

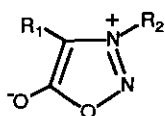
GENERATION OF THE DIHYDRO-5H-THIAZOLO[3,2-a]-PYRIDIN-3-ONE RING SYSTEM BY PROTON LOSS FROM ISOTHIOMÜNCHNONES‡

Albert Padwa* and Zhijia J. Zhang

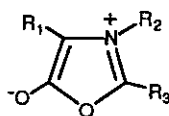
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Abstract - Dihydro-5H-thiazolo[3,2-a]pyridin-3-ones are easily generated by proton loss from isothiomünchnones. The closely related tetrahydro-2H-pyrido[2,1-b]-[1,3]thiazin-4-one ring system was prepared by treating piperidine-2-thione with acryloyl chloride. These cyclic *S,N*-ketene acetals undergo smooth reaction with different electrophiles in the presence of Lewis acids.

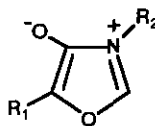
Mesoionic compounds have been known for many years and have been extensively utilized as substrates in 1,3-dipolar cycloadditions.¹⁻³ Of the known mesoionic heterocycles, the structure, physical properties, and reactions of sydnones, münchnones, and isomünchnones have drawn the closest scrutiny.⁴⁻¹⁹ The anhydro-4-hydroxythiazolium hydroxides (isothiomünchnones) represent another class of mesoionics which have not been as extensively studied as the other members of this mesoionic family.²⁰⁻²⁴ Interest in this ring system may be attributed to 1) its ease of preparation from simple thioamides,²⁰ 2) the interesting physical properties it possesses, and 3) the propensity for its thiocarbonyl ylide dipole to undergo 1,3-dipolar cycloaddition with a wide range of dipolarophiles to produce complex heterocyclic ring systems.²⁰⁻²⁴ In virtually every investigation to date, at least one of the substituents (*i.e.*, R₁, R₂ or R₃) present on the isothiomünchnone backbone has been an aryl group. This is presumably due to electronic stabilization of the dipole to a sufficient degree to allow for its isolation. In order to broaden the



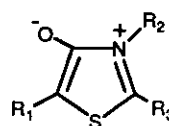
Sydones



Münchnones



Isomünchnones



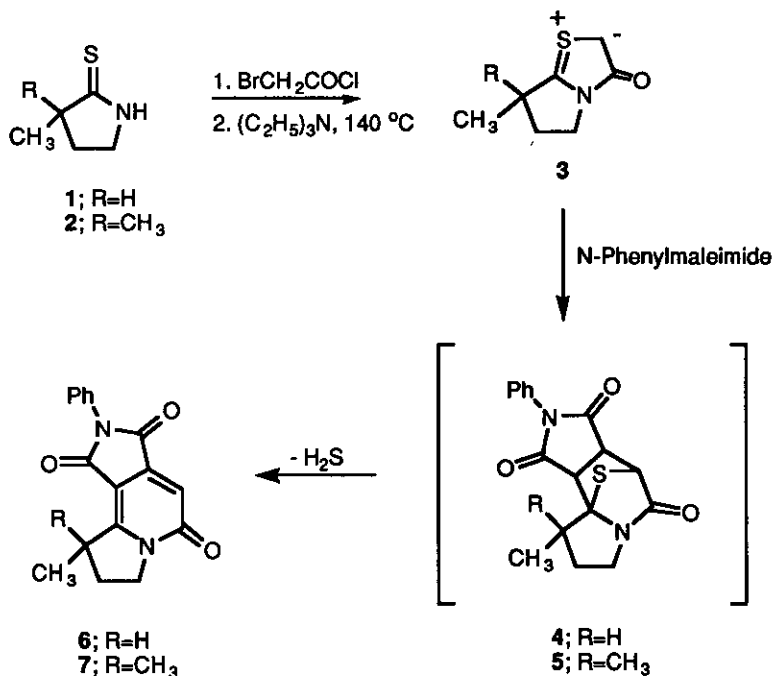
Isothiomünchnones

utility of these mesoionic compounds for synthesis, we thought it worthwhile to investigate the possibility of generating transient anhydro-4-hydroxythiazolium hydroxides in which the peripheral substituents R₁, R₂, and R₃ were of the alkyl, rather than aryl, variety. The results of this investigation are reported herein.

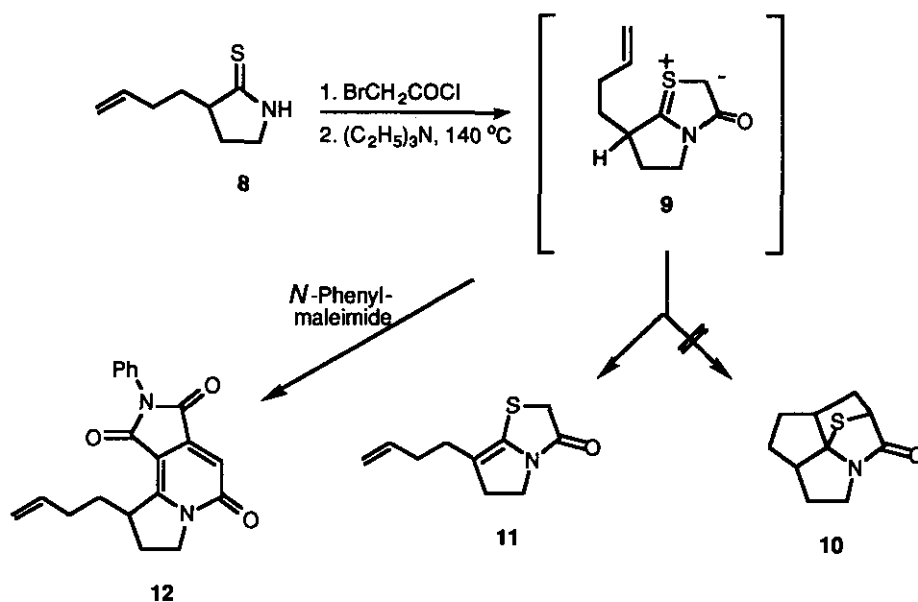
‡ Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday.

RESULTS AND DISCUSSION

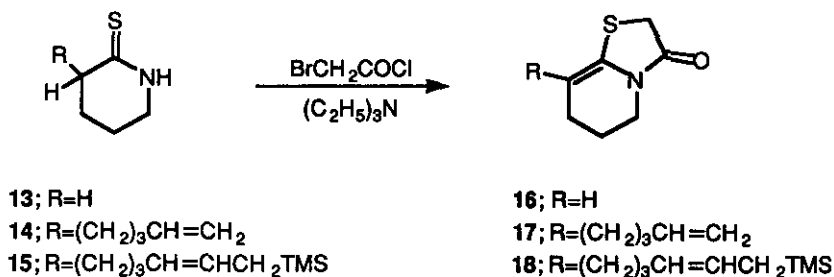
Our study commenced with an examination of simple cyclic thiolactams as mesoionic precursors. Sequential treatment of thiolactams (1) and (2) with bromoacetyl chloride and triethylamine in the presence of one equiv of *N*-phenylmaleimide afforded pyridones (6) and (7) in good yield. These compounds are derived by dipolar cycloaddition of the mesoionic species (3) with the added dipolarophile to give cycloadducts (4) or (5) as transient species which subsequently eliminate hydrogen sulfide.²⁵



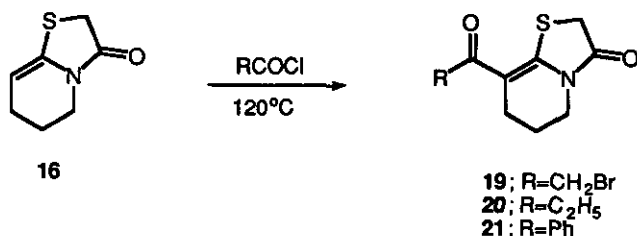
Intramolecular 1,3-dipolar cycloaddition reactions represent one of the most efficient methods for the generation of complex ring systems.²⁶ In connection with our continuing interest in this area,²⁷ we decided to investigate the cycloaddition behavior of anhydro-4-hydroxythiazolium hydroxides which possess tethered alkenes.²⁸ With this in mind, thiolactam (8) was treated under the standard conditions for dipole formation and cycloaddition. However, no product of dipolar cycloaddition across the alkenyl π -bond (*i.e.*, 10) was detected in the reaction mixture. Instead, pyrrolo[1,2-*b*]thiazolone (11) was isolated in 79% yield. This compound is derived by elimination of the proton α to the dipole center. Apparently, proton loss to give the *S,N*-ketene acetal (11) is faster than intramolecular dipolar cycloaddition across the unactivated π -bond. When the reaction was carried out in the presence of excess (2 equiv) *N*-phenylmaleimide, however, pyridone (12) could be isolated but only in 23% yield. The remaining product corresponded to pyrrolo[1,2-*b*]thiazolone (11).



