Pergamon

Tetrahedron 54 (1998) 6987–6998

TETRAHEDRON

SYNTHESIS OF OXAZINES AND THIAZINES BY CYCLODEHYDRATION OF HYDROXY AMIDES AND THIOAMIDES[§]

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Received 6 January 1998; revised 18 February 1998; accepted 19 February 1998

Abstract: Dihydro-1,3-oxazines and -thiazines were obtained by cyclodehydration of hydroxy amides and thioamides with PEG-linked Burgess reagent or under Mitsunobu conditions. Yields were generally higher with polymer-Burgess reagent, but both conditions failed to cyclize δ- and ε-hydroxy amide precursors. In contrast, Burgess reagent was successful for the cyclodehydration of δ-hydroxy thioamide to give the expected thiazepine heterocycle, whereas the Mitsunobu reaction provided only thioacyl pyrrolidine. Both sets of reaction conditions led to thioacyl piperidine in the cyclodehydration of ε-hydroxy thioamide. Thiolysis of oxazines provided hydroxy thioamide intermediates in moderate to good yield, thus establishing a new protocol for the conversion of oxazines to thiazines.

Introduction

The broad utility of 5,6-dihydro-4*H*-[1,3]oxazines **1** in organic synthesis has received considerable attention.[1] These heterocycles have been shown to be stable to cold basic solutions, but are labile in acidic media and ring-open to form 3-aminopropyl esters **2** (Scheme 1).[2] Subsequent rearrangement occurs in basic media to form 3-hydroxypropylamides. Reduction of the imine bond can be accomplished with sodium borohydride to afford the tetrahydro derivatives **3** which serve as masked aldehyde equivalents.[3] *N*-Alkylation is also possible; subsequently Grignard reagents can be added to the imine;[4] further treatment with NaH will induce tautomerization, leading to the exocyclic double bond in **4**, which will undergo addition to electrophiles. Oxazines will also undergo cycloaddition reactions with ketenes and epoxides to yield bicyclic compounds **5**[5] and **6**,[6] respectively. Other useful aspect of oxazine chemistry include nucleophilic additions and enolate anion alkylations, exemplified with structures **7** and **8**.

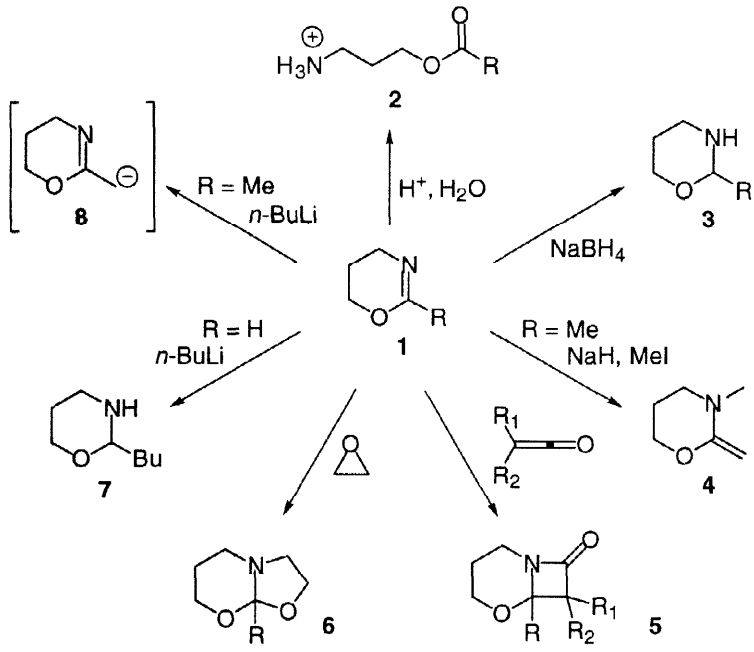
The major methods for the preparation of 5,6-dihydro-4*H*-[1,3]oxazines are based on the mineral acid-catalyzed cyclocondensation of activated caboxylic acids or nitriles with 3-halo- and 3-hydroxypropylamines,[1,7,8] ring closure of γ-haloalkylamides,[9] Diels-Alder addition of *N*-acylimines and alkenes,[10] and acid-catalyzed amidoalkylation of terminal olefins.[11] Recently, Badiang and Aubé

§ Dedicated to our colleague and friend Professor Madeleine M. Joullié in celebration of forty years of distinguished teaching and research at the University of Pennsylvania.

0040-4020/98/$19.00
PII: S0040-4020(98)00341-X

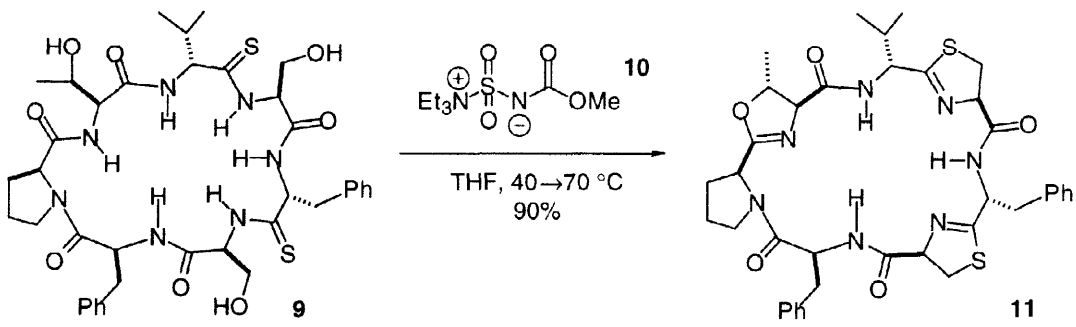
reported a novel one-step conversion of aldehydes to oxazines with 1,3-azido alcohols.[12] Fewer routes are available for the preparation the sulfur-analogs of **1**, 5,6-dihydro-4*H*-[1,3]thiazines.[13] Cyclization of γ-hydroxy and γ-halo amides in the presence of P_2S_5 leads to thiazines. Base-catalyzed processes leading to oxazines are less apparent; however, ring formation will occur by deprotonation of isonitriles, followed by treatment with an epoxide.[14] This method can also be adapted for the synthesis of thiazines by substituting an episulfide, and promoting ring closure by treatment with CuO.[15]

