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

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6 *This article is part of a Special Issue dedicated to celebrating the 200th Anniversary of Dalhousie*
7 *University and to highlight the chemical research being performed by faculty and alumni*

10 **Abstract**

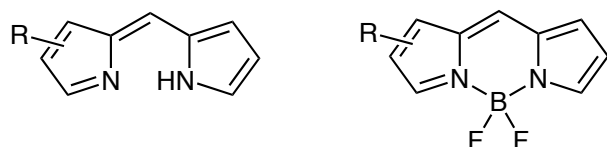
11 The synthesis of symmetric α -free *meso*-H-dipyrrin hydrobromides from 5-H-2-formyl pyrroles
12 was investigated. The self-condensation produces regioisomeric dipyrrins through adoption of
13 two mechanistic pathways. The key difference between the two pathways lies in which position
14 of the pyrrole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

18
19 **Keywords:** Dipyrrins, pyrroles, steric effects, condensation, synthesis

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22 Introduction

23 Although historically used as a building block for porphyrins,¹ in recent years the dipyrrinato
24 unit²⁻⁶ (Figure 1) has come to be appreciated as a useful chromophore by which to invoke
25 desirable features such as energy transfer and storage.^{7, 8} There are numerous reports describing
26 the use of dipyrrinato complexes in applications as diverse as biological stains/probes, light
27 harvesters and anticancer agents.⁹ Of the dipyrrinato complexes, boron difluoride complexes are
28 the most thoroughly studied due to their high thermal and photochemical stability, chemical
29 robustness, high fluorescence quantum yields and tuneable fluorescence properties. These
30 complexes are formally known as 4,4'-difluoro-4-bora-diaza-s-indacenes and are commonly
31 referred to as *F*-BODIPYs (Figure 1). Beyond the established utility of *F*-BODIPYs,¹¹⁻¹⁴ the
32 luminescence properties of these complexes, and those of other metals,¹⁰⁻¹² have fostered the use
33 of this framework in dye-sensitized solar cells and catalysts for hydrogenation and
34 hydroamination,¹³⁻¹⁶ all pointing towards a promising future for this underdeveloped ligand.



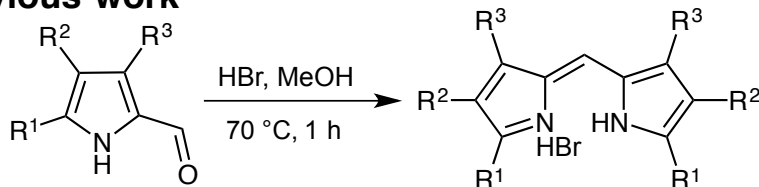
35
36 **Figure 1** Dipyrrin (left) and *F*-BODIPY (right)

37 Based on a one-pot approach to transform 2-formyl pyrroles into *F*-BODIPYs,¹⁷ we
38 previously reported the efficient synthesis of symmetric *meso*-H-dipyrrins from 2-formyl
39 pyrroles in the presence of acid (Scheme 1, top).¹⁸ Using methanol as a solvent, and heating 2-
40 formyl pyrroles at 70 °C for 1 hour in the presence of excess aqueous 48% hydrobromic acid, we
41 produced the requisite symmetric dipyrrin hydrobromide salts in moderate-to-high isolated yields
42 (60-90%). Substituents such as alkyl, keto, alkanolate and conjugated esters were well tolerated.
43 As well as being convenient and efficient, this strategy complements existing literature methods

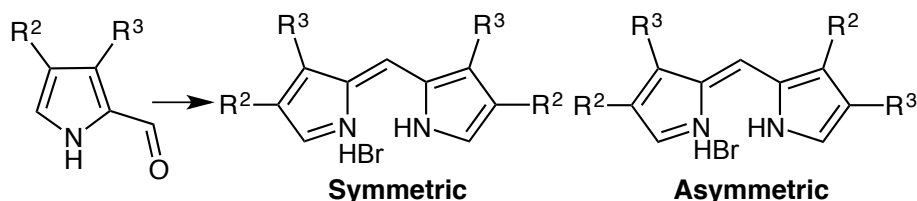
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44 by enabling the high-yielding synthesis of symmetric dipyrrens from pyrroles that bear electron
45 withdrawing functional groups.

