ON THE SYNTHESIS OF THIENO[*C*]-FUSED 1,5-NAPHTHYRIDINE-9-OXIDES AND 5-OXIDES

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Abstract-Three different methods have been developed for the synthesis of the six isomeric thieno[*c*]-1,5-naphthyridine-5-oxides and 9-oxides; direct oxidation of the naphthyridines with *m*-chlorobenzoic acid, Pd(0)-catalyzed coupling between formylthiopheneboronic acids or formyltrialkylstannylthiophenes and *o*-bromoamino derivatives of pyridine-*N*-oxides, and coupling between the same type of thiophene derivatives and nitropyridines. The unsymmetrical biaryls so obtained underwent a reductive cyclization when treated with ammoniacal ferrous sulphate. In the latter cases the yield in the coupling reaction was increased when copper(II) oxide was used as a co-reagent. The ^{13}C-nmr spectra of all six thieno[*c*]naphthyridines are discussed.

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 compounds with angular annelation (for review cf. ref.[1]). These types of compounds have become easily available by the Pd(0)-catalyzed coupling

reactions for instance between *o*†-aminohalothiophene derivatives and *o*-formylthiopheneboronic acids or *o*-formylthiophene tin derivatives.[2,3] Extensive experimental studies of electrophilic nitration of many of the isomeric dithienopyridines[4,5] as well as theoretical calculations[4,6] have been carried out. We have recently also expanded the Pd(0)-catalyzed coupling reactions to the syntheses of the six thieno-fused 1,5- and 1,6-naphthyridines.[7] However these compounds are very resistant to electrophilic nitration and very harsh conditions have to be used.[8] It is well known that aza-containing heterocycles are strongly activated towards aromatic nitration upon *N*-oxidation.[9] We therefore hoped that it would be possible to carry out electrophilic substitution on the isomeric *N*-oxides of these thieno-fused naphthyridines under milder conditions and to study the effect of the mode of annelation. Deoxygenation could then be used in order to prepare the substituted parent compounds.

We have previously carried out nitration[10] and bromination[11] of the six thieno analogues of phenanthridine-*N*-oxide. Furthermore, it has been shown that nucleophilic addition-elimination reactions of azine-*N*-oxides have a wide applicability in the syntheses of various derivatives.[9] In addition, we also wanted to find out if selectivity could be obtained in mono-*N*-oxidation of these systems, containing two non-equivalent pyridinic nitrogens.

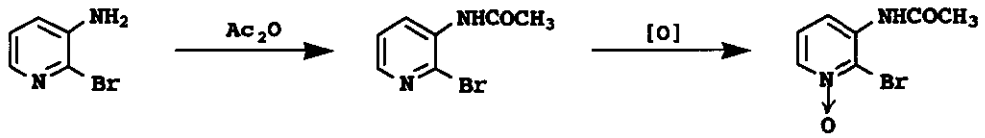
All isomeric thieno[*c*]fused quinoline-*N*-oxides and isoquinoline-*N*-oxides have previously been prepared by Pd(0)-catalyzed coupling of *o*-bromonitrobenzene with *o*-formylthiopheneboronic acids and of *o*-bromonitrothiophenes with *o*-formylbenzeneboronic acid, followed by reductive ring-closure using ferrous sulphate in aqueous ammonia.[12,13] A similar strategy was also used for the syntheses of six of the nine isomeric dithienopyridine-*N*-oxides.[14] It was therefore natural to try this approach for the syntheses of some of the target compounds.

† For convenience *ortho* is used for adjacent positions in thiophene.

RESULTS

Synthesis of 9-*N*-oxides of thieno[*c*]fused 1,5-naphthyridine.

A suitable starting material for the syntheses of thieno[2,3-*c*]-1,5-naphthyridine-9-oxide (**2**), thieno[3,4-*c*]-1,5-naphthyridine-9-oxide (**3**) and thieno[3,2-c]-1,5-naphthyridine-9-oxide (**4**) was 2-bromo-3-acetamidopyridine-*N*-oxide (**1**) which was prepared from 2-bromo-3-acetamidopyridine in excellent yield by the action of *m*-chloroperbenzoic acid. Magnesium monoperoxyphthalate hexahydrate (MMPP) has recently been considered as a more cost effective and less hazardous oxidation agent for *N*-oxidation of pyridines.[15] However, by using MMPP in our cases yields were low.



