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Regioselective Substituent Effects upon the Synthesis of Dipyrrins from 2-Formyl Pyrroles

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Abstract

The synthesis of symmetric α-free *meso*-H-dipyrrin hydrobromides from 5-H-2-formyl pyrroles was investigated. The self-condensation produces regioisomeric dipyrrins through adoption of two mechanistic pathways. The key difference between the two pathways lies in which position of the pyrrole directs nucleophilic attack. Through a systematic study involving various substituted and/or isotopically labelled 5-H-2-formyl pyrroles, we herein provide evidence to suggest that not only do two mechanistic pathways exist, but that the steric bulk of the substituent adjacent to the 5-unsubstituted position influences which pathway dominates.

Keywords: Dipyrrins, pyrroles, steric effects, condensation, synthesis

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Introduction

Although historically used as a building block for porphyrins,[1] in recent years the dipyrrinato unit[2-6] (Figure 1) has come to be appreciated as a useful chromophore by which to invoke desirable features such as energy transfer and storage.[7, 8] There are numerous reports describing the use of dipyrrinato complexes in applications as diverse as biological stains/probes, light harvesters and anticancer agents.[9] Of the dipyrrinato complexes, boron difluoride complexes are the most thoroughly studied due to their high thermal and photochemical stability, chemical robustness, high fluorescence quantum yields and tuneable fluorescence properties. These complexes are formally known as 4,4'-diflouro-4-bora-diaza-s-indacenes and are commonly referred to as *F*-BODIPYs (Figure 1). Beyond the established utility of *F*-BODIPYs,[11–14] the luminescence properties of these complexes, and those of other metals,[10-12] have fostered the use of this framework in dye-sensitized solar cells and catalysts for hydrogenation and hydroamination,[13-16] all pointing towards a promising future for this underdeveloped ligand.

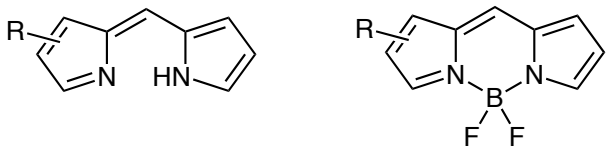
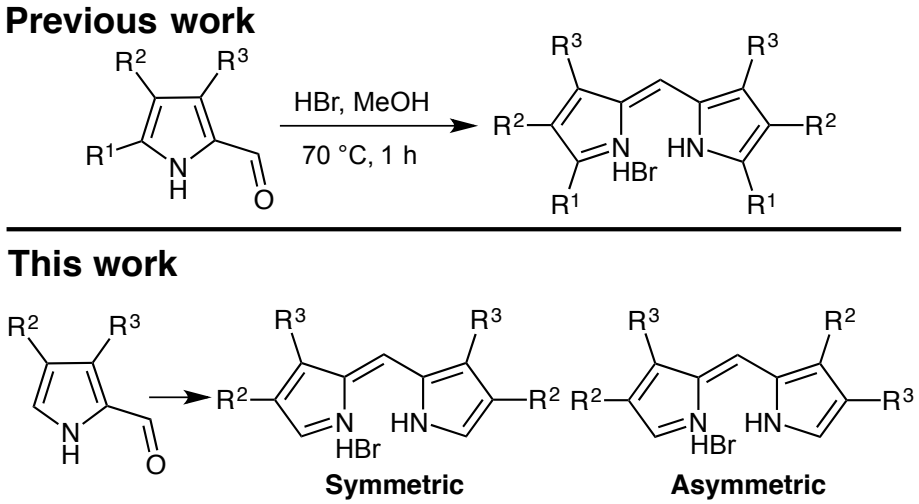


Figure 1 Dipyrrin (left) and *F*-BODIPY (right)

Based on a one-pot approach to transform 2-formyl pyrroles into *F*-BODIPYs,[17] we previously reported the efficient synthesis of symmetric *meso*-H-dipyrrins from 2-formyl pyrroles in the presence of acid (Scheme 1, top).[18] Using methanol as a solvent, and heating 2-formyl pyrroles at 70 °C for 1 hour in the presence of excess aqueous 48% hydrobromic acid, we produced the requisite symmetric dipyrrin hydrobromide salts in moderate-to-high isolated yields (60-90%). Substituents such as alkyl, keto, alkanoate and conjugated esters were well tolerated. As well as being convenient and efficient, this strategy complements existing literature methods

by enabling the high-yielding synthesis of symmetric dipyrrins from pyrroles that bear electron withdrawing functional groups.



