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Synthesis of mono-, bis- and tris-tridentate ligands based on 5′-substituted-2,2′-bipyridine-6-carboxylic acid

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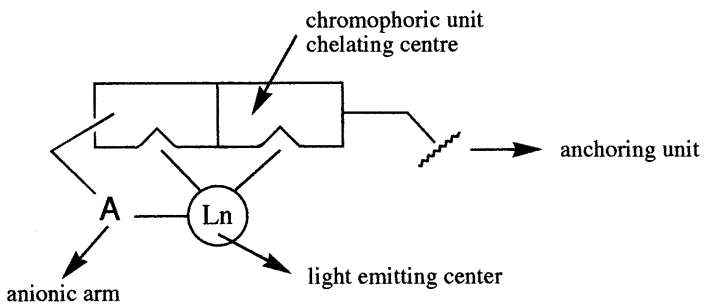
Abstract—The synthesis of 5′-methyl-2,2′-bipyridine-6-carboxylic acid is described starting from the pivotal 5′-methyl-6-bromo-2,2′-bipyridine building block. Functionalisation of the latest at the 5′-methyl position gives access to the 5′-bromomethyl, 5′-hydroxymethyl and 5′-aminomethyl derivatives. Upon nucleophilic substitution, the hydroxy and amino derivatives react with the 5′-bromomethyl compound to give quasi-linear and podand type intermediates. Thanks to a carboalkoxylation reaction at the 6-bromo position of the different intermediates, followed by a saponification reaction, mono-, bis- and tris-tridentate ligands are obtained, which are particularly well suited for the complexation of lanthanide(III) cations.

The recent advances in the development of time-resolved fluoroimmunoassays[1] and the remarkable photophysical properties of some lanthanide complexes such as their long lived excited states have attracted much attention of the scientific community. It appears that the utilisation of these complexes for potential biomedical applications have to fulfil inescapable criteria[2] such as water solubility and high thermodynamic stability in biological media, avoiding the possible release of the toxic free lanthanide cations. Concerning the so-called antenna effect,[3] high molar absorptivities, efficient ligand to metal energy transfer and long lived excited states with effective shielding of the lanthanide cations from the solvent are required. Furthermore, assuming that a coordination number of nine is commonly encountered for lanthanide complexes, the coordination of three tridentate ligands (Eq. (1)) should allow the complete filling of the first coordination sphere around the metal and avoid water coordination.

Following our synthetic efforts to obtain lanthanide complexes fulfilling as much as possible these requirements,[4] we focused our attention toward the design of 2,2′-bipyridine-6-carboxylic acid **1**, substituted at the 5′ position by a methyl group. Further derivatisation of **1** provides the skill for the construction of the bis- or tris-tridentate ligands **2** and **3** (Eq. (2)).



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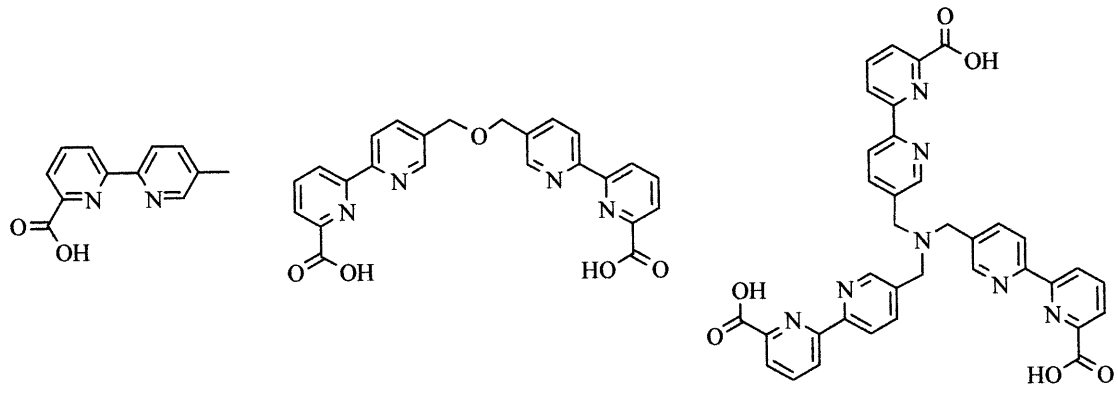