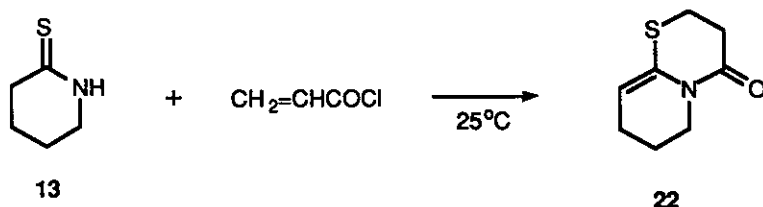
Sequential treatment of thiolactams (13-15) with bromoacetyl chloride and triethylamine resulted in a related transformation producing tetrahydro-5*H*-thiazolo[3,2-*a*]pyridines (16-18) in 80-85% yield. Again, no internal cycloaddition was detected with thiolactams (14) and (15). During the course of preparing 16, we noted the presence of a minor by-product which was substantially enhanced when excess



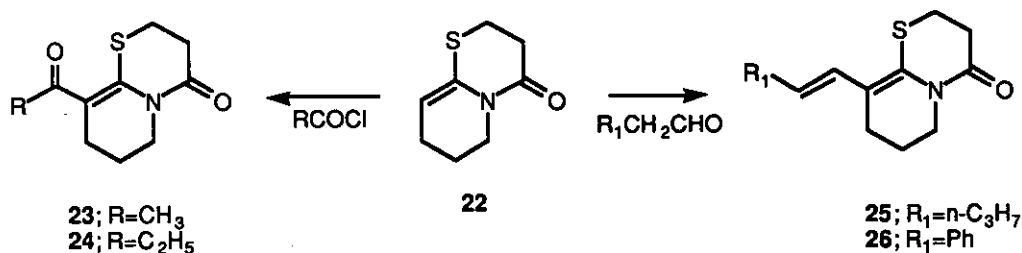
bromoacetylchloride was used. Further experimentation demonstrated that 16 reacted further with the excess acid chloride at 120°C to ultimately produce the acylated tetrahydrothiazolo[3,2-*a*]pyridine (19). A related set of reactions occurred when propionyl and benzoyl chloride were allowed to react with 16 producing compounds (20) and (21) in good yield.

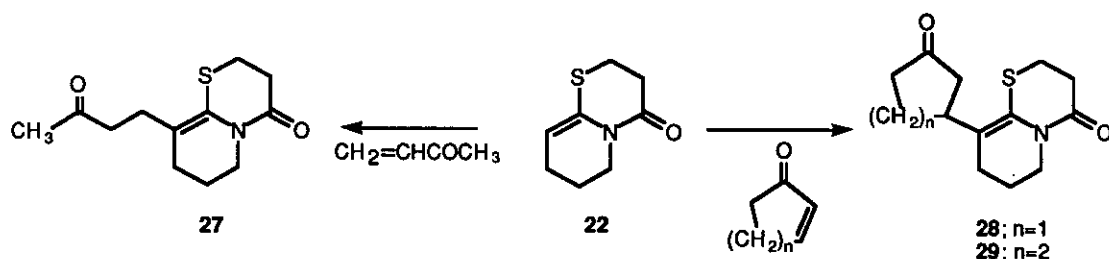


Silyl ketene *O,O*-acetals have successfully been used as the functional equivalents of ester enolates.²⁹ These ketene silyl acetals react with carbonyl³⁰ and α,β -unsaturated carbonyl compounds³¹ in the presence of Lewis acids to give the corresponding adducts in good yield. Silyl substituted *S,N*-ketene acetals, on the other hand, have not been as extensively utilized in organic synthesis. These hetero-substituted acetals are generally formed from the corresponding thioamide by allowing the lithium enethiolate to react with a trialkyl substituted silyl halide.³² The resulting *S*-silyl *S,N*-ketene acetal has been reported to undergo stereo and regioselective aldol type reactions with aldehydes and α -enones.³² Very little is known about the chemical behavior of *S,N*-ketene acetals which do not possess a silyl group on the sulfur atom. Since *S,N*-ketene acetal (**16**) was found to react with acid chlorides in the absence of a Lewis acid, we decided to study the chemical behavior of this system as well as the closely related pyridothiazine **22** with a variety of electrophilic reagents. Pyrido[2,1-*b*] [1,3]thiazine (**22**) was prepared in good yield (86%) by treating piperidine-2-thione (**13**) with acryloyl chloride. Compound (**22**) reacts smoothly with acid chlorides, aldehydes, and α,β -unsaturated ketones in either dimethoxyethane or THF.

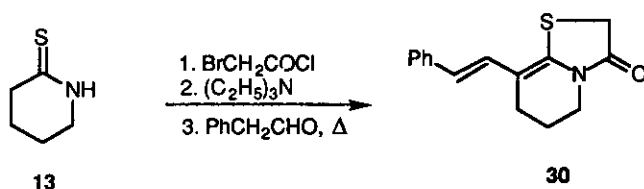


The effect of the reaction conditions on the overall yield was studied and the best result was achieved when the reaction was carried out at 0°C to room temperature in the presence of a Lewis acid. The reactions also proceeded thermally at 140°C . Thus, *S,N*-ketene acetal (**22**) reacted with acetyl or propionyl chloride to give tetrahydro-2*H*-pyrido[2,1-*b*] [1,3]thiazin-4-ones (**23**) and (**24**) in 60% and 80% yield, respectively. Reaction with valeraldehyde and benzaldehyde gave the 1,2-addition products (**25**) and (**26**) in good yield (ca 70%). Condensation of **22** with α -enones such as methyl vinyl ketone, cyclopentenone or cyclohexenone, afforded only the 1,4-addition products (*i.e.*, **27-29**) in essentially quantitative yield.

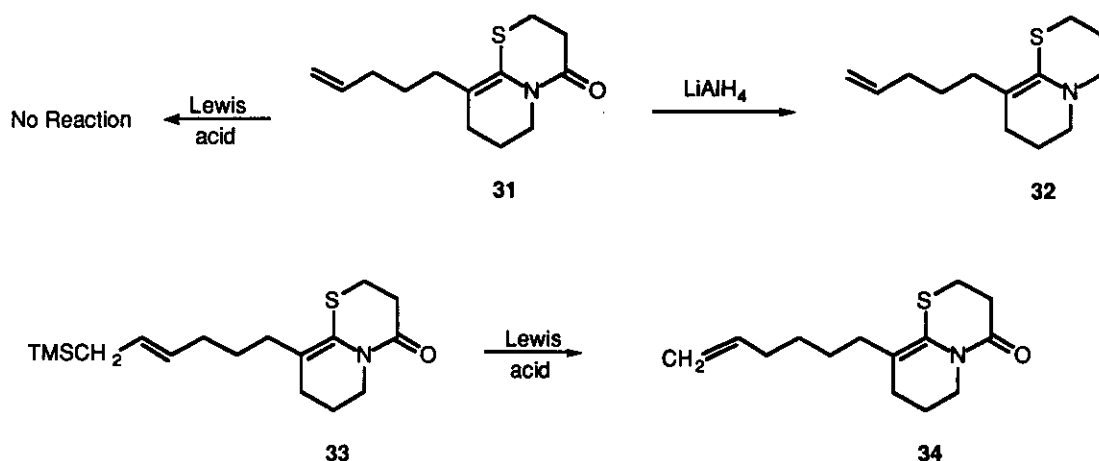




We also investigated the reaction of piperidine-2-thione (13) with bromoacetyl chloride and phenylacetaldehyde which afforded dihydro-5*H*-thiazolo[3,2-*a*]pyridin-3-one (30) in 77% yield. Presumably, the initial reaction of 13 produces 16 which reacts further with the aldehyde to give the 1,2-addition product 30.

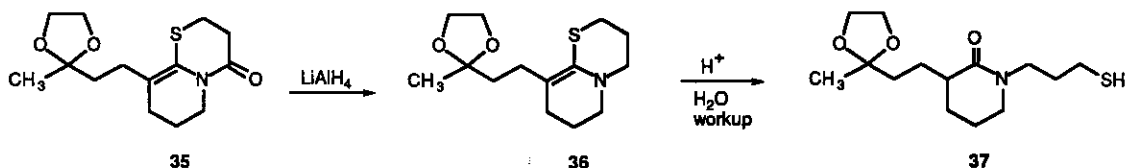


Electrophilic cyclization reactions of iminium ions and related intermediates (Mannich cyclizations) constitute some of the most important methods for preparing nitrogen heterocycles.³³ Recent years have witnessed the important development of the cyclization chemistry of α -*N*-acyliminium ions.³⁴ This initiating functionality is more reactive than a simple iminium ion and, thus, will react with a wider range of intramolecular nucleophiles. During the course of our studies, it occurred to us that the Lewis acid induced cyclization of alkenyl substituted *S,N*-ketene acetals might provide an interesting method for the synthesis of nitrogen heterocycles. We hoped that the *S,N*-ketene acetal moiety might be nucleophilic enough to generate an *N*-acyl iminium ion when treated with an appropriate Lewis acid. Toward this end,

