Substituted Dipyridylethenes and -ethynes and Key Pyridine Building Blocks

Paul-Michael Windscheif, Fritz Vögtle*

Institut für Organische Chemie und Biochemie der Universität Bonn, Gerhard-Domagk-Straße 1, D-53121 Bonn 1, Germany

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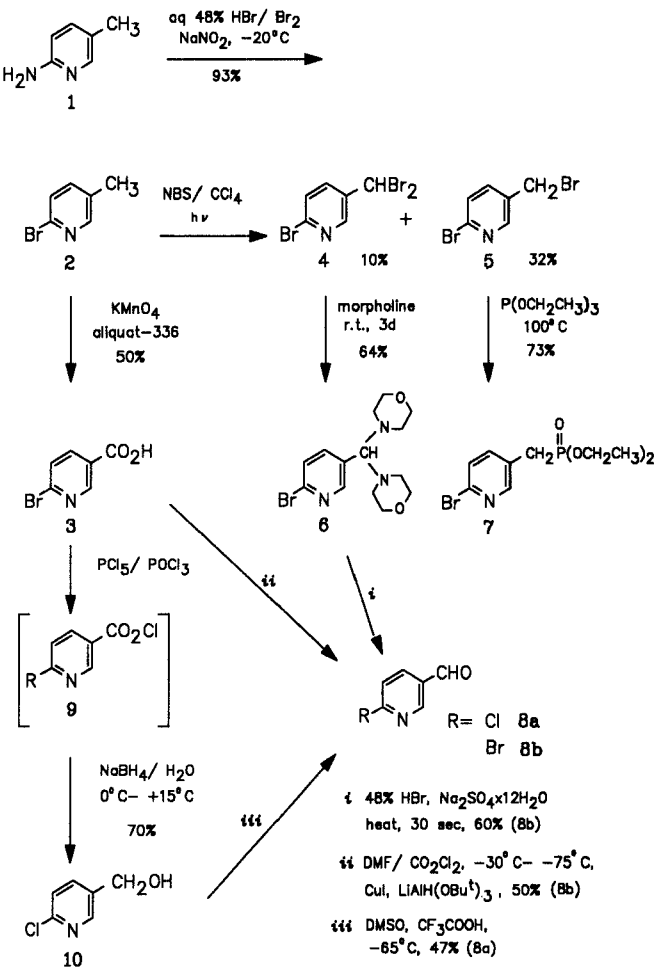
Various new 2,5-disubstituted pyridines were prepared. The 2-substituted 5-formylpyridines **8**, **15a–b** were obtained by reduction of the nicotinic acid **3**, hydrolysis of the bis(morpholino)methylpyridine **6** or the reaction of 5-bromopyridines **12** and **14** with lithium butoxide in DMF. Dipyridylethenes **16a–b,e** were synthesized by Wadsworth–Emmons reaction with pyridyl phosphonate **7** or by coupling of the aldehydes by McMurry reaction to the ethenes **16c–d**. After bromination of the C=C double bond of the dipyridylethenes **16a–d**, dipyridylacetylenes **18a–d** were obtained via elimination of the 1,2-dipyridyl-1,2-dibromoethanes **17a–d**.

Substituted pyridines have attracted considerable attention because of their many uses in heterocyclic chemistry, complex chemistry and industrial chemistry. Far less work has been reported on specifically 2,5-disubstituted pyridines compared with 2,6- and 2,4-disubstituted pyridines. Pyridine derivatives are useful precursors for pharmacological[1] compounds, for the preparation of liquid crystals,[2] the synthesis of polymers or as ligands for transition metal cations. After coupling 2-halopyridine via $Ni(COD)_2$,[3] or after oxidation of the thiomethylpyridine to pyridylsulfenyl compounds[4] and coupling with ethylmagnesium bromide it might be possible to get new poly-2,2′-bipyridine polymers. In addition 2,2′-bipyridines are of interest in supramolecular[5] chemistry or as ruthenium complexes for splitting of water[6] or intercalation in DNA.[7]

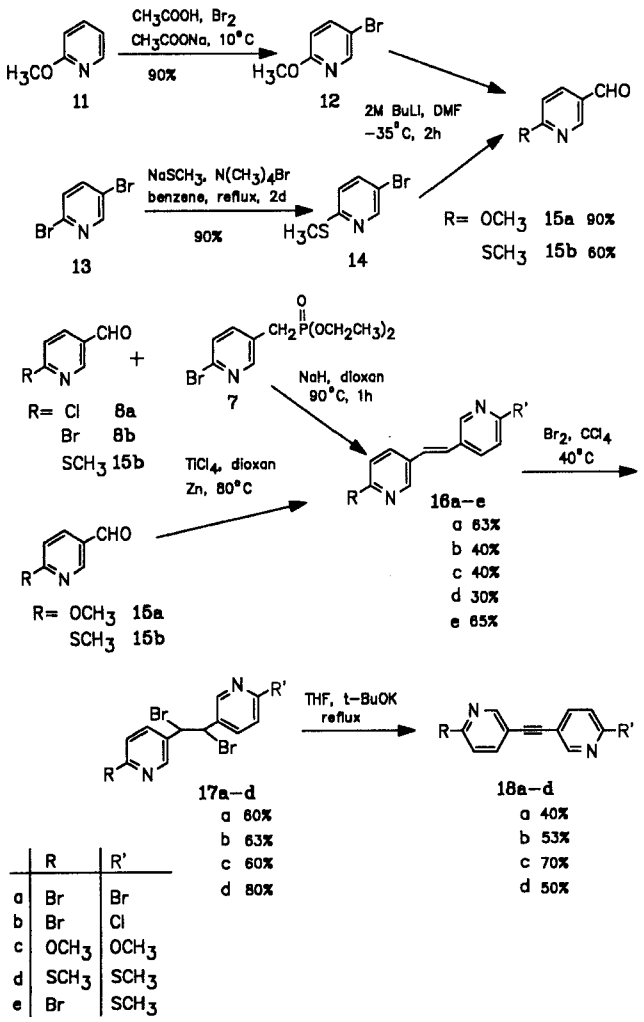
Here we report the preparation of 2,5-disubstituted pyridines which can be used as building blocks for new heterocyclic supramolecular assemblies, polymers and pharmacological active substances. We first prepared 2-bromo-5-methylpyridine (**2**) in 93% yield, compared with 43% of a previously[8] reported procedure. Special regard to the temperature is required during the reaction of 2-amino-5-methylpyridine[9] (**1**) with bromine in hydrobromic acid. The bromination of the methyl group of **2** with *N*-bromosuccinimide using a 300 Watt photo lamp gave 2-bromo-5-bromomethylpyridine (**5**) in 31% yield and 2-bromo-5-dibromomethylpyridine (**4**) in 10% yield. The purification with hydrobromic acid reported earlier[10] seems not to be optimal. Instead a chromatographic separation of the starting compound **2** and of the two brominated products **4** and **5** was necessary. Diethyl (6-bromo-3-pyridylmethyl)phosphonate (**7**) was obtained by heating the bromomethyl compound **5** in triethyl phosphite. Further purification by liquid chromatography was required (73% yield).[11] 2-Bromo-5-methylpyridine (**2**) was oxidized to 6-bromonicotinic acid[12] (**3**) in 50% yield as reported earlier.

