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Nitration of dithieno[3,2-*b*:3',2'-*d*]pyridine (**4**) and dithieno[3,2-*b*:3',4'-*d*]pyridine (**5**) has been studied. Nitration of **4** occurred in both positions of the C ring, while **5** was predominantly substituted on the 3,4-fused ring. The structures of the nitro derivatives were proven by extensive use of  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectroscopy.

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In connection with our interest in the effect of the mode of annelation on reactivity and orientation in electrophilic substitution of tricyclic hetero systems, we have previously studied the nitration of dithieno[3,4-*b*:3',4'-*d*]pyridine **1** [1], dithieno[2,3-*b*:3',2'-*d*]pyridine **2** [2] and dithieno[3,4-*b*:3',2'-*d*]pyridine **3** [2]. Nitration of **1** and **2** has also been investigated by means of theoretical calculations [1,3]. We have now studied the nitration of two further systems, namely dithieno[3,2-*b*:3',2'-*d*]pyridine (**4**) and dithieno[3,2-*b*:3',4'-*d*]pyridine (**5**).

Compound **4** was nitrated with concentrated nitric acid in trifluoroacetic acid (TFA) at the boiling point of the solvent. Urea was added to the reaction mixture in order to suppress the nitrous acid catalyzed nitration. Ring system **4** is characterized by low reactivity towards electrophilic nitration. Positional selectivity is low between substitution at the 2-position (40%) and the 3-position (60%). Highly insoluble nitro derivatives, with mp 262-264° (**6**) and 303-305° (**7**), were isolated in similar amounts (36% **6** and 44% **7**) by chromatography on silica gel. Low reactivity of 2,3- or 3,2-fused systems is characteristic of dithienopyridines. For example, nitration of **2** is two orders of magnitude slower than that of **1** [3]. Deactivation effects of the 2,3- or 3,2-fused thiophene rings are compared to the 3,4-fused one have already been discussed in a previous publication [3]. Another similarity to the previous results is the higher reactivity of the C ring in comparison to the A ring.

The small long range coupling between  $\text{H}^5$  and  $\text{H}^8$  is typical of dithienopyridine systems [4,5] and also their derivatives. The thiophene doublet is combined with a long range coupling in the  $^1\text{H}$  nmr spectrum of **6** and **7** (Table 1) indicating that both thiophene protons remained unchanged in the A ring.

The  $\alpha$  and  $\beta$  carbons of thiophene can be differentiated by measuring their C-H coupling constants. In the case of nitro compounds,  $^1J_{\text{CH}}$  coupling constants above 190 Hz are characteristic of the  $\alpha$ -position of thiophene, while lower values are characteristic of the  $\beta$ -position. Two of the four  $^1J_{\text{CH}}$  couplings are lower than 190 Hz in the  $^{13}\text{C}$  nmr spectrum of **6** (Table 2) showing the presence of two free  $\beta$ -positions of thiophene rings. This indicates nitration at the 2-position. On the other hand, only one  $^1J_{\text{CH}}$  coupling lower than 190 Hz appears in  $^{13}\text{C}$  nmr spectrum of **7** showing substitution at the 3-position.

The nitration of **5** could be carried out under milder conditions at room temperature. This reaction was faster than that of the 2,3- or 3,2-fused systems **2** and **4** but considerably slower than that of the 3,4-fused system **1**. One minor isomer, **8**, and a major product, **9**, could be isolated. The isomer distribution shows that the 8-position of the A ring is nitrated twice as fast as the 2-position of the C ring. The latter thiophene ring is activated by the nearby ring nitrogen and it is deactivated by the annelation (*i.e.* 3,2-fusion). It should be pointed out that isomer substituted at the 6-position has not been obtained by nitration of **1** or **5**. Similarly, substitution at the 7-position has not been detected for **2**, **3** or **4**. As we have demonstrated [1,3], this is the consequence of the effects of the ring nitrogen, which destabilizes the Wheland intermediates substituted at the 6- and 7-position in case of 3,4-fused and 2,3- or 3,2-fused A rings respectively. If the nitration takes place through the conjugated acid, the field effect of the protonated nitrogen results in a high activation barrier in nitration at the 6-position [3]. Polarity of the ring nitrogen can be changed by oxidation, which may lead to reversal of regioselectivity, as was demonstrated for *N*-oxides of **1** and **2** [6,7].

Table 1

Proton NMR Shifts (ppm) and Coupling Constants (Hz) [a], in Dimethyl Sulfoxide- $d_6$  (**6**, **7**) or in Deuteriochloroform (**8**, **9**)

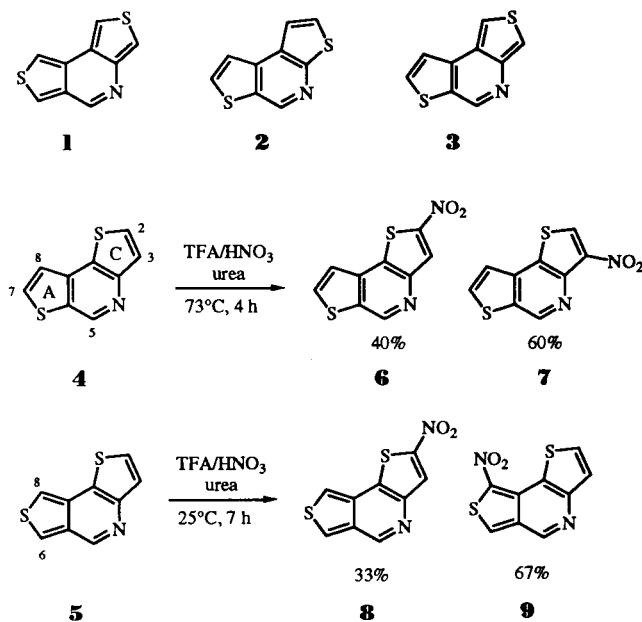
	H <sup>2</sup>	H <sup>3</sup>	H <sup>5</sup>	H <sup>6</sup>	H <sup>7</sup>	H <sup>8</sup>	$^2J_{\text{HH}}$	$^3J_{\text{HH}}$	$^4J_{\text{HH}}$
<b>6</b>	-	8.76	9.54		8.46	8.08	5.87,8		0.85,8
<b>7</b>	9.30	-	9.54		8.45	8.05	5.47,8		0.75,8
<b>8</b>	-	8.41	9.11	8.29		7.99	-	3.0 <sub>6,8</sub>	0.95,8
<b>9</b>	7.76	7.94	9.04	8.53		-	5.52,3		-

