

3,3'-*N,N'*-Bis(amino)-2,2'-bipyridine – An unusually methylation-resistant amine

Danielle M. Chisholm, Robert McDonald, and J. Scott McIndoe

Abstract: Methylation of aromatic amino groups is usually straightforward, but the formation of two intramolecular hydrogen bonds in 3,3'-*N,N'*-bis(amino)-2,2'-bipyridine and (or) the potential for ring methylation prevents the clean tetramethylation of this molecule. Numerous attempts to make 3,3'-*N,N'*-bis(dimethylamino)-2,2'-bipyridine produced only complex mixtures of variously methylated products, and the only isolated molecule was 3,3'-*N,N'*-bis(methylamino)-2,2'-bipyridine, for which an X-ray crystal structure was obtained.

Key words: Proton-sponge, methylation, electrospray ionization mass spectrometry, bipyridine ligands.

Résumé : La méthylation des amines aromatiques est une réaction généralement simple mais, dans le cas de la 3,3'-*N,N'*-bis(amino)-2,2'-bipyridine, la formation de deux liaisons hydrogènes intramoléculaires et (ou) la possibilité de méthylation des hétérocycles empêche la réaction de tétraméthylation propre de cette molécule. Plusieurs essais de préparation de la 3,3'-*N,N'*-bis(diméthylamino)-2,2'-bipyridine n'ont conduit qu'à la formation de mélanges complexes de produits de degrés de méthylation divers et la seule molécule qui a pu être isolée est la 3,3'-*N,N'*-bis(méthylamino)-2,2'-bipyridine dont la structure a été caractérisée par diffraction des rayons-X.

Mots-clés : éponge à protons, méthylation, spectrométrie de masse avec ionisation par électronébulisation, ligands bipyridine.

[Traduit par la Rédaction]

1,8-Bis(dimethylamino)naphthalene (Proton-sponge), was first reported by Brown and Letang in 1941,¹ and in the late 1960s Alder et al.² drew attention to the fact that this molecule was unusually basic. Alder et al.² demonstrated how the sequential addition of methyl groups to 1,8-bis(amino)naphthalene increased the pK_a slowly until the fourth substitution, which increased the pK_a from 6.4 to 12.3. The high basicity is due to a number of factors. The bulky nature of the dimethylamino groups and their close proximity to one another induces steric repulsion between the lone pairs of electrons on the two nitrogen centres. To relieve some of the repulsion the naphthalene system twists out of plane by $\sim 30^\circ$,² and the steric strain is easily relieved through association of a proton. The lone pairs on each nitrogen centre can become equally involved^{3,4} in hydrogen bonding with the proton and are no longer repelled by one another, allowing the naphthalene ring to return to planarity.⁵ The spatial arrangement of the dimethylamino groups allows access to only a proton, and anything larger will not fit comfortably (a notable exception being a highly reactive palladium fragment).⁶ Many new proton sponges have since been introduced (see Fig. 1 for examples).⁷⁻⁹ Staab et al.^{10,11} showed that it was not just the proximity of the nitrogen centres that determined the strength of basicity but also the linearity of the resulting hydrogen bonds, hence the low basicity of struc-

tures 1(*d*) and 1(*e*). The superbases¹² 1,8-bis(hexamethyltri-aminophosphazenylnaphthalene)¹³ contains a combination of basic phosphazenes and proton sponge structure to achieve a pK_a of 29.9 in acetonitrile, almost 10^{12} more basic than 1,8-bis(dimethylamino)naphthalene.

The exclusive and strong association of a proton to these types of molecules makes them perfect handles for study using electrospray ionization mass spectrometry (ESI-MS).¹⁴ Eliminating the possibility for multiple charge pathways greatly simplifies mass spectra, making this particular type of molecule very attractive. The only obstacle is adding this convenient probe to molecules of interest; in our research that equates to spectator ligands in catalytic reactions.¹⁵⁻¹⁸ This end has been achieved previously in our group through altering triphenylphosphine by replacing one phenyl group with a proton sponge. (1,8-Bis(dimethylamino)naphthalene-2-yl)diphenylphosphine was synthesized and used to show that ESI-MS investigations of neutral metal complexes was possible when a chargeable ligand was employed.¹⁹

The direction we had envisioned for this work was toward molecules that would possess a similarly highly basic site once bound to a metal centre. We were drawn to the scaffold of the fluorene-type sponges 1(*b*) introduced by Staab and Saube⁸ because of the similarity they bore to the orientation of 2,2'-bipyridine ("bipy") chelating to a metal. Increasingly large atoms (O, S, Se, and Te) could replace the methylene

