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Through the use of Pd(0)-catalyzed coupling between 2- and 4-formyl-3-thiopheneboronic acid and 4-iodo-3-aminopyridine (**1**) and 3-bromo-2-aminopyridine, convenient one-pot procedures for the preparation of thieno[2,3-*c*]-1,7-naphthyridine (**2**), thieno[3,4-*c*]-1,7-naphthyridine (**3**), thieno[2,3-*c*]-1,8-naphthyridine (**6**) and thieno[3,4-*c*]-1,8-naphthyridine (**7**) have been developed. Thieno[3,2-*c*]-1,7-naphthyridine (**4**) and thieno[3,2-*c*]-1,8-naphthyridine (**8**) were obtained through the coupling of 2-tri-*n*-butylstannyl-3-thiophenylaldehyde with 2,2-dimethyl-*N*-(4-iodo-3-pyridinyl)propanamide and 3-bromo-2-acetamidopyridine (**1**). The yield of **8** was further increased when copper(II) oxide was used as the co-reagent. The <sup>13</sup>C nmr spectra of the six isomeric thieno[*c*]-fused 1,7- and 1,6-naphthyridines are discussed.

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### Introduction.

We have for some years been engaged in a study of the effects of the mode of annelation on the chemical and physical properties of new tricyclic heterocyclic systems with phenanthrene annelation pattern (for review *cf.* ref [1]).

Recently, we have developed convenient one-pot procedures involving Pd(0)-catalyzed cross couplings for the synthesis of thieno[*c*]-fused 1,5- and 1,6-naphthyridines [2], thieno[*c*]-fused 1,5-naphthyridine 9-oxides and 5-oxides [3], and thieno[*b*]-fused naphthyridines [4-6]. Extensive experimental studies and theoretical calculations of electrophilic substitution of many of the isomeric dithienopyridines [7,8] as well as the six thieno analogues of phenanthrene *N*-oxide [9,10] and thieno[*c*]-1,5-naphthyridines [11], have been carried out.

Theoretically there are 24 isomers of thieno-fused naphthyridines with an angular annelation pattern. In the present paper, the synthesis of the six remaining thieno[*c*]-1,7- and 1,8-naphthyridines will be described.

Many compounds isosteric or structurally similar to the thieno[*c*]naphthyridines show various kinds of biological activity, which gives additional interest to a study of these compounds.

The thieno[*c*]-1,8-naphthyridines might also be interesting, as there has been considerable interest in the behavior of 1,8-naphthyridine as a ligand (for a review *cf.* ref [12]).

### Results and Discussion.

#### Preparations.

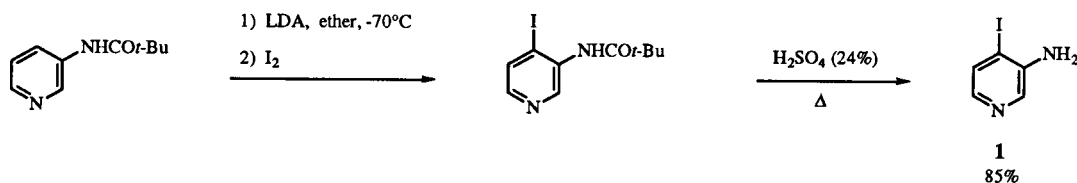
A suitable starting material for the syntheses of thieno[2,3-*c*]-1,7-naphthyridine (**2**), thieno[3,4-*c*]-1,7-naphthyridine (**3**) and thieno[3,2-*c*]-1,7-naphthyridine (**4**) was 4-iodo-3-aminopyridine (**1**), which was prepared from the readily available 2,2-dimethyl-*N*-(4-iodo-3-pyridinyl)propanamide by hydrolysis in dilute sulfuric acid (Scheme 1).

The Pd(0)-catalyzed coupling reaction of **1** with 2-formyl- and 4-formyl-3-thiopheneboronic acid gave thieno[2,3-*c*]-1,7-naphthyridine (**2**) and thieno[3,4-*c*]-1,7-naphthyridine (**3**) in 55% and 72% yield, respectively. The Pd(0)-catalyzed coupling reaction of **1** with 2-tributylstannyl-3-thiophenylaldehyde in *N,N*-dimethylformamide at 100° gave only thieno[3,2-*c*]-1,7-naphthyridine (**4**) in trace amounts. This could be explained by the observed severe decomposition of **1** under these reaction conditions (Scheme 2).

