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Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

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Abstract

Sulfenyl dipyrroles feature two pyrroles linked via a sulfenyl bridge. The synthesis of sulfenyl dipyrroles has typically involved SCl_2 as the sulfur source. However, SCl_2 is no longer readily available within North America and Europe. Herein we report a new synthesis of sulfenyl dipyrroles using SOCl_2 as the sulfur source and reductant. Although five new sulfenyl dipyrroles were synthesized and isolated via this route, functional group tolerance proved limited. A potential mechanism for the reaction, involving reduction of a sulfinyl moiety by SOCl_2 , is briefly explored.

Keywords

sulfur, pyrrole, organic synthesis, in-situ reduction of sulfinyl dipyrroles

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

Introduction

The sulfenyl dipyrrolic motif, featuring two pyrroles linked via a sulfenyl bridge (**1**, V = S, Figure 1), has been known since the 1930s.¹ The most common application of this motif involves its incorporation into thiacorroles and thiaporphyrinoids,² for use as electron-deficient ligands in metal complexation (Figure 1).³ To the best of our knowledge there are only a few reported examples of isolated sulfur-bridged dipyrroles (Figure 1, **1**);^{3a, 4} one example of a tripyrrole with two bridging sulfur atoms (**2**); and a few examples of acyclic (**3** and **4**)⁵ and cyclic (**5** and **6**)^{2a, 6} sulfur-bridged tetrapyrroles. Cyclic tetrapyrroles with three or four bridging sulfur atoms are unknown.

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

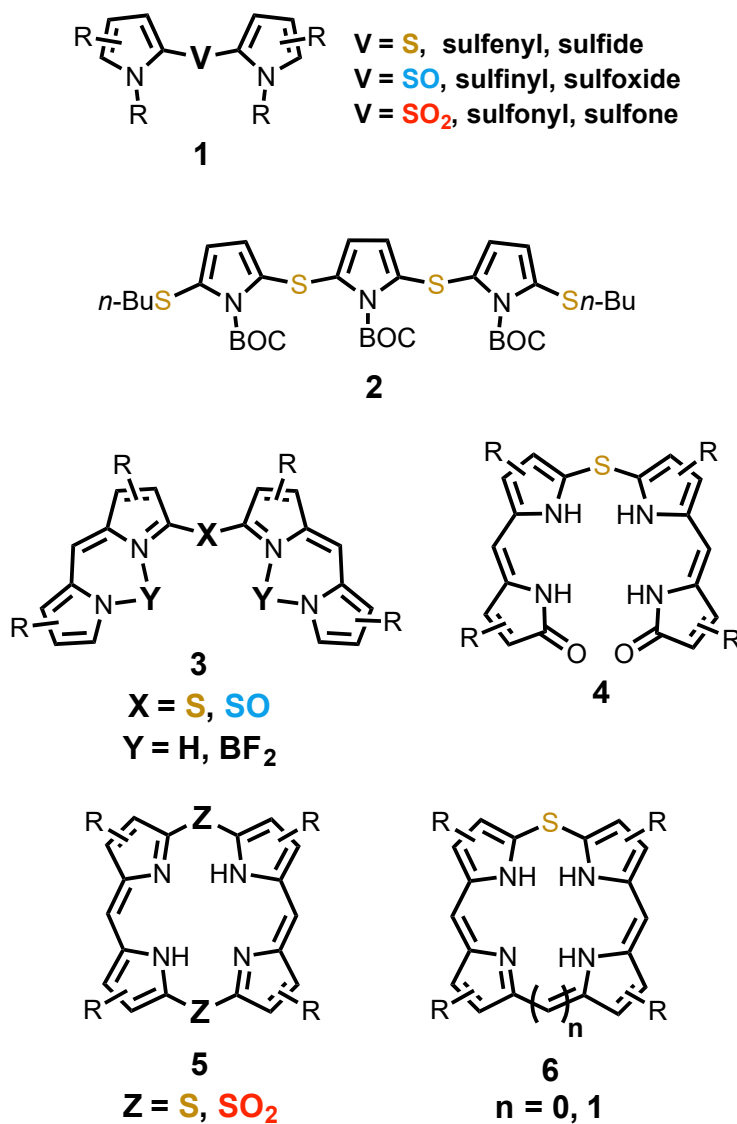


Figure 1: Examples of Known Sulfur-bridged Pyrroles

The synthesis of sulfenyl dipyrroles has remained largely unchanged since their discovery, typically involving the reaction of an α -free pyrrole with sulfur dichloride (SCl_2 , Figure 2, top).^{1, 2b, 4c, 7} Pyrroles and sulfenyl groups both tend to be electron-rich nucleophilic species, the combination of which would be expected to yield a very electron-rich and nucleophilic product. As such, pyrroles bearing electron-withdrawing groups are typically used to attenuate the electron-rich nature of these compounds, enabling controlled reactivity and

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

stabilizing the final product. A variation from the use of SCl_2 , and the first example of a 3,4,5-unsubstituted pyrrole being used for the preparation of a sulfenyl dipyrrole, was presented in 1987^{4c} and expanded upon in 1997.^{4a} This route involves reacting *N*-protected α -bromopyrroles with *n*-BuLi to generate a lithium salt that subsequently reacts with a bis(arylsulfonyl) sulfide to produce the requisite sulfenyl dipyrroles (Figure 2, top). Although this work presents an alternative to using SCl_2 , the requirement for strong base precludes tolerance of pyrroles that contain base-sensitive substituents. Further, if the synthetic goal is an N–H pyrrole, the presence of an *N*-protecting group mandates the eventual deprotection of the pyrrolic nitrogen atoms, which, whether facile⁸ or more challenging,^{4a} represents an additional step for consideration as regards to synthetic efficiency.

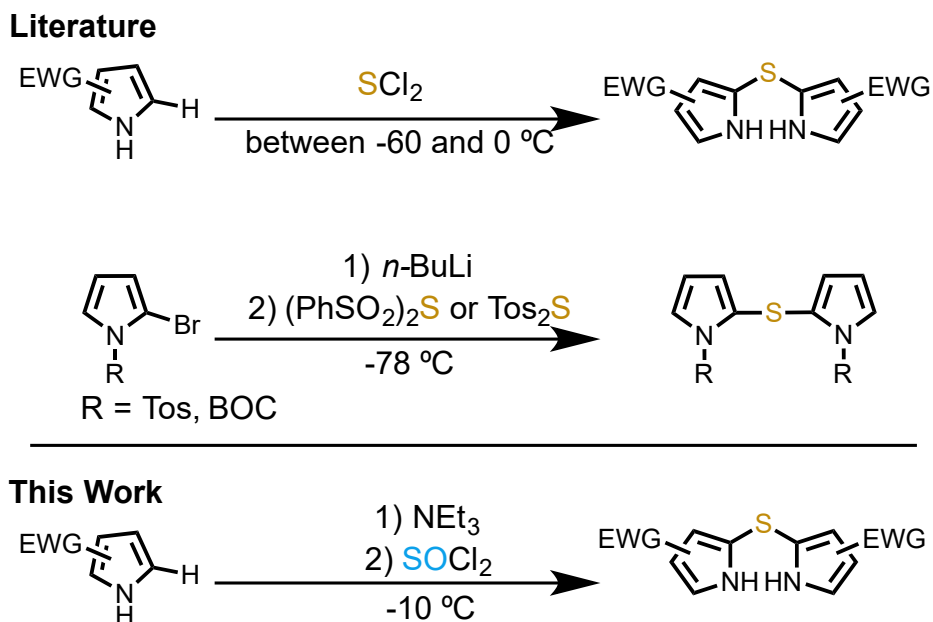


Figure 2: Previously Reported Syntheses of Sulfur-bridged Dipyrroles (Top); Synthesis of Sulfenyl Dipyrroles Using SOCl_2 (Bottom)

Although the simplicity of the synthetic approach to sulfenyl dipyrroles involving sulfur dichloride is appealing, this reagent is inaccessible to many researchers as it is not readily

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

available in North America and Europe. Producing sulfur dichloride on a modest research scale is quite challenging, as it requires chlorination of sulfur chloride, S_2Cl_2 , with Cl_2 gas.⁹ As such, we evaluated the utility of $SOCl_2$ for the purpose of linking two pyrroles via a sulfur-based bridge (Figure 2, bottom), cognizant that we could expect to amend the oxidation state at sulfur, post-reaction. Literature precedent^{4a} supports the notion that once a sulfur-bridged dipyrrole is in hand, there is the potential to access higher or lower oxidation state analogues. For example, aryl sulfides can be selectively oxidized to sulfoxides or sulfones using *m*-CPBA.^{4a} In addition, sulfones and sulfoxides can be reduced to sulfides, non-selectively, via deoxygenative atom transfer to a phosphine.¹⁰

