Sulfenylation Using Sulfoxides. Intramolecular Cyclization of 2- and 3-Acylpyrroles

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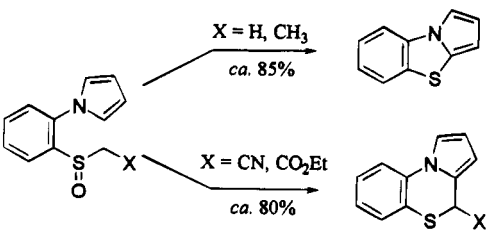
$AlCl_3$-catalyzed acylation of *N*-(phenylsulfonyl)pyrrole with 2-(ethylthio)benzoyl chloride followed by hydrolysis provided 2-(2-(ethylthio)benzoyl)pyrrole (**3**). Compound **3** was also available from ethyl 2-(ethylthio)benzoate and pyrrolylmagnesium chloride (Scheme 2). Oxidation ($NaIO_4$) gave the corresponding sulfoxide **4** which when refluxed 6 h in *p*-xylene (bp 138 °C) gave predominately the C-3 cyclization product **11** (51%) along with the rearrangement product **12** (17%). Conducting the thermal reaction in the presence of DMAP in refluxing toluene gave mainly the N-1 cyclization product **13** (46%) also accompanied by the rearrangement product **12** (20%). Formation of a 2*H*-pyrrole spirocyclic intermediate from thermally promoted intramolecular *ipso*-sulfenylation in **4** is suggested to account for the formation of **12**. The *N*-methyl derivative of **4** (*i.e.* **6**) produced **9** and **10** after 9 h at 138 °C; in the presence of DMAP only **9** is produced after 18 h at 138 °C. The 3-acyl sulfoxide **8** cyclized to **17** during 6.5 h at 138 °C. These results indicate that although sulfoxides are useful for intramolecular sulfenylation reactions, care must be taken in assigning structures to the product(s) because rearrangement may take place during and/or after the initial cyclization reaction. Addition of a basic amine to the reaction mixture may prevent acid-catalyzed rearrangements of the initially formed products.

Cyclization of pyrrole-containing sulfoxides is a useful technique for preparing a variety of *N,S*-heterocycles.[2,3] This approach utilizes either the intrinsic electrophilicity (thermal cyclization in refluxing xylene)[2b] or enhanced electrophilicity (by addition of a protic acid[2a] or TFAA[3]) of sulfoxides. As a group, these reactions are unusual, because the reaction conditions which lead to selective reaction *at sulfur* in alkyl-substituted sulfoxides[2–4] are widely used for Pummerer rearrangement of sulfoxides.[5] The reaction path may be diverted in one direction or the other by proper choice of reaction conditions and sulfoxide side chain (see Scheme 1): Sulfenylation products are favored when the side chain of an alkyl aryl sulfoxide is simple alkyl while Pummerer products are favored when the alkyl side chain contains an electron-withdrawing group on the α-carbon.[4b,5]

One of the major advantages of use of sulfoxides as sulfenylating agents over conventional techniques utilizing a sulfide/positive halogen source[6] (*e.g.* dimethyl sulfide/NCS) or thiol/halogen[7] is the absence of polyhalogenation or polysulfenylation of the product when more than one unsubstituted site is available.

Scheme 1

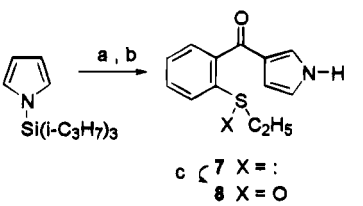


As part of our continuing investigation of sulfoxide electrophilic sulfenylation for preparation of pyrrole-containing *N,S*-heterocyclic compounds, we report the chemistry of 2- and 3-acylpyrroles *including evidence for a 2H-pyrrole spirocyclic intermediate in the cyclization of 2-acylpyrroles*.

Results and Discussion

Synthesis of 2- and 3-Acylpyrrole Sulfoxides. Required 2-acylpyrroles **4** and **5** were prepared via two routes from 2-(ethylthio)benzoic acid derivatives **1** (Scheme 2). In contrast to expectations based on literature reports,[8] no reaction took place when BF_3OEt_2 was used as the catalyst in the Friedel–Crafts reaction of **1a** with *N*-(phenylsulfonyl)pyrrole; however, $AlCl_3$[8,9] was effective.

