A New and Efficient Access to Thiazoline-4-carboxylates and Cysteine Derivatives Incorporating Cyclopropyl Groups[‡]

Marcus W. Nötzel,[a] Thomas Labahn,[b] Mazen Es-Sayed,[c] and Armin de Meijere*[a]

Dedicated to Professor Frank-Gerrit Klärner on the occasion of his 60th birthday

Keywords: Amides / Amino acids / Michael additions / Nitrogen heterocycles / Sulfur heterocycles

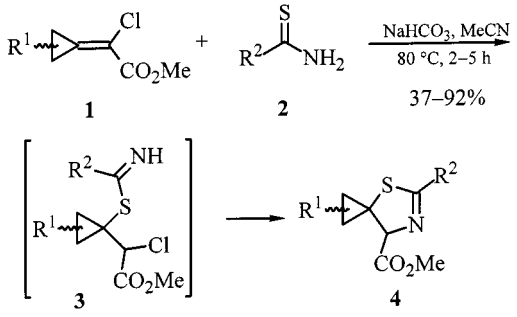
Under basic conditions ($NaHCO_3$, MeCN), thiocarboxamides **2**, including *N,N*-thioureas, cleanly undergo Michael addition onto 2-chloro-2-cyclopropylideneacetates **1**, attacking through the sulfur, and this is followed by an intramolecular substitution to afford 5-spirocyclopropane-annelated thiazoline-4-carboxylates **4** in 37–92% yields. The thiazolines **4** are cysteine derivatives that possess a cyclopropyl or substituted cyclopropyl group in place of the *gem*-dimethyl-substituted β-carbon atom of penicillamine; they can be hydrolyzed to the hydrochloride salt of the amino acid **5** by heating in acid. Under acidic conditions (CH_2Cl_2, HCl), the Michael adducts **7** of thioamides **2** onto **1** are formed in high to virtually quantitative yields. When treated with $NaHCO_3$ in MeCN, the adducts **7** cyclize to thiazolinecarboxylates **4** (51–82%), but in the presence of $Ti(OiPr)_4$ they form spirocyclopropane-annelated thiazinones **8** (19–88%).

Introduction

Natural amino acid homologues incorporating cyclopropyl groups are subjects of ever increasing interest as potential enzyme inhibitors[1] and conformationally restricted building blocks for peptidomimetics.[2] A wide range of biological activities has been discovered in such unnatural amino acid analogues and in small peptides containing them.[3] Quite a variety of such cyclopropane amino acids and their derivatives have been prepared by sequential Michael addition, nucleophilic substitution, and possible further transformations[4,5] from the highly reactive acrylate analogues methyl 2-chloro-2-cyclopropylideneacetates **1**.[6] However, cysteine derivatives that are β,β-disubstituted like penicillamine, but which possess a cyclopropane ring in place of the *gem*-dimethyl substituents, have not previously been described.[7] One route to cysteines is by hydrolysis of thiazoline-4-carboxylates, which can be prepared by treatment of thiobenzamide with α-chloroacrylates.[8] However, this method cannot be applied to α-chloro-β,β-dimethylacrylates, and so β,β-disubstituted cysteine derivatives (penicillamines) are not accessible by these means. In view of the fact that even weakly nucleophilic deprotonated primary carboxamides add to **1**, and that this addition, under appropriate conditions, is followed by an intramolecular substitution of the α-chlorine to give spirocyclopropanated oxazoline-4-carboxylates,[9] it was of interest to study the addition of primary thiocarboxamides to **1** as a possible way to obtain spirocyclopropane-annelated thiazoline-4-carboxylates **4**.

Results and Discussion

When an equimolar mixture of methyl 2-chloro-2-cyclopropylideneacetate (**1a**) and thiobenzamide (**2a**) was refluxed for 3 h in acetonitrile solution in the presence of sodium bicarbonate, methyl 2′-phenylspiro(cyclopropane-1,5′-thiazoline)-4′-carboxylate (**4a**) was isolated in 86% yield (Scheme 1). The structure was assigned on the basis of its ^1H and ^{13}C NMR spectra and MS data, and was rigorously proven by an X-ray crystal structure analysis.[10]



Scheme 1. For details see Table 1

[‡] Cyclopropyl Building Blocks in Organic Synthesis, 66. − Part 65 see: K. Miyazawa, S. Löhr, A. de Meijere, *Mol. Cryst. Liq. Cryst.*, in press; Part 64 see: C. Funke, M. Es-Sayed, A. de Meijere, *Org. Lett.* **2000**, 4249−4251.

[a] Institut für Organische Chemie der Georg-August-Universität Göttingen,
Tammannstrasse 2, 37077 Göttingen, Germany
Fax: (internat.) +49 551/399475
E-mail: Armin.deMeijere@chemie.uni-goettingen.de
[b] Institut für Anorganische Chemie der Georg-August-Universität Göttingen,
Tammannstrasse 4, 37077 Göttingen, Germany
[c] Bayer AG, Landwirtschaftszentrum,
Alfred-Nobel-Straße 50, Geb. 6510, 40789 Monheim, Germany

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/eurjoc or from the author.

