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Alkylthio Unit as an α-Pyrrole Protecting Group for Use in Dipyrromethane Synthesis

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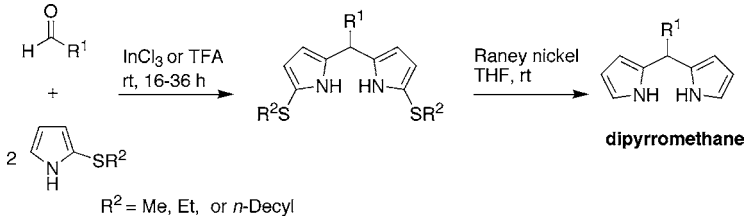

The synthesis of porphyrin precursors requires the successive introduction of substituents at the pyrrole α- and α′-positions (2- and 5-, respectively). An α-pyrrole substituent that serves as a temporary masking agent and is not deactivating would greatly facilitate such syntheses, particularly for β-(3,4)-unsubstituted pyrroles, but has heretofore not been available. A series of α-RS groups (R = Me, Et, *n*-decyl, Ph) have been investigated in this regard, including the determination of the kinetics of substitution at the pyrrolic 3-, 4-, and 5-positions and the application to dipyrromethane formation. The RS group was readily introduced into the pyrrole α-position by the reaction of 2-thiocyanatopyrrole (prepared from pyrrole, ammonium thiocyanate, and iodine) and the corresponding Grignard reagent RMgBr. Each 2-alkylthio group activated the pyrrole ring toward deuteration at the 3- or 5- (vs 4-) position. The dipyrromethane synthesis was carried out using a 2:1 ratio of 2-(RS)pyrrole/benzaldehyde with a catalytic amount of $InCl_3$ at room temperature in the absence of any solvent. The α-RS group was removed by hydrodesulfurization using Raney nickel or nickel complexes. This stoichiometric synthesis using the α-RS-protected pyrrole is in contrast to the traditional synthesis that employs an aldehyde and 25−100 mol equiv of pyrrole. Six meso-substituted dipyrromethanes were prepared by the reaction of 2-(*n*-decylthio)pyrrole/aldehyde/$InCl_3$ (2.2:1:0.2 ratio) followed by hydrodesulfurization. Other reactions of the 1,9-bis(RS)dipyrromethane include oxidation to give (i) the 1,9-bis(RS)dipyrrin or (ii) the 1,9-bis(RSO_2)dipyrromethane, which underwent subsequent complexation with dibutyltin dichloride. In summary, under mild reaction conditions, the 2-alkylthio group is readily introduced to the pyrrole nucleus, directs electrophilic substitution to the 5-position, and is readily removed as required for elaboration of porphyrinic precursors.

Introduction

The synthesis of porphyrinic macrocycles and related compounds requires the ability to carry out reactions at the pyrrolic α- and α′-positions (2- and 5-positions, respectively). The controlled introduction of a single substituent via electrophilic substitution can necessitate the use of an α-blocking group, particularly when the newly introduced substituent activates the pyrrole to further substitution. In the synthesis of naturally occurring porphyrins, which typically entails the use of 3,4-disubstituted pyrroles (e.g., **A**), an ester (or carboxylic acid) suffices to block the 2-position: substitution occurs at the 5-position, which contains the only open carbon in the pyrrolic nucleus (eq 1). Removal of the blocking carboxy moiety typically requires treatment at high temperature with a strong base, a strong acid, and/or a halogen reagent. Use of the halogen reagent affords the 2-halopyrrolic species, which is converted to the pyrrole with the open 2-position by catalytic hydrogenation.[1] In general, the use of a carboxylate (or other electron-withdrawing group) to block the 2-position in a pyrrole lacking substituents at the 3- and 4-positions (e.g., **B**, eq 2) is expected to present three problems: (1) sluggish reaction, (2) diminished selectivity for the direction of the incoming group to the

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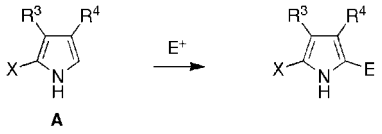
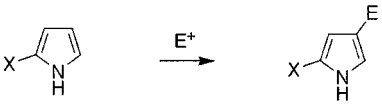
5-position vs the 4-position, and (3) harsh conditions for removal of the carboxylate group. To our knowledge, only one β-unsubstituted dipyrromethane has been prepared via this approach.[2] On the other hand, the incoming group could be directed rapidly to the 5-position with an α-blocking group that is not deactivating, but such a simple protective group for pyrroles has heretofore not been developed.



A (eq 1)

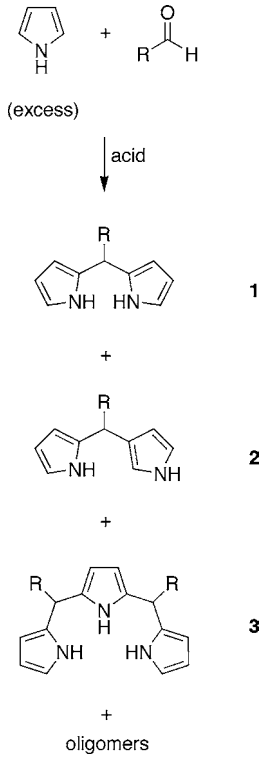


B (eq 2)

