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Pyrrolidine-Forming 1,3-Dipolar Cycloaddition of *N*-(Phenylthiomethyl)-α-amino Acid Esters

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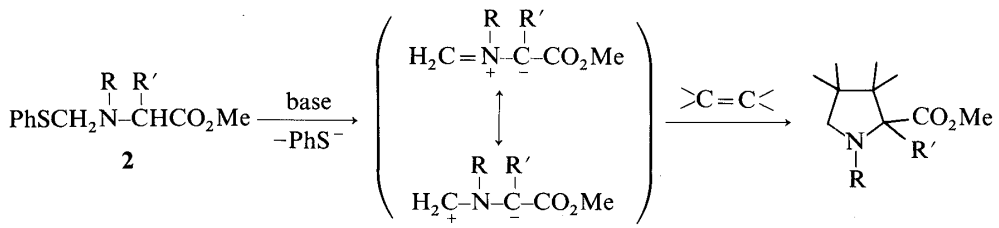
The sodium hydride-aided reaction of *N*-(phenylthiomethyl)-α-amino acid esters with α,β-unsaturated carboxylates results in a pyrrolidine-forming 1,3-dipolar cycloaddition. Thus, a new route to pyrrolidines, pyrrolizidines, and indolizidines has been provided.

Keywords——1,3-dipolar cycloaddition; *N*-(phenylthiomethyl)-α-amino acid ester; azomethine ylide; pyrrolidine; pyrrolizidine; indolizidine

The 1,3-dipolar cycloaddition of azomethine ylides[1] leading to alicyclic amines, five- and six-membered rings in particular, is of great synthetic interest because of the huge number of naturally occurring and physiologically active compounds that contain these ring systems.

As mentioned in the preliminary communication,[2] we found that the azomethine ylides (**1**) could be derived from *N*-phenylthiomethyl derivatives (**2**) of *N*-monosubstituted amino acid esters. It is considered that base treatment induces the release of phenylthiolate anion to form the azomethine ylide **1**, which then undergo 1,3-dipolar cycloaddition. We now wish to describe the details of this work.



2 **1**

N-Phenylthiomethyl derivatives of methyl esters of α-amino acids, *i.e.*, sarcosine, *N*-methylalanine, proline, and pipecolinic acid, were newly prepared by allowing the methyl esters to react with 35% aqueous formaldehyde and thiophenol in methanol under reflux. In addition, an *N*,*N*-bis(phenylthiomethyl) derivative of methyl glycinate was prepared by reaction with two molar equivalents of the reagents. The results and analytical data are summarized in Table I.

When methyl esters of *N*-phenylthiomethylated sarcosine and *N*-methylalanine were reacted with several olefinic dipolarophiles in the presence of sodium hydride in hexamethylphosphoramide (HMPA)-dimethoxyethane (DME), 1,3-dipolar cycloaddition proceeded smoothly to give pyrrolidines. The results are summarized in Table II. In most cases, the products were mixtures of regioisomers which were separated by silica gel column chromatography using diisopropyl ether–hexane as an eluent. The structures were determined on the

TABLE I. Preparation[a] of $PhSCH_2NCHCO_2Me$ (R on N, R′ on CH)

Compound No.	R	R′	Yield (%)	bp °C (mmHg) or mp °C (Recry. solv.)	Formula	Analysis (%) Calcd (Found) C	H	N
2a	CH_3	H	70	110—111 (0.1)	$C_{11}H_{15}NO_2S$	58.28 (58.65)	6.59 (6.71)	6.15 (6.22)
2b	CH_3	CH_3	70	111—113 (0.04)	$C_{12}H_{17}NO_2S$	60.24 (60.51)	7.16 (6.99)	5.85 (5.96)
2c	$-CH_2CH_2CH_2-$		84	119—120 (0.05)	$C_{13}H_{17}NO_2S$	62.14 (62.63)	6.82 (6.80)	5.57 (5.29)
2d	$-CH_2CH_2CH_2CH_2-$		53	142—143 (0.05)	$C_{14}H_{19}NO_2S$	63.38 (63.74)	7.22 (7.17)	5.28 (5.35)
2e	$PhSCH_2$	H	84	36—37 (Petr. ether)	$C_{17}H_{19}NO_2S_2$	61.25 (61.21)	5.75 (5.70)	4.20 (4.18)

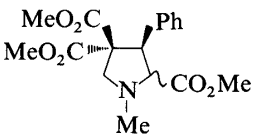
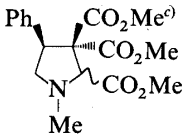
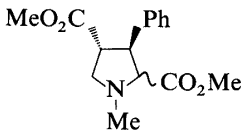
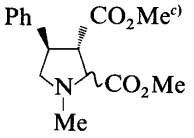
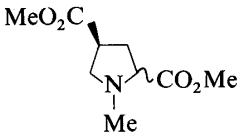
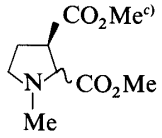
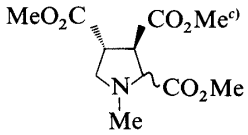
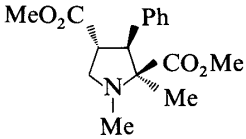
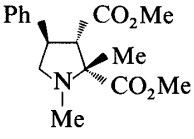
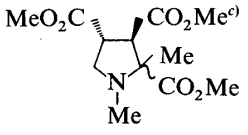
a) General procedures are given in Experimental.

basis of proton nuclear magnetic resonance (^{1}H-NMR) and ^{13}C-NMR spectral data (Table III).