Results and Discussion

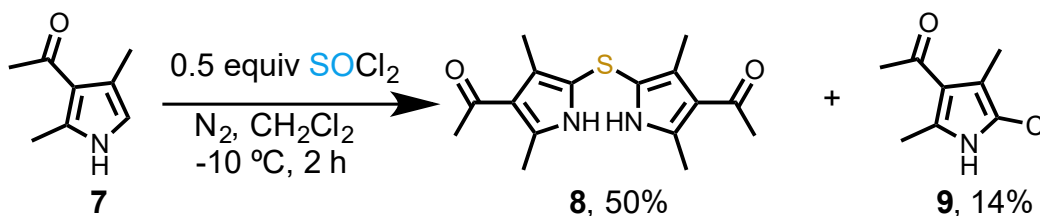
Treatment of *N*-protected α -lithiopyrroles (*n*-BuLi^{4a} or LTMP⁸) with $SOCl_2$ produces the requisite sulfinyl dipyrroles. Moreover, literature reports¹¹ indicate that $SOCl_2$, in the presence of a Lewis acid catalyst (e.g. $FeCl_3$ or $AlCl_3$), reacts with arenes such as benzene or thiophene to produce sulfinyl bridged diarenes. As $SOCl_2$ is more commonly used as a chlorinating agent, and is known to generate potent chlorinating agents such as Cl_2 and SO_2Cl_2 *in situ*,¹² a degree of chlorination was expected despite our goal of using this reagent as an electrophilic source of sulfur.^{4a, 11b, 12b, 13} Nevertheless, given the increased nucleophilicity of pyrrole cf. benzene and thiophene, we hypothesized that pyrroles could be reacted with $SOCl_2$ under catalyst-free conditions to produce sulfinyl-bridged dipyrroles without the requirement for prior α -lithiation. As the literature regarding such synthetic work is so limited, this project was heavily dependent on an investigation of fundamental reactivity.

The N-H pyrrole **7** (Scheme 1), easily prepared¹⁴ and bearing an acyl group in the β -position, was an accessible starting point from which to explore the reactivity of pyrroles and

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

SOCl_2 . The stabilizing effects imparted by the electron-withdrawing acyl group were anticipated to attenuate the nucleophilicity of the pyrrolic unit.^{4c, 7} In this way, enhanced stability under the acidic conditions could be expected, a particularly important consideration given the propensity of pyrroles to undergo polymerization under such conditions.¹⁵

Pyrrole **7** was reacted with 0.5 equiv SOCl_2 until complete consumption of the starting material was observed via TLC, i.e. 2 h (Scheme 1). To our surprise, the sulfenyl dipyrrole **8** was isolated as the major product alongside the chlorinated pyrrole **9**, both of which were bench-stable: the expected sulfoxide was not isolated, and not observed as a synthetic intermediate.



Scheme 1: Synthesis of Sulfenyl Dipyrrole **8** using SOCl_2

The structure of **8** was elucidated using both HRMS and NMR spectroscopy, with X-ray crystallographic analysis unequivocally confirming the sulfenyl bridge. The HRMS spectrum reported an accurate mass corresponding to two units of pyrrole **7** linked via a sulfenyl (-S-) bridge, indicating **8** was a sulfenyl, rather than sulfinyl (-S(O)-), dipyrrole. The ^1H NMR spectrum, collected in $\text{DMSO-}d_6$, contained the four signals of chemical shift and integration expected for the structure of **8**: three singlets with chemical shifts that ranged from 2.4-2.3 ppm, corresponding to the three distinct methyl groups of **8**, and a broad singlet at ~ 11 ppm, a shift typical of pyrrolic N-H protons in DMSO. Crystals of **8** were grown, via the slow evaporation of a solution of **8** in methanol, and then analyzed via single crystal X-ray diffraction to unequivocally confirm the presence of the sulfenyl bridge (Figure 3). The crystal structure of **8**

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

demonstrated a trans relationship, with respect to the pyrrolic units, across the sulfide-linkage.

The generation of a sulfenyl bridge in **8** indicated one of two things: either reduction of the sulfur atom originating with SOCl_2 occurred during or subsequent to the reaction with this sulfenyl source, or that a significant impurity in the SOCl_2 provided a sulfenyl source.

Given the surprising sulfenyl oxidation state of **8**, we attempted to rule out the presence of sulfur dichloride (SCl_2) and/or sulfur monochloride (S_2Cl_2) in the SOCl_2 used in our reactions,^{12a} both of which could result in the observed sulfenyl bridge. Thus, SOCl_2 was purified following literature procedure¹⁶ (twice fractionally distilled in the presence of triphenyl phosphite, vented through CaCl_2), and used the same day. Following treatment of pyrrole **7** with the purified SOCl_2 , **8** was again isolated as the major product and in a similar yield (Scheme 1), supporting the notion that sulfur-based impurities within the SOCl_2 reactant were not an appreciable source of **8**. In addition, treatment of **7** with thionyl bromide (SOBr_2) furnished sulfide **8**, albeit in reduced yield compared to the use of SOCl_2 . Reaction of **7** with SO_2Cl_2 returned only the chlorinated pyrrole.

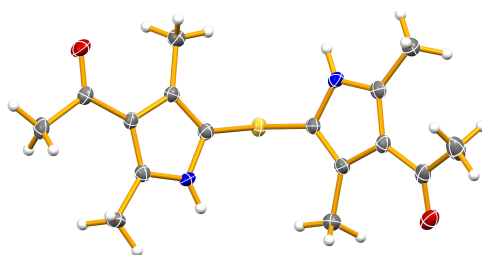
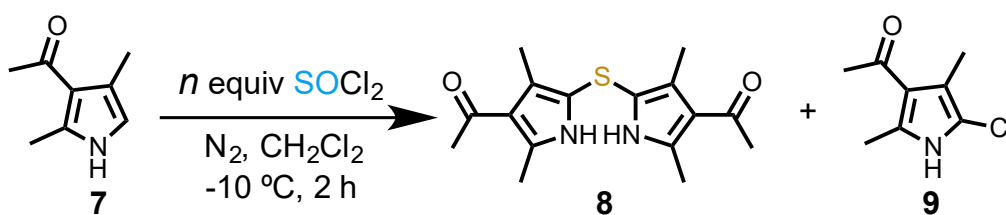


Figure 3: Crystal Structure of Sulfenyl Dipyrrole 8 (S = yellow, N = blue, O = red, C = grey, H = white); Thermal ellipsoids drawn at the 50% probability level.

In the absence of an obvious reducing agent we suspected that SOCl_2 had acted as a sacrificial reductant, as well as the source of the sulfenyl bridge, during the synthesis of **8**. Under

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

this assumption, a 1:1 ratio of **7**:SOCl₂ would be insufficient to furnish sulfide **8** in >50% yield (Scheme 1). Using an optimal reaction temperature of -10 °C (see Table S3, Supporting Information), we explored the effect of varying the stoichiometry of SOCl₂ upon the yield of **8** and **9** according to Scheme 2. The use of 0.8 equiv SOCl₂ furnished a modest improvement, with **8** being reproducibly isolated in 60% yield (Table 1, entry 2). However, the use of >0.9 equiv SOCl₂ was ineffective in promoting a further increase in the yield of **8** (entries 3-8).



Scheme 2: Exploring the Effects of Stoichiometry on the Synthesis of **8**

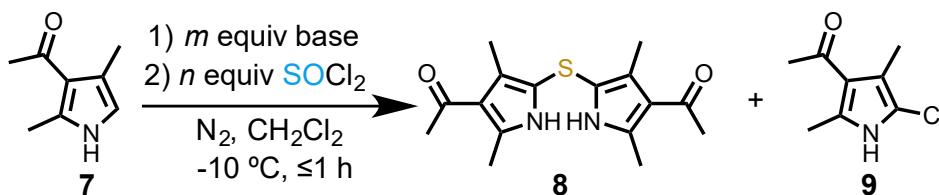
Table 1: Effects of Stoichiometry on the Synthesis of **8**

Entry	Equiv of SOCl ₂ (n)	Yield ^a of 8 (%)	Yield ^a of 9 (%)
1	0.5	50	14
2	0.8	60	16
3	0.9	50	20
4	1.0	48	23
5	1.1	43	14
6	3	48	13
7	5	50	13
8	7	37	14

^a Isolated yield.

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

The inherent reactivity of pyrroles renders them susceptible to polymerization under weakly acidic conditions,¹⁵ such as are produced in the presence of SOCl_2 .¹⁷ Pyrrole **7** and **9** could both be subject to this polymerization. To investigate the effects of the addition of mild organic nitrogenous bases to the reaction mixture (Scheme 3), 1.1 equiv NEt_3 was added to a solution of pyrrole **7** in CH_2Cl_2 , followed by the addition of 0.8 equiv SOCl_2 (Table 2, entry 1). This resulted in a drastically increased reaction rate such that consumption of starting material was observed after 25 min, cf. 2 hours in the absence of base, and the reaction furnished **8** with an increased and reproducible yield of 70%. Stirring this reaction mixture for 2 h did not result in an increased yield (entry 2). The use of 1.1 equiv SOCl_2 in the presence of NEt_3 resulted in a significant decrease in the yield of **8** (entry 3), and additional NEt_3 resulted in similarly decreased yield of **8** (entries 4 and 5). The order of the addition of the reagents proved vital, with NEt_3 added first to produce the optimal yield of **8** (compare entries 1 and 6). We explored the use of other nitrogenous bases (entries 7 – 12), but did not see increased yields of **8**. After a brief exploration of concentration, 0.01 M **7** in CH_2Cl_2 was deemed optimal.