The absence of a suitable α-blocking group for unsubstituted pyrroles has substantially affected a number of synthetic transformations. For example, the synthesis of β-unsubstituted dipyrromethanes is typically carried out by reaction of an aldehyde with excess pyrrole (up to 100 mol equiv), resulting in **1**, N-confused dipyrromethane (**2**), tripyrrane (**3**), and oligomeric byproducts (Scheme 1). The presence of excess pyrrole is required to trap the initially formed pyrrole−carbinol and thereby suppress the competitive self-oligomerization of the pyrrole−carbinol. Although considerable refinement has gone into streamlining the conditions for carrying out this reaction and purifying the product,[3−5] the use of such a large excess of pyrrole remains an inherent disadvantage. The availability of an α-blocking group that is not deactivating would enable the use of a stoichiometric amount of the protected pyrrole (2 mol equiv) and the aldehyde. Thompson and co-workers have recently reported a sulfonyl or 2,4-dinitrophenylsulfinyl group for protecting the α-pyrrole position, but again, both groups are deactivating.[6]

For applications in the synthesis of porphyrinic precursors, an ideal α-pyrrole protecting group would afford the following features: (1) mask the α-carbon toward electrophilic aromatic substitution, (2) direct electrophilic aromatic substitution to the pyrrole 5-position without deactivation of the pyrrole ring, (3) afford stability toward acidic conditions, (4) yield a crystalline product, and (5) undergo traceless cleavage under nonacidic conditions. In contemplating candidates for protection of the α-pyrrolic position, we considered the alkylthio moiety. In this regard, Muchowski and co-workers demonstrated that a 2-alkylthiopyrrole undergoes acylation selectively at the 5-position.[7] Thioethers also have been employed as traceless linkers in solid-phase chemistry.[8]

SCHEME 1



In this paper, we describe the use of the alkylthio unit as a traceless α-pyrrole protecting group. We have screened acid catalysts and characterized the kinetics of electrophilic aromatic substitution of 2-substituted pyrroles. Our study includes the development of a mild, solventless, and stoichiometric synthesis of β-unsubstituted dipyrromethanes bearing different substituents at the meso-position. Selective oxidation of the 1,9-bis(RS)-dipyrromethanes at the dipyrromethane unit or the sulfur moieties has been established. This work provides the foundation for the use of the alkylthio unit in pyrrole and porphyrin chemistry, masking the pyrrolic 2-position and activating the pyrrolic unit toward electrophilic substitution at the 5-position.

Results and Discussion

1. Syntheses of 2-(RS)pyrroles. We sought to prepare pyrrole derivatives bearing a series of α-RS groups, where R = methyl, ethyl, *n*-decyl, and phenyl groups. Several routes have been reported for the synthesis of 2-(RS)pyrroles lacking any other substituents, though none has been used to prepare an extensive set of homologues. The routes consist of (1) treatment of pyrrole with a dialkyl disulfide in the presence of sulfuric acid,[9] (2) reaction of 2-thiocyanatopyrrole with a Grignard reagent,[10,11] (3) cyclization of allyl isothiocyanate to give the pyrrole-2-

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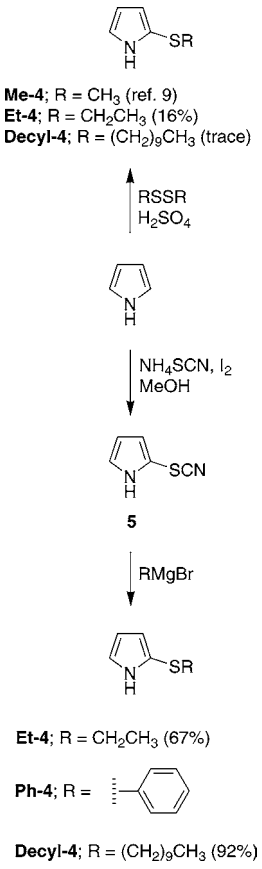
SCHEME 2



thiolate followed by reaction with an alkyl halide,[12] and (4) alkylation of pyrrole with an alkylsulfanyl chloride.[6,13] We explored the first two methods. 2-(Methylthio)pyrrole (**Me-4**) has been prepared by treatment of pyrrole with dimethyl disulfide in sulfuric acid,[9] but our attempts to extend this method to the ethyl and *n*-decyl analogues afforded compounds **Et-4** and **Decyl-4** in low yield (Scheme 2). The phenyl analogue **Ph-4** has been prepared by reaction of 2-thiocyanatopyrrole (**5**)[11] with phenylmagnesium bromide.[10] 2-Thiocyanatopyrrole (**5**), which is readily prepared by reaction of pyrrole, ammonium thiocyanate, and iodine in methanol, proved to be a versatile substrate. Thus, reaction of **5** with ethyl- or *n*-decylmagnesium bromide afforded **Et-4** or **Decyl-4** in 67 or 92% yield, respectively.

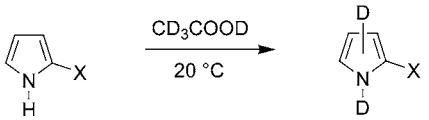
2. Kinetic Study of Deuteration of Pyrroles Bearing Different α-Substituents. The kinetics of deuterium exchange on **Me-4**, **Et-4**, **Ph-4**, and **Decyl-4** were examined to characterize the electronic effects of the various 2-substituents. The electronic effects of pyrrolic substituents have been examined by deuterium exchange, but no data are available for 2-RS substituents.[14−17] Of particular concern was to assess the effect of such groups on the reactivity of the 5-, 4-, and 3-positions on the pyrrole ring toward electrophilic aromatic substitution. For benchmarking purposes, other pyrroles examined include 2-methylpyrrole, 2-carboxypyrrole, and pyrrole itself. A full description of experimental methods and data is available in the Supporting Information.