The requisite 3-acyl sulfoxide **8** was prepared using the Muchowski process[10] (*N*-(triisopropylsilyl)pyrrole and **1a**), followed by directing group removal and oxidation (eq 1).



(1)

conditions: (a) **1a**, $AlCl_3$ (b) $(Bu)_4NF$, THF (c) $NaIO_4$, H_2O/CH_3OH

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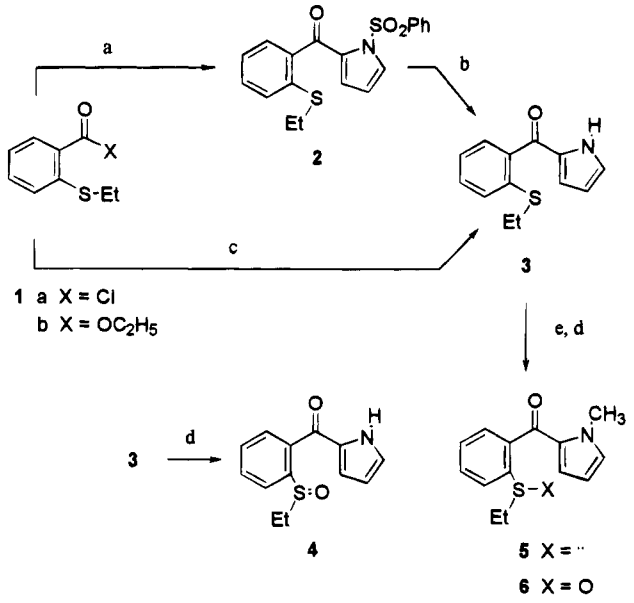
0022-3263/94/1959-8076$04.50/0

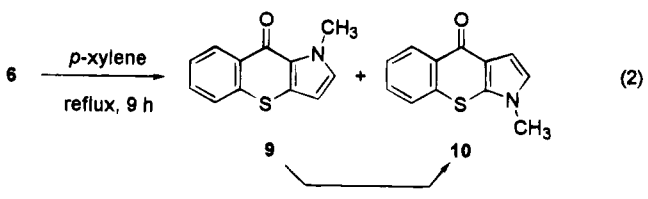
Scheme 2



[a] Conditions: (a) *N*-(phenylsulfonyl)pyrrole, $AlCl_3$ (33%), (b) CH_3OH, KOH (100%), (c) 2.2 equiv pyrrolylmagnesium chloride, toluene (60%), (d) $NaIO_4$, H_2O/CH_3OH, (e) $(CH_3O)_2SO_2$, Bu_4NHSO_4, benzene (73%).

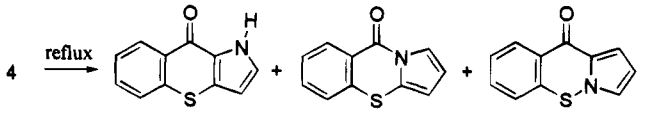
Pyrrole coupling constants and chemical shifts may be used to ascertain substitution patterns in acyl pyrroles.[11] For 2-acyl compounds **3** and **4**, H-5 (the most downfield pyrrole proton) was not always fully resolved from the aromatic envelope. However H-3 and H-4 (the most upfield pyrrole proton) were well resolved allowing differentiation between the 2- and 3-acyl isomers.

Sulfoxide Cyclization. Refluxing the *N*-methyl sulfoxide **6** in *p*-xylene solution for 9 h left only a trace of sulfoxide. Two products were isolated: compound **9** from cyclization to the "open" pyrrole 3-position and the rearrangement product **10**. Both were identified by comparison with authentic samples prepared from *N*-methylpyrrole and 2-(chlorocarbonyl)benzenesulfenyl chloride.[12] Muchowski[13] has observed that **9** rearranges to **10** upon heating (190 °C for 5 h) in polyphosphoric acid. Rearrangement of pyrrolyl sulfides under acidic conditions involves *ipso* protonation to a 2*H*- or 3*H*-pyrrole followed by preferential sulfur migration.[13] Although the reaction conditions used here are much milder, it is clear they are sufficient because the rearrangement can be prevented by conducting the reaction in the presence of 0.1 equiv of DMAP. In this case, the reaction was slower and more selective, producing only **9** after 18 h at reflux.



