Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 5039–5045

TETRAHEDRON

Synthesis of 4-functionalized terdendate pyridine-based ligands

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Received 31 October 2002; revised 24 April 2003; accepted 8 May 2003

Abstract—Four different 4-functionalised pyridine-based ligands were synthesized with aminomethyl, oxazolinyl, pyrazolyl and methylimidazolyl groups at the 2- and 6-position. The nitrogens of these groups together with the pyridine nitrogen can act as terdendate ligands for metal ions. Synthetic handles on the 4-position of the pyridine group were introduced via ether or ester bonds leading to monofunctional, bifunctional and amphiphilic ligands. © 2003 Published by Elsevier Science Ltd.

1. Introduction

Terdendate N-heterocyclic ligands have been used over the last century as effective and stable complexing agents for transition metal ions. These ligand-metal ion complexes have been used to build supramolecular coordination polymers,[1–4] dendrimers[5] or ordered architectures on surfaces[6] leading to new materials with interesting catalytic, photochemical and redox properties.[7] In the last decade the most used terdendate ligands for supramolecular systems were based on terpyridine groups.[2,4,8]

In this paper we describe the synthesis of four pyridine-based ligands with different nitrogen containing groups at the 2- and 6-positions and a functional group at the 4-position; these ligands can be seen as analogues of terpyridines. The aminomethyl, oxazolinyl, pyrazolyl and methylimidazolyl groups were introduced to yield planar terdendate ligands. These groups have been reported in literature to form stable complexes with metal ions. Bisaminomethylpyridine forms stable complexes with for example Cd^{2+}, Ni^{2+}, and Zn^{2+}.[9] Chiral derivatives of bisoxazolinylpyridines complexed with Rh^{3+} can act as catalysts for the reduction of ketones.[10] Ruthenium complexed bis(*N*-pyrazolyl)pyridine ligands described by Jameson et al. are both structural and redox analogues of terpyridine complexes.[11] Metal complexed methylimidazolyl groups have not often been reported, but structurally related benzimidazolyl ligands have been reported to form complexes with Ru^{2+} and Eu^{3+} with interesting redox and luminescent properties.[12–14]

The various chelating groups have a different preference for metal ions that they are able to coordinate. This is, amongst others, due to the fact that the chelating groups have different distances between the nitrogens of the groups at the 2- and 6-position: 4.12, 4.95, 4.81 and 4.59 Å for the aminomethyl, oxazolinyl, pyrazolinyl and methylimidazolyl pyridines respectively as seen from molecular modeling. For terpyridines this distance is 4.66 Å. The groups have different pK_a-values, which also influences the binding properties of metal ions.

The syntheses of 4-substituted pyridine ligands have been much less explored than ones that are not substituted at the 4-position. However, some 4-substituted terpyridines have been reported.[15] To use these kinds of ligands in supramolecular chemistry a synthetic handle opposite to the complexing site of the molecule is necessary to build in additional properties. The present work was aimed at the synthesis of bifunctional ligands suitable for building linear reversible coordination polymers. To obtain long coordination polymers, high complexation constants between metal ions and ligands are required. For that reason terdendate ligands were chosen that are also the most appropriate for complexing hexacoordinating metal ions.

The chelating moieties were prepared with a synthetic handle at the 4-position of the pyridine via ether or ester bonds, which makes these compounds useful as building blocks for supramolecular structures. The synthetic methods described here were used to obtain bifunctional, monofunctional and amphiphilic monofunctional ligands. Scheme 1 shows the general structure of the synthesized bifunctional ligands. The amphiphilic ligands can be used to provide micelles or bilayer structures with metal-ion coordinating groups, which can find application in catalysis, separation[16] or supramolecular chemistry.

