

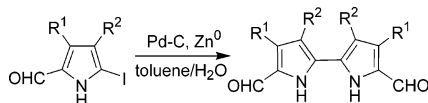
Improved Synthesis of Functionalized 2,2'-Bipyrroles

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A series of 2,2'-bipyrroles has been efficiently synthesized using an improved synthetic approach based on Pd(0)-catalyzed homocoupling of various 2-iodopyrroles. This new synthetic approach takes place at room temperature and in the presence of water. Functional groups such as formyl, ester, and nitrile are able to survive these reaction conditions. Solvents are found to play an important role in this reaction.

The 2,2'-bipyrrole motif occurs in a number of polypyrrole pigments, many of which have attracted increasing attention in coordination chemistry, medicinal chemistry, and material science.¹ 5,5'-Diformyl-2,2'-bipyrroles **1** are key synthetic precursors for porphycene **2**,^{2,3} sapphyrin **3**,⁴ and other expanded porphyrin analogues.⁵ Available synthetic routes to 2,2'-bipyrroles are limited^{3–4,6–7} to oxidative coupling and reductive coupling methodologies. Oxidative coupling⁶ works only in a limited number of cases and often in low yield, so reductive

couplings,^{3–4,7} usually the Ullmann reaction, are the most widely used for access to 2,2'-bipyrroles. Due to the drastic conditions of the Ullmann coupling reaction, sensitive substituents (such as formyl groups), cannot be carried through intact; thus, direct access to compound **1** is not possible. Since the original preparation of compounds of type **1** by Vogel and co-workers² during their synthesis of porphycene **2**, only a few variants of the seminal synthetic methodology have been described.^{3,7} All except one⁸ are based on the Ullmann-type dimerization of a preformed halopyrrole (Scheme 1).

Synthesis of **1**, as reviewed in detail in the literature,⁸ normally requires four key steps: (1) Ullmann coupling of a 2-iodopyrrole-5-carboxylic ester, (2) hydrolysis of the diester, (3) decarboxylation of the resulting 5,5'-dicarboxylic acid, and (4) Vilsmeier-type diformylation. The Ullmann synthesis of biaryls by the copper-induced reductive coupling of aromatic halides is of broad synthetic use.^{9a} Although some substrates will undergo Ullmann reductive coupling under mild conditions, the typical Ullmann coupling is conducted at high temperature.^{9b} Ullmann-type reductive couplings of pyrroles are best when there is one or more electron-withdrawing group present; high temperature is usually required.^{9b}

Recently, Liebeskind and co-workers reported an ambient-temperature Ullmann-type coupling reaction,^{9c} but the requirement of specific type of substrates or specific positions of the substituent limits its synthetic application. They stated that the “most noticeable limitation of this process is the lack of reaction of aromatic halide substrates not possessing a coordinating ortho-substituent”.^{9c} Sessler et al.^{7a} developed an efficient procedure for the preparation of alkyl-substituted 2,2'-bipyrroles by protection of the pyrrole nitrogen atom before an Ullmann-type coupling reaction; this was followed by deprotection of the resulting N-substituted 2,2'-bipyrroles. Vogel^{7b} et al. later improved the Sessler method by changing the solvent from DMF to toluene. Since the nature of substituents on the pyrrole ring greatly influences the performance of the literature reactions, thus precluding the synthesis of some attractive target compounds, the current number of compounds **1** is still very small.

The above synthetic limitations encouraged us to develop a new expedited methodology for the synthesis of bipyrroles **1**. Inspired by the rapidly developing field of metal-catalyzed coupling reactions, and especially some recently developed palladium-catalyzed couplings of aryl halides under mild

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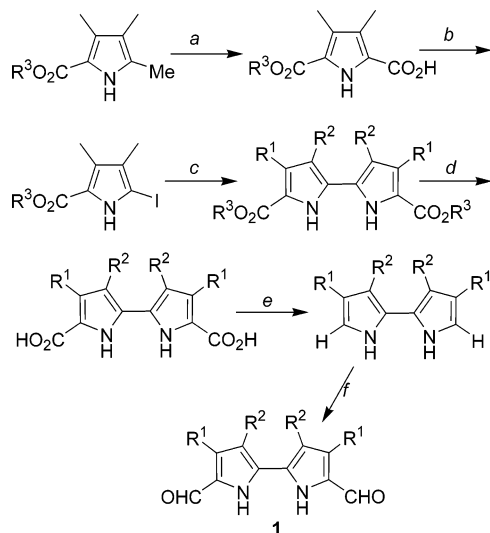
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SCHEME 1. Previous Methodologies for the Synthesis of 5,5'-Diformyl-2,2'-bipyrrroles 1


Steps: a) oxidation; b) iodination; c) Ullmann coupling; d) de-esterification; e) decarboxylation; f) Vilsmeier diformylation.

conditions,^{10–11} we decided to try different metals (other than copper) for homocoupling of iodopyrroles.