  1434−193X/01/0816−3025 $ 17.50+.50/0

Table 1. Synthesis of thiazoline-4-carboxylates **4** from thioamides **2** and methyl 2-chloro-2-cyclopropylideneacetates **1**

Michael acceptor	Thioamide	R^1	R^2	Product	Diastereomeric ratio	Yield (%)
1a	**2a**	H	Ph	**4a**	–	86
1a	**2b**	H	Me	**4b**	–	73
1a	**2c**	H	4-BrC_6H_4	**4c**	–	85
1a	**2d**	H	4-*t*BuC_6H_4	**4d**	–	77
1a	**2e**	H	4-$MeOC_6H_4$	**4e**	–	92
1a	**2f**	H	4-MeC_6H_4	**4f**	–	68
1a	**2g**	H	4-FC_6H_4	**4g**	–	67
1a	**2h**	H	2-C_4H_3S[a]	**4h**	–	53
1a	**2i**	H	NMe_2	**4i**	–	49
1a	**2j**	H	NMePh	**4j**	–	37
1a	**2k**	H	$O(CH_2CH_2)_2N$[b]	**4k**	–	39
1b	**2a**	Me	Ph	**4l**	1.2:1	51
1b	**2b**	Me	Me	**4m**	1.9:1	52
1b	**2e**	Me	4-$MeOC_6H_4$	**4n**	1.2:1	72
1c	**2a**	Et	Ph	**4o**	2.1:1:1	58
1c	**2b**	Et	Me	**4p**	1.7:1:1	78
1c	**2c**	Et	4-BrC_6H_4	**4q**	9.3:1.5:1	52
1c	**2d**	Et	4-*t*BuC_6H_4	**4r**	2.3:1.1:1	66
1d	**2a**	$(CH_2)_2OBn$	Ph	**4s**	2:1	52
1d	**2b**	$(CH_2)_2OBn$	Me	**4t**	1.1:1	77

[a] Thiophene-2-thiocarboxamide. – [b] Morpholine-4-carbothioic acid amide.

Under the same conditions, thioacetamide (**2b**), thiophene-2-thiocarboxamide (**2h**), substituted thiobenzamides **2c–g**, and *N*,*N*-disubstituted thiourea derivatives **2i–k** gave the corresponding thiazolines **4b–t**, in yields ranging from 37 to 92% (Table 1).

In the Michael additions of the thioamides **2a–e** to the 2′-substituted methyl 2-chloro-2-cyclopropylideneacetates **1b–d** to give **4l–t**, up to four diastereomers can be formed; only three or fewer were obtained, however, although with rather low selectivities [diastereomeric ratios (*dr*s) ranging from 1.7:1:1 to 2:1]. For comparison, treatment of **1c** with oxoamides exclusively gave only two diastereomers of the corresponding oxazoline-5-carboxylates, with *dr*s of up to 17:1.[9] The lower diastereoselectivities probably arise from the fact that higher reaction temperatures are required for cocyclization with thioamides, and that the Michael addition would be reversible at the temperature of 80 °C. In addition, the high temperature would favor an S_N1 mechanism for the intramolecular chlorine substitution resulting in ring-closure, thus causing the loss of any stereochemical information at C-2 in **3** that may arise from a diastereoselective protonation of the corresponding enolate as observed previously.[11] Therefore, more than two diastereomers were obtained in the cases of **4o–r**. The relative configuration of the major diastereomer of methyl 2′-(4-*tert*-butylphenyl)-spiro[2-ethylcyclopropane-1,5′(4′*H*)-thiazoline]-4′-carboxylate (**4r**) was proven by X-ray crystal structure analysis to be 2*R**,4′*S**,5′*R** (Figure 1).[10]

The new thiazoline-4-carboxylates **4** are suitable precursors for the cyclopropane analogue of penicillamines **5**. Refluxing of **4b** in water for 5 h produced the *N*-acetylcysteine methyl ester **6** in a yield of 93%. The free amino acid **5** was obtained in 89% yield by refluxing **4b** for 5 h in 3 N HCl (Scheme 2).