Previous work



This work



46

47 **Scheme 1** *meso*-H-dipyrren formation from 2-formyl pyrroles

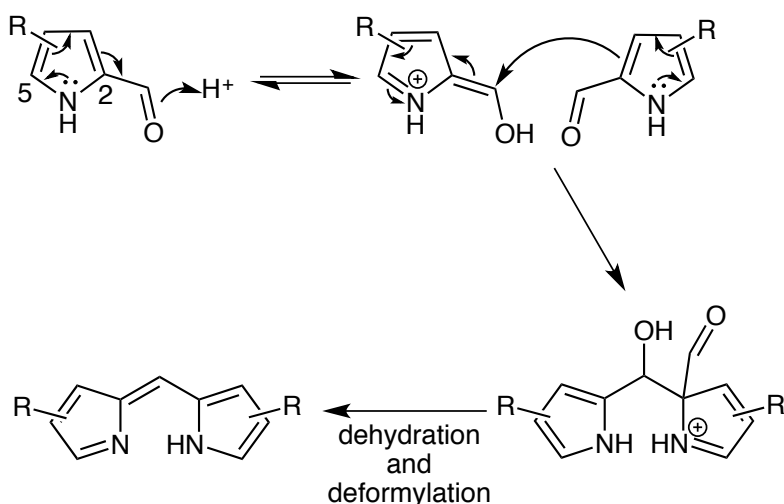
48 When subjected to these reaction conditions, a 5-H-2-formyl pyrrole (R¹ = H in Scheme
49 1, top) produced both symmetric and asymmetric regioisomers in a 9:1 ratio, respectively.¹⁸ The
50 reaction mechanism for formation of dipyrrens under these conditions was presumed to proceed
51 analogously to that for a fully substituted 2-formyl pyrrole,¹⁷ whereby the carbonyl carbon atom
52 of one pyrrole undergoes nucleophilic attack by another to generate the requisite dipyrren
53 (Scheme 2). However, this does not explain the presence of both asymmetric and symmetric
54 products. We suspected that by virtue of the unsubstituted 5-position, attack could originate from
55 either the 2- or 5-position of 5-H-2-formyl pyrroles. Thus, with two nucleophilic sites, two
56 possible regioisomeric dipyrrens could form (Scheme 1, bottom).

57 Results and Discussion

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

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



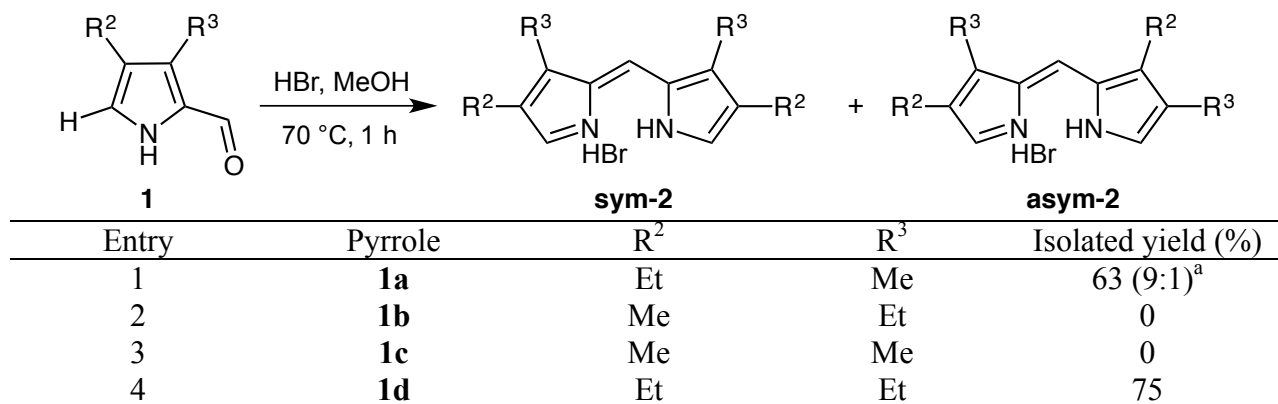
Scheme 2: Suggested pathway for the formation of symmetrical dipyrrens from fully substituted 2-formyl pyrroles

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 R² and R³. Upon exposure of the pyrroles to the reaction conditions typically used for dipyrren formation (HBr, MeOH, 70 °C, 1 h), evidence of a steric influence emerged. Indeed, when R² = Et (Table 1, entries 1 and 4), dipyrren formation was successful. On the contrary, when using pyrroles bearing R² = Me (entries 2 and 3) dipyrren 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 dipyrren formation via reaction at the position bearing the formyl group. In contrast, a methyl group at R² offers insufficient bulk to hinder reactivity at the adjacent unsubstituted α -position, and thus facilitates polymerization. Furthermore, it appears that increasing steric bulk at

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77 R² has a more pronounced effect than at R³: note that when R² is Me (**1b** and **1c**, entries 2 and 3)
 78 polymeric tars result no matter the nature of R³.