TABLE 1. Rate Constants *k* of Deuteration of 2-Substituted Pyrroles[a]

2-substituent	rate constants k ($\times 10^4$) in s^{-1} ($t_{1/2}$ in min) 5-H	4-H	3-H	Hammett substituent constant σ_m[b]
-CH_3	240 (0.04)	2.5 (45)	110 (0.7)	−0.12
-H[c]	2.2 (48)	0.35 (310)	0.35 (48)	0.00
-SCH_3	8.7 (13)	0.047 (2200)	8.8 (13)	0.15
-SCH_2CH_3	3.3 (34)	0.049 (2300)	2.8 (34)	0.18
-$S(CH_2)_9CH_3$	4.0 (28)	0.063 (1600)	3.7 (30)	
-SPh	0.25 (460)	0.015 (7000)	0.14 (780)	0.23
-COOH	*d*	*d*	*d*	0.37

[a] In neat CD_3COOD with a pyrrole (87 mM, CD_3COOD/pyrrole = 200:1) at 20 °C. See Supporting Information for details. [b] Reference 18. [c] Due to molecular symmetry, 2-H and 3-H are equivalent to 5-H and 4-H, respectively. [d] No significant change was observed after 2 days.

The studies were carried out by performing the deuteration of a given pyrrole in neat CD_3COOD at 20 °C in an NMR tube (eq 3) using 1,4-dichlorobenzene as an internal standard. The



(eq 3)

resonances corresponding to H^5, H^4, and H^3 steadily diminished in intensity over time. The kinetic data obtained obeyed the first-order rate expression quite closely, affording rate constants k (sec^{-1}) and $t_{1/2}$ (min) values for the various positions (Table 1). Two comparisons are noteworthy, the relative reactivity of the 3-, 4-, and 5-positions for a given 2-(RS)pyrrole and the overall reactivity of the 2-(RS)pyrrole vs the benchmark pyrroles. For pyrrole itself, the α-(2-,5-) positions were six times more reactive toward deuterium exchange vs the *β*-(3-,4-) positions, which is comparable to the results of Bean's study of pyrrole in dilute acid, where the corresponding reactivity difference was 1.6-fold.[14]

For a given 2-alkylthio-substituted pyrrole (**Me-4**, **Et-4**, and **Decyl-4**), the reactivity toward deuterium exchange decreased in the following order: 5-position ∼ 3-position > 4-position. The presence of the 2-phenylthio group deactivates the pyrrole ring; thus, deuterium exchange at all positions was very slow for **Ph-4**. With pyrrole-2-carboxylic acid, no significant deuterium−hydrogen exchange was observed after two days, so rate constants were not calculated.

To confirm that the observed deuterium exchange was not confounded with any chemical reactions (e.g., pyrrole polymerization) under the acidic conditions, the reverse hydrogen−deuterium exchange (dedeuteration) was examined. Thus, a solution of deuterated **Decyl-4** (>90% for D^5 and D^3 and >30% for D^4) in CD_3COOD containing 1,3,5-tribromobenzene as an internal standard was treated with CH_3COOH (1 mL) for 24 h at 20 °C. Integration of the resonances in the aromatic region showed >98% conversion of deuterium to hydrogen in the sample of **Decyl-4**. This experiment confirmed the integrity of the 2-alkylthiopyrrole core structure under the acidic conditions.

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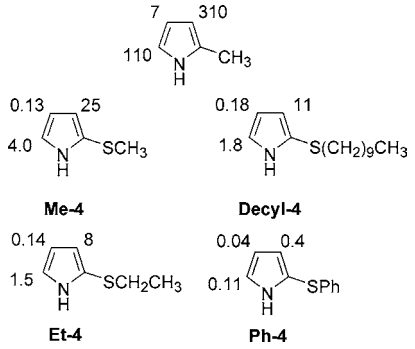
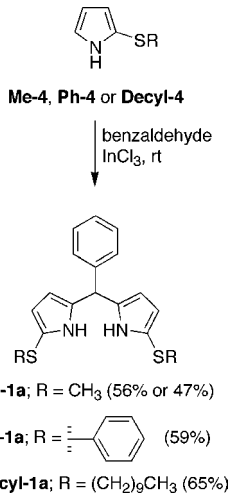


FIGURE 1. Reactivity of 2-(RS)pyrroles for deuterium exchange relative to exchange at the corresponding position of pyrrole. The value given for each position is the ratio of two rate constants.

SCHEME 3



Comparing the various 2-thiopyrroles with pyrrole, we note that the presence of alkylthio substitution has the following effect on each position toward deuterium exchange: (1) the 5-positions are slightly activated (1.5−4-fold), (2) the 4-positions are deactivated (5−7-fold), and (3) the 3-positions are strongly activated (8−25-fold). As expected, 2-methylpyrrole was strongly activated toward deuterium exchange at the 3- and 5-positions (>100 times) and at the 4-position (7 times).[16] Thus, the 2-alkylthiopyrroles lie intermediate in reactivity between pyrrole and 2-methylpyrrole. For ease of comparison, the relative reactivity for deuterium exchange at a given position for the various pyrroles compared to that of pyrrole itself is illustrated in Figure 1. It is noteworthy that these results are at odds with the expected electroneutrality or slight deactivation of alkylthio groups predicted by the Hammett substituent constants.[18]

3. Synthesis of Dipyrromethanes. A. Condensation Yielding 1,9-Bis(RS)dipyrromethanes. The condensation of **Me-4** and benzaldehyde (0.25 M) was performed in CH_2Cl_2 containing TFA (0.1 M) at room temperature, leading to dipyrromethane **Me-1a** in 56% yield (Scheme 3). The same reaction in the absence of CH_2Cl_2 (solventless) afforded **Me-1a** in 47% yield. In both cases, only 2.2 mol equiv of **Me-4** was employed, rather than 25−100 mol equiv as in the one-flask synthesis of dipyrromethanes from pyrrole and an aldehyde.

