Pergamon

Tetrahedron Vol. 51, No. 10, pp. 2929-2938, 1995

0040-4020/95 $9.50+0.00

0040-4020(95)00056-9

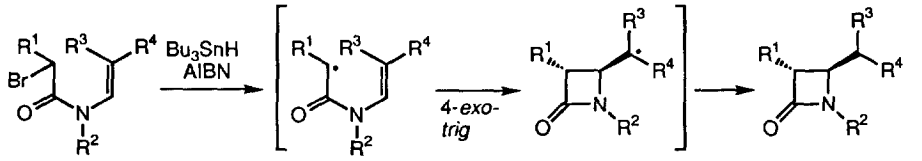
Uncatalyzed Cationic Olefin Cyclizations of *N*-Vinylic α-Chloro-α-thioacetamides. Formation of β- and γ-Lactams

Hiroyuki Ishibashi,* Tohru Nakaharu, Masako Nishimura, Atsuko Nishikawa, Chisato Kameoka, and Masazumi Ikeda

Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

Abstract: *N*-Vinylic α-chloro-α-thioacetamides were found to cyclize without a catalyst in two different manners depending upon the nature of the substituents at the terminus of the *N*-vinylic bond. Thus, bis(phenylthio)-substituted enamides **8a-c** cyclized in a 4-*exo-trig* manner to give 4-methylene-β-lactams **10a-c**, whereas mono(phenylthio)-, monophenyl-, diphenyl-, and dialkyl-substituted congeners **23a,b**, **28**, and **38** cyclized in a 5-*endo-trig* manner to give γ-lactams **26a,b**, **30**, and **39**, respectively. The product **38** was transformed into an anticonvulsant agent ethosuximide (**42**).

Recently, we[1] and Belletire[2] reported that the α-bromoamides **1** bearing the phenylthio or phenyl substituent(s) at the terminus of the *N*-vinylic bond, upon treatment with Bu_3SnH in the presence of azobis(isobutyronitrile) (AIBN), underwent radical cyclization to give β-lactams **4**. The effectiveness of a relatively difficult 4-*exo-trig* cyclization of the carbamoylmethyl radicals **2**, generated from **1**, may be attributable to the high stability of the resulting phenylthio or phenyl substituted radicals **3**. Since the phenylthio and phenyl groups are also capable of stabilizing the neighboring carbocations, we were then interested in the mode of cationic cyclization of *N*-vinylic α-chloro-α-thioacetamides (*e.g.*, **8**). We have found that the *N*-[2,2-bis(phenylthio)ethenyl]-α-chloro-α-thioacetamides **8** cyclized in a 4-*exo-trig* manner to give β-lactams **10**, whereas other enamides herein examined cyclized in a 5-*endo-trig* manner to give γ-lactams. Also intriguing was that the cyclizations were performed without the use of a catalyst such as Lewis acid.[3] The present paper describes the results of our works in this area including an application of the latter cyclization to the synthesis of an anticonvulsant agent ethosuximide (**42**).



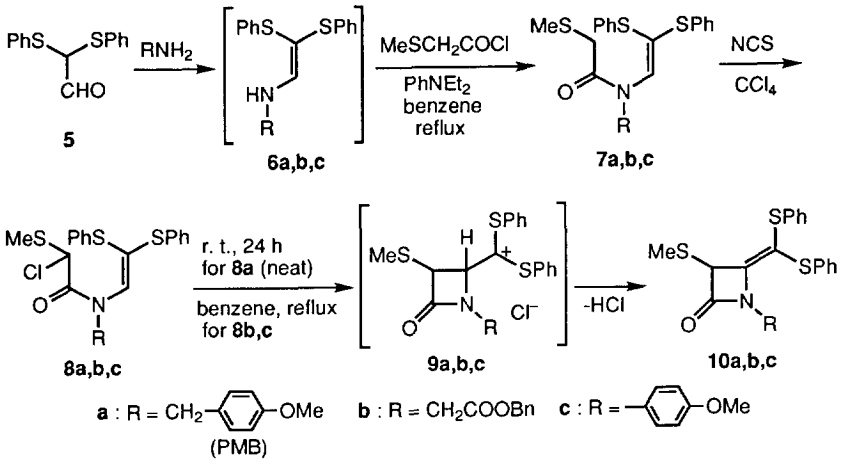
1 **2** **3** **4**

R^3 and/or R^4 = SPh or Ph

4-*Exo-Trig* Cyclization: Formation of β-Lactams

Condensation of bis(phenylthio)acetaldehyde (**5**) with an appropriate amine followed by acylation of the resulting enamines **6** (not imines) with (methylthio)acetyl chloride in refluxing benzene in the presence of

N,*N*-diethylaniline (without it for **7c**) gave the enamides **7a-c**, which were then treated with *N*-chlorosuccinimide (NCS) to give the corresponding α-chlorosulfides **8a-c**.



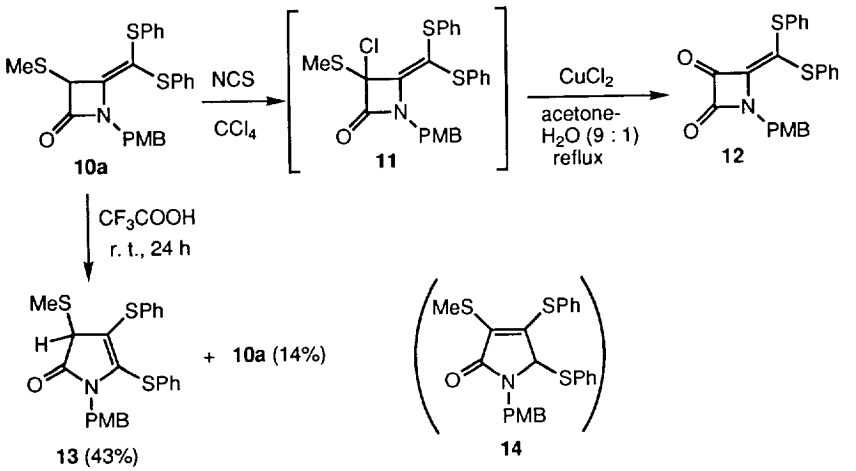
The chlorosulfide **8a** was rather stable in an appropriate solvent at room temperature, but, surprisingly, this compound was found to gradually cyclize just by standing at room temperature without the use of a catalyst and a solvent to give the β-lactam **10a** in 66% yield after 24 h. The IR spectrum of **10a** showed the bands at 1800 and 1625 cm^{-1}, clearly indicative of 4-methylene-2-azetidinone structure. The ^1H NMR spectrum exhibited two singlets due to the *S*-methyl protons and the C-3 methine proton at δ 2.18 and 4.68, respectively.

