Orientation Effects in the Nitration of the Dithieno[*b,d*]pyridine *N*-Oxides. Its Dependence on Acidity of the Reaction Medium

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The nitration of three dithienopyridine-*N*-oxides was investigated. The regiochemistry of the reaction was dependent on the reaction conditions used. Under strongly acidic conditions the positional preference is similar for the *N*-oxides and free bases. However, under mildly acidic or neutral conditions a completely different substitution pattern was obtained. In the latter case those ring positions were substituted which are expected to be unfavored or forbidden in electrophilic substitution of the free bases. The structures of the nitro derivatives were proven by extensive use of ^1H and ^{13}C nmr spectroscopy.

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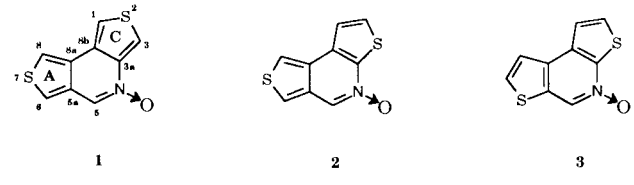
We have for some time been interested in understanding the regioselectivity of tricyclic heterocyclic systems with different angular annelation patterns. Previously, we reported our experimental and theoretical results on orientation in the nitration of the *cc*-fused dithieno[3,4-*b*:3′,4′-*d*]pyridine [1], which was predominantly substituted in the 1-position (78%) and to some extent in the 8-position (20%). Transition state energies calculated at the *ab initio* 3-21G(*) level were in good agreement with the experimental findings. On the other hand, nitration of the [*b,c*]-fused system dithieno[3,4-*b*:2′,3′-*d*]pyridine occurred in both positions of the *c*-fused thiophene rings [2], while the [*b,b*]-fused system dithieno[2,3-*b*:3′,2′-*d*]pyridine was predominantly substituted in the 2-position (70%) and the 1-position (30%) [2]. Again the calculated TS-energies were in good agreement with the experimental regioselectivity between the two thiophene rings. Calculations also reflected the much faster nitration rates of the [*c,c*]-fused systems compared to the [*b,b*]-fused systems [3]. We were therefore interested in comparing the reactivities of their *N*-oxides with those of the parent compounds. It should also be of interest to compare the reactivity and orientation in the nitration of these *N*-oxides with those of the six isomeric thienoquinoline *N*-oxides and thienoisoquinoline *N*-oxides, which have been nitrated under strongly acidic conditions with nitration occurring exclusively in the thiophene part [4]. The positional selectivities were in accord with calculated relative energies of Wheland intermediates, which refer to electrophilic substitution mechanism involving the conjugated acids as substrates [5]. The previous reports on the nitration reaction of aromatic *N*-oxides are quite interesting. A number of publications focus on the unusual, reaction condition dependent, product ratio of the nitration reaction [6,7]. The position of substitution depends on the acidity of the reaction medium and on the temperature.

Results and Discussion.

We found that the outcome of the reaction is strongly dependent on the reaction conditions. The reaction between the [*c,c*]-fused compound **1** and nitric acid in TFA at 40° causes unexpected decomposition of the substrate. No nitrated derivatives of **1** could be detected from this reaction mixture. A similar reaction using sulfuric acid and urea (in order to eliminate the nitrous acid catalyzed reaction), at room temperature or −15° resulted in 1:1 mixture of 1- and 8-monosubstituted derivatives of **1** (Figure 2). Using excess of nitric acid or sulfuric acid as solvent the reaction led to the 1,8-disubstituted product **6**. It should be noted that this substitution pattern is quite similar to that of the parent base [1]. Abandoning the sulfuric acid (but not the urea) from the above mentioned reaction conditions or adding a large amount of water to it, resulted in completely different products. No trace of the 1- or 8-substituted derivatives were detected, however a new mononitro derivative 6-nitrodithieno[3,4-*b*:3′,4′-*d*]-pyridine *N*-oxide (**7**) appears as the only nitrated product. Besides, partial decomposition of the ring system give rise to dark brown water soluble components.



1 2 3

Figure 1. Substrates of the nitration reactions.

