Nucleophilic Attack at Sulfoxide: The Methanethiol-Mediated Cleavage of a Thiane 1-Oxide

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Nucleophilic attack on tricoordinate sulfur has been reported in a large number of reactions, including sulfoxide racemization in acidic solution,[1] the Andersen procedure for the synthesis of chiral sulfoxides,[2] and the asymmetric synthesis of sulfinamides.[3] In the latter two cases, the reactions were reported to undergo a Walden inversion at the reaction center, presumably via an incipient σ-sulfurane intermediate.[4]

In the majority of these examples of nucleophilic attack at tricoordinate sulfur, the leaving group is a suitably activated heteroatom.[1] We now report a novel example of a nucleophilic substitution wherein the leaving group is a stabilized carbanion,[5] an enolate of a dithioate ester, and the nucleophile is methanethiolate.

Recently, Brown *et al.*[6] reported that during the synthesis of aprikalim (**2**), a member of a class of pharmacologically active agents classified as potassium channel openers,[7] exposure of tetrahydro-*S*-methyl-2-(3-pyridinyl)-2*H*-thiopyran-2-carbodithioate 1-oxide (**1**) to aqueous methylamine produced **2** in 40% yield as the sole isolated product. Upon repeating this experimental protocol, we discovered that in addition to **2**, a second product, the novel disulfide *N*-methyl-α-[4-(methyldithio)-butyl]-3-pyridineethanethioamide (**3**) was formed. We believe that **3** was formed via a sequence of reactions including a methanethiol-mediated ring fragmentation of the thiane oxide present in **1.** In this report, the identification and *de novo* synthesis of **3** together with studies supporting our mechanistic hypothesis are described.

Chemistry

Identification of 3. Reaction of **1** with aqueous methylamine resulted in the isolation of aprikalim (**2**, 57%) and a second, less polar product **3** (26%). Analysis of the ^{1}H NMR spectrum of **3** suggested the retention of the pyridine moiety, formation of the distinct thioamide (doublet at δ 3.13 and NH at δ 8.35), the presence of a heteroatom bonded methyl (singlet at δ 2.37), and a downfield methine coupled to a methylene (triplet at δ 3.70). The latter two signals were not present in the spectrum of **2**. The coupling pattern derived from 2D ^{1}H NMR experiments indicated five contiguous carbon atoms, four of which were methylenes.

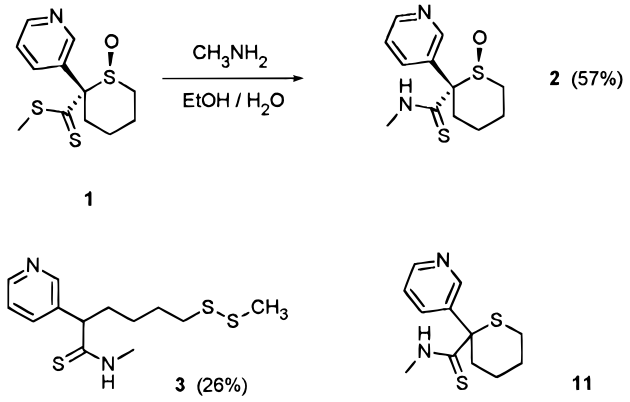

Figure 1.

Mass spectral analysis and combustion analysis suggested the formula $C_{13}H_{20}N_2S_3$, which differed from that of **2** by the addition of CH_4S and loss of oxygen. This, as well as other data from the various spectra, suggested the structure depicted in Figure 1. Attempts to obtain a crystal suitable for X-ray analysis were unsuccessful, so an independent synthesis of **3** was developed.

Synthesis of 3. Retrosynthetically, **3** was dissected into ethyl 3-pyridylacetate (**4**) and a suitably functionalized alkylating reagent. The potential instability of the disulfide to subsequent chemistry prompted the decision to install it late in the synthesis. This suggested that 1-iodo-4-(*tert*-butyldimethylsiloxy)butane is the initial electrophile.[8] The synthetic sequence that was developed is shown in Scheme 1. Of particular interest were the conditions to prepare the thioamide **8**. Sonication with phosphorus pentasulfide in THF proved to be more efficient than classically used procedures, such as Lawesson's reagent or phosphorus pentasulfide in pyridine, affording **8** in 73% yield.[9] The final conversion was accomplished in a one-pot procedure by the synthesis of the sodium salt of the thiol (from **10b**), followed by methyl methanethiosulfonate to afford **3** in 35% yield.[10]

This unambiguous linear synthetic route provided **3**, which was identical by (by TLC, IR, MS, ^{1}H NMR, and ^{13}C NMR) to the material isolated from the initial reaction.

