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Simple and efficient synthesis of pyrazole-fused porphyrins

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ABSTRACT

A simple and efficient method for the synthesis of pyrazole-fused porphyrins from readily available *N*-tosylhydrazones and 2-nitroporphyrins has been developed. This catalyst-free method can be applied to a wide range of substrates and demonstrate excellent tolerance to a variety of substituents.

Porphyrins are an important and interesting class of molecules in nature and have shown wide applications in catalysts, molecular sensing, artificial photosynthesis, nonlinear optical materials, molecular wires, medicine, and so forth.[1] The derivatization step is particularly important for the applications of porphyrin.[2] Thus, considerable efforts have been made to develop selective methods for allowing the effective functionalization of porphyrin. Up to now, there are some important methods that have been developed to modify porphyrin as a useful reaction platform such as bromination,[3] nitration,[4] and borylation.[5]

2-Nitroporphyrin,[4a] an easily accessible product by nitration of porphyrin, has attracted considerable attention in recent years because of their high versatility as intermediate for further derivatization. On the one hand, the nitro group can be converted to amino and diazonium groups, both of them are important synthetic tools for porphyrin derivatization.[6] On the other hand, the peripheral double bonds of *meso*-tetraarylporphyrins can be partially isolated from the macrocyclic conjugation pathway. So the 2-nitro substituted double bond has the similar reactivity of normal nitroalkenes. With this property, extensive researches have been made on 2-nitroporphyrins in nucleophilic substitution reactions. For example, 2-nitro group can be nucleophilically substituted by other groups including thiolates,[7] Grignard or organolithium reagents,[8] alkoxides,[9] 1,3-dicarbonyl compounds,[10] or azide ion.[11] Additionally, many other interesting reactions also have been investigated such as Diels–Alder cycloaddition,[12] sulfa-Michael/aldol cascade reaction,[13] and so on.[14]

N-Tosylhydrazones have emerged as useful reagents in many organic reactions.[15] Among these reactions, Tang's group developed a simple method for the synthesis of pyrazoles from *N*-tosylhydrazones and nitroalkenes.[16] This reaction and the property of 2-nitroporphyrins make it possible to synthesize pyrazole-fused porphyrins derivatives with *N*-tosylhydrazones. As part of our endeavor to synthesize porphyrin derivatives based on 2-nitroporphyrins,[13] we herein report a simple method for the synthesis of a series of new porphyrin derivatives by the reaction of 2-nitroporphyrins and *N*-tosylhydrazones under basic condition (Scheme 1).

In the initial study, we investigated the influence of the different base to the reaction of 2-nitroporphyrin **1a** and 4-methyl-*N*′-(4-nitrobenzylidene)benzenesulfonohydrazide **2a** (Table 1). In each case the experiment was conducted for 2 h with 1.5 equiv *N*-tosylhydrazone **2a** and 2 equiv base in *N*,*N*-dimethylformamide (DMF) at 80 °C. The progress of this reaction was monitored by TLC and the target products were purified by flash column chromatography on silica gel. As shown in Table 1, after 2 h, all tested bases could precede the reaction and provide the desired product **3a** except triethylamine (entry 1). We found that Cs_2CO_3 was the best base for this reaction (70% yield, entry 6), and K_2CO_3 and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were also both suitable bases with 61% and 65% yield, respectively (entries 2 and 4). The other bases such as NaH (entry 3) and *t*-BuOK (entry 5) were also tested with lower yields from 10% to 23%. Then we improved the reaction temperature to 100 °C to test the influence of temperature to this reaction (entry 7). The result showed the yield could not be markedly increased when improving the reaction temperature. We

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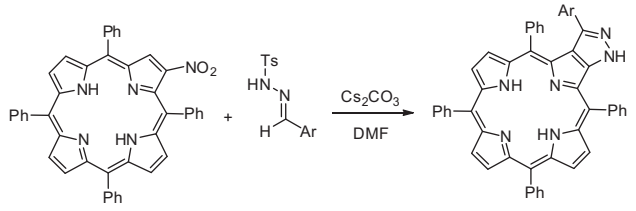
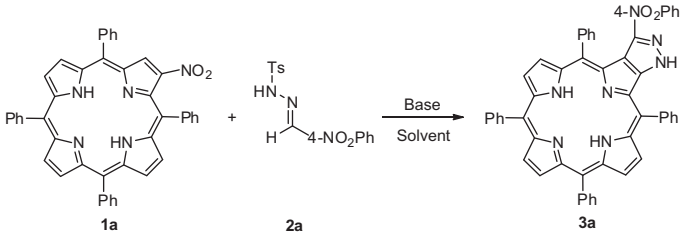


Scheme 1. Reaction of 2-nitroporphyrins with *N*-tosylhydrazone under catalyst-free conditions.