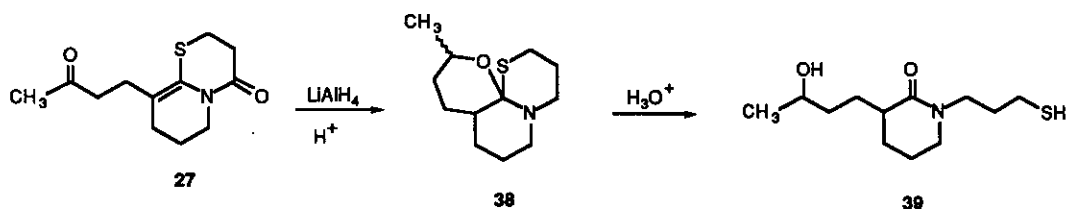


we prepared 9-pentenyl tetrahydropyridothiazinone (**31**) with the intention of inducing a cyclization reaction on the tethered π -bond. Unfortunately, all of our attempts to induce such a reaction failed to give a cyclized product. Reduction of **31** with LiAlH_4 afforded hexahydropyridothiazine (**32**) which also failed to cyclize under Lewis acid conditions. The ability of a silicon substituent to promote cationic cyclization has led to the emergence of organosilanes as particularly important functional groups for terminating electrophilic cyclization reactions.³⁵ With this in mind, we synthesized 9-(trimethylsilanylhex-4-enyl)tetrahydropyridothiazinone **33** and subjected it to a variety of Lewis acid conditions. The only material that was formed, however, corresponded to the protodesilylated product (**34**).

Since we were unable to induce Lewis acid cyclization of the 9-alkenyl substituted pyridothiazolinone system, we decided to examine the cyclization behavior of the 9-(3-oxo-butyl) system (*i.e.*, **27**). As was noted earlier, this compound is available in excellent yield by treating **22** with methyl vinyl ketone in the presence of a Lewis acid. Structure (**27**) was readily converted to the corresponding ketal (**35**) in the conventional way. Our expectation was that the cyclization of **35** could be brought about by use of 1 equiv, or just less than 1 equiv, of a strong mineral acid. We found, however, that treatment of **35** with 1.0 equiv of several acids (*i.e.*, $\text{CF}_3\text{CO}_2\text{H}$, H_2SO_4 , *p*-toluenesulfonic acid) did not result in ring cyclization. Reduction of **35** with LiAlH_4 gave **36** which produced the ring opened amide (**37**) when subjected to aqueous hydrolysis.



One last system we studied corresponded to the reductive cyclization of **27**. Reaction of **27** with lithium aluminum hydride followed by acidic workup afforded **38** in 65% yield as a 1:1-mixture of diastereomers. This compound was subsequently converted to piperidinone (**39**) when subjected to aqueous hydrolysis. The conversion of **27** to **38** is best interpreted as involving initial reduction of both the keto and amido carbonyl groups followed by an acid catalyzed protonation of the reactive *S,N*-ketene acetal. The neighboring hydroxyl group, in this case, is nucleophilic enough to trap the transient iminium ion prior to proton loss.



In conclusion, we have demonstrated that dihydro-5*H*-thiazolo[3,2-*a*]pyridin-3-ones can be easily prepared by proton loss from isothiomünchnones. The closely related tetrahydro-2*H*-pyrido[2,1-*b*][1,3]thiazin-4-one ring system was also prepared by treating piperidine-2-thione with acryloyl chloride. Both of these cyclic *S,N*-ketene acetals undergo reaction with different electrophiles in the presence of Lewis acids. We are continuing to explore the chemical behavior of these novel heterocyclic systems and will report additional findings at a later date.

EXPERIMENTAL SECTION

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in oven dried glassware under an atmosphere of extra dry nitrogen. Solutions were evaporated under reduced pressure with a rotatory evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate-hexane mixture as the eluent unless specified otherwise.

8-Methyl-2-phenyl-7,8-dihydro-6*H*-2,5*a*-diazoo-*as*-indacene-1,3,5-trione (6). To a solution containing 295 mg (2.6 mmol) of 3-methyl-pyrrolidine-2-thione³⁶ in 4 ml of 1,2-dimethoxyethane was added 233 μ l of (2.8 mmol) of bromoacetyl chloride. The resulting mixture was stirred at 25°C for 30 min, and this was followed by the addition of 0.7 ml (5.0 mmol) of triethylamine and the mixture was stirred for an additional 10 min. A 888 mg (5.2 mmol) sample of *N*-phenylmaleimide was added and the mixture was heated for 1.5 h at 140°C. After cooling to 25°C, the reaction mixture was filtered through a layer of silica gel. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 200 mg (27%) of 8-methyl-2-phenyl-7,8-dihydro-6*H*-2,5*a*-diazoo-*as*-indacene-1,3,5-trione (6) as a white solid; mp 88-90°C; ir (CHCl₃) 1717, 1667, 1626, 1358, and 1112 cm⁻¹; ¹H-nmr (300 MHz, CDCl₃) δ 1.50 (d, 3H, J=6.0 Hz), 1.98-2.08 (m, 1H), 2.42-2.52 (m, 1H), 3.86-3.96 (m, 1H), 4.09-4.18 (m, 1H), 4.23-4.32 (m, 1H), 6.92 (s, 1H), and 7.38-7.50 (m, 5H); ¹³C-nmr (75 MHz, CDCl₃) δ 18.2, 28.6, 38.4, 47.8, 101.9, 112.6, 126.1, 128.0, 128.8, 131.2, 141.7, 158.1, 161.7, 163.8, and 164.6; hrms Calcd for C₁₇H₁₄N₂O₃: 294.1004. Found: 294.1005.

8,8-Dimethyl-2-phenyl-7,8-dihydro-6*H*-2,5*a*-diazoo-*as*-indacene-1,3,5-trione (7). To a solution containing 100 mg (0.78 mmol) of 3,3-dimethylpyrrolidine-2-thione³⁶ in 3 ml of 1,2-dimethoxyethane was added 122 mg of (0.77 mmol) of bromoacetyl chloride. The resulting mixture was stirred at 25°C for 30 min, followed by the addition of 110 μ l (0.78 mmol) of triethylamine and the mixture was stirred for an additional 10 min. A 270 mg (1.5 mmol) sample of *N*-phenylmaleimide was added and the mixture was heated for 1 h at 140°C. After cooling to 25°C, the reaction mixture was filtered through a layer of silica gel. The solvent was removed under reduced pressure and the crude residue product was chromatographed on silica gel to give 110 mg (46%) of 8,8-dimethyl-2-phenyl-7,8-dihydro-6*H*-2,5*a*-diazoo-*as*-indacene-1,3,5-trione (7) as a white solid; mp 282-283°C; ir (CHCl₃) 1718, 1665, 1588, 1372,

1252, and 1113 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.64 (s, 6H), 2.17 (t, 2H, $J=7.5$ Hz), 4.22 (t, 2H, $J=7.5$ Hz), 6.95 (s, 1H), and 7.38-7.52 (m, 5H); ^{13}C -nmr (75 MHz, CDCl_3) δ 25.7 (CH_3), 36.8, 46.6, 47.9, 101.2, 112.9, 126.4, 128.3, 128.9, 131.3, 142.6, 161.6, 162.2, 163.8, and 164.7; Anal. Calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}_3$: C, 70.12; H, 5.23; N, 9.08. Found: C, 70.04; H, 5.24; N, 9.09.

7-Pent-4-enyl-5,6-dihydropyrrolo[1,2-*b*]thiazol-3-one (11). To a solution containing 5.1 g (60 mmol) of 2-pyrrolidinone in 100 ml of THF was added 80 ml of 1.6 M *n*-butyllithium at -78°C . The solution was allowed to warm to 25°C and stirred for 8 h. The solution was then cooled to -78°C and 9.8 g (50 mmol) of 5-iodo-1-pentene was added. This reaction mixture was allowed to warm to 25°C and stirred overnight. The mixture was poured into water, extracted with methylene chloride, and the organic layer was dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude residue was chromatographed on silica gel to give 5.8 g (70%) of 3-pent-4-enylpyrrolidinone as a colorless oil; ir (neat) 3227, 1693, 1450, 1268, and 905 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.30-1.50 (m, 2H), 1.70-1.85 (m, 2H), 2.00-2.15 (m, 2H), 2.20-2.35 (m, 3H), 3.29 (t, 2H, $J=7.2$ Hz), 4.90-5.05 (m, 2H), 5.70-5.90 (m, 1H), and 6.54 (s, 1H).

A solution of 4.4 g (29 mmol) of the above compound and 6.4 g (16 mmol) of Lawesson's reagent in 40 ml of 1,2-dimethoxyethane was heated at reflux for 4 h. The solvent was removed under reduced pressure and the crude residue was chromatographed on silica gel with methylene chloride as the eluent to give 4.0 g (82%) of 3-pent-4-enylpyrrolidinone-2-thione (**8**) as a white solid; mp $50-51^\circ\text{C}$; ir (neat) 1516, 1275, 1104, and 905 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.30-1.60 (m, 2H), 1.80-1.90 (m, 1H), 2.00-2.20 (m, 4H), 2.30-2.42 (m, 1H), 2.70-2.80 (m, 1H), 3.54 (t, 2H, $J=8.1$ Hz), 4.90-5.10 (m, 2H), 5.70-5.90 (m, 1H), and 8.28 (s, 1H).

