Synthesis of Substituted 2-Pyridyl-4-phenylquinolines

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Abstract: The acid-catalyzed condensation of o-aminobenzophenones with aromatic acetyl derivatives, in a basic methanol/tetrahydrofuran medium, has been used to prepare a series of substituted 2-pyridyl-4-phenylquinolines. Derivatives having two aza binding sites can act as asymmetric bidentate ligands to complex transition metals such as ruthenium, osmium or iridium. All the compounds were characterized by elemental analysis, Ei or FAB (+) MS, 1H- and 13C-NMR spectroscopies. Complete assignments of the 1H spectra were accomplished by using a combination of one- and two-dimensional NMR techniques.

Keywords: Quinoline derivatives, asymmetric bidentate aza-ligands, 2D-NMR.

Introduction

In the past few decades luminescent transition metal complexes based on polypyridine ligands, owing to their long-lived metal-to-ligand charge-transfer (MLCT) excited states, have already been used in various fields such as solar energy conversion [1], information storage [2], photocleavage of DNA [3], and oxygen sensors [4]. Although the photophysics and photochemistry of [Ru(bpy)3]2+ (bpy = 2,2’ bipiridine) have been the subject of extensive research [1–4], few other bidentate ligands, i.e. having two aza binding sites, have been prepared and the photophysical and/or photochemical
properties of their complexes with transition metals studied [5]. As a continuation of previous studies in this field [6], we now report the synthesis and characterization of the ligands shown in Scheme 1, with the aim of studying the photochemical properties of their complexes with transition metals such as ruthenium, osmium or iridium. Three of these asymmetric bidendate ligands (L2 – L4) are new. All the compounds were characterized by elemental analysis, EI or FAB mass, $^1$H and $^{13}$C NMR spectroscopies. Complete assignments of the $^1$H spectra of the various compounds were accomplished by using a combination of one- and two-dimensional NMR techniques.

**Scheme 1**

| Ligands | R$_1$ | R$_2$ | R$_3$ | Initials |
|---------|-------|-------|-------|----------|
| L$_1$   | H     | H     | H     | ph-pq    |
| L$_2$   | CH$_3$| H     | H     | mph-pq   |
| L$_3$   | CH$_3$| H     | CH$_3$| mph-mpq  |
| L$_4$   | H     | Br    | CH$_3$| brph-mpq |

**Results and discussion**

The literature describes numerous different ways to prepare substituted quinoline rings: i.e., by exploiting quinoline carboxamides [7], acid-catalyzed condensation of o-aminobenzophenones [8] with ketones [9], sequential vinylic substitution/annelation processes [10], reactions of N-arylnitrilium salts with acetylenes [11], cyclodehydration of o-vinyl anilides [12], intramolecular Wittig reactions [13], and cyclization of oximes [14]. Using o-isocyanostyrenes only symmetric biquinoline may be prepared [15]. Following the synthetic pathway previously used for the preparation of the unsubstituted ligand 4-phenyl-2-(2′-pyridyl)quinoline (L$_1$, ph-pq) [16], namely the acid-catalyzed condensation of o-amino-benzophenone with 2- acetylpyridine derivatives, as shown in Scheme 2, we have now synthetized the ligands 4-phenyl-7-methyl-2-(2′-pyridyl)quinoline (L$_2$, mph-pq) and 4-phenyl-7-methyl-2-[2′-(6′-methyl)pyridyl]-quinoline (L$_3$, mph-mpq).
The ligand 4-phenyl-6-bromo-2-[2’-(6’-methyl)-pyridyl]quinoline (L₄, brph-mpq) was obtained in a three synthetic steps (Scheme 3) starting from p-nitrobromobenzene.
2-Amino-5-bromobenzophenone (2) was obtained by condensation of $p$-nitro bromobenzene with phenylacetonitrile in a basic methanol/tetrahydrofuran medium to give 3-phenyl-5-bromo-2,1-benzisoxazole (1) (66%), which upon reductive cleavage (Fe/CH$_3$COOH) of the benzisoxazole ring was converted to the desired aminoketone 2 (70%). A subsequent Friedlander reaction [17] of the $o$-aminobenzophenone 2 with 2-acetyl-6-methylpyridine, using a mixture of m-cresol and phosphorous pentoxide gave ligand $L_4$ (71%). Table I reports the results of a complete $^1$H-NMR analysis of ligands $L_1$–$L_4$. Proton chemical shifts and $J$(H,H) values were measured at 500 MHz.