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

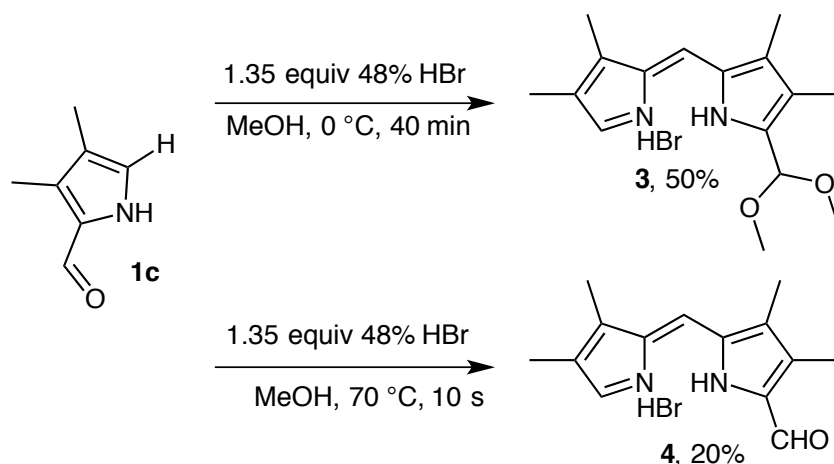


80 ^a **sym-2** was the major isomer produced

81 Given that exposure of **1c**, and a labelled variant **1c*** (see Supporting Information), to our
 82 dipyririn-formation conditions produced a polymeric tar (Table 1, entry 3), we evaluated whether
 83 thermal (not acid-catalyzed) deformylation, and/or condensation, of **1c** occurred at the reaction
 84 temperature (70 °C). However, despite heating a solution of **1c** in MeOH at 70 °C for prolonged
 85 periods of time, neither deformylation nor condensation occurred. This indicated that protonation
 86 of 2-formyl pyrroles is necessary for reaction to occur. Cognizant of this fact, the reaction
 87 conditions were modified to enable isolation of dipyririn rather than allow subsequent reaction to
 88 lead to polymerization. Exposure of a solution of **1c** to HBr at 0 °C resulted in isolation of the
 89 new acetal-containing dipyririn **3** (Scheme 3, top). As the acetal moiety of **3** is merely a protected
 90 formyl group formed under the acidic methanolic reaction conditions, this result suggested that
 91 nucleophilicity originated from the 5-position of pyrrole **1c**. When the reaction was repeated at
 92 70 °C (vessel immersed into oil bath held at 70 °C) and quenched after just 10 s, the new
 93 dipyririn **4** was isolated with no hint of the formation of **3** (Scheme 3, bottom). The retention of
 94 the formyl functionality of **4** provides further evidence for the nucleophilic role of the

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

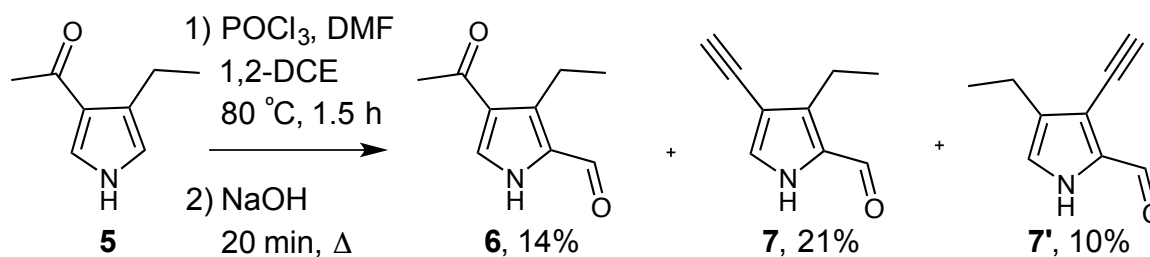


99 Isolation of the α -acetal and α -formyl dipyrrens **3** and **4** from the self-condensation of **1c**
100 indicated that attack from the unsubstituted 5-position of 5-H-2-formyl pyrroles was not only
101 possible, but was the only observed outcome when $R^2 = R^3 = \text{Me}$. We then utilised the labeled 5-
102 H-2-formyl pyrrole **1d***, bearing ethyl substituents at the 3- and 4-positions. As shown in Table
103 1, **1d** reacts to form dipyrryn: evidently the presence of the R^2 ethyl group adjacent to the
104 unsubstituted 5-position results in a significant change to reactivity (compare entries 2 and 3,
105 where $R^2 = \text{Me}$, with entry 4). Our goal with the labelled pyrrole **1d*** was to ascertain whether
106 nucleophilicity originated at the 2-position (to give the symmetric dipyrryn, **sym-2**) or the
107 unsubstituted 5-position (to give the asymmetric dipyrryn, **asym-2**). Incorporation of a deuterium
108 labell within the ethyl substituent would serve to differentiate the otherwise identical dipyrryn
109 products.

