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A Practical Synthesis of Meso-monosubstituted, β-Unsubstituted Porphyrins

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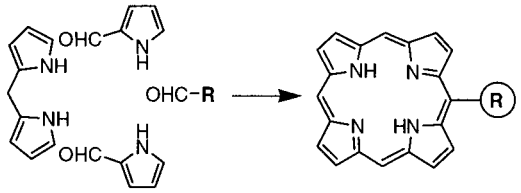
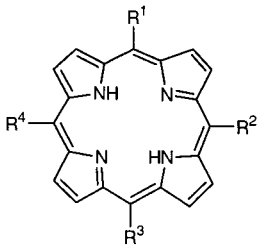
ABSTRACT



A simple straightforward synthesis for meso-monosubstituted, β-unsubstituted porphyrins is reported. Porphyrins of this type are easily prepared by condensation of dipyrromethane, pyrrole-2-carbaldehyde, and the desired aromatic or aliphatic aldehyde. The method can be used for a variety of functional groups with yields between 2 and 12%. In most cases, the 5,15-disubstituted porphyrin is obtained as a second product but can be removed easily.

In the past few decades, enormous progress has been made in synthetic porphyrin chemistry.[1] Today, porphyrins with nearly all sorts of substitution patterns are accessible. The synthetic strategies applied comprise direct methods such as condensations of pyrrole (or pyrrolic derivatives such as dipyrromethanes) with various aldehydes or total syntheses.[2] Alternatively, modifications of existing porphyrins utilize either electrophilic (e.g., formylation, halogenation, nitration)[3] or nucleophilic (e.g., organolithium chemistry)[4] aromatic substitution reactions. These methods provide convenient access to porphyrins with four (**6**), three (**5**), or two substituents (**3** or **4**) in the meso positions, regardless of whether the substituents are identical or different (Figure 1). And even the parent porphyrin without any substituents (porphine **1**) is now accessible in high yield.[5]



1	$R^1 = R^2 = R^3 = R^4 = H$	Porphine
2	$R^2 = R^3 = R^4 = H$	A-type
3	$R^3 = R^4 = H$	AB-type (5,10)
4	$R^2 = R^4 = H$	AB-type (5,15)
5	$R^4 = H$	ABC-type
6		ABCD-type

Figure 1. Types of meso-substituted porphyrins.

Nevertheless, several blank spots remain on the map of synthetic porphyrin chemistry. One of these is the synthesis

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(1) Kadish, K. M., Smith, K. M., Guilard, R., Eds. *The Porphyrin Handbook*; Academic Press: San Diego, 2000; Vol. 1.

(2) (a) Lindsey, J. S. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 1, pp 45−118. (b) Smith, K. M. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 1, pp 119−148.

(3) Jaquinod, L. In *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 2000; Vol. 1, pp 201−237.

(4) (a) Senge, M. O.; Kalisch, W. W.; Bischoff, I. *Chem. Eur. J.* **2000**, *6*, 2721−2738. (b) Feng, X.; Bischoff, I.; Senge, M. O. *J. Org. Chem.* **2001**, *66*, 8693−8700.

(5) Neya, S.; Funasaki, N. *Tetrahedron Lett.* **2002**, *43*, 1057−1058.

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of porphyrins with only one substituent, e.g., meso-monosubstituted, β-unsubstituted porphyrins (**2**). Though there are a number of occurrences where porphyrins of this type are referred to in previous studies, their synthesis either relied on the tedious monofunctionalization[6,7] of porphyrin **1** or they are described as byproducts for which synthesis and/or characterization often remain unclear.[8] Examples include mononitrated and monobrominated porphyrin,[6] (5-formylporphyrinato)copper(II),[7] and *tert*-butyl-[8a] and indolizine-substituted[9] porphyrins among others.[8b] Yields for the latter are typically $\leq$1%. To date, no practical synthesis for compounds of type **2** exists.

Yet, porphyrins of this type are of special interest because they offer the intriguing possibility of introducing additional substituents into the three other meso positions in a step-by-step procedure,[10] thereby opening the way to a rational synthesis of ABCD-tetrasubstituted porphyrins and to combinatorial porphyrin libraries. Moreover, in many physicochemical investigations, for example, in perturbation studies, meso-monosubstituted porphyrins are highly valuable reference compounds.[11]

In principle, compounds of type **2** are accessible by condensation of a bilane with a suitable aldehyde.[9] However, as bilane is highly unstable and difficult to prepare, the need exists for a synthesis that circumvents the use of bilane by utilization of simpler building blocks. One possible component to build porphyrins with unsubstituted meso positions is pyrrole-2-carbaldehyde **7**, which originally was used by Fischer in one of the first syntheses of porphine.[12] Another component that accounts for an unsubstituted meso position in the final porphyrin is dipyrromethane **8**, which is relatively stable and can easily be prepared in large quantities.[13] Thus, we planned to use a combination of **7** and **8** as an "equivalent" for the bilane, wherein the deactivating effect of the formyl group in **7** favors a reaction with **8** over self-condensation (Scheme 1).

