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An unprecedented regioselective lithiation of dipyrromethanes. Synthesis of *meso*-functionalized dipyrromethanes

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Abstract—Functionalization of *meso*-positions of dipyrromethanes, gives valuable intermediates through a highly regioselective lithiation–substitution sequence.

Dipyrromethanes are important intermediates for the preparation of synthetic porphyrins[1] and related compounds (dipyrrins, calix[*n*]pyrroles, chlorins, corroles). Unlike naturally occurring porphyrins, which are substituted at the β-positions and unsubstituted at the *meso*-positions (5-positions), synthetic porphyrins are invariably substituted at the *meso*-positions and lack substituents at the β-position. Dipyrromethanes are also frequently used as precursors to dipyrromethenes, which are important ligands in the design of macromolecular structures. Difluoroboron complexes of dipyrromethenes, (BODIPY) derivatives are used as fluorescent dyes for biological samples.[2] Access[3] to such building blocks has thus far relied mainly on one-pot condensations of pyrrole and the desired aldehydes in acidified solvents: $BF_3{\cdot}OEt_2/CH_2Cl_2$, acetic acid/DMF or THF, $SnCl_4/CH_2Cl_2$, *p*-toluenesulfonic acid/MeOH or toluene, or aqueous HCl/THF. In most of these syntheses a large pyrrole:aldehyde ratio (up to 400:1) is employed to drive the reaction to completion and to supress reactions leading to unwanted linear/cyclic oligomers. Further, the nonavailability of many functionalized aldehydes, the failure of aliphatic aldehydes to react and their propensity to show side reactions limit the scope of this route. The indirect synthesis through the use of perhydro 1,3-heterocycles,[4] was also attended by the formation of tripyrranes. Thus a direct route to *meso*-substituted dipyrromethanes is still required.

In this letter, we report our studies concerning the development of an approach to synthesize *meso*-substituted dipyrromethanes, which allows us, *inter alia*, to append a variety of substituents and is free of all of the limitations cited above. We capitalized on the successful and unprecedented generation of a carbanion (*n*-BuLi/THF, −20 °C) at the *meso*-position of a 5-unsubstituted dipyrromethane, and its reaction with a number of electrophiles.[5] The approach is single-pot and allows the introduction of a variety of substituents exclusively at the *meso*-position to furnish dipyrromethanes **2**. Further, no evidence of α-lithiation was observed under these reaction conditions.

5-Unsubstituted dipyrromethane **1a** was synthesized in a high yield, following the procedure reported[4] by us earlier. We initially examined the metallation of *N*,*N*′-dimethyldipyrromethane **1a** with 1.0–3.0 equiv of *n*-BuLi (−20 °C) and subsequent normal and inverse quenching with methanol-d_4 (Scheme 1) to determine the optimal conditions for metallation at the *meso*-position. Employing 3.0 equiv of the base, a deep red colored anion could be seen; a lower ratio of the base did not yield a persistent colored anion. Using 3.0 equiv of *n*-BuLi, for 1.0 equiv of **1a**, deuterium distribution (%-d_1 incorporation and location) in the resultant product was analyzed by a high field ^{1}H NMR analysis. However, no deuterium incorporation was observed at the *meso*-position as indicated by the exclusive isolation of **1a** (entry 1, Table 1); neither was deuterium incorporation observed

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Keywords: Dipyrromethane; Lithiation; Anions; *meso*-Substitution; *meso*-Porphyrins.

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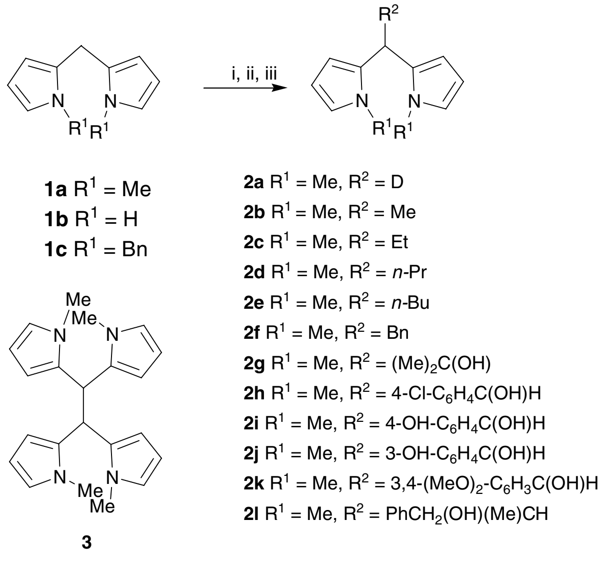

Scheme 1. Synthesis of *meso*-substituted dipyrromethanes. Reagents and conditions: (i) *n*-BuLi (3 equiv), THF, −20 °C; (ii) electrophile (2 equiv); (iii) NH_4Cl quenching.

Table 1. Synthesis of *meso*-substituted dipyrromethanes **2**

Entry	Electrophile	Product[a] **2**	Yield[b] (%)
1	CD_3OD	**2a**	0
2	Me_2SO_4	**2b**	32
3	EtBr	**2c**	61
4	*n*-PrBr	**2d**	55
5	*n*-BuBr	**2e**	38
6	BnCl	**2f**	51
7	MeCOMe	**2g**	54
8	4-Cl–C_6H_4CHO	**2h**	30
9	4-HO–C_6H_4CHO	**2i**	25
10	3-HO–C_6H_4CHO	**2j**	31
11	3,4-$(MeO)_2$–C_6H_3CHO	**2k**	55
12	$PhCH_2COMe$	**2l**	50
13	MeI	**2e**	68
14	ICl	**2e**	30
15	$BrCH_2COOEt$	**2e**	55
16	$CH_2{=}CHCH_2Br$	**2e**	35

[a] Compound **3** was formed in all entries in about 20% yield.

