A General One-Step Synthesis of Multidentate (Pyridylalkyl)amines from Mono-, Bis-, Tris- and Tetrakis(bromomethyl)benzenes: Potential Ligands for Supramolecular Assembly

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Abstract: The synthesis of new multidentate nitrogen-containing ligands is of ongoing interest. In this report, the one-step syntheses of a series of (pyridylalkyl)amine derivatives is described. The reported compounds contain both pyridine rings and sp^3-hybridized nitrogen as potential donor sites. The general synthetic method involves a room temperature reaction of mono-, bis-, tris-, or tetrakis(bromomethyl)benzenes with an excess of (pyridylmethyl)amine in tetrahydrofuran. The products can be purified by distillation, chromatography or recrystallization and are obtained in fair to good yields. The advantages of this synthetic method are the procedural simplicity and the ready availability of the starting materials. The applicability of these compounds in supramolecular chemistry is demonstrated by the reaction of two of the described ligands with silver(I) salts.

Key words: pyridines, amines, alkylations, ligands, supramolecular chemistry

Pyridylamines and structurally related compounds have been incorporated into a variety of synthetic targets including antitumor complexes,[1–8] supramolecular complexes and assemblies,[9–35] and ion receptors.[36–38] The presence of both pyridine and sp^3-nitrogen atoms give pyridylamines a high degree of versatility in the synthesis of these materials. The prevailing method for the synthesis of pyridylamines is the reductive amination of carbonyl compounds.[39] Although well-known, reductive amination is a two-step process and dependent on the availability of the corresponding carbonyl compounds. As an outgrowth of our research involving the design of new multidentate nitrogen-heteroaromatic ligands,[40–43] we sought a short and simple synthesis of bis(pyridylmethyl)amines (**4**–**9**) that did not require imine intermediates. As a result of this investigation, we report the syntheses of **4**–**9** and the related (pyridylalkyl)amines **1**–**3** and **10**–**18** by a one-step procedure (Figure 1). All of these compounds (most of which were previously unknown) possess multiple nitrogen binding sites and may thus serve as useful precursors of new supramolecular materials. In this regard, two specific examples of Ag(I)-guided supramolecular assembly are also described.

Despite the well-documented difficulty in controlling the degree of alkylation of nitrogen nucleophiles,[44] we believed a simple and direct approach to the synthesis of the desired (pyridylmethyl)amines might be the reaction of (bromomethyl)benzenes with 2-, 3- or 4-(aminomethyl)pyridine – all readily available materials. To test this approach, we first examined the reaction of benzyl bromide with 2-, 3- and 4-(aminomethyl)pyridine to give **1**–**3** (Equation 1). We found that stirring an excess of 2-(aminomethyl)pyridine with benzyl bromide in tetrahydrofuran (THF) for 18 hours at room temperature indeed gave **1**, isolated in 66% yield after filtration and distillation. Compound **1** was previously prepared in 46% yield via a conventional reductive amination route[45] (86% yield

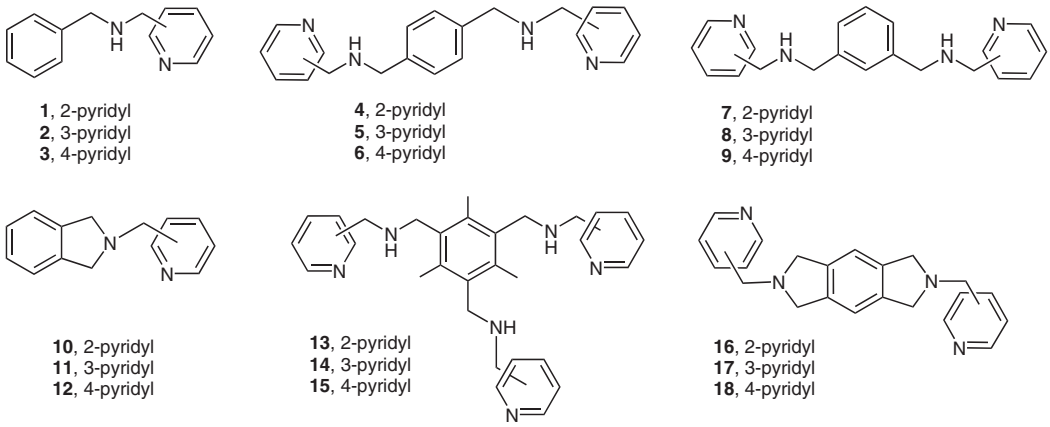

Figure 1 Compounds synthesized in this study

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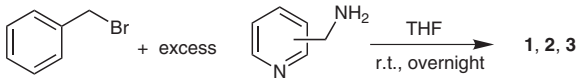
using a polymer supported reductive amination reaction[46]). This synthetic method also worked well with the other (aminomethyl)pyridine isomers; reaction of benzyl bromide with 3-(aminomethyl)pyridine gave **2** in 60% yield (prepared in 50% yield by reductive amination[47]), and reaction with 4-(aminomethyl)pyridine gave **3**[48] in 56% yield (Table 1).