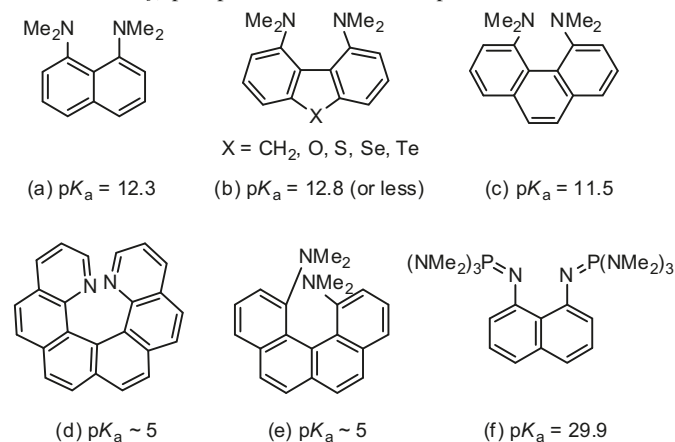
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Fig. 1. Some of the structures developed in the course of research into proton sponges based on (a) naphthalene,² (b) fluorene,⁸ (c) phenanthrene,⁸ (d) 1,16-diaza[6]helicene,¹⁰ (e) benzo[*c*]phenanthrene¹¹, and (f) phosphazene-substituted naphthalene.¹³



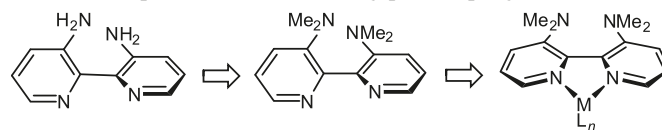
group with only minor detrimental effects on the basicity. To this end we pursued the functionalization of 2,2'-bipyridine. Bipy ligands are common in coordination chemistry^{20–22} so their incorporation into our investigations seemed like an appropriate choice. The idea was to substitute bipyridine at the 3 and 3' positions to arrive at 3,3'-*N,N'*-bis(dimethylamino)-2,2'-bipyridine and to rely on coordination to a metal centre to orient the two groups toward each other (Fig. 2).

Once the functionalized bipyridine has coordinated to the metal and the dimethylamino groups have adopted the expected orientation, addition of a proton source should render the entire complex amenable to ESI-MS analysis and provide the first example of a metal-containing proton sponge. The effect of the relatively flexible coordination environment of the metal was also of structural interest — it is possible, of course, that the metal coordinates to one pyridine nitrogen and one dimethylamino nitrogen. In this case, an identical site would be available on the other side of the ligand, which itself could bind another metal centre or H⁺.

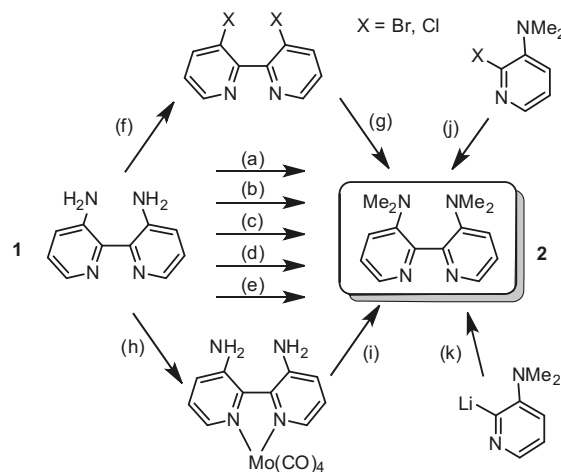
Synthesis of the known 3,3'-bis(amino)-2,2'-bipyridine (**1**) was straightforward.²³ However, tetramethylation of the molecule to replace all N–H bonds with N–CH₃ proved anything but simple. Tetramethylation of 3,3'-bis(amino)biphenyl and 1,8-bis(amino)naphthalene is routine, but the same approach on 3,3'-bis(amino)-2,2'-bipyridine failed, and we subsequently tried nine other routes without success (Scheme 1).

Route a in Scheme 1 involved sodium hydride and dimethylsulfate, based on Staab and Staupe's⁸ preparation of the fluorene-derived sponges. Route b adapted Giam and Hauck's²⁴ approach to the methylation of 3-aminopyridine to give 3-dimethylaminopyridine using formic acid and formaldehyde. Route c modified Sheppard's²⁵ methylation of *m*-trifluoromethylaniline to *m*-trifluoromethyl-*N,N*-dimethylaniline using trimethylphosphate and aqueous sodium hydroxide. Route d employed Charmant et al.'s²⁶ use of methyl iodide to methylate a benzylamine-substituted naphthalene proton sponge derivative. Route e used Shaw and Turner's²⁷ approach to methylating 2,2'-diaminobiphenyl to 2,2'-bis(dimethylamino)biphenyl using dimethyl sulfate and sodium hydroxide. All of these routes, to a greater or lesser extent, resulted in methylation, but always a complex mixture of

Fig. 2. Concept for a metal-containing proton sponge.



