The Syntheses and NMR Spectra of the Twelve Isomeric Thieno[*b*]fused Naphthyridines

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Through the use of Pd(0)-catalyzed couplings between 2-(2-trimethylstannyl-3-pyridyl)-1,3-dioxolane, 3-trimethylstannyl-2-pyridine carboxaldehyde, 3-trimethylstannyl-4-pyridine carboxaldehyde and 4-trimethylstannyl-3-pyridine carboxaldehyde with *t*-butyl-*N*-(3-bromo-2-thienyl)carbamate, *t*-butyl-*N*-(2-bromo-3-thienyl)carbamate and *t*-butyl-*N*-(4-bromo-3-thienyl)carbamate in *N,N*-dimethylformamide at 100°, using cupric oxide as a coreagent, all twelve isomeric thieno[*b*]naphthyridines have been synthesized in an one-pot procedure. A detailed study of the ^1H and ^{13}C nmr spectra of these isomers has been undertaken.

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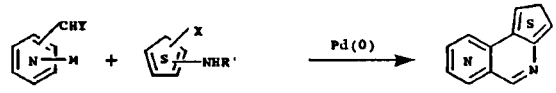
Introduction

The preparation, nmr spectra and chemical reactions of tricyclic heterocyclic aromatic systems with angular annelation pattern has been extensively studied in this laboratory in recent years. Such compounds as the dithieno[*b,d*]-pyridines were made available by using a modified Suzuki reaction between *o*-formylthiopheneboronic acids and amino protected *o*-haloaminothiophenes. Alternatively, *o*-formylstannylthiophenes (Stille reaction) were used as the organometallic reagent in these Pd(0)-catalyzed reactions (for review *cf* reference [1]). Using 2- and 4-formyl-3-thiopheneboronic acid and 2-(tributylstannyl)-3-thiophene carboxaldehyde as the organometallic reagent, and 3-amino-2-bromo- and 4-acetamido-3-bromopyridine as the *o*-aminobromo component, the six thieno[*c*]fused 1,5- and 1,6-naphthyridines were prepared [2]. In order to prepare the twelve isomeric thieno[*b*]naphthyridines, two approaches can be envisaged. The four isomeric *o*-formyl-(trialkylstannyl)pyridines or *o*-formylpyridineboronic acids

Scheme 1



M = $B(OH)_2$, SnR_3, R = Me, Bu; X = Br, I;
Y = O, OCH_2CH_2O; R' = CO_2t-Bu

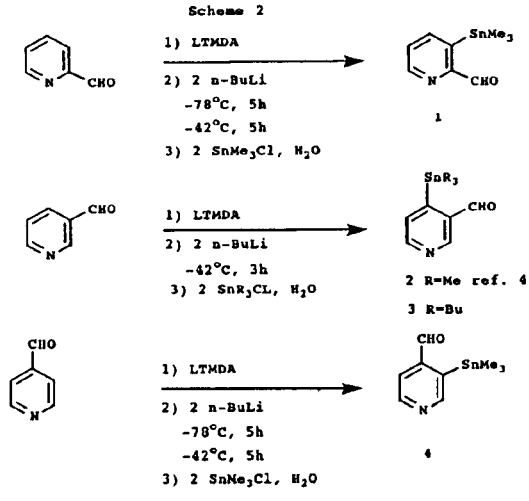
are coupled with the three *o*-aminohalothiophene derivatives (Scheme 1) or, alternatively, the four *o*-formylhalopyridines are coupled with *o*-amino(trialkylstannyl)thiophene derivatives or *o*-aminothiopheneboronic acid derivatives. In this paper the first-mentioned approach to the syntheses of the thieno[*b*]naphthyridines is described, and in all cases the tin derivatives were used as the organometallic reagent.

Results and discussion.

Three of the four isomeric *o*-formyl(trialkylstannyl)-pyridines were prepared by a convenient technique, recently introduced by Comins and Killpack [3], who *o*-metalated pyridine carboxaldehydes with butyllithium after protection of the carbonyl function through reaction with *N'*-lithio-*N*, *N*, *N'*-trimethylethylenediamine. Using this technique 2-pyridine carboxaldehyde gave 3-(trimethylstannyl)-2-pyridine carboxaldehyde (**1**) in 63% yield, after reaction with trimethylstannyl chloride. The lithiation of the protected 3-pyridine carboxaldehyde occurred selectively in the 4-position, and the resulting derivative gave 4-(tributylstannyl)-3-pyridine carboxaldehyde (**3**) in 32% yield, after reaction with tributylstannyl chloride. When our work was in progress, Kelly and Kim [4] reported the synthesis of 4-(trimethylstannyl)-3-pyridine carboxaldehyde (**2**) in 60% yield by the same approach. From 4-pyridine carboxaldehyde, as expected, 3-(trimethylstannyl)-4-pyridine carboxaldehyde (**4**) was obtained in 42% yield (Scheme 2).

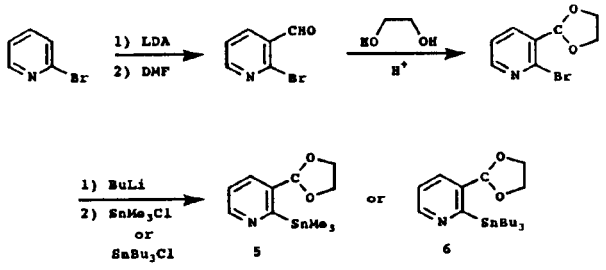
In order to obtain 2-(trimethylstannyl)- or 2-(tributylstannyl)-3-pyridine carboxaldehyde, the necessary starting material for the three thieno[*b*]-2,5-naphthyridines [5], another route obviously has to be used. Starting from 2-

Scheme 2



bromopyridine, 2-bromo-3-pyridine carboxaldehyde was prepared by metalation with lithium diisopropylamide followed by reaction with *N,N*-dimethylformamide [6,7]. The aldehyde was then protected by acetal formation with ethylene glycol. Halogen-metal exchange at -78° followed by reaction with trimethylstannyl chloride or tributylstannyl chloride then yielded 2-(2-trimethylstannyl-3-pyridyl)-1.3-dioxolane (**5**) and 2-(2-tributylstannyl-3-pyridyl)-1,3-dioxolane (**6**), respectively. In contrast to the corresponding acetals in the thiophene [8] and in the furan