Scheme 3: Exploring the Effects of Organic Bases on the Yield of **8**

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

Table 2: Effects of Organic Bases on the Yield of 8

Entry	Base	Equiv Base (<i>m</i>)	Equiv SOCl ₂ (<i>n</i>)	Yield ^a of 8 (%)	Yield ^a of 9 (%)
1	NEt ₃	1.1	0.8	70 ^b	14
2	NEt ₃	1.1	0.8	71 ^{b,c}	15
3	NEt ₃	1.1	1.1	28 ^b	18
4	NEt ₃	2	0.8	30 ^b	22
5	NEt ₃	5	0.8	23 ^b	3
6	NEt ₃	1.1	0.8	44 ^{b,d}	23
7	DIPEA	1.1	0.8	20	10
8	HNEt ₂	1.1	0.8	45	19
9	Aniline	1.1	0.8	50	20
10	Pyridine	1.1	0.8	68	27
11	DMAP	1.1	0.8	55	22
12	2,6-Di-tert-butyl-4-methylpyridine	1.1	0.8	48	27

^aIsolated yield; ^bstarting material consumed completely within 25 min, monitoring by TLC; ^c2 h reaction length; ^dSOCl₂ added first, NEt₃ added second.

Reacting SOCl₂ with pyrroles **10-14** in the presence of NEt₃, and altering the duration of the reaction in line with observed consumption of the starting material, gave a handful of new *N*-H and *N*-protected sulfenyl dipyrroles (**15-19**) in 7-64% yields (Figure 4). However, the use of a α -free pyrroles **20-24**, or the chlorinated pyrrole **9**, resulted in either polymerization or no reaction. A curious observation was the difference in reaction length (as determined by complete

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

consumption of the starting material according to TLC) required to furnish comparable yields of sulfides **15** and **16**. The reaction of pyrrole **10**,¹⁸ substituted with a benzyl ester in the 2-position, with 0.8 equiv SOCl₂ required heating at reflux temperature in CH₂Cl₂ for 20 h to furnish **15** in a 64% yield. However, the reaction of pyrrole **11**,¹⁸ substituted with a benzyl ester in the 3-position, with 0.8 equiv SOCl₂ required heating at reflux temperature in CH₂Cl₂ for only 2 h to furnish **16** in a 52% yield. This trend follows the anticipated reactivity of pyrroles, whereby substitution with an electron-withdrawing group at the α -position is expected to cause a greater decrease in nucleophilicity of the pyrrole when compared to the analogous β -substitution pattern.¹⁹

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

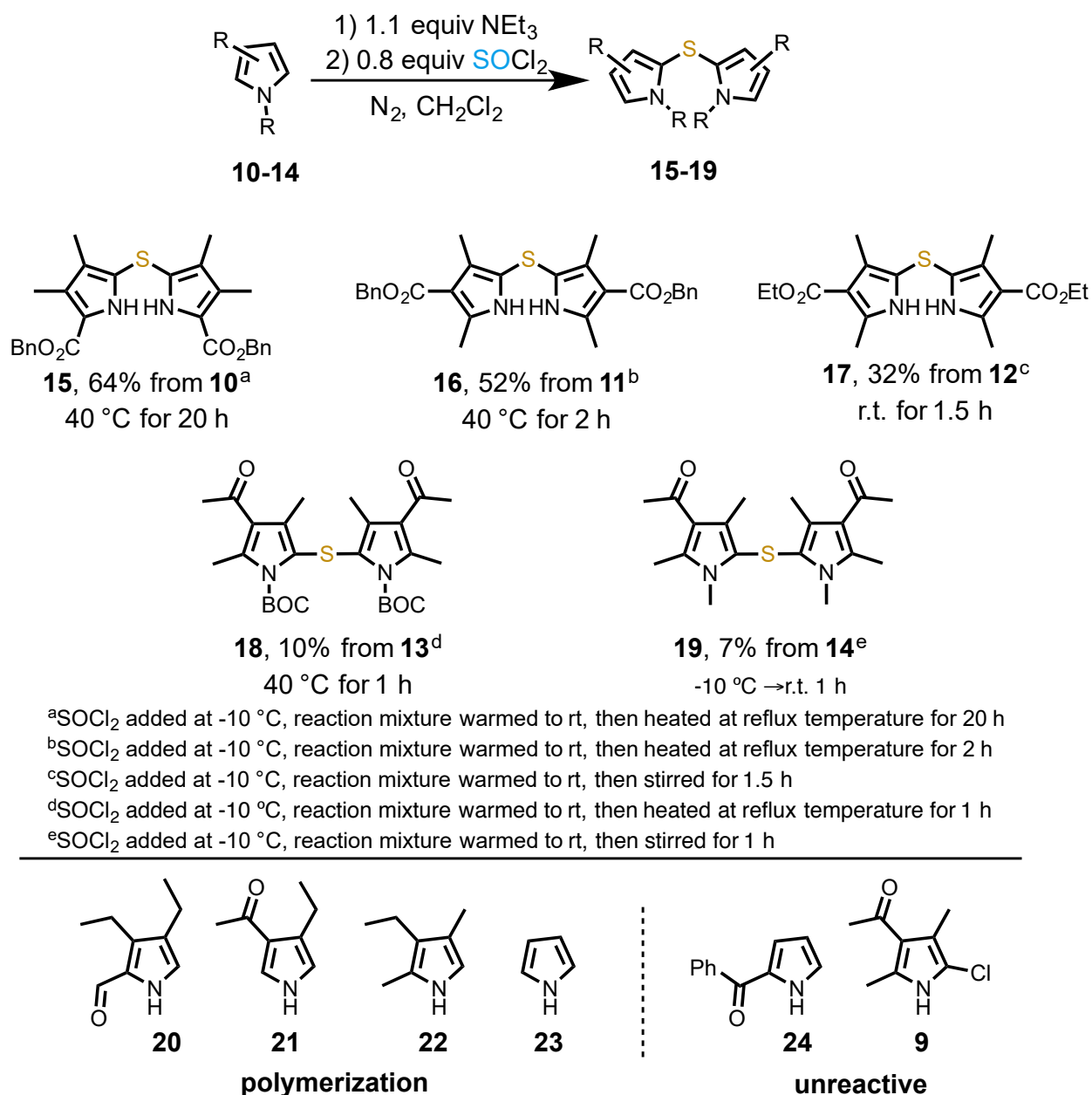


Figure 4: Synthesis of Sulfenyl Dipyrroles 15-19

Arenes typically react with SOCl₂ to produce diaryl sulfoxides (Ar-SO-Ar), but only in the presence of a catalyst.^{11a, 11b, 11d, 11e} However, arenes bearing multiple ethereal, i.e. electron-donating, substituents have been noted^{12b} to react in neat SOCl₂ to produce symmetrical diaryl sulfides (Figure 5, top), akin to our observations using pyrroles. Evidence to support the

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

hypothesis that the sulfenyl bridge may be formed as a result of reduction of a sulfinyl unit by unreacted SOCl_2 included isolation of the sulfenyl bridged product when the corresponding anisole-derived sulfoxide was reacted with neat SOCl_2 (Figure 5, bottom).

