Intramolecular Capture of Pummerer Rearrangement Intermediates. I. Synthesis of Pyrrolo[2,1-*c*][1,4]benzothiazines

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Treatment of 1-(2-alkylsulfinylphenyl)pyrroles with trifluoroacetic acid in refluxing toluene gives 4-substituted pyrrolo[2,1-*c*][1,4]benzothiazines in good yield when the alkyl group bears an electron withdrawing substituent on the α-carbon. In the absence of such a group, starting material is recovered. The sulfoxides are prepared by oxidation (*m*CBPA) of the corresponding sulfide. The sulfides are prepared from 2-aminobenzenethiol either by *S*-alkylation followed by conversion to the pyrrole using 1,4-dimethoxytetrahydrofuran in glacial acetic acid or by *S*-alkylation of 1-(2-phenylmercapto)pyrrole followed by oxidation to the sulfoxide.

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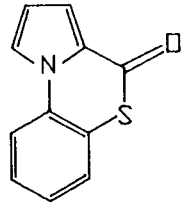
Thionium ions (-$^{+}$S=CH-), generated by treatment of sulfoxides with an acid or acylating agent (the Pummerer rearrangement) [1] or by other means [2] are useful synthetic intermediates. In addition to the traditional process in which α-chloro- or α-acetoxysulfides are formed [1], thionium ions react at carbon in a variety of other interesting reactions including the 'ene' reaction [3a], cationic polyolefin cyclizations [3b], Diels-Alder reactions [3c], intramolecular cyclization with carboxyl [4], phenolic [5], and similar nucleophiles, and they may act as the electrophilic species in aromatic substitution reactions with benzene derivatives [6-8] as well as heteroycles such as pyrrole, thiophene, and indole [9].



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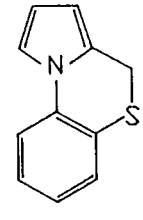

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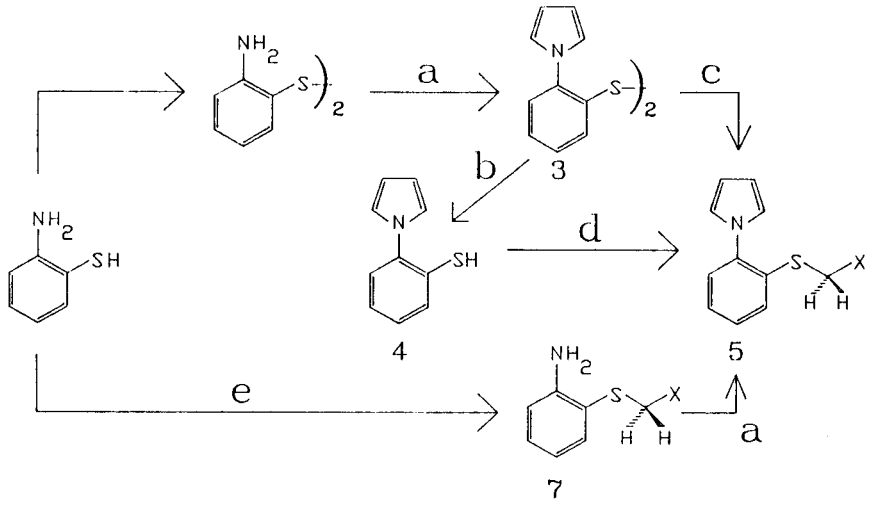
The work we report here utilizes this chemistry to prepare pyrrolo[2,1-*c*][1,4]benzothiazines **8** from sulfoxides **6** *via* the Pummerer rearrangement. Pyrrolo[2,1-*c*][1,4]benzothiazines constitute a little studied group of compounds as evidenced by the appearance in the literature of only two derivatives **1** and **2** [10,11]. The thiolactone **1** (precursor to **2** and potentially a useful precursor to 4-alkyl derivtives) is prepared in <20% overall yield from 2-aminobenzenethiol [10]. The alternative method we have developed leads directly to 4-substituted pyrrolo[2,1-*c*][1,4]benzothiazines and begins with the same starting material but is operationally simpler and proceeds in better overall yield than the reported procedure.