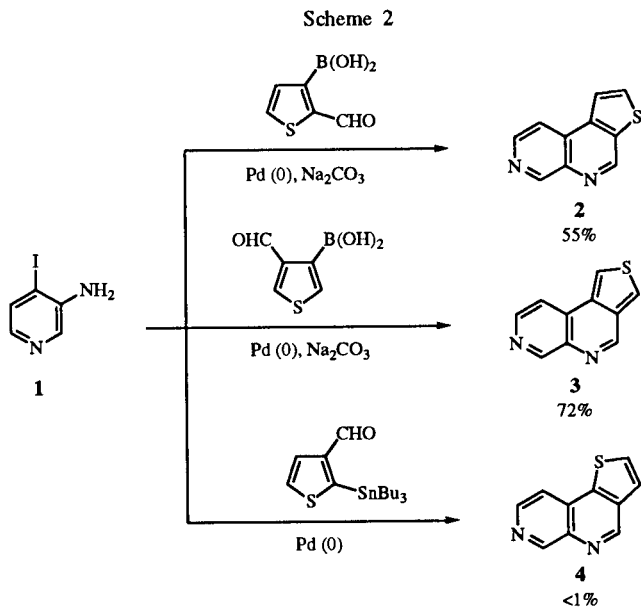
However, by using the more stable 2,2-dimethyl-*N*-(4-iodo-3-pyridinyl)propanamide as the coupling partner, **4** could be obtained in 44% yield after treatment with hydrochloric acid (Scheme 3).

We have previously found that the addition of copper(II) oxide increases the rate of the Pd(0)-catalyzed coupling of heteroaryl halides with heteroaryl stannanes [3.5.6]. However, the synthesis of **4** by this approach failed due to the

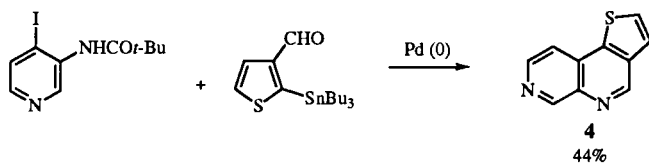
Scheme 1



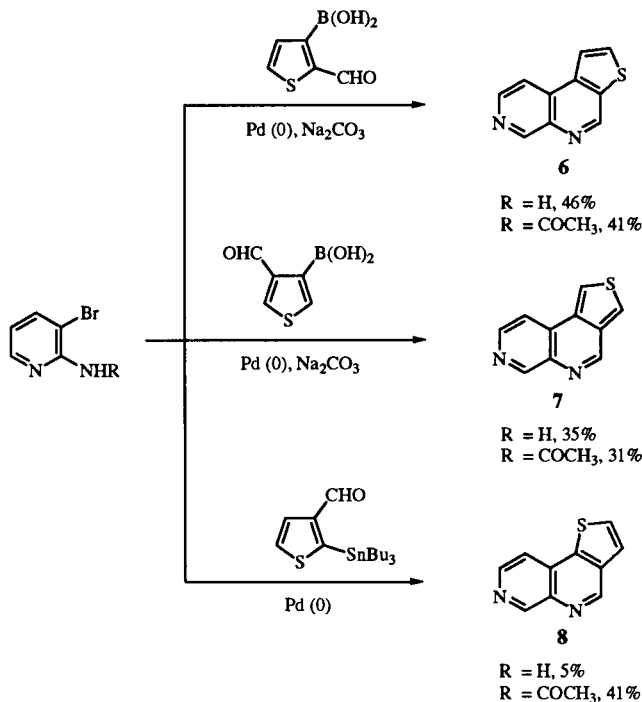
Scheme 2



Scheme 3



Scheme 4



formation of 3,3'-diformyl-2,2'-bithienyl from 2-(tributylstannyl)-3-thiophenylaldehyde in almost quantitative yield [13].

The Pd(0)-catalyzed coupling reactions shown below all proceeded in moderate yields, giving thieno[2,3-*c*]-1,8-naphthyridine (**6**), thieno[3,4-*c*]-1,8-naphthyridine (**7**) and thieno[3,2-*c*]-1,8-naphthyridine (**8**). It should be noted that only a 5% yield of **8** could be isolated in the coupling reaction of 3-bromo-2-aminopyridine with 2-tri-*n*-butylstannyl-3-thiophenylaldehyde, while 3-bromo-2-acetamidopyridine, under the same reaction conditions, gave **8** in 41% yield. This increased reactivity of the pyridine derivative upon *N*-acylation in the Pd(0)-catalyzed coupling has been observed previously [2] (Scheme 4).