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

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

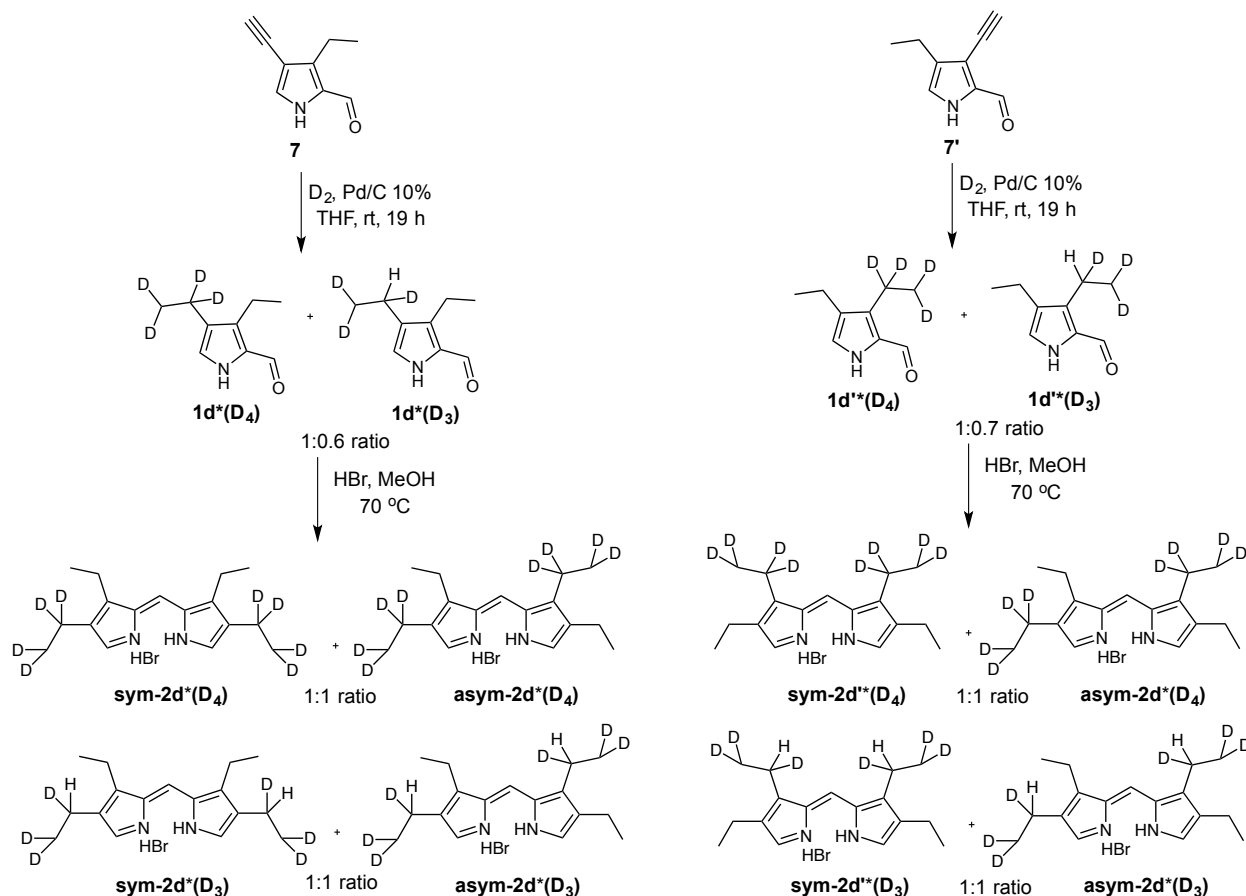


Scheme 4 Formylation of **5**

118 The terminal alkynyl group could potentially be deuterated and subsequently reduced to
119 give the desired D₁-labelled 5-H-2-formyl pyrrole **1d*** in two steps. However, treatment of **7**
120 with *n*BuLi,²⁸ followed by quenching with D₂O, resulted only in the degradation of the starting
121 material. Instead, the separated regioisomers **7** and **7'** were each reduced using D₂ gas to give
122 **1d*(D₄)** and **1d'*(D₄)**, alongside the D₃ analogues **1d*(D₃)** and **1d'*(D₃)** in a 1:0.6 and 1:0.7
123 ratio (Scheme 5). This was likely due to traces of HD in the D₂ gas supply as a result of air
124 permeation during the heavy water electrolysis for the generation of D₂,²¹ or the presence of trace
125 water during reaction.²² The two mixtures were each submitted to the acid-catalyzed
126 condensation reaction, under typical conditions, to afford the desired labelled α -free dipyrrens
127 bearing 6-8 deuterium labels (Scheme 5 shows the D₆ and D₈ variants). We determined the ratio
128 of products using the integration for two ¹H NMR signals of **2d'** and **2d'***, located at δ 2.5 and δ
129 2.7 (see Supporting Information). The ¹H NMR signals were assigned using 2-D methods, and
130 comparing to the unlabelled analogue **2d**. According to NMR spectroscopic analysis (¹H, ¹³C,
131 HMBC and HSQC) and based on the ratio of (D₄):(D₃) for the product outcome corresponding to

