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Gram-Scale Synthesis of a Bench-Stable 5,5''-Unsubstituted Terpyrrole

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Abstract

The controlled preparation of higher order oligopyrrolic species holds broad utility across the chemical and material sciences. Here, we describe the gram-scale synthesis of a bench-stable 5,5''-unsubstituted terpyrrole in excellent yield via a tandem Suzuki cross-coupling with *in situ* deprotection. The solution and solid-state stability as well as UV-vis, fluorescence, and single crystal X-ray diffraction structure are also detailed.

Graphical Abstract

The development of synthetic procedures that allow for the economic preparation of α,α' -linked pyrroles in an efficient and scalable manner continues to attract attention.^{1–5} To date, numerous routes toward β -functionalized and relatively stable bipyrroles⁶ as well as quaterpyrroles^{7,8} have been described. However, synthetic methods for the preparation of terpyrroles remain limited (Figure 1). The first workable approach to such species was detailed by Rapaport and co-workers and involved an acid catalyzed trimerization of pyrrole followed by Pd/C-catalyzed dehydrogenation.⁹ Following this, LeGeoff and co-workers,¹⁰ Meijer and co-workers,¹¹ and Sessler and co-workers¹² subjected 1,4-diketo precursors to Paal-Knorr conditions thus defining creation of the central pyrrole as the key synthetic step. More recently, Carretero and co-workers have implemented a 1,3-dipolar cycloaddition for the iterative construction of pyrrole subunits. Though elegant in nature, these and other

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ASSOCIATED CONTENT

Supporting Information

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¹H and ¹³C NMR characterization data of compound **1**, ¹H NMR stability studies and data, X-ray crystal data of compound **1**, as well as synthetic procedural notes and references (PDF)

Crystal structure of compound **1** (CIF)

routes¹³ suffer from poor to moderate overall yields. Moreover, they often require a pyrrole nitrogen protecting group or capping of the terminal α -position. They also suffer from long step counts and produce 5,5''-unsubstituted terpyrrole products that lack appreciable stability. We have therefore devoted effort toward the development of new methodologies that allow access to stable terpyrrole derivatives. Here, we present the gram-scale synthesis of a 5,5''-unsubstituted terpyrrole via a tandem Suzuki coupling protocol with *in situ* deprotection. The approach detailed here relies on commercially available and easily prepared precursors.

The ability of carbalkoxy substituents to attenuate the reactivity of pyrrole is well appreciated in building complex pyrrole-based structures.^{14–18} We thus postulated that incorporating β -ethyl ester functionalities into the central pyrrole would improve the stability of the resulting terpyrrole. Gratifyingly, the tandem Suzuki cross-coupling of an easily prepared dibromo pyrrole (**2**)¹⁹ with commercially available *N*-Boc-pyrrole-2-boronic acid (**3**, 2.4 equiv) furnished terpyrrole (**1**) in 92% yield on a greater than 5-g scale after purification. As shown in Scheme 1, the reaction conditions involved the use of PdCl₂(PPh₃)₂ (20 mol %) as the catalyst, K₂CO₃ (5 equiv) as a base, and a *N,N*-dimethylformamide/ H₂O mixture (5:1, v/v) as solvent with heating to 120 °C for 5 h.^{20,21}

The stability of the new 5,5''-unsubstituted terpyrrole species allowed single crystals suitable for X-ray diffraction analysis grown from slow evaporation of dichloromethane/hexanes (1:1, v/v).²² The resulting structure proved analogous to previously reported structurally characterized terpyrroles, as well as those analyzed by means of calculations.^{2,23–27} Specifically, compound **1** adopts an alternating planar—antiperiplanar—antiperiplanar conformation in the solid state (Figure 2). In the case of **1**, the β -carbethoxy groups are involved in hydrogen-bonding interactions with the pyrrole NH protons, as inferred from the NH to adjacent carbonyl bond distance of 1.98(3) Å (N₁–H to O) and 2.21(3) Å (N₂–H to O) (Figures S5 and S6).²⁸ As a result, the terminal pyrrole subunits are twisted relative to the central pyrrole with the NH portion pointed toward the carbonyl oxygen. The pyrrole—pyrrole torsional angles are 164.75° (N1 to N0) and 154.83° (N2 to N0).

UV—vis spectrophotometric analysis of terpyrrole **1** revealed a strong absorbance band at $\lambda_{\text{max}} = 327 \text{ nm}$ ($\epsilon = 17\,000 \text{ M}^{-1} \text{ cm}^{-1}$) (Figure 3a). The fluorescence profile was also determined with an emission maximum at 433 nm when excited at 327 nm in acetonitrile (Figure 3b).

¹H NMR spectroscopic studies were carried out to probe the stability of the new terpyrrole. Based on these studies, a 47% recovery was found when compound **1** was dissolved in CDCl₃ and maintained under laboratory conditions for 72 h and then subjected to purification by silica gel column chromatography (Figures S1 and S2). Terpyrrole **1** proved more stable as a solid. Based on ¹H NMR spectroscopic analyses, less than 1% degradation was seen over the course of 1 week (Figure S3).

