A Novel Class of Conformationally Constrained, Masked Cysteines: Synthesis of 2-Alkyl- and 2-Arylsulfanyl-1-aminocyclopropanecarboxylic Acids

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A convenient synthesis of 4-sulfanylmethylene-5(4*H*)-oxazolones **3** was realized starting from 4-(chloromethylene)oxazolone **1** and mercaptans **2**. Oxazolones **3** were used as starting materials for the preparation of unknown 2-sulfanyl-1-aminocyclopropanecarboxylic acid derivatives **5** and **7.** Oxazolones **3** were cyclopropanated at the exocyclic double bond with diazomethane, giving a mixture of the two (*Z*)- and (*E*)-spirocyclopropane oxazolones **4** with good diastereoselectivity. These were then treated with ethanol and DMAP to produce the corresponding carboxylates **5**. The trityl derivative **5d** was converted into a mixture of diastereoisomeric disulfides **6** using iodine in ethanol solution. Disulfides **6** are convenient synthons for the preparation of 3-sulfanyl-substituted 2,3-methanoamino acids **7**.

Introduction

In recent years significant attention has been focused on the preparation of conformationally constrained amino acids because their introduction into a peptide generates important changes in the peptide conformation by modulating its interaction with the active site of an enzyme or bioreceptor.[1] Different approaches making an amino acid stiff have been used: introducing an element of unsaturation in the chain (i.e. α,*β*-didehydroamino acids),[2] linking both the amino and carboxyl groups to a ring (cyclohexyl-,[3] cyclopentyl-,[4] and cyclopropylamino acids[5]), and synthesizing cyclic amino acids in which the amino or carbonyl groups are inside the ring.[6] In particular, the preparation of peptides containing methanoamino acids is of great interest because the cyclopropyl ring increases their rigidity as a result of the bond stretching imposed by the methylene bridge.[5,7] Furthermore, the unsaturated character of this molecular fragment hinders rotation around the $C_\alpha-C_\beta$ bond, giving, for 2,3-methanoamino acids substituted at C-3, two possible isomers (cis and trans). Their presence in the peptide chain is expected to have marked effects on the secondary structures, with consequent stabilization of the peptide toward enzyme cleavage.[8] Moreover, cyclopropaneamino acid derivatives possess, as single molecules, a wide spectrum of biological actions.[5b] So, the interest in the synthesis of these substrates is growing, but it is worth noting that the known synthetic procedures are lacking in the preparation of 2,3-methanoamino acids substituted with a sulfur atom at C-3. To prepare a new class of compounds with potential anticancer activity,[9] we have synthesized 2-alkylsulfanyl- or 2-arylsulfanyl-1-aminocyclopropanecarboxylic acid derivatives **5** and **7**, in which the cysteine skeleton exists.

The use of 4-ylidene-5(4*H*)-oxazolones as starting materials for the preparation of these compounds is common, because diazomethane easily adds to the exocyclic double bond of the oxazolone derivatives, making the cyclopropane ring.[5b,10] The compounds 4-alkylsulfanyl- or 4-arylsulfanylmethylene-5(4*H*)-oxazolones **3** are the key starting materials for the preparation of amino acid derivatives **5** and **7** through the cyclopropanation reaction of the exocyclic double bond.

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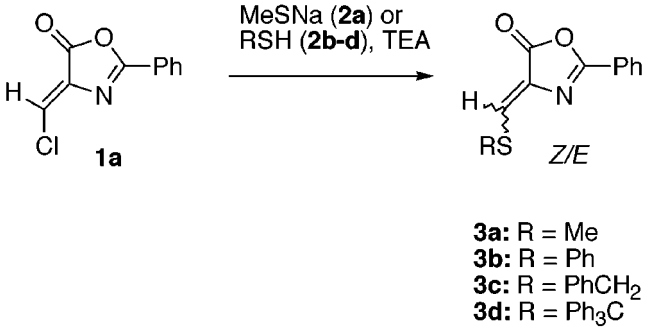
Scheme 1