The requisite sulfoxides **6** were readily prepared from 2-aminobenzenethiol. Preparation of **4**, a logical intermediate, has been reported [10]. In our hands however, the reported procedure for the reduction of the disulfide **3** to **4** was cumbersome as was reduction with sodium borohydride or lithium aluminum hydride. The observation that **3** is more readily soluble in aromatic solvents than ethers or alcohols led to a more convenient procedure using sodium *bis*(2-methoxyethoxy)aluminum hydride in toluene (Vitride^{R}). Alkylation of **4** and oxidation of the derived sulfides **5** with *m*-chloroperbenzoic acid under standard conditions (see Experimental) gave the desired sulfoxides **6**.

Although solubility of the disulfide was a problem, sulfides **5** could also be prepared from **3** by *in situ* generation of the anion of **4** in ethanol/DMF by reduction with sodium borohydride followed by treatment with the appropriate alkyl halide in ethanol. The simplest procedure, however, involved first alkylating 2-aminobenzenethiol to an anilinosulfide **7** followed by pyrrole formation [12]. This procedure is not as general as routes which put the pyrrole group in place first due to the potential incompatibility of the free amino group in **7** with functionality present in the alkylating agent. As a comparison of these routes note that *N*-(2-cyanomethylthiophenyl)pyrrole **5E** is prepared in 39, 47, and 68 percent overall yield, respectively, from 2-aminobenzenethiol *via* **4**, *in situ* alkylation, and *via* **7E**.

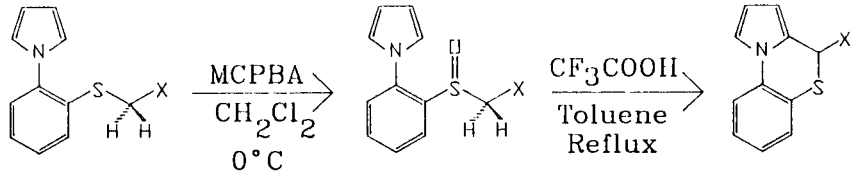
Pummerer rearrangement of **6** was conducted in refluxing toluene containing 2 equivalents of trifluoroacetic acid. Sulfoxides **6D-F** gave **8D-F** in 70-90% yield; under these conditions **6**A-C were recovered unchanged. *p*-Toluenesulfonic acid in refluxing toluene was also ineffective, causing decomposition of the sulfoxide without generating an isolable product. To date no other conditions tried have succeeded in producing any **8** from **6A-C**.

The course of the reaction was readily followed by tlc using van Erk reagent [13] to visualize the spots. The products were identified by spectroscopic means. The mass



A X=H B X=CH_3 C X=C_6H_5 D X=$CO_2C_2H_5$ E X=CN F X=COC_6H_5

a) 2,5-dimethoxytetrahydrofuran / CH_3COOH / Heat
b) $NaAl[OCH_2CH_2OCH_3]_2H_2$ / Toluene / Ice Bath
c) $NaBH_4$ / DMF / EtOH / RX d) RX / EtOH / KOH
e) Ref 12



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spectra showed a molecular ion at 18 mass units less than the corresponding sulfoxide indicating an overall loss of water had taken place. The products also showed a base peak at m/z 186 representing loss of the 4-substituent from the parent system. In the nmr spectra, the pyrrole hydrogens had shifted (1H into aromatic envelope and 2H into a symmetrical multiplet at δ 6.0-6.4) and H-4 of the cyclized product appeared in the range δ 4.75-5.55.