Scheme 1



Due to the ready availability of the starting materials, the cyclodehydration of β-hydroxy-α-amino acid derivatives represents an attractive pathway to the related five-membered oxazolines and thiazolines.[16] The use of Burgess reagent (**10**)[17] for the preparation of oxazolines[18] and thiazolines[19] under neutral reactions conditions allows for the selective assembly of these heterocycles on polyfunctionalized scaffolds (Scheme 2).[20]

Scheme 2



Similar cyclodehydrations have been achieved under Mitsunobu conditions[21] and by the use of thionyl chloride;[22] however, the latter protocols tend to be harsher and therefore more prone to epimerizations and side reactions.[18,19] In this paper, we report our studies on the use of Burgess reagent and Mitsunobu conditions for the preparation of oxazines and thiazines as well as larger heterocycles by cyclodehydration of readily available hydroxy amide and thioamide precursors.

Results and Discussion

Polyethylene-linked Burgess reagent **13**[17b] was selected for the cyclodehydration of amides **12** (Scheme 3). For comparison, each of these substrates was also subjected to Mitsunobu conditions. The results of these studies are summarized in Table 1.

Scheme 3

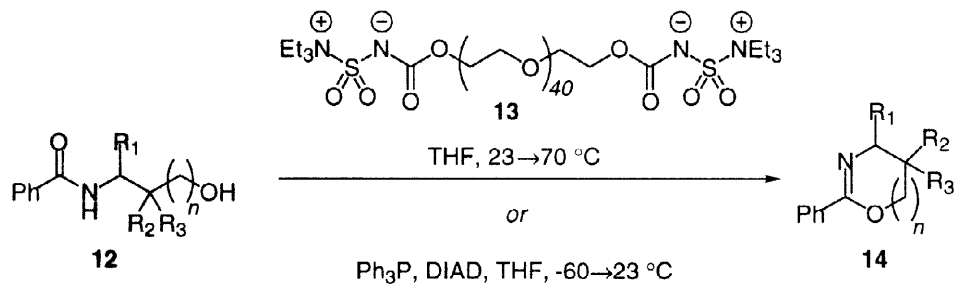


Table 1. Cyclodehydration of hydroxyamides **12** under Burgess and Mitsunobu conditions.

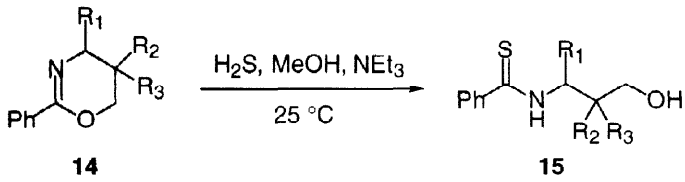
Entry	*n*	R_1	R_2	R_3	Product	Yield of PEG-Burgess Reaction	Yield of Mitsunobu Reaction
1	1	H	H	H	**14a**	42%	13%
2	1	H	Me	Me	**14b**	69%	71%
3	1	$CONMe_2$	H	H	**14c**	55%	40%
4	2	H	H	H	**14d**	-	-
5	3	H	H	H	**14e**	-	-

Treatment of *N*-acyl alcohol **12a** with 1.5 equiv of PEG-Burgess reagent **13** in THF at room temperature, followed by warming to 70 °C for 2 h, yielded the 5,6-dihydro-[1,3]oxazine **14a** in 42%

yield (entry 1). In contrast, the corresponding Mitsunobu reaction with triphenylphosphine and diisopropyl azodicarboxylate (DIAD) in THF provided only 13% of this oxazine. As expected,[23] introduction of a *gem*-dimethyl moiety facilitated cyclization, and both PEG-Burgess reagent and Ph_3P/DIAD performed similarly well in the preparation of oxazine **14b** (entry 2). For the cyclodehydration of the amide-substituted **12c**, PEG-Burgess was slightly superior to Mitsunobu conditions and provided oxazine **14c** in 55% yield (entry 3). However, increases in the chain length were not tolerated by either reagent, and no seven- or eight-membered heterocycles were obtained from hydroxy amides **14d** and **14e** (entries 4 & 5). In the latter cases, elimination of the alcohol was favored over cyclodehydration.

The conversion of oxazolines to thiazolines by selective thiolysis followed by cyclodehydration represents an efficient new strategy for the preparation of these heterocycles.[20i,24] We have now found that this method can also be used for the conversion of oxazines to thiazines. Thiolysis of oxazines **14a-c** with a solution of H_2S in MeOH/NEt_3 (1 : 1) at 25 °C provided the thioamides **15a-c** in 42-72% yield (Scheme 4, Table 2). The reaction time was dependent on the level of ring-substitution; the more highly substituted oxazine **14b** required 4 d to provide thioamide **15b** in 65% yield (entry 2) whereas thiolysis of the least substituted **14a** was complete in 6 h (entry 1). The dimethyl amide substituted **15c** was isolated in 72% yield after 1 d (entry 3).[25]

Scheme 4



14 **15**

Table 2. Thiolysis of oxazines **14**.