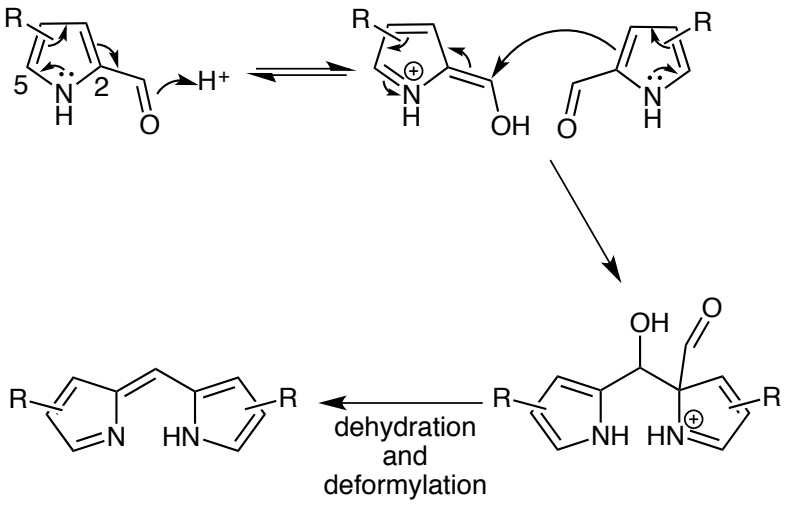
Scheme 1 *meso*-H-dipyrrin formation from 2-formyl pyrroles

When subjected to these reaction conditions, a 5-H-2-formyl pyrrole (R^1 = H in Scheme 1, top) produced both symmetric and asymmetric regioisomers in a 9:1 ratio, respectively.[18] The reaction mechanism for formation of dipyrrins under these conditions was presumed to proceed analogously to that for a fully substituted 2-formyl pyrrole,[17] whereby the carbonyl carbon atom of one pyrrole undergoes nucleophilic attack by another to generate the requisite dipyrrin (Scheme 2). However, this does not explain the presence of both asymmetric and symmetric products. We suspected that by virtue of the unsubstituted 5-position, attack could originate from either the 2- or 5-position of 5-H-2-formyl pyrroles. Thus, with two nucleophilic sites, two possible regioisomeric dipyrrins could form (Scheme 1, bottom).

Results and Discussion

Curious as to the origin of this regioselectivity, the reaction pathways for formation of α-free dipyrrins from 5-H-2-formyl pyrroles were investigated. Accordingly, several 5-H-2-formyl

pyrroles bearing alkyl and isotopically labelled substituents at the 3- and 4-positions were prepared, and their condensation products are reported herein.

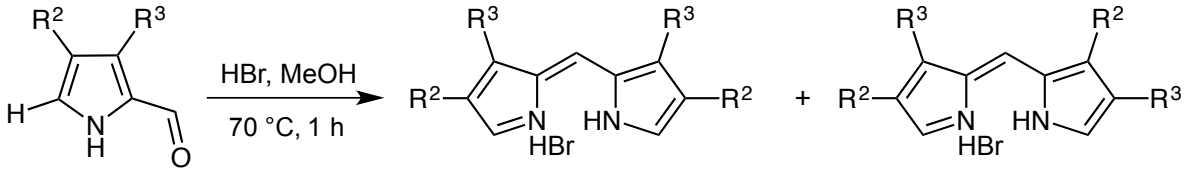


Scheme 2: Suggested pathway for the formation of symmetrical dipyrrins from fully substituted 2-formyl pyrroles

With the hypothesis that nucleophilic attack could occur from both the unsubstituted 5-position and the 2-formyl position of a 5-H-2-formyl pyrrole, we investigated four 5-H-2-formyl pyrroles **1a-d** with variation of methyl and ethyl substituents across R^2 and R^3. Upon exposure of the pyrroles to the reaction conditions typically used for dipyrrin formation (HBr, MeOH, 70 °C, 1 h), evidence of a steric influence emerged. Indeed, when R^2 = Et (Table 1, entries 1 and 4), dipyrrin formation was successful. On the contrary, when using pyrroles bearing R^2 = Me (entries 2 and 3) dipyrrin formation was not observed, and the reaction instead produced an intractable tar. These results suggest that an ethyl group provides sufficient steric bulk to hinder reaction at the adjacent α-position (5-H), and thus prevent polymerization by instead promoting the desired dipyrrin formation via reaction at the position bearing the formyl group. In contrast, a methyl group at R^2 offers insufficient bulk to hinder reactivity at the adjacent unsubstituted α-position, and thus facilitates polymerization. Furthermore, it appears that increasing steric bulk at

R^2 has a more pronounced effect than at R^3: note that when R^2 is Me (**1b** and **1c**, entries 2 and 3) polymeric tars result no matter the nature of R^3.

Table 1: *meso*-H-dipyrrin formation from alkyl substituted 5-H-2-formyl pyrrole **1**



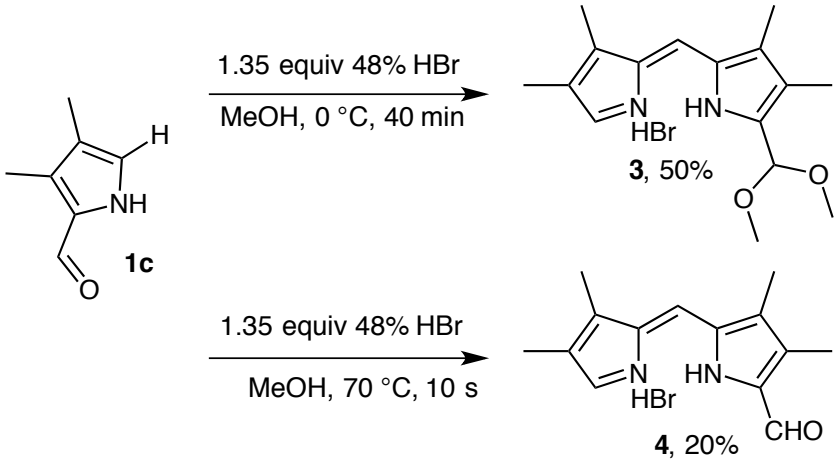
1 **sym-2** **asym-2**

Entry	Pyrrole	R^2	R^3	Isolated yield (%)
1	**1a**	Et	Me	63 (9:1)[a]
2	**1b**	Me	Et	0
3	**1c**	Me	Me	0
4	**1d**	Et	Et	75

