SOME ELECTROPHILIC SUBSTITUTION REACTIONS OF DITHIENO [2,3-b : 3', 4'-d]PYRIDINE

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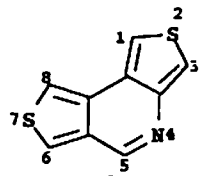
Abstract: Nitration, bromination and iodination of dithieno[2,3-*b*:3,4-*d*]pyridine have been studied and the results compared with those obtained for other isomeric systems. Nitration with concentrated nitric acid in trifluoroacetic acid gave selectively the 8-nitro isomer. The 8-bromo isomer was best obtained in 61% yield by bromination with *N*-bromosuccinimde in a biphasic system using picric acid as catalyst. Iodination was carried out with iodine and mercuric nitrate in dichloromethane and depending on the amount of iodine the 8-iodo and 6,8-diiodo derivatives were obtained.

Introduction

In connection with our work on electrophilic substitution on dithieno[*b,d*]pyridines, we have previously studied nitration of five of the nine isomers. The *c,c*-fused isomer, dithieno[3,4-*b*;3',4'-*d*]pyridine **1** , was studied in detail. Theoretical calcu-



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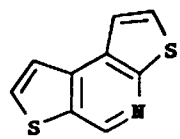

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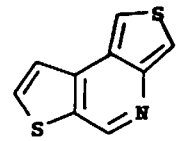

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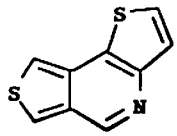
lations at the *ab initio* 21 G* level of the transition state complexes towards the Wheland intermediate agreed with the experimentally observed isomer distributions [1]. The 1-, 8-, and 3-nitro isomers were obtained in the relative proportions of 78%, 20% and 2%, respectively, upon nitration with concentrated nitric acid in trifluoroacetic acid at room temperature. Theoretical and experimental studies were also carried out with the *b,b*-fused system dithieno[2,3-*b*;3',2'-*d*]pyridine **2** . This system reacted much slower and a reaction temperature of 80 °C had to be used. Nitration took only place in the thiophenic ring of **2** to which the pyridinic nitrogen was bound and the 1- and 2-nitro isomer were obtained in the proportions of 43 to 57. These changed to 70 to 30 in boiling trifluoracetic acid [2, 3]. The substitution pattern of the *b,c*-fused systems is particularly interesting. Thus dithieno[3,4-*b*:3',2'-*d*]pyridine **3** is at room temperature only nitrated in the *c*-fused thiophene ring and the 1- and 3- isomers are isolated in about equal amounts, in contrast to the nitration of **1**, when only trace amounts of the 3-nitro derivative was obtained [2]. If the *b*-fused ring is bound to pyridinic nitrogen in a [*b,c*]-fused isomer, as in dithieno[3,2 *b*: 3',4'-*d*]pyridine **4** , nitration occurs in the 8-position of the *c*-fused ring (67%) and the 2-position of the *b*-fused ring (33%) [4].



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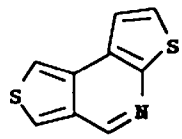

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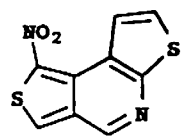

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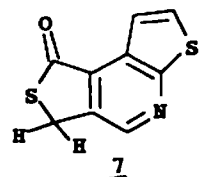

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We were therefore interested in studying the *b,c*-fused isomer dithieno-[2,3-*b*:3',4',-*d*]pyridine **5** where the *b*-fused ring has the same orientation as in **3**, and where the pyridinic nitrogen is bound to the *b*-fused ring, in order to compare orientation effects and reactivity.

