were washed with water and dried over sodium sulfate, and the solvent was evaporated. A solution of diazomethane in ether was added to an ethereal solution of the residue to obtain a pale yellow solution that was allowed to stand for 10 min at 25 °C. Evaporation of the solvent gave a mixture (25 mg) of two keto esters which was purified by LC on Partisil using 20% ether in hexane as eluant. Keto ester **9** (minor): oil; IR ($CHCl_3$) 1730, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (s, 3 H), 0.87 (d, 3 H, J = 6.8 Hz), 1.27 (s, 3 H), 2.38 (d, 1 H, J = 14 Hz), 2.46 (d, 1 H, J = 14 Hz), 2.68 (m, 1 H, J = 14, 10, 8 Hz); mass spectrum, m/z 266, 251, 235, 193, 192.

Ozonolysis of Arenarol (7). Silver oxide (400 mg) was added to a solution of arenarol (225 mg) in dry ether (25 mL) and the suspension was stirred for 1 h at 25 °C. The reaction mixture was filtered through Celite and the solvent was evaporated to obtain arenarone (166 mg). The arenarone (166 mg) was subjected to the ozonolysis procedure above to obtain a crude mixture of methyl esters (86 mg). A portion of the mixture was chromatographed by LC using 20% ether in hexane as eluant to obtain the keto ester **9** as the major product.

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Registry No. **2**, 71678-03-0; **3**, 96806-31-4; **5**, 71678-04-1; **6**, 96806-32-5; **7**, 87764-13-4; **8**, 96806-33-6; **9**, 96893-68-4; arenarone, 87764-16-7.

A Convenient Method for the Preparation of 2-(1-Aminoalkyl)thiazole-4-carboxylic Acids, Key Intermediates in the Total Synthesis of Naturally Occurring Antitumor Cyclopeptides

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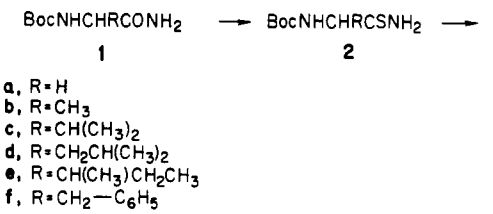
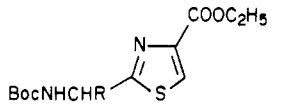
The structure of some naturally occurring peptides of significant biological and pharmaceutical interest have been found to possess the thiazole ring. Such is the case of thiostrepton,[1,2] bottromycin,[3] dysidenin,[4] or isodysidenin[5] and of the well-known antitumor drug bleomycin, which binds to DNA by intercalation of its bithiazole part.

In a continuing search for pharmacologically active natural products, it has been found that a series of cytotoxic cyclic peptides isolated from marine animals contain a 2-(1-aminoalkyl)thiazole-4-carboxylic acid moiety which appears to have been formed by biosynthetic condensation of an amino acid with cysteine. Structures of these compounds such as dolastatin (isolated from a mollusk[6]), ulicyclamide, ulithiacyclamide,[7] and patellamides[8-11] isolated from tunicates have been proposed, and a great deal of research has gone into establishing the mode of antitumor action of these drugs. For this purpose, it seems necessary to undertake the total synthesis of the peptides extracted from marine animals in very small amounts. Thiazole amino acids that may play a key role in the biological activity of the peptides are also important intermediates for their total synthesis. The preparations of (gly)Thz and (gln)Thz[12] recently described[13] involve a multiple step method. We propose here a simpler alternative method starting from commercially available α-amino carboxamides. Initial N-protection afforded *t*-Boc-*N*-α-amino carboxamides **1** (Scheme I) as shown by an IR carbamate band at 1665–1670 cm^{-1}. Thionation of amides by a modification of the initial procedure of Lawesson[14] using

Scheme I





3

3a, Boc-gly(Thz)OEt
b, Boc-ala(Thz)OEt
c, Boc-val(Thz)OEt
d, Boc-leu(Thz)OEt
e, Boc-ile(Thz)OEt
f, Boc-phe(Thz)OEt