Keywords: terdendate; ligand; coordination; supramolecular; surfactant.
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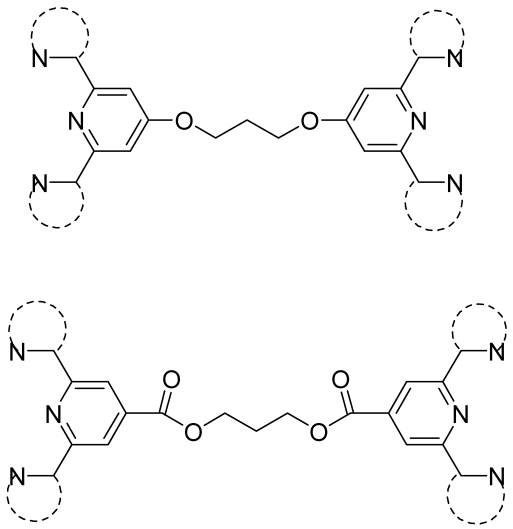
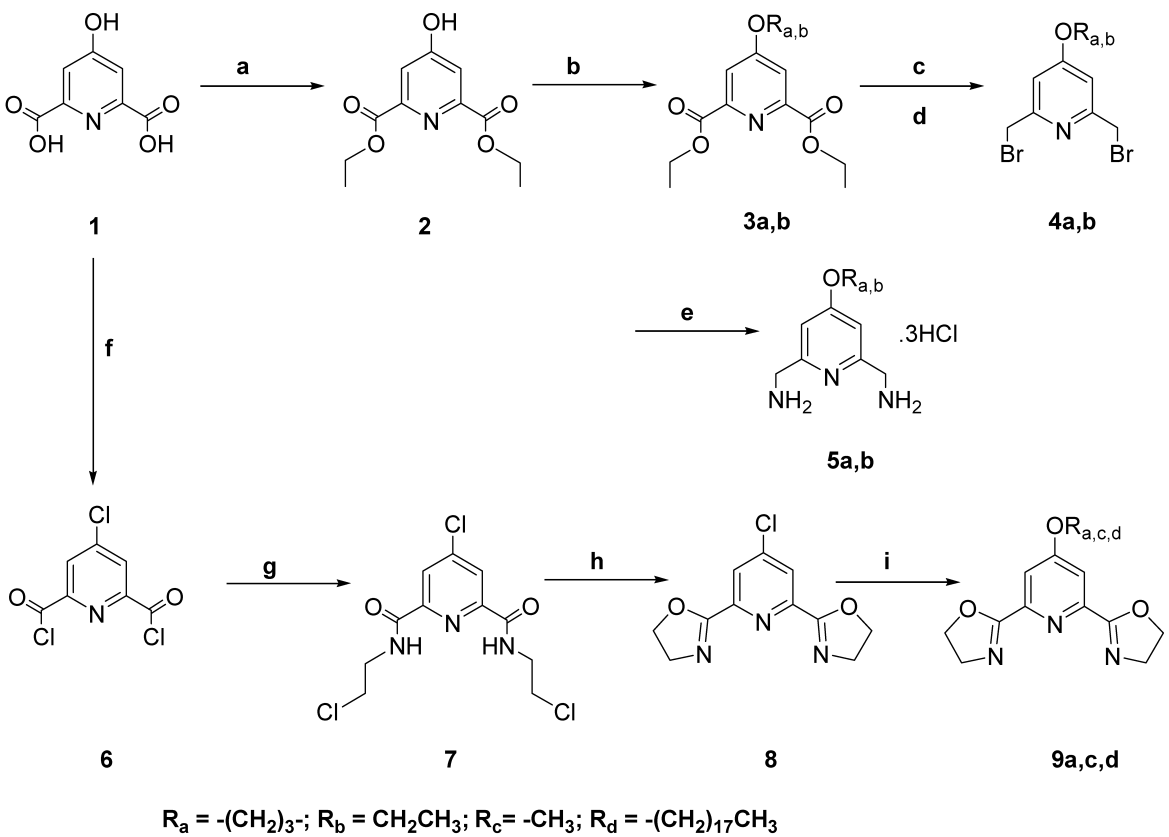
0040–4020/03/$ - see front matter © 2003 Published by Elsevier Science Ltd.
doi:10.1016/S0040-4020(03)00753-1



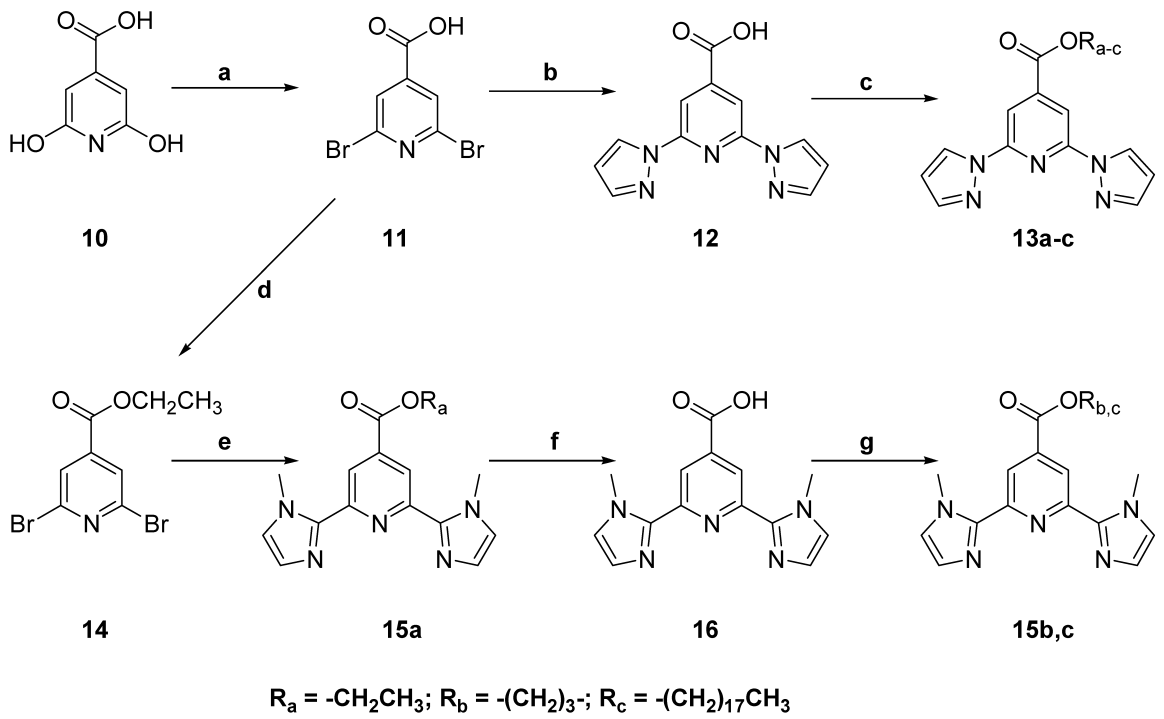
Scheme 1. General structures of the bifunctional terdendate ligands.