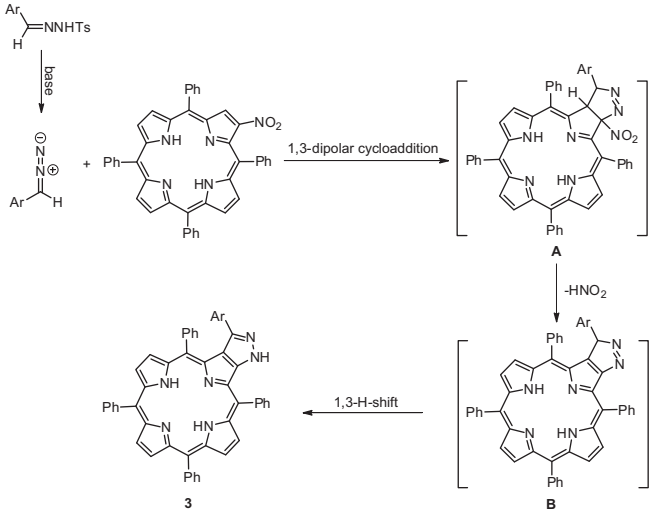
Table 1
Optimization of the reaction conditions



1a **2a** **3a**

Entry[a]	Base	Solvent	Hydrazone (equiv)	*t* (h)	*T* (°C)	Yield (%)
1	Et_3N	DMF	1.5	2	80	—
2	K_2CO_3	DMF	1.5	2	80	61
3	NaH	DMF	1.5	2	80	10
4	DBU	DMF	1.5	2	80	65
5	*t*-BuOK	DMF	1.5	2	80	23
6	Cs_2CO_3	DMF	1.5	2	80	70
7	Cs_2CO_3	DMF	1.5	2	100	72
8	Cs_2CO_3	THF	1.5	2	80	28
9	Cs_2CO_3	Toluene	1.5	2	80	Trace
10	Cs_2CO_3	Benzene	1.5	2	80	Trace
11	Cs_2CO_3	Dioxane	1.5	2	80	—
12	Cs_2CO_3	$CHCl_3$	1.5	2	60	—
13	Cs_2CO_3	DMF	3	2	80	76
14	Cs_2CO_3	DMF	7	1	80	85

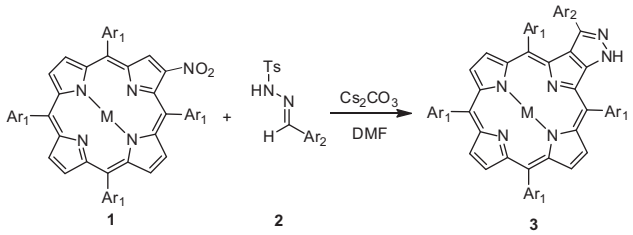
[a] Unless otherwise specified, all reactions were carried out on 0.015 mmol of **2a** in 0.5 mL of solvent.



Scheme 2. Possible reaction mechanism.

next examined the effect of solvent to the reaction (entries 8–12), and the best solvent was DMF. Tetrahydrofuran (THF) turned out to be a fair solvent in this reaction and afforded relatively low yield (28%). Aromatic solvents containing toluene and benzene were also

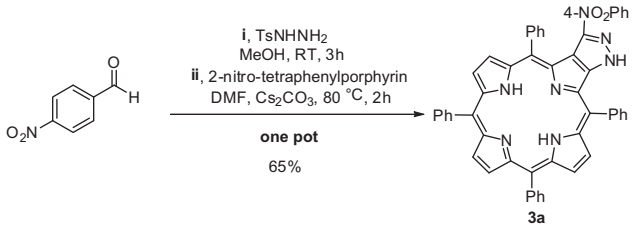
Table 2
Synthesis of pyrazole-fused porphyrins **3a**–**q**



1 **2** **3**

Entry[a]	Ar_1	Ar_2	M	Product	Yield (%)
1	Ph	4-NO_2-Ph	2H	**3a**	85
2	Ph	2-NO_2-Ph	2H	**3b**	60
3	Ph	4-CN-Ph	2H	**3c**	75
4	Ph	4-Cl-Ph	2H	**3d**	65
5	Ph	2-Cl-Ph	2H	**3e**	61
6	Ph	2,4-di-Cl-Ph	2H	**3f**	67
7	Ph	2,6-di-Cl-Ph	2H	**3g**	90
8	Ph	4-F-Ph	2H	**3h**	58
9	Ph	4-Br-Ph	2H	**3i**	62
10	Ph	Ph	2H	**3j**	54
11	Ph	4-CH_3-Ph	2H	**3k**	55
12	Ph	3-OCH_3-Ph	2H	**3l**	69
13	Ph	4-*t*Bu-Ph	2H	**3m**	58
14	Ph	4-Py	2H	**3n**	85
15	Ph	4-NO_2-Ph	Cu	**3o**	68
16	4-OCH_3-Ph	4-NO_2-Ph	Cu	**3p**	65
17	4-CH_3-Ph	4-NO_2-Ph	Cu	**3q**	78

[a] Reactions were performed with 2-nitroporphyrins **1** (0.05 mmol), *N*-tosylhydrazones **2** (0.35 mmol), and Cs_2CO_3 (0.45 mmol) in DMF (3 ml) at 80 °C.