Entry	R_1	R_2	R_3	Reaction Time	Product	Yield
1	H	H	H	6 h	**15a**	42%
2	H	Me	Me	4 d	**15b**	65%
3	$CONMe_2$	H	H	1 d	**15c**	72%

As anticipated from our studies on the cyclization of β-hydroxy thioamides to give thiazolines,[19a,24] cyclodehydration of thioamides **15** proved more facile due to the increased

nucleophilicity of the thioamide vs. the amide group (Scheme 5). Room temperature was sufficient to allow intramolecular nucleophilic displacement in the presence of either Burgess or Mitsunobu reagents. The use of PEG-Burgess reagent was again mostly superior to cylodehydration under Mitsunobu conditions (Table 3). Thioamide **15a** provided 51% of 5,6-dihydro-[1,3]thiazine **16a**, whereas only 21% of this heterocycle was obtained with Ph_3P/DIAD (entry 1). Similarly, yields for the polymer-Burgess cyclization of dimethyl- and amide-substituted thioamides **15b** and **15c** were increased (64% and 71%, respectively) vs. the Mitsunobu reactions (40% and 54%, respectively; entries 2 & 3).

Scheme 5

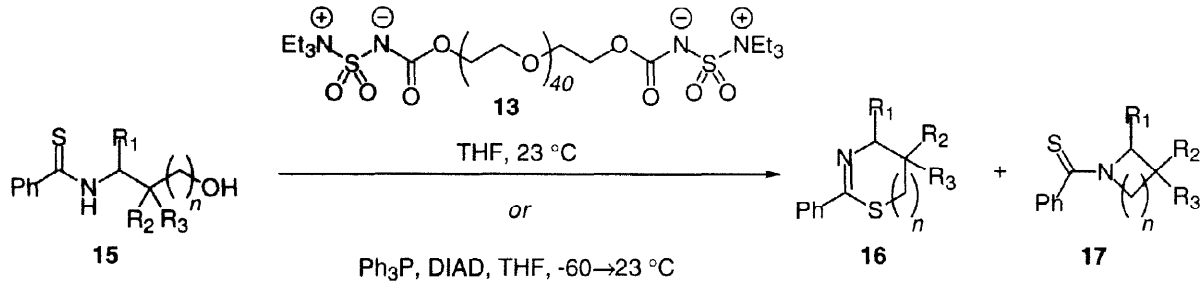


Table 3. Cyclodehydration of hydroxy thioamides **15** under Burgess and Mitsunobu conditions.

Entry	*n*	R_1	R_2	R_3	Product(s)	Yield of PEG-Burgess Reaction	Yield of Mitsunobu Reaction
1	1	H	H	H	**16a**	51%	21%
2	1	H	Me	Me	**16b**	64%	40%
3	1	$CONMe_2$	H	H	**16c**	71%	54%
4	2	H	H	H	**16d/17d**	17% (**16d**)[a]; 40% (**17d**)	76% (**17d**)
5	3	H	H	H	**17e**	38%	71%

[a] **16d** was isolated as the sole product in 58% yield using standard Burgess reagent **10**.

In contrast to the results observed for amides **12d** and **12e**, however, cyclodehydration of δ- and ε-hydroxy thioamides **15d** and **15e** competed now very effectively with elimination. In addition to 40% of thioacyl pyrrolidine **17d**, 17% of the 4,5,6,7-tetrahydro-[1,3]thiazepine **16d** was also obtained (entry 4).[26] Interestingly, thiazepine **16d** was the only product isolated after exposure of thioamide

15d to standard Burgess reagent **10**.[17b,19a] Currently, it is not yet clear what causes this considerable difference in chemoselectivity between the polymer-linked **13** and the low-molecular weight Burgess reagent **10**. In our control experiments, only substrate **15d** provided a different product distribution when exposed to reagent **10**. All other substrates provided comparable or lower yields of the same product isolated with reagent **13**. Since under the more reactive and more basic Mitsunobu conditions only the thioacyl pyrrolidine product **17d** was isolated from **15d**, it can be speculated that the improved leaving group ability of the polymer-linked sulfamoyl carbamate in **13** favors the kinetically preferred five-membered ring formation, whereas the less electron-withdrawing methyl sulfamoyl carbamate leaving group derived from **10** allows for the formation of the seven-membered heterocycle.[27] We plan to conduct further studies on modulating the reactivity of (carboxysulfamoyl)ammonium inner salts by attachment of electron-donating and -releasing substituents. Even with Burgess reagent **10**, cyclodehydration of ε-hydroxy thioamides **15e** provided only *N*-alkylated product **17e** (entry 5). The yield of this piperidide was clearly superior under the more basic Mitsunobu reaction conditions.

Conclusions

Our investigations demonstrate that although the reaction occurs slightly more slowly than in the oxazoline and thiazoline series, the Burgess cyclodehydration strategy can be applied to the synthesis of 5,6-dihydro-4*H*-[1,3]oxazines and thiazines in moderate to good yields. The mild reaction conditions using polyethyleneglycol-linked reagent that is readily separated from the reaction mixture provide generally superior yields compared to the Mitsunobu reaction for the conversion of γ-hydroxy amides and thioamides to six-membered heterocycles. Furthermore, we have been able to extend the oxazoline→thiazoline heterocycle conversion route to oxazines and thiazines. Thiolysis of oxazines provides a convenient, chemoselective access to thioamide precursors for thiazine formation.

