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ON 4,5-DISUBSTITUTION OF 3-THIOPHENE ALDEHYDE

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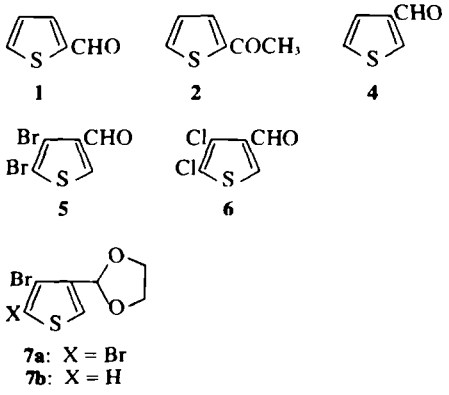
Abstract—The bromination and chlorination of 3-thiophene aldehyde in excess aluminium chloride have been investigated. Dihalogenation gave the 4,5-dihalo derivatives as the main products. This seems to be the first example of this substitution pattern for a 3-substituted thiophene.

Bromination of 2-thiophene aldehyde **1** and 2-acetylthiophene **2** in an excess of aluminium chloride **3** has been extensively investigated by Gol'dfarb *et al.*[1] While **1** in chloroform gives mainly 5 - bromo - 2 - formylthiophene upon bromination,[2] bromination of the complex between the carbonyl group in **1** or **2** and **3** gives the corresponding 4-brominated compounds. Thus, in electrophilic substitution the competition between the 4- and 5-positions of a 2-carbonylthiophene, which in **1** favors bromination at the 5-position, is changed when the carbonyl oxygen is complexed with **3**, making the carbonyl group even more electron attracting. The electron density decreases more in the 5-position than in the 4-position, analogous to the *p*- and *m*-positions in benzene, leaving the latter the most reactive. A similar complex between the carbonyl oxygen and a proton has been suggested by Gronowitz to explain the product distribution in the nitration of **1** under acidic conditions.[3] This assumption is in accordance with results by Gol'dfarb *et al.* on nitrations, brominations and chloromethylations of **1** and **2**.[4-7] Other electrophilic substitutions on 2-substituted thiophenes bearing a -I-M-substituent complexed with **3** have been carried out.[1,8-12,14] Furfural and 2-selenophene aldehyde have been brominated under the same conditions.[1,13] In some cases 4-substitution is accompanied with 5-substitution or 4,5-disubstitution. The corresponding reactions of 3-substituted thiophenes have not been investigated to the same extent.

Acylation of 3-acylthiophenes with 2.5 moleq. of **3** smoothly gives 2,4-diacylthiophenes.[8,12] Fournari *et al.* prepared 2 - bromo - 4 - formyl - thiophene by adding bromine to a refluxing solution of 3-thiophene aldehyde **4** and 2.5 moleq. of **3** in dichloromethane.[15]



1 **2** **4**

5 **6**

7a: X = Br
7b: X = H

Scheme 1.

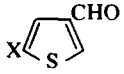
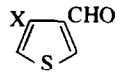
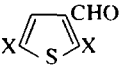
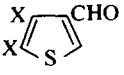
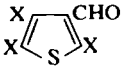
RESULTS