To a solution containing 200 mg (1.2 mmol) of **8** in 4 ml of 1,2-dimethoxyethane was added 117 μl of (1.4 mmol) of bromoacetyl chloride. The resulting mixture was stirred at 25°C for 30 min, followed by the addition of 329 μl (2.4 mmol) of triethylamine and the mixture was stirred for an additional 10 min. The mixture was then heated for 1 h at 140°C . After cooling to 25°C , it was filtered through a layer of silica gel. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 167 mg (79%) of 7-pent-4-enyl-5,6-dihydropyrrolo[1,2-*b*]thiazol-3-one (**11**) as a colorless oil; ir (neat) 1691, 1664, 1405, 1356, and 908 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.52 (quin, 2H, $J=7.5$ Hz), 2.00-2.12 (m, 4H), 2.86 (t, 2H, $J=8.1$ Hz), 3.71 (t, 2H, $J=8.1$ Hz), 4.00 (s, 2H), 4.96-5.09 (m, 2H), and 5.75-5.88 (m, 1H); ^{13}C -nmr (75 MHz, CDCl_3) δ 25.7, 26.2, 33.0, 35.2, 38.6, 41.1, 110.5, 114.6, 131.2, 137.7, and 164.3; hrms Calcd for $\text{C}_{11}\text{H}_{15}\text{NOS}$: 209.0874. Found: 209.0874.

The above reaction was also carried out in the presence of 2 equiv of *N*-phenylmaleimide. In addition to **11** (65%), it was possible to isolate 95 mg (23%) of 8-pent-4-enyl-2-phenyl-7,8-dihydro-6*H*-2,5a-diazo-*as*-indacene-1,3,5-trione (**12**) as a white solid; mp $49-50^\circ\text{C}$; ir (CHCl_3) 1718, 1684, 1627, 1368,

and 906 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.50-1.60 (m, 2H), 2.00-2.20 (m, 5H), 2.38-2.48 (m, 1H), 3.80-3.90 (m, 1H), 4.04-4.15 (m, 1H), 4.25-4.35 (m, 1H), 4.92-5.05 (m, 2H), 5.72-4.88 (m, 1H), 6.93 (s, 1H), and 7.38-7.52 (m, 5H); ^{13}C -nmr (75 MHz, CDCl_3) δ 25.8, 26.3, 32.0, 33.1, 43.5, 48.0, 102.1, 112.8, 114.9, 126.2, 128.1, 128.9, 131.2, 137.7, 141.7, 157.4, 161.8, 164.0, and 164.7; hrms Calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_3$: 348.1474. Found: 348.1475.

6,7-Dihydro-5H-thiazolo[3,2-a]pyridin-3-one (16). To a solution containing 745 mg (6.4 mmol) of piperidine-2-thione (13) in 15 ml of 1,2-dimethoxyethane was added 586 μl (7.1 mmol) of bromoacetyl chloride. After stirring at 25°C for 10 min, 1.8 ml (12.8 mmol) of triethylamine was added. The resulting mixture was heated at 130°C for 1 h, cooled, and then filtered through a layer of silica gel. The solvent was removed under reduced pressure and the crude residue was chromatographed on silica gel to give 780 mg (78%) of 6,7-dihydro-5H-thiazolo[3,2-a]pyridin-3-one (16) as a colorless oil; ir (neat) 1692, 1644, 1387, 1363, and 1250 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.82 (quin, 2H, $J=6.0$ Hz), 2.15 (q, 2H, $J=5.7$ Hz), 3.62 (t, 2H, $J=6.0$ Hz), 3.70 (s, 2H), and 4.81 (t, 1H, $J=4.2$ Hz); ^{13}C -nmr (75 MHz, CDCl_3) δ 20.0, 22.2, 31.9, 41.5, 97.7, 131.9, and 169.5; hrms Calcd for $\text{C}_7\text{H}_9\text{NOS}$: 155.0405. Found: 155.0405.

8-Pent-4-enyl-6,7-dihydro-5H-thiazolo[3,2-a]pyridin-3-one (17). To a solution containing 5.1 g (50 mmol) of piperidine-2-one in 100 ml of THF was added 70 ml of 1.6 M *n*-butyllithium at -78°C. The solution was allowed to warm to 25°C and was stirred for 8 h. The solution was then cooled to -78°C and 5.9 ml (50 mmol) of 5-bromo-1-pentene was added. This reaction mixture was allowed to warm to 25°C and stirred overnight. The mixture was poured into water, extracted with methylene chloride, and the organic layer was dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude residue was chromatographed on silica gel to give 5.6 g (67%) of 3-pent-4-enyl-piperidine-2-one as a colorless oil; ir (neat) 1652, 1481, and 897 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.25-1.40 (m, 4H), 1.50-1.65 (m, 2H), 1.70-1.95 (m, 2H), 1.95-2.00 (m, 2H), 2.05-2.10 (m, 1H), 3.17 (t, 2H, $J=2.1$ Hz), 4.80-5.00 (m, 2H), 5.75-5.90 (m, 1H), and 7.23 (s, 1H).

A solution of 10.3 g (62 mmol) of the above compound and 15 g (37 mmol) of Lawesson's reagent in 60 ml of 1,2-dimethoxyethane was heated at reflux for 4 h. The solvent was removed under reduced pressure and the crude residue was chromatographed on silica gel using methylene chloride as the eluent to give 9.1 g (81%) of 3-pent-4-enyl-piperidine-2-thione (14) as a white solid; mp 54-55°C; ir (neat) 1558, 1439, 1348, and 1110 cm^{-1} ; ^1H -nmr (360 MHz, CDCl_3) δ 1.30-1.65 (m, 4H), 1.75-1.95 (m, 4H), 2.00-2.25 (m, 2H), 2.60-2.75 (m, 1H), 3.20-3.45 (m, 2H), 4.90-5.25 (m, 2H), 5.70-5.95 (m, 1H), and 8.70 (s, 1H).

To a solution containing 113 mg (0.62 mmol) of 14 in 3 ml of 1,2-dimethoxyethane was added 59 μl (0.70 mmol) of bromoacetyl chloride. The resulting mixture was stirred at 25°C for 10 min and then 139 μl (1.4 mmol) of triethylamine was added. The mixture was heated at 140°C for 30 min and then filtered through

a layer of silica gel. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 117 mg (85%) of 8-pent-4-enyl-6,7-dihydro-5H-thiazolo[3,2-a]pyridin-3-one (**17**) as a yellow oil; ir (neat) 1659, 1390, 1252, and 906 cm^{-1} ; ^1H -nmr (360 MHz, CDCl_3) δ 1.45 (quin, 2H, $J=7.5$ Hz), 1.78 (quin, 2H, $J=5.9$ Hz), 1.89-2.13 (m, 6H), 3.51 (t, 2H, $J=5.9$ Hz), 3.65 (s, 2H), 4.89 (dd, 1H, $J=11.0$ and 0.9 Hz), 4.95 (dd, 1H, $J=17.2$ and 1.6 Hz), and 5.67-5.83 (m, 1H); ^{13}C -nmr (75 MHz, CDCl_3) δ 20.4, 21.12, 21.14, 32.2, 32.9, 41.1, 109.2, 114.3, 126.0, 138.0, and 169.1; Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{NOS}$: C, 64.53; H, 7.67; N, 6.27; S, 14.36. Found: C, 64.45; H, 7.68; N, 6.25; S, 14.44.

8-Hex-5-enyl-6,7-dihydro-5H-thiazolo[3,2-a]pyridin-3-one (18). To a solution containing 9.0 g (0.1 mol) of 1,4-butanediol in 100 ml of THF was added 64 ml of 1.6 M of *n*-butyllithium at -78°C and the mixture was stirred for 10 min at -78°C . A 13.2 g (88 mmol) sample of *t*-butyldimethylsilyl chloride was added and the reaction mixture was allowed to gradually warm to 25°C and stirred overnight. The mixture was poured into 200 ml of ether and washed several times with water. The ether solution was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give pure 4-*t*-butyldimethylsiloxy-1-butanol³⁷ as a colorless liquid; ir (neat) 2857, 1141, 1253, 830, and 784 cm^{-1} ; ^1H -nmr (360 MHz, CDCl_3) δ 0.08 (s, 6H), 0.91 (s, 9H), 1.60-1.72 (m, 4H), 2.58 (s, 1H), and 3.60-3.72 (m, 4H).