The products **3a** and **3b** show ^{1}H-NMR spectra markedly different from that of **3c**; the signals of the C_2, C_3, and C_5 protons are suggestive of the indicated structures, since the methine protons on C_2 and C_3 of **3a** and **3b** are coupled with each other at 3.63 (d), 4.43 (d, $J=7.2$ Hz) and 3.50 (d), 4.54 ppm (d, $J=8.6$ Hz), respectively, whereas in the case of the compound **3c** only the methine proton on C_2 appears as a singlet at 4.14 ppm. Further, the methylene protons on C_5 of **3a** show AB coupling at 2.62 (d) and 4.29 ppm (d, $J=10.7$ Hz), and those of **3b** do so at 3.39 (d) and 3.70 ppm (d, $J=12.9$ Hz), whereas ABX coupling at 2.93 (dd, $J=9.1$, 10.5 Hz) and 4.52 ppm (dd, $J=7.1$, 10.5 Hz) is seen in the case of **3c**. The stereochemistry of the methoxycarbonyl groups of **3a** and **3b** was determined on the basis of the chemical shifts of the ester methyls. The signals of the ester methyl oriented *cis* to the phenyl group in the five-membered ring appear at higher magnetic field owing to the shielding effect of the phenyl group.[3] Shifts (0.4—0.5 ppm) of the signals of two ester methyls to higher field are observed in the case of **3a**, whereas only one ester methyl signal is shifted in the case of **3b**. In contrast to the normal cycloaddition which gives **3a** and **3b**, the formation of **3c** is considered to result from the resonance hybrid of the intermediary azomethine ylide [$H_2C=\overset{+}{N}-\overset{-}{C}-CO_2Me \leftrightarrow H_2C-\overset{+}{N}=C-CO_2Me$]. The structures of the products obtained in the other experiments were similarly determined. As can be seen in entries 4 and 6 (Table II), the dipolarophiles, dimethyl maleate and dimethyl fumarate, gave the same products, but in different yields. The product in entry 4 was an isomeric mixture (3/1), whereas that in entry 6 was a single isomer.

Next, *N*,*N*-bis(phenylthiomethyl)glycine methyl ester was reacted with methyl cinnamate (*E*-form) under similar conditions. The results are summarized in Chart 1. In this case, the *N*-phenylthiomethyl-substituted pyrrolidine first formed can react further as another source of the azomethine ylide to give the corresponding pyrrolizidines. As indicated in Chart 1, the use of 1 mol eq of methyl cinnamate gave the pyrrolidine product (**9**) together with **10a—c** in 26% total yield, whereas the use of 2 mol eq gave the pyrrolizidines (**10a—c**) as major products in 29% yield. Thus a fascinating one-pot synthetic method for pyrrolizidine has been found. The product obtained in the former case was a single isomer (**9**) which was assigned the indicated

TABLE II. Synthesis of Pyrrolidines[a)]

Entry	Olefin	Reaction conditions	Product[b)]	Yield (%)
i) In the case of *N*-(phenylthiomethyl)sarcosine methyl ester (**2a**)				
1	$PhCH=C(CO_2Me)_2$	Reflux 9 h	 **3a** (*cis*: 1.3) **3b** (*trans*: 1.2)  **3c** (1)	71
2	$PhCH=CHCO_2Me$ (*E*)	r.t. 1.5 h	 **4a** (*cis*: 7.5) **4b** (*trans*: 1)  **4c**:**4d** (3.7:1.7)	84
3	$H_2C=CHCO_2Me$	r.t. 24 h	 **5a** (3)  **5b**:**5c** (1:0.1)	47
4	$MeO_2CCH=CHCO_2Me$ (*E* or *Z*)	*E*: r.t., 4 h *Z*: r.t., 7 h	 **6a**:**6b** (3:1)	
ii) In the case of *N*-methyl-*N*-(phenylthiomethyl)alanine methyl ester (**2b**)				
5	$PhCH=CHCO_2Me$ (*E*)	r.t. 21 h	 **7a** (1)  **7b** (2)	62
6	$MeO_2CCH=CHCO_2Me$ (*E* or *Z*)	*E*: 45 °C, 4 h *Z*: r.t., 7 h	 **8**	*E*: 33 *Z*: 15

a) Molar proportions, substrate : olefin : sodium hydride : HMPA = 1 : 1.2 : 2 : 1; solvent, DME. *b*) The ratio of the isomers is indicated in parentheses. This was determined on the basis of the NMR spectral data. *c*) The stereochemistry of this compound is not clear.

structure on the basis of its infrared (IR), NMR, and mass spectral (MS) data. On the other hand, the pyrrolizidine products obtained with 2 mol eq of methyl cinnamate were shown to be composed of three isomers by gas chromatographic (GC) analysis. The three compounds showed similar GC/MS splitting patterns, with peaks of $M^+ - OMe$ at 406 (*m*/*z*) instead of

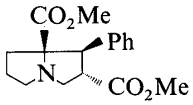
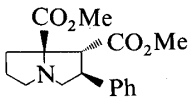
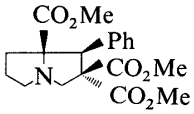
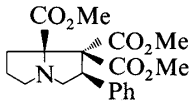
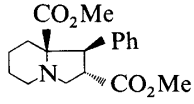
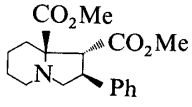
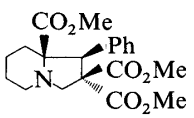
TABLE III. NMR Spectral Data for **4**—**8**

