Conversion of Amides and Lactams to Thioamides and Thiolactams Using Hexamethyldisilathiane

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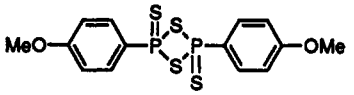
Received September 17, 1993•

Amides and lactams were converted to their corresponding thioamides and thiolactams employing a new protocol using hexamethyldisilathiane (TMS_2S). Oxophilic promoters were employed to generate Vilsmeier-type intermediates, the most efficient reagents being phosphorus oxychloride, triphosgene, and oxalyl chloride. Thionation of intermediate chloro iminium ions was accomplished *in situ* with TMS_2S. Yields were good to excellent for secondary and tertiary amides and lactams while yields for primary systems were poor.

Introduction

Thioamides are valuable intermediates in organic synthesis.[1] Accordingly, there are numerous procedures for their preparation from amides and lactams: Lawesson's reagent (1),[2a] P_2S_5,[2b] H_2S,[2c] $R_3OBF_4/NaSH$,[2d] R_2PSX,[2e] and $(Et_2Al)_2S$,[2f] to mention a few. Many of these methods require protracted reaction times, high temperatures, or inconvenient reaction conditions for their execution and are often accompanied by painful chromatographic separations to remove spent reagents from desired products.



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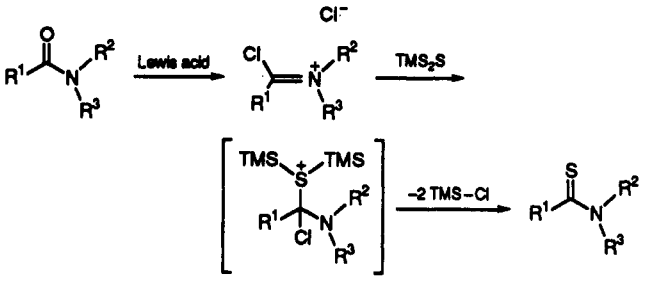
In conjunction with several projects within our laboratory, we required a clean and efficient method for converting amides to thioamides, where existing literature protocols failed to provide satisfactory results. Several recent reports in the literature demonstrated that hexamethyldisilathiane (TMS_2S) may be employed in the formation of thiocarbonyl compounds,[3] including a communication by Shiao, which illustrated that hexamethyldisilathiane may be used in converting nitriles to primary thioamides.[3h] To our knowledge, no attempts have been made at employing bis-TMS sulfide directly in the conversion of amides and lactams to their sulfur analogs.[3g] Herein we detail our efforts at converting amides to thioamides, by trapping Vilsmeier-type chloro iminium ion intermediates with hexamethyldisilathiane (Scheme 1).

Scheme 1



Results and Discussion

On the basis of literature precedence,[3] and related studies for tin, germanium, and lead analogs,[4] we were confident in the ability of TMS_2S to act as an efficient thionating agent. In order to ascertain the feasibility of this transformation, efforts were directed at the conversion of lactam **2g** to thiolactam **3g** under a variety of conditions. These results are summarized in Table 1.

Initially, it was hoped that the combined oxophilicity of silicon, the nucleophilicity of sulfur, and the inherent weak nature of the S–Si bond of TMS_2S would prove to sufficiently activate the amide carbonyl toward Group VI substitution. Regrettably, hexamethyldisilathiane was not reactive enough to effect this transformation (entry 1). Addition of either a complementary silicon source, such as TMSOTf, to activate the carbonyl oxygen, or use of fluoride (TBAF) to enhance the nucleophilicity of the sulfur did little to facilitate this reaction (entries 2 and 3).[3b,4]

It quickly became apparent that a method of activating the carbonyl group toward substitution was required. Indeed, Ricci found that in the preparation of thiocarbonyl units employing bis-TMS sulfide as a thionating agent,

• Abstract published in *Advance ACS Abstracts*, December 15, 1993.

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(2) (a) Scheibye, S.; Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 229. Thomsen, I.; Clausen, K.; Scheibye, S.; Lawesson, S.-O. *Org. Synth.* **1984**, *62*, 158 and references therein. For a comprehensive review of Lawesson's reagent, see: Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061. (b) Wakabayashi, T.; Kato, Y. *Jpn. Koha. Tokkyo Koho* **1978**, *78*, 56, 662.; *Chem. Abstr.* **1979**, *90*, 22818h. (c) Paquer, D.; Smadja, S.; Vialle, J. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1974**, *279*, 529. (d) Bodine, J. J.; Kaloustian, M. K. *Synth. Commun.* **1982**, *12*, 787. (e) Pedersen, B. S.; Lawesson, S.-O. *Bull. Soc. Chim. Belg.* **1977**, *86*, 693. (f) Ishi, Y.; Hirabayashi, T. Imaeda, H.; Ito, K. *Japan Patent* **1974**, *40*, 441; *Chem. Abstr.* **1975**, *82*, 156074f.

(3) (a) Schwabacher, A. W.; Maynard, T. L. *Tetrahedron Lett.* **1993**, *34*, 1269. (b) Degl'Innocenti, A.; Capperucci, A.; Mordini, A.; Reginato, G.; Ricci, A.; Cerreta, F. *Tetrahedron Lett.* **1993**, *34*, 873. (c) Steliou, K.; Salama, P.; Corriveau, J. *J. Org. Chem.* **1985**, *50*, 4969. (d) Ando, W.; Furuhata, T.; Tsumaki, H.; Sekiguchi, A. *Chem. Lett.* **1982**, 885. (e) Ricci, A.; Degl'Innocenti, A.; Capperucci, A.; Reginato, G. *J. Org. Chem.* **1989**, *54*, 19. (f) Segi, M.; Nakajima, T.; Suga, S.; Murai, S.; Ryu, I.; Ogawa, A.; Sonoda, N. *J. Am. Chem. Soc.* **1988**, *110*, 1976. (g) Steliou, K.; Mrani, M. *J. Am. Chem. Soc.* **1982**, *104*, 3104. (h) Lin, P.-Y.; Ku, W.-S.; Shiao, M.-J. *Synthesis* **1992**, 1219. (i) M. D. Mizhiritskii M. D.; Reikhsfel'd, V. O. *Zh. Obsch. Khim.* **1986**, 1373.