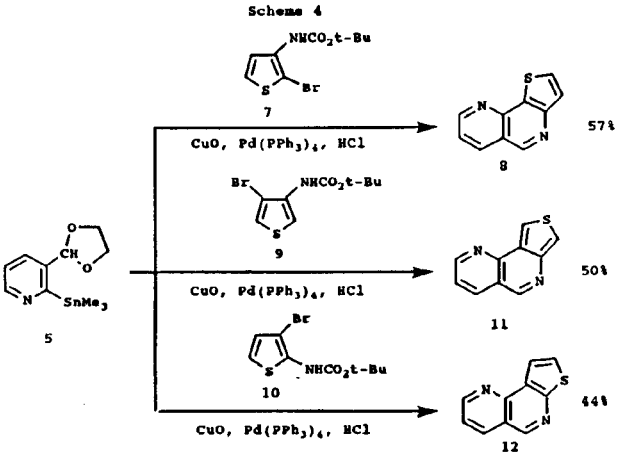
Scheme 3



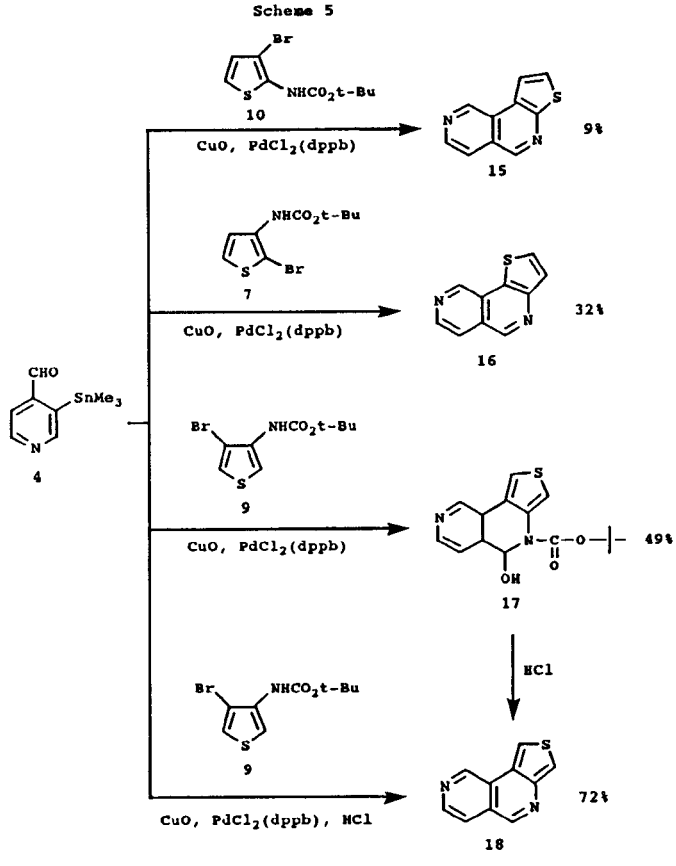
series [9], where the acetals are hydrolysed to the aldehydes without breaking the carbon-tin bond, this could not be achieved with **5** and **6**. Treatment with 1*M* hydrochloric acid, trityl fluoroborate [10], tartaric acid [11] or *trans*-acetalization with acetone [12], only led to cleavage of the carbon-tin bond or to no reaction at all.

We therefore used the acetals **5** and **6** directly in the Pd(0)-catalyzed coupling with the three *t*-butyl-*N*-(*o*-halothienyl)carbamates, expecting that treatment of the unsymmetrical coupled product with hydrochloric acid would produce the free aldehyde, which then would spontaneously ring-close to the tricyclic system. We found however, that the rate of the coupling and the yields were quite unsatisfactory. After experimenting with several co-reagents, we found that in the reaction of **5** with *t*-butyl-*N*-(2-bromo-3-thienyl)carbamate (**7**), cupric oxide gave the fastest reaction and best yield (57%) of thieno[3,2-*b*]-2,5-naphthyridine (**8**), with *tetrakis*(triphenylphosphine)-palladium(0) as catalyst [13,14]. We also tried some other Pd(0) catalysts, which in this case did not increase the yields. Recently another group has confirmed our findings of the beneficial effect of co-reagents on the yields and rates of Pd(0) catalyzed couplings [15]. We also found that coupling of **6** with **7** and of **3** with *t*-butyl-*N*-(4-bromo-3-thienyl)carbamate (**9**) failed, providing additional evidence for steric hindrance in the Stille coupling [16]. Coupling of **5** with **9** and with *t*-butyl-*N*-(3-bromo-2-thienyl)carbamate (**10**) gave thieno[3,4-*b*]-2,5-naphthyridine (**11**) and thieno[2,3-*b*]-2,5-naphthyridine (**12**) in 50% and 44% yield, respectively (Scheme 4). In our previous work on the thieno[*b,d*]pyridines, we found that *t*-butyl-*N*-(3-iodo-2-thienyl)carbamate (**13**) gave better yields than **10** both in the coupling with boronic acids [17] and tin derivatives [18]. However, **10** gives higher yields of **12** than **13** does (27%). In attempts to raise the low yields obtained in the syntheses of some thieno[*b*]naphthyridines, different reaction conditions were tried for the preparation of thieno[2,3-*b*]-2,7-naphthyridine (**14** in Scheme 7). Reacting **2** with **13** using *tetrakis*(triphenylphosphine)palladium(0) gave no product at all. We therefore decided to use the procedure described in [14] using dichloro(diphenylphosphinebutane)palladium(II)

Scheme 4

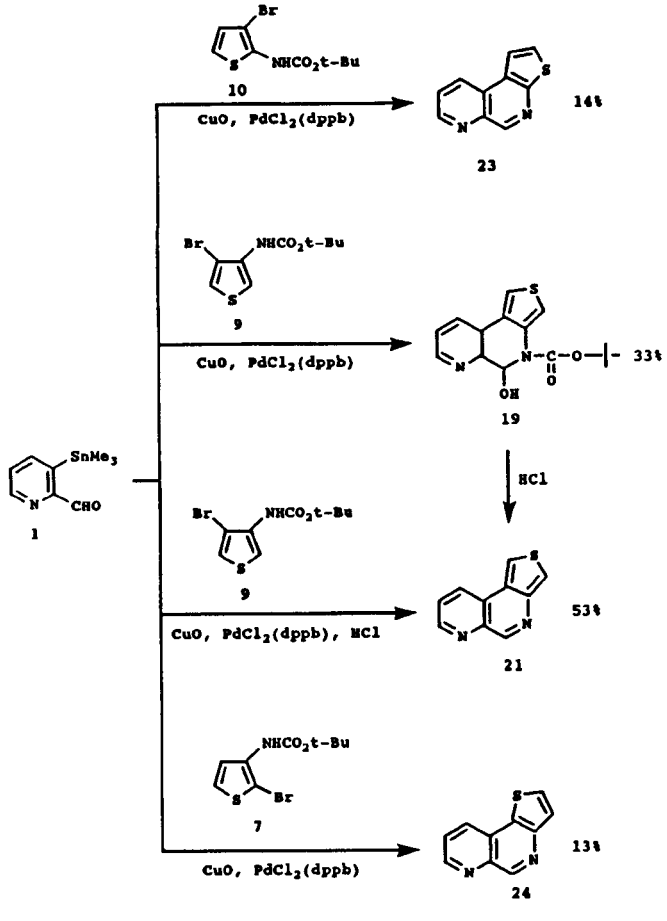


Scheme 5



[$PdCl_2$(dppb)] as catalyst and cupric oxide as the co-reagent in the coupling of **1**, **2** and **4** with **7**, **9** and **10**. Using **4** and **10** still gave a very unsatisfactory yield of thieno[2,3-*b*]-2,6-naphthyridine (**15**). Better yields were obtained in the reaction of **4** with **7**, which gave thieno[3,2-*b*]-2,6-naphthyridine (**16**) in 32% yield. As in the syntheses of dithieno[*b*,*d*]pyridines, in which the thiophene ring is annelated with its *c*-side [17], the reaction of