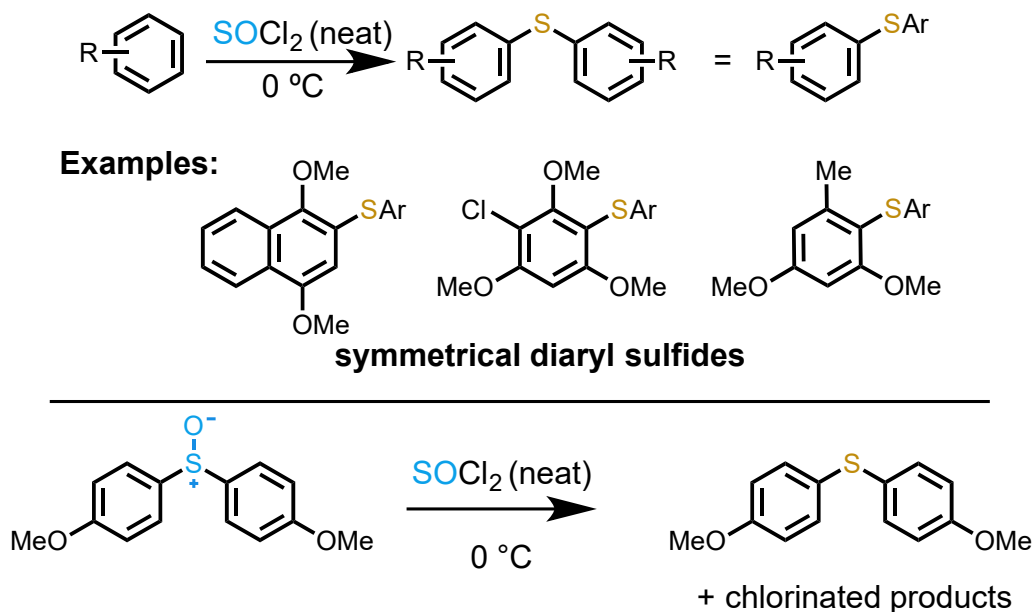
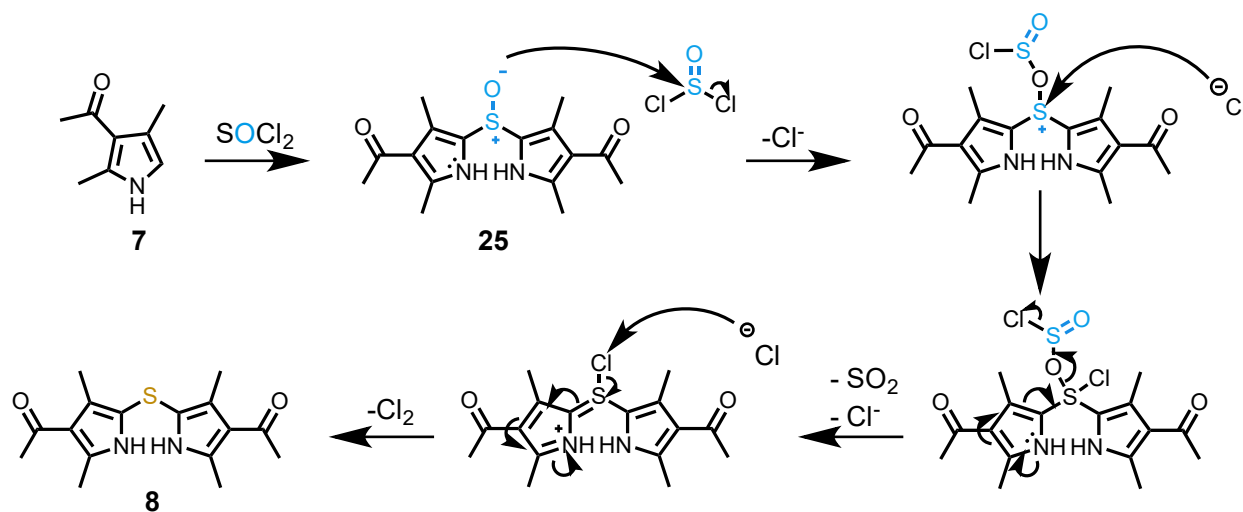


Figure 5: Diaryl Sulfides Formed in Neat SOCl_2 (Top); Treatment of Electron-rich Diaryl Sulfoxide Resulted in Formation of Diaryl Sulfide (Bottom)

With electron-rich arenes^{12b} and pyrroles reacting with SOCl_2 to form diaryl sulfides, yet less electron-rich arenes reacting with SOCl_2 to form diaryl sulfoxides,¹¹ it seems reasonable that sulfoxide **25** is initially formed en route to **8** (Scheme 4). This unobserved sulfoxide must be subject to rapid in-situ reduction, presumably first involving Swern-type reaction with SOCl_2 that is promoted by the electron-rich and conjugated nature of the pyrrole moiety. Subsequent attack by chloride, facilitated by resonance stabilization enabling sulfonium character at sulfur, would result in loss of SO_2 , generation of Cl_2 , and thereby reduction of **25** to produce **8**.

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride



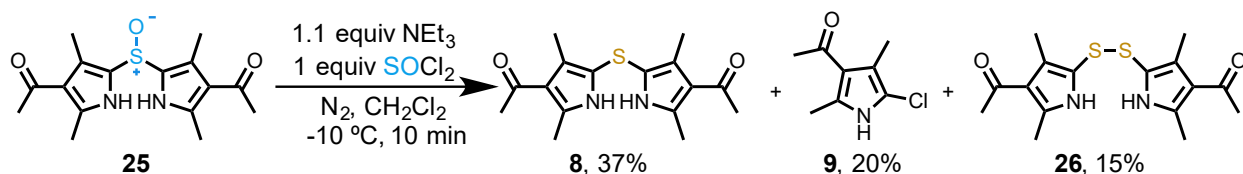
Scheme 4: Proposed Mechanism for the Formation of Sulfide **8 from the Reaction of Pyrrole **7** and SOCl_2**

To support the proposed mechanism involving evolution of SO_2 (Scheme 4), a solution of pyrrole **7** and 1.1 equiv NEt_3 , in CH_2Cl_2 , was treated with 0.8 equiv SOCl_2 at -10°C . A positive flow of N_2 over the reaction mixture was vented through an aqueous solution of KMnO_4 (0.005 M). Decolorization of the KMnO_4 solution was complete after 5 min, indicating reaction of SO_2 with KMnO_4 to produce aqueous MnSO_4 . This occurred considerably faster than when **7** was absent from the reaction flask and thus gaseous SOCl_2 was the only source of oxidant in the vented gas: given that pyrrole **7** and 0.8 equiv SOCl_2 reacted to produce **8** in 73% isolated yield, it would be unlikely that appreciable decolorization could be caused by the vented SOCl_2 .

Furthermore, when sulfoxide **25** (prepared via oxidation of **8** with *m*-CPBA) was treated with 1 equiv SOCl_2 , rapid consumption of **25** was accompanied by production of **8** (Scheme 5), thereby supporting our proposed mechanism (Scheme 4) involving in-situ reduction of the sulfoxide. Interestingly, the reaction of 1-[2,4-dimethyl-5-(4-methylphenyl)sulfinyl-1*H*-pyrrol-3-yl]ethanone, i.e. tolyl-S(O)-pyrrole, with SOCl_2 also resulted in formation of the corresponding

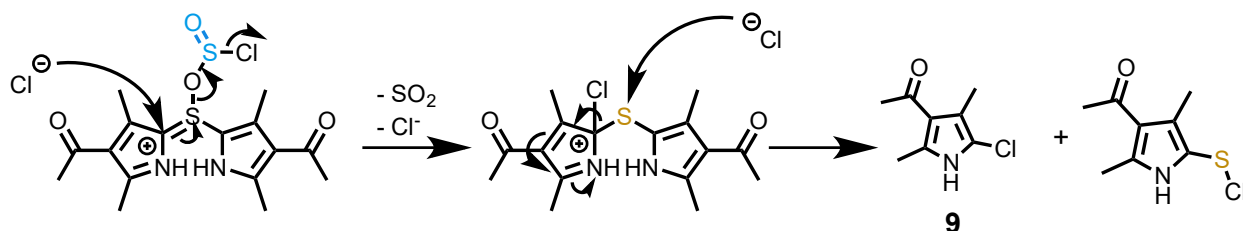
Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

sulfide, in contrast to the stability of ditolyl sulfoxide under these conditions.^{11a-c, 11e} Clearly, the conjugated electron-rich nature of the substituent(s) about sulfur is key to invoking the observed reduction of diaryl sulfoxides by SOCl_2 .



Scheme 5: Reduction of Sulfoxide **27** in the Presence of SOCl_2

The chlorinated pyrrole **9** and the disulfide **26** were also isolated from the reaction of **25** with SOCl_2 , suggesting cleavage of a C-S bond of **25** or a later intermediate. In further support of this suggestion, addition of pyrrole **14** to the reaction of **25** with SOCl_2 resulted in formation of the corresponding mixed, unsymmetrical diaryl sulfide. In keeping with our proposed mechanism, and subsequent to reaction of sulfoxide **25** with SOCl_2 , attack of the first intermediate by chloride at the α -position (rather than at sulfur as per the productive mechanism represented in Scheme 4) would enable formation of the 2-chloropyrrole **9**, as well as the corresponding sulfenyl chloride en route to **8**, **26** and the unsymmetrical diaryl sulfide formed in the presence of **14**.



Scheme 6: Proposed Formation of Sulfenyl Chloride

Through the course of this work, crystal structures were obtained for the two sulfenyl dipyrroles **8** and **15**, and the sulfinyl and sulfoxyl dipyrroles **25** and **27**, respectively. All of these

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

compounds contain N-H groups that form traditional N-H...O hydrogen bonds to oxygen acceptors in different molecules. A table of the hydrogen bonds has been included in the SI (Table S3) as have hydrogen bonding diagrams for each of the individual structures. Perhaps most interestingly, the unit cell, space group, packing and hydrogen bonding pattern in compounds **8** and **27** are all identical or nearly so. In both compounds, the N-H groups in the pyrrole rings are trans to one another across the central S bridge. So, the two unique N-H...O bonds, both of which involve carbonyl oxygen atoms as acceptors, form chains of hydrogen bonds that extend along the *c* axis when viewed in the *ac* plane. Each molecule participates in 4 hydrogen bonds, involving its two N-H groups as donors and its two C=O groups as acceptors. In Compound **27** the SO₂ oxygen atoms do not participate in the hydrogen bonding network, and as in compound **8**, it is the carbonyl oxygen atoms that act as the hydrogen bond acceptors. This results in a pattern of hydrogen bonding identical to that observed in compound **8**.