In a preparation of 2 - bromo - 4 - formylthiophene according to Fournari *et al.*, we obtained upon distillation a by-product **5**, m.p. 89.5–90.5°C. Elemental analysis, mass and NMR spectra showed it to be a dibromoformylthiophene. Since 2,5 - dibromo - 3 - formylthiophene melts at 47–49°C,[15,16] we investigated the by-product more closely. It was shown to be the previously unknown 2,3 - dibromo - 4 - formylthiophene as follows. Compound **5** was converted to its ethylene acetal **7a**, which was treated with one moleq. of *n*-butyllithium at −70°C, whereupon water was added. The resulting product was identified by GLC with an authentic sample of 2 - (4 - bromo - 3 - thienyl) - 1,3 - dioxolane **7b**.[17] Furthermore, its PMR spectrum showed an AB quartet at 7.46 and 7.27 δ, J = 3.5 Hz. The coupling constant is a little outside the normal region for a 3,4-disubstituted thiophene (2.8–3.2 Hz).[8] It is, however, clearly outside the ranges of 2,3- and 2,4-disubstituted thiophenes (4.9–6.0 and 1.2–1.9 Hz, respectively). However, the same coupling constant was found in cyclohexane solution by Gronowitz *et al.* for authentic **7b**.[17] Dibromination using 2 moleq. of bromine gave according to GLC the product distribution shown in Table 1. 2,5 - Dibromo - 3 - formylthiophene[15] and 2,3,5 - tribromo - 4 - formylthiophene (see below) were identified by comparison with authentic samples on GLC, the former also by its mass spectrum. In order to elucidate whether the formation of 2,5 - dibromo - 3 - formylthiophene was kinetically or thermodynamically controlled, a sample containing 85% of **5** and 12% of 2 - bromo - 4 - formylthiophene was refluxed in dichloromethane with 2.5 moleq. of **3**. Even after 22 h no change in the composition of the mixture was detected by GLC. The composition on dibromination therefore seems to be kinetically controlled.

Next we looked for isomeric monobromoformylthiophenes in the monobromination of **4**. Under GLC conditions that separated authentic samples of 2,3-, 2,4- and 3,4-bromoformylthiophenes we found only traces of the 3,4-isomer. This should be compared with the results of Östman, who on nitration of **4** in trifluoroacetic acid obtained considerable amounts of isomers of the main product, 2 - nitro - 4 - formylthiophene.[19] Belen'kii *et al.* acylated 3-acylthiophenes and obtained 2,4-diacylthiophenes in good yields but they reported nothing about isomers.[12]

For the preparation of **5** it is more convenient to use 1.6 moleq. of bromine, thus avoiding formation of the tribromothiophene aldehyde, which is difficult to remove from the product. Again in this case we found no isomers of 2 - bromo - 4 - formylthiophene, except for traces of the 3,4-isomer. However, for some reason, the ratio **5**: 2,5 -

Table 1. Composition of reaction mixtures obtained in the Experimental part

Compound	X = Br† 2.0 moleq. Br_2	X = Br‡ 1.6 moleq. Br_2	X = Br§ 1.0 moleq. Br_2	X = Cl‡
4	2.6	8.5	14	1.4
	7.2	34	74	2.7
		traces¶	traces¶	
	4.8	7.1	traces	2.9
	74	46	8.6	8?
	9.2	3.5	—	10

†NPGS 5%, 2 m, 150–200°C, 8°C/min. ‡OV 25, 3%, 3 m, 130–250°C, 8°C/min. §Reoplex 5%, 3 m, 120–200°C, 3°C/min. ¶For this detection, conditions § were used.

dibromo - 3 - formylthiophene is less favorable with 1.6 moleq. of bromine than with 2.0 moleq.

It was also possible to prepare 2,3,5 - tribromo - 4 - formylthiophene from **4** and **3** with a slight excess of bromine (3 moleq) in dichloromethane. However, bromination with 3 moleq. of bromine in dry chloroform without **3** gave only 2,5 - dibromo - 3 - formylthiophene.