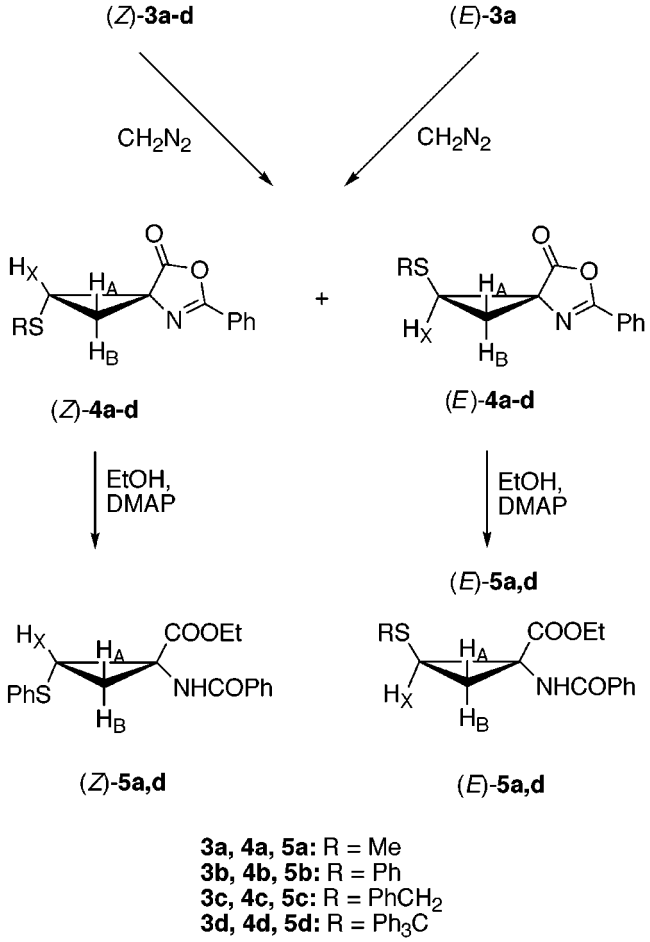
Results and Discussion

Oxazolones **3a**−**d** were prepared by reacting 4-(chloromethylene)-2-phenyl-5(4*H*)-oxazolone **1** with sodium thiomethoxide **2a** or mercaptans **2b**−**d** in the presence of triethylamine as a base at room temperature and in dichloromethane, in a method analogous to that described for the synthesis of β-alkylthio-α,β-didehydroamino acids.[2a] The reactions resulted in a mixture of two isomers, *Z* and *E*, from which the thermodynamically more stable *Z* isomer was isolated as the major product. Synthetically useful procedures[11] for the preparation of sulfanylmethyleneoxazolones **3** have been reported, but to our knowledge, chloroazlactone **1** was used as starting material only for the preparation of aryl derivatives. In that case, the presence of a Lewis acid ($AlCl_3$) is mandatory.[12] The use of **1** as the starting material takes advantage of good yields (70−90%) of oxazolones **3a**−**d** and short reaction times (30−60 min) (Scheme 1).

The IR spectra of compounds **3** show the typical absorption of the unsaturated carbonyl group of oxazolones (1740−1760 cm^{-1}) and the configuration assigned to compounds **3** was confirmed by ^1H NMR data reported in the literature for (*Z*)-**3a,c**.[11c]

In a typical procedure, pure isomers (*Z*)-**3a**−**d** were made to react with an excess of diazomethane at room temperature. The reactions were completed in 1−3 h, and the ^1H NMR analyses of the crude reaction mixtures showed the formation of two isomeric spirooxazolones, (*Z*)-**4a**−**d** and (*E*)-**4a**−**d**, in a variable ratio, but one in which the *Z* isomer is always the major one (*Z*/*E*: 3/1 to 5/1). The isomeric oxazolones **4** were obtained in satisfactory yields (54−73%): the major isomers (*Z*)-**4a**−**d** were isolated as pure compounds, whereas the (*E*)-**4b**−**d** isomers were isolated as small samples of pure compound. The isomeric ratio is in favor of the *Z* isomer, which possesses the same geometry at the double bond as the starting azlactone **3**, and the loss of this geometry in the cyclopropanation reaction is in agreement with the literature data.[10] This was confirmed by an independent experiment: Starting from pure oxazolone (*E*)-**3a** the reaction with diazomethane afforded the same isomeric spirocyclopropane oxazolones (*Z*)- and (*E*)-**4a** but in a reversed ratio (Scheme 2).

