Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 1793–1796

Catalytic etherification of N-protected tris(hydroxymethyl)aminomethane for the synthesis of ligands with C_3 symmetry

Nicolas Weibel, Loïc Charbonnière* and Raymond Ziessel*

Laboratoire de Chimie Moléculaire, associé 7509 au CNRS, ECPM-ULP, 25 rue Becquerel, 67087 Strasbourg Cedex, France

Received 28 November 2005; revised 21 December 2005; accepted 9 January 2006
Available online 26 January 2006

Abstract—The synthesis of two nonadentate ligands based on a *N*,*N*-dibenzylated-tris(hydroxy)methylaminomethane framework is described. The key step consists in tris-etherification of the precursor with elaborated pyridine and bipyridine derivatives and this was greatly improved by the introduction of catalytic amounts of tetrabutylammoniumiodide to the reaction mixture in DMF at room temperature. Analysis of the alkylation rates and an X-ray crystal structure of a bis-alkylated intermediate strongly support the presence of a tight intramolecular hydrogen bond, preventing a fast third alkylation step. The two acidic ligands were successfully prepared by combining a sequence of carboalkoxylation and hydrolysis of the corresponding esters. Both ligands react with europium and terbium chloride salts to generate water luminescent mononuclear complexes.

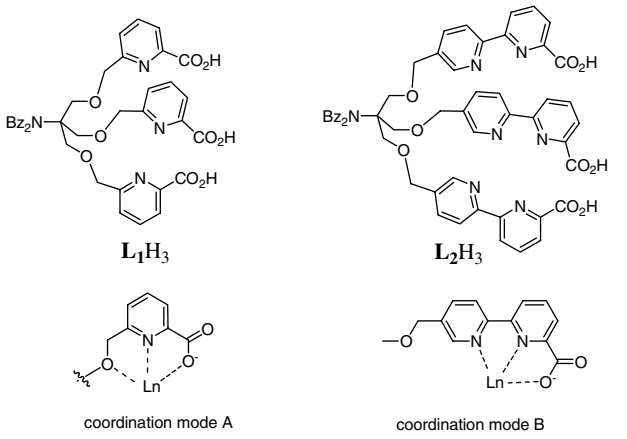
Gathering coordinating entities on a C_3 symmetrical podand type of structure is an elegant way to achieve increased stability for metal coordination. Providing that the link which connects the coordinating moieties to the central node is neither too short, avoiding steric congestion, nor too long, generating entropic disorder,[1] the improved thermodynamic control can result in superior efficiency regarding photo-chemical stability and photophysical properties.[2] In the case of lanthanide coordination chemistry, for which coordination numbers of nine are targeted for optimum photo-physical properties, tris-tridentate podand type structures can saturate the first coordination sphere of the lanthanide. Owing to their exceptional luminescence properties, such complexes are used as luminescent labels,[3] and thereby require the introduction of an activated group for labeling biological materials. The use of tris(hydroxymethyl)aminomethane (TRIS) is particularly attractive as this starting material provides both a C_3 symmetrical frame of alkoxy groups and an amino residue that should give access to orthogonal chemistry,[4] and potentially to the introduction of a labelling group.

Relatively few examples dealing with the use of TRIS as a starting material for C_3 symmetric ligands have been reported, and most of them rely on the nucleophilic attack of the hydroxy groups on sp^2 carbon atoms such as acyl chlorides[5] or α,β-unsaturated carbonyl compounds in 1,4 additions.[6] Williamson etherification reaction are more rare and require the use of severe experimental conditions and afford modest yields of trisalkylation.[7] In an effort to introduce elaborated tridentate coordination sites containing chromophoric units, we have investigated activation by alkylation of TRIS under various experimental conditions and with catalytic mediators. Results concerning the synthesis of two new C_3 symmetric ligands, $\mathbf{L}_1\mathbf{H}_3$ and $\mathbf{L}_2\mathbf{H}_3$, are described (Chart 1). After deprotonation, both ligands have tris-tridentate anionic arms able to compensate for the +III charge of the lanthanide cations. During the coordination, the formation of two five-membered chelate rings per arm appears to be a favorable option. $\mathbf{L}_1\mathbf{H}_3$ is designed so that the ether linkages are expected to take part in the coordination (mode A), whereas in $\mathbf{L}_2\mathbf{H}_3$ these groups are only envisaged as spacers in the C_3 framework (mode B).