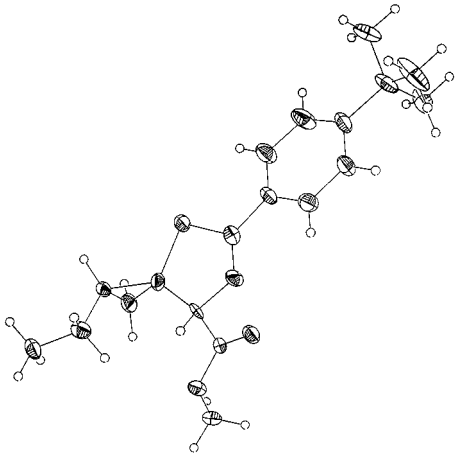
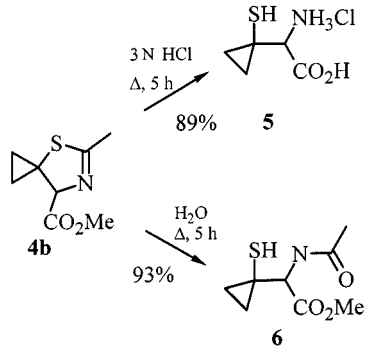
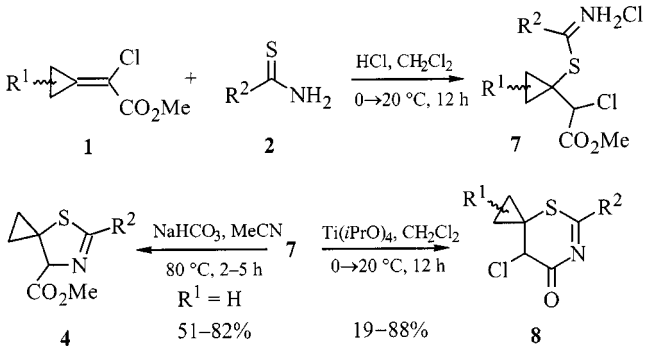


Figure 1. Structure of methyl 2′-(4-*tert*-butylphenyl)spiro[2-ethylcyclopropane-1,5′(4′*H*)-thiazoline]-4′-carboxylate (**4r**) (ref.[10])



Scheme 2

Treatment of methyl 2-chloro-2-cyclopropylideneacetate (**1a**) with thioamides **2**, at 0 °C for 12 h in dichloromethane saturated with hydrogen chloride, gave compounds **3** as their HCl adducts **7** in high to virtually quantitative yields. If compounds **7** were heated in acetonitrile at reflux in the presence of sodium bicarbonate, they also gave the spirocyclopropanated thiazolines **4**, but the yields in this two-step preparation (51−82%) were not quite as good as those for the single operation approach; and therefore only a few thiazolines **4a−c** were prepared in a pure form by this route. In most cases, competition with a six-membered ring-closure to give the corresponding 1,3-thiazin-4(5*H*)-ones **8** was observed. These latter could not be separated efficiently from the thiazolines **4**. Fortunately, though, this cyclization of the intermediates **7** occurred selectively in the presence of titanium tetraisopropoxide and gave the pure thiazinones **8** in good yields in most cases (Scheme 3 and Table 2). The structures could be assigned on the basis of their ^{1}H and ^{13}C NMR spectra and MS data, and that of compound **8a** was rigorously proven by an X-ray crystal structure analysis.[10]



1 **2** **7** **4** **8**

4	R^2	%
a	Ph	71
b	Me	51
c	4-BrC_6H_4	82

Scheme 3. For details see Table 2

Thiophene-2-thiocarboxamide (**2h**), substituted thiobenzamides **2c−e**, and *N*-substituted thioureas **2i**, **2j**, and **2l** under the same conditions gave the corresponding thiazinones **8b−k**, in yields ranging from 19 to 88% (Table 2).

In the Michael additions of the thioamides **2a**, **2c**, and **2d** to the 2′-substituted methyl 2-chloro-2-cyclopropylideneacetate **1c** to give **8i−k**, the observed diastereoselectivities were low [diastereomeric ratios (*dr*s) ranging from 3:1:1 to 2:1], as in the formation of the thiazolines **4l−t**. In these cases, the presence of the strong acid hydrogen chloride apparently results in the lack of diastereoselectivity.

The relative configuration of the major diastereomer of 5-(4-bromophenyl)-8-chloro-1-ethyl-4-thia-6-azaspiro[2.5]-oct-5-en-7-one (**8j**) was proven by an X-ray crystal structure analysis to be 1*S**,3*R**,8*R** (Figure 2).[10]

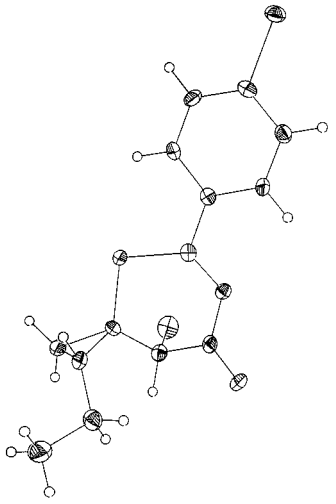


Figure 2. Structure of 5-(4-bromophenyl)-8-chloro-1-ethyl-4-thia-6-azaspiro[2.5]oct-5-en-7-one (**8j**) in the crystal (ref.[10])

Conclusion

Upon treatment with thiocarboxamides **2** under basic conditions, methyl 2-chloro-2-cyclopropylideneacetates

Table 2. Synthesis of thiazinones **8** from thioamides **2** and methyl 2-chloro-2-cyclopropylideneacetates **1**

Michael acceptor	Thioamide	R^1	R^2	Product	Diastereomeric ratio	Yield[a] (%)
1a	**2a**	H	Ph	**8a**	−	71
1a	**2c**	H	4-BrC_6H_4	**8b**	−	51
1a	**2d**	H	4-*t*BuC_6H_4	**8c**	−	78
1a	**2e**	H	4-$MeOC_6H_4$	**8d**	−	82
1a	**2h**	H	2-C_4H_3S[b]	**8e**	−	29
1a	**2i**	H	NMe_2	**8f**	−	80
1a	**2j**	H	NMePh	**8g**	−	80
1a	**2l**	H	NHMe	**8h**	−	19
1c	**2a**	Et	Ph	**8i**	2:1	54
1c	**2c**	Et	4-BrC_6H_4	**8j**	2:1	84
1c	**2d**	Et	4-*t*BuC_6H_4	**8k**	3:1:1	88

[a] Overall yields based on starting material **1**. − [b] Thiophene-2-thiocarboxamide.

