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N-Methylation and N-Oxidation of the Less Reactive Nitrogen Atom of a 2,3'-Bipyridine. Two General Methods for Polyazines[1]

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Abstract: 5-Carbamoyl-2,3'-bipyridine model compound was N-methylated or N-oxidized at the less reactive 2-pyridyl ring for the first time. Two different schemes were developed.

Directing a reaction to one selected annular nitrogen atom of a polyazine or a polycyclic polyazine is an old and continuing synthetic challenge. Especially difficult is the case where the desired reaction site is sterically hindered and/or electronically deactivated.

2,3'-Bipyridine (BPY) is a prototypical polyazine where the two annular nitrogen atoms demonstrate markedly different reactivities due to their geometry, the nitrogen atom of the 2-pyridyl ring being more sterically hindered and therefore much less nucleophilic than that of the 3'-pyridyl ring.

We have devised two different methods to achieve regiocontrolled functionalization of one annular nitrogen atom using a BPY as a model substrate. When it is desirable to functionalize the less reactive nitrogen atom in the 2-pyridyl ring of the BPY our first approach employs a three-step protection-functionalization-deprotection sequence on *preformed* BPY. A removable 2-(p-nitrophenyl)ethyl (NPE) protecting group is first bonded to the more reactive 3'-pyridyl nitrogen atom, the less reactive 2-pyridyl nitrogen atom then is functionalized by N-quaternization or N-oxidation and the protecting group is removed by base as p-nitrostyrene to give the desired final product. A simpler approach for the N-oxide employs an N-methyl protecting group, readily removed by the action of KI in heated DMF in a similar sequence of steps, Scheme 1.

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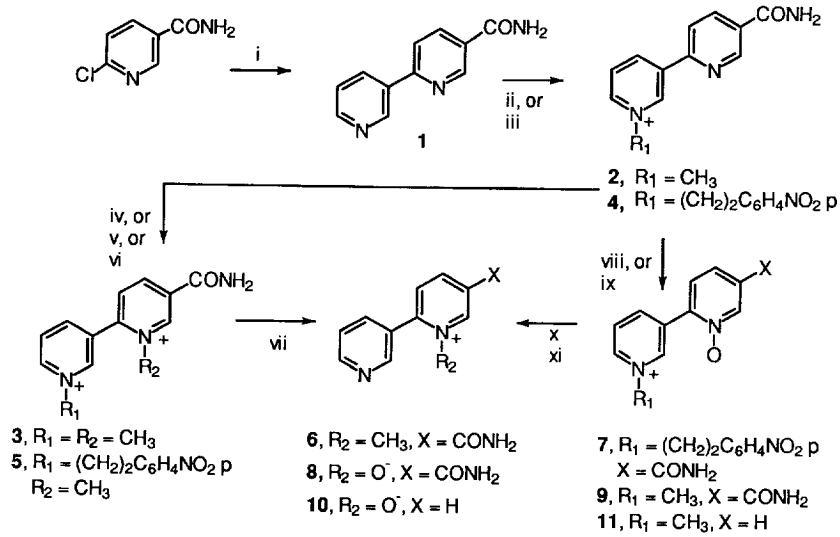
[1]Dedicated to Professor Charles W. Jefford on the occasion of his retirement.

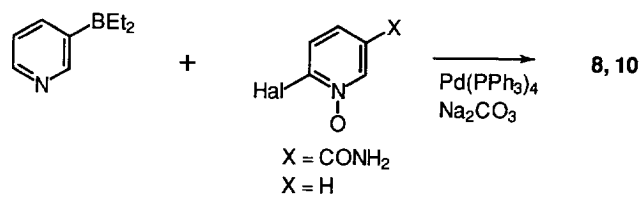
Scheme 1[a]



[a]Reagents: (i) Pd(Ph3)4, 3-Et2B-pyridine, THF, (ii) MeI, EtOAc, (iii) Br(CH2)2C6H4NO2, (iv) MeI, DMF, (v) MeI, sulfolane (vi) MeOTs, sulfolane, (vii) NaOAc, MeCN for **5**, (viii) MCPBA, sulfolane for **7**; peroxide, TFA for **9**, (ix) MCPBA, $CHCl_3$ for **11**, (x) NaOAc, MeCN for **7**, (xi) KI, DMF for **9** and **11**.