Ligand $\mathbf{L}_1\mathbf{H}_3$ is based on tridentate units made of 2-alkoxymethylene-6-carboxy-pyridine. The synthetic protocol to obtain $\mathbf{L}_1\mathbf{H}_3$ is described in Scheme 1. Starting from commercially available 2-amino-6-methyl-pyridine

* Corresponding authors. Tel.: +33 3 90 24 26 89; fax: +33 3 90 24 26 35; e-mail: ziessel@chimie.u-strasbg.fr

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.01.026

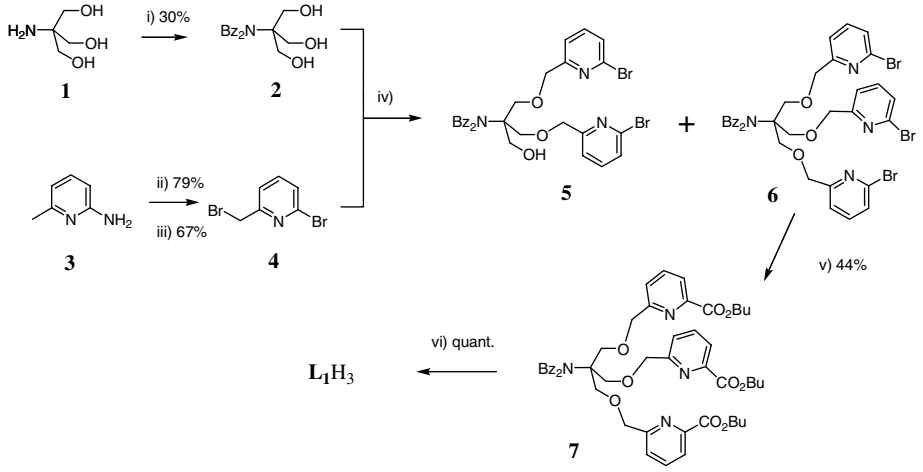


3, a Sandmeyer reaction[8] gave the intermediate 2-bromo-6-methyl-pyridine which is transformed into **4** by a radical bromination.[9] The N-protected TRIS derivative envisaged was the *N*,*N*-dibenzyl compound **2**, obtained by an adaptation of a literature procedure.[10] These protecting groups support acidic and basic conditions, and can in principle be deprotected by hydrogenolysis.

As described in Table 1, alkylation of **2** according to conventional procedures using NaH in dry THF at 65 °C led to a poor yield (41%) of the tris-alkylated product, **6**, and a substantial amount of the bis-alkylated intermediate **5** (22%). Changing the solvent to DMF in the presence of a catalytic amount of tetrabutylammonium iodide (TBAI) substantially improved the yield of the reaction, similar to what was observed for the TBAI assisted synthesis of phosphonates.[11] Under these conditions, the starting alkylating agent was consumed in one hour without the need to heat the solution. In the next step, the bromine groups in **6** were converted into butyl esters by a carboalkoxylation procedure catalyzed by low valent palladium.[12]

Compound **7** was isolated in 44% yield. In contrast to the case of the carboethoxylation of bromo-bipyridine derivatives,[12,13] the reaction with bromo-pyridines required higher reaction temperatures, provided by changing the nature of the alcohol (*n*-butanol instead of ethanol). Finally, ligand L_1H_3 was obtained quantitatively as its tetrahydrochloride salt after acidic hydrolysis of the ester groups.[14] A similar procedure was applied for the synthesis of ligand L_2H_3 (Scheme 2). Here again, the use of catalytic amounts of TBAI in DMF at room temperature proved to be very effective in improving the yield of the tris-etherification of **2** (Table 1). Insight into an understanding of the difficulties to achieve the third alkylation was gained by X-ray diffraction. Single crystals of compound **9** were obtained by slow diffusion of Et_2O into a CH_2Cl_2 solution of the compound (Fig. 1).

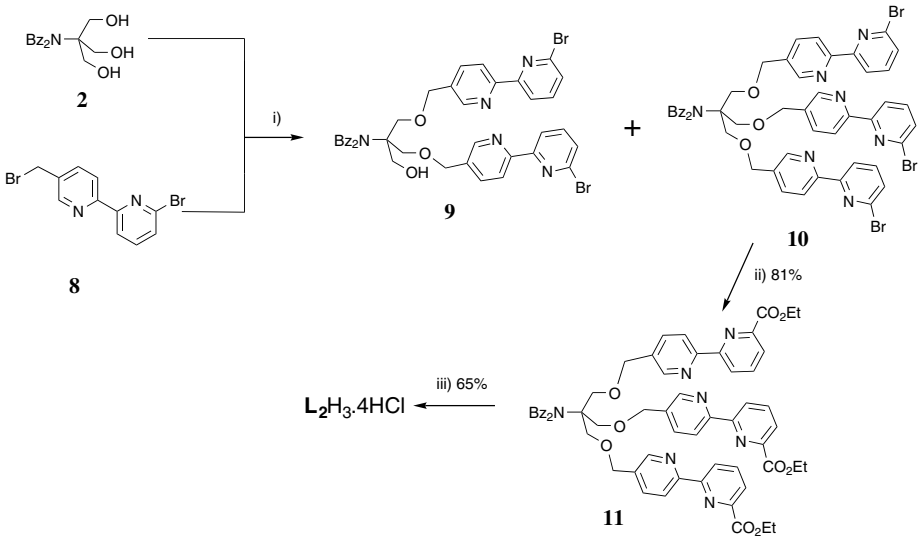
An interesting feature of the structure is the formation of a tight intramolecular hydrogen bond between the hydrogen atom of the remaining hydroxy group and