(2)

Scheme 3



Condition/ product distr. (%)	11	12	13
p-xylene only, 6 h	51	17	trace
0.1 eq DMAP, 29 h, toluene*	trace	20	46
0.1 eq Et_3N, 24 h, toluene*	10	15	69

* Based on recovered starting material

Sulfoxide **4**, in which cyclization can take place to N-1 or C-3, gave after 6 h in refluxing *p*-xylene predominately the C-3 cyclization product **11** and only a trace of the N-1 cyclization product **13** (Scheme 3). *Unexpectedly, the reaction mixture also contained a significant amount of the rearrangement product* ***12***.

Compound **12** is unlikely to arise by C → N acyl migration prior to cyclization, even though our previous work[2b] has shown that **12** is formed in very high yield from the corresponding *N*-acylpyrrole (*i.e.*, 1-[2-(ethylsulfinyl)benzoyl]pyrrole) in refluxing *p*-xylene. There is no precedence in the literature for rearrangement of a 2-acylpyrrole such as **4** into an *N*-acylpyrrole (normally, under conditions rigorous enough to cause acyl migration, thermodynamic equilibration may also take place, disfavoring the *N*-acyl isomer since the general order of thermodynamic stability for acyl pyrroles is 3-acyl > 2-acyl > *N*-acyl[14]). Refluxing the sulfide **3** (which cannot cyclize) in neat TFA for 37 h causes less than 50% conversion to the 3-acyl isomer, with no spectroscopic or chromatographic evidence for the presence of any of the 1-acyl isomer. 1-[2-(Ethylsulfinyl)benzoyl]pyrrole is not present as a contaminant in the samples of compound **4** used in this study at the limits detectable by NMR or TLC. Compound **12** does not form from the other reaction products either. Both compounds **12** and **11** are stable under prolonged reflux in *p*-xylene while **13** appears to produce only **11** under neutral or acidic conditions. As described below, **13** is quite stable in refluxing *p*-xylene in the presence of mild bases. *Compound* ***12*** *is most readily explained by an acyl migration from a spirocyclic intermediate and once it is formed, it does not revert to spirocycle*, nor does it undergo acid-catalyzed 1,2-acyl migration via C-protonated pyrroles.[14a]

While the relative amount of **12** formed in these reactions remained quite constant (Scheme 3), the product distribution between **11** and **13** could be dramatically influenced by addition of a basic amine to the reaction mixture. Compound **13**, a novel heterocycle, is less stable than **11** and it is converted to **11** at a rate dependent upon reaction conditions; it may be isolated in fair yield by conducting the thermal reaction in the presence of a

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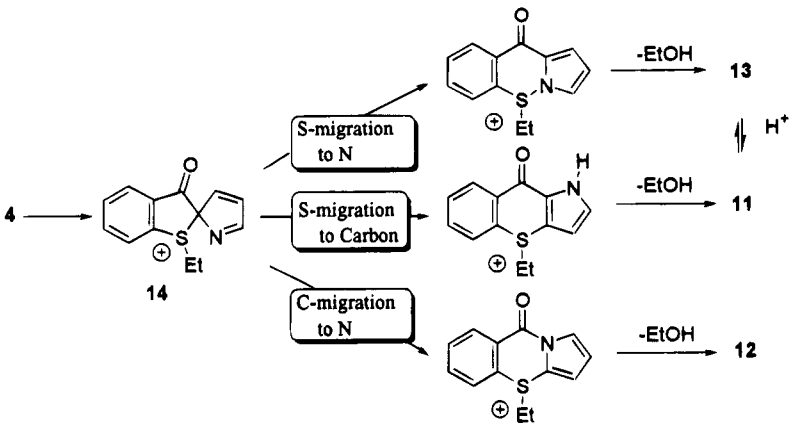
Scheme 4

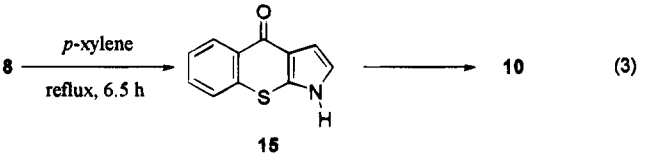


basic amine. The conversion of **13** into **11** is accompanied by some decomposition as evidenced by the appearance of a gummy tar on the walls of the reaction flask upon prolonged heating of pure **13** in *p*-xylene in the absence of base. These data are consistent with an acid-catalyzed equilibration promoted by weak proton sources, perhaps the protons on the α-carbon of unreacted sulfoxide (whose acidity may be thermally enhanced) or the glass surface of the reaction flask (as suggested by a referee).

