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A convenient synthesis of 6,6′-dimethyl-2,2′-bipyridine-4-ester and its application to the preparation of bifunctional lanthanide chelators

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Abstract—We describe a convenient scalable synthesis of 4-carbomethoxy-6,6′-dimethyl-2,2′-bipyridine based on the application of modified Negishi cross-coupling conditions. The use of this building block in the preparation of a number of dissymmetrically 6,6′-trisubstituted-2,2′-bipyridines and of bifunctional lanthanide chelators is also reported.

In coordination and metallosupramolecular chemistry, much attention is given to 2,2′-bipyridine (bpy) moiety because of its high binding affinity for a variety of metal ions and photophysical, photochemical, and electron transfer properties of bpy-metal complexes.[1] In particular, bpy chromophore is an efficient photosensitizer antenna to enhance the luminescence of Eu(III) and Tb(III) ions.[2] Such a photophysical property is promising for bioanalytical applications in fields such as fluoroimmunoassays, time-resolved fluorescence imaging or luminescent sensors.[3] Although a survey of the literature highlights the outstanding luminescence properties of lanthanide tags based on bpy chromophore,[2,4] only a few of these labels have been developed up to now.[5] This is due, amongst other reasons (such as kinetic stability of the Ln(III) complexes in biological media), to the lack of a reactive group in these systems for covalent attachment to proteins and biological analogues. So, there remains a need for bifunctional chelators[6] based on 2,2′-bipyridine.

In the course of our research on the design of lanthanide-containing chelating systems with potential applications as both luminescent labels and MRI contrast agents[7] and in order to develop biological labeling, we were interested in a convenient synthesis of 4-carbomethoxy-6,6′-dimethyl-2,2′-bipyridine (Compound **1**, Scheme 1). In this compound, derivatization at the 6,6′-positions is an attractive feature to introduce bpy unit in open-chain (**2**), macrocyclic (**3**), and macrobicyclic (**4**) structures, thus yielding photoactive ligands capable of forming stable lanthanide complexes. The aromatic ester functionality could be successfully converted to an amido–amino compound, which could be further coupled for vectorization to various biomolecules using heterobifunctional cross-linking reagents.[5a,8] Moreover, the photophysical properties of this chromophoric unit ($\lambda(\text{abs}) = 294$ nm, $\varepsilon = 10{,}900\ \text{M}^{-1}\,\text{cm}^{-1}$, $^3E_{00} = 22{,}400\ \text{cm}^{-1}$ in methanol solution)[9] are favorable for an efficient antenna effect for both Eu and Tb luminescence. In this Letter, we describe a convenient synthetic route for the preparation of **1** and its conversion into the corresponding bis(bromomethyl) and bis(hydroxymethyl) derivatives. In addition, we report the synthesis of three new multidentate ligands, monofunctionalized on the bpy moiety (**2**–**4**, Scheme 1).

The synthesis of the pivotal building block **1** was to be approached via a metal-catalyzed coupling of the two pyridine fragments **6** and **7** (Scheme 2). The trifunctionalized pyridine **7**, bearing an ester group, was obtained in one step from commercially available, but expensive, 2-chloro-6-methyl-isonicotinic acid **5** or in three steps starting from diethyl oxalate, acetone, and cyanoacetamide by improvement of literature procedures (51% yield from diethyl oxalate).[10]