For the preparation of seven- and eight-membered heterocycles, neither the Burgess reagent nor Mitsunobu cyclodehydration conditions are successful for the conversion of hydroxy amides. However, encouraging results have been obtained for the cyclodehydration of the corresponding hydroxy thioamides. Thiazepine, pyrrolidine, and piperidine products were obtained from the corresponding acyclic precursors in high selectivity depending on the reagent used. In particular, the chemoselectivity differences between standard Burgess reagent **10** and our polymer-linked variant **13** are noteworthy and will form the basis for further investigations on the mechanistic effects of the "non-participating" polymer backbone.

Experimental Section

General. Anhydrous solvents were freshly distilled from either sodium benzophenone ketyl, P_2O_5, or CaH_2. All reactions were performed in oven-dried glassware under an argon or nitrogen atmosphere. IR spectra were recorded on an IBM IR/32 spectrophotometer. NMR spectra were recorded in $CDCl_3$ unless stated otherwise on a Bruker AC-300 NMR spectrometer (300 MHz for ^1H NMR and 75 MHz for ^{13}C NMR) and are reported in ppm relative to tetramethylsilane (δ). Data are

reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, and coupling constants. Mass spectra were obtained on a VG-70-70 HF. Analytical TLC used Merck silica gel 60 F-254 plates, and flash chromatography on SiO_2 or florisil was used to separate and purify the crude reaction mixtures.

General procedure A for the preparation of γ-hydroxy amides. *N*-(3-Hydroxypropyl)benzamide (12a). A solution of 3.0 g (21.3 mmol) of 3-amino-1-propanol and 2.4 g (23.5 mmol) of Et_3N in 35 mL of CH_2Cl_2 was cooled to 0 °C, treated with 3.0 g (21.3 mmol) of benzoyl chloride and warmed to 25 °C over a period of 2 h with stirring. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in 20 mL of EtOAc and filtered. The filtrate was concentrated *in vacuo* and chromatographed on SiO_2 (EtOAc) to yield 2.9 g (77%) of **12a**[28] as a crystalline solid: R_f 0.39 (EtOAc); ^1H NMR δ 7.79 - 7.76 (m, 2 H), 7.52 - 7.41 (m, 3 H), 6.63 (bs, 1 H), 3.73 (t, 2 H, J = 5.6 Hz), 3.65 (q, 2 H, J = 5.9 Hz), 2.14 (bs, 3 H), 1.84 - 1.77 (m, 2 H).

***N*-(3-Hydroxy-2,2-dimethyl-propyl)-benzamide (12b).** According to the general procedure A, 3.41 g (24.3 mmol) of benzoyl chloride and 2.7 g (26.7 mmol) of Et_3N were allowed to react with 3.0 g (29.1 mmol) of 2,2-dimethyl-3-amino-1-propanol.[29] Purification on SiO_2 (EtOAc/Hexanes, 2:3) yielded 4.71 g (78%) of **12b** as a white, crystalline solid: Mp 107.6 - 108.6 °C; IR (KBr) 3303, 3289, 3275, 3189, 2957, 1641, 1578, 1557, 1039, 706 cm^{-1}; ^1H NMR δ 7.77 (d, 2 H, J = 7.2 Hz), 7.54 - 7.42 (m, 3 H), 6.69 (bs, 1 H), 3.93 (t, 1 H, J = 6.7 Hz), 3.25 (d, 2 H, J = 6.6 Hz), 3.26 - 3.24 (d, 2 H, J = 6.3 Hz), 0.94 (s, 6 H); ^{13}C NMR δ 169.0, 133.9, 131.6, 128.5, 126.9, 68.7, 47.3, 36.6, 22.7; MS (EI) *m/z* (rel intensity) 207 (M^+, 14), 177 (21), 134 (33), 105 (100), 77 (34); HRMS *m/z* calcd for $C_{12}H_{17}NO_2$: 207.1259, found 207.1261.

***N*-(1-Dimethylcarbamoyl-3-hydroxypropyl)-benzamide (12c).** *N,N*-Dimethylamine gas was bubbled into a stirred solution of 0.196 g of *N*-(2-oxo-tetrahydro-furan-3-yl)-benzamide[30] (0.95 mmol) in 2 mL of MeOH at 0 °C for 15 min. The reaction vessel was then sealed and stirred for 12 h at 25 °C. The solvent was removed *in vacuo* and the mixture was purified by chromatography on SiO_2 (MeOH/CH_2Cl_2, 1:20) to yield 0.218 g of **12c** (92%) as a white solid: Mp 127.4 - 128.1 °C; IR (KBr) 2950, 2936, 1641, 1629, 1537, 1459, 1421, 1309, 1258 cm^{-1}; ^1H NMR δ 7.83 - 7.81 (m, 2 H), 7.53 - 7.36 (m, 4 H), 5.25 - 5.18 (m, 1 H), 4.23 - 4.18 (m, 1 H), 3.73 - 3.59 (m, 2 H), 3.13 (s, 3 H), 3.00 (s, 3 H), 2.11 - 2.00 (m, 1 H), 1.62 - 1.53 (m, 1 H); ^{13}C NMR δ 171.7, 168.1, 132.0, 131.9, 128.6, 127.1, 57.8, 46.8, 37.0, 36.2, 35.7; MS (EI) *m/z* (rel intensity) 250 (M^+, 14), 206 (37), 178 (34), 105 (100), 77 (48), 72 (19); HRMS *m/z* calcd for $C_{13}H_{19}N_2O_3$: 250.1317, found 250.1325.