In the second method the desired nitrogen atom is functionalized *first* and *then* the two pyridine rings are cross-coupled together to generate the BPY using a palladium catalyst, a pyridyl borane and an N-functionalized halogenated pyridine, Scheme 2.

Scheme 2



Our model substrate selected to illustrate these two methods is 5-carbamoyl-2,3′-bipyridine (**1**). Not only is the 2-pyridyl ring sterically

deactivated for nucleophilic reactions but also the carbamoyl group presents substantial additional electronic deactivation. The 2-pyridyl ring in **1** is so deactivated that we were forced to devise new reaction conditions which differ markedly from those used in the first successful synthesis of 1-methyl-2,3'-bipyridinium ion.[1] The new conditions are likely to be more widely applicable to other substrates.

The regiocontrolled N-methylation of **1** at the 2-pyridyl nitrogen atom to give **6** and the regiocontrolled N-oxidation of the 2-pyridyl nitrogen atom of **1** to prepare **8** were achieved by the first route.

Using the second synthetic approach N-oxide **8** also was prepared but the cross-coupling route failed to provide N-methylated **6**.

RESULTS AND DISCUSSION

Pd-Catalyzed Cross-Coupling. Bipyridine **1** was readily prepared (92%) by a Suzuki[2-5] cross-coupling of diethyl-3-pyridylborane and 2-chloro-5-carbamoylpyridine with tetrakis(triphenylphosphine)palladium(0) and an aqueous carbonate buffer. The 5-methyl ester has been made by a similar route[6] but the isomeric 2-chloro-3-carbamoylpyridine did not couple with benzeneboronic acid in the presence of $Pd(dppb)Cl_2$.[7]

N-Methylation. Mono- and di-N-methylation of **1** was examined to obtain information about the reactivity of the two nitrogen atoms and, as seen below, to learn about the thermal instability of the diquaternized salt toward demethylation. The first N-methylation took place readily to provide **2**, 1'-methyl-5-carbamoyl-2,3'-bipyridinium iodide in 80% yield with MeI and 99% yield with methyl tosylate (MeOTs).

The conditions selected for the second N-methylation were dictated by the limited solubility of **2**, its diminished reactivity and subsequent thermal dequaternization. Our conditions used for the preparation of the diquaternized form of BPY itself, MeI in acetonitrile heated at 100 ^{0}C in a sealed tube,[1] were unsatisfactory.

Sulfolane solubilized monocation **2** and heating with excess MeOTs at 110 ^{0}C gave (**3**), 1,1'-dimethyl-5-carbamoyl-2,3'-bipyridinium ion (84%). Heated DMF and MeI was unsatisfactory because a mixture of mono (**2**) and diquaternized (**3**) products along with tetramethylammonium solvent decomposition product were isolated in low yields.

Addition of the Protecting Group and Diquaternization. The addition of the NPE protecting group to N-1' was achieved easily in 90% yield to provide monocation **4**.

Again, the second methylation step was a challenge. The solvent of choice proved to be sulfolane because of its good solvent properties and its inertness to the methylating agent. However, the yield of desired diquaternized **5** was only 15% using MeI because deprotection of the starting material by iodide ion followed by methylation to form dimethylated dication **3** was a competing process. Reverse phase column chromotography[8] proved useful in the separation of materials.

The yield of **5** improved to 85% with MeOTs. No dequaternization now was evident with the weakly nucleophilic tosylate counterion.

Attempts to attach other groups to N-1 of **4** were unsuccessful. Neither ethyl tosylate nor bromoacetonitrile nor benzyl bromide, the latter in the presence of silver salts,[9] could be made to react, providing further evidence of the markedly low reactivity of this atom.

An attempt was made to bond a 2-cyanoethyl group to the N-1′ atom of **1** with the expectation that it would be easier to remove by the action of base in the deprotection step.[10,11] However, the 2-cyanoethyl bromide alkylating agent only gave rise to low yields of the desired N-quaternized product.

Deprotection. Selection of conditions for the successful removal of the N-protecting group required several trials. The 2,2,6,6-tetramethylpiperidine base used in our earlier study[1] was unsatisfactory because of the difficulty encountered in removing it as its tosylate salt from the desired ionic product **6**, 1-methyl-5-carbamoyl-2,3′-bipyridinium ion. Dry sodium acetate in refluxing acetonitrile brought about the elimination of 4-nitrostyrene to regenerate the unsubstituted 3′-pyridyl ring and the formation of monomethylated product **6** (55%).

