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Direct synthesis of new cryptates based on the *N*,*C*-pyrazolylpyridine motif

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Abstract—An expeditious synthesis of new cryptands derived from *N*,*C*-pyrazolylpyridine and their full characterization is reported. Emission lifetimes of the europium and terbium cryptates were in the range of milliseconds and terbium quantum yield was high.
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The design and synthesis of macrocyclic ligands and their luminescent lanthanide (Ln) complexes are a fascinating area of research, owing to their importance in either basic or applied chemistry.[1] The ability of macrocyclic ligands to recognize Ln ions makes them valuable for the development of supramolecular devices, probes in biological systems, luminescence labels, and medical diagnostics.[2] However, the Ln luminescence in aqueous solution is substantially lowered due to the vibronic coupling of water molecules with the metal.

Macrobicyclic ligands possess a three-dimensional spherical cavity with special recognition sites, which may provide, to the bound ion, efficient shielding from solvent molecules.[3] Cryptates incorporating symmetrical bis-heteroaryl groups like 2,2′-bipyridine (Fig. 1a) showed exceptional luminescent properties specially with europium.[4] The tris-heteroaryl group 2,6-bis(*N*-pyrazolyl)-pyridine has been very effective in Ln sensitization (antenna effect) because, incorporated in chelates,[5] macrocycles,[6] or cryptates[7] (Fig. 1b–d) led to compounds with outstanding luminescent properties.

Along these lines, we found it very attractive to build a new series of cryptates similar to that of Figure 1a but with a heterocyclic motif similar to that of Figure 1b–d. Scheme 1 shows the expeditious synthesis used in this work.

It was accomplished in three steps from the potassium salt of 3-methylpyrazole, prepared in situ. The reaction

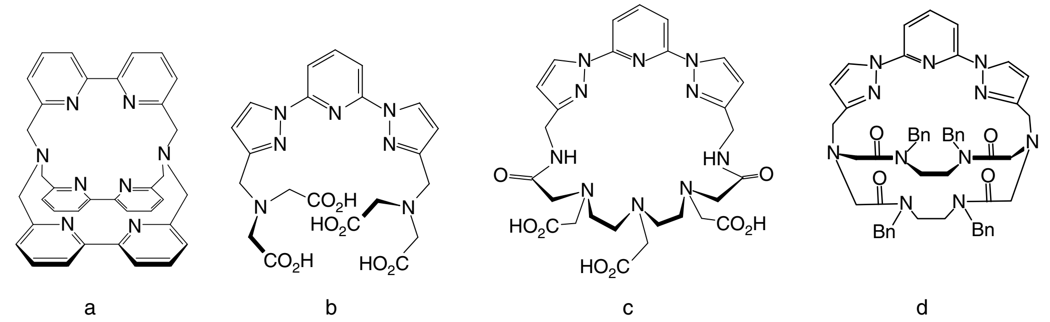

Figure 1. Some compounds prepared by our research group bearing outstanding luminescence properties.

Keywords: Lanthanide; Luminescence; Cryptand; Pyrazole.

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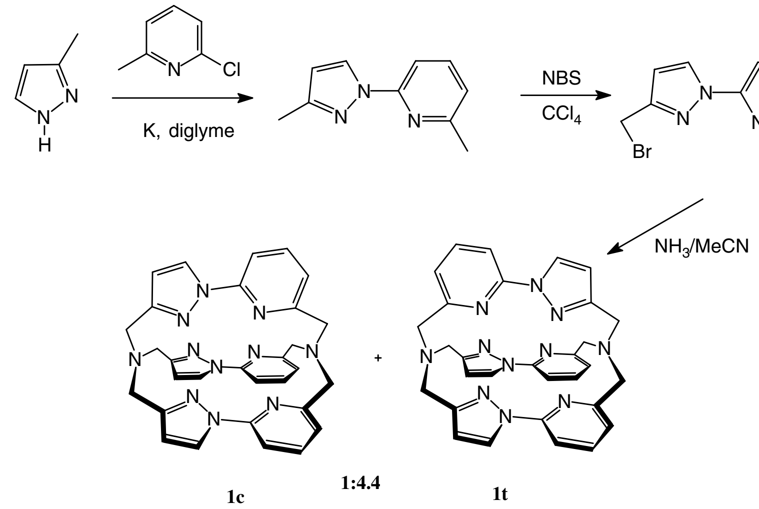


