On the Orientation in Lithiation and Bromination of Dithieno[3,4-*b*:3′,2′-*d*]pyridine

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The 3-position of dithieno[3,4-*b*:3′,2′-*d*]pyridine was found to be most reactive with regard to lithiation, bromination and halogen-metal exchange. The lithium compounds were trapped as the formyl derivatives by reaction with *N,N*-dimethylformamide.

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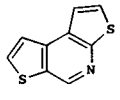
Introduction.

In connection with our interest in the effect of the mode of annelation on reactivity in tricyclic heterocyclic systems with angular annelation pattern, we have previously studied the lithiation with lithium diisopropylamide of dithieno[2,3-*b*:3′,2′-*d*]pyridine (**1**) [1]. Selective lithiation was observed in the 7-position. The result was in accordance with the relative acidities calculated on *ab initio* 3-21G* levels [1].

We have now studied the metalation of the *b,c*-fused system dithieno[3,4-*b*:3′,2′-*d*]pyridine (**2**) with lithium diisopropylamide at −70° using different reaction times. The lithium compounds were trapped as the formyl derivatives by reaction with *N,N*-dimethylformamide.

Using 1.2 equivalents of lithium diisopropylamide during 3-6 hours (Table 1, entries A, B, C, D) gave at most 34% of the 3-formyl derivative **3**, between 34 and 61% of the starting material was recovered, and 1-4% of the 1-isomer **4** was also obtained. After six hours reaction time the formation of about 2% of the 7-formyl derivative **5** was also observed. Using a reaction time of 16 hours increased the amount of **5** to 8%.



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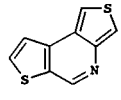

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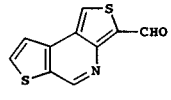

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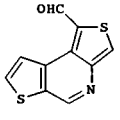

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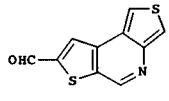

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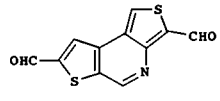

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Using 2.15 equivalents of lithium diisopropylamide led to a decrease in recovered starting material. The 3-isomer was formed in a yield of 42% together with small amounts of the 1- and 7-formyl derivatives and 20% of the 3,7-diformyl derivative **6** (*cf.* Table 1).

The structure of the monoformyl derivative **3**, was determined in a nuclear Overhauser effect (NOE) experiment. In deuterated dimethyl sulfoxide the compound showed five bands in its ^{1}H nmr spectrum. The bands at δ 8.14 and δ 8.35 have splittings of 5.15 Hz, characteristic for the coupling constant between the 2- and 3-proton in thiophene, showing that the formyl group is in the *c*-annelated ring. The remaining proton in the *c*-annelated ring absorbs at δ 9.14 and gave a coupling to the formyl proton of 1.2 Hz. The formyl proton absorbs at δ 10.66 and the proton at the 5-position at δ 9.41.

Table 1

Metalation of Dithieno[3,4-*b*:3′,2′-*d*]pyridine with Lithium Diisopropylamide Followed by Reaction with *N,N*-Dimethylformamide

Entry	LDA DMF mmole	Reaction time hours	**2**	**3**	**4**	**5**	**6**
			Yields in %				
A	1.2	3	61	21	4	–	–
B	1.2	4	40	38	3	–	–
C	1.2	6	34	43	1	2	–
D	1.2	16	31	33	1	8	–
E	2.15	5	9	42	3	5	20
F	2.50	6	–	50	–	–	29

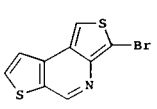
By irradiating the band at δ 8.14, enhancement was observed at δ 8.35 (25%) and at δ 9.14 (25%). Consequently the chemical shift for the proton in the 8-position is 8.14 ppm, the proton in the 7-position 8.35 ppm, the proton in the 1-position 9.14 ppm and the position first lithiated is the 3-position.

The structure of **3** was also proved in a chemical experiment. 3-Bromodithieno[3,4-*b*:3′,2′-*d*]pyridine underwent halogen metal exchange followed by treatment with *N,N*-dimethylformamide and the compound so obtained was identical with that in the preparation with lithium diisopropylamide and *N,N*-dimethylformamide.