It appeared that the chlorination of **4** with an excess of **3** might be a simple route to 2 - chloro - 4 - formylthiophene, previously prepared from the less accessible 4 - bromo - 2 - chlorothiophene by halogen-metal exchange and treatment with N,N-dimethylformamide.[20] It was, however, not possible to obtain the pure product by distillation through a 35 cm column filled with glass helices, which was due to rapid formation of a dichlorinated product. The trichlorinated aldehyde was also formed very easily. The products were identified on GLC–MS. The main dichlorinated compound was purified by recrystallisation, m.p. 58.9–59.9°C, and its oxime m.p. 146.5–147.6°C. 2,5 - Dichloro - 3 - formylthiophene is reported to melt at 24–24.5°C and its oxime at 129–131°C.[21] The present product therefore seems to be the hitherto unknown 2,3 - dichloro - 4 - formylthiophene **6**. The structure of **6** was confirmed by the C-H coupling constant of the unsubstituted carbon in the ^{13}C NMR spectrum. We found that in **5** $J_{C_5-H_5}$ was 194 Hz, and in 2,5 - dibromo - 3 - formylthiophene $J_{C_4-H_4}$ was 179 Hz. These values are in accordance with the values for monosubstituted thiophenes reported by Gronowitz *et al.*[22] They found $J_{C_\alpha-H_\alpha}$ to be 184–199 Hz and $J_{C_\beta-H_\beta}$ to be 164–177 Hz. The largest C-H coupling in **6** was 197 Hz, thus being a $C_\alpha-H_\alpha$ coupling, which proves the structure of **6**. For preparative purposes the reaction was followed on the gas chromatograph and interrupted at an early stage of the formation of the trichloroformylthiophene (the composition is presented in Table 1).

DISCUSSION

The substitution pattern on electrophilic substitution of thiophenes containing a -I-M-substituent in the 3-position has been discussed by one of the present authors.[3] The first substituent enters the 5-position, while the second enters the 2-position.[23] This was also found by Fournari *et al.* upon dibromination of **4** in chloroform without **3** as catalyst.[15] It was however observed that when the two α-positions were blocked with halogen atoms or with methyl groups, dinitration and disulfonation occurred easily in spite of the presence of a deactivating group when the last substituent entered. This was explained by a simple resonance theory applied to the substrate molecule.[3] According to resonance theory no good resonance structure can be drawn deactivating the 4-position. Resonance theory applied to the Wheland intermediates predicts the reactivity order to be $5 > 2 \approx 4$. Investigating nitration of 3-formyl-, 3-cyano- and 3-nitrothiophene in trifluoroacetic acid, Östman found, along with 5-substituted products (81–91%), appreciable amounts of 2,3- and 3,4-isomers.[19] The 2:4-ratios obtained in these substitutions were about 1.3, 1.4 and 2 for formyl-, cyano- and nitrothiophene, respectively. Thus, the experimental reactivity order in this case was $5 > 2 \approx 4$. Since electrophilic substitutions in thiophenes are known to be directed by the heteroatom to α-positions rather than to β-positions, one can state that the -I-M-substituent in the 3-position deactivates the 2-position more than the 4-position. In this context, Östman points out that the C_3–C_4 bond is slightly longer than the C_2–C_3 bond, which may make the inductive interaction between the substituent and the 4-position weaker than the interaction to the 2-position. This difference concerning the 2- and 4-positions in 3-substituted thiophenes is well known, both in electrophilic substitution (see Ref. 3 and references therein) and in PMR shifts.[24] Furthermore, the methyl groups in 2,3- and 3,2-methylnitrothiophenes are acidic, reacting with aldehydes under base catalysis, while the methyl groups in the 3,4-isomer do not.[25] Localisation energies for the substitutions in Ref. 19 are in qualitative agreement with experimental data.[26] In an MO LCAO SCF calculation of the total charges on the atoms of 3-thiophene aldehyde and its complex with a proton on the carbonyl oxygen, the highest electron density was found at C_5, the second highest (of the unsubstituted positions) at C_2, which is in accordance with the results of Östman[19] and also of other workers cited in Ref. 27.[27]

The results in the present paper show that in the 2 - halo - 4 - formylthiophenes complexed with **3**, the free

α-position is more deactivated than the free β-position, giving predominantly β-substitution on electrophilic halogenation. This seems to be the first example of this substitution pattern.[23] Since no 2 - bromo - 3 - formylthiophene was formed on bromination of **4**, we conclude that the 2,5 - dibromo - 3 - formylthiophene was formed from 2 - bromo - 4 - formylthiophene.