[a] **sym-2** was the major isomer produced

Given that exposure of **1c**, and a labelled variant **1c*** (see Supporting Information), to our dipyrrin-formation conditions produced a polymeric tar (Table 1, entry 3), we evaluated whether thermal (not acid-catalyzed) deformylation, and/or condensation, of **1c** occurred at the reaction temperature (70 °C). However, despite heating a solution of **1c** in MeOH at 70 °C for prolonged periods of time, neither deformylation nor condensation occurred. This indicated that protonation of 2-formyl pyrroles is necessary for reaction to occur. Cognizant of this fact, the reaction conditions were modified to enable isolation of dipyrrin rather than allow subsequent reaction to lead to polymerization. Exposure of a solution of **1c** to HBr at 0 °C resulted in isolation of the new acetal-containing dipyrrin **3** (Scheme 3, top). As the acetal moiety of **3** is merely a protected formyl group formed under the acidic methanolic reaction conditions, this result suggested that nucleophilicity originated from the 5-position of pyrrole **1c**. When the reaction was repeated at 70 °C (vessel immersed into oil bath held at 70 °C) and quenched after just 10 s, the new dipyrrin **4** was isolated with no hint of the formation of **3** (Scheme 3, bottom). The retention of the formyl functionality of **4** provides further evidence for the nucleophilic role of the

unsubstituted 5-position of **1c**. The small adjacent substituent (R^2 = Me) would provide little steric hindrance to the approach of the electrophile.

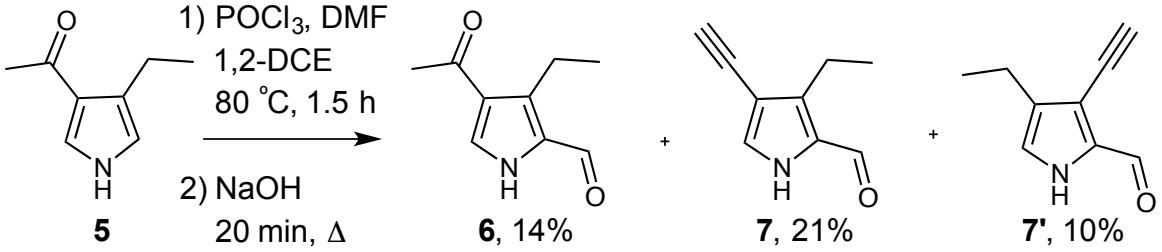


Scheme 3 Reaction of pyrrole **1c** at 0 °C and at 70 ºC

Isolation of the α-acetal and α-formyl dipyrrins **3** and **4** from the self-condensation of **1c** indicated that attack from the unsubstituted 5-position of 5-H-2-formyl pyrroles was not only possible, but was the only observed outcome when $R^2 = R^3$ = Me. We then utilised the labeled 5-H-2-formyl pyrrole **1d***, bearing ethyl substituents at the 3- and 4-positions. As shown in Table 1, **1d** reacts to form dipyrrin: evidently the presence of the R^2 ethyl group adjacent to the unsubstituted 5-position results in a significant change to reactivity (compare entries 2 and 3, where R^2 = Me, with entry 4). Our goal with the labelled pyrrole **1d*** was to ascertain whether nucleophilicity originated at the 2-position (to give the symmetric dipyrrin, **sym-2**) or the unsubstituted 5-position (to give the asymmetric dipyrrin, **asym-2**). Incorporation of a deuterium labell within the ethyl substituent would serve to differentiate the otherwise identical dipyrrin products.

The synthetic strategy for the preparation of the labelled 5-H-2-formyl pyrrole **1d*** began with Vilsmeier-Haack formylation of pyrrole **5**[19] (Scheme 4) with the intention of then effecting