The use of palladium-catalyzed reductive couplings in carbon–carbon bond-forming reactions has attracted considerable attention in modern synthetic organic chemistry.^{12a–e} These include the Stille,^{12b} Suzuki,^{12c} Heck,^{12d} and Sonogashira^{12e} coupling reactions to name only a few. Early usage of Pd–C as the catalyst for the Ullmann coupling, under phase-transfer conditions, required refluxing at 100 °C, but the high temperature for this reaction limits its application in the synthesis of biaryls possessing functional groups.¹²

Recently, Pd–C co-catalyzed biaryl synthesis was reported to take place at room temperature by simply adding water to the reaction conditions.¹¹ Meanwhile, 2-formyl-5-iodopyrroles have been used in Sonogashira coupling reactions with TMS–acetylene to build acetylenic and diacetylenic diformyl-dipyrroles.¹³ Encouraged by these results, we selected Pd–C as our catalyst and a mixture of organic solvents, along with water as a co-solvent. Though our procedure can be applied to the synthesis of all commonly available 5,5'-disubstituted 2,2'-bipyrrroles from the corresponding 5-substituted 2-iodopyrroles,¹⁴ we chose to demonstrate the approach using 5-formyl-2-iodopyrroles 4 because they are easily available, and if our

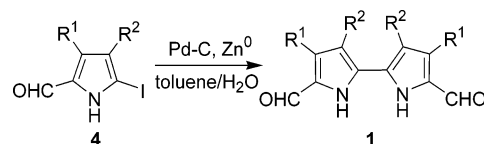
SCHEME 2. New Synthetic Route to 5,5'-Diformyl-2,2'-bipyrrroles 1


TABLE 1. Reductive Coupling of 2-Iodopyrroles 4 Using 10% Pd–C and Zn at Room Temperature in Toluene/Water (1:1)

Formyliodopyrrole	Diformyl-2,2'-bipyrrrole	Yield
 4a	 1a	35%
 4b	 1b	54%
 4c	 1c	41%
 4d	 1d	26%
 4e	 1e	40%

scheme was successful, could form bipyrrroles 1, critically important for porphycene synthesis, in one step.

After attempting several coupling systems, we settled on Pd–C with zinc as a suitable catalyst for the homocoupling of compound 4 at room temperature; the aldehyde group on the pyrrole ring was able to survive these conditions. We also discovered that toluene/water is a better solvent system than acetone/water.

Our overall synthesis of 2,2'-bipyrrroles from readily available 2-iodopyrroles 4a–e is shown in Scheme 2. In our synthetic approach, the homocoupling reactions of 2-iodopyrroles to generate 2,2'-bipyrrroles were performed in the solvent mixture of toluene/water (1:1) at room temperature under argon, with a combination of Pd–C and activated zinc metal as the catalyst. The reaction was easily followed using TLC since the target bipyrrroles display characteristic blue fluorescence under ultraviolet (366 nm) light. The yields of this coupling reaction were moderate, as shown in Table 1, and the aldehyde group was able to survive these mild reaction conditions. As usual in these coupling reactions, the major byproduct was the protiodehalogenated compound.

It was noticed that substituting toluene with acetone caused the yield of the protiodehalogenated product to increase. The reason that the toluene/water system gave the best results may be because toluene is able to stabilize the Pd-coupling intermediate, for which there is precedent in the literature.¹⁵ Another

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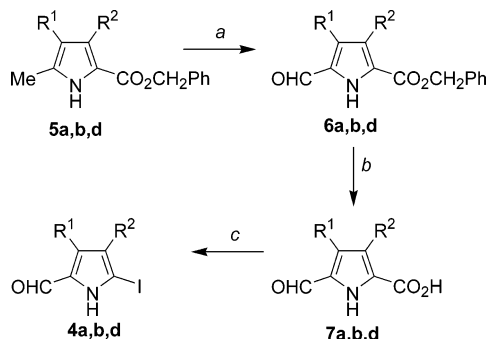
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(14) (a) For example, using benzyl 2-iodo-3,4-dimethylpyrrole-5-carboxylate and Pd–C/Zn in acetone/water, dibenzyl 3,3',4,4'-tetramethyl-2,2'-bipyrrrole-5,5'-dicarboxylate was obtained in 75% yield (Supporting Information). This bipyrrrole was previously obtained by oxidative coupling in 25% yield,^{14b} and by Ullmann coupling in 57% yield.^{14c} (b) Falk, H.; Flödl, H. *Monatsh. Chem.* **1988**, 119, 247. (c) Grigg, R.; Johnson, A. W. *J. Chem. Soc.* **1964**, 3315.

