Pergamon

Tetrahedron 58 (2002) 8573–8579

TETRAHEDRON

Pyridinium *N*-(2′-azinyl)aminides: regioselective synthesis of *N*-(2-pyridyl) substituted polyamines

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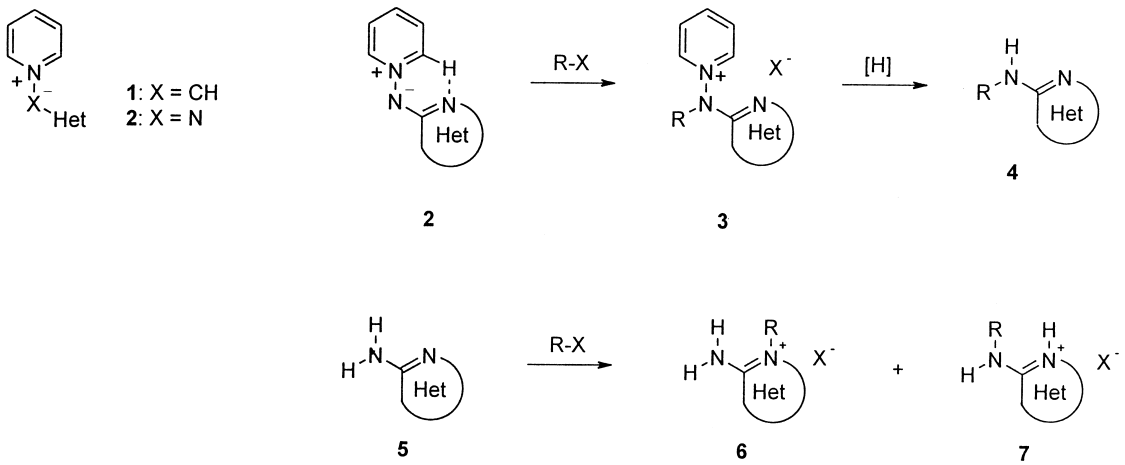
Received 16 May 2002; accepted 24 July 2002

Abstract—The regioselective alkylation of pyridinium-*N*-(2′-pyridyl)aminide with alkyl dihalides under mild conditions, followed by N–N bond reduction of the corresponding bis-salts, allowed an easy preparation of *N*,*N*′-bis(2-pyridyl)diamines. The same methodology has been applied to the synthesis of *N*,*N*′,*N*″-tris(2-pyridyl)triamines. © 2002 Elsevier Science Ltd. All rights reserved.

The role of polyamines in biological systems is well recognized and, over the last two decades, many functions of prokaryotic and eukaryotic cells have been shown to be polyamine dependent.[1–3] Natural and synthetic polyamines are potent cation-channel blockers and templates for the design of synthetic vectors with potential application in gene therapy.[3] A number of polyamine analogues have shown promise as anticancer agents[4,5] and a platinum complex linked by a bridging diamine showed biological activity against various human cancer cell lines.[6,7]

The synthetic approaches to polyamine chemistry have been recently reviewed, being the *N*-alkylation of amines the most widely used reaction in polyamine synthesis.[8] To avoid polyalkylation, excess of amine or a suitable protecting group have to be used but, in the field of diamines and polyamines, mono *N*-alkylation has been achieved using cesium hydroxide.[9] In the last years, we have been interested in heteroaryl-stabilized cycloiminium ylides **1**, as building blocks for the synthesis of heterocyclic derivatives[10–15] and, more recently, we are exploring the synthetic utility of pyridinium *N*-(2′-azinyl)aminides **2** (Scheme 1).[16–21] Some of our work in this field has been concerned with alkylation processes and in a preceding[21] paper we reported the regioselective synthesis of 2-alkylaminoazines **4** in a two-step method. As it is well known, the direct alkylation of heterocyclic amidines **5** is unsatisfactory as a preparative method, because mixtures of *N-endo*-substituted **6** and *N-exo*substituted **7** derivatives are obtained and, usually, alkylation mainly occurs at the most basic endocyclic nitrogen[22,23] (Scheme 1). However, when permanent nitride species, such as the pyridinium *N*-(2′azinyl)aminides **2**, are used, regioselective alkylation takes place at the exocyclic nitrogen, and the salts **3** are



Scheme 1.

Keywords: polyamines; pyridinium bis-salts; aminides; alkylation; ylids.

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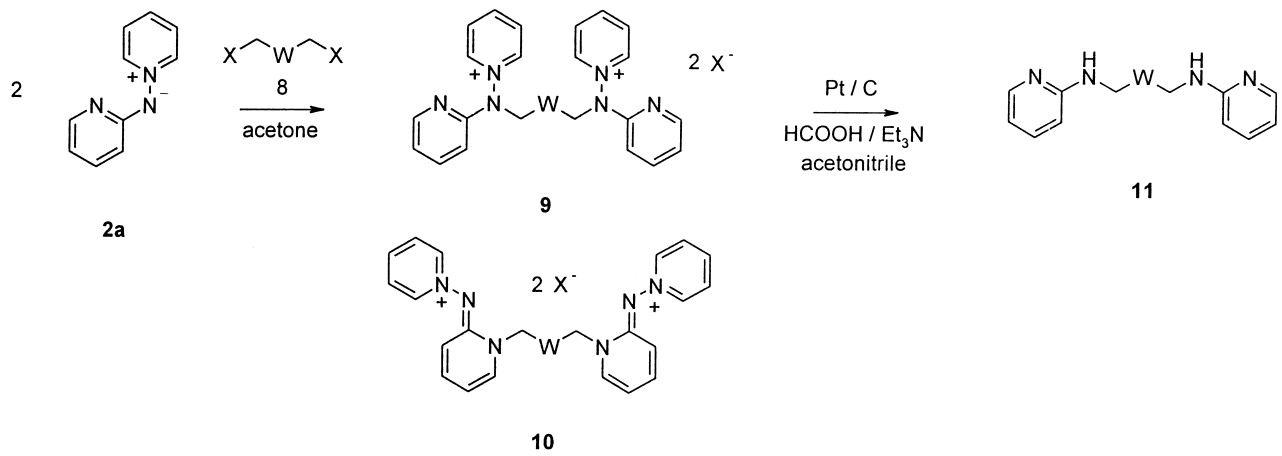
PII: S0040-4020(02)00901-8



Scheme 2.

obtained. Two factors can explain the observed regioselectivity, the stabilizing effect of the pyridinium moiety over the exocyclic *N*-aminide anion, and the existence of an intramolecular hydrogen bond blocking the α-nuclear nitrogen.[17] The final N–N bond reduction of the pyridinium salts affords the corresponding 2-alkylaminoazines **4**.

