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A facile one-pot preparation of *meso*-hydroxymethylporphyrins via a sequential S_NAr reaction with (2-pyridyldimethylsilyl)methyllithium followed by hydrolysis and aerobic oxidation

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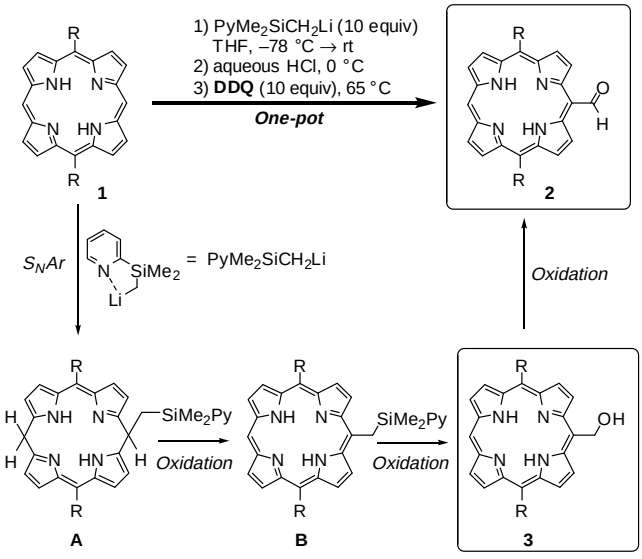
ABSTRACT

The first, direct *meso*-hydroxymethylation of 5,15-substituted porphyrins can effectively be obtained by a simple one-pot procedure involving a sequential S_NAr reaction of porphyrins with (2-pyridyldimethylsilyl)methyllithium, followed by hydrolysis and aerobic oxidation at ambient O_2 pressure.

Porphyrins and related tetrapyrrolic macrocycles are a class of chemically and biologically important heterocyclic compounds that have found broad applications in the areas of catalysis, medicine, and material science.[1,2] In this regard, a considerable effort has been devoted to the discovery of new approaches to the synthesis of various useful porphyrin systems.[3–5] It is known that hydroxymethyl-substituted porphyrins are among the most versatile building blocks that allow for subsequent transformations into more complicated porphyrin derivatives.[6] The typical procedure for the preparation of hydroxymethyl-substituted porphyrins involves a stepwise process through the traditional Vilsmeier formylation of porphyrins, followed by reduction.[7] However, to the best of our knowledge, no existing methods offer a direct introduction of the hydroxymethyl group into the porphyrin core.[8]

Recently, we have demonstrated a novel direct *meso* formylation of 5,15-disubstituted porphyrins **1** based on a one-pot three-step procedure via nucleophilic addition (S_NAr reaction)[4] with (2-pyridyldimethylsilyl)methyllithium ($PyMe_2SiCH_2Li$),[9] followed by hydrolysis and oxidation.[5c] As shown in Scheme 1, the process involves the DDQ-promoted oxidative conversion of silylmethyl-substituted dihydroporphyrins **A**, initially formed adducts by the S_NAr reaction, into *meso*-formylporphyrins **2** via the sequential generation of silylmethylporphyrins **B** and hydroxymethylporphyrins **3**.

Herein, we report an aerobic oxidation version of this reaction, which can effectively afford *meso*-hydroxymethylporphyrins **3** and not *meso*-formylporphyrins **2**. The crucial element of the reaction is the use of molecular oxygen instead of DDQ as an oxidizing agent,[10] which effectively brings about the conversion of **A** into **3**



Scheme 1. Reaction pathways for the direct *meso*-formylation of 5,15-disubstituted porphyrins using one-pot procedure involving S_NAr reaction with $PyMe_2SiCH_2Li$, followed by hydrolysis and DDQ oxidation.

but without further oxidation of the hydroxymethyl functionality to the CHO group, thereby facilitating the unprecedented direct *meso*-hydroxymethylation of the porphyrin core. This reported reaction proceeds at ambient O_2 pressure, and these mild, green, and economic conditions have been employed for 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 hydroxymethyl functionality attached at the *meso* position in good yields.

