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4-Alkoxy- and 4-Amino-2,2′-bipyrrole Synthesis

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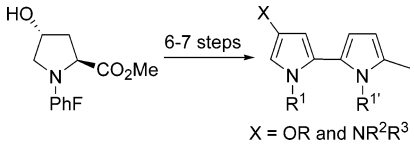
ABSTRACT



4-Alkoxy-2,2′-bipyrroles and the first examples of 4-amino-2,2′-bipyrroles have been synthesized by a diversity-oriented strategy from 4-hydroxyproline. The bipyrrole products offer interesting potential as building blocks for making pyrrole products, as demonstrated by the first synthesis of an amino prodigiosin analogue.

2,2′-Bipyrrole structures are components of natural products such as the prodigiosins,[1,2] streptorubin B and the tambjamines (Figure 1). Encompassed in expanded porphyrins[3,4]

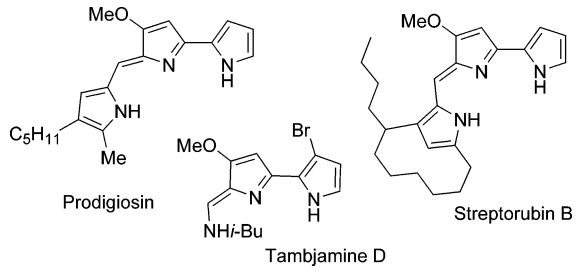


Figure 1. Representative natural products containing 2,2′-bipyrrole.

and conductive materials,[5,6] bipyrroles have served in a wide range of applications.

Among the synthetic routes that have been reported for making bipyrrole, few strategies have been diversity-oriented.[7−17] For example, toward achieving the first prodigiosin synthesis,[7] Rapoport introduced the construction of a series of bipyrroles by condensation of substituted pyrrole and Δ^1-pyrroline precursors, followed by dehydrogenation. Focused on the synthesis of the key 4-methoxy-2,2′-bipyrrole-5-carboxaldehyde intermediate employed in this

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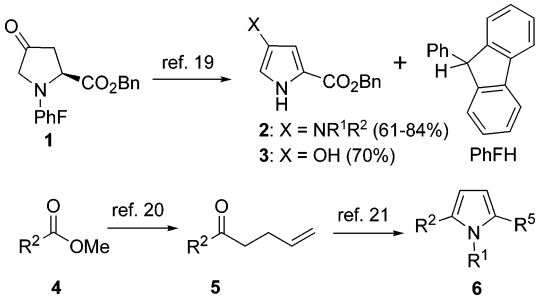
prodigiosin synthesis, four strategies were later achieved featuring intramolecular Pd(II)-promoted 2,2′-diary1 coupling,[9] amination of a vicinal tricarbonyl intermediate,[10] intermolecular oxidative coupling of pyrrole and pyrrole-2-carboxylate precursors with singlet oxygen,[15] and Pd-catalyzed cross-coupling of bromopyrrole and pyrrole boronate starting materials.[17] In addition, symmetrical 2,2′-bipyrroles have recently been prepared using hypervalent iodine(III)-induced oxidative couplings of 3-alkyl- and 3-arylpyrroles.[16]

Methology for enhancing the diversity of bipyrrole units is desired to further structure−activity relationship studies of interesting pyrrole products. For example, elaborating the B-ring methoxy group to provide other ethers has improved the therapeutic potential of certain prodigiosin analogues.[18] Moreover, to the best of our knowledge, the chemistry of 4-amino-2,2′-bipyrroles has yet to be explored.