The nitration of the [*b,c*]-fused ring system **2** in a strongly acidic medium gave predominantly 8-nitration with only a trace of 6-nitration (Figure 3). Use of excess nitric acid under these conditions resulted in dinitration at positions 2 and 8. The preference toward the *c*-fused ring (position 8) *versus* the *b*-fused (position 1 or 2) is in good agreement with the theoretical predictions [3]. However nitration with nitric acid under a conditions of mild acidity (TFA/nitric acid/urea) gave predominantly 6 nitration.

The nitration reaction of the [*b,b*]-fused *N*-oxide **3** in the presence of sulfuric acid results in 1- and 2-substituted

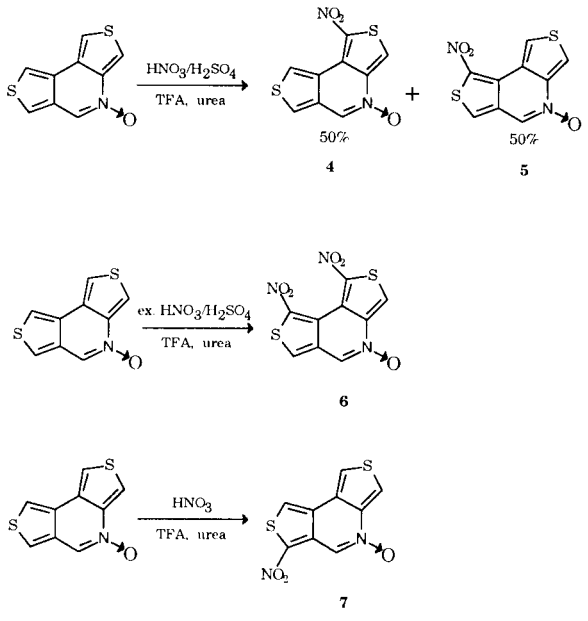


Figure 2. Nitration of dithieno[3,4-*b*:3',4'-*d*]pyridine *N*-oxide under strongly and mildly acidic conditions.

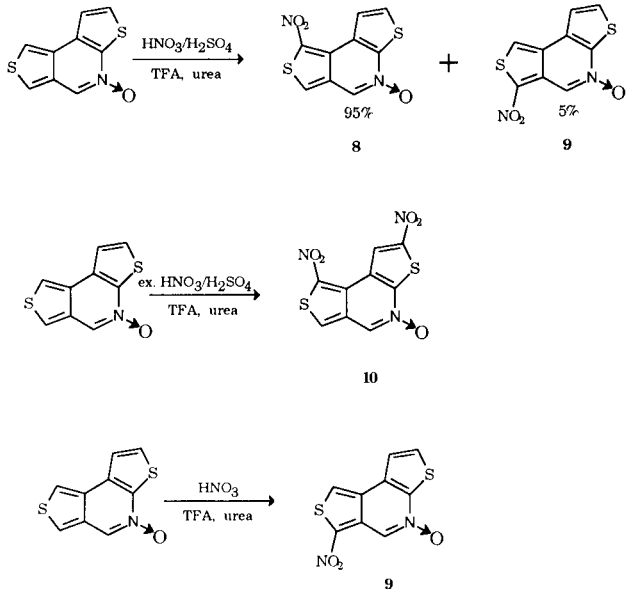


Figure 3. Nitration of dithieno[2,3-*b*:3',4'-*d*]pyridine *N*-oxide under strongly and mildly acidic conditions.

products, **12** and **13**. This position preference is the same that was obtained for nitration of the free base [2]. Unfortunately, separation of these two derivatives could not be achieved even by hplc, but the large difference in selectivity and the known ^{1}H nmr spectrum of the parent base [2] allowed their identification. This reaction was also accompanied by deoxygenation. Deoxygenation of *N*-oxides is not unprecedented as 4-nitropyridine has been obtained directly from the reaction of pyridine *N*-oxide with a nitrating mixture of sulfuric acid and nitric acid [6]. Nitration of **3** under mild acidic condition resulted in 5- and 7-substituted isomers (Figure 4). This substitution pattern is quite surprising. Substitution in the 5-position has not been observed before in the nitration of dithienopyridines. Nitration of *N*-oxides of thienopyridines or quinoline derivatives at the α position to nitrogen has not been reported either. The α position is usually favored by nucleophilic reagents [8].