N-Oxidation. (Nitrophenyl)ethylated material **4** was easily N-oxidized to **7** using 3-chloroperbenzoic acid[12] in sulfolane (57%) and the protecting group was removed using sodium acetate in acetonitrile to yield 5-carbamoyl-2,3′-bipyridine-1-oxide **8** (62%).

In view of the easy dealkylation of **3** by iodide ion, another route was explored, now using the N-methyl substituent on N-1′ as a protecting group. Iodide **2** was first converted to the tosylate at room temperature with MeOTs to generate volatile MeI in an anion exchange reaction in order to avoid oxidizing the iodide counterion and then N-oxidized (86%) in peroxytrifluoroacetic acid[13] to 5-carbamoyl-1′-methyl-2,3′-bipyridinium-1-oxide (**9**). Deprotection, this time removing the methyl group using KI in heated DMF, gave the more sterically hindered mono N-oxide **8** (55%).

On the parent BPY lacking the carbamoyl substituent, the same sequence of N-1′ protection with a methyl group followed by N-oxidation gave **11** which

then was deprotected thermally with KI in hot DMF to afford **10** (40%). N-oxidation of unprotected BPY has been reported along with spectroscopic properties.[14,15]

Palladium-Catalyzed Coupling to Prepare N-Oxide 10. A more direct route to **10** (68%) employed palladium-catalyzed cross-coupling[2-5] of diethyl-3-pyridylborane and 2-bromopyridine-1-oxide in aqueous carbonate. Although the 2-bromopyridine-1-oxide can undergo a facile nucleophilic substitution reaction with hydroxide ion to give a pyridone,[16] this potential side-reaction was not important. A 2-bromopyridine-1-oxide has been made to couple with a thienylboronic acid under similar conditions.[17]

Unsuccessful Palladium-Catalyzed Coupling to Prepare 6. Our ability to cross-couple diethyl-3-pyridylborane with N-methylated pyridinium, quinolinium and isoquinolinium halides having the halogen atom located beta to the annular nitrogen atom[18] encouraged us to attempt the preparation of **6** by such a route using a quaternized substrate having the halogen atom at an alpha position. Unfortunately, all attempts failed. Thus, coupling of the 3-pyridylborane and 2-bromo-1-methylpyridinium ion was unsuccessful using carbonate or bicarbonate buffers and tetrakis(triphenylphosphine)-palladium(0) or $Pd(dppe)_2Cl_2$ (dppe is 1,2-(diphenylphosphino)ethane).

CONCLUSIONS

The two methods for the preparation of carbamoyl N-oxide **8** may be compared, each ultimately starting with the 3-pyridylborane and a 2-halopyridine. The two-step palladium coupling route first making the N-oxide and then coupling the two reactants is shorter and gives **8** in 63% overall yield. The four-step sequence where the 2,3-bipyridine is prepared first by palladium coupling, protected, N-oxidized and then deprotected gives an overall yield of 29% for the route using the NPE protecting group and 43% for the methyl protection scheme. Although unsubstituted N-oxide **10** was synthesized by the two routes the starting points are not the same for both approaches to allow a meaningful comparison. The overall yield for the four-step route to the N-methylated carbamoyl **6** was 39%.

Our two methods would seem to be useful for the preparation of a variety of selectively N-derivatized polyazines.

EXPERIMENTAL

Reverse phase octadecylated silica gel was purchased from Aldrich. Kieselgel 60 was used for column chromotography.

