Chem. Pharm. Bull.
30(11)4015—4024(1982)

Syntheses of α-Alkylated β,γ-Unsaturated α-Amino Acids[1)]

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(Received May 8, 1982)

Various α-alkylated β,γ-unsaturated α-amino acids were synthesized by the deconjugative alkylation of methyl α-isocyanoalkylideneacetates followed by hydrolysis. In the mechanistic study, no marked differences in reactivity of the geometrical isomers of methyl 2-isocyano-3-phenyl-2-butenoate (*E*- and *Z*-**11a**) were observed. On the other hand, the double bound migration of unsymmetrical ($R^1 \neq R^2$) isocyano compounds (**11c**, **d**) proceeded regioselectively due both to the different acidities of the alkyl groups and to the stability of the carbanion formed on proton abstraction. Furthermore, direct synthesis of methyl α-isocyanocycloalkylideneacetates (**4a**, **b**, **d**) by the reaction of methyl isocyanoacetate with cyclic ketones was also investigated.

Keywords——deconjugative alkylation; α-isocyanoalkylideneacetates; geometrical isomers; regioselective; α-alkyl-α-isocyanoalk-1-enylacetates; α-alkylated β,γ-unsaturated α-amino acids

During recent years, studies on β,γ-unsaturated α-amino acids, some of which are naturally occurring antibiotics[2)] and irreversible inhibitors of amino acid metabolizing enzymes,[3)] have increased remarkably. Most especially, biochemical research on suicide enzyme inactivation, which entails the binding of pyridoxal phosphate with those amino acids having latent reactive double bonds, has received much attention not only in pharmacological but also in organic chemistry. Several synthetic methods have been described,[4)] including a facile preparative method using α-formylaminoacrylates reported by the present authors in 1979.[5)]

Most recently, some α-alkylated, β,γ-unsaturated α-amino acids have been found to inhibit irreversibly amino acid decarboxylases[6)] and considerable knowledge on the physiological role of polyamines has been accumulated due to the use of such inhibitors. Various synthetic studies on α-vinyl-α-amino acids such as alanine, ornithine, and 3,4-dihydroxyphenylalanine (DOPA) have been reported and a variety of practical methods for the introduction of a vinyl residue into an α-amino acid skeleton have recently been developed.[7)] These methods, however, are effective only for the synthesis of α-vinyl-α-amino acid derivatives and lack utility for the synthesis of other types of α-alkylated β,γ-unsaturated α-amino acids. In a previous communication[8)] related to the study of β,γ-unsaturated α-amino acids, we briefly described the synthesis of α-alkylated cycloalk-1-enylglycines by the use of deconjugative alkylation of α-isocyanoacrylates.

In the present paper, we describe our detailed investigation of the synthesis of α-alkylated cycloalk-1-enylglycines having various ring sizes and containing various heteroatoms in the ring. The method has also been extended to the synthesis of acyclic α-alkylated β,γ-unsaturated α-amino acids.[9)]

α-Alkylated Cycloalk-1-enylglycines

We have previously shown that saponification of methyl α-formylaminoacrylates caused the migration of the α,β-double bond to the β,γ-position owing to intramolecular proton abstraction at the γ-position.[5)] On the other hand, Cope *et al.* found[10)] that treatment of an ethylenemalonic ester or cyanoacetic ester with an alkyl halide in the presence of sodium alkoxide afforded an α-alkylated compound with accompanying double bond migration *via* the ambident ion. Taking the above information into consideration, we attempted to synthe-

size α-alkylated β,γ-unsaturated α-amino acids using the double bond migration approach.

First, the reaction of methyl *N*-formylcyclopentylideneglycinate (**1a**) with methyl iodide in the presence of NaH in THF was carried out. *N*-Methylation proceeded exclusively and resulted in the formation of methyl *N*-formyl-*N*-methyl-cyclopentylideneglycinate (**3**) in 81% yield (Chart 1). This result suggested that the electron-withdrawing effect of the formyl-