The above alcohol was dissolved in 200 ml of methylene chloride, to which 20 g of celite was added and 25 g (116 mmol) of pyridinium chlorochromate at 0°C was slowly added. The reaction mixture was stirred at 25°C for 2 h and then 200 ml of ether was added. The mixture was filtered through a layer of silica gel. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 13.9 g (79%) of 4-*t*-butyldimethylsiloxybutanal³⁸ as a colorless liquid; ir (neat) 1725, 1250, 1094, and 771 cm^{-1} ; ^1H -nmr (360 MHz, CDCl_3) δ 0.05 (s, 6H), 0.90 (s, 9H), 1.88 (t, 2H, $J=6.5$ Hz), 2.51 (t, 2H, $J=6.8$ Hz), 3.65 (t, 2H, $J=5.8$ Hz), and 9.80 (s, 1H).

To a solution containing 17.8 g (50 mmol) methyltriphenylphosphonium bromide in 100 ml THF was added 34 ml of 1.6 M *n*-butyllithium at 0°C and the mixture was stirred at 25°C for 1 h. A 7.4 ml (55 mmol) sample of (iodomethyl)trimethylsilane was added to above solution. The resulting mixture was stirred at 25°C for 1 h and then cooled to -78°C . To this mixture was added 32 ml of 1.6 M *n*-butyllithium and the reaction mixture was allowed to warm to 25°C and was stirred for 2 h. The mixture was cooled to -78°C and 8.0 g (40 mmol) of 4-*t*-butyldimethylsiloxybutanal in 10 ml of THF was added. The mixture was allowed to warm to 25°C and stirred for 20 h and was then poured into water, extracted with ether, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 9.0 g (80%) of 6-*t*-butyldimethylsiloxy-1-trimethylsilyl-2-hexene as a colorless liquid; ir (neat) 2853, 1464, 1248, 1099, and 775 cm^{-1} ; ^1H -nmr (360 MHz, CDCl_3) δ 0.01 (s, 9H), 0.06 (s, 6H), 0.91 (s, 9H), 1.48 (d, 2H, $J=8.6$ Hz), 1.55-1.62 (m, 2H), 2.05 (q, 2H,

$J=7.5$ Hz), 3.62 (t, 2H, $J=5.8$ Hz), and 5.25-5.45 (m, 2H).

A solution containing 8.0 g (28 mmol) of the above compound and 2.1 g (8.4 mmol) of pyridinium *p*-toluenesulfonate in 100 ml of absolute ethanol was stirred at 25°C for 20 h. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 3.4 g (71%) of 6-trimethylsilyl-hex-4-en-1-ol³⁹ as a colorless liquid; ir (neat) 2951, 1247, 1148, 1055, and 849 cm^{-1} ; ^1H -nmr (360 MHz, CDCl_3) δ 0.01 (s, 9H), 1.40 (s, 1H), 1.48 (d, 2H, $J=8.6$ Hz), 1.64 (quin, 2H, $J=7.2$ Hz), 2.10 (q, 2H, $J=7.2$ Hz), 3.67 (t, 2H, $J=6.5$ Hz), 5.23-5.32 (m, 1H), and 5.40-5.52 (m, 1H); ^{13}C -nmr (75 MHz, CDCl_3) δ -1.9, 18.4, 23.3, 32.6, 62.5, 126.0, and 126.6.

To a solution containing 3.0 g (17.4 mmol) of the above alcohol in 50 ml of methylene chloride was added 4.9 ml (35 mmol) of triethylamine at -40°C followed by the addition of 3.8 g (20 mmol) of tosyl chloride. The reaction mixture was allowed slowly to warm to 25°C and stirred for 20 h. The mixture was poured into ice water, extracted with methylene chloride, and dried over magnesium sulfate. The solvent was removed under reduced pressure to give 6-trimethylsilyl-4-hexenyl *p*-toluenesulfonate⁴⁰ as a colorless oil; ir (neat) 2950, 1245, 1172, 940, and 660 cm^{-1} ; ^1H -nmr (360 MHz, CDCl_3) δ 0.02 (s, 9H), 1.40 (d, 2H, $J=8.6$ Hz), 1.71 (quin, 2H, $J=7.2$ Hz), 2.00 (q, 2H, $J=7.2$ Hz), 2.46 (s, 3H), 4.04 (t, 2H, $J=6.1$ Hz), 5.10-5.25 (m, 2H), 7.35 (d, 2H, $J=7.9$ Hz), and 7.80 (d, 2H, $J=7.9$ Hz).

The above product was dissolved in 100 ml of acetone, to which 10.4 g (69 mmol) of sodium iodide was added. The resulting mixture was heated at reflux under a nitrogen atmosphere for 4 h. The reaction mixture was poured into ice water, extracted with hexane, washed with an aqueous solution of sodium thiosulfate, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 4.5 g (91%) of 6-iodo-1-trimethylsilyl-2-hexene;⁴¹ ir (neat) 2949, 1423, 1218, 1149, and 850 cm^{-1} ; ^1H -nmr (360 MHz, CDCl_3) δ 0.02 (s, 9H), 1.51 (d, 2H, $J=8.6$ Hz), 1.88 (quin, 2H, $J=7.2$ Hz), 2.11 (q, 2H, $J=6.9$ Hz), 3.22 (t, 2H, $J=6.9$ Hz), 5.25-5.35 (m, 1H), and 5.42-5.52 (m, 1H); ^{13}C -nmr (75 MHz, CDCl_3) δ -1.8, 6.6, 18.6, 27.7, 33.4, 124.9, and 127.0.

To a solution containing 2.3 g (23 mmol) of piperidine-2-one in 50 ml of THF was added 31 ml of 1.6 M *n*-butyllithium at -78°C. The reaction mixture was allowed to warm up to 25°C and was stirred for 5 h. The reaction mixture was cooled to -78°C and to this solution was added 4.4 g (15.6 mmol) of 6-iodo-1-trimethylsilyl-2-hexene in 10 ml of THF. The solution was allowed to warm to 25°C and stirred overnight. The mixture was poured into water, extracted with methylene chloride, and dried over magnesium sulfate. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 3.9 g (98%) of 3-(6-trimethylsilyl-4-hexenyl)piperidin-2-one as a colorless oil; ir (neat) 2858, 1649, and 850 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 0.00 (s, 9H), 1.45-1.58 (m, 6H), 1.70-1.85 (m, 2H), 1.85-2.10 (m, 4H), 2.22-2.32 (m, 1H), 3.29 (s, 2H), 5.20-5.45 (m, 2H), and

6.00 (s, 1H); ^{13}C -nmr (75 MHz, CDCl_3) δ -2.4, 17.7, 20.6, 25.5, 26.5, 26.6, 30.8, 40.2, 41.4, 124.7, 126.5, and 174.8.

A solution containing 3.0 g (11.9 mmol) of the above compound and 3.6 g (8.9 mmol) of Lawesson's reagent in 30 ml of 1,2-dimethoxyethane was heated at reflux for 5 h. The reaction mixture was filtered through a layer of silica gel. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel using methylene chloride as the eluent to give 2.64 g (83%) of 3-(6-trimethylsilylhex-4-enyl)piperidine-2-thione (**15**) as an oil; ir (neat) 2859, 1558, 1358, 1247, and 848 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 0.2 (s, 9H), 1.40-1.62 (m, 7H), 1.80-2.15 (m, 4H), 2.20-2.35 (m, 1H), 2.65-2.75 (m, 1H), 3.25-3.50 (m, 2H), 5.20-5.44 (m, 2H), and 8.80 (s, 1H); ^{13}C -nmr (75 MHz, CDCl_3) δ -1.8, 18.1, 18.7, 24.1, 26.7, 26.9, 34.6, 44.2, 46.1, 125.3, 126.7, and 206.5; hrms Calcd for $\text{C}_{14}\text{H}_{27}\text{NSSi}$: 269.1633. Found: 269.1633.

To a solution containing 102 mg (0.38 mmol) of **15** in 3 ml of 1,2-dimethoxyethane was added 38 μl (0.46 mmol) of bromoacetyl chloride and the reaction mixture was stirred for 20 h at 25°C. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 100 mg (83%) of 8-hex-5-enyl-6,7-dihydro-5H-thiazolo[3,2-a]pyridin-3-one (**18**); ir (neat) 2851, 1692, 1659, and 1387 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.40-1.55 (m, 4H), 1.85 (quin, 2H, $J=6.1$ Hz), 2.00 (t, 2H, $J=7.2$ Hz), 2.05-2.25 (m, 4H), 3.59 (t, 2H, $J=5.8$ Hz), 3.72 (s, 2H), 4.95-5.05 (m, 2H), and 5.78-5.90 (m, 1H); ^{13}C -nmr (75 MHz, CDCl_3) δ 20.7, 26.4, 26.6, 28.4, 32.6 (CH_2), 32.9, 33.5, 41.4, 110.0, 114.4, 126.1, 138.7, and 169.5; hrms Calcd for $\text{C}_{13}\text{H}_{19}\text{NOS}$: 237.1187. Found: 237.1186.