Table I

compd[a]	isolated yield, %	mp, °C	R_f
1a	62	94	0.02
b	74	123.5	0.07
c	90	157	0.03
d	92	144	0.23
e	90	166	0.11
f	96	148	0.08
2a	88	124.5	0.06
b	60	103	0.15
c	66	108	0.16
d	73	157.5	0.29
e	86	132	0.24
f	70	101	0.26
3a	75	133	0.42
b	35	89.5	0.34
c	42	125.5	0.64
d	33	92	0.38
e	63	103	0.66
f	39	111	0.75

[a] Satisfactory analyses were obtained for all compounds.

(1) Bodanszky, M.; Fried, J.; Sheehan, J. T.; Williams, N. J.; Alicino, J.; Cohen, A. I.; Keller, B. T.; Birkhimer, C. A. *J. Am. Chem. Soc.* **1964**, *86*, 2478–2490.
(2) Anderson, B.; Hodgkin, D. C.; Viswamitra, M. A. *Nature (London)* **1970**, *225*, 233–235.
(3) Waisvicz, J. M.; van der Hoeven, M. G.; te Nijenhuis, B. *J. Am. Chem. Soc.* **1957**, *79*, 4524–4527.
(4) Kazlauskas, R.; Lidgard, R. O.; Walls, R. J.; Vetter, W. *Tetrahedron Lett.* **1977**, 3183–3186.
(5) Charles, C.; Brackman, J. C.; Daloze, D.; Tursch, B.; Karlsson, R. *Tetrahedron Lett.* **1978**, 1519–1520.
(6) Pettit, G. R.; Kamano, Y.; Brown, P.; Gust, D.; Inoue, M.; Herald, C. L. *J. Am. Chem. Soc.* **1982**, *104*, 905–907.
(7) Ireland, C. M.; Sheuer, P. J. *J. Am. Chem. Soc.* **1980**, *102*, 5688–5691.
(8) Ireland, C. M.; Durso, A. R., Jr.; Newman, R. A.; Hacker, M. P. *J. Org. Chem.* **1982**, *47*, 1807–1811.
(9) Biskupiak, J. E.; Ireland, C. M. *J. Org. Chem.* **1983**, *48*, 2302–2304.
(10) Hamamoto, Y.; Endo, M.; Nakagawa, M.; Nakanishi, T.; Mizukawa, K. *J. Chem. Soc., Chem. Commun.* **1983**, 323–324.
(11) Wasylyk, J. M.; Biskupiak, J. E.; Costello, C. E.; Ireland, C. M. *J. Org. Chem.* **1983**, *48*, 4445–4449.
(12) Abbreviations for 2-(1-aminoalkyl)thiazole-4-carboxylic acid related to natural amino acids correspond to the Pettit's proposal.[6]
(13) Hamada, Y.; Kohda, K.; Shioiri, T. *Tetrahedron Lett.* **1984**, *25*, 5303–5306.
(14) Pedersen, B. S.; Scheibye, S.; Clausen, K.; Lawesson, S. O. *Bull. Soc. Chim. Belg.* **1978**, *87*, 293–297.

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2,4-bis(4-phenoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide (PTPS)[15] in anhydrous tetrahydrofuran at 20 °C is selective since the *tert*-butoxycarbonyl N-protecting group reacts with Lawesson's reagent at 110 °C[14] and ester is transformed into the thio ester function at 140 °C.[16] The thioamides **2** display an IR absorption decrease of approximately 10 cm^{-1} which is consistent with the amide (1620–1650 cm^{-1} range) → thioamide (1610–1640 cm^{-1} range) transformation.

The cyclization of thioamides **2** to thiazoles **3** was achieved by using ethyl bromopyruvate following the general procedure of Hantzsch already employed by us for the synthesis of bithiazoles related to bleomycin derivatives.[17,18] The NMR spectra of **3** show a single proton in the range δ 8.0–8.4 which is, with the 1220–1240 cm^{-1} IR absorption peak, indicative of the thiazolic moiety. A common feature for **2** and **3** lies in the weak intensity of the molecular peak as compared with the *m/e* 57 parent fragmentation in mass spectroscopy. The results are summarized in Table I.