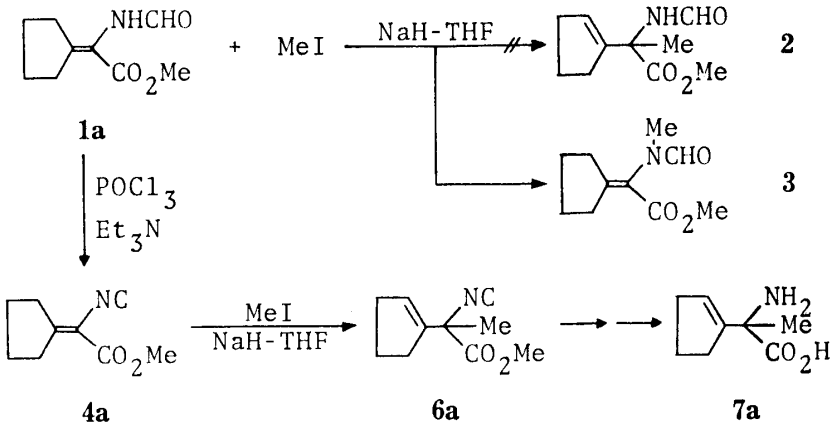
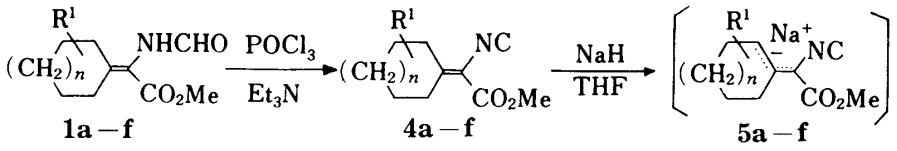
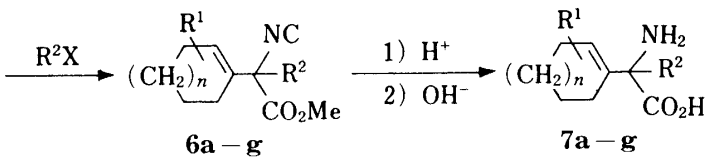


Chart 1

amino group was insufficient to cause abstraction of the allylic proton in this compound (**1a**). For this reason, both the strong electron-withdrawing character and easy conversion to an amino group of the isocyano function was considered. With methyl α-isocyanocyclopentylideneacetate (**4a**), prepared from **1a** by the method described in the previous paper,[8] the same reaction conditions caused both migration of the α,β-double bond to the β,γ-position and simultaneous α-alkylation, affording methyl α-(cyclopent-1-enyl)-α-isocyano-α-methylacetate (**6a**) in 84% yield. The infrared (IR) spectrum of **6a** showed the characteristic absorption of the isocyano group at 2140 cm^{-1} and of the ester group at 1750 cm^{-1} and the nuclear magnetic resonance (NMR) spectrum ($CDCl_3$) showed an olefinic proton signal at δ 5.86. Subsequently, hydrolysis of **6a** with 2 N methanolic hydrochloric acid followed by saponification with sodium



a: $n = 0$, R^1 = H
b: $n = 1$, R^1 = H
c: $n = 1$, R^1 = 4-Me
d: $n = 2$, R^1 = H
e: $n = 3$, R^1 = H
f: $n = 7$, R^1 = H



a: $n = 0$, R^1 = H, R^2 = Me
b: $n = 0$, R^1 = H, R^2 = $CH_2CH=CH_2$
c: $n = 1$, R^1 = H, R^2 = Me
d: $n = 1$, R^1 = 4-Me, R^2 = Et
e: $n = 2$, R^1 = H, R^2 = Et
f: $n = 3$, R^1 = H, R^2 = CH_2Ph
g: $n = 7$, R^1 = H, R^2 = *n*-Pr

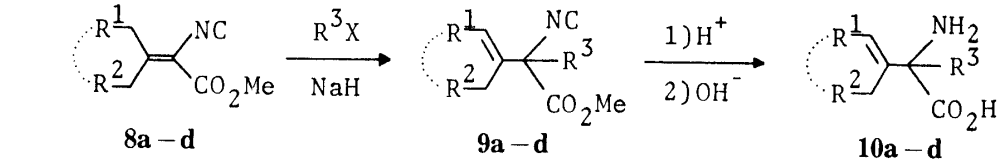
Chart 2

Table I. Yields and Physical Properties of **6**

Compd.	Yield (%)	IR ν_{max}^{film} cm^{-1}	>C=CH-	NMR ($CDCl_3$) δ OMe	NMR ($CDCl_3$) δ Other
6a	84	2140, 1752	5.86	3.81	1.79 (3H, s), 1.85—2.60 (6H, m)
6b	68	2150, 1750	5.90	3.80	0.93 (3H, t), 1.00—2.60 (12H, m)
6c	63	2130, 1750	5.80—6.00	3.76	1.71 (3H, s), 1.46—2.30 (3H, m)
6d	76	2140, 1750	5.86—6.10	3.80	0.95 (3H, broad d), 1.00 (3H, t), 1.30—2.50 (9H, m)
6e	76	2130, 1750	6.15	3.81	1.00 (3H, t), 1.15—2.50 (12H, m)
6f	76	2120, 1750	5.93	3.70	1.50 (8H, broad s), 1.90—2.50 (4H, m), 3.05, 3.50 (2H, ABq), 7.05—7.40 (5H, m)
6g	79	2140, 1748	5.74	3.78	0.89 (3H, t), 1.00—2.50 (24H, m)

