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Efficient synthesis and solid state analysis of 3-(1*H*-pyrrol-2-yl)quinoxalin-2(1*H*)-one and 2-(1*H*-pyrrol-2-yl)-1*H*-benzo[*d*]imidazole from pyrrolo-2-ylglyoxyl acid

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Abstract

The synthesis of new pyrrole-functionalized quinoxalines and benzimidazole is described. Our methodology involves the condensation between 2-oxo-2-(1*H*-pyrrol-2-yl)acetic acid and differently substituted 1,2-phenylene diamines. Depending on the substitution and on the reaction conditions, the synthesis leads to either the pyrrolyl-quinoxaline or -benzimidazole heterocycles. Further insights concerning the structural arrangement of the pyrrolyl-quinoxaline were obtained by solid state analysis, revealing an inverted pyrrole similar to that observed for 2,3-dipyrrolyl quinoxalines. This observation accounts for the fact that strong dipolar interactions or intermolecular H-bonds may govern the structural arrangement in the solid state.

Keywords: Quinoxaline; Benzimidazole; Chromophore; Heterocycles

Due to a large field of interest that ranges from pharmaceutical to material chemistry, the preparation of small heterocycles underwent a renewed interest in the recent years. In particular, quinoxalinone derivatives exhibit a privileged structure for drug design in medicinal chemistry. Indeed, acting as glutamate receptors[1] or serine protease inhibitors,[2] quinoxalin-2-ones were proven active for treating diseases of the central nervous system like Huntington, or Parkinson and Alzheimer diseases. Indole-substituted quinoxalinone was also proven active as vascular endothelial growth factor (VEGF) inhibitor.[3] In parallel, other small heterocycles such as benzimidazoles found applications both in medicinal[4] or material chemistry.[5]

During the course of our study on the development of pyrrole-based anion sensors, we have been interested in the preparation of pyrroles featuring α-linked heterocyclic chromophores that could 'report' on the coordination. Accordingly, we and others synthesized new 2,3-dipyrrolylquinoxalines (DPQ) by reacting 1,2-di(1*H*-pyrrol-2-yl)-ethane-1,2-diones and 1,2-diaminobenzenes.[6] As dipyrrolylquinoxalines displayed interesting anion binding properties, we decided to investigate whether the simultaneous presence of the two pyrrole subunits was an absolute requirement. Indeed, to date, neither solid state nor solution analyses evidenced an 'in–in' conformation (Fig. 1). In this Letter, we report the results we obtained when we carried out the reaction between 2-oxo-2-(1*H*-pyrrol-2-yl)acetic acid **1** and 1,2-diaminobenzene or 4,5-dinitro-1,2-diaminobenzene.

2-Oxo-2-(1*H*-pyrrol-2-yl)acetic acid **1** (Scheme 1) was prepared according to Birchall and Rees's method.[7] At −70 °C, pyrrole was reacted with 1 equiv of oxalyl chloride

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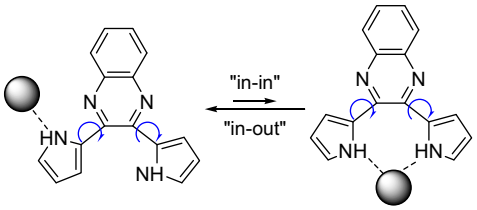


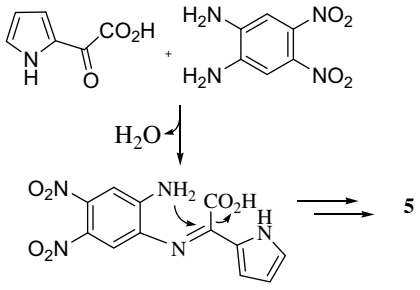
Fig. 1. Anion binding by DPQ: two possible conformations.

in dry diethyl ether. After usual work up, **1** was isolated in 70% yield. The following condensation between **1** and 1,2-diaminobenzene appeared very solvent dependant. Indeed, in ethanol—a solvent commonly used for Schiff-base type condensations—the expected 3-(1*H*-pyrrol-2-yl)quinoxalin-2(1*H*)-one **2** was isolated in poor yield (<15%) even in the presence of a dehydrating agent. By contrast, in refluxing toluene and in the presence of catalytic amounts of TFA,[8] we were able to isolate **2** in 62% yield.[9] Interestingly, when 4,5-dinitro-1,2-diaminobenzene was used instead of 1,2-phenylenediamine, the aforementioned conditions were not suitable anymore as the expected quinoxalinone **3** was isolated in less than 2% yield! Consequently, we re-investigated the experimental conditions for the preparation of **3**, and found out that reacting 3 equiv of 4,5-dinitro-1,2-diaminobenzene with 1 equiv of oxo-acid **1** in refluxing acetic acid for 7 days afforded **3** in 38% yield (see Table 1).[10]

On the other hand, further investigations concerning the outcomes of the condensation between **1** and 4,5-dinitro-1,2-diaminobenzene in refluxing toluene in the presence of a catalytic amount of TFA, revealed that the unexpected 2-(1*H*-pyrrol-2-yl)-1*H*-benzo[*d*]imidazole **5** was formed in 18% yield, as the major product.[11] Interestingly, the unsubstituted benzimidazole **4** was never observed, even in refluxing acetic acid.