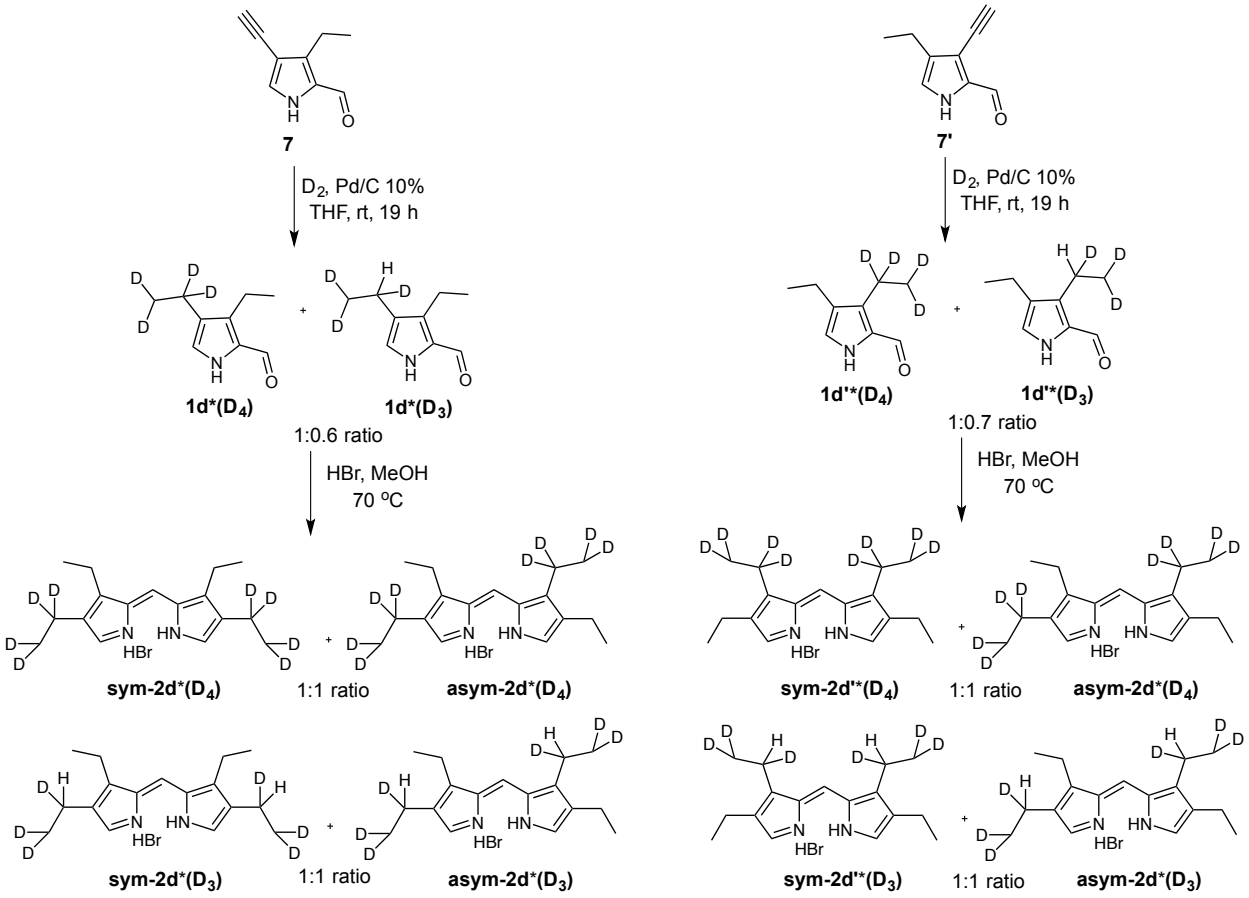
deuterative reduction of the acyl group. Surprisingly, the desired 5-H-2-formyl pyrrole **6** was obtained in only 14% yield. The remainder of the recovered material consisted of the two regioisomeric alkynes **7** and **7'** (Scheme 4).[20] The position of the alkynyl group in the major and minor isomer was assigned using 2-D NMR spectroscopy.



Scheme 4 Formylation of **5**

The terminal alkynyl group could potentially be deuterated and subsequently reduced to give the desired D_1-labelled 5-H-2-formyl pyrrole **1d*** in two steps. However, treatment of **7** with *n*BuLi,[28] followed by quenching with D_2O, resulted only in the degradation of the starting material. Instead, the separated regioisomers **7** and **7'** were each reduced using D_2 gas to give **1d*(D_4)** and **1d'*(D_4)**, alongside the D_3 analogues **1d*(D_3)** and **1d'*(D_3)** in a 1:0.6 and 1:0.7 ratio (Scheme 5). This was likely due to traces of HD in the D_2 gas supply as a result of air permeation during the heavy water electrolysis for the generation of D_2,[21] or the presence of trace water during reaction.[22] The two mixtures were each submitted to the acid-catalyzed condensation reaction, under typical conditions, to afford the desired labelled α-free dipyrrins bearing 6-8 deuterium labels (Scheme 5 shows the D_6 and D_8 variants). We determined the ratio of products using the integration for two ^{1}H NMR signals of **2d'** and **2d'***, located at δ2.5 and δ 2.7 (see Supporting Information). The ^{1}H NMR signals were assigned using 2-D methods, and comparing to the unlabelled analogue **2d**. According to NMR spectroscopic analysis (^{1}H, ^{13}C, HMBC and HSQC) and based on the ratio of **(D_4)**:**(D_3)** for the product outcome corresponding to