**Table I. $^1$H NMR parameters of ligands $L_1$ – $L_4$**

| Proton | $L_1$       | $L_2$       | $L_3$       | $L_4$       |
|--------|-------------|-------------|-------------|-------------|
| 3      | 8.53 s      | 8.47 s      | 8.48 s      | 8.57 s      |
| 5      | 7.96 d $J$=8.0 | 7.85 d $J$=9.0 | 7.22 d $J$=7.5 | 8.06 d $J$=2.0 |
| 6      | 7.56-7.50 m | 7.34 bd $J$=6.0 | 7.34 dd $J$=8.5, 1.5 | -          |
| 7      | 7.75 dt $J$=7.0, 1.5 | - | - | 7.79 dd $J$=7.0, 2.0 |
| 8      | 8.26 d $J$=8.5 | 8.05 bs     | 8.04 bs     | 7.23 d $J$=7.5 |
|     |     |     |     |     |
|-----|-----|-----|-----|-----|
| 3'  | 8.71 d | 8.69 d | 7.83 d | 8.45 d |
|     | J=7.5  | J=8.0  | J=8.5  | J=8.0  |
| 4'  | 7.90 dt | 7.88 dt | 7.77 t  | 7.77 t  |
|     | J=8.0, 2.0 | J=8.0, 1.5 | J=7.5  | J=8.0  |
| 5'  | 7.37 bt | 7.36 dt | 8.47 d  | 8.10 d  |
|     | J=6.5  | J=7.5, 1.5 | J=7.5  | J=8.0  |
| 6'  | 8.74 d | 8.73 dd | -       | -       |
|     | J=4.5  | J=4.5, 1.0 | -       | -       |
| Ph  | 7.62-7.50 m | 7.61-7.49 m | 7.61-7.50 m | 7.57-7.51 m |
| Py-CH₃ | - | - | 2.65 s | 2.64 s |
| q-CH₃ | - | 2.60 s | 2.59 s | - |

Notes: The spectra were obtained in deuterated chloroform (CDCl₃), chemical shifts in ppm, and coupling constants in Hz. Numbering pattern as shown in Schemes 2 and 3. Abbreviations used: bs = broad singlet, s = singlet, d = doublet, dd = double doublet, m = multiplet, t = triplet, dt = double triplet.

Assignments were aided by the use of 2D homonuclear chemical shift correlated ¹H-NMR (COSY) [18]. As an example, Figure 1 shows the COSY–45 experiment of L₁ and includes as the upper and left traces the related ¹H-NMR spectrum, both run in deuterated chloroform (CDCl₃). The 1H singlet at 8.53 ppm was easily assigned by the integration ratio to the quinoline proton H₃. A four-spin system is identified, through the COSY spectrum, as connecting the ¹H signals at 8.26, 7.96, 7.75, and 7.57-7.50 ppm. The doublet (ortho coupling) at 8.26 ppm and the double triplet at 7.75 ppm have been assigned to H₈ and H₇, respectively, by comparison with the literature ¹H data for L₁ in deuterated acetone [16].

The resonances for H₅ and H₆ could be assigned to the signals at 7.96 and 7.57-7.50 ppm, respectively. The ¹H double triplet at 7.90 ppm, diagnostic for a γ-pyridine [19], and involved in another four spin system connecting the ¹H signals at 8.74, 8.71, 7.90, and 7.37 ppm, was assigned to the pyridine proton H₄'. As a consequence of the meta and ortho couplings showed by H₄', the doublets at 8.74, 8.71, and the broad triplet at 7.37 ppm, that in turn are correlated themselves, were easily assigned at H₆', H₃', and H₅', respectively. It is worth noting that ortho, meta, and para cross-peaks are observable in the COSY-45 spectrum and can be distinguished from the number and/or the intensity of the spots.
Figure 1: 500 MHz $^1\text{H}/^1\text{H}$ COSY-45 spectrum of $L_1$ in deuterated chloroform. The upper and left traces are 1D proton spectrum of $L_1$.

The highest downfield shift experienced by the H$_{3'}$ protons, due to deshielding by the non-bonding electrons of the nitrogen on the pyridine ring, is indicative of an anti conformation for the ligands, in agreement with the conformation considered the most probable for bipyridine [5]. According to literature data [19], confirmed by our $^1\text{H}$-NMR analyses, these uncomplexed molecules show an anti conformation (as depicted in Schemes 1 - 3) that changes to a syn one
when they act as ligands by using the nitrogen of the pyridine and quinoline rings as binding sites. According to the inductive and/or mesomeric effects of the substituents, their introduction onto the skeleton of the N-N bidentate ligand L₁ influence the upfield and/or downfield chemical shift of the nearest protons, and the reactivity of these molecules as well. The structures of ligands L₁-L₄ was further confirmed by their ¹³C-NMR spectra (see Table II), which displayed the expected patterns.