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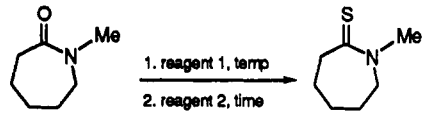
Table 1. Optimization of Thionation Conditions



2g 3g

entry	solvent	reagent 1 (conditions)	reagent 2 (conditions)	yield, %
1	$ClCH_2CH_2Cl$	3 equiv of TMS_2S, rt to reflux, 12 h		no reaction
2	$ClCH_2CH_2Cl$	1.5 equiv of TMSOTf, −78 °C	3.0 equiv of TMS_2S, −78 °C to reflux, 12 h	no reaction
3	$ClCH_2CH_2Cl$	3.0 equiv of TMS_2S, 0 °C to reflux	1.0 equiv of TBAF, at 0 °C	no reaction
4	CH_2Cl_2	1.05 equiv of BF_3·OEt_2, −78 °C to reflux	3.0 equiv of TMS_2S at −78 °C, 24 h	48
5	CH_2Cl_2	1.0 equiv of BCl_3, −78 °C to rt	3.0 equiv of TMS_2S at −78 °C, 24 h	53
6	CH_2Cl_2	1.5 equiv of SO_2Cl_2, −78 to 0 °C	3.0 equiv of TMS_2S at −78 °C, 12 h	dec
7	CH_2Cl_2	1.5 equiv of $SOCl_2$, −78 to 0 °C	3.0 equiv of TMS_2S at −78 °C, 12 h	dec
8	CH_2Cl_2	1.5 equiv of TfCl, −78 °C to rt	3.0 equiv TMS_2S at rt, 12 h	no reaction
9	CH_2Cl_2	1.5 equiv Tf_2O, −78 °C	3.0 equiv TMS_2S, −78 °C to rt, 12 h	61
10	CH_2Cl_2	2.8 equiv MeOTf, −78 °C to rt	4.2 equiv TMS_2S at 0 °C to rt, 12 h	no reaction
11	CH_2Cl_2	1.6 equiv ClCOCOCl, −78 to 0 °C	3.0 equiv TMS_2S at 0 °C, 1.5 h	21
12	CH_2Cl_2	1.1 equiv ClCOCOCl, −78 to 0 °C	2.6 equiv TMS_2S at 0 °C, 1.5 h	13
13	CH_2Cl_2	1.25 equiv BrCOCOBr, −40 to 0 °C	3.0 equiv TMS_2S at 0 °C, 12 h	66
14	CH_2Cl_2	2.6 equiv TMS_2S, −78 °C	1.1 equiv ClCOCOCl, −78 to 0 °C, 2.5 h	27
15	CH_2Cl_2	1.05 equiv triphosgene, 0 °C	3.0 equiv TMS_2S at 0 °C, 4 h	86
16	CH_2Cl_2	1.3 equiv $POCl_3$, −78 °C	3.5 equiv TMS_2S, −78 °C to rt, 4 h	91
17	CH_3CN	1.3 equiv $POCl_3$, −45 °C	3.5 equiv TMS_2S, −45 °C to rt, 12 h	76

Lewis acids such as $CoCl_2$ or TMSOTf were required to effect this transformation.[3b,e] Accordingly, a variety of Lewis acids were evaluated for their ability to accomplish this particular transformation. Initial investigation focused upon the use of boron-based Lewis acids in combination with hexamethyldisilathiane;[3g] however, in our hands, these were found to give only modest results. Boron trisulfide, generated *in situ*, is believed to be the active reagent in these transformations (entries 4 and 5).[3g,5]

At this point, another consideration suggested itself. The Vilsmeier reaction has long been known to convert amides to highly electrophilic iminium ions, which may then react with weakly nucleophilic groups such as aromatic rings.[6] We felt that such intermediates might provide a useful means of activating amides toward nucleophilic attack by TMS_2S. Accordingly, efforts were made at finding optimum conditions for forming and trapping these Vilsmeier intermediates. Use of sulfur-based promoters gave very disappointing results (entries 6–9), with only triflic anhydride providing moderate amounts of thiolactam **3g** (61%).

Attention was next turned to the application of carbon-based oxophilic promoters in the formation of iminium ions. Use of methyl triflate was not successful, presumably due to the lack of a nucleophile to initiate attack on the iminium ion intermediate; however, some limited success was obtained through use of oxalyl halide derivatives. Formation of chloro iminium ion intermediates was observed to take place by treating amides with oxalyl chloride at low temperature and then gradual warming to room temperature (method A). Two experimental indicators were useful in monitoring formation of these intermediates: the solutions were found to turn a distinctive pale amber color and, in the case of either oxalyl chloride or bromide, the evolution of gas (both CO_2 and CO) was observed. Use of oxalyl chloride provided marginal results with this substrate. Employing 1.6 equiv of oxalyl chloride resulted in a 21% yield of the desired product and reducing the equivalents of oxalyl chloride reduced yields of **3g**. In addition, increasing either the amount of oxalyl chloride, the amount of bis-TMS sulfide, or the time of the reaction did not noticeably affect the outcome. The more reactive oxalyl bromide proved to be superior to the chloride, providing 66% of the desired thiolactam (entries 11–14).