Scheme 2



The spirooxazolone (*Z*)-**4b** was treated with 4-(dimethylamino)pyridine (DMAP) in ethanol for 60 min at room temperature. Pure ethyl 1-benzoylamino-2-phenylsulfanylcyclopropanecarboxylate **5b** was isolated in 75% yield (Scheme 2). A useful synthetic improvement in the preparation of isomeric carboxylates **5b** was found with the possibility of performing a "one pot" reaction starting from oxazolone (*Z*)-**3b** and avoiding the isolation of the mixture of two oxazolones **4b**. In fact, reaction of (*Z*)-**3b** with diazomethane, solvent elimination, and reaction of the crude mixture with ethanol in the presence of DMAP for 60 min gave isomers (*Z*)- and (*E*)-**5b** in good yield (77%, 3:1). The same results were obtained starting from oxazolones **3a,c,d**: 2-alkylsulfanyl-1-benzoylaminocyclopropanecarboxylates **5a,c,d** were isolated in good yields (60−66%) as a mixture of two isomers (Scheme 2).

Structural assignments for compounds **4** and **5** have been made on the basis of IR, ^1H NMR (Table 1), and ^{13}C NMR spectral data as well as NOESY and COSY experiments, and the results are in agreement with the literature data.[10] The IR spectra of spirocyclopropane oxazolones **4** show a typical absorption at 1780−1800 cm^{-1} (lactone group), whereas the carbonyl ester group stretching at 1720 cm^{-1} is present in the spectra of compounds **5**. The ^1H NMR signals of protons on the cyclopropyl ring, in both compounds **4** and **5**, appear as an ABX system: the signals of H_X, as expected on the basis of their proximity to the S substituent, are at lower fields; the signals of geminal H_A and H_B could be assigned by their vicinal coupling constants J_{AX} and J_{BX} since it has been found that, for vicinal cyclopropyl ring protons,

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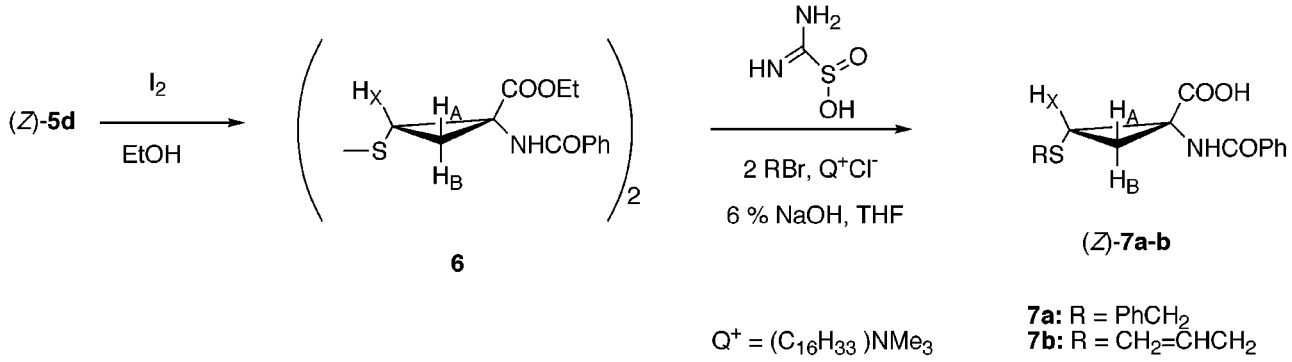
Table 1. ^{1}H NMR Data for Compounds 4−7