***N*-(4-Hydroxybutyl)-benzamide (12d).** According to the general procedure A, 3.0 g (21.3 mmol) of benzoyl chloride and 2.4 g (23.5 mmol) of Et_3N were reacted with 2.3 g (25.6 mmol) of 4-amino-1-butanol to yield 3.4 g (82%) of **12d**[31] as a white solid: ^1H NMR δ 7.78 - 7.75 (m, 2 H), 7.52-7.40 (m, 3 H), 6.55 (bs, 1 H), 3.73 (t, 2 H, J = 3.06 Hz), 3.50 (q, 2 H, J = 5.58 Hz), 1.88 (bs, 1 H), 1.79 - 1.62 (m, 4 H).

***N*-(5-Hydroxypentyl)-benzamide (12e).** According to the general procedure A, 3.0 g (25.6 mmol) of 5-amino-1-pentanol and 2.5 g (23.5 mmol) of Et_3N were reacted with 3.0 g (21.3 mmol) of benzoyl chloride to yield 2.9 g (68%) of **12e**:[28] ^1H NMR δ 7.77 - 7.74 (m, 2 H), 7.52 - 7.40 (m, 3 H), 6.21 (bs, 1 H), 3.67 (t, 2 H, J = 6.2 Hz), 3.47 (q, 2 H, J = 6.2 Hz), 1.71-1.42 (m, 9 H).

Preparation of polyethylene glycol-supported Burgess reagent 13. A solution of 6.0 g (3.0 mmol) of polyethylene glycol (M_w 2000) in 30 mL of benzene was dried azeotropically for 24 h in a Dean Stark apparatus and subsequently added dropwise to a solution of 0.55 mL (0.89 g, 6.3 mmol) of $ClS(O)_2NCO$ in 10 mL of dry benzene. The reaction mixture was stirred at 25 °C for 1 h, concentrated *in vacuo* and dried overnight *in vacuo* to yield a colorless residue which was used

without further purification. A solution of this residue in 20 mL of benzene was added dropwise to a solution of 1.6 mL (11.4 mmol) of Et_3N in 10 mL of dry benzene. The reaction mixture was stirred at 25 °C for 1 h, filtered, concentrated *in vacuo*, and dried *in vacuo* to yield 5.8 g (88%) of polymer-linked Burgess reagent. The colorless reagent was used without further purification.

General procedure B for the thiolysis of oxazines. *N*-(3-Hydroxypropyl)thiobenzamide (15a). A solution of 0.048 g (0.29 mmol) of oxazine **14a** in 1 mL of MeOH and 1 mL of Et_3N was cooled to 0 °C, saturated with H_2S gas and stirred at 25 °C for 6 h. The reaction mixture was then concentrated *in vacuo* and chromatographed on SiO_2 (EtOAc/Hexanes, 3:1) to yield 0.02 g (42%) of **15a** as a pale yellow oil: R_f 0.42 (EtOAc/Hexanes, 3:1); IR (neat) 3287, 3281, 3268, 3058, 2943, 1534, 1529, 1449, 1395 cm^{-1}; ^1H NMR δ 8.57 (bs, 1 H), 7.77 - 7.75 (m, 2 H), 7.47 - 7.34 (m, 3 H), 3.99 (q, 2 H, J = 5.6 Hz), 3.84 (t, 2 H, J = 5.3 Hz), 2.43 (bs, 1 H), 1.99 - 1.91 (m, 2 H); ^{13}C NMR δ 199.0, 141.6, 131.2, 128.6, 126.8, 61.5, 45.6, 30.3; MS (EI) *m/z* (rel intensity) 195 (M^+, 39), 177 (45), 150 (49), 121 (100), 105 (92), 77 (73); HRMS *m/z* calcd for $C_{10}H_{13}NOS$: 195.0718, found 195.0710.

***N*-(3-Hydroxy-2,2-dimethyl-propyl)-thiobenzamide (15b).** According to general procedure B, a solution of 0.460 g of **14b** (2.4 mmol) in 3 mL of MeOH and 3 mL of Et_3N was saturated with H_2S gas and allowed to react for 4 d. Chromatography on SiO_2 (EtOAc/Hexanes, 3:7) yielded 0.347 g of **15b** (65%) as a viscous yellow oil: IR (neat) 3274, 3063, 2948, 2871, 1725, 1534, 1048, 696 cm^{-1}; ^1H NMR δ 8.64 (bs, 1 H), 7.79 - 7.76 (m, 2 H), 7.49 - 7.36 (m, 3 H), 3.81 - 3.80 (d, 2 H, J = 5.6 Hz), 3.49 (d, 2 H, J = 5.6 Hz), 2.70 (t, 1 H, J = 5.6 Hz), 1.05 (s, 6 H); ^{13}C NMR δ 199.2, 141.5, 131.1, 128.4, 126.6, 70.3, 55.6, 36.2, 22.9; MS (EI) *m/z* (rel intensity) 223 (M^+, 38), 192 (18), 150 (66), 121 (100), 104 (21), 77 (28), 55 (13), 44 (20); HRMS *m/z* calcd for $C_{12}H_{17}NOS$: 223.1031, found 223.1035.

4-Hydroxy-*N,N*-dimethyl-2-thiobenzoyl-butyramide (15c). According to general procedure B, a solution of 0.320 g (1.38 mmol) of **14c** in 1 mL of MeOH and 1 mL Et_3N was saturated with H_2S gas, sealed, and allowed to stir at 25 °C for 1 d. Chromatography on SiO_2 (MeOH/CH_2Cl_2, 1:20) yielded 0.263 g of **15c** as a white solid: Mp 155.4 - 156.9 °C; ^1H NMR δ 8.81 (d, 1 H, J = 6.5 Hz), 7.85-7.61 (m, 2 H), 7.53-7.38 (m, 3 H), 5.84-5.77 (m, 1 H), 3.77-3.61 (m, 3 H, 2 H after D_2O shake), 3.16 (s, 3 H), 3.03 (s, 3 H), 2.20-2.09 (m, 1 H), 1.83-1.73 (m, 1 H); ^{13}C NMR δ 199.2, 171.0, 140.7, 131.7, 128.6, 126.9, 57.4, 53.0, 36.9, 36.2, 35.8.

