SYNTHESIS OF THE SIX ISOMERIC THIENO[*c*]-FUSED 1,5- AND 1,6-NAPHTHYRIDINES

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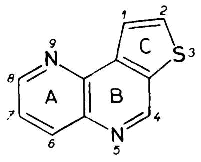
Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

Through the use of Pd(0)-catalyzed coupling between 2- and 4-formyl-3-thiopheneboronic acids and 3-amino-2-bromopyridine and 4-acetamido-3-bromopyridine, convenient one-pot procedures for the preparation of thieno[2,3-*c*]-1,5-naphthyridine, thieno[3,4-*c*]-1,5-naphthyridine, thieno-[2,3-*c*]-1,6-naphthyridine, and thieno[3,4-*c*]-1,6-naphthyridine have been developed. In order to obtain thieno[3,2-*c*]-1,6-naphthyridine 2-(tributylstannyl)-3-thiophene aldehyde had to be used, since the organometallic partner in the coupling reaction, 3-formyl-2-thiopheneboronic acid, is too easily deboronated. The effect of silver(I) oxide and thallium(I) carbonate on the coupling was studied. ^{1}H and ^{13}C NMR spectra of the six isomeric thieno[*c*]-fused 1,5- and 1,6-naphthyridines are discussed.

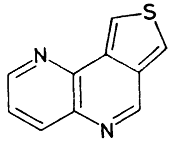
In connection with our interest in the effect of the mode of annelation on the physical and chemical properties of tricyclic heterocyclic systems with phenanthrene annelation pattern, dithienobenzenes have been investigated[1-3]. Recently, we developed convenient one-pot procedures involving Pd(0)-catalyzed cross-couplings for the synthesis of benzo- and thieno[*c*]-fused quinolines[4] and isoquinolines[5], thieno[*c*]-fused 1,8-naphthyridines[4], as well as all nine isomeric dithienopyridines[6-9]. NMR spectra of these systems have been analyzed[10,11] and a study of their substitution reactions is in progress.

Theoretically there exist 24 isomers of thieno-fused naphthyridines with an angular annelation pattern. In the present paper, the synthesis and NMR spectra of the six isomeric compounds, the three thieno[*c*]-1,5-naphthyridines (*I*–*III*) and the three thieno[*c*]-1,6-naphthyridines (*IV*–*VI*) will be described. As far as we could find, none of these parent compounds have been described in the literature, but the corresponding condensed thieno[2,3-*c*]naphthyridones (*VIII*) have been prepared through oxidative photocyclization reactions of (*VII*) (ref.[12]) (Scheme 1).

Many compounds isosteric or structurally similar to the compounds *I*–*VI* have shown various kinds of biological activity, which gives additional interest to a study of these systems.



I



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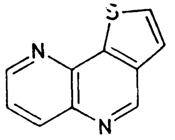

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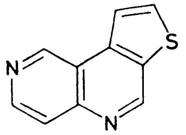

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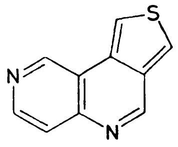

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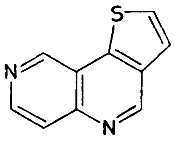

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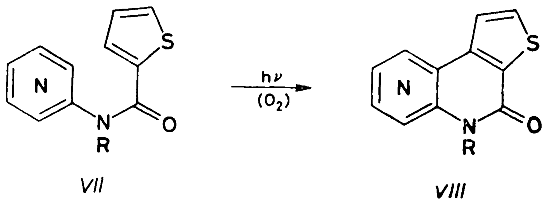
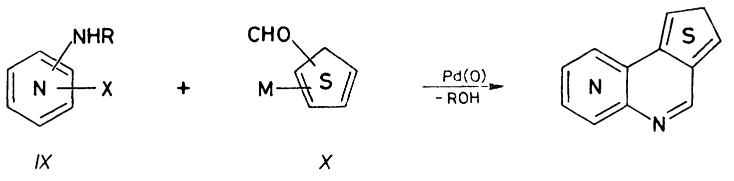


SCHEME 1

The strategy followed for the one-pot synthesis is modelled on the methods developed by us for the synthesis of the dithienopyridines. It uses the Pd(0)-catalyzed cross-coupling of *o*-formylarylboronic acids or *o*-formylaryltin trialkyl derivatives with *o*-amino- or protected *o*-aminoaryl halides. The coupled product ring-closes spontaneously during the reaction to the desired tricyclic system (Scheme 2). Snieckus



In formula IX : R = H, $COCH_3$, $CO_2C(CH_3)_3$; X = I, Br, Cl

In formula X : M = $B(OH)_2$, $SnBu_3$

SCHEME 2

and coworkers have independently developed an alternative approach for the one-pot synthesis of similar compounds, in which *o*-aminoarylboronic acids are coupled with *o*-formyl aryl halides[13].