	δ ($CDCl_3$), (J/Hz)							
compd	Ar	H_X	H_A	H_B	J_{AB}	J_{AX}	J_{BX}	
(*Z*)-**4a**	8.10−7.41	3.08	2.19	2.12	5.4	8.9	7.9	2.13 (SMe)
(*E*)-**4a**	8.01−7.40	3.30	1.95	2.34	5.7	8.2	9.0	2.13 (SMe)
(*Z*)-**4b**	8.01−7.12	3.38	2.34	2.20	5.7	8.9	7.6	
(*E*)-**4b**	8.01−7.15	3.59	2.07	2.48	5.9	8.1	9.0	
(*Z*)-**4c**	7.96−6.89	2.88	2.13	1.98	5.6	9.4	8.0	3.78 (SCH_2)
(*E*)-**4c**	8.06−6.88	3.09	1.79	2.24	5.9	8.3	9.4	3.74 (SCH_2)
(*Z*)-**4d**	7.97−7.03	2.73	2.01	1.82	5.8	9.9	8.5	
(*E*)-**4d**	7.97−7.04	3.02	1.70	2.16	6.0	8.5	10.0	
(*Z*)-**5a**	7.85−7.44	2.83	2.20	1.20	6.0	9.6	7.1	6.85 (NH, exch.), 4.19, 1.24 (OEt), 2.23 (SMe)
(*E*)-**5a**	7.90−7.42	2.69	1.89	1.58	6.1	7.5	9.5	6.75 (NH, exch.), 4.23, 1.26 (OEt), 2.28 (SMe)
(*Z*)-**5b**	7.80−7.21	3.14	2.46	1.45	6.2	9.5	7.0	6.59 (NH, exch.), 4.31−4.13 1.27 (OEt)
(*E*)-**5b**	7.79−7.21	2.96	2.15	1.91	6.4	7.3	9.5	6.82 (NH, exch.), 4.18, 1.19 (OEt)
(*Z*)-**5c**	7.53−7.21	2.74	2.15	1.17	6.1	9.8	7.4	5.71 (NH, exch.), 4.13, 1.20 (OEt), 3.75 (SCH_2, J = 13.7)
(*E*)-**5c**	7.76−7.27	2.39	2.01	1.66	6.2	7.6	9.6	6.53 (NH, exch.) 4.19, 1.27 (OEt), 3.86 (SCH_2, J = 13.4)
(*Z*)-**5d**[a]	7.56−7.11	2.66	2.24	1.28	6.2	10.2	7.6	5.32 (NH, exch.), 4.14−4.01 1.21 (OEt)
6[b]	7.82−7.40	3.26	2.29	1.58	6.4	9.4	6.8	6.73 (NH, exch.), 4.15, 1.22 (OEt)
(*Z*)-**7a**	7.57−7.21	3.89	2.22	1.15	6.3	9.9	7.4	5.60 (NH, exch.), 5.0−4.0 (OH, exch.), 3.81 (SCH_2, J = 13.7)
(*Z*)-**7b**	7.84−7.41	2.84	2.84	1.15	6.2	9.9	7.4	6.79 (NH, exch.), 6.8−6.1 (OH, exch.), 6.02−5.83, 5.28−5.19 (m, $CH{=}CH_2$) 3.27 (SCH_2, J = 7.7)

[a] The ^{1}H NMR spectrum of (*E*)-**5d** could be determined only on the diastereoisomeric mixture and shows characteristic signals at δ = 5.61 (s, NH), 2.61−2.53, 2.10−2.00, and 1.75−1.63 associated with H_X, H_A, and H_B, respectively. [b] Pure diastereoisomer. The ^{1}H NMR spectrum of the diastereoisomeric mixture of disulfides shows signals at δ = 7.85−7.40 (m, H_{arom}), 4.20−4.10, 1.26−1.18 (OEt), 3.36 (dd, J_{AX} = 9.4, J_{BX} = 6.8, H_X), 2.32−2.23 (m, H_A), and 1.58−1.53 (m, H_B).

Scheme 3



J_{cis} is larger than J_{trans}.[13] These results were also confirmed by independent NOESY experiments for compounds (*Z*)-**4d**, (*Z*)-**5a**,**c**, and (*E*)-**5c** in which the close spatial proximity of H_X and H_A in the *Z* isomers and H_X and H_B in the *E* isomer has been demonstrated. NOESY experiments confirmed the stereochemistry of compounds **5**. In fact, a positive Overhauser effect was pointed out between the H_X and the hydrogen linked to nitrogen in compound (*E*)-**5c**. As expected, this effect was absent for *Z* isomers. The configuration of compounds **4** follows from their transformation into the corresponding **5**. When pure compound (*Z*)-**4b** was treated with ethanol and DMAP, pure ester (*Z*)-**5b** was found. The ^{1}H NMR spectrum of this compound is in agreement with ^{1}H NMR spectra of compounds (*Z*)-**5a**,**c,d** (see Table 1).

The cyclopropanecarboxylate **5d** is a synthetically interesting substrate in which the trityl group linked to the sulfur atom can be easily removed. As depicted in Scheme 3, when compound (*Z*)-**5d** was treated with iodine in ethanol for 2 h, a mixture of diastereoisomeric disulfides **6** was obtained in good yield. The preparation of disulfides, which, as shown later, are synthetic equivalents of the corresponding thiol, is advantageous over the direct alkylation of the sulfur atom because it allows for the preparation of a series of cyclopropanecarboxylic acid derivatives **7**, while it avoids the steps involved in the preparation and hydrolysis of compounds **5**. This synthon is particularly useful when the mercaptan derivatives are not readily available or when a double bond is present in the alkyl group because of its reactivity with diazomethane. In the alkylation reaction, disulfides **6** were used as a diastereoisomeric mixture which is irrelevant to the configuration of the final products. As shown in Scheme 3, the alkylation of **6** was performed under phase-transfer catalysis in THF using aqueous sodium hydroxide (6%), CTACl as a catalyst, and the alkyl bromide (benzyl bromide and allyl bromide). The use of aminoiminomethanesulfinic acid[14] in the reaction mixture led to the reduction of disulfides **6** to the corresponding thiol, which was not isolated, and instead was directly alkylated. The hydrolytic conditions produced the acids **7** in satisfactory yields.

