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Reaction of 2-Amino-5,10,15,20-Tetraphenylporphyrinatonickel(II) with α,β-Unsaturated Acyl Chlorides: Synthesis of 2-pyridone-fused Porphyrin Derivatives

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Dedicated to Professor Pedro Joseph-Nathan on the occasion of his 65th birthday

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Abstract: The reactivity of 2-amino-5,10,15,20-tetraphenylporphyrinatonickel(II) with acryloyl and cinnamoyl chlorides was studied. The reaction with acryloyl chloride afforded the dihydro-2-pyridone fused porphyrin **3a** resulting from an aza-annulation reaction. The oxidation of **3a** afforded the corresponding 2-pyridone derivative. *N*-Acylation reaction is an important competing transformation, giving rise to amide derivatives. The structures of the novel compounds were established by NMR and mass spectrometry studies.
Keywords: Porphyrins, aza-annulation reactions, 2-pyridones, acyl chlorides.

Resumen: En el presente trabajo se estudió la reactividad de 2-amino-5,10,15,20-tetrafenilporfirinatoníquel(II) con los cloruros de acriloílo y cinamoílo. De la reacción de aza-anulación con cloruro de acriloílo resultó la porfirina **3a** que posee un anillo de dihidro-2-piridona fundido. La oxidación de **3a** permitió la obtención del derivado de 2-piridona correspondiente. La reacción de *N*-acilación es una importante transformación competitiva, que origina los derivados de amida. La estructura de los nuevos compuestos fue establecida por estudios de RMN y por Espectrometría de Masa.
Palabras-clave: Porfirinas, reacciones de aza-anulación, 2-piridonas, cloruros de acilo.

Introduction

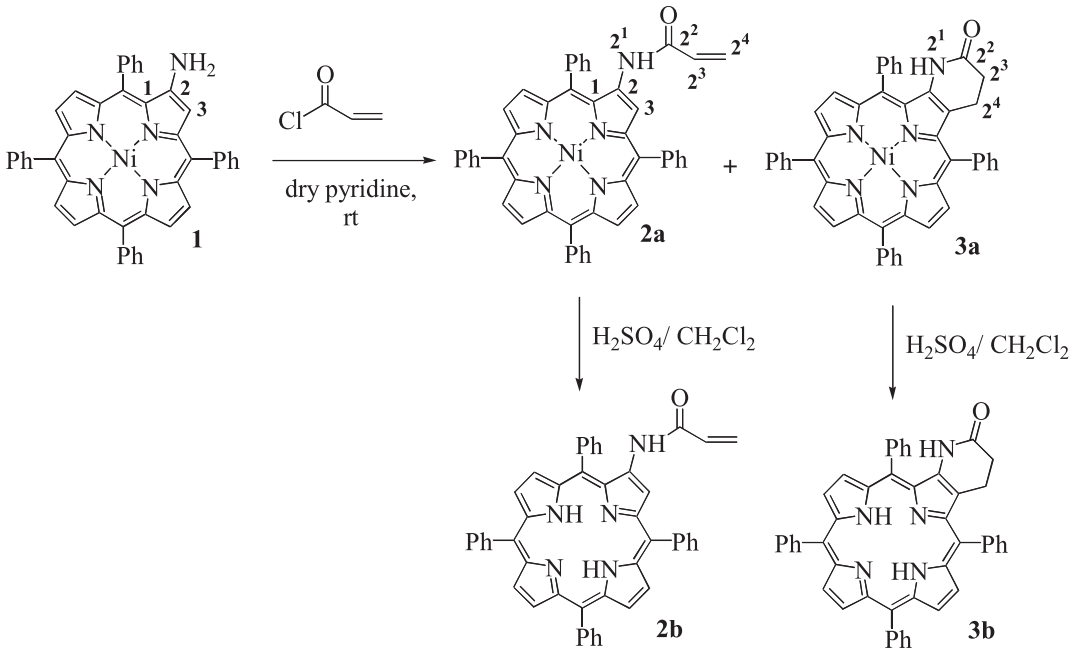
Porphyrin derivatives are widely distributed in Nature, playing essential roles in vital processes such as photosynthesis, oxygen transport and storage. Moreover, the intensive studies carried out in the last decades by many research groups have pointed out certain important applications of these compounds in medicine, in catalysis, and as sensors, biocides, or as components of new electronic materials [1]. The search for new tetrapyrrolic macrocycles with adequate features for specific applications has become the target of several work programs. In particular, our group has been devoting a great effort to establish new methods for the introduction of suitable functionalities starting with readily available porphyrin macrocycles, aiming to improve their properties and potential applications [2]. Part of that work has been related with the functionalization of β-pyrrolic positions *via* 2-amino-tetraarylporphyrins [3-7].