**Table II.** ¹³C NMR parameters of ligands L₁ – L₄

| Carbon | L₁  | L₂  | L₃  | L₄  |
|--------|-----|-----|-----|-----|
| 2      | 156.40 | 156.54 | 155.97 | 156.35 |
| 3      | 119.24 | 118.48 | 118.62 | 118.85 |
| 4      | 149.23 | 149.02 | 148.88 | 148.24 |
| 5      | 125.82 | 125.47 | 125.45 | 128.55 |
| 6      | 128.30 | 129.03 | 128.90 | 120.80 |
| 7      | 129.39 | 139.62 | 139.55 | 132.79 |
| 8      | 130.21 | 129.20 | 129.16 | 131.87 |
| 9      | 148.51 | 148.74 | 148.70 | 147.08 |
| 10     | 126.78 | 124.78 | 124.76 | 123.80 |
| 2’     | 155.64 | 155.59 | 155.88 | 155.31 |
| 3’     | 121.87 | 121.78 | 118.82 | 120.11 |
| 4’     | 136.94 | 136.87 | 137.05 | 137.11 |
| 5’     | 124.03 | 123.92 | 123.48 | 123.79 |
| 6’     | 149.17 | 149.11 | 157.90 | 158.04 |
| 1”     | 138.40 | 138.55 | 138.74 | 137.88 |
| 2”/6”  | 128.44 | 128.41 | 128.43 | 128.69 |
| 3”5”   | 129.67 | 129.63 | 129.64 | 129.55 |
| 4”     | 126.78 | 128.21 | 128.17 | 127.93 |
| Py-CH₃ | -   | -   | 24.64 | 24.61 |
| q-CH₃  | -   | 21.66 | 21.67 | -   |

Notes: [a] The spectra were obtained in deuterated chloroform (CDCl₃), (chemical shifts in ppm); [b] Numbering patterns as shown in Schemes 2 and 3.

**Conclusions**

We report the synthesis of a series of bidentate aza chelating molecules, based on a substituted 2-pyridyl-4-phenylquinoline skeleton, that may be useful for the complexation of metal cations such as Ru, Os, and Ir. These complexes, owing to their asymmetry, may display new and interesting photophysical properties.
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Experimental

General

The starting materials 2-acetylpyridine, 2-aminobenzophenone, 2-amino-4-methylbenzophenone, p-nitrobromobenzene, and phenylacetoneitrile were purchased from Aldrich. All other chemicals were reagent grade. 6-Methyl-2-acetylpyridine [20] and the ligand 4-phenyl-2-(2’-pyridyl)pyridine (L₁) [16], were prepared as described in the literature. All reactions were performed under an inert atmosphere of nitrogen except when otherwise stated and the solvents were dried and stored under nitrogen and over 4Å molecular sieves. Melting points are uncorrected. Elemental analyses were determined by a commercial laboratory. ¹H- and ¹³C-NMR spectra were performed in deuterated chloroform (CDCl₃) with a Varian INOVA 500 instrument. Chemical shifts were calibrated relative to the solvent resonance considered at 7.26 ppm for residual CHCl₃ and at 77.0 ppm for CDCl₃. The analysis of the proton spectra was carried out according to the rules for the first-order splitting with the help of integral intensities. The ¹³C-NMR spectra were measured with full decoupling from the protons, and the signals were assigned with the help of SCS. The quaternary carbon atoms and CH groups were differentiated by means of the APT pulse sequence. Positive ion FAB mass spectra were obtained on a Kratos MS 50 S double-focusing mass spectrometer equipped with a standard FAB source, using 3-nitrobenzyl alcohol as a matrix. The yields, melting points and elemental analyses of the ligands synthetized are presented in Table III. The ¹H- and ¹³C-NMR spectra with signal assignments are given in Tables I and II, respectively.