The structure of the 7-formyl derivative followed directly from the presence of the characteristic J_{13}-coupling constant of 3.30 Hz and the expected α-reactivity of thiophene derivatives.

The structure of the diformyl derivative was also confirmed by a NOE experiment. By irradiating the absorp-

tion due to the proton in the 8-position two enhancements were observed, for the 7-formyl absorption (40%) and the other must be for the absorption due to the proton in the 1-position (20%).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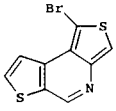
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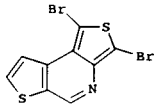
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When dithieno[3,4-*b*:3',2'-*d*]pyridine (**2**) was brominated with bromine in a buffer system [2] the product contained four components, **2** and **7-9**, and the yields were 13, 32, 8 and 10%. When **2** was treated with 2.6 equivalents of bromine under the same conditions at 0° **9** was obtained in 72% yield. Brominating with *N*-bromosuccinimide in chloroform, **9** could also be achieved, however the yield was only 43%.

The relative reactivity of the 1- and 3-bromines in halogen metal exchange was studied. The monobromo derivative obtained after hydrolysis gave in its ^{1}H nmr spectrum a chemical shift characteristic for the proton in the 3-position. Furthermore the remaining bromine in the 1-position influences the proton in the 8-position with a large bay effect. The chemical shift is increased from 7.73 ppm to 8.45 ppm. The hydrolysis product contained **2, 8** and **9** in the proportions 8:34:34. When 2.40 equivalents of butyllithium was used in the halogen metal exchange of **9** followed by hydrolysis, **2** was obtained in a yield of 78%.

EXPERIMENTAL

Melting points are uncorrected. The ^{1}H nmr spectra were recorded on a Varian XL-300 spectrometer. The mass spectra were recorded on a Jeol JMS-SZ 102 spectrometer. For hplc a preparative polygosil/silica column (250 x 20) was used.

General Procedure for the Reaction of Dithieno[3,4-*b*:3',2'-*d*]pyridine (**2**) with Lithium Diisopropylamide and *N,N*-Dimethylformamide, Entries A-D in Table 1.

A 250 ml three necked flask was flushed with nitrogen and charged with 0.32 ml (2.40 mmoles) of anhydrous diisopropylamine in 10 ml of anhydrous ether and cooled to −10°, whereupon 1.20 ml (2.40 mmoles) of 2*N* butyllithium was added under stirring. After stirring for 30 minutes the reaction mixture was cooled to −78° and 382 mg (2.00 mmoles) of dithieno[3,4-*b*:3',2'-*d*]pyridine [3] in 100 ml of anhydrous ether was added dropwise for 90 minutes, whereupon 0.20 ml (2.40 mmoles) of *N,N*-dimethylformamide in 10 ml of anhydrous ether was added dropwise. After reaction times given in Table 1, the reaction mixture was allowed to reach 0° and 10 ml of 2*N* hydrochloric acid was added under stirring. The stirring was continued for 30 minutes and the *p*H adjusted to about 3. The phases were separated and the water phase extracted with ether. The combined ether phases were washed with ice-water, sodium hydrogen carbonate to neutral *p*H and ice-water again. If necessary the ethereal solution was treated with charcoal before drying over magnesium sulfate.

3-Formyldithieno[3,4-*b*:3',2'-*d*]pyridine (**3**).

After evaporation the crude product was chromatographed on silica 60 using ethyl acetate/ether (1:10) as eluent, followed by hplc with heptane/ethyl acetate (70:30) as eluent. The yield is given in Table 1. The substance was sublimed at 175°/0.2 mm Hg; ir: ν CO 1640 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 10.82 (d, 1H, CHO, J = 1.25 Hz), 9.18 (d, 1H, 5-H, J = 0.70 Hz), 8.37 (d, 1H, 1-H, J = 1.25 Hz), 7.91 (d, 1H, 7-H, J = 5.20 Hz), 7.81 (dd, 1H, 8-H, J = 5.20, 0.70 Hz).