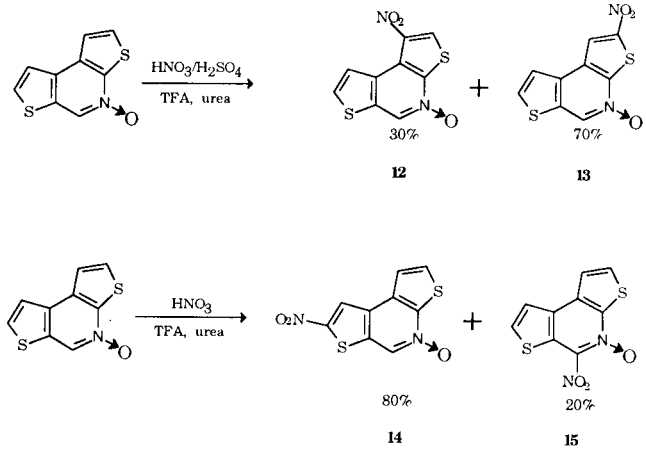


Figure 4. Nitration of dithieno[2,3-*b*:3',2'-*d*]pyridine *N*-oxide under strongly and mildly acidic conditions.

Based on kinetic measurements, Gleghorn *et al* [6] concluded that the nitration of quinoline *N*-oxide take place through the conjugate acid under strongly acidic conditions. It is very probable that this also is the case for the nitration of dithienopyridine *N*-oxides in TFA-sulfuric acid mixtures. The similarity with the substitution pattern of the free bases, in accordance with the theoretical calculations, seems to support an electrophilic substitution mechanism in this case. The substrate of the nitration reaction under mild acidic conditions is probably the unprotonated *N*-oxide, similarly to the quinoline or cinnoline *N*-oxide nitration [6].

As it is assumed that the nitration under mild acidic conditions take place through the free base, we felt it necessary to investigate the substitution reactions under neutral conditions.

A nitration reaction of the [*b*,*c*]-fused *N*-oxide **2** with nitrogen dioxide/nitrogen tetroxide in dichloromethane was carried out. This reaction showed a preference for nitration in a different position, the 2 position (Figure 5). The product substituted in the 6-position, **9**, which was the only mononitrated product of nitration of **2** under mild acidic conditions, was obtained as a minor component. The nitration of the *cc*-fused *N*-oxide (**1**) with nitrogen dioxide/nitrogen tetroxide in dichloromethane resulted in a complicated mixture, mainly decomposition products of the starting material. However the 6-nitro isomer **7** could

not detected in the reaction mixture. The nitration of the [*b,b*]-fused system **3** was also attempted, but only the unreacted starting material could be detected after a reaction time of 3 hours. The nitration by this reagent (nitrogen dioxide/nitrogen tetroxide) involves nitrosonium ion catalysis in some way [9]. Taking into account the essentially different reactivity and substitution pattern of the dithienopyridine *N*-oxides under conditions of nitrogen dioxide/nitrogen tetroxide nitration compared to those of mild acidic conditions, it can be concluded that nitrous acid catalyzed reaction seems to be unlikely in the latter case. It should also be pointed out that in case of nitric acid nitrations, urea was added in high concentration in order to suppress the nitrous acid catalysis.

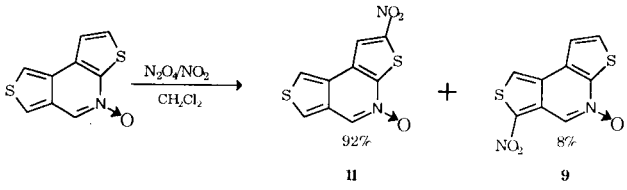


Figure 5. Nitration of dithieno[2,3-*b*:3',4'-*d*]pyridine *N*-oxide with nitrogen tetroxide-nitrogen dioxide under neutral conditions.

Further evidence indicating that the reaction might be a nitronium ion mediated process was obtained in the nitration with nitronium tetrafluoroborate in sulfolane. Under these conditions nitration of **1** occurred in position 6 yielding **7** and nitration of **3** in positions 7 and 5 yielding **14** and **15** respectively. These products are identical with those found in the nitration under mild acidic conditions. No trace of the products formed in nitration under strongly acidic conditions could be detected.