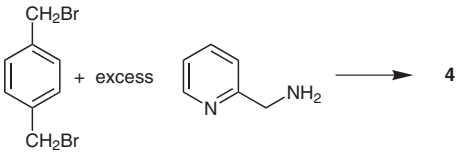
Equation 1

Table 1 Product Yields for (Pyridylalkyl)amines

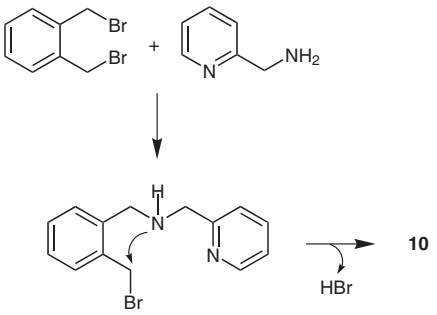
Product	Yield (%)[a]
1	66
2	60
3	56
4	20
5	42
6	42
7	–[b]
8	40
9	37
10	48
11	62
12	59
13	28
14	49
15	13
16	46
17	46
18	38

[a] Purified yields.
[b] Could not be purified by chromatography.

With these results in hand, we next applied this method to reactions involving α,α′-dibromoxylenes. We were pleased to find that reaction of an excess of 2-(aminomethyl)pyridine with α,α′-dibromo-*p*-xylene under the same conditions gave **4**, although in modest yield (20%; Equation 2). In subsequent experiments, this method was applied successfully for the syntheses of **5**, **6**, **8** and **9**, all in reasonable yields (see Table 1). For the synthesis of **7**, we believed the product was obtained, but we were unable to achieve a satisfactory separation using chromatography. All of these compounds were isolated as hygroscopic, colored oils except for **5**, which slowly solidified. Reactions of α,α′-dibromo-*o*-xylene with the various (aminomethyl)pyridines gave unexpected results. In these cases, we did not obtain the expected bis-substituted products, but rather the previously unknown cyclized bidentate (pyridylalkyl)amines **10**–**12** in 48–62% purified yields. Compounds **10**–**12**, isolated as colored oils, were clearly formed as a result of an intramolecular cyclization of the monosubstituted intermediate (Scheme 1).

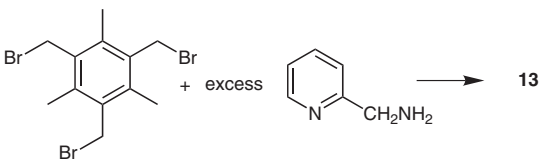


Equation 2



Scheme 1 Reaction mechanism for the synthesis of **10**

Multidentate 1,3,5-trisubstituted benzenes are attractive synthetic targets due to their utility in supramolecular chemistry[49–55] and actinide sequestration.[56] Accordingly, the reactions of 2-, 3- and 4-(aminomethyl)pyridine with 1,3,5-tris(bromomethyl)mesitylene[57] proceeded in the expected fashion (Equation 3, using **13** as an example), giving the new trisubstituted compounds **13**–**15** in 28%, 49% and 13% yields, respectively. Compounds **13**–**15** were initially isolated as hygroscopic oils, but **14** slowly solidified on standing, giving a collection of both fan-shaped and cube-shaped crystals. Redissolving a portion of these crystals in acetone, followed by slow evaporation, gave a collection of colorless X-ray quality crystals. Subsequent crystallographic analysis revealed the expected structure of **14** as shown in Figure 2 (see also Table 2).



Equation 3

The intramolecular cyclization illustrated in the syntheses of **10**–**12** (Scheme 1) suggested to us that reaction of (aminomethyl)pyridines with 1,2,4,5-tetrakis(bromomethyl)benzene could give novel polycyclic products.

