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A convenient preparative method for anionic tris(substituted pyrazolyl)methane ligands

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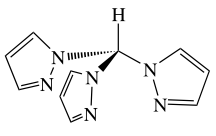
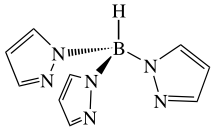
Abstract—The synthesis of tris[3-(6-carboxypyridin-2-yl)pyrazol-1-yl]methane is described in a linear multi-step protocol. The pyridyl-pyrazolyl arms are first constructed before being condensed with chloroform. Careful study of the condensation reaction shows the presence of an isomeric form of the tris(pyrazolyl)methane derivative in which one of the pyrazolyl substituents is linked through the nitrogen atom at the 2 position of the pyrazol. After acid-catalysed isomerisation to the desired isomer, the intermediate compound was subjected to a carboalkoxylation reaction and a subsequent hydrolysis. These are some rare examples of reactions directly occurring on the tris(pyrazolyl)methane platforms.

Tris(pyrazolyl)methane[1] (TPM) and the isoelectronic tris(pyrazolyl)borate[2] (TPB) have raised a lot of interest in the field of coordination chemistry[3] due to their shape and pre-organised structure and to relatively easy synthetic access. From these so called *scorpionates*, numerous derivatives were developed by functionalisation of the pyrazolyl rings, some of them being used as artificial enzymes.[4] For coordination purposes, the functionalisation of the position 3 of pyrazols was particularly attractive as it may lead to the introduction of further coordinating functionalities such as methylsulfanylphenyl,[5] carboxylic acids[6] or pyridyl rings.[7] In this last case, the chelating arms have been shown to be very efficient chromophores for providing an antenna effect with lanthanide cations.[8] Such ligands are thus expected to be relevant targets for the design of time-resolved luminescent probes in particular in the case of terbium complexes.[9] Whatever their application, the main drawback of these polyheteroaromatic ligands and their complexes is their low solubility and instability in water solutions.

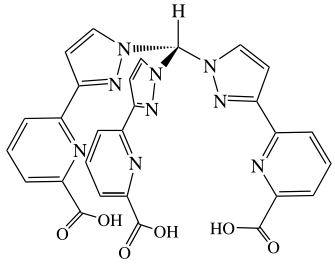
The present work describes the synthesis of ligand $\mathbf{LH_3}$, which combines the basic tris(pyrazolyl)methane (TPM) framework, three pyridyl-pyrazolyl chromophores and carboxylate functions attached on the pyridine moieties. The combination of these three functions is expected to provide a ligand with a pre-organised complexation pocket well suited for lanthanide complexation. These complexes should exhibit interesting photo-physical properties and thermodynamic stability in aqueous solvents.



TPM



TPB



LH_3

Keywords: tris(pyrazolyl)methane; bipyridine carboxylate; scorpionate; water solubility.
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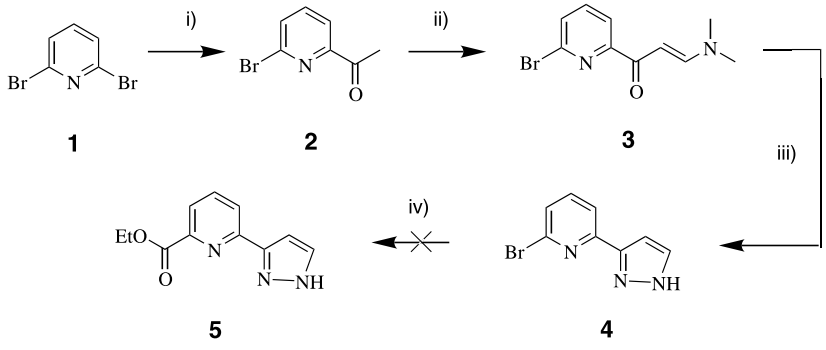
Our first attempt to synthesise $\mathbf{LH_3}$ was based on the preparation of an ester precursor **5**, which should then be condensed with chloroform to afford an ester precursor of $\mathbf{LH_3}$. Starting from the commercially available 2,6-dibromopyridine **1**, 2-acetyl-6-bromopyridine **2**, was obtained according to a literature procedure.[10] Reaction of **2** with neat *N*,*N*-dimethylformamide dimethylacetal gave 3-dimethylamino-1-(6-bromopyridin-2-yl)prop-2-en-1-one **3** in 77% yield. When **3** is reacted with hydrazine hydrate in hot methanol in a Schlenk tube, the pyrazolyl ring is formed in quantitative yield, leading to **4** (Scheme 1). Unfortunately, all our efforts to obtain compound **5** by a conventional carboalkoxylation procedure, in which **5** was reacted with bubbling CO in a hot EtOH/Et_3N mixture using 5% [$Pd(PPh_3)_2Cl_2$] as catalyst,[11] remained unsuccessful. This disappointing result was nevertheless in agreement with previous findings,[12] in which this kind of reaction was showed to be poorly efficient in the presence of secondary aliphatic amines. In order to overcome this drawback, it was decided to realise the condensation of compound **4** with chloroform leading to the **TPM** framework **6**.