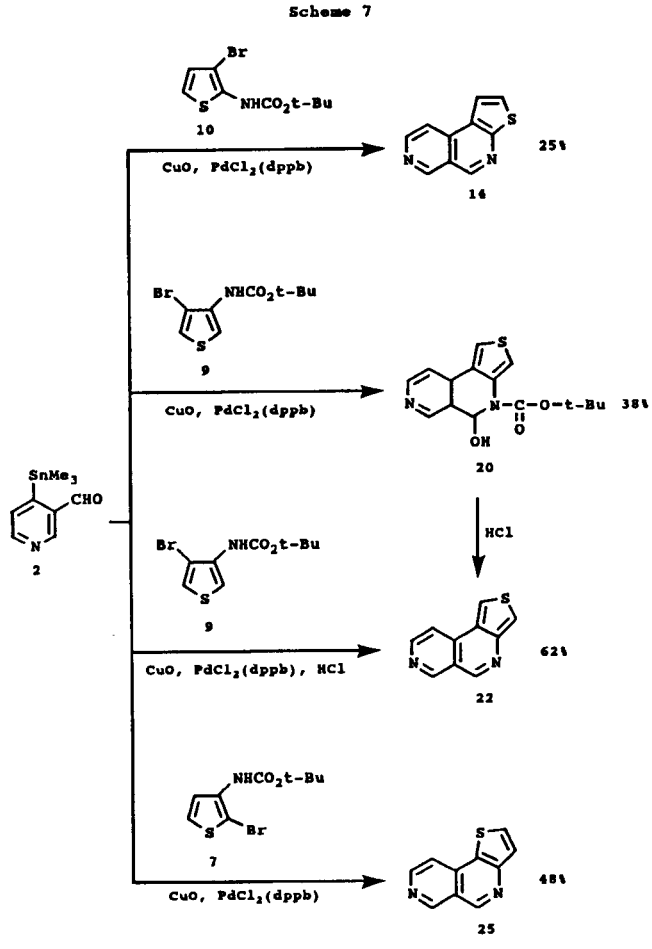
Scheme 6



4 with **9** gave 4-carbo-*t*-butoxy-5-hydroxy-4,5-dihydrothieno[3,4-*b*]-2,6-naphthyridine (**17**) as an intermediate, which was aromatized to thieno[3,4-*b*]-2,6-naphthyridine (**18**) by refluxing with 2*M* hydrochloric acid (Scheme 5).

This type of intermediate was also obtained in the reaction of **1** and **2** with **9**, which gave 4-carbo-*t*-butoxy-5-hydroxy-4,5-dihydrothieno[3,4-*b*]-2,8-naphthyridine (**19**) and 4-carbo-*t*-butoxy-5-hydroxy-4,5-dihydrothieno[3,4-*b*]-2,7-naphthyridine (**20**). These products were aromatized in the same way to thieno[3,4-*b*]-2,8-naphthyridine (**21**) and thieno[3,4-*b*]-2,7-naphthyridine (**22**). Both in the preparation of thieno[2,3-*b*]-2,8-naphthyridine (**23**) from **1** and **10** and of thieno[3,2-*b*]-2,8-naphthyridine (**24**) from **1** and **7** the yields were very low (Scheme 6), while in the

Scheme 7

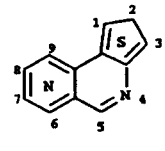


reaction of **2** with **7** and **10** better yields of thieno[3,2-*b*]-2,7-naphthyridine (**25**) and thieno[2,3-*b*]-2,7-naphthyridine (**14**) were obtained (Scheme 7).

As our main preliminary goal was to prepare all twelve isomers for a study of their spectral properties, we have not yet optimized the yields. As can be seen from the Schemes, especially the yields in the reaction with **7** leading to the [2,3-*b*]fused systems are in most cases quite unsatisfactory. It is possible that the other approach switching the positions of the halogen and the tin substituents, might give better yields.

NMR Spectra.

A detailed study of ^1H and ^{13}C spectra of all twelve isomers has been undertaken, in order to be able to study the substitution patterns in these tricyclic molecules. The labeling of positions is shown below.



^{1}H NMR spectra.

Assignments of ^{1}H chemical shifts and coupling constants of these compounds are given in the experimental part. The chemical shifts of the thieno[*b*]naphthyridines followed in principal what could be expected from a comparison with the shifts of structurally related systems, such as thieno[*c*]pyridines [19-21], naphthyridines [22] and thieno[*c*]fused 1,5 and 1,6-naphthyridines [2]. A characteristic shift order for the compounds is that 5-H and the protons α to the nitrogen in the A ring are most deshielded, followed by the proton γ to the nitrogen atom, and finally the thiophene protons and the proton β to the nitrogen in the A ring come into resonance. This is true for all isomers except **11**, where 1-H in the thiophene ring resonates 0.33 ppm downfield from 6-H. The protons α to the sulfur atom in the [3,2-*b*]fused systems resonate at lower field than the protons β to the sulfur atom; this is also the case in thiophene [23] and dithieno[3,2-*b*:*d*]pyridines [17,18], and in the thieno[*c*]fused 1,5- and 1,6-naphthyridines [2]. The reverse is true for the [2,3-*b*]fused systems. The β proton in the [2,3-*b*]fused systems gets more deshielded as the nitrogen atom in the A ring moves closer to the thiophene moiety. In the [3,4-*b*]fused systems, 1-H resonates at higher frequency than 3-H in all isomers. The thiophene protons appear as an AB quartet, with characteristic 2-3 and 2-5 coupling constants, 5.4-5.9 Hz and 3.2-3.4 Hz, respectively. Unambiguous shift assignments of the thiophene protons were based on ^{1}H-^{13}C HETCOR NMR spectra (Figure 1). The coupling constants in the naphthyridine moiety of the thieno[*b*]-