In particular, we have shown that 2-amino-5,10,15,20-tetraphenylporphyrinatonickel(II) reacts with α,β-unsaturated ketones and aldehydes affording fused pyridoporphyrins, thus demonstrating that such porphyrin amino derivative can behave as an aromatic amine or as an enamine [3,4]. Knowing that nitrogen heterocycles with a 2-pyridone core can be obtained via aza-annulation of enamines with α,β-unsaturated acid derivatives [8,9] we decided to investigate the reactivity of 2-amino-5,10,15,20-tetraphenylporphyrinatonickel(II) (**1**) with acryloyl and cinnamoyl chlorides. In such way, we were able to make use of the enamine behavior thus originating a fused-2-pyridone ring in two macrocycle β-pyrrolic positions, such new fused ring being a structural feature present in many biologically active compounds [10]. We also obtained the amide derivatives, which express the predominant amine character of **1**.

Results and Discussion

The starting porphyrin used in these reactions, 2-amino-5,10,15,20-tetraphenylporphyrinatonickel(II) (**1**), was obtained *via* nitration of the nickel(II) complex of 5,10,15,20-tetraphenylporphyrin with copper(II) nitrate in acetic anhydride, followed by reduction with tin(II) chloride [11].

The reaction of **1** with acryloyl chloride was carried out at room temperature in dry pyridine and under an atmosphere protected against moisture. After stirring for 30 minutes the solvent was removed under vacuum, the residue was dissolved in dichloromethane and the mixture neutralized with acidic water. The organic layer was then washed with water and dried over sodium sulfate. Separation by preparative thin layer chromatography, using a 1:1 mixture of dichloromethane and petroleum ether as eluent, afforded compounds **2a** and **3a** in 58% and 27% yields, respectively. After structural characterization by spectroscopic techniques (^{1}H and ^{13}C NMR, MS and UV-Vis) we were able to assign the less polar compound to amide **2a** and the more polar one to the dihydro-2-pyridone-fused porphyrin **3a** (Scheme 1).



Scheme 1

The mass spectra (FAB^+) of compounds **2a** and **3a** show the parent ion at *m/z* 739 ($[M]^{+\cdot}$) in agreement with the proposed structures. The ^1H NMR spectrum of amide **2a** is consistent with a β-substituted porphyrin derivative, with the resonance of H-3 appearing as a singlet at δ 9.35. In the same spectrum, the resonances of the vinylic protons are easily identified: H-2^3 appears as a double doublet at δ 5.52 ppm due to *cis* (J = 10.2 Hz) and *trans* (J = 16.2 Hz) couplings with the vicinal protons *cis*-H-2^4 (doublet at δ 5.56) and *trans*-H-2^4 (doublet at δ 6.28).

In the case of dihydropyridone **3a**, the ^1H NMR spectrum shows only the resonances of six β-pyrrolic protons, which seems to indicate a β-fused derivative. The resonances of protons of H-2^3 and H-2^4 appear as two triplets (J = 7.7 Hz), at δ 2.74 and δ 2.60 ppm, respectively. The ^{13}C NMR spectrum confirms the proposed structure showing the resonance corresponding to the carbonyl group at δ 169.8 and the resonance of the two methylenic carbons at δ 22.0 and δ 31.2.

When the reaction was performed with cinnamoyl chloride (Scheme 2), under the conditions described above, compound **4a** was obtained in 66% yield as the only product.