The specific constitution of the spirocyclic intermediate formed initially from **4** is not known, but may involve a sulfonium sulfur migration (such as intermediate **14** in Scheme 4). The migratory aptitude of a sulfonium species relative to acyl has not been reported directly, but 2-(dimethylsulfonium)pyrrole rearranges to 3-(dimethylsulfonium)pyrrole[15] in refluxing TFA over 2–4 h. These are roughly the same conditions and time scale used for rearrangement of *N*-tosyl-2-(alkylthio)pyrroles to *N*-tosyl-3-(alkylthio)pyrroles.[16] Alkylthio has a higher migratory aptitude than carbethoxy in 2*H*-pyrroles.[17]

The rate of cyclization of both **4** and **6** is slower in *p*-xylene in the presence of an amine than in refluxing *p*-xylene alone. The amine acid scavenger therefore not only prevents acid-catalyzed conversion of **9** → **10** and **13** → **11** but apparently also reduces sulfoxide sulfur reactivity by preventing activation via protonation of the sulfoxide oxygen. DMAP is very effective at catalyzing acylation reactions by forming an intermediate acyl pyridinium species;[18] we have no evidence for a similar process involving a transient species containing a sulfoxide sulfur–amine nitrogen bond. We also thought that perhaps the amine could assist the reaction of **4** by aiding removal of the pyrrole proton in the intermediate 2*H*-pyrrole. However, the reactivity of **4** and the *N*-methyl derivative **6** is not significantly different.

After the novel and exciting chemistry of the 2-acyl pyrrole **4**, the chemistry of the 3-acyl analog **8** was anticlimactic. Heating the compound in *p*-xylene for 6.5 h produced the expected **15**. This product could be the result of cyclization of **8** or preferential sulfur migration from a spirocyclic intermediate. Compounds **8** and **15** have the same R_f values in a variety of solvents making it difficult to ascertain when the **8** → **15** conversion was complete. This problem also made purification of **15** difficult. Purification and spectroscopic analysis were conducted after *N*-methylation of **15** to **10** with either dimethyl sulfate or methyl iodide under phase transfer conditions.



(3)

Formation of spirocyclic intermediates in the electrophilic reactions of sulfoxides is a novel process. Further work is necessary to fully understand the process and additional work to exploit the technique in heterocyclic synthesis is underway.

Experimental Section

Melting points are reported uncorrected. NMR spectra were recorded at 200 MHz (^{1}H) or 75 MHz (^{13}C) in $CDCl_3$ unless otherwise specified. The following compounds were prepared following published procedures: 2-(ethylthio)benzoic acid;[19] *N*-phenylsulfonylpyrrole;[20] *N*-(triisopropylsilyl)pyrrole.[10] Unless otherwise noted "workup" refers to partitioning the reaction mixture between CH_2Cl_2 and H_2O followed by washing the organic layer with the appropriate aqueous solution (brine, 5% HCl, or 5% $NaHCO_3$) and drying over Na_2SO_4. Solvent was removed by rotary evaporation under aspirator vacuum and the crude product was either distilled, flash chromatographed over SiO_2, or recrystallized as specified in the text.

Ethyl 2-(Ethylthio)benzoate (1b). A mixture of 2-(ethylthio)benzoic acid (15 g, 0.082 mol), concentrated H_2SO_4 (3.1 mL), and EtOH (250 mL) was refluxed for 22 h, at which time it was concentrated to about one-half its original volume *in vacuo*. The mixture was worked up to give a cloudy yellow liquid which was distilled (bp 172–182 °C) under aspirator vacuum to give **1b** (14 g, 82%) as a colorless clear liquid: IR (neat) 1710 cm^{-1}; partial ^{1}H NMR δ 7.96–7.91 (m, 1H), 4.34 (q, J = 7.1 Hz, 2H), 2.90 (q, J = 7.4 Hz, 2H), 1.39–1.31 (m, 6H); MS [*m/z* (relative intensity)] 210 (M^+, 69), 149 (100). This compound was used without further purification.