In conclusion, the goal of our research was attained by the preparation of new 3-sulfanyl substituted 2,3-methanoamino acid derivatives **5** and **7**, which cannot be obtained by the apparently straightforward route of nucleophilic substitution of a chloride atom in the known

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Table 2. Elemental Analyses

compound	formula	mw	calcd (%)			found (%)		
			C	H	N	C	H	N
(*E*)-**3a**	$C_{11}H_9NO_2S$	219.26	60.26	4.14	6.39	60.11	4.10	6.30
(*Z*)-**3b**	$C_{16}H_{11}NO_2S$	281.33	68.31	3.94	4.98	68.05	4.09	4.78
(*E*)-**3c**	$C_{17}H_{13}NO_2S$	295.36	69.13	4.44	4.74	69.03	4.24	4.68
(*Z*)-**3d**	$C_{29}H_{21}NO_2S$	447.55	77.83	4.73	3.13	77.67	4.78	3.02
(*Z*)-**4a**	$C_{12}H_{11}NO_2S$	233.28	61.78	4.75	6.00	61.50	4.85	5.91
(*Z*)-**4b**	$C_{17}H_{13}NO_2S$	295.36	69.13	4.44	4.74	69.25	4.32	4.84
(*E*)-**4b**	$C_{17}H_{13}NO_2S$	295.36	69.13	4.44	4.74	69.00	4.57	4.61
(*Z*)-**4c**	$C_{18}H_{15}NO_2S$	309.38	69.88	4.89	4.53	70.01	4.99	4.42
(*E*)-**4c**	$C_{18}H_{15}NO_2S$	309.38	69.88	4.89	4.53	69.70	4.95	4.44
(*Z*)-**4d**	$C_{30}H_{23}NO_2S$	461.58	78.06	5.02	3.03	78.18	5.10	3.15
(*E*)-**4d**	$C_{30}H_{23}NO_2S$	461.58	78.06	5.02	3.03	77.92	5.14	2.98
(*Z*)-**5a**	$C_{14}H_{17}NO_3S$	279.35	60.19	6.13	5.01	60.30	6.25	5.23
(*Z*)-**5b**	$C_{19}H_{19}NO_3S$	341.42	66.84	5.61	4.10	66.99	5.70	4.23
(*E*)-**5b**	$C_{19}H_{19}NO_3S$	341.42	66.84	5.61	4.10	66.68	5.73	4.01
(*Z*)-**5c**	$C_{20}H_{21}NO_3S$	355.45	67.58	5.95	3.94	67.42	5.88	3.83
(*E*)-**5c**	$C_{20}H_{21}NO_3S$	355.45	67.58	5.95	3.94	67.63	6.04	3.82
(*Z*)-**5d**	$C_{32}H_{29}NO_3S$	507.65	57.71	5.76	2.76	57.55	5.88	2.69
6	$C_{26}H_{28}N_2O_6S_2$	528.64	59.07	5.34	5.30	59.00	5.29	5.25
(*Z*)-**7a**	$C_{18}H_{17}NO_3S$	327.40	66.04	5.23	4.28	65.89	5.33	4.13
(*Z*)-**7b**	$C_{14}H_{15}NO_3S$	277.34	60.63	5.45	5.05	60.50	5.61	4.98

2-chloro-1-aminocyclopropanecarboxylic acid[10d] with mercaptan derivatives, as has been demonstrated by the literature data[15] to be known and been verified by ourselves. Our process has the advantage of showing a good diastereoselectivity, the *Z* isomers being highly prevalent over the *E* ones. These compounds are conformationally constrained cysteine analogues, and for this reason, can contribute to the study of their conformational effects in biologically interesting peptides.