Scheme 1. Reagents and conditions: (i) benzyl bromide (2.2 equiv), $NaHCO_3$ (2.2 equiv), TBAI (0.1 equiv), H_2O, 100 °C, 30%;[10] (ii) HBr 48%, Br_2 −20 °C/$NaNO_2$ (4 equiv), 0 °C, 79%;[8] (iii) NBS (1.1 equiv), AIBN (cat.), hv, CH_2Cl_2/H_2O (1/1), reflux, 67%;[9] (iv) see Table 1 for experimental conditions; (v) *n*-BuOH/$(i\text{Pr})_2\text{EtN}/CH_2Cl_2$ (10/5/3), $[Pd(PPh)_3Cl_2]$ (0.05 mol equiv per Br), CO (1 atm.), 120 °C, 44%; (vi) HCl 6 N, 60 °C, quant.

Table 1. Reaction conditions for the etherification of **2** with compounds **4** and **8**

Entry	Alkylating agent	Solvent	Temperature (°C)	Reaction time (h)	Number of NaH (equiv)	Number of TBAI (equiv)	Yields of ethers formed	
1	**4**	THF	65	28	4	—	**6** (41%)	**5** (22%)
2	**4**	DMF	25	1	4.5	0.1	**6** (75%)	
3	**8**	THF	70	25	9	—	**10** (55%)	
4	**8**	DMF	70	24	9	—	**10** (19%)	**9** (25%)
5	**8**	DMF	25	19	4.5	0.1	**10** (87%)	



Scheme 2. Reagents and conditions: (i) see Table 1; (ii) $EtOH/Et_3N/CH_2ClCH_2Cl$ (4/4/1), $[Pd(PPh_3)_2Cl_2]$ (7% mol equiv per Br), CO (1 atm.), 70 °C, 81%; (iii) NaOH (4 equiv), $MeOH/H_2O$ (4/1), 60 °C, dil HCl, 65%.

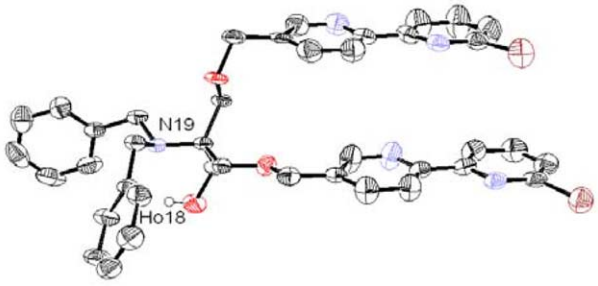


Figure 1. ORTEP view of compound **9** (ellipsoids drawn at 50% probability).

the central nitrogen atom ($d_{N19–H18} = 2.084$ Å, angle (OHN) = 107.0°). It is surmised that this hydrogen bond is responsible for the difficulty to effect the etherification reaction on the third hydroxy group of the TRIS. The two bipyridyl arms of **9** are co-facially arranged in an anti-conformation, but at a rather long distance (4.77 Å), and no particular π-stacking interaction is foreseen.

Catalytic enhancement of nucleophilic substitution by iodide, a better nucleophile and electrophile than bromide[15] is well established, but should be tempered in that case, as the nucleophilic power of halides has been shown to be reversed within the series when using aprotic polar solvents.[16] In our case, the catalytic activity of TBAI is clearly demonstrated (see Table 1, entry 4), but the exact influence may arise from a subtle balance between hydrogen bonding disruption and nucleophilicity enhancement.

