2-Amino-3,4-diethylpyrrole derivatives: New building blocks for coiled structures†

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The synthesis of a multicomponent, mixed oligomer containing α-aminopyrrole is described; this system adopts a coiled structure in the solid state and serves as a prototype of a possible new class of hydrogen bond based helicates.

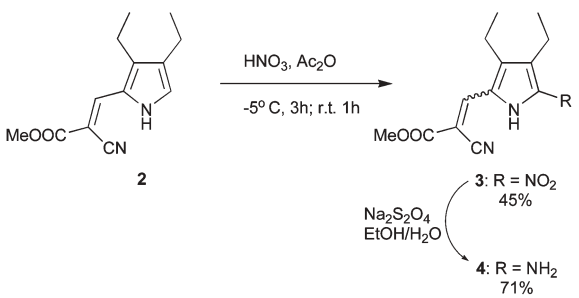
The design and synthesis of molecules and organized assemblies with controlled geometries represents a current challenge in supramolecular chemistry.[1] One of the more powerful approaches to achieving such structures involves the use of inter- and intramolecular hydrogen bond interactions. Examples of systems constructed in this manner run the gamut from modified nucleobases assembled in metal-free G-quartets[2] to DNA-mimicking helical superstructures,[3] with particular focus being devoted to the generation of topographically nonplanar entities, such as foldamers,[4] rotaxanes, catenanes, pretzelanes, and knots.[5] We have contributed to this area with several biimidazole- and oligopyrrole-carbonyl based systems, chemistry that has also been developed in a different fashion by the group of Gale.[6] In this paper, we describe the synthesis of a new oligopyrrole amide system (**1**) that is based on the use of an α-aminopyrrole. This open-chain system adopts a coiled conformation in the solid state.

The synthesis of **1** is predicated on the availability of a functionalized α-aminopyrrole precursor. α-Aminopyrroles are not, however, readily available precursors.[7] The very few literature reports of α-aminopyrroles involve systems that contain electron-withdrawing groups in the β-pyrrolic positions and/or 1-*N*-pyrrole substitution.[8–10] To the best of our knowledge, there are no reports of α-amino derivatives of more electron-rich pyrrole moieties. However, such species would represent potentially important building blocks for the synthesis of a wide-range of *meso*-aza macrocycles, as well as variety of aza-linked open-chain receptor systems.[11] Thus, a major goal of this work was to develop the chemistry of such α-aminopyrroles.

There are two main routes to α-aminopyrroles reported in the literature. The first involves the synthesis of an α-nitropyrrole derivative, followed by hydrogen or Clemmensen-type reduction,[9] while the second involves building up the pyrrole-ring from appropriate building blocks.[8,10] In both cases the resulting α-aminopyrroles contained electron-withdrawing groups in the β-pyrrolic positions, as noted above. Because it is potentially more versatile, we elected to study further the first of these strategies. In particular, we sought to find reduction conditions that would allow us to isolate α-aminopyrroles that contained solubilizing alkyl substituents in the β-pyrrolic positions, even though such species were recognized as being potentially unstable.

A number of literature-inspired[9] procedures were tested using the carbonyl-protected 3,4-diethyl-2-nitropyrrole **3** (Scheme 1), which was obtained, as two inseparable isomers (see ESI†), by nitrating the corresponding α-free species **2**. None of these yielded the desired aminopyrrole product **4**. Either no evidence of reaction was observed (hydrogenation over Pd/C up to 500 psi) or extensive decomposition was seen (Clemmensen-type reductions). By contrast, the use of milder reduction conditions (ethanolic solution of sodium dithionite) in combination with a quick work-up, yielded the desired product (**4**), as two isomers, in moderate to high yield (Scheme 1). It is to be noted that, as expected, this α-amino pyrrole derivative proved rather unstable; it was found to decompose in air within 15 minutes of its isolation. However, compound **4** proved significantly more stable than various other α-aminopyrroles having alkyl substituents in the β-pyrrolic positions;[12] indeed it proved possible to store it for extended periods (5 days) at low temperatures (4 °C) in the absence of oxygen, after which appreciable decomposition was observed.

Structural proof for the α-aminopyrrole **4** came from a single crystal X-ray analysis, obtained by slow evaporation of a dichloromethane solution of **4** maintained under an inert atmosphere.‡ To the best of our knowledge, this represents the first solid-state structure determined for an aminopyrrole. As shown in Fig. 1, compound **4** forms hydrogen bonded ribbons in the solid state that are held together by two NH···O hydrogen bonds (N1H···O1, 3.11 Å, 136°; N2H···O1, 2.81 Å, 157°).



Scheme 1 Synthesis of α-nitro- and α-aminopyrrole derivatives **3** and **4**, respectively.