5-Carbamoyl-2,3'-bipyridine (1). Diethyl-3-pyridylborane 0.809 g (5.5 mmol), 6-chloronicotinamide 1.04 g (6.63 mmol), and tetrakis(triphenylphosphine)-palladium(0) 0.683 g (0.591 mmol) were added to 25 mL of degassed THF. After stirring for 5 min, potassium carbonate (1.61 g) dissolved in 13 mL of degassed water was added and the solution was stirred at reflux for 6 h. The reaction mixture was cooled to 0 °C and the catalyst was removed under nitrogen. To the filtrate, 50 mL of EtOAc was added and the aqueous layer was removed. The organic layer was extracted twice with 10 mL portions of 2M HCl. The acid washes were combined and made basic with sodium carbonate to give a precipitate which was collected and recrystallized from water to afford 1.02 g (92% yield) of a white solid (mp 227-229 °C decomp.). H^1 NMR (DMSO-d_6) δ 9.25 (1H, s), 9.15 (1H, d, J = 1.5 Hz), 8.63 (1H, dd, J = 1.5 and 6 Hz), 8.5 (1H, dd, J = 2 and 8 Hz), 8.36 (1H, dd, J = 2 and 8 Hz), 8.07 (1H, d, J = 8 Hz), 7.60 (1H, dd, J = 6 and 8 Hz). Anal Calcd. for $C_{11}H_9ON_3.1/4H_2O$: C, 64.86: H, 4.70; N, 20.63. Found: C, 65.24; H, 4.50; N, 20.93.

5-Carbamoyl-1'-methyl-2,3'-bipyridinium Iodide (2a). Compound **1** and excess MeI in EtOAc gave crystals of **2** after stirring at room temperature overnight. Trituration with hot methanol yielded pale yellow crystals (80% yield, mp >250 °C). H^1 NMR (CD_3OD) δ 9.47 (1H, s), 9.13 (1H, d, J = 2 Hz), 9.07 (1H, d, J = 8 Hz), 8.92 (1H, d, J = 6 Hz), 8.42 (1H, dd, J = 6 and 8 Hz), 8.22 (1H, t, J = 6 and 8 Hz), 8.15 (1H, d, J = 8 Hz), 4.52 (CH_3, s). Anal. Calcd. for $C_{12}H_{12}ON_3I$: C, 42.25; H, 3.55; N, 12.32. Found: C, 42.01; H, 3.54; N, 12.61.

5-Carbamoyl-1'-methyl-2,3'-bipyridinium Tosylate (2b). Compound **1** and excess MeOTs in CH_3CN gave crystals of **2** after stirring at reflux overnight. Filtration of the hot solution and then two washes with hot CH_3CN gave beige crystals (99% yield, mp 185-192 °C, decomp.). H^1 NMR (DMSO-d_6) δ 9.71 (1H, s), 9.20 (2H, m), 9.03 (1H, d, J = 6 Hz), 8.46 (1H, dd, J = 2 and 9 Hz), 8.33 (1H, bd, J= 9 Hz), 8.23 (1H, dd, J= 6 and 9 Hz), 7.75 (1H, bs), 7.45 (2H, d, 9 Hz), 7.08 (2H, d, 9 Hz) 4.44 (3H, s), 2.26 (3H, s). Anal. Calcd. for $C_{19}H_{19}O_4N_3S$: C, 59.20; H, 4.97; N, 10.90. Found: C, 58.85; H, 4.90; N, 10.80.

5-Carbamoyl-1,1'-dimethyl-2,3'-bipyridinium Diiodide (3a). Salt **2** was dissolved in dry DMF with excess MeI and heated to 95 °C in a sealed tube overnight. The tube was cooled and the solids were collected. The solids

were triturated with hot methanol to give orange needle-like crystals which were recrystallized from water and isopropyl alcohol to yield (25%) of orange needle-like crystals (mp >250 °C). H^1 NMR (D_2O), δ 9.60 (1H, s), 9.35 (1H, s), 9.20 (1H, d, J = 8.3 Hz), 9.13 (1H, d, J = 6 Hz), 8.94 (1H, d, J = 8 Hz), 8.43 (1H, dd, J = 6 and 8 Hz), 8.36 (1H, d, J = 8 Hz), 4.6 (CH_3, s), 4.38 (CH_3, s). Anal. Calcd. for $C_{13}H_{16}ON_3I_2.1/2H_2O$: C, 31.73; H, 3.28; N, 8.54. Found: C, 31.59; H, 3.18; N, 8.48.