The hydrogen bonding patterns observed in compounds **15** and **25** are quite different from those in the previous two compounds. In **15** and **25** the pyrrole rings, and thus the N-H groups, are in a cis disposition across the central sulfur bridge. In both of these compounds, the two N-H groups of one molecule form hydrogen bonds to the same oxygen atom in a second molecule. Even more specifically, pairs of molecules form discrete dimers as they act as both donors (2) and acceptors (2) in the 4 hydrogen bonds formed between two molecules. The hydrogen bonding pattern does, however, differ between **15** and **25** because the hydrogen bond acceptor in **15** is a carbonyl oxygen atom (as in **8** and **27**) while in compound **25** the acceptor is the central oxygen atom of the SO group. In compound **15** the hydrogen bonding region of the two molecules of the dimer are coplanar while in **27** they are completely intertwined.

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

The C¹-S and C⁹-S bond lengths of **8** are similar to each other, at 1.755(3) Å and 1.744(2) Å, respectively. In addition, the C¹-S and C⁹-S bond lengths of **15**, **25**, and **27** are similar to those of **8**. The higher oxidation state of the sulfur atom in either **25** or **27** does not appear to have a significant effect on the length of the C-S bonds, nor does the dimeric nature of **15** and the identity and position of the electron-withdrawing group (acyl vs. benzyl ester). However, a notable difference can be seen in the C¹-S-C⁹ bond angles. Comparing **8** and **15**, i.e. 105.8(1)° and 101.4(2)°, respectively, the narrowing of the S-C⁹ bond angle from **8** to **15** may be a result of the dimeric nature of **15**, where the hydrogen bonding between two molecular units forces the sulfide bond angle to narrow. The C¹-S-C⁹ bond angle of sulfoxide **25**, 104.5(4)° is comparable to that of **8**, while the bond angle of sulfone **27** is 109.56(5)°.

Given that the central bond angles between the two pyrrole units of each of **8**, **15**, **25** and **27** are in accordance with sp³ hybridization at sulfur, it seems reasonable to conclude that the two pyrroles do not share a common π -system. We would expect there to be little electronic communication between the two aryl substituents of the sulfide, sulfoxide or sulfone. Further evidence to support this can be seen by comparing **8**, **15**, **25**, and **27** to the analogous conjugated system of a dipyrin, a pyrrole linked to an azafulvene via an sp² bridging carbon, which features central bond angles in the range of 120-135 °.²⁰ To the best of our knowledge these are the first examples of sulfenyl, sulfinyl and sulfonyl dipyrrole crystal structures.

These crystal structures are in-line with those of similar reported aryl sulfides. The sulfide bond lengths of **8** and **15** are comparable (± 0.02 - 0.05 Å) to those seen in similar aryl sulfides **28** and **29** (Figure 6).²¹ The C¹-S-C⁹ bond angle of **8** is similar to that of the electron-rich **28** (106.4°), while the bond angle of **15** is more similar to that of electron-poor **29** (100.8°). The

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

C–S bond lengths of sulfoxide **25** and sulfone **27**, are comparable (± 0.02 - 0.05 Å) to their literature partners, **30**²² and **31**,²³ respectively. The C¹-S-C⁹ bond angle of **25** ($104.5(4)^\circ$) is 6° wider than that of sulfoxide **31** (98.5°), and the same bond angle of sulfone **27** ($109.56(5)$) is 5° wider than that of sulfone **31** (104.4°).

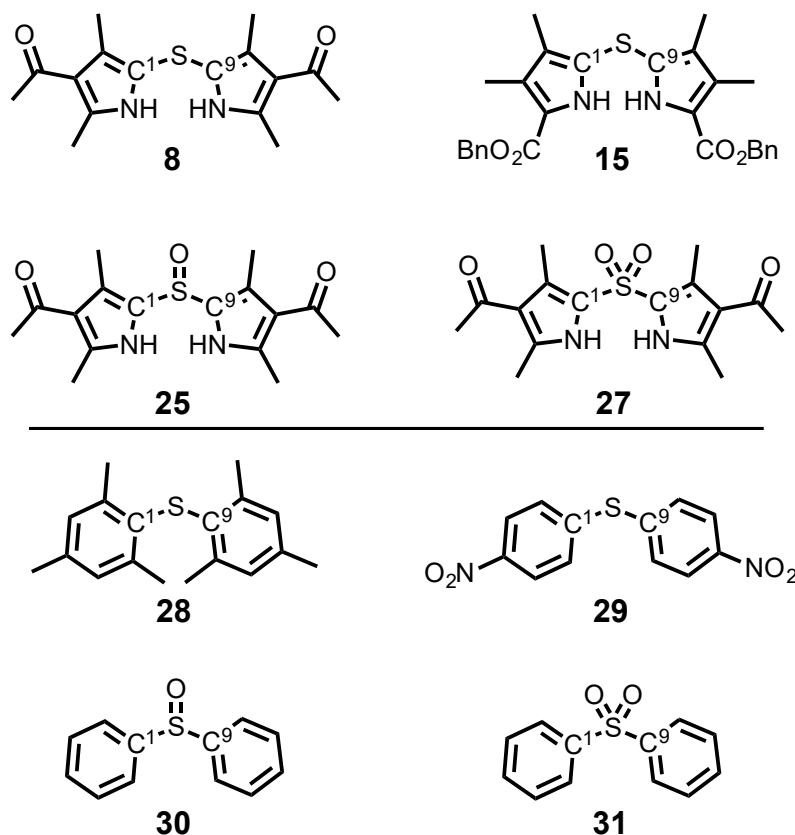


Figure 6: Sulfenyl Dipyrroles (8 and 15), Sulfinyl Dipyrrole (25), and Sulfonyl Dipyrrole (27) (Top); Comparative Compounds with Published Solved Crystal Structures (Bottom)

4.4 Conclusion

The synthesis of sulfur-bridged dipyrroles has been explored using SOCl_2 as the sulfur source. Although functional group tolerance to treatment of pyrroles with SOCl_2 proved limited, five new sulfenyl dipyrroles were synthesized and isolated, and a mechanistic rationale for the reaction, involving reduction of sulfur, was explored.

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

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Experimental

All chemicals were used as received unless indicated otherwise. Compounds **7**,¹⁴ **10**,¹⁸ **11**,¹⁸ **12**,¹⁸,²⁴ **13**,²⁵ **14**,²⁶ **20**,²⁷ **21**,²⁸ **24**,²⁹ and **30**²⁵ were prepared according to literature procedures. Thionyl chloride was purified via two separate fractional distillations over triphenyl phosphite, venting through CaCl₂, following a literature procedure,¹⁶ to furnish SOCl₂ with boiling point 75-76 °C under atmospheric pressure with a faint yellow colour when in large quantity, matching the literature data.¹⁶ Sulfuryl chloride was purified via fractional distillation following a literature procedure.^{12a} Moisture and air-sensitive reactions were performed in flame-dried glassware under a positive pressure of nitrogen unless indicated otherwise. Moisture- and air-sensitive compounds were introduced via gas-tight oven-dried syringe or cannula through a rubber septum. Flash chromatography was performed using Silicycle ultra-pure silica (230-400 mm). NMR spectra were recorded using 500 or 300 MHz spectrometers. ¹H chemical shifts (δ) are expressed in parts per million (ppm) relative to tetramethylsilane using residual solvent signal, from deuterated solvent, as internal standard (chloroform, 7.16 ppm; dichloromethane 5.31 ppm; DMSO 2.50 ppm). ¹³C chemical shifts (δ) are expressed in parts per million (ppm) relative to tetramethylsilane using deuterated solvent as internal standard spectra (CDCl₃, 77.16 ppm;

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

CD₂Cl₂, 53.84 ppm; DMSO-*d*₆ 128.06 ppm). Splitting patterns are indicated as follows: br s, broad singlet; s, singlet; d, doublet; m, multiplet. All coupling constants (*J*) are reported in hertz (Hz). Mass spectra were obtained using TOF and LCQ Duo ion trap instruments operating in ESI⁺ - or APCI-mode, as indicated. Melting points were determined using a Fisher-Johns melting point apparatus, and are uncorrected. Use of 10 μ L, 25 μ L, 250 μ L, 500 μ L, 1000 μ L, and 5000 μ L Hamilton Company[®] syringes enabled greater accuracy when adding appropriately small volumes (<5000 μ L). Error associated with each syringe was $\pm 1\%$ of the nominal volume.³⁰ Deposition Numbers 2021365 to 2021368 (see Table S2, Supporting Information) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service via www.ccdc.cam.ac.uk/structures.

1,1'-[Thiobis(2,4-dimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (8): prepared using four methods.

