Polychlorination of Thiophene. A Reinvestigation

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Some old controversies in the literature with regard to the structures of trichlorothiophenes have been elucidated. In the course of these studies, we found that the best method for the preparation of 2,3,5-trichlorothiophene is the direct chlorination of thiophene in the presence of catalytic amounts of ferric chloride. If 2,5-dichlorothiophene is available 2,3,5-trichlorothiophene can also be obtained in good yields through chlorination with thionyl chloride and sulfuryl chloride, using aluminum trichloride as catalyst.

In connection with our interest in perchlorinated trithienylmethyl derivatives, we needed efficient methods for the preparation of 2,3,5-trichlorothiophene (1) and 2,3,4-trichlorothiophene (2). Direct chlorination of thiophene in the absence of solvents and catalysts gives vary-

ing mixtures of addition and substitution products depending on the reaction and work-up conditions [1-3]. Work-up by heating with alcoholic potassium hydroxide in order to destroy addition products was introduced already by Victor Meyer [4] and he reported the formation of minor amounts of a trichlorothiophene fraction. Steinkopf and Köhler used the same chlorination conditions and using fractional distillation and purification *via* mercury derivatives, they obtained a trichloro derivative in low yield, which they believed to be 2,3,5-trichlorothiophene. They also prepared 2,3,4-trichlorothiophene by entrainment Grignard reaction of tetrachlorothiophene,
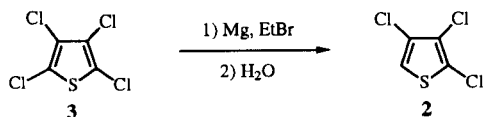
followed by hydrolysis. Rahman *et al.* have prepared 2 through halogen-metal exchange followed by the acid hydrolysis of trichloro-2-thienylmagnesium halide [5,6]. Hartough *et al.* on the other hand reported that in the chlorination of thiophene with one equivalent of chlorine at 50° followed by solid caustic sodium hydroxide-potassium hydroxide gave 7.3% of 2,3,4-trichlorothiophene and only 0.2% of 2,3,5-trichlorothiophene. They based

their structure assignment on the fact that chlorination of 2,5-dichlorothiophene only yielded the isomer, which they had assigned to be the 2,3,5-trichloro derivative and draw the conclusion that the other isomer had to be the 2,3,4-trichloro isomer. No yields are mentioned. It is of course clear that this cannot be considered to be binding evidence, as addition of chlorine to 2,5-dichlorothiophene followed by elimination could give the 2,3,4-trichloro isomer *via* addition-elimination reactions. Stronger evidence for the assignments was perhaps that the compound assigned to be 2,3,4-trichlorothiophene was claimed to react with mercuric chloride, while the other isomer did not. However, no experimental details were given. This reaction is considered to be characteristic for thiophenes having an α-hydrogen [7,8]. In 1961 Profft and Solf carried out glc analysis on the chlorination product obtained according to the procedure of Hartough *et al.* and in the published glc only traces of 2,3,5-trichlorothiophene is present [9]. On the other hand in a later glc study in connection with a determination of the ^{1}H nmr parameters of all chlorothiophenes, the formation of both trichlorothiophenes in the chlorination of thiophene according to Hartough are reported. Their retention times are given but the relative proportions are not reported [10].

Using four moles of chlorine per mole of thiophene and allowing the temperature during chlorination to rise to 190°, so that pyrolysis of addition products occured gave, upon tedious fractionation, 2,3,4-trichlorothiophene and 2,3,5-trichlorothiophene in 7.5% and 35% yield, respectively. When the molar proportion of chlorine to thiophene was raised to 7.5:1 and the temperature during chlorination allowed to increase to 205°, 2,3,5-trichlorothiophene and tetrachlorothiophene were obtained in 15% and 70% yield, respectively [3].

In order to clear the inconsistencies in the literature and to find out if direct chlorination of thiophene with the appropriate amounts of chlorine could be used as a preparative and selective route to 2,3,5-trichlorothiophene (1), we reinvestigated the direct chlorination of thiophene.