[O]: *m*-CPBA, 91%
MMPP, 43%

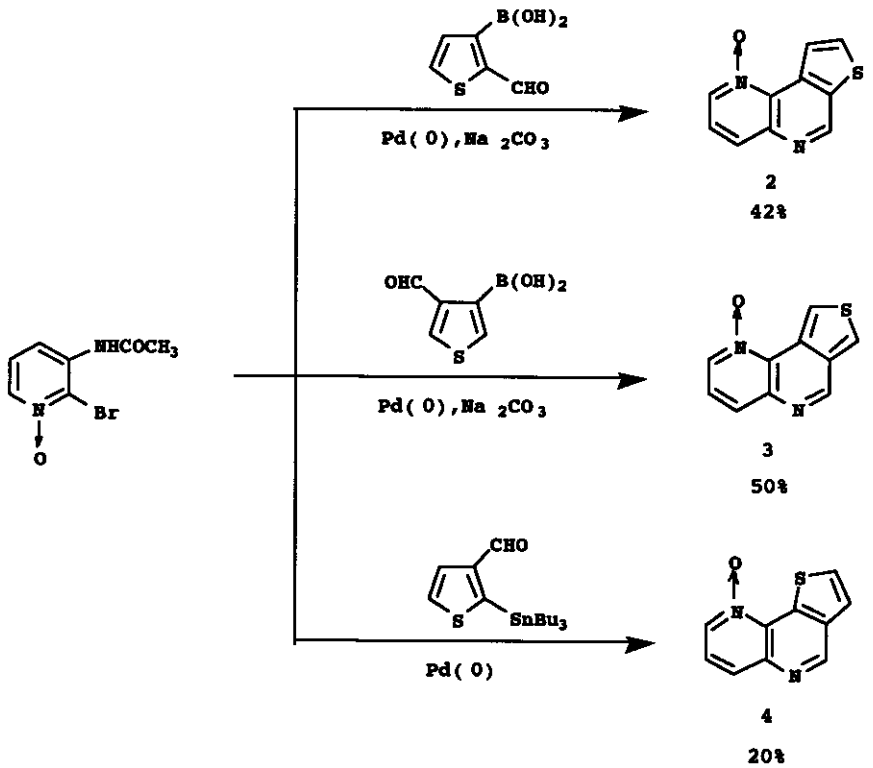
1

The Pd(0)-catalyzed coupling reaction of **1** with 2-formyl- and 4-formyl-3-thiopheneboronic acids gave **2** and **3** in 42 and 50 % yields, respectively. The Pd(0)-catalyzed coupling reaction of **1** with 2-tributylstannyl-3-thiophenecarbaldehyde gave **4** in a low yield of 20%.

We have previously found that the addition of silver(I) oxide increases the rate of the Pd(0)-catalyzed coupling of heteroaryl halides with heteroaryl stannanes (method A).[7,16] However, the synthesis of **4** by this approach failed due to the formation of 3,3´-diformyl-2,2´-bithienyl in almost quantitative yield.[17] When the tin compound was added slowly over a period of 25 min (method B) **4** was obtained in 10% yield. During the progress of this work, we discovered that copper(II) oxide can be an even better co-reagent than silver(I) oxide in the Pd(0)-catalyzed coupling.[18] By using copper(II) oxide as co-reagent, the yield of **4** could be increased to 33%. Only small amounts

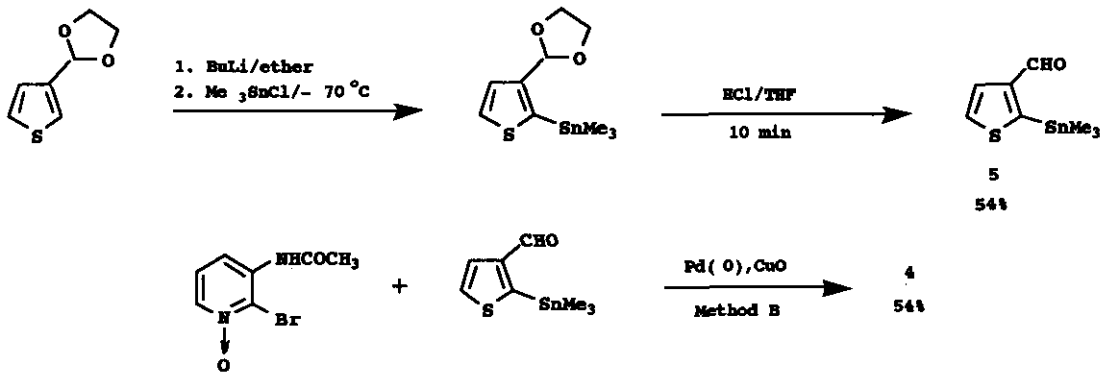
of 3,3'-diformyl-2,2´-bithienyl were formed.

Considering the possibility that the low reactivity of **1** could be caused by sterical hindrance, 2-trimethylstannyl-3-thiophenecarbaldehyde (**5**) was used in the coupling reaction. 2-Trimethylstannyl-3-thiophenecarbaldehyde was prepared by hydrolysis of 2-trimethylstannyl-3-thienyl-1,3-dioxolane with 1 N hydrochloric acid in refluxing tetrahydrofuran. A recently developed method[19] of the metalation of the α-aminoalkoxide of 3-thiophenecarbaldehyde was also attempted for a direct synthesis of **5**. However, upon reaction with trimethylstannyl chloride, 2,5-di(trimethylstannyl)-3-thiophenecarbaldehyde was obtained as the main product.