The ^1H NMR spectrum of compound **4a** shows the resonance of H-3 as a singlet at δ 9.37, indicating that this is a β-substituted derivative. The resonance of protons H-2^3 and H-2^4 appears as doublets at δ 5.78 and δ 7.60. H-2^4 is more deshielded than H-2^3 due to the mesomeric and anisotropic deshielding effects of the carbonyl and phenyl groups. The mass spectrum confirms the proposed structure for **4a** showing a peak at *m/z* 816 ($[M+H]^+$).

The free bases **2b**, **3b** (Scheme 1) and **4b** (Scheme 2) were obtained by demetallation of the corresponding nickel complexes with 5% of sulfuric acid in dichloromethane. After neutralization, the usual work-up and chromatography, the new derivatives were isolated in moderated to high yields: **2b** (73%), **3b (**60%) and **4b** (91%). The structural characterization of the free bases was based on spectroscopic data; the ^1H NMR spectra of these free bases are very similar to those due to their metal complexes, the major difference being the typical appearance in the free bases of the signals corresponding to

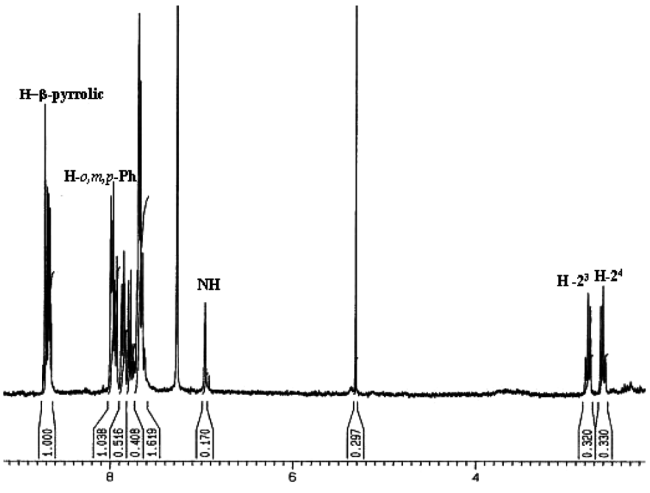
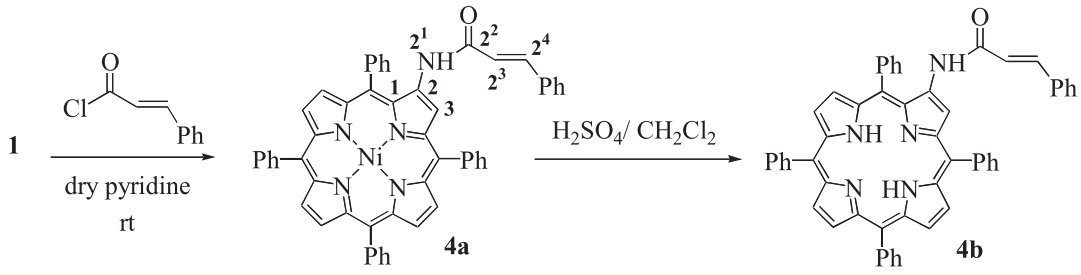
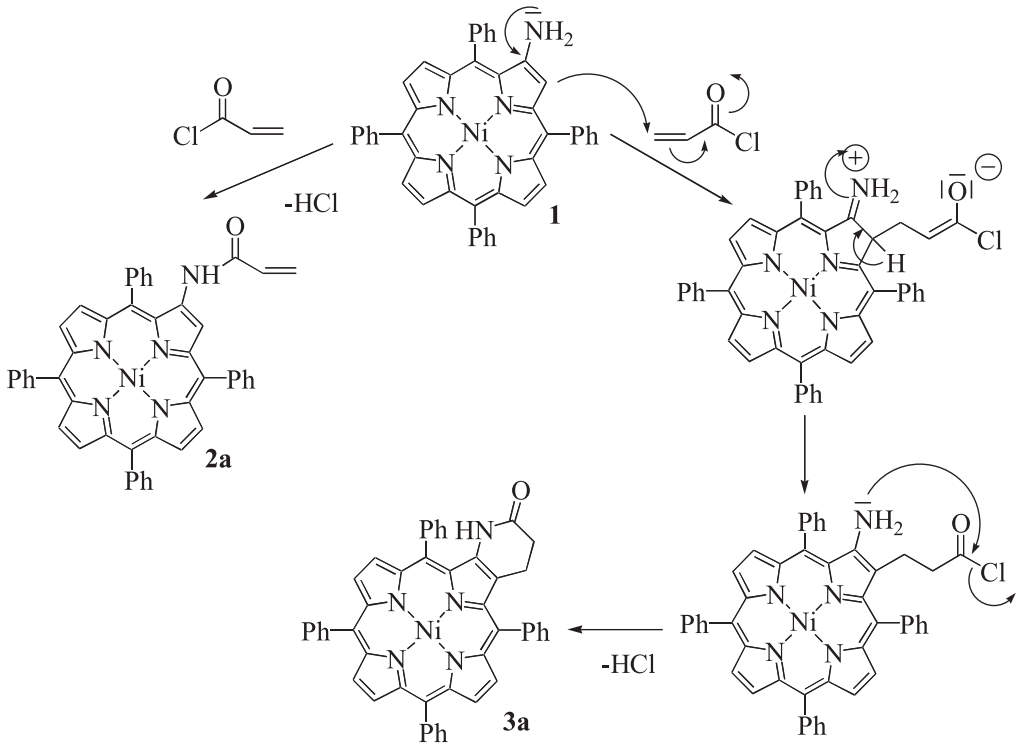