Keywords: Bipyridine; Bifunctional chelators; Lanthanides.
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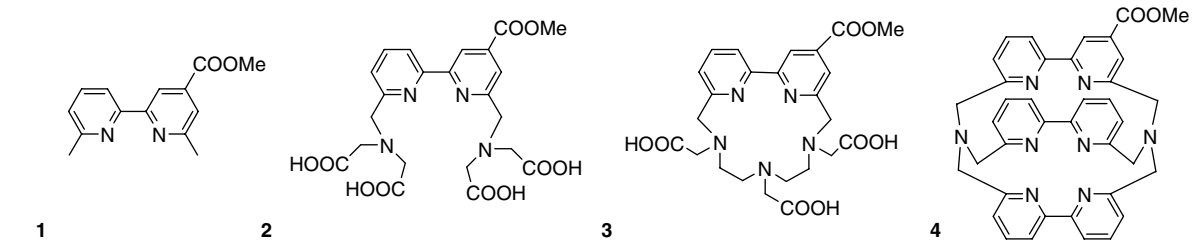
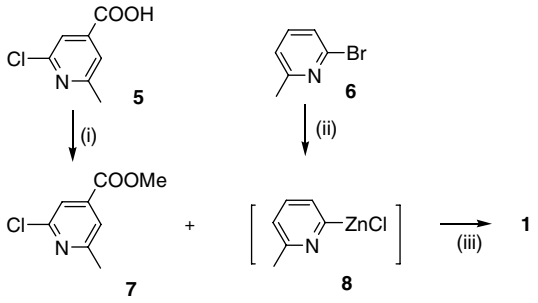


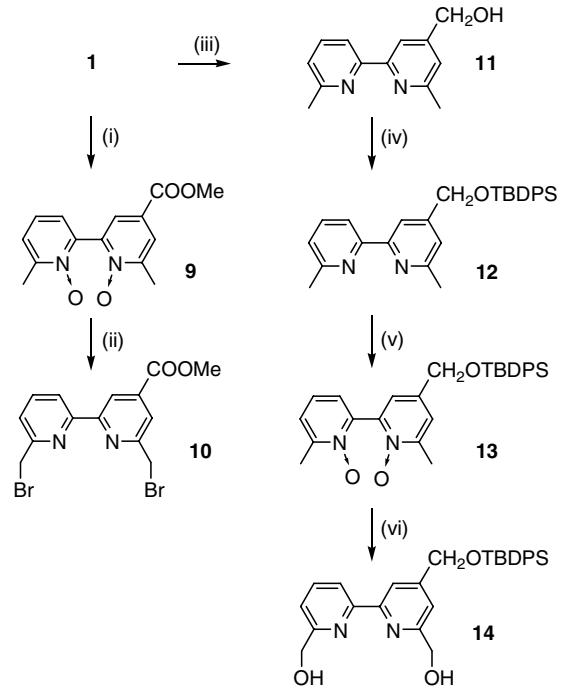
Scheme 1.



Scheme 2. Reagents and conditions: (i) MeOH, HCl, reflux, 6 h (92%); (ii) *n*-BuLi, THF, $ZnCl_2$, −78 °C to rt; (iii) $PdCl_2$–$(PPh_3)_2$, DIBAH, THF, reflux, 1.5 h (84%).

After attempting several methodologies using metal-catalyzed coupling,[11] it was found that a modified Negishi cross-coupling reaction was the most effective for the preparation of bipyridine derivative **1**. The pyridylzinc chloride compound **8** was satisfactorily prepared from 2-bromo-6-methyl-pyridine (**6**) by halogen–metal exchange with *n*-butyllithium, followed by transmetallation with $ZnCl_2$. Cross-coupling reaction of **7** with **8** in the presence of 5 mol % of a catalyst[12] prepared from $PdCl_2$–$(PPh_3)_2$ and DIBAH (2 equiv) in refluxing THF afforded compound **1** in 84% isolated yield.[13] This reaction was adapted to a 10 g scale, with no significant loss of yield or efficiency. The target compound **1** was previously described by a Stille-type cross-coupling reaction on 2-hydroxy-4-carbomethoxy-6-methyl pyridine derivatives.[14] The new synthetic path proposed here is more convenient: it is more reliable and shorter, presents no purification or toxicity problems (since organotin compounds are not used) and does not require triflate as a coupling component to provide satisfying yield.[14] In compound **1**, both the ester function and the methyl groups at the 6,6′-positions are available for different functionalization reactions which are depicted in Scheme 3.