Experimental

The reactions were carried out in dried glassware. Reagents and solvents were handled by using standard syringe techniques. Melting points are uncorrected. The ^{1}H NMR spectra were recorded on a Varian XL-300 spectrometer using deu-

teriochloroform as solvent. The mass spectra were recorded on a Jeol JMS-SX 102 spectrometer. Flash column chromatography was carried out using Merck silica gel 60. Heptane, pentane, ethyl acetate, dichloromethane and tetrachloromethane were freshly distilled over molecular sieves, chloroform over phosphorous pentoxide and diethyl ether from sodium dispersion prior to use. For HPLC a preparative polygosil/silica column (250x20) was used. The elemental analyses were carried out by Domis and Kolbe, Microanalytisches Laboratorium, Mülheim a. d. Ruhr, Germany.

Nitration of dithieno[2,3-*b*:3',4'-*d*]pyridine 5

To a stirred solution of 573 mg (3.0 mmoles) of sublimed **5** [5] and 1.20 g (20 mmoles) of urea in 20 ml of trifluoroacetic acid 3.0 ml (72 mmoles) of concentrated nitric acid (d = 1.5 g/ml) was added. The reaction mixture was stirred at room temperature for two days. After evaporation the residue was neutralized by a solution of sodium hydrogen carbonate. The so obtained water phase was extracted several times with ether. The combined ether phases were washed with water, dried over magnesium sulfate and evaporated. The crude product was chromatographed using ethyl acetate/heptane (1:5) as eluent giving the less polar component **7** and ether/heptane (1:1) as eluent for the more polar component **6**.

8-Nitrodithieno[2,3-*b*:3',4'-*d*]pyridine 6

The fractions containing the more polar component were evaporated giving 411 mg (58%) of **6**. After further HPLC purification using heptane/ethyl acetate (80:20) as eluent, **6** was recrystallized from dichloromethane and sublimed at 150 °C/1 mm Hg. Mp for the yellow crystals 178-180 °C; IR (potassium bromide): ν 1385 cm^{-1} (NO_2): ^{1}H NMR: δ 8.90 (s, 1H, H5), 8.70 (d, 1H, H1, J = 5.95 Hz), 8.50 (s, 1H, H6), 7.65 (d, 1H, H2, J = 5.95 Hz).

Anal. Calcd. for $C_9H_4O_2N_2S_2$: C, 45.72; H, 1.67; MW, 235.9714. Found: C, 45.73; H, 2.09; MW, 235.9713 (HRMS).

8-Hydroxydithieno[2,3-*b*:3',4'-*d*]pyridine in keto form 7

When the fractions containing the less polar component were evaporated 31 mg (5%) of **7** was obtained after recrystallization from ether. Heptane/ethyl acetate (90:10) were used as eluent for HPLC purification. After sublimation at 158 °C/ 1 mm Hg mp was 194-196 °C; IR (potassium bromide): ν 1675 cm^{-1} (CO); ^{1}H NMR: δ 8.70 (d, 1H, H5, J = 0.40 Hz), 8.60 (dd, 1H, H1 J = 5.90, 0.40 Hz), 7.60 (d, 1H, H2, J = 5.90 Hz), 4.70 (s, 2H, CH_2).

HRMS calcd. for $C_9H_5ONS_2$: 206.9813. Found: 206.9818.

Bromination of dithieno[2,3-*b*:3',4'-*d*]pyridine 5

To a stirred solution of 1.91 g (0.01 mole) of **5**, 3.40 g (0.024 mole) of sodium monohydrogen orthophosphate, 4.00 g (0.024 mole) of sodium hydrogen carbonate and 2.40 g (0.02 mole) of magnesium sulfate in 200 ml of chloroform 0.57 ml (0.011 mole) of bromine in 100 ml of chloroform was added dropwise during two hours at 0 °C. The stirring was continued at room temperature and the reaction was followed by thin layer chromatography. After 8 hours the reaction mixture was poured into ice-water and the phases were separated. The water phase was extracted with chloroform and the combined phases were washed with water, treated with charcoal and dried over magnesium sulfate. After evaporation the residue was chromatographed on silica gel using ethyl acetate/heptane (1:6) as eluent and the tribromo and the dibromo deriva-