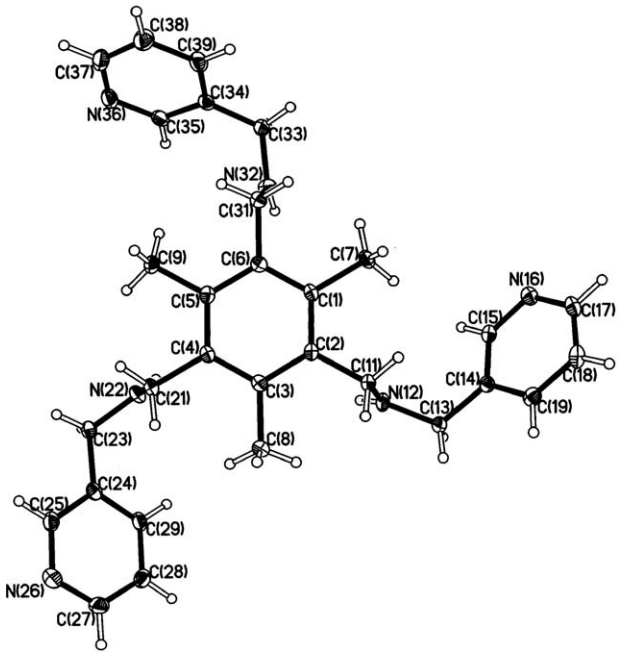
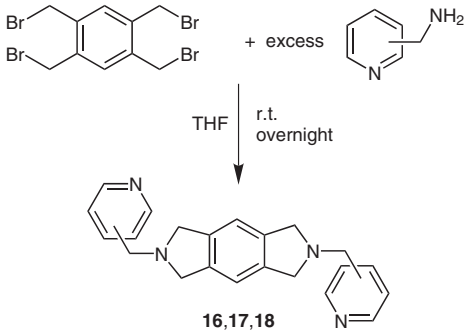


Figure 2 ORTEP plot of **14** (50% ellipsoids); does not include two water molecules, which are part of the unit cell

Accordingly, reactions of 2-, 3- and 4-(aminomethyl)pyridine with 1,2,4,5-tetrakis(bromomethyl)benzene gave previously unknown compounds **16**–**18** in 46%, 46% and 38% yields, respectively (Equation 4). Compounds **16**–**18** were purified by recrystallization and isolated as slightly colored crystalline solids. Besides the usual characterization by spectroscopic and combustion analyses, the structure of **18** was confirmed by single crystal X-ray analysis.



Equation 4

During the course of this investigation, we learned that the synthetic method described herein works only with bromomethylbenzenes and not the corresponding chloromethylbenzenes. Furthermore, we found that adding an external base instead of an excess of the (aminomethyl)pyridine is ineffective. Bases we have examined to this effect include sodium hydroxide, potassium hydroxide, pyridine and triethylamine. Therefore, an excess of the (aminomethyl)pyridine is necessary to provide a proton acceptor for the reaction. If so desired, the excess (aminomethyl)pyridine can be recycled by distillation. Some of the low product yields may be attributed to the fact that the products themselves may be protonated during the reaction and therefore removed during the filtration step. To address this issue, we repeated the synthesis of **16** but stirred the reaction mixture with pulverized potassium hydroxide for 1.5 hours before filtration. The result was a marginal increase in yield after recrystallization (57% vs 46%), which nonetheless suggests that some protonation of product may be occurring during the reaction.

Table 2 Selected Crystallographic Data for compounds **14**, **19** and **20**

	14	**19**	**20**
Formula	$C_{30}H_{36}N_6 \cdot 2H_2O$	$C_{20}H_{22}N_4AgNO_3$	$C_{25}H_{26}AgF_3N_4O_{3.5}S$
FW	516.68	488.30	635.43
Crystal system	triclinic	rhombohedral	triclinic
Space group	$P\bar{1}$	$R\bar{3}$	$P\bar{1}$
a (Å)	10.207(3)	32.9201(15)	8.836(2)
b (Å)	11.812(3)	32.9201(15)	10.759(3)
c (Å)	13.956(3)	9.9920(9)	15.420(4)
α (°)	113.858(4)	90	95.544(4)
β (°)	100.138(5)	90	91.344(4)
γ (°)	101.997(5)	120	108.471(4)
V (Å^3)	1440.2(6)	9377.9(10)	1381.6(6)
Z	2	18	2
R_1 [I > 2σ(I)]	0.062	0.076	0.135
wR_2 (all data)	0.164	0.216	0.303