Mechanistic Studies. A minimum of two mechanistic paths appeared to be involved: the direct displacement of methanethiol by methylamine to produce **2** (Figure 1) and an alternative pathway leading to **3** (Figure 2). With the identity of **3** verified by independent synthesis, a series of experiments were designed to ascertain the mechanistic course of the reaction(s) leading to **3**. The structural reorganization observed in the formation of **3** obviously involved two general reactions: a ring fragmentation and a net reduction at sulfur, in addition to the amide formation which released methanethiol. The methanethiol produced in the formation of **2**, which under the reaction conditions could exist in

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(3) Nudelman, A.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 3869. Williams, T. R.; Nudelman, A.; Booms, R. E.; Cram, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 4684.
(4) Reference 1, p 157.
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(7) Gopalakrishnan, M.; Janie, R. R.; Triggle, D. J. *Drug Dev. Res.* **1993**, *28*, 95. Empfield, J. R.; Russell, K. *Annu. Reports Med. Chem.* **1995**, *30*, 81. Lawson, K. *Pharmcol. Ther.* **1996**, *70*, 39.
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(9) Raucher, S.; Klein, P. *J. Org. Chem.* **1981**, *46*, 3558.
(10) Smith, D. J.; Maggio, E. T.; Kenyon, G. L. *Biochemistry* **1975**, *14*, 766.

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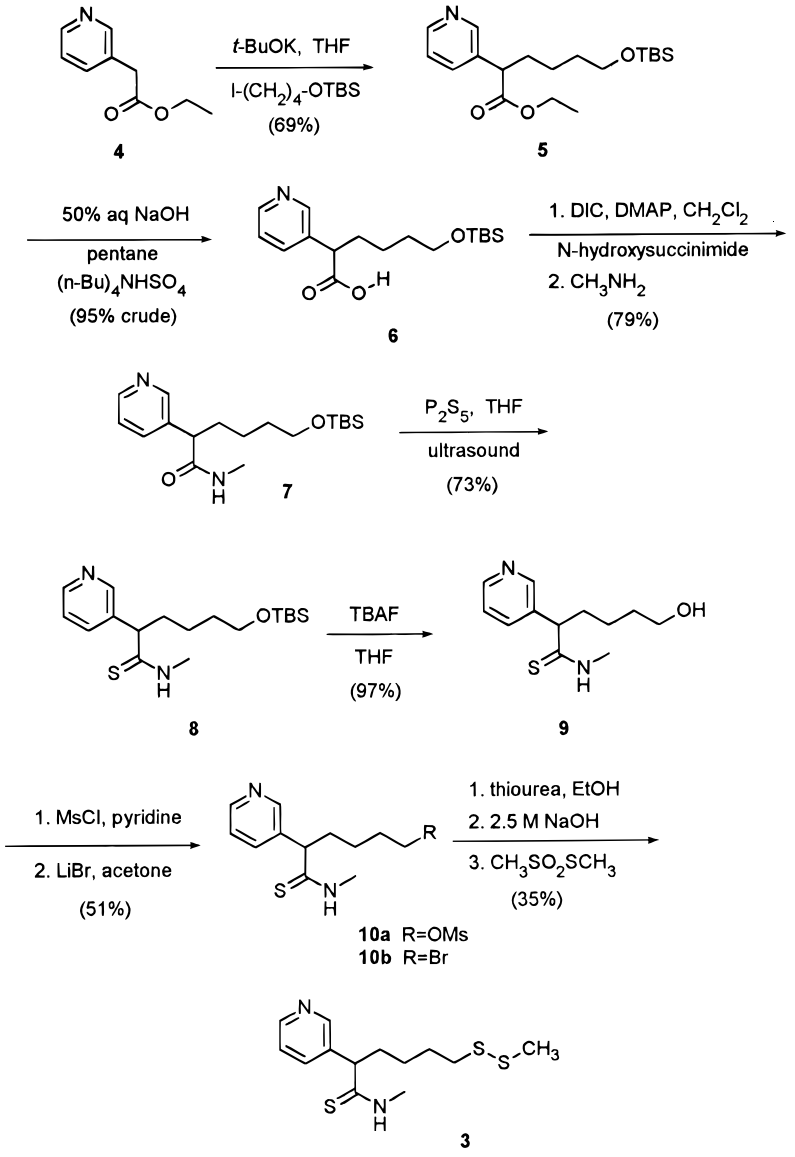
Scheme 1



equilibrium with methylammonium methanethiolate,[11] was believed to be the primary participant in the reactions leading to **3** (*vide infra*). Several possible reaction pathways were envisioned for the formation of **3**. The first involved displacement of methanethiol to form **2**, followed by reduction to the sulfide and subsequent attack at sulfur to cleave the thiane ring (in either order, amide/reduction → cleavage). A second possibility involved the initial reduction to the sulfide and then amide formation/ring cleavage (in either order, reduction/amide → cleavage). Alternatively, attack directly on the sulfoxide was followed by reduction/disulfide formation and amide formation (again, in either order, cleavage/reduction → amide). In all cases, the reaction sequences leading to **3** relied on thioamide formation (in any pathway) to maintain the source of methanethiol necessary for the subsequent chemistry.