Table II. Yields, Physical Properties, and Analytical Data of **7**

Compd.	Yield (%)	mp (°C, dec.)	IR ν_{max}^{KBr} cm^{-1}	NMR (CF_3CO_2D) δ >C=CH-	Analysis (%) Calcd (Found) C	H	N
7a	69	281—283	3420, 2090, 1620, 1593	6.19	61.91 (61.79	8.44 8.57	9.03 8.97)
7b	56	240—243	3400, 2090, 1630, 1595	6.17	66.97 (66.98	9.71 9.71	7.10 6.87)
7c	53	264—267	3420, 2070, 1630, 1595	6.25	63.88 (63.76	8.93 8.98	8.28) 8.15
7d	51	252—254	3420, 2070, 1630, 1595	6.15	66.97 (66.79	9.71 9.87	7.10 7.02)
7e	42	248—249	3420, 2100, 1625, 1590	6.35	66.97 (66.90	9.71 9.83	7.10 7.04)
7f	72	240—242	3430, 1630, 1520	6.21	74.69 (74.49	8.48 8.39	5.12 5.03)
7g	73	227—229	3430, 1627, 1595	5.96	72.55 (72.39	11.10 11.21	4.98 4.81)



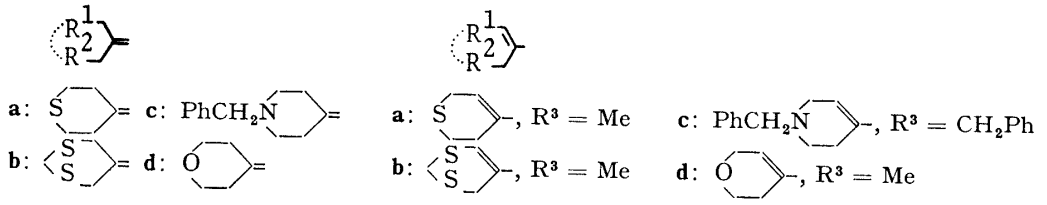


Chart 3

hydroxide gave α-(cyclopent-1-enyl)-α-methylglycine (**7a**) in 84% yield. In the same way, various other α-alkyl-α-(cycloalk-1-enyl)glycines (**7a—g**) were prepared in good yields as shown in Chart 2. These results are summarized in Tables I and II.

The synthesis of α-alkylated α-(cycloalk-1-enyl)glycines which includes heteroatoms (O, S, N) in the ring was also investigated using the above method (Chart 3). The corresponding

α-alkylated β,γ-unsaturated α-amino acids (**10a—d**) were obtained in good yields without formation of sulfonium or ammonium halide salts. These results are summarized in Tables III and IV.

Table III. Yields and Physical Properties of **9**

Compd.	Yield (%)	IR ν_{max}^{film} cm^{-1}	>C=CH–	NMR ($CDCl_3$) δ	
				OMe	Other
9a	69	2145, 1750	6.03—6.30	3.82	1.78 (3H, s), 2.20—2.50 (2H, m), 2.50—3.00 (2H, m), 3.15—3.40 (2H, m)
9b	82	2120, 1740	6.60	3.85	1.83 (3H, s), 3.30 (2H, s), 3.94 (2H, s)
9c	79	2130, 1745	5.85—6.10	3.75	2.10—3.40 (8H, m), 3.60 (2H, s), 7.30 (5H, br s), 7.35 (5H, s)
9d	71	2140, 1750	5.90—6.10	3.83	1.79 (3H, s), 2.00—2.35 (2H, m), 3.79 (2H, t), 4.15—4.35 (2H, m)