EXPERIMENTAL

M.ps are uncorrected. The PMR spectra were recorded in $CDCl_3$ solution on a Varian A-60 NMR spectrometer. ^{13}C NMR spectra were recorded in $(CD_3)_2CO$ solutions on a JEOL FX-60 NMR spectrometer. The shifts were obtained from proton decoupled spectra with TMS as internal standard. GLC analyses were carried out on a Perkin–Elmer 900 gas chromatograph with a FID detector and were integrated with a Varian Aerograph model 480. The MS were recorded on an LKB A 9000 mass spectrometer. Peak clusters in the MS of compounds containing bromine and chlorine showed the expected isotopic patterns.

2 - *Bromo* - 3 - *formylthiophene* (preparation modified and sample submitted by T. Dahlgren),[28] 3 - *bromo* - 4 - *formylthiophene*,[28] 2 - (3 - *bromo* - 4 - *thienyl*) - 1,3 - *dioxolane*[17] and 2,5 - *dibromo* - 3 - *formylthiophene*[15] were prepared according to methods described in the literature.

^{13}C NMR *of* 2,5 - *dibromo* - 3 - *formylthiophene*. δ 113.8, 124.3 (C_2, C_5), 129.7 (C_4), 140.4 (C_3), 183.4 (C_{ald}), $J_{C_4-H_4}$ 179 Hz.

Monobromination of 3-thiophene aldehyde was carried out according to Ref. 15, starting from 5.0 g (0.0446 mol) of **4**, 150 ml of dichloromethane, 14.5 g of **3** and 7.1 g (0.0444 mol) of dry bromine dissolved in 5 ml of dichloromethane. After hydrolysis and washing with 6 M hydrochloric acid and sodium hydrogen carbonate, the reaction mixture was analysed by GLC (Reoplex 5%, 3 m, 120–200°C, 3°C/min, gas flow 10 ml/min). These conditions separated 2,3-, 2,4- and 3,4-bromoformylthiophenes satisfactorily. Their retention times increased in this order. The composition of the reaction mixture is given in Table 1.

2,3 - *Dibromo* - 4 - *formylthiophene* **5**. 3-Thiophene aldehyde (22.1 g, 0.197 mol) was dissolved in 700 ml of dry dichloromethane and the solution was cooled with ice-water. Aluminium chloride (65 g, 0.49 mol) was added, with stirring, in four portions. The dark solution was heated to reflux and a solution of dry bromine (50.5 g, 0.315 mol) in dichloromethane (50 ml) was added dropwise over a 45 min period. The mixture was refluxed for 3 h and then poured onto crushed ice. The phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were washed twice with 6 M HCl, once with $NaHCO_3$ and finally with water. After drying ($MgSO_4$) and evaporation, a solid (45.5 g) was obtained which was distilled at reduced pressure. The fraction (28.0 g) boiling at 86–112°C/0.3–0.5 mmHg showed the composition given in Table 1. Recrystallisation from ligroin gave 18.7 g (43% calcd. on bromine) of the title compound, m.p. 89.5–90.5°C. GLC (OV 25, 3%, 3 m, 130–250°C) showed only one peak. (Found: C 21.8; H 0.72; Br 59.8. $C_5H_2Br_2OS$ (270.0) requires: C 22.3; H 0.75; Br 59.2%). PMR: δ 8.20 (s, 1, H_5), 9.84 (s, 1, CHO). ^{13}C NMR: δ 114.4, 114.8 (C_3 and C_4), 138.5 (C_2 and C_5), 184.2 (C_{ald}), $J_{C_5-H_5}$ 194 Hz. MS (direct inlet): Found: *m/e* 268, 270, 272 (M^+); 267, 269, 271 (100%, loss of H); 239, 241, 243 (loss of CHO) calcd. for $C_5H_2{}^{79}Br_2OS$: *m/e* 268. MS of 2,5 - dibromo - 3 - formylthiophene (via GLC) showed the same peaks. GLC of a distillation fraction boiling at 50–70°C/0.3 mmHg under conditions given above for monobromination of 3-thiophene aldehyde showed only traces of 3 - bromo - 4 - formylthiophene and no 2 - bromo - 3 - formylthiophene.