The condensation of pyrrole and benzaldehyde typically affords 5-phenyldipyrromethane (**1**), N-confused 5-phenyldipyrromethane (**2**), and 5,10-diphenyltripyrrane (**3**), as illustrated in Scheme 1, when R = phenyl. To assess the cleanliness of the reaction yielding **Me-1a**, each fraction obtained from column chromatography was analyzed by gas chromatography (GC), gas chromatography mass spectrometry (GC−MS), and ^{1}H NMR spectroscopy. GC and GC−MS analyses showed two dominant peaks (t_R = 19.3 and 19.6 min) that gave the same molecule ion peak (m/z = 312); the former was due to dipyrromethane **Me-1a**, and the latter was due to a putative N-confused dipyrromethane byproduct. A similar chromatogram was observed in the condensation of pyrrole and benzaldehyde.[5] No tripyrrane species were observed. This demonstrated the stability of the methylthio protecting group toward the dipyrromethane-forming reaction conditions.

TABLE 2. Acid Screening Experiments for the Condensation of 2-(Methylthio)pyrrole (Me-4) and Benzaldehyde[a]

acid	product/N-confused byproduct ratio[b]	darkness[c]
TFA	3.3:1	brown
$InCl_3$	6.1:1	yellow
$MgBr_2$[d]	5.9:1	orange
$Sc(OTf)_3$	3.4:1	orange
$Yb(OTf)_3$	4.4:1	light yellow

[a] Condensations (solventless) were performed with a 2:1:0.1 ratio of **Me-4**/benzaldehyde/acid at room temperature for 1 h. [b] Only the peaks of **Me-1a** (t_R = 19.3 min) and the putative N-confused byproduct (t_R = 19.6 min) are considered; the peak assigned to 2-benzyl-5-(methylthio)pyrrole (t_R = ~13.2 min) was observed in all cases but not taken into consideration. [c] Relative darkening of the reaction mixture after quenching with base. [d] The reaction time was 16 h.

The effects of TFA or a mild Lewis acid ($InCl_3$, $MgBr_2$, $Yb(OTf)_3$, or $Sc(OTf)_3$) on the reaction course in the solventless synthesis were examined. The cleanliness of the reaction was determined quantitatively by the ratio of the dipyrromethane **Me-1a** and the byproducts (detectable by GC analysis), and qualitatively by the darkness of the reaction mixture.[5] The darkening of the reaction mixture signals the formation of the materials that decrease the yield and complicate the purification (such materials are difficult to quantitate by GC).[5] The results are summarized in Table 2. Considering all factors, $InCl_3$ afforded the best results with dipyrromethane **Me-1a** and was chosen as the catalyst for further studies.

The conditions using $InCl_3$ were applied with other 2-(RS)-pyrroles in an effort to find substrates that afford an increase in the ratio of dipyrromethane/N-confused byproduct and also limit reliance on extensive chromatography for purification. The reaction mixture obtained from **Ph-4** contained **Ph-1a** and no detectable quantity of N-confused byproduct, whereas that of **Decyl-4** gave **Decyl-1a** and the N-confused byproduct in ≥20:1 ratio. The ^{1}H NMR analysis showed the remaining starting material, **Ph-4** or **Decyl-4**, in such reaction mixtures at the level of ~25 or ~5%, respectively. Attempts to separate each dipyrromethane, **Ph-1a** or **Decyl-1a**, by recrystallization of the reaction mixture were unsuccessful. Purification by passage over a short chromatographic column gave **Ph-1a** or **Decyl-1a** in 59 or 65% yield, respectively.

B. Hydrodesulfurization of 1,9-Bis(RS)dipyrromethanes. Carbon−sulfur bond cleavage can be achieved using a variety of metallic or organometallic reagents, of which Raney nickel has been used the most frequently.[19] Accordingly, removal of

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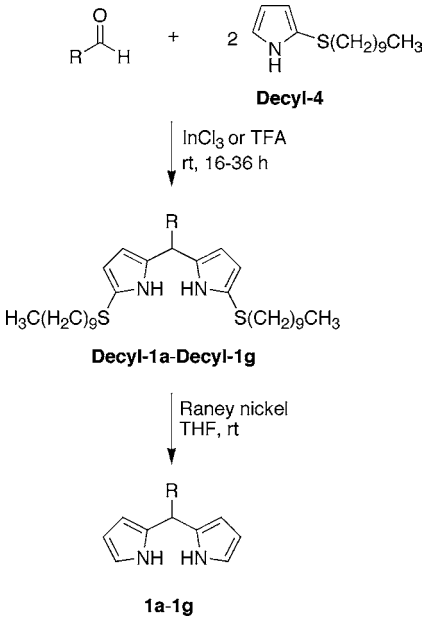
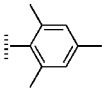
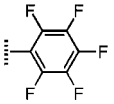
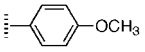
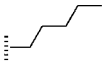
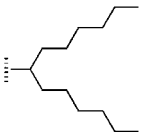
SCHEME 4



the methylthio units from dipyrromethane **Me-1a** was carried out by reduction with Raney nickel in refluxing EtOH. The workup procedure requires filtration through a silica pad to remove polar components and the remaining Raney nickel. The deprotected product **1a** was obtained in 97% yield. Application of the same conditions to **Ph-1a** afforded an incomplete reaction and the formation of several pyrrolic byproducts. This observation was consistent with Brückner's report, wherein the formation of coupling byproducts occurred in the reductive desulfurization of di-2-pyrrolylthione with Raney nickel.[20] In the case of **Decyl-1a**, Raney-nickel deprotection afforded **1a** in 69% yield. The use of other reagents (e.g., nickel boride generated in situ from $NiCl_2$ and $NaBH_4$) did not afford better results.