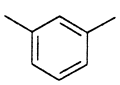
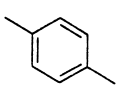
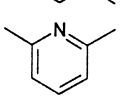
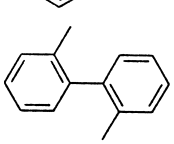
This paper presents the results obtained in the synthesis of some *N*,*N*′-bis(2-pyridyl)diamines **11** from *N*-(2′-pyridyl)-aminide **2a** (Het=2-pyridyl) and the corresponding dihaloderivatives (molar ratio 2:1), by applying the two-step method previously described. The same methodology allows the synthesis of *N*,*N*′,*N*″-tris(2-pyridyl)triamines **15**. Preparation of the starting pyridinium *N*-aminides **2** has been previously described.[17,18]

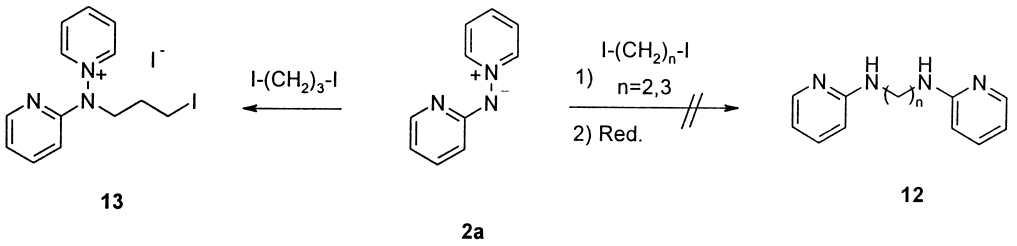
1. Results and discussion

Different dihaloderivatives **8** were reacted at room temperature with the *N*-(2′-pyridyl)aminide **2a** to produce the bis-pyridinium salts **9** as the main products (Scheme 2). Reduction with formic acid/triethylamine in the presence of Pt/C,[18] afforded the corresponding diamines **11** (Table 1). The alkylation process employing a benzylic dihaloderivative, as α,α′-dibromoxylenes, 2,2′-bis(bromomethyl)-1,1′-biphenyl or 2,5-bis(bromomethyl)pyridine, afforded a quantitative yield of the bis-salts **9i–m** (Table 1), in a highly regioselective process, where no traces of the regioisomers **10** were detected in the reaction mixture.

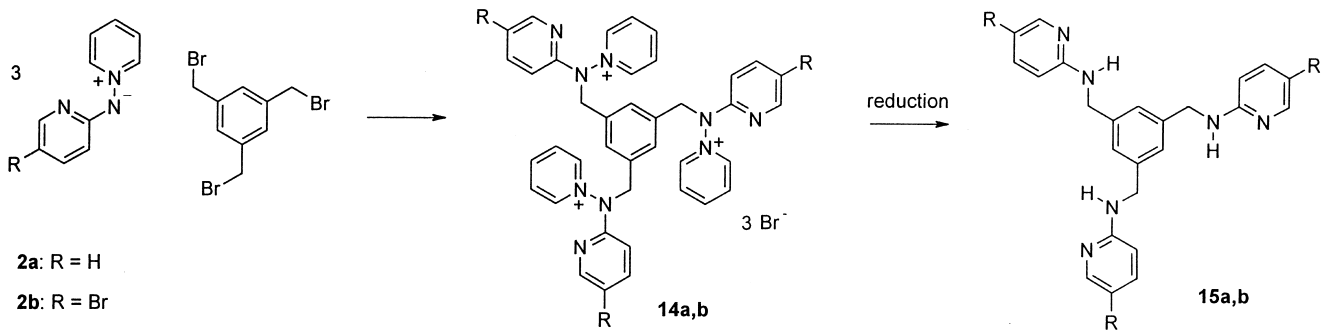
The same process, when applied to the less reactive

Table 1. Compounds **9a–m** and **11a–m** obtained

Compound **9**	W	X	Reaction time (days)	Yield (%)	Compound **11**	Yield (%)
a	$(CH_2)_4$	I	3	50	**a**	45
b	$(CH_2)_5$	I	3	58	**b**	49
c	$(CH_2)_6$	I	3	54	**c**	42
d	$(CH_2)_7$	Br	5	40	**d**	64
e	$(CH_2)_8$	Br	5	40	**e**	43
f	$(CH_2)_9$	Br	9	55	**f**	70
g	$(CH_2)_2O(CH_2)_2$	Br	7	50	**g**	40
h	$(CH_2)_2O(CH_2)_2O(CH_2)_2$	I	7	46	**h**	51
i		Br	2	96	**i**	60
j		Br	2	97	**j**	50
k		Br	2	95	**k**	55
l		Br	2	90	**l**	47
m		Br	1	97	**m**	85



Scheme 3.



Scheme 4.

aliphatic dihaloderivatives took place in the same way, yielding the bis-salts **9a–h** as the main products, but also the corresponding ring alkylated derivatives **10** in a rough 10–15% yield, detected by ^{1}H NMR. As chain length increases, longer time was necessary to obtain a similar conversion, and in compounds **9a–f** about a 15% of starting aminide **2a** was always detected. On the contrary, with short dialkylating agents, like in the synthesis of **12** (Scheme 3) from 1,2-diiodoethane or 1,3-diiodopropane, no bis-alkylation was observed on **2a**, probably due to electronic repulsion in the intermediate salt. With diiodoethane, **2a** was recovered as hydroiodide, indicating a predominance of the elimination process, while compound **13** was obtained from 1,3-diiodopropane.

When 1-bromo-2-(2-bromoethoxy)ethane or 1-iodo-2-[2-(2-iodoethoxy)ethoxy]ethane were used as alkylating agents, the bis-salts **9g** and **9h** were obtained with similar yields than analogous compounds **9b** and **9e**. Monoalkylation product was detected in the synthesis of **9g** and, when the reaction mixture was reduced, 4-pyridin-2-yl morpholine[24] was obtained together with the diamine **11g**.

When the process was applied to the synthesis of tris-salts **14**, (Scheme 4) the process occurred with high regioselectivity and yield. In this case, a mixture of acetonitrile and *N*,*N*-dimethylformamide was used as solvent, to avoid precipitation of the intermediates bis-salts, insolubles in acetone, the usual solvent. Then, the usual reduction with formic acid/triethylamine–Pd/C produced the triamines **15**.

As a conclusion, the use of pyridinium *N*-aminides like **2a**,**b**, can be a good way to produce di- or polialkylamino derivatives bearing 2-aminoheterocyclic fragments, where properties like basicity, or coordinating ability, can be easily modulated.