2. Results and discussion

As starting compounds for all metal ion complexing agents described here either 4-hydroxypyridine-2,6-dicarboxylic acid (chelidamic acid) or 2,6-dihydroxyisonicotinic acid were used. Scheme 2 shows the synthesis of the aminomethyl- and oxazolinylpyridines both starting from chelidamic acid. The aminomethyl ligands **5a** and **b**, were prepared by a five-step procedure. Chelidamic acid **1** was esterified in ethanol containing $SOCl_2$ to give diethylester **2** in 87% yield.[17] Diester **2** was treated with the appropriate bromoalkane in 2-butanone using K_2CO_3 as a base to give bifunctional compound **3a** (86%) and monofunctional compound **3b** (70%). Subsequently, the ester groups were reduced to hydroxymethyl groups with $NaBH_4$ in ethanol. It was possible to isolate the 2,6-bis(hydroxymethyl)-pyridines by crystallization in cold water, but that method gave very low yields. Horváth et al. already described very low yields of similar compounds upon isolation and noticed less loss of material when the crude product was used for the next reaction.[18] For that reason we also used the crude alcohol for the next step. To transform the alcohol functionality into a better leaving group several methods were attempted. Tosylation gave a poor yield (24%) for the bifunctional compound. Mesylation gave a product that seemed not stable upon isolation. Bromination was first tried using 48% HBr, but the compounds were not stable in this very acidic environment. Bromination by PBr_3 according to a method described by Takalo et al. gave a stable product with moderate yields (45–72% for two steps).[19] In the last step the bromines were replaced using hexamethylenetetramine in dichloromethane. The complex that was formed was subsequently hydrolyzed with acid yielding the protonated ligands **5a** and **b**. To desalt these water-soluble compounds C18-reversed phase column chromatography was used with water as eluens. The HCl



Scheme 2. (a) $SOCl_2$, EtOH (87%); (b) **3a**: $Br(CH_2)_3Br$, K_2CO_3, MEK (86%) **3b**: CH_3CH_2Br, K_2CO_3, MEK (70%); (c) $NaBH_4$, EtOH, not purified; (d) PBr_3, $CHCl_3$ (step c and d together **4a**: 72%, **4b**: 45%); (e) 1. Hexamethylenetetramine, CH_2Cl_2, 2. HCl, EtOH, H_2O (**5a**: 22%, **5b**: 27%); (f) $SOCl_2$, DMF, not purified; (g) 1. 2-aminoethanol, triethylamine, CH_2Cl_2, 2. $SOCl_2$ (step f and g together 54%); (h) NaH, THF (96%); (i) **9a**: NaH, DMF, 1,3-propanediol (73%) **9c**: NaOMe, MeOH (71%) **9d**: NaH, DMF, benzene, 1-octadecanol (38%).



Scheme 3. (a) $POBr_3$, autoclave (41%); (b) KH, pyrazole, diglyme (67%); (c) **13a**: H_2SO_4, EtOH (74%) **13b**: DCC, DMAP, CH_2Cl_2, 1,3-propanediol (36%) **13c**: DCC, DMAP, CH_2Cl_2, 1-octadecanol (83%); (d) H_2SO_4, EtOH (93%); (e) 1-methyl-2-tributylstannylimidazole, $(Ph_3P)_4Pd$, toluene (79%); (f) KOH, EtOH, H_2O (79%); (g) **15b**: DCC, CH_2Cl_2, DMAP, 1,3-propanediol (53%) **15c**: DCC, CH_2Cl_2, DMAP, 1-octadecanol (89%).

contents and purity of these compounds were determined with a potentiometric titration.

The synthesis of oxazolinylpyridine ligands **9a**,**c**,**d** started with preparing acid chloride **6** in $SOCl_2$.[20] This acid chloride was converted into the corresponding 4-chloro-bis(2-chloroethyl)-2,6-pyridinedicarboxamide **7**, by treatment with aminoethanol and subsequently $SOCl_2$ (54%) similar to the method used by Nishiyama et al.[10] Compound **7** was ring closed using NaH in THF to give 4-chloro-2,6-di-oxazolinylpyridine **8**. This compound is an ideal building block; the chloro group can easily be derivatized with all kinds of groups. We used methanol and octadecanol in order to obtain the monofunctional ligands, **9c** and **d**, and propanediol was used to obtain the bifunctional ligand, **9a** (37–73%).

In Scheme 3 the synthesis of pyrazolyl- and methyl-imidazolylpyridines is depicted both starting from isonicotinic acid **10**. The hydroxyl groups were replaced by bromines using $POBr_3$ according to a procedure from literature yielding compound **11**,[21] which is used for the synthesis of both types of ligands. In the case of the pyrazolylpyridine ligands the pyrazolyl groups were introduced using KH as a base. This yielded compound **12** with a carboxylic acid group at the 4-position of the pyridine that can be used as a synthetic handle to introduce other functional groups via for example ester bonds.[22] This was done with propanediol, which gave bifunctional ligand **13a**, and with ethanol and octadecanol, which gave monofunctional ligands **13b** and **c**, respectively. In the case of the methylimidazolyl ligands the carboxylic acid group at the 4-position was first protected as an ethyl ester to give **14**. Then the bromine groups were replaced by 1-methylimidazolyl groups by reaction with 1-methyl-2-tributylstannylimidazole[23] in toluene with $(Ph_3P)_4Pd$ as a catalyst yielding compound **15a** in 79%. This compound is already a monofunctional ligand with a short ethyl tail. To introduce other functionalities the ester was hydrolyzed in a basic solution to compound **16** and esterified again using propanediol and octadecanol to give a bifunctional and an amphiphilic ligand (**15b** and **c**) respectively.

In conclusion, we have presented in this paper the synthesis of four different kinds of 4-functionalized terdendate pyridine-based ligands. For each case, the synthesis of both bifunctional and monofunctional ligands is described. Using the methods described here, it will be possible to synthesize dervatives with other spacers and tails. The ligands can find application in supramolecular chemistry, reversible coordination polymers, catalysis and separation. Studies on the complexation behavior of these ligands with transition metal ions are currently in progress.