In conclusion, we have developed a facile synthesis of a new, bench-stable terpyrrole amenable to preparation on gram scale using commercially available and easily prepared precursors. The importance of bipyrrole, terpyrrole, and tetrapyrrole building blocks in

expanded porphyrin and porphyrin analogue chemistry leads us to predict that precursors such as **1** will have a role to play in accessing new porphyrinoid and oligopyrrolic constructs.

EXPERIMENTAL SECTION

General Information.

All reagents and solvents were purchased from commercial supplies and used without further purification. Analytical thin-layer chromatography (TLC) was performed using commercial precoated silica gel plates containing a fluorescent indicator. Column chromatography was carried out using silica gel (0.040–0.063 mm). High-resolution mass spectra (HRMS) were measured using an Ion Spec Fourier Transform mass spectrometer (9.4 T). Proton and carbon NMR spectra were recorded using a Varian 400 spectrometer or Bruker Avance III 500 MHz instrument at room temperature, and chemical shifts are reported in ppm using TMS or solvent residual signals as internal reference standards. Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported in terms of chemical shift. All NMR spectroscopic solvents were purchased from Cambridge Isotope Laboratories. UV-vis spectra were recorded from 250 to 800 nm using a Varian Cary 5000 spectrophotometer at room temperature. Fluorescence spectra were recorded on a Photon Technology International Fluorescence Master fluorimeter. The source was a 75 W xenon short arc lamp. A cell length of 10 mm and spectroscopic grade acetonitrile were used for all UV-vis and fluorescence studies.

$\text{PdCl}_2(\text{PPh}_3)_2$ was purchased from Strem Chemicals Inc. and used as received. *N*-Boc-pyrrole-2-boronic acid (**3**) was purchased from Frontier Scientific and used as received. Ethyl 2,5-dibromopyrrole-3,4-dicarboxylate¹⁹ is a known compound and was prepared following reported procedures.

Diethyl 1H,1' H,1'' H-[2,2':5',2''-Terpyrrole]-3',4'-dicarboxylate(1).—An oven-dried round-bottom flask containing diethyl 2,5-dibromopyrrole-3,4-dicarboxylate (**2**) (7.0 g, 0.019 mol), $\text{PdCl}_2(\text{PPh}_3)_2$ (2.66 g, 0.0038 mol, 20 mol %), *N*-Boc-pyrrole-2-boronic acid (**3**) (9.6 g, 0.046 mol, 2.4 equiv), and K_2CO_3 (13.1 g, 0.094 mol, 5 equiv) was degassed with a strong flow of N_2 for 15 min. At the same time a round-bottom flask containing *N,N*-dimethylformamide (200 mL) and H_2O (40 mL) was degassed with N_2 for 15 min. The DMF/ H_2O (5:1, v/v) solution was added to the solids via cannula, and the reaction mixture was transferred to an oil bath and then heated to 120 °C for 5 h. N_2 was bubbled through the solvent for the first 15 min, and then a nitrogen atmosphere was maintained for the entire reaction time. The reaction flask was then transferred to a rotary evaporator, and the solvent was removed under reduced pressure (<40 mbar at 80 °C). The resultant crude solid was taken up in dichloromethane and purified by flash column chromatography over silica gel to yield a pale oil with a yellow tint. The oil was taken up in dichloromethane/hexanes (25 mL; 1/1, v/v), and the solvent was removed *in vacuo* (<20 mbar at 40 °C). This procedure for dissolution and removal of solvent was repeated three times. The resultant solid was taken up in dichloromethane (35 mL), and hexanes were added until precipitation occurred. The

mixture was warmed to 40 °C, allowed to cool slowly to room temperature, and cooled in an ice bath for 15 min followed by filtering to yield **1** as a cream-white solid (5.99 g, 92% yield). ¹H NMR (400 MHz, CDCl₃): δ 11.07 (s, 2H), 8.62 (s, 1H), 6.91 (tt, *J* = 2.5, 1.1 Hz, 2H), 6.50 (ddt, *J* = 3.6, 2.3, 1.2 Hz, 2H), 6.29 (dtd, *J* = 3.6, 2.6, 1.0 Hz, 2H), 4.31 (qd, *J* = 7.2, 1.0 Hz, 4H), 1.35 (td, *J* = 7.2, 1.0 Hz, 6H) ppm. ¹³C NMR (101 MHz, CDCl₃) δ 167.4, 129.7, 122.7, 119.9, 110.0, 109.5, 106.8, 61.3, 14.3 ppm. HRMS (ESI⁺) *m/z*: [M + Na]⁺ calcd for C₁₈H₁₉N₃O₄Na, 364.1268; found, 364.1259.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- (20). Pd(dppf)Cl₂ (20 mol%) under analogous conditions gave terpyrrole 1 in 83% yield.₂
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Figure 1.
Synthetic routes for the preparation of terpyrrole.

Figure 2. ORTEP plot (thermal ellipsoids set at the 50% probability) of the single crystal X-ray diffraction structure of terpyrrole **1** viewed from the (a) top and (b) side. Hydrogen atoms are removed for clarity.

Figure 3.

(a) UV-vis and (b) emission spectra of terpyrrole **1** recorded in acetonitrile ($[1] = 15 \mu\text{M}$).

Scheme 1.

Synthesis of Terpyrrole (1) Using a Tandem Suzuki Cross-Coupling and an Associated in Situ Deprotection Protocol