The use of copper(II) oxide was in this case successful, and the yield of **8** could be raised to 61%.

### <sup>13</sup>C NMR Spectra.

Unambiguous assignments of the <sup>13</sup>C nmr signals and the carbon-proton coupling constants of the thieno[*c*]naphthyridine are given in Tables 1 and 2. Assignments were confirmed by proton decoupled <sup>13</sup>C spectra, proton-coupled <sup>13</sup>C spectra and <sup>1</sup>H-<sup>13</sup>C HETCOR spectra.

Table 1

<sup>13</sup>C NMR Chemical Shifts (in ppm) of the Thienonaphthyridines 2-4 and 6-8

Compound	1C	2C	3C	4C	6C	7C	8C	9C
<b>2</b>	121.7	132.8		146.6	153.8		144.7	116.2
<b>3</b>	119.4		125.6	150.2	152.3		146.7	116.6
<b>4</b>		129.2	124.2	148.2	154.2		144.7	116.1
<b>6</b>	121.5	133.3		148.1		151.4	122.0	132.6
<b>7</b>	117.3		125.6	152.0		150.0	122.5	132.3
<b>8</b>		127.8	123.9	149.5		151.8	122.2	132.6

Table 2

J<sub>CH</sub> Values (Hz) of the Thienonaphthyridines 2-4, 6-8

Compound	1C	2C	3C	4C	6C	7C	8C	9C
<b>2</b>								
<sup>1</sup> J <sub>CH</sub>	171.1	187.0		185.0	181.2		180.2	163.6
<sup>2</sup> J <sub>CH</sub>	4.1	6.8					2.4	7.6
<sup>3</sup> J <sub>CH</sub>					10.4		12.7	
<b>3</b>								
<sup>1</sup> J <sub>CH</sub>	187.6		189.0	182.0	180.5		179.6	161.7
<sup>2</sup> J <sub>CH</sub>							2.0	8.4
<sup>3</sup> J <sub>CH</sub>	4.7		4.6	2.8	10.9		12.2	
<b>4</b>								
<sup>1</sup> J <sub>CH</sub>		187.9	172.4	181.6	181.4		180.7	163.0
<sup>2</sup> J <sub>CH</sub>		7.0	4.0				1.9	7.8
<sup>3</sup> J <sub>CH</sub>					10.7		12.7	
<b>6</b>								
<sup>1</sup> J <sub>CH</sub>	170.6	186.4		183.8		179.7	165.0	162.0
<sup>2</sup> J <sub>CH</sub>	4.0	6.8				3.5	8.7	
<sup>3</sup> J <sub>CH</sub>						8.1		6.4
<b>7</b>								
<sup>1</sup> J <sub>CH</sub>	186.8		187.9	181.8		179.9	164.7	161.1
<sup>2</sup> J <sub>CH</sub>						3.3	8.6	
<sup>3</sup> J <sub>CH</sub>	4.7		4.9	2.8		7.9		6.6
<b>8</b>								
<sup>1</sup> J <sub>CH</sub>		187.8	172.2	180.4		179.5	165.4	162.3
<sup>2</sup> J <sub>CH</sub>		7.1	3.5			3.5	8.8	
<sup>3</sup> J <sub>CH</sub>			1.9			8.0		6.5

From the results listed in Table 1, it can be noted that the carbons  $\alpha$  to the nitrogen resonate at lowest field. At higher field follow the chemical shifts of the carbons in the thiophene ring and the carbons  $\beta$  to the nitrogen. Interestingly, the C9-carbon in **2-4** resonates at the highest field of all carbons in this investigation. This resonance also deviates up-field from the parent 1,7-naphthyridine by 4 ppm [14]. However, the other resonances in the pyridine part followed firmly the same pattern as observed for the 1,7- and 1,8-naphthyridines [14].

In thiophene the  $^{13}\text{C}$  chemical shift of the  $\alpha$  carbons is smaller than that of the  $\beta$ -carbons, while in our fused systems, the  $^{13}\text{C}$  chemical shifts of the  $\alpha$ -carbons are larger than those of the  $\beta$ -carbons. This pattern has previously been observed in the thieno[*c*]-fused 1,5- and 1,6-naphthyridines [2], thieno[*b*]naphthyridines [6] and thieno[*c*]quinolines [15].