1,1'-[Thiobis(2,4-dimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (8) via reaction of 7 with SOCl₂

In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (32 μ L, 0.44 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of 7 (81 mg, 0.59 mmol) and NEt₃ (90 μ L, 0.65 mmol) in anhydrous CH₂Cl₂ (6 mL). The reaction mixture was stirred at -10 °C, under nitrogen, for 25 min. Methanol (2 mL) was added to quench the reaction, and the reaction mixture was then concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (62 mg, 70%). M.p. 250-252 °C (decomp); ¹H NMR (500 MHz; CDCl₃) δ 7.98 (br s, 2H), 2.46 (s, 6H), 2.44 (s, 6H), 2.40 (s, 6H); ¹H NMR (500 MHz; DMSO-*d*₆) δ 11.13 (br s, 2H), 2.40 (s, 6H), 2.32 (s, 6H), 2.29 (s, 6H); ¹³C {¹H} NMR (126 MHz; DMSO-*d*₆) δ 193.5, 136.5, 124.3, 120.9, 115.8, 30.7, 14.5, 12.7; HRMS-APCI (*m/z*): [M+H]⁺ calculated for

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

$C_{16}H_{21}N_2O_2S$ 305.1318; found 305.1321; HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_{16}H_{20}N_2O_2SNa$ 327.1138; found 327.1128. **1-(5-Chloro-2,4-dimethyl-1H-pyrrol-3-yl)ethanone (9)** was also isolated, as an off-white solid (19 mg, 19%). M.p. 178-180 °C (decomp.); (500 MHz; DMSO- d_6) δ 11.70 (br s, 1H), 2.37 (s, 3H), 2.30 (s, 3H), 2.10 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz; DMSO- d_6) δ 193.2, 133.7, 120.5, 114.5, 110.3, 30.6, 14.2, 11.2; HRMS-ESI (m/z): $[M-H]^-$ calculated for $C_8H_9^{35}ClNO$ 170.0378; found 170.0376; HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_8H_{10}^{35}ClNONa$ 194.0343; found 194.0339. 1H NMR reported in both $CDCl_3$ and DMSO- d_6 to correct a misreport of NMR solvent in previous literature.³¹

1,1'-[Thiobis(2,4-dimethyl-1H-pyrrol-3,5-diyl)]bisethanone (8) via reaction of 7 with SOBr₂

In an oven-dried round-bottom equipped with a stir bar, cold thionyl bromide (48 μ L, 0.62 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **7** (114 mg, 0.830 mmol) and NEt_3 (127 μ L, 0.913 mmol) in anhydrous CH_2Cl_2 (8 mL). The reaction mixture was stirred at -10 °C, under nitrogen, for 15 min. Methanol (2 mL) was added to quench the reaction, and the reaction mixture was then concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (23 mg, 18%). M.p. 249-252 °C (decomp); 1H NMR (300 MHz; DMSO- d_6) δ 11.15 (br s, 2H), 2.39 (s, 6H), 2.31 (s, 6H), 2.28 (s, 6H); HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_{16}H_{20}N_2O_2SNa$ 327.1138; found 327.1145; in accordance with our previous data. **1-(5-Bromo-2,4-dimethyl-1H-pyrrol-3-yl)ethanone** was also isolated, as an off-white solid (11 mg, 10 %). M.p. 50-53 °C (decomp); 1H NMR (500 MHz; $CDCl_3$) δ 8.02 (br s, 1H), 2.49 (s, 3H), 2.42 (s, 3H), 2.22 (s, 3H); HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_8H_{10}^{79}BrNONa$ 237.9838; found 237.9842. ^{13}C NMR data not collected due to the instability of this compound.

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

1,1'-[Thiobis(2,4-dimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (8) via treatment of 7 with S₂Cl₂

In an oven-dried round-bottom equipped with a stir bar, S₂Cl₂ (50 μ L, 0.64 mmol) was added to a cooled solution (0 °C) of **7** (169 mg, 1.23 mmol) in CH₂Cl₂ (12 mL). Immediately upon addition of S₂Cl₂ the reaction mixture became thick with solid. The reaction mixture was stirred for 10 min, whereupon distilled water (1 mL) was added to quench the reaction. The solid was then collected via suction filtration, and dissolved in THF. The resulting solution was dried with MgSO₄ and concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (30 mg, 16%); M.p. 250-252 °C (decomp); ¹H NMR (300 MHz; DMSO-*d*₆) δ 11.23 (br s, 2H), 2.39 (s, 6H), 2.31 (s, 6H), 2.28 (s, 6H); HRMS-ESI (*m/z*): [M+Na]⁺ calculated for C₁₆H₂₀N₂O₂SNa 327.1138; found 327.1130. **1,1'-[Dithiobis(2,4-dimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (26)** was also isolated, as an off-white solid (50 mg, 24%). M.p. 184-186 °C; ¹H NMR (500 MHz; DMSO-*d*₆) δ 11.63 (br s, 2H), 2.43 (s, 6H), 2.29 (s, 6H), 1.80 (s, 6H); ¹³C {¹H} NMR (126 MHz; DMSO-*d*₆) δ 193.5, 139.1, 129.8, 121.7, 115.8, 30.7, 14.5, 11.9; HRMS-ESI (*m/z*): [M+Na]⁺ calculated for C₁₆H₂₀N₂O₂S₂Na 359.0858; found 359.0845.

1,1'-[Thiobis(2,4-dimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (8) via treatment of 25 with SOCl₂

In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (8 μ L, 0.1 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **25** (29 mg, 0.1 mmol) and NEt₃ (14 μ L, 0.1 mmol) in anhydrous CH₂Cl₂ (2 mL). The reaction mixture was stirred at -10 °C, under nitrogen, for 10 min. Methanol (1 mL) was added to quench the reaction, and the reaction mixture was then concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the desired product as

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

an off-white solid (10 mg, 37%). M.p. 250-252 °C (decomp); ^1H NMR (300 MHz; DMSO- d_6) δ 11.16 (br s, 2H), 2.39 (s, 6H), 2.31 (s, 6H), 2.28 (s, 6H); HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2\text{SNa}$ 327.1138; found 327.1128. **1-(5-Chloro-2,4-dimethyl-1H-pyrrol-3-yl)ethanone (9)** was also isolated, as an off-white solid (10 mg, 20%). ^1H NMR (500 MHz; CDCl_3) δ 8.02 (br s, 1H), 2.48 (s, 3H), 2.41 (s, 3H), 2.21 (s, 3H). **1,1'-[Dithiobis(2,4-dimethyl-1H-pyrrol-3,5-diyl)]bisethanone (26)** was also isolated, as an off-white solid (8 mg, 14%). ^1H NMR (500 MHz; DMSO- d_6) δ 11.63 (br s, 2H), 2.43 (s, 6H), 2.29 (s, 6H), 1.80 (s, 6H).

1-(5-Chloro-2,4-dimethyl-1H-pyrrol-3-yl)ethanone (9)

The title compound was prepared according to a modified literature procedure.³² In an oven-dried round-bottom equipped with a stir bar, **7** (2.02 g, 14.7 mmol) was dissolved in anhydrous CH_2Cl_2 (150 mL) and cooled to -10 °C under N_2 . Freshly distilled, chilled, SO_2Cl_2 (1.2 mL, 15 mmol, -8 °C) was slowly added to the reaction mixture. The reaction mixture was stirred for 30 min, whereupon methanol (10 mL) was added to quench the reaction. The reaction mixture was then concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 30%→50% ethyl acetate/hexanes, to yield the desired product as an off-white solid (1.64 g, 53%). ^1H NMR (500 MHz; DMSO- d_6) δ 11.70 (br s, 1H), 2.37 (s, 3H), 2.30 (s, 3H), 2.10 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz; DMSO- d_6) δ 193.2, 133.7, 120.4, 114.5, 110.3, 30.6, 14.2, 11.2; HRMS-ESI (m/z): $[\text{M}-\text{H}]^-$ calculated for $\text{C}_8\text{H}_9\text{ClNO}$ 170.0378; found 170.0376; HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_8\text{H}_{10}\text{ClNONa}$ 194.0343; found 194.0339. ^1H NMR reported in both CDCl_3 and DMSO- d_6 to correct a previous misreport of NMR solvent.³¹

tert-Butyl Ester 3-Acetyl-2,4-dimethyl-1H-pyrrole-1-carboxylic Acid (13)

The title compound was prepared following a modified literature procedure.²⁵ In an oven-dried round-bottom equipped with a stir bar, di-*tert*-butyl dicarbonate (1.04 g, 4.68 mmol) was

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

dissolved in anhydrous acetonitrile (9 mL) and the mixture then bubbled with N₂ gas for 10 min to prepare Solution One. In a second oven-dried round-bottom equipped with a stir bar, a solution of pyrrole **7** (212 mg, 1.55 mmol) and DMAP (24 mg, 0.22 mmol) in anhydrous acetonitrile (15 ml) was bubbled with N₂ for 10 min under N₂ to prepare Solution Two. Solution One was added to Solution Two, slowly via cannula. The resulting solution was stirred until **7** was consumed (20 min), according to analysis using TLC. The reaction solvent and excess di-*tert*-butyl dicarbonate were removed *in vacuo*, and the resulting residue was purified via column chromatography on silica, eluting with 15% ethyl acetate/hexanes, to yield the title compound as an off-white solid (320 mg, 87%). ¹H NMR (500 MHz; CDCl₃) δ 6.92-6.91 (m, 1H), 2.69 (s, 3H), 2.44 (s, 3H), 2.19-2.19 (m, 3H), 1.59 (s, 9H); ¹³C{¹H} NMR (126 MHz; CDCl₃) δ 196.9, 149.0, 137.2, 126.1, 119.9, 118.7, 84.2, 31.6, 27.9, 14.2, 13.1; HRMS-ESI (*m/z*): [M+Na]⁺ calculated for C₁₃H₁₉NO₃Na 260.1257; found 260.1264.

