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5,5-Dialkyldipyrromethane as a precursor for the synthesis of calix[4]phyrins and pseudocorroles using MacDonald [2+2] condensations

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Abstract—The reaction of formylated dialkyldipyrromethanes with 5,5-dialkyl or 5-aryldipyrromethanes afforded *meso*-tetraalkyl or dialkylaryl-calix[4]phyrins, respectively. Templating with Ni(II) was needed to get these compounds in acceptable yields. From these MacDonald condensations, trisubstituted pseudocorroles were also isolated as Ni(II) chelates.

Calix[4]phyrins (porphodimethenes) are porphyrin analogues, partly having the conjugated character of porphyrins and partly the nonconjugated character of calixpyrroles, which have been intensively studied during the last few years.[1] Since these hybrid molecules showed to be not only interesting intermediates in the oxidation pathway of porphyrinogen to porphyrins[2] or in the synthesis of chlorins by isomerization,[3] but also are promising as receptors for anion and small neutral molecules,[4] several new methods of their synthesis have been developed. They have been synthesized by reductive alkylation of porphyrins,[5] by dealkylation of calix[4]pyrroles,[2] and recently reported methods included the reaction of acetone or vicinal diketones with 5-aryldipyrromethanes,[4a,c,6] dialkyldipyrromethane with aromatic aldehydes,[1,7] or the condensation of pyrrole with sterically encumbered aldehydes.[8] Nevertheless, the ability to vary substituents at the *meso* positions of the tetrapyrrolic macrocycle still remains rather limited. To date, the only known approach to the preparation of calix[4]phyrins that are asymmetrically substituted at sp^3 centres uses a metallated porphyrin as the starting material.[5c]

Inspired by the previously reported work on the MacDonald [2+2] condensation reactions of dipyrromethanes with bisformyldipyrromethanes leading to asymmetrically substituted 5,15-diphenylporphyrins,[9] and on the other hand, the successful application of similar reaction to the synthesis of unstable porphodimethenes bearing solely alkyl groups at β-positions of pyrroles,[3] we tried to expand the synthetical utility of this classical method to β-unsubstituted *meso*-tetraalkylporphodimethenes. In this letter, preliminary results of this study are presented.

Initially, we examined a simple macrocyclization of the monoformylated pyrrolic precursor. The requisite 1-formyl-5,5-dipropyldipyrromethane (**2**) was obtained from **1** in 58% yield using the Clezy-modified Vilsmeier-Haack procedure (Scheme 1).[10–12] As we hoped, the acid-catalyzed condensation of **2** afforded the symmetrical macrocycle **4a** as yellow crystals, but even after some optimization of the procedure, the product was isolated in a disappointingly low yield (5.5%). Presumably, this was a consequence of high steric strain involved in the formation of the tetraalkylporphyrinogen intermediate, like in the case of the analogous porphyrin synthesis.[9] In order to confer a favourable configuration of the intermediate compound and improve the yield, we employed a metal cation template strategy. The metal cation of choice for incorporation as a template was Ni(II), since its complexes with porphodimethenes are rather well known. Their complexes could easily be separated by flash chromatography and, being diamagnetic, could