2-[2-(Ethylthio)benzoyl]-1-(phenylsulfonyl)pyrrole (2). A mixture of 2-(ethylthio)benzoic acid (7.5 g, 41 mmol), $SOCl_2$ (3.6 mL, 49 mmol, 1.2 equiv), and benzene (100 mL) was refluxed for 3 h. After solvent removal, the resulting yellow oil was dissolved in 1,2-dichloroethane (40 mL) and added over

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5 min to a suspension of $AlCl_3$ (6.0 g, 45 mmol, 1.2 equiv) in 1,2-dichloroethane (40 mL). After the resulting red mixture was stirred for 10 min, a solution of *N*-(phenylsulfonyl)pyrrole (7.8 g, 37 mmol, 1.0 equiv) in 1,2-dichloroethane (20 mL) was added dropwise over 20 min. After stirring for 2 h at room temperature, the mixture was dumped into 250 mL of ice–water. After the ice melted, the layers were separated and the aqueous layer was extracted twice with 1,2-dichloroethane. After washing the combined organics with H_2O and drying (Na_2SO_4), the volatiles were removed *in vacuo* to give an oily dark brown solid. After recrystallization from EtOH, **2** (4.6 g, 33%) was obtained as a light brown solid. This solid was used without further purification in subsequent reactions; however, analytically pure material may be obtained by recrystallization from EtOAc/hexane and then from EtOH (mp 101–102 °C): IR (KBr) 1648, 1336, 1163 cm^{-1}; partial ^1H NMR δ 8.11 (m, 2H), 7.83 (dd, J = 1.80, 3.2 Hz, 1H), 6.52 (dd, J = 1.8, 3.7 Hz, 1H), 6.29 (dd, J = 3.2, 3.7 Hz, 1H); MS [*m/z* (relative intensity)] 371 (M^+, 1.8), 94 (100). Anal. Calcd for $C_{19}H_{17}NO_3S_2$: C, 61.43; H, 4.61; N, 3.77. Found: C, 61.47; H, 4.58; N, 3.69.

2-[2-(Ethylthio)benzoyl]pyrrole (3). To an ice-cold solution of methylmagnesium chloride (42 mL of 3 M solution in THF, 0.13 mol) in toluene (165 mL) under N_2 was added carefully pyrrole (8.4 g, 0.126 mol) over 10 min. After warming to room temperature, the solution was heated at 55 °C for 50 min, at which time a solution of **1b** (12 g, 0.06 mol) in toluene (18 mL) was added dropwise under N_2. The reaction mixture was refluxed for 12 h. After cooling to room temperature, the reaction was quenched by the addition of saturated NH_4Cl solution (225 mL) and worked up. The resulting crude black oily solid was chromatographed ($CHCl_3$) to yield a dark brown solid. Recrystallization (EtOAc/hexane) gave **3** (8.1 g, 61%) as a tan solid (mp 79–80 °C): IR (KBr) 1600 cm^{-1}; ^1H NMR δ 7.56 (m, 1H), 7.43 (m, 2H), 7.23 (m, 2H), 6.64 (m, 1H), 6.27(m, 1H), 2.93 (q, J = 7.4 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H). Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.67; N, 6.06. Found: C, 67.53; H, 5.54; N, 6.02. This compound could also be prepared in quantitative yield from **2** using the hydrolysis method of Kakushima and Frenette.[16]

2-[2-(Ethylsulfinyl)benzoyl]pyrrole (4). Compound **3** (10 g, 0.043 mol), $NaIO_4$ (12 g, 0.056 mol, 1.3 equiv), MeOH (100 mL), CH_2Cl_2 (70 mL), and H_2O (72 mL) were stirred at rt for 24 h. The layers were separated; the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL) and the extract combined with the original CH_2Cl_2 layer. The combined organic extract was dried (Na_2SO_4) and rotary evaporated under vacuum to give a dark orange-yellow solid. Chromatography ($CHCl_3$) afforded **4** contaminated with some unreacted starting material. Trituration with warm benzene and filtration gave of **4** (7.3 g, 68%) as an off-white solid (mp 155–159 °C). This compound was typically used without further purification in subsequent reactions but can be recrystallized from EtOAc/EtOH to give an analytically pure sample (mp 160–161 °C): IR (KBr) 1613, 1035 cm^{-1}; ^1H NMR (acetone-d_6/DMSO-d_6) δ 8.18 (dd, 1H), 7.99 (dd, 1H), 7.87 (td, 1H), 7.71 (td, 1H), 7.30 (dd, J = 1.4, 2.4 Hz, 1H), 6.81 (dd, J = 1.4, 3.9 Hz, 1H), 6.32 (dd, J = 2.4, 3.9 Hz, 1H), 3.1 (br s), 3.08 (d of m, 2H), 1.31 (t, J = 7.5 Hz, 3H); MS [*m/z* (relative intensity)] 247 (M^+, 8.8), 218 (100). Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66. Found: C, 63.16; H, 5.24; N, 5.55.