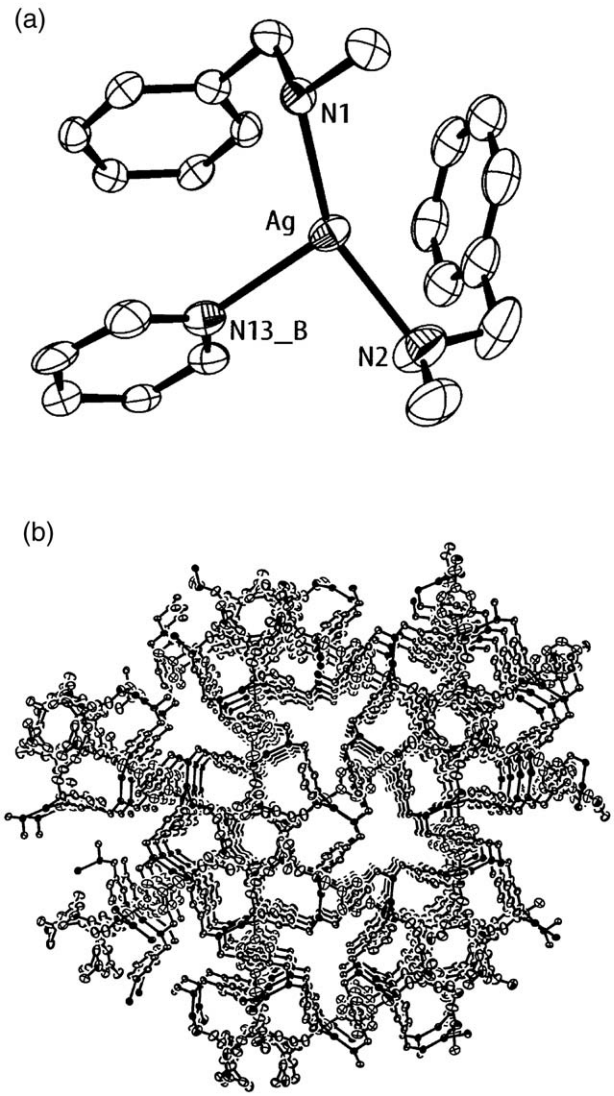


Figure 3 (a) Subunit of three-dimensional polymer **19**; (b) view down the crystallographic *c* axis; in both (a) and (b), hydrogen atoms and nitrate groups are omitted for clarity

In order to demonstrate the application of these ligands in supramolecular assembly, we reacted **5** and **18** with Ag(I) salts. In one experiment, compound **5** was mixed with silver nitrate in an acetone–water mixture. Visually colorless crystals formed after three days of slow solvent evaporation. X-ray crystallographic analysis (Table 2) revealed the assembly of a three-dimensional polymer (**19**). A subunit of the structure is shown in Figure 3(a). The silver ions in the polymer are three-coordinate and exist in a distorted T-shaped geometry, with two sp^3-nitrogen atoms from different ligand molecules forming the ends of the T-crossbar (N1–Ag–N2 152.8°). The third donating atom to the silver is a pyridine nitrogen (N13_B) from a *third* ligand molecule. Viewing the structure down the crystallographic *c*-axis reveals a regular repeating pattern with well-defined channels of varying size [Figure 3(b)]. During the course of this work, Zhu et al. also reported the interaction of **5** with silver nitrate.[58] Interestingly, in this case, an infinite *one-dimensional* polymer was obtained in which N–Ag–N interactions served to link individual ligand molecules end-to-end. The difference in structure may possibly be attributed to the different solvent system used to grow the crystals (EtOH–H_2O in this case).

In a second experiment, compound **18** was reacted with silver triflate in a THF–H_2O mixture. Within one hour, numerous small crystals had formed on the sides of the reaction vial. X-ray structural characterization indicated the formation of an infinite linear polymer (**20**) consisting of alternating Ag(I) ions and molecules of **18**. Each Ag(I) was bound quasi-linearly to two pyridine nitrogen atoms from adjacent molecules of **18** (N–Ag–N 169.2°). In this case, the sp^3-hybridized nitrogen atoms of **18** were not involved in Ag–N bonding. Each linear polymer chain was tethered to a single nearby chain by Ag–Ag interactions (Ag–Ag 3.258 Å), thus giving the overall structure the appearance of a ladder with the Ag–Ag interactions being the rungs (Figure 4).

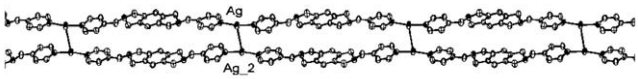


Figure 4 Ladder-like structure of **20**; hydrogen atoms and triflate groups are omitted for clarity

In conclusion, we have synthesized a series of (pyridylalkyl)amine derivatives using a simple one-step method based on N-alkylation chemistry. These compounds possess multiple nitrogen binding sites and therefore are attractive from a ligand application standpoint, as demonstrated by the formation of supramolecular polymers from the reactions of **5** and **18** with Ag(I) salts. Although our reported yields are generally modest, we believe the simplicity of this method and the ready availability of the starting materials make this an attractive preparative approach. We are continuing our investigation into these materials as ligands for supramolecular assemblies.