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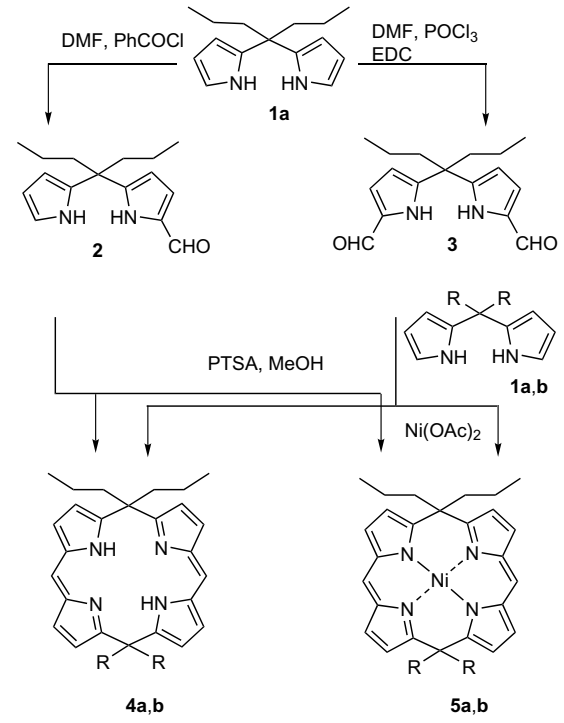
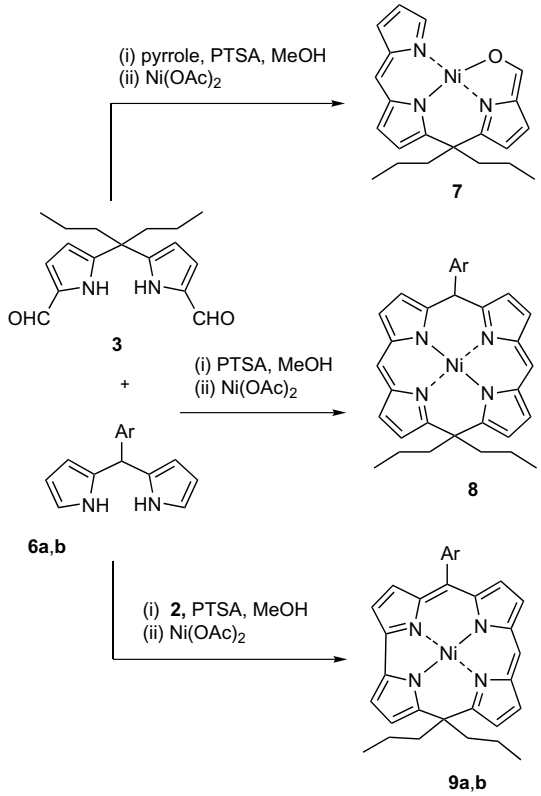


Reactants	Product	R,R	Yield (%)
2	**4a**	*n*-propyl	5.5
1a, **3**	**4a**	*n*-propyl	3.0
1b, **3**	**4b**	- $(CH_2)_5$-	1.5
2	**5a**	*n*-propyl	21
1a, **3**	**5a**	*n*-propyl	18
1b, **3**	**5b**	$(CH_2)_5$	28

Scheme 1.

be analyzed by NMR spectroscopy. Condensation of **2** in the presence of nickel acetate provided a reliable route to the metallated macrocycle **5a**[13] obtained in a reasonable 21% yield. Similar procedures were applied to condensations of dipyrromethane **1b** derived from cyclohexanone, with **3**[14] giving asymmetrical free-base and metallated macrocycles **4b** and **5b**, respectively (Scheme 1).



Reactants	Product	Ar	Yield (%)
3, **6a**	**8**	4-$CH_3OC_6H_4$	7.7
3, **6a**	**9a**	4-$CH_3OC_6H_4$	3.6
3, **6b**	**9b**	2,6-$Cl_2C_6H_3$	2.9
3, **6b**	**7**	2,6-$Cl_2C_6H_3$	2.3
3, pyrrole	**7**		6.0
2, **6a**	**9a**	4-$CH_3OC_6H_4$	10.0

Scheme 2.

When the same conditions were applied to the condensation of dipyrromethanes **6a** and **b** with **3**, three types of products were isolated: the expected calix[4]phyrin **8**, the contracted macrocycle **9a** and **b** and the tripyrrolic chelate **7**, dependent on the nature of the aryl substituent (Scheme 2). From the reaction using *p*-methoxyphenyl derivative **6a**, we isolated the *meso*-trisubstituted calix[4]phyrin **8**[15] and a small amount of corrole-type macrocycle **9a**.[16] The latter compound was also obtained from dipyrromethanes **2** and **6a**. The skeleton of this compound is isomeric to corrole. Since the term isocorrole is already reserved for [2.0.1.0]-tetraphyrins, we will call these compounds pseudocorroles. The compound **8** could not be converted to the isoporphyrin[17] on oxidation.

Attempted condensation of the more sterically hindered substrate **6b** with **3** did not give any calix[4]phyrin, but afforded macrocycle **9b** (2.9% yield) and compound **7**[18] (2.3% yield). The latter could also be obtained from dipyrromethane **3** and pyrrole. Apparently, pyrrole did form under the reaction conditions by decomposition of the unstable aryldipyrromethane **6b**.