3. Experimental

3.1. General

All solvents were of p.a. quality and reactions were carried out under dry N_2 when dry atmosphere was required. Chemicals were purchased and used without further purification. 4-Hydroxypyridine-2,6-dicarboxylic acid (chelidamic acid) was obtained from 4-oxo-4*H*-pyrane-2,6-dicarboxylic acid (chelidonic acid).[24] Diethyl 4-hydroxypyridine-2,6-dicarboxylate, **2**,[17] 4-chloro-2,6-pyridine-

dicarbonyl dichloride, **6**,[20] 2,6-dibromoisonicotinic acid **11**,[21] ethyl 2,6-dibromoisonicotinate **14**[21,25] and 1-methyl-2-tributylstannylimidazole[23] were prepared according to literature. ^{1}H NMR (200 MHz) and ^{13}C NMR spectra were recorded on a Bruker AC200 spectrometer at room temperature. MS and HRMS data were obtained with a Finnigan MAT 95 spectrometer. Elemental analysis was performed with an Elemental Analyser EMASyst1106. Some of the compounds were too hygroscopic to obtain correct elemental analyses. UV spectra of the final products were measured on a Perkin Elmer Lambda 18 UV/VIS spectrometer.

3.1.1. Tetraethyl 4,4′-(1,3-propoxy)-bis-2,6-pyridinedicarboxylate 3a. A mixture of compound **2** (8.3 g, 34.7 mmol), 1,3-dibromopropane (3.5 g, 17.3 mmol) and 10.4 g K_2CO_3 were refluxed in 2-butanone for 3 days under a N_2 atmosphere. The solvent was evaporated and CH_2Cl_2 was added to the residue. Salts were removed by filtration and the filtrate was concentrated and purified using column chromatography (1% MeOH in CH_2Cl_2). Yield: 86% oil (7.2 g, 14.9 mmol). ^{1}H NMR ($CDCl_3$): δ 1.41 (t, J=7.1 Hz, 12 H, CH_3), 2.38 (m, J=5.8 Hz, 2H, CH_2), 4.35 (q, J=5.8 Hz, 4H, OCH_2), 4.46 (q, J=7.2 Hz, 8H, CH_2OC=O), 7.77 (s, 4H, aromatic H). $C_{25}H_{30}N_2O_{10}$: calcd C 57.9, H 5.8, N 5.4; found C 58.1, H 5.8, N 5.5.

3.1.2. Diethyl 4-ethoxy-2,6-pyridinedicarboxylate 3b. Yield: 70% oil. ^{1}H NMR ($CDCl_3$): δ 1.44 (t, J=6.8 Hz, 6H, CH_3), 1.47 (t, J=5.9 Hz, 3H, CH_3), 4.21 (q, J=7.0 Hz, 2H, OCH_2), 4.46 (q, J=7.1 Hz, 8H, CH_2OC=O), 7.76 (s, 2H, aromatic H). $C_{13}H_{17}NO_5$: calcd C 58.4, H 6.4, N 5.2; found C 58.3, H 6.5, N 5.1.

3.1.3. 4,4′-(1,3-Propoxy)-bis[2,6-bis(bromomethyl)pyridine] 4a. Compound **3a** (1.1 g, 2.3 mmol) was dissolved in 30 mL absolute ethanol at 0°C. In small amounts $NaBH_4$ (1.4 g, 37 mmol) was added. The reaction mixture was stirred for another 0.5 h at 0°C and then refluxed overnight. The solvent was removed, 25 mL of a saturated $NaHCO_3$ solution was added and the mixture was subsequently refluxed for 1 h. The solvent was evaporated and the crude 4,4′-(1,3-propoxy)-bis[2,6-bis(hydroxymethyl)pyridine] was used without purification for the next reaction step. ^{1}H NMR (D_2O/MeOD): δ 2.32 (quint, J=6.0 Hz, 2H, CH_2), 4.31 (t, J=6.1 Hz, 4H, CH_2O), 4.61 (s, 8H, CH_2OH), 6.98 (s, 4H, aromatic H).

PBr_3 (4.11 g, 15.2 mmol) in 35 mL $CHCl_3$ was added dropwise to a suspension of 4,4′-(1,3-propoxy)-bis[2,6-bis(hydroxymethyl)pyridine] (0.71 g, 2.0 mmol) in 60 mL $CHCl_3$ at room temperature. This reaction mixture was refluxed overnight. To the cooled reaction mixture was added 25 mL of a 5% $NaHCO_3$ solution and the mixture was stirred for another hour until the system became clear. The organic layer was washed with water and dried over Na_2SO_4. The crude product was purified using column chromatography (0.5% MeOH in CH_2Cl_2). Yield: 72% (0.87 g, 1.4 mmol) for two steps, mp 129°C. ^{1}H NMR ($CDCl_3$): δ 2.32 (quint, J=5.9 Hz, 2H, CH_2), 4.21 (q, J=5.9 Hz, 4H, CH_2O), 4.47 (s, 8H, CH_2OH), 6.90 (s, 4H, aromatic H). $C_{17}H_{18}N_2O_2Br_4$: calcd C 33.9, H 3.0, N 4.6; found C 33.9, H 2.9, N 4.4.

3.1.4. 2,6-Bis(bromomethyl)-4-ethoxypyridine 4b. 2,6-bis(hydroxymethyl)-4-ethoxypyridine: ^{1}H NMR (D_2O/MeOD): δ 1.41 (t, J=7.0 Hz, 3H, CH_3), 4.20 (q, J=7.0 Hz, 2H, CH_2O), 4.62 (s, 4H, CH_2OH), 6.95 (s, 2H, aromatic H).