On the other hand, cyclizations of the α-chlorosulfides **8b** and **8c** were achieved by heating them in boiling benzene to give the corresponding β-lactams **10b** and **10c** in 62 and 54% yields, respectively.

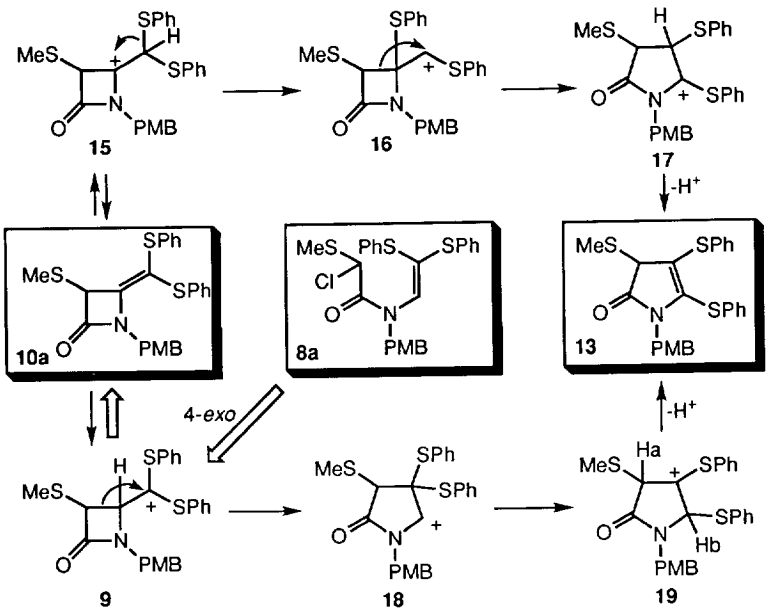
Formation of **10** from **8** may be explained in terms of a 4-*exo-trig* cyclization of **8** followed by dehydrochlorination of the resulting cationic intermediate **9** stabilized by two phenylthio groups.

Treatment of the β-lactam **10a** with NCS gave the chlorosulfide **11**, which wa then treated with $CuCl_2$ in aqueous acetone under reflux[4] to give the azetidine-2,3-dione **12** in 51% yield (based on **10a**).[5] The IR spectrum of **12** showed two carbonyl bands at 1830 and 1800 cm^{-1}. On the other hand, a solution of **10a** in trifluoroacetic acid was allowed to stand at room temperature overnight to give the ring-expansion product **13** in 43% yield together with the recovered **10a** (14%). The structure of **13** was deduced from the spectroscopic evidence. The IR spectrum showed the band at 1690 cm^{-1} due to the five-membered enamide, and the ^1H NMR spectrum exhibited two singlets due to the S-methyl protons at δ 2.16 and the C_3 methine proton at δ 4.70, respectively. Another possible structure **14** may be ruled out since the signal due to the S-methyl protons of **14** should appear at lower field like that (δ 2.56) of the S-methyl protons of **26a** (*vide infra*).

Two routes may be considered for the formation of **13** from **10a**. Thus, protonation of **10a** gives either the nitrogen-stabilized cation **15** or the sulfur-stabilized cation **9**. The cation **15** undergoes 1,2-phenylthio migration to give the new cation **16**. Ring-expansion of **16** followed by deprotonation of the resulting five-membered cation **17** provides **13**. On the other hand, ring-expansion of the cation **9** gives the new cation **18**,

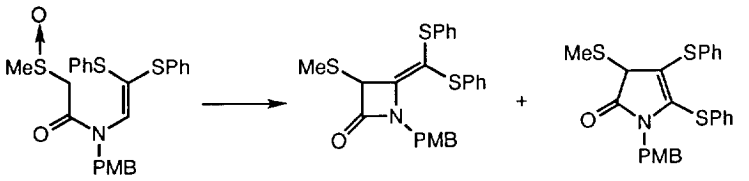


which then undergoes 1,2-shift of the phenylthio group to give **19**. A subsequent elimination of the proton at C-5 position (Hb) provides **13**. However, the proton at C-3 position (Ha) of **19** might be more acidic than was Hb, and hence the alternate lactam **14** might result. The cation **9** is an intermediate for the formation of **10a** from the chloride **8a**, so that the possibility of a rearrangement of **9** to **18** may be ruled out.



We also examined the reaction of the sulfoxide **20** under the Pummerer rearrangement conditions.[6] Thus, when the sulfoxide **20**, prepared by oxidation of **7a** with MCPBA, was treated with trifluoroacetic anhydride (TFAA) in CH_2Cl_2 at 0 °C and then at room temperature, the β-lactam **10a** and the γ-lactam **13** were obtained in 21 and 31% yields, respectively. On the other hand, treatment of **20** with *p*-toluenesulfonic

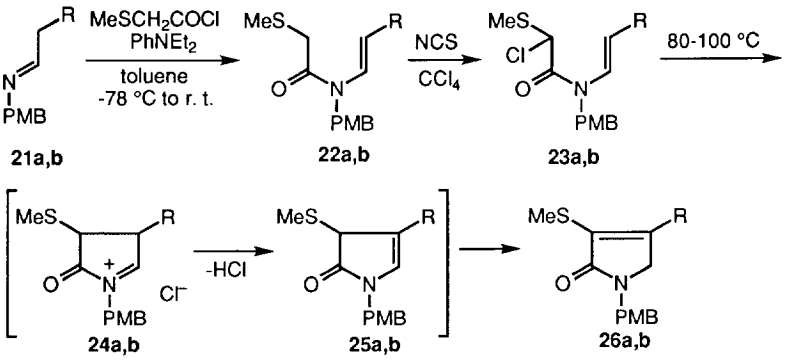
acid in boiling 1,2-dichloroethane gave **10a** and **13** in 6 and 44% yields, respectively. Formation of **13** in each case might be the result of a rearrangement of the initially formed β-lactam **10a** under the acidic conditions employed.