General procedure C for the preparation of γ-hydroxy thiobenzamides with Lawesson's reagent. *N*-(4-Hydroxybutyl)thiobenzamide (15d). A solution of 0.388 g (5.7 mmol) of imidazole and 0.86 g (5.7 mmol) of TBDMS-Cl in 25 mL of CH_2Cl_2 was cooled to 0 °C and treated dropwise with a solution of 1.0 g (5.8 mmol) of hydroxy amide **12d** in 5 mL of CH_2Cl_2, and warmed to 25 °C over a period of 2 h. The reaction mixture was filtered and concentrated *in vacuo* to give crude silyl ether which was used directly for the next reaction: R_f 0.34 (EtOAc/Hexanes, 3:7).

A solution of 1.7 g (4.27 mmol) of Lawesson's reagent in 14 mL of THF was treated dropwise with a solution of 1.2 g (3.88 mmol) of silyl ether in 2 mL of THF and stirred for 12 h at 25 °C. The reaction mixture was concentrated *in vacuo* and filtered through SiO_2 topped with basic alumina (EtOAc/Hexanes, 3:7) to give thioamide which was used directly for the next reaction: R_f 0.42 (EtOAc/Hexanes, 3:7).

A solution of 0.27 g (1.1 mmol) of thioamide in 4 mL of THF was treated with 0.30 g (1.16 mmol) of tetrabutylammonium fluoride and stirred for 0.5 h at 25 °C. The reaction mixture was concentrated and purified on SiO_2 (EtOAc) to yield 0.12 g (53%) of **15d** as a viscous yellow oil: R_f 0.42 (EtOAc); IR (neat) 3392, 3363, 3284, 2936, 1535, 1450, 1394, 1055 cm^{-1}; ^1H NMR δ 8.30 (bs, 1 H), 7.76-7.73 (m, 2 H), 7.46-7.36 (m, 3 H), 3.84 (q, 2 H, J = 6.7 Hz), 3.73 (t, 2 H, J = 5.9 Hz), 1.93-

1.84 (m, 3 H), 1.75-1.67 (m, 2 H); ^{13}C NMR δ 198.9, 141.8, 130.9, 128.4, 126.7, 62.2, 46.7, 29.6, 24.7.

N-(5-Hydroxypentyl)-thiobenzamide (15e). According to the general procedure C, 1.0 g (4.83 mmol) of **12e** was reacted with 0.8 g (5.31 mmol) of TBDMS-Cl, 0.36 g (5.31 mmol) of imidazole, 2.14 g (5.31 mmol) of Lawesson's reagent, and 1.4 g (5.07 mmol) of TBAF. Purification on SiO_2 yielded 0.54 g (51%, 3 steps) of **15e** as a viscous yellow oil: R_f 0.34 (EtOAc); IR (neat) 3247, 2934, 1535, 1460, 695 cm^{-1}; ^{1}H NMR δ 7.81 (bs, 1 H), 7.72 - 7.70 (m, 2 H), 7.47 - 7.34 (m, 3 H), 3.81 (q, 2 H, J = 5.8 Hz), 3.65 (t, 2 H, J = 6.3 Hz), 1.83 - 1.47 (m, 7 H); ^{13}C NMR δ 187.7, 130.5, 119.7, 117.0, 115.1, 57.0, 35.2, 20.5, 16.2, 11.9; MS (EI) *m/z* (rel intensity) 223 (M^+, 49), 190 (29), 178 (15), 164 (14), 150 (41), 138 (13), 121 (100), 104 (63); HRMS *m/z* calcd for $C_{12}H_{17}NOS$: 223.1031, found 223.1032.

General procedure D for cyclodehydration of γ-hydroxy amides and thioamides with PEG-Burgess reagent. 2-Phenyl-5,6-dihydro-4H-[1,3]oxazine (14a). To a solution of 0.05 g (0.28 mmol) of hydroxy amide **12a** in 2 mL of dry THF was added 0.08 g (0.34 mmol) of PEG-Burgess reagent **13**. The reaction mixture was stirred at 25 °C for 1.5 h, warmed to 70 °C and allowed to react for 2 h. The solution was concentrated *in vacuo* and filtered through a pad of SiO_2 to yield 0.019 g (42%) of **14a**[32] as a pale yellow oil: ^{1}H NMR δ 7.91 - 7.87 (m, 2 H), 7.41 - 7.34 (m, 3 H), 4.39 (t, 2 H, J = 5.4 Hz), 3.61 (t, 2 H, J = 5.8 Hz), 2.02 - 1.95 (m, 2 H).

According to general procedure E, 0.05 g (0.28 mmol) of **12a**, 0.11 g (0.42 mmol) of triphenylphosphine and 0.068 g (0.39 mmol) of DIAD yielded 6 mg (13%) of **14a** as a pale yellow oil.

