

Synthesis of Symmetric *meso*-H-Dipyrin Hydrobromides from 2-Formylpyrroles

Kate-lyn A. R. Lund, Alison Thompson*

Department of Chemistry, Dalhousie University, 6274 Coburg Road, PO BOX 15000, Halifax, Nova Scotia, B3H 4R2, Canada
Fax +1(902)4941310; E-mail: Alison.Thompson@Dal.ca

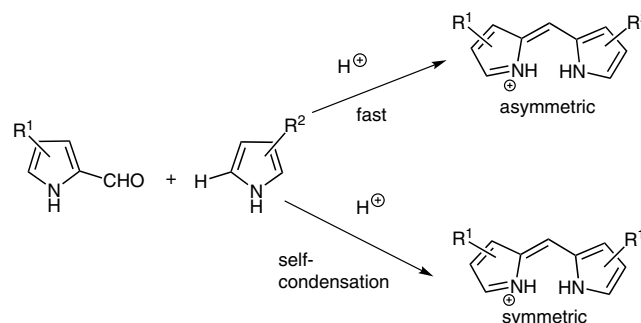
Received: 16.01.2014; Accepted after revision: 04.03.2014

Abstract: The reaction of 2-formylpyrroles in acidic methanol gives the corresponding symmetric, *meso*-H-4,6-dipyrin hydrobromides. This convenient strategy involves initial deformylation under the acidic conditions, followed by immediate in situ reaction of the resulting α -free pyrrole with the remaining 2-formylpyrrole in solution to give the dipyrin hydrobromide salt in good yield.

Key words: pyrrole, condensation, coupling, conjugation, dipyrin

The conjugated π -system of dipyrins^{1,2} consists of two pyrrolic units linked by a methine bridge. Traditionally of interest as a building block for porphyrins, the dipyrinato unit is now appreciated as a useful chromophore by which to invoke desirable features such as energy transfer and storage by the corresponding complexes.^{3,4} Beyond the established utility of *F*-BODIPYs, i.e. $-\text{BF}_2$ complexes of dipyrins,^{5–8} the luminescence properties⁹ of the ligand and other dipyrinato complexes have fostered the recent use of this framework as a component of dye-sensitized solar cells.^{10,11} Furthermore, Fe and Co dipyrinato complexes have recently been shown to catalyze the amination of C–H bonds,^{12,13} following earlier work regarding Ir and Rh dipyrinato complexes as hydrogenation catalysts.¹⁴ Indeed, there are numerous recent reports describing the use of dipyrinato complexes in applications as diverse as biological stains/probes, light harvesters and anticancer agents,^{15–20} all pointing towards a promising future for this underdeveloped ligand.

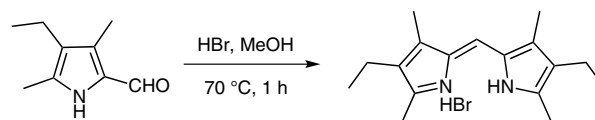
The most common synthetic route to dipyrins is the MacDonald coupling,^{21,22} an acid-catalyzed condensation of a 2-formylpyrrole with a pyrrole that is unsubstituted in the 2-position, i.e., α -free (Scheme 1).^{1,2} Upon the addition of aqueous HBr to a 2-formylpyrrole and an α -free pyrrole, a dramatic color change typically ensues, turning the solution an immediate orange/brown/brick-red color dependent upon the nature of the substrates. Rapid precipitation of the dipyrin hydrobromide salt occurs (Scheme 1, top). Both the color change and the precipitation are delayed when the α -free pyrrole is electron-poor; the presence of electron-withdrawing substituents decreases the nucleophilicity of the pyrrole.²³ In some cases, an undesired symmetric dipyrin forms under these conditions, resulting from competitive self-condensation of the 2-formylpyrrole (Scheme 1, bottom).²



Scheme 1 MacDonald coupling to generate an asymmetric dipyrin (top); when R^2 = electron-withdrawing group, the MacDonald coupling is uncompetitive and a symmetric dipyrin forms (bottom)

Symmetrical dipyrins are usually prepared via: a) reacting two equivalents of an α -free pyrrole with formic acid; b) acid-catalyzed hydrolysis, decarboxylation and condensation of pyrrole-2-carboxylates in formic acid; or c) a MacDonald coupling in which the α -free component and the 2-formylpyrrole have the same substitution pattern.²⁴ Wu and Burgess reported the preparation of symmetric *F*-BODIPYs from 2-formylpyrroles, eliminating the use of an α -free pyrrole.²⁵ BODIPYs were isolated via in situ trapping of the dipyrin, demonstrating the one-pot synthesis of BODIPYs from 2-formylpyrroles. As such, just as α -free pyrroles can be generated via the acid-catalyzed decarboxylation of 2-carboxylate pyrroles so the precedent was demonstrated for the deformylation of 2-formylpyrroles.