Compound No.	^{1}H-NMR δ ($CDCl_3$, J=Hz)	^{13}C-NMR δ ($CDCl_3$)
3a	2.42 (3H, s, NCH_3), 2.62 (1H, d, J=10.7, 5-CH_A), 3.10 (3H, s, OCH_3), 3.29 (3H, s, OCH_3), 3.63 (1H, d, J=7.2, 2-CH), 3.79 (3H, s, OCH_3), 4.29 (1H, d, J=10.7, 5-CH_B), 4.43 (1H, d, J=7.2, 3-CH), 7.12—7.41 (5H, m, C_6H_5)	41.4 (q, NCH_3), 51.1 (q, OCH_3), 51.9 (q, OCH_3), 53.0 (q, OCH_3), 54.1 (d, 3-C), 61.2 (t, 5-C), 63.7 (s, 4-C), 72.7 (d, 2-C), 127.4, 127.8, 129.7, 137.3 (d, d, d, s, C_6H_5), 168.4 (s, C=O), 170.2 (s, C=O), 171.7 (s, C=O)
3b	2.49 (3H, s, NCH_3), 3.10 (3H, s, OCH_3), 3.39 (1H, d, J=12.9, 5-CH_A), 3.50 (1H, d, J=8.6, 2-CH), 3.66 (3H, s, OCH_3), 3.70 (1H, d, J=12.9, 5-CH_B), 3.77 (3H, s, OCH_3), 4.54 (1H, d, J=8.6, 3-CH), 7.27 (5H, s, C_6H_5)	40.6 (q, NCH_3), 52.2 (q, OCH_3), 53.3 (q, 2× OCH_3), 54.3 (d, 3-C), 62.3 (t, 5-C), 64.9 (s, 4-C), 73.6 (d, 2-C), 127.8, 128.4, 129.3, 137.8 (d, d, d, s, C_6H_5), 169.0 (s, C=O), 171.1 (s, C=O), 172.1 (s, C=O)
3c	2.50 (3H, s, NCH_3), 2.93 (1H, dd, J=9.1, 10.5, 5-CH_A), 3.13 (3H, s, OCH_3), 3.39 (1H, dd, J=7.1, 9.1, 4-CH), 3.68 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 4.14 (1H, s, 2-CH), 4.52 (1H, dd, J=7.1, 10.5, 5-CH_B), 7.28 (5H, s, C_6H_5)	40.7 (q, NCH_3), 49.9 (d, 4-C), 52.4 (q, OCH_3), 53.0 (q, 2×OCH_3), 60.1 (t, 5-C), 69.0 (s, 3-C), 74.0 (d, 2-C), 127.7, 128.3, 129.3, 137.6 (d, d, d, s, C_6H_5), 169.2 (s, C=O), 169.4 (s, C=O), 171.4 (s, C=O)
4a	2.42 (3H, s, NCH_3), 2.68 (1H, t, J=7.3, 5-CH_A), 3.18 (3H, s, OCH_3), 3.31—3.73 (3H, m, 2-CH, 4-CH, 5-CH_B), 3.61 (3H, s, OCH_3), 3.98 (1H, dd, J=7.2, 9.2, 3-CH), 7.23 (5H, s, C_6H_5)	40.3 (q, NCH_3), 49.6 (d, 4-C), 50.9 (q, OCH_3), 51.1 (q, OCH_3), 51.9 (d, 3-C), 58.6 (t, 5-C), 73.0 (d, 2-C), 127.1, 128.2, 128.4, 140.0 (d, d, d, s, C_6H_5), 170.8 (s, C=O), 173.6 (s, C=O)
4b	2.44 (3H, s, NCH_3), 2.81—3.32 (2H, m, 4-CH, 5-CH_A), 3.24 (1H, d, J=8.3, 2-CH), 3.56 (1H, dd, J=3.3, 8.6, 5-CH_B), 3.68 (3H, s, $(OCH_3)_2$), 3.95 (1H, dd, J=6.6, 8.3, 3-CH), 7.28 (5H, s, C_6H_5)	40.3 (q, NCH_3), 50.7 (d, 4-C), 51.8 (q, OCH_3), 52.1 (q, OCH_3), 52.2 (d, 3-C), 58.5 (t, 5-C), 75.3 (d, 2-C), 127.2, 127.6, 128.7, 141.3 (d, d, d, s, C_6H_5), 172.2 (s, C=O), 173.4 (s, C=O)
4c	2.47 (3H, s, NCH_3), 2.67 (1H, t, J=8.8, 5-CH_A), 3.18—3.55 (3H, m, 2-CH, 4-CH, 5-CH_B), 3.62 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.94 (1H, t, J=7.6, 3-CH), 7.29 (5H, s, C_6H_5)	40.1 (q, NCH_3), 46.5 (d, 3-C), 51.7 (q, OCH_3), 52.0 (q, OCH_3), 55.0 (d, 4-C), 62.8 (t, 5-C), 69.9 (d, 2-C), 126.9, 127.4, 128.7, 141.8 (d, d, d, s, C_6H_5), 171.2 (s, C=O), 172.0 (s, C=O)
4d	2.44 (3H, s, NCH_3), 2.84—3.57 (5H, m, 2-CH, 3-CH, 4-CH, 5-CH_2), 3.64 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 7.12—7.48 (5H, m, C_6H_5)	40.5 (q, NCH_3), 47.0 (d, 3-C), 51.9 (q, OCH_3), 52.0 (q, OCH_3), 56.6 (d, 4-C), 63.2 (t, 5-C), 70.9 (d, 2-C), 126.8, 127.4, 128.6, 143.4 (d, d, d, s, C_6H_5), 172.1 (s, C=O), 173.1 (s, C=O)
5a	2.44 (3H, s, NCH_3), 1.99—2.64, 2.99—3.38 (6H, m, 2-CH, 3-CH_2, 4-CH, 5-CH_2), 3.72 (3H, s, OCH_3), 3.76 (3H, s, OCH_3)	28.0 (t, 3-C), 40.9 (q, NCH_3), 47.5 (d, 4-C), 52.2 (q, $(OCH_3)_2$), 55.7 (t, 5-C), 70.2 (d, 2-C), 172.6 (s, C=O), 174.2 (s, C=O)
5b	2.40 (3H, s, NCH_3), 2.17—2.70, 2.89—3.52 (6H, m, 2-CH, 3-CH, 4-CH_2, 5-CH_2), 3.70 (3H, s, OCH_3), 3.74 (3H, s, OCH_3)	32.9 (t, 4-C), 40.5 (q, NCH_3), 41.4 (d, 3-C), 51.9 (q, $(OCH_3)_2$), 58.2 (t, 5-C), 67.3 (d, 2-C), 173.0 (s, C=O), 174.1 (s, C=O)
5c	2.42 (3H, s, NCH_3), 2.17—2.70, 2.89—3.52 (6H, m, 2-CH, 3-CH, 4-CH_2, 5-CH_2), 3.70 (3H, s, OCH_3), 3.74 (3H, s, OCH_3)	32.5 (t, 4-C), 40.5 (q, NCH_3), 41.6 (d, 3-C), 52.1 (q, $(OCH_3)_2$), 58.8 (t, 5-C), 66.9 (d, 2-C), 173.2 (s, C=O), 174.4 (s, C=O)
6a	2.40 (3H, s, NCH_3), 2.77 (1H, dd, J=9.2, 10.4, 5-CH_A), 3.31—3.45 (4H, m, 2-CH, 3-CH, 4-CH, 5-CH_B), 3.67 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.75 (3H, s, OCH_3)	40.3 (q, NCH_3), 45.3 (d, 3-C), 50.1 (d, 4-C), 52.1 (q, OCH_3), 52.4 (q, $(OCH_3)_2$), 58.0 (t, 5-C), 70.1 (d, 2-C), 171.5 (s, C=O), 172.6 (s, C=O), 172.7 (s, C=O)