Yield: 45% (for two steps), mp 71°C. ^{1}H NMR ($CDCl_3$): δ 1.44 (t, J=7.0 Hz, 3H, CH_3), 4.12 (q, J=7.0 Hz, 2H, CH_2O), 4.47 (s, 4H, CH_2Br), 6.87 (s, 2H, aromatic H). $C_9H_7NOBr_2$: calcd C 35.5, H 2.3, N 4.6; found C 35.3, H 2.6, N 4.4.

3.1.5. 4,4′-(1,3-Propoxy)-bis[2,6-bis(aminomethyl)pyridine] hexahydrochloride 5a. To a refluxing solution of hexamethylenetetramine (0.9 g, 6.4 mmol) in 20 mL CH_2Cl_2 a solution of **5a** (0.87 g, 1.45 mmol) in CH_2Cl_2 was added dropwise. This reaction mixture was refluxed overnight. The obtained precipitate was filtered, dissolved in a mixture of 10 mL ethanol and 10 mL water and acidified to pH 3 with concentrated HCl. This mixture was stirred for 3 h and kept at pH <4 at 40°C. The solvent was removed and the crude product was purified and desalted using C18-reversed phase column chromatography with water as eluents. The product was recrystallised with water/acetone. Yield: 22% (0.18 g, 0.32 mmol), mp >300°C. ^{1}H NMR (D_2O): δ 2.15 (quint, J=6.0 Hz, 2H, CH_2), 4.07 (s, 8H, CH_2N), 4.10 (m, J=6.0 Hz, 4H, CH_2O), 6.78 (s, 4H, aromatic H); ^{13}C NMR (D_2O): δ 30.20 (CH_2) 45.53 (4×CH_2NH_2), 68.08 (2×OCH_2), 111.27 (4×CH), 156.24 (4×CN), 169.35 (2×CO). $C_{17}H_{32}N_6O_2Cl_6$: calcd C 36.1, H 5.7, N 14.9; found C 36.5, H 5.4, N 15.1. UV (H_2O): λ_{max} (log ε)=219 nm (4.71).

3.1.6. 2,6-Bis(aminomethyl)-4-ethoxypyridine trihydrochloride 5b. Yield: 27%, mp >300°C. ^{1}H NMR (D_2O): δ 1.33 (t, J=7.0 Hz, 3H, CH_3), 4.16 (q, J=7.0 Hz, 2H, OCH_2), 4.24 (s, 4H, CH_2N), 6.95 (s, 2H, aromatic H); ^{13}C NMR (D_2O): δ 16.44 (CH_3), 45.54 (2×CH_2NH_2), 67.78 (OCH_2), 111.38 (2×CH), 156.16 (2×CN), 169.41 (CO). $C_9H_{18}N_3OCl_3$: calcd C 37.2, H 6.2, N 14.5; found C 37.4, H 6.0, N 14.8. UV (H_2O): λ_{max} (log ε)=211 nm (4.23).

3.1.7. 4-Chloro-*N*^{2},*N*^{6}-bis(2-chloroethyl)-2,6-pyridinedicarboxamide 7. To a solution of 2-aminoethanol (1.62 g, 20.6 mmol) and triethylamine (7.92 g, 78.3 mmol) in CH_2Cl_2 (50 mL) was slowly added a solution of 2.03 g (10.0 mmol) acid chloride **6** in CH_2Cl_2 (50 mL) at 0°C. The mixture was stirred for 24 h at room temperature. Then $SOCl_2$ (33 mL) was added at 0–10°C, and the mixture was refluxed for 9 h and poured slowly into ice water. The organic layer was collected, washed with brine and dried over Na_2SO_4. The product was purified by column chromatography (5% ether in CH_2Cl_2). Yield: 54% (1.76 g, 5.4 mmol), mp 173–174°C. ^{1}H NMR ($CDCl_3$): δ 3.74 (t, J=5.1 Hz, 4H, CH_2Cl), 3.83 (q, J=5.4 Hz, 4H, CH_2N), 8.10 (s, 2H, NH), 8.34 (s, 2H, aromatic H). HRMS calcd for $C_{11}H_{12}N_3O_2Cl_3$ 322.9995; found 322.9991.

3.1.8. 4-Chloro-2,6-di(4,5-dihydro-1,3-oxazol-2-yl)pyridine 8. To a suspension of NaH (0.68 g, 60% oil, 17.0 mmol) in THF (12 mL) was added a solution of **7** (1.76 g, 5.4 mmol) in THF (25 mL). The mixture was stirred overnight. After filtration and concentration, the residue was extracted with ether. The extract gave a solid upon

evaporation of the solvent, which was recrystallised from hexane/ethyl acetate to give **8** as white needles. Yield: 96% (1.3 g, 5.17 mmol), mp 179–180°C. IR (KBr disk) 1636, 1562, 1385, 1275, 1124, 945, 783 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.09 (t, J=9.5 Hz, 4H, CH_2), 4.56 (t, J=9.4 Hz, 4H, CH_2), 8.16 (s, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 55.09 (2×CH_2N), 68.57 (2×CH_2O), 125.72 (2×CH), 145.44 (2×CN), 147.94 (CCl), 162.62 (2×OC=N). HRMS calcd for $C_{11}H_{10}N_3O_2Cl$ 251.0462; found 251.0462.