2. Experimental

All melting points were determined in open capillary tubes, on a Gallenkamp MFB-595-010M and are uncorrected. IR spectra were obtained on a Perkin–Elmer FTIR 1725X spectrometer. ^{1}H and ^{13}C NMR (300 and 75 MHz, respectively) spectra were recorded on a Varian Unity 300 MHz spectrometer at room temperature. Chemical shifts are given in ppm (δ) relative to TMS. Coupling constants (J) are in hertz (Hz), and signals are described as follows: s, singlet; d, doublet; t, triplet; br., broad; m, multiplet; ap., apparent; etc. Mass spectra (*m*/*z*, *I*%) were recorded on a VG AutoSpec (Micromass Instrument). Elemental analyses were carried out on a Heraeus Rapid CHN analyzer and are within 0.4% of the theoretical values for all the new compounds described. All reagents were obtained from commercial sources and used without further purification. All solvents were purified, dried and finally distilled before use following reported procedures.[25] TLC analyses were performed on silica gel 60 plates F_{254} (Macherey–Nagel) and flash purifications were carried out on silica gel 60 (40–63 μm, Merck) and/or employing Biotage columns, using the solvent eluting reported for each case. Spots were visualized under UV light. Ylides **2a**,**b** have been previously described.[17,18]

2.1. Preparation of pyridinium salts 9a–m and 14a,b

General method. To a solution of the pyridinium *N*-(2′-pyridyl)aminide **2a** (514 mg, 3 mmol) in acetone (15 mL), the corresponding dihalide (1.4 mmol) was added, and the mixture was stirred at room temperature until no progress was observed by TLC. The salts were obtained either as solids, which were filtered, washed with acetone and recrystallized or as oils, which were washed with diethyl ether and used in the next step without further purification.

To obtain **9g** and **9h**, THF (15 mL) was used as solvent. The salts **14** were obtained in the same way from pyridinium *N*-(2′-pyridyl)aminide **2a** (770 mg, 4.5 mmol) for **14a** or from pyridinium *N*-(5′-bromo-2′-pyridyl)aminide **2b** (1.13 g, 4.5 mmol) for **14b**, and 2,4,6-tris(bromomethyl)-mesitylene[26] (500 mg, 1.4 mmol) in a mixture of aceto-nitrile (13.5 mL) and *N*,*N*-dimethylformamide (1.5 mL).

2.1.1. 1-{4-[(Pyridin-1-ium-pyridin-2-ylamino)butyl]-pyridin-2-ylamino}pyridinium diiodide (9a). Yellow solid (456 mg, 50%, methanol), mp 233–234°C; [Found: C, 44.21; H, 4.04; N, 12.76. $C_{24}H_{26}I_2N_6$ requires C, 44.19; H, 4.02; N, 12.88%]; ν_{max} (KBr) 3008, 1917, 1473, 1429 cm^{-1}; δ_H (300 MHz, CD_3OD) 9.24 (4H, dd, *J*=5.2, 1.2 Hz, *H*2(6)); 8.82 (2H, tt, *J*=7.6, 1.2 Hz, *H*4); 8.31 (4H, dd, *J*=7.6, 5.2 Hz, *H*3(5)); 8.12 (2H, dd, *J*=4.8, 1.6 Hz, *H*6′); 7.83 (2H, ddd, *J*=8.7, 7.3, 1.6 Hz, *H*4′); 7.08 (4H, m, *H*3′(5′)); 4.26 (4H, br.t, CH_2–N); 1.89 (4H, m, CH_2–C).

2.1.2. 1-{5-[(Pyridin-1-ium-pyridin-2-ylamino)pentyl]-pyridin-2-ylamino}pyridinium diiodide (9b). Brown oil (500 mg, 50% for **11b**); δ_H (300 MHz, CD_3OD) 9.27 (4H, dd, *J*=5.9, 1.3 Hz, *H*2(6)); 8.81 (2H, tt, *J*=7.0, 1.3 Hz, *H*4); 8.32 (4H, dd, *J*=7.0, 5.9 Hz, *H*3(5)); 8.10 (2H, dd, *J*=5.3, 1.8 Hz, *H*6′); 7.83 (2H, ddd, *J*=8.7, 7.3, 1.8 Hz, *H*4′); 7.13 (2H, d, *J*=8.7 Hz, *H*3′); 7.06 (2H, dd, *J*=7.3, 5.3 Hz, *H*5′); 4.21 (4H, br.t, CH_2–N); 1.72 (6H, m, CH_2–C).

2.1.3. 1-{6-[(Pyridin-1-ium-pyridin-2-ylamino)hexyl]-pyridin-2-ylamino}pyridinium diiodide (9c). Yellow solid (514 mg, 54%, ethanol), mp 210–212°C; [Found: C, 46.14; H, 4.35; N, 12.45. $C_{26}H_{30}I_2N_6$ requires C, 45.90; H, 4.44; N, 12.35%]; ν_{max} (KBr) 3012, 1619, 1468, 1432 cm^{-1}; δ_H (300 MHz, CD_3OD) 9.25 (4H, dd, *J*=5.8, 1.4 Hz, *H*2(6)); 8.83 (2H, tt, *J*=7.3, 1.4 Hz, *H*4); 8.33 (4H, dd, *J*=7.3, 5.8 Hz, *H*3(5)); 8.09 (2H, dd, *J*=5.0, 1.9 Hz, *H*6′); 7.84 (2H, ddd, *J*=8.7, 7.3, 1.9 Hz, *H*4′); 7.16 (2H, d, *J*=8.7 Hz, *H*3′); 7.07 (2H, dd, *J*=7.3, 5.0 Hz, *H*5′); 4.21 (4H, t, *J*=7.6 Hz, CH_2–N); 1.67 (4H, m, CH_2β); 1.55 (4H, m, CH_2γ).

2.1.4. 1-{7-[(Pyridin-1-ium-pyridin-2-ylamino)heptyl]-pyridin-2-ylamino}pyridinium dibromide (9d). Brown oil (420 mg, 50% total yield, 42% for **2d**); δ_H (300 MHz, CD_3OD) 9.21 (4H, dd, *J*=5.8, 1.2 Hz, *H*2(6)); 8.80 (2H, tt, *J*=7.2, 1.2 Hz, *H*4); 8.31 (4H, dd, *J*=7.2, 5.8 Hz, *H*3(5)); 8.10 (2H, dd, *J*=4.8, 1.9 Hz, *H*6′); 7.81 (2H, ddd, *J*=8.7, 7.3, 1.9 Hz, *H*4′); 7.12 (2H, d, *J*=8.7 Hz, *H*3′); 7.07 (2H, dd, *J*=7.3, 4.8 Hz, *H*5′); 4.20 (4H, t, *J*=7.5 Hz, CH_2–N); 1.65 (4H, m, CH_2β); 1.45 (6H, m, CH_2γ and CH_2δ).