While generation of the chloro iminium ion intermediates was mediocre using the oxalyl chloride method in the case of **2g**, it should be noted that for several other substrates, (**2b**, Table 2, and **5a,b,f–h**, Table 3) this reagent proved to be an excellent choice for generating and trapping chloro iminium ions with TMS_2S. Limitations to the effectiveness of oxalyl chloride appear to be restricted to systems where no protons are located α to the carbonyl. It is hypothesized that during the slow formation of these Vilsmeier intermediates, isomerization to the enamine may be occurring with subsequent side reactions taking place either *via* dimerization[7] (path A) or reaction with oxalyl chloride[8] (path B, Scheme 2). Indeed, pathway B does seem to be competing with trapping of the Vilsmeier intermediate, as **4g** (Figure 1) was isolated in 18% yield in entry 11 (Table 1). In an effort to circumvent any side reactions of the chloro iminium ion intermediate, attempts were made at generating iminium ions in the presence of TMS_2S (entry 14); however, yields were only slightly improved by this approach. Further investigation of alternative promoters led to the discovery that triphosgene[9] may also be employed in this transformation to good advantage (entry 15, Table 1). Triphosgene also provided a convenient method for monitoring the formation of these Vilsmeier intermediates as the evolution of CO_2 occurred

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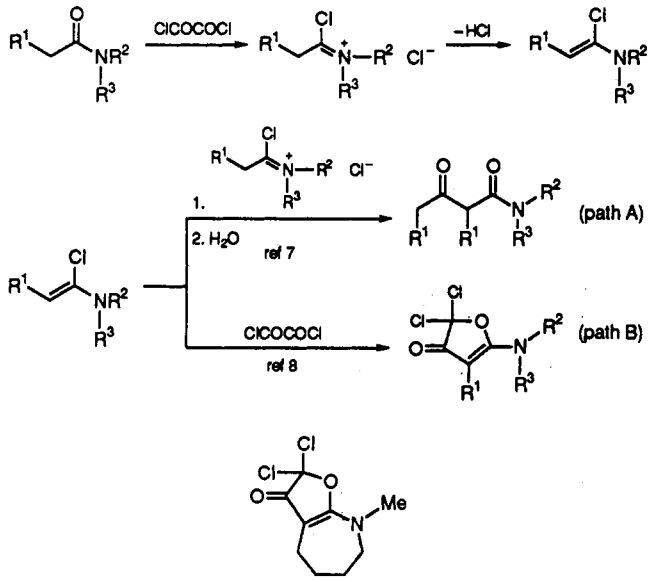
(9) (a) Eckert, H.; Forster, B. *Angew. Chem.* **1987**, *99*, 922. (b) Eckert, H.; Forster, B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 894. (c) Councler, C. *Ber. Dtsch. Chem. Ges.* **1880**, 1697. (d) Bayer and Co., DRP (1901); *Chem. Zentrabl.* **1901**, *72 II*, 69. (e) Marotta, D. *Gazz. Chim. Ital.* **1929**, *59*, 955. (f) Nekrassow, W.; Melnikow, N. *J. Prakt. Chem.* **1930**, *NF 126*, 81.

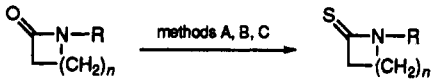
Scheme 2



4g

Figure 1. Side product from the reaction of oxalyl chloride with **2g** (entry 11, Table 1).

Table 2. Preparation of Thiolactams Using Hexamethyldisilathiane



2a-g **3a-g**

compd	n	R	method[a]	time, h	% yield with TMS_2S	% yield with Lawesson's reagent
2a	1	benzyl	C	48	70 (97)[b]	92
2b	2	Me	C	4	82	95[c]
2c	2	Et	C	6	92	83
2d	2	vinyl	A, B, C	24	dec	24[d]
2e	2	H	C	24	73	75[d]
2f	3	Me	C	6	88	95
2g	4	Me	C	6	91	94

[a] A: oxalyl chloride/TMS_2S/CH_2Cl_2. B: triphosgene/TMS_2S/CH_2Cl_2. C: $POCl_3$/TMS_2S/CH_2Cl_2. [b] Yield based upon recovered starting material. [c] Reference 13. [d] Reference 10.

with concomitant formation of the iminium ion (method B). Phosphorus oxychloride was also examined as a promoter for this transformation. Perhaps not surprisingly, use of the traditional method of Vilsmeier intermediate formation proved to be excellent in forming and trapping chloro iminium ions (entry 16, Table 1; method C). An additional bonus found in using this strategy was that purification of reaction products was accomplished by a simple aqueous workup, followed by filtration through a short plug of silica gel. This was particularly gratifying in light of the painful chromatographic separations which often accompany transformations using Lawesson's reagent.

With a feasible method for the thionation of amides and lactams established, we next set out to determine the generality of this new methodology by examining a variety of systems. The results for the formation of several thiolactams are summarized in Table 2 and, where possible, comparisons are made to yields obtained using Lawesson's reagent. In this study, both the ring size and the nitrogen substituent were varied in order to ascertain the flexibility of the protocol. Ring size does not seem to play a significant factor in the formation of thiolactams using this methodology except for β-lactams. Formation of Vilsmeier intermediates of 1-alkyl-2-azetidinones was much slower than other tertiary systems due to reduced lone pair participation by nitrogen because of ring strain. In addition, this reaction seemed to be relatively tolerant of the substituent on nitrogen, with the exceptions of **2d** and **2e**. For 2-pyrrolidinone, it is observed that secondary lactams are much less reactive than their corresponding tertiary systems, again probably due to reduced lone pair participation by nitrogen. In the case of **2d**, both Lawesson's reagent[10] and phosphorous pentasulfide[11] fail to give entirely satisfactory results, probably due to polymerization.[12] In instances where systems appeared to be much less reactive, use of excess reagents, longer reaction times, higher reaction temperatures, or additives such as DMAP did not appear to significantly improve these reactions. In general, yields were found to be comparable to those obtained using Lawesson's reagent.

Heartened by these results, efforts were next directed at the conversion of amides to thioamides using our new methodology. Again, comparisons were made with yields obtained using Lawesson's reagent and these results are summarized in Table 3. Primary, secondary, and tertiary amides were examined using various substituents for R^1, R^2, and R^3. Tertiary benzamide **5b** was found to be somewhat less reactive than other tertiary aliphatic amides, requiring 8 h for complete formation of the Vilsmeier reagent, and secondary amides were found to be considerably less reactive than tertiary systems but still provided satisfactory results (**5e**). A serious limitation of this reaction becomes apparent upon examining primary systems, as poor yields for **6c** were observed; other primary systems examined employing this strategy failed to provide any observable product. This is in accord with the general reactivity trend of lactams and easily explained by levels of lone pair participation by nitrogen. Again, use of higher reaction temperatures, greater equivalents of reagents, longer reaction times, or additives such as DMAP did not improve the yield.