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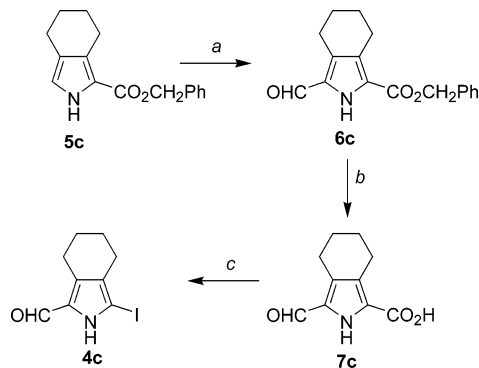
SCHEME 3. Synthesis of 2-Formyl-5-iodopyrroles 4a,b,d from Benzyl 2-Methylpyrrole-5-carboxylates 5a,b,d


Reagents: a) CAN, HOAc, THF–H₂O; b) Pd–C, H₂, THF; c) I₂, KI, NaHCO₃, C₂H₄Cl₂–H₂O.

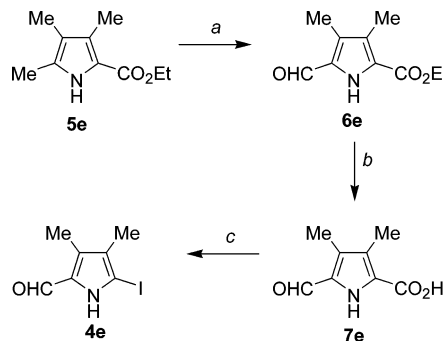
issue worth mentioning is that water plays an important role in this reaction:¹⁶ first, it increased the reaction rate compared with the anhydrous system, and second, we believe it allows the reaction to be performed at room temperature. Under anhydrous conditions, when acetone or toluene was used as the solvent, no reaction occurred and all the starting materials were recovered after periods up to 4 days.

The key starting materials, 2-formyl-5-iodopyrroles **4a–e** are very easy to generate in three steps from the corresponding 2-methylpyrrole in high yields (as shown in Scheme 3), involving (1) regioselective oxidation of the α -methyl group of pyrrole **5**¹⁷ using ceric ammonium nitrate¹⁸ to give pyrrole **6**,¹⁸ (2) catalytic debenzoylation of the esters using Pd–C in THF under H₂ to give pyrrole **7**, and (3) direct iodination to generate pyrrole **4**. An alternative method was used to prepare pyrrole **6c** from **5c**^{17g} through a Vilsmeier reaction (92% yield) as shown in Scheme 4. As for ethyl ester **4e** in Scheme 5, effective hydrolysis with LiOH in THF without aldehyde protection was achieved in >90% yield according to a literature procedure.¹³ The yield in each step is very high, and there is normally no need for chromatography. The overall yield for the three steps is generally higher than 65%.

The photophysical properties of 5,5'-dialdehyde-2,2'-bipyrroles **1** are summarized in Table 2. As previously observed with certain 2,2'-bipyrroles²⁰ (and even with arylpyrroles),²¹ all the functionalized bipyrroles shown in Table 2 are highly luminescent materials at room temperature. Their absorptions occur between 231 and 401 nm, and they are strongly luminous at ~410 nm. We observed large Stokes shifts for most of the

SCHEME 4. Synthesis of 2-Formyl-5-iodopyrrole 4c from Benzyl Pyrrole-5-carboxylate 5c


Reagents: a) POCl₃, DMF, CH₂Cl₂, AcONa; b) Pd–C, H₂, THF; c) I₂, KI, NaHCO₃, C₂H₄Cl₂–H₂O.

SCHEME 5. Synthesis of 2-Formyl-5-iodopyrrole 4e from Ethyl 2-Methylpyrrole-5-carboxylate 5e


Reagents: a) CAN, HOAc, THF–H₂O; b) LiOH, THF; c) I₂, KI, NaHCO₃, C₂H₄Cl₂–H₂O.