5-*Endo-Trig* Cyclization: Formation of γ-Lactams

In contrast with the chlorosulfides **8**, other chlorosulfides including diphenyl substituted congener **28** herein examined were found to cyclize in a 5-*endo-trig* manner to give γ-lactams.

The chlorosulfides **23a,b** were prepared by a) condensation of (phenylthio)acetaldehyde or phenylacetaldehyde with *p*-methoxybenzylamine, b) acylation of the resulting imines **21a,b** with (methylthio)acetyl chloride in the presence of *N,N*-diethylaniline, and c) chlorination of the enamides **22a,b** with NCS.

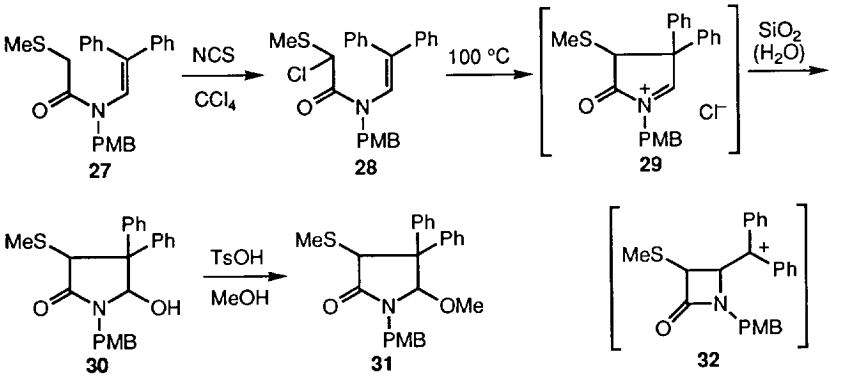


a : R = SPh, **b** : R = Ph

The mono(phenylthio)-substituted compound **23a** was found to cyclize at 80 °C in the absence of a catalyst and a solvent to give the unsaturated five-membered lactam **26a** in 35% yield.[7] Formation of **26a** may be explained in terms of a 5-*endo-trig* cyclization leading to the acyliminium salt **24a**.[8] This step is then followed by dehydrochlorination and subsequent conjugation of the double bond of the cyclic enamide **25a** to give **26a**. Similarly the phenyl-substituted compound **23b** afforded **26b** in 30% yield.[10]

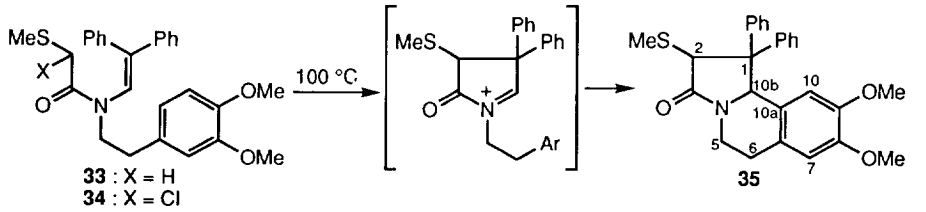
The diphenyl-substituted congener **28**, prepared according to a procedure similar to that described for **8**, upon heating without a solvent at 100 °C, also gave the five-membered lactam **30** (mp 192-194 °C) in 58% yield: no β-lactam was detected in the crude reaction mixture. The ^{1}H NMR spectrum of **30** showed it to be a single stereoisomer, though the exact stereochemistry was unknown. Formation of **30** might be the result of a 5-*endo-trig* cyclization of **28** followed by reaction of the resulting acyliminium salt **29** with water during the

course of the chromatographic separation of the reaction mixture. It was therefore presumed that the diphenyl-substituted carbocation **32**, which might be formed by 4-*exo-trig* cyclization of **28**, was less stable than was the acyliminium ion **29**.



The lactam **30** thus obtained was allowed to stand at room temperature in methanol in the presence of a catalytic amount of *p*-toluenesulfonic acid to give the corresponding 5-methoxy derivative **31** (mp 146-148 °C) as a single stereoisomer.

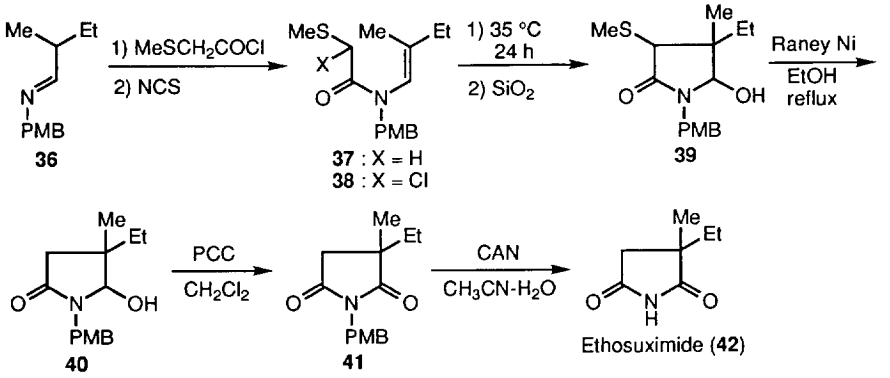
The intramolecular attack of an aromatic ring on the acyliminium ion such as **29** might give fused pyrrolidine derivatives.[11] Indeed, heating chlorosulfide **34**, bearing the 2-(3,4-dimethoxyphenyl)ethyl group on the nitrogen atom, in refluxing benzene provided the tricyclic compound **35** in 50% yield as a single stereoisomer.



Thus, it was found that even the cyclization of a compound having two substituents at the terminus of the *N*-vinylic bond (*e.g.*, **28**), the 5-*endo-trig* cyclization took place smoothly, giving γ-lactams in good yield, so we then examined the application of the method to the synthesis of an anticonvulsant agent ethosuximide (**42**).[12]

Condensation of commercially available 2-methylbutanal with *p*-methoxybenzylamine followed by acylation of the resulting imine **36** with (methylthio)acetyl chloride gave, in 59% yield, the enamide **37**, which was treated with NCS to give the requisite chlorosulfide **38**. This compound cyclized at relatively low temperature (35 °C) without a solvent to give the expected 5-hydroxy-2-pyrrolidinone **39** in 64% yield after treatment of the crude material with silica gel. The ^{1}H NMR spectrum of **39** showed it to be a *ca.* 4 : 1 mixture of two major isomers of possible four diastereoisomers. Treatment of **39** with Raney nickel in boiling ethanol gave **40** as a mixture of two stereoisomers in a ratio of *ca.* 4 : 1. Oxidation of **40** with

pyridinium chlorochromate (PCC) followed by deprotection of the *p*-methoxybenzyl group of **41** with cerium (IV) ammonium nitrate (CAN) gave ethosuximide (**42**).