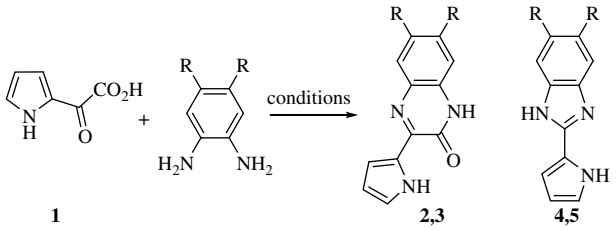
A possible explanation for the formation of **5** involves the primary attack of one amino-group on the 'activated' keto-carbonyl leading to an imine-intermediate. The electrophilic imine carbon atom is then intra-molecularly trapped by the second amine. Following, in the drastic oxidizing conditions used here, the resulting 2,3-dihydrobenzimidazole is readily oxidized to the corresponding 2-pyrrolo-benzimidazole **5** upon decarboxylation.

Information concerning the structural arrangement of the quinoxalinone in the solid state was obtained by single



Scheme 1. Proposed mechanism for the formation of **5**.

Table 1
Access to the quinoxalinone or benzimidazole derivatives



1 **2,3** **4,5**

Entry	R	Conditions	Product (yield)[a]	Product (yield)[a]
1	H	PhMe/$TFA_{cat.}$	**2** (62%)	**4** (0%)
2	NO_2	PhMe/$TFA_{cat.}$	**3** (2%)	**5** (18%)
3	NO_2	AcOH	**3** (38%)	**5** (0%)

[a] Yields refer to those of pure isolated products characterized by spectroscopic methods.

crystal diffraction analyses of **2** grown by slow evaporation of a dichloromethane solution.[12] The structure belongs to the $P\bar{1}$ space group and is almost planar with a torsion angle (N4–C3–C22–N21) of 11.4°. In the solid state, **2** displays the amide tautomeric form with a C2–O1 bond distance of 1.24 Å (Fig. 2a). As it has already been observed for dipyrrolylquinoxaline (DPQ),[13] the structure reveals an inverted pyrrole with the NH pointing toward the quinoxalinone nitrogen N4. This observation confirms that in the solid state, the steric hindrance resulting from the close proximity of the two pyrrole rings in DPQs is not responsible for this unexpected conformation. Conversely, this observation accounts for dipolar interactions in the solid state as no intramolecular N21···H···N4 hydrogen bond is evidenced presently. The supramolecular assembly of quinoxalinone **2** reveals an interesting arrangement with two adjacent, antiparallel quinoxalinones distanced of 3.35 Å (C2–C3–C9–C10–N1–N2, Fig. 2b). In addition to intermolecular π stacking interactions, the stability of the supramolecular assembly is also insured by an efficient H-bond network between the amide oxygen O1 of one quinoxalinone and the pyrrolic NH of a neighbor. The distance between O1 and N21 was measured at 2.95 Å (Fig. 2b).

As simple DPQ were proven efficient anion sensors in organic medium, we have also been interested in evaluating the anion binding properties of the monopyrrole analogue **2**. Unfortunately, both UV–vis and NMR titrations of **2** with halides revealed the absence of noticeable affinities of **2** for anions. This result surprised us as the presence of the carbonyl group was expected to enhance the H-bond donor character of the pyrrole NH. Thus, this result confirms that while not acting in an intramolecular, synergetic way, the presence of the two pyrroles in DPQ-like systems constitutes a requirement for the observation of good anion binding affinities.[14]

In conclusion, we have demonstrated that pyrrolo-quinoxalinone–DPQ mono-pyrrole analogues—can be prepared by condensating 2-oxo-2-(1*H*-pyrrol-2-yl)acetic acid **1** with 1,2-phenylenediamine. Depending on the