[a] Subscript numbers refers to the coupling protons.

Table 2  
Carbon NMR Shifts and Carbon-hydrogen Coupling Constants,  
in 80% Formic Acid 20% Dimethyl Sulfoxide-d<sub>6</sub> mixture

		C <sup>2</sup>	C <sup>3</sup>	C <sup>3a</sup>	C <sup>5</sup>	C <sup>5a</sup>	C <sup>6</sup>	C <sup>7</sup>	C <sup>8</sup>	C <sup>8a</sup>	C <sup>8b</sup>
<b>6</b>	δ	138.6	122.5	156.9	143.0	136.3		149.8	124.7	146.4	133.9
	<sup>1</sup> J <sub>CH</sub>		185.3		194.3			191.2	178.5		
	<sup>2</sup> J <sub>CH</sub>		—		—			6.9	4.5		
<b>7</b>	δ	140.8	139.1	147.3	141.9	132.8		150.9	124.1	135.1	132.6
	<sup>1</sup> J <sub>CH</sub>	198.6			195.4			191.0	178.7		
	<sup>2</sup> J <sub>CH</sub>	—			—			6.9	4.4		
<b>8</b>	δ	154.0	123.1	134.1	149.2	133.3	143.6		124.1	133.4	131.4
	<sup>1</sup> J <sub>CH</sub>		184.1		191.2		202.3		198.4		
	<sup>3</sup> J <sub>CH</sub>		—		2.8		4.9, 2.2		5.5		
<b>9</b>	δ	138.7	121.7	141.4	146.2	132.5	149.3		143.3	130.7	128.7
	<sup>1</sup> J <sub>CH</sub>	190.7	178.7		195.3		199.1				
	<sup>2</sup> J <sub>CH</sub>	5.1	4.1								
	<sup>3</sup> J <sub>CH</sub>				3.0		2.5				

## Scheme



Long range coupling between H<sup>5</sup>-H<sup>8</sup> is present in the <sup>1</sup>H nmr spectrum of **8** and it is combined with the coupling of thiophenic protons indicating that the C ring is nitrated (Table 1). One C-H coupling under 190 Hz appears in the <sup>13</sup>C nmr spectrum of **8** indicating that the β-position is unsubstituted in the C ring. Consequently, the nitration occurred at the 2-position. The H<sup>5</sup>-H<sup>8</sup> long range coupling is missing from the <sup>1</sup>H nmr spectrum of **9**, while the thiophenic α-β coupling (5.5 Hz) is retained indicating substitution at the 8-position. A further proof is that all of the four <sup>1</sup>J<sub>CH</sub> couplings are split into doublets. Such a coupling scheme is only possible for the 8-nitro derivative. In all other cases (except the highly unlikely 5-substitution), one of the <sup>2</sup>J<sub>CH</sub> or <sup>3</sup>J<sub>CH</sub> couplings should be missing (Table 2).

## EXPERIMENTAL

## General Procedure for Nitration.

To a solution of 0.2 g (1.0 mmole) of dithienopyridine [**4**] and 0.4 g (6.7 mmole) urea in 10 ml of trifluoroacetic acid (TFA), 1.0 ml (24 mmole) of concentrated nitric acid (d = 1.5 g/cm<sup>3</sup>) was added and the mixture was refluxed for 4 hours (**4**) or stirred at room temperature for 7 hours (**5**). The solvent was evaporated and the residue was neutralized by sodium bicarbonate solution.

2- and 3-Nitrodithieno[3,2-b:3',2'-d]pyridine **6**, **7**.

The crude product was separated by silica gel chromatography (benzene-acetic acid, 4:1) yielding 0.09 g (36%) of **6** and 0.11 g (44%) of **7**, mp 262-264° for **6** and 303-305° for **7**; ms: m/z 236 (M<sup>+</sup>).

Anal. Calcd. for C<sub>9</sub>H<sub>4</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>: C, 45.8; H, 1.7; N, 11.9. Found for **6**: C, 45.5; H, 1.5; N, 11.9; for **7**: C, 45.6; H, 1.8; N, 11.7.

2- and 8-Nitrodithieno[3,2-b:3',4'-d]pyridine **8**, **9**.

The crude product was separated by silica gel chromatography (ether-chloroform, 10:1) yielding 0.05 g (18%) of **8** and 0.13 g (50%) of **9**, mp 242-245° for **8** and **9** is decomposed above 215°; ms: m/z 236 (M<sup>+</sup>).

Anal. Calcd. for C<sub>9</sub>H<sub>4</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub>: C, 45.8; H, 1.7; N, 11.9. Found for **8**: C, 45.9; H, 1.8; N, 11.9; for **9**: C, 45.8; H, 1.8; N, 11.8.

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