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† Electronic supplementary information (ESI) available: Synthetic details and full X-ray data. See DOI: 10.1039/b602956f

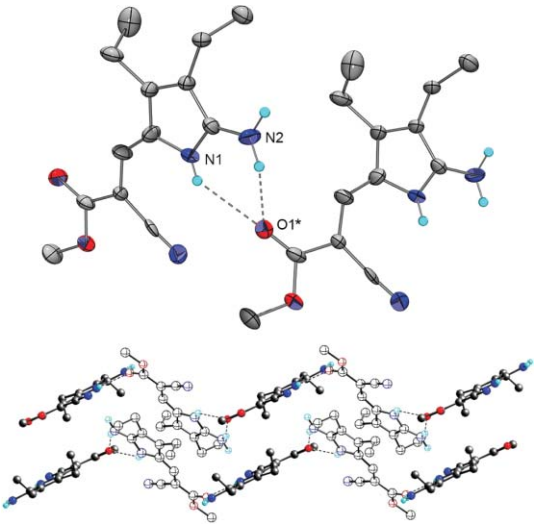
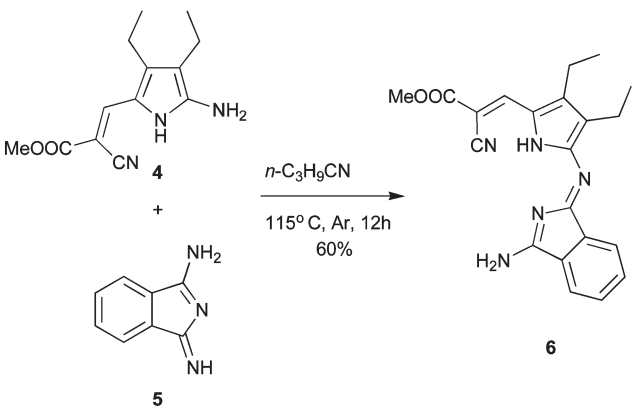


Fig. 1 ORTEP-PovRay rendered view of the solid-state structure of **4** as determined from single crystal X-ray diffraction analysis. The atom O1* is at equivalent position (x, ½ − y, ½ + z). All hydrogen atoms, except those present on the amino and pyrrolic nitrogen atoms have been removed for clarity. The displacement ellipsoids for the non-hydrogen atoms are scaled to the 50% probability level.

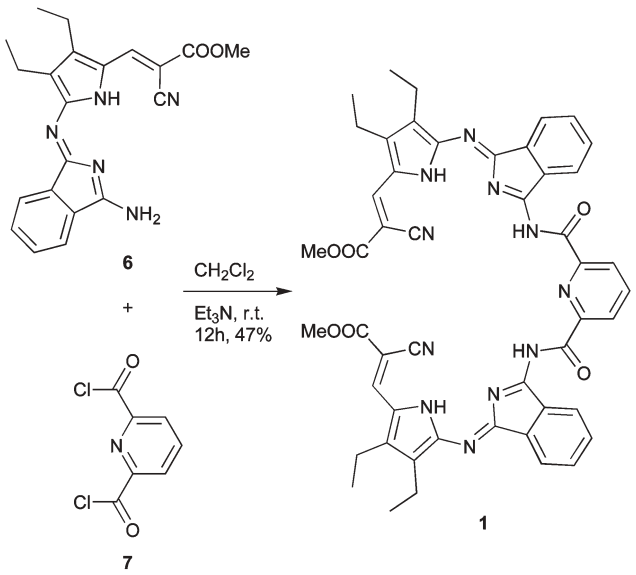
Once the α-aminopyrrole **4** was in hand, it was reacted with commercially available 1,3-diiminoisoindoline, **5**. The reaction was performed in *n*-butyronitrile heated to reflux (temp. = 117 °C) under an argon atmosphere. It was observed that the use of higher boiling solvents, and hence higher reaction temperatures led to the formation of phthalocyanine. Chromatographic workup of the reaction mixtures (silica gel, eluent: 2% MeOH in CH_2Cl_2) led to the isolation of the monopyrrolyl-isoindoline derivative **6** in 60% yield (Scheme 2).

The target compound **1** was synthesized by subjecting a dry CH_2Cl_2 solution of monopyrrolyl-isoindoline, **6**, to reaction with pyridine-2,6-dicarbonyl dichloride, **7**, in the presence of Et_3N; Scheme 3. The reaction was allowed to stir at room temperature for a period of 12 h. After workup, purification was effected by column chromatography over alumina using 1% MeOH in CH_2Cl_2 as the eluent; this afforded compound **1** in 47% yield.

Structural proof for compound **1** came from a single crystal X-ray analysis, as depicted in Fig. 2. The crystal structure of **1**



Scheme 2 Synthesis of monopyrrolyl-isoindoline, **6**.



Scheme 3 Synthesis of compound **1**.