Scheme 1.

of the pyrazolate with 2-chloropycoline afforded dimethyl pyridinepyrazole,[8] which was transformed into the dibromide derivative by radical bromination with NBS.[9] Treatment with anhydrous ammonia (autoclave; dry acetonitrile at 100 °C, sodium carbonate) afforded the sodium cryptates in reasonable yield as a **1c**:**1t** mixture in 1:4.4 ratio, slightly above the 1:3 proportion expected on strict statistical grounds.[10]

The higher ratio of **1t** may be easily explained if we reasonably simplify the complex mechanism of this reaction in a stepwise manner. No doubt the first process must be the replacement of bromine by ammonia. Since the latter is added deficiency with respect to the dibromo derivative (2:3 ratio), a mixture of the two possible monoamines together with unreacted starting material and a small amount of diamine should be produced. The second step should be the coupling of two pyrazolepyridine units to form a macrocycle. We have observed that no high dilution conditions were necessary in the cryptate formation suggesting a template effect of the sodium cation. Therefore, a slight bias in the coupling of the pyrazolepyridine units to form the non-symmetric macrocycle, templated by the intercourse of sodium, would explain the obtained **1c**:**1t** ratio.

It should be noted that since the *N*,*C*-pyrazolepyridine moiety is non-symmetric, the coupling of three units led to the two isomeric criptands. Isomer **1c** has the three pyridine (or pyrazole) rings bonded to the same bridgehead nitrogen and therefore bears C_{3v} symmetry whilst the different arrangement of one subunit renders isomer **1t** of lower symmetry (C_{1v}).

Unfortunately, we have not been able to separate the two isomers by the usual techniques. However, since their photophysical properties are expected to be quite similar, we believed it would be worth carrying out the pertinent lanthanide complexation and report the luminescence studies on the mixture which, nevertheless, has been fully characterized by 1D and 2D ^{1}H and ^{13}C NMR spectra.

As an example, Figure 2 shows the assignment of the methylene protons. The highly symmetric **1c** gave two singlets at 3.84 and 3.82 ppm (triangles in Fig. 2), the most deshielded one corresponding to the CH_2 groups bonded to the pirazole rings as indicated by HMBC data. The lower symmetry of **1t** makes the protons of its methylene groups marked with circles to be diastereotopic, thus leading to two AB systems at 3.91/3.81 and 3.80/3.73 ppm, with typical geminal couplings of 14.5 Hz. On the other hand, the symmetry plane of **1t** forces the protons of each methylene of the overturned pyrazolepyridine unit to be isochronous therefore giving the corresponding singlets [diamond (3.92 ppm) and square (3.71 ppm) in Fig. 2]. The relative areas of the signals belonging to **1c** and **1t** were in the aforementioned 1:4.4 ratio. Complete assignment of all proton and carbon signals was performed by means of HMQC and HMBC spectra whose discussion is omitted for the sake of brevity.

Since we were unable to resolve the **1c**,**t** mixture, we have performed the six-step sequence depicted in Scheme 2 to selectively prepare **1c**. Overall yield was low (<10%) and improvement of the reaction conditions is currently in progress. Yet, as expected, the photophysical study of the small amount of **1c** obtained in the first run resulted identical to that of the 1:4.4 mixture, even though **1c** is its minor component.

The Eu(III), Tb(III), and Gd(III) complexes of the mixture of ligands **1c**,**t** were prepared by ion exchange on the sodium cryptates by 36–48 h reflux in the presence of an excess of the corresponding $LnCl_3$ in methanol/water 1:1. The reaction was followed by UV/vis (Table 1) and luminescence data (Table 2).