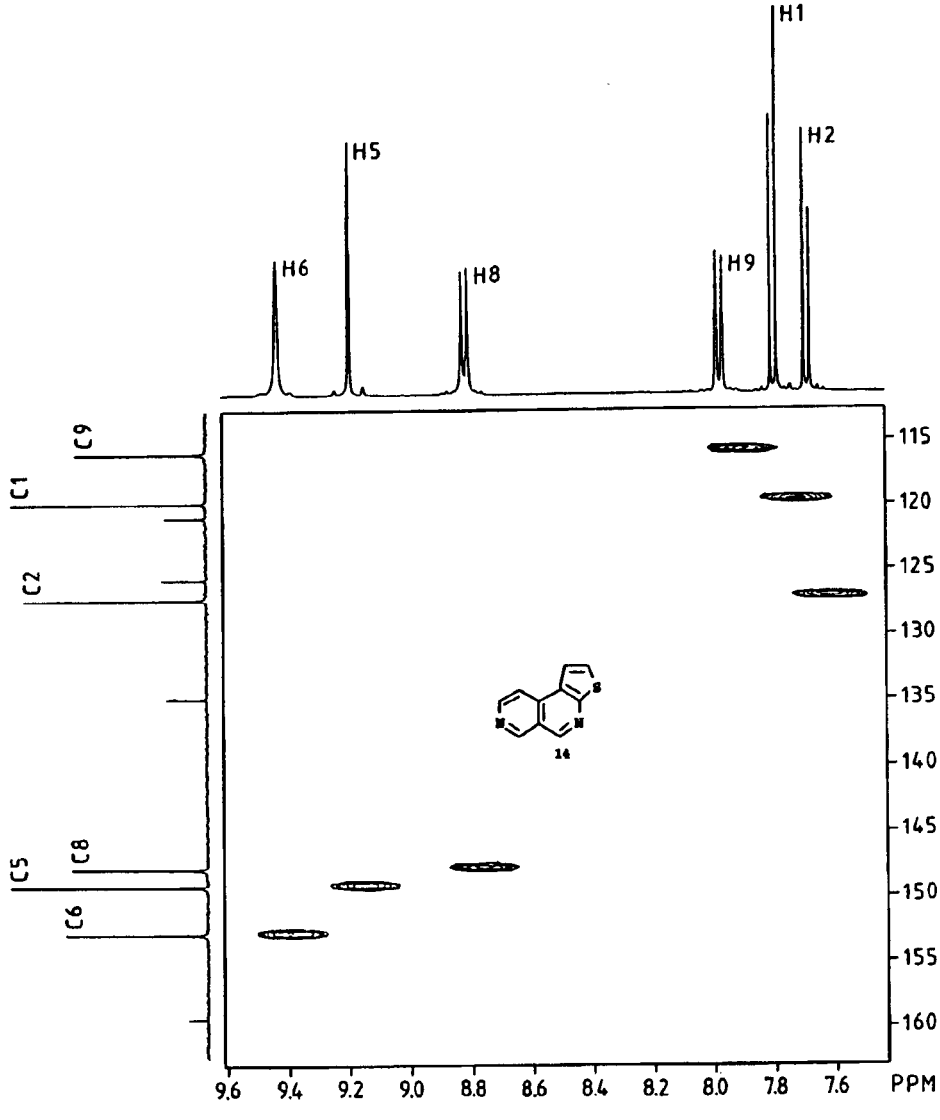


Figure 1. ^{1}H - ^{13}C HETCOR spectrum of **14**.

Table 1

^{13}C nmr Chemical Shifts for the Thieno[*b*]naphthyridines

Compound	C_1	C_2	C_3	C_5	C_6	C_7	C_8	C_9
8		128.9	126.0	151.0	136.6	122.1	153.8	
11	118.8		120.1	153.0	136.0	122.4	155.3	
12	120.6	126.5		149.6	136.2	121.7	153.9	
14	119.7	127.3		149.2	152.8		147.8	116.0
15	118.9	128.3		148.4	119.9	144.4		148.0
16		128.0	126.2	149.9	120.3	144.8		147.8
18	115.7		121.2	152.2	120.7	147.1		146.6
21	116.4		120.4	155.1		149.9	125.5	130.8
22	118.6		120.5	152.0	151.5		150.1	116.5
23	119.5	127.6		151.1		150.4	125.0	131.0
24		128.1	126.3	152.6		150.7	125.2	131.0
25		129.7	126.5	150.6	153.1		148.0	115.8

2,5-naphthyridines fall in the intervals $J_{6,7}$ = 7.9-8.2 Hz, $J_{6,8}$ = 1.7-1.8 Hz and $J_{7,8}$ = 4.4-4.7 Hz; for the thieno[*b*]-2,6-naphthyridines $J_{5,6}$ = 0.9 Hz $J_{6,7}$ = 5.2-5.6 Hz; for the thieno[*b*]-2,7-naphthyridines $J_{8,9}$ = 5.4-5.6 Hz and for the thieno[*b*]-2,8-naphthyridines $J_{7,8}$ = 4.4-4.7 Hz, $J_{5,8}$ = 0.8 Hz, $J_{7,9}$ = 1.7-1.8 Hz and $J_{8,9}$ = 7.9-8.2 Hz. These values are all also characteristic for the parent naphthyridines [22], except for the $J_{5,8}$ coupling, which is only observed in compound **24**, in contrast to 1,6 and 1,7-naphthyridines, where it is of the order of 0.9 Hz. A coupling between the 5- and 6-protons is observed in the spectrum of compound **16**, which has not been reported for the corresponding naphthyridine.

^{13}C Chemical Shift Assignments.

Unambiguous assignments of the ^{13}C nmr signals of these systems are given in Table 1. Assignments were based on proton-decoupled ^{13}C spectra, proton-coupled ^{13}C spectra and ^{1}H-^{13}C HETCOR spectra. The carbons α to the nitrogen atoms resonate at the lowest field. At higher field follow first the carbons γ to the nitrogen atoms, and then at highest field the carbons β to the nitrogen atoms and the carbons in the thiopene ring. In contrast to thiophene [23], the ^{13}C chemical shifts of the α carbons are larger than those for the β carbons. This is in accordance with all observations for thieno-fused systems. In the [3,4-*b*]fused systems 1-C and 3-C fell in the region 115.7-118.8 ppm and 120.1-121.2 ppm, respectively. This deshielding of the carbon closer to the nitrogen atom is additional evidence for the assignments of the 1 and 3 carbons. The shifts of the naphthyridine moiety are in good agreement with those of the corresponding naphthyridines [24].