The original reaction was performed in ethanol (95%) with excess aqueous methylamine at room temperature over a period of 3−5 h. Subsequent experimental runs established that the reaction was complete within 30 min and that the product ratio did not change with time. Treatment of both **2** and its reduced counterpart **11**[6] (Figure 1) with a 10-fold excess of sodium methanethiolate in 95% ethanol overnight at room temperature, or in mixtures of sodium methanethiolate and aqueous methylamine in ethanol, afforded only starting material. The stability of **2** to the reaction conditions, as well as to excess sodium methanethiolate, eliminated its consideration as an intermediate. Methanethiol did not appear to function as a reducing reagent under these conditions.[12] The stability of **11** to excess sodium methanethiolate eliminated cyclic thianethioamides as intermediates leading to **3**. Thus, ring fragmentation occurred prior to thioamide formation.

To determine the oxidation state of the sulfur at which the cleavage occurred, **1** and **12**[6] were synthesized (Scheme 2) and allowed to react independently with 3 equiv of sodium methanethiolate in ethanol. In the case of **1**, three products were isolated in the 30 min experiment. The sulfide **12** was formed in low yield (3%), presumably via reduction by methanethiol. The major

(11) Methanethiol pK_a 10.3; Methylamine pK_a 10.6; see: March, J. In *Advanced Organic Chemistry; Reactions, Mechanism, and Structure*, 4th ed.; Wiley: New York, New York, 1992, p 248 and references cited therein.

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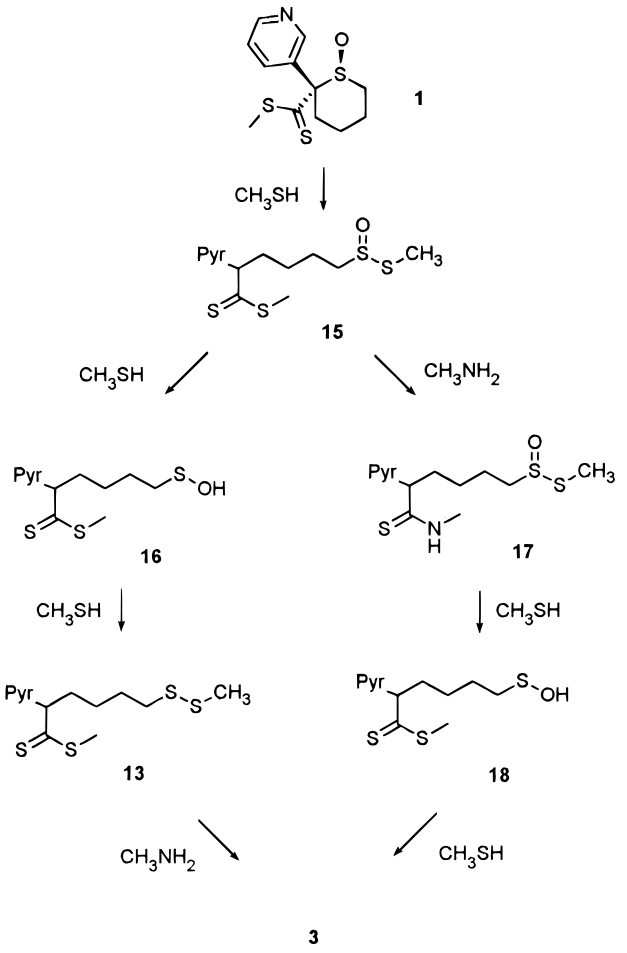
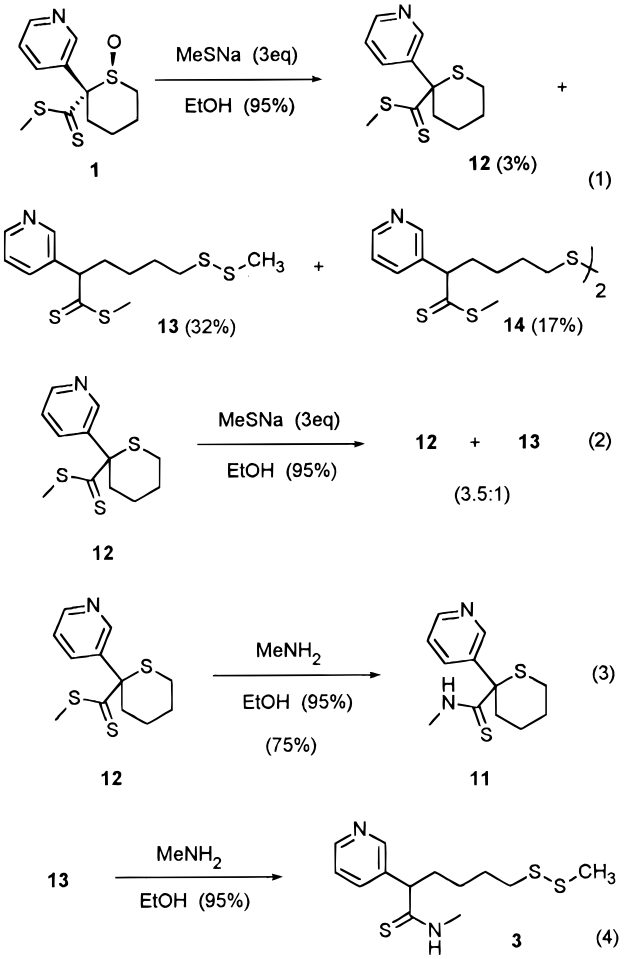


Figure 2. Proposed mechanism for the formation of **3**.

products **13** (32%) and **14** (17%) were formed by nucleophilic attack on sulfur. Reaction of **12** for 3 h under identical conditions provided only **12** and **13** in a 3.5:1 ratio. These results strongly implied that attack on the sulfoxide sulfur was the initial event leading to **3**, but did not discount the intermediacy of **12**. Submission of **12** to the original reaction conditions resulted in only **11** and no ring fragmented products, ruling out **12** as an intermediate in the reaction pathway. However, an additional experiment confirmed the potential intermediacy of **13** (Scheme 2). Reaction of **13** with aqueous methylamine in ethanol produced *only* **3**.