3.1.9. 4,4′-(1,3-Propoxy)-bis[2,6-di(4,5-dihydro-1,3-oxazol-2-yl)pyridine] 9a. To a suspension of NaH (0.08 g, 60% oil, 2 mmol) in dry DMF was added 0.08 g (1.0 mmol) of 1,3-propanediol. After stirring at room temperature for 1 h compound **8** was added (0.50 g, 2.0 mmol) and the mixture was heated at 40°C for 2 days. The solvent was evaporated and the residue was extracted using hot ethyl acetate to give **9a** as a white solid. Yield: 73% (0.37 g, 0.7 mmol), mp 207–209°C. ^1H NMR (CD_3OD): δ 2.11 (m, J=6.0 Hz, 2H, CH_2), 3.81 (t, J=9.6 Hz, 8H, CH_2), 4.12 (t, J=6.0 Hz, 4H, CH_2O), 4.29 (t, J=9.8 Hz, 8H, CH_2), 7.41 (s, 4H, aromatic H); ^{13}C NMR (CD_3OD): δ 30.48 (CH_2), 56.49 (4×CH_2N), 67.47 (4×CH_2O), 70.86 (2×CH_2O) 116.01 (4×CH), 150.40 (2×CN), 166.47 (4×OC=N), 168.67 (CO). $C_{25}H_{26}N_6O_6{\cdot}0.8H_2O$: calcd C 57.6, H 5.3, N 16.1; found C 57.8, H 5.2, N 15.9. UV (CH_3OH): λ_{max} (log ε)=210 nm, (4.64), 229 nm (4.55).

3.1.10. 2,6-Di(4,5-dihydro-1,3-oxazol-2-yl)-4-methoxypyridine 9c. Sodium (0.137 g, 0.596 mmol) was added to 10 mL methanol. After 15 minutes compound **8** (1.0 g, 4.0 mmol) was added. The mixture was heated at 40°C for 24 h. The solvent was evaporated and the residue was extracted using hot ethyl acetate to give **9c** as a white solid. Yield: 71% (0.70 g, 2.8 mmol), mp 218–220°C. ^1H NMR (CD_3OD): δ 3.91 (s, 3H, OCH_3), 4.18 (t, J=9.4 Hz, 4H, CH_2), 4.50 (t, J=9.7 Hz, 4H, CH_2), 7.62 (s, 2H, aromatic H); ^{13}C NMR (CD_3OD): δ 55.43 (CH_3O), 56.68 (2×CH_2N), 69.85 (2×CH_2O), 112.98 (2×CH), 149.22 (2×CN), 165.39 (2×OC=N), 168.60 (CO). $C_{12}H_{13}N_3O_3$: calcd C 58.3, H 5.3, N 17.0; found C 58.0, H 5.3, N 17.0. HRMS calcd for $C_{12}H_{13}N_3O_3$ 247.0957; found 247.0963. UV (CH_3OH): λ_{max} (log ε)=210 nm (4.38), 231 nm (4.32).

3.1.11. 2,6-Di(4,5-dihydro-1,3-oxazol-2-yl)-4-octadecyloxy-pyridine 9d. To a suspension of NaH (0.08 g, 60% in oil, 2 mmol) in dry DMF was added 1-octadecanol (0.54 g, 2.0 mmol) and this mixture was stirred for 1 h. at room temperature. Compound **8** was added (0.50 g, 2.0 mmol) and the reaction mixture was heated at 40°C for 2 days. The solvent was evaporated and the residue was extracted with hot ethyl acetate. After evaporation the residue was washed with hot hexane and recrystallised from ethanol to give **9d** as a white solid. Yield: 38% (0.37 g, 0.8 mmol), mp 116–117°C. ^1H NMR ($CDCl_3$): δ 0.86 (t, J=6.5 Hz, 3H, CH_3), 1.24 (m, 30H, CH_2), 1.79 (m, 2H, CH_2), 4.11 (t, J=6.6 Hz, 4H, CH_2), 4.09 (m, J=9.3 Hz, 2H, OCH_2), 4.51 (t, J=8.8 Hz, 4H, CH_2), 7.64 (s, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 14.15 (CH_3), 22.70–31.94 (16×CH_2), 54.99 (2×CH_2N), 68.34 (2×CH_2O), 68.82 (OCH_2), 112.04 (2×CH), 148.13 (2×CN), 163.65 (2×OC=N), 166.01 (CO). $C_{29}H_{47}N_3O_3{\cdot}1.4H_2O$: calcd C 68.2, H 9.8, N 8.2; found C 68.2, H 9.4, N 8.1. HRMS calcd for $C_{29}H_{47}N_3O_3$ 485.3617; found 485.3615. UV (CH_3OH): λ_{max} (log ε)=210 nm (4.35), 232 nm (4.30).

3.1.12. 2,6-Di(1*H*-pyrazol-1-yl)isonicotinic acid 12. To a solution of pyrazole (2.43 g, 35 mmol) in anhydrous diglyme (50 mL) was added KH (33 mmol, oil-free) and the mixture was stirred at room temperature for 2 h. 2,6-Dibromoisonicotinic acid **11** (2.81 g, 10 mmol) was added in one portion. The resulting mixture was stirred at 130°C for 3 days. The solvent was removed under vacuum. Water was added and the mixture was acidified. The obtained precipitate was filtered and purified by dissolving in methylene chloride, adding methanol, and slowly removing the methylene chloride on a rotatory evaporator. The solid material was isolated by filtration. Yield: 67% (1.7 g, 6.7 mmol), mp 263–265°C. ^1H NMR ($CDCl_3/CD_3OD$): δ 6.52 (dd, J=1.4 and 2.6 Hz, 2H, CH=C), 7.76 (d, J=1.4 Hz, 2H, CH=N), 8.31 (s, 2H, aromatic H), 8.60 (d, J=2.6 Hz, 2H, CH=N); ^{13}C NMR ($CDCl_3/CD_3OD$): δ 108.15 (2×CH), 108.99 (2×CH), 127.38 (2×NCH), 142.57 (2×N=CH), 144.16 (C), 150.41 (2×NCN), 165.36 (CO_2H). HRMS calcd for $C_{12}H_9N_5O_2$ 255.0756; found 255.0760.