8-(2-Bromoacetyl)-6,7-dihydro-5H-thiazolo[3,2-a]pyridin-3-one (19). To a solution containing 200 mg (1.7 mmol) of piperidine-2-thione in 5 ml of 1,2-dimethoxyethane was added 315 μl (3.8 mmol) of bromoacetyl chloride. After stirring at 25°C for 10 min, 484 μl (3.5 mmol) of triethylamine was added. The resulting mixture was heated at 140°C for 1 h. The crude product was filtered through a layer of silica gel. The solvent was removed under reduced pressure and the crude product was subjected to chromatography on silica gel to give 285 mg (60%) of 8-(2-bromoacetyl)-6,7-dihydro-5H-thiazolo[3,2-a]pyridin-3-one (**19**) as a white solid; mp 137-138°C; ir (CHCl_3) 1714, 1636, 1500, 1174, and 1091 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 2.00 (t, 2H, $J=4.8$ Hz), 2.65 (t, 2H, $J=5.1$ Hz), 3.60-3.85 (m, 4H), and 4.25 (s, 2H); ^{13}C -nmr (75 MHz, CDCl_3) δ 20.0, 23.2, 32.2, 42.0, 45.9, 105.8, 145.0, 172.2, and 188.8; hrms Calcd for $\text{C}_9\text{H}_{10}\text{BrNO}_2\text{S}$: 274.9616. Found: 274.9614.

Preparation of 8-Propionyl-6,7-dihydro-5H-thiazolo[3,2-a]pyridin-3-one (20). To a solution containing 200 mg (1.7 mmol) of piperidine-2-thione in 5 ml of 1,2-dimethoxyethane was added 158 μl (1.9 mmol) of bromoacetyl chloride. After stirring for 10 min at 25°C, 484 μl (3.5 mmol) of triethylamine was added. After stirring for another 10 min at 25°C, 727 μl of propionyl chloride was added. The resulting mixture was heated to 140°C for 1 h. The crude mixture was filtered through a layer of silica

gel. The solvent was removed under reduced pressure and the crude residue was chromatographed on silica gel to give 234 mg (64%) of 8-propionyl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyridin-3-one (**20**) as a white solid; mp 115-116°C; ir (CHCl₃) 1714, 1642, 1435, 1172, and 1101 cm⁻¹; ¹H-nmr (360 MHz, CDCl₃) δ 1.30 (t, 3H, J=7.2 Hz), 1.94 (quin, 2H, J=5.8 Hz), 2.51 (t, 2H, J=7.2 Hz), 2.57 (t, 2H, J=5.8 Hz), 3.63 (s, 3H), and 3.66 (t, 2H, J=5.8 Hz); ¹³C-nmr (75 MHz, CDCl₃) δ 7.7, 19.9, 23.4, 32.0, 32.2, 41.6, 107.7, 150.5, 171.9, and 198.8; Anal. Calcd for C₁₀H₁₃NO₂S: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.76; H, 6.22; N, 6.63.

8-Benzoyl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyridin-3-one (21**).** To a solution containing 102 mg (0.89 mmol) of piperidine-2-thione in 3 mL of 1,2-dimethoxyethane was added 80 μl (0.97 mmol) of bromoacetyl chloride. The resulting mixture was stirred at 25°C for 10 min and then 247 μl (1.8 mmol) of triethylamine was added. After stirring for another 10 min at 25°C, 515 μl (4.5 mmol) of benzoyl chloride was added. The mixture was heated at 140°C for 2 h and then filtered through a layer of silica gel. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 126 mg (55%) of 8-benzoyl-6,7-dihydro-5*H*-thiazolo[3,2-*a*]pyridin-3-one (**21**) as a white solid; mp 137-138°C; ir (neat) 1706, 1620, 1379, 1282, and 983 cm⁻¹; ¹H-nmr (300 MHz, CDCl₃) δ 1.86 (quin, 2H, J=5.7 Hz), 2.61 (t, 2H, J=5.7 Hz), 3.67 (s, 3H), 3.70 (t, 2H, J=5.7 Hz), and 7.35-7.55 (m, 5H); ¹³C-nmr (75 MHz, CDCl₃) δ 20.6, 26.5, 32.4, 42.5, 108.0, 127.3, 128.1, 130.5, 139.6, 154.5, 172.3, and 193.9; hms Calcd for C₁₄H₁₃NO₂S: 259.0667. Found: 259.0667.

Preparation of 3,6,7,8-Tetrahydro-2*H*-pyrido[2,1-*b*][1,3]thiazin-4-one (22**).** To a solution containing 1.25 g (10.9 mmol) of piperidine-2-thione in 10 ml of 1,2-dimethoxyethane was added 0.88 ml (10.9 mmol) of acryloyl chloride. The resulting solution was stirred at 25°C for 1 h and then heated at reflux for 30 min. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 1.59 g (86%) of 3,6,7,8-tetrahydro-2*H*-pyrido[2,1-*b*][1,3]thiazin-4-one (**22**) as a colorless oil; ir (neat) 1652, 1613, 1367, and 772 cm⁻¹; ¹H-nmr (300 MHz, CDCl₃) δ 1.65 (quin, 2H, J=6.0 Hz), 1.94 (q, 2H, J=4.2 Hz), 2.63-2.73 (m, 4H), 3.65 (t, 2H, J=6.0 Hz), and 4.92 (t, 1H, J=4.2 Hz); ¹³C-nmr (75 MHz, CDCl₃) δ 21.2, 22.8, 23.1, 35.4, 41.2, 108.2, 128.6, and 166.3; hms Calcd for C₈H₁₁NOS: 169.0561. Found: 169.0561.

9-Acetyl-3,6,7,8-tetrahydro-2*H*-pyrido[2,1-*b*][1,3]thiazin-4-one (23**).** A solution containing 1.33 g (7.9 mmol) of **22** and 2.8 ml (39 mmol) of acetyl chloride in 6 ml of 1,2-dimethoxyethane was heated at 140°C for 1 h. The mixture was filtered through a layer of silica gel. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 1.0 g (60%) of 9-acetyl-3,6,7,8-tetrahydro-2*H*-pyrido[2,1-*b*][1,3]thiazin-4-one (**23**) as a white solid; mp 175-176°C; ir (CHCl₃) 1678, 1486, 1349, and 1151 cm⁻¹; ¹H-nmr (300 MHz, CDCl₃) δ 1.87 (quin, 2H, J=5.7 Hz), 2.23 (s, 3H), 2.54 (t, 2H, J=6.6 Hz), 2.78-2.88 (m, 4H), and 3.84 (t, 2H, J=5.7 Hz); ¹³C-nmr (75 MHz, CDCl₃)

δ 21.3, 22.0, 26.1, 28.0, 34.8, 41.6, 113.7, 147.4, 169.1, and 196.9; Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.88; H, 6.23; N, 6.60.

9-Propionyl-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (24). A solution containing 100 mg (0.59 mmol) of **22** and 257 μ l (3.0 mmol) of propionyl chloride in 2 ml of 1,2-dimethoxyethane was heated at 140°C for 5 h. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 110 mg (83%) of 9-propionyl-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (**24**) as a white solid; mp 143-144°C; ir (CHCl₃) 1674, 1488, 1343, 1279, 1099, and 1018 cm⁻¹; ¹H-nmr (300 MHz, CDCl₃) δ 1.10 (t, 3H, J=7.2 Hz), 1.86 (quin, 2H, J=5.7 Hz), 2.45-2.56 (m, 4H), 2.78-2.82 (m, 4H), and 3.83 (t, 2H, J=5.7 Hz); ¹³C-nmr (75 MHz, CDCl₃) δ 7.7, 21.4, 22.2, 25.2, 32.7, 34.9, 41.8, 113.8, 147.0, 169.3, and 199.7; Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.69; H, 6.65; N, 6.27.

9-Pent-1-enyl-3,6,7,8-tetrahydro-2H-pyrido-[2,1-b][1,3]thiazin-4-one (25). A solution containing 100 mg (0.59 mmol) of **22** and 315 μ l (3.0 mmol) of valeraldehyde in 2 ml of 1,2-dimethoxyethane was heated at 140°C for 10 h. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 98 mg (70%) of 9-pent-1-enyl-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (**25**) as a colorless oil; ir (neat) 1965, 1651, 1543, 1377, and 1072 cm⁻¹; ¹H-nmr (300 MHz, CDCl₃) δ 0.89 (t, 3H, J=7.2 Hz), 1.30-1.42 (m, 2H), 1.75-1.85 (m, 2H), 2.09 (q, 2H, J=7.2 Hz), 2.27 (t, 2H, J=6.3 Hz), 2.87 (s, 4H), 3.81 (t, 2H, 6.2 Hz), 5.58-5.65 (m, 1H), and 6.50 (d, 1H, J=15.3 Hz); ¹³C-nmr (75 MHz, CDCl₃) δ 13.6, 21.5, 22.7, 22.8, 24.6, 35.3, 35.6, 41.8, 117.8, 126.6, 127.4, 129.5, and 167.7; hrms Calcd for $C_{13}H_{19}NOS$: 237.1187. Found: 237.1187.