2.1.5. 1-{8-[(Pyridin-1-ium-pyridin-2-ylamino)octyl]pyridin-2-ylamino}pyridinium dibromide (9e). Yellow solid (344 mg, 40%, ethanol/ethyl acetate), mp 202–203°C; [Found: C, 54.95; H, 5.59; N, 13.45. $C_{28}H_{34}Br_2N_6$ requires C, 54.74; H, 5.58; N, 13.68%]; ν_{max} (KBr) 3005, 2932, 1617, 1472, 1433 cm^{-1}; δ_H (300 MHz, CD_3OD) 9.22 (4H, dd, *J*=5.2, 1.2 Hz, *H*2(6)); 8.80 (2H, tt, *J*=7.3, 1.2 Hz, *H*4); 8.30 (4H, dd, *J*=7.3, 5.2 Hz, *H*3(5)); 8.10 (2H, dd, *J*=4.8, 1.7 Hz, *H*6′); 7.82 (2H, ddd, *J*=8.5, 7.2, 1.7 Hz, *H*4′); 7.10 (2H, d, *J*=8.5 Hz, *H*3′); 7.07 (2H, dd, *J*=7.2, 4.8 Hz, *H*5′); 4.15 (4H, t, *J*=7.5 Hz, CH_2–N); 1.61 (4H, m, CH_2β); 1.37 (8H, m, CH_2γ, CH_2δ and CH_2ε).

2.1.6. 1-{[9-(Pyridin-1-ium-pyridin-2-ylamino)nonyl]-pyridin-2-ylamino}pyridinium dibromide (9f). Brown oil (484 mg, 55%, total yield, 35% for **9f**); δ_H (300 MHz, CD_3OD) 9.23 (4H, dd, *J*=6.8, 1.2 Hz, *H*2(6)); 8.82 (2H, tt, *J*=7.7, 1.2 Hz, *H*4); 8.31 (4H, dd, *J*=7.7, 6.8 Hz, *H*3(5)); 8.10 (2H, dd, *J*=5.0, 1.8 Hz, *H*6′); 7.84 (2H, ddd, *J*=8.6, 7.3, 1.8 Hz, *H*4′); 7.12 (2H, d, *J*=8.6 Hz, *H*3′); 7.07 (2H, dd, *J*=7.3, 5.0 Hz, *H*5′); 4.15 (4H, t, *J*=7.5 Hz, CH_2–N); 1.61 (4H, m, CH_2β); 1.37 (10H, m, CH_2γ, CH_2δ and CH_2ε).

2.1.7. 1-{[3-Oxa-5-(pyridin-1-ium-pyridin-2-ylamino)-pentyl]pyridin-2-ylamino}pyridinium dibromide (9g). Brown oil (442 mg, 55%, total yield, 50% for **9g**); δ_H (300 MHz, CD_3OD) 9.20 (4H, dd, *J*=6.7, 1.4 Hz, *H*2(6)); 8.75 (2H, tt, *J*=7.8, 1.4 Hz, *H*4); 8.24 (4H, dd, *J*=7.8, 6.7 Hz, *H*3(5)); 8.11 (2H, ddd, *J*=4.9, 1.8, 0.9 Hz, *H*6′); 7.80 (2H, ddd, *J*=8.7, 7.0, 1.8 Hz, *H*4′); 7.06 (2H, dd, *J*=7.0, 4.9 Hz, *H*5′); 6.97 (2H, d, *J*=8.7 Hz, *H*3′); 4.31 (4H, t, *J*=4.9 Hz, CH_2O); 3.79 (4H, t, CH_2N).

2.1.8. 1-{[3,6-Dioxa-8-(pyridin-1-ium-pyridin-2-ylamino)-octyl]pyridin-2-ylamino} pyridinium diiodide (9h). Brown oil (748 mg, 75%, total yield, 46% for **9h**); δ_H (300 MHz, CD_3OD) 9.26 (4H, dd, *J*=6.8, 1.3 Hz, *H*2(6)); 8.82 (2H, tt, *J*=7.8, 1.3 Hz, *H*4); 8.31 (4H, dd, *J*=7.8, 6.8 Hz, *H*3(5)); 8.11 (2H, ddd, *J*=4.9, 1.8, 0.9 Hz, *H*6′); 7.83 (2H, ddd, *J*=8.6, 7.3, 1.8 Hz, *H*4′); 7.06 (4H, m, *H*3′ and 5′); 4.41 (4H, t, *J*=4.7 Hz, CH_2O); 3.78 (4H, t, *J*=4.7 Hz, CH_2N); 3.38 (4H, s, (OCH_2)$_2$).

2.1.9. 1-{[2-(Pyridin-1-ium-pyridin-2-ylaminomethyl)-benzyl]pyridin-2-ylamino}pyridinium dibromide (9i). Pale yellow solid (815 mg, 96%, ethanol/ethyl acetate), mp 218–219°C; [Found: C, 55.41; H, 4.61; N, 13.61. $C_{28}H_{26}Br_2N_6$ requires C, 55.46; H, 4.32; N, 13.86%]; ν_{max} (KBr) 2995, 1586, 1470, 1428, 775, 691 cm^{-1}; δ_H (300 MHz, CD_3OD) 9.27 (4H, dd, *J*=6.8, 1.6 Hz, *H*2(6)); 8.70 (2H, tt, *J*=7.7, 1.6 Hz, *H*4); 8.20 (6H, m, *H*3(5) and *H*6′); 7.83 (2H, ddd, *J*=8.7, 7.5, 1.6 Hz, *H*4′); 7.16 (6H, m, *H*–Ar and *H*5′); 7.05 (2H, d, *J*=7.5 Hz, *H*3′); 5.68 (4H, s, CH_2).

2.1.10. 1-{[3-(Pyridin-1-ium-pyridin-2-ylaminomethyl)-benzyl]pyridin-2-ylamino}pyridinium dibromide (9j). White solid (823 mg, 96%, ethanol/ethyl acetate), mp 227–228°C; [Found: C, 55.76; H, 4.40; N, 14.10. $C_{28}H_{26}Br_2N_6$ requires C, 55.46; H, 4.32; N, 13.86%]; ν_{max} (KBr) 3012, 1574, 1468, 1427, 773, 682 cm^{-1}; δ_H (300 MHz, CD_3OD) 9.17 (4H, dd, *J*=6.8, 1.2 Hz, *H*2(6)); 8.68 (2H, tt, *J*=7.6, 1.2 Hz, *H*4); 8.16 (6H, m, *H*3(5) and *H*6′); 7.86 (2H, ddd, *J*=8.5, 8.0, 1.6 Hz, *H*4′); 7.62 (1H, br.s, *H*-2″); 7.34 (3H, m, *H*4″(6″) and *H*5″); 7.15 (4H, m, *H*3′ and 5′); 5.37 (4H, s, CH_2).

2.1.11. 1-{[4-(Pyridin-1-ium-pyridin-2-ylaminomethyl)-benzyl]pyridin-2-ylamino}pyridinium dibromide (9k). White solid (806 mg, 95%, ethanol), mp >290°C; [Found: C, 55.34; H, 4.34; N, 13.63. $C_{28}H_{26}Br_2N_6$ requires C, 55.46; H, 4.32; N, 13.86%]; ν_{max} (KBr) 3009, 2934, 1621, 1468, 1427, 643 cm^{-1}; δ_H (300 MHz, CD_3OD) 9.15 (4H, dd,

J=6.8, 1.2 Hz, $H2(6)$); 8.73 (2H, tt, J=7.8, 1.2 Hz, $H4$); 8.17 (6H, m, $H3(5)$ and $H6'$); 7.86 (2H, ddd, J=8.8, 7.5, 1.8 Hz, $H4'$); 7.41 (4H, s, H–Ar); 7.17 (4H, m, $H3'$ and $5'$); 5.35 (4H, s, CH_2).