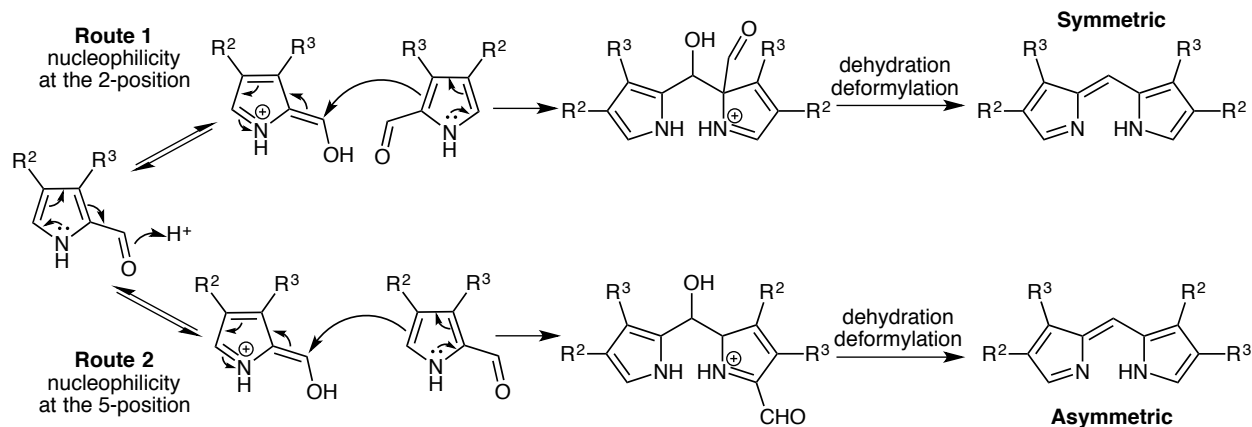
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132 reaction of **1d*** regioisomers, **sym-2d*** and **asym-2d*** were obtained in a 1:1 ratio. Likewise,
133 reaction of **2d'*** led to a 1:1 mixture of **sym-2d'*** and **asym-2d'***, again with the expected
134 (**D₄**):(**D₃**) isomeric ratio.



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144 nucleophilicity at the unsubstituted 5-position of 5-H-2-formyl pyrroles becomes competitive
145 (Route 2, Scheme 6). Notwithstanding that the analysis of products resulting from the self-
146 condensation of **1d*** or **1d'*** is complicated by the presence of pyrroles containing D₃ and D₄
147 labels, it is clear that a mixture of both symmetric and asymmetric dipyrrens form from **1d**. In the
148 self-condensation of **1c** (R² = R³ = Me), dipyrren formation presumably proceeds through Route
149 2, and the asymmetric product is formed before polymerization begins to dominate. However,
150 when R² = R³ = Et, a 1:1 ratio of symmetric and asymmetric products was observed, thereby
151 suggesting that the influence of increased steric bulk decreased the nucleophilicity of the
152 adjacent 5-position such that both routes are equally preferred, and thus an equal mixture of
153 dipyrren isomers is obtained.



155 **Scheme 6** Proposed mechanistic routes for formation of symmetric and asymmetric dipyrrens
156 from 5-H-2-formyl pyrroles

157 Hailing back to the reaction of **1a** (Table 1, entry 1), which spurred our initial
158 investigation, we believe that our findings help support a rationale for the acquired 9:1
159 symmetric:asymmetric product ratio. Pyrrole **1a** has a methyl group (R³ = Me) adjacent to the 2-
160 formyl group and an ethyl group (R² = Et) adjacent to the unsubstituted 5-position. The ethyl
161 group renders the adjacent 5-position somewhat sterically hindered and decreases the likelihood

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

165 **Conclusion**

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

173 **Experimental Section**

174 All chemicals were purchased and used as received unless otherwise indicated. Moisture-
175 sensitive reactions were performed in oven-dried glassware and under a positive pressure of
176 nitrogen. Air- and moisture-sensitive compounds were introduced via syringe or cannula through
177 a rubber septum. Flash chromatography was performed using ultra-pure silica (230-400 mm).
178 NMR spectra were recorded using a 500 MHz spectrometer instrument using CDCl₃ as solvents
179 and are reported in parts per million (ppm) against solvent peaks referenced as follows: CDCl₃ at
180 7.26 ppm for ¹H and at 77.16 ppm for ¹³C; CD₂Cl₂. at 5.31 ppm for ¹H and at 53.84 ppm for ¹³C.
181 Coupling constants (*J*) are given in Hertz (Hz). Mass spectra were obtained using TOF and LCQ
182 Duo ion trap instruments operating in ESI^{+/-} mode, as indicated.

183

184

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185 **General Procedure for the preparation of 2**

186 HBr (48% aqueous solution, 0.5 mL) was added drop-wise to a solution of 2-formyl pyrrole **1**
187 (0.4 mmol) in MeOH (1 mL) and the solution was slowly heated to 70 °C and stirred, monitoring
188 visually and by TLC. If the mixture had not visibly polymerized (black reaction mixture and
189 intractable tar), and all starting material was consumed, the reaction mixture was cooled to room
190 temperature and stored in the freezer for 19 h. If product formed, the precipitate was isolated via
191 filtration to provide dipyrrin **2** as a crystalline solid.