8-Bromodithieno[2,3-*b*:3',4'-*d*]pyridine 8

The fractions containing the more polar component were evaporated giving 1.03 g (38%) of **8** as pale yellow crystals, which after recrystallization from ether (charcoal treatment) become white. Further purification by HPLC using heptane/ethyl acetate (80:20) as eluent gave a compound, which after sublimation at 119 °C/1mm Hg had mp 141-143 °C; ^{1}H NMR: δ 8.85 (s, 1H, H5), 8.30 (d, 1H, H1, J = 5.85 Hz), 8.10 (s, 1H, H6), 7.55 (d, 1H, H2, J = 5.85 Hz).

Anal. Calcd. for $C_9H_4BrNS_2$: C, 40.01; H, 1.49; N, 5.19; MW, 270.19. Found: C, 39.83; H, 1.67; N, 4.92; MW, 269/271.

6,8-Dibromodithieno[2,3-*b*:3',4'-*d*]pyridine 9

The fractions containing the more polar component in the first separation step were evaporated giving 628 mg (18%) yellow crystals recrystallized from dichloromethane/pentane (charcoal treatment). Further purification by HPLC using heptane/ethyl acetate (90:10) as eluent gave a compound, which after sublimation at 141 °C/1 mm Hg had mp 167-169 °C; ^{1}H NMR: δ 8.75 (s, 1H, H5), 8.30 (d, 1H, H1, J = 5.80 Hz), 7.60 (d, 1H, H2, J = 5.80 Hz).

Anal. Calcd. for $C_9H_3Br_2NS_2$: C, 30.98; H, 0.87; N, 4.01; MW, 348.88. Found: C, 30.68; H, 0.76; N, 4.10; MW, 347/349/351.

2,6,8-Tribromodithieno[2,3-b:3',4'-d]pyridine 10

The fractions containing the less polar component in the first separation step were evaporated giving 127 mg (3%) of **10** as yellow crystals, which were recrystallization from dichloromethane/pentane. After further purification by HPLC using heptane/ethyl acetate (90:10) as eluent and sublimation at 169 °C/1 mm Hg the mp was 196-198 °C; ^{1}H NMR: δ 8.70 (s, 1H, H5), 8.25 (s, 1H, H1).

HRMS calcd. for $C_9H_2Br_3NS_2$: 424.7178. Found: 424.7177.

Bromination of 5 with 2.6 equivalents of bromine

From 1.91 g (10.0 mmoles) of **5**, 4.00 g (0.028 mole) of sodium monohydrogen orthophosphate, 9.5 g (11 mmoles)) of sodium hydrogen carbonate and 2.80 g (0.024 mole) of magnesium sulfate in 200 ml of chloroform 1.35 ml (0.026 mole) of bromine in 100 ml of chloroform was added dropwise during two hours at 0 °C the reaction was performed as described above. After work-up 351 mg (13%) of **8**, 838 mg (24%) of **9**, 342 mg (8%) of **10**, 698 mg (20%) of **11** and and 54 mg (2%) of **12** were obtained.

2,8-Dibromodithieno[2,3-*b*:3,4-*d*]pyridine 11

The fractions containing **11** were treated with charcoal, evaporated and recrystallized from ether or further purified by HPLC using heptane/ethyl acetate (80:20) as eluent. After sublimation at 148 °C/1 mm Hg mp was 176.5-178.5 °C; ^{1}H NMR: δ 8.80 (s, 1H, H5), 8.30 (s, 1h, H1), 8.10 (s, 1H, H6).

Anal. Calcd. for $C_9H_3Br_2NS_2$: C, 30.98; H, 0.87; MW, 348.88. Found: 30.67; H, 0.72; MW, 347/349/351.

