Synthesis of symmetric meso-*H* dipyrrin hydrobromides from 2-formyl pyrroles

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Received:

Abstract: The reaction of 2-formyl pyrroles in acidic methanol gives the corresponding symmetric, *meso*-H 4,6-dipyrrin 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-formyl pyrrole in solution to give the dipyrrin hydrobromide salt in good yield.

Key words: Pyrrole, condensation, coupling, conjugation, dipyrrin.

The conjugated π-system of dipyrrins[1,2] consists of two pyrrolic units linked by a methine bridge. Traditionally of interest as a building block for porphyrins, the dipyrrinato 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. $-BF_2$ complexes of dipyrrins,[5-8] the luminescence properties[9] of the ligand and other dipyrrinato complexes have fostered the recent use of this framework as a component of dye-sensitized solar cells.[10,11] Furthermore, Fe and Co dipyrrinato complexes have recently been shown to catalyze the amination of C–H bonds,[12,13] following earlier work regarding Ir and Rh dipyrrinato complexes as hydrogenation catalysts.[14] Indeed, there are numerous recent reports describing the use of dipyrrinato complexes in applications as diverse as biological stains/probes, light harvesters and anti-cancer agents,[15-20] all pointing towards a promising future for this under-developed ligand.

The most common synthetic route to dipyrrins is the MacDonald coupling,[21,22] an acid-catalyzed condensation of a 2-formyl pyrrole with a pyrrole that is unsubstituted in the 2-position, i.e., α-free (Figure 1).[1,2] Upon the addition of aqueous HBr to a 2-formyl pyrrole and an α-free pyrrole, a dramatic colour change typically ensues, turning the solution an immediate orange/brown/brick-red colour dependent upon the nature of the substrates. Rapid precipitation of the dipyrrin bromine salt occurs (Figure 1, top). Both the colour 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 dipyrrin forms under these conditions, resulting from competitive self-condensation of the 2-formyl pyrrole (**Figure 1**, bottom).[2]

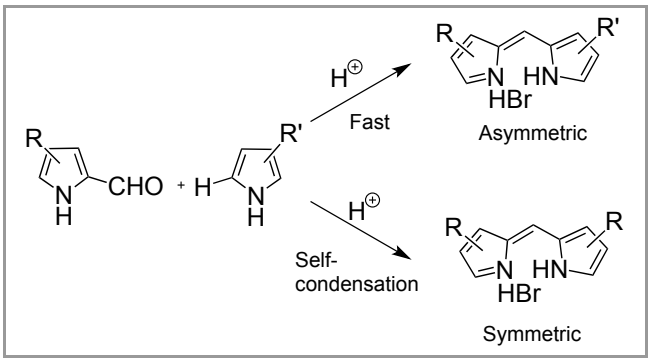


Figure 1 MacDonald coupling to generate an asymmetric dipyrrin (top); when R' = electron-withdrawing group, the MacDonald coupling is uncompetitive and a symmetric dipyrrin forms (bottom)

Symmetrical dipyrrins are usually prepared *via*; a) reacting two equiv 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-formyl pyrrole have the same substitution pattern.[24] Wu and Burgess reported the preparation of symmetric *F*-BODIPYs from 2-formyl pyrroles, eliminating the use of an α-free pyrrole.[25] BODIPYs were isolated via *in situ* trapping of the dipyrrin, demonstrating the one-pot synthesis of BODIPYs from 2-formyl pyrroles. 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-formyl pyrroles.