While this procedure seems to be sensitive to the level of substitution on nitrogen, it was gratifying to observe that this reaction was relatively insensitive to the size of the alkyl groups on nitrogen or α to the carbonyl. Having large substituents at R^1, R^2, and R^3 does not seem to significantly influence the outcome of the reaction (**5f,g**). Both oxalyl chloride and phosphorus oxychloride were both found to be quite effective in mediating iminium ion formation; however, it should be noted that oxalyl chloride was only effective in instances where no protons were α to the carbonyl (**5a,b,f–h**), *vide supra*. Yields were found to be consistent with those observed for lactams, and aside from the aforementioned poor reactivity of the primary amides, our methodology was found to give results comparable to those of Lawesson's reagent.

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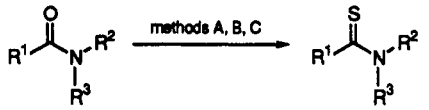
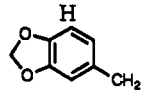
(13) Yde, B.; Yousif, N. M.; Pedersen, U.; Thomsen, I.; Lawesson, S.-O. *Tetrahedron* **1984**, *40*, 2047.
(14) Raucher, S.; Kein, P. *Tetrahedron Lett.* **1980**, *21*, 4061.

Table 3. Preparation of Thioamides Using Hexamethyldisilathiane



5a-i 6a-i

compd	R^1	R^2	R^3	method[a]	time	% yield with TMS_2S	% yield with Lawesson's reagent
5a	Ph	$-(CH_2)_4-$	$-(CH_2)_4-$	A	3 h	93	99
5b	Ph	Me	Me	A	12 h	100	89[b]
5c	Ph	H	H	C	5 days	30	92[c]
5d	Me	$-(CH_2)_4-$	$-(CH_2)_4-$	C	12 h	91	96[c]
5e	Me	Me	H	C	24 h	77	89
5f	t-Bu	$-(CH_2)_4-$	$-(CH_2)_4-$	A	3 h	92	86
5g	H	$-(CH_2)_5-$	$-(CH_2)_5-$	A	3 h	93	100
5h	H	i-Pr	i-Pr	A	12 h	97	86
5i		$-(CH_2)_4-$	$-(CH_2)_4-$	C	12 h	91	100

[a] A: oxalyl chloride/TMS_2S/CH_2Cl_2. B: triphosgene/TMS_2S/CH_2Cl_2. C: $POCl_3$/TMS_2S/CH_2Cl_2. [b] Reference 14. [c] Reference 2a.

Conclusion

Intercepting Vilsmeier intermediates with hexamethyldisilathiane proves to be an effective method for converting secondary and tertiary amides and lactams to their corresponding sulfur analogs. In general, these reactions may be performed at low temperatures and reaction were complete in a relatively short period of time. Purification of these compounds was simple, and considering the numerous efficient methods for preparing hexamethyldisilathiane,[15] this procedure should be amenable to large-scale production of the thioamides at relatively low cost.

Experimental Section

Melting points are reported uncorrected. Infrared spectra were recorded with a Perkin-Elmer 1800 FTIR spectrometer. ^1H NMR and ^{13}C NMR (APT[16]) spectra were obtained using Varian Gemini 200-MHz and GE QE 300-MHz NMR spectrometers. Exact mass measurements were obtained at the Purdue University Mass Spectrometry Laboratory. Methylene chloride and benzene were distilled over CaH_2, and hexamethyldisilathiane was obtained commercially from the Aldrich Chemical Co. Unless otherwise stated, all reactions were performed under an inert argon atmosphere. General methods for the preparation of thioamides and thiolactams are as follows.

Method A. A solution of ~1.0 mmol of amide or lactam in 2 mL of dry CH_2Cl_2 was cooled to −78 °C and 0.14 mL (1.5 mmol, 1.5 equiv) of oxalyl chloride was added dropwise over 10 min. The resulting solution was stirred for an additional 10 min, and the bath was removed to permit gradual warming to 0 °C. After 30 min, the solution turned a pale amber color and gas evolution (CO_2 and CO) was observed. Gas evolution ceased after approximately 30 min, and at this point 0.65 mL (3.1 mmol, 3.1 equiv) of TMS_2S (STENCH!) was added dropwise. The reaction mixture was warmed to room temperature over 1–3 h (see tables), and the progress of the reaction was monitored *via* TLC. Upon completion, the reaction mixture was concentrated *in vacuo* and filtered through a short plug of 60–200-mesh silica gel. Pure samples of desired thioamides were obtained upon concentration of the eluent.

Method B. To a solution of ~1.0 mmol of amide or lactam in 5 mL of dry CH_2Cl_2 at 0 °C was added 313 mg (1.05 mmol, 1.05 equiv) of triphosgene in portions, and the resulting solution was warmed to room temperature over 1 h. During the course of this interval, the solution turned a pale amber color and gas (CO_2) evolved from the solution. When gas evolution ceased, 0.64 mL (3.05 mmol, 3.05 equiv) of TMS_2S (STENCH!) was added dropwise over 5 min. The course of the reaction was monitored *via* TLC, and reactions were typically complete within 1–3 h. Upon completion, the reaction mixture was diluted with 10 mL of water and the layers were separated. The aqueous phase was extracted with 3 × 10 mL of CH_2Cl_2 and combined organics were dried over Na_2SO_4, concentrated *in vacuo*, and filtered through a short plug of 60–200-mesh silica gel. Concentration of the eluent afforded pure thioamides or thiolactams.

Method C. A solution of ~1.0 mmol of amide or lactam in 2 mL of dry CH_2Cl_2 was cooled to −78 °C and 0.12 mL (1.3 mmol, 1.3 equiv) of phosphorus oxychloride was added dropwise over 10 min. The solution turned a pale amber color after approximately 10 min at −78 °C. Formation of the chloro iminium ion intermediate was monitored by disappearance of the starting material by TLC. (Note: Warming to room temperature may be required to ensure complete formation of the Vilsmeier intermediate. In instances where complete iminium ion formation was not observed, TMS_2S (STENCH!) was added after 30 min.) After 30 min, the solution was treated with 0.65 mL (3.1 mmol, 3.1 equiv) of TMS_2S and the resulting mixture was allowed to warm to room temperature for approximately 1–4 h (see tables). Upon completion of the reaction, 10 mL of water was added and the layers were separated. The aqueous phase was extracted with 3 × 10 mL of CH_2Cl_2 and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to afford a pale yellow oil which was filtered through a short plug of 60–200-mesh silica gel. The eluent was concentrated *in vacuo* to afford pure samples of the desired thioamides and thiolactams.

