Thiol-Mediated Free Radical Cyclization of Alkenyl and Alkynyl Isocyanides

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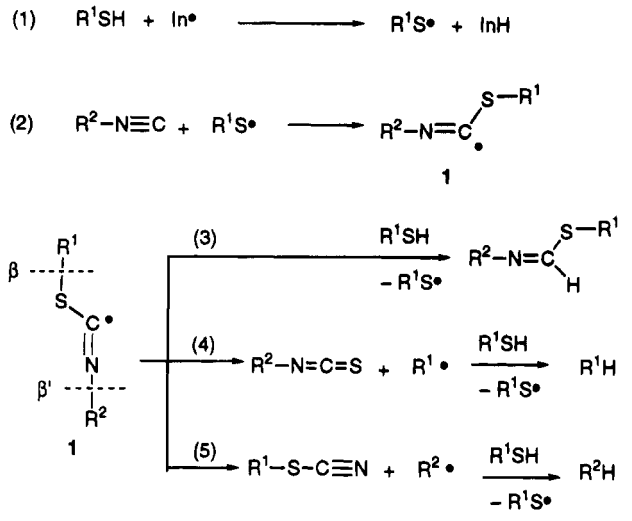
Thiol-mediated free radical cyclizations of but-3-enyl and but-3-ynyl isocyanides of types **6**–**8** give new access to 3,5-disubstituted 2-(alkyl- and 2-(arylthio)pyrrolines **11**, **12**, and **18**. When 2-mercaptoethanol is used with the same isocyanides the reaction results in pyroglutamates **16**, **17**, or **19**. These cyclizations involve the formation of a new carbon–carbon bond through intramolecular addition of a carbon-centered thioimidoyl radical to a carbon–carbon multiple bond. Although cyclic products are usually obtained in high yields, in a few cases a competing radical degradation process leading to isothiocyanates was observed. Isocyanide **8a** carrying an allyl(phenyl) sulfide moiety isomerizes to 2-(phenylthio)pyrroline **24** in a series of sequential steps.

Free radical reactions of isocyanides with thiols were reported by Saegusa and co-workers more than twenty years ago.[1] These authors observed that alkyl and phenyl isocyanides react with primary thiols yielding (alkylthio)formimidate, with tertiary thiols giving isothiocyanates, and with secondary thiols affording mixtures of thioformimidates and isothiocyanates. As delineated in eqs 1–4, addition of a thiyl radical to the isocyanide group



affords a carbon-centered imidoyl radical **1** (eq 2). Direct hydrogen atom transfer from thiol to radical **1** gives a thioimidate in propagating step (3), while β-cleavage of a C–S bond leads to the corresponding isothiocyanate and alkane R^1H in propagating process (4). Although these authors did not observe any deamination product R^2H that would result from β' cleavage of a C–N bond according to (5), this process was inferred in a more recent study based on ESR spectroscopy.[2] No synthetic work based on these observations has followed. We postulated that Saegusa's findings bear a great potential for the synthesis of cyclic compounds. To effectuate this idea we conceived radicals of type **1** in which appendage R^1, or R^2, comprises a suitably positioned radicophilic functionality which will encourage ring closure over the possibly competitive processes (3)–(5). In the present paper we apply this concept to the synthesis of highly substituted pyrrolines and 5-oxopyrrolidines using a novel thiol induced cyclization of various but-3-enyl isocyanides and but-3-ynyl isocyanides.[3,4]

Isocyanides of types **6**, **7**, and **8** were obtained in a few steps by derivatization of glycine imines **2** through the corresponding formyl derivatives **3**, **4**, and **5** using standard methods (Scheme 1 and Experimental Section).

Reactions of isocyanides of type **6** with benzenethiol, ethanethiol and esters of ω-mercapto carboxylic acids are described in Scheme 2 and Table 1. AIBN was used as initiator and reactions were conducted in dry degassed toluene. It was found that benzenethiol, ethanethiol, and methyl 4-mercaptobutyrate react with alkenylisocyanides giving the corresponding 2-(arylthio)- or 2-(alkylthio)-1-pyrroline derivatives (Table 1, entries 1–9). Thiyl radical ($R^5S^•$) adds to an isocyanide **6** generating a thioimidoyl radical **9** which undergoes 5-*exo* cyclization giving radical **10** (Scheme 2). Hydrogen atom abstraction from R^5SH affords the *cis*- and *trans*-pyrrolines **11** and **12** and $R^5S^•$ which continues the chain. Yields are usually high (Table 1, entries 1–5) but decrease (entries 6–9) when the double bond is substituted at the site of imidoyl radical addition (*cf.* Scheme 2, **9** → **10** R^1 = Me). In these slower cyclizations better results are obtained with ethanethiol than with benzenethiol. In the reaction of compound **6d**, at 110 °C degradation to isothiocyanate (*cf.*, **9** → **13**) becomes a competing process (Table 1, entry 9). In reactions involving a thiol which may give a stabilized free radical through homolysis of its C–S bond, isothiocyanate formation competes with cyclization even when the double bond involved in the intramolecular 5-*exo* addition is not sterically hindered. This is the case for the reaction between methyl mercaptoacetate and isocyanide **6c**. As shown in entries 10–13, control over these two competing reactions may be gained by adequate temperature adjustment. Thus in reactions run at temperatures over 40 °C isothiocyanate **13c** was obtained as the major product, while in a reaction performed at

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(1) Saegusa, T.; Kobayashi, S.; Ito, Y. *J. Org. Chem.* **1970**, *35*, 2118.

(2) Blum, P. M.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1313.

(3) Preliminary report: Bachi, M. D.; Lasanow, D. *Synlett* **1990**, 551.

(4) Preliminary report: Bachi, M. D.; Balanov, A.; Bar-Ner, N.; Bosch, E.; Denenmark, D.; Mizhiritskii, M. *Pure Appl. Chem.* **1993**, *65*, 595.

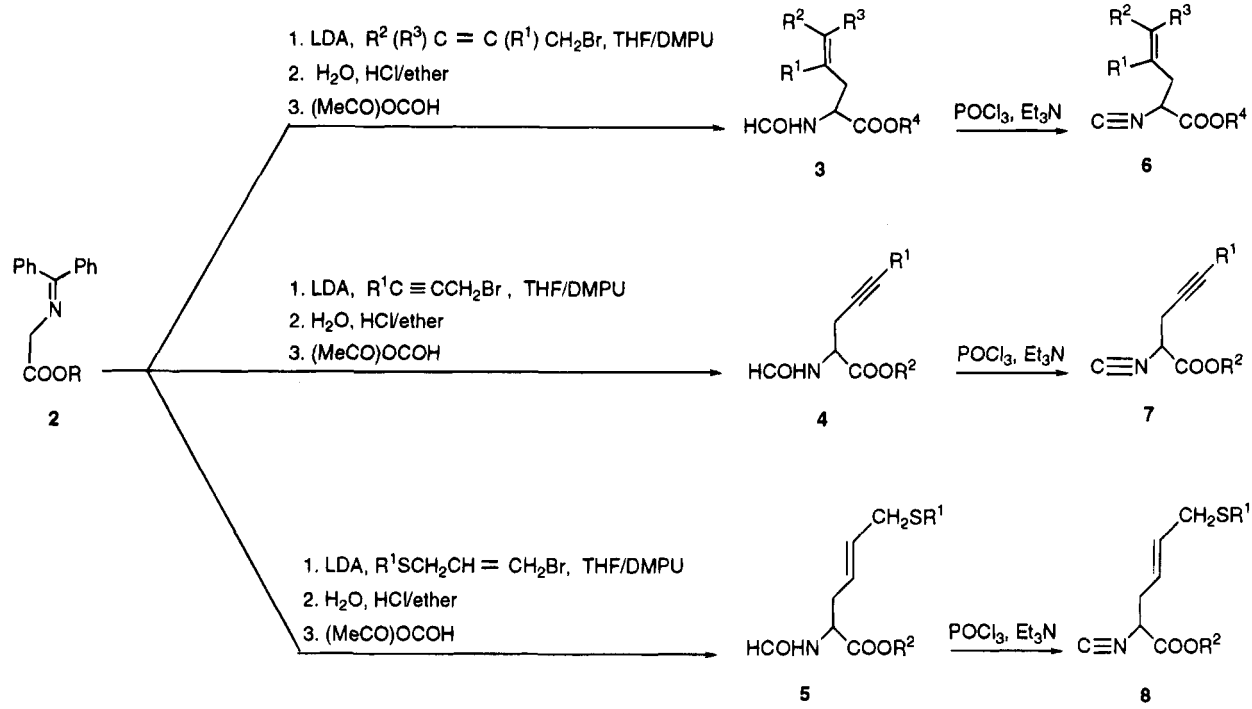
0022-3263/94/1959-7752$04.50/0

Table 1. Reactions of Isocyanides of Type 6 with Thiols and AIBN[a]

