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Synthesis of functionalized dipyrrolyldiketones, precursors of quinoxaline-containing macrocycles

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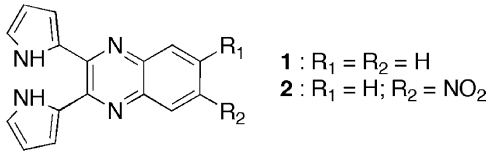
Abstract—In the general context of molecular recognition, the need to design new ligands able to selectively bind small analytes is currently being subjected to intensive research. In this respect, and considering that polypyrrole ligands can play crucial roles in this area, we developed the synthesis of a new class of per-alkyl dipyrrolyldiketone building blocks. Further functionalization including oxidation, and conversion to the corresponding aza-analogue dimer of indolizine is described.

In recent years, the concept of molecular recognition of anions has attracted much attention.[1,2] In particular, it is now well established that properly designed systems able to produce optical or redox signals upon selective complexation of an analyte will shortly play a crucial role in areas as different as environmental or medicinal science. Among the different possibilities, the design of a sensor that produces a visual signal upon binding is undoubtedly the most convenient and the most promising.[3,4] For instance, an ultimate goal involves the preparation of a pH-paper-like system that would signal nitrates in tap water through a simple color change. This approach requires the development of molecules bearing at least a coordinating unit and a reporter. The latter is necessary to signal the coordination of the analyte through a macroscopic signal (visual or else).

A few years ago, Sessler and co-workers demonstrated that dipyrrolylquinoxalines (DPQ) present the topological features matching these requirements (Scheme 1).[5]

In this case, the two pyrrole units bind anions via the pyrrole NH functions whilst the quinoxaline unit acts as a chromogenic reporter and displays a color change when halides are bound to the ligand. Despite these



Scheme 1.

encouraging pioneering results, the DPQ approach still requires improvements. In particular, enhancing the affinity and/or the selectivity of the system toward anions is crucial, especially if use of polar solvents such as water is envisioned. To this end, two modifications of the skeleton of the sensor are of interest. First, the electron deficiency of the chelating system can be raised.[5,6] In this case, the hydrogen-binding ability of the ligand is enhanced leading to a higher affinity toward anions. This modification was tested and proved to be efficient. Thus, in dichloromethane, when $R_1 = R_2 = H$, $K_a(F^-) = 18{,}200\,M^{-1}$ whereas when $R_1 = H$ and $R_2 = NO_2$, $K_a(F^-) = 118{,}000\,M^{-1}$. Second, the number of hydrogen-bond donors can be increased. This second approach requires further functionalization of the DPQ chelating unit. To the best of our knowledge, if we do not consider modifications of the reporter, the only modifications reported up to now concern the formylation of the pyrrole α-free positions followed by reaction with an excess of pyrrole.[7] The main reason for the limited numbers of modifications performed on the DPQ core is attributable to the poor reactivity of the pyrrole

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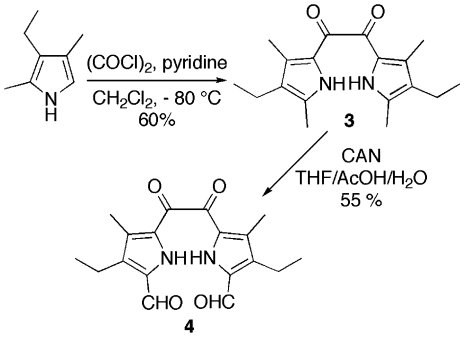
α-free positions, and the rather low solubility of the ligand in most organic solvents. In order to circumvent this problem, we decided to develop the preparation of per-alkyl DPQ.

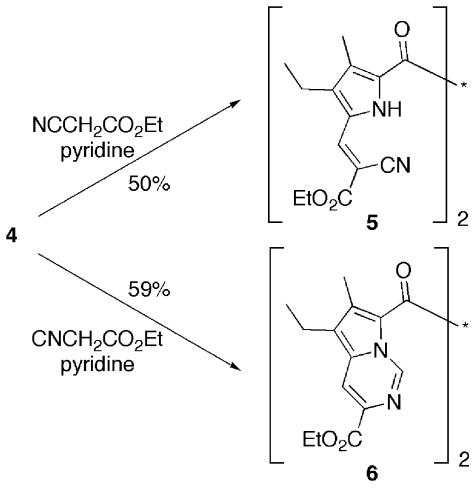
Herein, we wish to report the first results we obtained using this methodology. In particular we describe the preparation of the highly soluble per-alkyl diketone (**3**) and its efficient conversion to the corresponding dialdehyde (**4**). We also report the selective protection of the aldehyde functions and demonstrate that **4** can be easily converted into the unprecedented bis(pyrrolo-pyrimidine) ethanedione (**6**). The latter was fully characterized including by X-ray structural determination.