The determination of the substitution positions were achieved using 1D ^{1}H nmr and ^{13}C nmr and 2D HETCOR techniques. The ^{1}H nmr spectra of **4, 7, 9, 11, 12, 13** and **14** show long range coupling between H^5 and H^8 (Table 1). This proves that these positions remained unchanged. The small long range coupling is characteristic of the dithienopyridine systems [10,11] and also their derivatives [1,2]. The missing long range coupling in the ^{1}H nmr spectrum of **5** and **8** identified these products as 8-nitro derivatives. Both the long range coupling and H^5 singlet are missing from the ^{1}H spectrum of **15**, which in combination with the presence of thiophene doublets (^2J = 5.5, 5.7 Hz) indicates substitution in position 5. The thiophene doublet is combined with a long range coupling in the ^{1}H nmr spectrum of **4, 11, 12** and **13** indicating that both of the thiophene protons remained unchanged in the ring A. If the long range coupling is combined with a singlet, the nitration must have taken place at the thiophenic α position of the ring A (in position 6 for nitration of **1** and **2**, in position 7 for **3**). According to this, **7** and **9** are assigned as 6-nitro derivatives and **14** as 7 nitro derivative. The downfield shift ($\approx$1 ppm) induced on H^8 when the nitro group is situated on the angular peri position C^1 or *vice versa* is also characteristic to the [*b,d*]-annelated dithienopyridine systems [1,2]. Appearance of a downfield *dd* in the nmr spectrum of **4** and **12** identifies them as 1-nitro derivatives. Missing H-H couplings from the ^{1}H nmr spectrum of dinitrated derivatives **6** and **10** indicate that the disubstitution has occurred in different thiophene rings and that one of the substitution position must be position 8 (otherwise at least the long range coupling should appear). The large downfield shift of H^1 (9.44 ppm) of compound **10** in

Table 1

Proton NMR Shifts (ppm) and Coupling Constants (Hz) [a], (Deuteriochloroform)

	H^1	H^2	H^3	H^5	H^6	H^7	H^8	$^2J_{HH}$	$^3J_{HH}$	$^4J_{HH}$ [b]
4	–		8.64	8.44	7.81		9.33		$3.1_{6,8}$	$0.8_{5,8}$
5	9.38		8.41	8.31	7.86		–		$3.8_{1,3}$	–
	(9.30) [c]		(8.45)	(8.65)	(8.51)					
6	–		8.38	8.58	7.88		–		–	–
7	7.97		8.34	9.26	–		7.98		$3.4_{1,3}$	$0.8_{5,8}$
8	8.68	7.71		8.62	8.16		–	$5.7_{1,2}$	–	–
	(8.42) [c]	(8.03)		(9.02)	(8.85)					
9	7.68	7.76		9.49	–		8.18	$5.6_{1,2}$	–	$0.8_{5,8}$
	(8.09) [c]	(8.14)		(9.08)			(9.10)			
10	9.44	–		8.75	8.27		–	–	–	–
11	8.44	–		8.76	8.02		8.02 [d]	–	$3.0_{6,8}$	$0.9_{5,8}$
12	–	8.81		8.96		7.90	8.41	$5.7_{7,8}$		$0.8_{5,8}$
13	8.47	–		8.97		7.94	7.73	$5.4_{7,8}$		$0.8_{5,8}$
14	7.68	7.81		8.76		–	8.46	$5.7_{1,2}$		$0.8_{5,8}$
15	7.73	7.92		–		7.91	7.67	$5.5_{1,2}$, $5.7_{7,8}$		–

[a] Subscript numbers refers to the coupling protons. [b] Long-range coupling. [c] Chemical shifts in DMSO-d_6 are given in parenthesis. [d] The crude product exhibited non-equivalence for H^6 and H^8. The latter clearly resolved into dd.

