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Simple and Catalyst-Free Synthesis of *meso*-O-, -S-, and -C-Substituted Porphyrins

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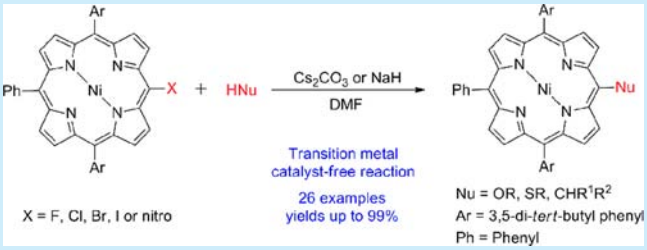
Supporting Information

ABSTRACT: A simple and efficient method for the *meso*-functionalization of porphyrin has been developed. Kinetic studies of *meso*-fluoro-, -chloro-, -bromo-, -iodo-, and -nitro-substituted porphyrins (Ni) with phenol reveal that the reaction undergoes a typical aromatic nucleophilic substitution (S_NAr) process. This catalyst-free method can be performed with *meso*-brominated porphyrins and oxygen-, sulfur-, and carbon-based nucleophiles to achieve a wide variety of *meso*-substituted porphyrins.



Porphyrins are an important class of functional molecules in nature and have shown diverse potential applications in catalysis, material science, medicine, and so forth.[1] The performance of porphyrins in these areas has often been found to be intimately dependent on their peripheral substituents.[2] Considerable efforts have therefore been devoted to the synthesis of such structures, especially on the unsymmetrically substituted porphyrins.[2] The outer rim substituents, until now, have been mostly introduced into the pyrrole and aldehyde precursors before the porphyrin-forming procedure.[3] However, this method often results in mixed condensation products and needs a tedious chromatographic workup. Likewise, use of acid-labile groups and sterically hindered residues is problematic.[4] Thus, interest has shifted toward the use of a postmodification strategy to obtain unsymmetrically substituted porphyrins via direct derivatization of easily accessible porphyrin synthons such as haloporphyrin, formylporphyrin, and nitroporphyrin synthesized by classic but still useful electrophilic substitutions.[5] Recently, efforts have mainly been focused on the nucleophilic reactions of *meso*-unsubstituted porphyrins with organometallic reagents followed by oxidation[6] and transition-metal-catalyzed C−heteroatom[7] or C−C bond formation reactions.[8] But the metal reagents and specific ligands involved in these methods will hamper their widespread applications. Thus, there remains a need to develop an alternative way to achieve these unsymmetrically substituted porphyrins with improved generality and practicality.

Aromatic nucleophilic substitution (S_NAr) reaction of aryl halides is an important method for the modification of electron-deficient aromatic compounds, but it has rarely been applied in the synthesis of porphyrin derivatives except for several examples reported.[9] Herein, we report a facile S_NAr reaction of easily accessible *meso*-halo- or -nitro-substituted porphyrins with oxygen-, sulfur-, and carbon-based nucleophiles under mild conditions to give the corresponding *meso*-derivatives in high yield (Figure 1).[10]

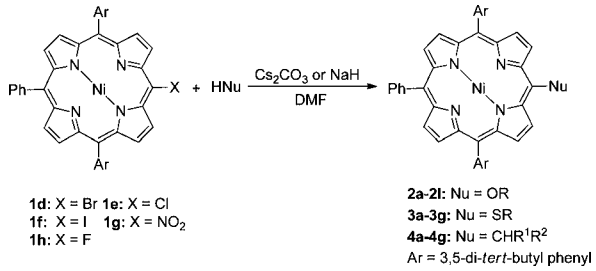


Figure 1. S_NAr reactions of *meso*-substituted porphyrins (Ni) with various nucleophilic substrates.

The *meso*-brominated porphyrin 5-bromo-10,20-di(3,5-di-*tert*-butylphenyl)-15-phenylporphyrin (**1a**), which can be readily prepared via convenient bromination, and its metal complexes (**1b**, **1c**, and **1d**) have been initially used as representative halogenated porphyrin precursors to evaluate the reaction conditions. As shown in Table 1, the solvent is found to be critical for the transformation. The reaction went smoothly in DMF (entry 1), while no reaction occurred in toluene or 1,4-dioxane (entries 2 and 3). That can be ascribed to the effective transition-state stabilization by amide solvent.[11] Further screening of bases indicated that Cs_2CO_3 worked best for the synthesis, and partial decomposition of starting material was observed when a stronger base such as *t*-BuOK was used (entries 4−7).