5-Carbamoyl-1,1'-dimethyl-2,3'-bipyridinium Ditosylate (3b). Salt **2** (0.519 mmol) was added to distilled sulfolane (10 mL) with MeOTs (0.887 mmol) and stirred overnight at 110 °C. The solution was cooled and the product precipitated with 1:1 EtOAc/Et_2O. The product was collected and recrystallized with MeOH and EtOAc to give an off-white solid (84% yield, mp >200 °C). H^1 NMR (DMSO-d_6), δ 9.65 (1H, s), 9.36 (1H, s), 9.21 (1H, d, J = 5 Hz), 9.05 (1H, d, J = 8 Hz), 8.85 (1H, d, J = 8 Hz), 8.65 (1H, s), 8.37-8.27 (3H, m), 7.42 (4H, d, J = 8 Hz), 7.08 (4H, d, J = 8 Hz), 4.42 (CH_3, s), 4.24 (CH_3, s), 2.26 (6H, s). Anal. Calcd. for $C_{27}H_{29}O_7N_3S_2.H_2O$: C, 54.99; H, 5.29; N, 7.13. Found: C, 55.24; H, 4.98; N, 6.99.

5-Carbamoyl-1'-(2-(4-nitrophenyl)ethyl)-2,3'-bipyridinium Iodide (4). A mixture of 1.52 g (6.61 mmol) of 2-(4-nitrophenyl)ethyl bromide and 3 g (20 mmol) of NaI in 20 mL of acetone was stirred at reflux. The suspension was allowed to cool and the insoluble materials were removed. The filtrate was concentrated and 20 mL of EtOAc was added. The insoluble solids were removed and the filtrate was concentrated to yield p-nitrophenethyl iodide. This was dissolved in 25 mL of 1,4-dioxane and to this 1.3 g of **1** (6.5 mmol) was added. The suspension was heated at reflux overnight. While the suspension was still hot the insoluble material was filtered off and the resultant yellow solids were triturated with hot 1,4-dioxane to yield 3.1 g of a yellow solid (90% yield, mp >200 °C). H^1 NMR (DMSO-d_6), δ 9.8 (1H, s), 9.22 (1H, d, J = 8 Hz), 9.20 (1H, d, J = 2 Hz), 9.02 (1H, d, J = 7.0 Hz), 8.43 (1H, dd, J = 2 and 8 Hz), 8.26 (H, d, J = 8 Hz), 8.22 (1H, dd, J = 7 and 8 Hz), 8.20 (2H, Ph, d), 7.58 (2H, Ph, d), 5.0 (2H, t, J = 7 Hz), 3.43 (2H, t, J = 7 Hz). Anal. Calcd. for $C_{19}H_{17}O_3N_4I$: C, 47.91; H, 3.53; N, 11.76. Found: C, 47.85; H, 3.60; N, 11.77.

5-Carbamoyl-1-methyl-1'-(2-(4-nitrophenyl)ethyl)-2,3'-bipyridinium Diiodide (5a). A solution of 200 mg (0.42 mmol) of **4** in 3 mL of sulfolane and 1 mL of MeI (16 mmol) in a sealed tube was heated at 120 °C overnight. The mixture was cooled to 0 °C and then precipitated with 8 mL of EtOAc. After filtration the oily brown solid was dissolved in methanol, concentrated and coated onto

200 mg of octadecyl functionalized silica gel. This material was then added to the top of a reverse phase silica gel column and eluted with H_2O.[8] Removal of the water gave an orange oil which crystallized on standing. The solid was recrystallized from methanol and EtOAc to afford 65 mg of yellow crystals (15% yield, mp >200 °C). H^1 NMR (DMSO-d_6). δ 9.63 (1H, s), 9.48 (1H, s), 9.22 (1H, d, J = 6 Hz), 9.03 (1H, d, J = 8 Hz), 8.90 (1H, d, J = 7 Hz), 8.65 (1H, s, NH), 8.39 (1H, dd, J = 6 and 8 Hz), 8.30 (1H, d), 8.27 (1H, s, NH), 8.18 (2H, d, Ph), 7.54 (2H, d, Ph), 4.98 (2H, t, J = 7 Hz), 4.19 (3H, s, CH_3), 3.45 (2H, t, J = 7 Hz). Anal. Calcd. for $C_{20}H_{20}O_3N_4I_2$: C, 38.85; H, 3.26; N, 9.06: Found: C, 38.78; H, 3.50; N, 8.99.