2.1.12. 1-{[6-(Pyridin-1-ium-pyridin-2-ylaminomethyl)-pyridin-2-ylmethyl]pyridin-2-ylamino}pyridinium dibromide (9l). White solid (765 mg, 90%, ethanol), mp 182–183°C; [Found: C, 53.23; H, 4.37; N, 15.91. $C_{27}H_{25}Br_2N_7$ requires C, 53.40; H, 4.15; N, 16.14%]; ν_{max} (KBr) 3010, 1588, 1471, 1430, 780, 685 cm^{-1}; δ_H (300 MHz, CD_3OD) 9.28 (4H, dd, J=6.8, 1.5 Hz, $H2(6)$); 8.73 (2H, tt, J=7.9, 1.5 Hz, $H4$); 8.21 (4H, dd, J=7.9, 6.8 Hz, $H3(5)$); 8.10 (2H, ddd, J=4.8, 2.0, 0.8 Hz, $H6'$); 7.90 (1H, t, J=7.9 Hz, $H4''$); 7.74 (2H, ddd, J=8.9, 7.3, 2.0 Hz, $H4'$); 7.59 (2H, d, J=7.9 Hz, $H3''(5'')$); 7.05 (2H, dd, J=7.3, 4.8 Hz, $H5'$); 6.90 (2H, d, J=8.9 Hz, $H3'$); 5.56 (4H, s, CH_2).

2.1.13. 1-{[2′-(Pyridin-1-ium-pyridin-2-ylaminomethyl)-biphenyl-2-ylmethyl]pyridin-2-ylamino}pyridinium dibromide (9m). Beige solid (930 mg, 97%, ethanol/ethyl acetate), mp 221–223°C; [Found: C, 59.21; H, 4.47; N, 12.14. $C_{34}H_{30}Br_2N_6$ requires C, 59.29; H, 4.71; N, 12.28]; ν_{max} (KBr) 3011, 1617, 1588, 1468, 1427, 773, 687 cm^{-1}; δ_H (300 MHz CD_3OD) 9.02 (4H, dd, J=6.8, 1.4 Hz, $H2(6)$); 8.81 (2H, tt, J=7.8, 1.4 Hz, $H4$); 8.24 (4H, dd, J=7.8, 6.8 Hz, $H3(5)$); 8.11 (2H, dd, J=4.9, 1.8 Hz, $H6'$); 7.72 (2H, ddd, J=8.5, 7.3, 1.8 Hz, $H4'$); 7.52 (2H, dd, J=7.2, 1.9 Hz, H–Ar); 7.44 (2H, td, J=7.2, 1.9 Hz, H–Ar); 7.40 (2H, td, J=7.2, 1.9 Hz, H–Ar); 7.15 (2H, dd, J=7.2, 1.9 Hz, H–Ar); 7.08 (2H, dd, J=7.3, 4.9 Hz, $H5'$); 6.66 (2H, d, J=8.5 Hz, $H3'$); 5.37 (2H, d, J=14.8 Hz, CH_2); 5.12 (2H, d, J=14.8 Hz, CH_2).

2.1.14. 1-[3-Iodoethyl(pyridin-2-yl)amino]pyridinium iodide (13). White solid (666 mg, 95%, ethanol/ethyl acetate), mp 181–182°C; [Found: C, 33.36; H, 3.22; N, 9.08 $C_{13}H_{15}I_2N_3$ requires C, 33.43; H, 3.24; N, 9.00%]; ν_{max} (KBr) 3003, 1637, 1617, 1513 cm^{-1}; δ_H (300 MHz, CD_3OD) 9.74 (2H, dd, J=6.7, 1.4 Hz, $H2(6)$); 9.07 (1H, tt, J=7.9, 1.4 Hz, $H4$); 8.58 (2H, dd, J=7.9, 6.7 Hz, $H3(5)$); 8.53 (1H, dd, J=6.4, 1.6 Hz, $H6'$); 8.21 (1H, ddd, J=9.0, 7.6, 1.6 Hz, $H4'$); 7.50 (1H, ddd, J=7.6, 6.4, 1.3 Hz, $H5'$); 6.88 (1H, d, J=9.0 Hz, $H3'$); 4.85 (2H, ap.t, J=5.7 Hz, CH_2–N); 4.46 (2H, t, J=6.0 Hz, CH_2–I); 2.78 (2H, m, CH_2).

2.1.15. 1-{[3,5-Bis(pyridin-1-ium-pyridin-2-ylamino-methyl)benzyl]pyridin-2-ylamino}pyridinium tribromide (14a). Yellow solid (914 mg, 75%, ethanol), mp >290°C; [Found: C, 53.54; H, 4.27; N, 14.25. $C_{39}H_{36}Br_3N_9$ requires C, 53.81; H, 4.17; N, 14.48%]; ν_{max} (KBr) 3008, 1619, 1467, 1432, 779, 686 cm^{-1}; δ_H (300 MHz, CD_3OD) 9.21 (6H, dd, J=6.0, 1.4 Hz, $H2(6)$); 8.68 (3H, tt, J=8.1, 1.4 Hz, $H4$); 8.18 (9H, m, $H3(5)$ and $H6'$); 7.83 (3H, ddd, J=8.4, 7.3, 2.1 Hz, $H4'$); 7.61 (3H, s, H–Ar); 7.15 (3H, dd, J=7.3, 4.8 Hz, $H5'$); 7.03 (3H, d, J=8.4 Hz, $H3'$); 5.38 (6H, s, CH_2).

2.1.16. 1-{[3,5-Bis(pyridin-1-ium-5-bromopyridin-2-yl-aminomethyl)benzyl]-5-bromopyridin-2-ylamino}pyridinium tribromide (14b). White solid (1.2 g, 77%, ethanol/ethyl acetate), mp >170°C (dec.); [Found: C, 41.98; H, 3.28, N, 11.07. $C_{39}H_{33}Br_6N_9$ requires C, 42.31; H, 3.00; N, 11.39]; ν_{max} (KBr) 3024, 1618, 1577, 1465, 1372, 1001, 678 cm^{-1}; δ_H (300 MHz, CD_3OD) 9.30 (6H, dd, J=6.7, 1.3 Hz, $H2(6)$); 8.75 (3H, tt, J=7.8, 1.3 Hz, $H4$); 8.27 (3H, br. d, J=2.2 Hz, $H6'$); 8.25 (6H, dd, J=7.8, 6.7 Hz, $H3(5)$); 8.02 (3H, dd, J=8.9, 2.2 Hz, $H4'$); 7.65 (3H, s, H–Ar); 7.09 (3H, d, J=8.9 Hz, $H3'$); 5.45 (6H, s, CH_2).