	isocyanides 6							pyrrolines 11 + 12								isothiocyanate 13					
entry		R^1	R^2	R^3	R^4	R^5SH, R^5	temp, °C	time, h		R^1	R^2	R^3	R^4	R^5	yield, %	11/12 ratio[b]		R^1	R^2	R^3	R^4	yield, %
1	**a**	H	H	H	^{t}Bu	Ph	110	1.0	**k**	H	H	H	^{t}Bu	Ph	74	1:1.1	–					–
2	**a**					Et	110	1.5	**l**	H	H	H	^{t}Bu	Et	83	1.4:1	–					–
3	**b**	H	H	H	Et	Et	40	1.5	**m**	H	H	H	Et	Et	85	1.2:1	–					–
4	**c**	H	Me	Me	Et	Et	40	1.5	**n**	H	Me	Me	Et	Et	83	1.4:1	–					–
5	**c**	H	Me	Me	Et	$(CH_2)_3$-CO_2Me	85	2.0	**o**	H	Me	Me	Et	$(CH_2)_3$-CO_2Me	84	1:1	–					–
6	**d**	Me	H	H	^{t}Bu	Ph	40	1.5	**p**	Me	H	H	^{t}Bu	Ph	traces	–	–					–
7	**d**					Ph	110	1.5	**p**						30	–						–
8	**d**					Et	40	3.5	**q**	Me	H	H	^{t}Bu	Et	56	–	**d**	Me	H	H	^{t}Bu	–
9	**d**					Et	110	2.5	**q**						50	–	**d**					10
10	**c**	H	Me	Me	Et	CH_2CO_2Me	45	3.0	**r**	H	Me	Me	Et	CH_2CO_2Me	38	1:1	**c**	H	Me	Me	Et	57
22	**c**						5[c]	2.0	**r**						58	1:1	**c**					36
12	**c**						−20[c]	4.5	**r**						70	1:1	**c**					28
13	**c**						−60[c]	8.5	**r**						78	1:1	**c**					2

[a] Reactions were performed with 0.02 M solutions of isocyanide in degassed dry toluene, thiol (1.15 equiv), and AIBN (0.15 equiv). [b] Tentative assignments by ^{1}H NMR. [c] Irradiated with Hanovia E-H4 lamp (cobalt filter, Pyrex vessel).

Scheme 1



−60 °C the desired pyrrolines **11r** and **12r** were obtained in high yield.

The reaction of alkenylisocyanide **6a** and mercaptoethanol affords *cis* and *trans* pyroglutamates **16** and **17** (72%, 1:2.5 *cis/tans* ratio). Evidently, the product of free radical cyclization is the 2-((hydroxyethyl)thio)-Δ^1-pyrroline **14** shown in Scheme 3. It was originally assumed that this compound is transformed to *tert*-butyl 4-methylpyroglutamates **16/17** through the intermediacy of the *ortho* derivative **15** which undergoes hydrolysis during chromatography on silica gel.[3,5] However, recent observations in this laboratory indicate that pyroglutamates **16/17** are probably obtained from intermediates **14** and **15** in a thermal process.[6]

It occurred to us that a still broader field of application of the reaction shown in Scheme 2 would open up if instead of the isolated double bond present in isocyanides **6** more highly functionalized radical traps are used. For this purpose we synthesized isocyanides of types **7** and **8** (Scheme 1) and studied their free radical reactions with thiols. Reaction of silylalkynyl isocyanides of type **7** with aliphatic thiols were found to follow the same pattern of isocyanides **6** but required a higher temperature. As shown in Scheme 4 and Table 2 the corresponding silylmethylidene pyrrolines **18** were obtained with primary thiols, the silylmethylidene pyroglutamate **19** with mercaptoethanol, and isothiocyanate **20** with *tert*-dodecanethiol.

5-*Exo-trig* intramolecular additions of carbon radicals to the double bond of allyl sulfides[7,8] or allylstannane[9] lead, through the β-elimination of the radical leaving group, to cyclic products having an alkylene side chain

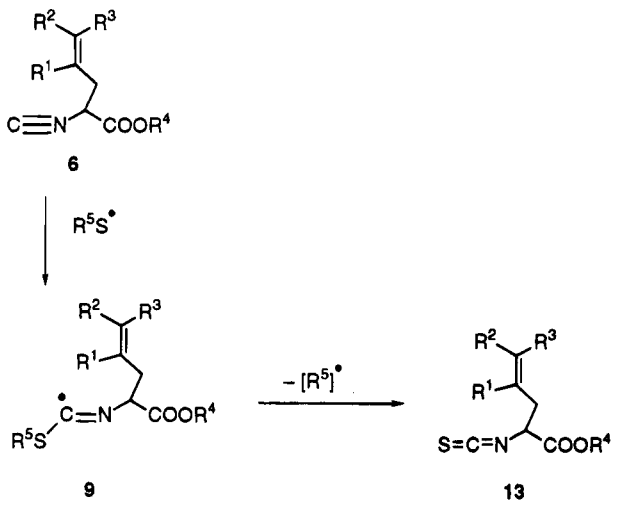
(5) Meyers, A. I.; Ford, M. E. *Tetrahedron Lett.* **1975**, 2861.
(6) Observed spectoscopically by A. Melman in a related reaction, presently under investigation.
(7) Uneo, Y.; Chino, K.; Okawara, M. *Tdetrahedron Lett.* **1982**, *23*, 2575.
(8) Boger, D. L.; Coleman, R. S. *J. Am. Chem. Soc.* **1988**, *110*, 4796.
(9) Keck, G. E.; Cressman, E. N. K.; Enholm, E. J. *J. Org. Chem.* **1989**, *54*, 4345.

Table 2. Reactions of Isocyanides of Type 7 with Thiols and AIBN[a]

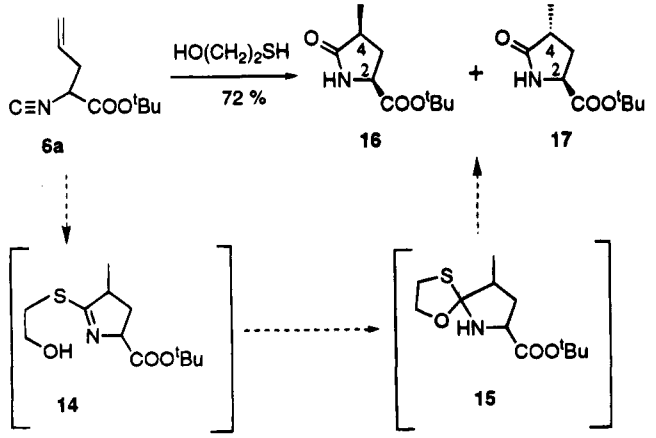
entry	isocyanide 7	R^1	R^2	R^3SH, R^3	product 18, 19, or 20	R^1	R^2	R^3	yield, %
1	**a**	TBDPS	^{t}Bu	Et	**18k**	TBDPS	^{t}Bu	Et	72
2	**b**	TBDPS	Et	Et	**18l**	TBDPS	Et	Et	70
3	**b**	TBDPS	Et	$(CH_2)_2CO_2Me$	**18m**	TBDPS	Et	$(CH_2)_2CO_2Me$	60
4	**c**	TBDMS	Et	Et	**18n**	TBDMS	Et	Et	90
5	**b**	TBDPS	Et	$(CH_2)_2OH$	**19b**	TBDPS	Et	–	84
6	**c**	TBDMS	Et	$(CH_2)_2OH$	**19c**	TBDMS	Et	–	81
7	**b**	TBDPS	Et	$^tC_{12}H_{25}$	**20b**	TBDPS	Et	–	60

[a] Reactions were performed with 0.02 M solution of isocyanide in degassed dry toluene, thiol (1.15 equiv) and AIBN (0.15 equiv) at 100–110 °C.