Scheme 1. Attempted routes to 3,3'-*N,N'*-bis(dimethylamino)-2,2'-bipyridine (**2**).

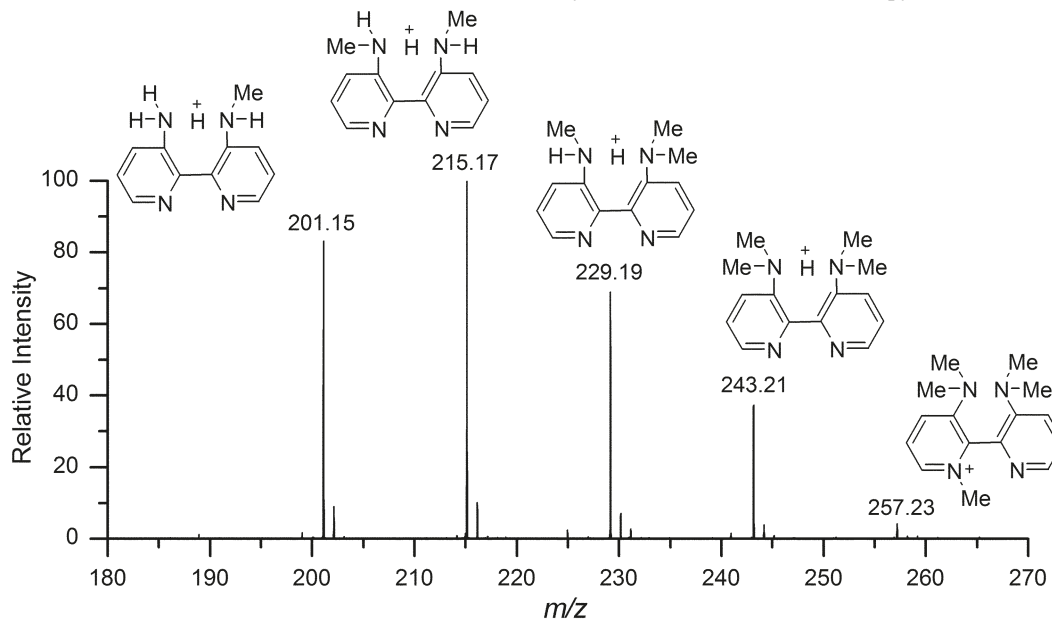


products was obtained and we were never successful in isolating the desired compound. Figure 3 illustrates a typical ESI-MS obtained from these reaction mixtures. Separating the different components by chromatography proved unsuccessful. Note that ESI-MS does not distinguish between ring methylation (+15 Da, positively charged) or replacement of one H for the Me and protonation (+15 Da, positively charged), so the following spectrum contains both series, i.e., [C₁₀N₄Me_{*n*}H_(4-*n*)]⁺ (*n* = 1–5) and [C₁₀N₄Me_{*n*}H_(4-*n*) + H]⁺ (*n* = 1–4). The ¹H NMR mixture, which showed the presence of both types of methyl groups (methylamine and methylpyridinium). Pyridines may be directly methylated by dimethylsulfate²⁸ or methyl iodide²⁹ in the absence of added strong base.

The one compound successfully isolated was the dimethylated neutral compound 3,3'-bis(methylamino)-2,2'-bipyridine (**3**) by fractional crystallization in 25% yield. Monomethylation of each amino group allows for two separate hydrogen bonds between the amine hydrogen and the pyridine nitrogen in opposite rings. Crystals of **3** were obtained from the reaction of **1** with sodium hydride and methyl iodide and were isolated by slow evaporation of diethyl ether. An X-ray crystal structure of this molecule was obtained (Fig. 4). This compound was spectroscopically characterized previously by ¹H and ¹⁵N NMR without preparative details.³⁰

The bipyridine core of **3** is very similar to unsubstituted 2,2'-bipyridine with respect to bond lengths and angles. The C–N1 and C–C bond lengths in the two equivalent pyridine rings average 1.34 and 1.40 Å, respectively, whereas the average bond angle is 120.0°. The comparative numbers for 2,2'-bipyridine are 1.36 and 1.39 Å and 120.8°, respectively.³¹ As with 2,2'-bipyridine, N1 and N1' are arranged trans to one another, but whereas 2,2'-bipyridine is coplanar, the two equivalent pyridine rings of **3** lie in parallel planes separated by 0.06 Å. The presence of the hydrogen bonds

Fig. 3. Positive ion ESI-MS in CH₂Cl₂ of the mixture obtained from methylation of 3,3'-bis(amino)-2,2'-bipyridine with Me₂SO₄ and NaOH.