5-Carbamoyl-1-methyl-1′-(2-(4-nitrophenyl)ethyl)-2,3′-bipyridinium Ditosylate (5b). A mixture of 500 mg (1.05 mmol) of **4**, 10 ml of sulfolane, and 1.0 g (5.4 mmol) of MeOTs was heated at 115 °C overnight. The solution was cooled to 0 °C and then precipitated with 10 mL of EtOAc. The solid was collected and washed 3 times with 20 mL portions of EtOAc to give 600 mg of a white solid (85% yield, mp >220 °C). H^1 NMR (DMSO-d_6). δ 9.63 (1H, s), 9.48 (1H, s), 9.22 (1H, d, J = 7 Hz), 9.03 (1H, d, J = 9 Hz), 8.90 (1H, d, J = 7 Hz), 8.65 (1H, s, NH), 8.39 (1H, dd, J = 7 and 9 Hz), 8.30 (1H, d, J = 9 Hz), 8.27 (1H, s, NH), 8.18 (2H, d, Ph), 7.54 (2H, d, Ph), 7.50 (4H, d, Ph of OTs), 7.08 (4H, d, Ph of OTs), 4.98 (2H, t, CH_2), 4.19 (3H, s, CH_3), 3.45 (2H, t, CH_2), 2.22 (6H, s, CH_3 of OTs). Anal. Calcd. for $C_{34}H_{34}N_4O_9S_2$: C, 57.76; H, 4.89; N, 7.93. Found: C, 58.20; H, 5.01; N, 8.07.

5-Carbamoyl-1-methyl-2,3′-bipyridinium Diperchlorate (6). A suspension of 1.0 g (1.4 mmol) of the tosylate of **5b**, 30 mL of acetonitrile, and 0.14 g (1.7 mmol) of sodium acetate was heated at reflux for 48 h. The suspension was cooled to 0 °C and the insoluble NaOTs was collected. The filtrate was concentrated to a brown oil which was taken up in 20 mL of H_2O and 20 mL of EtOAc. The H_2O was then diluted with 80 mL of methanol and then mixed with 500 mg of octadecyl functionalized silica gel and concentrated to a powder. This material was placed on top of a reverse phase silica gel column and eluted with H_2O. Removal of the water gave a yellow oil. Addition of 30 mL of EtOAc caused the oil to solidify yielding 325 mg of a light brown solid (55% yield, mp >200 °C). H^1 NMR (DMSO-d_6). δ 9.62 (1H, s), 9.00 (1H, d, J = 8 Hz), 8.85 (2H, m), 8.65 (1H, s, NH), 8.28 (1H, d J = 8 Hz), 8.22 (1H, s, NH), 8.18 (1H, d, J = 8 Hz), 7.70 (1H, dd, J = 5 and 8 Hz), 7.45 (2H, d, Ph), 7.10 (2H, d, Ph), 4.22 (3H, s, N-CH_3), 2.29 (3H, s CH_3 of OTs). This material was converted to its perchlorate salt on the addition of perchloric acid-EtOAc. Anal. Calcd for $C_{12}H_{13}Cl_2N_3O_9$: C, 34.80; H, 3.16; N, 10.14: Found: C, 34.53; H, 3.15; N, 10.00.

5-Carbamoyl-1'-(2-(4-nitrophenyl)ethyl)-2,3'-bipyridinium-1-oxide Tosylate (7). The iodide salt was first converted to the tosylate salt as follows. To a suspension of **4** (500 mg, 1.04 mmol) in 50 mL of acetonitrile was added MeOTs (200 mg, 1.07 mmol). The suspension was stirred under a stream of nitrogen for two days. The precipitate was a white solid (540 mg, 1.04 mmol) which was suspended in 20 mL of sulfolane and 50% m-chloroperbenzoic acid (763 mg, 4.42 mmol). The reaction was stirred at room temperature for 3 days and the product was precipitated with 50 mL of 1:1 EtOAc:diethyl ether. The white precipitate was filtered and dried under vacuum to give **7**, 320 mg (mp >220 °C, 57 % yield). H^1 NMR (DMSO-d_6): δ 9.72 (1H, s), 9.08 (2H, m), 8.84 (1H, s), 8.22 (1H, dd, J = 5 and 8 Hz), 8.19 (3H, d, J = 9 Hz, Ph and NH), 7.95 (3H, m), 7.57 (2H, d, J = 8 Hz, Ph), 7.44(2H, d, Ph OTs), 7.08 (2H, d, Ph OTs), 4.96 (2H, m, CH_2), 3.50 (2H, m, CH_2), 2.28 (3H, s, CH_3). Anal. Calcd. for $C_{26}H_{24}N_4O_7S$: C, 58.20; H, 4.51; N, 10.44. Found: C, 58.24; H, 4.51; N, 10.38.