1a–d undergo a domino transformation, involving a Michael addition followed by an intramolecular nucleophilic substitution, to afford 5-spirocyclopropane-annelated thiazoline-4-carboxylates **4**. Alternatively, compounds **4** could also be obtained in two steps by initial preparation of the Michael adducts **7** of thioamides **2** with the chloroester **1a** under acidic conditions, in high to virtually quantitative yields, followed by cyclization of the adducts **7** under basic conditions. Titanium tetraisopropoxide mediated cyclization of the adducts **7** gave thiazinones **8**. The thiazoline-4-carboxylates **4** are protected cysteine derivatives.

Experimental Section

General Remarks: All chemicals used are commercially available except for methyl 2-chloro-2-cyclopropylideneacetate (**1**),[12] which was prepared by the literature method,[6] and some of the thioamides, which were prepared according to a published general procedure.[13] All reactions were performed in anhydrous solvents under an atmosphere of N_2. Solvents were distilled under N_2 from sodium benzophenone (THF) or CaH_2 (DMF). All other reagents and solvents, such as hexanes (LP) and diethyl ether (Et_2O), were purified by standard procedures. – Reactions were monitored by thin layer chromatography on silica gel plates (Macherey–Nagel SIL G/UV_{254}). The chromatograms were viewed under UV light or by staining with Merck ninhydrin spray reagent. Silica gel 60 (I, 0.063–0.200 mm, 230–400 mesh), obtained from Merck, and silica gel 60 (II, 0.004–0.063 mm, 230–400 mesh, "flash"), obtained from Macherey–Nagel, were used for column chromatography. Eluents were distilled before use. – NMR spectra were recorded at 250 MHz (^{1}H) and at 62.9 MHz (^{13}C) in $CDCl_3$; for the cysteine **5**, D_2O was used as solvent. Chemical shifts δ are reported in ppm relative to $CHCl_3$ (^{1}H, δ = 7.26), $CDCl_3$ (^{13}C, δ = 77.0) and HDO (^{1}H, δ = 4.65) as internal standard. – Melting points are uncorrected.

Methyl 2′-Arylspiro[cyclopropane-1,5′(4′*H*)-thiazoline]-4′-carboxylates 4. – General Procedure (GP 1): A solution of the respective methyl 2-chloro-2-cyclopropylideneacetate **1**, thioamide **2** (1 equivalent), and $NaHCO_3$ in freshly dried acetonitrile (20 mL) was heated under reflux for 5 h. After filtration (200 mL of Et_2O, column 1.5 × 3 cm; 5 g of silica gel) the solvent was evaporated in vacuo. The dark yellow residue was subjected to column chromatography (LP/Et_2O = 5:1, 300 mL; 1:1, 500 mL; column 1.5 × 30 cm; 30 g of silica gel).

Methyl 2′-Arylspiro[cyclopropane-1,5′(4′*H*)-thiazoline]-4′-carboxylates 4. – General Procedure (GP 2): Under an atmosphere of nitrogen, the respective methyl 2-chloro-2-cyclopropylideneacetate **1** and thioamide **2** (1 equivalent) were added at 0 °C to a freshly prepared solution of hydrogen chloride in anhydrous dichloromethane. The solution was allowed to warm up to ambient temperature overnight. The solvent was removed and the yellow residue and $NaHCO_3$ were dissolved in 20 mL of freshly dried acetonitrile and refluxed for 5 h. After filtration (200 mL of Et_2O, column 1.5 × 3 cm; 5 g of silica gel), the solvent was evaporated in vacuo. The dark yellow residue was chromatographed (LP/Et_2O = 5:1, 300 mL; 1:1, 500 mL; column 1.5 × 30 cm; 30 g of silica gel).