3.1.13. Ethyl 2,6-di(1*H*-pyrazol-1-yl)isonicotinate 13a. A mixture of compound **12** (0.26 g, 1.0 mmol) and concentrated H_2SO_4 (0.5 mL) in 10 mL of ethanol was heated for 3 h. The solvent was removed by evaporation and water was added to the residue. The precipitate was filtered and purified by recrystallization from ethanol/water to give a white solid. Yield: 74% (0.21 g, 0.7 mmol), mp 143–144°C. ^1H NMR ($CDCl_3$): δ 1.43 (t, J=7.16 Hz, 3H, CH_3), 4.45 (q, J=7.1 Hz, 2H, OCH_2), 6.50 (dd, J=1.4 and 2.6 Hz, 2H, CH=C), 7.79 (d, J=1.3 Hz, 2H, CH=N), 8.37 (s, 2H, aromatic H), 8.56 (d, J=2.6 Hz, 2H, CH=N); ^{13}C NMR ($CDCl_3$): δ 14.23 (CH_3), 62.15 (OCH_2), 108.35 (2×CH), 109.09 (2×CH), 127.16 (2×NCH), 142.76 (2×N=CH), 143.55 (C), 150.68 (2×NCN), 163.93 (CO_2). $C_{14}H_{13}N_5O_2$: calcd C 59.3, H 4.6, N 24.7; found C 58.9, H 4.4, N 24.3. UV (CH_3OH): λ_{max} (log ε)=208 (4.22), 248 (4.45), 268 (4.08), 331 nm (4.02).

3.1.14. 1,3-Propyl bis-[2,6-di(1*H*-pyrazol-1-yl)isonicotinate] 13b. A mixture of 0.26 g (1.0 mmol) of compound **12** in 10 mL CH_2Cl_2, DCC (0.46 g, 2.2 mmol), 0.04 g (0.5 mmol) of 1,3-propanediol and a catalytic amount of DMAP was stirred for 2 days. The precipitate was removed by filtration, the filtrate was concentrated and the residue was purified by column chromatography (0.3% MeOH in CH_2Cl_2). Yield: 36% (0.10 g, 0.2 mmol), mp 223–225°C. ^1H NMR ($CDCl_3$): δ 2.36 (quint, J=5.8 Hz, 2H, CH_2), 4.61 (t, J=5.8 Hz, 4H, OCH_2), 6.46 (dd, J=1.3 and 2.3 Hz, 2H, CH=C), 7.69 (d, J=1.2 Hz, 2H, CH=N), 8.29 (s, 2H, aromatic H), 8.45 (d, J=2.4 Hz, 2H, CH=N); ^{13}C NMR ($CDCl_3/CD_3OD$): δ 30.62 (CH_2), 63.65 (2×CH_2O), 108.25 (4×CH), 108.81 (4×CH), 127.21 (4×NCH), 142.67 (2×N=CH), 142.85 (2×C), 150.35 (4×NCN), 163.92 (2×CO_2). $C_{27}H_{22}N_{10}O_4$: calcd C 58.9, H 4.0, N 25.4; found C 58.8, H 3.9, N 25.6. UV (CH_2Cl_2): λ_{max} (log ε)=249 nm (4.64), 270 nm (4.56), 334 nm (4.52).

3.1.15. Octadecyl 2,6-di(1*H*-pyrazol-1-yl)isonicotinate 13c. Yield: 83%, mp 91–93°C. ^1H NMR ($CDCl_3$): δ 0.86 (t, J=6.8 Hz, 3H, CH_3), 1.30 (m, 30H, CH_2), 1.79 (m,

J=7.1 Hz, 2H, CH_2), 4.38 (t, J=6.8 Hz, 2H, OCH_2), 6.55 (dd, J=1.2 and 2.4 Hz, 2H, CH═C), 7.80 (d, J=1.2 Hz, 2H, CH═N), 8.38 (s, 2H, aromatic H), 8.57 (d, J=2.4 Hz, 2H, CH═N); ^{13}C NMR ($CDCl_3$): δ 14.10 (CH_3), 22.66–31.89 (16×CH_2), 66.34 (OCH_2), 108.34 (2×CH), 109.11 (2×CH), 127.14 (2×NCH), 142.74 (2×N═CH), 143.59 (C), 150.69 (2×NCN), 164.03 (CO_2). $C_{30}H_{45}N_5O_2$: calcd C 71.0, H 8.9, N 13.8; found C 70.9, H 9.1, N 13.4. UV (CH_3OH): λ_{max} (log ε)=208 (4.13), 248 (4.36), 268 (3.99), 330 nm (3.91).