All NMR spectra were obtained on a 400 MHz Bruker Avance DRX multinuclear NMR spectrometer. Elemental analyses were obtained from Galbraith Laboratories Inc., or by using a CE Elantech Thermo-Finnigan Flash 1112 CHN elemental analyzer. 1,3,5-Tris(bromomethyl)mesitylene was prepared using a literature procedure.[57] All other starting materials were obtained commercially from Sigma–Aldrich or Acros and used as received.

Alkylation; Typical Procedure

All reactions were performed under an atmosphere of dry nitrogen. The synthesis of compound **1** is representative of the alkylation procedure. BnBr (1.19 mL, 10 mmol) in THF (100 mL) was added to a round-bottom flask and 2-(aminomethyl)pyridine (2.03 mL, 20 mmol) was added by syringe. The reaction mixture was stirred overnight at r.t. then the precipitated salts were filtered off and the solvent was removed under reduced pressure. Fractional distillation of the remaining yellow-brown liquid gave **1**; yield: 1.3g (66%); colorless liquid; bp 140 °C/1 mmHg (Lit.[45] 180 °C/0.1 mm Hg).

The spectral characterization data for **1** has been reported previously.[45]

2

The general method was used with the following reagent amounts: BnBr (1.19 mL, 10 mmol), 3-(aminomethyl)pyridine (2.03 mL, 20 mmol) and THF (100 mL); yield: 1.19 g (60%); pale-yellow liquid; bp 135°C/0.05 mm Hg.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.90 (br s, 1 H), 3.83 (s, 4 H), 7.26–7.36 (m, 6 H), 7.72 (d, *J* = 7.7 Hz, 1 H), 8.52 (d, *J* = 4.6 Hz, 1 H), 8.59 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 50.36, 53.13, 123.34, 127.11, 128.11, 128.45, 135.48, 135.79, 139.79, 148.52, 149.77.

Anal. Calcd for $C_{13}H_{14}N_2$: C, 78.75; H, 7.12; N, 14.13. Found: C, 78.99; H, 7.17; N, 14.29.

3

The general method was used with the following reagent amounts: BnBr (1.19 mL, 10 mmol), 4-(aminomethyl)pyridine (2.03 mL, 20 mmol) and THF (100 mL). Flash chromatography on silica gel (CH_2Cl_2–MeOH, 10:1) gave **3**; yield: 1.1 g (56%); brown liquid.

The spectral characterization data for **3** has been reported previously.[48]

4

The general method was used with the following reagent amounts: α,α′-dibromo-*p*-xylene (2.63 g, 10 mmol), 2-(aminomethyl)pyridine (4.08 mL, 40 mmol) and THF (100 mL). Flash chromatography on silica gel (MeOH–CH_2Cl_2, 1:9) gave **4**; yield: 0.63 (20%); thick yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.85 (s, 4 H), 3.94 (s, 4 H), 7.17 (t, *J* = 5.0 Hz, 2 H), 7.31–7.33 (br, 6 H), 7.64 (dt, *J* = 7.7, 1.7 Hz, 2 H), 8.56 (d, *J* = 4.7 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 53.16, 54.37, 121.9, 122.33, 128.33, 136.38, 138.73, 149.27, 159.61.

Anal. Calcd for $C_{20}H_{22}N_4 \cdot 0.5H_2O$: C, 73.36; H, 7.08. Found: C, 72.98; H, 7.35.

5

The general method was used with the following reagent amounts: α,α′-dibromo-*p*-xylene (2.64 g, 10 mmol), 3-(aminomethyl)pyridine (4.06 mL, 40 mmol) and THF (100 mL). Flash chromatography on silica gel (MeOH–acetone, 1:2) gave **5**; yield: 1.33 g (42%); thick yellow liquid that slowly solidified on standing; mp 67 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.81 (s, 4 H), 3.83 (s, 4 H), 7.25–7.28 (m, 2 H), 7.32 (br s, 4 H), 7.70–7.72 (m, 2 H), 8.51 (dd, *J* = 4.8, 1.5 Hz, 2 H), 8.59 (d, *J* = 1.6 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 50.40, 52.87, 123.33, 128.23, 135.56, 135.75, 138.78, 148.49, 149.73.

Anal. Calcd for $C_{20}H_{22}N_4 \cdot H_2O$: C, 71.40; H, 7.19; N, 16.65. Found: C, 71.28; H, 6.82; N, 16.40.