1-Benzylazetidine-2-thione (3a). A solution of 164 mg (1.02 mmol) of lactam in 5 mL of CH_2Cl_2 was subjected to the conditions specified in method C. Purification was accomplished by flash chromatography employing 60–200-mesh silica gel, eluting with 1:1 EtOAc/hexane to give 46 mg of recovered **2a** and 127 mg (70% yield, 97% based upon recovered starting material) of **3a** as a light brown oil: IR ($CDCl_3$) 2962, 1506, 1350, 1264, 1172, 1072 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34 (m, 5 H), 4.68 (s, 2 H), 3.68 (t, J = 3.53 Hz, 2 H), 3.04 (t, J = 3.53 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.49 (e), 134.02 (e), 128.91 (o), 128.59 (o), 128.14 (o), 49.3 (e), 47.19 (e), 39.78 (e); MS (EI, 70 eV) m/e 177 (M^+, 25.48), 148 (14.88), 91 (base), 65 (18.55); HRMS (EI) exact mass calcd for $C_{10}H_{11}NS$ 177.0612 (M^+), found 177.0610. Anal. Calcd for $C_{10}H_{11}NS$: C, 67.76; H, 6.25; N, 7.9; S, 18.09. Found: C, 67.57; H, 5.93; N, 7.88; S, 17.95.

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Preparation of 3a Using Lawesson's Reagent.[10] To a solution of 123.4 mg (0.77 mmol) of **2a** in 5 mL of dry benzene was added 362 mg (0.9 mmol, 1.15 equiv) of Lawesson's reagent, and the reaction mixture was heated to reflux, under argon for 4 h. After being cooled to room temperature, the homogeneous solution was concentrated *in vacuo* and purified by flash chromatography, using 1 × 6 in. of 60–200-mesh silica gel, eluting with 3:7 to 1:1 EtOAc/hexanes. Concentration provided 125.4 mg (92%) of **3a** as a light brown oil which gave spectral characteristics identical to those reported above.

1-Methylpyrrolidine-2-thione (3b).[17] A solution of 176 mg (1.78 mmol) of lactam in 5 mL of CH_2Cl_2 was subjected to the conditions specified in method C. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting with 1:1 EtOAc/hexane to give 166 mg (82%) of **3b** as a colorless oil: IR (film) 2952, 2878, 1698, 1540, 1400, 1312, 1254, 1124 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.72 (t, J = 7.1 Hz, 2 H), 3.2 (s, 3 H), 2.97 (t, J = 7.8 Hz, 2 H), 2.06 (q, J = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 200.95 (e), 57.03 (e), 44.55 (e), 35.36 (o), 19.28 (e); MS (EI, 70 eV) m/e 115 (M^+, base), 100 (3.9), 82 (19.8), 73 (22.3), 58 (17.8); HRMS (EI) exact mass calcd for C_5H_9NS 115.0456 (M^+), found 115.0453.

1-Ethylpyrrolidine-2-thione (3c).[18] A solution of 0.12 mL (1.05 mmol) of lactam in 2 mL of CH_2Cl_2 was subjected to the conditions specified in method C. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting with 1:1 Et_2O/pentane, to give 125 mg (92%) **3c** as a pale yellow oil: IR ($CDCl_3$) 2984, 1516, 1328, 1124 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.78 (q, J = 7.28 Hz, 2 H), 3.69 (t, J = 7.34 Hz, 2 H), 3.00 (t, J = 8 Hz, 2 H), 2.02 (m, 2 H), 1.20 (t, J = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.18 (e), 53.96 (e), 44.94 (e), 42.7 (e), 19.38 (e), 11.14 (o); MS (EI, 70 eV) m/e 129 (M^+, base), 114 (4.8), 87 (21.7), 68 (23.5), 58 (18.5); HRMS (CI, isobutane) exact mass calcd for $C_7H_{13}NS$ 130.0690 (M^+ + H), found 130.0687.

Preparation of 3c Using Lawesson's Reagent.[10] To a solution of 0.12 mL (1.05 mmol) of **2c** in 5 mL of dry benzene was added 531 mg (1.3 mmol, 1.25 equiv) of Lawesson's reagent, and the reaction mixture was heated to reflux, under argon for 4 h. After being cooled to room temperature, the homogeneous solution was concentrated *in vacuo* and purified by flash chromatography, using 1 × 6 in. of 60–200-mesh silica gel, eluting with 3:7 to 1:1 EtOAc/hexanes. Concentration provided 113 mg (83%) of **3c** as a pale yellow oil which gave spectral characteristics identical to those reported above.

Pyrrolidine-2-thione (3e).[19] A solution of 0.1 mL (1.3 mmol) of lactam in 3 mL of CH_2Cl_2 was subjected to the conditions specified in method C. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting with 1:1 EtOAc/hexane, to give 97.2 mg (73%) of **3e** as a white solid: mp 111–112 °C; IR ($CDCl_3$) 3416, 3178, 2892, 1538, 1528, 1476, 1350, 1311, 1113, 1064 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.15 (br s, 1 H), 3.60 (t, J = 7.2 Hz, 2 H), 2.84 (t, J = 7.9 Hz, 2 H), 2.13 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.24 (e), 49.56 (e), 43.22 (e), 22.64 (e); MS (EI, 70 eV) m/e 101 (M^+, base), 86 (2.6), 71 (11), 59 (8.3), 46 (6.8); HRMS (EI) exact mass calcd for C_4H_7NS 101.0299 (M^+ + H), found 101.0299.