TABLE 2. Photophysical Data for 5,5'-Diformyl-2,2'-bipyrroles **1 in CH₂Cl₂ at Room Temperature**

compd	absorption $\lambda_{\max}$ nm (log ϵ)	emission ^a $\lambda_{\max}$ (nm)	fluorescence ^b quantum yield	Stokes shift (nm)
1a	233 (4.08), 280 (3.90), 363 (4.32)	410	0.356	37
1b	232 (4.21), 268 (4.00), 361 (4.41)	410	0.321	49
1c	235 (4.27), 382 (4.59), 401 (4.58)	415	0.411	14
1d	232 (4.04), 262 (3.82), 356 (4.24)	408	0.326	52
1e	231 (3.79), 275 (3.64), 361 (4.05)	410	0.320	49

^a Excitation at 350 nm. ^b Calculated using quinine sulfate 5% H₂SO₄ solution as the standard.

bipyrroles, between 37 and 52 nm, except for bipyrrole **1c**, which has a Stokes shift of 14 nm and a strong red-shifted long wavelength absorption band compared with the other bipyrroles. Bipyrrole **1c** was also found to have the largest quantum yield of all the bipyrroles studied. Since these bipyrroles are blue luminous materials, they may find application in the material science area as blue-light-emitting devices.

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In summary, we have developed an improved general methodology for the synthesis of 2,2'-bipyrroles, and more specifically, of 5,5'-diformyl-2,2'-bipyrroles **1**; the formyl group was our benign functionality because of the importance of diformylbipyrroles in the synthesis of porphycene and related macrocycles.² This improved synthetic method uses Pd–C and activated metallic zinc as the catalysts, and the presence of water in the reaction system is critically important. These mild reaction conditions allow functional groups such as formyl, ester, and nitrile to be carried through the sequence intact. By using this improved route, six 5,5'-diformyl-2,2'-bipyrroles **1** were synthesized in four steps each from commonly available monopyrroles. The bipyrroles are strongly luminescent, and the new approach should provide a ready access to new materials for light-emitting devices.

Experimental Section

General Procedure for the Reductive Coupling of 4. Activated zinc was obtained by washing zinc dust with 3 M HCl, then filtering through filter paper, washing successively with water, ethanol, and diethyl ether, and then drying under vacuum. The following describes the reductive coupling of **4a** as a representative example of the procedure for synthesis of 5,5'-diformyl-2,2'-bipyrroles **1**. A mixture of Pd–C (10.0 mg, 10%) and activated zinc dust (100 mg, 1.5 mmol) was placed in a dry 50 mL round-bottom flask. After being evacuated, the flask was filled with argon. Then, 4 mL of toluene/water (1:1) was added and the mixture was stirred at room temperature under argon for 15 min. 2-Iodopyrrole (132 mg, 0.5 mmol) in 8 mL of toluene was added through a syringe. Finally, 8 mL of distilled water was added and the mixture was stirred vigorously at room temperature under argon. The reaction was usually complete within 24 h. [Using TLC to follow reaction progress, all of the five 5,5'-diformyl-2,2'-bipyrroles **1** display a characteristic blue fluorescence under UV irradiation (around 366 nm) on silica gel TLC plates. Their CH₂Cl₂, acetone, DMSO, and THF solutions also show strong blue luminescence under the same wavelength illumination at ambient conditions, unlike the starting material monopyrroles **4**]. The reaction was stopped when all starting material was used up (TLC); CH₂Cl₂ (40 mL) was added to the mixture and it was sonicated to form two layers. After the water layer was removed, the remaining solution was filtered through Celite which was washed three times with CH₂Cl₂ (100 mL). The organic solvents were collected and dried over anhydrous Na₂SO₄ before evaporation under vacuum. The pure target compounds were separated using a silica gel column eluted with EtOAc/hexane (1:2). Further purification can be performed by recrystallization from CH₂Cl₂/hexane or from ethanol.

3,3'-Diethyl-5,5'-diformyl-4,4'-dimethyl-2,2'-bipyrrole 1a.^{4c} After the silica gel column was used for the separation, the title compound was obtained as a white solid in 35% yield (23.7 mg, 35%). mp 240–242 °C (lit^{4c} mp 241–242 °C). ¹H NMR (250 MHz, CDCl₃) δ 11.71(s, 2H), 9.61 (s, 2H), 2.74–2.71 (m, 4H), 1.95 (s,

6H), 1.56–1.10 (m, 6H). ¹³C NMR (250 MHz, CDCl₃) ppm 177.8, 135.9, 128.9, 128.2, 119.2, 16.9, 16.1, 9.3. HRMS (ESI) Calcd for C₁₆H₂₁N₂O₂ [M + H]⁺: 273.1597. Found: 273.1601.