Note: The ^1H NMR of **4** in $CDCl_3$ was complex due to coupling between the pyrrole NH and the carbon-bound pyrrole protons, where $J_{1,4}$ is about equal to $J_{4,5}$. The spectrum was as follows: δ 8.27 (dd), 7.94 (dd), 7.76 (td), 7.57 (td), 7.20 (td), 6.82 (ddd), 6.33 (dt), 3.08 (d of m), 1.31 (t, J = 7.49 Hz).

2-[2-(Ethylthio)benzoyl]-1-methylpyrrole (5). A solution of **3** (5 g, 22 mmol) in benzene (30 mL) was added dropwise over 10 min to a stirred mixture containing 50% NaOH (45 mL), dimethyl sulfate (2.3 mL, 24 mmol), tetrabutylammonium hydrogen sulfate (367 mg, 1.1 mmol), and benzene (30 mL). The resulting two-phase solution was stirred vigorously at room temperature for 35 min and then the mixture was dumped onto 100 mL of cracked ice and stirred until the ice melted. After workup the dark brown oil was chromatographed ($CHCl_3$) to give **5** (3.9 g, 73%) as a brown solid. This solid was used without further purification in subsequent reactions; however, analytically pure white solid can be obtained by recrystallization from EtOH (mp 53–56 °C): IR (KBr) 1627 cm^{-1}; ^1H NMR δ 7.43–7.14 (m, 4H), 6.9 (distorted t, 1H), 6.45 (dd, J = 1.6, 4.1 Hz, 1H), 6.08 (dd, J = 2.5, 4.1 Hz, 1H), 4.05 (s, 3H), 2.89 (q, J = 7.4 Hz, 2H), 1.23 (t, J = 7.4 Hz, 3H); MS [*m/z* (relative intensity)] 245 (M^+, 49), 216 (100). Anal. Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.34; H, 6.19; N, 5.61.

2-[2-(Ethylsulfinyl)benzoyl]-1-methylpyrrole (6). A mixed phase $NaIO_4$ oxidation procedure was employed initially using **5** (3 g, 12 mmol), $NaIO_4$ (3.4 g, 16 mmol, 1.3 equiv), CH_2Cl_2 (45 mL), MeOH (50 mL), and H_2O (45 mL), but these conditions gave a very slow oxidation. After stirring at room temperature for 29.5 h, most of the CH_2Cl_2 was removed *in vacuo* and an additional 20 mL of MeOH was added. After stirring at room temperature for an additional 75 min, the reaction was complete. After the usual workup, **6** (3.1 g, 98%) was obtained as a light yellow solid Analytically pure material can be obtained by recrystallization from EtOAc (mp 111–113 °C): IR (KBr) 1605, 1063 cm^{-1}; ^1H NMR δ 8.25–8.21 (m, 1H), 7.78–7.69 (m, 2H), 7.57–7.49 (m, 1H), 6.96 (distorted t, 1H), 6.63 (dd, J = 1.66, 4.08 Hz, 1H), 6.16 (dd, J = 2.20, 4.08 Hz, 1H), 4.02 (s, 3H), 3.10 (dm, 2H), 1.33 (t, J = 7.49 Hz, 3H); MS [*m/z* (relative intensity)] 261 (M^+, 6), 96 (100). Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.33; H, 5.72; N, 5.32.

