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One-Pot Synthesis of *meso*-Formylporphyrins by S_NAr Reaction of 5,15-Disubstituted Porphyrins with (2-Pyridyldimethylsilyl)methyllithium

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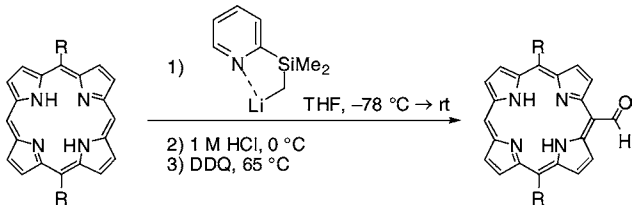
ABSTRACT



A simple, one-pot procedure that converts 5,15-substituted porphyrins into the corresponding *meso*-formylated porphyrins has been developed. The method, based on a new synthetic concept for functionalized porphyrins utilizing the (2-pyridyldimethylsilyl)methyl group as a latent formyl functionality, affords the desired product in good yield and is especially appropriate for the direct formylation of free base porphyrins, which has never been achieved by known methods.

The synthesis of porphyrins is of significant interest because of their wide potential applications in catalysis, medicine, and molecular materials.[1,2] A number of synthetic strategies and intermediates have been developed to constitute porphyrin systems.[3−5] Formylporphyrins are arguably among the most useful precursors for subsequent transformations to synthesize more complicated porphyrin derivatives.[6] The typical method for introducing a formyl group into the porphyrin core involves the Vilsmeier formylation and related reactions. However, these methods usually work well only with Ni(II) and Cu(II) complexes which lack acid-sensitive functional groups, as the formylation requires use of strong

(1) *The Porphyrin Handbook*; Kadish, K. M., Smith, K. M., Guilard, R., Eds.; Academic Press: San Diego, 1999−2003; Vols. 1−20.

(2) We have developed porphyrin-based Lewis acid catalysts that can promote regio- and stereoselective isomerization of epoxides to carbonyl compounds and Claisen rearrangement of allylvinyl ethers; see: (a) Suda, K.; Baba, K.; Nakajima, S.; Takanami, T. *Chem. Commun.* **2002**, 2570−2571. (b) Suda, K.; Kikkawa, T.; Nakajima, S.; Takanami, T. *J. Am. Chem. Soc.* **2004**, *126*, 9554−9555. (c) Takanami, T.; Hayashi, M.; Suda, K. *Tetrahedron Lett.* **2005**, *46*, 2893−2896. (d) Takanami, T.; Hayashi, M.; Iso, K.; Nakamoto, H.; Suda, K. *Tetrahedron* **2006**, *62*, 9467−9474.

(3) For some examples of leading works on functionalization reactions of porphyrins, see: (a) DiMagno, S. G.; Lin, V. S.-Y.; Therien, M. J. *J. Am. Chem. Soc.* **1993**, *115*, 2513−2515. (b) Boyle, R. W.; Johnson, C. K.; Dolphin, D. *J. Chem. Soc., Chem. Commun.* **1995**, 527−528. (c) Yamaguchi, S.; Katoh, T.; Shinkubo, H.; Osuka, A. *J. Am. Chem. Soc.* **2007**, *129*, 6392−6393. (d) Liu, C.; Shen, D.-M.; Chen, Q.-Y. *J. Org. Chem.* **2007**, *72*, 2732−2736.

(4) Senge et al. have developed a unique, yet useful, method for the preparation of *meso*-substituted porphyrins utilizing an S_NAr reaction with organolithium reagents: (a) Senge, M. O. *Acc. Chem. Res.* **2005**, *38*, 733−743. (b) Senge, M. O.; Hatscher, S. S.; Wiehe, A.; Dahms, K.; Kelling, A. *J. Am. Chem. Soc.* **2004**, *126*, 13634−13635. (c) Dahms, K.; Senge, M. O.; Bakar, M. B. *Eur. J. Org. Chem.* **2007**, 3833−3848 and references cited therein.

(5) We have reported metal-catalyzed amination and cyanation of porphyrins: (a) Takanami, T.; Hayashi, M.; Hino, F.; Suda, K. *Tetrahedron Lett.* **2003**, *44*, 7353−7357. (b) Takanami, T.; Hayashi, M.; Chijimatsu, H.; Inoue, W.; Suda, K. *Org. Lett.* **2005**, *7*, 3937−3940.

(6) For reviews, see: (a) Balakumar, A.; Muthukumaran, K.; Lindsey, J. S. *J. Org. Chem.* **2004**, *69*, 5112−5115. (b) Ponomarev, G. V. *Chem. Heterocycl. Compd.* **1994**, *30*, 1444−1465.