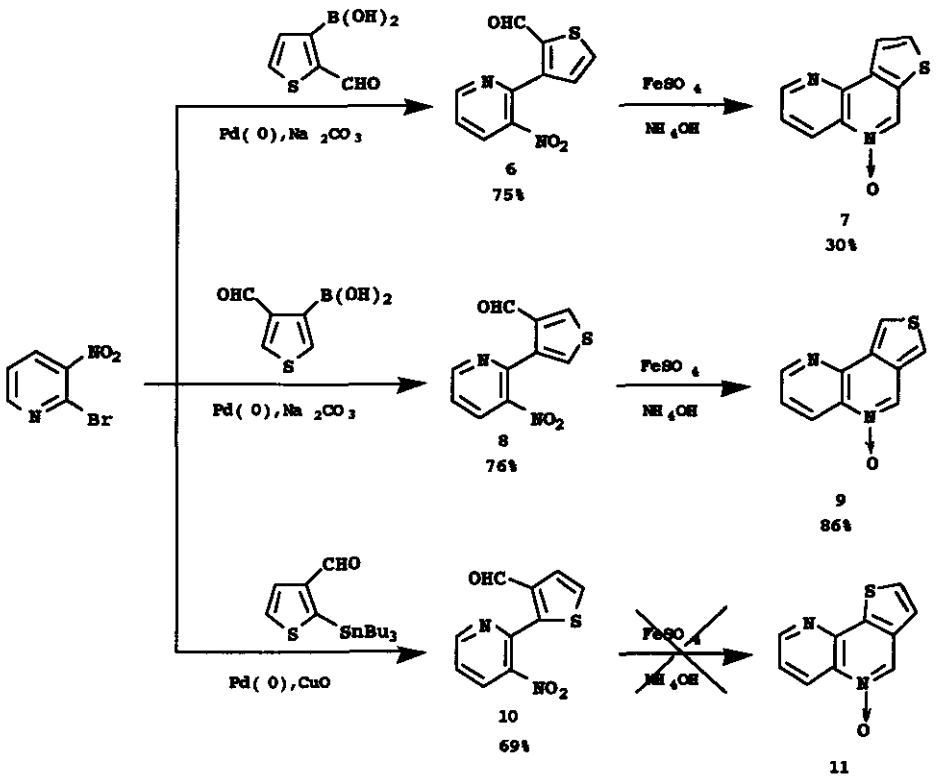
By using **5** in the coupling reaction, **4** could be obtained in 46% yield. Copper(II) oxide favoured the formation of 3,3´-diformyl-2,2´-bithienyl and lowered the yield of **4**. By using METHOD B the yield could be further raised

to 54 %.



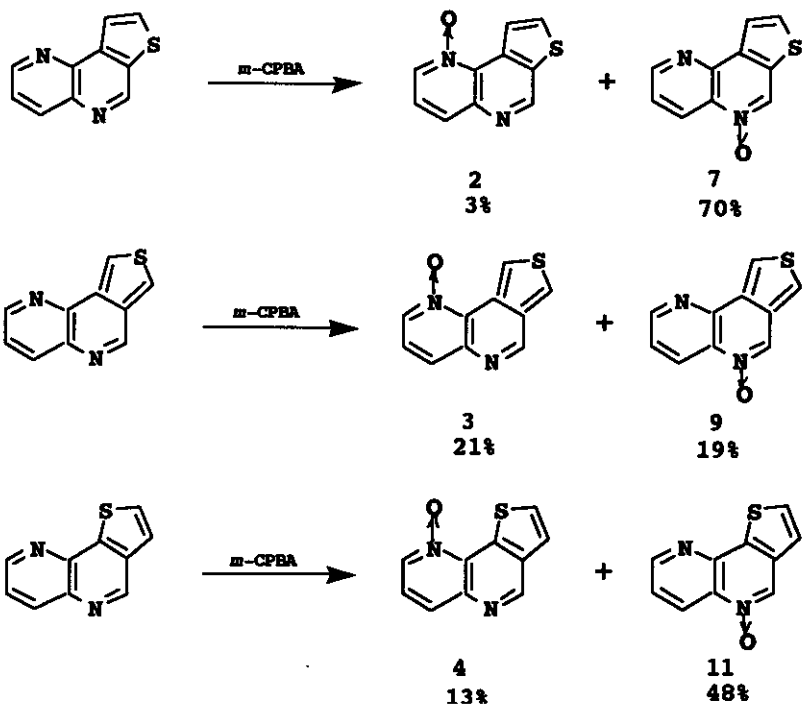
Synthesis of 5-*N*-oxides of thieno[*c*]fused 1,5-naphthyridine

The Pd(0)-catalyzed coupling reactions shown below all proceeded in good yields, giving 3-(3-nitropyridine-2-yl)-2-thiophenecarbaldehyde(**6**), 3-(3-



nitropyridin-2-yl)-4-thiophenecarbaldehyde (**8**) and 2-(3-nitropyridin-2-yl)-3-thiophenecarbaldehyde (**10**). It should be noted that **10** could be isolated in only 16% yield if the coupling reaction of 2-bromo-3-nitropyridine with 2-tri-n-butylstannyl-3-thiophenecarbaldehyde was performed without copper(II) oxide.

