Rational Synthesis of Meso-Substituted Porphyrins Bearing One Nitrogen Heterocyclic Group

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Tailoring the perimeter of the porphyrin macrocycle with diverse substituents in defined patterns is essential for studies in biomimetic and materials chemistry.^{1,2} Small nitrogen heterocycles are substituents of particular interest,³ providing sites for metal coordination, hydrogenbonding, alkylation (water solubilization), and modulation of the electronic properties of the porphyrin. Indeed, pyridine substituents have yielded a broad array of metal-coordinated multiporphyrin architectures,⁴ imidazole groups have yielded stacked multiporphyrin assemblies,⁵ and quinoline,⁶ pyrimidine/purine,^{7,8} or pyrazole⁹ units have enabled molecular recognition and selfassembly studies of porphyrins with complementary molecules. In these diverse architectures, a recurring pattern entails the incorporation of one heterocyclic group and three nonheterocyclic groups at the four meso positions of a porphyrin.

Despite the widespread attraction of porphyrins bearing a single nitrogen heterocyclic group,¹⁰ the synthesis of such porphyrins has presented vexing challenges. The prevalent method of synthesis involves a mixed aldehyde condensation with pyrrole via the Adler method in refluxing propionic acid.¹¹ This statistical approach affords a mixture of up to six porphyrins, from which the desired porphyrin is typically separated by laborious chromatography. For many nonheterocyclic aldehydes the milder conditions of the two-step one-flask synthesis (at room temperature in CH₂Cl₂ with TFA or BF₃-etherate followed by oxidation with DDQ) are attractive, generally affording higher yields and more tractable non-porphyrin byproducts.¹ However, small heterocyclic aldehydes generally fail in this method, which has been attributed to the poor solubility of the heterocyclic aldehyde (or its intermediate reaction products with pyrrole) in acidified CH₂Cl₂ or CHCl₃. Indeed, the room-temperature pyrrolealdehyde condensation has succeeded with more soluble heterocyclic aldehydes, such as pyrimidinecarboxaldehydes bearing bulky groups adjacent to both nitrogens,¹² pyrazolecarboxaldehydes bearing protecting groups (benzyl, SEM) on one of the nitrogens,¹³ or benzaldehydes to which heterocycles are attached.¹ A complementary approach has been developed for the Pd-mediated attachment of heterocyclic groups to a dihalogenated porphyrin, thereby avoiding the acid-catalyzed condensations with heterocyclic aldehydes.¹⁴ Still, a direct and nonstatistical method is required to avoid performing additional synthetic steps and extensive chromatographic separation of multiple porphyrin products.

We now report such a method for the preparation of porphyrins bearing one nitrogen heterocycle. Our approach builds on our recent success in developing two reactions: (1) a one-flask synthesis of dipyrromethanes and (2) the condensation of the dipyrromethane and a dipyrromethane-dicarbinol. For both reactions we have identified conditions (solvent, catalyst, temperature) that are suitable for the heterocyclic substrates.

Dipyrromethanes are available via the one-flask roomtemperature condensation of an aldehyde with excess pyrrole (in the absence of any solvent) in the presence of TFA or BF₃-etherate.^{15,16} This reaction has been used to prepare dipyrromethanes bearing a wide variety of substituents.¹ The dipyrromethane-forming reaction also can be performed at elevated temperature in the absence of added acid, albeit in lower yield than with acid at room temperature.¹⁶ Upon application of the standard procedure at room temperature with acid to a set of heterocyclic aldehydes (2-, 3-, or 4-pyridinecarboxaldehyde, quinoline-3-carboxaldehyde, imidazole-2-carboxaldeyde, uracil-5-carboxaldehyde) with pyrrole, no dipyrromethane was obtained.¹⁷ While the "high-temperature no-acid" conditions have had no utility with anyl or aliphatic aldehydes, we felt the ability to forego any acid warranted examination in this case, given that identifying a suitable acidic medium for heterocyclic aldehydes has proved so problematic. Upon performing the pyrrole-aldehyde

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^a All reactions were performed with 14 mol of pyrrole per mol of aldehyde in the absence of any solvent. ^b With addition of TFA (See Supporting Information).

reaction without added acid at 85 °C overnight, the desired dipyrromethanes **1a**-**c** were obtained in reasonable yields as shown in Table 1. Dipyrromethanes 1d,e required higher temperatures and also were obtained after heating overnight. Uracil-5-carboxaldehyde afforded only a small amount of dipyrromethane upon application of the acidic conditions at room temperature or using elevated temperature without acid. In this case the desired dipyrromethane 1f was obtained upon condensation with pyrrole in the presence of TFA (0.3 equiv) at 60 °C for 1 h. The dipyrromethanes generally were purified by removal of excess pyrrole by high-vacuum distillation, filtration of the crude mixture over an alumina pad, bulb-to-bulb distillation to remove the dipyrromethane from oligomeric materials, and final crystallization to remove any N-confused dipyrromethane. Dipyrromethanes 1d and 1f were not distilled but were chromatographed and then crystallized.