5,5'-Diformyl-4,4'-bis(2-methoxycarbonyl)ethyl)-3,3'-dimethyl-2,2'-bipyrrole 1b. After separation by use of the silica gel column, the title compound was obtained as a white solid in 54% yield (52.4 mg). mp >330 °C (dec). ¹H NMR (250 MHz, DMSO-*d*₆) δ 11.7 (s, 2H), 9.60(s, 2H), 3.57 (s, 6H), 3.00–2.95 (m, 4H), 2.58–2.48 (m, 4H), 1.93 (s, 6H). ¹³C NMR (250 MHz, CDCl₃) δ 178.3, 172.6, 131.7, 129.3, 127.8, 119.7, 51.3, 34.5, 19.2, 9.3. Anal. Calcd for C₂₀H₂₄N₂O₆·0.5H₂O: C, 60.47; H, 6.34; N, 7.05. Found: C, 60.6; H, 6.1; N, 6.9. HRMS (ESI) Calcd for C₂₀H₂₅N₂O₆[M + H]⁺: 389.1707. Found: 389.1707.

3:4,3':4'-Bisbutano-5,5'-diformyl-2,2'-bipyrrole 1c. After separation by use of the silica gel column, the title compound was obtained as a white solid in 41% yield (30.3 mg). mp >310 °C (dec). ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.50 (s, 2H), 9.54 (s, 2H), 2.80 (m, 4H), 2.50 (m, 4H), 1.67 (br, 8H). ¹³C NMR (250 MHz, DMSO-*d*₆) δ 177.3, 128.4 (2C), 126.9, 121.6, 22.9, 22.4, 21.8, 21.2. Anal. Calcd for C₁₈H₂₀N₂O₂·H₂O: C, 68.77; H, 7.05; N, 8.91. Found: C, 69.1; H, 6.7; N, 8.6. HRMS (ESI) Calcd for C₁₈H₂₁N₂O₂ [M + H]⁺: 297.1597. Found: 297.1605.

4,4'-Bis(2-cyanoethyl)-5,5'-diformyl-3,3'-dimethyl-2,2'-bipyrrole 1d. After separation by use of the silica gel column, the title compound was obtained as a white solid in 26% yield (20.9 mg). mp >330 °C (dec). ¹H NMR (250 MHz, acetone-*d*₆) δ 9.71 (s, 2H), 9.65 (s, 2H), 3.18–3.12 (m, 4H), 2.71–2.65 (m, 4H), 2.18 (s, 6H). ¹³C NMR (250 MHz, acetone-*d*₆) δ 178.9, 131.0, 130.7, 128.3, 121.4, 120.2, 20.8, 19.0, 9.7. Anal. Calcd for C₁₈H₁₈N₄O₂·0.25H₂O: C, 66.18; H, 5.70; N, 17.15. Found: C, 66.4; H, 5.3; N, 17.4. HRMS (ESI) Calcd for C₁₈H₁₉N₄O₂ [M + H]⁺: 323.1502. Found: 323.1504.

5,5'-Diformyl-3,3',4,4'-tetramethyl-2,2'-bipyrrole 1e.^{4a} After separation by use of the silica gel column, the title compound was obtained as a white solid in 40% yield (24.4 mg). mp >307 °C (dec) [lit^{4a} mp 305–307 °C (dec)]. ¹H NMR (250 MHz, DMSO-*d*₆) δ 11.66 (s, 2H), 9.61 (s, 2H), 2.25 (s, 6H), 1.91 (s, 6H). ¹³C NMR (250 MHz, DMSO-*d*₆) δ 177.9, 129.5 (2C), 128.1, 119.9, 9.4, 9.0. HRMS (ESI) Calcd for C₁₄H₁₇N₂O₂ [M + H]⁺: 245.1284. Found: 245.1289.

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Supporting Information Available: Synthetic procedures for compounds **6a–d**, **4a–d**, and dibenzyl 3,3',4,4'-tetramethyl-2,2'-bipyrrole-5,5'-dicarboxylate, spectroscopic characterization and ¹H NMR/¹³C NMR spectra of compounds **1a–e**, **6a–d**, **4a–d**, and dibenzyl 3,3',4,4'-tetramethyl-2,2'-bipyrrole-5,5'-dicarboxylate; ESI HRMS spectra for compounds **1a–e**, **4c**, **4d**, and dibenzyl 3,3',4,4'-tetramethyl-2,2'-bipyrrole-5,5'-dicarboxylate. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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