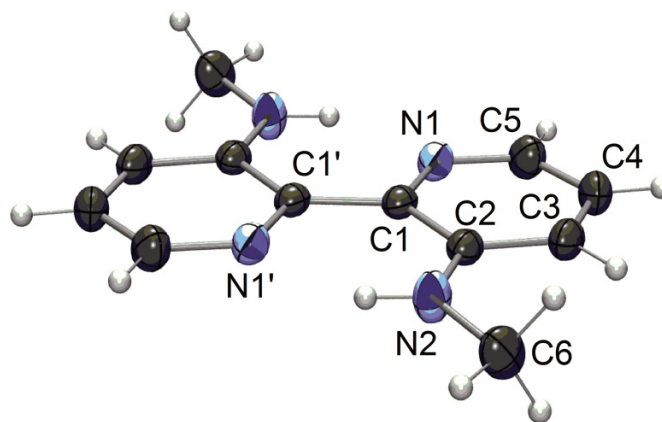


(N1–H length = 1.962 Å and N1–H–N2' bond angle = 133.3°) is evident from the structure, and they are essentially the same as that in **1** (1.947 Å and 132.8°). A hydrogen bond can be classified as strong, moderate, or weak by evaluating factors such as bond length, bond angles, and comparison of the lengths of the hydrogen bond and the covalent bond between the hydrogen and the atom to which it is bonded,³² and the H bonds here fall into the “moderate” category (1.5–2.2 Å and 130°–180°). There is no intermolecular H bonding evident in the packing of **3**.

Because **3** has two moderate-strength intramolecular hydrogen bonds, as does **1** (and also presumably the intermediate 3,3'-*N,N'*-(amino)(methylamino)-2,2'-bipyridine, although it has not been characterized), this feature may partially account for these molecules being unusually resistant to further methylation. Forcing conditions (neat MeI) seemed to be able to tri- and tetramethylate **1**, but also caused ring methylation of a pyridine nitrogen, further complicating the product mixture.

As an alternate synthetic approach, we tried cross-coupling various derivatives of 3-dimethylaminopyridine. 3-Dimethylaminopyridine³⁰ and 2-chloro-3-dimethylaminopyridine³¹ were made from nitropyridine species, which were reduced using SnCl₂·2H₂O in HCl, and the subsequent aminopyridine was methylated using formic acid and formaldehyde to give 3-dimethylaminopyridine and 2-chloro-3-dimethylaminopyridine. The copper-catalyzed Ullmann coupling of 2 equiv of 2-chloro-3-dimethylaminopyridine (Scheme 1, route j) failed to proceed. Route k, the iron-catalyzed cross-coupling³³ of 2-chloro-3-dimethylaminopyridine and 3-dimethylamino-2-lithiopyridine (easily generated in situ using *n*-BuLi in THF and the formation verified through independent quenching experiments) did not generate a product. Several competing factors are thought to have limited the success of the coupling reactions of 2-chloro-3-dimethylaminopyridine. Whereas electron-withdrawing groups (e.g., NO₂) located ortho to the halogen activate the molecule, electron-donating groups (e.g., NMe₂) have the opposite effect. Particularly bulky substitu-

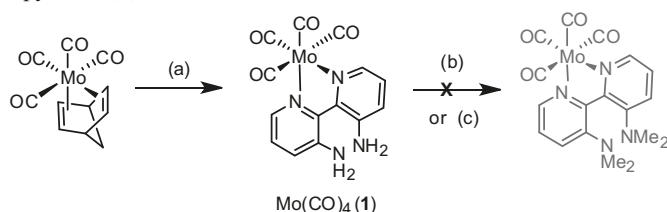
Fig. 4. Perspective view of **3** showing the atom-labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 70% probability level. Hydrogen atoms are shown with arbitrarily small thermal parameters. Primed atoms are related to unprimed ones via the crystallographic inversion centre (1/2, 0, 1/2) at the midpoint of the C1–C1' bond. Broken lines indicate hydrogen-bonded N–H···N interactions. Selected interatomic distances (Å): C1–C1' = 1.487(2), N1–N2' = 2.645(2), N1–C1 = 1.346(2), N1–C5 = 1.332(2), N2–C2 = 1.354(2), and N2–C6 = 1.442(2). Selected bond angles (°): N2–C2–C1 = 122.9(1) and C1–N1–C5 = 121.3(1). Selected torsion angle (°): N1–C1–C2–N2 = 178.6(1).



ents in this position will also hinder the formation of coupled products.³⁴ Similar complications seem plausible for the attempted iron-catalyzed coupling.