The mechanism proposed for this process, shown in Figure 1, involves formation of the thionium ion **9** from a

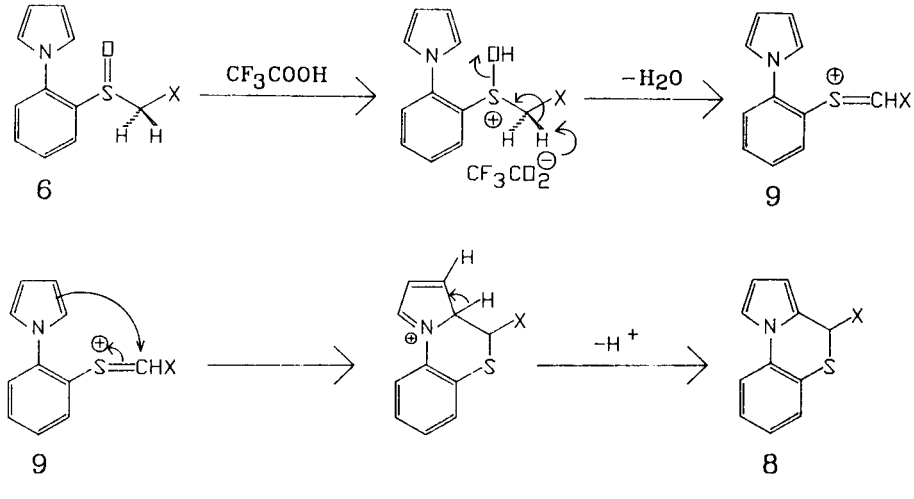

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Figure 1

Table

Physical and Spectral Data for 1-(2-alkylsulfinylphenyl)pyrroles

Compound 6	Alkyl Group	Yield (%)	mp (°C)	Partial NMR (δ)	IR (cm^{-1})	MS [m/z (Relative Intensity)]	Elemental Analysis Calcd/Fnd		
A	CH_3	95	102-102.5	2.20 (s, 3H), 6.39 (t, 2H, J = 2.0 Hz), 6.88 (t,2H, J = 2.0 Hz)	1055	205 (M^+, 17%), 190 (12), 174 (14), 162 (69) 158 (88), 148 (31), 130 (100), 109 (66)	64.36 64.44	5.40 5.51	6.82 6.72
B	CH_2CH_3	80	76-77.5	0.95 (t, 3H, J = 7.4 Hz), 1.5-2.7 (m, 2H), 6.40 (t, 2H, J = 2.6 Hz), 6.91 (t, 2H, J = 2.6 Hz)	1040	219 (M^+, 96), 190 (80) 174 (62), 162 (100), 158 (46), 148 (60), 130 (67), 109 (77)	65.72 65.61	5.97 5.83	6.39 6.34
C	$CH_2C_6H_5$	88	128-129	3.21 (.5 of AB q, 1H, J = 13.0 Hz), 3.53 (.5 of AB q, 1H, J = 13.0 Hz), 6.48 (t, 2H, J = 2 Hz)	1035	281 (M^+, 7), 264 (16) 173 (8), 148 (10), 109 (14), 91 (100)	72.57 72.38	5.37 5.41	4.98 4.86
D	CH_2CN	71	109-110	2.35 (.5 of AB q, 1H, J = 16.4 Hz), 3.43 (.5 of AB q, 1H, J = 16.4 Hz), 6.42 (t, 2H, J = 2.2 Hz) 6.90 (t, 2H, J = 2.2 Hz)	2235, 1060	230 (M^+, 2), 190 (15) 173 (5), 162 (17), 148 (23), 109 (27), 40 (100)	62.59 62.68	4.38 4.48	12.16 12.06
E	$CH_2CO_2C_2H_5$	88	66-67	1.1 (t, 3H, J = 7.0 Hz) 2.78 (.5 of AB q, 1H, J = 13.5 Hz) 3.18 (.5 of AB q, 1H, J = 13.5 Hz) 4.03 (q, 2H, J = 7.0 Hz) 6.38 (t, 2H, J = 2 Hz) 6.90 (t, 2H, J = 2 Hz)	1730, 1040	277 (M^+, 2) 190 (5) 175 (7), 162 (13) 148 (13), 109 (22) 42 (100)	60.63 60.62	5.45 5.39	5.05 5.03
F	COC_6H_5	98	86-87	3.47 (.5 of AB q, 1H, J = 14.0 Hz), 3.83 (.5 of AB q, 1H, J = 14.0 Hz) 6.40 (t, 2H, J = 2.2 Hz) 6.97 (t, 2H, J = 2.2 Hz)	1680, 1060	309 (M^+, 8), 204 (28), 190 (11), 173 (70), 162 (35), 148 (41), 109 (37), 105 (100)	69.88 69.72	4.89 4.87	4.53 4.54