The desired dipyrromethane-dicarbinols were prepared in a two-step process (Scheme 1).¹⁸⁻²⁰ Treatment of 5-phenyldipyrromethane with ethylmagnesium bromide followed by benzoyl chloride afforded the 1,9-diacyldipyr-



3-dicarbinol. R = CH₃

romethane **2** in good yield. Similar reaction of 5-(*p*-tolyl)dipyrromethane with *p*-toluoyl chloride gave the diacyldipyrromethane 3. Reduction of the diacyldipyrromethanes with NaBH₄ in THF-methanol afforded the corresponding dipyrromethane-dicarbinols, which were not characterized but were used immediately in the subsequent reaction.

The reaction of a dipyrromethane and a dipyrromethane-dicarbinol provides a means of preparing a porphyrin bearing a regiospecific pattern of meso substituents (Scheme 2).^{18–20} The success of this approach hinges on the absence of acid-promoted scrambling of the dipyrromethane and dipyrromethane-dicarbinol. We recently developed conditions (30 mM TFA in CH₃CN at room temperature for 5 min followed by oxidation with DDQ) for this reaction that give 20-30% yields without detectable scrambling.^{20,21} (The condensation of a dipyrromethane and an aldehyde under similar conditions proceeds without detectable scrambling.²²) Given the expectation that heterocyclic substrates behave differ-

⁽¹⁷⁾ Two examples of one-flask syntheses of dipyrromethanes bearing heterocyclic substituents have been reported but without delineation of scope. Reaction of 4-pyridinecarboxaldehyde and pyrrole in the presence of gaseous HCl afforded 5-(4-pyridyl)dipyrromethane (Nagarkatti, J. P.; Ashley, K. R. Synthesis 1974, 186-187). Reaction of a uridinecarboxaldehyde with pyrrole in CHCl3 containing SnCl4 afforded the corresponding dipyrromethane (Cornia, M.; Binacchi, S.; Del Soldato, T.; Zanardi, F.; Casiraghi, G. J. Org. Chem. 1995, 60, 4964-4965)

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ently in acidified solvents than most aromatic compounds, we surveyed the effects of various amounts of TFA on the reaction course with dipyrromethanes 1a-eand dipyrromethane-dicarbinol 2-dicarbinol in acetonitrile. The reactions were monitored by treating small reaction aliquots with excess DDQ followed by absorption spectroscopy in order to determine the overall porphyrin yield. For each dipyrromethane examined, the reactions with 75 mM acid were complete in 5 min and the yield remained constant over 1 h. At 0.6 mM TFA, the reactions were slower but the yields were higher. The only exception occurred with the imidazole-dipyrromethane 1e, which gave only trace amounts of porphyrin with low TFA, and about 2% yield with 75 mM TFA. A synopsis of the results is provided in Table 2 (see Supporting Information for comprehensive data). The superior results obtained with trace acid catalysis are counter to the expectation that excess acid is required to overcome the basicity of the pyridine-like nitrogen atom.

These conditions were applied to prepare the porphyrins **4a**–**g**. In the synthesis of porphyrins **4a**–**d**, **4f**, and 4g (condensation at 0.6 mM), only a single porphyrin product was observed on chromatography, making purification quite straightforward. The isolated yields were essentially identical to those determined by spectroscopic monitoring of the reactions. The absence of scrambling in these reactions was confirmed by examining the crude reaction mixtures.²³ (The reaction with the imidazoledipyrromethane 1e at 75 mM TFA gave tetraphenylporphyrin in an amount comparable to that of the desired porphyrin 4e.) Porphyrins 4b, 4f, and 4g also were prepared at the semipreparative scale ($\sim 1-4$ mmol

Table 2. Conditions for the Synthesis of the Porphyrins^a

		yield (%) ^b		
porphyrin	TFA (mM)	5 min	1 h	other time
4a	0.6	5.7	20	
	75	11	11	
4b	0.6	trace	4.2	9.2 (4 h)
	75	7.1	7.3	
4 c	0.6	0	1.9	6.5 (6 h)
	75	3.9	3.9	
4d	0.6	2.1	9.7	11 (2 h)
	75	6.1	5.9	
4e	0.6	0	0	
	75	1.5	1.5^{c}	
4f	0.6	21	21^d	
	75	_	_	