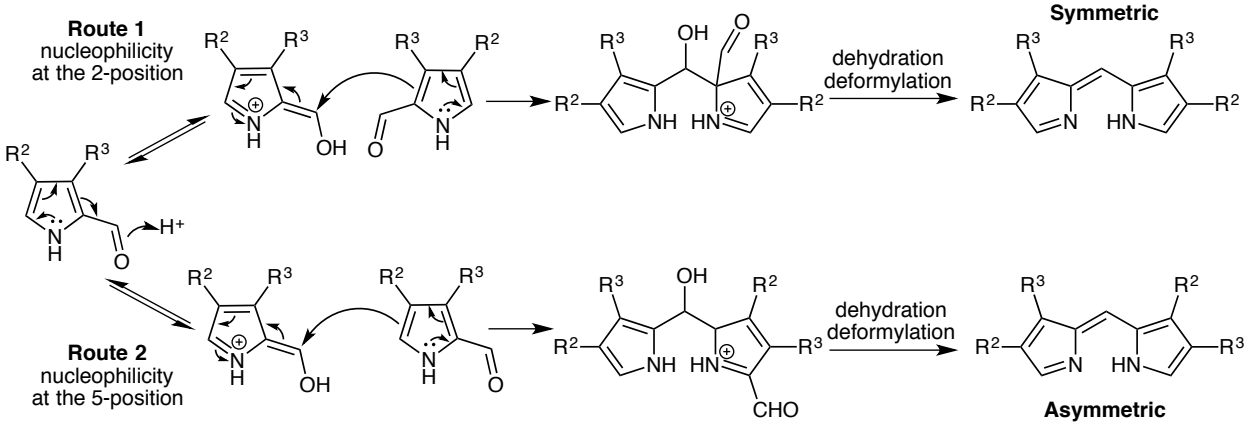
reaction of **1d*** regioisomers, **sym-2d*** and **asym-2d*** were obtained in a 1:1 ratio. Likewise, reaction of **2d'*** led to a 1:1 mixture of **sym-2d'*** and **asym-2d***, again with the expected **(D_4)**:**(D_3)** isomeric ratio.



Scheme 5 Synthesis of the labelled α-free dipyrrin **2d***

The production of both symmetric and asymmetric dipyrrins indicates that the reaction can proceed via two pathways (Scheme 6), with nucleophilicity originating at both the 5-unsubstituted and 2-formyl positions of **1d**. Route 1 (Scheme 6, top) involves nucleophilic attack from the 2-formyl position onto the formyl group of another molecule. Subsequent loss of water and deformylation gives the symmetric dipyrrin. Given the very high yields of dipyrrins obtained when exposing tri-substituted pyrroles to these reaction conditions (R^1, R^2, $R^3 \neq H$ in Scheme 1),[18] this pathway must operate efficiently. However, in the case of 5-unsubstituted pyrroles,

nucleophilicity at the unsubstituted 5-position of 5-H-2-formyl pyrroles becomes competitive (Route 2, Scheme 6). Notwithstanding that the analysis of products resulting from the self-condensation of **1d*** or **1d'*** is complicated by the presence of pyrroles containing D_3 and D_4 labels, it is clear that a mixture of both symmetric and asymmetric dipyrrins form from **1d**. In the self-condensation of **1c** ($R^2 = R^3 = Me$), dipyrrin formation presumably proceeds through Route 2, and the asymmetric product is formed before polymerization begins to dominate. However, when $R^2 = R^3 = Et$, a 1:1 ratio of symmetric and asymmetric products was observed, thereby suggesting that the influence of increased steric bulk decreased the nucleophilicity of the adjacent 5-position such that both routes are equally preferred, and thus an equal mixture of dipyrrin isomers is obtained.



Scheme 6 Proposed mechanistic routes for formation of symmetric and asymmetric dipyrrins from 5-H-2-formyl pyrroles

Hailing back to the reaction of **1a** (Table 1, entry 1), which spurred our initial investigation, we believe that our findings help support a rationale for the acquired 9:1 symmetric:asymmetric product ratio. Pyrrole **1a** has a methyl group ($R^3 = Me$) adjacent to the 2-formyl group and an ethyl group ($R^2 = Et$) adjacent to the unsubstituted 5-position. The ethyl group renders the adjacent 5-position somewhat sterically hindered and decreases the likelihood

of nucleophilic attack from the 5-position (Scheme 6, Route 2), thus limiting asymmetric dipyrrin production. In this way, we would expect nucleophilic attack from the 2-position of **1a** to dominate (Scheme 6, Route 1) to thus give the symmetric dipyrrin as the major product.

Conclusion

In conclusion, the reaction pathway for formation of *meso*-H-dipyrrins from 5-H-2-formyl pyrroles was investigated. We found that nucleophilic attack can originate from the 2-position (bearing the formyl group, Route 1) or from the unsubstituted 5-position (Route 2) of 5-H-2-formyl pyrroles, resulting in symmetric or asymmetric regioisomers, respectively. Steric effects imparted by the substituents in the 4-position influence the course of reactivity: the presence of bulkier groups adjacent to the unsubstituted 5-position promotes formation of the symmetric dipyrrin akin to the case when 2,4,5-trisubstituted 2-formyl pyrroles are used.

Experimental Section

All chemicals were purchased and used as received unless otherwise indicated. Moisture-sensitive reactions were performed in oven-dried glassware and under a positive pressure of nitrogen. Air- and moisture-sensitive compounds were introduced via syringe or cannula through a rubber septum. Flash chromatography was performed using ultra-pure silica (230-400 mm). NMR spectra were recorded using a 500 MHz spectrometer instrument using $CDCl_3$ as solvents and are reported in parts per million (ppm) against solvent peaks referenced as follows: $CDCl_3$ at 7.26 ppm for ^{1}H and at 77.16 ppm for ^{13}C; CD_2Cl_2. at 5.31 ppm for ^{1}H and at 53.84 ppm for ^{13}C. Coupling constants (*J*) are given in Hertz (Hz). Mass spectra were obtained using TOF and LCQ Duo ion trap instruments operating in $ESI^{+/-}$ mode, as indicated.