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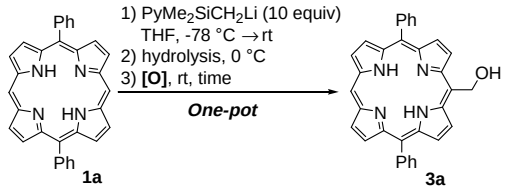


hydrolysis	[O]	time (h)	**3a**
1 M HCl	O_2	2	56 %[a]
H_2O	O_2	1.5	76 %[a]
H_2O	air	8	71 %[a]

[a] Isolated yield.

Scheme 2. Direct *meso*-hydroxymethylation of 5,15-diphenylporphyrin by S_NAr reaction using $PyMe_2SiCH_2Li$, hydrolysis, and aerobic oxidation.

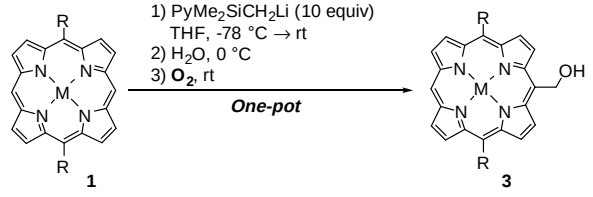
In previous work, the sequential treatment of 5,15-diphenylporphyrin **1a** with 10 equiv of $PyMe_2SiCH_2Li$ at −78 °C, followed by 1 M HCl at 0 °C and 10 equiv of DDQ at 65 °C, afforded the corresponding 10-formyl-5,15-diphenylporphyrin **2a** in 91% yield.[5c] On the other hand, a similar reaction using dioxygen instead of DDQ as an oxidizing agent at ambient temperature and pressure resulted in the formation of 10-hydroxymethyl-5,15-diphenylporphyrin **3a** in 56% yield along with an inseparable complex mixture of byproducts (Scheme 2).[11] Upon further investigation of the reaction conditions, conducting the aerobic oxidation under nearly neutral conditions was found to produce a substantial improvement. Thus, a solution of **1a** in tetrahydrofuran was treated in the following order: 10 equiv of $PyMe_2SiCH_2Li$ at −78 °C to room temperature, H_2O at 0 °C, and aerobic oxidation for 1.5 h at ambient temperature and O_2 pressure. Under these conditions, the reaction proceeded cleanly to provide a 76% yield of the desired *meso*-hydroxymethylporphyrin **3a** without byproducts other than a trace amount (<5%) of the *meso*-formylporphyrin **2a**, which could be detected in the ^1H NMR spectrum of the crude reaction mixture. Essentially, the same result was also obtained using air in lieu of pure dioxygen as an oxidizing agent, although a prolonged oxidation reaction time (8 h) was necessary to complete the reaction.

The hydroxymethylation reaction with various porphyrins is summarized in Table 1.[12] As can be observed, this process was found to have a wide scope with regard to the central metal ions and peripheral substituents of the porphyrin ring. For example, 5,15-diarylporphyrins with electron-rich, electron-neutral, and electron-poor aromatic moieties on the porphyrin core are all compatible with the reaction conditions (entries 1–5). The hydroxymethylation was applicable to the substrate **1f** containing a silyl functionality, leaving the functional group untouched (entry 6). 5,15-Di(*iso*-butyl)porphyrin **1g** could also participate as a substrate in the reaction, furnishing the hydroxymethylporphyrin in 66% yield (entry 7). This process is not limited to free-base porphyrins; both nickel and zinc complexes could be substituted to obtain the *meso* hydroxymethyl-substituted complexes in good yields (entries 8–15). It is of note that the central metal ions of these metal complexes were entirely preserved during the hydroxymethylation (entries 12–15); in contrast, complete demetallation from zinc porphyrin complexes was observed in our previous *meso*-formylation with DDQ as an oxidizing agent.[5c]