From previous investigations, it was evident that a drawback in the use of arylboronic acids in the coupling reaction is that deboronation might be a competing reaction in aqueous media, especially when the aryl group is π-excessive[8]. In such cases, Pd-catalyzed cross-coupling of organotin reagents with aryl halides, extensively studied by Stille and others[14], can be advantageously used. They are usually more stable but more toxic and expensive than the boronic acids. Because of these two main drawbacks of organotin compounds, we chose to use boronic acids whenever possible.

RESULTS AND DISCUSSION

Preparation

The Pd(0)-catalyzed reaction between 2-chloro-3-aminopyridine and 2-formyl-3-thiopheneboronic acid gave low yields of *I* (Table I). Since the reactivity in the

TABLE I

Reaction conditions for the coupling of boronic acids *X* with *o*-bromoamino- or acetamidopyridines *IX*

X	Equivalent	*IX* -NHR	-X	Base	Reaction time	Yield %	Product
2-CH=O 3-B(OH)$_2$	1·1	3-NH$_2$	2-Cl	Na$_2$CO$_3$	50—60 min	18	*Ia*
	1·1	3-NH$_2$	2-Br	Na$_2$CO$_3$	40—50 min	41	*Ib*
	1·5	3-NH$_2$	2-Br	Na$_2$CO$_3$	50—60 min	60	*Ic*
	1·1	4-NH$_2$	3-Br	Na$_2$CO$_3$	—^{b}	10^c	*IVa*
	1·1	4-NH$_2$	3-Br	NaHCO$_3$	—^{b}	8^c	*IVb*
	1·1	4-NH$_2$	3-Br	TEA^a	15 h	30^c	*IVc*
	1·5	4-NH$_2$	3-Br	Na$_2$CO$_3$	—^{b}	14	*IVd*
	1·5	4-NHCOCH$_3$	3-Br	Na$_2$CO$_3$	20—25 min	73	*IVe*
3-CH=O 4-B(OH)$_2$	1·1	3-NH$_2$	2-Br	Na$_2$CO$_3$	150—170 min	55	*IIa*
	1·25	3-NH$_2$	2-Br	Na$_2$CO$_3$	200—220 min	62	*IIb*
	1·25	4-NHCOCH$_3$	3-Br	Na$_2$CO$_3$	25—30 min	68	*V*
3-CH=O 2-B(OH)$_2$	1·5	3-NH$_2$	2-Br	TEA^a	24 h	18	*IIIa*
	1·5	3-NH$_2$	2-Br	Tl$_2$CO$_3$	2—4 min	29^c	*IIIb*

[a] When triethylamine (TEA) was used as base, the reaction was carried out in dimethylformamide; for details, see ref.[1]. [b] The reaction mixture was refluxed for approximately 2 h. No degradation of the product was observed during prolonged reflux. [c] The yield was estimated from GLC.

oxidative addition of Pd(0) to aryl halides increases in the series PhI > PhBr > PhCl (ref.[15]), we turned to 2-bromo-3-aminopyridine and obtained a three-fold increase in the yield of *I*. However, deboronation still occurred, and after 40 min of reflux, the formation of 35% of 2-thiophene aldehyde was observed. (This by-product was isolated and had an R_F-value on GLC identical as 2-formylthiophene[36], *m*/*z*: 112.) Therefore 1·5 equivalents of 2-formyl-3-thiopheneboronic acid were used, which gave a 60% yield of *I*.