2.2. Reduction of pyridinium salts

General method. Platinum on charcoal (5%) (260 mg) was suspended into a solution of the pyridinium bis-salts (0.6 mmol) in CH_3CN (9 mL) and cooled in an ice bath with stirring. Formic acid (98%, 2.6 mL) in CH_3CN (4.5 mL) and then triethylamine (6.2 mL) in the same solvent (9 mL) were added dropwise. The reaction mixture was refluxed for 4 h. The resulting suspension was filtered through Celite, the filtrate was evaporated, made basic with saturated aq. solution of potassium carbonate and extracted with ethyl acetate (3×25 mL). The combined organic phases were dried over $MgSO_4$, filtered and evaporated to dryness. The residue was purified by flash chromatography (ethyl acetate) and finally, recrystallized and identified. Reduction of pyridinium tris-salts **14** was accomplished in the same way, using platinum on charcoal (5%) (390 mg) in CH_3CN (13.5 mL), formic acid (3.9 mL) in CH_3CN (6.6 mL) and triethylamine (9.3 mL) in the same solvent (13.5 mL).

2.2.1. *N,N′*-Dipyridin-2-yl-butane-1,4-diamine (11a). White solid (65 mg, 45%, ethyl acetate/hexane), mp 151–152°C; [Found: C, 69.23; H, 7.53; N, 22.82. $C_{14}H_{18}N_4$ requires C, 69.39; H, 7.49; N, 23.12%]; ν_{max} (KBr) 3241, 2937, 2867, 1604, 1440 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.06 (2H, ddd, J=5.0, 2.0, 0.8 Hz, $H6$); 7.39 (2H, ddd, J=8.4, 6.5, 2.0 Hz, $H4$); 6.54 (2H, ddd, J=6.5, 5.0, 2.0 Hz, $H5$); 6.36 (2H, br.d, J=8.4 Hz, $H3$); 4.62 (2H, br.s, HN); 3.31 (4H, m, CH_2N); 1.72 (4H, m, CH_2). δ_C (75 MHz, $CDCl_3$) 158.4 ($C2$), 147.7 ($C6$), 137.1 ($C4$), 112.4 ($C5$), 106.4 ($C3$), 41.5 (CH_2N), 26.7 (CH_2).

2.2.2. *N,N′*-Dipyridin-2-yl-pentane-1,5-diamine (11b). Creamy solid (75 mg, 49%, ethyl acetate/hexane), mp 148–149°C; [Found: C, 69.90; H, 7.91; N, 21.72. $C_{15}H_{20}N_4$ requires C, 70.28; H, 7.86; N, 21.86%]; ν_{max} (KBr) 3312, 2933, 2857, 1614, 1468 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.06 (2H, ddd, J=5.0, 1.9, 0.9 Hz, $H6$); 7.40 (2H, ddd, J=8.5, 6.5, 1.9 Hz, $H4$); 6.55 (2H, ddd, J=6.5, 5.0, 0.9 Hz, $H5$); 6.35 (2H, dt, J=8.5, 0.9 Hz, $H3$); 4.50 (2H, br.s, HN); 3.26 (4H, ap.q, J=6.7 Hz, CH_2N); 1.67 (4H, m, $CH_2\beta$), 1.51 (2H, m, $CH_2\gamma$). δ_C (75 MHz, $CDCl_3$) 158.8 ($C2$), 148.1 ($C6$), 137.4 ($C4$), 112.7 ($C5$), 106.5 ($C3$), 42.0 (CH_2N), 29.4 ($CH_2\beta$), 24.5 ($CH_2\gamma$).

2.2.3. *N,N′*-Dipyridin-2-yl-hexane-1,6-diamine (11c). White solid (68 mg, 42%, ethyl acetate/hexane), mp 151–152°C (lit.[27] 151–153°C); [Found: C, 70.70; H, 8.16; N, 20.37. $C_{16}H_{22}N_4$ requires C, 71.08; H, 8.20; N, 20.72%]; ν_{max} (KBr) 3285, 2933, 2850, 1610, 1457 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.06 (2H, dd, J=4.9, 1.8 Hz, $H6$); 7.40 (2H, ddd, J=8.5, 7.1, 1.8 Hz, $H4$); 6.54 (2H, ddd, J=7.1, 4.9, 0.8 Hz, $H5$); 6.36 (2H, br.d, J=8.5 Hz, $H3$); 4.50 (2H, br.s, HN); 3.25 (4H, ap.q, J=7.0 Hz, CH_2N); 1.64 (4H, m,

CH_2β), 1.45 (4H, m, CH_2γ). δ_C (75 MHz, $CDCl_3$) 158.5 (*C*2), 147.8 (*C*6), 137.1 (*C*4), 112.3 (*C*5), 106.1 (*C*3), 41.8 (*C*H_2N), 29.2 (*C*H_2β), 26.5 (*C*H_2γ).

2.2.4. *N*,*N*′-Dipyridin-2-yl-heptane-1,7-diamine (11d). White solid (109 mg, 64%, ethyl acetate/hexane), mp 100–101°C; [Found: C, 71.63; H, 8.44; N, 19.66. $C_{17}H_{24}N_4$ requires C, 71.79; H, 8.51; N, 19.70%]; ν_{max} (KBr) 3279, 2928, 2854, 1611, 1475 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.03 (2H, ddd, *J*=5.0, 1.8, 0.9 Hz, *H*6); 7.37 (2H, ddd, *J*=8.6, 6.9, 1.8 Hz, *H*4); 6.51 (2H, ddd, *J*=6.9, 5.0, 0.9 Hz, *H*5); 6.33 (2H, dt, *J*=8.6, 0.9 Hz, *H*3); 4.53 (2H, br.s, *H*N); 3.20 (4H, ap.q, *J*=7.0 Hz, CH_2N); 1.59 (4H, m, CH_2β), 1.37 (6H, m, CH_2γ and CH_2δ). δ_C (75 MHz, $CDCl_3$) 158.8 (*C*2), 148.1 (*C*6), 137.4 (*C*4), 112.5 (*C*5), 106.3 (*C*3), 42.2 (*C*H_2N), 29.4 (*C*H_2β), 29.1 (*C*H_2γ), 26.9 (*C*H_2δ).

2.2.5. *N*,*N*′-Dipyridin-2-yl-octane-1,8-diamine (11e). White solid (77 mg, 43%, ethyl acetate/hexane), mp 111–112°C; [Found: C, 72.18; H, 8.83; N, 18.81. $C_{18}H_{26}N_4$ requires C, 72.44; H, 8.78; N, 18.77%]; ν_{max} (KBr) 3330, 2927, 2854, 1610, 1478 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.05 (2H, ddd, *J*=5.6, 1.8, 0.8 Hz, *H*6); 7.41 (2H, ddd, *J*=8.4, 6.0, 1.8 Hz, *H*4); 6.54 (2H, ddd, *J*=6.0, 5.6, 0.8 Hz, *H*5); 6.37 (2H, br.d, *J*=8.4 Hz, *H*3); 4.58 (2H, br.s, *H*N); 3.23 (4H, m, CH_2N); 1.61 (4H, m, CH_2β), 1.35 (8H, m, CH_2γ and CH_2δ). δ_C (75 MHz, $CDCl_3$) 158.4 (*C*2), 147.5 (*C*6), 137.2 (*C*4), 112.2 (*C*5), 106.1 (*C*3), 41.9 (*C*H_2N), 29.2 (*C*H_2β), 28.9 (*C*H_2γ), 26.6 (*C*H_2δ).