The UV–vis spectra of the lanthanide cryptates showed the characteristic bands for the pyrazolylpyridine chromophore (255 and 280 nm) that suffered a bathochromic shift of 9 nm when complexed to Ln similarly to what happened in related Eu(III) and Tb(III) complexes with ligands derived from 2,6-bis(*N*-pyraz-

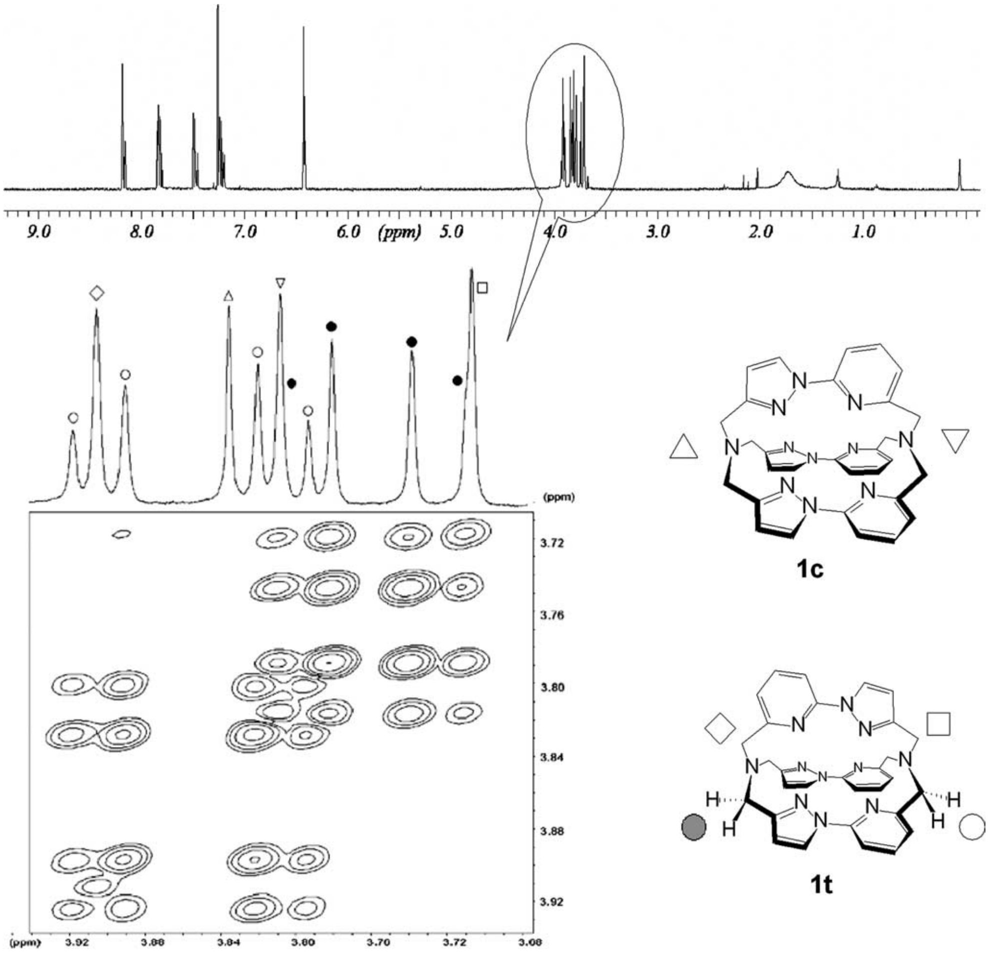
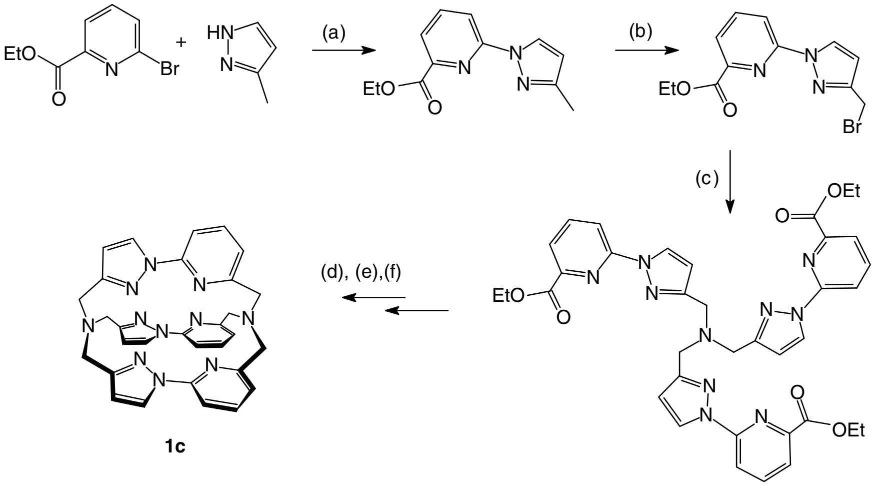