Bromination of 3 - *thiophene aldehyde with* 2 *moleq. of bromine* was carried out in the same manner. The product composition is given in Table 1.

2 - (2,3 - *Dibromo* - 4 - *thienyl*) - 1,3 - *dioxolane* **7a**. To 30 ml of dry benzene the following compounds were added: 2,3 - dibromo - 4 - formylthiophene (9.8 g, 0.0363 mol), ethylene glycol (2.8 g), and some crystals of *p*-toluene sulfonic acid. The mixture was refluxed over night with water separation. After cooling, the solution was washed twice with $NaHCO_3$ solution, and once with water. The residue after drying and evaporation was distilled *in vacuo*, yielding 8.2 g (72%) of the title compound, b.p. 179–182°C/13 mmHg. PMR: δ 7.46 (d, 1, H_5), 5.82 (d, 1, CH), 4.03 (4, CH_2CH_2), $J_{5,CH}$ 0.6 Hz.

2 - (4 - *Bromo* - 3 - *thienyl*) - 1,3 - *dioxolane* **7b**. 2 - (2,3 - Dibromo - 4 - thienyl) - 1,3 - dioxolane (3.14 g, 0.010 mol) was dissolved in dry ether (20 ml). The solution was cooled under a stream of dry nitrogen to −70°C, whereupon a solid appeared. *n*-Butyllithium (7.0 ml of a 1.46 M solution in hexane, 0.0102 mol) was added dropwise. After stirring for 15 min, the cooling bath was removed, and when the mixture had reached room temperature (at which stage the solid had dissolved again), water was added dropwise. The phases were separated and the ether phase washed once with water and once with sat. NaCl solution. The product obtained after drying and evaporation weighed 1.8 g. GLC (BDS 10%, 2 m, 200°C) showed one main component which was identified with an authentic sample of the title compound. PMR: δ 7.46 (quart., 1, H_2), 7.27 (d, 1, H_5), 5.89 (d, 1, CH), 4.02 (m, 4, CH_2CH_2), J_{24} 3.5 Hz, $J_{2,CH}$ 0.6 Hz. Lit. values (in cyclohexane extrapolated to infinite dilution): δ 7.18 (H_2), 7.05 (H_5), J_{25} 3.5 Hz, $J_{5,CH}$ 0.7 Hz.[17]

2,3,5 - *Tribromo* - 4 - *formylthiophene*. To an ice-cooled solution of 3-thiophene aldehyde (11.5 g, 0.103 mol) in dichloromethane (350 ml), was added aluminium chloride (33 g, 0.25 mol) in two portions with stirring. The solution was heated to reflux, and bromine (50.0 g, 0.312 mol) dissolved in dichloromethane (50 ml) added over a period of 35 min. After refluxing for 4 h, GLC (OV 25, 3%, 3 m, 130–250°C, 8°C/min) showed considerable amounts of 2,3 - dibromo - 4 - formylthiophene along with the title compound (main product). An additional 8.6 g of bromine (total 0.367 mol) was added dropwise, and after refluxing for an additional 5 h the reaction was interrupted. The solution was poured onto crushed ice, and after separation of the phases, the aqueous phase was extracted with dichloromethane. The combined organic layers were washed twice with 6 M HCl, and then with $NaHCO_3$ solution, sodium thiosulfate solution, $NaHCO_3$ solution and water. Drying and evaporation gave a slightly yellow solid which was recrystallised from ligroin, giving the title compound (25.0 g, 70%), m.p. 99.9–101.3°C. The product was 96% pure according to GLC. Analytical sample m.p. 100.5–102.0°C (ethanol). (Found: C 17.1; H 0.23; Br 69.6. C_5HBr_3OS (348.9) requires: C, 17.2; H 0.29; Br 68.7%). PMR: δ 9.80.