192 **1-Dimethoxymethyl-2,3,7,8-tetramethyl-5-*H*-4,6-dipyrrin hydrobromide (3)**

193 The title compound was synthesized following a modified literature procedure.¹⁸ Chilled (0 °C)
194 aqueous HBr (48%, 50 µL) was added to a solution of **1c** (40.5 mg, 0.329 mmol) in methanol
195 (3.3 mL) at 0 °C. Red precipitate began to form after 5 min of stirring. The reaction mixture was
196 stirred for 1 h, and the solid was collected via suction filtration, yielding the title compound as a
197 dark red solid (23 mg, 50%). M.p. 196-200 °C (decomp.); ¹H NMR (500 MHz; CDCl₃) δ 13.56
198 (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,
199 3H), 2.28 (s, 3H), 2.14 (s, 3H), 2.07 (s, 3H); ¹³C {¹H} NMR (126 MHz; CDCl₃) δ 152.6, 144.5,
200 143.3, 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
201 (*m/z*): [M+H]⁺ calculated for C₁₆H₂₃N₂O₂ 275.1754; found 275.1751.

202 **1-Formyl-2,3,7,8-tetramethyl-5-*H*-4,6-dipyrrin hydrobromide (4)**

203 The title compound was synthesized following a modified literature procedure.¹⁸ Aqueous HBr
204 (48%, 50 µL) was added to a solution of **1c** (37 mg, 0.300 mmol) in methanol (3 mL) at reflux
205 temperature. After 5-10 seconds the mixture turned a dark red, and the reaction vessel was
206 immediately plunged into an ice bath (≤0 °C), followed by addition of ether to dilute the mixture
207 and assist in rapid cooling. The resulting ethereal solution was concentrated *in vacuo*, keeping

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208 the temperature below 25 °C, until a solid precipitate formed. The precipitate was collected via
209 suction filtration and washed with ether to yield the title compound (14 mg, 20%). M.p. 185-189
210 °C (decomp); ¹H NMR (300 MHz; CDCl₃) δ 14.19 (br s, 1H), 13.64 (br s, 1H), 10.69 (s, 1H),
211 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); ¹³C{¹H}
212 NMR (126 MHz; CDCl₃) δ 184.2, 149.8, 147.6, 142.4, 141.6, 131.9, 128.9, 127.8, 127.8, 125.2,
213 10.7, 10.3, 10.0, 9.7; HRMS-ESI (*m/z*): [M+H]⁺ calculated for C₁₄H₁₇N₂O₁ 229.1335; found
214 229.1340.

215 **3-Acetyl-4-ethylpyrrole (5)**

216 The title compound was synthesized following a modified literature procedure.²³ A solution of 3-
217 hexen-2-one (8.8 g, 90 mmol) and TosMIC (17.8 g, 91.2 mmol) in a mixture of anhydrous
218 DMSO/Et₂O (450 mL, 1:2) was slowly added to a well-stirred suspension of sodium hydride (8
219 g, 200 mmol, 60% in oil) in anhydrous ether (180 mL) via cannula transfer. After completion of
220 the addition, the mixture was stirred at room temperature for 1 h, then treated with water to
221 quench excess NaH, and thoroughly extracted with ethyl acetate (4 x 350 mL). The combined
222 organic extracts were washed with brine (12 x 300 mL), dried over anhydrous Na₂SO₄, and the
223 solvent removed *in vacuo* to furnish a dark brown oil. The oil was placed in a freezer overnight,
224 producing a greasy solid which was continually extracted with pentane for 26 hours (Soxhlet) to
225 yield the desired product as a light brown solid after removal of the solvent *in vacuo* (7.9 g,
226 63%). ¹H NMR (300 MHz; CDCl₃) δ 8.44 (br s, 1H), 7.37-7.36 (m, 1H), 6.59-6.57 (m, 1H), 2.80
227 (q, *J* = 7.4 Hz, 2H), 2.40 (s, 3H), 1.20 (t, *J* = 7.4 Hz, 3H), in accordance with literature.¹⁹

228 **4-Acetyl-3-ethyl-2-formylpyrrole (6)**

229 The title compound and alkynyl by-products were synthesized following a modified literature
230 procedure.^{20, 24} POCl₃ (2.04 mL, 21.9 mmol) was added, drop-wise, at 0 °C under N₂ to DMF (16