Indeed, condensation of 2 equiv of **7** with **8** and benzaldehyde afforded the desired 5-phenylporphyrin **9a** in 5% yield.

Scheme 1

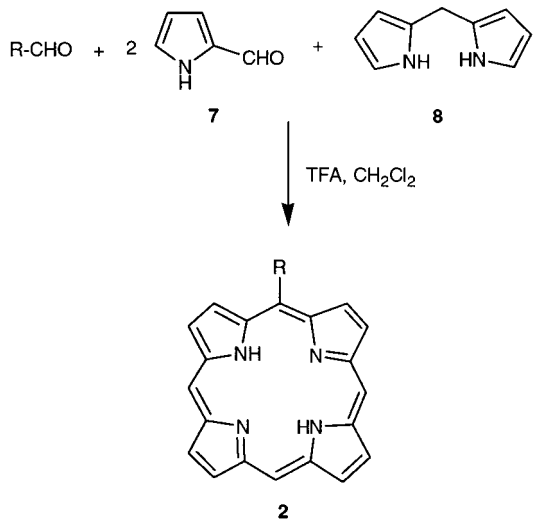
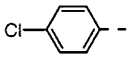
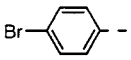
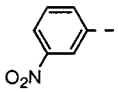
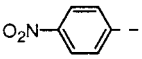
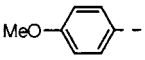
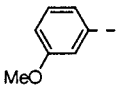
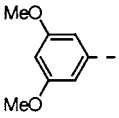
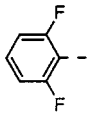
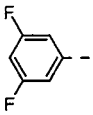


Table 1. Products and Yields after Purification for the Condensation Reaction of Pyrrole-2-carbaldehyde and Dipyrromethane with Various Aldehydes

	R-CHO		
	R =	%-yield **a**	%-yield **b**
9		5	5
10		4	1
11		6	3
12		3	5
13		2	—
14		12	—
15		5	6
16		6	—
17		2	15
18		3	2
19		7	—
20		11	7

We tested this method with a series of aldehydes and found that it tolerates aldehydes with a variety of functional groups, including those amenable for use in subsequent C−C-coupling reactions (e.g., **10** or **11**), for the preparation of hydrophilic porphyrins (e.g., **14**−**16** after deprotection of the methyl ether) for medicinal applications (or **17** and **18** for in vivo ^{19}F NMR), and for superstructured porphyrins (**12** or **13** and related amino compounds) (Table 1).

(6) (a) Drach, J. E.; Longo, F. R. *J. Org. Chem.* **1974**, *39*, 3282−3284. Callot, H. J.; Schaeffer, E. *J. Chem. Res., Synop.* **1978**, 51. (b) Nudy, L. R.; Coffey, J. C.; Longo, F. R. *J. Heterocycl. Chem.* **1982**, *19*, 1589−1590. Nudy, L. R.; Hutchinson, H. G.; Schieber, C.; Longo, F. R. *Tetrahedron* **1984**, *40*, 2359−2363. Nudy, L. R.; Schieber, C.; Longo, F. R.; Agarwala, V. S. *Heterocycles* **1987**, *26*, 1797−1803.

Generally, both aliphatic and aromatic aldehydes may be used in this reaction. The yields of the monosubstituted porphyrins **9a**−**20a** vary between 2 and 12%, which is quite satisfactory given the low yields often observed in porphyrin syntheses employing condensation reactions and the inaccessibility of the target porphyrins by other methods. The 5,15-disubstituted porphyrin (**b** in Table 1), which in most cases is obtained as a second product, can easily be separated from the monosubstituted porphyrin by column chromatography.

In practical terms, the yields and relative formation of mono- versus disubstituted product observed for the individual reactions do not depend so much on the electronic effects of the substituents but on the solubility of the monosubstituted product versus that of the disubstituted porphyrin. In most cases, the disubstituted porphyrin is much less soluble than the monosubstituted porphyrin and thus is either simply retained on the chromatography column or easily separated. For example, for compounds **16a** and **19a**, simple filtration of the crude reaction mixture through a short silica column is sufficient for purification, while the others require a standard column chromatographic separation.[14]

In conclusion, we have developed a simple and straightforward method that provides the first systematic access to meso-monosubstituted, β-unsubstituted porphyrins. Currently, we are expanding the methodology described herein and using the monosubstituted porphyrins as precursors in the development of a rational synthesis of 5,10- (**3**) and 5,15-disubstituted porphyrins (**4**).