Preparation of the per-alkyl diketone (**3**) was achieved using the experimental procedure developed for the preparation of the substituent-free dipyrrolyldiketone.[8] Condensation of the commercially available 3-ethyl-2,4-dimethyl-1*H*-pyrrole with a stoichiometric amount of oxalyl chloride in the presence of dry pyridine (Scheme 2) afforded the expected diketone (**3**) in 60% yield. Conveniently, the pure diketone was directly isolated from the crude mixture by simple washings with petroleum ether and methanol.

We then investigated the possibility of further functionalizing the new dipyrrolyldiketone building block (**3**). Considering the importance of the α-formyl pyrroles in macrocyclic chemistry we decided to oxidize the α-methyl positions to aldehydes. To this end, and taking advantage of the presence of the two α′-carbonyl groups,[9] we considered the use of cerium ammonium nitrate (CAN) that proved to be efficient in the case of electron deficient 5-ethyl ester-2-methyl pyrroles.[10] Additionally, it was shown not being dependent on the β-substitution. Thus, we reacted 8.6 equiv of CAN with **3** in a mixture of THF, acetic acid, and water and isolated the expected dialdehyde **4** in 55% yield. Ultimately, we tested the reactivity of the aldehyde functions. As Schiff-base chemistry involving the unprotected molecule only led to polymers, we decided to selectively protect the CHO functions. With this end in view, we decided to convert the aldehyde function to the corresponding 2-cyano-3-acrylate derivative (Scheme 3).[11] Commonly used in oligopyrrole chemistry, this protection is stable in acidic media and therefore appropriated to Schiff-base chemistry. In toluene, reaction of **4** with



Scheme 2.



Scheme 3.

4 equiv of ethyl cyanoacetate in the presence of pyridine afforded the expected diprotected adduct (**5**) in 55% yield.[12] Thus, the remaining carbonyl groups are available for further, unambiguous reactions.

In parallel, we also tested the reactivity of the aldehyde functions by reacting them with ethyl isocyanoacetate. Indeed, it has lately been reported that condensation of ethyl isocyanoacetate with formyl pyrrole conveniently leads to 3-ethoxycarbonylpyrrolo[1,2-*c*]pyrimidine.[13] The latter heterocycles, although rare in nature, are present in variolins, a family of alkaloids isolated from marine sponge *Kirkpatrickia varialosa*, which have antitumor and antiviral activity.[14] Additionally, pyrrolo[1,2-*c*]pyrimidine can be considered as aza analogues of the more common indolizines. Using the experimental procedure described above, the condensation of **4** with ethyl isocyanoacetate afforded the expected symmetrical bis-pyrrolo[1,2-*c*]pyrimidine (**6**) in 59% yield (Scheme 3).

Comparison of the ^{1}H NMR spectra for compounds **5** and **6** revealed striking similarities. Indeed, in both cases, the number of signals, the multiplicity, and the integration are identical. Whereas the chemical shifts are approximately the same, the major difference lies on the singlet that resonates at low field. On one hand, in the case of **5**, it appears as a broad singlet corresponding to the NH signal (Table 1). On the other hand, a sharp signal attributed to the CH located between the nitrogen atoms appears at 10.55 ppm in the case of **6**. However, unambiguous structural determination was established on the basis of ^{13}C and two dimensional NMR spectra.

Definitive structural assignment for **6** was further confirmed by X-ray diffraction analyses.[15] X-ray quality single crystals were obtained from slow evaporation of a dichloromethane solution of **6**. X-ray crystal structure of the yellow plates of **6** reveals two planar pyrrolopyrimidine sub-units linked together by the dicarbonyl linkage. The two carbonyl functions appeared to be almost perpendicular with a dihedral angle nearing 84°. This torsion angle also corresponds to the torsion

Table 1. ^{1}H NMR data for compounds **5** and **6**

	δ/m/I[a]	δ/m/I[a]	δ/m/I[a]	δ/m/I[a]
5	1.09/t/6H	1.40/t/6H	2.44/s/6H	2.64/q/4H
6	1.18/t/6H	1.59/t/6H	2.23/s/6H	2.75/q/4H
5	4.38/q/4H	8.08/s/2H	12.03/br s/2H	
6	4.50/q/4H	8.27/s/2H	10.55/s/2H	

[a] δ/m/I: δ(ppm)/multiplicity/integration.