The tris-bromobipyridine intermediate **10** was then converted into the tris-ester **11** by the above mentioned carboethoxylation procedure,[12] under conventional conditions of solvent and temperature. Note that the carboalkoxylation is more efficient compared to the preparation of **7** and the use of a high boiling solvent could be avoided. Finally, **11** was saponified with methanolic NaOH to afford $\mathbf{L}_2H_3$ as a tetrahydrochloride salt after acidification of the medium.[17] Preliminary investigations of the complexation of $\mathbf{L}_1H_3$ and $\mathbf{L}_2H_3$ with lanthanide chloride salts (Ln = Eu and Tb) in water clearly indicate the formation of luminescent mononuclear complexes and complexes of $[Ln(\mathbf{L}_2)]{\cdot}xH_2O$ formulae were isolated with $\mathbf{L}_2$ and characterized by elemental analysis, IR and FAB mass spectrometry. As evidenced on Figure 2, the complexation of $\mathbf{L}_2$ by europium leads to a bathochromic shift of the ligand centered π–π^* transitions (from $\lambda = 290$ nm ($\varepsilon = 32{,}800\ M^{-1}\,cm^{-1}$) for $\mathbf{L}_2$ to 305 nm ($\varepsilon = 23{,}400\ M^{-1}\,cm^{-1}$) for $[Eu(\mathbf{L}_2)]$) with appearance of the europium centered emission upon ligand excitation (quantum yield = 1.2%).[18] Nevertheless, fluorescence spectra revealed the presence of the remaining ligand centred fluorescence around 450 nm that can be attributed either to a bad intersystem crossing efficiency or to a partial decoordination of the ligand. Deeper photo-physical studies, in particular the examination of the excited state lifetimes in water and deuterated

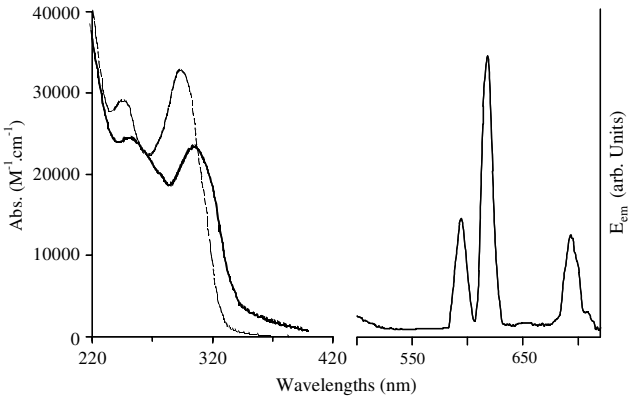


Figure 2. Absorption spectra of $\mathbf{L}_2H_3$ (dashed line) and $[Eu\mathbf{L}_2]$ (bold line) and emission spectra of $[Eu(\mathbf{L}_2)]$ in water (TRIS/HCl buffer, 0.01 M, pH = 7.0).

water, point to the presence of two species in solution. In the case of $\mathbf{L}_2$, the longest lived species ($\tau = 1.23$ ms, 25%) corresponds to the expected complex with the tris-tridentate units wrapping around the first coordination sphere of the europium atom, while the shortest one ($\tau = 0.27$ ms, 75%) contains three coordinated water molecules in the first coordination sphere, pointing to the decoordination of one of the three tridentate arm.[19]

In short, we succeeded in alkylating a di-N-protected trishydroxymethylaminomethane framework with brominated pyridine or bipyridine modules. Alkylation is, however, partially inhibited by an intramolecular hydrogen bond in the bis-alkylated intermediate species. The resulting bromo groups were adequately transformed into the ester and acid forms via a carboalkoxylation/hydrolysis sequence. These new C_3-like podands form mononuclear complexes with europium with ligand centred sensitization of the europium emission (antenna effect). Work in progress concentrates on the determination of the structure of the complexes in solution and on the complexation of other lanthanide cations.