We bubbled chlorine into thiophene at 50° and followed the reaction by glc. The chlorination was stopped, when most of the 2,5-dichlorothiophene had disappeared (after about 4 hours), and the weight increase of the product indicated that on the average three chlorines were added to thiophene. The composition of the crude product was analyzed by glc/ms and ^{1}H and ^{13}C nmr. The following non-calibrated relative proportions were obtained: 2,5-dichlorothiophene (**4**, 14%), 2,3,5-trichlorothiophene (**1**, 35%), pentachlorothiolene (8%), pentachlorothiolane (6%), hexachlorothiolane (**11**, 10%) and higher substituted derivatives (27%).

One part of the product was dehydrochlorinated with solid sodium hydroxide-potassium hydroxide according to Hartough [2]. Analysis of the product now showed the following proportions: 2,5-dichlorothiophene (9%), 2,3,5-trichlorothiophene (55%, J_{CH} = 179.6 Hz), 2,3,4-trichlorothiophene (**2**, 14%, J_{CH} = 194.7 Hz [11]), and tetrachlorothiophene (**3**, 21%). The same composition of the product was obtained upon refluxing the reaction mixture for several hours with ethanolic potassium hydroxide.

Another part of the crude reaction product was distilled *in vacuo* at 45-85°/10 mm Hg prior to removal or destruction of the addition products by alkali treatment, yielding 9% of 2,5-dichlorothiophene and 23% of 2,3,5-trichlorothiophene free from the 2,3,4-trichloro isomer.
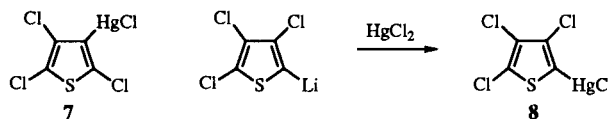
We found that the formation of addition products could not be avoided by carrying out the chlorination at room temperature. After two hours 2,5-dichlorothiophene (42%) and addition products were formed. Using an even lower temperature and carbon tetrachloride as solvent also gave addition products.

We could confirm Steinkopf and Köhlers results that 2,3,5-trichlorothiophene did not react with an saturated aqueous solution of mercuric chloride and aqueous sodium acetate, used by Volhard [8] to prepare 3,4,5-trichloro-2-thienylmercuric chloride. Steinkopf and Köhler [1] also reported that 2,3,4-trichlorothiophene reacted very slowly under these conditions and gave only 18% yield of 3,4,5-trichloro-2-thienylmercuric chloride after a reaction time of two weeks. Both isomeric trichlorothienylmercuric chlorides were, however,
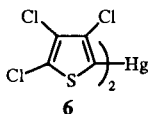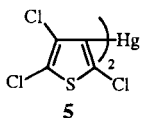

obtained in an indirect way by reaction with mercuric oxide in glacial acetic acid to *bis*-(2,4,5-trichloro-3-thienyl)mercury(II) (**5**) and *bis*-(3,4,5-trichloro-2-

thienyl)mercury(II) (**6**), which upon reaction with mercuric chloride in acetone gave 2,4,5-trichloro-3-thienylmercuric chloride (**7**) and 3,4,5-trichloro-2-thienyl-


mercuric chloride (**8**), which also later has been obtained from 3,4,5-trichloro-2-thienyllithium and mercuric chloride [12]. We could also confirm Steinkopf and Köhlers result that the isomeric mercury derivatives had very similar melting points and gave no melting-point depression with each other. The statement in Hartoughs monography that "Only in the case of Steinkopf's 2,3,5-trichloro-4-thiophenemercuric chloride, which was later shown to be 2,3,4-trichlor-5-thiophenemercuric chloride" is not correct [13].

The two isomeric trichlorothienylmercuric chlorides were reacted with bromine in dichloromethane according to Steinkopf and Köhler and we obtained in this way 2-bromo-3,4,5-trichlorothiophene (**9**), mp 42-43° from 3,4,5-trichloro-2-thienyl mercuric chloride and 3-bromo-2,4,5-trichlorothiophene (**10**), mp 36-37° from 2,4,5-trichloro-3-thienylmercuric chloride. A mixed melting
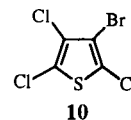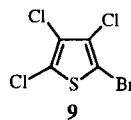

point of 38-39° was obtained. The compounds showed different ^{13}C nmr shifts and different retention times upon glc. According to Steinkopf and Köhler [1] both compounds have the same melting points (50.5-51.0°) and give no melting point depression. They also claimed that this was true for the isomeric iodo derivatives and acetyl-trichlorothiophenes prepared from the mercury derivatives. As Hartough pointed out there must have been some confusion.