Methyl 2′-Phenylspiro[cyclopropane-1,5′(4′*H*)-thiazoline]-4′-carboxylate (4a). – Method A: Methyl 2-chloro-2-cyclopropylideneacetate (**1a**) (83 mg, 0.57 mmol), thiobenzamide (**2a**) (78 mg, 0.57 mmol), and $NaHCO_3$ (1.00 g, 11.9 mmol) were heated for 5 h according to GP 1 to yield 121 mg (86%) of **4a** as a colorless solid, m.p. 51 °C, R_f = 0.56 (LP/Et_2O 1:1). – *Method B:* Methyl 2-chloro-2-cyclopropylideneacetate (**1a**) (201 mg, 1.37 mmol), thiobenzamide **2** (188 mg, 1.37 mmol), and $NaHCO_3$ (1.00 g, 11.9 mmol) were allowed to react according to GP 2 to yield 241 mg (71%) of **4a** as a colorless solid, m.p. 51 °C, R_f = 0.56 (LP/Et_2O 1:1). – IR (film): $\tilde{\nu}$ = 3064, 2952, 1734, 1596, 1447, 1256, 1028 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 1.04–1.11 (m, 4 H, *c*-Pr), 3.67 (s, 3 H, OCH_3), 4.88 (s, 1 H, 4-H), 7.34–7.77 (m, 3 H, Ph), 7.80 (d, *J* = 2.9 Hz, 2 H, Ph). – ^{13}C NMR ($CDCl_3$, DEPT): δ = 9.2, 16.4 (–, *c*-Pr), 33.7 (C_{quat}, C-5′), 55.2 (+, OCH_3), 82.5 (+, C-4′), 128.2, 128.4 (+, Ph), 129.0 (C_{quat}, Ph), 131.6 (+, Ph), 168.9, 171.7 (C_{quat}, C-2′, CO_2Me). – MS (70 eV): *m*/*z* (%) = 247 (5) [M^+], 188 (100) [$M^+ - CO_2Me$]. – $C_{13}H_{13}NO_2S$ (247.31): calcd. C 63.14, H 5.30, N 5.66; found C 63.31, H 5.10, N 5.01.

Methyl 2′-Phenylspiro[2-methylcyclopropane-1,5′(4′*H*)-thiazoline]-4′-carboxylate (4l): Methyl 2-chloro-2-(2′-methylcyclopropylidene)-acetate (**1b**) (218 mg, 1.36 mmol), thiobenzamide (**2a**) (186 mg, 1.36 mmol), and $NaHCO_3$ (1.00 g, 11.9 mmol) were heated for 5 h according to GP 1 to yield 181 mg (51%) of **4l** as a colorless oil, *dr* 1.2:1, R_f = 0.35 (LP/Et_2O 2:1). – IR (film): $\tilde{\nu}$ = 2954, 1734, 1603, 1576, 1524, 1448, 1167 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 0.62–0.79 (m, 1 H, *c*-Pr), 1.12–1.29 (m, 5 H, *c*-Pr, CH_3), 3.70 (s, 3 H, OCH_3, isomer B), 3.71 (s, 3 H, OCH_3, isomer A), 4.90 (s, 1 H, 4′-H, B), 5.01 (s, 1 H, 4′-H, A), 7.37–7.42 (m, 3 H, Ph), 7.77–7.83 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$, DEPT): Isomer A: δ = 13.4 (+, C-2), 15.4 (–, C-3), 23.2 (+, CH_3), 37.5 (C_{quat}, C-5′), 52.2 (+, OCH_3), 83.6 (+, C-4′), 128.3, 128.5, 131.6 (+, Ph), 133.1 (C_{quat}, Ph), 169.5, 172.6 (C_{quat}, C-2′, CO_2Me); Isomer B: δ = 15.5 (–, C-3), 16.1 (+, C-2), 21.4 (+, CH_3), 37.5 (C_{quat}, C-5′), 52.2 (+, OCH_3), 83.4 (+, C-4′), 128.3, 128.5, 131.6 (+, Ph), 133.1 (C_{quat}, Ph), 171.7, 172.3 (C_{quat}, C-2′, CO_2Me). – MS (70 eV): *m*/*z* (%) = 261 (7) [M^+], 202 (100) [$M^+ - CO_2Me$]. – $C_{14}H_{15}NO_2S$ (261.33): calcd. C 64.34, H 5.79, N 5.36; found C 64.00, H 5.50, N 5.09.

Methyl 2′-Phenylspiro[2-ethylcyclopropane-1,5′(4′*H*)-thiazoline]-4′-carboxylate (4o): Methyl 2-chloro-2-(2′-ethylcyclopropylidene)acetate (**1c**) (343 mg, 1.96 mmol), thiobenzamide (**2a**) (270 mg, 1.97 mmol), and $NaHCO_3$ (1.00 g, 11.9 mmol) were heated for 5 h according to GP 1 to yield 311 mg (58%) of **4o** as a colorless oil, *dr* 2.1:1:1, R_f = 0.33 (LP/Et_2O 3:1). – IR (film): $\tilde{\nu}$ = 2958, 1734, 1597, 1577, 1167 cm^{-1}. – ^{1}H NMR ($CDCl_3$): δ = 0.82–1.47 (m, 8 H, *c*-Pr, CH_2CH_3), 3.72 (s, 3 H, OCH_3), 4.87 (s, 1 H, 4′-H, isomer C), 4.92 (s, 1 H, 4′-H, isomer B), 4.98 (s, 1 H, 4′-H, isomer A), 7.35–7.45 (m, 3 H, Ph), 7.79–7.86 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$, DEPT): δ = 13.3 (–, C-3, C), 13.50 (+, C-2, A), 13.53 (+, C-2, C), 13.7 (+, C-2, B), 13.8 (–, C-3, A), 14.6 (–, C-3, B), 20.4 (–, CH_2CH_3, C), 22.6 (–, CH_2CH_3, A), 24.3 (–, CH_2CH_3, B), 27.8 (+, CH_2CH_3, A), 28.1 (+, CH_2CH_3, B), 30.3 (+, CH_2CH_3, C), 37.3 (C_{quat}, C-5′, A), 39.5 (C_{quat}, C-5′, C), 40.5 (C_{quat}, C-5′, B), 52.1 (+, OCH_3), 83.4 (+, C-4′), 127.3, 128.6, 131.5 (+, Ph), 133.0 (C_{quat}, Ph), 169.6, 172.3 (C_{quat}, C-2′, CO_2Me). – MS (70 eV): *m*/*z* (%) = 275 (1) [M^+], 216 (100) [$M^+ - CO_2Me$]. – $C_{15}H_{17}NO_2S$ (275.36): calcd. C 65.43, H 6.22, N 5.09; found C 65.37, H 6.02, N 5.01.