In our earlier explorations of new methodology for pyrrole synthesis, 4-aminopyrrole-2-carboxylates **2** were found to be effectively prepared by reacting 4-oxo-*N*-(PhF)prolinate **1** with an amine and catalytic acid at 50 °C in a polar solvent [PhF = 9-(9-phenylfluorenyl)].[19] 4-Hydroxypyrrole-2-carboxylate **3** was similarly made on treatment of 4-oxoprolinate **1** with aqueous ammonium hydroxide and *p*-TsOH in THF (Scheme 1).[19] In addition, 1,2,5-trisubstituted pyrroles **6** were

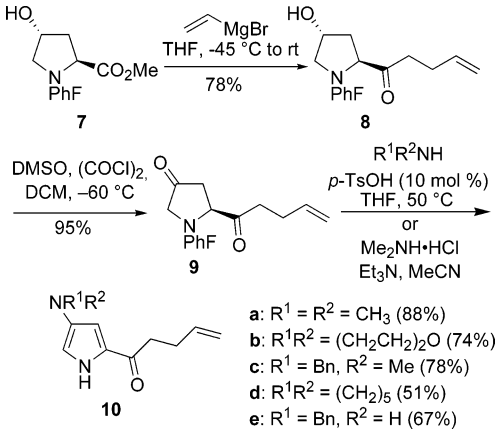
Scheme 1. Prior Methodology for Pyrrole Synthesis



prepared by a practical three-step protocol featuring the synthesis of homoallylic ketone **5** by exposure of methyl ester **4** to excess of vinylmagnesium bromide in the presence of a catalytic amount of a copper salt (Scheme 1),[20] followed by olefin oxidation and Paal-Knorr condensation.[21] Novel syntheses of 4-alkoxy- and 4-amino-2,2′-bipyrroles have now been developed using strategies that combine elements of these past methods for substituted pyrrole synthesis.

4-Alkoxy- and 4-amino-2,2′-bipyrroles were synthesized from 4-hydroxyproline as an inexpensive starting material.[22] As reported, homoallylic ketone **8** was prepared in 78% yield from 4-hydroxy-*N*-(PhF)prolinate **7** by the addition of freshly prepared vinylmagnesium bromide in THF (Scheme 2).[20]

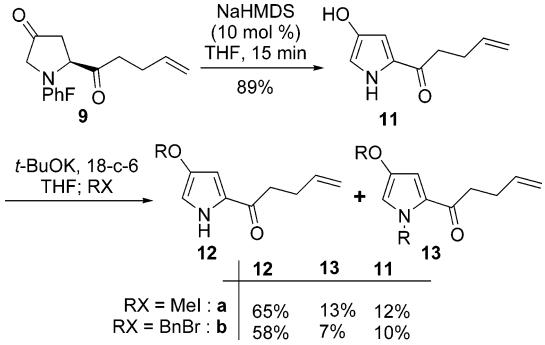
Scheme 2. Synthesis of 2-Acyl-4-aminopyrroles **10**



Oxidation of alcohol **8** was performed using oxalyl chloride and dimethyl sulfoxide to furnish 4-oxopyrrolidine **9** in 95% yield after purification by column chromatography.[23] 2-Acyl-4-aminopyrroles **10b**−**e** were prepared under similar conditions previously used to make amino pyrrole-2-carboxylates **2**. Treatment of 4-oxopyrrolidine **9** with a primary or secondary amine in the presence of a catalytic amount of *p*-toluenesulfonic acid in warm THF caused elimination of 9-phenylfluorene (PhFH) and formation of the desired pyrroles **10b**−**e** in 51−78% yields. In the case of 4-dimethylaminopyrrole **10a**, Et_3N (110 mol %) was used to partially neutralize dimethylamine hydrochloride (300 mol %) in acetonitrile prior to reaction with ketone **9**.

Alternatively, 2-acyl-4-hydroxypyrrole **11** was prepared in 89% yield by exposure of ketone **9** with a catalytic amount of sodium bis(trimethylsilyl)amide (10 mol %) in THF for 15 min (Scheme 3). *O*-Alkylation of 4-hydroxypyrrole **11**

Scheme 3. Synthesis of 2-Acyl-4-alkoxypyrroles **12**



was accomplished by deprotonation with potassium *tert*-butoxide followed by the addition of methyliodide or

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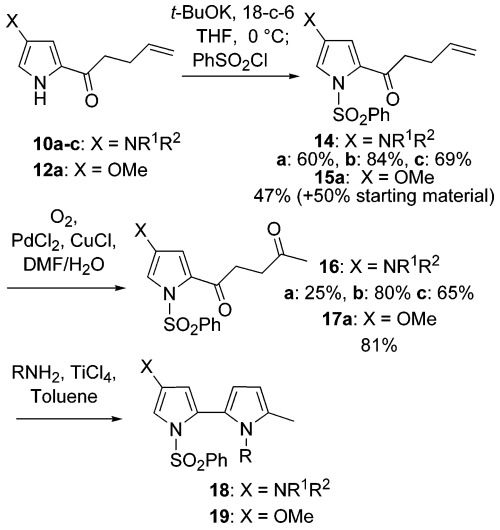
benzylbromide in, respectively, 65% and 58% yield. Under these conditions, some *N*- and *O*-bisalkylated side product **13** was also obtained together with starting material (Scheme 3).