Analogous to a method[13] described, 2-bromo-5-dibromomethylpyridine (**4**) was stirred with morpholine. The precipitate of bis(morpholino)methylpyridine **6** was isolated in 64% yield. Different methods are used to obtain the aldehydes **8a,b**, and **15a,b**. After the hydrolysis of **6** with 48% hydrobromic acid, 2-bromo-5-formylpyridine[14] (**8b**) was isolated in 60% yield. The nicotinic acid



3 was reduced with $LiAlH(OBu\text{-}t)_3$ in analogy to a previously reported procedure by Fujisawa[15] and the aldehyde **8b** was isolated after purification via liquid chromatography in 50% yield. Otherwise the bromine in the α-position of the nicotinic acid **3** was exchanged to the chlorine substituent by reaction with phosphoric chloride in phosphoryl chloride to nicotinic acid chloride **9**. Reduction with $NaBH_4$ yielded the 6-chloronicotinyl alcohol **10** in 70% yield. Therefore 6-chloronicotinaldehyde[16] (**8a**) was isolated after the Swern[17] oxidation with anhydrous DMSO and trifluoroacetic anhydride from its corresponding alcohol **10** in 47% yield. As reported earlier by Kompis,[18] 2-methoxypyridine (**11**) reacted in a modified preparation with bromine and sodium acetate in glacial acetic acid to 5-bromo-2-methoxypyridine (**12**) in 92% yield instead of 42%. Analogous to a method described by Oae,[19] 2,5-dibromopyridine (**13**) was reacted with sodium methanethiolate to give 5-bromo-2-methylsulfenylpyridine (**14**) in 90% yield. The carbaldehydes **15a** and **b** were prepared as reported for 2-methoxypyridine-5-carbaldehyde[20] **15a**. The aldehydes **15a,b** were prepared from the corresponding 5-bromopyridines **12**

and **14** with butyllithium in DMF in 90 and 60% yield, respectively. The dipyridylethenes **16a–b,e** were prepared via Wadsworth–Emmons reaction[21] in dioxane with sodium hydride (45% suspension), from pyridine phosphoric ester **7** and the corresponding aldehydes **8a–b** and **15b** in 63, 40 and 65% yield. The alternative reaction with low valent titanium[22] (McMurry reaction) was used for the formation of the double bond of the dipyridylethenes **16c,d** with the aldehydes **15a,b**. These aldehydes were added to a heated solution of titanium(IV) chloride, pyridine and zinc in dioxane and the ethenes were isolated in 40 and 30% yield, respectively. After bromination[23] of the ethenes to **17a–d** with bromine in carbon tetrachloride, elimination with potassium *tert*-butoxide followed. The di(pyridine)ethynes **18a–d** were isolated as colourless powders after chromatographic purification in 40, 53, 70, and 50% yield, respectively. The ethenes **16a–e** and ethynes **18a–d** might be useful precursors for molecular wires and π-conjugated type polymers with non linear optic (NLO), photo- and electroluminescence[24] properties or for cationic host molecules with properties of a photoswitching π-acceptor.[25]



We believe that the above paths to 2,5- or 3,6-disubstituted pyridines represent an addition to the preparation of more often documented 2,6- and 2,4-disubstituted pyridines, as reactive precursors for new developments in the various fields in which heterocyclic chemistry is required.

Mp's were determined with the microscope heating table, Reichert (AU-Wien) and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200, WM-250 and WH-90 instruments, Bruker Physik (D-Karlsruhe). E.I. mass spectra were obtained on MS-30 and MS-50 A.E.I (GB-Manchester) and GC-MS: GC on a HP 5890 (capillary column, crosslinked methylsilicone; 25 mm × 0.2 mm 0.33 μm layer of thickness; 12.5 m; no. 394-01-26-8) and MS on HP 5989 A Hewlett Packard Company (USA Palo Alto) instruments. The temperature gradient was 20 °C/min (max. 280 °C) and the parameters of the ionisation source 70 eV, 200 °C. IR spectra were registered on a Unicam SP-1100, Pye Unicam Ltd. Organic solvents were purified by standard procedures. The pyridines **1**, **11** and **13** were commercially available. Compounds **4**, **5**, **7**, **8b**, **12**, **14**, **15a,b**, **16a–d**, **17b** and **18a,c** gave C,H,N ± 0.4%.

2-Bromo-5-methylpyridine (2):[26]

Powdered 2-amino-5-methylpyridine (30.0 g, 0.277 mol) was added with vigorous stirring in portions to 48% hydrobromic acid (150 mL) at 20–30 °C. After all of the compound was dissolved, the mixture was cooled at −15 to −20 °C. To this suspension, cooled bromine (40 mL, 0.778 mol) was added dropwise over 10 min, maintaining the temperature at −20 °C. The paste became more mobile and was stirred for 90 min at this temperature. Then sodium nitrite (51.0 g, 0.739 mol) in water (75 mL) was added dropwise. After this the reaction mixture was allowed to warm to +15 °C over 1 h and was stirred for additional 45 min at the same temperature. The mixture was cooled to −15 to −20 °C and treated with cooled aq NaOH (200 g, 5 mol NaOH, in 500 mL H_2O). During the addition temperature should not rise above −10 °C. The mixture was allowed to warm to r.t. and stirred for 1 h. The aqueous layer was extracted with Et_2O and the organic phase dried with Na_2SO_4. The Et_2O extracts were evaporated under vacuum and the residue subjected to solid vacuum distillation (colourless crystals, 44.5 g, 93%) (lit. 43%), mp 41 °C.

^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 2.26 (d, 3H, CH_3, ^5J = 0.8 Hz), 7.33 (s, 1H, $H_{pyridyl}$), 7.34 (s, 1H, $H_{pyridyl}$), 8.16 (m, 1H, $H_{pyridyl}$).