The one- and two-bond  $^1\text{H}$ - $^{13}\text{C}$  coupling constants in the pyridine rings were of the same magnitude as observed in pyridine [16]. Characteristic long-range coupling constants fall in defined intervals of  $J_{6,8} = 10.4\text{--}10.9$  Hz and  $J_{8,6} = 12.2\text{--}12.7$  Hz for **2-4** and  $J_{7,9} = 7.9\text{--}8.1$  Hz and  $J_{9,7} = 6.4\text{--}6.6$  Hz, for **6-8**. The expected coupling constant  $J_{9,6}$  is missing in **2-4**.

Long-range couplings between the thiophene ring and the azomethine linkage were observed in the [3,4-*c*] and [3,2-*c*] fused systems. In the isosteric thienoquinolines this long-range coupling was only observed in the [3,4-*c*] fused system [15]. However,  $J_{\text{C}_4\text{H}_3}$  could not be observed in **4** and

**8**, probably due to line width effects for the azomethine carbons, the resonance line width ( $\Delta\nu_{1/2}$ ) of which was around 4 Hz. The thiophene  $\alpha$  and  $\beta$  resonances in the [2,3-*c*] fused system could be differentiated by means of their HETCOR spectra, which showed C-H interaction between the  $\beta$  carbon and a proton doublet belonging to  $J_{\text{H}_1\text{H}_4}$  (Figure 1).

The one-bond  $^1\text{H}$ - $^{13}\text{C}$  coupling constants for  $\text{C}_\alpha\text{H}_\alpha$  and  $\text{C}_\beta\text{H}_\beta$  in the thiophene part fall in the intervals of 187.0-189 Hz and 170.6-172.4 Hz, respectively. The two-bond  $^1\text{H}$ - $^{13}\text{C}$  coupling constants for  $\text{C}_\alpha\text{H}_\beta$  were usually around 3 Hz larger than those of  $\text{C}_\beta\text{H}_\alpha$ .

## EXPERIMENTAL

The nmr spectra were recorded on a Varian XL-300 spectrometer. Deuteriochloroform was used as solvent for all substances. Sample concentrations were 5 mg/ml for the  $^1\text{H}$  nmr spectra. Sample concentrations for the  $^{13}\text{C}$  nmr and HETCOR spectra were 30 mg/ml. The mass spectra were recorded on a JEOL JMS-SX 102 spectrometer (70 eV). The elemental analyses were carried out by Dornis und Kolbe, Mülheim, Germany. All melting points are uncorrected. The thieno[*c*]naphthyridines were all chromatographed on a Polygosil HPLC-column, 250 x 20 mm. Eluents are given below.

### 4-Iodo-3-aminopyridine (**1**).

A 250 ml one-necked flask, equipped with condenser and magnetic stirring, was charged with 3.04 g (0.01 mole) of 2,2-dimethyl-*N*-(4-iodo-3-pyridinyl)propanamide [17] and 100 ml of dilute sulfuric acid (24%). The mixture was refluxed for 1 hour and allowed to attain room temperature. The reaction mixture was neutralized with 4 *N* sodium hydroxide and solid sodium hydrogen carbonate, extracted with chloroform and finally dried over magnesium sulfate. Recrystallization from petroleum ether (40-60) gave 1.88 g (85%) of **1** as white needles, mp 50-51°; ms: *m/z* (%) 221 (5), 220 (100,  $\text{M}^+$ ), 93 (21), 69 (6), 66 (14), 65 (6), 39 (8);  $^1\text{H}$  nmr:  $\delta$  8.05 (s, 1H,  $\text{H}_1$ ), 7.62 (d, 1H,  $\text{H}_5$ ), 7.58 (d, 1H,  $\text{H}_4$ ), 4.26 (broad s, 2H,  $\text{NH}_2$ ).

*Anal.* Calcd. for  $\text{C}_5\text{H}_5\text{IN}_2$ : C, 27.30; H, 2.29; N, 12.73. Found: C, 27.38; H, 2.34; N, 12.58.