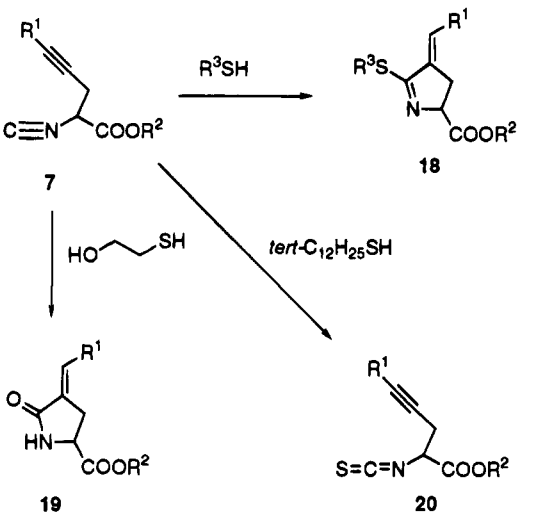
Scheme 2



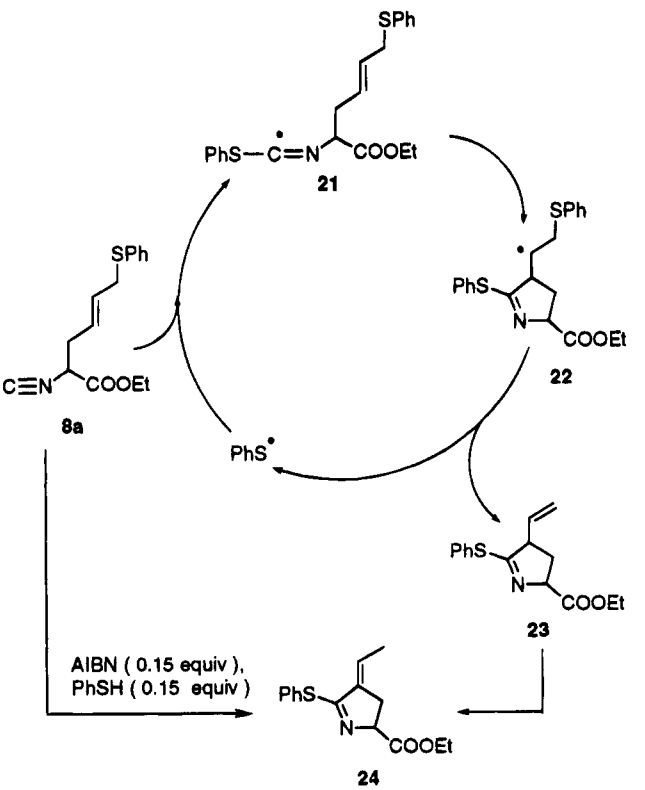
Scheme 3



Scheme 4



Scheme 5



on the site of the ring closure. Such cyclizations are expected to be faster than those engaging isolated double or triple bonds.[10] We visualized that isocyanides of type **8** carrying a suitably positioned allyl(phenyl) sulfide moiety may undergo thiyl-mediated radical cyclization to 3-alkylene pyrrolines, isomeric to 3-alkylidenepyrrolines **18**.

The realization of this idea is shown in Scheme 5 for compound **8a** in which the leaving group is a phenylthiyl

(10) Curran, D. P.; van Elburg, P. A.; Giese, B.; Gigles, S. *Tetrahedron Lett.* **1990**, *31*, 2861.

Table 3. Isomerization of Isocyanide 8a to Pyrroline 24[a]

entry	[M][b] **8a**	time, h	pyrroline **24**, yield	recovered **8a**, yield
1	0.005	2.5	85%	7%
2	0.02	4	71%	16%
3	0.2	1.5	76%	7%

[a] Reactions were performed in dry degassed toluene at 110 °C with PhSH (0.15 equiv) and AIBN (0.15 equiv). [b] Initial concentration.

radical. Thus, isocyanide **8a** is converted into 2-(phenylthio)pyrroline **24** when heated to 110 °C in the presence of a catalytic amount of benzenethiol and AIBN. This reaction is viewed as a series of sequential steps: *intermolecular addition* (**8a** → **21**), *intramolecular addition* (**21** → **22**), and *elimination* (**22** → **23**), or alternatively, conversion of **21** into **23** in *one concerted step*. This is an isomerization involving cyclization accompanied by migration of a phenylthiyl group from a terminal position of an allylic system on the open chain isocyanide **8a** to position-2 of vinylpyrroline **23**. In a subsequent step double bond migration leads to the more stable conjugated ethylidene pyrroline **24**. Cyclizations based on free radical additions to carbon-carbon multiple bonds using thiols (Tables 1 and 2), stannanes,[11-13] or silanes[14] as radical sources are exposed to a competing direct reduction of the open-chain radical intermediate. To minimize the effect of this side reaction, cyclizations are usually performed under high dilution conditions. Cyclization of isocyanide **8a** occurs in the absence of a hydrogen donor and therefore can also be performed in concentrated solutions. Indeed, this reaction is independent of **8a** initial concentration within the measured range of 0.005 to 0.2 M (Table 3).

While none or very low diastereoselctivty was observed in the cyclization of isocyanides **6a-c** into *cis*/*trans* pyrrolines **11** and **12**, the mercaptoethanol mediated cyclization of **6a** affords *cis* 4-methylpyroglutamate **16** and its *trans* isomer **17** in 1:2.5 ratio respectively. This compound was previously obtained by a different method as a 1:1 *cis*/*trans* mixture but no spectral assignment to individual isomers was given.[15] Since reported ^{1}H NMR assignments for *cis* or *trans* urethane derivatives related to **16** and **17** are inconsistent[16-19,20a] we determined the configuration of *cis* isomer **16**, by X-ray diffraction.[21] The ^{1}H NMR spectrum of the *cis* isomer **16** exhibits the following relevant signals, 1.76 (ddd, $J_{H^{3\alpha}H^{3\beta}}$ = 12.72, $J_{H^{3\alpha}H^{4\alpha}}$ = 9.24, and $J_{H^{3\alpha}H^{2\alpha}}$ = 8.22 Hz, $H^{3\alpha}$), 2.66 (ddd, $J_{H^{3\beta}H^{3\alpha}}$ = 12.76, $J_{H^{3\beta}H^{2\alpha}}$ = 8.20, and $J_{H^{3\beta}H^{4\alpha}}$ = 8.20 Hz, $H^{3\beta}$), and 4.09 (dd, $J_{H^{2\alpha}H^{3\alpha}}$ = 7.9 and $J_{H^{2\alpha}H^{3\beta}}$ = 7.9 Hz, $H^{2\alpha}$), and the spectrum of the *trans* isomer **17**; 2.04 (ddd, $J_{H^{3\alpha}H^{3\beta}}$ = 12.52, $J_{H^{3\alpha}H^{4\beta}}$ = 8.55, and $J_{H^{3\alpha}H^{2\alpha}}$ = 8.55 Hz, $H^{3\alpha}$), 2.48 (ddd, $J_{H^{3\beta}H^{3\alpha}}$ = 12.46, $J_{H^{3\beta}H^{4\beta}}$ = 8.94, and $J_{H^{3\beta}H^{2\alpha}}$ = 3.28 Hz, $H^{3\beta}$), and 4.05 (m, $J_{H^{2\alpha}H^{3\alpha}}$ = 8.99 and $J_{H^{2\alpha}H^{3\beta}}$ = 3.05 Hz, $H^{2\alpha}$). It is noted that, $\Delta(\delta H^{3\beta} - \delta H^{3\alpha})$ is greater for the *cis* isomer (0.9 ppm) than for *trans* isomer (0.44 ppm), while $\Delta(J_{H^{2\alpha}H^{3\alpha}} - J_{H^{2\alpha}H^{3\beta}})$ is smaller for the *cis* isomer (~0 Hz) than for the *trans* isomer (~6 Hz). Comparable characteristic features were observed in the NMR spectrum of a series of *cis*/*trans* 4-alkyl-5-(thioxo) pyrrolidine-2-carboxylic acid esters.[22] A similar trend was also observed in the spectra of a *cis*/*trans* 4-benzylpyroglutamate[17] and *cis*/*trans* N-BOC protected 4-alkylpyroglutamic acid esters.[20] A qualitatively similar pattern observed in the NMR spectra of the diastereoisomeric mixtures of pyrrolines **11** and **12** served us for the tentative assignment of their stereochemistry (Table 1). The assignment of *E* configuration to 4-alkylidene pyrrolines **18k-n** and **24** derives from the expectation that under the employed reaction conditions thiyl radicals should induce thermodynamic control.[23]

In summary, thiyl radical mediated 5-*exo*-*trig* and 5-*exo*-*dig* cyclizations of alkenyl- and alkynyl isocyanides open a new access to highly functionalized pyrrolidine derivatives.

Experimental Section

General. For general procedures see ref 24. Signal assignments to compounds **11** and **12** derive from NMR spectra of mixtures of *cis* and *trans* isomers and were corroborated by pertinent decoupling experiments.

***tert*-Butyl 2-Formamidopent-4-enoate (3a).** *N*-(Diphenylmethylene)glycine *tert*-butyl ester (4.1 g, 13.9 mmol) was alkylated with allyl bromide using LDA [(13.9 mmol) obtained from diisopropylamine (1.96 mL) and *n*-BuLi (1 equiv, 1.5M in hexane)] in THF (30 mL) and DMPU (1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone) (4 mL) at −78 °C.[25,26] Hydrolysis (1 *N* aqueous HCl, ether) of the alkylated imine afforded crude amine which was formylated (aceticformic anhydride in ether). Flash chromatography (Hex/EtOAc, 1:1) of the product gave the title compound **3a** (30%, 2 steps); IR (neat) 3296, 1737, 1670 cm^{-1}; ^{1}H NMR δ 1.46 (s, 9H), 2.51-2.56 (m, 1H), 2.57-2.62 (m, 1H), 4.65 (dd, J = 13.3, 5.5 Hz, 1H), 5.11-5.20 (m, 2H), 5.63-5.74 (m, 1H), 6.15 (br s, 1H), 8.20 (s, 1H). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.30; H, 8.54; N, 7.03. Found: C, 59.96; H, 8.62; N, 6.92.