3-Bromo-4-aminopyridine reacted even more slowly than 2-bromo-3-aminopyridine with 2-formyl-3-thiopheneboronic acid, giving a very low yield of thieno[2,3-*c*]-1,6-naphthyridine (*IV*). This is not unexpected, since the 3-bromo isomer is much less reactive in nucleophilic aromatic substitution and consequently in oxidative insertion than the 2-bromo isomer. Using the same technique as in our phenanthridine synthesis[5], using 3-bromo-4-acetamidopyridine, a dramatic increase of the yield to 73% was achieved.

4-Formyl-3-thiopheneboronic acid appeared to be more stable under the reaction conditions than 2-formyl-3-thiopheneboronic acid, and good yields of thieno[3,4-*c*]-1,5-naphthyridine (*II*) and thieno[3,4-*c*]-1,6-naphthyridine (*V*) were obtained with 2-bromo-3-aminopyridine and 3-bromo-4-acetamidopyridine, respectively.

TABLE II

Reaction conditions for the coupling of 2-(tributylstannyl)-3-thiophene aldehyde with *o*-bromoamino- or acetamidopyridine *IX*

Equivalent of aldehyde	-NHR	-X	Base	Reaction time	Yield %	Product
1·1	3-NH_2	2-Br	none	30 h	52	*IIIc*
1·1	3-$NHCOCH_3$	2-Br	none	8 h	69	*IIId*
1·1	3-$NHCOCH_3$	2-Br	Ag_2O	—[a]	48[c]	*IIIe*
1·1	3-$NHCOCH_3$	2-Br	Ag_2O	—[a]	40[b,c]	*IIIf*
1·6	3-$NHCOCH_3$	2-Br	Ag_2O	2—3 min	69	*IIIg*
1·6	3-NH_2	2-Br	Ag_2O	10—15 min	71	*IIIh*
1·1	3-NH_2	2-Br	Tl_2CO_3	—[a]	11[c]	*IIIi*
1·1	4-$NHCOCH_3$	3-Br	none	10 h	60	*VIa*
1·6	4-$NHCOCH_3$	3-Br	Ag_2O	—[a]	21[c]	*VIb*
1·6	4-NH_2	3-Br	Ag_2O	—[a]	34[c]	*VIc*

[a] The reaction mixture was refluxed for approximately 2 h. No degradation of the product was observed during prolonged reflux. [b] The reaction temperature was 50°C. [c] The yield was estimated from GLC.

As 3-formyl-2-thiopheneboronic acid is easily hydrolyzed in aqueous media, anhydrous conditions (triethylamine in DMF), first introduced by Gaudino et al.[16], were used. However, thieno[3,2-*c*]-1,5-naphthyridine (*III*) was only obtained in 18% yield. We therefore turned to the tin methodology, using 2-(tributylstannyl)-3-thiophene aldehyde, which gave *III* and thieno[3,2-*c*]-1,6-naphthyridine (*VI*) in 69% and 60% yield, respectively, in the reaction with 3-acetamido-2-bromopyridine and 4-acetamido-3-bromopyridine. However, long reaction times had to be used (8 to 30 h). We found that the addition of silver(I) oxide greatly increased the rate of coupling of 3-amino-2-bromopyridine with the tin derivative, and after 15 min a 71% yield of *III* was obtained, with 1·6 equivalents of the tin derivative. (For the use of silver(I) oxide in Pd(0)-catalyzed couplings, cf. ref.[17].) However, to our surprise, the use of silver(I) oxide in the coupling of 4-amino- or 4-acetamido-3-bromothiophene with 2-(tributylstannyl)-3-thiophene aldehyde led to a sharp decrease in the yield of *VI*. The low yields were due to the formation of 3,3′-diformyl-2,2′-

TABLE III

^{1}H NMR chemical shifts (in ppm) of the thienonaphthyridines *I*—*VI*

Compound	H(1)	H(2)	H(3)	H(4)	H(6)	H(7)	H(8)	H(9)
I	8·34	7·92	(S)	9·37	8·52	7·67	9·01	(N)
II	8·57	(S)	8·17	9·12	8·31	7·56	8·83	(N)
III	(S)	7·74	7·66	9·33	8·52	7·67	8·97	(N)
IV	8·14	8·05	(S)	9·50	8·08	8·82	(N)	9·77
V	8·18	(S)	8·19	9·18	7·82	8·74	(N)	9·52
VI	(S)	7·69	7·67	9·43	8·03	8·81	(N)	9·60