^{13}C NMR (22.63 MHz, $CDCl_3$, 20 °C): δ = 17.67 (CH_3), 127.46 (CH), 132.48 (C), 138.96 (C), 139.31 (CH), 150.41 (CH).

GC-MS (retention time, 5.03 min): m/z = 173/171 (M^+, 33,33%), 92 (M^+ −Br, 92%).

2-Bromo-5-bromomethylpyridine (5):[27]

2-Bromo-5-methylpyridine (10.0 g, 0.058 mol) and powdered NBS (*N*-bromosuccinimide) (10.33 g, 0.0581 mol) were refluxed in CCl_4 (150 mL) under irradiation with a 300 Watt lamp. After 3.5 h the mixture was allowed to cool and the succinimide was filtered off, the filtrate concentrated, $CHCl_3$ (100 mL) added, the organic layer washed with saturated aq $NaHCO_3$, dried with Na_2SO_4 and concentrated to an oil. The crude product was purified by column chromatography (silica gel, 150–270 mesh ASTM; toluene/$CHCl_2$ 1:19 v/v): educt **2** (R_f = 0.439), compound **5** (R_f = 0.55), compound **4** (R_f = 0.64).

5 (4.6 g, 31.5%), mp 59 °C.

^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.44 (s, 2H, CH_2Br), 7.44 (dd, 1H, $H_{pyridyl}$, ^3J = 8.6 Hz, ^5J = 0.8 Hz), 7.57 (dd, 1H, $H_{pyridyl}$, ^3J = 8.6 Hz, ^4J = 2.9 Hz), 8.34 (dd, 1H, $H_{pyridyl}$, ^4J = 2.9 Hz, ^5J = 0.8 Hz).

^{13}C NMR (22.63 MHz, $CDCl_3$, 20 °C): δ = 28.42 (CH_2Br), 128.24 (CH), 133.06 (C), 139.15 (CH), 141.87 (CBr), 149.96 (CH).

GC-MS (retention time 7.6 min, MS-30): m/z = 249/251/253 (M^+, 5, 10, 5%), 170/172 (M^+ −Br, 100, 97%).

4 (1.9 g, 10%), mp 91 °C.

^{1}H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 6.56 (d, 1H, $CHBr_2$, ^5J = 0.7 Hz), 7.51 (ddd, 1H, $H_{pyridyl}$, ^3J = 8.4 Hz, 2 × ^5J = 0.7 Hz), 7.83 (dd, 1H, $H_{pyridyl}$, ^3J = 8.4 Hz, ^4J = 2.8 Hz), 8.41 (dd, 1H, $H_{pyridyl}$, ^4J = 2.8 Hz, ^5J = 0.7 Hz).

^{13}C NMR (22.63 MHz, $CDCl_3$, 20 °C): δ = 35.70 ($CHBr_2$), 128.60 (CH), 137.40 (C), 137.85 (CH), 143.26 (Br), 146.59 (CH).

GC-MS (retention time 8.9 min; MS-30, 70 eV): m/z = 327, 329, 331, 333 (M^+, 0.25, 1, 1, 0.25), 248/250/252 (M^+ −Br, 50/100/48).

Diethyl (6-Bromo-3-pyridylmethyl)phosphonate (7):

2-Bromo-5-bromomethylpyridine (12.0 g, 0.0479 mol) and triethyl phosphite (8.8 mL, 0.0479 mol, 8.4 g) were heated in a 50 mL flask equipped with a bridge for continuous distillation of ethyl bromide. After the mixture was cooled, the brownish oil was purified by flash column chromatography (silica gel 230–400 mesh ASTM; MeOH/AcOEt 1:20 v/v, R_f = 0.47) to give compound **7** (11 g, 73%), a liquid at 20 °C.

^1H NMR (200 MHz, $CDCl_3$, 20 °C): δ = 1.1 (t, 6H, CH_3, ^3J = 7.5 Hz), 2.95 [d, 2H, CHP, ^2J (^{31}P–^1H) = 21.5 Hz], 3.90 (dq, 4H, OCH_2, ^3J = 7.5 Hz), 7.28 (d, 1H, $H_{pyridyl}$, ^3J = 8.3 Hz), 7.40 (dt, 1H, $H_{pyridyl}$, ^3J = 8.3 Hz, ^4J = 2.5 Hz), 8.10 (t, 1H, $H_{pyridyl}$, ^4J = 2.5 Hz).

^{13}C NMR (22.63 MHz, $CDCl_3$, 20 °C): δ = 15.92 [d, CH_3, ^3J (^{13}C–^{31}P = CP) = 6 Hz], 29.76 (d, CH_2P, $^1J_{CP}$ = 139.9 Hz), 61.9 (d, OCH_2, $^2J_{CP}$ = 7 Hz), 127.16 (d, C, $^2J_{CP}$ = 8 Hz), 127.34 (d, CH, $^3J_{CP}$ = 3 Hz), 139.39 (d, CH, $^3J_{CP}$ = 5 Hz), 140.02 (d, CBr, $^5J_{CP}$ = 4 Hz), 150.36 (d, CH, $^3J_{CP}$ = 8 Hz).

IR (KBr/liquid): ν = 1030/1070 (P=O, P–O) vs, 980 (P–O) s, 1100 cm^{-1} (P=O) s.

GC–MS (retention time 8.4 min): m/z = 307, 309 (M^+, 8, 8), 280/278 (M^+ $-CH_2CH_3$, 8), 170, 171, 172, 173 [M^+ $-PO(OCH_2CH_3)_2$, 38, 40, 37, 34], 91 [M^+ $-PO(OCH_2CH_3)_2$, −Br, 100].

6-Bromonicotinic Acid (3)[28]

2-Bromo-5-methylpyridine (20.0 g, 0.116 mol) and phase transfer catalyst Aliquat-336 (0.5 mL) were heated in water (400 mL). Powdered potassium permanganate (51.0 g, 0.323 mol) was added in portions over 3 h and the mixture was heated for additional 90 min. The solid was filtered off, washed with hot water and the combined filtrates were concentrated to ca. 150 mL. This was acidified with 48% hydrobromic acid and stored for 12 h at 6 °C. The precipitate was filtered off, dried in air, recrystallized from H_2O (750 mL) and dried to give colourless plates (11.8 g, 50%) [lit. 60–69%], mp 195 °C.

^1H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 7.65 (d, 1H, $H_{pyridyl}$, ^3J = 8.4 Hz), 8.2 (dd, 1H, $H_{pyridyl}$, ^3J = 8.4 Hz, ^4J = 2.4 Hz), 9.05 (dd, 1H, $H_{pyridyl}$, ^4J = 2.4 Hz).