9-Styryl-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (26). To a solution containing 131 mg (0.78 mmol) of **22** and 453 μ l (3.9 mmol) of phenylacetaldehyde in 3 ml of THF was added 96 μ l (0.78 mmol) of boron trifluoride etherate at 0°C. The resulting mixture was stirred at 25°C for 10 h. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 148 mg (67%) of 9-styryl-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (**26**) as a colorless oil; ir (neat) 1654, 1554, 1282, 1157, and 691 cm⁻¹; ¹H-nmr (360 MHz, CDCl₃) δ 1.95 (quin, 2H, J=5.5 Hz), 2.47 (t, 2H, J=5.5 Hz), 2.95-3.02 (m, 4H), 3.94 (t, 2H, J=5.5 Hz), 6.54 (d, 1H, J=15.8 Hz), and 7.20-7.48 (m, 6H); ¹³C-nmr (75 MHz, CDCl₃) δ 22.3, 22.6, 24.4, 35.6, 41.9, 117.4, 125.9, 126.3, 126.4, 126.9, 128.4, 129.9, 137.7, and 167.4; hrms Calcd for $C_{16}H_{17}NOS$: 271.1031. Found: 271.1031.

9-(3-Oxo-butyl)-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (27). To a solution containing 1.39 g (8.22 mmol) of **22** and 1.0 ml (12.3 mmol) of methyl vinyl ketone in 15 ml of acetonitrile was added 0.5 ml (8.7 mmol) of acetic acid at 25°C. The resulting mixture was heated at reflux for 10 h. The solvent was removed under reduced pressure and the crude product was

chromatographed on silica gel to give 1.88 g (95%) of 9-(3-oxobutyl)-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (**27**) as a colorless oil; ir (neat) 1708, 1650, 1274, and 1022 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.78-1.88 (m, 2H), 2.11 (t, 2H, $J=6.6$ Hz), 2.16 (s, 3H), 2.42 (t, 2H, $J=6.6$ Hz), 2.55 (t, 2H, $J=6.6$ Hz), 2.85 (s, 4H), and 3.78 (t, 2H, $J=5.7$ Hz); ^{13}C -nmr (75 MHz, CDCl_3) δ 21.6, 22.7, 27.7, 27.9, 29.5, 35.2, 41.1, 118.4, 124.4, 167.1, and 207.8; hrms Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_2\text{S}$: 239.0980. Found: 239.0979.

9-(3-Oxo-cyclopentyl)-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (28). To a solution containing 125 mg (0.74 mmol) of **22** and 310 μl (3.7 mmol) of 2-cyclopentenone in 3 ml of THF was added 93 μl (0.75 mmol) of boron trifluoride etherate at 0°C . The resulting mixture was stirred at 25°C for 10 h. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 169 mg (91%) of 9-(3-oxocyclopentyl)-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (**28**) as a white solid; mp $114\text{--}115^\circ\text{C}$; ir (neat) 1738, 1650, 1600, 1334, and 1151 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.75-1.85 (m, 4H), 2.05-2.15 (m, 4H), 2.20-2.40 (m, 2H), 2.87 (s, 4H), 3.40-3.52 (m, 1H), and 3.75-3.87 (m, 2H); ^{13}C -nmr (75 MHz, CDCl_3) δ 21.4, 22.6, 23.0, 26.5, 35.2, 38.0, 39.7, 41.3, 41.4, 118.6, 125.1, 167.0, and 217.5; Anal. Calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_2\text{S}$: C, 62.12; H, 6.82. Found: C, 62.06; H, 6.79.

9-(3-Oxocyclohexyl)-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (29). To a solution containing 127 mg (0.75 mmol) of **22** and 363 μl (3.8 mmol) of 2-cyclohexenone in 3 ml of THF was added 93 μl (0.75 mmol) of boron trifluoride etherate at 0°C . The resulting mixture was stirred at 25°C for 10 h. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 185 mg (93%) of 9-(3-oxocyclohexyl)-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (**29**) as an oil; ir (neat) 1704, 1649, 1266, 1157, 923, and 728 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.60-1.82 (m, 5H), 2.00-2.12 (m, 3H), 2.20-2.35 (m, 4H), 2.83 (s, 4H), 3.00-3.10 (m, 1H), and 3.73-3.82 (m, 2H); ^{13}C -nmr (75 MHz, CDCl_3) δ 21.4, 22.6, 22.9, 24.9, 28.7, 35.1, 40.6, 41.2, 41.7, 44.9, 120.5, 124.4, 167.2, and 210.1; hrms Calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_2\text{S}$: 265.1136. Found: 265.1136.

8-Styryl-6,7-dihydro-5H-thiazolo[3,2-a]pyridin-3-one (30). To a solution containing 111 mg (0.61 mmol) of piperidine-2-thione (**13**) in 3 ml of 1,2-dimethoxyethane was added 55 μl (0.67 mmol) of bromoacetyl chloride. The resulting mixture was stirred at 25°C for 10 min and then 169 μl (1.2 mmol) of triethylamine was added. After stirring for another 10 min at 25°C , 510 μl of phenylacetaldehyde was added. The mixture was heated at 140°C for 3 h and then filtered through a layer of silica gel. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 177 mg (77%) of 8-styryl-6,7-dihydro-5H-thiazolo[3,2-a]pyridin-3-one (**30**) as an oil; ir (neat) 1695, 1611, 1388, and 1255 cm^{-1} ; ^1H -nmr (360 MHz, CDCl_3) δ 1.98 (quin, 2H, $J=5.8$ Hz), 2.48 (t, 2H, $J=5.8$ Hz), 3.70 (t, 2H, $J=5.8$ Hz), 3.84 (s, 2H), 6.45 (d, 1H, $J=15.4$ Hz), 6.80 (d, 1H, $J=15.4$ Hz), and 7.20-7.50

(m, 5H); ^{13}C -nmr (75 MHz, CDCl_3) δ 20.0, 22.9, 32.3, 41.6, 109.2, 124.2, 124.6, 125.6, 126.6, 128.4, 133.1, 137.5, and 169.6; hrms Calcd for $\text{C}_{15}\text{H}_{15}\text{NOS}$: 257.0874. Found: 257.0874.

9-Pent-4-enyl-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (31). To a solution containing 3.7 g (20 mmol) of 3-pent-4-enylpiperidine-2-thione (**14**) in 20 ml of 1,2-dimethoxyethane was added 1.7 ml (20 mmol) of acryloyl chloride. The resulting solution was stirred at 25°C for 1 h. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 4.1 g (87%) of 9-pent-4-enyl-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (**31**) as a colorless oil; ir (neat) 1650, 1615, 1383, 1155, and 903 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.51 (quin, 2H, $J=7.5$ Hz), 1.80 (quin, 2H, $J=6.0$ Hz), 2.05-2.22 (m, 6H), 2.87 (s, 4H), 3.80 (t, 2H, $J=6.0$ Hz), 4.85-5.05 (m, 2H), and 5.80-5.90 (m, 1H); ^{13}C -nmr (75 MHz, CDCl_3) δ 21.7, 22.8, 26.6, 27.7, 33.1, 33.3, 35.2, 41.2, 114.3, 120.3, 123.6, 137.9, and 167.0; hrms Calcd for $\text{C}_{13}\text{H}_{19}\text{NOS}$: 237.1187. Found: 237.1185.

9-Pent-4-enyl-2,3,4,6,7,8-hexahydropyrido[2,1-b][1,3]thiazine (32). To a solution containing 237 mg (1.0 mmol) of **31** in 15 ml ether was slowly added 76 mg (2.0 mmol) of lithium aluminum hydride. The resulting mixture was heated at reflux for 1 h and then a small amount of water was carefully added at 0°C. The solid was filtered and the solvent was removed under reduced pressure to give 73 mg (35%) of 9-pent-4-enyl-2,3,4,6,7,8-hexahydropyrido[2,1-b][1,3]thiazine (**32**) as a colorless oil; ir (neat) 1637, 1436, 1283, and 906 cm^{-1} ; ^1H -nmr (360 MHz, CDCl_3) δ 1.45 (quin, 2H, $J=7.5$ Hz), 1.78 (quin, 2H, $J=5.8$ Hz), 2.02-2.09 (m, 6H), 2.19 (t, 2H, $J=7.5$ Hz), 2.66 (t, 2H, $J=5.8$ Hz), 2.79 (t, 2H, $J=5.8$ Hz), 2.90 (t, 2H, $J=5.1$ Hz), 4.90-5.05 (m, 2H), and 5.78-5.90 (m, 1H); ^{13}C -nmr (75 MHz, CDCl_3) δ 20.9, 26.3, 27.2, 27.7, 27.9, 33.2, 33.2, 53.3, 53.6, 113.5, 116.4, 131.6, and 138.5; hrms Calcd for $\text{C}_{13}\text{H}_{21}\text{NS}$: 223.1395. Found: 223.1394.