Ethyl 2-Formamido-5-methylhex-4-enoate (3c). Compound **3c** was prepared according to the procedure described for the preparation of formyl **3a** but starting from *N*-(diphenylmethylene)glycine ethyl ester (16.5 mmol). Flash chromatography (Hex/EtOAc, 1:1) of the product gave the title compound **3c** (67%, 2 steps); IR (neat) 3302 (NH), 1741, 1523, 1665 cm^{-1}; ^{1}H NMR δ 1.28 (t, J = 7.12 Hz, 3H), 1.60 (s, 3H), 1.70 (s, 3H), 2.49 (ddd, J = 14.32, 6.95, 7.0 Hz, 1H), 2.62 (ddd, J = 14.32, 7.11, 7.11 Hz, 1H), 4.20 (q, J = 7.12 Hz, 2H), 4.71 (ddd, J = 7.91, 7.91, 5.47 Hz, 1H), 4.98 - 5.03 (m, 1H), 6.14 (br s, 1H), 8.20 (s, 1H). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.30; H, 8.54; N, 7.04. Found: C, 60.03; H, 8.69; N, 6.99.

***tert*-Butyl 2-Formamido-4-methylpent-4-enoate (3d).** Compound **3d** was prepared according to the procedure

(11) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergammon Press: Oxford, 1986.
(12) Neumann, W. P. *Synthesis* **1987**, 665.
(13) Curran, D. P. *Synthesis* **1988**, 417.
(14) Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* **1989**, *30*, 681.
(15) Kanemasa, K.; Tatsukawa, A.; Wada, E. *J. Org. Chem.* **1991**, *56*, 2875.
(16) Baldwin, J. E.; Miranda, T.; Moloney, M.; Hokelek, T. *Tetrahedron* **1989**, *45*, 7459.
(17) Dikshit, D. K.; Panday, S. *J. Org. Chem.* **1992**, *57*, 1920.
(18) August, R. A.; Khan, J. A.; Moody, C. M.; Young, D. W. *Tetrahedron Lett.* **1992**, *33*, 4617.
(19) Langlois, N.; Rojas, A. *Tetrahedron Lett.* **1993**, *34*, 2477.
(20) (a) Ezquerra, J.; Pedregal, C.; Rubio, A.; Yruretagoyena, B.; Escribano, A.; Sanchezferrando, F. *Tetrahedron* **1993**, *49*, 8665. (b) In the spectra of *cis* isomers, H^3 hydrogen atoms were assigned signals at higher field than the assignments for H^2 and H^3 in this article were inverted.
(21) (a) We thank Dr. Felix Frolow for X-ray diffraction analysis of compound **16**. (b) The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 IEZ, U.K.
(22) Bachi, M. D.; Bar-Ner, N.; Mizhiritskii, M.; Konstantinovskii, L. Manuscript in preparation.
(23) Griesbaum, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 273.
(24) Bachi, M. D.; Bosch, E.; Denenmark, D.; Girsh, D. *J. Org. Chem.* **1992**, *57*, 6803.
(25) Stork, G.; Leony, Y. W.; Touxin, A. M. *J. Org. Chem.* **1976**, *41*, 3491.
(26) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663.

described for the preparation of formyl **3a** starting from *N*-(diphenylmethylene)glycine *tert*-butyl ester (17.5 mmol). Flash chromatography (Hex/EtOAc, 4:1) of the product gave the title compound **3d** (70%, 2 steps); IR (neat) 3301, 1737, 1670 cm^{-1}; ^1H NMR δ 1.47 (s, 9H, $C(CH_3)_3$), 1.77 (s, 3H), 2.41 (dd, J = 13.96, 7.76 Hz, 1H), 2.55 (dd, J = 13.90, 6.11 Hz, 1H), 4.68 (m, 1H), 4.76 (dd, J = 1.76, 0.83 Hz, 1H), 4.85 (m, 1H), 6.00 (br s, 1H), 8.19 (s, 1H). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.97; H, 8.92; N, 6.57. Found: C, 61.97; H, 9.11; N, 6.28.

***tert*-Butyl 2-Formamido-5-(*tert*-butyldiphenylsilyl)-pent-4-ynoate (4a).** Compound **4a** was prepared according to the procedure described for the preparation of formyl **3a** starting from *N*-(*p*-chlorophenylmethylene)glycine *tert*-butyl ester (12 mmol) instead of *N*-(diphenylmethylene)glycine *tert*-butyl ester. Flash chromatography (Hex/EtOAc, 7:3) of the product gave the title compound **4a** (67%, 2 steps); mp 98 °C (Hex); IR (neat) 3300, 2180, 1737, 1686 cm^{-1}; ^1H NMR δ 1.05 (s, 9H), 1.46 (s, 9H), 2.96 (dd, J = 17.16, 3.75 Hz, 1H), 3.10 (dd, J = 17.16, 5.01 Hz, 1H), 4.73 (br ddd, J = 7.51, 4.83, 3.66 Hz, 1H), 6.47 (br d, J = 7.08 Hz, 1H), 7.35–7.39 (m, 6H), 7.73–7.76 (m, 4H), 8.24 (s, 1H). Anal. Calcd for $C_{26}H_{33}NO_3Si$: C, 71.72; H, 7.59; N, 3.22. Found: C, 71.43; H, 7.36; N, 3.23.

Ethyl 2-Formamido-5-(*tert*-butyldiphenylsilyl)pent-4-ynoate (4b). Compound **4b** was prepared according to the procedure described for the preparation of formyl **3a** starting from *N*-(diphenylmethylene)glycine ethyl ester (12 mmol). Flash chromatography (Hex/EtOAc, 4:1) of the product gave the title compound **4b** (60%, 2 steps); IR (neat) 3176, 2183, 1746, 1647 cm^{-1}; ^1H NMR δ 1.06 (s, 9H), 1.27 (t, J = 7.14 Hz, 3H), 3.04 (d, J = 4.47 Hz, 2H), 4.26 (m, 2H), 4.68 (m, 1H), 6.47 (br NH), 7.36–7.40 (m, 6H), 7.73–7.76 (m, 4H), 8.25 (s, 1H). Anal. Calcd for $C_{24}H_{29}NO_3Si$: C, 70.76; H, 7.13; N, 3.44. Found: C, 70.47; H, 7.14; N, 3.74.

Ethyl 2-Formamido-5-(*tert*-butyldimethylsilyl)pent-4-ynoate (4c). Compound **4c** was prepared according to the procedure described for the preparation of formyl **3a** starting from *N*-(*p*-chlorophenylmethylene)glycine ethyl ester (12 mmol) instead of *N*-(diphenylmethylene)glycine ethyl ester. Flash chromatography (Hex/EtOAc, 7:3) of the product gave the title compound **4c** (48%, 2 steps); IR (neat) 3326, 2182, 1740, 1684 cm^{-1}; ^1H NMR δ 0.08 (s, 6H), 0.91 (s, 9H), 1.31 (dd, J = 4.70, 2.40 Hz, 2H), 4.26 (m, 2H), 4.79 (ddd, J = 8.23, 4.30, 4.05 Hz, 1H), 6.40 (br s, 1H), 8.26 (s, 1H). Anal. Calcd for $C_{14}H_{25}NO_3Si$: C, 59.36; H, 8.83; N, 4.95. Found: C, 59.22; H, 8.57; N, 5.00.

Ethyl 2-Formamido-5-(phenylthio)pent-4-enoate (5a). Compound **5a** was prepared according to the procedure described for the preparation of formyl **3a** starting from *N*-(diphenylmethylene)glycine ethyl ester (8.8 mmol). Flash chromatography (Hex/EtOAc, 1:1) of the product gave the title compound **5a** (60%, 2 steps); IR (neat) 1741, 1669, 1691, 3350 cm^{-1}; ^1H NMR δ 1.27 (t, J = 7.15 Hz, 3H), 2.51 (br dd, J = 8.00, 7.4 Hz, 2H), 3.48 (dd, J = 13.96, 6.52 Hz, 1H), 3.55 (dd, J = 13.95, 7.49 Hz, 1H), 4.19 (q, J = 7.16 Hz, 2H), 4.65 (dt, J = 8.00, 4.75 Hz, 1H), 5.34 (dt, J = 15.0, 7.4 Hz, 1H), 5.57 (dt, J = 15.0, 7.6 Hz, 1H), 5.66 (br d, 1H), 7.20–7.32 (m, 5H), 7.98 (s, 1H). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.43; H, 6.48; N, 4.78; S, 10.92. Found: C, 16.58; H, 6.75; N, 4.84; S, 10.63.