^{13}C-^{1}H Coupling Constants

Unambiguous assignments of the carbon-proton coupling constants are given in Table 2. The assignments were based on the proton-coupled ^{13}C nmr spectra. The α and β positions in the thieno[2,3-*b*]naphthyridines and the thieno[3,2-*b*]naphthyridines were determined through their characteristic ^{1}J couplings in the proton-coupled ^{13}C spectra. The one-bond coupling constants, C(α)H(α) and C(β)H(β) in the thiophene ring, fall in the interval 184.3-190.7 Hz and 169.7-173.1 Hz, respectively. These values are in good agreement with those found in thiophene [25] and dithienopyridines [26]. The assignment of 1-C and 3-C in the [3,4-*b*]fused systems was based on the characteristic difference in the three-bond couplings $J_{1,3}$ (5.3-5.4 Hz) and $J_{3,1}$ (3.3-3.6 Hz). This difference is also found for dithieno[3,4-*b*:*d*]pyridines [26], where $J_{1,3}$ is 5.0-5.6 Hz and $J_{3,1}$ is 3.1-3.5 Hz, and for thieno[3,4-*c*]isoquinoline [27] where $J_{1,3}$ is 5.0 Hz and $J_{3,1}$ is 3.3 Hz. This analogy is only valid if the nitrogen atom in the B ring is in the 5 position; if it is in the 6 position, the coupling constants across the sulfur atom are almost the same. In the naphthyridine moiety of the molecules the one- and two-bond ^{1}H-^{13}C coupling constants in the A-ring were in most cases of the same magnitude as those observed by Miyajima and co-workers in pyridine [28].

Long-range coupling constants are in the intervals $J_{7,9}$ = 7.3-7.5 Hz and $J_{9,7}$ = 5.8-6.1 Hz for the thieno[*b*]-2,8-naphthyridines, $J_{5,6}$ = 2.9-3.3 Hz, $J_{6,5}$ = 1.9-2.6 Hz, $J_{6,8}$ = 10.6-11.1 Hz and $J_{8,6}$= 11.7-12.2 Hz for the thieno[*b*]-2,7-naphthyridines, $J_{5,6}$ = 4.7-5.2 Hz, $J_{6,5}$ = 1.9-2.1 Hz, $J_{7,9}$ = 11.6-12.0 Hz and $J_{9,7}$ = 10.6-11.2 Hz for the thieno[*b*] 2.6-naphthyridines and $J_{5,6}$ = 4.7 Hz, $J_{6,5}$ = 2.5-3.0 Hz, $J_{6,8}$ = 6.0-6.3 Hz and $J_{8,6}$ = 7.2-7.8 Hz for the thieno[*b*]-2,5-naphthyridines. For compound **18** no coupling was observed between 6-C and 5-H. There is a strong interaction over the three bonds across the nitrogen in the A ring, leading to coupling constants of the magnitude of about 12 Hz in the 2,6- and 2,7-naphthyridines. This is also the case in pyridine [28] and isoquinoline [29].

Table 2

^{13}C Coupling Constants for the Thieno[*b*]naphthyridines.

Compound	C_1	C_2	C_3	C_5	C_6	C_7	C_8	C_9
8								
$^1J_{CH}$		186.6	171.9	180.0	164.4	166.2	179.4	
$^2J_{CH}$		6.7	3.9			8.7	3.6	
$^3J_{CH}$				4.7	6.0, 2.9		7.5	
11								
$^1J_{CH}$	190.7		188.4	179.8	162.4	165.7	179.1	
$^2J_{CH}$						8.5	3.3	
$^3J_{CH}$	5.3		3.6	4.7	6.3, 2.5		7.2	
12								
$^1J_{CH}$	173.1	186.1		181.5	163.0	165.8	179.0	
$^2J_{CH}$	3.5	6.5				8.8	3.6	
$^3J_{CH}$				4.7	6.0, 3.0		7.8	
14								
$^1J_{CH}$	170.4	187.2		182.1	180.1		180.3	163.2
$^2J_{CH}$	3.0	5.4					2.3	8.5
$^3J_{CH}$				2.9	1.9, 10.6		12.2	
15								
$^1J_{CH}$	170.6	187.0		183.4	164.8	181.6		180.6
$^2J_{CH}$	3.0	5.4			6.7	2 3		
$^3J_{CH}$				4.7	2.1	12.0		10.6
16								
$^1J_{CH}$		188.1	172.6	181.8	163.2	181.9		180.7
$^2J_{CH}$		7.0	4.0		7.1	2.3		
$^3J_{CH}$				4.7	1.9	11.9		10.6
18								
$^1J_{CH}$	187.3		189.2	181.8	163.6		181.4	179.4
$^2J_{CH}$					8.3		2.5	
$^3J_{CH}$	5.4		3.3	5.2			11.6	11.2
21								
$^1J_{CH}$	186.5		188.9	183.1		180.3	160.2	162.6
$^2J_{CH}$						3.2	8.9	
$^3J_{CH}$	5.4		3.3			7.3		6.1
22								
$^1J_{CH}$	187.3		189.2	180.5	178.9		180.0	163.4
$^2J_{CH}$							2.5	8.3
$^3J_{CH}$	5.4		3.4	3.3	1.9, 11.1		11.7	
23								
$^1J_{CH}$	169.7	186.7		184.3		180.4	164.7	163.7
$^2J_{CH}$	3.1	5.3				3.4	9.1	
$^3J_{CH}$						7.5		5.9
24								
$^1J_{CH}$		187.9	172.3	182.9		180.9	165.0	164.0
$^2J_{CH}$		6.9	3.9			3.4	9.1	
$^3J_{CH}$						7.4		5.8
25								
$^1J_{CH}$		184.3	172.7	180.4	181.2		180.4	164.5
$^2J_{CH}$		7.0	3.8				2.3	8.3
$^3J_{CH}$				2.9	2.6, 10.6		12.2	

EXPERIMENTAL

The ^1H 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 ^1H nmr spectra. Sample concentrations for the ^{13}C nmr and HETCOR spectra were 30 mg/ml. High resolution mass spectra were recorded on a JEOL JMS-SX 102 spectrometer. The elemental analyses were carried out by Dornis und Kolbe, Mühlheim, Germany. All melting points are uncorrected.

2- and 3-Pyridine carboxaldehyde and *N, N, N'*-trimethylethylenediamine were purchased from Janssen. 4-Pyridine carboxaldehyde was purchased from Sigma. Trimethyltin chloride

was purchased from Aldrich. Tributyltin chloride and 2-bromopyridine were purchased from Merck. *N,N*-Dimethylformamide, petroleum ether (40-60°) and ethyl acetate were distilled and kept over molecular sieves prior to use. Tetrahydrofuran and diethyl ether were distilled over sodium. All other solvents were purchased from the manufacturer in analytical grade and used without further purification. *Tetrakis* (triphenylphosphine)palladium(0) [30], dichloro (diphenylphosphinebutane)palladium(II) [31], 2-bromo-3-pyridinecarboxaldehyde [6,7], *t*-butyl-*N*-(3-bromo-2-thienyl)carbamate [17], *t*-butyl-*N*(3-iodo-2-thienyl)carbamate [17], *t*-butyl-*N*-(2-bromo-3-thienyl)carbamate [17], *t*-butyl-N-(4-bromo-3-thienyl)carbamate [17] and 4-trimethylstannyl-3-pyridinecarboxaldehyde [4] were prepared by published procedures.