References and notes

1. Koeller, S.; Bernardinelli, G.; Bocquet, B.; Piguet, C. *Chem. Eur. J.* **2003**, *9*, 1062.
2. Belser, P.; De Cola, L.; Von Zelewsky, A. *J. Chem. Soc., Chem. Commun.* **1988**, 1057.
3. Weibel, N.; Charbonnière, L. J.; Guardigli, M.; Roda, A.; Ziessel, R. *J. Am. Chem. Soc.* **2004**, *126*, 4888.
4. Sohna Sohna, J.-E.; Fages, F. *Tetrahedron Lett.* **1997**, *38*, 1381.
5. Gillies, E. R.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2002**, *124*, 14137.
6. (a) Newkome, G. R.; Lin, X. *Macromolecules* **1991**, *24*, 1443; (b) Newkome, G. R.; Moorefield, C. N.; Baker, G. R. *Aldrichim. Acta* **1992**, *25*, 31; (c) Viguier, R.; Serratrice, G.; Dupraz, A.; Dupuy, C. *Eur. J. Inorg. Chem.* **2001**, 1789.
7. Dupuis, C.; Viguier, R.; Dupraz, A. *Synth. Commun.* **2001**, *31*, 1307.
8. Adams, R.; Miyano, S. *J. Am. Chem. Soc.* **1954**, *76*, 3168.
9. Bedel, S.; Ulrich, G.; Picard, C. *Tetrahedron Lett.* **2002**, *43*, 1697.
10. Dupraz, A.; Guy, P.; Dupuy, C. *Tetrahedron Lett.* **1996**, *37*, 1237.
11. Cohen, R. J.; Fox, D. L.; Eubank, D. L.; Salvatore, R. N. *Tetrahedron Lett.* **2003**, *44*, 8617.
12. El Ghayoury, A.; Ziessel, R. *J. Org. Chem.* **2000**, *65*, 7757.
13. Charbonnière, L.; Weibel, N.; Ziessel, R. *J. Org. Chem.* **2002**, *67*, 3933.
14. Compound $\mathbf{L}_1H_3{\cdot}4HCl{\cdot}2H_2O$: ^{1}H NMR ($CD_3OD$, 200 MHz): δ 4.30 (s, 6H), 4.87 (s, 4H), 4.94 (s, 6H), 7.17–7.28 (m, 10H), 7.80–7.84 (m, 3H), 8.18–8.24 (m, 6H); ^{13}C NMR (CD_3OD, 50 MHz): δ 57.9, 69.7, 71.6, 74.1, 127.1, 129.3, 130.2, 130.7, 131.4, 132.5, 145.2, 145.8, 156.7, 163.7; FAB$^+$/MS: *m*/*z* 707.3 ($[\mathbf{L}_1H_3{+}H]^+$, 100%). Anal. Calcd for $C_{39}H_{38}N_4O_9{\cdot}4HCl{\cdot}2H_2O$: C, 52.71; H, 5.22; N, 6.30. Found: C, 52.52; H, 4.98; N, 6.14; IR (KBr, cm^{-1}): 3435 (s), 2966 (w), 2933 (w), 1636 (m, $\nu_{COO,asym.}$), 1439 (w), 1384 (m, $\nu_{COO,sym.}$), 1275 (w), 1076 (w), 1010 (w); UV–vis (0.01 M Tris/HCl buffer, pH = 7.0, λ_{max}, nm (ε_{max}, M^{-1} cm^{-1})): 268 (14,600).
15. March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley Interscience, 1985; p 304.
16. Weaver, W. M.; Hutchison, J. D. *J. Am. Chem. Soc.* **1964**, *86*, 261.
17. Compound $\mathbf{L}_2H_3{\cdot}4HCl{\cdot}H_2O$: ^{1}H NMR ($CD_3OD$, 400 MHz): δ 3.74 (s, 6H), 4.08 (s, 4H), 4.51 (s, 6H), 7.04–7.15 (m, 6H), 7.24–7.30 (m, 4H), 7.76 (dd, 3H, $^3J = 8.5$ Hz, $^4J = 2.0$ Hz), 7.94 (t, 3H, $^3J = 8.0$ Hz), 8.03 (d, 3H, $^3J = 7.0$ Hz), 8.30 (d, 3H, $^3J = 8.0$ Hz), 8.32 (d, 3H, $^3J = 8.5$ Hz), 7.49 (s, 3H); FAB$^+$/MS: *m*/*z* 847.2 ($[\mathbf{L}_2H_3{-}C_7H_7{+}H]^+$, 25%), 938.2 ($[\mathbf{L}_2H_3{+}H]^+$, 100%). Anal. Calcd for $C_{54}H_{47}N_7O_9{\cdot}4HCl{\cdot}H_2O$: C, 58.86; H, 4.85; N, 8.90. Found: C, 58.69; H, 4.88; N, 8.82; IR (KBr, cm^{-1}): 3445 (s), 1635 (m, $\nu_{COO,asym.}$), 1384 (m, $\nu_{COO,sym.}$), 1262 (w), 1096 (w); UV–vis (0.01 M Tris/HCl buffer, pH = 7.0, λ_{max}, nm (ε_{max}, M^{-1} cm^{-1})): 242 (27,600), 290 (32,800).
18. Absolute quantum yields determined relatively to $[Ru(bipyridine)_3]Cl_2$ in air equilibrated water (2.8%) Nakamura, K. *Bull. Chem. Soc. Jpn.* **1982**, *5*, 2697.
19. Mameri, S.; Charbonnière, L.; Ziessel, R. *Inorg. Chem.* **2004**, *43*, 1819.