***tert*-Butyl 2-Isocyanopent-4-enoate (6a).** To a cold solution (0 °C) of formyl **3a** (545 mg, 2.7 mmol) in CH_2Cl_2 (6 mL) were added diisopropylamine (1.4 mL, 9.45 mmol) and phosphoryl chloride (0.3 mL, 3 mmol). The solution was stirred at 0 °C for 1 h and was poured into ice-water (37 g) containing $NaHCO_3$ (3.7 g). After stirring for 2 h , water (30 mL) and CH_2Cl_2 (30 mL) were added, the organic layer was separated, washed with water (3 × 10 mL) and dried (Na_2SO_4). The solvent was evaporated and flash chromatography (Hex/EtOAc, 4:1) of the residue afforded the title compound **6a** (456 mg, 93% yield); IR (neat) 2148, 1750 cm^{-1}; ^1H NMR δ 1.50 (s, 9H), 2.62 (m, 2H), 4.20 (dd, J = 7.06, 5.21 Hz, 1H), 5.25 (m, 2H), 5.81 (dddd, J = 17.14, 9.97, 7.10, 7.10 Hz, 1H). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.30; H, 8.29; N, 7.73. Found: C, 66.80; H, 8.30; N, 7.69.

Ethyl 2-Isocyanopent-4-enoate (6b). Compound **6b** was prepared from *N*-(diphenylmethylene)glycine ethyl ester (10 mmol) according to the procedures described for the preparation of formyl **3a** and isocyanide **6a**. Flash chromatography (Hex/EtOAc, 4:1) of the formylated product afforded the title compound **6b** (30%, 3 steps); IR (neat) 2149, 1755 cm^{-1}; ^1H NMR δ 1.31 (t, J = 7.15 Hz, 3H), 2.64–2.70 (m, 2H), 4.28 (q, J = 7.15 Hz, 2H), 4.31 (t, J = 5.17 Hz, 1H), 5.24–5.29 (m, 2H), 5.76–5.86 (m, 1H). Anal. Calcd for $C_8H_{11}NO_2$: C, 62.74; H, 7.19; N, 9.14. Found: C, 62.53; H, 7.08; N, 9.14.

Ethyl 2-Isocyano-5-methylhex-4-enoate (6c). Compound **6c** was prepared from formyl **3c** (498 mg, 2.5 mmol) according to the procedure described for the preparation of isocyanide **6a**. Flash chromatography (Hex/EtOAc, 8:2) of the product gave isocyanide **6c** (381 mg, 84%); IR (neat) 2149, 1757 cm^{-1}; ^1H NMR δ 1.32 (t, J = 7.14 Hz, 3H), 1.67 (s, 3H), 1.76 (s, 3H), 2.65 (dd, J = 6.7, 6.7 Hz, 2H), 4.24 (t, J =6.33 Hz, 1H), 4.27 (q, J = 7.14 Hz, 2H), 5.18 - 5.14 (m, 1H). Anal. Calctd for $C_9H_{15}NO_2$: C, 66.27; H, 8.34. Found: C, 66.58; H, 8.31.

***tert*-Butyl 2-Isocyano-4-methylpent-4-enoate (6d).** To a cold solution (0 °C) of formyl **3d** (1.46 g, 6.9 mmol) in CH_2Cl_2 (60 mL) were added triethylamine (3.4 mL, 24.2 mmol) and phosphoryl chloride (0.7 mL, 7.6 mmol). Stirring was continued at 0 °C for 2.5 h. The reaction mixture was poured into ice-water (86 g) containing $NaHCO_3$ (8.6 g). After stirring for 2 h , CH_2Cl_2 (200 mL) was added, the organic layer was separated, washed with water (3 × 25 mL) and dried (Na_2SO_4). The solvent was evaporated and flash chromatography (Hex/EtOAc, 4:1) of the residue afforded the title compound **6d** (1.28 mg, 96% yield); IR (neat) 2150, 1751 cm^{-1}; ^1H NMR δ 1.50 (s, 9H), 1.79 (s, 3H), 2.56 (dd, J = 14.2, 8.69 Hz, 1H), 2.62 (dd, J = 14.2, 5.26 Hz, 1H), 4.27 (dd, J = 8.68, 5.45 Hz, 1H), 4.97 (s, 1H), 4.98 (s, 1H).

***tert*-Butyl 2-Isocyano-5-(*tert*-butyldiphenylsilyl)pent-4-ynoate (7a).** Compound was prepared from formyl **4a** (905mg, 2.1 mmol) according to the procedure described for the preparation of isocyanide **6d**. Flash chromatography (Hex/EtOAc, 7:3) of the product afforded the title compound **7a** (744 mg, 85% yield); IR (neat) 2184, 2150, 1755 cm^{-1}; ^1H NMR δ 1.09 (s, 9H), 1.47 (s, 9H), 3.07 (d, J = 6.04 Hz, 2H), 4.37 (t, J = 5.87 Hz, 1H), 7.34–7.38 (m, 6H), 7.77–7.79 (m, 4H). Anal. Calcd for $C_{26}H_{31}NO_2Si$: C, 74.82; H, 7.43; N, 3.36. Found: C, 74.42; H, 7.52; N, 3.46.

Ethyl 2-Isocyano-5-(*tert*-butyldiphenylsilyl)pent-4-ynoate (7b). Compound **7b** was prepared from formyl **4b** (2.7g, 6.6mmol) according to the procedure described for the preparation of isocyanide **6d**. Flash chromatography (Hex/EtOAc, 7:3) of the product afforded the title compound **7b** (2.5 g, 96% yield); IR (neat) 2185, 2151, 1759, 1747 cm^{-1}; ^1H NMR δ 1.09 (s, 9H), 1.26 (t, J = 7.09 Hz, 3H), 3.08 (d, J = 5.91 Hz, 2H), 4.27 (q, J = 7.11Hz, 2H), 4.48 (t, J = 5.91 Hz, 1H), 7.35–7.40 (m, 6H), 7.76–7.79 (m, 4H). Anal. Calcd for $C_{24}H_{27}NO_2Si$: C, 74.04; H, 6.94; N, 3.60. Found: C, 74.14; H, 6.92; N, 3.78.

Ethyl 2-Isocyano-5-(*tert*-butyldimethylsilyl)pent-4-ynoate (7c). Compound **7c** was prepared from formyl **4c** (726mg, 2.3mmol) according to the procedure described for the preparation of isocyanide **6d**. Flash chromatography (Hex/EtOAc, 7:3) of the product afforded the title compound **7c** (580 mg, 95% yield); IR (neat) 2183, 2151, 1755 cm^{-1}; ^1H NMR δ 0.10 and 0.11 (two s, 6H), 0.94 (s, 9H), 1.34 (t, J = 7.14 Hz, 3H), 2.90 (d, J = 6.03 Hz, 2H), 4.30 (q, J = 7.14 Hz, 2H), 4.38 (t, J = 6.07 Hz, 1H). Anal. Calcd for $C_{14}H_{23}NO_2Si$: C, 63.39; H, 8.67; N, 5.25. Found: C, 63.64; H, 8.63; N, 5.05.

Ethyl 2-Isocyano-5-(phenylthio)hex-4-enoate (8a). Compound **8a** was prepared from formyl **5a** (136 mg, 0.464 mmol) according to the procedure described for the preparation of isocyanide **6a**. Flash chromatography of the product (Hex/EtOAc, 7:3) gave isocyanide **8a** (100mg, 75%); IR (neat) 2149, 1750 cm^{-1}; ^1H NMR δ 1.29 (t, J = 7.1, 3H), 2.62 - 2.54 (m, 2H), 3.54 (d, J = 7.0 Hz, 2H), 4.17 (dd, J = 7.49, 5.00 Hz, 1H), 4.23 (q, J = 7.1, 2H), 5.53 (dtt, J = 15.15, 7.17, 1.2 Hz, 1H), 5.75 (dtt, J = 15.16, 6.94, 1.2 Hz, 1H), 7.35 - 7.18 (m, 5H).

2*H*-Pyrrole-2-carboxylic Acid, 3,4-Dihydro-4-methyl-5-(phenylthio), *tert*-Butyl Esters (11k/12k). *Procedure A.* A solution of isocyanide **6a** (242 mg, 1.3 mmol), benzenethiol (0.18 mL, 1.43 mmol), and AIBN (40 mg, 0.19 mmol) in dry toluene (65 mL) was stirred at 110 °C for 1 h. The solvent

was evaporated and flash chromatography (Hex/EtOAc, 4:1) of the residue afforded a mixture of the title compounds **11k/12k** (288.5 mg, 74% yield; **11k/12k**, 1:1.1). *Procedure B.* To a solution of isocyanide **6a** (163.5 mg, 0.9 mmol) in dry toluene (30 mL) at 110 °C was added a solution of AIBN (30 mg, 0.02 mmol) and benzenethiol (0.12 mL, 0.99 mmol) in dry toluene (10 mL) during 1 h. When TLC indicated the complete consumption of starting material (~1 h) the solvent was evaporated. Flash chromatography (Hex/EtOAc, 4:1) of the residue afforded a mixture of the title compounds **11k/12k** (79 mg, 30% yield; **11k/12k**, 1:1.2): IR (neat) 1734, 1593 cm^{-1}; ^1H NMR of **11k**: δ 1.29 (d, J = 7.18 Hz, 3H), 1.46 (s, 9H), 1.73 (ddd, J = 12.82, 6.35, 6.35 Hz, 1H), 2.53 (ddd, J = 12.96, 9.00, 9.00 Hz, 1H), 2.9–3.1 (m, 1H), 4.49 (ddd, J = 8.78, 6.17, 0.95 Hz, 1H), 7.36–7.61 (m, 5H); ^1H NMR of **12k**: δ 1.27 (d, J = 7.19 Hz, 3H), 1.46 (s, 9H), 1.86 (ddd, J = 12.92, 8.60, 6.66 Hz, 1H), 2.34 (ddd, J = 12.96, 8.47, 4.68 Hz, 1H), 3.1–3.2 (m, 1H), 4.58 (ddd, J = 8.60, 4.84, 1.31 Hz, 1H), 7.36–7.61 (m, 5H).