The reactivity of porphyrin substrates was also dependent on the central metal ion. When Cu(II) and Ni(II) were inserted into the porphyrin core, the reactivity of the resultant metalloporphyrin was obviously enhanced (entries 9 and 10).[12] In sharp contrast, Zn(II) porphyrin (**1b**) can hardly react with phenol (entry 8). That can be attributed to the

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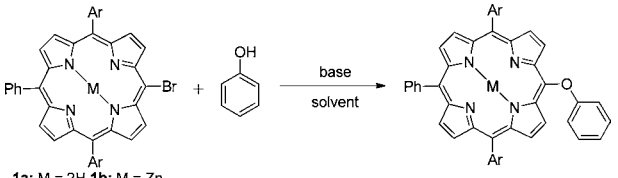
Table 1. S_NAr Reaction of *meso*-Bromoporphyrin (M = 2H/Zn/Cu/Ni) with Phenol under Various Conditions[a]



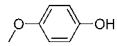
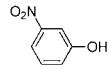
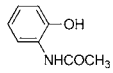
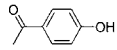
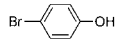
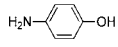
entry	M	base	solvent	product	temp (°C)	yield[e] (%)
1	2H	K_2CO_3	DMF	**2H2a**	100	74
2[b]	2H	K_2CO_3	1,4-dioxane		100	0
3[b]	2H	K_2CO_3	toluene		100	0
4[b]	2H		DMF		100	0
5[b]	2H	Na_3PO_4	DMF	**2H2a**	100	7
6[c]	2H	*t*-BuOK	DMF		100	0
7	2H	Cs_2CO_3	DMF	**2H2a**	100	84
8[b]	Zn	Cs_2CO_3	DMF		100	0
9	Cu	Cs_2CO_3	DMF	**Cu2a**	100	89
10	Ni	Cs_2CO_3	DMF	**2a**	100	99
11[d]	Ni	Cs_2CO_3	DMF	**2a**	100	99
12	Ni	Cs_2CO_3	DMF	**2a**	120	99
13	Ni	Cs_2CO_3	DMF	**2a**	80	80
14	Ni	Cs_2CO_3	DMF	**2a**	60	45

[a]Reactions were carried out in the indicated solvent (3.0 mL) with porphyrin (30.0 mg, 1.0 equiv), phenol (1.4 equiv), and indicated base (2.0 equiv) under N_2 atmosphere for 1 h. [b]Recovery of starting materials. [c]Decomposition of porphyrin was observed. [d]Compound **1d** was dissolved in dichloromethane (50 mL) and washed with edetate disodium (0.1 N, 50 mL) to remove possible free nickel(II) ions before use. [e]Isolated yield.

relative electropositivity for zinc(II) (Pauling electronegativity 1.65) in comparison to copper(II) and nickel(II) (Pauling electronegativity 1.90 and 1.91, respectively). Thus, zinc porphyrin will have greater electron density on the periphery and show lower activity in the S_NAr reaction.[13] Temperature is another factor that affects the conversion and yield. An elevated temperature was needed for effective transformation, as decreased reactivity was observed when the reaction temperature was below 100 °C (entries 13 and 14). In addition, treating the Ni(II) porphyrin with edetate disodium before use, in order to remove any free metal ions that may exist, resulted in no change for the conversion (entries 10 and 11). That is quite different from the reported nickel(II) catalyzed cross-coupling reaction, and in that case the nickel(II) catalyst is essential.[14]