TABLE III. (continued)

Compound No.	^{1}H-NMR δ ($CDCl_3$, J=Hz)	^{13}C-NMR δ ($CDCl_3$)
6b	2.39 (3H, s, NCH_3), 2.77 (1H, t, J=10.3, 5-CH_A), 3.27—3.47 (4H, m, 2-CH, 3-CH, 4-CH, 5-CH_B), 3.72 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.77 (3H, s, OCH_3)	39.6 (q, NCH_3), 44.8 (d, 3-C), 49.4 (d, 4-C), 51.6 (q, OCH_3), 52.2 (q, $(OCH_3)_2$), 57.3 (t, 5-C), 68.8 (d, 2-C), 170.8 (s, C=O), 171.2 (s, C=O), 173.4 (s, C=O)
7a	1.33 (3H, s, CCH_3), 2.29 (3H, s, NCH_3), 3.29—3.44 (2H, m, 3-CH, 4-CH), 3.39 (3H, s, OCH_3), 3.55 (3H, s, OCH_3), 3.58 (2H, d, J=6.0, 5-CH_2), 7.22 (5H, s, C_6H_5)	20.4 (q, CCH_3), 34.8 (q, NCH_3), 46.3 (d, 4-C), 50.7 (q, OCH_3), 51.8 (q, OCH_3), 56.8 (t, 5-C), 59.4 (d, 3-C), 73.8 (s, 2-C), 127.5, 128.3, 128.6, 137.3 (d, d, d, s, C_6H_5), 172.8 (s, C=O), 174.6 (s, C=O)
7b	1.24 (3H, s, CCH_3), 2.31 (3H, s, NCH_3), 3.15 (2H, d, J=4.9, 5-CH_2), 3.62 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 3.60—3.89 (2H, m, 3-CH, 4-CH), 7.16—7.46 (5H, m, C_6H_5)	15.9 (q, CCH_3), 35.1 (q, NCH_3), 44.9 (d, 3-C), 51.7 (q, OCH_3), 51.9 (q, OCH_3), 60.3 (d, 4-C), 61.1 (t, 5-C), 70.3 (s, 2-C), 126.8, 127.8, 128.6, 141.7 (d, d, d, s, C_6H_5), 171.9 (s, C=O), 174.0 (s, C=O)
8	1.56 (3H, s, CCH_3), 2.21 (3H, s, NCH_3), 3.08 (2H, dd, J=6.4, 12.8, 5-CH_2), 3.28—3.59 (2H, m, 3-CH, 4-CH), 3.66 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.73 (3H, s, OCH_3)	21.5 (q, CCH_3), 34.7 (q, NCH_3), 43.3 (d, 3-C), 51.1 (q, OCH_3), 52.0 (q, OCH_3), 52.2 (q, OCH_3), 56.2 (d, 4-C), 56.4 (t, 5-C), 70.7 (s, 2-C), 171.4 (s, C=O), 171.5 (s, C=O),174.5 (s, C=O)

TABLE IV. Synthesis of Pyrrolizidines and Indolizidines[a]

Entry	Olefin	Reaction conditions	Product[b]		Yield (%)
i) In the case of *N*-(phenylthiomethyl)proline methyl ester (**2c**)					
7	$PhCH=CHCO_2Me$	Reflux 20 h	 **11a** (1)	 **11b** (1)	42
8	$PhCH=C(CO_2Me)_2$	Reflux 43 h	 **12a** (3) **11a** (0.1)	 **12b** (1) **11b** (4)	56
ii) In the case of *N*-(phenylthiomethyl)pipecolinic acid methyl ester (**2d**)					
9	$PhCH=CHCO_2Me$	60 °C 5 h	 **13a** (1)	 **13b** (2)	53
10	$PhCH=C(CO_2Me)_2$	Reflux 3 h	 **14a** (3)	**13a** (5)	59