Dibenzyl Ester 5,5'-Thiobis[3,4-dimethyl-1*H*-pyrrole-2-carboxylic Acid] (**15**)

In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (15 μ L, 0.21 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **10**¹⁸ (64 mg, 0.28 mmol) and NEt₃ (43 μ L, 0.31 mmol) in anhydrous CH₂Cl₂ (3.5 mL). The reaction mixture was stirred at -10 °C and allowed to warm to room temperature (20-25 °C), under N₂. Once at room temperature, the reaction mixture was heated at reflux temperature for 20 h. Methanol (1 mL) was added to quench the reaction, and the reaction mixture was then concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 15% ethyl acetate/hexanes, to yield the title compound as an off-white solid (44 mg, 64%). M.p. 195-197 °C; ¹H NMR (500 MHz; DMSO-*d*₆) δ 11.68 (br s, 2H), 7.44-7.42 (m, 4H), 7.41-7.37 (m, 4H), 7.36-7.32 (m, 2H), 5.31 (s, 4H), 2.14 (s, 6H), 2.04 (s, 6H); ¹³C{¹H} NMR (126 MHz; DMSO-*d*₆)

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

δ 160.3, 136.5, 128.4, 127.9, 127.7, 125.7, 123.9, 121.5, 120.0, 65.1, 10.7, 9.4; HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_{28}H_{28}N_2O_4SNa$ 511.1662; found 511.1660. **Benzyl ester 3,4-dimethyl-5-chloro-1H-pyrrole-2-carboxylic acid** was also isolated, as an off-white solid (8 mg, 11 %). M.p. 153-155 °C; 1H NMR (500 MHz; $CDCl_3$) δ 8.82 (br s, 1H), 7.42-7.32 (m, 5H), 5.31 (s, 2H), 2.28 (s, 3H), 1.95 (s, 3H). $^{13}C\{^1H\}$ NMR (126 MHz; $CDCl_3$) δ 160.7, 136.4, 128.7 (three overlapping signals), 128.34, 128.31, 117.9, 117.4, 66.0, 11.1, 8.7; HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_{14}H_{14}^{35}ClNO_2Na$ 286.0605; found 286.0601.

Dibenzyl Ester 5,5'-Thiobis[2,4-dimethyl-1H-pyrrole-3-carboxylic acid] (16)

In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (16 μ L, 0.21 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **11**¹⁸ (70 mg, 0.31 mmol) and NEt_3 (47 μ L, 0.34 mmol) in anhydrous CH_2Cl_2 (3.0 mL). The reaction mixture was stirred at -10 °C and allowed to warm to room temperature (20-25 °C), under N_2 . Once at room temperature, the reaction mixture was heated at reflux temperature for 2 h. Methanol (1 mL) was added to quench the reaction, and the reaction mixture was then concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 15% ethyl acetate/hexanes, to yield the title compound as an off-white solid (39 mg, 52%). M.p. 197-200 °C; 1H NMR (500 MHz; $CDCl_3$) δ 7.96 (br s, 2H), 7.41-7.39 (m, 4H), 7.37-7.36 (m, 4H), 7.32-7.29 (m, 2H), 5.26 (s, 4H), 2.42 (s, 6H), 2.38 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz; $CDCl_3$) δ 165.3, 137.8, 136.9, 128.7, 128.2, 128.1, 126.7, 115.6, 111.9, 65.5, 14.5, 12.5; HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_{28}H_{28}N_2O_4SNa$ 511.1662; found 511.1641. **Benzyl ester 2,4-dimethyl-5-chloro-1H-pyrrole-3-carboxylic acid** was also isolated, as an off-white solid (12 mg, 14 %). M.p. 154-156 °C; 1H NMR (500 MHz; $CDCl_3$) δ 7.99 (br s, 1H), 7.46-7.44 (m, 2H), 7.41-7.38 (m, 2H), 7.36-7.33 (m, 1H), 5.32 (s, 2H), 2.49 (s, 3H), 2.21 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz;

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

CDCl₃) δ 165.2, 136.9, 134.6, 128.6, 128.1, 128.0, 117.0, 111.4, 110.7, 65.5, 14.1, 11.1; HRMS-ESI (m/z): [M+Na]⁺ calculated for C₁₄H₁₄³⁵CINO₂Na 286.0605; found 286.0606.

Diethyl Ester 5,5'-Thiobis[2,4-dimethyl-1H-pyrrole-3-carboxylic acid] (17)

In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (17 μ L, 0.23 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **12**¹⁸ (52 mg, 0.32 mmol) and NEt₃ (50 μ L, 0.36 mmol) in anhydrous CH₂Cl₂ (3 mL). The reaction mixture was stirred at -10 °C and allowed to warm to room temperature (20-25 °C), under N₂. Once at room temperature, the reaction mixture was stirred for 1.5 h. Methanol (1 mL) was added to quench the reaction, and the reaction mixture was then concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 15% ethyl acetate/hexanes, to yield the title compound as an off-white solid (19 mg, 32%). M.p. 189-192 °C; ¹H NMR (500 MHz; CDCl₃) δ 7.90 (br s, 2H), 4.26 (q, J = 7.1 Hz, 4H), 2.44 (s, 6H), 2.39 (s, 6H), 1.34 (t, J = 7.1 Hz, 6H); ¹³C {¹H} NMR (126 MHz; CDCl₃) δ 165.8, 137.5, 126.5, 115.6, 112.2, 59.5, 14.6, 14.3, 12.4; HRMS-ESI (m/z): [M+Na]⁺ calculated for C₁₈H₂₄N₂O₄SNa 387.1349; found 387.1344.

Di-*tert*-butyl Ester 5,5'-Thiobis[3-acetyl-2,4-dimethyl-1H-pyrrole-1-carboxylic acid] (18)

In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (33 μ L, 0.45 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **13** (142 mg, 0.586 mmol) and NEt₃ (92 μ L, 0.66 mmol) in anhydrous CH₂Cl₂ (6 mL). The reaction mixture was stirred at -10 °C and allowed to warm to room temperature (20-25 °C), under N₂, then heated at reflux temperature for 1 h. Methanol (2 mL) was added to quench the reaction, and the reaction mixture then concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the title compound as an off-white solid (15 mg, 10%). ¹H NMR (500 MHz; CDCl₃) δ 2.51 (s, 6H), 2.39 (s, 6H), 2.07 (s, 6H), 1.59 (s,

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

18H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz; CDCl_3) δ 196.6, 148.9, 137.1, 126.1, 124.9, 120.5, 85.8, 31.8, 28.0, 14.3, 12.6; HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}_6\text{SNa}$ 527.2186; found 527.2204.

1,1'-[Thiobis(1,2,4-trimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (19)

In an oven-dried round-bottom equipped with a stir bar, cold thionyl chloride (30 μL , 0.41 mmol, $-8\text{ }^\circ\text{C}$) was slowly added to a cooled solution ($-10\text{ }^\circ\text{C}$, salt/ice) of **14** (84 mg, 0.56 mmol) and NEt_3 (85 μL , 0.61 mmol) in anhydrous CH_2Cl_2 (6 mL). The reaction mixture was removed from the cold bath and stirred for 1 h, under N_2 . Methanol (2 mL) was added to quench the reaction, and the reaction mixture was concentrated *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 50% ethyl acetate/hexanes, to yield the title compound as an off-white solid (6 mg, 7%). ^1H NMR (500 MHz; CDCl_3) δ 3.44 (s, 6H), 2.51 (s, 6H), 2.45 (s, 6H), 2.43 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz; CDCl_3) δ 195.4, 138.2, 125.2, 122.0, 118.3, 31.5, 31.4, 14.1, 13.0; HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_2\text{SNa}$ 355.1451; found 355.1436.