6

The general method was used with the following reagent amounts: α,α′-dibromo-*p*-xylene (2.62 g, 10 mmol), 4-(aminomethyl)pyridine (4.1 mL, 40 mmol) and THF (150 mL). Flash chromatography on silica gel (MeOH–acetone, 1:2) gave **6**; yield: 1.3 g (42%); thick yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.81 (s, 4 H), 3.84 (s, 4 H), 7.30–7.32 (m, 8 H), 8.55–8.56 (m, 4 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 51.81, 52.90, 122.97, 128.26, 138.75, 149.37, 149.77.

Anal. Calcd for $C_{20}H_{22}N_4 \cdot H_2O$: C, 71.40; H, 7.19; N, 16.65. Found: C, 71.48; H, 7.27; N, 16.97.

8

The general method was used with the following reagent amounts: α,α′-dibromo-*m*-xylene (2.63 g, 10 mmol), 3-(aminomethyl)pyridine (4.06 mL, 40 mmol) and THF (150 mL). Flash chromatography on silica gel (MeOH–acetone, 1:2) gave **8**; yield: 1.26 g (40%); orange liquid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.82 (s, 4 H), 3.88 (s, 4 H), 7.23–7.24 (m, 6 H), 7.71 (d, *J* = 7.7 Hz, 2 H), 8.52 (d, *J* = 3.5 Hz, 2 H), 8.59 (br s, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 50.51, 53.12, 123.34, 126.89, 127.82, 128.56, 135.51, 135.77, 140.13, 148.48, 149.72.

Anal. Calcd for $C_{20}H_{22}N_4 \cdot 0.5H_2O$: C, 73.36; H, 7.08; N, 17.11. Found: C, 73.94; H, 7.46; N, 16.81.

9

The general method was used with the following reagent amounts: α,α′-dibromo-*m*-xylene (1.31 g, 5 mmol), 4-(aminomethyl)pyridine (2.03 mL, 20 mmol) and THF (75 mL). Flash chromatography on silica gel (MeOH–acetone, 1:2) gave **9**; yield: 0.58 g (37%); thick yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.81 (s, 4 H), 3.84 (s, 4 H), 7.26–7.32 (m, 8 H), 8.54–8.55 (br, 4 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 51.88, 53.13, 122.95, 126.94, 127.81, 128.60, 140.03, 149.31, 149.73.

Anal. Calcd for $C_{20}H_{22}N_4 \cdot 1.5H_2O$: C, 69.54; H, 7.29; N, 16.22. Found: C, 69.79; H, 7.09; N, 16.18.

10

The general method was used with the following reagent amounts: α,α′-dibromo-*o*-xylene (1.32 g, 5 mmol), 2-(aminomethyl)pyridine (2.04 mL, 20 mmol) and THF (100 mL). Flash chromatography on silica gel (acetone) gave **10**; yield: 0.5 g (48%); thick dark-brown oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.05 (s, 4 H), 4.10 (s, 2 H), 7.20 (br s, 5H), 7.52 (d, *J* = 7.8 Hz, 1 H), 7.70 (dt, *J* = 7.6, 1.8 Hz, 1 H), 8.59–8.60 (m, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 59.05, 61.75, 122.10, 122.25, 122.98, 126.70, 136.60, 139.97, 149.15, 158.98.

Anal. Calcd for $C_{14}H_{14}N_2 \cdot 0.5H_2O$: C, 76.68; H, 6.89; N, 12.78. Found: C, 76.33; H, 6.41; N, 12.61.

11

The general method was used with the following reagent amounts: α,α′-dibromo-*o*-xylene (1.32 g, 5 mmol), 3-(aminomethyl)pyridine (1.27 mL, 12.5 mmol) and THF (100 mL). The crude oil was dissolved in acetone and filtered through a silica gel column. The solvent was removed under reduced pressure to give **11**; yield: 0.65 g (62%); dark oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.95 (s, 2 H), 3.97 (s, 4 H), 7.21 (br s, 4 H), 7.29–7.32 (m, 1 H), 7.80 (d, *J* = 7.4 Hz, 1 H), 8.55 (d, *J* = 4.5 Hz, 1 H), 8.64 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 57.36, 58.86, 122.26, 123.42, 126.78, 134.39, 136.45, 139.69, 148.61, 149.95.

Anal. Calcd for $C_{14}H_{14}N_2 \cdot 0.5H_2O$: C, 76.68; H, 6.89; N, 12.78. Found: C, 76.07; H, 7.00; N, 12.40.