Table 2

Carbon NMR Shifts and C-H Coupling Constants (DMSO-d_6)

		C^1	C^2	C^3	C^{3a}	C^5	C^{5a}	C^6	C^8	C^{8a}	C^{8b}
4	δ	138.3		125.7	125.1	128.9	132.5	123.8	130.2	123.4	121.4
	$^1J_{CH}$			199.8		190.2		193.2	195.8		
	$^3J_{CH}$			–		3.7		2.6, 5.27	4.5		
5	δ	130.7		118.8	140.9	127.3	131.6	130.7	127.1	123.8	121.8
	$^1J_{CH}$	195.5		197.7		190.8		195.5			
	$^3J_{CH}$	[a]		4.1		3.5		[a]			
6	δ	147.4		123.7	138.9	128.7	132.5	128.9	146.8	118.9	118.7
	$^1J_{CH}$			202.1		193.1		198.4			
	$^3J_{CH}$			–		3.5		2.6			
7	δ	119.9		122.3	138.6	126.7	127.6	128.1	127.0	124.2	121.4
	$^1J_{CH}$	197.6		193.5		195.0			194.3		
	$^3J_{CH}$	4.0		5.6		–			–		
8	δ	126.3	127.8		143.5	127.2	133.1	132.7	124.2	123.8	123.6
	$^1J_{CH}$	177.8	191.7			193.6		197.2			
	$^2J_{CH}$	5.0	7.3			–		–			
	$^3J_{CH}$	–	–			3.6		3.1			
9	δ	122.8	131.1		145.5	126.1	128.5	139.3	128.9	128.3	127.0
	$^1J_{CH}$	176.0	191.9			196.5			196.1		
	$^2J_{CH}$	4.2	6.4			–		–			
	$^3J_{CH}$	–	–			–		–			

[a] Unresolved multiplet (The coupling obscured due to overlap).

compared to the H^1 shift of the 2-nitro derivative **11** (8.44 ppm) refers to 2,8 dinitration. Such a downfield shift is missing from the ^1H nmr spectrum of **6** involving a missing H^1 proton, which identified **6** as 1,8-dinitro derivative. (In case of the 8-nitro derivative **5** of the same ring system, H^1 is shifted to 9.38 ppm, while the highest chemical shift found for the dinitro derivative **6** is only 8.58 ppm.) The thiophene α and β carbons can be differentiated by measuring of their C-H coupling constants. The $^1J_{CH}$ constants are about 195 Hz and 175 Hz for α and β carbons respectively (Table 2). Geminal C-H couplings ($^1J_{CH}$) appearing in the ^{13}C spectrum of **8** (δ = 126.3 ppm) and **9** (δ = 122.8 ppm) indicate that only the thiophenic β position (position 1) remained intact. The HETCOR spectrum of **8** shows C-H interaction between the carbon atom at 126.3 ppm and a proton doublet at 8.42 ppm, while the HETCOR spectrum of **9** shows a correlation between the ^{13}C shift at 122.8 ppm and ^1H doublet at 8.09 ppm. This supports the ^1H nmr assignment that the nitration has taken place on the *c*-fused ring. The appearance of long range couplings of the protonated carbon atoms ($^2J_{CH}$, $^3J_{CH}$) indicates intact positions close to each other. If all of the protonated carbon atoms show such long range couplings the monosubstitution of ring systems **1** or **2** must take place at position 8. (If any other position was nitrated, one of the long range couplings ($^2J_{CH}$, $^3J_{CH}$) should be missing.) Such a coupling pattern was found for derivatives **5** and **8**. If the monosubstituted products of **1** or **2** show two long range couplings to the same carbon atom, then positions 6 and 8 must be unsubstituted. This coupling pattern was found for the ^{13}C shift at 123.8 ppm for nitro derivative **4**. Two long range couplings appear in the ^{13}C nmr spectrum of the disubstituted derivative **6**. As the proton spectrum clearly indicates that the disubstitution must take place on different rings, these two couplings are further evidences for intact C^6 and C^5 positions.