TABLE IV

^{1}H NMR coupling constants (*J* in Hz) of the thienonaphthyridines *I*—*VI*

Compound	*J*(1, 2)	*J*(1, 3)	*J*(1, 4)	*J*(2, 3)	*J*(6, 7)	*J*(6, 8)	*J*(6, 9)	*J*(7, 8)
I	5·3	—	0·8	—	8·4	1·7	—	4·3
II	—	3·1	0·9	—	8·2	1·7	—	4·6
III	—	—	—	5·3	8·4	1·6	—	4·3
IV	5·3	—	0·8	—	5·8	—	0·8	—
V	—	2·9	0·8	—	5·5	—	0·6	—
VI	—	—	—	5·3	5·8	—	0·8	—

-bithienyl from 2-(tributylstannyl)-3-thiophene aldehyde. 3,3'-Diformyl-2,2'-bithienyl was isolated from the reaction mixture by liquid chromatography, and after recrystallization from benzene had the same melting point as reported in the literature[37] (155–157°C). ^{1}H NMR, δ: 7·49 q, 2 H (H-4, $J_{4,5} = 5{\cdot}4$, $J_{4,\mathrm{CHO}} = 0.8$); 7·64 d, 2 H (H-5); 9·86 s, 2 H (CHO).

Kishi et al.[17] have found that the rate of Pd-catalyzed coupling reactions of boronic acids can be accelerated by adding thallium(I) hydroxide, and Suzuki et al.[18] have in some cases found that thallium(I) hydroxide or carbonate has an accelerating effect in the cross-coupling of alkyl boronates with alkenyl and aryl halides. However, the addition of thallium(I) carbonate had a detrimental effect on the yield of *III*, both when boronic acids or tin derivatives were used (cf. Tables I and II).

^{1}H NMR *Spectra*

^{1}H NMR data for the thienonaphthyridines are given in Tables III and IV. The assignments of the ^{1}H NMR signals were confirmed by ^{1}H–^{13}C HETCOR spectra. The chemical shifts of the thienonaphthyridines followed principally what could be expected, from a comparison with the shifts of structurally related systems such as thieno[*c*]pyridines[19–21] and naphthyridines[22].

In the [2,3-*c*]-fused systems the protons α to the sulfur resonates at higher field than the protons β to sulfur. This has previously been observed in the isosteric thieno[2,3-*c*]quinoline[5], and is opposite to the case of thieno[2,3-*c*]pyridine[19,20]. Furthermore, the difference in chemical shift of the H(1) and H(2) protons in *I* is comparably larger than that of thienoquinoline (0·42 and 0·13 ppm). This may indicate that the nitrogen in the A-ring (see Scheme 1) is deshielding the H(1) proton. This deshielding effect by nitrogen is also found when the chemical shifts of the H(1) protons of benzo[*c*]-1,5-naphthyridine[23] and benzo[*c*]isoquinoline[24] are compared. As the nitrogen atom in the A-ring moves away from the thiophene moiety, as in *IV*–*VI*, the α protons become less deshielded. This clearly demonstrates how the distance between the nitrogen in the A-ring and the thiophene protons influences their chemical shifts.

The coupling constants in the pyridine part are in good agreement with earlier observations[22], and the characteristic long-range couplings in 1,5- and 1,6-naphthyridine, $J_{6,8} = 1{\cdot}6-1{\cdot}7$ Hz and $J_{6,9} = 0{\cdot}6-0{\cdot}8$ Hz, were also found in our systems.

The long-range couplings between the protons in the thiophene ring and the azomethine proton in the [2,3-*c*]- and [3,4-*c*]-fused systems are in the range 0·8 to 0·9 Hz. This long-range coupling is not observed in the [3,2-*c*]-fused system. The coupling constants in the thiophene part are $J_{1,2} = J_{2,3} = 5{\cdot}3$ Hz and $J_{1,3} = 2{\cdot}9-3{\cdot}1$ Hz, which are in the intervals characteristic for thiophene derivatives[25].

^{13}C NMR *Spectra*

From the results listed in Table V, it may be noted that the carbons α to the nitrogen resonates at the lowest field. At higher field follow the chemical shifts of the carbons in the thiophene ring and the carbon β to the nitrogen in the A-ring.