The observed C_1 extrusion has been earlier reported (deformylation or demethylation) in case of templated syntheses of corroles with manganese(III) or cobalt-(III).[19,20] On the other hand, recently Callot and co-workers have published the formation of divalent corroles by ring contraction of *meso*-tetraarylporphyrins Ni(II) complexes.[21]

The method described here, utilizing readily available pyrrole precursors, allows for a variable substitution at sp^3 centres of calix[4]phyrin without the need for a porphyrin intermediate. Although free-base macrocycles could be prepared in this way, much better yields were obtained from templated syntheses leading to metal complexed products. In case of aryl substituted dipyrromethane the expected dialkylaryl-calix[4]phyrin was formed next to a contracted, corrole-like system, and with a more sterically hindered aryl substituent, the latter became the only isolated macrocyclic product.

The nickel(II) complexes of pseudocorrole reported herein are, to the best of our knowledge, the first examples of *meso*-dialkylated derivatives of this corrole tautomer.

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11. 1-Formyl-5,5-di(*n*-propyl)dipyrromethane (**2**): To a stirred solution of dipyrromethane **1a** (1.15 g, 5 mmol) in 10 mL of dry DMF cooled with ice-water bath was added dropwise a solution of benzoyl chloride (0.75 g, 5.4 mmol) in 2 mL of DMF under Ar. The mixture was stirred for 30 min at 0 °C, then allowed to warm to room temperature for 1.5 h. The solution was then diluted with Et_2O (50 mL) and extracted with water (3×15 mL), washed with Et_2O (1×10 mL), adjusted to pH 8 with Na_2CO_3 solution, left overnight, cooled and the yellow precipitate was filtered off. The crude product was purified by CC on alumina (neutral) with CH_2Cl_2 as the eluent followed by filtration through a pad of silica gel washed with CH_2Cl_2. Treating with pentane after an evaporation of most of the solvent gave 0.75 g (58%) of compound **2** as cream-white crystals.
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13. 5,5,15,15-[Tetrakis(*n*-propyl)-5,15-dihydroporphyrinato]-nickel (**5a**): A solution of bisformyldipyrromethane **3** (29 mg, 0.1 mmol) and dipyrromethane **1a** (23 mg, 0.1 mmol) in 15 mL of methanol was degassed with Ar and stirred at room temperature for 30 min., then a solution of *p*-toluenesulfonic acid (38 mg, 0.2 mmol) in 2 mL of methanol was added in one portion and stirring continued for 5 min. A solution of $Ni(OAc)_2 \times 4H_2O$ (249 mg, 1.0 mmol) in 10 mL of methanol was added and the mixture was stirred for 8 h, then 40 mL of water was added and the mixture extracted with CH_2Cl_2 (40+20 mL), the combined organic layers were washed with $NaHCO_3$ solution, water, brine, dried with Na_2SO_4, the solvents were evaporated and the residue purified by CC silica gel (heptane–CH_2Cl_2 5:2) to afford 11 mg (18%) of compound **5a**; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.01$ (t, $J = 7.3$ Hz, 12H, CH_3), 1.45 (m, 8H, CH_2), 2.47 (br s, 8H, CH_2), 6.19 (d, $J = 4.4$ Hz, 4H, $CH_{\beta\text{-pyrrole}}$), 6.74 (m, 6H, $CH_{\beta\text{-pyrrole}}$ and CH_{meso}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.7$, 18.4, 42.8 (br, propyl carbons), 46.9, 115.8 (CH pyrrole), 128.5 (*meso* CH), 130.5 (CH pyrrole),

135.3 (C pyrrole), 164.7 (C pyrrole); ES-MS (*m*/*z*): 537.2 [MH^+], UV–vis (CH_2Cl_2) λ_{max} ($\log\varepsilon$) = 307.9 (3.752), 423.3 (4.716), 518.0 (4.288).