General Procedure for the Stannylation of Pyridine carboxaldehydes **1**,**3** and **4**.

To a stirred solution of 6.12 ml (48 mmoles) of *N,N,N'*-trimethylethylenediamine in 150 ml of anhydrous tetrahydrofuran, 21.4 ml 2.06 *M* butyllithium was added at -78°. After 15 minutes, 4.3 g (40 mmoles) of the appropriate pyridine carboxaldehyde was added, and the mixture was stirred at -78° for 15 minutes; then 38.8 ml of a 2.06 *M* butyllithium was added and the stirring was continued at the indicated temperatures and times. After cooling to -78°, 16.7 g (84 mmoles) of trimethyltin chloride or 27.3 g (84 mmoles) of tributyltin chloride in 100 ml of anhydrous tetrahydrofuran was added over a couple of minutes. The reaction was allowed to reach room temperature. It was quenched with 200 ml of cold brine and extracted with 3 x 300 ml of diethyl ether. The organic phase was dried over potassium carbonate and evaporated. The crude product was purified by column chromatography (petroleum ether-ethyl acetate, 4:1).

3-(Trimethylstannyl)-2-pyridine carboxaldehyde (**1**).

After chromatography 6.9 g (63%) of the title compound was obtained as a yellow oil; ^{1}H nmr: δ 0.31 (s, 9H, CH_3), 7.46 (dd, 1H, 5-H, J = 4.8, 7.4 Hz), 8.05 (ddd, 1H, 4-H, J = 0.8, 1.7, 7.4 Hz), 8.75 (dd, 1H, 6-H, J = 1.7, 4.8 Hz), 10.05 (d, 1H, CHO, J = 0.8 Hz); ms: m/z 270 (M^+, 6), 256 (100), 241 (10), 226 (30), hrms: m/z Calcd.for $C_9H_{14}ONSn$ $(M+H)^+$: 272.0098. Found: 272.0094.

4-(Tributylstannyl)-3-pyridine carboxaldehyde (**3**).

The title compound, 5.1 g (32%) was obtained as a yellow oil; ^{1}H nmr: δ 0.8-1.5 (m, 27H, C_4H_9), 7.65 (d, 1H, 5-H, J = 4.6 Hz), 8.67 (d, 1H, 6-H, J = 4.6 Hz), 8.95 (s, 1H, 2-H), 10.09 (s, 1H, CHO; ms: m/z 396 (M^+, 10), 340 (100), 284 (10), 226 (45); hrms: Calcd. for $C_{18}H_{32}ONSn$ $(M+H)^+$: 398.1506. Found: 398.1496.

3-(Trimethylstannyl)-4-pyridine carboxaldehyde (**4**).

The title compound, 4.6 g (42%) was isolated as a yellow oil; ^{1}H nmr: δ 0.32 (s, 9H, CH_3), 7.66 (d, 1H, 5-H, J = 4.9 Hz), 8.87 (d, 1H, 6-H, J =4.9 Hz), 8.91 (s, 1H, 2-H), 10.04 (s, 1H, CHO); ms: m/z 270 (M^+, 2), 256 (100), 241 (5), 226 (55); hrms: m/z Calcd. for $C_9H_{14}ONSn$ $(M+H)^+$: 272.0098. Found: 272.0086.

2-(2-Bromo-3-pyridyl)-1,3-dioxolane.

In a one-neck flask 24 g (0.13 mole) of 2-bromo-3-pyridinecarboxaldehyde, 39 g (0.63 mole) of ethylene glycol, 150 ml of toluene and a few chips of *p*-toluene sulphonic acid was refluxed with water separation until no more water separated (24 hours). The toluene layer was washed with 100 ml of sodium hydrogen carbonate solution and 100 ml of water and then dried over magnesium sulfate. The product was filtered, evaporated and then purified by column chromatography using petroleum ether/ethyl acetate (7:3) as eluent; 27 g (90%) of product was obtained as colourless needles, mp 48-50°; ^{1}H nmr: δ 4.12 (m, 4H, CH_2), 6.04 (s, 1H, CH), 7.31 (dd, 1H, 5-H, J = 4.7, 7.7 Hz), 7.89 (dd, 1H, 4-H, J = 1.9, 7.7Hz), 8.37 (dd, 1H, 6-H, J = 1.9, 4.7 Hz); ms: m/z 230 (M^+, 20), 186 (10), 157 (5), 150 (25), 78 (25); hrms: m/z Calcd. for $C_8H_8NO_2Br$: 228.9738. Found: 228.9741.

General Procedure for the Synthesis of 2-(2-Trimethylstannyl-3-pyridyl)-1,3-dioxolane (**5**) and 2-(2-Tributylstannyl-3-pyridyl)-1,3-dioxolane (**6**).

A solution of 12 g (52 mmoles) of 2-(2-bromo-3-pyridyl)-1,3-dioxolane in 480 ml of anhydrous diethyl ether was added slowly to 32 ml of 2.06 *M* butyllithium in 30 ml diethyl ether at -78°. The resulting red solution was stirred for 10 minutes and then added to a suspension of 10.4 g (52 mmoles) of trimethyltin chloride or 16.9 g (52 mmoles) of tributyltin chloride in 240 ml diethyl ether, also at -78°. The reaction mixture was allowed to slowly warm to room temperature. The product was filtered and then distilled.

2-(2-Trimethylstannyl-3-pyridyl)-1,3-dioxolane (**5**).

The procedure described above gave 10.6 g (65%) of a yellow oil with a bp 100-105°/2 mm Hg; ^{1}H nmr δ 0.35 (s, 9-H, CH_3), 4.06 (m, 4H, CH_2), 5.85 (s, 1H, CH), 7.17 (dd, 1H, 5-H, J = 4.8, 8.0 Hz), 7.72 (dd, 1H, 4-H, J = 1.7, 8.0), 8.72 (dd, 1H, 6-H, J = 1.7, 4.8 Hz); ms: m/z 314 (M^+, 1), 300 (100), 270 (10), 256 (90), 150 (35); hmrs: m/z Calcd. for $C_{10}H_{14}O_2NSn$: 300.0047. Found: 300.0045.

2-(2-Tributylstannyl-3-pyridyl)-1,3-dioxolane (**6**).

From the above procedure 9.1 g (40%) of a yellow oil with a bp 150-170°/3 mm Hg was obtained; ^{1}H nmr δ 0.88 1.52 (m, 27H, C_4H_9, 4.08 (m, 4H, CH_2), 5.77 (s, 1H, CH), 7.15 (dd, 1H, 5-H, J = 4.7, 7.9 Hz), 7.73 (dd, 1H, 4-H, J = 1.7, 7.9 Hz), 8.71 (dd, 1H, 6-H, J = 1.7, 4,7); ms: m/z 440 (M^+, 5), 384 (80), 291 (90), 235 (90), 179 (100); hrms: m/z Calcd. for $C_{20}H_{36}O_2SnN$: 442.1768. Found: 442.1772.