### 3-Bromo-2-acetamidopyridine (**5**).

A 50 ml two-necked flask, equipped with condenser, thermometer and magnetic stirring, was charged with 1.45 g (8.4 mmoles) of 3-bromo-2-aminopyridine [18] and 18 ml of acetic anhydride. The mixture was stirred at 100° for 14 hours. The reaction mixture was evaporated and the residue diluted with 75 ml of diethyl ether. The organic phase was extracted with four 60 ml portions of 2 *N* sodium hydroxide and neutralized with concentrated hydrochloric acid. The aqueous phase was extracted with five 70 ml portions of dichloromethane and the combined organic phases were finally dried over sodium sulfate. Recrystallization from *n*-pentane gave 1.61 g (89%) of **5** as white needles, mp 96-97°; ms: *m/z* (%) 316 (9,  $\text{M}^+ + 1$ ), 314 (9,  $\text{M}^+$ ), 174 (96), 172 (100), 135 (21), 93 (56), 66 (11), 43 (15);  $^1\text{H}$  nmr:  $\delta$  8.34 (dd, 1H,  $\text{H}_6$ ), 7.87 (dd, 1H,  $\text{H}_4$ ), 6.95 (dd, 1H,  $\text{H}_5$ ), 2.46 (s, 3H,  $\text{CH}_3$ ), 1.47 (s, 1H, NH),  $J_{4,5} = 7.9$ ,  $J_{4,6} = 1.5$ ,  $J_{5,6} = 4.8$ .

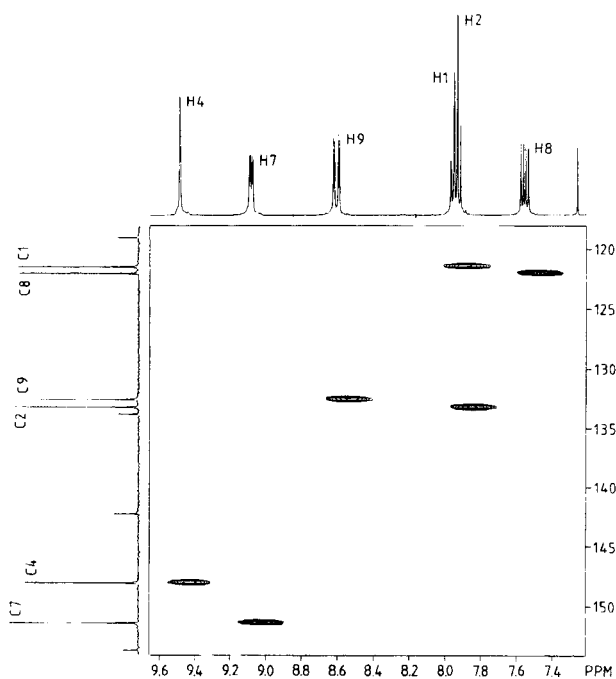


Figure 1

*Anal.* Calcd. for  $C_7H_7BrN_2O$ : C, 39.10; H, 3.28; N, 13.03. Found: C, 39.15; H, 3.29; N, 12.94.

General Procedure for the Preparation of Thienonaphthyridines **2,3,6** and **7** via Boronic Acids.

A 50 ml three-necked flask, equipped with condenser, magnetic stirrer, thermometer and a nitrogen inlet, was charged with 2.5 mmoles of the appropriate pyridine derivative, 0.14 g (0.125 mmole) of tetrakis(triphenylphosphine)palladium(0) [19] and 10 ml of 1,2-dimethoxyethane. After stirring for 10 minutes, 0.59 g (3.75 mmoles) of 2-formyl- or 0.49 g (3.125 mmoles) of 4-formyl-3-thiopheneboronic acid [20] was added, followed by 7.5 ml of an aqueous solution of sodium carbonate (1.5 *M* or 1.25 *M*, respectively). The reaction mixture was refluxed for 1 hour for **2** or **3**, 1.5 hours for **6** or 2.5 hours for **7** with vigorous stirring. The organic phase was evaporated and 20 ml of 2 *N* hydrochloric acid was added to the residue. The aqueous phase was washed with ether, neutralized with 2 *N* sodium hydroxide and extracted several times with chloroform. The organic phase was dried over magnesium sulphate and finally subjected to chromatography.