The next step was to try to inhibit the formation of the intramolecular hydrogen bonds and to block ring methylation. Coordination of **1** to a metal centre engages the lone pairs of the pyridine nitrogen so they are no longer available to form hydrogen bonds with an amine hydrogen or to be methylated. Mo(CO)₄ (norbornadiene) was selected for this task (Scheme 2).^{35,36} Displacement of norbornadiene³⁷ with **1** to give Mo(CO)₄(**1**) (Scheme 1, step h), effectively removed the

Scheme 2. Attempted routes to 3,3'-*N,N'*-bis(dimethylamino)-2,2'-bipyridine (**2**).



possibility of the formation of intramolecular hydrogen bonds within the bipyridine molecule. Confirmation that coordination had occurred through both pyridine nitrogen centres was obtained through comparison to the IR stretching frequencies of Mo(CO)₄(2,2'-bipyridine).^{38,39} Sodium hydride and dimethyl sulfate were used to methylate Mo(CO)₄(**1**), but upon completion of step i the IR spectrum did not contain any CO-stretching frequencies, and the ESI-MS spectrum showed products containing one to four methyl groups as well as starting material. The procedure involving sodium hydride and methyl iodide described previously gave a mixture of methylated products as before.

A final attempt (Scheme 1, routes f and g) involved aminating 3,3'-bis(halo)-2,2'-bipyridines^{40–42} with a lithium aminoborane reagent (LAB) made from *n*-BuLi and BH₄NMe₂ in tetrahydrofuran.⁴³ However, upon addition of the LAB to the bis(halogen) species none of the desired product was observed upon workup.

Conclusions

3,3'-Bis(amino)-2,2'-bipyridine (**1**) is unusually difficult to tetramethylate or to prepare by numerous other methods commonly used to construct similar molecules. The key structural feature likely to be responsible for this behaviour is the pyridine nitrogens, which can form two intramolecular hydrogen bonds in the un-, mono- and dimethylated compounds that may interfere with further methylation. These hydrogen bonds are in clear evidence in the X-ray crystal structure of 3,3'-bis(methylamino)-2,2'-bipyridine (**3**). The pyridine nitrogens are also susceptible to methylation themselves, further complicating the reactivity of **1**.

Experimental

All synthesis was performed under an inert atmosphere of N₂ using standard glovebox or Schlenk procedures. 2-Chloro-3-dimethylamino pyridine, 3,3'-diamino-2,2'-bipyridine,²³ and Mo(CO)₄(norbornadiene)^{35,37} were made by literature methods. All other chemicals were used as obtained (Sigma-Aldrich, Oakville, Ontario). Solvents were HPLC grade and purified on an MBraun solvent purification system (SPS). Gases were obtained from Airgas (Calgary, Alberta). NMR spectra were collected on either an AV-300 or an AV-360 Bruker spectrometer. Internal reference was made to CHCl₃ (1H *d* = 7.26 ppm). All mass spectra were obtained on a Micromass Q-ToF micro hybrid quadrupole/time-of-flight mass spectrometer in positive ion mode using pneumatically assisted electrospray ionization with a capillary voltage of 2900 V, a source temperature of 100 °C, and a desolvation temperature of 180 °C. Solutions

were run in dichloromethane and introduced to the mass spectrometer by a syringe pump at a rate of 2 mL/h. Internal calibrants for accurate mass experiments were protonated triphenylphosphine oxide ([C₁₅H₁₈PO + H]⁺ = 278.0939 *m/z*), tetrapropylammonium bromide ([C₁₂H₂₈N]⁺ = 186.2222 *m/z*), and tetrabutylammonium bromide ([C₁₆H₃₆N]⁺ = 242.2848 *m/z*) as indicated where applicable. Higher mass accuracy is provided in these instances.

3,3'-Bis(methylamino)-2,2'-bipyridine (**3**)

Sodium hydride (0.052 g, 2.2 mmol) was added to (3,3'-diamino-2,2'-bipyridine (0.104 g, 0.55 mmol) in THF (5 mL) and stirred for 30 min resulting in bubbling and giving a yellow solution. Methyl iodide (0.31 g, 0.14 mL, 2.2 mmol) was added and the solution was refluxed for 90 min. Sodium hydroxide was added (3 mol/L, 1 mL) and the mixture extracted with diethyl ether (4 × 10 mL) until no colour remained in the aqueous phase. The organic phase was dried over magnesium sulfate and reduced in volume via a rotary evaporator. The yellow solid was redissolved with a minimal amount of diethyl ether and cooled to –5 °C to give yellow crystalline material (30 mg, 25%); mp = 148–150 °C. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 2.92 (s, 6H), 7.06 (dd, ³J_{HH} = 1.53, 8.37 Hz, 2H), 7.15 (dd, ³J_{HH} = 4.55, 8.42 Hz, 2H), 7.91 (dd, ³J_{HH} = 1.62, 4.47 Hz, 2H), 9.43 (s, 2H). ¹³C NMR (500 MHz, CDCl₃) δ (ppm): 29.80, 117.69, 123.30, 133.13, 140.25, 145.81. ESI-MS (+ve, CH₂Cl₂ + formic acid) *m/z* experimental: 215.1298 [C₁₂H₁₄N₄ + H]⁺; calcd: 215.1297.