While the detailed mechanism has not yet been experimentally confirmed, we tentatively assume the reaction pathway of the hydroxymethylation as shown in Scheme 3. In this reaction pathway, the oxidative conversion of the intermediary **B** into the *meso*-hydroxymethylporphyrin **3** proceeds by a Fleming-Tamao oxidation mechanism,[13] in which hydrogen peroxide, generated in situ from aerobic oxidation of dihydroporphyrin **A**, is mainly responsible for the oxidation of the silyl group to the hydroxyl group.[14] Indeed, a brief experiment using aqueous hydrogen peroxide as an oxidant under an anaerobic condition resulted in the transformation of porphyrin **1a** into the *meso*-hydroxymethyl derivative **3a** in 53% yield, although the reaction conditions have not yet been optimized. Further experiments will be necessary to obtain insights into the precise mechanism of the hydroxymethylation.

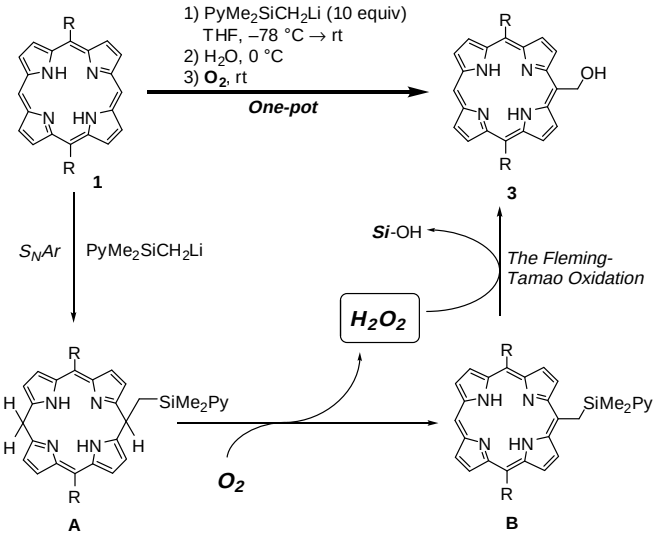
In summary, we have developed an efficient one-pot procedure for the first, direct hydroxymethylation of 5,15-disubstituted porphyrins at the *meso* position. This involves a sequential S_NAr reac-

Table 1
One-pot conversion of 5,15-disubstituted porphyrins into *meso*-hydroxymethylporphyrins by S_NAr reaction using $PyMe_2SiCH_2Li$, hydrolysis, and aerobic oxidation



Entry	Substrate	M	R	Product	Yield[a] (%)
1	**1a**	2H	Ph	**3a**	76
2	**1b**	2H	*p*-Tolyl	**3b**	70
3	**1c**	2H	3-$MeOC_6H_4$	**3c**	75
4	**1d**	2H	3,4,5-$(MeO)_3C_6H_2$	**3d**	55
5	**1e**	2H	3-$CF_3C_6H_4$	**3e**	56
6	**1f**	2H	4-(*i*-$Pr_3SiC{\equiv}C)C_6H_4$	**3f**	71
7	**1g**	2H	*i*-Bu	**3g**	66
8	**Ni-1a**	Ni	Ph	**Ni-3a**	82
9	**Ni-1b**	Ni	*p*-Tolyl	**Ni-3b**	70
10	**Ni-1d**	Ni	3,4,5-$(MeO)_3C_6H_2$	**Ni-3d**	72
11	**Ni-1f**	Ni	4-(*i*-$Pr_3SiC{\equiv}C)C_6H_4$	**Ni-3f**	72
12	**Zn-1a**	Zn	Ph	**Zn-3a**	57
13	**Zn-1c**	Zn	3-$MeOC_6H_4$	**Zn-3c**	83
14	**Zn-1f**	Zn	4-(*i*-$Pr_3SiC{\equiv}C)C_6H_4$	**Zn-3f**	62
15	**Zn-1g**	Zn	*i*-Bu	**Zn-3g**	65

[a] Isolated yield.