Scheme 3. One-pot reaction of 4-nitrobenzaldehyde to form **3a**. Reaction condition: (i) 4-nitrobenzaldehyde (0.35 mmol), $TsNHNH_2$ (0.35 mmol), MeOH, rt, 3 h; (ii) 2-nitro-tetraphenylporphyrin (0.05 mmol), Cs_2CO_3 (0.45 mmol), DMF, 80 °C, 2 h.

tested (entries 9 and 10), but just with trace product **3a**. The other solvents such as dioxane and $CHCl_3$ could not get any product under the same reaction condition (entries 11 and 12). Inspired by the excellent results, we also investigated the quantity of used *N*-tosylhydrazone. The reaction yield was surprisingly improved when the amount of *N*-tosylhydrazone was increased (entries 13 and 14). Up to 85% yield was achieved using 7 equiv of *N*-tosylhydrazone and the reaction time was decreased to 1 h (entry 14).

The structure of product **3a** was unambiguously established from its spectroscopic data, especially HRMS, ^1H, and ^{13}C. The mass spectrometry of product **3a** displayed the molecular ion peak at *m*/*z* 776.2769 (calcd 776.2768 for $[M+H]^+$), which indicated the desired pyrazole-fused product was produced in the reaction. The UV–Vis absorption spectra of **3a** demonstrated the sort band accompanied by Q bands. These were consistent with our NMR results (^1H and ^{13}C) of **3a** (Supporting information). The ^1H NMR spectrum of **3a** (298 K, $CDCl_3$) was characterized by the inner NH signal (22, 24 NH) of the pyrrole at δ −2.74 and −2.72 ppm, and six β-pyrrole proton signals in the region of δ 8.66–8.98 ppm. The broad peak at δ 9.29 ppm was assigned to the proton of NH which was located on the pyrazole segment, which was confirmed by the deuterium exchange experiment with D_2O.

A plausible mechanism for the formation of pyrazole-fused porphyrin is outlined in Scheme 2. The first step was the classic 1,3-dipolar cycloaddition reaction of 2-nitroporphyrin and diazo dipolar which generated in situ by the reaction of tosylhydrazone and base, the resulting pyrazoline-fused chlorin intermediate **A** was transformed into pyrazole-fused porphyrin intermediate **B** via elimination of nitrous acid. The final product **3** was formed by [1,3]-*H*-migration of pyrazole-fused porphyrin intermediate **B**.

Next, under the above optimized conditions, we then proceeded to synthesize a variety of pyrazole-fused porphyrins to test the generality and scope of the method (Table 2). At first, we examined the substrate scope of the *N*-tosylhydrazones, which were derived from aromatic aldehydes. For example, the *N*-tosylhydrazones bearing a range of electron-withdrawing and electron-donating substituents were successfully converted to the corresponding products in moderate to high yields (**3a**–**3m**). In addition, the *N*-tosylhydrazones derived from heteroaromatic aldehyde also worked well to give the corresponding product in moderate yields (**3n**). And then, we also tested the scope of the porphyrin, 2-nitro-tetraphenylporphyrin Cu(II) was tested and also afforded the desired product in moderate yields (**3o**). Moreover, 4-OCH_3Ph and 4-CH_3Ph-substituted 2-nitroporphyrins Cu(II) were also suitable substrates to this reaction and afforded the corresponding products (**3p** and **3q**) in moderate yields. It is noteworthy that the reaction proceeded with a high level of regioselectivity and no isomer was detected in all substituents.

It is worthy to note that we also developed a one-pot procedure to perform this reaction. The 1:1 stoichiometry reaction of 4-nitrobenzaldehyde and tosylhydrazide to produce 4-Methyl-*N*′-(4-nitrobenzylidene)benzenesulfonohydrazide was completed in MeOH for 3 h. After removal of the solvent, subjection of the resulting residue to the porphyrins synthesis conditions with 2-nitro-tetraphenylporphyrin generated 3a with 65% yield which was just a little diminished compared with the separate steps (Scheme 3). This one-pot method is a viable option, and in most cases, *N*-tosylhydrazones can be prepared without purification in a similar manner.

In conclusion, we have developed a facile method for the preparation of pyrazole-fused porphyrins from *N*-tosylhydrazones and 2-nitroporphyrins. The efficient and simple reaction shows excellent tolerance to a variety of substituents, including both electron-donating and electron-withdrawing groups. The reaction provides moderate-to-excellent yields of a wide variety of products, and can be performed as a one-pot procedure without transition-metal catalysts. The pyrazole-fused porphyrins can be used as reagent of photodynamic therapy and as derivatization platform due to the bioactivity and reactivity of pyrazole. Further studies on the properties of these new and potentially valuable porphyrins are currently under investigation.

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Supplementary data

Supplementary data (a description of the synthesis and characterization of all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.02.020.

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