The chemical shifts of the carbons in the A-ring show almost the same pattern as observed for the naphthyridines[27]. In thiophene the ^{13}C chemical shifts of the α carbons are smaller than those of the β-carbons[26], while in our fused systems, the ^{13}C chemical shifts of the α-carbons are larger than those of the β-carbons. This pattern was previously observed in this laboratory[10] in the isosteric thieno[*c*]quinolines. Again (as with H(1) in the ^{1}H NMR spectra) there is a trend of less deshielding of C(1) on going from 1,5-naphthyridine to 1,6-naphthyridine.

Assignments of the carbon–proton coupling constants of the thieno[*c*]naphthyridines are given in Table VI. The one and two bond ^{1}H–^{13}C coupling constants in the A-ring were in general of the same magnitude as observed by Miyajima, and coworkers in pyridine[28]. Characteristic long-range coupling constants fall in defined intervals of $J_{6,8}$ = 6·1 – 6·3 Hz and $J_{8,6}$ = 7·8 – 8·0 Hz for *I – III*, $J_{6,9}$ = 1·2 to 1·5 Hz, $J_{7,9}$ = 12·4 – 12·8 Hz and $J_{9,7}$ = 11·4 – 11·8 Hz for *IV – VI*. The strong coupling across the nitrogen has for example also been observed in isoquinoline[29]. These long-range couplings seem to be a powerful tool for studying substitution in the A-ring.

The one bond ^{1}H–^{13}C coupling constants for C(α)H(α) and C(β)H(β) in the thiophene part fall in the intervals 185·9 – 190·8 Hz and 170·8 – 173·8 Hz. The two bond ^{1}H–^{13}C coupling constants for C(α)H(β) were 6·6 – 7·8 Hz, which were approximately 2 Hz larger than those of C(β)H(α).

Long-range couplings between the thiophene ring and the azomethine linkage were observed in both the [3,4-*c*]- and the [3,2-*c*]-fused systems. In the isosteric thienoquinolines this long-range coupling was only observed in the [3,4-*c*]-fused

TABLE V

^{13}C NMR chemical shifts (in ppm) of the thienonaphthyridines *I – VI*

Compound	C(1)	C(2)	C(3)	C(4)	C(6)	C(7)	C(8)	C(9)
I	122·7	132·1	(S)	145·8	137·4	123·2	149·9	(N)
II	119·6	(S)	125·0	149·4	136·8	123·1	148·9	(N)
III	(S)	129·4	123·7	147·2	137·8	123·5	150·1	(N)
IV	120·7	123·9	(S)	149·5	122·5	146·5	(N)	148·2
V	116·4	(S)	126·4	153·1	122·7	148·1	(N)	146·7
VI	(S)	127·4	123·9	150·7	122·8	146·7	(N)	148·0

TABLE VI

J_{CH} values (in Hz) of the thienonaphthyridines *I*–*VI*

	$^1J_{CH}$	$^2J_{CH}$	$^3J_{CH} + {}^4J_{CH}$
I	C1H1 173·8	C1H2 4·5	C6H8 6·1
	C2H2 185·9	C2H1 7·8	C8H6 7·8
	C4H4 183·3	C7H8 9·1	
	C6H6 164·3	C8H7 3·3	
	C7H7 164·3		
	C8H8 178·7		
II	C1H1 190·8	C7H8 8·7	C1H3 4·8
	C3H3 188·2	C8H7 3·2	C3H1 5·1
	C4H4 181·2	C3H4 1·3	C6H8 6·5
	C6H6 163·4	C4H3 3·0	C8H6 7·7
	C7H7 164·3		
	C8H8 178·6		
III	C2H2 186·4	C2H3 6·6	C3H4 1·3
	C3H3 170·8	C3H2 3·9	C4H3 1·2
	C4H4 180·2	C7H8 9·5	C6H8 6·3
	C6H6 164·5	C8H7 3·3	C8H6 8·0
	C7H7 164·4		
	C8H8 179·2		
IV	C1H1 171·3	C1H2 4·2	C6H9 1·2
	C2H2 186·5	C2H1 6·7	C7H9 12·8
	C4H4 183·2	C6H7 7·6	C9H7 11·4
	C6H6 164·9	C7H6 2·6	
	C7H7 179·6		
	C9H9 178·6		
V	C1H1 187·5	C6H7 8·0	C1H3 4·8
	C3H3 188·8	C7H6 2·7	C3H1 4·7
	C4H4 181·0	C3H4 1·0	C6H9 1·3
	C6H6 164·5	C4H3 2·6	C7H9 12·4
	C7H7 179·7		C9H7 11·8
	C9H9 177·4		
VI	C2H2 188·1	C2H3 6·9	C3H4 1·3
	C3H3 171·8	C3H2 4·1	C4H3 1·3
	C4H4 180·3	C6H7 7·7	C6H9 1·5
	C6H6 165·2	C7H6 2·6	C7H9 12·7
	C7H7 180·3		C9H7 11·4
	C9H9 178·7		