Fig. 1. ^1HNMR spectrum of compound **3a**.



Scheme 2



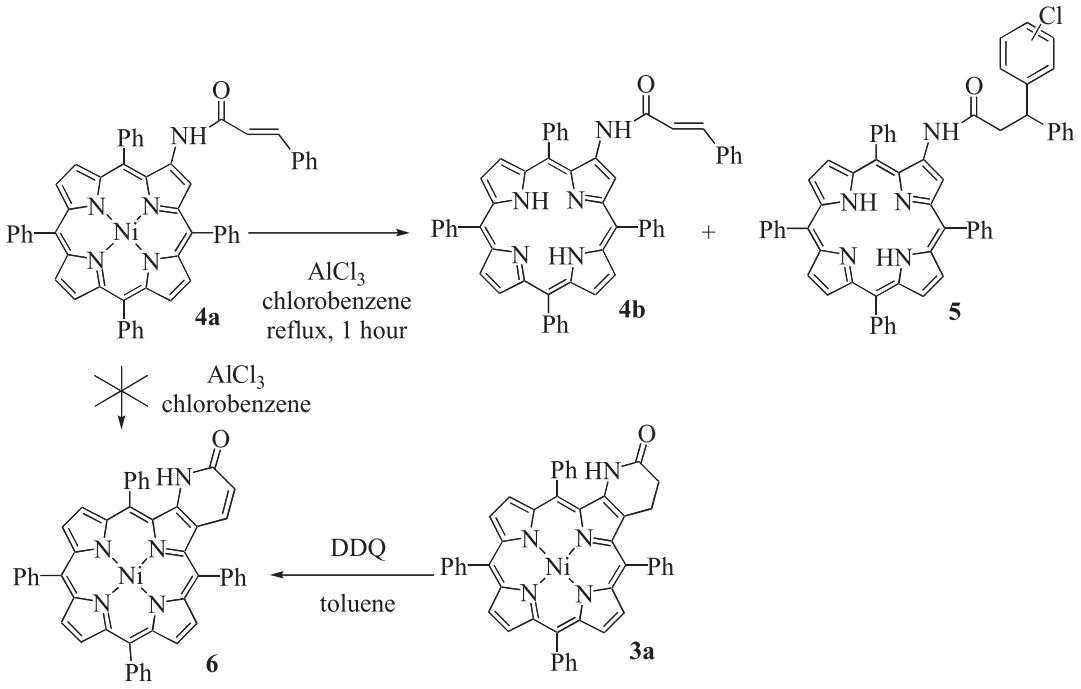
Scheme 3

the internal NH resonances at ca. δ -2.8. Once again, the mass spectra confirm the proposed structures, showing peaks at *m/z* 683 $[M]^{+\cdot}$ for **2a** and **3b** and at 760 $[M+H]^{+}$ for **4b**.