C. Scope of Application. The synthesis of dipyrromethanes bearing diverse meso-substituents was examined using the solventless synthesis with 2-(*n*-decylthio)pyrrole followed by Raney-nickel mediated hydrodesulfurization of the resulting dipyrromethane (Scheme 4). Each of the target dipyrromethanes (**1a**,[21] **1b**,[22] **1c**,[3] **1d**,[23] **1e**,[24] **1f**,[25] and **1g**[26]) is known, and **1a**−**f**[5] and **1g**[26] have been prepared recently by the solventless synthesis method using pyrrole in large excess (typically 100 mol equiv).[5] The solventless condensation herein was carried out initially using a 2:1:0.1 ratio of **Decyl-4**/aldehyde/$InCl_3$ at room temperature for 2 h. However, ^{1}H NMR analysis of the reaction mixtures showed ∼5% incompletion; hence, the ratio was increased to 2.2:1:0.2 and the reaction time was lengthened to 16 h. This slight modification resulted in complete consumption of the aldehydes. Attempts to use molecular sieves to remove the large quantity of water generated (∼1.8 M) were unsuccessful (see Supporting Information). The application of these conditions generally gave good results. However, the swallowtail aldehyde 7-formyltridecane[27] reacted sluggishly and required 36 h for completion. Mesitaldehyde reacted smoothly upon use of TFA instead of $InCl_3$.

TABLE 3. Synthesis of Dipyrromethanes[a]

Product	Meso-substituent	% Yield
1a		66
1b		48
1c[b]		66
1d		58
1e		38
1f[c]		53
1g[c,d]		63

[a] The condensations were carried out using a molar ratio of 2-(*n*-decylthio)pyrrole/aldehyde/$InCl_3$ of 2.2:1.0:0.2 for 16 h at room temperature in the absence of any solvent. $InCl_3$ was removed by precipitation with hexanes. The crude product was hydrodesulfurized with Raney nickel at room temperature. The solid dipyrromethane product was isolated by precipitation. [b] TFA (0.23 mol equiv) was employed in place of $InCl_3$; the condensation was carried out for 1.75 h, and the condensation reaction mixture was worked up by aqueous−organic extraction. [c] Column chromatography afforded the product as an oil. [d] The condensation was carried out for 36 h.

A simple method for the removal of $InCl_3$ entails precipitation upon addition of powdered NaOH,[5] but traces of base deactivate Raney nickel.[28] To achieve a streamlined procedure for condensation/hydrodesulfurization, the crude dipyrromethane reaction mixture was treated with hexanes, causing precipitation of $InCl_3$ while keeping the 1,9-bis(*n*-decylthio)dipyrromethane in solution. The sole exception occurred in the synthesis of dipyrromethane **1c** where TFA catalysis was employed, whereupon the reaction mixture was neutralized by 0.1 N aqueous NaOH.

The resulting crude residue directly underwent hydrodesulfurization with Raney-nickel slurry in THF at room temperature for 1−2 h. The standard workup included removal of Raney nickel by filtration followed by silica pad filtration or flash column chromatography. The yield of each dipyrromethane ranged from 38 to 66% (Table 3).

4. Additional Transformations. A. Oxidation Processes. Dipyrromethanes typically undergo oxidation to give the cor-

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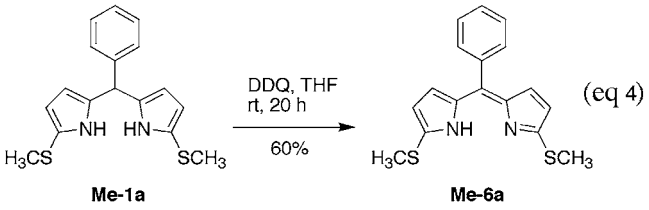
responding dipyrrin, which can be a useful transformation in the preparation of porphyrin precursors. The 1,9-bis(RS)-dipyrromethanes differ from more simple dipyrromethanes because they have two sites of reactivity toward oxidants, the dipyrromethane motif and the two thioethers. Treatment of the protected dipyrromethane **Me-1a** with DDQ gave the corresponding dipyrrin **Me-6a** in 60% yield (eq 4). Treatment of



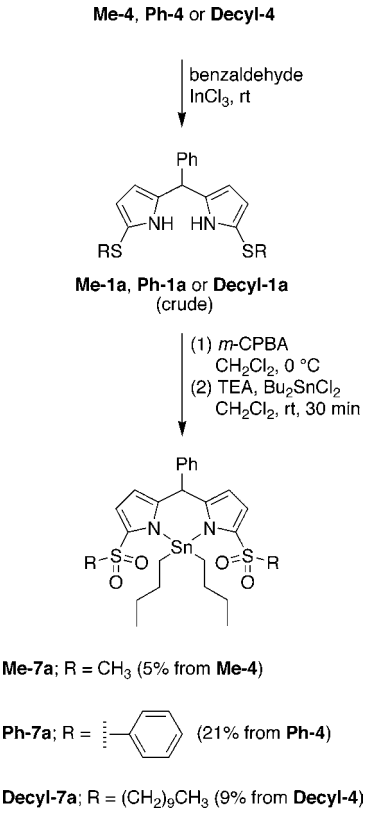
Me-1a **Me-6a** (eq 4)

dipyrrin **Me-6a** with zinc acetate did not afford the corresponding bis(dipyrrinato)zinc complex, unlike dipyrromethanes lacking 1,9-substituents.[29]