Steinkopf and Köhlers result that 2,3,5-trichlorothiophene is not formed by direct chlorination of intermediate 2,5-dichlorothiophene, as previously reported [3] was also confirmed by us. Direct chlorination of 2,5-dichlorothiophene at 50° for four hours gave hexachlorothiolane (64%), higher substituted derivatives (15%) and pentachlorothiolene (9% glc/ms). Dehydrochlorination with ethanolic potassium hydroxide gave tetrachlorothiophene (89%), 2,3,5-trichlorothiophene (4%) and 2,3,4-trichlorothiophene (2%).
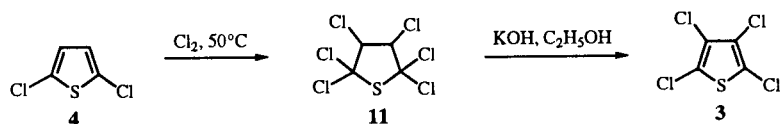
Chlorination of 2,5-dichlorothiophene in the presence of hydrogen chloride or 37% hydrochloric acid on the other hand gave 2,3,5-trichlorothiophene in 58% yield and tetrachlorothiophene in 16% yield. The reaction was much slower than in the common chlorination of thiophene.

Chlorination of 3-chlorothiophene (12) gave after 20 minutes at 50° 78% of 2,3,5-trichlorothiophene, 5% of 2,3,4-trichlorothiophene, 3% of tetrachlorothiophene and
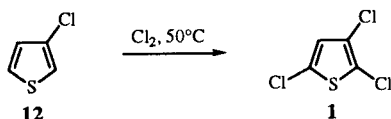
addition compounds (12%). Longer reaction times, one and a half hour, at 50° gave mainly 2,3,5-trichlorothiophene (61%) and a larger amount of addition compounds (32%). Chlorination of 3-chlorothiophene in ice-cold carbon tetrachloride gave 2,3-dichlorothiophene (13) in 85%
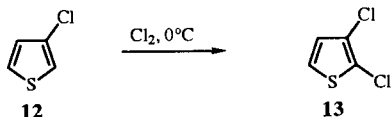
yield together with 14% of 2,3,5-trichlorothiophene. Longer reaction times, three hours, increased the amounts of addition products (58%) and only 27% of 2,3-dichlorothiophene and 6% of 2,3,5-trichlorothiophene were formed. As previously observed, further non-catalytic chlorination of 2,3,5-trichlorothiophene did not occur even after 24 hours of reaction [3]. If the chlorination of 2,3,5-trichlorothiophene was carried out in the presence of hydrochloric acid pentachlorothiolene was obtained.

During the course of our investigation we found that ferric chloride was an efficient catalyst for the dehydrochlorination of the addition products at 35-40°. After a few hours only traces of addition products were detected by glc. Extensive chlorination of thiophene, where all 2,5-dichlorothiophene was consumed, yielded only 14% of 2,3,5-trichlorothiophene and higher substituted addition products. If the product was treated with a catalytic amount (1 mole %) of ferric chloride, 2,3,5-trichlorothiophene and tetrachlorothiophene was obtained in 23% and 48% isolated yield, respectively. This method is more

convenient than the high temperature chlorination mentioned above [3]. Tetrachlorothiophene has also been prepared by reaction of hexachlorobutadiene with sulfur [14].
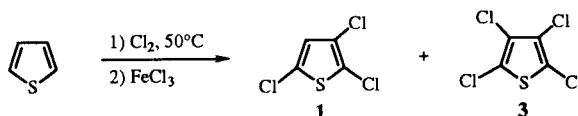
If the chlorination was carried out in carbon tetrachloride, the reaction mixture consisted of 2,5-dichlorothiophene (8%), 2,3,5-trichlorothiophene (32%) and higher substituted derivatives. After treatment with ferric chloride (1 mole %) 59% of 2,3,5-trichlorothiophene and 11% of tetrachlorothiophene was isolated. The yield of 2,3,5-trichlorothiophene has not yet been optimized and it seems reasonable that higher yields can be achieved.