3,3'-Dichloro-2,2'-bipyridine^{40,41}

To a cold solution (0 °C) of sodium nitrite (370.2 mg, 5.4 mmol) in concentrated sulfuric acid (4 mL) was slowly added a solution of 3,3'-diamino-2,2'-bipyridine (453.2 mg, 2.4 mmol) in glacial acetic acid (4 mL) and stirred for 30 min. The ice bath was removed and the reaction stirred at room temperature for 30 min and then cooled to 0 °C. A cold solution of copper(I) chloride (2.09 g, 210 mmol) in concentrated hydrochloric acid (5 mL) was then added. The reaction was kept at low temperature to keep the evolution of gas at a slow rate. After 25 min the reaction was heated to 70 °C until the effervescence stopped, water was added (14 mL), and the reaction stirred overnight. The green-blue cloudy reaction mixture was filtered and the retrieved blue crystals dissolved in water (15 mL), made alkaline using saturated aqueous sodium hydroxide, and sodium cyanide was (0.5 g, 10 mmol) added. *CAUTION: solution must be alkaline before addition of sodium cyanide to prevent the formation of toxic hydrogen cyanide (HCN).* The aqueous mixture was extracted with dichloromethane (2 × 25 mL) that was washed once with water (50 mL), dried over magnesium sulfate, taken to near dryness on the rotary evaporator, and dried under high vacuum to give a shiny yellow solid (111.1 mg, 20% yield); mp = 125–128 °C. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.36 (dd, ³J_{HH} = 4.55, 8 Hz, 2H), 7.84 (dd, ³J_{HH} = 1.41, 8 Hz, 2H), 8.64 (dd, ³J_{HH} = 1.41, 4.55 Hz, 2H). ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 124.5, 131.0, 137.4, 147.5, 155.7. ESI-MS (+ve, CH₂Cl₂ + formic acid) *m/z* experimental: 224.9848 [C₁₀H₆Cl₂N₂ + H]⁺; calcd: 224.9986.

3,3'-Dibromo-2,2'-bipyridine^{40,41}

The same as for 3,3'-dichloro-2,2'-bipyridine but with CuBr in place of CuCl. 3,3'-Diamino-2,2'-bipyridine (505.7 mg, 2.72 mmol). White solid retrieved (83.6 mg, 10% yield); mp = 148–150 °C. ¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.28 (dd, ³J_{HH} = 4.45, 8 Hz, 2H), 8.02 (dd, ³J_{HH} = 1.4, 8 Hz, 2H), 7.1 (dd, ³J_{HH} = 1.4, 4.45 Hz, 2H). ¹³C NMR (300 MHz, CDCl₃) δ (ppm): 120.4, 124.9, 140.7, 148.1, 157.1. ESI-MS (+ve, CH₂Cl₂ + formic acid) *m/z* experimental: 314.8899 [C₁₀H₆Br₂N₂ + H]⁺; calcd: 314.8956.

3,3'-N,N'-Bis(dimethylamino)-2,2'-bipyridine (2), attempted syntheses**Route a — Methylation of 3,3'-diamino-2,2'-bipyridine with dimethyl sulfate⁸**

Sodium hydride (320 mg, 13.33 mmol) was added to a solution of 3,3'-diamino-2,2'-bipyridine (0.392 g, 2.11 mmol) in tetrahydrofuran in four equal portions to give a cloudy yellow suspension. Dimethyl sulfate (2.4 mL, 1.80 g, 14.3 mmol) was slowly added and the mixture was refluxed for 3 h to give a brown slurry. Methanol (300 mL) was added to the room temperature reaction and the entire mixture poured over sodium hydroxide (saturated aq, 15 mL). The volume was reduced via rotary evaporator, water (200 mL) was added, and the mixture extracted with ether (200 mL, 4 × 100 mL). The volume of the bright orange organic solution was brought to ~50 mL on the rotary evaporator and then under high vacuum. The organic layer was then washed with dilute hydrochloric acid (3 × 30 mL), dried over magnesium sulfate and taken to dryness on the rotary evaporator to give an orange solid. ESI-MS analysis showed no starting material or any methylated products.

Route b — Methylation of 3,3'-diamino-2,2'-bipyridine with formaldehyde / formic acid²⁴

3,3'-Diamino-2,2'-bipyridine (100 mg, 0.537 mmol) was refluxed in formic acid (8 mL) and formaldehyde (8 mL) for 8 h to give a bright yellow solution. Hydrochloric acid (4 mol/L, 20 mL) was added and the solution was taken to near dryness on high vacuum. The yellow-orange solid was taken up in distilled water (15 mL) and 18 mol/L sodium hydroxide (10 mL) was added to give a murky brown mixture. The slurry was extracted with benzene (5 × 15 mL) and the organic layer was dried with magnesium sulfate and then taken to near dryness. Starting material was recovered unchanged; no methylated products were identified.

