (11) offer ready access to thienyl ketones and it has been previously shown in this laboratory (12) that an aldehyde

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[1] This investigation was aided by a grant from the Office of Naval Research. The analyses were carried out by Dr. F. Buhler of this Department.

[2] For Paper IV of this series see Crowe and Nord, *Nature*, **163**, May, (1949)

[3] Abridged from a part of the dissertation presented in partial fulfillment of the requirments for the degree of Doctor of Philosophy to the Graduate Faculty of Fordham University, 1949.

TABLE I

ALKYL THIOPHENES PREPARED VIA WOLFF-KISHNER REDUCTION

CARBONYL COMPOUND	DECOMPOSITION TEMP. (°C) OF HYDRAZONES	PRODUCT	YIELD %	B.P., °C	n_D^{20}	ANAL.			
						Calc'd		Found	
						C%	H%	C%	H%
Thiophene-2-aldehyde	90–100	2-Methylthiophene	78	112 –113[a]	1.5203[a]	61.07	6.16	60.85	6.10
2-Acetylthiophene	125–140	2-Ethylthiophene	91	133 –134.5[b]	1.5122	64.23	7.18	64.3	7.45
2-Propanoylthiophene	115–130	2-Propylthiophene	89	158 –159[c]	1.5050[c]	66.61	7.99	66.4	8.17
5-Methylthiophene-2-aldehyde	105–115	2,5-Dimethylthiophene	78	135 –136[d]	1.5132[d]	64.23	7.18	64.45	7.46
3-Methylthiophene-2-aldehyde	105–115	2,3-Dimethylthiophene	82	139.5–140.5[e]	1.5188[e]	64.23	7.18	64.4	7.35
5-Ethylthiophene-2-aldehyde	120–130	2-Methyl-5-ethylthiophene	81	159 –161[f]	1.5074[f]	66.61	7.99	66.95	8.19
5-Propylthiophene-2-aldehyde	115–125	2-Methyl-5-propylthiophene	83	179.5–180.5	1.5026	68.51	8.69	68.2	8.79
5-Chlorothiophene-2-aldehyde	100–120	2-Methyl-5-chlorothiophene	70	153.5–154.5[g]	1.5360[g]	45.25	3.80	45.28	4.01
2,5-Dimethylthiophene-3-aldehyde	120–130	2,3,5-Trimethylthiophene	74	163 –164[h]	1.5131[h]	66.61	7.99	66.4	8.00
2,3-Dimethylthiophene-5-aldehyde	115–130	2,3,5-Trimethylthiophene	80	163 –164[h]	1.5131[h]	66.61	7.99	66.5	8.10
2,3,5-Trimethylthiophene-4-aldehyde	120–130	2,3,4,5-Tetramethylthiophene	70	187 –189[i]	1.5196	68.51	8.69	68.2	8.48

[a] Ref. (6) gives b.p. 112.5°; n_D^{20} 1.5203.

[b] Ref. (3) gives b.p. 132–134°.

[c] Ref. (1d) gives b.p. 157–160°; n_D^{20} 1.5048.

[d] Ref. (7) gives b.p. 135.5–136°; n_D^{19} 1.51418.

[e] Ref. (4) gives b.p. 140.2–141.2°; n_D^{20} 1.5192.

[f] Ref. (4) gives b.p. 159.8–160.4; n_D^{20} 1.5073.

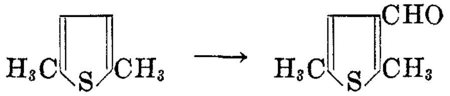
[g] Ref. (8) gives b.p. 153.7°; n_D^{17} 1.5367.

[h] Ref. (9) gives b.p. 163–165°/746 mm; n_D^{20} 1.5131.

[i] Ref. (10) gives b.p. 182–184°.

group can be introduced directly into thiophene and some substituted derivatives by means of the N-methylformanilide synthesis. Thus the facile reduction of these compounds offers a convenient way to obtain alkylated thiophenes. It, therefore, was deemed advisable to attempt the preparation of tetramethylthiophene to test the suitability of the reaction in both the α- and β-positions.

In forming thiophene aldehydes by means of the N-methylformanilide synthesis the entering aldehyde group ordinarily occupied any free α-position. If, however, both α-positions possess substituents, as in 2,5 dimethylthiophene, it is possible to obtain formylation in the β-position giving 2,5 dimethylthiophene-3-aldehyde (I).

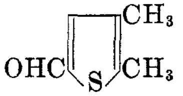


(I)

The aldehyde so obtained was oxidized to the corresponding acid and a mixed melting point with an authentic sample of 2,5-dimethyl-3-thiophenecarboxylic acid showed no depression, thus indicating that the aldehyde group had entered in the β-position. Reduction of I *via* the Wolff-Kishner method gave 2,3,5-trimethylthiophene and treatment of this with N-methylformanilide and phosphorus oxychloride gave 2,3,5-trimethylthiophene-4-aldehyde, which was again reduced to give 2,3,4,5-tetramethylthiophene.

It has also been found that 2,3-dimethylthiophene can be formylated to yield a dimethylthiophene aldehyde, which as expected proved to have the aldehyde group in the free α-position (II). This was shown by its conversion to the corresponding trimethylthiophene, which had the same physical constants as the 2,3,5-trimethylthiophene prepared from I. Furthermore, the N-methylformanilide synthesis when applied to the trimethylthiophene derived from II gave 2,3,5-trimethylthiophene-4-aldehyde, the semicarbazone of which showed no depression of its melting point, when mixed with an authentic sample. Therefore II is 2,3-dimethylthiophene-5-aldehyde.