The experimental results presented herein show fundamental similarities of orientation effects in the nitration of dithienopyridines and their *N*-oxides under strongly acidic conditions. The similarity of these effects in the nitration of thienoquinoline *N*-oxides and isothienoquinoline *N*-oxides [4] to the dithienopyridine *N*-oxide analogs is also obvious. Thieno[3,4-*b*]quinoline *N*-oxide is substituted at the thiophenic 1 position, similarly to the [*c,c*]-fused dithienopyridine *N*-oxide **1**. Nitration of thieno[3,4-*c*]isoquinoline *N*-oxide results in 1-nitro product, which is analog with the 8-nitro substituted derivative of **2**. Thieno[2,3-*b*]-quinoline *N*-oxide which is considered to be the benzo-analogue of **3** is nitrated exclusively at position 2, while the nitration of **3** occured predominantly in the 2-position and to a minor extent in the 1-position (Figure 4). However, the nitration of *N*-oxides under mildly acidic or neutral conditions leads to a completely different substitution pattern. The orientation effects do not show any analogy with the nitration of the conjugated acid, the thieno(iso)-quinoline *N*-oxides or the parent bases. Further investiga-

tion of the mechanism of this reaction seems to be important [12].

EXPERIMENTAL

The nmr spectra were recorded on a Varian XL-300 spectrometer. The high resolution mass spectra data were obtained on a Finnigan 4021 spectrometer (70 eV).

General Procedure I. Nitration Under Strongly Acidic Conditions.

To a mixture of 96% sulfuric acid (0.70 ml, 12.6 mmoles) trifluoracetic acid (10 ml) at −15° was added urea (36 mg, 0.6 mmole) and the *N*-oxide [11] (104 mg, 0.5 mmole). After stirring the mixture for 10 minutes, 65% nitric acid (0.04 ml, 0.57 mmole) was added. After 10 minutes the reaction mixture was poured onto ice and made alkaline with sodium bicarbonate solution. The resulting precipitate was extracted with chloroform. The organic layer was dried on magnesium sulfate and evaporated. The crude product was separated by usual silica gel chromatography or by hplc.

General Procedure **II**. Nitration Under Mild Acidic Conditions.

To a stirred solution of urea (90 mg, 1.5 mmoles) in trifluoracetic acid (10 ml) at 0° was added the *N*-oxide [11] (104 mg, 0.5 mmole). After stirring for 5 minutes, 65% nitric acid was introduced (0.1 ml, 1.5 mmoles). The reaction mixture was then stirred for further 60 minutes after which it was subjected to the above mentioned workup procedure.

1- and 8-Nitrodithieno[3,4-*b*:3′,4′-*d*]pyridine *N*-Oxides **4** and **5**.

The crude product resulting from the general procedure I was separated by semi-preparative normal phase hplc (Nucleosil sil 500 x 1″, chloroform-ethanol, 95:5) into 1-nitro isomer **4** and 8-nitro isomer **5**; isolated yields for **4**, 31 mg (25%) and for **5**, 28 mg (22%), mp 196-198° for **4** and 227° for **5**; ms: m/z 252, **4** and **5**.

Anal. Calcd. for $C_9H_4N_2O_3S_2$: C, 42.9; H, 1.6; N, 11.1. Found for **4**: C, 42.7; H, 1.7; N, 11.0. Found for **5**: C, 42.8; H, 1.7; N, 11.0.

1,8-Dinitrodithieno[3,4-*b*:3′,4′-*d*]pyridine *N*-Oxide **6**.

The reaction was carried out according to general procedure I, but 10-fold excess of nitric acid was used. After silica gel chromatography (chloroform-ethanol, 9:1) 50 mg (34%) of **6** was isolated, mp 180-181°, hrms: m/z Calcd. for $C_9H_3N_3O_5S_2$: (296.9514). Found: 296.9512.

6-Nitrodithieno[3,4-*b*:3′,4′-*d*]pyridine-*N*-Oxide **7**.

The crude product which resulted by the general procedure II was isolated by column chromatography (chloroform-ethanol, 1:1) to give 66 mg (52%) of **7**, mp >340°; ms: m/z 252.

Anal. Calcd. for $C_9H_4N_2O_3S_2$: C, 42.9; H, 1.6; N, 11.1. Found: C, 42.7; H, 1.6; N, 10.9.

8-Nitrodithieno[2,3-*b*:3′,4′-*d*]pyridine *N*-Oxide **8**.

Nitration was carried out according to the general procedure I. The crude product was separated by silica gel column chromatography (chloroform-ethanol, 9:1), yielding 60 mg (47%) **8** and 3 mg (2%) of **9**, mp of **8**; 202-204°; ms: m/z 252.