1-Methylpiperidine-2-thione (3f). A solution of 0.12 mL (1.06 mmol) of lactam in 2 mL of CH_2Cl_2 was subjected to the conditions specified in method C. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting with 1:1 Et_2O/pentane, to give 121 mg (88.5%) of **3f** as a white solid: mp[20] 36–37 °C; IR[21] ($CDCl_3$) 2954, 1538, 1354,1332, 1126, 1098, 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.45 (s, 3 H), 3.45 (t, J = 6.07 Hz, 2 H), 2.98 (t, J = 6.30 Hz, 2 H), 1.89 (m, 2 H), 1.72 (m, 2 H); ^{13}C NMR[22] ($CDCl_3$, 75 MHz) δ 199.4 (e), 53.04 (e), 43.34 (o), 41.37 (e), 22.92 (e), 20.62 (e); MS (EI, 70 eV) m/e 129 (M^+, base), 115 (21.43), 114 (25.34), 73 (23.02), 68 (38.14), 55 (22.94); HRMS (EI) exact mass calcd for $C_6H_{11}NS$ 129.0612 (M^+), found 129.0609.

Preparation of 3f Using Lawesson's Reagent.[10] To a solution of 0.12 mL (1.06 mmol) of **2f** in 5 mL of dry benzene was added 491 mg (1.2 mmol, 1.15 equiv) of Lawesson's reagent, and the reaction mixture was heated to reflux, under argon for 4 h. After being cooled to room temperature, the homogeneous solution was concentrated *in vacuo* and purified by flash chromatography, using 1 × 6 in. of 60–200-mesh silica gel, eluting with 3:7 to 1:1 EtOAc/hexanes. Concentration provided 131 mg (95%) of **3f** as a white solid which gave spectral characteristics identical to those reported above.

Hexahydro-1-methyl-2*H*-azepine-2-thione (3g). A solution of 0.13 mL (1.01 mmol) of lactam in 2 mL of CH_2Cl_2 was subjected to the conditions specified in method C. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting with 1:1 EtOAc/hexane, to give 132 mg (91%) of **3g** as a white solid: mp 45–46 °C; IR ($CHCl_3$) 2949, 1522, 1398, 1342, 1120, 1062 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.67 (m, 2 H), 3.50 (s, 3 H), 3.11 (m, 2 H), 1.70 (m, 6 H); ^{13}C NMR[22] ($CDCl_3$, 75 MHz) δ 205.76 (e), 55.92 (e), 46.6 (e), 45.2 (o), 29.03 (e), 26.22 (e), 24.46 (e); MS (EI, 70 eV) m/e 143 (M^+, base), 128 (19.4), 110 (39.2); HRMS (EI) exact mass calcd for $C_7H_{13}NS$ 143.0769 (M^+), found 143.0772.

Preparation of 3g Using Lawesson's Reagent.[10] To a solution of 0.13 mL (1.01 mmol) of **2g** in 5 mL of dry benzene was added 424 mg (1.05 mmol, 1.0 equiv) of Lawesson's reagent, and the reaction mixture was heated to reflux, under argon for 4 h. After being cooled to room temperature, the homogeneous solution was concentrated *in vacuo* and purified by flash chromatography, using 1 × 6 in. of 60–200-mesh silica gel, eluting with 3:7 to 1:1 EtOAc/hexanes. Concentration provided 136 mg (94%) of **3g** as a white solid which gave spectral characteristics identical to those reported above.

Furanone (4g) was obtained as a side product from method A in 18% yield as a white solid: mp 109.5–110.5 °C; IR ($CDCl_3$) 2940, 2864, 1710, 1604, 1484, 1484, 1446, 1386, 1020, 884 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.46 (t, J = 5.5 Hz, 2H), 3.17 (s, 3H), 2.37 (t, J = 6.3 Hz, 2H), 1.89 (m, 2H), 1.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 185 (e), 171.27 (e), 103.36 (e), 87.6 (e), 55.11 (e), 38.48 (o), 27.95 (e), 25.44 (e), 21.3 (e); MS (EI, 70 eV) m/e 239 (M^+ + 4, 6.4), 237 (M^+ + 2, 53), 235 (M^+, 92), 200 (16.7), 172 (84.8), 136 (28.8), 109 (70.4), 81 (base), 68 (43); HRMS (EI) exact mass calcd for $C_9H_{11}Cl_2NO_2$ 235.0167 (M^+), found 235.0163. Anal. Calcd for $C_9H_{11}Cl_2NO_2$: C, 45.79; H, 4.70; Cl, 30.03; N, 5.93. Found: C, 45.59; H, 4.39; Cl, 29.91; N, 5.88.

1-(Thiobenzoyl)pyrrolidine (6a).[23] A solution of 200 mg (1.14 mmol) of amide in 5 mL of CH_2Cl_2 was subjected to the conditions specified in method A. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting with 1:1 EtOAc/hexane, to give 204 mg (93%) of **6a** as a white solid: mp 72–74 °C; IR (film) 2974, 1496, 1472, 1452, 1326, 1266, 1244, 1174, 1004 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.29 (s, 5 H), 3.91 (t, J = 6.2 Hz, 2 H), 3.4 (t, J = 6.2 Hz, 2 H), 2.02–1.90 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 197.28 (e), 143.95 (e), 128.62 (e), 128.2 (o), 125.54 (o), 53.52 (e), 53.13 (e), 26.1 (e), 24.27 (e); MS (EI, 70 eV) m/e 191 (M^+, base), 158 (19.3), 130 (90.4), 121 (75.4), 70 (44.2); HRMS (EI) exact mass calcd for $C_{11}H_{13}NS$ 191.0769 (M^+), found 191.0761.

Preparation of 6a Using Lawesson's Reagent.[10] To a solution of 195 mg (1.1 mmol) of **5a** in 10 mL of dry benzene was added 540 mg (1.3 mmol, 1.2 equiv) of Lawesson's reagent, and the reaction mixture was stirred for 12 h at room temperature, under argon. The heterogeneous solution was concentrated *in vacuo* and purified by flash chromatography, using 1 × 6 in. of 60–200-mesh silica gel, eluting with 3:7 to 1:1 EtOAc/hexanes. Concentration provided 210 mg (99%) of **6a** as a white solid which gave spectral characteristics identical to those reported above.