#### Thieno[2,3-*c*]-1,7-naphthyridine (**2**).

This compound was chromatographed with heptane/ethyl acetate/2-propanol, 40:50:10 and 256 mg (55%) was obtained by the coupling of 4-iodo-3-aminopyridine with 2-formyl-3-thiopheneboronic acid, mp 138-140°; ms: *m/z* (%) 188 (5), 187 (14), 186 (100,  $M^+$ ), 185 (43), 160 (9), 159 (11), 158 (4), 114 (5);  $^1H$  nmr:  $\delta$  9.56 (d, 1H,  $H_6$ ), 9.37 (d, 1H,  $H_4$ ), 8.71 (d, 1H,  $H_8$ ), 8.03 (dd, 1H,  $H_9$ ), 7.97 (dd, 1H,  $H_1$ ), 7.94 (d, 1H,  $H_2$ ),  $J_{1,2} = 5.3$ ,  $J_{1,4} = 0.8$ ,  $J_{6,9} = 0.9$ ,  $J_{8,9} = 5.6$ .

*Anal.* Calcd. for  $C_{10}H_6N_2S$ : C, 64.45; H, 3.25; N, 15.04. Found: C, 64.56; H, 3.35; N, 14.84.

#### Thieno[3,4-*c*]-1,7-naphthyridine (**3**).

This compound was chromatographed with heptane/ethyl acetate/2-propanol, 60:30:10 and 335 mg (72%) was obtained by the coupling of 4-iodo-3-aminopyridine with 4-formyl-3-thiopheneboronic acid, mp 149-150°; ms: *m/z* (%) 188 (5), 187 (13), 186 (100,  $M^+$ ), 185 (34), 160 (6), 159 (11), 158 (4), 114 (5);  $^1H$  nmr:  $\delta$  9.32 (d, 1H,  $H_6$ ), 9.11 (d, 1H,  $H_4$ ), 8.68 (d, 1H,  $H_8$ ), 8.24 (dd, 1H,  $H_1$ ), 8.16 (d, 1H,  $H_3$ ), 7.97 (dd, 1H,  $H_9$ ),  $J_{1,3} = 2.9$ ,  $J_{1,4} = 0.9$ ,  $J_{6,9} = 0.8$ ,  $J_{8,9} = 5.3$ .

*Anal.* Calcd. for  $C_{10}H_6N_2S$ : C, 64.45; H, 3.25; N, 15.04. Found: C, 64.46; H, 3.34; N, 14.93.

#### Thieno[2,3-*c*]-1,8-naphthyridine (**6**).

This compound was chromatographed with heptane/ethyl acetate/2-propanol, 60:30:10 and 214 mg (46%) was obtained by the coupling of 3-bromo-2-aminopyridine with 2-formyl-3-thiopheneboronic acid. The compound was obtained as a pale yellow oil, which slowly turned solid in the refrigerator. No elemental analysis was attempted as it slowly decomposed at room temperature, mp 72-76° dec; ms: *m/z* (%) 188 (10), 187 (28), 186 (100,  $M^+$ ), 185 (49), 160 (11), 159 (20), 133 (10), 93 (11), 69 (28);  $^1H$  nmr:  $\delta$  9.52 (d, 1H,  $H_4$ ), 9.11 (dd, 1H,  $H_7$ ), 8.66 (dd, 1H,  $H_9$ ), 8.00 (dd, 1H,  $H_1$ ), 7.96 (d, 1H,  $H_2$ ), 7.60 (dd, 1H,  $H_8$ ),  $J_{1,2} = 5.3$ ,  $J_{1,4} = 0.7$ ,  $J_{7,8} = 4.3$ ,  $J_{7,9} = 1.9$ ,  $J_{8,9} = 8.2$ ; hrms Calcd. for  $C_{10}H_6N_2S$ : 186.0252. Found: 186.0252.

#### Thieno[3,4-*c*]-1,8-naphthyridine (**7**).

This compound was chromatographed with heptane/ethyl acetate/2-propanol, 35:55:10 and 163 mg (35%) and was obtained by

the coupling of 3-bromo-2-aminopyridine with 4-formyl-3-thiopheneboronic acid, mp 144-147°; ms: *m/z* (%) 187 (14), 186 (100,  $M^+$ ), 185 (21), 159 (10), 142 (5), 133 (10), 114 (7), 93 (7);  $^1H$  nmr:  $\delta$  9.30 (d, 1H,  $H_4$ ), 9.11 (dd, 1H,  $H_7$ ), 8.66 (dd, 1H,  $H_9$ ), 8.12 (dd, 1H,  $H_1$ ), 8.19 (d, 1H,  $H_3$ ), 7.60 (dd, 1H,  $H_8$ ),  $J_{1,3} = 3.0$ ,  $J_{1,4} = 0.9$ ,  $J_{7,8} = 4.6$ ,  $J_{7,9} = 1.9$ ,  $J_{8,9} = 7.9$ .