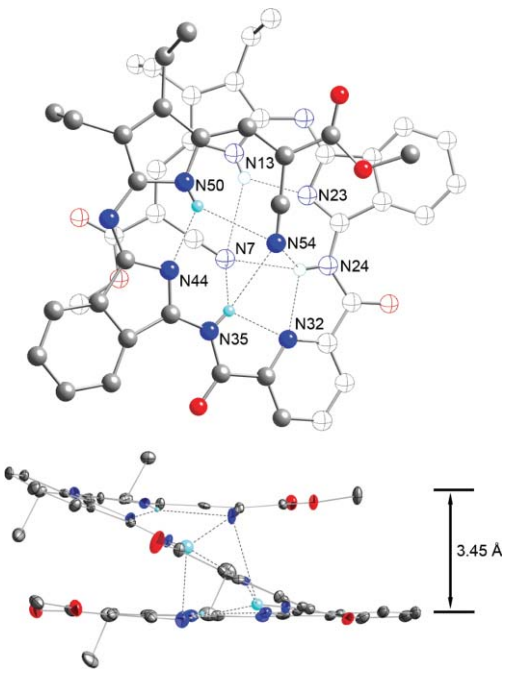


Fig. 2 CrystalMaker rendered top and side views of the X-ray structure of **1**. All hydrogen atoms except those on the pyrrolic and amide nitrogen atoms have been removed for clarity. The displacement ellipsoids for the non-hydrogen atoms are scaled to the 50% probability level.

reveals a helical arrangement in the solid state, with a pitch of 3.45 Å between the two pyrrole moieties.§ In the unit cell, both enantiomers (*M* and *P*) are present. There are no intermolecular interactions between individual molecules, as judged by the extent of separation. The helical structure is stabilized by ten intramolecular hydrogen bond interactions. Of the ten hydrogen bonds present, four are bifurcated, being formed between the pyrrole NH hydrogen atoms and the N atoms in position 2 of the isoindoline moieties (imine nitrogens), and within the nitrile moiety

(N13H···N7, 3.30 Å, 143°; N13H···N23, 2.63 Å, 129°, and N50H···N44, 2.67 Å, 128°; N50···N54, 3.26 Å, 143°).

The other six hydrogen bonds that are formed consist of two sets of trifurcated hydrogen bonds that rely on the amide NH hydrogen atoms as the hydrogen bond donor atoms. The counterparts in these interactions are the N atoms of both nitrile functionalities, as well as the pyridine nitrogen atom. These trifurcated interactions may be described using the following parameters: for the N24H amide hydrogen atom: N24H···N7, 3.29 Å, 157°; N24H···N32, 2.68 Å, 109°; N24H···N54, 3.34 Å, 107°, and for the N35H amide hydrogen atom: N35H···N7, 3.24 Å, 123°; N35H···N32, 2.69 Å, 111°; N35H···N54, 3.37 Å, 145°.

The solution phase structure of **1** is still being studied in detail. However, based on the upfield shifts for the OMe protons (2.85 ppm in **1** *vs.* 3.76–3.94 ppm in **3**, **4** and **6**), we believe that the open-chain system **1** adopts a folded, coil-like conformation in $CDCl_3$.

In summary, 2-amino-3,4-diethylpyrrole (**4**) provides a new, and potentially useful building block for the construction of more elaborate molecular architectures, including the open-chain systems described in this initial report. The ability of the latter to adopt coil-like conformations stabilized by multiple hydrogen bond interactions leads to the consideration that they could have a role to play as molecular receptors for appropriately targeted substrates. Systems such as coil **1** are also of interest because their 3-dimensional structure could be made to vary as a function of environment (*e.g.*, dissolving in competitive H-bonding solvents *vs.* isolating neat in the solid state). To the extent this proves true, it could provide a means for effecting molecular switching. Further studies of **4** and its derivatives, including a detailed analysis of the properties of **1** in solution, are currently ongoing in our laboratory.

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Notes and references

‡ For compound **4**, the data were collected on a Nonius Kappa CCD diffractometer using a graphite monochromator with MoKα radiation. Standard procedures were followed. Crystal data: $C_{13}H_{17}N_3O_2$, M_r = 247.30, T = 153(2) K, monoclinic, space group $P2_1/c$, a = 10.5504(10), b = 9.0899(8), c = 13.5949(14) Å, β = 96.867(4), V = 1294.4(2) Å^3, ρ_{calc} = 1.269 Mg m^{-3}, μ = 0.088 mm^{-1}, Z = 4, reflections collected: 3999, independent reflections: 2273 (R_{int} = 0.0875), final R indices [$I > 2\sigma(I)$]: $R1$ = 0.1189, w$R2$ = 0.1647, R indices (all data): $R1$ = 0.1945, w$R2$ = 0.1888. CCDC 299138. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b602956f

§ The same data collection and analysis procedures were used for compound **1** as were for **4**. Crystal data: $C_{49}H_{43}N_{11}O_6$, M_r = 881.94, T = 153(2) K, triclinic, space group $P\bar{1}$, a = 12.7239(4), b = 13.6559(5), c = 15.0447(7) Å, α = 65.588(2), β = 69.964(2), γ = 67.954(2)°, V = 2151.24(14) Å^3, ρ_{calc} = 1.362 Mg m^{-3}, μ = 0.093 mm^{-1}, Z = 2, reflections collected: 28488, independent reflections: 7477 (R_{int} = 0.157), final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0621, w$R2$ = 0.1211, R indices (all data): $R1$ = 0.1187, w$R2$ = 0.1466. CCDC 299137. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b602956f

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