General Procedure for the Preparation of the Thieno[*b*]naphthyridines.

A mixture of 0.55 g (2.0 mmoles) of the appropriate *o*-bromothienylcarbamate or 0.65 g (2.0 mmoles) of the *o*-iodothienylcarbamate (2.0 mmoles), 0.060 g (0.10 mmole) of dichloro(diphenylphosphinebutane)palladium(II) or 0.115 g (0.10 mmole) *tetrakis* triphenylphosphinepalladium(0) and 0.16 g (2.0 mmoles) of cupric oxide in 8 ml of *N,N*-dimethylformamide was stirred at 100° under nitrogen. After 5 minutes, 0.81 g (3.0 mmoles) of the appropriate trimethylstannylpyridine carboxaldehyde or 0.94 g (3.0 mmoles) of 2-(2-trimethylstannyl-3-pyridyl)-1,3-dioxolane in 2 ml of *N,N*-dimethylformamide was added all at once to the reaction mixture. After the starting materials were consumed (see compound data), the reaction mixture was allowed to reach room temperature. In the syntheses of compounds **8, 11, 12, 18, 21** and **22**, 5 ml of 2*M* hydrochloric acid was added to the reaction mixture. These solutions were then heated at 100° for 1 hour, allowed to reach room temperature and neutralized with 5 ml of 2*M* sodium hydroxide solution. For all of the thieno[*b*]naphthyridines, the precipitate was fil-

tered off and the filtrate was evaporated. The residue was subjected to chromatography using ethyl acetate as eluent and sublimated at 30° below the mp at 2 mm Hg. Compounds **17, 19** and **20** were not sublimated, but were recrystallized from ethanol.

Thieno[3,2-b]-2,5-naphthyridine (**8**).

The starting materials were consumed after 3 hours and the product, 0.21 g (57%), was isolated as white crystals, mp 120-122°; ^{1}H nmr: ms: see ref [13].
Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.45; H, 3.25; N, 15.04. Found: C, 64.61; H, 3.41; N, 14.81.

Thieno[3,4-*b*]-2,5-naphthyridine (**11**).

The starting materials were consumed after 1 hour and the product, 0.19 g (50%) was isolated as white crystals, mp 86-88°; ^{1}H nmr: ms: see ref [13].
Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.45; H, 3.25; N, 15.04. Found: C, 64.58; H, 3.31; N, 14.96.

Thieno[2,3-*b*]-2,5-naphthyridine (**12**).

The starting materials were consumed after 80 minutes and the product, 0.16 g (44%), was obtained as white crystals, mp 117-119°; ^{1}H nmr: ms: see ref. [13].
Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.45; H, 3.25; N, 15.04. Found: C, 64.24; H, 3.30; N, 14.06.

Thieno[2,3-*b*]-2,7-naphthyridine (**14**).

The starting materials were consumed after 4 hours and the product, 93 mg (25%), was isolated as white crystals, mp 112-116°; ^{1}H nmr: δ 7.72 (d, 1H, 2-H, J = 5.9 Hz), 7.84 (d, 1H, 1-H, J = 5.9 Hz), 8.03 (d, 1H, 9-H, J = 5.4 Hz), 8.87 (d, 1H, 8-H, J = 5.4), 9.24 (s, 1H, 5-H), 9.49 (s, 1H, 6-H); ms: m/z 186 (100), 159 (12), 142 (5), 114 (8), 92 (6).
Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.45; H, 3.25; N, 15.04. Found C, 64.44; H, 3.25; N, 15.04.

Thieno[2,3-*b*]-2,6-naphthyridine (**15**).

The starting materials were consumed after 80 minutes and the product, 33.5 mg (9%), was isolated as white crystals, mp 130-131°; ^{1}H nmr: δ 7.79 (d, 1H, 2-H, J = 5.8 Hz), 7.88 (d, 1H, 6-H, J = 5.6 Hz), 7.98 (d, 1H, 1-H, J = 5.8 Hz), 8.79 (d, 1H, 7-H, J = 5.6 Hz), 9.15 (s, 1H, 9-H), 9.76 (s, 1H, 5-H).
Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.45; H, 3.25; N, 15.04. Found: C, 64.41; H, 3.41; N, 14.81.

Thieno[3,2-*b*]-2,6-naphthyridine (**16**).

The starting materials were consumed after 100 minutes and the product, 0.12 g (32%), was isolated as white crystals, mp 131-132°; ^{1}H nmr: δ 7.76 (d, 1H, 3-H, J = 5.4 Hz), 7.81 (d, 1H, 2-H, J = 5.4 Hz), 7.87 (dd, 1H, 6-H, J = 0.9, 5.6 Hz), 8.78 (d, 1H, 7-H, J = 5.6 Hz), 9.24 (d, 1H, 5-H, J = 0.9 Hz), 9.59 (s, 1H, 9-H); ms: m/z 186 (100), 159 (40), 142 (12), 93 (18), 87 (20).
Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.45; H, 3.25; N, 15.04. Found: C, 64.59; H, 3.35; N, 14.86.

4-Carbo-*t*-butyloxy-5-hydroxy-4,5-dihydrothieno[3,4-*b*]-2,6-naphthyridine (**17**).

The starting materials were consumed after 1 hour and the product, 0.30 g (49%), was isolated as white crystals, mp 193-194°; ^{1}H nmr: δ 1.61 (s, 9H, CH_3), 4.92 (s, 1H, OH), 6.85 (s, 1H, 5-H), 7.47 (d, 1H, 6-H, J = 5.2 Hz), 7.50 (d, 1H, 3-H, J = 3.2 Hz), 7.70 (d, 1H, 1-H, J = 3.2 Hz), 8.55 (d, 1H, 7-H, J = 5.2 Hz), 8.55 (s, 1H, 9-H); ms: m/z 305 (37 M^++1), 287 (75), 231 (100), 187 (100), 93 (30); hrms m/z Calcd. for $C_{15}H_{17}O_3N_2S$: 305.0960 Found: 305.0961.

Thieno[3,4-*b*]-2,6-naphthyridine (**18**).

The starting materials were consumed after 80 minutes and the product, 0.27 g (72%), was isolated as white crystals, mp 165-169°; ^{1}H nmr: δ 7.69 (d, 1H, 6-H, J = 5.2 Hz), 8.07 (d, 1H, 3-H, J = 3.2 Hz), 8.17 (d, 1H, 1-H, J = 3.2 Hz), 8.80 (d, 1H, 7-H, J = 5.2) Hz, 8.99 (s, 1H, 5-H), 9.59 (s, 1H, 9-H); ms: m/z 186 (100), 159 (20), 142 (12), 114 (8), 93 (7).
Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.45; H, 3.25; N, 15.04. Found: C, 64.55; H, 3.26; N, 15.10.