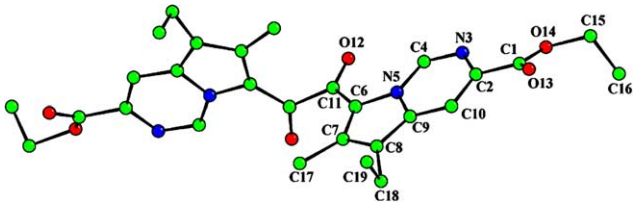


Figure 1.

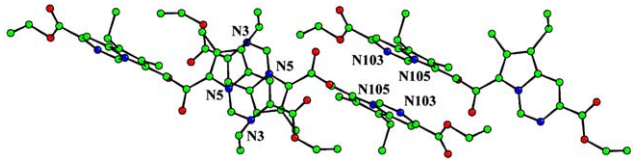


Figure 2.

angle between the two pyrrolopyrimidine moieties as atoms O12–C11–C6 and N5 are coplanar (Fig. 1).

The crystal packing displays supramolecular assemblies resulting from Π-stacking interactions between two adjacent molecules. The pyrrolopyrimidine moieties arrange each other in a cofacial, head-to-tail manner, maximizing the electronic overlapping (Fig. 2). Thus, the spatial arrangement appears as parallel supramolecular chains according to a $P2_1/c$ space group.

In conclusion, we have reported the synthesis of a highly soluble per-alkyl dipyrrolyldiketone. After oxidation and protection of the formyl groups using isocyanoacetate, the corresponding bis-pyrrolopyrimidine was isolated and fully characterized, including by X-ray crystal structure. To the best of our knowledge, this constitutes the first example of a pyrrolopyrimidine crystal structure. Work is currently in progress in our laboratory in order to establish if, taking advantage of the propensity to self assemble, an electron transfer could be evidenced in solution. In parallel, macrocyclic chemistry incorporating these new building blocks is currently under investigation.

Acknowledgements

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12. Typical experimental procedure for the preparation of **5**: Under argon, a 50 mL round-bottom-flask was charged with the diformyl-diketone **4** (100 mg, 0.30 mmol), anhydrous toluene (7 mL), ethyl cyanoacetate (138 mg, 1.2 mmol), and freshly distilled pyridine (12 μL, 0.086 mmol). The reaction mixture was brought to reflux for 12 h. After cooling, the solvent was removed under reduced pressure and the residue was poured on a fritted funnel and washed with petroleum ether. The resulting powder was then dissolved in CH_2Cl_2 and evaporated to dryness affording 90 mg of the expected diprotected dialdehyde **5** in 55% yield.
^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (t, $J = 7.6$ Hz, 6H, CH_2CH_3), 1.40 (t, $J = 7.2$ Hz, 6H, CH_2CH_3), 2.44 (s, 6H, CH_3), 2.64 (q, $J = 7.6$ Hz, 4H, CH_2CH_3), 4.38 (q, $J = 7.2$ Hz, 4H, CH_2CH_3), 8.08 (s, 2H, CH), 12.03 (br s, 2H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 14.2, 16.1, 17.0, 62.6, 98.0, 116.7, 127.9, 131.3, 133.0, 138.2, 138.9, 162.7, 178.8; MS (MALDI-TOF) calcd for $C_{28}H_{30}N_4O_6$: $(M+H)^+$ 519.4. Found 519; Anal Calcd for $C_{28}H_{30}N_4O_6$: C, 64.85; H, 5.83; N, 10.80; Found: C, 64.76; H, 6.31; N, 15.88.
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15. Crystallographic data for **6**: ($C_{28}H_{30}N_4O_6$: M = 518.22), Yellow plate, monoclinic, space group $P2_1/c$, $Z = 4$, $a = 15.865(2)$, $b = 8.878(2)$, $c = 18.552(3)$ Å, $\beta = 95.99(1)°$, $V = 2598.7(7)$ Å^3, ρ calcd = 1.33 g cm^{-3}, $F(000) = 1096$, $\mu = 0.095$ mm^{-1}. A total of 14,726 reflections were measured (range 1–25.5°), 4694 unique ($R_{int} = 0.07$), on a Kappa CCD diffractometer using graphite monochromatized MoK_α radiation ($\lambda = 0.710730$ Å) at 295 K. The structure was refined on F to $R = 0.0808$, $R_w = 0.0890$ (1696 reflections with $I > 2\sigma(I)$), and a goodness of fit = 1.153 for 204 refined parameters. CCDC 243103 contains the supplementary crystallographic data for this paper.