5-Bromodithieno[2,3-*b*:3,4-*d*]pyridine 12

The fractions containing **12** were evaporated and the residue, pale yellow crystals, was further purified by HPLC using

heptane/ethyl acetate (85:15) as eluent. After sublimation at 128 °C/1 mm Hg mp was 153-155; ^{1}H NMR: δ 8.10 (d,1H, H6, J = 3.10 Hz), 7.80 (d, 1H, H8, J = 3.10 Hz), 7.60 (d, 1H, H2, J = 5.80 Hz), 7.40 (d, 1H, H1, J = 5.80 Hz).

Anal. Calcd. for $C_9H_4BrNS_2$: C, 40.01; H, 1.49; N, 5.19; MW, 268.8941. Found: C, 39.67; H, 1.38; N, 4.73; MW, 269/271; 268.8958 (HRMS).

8-Bromodithieno[2,3-*b*:3',4'-*d*]pyridine 8 obtained in bromination with *N*-bromosuccinimide

To a suspension of 1.96 g (11.0 mmoles) of *N*-bromosuccinimide in 50 ml of tetrachloromethane 1.91 g (10 moles) of **5** and 23.0 mg (0.10 mmole) of picric acid was added. The reaction mixture was stirred at room temperature for 3-4 hours. After filtration of succinimide the filtrate was washed with saturated sodium hydrogen carbonate and water, treated with charcoal and dried over magnesium sulfate. The residue after evaporation was 1.65 g (61%) of **8**, which was purified and had the some physical properties as described above.

8-Iododithieno[2,3-*b*:3,4-*d*]pyridine 13

To a suspension of 764 mg (4.00 mmoles) of sublimed **5**, 1.0 g (12 mmoles) of sodium hydrogen carbonate and 1.63 g (5.00 mmoles) of mercury(II) nitrate in 10 ml of dichloromethane 1.27 g (5.00 mmoles) of iodine was added. The reaction mixture was stirred at room temperature for three hours. The precipitate formed was filtered off and the filtrate was washed with saturated aqueous sodium thiosulfate solution and water. The organic phase was treated with charcoal, dried over magnesium sulfate and evaporated. The residue was chromatographed using ethyl acetate/heptane (1:10) and (1:5) as eluents. Evaporation of the fractions containing **13** gave 520 mg (41%). After further purification by HPLC and sublimation at 140 °C/1 mm Hg mp was 161-163 °C; ^{1}H NMR: δ 8.90 (s, 1H, H5), 8.60 (d, 1H, H1, J = 5.90 Hz), 8.30 (s, 1H, H6), 7.55 (d, 1H, H2, J = 5.90 Hz).

HRMS calcd. for C_9H_4INS: 316.8830. Found: 316.8833.

6,8-Diiododithieno[2,3-*b*:3,4-*d*]pyridine 14

In a procedure as described above **14** was obtained from 764 mg (4.00 mmoles) of **5**, 2.0 g (24 mmoles) of sodium hydrogen carbonate, 3.26 g (10 mmoles) of mercury(II) nitrate 20 ml of dichloromethane and 2.54 g (10 mmoles) of iodine. The fractions containing **14** were treated with charcoal and evaporated, the residue was either recrystallized from ether or further purified by HPLC using heptane/ethyl acetate (90:10) as eluent. After sublimation at 148 °C/1 mm Hg mp was 174.5-176.5 °C; ^{1}H NMR: δ 8.70 (d, 1H, H5; J = 0.40 Hz), 8.60 (dd, 1H, H1, J = 5.90, 0.40 Hz), 7.60 (d, 1H, H2, J = 5.90 Hz).

Anal. Calcd. for $C_9H_3I_2NS_2$: C, 24.39; H, 0.68; N, 3.16; Mw, 443.10. Found: C, 24.29; H, 0.78; N, 3.08; MW, 443.