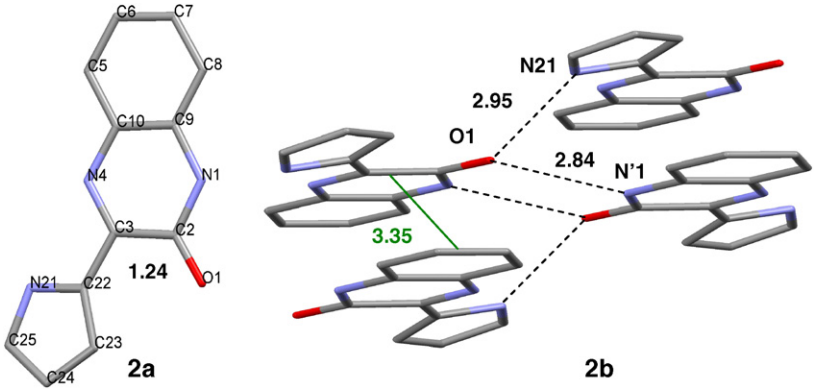


Fig. 2. Top and side view of **2**. Dashed lines indicate hydrogen bonding interactions.

experimental conditions and on the substitution of the aromatic diamine, the biologically relevant 2-pyrrolo-benzimidazole could also be isolated at the expense of the expected quinoxalinone. The X-ray crystal structure of the quinoxalinone revealed a flat conformation with an inverted pyrrole similar to what was observed for DPQ. However, by contrast with DPQ, quinoxalinone **2** did not display any anion binding affinity. Further work is currently in progress in our Laboratory for generalizing our synthetic approach and in bringing more insights in the coordinating properties of the newly prepared heterocycles.

Acknowledgement

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9. *Experimental procedure for the preparation of* **2**: Under nitrogen, a 100 mL round bottom flask equipped with a stir bar, a nitrogen inlet and a Dean–Stark assembly, was charged with the keto acid **1** (2 mmol, 278 mg), 1,2-diaminobenzene (2 mmol, 217 mg) and 20 mL of dry toluene. The mixture was brought to reflux and heated for 4 h in the presence of a catalytic amount of trifluoroacetic acid (10%). After removing the solvent in vacuo, the residue was taken in CH_2Cl_2 (50 mL) and washed with $NaHCO_3$ aq The organic layer was separated and washed with water and brine. After drying over anhydrous Na_2SO_4, the solution was filtered and evaporated to dryness. The residue was purified by silica gel column chromatography using CH_2Cl_2/cyclohexane: 9/1 as eluent. The expected quinoxalinone **2** (261 mg) was isolated in 62% yield.
^{1}H NMR (400 MHz, DMSO-d_6) δ 6.24 (m, 1H, H_{pyr}), 7.06 (m, 1H, H_{pyr}), 7.29 (d, $J = 7.3$ Hz, 2H, H_{Ar}), 7.42 (m, 2H, $H_{Ar} + H_{pyr}$), 7.72 (d, $J = 8.3$ Hz, 1H, H_{Ar}), 11.68 (s, 1H, HOH or NH), 12.47 (s, 1H, HOH or NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 109.8, 115.0, 115.8, 123.4, 123.6, 127.2, 128.1, 128.2, 130.7, 132.2, 146.4, 153.7. HRMS (MALDI-Tof): calcd for $C_{12}H_9N_3O$ $[M]^+$ 211.0740; found 211.0837.
10. Structural characterization of **3**: ^{1}H NMR (400 MHz, DMSO-d^6) δ 6.35 (m, 1H, H_{pyr}), 7.27 (m, 1H, H_{pyr}), 7.62 (m, 1H, H_{pyr}), 7.86 (s, 1H, H_{Ar}), 8.28 (s, 1H, H_{Ar}), 11.98 (s, 1H, HOH), 13.08 (s, 1H; HNH); ^{13}C NMR (100 MHz, DMSO-d_6) 112.2, 113.3, 120.4, 124.8, 128.0, 128.6, 134.9; 135.1, 138.1, 140.8, 150.5, 154.3; HRMS (EI): calcd for $C_{12}H_7N_5O_5$ $[M]^{+\cdot}$ 301.0447; found 301.0446.
11. **5** was prepared according to the aforementioned methodology. The expected benzimidazole was isolated in 18% yield after 7 days reflux. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.34 (m, 1H, H_{pyr}), 7.11 (m, 2H, H_{pyr}), 8.30 (s, 2H, H_{Ar}), 12.20 (s, 1H, HNH), 13.73 (s, 1H, HNH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 111.1, 113.2, 121.8, 124.9, 138.8, 154.3; HRMS (ESI): calcd For $C_{11}H_8N_5O_4$ $[M+H]^+$ 274.0570; found 274.0572.
12. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC-668342. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).
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14. Similarly, it was also demonstrated (see Ref. 6c) that a SEM monoprotected DPQ does not bind anion effectively.