The synthesis, here applied to six thiazole amino acids found in the structure of ulicyclamide, ulithiacyclamide, and patellamides, is very general and could be used starting from any L- or D-amino acids in good yields. The absence of any racemization during the two main steps of the synthesis has been verified using ^1H NMR and ^{13}C NMR. The least-square linear regression analyses of the C–multiple bond and α atoms for the amides and corresponding thioamides indicate the presence of a single enantiomer, as substantiated by the following relations:

$$\delta_{C=S} = 1.475 \times \delta_{C=O} - 48.136 \qquad (r = 0.983)$$

$$\delta_{C_\alpha(C=S)} = 1.008 \times \delta_{C_\alpha(C=O)} + 5.164 \qquad (r = 0.997)$$

Experimental Section

Melting points were determined on a Tottoli melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 177 grating infrared spectrophotometer using potassium bromide pellets. ^1H and ^{13}C spectra in $CDCl_3$ solutions were recorded on Cameca 350-MHz and Bruker WP 80 SY spectrometers, respectively, with tetramethylsilane as internal standard. Electron impact mass spectra were recorded on a Ribermag R10-10 (combined with Riber 400 data system) mass spectrometer at 70 eV by using direct insertion. TLC monitoring of all reactions was performed with Merck silica gel 60 F 254 precoated sheets (0.2 mm) with CH_2Cl_2–ethyl acetate (9:1, v/v) as developing system. Spots were detected with ultraviolet light and/or ninhydrin.

Typical Procedure for the Preparation of N-Protected α-Amino Carboxamides 1. *N*-Boc-valinamide (1c). To a solution of 2.18 g of di-*tert*-butyl dicarbonate (10 mmol) in dry CH_2Cl_2 (50 mL) were added 1.5 g of L-valinamide hydrochloride (10 mmol) and 2.1 g of triethylamine (20 mmol). The reaction mixture was refluxed for 3 h. Triethylamine salts were extracted twice by 10 mL of water, and the organic phase was evaporated in vacuo to give 1.9 g (90% yield) of an oily residue which readily crystallized upon standing at room temperature: R_f 0.03; mp 157 °C; IR 1630 (C=O), 1670 (Boc); ^{13}C NMR δ 59.6 (d, C_α), 174.5 (s, C=O). Anal. Calcd for $C_{10}H_{20}N_2O_3$: C, 55.53; H, 9.32; N, 12.95; O, 22.19. Found: C, 55.66; H, 9.31; N, 12.83; O, 22.07.

Typical Procedure for the Preparation of N-Protected α-Amino Thiocarboxamides 2. *N*-(*tert*-Butoxycarbonyl)-valinethioamide (2c). To a solution of amide **1c** (1.365 g, 6.3 mmol) in dry THF (10 mL) was added PTPS (2.0 g, 3.8 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature until the starting material was consumed (6 h), as monitored by thin-layer chromatography (silica gel, 9:1 dichloromethane–ethyl acetate). The solvent was evaporated and the thick residue was chromatographed on a silica gel column (eluted with CH_2Cl_2–ethyl acetate, 9:1). The resulting oil (1.8 g, 66%) crystallized on standing (white crystals): R_f 0.16; mp 109 °C; IR 1630 (C=S), 1680 (Boc); ^{13}C NMR δ 65.5 (d, C_α), 209.4 (s, C=S); mass spectrum, *m/e* (relative intensity) 232 (26, M^+) 57 (100). Anal. Calcd for $C_{20}H_{20}N_2O_2S$: C, 51.69; H, 8.68; N, 12.06; O, 13.77; S, 13.80. Found: C, 51.77; H, 8.73; N, 12.12; O, 13.89; S, 13.74.