^{13}C NMR (69.79 MHz, DMSO, 20 °C): δ = 126.5 (CH), 128.2 (CH), 139.8 (CH), 145.8 (C), 151.3 (C), 165.7 (COOH).

GC-MS (retention time 6.8 min): m/z = 203/201 (M^+, 67/70), 156/158 (M^+ $-CO_2$, 7/7), 122 (M^+ −Br, 100), 78 (M^+ − Br, $-CO_2$, 22).

IR (KBr/solid): 1690 cm^{-1} (C=O) vs.

2-Chloro-5-hydroxymethylpyridine (10):

A mixture of **3** (5.0 g, 0.0247 mol), phosphoric chloride (5.6 g, 0.0270 mol) and phosphoryl chloride (2.8 mL, 0.0306 mol, 4.69 g) was refluxed for 90 min. After cooling, the liquid was distilled off and sodium borohydride (3.37 g, 0.09 mol in 60 mL water) was added dropwise at 0 °C, such that the temperature was not allowed to raise above 15 °C. The mixture was stirred for 2 h, saturated with NaCl and extracted with Et_2O. The organic layer was dried, the solvent removed and colourless crystals of **10** were isolated: 2.5 g (70.3%), mp 40 °C (lit. 39–40 °C).[29]

^1H NMR (90 MHz, $CDCl_3$, 20 °C): δ = 4.72 (s, 2 × 2H, CH_2), 7.33 (d, 1H, $H_{pyridyl}$, ^3J = 8.4 Hz), 7.63 (dd, 1H, $H_{pyridyl}$, ^4J = 2.6 Hz, ^3J = 8.4 Hz), 8.37 (d, 2 × 1H, $H_{pyridyl}$, ^4J = 2.6 Hz).

MS-50 (HRMS 70 eV, 180 °C, m/z): Calc. 143.0132. Found 143.0130 (M^+ 94/30), 142/144 (M^+, −H, 82/42), 114/116 (M^+ −CHO, 94/30), 78 (M^+ −Cl, $-CH_2O$, 100).

6-Chloro-3-pyridinecarbaldehyde (8a) by Oxidation of 10:

Anhydrous DMSO (2.51 g, 32.2 mmol) and CH_2Cl_2 (25 mL) were cooled to −75 °C and during a period of 15 min trifluoroacetic acid (3.7 mL, 25.4 mmol, 5.34 g) in CH_2Cl_2 (8.5 mL) was added dropwise. After 10 min, **10** (3.14 g, 21.9 mmol) dissolved in CH_2Cl_2 (8.5 mL) was added and the mixture stirred for 1 h at −60 °C. The mixture was quenched with Et_3N (6.6 mL), allowed to warm to r.t. and water (25 mL) was added. After extraction with CH_2Cl_2, the organic phase was dried and the solvent removed. The crude product was distilled in vacuum: 1.45 g (46.8%) of **8b**, mp 71 °C.

^1H NMR (90 MHz, $CDCl_3$, 20 °C): δ = 7.50 (ddd, 1H, $H_{pyridyl}$, ^3J = 8.25 Hz, ^5J = 0.75 Hz, ^4J = 2.4 Hz), 8.15 (dd, 1H, $H_{pyridyl}$, ^3J = 8.25 Hz, ^4J = 2.4 Hz), 8.89 (dd, 1H, $H_{pyridyl}$, ^4J = 2.5 Hz, ^5J = 0.75 Hz), 10.06 (d, 1H, H_{CHO}, ^4J = 2.4 Hz).

MS-50 (HRMS 70 eV, 180 °C, m/z): Calc. 140.9976. Found 140.9980 (M^+, 100%), 112/114 (M^+ −CO, 55/18), 76 (M^+ −CHO, −Cl, 14).

IR (KBr, solid): 1710 cm^{-1} (C=O) vs.

2-Bromo-5-(dimorpholinomethyl)pyridine (6):

2-Bromo-5-(dibromomethyl)pyridine (1.8 g, 0.055 mol) was stirred in morpholine (8 mL, 0.0917 mol) in an open flask at r.t. for 3 d. The mixture was poured onto ice and stirred for additional 3 h at 5 °C. Then the precipitate was collected by vacuum filtration, washed with cooled water, and dried with phosphorus pentoxide to give microcrystalline **6** (1.2 g, 63.9%), mp 115–117 °C.

^1H NMR (200 MHz, $CDCl_3$ 20 °C): δ = 2.36 (m), 2.80 (t), 3.61 (m), 7.41 (dd, 1H, $H_{pyridyl}$, ^3J = 8.2 Hz, ^4J = 2.4 Hz), 7.49 (dd, 1H, $H_{pyridyl}$, ^3J = 8.2 Hz, ^5J = 0.7 Hz), 8.17 (dd, 1H, $H_{pyridyl}$, ^4J = 2.4 Hz, ^5J = 0.7 Hz).

MS-50 (HRMS, 70 eV, 180 °C, m/z): Calc. 343.0711/341.0739. Found 343.0721/341.0740 (M^+), 342.065/340.069 (M^+ −H, 0.13/0.11), 256.988/254.986 (M^+ $-C_4H_8NO$, 100/99), 170/172 (M^+ $-2 \times C_4H_8NO$, 8/8).

6-Bromo-3-pyridinecarbaldehyde (8b):

(a) By hydrolysis of **6**:

Compound **6** (0.77 g, 0.00266 mol) was heated for 30 s in water (3 mL) and 48% hydrobromic acid (3 mL). Directly $Na_2SO_4 \cdot 12H_2O$ (4.5 g, 0.1 mol) was added and filtered. The filtrate was extracted with CH_2Cl_2, the organic layer dried and the solvent removed. The residue was purified by column chromatography (silica gel 140–270 mesh ASTM; MeOH/toluene/EtOAc/CH_2Cl_2 1:9:19:180 v/v/v/v) (R_f = 0.69); 0.25 g (60%), mp 100 °C.

(b) By reduction of **3**:

To a cooled (−20 °C) solution of anhydr. DMF (6 mL, 5.7 g, 0.078 mol) in anhydr. CH_2Cl_2 (12 mL) under an inert atmosphere, oxalyl chloride (1.88 mL, 2.78 g, 0.0219 mol) was added. After 90 min, the solvent was removed in vacuum. Then anhydr. acetonitrile (11.3 mL) and THF (23 mL) were added at −30 °C and a mixture of 6-bromonicotinic acid (1.5 g, 7.4 mmol) dissolved in THF (11.3 mL) and pyridine (0.25 mL) was added dropwise. The mixture was stirred for 90 min at −30 °C, cooled to −75 °C and a trace of copper(I) iodide and lithium tri-*tert*-butoxyaluminium hydride[30] (3.75 g, 14.7 mmol) were added. After 15 min the mixture was quenched with 7% hydrobromic acid. The mixture was allowed to warm to r.t. and extracted with Et_2O. The organic layer was washed with saturated aq $NaHCO_3$, saturated aq NaCl, dried and purified with column chromatography v.s. to give compound **8b** (0.7 g, 50.8%).