General Procedure for the preparation of 2

HBr (48% aqueous solution, 0.5 mL) was added drop-wise to a solution of 2-formyl pyrrole **1** (0.4 mmol) in MeOH (1 mL) and the solution was slowly heated to 70 ºC and stirred, monitoring visually and by TLC. If the mixture had not visibly polymerized (black reaction mixture and intractable tar), and all starting material was consumed, the reaction mixture was cooled to room temperature and stored in the freezer for 19 h. If product formed, the precipitate was isolated via filtration to provide dipyrrin **2** as a crystalline solid.

1-Dimethoxymethyl-2,3,7,8-tetramethyl-5-*H*-4,6-dipyrrin hydrobromide (3)

The title compound was synthesized following a modified literature procedure.[18] Chilled (0 °C) aqueous HBr (48%, 50 μL) was added to a solution of **1c** (40.5 mg, 0.329 mmol) in methanol (3.3 mL) at 0 °C. Red precipitate began to form after 5 min of stirring. The reaction mixture was stirred for 1 h, and the solid was collected via suction filtration, yielding the title compound as a dark red solid (23 mg, 50%). M.p. 196-200 °C (decomp.); ^{1}H NMR (500 MHz; $CDCl_3$) δ 13.56 (br s, 1H), 13.23 (br s, 1H), 7.66-7.64 (m, 1H), 7.27 (s, 1H), 6.05 (s, 1H), 3.55 (s, 6H), 2.30 (s, 3H), 2.28 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz; $CDCl_3$) δ 152.6, 144.5, 143.3, 142.1, 128.1, 126.8, 125.7, 124.7, 123.1, 99.9, 56.2, 10.4, 10.3, 10.1, 9.5; HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{16}H_{23}N_2O_2$ 275.1754; found 275.1751.

1-Formyl-2,3,7,8-tetramethyl-5-*H*-4,6-dipyrrin hydrobromide (4)

The title compound was synthesized following a modified literature procedure.[18] Aqueous HBr (48%, 50 μL) was added to a solution of **1c** (37 mg, 0.300 mmol) in methanol (3 mL) at reflux temperature. After 5-10 seconds the mixture turned a dark red, and the reaction vessel was immediately plunged into an ice bath (≤0 °C), followed by addition of ether to dilute the mixture and assist in rapid cooling. The resulting ethereal solution was concentrated *in vacuo*, keeping

the temperature below 25 °C, until a solid precipitate formed. The precipitate was collected via suction filtration and washed with ether to yield the title compound (14 mg, 20%). M.p. 185-189 °C (decomp); ^{1}H NMR (300 MHz; $CDCl_3$) δ 14.19 (br s, 1H), 13.64 (br s, 1H), 10.69 (s, 1H), 7.99-7.97 (m, 1H), 7.48 (s, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 2.33 (s, 3H), 2.15 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz; $CDCl_3$) δ 184.2, 149.8, 147.6, 142.4, 141.6, 131.9, 128.9, 127.8, 127.8, 125.2, 10.7, 10.3, 10.0, 9.7; HRMS-ESI (*m/z*): $[M+H]^+$ calculated for $C_{14}H_{17}N_2O_1$ 229.1335; found 229.1340.

3-Acetyl-4-ethylpyrrole (5)

The title compound was synthesized following a modified literature procedure.[23] A solution of 3-hexen-2-one (8.8 g, 90 mmol) and TosMIC (17.8 g, 91.2 mmol) in a mixture of anhydrous DMSO/Et_2O (450 mL, 1:2) was slowly added to a well-stirred suspension of sodium hydride (8 g, 200 mmol, 60% in oil) in anhydrous ether (180 mL) via cannula transfer. After completion of the addition, the mixture was stirred at room temperature for 1 h, then treated with water to quench excess NaH, and thoroughly extracted with ethyl acetate (4 x 350 mL). The combined organic extracts were washed with brine (12 x 300 mL), dried over anhydrous Na_2SO_4, and the solvent removed *in vacuo* to furnish a dark brown oil. The oil was placed in a freezer overnight, producing a greasy solid which was continually extracted with pentane for 26 hours (Soxhlet) to yield the desired product as a light brown solid after removal of the solvent in vacuo (7.9 g, 63%). ^{1}H NMR (300 MHz; $CDCl_3$) δ 8.44 (br s, 1H), 7.37-7.36 (m, 1H), 6.59-6.57 (m, 1H), 2.80 (q, J = 7.4 Hz, 2H), 2.40 (s, 3H), 1.20 (t, J = 7.4 Hz, 3H), in accordance with literature.[19]

4-Acetyl-3-ethyl-2-formylpyrrole (6)