2,3 - *Dichloro* - 4 - *formylthiophene*. To an ice-cooled solution of 3-thiophene aldehyde (12.8 g, 0.125 mol) in dichloromethane (220 ml), was added aluminium chloride (40 g) in portions with stirring. With continued stirring and cooling, dry chlorine gas was bubbled through the solution. The reaction was interrupted when GLC (BDS 10%, 2 m, 150–200°C, 8°C/min) showed the composition given in Table 1. After separation of the phases, the aqueous phase was extracted once with dichloromethane. The combined organic phases were washed twice with 6 M HCl, whereupon ice and sodium hydrogen sulfite solution were added. After shaking, the two-phase system was strongly acidified with conc. HCl. The phases were separated after shaking and the organic layer was washed twice with $NaHCO_3$ solution. Drying and evaporation gave a yellowish solid (18.6 g), which was recrystallised twice from ligroin, yielding the title compound (9.7 g), m.p. 58.3–59.3°C. From the mother liquor of the second recrystallisation, an additional 0.2 g was obtained, m.p. 54.5–58.0°C. Both samples contained only one component according to GLC. The total yield was 44%. The analytical sample m.p. 58.9–59.9°C (ethanol) (lit. value for 2,5 - dichloro - 3 - formylthiophene 24–24.5°C[21]). This solvent had the disadvantage of rapid acetal formation, so ligroin was preferred. (Found: C 33.6; H 1.21; Cl 39.6. $C_5H_2Cl_2OS$ (181.0) requires: C 33.2; H 1.11; Cl 39.2%). PMR: δ 8.05 (s, 1, H_5), 9.84 (s, 1, CHO). ^{13}C NMR: δ 124.0, 127.3 (C_3 and C_4), 135.1 (C_5), 136.8 (C_2), 183.6 (C_{ald}), $J_{C_5-H_5}$ 197 Hz. MS (via GLC): Found: *m/e* 180, 182, 184 (M^+), 179, 181, 183 (100%, loss of H), 151, 153, 155 (loss of CHO). Calcd. for $C_5H_2{}^{35}Cl_2OS$: 180.

Spectra of other components in the mixture: 2 - Chloro - 4 - formylthiophene: MS (via GLC): Found: *m/e* 146, 148 (M^+), 145, 147 (100%, loss of H), 117, 119 (loss of CHO). Calcd. for $C_5H_3{}^{35}ClOS$: 146. PMR (from a contaminated distillation fraction): δ 7.93 (d, 1, H_2), 7.32 (d, 1, H_4), 9.75 (s, 1, CHO), J 1.6 Hz. Lit. values for 2 - chloro - 4 - formylthiophene (CCl_4): δ 7.90, 7.32, 9.78, J 1.6 Hz.[20] 2,5 - Dichloro - 3 - formylthiophene: MS (via GLC): Found: *m/e* 180, 182, 184 (M^+), 179, 181, 183 (100%, loss of H), 151, 153, 155 (loss of CHO). Calcd. for $C_5H_2{}^{35}Cl_2OS$: 180. 2,3,5 -

Trichloro - 4 - formylthiophene: MS (via GLC): Found: *m/e* 214, 216, 218, 220 (M^+), 213, 215, 217, 219 (100%, loss of H), 185, 187, 189, 191 (loss of CHO). Calcd. for $C_5H^{35}Cl_3OS$: 214. PMR (from a sample containing mainly 2,3 - dichloro - 4 - formylthiophene): δ 9.95.

The oxime of 2,3 - dichloro - 4 - formylthiophene was prepared and sublimed at 145°C/2 mmHg, m.p. 146.5–147.6°C (sealed capillary). Lit. value for the oxime of 2,5 - dichloro - 4 - formylthiophene, m.p. 129–131°C.[21]

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