Chlorination of thiophene to 2-chlorothiophene and 2,5-dichlorothiophene has recently been achieved in almost quantitative yield using one and two equivalents of N-chlorosuccinimide in hexane in the presence of catalytic amounts of 70% perchloric acid [15]. Previously sulfuryl chloride was used for the preparation of these compounds [16,17]. This reagent could not be used for further chlorination. We found, however, that chlorination of 2,5-dichlorothiophene with a mixture of thionyl chloride and sulfuryl chloride at 0-5° in the presence of aluminum trichloride gave 2,3,5-trichlorothiophene in 52%
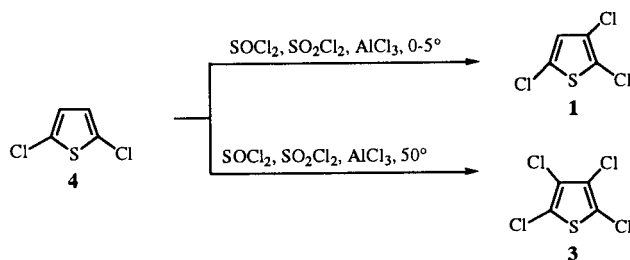
yield. If the reaction mixture was heated to 50° over night tetrachlorothiophene was obtained in 46% yield.

We thus found that the best method for the preparation of 2,3,5-trichlorothiophene is the direct chlorination of thiophene in the presence of catalytic amounts of ferric chloride. If 2,5-dichlorothiophene is available 2,3,5-trichlorothiophene can be obtained in good yield through

chlorination with thionyl chloride and sulfuryl chloride using aluminum trichloride as catalyst.

EXPERIMENTAL

Melting points are uncorrected. The ^1H and ^{13}C nmr were recorded on a Varian XL-300 spectrometer. The mass spectra were recorded on a JEOL JMS-SX 102 spectrometer. The glc analyses were carried out on a Varian 3300 gas chromatograph using an OV-17 (3%, 2 m) column and a temperature gradient of 10°/minute. Identification of the components in the reaction products were made by coinjection of autentic samples in the glc analyses and by matching mass spectra. The retention times for the authentic chlorothiophenes under the above conditions are as follows:

Compound:	2-	2,5-	2,3-	2,3,5-	2,3,4-	2,3,4,5-
Rt (minutes):	1.15	1.85	2.31	3.18	3.94	5.03

2-Chlorothiophene.

This compound was prepared from thiophene and N-chlorosuccinimide in the presence of perchloric acid [15].

3-Chlorothiophene.

This compound was prepared from 3-bromothiophene by halogen-metal exchange and treatment with chlorine [18].

2,3-Dichlorothiophene.

To a solution of 4.74 g (40.0 mmoles) of 3-chlorothiophene in 15 ml of carbon tetrachloride chlorine was bubbled at 0° for 45 minutes. The reaction mixture was warmed to 50° and nitrogen was bubbled through the reaction mixture for 10 minutes. After evaporation distillation gave 4.4 g (72%) of the title compound bp 59-62°/10 mm Hg (lit [19] 173-174°), and 0.6 g (8%) of 2,3,5-trichlorothiophene.

2,3,4-Trichlorothiophene.

This compound was obtained by lithiation of tetrachlorothiophene followed by hydrolysis [20].

Chlorination of Thiophene.

Method A.

To 42.0 g (0.50 mole) of thiophene 400-450 g of chlorine was bubbled under magnetical stirring. The temperature rose to 50° and was kept at this temperature by means of a water bath for 8.5 hours. A vigorous stream of nitrogen was then bubbled through the reaction mixture for 20 minutes. The reaction mixture was diluted with 75 ml of anhydrous carbon tetrachloride and 0.81 g (5.00 mmoles) of ferric chloride was added. The stirring was continued at 35-40° for three hours, whereupon nitrogen was bubbled through the reaction mixture for 10 minutes. After filtration the reaction mixture was washed with two 100 ml portions of water, dried over magnesium sulfate and evaporated. The residue was distilled in vacuo.

2,3,5-Trichlorothiophene.

The yield was 21.6 g (23%), bp 77-79°/8 mm Hg (lit [18] bp 198°); ^{13}C nmr (deuteriochloroform): δ 121.3 (d, J = 179.6 Hz), 123.0, 126.0, 126.8.

Tetrachlorothiophene.

The yield was 53.3 g (48%), bp 61-64°/1.2 mm Hg, mp 29.0-30.0° (methanol) (lit [14] mp 29.5-29.7°).

Method B.