α-(1-Mercaptocyclopropyl)glycine Hydrochloride (5): Under an atmosphere of nitrogen, methyl 2′-methylspiro(cyclopropane-1,5′-thiazoline)-4′-carboxylate (**4b**) (111 mg, 0.598 mmol) was heated for 5 h in 10 mL of 3 N hydrochloric acid. The aqueous layer was extracted three times with diethyl ether (10 mL each), and the water was removed in vacuo. The yield was 98 mg (89%) of **5** as a colorless solid, m.p. 198 °C (dec.). – IR (film): $\tilde{\nu}$ = 3408, 2925, 1743,

1513, 1409, 1210, 1109, 862 cm^{-1}. – ^1H NMR (D_2O): δ = 0.82–1.21 (m, 4 H, *c*-Pr), 3.43 (s, 1 H, 2-H). – ^{13}C NMR (D_2O, DEPT): δ = 18.3, 20.2 (–, *c*-Pr), 21.2 (C_{quat}, C-3), 64.1 (+, C-2), 172.3 (C_{quat}, CO_2H). – MS (ESI): *m/z* (%) = 148 (17) [M^+].

***N*-Acetyl-α-(1-mercaptocyclopropyl)glycine Methyl Ester (6):** Under an atmosphere of nitrogen, methyl 2′-methylspiro(cyclopropane-1,5′-thiazoline)-4′-carboxylate (**4b**) (136 mg, 0.734 mmol) was heated for 5 h in 10 mL of water. The aqueous layer was extracted three times with diethyl ether (10 mL each) and the water was removed in vacuo. The yield was 139 mg (93%) of **6** as a colorless solid, m.p. 156 °C. – IR (film): $\tilde{\nu}$ = 2976, 2863, 1740, 1684, 1382, 1350, 1120 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 0.95–1.48 (m, 4 H, *c*-Pr), 2.10 (s, 3 H CH_3CO), 3.78 (s, 3 H, CO_2CH_3), 4.25 (d, *J* = 8.8 Hz, 1 H, 2-H). – ^{13}C NMR ($CDCl_3$, DEPT): δ = 15.8, 18.5 (–, *c*-Pr), 23.1 (+, CH_3CO), 32.2 (C_{quat}, C-3), 52.6 (+, OCH_3), 57.6 (+, C-2), 169.9, 170.7 (C_{quat}, CH_3CO, CO_2Me). – MS (70 eV): *m/z* (%) = 203 (10) [M^+], 202 (100), 170 (72) [M^+ – SH], 144 (4) [M^+ – CO_2Me]. – $C_8H_{13}NO_3S$ (203.25): calcd. C 47.28, H 6.45; found C 47.03, H 6.20.

5-Aryl-8-chloro-4-thia-6-azaspiro[2.5]oct-5-en-7-ones 8. – General Procedure (GP 3): Under an atmosphere of nitrogen, methyl 2-chloro-2-cyclopropylideneacetates **1** and a thioamide **2** (1 equivalent) were added at 0 °C to a freshly prepared solution of hydrogen chloride in anhydrous dichloromethane. The solution was allowed to warm up to ambient temperature overnight. The solvent was removed, and the yellow residue was dissolved in dichloromethane under nitrogen. Titanium tetraisopropoxide was added at 0 °C and the solution was allowed to warm up to ambient temperature overnight. Water (2 mL) was then added, and the solution was stirred for 2 h. The aqueous layer was extracted three times with dichloromethane (10 mL each). The combined organic layers were dried with $MgSO_4$, and the solvent was removed in vacuo. The dark yellow residue was subjected to column chromatography (LP/Et_2O = 2:1, 300 mL; 1:1, 500 mL; column 1.5 × 30 cm; 30 g of silica gel).