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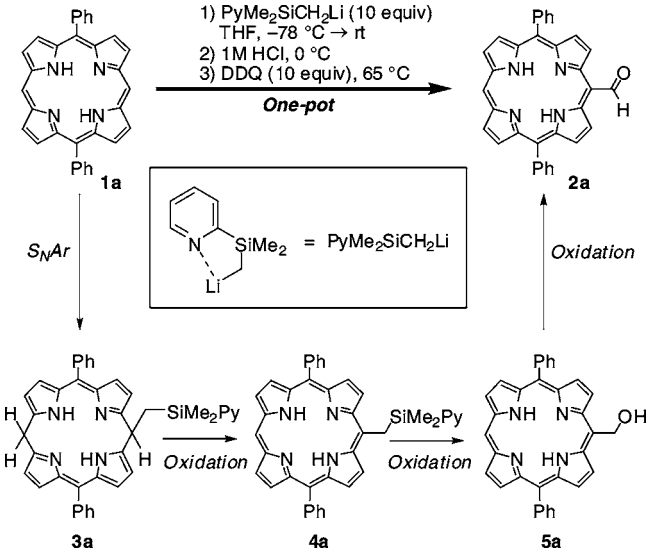
acidic conditions.[6,7] In addition, the demetalation of the resulting formyl-substituted metal complexes to the corresponding free bases also requires harsh acidic conditions such as CF_3COOH in H_2SO_4.[6,7]

Recently, significant progress has been made by Senge et al. for the preparation of *meso*-formylporphyrins through a stepwise procedure that involves a nucleophilic addition (S_NAr reaction) of 2-lithio-1,3-dithiane to 5,15-disubstituted porphyrins to generate the corresponding *meso*-(1,3-dithianyl)-porphyrins and the subsequent oxidative conversion of the dithianyl moiety into the CHO group.[4b] This creative approach is simple in its operation and can be applied under basic conditions for the preparation of *meso*-formylated Ni(II) complexes with yields ranging from 50% to 54%. However, unfortunately, when free base porphyrins are used as substrates in the reaction, the yields do not exceed 47%, and no improved conditions have since been reported. As a consequence, there still exists a need for a more efficient and general approach to formylporphyrins, particularly free base formylporphyrins.[8]

Among the numerous applications of silicon in organic synthesis, aryldimethylsilyl groups occupy a special niche in their use as the masked form of the hydroxyl group.[9] Therefore, we envisioned that porphyrins bearing (aryldimethysilyl)methyl moieties as a hydroxymethyl group surrogate would serve as an excellent platform to access formylporphyrins. Here, we report an efficient direct conversion of 5,15-disubstituted porphyrins to the corresponding *meso*-formylporphyrins by utilizing a facile one-pot protocol that involves a S_NAr reaction with (2-pyridyldimethylsilyl)methyl lithium ($PyMe_2SiCH_2Li$)[10] followed by hydrolysis and oxidation. The synthesis can be performed under mild conditions with a range of 5,15-diaryl- and 5,15-dialkyl-substituted free base porphyrins as well as their metal complexes, providing a new series of porphyrins with a formyl functionality attached at the *meso* position in good to high yields.

We selected $PyMe_2SiCH_2Li$ as a nucleophilic hydroxymethylating agent for the sequential synthesis of *meso*-formylporphyrins via *meso*-hydroxymethylporphyrin formation not only because of the facile convertibility of its 2-pyridyldimethylsilyl ($PyMe_2Si$) group to the hydroxyl group but also because of its eminent availability; the lithium reagent can readily be prepared by the deprotonation of 2-pyridyltrimethylsilane, a commercially available reagent, with *t*-BuLi in ether at −78 °C in a nearly quantitative yield.[10] Thus, a solution of 5,15-diphenylporphyrin **1a** in THF was treated in the following order with 10 equiv of $PyMe_2SiCH_2Li$ at −78 °C to room temperature, aqueous HCl at 0 °C, and then 10 equiv of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) at 65 °C (Scheme 1). We were pleased to observe that this reaction sequence directly provided 91% yield of the desired *meso*-formylated free base **2a**. This result shows that 5,15-disubstituted porphyrin **1a** can readily be converted to the *meso*-formylated porphyrin **2a** by a one-pot synthesis without the requirement to isolate the intermediary products such as *meso*-silylmethyl- and *meso*-hydroxymethylporphyrins, **4a** and **5a**, and their precursor dihydroporphyrins **3a**.[11,12]

Scheme 1. Direct Conversion of 5,15-Diphenylporphyrin **1** to *meso*-Formylporphyrin **2** via S_NAr Reaction with $PyMe_2SiCH_2Li$



(7) (a) Johnson, A. W.; Oldfield, D. *J. Chem. Soc. C* **1966**, 794−798. (b) Inhoffen, H. H.; Fuhrhop, J.-H.; Voigt, H.; Brockmann, H., Jr. *Justus Liebigs Ann. Chem.* **1966**, *695*, 133−143. (c) Smith, K. M.; Bisset, G. M. F.; Tabba, H. D. *J. Chem. Soc., Perkin. Trans. 1* **1982**, 581−585. (d) Ando, A.; Yamazaki, M.; Komura, M.; Sano, Y.; Hattori, N.; Omote, M.; Kumadaki, I. *Heterocycles* **1999**, *50*, 913−918 and references cited therein.