Figure 2. Assignment of methylene signals to the 1:4.4 mixture of cryptands **1c**,**t**.



Scheme 2. Reagents and conditions: (a) (1) pyrazole, K(metal), diglyme, 80 °C; (2) 6-bromo-2-ethoxycarbonylpyridine, 60 °C, 60 h; (b) NBS, CCl_4, reflux, 24 h; (c) NH_3, CH_3CN, Na_2CO_3, 100 °C, 12 h; (d) $NaBH_4$, EtOH, 60 °C, 14 h; (e) PBr_3, CH_3CN, reflux, 3 h; (f) NH_3, CH_3CN, Na_2CO_3, 100 °C, 20 h.

olyl)pyridine[11] or 2,2′-bipyridine.[12] Slight electronic and/or conformational perturbations should be the source of the absorption variations upon metal exchange.

The emission spectra of the Eu(III) and Tb(III) complexes, excited into their lowest energy, ligand-centered absorption band showed the well-known, structured luminescence of the lanthanide ions, with the highest

Table 1. Wavelength maxima and molar absorption coefficients of Eu(III) and Tb(III) complexes of compounds **1c**,**t** (water)

	Cryptate complex					
	Na^+		Eu(III)		Tb(III)	
λ_{abs} (nm)	255	280	263	289	263	289
ε (10^3 M^{-1} cm^{-1})	33.9	23.9	33.0	30.8	22.9	26.4

Table 2. Lifetimes (ms) measured in H_2O and D_2O at rt and 77 K, quantum yields (ϕ) of the metal-centered emission of the complexes and number of water molecules (n)

1c,t	$\tau^{300\,K}_{H_2O}$	$\tau^{300\,K}_{D_2O}$	$\tau^{77\,K}_{D_2O}$	ϕ	n
Eu(III)	0.43	1.64	2.01	>0.01	1.8
Tb(III)	1.30	2.77	3.04	0.38	1.8

intensity band at 615 and 545 nm for Eu(III) and Tb(III), respectively (correspondingly $^5D_0$–$^7F_2$ and $^5D_4$–$^7F_5$). The accordance between absorption and excitation spectra proves that energy is efficiently transferred from the *N*,*C*-pyrazolylpyridine chromophores to the lanthanides. Measurement of the luminescence decay showed mono-exponential curves, suggesting a unique chemical environment of the lanthanide ion.

Although the luminescence lifetimes and quantum yields at room temperature in water (Table 2) were shorter than others obtained with chelates based on pyrazolylpyridine motifs, the measured values resulted in the range[13] or even much longer[14,15] than those observed for other cryptates.