Scheme 3. Plausible reaction pathway for the one-pot *meso*-hydroxymethylation of 5,15-disubstituted porphyrins.

tion with $PyMe_2SiCH_2Li$, followed by hydrolysis and aerobic oxidation at ambient O_2 pressure. This process can readily accommodate a wide variety of substrates including 5,15-dialkyl- and 5,15-diaryl-substituted free-base porphyrins and their metal complexes, affording the corresponding *meso*-hydroxymethylporphyrins in good yields. Further investigations into the utility of the products, that is, *meso*-hydroxymethylporphyrins, as building blocks for the construction of porphyrin derivatives that show various useful functions are currently underway.

Acknowledgments

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12. Typical procedure for the one-pot hydroxymethylation of 5,15-disubstituted porphyrins: An oven-dried 100 mL round-bottomed flask equipped with a magnetic stirring bar and a three-way stopcock was charged with a porphyrin **1** (0.1 mmol). The flask was evacuated and flushed with argon (three times), and then absolute THF (40 mL) was added. To the solution was added an ethereal solution of $PyMe_2SiCH_2Li$ (prepared by adding 0.65 mL of 1.58 M *t*BuLi in pentane to a solution of 1.2 mmol 2-pyridyltrimethylsilane in 1.5 mL of ether, followed by stirring at −78 °C for 2 h)[9] via a cannula at −78 °C. After being stirred at −78 °C for 5 min, the cooling bath was removed and the mixture was stirred at room temperature. The reaction was complete within 3 h, having been monitored by TLC. Upon completion of the reaction, the mixture was cooled to 0 °C, and then 5 mL of H_2O was added. After being stirred at 0 °C for 10 min, the mixture was stirred under O_2 (using a balloon) at room temperature for 1–5 h, and poured into brine. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were combined, concentrated in vacuo, and subjected to chromatography on silica gel using 2–10% hexane/CH_2Cl_2 as an eluent to give the *meso*-hydroxymethylporphyrin **3**. All the compounds reported herein showed spectral data consistent with the assigned structures. Selected data: For **3a**: ^{1}H NMR ($CDCl_3$) δ: 10.20 (1H, s), 9.66 (2H, d, J = 4.7 Hz), 9.30 (2H, d, J = 4.4 Hz), 9.04 (2H, d, J = 4.7 Hz), 8.98 (2H, d, J = 4.4 Hz), 8.22 (4H, d, J = 6.6 Hz), 7.86–7.74 (6H, m), 7.02 (2H, s), 3.73 (1H, br), −3.14 (2H, s); IR (KBr): 3308, 1597, 1561, 1484, 1440, 1406, 976, 957, 921, 850, 794, 724, 704 cm^{-1}; HRMS-FAB$^+$ ([M+H]$^+$): calcd for $C_{33}H_{25}N_4O$: 493.2028. Found 493.2023. For **3f**: ^{1}H NMR ($CDCl_3$) δ: 10.21 (1H, s), 9.68 (2H, d, J = 4.9 Hz), 9.32 (2H, d, J = 4.8 Hz), 9.03 (2H, d, J = 4.9 Hz), 8.97 (2H, d, J = 4.8 Hz), 8.16 (4H, d, J = 7.9 Hz), 7.90 (4H, d, J = 7.9 Hz), 7.03 (2H, s), 3.73 (1H, br), 1.33–1.01 (42H, m), −3.16 (2H, s); IR (KBr): 3614, 2943, 2866, 2152, 1651, 1550, 1466, 1068, 995, 798, 671 cm^{-1}; HRMS-FAB$^+$ ([M+H]$^+$): calcd for $C_{55}H_{65}N_4OSi_2$: 853.4697. Found 853.4703.
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