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Simple route to *meso*-substituted *trans*-A_2B_2-porphyrins bearing pyridyl units

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Abstract—We have developed a methodology that affords regioisomerically pure *trans*-A_2B_2-porphyrins bearing pyridyl substituents. The optimal conditions for their synthesis were identified by the modification of known conditions for the reaction of dipyrromethanes with aromatic aldehydes. A total of five new porphyrins were synthesized. © 2003 Elsevier Science Ltd. All rights reserved.

Among the great diversity of porphyrins with a specific pattern of substituents, pyridyl substituted porphyrins have recently received great attention. Such compounds and their metal complexes have been used in the construction of arrays, formed by hydrogen bonds,[1,2] or by the coordination of exocyclic ligands.[3–7] Some of these arrays have been investigated as biomimetic models of photosynthetic systems.[8] Water-soluble quaternary salts derived from pyridylporphyrins have been studied as photosensitizers in photodynamic therapy (PDT).[9] They strongly interact with nucleotides[10] and with DNA,[11,12] which has ultimately led to the discovery of their role as DNA cleaving agents.[13] Furthermore, their metal complexes have been found to exhibit some catalytic activity in the electrochemical reduction of dioxygen[14] and nitric oxide.[15] Their manganese complexes are promising compounds in the development of the superoxide dismutase (SOD) mimic.[16] In particular *meso*-substituted *trans*-A_2B_2-porphyrins possessing two pyridyl units have often been used as building blocks in the construction of supramolecular assemblies,[4,17–21] in DNA binding studies,[22] as chemosensors[23] or artificial enzymes.[24]

In spite of the progress in the synthesis of porphyrins, compounds bearing one, two or three pyridyl units are still synthesized almost exclusively via the mixed aldehyde condensation under Adler's conditions followed by tedious chromatographical separation of the six regioisomers,[2,17,20–22,25–28] or via post-functionalization.[4,29,30] This situation simply reflects the fact that synthetic methodology for the rational synthesis of mono-pyridyl porphyrins and *trans*-A_2B_2-pyridyl porphyrins has only been developed in recent years.[31,32] Although there are isolated examples of the synthesis of these molecules via condensation of dipyrromethanes (DPMs) with aldehydes, they do not represent a comprehensive methodology due to such reasons as the use of the specific, bulky groups bearing aldehydes,[33–35] the lack of experimental details,[8,12] or the use of DPMs unsubstituted at the 5-position (less sensitive to scrambling).[36,37] The most promising approach to date (in terms of generality) consists of self-condensation of dipyrromethane-monocarbinols.[32] The present report describes what we believe to be a comprehensive method for the synthesis of *trans*-A_2B_2-bis(pyridyl)porphyrins.

The most popular method for the synthesis of *meso*-substituted *trans*-A_2B_2-porphyrins is by reaction of dipyrromethanes with aldehydes.[38] For sterically hindered dipyrromethanes, the reaction is conducted in CH_2Cl_2 in the presence of 1.8 equiv. of TFA (versus aldehydes). The major problem with the synthesis of porphyrins comprising amino groups results from the interaction of an acidic catalyst with substrates[39,40] (salts are formed which sometimes precipitate). In such cases the real concentration of acid is unknown and it is difficult to predict the amount of acid catalyst necessary for the reaction to proceed effectively. Very recently we developed a comprehensive methodology that afforded *trans*-A_2B-corroles bearing substituents with basic nitrogen atoms at *meso*-positions via the condensation of dipyrromethanes with aldehydes followed by the radical oxidative cyclization of bilanes.[41]

Keywords: porphyrin; pyridine; dipyrromethane; scrambling.