(2)

1 2 3

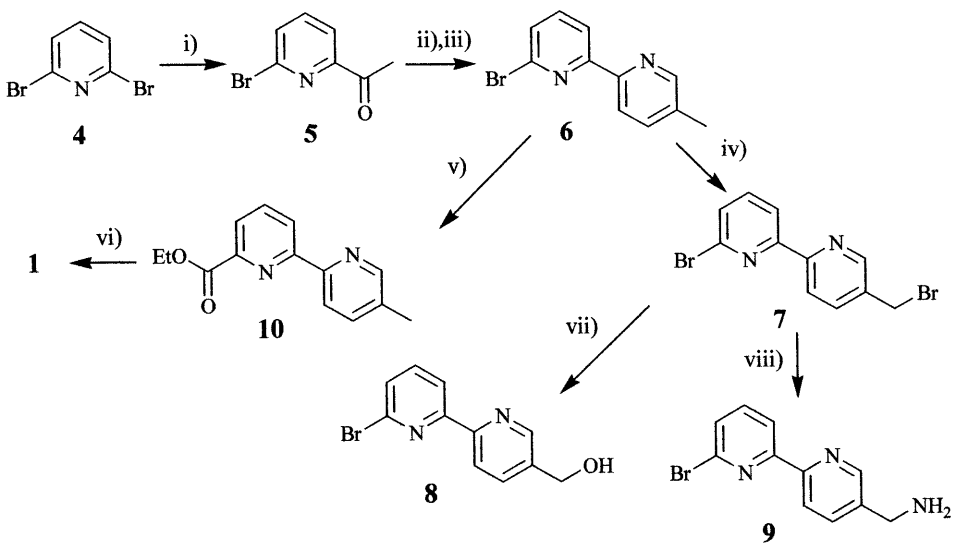
In their anionic forms, these ligands are expected to be extremely well suited for the coordination to lanthanide cations, with a chromophoric unit able to transfer energy absorbed by the ligand to a potentially light emitting metal such as europium or terbium.[4]

The synthesis of all compounds described herein are centred around a new synthetic protocol for obtaining the pivotal building block 6-bromo-5′-methyl-2,2′-bipyridine, **6**.[5] This compound can be further activated either at the 6- or 5′-positions independently. Derivative **6** is obtained in two steps from the commercially available 2,6-dibromopyridine **4** which is first transformed to 2-bromo-6-acetylpyridine **5** according to literature procedure.[6] Reaction of **5** with iodine in refluxing pyridine afforded the acetylpyridinium iodide salt in nearly quantitative yield (95%). The pyridinium salt reacted with methacrolein in hot formamide according to the methodology developed by Kröhnke[7] to give **6** in a reasonable 68% yield (Scheme 1).