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(7) Schloezer, R.; Fuhrhop, J.-H. *Angew. Chem.* **1975**, *87*, 388−389.

(8) (a) Song, X.-Z.; Jentzen, W.; Jaquinod, L.; Khoury, R. G.; Medforth, C. J.; Jia, S.-L.; Ma, J.-G.; Smith, K. M.; Shelnutt, J. A. *Inorg. Chem.* **1998**, *37*, 2117−2128. (b) Cavaleiro, J. A. S.; Neves, M. G. P. M.; Medforth, C. J.; Smith, K. M. *Heterocycles* **1994**, *37*, 213−218. Silva, A. M. G.; Tomé, A. C.; Neves, M. G. P. M. S.; Cavaleiro, J. A. S. *Tetrahedron Lett.* **2000**, *41*, 3065−3068.

(9) Matsumoto, K.; Ogasawara, A.; Kimura, S.; Hayashi, N.; Machiguchi, T. *Heterocycles* **1998**, *48*, 861−864.

(10) Senge, M. O.; Bischoff, I. *Eur. J. Org. Chem.* **2001**, 1735−1751.

(11) Kuz'mitskii, V. A.; Gael, V. I.; Mazurenko, A. S. *Zh. Fiz. Khim.* **1995**, *69*, 276−281. do Monte, S. A.; Braga, M. *Chem. Phys. Lett.* **1998**, *290*, 136−142. Shediac, R.; Gray, M. H. B.; Uyeda, H. T.; Johnson, R. C.; Hupp, D. T.; Angiolillo, P. J.; Therien, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 7017−7033.

(12) Fischer, H.; Gleim, W. *Justus Liebigs Ann. Chem.* **1935**, *521*, 157−160.

(13) Lee, C.-H.; Lindsey, J. S. *Tetrahedron* **1994**, *50*, 11427−11440.

(14) For example, the synthesis of 5-(4-methoxyphenyl)-porphyrin **14a** is as follows: 380 mg (4.00 mmol) of **7**, 300 mg (2.06 mmol) of **8**, and 0.25 mL (2.06 mmol) of 4-methoxybenzaldehyde were dissolved in 1 L of dry dichloromethane under argon. To this solution was added 70 μL (0.9 mmol) of TFA, and the reaction mixture was shielded from ambient light and stirred for 16 h in the dark. After this time, 1.3 g (5.73 mmol) of DDQ suspended in about 100 mL of dry dichloromethane was added and the mixture stirred for another 60 min. Then, 1.5 mL of triethylamine was added and the reaction mixture concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel using 2:1 v/v dichloromethane/hexane as the eluent. Recrystallization from dichloromethane/methanol afforded 99 mg (0.24 mmol, 12%) of 5-(4-methoxyphenyl)-porphyrin **14a** as purple crystals: mp 286 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.29 (2H, s, 10, 20-C_{meso-H}), 10.21 (1H, s, 15-C_{meso-H}), 9.46 (2H, *AB*, ^3J = 4.4 Hz, 12,18-$C_{\beta-H}$), 9.44 (2H, *AB*, ^3J = 4.4 Hz, 13,17-$C_{\beta-H}$), 9.39 (2H, *AB*, ^3J = 4.5 Hz, 2,8-$C_{\beta-H}$), 9.11 (2H, *AB*, ^3J = 4.5 Hz, 3,7-$C_{\beta-H}$), 8.16 (2H, *AB*, ^3J = 8.6 Hz, Ar_{o-H}), 7.32 (2H, *AB*, ^3J = 8.6 Hz, Ar_{m-H}), 4.11 (3H, s, C*H*$_3$), −3.60 ppm (2H, br s, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.49 (C28), 135.79 (C26, C30), 134.05 (C25), ∼131 (C2, C3, C7, C8, C12, C13, C17, C18), 119.42 (C5), 112.39 (C27, C29), 104.59 (C10, C20), 103.36 (C15), 55.61 ppm (C31); MS (EI, 310 °C, 80 eV) *m*/*z* (%) 416 (100) $[M]^{\bullet+}$, 401 (4) $[M - CH_3]^+$, 385 (1) $[M - OCH_3]^+$, 208 (13) $[M]^{2+}$; UV−vis (CH_2Cl_2) λ_{max} (lg ϵ) 405 nm (5.13), 499 (4.11), 539 (3.60), 575 (3.64), 628 (3.12); HRMS (EI) [$C_{27}H_{20}N_4O$ [M^+]] calcd 416.16371, found 416.16522.