Scheme 2



Discussion

The unexpected observation of a second product in the reaction of **1** with aqueous methylamine resulted in the discovery of a reaction in which methanethiolate attacked the sulfoxide sulfur of **1** and produced the novel disulfide **3**. The identity of **3** was confirmed through an independent, unambiguous synthetic route. A series of related experiments has resulted in the refined mechanism for the formation of **3** which is proposed in Figure 2.

The sulfur in the thiane 1-oxide ring of **1** is attacked by methanethiol leading to the thiosulfinate **15**. This occurs only with **1** prior to thioamide formation; **2** is inert to further transformations. A possible explanation for the differences observed in the reactivity of the thioamide and carbodithioate **13** may be related to the greater degree of atropisomerism observed in thioamides.[13] This increase in the double bond character in the nitrogen–carbon bond may prohibit or reduce suitable resonance stabilization of the incipient anion formed α to the thiocarbonyl, which is consistent with the stabilization of this anion being the driving force for this fragmentation.[5]

The thiosulfinate then reacts with a second molecule of methanethiol to afford one molecule of dimethyl disulfide and the sulfenic acid **16.** The sulfenic acid then undergoes attack at sulfur to form the unsymmetrical disulfide **13** and a molecule of water. The latter sequence, **15** → **16** → **13**, is consistent with the literature reports of the reaction of thiosulfinates with thiols to produce disulfides via the intermediacy of sulfenic acids.[14] Finally, the dithioester **13** is converted to the thioamide **3** via displacement with methylamine. Alternatively, the sequence of **17** → **18** → **3** may occur. The current experimental evidence does not allow the differentiation between these two pathways, and indeed both may be operable. The stoichiometry of this reaction mechanism, 3 mol of methanethiol per mol of sulfoxide, suggests the maximum yield of **3** to be 33%. Experimentally, a yield of 26% was observed.

In summary, a novel reaction involving a methanethiol-mediated nucleophilic attack at tricoordinate sulfur has been reported which has resulted in the

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synthesis of the disulfide **3**. Mechanistic evidence has been presented that the driving force for this reaction is resonance stabilization of the incipient anion formed α to the carbodithioate moiety of **1**. Further extension of this work to the synthesis of unsymmetrical disulfides and related ring fragmentation reactions will be reported in due course.

Experimental Section

High-resolution mass spectra, infrared spectra, ultraviolet spectra, and combustion analyses were obtained by the Structural, Analytical and Medicinal Chemistry Unit of Pharmacia & Upjohn. ^{1}H-NMR spectra were recorded at 300 MHz and ^{13}C spectra at 75 MHz. Chemical shifts are reported as δ units relative to TMS.

Thin-layer chromatography was conducted with E. Merck Kieselgel 60 F_{254} 0.25 mm glass plates. Column chromatography was performed with E. Merck silica gel (230−400 mesh). All solvents for chromatography were Burdick and Jackson or Fisher Reagent grade. All nonaqueous reactions were carried out under a nitrogen atmosphere unless otherwise described. Extractions were followed by the combination of organics, drying with anhydrous Na_2SO_4, and concentration *in vacuo*. Melting points are uncorrected. Compounds **1**, **11** and **12** were synthesized as described by Brown *et al*.[6]

Tetrahydro-*N*-methyl-2-(3-pyridinyl)-2*H*-thiopyran-2-carbothioamide 1-Oxide (2) and *N*-Methyl-α-[4-(methyldithio)butyl]-3-pyridineethanethioamide (3). To a well-stirred solution of **1** (105 mg, 0.35 mmol) in ethanol (8.0 mL) was added a solution of 40% aqueous methylamine (0.5 mL, 6.5 mmol) in ethanol (0.8 mL). The reaction mixture was stirred for 3 h, and then an additional aliquot of aqueous methylamine (0.25 mL, 3.3 mmol) in ethanol (0.4 mL) was added. The solution was stirred an additional 2 h, concentrated, and diluted with acetonitrile. The resulting precipitate was collected to afford 21 mg of **2** (29%). The filtrate was concentrated and chromatographed (10% MeOH/ethyl acetate) to afford an additional 28 mg (28%) of **2** and 29 mg (26%) of **3**.