2*H*-Pyrrole-2-carboxylic Acid, 3,4-Dihydro-4-methyl-5-(ethylthio), *tert*-Butyl Esters (11l/12l). A solution of isocyanide **6a** (170 mg, 0.94 mmol), ethanethiol (0.11 mL, 1.31 mmol), and AIBN (30 mg, 0.14 mmol) in dry toluene (55 mL) was stirred at 110 °C in a sealed tube for 1.5 h. The solvent was evaporated and flash chromatography ($CHCl_3$) of the residue afforded a mixture of the title compounds **11l/12l** (196 mg, 83% yield; **11l/12l**, 1.4:1); IR (neat) 1735, 1582 cm^{-1}; ^1H NMR of **11l**: δ 1.21 (d, J = 7.14 Hz, 3H), 1.34 (t, J = 7.41 Hz, 3H), 1.48 (s, 9H), 1.65 (ddd, J = 12.84, 7.33, 7.32 Hz, 1H), 2.53 (ddd, J = 12.80, 8.66, 8.65 Hz, 1H), 2.86–3.23 (m, 3H),4.46 (ddd, J = 8.40, 7.22, 1.18 Hz, 1H); ^1H NMR of **12l**: δ 1.17 (d, J = 7.19 Hz, 3H), 1.35 (t, J = 7.39 Hz, 3H),1.46 (s, 9H), 1.85 (ddd, J = 12.88, 8.60, 7.19 Hz, 1H), 2.33 (ddd, J = 12.92, 8.52, 4.40 Hz,1H), 2.86–3.23 (m, 3H), 4.62 (ddd, J = 8.70, 4.44, 1.09 Hz, 1H). Anal. Calcd for $C_{12}H_{21}NO_2S$: C, 59.26; H, 8.64; N, 5.76; S, 13.17. Found:C, 59.52; H, 8.94; N, 5.74; S, 12.95.

2*H*-Pyrrole-2-carboxylic Acid, 3,4-Dihydro-4-methyl-5-(ethylthio), Ethyl Esters (11m/12m). Cyclization of isocyanide **6b** (218 mg, 1.4 mmol) was performed according to the procedure described for the preparation of compounds **11l/12l** but at 40 °C. Flash chromatography ($CHCl_3$) of the products afforded a mixture of the title compounds **11m/12m** (259 mg, 85% yield; **11m/12m**, 1.2:1); IR (neat) 1735, 1580 cm^{-1}; ^1H NMR δ 1.19 (d, J = 7.16 Hz, 3H), 1.23 (d, J = 7.08 Hz, 3H), 1.28 (t, J = 7.12 Hz, 3H), 1.29 (t, J = 7.12 Hz, 3H), 1.35 (t, J = 7.40 Hz, 3H), 1.36 (t, J = 7.40 Hz, 3H), 1.74 (ddd, J = 12.80, 8.10, 7.96 Hz, 1H, **11m**), 1.89 (m, 1H, **12m**), 2.41 (ddd, J = 12.81, 8.54, 4.27 Hz, 1H, **12m**), 2.55 (ddd, J = 12.82, 8.54, 8.54 Hz, 1H, **11m**), 2.93–3.14 (m, 3H), 4.19 (q, J = 7.16 Hz, 2H), 4.22 (qd, J = 7.15, 2.25 Hz, 2H), 4.55 (dd, J = 7.74, 7.67 Hz, 1H, **11m**), 4.73 (dd, J = 8.62, 4.45 Hz, 1H, **12m**). Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.78; H, 7.96; N, 6.50; S, 14.89. Found: C, 55.81; H, 8.20; N, 6.44; S, 14.42.

2*H*-Pyrrole-2-carboxylic Acid, 3,4-Dihydro-4-isopropyl-5-(ethylthio), Ethyl Esters (11n/12n). Cyclization of isocyanide **6c** (144 mg, 0.79 mmol) was performed according to the procedure described for the preparation of compounds **11l/12l** but at 40 °C. Flash chromatography ($CHCl_3$) of the products afforded a mixture of the title compounds **11n/12n** (161 mg, 83% yield; **11n/12n**, 1.4:1); IR (neat) 1737, 1586 cm^{-1}; ^1H NMR of **11n**: δ 0.79 (d, J = 6.74 Hz, 3H,), 0.95 (d, J = 6.87 Hz, 3H), 1.28 (t, J = 7.13 Hz, 3H), 1.37 (t, J = 7.4 Hz, 3H), 1.90 (ddd, J = 13.20, 7.96, 7.96 Hz, 1H), 2.29 (ddd, J = 13.16, 9.29, 9.28 Hz, 1H), 2.91–3.21 (m, 4H), 4.17–4.50 (m, 2H), 4.55 (ddd, J = 8.96, 7.54, 1.48 Hz, 1H); ^1H NMR of **12n**: δ 0.78 (d, J = 6.71 Hz, 3H), 0.96 (d, J = 6.87 Hz, 3H), 1.29 (t, J = 7.14 Hz, 3H), 1.34 (t, J = 7.40 Hz, 3H), 2.04–2.18 (m, 2H), 2.91–3.21 (m, 4H), 4.63 (ddd, J = 7.80, 5.98, 1.61 Hz, 1H). Anal. Calcd for $C_{12}H_{21}NO_2S$: C, 59.26; H, 8.64; N, 5.76. Found: C, 59.37; H, 8.93; N, 5.48.

2*H*-Pyrrole-2-carboxylic Acid, 3,4-dihydro-4-isopropyl-5-(((methoxycarbonyl)propyl)thio) Ethyl Esters (11o/12o). Cyclization of isocyanide **6c** (282 mg, 1.56 mmol) was performed according to the procedure described for the preparation of compounds **11l/12l**. Flash chromatography (Hex/EtOAc, 4:1) of the products afforded a mixture of the title compounds **11o/12o** (415 mg, 84% yield; **11o/12o**, 1:1); IR (neat) 1739, 1585 cm^{-1}; ^1H NMR of **11o**: δ 0.80 (d, J = 6.90 Hz, 3H), 0.95 (d, J = 6.88 Hz, 3H), 1.30 (t, J = 7.13 Hz, 3H), 1.91 (ddd, J = 13.18, 7.87, 8.00 Hz, 1H), 1.99–2.07 (m, 2H), 2.08 - 2.19 (m, 1H), 2.29 (ddd, J = 13.17, 9.45, 9.00 Hz, 1H), 2.45 (t, J = 7.47 Hz, 2H), 2.93 (dddd, J = 9.63, 8.51, 3.72, 1.68 Hz, 1H), 3.09 (dt, J = 13.12, 7.17 Hz, 1H), 3.19 (dt, J = 13.10, 7.06 Hz, 1H), δ 3.68 (s, 3H), 4.16–4.28 (m, 2H), 4.54 (ddd, J = 8.98, 7.66, 1.68 Hz, 1H); ^1H NMR of **12o**: δ 0.77 (d, J = 6.82 Hz, 3H), 0.95 (d, J = 6.88 Hz, 3H), 1.28 (t, J = 7.13 Hz, 3H), 1.98–2.16 (m, 1H), 1.98–2.04 (m, 2H), 2.44 (t, J = 7.51 Hz, 2H), 3.01 (dddd, J = 9.56, 6.03, 3.57, 1.64 Hz, 1H), 3.09 (dt, J = 13.16, 6.16 Hz, 1H), 3.15 (dt, J = 13.16, 7.13 Hz, 1H), 3.68 (s, 3H), 4.18 (q, J = 7.12 Hz, 2H), 4.60 (ddd, J = 8.73, 5.83, 1.65 Hz, 1H). Anal. Calcd for $C_{15}H_{25}NSO_4$: C, 57.14; H, 7.94; N, 4.44. Found: C, 56.84; H, 8.12; N, 4.35.