14. Recently, a modified preparation of compound **3** was reported by Veauthier, J. M.; Cho, W.-S.; Lynch, V. M.; Sessler, J. L. *Inorg. Chem.* **2004**, *43*, 1220–1228.
15. Spectroscopic data of compound **8**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (m, 6H, CH_3), 1.32–1.46 (m, 4H, CH_2), 2.08 (br s, 2H, CH_2), 2.75 (br s, 2H, CH_2), 3.78 (s, 3H, OCH_3), 5.26 (s, 1H, CH_{meso}), 6.21 (m, 4H, $H_{\beta\text{-pyrrole}}$), 6.75 (d, J = 4.02 Hz, 2H, $H_{\beta\text{-pyrrole}}$), 6.78 (d, J = 4.4 Hz, 2H, $H_{\beta\text{-pyrrole}}$), 6.80 (s, 2H, CH_{meso}), 6.94 (AA′BB′, 2H, H_{phenyl}), 7.91 (br d, J = 7.3, 2H, H_{phenyl}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.6, 14.8, 18.3, 18.6 (propyl), 46.9, 47.1 (C macrocycle), 55.3 (OMe), 114.3 (CH Ar), 116.2, 117.0, 128.9, 129.2 (CH Ar), 131.1, 131.3, 133.9 (C Ar), 135.4, 135.5, 158.5 (C Ar), 165.1; ES-MS (*m*/*z*): 557.2 [$M^+ - 1$], UV–vis (CH_2Cl_2) λ_{max} ($\log\varepsilon$) = 310.0 (4.093), 423.8 (4.614), 521.0 (4.396).
16. Spectroscopic data of compound **9a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.52–0.77 (m, 10H, CH_2CH_3), 2.42–2.60 (m, 4H, CH_2), 3.88 (s, 3H, OCH_3), 6.46 (d, J = 4.0 Hz, 1H, $H_{\beta\text{-pyrrole}}$), 6.77 (d, J = 4.4 Hz, 1H, $H_{\beta\text{-pyrrole}}$), 6.87 (d, J = 4.9 Hz, 1H, $H_{\beta\text{-pyrrole}}$), 6.93 (d, J = 4.9 Hz, 1H, $H_{\beta\text{-pyrrole}}$), 6.96–7.02 (m, 3H, $H_{\beta\text{-pyrrole}}$ and H_{phenyl}), 7.02 (d, J = 4.6 Hz, 1H, $H_{\beta\text{-pyrrole}}$), 7.07 (d, J = 4.4 Hz, 1H, $H_{\beta\text{-pyrrole}}$), 7.27 (s, 1H, CH_{meso}), 7.34 (d, J = 4.6 Hz, 1H, $H_{\beta\text{-pyrrole}}$), 7.41 (AA′BB′, 2H, H_{phenyl}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 16.0, 39.7 (propyl), 49.3 (C macrocycle), 55.4 (OMe), 111.6, 113.3 (CH Ar), 118.8, 121.0, 121.2, 123.6, 125.6, 127.6 (C macrocycle), 128.3, 129.6 (C Ar), 132.4 (CH Ar), 132.7, 133.7, 136.9, 137.6, 140.5, 141.0, 148.8, 153.8, 159.6 (C Ar), 161.9, 168.7; ES-MS (*m*/*z*): 554.2 [M^+], UV–vis (CH_2Cl_2) λ_{max} ($\log\varepsilon$) = 304.4 (4.057), 403.4 (4.511), 448.3 (4.717), 642.3 (3.734), 809.1 (3.835), 892.0 (4.089).
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18. Spectroscopic data of compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.73 (t, J = 7.2 Hz, 6H, CH_3), 0.79–0.88 (m, 4H, CH_2), 1.85–1.95 (m, 4H, CH_2), 6.21 (d, J = 4.4 Hz, 1H, $H_{\beta\text{-pyrrole}}$), 6.41 (d, J = 4.4 Hz, 1H, $H_{\beta\text{-pyrrole}}$), 6.42 (d, J = 4.0 Hz, 1H, $H_{\beta\text{-pyrrole}}$) 6.93 (s, 1H, CH_{meso}), 6.96 (dd, J = 4.0 Hz, 1.1 Hz, 1H, $H_{\beta\text{-pyrrole}}$), 7.01 (d, J = 4.4 Hz, 1H, $H_{\beta\text{-pyrrole}}$), 7.06 (d, J = 4.0 Hz, 1H, $H_{\beta\text{-pyrrole}}$), 7.64 (d, J = 1.1 Hz, 1H, $H_{\alpha\text{-pyrrole}}$), 7.69 (s, 1H, H–C–O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 18.3, 46.6 (propyl), 50.6 (C macrocycle), 112.2, 116.6, 117.6, 123.6, 129.3, 129.9, 133.2, 133.9, 134.2, 142.1, 147.9, 155.4, 165.2, 176.4; ES-MS (*m*/*z*): 394.1 [M^++3], 392.1 [MH^+], UV–vis (CH_2Cl_2) λ_{max} ($\log\varepsilon$) = 322.4 (4.218), 356.4 (3.991), 436.4 (4.148), 522.7 (4.346).
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