In conclusion, we revealed that *N*-vinylic α-chloro-α-thioacetamides cyclized without a catalyst and, in some cases, without a solvent to give β- or γ-lactams. In contrast to the radical cyclizations of the α-bromoamides **1** which usually gave 4-*exo-trig* cyclization products **4**, the cationic cyclization of the α-chlorosulfides herein examined proceeded, in general, in a 5-*endo-trig* manner to give γ-lactams. Only the exception was the cyclization of the bis(phenylthio)-substituted compounds **8**, which provided β-lactams **10** *via* the stable intermediates **9**. The 5-*endo-trig* cyclizations of *N*-vinylic α-chloro-α-thioacetamides offer a useful procedure for the synthesis of poly-functionalized five-membered nitrogen-containing heterocycles.

Experimental Section

Melting points are uncorrected. IR spectra were recorded on a JASCO IRA-100 spectrophotometer. ^{1}H NMR spectra were measured on a JEOL JNM-PMX 60 (60 MHz), JEOL JNM-EX 270 (270 MHz), or Varian XL-300 (300 MHz) spectrometer, and δ values are quoted relative to tetramethylsilane. Exact MS determinations were obtained on a Hitachi M-80 instrument operating at 20 eV. Column chromatography was performed on Silica gel 60 PF_{254} (Nacalai Tesque, Inc.) under pressure.

***N*-(4-Methoxybenzyl)-α-methylthio-*N*-[2,2-bis(phenylthio)ethenyl]acetamide (7a).** A mixture of bis(phenylthio)acetaldehyde (**5**)[1e] (500 mg, 1.92 mmol) and *p*-methoxybenzylamine (263 mg, 1.92 mmol) in benzene (20 ml) was stirred at room temperature for 2 h in the presence of $MgSO_4$ (10 g). After $MgSO_4$ had been removed by filtration, *N,N*-diethylaniline (287 mg, 1.92 mmol) was added to the filtrate containing the enamine **6a** [^{1}H NMR ($CDCl_3$, 60 MHz) δ 3.72 (3H, s), 4.15 (2H, d, J = 6 Hz, NCH_2, 5.0-5.7 (1H, br, NH), 6.7-7.5 (15H, m)], and the mixture was heated under reflux. To this refluxing mixture was added dropwise a solution of (methlthio)acetyl chloride (478 mg, 3.84 mmol) in dry benzene (2 ml), and the mixture was further refluxed for 30 min. The reaction mixture was washed with water, and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane-AcOEt, 7:1) to give **7a** (788 mg, 88%) as an oil: IR (CCl_4) ν 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$, 60 MHz) δ 2.15 (3H, s), 3.24 (2H, s), 3.75 (3H, s), 4.80 (2H, s), 6.7-7.5 (13H, m), 6.80 (2H, d, J = 8 Hz). *Anal.* Calcd for $C_{25}H_{25}NO_2S_3$: C, 64.21; H, 5.39; N, 3.00. Found: C, 63.71; H, 5.40; N, 3.37.

***N*-Benzyloxycarbonylmethyl-α-methylthio-*N*-[2,2-bis(phenylthio)ethenyl]acetamide (7b).** According to a procedure similar to that described above for **7a**, the enamine **6b**, prepared from **5** (514 mg, 1.97 mmol) and glycine benzyl ester (325 mg, 1.97 mmol), was treated with (methylthio)acetyl chloride (491 mg, 3.94 mmol). After workup, the crude material was chromatographed on silica gel (hexane-AcOEt, 7:1) to

give **7b** (763 mg, 78%) as an oil: IR (CCl_4) ν 1750, 1670 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.11 (3H, s), 3.25 (2H, s), 4.48 (2H, s), 5.10 (2H, s), 7.1-7.4 (16H, m). *Anal.* Calcd for $C_{25}H_{25}NO_3S_3$: C, 63.00; H, 5.08; N, 2.83. Found: C, 62.60; H, 5.09; N, 3.14.

***N*-(4-Methoxyphenyl)-α-methylthio-*N*-[2,2-bis(phenylthio)ethenyl]acetamide (7c).** A mixture of **5** (260 mg, 1 mmol) and *p*-anisidine (123 mg, 1 mmol) in benzene (20 ml) was heated under reflux for 2 h with removal of water. The solvent was evaporated off, the residue containing the enamine **6c** was dissolved in toluene (30 ml), and the mixture was heated under reflux. To this refluxing mixture was added dropwise a solution of (methylthio)acetyl chloride (187 mg, 1.5 mmol) in benzene (1 ml), and the mixture was further heated under reflux for 18 h. The reaction mixture was washed with a saturated $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane-AcOEt, 7:1) to give **7c** (200 mg, 44%) as an oil: IR (CCl_4) ν 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.20 (3H, s), 3.15 (2H, s), 3.77 (3H, s), 6.6-7.5 (14H, m), 7.59 (1H, s). *Anal.* Calcd for $C_{24}H_{23}NO_2S_3$: C, 63.55: H, 5.11; N, 3.09. Found: C, 63.33; H, 5.16; N, 3.43.

General Procedure for the Preparation of β-Lactams 10a-c. To a solution of **7a-c** (2 mmol) in CCl_4 (10 ml) was added NCS (267 mg, 2 mmol) by portions at room temperature, and the mixture was stirred at the same temperature for 15h. The precipitated succinimide was filtered off, and the filtrate was concentrated *in vacuo* to give the chlorides **8a-c** in nearly quantitative yields. In the case of the chloride **8a**, this material was allowed to stand at room temperature without the use of a solvent for 24 h, and the reaction mixture was chromatographed on silica gel (hexane-AcOEt, 10:1). On the other hand, the chlorides **8b** or **8c** was dissolved in benzene (5 ml) and the whole was heated under reflux for 2 h. The solvent was evaporated off, and the residue was chromatographed on silica gel (hexane-AcOEt, 7:1). The following oily compounds were thus obtained.