2*H*-Pyrrole-2-carboxylic Acid, 3,4-Dihydro-4-dimethyl-5-(phenylthio), *tert*-Butyl Ester (11p). Cyclization of isocyanide **6d** (390 mg, 2 mmol) was performed according to the procedure described for the preparation of compounds **11l/12l** but using benzenethiol instead of ethanethiol. Flash chromatography (Hex/EtOAc, 4:1) of the product afforded the title compound **11p** (178 mg, 30% yield); IR (neat) 1737, 1590 cm^{-1}; ^1H NMR δ 1.27 (s, 3H), 1.35 (s, 3H), 1.46 (s, 9H), 2.02 (dd, J = 12.80, 6.26 Hz, 1H), 2.18 (dd, J = 12.80, 8.60 Hz, 1H), 4.49 (dd, J = 8.60, 6.26 Hz, 1H), 7.32–7.39 (m, 3H), 7.58–7.61 (m, 2H); ^{13}C NMR δ 23.3, 27.1, 27.3, 28.7, 44.1, 56.6, 72.0, 81.6, 129.4, 129.7, 134.8, 172.9. Anal. Calcd for $C_{17}H_{23}NO_2S$: C, 66.88; H, 7.54; N, 4.59; S, 10.49. Found: C, 66.93; H, 7.64; N, 4.54; S, 10.45.

2*H*-Pyrrole-2-carboxylic Acid, 3,4-Dihydro-4-dimethyl-5-(ethylthio), *tert*-Butyl Ester (11q). Cyclization of isocyanide **6d** (294 mg, 1.5 mmol) was performed according to the procedure described for the preparation of compounds **11l/12l** but at 40 °C for 3.5 h. Flash chromatography (Hex/EtOAc, 4:1) of the product afforded the title compound **11q** (214 mg, 56% yield); IR (neat) 1739, 1588 cm^{-1}; ^1H NMR δ 1.17 (s, 3H), 1.22 (s, 3H), 1.33 (t, J = 7.56 Hz, 3H), 1.47 (s, 9H), 1.95 (dd, J = 12.70, 6.97 Hz, 1H), 2.16 (dd, J = 12.64, 8.41 Hz, 1H), 2.94–3.02 (m, 1H), 3.04–3.14 (m, 1H), 4.51 (dd, J = 8.88, 7.00 Hz, 1H). Anal. Calcd for $C_{13}H_{23}NO_2S$: C, 60.70; H, 8.95; N, 5.45; S, 12.45. Found: C, 60.92; H, 9.07; N, 5.70; S, 12.12.

2*H*-Pyrrole-2-carboxylic Acid, 3,4-Dihydro-4-isopropyl-5-(((methoxycarbonyl)methyl)thio), Ethyl Esters (11r/12r). A solution of isocyanide **6c** (90 mg, 0.5 mmol), methyl mercaptoacetate (56 mg, 0.55 mmol) and AIBN (16mg, 0.1 mmol) in toluene (25 mL) was cooled to −60 °C under argon atmosphere by means of CH_2Cl_2/dry ice cooling bath. The solution was irradiated with Hanovia lamp for 9 h and then the solvent was evaporated. Flash chromatography (Hex/EtOAc, 8:2) afforded a mixture of the title compounds **11r/12r** (112 mg, 78% yield; **11r/12r**, 1:1), isothiocyanate **13c** (2 mg, 2%), and starting isocyanide **6c** (4 mg, 4%); IR (neat): 1740, 1591 cm^{-1}; ^1H NMR of **11r**: δ 0.83 (d, J = 7.46 Hz, 3H), 0.96 (d, J = 6.85 Hz, 3H), 1.29 (t, J = 4.18 Hz, 3H), 1.94 (ddd, J = 13.16, 8.22, 8.03 Hz, 1H), 2.07–2.27 (m, 1H), 2.31 (ddd, J = 13.17, 9.33, 9.04 Hz, 1H), 2.99 (dddd, J = 9.60, 8.57, 3.77, 1.78 Hz, 1H), 3.74 (s, 3H), 3.95 and 3.91 (two d, J = 16.07 Hz, 2H), 4.15–4.25 (m, 2H), 4.53 (ddd, J = 8.99, 7.78, 1.76 Hz, 1H); ^1H NMR of**12r**: δ 0.81 (d, J = 6.85 Hz, 3H), 0.97 (d, J = 6.87 Hz, 3H), 1.28 (t, J = 4.13 Hz, 3H), 2.07–2.27 (m, 1H), 2.07 - 2.21 (m, 2H), 3.05 - 3.10 (m, 1H), 3.73 (s, 3H), 3.89 and 3.96 (two d, J = 16.05 Hz, 2H), 4.15–4.25 (m, 2H), 4.61 (ddd, J = 8.74, 5.95, 1.73 Hz, 1H). Anal. Calcd for $C_{13}H_{21}NO_4S$: C, 54.33; H, 7.37; N, 4.87; S, 11.16. Found: C, 54.62; H, 7,33; N, 4.89; S, 10.86.

***tert*-Butyl *cis*-4-Methyl-5-oxopyrrolidine-2-carboxylate (16) and *tert*-Butyl *trans*-4-Methyl-5-oxopyrrolidine-2-carboxylate (17).** Cyclization of isocyanide **6a** (261 mg, 1.4 mmol) was performed according to the procedure described for the preparation of compounds **11l/12l** but using mercaptoethanol instead of ethanethiol at 40 °C. Flash chromatography (Hex/EtOAc, 1:1) of the products afforded the title compounds **16/17** (200 mg, 72% yield; **16/17**, 1:2.5); *cis* isomer **16**: mp 87 °C (Hex); IR (nujol) 3198, 1742, 1699 cm^{-1}; ^1H NMR δ 1.23 (d, J = 7.12 Hz, 3H), 1.49 (s, 9H), 1.76 (ddd, J = 12.72, 9.24, 8.22

Hz, 1H), 2.50 (ddq, J = 8.88, 8.88, 7.16 Hz, 1H), 2.66 (ddd, J = 12.76, 8.20, 8.20 Hz, 1H), 4.09 (dd, J = 7.9, 7.9 Hz, 1H), 6.09 (br s, 1H). Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.29; H, 8.54; N, 7.03. Found: C, 60.39; H, 8.20; N, 7.16; *trans* isomer **17**: mp 97.5 °C (Hex); IR (nujol) 3258, 1735, 1707,1662 cm^{-1}; ^{1}H NMR δ 1.22 (d, J = 6.91 Hz, 3H), 1.47 (s, 9H), 2.04 (ddd, J = 12.52, 8.55, 8.55 Hz, 1H), 2.48 (ddd, J = 12.46, 8.94, 3.28 Hz, 1H), 2.51 (ddq, J = 8.53, 8.53, 6.98 Hz, 1H), 4.05 (ddd, J = 8.99, 3.05, 0.74 Hz, 1H), 6.17 (br s, 1H); ^{13}C NMR δ 16.5, 28.6, 34.2, 35.1, 54.8, 83.0, 172.0, 180.9. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.29; H, 8.54; N, 7.03. Found: C, 59.89; H, 8.28; N, 6.84.

2*H*-Pyrrole-2-carboxylic Acid, 3,4-Dihydro-4-((*tert*-butyldiphenylsilyl)methylidene)-5-(ethylthio), *tert*-Butyl Ester (18k). Cyclization of isocyanide **7a** (246 mg, 0.59 mmol) was performed according to the procedure described for the preparation of compounds **11l/12l**. Flash chromatography (Hex/EtOAc, 7:3) of the product afforded the title compound **18k** (200.5 mg, 72% yield); IR (neat) 1734, 1705, 1615, 1547 cm^{-1}; ^{1}H NMR δ 1.07 (s, 9H), 1.33 (s, 9H), 1.40 (t, J = 7.38 Hz, 3H), 2.03 (ddd, J = 18.11, 3.22, 3.22 Hz, 1H), 2.19 (ddd, J = 18.09, 8.13, 2.79 Hz, 1H), 3.09 (dq, J = 13.86, 7.38 Hz, 1H), 3.23 (dq, J = 13.85, 7.36 Hz, 1H), 4.46 (dd, J = 8.16, 3.55 Hz, 1H), 6.39 (m, 1H), 7.33−7.40 (m, 6H), 7.62−7.72 (m, 4H). Anal. Calcd for $C_{28}H_{37}NO_2SSi$: C, 70.15; H, 7.72; N, 2.92. Found: C,70.30; H, 7.66; N, 2.68.

2*H*-Pyrrole-2-carboxylic Acid, 3,4-Dihydro-4-((*tert*-butyldiphenylsilyl)methylidene)-5-(ethylthio), Ethyl Ester (18l). Cyclization of isocyanide **7b** (2.5 g, 6.4 mmol) was preformed according to the procedure described for the preparation of compounds **11l/12l**. Flash chromatography (Hex/EtOAc, 4:1) of the product afforded the title compound **18l** (2 g,70% yield); IR(neat) 1738, 1616,1546 cm^{-1}; ^{1}H NMR δ 1.07 (s, 9H), 1.17 (t, J = 7.13 Hz, 3H), 1.41 (t, J = 7.40 Hz, 3H), 2.16 (ddd, J = 17.94, 4.32, 2.66 Hz, 1H), 2.22 (ddd, J = 17.96, 7.45, 2.70 Hz, 1H), 3.11−3.16 (m, 1H), 3.21−3.24 (m, 1H), 4.08 (q, J = 7.11 Hz, 2H), 4.54 (dd, J = 7.42, 4.34 Hz, 1H), 6.44 (m, 1H), 7.36−7.38 (m, 6H), 7.61−7.63 (m, 4H). Anal. Calcd for $C_{26}H_{33}NO_2SSi$: C, 69.18; H, 7.32; N, 3.10; S, 7.09. Found: C, 69.30; H, 7.36; N, 3.40; S, 6.91.