12

The general method was used with the following reagent amounts: α,α′-dibromo-*o*-xylene (1.32 g, 5 mmol), 4-(aminomethyl)pyridine (1.26 mL, 12.5 mmol) and THF (100 mL). The crude oil was dis-

solved in acetone and filtered through a silica gel column. The solvent was removed under reduced pressure to give **12**; yield: 0.61 g (59%); dark oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.94 (s, 2 H), 3.98 (s, 4 H), 7.22 (br s, 4 H), 7.37 (d, *J* = 5.3 Hz, 2 H), 8.57–8.59 (m, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 59.05, 122.32, 123.60, 126.89, 139.68, 148.23, 149.83.

Anal. Calcd for $C_{14}H_{14}N_2 \cdot H_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 74.48; H, 6.38; N, 12.14.

13

The general method was used with the following reagent amounts: 1,3,5-tris(bromomethyl)mesitylene (1.006 g, 2.5 mmol), 2-(aminomethyl)pyridine (1.60 mL, 15 mmol) and THF (50 mL). EtOAc was added to the crude product and the colorless solid formed was filtered off and the filtrate was concentrated under reduced pressure. Flash chromatography on silica gel [acetone–MeOH (3:1) then 100% MeOH] gave **13**; yield: 0.34 g (28%); thick yellow oil.

^{1}H NMR (acetone-d_6, 400 MHz): δ = 2.39 (s, 9 H), 3.81 (s, 6 H), 4.03 (s, 6 H), 7.18 (t, *J* = 5.8 Hz, 3 H), 7.40 (d, *J* = 7.7 Hz, 3 H), 7.66 (t, *J* = 6.2 Hz, 3 H), 8.56 (d, *J* = 3.7 Hz, 3 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 15.14, 48.45, 55.63, 122.22, 122.56, 135.16, 135.73, 136.70, 149.35, 167.05.

Anal. Calcd for $C_{30}H_{36}N_6 \cdot 2H_2O$: C, 69.74; H, 7.80; N, 16.27. Found: C, 69.30; H, 7.33; N, 16.67.

14

The general method was used with the following reagent amounts: 1,3,5-tris(bromomethyl)mesitylene (1.01 g, 2.5 mmol), 3-(aminomethyl)pyridine (1.50 mL, 15 mmol) and THF (50 mL). Flash chromatography on silica gel [acetone–MeOH (2:1) then MeOH–acetone (2:1)] gave **14** as a thick yellow oil in 49% yield (0.63 g). When left exposed to air, **14** crystallized after one week to give fan-shaped and cubic crystals. Slowly evaporating an acetone solution of **14** gave colorless X-ray quality crystals; mp 56–59 °C

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.88 (br, 3 H), 2.31 (s, 9 H), 3.74 (s, 6 H), 3.91 (s, 6 H), 7.28 (d, *J* = 12 Hz, 3 H), 7.77 (d, *J* = 7.6 Hz, 3 H), 8.54 (d, *J* = 4.5 Hz, 3 H), 8.62 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 15.89, 48.43, 52.00, 123.77, 134.98, 135.96, 136.33, 148.96, 150.16.

Anal. Calcd for $C_{30}H_{36}N_6 \cdot 2H_2O$: C, 69.74; H, 7.80; N, 16.27. Found: C, 70.36; H, 7.90; N, 16.11.

15

The general method was used with the following reagent amounts: 1,3,5-tris(bromomethyl)mesitylene (1.02 g, 2.5 mmol), 4-(aminomethyl)pyridine (1.50 mL, 15 mmol) and THF (50 mL). Flash chromatography on silica gel (MeOH–acetone, 2:1) gave **15**; yield: 0.17 g (13%); thick yellow oil.

^{1}H NMR (acetone-d_6, 400 MHz): δ = 2.37 (s, 9 H), 3.72 (s, 6 H), 3.92 (s, 6 H), 7.42 (s, 6 H), 8.51 (d, *J* = 4.3 Hz, 6 H).

^{13}C NMR (acetone-d_6, 100 MHz): δ = 15.14, 48.42, 53.10, 123.48, 134.96, 135.83, 149.94, 150.52.

Anal. Calcd for $C_{30}H_{36}N_6 \cdot H_2O$: C, 72.26; H, 7.68; N, 16.85. Found: C, 72.21; H, 7.60; N, 16.41.