Almost two water molecules were detected in the first coordination sphere (de Horrocks,[16] Parker,[17] and Kimura[18] methods). From the various possible arrangements calculated by semiempirical and molecular mechanics calculations for cryptate **1c** as a representative example (Hyperchem, AM1 and MM+), the finding of a relatively high water coordination fits better with a structure similar to that of A (Fig. 3), where the pyrazolylpyridine arms would embrace less symmetrically the metal as in B, hence leaving it more exposed to external coordination. Both calculated structures A and B are similar to those in the literature for aqua-chloro-(*N*,*N*-bis(2,2′bipyridine-6,6′dimeth-yl)-2,2′-bipyridine-6,6′-bis- (methylamine))-terbium(III) dichloride dihydrate[19] (A-like) and sodium tris(2,2′-bipyridine)cryptate acetonitrile solvate[20] (B-like). Unfortunately, at the moment of the writing of this letter, it has been not possible to get crystals either from the isomer mixture or pure **1c**.

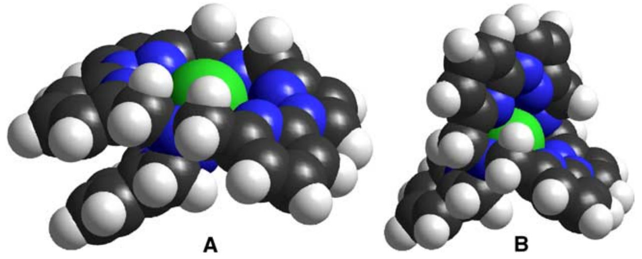


Figure 3. Molecular modeling (Hyperchem, AM1/MM+) of cryptate **1c**. The metal atom was forced to rest at the geometrical center of the cryptands.

Larger lifetimes were observed in D_2O [factors of ca. 4 for Eu(III) and 2 for Tb(III)] stressing that the cryptates were in fact sensitive to vibronic deactivation via O–H oscillators. The lower effect exerted by solvent deuteration on Tb(III) complexes, as compared to Eu(III) ones, may indicate the lower probability of the former metal to couple with O–H vibronic deactivation,[21] probably because of the higher gap that Tb(III) bears between its lowest luminescent and highest ground states.

On the other hand, the larger lifetimes observed at low temperature, especially in Eu(III) cryptates, hint to the higher feasibility of non-emitting LMCT states for Eu(III) and/or additional non-radiative pathways, less accessible in the case of Tb(III).[22] Furthermore, the larger size of Tb(III) [ionic radius of 1.18 Å as compared to 1.07 Å of Eu(III)], might make it to be in closer contact to the nitrogen atoms, fact that no doubt should contribute to the much higher quantum yield observed in the Tb(III) cryptates (Table 2).

In conclusion, we have reported a straightforward synthetic method to obtain a mixture of new cryptands based on the pyrazolylpyridine motif, which allowed us to quickly assert that these compounds gave Ln complexes with quite valuable luminescence properties. The also reported preliminary, yet successful result in the selective preparation of the symmetric isomer **1c** paves the road to the synthesis of this kind of cryptands with additional functionality in the aromatic rings, in order to serve specific practical applications as luminescent probes in biological systems. Work is under way.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.09.020.