3.1.16. Ethyl 2,6-bis(1-methyl-1*H*-imidazol-2-yl)isonicotinate 15a. A mixture of 2.97 g (9.6 mmol) of compound **14**, 1-methyl-2-tributylstannylimidazole (9.6 g, 26 mmol) and $(Ph_3P)_4Pd$ (0.29 g, 0.02 mmol) was heated under N_2 in toluene (100 mL) for 12 h. After cooling the solvent was removed and the residue was purified by column chromatography on silica gel (5% MeOH in CH_2Cl_2/MeOH). Yield: 79% (2.35 g, 7.6 mmol), mp 148–150°C. ^{1}H NMR ($CDCl_3$): δ 1.40 (t, J=7.1 Hz, 3H, CH_3), 4.12 (s, 6H, NCH_3), 4.41 (q, J=7.1 Hz, 2H, OCH_2), 7.02 (d, J=1.2 Hz, 2H, CHN), 7.18 (d, J=1.0 Hz, 2H, CHN), 8.62 (s, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 14.29 (CH_3), 61.90 (OCH_2), 121.71, (2×CH), 124.53 (2×CH), 128.86 (2×CH), 139.66 (C), 144.72 (C), 150.34 (C), 164.58 (CO_2). $C_{16}H_{17}N_5O_2$·0.2H_2O: calcd C 61.0, H 5.6, N 22.2; found C 61.3, H 5.4, N 21.9. HRMS calcd for $C_{16}H_{17}N_5O_2$ 311.1382; found 311.1374. UV (CH_3OH): λ_{max} (log ε)=279 (4.32), 341 nm (4.06).

3.1.17. 2,6-Bis(1-methyl-1*H*-imidazol-2-yl)isonicotinic acid 16. A mixture of compound **15a** (3.2 g, 10.3 mmol), 1.15 g of KOH, dissolved in 20 mL of water and 50 mL of ethanol was refluxed for 2 hours. Ethanol was removed by evaporation and water was added to the residue. The mixture was acidified with 1N HCl to pH ~6.2, which gave compound **16** as a white solid. Yield: 79% (2.3 g, 8.1 mmol), mp 315–318°C. ^{1}H NMR (D_2O): δ 3.78 (s, 6H, NCH_3), 7.09 (d, J=1.2 Hz, 2H, CHN), 7.16 (d, J=1.0 Hz, 2H, CHN), 7.97 (s, 2H, aromatic H); ^{13}C NMR (D_2O/CD_3OD): δ 121.12 (2×CH), 126.27 (2×CH), 128.30 (2×CH), 139.64 (C), 144.09 (C), 150.27 (C), 164.77 (CO_2). HRMS calcd for $C_{14}H_{13}N_5O_2$ 283.1069; found 283.1059.

3.1.18. 1,3-Propyl bis-[2,6-bis(1-methyl-1*H*-imidazol-2-yl)isonicotinate] 15b. A mixture of 0.28 g (1.0 mmol) of compound **16** in 10 mL CH_2Cl_2, 2.2 mmol of DCC, 0.04 g (0.5 mmol) of propanediol and a catalytic amount of DMAP was stirred for 2 days at room temperature. The precipitate was removed by filtration, the filtrate was concentrated and the residue was purified by column chromatography (5% MeOH in CH_2Cl_2). The product was recrystallized from MeOH/hexane. Yield: 53% (0.16 g, 0.3 mmol), mp 220–222°C. ^{1}H NMR ($CDCl_3$): δ 2.30 (quint, J=6.2 Hz, 2H, CH_2), 4.07 (s, 12H, NCH_3), 4.53 (t, J=6.2 Hz, 4H, OCH_2), 7.02 (d, J=1.2 Hz, 4H, CHN), 7.18 (d, J=1.0 Hz, 2H, CHN), 8.61 (s, 4H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 27.82 (CH_2), 62.46 (2×OCH_2), 121.60 (4×CH), 124.72 (4×CH), 128.24 (4×CH), 139.29 (2×C), 144.21 (2×C), 150.01 (2×C), 164.34 (2×CO_2). HRMS calcd for $C_{31}H_{30}N_{10}O_4$ 606.2451; found 606.2442. UV (CH_3OH): λ_{max} (log ε)=279 nm (4.75), 342 nm (4.30).

3.1.19. Octadecyl 2,6-bis(1-methyl-1*H*-imidazol-2-yl)isonicotinate 15c. A mixture of 0.30 g (1.1 mmol) of compound **16** in 10 mL CH_2Cl_2, 1.2 mmol of DCC, 0.27 g (1.0 mmol) of octadecanol and a catalytic amount of DMAP was stirred for 2 days at room temperature. The precipitate was removed by filtration, the filtrate was concentrated and the residue was purified by column chromatography (5% MeOH in CH_2Cl_2). The product was recrystallized from MeOH/hexane. Yield: 89% (0.48 g, 0.9 mmol), mp 98–99°C. ^{1}H NMR ($CDCl_3$): δ 1.25 (t, J=6.5 Hz, 3H, CH_3), 1.24 (m, 30H, CH_2), 1.70 (quint, J=7.1 Hz, 2H, CH_2), 4.08 (s, 6H, NCH_3), 4.45 (t, J=6.8 Hz, 2H, OCH_2), 7.02 (d, J=1.2 Hz, 2H, CHN), 7.18 (d, J=1.0 Hz, 2H, CHN), 8.61 (s, 2H, aromatic H); ^{13}C NMR ($CDCl_3$): δ 14.15 (CH_3), 22.71–35.85 (16×CH_2), 66.15 (OCH_2), 121.74 (2×CH), 124.45 (2×CH), 128.87 (2×CH), 139.72 (C), 144.75 (C), 150.33 (C), 164.71 (CO_2). HRMS calcd for $C_{32}H_{49}N_5O_2$ 535.3886; found 535.3887. UV (CH_3OH): λ_{max} (log ε)=280 (4.26), 341 nm (3.99).

Acknowledgements

The authors would like to thank A. van Veldhuizen for NMR measurements, E. van der Klift for elemental analysis, M. A. Posthumus for HRMS and A. Koudijs for help with the synthetic work. The research of D. Branowska has been made possible by a fellowship of the Netherlands Ministry of Agriculture, Nature Management and Fisheries.

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