2: IR (mull) cm^{-1} 3186, 1560, 1445, 1037; ^{1}H NMR ($CDCl_3$, δ) 1.49−1.54 (m, 1H), 1.63−1.68 (m, 2H), 2.08−2.12 (m, 1H), 2.27−2.32 (m, 1H), 2.68 (ddd, J = 2.9, 11.6, 14.7 Hz, 1H), 2.96 (dddd, J = 1.5, 3.8, 3.8, 13.7 Hz, 1H), 3.01 (d, J = 4.80 Hz, 3H), 3.78 (ddd, J = 3.9, 12.6, 14.0 Hz, 1H), 7.29 (ddd, J = 1.1, 4.8, 8.3 Hz, 1H), 8.11 (ddd, J = 1.6, 2.5, 8.3 Hz, 1H), 8.45 (dd, J = 1.6, 4.8 Hz, 1H), 8.50 (dd, J = 1.6, 2.5 Hz, 1H), 8.88 (bs, 1H); ^{13}C NMR ($CDCl_3$, ppm) 15.6, 21.0, 25.7, 32.6, 45.2, 70.2, 123.7, 134.4, 135.3, 148.0, 149.3, 200.4; MS (EI) *m*/*z* 177 (100), 268 (M^+ + 1, 91), 251 (21). Anal. Calcd for $C_{12}H_{16}N_2OS_2$: C, 53.70; H, 6.01; N, 10.44. Found: C, 53.48; H, 6.04; N, 10.36.

3: IR (mull) cm^{-1} 3188, 1592, 1581, 1427, 1381; ^{1}H NMR ($CDCl_3$, δ) 1.20−1.35 (m, 1H), 1.35−1.49 (m, 1H), 1.62−1.76 (m, 2H), 1.88 (m, 1H), 2.37 (s, 4H), 2.67 (t, J = 7.3 Hz, 2H), 3.13 (d, J = 4.7 Hz, 3H), 3.70 (t, J = 7.5 Hz, 1H), 7.30 (dd, J = 4.8, 8.0 Hz, 1H), 8.02 (dt, J = 1.9, 8.0 Hz, 1H), 8.35 (bs, 1H), 8.39 (d, J = 2.1 Hz, 1H), 8.49 (dd, J = 1.6, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm) 23.2, 26.2, 28.6, 32.9, 35.3, 37.5, 57.4, 123.7, 135.4, 137.1, 148.6, 149.0, 205.8; MS (FAB) *m*/*z* 301 (M^+ + 1, 100), 253 (47), 302 (25). Anal. Calcd for $C_{13}H_{20}N_2S_3$: C, 51.96; H, 6.71; N, 9.32. Found: C, 51.90; H, 6.76; N, 9.18.

Ethyl α-(4-(*tert*-butyldimethylsiloxy)butyl)-3-pyridineethanecarboxylate (5). To a well-stirred solution of potassium *tert*-butoxide (35 mL, 35.0 mmol, 1.0 M in THF) in anhydrous THF (30 mL) cooled to 0 °C was slowly added ethyl 3-pyridylacetate (**10**) (4.80 g, 29.1 mmol) followed by 1-((*tert*-butyldimethylsilyl)oxy)-4-iodobutane[7] (10.1 g, 32.0 mmol) as a solution in THF (30 mL). The solution was warmed to rt, stirred for 20 min, poured into water, and extracted with ethyl acetate. Chromatography (1:1 hexane/ethyl acetate) afforded 7.07 g (69%) of **5** as a yellow oil: IR (film) cm^{-1} 2953, 1736, 1575; ^{1}H NMR ($CDCl_3$, δ) 0.0 (s, 6H), 0.85 (s, 9H), 1.20 (t, J = 9.0 Hz, 3H), 7.24 (dd, J = 4.8, 7.8 Hz, 1H), 7.67 (dt, J = 2.0, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm) 13.9, 18.1, 20.2, 25.7, 33.0, 34.3, 52.5, 60.7, 62.5, 122.8, 134.1, 138.0, 147.6, 148.2, 174.8; MS (EI) *m*/*z* 294 (100), 266 (23), 295 (22), 351 (M^+, 4).

α-(4-(*tert*-Butyldimethylsiloxy)butyl)-3-pyridineethanecarboxylic Acid (6). A biphasic solution of **5** (7.08 g, 20.2 mmol), tetra-*n*-butylammonium hydrogen sulfate (76 mg, 0.22 mmol), 50% aqueous NaOH (8.0 mL), and pentane (28 mL) was vigorously stirred for 5 h.[15] The solution was diluted with water and neutralized with 5% HCl. The mixture was extracted with 10% MeOH/$CHCl_3$. This afforded 4.04 g of **6** as a yellow oil which was not further purified: IR (film) cm^{-1} 2929, 1708, 1592; ^{1}H NMR ($CDCl_3$, δ) 0.0 (s, 6H), 0.85 (s, 9H); 3.33 (t, J = 6.9 Hz, 1H), 3.50 (t, J = 6.4 Hz, 2H), 7.10 (dd, J = 4.9, 7.8 Hz), 7.57 (bd, J = 7.9 Hz, 1H), 8.30 (bd, J = 4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm) 18.3, 23.8, 25.6, 25.9, 32.5, 33.2, 51.1, 62.8, 123.5, 136.2, 136.9, 146.9, 148.9, 178.7; MS *m*/*z* 266 (100), 146 (25), 248 (21), 323 (M^+, 3).