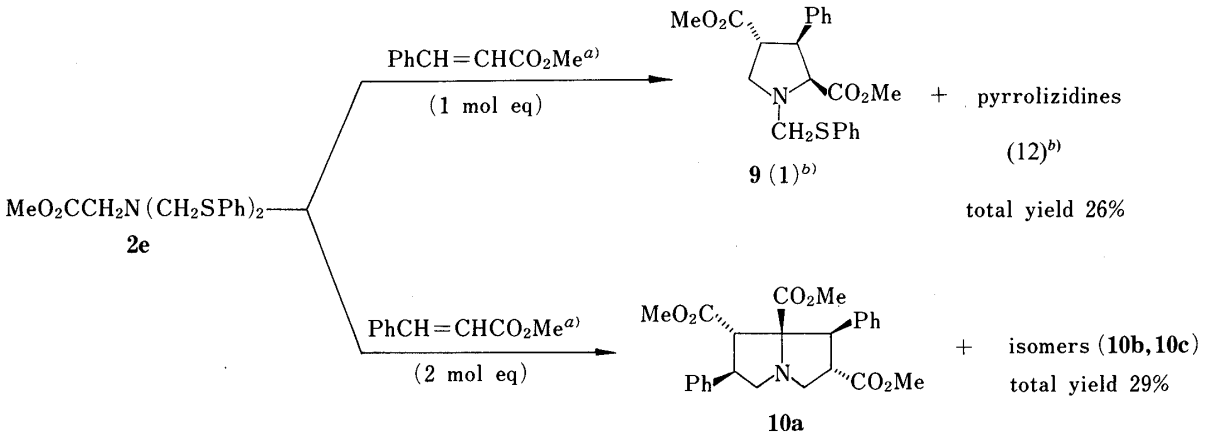
a) Molar proportions, substrate : olefin : sodium hydride : TMEDA = 1 : 1.2 : 2 : 1; solvent, DME. *b*) The ratio of the isomers is indicated in parentheses.

TABLE V. NMR Spectral Data for **11**—**14**

Compound No.	^{1}H-NMR δ ($CDCl_3$, J=Hz)	^{13}C-NMR δ ($CDCl_3$)
11a	1.70—2.23 (4H, m, 6-CH_2, 7-CH_2), 2.36—3.44 (4H, m, 3-CH_2, 5-CH_2), 3.31 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.66—4.15 (2H, m, 1-CH, 2-CH), 7.22 (5H, s, C_6H_5)	26.1, 34.9 (t, t, 6-C, 7-C), 49.5 (d, 2-C), 51.5 (q, OCH_3), 51.8 (q, OCH_3), 55.9 (t, 5-C), 57.8 (d, 1-C), 58.0 (t, 3-C), 82.2 (s, 8-C), 127.4, 127.6, 128.3, 136.7 (d, d, d, s, C_6H_5), 173.3 (s, C=O), 173.9 (s, C=O)
11b	1.52—2.14 (4H, m, 6-CH_2, 7-CH_2), 2.28—3.52 (4H, m, 3-CH_2, 5-CH_2), 3.54 (3H, s, OCH_3), 3.66—3.97 (2H, m, 1-CH, 2-CH), 3.79 (3H, s, OCH_3), 7.27 (5H, s, C_6H_5)	26.1, 32.3 (t, t, 6-C, 7-C), 45.2 (d, 1-C), 51.8 (q, OCH_3), 52.7 (q, OCH_3), 56.9 (t, 5-C), 58.5 (d, 2-C), 61.2 (t, 3-C), 77.7 (s, 8-C), 127.0, 127.7, 128.6, 139.0 (d, d, d, s, C_6H_5), 172.1 (s, C=O), 175.2 (s, C=O)
12a	1.55—2.94 (6H, m, $(CH_2)_3$), 3.11 (3H, s, OCH_3), 3.15 (3H, s, OCH_3), 3.38 (1H, d, J=12.9, 3-CH_A), 3.78 (3H, s, OCH_3), 4.41 (1H, d, J=12.9, 3-CH_B), 4.54 (1H, s, 1-CH), 7.20 (5H, s, C_6H_5)	24.2, 37.3 (t, t, 6-C, 7-C), 51.4 (q, OCH_3), 52.1 (q, OCH_3), 53.2 (q, OCH_3), 55.8 (t, 5-C), 59.2 (d, 1-C), 60.5 (t, 3-C), 66.3 (s, 2-C), 84.2 (s, 8-C), 127.2, 127.8, 129.3, 138.3 (d, d, d, s, C_6H_5), 168.2 (s, C=O), 172.0 (s, C=O), 174.6 (s, C=O)
12b	1.90—2.56 (6H, m, $(CH_2)_3$), 3.20—3.60 (2H, m, 3-CH_2), 3.36 (3H, s, OCH_3), 3.57 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 4.81 (1H, dd, J=7.5, 10.7, 2-CH), 7.04—7.40 (5H, m, C_6H_5)	29.5, 31.3 (t, t, 6-C, 7-C), 52.0 (q, OCH_3), 52.1 (q, OCH_3), 52.6 (q, OCH_3), 53.7 (t, 5-C), 55.9 (d, 2-C), 58.2 (t, 3-C), 69.4 (s, 1-C), 83.5 (s, 8-C), 127.5, 127.9, 129.7, 136.4 (d, d, d, s, C_6H_5), 168.9 (s, C=O), 169.9 (s, C=O), 173.9 (s, C=O)
13a	1.11—1.91 (8H, m, $(CH_2)_4$), 2.11—3.01 (2H, m, 3-CH_2), 3.21 (3H, s, OCH_3), 3.34—3.68 (2H, m, 1-CH, 2-CH), 3.52 (3H, s, OCH_3), 7.05 (5H, s, C_6H_5)	22.1, 23.5, 32.7 (t, t, t, 6-C, 7-C, 8-C), 45.6 (t, 5-C), 46.1 (d, 2-C), 50.4 (q, OCH_3), 51.7 (q, OCH_3), 54.1 (t, 3-C), 58.8 (d, 1-C), 73.9 (s, 9-C), 127.3, 128.1, 128.1, 137.5 (d, d, d, s, C_6H_5), 173.1 (s, C=O), 174.7 (s, C=O)
13b	1.20—2.14 (8H, m, $(CH_2)_4$), 2.77—3.03 (2H, m, 3-CH_2), 3.21—4.06 (2H, m, 1-CH, 2-CH), 3.64 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 7.26 (5H, s, C_6H_5)	21.0, 21.8, 27.4 (t, t, t, 6-C, 7-C, 8-C), 44.8 (d, 1-C), 45.8 (t, 5-C), 51.7 (q, OCH_3), 52.0 (q, OCH_3), 57.6 (t, 3-C), 61.2 (d, 2-C), 70.4 (s, 9-C), 126.7, 127.7, 128.6, 142.7 (d, d, d, s, C_6H_5), 171.8 (s, C=O), 174.2 (s, C=O)
14	1.08—2.30 (8H, m, $(CH_2)_4$), 3.03 (3H, s, OCH_3), 3.15 (3H, s, OCH_3), 3.40 (1H, d, J=7.0, 3-CH_A), 3.77 (3H, s, OCH_3), 4.23 (1H, d, J=7.0, 3-CH_B), 4.26 (1H, s, 1-CH), 7.22 (5H, s, C_6H_5)	19.7, 22.6, 30.5 (t, t, t, 6-C, 7-C, 8-C), 44.9 (t, 5-C), 50.8 (q, OCH_3), 51.9 (q, OCH_3), 53.1 (q, OCH_3), 56.5 (t, 3-C), 60.1 (d, 1-C), 64.0 (s, 2-C), 74.3 (s, 9-C), 127.0, 127.5, 129.6, 138.4 (d, d, d, s, C_6H_5), 172.1 (s, C=O), 172.5 (s, C=O), 175.6 (s, C=O)