Anal. Calcd. for $C_{10}H_5NOS_2$: C, 54.77; H, 2.30; N, 6.39; MW 219.29. Found: C, 54.4; H, 2.26; N, 6.11; MW 219.

1-Formyldithieno[3,4-*b*:3',2'-*d*]pyridine (**4**).

After evaporation the crude product was chromatographed on silica 60 using ethyl acetate/petroleum ether (2:1) as eluent, followed by hplc with heptane/ethyl acetate (70:30) as eluent. The yield is given in Table 1. The substance was sublimed at 173°/0.2 mm Hg; ir: ν CO 1645 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.66 (d, 1H, CHO, J = 1.25 Hz), 9.41 (s, 1H, 5-H), 9.14 (d, 1H, 3-H), 8.35 (d, 1H, 7-H, J = 5.15 Hz), 8.14 (dd, 1H, 8-H, J = 0.70, 5.15 Hz).

Anal. Calcd. for $C_{10}H_5NOS_2$: C, 54.77; H, 2.30; S, 29.25; MW 219.29. Found: C, 54.83; H, 2.46; S, 29.22; MW 219.

7-Formyldithieno[3,4-*b*:3',2'-*d*]pyridine (**5**).

After evaporation the crude product was chromatographed on silica 60 using ethyl acetate/ether (1:10) as eluent. Yield is given in Table 1. The substance was sublimed at 161°/0.4 mm Hg; ir: ν CO 1670 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 10.20 (s, 1H, CHO), 9.00 (d, 1H, 5-H, J = 0.80 Hz), 8.36 (d, 1H, 8-H, J = 0.80 Hz), 8.12 (d, 1H, 3-H, J = 3.30 Hz), 7.93 (d, 1H, 1-H, J = 3.30 Hz).

Anal. Calcd. for $C_{10}H_5NOS_2$: C, 54.77; H, 2.30; N, 6.39; MW 219.29. Found: C, 54.61; H, 2.37; N, 6.29; MW 219.

3,7-Diformyldithieno[3,4-*b*:3',2'-*d*]pyridine (**6**).

This compound was prepared according to the general procedure entries E and F in Table 1. Upon evaporation **6** crystallized and could be separated from the monoformyl derivatives and the starting material by filtration. The substance was sublimed at 178°/0.2 mm Hg; ir: ν CO 1640, 1675 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 10.66 (s, 1H, CHO), 10.26 (s, 1H, CHO), 9.53 (s, 1H, 5-H), 9.22 (s, 1H, 3-H), 8.97 (s, 1H, 8-H).

Anal. Calcd. for $C_{11}H_5NO_2S_2$: C, 53.42; H, 2.04; N, 5.67; MW 247.30. Found: C, 53.37; H, 2.41; N, 5.79; MW 247.

Bromination of Dithieno[3,4-*b*:3',2'-*d*]pyridine with 1.3 Equivalents of Bromine.

A flask flushed with nitrogen was charged with 382 mg (2.00 mmoles) of sublimed dithieno[3,4-*b*:3',2'-*d*]pyridine, 840 mg (4.80 mmoles) of dipotassium monohydrogen orthophosphate, 266 mg (3.20 mmoles) of sodium bicarbonate and 480 mg (4.00 mmoles) of magnesium sulfate in 100 mg of chloroform, whereupon 0.15 ml (2.60 mmoles) of bromine in 50 ml of chloroform was added dropwise at 0° with stirring. The stirring was continued for five hours at room temperature and the reaction was followed by thin layer chromatography. 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 treated with charcoal and dried over magnesium sulfate. After evapora-

tion the residue was chromatographed on thin layer silica using ethyl acetate/petroleum ether (1:4) as eluent, and the main component could be isolated. The minor components in the remaining fractions were separated by hplc using heptane/ethyl acetate (70:30) as eluent.

3-Bromodithieno[3,4-*b*:3′,2′-*d*]pyridine (**7**).