From a mechanistic point of view, the formation of amides and pyridones as reaction products reflects the dual behavior of 2-aminoporphyrin **1** as amine and enamine as shown in Scheme 3. Amides **2a** and **4a** are the result of the *N*-acylation while the formation of dihydropyridone **3a** results from an aza-annulation reaction initiated by the Michael addition of the enamine followed by an intramolecular *N*-acylation.

The fact that the reaction with cinnamoyl chloride did not afford any pyridone derivatives might be related with steric or electronic effects due to the phenyl group on the β-carbon of the acyl chloride. Even when the reaction was carried out at 80 ºC no pyridone products were formed.

Aluminum(III) chloride has been used as Lewis acid catalyst in the cyclization of cinnamanilides to quinolones [12]. In those reactions the phenyl group is lost. We applied this synthetic methodology with derivative **4a** expecting to obtain **6** (Scheme 4). The $AlCl_3$ was added to a solution of **4a** in chlorobenzene under stirring and then the mixture was refluxed for 1 h. After this period, the analytical TLC showed the complete conversion of starting porphyrin into two new products. The reaction mixture was purified by preparative thin layer chromatography using dichloromethane as eluent. The spectroscopic studies carried out with the two products **4b**



Scheme 4

(33%) and **5** (14%) revealed that none of them have the expected fused structure **6**.

Compound **4b**, the more polar one, was identified as the amide free base derivative.

As far as the characterization of compound **5** is concerned, the presence of a peak at *m/z* 872 ($[M+H]^+$) seems to indicate demetallation and addition of one molecule of solvent to **4a**. The ^{1}H NMR spectrum confirms this assumption showing the signals corresponding to the resonance of the H-2^3 protons as two overlapped doublets at δ 2.63-2.66 while the resonance of H-2^4 appears as a triplet at δ 4.64 (J = 7.6 Hz). We were not able to identify the position of the chlorine atom in the chlorophenyl group since the signals of the protons due to this phenyl ring are masked with the signals corresponding to the resonances of the porphyrin phenyl protons. However, we believe that, due to steric factors, the electrophilic attack at the chlorobenzene occurs preferentially in the *para* position.

It is worth to refer that we were able to obtain the fused derivative **6** by oxidation of compound **3a** with DDQ. The reaction occurred in toluene at room temperature for 3 days and compound **6** was obtained as the main reaction product (52% yield). The ^{1}H NMR spectrum confirms that it is a β-fused derivative showing the resonances of only six β-pyrrolic protons (δ 8.67-8.74). The signals of protons H-2^3 and H-2^4 appear as two doublets (J = 9.7 Hz) at, respectively, δ 6.41 and δ 6.88. The mass spectrum (FAB) shows the expected $[M+H]^+$ ion at *m/z* 738.

Conclusion

2-Amino-5,10,15,20-tetraphenylporphyrinatonickel(II) reacts with acryloyl chloride to afford the corresponding amide and a dihydro-2-pyridone-fused porphyrin derivative; this compound is easily oxidised with DDQ to the corresponding 2-pyridone.

The reaction of aminoporphyrin **1** with cinnamoyl chloride affords only the corresponding amide **4a**. Under Friedel-Crafts conditions this compound reacts with chlorobenzene to afford the addition product **5**.

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded on Bruker AMX 300 NMR spectrometer (at 300.13 and 75.47 MHz, respectively), $CDCl_3$ was used as solvent and TMS as internal reference. The chemical shifts are expressed in δ (ppm) and the coupling constants (J) in Hertz [Hz]. Mass spectra were recorded on VG AutoSpec Q mass spectrometer using $CHCl_3$ as solvent and 3-nitrobenzyl alcohol (NBA) as matrix.