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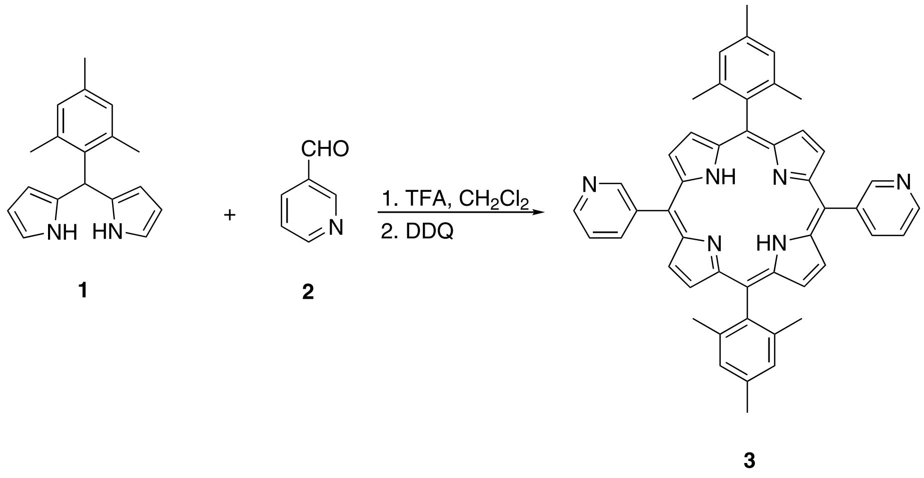
During these studies we found that related porphyrins are also formed under these conditions in small amounts. Encouraged by these results we aimed to find the reaction conditions under which porphyrins would be the major products. The reaction of mesityldipyrromethane (MesDPM) **1** and 3-pyridinecarboxaldehyde **2** was chosen as a model system for the optimization study (Scheme 1, Table 1). Initially, we found that under the optimized conditions for the reaction of neutral aromatic aldehydes,[38] 3-pyridinecarboxaldehyde **2** reacted with mesityldipyrromethane **1** to afford the respective porphyrin **3** in 32% yield. The gradual increase in the concentration of TFA to 4 equiv. led to an appreciable increase in the yield up to 39% (Table 1, entries 1–3). A further increase in the amount of TFA resulted in a decrease in the yield. Moreover in such cases problems with the separation of porphyrin **3** due to the extensive formation of additional side-products occurred (Table 1, entries 4 and 5). Prolongation of the reaction time did not improve the yield, and eventually led to scrambling (Table 1, entries 6–8). Regardless of the concentration of TFA we also observed the formation of an appreciable amount of hexaphyrin, which was identified using ESI-MS, but not purified due to its instability. A key concern upon the exposure of dipyrromethanes to acidic media is the occurrence of acidolysis, yielding fragments that could recombine to form products with undesired substitution patterns (i.e. scrambling). No scrambling was observed even when a high concentration of TFA (5 equiv.) was used, which is in full agreement with the results obtained for the condensation of MesDPM and aldehydes leading to *trans*-A_2B_2-porphyrins.[38] It has to be emphasized that judging from TLC and ESI-MS the respective *trans*-A_2B-corrole was always present as a side product in these reactions (~1% yield).

The optimized procedure[†] was subsequently used in the preparation of *trans*-A_2B_2-porphyrins from MesDPM **1** and isomeric pyridinecarboxaldehydes **6** and **7** (Scheme 2). Porphyrins **8** and **9** were obtained in 23 and 13%



Scheme 1.

Table 1. Optimization of the conditions for the reaction of mesityldipyrromethane **1** with aldehyde **2**[a]

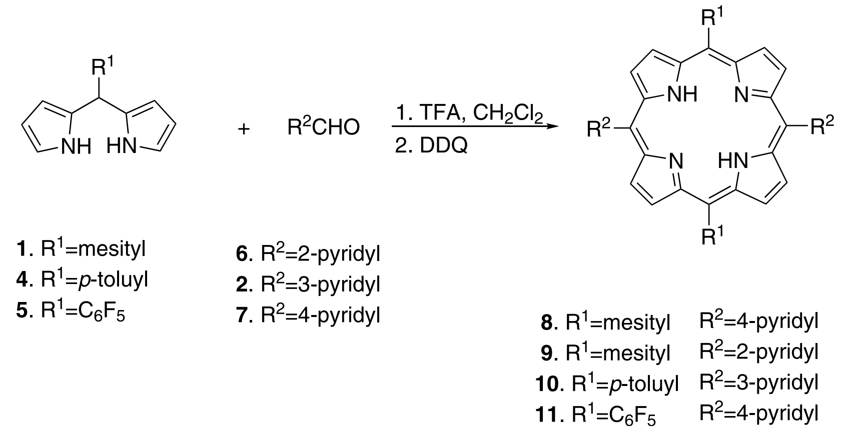
Entry	TFA (mmol)/ald. **2** (mmol)	Time of first step (h)	Yield of porphyrin **3** (%)[b]
1	1.8	0.5	32
2	3	0.5	38
3	4	0.5	39
4[c]	5	0.5	39
5	10	0.5	31
6	3	1	37
7	3	3	36
8	4	17	[c]

[a] All reactions were performed under the following constant conditions: For 1st step: CH_2Cl_2, MesDPM:aldehyde **2** = 1:1, [MesDPM] = 0.01, rt. For 2nd step: DDQ:MesDPM = 1.5:1, CH_2Cl_2, rt.