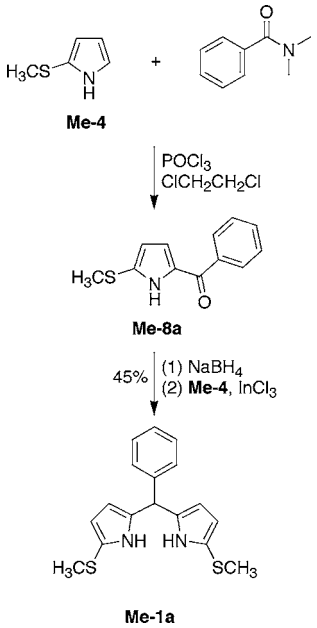
Oxidation of the alkylthio group provides an alternative to the use of Raney nickel for carbon−sulfur cleavage. Indeed, a 2-(methylthio)pyrrole was converted to the corresponding sulfone using *m*-CPBA,[6,30] and reductive desulfonation of pyrrolic compounds has been achieved with Bu_3SnH (photochemically)[30] or with Na(Hg) and Na_2HPO_4 in EtOH.[31] We found that 2-(*n*-decylthio)pyrrole (**Decyl-4**) was converted with *m*-CPBA to the corresponding 2-(*n*-decylsulfonyl)pyrrole in 69% yield. Thus, each crude dipyrromethane reaction mixture, prepared by the condensation of benzaldehyde and **Me-4**, **Ph-4**, or **Decyl-4** via the solventless approach, was subjected to oxidation with *m*-CPBA. In two cases examined in detail (reaction of **Ph-4** or **Decyl-4**), the corresponding bis(sulfone) was isolated in ∼75% crude yield and at least 70% purity but proved difficult to purify to homogeneity. To facilitate isolation of the intermediate sulfone prior to desulfonation, we explored the use of tin complexation,[32] which afforded excellent results with the structurally similar 1,9-diacyldipyrromethanes. Tin complexation was carried out with Bu_2SnCl_2 in the presence of TEA (Scheme 5). After filtration through a silica pad, **Me-7a** or **Decyl-7a** was isolated as a viscous oil in 5 or 9% yield, respectively. **Ph-7a** was obtained as platelike crystals in 21% yield upon recrystallization. The low overall yields likely stem from inefficient tin complexation. The X-ray crystal structure of tin complex **Ph-7a** shows one O atom of each sulfonyl group coordinated with the Sn atom, resulting in slight elongation of the S═O bond (see Supporting Information). The superior yield of Raney-nickel hydrodesulfurization made this the method of choice for deprotection.

B. Stepwise Synthesis of Dipyrromethanes. The presence of the 2-RS substituent opens the possibility of a stepwise synthesis of dipyrromethanes. Thus, pyrrole **Me-4** was acylated by *N*,*N*-dimethylbenzamide in the presence of phosphorus oxychloride following an established procedure[7] to obtain 5-benzoyl-2-(methylthio)pyrrole (**Me-8a**) (Scheme 6). $NaBH_4$ reduction of **Me-8a** led to the corresponding carbinol derivative. Condensation of the carbinol derivative with a stoichiometric amount of pyrrole **Me-4** in the presence of $InCl_3$ (0.1 equiv) gave **Me-1a** in 45% yield. This route illustrates the potential for exploitation of the 2-alkylthio group in stepwise syntheses of pyrromethane compounds.

SCHEME 5



SCHEME 6



Outlook

The rational synthesis of porphyrins requires the ability to prepare precursors such as dipyrromethanes in a controlled

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manner. For β-substituted pyrroles, the α-carboxy group has proved to be an effective masking agent, enabling introduction of an α′-substituent. For β-unsubstituted pyrroles, which have three sites open for reaction and are less electron rich than typical β-substituted pyrroles, an α-masking agent that is not deactivating is highly desirable. The studies reported herein have established the relative activity of the 3-, 4-, and 5-positions in a 2-(RS)-substituted pyrrole toward deuteration. In general, the 5-position of a 2-(alkylthio)-substituted pyrrole is ∼1.5−4 times more reactive toward deuteration vs that of pyrrole itself. The order of reactivity toward deuteration in a given 2-(RS)pyrrole was 5-position ∼ 3-position > 4-position; however, upon acid-catalyzed reaction with an aldehyde, the dominant product is the desired dipyrromethane. The relative lack of reactivity at the 3-position in this substitution process (vs deuteration) may stem from steric hindrance of the bulky 2-alkylthio group. The 2-(*n*-decylthio) group was chosen for use in a study of dipyrromethane formation. The ability to form dipyrromethanes with the use of a stoichiometric quantity of the pyrrole compound can be contrasted with the existing one-flask synthesis of dipyrromethanes, which typically employs 25−100 mol equiv of pyrrole relative to the aldehyde. Taken together, this work establishes the foundation for the use of the 2-alkylthio group as a protecting group in pyrrole chemistry, including introduction and removal under mild conditions and exploitation for directing electrophilic substitution at the 5-position.

Experimental Section

Effect of α-Pyrrole Substituents: Kinetic Study of Deuteration. A solution of CD_3COOD (600 μL, 10.5 mmol) was added to an α-substituted pyrrole (52 μmol) in an NMR tube at 20 °C. Kinetic measurements were made by ^{1}H NMR spectroscopy to at least 90% exchange for the protons undergoing fast exchange and to at least 60% exchange for those undergoing slow exchange (see Supporting Information).