***N*-Methyl-α-(4-(*tert*-butyldimethylsiloxy)butyl)-3-pyridineethaneamide (7).** To a cold (0 °C), well-stirred solution of **6** (6.15 g, 19.0 mmol) in CH_2Cl_2 (in 95 mL) was added *N*-hydroxysuccinimide (2.32 g, 20.2 mmol), 1,3-diisopropylcarbodiimide (2.57 g, 20.4 mmol), and 4-dimethylaminopyridine (120 mg, 0.98 mmol) in sequence. The solution was warmed to rt, stirred for 1 h, and filtered. Methylamine was bubbled into the filtrate for 2 min. The solution was stirred an additional 10 min, poured into water, and extracted with ethyl acetate. Chromatography (5% MeOH/ethyl acetate) afforded 5.05 g (79%) of **7** as a yellow oil which solidified: mp 58−61 °C; IR (mull) cm^{-1} 3276, 1644, 1565; ^{1}H NMR ($CDCl_3$, δ) 0.0 (s, 6H), 0.85 (s, 9H), 2.76 (d, J = 4.8 Hz, 3H), 3.26 (t, J = 7.6 Hz, 1H), 3.55 (t, J = 6.4 Hz, 2H); 7.26 (dd, J = 5.4, 7.6 Hz, 1H), 7.76 (dt, J = 1.9, 8.0 Hz, 1H), 8.44 (d, J = 2.1 Hz, 1H), 8.49 (dd, J = 1.6, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm) 18.1, 23.7, 25.7, 26.2, 32.2, 33.1, 50.5, 62.6, 123.5, 134.9, 135.6, 148.4, 149.2, 172.9; MS (EI) *m*/*z* 279 (100), 280 (21), 321 (M^+, 4). Anal. Calcd for $C_{18}H_{32}N_2O_2Si$: C, 64.24; H, 9.59; N, 8.32. Found: C, 64.40; H, 9.83; N, 8.31.

***N*-Methyl-α-(4-(*tert*-butyldimethylsiloxy)butyl)-3-pyridineethanethioamide (8).** To a solution of **7** (3.04 g, 9.0 mmol) in anhydrous THF (125 mL) was added P_2S_5 (2.10 g, 4.7 mmol). The solution was sonicated in an ultrasound bath for 20 min, and additional P_2S_5 (2.07 g, 4.7 mmol) was added. The solution was sonicated an additional 45 min, poured into water, and neutralized with aqueous $NaHCO_3$. The solution was extracted repeatedly with ethyl acetate. Chromatography (5% MeOH/ethyl acetate) afforded 1.61 g (50%) of **8** as a white solid: IR (mull) cm^{-1} 3190, 1591, 1389; ^{1}H NMR ($CDCl_3$, δ) 0.0 (s, 6H), 0.85 (s, 9H) 3.12 (d, J = 4.7 Hz, 3H), 3.56 (t, J = 6.3 Hz, 2H), 3.72 (t, J = 7.5 Hz, 1H), 7.28 (dd, J = 4.8, 8.4 Hz, 1H), 7.96 (bd, J = 9.0 Hz, 1H), 8.19 (bs, 1H), 8.40 (bd, J = 2.2 Hz, 1H), 8.48 (dd, J = 1.6, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm) 18.2, 23.8, 25.8, 32.34, 32.9, 35.4, 57.7, 62.7, 123.7, 135.4, 136.4, 148.5, 149.0, 206.1; MS (EI) *m*/*z* 295 (100), 164 (15), 352 (M^+, 4). Anal. Calcd for $C_{18}H_{32}N_2OSSi$: C, 61.31; H, 9.15; N, 7.95. Found: C, 61.03; H, 9.34; N, 7.82.

***N*-Methyl-α-(4-(hydroxyl)butyl)-3-pyridineethanethioamide (9).** To a cold (0 °C), well-stirred solution of **8** (1.60 g, 4.53 mmol) in of anhydrous THF (20 mL) was added TBAF (9.1 mL, 9.1 mmol, 1.0 M solution in THF). The solution was warmed to rt, and after 1 h, additional TBAF (4.5 mL, 4.5 mmol) was added. The reaction was stirred overnight, poured into brine, and extracted with ethyl acetate. Chromatography (10% MeOH/ethyl acetate) afforded 1.05 g (97%) of **9** as a white solid: IR (mull) cm^{-1} 3229, 1580, 1481; ^{1}H NMR (CD_3OD, δ) 3.00 (s, 3H), 3.50 (t, J = 6.5 Hz, 2H), 3.85 (dd, J = 6.3, 8.9 Hz, 1H), 7.33 (dd, J = 5.0, 8.0 Hz, 1H), 7.98 (dt, J = 1.8, 8.0 Hz, 1H), 8.37 (dd, J= 1.5, 4.9 Hz, 1H), 8.52 (d, J = 2.1 Hz, 1H); ^{13}C NMR (CD_3OD, ppm) 24.9, 32.7, 33.2, 36.3, 57.7, 62.5, 124.8, 137.6, 139.2, 148.4, 149.5, 207.0; MS (EI) *m*/*z* 166 (100), 205 (99), 238 (M^+, 24). Anal. Calcd for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61; N, 11.75. Found: C, 60.28; H, 7.64; N, 11.43.