We herein report the efficient synthesis and isolation of symmetric, *meso*-H-dipyrins formed from 2-formylpyrroles in the presence of acids (Scheme 2). As well as being extremely convenient, this strategy complements existing methods by enabling the high-yielding synthesis of symmetric dipyrins where the α -free pyrrole has electron-withdrawing functional groups or may not be easily accessed.



Scheme 2 Dipyrin hydrobromides from 2-formylpyrroles

To investigate the formation of dipyrins via acid-catalyzed deformylation (Scheme 2), 3,5-dimethyl-4-ethyl-2-

formylpyrrole (**1a**) was chosen as a test substrate (Table 1). First, a methanolic solution of **1a** and 1.1 equivalents of 48% aqueous HBr were stirred at room temperature. Although analysis using TLC indicated that some dipyrin had formed after 48 hours, significant amounts of starting material remained (entry 1). Elevating the reaction temperature to 40 °C induced a gradual color change and the precipitation of the product after five hours (entry 2). However, heating the reaction mixture at 70 °C for just two hours returned a 72% yield of the required dipyrin hydrobromide (entry 3), and the yield was elevated to 84% after just one hour with the use of excess HBr (entry 4). The use of acetic acid, acetonitrile or dichloroethane was also somewhat effective, but longer reaction times were required and lower yields resulted (entries 5–7). The use of TFA as acid was effective (entry 8), but for convenience we decided to pursue the more crystalline hydrobromide salts. Presumably,²⁵ the mechanism involves (some of) the 2-formylpyrrole undergoing deformylation to give the α -free analogue which immediately undergoes rapid condensation, at 40 °C, with the remaining unreacted 2-formylpyrrole; this was supported using ¹H NMR spectroscopy to monitor a reaction in MeOD. However, the regioselective formation of **2c** potentially points to some concerted character.

Table 1 Examining the Effect of Acid, Temperature and Solvent on the Conversion of **1a** into **2a**

Entry	Solvent	Temp (°C)	Time (h)	Acid (equiv)	Isolated yield (%)
1	MeOH	r.t.	>48	HBr (1.1)	incomplete
2	MeOH	40	5	HBr (1.1)	70
3	MeOH	70	2	HBr (1.1)	78
4	MeOH	70	1	HBr (excess)	84
5	AcOH	70	4	HBr (excess)	67
6	MeCN	70	2.5	HBr (excess)	50
7	DCE	70	4.5	HBr (excess)	70
8	MeOH	70	24	TFA (excess)	74

A variety of 2-formylpyrroles were then subjected to the optimized reaction conditions to evaluate the scope of the methodology (Table 2). Analogues bearing alkyl (**2a–e**), keto (**2f–h**), alkanoate (**2g–j**) and conjugated ester (**2k,l**) substituents all reacted as expected to give the requisite dipyrin salts. For the cases where yields are only moderate, the microcrystallinity of these dipyrins hampered isolation, e.g. **2h**. Furthermore, the ethoxy groups of **1g** and **1h** inevitably underwent exchange in acidic methanol, and gave the methyl ester-containing dipyrins **2g** and **2h**, respectively.

Overall, the synthesis of symmetric dipyrins via the respective 2-formylpyrrole under acidic conditions in meth-

Table 2 Dipyrin Hydrobromide Salts from 2-Formylpyrroles

Dipyrin	R ¹	R ²	R ³	Isolated yield (%)
2a	Me	Et	Me	84
2b	Me	Me	Me	72
2c	Me	Et	H	63 ^a
2d	Me	(CH ₂) ₄ Me	Me	79
2e	Me	(CH ₂) ₆ Me	Me	75
2f	Me	Ac	Me	83
2g	Et	COCH ₂ CH ₂ CO ₂ Me	Me	79
2h	Et	CO(CH ₂) ₄ CO ₂ Me	Me	50
2i	Me	CH ₂ CO ₂ Me	Me	65
2j	Me	CH ₂ CH ₂ CO ₂ Me	Me	84
2k	Me	CO ₂ Bu	Me	79
2l	Me	CO ₂ Bn	Me	90

^a Ratio of symmetric:asymmetric dipyrins = 9:1.

anol, is convenient and high yielding at elevated temperatures.^{26,27}

Acknowledgment

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC).