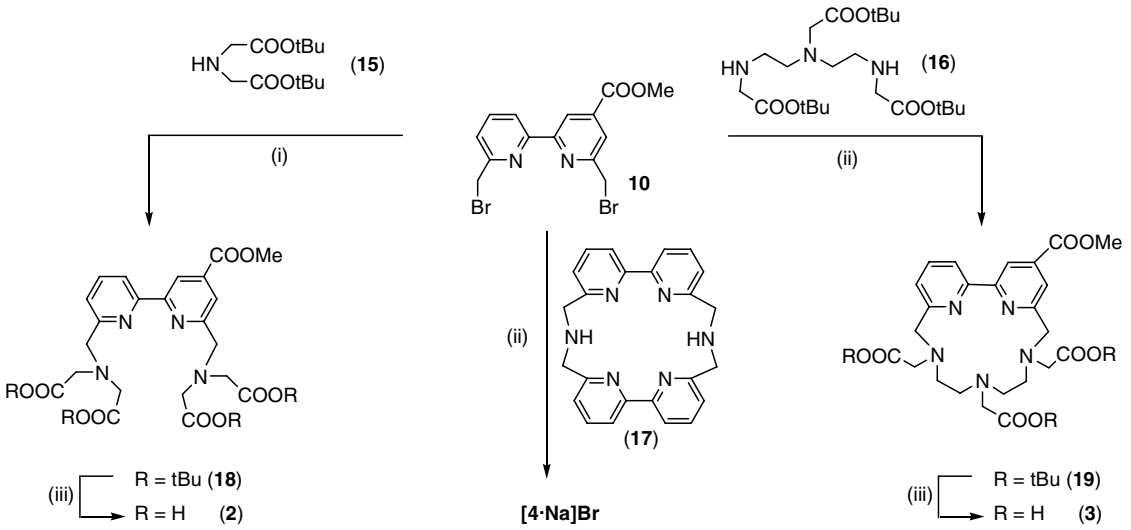
The introduction of bromomethyl functionality at the 6,6′-positions was achieved by employing an N,N′-oxidation process, including a Boeckelheide rearrangement followed by a pseudohalogen exchange.[15] Thus, 1,1′-dioxide **9** derivative was treated with acetic anhydride and the resulting rearranged diacetate was displaced with HBr in glacial acetic acid to yield dibromide **10** in 59% yield from **1**. In our hands, this two step procedure provided substantially better yields than the direct dimethyl functionalization of **1** by classical free-radical halogenation with *N*-bromosuccinimide (NBS).



Scheme 3. Reagents and conditions: (i) *m*-CPBA, CH_2Cl_2, rt, 19 h (95%); (ii) (a) Ac_2O, 120 °C, 16 h; (b) HBr, AcOH, 70 °C, 7 h (62%); (iii) $NaBH_4$, MeOH (82%); (iv) TBDPSCl, imidazole, DMF, rt, 48 h (94%); (v) *m*-CPBA, $CHCl_3$, rt, 24 h (78%); (vi) (a) Ac_2O, 100 °C, 18 h; (b) K_2CO_3, MeOH–H_2O, rt, 2 h (63%).

4-Hydroxymethyl-6,6′-dimethyl-2,2′-bipyridine **11** can be obtained in high yield by reduction of ester **1** with excess of $NaBH_4$ in methanol. Moreover, the monoprotected triol **14** was obtained in three steps starting from alcohol **11**. First, the protective group was introduced by treatment with *tert*-butyldiphenylsilyl chloride in the presence of imidazole. Following the methodology developed for the **1** → **10** conversion, compound **12** was oxidized with *m*-CPBA, to yield the corresponding dioxide **13** in 78% yield. Treatment of **12** with acetic anhydride and subsequent hydrolysis of the rearranged diacetate with K_2CO_3 in a MeOH–H_2O mixture afforded the building block **14** in 63% yield.

In a second part of this work, we used the reactivity of bromomethyl groups in **10** with respect to nucleophilic substitution reactions by secondary amines. The reaction of dibromide **10** with di-*tert*-butyliminodiacetate **15**, open-chain triamine **16**,[16] and macrocyclic diamine **17**,[17] in the presence of Na_2CO_3 as a base, gave the corresponding ligands **18**, **19**, and **4**, respectively (Scheme



Scheme 4. Reagents and conditions: (i) **15** (2 equiv), Na_2CO_3 (10 equiv), CH_3CN, reflux, 17 h, [reactant **10**] = 12.5×10^{-3} M, 91%; (ii) **16** or **17** (1 equiv), Na_2CO_3 (10 equiv), CH_3CN, reflux, 16 or 48 h, [reactants] = 2×10^{-3} M, 51% (**19**), 47% ([**4·Na**]**Br**); (iii) CF_3COOH, CH_2Cl_2, rt, 24 h, 87% (**2**), 97% (**3**).