To a solution of 42.0 g (0.50 mole) of thiophene in 75 ml of carbon tetrachloride, 400-450 g of chlorine was bubbled into the solution. The temperature was in the beginning not allowed to exceed 60° and after 9 hours it was 30°. A catalytic amount of ferric chloride was added and introduction of chlorine was continued for another hour. At 50° nitrogen was bubbled through the reaction mixture for 20 minutes. After cooling to 30°, 0.81 g (5.0 mmoles) of ferric chloride was added and the stirring was continued for 3 hours at 35-40°. The same work-up procedure as described above gave 55.3 g (59%) of 2,3,5-trichlorothiophene and 12.2 (11%) of tetrachlorothiophene.

Method C.

The same chlorination procedure and treatment with nitrogen as in A, but then 4.8 g of potassium hydroxide was added at 80° to the reaction mixture over a period of two hours followed by 12.0 g of sodium hydroxide in portions. The reaction mixture was refluxed for two days and worked up as described above. Distillation gave 16.9 g (17%) of 2,3,5-trichlorothiophene and 32.1 g (29%) of tetrachlorothiophene.

Chlorination of 2,5-Dichlorothiophene.

Method A.

A solution of 15.3 g (0.10 mole) of 2,5-dichlorothiophene [15] in 40 ml of carbon tetrachloride was treated with hydrogen chloride gas at 40-45° for five minutes. Then chlorine was bubbled through the solution for six hours, now and then interrupted by introduction of hydrogen chloride gas. In order to remove excess chlorine and hydrochloric acid, nitrogen was bubbled through the reaction mixture for 15 minutes, after which 0.16 g (1.0 mmole) of ferric chloride was added and the reaction mixture stirred at 35-40° for two hours. After treatment with nitrogen for 15 minutes the reaction mixture was filtered, washed with two portions of water, dried over magnesium sulfate and evaporated. Distillation gave 10.8 g (58%) of 2,3,5-trichlorothiophene and 3.5 g (16%) of tetrachlorothiophene.

Method B.

To a solution of 30.6 g (0.20 mole) of 2,5-dichlorothiophene [15] in 15 ml of thionyl chloride and 30 ml of sulfuryl chloride cooled to 0-5°, 5.0 g of aluminum chloride was added in portions. The reaction mixture was stirred at 0-5° for one hour and then at room temperature for four hours, after which it was carefully poured into cold 6 M hydrochloric acid. After addition of chloroform the phases were separated and the organic phase washed with water and 10% sodium hydrogen carbonate solution followed by drying over magnesium sulfate and evaporation. Distillation in vacuo gave 19.5 g (52%) of 2,3,5-trichlorothiophene with the same physical properties as described above.

Method C.

The reaction was performed as described in method B with the difference that the reaction temperature was 50° and that the reaction was left at this temperature under stirring over night. Upon work-up 20.4 g (46%) of tetrachlorothiophene was obtained with the same physical properties as described above.

2-Bromo-3,4,5-trichlorothiophene.

A solution of 122 mg (0.289 mmole) of (3,4,5-trichloro-2-thienyl)mercuric chloride [1,12] in 1.0 ml of dichloromethane was treated with 60 mg (0.38 mmole) of bromine in 3.0 ml of dichloromethane. The reaction mixture was stirred at room temperature for 30 minutes and evaporated. The residue was taken up in 5.0 ml of chloroform and after filtration and evaporation 50 mg (62%) of the title compound was obtained as white crystals; mp 42-43° from ethanol (correction of lit [1] 50.5°); retention time = 4.66 minutes; ^{13}C nmr (deuteriochloroform): δ 105.0, 123.2, 124.0, 125.7; hrms calcd. for $C_4{}^{79}Br^{35}Cl_3S$: 263.7969. Found: 263.7963.

3-Bromo-2,4,5-trichlorothiophene.

This compound was prepared as described above from (2,4,5-trichloro-3-thienyl)mercuric chloride [1] giving 44 mg (55%) as white crystals, mp 36-37° from ethanol followed by ether (correction of lit [1] 50.5-51.0°); retention time = 4.61 minutes; ^{13}C nmr (deuteriochloroform): δ 111.4, 121.8, 123.6, 124.7; hrms calcd. for $C_4{}^{79}Br^{35}Cl_3S$: 263.7969. Found: 263.7972.

Acknowledgements.

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