***N,N*-Dimethylthiobenzamide (6b).**[19] A solution of 165 mg (1.1 mmol) of amide in 5 mL of CH_2Cl_2 was subjected to the conditions specified in method A. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting

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with 1:1 Et_2O/pentane, to give 183 mg (100%) of **6b** as a colorless crystalline solid: mp 66–67 °C; IR ($CDCl_3$) 2938, 1518, 1394, 1142, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.314 (m, 5 H), 3.59 (s, 3 H), 3.15 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.15 (e), 143.26 (e), 128.46 (o), 128.22 (o), 125.62 (o), 44.06 (o), 43.13 (o); MS (EI, 70 eV) *m/e* 165 (M^+, 79.0), 164 (base), 131 (12.9), 121 (72), 77 (26.17); HRMS (EI) exact mass calcd for $C_9H_{11}NS$ 164.0534 (M^+ – H), found 164.0531.

Thiobenzamide (6c). A solution of 124.7 mg (1.02 mmol) of amide in 5 mL of CH_2Cl_2 was subjected to the conditions specified in method C. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting with 1:1 EtOAc/hexane, to give 42 mg (30%) of **6c** as a pale yellow solid: mp[3h] 116–117; IR[19] ($CDCl_3$) 3496, 3380, 1600, 1370, 1328, 1280 1184, 1076 cm^{-1}; ^1H NMR[3h] ($CDCl_3$, 300 MHz) δ 7.87 (d, J = 7.13 Hz, 2 H), 7.75 (br s, 1 H), 7.52 (t, J = 7.4 Hz, 1 H), 7.41 (m, 2 H), 7.23 (br s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.14 (e), 131.99 (o), 128.47 (o), 126.85 (o); MS (EI, 70 eV) *m/e* 137 (M^+, base), 121 (25.2), 104 (38.8), 77 (21.6); HRMS (EI) exact mass calcd for C_7H_7NS 137.0299 (M^+ + H), found 137.0299.

1-(Thioacetyl)pyrrolidine (6d).[24] A solution of 115.4 mg (1.03 mmol) of amide in 2 mL of CH_2Cl_2 was subjected to the conditions specified in method C. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting with 1:1 EtOAc/hexane, to give 120 mg (91%) of **6d** as a white solid: mp[2a] 64–65 °C; IR ($CDCl_3$) 2980, 2878, 1494, 1476, 1455, 1332, 1260, 1230, 1220, 1104 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.79 (m, 2 H), 3.56 (m, 2 H), 2.54 (s, 3 H), 2.0 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.69 (e), 53.5 (e), 51.18 (e), 32.71 (o), 26.32 (e), 24.51 (e); MS (EI, 70 eV) *m/e* 129 (M^+, base), 115 (41.7), 96 (12.7), 70 (37.2), 68 (64.56); HRMS (EI) exact mass calcd for $C_6H_{11}NS$ 129.0612 (M^+ + H), found 129.0612.

***N*-Methylthioacetamide (6e).**[25] A solution of 0.1 mL (1.3 mmol) of amide in 5 mL of CH_2Cl_2 was subjected to the conditions specified in method C. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting with 1:1 Et_2O/pentane, to give 96.5 mg (77%) of **6e** as a white solid: mp 56–57 °C; IR ($CDCl_3$) 3414, 3244, 2972, 2938, 1554, 1360, 1212, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.98 (br s, 1 H), 3.12 and 3.10 (s, 3 H), 2.52 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.4 (e), 33.56 (o), 32.99 (o); MS (EI, 70 eV) *m/e* 89 (M^+, base), 74 (13), 59 (32), 56 (38); HRMS (EI) exact mass calcd for C_3H_7NS 89.0299 (M^+ + H), found 89.0294.

Preparation of 6e Using Lawesson's Reagent.[10] To a solution of 0.10 mL (1.3 mmol) of **5e** in 5 mL of dry benzene was added 610 mg (1.5 mmol, 1.15 equiv) of Lawesson's reagent, and the reaction mixture was stirred for 12 h at room temperature, under argon. The heterogeneous solution was concentrated *in vacuo* and purified by flash chromatography, using 1 × 6 in. of 60–200-mesh silica gel, eluting with 3:7 to 1:1 EtOAc/hexanes. Concentration provided 104 mg (89%) of **6e** as a white solid which gave spectral characteristics identical to those reported above.

1-(Thiopivaloyl)pyrrolidine (6f).[23] A solution of 200 mg (1.3 mmol) of amide in 5 mL of CH_2Cl_2 was subjected to the conditions specified in method A. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting with 1:1 EtOAc/hexane, to give 214 mg (92%) of **5f** as a pale yellow solid: mp 33–35 °C; IR (film) 2970, 1420, 1364, 1260, 1152, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.76 (m, 4 H), 1.90 (m, 4 H), 1.30 (s, 9 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 208.76 (e), 57.46 (e), 52.63 (e), 43.3 (e), 29.98 (o), 27.05 (e), 22.68 (e); MS (EI, 70 eV) *m/e* 171 (M^+, 87.7), 156 (21.2), 129 (34.4), 114 (90.7), 70 (base); HRMS (EI) exact mass calcd for $C_9H_{17}NS$ 171.1082 (M^+), found 171.1078. Anal. Calcd for $C_9H_{17}NS$: C, 63.1; H, 10.00; N, 8.18; S, 18.72. Found: C, 63.10; H, 9.64; N, 8.18; S, 18.44.

Preparation of 6f Using Lawesson's Reagent.[10] To a solution of 180 mg (1.16 mmol) of **5f** in 10 mL of dry benzene was added 563 mg (1.4 mmol, 1.2 equiv) of Lawesson's reagent, and the reaction mixture was stirred for 48 h at room temperature, under argon. The heterogeneous solution was concentrated *in vacuo* and purified by flash chromatography, using 1 × 6 in. of 60–200-mesh silica gel, eluting with 3:7 to 1:1 EtOAc/hexanes. Concentration provided 171 mg (86%) of **6f** as a pale yellow solid which gave spectral characteristics identical to those reported above.