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231 mL). The mixture was allowed to warm to room temperature, and then stirred for 15 minutes.
232 This mixture was added drop-wise to a solution of 3-acetyl-4-ethylpyrrole (**5**) (2.00 g, 14.6
233 mmol) in DCE (49 mL), at 0 °C under N₂. The resulting mixture was heated to 80 °C and stirred
234 for an additional 80 minutes. Aqueous NaOH (2 M) was added to the reaction until pH > 8 and
235 the resulting emulsion was heated at reflux temperature for 20 minutes. After cooling to room
236 temperature, water (50 mL) was added, and the reaction mixture extracted with EtOAc (3 x 50
237 mL). The combined organic fractions were washed with brine (50 mL), dried over anhydrous
238 Na₂SO₄, and concentrated *in vacuo*. The crude mixture was purified via column chromatography
239 on silica, eluting with an EtOAc/hexanes gradient (20/80, 30/70) to afford the desired product **6**
240 as a brown solid (0.33 g, 14%), along with the two 4-alkynyl-2-formylpyrroles **7** (0.44, 21%) and
241 **7'** (0.22 g, 10%). **6**: M.p. 119-123 °C; ¹H NMR (500 MHz; CDCl₃) δ 10.03 (br s, 1H), 9.74 (s,
242 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); ¹³C {¹H}
243 NMR (126 MHz; CDCl₃) δ 193.5, 179.1, 140.4, 130.7, 130.4, 125.0, 28.5, 17.9, 16.7; HRMS-
244 ESI (*m/z*): [M+Na]⁺ calculated for C₉H₁₁NO₂Na 188.0682; found 188.0680.

245 **3-Ethyl-4-ethynyl-2-formylpyrrole (7)**

246 M.p. 80 °C (blackened), followed by melting at 119-120 °C; ¹H NMR (500 MHz; CDCl₃) δ 9.64
247 (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
248 Hz, 3H); ¹³C {¹H} NMR (125 MHz; CDCl₃) δ 177.9, 141.6, 129.6, 128.6, 106.8, 79.6, 76.3, 18.0,
249 16; HRMS-ESI (*m/z*): [M+Na]⁺ calculated for C₉H₉NONa 170.0576; found 170.0575.

250 **4-Ethyl-3-ethynyl-2-formylpyrrole (7')**

251 M.p. 95 °C (blackened), followed by melting at 104-105 °C; ¹H NMR (500 MHz; CDCl₃) δ 9.68
252 (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,

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253 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125 MHz; CDCl_3) δ 178.5, 134.2, 132.5, 123.3, 114.7, 83.8, 75.2, 18.8,
254 14.5; HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_9\text{H}_9\text{NONa}$ 170.0576; found 170.0578.

255 Pyrroles **1d*(D₃)** and **1d*(D₄)**

256 A mixture of pyrrole **7** (0.30 g, 2.04 mmol) and Pd (10% on activated carbon, 30 mg, 10% w/w)
257 in THF (25 mL) was stirred at room temperature under deuterium atmosphere for 19 hours. The
258 reaction mixture was filtered through Celite[®], which was then washed with MeOH ($\times 3$). The
259 combined washings were concentrated under reduced pressure and the crude mixture was
260 purified via column chromatography on SiO_2 (hexanes:EtOAc, 70:30) to give a pale yellow solid
261 (0.27 g), containing both **1d*(D₄)** and **1d*(D₃)** in a 1:0.6 ratio. The following data correspond to
262 the deuterated compound **1d*(D₄)**. ^1H NMR (CD_2Cl_2 , 500 MHz) 10.58 (br s, 1H), 9.62 (s, 1H),
263 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).
264 Multiplet at 2.43-2.44 ppm is the result of the CHD group of the deuterated compound **1d*(D₃)**.
265 ^{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
266 (m, CD_2), 17.3 (CH_2), 17.2 (CH_3). HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calcd for $\text{C}_9\text{H}_9\text{D}_4\text{NNaO}$,
267 178.1140; found, 178.1139.

268 Pyrroles **1d'*(D₃)** and **1d'*(D₄)**

269 A mixture of pyrrole **7'** (0.19 g, 1.28 mmol) and Pd (10% on activated carbon, 19 mg, 10% w/w)
270 in THF (16 mL) was stirred at room temperature under deuterium atmosphere for 19 hours. The
271 reaction mixture was filtered through Celite[®], which was then washed with MeOH ($\times 3$). The
272 combined washings were concentrated under reduced pressure and the crude mixture was
273 purified via column chromatography on SiO_2 (hexanes:EtOAc, 70:30) to give a pale yellow solid
274 (0.13 g), containing both **1d'*(D₄)** and **1d'*(D₃)** in a 1:0.7 ratio. The following data correspond to
275 the deuterated compound **1d'*(D₄)**. ^1H NMR (CD_2Cl_2 , 500 MHz) 9.58 (s, 1H), 9.34 (br s, 1H),

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276 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).
277 Multiplet at 2.69-2.74 ppm is the result of the CHD group of the deuterated compound *cis*-
278 **1d*(D₄)**. ¹³C NMR (CD₂Cl₂, 125 MHz) 177.7, 137.1, 129.4, 127.7, 124.0, 18.0 (CH₂), 17.2-16.3
279 (m, CHD₂ and CD₂), 14.9 (CH₃). HRMS-ESI (m/z): [M+Na]⁺ calcd for C₉H₉D₄NNaO, 178.1140;
280 found, 178.1138.