1-(4-Methoxybenzyl)-3-methylthio-4-[bis(phenylthio)methylene]azetidin-2-one (10a): 66% yield; IR (CCl_4) ν 1800, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.18 (3H, s), 3.75 (3H, s), 4.68 (1H, s), 4.83, 4.90 (1H each, AB q, J = 15.0 Hz), 6.72 (2H, d, J = 8.6 Hz), 6.94-7.0 (2H, m), 7.14-7.28 (10H, m). *Anal.* Calcd for $C_{25}H_{23}NO_2S_3$: C, 64.49; H, 4.98; N, 3.01. Found: C, 64.78; H, 4.95; N, 3.17.

1-Benzyloxycarbonylmethyl-3-methylthio-4-[bis(phenylthio)methylene]azetidin-2-one (10b): 62% yield; IR (CCl_4) ν 1805, 1745, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.19 (3H, s), 4.46 (2H, s), 4.70 (1H, s), 4.97 (2H, s), 7.20 (15H, br s). *Anal.* Calcd for $C_{26}H_{23}NO_3S_3$: C, 63.26; H, 4.70; N, 2.84. Found: C, 62.95; H, 4.60; N, 2.78.

1-(4-Methoxyphenyl)-3-methylthio-4-[bis(phenylthio)methylene]azetidin-2-one (10c): 54% yield; IR (CCl_4) ν 1800, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.30 (3H, s), 3.76 (3H, s), 4.83 (1H, s), 6.7-7.6 (12H, m), 6.80 (2H, d, J = 8 Hz). *Anal.* Calcd for $C_{24}H_{21}NO_2S_3$: C, 63.83; H, 4.69; N, 3.10. Found: C, 63.77; H, 4.82; N, 2.81.

1-(4-Methoxybenzyl)-4-[bis(phenylthio)methylene]azetidine-2,3-dione (12). To an ice cooled solution of **10a** (150 mg, 0.32 mmol) in CCl_4 (5 ml) was added NCS (43 mg, 0.32 mmol) by portions, and the mixture was stirred at room temperature for 15 h. The precipitated succinimide was filtered off, the filtrate was concentrated *in vacuo*, and the residue containing the chlorosulfide **11** was dissolved in acetone (9 ml). To this solution was added a solution of $CuCl_2 \cdot 2H_2O$ (218 mg, 1.28 mmol) in water (1 ml), and the mixture was heated under reflux for 8 h. Acetone was removed by evaporation, water (10 ml) was added to the residue, and the whole was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane-AcOEt, 4:1) to give **12** (79 mg, 59%) as an oil: IR (CCl_4) ν 1830, 1800, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 3.73 (3H, s), 5.13 (2H, s), 6.6-7.4 (12H, m), 6.70 (2H, d, J = 8 Hz); exact mass calcd for $C_{24}H_{19}NO_3S$ 433.0804, found 433.0802.

1-(4-Methoxybenzyl)-4-methylthio-4,5-di(phenylthio)-3*H*-pyrrol-2(1*H*)-one (13). A solution of **10a** (99 mg, 0.21 mmol) in trifluoroacetic acid (1 ml) was allowed to stand at room temperature overnight. The reaction mixture was neutralized with a saturated $NaHCO_3$ solution, and the whole was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane-AcOEt, 7:1). The first eluate gave **10a** (14 mg, 14%). The second eluate gave **13** (43 mg, 43%) as an yellow oil: IR (CCl_4) ν 1690, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.16 (3H, s), 3.73 (3H, s), 4.24 (1H, d, J = 14.5 Hz), 4.70 (1H, s), 5.10 (1H, d, J = 14.5 Hz), 6.74 (2H, d, J = 8 Hz), 7.05 (2H, d, J = 8 Hz), 7.24 (10H, s); exact mass calcd for $C_{25}H_{23}NO_2S_3$ 465.0891, found 465.0894.

Formation of 10a and 13 from the Sulfoxide 20. To a solution of **7a** (788 mg, 1.68 mmol) in CH_2Cl_2 (60 m l) was added dropwise a solution of *m*-chloroperbenzoic acid (80%) (362 mg, 1.68 mml) in CH_2Cl_2

(25 ml) at 0 °C, and the mixture was stirred at the same temperature for 1 h. The reaction mixture was washed with a saturated $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (benzene-acetone, 3:1) to give *N*-(4-methoxybenzyl)-α-methylsulfinyl-*N*-[2,2-bis(phenylthio)ethenyl]acetamide (**20**) (450 mg, 55%), which was used immediately in the next stage. **Method A.** Trifluoroacetic anhydride (139 mg, 0.66 mmol) was added to a solution of **20** (160 mg, 0.33 mmol) in CH_2Cl_2 (5 ml) at 0 °C, and the mixture was stirred at room temperature for 15 h. The reaction mixture was washed with a saturated $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane-AcOEt, 10:1). The first eluate gave **10a** (33 mg, 21%). The second eluate gave **13** (47 mg, 31%). **Method B.** *p*-Toluenesulfonic acid monohydrate (40 mg, 0.21 mmol) was added to a solution of **20** (100 mg, 0.21 mmol) in 1,2-dichloroethane (5 ml), and the mixture was heated under reflux for 1 h. After workup as described above, the crude material was purified by chromatography on silica gel (hexane-AcOEt, 7:1). The first eluate gave **10a** (6 mg, 6%). The second eluate gave **13** (43 mg, 44%).

***N*-(4-Methoxybenzyl)-α-methylthio-*N*-[2-(phenylthio)ethenyl]acetamide (22a).** 4-Methoxybenzylamine (2.06 g, 15 mmol) and $MgSO_4$ (10 g) were added successively to a solution of (phenylthio)acetaldehyde[6] (2.28 g, 15 mmol) in diethyl ether (20 ml), and the mixture was stirred at the same temperature for 2 h. $MgSO_4$ was filtered off, the filtrate was concentrated *in vacuo*, and the residue containing the imine **21a** was dissolved in dry toluene (20 ml). To this solution were added successively *N,N*-diethylaniline (2.25 g, 15 mmol) and (methylthio)acetyl chloride (2.8 g, 22.5 mmol) at -78 °C, and the mixture was stirred for 24 h during which time the bath temperature raised to room temperature. The reaction mixture was washed with water, and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane-AcOEt, 5:1) to gvie **22a** (1.54 g, 29%) as an oil: IR (CCl_4) ν 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.21 (3H, s), 3.46 (2H, br s), 3.78 (3H, s), 4.89 (2H, s), 5.63 (1H, d, J = 13 Hz), 5.7-7.3 (10H, m). *Anal.* Calcd for $C_{19}H_{21}NO_2S_2$: C, 63.48; H, 5.89; N, 3.90. Found: C, 63.33; H, 5.92; N, 3.72.