***N*-Methyl-α-(4-(methanesulfonyl)butyl)-3-pyridineethanethioamide (10a).** To a cold (0 °C), well-stirred solution of **9** (251 mg, 1.05 mmol) in pyridine (5 mL) was added methanesulfonyl chloride (0.09 mL, 1.16 mmol). The solution was stirred for 0.5 h, poured into water, and extracted with ethyl acetate. The aqueous layer was treated with aqueous $NaHCO_3$ and extracted with ethyl acetate. Chromatography of the combined extracts (10% MeOH/ethyl acetate) afforded 313 mg (94%) of **10a** as a pale orange oil: IR (mull) cm^{-1} 3218, 3056, 1562; ^{1}H NMR ($CDCl_3$, δ) 2.99 (s, 3H), 3.11 (d, J = 4.8 Hz, 3H),

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3.75 (t, J = 7.3 Hz, 1H), 4.21 (t, J = 6.3 Hz, 2H), 7.28 (dd, J = 6.0, 8.2 Hz, 1H), 7.95 (dt, J = 2.0, 8.0 Hz, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.48 (dd, J = 1.6, 4.8 Hz, 1H), 8.96 (bd, J = 4.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm) 23.4, 28.6, 32.8, 34.9, 37.2, 56.8, 69.9, 123.7, 135.5, 136.5, 148.4, 148.8, 205.4; MS (EI) m/z 242 (59), 221 (38), 204 (2), 316 (M^+, 1).

***N*-Methyl-α-(4-(bromo)butyl)-3-pyridineethanethioamide (10b).** To a cold (0 °C), well-stirred solution of mesylate **10a** (2.67 g, 7.18 mmol) in acetone (21 mL) was added lithium bromide (6.27 g, 71.8 mmol). The reaction mixture was allowed to warm to rt and was stirred overnight. The solution was concentrated, suspended in ethyl acetate, and filtered. The solids were washed with ethyl acetate. The filtrate was washed with aqueous $NaHCO_3$ and extracted with ethyl acetate. Chromatography of the combined extracts (10% MeOH/ethyl acetate) afforded 1.58 g (62%) of **10b** as a white solid: IR (mull) cm^{-1} 3185, 1590, 1571, 1278; ^{1}H NMR ($CDCl_3$, δ) 3.19 (d, J = 4.7 Hz, 3H), 3.45 (t, J = 6.7 Hz, 2H), 3.77 (t, J = 7.5 Hz, 1H), 7.38 (dd, J = 4.8, 7.8 Hz, 1H), 8.05 (dt, J = 1.9, 8.1 Hz, 1H), 8.44 (d, J = 2.1 Hz, 1H), 8.53 (bs, 1H), 8.58 (dd, J = 1.7, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm) 26.2, 32.4, 33.1, 33.6, 35.0, 57.5, 124.0, 135.6, 136.6, 148.8, 149.1, 205.8; MS (EI) m/z 221 (100), 222 (15), 300 (M^+, 1). Anal. Calcd for $C_{12}H_{17}BrN_2S$: C, 47.85; H, 5.69; N, 9.30. Found: C, 47.79; H, 5.70; N, 9.15.

***N*-Methyl-α-(4-(methyldithio)butyl)-3-pyridineethanethioamide (3).** A well-stirred solution of **10b** (1.33 g, 4.42 mmol) and thiourea (342 mg, 4.49 mmol) in ethanol (95%, 2.2 mL) was refluxed for 2 h and cooled to 0 °C, and aqueous NaOH (1.78 mL, 4.43 mmol, 2.5 M) was added. The solution was refluxed for 40 min and cooled to 0 °C, and a solution of methyl methanethiolsulfonate (0.45 mL, 4.38 mmol) in ethanol (95%, 0.9 mL) was added. The solution was warmed to rt and stirred 30 min. The reaction mixture was poured into water, treated with aqueous $NaHCO_3$, and extracted with ethyl acetate. Chromatography (10% MeOH/ethyl acetate) afforded 673 mg of a pale yellow oil which was rechromatographed (5% MeOH/ethyl acetate) to afford 460 mg (35%) of **3** as a white solid. This material was identical to the rearrangement product (by TLC, IR, MS, ^{1}H NMR, and ^{13}C NMR).

Mechanistic Experiments. 2/MeSNa. To a well-stirred solution of **2** (106 mg, 0.37 mmol) in ethanol (95%, 2.5 mL) was added MeSNa (78 mg, 1.11 mmol). The reaction mixture was stirred overnight at rt, diluted with brine, and extracted with chloroform. No changes were observed by TLC. Chromatography (10% MeOH/ethyl acetate) gave 98 mg of recovered **2** which was identical to an authentic sample.