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

282 HBr (48% aqueous solution, 0.4 mL) was added drop-wise to a solution of **1d*(D₄)** and *cis*-
283 **1d*(D₃)** (0.04 g, 0.26 mmol) in MeOH (0.8 mL) and the solution was slowly heated to 70 °C and
284 stirred for 5 minutes until complete consumption of the starting material according to TLC
285 analysis. The reaction mixture was cooled to room temperature and stored in the freezer for 19 h.
286 Filtration resulted in isolation of the precipitate as a crystalline dark green solid (22 mg)
287 containing dipyrrins **sym-2d*** and **asym-2d*** from aldehyde **1d*(D₄)** and **1d*(D₃)**, both in a 1:1
288 ratio. The following data correspond to **sym-2d*(D₄)**. ¹H NMR (CDCl₃, 500 MHz) 13.28 (br s,
289 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),
290 1.18-1.17 (m, 1H). Multiplet at 2.48 ppm is the result of the CH₂ group of the **asym-2d*** from
291 **1d*(D₄)** and **1d*(D₃)**. ¹³C NMR (CDCl₃, 125 MHz) 148.9, 141.7, 131.7, 127.4, 123.2, 18.2,
292 18.1-17.3 (m, CD₂), 17.9, 16.7, 16.6-15.7 (m, CHD₂), 14.3. Carbons at 17.9 and 14.3 ppm are the
293 results of the CH₃ (×2) and CH₂ (×2), respectively, of the **asym-2d*** from **1d*(D₄)** and **1d*(D₃)**.
294 HRMS-ESI (m/z): [M-Br]⁺ calcd for C₁₇H₁₇D₈N₂, 265.2514; found, 265.2509.

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

296 HBr (48% aqueous solution, 0.4 mL) was added drop-wise to a solution of **1d'*(D₄)** and **1d'*(D₃)**
297 (0.04 g, 0.26 mmol) in MeOH (0.8 mL) and the solution was slowly heated to 70 °C and stirred
298 for 5 minutes until complete consumption of the starting material according to TLC analysis. The

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299 reaction mixture was cooled to room temperature and stored in the freezer for 19 h. Filtration
300 resulted in isolation of the precipitate as a crystalline dark green solid (22 mg) containing
301 dipyrrins **sym-2d'*** and **asym-2d'*** from aldehyde **1d'***(**D**₄) and **1d'***(**D**₃), both in a 1:1 ratio. The
302 following data correspond to **sym-2d'***. ¹H NMR (CDCl₃, 500 MHz) 13.28 (br s, 2H), 7.74 (d,
303 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,
304 1H). Multiplet at 2.70 ppm is the result of the CH₂ group of the **asym-2c'*** from **1d'***(**D**₄) and
305 **1d'***(**D**₃). ¹³C NMR (CDCl₃, 125 MHz) 148.9, 141.7, 131.7, 127.4, 123.2, 18.1, 17.9, 17.3-18.1
306 (m, CD₂), 16.6-15.7 (m, CHD₂), 14.3. Carbons at 16.8 and 18.1 ppm are the results of the CH₃
307 (×2) and CH₂ (×2), respectively, of the **asym-2d'*** from **1d'***(**D**₄) and **1d'***(**D**₃). HRMS-ESI (*m/z*):
308 [M-Br]⁺ calcd for C₁₇H₁₇D₈N₂, 265.2514; found, 265.2509.

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313 Supplementary Material

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

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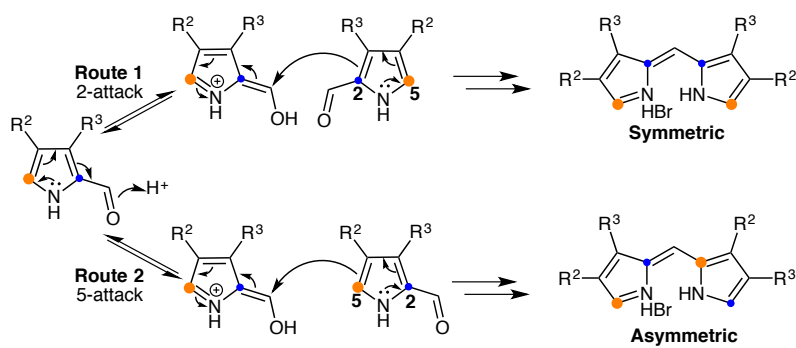
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Regioselective Substituent Effects upon the Synthesis of Dipyrroles from 2-Formyl Pyrroles

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351 TOC artwork



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