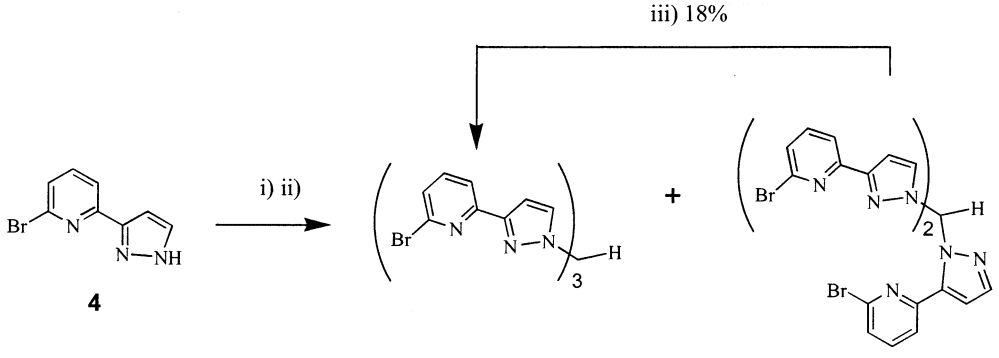
The condensation was conducted under conditions similar to previously reported results,[14] in which **4** was first suspended in water in the presence of Na_2CO_3, resulting in an exothermal reaction probably due to deprotonation of the pyrazol. This mixture was then added to $CHCl_3$ containing triethylbenzyl ammonium chloride as a phase transfer catalyst. The biphasic mixture was then refluxed, resulting in the slow formation of two new compounds, as evidenced by TLC analysis of the organic layer (Scheme 2, protocol ii).

After column chromatography, the second eluting product (R_f=0.54, SiO_2, CH_2Cl_2/MeOH 97/3) was characterised as the expected TPM adduct **6**. On the basis of its ^1H and ^{13}C NMR spectra[13] and according to literature data,[14,15] the first eluting compound (R_f= 0.59, same conditions) was identified as being **7**, an isomeric form of **6** in which one of the pyrazolyl ring is linked through the N2 nitrogen atom.

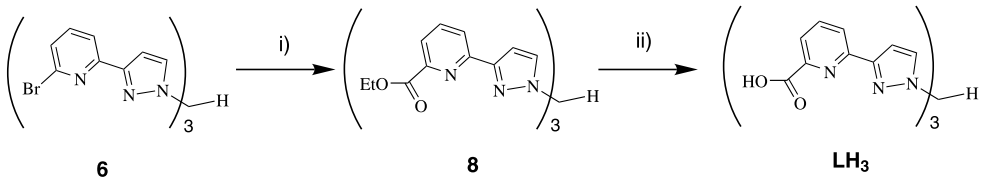
Treatment of **7** with *p*-toluenesulfonic acid in toluene led to isomerisation to **6**, but during this process, the product partly decomposed with the formation of the



Scheme 1. *Reagents and conditions*: (i) *n*-BuLi, THF, −78°C then $CH_3C(O)NMe_2$;[10] (ii) neat $Me_2NCH(OMe)_2$, 100°C, 2 h, 77%; (iii) $H_2NNH_2{\cdot}H_2O$, MeOH, 80°C, 45 min, quantitative; (iv) [$Pd(PPh_3)_2Cl_2$], EtOH, Et_3N, CO (1 atm.), 70°C, 15 h.