Attempts to oxidize olefins **10a**−**e** using the Tsuji−Wacker protocol (O_2, $PdCl_2$, CuCl),[24] ozonolysis, and OsO_4/$NaIO_4$ conditions[25] all led to decomposition of the electron-rich pyrrole ring. The protection of pyrroles **10** and **12** with an electron-withdrawing group was pursued to reduce nucleophilicity;[26] however, moderate electron-withdrawing groups, such as Boc at the 1-position and a carboxylate at the 2-position, failed to prevent pyrrole decomposition during Tsuji−Wacker oxidation. Protection of the nitrogen of pyrroles **10a**−**c** and **12a** as the corresponding phenylsulfonamides **14a**−**c** and **15a** was achieved by reacting the pyrrolyl anion, formed with potassium *tert*-butoxide, with phenylsulfonyl chloride in THF. The influence of the sulfonamide on the electron density of the aromatic ring was indicated by comparison of the ^{1}H NMR spectra of pyrroles **10b** and **14b** in which the chemical shifts of the ring protons at 6.60 and 6.55 ppm were deshielded, respectively, on sulfonylation to 7.20 and 6.75 ppm.

In the case of 4-dimethylaminopyrrole **10a**, besides the desired sulfonamide **14a** (60% yield), the corresponding 2-phenylsulfonylpyrrole was isolated as a side product in 8% yield. With sulfonamide protected pyrroles **14a**−**c** and **15a** in hand, the Tsuji−Wacker oxidation protocol performed effectively to convert the homoallylic ketones into 1,4-diones **16a**−**c** and **17a** in yields of 25−81% after purification by column chromatography (Scheme 4).

Scheme 4. Synthesis of 2,2′-Bipyrroles **18** and **19**



In the Paal−Knorr annulation, 1,4-diones **16a**−**c** and **17a** failed to react under a variety of condensation conditions, presumably due to the influence of the relatively electron-deficient aromatic ring on the neighboring carbonyl group.[8] By employing a modification of the Paal−Knorr condensation that had been used to make sterically crowded 1,2,5-trisubstituted pyrroles,[8,27] annulation was achieved by exposing 1,4-diketones **16b**−**c** and **17a** to primary amines in the presence of stoichiometric $TiCl_4$ (Scheme 4). Ammonia failed to react with 1,4-diketone **16b** under similar conditions; however, aniline reacted with **17a** to give bipyrrole **19a** in 94% yield. Using the same conditions, 2-(*p*-nitrophenyl)-ethylamine and 2-(phenylthio)ethylamine gave incomplete conversion to bipyrroles **18c** and **19b**, respectively, and significant amounts (>50%) of starting material were recovered. Using this Paal−Knorr condensation protocol, six examples of 4-amino-2,2′-bipyrroles **18a**−**f** and two different 4-methoxy-2,2′-bipyrroles **19a**,**b** were prepared in 33−94% yields after purification by chromatography over silica gel (Figure 2).