^1H NMR (90 MHz, CD_2Cl_2, 20 °C): δ = 7.65 (dt, 1H, $H_{pyridyl}$, ^3J = 8.25 Hz, ^5J = 0.5 Hz), 7.95 (dd, 1H, $H_{pyridyl}$, ^3J = 8.25 Hz, ^4J = 2.5 Hz), 8.75 (dd, 1H, $H_{pyridyl}$, ^4J = 2.5 Hz, ^5J = 0.5 Hz), 10.05 (d, 1H, H_{CHO}, ^5J = 0.5 Hz).

^{13}C NMR (62.97 MHz, $CDCl_3$, 20 °C): δ = 128.87 (CH), 130.43 (C), 137.41 (CH), 148.09 (C), 152.35 (CH), 189.41 (CHO).

GC-MS (retention time 4.1 min) m/z = 187/185 (M^+, 100/100), 156/158 (M^+ −CHO, 33/33), 106 (M^+ −Br, 23), 78 (M^+ −Br, −CHO, 56).

IR (KBr/solid): ν = 1710 cm^{-1} (C=O) vs.

(*E*)-1,2-Bis(6-bromo-3-pyridyl)ethene (16a):

To a stirred suspension of NaH (250 mg, 4.7 mmol, 60% oil dispersion) in dioxane (15 mL) and diethyl (2-bromo-5-methylpyri-

dyl)phosphonate (1.8 g, 4.7 mmol), a solution of 2-bromo-5-pyridinecarbaldehyde (1.0 g, 5.3 mmol) in dioxane (10 mL) was added dropwise. A colourless precipitate was formed immediately. The reaction mixture was heated for an additional 1 h at 90 °C and then was poured onto ice. After 1 h the residue was collected by vacuum filtration and washed with water and light petroleum (40/60) and **16a** was isolated: 1.0 g (60%), mp 265 °C.

^{1}H NMR (200 MHz, DMSO-d_6, 20 °C): δ = 7.52 (s, 2H, CH_{alken}), 7.71 (dd, 2H, $H_{pyridyl}$, ^3J = 8.3 Hz, ^5J = 0.8 Hz), 8.03 (dd, 2H, $H_{pyridyl}$, ^3J = 8.3 Hz, ^4J = 2.5 Hz), 8.58 (dd, 2H, $H_{pyridyl}$, ^4J = 2.5 Hz, ^5J = 0.8 Hz).

IR (KBr/solid): ν = 1030/1000 cm^{-1} (E- = CH_2) s.

MS-50 (70 eV, 180 °C, *m/z*): Calc. 337.9050. Found 337.9049.

GC-MS (retention time 13.4 min): *m/z* = 338/340/342 (M^+ 51/94/46), 259/261 (M^+ −Br, 14/12), 179/180 (M^+ −2Br, 76/32).

1,2-Dibromo-1,2-bis(6-bromo-3-pyridyl)ethane (17a):
A solution of (0.5 g, 3.1 mmol) bromine in CCl_4 (20 mL) was added dropwise over 2 h to a suspension of 1,2-bis(6-bromo-3-pyridyl)ethene **(16a)** (1 g, 2.9 mmol) and CCl_4 (20 mL). The mixture was stirred for an additional 2 d at 40 °C. The solvent was evaporated, the precipitate was filtered off, and washed with MeOH and dried in air to give **17a** (0.87 g, 60%), mp 229–31 °C.

^{1}H NMR (200 MHz, DMSO-d_6, 20 °C): δ = 6.37 (s, 2H, CHBr), 7.84 (dd, 2H, $H_{pyridyl}$, ^5J = 0.8 Hz, ^3J = 8.5 Hz), 8.08 (dd, 2H, $H_{pyridyl}$, ^4J = 2.5 Hz, ^3J = 8.5 Hz), 8.66 (dd, 2H, $H_{pyridyl}$, ^4J = 2.5 Hz, ^5J = 0.8).

MS-50 (HRMS 70 eV, 180 °C, *m/z*): Calc. 495.7421. Found 495.7420.

Bis(6-bromo-3-pyridyl)acetylene (18a):
Anhydr. THF (20 mL), potassium (180 mg, 4.6 mmol) and *tert*-butyl alcohol (400 mg, 5.5 mmol) were refluxed and dibromoethane (1.0 g, 2.14 mmol) was added in portions. After 45 min the brown solution was cooled and saturated aq NaCl (50 mL) was added, the organic layer was separated and dried (Na_2SO_4). The residue was chromatographed (silica gel, 140–170 mesh ASTM; MeOH/toluene/EtOAc/CH_2Cl_2 1:9:19:180 v/v/v/v; R_f = 0.81) to give **18a** (289 mg, 40%), mp 230–233 °C.

^{1}H NMR (90 MHz, CD_2Cl_2, 20 °C): δ = 7.50 (dd, 2H, $H_{pyridyl}$, ^3J = 8.5 Hz, ^5J = 0.8 Hz), 7.69 (dd, 2H, $H_{pyridyl}$, ^3J = 8.5 Hz, ^4J = 2.3 Hz), 8.50 (dd, 2H, $H_{pyridyl}$, ^4J = 2.3 Hz, ^5J = 0.8 Hz).

GC-MS (retention time 10.7 min, MS-50; HRMS, 70 eV, 180 °C, m/z): Calc. 335.8890 Found 335.8890.

(*E*)-1-(6-Bromo-3-pyridyl)-2-(chloro-3-pyridyl)ethene (16b):
This was prepared by a method analogous to that used for **16a**. Thus, from **8a** (1.0 g, 7.06 mmol) and **7** (2.2 g, 7.3 mmol) crystalline product **16b** was isolated: 0.65 g (63%), mp 250 °C (DMSO).

^{1}H NMR (200 MHz, DMSO, 20 °C): δ = 7.46 (s, 2H, CH=CH), 7.56 (d, 1H, $H_{pyridyl}$, ^3J = 8.5 Hz), 7.69 (d, 1H, $H_{pyridyl}$, ^3J = 8.5 Hz), 8.02 (dd, 1H, $H_{pyridyl}$, ^3J = 8.5 Hz, ^4J = 2.5 Hz), 8.13 (dd, 1H, $H_{pyridyl}$, ^3J = 8.5 Hz, ^4J = 2.5 Hz), 8.57 (d, 1H, $H_{pyridyl}$, ^4J = 2.5 Hz), 8.60 (d, 1H, $H_{pyridyl}$, ^4J = 2.5 Hz).