Experimental Section

General. Melting points are uncorrected. IR spectra obtained by the Nujol method were measured using NaCl. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ at 200 and 50 MHz, respectively, with $CHCl_3$ as the internal standard. Ethanol-free CH_2Cl_2 was used in all experiments. Oxazolone **1a**[10d] is a known compound. Elemental analyses of all compounds appear in Table 2.

General Procedure for the Preparation of 4-(Alkylsulfanylmethylene)- and 4-(Phenylsulfanylmethylene)-2-phenyl-5(4*H*)-oxazolones 3. A solution of 4-(chloromethylene)-2-phenyl-5(4*H*)-oxazolone (**1**) (207 mg, 1 mmol) and sodium thiomethoxide **2a** (105 mg, 1.5 mmol) or mercaptans **2c**−**d** (1 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature. Triethylamine (0.14 mL, 1 mmol) was added dropwise (except for **3a**) over a few minutes, and stirring was continued until the starting material **1** disappeared (30−60 min), after which the organic layer was washed with a solution of HCl (10%, 10 mL), and H_2O (10 mL) and dried over Na_2SO_4. After solvent elimination, the crude reaction mixture was recrystallized from CH_2Cl_2/Et_2O, and the pure isomer (*Z*)-**3** was isolated. Silica-gel (*n*-pentane/CH_2Cl_2, 1:0 to 0:1) column chromathography of the mother liquor gave two fractions, one containing the pure *Z* isomer and the other a mixture of *E* and *Z* isomers. The pure *E* isomer was isolated only in the case of **3a,c** after recrystallization of the mixture of isomers. In the case of **3d** only the *Z* isomer was obtained. The ratio of isomers is indicated below.

4-(Methylsulfanylmethylene)-2-phenyl-5(4*H*)-oxazolone (3a): total yield 85% (*Z*/*E*: 9:1). (*Z*)-**3a**: mp 143 °C (141 °C);[8c] IR ν_{max} 1740 cm^{-1}; ^{1}H NMR δ 8.09−7.45 (m, 6 H), 2.70 (s, 3 H). (*E*)-**3a**: mp 139 °C; IR ν_{max} 1740 cm^{-1}; ^{1}H NMR δ 8.01−7.46 (m, 5 H), 7.63 (s, 1 H), 2.60 (s, 3 H).

2-Phenyl-4-(phenylsulfanylmethylene)-5(4*H*)-oxazolone (3b): total yield 70% (*Z*/*E*: 2.3:1). (*Z*)-**3b**: mp 106 °C; IR ν_{max} 1770 cm^{-1}; ^{1}H NMR δ 8.14−7.40 (m, 10 H), 7.62 (s, 1 H). (*E*)-**3b**: IR ν_{max} 1770 cm^{-1}; ^{1}H NMR δ 8.14−7.40 (m, 10 H), 7.88 (s, 1 H).

4-(Benzylsulfanylmethylene)-2-phenyl-5(4*H*)-oxazolone (3c): total yield 83% (*Z*/*E*: 5.5:1). (*Z*)-**3c**: mp 122 °C (122 °C);[8c] IR ν_{max} 1780 cm^{-1}; ^{1}H NMR δ 8.08−7.30 (m, 11 H), 4.30 (s, 2 H). (*E*)-**3c**: mp 119 °C (CH_2Cl_2/Et_2O); IR ν_{max} 1780 cm^{-1}; ^{1}H NMR δ 7.99−7.46 (m, 10 H), 7.61 (s, 1 H), 4.15 (s, 2 H).

2-Phenyl-4-(tritylsulfanylmethylene)-5(4*H*)-oxazolone (3d): total yield 84%. (*Z*)-**3d**: mp 185 °C; IR ν_{max} 1780 cm^{-1}; ^{1}H NMR δ 8.10−7.27 (m, 20 H), 7.15 (s, 1 H).

General Procedure for Preparation of 1-Alkylsulfanyl- and 1-Arylsulfanyl-5-phenyl-6-oxa-4-azaspiro[2.4]ept-4-en-7-ones 4. (*Z*)-Oxazolone **3** (1 mmol) was dissolved in CH_2Cl_2 and an ethereal solution of diazomethane (1.5 mmol, 6 mL, 0.25 M) was added to it. The mixture was allowed to stand at room temperature until nitrogen evolution ceased (1−3 h). After solvent evaporation and crystallization from CH_2Cl_2, pure oxazolones (*Z*)-**4a,b** were obtained. The mother liquor, in the case of **4a,b**, and the crude reaction mixture, in the case of **4c,d**, were chromatographed [2-cm-width plate; silica-gel Kieselgel 60 (Merck); 230−400-mesh ASTM; cyclohexane/EtOAc (9:1) eluant; 6 mL/min flow rate] to give two fractions, one containing pure *Z* isomer **4** and the other a mixture of *Z* and *E* isomers. The pure *E* isomer was isolated in the case of **4b**−**d** by recrystallization. The ratio of isomers is indicated below. ^{1}H NMR data are given in Table 1.