3-[2-(Ethylthio)benzoyl]pyrrole (7). A mixture of 2-(ethylthio)benzoic acid (5.3 g, 29 mmol), $SOCl_2$ (2.7 mL, 38 mmol), and benzene (100 mL) was refluxed for 17 h. After solvent removal, the resulting yellow oil was dissolved in CH_2Cl_2 (30 mL) and added dropwise over 15 min to a suspension of $AlCl_3$ (4.2 g, 32 mmol) in CH_2Cl_2 (30 mL) that had been cooled in an ice bath. The resulting dark red mixture was stirred for 15 more min at 0 °C, at which time a solution of *N*-(triisopropylsilyl)pyrrole (6.4 g, 29 mmol) in CH_2Cl_2 (15 mL) was added over 5 min. The reaction mixture was stirred for 30 min at 0 °C and then at room temperature for 1 h. After pouring the reaction mixture into 200 mL of ice–H_2O and workup, the black liquid was immediately chromatographed ($CHCl_3$) to give 6.7 g (<60%) of brown oil which according to ^1H NMR was still contaminated with unreacted 1-(triisopropylsilyl)pyrrole: ^1H NMR δ 7.47–7.31 (m), 7.25–7.14 (m), 6.71 (m), 2.86 (q, J = 7.4), 1.48–1.27 (m), 1.22 (t, J = 7.4 Hz), 1.08 (s). For ease of purification the mixture was subjected to blocking group removal: a solution of tetrabutylammonium fluoride trihydrate (5.3 g, 17 mmol) and the crude (triisopropylsilyl)-pyrrole derivative (6.5 g, 17 mmol) in THF (55 mL) was stirred for 1 h then diluted with diethyl ether (80 mL) and the mixture was washed twice with H_2O. After drying (Na_2SO_4), the volatiles were removed *in vacuo* and the crude product was chromatographed ($CHCl_3$) and recrystallized (EtOAc/hexane) to give **7** (0.9 g, 23% yield based on (triisopropylsilyl)pyrrole as an off-white solid: mp 100 °C; IR (KBr) 3225, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.05 (br s, 1H), 7.44–7.32 (m, 3H), 7.22 (m, 1H), 7.13 (m, 1H), 6.77 (m, 1H), 6.67 (td, J = 1.5, 2.8 Hz, 1H), 2.88 (q, J = 7.4 Hz, 2H), 1.22 (t, J = 7.4 Hz, 3H); MS [*m/z* (relative intensity)] 231 (M^+, 27), 202 (100). Anal. Calcd for $C_{13}H_{13}NOS$: C, 67.50; H, 5.67; N, 6.06. Found: C, 67.41; H, 5.48; N, 6.15.

3-[2-(Ethylsulfinyl)benzoyl]pyrrole (8). A solution of $NaIO_4$ (0.8 g, 3.9 mmol, 1.3 equiv) in H_2O (18 mL) was added all at once to a solution of **7** (0.7 g, 3 mmol) in MeOH (30 mL). After several minutes of stirring, some white solid had formed in the solution. After stirring for 2 h the reaction mixture was worked up to give a solid. Recrystallization (EtOAc) yielded **8** (0.4 g, 57%): mp 179–180 °C; IR (KBr): 3206, 1621, 1060 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.8 (br s, 1H), 8.08–8.04 (m, 1H), 7.89–7.80 (m, 2H), 7.71–7.63 (m, 1H), 7.39 (m, 1H), 6.96 (m, 1H), 6.55 (m, 1H), 2.98 (dm, 2H), 1.14 (t, J = 7.4 Hz, 3H); MS [*m/z* (relative intensity)]: 247 (M^+, 4), 94 (100). Anal. Calcd for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66. Found: C, 63.25; H, 5.44; N, 5.60.

Cyclization of 4. Refluxing *p*-Xylene. A suspension of **4** (1 g, 4 mmol) in *p*-xylene (40 mL) was heated to reflux in a flask covered with foil to exclude light. The solid dissolved to

give a clear yellow solution. After refluxing for 6 h, the volatiles were removed in vacuo to give a very dark solid. Chromatography gave 140 mg (17%) of **12** and 400 mg (51%) of **11**.

1*H*,9*H*-[1]Benzothiopyrano[3,2-*b*]pyrrol-9-one (11). Recrystallization from EtOH gave pink crystals (mp 189–192 °C): IR (KBr) 3167, 1624 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.52 (m, 1H), 7.88–7.84 (m, 1H), 7.71–7.54 (m, 3H, containing d at 7.6, J = 2.8 Hz), 6.64 (d, J = 2.8 Hz, 1H); MS [*m/z* (relative intensity)] 201 (M^+, 100). Anal. Calcd for $C_{11}H_7NOS$: C, 65.65; H, 3.51; N, 6.96. Found: C, 65.58; H, 3.67; N, 6.84.