[b] Isolated yields.

[c] Scrambling was observed.

[†] General procedure for the preparation of porphyrins starting from sterically hindered dipyrromethanes and various pyridinecarboxaldehydes: Samples of mesityldipyrromethane **1** (105 mg, 0.40 mmol) and an aldehyde (0.40 mmol) were dissolved in CH_2Cl_2 (40 mL). To the resulting solution TFA (124 μL, 1.6 mmol) was added, and the reaction was stirred at room temperature. After 30 min, Et_3N (223 μL, 1.6 mmol) was added and the whole reaction mixture was evaporated to the dryness, redissolved in dioxane (10 mL) and a solution of DDQ (136 mg, 0.6 mmol) in dioxane was added. The reaction mixture was refluxed for 2 h, then an additional portion of DDQ (45 mg, 0.2 mmol) was added and heating was continued for 1 h.



Scheme 2.

yields, respectively.[‡] It is noteworthy that porphyrins **3**, **8** and **9** are not available via Adler's route because mesitaldehyde does not form porphyrins under these reaction conditions. In order to prove the scalability of this process, a large scale preparation of porphyrins **3** and **8** was attempted. These reactions, performed at 2 or 4 mmol scale (five or ten times greater than the standard experiments described in this paper) furnished 140–600 mg of porphyrins **3** and **8** in essentially the same yield as on the small scale (37 and 20%, respectively).

Like Lindsey et al.[38] we found that simple addition of a stoichiometric or larger amount of DDQ to the reaction mixture afforded porphyrins contaminated with chlorines. Moreover, the direct use of Lindsey's protocol (consisting of the addition of an extra amount of DDQ to partially purified porphyrins/chlorin mixture in toluene) did not work with our compounds for the following reasons: (a) the porphyrins were not soluble in toluene, (b) DDQ present in high excess formed very polar addition products with the porphyrins (presumably *N*-arylated) which drastically decreased yields of the desired porphyrins. Therefore we established another procedure consisting of the neutralization of the reaction mixture with NEt_3, evaporation to dryness, dissolution in 1,4-dioxane, followed by refluxing with DDQ.

We expected that the optimized conditions for sterically hindered dipyrromethanes, when applied to reactions involving sterically unhindered dipyrromethanes, would lead to extensive scrambling. Therefore various amounts of TFA (1, 2 and 3 equiv. versus amount of aldehydes) were screened in the reaction of dipyrromethane **4** with aldehyde **2**. No detectable scrambling (Level 0) was observed according to ESI-MS and TLC under all these conditions, and yields of the expected porphyrin **10** were 7, 13, and 19%, respectively.

The optimized conditions for the preparation of porphyrin **10**[§] were successfully applied to the synthesis of porphyrin **11** from pentafluorophenyldipyrromethane **5** and 4-pyridinecarboxaldehyde **7** (8% yield) (Scheme 2). The absence of scrambling in the reaction of dipyrromethanes **4** and **5** with aldehydes **2** and **6** at a

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[‡] All new compounds described in this work gave satisfactory spectroscopic data (^1H NMR, MS, UV). Exemplary details of purification and spectroscopic data: Following the general procedure starting from 5-mesityldipyrromethane (1.06 g, 4.00 mmol) and 3-pyridinecarboxaldehyde (380 μL, 4.00 mmol). The crude reaction mixture was evaporated with silica and chromatographed (silica, CH_2Cl_2/acetone, 99:1, then 97:3, 95:5, 93:7, 90:10). Two subsequent dry column vacuum chromatographies,[42] (silica, CH_2Cl_2/acetone, 99:1, then 97:3, 95:5, 93:7) afforded pure porphyrin **3** (519 mg, 37%). The resulting violet crystals were recrystallized from $CHCl_3$/hexanes. $R_f=0.55$ (silica, CH_2Cl_2/acetone 9:1); ^1H NMR ($CDCl_3$) δ −2.63 (s, 2H), 1.84 (s, 12H) 2.63 (s, 6H), 7.29 (s, 4H), 7.73 (dd, $J_1=7.5$ Hz, $J_2=5.5$ Hz, 2H), 8.52 (br d, $J=6.0$ Hz, 2H), 8.75 (s, 8H), 9.03 (dd, $J_1=4.5$ Hz, $J_2=1.5$ Hz, 2H), 9.40 (m, 2H); ESI-MS obsd 701.3 [M+H$^+$]; ESI-HR obsd 701.3423 [M+H$^+$], calcd exact mass 701.3387 ($C_{48}H_{41}N_6$); λ_{abs} (toluene, $\varepsilon\times10^{-3}$) 419 (382), 515 (17), 547 (6.4), 593 (4.9), 647 (1.6) nm. Anal. calcd for $C_{48}H_{40}N_6$: C, 82.26; H, 5.75; N, 11.99. Found: C, 82.14; H, 5.89; N, 11.77.