protonated sulfoxide followed by intramolecular capture to **8**. The lack of reactivity of **6A-C** relative to **6D-F** may be due to the absence of an electron withdrawing group in the former. Apparently without the acidifying electron withdrawing group on the carbon alpha to the sulfoxide group, trifluoroacetate ion is not basic enough to generate the thionium ion.

We continue to investigate this ring system using the functionalizable 4-substituents in **6D-F** to prepare derivatives of medicinal interest and searching for conditions that will induce cyclization of "unactivated" sulfoxides.

EXPERIMENTAL

All melting points and boiling points are uncorrected. Infrared (ir) spectra were determined on a Perkin-Elmer 735B grating infrared spectrometer and nuclear magnetic resonance (nmr) spectra were recorded in chloroform-d solution on Varian EM-360 or XL-200 spectrometers. Chemical shifts are reported as δ values relative to tetramethylsilane (TMS).

1-(2-Mercaptophenyl)pyrrole (**4**).

A stirred, nitrogen blanketed solution of the pyrrolodisulfide **3** (40.0 g, 0.114 mole) in toluene (800 ml) was cooled on an ice bath while sodium *bis*(2-methoxyethoxy)aluminum hydride (Red-Al purchased from Aldrich Chemical Co., 87 ml of 1*M* solution in toluene diluted with an additional 200 ml of toluene, 0.295 mole) was added dropwise over 80 minutes. After warming to room temperature the mixture was refluxed for 1.75 hours. The mixture was again cooled in an ice bath and acidified (*p*H 2) with 3 *N* hydrochloric acid. The organic layer was separated, dried (sodium sulfate), and the solvent evaporated *in vacuo* to give a dark brown oil. Vacuum distillation gave 26.9 g (67%) of a colorless oil, bp 119-121/1.0 Torr (lit bp 90°/0.1 Torr [9]); ^1H nmr: 3.28 (s, 1H), 6.30 (t, 2H, J = 2.5 Hz), 6.73 (t, 2H, J = 2.5 Hz), 6.97-7.38 (m, 4H); ir (neat): 2560 (-SH stretch) cm^{-1}.

Reduction/Alkylation of *bis*(2-Pyrrolophenyl)disulfide (**3**).

Under a blanket of nitrogen, disulfide **3** (10.4 g, 0.030 mole) in DMF (60 ml) was added to absolute ethanol (200 ml) and the resulting brown suspension was heated to reflux. Sodium borohydride (2.3 g, 0.06 mole) was then added carefully, in portions, through the top of the condenser over a period of 20 minutes. When the addition was complete, the mixture was allowed to cool to room temperature and ethyl chloroacetate (7.4 g, 0.061 mole) in ethanol (100 ml) was then added dropwise over 1 hour. After stirring overnight at room temperature the reaction mixture

was reduced to one-half of the original volume *in vacuo*, then poured into an equal volume of water, and extracted twice with 100 ml portions of ether. Drying (magnesium sulfate) and evaporation of the solvent *in vacuo* gave **5D** as a brown oil (11.3 g, 72%). Vacuum distillation gave an analytical sample as a slightly pinkish oil, bp 160-163°C/0.7 Torr (lit [14]: 125°/0.1 Torr); ^{1}H nmr: 1.15 (t, 3H, J = 7.0 Hz), 3.29 (s, 2H), 4.10 (q, 2H, J = 7.0 Hz), 6.34 (t, 2H, J = 2.5 Hz), 6.92 (t, 2H, J = 2.5 Hz), 7.30 (d, 3H, J = 4.0 Hz), 7.37-7.67 (m, 1H); ir (neat): 1735 cm^{-1}; ms: [m/z (relative intensity)]: 261 (M$^+$, 19), 188 (19), 174 (100), 173 (36), 154 (16), 115 (10).