system. All these data seem to be a powerful tool for studying substitution in the thiophene part.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian XL-300 spectrometer. Deuteriochloroform was used as solvent for all six thienonaphthyridines, as well as for 3,3'-diformyl-2,2'-bithienyl. Hexadeuterioacetone was used as solvent for 2-bromo-3-acetamidopyridine. Sample concentrations were 10 mg/ml for the ^{1}H NMR spectra and 50 mg/ml for the ^{13}C NMR and HETCOR spectra. In the ^{1}H-coupled ^{13}C spectra, 300—450 incremented FID's were acquired over spectral widths of 2 600—3 400 Hz, each FID with 32 768 data points. The acquisition time was 4 or 5 s and the relaxation delay in the range of 4—6 s. The HETCOR experiments were carried out with 512 data points and 64 increments. The acquisition time was close to 0·1 s and the relaxation delay 1·0 s. The 2D spectral width was around 750 Hz.

The mass spectra were recorded on a Finnigan 4021 spectrometer. GLC analyses were carried out on a Varian 1400 gas chromatograph using OV-17, 3% or OV-101, 3% column. The elemental analyses were carried out by Dornis und Kolbe, Mülheim, West Germany (*I*—*III*) and by Mikrokemi, Uppsala, Sweden (*IV*—*VI*), who also made the analysis of 2-bromo-3-acetamidopyridine. All melting points are uncorrected. The thieno[*c*]-naphthyridines were all chromatographed on silica gel 60 using 100% ethyl acetate (*I*—*III*), or a mixture of chloroform and methanol (95 : 5) (*IV*—*VI*) as eluents. They were always finally purified by sublimation at approximately 30°C below their melting point and at 1—2 mm Hg. Melting points, elemental analyses and MS data for the thienonaphthyridines are given in Table VII.

2-Bromo-3-acetamidopyridine

A 100 ml two-necked flask, equipped with condenser, thermometer and magnetic stirring, was charged with 5·19 g (0·03 mol) of 2-bromo-3-aminopyridine[30] and 50 ml of freshly distilled

TABLE VII

Melting points (uncorrected) and elemental analyses[a] for some thienonaphthyridines

Compound[b]	M.p., °C	Found % C	 % H	 % N
I	73—74	64·56	3·40	15·08
II	96—98	64·55	3·23	15·20
III	99—101	64·58	3·29	15·12
IV	139—141	64·3	3·2	14·9
V	148—160	64·2	3·1	14·9
VI	144—146	64·2	3·1	15·1

[a] For $C_{10}H_6N_2S$ (186·2) calculated: 64·45% C, 3·25% H, 15·04% N. [b] Mass spectra: 187, 186 (100%, M^+), 185, 160, 159, 142, 115, 114, 93, 87, 69, 63, 50, 45, 39. The intensities of the fragments were different for *I*—*VI*.

acetic anhydride. The mixture was stirred at 100°C for a couple of minutes. After cooling the reaction mixture to room temperature, it was evaporated and the residue diluted with 300 ml of ether. The organic phase was extracted with three 300 ml portions of cold 2M sodium hydroxide solution, which was treated on ice with 300 ml of saturated sodium hydrogen carbonate and approximately 150 ml of concentrated aqueous hydrogen chloride. The aqueous phase was extracted with three 400 ml portions of dichloromethane, the combined organic phase was washed with 200 ml of water and finally dried over sodium sulfate. After removal of the dichloromethane by evaporation, the residue was recrystallized once from pentane. This gave 4·7 g (73%) of the title compound as long needles, melting at 85–87°C. ^{1}H NMR spectrum: 2·23 s, 3 H (CH_3); 7·41 q, 1 H (H-5, $J(5, 6) = 5·45$); 8·12 q, 1 H (H-6, $J(5, 6) = 5·45$); 8·45 o, 1 H (H-4, $J(4, 5) = 8·2$, $J(4, 6) = 1·8$, $J(4, NH) = 2·1$); 8·62 broad s, 1 H (NH). Mass spectrum: m/z (%) 216 (5, $M^+ + 1$); 214 (6, $M^+ - 1$); 174 (41); 172 (43); 135 (100); 93 (80); 60 (15); 43 (48). For $C_7H_7BrN_2O$ (215·1) calculated: 39·10% C, 3·28% H, 37·16% Br, 13·03% N; found: 38·9% C, 3·2% H, 37·2% Br, 12·8% N.