2*H*-Pyrrole-2-carboxylic Acid, 3,4-Dihydro-4-((*tert*-butyldiphenylsilyl)methylidene)-5-(((methoxycarbonyl)-ethyl)thio), Ethyl Ester (18m). Cyclization of isocyanide **7b** (526 mg, 1.35 mmol) was performed according to the procedure described for the preparation of compounds **11l/12l** but using methyl 3-mercaptopropionate instead of ethanethiol. Flash chromatography (Hex/EtOAc, 8.5:1.5) of the product afforded the title compound **18m** (396 mg, 60% yield); IR (neat) 1739, 1609, 1546 cm^{-1}; ^{1}H NMR δ 1.07 (s, 9H), 1.19 (t, J = 7.13 Hz, 3H), 2.16 (ddd, J = 17.97, 4.43, 2.73 Hz, 1H), 2.21 (ddd, J = 17.95, 7.22, 2.71 Hz, 1H), 2.86 (m, 2H), 3.36 (ddd, J = 13.65, 6.89, 6.89 Hz, 1H), 3.43 (ddd, J = 13.58, 6.82, 6.82 Hz, 1H), 3.73 (s, 3H), 4.09 (q, J = 7.16 Hz, 2H), 4.53 (dd, J = 7.24, 4.51 Hz, 1H), 6.39 (app t, J = 2.66 Hz, 1H), 7.34−7.42 (m, 6H), 7.62−7.66 (m, 4H). Anal. Calcd for $C_{28}H_{35}NO_4SSi$: C, 66.01; H, 6.87; N, 2.75; S, 6.28. Found: C, 66.31; H, 6.86; N, 2.43; S, 6.46.

2*H*-Pyrrole-2-carboxylic Acid, 3,4-Dihydro-4-((*tert*-butyldimethylsilyl)methylidene)-5-(ethylthio), Ethyl Ester (18n). Cyclization of isocyanide **7c** (178 mg, 0.67 mmol) was performed according to the procedure described for the preparation of compounds **11l/12l**. Flash chromatography (Hex/EtOAc, 8.5:1.5) of the product afforded the title compound **18n** (165 mg, 90% yield); IR (neat) 1740, 1615, 1547 cm^{-1}; ^{1}H NMR δ 0.13 (s, 6H), 0.92 (s, 9H), 1.30 (t, J = 7.13 Hz, 3H), 1.37 (t, J = 7.40 Hz, 3H), 2.85 (ddd, J = 17.20, 4.42, 2.74 Hz, 1H), 2.94 (ddd, J = 17.25, 7.90, 2.62 Hz, 1H), 3.08 (dq, J = 12.90, 7.40 Hz, 1H), 3.18 (dq, J = 12.92, 7.40 Hz, 1H), 4.23 (q, J = 7.14 Hz, 2H), 4.70 (dd, J = 7.92, 4.42 Hz, 1H), 5.99 (app t, J = 2.66, 1H). Anal. Calcd for $C_{16}H_{29}NO_2SSi$: C, 58.71; H, 8.86; N, 4.28; S, 9.78. Found: C, 58.56; H, 8.57; N, 4.28; S, 9.36.

Ethyl 4-((*tert*-Butyldiphenylsilyl)methylidene)-5-oxopyrrolidine-2-carboxylate (19b). Cyclization of isocyanide **7b** (633 mg, 1.62 mmol) was performed according to the procedure described for the preparation of compounds **11l/12l**. Flash chromatography (Hex/EtOAc, 7:3) of the product afforded the title compound **19b** (551 mg, 84% yield); mp 76 °C (Hex/CH_2Cl_2); IR (neat) 3199, 3097, 1748, 1701, 1623 cm^{-1}; ^{1}H NMR δ 1.08 (s, 9H, $C(CH_3)_3$), 1.16 (t, J = 7.14 Hz, 3H, CH_3), 2.23 (ddd, J = 18.42, 3.15, 3.15 Hz, 1H), 2.45 (ddd, J = 18.40, 9.22, 2.90 Hz, 1H), 4.00 (ddd, J = 9.38, 3.90, 0.52 Hz, 1H), 4.09 (q, J = 7.13 Hz, 2H), 6.19 (br s, 1H), 7.19 (m, 1H), 7.35−7.43 (m, 6H), 7.63−7.66 (m, 4H); ^{13}C NMR δ 14.7, 14.8, 19.0, 52.8, 62.3, 126.6, 127.7, 128.6, 130.3, 133.5, 133.6, 136.6, 136.7, 148.1, 170.0, 172.0.

Ethyl 4-((*tert*-Butyldimethylsilyl)methylidene)-5-oxopyrrolidine-2-carboxylate (19c). Cyclization of isocyanide **7c** (213 mg, 0.80 mmol) was performed according to the procedure described for the preparation of compounds **11l/12l** but using mercaptoethanol instead of ethanethiol. Flash chromatography (Hex/EtOAc, 1:1) of the product afforded the title compound **19c** (186 mg, 81%); IR(neat) 3193, 1748, 1701 cm^{-1}; ^{1}H NMR δ 0.15 (s, 6H), 0.92 (s, 9H), 1.31 (t, J = 7.14 Hz, 3H), 2.97 (ddd, J = 17.63, 4.33, 2.79 Hz, 1H), 3.20 (ddd, J = 9.21, 4.37, 0.69 Hz, 1H), 4.24 (q, J = 7.15 Hz, 2H), 4.26 (ddd, J = 9.21, 4.37, 0.69 Hz, 1H), 6.20 (br s, 1H). 6.75 (m, 1H). Anal. Calcd for $C_{14}H_{25}NO_3Si$: C, 59.33; H, 8.89; N, 4.94. Found: C, 59.65; H, 8.88; N, 4.60.

Ethyl 5-(*tert*-Butyldiphenylsilyl)-2-isothiocyano-pent-4-enoate (20b). Reaction of isocyanide **7b** (745 mg, 1.9 mmol) was performed according to the procedure described for the preparation of compounds **11l/12l** but using *tert*-dodecanethiol instead of ethanethiol. Flash chromatography (Hex/EtOAc, 4:1) of the product afforded the title compound **20b** (454 mg, 60% yield); IR (neat) 2183, 2074, 1748 cm^{-1}; ^{1}H NMR δ 1.10 (s, 9H), 1.29 (t, J = 7.14 Hz, 3H), 3.02 (dd, J = 16.98, 5.22 Hz, 1H), 3.07 (dd, J = 17.0, 6.03 Hz, 1H), 4.28 (two q, J = 7.14 Hz, 2H), 4.48 (dd, J = 6.0, 5.25 Hz, 1H), 7.38−7.41 (m, 6H), 7.79−7.82 (m, 4H); ^{13}C NMR δ 14.8, 19.2, 26.2, 27.7, 58.9, 63.7, 85.7 , 103.8, 128.4, 130.0, 130.2, 133.6, 133.7, 136.3, 140.2, 167.7. Anal. Calcd for $C_{24}H_{27}NO_2SSi$: C, 68.40; H, 6.41; N, 3.32; S, 7.60. Found: C, 68.82; H, 6.71; N, 3.28; S,8.03.

2*H*-Pyrrole-2-carboxylic Acid, 3,4-Dihydro-4-ethylidene-5-(phenylthio), Ethyl Ester (24). To a boiling solution of isocyanide **8a** (423 mg, 1.5 mmol) in toluene (75 mL), thiophenol (25 mg, 0.23 mmol), and AIBN (37 mg, 0.23 mmol) were added in 3 portions during 1 h. After an additional 30 min the solvent was evaporated. Flash chromatography (Hex/EtOAc, 7:3) resulted in thioimidate **24** (313 mg, 76%) and starting isocyanide **8a** (29 mg, 7%); IR (neat) 1736, 1549 cm^{-1}; ^{1}H NMR δ 1.27 (t, J = 7.1 Hz, 3H), 1.84 (d, J = 7.0 Hz, 3H), 2.79 - 2.97 (m, 2H), 4.18 (q, J = 7.1 Hz, 2H), 4.79 (dd, J = 8.6, 4.1 Hz, 1H), 6.20 −6.21 (m, 1H), 7.39−7.64 (m, 5H). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.45; H, 6.18; N, 5.09; S, 11.64. Found: C, 65.47; H, 6.40; N, 4.89; S, 11.75.

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Supplementary Material Available: ^{1}H NMR spectra for compounds **6c**, **6d**, **8a**, **11k/12k**, and **19b**, ^{13}C NMR for compound **19b**, and ORTEP drawing and details of X-ray data acquisition for *tert*-butyl *cis*-4-methyl-5-oxopyrrolidine-2-carboxylate (**16**) (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.