3-phenyl-5-bromo-2,1-benzisoxazole (I): Phenylacetoneitrile (1.75 g, 15 mmol) was slowly added to a vigorously stirred solution of potassium hydroxide (17.76 g, 310 mmol) in methanol (35 mL) at room temperature. After dissolution was complete, 36 mL of a methanol/tetrahydrofuran (2 : 1 v/v) solution containing p-nitrobromobenzene (3.0 g, 15 mmol) was added dropwise at 0 °C. The resulting dark mixture was stirred at 0 °C for 3 hours, at room temperature for 4 hours, refuxed overnight, and then poured into ice-water (300 mL), filtered, washed successively with cold water and methanol and recrystallized from methanol to afford compound I as yellow crystals; 2.22 g (66%); m.p. 112 °C; ¹H-NMR (CDCl₃) δ: 8.05 (bs, 1H, benzisoxazole H₄); 7.99 (d, 2H, J = 7.0 Hz, phenyl H²/H⁶'); 7.58 (m, 3H, phenyl H⁴ and H³/H⁵'); 7.53 (dd, 1H, J = 10.0, 2.5 Hz, benzisoxazole H⁶'); 7.38 (dd, 1H, J = 10.0, 1.5 Hz, benzisoxazole H⁷); MS, m/z 274 (MH⁺). Anal. Calcd. for C₁₃H₈BrNO: C, 56.95; H, 2.92; N, 5.11. Found: C, 57.19; H, 3.03; N, 4.86.
**2 Amino-5-bromo-benzophenone (2):** Following the procedure of Simpson and Stephenson [21], a solution, containing 0.44 g (1.6 mmol) of 1 in acetic acid (70 mL), was heated on a water-bath, and 1.0 g (18 mmol) of iron powder was added over 2.5 hours, during which time, 12 ml of water was also added. The mixture was filtered while hot and then 100 ml of water was added. The yellow precipitate was collected by filtration, washed with cold water until the water washings were clear and dried. The product was purified by column chromatography (silica; cyclohexane / ethyl acetate 9:1) followed by recrystallization from ethanol-water to afford 2 as a yellow powder; 0.31 g (70 %); m.p. 105 °C; \(^1\)H-NMR (CDCl\(_3\)) \(\delta\): 7.63 (d, 2H, \(J = 8.5\) Hz, phenyl H\(^{2'/H6'}\)); 7.55 (m, 2H, benzene H\(^6\) and phenyl H\(^4\)); 7.49 (d, 2H, \(J = 8.5\) Hz, phenyl H\(^3'/H5'\)); 7.36 (dd, 1H, \(J = 9.0, 2.0\) Hz, benzene H\(^3\)); 6.65 (d, 1H, \(J = 8.5\) Hz, benzene H\(^3\)); 6.05 (bs, 2H, NH\(_2\)), MS, \(m/z\) 276 (MH\(^+\)). Anal. Calcd. for C\(_{13}\)H\(_{10}\)BrNO: C, 56.54; H, 3.62; N, 5.07. Found: C, 56.28; H, 3.59; N, 4.95

The synthesis of L\(_4\) is given below as a general procedure for the synthesis of ligands.

**4-phenyl-6-bromo-2-(2’-(6’-methyl)-pyridyl)quinoline (L\(_4\)):** A mixture of \(m\)-cresol (25 mL) and phosphorus pentoxide (0.81 g, 5.7 mmol) was stirred at 145 °C for 2.5 hours to afford a homogeneous solution. After cooling, 2-amino-5-bromobenzophenone (4.08 g, 15 mmol) and 2-acetyl-6-methyl-pyridine (2.03 g, 15 mmol) were added, followed by additional \(m\)-cresol (20 mL) to rinse the powder funnel. The reaction mixture was heated at 135 °C overnight. After cooling, the dark solution was poured into ethanol (200 mL) containing triethylamine (20mL). The resulting light grey precipitate was collected by filtration, continuously extracted with a solution of ethanol/triethylamine for 24 hours, and recrystallized from \(n\)-hexane/methylene chloride to give L\(_4\) as an off white powder; 3.96 g (71%); m.p. = 212 °C.; MS, \(m/z\) 375 (MH\(^+\)).

**Table III.** Melting points, yield and elemental analyses of ligands L\(_1\) – L\(_4\)

| Ligand | Recrystallization Solvent(s) | M.p: \(^\circ\)C | Yield (%) | Formula / M. w. | Elemental Analysis Calculated/Found (%) |
|--------|-----------------------------|------------------|-----------|----------------|----------------------------------------|
| L\(_1\) | EtOH                        | 152              | 70        | C\(_{20}\)H\(_{14}\)N\(_2\) 296.35 | C 85.05, H 5.00, N 9.90 |
| L\(_2\) | EtOH / CHCl\(_3\)           | 138              | 62        | C\(_{21}\)H\(_{16}\)N\(_2\) 296.35 | C 85.10, H 5.44, N 9.45 |
| L\(_3\) | EtOH / H\(_2\)O             | 194              | 60        | C\(_{22}\)H\(_{18}\)N\(_2\) 310.38 | C 85.02, H 5.63, N 9.32 |
| L\(_4\) | \(n\)-C\(_6\)H\(_{12}\) / CH\(_2\)Cl\(_2\) | 212              | 71        | C\(_{21}\)H\(_{15}\)BrN\(_2\) 375.26 | C 67.21, H 4.03, N 7.46 |
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Sample Availability: Available from the authors.

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