However, reduction of **6**, **8**, and **10** with ferrous sulphate in aqueous ammonia gave only thieno[3,4-*c*]-1,5-naphthyridine-5-oxide (**9**) in resonable yield. Upon heating, **6** and **10** decomposed rapidly.



The mode of annelation has a great effect on the reactivity of the pyridinic nitrogens. Thus thieno[2,3-*c*]-1,5-naphthyridine was almost exclusively oxidized at the 5-nitrogen, giving a convenient access to thieno[2,3-*c*]-1,5-napthyridine-5-oxide (**7**). The oxidation of thieno[3,2-*c*]-1,5-naphthyridine with *m*-CPBA gave a mixture of 9-oxide (**4**) (13 %) and 5-oxide (**11**) (48 %), which could be separated by hplc. On the other hand no selectivity was ob-

served in the oxidation of thieno[3,4-*c*]-1,5-naphthyridine which gave about equal amounts of the 9-oxide (**3**) and the 5-oxide (**9**) in low total yield. Oxidation at the sulfur was not observed under these reaction conditions.

^{13}C Nmr spectra

Unambiqous assignments of the ^{13}C nmr signals and the carbon-proton coupling constants of the thieno[*c*]naphthyridine-*N*-oxides are given in Tables 1 and 2. Assignments were confirmed by proton decoupled ^{13}C spectra, proton-coupled ^{13}C spectra and ^{1}H-^{13}C HETCOR spectra.

Characteristic chemical shift changes, compared with the parent thieno[c]-1,5-naphthyridines[7] could be observed in these systems depending on the position of the *N*-oxide. *N*-Oxidation thus leads primarily to carbon shielding of the carbon atoms α and γ to the NO group.

Table 1. ^{13}C Nmr chemical shifts (in ppm) of the thienonaphthyridine-*N*-oxides (**2-4,7,9,11**).

Compound	1C	2C	3C	4C	6C	7H	8H
2	127.4	132.3	-	147.6	127.6	122.5	137.0
3	126.8	-	125.2	151.3	126.5	122.2	137.7
4	-	132.7	122.6	149.2	127.5	121.8	135.3
7	122.8	130.6	-	131.0	129.1	123.6	151.8
9	121.7	-	121.0	130.6	129.2	123.4	151.0
11	-	131.4	122.7	132.0	129.7	123.8	152.0

The one bond ^{1}H-^{13}C coupling constants for all carbon nuclei in the pyridine rings were higher than those observed for the corresponding carbons in the parent compound, especially the α and γ carbons in **2-4** and the γ and azomethine carbons in **7,9** and **11**. Similar changes have been observed in aromatic

heterocycles upon *N*-oxidation.[20,21]

The two and three bond $^{1}H-^{13}C$ coupling constants in the terminal pyridine ring fall in defined intervals, J_{68}=6.6-6.9 Hz, J_{78}=3.9-4.0 Hz, J_{86}=8.5-8.8 Hz and J_{87}=3.8-4.2 Hz for **2-4** and J_{68}=6.0-6.3 Hz, J_{78}=8.8-9.0 Hz, J_{86}=7.8-8.0 Hz and J_{87}=3.3-3.4 Hz for **7,9** and **11**.

Table 2. J_{CH} values (Hz) of the thienonaphthyridine-N-oxides (**2-4,7,9,11**).

	C1	C2	C3	C4	C6	C7	C8
2							
$^{1}J_{CH}$	182.2	187.0		184.1	170.5	167.9	187.1
$^{2}J_{CH}$	5.2	9.3				3.9	4.2
$^{3}J_{CH}$					6.8		8.5
3							
$^{1}J_{CH}$	200.9		189.2	182.0	169.2	167.5	187.5
$^{2}J_{CH}$						4.0	4.1
$^{3}J_{CH}$	4.2		5.3, 1.3	3.1	6.9		8.5
4							
$^{1}J_{CH}$		183.7	171.9	180.8	170.3	167.8	187.5
$^{2}J_{CH}$		5.8	3.6			4.0	3.8
$^{3}J_{CH}$			1.4	3.3		6.6	8.8
7							
$^{1}J_{CH}$	175.0	187.6		187.9	172.0	167.2	180.7
$^{2}J_{CH}$	4.6	7.8				9.0	3.4
$^{3}J_{CH}$					6.3		8.0
9							
$^{1}J_{CH}$	191.8		189.1	184.6	171.5	167.2	180.5
$^{2}J_{CH}$						8.8	3.3
$^{3}J_{CH}$	5.0		5.2, 2.5		6.3		7.8
11							
$^{1}J_{CH}$		185.8	172.2	185.6	172.2	167.6	181.1
$^{2}J_{CH}$		8.1	5.0			9.0	3.3
$^{3}J_{CH}$			2.0		6.0		8.0