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

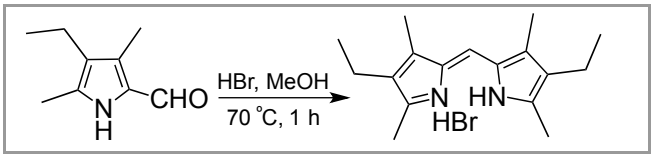


Figure 2 Dipyrrin hydrobromides from 2-formyl pyrroles

To investigate the formation of dipyrrins via acid-catalyzed deformylation (Figure 2), 3,5-dimethyl-4-

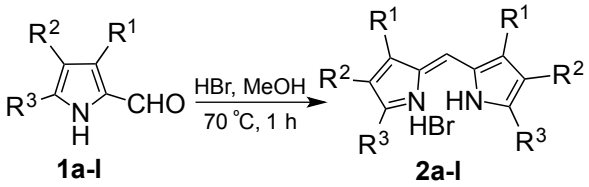
ethyl-2-formylpyrrole **(1a)** was chosen as a test substrate (Table 1). First, a methanolic solution of **1a** and 1.1 equiv of 48% aqueous HBr were stirred at room temperature. Although analysis using TLC indicated that some dipyrrin had formed after 48 hours, significant amounts of starting material remained (entry 1). Elevating the reaction temperature to 40 ºC induced a gradual colour change and the precipitation of the product after 5 hours (entry 2). However, heating the reaction mixture at 70 ºC for just 2 hours returned a 72% yield of the required dipyrrin hydrobromide (entry 3), and the yield was elevated to 84% after just 1 hour with the use of excess HBr (entry 4). The use of acetic acid, acetonitrile or dichloroethane were 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-formyl pyrrole undergoing deformylation to give the α-free analog which immediately undergoes rapid condensation, at 40 ºC, with the remaining unreacted 2-formyl pyrrole: this was supported using ^{1}H NMR spectroscopy to monitor a reaction in MeOD. However, the regioselective formation of **2c** potentially points to some concerted character.

A variety of 2-formyl pyrroles were then subjected to the optimized reaction conditions to evaluate the scope of the methodology (Table 2). Analogs bearing alkyl (**2a-e**), keto (**2f-h**), alkanoate (**2g-j**) and conjugated ester (**2k-l**) substituents all reacted as expected to give the requisite dipyrrin salts. For the cases where yields are only moderate, the microcrystallinity of these dipyrrins 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 dipyrrins **2g** and **2h**.

Table 1 Examining the effect of acid, temperature and solvent on the conversion of **1a** into **2a**

entry	solvent	temperature (ºC)	time (h)	acid (equiv)	isolated yield (%)
1	MeOH	rt	>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

Table 2 Dipyrrin hydrobromide salts from 2-formyl pyrroles



1a-l **2a-l**

dipyrrin	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	$(CH_2)_4CH_3$	Me	79
2e	Me	$(CH_2)_6CH_3$	Me	75
2f	Me	Ac	Me	83
2g	Et	$COCH_2CH_2CO_2Me$	Me	79
2h	Et	$CO(CH_2)_4CO_2Me$	Me	50
2i	Me	CH_2CO_2Me	Me	65
2j	Me	$CH_2CH_2CO_2Me$	Me	84
2k	Me	CO_2Bu	Me	79
2l	Me	CO_2Bn	Me	90

[a]9:1 ratio of symmetric:asymmetric dipyrrins

Overall, the synthesis of symmetric dipyrrins *via* the respective 2-formyl pyrrole under acidic conditions in methanol, is convenient and high yielding at elevated temperatures.[26,27]

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

Acknowledgment

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

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(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-formyl pyrrole (100 mg, 1 equiv) in methanol (2 mL). The reaction mixture was then heated at reflux temperature, with stirring, for one hour or until all starting material was consumed, monitored using thin layer chromatography (30% ethyl acetate/hexanes). The precipitated product was collected using suction filtration and the residue was washed with diethyl ether 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 ºC (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 12.90 (br s, 2H), 7.01 (s, 1H), 2.65 (s, 6H), 2.41 (q, 4H), 2.25 (s, 6H), 1.06 (t, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) 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 $C_{17}H_{25}N_2$ 257.2012; found, 257.2018.

Synthesis of meso-*H* dipyrrin hydrobromides