Anal. Calcd. for $C_9H_4N_2O_3S_2$: C, 42.9; H, 1.6; N, 11.1. Found: C, 42.5; H, 1.9; N, 10.8.

6-Nitrodithieno[2,3-*b*:3′,4′-*d*]pyridine *N*-Oxide **9**.

Nitration was carried out according to the general procedure II. The crude product was separated by silica gel column chromatography (chloroform-ethyl acetate, 1:1) yielding 51 mg (40%) of isolated product, mp 209-212°; ms: m/z 252.

Anal. Calcd. for $C_9H_4N_2O_3S_2$: C, 42.9; H, 1.6; N, 11.1. Found: C, 42.8; H, 1.7; N, 10.9.

2,8-Dinitrodithieno[2,3-*b*:3′,4′-*d*]pyridine *N*-Oxide **10**.

The reaction was carried out according to the general procedure I, but a 10-fold excess of nitric acid was used at 0°. After silica gel chromatography (chloroform-ethanol, 9:1) 64 mg (42%) of product was isolated, mp 203-205°; hrms: m/z Calcd. for $C_9H_3N_3O_5S_2$ (296.9514). Found: 296.9513.

2-Nitrodithieno[2,3-*b*:3′,4′-*d*]pyridine *N*-Oxide **11**.

To a solution of **2** [11] (125 mg, 0.6 mmole) in dry dichloromethane (60 ml) was added 0.16 mole/ℓ of nitrogen tetroxide solution in dichloromethane (6.0 ml, 0.48 mmole). The reaction mixture was protected from light and stirred at room temperature for 45 minutes after which the solvent was evaporated. The crude product was subjected to silica gel column chromatography (chloroform-ethyl acetate, 1:1) resulting in 48 mg (38%) of the 2-nitro derivative **11** and 3% of the 6-nitro derivative **9**, of **11**, 209-211°; ms: m/z 252.

Anal. Calcd. for $C_9H_4N_2O_3S_2$: C, 42.9; H, 1.6; N, 11.1. Found: C, 42.5; H, 1.8; N, 10.7.

1- and 2-Nitrodithieno[2,3-*b*:3′,2′-*d*]pyridine *N*-Oxides **12** and **13**.

The crude product which resulted from the general procedure I was separated by silica gel chromatography (chloroform-ethyl acetate, 1:1) yielding 54 mg (44%) of a mixture of **12** and **13** and a mixture of deoxygenated products (5 mg, 4%). Unfortunately, **12** and **13** could not separated even by hplc.

5- and 7-Nitrodithieno[2,3-*b*:3′,2′-*d*]pyridine *N*-Oxide **15** and **14**.

The crude product resulted from the general procedure II was separated by silica gel chromatography (chloroform-ethanol, 9:1 and chloroform-ethyl acetate, 9:1) into the 5-nitro isomer **15** (13 mg, 10%) and the 7 nitro isomer **14** (50 mg, 40%), mp 196-198° for **15** and 262-264° for **14**; ms: m/z 252 for **14** and **15**.

Anal. Calcd. for $C_9H_4N_2O_3S_2$: C, 42.9; H, 1.6; N, 11.1. Found for **15**: C, 42.7; H, 1.7; N, 11.0.

Nitration with Nitronium Tetrafluoroborate in Sulfolane.

A stock solution of nitronium tetrafluoroborate was prepared by transferring 50 ml of purified sulfolane containing 5% dichloromethane under nitrogen pressure to 0.19 g of the salt (preweighted in a glove-box). Twenty ml of the solution was transferred by nitrogen into a flask containing 30 mg (0.15 mmole) of the *N*-oxide **1** or **3**. The homogeneous mixture was stirred at room temperature for 4 hours. The reaction mixture was then diluted with water and extracted by chloroform. The organic phase was dried and evaporated. The hplc analysis of the residue obtained by nitration of **1** contained only the 6-nitro isomer **7**, while nitration of **3** resulted in the 7- and 5-nitro derivatives **14** and **15** in a ratio of 94:6.

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[12] A study on the mechanistic details of the nitration under mild acidic conditions is in preparation.