General procedure E for the Mitsunobu cyclodehydration of γ-hydroxy amides and thioamides. 5,5-Dimethyl-2-phenyl-5,6-dihydro-4H-[1,3]oxazine (14b). A stirred solution of 0.5 g (2.42 mmol) of **12b** and 0.95 g (3.62 mmol) of triphenylphosphine in 5 mL of THF was cooled to -60 °C and treated dropwise with 0.683 g (3.38 mmol) of DIAD and allowed to warm to 25 °C overnight. The mixture was concentrated *in vacuo* and chromatographed on SiO_2 (EtOAc/Hexanes, 1:9) to yield 0.46 g (71%) of **14b** as a white, crystalline solid: Mp 55.4 - 56.2 °C; IR (KBr) 2952, 2899, 1660, 1466, 1448, 1343, 1278, 1116, 1072, 782 cm^{-1}; ^{1}H NMR δ 7.94 - 7.91 (m, 2 H), 7.42 - 7.33 (m, 3 H), 3.90 (s, 2 H), 3.31 (s, 2 H), 1.00 (d, 6 H, J = 6.0 Hz); ^{13}C NMR δ 154.3, 133.6, 130.2, 127.9, 126.9, 74.3, 55.6, 27.5, 23.4; MS (EI) *m/z* (rel intensity) 189 (M^+, 29), 134 (39), 105 (100), 77 (31), 56 (19); HRMS *m/z* calcd for $C_{12}H_{15}NO$: 189.1154, found 189.1150.

According to general procedure D, a solution of 0.10 g (0.48 mmol) of **12b** and 0.96 g (0.72 mmol) of **13** in 3 mL of THF yielded 67 mg (69%) of **14b** as a white, crystalline solid.

2-Phenyl-5,6-dihydro-4H-[1,3]oxazine-4-carboxylic acid dimethyl amide (14c). According to general procedure D, 0.12 g (0.47 mmol) of **12c** and 0.98 g (0.74 mmol) of **13** yielded 0.06 g (55%) of **14c** as a white crystalline solid: Mp 112.4 - 113.2 °C; IR (neat) 2915, 2833, 1604, 1573, 1429, 707 cm^{-1}; ^{1}H NMR δ 7.95 - 7.91 (m, 2 H), 7.44 - 7.32 (m, 3 H), 4.62 - 4.49 (m, 2 H), 4.42 - 4.35 (m, 1 H), 3.37 (s, 3 H), 2.99 (s, 3 H), 2.40 - 2.30 (m, 1 H), 2.04 - 1.94 (m, 1 H); ^{13}C NMR δ 170.9, 155.9, 133.6, 130.5, 127.9, 127.1, 63.6, 52.1, 37.4, 25.9, 23.2; MS (EI) m/z (rel intensity) 232 (M^+, 37), 160 (98), 130 (43), 105 (100), 77 (70), 51 (29); HRMS *m/z* calcd for $C_{13}H_{16}N_2O_2$: 232.1212, found 232.1227.

According to general procedure E, a solution of 0.41 g (1.64 mmol) of **12c** and 0.65 g (2.47 mmol) of triphenylphosphine in 2.1 mL of dry THF yielded 0.15 g (40%) of **14c** as a pale yellow oil.

2-Phenyl-5,6-dihydro-4H-[1,3]thiazine (16a). According to the general procedure D, 0.02 g (0.12 mmol) of hydroxy thioamide **15a** was reacted with 0.241 g (0.18 mmol) of PEG-Burgess reagent **13** to yield 0.012 g (51%) of **16a**[33] as a pale yellow oil: R_f 0.46 (EtOAc/Hexanes 3:1); ^{1}H NMR δ 7.78-

7.75 (m, 2 H), 7.41-7.36 (m, 3 H), 3.92 (t, 2 H, J = 5.5 Hz), 3.16 (t, 2 H, J = 6.1 Hz), 1.92 (quint, 2 H, J = 5.9 Hz).

According to general procedure E, a solution of 0.023 g (0.12 mmol) of **15a** and 0.05 g (0.18 mmol) of triphenylphosphine in 2 mL of dry THF was cooled to -60 °C and treated with 0.034 g (0.17 mmol) of DIAD to yield 0.006 g (21%) of **16a** as a pale yellow oil.

5,5-Dimethyl-2-phenyl-5,6-dihydro-4H-[1,3]thiazine (16b). According to general procedure E, 0.100 g (0.45 mmol) of **15b** was treated with 0.18 g (0.67 mmol) of triphenylphosphine and 0.13 g (0.63 mmol) of DIAD at -60 °C, and warmed to 25 °C. The reaction mixture was concentrated *in vacuo* and chromatographed on SiO_2 (EtOAc/CH_2Cl_2/Hexanes, 0.5:1:8.5) to yield 0.037 g (40%) of **16b** as a yellow solid: Mp 64.6 - 65.4 °C; IR (neat) 3066, 2959, 2921, 1617, 1240, 1033, 6889 cm^{-1}; ^1H NMR δ 7.81 - 7.77 (m, 2 H), 7.43 - 7.34 (m, 3 H), 3.61 (s, 2 H), 2.86 (s, 2 H), 1.09 (s, 6 H); ^{13}C NMR δ 157.2, 139.1, 130.2, 128.2, 126.2, 59.8, 38.3, 26.0, 24.0; MS (EI) *m/z* (rel intensity) 205 (M^+, 62), 149 (37), 121 (100), 104 (55), 84 (24), 77 (18), 56 (23), 49 (30); HRMS calcd for $C_{12}H_{15}NS$: 205.0925, found 205.0923.

According to the general procedure D, 0.05 g (0.22 mmol) of hydroxy thioamide **15b** was reacted with 0.450 g (0.34 mmol) of **13** in 1 mL of THF at 25 °C for 1 h, and warmed to 70 °C for 2 h. The reaction mixture was concentrated *in vacuo* and chromatographed on SiO_2 (EtOAc/CH_2Cl_2/Hexanes, 0.5:1:8.5) to yield 0.029 g (64%) of **16b** as a yellow solid.