1-Methylsulfanyl-5-phenyl-6-oxa-4-azaspiro[2.4]ept-4-en-7-one (4a): total yield 70% (*Z*/*E*: 3:1). (*Z*)-**4a**: mp 137 °C (CH_2Cl_2/Et_2O); IR ν_{max} 1780 cm^{-1}.

5-Phenyl-1-phenylsulfanyl-6-oxa-4-azaspiro[2.4]ept-4-en-7-one (4b): total yield 73% (*Z*/*E*: 3:1). (*Z*)-**4b**: mp 165 °C (CH_2Cl_2/Et_2O); IR ν_{max} 1795 cm^{-1}; ^{13}C NMR δ 26.3 (C-2), 35.6 (C-1), 54.0 (C-3), 126.3−135.4 (H_{arom}), 163.4 (C-5), 177.2 (C-7). (*E*)-**4b**: mp 99 °C (CH_2Cl_2/Et_2O); IR ν_{max} 1795 cm^{-1}.

1-Benzylsulfanyl-5-phenyl-6-oxa-4-azaspiro[2.4]ept-4-en-7-one (4c): total yield 54% (*Z*/*E*: 5:1). (*Z*)-**4c**: mp 131 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 1800 cm^{-1}. (*E*)-**4c**: mp 88 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 1800 cm^{-1}.

5-Phenyl-1-tritylsulfanyl-6-oxa-4-azaspiro[2.4]ept-4-en-7-one (4d): total yield: 67% (*Z*/*E*: 3:1). (*Z*)-**4d**: mp 75 °C (CH_2Cl_2/*i*-PrOH); IR ν_{max} 1795 cm^{-1}. (*E*)-**4d**: mp 143−144 °C (CH_2Cl_2/*i*-PrO_2); IR ν_{max} 1795 cm^{-1}.

Ethyl (*Z*)-1-Benzoylamino-2-phenylsulfanylcyclopropanecarboxylate (5b). Compound (*Z*)-**4b** (40 mg, 0.12 mmol) was dissolved in EtOH (1.5 mL) and stirred at room temperature in the presence of DMAP (3.3 mg, 0.12 mmol) for 1 h. The ethanol was removed in a vacuum, and the oil was dissolved in CH_2Cl_2 (5 mL) and washed with 10% citric acid (2 × 5 mL). The organic layer was dried over Na_2SO_4. After

(15) Aksenov, V. S.; Terent'eva, G. A.; Savinykh, Y. V. *Russ. Chem. Rev.* (*Engl. Transl.*) **1980**, *49*, 549.

solvent evaporation, the oil was recrystallized from CH_2Cl_2/Et_2O, giving pure (*Z*)-**5b** (31 mg, 75%): mp 167 °C.

General Procedure for Preparation of (*Z*)-Ethyl 2-Alkylsulfanyl- and 2-Arylsulfanyl-1-benzoylaminocyclopropanecarboxylates 5. (*Z*)-Oxazolone **3** (1 mmol) was reacted with diazomethane as indicated above. After solvent evaporation, the oil was dissolved in EtOH (10 mL), and DMAP (122 mg, 1 mmol) was added. The reaction was stirred at room temperature for 1 h. The ethanol was removed in a vacuum, and the residual oil was dissolved in CH_2Cl_2 (10 mL) and washed with 10% citric acid (2 × 10 mL). The organic layer was dried over Na_2SO_4. After solvent evaporation, the oil was chromatographed on silica gel (CH_2Cl_2/Et_2O, 1:0 to 20:1) to give two fractions, one containing the pure *Z* isomer **5** and the other containing a mixture of *Z* and *E* isomers **5**. The pure *E* isomers were isolated in the case of **5b,c** by recrystallization. The ratio of isomers is indicated below. ^{1}H NMR data are given in Table 1.

Ethyl 1-Benzoylamino-2-methylsulfanylcyclopropanecarboxylate (5a): total yield 66% (*Z*/*E*: 3:1). (*Z*)-**5a**: mp 107 °C (CH_2Cl_2/Et_2O); IR ν_{max} 3300, 1720, 1640 cm^{-1}.