2.2.6. *N*,*N*′-Dipyridin-2-yl-nonane-1,9-diamine (11f). White solid (131 mg, 70%, ethyl acetate/hexane), mp 141–142°C; [Found: C, 72.70; H, 9.21; N, 17.58. $C_{19}H_{28}N_4$ requires C, 73.04; H, 9.03; N, 17.93%]; ν_{max} (KBr) 3288, 2928, 2849, 1614, 1517, 1475 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.06 (2H, dd, *J*=5.1, 2.1 Hz, *H*6); 7.40 (2H, ddd, *J*=8.6, 7.1, 2.1 Hz, *H*4); 6.54 (2H, ddd, *J*=7.1, 5.1, 0.7 Hz, *H*5); 6.37 (2H, br.d, *J*=8.6 Hz, *H*3); 4.47 (2H, br.s, *H*N); 3.23 (4H, m, CH_2N); 1.61 (4H, m, CH_2β), 1.36 (10H, m, CH_2γ, CH_2δ and CH_2ε). δ_C (75 MHz, $CDCl_3$) 158.6 (*C*2), 147.9 (*C*6), 137.8 (*C*4), 112.3 (*C*5), 106.0 (*C*3), 41.9 (*C*H_2N), 29.2 (*C*H_2β), 29.1 (*C*H_2γ), 28.9 (*C*H_2δ), 26.7 (*C*H_2ε).

2.2.7. *N*,*N*′-Di-piridin-2-yl-3-oxo-pentane-1,5-diamine (11g). Yellowish oil (62 mg, 40%); ν_{max} (KBr) 3350, 1606, 1515, 771 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.06 (2H, dd, *J*=5.1, 1.9 Hz, *H*6); 7.35 (2H, ddd, *J*=8.3, 7.1, 1.9 Hz, *H*4); 6.53 (2H, ddd, *J*=7.1, 5.1, 0.9 Hz, *H*5); 6.37 (2H, br.d, *J*=8.3 Hz, *H*3); 4.91 (2H, br.s, *H*N); 3.64 (4H, t, *J*=5.3 Hz, CH_2O); 3.48 (4H, q, *J*=5.3 Hz, CH_2N). δ_C (75 MHz, $CDCl_3$) 158.3 (*C*2), 147.4 (*C*6), 136.8 (*C*4), 112.3 (*C*5), 107.2 (*C*3), 69.39 (*C*H_2O), 41.3 (*C*H_2N). MS (EI 70 eV) *m*/*z* 78 (51), 94 (55), 107 (93), 119 (33), 139 (100), 258 (M^+ 8); exact mass calcd for $C_{14}H_{18}N_4O$ 258.1481, found 258.1470.

2.2.8. *N*,*N*′-Di-piridin-2-yl-3,6-dioxo-octane-1,8-diamine (11h). Yellowish oil (92 mg, 51%); ν_{max} (KBr) 3360, 1606, 1516, 773 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.05 (2H, ddd, *J*=5.1, 1.9, 0.9 Hz, *H*6); 7.36 (2H, ddd, *J*=8.5, 7.1, 1.9 Hz, *H*4); 6.53 (2H, ddd, *J*=7.1, 5.1, 0.9 Hz, *H*5); 6.38 (2H, br.d, *J*=8.5 Hz, *H*3); 5.25 (2H, br.s, *H*N); 3.69 (4H, t, *J*=4.9 Hz, CH_2O); 3.64 (4H, s, CH_2O); 3.50 (4H, br.q, *J*=4.9 Hz, CH_2N). δ_C (75 MHz, $CDCl_3$) 158.3 (*C*2), 147.9 (*C*6), 137.3 (*C*4), 112.8 (*C*5), 107.6 (*C*3), 70.4 (*C*H_2O), 70.0 (*C*H_2O), 41.8 (*C*H_2N). MS (EI 70 eV) *m*/*z* 78 (41), 94 (38), 107 (100), 121 (22), 183 (83), 302 (M^+ 4); exact mass calcd for $C_{16}H_{22}N_4O_2$ 302.1743, found 302.1743.

2.2.9. 2-(Pyridin-2-ylaminomethyl)benzylpyridin-2-ylamine (11i). White solid (105 mg, 60%, ethyl acetate), mp 154–156°C; [Found: C, 74.47; H, 6.47; N, 19.02. $C_{18}H_{18}N_4$ requires C, 74.46; H, 6.25; N, 19.29%]; ν_{max} (KBr) 3239, 1608, 1511, 1482, 776 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.08 (2H, ddd, *J*=5.6, 2.0, 0.8 Hz, *H*6); 7.38 (4H, m, *H*4 and *H*–Ar); 7.26 (2H, m, *H*–Ar), 6.58 (2H, ddd, *J*=5.6, 5.0, 0.8 Hz, *H*5); 6.38 (2H, br.d, *J*=8.4 Hz, *H*3); 5.21 (2H, br.s, *H*N); 4.60 (4H, br.s, CH_2). δ_C (75 MHz, $CDCl_3$) 157.9 (*C*2), 147.4 (*C*6), 137.8 (*C*–Ar), 137.1 (*C*4), 128.7 (*C*–Ar), 127.5 (*C*–Ar), 112.7 (*C*5), 107.3 (*C*3), 43.5 (*C*H_2).

2.2.10. 3-(Pyridin-2-ylaminomethyl)benzylpyridin-2-ylamine (11j). White solid (87 mg, 50%, ethyl acetate), mp 129–130°C; [Found: C, 74.19; H, 6.33; N, 18.91. $C_{18}H_{18}N_4$ requires C, 74.46; H, 6.25; N, 19.29%]; ν_{max} (KBr) 3256, 1614, 1521, 1491, 771 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.08 (2H, dd, *J*=5.2, 1.8 Hz, *H*6); 7.38 (3H, m, *H*4 and *H*–Ar); 7.27 (3H, m, *H*–Ar), 6.58 (2H, ddd, *J*=6.0, 5.2, 0.8 Hz, *H*5); 6.34 (2H, br.d, *J*=8.4 Hz, *H*3); 4.96 (2H, br.t, *J*=5.6 Hz, *H*N); 4.48 (4H, d, *J*=5.6 Hz, CH_2). δ_C (75 MHz, $CDCl_3$) 158.2 (*C*2), 147.7 (*C*6), 139.3 (*C*–Ar), 137.2 (*C*4), 128.6 (*C*–Ar), 126.1 (*C*–Ar), 125.9 (*C*–Ar), 112.8 (*C*5), 106.5 (*C*3), 45.9 (*C*H_2).