5-Carbamoyl-2,3'-bipyridine-1-oxide (8) by NPE Deprotection. To 50 mL of acetonitrile was added **7** (320 mg, 0.596 mmol) and dry sodium acetate (100 mg, 1.19 mmol). The solution was stirred at reflux for 24 h. The insoluble solids were removed and the filtrate was concentrated onto 20 g of silica gel and added to a column which was eluted with 70% EtOAc and 30% MeOH to give 90 mg of a white solid (62% yield, mp >220°C). H^1 NMR (DMSO-d_6): δ 8.96 (1H, d, J = 2 Hz), 8.60 (1H, dd, J = 2, 5 Hz), 8.52 (1H, s), 8.27 (1H, dt, J = 2, 2 and 9 Hz), 7.71 (1H, d, J = 9 Hz), 7.61 (1H, d, J = 9 Hz), 7.48 (1H, dd, J = 5 and 9 Hz). Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.23; H, 4.22; N, 19.55.

5-Carbamoyl-1'-methyl-2,3'-bipyridinium-1-oxide Tosylate (9): To trifluoroacetic acid (10 mL) was added **2** (750 mg, 1.95 mmol) and urea-H_2O_2 complex (320 mg). The solution was stirred overnight at room temperature with an additional 100 mg addition of the urea-H_2O_2 complex after the first 2 h. The mixture was diluted with 10 mL of water and the product was precipitated with isopropyl alcohol to give after filtration 700 mg of a yellow solid (86% yield, mp >200 °C). ^1H NMR (DMSO-d_6): δ 9.60 (s, 1H), 9.07 (m, 2H), 8.85 (s, 1H), 8.38 (s, NH), 8.25 (dd, 1H, 6 and 9 Hz), 8.03 (d, 1H, 9 Hz), 7.95 (bd, 2H, 9 Hz), 7.48 (d, 2H, 9 Hz), 7.11 (d, 2H, 9 Hz), 4.42 (s, 3H), 2.26 (s, 3H, NCH_3). Anal. Calcd. for $C_{19}H_{19}N_3O_5S.0.5H_2O$: C, 55.60; H, 4.91; N, 10.24. Found: C, 55.22; H, 4.59; N, 10.47.

5-Carbamoyl-2,3'-bipyridine-1-oxide (8) by Demethylation. To **9** (340 mg, 0.847 mmol) dissolved in 20 mL of DMF was added KI (280 mg, 1.68 mmol). The

mixture was heated at 120 °C for 36 h and then concentrated to a brown oil and dissolved in 40 mL of MeOH. The insoluble material was removed and the filtrate was concentrated onto 50 g of silica gel and added to the top of a silica gel column which then was eluted with 80% EtOAc and 20% MeOH to yield 100 mg of a white solid. (55% yield, mp >220°C). The ^{1}H NMR (DMSO-d_6) was the same as the above.

1'-Methyl-2,3'-bipyridinium-1-oxide Tosylate (11). To 20 mL of CH_2Cl_2 was added 2,3'-bipyridine (500 mg, 3.20 mmol) and MeOTs (600 mg, 3.22 mmol). The solution was stirred at room temperature for 24 h. The solvent was concentrated to yield 1.10 grams (3.20 mmol) of a slightly yellow oil which was added to 30 mL of $CHCl_3$ and 50% of m-chloroperbenzoic acid (2.21 g, 12.8 mmol). The solution was stirred at room temperature for 48 h. The $CHCl_3$ was washed once with 30 mL of water. The aqueous layer was separated and concentrated to 800 mg of yellow oil; this crude material was used directly for the deprotection step. H^1 NMR (DMSO-d_6): δ 9.58 (1H, s), 9.05 (2H, m), 8.50 (1H, d, J = 5 Hz), 8.24 (1H, dd, J = 5 and 8 Hz), 7.85 (1H, dd, J = 8 and 8 Hz), 7.60 (2H, m), 7.48 (2H, d, Ph), 7.05 (2H, d, Ph), 4.40 (3H, s, NCH_3), 2.25 (3H, s, CH_3).