The UV-Vis spectra were recorded on an Uvikon spectrophotometer using $CHCl_3$ as solvent. Melting points were measured on a Reichert Thermovar apparatus fitted with a microscope and are uncorrected. Preparative thin layer chro-

matography was carried out on 20 × 20 cm glass plates coated with Merck 60 silica gel (0.5 mm thick). Column chromatography was carried in silica gel (Merck, 230-400 mesh). Analytical TLC was carried out on precoated sheets with silica gel (Merck 60, 0.2 mm thick).

Reaction of 2-amino-5,10,15,20-tetraphenylporphyrinatonickel(II) with α,β-unsaturated acyl chlorides. General procedure:

To a stirred solution of 2-amino-5,10,15,20-tetraphenylporfirinatonickel(II) **1** (~7 mg, $1.0x10^{-2}$ mmol) in dry pyridine (1 mL) was added either acryloyl chloride (0.05 mL, $6.2x10^{-1}$ mmol) or cinnamoyl chloride (6.0 mg, $3.6x10^{-2}$ mmol). The reaction mixture was protected against moisture and stirred at room temperature until complete consumption of the starting porphyrin (~30 min., confirmed by TLC). After solvent removal under vacuum, the residue was dissolved in dichloromethane, neutralized with acidic water and washed with water. The organic layer was dried over sodium sulfate and its components were separated by preparative thin-layer chromatography using a 1:1 mixture of dichloromethane/ petroleum ether as eluent.

2a: 4.6 mg (58% yield); mp >300ºC; UV-Vis ($CHCl_3$) λ_{max} (log ε) 417 (5.33), 533 (4.22) nm; ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 5.52 (1H, dd, *J* = 10.2, 16.2 Hz, H-2^3), 5.66 (1H, d, *J* = 10.2 Hz, H-2^4), 6.28 (1H, d, *J* = 16.2 Hz, H-2^4), 7.60-7.68 (10H, m, H-*m,p*-Ph), 7.79-7.86 (2H, m, H-*m,p*-Ph), 7.95-8.04 (9H, m, H-*o*-Ph, NH), 8.59 (1H, d, J = 4.9 Hz, H-β), 8.66-8.73 (5H, m, H-β), 9.35 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 115.0, 118.4, 119.0, 119.7, 120.6, 126.9, 127.1, 127.8, 127.9, 128.5, 129.3, 130.6, 131.2, 131.9, 132.1, 132.2, 132.3, 132.5, 132.8, 133.5, 133.60, 133.64, 139.1, 139.4, 140.5, 141.7, 141.8, 142.1, 142.4, 142.7, 142.8, 143.0, 161.9 (C=O); FABMS *m/z* for $C_{47}H_{31}N_5ONi$ ($[M]^{+\cdot}$) 739.

3a: 2.1 mg (27% yield); mp >300ºC; UV-Vis ($CHCl_3$) λ_{max} (log ε) 416 (5.39), 534 (4.22) nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.60 (2H, t, J = 7.7 Hz, H-2^4), 2.74 (2H, t, J = 7.7 Hz, H-2^3), 6.95 (1H, s, NH), 7.64-7.70 (9H, m, H-*m,p*-Ph), 7.76 (2H, brd, J = 7.0 Hz, H-*m,p*-Ph), 7.83-7.87 (3H, m, H-*o,m*-Ph or H-*p*-Ph), 7.92-7.99 (6H, m, H-*o*-Ph), 8.64-8.71 (6H, m, H-β); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.0 (C-2^4), 31.2 (C-2^3), 115.2, 117.0, 119.2, 119.7, 122.8, 127.0, 127.3, 127.8, 128.3, 128.4, 129.0, 129.6, 131.3, 132.1, 132.3, 132.4, 132.6, 132.7, 133.6, 133.6, 137.3, 138.5, 140.4, 141.8, 142.1, 142.2, 142.6, 143.4, 169.8 (C=O); FABMS *m/z* for $C_{47}H_{31}N_5ONi$ ($[M]^{+\cdot}$) 739.