^a All reactions were performed using 2.5 mM dipyrromethane and 2.5 mM dipyrromethane-dicarbinol (2-dicarbinol) in acetonitrile containing TFA at room temperature for the time indicated, followed by oxidation with DDQ at room temperature. ^b Yields determined spectroscopically. ^c Scrambling was observed; thus, this yield represents the total yield of all porphyrins formed. d 30

dipyrromethane). In each case the pure porphyrin was isolated by filtration over alumina, chromatography on one silica column, and crystallization. The yields are

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⁽²³⁾ To probe acid-catalyzed scrambling during porphyrin-forming reactions, we applied an LD-MS assay for examining crude reaction mixtures, enabling identification of scrambling that might be missed following chromatographic workup.²² The crude reaction mixtures in the synthesis of porphyrin 4d or 4f (0.6 mM TFA) each gave a dominant peak in the mass spectrum corresponding to the expected porphyrin with no peaks corresponding to scrambled porphyrin products. Attempts to scrutinize putative scrambling processes in the reactions affording the pyridyl-substituted porphyrins 4a-c were stymied by insufficient mass differences among potential scrambled products (C6H5 = 77 Da; $C_5H_4N = 78$ Da). The crude reaction mixture obtained with the pyridyl-substituted porphyrin 4g was examined. A dominant molecule ion peak was observed, and no other peaks were observed which could be assigned as scrambled porphyrins, indicating the integrity of the dipyrromethanes under the mild reaction conditions.

modest (4-20%) but generally exceed those of mixed aldehyde condensations.

In summary, we have identified conditions for two reactions that enable the rational synthesis of porphyrins bearing one small heterocyclic group. In the synthesis of dipyrromethanes, reaction of a heterocyclic aldehyde and excess pyrrole occurs at elevated temperatures without added acid. In the synthesis of the porphyrin, reaction of a dipyrromethane and a dipyrromethane-dicarbinol occurs with trace acid catalysis (0.6 mM TFA) in the polar solvent acetonitrile. The use of little or no acid in these reactions appears to be novel, as excess acid has typically been employed with heterocyclic substrates. The desired porphyrin was obtained without statistical reactions and was purified in a straightforward manner. This approach should prove useful for the preparation of a broad variety of porphyrins bearing a single heterocyclic substituent.

Experimental Section

General. Bulb-to-bulb distillation was performed using a standard-size Kugelrohr short-path distillation apparatus (Aldrich). All reagents were obtained commercially except for uracil-5-carboxaldehyde, which was prepared as described in the literature.²⁴ Porphyrins (from crude reaction mixtures, or following purification) were analyzed by laser desorption ionization mass spectrometry (LD-MS) without a matrix.²⁵

Synthesis of Dipyrromethanes (general procedure). An aldehyde (20 mmol) was added to pyrrole (280 mmol, 20 mL), and the resulting mixture was stirred for 15 or 24 h at the temperature specified in Table 1. Then the reaction mixture was evaporated to dryness and chromatographed on alumina (column

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size 25 \times 4 cm) with CH₂Cl₂ and then CH₂Cl₂:ethyl acetate (4:1). Appropriate fractions were collected, affording a dark brown mixture. Bulb-to-bulb distillation afforded the desired dipyrromethane which then was crystallized.

Synthesis of Porphyrins (general procedure). Samples of the dipyrromethane (0.072 mmol) and the dipyrromethanedicarbinol (0.072 mmol) were dissolved in acetonitrile (29.0 mL) at room temperature and protected from light, and then TFA (0.018 mmol, 0.60 mM) was added. The reactions were monitored by treating small reaction aliquots with excess 2,3-dichloro-5,6dicyano-1,4-benzoquinone (DDQ) followed by absorption spectroscopy (418 nm, assuming $\epsilon = 5 \times 10^5 \text{ M}^{-1} \text{ cm}^{-1}$) in order to determine the overall porphyrin yield.²⁶ The reaction mixture was stirred for the period described in Table 2 at room temperature before adding DDQ (0.216 mmol). (As little as 0.055 mmol DDQ has been employed in these reactions with no apparent decrease in porphyrin yield.) After 1 h the solvent was evaporated and the residue was filtered over a pad of alumina (CH₂Cl₂, CH₂Cl₂:ethyl acetate). The porphyrin fraction was chromatographed on a silica column (CHCl₃) to remove small amounts of non-porphyrin pigments, affording a highly pure product. Crystallization was then performed to remove nonporphyrinic materials that gave peaks in the aliphatic region of the ¹H NMR spectrum.

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Supporting Information Available: Detailed synthetic procedures for the preparation of 1a-f, 2, 3, 4a-g; ¹H NMR spectra of dipyrromethanes 1a-f; ¹H NMR and LD-MS spectra of porphyrins 4a-g; a table of data concerning the effects of acid concentration on the yields of porphyrins 4a-e. This material is available free of charge via the Internet at http://pubs.acs.org.

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