General Procedure for the Preparation of Thienonaphthyridines *I*, *II*, *IV* and *V* via Boronic Acids

A 100 ml three-necked flask, equipped with condenser, magnetic stirrer, thermometer and a nitrogen inlet, was charged with 0·005 mol of the appropriate pyridine derivative, 3 mole % of tetrakis(triphenylphosphine)palladium(0) (ref.[31]) and 1,2-dimethoxyethane. 1,2-Dimethoxyethane (10 ml) was used when 2-chloro-3-aminopyridine (purchased from FLUKA), 2-bromo-3-aminopyridine[30] or 3-bromo-4-aminopyridine[32] was used in the coupling reaction. With 3-bromo-4-acetamidopyridine[33], 25 ml of 1,2-dimethoxy ethane was used. After stirring for 10 min, the appropriate formylboronic acid was added (2- or 4-formyl-3-thiopheneboronic acid[34]), followed by 15 ml of aqueous solution of $NaHCO_3$ or Na_2CO_3 (1M or 1·5 M solutions when 1·1 or 1·5 equivalents of boronic acid was used, respectively). The reaction mixture was refluxed with vigorous stirring. After the starting materials were consumed, the organic phase was removed at reduced pressure. The residue was extracted with three portions of chloroform, washed with water and dried over magnesium sulfate. After evaporation, the residue was chromatographed and finally sublimated at reduced pressure.

General Procedure for the Preparation of Thienonaphthyridines in Experiments *IIIc*, *IIId* and *VIa* via 2-(Tributylstannyl)-3-thiophene Aldehyde

A 50 ml three-necked flask, equipped with condenser, magnetic stirrer, thermometer and a nitrogen inlet was charged with 0·005 mol of the appropriate pyridine derivative, 3 mole % of tetrakis(triphenylphosphine)palladium(0), 0·0055 mol of 2-(tributylstannyl)-3-thiophene aldehyde[7] and 30 ml of anhydrous dimethylformamide. The reaction mixture was stirred at 100°C until the starting materials were consumed. After cooling the reaction mixture to room temperature, the organic solvent was removed under reduced pressure. The residue was filtered through a pad of neutral alumina using ethyl acetate as eluent. The filtrate was evaporated and the residue was chromatographed and finally sublimed at reduced pressure.

General Procedure for Preparation of Thienonaphthyridines in Experiments *IIIb*, *IIId*–*IIIi*, *VIb* and *VIc* Using Silver(I) Oxide or Thallium(I) Carbonate

A 100 ml three-necked flask, equipped with condenser, magnetic stirrer, thermometer and a nitrogen inlet, was charged with 0·005 mol of the appropriate pyridine derivative, 5 mole %

of tetrakis(triphenylphosphine)palladium(0), 0·005 mol of silver(I) oxide or 0·0075 mol of thallium(I) oxide and 50 ml of anhydrous dimethylformamide. After the reaction mixture had been stirred at 100°C for 5 min, 2-(tributylstannyl)-3-thiophene aldehyde or 3-formyl-2-thiopheneboronic acid[35] in 10 ml of dimethylformamide was added. When *o*-bromoacetamidopyridines were used in the coupling reaction, 5 ml of 2M hydrogen chloride was added when the starting materials were consumed, and stirred at 100°C for one more minute. After cooling the reaction mixture to room temperature, the precipitate was filtered off and the filtrate was filtered through a pad of neutral alumina using ethyl acetate as eluent. The filtrate was evaporated, and chromatographed and finally sublimed at reduced pressure.

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