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8. Potassium (1.83 g, 46.9 mmol) was added in small portions to a solution of 3-methylpyrazole (3.70 g, 47.01 mmol) in diglyme (300 mL) at rt and then the mixture was heated at 80 °C. When the metal was dissolved, 2-chloro-6-methylpyridine (4.00 g, 31.27 mmol) was added in one portion and the reaction was stirred at 140 °C for 4 days. The mixture was filtered and the solvent evaporated in vacuo. The resulting oil was flash chromatographed on silica gel (hexane/ethyl acetate 7:1). The final product was obtained as pale-yellow oil (4.14 g, 76%). ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.43 (1H, d, $J = 2.5$ Hz, Pz-H_5); 7.67 (1H, d, $J = 8.2$ Hz, Py-H_3); 7.58 (1H, dd, $J = 8.2$ and 7.1 Hz, Py-H_4); 6.92 (1H, d, $J = 7.1$ Hz, Py-H_5); 6.19 (1H, d, $J = 2.5$ Hz, Pz-H_4); 2.49 (3H, s, CH_3-Py); 2.34 (3H, s, CH_3-Pz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 156.7 (Py-C_6), 150.8 (Pz-C_3), 150.4 (Py-C_2), 138.1 (Py-C_4), 127.1 (Pz-C_5), 119.7 (Py-C_3), 108.3 (Pz-C_4), 107.1 (Py-C_5), 23.7 (Py-CH_3), 13.4 (Pz-CH_3). MS (L-SIMS+): 174.1 (M+H).
9. A mixture of 6-methyl-2-(3-methylpyrazol-1-yl)pyridine (800 mg, 4.62 mmol), *N*-bromosuccinimide (NBS) (1.64 g, 9.24 mmol), and dibenzoylperoxide (5 mg), was refluxed in carbon tretrachloride for 18 h, and then filtered at rt. The filtrate was evaporated and the resulting oily residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 1:1). The product was isolated as a white solid, which was recrystallized from hexane, 273 mg, (19%); mp 78–79 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm): 8.55 (1H, d, $J = 2.7$ Hz, Pz-H_5); 7.87 (1H, dd, $J = 1.5$ and 8.2 Hz, Py-H_3); 7.80 (1H, dd, $J = 6.9$ and 8.2 Hz, Py-H_4); 7.31 (1H, dd, $J = 1.5$ and 6.9 Hz, Py-H_5); 6.52 (1H, d, $J = 2.7$ Hz, Pz-H_4); 4.55 (2H, s, CH_2-Py); 4.52 (2H, s, CH_2-Pz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 155.5 (Py-C_6), 151.7 (Py-C_2), 150.7 (Pz-C_3), 139.7 (Py-C_4), 128.6 (Pz-C_5), 121.0 (Py-C_3), 111.7 (Pz-C_4), 107.9 (Py-C_5), 33.2 (Py-CH_2), 24.9 (Pz-CH_2). MS (L-SIMS+): 330, 332 (M+H), 334.
10. A mixture of 6-bromomethyl-2-(3-bromomethyl-pyrazol-1-yl)pyridine (388 mg, 1.17 mmol), sodium carbonate (189 mg) and 1 mL of a solution ammonia in acetonitrile (0.79 M) in dry acetonitrile (80 mL) was introduced in an autoclave, heated at 100 °C for 24 h, and then filtered at rt. The filtrate was evaporated and the resulting light-yellow residue was purified by recrystallization from methanol to yield a pale-yellow solid (80 mg, 32%) corresponding to the mixture 1:4.4 of cryptates **1c** and **1t**. Mp $>$300 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) **1c**: 8.17 (3H, d, $J = 2.6$ Hz, Pz-H_5); 7.82 (3H, dd, $J = 4.6$ and 5.0 Hz, Py-H_4); 7.46 (3H, d, $J = 4.6$ Hz, Py-H_3); 7.19 (3H, d, $J = 5.0$ Hz, Py-H_5); 6.42 (3H, d, $J = 2.6$ Hz, Pz-H_4); 3.84 (6H, s, CH_2-Py); 3.81 (6H, s, CH_2-Pz). Compound **1t** 8.19 (2H, d, $J = 2.6$ Hz, Pz-H_5); 8.17 (1H, d, $J = 2.6$ Hz, Pz-H_5); 7.83 (2H, dd, $J = 4.6$ and 5.0 Hz, Py-H_4); 7.82 (1H, dd, $J = 4.6$ and 5.0 Hz, Py-H_4); 7.50 (2H, d, $J = 4.6$ Hz, Py-H_3); 7.46 (1H, d, $J = 4.6$ Hz, Py-H_3); 7.23 (2H, d, $J = 5.0$ Hz, Py-H_5); 7.19 (1H, d, $J = 5.0$ Hz, Py-H_5); 6.42 (3H, d, $J = 2.6$ Hz, Pz-H_4); 3.91 (2H, s, CH_2-Py); 3.91–3.81 (4H, AB system, $J = 14.5$ Hz, CH_2-Pz); 3.80–3.73 (4H, AB system, $J = 14.5$ Hz, CH_2-Py); 3.71 (2H, s, CH_2Pz). MS (L-SIMS+): 564.2 (M+Na).
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