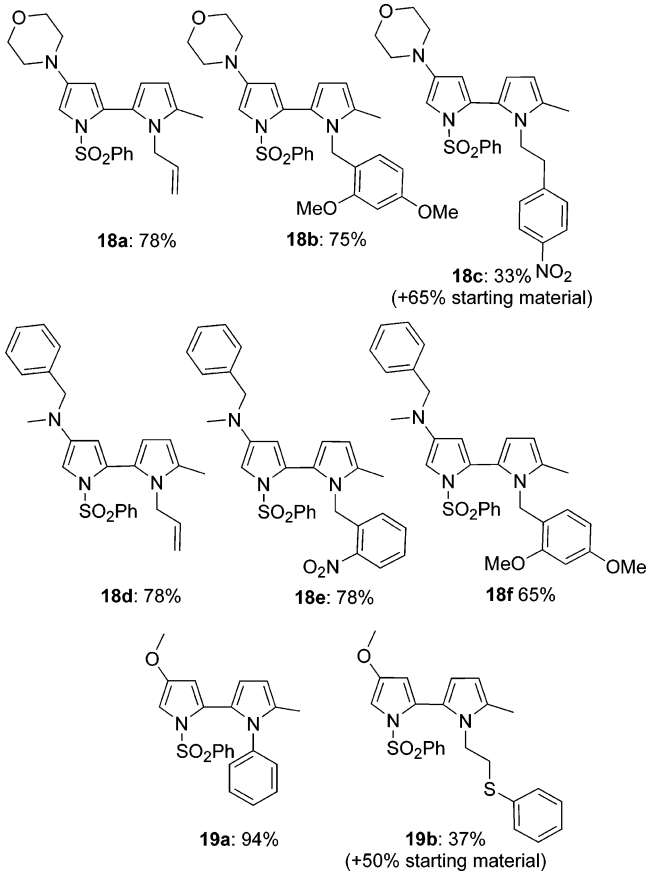


Figure 2. 4-Amino- and 4-methoxy-2,2′-bipyrroles **18** and **19**.

Finally, to demonstrate the utility of the bipyrrole products, 4-morpholino-2,2′-bipyrrole **18a** was employed in the first synthesis of a 4-aminoprodigiosin analogue (Scheme 5). Removal of the sulfonamide from aminobipyrrole **18a** was

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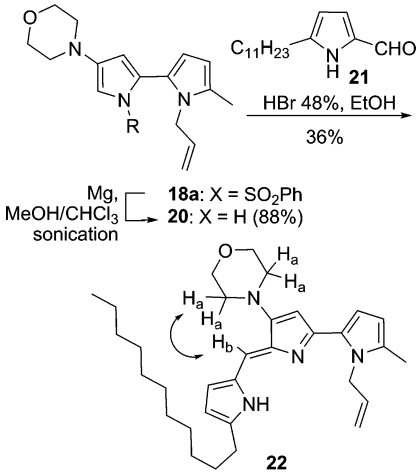
Scheme 5. Synthesis and Conformational Analysis of 4-Morpholinoprodigiosin **22** (double tipped arrows indicate characteristic observed NOE)



more difficult than anticipated, and many previously reported conditions for desulfonylation were unsuccessful.[28−38] Deprotection of sulfonamido bipyrrole **18a** was successfully achieved using magnesium turnings in a methanol/chloroform (99:1) mixture under ultrasonic irradiation for 5 min to provide bipyrrole **20**.[26] 2-Undecylpyrrole-5-carboxaldehyde **21** was prepared by formylation[39] of 2-undecylpyrrole.[40] The condensation of pyrrole aldehyde **21** with bipyrrole **20** was performed in EtOH on addition of a catalytic quantity of 48% aq HBr. The red pigment 4-morpholinoprodigiosin **22** was separated from unreacted formylpyrrole **21** by preparative HPLC and isolated as its TFA salt in 36% yield. Saturation of the upfield signals for the morpholine methylene protons (H_a) caused NOE enhancement of the dipyrrolomethene proton signal (H_b) indicative of their close proximity in the β-conformer in $CDCl_3$ (Scheme 5).

4-Hydroxyproline was used as precursor for making a set of 1,1′-disubstituted 4-alkoxy- and 4-amino-2,2′-bipyrroles. Among these first examples of 4-amino-2,2′-bipyrroles, morpholino adduct **18a** was also used to prepare the first 4-aminoprodigiosin **22**. Considering the power of this method for providing bipyrroles with varying ring substituents and the growing use of such intermediates for the synthesis of natural products and pyrrole analogues exhibiting interesting activity, this approach should be of general interest and utility for the community engaged in medicinal chemistry and material science.

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Supporting Information Available: Experimental details and spectroscopic characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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