*Anal.* Calcd. for  $C_{10}H_6N_2S$ : C, 64.45; H, 3.25; N, 15.04. Found: C, 64.58; H, 3.35; N, 14.89.

General Procedure for the Preparation of Thieno[3,2-*c*]-1,7-naphthyridine (**4**) and Thieno[3,2-*c*]-1,8-naphthyridine (**8**) via 2-Trialkylstannyl-3-thiophenylaldehyde.

A 25 ml three-necked flask, equipped with condenser, magnetic stirrer, thermometer and a nitrogen inlet, was charged with 2.5 mmoles of the appropriate pyridine derivative, 0.15 g (0.125 mmoles) of tetrakis(triphenylphosphine)palladium(0), 1.14 g (2.75 mmoles) of 2-tri-*n*-butylstannyl-3-thiophenylaldehyde [21], 0.20 g (2.5 mmoles) of copper(II) oxide and 15 ml of *N,N*-dimethylformamide. The reaction mixture was stirred at 100° until the starting materials were consumed.

When 2,2-dimethyl-*N*-(4-iodo-3-pyridinyl)propanamide was used as coupling partner, 5 ml of 2 *N* hydrochloric acid was added to the reaction mixture after the starting materials were consumed. The reaction mixture was refluxed for 1 hour, allowed to attain room temperature and neutralized with sodium hydroxide.

The organic phase was evaporated and 20 ml of 2 *N* hydrochloric acid was added to the residue. The aqueous phase was washed with ether, neutralized with 2 *N* sodium hydroxide and extracted several times with chloroform. The organic phase was dried over magnesium sulphate and finally subjected to chromatography.

#### Thieno[3,2-*c*]-1,7-naphthyridine (**4**).

This compound was chromatographed with heptane/ethyl acetate/2-propanol, 60:30:10 and 205 mg (44%) was obtained by the coupling of 2,2-dimethyl-*N*-(4-iodo-3-pyridinyl)propanamide with 2-tri-*n*-butylstannyl-3-thiophenylaldehyde, mp 99-103°; ms: *m/z* (%) 188 (7), 187 (18), 186 (100,  $M^+$ ), 185 (23), 160 (25), 159 (14), 133 (5), 114 (5);  $^1H$  nmr:  $\delta$  9.60 (d, 1H,  $H_6$ ), 9.39 (s, 1H,  $H_4$ ), 8.72 (d, 1H,  $H_8$ ), 7.94 (dd, 1H,  $H_9$ ), 7.78 (d, 1H,  $H_2$ ), 7.69 (d, 1H,  $H_3$ ),  $J_{2,3} = 5.3$ ,  $J_{6,9} = 0.8$ ,  $J_{8,9} = 5.6$ .

*Anal.* Calcd. for  $C_{10}H_6N_2S$ : C, 64.45; H, 3.25; N, 15.04. Found: C, 64.59; H, 3.37; N, 14.95.

#### Thieno[3,2-*c*]-1,8-naphthyridine (**8**).

This compound was chromatographed with heptane/ethyl acetate/2-propanol; 45:45:10 and 284 mg (61%) was obtained by the coupling of 3-bromo-2-acetamidopyridine with 2-tri-*n*-butylstannyl-3-thiophenylaldehyde in the presence of copper(II) oxide, mp 119-121°; ms: *m/z* (%) 187 (13), 186 (100,  $M^+$ ), 185 (14), 160 (9), 159 (10), 69 (12), 57 (12), 55 (9), 43 (9);  $^1H$  nmr:  $\delta$  9.47 (s, 1H,  $H_4$ ), 9.12 (dd, 1H,  $H_7$ ), 8.51 (dd, 1H,  $H_6$ ), 7.68 (d, 1H,  $H_2$ ), 7.65 (d, 1H,  $H_3$ ), 7.58 (dd, 1H,  $H_8$ ),  $J_{2,3} = 5.3$ ,  $J_{7,8} = 4.34$ ,  $J_{7,9} = 1.9$ ,  $J_{8,9} = 8.1$ .

*Anal.* Calcd. for  $C_{10}H_6N_2S$ : C, 64.45; H, 3.25; N, 15.04. Found: C, 64.62; H, 3.39; N, 15.14.

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