Direct Bromination of Dithieno[3,4-*b*:3′,4′-*d*]pyridine and Dithieno[2,3-*b*:3′,2′-*d*]pyridine

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Bromination of dithieno[3,4-*b*:3′,4′-*d*]pyridine (**1**) and dithieno[2,3-*b*:3′,2′-*d*]pyridine (**2**) has been studied. Disubstitution occurred at both positions of the C ring. The substitution pattern is found to be similar to that of the nitration reaction. The structures of bromo derivatives were established by ^{1}H and ^{13}C nmr spectroscopy.

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In preceding papers we have reported our experimental and theoretical results concerning the effect of the mode of annelation in nitration of dithienopyridines [1-4]. The present study was undertaken in order to investigate the regioselectivity in bromination of dithieno[3,4-*b*:3′,4′-*d*]-pyridine (**1**) and dithieno[2,3-*b*:3′,2′-*d*]pyridine (**2**).

Bromination of **1** and **2** was attempted in different ways. However, the reaction under acidic conditions led to decomposition of the starting material. This is somewhat surprising, because these ring systems could be nitrated even under strongly acidic conditions. In order to avoid the acidic medium, the reaction was carried out under mild, aprotic conditions [5]. Compounds **1** and **2** could be brominated with bromine in chloroform containing a chloroform soluble buffer salt, dipotassium monohydrogen phosphate, sodium bicarbonate and magnesium sulphate (to adsorb the water).

Using these conditions, compound **1** gave the 1,3-dibrominated derivative **3**. The reaction could not stopped at formation of the monobrominated derivatives. The ease of disubstitution may be due to the fact that the entry of the first bromine activates the other position of the same thiophene ring. Nitration gave mainly 1-nitro derivative and 3- and 8-nitro derivatives as minor products [1]. Although the first substitution position cannot be determined, the 3-position of **1** seems more reactive in bromination than in nitration. Transition state energies calculated for nitration of the conjugate acid predict 1 > 8 > 3 > > 6 positional preference, while the stability sequence of the Wheland intermediates of free base suggests 1 ≈ 3 > 8 > > 6 preference [5].

Mass spectroscopy was especially useful in establishing the number of bromine atoms in the product. The substitution positions were proven by ^{1}H and ^{13}C nmr spectroscopy. The small long-range coupling between H^5 and H^8 is typical of dithienopyridine systems [7] and their derivatives [1,2,4]. The thiophene doublet is combined with a long-range coupling in the ^{1}H nmr spectrum of **3** (Table 1) indicating that the disubstitution took place at the C ring. A further confirmation of the 1,3-disubstitution is that all of the three $^1J_{CH}$ couplings are split into doublets (one of them, C^6-H^6, into a quartet, see Table 2). If the substitutions took place at the A ring, C^5-H^5 should not be split further, because the C^5-H^6 long-range coupling should be missing.

Bromination of **2** is a considerably slower process than that of **1**, similar to their nitration [3]. The dependence of

Table 1

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

	H^5	H^6	H^7	H^8	$^2J_{HH}$	$^3J_{HH}$	$^4J_{HH}$
3	8.73	7.99		8.45		$2.9_{6,8}$	$0.9_{5,8}$
4	9.07		7.91	8.53	$5.5_{7,8}$		$0.8_{5,8}$

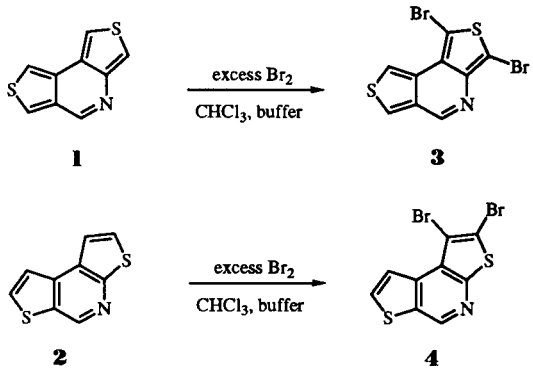
[a] Subscript numbers refer to the coupling protons.

Table 2

Carbon NMR Shifts and Carbon-hydrogen Coupling Constants (Hz) in Deuteriochloroform

		C^1	C^2	C^3	C^{3a}	C^5	C^{5a}	C^6	C^7	C^8	C^{8a}	C^{8b}
3	δ	103.2		108.0	143.5	149.8	130.3	126.5		118.7	132.1	125.2
	$^1J_{CH}$					182.5		188.5		189.9		
	$^3J_{CH}$					3.0		5.1, 1.0		5.0		
4	δ	119.9	111.8		145.7	140.2	136.8		148.0	123.5	145.6	130.9
	$^1J_{CH}$					195.2			190.3	178.7		
	$^2J_{CH}$					2.1 [a]			7.0	4.4		

[a] C^5-H^7 coupling.



1 3

2 4

reactivity on the annelation has been discussed in a preceding publication [3]. Reaction of **2** with an equimolecular amount of bromine resulted in a mixture of mono- and dibromo derivatives and part of the starting material. Monobromo isomers could not be separated from each other. However, according to the ^{1}H nmr spectrum of the reaction mixture, the ratio of 1- and 2-substituted derivatives is 1:2. By applying an excess amount of bromine, the 1,2-dibromo derivative **4** was obtained. Here again, the dibromination may be due to the activating effect of the first entering bromine. Similar to the bromination, the nitration of **2** also resulted in 1- and 2-substituted derivatives [2].

Dibromination could be established from the mass spectrum of **4**. The combination of H^7–H^8 coupling and H^5–H^8 long-range coupling indicates that the disubstitution occurred at the C ring. The presence of a relatively small $^1J_{CH}$ coupling (178 Hz) in the ^{13}C nmr spectrum of **4** shows that at least one β-position must be unsubstituted. Based on these spectroscopic data, compound **4** was identified as the 1,2-disubstituted isomer.

EXPERIMENTAL

General Procedure for Bromination.

Dithienopyridine (0.1 g, 0.5 mmole) was dissolved in 5 ml of chloroform containing 0.22 g (1.3 mmoles) of dipotassium hydrogen phosphate, 0.07 g (0.8 mmole) of sodium bicarbonate and 0.12 g (1.0 mmole) of magnesium sulphate. To this mixture, in the case of bromination of **1**, 0.23 g (0.07 ml, 1.4 mmoles), while in the case of bromination of **2**, 0.85 g (0.26 ml, 5.2 mmoles) of bromine was added in small portions. The mixture was stirred at room temperature for 24 hours for **1** or 60 hours for **2**, whereupon water was added to the reaction mixture. The organic phase was separated, dried and evaporated.

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

The crude product was separated by silica gel chromatography (chloroform-ether, 40:1) yielding 0.12 g (65%) of **3**, mp 149-150°; ms: m/z 348, 349, 350 (M^+).

Anal. Calcd. for $C_9H_3NS_2Br_2$: C, 30.9; H, 0.9; N, 4.0. Found: C, 30.6; H, 0.7; N, 3.7.

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

The crude product was separated by silica gel chromatography (dichloromethene-cyclohexane, 4:1) yielding 0.16 g (88%) of **4**, mp 191-192°; ms: m/z 348, 349, 350 (M^+).

Anal. Calcd. for $C_9H_3NS_2Br_2$: C, 30.9; H, 0.9; N, 4.0. Found: C, 30.7; H, 0.7; N, 3.8.

REFERENCES AND NOTES

† On leave of absence from Ain Shams University, Abbassia, Cairo, Egypt.

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