Anal. Calcd. for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.40; H, 5,85; N, 5.41.

The cyano derivative **5E** was prepared similarly in 77% yield.

Alkylation of 1-(2-Mercaptophenyl)pyrrole (**4**).

Under a blanket of nitrogen, potassium hydroxide solution (0.0285 mole, 0.3 *M* in 80% ethanol) was added dropwise to a stirred solution of **4** (0.0285 mole) in 250 ml of absolute ethanol. After stirring an additional 20 minutes, the alkyl halide (0.0286 mole) in absolute ethanol (250 ml) was added dropwise. After stirring overnight, the reaction mixture was filtered and the filtrate reduced to one half the original volume *in vacuo*. An equal volume of water was added and the murky solution extracted with chloroform (2 x 200 ml). The combined organic layers were washed with water then 5% aqueous potassium hydroxide, and dried over sodium sulfate. Evaporation of the volatiles *in vacuo* gave the crude product which was purified by either distillation or crystallization. Yields and physical data for the products are as follows:

5, X = C_6H_5.

This compound was obtained in 89% yield, mp 86-87°C; ^{1}H nmr: 3.76 (s, 2H), 6.30 (t, 2H, J = 2.5 Hz), 6.83 (t, 2H, J = 2.5 Hz), 7.20 (m, 9H); ms: [m/z (relative intensity)]: 265 (M$^+$, 13), 175 (14), 174 (100), 173 (30), 91 (45), 65 (15).

Anal. Calcd. for $C_{17}H_{15}NS$: C, 76.94; H, 5.70; N, 5.28. Found: C, 76.93; H, 5.76; N, 5.24.

5, X = CN.

This compound was obtained in 88% yield, bp 160-162°C/0.8 Torr (lit [14]: 146°C/0.15 Torr); ^{1}H nmr: 3.03 (s, 2H), 6.31 (t, 2H, J = 2.2 Hz), 6.85 (t, 2H, J = 2.2 Hz), 7.13-7.70 (m, 4H); ir (neat): 2225 cm^{-1}; ms: [m/z (relative intensity)]: 214 (M$^+$, 42), 174 (100), 51 (15), 50 (11), 45 (23).

Anal. Calcd. for $C_{12}H_{10}N_2S$: C, 67.26; H, 4.701; N, 13.07. Found: C, 67.33; H, 4.76; N, 12.99.

5, X = COC_6H_5.

This compound was obtained in 89% yield as an oily semisolid; ^{1}H nmr: 3.85 (s, 2H), 6.28 (t, 2H, J = 2.2 Hz), 6.87 (t, 2H, J = 2.2 Hz), 7.00-7.67 (m, 8H), 7.67-8.00 (m, 1H); ir (neat): 1670 cm^{-1}; ms: [m/z (relative intensity)] 293 (M$^+$, 58), 276 (11), 275 (43), 274 (23), 243 (11), 188 (91), 186 (13), 174 (82), 155 (29), 154 (24), 149 (13), 115 (12), 105 (100).

Satisfactory combustion analysis could not be obtained for this compound. It was used directly to prepare the crystalline sulfoxide.

N-(2-Methylthiophenyl)pyrrole (**5a**).