After evaporation 173 mg (32%) was obtained as white crystals. The substance was sublimed at 133-134°/2.8 mm Hg, mp 163.0-164.5°; ^{1}H nmr (deuteriochloroform): δ 9.03 (s, 1H, 5-H), 7.87 (s, 1H, 1-H), 7.82 (d, 1H, 7-H, J = 5.15), 7.71 (d, 1H, 8-H, J = 5.15).

Anal. Calcd. for $C_9H_4BrNS_2$: C, 40.01; H, 1.49; N, 5.19; MW, 270.19. Found: C, 40.08; H, 1.53; N, 5.21; MW, 269/271.

1-Bromodithieno[3,4-*b*:3′,2′-*d*]pyridine (**8**).

After evaporation 43.3 mg (8.00%) of **8** was obtained as white crystals. The substance was sublimed at 92°/1 mm Hg, mp 114.5-116.0°; ^{1}H nmr (deuteriochloroform): δ 8.92 (s, 1H, 5-H), 8.45 (dd, 1H, 8-H, J = 0.70, 5.25 Hz), 8.00 (s, 1H, 3-H), 7.83 (d, 1H, 7-H, J = 5.25 Hz).

Calcd. for $C_9H_4BrNS_2$: 268.8968. HRms Found: M+H 269.9044.

1,3-Dibromodithieno[3,4-*b*:3′,2′-*d*]pyridine (**9**).

A flask flushed with nitrogen was charged with 955 mg (5.00 mmoles) of sublimed dithieno[3,4-*b*:3′,2′-*d*]pyridine, 2.10 g (12.0 mmoles) of dipotassium monohydrogen orthophosphate, 0.70 g (8.0 mmoles) of sodium carbonate and 1.20 g (10.0 mmoles) of magnesium sulfate in 100 ml of chloroform, whereupon 0.70 ml (13.0 mmoles) of bromine in 50 ml of chloroform was added dropwise with stirring at 0°. The stirring was continued for 48 hours at room temperature and the reaction followed by thin layer chromatography until the starting material was consumed. The reaction mixture was poured into ice-water and the phases were separated. The aqueous phase was extracted three times with chloroform and the combined chloroform phases were washed with water, treated with charcoal and dried over magnesium sulfate. After evaporation the residue was chromatographed on silica 60 using ethyl acetate/petroleum ether (1:10) as eluent, giving 1.10 g (63%) of **9** as yellow crystals. The substance was sublimed at 124°/1.0 mm Hg, mp 148.5-150.0°; ^{1}H nmr (deuteriochloroform): δ 8.96 (s, 1H, 5-H), 8.40 (dd, 1H, 8-H, J = 1.30, 5.20 Hz), 7.85 (d, 1H, 7-H, J = 5.20 Hz).

Anal. Calcd. for $C_9H_3Br_2NS_2$: C, 30.98; H, 0.87; MW, 348.88. Found: C, 31.13; H, 0.95; MW, 347/349/351.

Halogen-metal Exchange of 1,3-Dibromo[3,4-*b*:3′,2′-*d*]pyridine (**9**) with 1.2 Equivalents of Butyllithium Followed by Reaction with Methanol.

A flask flushed with nitrogen was charged with 419 mg (1.20 mmoles) of **9** in 100 ml of anhydrous ether and at −70° 0.72 ml of 2*N* butyllithium in hexane diluted with 10 ml of anhydrous ether was added with stirring. After stirring for an additional 30 minutes, 1.0 ml methanol was added to the reaction mixture, which then was allowed to reach room temperature. The solvents were evaporated and the residue taken up in chloroform. The chloroform solution was dried over magnesium sulfate and evaporated. The product contained three components, which were separated by chromatography on thin layer silica using ethyl acetate/petroleum ether (1:4) as eluent followed by hplc using heptane/ethyl acetate (70:30) as eluent. After evaporation of the different fractions, the three components obtained were identical with **9**, **8** and **2** in yields of 144.1 mg (34%), 110.3 mg (34%) and 17.8 mg (34%), respectively.

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