4a: 5.6 mg (66% yield); mp >300ºC; UV-Vis ($CHCl_3$) λ_{max} (log ε) 419 (5.42), 534 (4.27) nm; ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 5.78 (1H, d, *J* = 15.5 Hz, H-2^3), 7.43-7.47 (5H, m, H-2^4-Ph), 7.60 (1H, d, *J* = 15.5 Hz, H-2^4), 7.64-7.71 and 7.85-7.95 (13H, 2m, H-*m,p*-Ph, NH), 7.95-8.01 and 8.06-8.09 (8H, 2m, H-*o*-Ph), 8.62 (1H, δ, *J* = 5.0 Hz, H-β), 8.67-8.74 (m, 3H, H-β), 8.71 (2H, s, H-12,13), 9.37 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 115.0, 118.4, 119.0, 119.7, 120.5, 126.9, 127.1, 127.8, 128.7, 129.0, 130.0, 131.2, 131.9, 132.0, 132.1, 132.2, 132.3, 132.5, 132.8, 132.9, 133.5, 133.6, 133.6, 134.0, 134.7, 139.4, 139.6, 140.6, 141.7, 142.0, 142.1, 142.4, 142.8, 143.0, 162.3 (C=O); FABMS *m/z* for $C_{53}H_{35}N_5ONi$ ($[M+H]^+$) 816.

Demetallation of the compounds. General Procedure: The metal complex was dissolved in dichloromethane and treated with sulfuric acid (5%) under stirring at room temperature until total demetallation (monitored by TLC). The reaction mixture was then neutralised with a saturated aqueous solution of sodium carbonate, washed with water, extracted with dichloromethane and dried over sodium sulfate. The solvent was removed and the residue was taken into dichloromethane and purified by column chromatography using dichloromethane as eluent.

2b: 6.4 mg (73% yield); mp >300ºC; UV-Vis ($CHCl_3$) λ_{max} (log ε) 421 (5.46), 518 (4.37), 551 (3.73), 591 (3.83), 646 (3.44) nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ -2.82 (2H, brs, NH), 5.60 (1H, dd, *J* = 10.2, 16.4 Hz, H-2^3), 5.71 (1H, dd, *J* = 1.4, 10.2 Hz, H-2^4), 6.34 (1H, dd, *J* = 1.4, 16.4 Hz, H-2^4), 7.73-7.79 and 7.91-7.97 (13H, 2m, H-*m,p*-Ph, NH), 8.18-8.26 (8H, m, H-*o*-Ph), 8.62 (1H, d, *J* = 4.9 Hz, H-β), 8.79-8.87 (3H, m, H-β), 8.85 (2H, s, H-12,13), 9.45 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 114.2, 116.1, 120.0, 120.5, 121.1, 126.6, 126.7, 126.8, 127.8, 127.9, 128.5, 129.4, 129.8, 130.7, 133.4, 134.3, 134.4, 134.6, 140.7, 141.8, 142.1, 142.2, 162.3 (C=O); FABMS *m/z* for $C_{47}H_{33}N_5O$ ($[M]^{+\cdot}$) 683.

3b: 3.3 mg (60% yield); mp >300ºC; UV-Vis ($CHCl_3$) λ_{max} (log ε) 422 (5.14), 518 (4.13), 551 (3.54), 591 (3.65), 646 (3.23) nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ -2.92 (2H, brs, NH), 2.66 (2H, t, *J* = 7.6 Hz, H-2^4), 2.84 (2H, t, *J* = 7.6 Hz, H-2^3), 7.06 (1H, s, NH), 7.70-7.98 (12H, m, H-*m,p*-Ph), 8.08-8.10 and 8.16-8.23 (8H, 2m, H-*o*-Ph), 8.66 (1H, d, *J* = 4.7 Hz, H-β), 8.70 (1H, d, *J* = 4.7 Hz, H-β), 8.81-8.83 (4H, m, H-β); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.6 (C-2^4), 29.7 (C-2^3), 116.1; 120.0, 120.5, 121.0, 126.7, 126.8, 126.8, 127.8, 127.9, 128.5, 129.4, 130.7, 133.4, 134.3, 134.4, 134.6, 140.7, 141.8, 142.1, 142.2, 162.3 (C=O); FABMS *m/z* for $C_{47}H_{33}N_5O$ ($[M]^{+\cdot}$) 683.