9-(6-Trimethylsilylhex-4-enyl)-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (33). To a solution containing 100 mg (0.37 mmol) of 3-(6-trimethylsilylhex-4-enyl)piperidine-2-thione (**15**) in 3 ml of 1,2-dimethoxyethane was added 36 μl (0.44 mmol) of acryloyl chloride. The reaction mixture was stirred at 25°C for 2 h. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 100 mg (83%) of 9-(6-trimethylsilylhex-4-enyl)-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (**33**) as a colorless oil; ir (neat) 1654, 1617, 1381, 1151, and 853 cm^{-1} ; ^1H -nmr (360 MHz, CDCl_3) δ 0.01 (s, 9H), 1.40-1.55 (m, 4H), 1.82 (quin, 2H, $J=5.8$ Hz), 2.01 (q, 2H, $J=7.2$ Hz), 2.17 (t, 2H, $J=6.5$ Hz), 2.20 (t, 2H, $J=7.5$ Hz), 2.87 (s, 4H), 3.80 (t, 2H, $J=5.8$ Hz), and 5.25-5.45 (m, 2H); ^{13}C -nmr (75 MHz, CDCl_3) δ -1.9, 18.3, 21.9, 23.1, 26.7, 27.8, 28.0, 33.8, 35.5, 41.4, 120.8, 123.7, 125.7, 126.7, and 167.3; hrms Calcd for $\text{C}_{17}\text{H}_{29}\text{NOSSi}$: 323.1739. Found: 323.1738.

9-Hex-5-enyl-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (34). To a solution containing 108 mg (0.33 mmol) of **32** in 5 ml of methylene chloride was added 106 μl (1.3 mmol) of

trifluoroacetic acid. The reaction mixture was stirred at 25°C for 20 h. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel to give 76 mg (90%) of 9-hex-5-enyl-3,6,7,8-tetrahydro-2H-pyrido[2,1-b][1,3]thiazin-4-one (**34**) as a colorless oil; ir (neat) 1652, 1611, 1276, and 885 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.38-1.50 (m, 4H), 1.80 (quin, 2H, $J=6.0$ Hz), 2.00-2.20 (m, 6H), 2.85 (s, 4H), 3.82 (t, 2H, $J=6.5$ Hz), 4.90-5.08 (m, 2H), and 5.75-5.80 (m, 1H); ^{13}C -nmr (75 MHz, CDCl_3) δ 22.1, 23.2, 27.2, 28.1, 28.6, 33.5, 33.9, 35.6, 41.6, 114.4, 121.0, 123.7, 138.7, and 167.5; hrms Calcd for $\text{C}_{14}\text{H}_{21}\text{NOS}$: 251.1344. Found: 251.1343.

9-[3-(2-Methyl[1,3]dioxolan-2-yl)propyl]-2,3,4,6,7,8-hexahydropyrido[2,1-b][1,3]thiazine (**36**). To a solution containing 183 mg (0.65 mmol) of 9-[3-(2-methyl[1,3]dioxolan-2-yl)propyl]-2,3,4,6,7,8-hexahydropyrido[2,1-b][1,3]thiazin-4-one (**35**) in 5 ml of THF and 10 ml of ether was carefully added 38 mg (1.0 mmol) of lithium aluminum hydride and the resulting solution was heated at reflux for 1 h. To this mixture was added 20 μl of water at 0°C. The resulting solid was filtered and the solvent was removed under reduced pressure to give 142 mg (82%) of 9-[3-(2-methyl[1,3]dioxolan-2-yl)propyl]-2,3,4,6,7,8-hexahydropyrido[2,1-b][1,3]thiazine (**36**) as a colorless oil; ir (neat) 1635, 1375, 1050, and 860 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.19 (s, 3H), 1.45-1.70 (m, 4H), 1.92 (t, 4H, $J=5.7$ Hz), 2.18-2.15 (m, 2H), 2.53 (t, 2H, $J=5.7$ Hz), 2.65 (t, 2H, $J=5.7$ Hz), 2.76 (t, 2H, $J=5.1$ Hz), and 3.80 (s, 4H); ^{13}C -nmr (75 MHz, CDCl_3) δ 21.1, 23.3, 26.3, 27.6, 28.0, 28.4, 37.1, 53.2, 53.6, 64.2, 109.5, 115.7, and 131.6; hrms Calcd for $\text{C}_{14}\text{H}_{23}\text{NO}_2\text{S}$: 269.1449. Found: 269.1449.

1-(3-Mercaptopropyl)-3-[2-(methyl[1,3]dioxolan-2-yl)ethyl]piperidin-2-one (**37**). A solution containing 140 mg (0.52 mmol) of **36** and 4 μl of trifluoroacetic acid in 4 ml of anhydrous THF was heated at reflux for 5 h. The solvent was removed under reduced pressure and the reaction was worked up in the normal fashion to give 1-(3-mercaptopropyl)-3-[2-(methyl[1,3]dioxolan-2-yl)ethyl]piperidin-2-one (**37**) (90%) as a colorless oil; ir (neat) 2860, 1620, 1295, and 1035 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.30 (s, 3H), 1.50-2.05 (m, 11H), 2.20-2.35 (m, 1H), 2.49 (q, 2H, $J=7.2$ Hz), 3.26 (t, 2H, $J=6.6$ Hz), 3.43 (t, 2H, $J=7.2$ Hz), and 3.91 (s, 4H); ^{13}C -nmr (75 MHz, CDCl_3) δ 21.4, 21.7, 23.5, 26.1, 31.1, 36.1, 40.9, 45.5, 47.8, 54.3, 109.7, and 172.3; hrms Calcd for $\text{C}_{14}\text{H}_{25}\text{NO}_3\text{S}$: 287.1555. Found: 287.1555.

13-Methyl-14-oxa-2-thia-6-azatricyclo[8.4.0.0^{1,6}]tetradecane (**38**). To a solution containing 239 mg (1 mmol) of **27** in 10 ml of ether and 5 ml of THF was slowly added 60 mg (1.6 mmol) of lithium aluminum hydride. The resulting mixture was heated at reflux for 2 h. After cooling the solution to 25°C, 50 μl of water was slowly added *via* syringe. The solid that formed was filtered and the solvent was removed under reduced pressure to give 13-methyl-14-oxa-2-thia-6-aza-tricyclo[8.4.0.0^{1,6}]tetradecane (**38**) as a colorless oil in 65% yield as a 1:1 mixture of diastereoisomers; ir (neat) 2840, 1440, 1075, and 1030 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.20 (d, 1.5H, $J=5.1$ Hz), 1.27 (d, 1.5H, $J=5.1$ Hz), 1.35-1.45

(m, 4H), 1.55-1.90 (m, 6H), 2.00-2.20 (m, 1H), 2.15-2.25 (m, 1H), 2.40-2.55 (m, 2H), 2.65-2.80 (m, 1H), 2.98 (dt, 0.5H, $J=10.5$ and 2.4 Hz), 3.18 (dt, 0.5H, $J=10.5$ and 2.4 Hz), 3.63-3.70 (m, 0.5H), 3.88 (dt, 0.5H, $J=10.5$ and 3.0 Hz), 4.10-4.20 (m, 0.5H), and 4.40-4.50 (m, 0.5H); ^{13}C -nmr (75 MHz, CDCl_3) δ 16.9, 21.4, 21.7, 24.5, 24.7, 24.8, 25.5, 25.8, 26.1, 27.2, 27.7, 27.9, 33.9, 38.4, 46.2, 46.7, 48.6, 48.9, 51.7, 67.9, 68.0, 68.7, 97.6, and 103.2; hrms Calcd for $\text{C}_{12}\text{H}_{21}\text{NOS}$: 227.1344. Found: 227.1344.

3-(3-Hydroxybutyl)-1-(3-mercaptopropyl)piperidin-2-one (39). A solution containing 90 mg (0.37 mmol) of **38** and 10 μl of acetic acid in 5 ml of acetonitrile was stirred at 25°C for 20 h. Removal of the solvent under reduced pressure afforded 3-(3-hydroxybutyl)-1-(3-mercaptopropyl)piperidin-2-one (**39**) (90%) as a colorless oil; ir (neat) 1614, 1493, 1361, and 1280 cm^{-1} ; ^1H -nmr (300 MHz, CDCl_3) δ 1.39 (d, 3H, $J=6.0$ Hz), 1.40-1.60 (m, 4H), 1.60-1.80 (m, 2H), 1.80-1.95 (m, 5H), 2.25-2.35 (m, 1H), 2.46 (q, 2H, $J=6.9$ Hz), 3.25 (t, 2H, $J=4.5$ Hz), 3.41 (t, 2H, $J=7.2$ Hz), 3.70 (sex, 1H, $J=5.7$ Hz), and 5.00 (s, 1H); ^{13}C -nmr (75 Hz, CDCl_3) δ 21.6, 21.8, 22.9, 26.1, 27.4, 31.0, 36.0, 41.0, 45.8, 48.0, 67.2, and 173.0; hrms Calcd for $\text{C}_{12}\text{H}_{23}\text{NO}_2\text{S}$: 245.1449. Found: 245.1448.

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