Typical Procedure for the Preparation of 2-[(N-Protected)-1-aminoalkyl]thiazole-4-carboxylic Esters 3. Ethyl 2-[*N*-(Butoxycarbonyl)valyl]thiazole-4-carboxylate (3c). A mixture of 1.16 g (5 mmol) of **2c** and 0.63 mL (5 mmol) of ethyl bromopyruvate in 20 mL of dry ether was stirred at room temperature for 2 days. Filtration of the precipitate and evaporation of the filtrate afforded a residue which was submitted to column chromatography (silica gel, dichloromethane–ethyl acetate, 9:1). Evaporation of the solvents gave an oil which soon crystallized (0.7 g, 42%): R_f 0.64; mp 125.5 °C; IR 1235 (C–H thiazole), 1697 (Boc); ^1H NMR δ 4.9 (dd, H_α), 8.0 (s, 5-ThzH); mass spectrum, *m/e* (relative intensity) 328 (3, M^+), 57 (100). Anal. Calcd for $C_{15}H_{24}N_2O_4S$: C, 54.86; H, 7.37; N, 8.53; O, 19.49; S, 9.76. Found: C, 55.91; H, 7.43; N, 8.50; O, 19.53; S, 9.71.

Registry No. **1a**, 35150-09-5; **1b**, 81587-17-9; **1c**, 35150-08-4; **1d**, 96928-99-3; **1e**, 96929-00-9; **1f**, 88463-18-7; **2a**, 89226-13-1; **2b**, 96929-01-0; **2c**, 96929-02-1; **2d**, 96929-03-2; **2e**, 96929-04-3; **2f**, 88815-90-1; **3a**, 96929-05-4; **3b**, 96929-06-5; **3c**, 96929-07-6; **3d**, 96929-08-7; **3e**, 96929-09-8; **3f**, 96929-10-1; ethyl bromopyruvate, 70-23-5; L-valinamide hydrochloride, 3014-80-0.

(15) Lajoie, G.; Lépine, F.; Maziak, L.; Belleau, B. *Tetrahedron Lett.* **1983**, *24*, 3815–3818.
(16) Clausen, K.; Thorsen, M.; Lawesson, S. O. *Chem. Scr.* **1982**, 14–18.
(17) Houssin, R.; Bernier, J. L.; Hénichart, J. P. *J. Heterocycl. Chem.* **1984**, *21*, 465–469.
(18) Houssin, R.; Bernier, J. L.; Hénichart, J. P. *J. Heterocycl. Chem.* **1984**, *21*, 681–683.

Synthesis and Reactivities of Trimethylsilyl-Substituted Tetrathia- and Tetraselenafulvalenes

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Recently numerous investigations on "Organic metals" have been reported.[1] The term organic metals refers to organic compounds which exhibit electrical conductivity close to that of metals. The compounds mostly consist of donor–acceptor complexes of tetrathiafulvalene (TTF), tetraselenafulvalene (TSeF), and their derivatives. There has been an enormous amount of research on the synthesis and properties of TTF and TSeF compounds.[2] However, in general, the preparation methods require multistep routes and involve unstable intermediates.

We have disclosed recently a synthesis of alkoxycarbonyl-substituted TTF and TSeF compounds from the reactions of CS_2 or CSe_2 with bis(alkoxycarbonyl)-acetylenes under high pressure.[3,4] We now report the one-step synthesis and reactivity of versatile trimethylsilyl-substituted TTF and TSeF derivatives as shown in Scheme I. In a typical reaction, bis(trimethylsilyl)-acetylene and CS_2 were dissolved in hexane and the solution was pressurized under 5000 atm at 120–130 °C for 12

(1) For recent reviews, see: Proceedings of the International Conference on "Synthetic Low-Dimensional Conductors and Superconductors", Les Arcs, France, December, 1982.
(2) Narita, M.; Pittman, C.U., Jr. *Synthesis* **1976**, *7*, 425.
(3) Rice, J. E.; Okamoto, Y. *J. Org. Chem.* **1981**, *46*, 446.
(4) Rice, J. E.; Wojciechowski, P.; Okamoto, Y. *Heterocycles* **1982**, *18*, 191.

0022-3263/85/1950-2788$01.50/0