Dimethyl sulfate (3.60 g, 0.0285 mole) was added under nitrogen, to a stirred mixture of **4** (5 g, 0.0285 mole) and anhydrous potassium carbonate (4.33 g, 0.031 mole) in 25 ml of dry acetone. The gel resulting from this addition was broken up and the mixture refluxed for 17 hours during which time the color gradually turned deep orange. The cooled mixture was filtered through a pad of florisil, the florisil rinsed with acetone, and the combined filtrate evaporated to dryness *in vacuo*. The residue was taken into chloroform and washed with 5% aqueous potassium hydroxide dried over sodium sulfate and the solvent removed *in vacuo* to give 5.6 g (86%) of a brown oil. Distillation gave an analytical sample (pale yellow oil, bp 115-117/0.8 Torr); ^{1}H nmr: 2.18 (s, 3H), 6.29 (t, 2H, J = 2.2 Hz), 6.83 (t, 2H, J = 2.2 Hz), 7.03-7.50 (m, 4H); ir (neat): 2920, 1500, 1425, 1335, 1080, 760, 730 cm^{-1}; ms: [m/z (relative intensity)] 189 (M$^+$, 79), 188 (M-1, 22), 174 (100), 156 (10), 147 (9), 135 (9), 116 (9), 115 (18).

Anal. Calcd. for $C_{11}H_{11}NS$: C, 69.80; H, 5.86; N, 7.40. Found: C, 69.92; H, 5.96; N, 7.39.

General Procedure for the Preparation of Sulfoxides **6**.

To a stirred solution of the sulfide **5** (0.020 mole) in dichloromethane (60 ml) at 0° was added dropwise *m*-CPBA (assumed to be 85%, 0.021 mole) in cold dichloromethane (about 100 ml) over about 1 hour. After an additional 1 hour at 0° the reaction mixture was stored in the freezer overnight (-25°). The mixture was then filtered and the filter cake rinsed with dichloromethane. The filtrate was washed with 5% aqueous potassium carbonate (2 x 250 ml), dried over sodium sulfate, and the solvent evaporated *in vacuo* to give the product as a brown semisolid. The crude product was recrystallized from either hexanes or ethanol to give the pure sulfoxides listed in the Table.

Preparation of Pyrrolo[2,1-*c*][1,4]benzothiazines (**8**).

To a solution of sulfoxide **6** (2.0 mmoles) in 25 ml of toluene was added, under nitrogen, trifluoroacetic acid (4.0 mmoles). As the addition proceeded the solution became a deep yellow color. When the addition was complete (about 15 minutes) the solution was refluxed for 3 hours during which time the reaction mixture became deep red. Evaporation of volatiles and chromatography of the residue on alumina (1 x 8'' column) eluted with 1:1 hexanes/benzene gave the following derivatives:

8, X = CN.

This compound was obtained in 76% yield, mp 101°; ir (crystallized melt): 2240 cm^{-1}; nmr (deuteriochloroform): 7.67-6.88 (m, 5H), 6.25 (m, 2H), 4.93 (s, 1H); ms: [m/z (relative intensity)] 212 (M$^+$, 41), 186 (100).

Anal. Calcd. for $C_{11}H_8N_2S$: C, 67.90; H, 3.80; N, 13.20. Found: C, 67.70; H, 3.91; N, 13.02.

8, X = CO_2C_2H.

This compound was obtained in 71% yield bp 140-150° (bath temperature)/0.5 Torr; ir (neat): 1735 cm^{-1}; nmr (deuteriochloroform): 7.67-7.00 (m, 5H), 6.50-6.00 (m, 2H), 4.75 (s, 1H), 4.03 (q, 2H, J = 7.0 Hz), 1.00 (t, 3H, 7.0 Hz); ms: [m/z (relative intensity)] 259 (M$^+$, 11), 186 (100).

Anal. Calcd. for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40. Found: C, 64.97; H, 4.90; N, 5.46.

8, X = COC_6H_5.

This compound was obtained in a yield of 86%, mp 106-107°; ir (crystallized melt): 1660 cm^{-1}; 8.03-7.67 (m, 1H), 7.54-6.83 (m, 4H), 6.30 (t, 1H, J = 2.5 Hz), 6.02 (m, 1H), 5.55 (s, 1H); ms: [m/z (relative intensity)] 291 (M$^+$, 4), 186 (100).

Anal. Calcd. for $C_{18}H_{13}NOS$: C, 74.20; H, 4.50; N, 4.81. Found: C, 74.08; H, 4.50; N, 4.81.

Acknowledgement.

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