2/MeSNa/Methylamine. To a well-stirred solution of **2** (106 mg, 0.37 mmol) in ethanol (95%, 2.5 mL) was added MeSNa (79 mg, 1.11 mmol) and aqueous methylamine (40%, 0.6 mL, 7.0 mmol). The reaction mixture was stirred overnight at rt, diluted with brine, neutralized with 5% HCl, and extracted with chloroform. No changes were observed by TLC. This provided 99 mg of recovered **2** as a white solid, which was identical to an authentic sample.

11/MeSNa. To a well-stirred solution of **11** (34.5 mg, 0.14 mmol) in ethanol (95%, 1.0 mL) was added MeSNa (30 mg, 0.43 mmol). The reaction mixture was stirred overnight at rt, diluted with brine, and extracted with ethyl acetate. No changes were observed by TLC. Chromatography (2:1 ethyl acetate/hexane) gave 15 mg of recovered **11** which was identical to an authentic sample.

11/MeSNa/Methylamine. To a well-stirred solution of **11** (51 mg, 0.24 mmol) in ethanol (95%, 1.6 mL) was added MeSNa (44 mg, 0.62 mmol) and aqueous methylamine (40%, 0.31 mL, 2.7 mmol). The reaction mixture was stirred overnight at rt, diluted with saturated ammonium chloride, and extracted with ethyl acetate. No changes were observed by TLC. This provided 44 mg of recovered **11** as a white solid which was identical to an authentic sample.

***S*-Methyl-α-(4-(methydithio)butyl)-3-pyridineethanecarbodithioate (13) and *S*-Methyl-α-(4-thiobutyl)-3-pyridineethanecarbodithioate Disulfide Derivative 14.** To a cold (0 °C), well-stirred solution of **1** (631 mg, 2.21 mmol) in ethanol (95%, 16 mL) was added MeSNa (477 mg, 6.81 mmol). The solution was stirred for 5 min, warmed to rt, and stirred an additional 30 min. The solution was poured into water and extracted with three portions of ethyl acetate. Chromatography (elution with 1:1 hexane/ethyl acetate, followed by 2:1 ethyl acetate/hexane, and finally 3:1 ethyl acetate/hexane) afforded 17 mg (3%) of **12** (identical with authentic material),[6] 227 mg (32%) of **13,** and 102 mg (17%) of **14**.

(13): IR (film) cm^{-1} 2912, 1585, 1476, 1422; ^{1}H NMR ($CDCl_3$, δ) 2.36 (s, 3H), 2.58 (s, 3H), 2.65 (t, J = 7.1 Hz, 2H), 4.41 (t, J = 7.4 Hz, 1H), 7.33 (dd, J = 5.0, 8.0 Hz, 1H), 7.91 (bd, J = 8.0 Hz, 1H), 8.50 (dd, J = 1.6, 4.92 Hz, 1H), 8.64 (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, ppm) 19.4, 23.0, 25.9, 28.4, 36.0, 37.3, 62.2, 123.6, 136.2, 136.7, 146.9, 147.8; MS (EI) m/z 271 (100), 224 (81), 180 (26), 317 (M^+, 3).

(14): IR (film) cm^{-1} 2923, 1573, 1422; ^{1}H NMR ($CDCl_3$, δ) 4.34 (t, J = 7.4 Hz, 1H), 7.20 (dd, J = 4.8, 7.9 Hz, 1H), 7.78 (dt, J = 1.9, 8.0 Hz, 1H), 8.44 (bd, J = 3.9 Hz, 1H), 8.57 (bs, 1H); ^{13}C NMR ($CDCl_3$, ppm) 19.4, 25.9, 28.5, 35.9, 38.2, 62.2, 123.3, 135.2, 136.2, 147.9, 148.7; MS (FAB) m/z 270 (100), 541(M^+ + 1, 89), 224 (88).

12/MeSNa. To a well-stirred solution of **12** (104 mg, 0.39 mmol) in ethanol (95%, 5.0 mL) was added MeSNa (83 mg, 1.19 mmol). The reaction mixture was at rt for 5 h, diluted with saturated ammonium chloride, and extracted with ethyl acetate. This provided 97 mg of a yellow oil. ^{1}H NMR analysis of the product gave a 3.5:1 ratio of **12** to **13** through integration analysis.

12/Methylamine. To a well-stirred solution of **12** (53 mg, 0.19 mmol) in ethanol (95%, 4.5 mL) was added aqueous methylamine (40%, 0.4 mL, 5.2 mmol). The reaction mixture was stirred at rt for 2.75 h, diluted with water, and extracted with ethyl acetate. Chromatography (2:1 ethyl acetate/hexane) gave 37 mg (75%) of **11** which was identical to an authentic sample.

13/Methylamine. To a well-stirred solution of **13** (49.7 mg, 0.16 mmol) in ethanol (95%, 1.5 mL) was added aqueous methylamine (40%, 14 mL, 0.16 mmol). The reaction mixture was stirred at rt for 2 h, diluted with water, and extracted with ethyl acetate. Chromatography (5% MeOH/ethyl acetate) gave 19 mg (40%) of **3** which was identical to an authentic sample.

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Supporting Information Available: Physical data (^{1}H NMR spectral data) for **5**, **6**, **7**, **8**, **9**, **10a**, **10b**, **13**, and **14** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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