The title compound and alkynyl by-products were synthesized following a modified literature procedure.[20, 24] $POCl_3$ (2.04 mL, 21.9 mmol) was added, drop-wise, at 0 °C under N_2 to DMF (16

mL). The mixture was allowed to warm to room temperature, and then stirred for 15 minutes. This mixture was added drop-wise to a solution of 3-acetyl-4-ethylpyrrole **(5)** (2.00 g, 14.6 mmol) in DCE (49 mL), at 0 °C under N_2. The resulting mixture was heated to 80 °C and stirred for an additional 80 minutes. Aqueous NaOH (2 M) was added to the reaction until pH > 8 and the resulting emulsion was heated at reflux temperature for 20 minutes. After cooling to room temperature, water (50 mL) was added, and the reaction mixture extracted with EtOAc (3 x 50 mL). The combined organic fractions were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude mixture was purified via column chromatography on silica, eluting with an EtOAc/hexanes gradient (20/80, 30/70) to afford the desired product **6** as a brown solid (0.33 g, 14%), along with the two 4-alkynyl-2-formylpyrroles **7** (0.44, 21%) and **7'** (0.22 g, 10%). **6**: M.p. 119-123 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ 10.03 (br s, 1H), 9.74 (s, 1H), 7.61-7.60 (m, 1H), 3.11 (q, J = 7.5 Hz, 2H), 2.44 (s, 3H), 1.26 (t, J = 7.5 Hz, 4H); ^{13}C{^{1}H} NMR (126 MHz; $CDCl_3$) δ 193.5, 179.1, 140.4, 130.7, 130.4, 125.0, 28.5, 17.9, 16.7; HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for $C_9H_{11}NO_2Na$ 188.0682; found 188.0680.

3-Ethyl-4-ethynyl-2-formylpyrrole (7)

M.p. 80 °C (blackened), followed by melting at 119-120 ºC; ^{1}H NMR (500 MHz; $CDCl_3$) δ 9.64 (s, 1H), 9.46 (br s, 1H), 7.23-7.22 (m, 1H), 3.10 (s, 1H), 2.85 (q, J = 7.6 Hz, 2H), 1.30 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz; $CDCl_3$) δ 177.9, 141.6, 129.6, 128.6, 106.8, 79.6, 76.3, 18.0, 16; HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for C_9H_9NONa 170.0576; found 170.0575.

4-Ethyl-3-ethynyl-2-formylpyrrole (7')

M.p. 95 °C (blackened), followed by melting at 104-105 ºC; ^{1}H NMR (500 MHz; $CDCl_3$) δ 9.68 (s, 1H), 9.28 (br s, 1H), 6.86 (br s, 1H), 3.35 (s, 1H), 2.58 (q, J = 7.6 Hz, 2H), 1.23 (t, J = 7.6 Hz,

3H); $^{13}C\{^{1}H\}$ NMR (125 MHz; $CDCl_3$) δ 178.5, 134.2, 132.5, 123.3, 114.7, 83.8, 75.2, 18.8, 14.5; HRMS-ESI (*m/z*): $[M+Na]^+$ calculated for C_9H_9NONa 170.0576; found 170.0578.

Pyrroles 1d*(D_3) and 1d*(D_4)

A mixture of pyrrole **7** (0.30 g, 2.04 mmol) and Pd (10% on activated carbon, 30 mg, 10% w/w) in THF (25 mL) was stirred at room temperature under deuterium atmosphere for 19 hours. The reaction mixture was filtered through Celite®, which was then washed with MeOH (×3). The combined washings were concentrated under reduced pressure and the crude mixture was purified via column chromatography on SiO_2 (hexanes:EtOAc, 70:30) to give a pale yellow solid (0.27 g), containing both **1d*(D_4)** and **1d*(D_3)** in a 1:0.6 ratio. The following data correspond to the deuterated compound **1d*(D_4)**. ^{1}H NMR (CD_2Cl_2, 500 MHz) 10.58 (br s, 1H), 9.62 (s, 1H), 6.85 (d, 1H, J = 3.0 Hz), 2.77 (q, 2H, J = 7.6 Hz), 1.24 (t, 3H, J = 7.6 Hz), 1.17 (br s, 1H). Multiplet at 2.43-2.44 ppm is the result of the CHD group of the deuterated compound **1d*(D_3)**. ^{13}C NMR (CD_2Cl_2, 125 MHz) 177.9, 138.0, 129.4, 127.5, 125.2,13.9-14.7 (m, CHD_2), 17.8-16.9 (m, CD_2), 17.3 (CH_2), 17.2 (CH_3). HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_9H_9D_4NNaO$, 178.1140; found, 178.1139.

Pyrroles 1d'*(D_3) and 1d'*(D_3)

A mixture of pyrrole **7'** (0.19 g, 1.28 mmol) and Pd (10% on activated carbon, 19 mg, 10% w/w) in THF (16 mL) was stirred at room temperature under deuterium atmosphere for 19 hours. The reaction mixture was filtered through Celite®, which was then washed with MeOH (×3). The combined washings were concentrated under reduced pressure and the crude mixture was purified via column chromatography on SiO_2 (hexanes:EtOAc, 70:30) to give a pale yellow solid (0.13 g), containing both **1d'*(D_4)** and **1d'*(D_3)** in a 1:0.7 ratio. The following data correspond to the deuterated compound **1d'*(D_4)**. ^{1}H NMR (CD_2Cl_2, 500 MHz) 9.58 (s, 1H), 9.34 (br s, 1H),

6.87 (d, 1H, J = 3.0 Hz), 2.46 (q, 2H, J = 7.6 Hz), 1.19 (t, 3H, J = 7.6 Hz), 1.15 (br s, 1H). Multiplet at 2.69-2.74 ppm is the result of the CHD group of the deuterated compound ***cis*-1d*(D$_4$)**. ^{13}C NMR (CD_2Cl_2, 125 MHz) 177.7, 137.1, 129.4, 127.7, 124.0, 18.0 (CH_2), 17.2-16.3 (m, CHD_2 and CD_2), 14.9 (CH_3). HRMS-ESI (*m/z*): $[M+Na]^+$ calcd for $C_9H_9D_4NNaO$, 178.1140; found, 178.1138.