Scheme 2. *Reagents and conditions*: Protocol (i) H_2O, Na_2CO_3, $CHCl_3$, $Bz(Et)_3NCl$, reflux, 19 h; extraction; PhMe, CF_3COOH, 110°C, 1 day, 38% overall yield for compound **6**. Protocol (ii) H_2O, Na_2CO_3, $CHCl_3$, $Bz(Et)_3NCl$, reflux, 19 h; purification by chromatography. (iii) PhMe, *p*-TsOH, reflux 15 h, 18%.



Scheme 3. *Reagents and conditions*: (i) $[Pd(PPh_3)_2Cl_2]$, EtOH, Et_3N, CO (1 atm.), 70°C, 15 h, 68%; (ii) NaOH, EtOH, H_2O, 70°C, 3 h then conc. HCl, 88%.

starting material **4**, and **6** was recovered in only 18% after purification (protocol iii). The presence of traces of water in the *p*-toluenesulfonic acid used probably plays an important rule in this decomposition process. As a result of the difficulties encountered during the purification process, we decided to run the isomerisation process directly on the crude reaction mixture obtained after aqueous work-up and to change *p*-TsOH to CF_3CO_2H (protocol i). In these conditions, the isomer **7** is not isolated before the acidic treatment and **6** can be obtained in 38% overall yield after purification.

When **6** was submitted to a carboethoxylation reaction promoted by palladium(0), the triethyl ester **8** was isolated in fair yield, without any major side-reaction (Scheme 3). Such mild synthetic conditions are of great interest as the use of more conventional procedures such as halogen–metal exchanges often require the use of hard bases which may led to deprotonation of the central carbon atom.[16]

In a final step, the ester functions were saponified in a methanol/water mixture containing NaOH and $\mathbf{LH_3}$ was recovered by acidification with concentrated HCl.[17] Preliminary experiments with lanthanide cations showed the ligand to form stable [Ln**L**] water soluble complexes. In the case of europium and terbium, bright red and green emissions were respectively observed upon UV irradiation, indicative of a ligand to metal energy transfer. The measured excited state lifetimes are respectively of 0.28 and 1.00 ms for europium and terbium in water with quantum yields of 2 and 15%, respectively. Further experiments are currently in progress for a full characterisation of the photo-physical properties of the ligand and complexes.[18]

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13. Selected data for compound **7**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 6.77 (d, 1H, $^3J=2.0$ Hz), 7.00 (d, 2H, $^3J=2.5$ Hz), 7.36 (dd, 2H, $^3J=7.5$ Hz, $^4J=1.0$ Hz), 7.41–7.44 (m, 1H), 7.52 (t, 2H, $^3J=7.5$ Hz), 7.59–7.69 (m, 3H), 7.84 (d, 2H, $^3J=2.5$ Hz), 7.93 (dd, 2H, $^3J=7.5$ Hz, $^4J=1.0$ Hz), 9.84 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 82.0, 106.3, 108.6, 119.3, 121.2, 127.1, 127.7, 131.8, 138.8, 139.6, 140.2, 140.9, 141.6, 141.7, 148.9, 152.0, 152.9. For comparison, compound **6**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.07 (d, 3H, $^3J=3$ Hz), 7.42 (dd, 3H, $^3J=8.0$ Hz, $^4J=1.0$ Hz), 7.57 (t, 3H, $^3J=7.5$ Hz), 7.65 (d, 3H, $^3J=2.5$ Hz), 7.93 (dd, 3H, $^3J=7.5$ Hz, $^4J=1.0$ Hz), 8.52 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 84.0, 107.0, 119.2, 127.5, 131.1, 139.0, 141.8, 152.4, 152.9.
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17. Selected data for $\mathbf{LH_3}$: ^{1}H NMR (d_6-DMSO): δ 7.19 (d, 3H, $^3J=2.5$ Hz), 7.99–8.10 (m, 6H), 8.15–8.20 (m, 3H), 8.22 (d, 3H, $^3J=2.5$ Hz), 9.35 (s, 1H). ^{13}C NMR (d_6-acetone): δ 84.4, 107.6, 124.3, 126.8, 133.2, 139.8, 147.9, 151.7, 153.5, 165.6. FABMS: m/z 578.3 (100%, M+H$^+$), 533.2 (15, M–CO_2+H$^+$). Anal. calcd for $C_{28}H_{19}N_9O_6\cdot 2HCl$: C, 51.71; H, 3.25; N, 19.38. Found: C, 51.59; H, 3.16; N, 19.29. IR: 2972, 2926, 2890, 1720, 1587, 1447, 1341, 1248, 1083, 1050.
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