***N*-(4-Methoxybenzyl)-α-methylthio-*N*-(2-phenylethenyl)acetamide (22b).** According to a procedure similar to that described above for the preparation of **22a**, *p*-methoxybenzylamine (1.37 g, 10 mmol) was allowed to react successively with phenylacetaldehyde (90%) (1.34 g, 10 mmol) and (methylthio)acetyl chloride (1.87 g, 15 mmol), and the crude material was chromatographed on silica gel (hexane-AcOEt, 5:1) to give **22b** (3.27 g, 63%): mp 87-89 °C (hexane-AcOEt); IR (CCl_4) ν 1660, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.16 (3H, s), 3.48 (2H, br s), 3.63 (3H, s), 4.85 (2H, s), 5.93 (1H, d, J = 14 Hz), 5.65-7.4 (10H, m). *Anal.* Calcd for $C_{19}H_{21}NO_2S$: C, 69.70; H, 6.46; N, 4.28. Found: C, 69.94; H, 6.47; N, 4.63.

1-(4-Methoxybenzyl)-3-methylthio-4-phenylthio-5*H*-pyrrol-2(1*H*)-one (26a). *N*-Chlorosuccinimide (48 mg, 0.36 mmol) was added by portions to a solution of **22a** (130 mg, 0.36 mmol) in CCl_4 (15 ml) at 0 °C, and the mixture was stirred at room temperature for 2 h. The precipitated succinimide was filterted off, and the filtrate was concentrated *in vacuo* to give the chloride **23a** [δ 5.82 (1H, s, CHCl)] in nearly quantitative yield. This material was then heated without a solvent at 40 °C for 2 h and then at 80 °C for 1 h, and the crude reaction mixture was chromatographed on silica gel (hexane-AcOEt, 1:1) to give **26a** (42 mg, 32 %) as an oil: IR (CCl_4) ν 1685, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.56 (3H, s, SMe), 3.49 (2H, s, H-5), 3.76 (3H, s, OMe), 4.45 (2H, s, ArCH_2), 6.78, 7.06 (2H each, AB q, J = 9 Hz, ArH), 7.2-7.5 (5H, m, ArH). *Anal.* Calcd for $C_{19}H_{19}NO_2S_2$: C, 63.84; H, 5.36; N, 3.92. Found: C, 63.51; H, 5.45; N, 4.08.

1-(4-Methoxybenzyl)-3-methylthio-4-phenyl-5*H*-pyrrol-2(1*H*)-one (26b). According to a procedure similar to that described above for the preparation of **26a**, the enamide **22b** (272 mg, 0.83 mmol) was treated with NCS (111 mg, 0.83 mmol), and the resulting chlorosulfide **23b** was heated without a solvent at 100 °C for 30 min. The crude material was chromatographed on silica gel (hexane-AcOEt, 5:1) to give **26b** (82 mg, 30%) as an oil: IR (CCl_4) ν 1700, 1610 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.55 (3H, s, SMe), 3.73 (3H, s, OMe), 4.08 (2H, s, H-5), 4.63 (2H, s, ArCH_2), 6.82 (2H, d, J = 9 Hz, ArH), 7.1-7.8 (7H, m, ArH). *Anal.* Calcd for $C_{19}H_{19}NO_2S$: C, 70.13; H, 5.89; N, 4.30. Found: C, 69.87; H, 5.89; N, 4.57.

***N*-(4-Methoxybenzyl)-α-methylthio-*N*-(2,2-diphenylethenyl)acetamide (27).** According to a procedure similar to that described above for the preparation of **7a**, *p*-methoxybenzylamine (0.7 g, 5.1 mmol) was allowed to react successively with diphenylacetaldehyde (1.0 g, 5.1 mmol) and (methylthio)acetyl chloride (1.25 g, 10.2 mmol), and the crude material was chromatographed on silica gel (hexane-AcOEt, 3:1) to give **27** (3.27 g, 63%) as an oil: IR (CCl_4) ν 1665 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.16 (3H, s), 3.25 (2H, s), 3.76 (3H, s), 4.40 (2H, s), 6.58 (1H, s), 6.83 (2H, d, d, J = 9 Hz), 7.0-7.5 (12H, m). *Anal.* Calcd for $C_{25}H_{25}NO_2S$: C, 74.41; H, 6.24; N, 3.47. Found: C, 74.28; H, 6.18; N, 3.84.

5-Hydroxy-1-(4-methoxybenzyl)-3-methylthio-4,4-diphenylpyrrolidin-2-one (30). According to a procedure similar to that described above for the preparation of **26a**, the enamide **27** (349 mg, 0.87 mmol) was tereated with NCS (116 mg, 0.87 mmol), and the resulting chlorosulfide **28** was heated without a solvent at 100 °C for 30 min. The crude material containing the acyliminium salt **29** was chromatographed on silica gel (hexane-AcOEt, 3;1) to give **30** (211 mg, 58%): mp 192-194 °C (hexane-AcOEt); IR (KBr) ν 3400, 3190, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.13 (3H, s, SMe), 2.30 (1H, d, J = 9 Hz, OH), 3.77 (3H, s, OMe), 4.13 (1H, d, J = 14 Hz, one of NCH_2), 4.26 (1H, s, H-3), 4.92 (1H, d, J = 14 Hz, one of NCH_2), 5.66 (1H, d, J = 9 Hz, H-5), 6.7-7.5 (14H, m). *Anal.* Calcd for $C_{25}H_{25}NO_3S$: C, 71. 57; H, 6.01; N, 3.34. Found: C, 71.97, H, 6.23; N, 3.46.