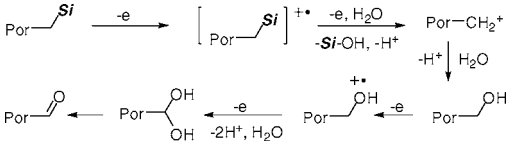
(8) A multi-step total synthesis of free base *meso*-formylporphyrins has been reported by Lindsey et al.; see ref 6a.

(9) For reviews: (a) Colvin, E. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 641−651. (b) Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599−7662.

(10) (a) Itami, K.; Mitsudo, K.; Yoshida, J. *Tetrahedron Lett.* **1999**, *40*, 5533−5536. (b) Itami, K.; Mitsudo, K.; Yoshida, J. *Tetrahedron Lett.* **1999**, *40*, 5537−5540. (c) Itami, K.; Kamei, T.; Mitsudo, K.; Nokami, T.; Yoshida, J. *J. Org. Chem.* **2001**, *66*, 3970−3976.

(11) Although we have failed in isolating *meso*-hydroxymethylporphyrin **5a**, a key synthetic intermediate in this formylation, TLC analysis showed that the hydroxymethyl derivative **5a** transiently appears during the course of the reaction: the R_f value (0.21, THF/hexane = 1:2) of the hydroxymethyl derivative **5a** proved to be identical to that of an authentic sample independently prepared by the reduction of the *meso*-formylporphyrin **2a** with $NaBH_4$ in THF/MeOH (3:1) at room temperature.

(12) Although details of the oxidation processes of silylmethylporphyrin **4** and hydroxymethylporphyrin **5** are not yet clear, we tentatively assume the mechanism depicted in the following scheme, where each oxidation reaction is initiated by a single-electron transfer from the respective compounds, **4** and **5** (see refs 13 and 14), to DDQ, a well-known electron acceptor (see refs 15 and 16). Further experiments are currently underway to elucidate the mechanism in detail.



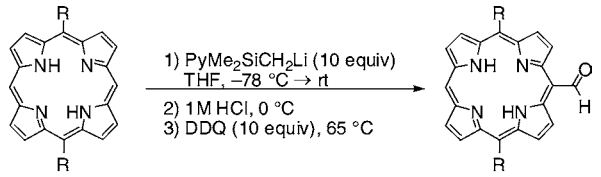
(13) For reviews on electron-transfer oxidation of organosilicon compounds, see: (a) Yoshida, J.; Nishiwaki, K. *J. Chem. Soc., Dalton Trans* **1998**, 2589−2596. (b) Yoshida, J. In *Electrochemistry V, Topics in Current Chemistry, Vol. 170*; Steckhan, E., Ed.; Springer-Verlag: Berlin, 1994; pp 39−81.

(14) For reviews on electron-transfer oxidation of alcohols, see: (a) Shono, T. *Electroorganic Chemistry as a New Tool in Organic Synthesis*; Springer-Verlag: Berlin, 1984; pp 29−38. (b) Torii, S. *Electroorganic Synthesis*; Kodansha-VCH: Tokyo, 1985; pp 239−248.

(15) Foster, R.; Foreman, M. L. In *The Chemistry of the Quinonoid Compounds, Part 1*; Patai, S., Ed.; Wiley: New York, 1974; pp 257−333.

A series of examples of this one-pot protocol are shown in Table 1. As a whole, a facile and efficient *meso*

Table 1. One-Pot Conversion of Free Base 5,15-Disubstituted Porphyrins to *meso*-Formylporphyrins by S_NAr Reaction with $PyMe_2SiCH_2Li$, Hydrolysis and Oxidation with DDQ



1 **2**

entry	substrate	R	product	yield[a] (%)
1	**1a**	Ph	**2a**	91
2	**1b**	*p*-tolyl	**2b**	82
3	**1c**	3-(H_2C=CH)C_6H_4	**2c**	90
4	**1d**	4-(*i*-Pr_3SiC≡C)C_6H_4	**2d**	71
5	**1e**	3,5-(*t*-Bu)$_2C_6H_3$	**2e**	80
6	**1f**	2,4,6-$Me_3C_6H_2$	**2f**	61
7	**1g**	3-(MeO)C_6H_4	**2g**	78
8	**1h**	3,4,5-$(MeO)_3C_6H_2$	**2h**	70
9	**1i**	3-$(CF_3)C_6H_4$	**2i**	71
10	**1j**	*i*-Bu	**2j**	79