4). Following precedents of the Lehn research group,[18] the 18-membered macrobicycle **4** was isolated as sodium cryptate in 47% yield after chromatography.[19] A template effect of the sodium cation was also observed for the formation of the 15-membered macrocycle **19**. In this case, an aqueous workup in the presence of ethylenediaminetetraacetic acid (EDTA) to remove Na^+ and purification by chromatography afforded the free ligand in 51% yield. Finally, the selective deprotection of the *tert*-butyl ester groups of derivatives **18** and **19** with trifluoroacetic acid at room temperature gave, respectively, triacids **2** and **3** in high yields.[19]

Mononuclear Ln^{3+} complexes (Eu, Tb, Gd) of these ligands were easily obtained (Scheme 5) by treating a solution of free ligands **2**, **3** or sodium cryptate **4** with $LnCl_3$ salts in aqueous solution at room temperature (**2** and **3**) or in methanol solution at reflux ([**4·Na**]**Br**). The examination of the luminescence lifetimes of europium complexes in water and deuterated water suggests the presence of one (**2·Ln**, **3·Ln**), and two (**4·Ln**) coordinated water molecules in the first coordination sphere of the lanthanide.[20] Preliminary physicochemical results showed that these complexes exhibit very interesting luminescence or relaxometric properties in aqueous solutions. The measured excited-state lifetimes are, respectively, of 0.58 and 1.05 ms for **2·Eu** and **3·Tb**, and upon excitation in the bpy chromophore the emission quantum yields are 6% and 10%, respectively. Compound **4·Gd** exhibits a high proton relaxivity ($r_1 = 13.55\ s^{-1}\ mM^{-1}$ at 20 MHz and 37 °C) in accordance with the presence of two inner sphere water molecules in this cryptate.

In conclusion, we have described a practical and efficient approach for the preparation of 4-carbomethoxy-6,6′-dimethyl-2,2′-bipyridine, **1**. We have further shown that **1** is a versatile precursor to the corresponding bromomethyl and hydroxymethyl derivatives, which are common moieties for further reactions. As first applications, a set of three bpy-based ligands bearing an ester function for further grafting on biological material were prepared. Further studies on their corresponding lanthanide complexes are currently in progress.

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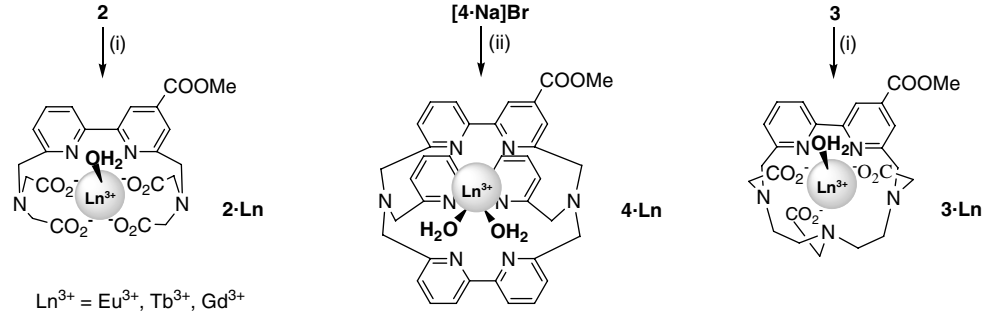

Scheme 5. Reagents and conditions: (i) $LnCl_3 \cdot 6H_2O$ (1.1 equiv), H_2O, rt, diluted NaOH; (ii) $LnCl_3 \cdot 6H_2O$ (1.1 equiv), MeOH, reflux.

Vander Elst, and Dr. S. Laurent (NMR and Molecular Imaging Laboratory, University of Mons-Hainaut, Belgium) for the determination of NMR relaxation measurements.