2.2.11. 4-(Pyridin-2-ylaminomethyl)benzylpyridin-2-ylamine (11k). White solid (96 mg, 55%, ethyl acetate), mp 191–193°C; [Found: C, 74.34; H, 6.35; N, 18.99. $C_{18}H_{18}N_4$ requires C, 74.46; H, 6.25; N, 19.29%]; ν_{max} (KBr) 3245, 1599, 1533, 1458, 770 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.08 (2H, dd, *J*=5.2, 1.8 Hz, *H*6); 7.40 (2H, ddd, *J*=8.6, 7.2, 1.8 Hz, *H*4); 7.33 (4H, s, *H*–Ar), 6.59 (2H, ddd, *J*=7.2, 5.2, 0.8 Hz, *H*5); 6.37 (2H, br.d, *J*=8.6 Hz, *H*3); 4.96 (2H, br.t, *J*=6.0 Hz, *H*N); 4.49 (4H, d, *J*=6.0 Hz, CH_2). δ_C (75 MHz, $CDCl_3$) 158.1 (*C*2), 147.6 (*C*6), 139.2 (*C*–Ar), 137.2 (*C*4), 127.4 (*C*–Ar), 112.8 (*C*5), 106.6 (*C*3), 37.6 (*C*H_2).

2.2.12. [6-(Pyridin-2-ylaminomethyl)pyridin-2-ylmethyl]pyridin-2-ylamine (11l). White solid (82 mg, 47%, ethyl acetate/hexane), mp 153–155°C (lit.[28] 147–149); [Found: C, 69.92; H, 6.02; N, 24.30. $C_{17}H_{17}N_5$ requires C, 70.08; H, 5.88; N, 24.04%]; ν_{max} (KBr) 3268, 1610, 1519, 772 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.10 (2H, dd, *J*=5.0, 1.8 Hz, *H*6); 7.58 (1H, t, *J*=8.9 Hz, *H*4′); 7.41 (2H, ddd, *J*=8.5, 7.2, 1.8 Hz, *H*4); 7.23 (2H, d, *J*=8.9 Hz, *H*3′(5′)); 6.59 (2H, dd, *J*=7.2, 5.0 Hz, *H*5); 6.49 (2H, d, *J*=8.5 Hz, *H*3); 5.72 (2H, br.s, *H*N); 4.63 (4H, d, *J*=4.1 Hz, CH_2). δ_C (75 MHz, $CDCl_3$) 158.1 (*C*2), 157.2 (*C*2′, 6′), 147.6 (*C*6), 136.9 (*C*4′), 137.1 (*C*4), 119.6 (*C*3′,5′), 112.7 (*C*5), 107.3 (*C*3), 46.8 (*C*H_2).

2.2.13. [(2′-Pyridin-2-ylaminomethyl)biphenyl-2-ylmethyl]pyridin-2-ylamine (11m). White solid (187 mg, 85%, ethyl acetate/hexane), mp 151–153°C; [Found: C, 78.32; H, 6.13; N, 14.96. $C_{24}H_{22}N_4$ requires C, 78.66; H, 6.05; N, 15.29%]; ν_{max} (KBr) 3228, 1595, 1437, 772 cm^{-1};

δ_H (300 MHz, $CDCl_3$) 8.00 (2H, dd, J=5.0, 2.0 Hz, *H*6); 7.49 (2H, m, *H*–Ar); 7.30 (6H, *H*4 and *H*–Ar); 7.19 (2H, m, *H*–Ar); 6.51 (2H, ddd, J=7.2, 5.0, 0.9 Hz, *H*5); 6.23 (2H, br. d, J=8.5 Hz, *H*3); 5.1 (2H, br. t, J=5.6 Hz, *H*N); 4.27 (4H, m, CH_2). δ_C (75 MHz, $CDCl_3$) 158.4 (*C*2), 147.9 (*C*6), 139.8 (*C*2′), 137.2 (*C*4), 137.0 (*C*1′), 129.6 (*C*–Ar), 128.2 (*C*–Ar), 127.8 (*C*–Ar), 127.0 (*C*–Ar), 112.8 (*C*5), 106.9 (*C*3), 43.9 (CH_2).

2.2.14. 3,5-Bis-(pyridin-2-ylaminomethyl)benzylpyridin-2-ylamine (15a). White solid (178 mg, 75%, ethyl acetate/hexane), mp 145–146°C; [Found: C, 72.69; H, 6.20; N, 20.97. $C_{24}H_{24}N_6$ requires C, 72.70; H, 6.10; N, 21.20%]; ν_{max} (KBr) 3239, 1599, 1458, 773 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.05 (3H, dd, J=4.8, 2.0 Hz, *H*6); 7.36 (3H, ddd, J=8.5, 7.2, 2.0 Hz, *H*4); 7.24 (3H, s, *H*–Ar); 6.56 (3H, dd, J=7.2, 4.8 Hz, *H*5); 6.32 (3H, d, J=8.5 Hz, *H*3); 5.03 (3H, br.s, *H*N); 4.45 (6H, br.s, CH_2). δ_C (75 MHz, $CDCl_3$) 158.1 (*C*2), 147.6 (*C*6), 139.8 (*C*1′, 3′, 5′), 137.2 (*C*4), 124.9 (*C*2′, 4′, 6′), 112.8 (*C*5), 106.7 (*C*3), 45.8 (CH_2).

2.2.15. 3,5-Bis-(5-bromopyridin-2-ylaminomethyl)benzylpyridin-5-bromo-2-ylamine (15b). Pale yellow solid (266 mg, 70%, ethyl acetate/hexane), mp 170–171°C; [Found: C, 45.87; H, 3.36; N, 13.03. $C_{24}H_{21}Br_3N_6$ requires C, 45.53; H, 3.34; N, 13.27%]; ν_{max} (KBr) 3234, 1590, 1455, 802 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.99 (3H, d, J= 2.5 Hz, *H*6); 7.42 (3H, dd, J=8.9, 2.5 Hz, *H*4); 7.19 (3H, s, *H*–Ar); 6.22 (3H, d, J=8.9 Hz, *H*3); 5.17 (3H, br. t, J= 5.9 Hz, *H*N); 4.42 (6H, d, J=5.9 Hz, CH_2). δ_C (75 MHz, $CDCl_3$) 157.2 (*C*2), 148.9 (*C*6), 140.1 (*C*1′, 3′, 5′), 140.0 (*C*4), 125.5 (*C*2′, 4′, 6′), 108.5 (*C*3), 107.5 (*C*5), 46.2 (CH_2).

Acknowledgements

The authors wish to thank the Comisión Interministerial de Ciencia y Tecnología (CICYT-2FD97-1248) for financial support, and the Ministerio de Educación y Cultura (MEC) for a studentship (M. J. R.).

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