Acid Screening Experiment. All experiments were carried out in the absence of a solvent. Each experiment employed benzaldehyde (42.6 mg, 401 μmol), **Me-4** (91.0 mg, 804 μmol), and an acid (40 μmol, 0.1 equiv relative to benzaldehyde) [TFA (3.1 μL), $InCl_3$ (8.9 mg), $MgBr_2$ (7.4 mg), $Yb(OTf)_3$ (25 mg) or $Sc(OTf)_3$ (20 mg)]. The reaction was monitored by thin-layer chromatography (TLC) analysis and stopped after the consumption of benzaldehyde was complete. In each case, the reaction was quenched by adding 0.1 N aqueous NaOH and ethyl acetate after 1 h (with the exception of the reaction using $MgBr_2$, which took 16 h). After drying and concentrating to dryness, each crude mixture was analyzed by ^{1}H NMR spectroscopy and GC. ^{1}H NMR spectra showed compound **Me-1a** as the main component and small peaks of the unreacted 2-(methylthio)pyrrole. A peak due to an N-confused byproduct could not be clearly observed. Therefore, GC analysis was employed to compare the yield and the cleanliness of the reaction, as described in Table 1. The solution for the GC analysis was prepared by diluting 5.0 mg of the crude mixture in 0.45 mL of THF.

1,9-Bis(methylthio)-5-phenyldipyrromethane (Me-1a). Several conditions were investigated. The title compound was obtained both under solution and under solventless conditions. The preferred solventless condition was employed for the acid screening study.

Solution Synthesis. A mixture of benzaldehyde (42.6 mg, 401 μmol, 0.25 M) and **Me-4** (100 mg, 884 μmol, 2.2 equiv) in CH_2Cl_2 (1.6 mL) was degassed for 5 min at room temperature. TFA (12.0 μL, 156 μmol, 0.1 M) was added. The reaction was stopped after 30 min, when the consumption of benzaldehyde was complete (by TLC and ^{1}H NMR spectroscopy). The violet reaction mixture was treated with a mixture of 0.1 N aqueous NaOH and ethyl acetate (10 mL, 1:1). The resulting orange mixture was extracted with CH_2Cl_2. The organic phase was collected, dried (Na_2SO_4), and concentrated. The crude mixture was passed through a silica column (hexanes/ethyl acetate (8:1), 2.5 cm diameter × 18 cm in height). Four fractions were obtained. The first fraction (yellow, $R_f = 0.50$) contained unknown pyrrole derivatives (by ^{1}H NMR analysis). The second fraction (colorless) consisted of unreacted **Me-4** ($R_f = 0.45$). The third fraction ($R_f = 0.21$) contained the product (**Me-1a**) in the form of a viscous yellow oil (71 mg, 56%), which solidified after 24 h at −15 °C. The last fraction had the same color and retention ($R_f = 0.21$) as that of the product, but ^{1}H NMR, GC, and GC-MS analyses indicated the presence of a mixture containing an N-confused dipyrromethane. Characterization data for **Me-1a**: mp 90−91 °C; ^{1}H NMR (THF-d_8) δ 2.22 (s, 6H), 5.32 (s, 1H), 5.55−5.58 (m, 2H), 6.06−6.08 (m, 2H), 7.13−7.26 (m, 5H), 10.14 (br s, 2H); ^{13}C NMR (THF-d_8) δ 21.8, 45.5, 109.4, 115.1, 121.6, 127.2, 128.9, 129.4, 136.8, 143.7; FAB−MS obsd 314.0918, calcd 314.0911 ($C_{17}H_{18}N_2S_2$).

Solventless Synthesis. A mixture of benzaldehyde (85.2 mg, 0.802 mmol) and **Me-4** (182 mg, 1.61 mmol, 2.0 equiv) was treated with TFA (6.2 μL, 80 μmol, 0.1 equiv) at room temperature. After 15 min, the reaction mixture became viscous and the stirring was very slow. Benzaldehyde was completely consumed within 1 h (by TLC). Workup and purification as described above gave **Me-1a** (0.12 g, 47%) with characterization data consistent with those described above.

Stepwise Synthesis. A solution of pyrrole **Me-8a** (30.0 mg, 0.138 mmol) in THF/MeOH (3.0 mL, 10:1) was treated with $NaBH_4$ (15.7 mg, 0.415 mmol) at room temperature for 20 min. The reaction mixture was poured in a mixture of saturated aqueous NH_4Cl (10 mL) and CH_2Cl_2 (10 mL). The organic phase was separated, washed with water, dried (Na_2SO_4), and concentrated to dryness. A mixture of the resulting residue and pyrrole **Me-4** (15.6 mg, 0.138 mmol) was dissolved in toluene (1.3 mL) and treated with $InCl_3$ (30.5 mg, 0.139 mmol) at room temperature. After 30 min, the reaction mixture was washed with 1 M aqueous NaOH. The organic layer was dried (Na_2SO_4), concentrated, and chromatographed [silica, hexanes/ethyl acetate (8:1)], affording a yellow oil (20 mg, 45%) that solidified after 24 h at −15 °C. Characterization data were consistent with those described above.