Halogen-metal exchange of 6,8-dibromodithieno[2,3-*b*:3',4'-*d*] pyridine 9

A flask flushed with nitrogen was charged with 698 mg (2.00 mmoles) of sublimed **9** in 100 ml of anhydrous ether at -70 °C and 1.20 ml of 2M butyllithium in cyclohexane diluted with 10 ml of anhydrous ether was under stirring added very slowly. After completed addition the reaction mixture was stirred for another five min, whereupon 1.0 ml of water was added and the reaction mixture was allowed to reach room temperature. The phases were separated and the organic phase washed with water, dried over magnesium sulfate and evaporated. According to thin layer chromatography the

product contained three components, which were separated by column chromatography using ethyl acetate/heptane (1:4) as eluent. The result was 259 mg (48%) of **8**, 167 mg (24%) of **9** and 23 mg (6%) of **5**.

Results and Discussion

The nitration was carried out under similar conditions with concentrated nitric acid in trifluorocetic acid. Urea was added to the reaction mixture to suppress the nitrous acid catalysed nitration. The reaction was carried out both at room temperature and under reflux. The nitration was smooth and to our surprise only one mononitro isomer was obtained in 58% yield, which was proven to be the 8-nitro isomer **6** . No substitution was observed in the *b*-fused ring as in **4** and no nitration in the other position of the *c*-fused ring as in **3**. The formation of a second component (**7**, 5%) was also observed. After reflux for one hour the yield of **6** decreased to 36% and the yield of **7** increased to 12% together with starting material. After refluxing for 2.5 hours only **7** could be detected.

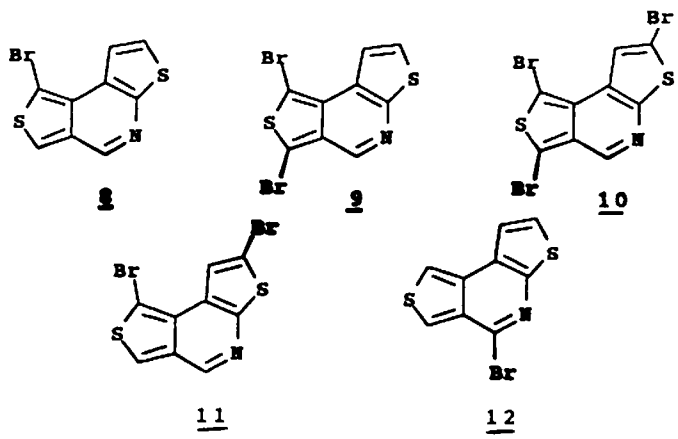
The structure of **6** was proven by ^{1}H NMR spectroscopy. The thiophenic doublets at δ 8.70 (H1) and 7.65 (H2) show the characteristic J_{23}-coupling (5.95 Hz). The characteristic down field shift of the proton in the 1-position from 7.50 ppm in the starting material to 8.70 ppm, more than one ppm, shows a large bay-effect and proves the presence of the nitro group in the 8-position [2,6].

IR and NMR spectra proved that **7** was the 8-oxo derivative. In the IR spectrum an absorption at 1675 cm^{-1}, charateristic for the carbonyl group in α,β-unsaturated γ-thiolactones [7], was observed. The ^{1}H NMR spectrum showed four absorptions with the relative intensities 1:1:1:2 at δ 8.70, 8.60, 7.60 and 4.70. The peak at lowest field due to the proton in the 5-position showed a splitting of 0.40 Hz. A coupling constant of this magnitude has previously been observed between the protons in the 1- and 5-positions [5]. The protons in the C-ring had the 2,3-coupling constant of 5.90 Hz. In a nuclear Overhouser effect experiment irradiation of the two protons at δ 4.70 enhanced the absorption due to the proton in the 5-position with 20%, showing the neighbourhood of the methylene protons and the proton in the 5-position.

In the bromination of **1** and **2** the monobromo isomers could not be separated, when bromine in chloroform and buffer was used. However, with excess bromine good yields of the 1,3-dibromo derivative of **1** and the 1,2-derivative of **2** was obtained [8]. Bromination of **3** with bromine in a buffer system gave a mixture of the 3-bromo-, 1-bromo- and 1,3-dibromo-derivatives in 32%, 8% and 10% yield, besides starting material. Bromination with 2.6 equivalents of bromine under the same conditions at 0 °C gave the 1,3-dibromo derivative in 72% yield. Bromination with *N*-bromosuccinimide gave a lower yield of the 1,3-dibromo derivative [9].