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13. A solution of *n*-BuLi (1.5 M in hexane, 1.1 equiv) was slowly added to a stirred solution of 1.02 g (5.93 mmol, 1 equiv) of bromopicoline **6** in 10 mL of anhydrous THF at −78 °C, and the resulting mixture was stirred for 15 min at this temperature. Then, a 0.44 M solution of anhydrous $ZnCl_2$ (1.1 equiv) in THF was added, and the stirring was continued for 30 min at room temperature. In a separate flask, a solution of 715 mg (3.85 mmol) of **7** in 5 mL of anhydrous THF was added to a solution containing 5 mol % of a catalyst prepared by reaction of a 0.014 M solution of Cl_2Pd–$(PPh_3)_2$ with 2 equiv of diisobutylaluminium hydride (1.0 M in hexane) and the mixture was stirred at room temperature for 10 min. The pyridylzinc chloride solution prepared above was then added dropwise, and the resulting mixture was heated at reflux for 1.5 h, cooled, and poured into saturated aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O and the organic extracts were concentrated to give a solid residue which was purified by flash chromatography over alumina (petroleum ether/ether 90:10), to yield 827 mg (84%) of compound **1** as a white solid. Mp: 122–123 °C (lit.[14] 116–117 °C). IR (KBr pellet): ν 1733 (C=O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.64 (s, 3H), 2.69 (s, 3H), 3.97 (s, 3H), 7.18 (d, 1H, $J = 7.8$ Hz), 7.69 (t, 1H, $J = 7.8$ Hz), 7.71 (s, 1H), 8.19 (d, 1H, $J = 7.8$ Hz), 8.71 (s, 1H). MS (DCI/NH_3): $m/z = 243$ [MH^+, 100%].
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19. *Selected data for compounds* **2**, **3**, *and* [**4**·**Na**]**Br**. Compound **2**: pale grey solid. Mp ≈180 °C (dec.). IR (KBr pellet): ν 1728, 1685 (C=O). ^{1}H NMR (CD_3OD, 300 MHz): δ 3.58 (s br, 8H), 4.06 (s, 3H), 4.20 (s br, 2H), 4.26 (s br, 2H), 7.61 (d, $J = 7.2$ Hz, 1H), 8.08 (s, 1H), 8.15 (t, $J = 7.2$ Hz, 1H), 8.41 (d, $J = 7.2$ Hz, 1H), 8.74 (s, 1H). HRMS-FAB$^+$ calcd for $[M+H]^+$ ($C_{22}H_{25}N_4O_{10}$) 505.15707, found 505.15742. Compound **3**: pale grey solid. Mp > 280 °C (dec.). IR (KBr pellet): ν 1728, 1685 (C=O). ^{1}H NMR (CD_3OD, 300 MHz): δ 2.55 (br m, 2H), 2.87 (br m, 4H), 3.10 (m, 2H), 3.39 (m, 2H), 3.60 (m, 2H), 3.90 (m, 2H), 4.07 (s+m, 5H), 4.30 (m, 2H), 7.64 (d, $J = 8.1$ Hz, 1H), 8.09 (s, 1H), 8.20 (t, $J = 7.5$ Hz, 1H), 8.47 (d, $J = 8.1$ Hz, 1H), 8.79 (s, 1H). HRMS-FAB$^+$ calcd for $[M+H]^+$ ($C_{24}H_{30}N_5O_8$) 516.20944, found 516.20965. Compound [**4**·**Na**]**Br** complex: yellow solid. Mp ≈280 °C (dec.). IR (KBr pellet): ν 1728 (C=O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.81 (br s, 10H); 3.91 (br s, 2H); 3.95 (s, 3H); 7.28 (m, 4H); 7.77–7.94 (m, 12H); 8.35 (s, 1H). HRMS-FAB$^+$ calcd for $[M+Na]^+$ ($C_{38}H_{32}N_8O_2Na$) 655.25459, found 655.25382. Anal. Calcd for $C_{38}H_{32}N_8O_2NaBr{\cdot}2H_2O$: C, 59.15; H, 4.70; N, 14.52. Found: C, 58.82; H, 4.89; N, 14.28.
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