1-(Thioformyl)piperidine (6g). A solution of 206 mg (1.82 mmol) of lactam in 5 mL of CH_2Cl_2 was subjected to the conditions specified in method A. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting with 1:1 Et_2O/pentane, to give 218 mg (93%) of **6g** as a colorless oil: IR (film) 2936, 2859, 1510, 1448, 1242, 1210, 1133, 1109, 1009 cm^{-1}; ^1H NMR[26] ($CDCl_3$, 200 MHz) δ 9.19 (s, 1 H), 3.98 (t, J = 5.6 Hz, 2 H), 3.57 (t, J = 5.6 Hz, 2 H), 1.64 (br s, 6 H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 185.55 (o), 56.44 (e), 45.79 (e), 26.63 (e), 24.74 (e), 24.13 (e); MS (EI, 70 eV) *m/e* 129 (M^+, base), 100 (13.2), 96 (37.6), 84 (43.4), 69 (34.3), 55 (40); HRMS (EI) exact mass calcd for $C_6H_{11}NS$ 129.0612 (M^+), found 129.0609. Anal. Calcd for $C_9H_{11}NS$: C, 55.77; H, 8.58; N, 10.84; S, 24.81. Found: C, 55.46; H, 8.30; N, 10.71; S, 24.51.

Preparation of 6g Using Lawesson's Reagent.[10] To a solution of 191 mg (1.7 mmol) of **5g** in 10 mL of dry benzene was added 819 mg (2.0 mmol, 1.2 equiv) of Lawesson's reagent, and the reaction mixture was stirred for 12 h at room temperature, under argon. The heterogeneous solution was concentrated *in vacuo* and purified by flash chromatography, using 1 × 6 in. of 60–200-mesh silica gel, eluting with 3:7 to 1:1 EtOAc/hexanes. Concentration provided 217 mg (100%) of **6g** as a colorless oil which gave spectral characteristics identical to those reported above.

***N,N*-Diisopropylthioformamide (6h).** A solution of 0.15 mL (1.03 mmol) of amide in 5 mL of CH_2Cl_2 was subjected to the conditions specified in method A. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting with 1:1 Et_2O/pentane, to give 145 mg (97%) of **6h** as a pale yellow solid: mp[27] 67–68 °C; IR ($CDCl_3$) 2980, 2936, 1499, 1456, 1304, 1146, 1018 cm^{-1}; ^1H NMR[28] ($CDCl_3$, 300 MHz) δ 9.35 (s, 1 H), 5.65 (septet, J = 6.8 Hz, 1 H), 3.82 (septet, J = 6.8 Hz, 1 H), 1.31 (d, J = 6.9 Hz, 6 H), 1.21 (d, J = 6.9 Hz, 6 H); ^{13}C NMR[25] ($CDCl_3$, 75 MHz) δ 184.46 (o), 48.48 (o), 48.39 (o), 24.08 (o), 19.03 (o); MS (EI, 70 eV) *m/e* 145 (M^+, 45.3), 102 (38.7), 70 (13.6), 58 (base); HRMS (EI) exact mass calcd for $C_7H_{15}NS$ 145.0925 (M^+), found 145.0922.

Preparation of 6h Using Lawesson's Reagent.[10] To a solution of 0.15 mL (1.0 mmol) of **5h** in 5 mL of dry benzene was added 461 mg (1.14 mmol, 1.14 equiv) of Lawesson's reagent, and the reaction mixture was stirred for 12 h at room temperature, under argon. The heterogeneous solution was concentrated *in vacuo* and purified by flash chromatography, using 1 × 6 in. of 60–200-mesh silica gel, eluting with 3:7 to 1:1 EtOAc/hexanes. Concentration provided 128 mg (86%) of **6h** as a yellow solid which gave spectral characteristics identical to those reported above.

2-(1,3-Benzodioxol-5-yl)-1-(thioacetyl)pyrrolidine (6i). A solution of 238 mg (1.02 mmol) of amide in 5 mL of CH_2Cl_2 was subjected to the conditions specified in method C. Purification was accomplished by filtration through a short plug of 60–200-mesh silica gel, eluting with 1:1 EtOAc/hexane, to give 233 mg (91%) of **6i** as a waxy white solid: mp 86–87 °C; IR ($CHCl_3$) 2880, 1504, 1490, 1452, 1332, 1246, 1184, 1156, 1088 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.91 (s, 1 H), 6.74 (s, 2 H), 5.93 (s, 2 H), 4.08 (s, 2 H), 3.85 (t, J = 6.5 Hz, 2 H), 3.54 (t, J = 6.7 Hz, 2 H), 1.97 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.03 (e), 147.82 (e), 146.46 (e), 129.04 (e), 121.6 (o), 108.9 (o), 108.23 (o), 100.96 (e), 54.16 (e), 50.83 (e), 50.79 (e), 26.46 (e), 24.27 (e); MS (EI, 70 eV) *m/e* 249 (M^+, 45.5), 216 (2.64), 178 (9.66), 135 (23.1), 114 (base); HRMS (EI) exact mass calcd for $C_{13}H_{15}NO_2S$ 249.0824 (M^+), found 249.0819. Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62; S, 12.86. Found: C, 62.45; H, 6.22; N, 5.75; S, 12.95.

Preparation of 6i Using Lawesson's Reagent.[10] To a solution of 257 mg (1.1 mmol) of **5i** in 20 mL of dry benzene was

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added 519 mg (1.3 mmol, 1.15 equiv) of Lawesson's reagent, and the resulting heterogeneous mixture was heated to reflux for 6 h. After being cooled to room temperature, the solution was concentrated *in vacuo* and purified by flash chromatography using 1.25 × 6 in. of 60–200-mesh silica gel, eluting with 3:7 EtOAc/hexanes. Concentration provided 286 mg (100%) of **6i** as a white solid which gave spectral and physical characteristics identical to those reported above.

Acknowledgment. We thank the National Institutes of Health (GM 32693) for support of this work. We are grateful to A. Rothwell for supplying mass spectra and to Dr. H.-P. D. Lee for supplying elemental analyses.

Supplementary Material Available: ^{1}H and ^{13}C NMR spectra of previously unreported compounds **3a**, **3c**, **3g**, **4g**, **6g**, **6h**, and **6i** (14 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 the ACS; see any current masthead page for ordering information.