5-Methoxy-1-(4-methoxybenzyl)-3-methylthio-4,4-diphenylpyrrolidin-2-one (31). *p*-Toluenesulfonic acid monohydrate (2 mg) was added to a solution of **30** (50 mg, 0.12 mmol) in methanol (2 ml) and the mixture was allowed to stand at room temperature overnight. The solvent was evaporated off and the residue was chromatographed on silica gel (hexane-AcOEt, 7:1) to give **31** (43 mg, 84%): mp 146-148 °C (hexane-AcOEt); IR (CCl_4) ν 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.16 (3H, s, SMe), 2.93 (3H, s, C_5-OMe), 3.82 (3H, s, OMe), 4.13 (1H, d, J = 14 Hz, one of NCH_2), 4.32 (1H, s, H-3), 5.06 (1H, d, J = 14 Hz, one of NCH_2), 5.20 (1H, s, H-5), 6.5-7.5 (14H, m). *Anal.* Calcd for $C_{26}H_{27}NO_3S$: C, 72.03; H, 6.28; N, 3.23. Found: C, 71.76; H, 5.99; N, 3.54.

***N*-[2-(3,4-Dimethoxyphenyl)ethyl]-α-methylthio-*N*-(2,2-diphenylethenyl)acetamide (33).** According to a procedure similar to that described above for the preparation of **7a**, 2-(3,4-dimethoxyphenyl)ethylamine (906 mg, 5 mmol) was allowed to react successively with diphenylacetaldehyde (976 mg, 5 mmol) and (methylthio)acetyl chloride (1.25 g, 10 mmol), and the crude material was chromatographed on silica gel (hexane-AcOEt, 5:1) to give **33** (1.61 g, 72%) as an oil: IR (CCl_4) ν 1655 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 2.20 (3H, s), 2.75 (2H, br t, J = 7 Hz), 3.22, 3.30 (total 2H, both s), 3.3-3.7 (2H, m), 3.86 (6H, s), 6.57 (1H, s), 6.6-6.9 (3H, m), 7.0-7.5 (10H, m); exact mass calcd for $C_{27}H_{29}NO_3S$ 447.1869, found 447.1844.

1,2,3,5,6,10b-Hexahydro-8,9-dimethoxy-2-methylthio-1,1-diphenylpyrrolo[2,1-a]isoquinolin-3-one (35). According to a procedure similar to that described above for the preparation of **26a**, the enamide **33** (271 mg, 0.61 mmol) was treated with NCS (81 mg, 0.61 mmol), and the resulting chlorosulfide **34** was heated without a solvent at 100 °C for 30 min. The crude material was chromatographed on silica gel (hexane-AcOEt, 3;1). The first eluate gave **33** (65 mg, 24%). The second eluate gave **35** (47%): mp 204-206 °C (hexane-AcOEt); IR (KBr) ν 1690 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.0-2.15 (1H, m, one of H-6), 2.13 (3H, s, SMe), 2.30 (1H, br d, J = ca. 15 Hz, one of H-6), 2.87 (1H, td, J = 12.5, 3.3 Hz, one of H-5), 3.66 (3H, s, OMe), 3.73 (3H, s, OMe), 3.97 (1H, s, H-2), 4.39 (1H, ddd, J = 12.5, 5.0, 1.3 Hz, one of H-5), 6.15 (1H, s), 6.27 (1H, s), 6.86-7.06 (5H, m), 7.00 (1H, s, H-10b), 7.35-7.55 (5H, m). *Anal.* Calcd for $C_{27}H_{27}NO_3S$: C, 72.78; H, 6.11; N, 3.14. Found: C, 72.62; H, 5.90; N, 3.16.

***N*-(2-Methylbut-1-enyl)-*N*-(4-methoxybenzyl)-α-(methylthio)acetamide (37).** According to a procedure similar to that described above for the preparation of **22a**, *p*-methoxybenzylamine (1.37 g, 10 mmol) was allowed to react successively with 2-methylbutanal (861 mg, 10 mmol) and (methylthio)acetyl chloride (1.87 g, 15 mmol), and the crude material was chromatographed on silica gel (hexane-AcOEt, 7:1) to give **37** (1.72 g, 59%) as an oily mixture of two stereoisomers in a ratio of ca. 5:1: IR (CCl_4) ν 1640 cm^{-1}; ^1H NMR for the major stereoisomer ($CDCl_3$, 60 MHz) δ 0.98 (3H, t, J = 7 Hz), 1.47 (3H, br s), 1.99 (2H, br t, J = *ca.* 7 Hz), 2.20 (3H, s), 3.20 (2H, s), 3.78 (3H, s), 4.54 (2H, s), 5.86 (1H, br s), 6.79, 7.19 (2H each, ABq, J = 9 Hz); exact mass calcd for $C_{16}H_{23}NO_2S$ 293.1449, found 293.1443.

4-Ethyl-5-hydroxy-1-(4-methoxybenzyl)-4-methyl-3-(methylthio)pyrrolidin-2-one (39). According to a procedure similar to that described above for the preparation of **26a**, the enamide **37** (572 mg, 1.95 mmol) was tereated with NCS (261 mg, 1.95 mmol), and the resulting chlorosulfide **38** was allowed to stand at 35 °C without a solvent overnight. After heating the mixture at 60 °C for 30 min, benzene (10 ml) and silica gel (5 g) were added to the reaction mixture, and the whole was stirred vigorously for 1 h. The silica gel was filtered off, the filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel (hexane-AcOEt, 3;1) to give **39** (389 mg, 64%): mp 136-139 °C (hexane-AcOEt); IR (CCl_4) ν 3410, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.6-1.9 (8H, m), 2.28, 2.30 [total 3H (*ca.* 1:4), both s], 3.33, 3.40 [total 1H (*ca.* 1:4), both s], 3.80 (3H, s), 3.9-5.2 (4H, m), 6.7-7.4 (4H, m). *Anal.* Calcd for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53. Found: C, 61.70; H, 7.39; N, 4.20.