Ethyl 1-Benzoylamino-2-phenylsulfanylcyclopropanecarboxylate (5b): total yield 77% (*Z*/*E*: 3:1). (*Z*)-**5b**: mp 167 °C (CH_2Cl_2/Et_2O); IR ν_{max} 3250, 1720, 1620 cm^{-1}. (*E*)-**5b**: mp 117 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 3250, 1720, 1620 cm^{-1}.

Ethyl 1-Benzoylamino-2-benzylsulfanylcyclopropanecarboxylate (5c): total yield 67% (*Z*/*E*: 5:1). (*Z*)-**5c**: mp 135 °C (CH_2Cl_2/Et_2O); IR ν_{max} 3300, 1720, 1640 cm^{-1}; ^{13}C NMR δ 14.3 (Me), 23.2 (C-3), 31.7 (C-2), 38.2 (SCH_2), 38.9 (C-1), 61.6 (OCH_2), 127.2−139.1 (H_{arom}), 168.4 (CONH), 170.8 (COOEt). (*E*)-**5c**: mp 102 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 3300, 1720, 1640 cm^{-1}.

Ethyl 1-Benzoylamino-2-tritylsulfanylcyclopropanecarboxylate (5d): total yield 60% (*Z*/*E*: 5:1). (*Z*)-**5d**: mp 136 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 3300, 1720, 1640 cm^{-1}; ^{13}C NMR δ 14.3 (Me), 23.0 (C-3), 30.9 (C-2), 38.0 (C-1), 61.5 (OCH_2), 127.2−134.1 (H_{arom}), 168.2 (CONH), 170.4 (COOEt).

Bis(2-Benzoylamino-2-ethoxycarbonylcyclopropyl)-disulfide (6). The ester **5d** (507 mg, 1 mmol) was dissolved in EtOH (2 mL), and a solution of iodine in aqueous ethanol (8 mL, 0.125 M, EtOH/H_2O, 7:1) was added and stirring was continued for 2 h. A solid was separated. After solvent evaporation, the solid was taken up with CH_2Cl_2 (10 mL) and washed with a solution of sodium thiosulfate and then with H_2O. After being dried over Na_2SO_4 and recrystallized from CH_2Cl_2/*i*-Pr_2O, a mixture of diastereoisomeric disulfides **6** (215 mg) was isolated. A further crop of **6** (40 mg) was obtained from the mother liquor when it was chromatographed on silica-gel (CH_2Cl_2/Et_2O, 1:0 to 7:1): total yield: 97%. A pure amount of one of the two diastereoisomers was isolated by a further recrystallization: mp 214 °C (EtOH/H_2O); IR ν_{max} 3200, 1705, 1640 cm^{-1}.

General Procedure for the Preparation of (*Z*)-2-Alkylsulfanyl- 1-benzoylaminocyclopropane Carboxylic Acids 7. To a solution of disulfides **6** (0.2 mmol), aminoiminosulfinic acid (0.2 mmol), alkyl bromide (0.42 mmol), and CTACl (0.0032 mg, 0.01 mmol) in THF (2 mL) under nitrogen was added an aqueous solution of NaOH (1.5 mL, 6%). The two-phase system was vigorously stirred under reflux for 2 h. After solvent evaporation, the mixture was taken up with CH_2Cl_2 (10 mL) and washed with H_2O (2 × 10 mL). The matched aqueous layers were acidified with HCl (10%, Congo Red) and extracted with CH_2Cl_2 (2 × 10 mL). After drying over Na_2SO_4, compound **7a** was recrystallized from CH_2Cl_2, giving a pure product (47 mg). The mother liquor of **7a** and the reaction mixture of **7b** were chromatographed on silica gel (CH_2Cl_2/Et_2O, 1:0 to 2:1) giving the corresponding pure compounds.

(*Z*)-1-Benzoylamino-2-benzylsulfanylcyclopropanecarboxylic Acid (7a): total yield 74%; mp 173−174 °C (CH_2Cl_2); IR ν_{max} 3300, 1685, 1620 cm^{-1}.

(*Z*)-Benzoylamino-2-allylsulfanylcyclopropanecarboxylic Acid (7b): total yield 67%; mp 166 °C (CH_2Cl_2/*i*-Pr_2O); IR ν_{max} 3300, 1690, 1620 cm^{-1}.

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