General Procedure for Dipyrromethane Synthesis Using an *n*-Decylthio α-Pyrrole Protecting group, Exemplified for 5-Phenyldipyrromethane (1a). A mixture of benzaldehyde (0.796 g, 7.50 mmol) and **Decyl-4** (3.95 g, 16.5 mmol) in the absence of any solvent was treated with $InCl_3$ (0.332 g, 1.50 mmol) in a loosely closed reaction vessel without deaeration. The heterogeneous mixture was stirred magnetically at room temperature for 16 h. The resulting violet mixture was treated with hexanes (5 mL), affording a brownish mixture. The mixture was filtered through a sintered glass funnel. The filtered material was washed with a small amount of hexanes. The filtrate was concentrated to dryness, affording a brown residue. The flask containing the crude brown residue was placed on a balance. A solid portion of 30.0 g of wet Raney nickel was removed from a Raney-nickel−THF slurry by a spatula and added directly to the flask containing the brown residue. Reagent grade THF (5.0 mL) was added to wash the inner walls of the flask. The mixture was stirred at room temperature for 1 h. The mixture was filtered through a sintered glass funnel to remove the Raney nickel. The filtered material was washed with THF (∼150 mL). The filtrate was concentrated to dryness. The resulting crude residue was dissolved in a small quantity of hexanes/toluene (1:2) and placed on top of a silica pad (3 cm diameter × 2 cm in height). The silica pad was eluted with hexanes/toluene [(1:2), ∼200 mL]. The first fraction contained 2-benzyl-5-(methylthio)pyrrole, 2-(methylthio)pyrrole, and unknown pyrrolic byproducts as determined by GC analysis (and subsequent GC-MS analysis and ^{1}H NMR spectroscopy). The second fraction contained predominantly the title compound accompanied by a trace amount of the byproducts. The second fraction was concentrated to dryness. The resulting yellowish solid was treated with hexanes (∼20 mL), and the slurry

was heated until the solvent refluxed. After a few minutes, the slurry was filtered. The filtrate, which contained less polar byproducts and only a small quantity of product, was discarded. The filtered material (white) was washed with a small amount of hexanes and then collected, affording a white solid (1.10 g, 66%): mp 98−99 °C (lit.[21] 100.2−101.1 °C); ^{1}H NMR δ 5.49 (s, 1H), 5.92−5.98 (m, 2H), 6.15−6.22 (m, 2H), 6.65−6.75 (m, 2H), 7.22−7.36 (m, 5H), 7.94 (br s, 2H); ^{13}C NMR δ 43.9, 107.2, 108.4, 117.2, 127.0, 128.4, 128.6, 132.5, 142.0. Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.05; H, 6.44; N, 12.33.

1,9-Bis(methylthio)-5-phenyldipyrrin (Me-6a). Following a standard procedure,[29] a solution of **Me-1a** (20.0 mg, 63.6 μmol) in THF (0.64 mL) was treated with DDQ (17.3 mg, 73.2 μmol) at room temperature for 24 h. The mixture was concentrated and chromatographed (hexanes/ethyl acetate (5:1) containing 1% TEA), affording a yellow viscous solid (12 mg, 60%): ^{1}H NMR (THF-d_8) δ 2.64 (s, 6H), 6.32 (d, J = 4.4 Hz, 2H), 6.45 (d, J = 4.4 Hz, 2H), 7.43 (s, 5H); ^{13}C NMR (THF-d_8) δ 16.0, 30.7, 119.0, 128.6, 128.9, 129.4, 131.7, 134.2, 138.0, 142.2, 151.8; FAB−MS obsd 313.0836, calcd 313.0833 [$(M + H)^+$, M = $C_{17}H_{16}N_2S_2$]; λ_{abs} 336, 474 nm.

Dibutyl[5,10-dihydro-1,9-bis(methylsulfonyl)-5-phenyldipyrrinato]tin(IV) (Me-7a). Following the solventless synthesis of **Me-1a** described above, a mixture of benzaldehyde (85.2 mg, 0.802 mmol) and **Me-4** (182 mg, 1.61 mmol) was treated with $InCl_3$ (17.8 mg, 80.0 μmol) at room temperature. After 1 h, TLC showed the reaction to be complete. The reaction mixture was diluted with ethyl acetate and washed with 0.1 M aqueous NaOH. The organic phase was separated, washed with water, dried (Na_2SO_4), and concentrated to dryness. Following a published procedure,[30] the residue was dissolved in CH_2Cl_2 (15 mL) and cooled to 0 °C in an ice bath. The solution was treated with *m*-CPBA (428 mg, 77% purity from commercial supplier, 1.91 mmol), and the mixture was stirred at 0 °C for 4 h. After warming to room temperature, the reaction mixture was washed with saturated aqueous $NaHCO_3$. The organic phase was separated, washed with water, dried (Na_2SO_4), and concentrated. Following a standard method,[32] the crude mixture was redissolved in CH_2Cl_2 (3 mL). TEA (0.265 mL, 1.91 mmol) was added. The reaction mixture was treated with Bu_2SnCl_2 (193 mg, 0.635 mmol) for 30 min and then filtered through a silica pad (CH_2Cl_2), affording a pale yellow viscous oil (25 mg, 5%): ^{1}H NMR (THF-d_8) δ 0.70−0.77 (m, 6H), 0.86−1.21 (m, 4H), 1.28−1.42 (m, 4H), 1.58−1.67 (m, 4H), 3.14 (s, 6H), 5.54 (s, 1H), 6.22 (d, J = 3.2 Hz, 2H), 6.89 (d, J = 3.2 Hz, 2H), 6.98−7.01 (m, 2H), 7.09−7.20 (m, 3H); ^{13}C NMR (THF-d_8) δ 13.84, 13.94, 26.6, 27.11, 27.14, 27.4, 28.0, 29.4, 45.9, 114.1, 116.4, 127.1, 128.6, 129.0, 132.6, 144.8, 145.9; FAB−MS obsd 611.1087, calcd 611.1060 [$(M + H)^+$, M = $C_{25}H_{34}N_2O_4S_2Sn$].

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Supporting Information Available: Complete Experimental Section, including procedures for kinetic experiments and extensive kinetic data; procedures for the synthesis of all new compounds; and ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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