the molecular ion peaks. A major component (**10a**) was isolated in the pure state by column chromatography and assigned the indicated structure on the basis of its NMR spectrum. The other two components were considered to be regio- or stereoisomers on the basis of the ^{13}C-NMR spectrum and GC/MS of the mixture.

Methyl esters of *N*-phenylthiomethyl derivatives of alicyclic amino acids, *i.e.*, proline and pipecolinic acid, were then reacted with olefinic dipolarophiles to give pyrrolizidines and indolizidines. Since in these cases tetramethylethylenediamine (TMEDA) was more efficient as a co-solvent than HMPA, the reaction was carried out in the NaH–TMEDA/DME system. The results are summarized in Table IV. The products **11a** and **11b** in entry 8, and **13a** in entry 10 are regarded as species formed from **12a**, **12b**, and **14a**, respectively, through hydrolysis and decarboxylation during the course of the isolation procedures. Assignment of the structures shown in Table IV, are based on ^{1}H- and ^{13}C-NMR spectral data (see Table V).



a) Reaction conditions: base, NaH; solvent, HMPA–DME; room temperature; time, 8 h. *b*) Ratio of the products.

Chart 1

In summary, this base-promoted 1,3-dipolar cycloaddition should be valuable for synthesizing pyrrolidines, pyrrolizidines, and indolizidines in good yields by a simple procedure.

Experimental

All melting and boiling points are uncorrected. IR spectra were measured with a Hitachi EPI-G2 infrared spectrometer. NMR spectra were taken on a JEOL JNM90Q spectrometer (90 MHz) and all chemical shifts are given downfield from tetramethylsilane (TMS). MS were recorded on a Hitachi RMS-4 MS spectrometer.

***N*-(Phenylthiomethyl)-α-amino Acid Methyl Ester (2a—d)**——General Procedure: First 35% aq. formaldehyde (18.0 g, 0.210 mol) and then thiophenol (19.2 g, 0.175 mol) was added to a stirred solution of α-amino acid methyl ester (0.175 mol) in 100 ml of methanol. After being stirred under reflux for 4 h, the reaction mixture was concentrated and the residue was extracted with benzene. The benzene solution was washed with 30% aq. potassium carbonate and dried over $MgSO_4$. After removal of the benzene, the residual oil was subjected to distillation. *N*-(Phenylthiomethyl)proline methyl ester (**2c**) was purified by silica gel column chromatography ($CHCl_3$: AcOEt = 1 : 3) because of its lability to heat, and an analytical sample was obtained by careful distillation of the eluted product. The physical and analytical data of the compounds are summarized in Table I.

***N*,*N*-Bis(phenylthiomethyl)glycine Methyl Ester (2e)**——First 35% aq. formaldehyde (39.0 g, 0.48 mol) and then thiophenol (44.0 g, 0.4 mol) were added to a stirred solution of glycine methyl ester (17.8 g, 0.2 mol) in 100 ml of methanol. After being stirred under reflux for 4 h, the reaction mixture was concentrated and the residue was extracted with benzene. The benzene solution was washed with 30% aq. potassium carbonate and dried over $MgSO_4$. After removal of the benzene, the oily residue was solidified by trituration with petr. ether, and recrystallized from petr. ether to give the pure product. The physical and analytical data of this compound are listed in Table I.