2-Phenyl-5,6-dihydro-4H-[1,3]thiazine-4-carboxylic acid dimethyl amide (16c). According to general procedure E, a solution of 0.045 g (0.173 mmol) of **15c** and 0.068 g (0.259 mmol) of triphenylphosphine in 3 mL of THF was cooled to -60 °C, treated dropwise with 0.049 g (0.242 mmol) of DIAD and allowed to warm slowly to 25 °C with stirring over a period of 12 h. The solvent was removed *in vacuo*, and the mixture was chromatographed on SiO_2 (EtOAc) to yield 0.023 g (54%) of **16c** as a colorless oil: IR (neat) 2940, 2852, 1592, 1567, 1454, 770, 701 cm^{-1}; ^1H NMR δ 7.82 - 7.79 (m, 2 H), 7.44 - 7.26 (m, 3 H), 4.65 - 4.57 (dd, 1 H, J = 5.5 Hz, 11.6 Hz), 3.42 - 3.33 (m, 1 H), 3.27 (s, 3 H), 3.24-3.14 (m, 1 H), 3.02 (s, 3 H), 2.14 - 1.89 (m, 2 H); ^{13}C NMR δ 171.2, 160.0, 139.2, 130.5, 128.2, 126.5, 58.0, 37.5, 36.0, 24.8, 20.9; MS (EI) m/z (rel intensity) 248 (M^+, 14), 223 (14), 221 (25), 189 (16), 160 (32), 121 (100), 105 (69), 77 (43); HRMS calcd for $C_{13}H_{16}N_2OS$: 248.0983, found 248.0993.

According to general procedure D, a solution of 0.02 g (0.075 mmol) of **15c** and 1.496 g (1.13 mmol) of **13** in 1.5 mL of THF was stirred at 25 °C for 1 h, then warmed to 70 °C for 2 h to yield 0.023 g (71%) of **16c** as a colorless oil.

2-Phenyl-4,5,6,7-tetrahydro-[1,3]-thiazepine (16d). According to general procedure D, 0.05 g (0.24 mmol) of **15d** was treated with 0.48 g (0.36 mmol) of PEG-Burgess reagent **13** in 2 mL of THF at 25 °C for 1 h, then warmed to 80 °C and stirred for 2 h, concentrated *in vacuo*, and chromatographed on SiO_2 (EtOAc/Hexanes, 1:9) to yield 0.018 g (40%) of **17d**[34] as a white solid and 0.008 g (17%) of **16d** as a viscous yellow oil: IR (neat) 3072, 2940, 2859, 2363, 1604, 1447, 1222, 764 cm^{-1}; ^1H NMR δ 7.97-7.93 (m, 2 H), 7.42 - 7.35 (m, 3 H), 4.09 - 4.05 (m, 2 H), 2.92 - 2.88 (m, 2 H), 2.10 - 2.03 (m, 2 H), 1.91 - 1.85 (m, 2 H); ^{13}C NMR δ 163.9, 139.9, 130.6, 128.6, 128.2, 53.9, 30.9, 28.1, 25.7.

Preparation of 16d by cyclodehydration with Burgess reagent 10. A solution of 0.12 g (0.57 mmol) of **15d** was treated with 0.162 g (0.69 mmol) of Burgess reagent **10** in 2 mL of THF at 25 °C for 2 d, concentrated *in vacuo*, and chromatographed on SiO_2 (EtOAc/Hexanes, 1:9) to yield 0.063 g (58%) of **16d** as a viscous yellow oil.

1-(Thiobenzoyl)pyrrolidine (17d). A solution of 0.07 g (0.33 mmol) of thiobenzamide **15d** and 0.13 g (0.50 mmol) of triphenylphosphine in 2 mL of THF was cooled to -60 °C, treated dropwise with of 0.09 g (0.47 mmol) of DIAD and allowed to warm to 25 °C over a period of 4 h. The reaction mixture was then concentrated *in vacuo* and chromatographed on SiO_2 (EtOAc) to yield 0.48 g (76%) of **17d**[34] as a white solid: ^{1}H NMR δ 7.37 - 7.32 (m, 5 H), 4.01 - 3.96 (t, 2 H, J = 6.7 Hz), 3.47 (t, 2 H, J = 6.7 Hz), 2.14 - 2.19 (m, 4 H).

Phenyl-piperidin-1-yl-methanone (17e). A solution of 0.05 g (0.21 mmol) of thiobenzamide **15e** and 0.08 g (0.31 mmol) of triphenylphosphine in 2 mL of THF was cooled to -60 °C, treated dropwise with 0.06 g (0.29 mmol) of DIAD and allowed to warm to 25 °C over a period of 4 h. The reaction mixture was then concentrated *in vacuo* and chromatographed on SiO_2 (EtOAc) to yield 0.03 g (71%) of **17e**[35] as a yellow oil: ^{1}H NMR δ 7.34 - 7.25 (m, 5 H), 4.35 (t, 2 H, J = 5.1 Hz), 3.52 - 3.48 (m, 2 H), 1.85 - 1.70 (m, 4 H), 1.56 (quint, 2 H, J = 6 Hz).

According to the general procedure D, 0.05 g (0.21 mmol) of **15e** was treated with 0.422 g (0.32 mmol) of PEG-Burgess reagent **13** in 2 mL of THF at 25 °C for 1 h, then warmed to 80 °C and stirred for 2 h, concentrated *in vacuo*, and chromatographed to yield 0.018 g (38%) of **17e** as a yellow oil.

Acknowledgment. This work has been supported by the National Institutes of Health (GM 55433). *P. W.* thanks the A. P. Sloan and the Camille Dreyfus Foundations for Fellowships.

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