Bromination of **5** under mild aprotic conditions with 1.1 equivalents of bromine in chloroform using sodium mono hydrogen orthophosphate, sodium bicarbonate and magnesium sulphate as buffer [10] lead to a mixture of the 8-bromo derivative **8** , the 6,8-dibromo derivative **9** and the 2,6,8-tribromo derivative **10** . Trace amounts of the 2,8-dibromo derivative **11** was observed by thin layer chromatography. The compounds were extremely difficult to separate (for details cf experimental part), but by repeated chromatography **8**, **9** and **10** were isolated in 38%, 18% and 3% yield, respectively. Following the reaction with thinlayer chromatography showed that **9** was formed after a reaction time of 2.5 hours and then formation of **10** could be observed. The major compound 8 was difficult to detect although a large number of elution systems were tried, as the retention time was similar to that of **5**. The bromination could not be stopped at the monobromo derivative. After one hour only small amounts of 8 were obtained.

Using excess of bromine, gave in addition to **8**, **9** and **10** up to 20% of **11** at the expence of **8**. The reason for this could be that the bromination is reversible and that the 2,8-dibromo derivative is the more stable one. Similar results were observed in the bromination of 3-phenylthiophene [11,12]. Also small amounts of the 5-bromo derivative **12** was observed.



8 9 10

11 12

Substitution in this position has previously only been found in the nitration of the *N*-oxide of **2** [13]. Using three equivalents of bromine gave **9** as the most favoured component. The product distributions which were obtained are summarized in Table 1.

Table 1

Product distribution (%) in the bromination of dithieno[2,3-*b*:3',4',-*d*]pyridine **5** as a function of the amount of bromine.

Equivalents	Compound				
of bromine	**8**	**9**	**10**	**11**	**12**
1.1	38	18	3	trace	-
2.2	16	26	10	18	-
2.6	13	24	8	20	2
3.0	11	37	8	20	2

In order to find more selective methods for bromination, tetrabutylammonium perbromide in dichloromethane in the presence of excess of sodium hydrogen carbonate [14] was applied. However, the total yield was 18% of **8** and 10% of **9**. Bromination with *N*-bromosuccinimide in chloroform at room temperature or by refluxing could also be achieved (Table 2). Unfortunately the yields were quite small in spite of the easier work-up pocedure.

Table 2

Product distribution (%) in the bromination of dithieno[2,3-*b*:3',4',-*d*]pyridine **5** as a function of the reaction conditions.

Equivalents	Catalyst	Time, temp.	Compounds			
of NBS			**8**	**9**	**10**	**11**
1.1	------	1 day, rt	19	13	3	-
1.1	$HClO_4$	2-3 h, rt	28	22	3	2
1.1	Pic.a	4-5 h, rt	61	trace	-	-
2.2	-"-	5-7 h, rt	7	49	3	5

When this work was in progress, a paper by Goldberg and Alper [15] described biphasic electrophilic halogenation of activated aromatics and heteroaromatics with *N*-halosuccinimides, catalyzed by perchloric acid. It seemed very promising, as

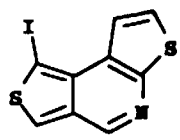
they could transform thiophene to either 2-bromothiophene or 2,5-dibromothiophene in almost quantitative yields, by using either one or two equivalents of *N*-bromosuccinimide.

When we used perchloric acid as catalyst, the reaction was vigorous and after about 15 minutes **9** had been formed and after 2.5 hours no starting material could be detected. After work-up only low yields of brominated products were obtained (cf. Table 2). We therefore used the weaker catalyst, picric acid, and managed in this way to obtain a 61% yield of **8** and trace amounts of **9** by using 1.1 equivalents of *N*-bromosuccinimide at room temperature and a reaction time of 4-5 hours. With 2.2 equivalents 49% of **9** was obtained after 6-7 hours at room temperature, together with small amounts of **8**, **10** and **11** (Table 2).