MS-30 (70 eV, 180 °C): *m/z* = 294/296/298 (M^+ 82%/100/30), 259/261 (M^+ −Cl, 6/4), 215 (M^+ −Cl, −Br, 15).

IR (KBr/solid): 1095 cm^{-1} (E- = CH_2).

1,2-Dibromo-1-(6-bromo-3-pyridyl)-2-(6-chloro-3-pyridyl)ethane (17b):
This compound was prepared by a method analogous to that used for **17a**. Thus, from the ethene **16b** (1.8 g, 8.1 mmol), colourless crystals of **17b** (2.2 g, 71.4%) were isolated, mp 225–226 °C.

^{1}H NMR (200 MHz, DMSO, 20 °C): δ = 6.38 (s, 2H, CHBr), 7.70 (dd, 1H, $H_{pyridyl}$, ^5J = 0.8 Hz, ^3J = 8.0 Hz), 7.84 (dd, 1H, $H_{pyridyl}$, ^5J = 0.8 Hz, ^3J = 8.0 Hz), 8.08 (dd, 1H, $H_{pyridyl}$, ^4J = 2.4 Hz, ^3J = 8.0 Hz), 8.19 (dd, 1H, $H_{pyridyl}$, ^4J = 2.4, ^3J = 8.0 Hz), 8.66 (dd, 1H, $H_{pyridyl}$, ^4J = 2.4 Hz, ^5J = 0.8 Hz), 8.68 (dd, 1H, $H_{pyridyl}$, ^4J = 2.4 Hz, ^5j = 0.8 Hz).

MS-30 (70 eV, 180 °C): *m/z* = 452/454/456/458 (M^+ 0.2%/1.2/1.5/0.5), 419/421 (M^+ −Cl, 0.1/0.2), 373/375/377/379 (M^+ −Br, 15/30/25/4), 294/296/298 (M^+ $-Br_2$, 92/100/60), 215/217 (M^+ $-Br_3$, 25/8), 180/179 (M^+ $-Br_3Cl$/ $-Br_3ClH$, 15/45).

1-(2-Bromo-5-pyridyl)-2-(2-chloro-5-pyridyl)acetylene (18b):
This was prepared by a method analogous to that used for **18a**. Thus, from bispyridylethane **17b** (270 mg, 0.59 mmol), **18b** (92 mg, 53.2 was isolated as a colourless powder; R_f = 0.81, mp 212–213 °C (cyclohexane).

^{1}H NMR (200 MHz, CD_2Cl_2, 20 °C): δ = 7.35 (dd, 1H, $H_{pyridyl}$, ^5J = 0.75 Hz, ^3J = 8.25 Hz), 7.5 (dd, 1H, $H_{pyridyl}$, ^5J = 0.75 Hz, ^3J = 8.25 Hz), 7.77 (dd, 1H, $H_{pyridyl}$, ^4J = 2.5 Hz, ^3J = 8.25 Hz), 7.78 (dd, 1H, $H_{pyridyl}$, ^4J = 2.5 Hz, ^3J = 8.25 Hz), 8.49 (dd, 1H, $H_{pyridyl}$, ^4J = 2.5 Hz, ^5J = 0.75 Hz), 8.52 (dd, 1H, $H_{pyridyl}$, ^4J = 2.5 Hz, ^5J = 0.75 Hz).

MS-50 (HRMS 70 eV, 180 °C, m/z): Calc. 291.9398, Found 291.9400 (M^+, 78%), 213/217 (M^+ −Br, 80/25), 178/177 (M^+ −BrCl/ −BrClH, 40/10).

5-Bromo-2-methoxypyridine (12):[31]
A cooled solution of bromine (44.2 mL, 138.7 g, 0.867 mol) in glacial acetic acid (150 mL) was dropped with vigorous stirring into a suspension of 2-methoxypyridine (90.0 g, 0.82 mol) and sodium acetate (70.0 g, 0.85 mol) in AcOH (250 mL) at 10 °C. The reaction was stirred for 12 h at r.t. Then it was concentrated to 1/3 of its volume and poured onto broken ice (800 mL). 5 M aq NaOH was added at 10 °C until the mixture reached alkaline. After extraction with Et_2O the organic phase was dried (Na_2SO_4) and the oil distilled to give **12** 140 g, 90%) (lit., 41%), at 20 °C (bp 69 °C/0.1 Torr).

^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 3.8 (s, 3H, OCH_3), 6.52 (d, 2H, ^3J = 8.7 Hz), 7.5 (dd, 2H, ^3J = 8.7 Hz, ^4J = 2.6 Hz).

^{13}C NMR (90 MHz, $CDCl_3$, 20 °C): δ = 162.87 (C), 147.4 (CH), 140.8 (CH), 112.5 (CH), 111.6 (C), 53.5 (CH_3).

GC-MS (retention time 4.9 min): *m/z* = 186/188/187/189 [M^+ (+H), 50%/48/35/33], 157/158/159/160 (M^+ $-OCH_3$, 24/24/25), 78 (M^+ $-OCH_3$, −Br, 100).

6-Methoxy-3-pyridinecarbaldehyde (15a):[32]
5-Bromo-2-methoxypyridine (69.0 g, 0.37 mol) in anhydr. Et_2O (500 mL) was stirred under an inert atmosphere at −35 °C. BuLi (2 M; 210 mL in hexane) was dropped into the solution. At the same temperature anhydr. DMF (59 mL, dried over anhydr. $CuSO_4$ and molecular sieve 3Å and distilled) was added and the mixture was allowed to warm to 0 °C over 2 h. Then the mixture was quenched with 5% aq NH_4Cl (200 mL). The aqueous phase was separated and extracted with CH_2Cl_2, the organic phases were dried and the solvent was removed at 30 °C/20 Torr. The residue was distilled in vacuum and 45 g (90%, analogous lit.) of **15a** was obtained; mp 47 °C.

^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 9.9 (s, 1H, CHO), 8.6 (d, 1H, $H_{pyridyl}$, ^4J = 2.3 Hz), 8.03 (dd, 1H, $H_{pyridyl}$, ^3J = 8.7 Hz, ^4J = 2.3 Hz), 6.8 (d, 1H, $H_{pyridyl}$, ^3J = 2.3 Hz), 4.0 (s, 3H, CH_3).