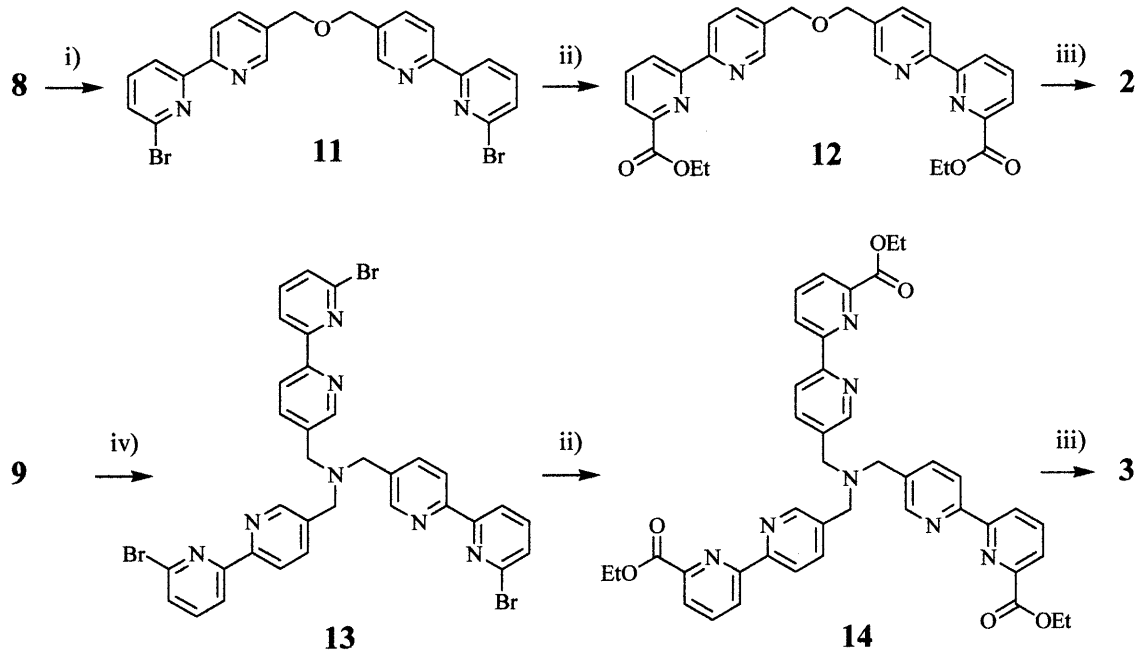
Activation of the 5′-position of the bipyridine derivative **6** was achieved by a radicalar bromination using NBS in hot CCl_4 in the presence of AIBN as photoiniator. The mono-brominated compound **7** was isolated in reasonable yields either by column chromatography (55%) or careful successive recrystallisations in hot CCl_4 (35%). Reaction of **7** with excess NaOAc in hot DMF followed by subsequent saponification of the ester gave the 5′-hydroxymethyl compound **8**, while a Delépine reaction between **7** and hexamethylenetetramine followed by acid hydrolysis of the ammonium salt afforded the corresponding amino derivative **9** in fair yield. The set of reactions are sketched in Scheme 1.

Carboethoxylation of **6** in the presence of catalytic amounts of $[Pd(PPh_3)_2Cl_2]$ in an $EtOH/Et_3N$ mixture under a CO atmosphere is straightforward and afforded the ester **10**, which, upon hydrolysis with concentrated HCl in a H_2O/EtOH solution, gave the tridentate ligand **1**.[8]

Activation of the 5′-position of the bipyridine unit is particularly interesting, as it should bring about a large variety of reactions with nucleophilic and electrophilic compounds, allowing the easy grafting of these



Scheme 1. (i) ^{n}BuLi, Et_2O, $(CH_3)_2NCOCH_3$; (ii) I_2, pyridine, 95%; (iii) $CH_2{=}CH(CH_3)C(O)H$, formamide, 68%; (iv) NBS, CCl_4, AIBN, 55%; (v) $[Pd(PPh_3)_2Cl_2]$ (0.05 equiv.), EtOH, Et_3N, CO, 98%; (vi) HCl, EtOH, H_2O, 90%; (vii) (a) NaOAc, DMF; (b) NaOH, H_2O, MeOH; (c) HCl (78% for the three steps); (viii) (a) hexamethylenetetramine, CH_2Cl_2; (b) HCl, EtOH (78% for the two steps).



Scheme 2. (i) (a) NaH, THF, rt, 1 h; (b) **7** (1.3 equiv.), 80°C, 12 h (84%); (ii) $[Pd(PPh_3)_2Cl_2]$ (0.05 equiv. per Br atom), EtOH, Et_3N, CO (1 atm), 80°C, 12 h (39% for **11** and 33% for **13**); (iii) (a) NaOH, MeOH, H_2O, 100°C, 2 h; (b) HCl dil. (89% for **2** and 51% for **3**); (iv) **7** (2.2 equiv.), Na_2CO_3, CH_3CN, 80°C, 48 h (87%).

bipyridine fragments on pre-organised platforms. Specifically, as examples of such reactions, compounds **8** and **9** can be used in nucleophilic substitution reactions with **7** to generate the ether bridged compound **11** and the podand **13** (Scheme 2). Furthermore, applying the previously described carboalkoxylation process to these brominated bipyridines allowed the synthesis of their ethyl ester derivatives **12** and **14** which, upon basic treatment and subsequent neutralisation, afforded the quasi-linear bis-bidentate and podand type tris-tridentate ligands **2**[9] and **3**,[10] respectively. Interestingly, in the case of the tertiary amine **14**, the ester functions are easily hydrolysed to their corresponding acid, explaining the relative low yield obtained for the preparation of **14**. Applying the saponification process directly on a crude sample of **14** obtained by evaporation of the solvents after the carboalkoxylation reaction allow us to isolate the tripod **3** in a far better yield (90%).