4-Ethyl-5-hydroxy-1-(4-methoxybenzyl)-4-methylpyrrolidin-2-one (40). Raney nickel (W-2) (*ca.* 1 g) was added to a solution of **39** (184 mg, 0.59 mmol) in ethanol (5 ml), and the whole was heated under reflux for 3 h. The Raney nickel was filtered off, the filtrate was concentrated *in vacuo*, and the residue was

chromatographed on silica gel (hexane-AcOEt, 3:1) to give **40** (72 mg, 58%): mp 65-68 °C (hexane-AcOEt); IR (CCl_4) ν 3350, 1670 cm^{-1}; ^1H NMR for the major isomer ($CDCl_3$, 300 MHz) δ 0.89 (3H, t, *J* = 7.6 Hz), 0.91 (3H, s), 1.48-1.57 (2H, m), 1.98-2.06 (1H, br), 2.08 (1H, d, *J* = 16.6 Hz), 2.40 (1H, d, *J* = 16.6 Hz), 3.80 (3H, s), 4.14 (1H, d, *J* = 14.6 Hz), 4.55 (1H, br d), 4.78 (1H, d, *J* = 14.6 Hz), 6.86 (2H, d, *J* = 8.6 Hz), 7.22 (2H, d, *J* = 8.6 Hz); ^1H NMR for the minor isomer ($CDCl_3$, 300 MHz) δ 0.78 (3H, t, *J* = 7.4 Hz), 1.05 (3H, s), 1.26-1.39 (2H, m), 1.58 (1H, s), 2.23 (1H, d, *J* = 17.0 Hz), 2.32 (1H, dd, *J* = 17.0, 1.0 Hz), 3.80 (3H, s), 4.14 (1H, d, *J* = 14.6 Hz), 4.47 (1H, br d), 4.77 (1H, d, *J* = 14.6 Hz), 6.86 (2H, d, *J* = 8.6 Hz), 7.22 (2H, d, *J* = 8.6 Hz). *Anal.* Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.01; H, 8.15; N, 5.44.

4-Ethyl-1-(4-methoxybenzyl)-4-methylpyrrolidine-2,5-dione (41). To a stirred suspension of pyridinium chlorochromate (PCC) (103 mg, 0.48 mmol) in CH_2Cl_2 (2 ml) was added a solution of **40** (64 mg, 0.24 mmol) in CH_2Cl_2 (1 ml) at room temperature, and the stirring was continued for 2 h. The precipitates were removed by filtration and washed with diethyl ether. The combined organic layers were washed with 5% HCl, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane-AcOEt, 3:1) to give **41** (40 mg, 56%): mp 65-67 °C (hexane-AcOEt); IR (CCl_4) ν 1775, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.78 (3H, t, *J* = 7 Hz), 1.26 (3H, s), 1.4-1.9 (2H, m), 2.36, 2.63 (1H each, ABq, *J* = 18 Hz), 3.78 (3H, s), 4.57 (2H, s), 6.80, 7.32 (2H each, ABq, *J* = 9 Hz). *Anal.* Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.03; H, 7.37; N, 5.60.

Ethosuximide (42). To a stirred solution of **41** (133 mg, 0.5 mmol) in acetonitrile (1 ml) was added dropwise a solution of cerium (IV) ammonium nitrate (577 mg, 1.0 mmol) in water (4 ml) at room temperature, and the stirring was continued for 1 h. Water (10 ml) was added to the reaction mixture and the whole was extracted with AcOEt. The organic phase was washed with brine and dried over $MgSO_4$. The solvent was evaporated off to give ethosuximide containing an inseparable by-product, so that the residue was dissolved in a mixture of ethanol (7 ml) and ammonia solution (28%) (3 ml) and the mixture was heated in a sealed at 100 °C for 2 h. Water (20 ml) was added to the reaction mixture and the whole was extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$, the solvent was evaporated off, and the residue was chromatographed on silica gel (hexane-AcOEt, 2:1) to give pure ethosuximide (**42**) (33 mg, 47%), whose melting point (38.5-40 °C) and spectral data were identical with those of an authentic sample purchased from Sigma Chemical Co. (mp 39-41 °C): IR (CCl_4) ν 3430, 3230, 1785, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 60 MHz) δ 0.93 (3H, t, *J* = 7 Hz), 1.33 (3H, s), 1.5-1.9 (2H, m), 2.45, 2.70 (1H each, ABq, *J* = 18 Hz), 8.5-9.3 (1H, br).

References and Notes

1. (a) Ishibashi, H.; Nakamura, N.; Sato, T.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* **1991**, *32*, 1725. (b) Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* 1992, 2399. (c) Ishibashi, H.; Kameoka, C.; Yoshikawa, A.; Ueda, R.; Kodama, K.; Sato, T.; Ikeda, M. *Synlett* **1993**, 649. (d) Ishibashi, H.; Kameoka, C.; Sato, T.; Ikeda, M. *Synlett* **1994**, 445. (e) Ishibashi, H.; Kameoka, C.; Iriyama, H.; Kodama, K.; Sato, T.; Ikeda, M. *J. Org. Chem.* in press.
2. Fremont, S.L.; Belletire, J.L.; Ho, D.M. *Tetrahedron Lett.* **1991**, *32*, 2335.
3. For reviews of the carbon-carbon bond forming reactions using α-chlorosulfides, see Ishibashi, H.; Ikeda, M. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 330; Ishibashi, H. *Yakugaku Zasshi* **1989**, *109*, 685; Ishibashi, H.; Ikeda, M. *Rev. Heteroatom Chem.* **1992**, vol 7, 191.
4. Ishibashi, H.; Matsuoka, K.; Ikeda, M. *Chem. Pharm. Bull.* **1991**, *39*, 1854.
5. An analogous transformation of 3-(phenylthio)azetidin-2-ones to azetidine-2,3-diones has been reported, see Manhas, M.S.; Bari, S.S.; Bhawal, B.M.; Bose, A.K. *Tetrahedron Lett.* **1984**, *25*, 4733.
6. Ishibashi, H.; Ikeda, M.; Maeda, H.; Ishiyama, K.; Yoshida, M.; Akai, S.; Tamura, Y. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1099 and references cited therein.
7. IR spectrum of the crude reaction mixture showed the presence of a trace amount of β-lactam (ν 1765 cm^{-1}), but no such compound was isolated as a pure form.
8. Although the 5-*endo-trig* cyclization has been recognized as a disfavored process,[9] a few examples of such type of cyclization have been reported, see (a) Grigg, R.; Kemp, J.; Malone, J.; Tangthongkum, A. *J. Chem. Soc., Chem. Commun.* **1980**, 648. (b) Tamura, Y.; Maeda, H.; Akai, S.; Ishibashi, H. *Tetrahedron Lett.* **1982**, *23*, 2209.
9. Baldwin, J.E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
10. Heating **23b** in boiling benzene gave a complex mixture of products containing the dechlorinated compound **22b**.
11. Speckamp, W.N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.
12. Kaestner, I.; Kermes, U.; Rougerie, A. *Acta Biol. Med. Ger.* **1971**, *27*, 451.

(*Received in Japan* 9 *December* 1994; *accepted* 13 *January* 1995)