1,1'-[Sulfinylbis(2,4-dimethyl-1*H*-pyrrol-3,5-diyl)]bisethanone (25)

The title compound and sulfone **27** were prepared and isolated from the same reaction using a modified literature procedure.^{4a} A solution of *m*-CPBA ($\leq 77\%$, 430 mg, 1.59 mmol) in DMF (18 mL) was added, drop-wise under N_2 , to a solution of **8** (502 mg, 1.65 mmol) in DMF (36 mL). After complete addition of the *m*-CPBA solution (8 min), the resulting reaction mixture was stirred at $0\text{ }^\circ\text{C}$ until all starting material had been consumed (1 h, monitoring via TLC). The reaction mixture was diluted with CHCl_3 (100 mL) and then washed with saturated NaHCO_3 (50 mL), followed by thorough washing with H_2O ($5 \times 50\text{ mL}$). The organic layer was dried with Na_2SO_4 and the solvent then removed *in vacuo*. The resulting residue was purified via column

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

chromatography on silica, eluting with 50→100% ethyl acetate/hexanes, to yield the desired product as an off-white solid (248 mg, 48%), which began to noticeably degrade under ambient conditions (open-air, 20 °C) after 3 days. The title compound appeared to be stable at low temperatures (-20 °C, weeks). M.p. 132-134 °C, decomp 138 °C; ^1H NMR (500 MHz; CDCl_3) δ 11.41 (br s, 2H), 2.49 (s, 6H), 2.36 (s, 6H), 2.31 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz; CDCl_3) δ 194.5, 141.3, 127.5, 122.6, 122.0, 31.2, 15.2, 12.2; HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_3\text{SNa}$ 343.1087; found 343.1076. **1,1'-[Sulfonylbis(2,4-dimethyl-1H-pyrrol-3,5-diyl)]bisethanone (27)** was also isolated, as an amorphous white solid (111 mg, 20%). ^1H NMR (500 MHz; $\text{DMSO}-d_6$) δ 12.11 (br s, 2H), 2.45 (s, 6H), 2.33 (s, 6H), 2.31 (s, 6H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz; $\text{DMSO}-d_6$) δ 194.3, 138.4, 125.4, 124.5, 122.4, 31.1, 14.1, 11.3; HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_4\text{SNa}$ 359.1036; found 359.1035.

1-[5-[(4-Acetyl-3,5-dimethylpyrrol-2-yl)thio]-1,2,4-trimethyl-1H-pyrrol-3-yl]ethanone

Cold thionyl chloride (17 μL , 0.24 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of **25** (76 mg, 0.24 mmol), **14** (361 mg, 2.41 mmol), and NEt_3 (26 μL , 0.26 mmol) in anhydrous CH_2Cl_2 (5 mL), under nitrogen. Prior to cooling and thionyl chloride addition, the reaction mixture required 10 min of stirring at room temperature for all solid reagents to completely dissolve. Once thionyl chloride had been added, the reaction mixture was stirred at -10 °C until **25** was consumed (20 min), according to analysis using TLC. The reaction solvents were removed *in vacuo* and the resulting residue was crudely purified via column chromatography on silica, eluting with 25% ethyl acetate/hexanes→100% ethyl acetate. The resulting (impure) solid was fully purified using preparative TLC, using 100% ethyl acetate as the eluent. A single preparative TLC plate was cycled 3 times (run TLC plate in 100% ethyl acetate; air dry; run; air dry; run third and final time) to enable ideal separation and furnish the

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

title compound as an off-white amorphous solid (6 mg, 8%). ^1H NMR (500 MHz; CDCl_3) δ 7.82 (s, 1H), 3.55 (s, 3H), 2.55 (s, 3H), 2.47 (s, 3H), 2.44-2.42 (m, 9H), 2.39 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz; CDCl_3) δ 195.4, 194.9, 138.4, 136.9, 126.5, 123.8, 122.2, 122.1, 118.7, 116.2, 31.44, 31.42, 31.1, 15.5, 14.1, 13.1 (two overlapping signals); HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_2\text{SNa}$ 341.1294; found 341.1304. **1-(5-Chloro-1,2,4-trimethyl-1H-pyrrol-3-yl)ethanone** was also isolated, as an off-white amorphous solid (15 mg, 4% from **14**). ^1H NMR (500 MHz; CDCl_3) δ 3.48 (s, 3H), 2.49 (s, 3H), 2.41 (s, 3H), 2.24 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz; CDCl_3) δ 195.1, 134.7, 121.2, 115.2, 114.6, 31.4, 30.8, 12.7, 12.4; HRMS-ESI (m/z): $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_9\text{H}_{12}^{35}\text{ClN}_2\text{O}$ 208.0500; found 208.0496.

1-[2,4-Dimethyl-5-(4-methylphenyl)sulfinyl-1H-pyrrol-3-yl]ethanone

The title compound was prepared according to a modified literature procedure.^{4a} To a solution of 1-[2,4-dimethyl-5-(4-methylphenyl)thio-1H-pyrrol-3-yl]ethanone (155 mg, 0.598 mmol) in DMF (12 mL) at $-10\text{ }^\circ\text{C}$, was added, dropwise, a solution of *m*-CPBA (120 mg, 0.610 mmol) in DMF (6 mL), under N_2 . After 2 h, the reaction mixture was diluted with methanol (5 mL) and concentrated under reduced pressure. Water (60 mL) was added to the reaction mixture, and the aqueous layer thoroughly extracted with CH_2Cl_2 (5×20 mL). The combined organic fractions were washed with water (2×50 mL) and brine (50 mL), and then dried with Na_2SO_4 . The reaction mixture was concentrated *in vacuo*, then purified via column chromatography on silica eluting with 15% ethyl acetate/hexanes \rightarrow 25% ethyl acetate/hexanes to yield the title compound as an off-white amorphous solid (103 mg, 63%). ^1H NMR (500 MHz; CDCl_3) δ 9.94 (s, 1H), 7.45 (d, $J = 8.2$ Hz, 2H), 7.27 (d, $J = 8.1$ Hz, 2H), 2.49 (s, 3H), 2.40-2.39 (m, 6H), 2.38 (s, 3H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126 MHz; CDCl_3) δ 194.8, 141.5, 140.79, 140.76, 140.4, 130.2, 127.4, 124.9,

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

122.3, 31.2, 21.5, 15.2, 12.4; HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_{15}H_{17}NO_2SNa$ 298.0872; found 298.0870; in accordance with literature.³³

1-[2,4-Dimethyl-5-(4-methylphenyl)thio-1*H*-pyrrol-3-yl]ethanone: prepared using two methods.

1-[2,4-Dimethyl-5-(4-methylphenyl)thio-1*H*-pyrrol-3-yl]ethanone via treatment of 7 and *p*-toluenesulfonyl chloride with PPh_3 . The title compound was prepared according to a modified literature procedure.^{10a} Pyrrole 7 (51 mg, 0.37 mmol), *p*-toluenesulfonyl chloride (137 mg, 0.719 mmol) and tricyclohexylphosphine (294 mg, 0.929 mmol) were dissolved in anhydrous dioxane (1.5 mL) under N_2 at room temperature (20 °C). Once completely in solution, the reaction mixture was heated at 50 °C for 20 h. The reaction solvent was removed *in vacuo*, and the resulting residue purified via column chromatography on silica eluting with 25% ethyl acetate/hexanes to yield the title compound as an off-white amorphous solid (70 mg, 72%). 1H NMR (500 MHz; $CDCl_3$): δ 8.10 (br s, 1H), 7.04 (d, $J = 8.0$ Hz, 2H), 6.91 (d, $J = 8.2$ Hz, 2H), 2.51 (s, 3H), 2.46 (s, 3H), 2.37 (s, 3H), 2.28 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz; $CDCl_3$) δ 195.2, 137.7, 135.7, 134.4, 130.0, 128.9, 126.3, 122.6, 113.6, 31.1, 21.0, 15.4, 13.2; HRMS-ESI (m/z): $[M+Na]^+$ calculated for $C_{15}H_{17}NOSNa$ 282.0923; found 282.0911. Although this is a known compound,³⁴ 1H and ^{13}C NMR data have not been previously reported.

1-[2,4-Dimethyl-5-(4-methylphenyl)thio-1*H*-pyrrol-3-yl]ethanone via treatment of 1-[2,4-dimethyl-5-(4-methylphenyl)sulfinyl-1*H*-pyrrol-3-yl]ethanone with $SOCl_2$

Cold thionyl chloride (15 μ L, 0.20 mmol, -8 °C) was slowly added to a cooled solution (-10 °C, salt/ice) of 1-[2,4-dimethyl-5-(4-methylphenyl)sulfinyl-1*H*-pyrrol-3-yl]ethanone (51 mg, 0.18 mmol) and NEt_3 (28 μ L, 0.20 mmol) in anhydrous CH_2Cl_2 (2 mL). The reaction mixture was stirred at -10 °C, under nitrogen, for 9 min. Methanol (1 mL) was added to quench the reaction,

Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

and the solvent was then removed *in vacuo*. The resulting residue was purified via column chromatography on silica, eluting with 20% ethyl acetate/hexanes, to yield the title compound as an off-white solid (7 mg, 15%). $^1\text{H NMR}$ (500 MHz; CDCl_3): δ 8.10 (br s, 1H), 7.04 (d, $J = 8.0$ Hz, 2H), 6.91 (d, $J = 8.2$ Hz, 2H), 2.51 (s, 3H), 2.46 (s, 3H), 2.37 (s, 3H), 2.28 (s, 3H).

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Synthesis of sulfenyl dipyrroles via reaction of α -free pyrroles with thionyl chloride

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