[b] Isolated purified (column chromatography: silica gel: 60–120 mesh, ethyl acetate/hexane mixtures as eluent) yields.

on the pyrrole *C*-rim.[8] We believe that the rapid deuterium exchange of d_4-methanol with excess *n*-BuLi present, meant that it was not available for quenching the *meso*-anionic species. This interpretation is supported by the quantitative trapping of the *meso*-anionic species with a number of other electrophiles (Table 1).

Typically, treatment of dipyrromethane **1a** with 3.0 equiv[9] of freshly prepared *n*-BuLi (1.6 N in hexanes) in THF at −20 °C, under a blanket of dry nitrogen gas, followed by stirring to reach room temperature yielded a red colored solution. After 0.3 h at room temperature, the reaction mixture was cooled to −20 °C and 2.0 equiv of ethyl bromide was added, and the reaction mixture was allowed to warm to room temperature then quenched with saturated aqueous NH_4Cl solution to obtain the *meso*-substituted product **2c** after chromatographic purification.

The synthesis of various *meso*-substituted dipyrromethanes **2** is summarized in Scheme 1. The reaction proceeded smoothly with a range of electrophiles such as alkyl halides, aralkyl halides, aldehydes, and ketones. The formation of **2b–l** (Table 1) was attended by the formation of dipyrromethane dimer **3**, which could arise from a metal–halogen interchange[10] reaction of the initially formed *meso*-anionic species of **1a** and the lithium halide present in *n*-BuLi. However, the isolated yield of **2b–l** was strongly dependent on the specific conditions employed, in addition to the amount of the base used for deprotonation. For example, allowing the reaction to warm to −10 °C from −20 °C, after the initial addition of *n*-BuLi, enhanced the yield of dimer **3**. The formation of dimer **3** is interesting as it could serve as an intermediate for the synthesis of *meso*-linked porphyrinoids.[11] It was also formed when metallated **1a** was quenched with saturated NH_4Cl, without adding an electrophile. Further, the reactions of the anion of **1a** with electrophiles such as methyl iodide, iodine monochloride, ethyl bromoacetate, and allyl bromide, furnished **3** along with **2e**, presumably through metal–halogen exchange followed by nucleophilic substitution with *n*-BuLi.

All compounds were fully characterized by NMR (^{1}H and ^{13}C) spectroscopy, mass spectrometry, and microanalytical analysis and in the case of **3**, single crystal X-ray diffraction analysis[12] (Fig. 1).

Similar reactions were attempted with **1b**, but *meso*-metalation could not be achieved, presumably due to the presence of the much more acidic pyrrolic *N*-hydrogens. Thus, to convert dipyrromethane **1b** into **1c**, potassium *tert*-butoxide could be employed as a base.

The reaction of **1c** with *n*-BuLi under similar conditions did not furnish the desired *meso*-substituted dipyrromethanes, but instead, benzylic substitution was observed.

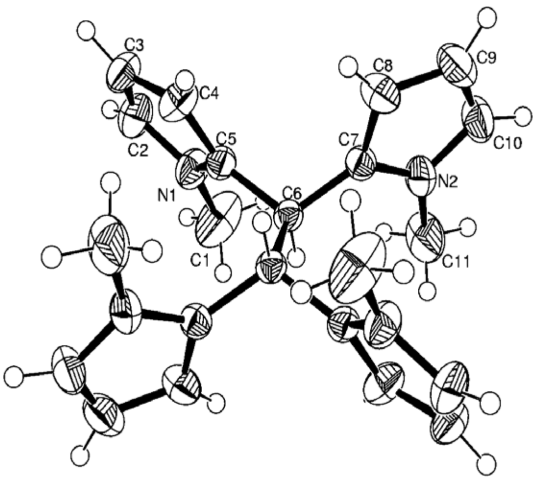

Figure 1. X-ray crystal structure of **3** showing a stereoview of the molecule and the labeling scheme used in the structure analysis.

Thus, treatment of **1c** with *n*-BuLi, using less than 3.0 equiv, gave no anion formation, but when 3.0 equiv were added, a colored anionic species was formed, which upon quenching with ethyl bromide (2.0 equiv) furnished diethyl derivative 2,2-bis-[1-(1-phenylpropyl)-1*H*-pyrrol]methane (see Supplementary data), substituted at the benzylic carbons, in a quantitative yield.[13] In none of these reactions was formation of a product corresponding to **3**, that is, dimeric dipyrromethane, observed.

In summary, we have shown that the *meso*-position of the *N*-methyldipyrromethanes can be elaborated using a metallation–substitution sequence. The methodology is simple and furnishes the products in good to high yields. The fact that the dipyrromethanes come 'prefunctionalized' at the *meso*-position, means that they could be used as precursors of *meso*-porphyrins, calix[4]pyrroles[14] and related systems for a range of applications. Work is in progress to develop similar reactions of N-unsubstituted dipyrromethanes through protection with groups other than alkyl.

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Supplementary data

Experimental procedures and spectral data for all compounds are given in the Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.11.056.

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13. Even by employing *sec*-BuLi (3.0 or 6.0 equiv), followed by quenching with ethyl bromide, *meso*-substitution was not observed. After the addition of approx. 3.0 equiv of the base the color of the reaction turned red, which subsequently turned green, quenching of which yielded a product mixture indicative of benzylic substitution.
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