Long-range couplings between the thiophene ring and the azo-methine proton were observed in the [3,4-*c*] and [3,2-*c*]-fused systems. In the isosteric thienoquinolines and thienoquinoline-*N*-oxides this long-range coupling was only observed in the [3,4-*c*]-fused system.[22,13] However, J_{C4H3} could not be observed in **9** and **11**, due to line width effects for the carbons α to the *N*-oxide. This α-carbon resonance was always broader than the other lines by about 2-3 Hz. The same phenomenon has previously been observed in various mono and diaza-*N*-oxides.[20,23]

The one bond ^{1}H-^{13}C coupling constants for $C_{\alpha}H_{\alpha}$ and $C_{\beta}H_{\beta}$ in the thiophene part fall in the intervals of 187.0-200.9 Hz and 171.9-182.2 Hz, respectively. The two bond ^{1}H-^{13}C coupling constants for $C_{\alpha}H_{\beta}$ were at least always 2 Hz larger than those of $C_{\beta}H_{\alpha}$.

EXPERIMENTAL

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}H nmr spectra. Sample concentrations for the ^{13}C nmr and HETCOR spectra were 30 mg/ml. The ir spectra were taken on a Perkin-Elmer 298 spectrophotometer. The mass spectra were recorded on a Finnigan 4021 spectrometer (70 eV). High resolution mass spectra were recorded on a JEOL JMS-SX 102 spectrometer. Methane was used in the chemical ionization experiments. The elemental analyses were carried out by Dornis und Kolbe, Mülheim, Germany (**2,3,9**) and by Mikrokemi, Uppsala, Sweden (**1,11**). All melting points are uncorrected.

m-Chlorperbenzoic acid (*m*-CPBA) and magnesium monoperoxyphthalate hexahydrate (MMPP) were purchased from Merck. *N,N,N'*-Trimethylethylenediamine was purchased from Janssen Chimica. Amberlyst A-21 anion exchanger was purchased from Sigma. Diisopropylamine, dimethylformamide, n-heptane and ethyl

acetate were distilled and kept over molecular sieves prior to use. Chloroform, used in chromatography, was dried by distillation over phosphorous pentoxide. All other solvents were purchased from the manufacturer in analytical grade and used without further purification.

Preparation of 2-bromo-3-acetamidopyridine-*N*-oxide (1)

a) via *m*-CPBA.

To a stirred mixture of 4.30 g (0.02 mol) of 2-bromo-3-acetamidopyridine,[7] 3.0 g (0.025 mol) magnesium sulphate and 40 ml of chloroform, 7.92 g (0.032 mol) of *m*-CPBA was added in small portions over a period of 30 min at room temperature. After 24 h chloroform was evaporated and the residue was filtered through a pad of anion exchanger with acetonitrile as eluent. After evaporation the crude product was chromatographed on silica gel using chloroform/methanol (90:10) as eluent, giving 4.20 g (91%) of the title compound, mp 158-159°C; ir(KBr): νNH 3280,1585, νCO 1685, νNO 1240 cm^{-1}; ^1H nmr: δ 8.76 (broad s, 1H, NH), 8.19 (q, 1H, H_6), 8.02 (m, 1H, H_4), 7.34 (dd, 1H, H_5), 2.24 (s, 2H, CH_3), J_{45} = 8.5, J_{46} = 1.3, J_{56} = 6.5, J_{4NH} = 2.7 Hz. *Anal.* Calcd for $C_7H_7N_2O_2Br$: C, 36.39; H, 3.05; N, 12.12. Found: C, 36.5; H, 2.9; N, 12.0.

b) via MMPP.

To a stirred mixture of 4.30 g (0.02 mol) of 2-bromo-3-acetamidopyridine in 40 ml of glacial acetic acid, 9.92 g (0.02 mol) of MMPP was carefully added at 80-85°C. After 24 h the reaction mixture was cooled and evaporated. The residue was neutralized with 1 M sodium bicarbonate and subjected to continous extraction with chloroform. After chromatography on silica gel using cloroform/methanol (90:10) as eluent, this gave 2.0 g (43%) of a compound identical to that described in procedure a.

General procedure for the preparation of thienonaphthyridine-9-oxides (2,3) and biaryls (6,8) via boronic acids

A 100 ml three-necked flask, equipped with condenser, mechanical stirrer and a nitrogen inlet, was charged with (0.01 mol) of 2-bromo-3-acetamidopyridine-*N*-oxide or 2-bromo-3-nitropyridine,[24] 0.58 g (0.0005 mol) of tetrakis-(triphenylphosphine)palladium(0)[25] and 50 ml of 1.2-dimethoxyethane. After stirring for 10 min, 2.34 g (0.015 mol) of 2-formyl- or 1.95 g (0.0125 mol) of 4-formyl-3-thiopheneboronic acid[26] was added, followed by 30 ml of aqueous solution of sodium carbonate (1.5 M or 1.25 M, respectively). The reaction mixture was refluxed for 2 h (**2,3**) or 1 h (**6,8**) with vigorous stirring. The organic phase was evaporated and extracted several times with chloroform and finally chromatographed on silica gel.