Pyrrolidines (3—8)——General Procedure: *N*-(Phenylthiomethyl)sarcosine methyl ester (**2a**) or *N*-methyl-*N*-(phenylthiomethyl)alanine methyl ester (**2b**) (20 mmol) was added at room temperature to a stirred suspension of sodium hydride (1.6 g, 40 mmol) in DME (20 ml) containing HMPA (3.6 ml) under a nitrogen atmosphere. After stirring of the ice-cooled mixture for 5 min, a solution of a dipolarophile (24 mmol) in DME was added. The reaction mixture was stirred under the conditions described in Table II. Insoluble material was filtered off and the filtrate was concentrated under reduced pressure. A benzene solution of the residue was washed with 30% aq. potassium carbonate and dried over $MgSO_4$. After removal of the benzene, purification of the product and isolation of the isomer from the residue were carried out as follows.

In entry 1 (Table II), the residue was subjected to column chromatography (silica gel, iso-Pro_2O : hexane = 1 : 2). The product **3a** was obtained as a solid and the isomers **3b** and **3c** were isolated as oils. **3a**: mp 108—110 °C (from MeOH). IR ν_{max}^{KBr} cm^{-1}: 1746 (C=O). MS (*m/z*): 335 (M^+). *Anal.* Calcd for $C_{17}H_{21}NO_6$: C, 60.88; H, 6.31; N, 4.18. Found: C, 60.98; H, 6.21; N, 4.10. **3b**: IR ν_{max}^{neat} cm^{-1}: 1745 (C=O). MS (*m/z*): 335 (M^+). **3c**: IR ν_{max}^{neat} cm^{-1}: 1745 (C=O). MS (*m/z*): 335 (M^+).

In entries 2, 3, and 4, the residue was distilled under reduced pressure and the distillate was subjected to elemental analysis. Each isomer was isolated as an oil from the distillate by column chromatography (silica gel, iso-Pro_2O : hexane = 1 : 2). **4(a—d)**: bp 120—121 °C (2 mmHg). *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.64; H, 6.89; N, 5.12. The IR spectra and MS of **4a**, **4b**, **4c** and **4d** showed patterns similar to each other,

containing an absorption band at 1740 cm^{-1} (C=O) and a peak at 246 *m/z* ($M^+ - OMe$), respectively. **5(a—c)**: bp 132—133 °C (17 mmHg). *Anal.* Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.36; H, 7.44; N, 6.85. The IR spectra and MS of **5a**, **5b**, and **5c** showed patterns similar to each other, containing an absorption band at 1745 cm^{-1} (C=O) and a peak at 201 *m/z* (M^+), respectively. **6(a—b)**: bp 120—121 °C (1 mmHg). *Anal.* calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40. Found: C, 51.15; H, 6.64; N, 5.41. The IR spectra and MS of **6a** and **6b** showed patterns similar to each other, containing an absorption band at 1735 cm^{-1} (C=O) and a peak at 259 *m/z* (M^+), respectively. In the case of the reaction with dimethyl maleate, the same products as with dimethyl fumarate were obtained.

In entry 5, the residue was subjected to column chromatography (silica gel, iso-Pro_2O : benzene = 1 : 9) to afford pure compounds **7a** and **7b**. **7a**: mp 78—79 °C (EtOH). IR ν_{max}^{KBr} cm^{-1}: 1739 (C=O). MS (*m/z*): 291 (M^+). *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.88; H, 7.28; N, 4.79. **7b**: mp 49—50 °C (EtOH). IR ν_{max}^{KBr} cm^{-1}: 1739 (C=O). MS (*m/z*): 291 (M^+) *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.95; H, 7.27; N, 4.81. Found: C, 65.73; H, 7.26; N, 4.83.

In entry 6, the residue was subjected to column chromatography (silica gel, iso-Pro_2O : benzene = 1 : 6) to afford a single product (**8**) in both cases. **8**: bp 99—100 °C (1 mmHg). IR ν_{max}^{neat} cm^{-1}: 1738 (C=O). MS (*m/z*): 242 ($M^+ - OMe$). *Anal.* Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.72; H, 7.00; N, 5.18.

Ratios of isomers, shown in Table II, were calculated on the basis of GC or ^{1}H-NMR spectra of the crude products. The ^{1}H- and ^{13}C-NMR data are collected in Table III.

Pyrrolizidines (11, 12) and Indolizidines (13, 14)——The reactions were carried out in a manner similar to that described for pyrrolidines (**3—8**) using *N*-(phenylthiomethyl)proline methyl ester (**2c**) or *N*-(phenylthiomethyl)-pipecolinic acid methyl ester (**2d**) (15 mmol), dipolarophile (18 mmol), sodium hydride (30 mmol), and TMEDA (15 mmol) in 50 ml of DME. After completion of the reaction, insoluble material was filtered off and the filtrate was concentrated under reduced pressure. A benzene solution of the residue was washed with 30% aq. potassium carbonate and dried over $MgSO_4$. After removal of the benzene, purification of the product and isolation of the isomers from the residue were carried out as follows.

In entry 7 (Table IV), the residue was distilled under reduced pressure and the distillate was subjected to elemental analysis. **11a, b**: bp 151—152 °C (0.03 mmHg). *Anal.* Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.45; H, 7.15; N, 4.50. Two isomers (**11a** and **11b**) were isolated as oils from the distillate by column chromatography (silica gel, AcOEt : benzene = 1 : 4). **11a**: IR ν_{max}^{neat} cm^{-1}: 1738 (C=O). MS (*m/z*): 272 ($M^+ - OMe$). **11b**: IR ν_{max}^{neat} cm^{-1}: 1735 (C=O). MS (*m/z*): 272 ($M^+ - OMe$).