4b: 8.0 mg (91% yield); mp >300ºC; UV-Vis ($CHCl_3$) λ_{max} (log ε) 423 (5.26), 519 (4.26), 553 (3.63), 592 (3.72), 647 (3.24) nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ -2.80 (2H, s, NH), 5.88 (1H, d, *J* = 15.5 Hz, H-2^3), 7.46-7.54 (5H, m, H-2^4-Ph), 7.66 (1H, d, *J* = 15.5 Hz, H-2^4), 7.75-7.77 and 7.95-8.06 (13H, 2m, H-*m,p*-Ph, NH), 8.20-8.22 and 8.29-8.31 (8H, 2m, H-*o*-Ph), 8.66 (1H, d, *J* = 4.8 Hz, H-β), 8.79 (2H, brs, H-12,13), 8.82-8.87 (3H, m, H-β), 9.46 (1H, s, H-3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 116.0, 120.0, 120.5, 120.6, 121.0, 126.7, 126.8, 126.9, 127.7, 127.8, 127.9, 128.6, 129.0, 129.1, 130.0, 133.5, 134.4, 134.5, 134.6, 134.7, 140.9, 141.8, 142.0, 142.1, 142.2, 162.7 (C=O); FABMS *m/z* for $C_{53}H_{37}N_5O$ ($[M+H]^+$) 760.

Attempted cyclization of 4a

To a stirred solution of compound **4a** (2.1 mg, $2.6x10^{-3}$ mmol) in chlorobenzene (1.5 mL) was added aluminum(III) chloride (2.1 mg, $1.6x10^{-2}$ mmol). The resulting mixture was refluxed for 1 hour and then neutralized with a saturated aqueous solution of sodium carbonate, washed with water and extracted with dichloromethane. The organic layer was dried over sodium sulfate and concentrated under reduced pressure. Reaction products were purified by preparative TLC using dichloromethane as eluent.

5: 0.3 mg (14% yield); UV-Vis ($CHCl_3$) λ_{max} 420 (100%), 517 (6.7%), 550 (3.4%), 591 (3.8%), 646 (2.4%) nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ -2.86 (2H, s, NH), 2.63-2.66 (2H, 2 overlapped d, H-2^3), 4.64 (1H, t, *J* = 7.6 Hz, H-2^4), 7.13-7.21 (5H, m, H-2^4-Ph), 7.28-7.34 (4H, m, H-2^4-Ph), 7.72-7.78 and 7.83-7.96 (13H, 2m, H-*m,p*-Ph, NH), 8.14-8.20 (8H, m, H-*o*-Ph), 5.58 (1H, d, J = 4.8 Hz, H-β), 8.78 (2H, brs, H-12,13), 8.82-8.85 (2H, m, H-β), 9.29 (1H, s, H-3); FABMS *m/z* for $C_{59}H_{42}ClN_5O$ ([M+H]$^+$) 872.

Oxidation of 3a with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

Compound **3a** (2.1 mg, 2.84×10^{-3} mmol) was dissolved in toluene (1 mL) and DDQ (2.3 mg) was added. The reaction mixture was stirred at room temperature for 3 days and then the solvent removed under vacuum. The obtained residue was taken up with dichloromethane, washed with an aqueous solution saturated with sodium carbonate and the organic layer dried over sodium sulfate. Purification by column chromatography, using dichloromethane as eluent, afforded pure compound **6** (1.2 mg, 52% yield); UV-Vis ($CHCl_3$) λ_{max} 423 (100%), 537 (9.3%) nm; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.41 (1H, d, *J* = 9.6 Hz, H-2^3), 6.88 (1H, d, *J* = 9.6 Hz, H-2^4), 7.64-7.99 (20H, m, H-*o,m,p*-Ph), 8.43 (1H, s, NH), 8.67-8.74 (6H, m, H-β); FABMS *m/z* for $C_{47}H_{29}N_5O$ ([M+H]$^+$) 738.

Acknowledgments

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