8-Chloro-5-phenyl-4-thia-6-azaspiro[2.5]oct-5-en-7-one (8a): Methyl 2-chloro-2-cyclopropylideneacetate (**1a**) (500 mg, 3.41 mmol), thiobenzamide (**2a**) (468 mg, 3.41 mmol), and titanium tetraisopropoxide (808 µL, 2.74 mmol) were allowed to react according to GP 3 to yield 607 mg (71%) of **8a** as a yellow solid, m.p. 68 °C, R_f = 0.50 (LP/Et_2O 1:1). – IR (film): $\tilde{\nu}$ = 3403, 2976, 1734, 1653, 1507, 1214, 1177 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 1.10–1.44 (m, 4 H, *c*-Pr), 4.05 (s, 1 H, 8-H), 7.43 (t, *J* = 7.2 Hz, 2 H, Ph), 7.55–7.61 (m, 1 H, Ph), 8.03 (d, *J* = 7.2 Hz, 2 H, Ph). – ^{13}C NMR ($CDCl_3$, DEPT): δ = 12.3, 17.9 (–, *c*-Pr), 26.4 (C_{quat}, C-3), 57.0 (+, C-8), 127.5, 128.8, 133.8 (+, Ph), 135.8 (C_{quat}, Ph), 172.1 (C_{quat}, C-5), 179.9 (C_{quat}, C-7). – MS (70 eV): *m/z* (%) = 253/251 (38/100) [M^+], 216 (38) [M^+ – Cl]. – $C_{12}H_{10}ClNOS$ (251.73): calcd. C 57.26, H 4.00, N 5.56; found C 57.49, H 4.16, N 5.68.

8-Chloro-1-ethyl-5-phenyl-4-thia-6-azaspiro[2.5]oct-5-en-7-one (8i): Methyl 2-chloro-2-(2′-ethylcyclopropylidene)acetate (**1c**) (107 mg, 0.613 mmol), thiobenzamide (**2a**) (84.0 mg, 0.612 mmol), and titanium tetraisopropoxide (181 µL, 0.613 mmol) were allowed to react according to GP 3 to yield 92 mg (54%) of **8i** as a colorless oil, *dr* 2:1, R_f = 0.62 (LP/Et_2O 1:1). – IR (film): $\tilde{\nu}$ = 3356, 3062, 1733, 1653, 1457, 1387, 1201 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 0.80–1.88 (m, 8 H, *c*-Pr, CH_2CH_3), 4.10 (s, 1 H, 8-H, isomer B), 4.25 (s, 1 H, 8-H, isomer A), 7.42–7.56 (m, 2 H, Ph), 7.58–7.62 (m, 1 H, Ph), 8.02–8.08 (m, 2 H, Ph). – ^{13}C NMR ($CDCl_3$, DEPT): δ = 13.7 (+, C-1), 18.6 (–, C-2, A), 20.6 (–, C-2, B), 21.8 (–, CH_2CH_3, A), 24.5 (–, CH_2CH_3, B), 30.6 (C_{quat}, C-3, B), 30.9 (C_{quat}, C-3, A), 34.7 (+, CH_2CH_3), 53.8 (+, C-8, A), 54.0 (+, C-8, B), 127.4, 128.8, 133.8 (+, Ph), 135.8 (C_{quat}, Ph), 172.4 (C_{quat}, C-5, B), 172.5 (C_{quat}, C-5, A), 180.6 (C_{quat}, C-7). – MS (70 eV): *m/z* (%) = 281/279 (1/5) [M^+], 262 (32). – $C_{14}H_{14}ClNOS$ (279.78): calcd. C 60.10, H 5.04, N 5.00; found C 59.75, H 4.80, N 4.84.

5-(4-*tert*-Butylphenyl)-8-chloro-1-ethyl-4-thia-6-azaspiro[2.5]oct-5-en-7-one (8k): Methyl 2-chloro-2-(2′-ethylcyclopropylidene)acetate (**1c**) (204 mg, 1.17 mmol), 4-*tert*-butylthiobenzamide (**2d**) (226 mg, 1.17 mmol), and titanium tetraisopropoxide (700 µL, 2.37 mmol) were allowed to react according to GP 3 to yield 346 mg (88%) of **8k** as a colorless oil, *dr* 3:1:1, R_f = 0.54 (LP/Et_2O 2:1). – IR (film): $\tilde{\nu}$ = 2964, 2873, 1695, 1521, 1223, 1191, 1110 cm^{-1}. – ^1H NMR ($CDCl_3$): δ = 0.80–1.90 (m, 8 H, *c*-Pr, CH_2CH_3), 1.31 [s, 9 H, $C(CH_3)_3$], 3.95 (s, 1 H, 8-H, isomer B), 4.06 (s, 1 H, 8-H, isomer C), 4.23 (s, 1 H, 8-H, isomer A), 7.44 (d, *J* = 8.4 Hz, 2 H, Ph), 8.00 (d, *J* = 8.4 Hz, 2 H, Ph). – ^{13}C NMR ($CDCl_3$, DEPT): δ = 13.6 (+, C-1), 18.5 (–, C-2, A), 18.9 (–, C-2, B), 20.5 (–, C-2, C), 21.7 (–, CH_2CH_3, B), 22.4 (–, CH_2CH_3, A), 26.3 (–, CH_2CH_3, C), 30.7 (C_{quat}, C-3), 30.9 [+, $C(CH_3)_3$], 34.6 (+, CH_2CH_3), 35.1 [C_{quat}, $C(CH_3)_3$], 53.9 (+, C-8, B), 54.1 (+, C-8, A), 58.3 (+, C-8, C), 125.7, 127.3 (+, Ph), 133.0, 157.9 (C_{quat}, Ph), 172.5 (C_{quat}, C-5), 180.4 (C_{quat}, C-7). – MS (70 eV): *m/z* (%) = 337/335 (37/62) [M^+], 300 (17) [M^+ – Cl]. – $C_{18}H_{22}ClNOS$ (335.89): calcd. C 64.37, H 6.60, N 4.17; found C 64.71, H 6.99, N 4.01.