Thieno[2,3-*c*]-1,5-naphthyridine-9-oxide (2)

Chloroform/methanol (98:2) was used as eluent and **2** was obtained in 42% as colourless needles, mp 205-207°C (heptane). ^{1}H Nmr: δ 9.42 (d, 1H, H_4), 9.28 (dd, 1H, H_1), 8.65 (dd, 1H, H_8), 8.16 (dd, 1H, H_6), 8.02 (d, 1H, H_2), 7.56 (dd, 1H, H_7), J_{12} = 5.4, J_{14} = 0.8, J_{67} = 8.6, J_{68} = 1.0, J_{78} = 6.2 Hz; ms: m/z 202 (M^+),186 (M^+-O), 174 (186-HCN), 147 (186-CHS), 121. *Anal.* Calcd for $C_{10}H_6N_2O$: C, 59.39; H, 2.99; N, 13.85. Found: C, 59.62; H, 3.10; N, 13.84.

Thieno[3,4-*c*]-1,5-naphthyridine-9-oxide (3)

Chloroform/methanol (98:2) was used as eluent and **3** was obtained in 50% yield as pale yellow needles, mp 193-196°C (heptane). ^{1}H Nmr :δ 9.72 (dd, 1H, H_1), 9.14(d, 1H, H_4), 8.57 (dd, 1H, H_8), 8.24 (d, 1H, H_3), 7.98 (dd, 1H, H_6), 7.48 (dd, 1H, H_7), J_{13} = 3.2, J_{14} = 0.8, J_{67} = 8.3, J_{68} = 0.8, J_{78} = 6.5 Hz; ms: m/z 202 (M^+),186 (M^+-O), 175 (M^+-HCN), 174 (186-HCN), 130; *Anal.* Calcd for $C_{10}H_6N_2O$: C, 59.39; H, 2.99; N, 13.85. Found: C, 59.33; H, 2.93; N,

12.75.

3-(3-Nitropyridin-2-yl)-2-thiophenecarbaldehyde (6)

Heptane/ethyl acetate (70:30) was used as eluent and **6** was obtained in 75% yield mp 116°C (decomp.). Ir (KBr): νCH 3110,3070, νCO 1645, νNO_2 1345 cm^{-1}; ^1H nmr: δ 9.90 (d, 1H ,CHO), 8.86 (dd, 1H, $H_{6'}$), 8.35 (dd, 1H, $H_{4'}$), 7.76 (dd, 1H, H_5), 7.58 (dd, 1H, $H_{5'}$), 7.18 (d, 1H, H_4), J_{CHO-5} = 1.0, J_{45} = 5.1, $J_{4'5'}$ =8.3, $J_{4'6'}$ = 1.5, $J_{5'6'}$ = 4.7; HRms calcd for $C_{10}H_5O_3N_2S$ $(M-H)^+$: 233.0020, found: 233.0023.

3-(3-Nitropyridin-2-yl)-4-thiophenecarbaldehyde (8)

Heptane/ethyl acetate (50:50) was used as eluent and **8** was obtained in 76% yield, mp 167-168°C. Ir(KBr): ν CH 3070, ν CO 1650, νNO_2 1340; ^1H nmr: δ 9.84 (d, 1H, CHO), 8.85 (dd, 1H, $H_{6'}$), 8.43 (dd, 1H, $H_{4'}$), 8.21 (d, 1H, H_5), 7.58 (dd, 1H, H_2), 7.54 (dd, 1H, $H_{5'}$), J_{CHO-2} = 0.9, J_{25} = 3.2, $J_{4'5'}$ = 8.3 $J_{4'6'}$ = 1.5, $J_{5'6'}$ = 4.8; HRms calcd for $C_{10}H_5O_3N_2S$: 233.0020, found 233.0022.

2-Trimethylstannyl-3-thiophenecarbaldehyde (5)

A reaction mixture consisting of 9.57 g (0.03 mol) of 2-(2-trimethylstannyl-3-thienyl)-1,3-dioxolane,[27] 60 ml of tetrahydrofuran and 15 ml of 1 M hydrochloric acid was refluxed for 10 min. Upon work up, 150 ml of ether was added to the reaction mixture and the organic phase was separated. The water phase was extracted three times with ether and the combined organic phases were washed with saturated sodium bicarbonate solution, and dried over sodium sulfate. After evaporation, the residue was distilled at reduced pressure(80-82°C/1 mm Hg) to give 4.48 g (54%) of the title compound as a white solid, mp 48-50°C. Ir(KBr): ν CH 2980,2920, ν CO 1665 cm^{-1}; ^1H nmr: δ 9.95 (s, 1H, CHO),7.66 (d, 1H, H_4),7.64 (d, 1H, H_5), 0.41 (m, 9H, CH_3), J_{45} = 5.8 Hz;

HRms calcd for $C_8H_{13}OSSn$ $(M+H)^+$: 276.9709, found 276.9711.