Route c — Methylation of 3,3'-diamino-2,2'-bipyridine with trimethylphosphate²⁵

3,3'-Diamino-2,2'-bipyridine (0.500 g, 2.69 mmol) was added to trimethylphosphate (0.785 g, 5.60 mmol), and the resulting yellow solution was heated at 200 °C for 2 h to give a black sticky substance. Sodium hydroxide (15% aq, 10 mL) and water (15 mL) were added and the mixture stirred for 2 h. The black mixture was extracted with diethyl ether (3 × 20 mL) and the organic layer was dried with magnesium sulfate and sodium hydroxide pellets and then dried under high vacuum. NMR of the resulting orange-brown oil showed an indistinguishable mixture of products.

Route d — Methylation of 3,3'-diamino-2,2'-bipyridine with methyl iodide²⁶

Sodium hydride (0.633 g, 26.4 mmol) was added to a solution of 3,3'-diamino-2,2'-bipyridine (0.123 g, 0.659 mmol) in THF and stirred for 90 min. Methyl iodide (0.375 g, 0.16 mL, 2.64 mmol) was then added and the mixture refluxed for 1 h. After cooling to room temperature, the mixture was poured over sodium hydroxide (3 mol/L, 15 mL) and stirred for 30 min. The aqueous layer was extracted with diethyl ether (2 × 50 mL) and the organic layer was passed through an alumina plug to give a clear yellow solution. The ether was removed to give an orange-yellow oil, an inseparable mixture of the desired product and partially (and over-) methylated by-products. ESI-MS (+ve, CH₂Cl₂ + formic acid) *m/z*: 201.15 [C₁₁H₁₂N₄ + H]⁺, 215.17 [C₁₂H₁₄N₄ + H]⁺, 229.19 [C₁₃H₁₆N₄ + H]⁺, 243.21 [C₁₄H₁₈N₄ + H]⁺, 257.23 [C₁₅H₂₁N₄]⁺.

Route e — Methylation of 3,3'-diamino-2,2'-bipyridine with dimethyl sulfate²⁷

Dimethyl sulfate (0.70 mL, 0.526 g, 4.17 mmol) was added to a suspension of 3,3'-diamino-2,2'-bipyridine (0.174 g, 0.935 mmol) in water (5 mL) in portions (0.21, 0.21, and 0.28 mL), and after each addition was shaken for 10 min and made alkaline with sodium hydroxide (10% aq). The yellow solution was heated at 100 °C for 15 min. The water was removed to give an orange-yellow oil, an inseparable mixture of the desired product, and partially (and over-) methylated by-products. ESI-MS (+ve, CH₂Cl₂ + formic acid) *m/z*: 201.15 [C₁₁H₁₂N₄ + H]⁺, 215.17 [C₁₂H₁₄N₄ + H]⁺, 229.19 [C₁₃H₁₆N₄ + H]⁺, 243.21 [C₁₄H₁₈N₄ + H]⁺, 257.23 [C₁₅H₂₁N₄]⁺.

Step f — Demethylation of 3,3'-N,N'-bis(dimethylamino)-2,2'-pyridine-pyridinium iodide

Pyridinium chloride (6.58 g, 56.9 mmol) was added to 3,3'-N,N'-bis(dimethylamino)-2,2'-pyridine-pyridinium iodide (0.170 g, 0.659 mmol) and heated at 225 °C for 10 min. ESI-MS (+ve, CH₂Cl₂ + formic acid) *m/z*: 201.15 [C₁₁H₁₂N₄ + H]⁺, 215.17 [C₁₂H₁₄N₄ + H]⁺.

Step g — Halogen substitution of 3,3'-bis(chloro)-2,2'-bipyridine

LiH₃BN(Me)₂ was made according to literature procedures.⁴³ LiH₃BNMe₂ (0.95 mol/L, 0.27 mL, 0.25 × 10⁻⁴ mol) was added to 3,3'-dichloro-2,2'-bipyridine (50.8 mg, 0.22 mmol) in THF (1 mL) at 0 °C to give a deep red solution. The reaction was stirred at 0 °C for 15 min and then at room temperature for 90 min. HCl (3 mol/L, 3.3 mL) and methanol (3.3 mL) were then added at 0 °C and the mixture was stirred for 15 min. The reaction was refluxed overnight, the volume reduced to ~5 mL, made alkaline with saturated sodium hydroxide, and extracted with CH₂Cl₂ (3 × 10 mL). The peach-coloured organic layer was dried with MgSO₄ and reduced to a solid that proved to be unreacted starting material. ESI-MS (+ve, CH₂Cl₂) *m/z*: 230.31 [C₁₀H₆Cl₂N₂ + Li]⁺.