Under the optimized conditions, compound **1d** was further employed to react with substituted phenol and aliphatic alcohol (Table 2). Electron-rich and -poor phenol derivatives, as well as more sterically hindered 2-acetylaminophenol, could all be transformed to the corresponding *meso*-substituted porphyrins in high yield (entries 2−6). Substrates with an amino group (entry 7) also worked smoothly with good selectivity, and no N-substituted product was observed. When it came to the fused-ring aromatic compounds or heterocycle substrates (entries 8 and 9), *meso*-aryloxy-substituted products could be obtained efficiently. Aliphatic alcohols were also employed in the reaction, but they did not work under the same conditions. A stronger base such as NaH must be used to promote this transformation, and the *meso*-alkoxy-substituted porphyrins

Table 2. S_NAr Reaction of 1d with Phenol Derivatives and Alcohols[a]

entry	ROH	time (h)	temp (°C)	product	yield (%)[c]
1		1	100	**2a**	99
2		1	100	**2b**	97
3		1	100	**2c**	86
4		1	100	**2d**	75
5		1	100	**2e**	83
6		1	100	**2f**	83
7		1	100	**2g**	88
8		1	100	**2h**	91
9		1	100	**2i**	79
10[b]		8	20	**2j**	68
11[b]		8	20	**2k**	72
12[b]		8	20	**2l**	23

[a]For entries 1−9, reactions were carried out in DMF (3.0 mL) under N_2 atmosphere with **1d** (30.0 mg, 1.0 equiv), phenol derivatives (1.4 equiv), and Cs_2CO_3 (2.0 equiv). Entries 10−12, 10.0 equiv of NaH, and alcohols were used. [b]Partial decomposition of porphyrin was observed. [c]Isolated yield.

were obtained at room temperature in moderate yield (entries 10−12).

To our delight, the reaction was not limited to oxygen-based nucleophiles. Multiple kinds of sulfur-based nucleophiles were found to be suitable for this process. As shown in Table 3, in addition to 4-methylbenzenethiol (entry 1), **1d** could be coupled smoothly to other electron-rich or -poor aromatic thiols, such as 4-methoxythiophenol and 4-fluorothiophenol, affording *meso*-sulfanyl-substituted porphyrins (entries 2 and 3). 2-Naphthalenethiol could also participate as a suitable substrate, furnishing the desired product in 71% yield (entry 4). When aliphatic thiols 1-propanethiol and benzylmercaptan were used, *meso*-alkylsulfanyl-substituted porphyrins could also be easily obtained (entries 5 and 6). It is worthwhile to point out that dithiol substrate could react with **1d** to afford diporphyrin **3g** in 79% yield (entry 7). That should be a practical way to construct some functional face-to-face diporphyrins.

The results mentioned above encouraged us further to extend the scope of substrates to carbon-based nucleophiles (Table 4). For example, **1d** reacted with malononitrile and ethylcyanacetate to afford cyano-contained porphyrins **4a** and **4b** in 89 and 91% yields, respectively (entries 1 and 2). The cyano-substituted porphyrins are thought to be one of the most important precursors for their valuable transformation to some functional groups such as aldehydes, amines, amides, and acid derivatives. 1,3-Diketones and malonate-type nucleophiles could also react with **1d** successfully to provide the

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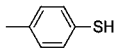
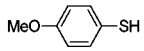
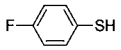
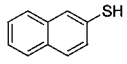
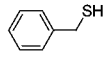
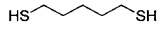
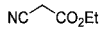
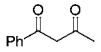
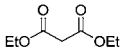
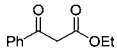
Table 3. S_NAr Reaction of 1d with Sulfur-Based Nucleophiles[a]

entry	RSH	product	yield (%)[d]
1		**3a**	87
2		**3b**	95
3		**3c**	93
4		**3d**	71
5[b]		**3e**	95
6		**3f**	81
7[c]		**3g**	79

[a]Reactions were carried out in DMF (3.0 mL) under N_2 atmosphere with **1d** (30.0 mg, 1.0 equiv), RSH (1.4 equiv), and Cs_2CO_3 (2.0 equiv) at 100 °C for 1 h. [b]The product was purified by recrystallization since it easily decomposed on silica gel. [c]0.5 equiv of 1,5-pentanedithiol was used. [d]Isolated yield.