Dipyrrins sym-2d* sym and asym-2d* from 1d*

HBr (48% aqueous solution, 0.4 mL) was added drop-wise to a solution of **1d*(D$_4$)** and ***cis*-1d*(D$_3$)** (0.04 g, 0.26 mmol) in MeOH (0.8 mL) and the solution was slowly heated to 70 ºC and stirred for 5 minutes until complete consumption of the starting material according to TLC analysis. The reaction mixture was cooled to room temperature and stored in the freezer for 19 h. Filtration resulted in isolation of the precipitate as a crystalline dark green solid (22 mg) containing dypirrins **sym-2d*** and **asym-2d*** from aldehyde **1d*(D$_4$)** and **1d*(D$_3$)**, both in a 1:1 ratio. The following data correspond to **sym-2d*(D$_4$)**. ^{1}H NMR ($CDCl_3$, 500 MHz) 13.28 (br s, 2H), 7.74 (d, 2H, J = 3.0 Hz), 7.28 (br s, 1H), 2.72 (q, 4H, J = 7.6 Hz), 1.21 (t, 6H, J = 7.6 Hz), 1.18-1.17 (m, 1H). Multiplet at 2.48 ppm is the result of the CH_2 group of the **asym-2d*** from **1d*(D$_4$)** and **1d*(D$_3$)**. ^{13}C NMR ($CDCl_3$, 125 MHz) 148.9, 141.7, 131.7, 127.4, 123.2, 18.2, 18.1-17.3 (m, CD_2), 17.9, 16.7, 16.6-15.7 (m, CHD_2), 14.3. Carbons at 17.9 and 14.3 ppm are the results of the CH_3 (×2) and CH_2 (×2), respectively, of the **asym-2d*** from **1d*(D$_4$)** and **1d*(D$_3$)**. HRMS-ESI (*m/z*): $[M–Br]^+$ calcd for $C_{17}H_{17}D_8N_2$, 265.2514; found, 265.2509.

Dipyrrins sym-2d'* sym and asym-2d* from 1d'*

HBr (48% aqueous solution, 0.4 mL) was added drop-wise to a solution of **1d'*(D$_4$)** and **1d'*(D$_3$)** (0.04 g, 0.26 mmol) in MeOH (0.8 mL) and the solution was slowly heated to 70 ºC and stirred for 5 minutes until complete consumption of the starting material according to TLC analysis. The

reaction mixture was cooled to room temperature and stored in the freezer for 19 h. Filtration resulted in isolation of the precipitate as a crystalline dark green solid (22 mg) containing dypirrins **sym-2d'*** and **asym-2d*** from aldehyde **1d'*(D$_4$)** and **1d'*(D$_3$)**, both in a 1:1 ratio. The following data correspond to **sym-2d'***. ^{1}H NMR ($CDCl_3$, 500 MHz) 13.28 (br s, 2H), 7.74 (d, 2H, J = 3.0 Hz), 7.28 (br s, 1H), 2.48 (q, 4H, J = 7.6 Hz), 1.21 (t, 6H, J = 7.6 Hz), 1.18-1.17 (m, 1H). Multiplet at 2.70 ppm is the result of the CH_2 group of the **asym-2c*** from **1d*(D$_4$)** and **1d'*(D$_3$)**. ^{13}C NMR ($CDCl_3$, 125 MHz) 148.9, 141.7, 131.7, 127.4, 123.2, 18.1, 17.9, 17.3-18.1 (m, CD_2), 16.6-15.7 (m, CHD_2), 14.3. Carbons at 16.8 and 18. 1 ppm are the results of the CH_3 (×2) and CH_2 (×2), respectively, of the **asym-2d*** from **1d'*(D$_4$)** and **1d'*(D$_3$)**. HRMS-ESI (*m/z*): $[M–Br]^+$ calcd for $C_{17}H_{17}D_8N_2$, 265.2514; found, 265.2509.

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Supplementary Material

Supplementary material is available with the article through the journal Web site at XXX.

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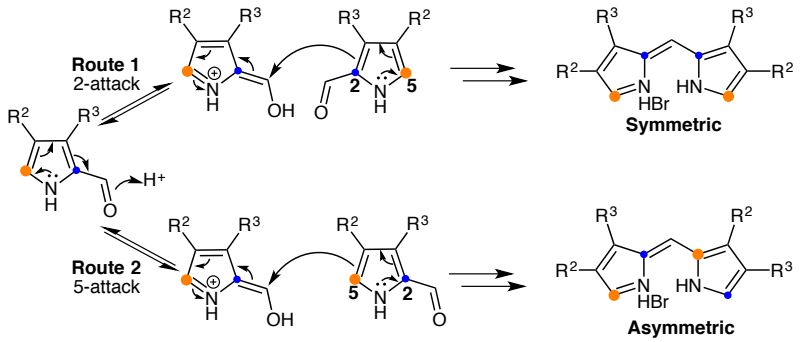
351 **TOC artwork**



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