[§] General procedure for the preparation of porphyrins starting from sterically unhindered dipyrromethanes and various pyridinecarboxaldehydes: Samples of dipyrromethane (0.40 mmol) and an aldehyde (0.40 mmol) were dissolved in CH_2Cl_2 (40 mL). To the resulting solution TFA (93 μL, 1.2 mmol) was added and the reaction was stirred at room temperature. After 30 min, the supernatant was decanted and THF (20 ml) was added to the residue followed by Et_3N (167 μL, 1.2 mmol). Both organic fractions were combined and DDQ (136 mg, 0.60 mmol) was added as a solution in THF and the reaction mixture was stirred for 1 h. Following the general procedure starting from 5-(4-methylphenyl)dipyrromethane (95 mg, 0.40 mmol) and 3-pyridinecarboxaldehyde (38 μL, 0.4 mmol). The crude mixture was filtered through a silica pad (dry column vacuum chromatography, 60×150 mm, CH_2Cl_2/acetone, 95:5, then 90:10). After evaporation, the crude product was dissolved in $CHCl_3$ and chromatographed (silica, CH_2Cl_2 then CH_2Cl_2/acetone, 99:1, then 97:3, 95:5). The resulting crystals were crystallized from $CHCl_3$/cyclohexane (24 mg, 19%). $R_f=0.49$ (silica, CH_2Cl_2/acetone 8:2); ^1H NMR ($CDCl_3$) δ −2.78 (s, 2H), 2.71 (s, 6H), 7.57, 8.09 (AA′BB′, $J=7.0$ Hz, 2×4H), 7.74 (dd, $J_1=7.5$ Hz, $J_2=5.0$ Hz, 2H), 8.51 (d, $J=7.5$ Hz, 2H), 8.78 (d, $J=4.0$ Hz, 4H), 8.93 (d, $J=4.5$ Hz, 4H), 9.04 (dd, $J_1=5.0$ Hz, $J_2=1.0$ Hz, 2H), 9.4–9.5 (m, 2H). ESI-MS obsd 645.3 [M+H$^+$]; ESI-HR obsd 645.2781 [M+H$^+$], calcd exact mass 645.2761 ($C_{44}H_{33}N_6$); λ_{abs} (toluene, $\varepsilon\times10^{-3}$) 420 (332), 516 (15), 550 (7.0), 590 (4.2), 648 (2.8) nm.

higher concentration of acid than applied in the earlier condensation[38] of sterically unhindered dipyrromethanes and aldehydes could be explained by a consideration of the basicity of the different reactants. The weakly basic nature of a pyrrolic unit in dipyrromethanes provides little capacity for buffering acid in reactions of the dipyrromethanes. By comparison, the pyridine motif in aldehyde **2** is basic ($pK_a = 4.81$), and it is likely that this molecule buffers TFA, affording an effective acidity within a range that safely avoids acidolysis of DPM.

The precipitation of an amorphous residue was observed during the course of condensation of unhindered DPMs **4** and **5** with aldehydes **2** and **6**, which could affect the yield. Therefore attempts to improve the yield were performed by replacing pure CH_2Cl_2 as a solvent with a mixture of CH_2Cl_2 with DMF, MeOH and THF (4:1) respectively or with pure MeCN. Unfortunately this drastically diminished the yield of porphyrins and/or led to scrambling. An alternative pathway was attempted starting from 5-(3-pyridyl)dipyrromethane and *p*-tolualdehyde but the yield of porphyrin **10** was only 0.6%. It is worth pointing out that in the case of porphyrins derived from unhindered dipyrromethanes the simple addition of a stoichiometric amount of DDQ is sufficient to obtain porphyrins free of chlorines.

Conclusions: *trans*-A_2B_2-Bis(pyridyl)porphyrins can be effectively synthesized from dipyrromethanes and pyridine derived aldehydes. Both sterically hindered and unhindered dipyrromethanes can be transformed into porphyrins in moderate to good yields without scrambling. We believe that the availability of this methodology will accelerate physicochemical and biochemical studies of *trans*-A_2B_2-bis(pyridyl)porphyrins and their derivatives.

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