Attempted synthesis of 2-trimethylstannyl-3-thiophenecarbaldehyde (5) from 3-formylthiophene

This synthesis was performed according to the procedure in ref. 19 from 3.33 g (0.033 mol) of 3-thiophenecarbaldehyde, 4.6 ml (0.036 mol) of *N,N,N'*-trimethylethylenediamine, 0.033 mol of butyllithium, 4.7 ml (0.033 mol) of diisopropylamine, once again 0.060 mol of butyllithium and finally 5.98 g (0.030 mol) of trimethyltin chloride. After work up the reaction mixture was chromatographed on silica gel using petroleum ether/ethyl acetate (95:5) as eluent, giving 2,5-di(trimethylstannyl)-3-thiophenecarbaldehyde, 2-trimethylstannyl-3-thiophenecarbaldehyde and 5-trimethylstannyl-3-thiophenecarbaldehyde in 37%, 3% and 9% yield, respectively.

2,5-Di-(trimethylstannyl)-3-thiophenecarbaldehyde

This compound was obtained as a pale yellow liquid, bp 142-144°C/1.5 mm Hg; ir: ν CH 2910, νCO 1665; ^{1}H nmr: δ 10.00 (s, 1H, CHO), 7.75 (s, 1H, H_4), 0.41 (m, 18H, CH_3); HRms calcd for $C_{11}H_{21}OSSn_2(M+H)^+$: 440.9357, found 440.9357.

5-Trimethylstannyl-3-thiophenecarbaldehyde

This compound was obtained as a pale yellow solid, mp 42-44°C; ir(KBr): ν CH 2910, νCO 1670 cm^{-1}; ^{1}H nmr: δ 10.00 (d, 1H, CHO), 8.37 (s, 1H, H_2), 7.62 (d, 1H, H_4), 0.41 (m, 9H, CH_3), J_{24} = 0.90 Hz; HRms calcd for $C_8H_{12}OSSn$ $(M+H)^+$: 275.9631, found 275.9630.

Procedure for the preparation of thieno[3,2-*c*]-1,5-naphthyridine-9-oxide (4) and 2-(3-nitropyridin-2-yl)-3-thiophenecarbaldehyde (10) via 2-trialkylstannyl-3-thiophenecarbaldehyde

A 100 ml three-necked flask, equipped with condenser, magnetic stirrer and a

nitrogen inlet, was charged with 0.01 mol of the appropriate pyridine derivative, 0.58 g (0.0005 mol) of tetrakis(triphenylphosphine)palladium(0), 4.42 g (0.011 mol) of 2-tri-n-butylstannyl-3-thiophenecarbaldehyde[3] or 3.03 g (0.011 mol) of 2-trimethylstannyl-3-thiophenecarbaldehyde and 60 ml of dimethylformamide. The reaction mixture was stirred at 100°C until the starting materials were consumed. After cooling the reaction mixture to room temperature, it was evaporated. The residue was purified by chromatography on silica gel.

Thieno[3,2-*c*]-1,5-naphthyridine-9-oxide (4)

This compound was obtained in 20% yield after 120 min from 2-tributylstannyl-3-thiophenecarbaldehyde and in 46% yield after 60 min from 2-trimethylstannyl-3-thiophenecarbaldehyde. Chloroform/methanol (98:2) was used as eluent

giving **4**, mp 215-218°C; ^{1}H nmr: δ 9.42 (s, 1H, H_4), 8.71 (dd, 1H, H_8), 8.23 (dd, 1H, H_6), 7.91 (d, 1H, H_2), 7,78 (d, 1H, H_3), 7.60 (dd, 1H, H_7), J_{23} = 5.4, J_{67} = 8.6, J_{68} = 0.9, J_{78} = 6.3 HZ; ms: m/z 203 (M^+), 202 (M^+), 186 (M^+-O), 174 (186-O), 147 (186-CHS);HRms calcd for $C_{10}H_6N_2OS$ $(M+H)^+$: 202.0201, found 202.0200.

2-(3-Nitropyridin-2-yl)-3-thiophenecarbaldehyde (10)

This compound was obtained in 16% yield after 24 h from 2-tributylstannylthiophenecarbaldehyde, heptane/ethyl acetate (50:50) giving **10**, mp 110°C (decomp.); ir(KBr): ν CH 3100,3080, νCO 1665, νNO_2 1350 cm^{-1}; ^{1}H nmr: δ 9.82 (s, 1H, CHO), 8.89 (dd, 1H, $H_{6'}$), 8.40 (dd, 1H, $H_{4'}$), 7.62 (d, 1H, H_4), 7.56 (dd, 1H, H_5), 7.49 (d, 1H, H_5), J_{45} = 5.4, $J_{4'5'}$ = 8.0, $J_{4'6'}$ = 1.5, $J_{5'6'}$ = 4.8 Hz; HRms calcd for $C_{10}H_7O_3NS$ $(M+H)^+$: 235.0177, found 235.0179.