^{13}C NMR (62.97 MHz, $CDCl_3$, 20 °C): δ = 189.5 (CH), 167.7 (C), 152.9 (CH), 137.4 (CH), 126.7 (C), 112.1 (CH), 54.3 (CH_3).

IR (KBr, solid): ν = 1710 cm^{-1} (C=O) s.

GC–MS (retention time 5.16 min): *m/z* = 137/136 (M^+/M^+ −H, 100%/99), 108 (M^+ −CHO, 40) 107 (M^+ $-OCH_3$, +H, 63), 78 (M^+ −CHO, $-OCH_3$, 43).

1,2-Bis(2-methoxy-5-pyridyl)ethene (16c):
Under an inert atmosphere, titanium(IV) chloride (0.97 mL, 1.68 g, 8.9 mmol) and pyridine (1.5 mL) were stirred in dioxane (150 mL) at r.t. After 10 min zinc (0.58 g, 8.9 mmol) was added; the colour of the solution changed from yellow to green, and the solution was then heated for 2 h at 80 °C. Methoxypyridinecarbaldehyde **15a** (0.4 g, 2.96 mmol) solved in dioxane (3 mL) was dripped into the mixture and refluxed for 12 h at 80 °C. The solution was poured into a beaker, cooled to −14 °C, under vigorous stirring quenched with saturated aq Na_2CO_3 and stirred for additional 1 h. The mixture was extracted with Et_2O, the organic layers were dried and the solvent was removed under reduced pressure. Further purification by column chromatography (silica gel 140–270 mesh ASTM;

MeOH/EtOAc/CH_2Cl_2, 1:9:19:180 v/v/v/v; R_f = 0.38) gave **16c** (142 mg, 40%), mp 165°C.

^{1}H NMR (250 MHz, $CDCl_3$, 20°C): δ = 8.18 (d, 2H, Pyridyl-H, ^4J = 2.2 Hz), 7.77 (dd, 2H, $H_{pyridyl}$, ^3J = 8.4 Hz, ^4J = 2.2 Hz), 6.90 (s, 2H, C=C-H), 6.75 (d, 2H, $H_{pyridyl}$, ^3J = 8.4 Hz), 3.95 (s, 6H, OCH_3).

^{13}C NMR (62.97 MHz, $CDCl_3$, 20°C): δ = 163.73 (C), 145.81 (CH), 135.26 (CH), 126.53 (C), 124.12 (CH), 111.2 (CH), 53.65 (CH_3).

1,2-Dibromo-1,2-bis(6-methoxy-3-pyridyl)ethane (17c):
This compound was prepared by a method analogous to that used for **17a**. Thus, from ethene **16c** (500 mg, 2.06 mmol) crystalline **17c** (496 mg, 60%) was isolated, mp 185°C.

^{1}H NMR (250 MHz, DMSO-d_6, 20°C): δ = 8.40 (d, 2H, $H_{pyridyl}$, ^4J = 2.2 Hz), 8.05 (dd, 2H, $H_{pyridyl}$, ^3J = 8.4 Hz, ^4J = 2.2 Hz), 6.95 (d, 2H, $H_{pyridyl}$, ^3J = 8.4 Hz), 6.3 (s, 2H, CHBr), 3.95 (s, 6H, OCH_3).

MS-50 (HRMS 70 eV, 180°C, m/z): Calc 399.9422. Found 399.9436; (M^+), 320/321/322/323/324 (M^+ −Br, 1%/32/5/31/4), 241/242/243/244 (M^+ −2Br, 35/100/33/5).

1,2-Bis(6-methoxy-3-pyridyl)ethyne (18c):
This compound was prepared by a method analogous to that used for **18a**. Thus, from bispyridylethane **17c** (0.8 g, 1.99 mmol), **18c** was isolated: yield 410 mg (70%) (R_f = 0.72), mp 110°C (cyclohexane).

^{1}H NMR (250 MHz, $CDCl_3$, 20°C): δ = 8.3 (d, 2H, $H_{pyridyl}$, ^4J = 2.3 Hz), 7.65 (dd, 2H, $H_{pyridyl}$, ^3J = 8.3 Hz, ^4J = 2.3 Hz), 6.7 (d, 2H, $H_{pyridyl}$, ^3J = 8.3 Hz), 3.9 (s, 6H, OCH_3).

^{13}C NMR (62.97 MHz, $CDCl_3$, 20°C): δ = 163.36 (C), 149.92 (CH), 140.99 (CH), 112.87 (C), 110.68 (CH), 87.49 (C), 53.64 (OCH_3).

GC-MS (retention time 11.4 min): m/z = 240 (M^+ 100%), 211 ($M^+ - 2 \times CH_3 + H$, 34), 179 ($M^+ - 2 \times OCH_3$, 4).

MS-50 (HRMS 70 eV, 180°C, m/z): Calc. 240.0898. Found 240.0895.

3-Bromo-6-methylthiopyridine (14):
2,5-Dibromopyridine **(13)** (1.0 g, 0.42 mol), sodium methanethiolate (4.0 g, 0.057 mol, as 15% aqueous solution) and *N*-tetrabutylammonium bromide (0.5, 1.6 mmol) were refluxed for 2 d in benzene (20 mL). The organic layer was separated and the aqueous layer extracted with CH_2Cl_2. The organic layers were dried, evaporated and the remaining oil vacuum distilled: yield 8.6 g (90%) colourless solid, mp 42°C.

^{1}H NMR (250 MHz, $CDCl_3$, 20°C): δ = 8.45 (d, 1H, $H_{pyridyl}$, ^4J = 2.3 Hz), 7.55 (dd, 1H, $H_{pyridyl}$, ^3J = 8.6 Hz, ^4J = 2.3 Hz), 7.05 (d, 1H, $H_{pyridyl}$, ^3J = 8.6 Hz), 2.5 (s, 1H, CH_3).

^{13}C NMR (22.67 MHz, $CDCl_3$, 20°C): δ = 158.73 (C), 150.22 (CH), 138.24 (CH), 122.64 (CH), 115.74 (C).

GC-MS (retention time 6.8 min): m/z = 203/205 (M^+, 51%/45), 157/159 ($M^+ - SCH_3$, 25/23), 78 ($M^+ - SCH_3$, −Br, 100).

6-Methylthio-3-pyridinecarbaldehyde (15b):
This compound was prepared by a method analogous to that used for **16c**. Thus, from 3-bromo-6-methylthiopyridine **(14)** (2.0 g, 0.0146 mol) colourless crystals of **15b** (1.34 g, 60%) were isolated, mp 41°C.