Acknowledgments

This work was supported financially by the Fonds der Chemischen Industrie and Bayer AG, as well as through generous gifts of chemicals by BASF AG. M. N. is particularly grateful to Bayer AG for a two months stay in their Agricultural Research Station. The authors are indebted to Dr. Burkhard Knieriem, Göttingen, for his careful reading of the final manuscript.

[1] [1a] M. C. Pirrung, J. Cao, J. Chen, *J. Org. Chem.* **1995**, *60*, 5790–5794. – [1b] M. C. Pirrung, H. Han, J. Chen, *J. Org. Chem.* **1996**, *61*, 4527–4531. – [1c] M. C. Pirrung, L. M. Kaiser, J. Chen, *Biochemistry* **1993**, *32*, 7445–7450.

[2] K. Burgess, K.-K. Ho, D. Moye-Sherman, *Synlett* **1994**, 575–583.

[3] [3a] J. Salaün, *Top. Curr. Chem.* **1999**, *207*, 1–88. – [3b] J. Salaün, M. S. Baird, *Curr. Med. Chem.* **1995**, *2*, 511–542. – [3c] Z. Huang, Y.-B. He, K. Raynor, M. Tallent, T. Reisine, M. Goodman, *J. Am. Chem. Soc.* **1992**, *114*, 9390–9401. – [3d] Y.-F. Zhu, T. Yamazaki, J. W. Tsang, S. Lok, M. Goodman, *J. Org. Chem.* **1992**, *57*, 1074–1081.

[4] [4a] A. de Meijere, L. Wessjohann, *Synlett* **1990**, 20–32. – [4b] A. de Meijere, in: *New Aspects of Organic Chemistry II, Proceedings of the Fifth International Kyoto Conference on New Aspects of Organic Chemistry – IKCOC 5*, Kyoto, Nov. 11 – Nov. 15 **1991**, (Ed.: Y. Oshiro) Kodansha, Tokyo **1992**, p. 181. – [4c] A. de Meijere, S. I. Kozhushkov, L. Hadjiarapoglou, *Top. Curr. Chem.* **1999**, *207*, 149–227. – [4d] L. Wessjohann, N. Krass, D. Yu, A. de Meijere, *Chem. Ber.* **1992**, *125*, 867–882. – [4e] M. Tamm, M. Thutewohl, C. Ricker, M. T. Bes, A. de Meijere, *Eur. J. Org. Chem.* **1999**, 2017–2024. – [4f] L. Wessjohann, K. Giller, B. Zuck, L. Skattebøl, A. de Meijere, *J. Org. Chem.* **1993**, *58*, 6442–6450.

[5] [5a] M. Es-Sayed, C. Gratkowski, N. Krass, A. de Meijere, *Synlett* **1992**, 962–964. – [5b] M. Es-Sayed, C. Gratkowski, N. Krass, A. I. Meyers, A. de Meijere, *Tetrahedron Lett.* **1993**, *34*, 289–292.

[6] T. Liese, F. Seyed-Mahdavi, A. de Meijere, *Org. Synth.* **1990**, *69*, 148–153.

[7] Some other penicillamine analogues have been prepared: [7a] C. F. Stanfield, W. L. Cody, V. J. Hruby, *J. Org. Chem.* **1986**, *51*,

5153−5156. − [7b] H. T. Nagasawa, J. E. Elberling, J. C. Roberts, *J. Med. Chem.* **1987**, *30*, 1373−1378.
[8] F. Effenberger, T. Beisswenger, F. Dannenhauer, *Chem. Ber.* **1988**, *121*, 2209−2223.
[9] M. W. Nötzel, M. Tamm, T. Labahn, M. Noltemeyer, M. Es-Sayed, A. de Meijere, *J. Org. Chem.* **2000**, *65*, 3850−3852.
[10] Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-154095 (**4a**), CCDC-160644 (**4r**), CCDC-154094 (**8a**), and CCDC-160645 (**8j**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, U.K. − [10a] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **1990**, *46*, 467. − [10b] G. M. Sheldrick, *SHELXL-93, program for crystal structure refinement*, University of Göttingen, **1993**.
[11] C. Funke, A. de Meijere, unpublished results.
[12] The immediate precursor to **1**, 1-chloro-1-(trichloroethenyl)cyclopropane, is commercially available from Merck−Schuchardt.
[13] D. Brillon, *Synth. Comm.* **1990**, *20*, 3085−3095.

Received December 22, 2000
[O00652]