Procedure for the preparation of 4 and 10 using silver(I) oxide and copper(II) oxide as co-reagents.

A 100 ml three-necked flask, equipped with condenser, magnetic stirrer and a nitrogen inlet, was charged with 0.01 mol of the appropriate metal-oxide, 0.01 mol of the appropriate pyridine derivative and 0.58 g (0.0005 mol) of tetrakis(triphenylphosphine)palladium(0) in 50 ml of dimethylformamide. The reaction mixture was stirred at 100°C for 5 min, whereupon 0.011 mol of the appropriate tin compound was added all at once *(METHOD A)* or dropwise during 25 min *(METHOD B)*. The reaction mixture was stirred at 100°C until the starting materials were consumed (25 - 120 min). After cooling the reaction mixture to room temperature, the precipitate was filtered off and the filtrate was evaporated. The residue was purified by chromatography as above. The yields of **4** are discussed in the text. The coupling reaction of 2-bromo-3-nitropyridine with 2-tributylstannyl-3-thiophenecarbaldehyde in the presence of copper(II) oxide gave **10** in 69% yield after 40 min.

General procedure for the preparation of thieno[*c*]-1,5-naphthyridine-5-oxides (7,9)

These compounds were prepared according to the procedure described in ref. 12, from 1.2 g (0.005 mol) of biaryl, 13.9 g (0.05 mol) of ferrous sulfate heptahydrate in 30 ml of water, 5 drops of 2 N hydrochloric acid and 35 ml of 25% aqueous ammonia. After workup, the residue was recrystallized from acetonitrile giving 30 and 86% of **7** and **9**, respectively.

Thieno[2,3-*c*]-1,5-naphthyridine-5-oxide (7)

This compound was obtained as colourless prisms, mp 215-217°C; ^{1}H nmr: δ 9.15 (dd, 1H, H_6), 9.08 (dd, 1H, H_8), 9.03 (d, 1H, H_4), 8.22 (dd, 1H, H_1), 7.83 (d, 1H, H_2), 7.73 (dd, 1H, H_7), J_{12} = 5.3, J_{14} = 0.8, J_{67} = 8.7, J_{68} = 1.6, J_{78} = 4.3 Hz; ms: m/e 202 (M^+), 186 (M^+-O), 174 (186-HCN), 147 (186-CHS), 129;

HRms calcd for $C_{10}H_6N_2OS$: 202.0201, found 202.0201.

Thieno[3,4-*c*]-1,5-naphthyridine-5-oxide (9)

This compound was obtained as pale yellow prisms, mp 210-212°C; ^1H nmr: δ 9.02 (dd, 1H, H_6), 8.94 (dd, 1H, H_8), 8.76 (d, 1H, H_4), 8.58 (dd, 1H, H_1), 7.87 (d, 1H, H_3), 7.66 (dd, 1H, H_7), J_{13} = 3.1, J_{14} = 0.9, J_{67} = 8.5, J_{68} = 1.6, J_{78} = 4.6 Hz; ms: m/e 202 (M^+), 186 (M^+-O), 174 (186-HCN), 147 (186-CHS), 129. *Anal.* Calcd for $C_{10}H_6N_2O$: C,59.39; H,2.99; N,13.85. Found: C,59.15; H,3.04; N,13.82.

General procedure for the reaction of thienonaphthyridines with *m*-CPBA.

To a stirred mixture, consisting of 0.93 g (0.005 mol) of the appropriate thienonaphthyridine, 0.5 g of magnesium sulphate and 10 ml of chloroform, 1.36 g (0.005 mol) of *m*-CPBA was added at room temperature. After 10 min, (prolonged stirring did not improve the yields) 200 ml of chloroform were added to the reaction mixture. The phases were separated and the organic phase was washed with 50 ml of 1M sodium carbonate, 50 ml water and dried over magnesium sulphate. After evaporation the residue was subjected to chromathography on a reversed phase hplc Dynamax C_{18}-column. Acetonitrile/-water (25:75) was used as eluent for **2,3,7** and **9** and acetonitrile/water (15:85) for **4** and **11** giving **2,3,4,7,9** and **11** in 3,21,13,70,19 and 48% yields, respectively.

Thieno[2,3-*c*]-1,5-naphthyridine-5-oxide (11)

This compound was obtained as small yellow needles, mp 239-241°C (acetonitrile). ^1H Nmr: δ 9.17 (dd, 1H, H_6), 9.04 (dd, 1H, H_8), 9.00(s, 1H, H_4), 7.81 (d, 1H, H_2), 7.73 (dd, 1H, H_7), 7.43 (d, 1H, H_3), J_{23} = 5.3, J_{67} = 8.7, J_{68} = 1.6, J_{78}=4.4 Hz; ms: m/z 202 (M^+),186 (M^+-O), 174 (186-HCN), 147 (186-

CHS), 129. *Anal.* Calcd for $C_{10}H_6N_2O$: C,59.39; H,2.99; N,13.85. Found: C,59.0; H,2.9; N,13.5.

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