In entry 8, the residue was subjected to column chromatography (silica gel, AcOEt : benzene = 1 : 4) to afford four compounds, two of which were identified as **11a** and **11b** by direct comparison of their MS and NMR spectra with those described above. **12a**: Oil. IR ν_{max}^{neat} cm^{-1}: 1720, 1755 (C=O). MS (*m/z*): 330 ($M^+ - OMe$). **12b**: mp 103—104 °C (hexane). IR ν_{max}^{KBr} cm^{-1}: 1722, 1756 (C=O). MS (*m/z*): 330 ($M^+ - OMe$). *Anal.* Calcd for $C_{19}H_{23}NO_6$: C, 63.14; H, 6.42; N, 3.88. Found: C, 63.49; H, 6.57; N, 3.86.

In entry 9, the residue was distilled under reduced pressure and the distillate was subjected to elemental analysis. **13a, b**: bp 159—157 °C (0.05 mmHg). *Anal.* Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.31; N, 4.41. Found: C, 68.39; H, 7.48; N, 4.12. Two isomers (**13a** and **13b**) were isolated from the distillate by column chromatography (silica gel, iso-Pro_2O : benzene = 1 : 3). **13a**: mp 82—83 °C (hexane). IR ν_{max}^{KBr} cm^{-1}: 1734 (C=O). MS (*m/z*): 286 ($M^+ - OMe$). **13b**: Oil, IR ν_{max}^{neat} cm^{-1}: 1735 (C=O). MS (*m/z*): 286 ($M^+ - OMe$).

In entry 10, the residue was subjected to column chromatography (silica gel, iso-Pro_2O : benzene = 1 : 1) to afford two compounds, one of which was identified as **13a** by direct comparison of its NMR spectrum with that described above. **14**: mp 118—119 °C (petr. ether). IR ν_{max}^{KBr} cm^{-1}: 1733 (C=O). MS (*m/z*): 344 ($M^+ - OMe$). *Anal.* Calcd for $C_{20}H_{25}NO_6$: C, 63.98; H, 6.71; N, 3.73. Found: C, 64.00; H, 6.66; N, 3.76.

Ratios of isomers, shown in Table IV, were calculated on the basis of GC or ^{1}H-NMR spectra of the crude products. The ^{1}H- and ^{13}C-NMR data are collected in Table V.

Reaction of *N,N*-Bis(phenylthiomethyl)glycine Methyl Ester (2e) with Methyl Cinnamate——In the case of 1 mol eq of methyl cinnamate, this reaction was carried out in a manner similar to that described for pyrrolidines (**3—8**), using **2e** (1.0 g, 3 mmol) and methyl cinnamate (0.5 g, 3 mmol) as a dipolarophile. The pyrrolidine derivative (**9**) was isolated in a pure state by column chromatography (silica gel, iso-Pro_2O : hexane = 1 : 1), and the structure was determined on the basis of the spectral data. **9**: Oil. IR ν_{max}^{neat} cm^{-1}: 1755 (C=O). MS (*m/z*): 275 ($M^+ - PhSH$). ^{1}H-NMR δ ($CDCl_3$, *J*=Hz); 3.05 (3H, s, OCH_3), 3.26 (1H, d, *J*=6.7, 2-CH), 3.28—3.47 (2H, m, 4-CH, 5-CH_A), 3.64 (3H, s, OCH_3), 3.94 (1H, dd, *J*=6.0, 10.1, 5-CH_B), 4.01 (1H, t, *J*=6.7, 3-CH), 4.59 (1H, d, *J*=9.1, NCH_AS), 4.78 (1H, d, *J*=9.1, NCH_BS), 7.25 (5H, s, C_6H_5), 7.20—7.50 (5H, m, SC_6H_5). ^{13}C-NMR δ ($CDCl_3$): 48.7 (d, 4-C), 50.6 (d, 3-C), 51.0 (q, OCH_3), 52.0 (q, OCH_3), 53.7 (t, 5-C), 60.0 (t, NCH_2S), 66.7 (d, 2-C), 126.6, 127.3, 128.2, 129.0, 131.5, 136.9, 139.5 (d, d, d, d, d, s, s, 2 × C_6H_5), 170.4 (s, CO), 173.2 (s, CO). The other products were determined to be pyrrolizidine derivatives by GC/MS comparison with **10a—c** obtained in the next experiment.

In the case of 2 mol eq of methyl cinnamate, this reaction was carried out in a manner similar to that described for pyrrolidines (**3—8**), using **2e** (10 g, 30 mmol) and methyl cinnamate (9.6 g, 60 mmol) as a dipolarophile. The crude product was determined to be a mixture of three isomers by GC/MS spectral analysis. Namely, the GC of the product

showed three peaks and the MS of each peak have the same highest fragment peak [406 (*m/z*), $M^+ - OMe$] and similar fragment patterns. The main product (**10a**) was isolated in a pure state by column chromatography (silica gel, AcOEt : hexane = 1 : 1). **10a**: Oil. IR ν_{max}^{neat} cm^{-1}: 1741 (C=O). ^{1}H-NMR δ ($CDCl_3$): 2.98—4.22 (8H, m, 1-CH, 2-CH, 3-CH_2, 5-CH_2, 6-CH, 7-CH), 3.41 (3H, s, OCH_3), 3.56 (6H, s, $2 \times OCH_3$), 7.25 (10H, s, $2 \times C_6H_5$). ^{13}C-NMR δ ($CDCl_3$): 47.4, 50.2 (d, d, 2-C, 7-C), 51.9 (q, $2 \times$ O–C), 52.1 (q, O–C), 53.3, 57.6 (d, d, 1-C, 6-C), 57.7, 59.7 (t, t, 3-C, 5-C), 83.4 (s, 8-C), 127.2, 127.5, 128.2, 128.7, 136.7, 138.6 (d, d, d, d, s, s, $2 \times C_6H_5$), 172.3 (s, CO), 172.5 (s, CO), 173.4 (s, CO). The ^{13}C-NMR spectrum of the mixture of **10b** and **10c** was quite similar to that of **10a**.

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References and Notes

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