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

References and Notes

- Wood, T. E.; Thompson, A. *Chem. Rev.* **2007**, *107*, 1831.
- Wood, T. E.; Uddin, I. M.; Thompson, A. In *Handbook of Porphyrin Science*; Kadish, K. M.; Smith, K.; Guillard, R., Eds.; World Scientific: New Jersey, **2010**, 235.
- Khan, T. K.; Bröring, M.; Mathur, S.; Ravikanth, M. *Coord. Chem. Rev.* **2013**, *257* (15–16), 15 2348.
- Mondal, P.; Chaudhary, A.; Rath, S. P. *Dalton Trans.* **2013**, *42*, 12381.
- Benstead, M.; Mehl, G. H.; Boyle, R. W. *Tetrahedron* **2011**, *67*, 3573.
- Boens, N.; Leen, V.; Dehaen, W. *Chem. Soc. Rev.* **2012**, *41*, 1130.
- Loudet, A.; Burgess, K. *Chem. Rev.* **2007**, *107*, 4891.
- Ziessel, R.; Ulrich, G.; Harriman, A. *New J. Chem.* **2007**, *31*, 496.
- Baudron, S. A. *Dalton Trans.* **2013**, *42*, 7498.

- (10) Li, G.; Bomben, P. G.; Robson, K. C. D.; Gorelsky, S. I.; Berlinguette, C. P.; Shatruk, M. *Chem. Commun.* **2012**, 48, 8790.
- (11) Li, G.; Hu, K.; Yi, C.; Knappenberger, K. L.; Meyer, G. J.; Gorelsky, S. I.; Shatruk, M. *J. Phys. Chem. C* **2013**, 117, 17399.
- (12) Hennessy, E. T.; Betley, T. A. *Science* **2013**, 340, 591.
- (13) King, E. R.; Hennessy, E. T.; Betley, T. A. *J. Am. Chem. Soc.* **2011**, 133, 4917.
- (14) Yadav, M.; Singh, A. K.; Pandey, D. S. *Organometallics* **2009**, 28, 4713.
- (15) Ding, Y.; Li, X.; Li, T.; Zhu, W.; Xie, Y. *J. Org. Chem.* **2013**, 78, 5328.
- (16) Gupta, R. K.; Pandey, R.; Sharma, G.; Prasad, R.; Koch, B.; Srikrishna, S.; Li, P.-Z.; Xu, Q.; Pandey, D. S. *Inorg. Chem.* **2013**, 52, 3687.
- (17) Gupta, R. K.; Sharma, G.; Pandey, R.; Kumar, A.; Koch, B.; Li, P.-Z.; Xu, Q.; Pandey, D. S. *Inorg. Chem.* **2013**, 52, 13984.
- (18) Hall, J. D.; McLean, T. M.; Smalley, S. J.; Waterland, M. R.; Telfer, S. G. *Dalton Trans.* **2010**, 39, 437.
- (19) Klein, J. H.; Sunderland, T. L.; Kaufmann, C.; Holzapfel, M.; Schmiedel, A.; Lambert, C. *Phys. Chem. Chem. Phys.* **2013**, 15, 16024.
- (20) McLean, T. M.; Moody, J. L.; Waterland, M. R.; Telfer, S. G. *Inorg. Chem.* **2012**, 51, 446.
- (21) MacDonald, S. F. *J. Chem. Soc. C* **1952**, 4176.
- (22) Shanmugathan, S.; Edwards, C.; Boyle, R. W. *Tetrahedron* **2000**, 56, 1025.
- (23) Paine, J. B. III. In *The Porphyrins*; Vol. I; Dolphin, D., Ed.; Chap. 4; Academic Press: New York, **1978**, 101.
- (24) Tu, B.; Wang, C.; Ma, J. *Org. Prep. Proced. Int.* **1999**, 31, 349.
- (25) Wu, L.; Burgess, K. *Chem. Commun.* **2008**, 4933.
- (26) **General Procedure for the Synthesis of meso-H-4,6-Dipyrrin Hydrobromides:** Aqueous HBr (48%, 1 mL) was added to a solution of 2-formylpyrrole (100 mg, 1 equiv) in MeOH (2 mL). The reaction mixture was then heated at reflux temperature, with stirring, for 1 h or until all starting material was consumed, monitored using thin layer chromatography (30% EtOAc–hexanes). The precipitated product was collected using suction filtration and the residue was washed with Et₂O to yield the respective meso-H-4,6-dipyrrin hydrobromide.
- (27) 1,3,7,9-Tetramethyl-2,8-diethyl-4,6-dipyrrin Hydrobromide (**2a**): The title compound was isolated as a red solid (93 mg, 84% yield); mp 225 °C (dec.). ¹H NMR (300 MHz, CDCl₃): δ = 12.90 (br s, 2 H), 7.01 (s, 1 H), 2.65 (s, 6 H), 2.41 (q, 4 H), 2.25 (s, 6 H), 1.06 (t, 6 H). ¹³C NMR (125 MHz, CDCl₃): δ = 153.9, 141.4, 130.7, 126.3, 118.8, 17.4, 14.6, 13.0, 10.2. HRMS (ESI): *m/z* [M + H]⁺ calcd for C₁₇H₂₅N₂: 257.2012; found: 257.2018.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.