Table 4. S_NAr Reaction of 1d with Carbon-Based Nucleophiles[a]

entry	$CH_2R^1R^2$	product	time (h)	yield (%)[e]
1[b]		**4a**	1	89
2[c]		**4b**	2	91
3		**4c**	2	73
4[c]		**4d**	2	65
5[d]		**4e**	6	62
6[c]		**4f**	4	77
7[c]		**4g**	4	90

[a]Reactions were carried out in DMF (3.0 mL) under N_2 atmosphere with **1d** (30 mg, 1.0 equiv), $CH_2R^1R^2$ (1.4 equiv), and Cs_2CO_3 (2.0 equiv) at 100 °C for 1−6 h. [b]The product was separated by recrystallization from CH_2Cl_2/MeOH since it strongly absorbed and decomposed on silica gel. [c]Enantiomers were not separated, and keto−enol tautomeriztion was observed for compounds **4c**, **4d**, **4f**, and **4e**. [d]Partial decomposition of porphyrins was observed. [e]Isolated yield.

corresponding *meso*-carbon-based products in moderate to high yields (entries 3−7).

In order to obtain deeper insights into the mechanism, *meso*-F- (**1h**), -Cl- (**1e**), -I- (**1f**), and -nitro- (**1g**) substituted porphyrins(Ni) were also prepared. Reaction rate constants of *meso*-F-, -Cl-, -Br-, -I-, and -NO_2-substituted porphyrins(Ni) with phenol were further measured and ranked.[15]

All kinetic measurements (in triplicate) were conducted under pseudo-first-order conditions

$$kt = -2.303 \log(C/C_0) + b$$

where C/C_0 is the ratio of 5-substituted porphyrins(Ni) in the mixture at time t to the initial concentration. Values of the term $[-\log(C/C_0)]$ were plotted against t. Since the reaction of 5-fluoroporphyrin(Ni) was too fast to be measured, we finally obtained four sets of reactivity data. As shown in Figure 2,

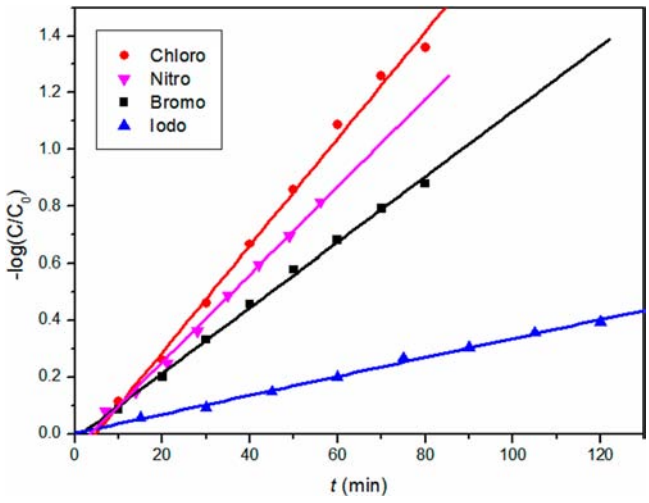


Figure 2. Kinetic plots for the reaction of *meso*-Cl, -Br-, -I-, and -NO_2-substituted porphyrins (Ni) with phenols.

reactivity of the substituted porphyrins(Ni) was measured in the order Cl > NO_2 > Br > I (known as the "element effect", Figures S1−S5 and Tables S1−S5 in the Supporting Information), which is consistent with the reported classic S_NAr reaction.[16] Most aromatic nucleophilic substitution reactions were thought to proceed via a Meisenheimer complex or a σ-complex intermediate procedure,[17] and the rate-determining step[18] might be the formation or decomposition of Meisenheimer complex. Based on the results measured above, we propose the reaction may proceed through an addition−elimination process with the addition of nucleophiles being rate-determining step.

In conclusion, we have developed a facile and effective catalyst-free method for the preparation of *meso*-O, -S-, and -C-substituted porphyrins from *meso*-brominated porphyrin. Most of the reactions can be completed within 1 h and in high yield except that relatively long reaction times were needed for the carbon-based nucleophiles. Kinetic investigation shows that the reaction adopts a typical nucleophilic aromatic substitution (S_NAr) procedure. The general simple methodology will grant access to a variety of *meso*-functionalization of porphyrins that could be applied in catalysts, photodynamic therapy agents, and nonlinear optical materials.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characteristic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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