Step h — Mo(CO)₄(3,3'-diamino-2,2'-bipyridine)

Mo(CO)₄(norbornadiene) was made according to the literature preparation. Mo(CO)₄(nbd) (164.1 mg, 0.548 mmol) was added to a solution of 3,3'-diamino-2,2'-bipyridine

(100.1 mg, 0.538 mmol) in benzene (5 mL) and the reaction was refluxed for 3 h covered in aluminum foil. The benzene was removed under high vacuum and the brown solid taken up in dichloromethane to give a red solution. Layering of hexanes over the red dichloromethane solution produced a yellow precipitate. IR (CH_2Cl_2) ν_{CO} (cm^{-1}): 2013, 1901, 1871, 1824.

Step i — Methylation of $\text{Mo}(\text{CO})_4(3,3'$ -diamino-2,2'-bipyridine) with dimethyl sulfate and methyl iodide

Reduction procedures were followed as above for sodium hydride / dimethyl sulfate^{8,26} and sodium hydride / methyl iodide²⁶ using the metal complex in place of free 3,3'-diamino-2,2'-bipyridine. For NaH/ Me_2SO_4 : ESI-MS (+ve, CH_2Cl_2) m/z : 201.15 [$\text{C}_{11}\text{H}_{12}\text{N}_4 + \text{H}$]⁺, 215.17 [$\text{C}_{12}\text{H}_{14}\text{N}_4 + \text{H}$]⁺, 229.19 [$\text{C}_{13}\text{H}_{16}\text{N}_4 + \text{H}$]⁺, 243.21 [$\text{C}_{14}\text{H}_{18}\text{N}_4 + \text{H}$]⁺. For NaH/MeI: ESI-MS (+ve, CH_2Cl_2 + formic acid) m/z : 201.15 [$\text{C}_{11}\text{H}_{12}\text{N}_4 + \text{H}$]⁺, 215.17 [$\text{C}_{12}\text{H}_{14}\text{N}_4 + \text{H}$]⁺, 229.19 [$\text{C}_{13}\text{H}_{16}\text{N}_4 + \text{H}$]⁺, 243.21 [$\text{C}_{14}\text{H}_{18}\text{N}_4 + \text{H}$]⁺, 257.23 [$\text{C}_{14}\text{H}_{18}\text{N}_4 + \text{H}$]⁺.

Route j — Homo-coupling of 2-chloro-3-dimethylaminopyridine

2-Chloro-3-dimethylaminopyridine (1.42 g, 9.14 mmol) was added to a slurry of activated copper (1.45 g, 22.79 mmol) in dry DMF (35 mL) and refluxed overnight. The hot reaction mixture was poured over H_2O (400 mL) and isolated via suction filtration and extracted with dioxane via a Soxhlet apparatus. The dioxane was removed on a rotary evaporator, the solid taken up in CH_2Cl_2 , washed with aqueous ammonia followed by H_2O , and dried over MgSO_4 . NMR (300 MHz, CDCl_3) showed no coupled product.

Route k — Coupling of 2-chloro-3-dimethylaminopyridine and 3-dimethylaminopyridine³³

A 1:1 solution of *n*-BuLi/TMEDA (*n*-BuLi, 1.6 mol/L in hexanes, 4.09 mL, 6.54 mmol) was added via cannula to a solution of 3-dimethylaminopyridine (0.799 g, 6.54 mmol) in THF at -78°C and stirred for 3 h to give a bright orange solution. In a separate Schlenk flask, 2-chloro-3-dimethylaminopyridine (0.872 g, 5.56 mmol) was added to a solution of $\text{Fe}(\text{acac})_3$ (96.9 mg, 2.74×10^{-4} mol) and *N*-methyl-2-pyrrolidone (3.19 g, 3.1 mL, 32.15 mmol) in dry THF (30 mL) to give a deep red-orange solution that was cooled to -78°C . The 3-dimethylaminopyridine solution was then transferred via cannula to the 2-chloro-3-dimethylaminopyridine solution to give a deep red-purple colour and the stirred at -78°C for 1 h before being allowed to warm to room temperature. Concentrated HCl (10 mL) was then added and the mixture stirred for 1 h. The solution was made alkaline with sodium hydroxide (1 mol/L, 10 mL), extracted with diethyl ether (4 \times 50 mL), dried with MgSO_4 , and then taken to dryness on a rotary evaporator to give a yellow-orange solid, a mixture of starting materials. ESI-MS (+ve, CH_2Cl_2 + formic acid) m/z : 157.05 [$\text{C}_6\text{H}_9\text{ClN}_2 + \text{H}$]⁺, 123.09 [$\text{C}_6\text{H}_{10}\text{N}_2 + \text{H}$]⁺.

Supplementary data

Supplementary data (full X-ray diffraction data and the ¹H NMR spectrum of the mixture of products from methylation) are available with the article through the journal Web site (www.nrcresearchpress.com/cjc).

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