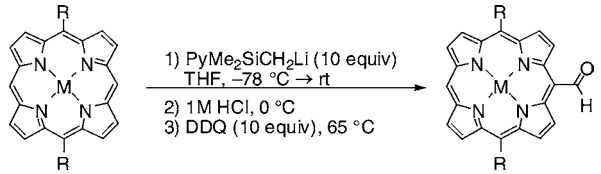
[a] Isolated yield.

formylation of various 5,15-disubstituted free bases was observed, and the yields obtained did not fall below 60% for all the substrates examined. The reactions of 5,15-diarylporphyrins **1b**−**e**, of which the aliphatic moiety on the phenyl ring is Me, CH_2=CH, *i*-Pr_3SiC≡C, and even *t*-Bu, proceed in good to high yields (entries 2−5), whereas a slightly lower yield is observed for the substrate **1f** having ortho-substituted phenyl ring (entry 6); the reason for this is probably because the *meso* carbon is more sterically hindered by the ortho substituents on the phenyl ring. Moreover, regardless of whether R is an electron-poor or electron-rich aromatic group, a good yield is typically obtained (entries 7−9). This protocol is not limited to 5,15-diarylporphyrins; 5,15-di(isobutyl)porphyrin **1j** could readily participate as a substrate in the reaction, furnishing the formylporphyrin **2j** in 79% yield (entry 10).

We also explored the one-pot protocol for the formylation of metalloporphyrin complexes such as Ni(II), Cu(II), and Zn(II) complexes of diaryl- and dialkyl-substituted porphyrins. As shown in Table 2, under the same reaction conditions, both Ni(II) and Cu(II) complexes could be substituted to obtain the *meso*-formyl-substituted complexes in good to high yields (entries 1−6). The Zn(II) complexes could also undergo the formylation, the corresponding demetalated free base formylporphyrins being isolated as the

(16) Several groups have reported that DDQ can oxidize aryl methanols to aromatic aldehydes; see: Branytska, O.; Neumann, R. *Synlett* **2004**, 1575−1576 and references cited therein.

Table 2. One-Pot Conversion of Metal Complexes of 5,15-Disubstituted Porphyrins to *meso*-Formylporphyrins by S_NAr Reaction with $PyMe_2SiCH_2Li$, Hydrolysis, and Oxidation with DDQ



M-1 **M-2**

entry	substrate	M	R	product	yield[a] (%)
1	**Ni-1a**	Ni	Ph	**Ni-2a**	83
2	**Ni-1g**	Ni	3-(MeO)C_6H_4	**Ni-2g**	81
3	**Ni-1j**	Ni	*i*-Bu	**Ni-2j**	77
4	**Cu-1a**	Cu	Ph	**Cu-2a**	73
5	**Cu-1g**	Cu	3-(MeO)C_6H_4	**Cu-2g**	65
6	**Cu-1j**	Cu	*i*-Bu	**Cu-2j**	67
7	**Zn-1a**	Zn	Ph	**2a**[b]	87
8	**Zn-1g**	Zn	3-(MeO)C_6H_4	**2g**[b]	70
9	**Zn-1j**	Zn	*i*-Bu	**2j**[b]	73

[a] Isolated yield. [b] The corresponding *meso*-formylated free bases (M = 2H) were isolated as the products.

sole products in good yields (entries 7−9). Although the formylated Zn(II) complexes could easily be prepared by the metal insertion reactions of the free base formylporphyrins with $Zn(OAc)_2$, further optimization will be necessary to prevent the demetalation during the formylation.[17]

In summary, a new method for the synthesis of *meso*-formylporphyrins starting from 5,15-disubstituted porphyrins has been developed. This simple one-pot methodology utilizing the silylmethyl group as a latent formyl functionality makes it possible to carry out the direct *meso*-formylation of an array of 5,15-disubstituted porphyrins, particularly their free bases, which has never been achieved by known methods. Therefore, our novel formylation procedure described herein will provide a new alternative and practical method. Further investigations into this and the related functionalization of porphyrins are ongoing in our laboratories.

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Supporting Information Available: Detailed experimetal procedures and characterization data for each compound. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Treatment of free base *meso*-formylporphyrins with an excess amount of $Zn(OAc)_2$ in CH_2Cl_2/MeOH (3:1) at room temperature gave the corresponding Zn(II) complexes in quantitative yields.