^{1}H NMR (250 MHz, $CDCl_3$, 20°C): δ = 9.95 (s, 1H, CHO), 8.8 (s, 81H, $H_{pyridyl}$), 7.9 (dd, 1H, $H_{pyridyl}$, ^3J = 2.2 Hz, ^4J = 8.4 Hz), 7.25 (d, 1H, $H_{pyridyl}$, ^3J = 8.4 Hz), 2.6 (s, 3H, SCH_3).

^{13}C NMR (62.97 MHz, $CDCl_3$, 20°C): δ = 190.0 (CHO), 167.78 (C), 152.59 (CH), 134.18 (CH), 127.70 (C), 121.61 (CH).

IR (KBr/solid): 1710 cm^{-1} (C=O) vs.

GC-MS (retention time 6.98 min): m/z = 153/152 (M^+/M^+ −H, 100, 57), 138 ($M^+ - CH_3$, 1), 124 (M^+ −CHO, 7), 107 ($M^+ - SCH_3$, +H, 52), 78 ($M^+ - SCH_3$, −CHO, +H, 34).

(*E*)-1,2-Bis(6-methylthio-3-pyridyl)ethene (16d):
This compound was prepared by a method analogous to that used for **16c**. Thus, from 6-methylthiopyridine-3-carbaldehyde **(15b)** (1.0 g, 6.5 mmol), microcrystalline **16d** (260 mg, 30%) was isolated: R_f = 0.3, mp 171°C.

^{1}H NMR (250 MHz, $CDCl_3$, 20°C): δ = 2.6 (s, 6H, $-SCH_3$), 7.0 (s, 2H, HC=C), 7.17 (d, 2H, $H_{pyridyl}$, ^3J = 8.4 Hz), 7.67 (dd, 2H, $H_{pyridyl}$, ^3J = 8.4 Hz, ^4J = 2.2 Hz), 8.5 (d, 2H, $H_{pyridyl}$, ^4J = 2.2 Hz).

^{13}C NMR (62.97 MHz, $CDCl_3$, 20°C): δ = 13.46 (CH_3), 121.44 (CH), 125.37 (CH), 128.44 (C), 132.38 (CH), 148.36 (CH), 159.41 (C).

GC-MS (retention time 14.5 min): m/z = 274 (M^+, 100%), 259 ($M^+ - CH_3$, 50%), 227 ($M^+ - SCH_3$, 8).

1,2-Dibromo-1,2-bis(6-methylthio-3-pyridyl)ethane (17d):
This compound was prepared by a method analogous to that used for **17a**. Thus, from ethene **16d** (200 mg, 0.73 mmol), **17d** (269 mg, 85%) was isolated, mp 251°C.

^{1}H NMR (250 MHz, DMSO-d_6, 20°C): δ = 2.55 (s, 6H, $-SCH_3$), 6.35 (s, 2H, CHBr), 7.45 (d, 2H, $H_{pyridyl}$, ^3J = 8.4 Hz), 8.0 (dd, 2H, $H_{pyridyl}$, ^3J = 8.4 Hz, ^4J = 2.2 Hz), 8.7 (d, 2H, $H_{pyridyl}$, ^4J = 2.2 Hz).

MS-50 (HRMS, 70 eV, 180°C, m/z): Calc. 431.8964. Found 431.8964 (M^+), 355/353 (M^+ −Br, 10/10), 273/274/275/276 ($M^+ - {}^2Br$, 25/100/50/30).

1,2-Bis(6-methylthio-3-pyridyl)ethyne (18d):
This compound was prepared by a method analogous to that used for **18a**. Thus, from bispyridylethane **17d** (250 mg, 0.57 mmol (microcrystalline **18d** (78 mg, 50%) was isolated (R_f = 0.7), mp 148–149°C.

^{1}H NMR (250 MHz, $CDCl_3$, 20°C): δ = 8.55 (d, 2H, $H_{pyridyl}$, ^4J = 2.3 Hz), 7.55 (dd, 2H, $H_{pyridyl}$, ^3J = 8.3 Hz, ^4J = 2.3 Hz), 7.15 (d, 2H, $H_{pyridyl}$, ^3J = 8.3 Hz), 2.55 (s, 6H, SCH_3).

^{13}C NMR (62.97 MHz, $CDCl_3$, 20°C): δ = 160.2 (C), 151.9 (CH), 138.0 (CH), 120.9 (CH), 115.2 (C), 89.0 (C), 13.4 (SCH_3).

GC-MS (retention time 13.9 min): m/z = 272 (M^+, 100%); 226 ($M^+ - SCH_2$, 6), 180 ($M^+ - 2 \times SCH_3$, 3).

MS-50 (HRMS 70 eV, 180°C, m/z): Calc. 272.0442. Found 272.0442.

(*E*)-1-(6-Bromo-3-pyridyl)-2-(6-methylthio-3-pyridyl)ethene (16e):
This compound was prepared by a method analogous to that used for **16a**. Thus, from 6-methylthiopyridine-3-carbaldehyde **(15b)** (250 mg, 2.1 mmol) and **7** (600 mg, 1.95 mmol), **16e** (0.64 g, 65%) was isolated, mp 140–141°C.

^{1}H NMR (250 MHz, $CDCl_3$, 20°C): δ = 2.59 (s, 3H, SCH_3), 7.35 (d, 2H, HC=CH, ^3J_E = 10.38 Hz), 7.5 (d, 1H, $H_{pyridyl}$, ^3J = 8.4 Hz), 7.57 (s, 1H, $H_{pyridyl}$), 7.8 (d, 1H, $H_{pyridyl}$, ^3J = 8.3 Hz), 8.05 (m, 1H, $H_{pyridyl}$), 8.75 (d, 1H, $H_{pyridyl}$, ^4J = 2.4 Hz), 8.85 (d, 1H, $H_{pyridyl}$, ^4J = 2.2 Hz).

^{13}C NMR (62.97 MHz, $CDCl_3$, 20°C): δ = 148.56 (CH), 148.45 (CH), 134.94 (CH), 132.39 (CH), 128.05 (CH), 127.69 (CH), 123.95 (CH), 121.40 (CH), 13.33 (SCH_3); C_q not resolved.

GC-MS (retention time 13.9 min): m/z = 308, 306 (M^+ 100%, 70), 261, 263 ($M^+ - SCH_3$), 20, 15).

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^{1}H NMR (90 MHz, $CDCl_3$): δ = 5.8 [d, 2H, CH_2, ^2J (^{1}H-^{31}P) = 16 Hz], 7.15 (d, 1H, $H_{pyridyl}$, ^3J = 8.5 Hz), 7.4–8.0 (m, 17H, H_{aryl}).
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