In summary, the development of asymmetrically disubstituted bipyridines such as **7**, **8** and **9** opens the way to a potentially large family of tridentate ligands, among which **2** and **3** are archetypal members. Our interest is currently directed toward the chemical and photophysical behaviours of their lanthanide complexes, as well as to the anchoring of the 2,2′-bipyridine-6-carboxylic acid fragment on extended pre-organised architectures. It is acknowledged that anionic derivatives (e.g. diethylenetriaminetetraacetic)[11] strongly stabilise trivalent lanthanides salts and also that α,α′-bipyridine units effectively act as molecular transformers.[12] The ligands described here combined both skills within the same frame.

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8. 5′-Methyl-2,2′-bipyridine-6-carboxylic acid (**1**): mp = 250–251°C. ^{1}H NMR (DMSO-d_6): δ 2.65 (s, 3H), 8.16–8.30 (m, 2H), 8.49 (dd, 1H, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 8.56–8.77 (m, 3H). ^{13}C NMR (DMSO-d_6): δ 18.9, 125.4, 126.8, 128.9, 141.4, 142.2, 143.2, 145.8, 147.8, 149.0, 149.7, 167.8. IR (KBr pellets, cm^{-1}): 1744 (ν_{CO}), 1551, 1465 ($\nu_{C=C}$, $\nu_{C=N}$). Anal. calcd for $C_{12}H_{10}N_2O_2 \cdot 0.1H_2O$: C, 66.72; H, 4.76; N, 12.97. Found: C, 66.82; H, 4.95; N, 12.63.
9. Bis-[(6-carboxy-2,2′-bipyridine-5-yl)methyl]ether (**2**): mp = 217–218°C. ^{1}H NMR (DMSO-d_6): δ 4.75 (s, 4H), 8.08 (dd, 2H, ^3J = 8.5 Hz, ^4J = 2.0 Hz), 8.15 (t, 2H, ^3J = 7.5 Hz), 8.58 (d, 2H, ^3J = 8.0 Hz), 8.60 (d, 2H, ^3J = 7.0 Hz), 8.61 (d, 2H, ^3J = 7.0 Hz), 8.75 (s, br, 2H). ^{13}C NMR (DMSO-d_6): δ 69.0, 121.3, 123.8, 125.1, 135.0, 137.9, 139.0, 147.6, 148.0, 152.8, 153.8, 165.8. Anal. calcd

for $C_{24}H_{18}N_4O_5 \cdot H_2O$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.48; H, 4.42; N, 11.88.

10. Tris-[(6-carboxy-2,2′-bipyridine-5-yl)methyl]amine (**3**): decomp. at $T>220$°C. ^{1}H NMR (DMSO-d_6): δ 4.14 (s, 6H), 8.03 (s, 3H), 8.05 (s, 3H), 8.14 (d, 3H, $^3J=8.5$ Hz), 8.37 (d, 3H, $^3J=7.0$ Hz), 8.40 (d, 3H, $^3J=8.5$ Hz), 8.65 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 54.6, 121.0, 123.8, 125.1, 135.5, 138.9, 140.4, 147.9 (2C), 150.7, 153.9, 165.7. IR (KBr pellets, cm^{-1}): 3411 (ν_{OH}), 1729 (ν_{CO}), 1640, 1619 ($\nu_{C=C}$, $\nu_{C=N}$). Anal. calcd for $C_{36}H_{27}N_7O_6 \cdot 0.5H_2O$: C, 65.25; H, 4.26; N, 14.80. Found: C, 65.61; H, 4.38; N, 14.64.
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