4-Carbo-*t*-butyloxy-5-hydroxy-4,5-dihydrothieno[3,4-*b*]-2,8-naphthyridine (**19**).

The starting materials were consumed after 1 hour and the product, 0.20 g (33%), was isolated as white crystals, mp 130-131°; ^{1}H nmr: δ 1.59 (s, 9H, CH_3), 4.40 (s, 1H, OH), 6.90 (s, 1H, 5-H), 7.38 (dd, 1H, 8-H, J = 4.8, 7.9 Hz), 7.60 (d, 1H, 3-H, J = 3.0 Hz), 7.61 (d, 1H, 1-H, J = 3.0 Hz), 8.02 (dd, 1H, 9-H, J = 1.6, 7.9 Hz), 8.56 (dd, 1H, 7-H, J = 1.6, 4.8 Hz); ms: m/z 305 (25 M^++1), 231 (65), 187 (100), 93 (56); hrms: m/z Calcd. for $C_{15}H_{17}O_3N_2S$: 305.0960. Found: 305.0963.

4-Carbo-*t*-butyloxy-5-hydroxy-4,5-dihydrothieno[3,4-*b*]-2,7-naphthyridine (**20**).

The starting materials were consumed after 80 minutes and the product, 0.23 g (38%), was isolated as white crystals, mp 130-131°; ^{1}H nmr: δ 1.59 (s, 9H, CH_3), 4.51 (s, 1H, OH), 6.78 (s, 1H, 5-H), 7.35 (d, 1H, 9-H, J = 4.9 Hz), 7.46 (d, 1H, 3-H, J = 3.2 Hz), 7.62 (d, 1H, 1-H, J = 3.2 Hz), 8.42 (d, 1H, 8-H, J = 4.9 Hz), 8.83 (s, 1H, 6-H); ms: m/z 305 (100 M^++1), 249 (55), 232 (35), 187 (75), 93 (45); hrms: m/z Calcd. for $C_{15}H_{17}O_3N_2S$ 305.0960. Found: 305.0963.

Thieno[3,4-*b*]-2,8-naphthyridine (**21**).

The starting materials were consumed after 1 hour and the product, 0.20 g (53%), was isolated as white crystals, mp 118-120°; ^{1}H nmr: δ 7.63 (dd, 1H, 8-H, J = 4.5, 8.1 Hz), 8.01 (d, 1H, 3-H, J = 3.2 Hz), 8.05 (d, 1H, 1-H, J = 3.2 Hz), 8.45 (dd, 1H, 9-H, J = 1.5, 8.1 Hz), 8.89 (dd, 1H, 7-H, J = 1.5, 4.5 Hz), 9.10 (s, 1H, 5-H); ms: m/z 186 (100), 159 (6), 142 (5), 137 (5), 114 (6).
Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.45; H, 3.25; N, 15.04. Found: C, 64.59; H, 3.34; N, 14.81.

Thieno[3,4-*b*]-2,7-naphthyridine (**22**).

The starting materials were consumed after 1 hour and the product, 0.23 g (62%), was isolated as white crystals, mp 157-164°; ^{1}H nmr: δ 7.98 (d, 1H, 9-H, J = 5.5 Hz), 8.02 (d, 1H, 3-H, J = 3.2 Hz), 8.20 (d, 1H, 1-H, J = 3.2 Hz), 8.84 (d, 1H, 8-H, J = 5.5 Hz), 8.97 (s, 1H, 5-H), 9.20 (s, 1H, 6-H); ms: m/z 186 (100), 159 (12), 142 (5), 114 (7), 97 (7); hrms: m/z Calcd. for $C_{10}H_6N_2S$: 186.0252. Found: 186.0253.

Thieno[2,3-*b*]-2,8-naphthyridine (**23**).

The starting materials were consumed after 6 hours and the title compound, 52.1 mg (14%), was isolated as white crystals, mp 110-111°; ^{1}H nmr δ 7.69 (dd, 1H, 8-H, J = 4.2, 8.4 Hz), 7.71 (d, 1H, 2-H, J = 5.9 Hz), 7.81 (d, 1H, 1-H, J = 5.9 Hz), 8.55 (d, 1H, 9-H, J = 1.6, 8.4), 9.02 (d, 1H, 7-H, J = 1.6, 4.2 Hz), 9.36 (s, 1H, 5-H); ms: m/z 186 (100), 159 (12), 142 (12), 114 (10), 93 (11).

Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.45; H, 3.25; N, 15.04. Found: C, 64.74; H, 3.43; N, 14.62.

Thieno[3,2-*b*]-2,8-naphthyridine (**24**).

The starting materials were consumed after 2 hours and the product, 48.4 mg (13%), was obtained as fine white crystals, mp 128-131°; ^{1}H nmr: δ 7.68 (dd, 1H, 8-H, J = 4.3, 8.4 Hz), 7.73 (d, 1H, 3-H, J = 5.4 Hz), 7.76 (d, 1H, 2H, J = 5.4 Hz), 8.41 (ddd, 1H, 9-H, J = 0.8, 1.6, 8.4 Hz), 9.03 (dd, 1H, 7-H, J = 1.6, 4.3 Hz), 9.45 (d, 1H, 5-H, J = 0.8 Hz); ms: m/z 186 (100), 159 (8), 142 (7), 133 (6), 93 (5).

Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.45; H, 3.25; N, 15.04. Found: C, 65.01; H, 3.60; N, 14.65.

Thieno[3,2-*b*]-2,7 -naphthyridine (**25**).

The starting materials were consumed after 140 minutes and the product, 0.18 g (48%), was isolated as white crystals, mp 140-141°; ^{1}H nmr: δ 7.74 (d, 1H, 3-H, J = 5.4 Hz), 7.84 (d, 1H, 9-H, J = 5.6 Hz), 7.85 (d, 1H, 2-H, J = 5.4 Hz), 8.80 (d, 1H, 8-H, J = 5.6 Hz), 9.30 (s, 1H, 5-H), 9.44 (s, 1H, 6-H); ms: 186 (100), 159 (17), 133 (7), 114 (7), 93 (8).

Anal. Calcd. for $C_{10}H_6N_2S$: C, 64.45; H, 3.25; N, 15.04. Found: C, 64.63; H, 3.35; N, 14.86.

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[5] For convenient comparison with the *c*-fused systems, we wished to consider all the twelve systems as *b*-fused system. Thus compounds **8, 11** and **12** are called thieno[*b*]-2,5-naphthyridines. The correct names we believe should be thieno[*h*]-1,6-naphthyridines. In the same way, we believe the correct names for compounds **21, 23** and **24** should be thieno[*f*]-1,7-naphthyridines, but they are called thieno[*b*]-2,8-naphthyridines.

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