16

The general method was used with the following reagent amounts: 1,2,4,5-tetrakis(bromomethyl)benzene (1.11 g, 2.5 mmol), 2-(aminomethyl)pyridine (2.6 mL, 25 mmol) and THF (50 mL). The crude yellow semi-solid was rinsed thoroughly with Et_2O to give **16**; yield: 0.39 g (46%); fine colorless crystalline solid; mp 134–136 °C (EtOAc).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 4.03 (s, 8 H), 4.10 (s, 4 H), 7.02 (s, 2 H), 7.21 (t, *J* = 6.0 Hz, 2 H), 7.52 (d, *J* = 7.8 Hz, 2 H), 7.70 (t, *J* = 7.8 Hz, 2 H), 8.60 (d, *J* = 4.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 59.3, 62.2, 116.7, 122.6, 123.5, 137.0, 139.1, 149.6, 159.2.

Anal. Calcd for $C_{22}H_{22}N_4$: C, 77.03; H, 6.47; N, 16.42. Found: C, 76.86; H, 6.72; N, 16.19.

17

The general method was used with the following reagent amounts: 1,2,4,5-tetrakis(bromomethyl)benzene (3.41 g, 7.6 mmol), 3-(aminomethyl)pyridine (4.6 mL, 45 mmol) and THF (150 mL). The crude yellow solid was recrystallized (EtOAc–hexane) to give **17**; yield: 1.20 g (46%); pink needles; mp 190–198 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.93 (s, 12 H), 7.02 (s, 2 H), 7.31 (t, *J* = 5.1 Hz, 2 H), 7.80 (d, *J* = 7.5 Hz, 2 H), 8.55 (d, *J* = 4.3 Hz, 2 H), 8.64 (s, 2 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 57.9, 59.1, 116.9, 123.9, 134.7, 136.9, 139.1, 149.2, 150.5.

Anal. Calcd for $C_{22}H_{22}N_4$: C, 77.03; H, 6.47; N, 16.42. Found: C, 77.09; H, 6.53; N, 16.55.

18

The general method was used with the following reagent amounts: 1,2,4,5-tetrakis(bromomethyl)benzene (1.02 g, 2.3 mmol), 4-(aminomethyl)pyridine (1.6 mL, 16 mmol) and THF (50 mL). The crude orange-red solid was recrystallized (EtOAc) to give **18**; yield: 0.35 g (38%); brown needles; mp 187–190 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.94 (s, 4 H, NCH_2), 3.96 (s, 8 H, NCH_2), 7.03 (s, 2 H, Ph-H), 7.38 (d, *J* = 4.7 Hz, 4 H, Py-H), 8.59 (t, *J* = 5.1 Hz, 4 H, Py-H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 59.2, 59.5, 124.0, 116.9, 139.0, 150.4.

Anal. Calcd for $C_{22}H_{22}N_4$: C, 77.03; H, 6.47; N, 16.42. Found: C, 77.81; H, 6.55; N, 16.81.

19

A solution of **5** (0.032 g, 0.1 mmol) in acetone (5 mL) and a solution of silver nitrate (0.017 g, 0.1 mmol) in H_2O (2 mL) were layered in a vial. The vial was kept in the dark without a lid. After 3 days, visually colorless crystals had formed. The crystals were filtered, washed with deionized water, and air-dried; mp 131 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.67 (s, 4 H), 3.71 (s, 4 H), 7.28 (br, 4 H), 7.34–7.37 (m, 2 H), 7.76 (d, *J* = 6.8 Hz, 2 H), 8.42 (d, *J* = 4.7 Hz, 2 H), 8.47 (s, 2 H).

20

A solution of **18** (0.010 g, 0.029 mmol) was dissolved in boiling THF in a vial. After the solution cooled, a solution of silver triflate (0.029 M in H_2O; 1 mL, 0.029 mmol) was added dropwise with swirling. The solution was allowed to slowly evaporate over 1 h, during which time numerous small clear crystals formed on the side of the vial; mp 170 °C

^{1}H NMR (CD_3CN, 400 MHz): δ = 3.90 (s, 8 H), 3.94 (s, 4 H), 7.06 (s, 2 H), 7.42 (d, *J* = 4.7 Hz, 4 H), 8.52 (d, *J* = 4.6 Hz, 4 H).

X-ray Crystallography

Data for compounds **14**, **19** and **20**[60] were collected on a Bruker APEX diffractometer, equipped with a CCD detector. The structures were solved by direct-methods and subsequent difference

Fourier syntheses using SHELXTL program package.[59] The X-ray analysis of **19** revealed that one pyridine group [C(21)–C(26) and C(21′)–C(26′)] and the nitrate counter-ion were disordered. Table 2 contains the crystal data for compounds **14**, **19**, and **20**. Figure 3 and Figure 4 were generated using the software program *ORTEP-3 for Windows*, version 1.08.[61]

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