Mass spectrum showed that **8** contained only one bromine. ^{1}H NMR showed the characteristic 2,3-coupling constant of 5.85 Hz for the C-ring and a down field shift of the absorption due to the proton in the 1-position giving evidence for that the bromo substituent is in the 8-position. The mass spectrum of **9** showed a pattern characteristic for a dibromo derivtive. The C-ring containing two protons with the coupling constant of 5.80 Hz, concequently **9** is the 6,8-dibromo derivative. Mass spectrum of **10** gave that it is a tribromo derivative and the ^{1}H NMR showed two singlets, besides the one due to the proton in the 5-position, there is one at δ 8.25, in the same region as the absorption due to the proton in the 1-position of **8** and **9**. The conclusion is that **10** is the 2,6,8-tribromo derivative. The dibromo derivative **11** gave a ^{1}H NMR consisting of three singlets at δ 8.80, 8.30 and 8.10, which can be asigned to the 5-, 1- and 6-proton, respectively. The monobromo derivative **12** showed in its ^{1}H NMR spectrum four doublets, which two and two had splittings of 3.10 and 5.80 Hz, respectively, giving evidence for that both the A-ring and the C-ring are not substituted. Furthe more there was no absorption in the region of d 8.95, consequently **12** is the 5-monobromo derivative.

Many methods for the iodination of thiophenes are known. Iodine and mercuric oxide is a generally used method, the drawback of this method is that only half of the iodine is consumed [16,17]. A way to circumvent this drawback is to oxidize the hydroiodic acid back to iodine. For this purpose nitric acid [18] or iodic acid [17,19] have been used numerous times. However, when we tried the mercuric oxide method and iodine-iodic acid method only low yields of iodinated products were obtained.

A recent paper described the syntheses of different iodinated aromatic compounds in good yields, using iodine and a mercury(II) salt such as the chloride, nitrate or triflate in dichloromethane at room temperature [20]. We therefore applied



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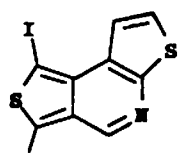

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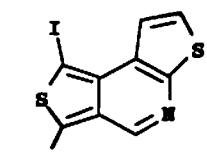

15

this reaction to **5** using 1.25 equivalents of iodine. The 8-iodo derivative **13** was obtained in 41% yield together with small amounts of the 6,8-diiodo derivative **14** . Using 2.5 equivalents of iodine gave after 4-5 hours at room temperature only **14** in 34% yield. Although the yields are lower the work-up of the products is much easier than in the bromo case. Longer reaction times (over night) gave according to mass spectrum a mercurated compound, which probably is the 8-iodo-6-iodomercury derivative **15** . However, it was not possible to grow crystals good enough for X-ray crystallography. The structures of **13** and **14** were determined by mass and NMR spectroscopy in analogy with those of the corresponding bromo derivatives, **8** and **9**.

We have previously studied the halogen-metal exhange of the 1,3-dibromo derivative of **3** with butyllithium and through

reaction with suitable electrophiles prepared various 1,3-difunctionalized derivatives [21]. Halogen-metal exchange of **9** with butyllithium at -70 °C in anhydrous ether followed by hydrolysis gave **8** (48%), **9**, (24%) and **5** (6%). No 6-bromo derivative could be detected. The behaviour was thus very similar to that of **3** [21]. Halogen-metal exchange of **9** with 2.20 equivalents of butyllithium followed by hydrolysis gave 89% of **5**. The dilithiation was complete in 20-25 min at -70 °C. Thus compound **9** appears to be a promising starting material for various 6,8-disubstituted derivatives of **5** of potential biological interest, through halogen-metal exchange followed by various electrophiles.

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