(II)



Attempts to apply the N-methylformanilide synthesis to 2,5-dichlorothiophene were unsuccessful, probably due to the fact that the hydrogen atoms in the β-positions in this compound do not have the required mobility.

EXPERIMENTAL[4]

The procedure for the reduction of the carbonyl compounds was the same for all of the substances listed in Table I. As an example, the preparation of 2-methylthiophene is given.

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[4] The thiophene used in these preparations was obtained through the courtesy of Drs. W. M. Holaday and G. A. Harrington of the Socony-Vacuum Oil Company.

2-Methylthiophene. Thiophene-2-aldehyde (28 g., 025 mole), 50 ml. of hydrazine hydrate (85%), and 200 cc. of ethylene glycol were placed in a 1-l. round-bottom flask fitted with a thermometer extending below the surface of the reaction mixture and arranged for distillation. The solution was heated to 130–160° and water and excess hydrazine distilled over. After thirty minutes a small amount of water-insoluble material was separated from the distillate and returned to the reaction flask. The solution was cooled below 60°, 50 g. of potassium hydroxide pellets was added, and an efficient reflux condenser was fitted to the flask. Heating was again applied with occasional shaking to bring the hydroxide into solution. A vigorous reaction with evolution of nitrogen occurred at 90–100°. After the reaction had subsided, the mixture was refluxed for fifteen minutes and then the methylthiophene was distilled from the reaction mixture. The distillate was extracted with ether, the ether extract washed with 6 *N* hydrochloric acid, dried over calcium chloride, the ether removed and the residual liquid fractionated over sodium. There was obtained 19.1 g. (78%) of 2-methylthiophene, b.p. 112–113°.

2,5-Dimethylthiophene-3-aldehyde. 2,5-Dimethylthiophene (56 g., 0.5 mole), 81.1 g. of N-methylformanilide (0.6 mole), and 92 g. of phosphorus oxychloride (0.6 mole) were placed in a flask fitted with a reflux condenser and the solution heated on a steam-bath until a vigorous evolution of hydrogen chloride gas commenced. Heating was removed until the reaction had subsided, then the flask was placed on a steam-bath for twenty minutes. At the end of this time cooling was applied and the contents of the flask carefully neutralized with aqueous sodium acetate. The mixture was then steam-distilled until no further oil came over. The distillate was extracted with ether, the ether extract washed with 6 *N* hydrochloric acid and with 5% sodium bicarbonate solution, dried over sodium sulfate and rectified. There was obtained 19.6 g. of 2,5-dimethylthiophene-3-aldehyde, b.p. 77–82°/4 mm.; n_D^{20} 1.5620. Fourteen grams of 2,5-dimethylthiophene were recovered in the fractionation. The yield of the aldehyde calculated on the basis of the utilized dimethylthiophene was 40%. The *semicarbazone* had m.p. 228–230°d.

Anal. Calc'd for $C_8H_{11}N_3OS$: N, 21.30. Found: N, 21.45.

The *acid* obtained by permanganate oxidation between 10–20° had m.p. 115–116°. A mixed m.p. with an authentic sample of 2,5-dimethylthiophene-3-carboxylic acid (13) showed no depression.

Anal. Calc'd for $C_7H_8O_2S$: C, 53.85; H, 5.15.
Found: C, 53.9; H, 5.15.

2,3-Dimethylthiophene-5-aldehyde. 2,3-Dimethylthiophene (33.6 g., 0.3 mole), 54 g. of N-methylformanilide (0.4 mole), and 61.3 g. of phosphorus oxychloride (0.4 mole) were placed in a round-bottom flask fitted with an efficient reflux condenser. The solution was allowed to heat up, until evolution of hydrogen chloride gas began. At this point, cooling was immediately applied by means of an ice-water bath. After the reaction had subsided, the flask was heated on the steam-bath for twenty minutes. Cooling was again applied and after careful neutralization with excess aqueous sodium acetate, the same isolation procedure as above was followed. There was obtained 35.4 g. (84.5%) of 2,3-dimethylthiophene-5-aldehyde, b.p. 80–85°/3 mm.; n_D^{20} 1.5770. The *semicarbazone* had m.p. 222–225°d.

Anal. Calc'd for $C_8H_{11}N_3OS$: N, 21.3. Found: N, 21.04.

2,3,5-Trimethylthiophene-4-aldehyde. 2,3,5-Trimethylthiophene (31.5 g., 0.25 mole), 67.6 g. of N-methylformanilide (0.5 mole), and 76.7 g. of phosphorus oxychloride (0.5 mole) were mixed in a flask fitted with a reflux condenser. The mixture was placed on a steam-bath until a vigorous evolution of hydrogen chloride gas began. Heating was removed until the reaction had subsided, and then was continued for twenty minutes. Following the same neutralization and isolation procedure as above, there was obtained upon rectification 15.8 g. of 2,3,5-trimethylthiophene-4-aldehyde, b.p. 87–91°/3mm., n_D^{20} 1.5553. During fractionation 8.5 g. of 2,3,5-trimethylthiophene was recovered. Therefore the yield of aldehyde on the basis of utilized methyl compound was 58%. The *semicarbazone* had a m.p. 179–180°.

Anal. Calc'd for $C_8H_{11}N_3OS$: N, 19.89. Found: N, 19.90.

SUMMARY

1. A modified Wolff-Kishner reduction has been applied to nine thiophene aldehydes and two thienyl ketones to give the corresponding alkylthiophenes in yields amounting to 70–91%.

2. The N-methylformanilide aldehyde synthesis has been utilized to prepare 2,3-dimethylthiophene-5-aldehyde, 2,5-dimethylthiophene-3-aldehyde, and 2,3,5-trimethylthiophene-4-aldehyde.

New York 58, N. Y.

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