DMAP in Refluxing Toluene. A mixture of DMAP (0.12 g, 1 mmol), **4** (2.5 g, 10.1 mmol), and toluene (115 mL) was refluxed in a foil-covered flask for 29 h, at which time the solvent was removed *in vacuo*. The resulting crude solid was chromatographed ($CHCl_3$) to give 110 mg of **12** (20% based on recovered starting material), 510 mg of **13** (46% based on recovered starting material), and 1.10 g of unreacted starting material. A small amount of **11** was detected by TLC but was not isolated.

Pyrrolo[1,2-*b*][1,2]benzothiazin-10-one (13). Compound **13** can be recrystallized (EtOAc/hexane) to give an analytically pure yellow-orange solid (mp 100–102 °C): IR (KBr) 1605 cm^{-1}; ^1H NMR δ 8.50 (dd, J = 1.6, 8.0 Hz, 1H), 7.60–7.36 (m, 3H, containing dd at 7.48, J = 1.5, 4.2 Hz, 1H), 7.27–7.23 (m, 1H), 7.15 (dd, J = 1.5, 2.6 Hz, 1H), 6.60 (dd, J = 2.6, 4.2 Hz, 1H); ^{13}C NMR δ 172.3, 135.3, 132.8, 131.7, 129.5, 127.4, 126.5, 125.9, 121.0, 116.4, 112.8; MS [*m/z* (relative intensity)] 201 (M^+, 100). Anal. Calcd for $C_{11}H_7NOS$: C, 65.65; H, 3.51; N, 6.96. Found: C, 65.61; H, 3.56; N, 6.91.

Et_3N in Refluxing Toluene. Triethylamine (0.017 mL, 0.12 mmol), **4** (0.3 g, 1.2 mmol), and toluene (15 mL) were combined and refluxed with stirring for 24 h. After removal of volatiles *in vacuo*, a light brown oil was obtained which solidified to a dark gold solid. Chromatography (1:1 $CHCl_3$/hexane) yielded 24 mg (15% based on recovered starting material) of **12**, 114 mg (69% based on recovered starting material) of **13**, and 115 mg of light brown solid which proved by NMR to be a mixture of starting material and **11**. By integration, the approximate amounts for the mixture were 93 mg of **4** and 22 mg (13% based on recovered starting material) of **11**.

Cyclization of 6. Compound **6** (370 mg, 142 mmol) was refluxed in *p*-xylene for 9 h. Over time, the reaction mixture changed from clear and colorless to opaque, dark brown. Chromatography on SiO_2 ($CHCl_3$) gave **9** (160 mg, 52%) and then **10** (8.1 mg, 3%); both compounds were compared spectroscopically and chromatographically with authentic samples.[13] Longer reflux times caused a gradual disappearance of the higher R_f spot (**9**) with a corresponding increase in intensity of the lower R_f spot (**10**).

Cyclization of 8. 1*H*,4*H*-[1]Benzothiopyrano[2,3-*b*]-pyrrol-4-one (17). A mixture of **8** (1.1 g, 4.2 mmol) and *p*-xylene (50 mL) was refluxed for 5.5 h. After discontinuing reflux, the hot orange solution was decanted away from a black residue on the flask walls. After removing the volatiles *in vacuo*, an orange solid (400 mg), the title compound, was obtained. Recrystallization of a small amount of the solid from MeOH yielded orange crystals (mp 202–208 °C dec), which according to ^1H NMR were contaminated with a little starting material: IR (KBr) 1605 cm^{-1}; ^1H NMR (acetone-d_6) δ 11.3 (br s, 1H), 8.64 (m, 1H), 7.81–7.52 (m, 3H), 7.28 (d, J = 3.2 Hz, 1H), 6.93 (d, J = 3.2 Hz, 1H); MS [*m/z* (relative intensity)]: 201 (M^+, 100). The structure of this compound was established by comparison of the methylation product with authentic samples of compounds **9** and **10**:[13] Compound **15** (17 mg, 0.08 mmol), Bu_4NHSO_4 (1.4 mg, 5 mol %), and dimethyl sulfate (0.012 mL, 0.12 mmol) were added to a mixture of 0.6 mL of benzene and 0.5 mL of 50% aqueous NaOH. After stirring 45 min, the mixture was worked up to give a dark red oil which, after chromatography ($CHCl_3$), gave 9 mg (52%) of **10** as an orange yellow solid.

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