2,3'-Bipyridine-1-oxide (10) by Deprotection: Crude **11** (300 mg, 0.840 mmol) was dissolved in 10 mL of DMF and KI (280 mg, 1.68 mmol) was added. The reaction was heated at 120 °C for 24 h and then concentrated to a brown oil and dissolved in MeOH. The insoluble material was removed and the filtrate was concentrated onto 10 g of silica gel and added to the top of a silica gel column which then was eluted with 90% EtOAc and 10% MeOH to yield 60 mg of a white solid (mp 135-137 °C, 40% yield). H^1 NMR (DMSO-d_6) δ 8.95 (1H, d, J = 2 Hz), 8.63 (1H, dd, J = 2 and 5 Hz), 8.37 (1H, dd, J = 2 and 6 Hz), 8.27 (1H, dt, J = 2, 2 and 9 Hz), 7.73 (1H, dd, J = 2 and 8 Hz), 7.52 (1H, dd, J = 5 and 9 Hz), 7.44 (2H, m). Anal. Calcd. for $C_{10}H_7N_2O$: C, 69.75: H, 4.63; N, 16.27: Found C, 70.03; H, 4.69; N, 16.29.

6-Chloronicotinamide-1-oxide: 6-Chloronicotinamide (800 mg, 5.75 mmol) and urea-H_2O_2 complex (930 mg) were dissolved in 10 mL of trifluoroacetic acid. The solution was stirred overnight at room temperature with the addition of 300 mg urea-H_2O_2 after each of the first two hours. The reaction was diluted with 50 mL of H_2O and 50 mL of EtOAc. The organic layer was separated and the aqueous layer was extracted 3 times with 50 mL of EtOAc. The extracts were combined, dried, and concentrated to a clear liquid. Column chromotography with silica gel and 80% EtOAc/20% MeOH gave 850 mg of an off-white solid (86% yield, mp 124-128 °C). H^1 NMR (DMSO-d_6) δ 8.80 (d, 1H, J = 2 Hz), 8.24

(s, 1H), 7.88 (d, 1H, J = 9 Hz), 7.82 (s, 1H), 7.70 (dd, 1H, J = 2 and 9 Hz). Anal. Calcd. for $C_5H_5N_2O_2Cl$ .1/3 H_2O: C, 40.35: H, 3.20; N, 16.69: Found C, 40.50; H, 2.91; N, 15.24.

Pd-Catalyzed Coupling to Prepare 5-Carbamoyl-2,3'-Bipyridine-1-oxide (8): 6-Chloronicotinamide-1-oxide (175 mg, 1.01 mmol), diethyl-3-pyridyl borane (150 mg, 1.01 mmol), and tetrakis(triphenylphosphine)palladium(0) (200 mg, 0.173 mmol) were added to 20 mL of degassed THF. The suspension was stirred under nitrogen for 5 min and then K_2CO_3 (280 mg, 2.03 mmol) in 10 mL of water was added. The solution was heated at reflux for 24 h and then cooled to 0 °C and the black insoluble solid was removed by filtration. The reaction was diluted with 30 mL of water and 30 mL EtOAc. The aqueous layer was separated and concentrated to a yellow solid which was triturated with hot MeOH. Solids were collected and the filtrate was concentrated to a white solid which was recrystallized with 95% EtOH and EtOAc to give 160 mg of a white solid (73% yield, mp> 220 °C). The ^{1}H NMR (DMSO-d_6) was the same as that above.

Pd-Catalyzed Coupling to Prepare 2,3'-Bipyridine-1-oxide (10): 2-Bromopyridine-1-oxide hydrochloride (500 mg, 2.38 mmol), diethyl-3-pyridyl borane (350 mg, 2.38 mmol) and tetrakis(triphenylphosphine)palladium(0) (300 mg, 0.260 mmol) were added to 30 mL of degassed THF. The suspension was stirred under nitrogen for 5 min and then K_2CO_3 (1.65 g, 12.0 mmol) in 15 mL of water was added. The solution was heated at reflux for 48 h and then cooled to 0 °C and the catalyst was collected. To the filtrate was added 30 mL of EtOAc and 30 mL water. The aqueous layer was separated and concentrated to a white solid which was triturated with 20 mL of MeOH; the solid material was collected. The methanolic layer was concentrated to 280 mg of a white solid (mp 136-137 °C, 68% yield). The H^1 NMR (DMSO-d_6) was the same as that above.

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