Table IV. Yields, Physical Properties, and Analytical Data of **10**

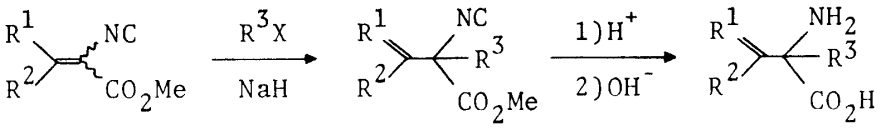
Compd.	Yield (%)	mp (°C, dec.)	IR ν_{max}^{KBr} cm^{-1}	NMR (CF_3CO_2D) δ >C=CH–	Analysis (%) Calcd (Found)			
					C	H	N	S
10a	68	251—253	3430, 1615, 1590	6.30—6.50	51.31 (51.19	7.00 7.05	7.48 7.40	17.12 17.01)
10b	71	216—217	3400, 1620, 1597	6.88	40.95 (40.69	5.40 5.45	6.82 6.81	31.24 31.02)
10c	59	168—171	3410, 1620	6.25—6.50	74.97 (74.68	7.19 7.30	8.33 8.39)	
10d	64	276—278	3420, 2120, 1640, 1590	6.10—6.40	56.13 (55.96	7.65 7.49	8.18 8.00)	

Acyclic α-Alkylated β,γ-Unsaturated α-Amino Acids

Moreover, these reactions can be extended to the synthesis of acyclic α-alkylated β,γ-unsaturated α-amino acids. Various α-isocyanoacrylic acid esters (**11a—e**) were synthesized *via* α-formylaminoacrylic acid esters by the reaction of isocyanoacetate with various ketones or an aldehyde according to a standard method.[18,19] Alkylation of methyl 2-isocyano-3-methyl-2-butenoate (**11b**, $R^1=R^2=CH_3$) was then carried out using benzyl bromide in the presence of NaH to afford (75%) the expected compound (**12c**). Subsequently, hydrolysis followed by saponification of **12c** gave α-benzylisodehydrovaline (**13c**) in good yield (Chart 4).

On the other hand, unsymmetrical ($R^1\neq R^2$) α-isocyanoacrylic acid esters (**11a** and **11c—e**) were obtained as mixtures of (*E*)- and (*Z*)-isomers.[11,12] In order to examine the differential reactivity of (*E*)- and (*Z*)-isomers, as a typical example, (*E*)-**11a** and (*Z*)-**11a** were allowed to react separately with methyl iodide as described above. Methyl 2-isocyano-2-methyl-3-phenyl-3-butenoate (**12a**) was obtained in 85% and 82% yields from (*E*)-**11a** and (*Z*)-**11a**, respectively, and no marked differences in reactivity of the geometrical isomers were observed (Chart 5).

In the cases of α-isocyano compounds (**11c** and **11d**) possessing alkyl substituents ($R^1\neq R^2$) such as methyl, ethyl or isopropyl groups, the possibility of the abstraction of two different protons had to be considered. In order to investigate the direction of the double bond migration, the reaction of methyl 2-isocyano-3-methyl-2-pentenoate (**11c**) with benzyl bromide was investigated. The vinyl compound (**12e**) resulting from proton abstraction at the methyl



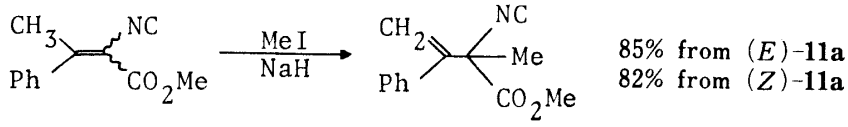
11a: R^1 = Me, R^2 = Ph
11b: R^1 = Me, R^2 = Me
11c: R^1 = Me, R^2 = Et
11d: R^1 = Me, R^2 = iso-Pr
11e: R^1 = iso-Pr, R^2 = H

12

13

a: $R^1 = CH_2$, R^2 = Ph, R^3 = Me
b: $R^1 = CH_2$, R^2 = Ph, R^3 = Et
c: $R^1 = CH_2$, R^2 = Me, $R^3 = CH_2Ph$
d: $R^1 = CH_2$, R^2 = Me, R^3 = 3,4-methylenedioxy-CH_2Ph
e: $R^1 = CH_2$, R^2 = Et, $R^3 = CH_2Ph$
f: $R^1 = CH_2$, R^2 = Et, R^3 = 3,4-methylenedioxy-CH_2Ph
g: $R^1 = CH_2$, R^2 = iso-Pr, $R^3 = CH_2Ph$
h: $R^1 = CH_2$, R^2 = iso-Pr, R^3 = 3,4-methylenedioxy-CH_2Ph
i: $R^1 = C(CH_3)_2$, R^2 = H, $R^3 = CH_2Ph$

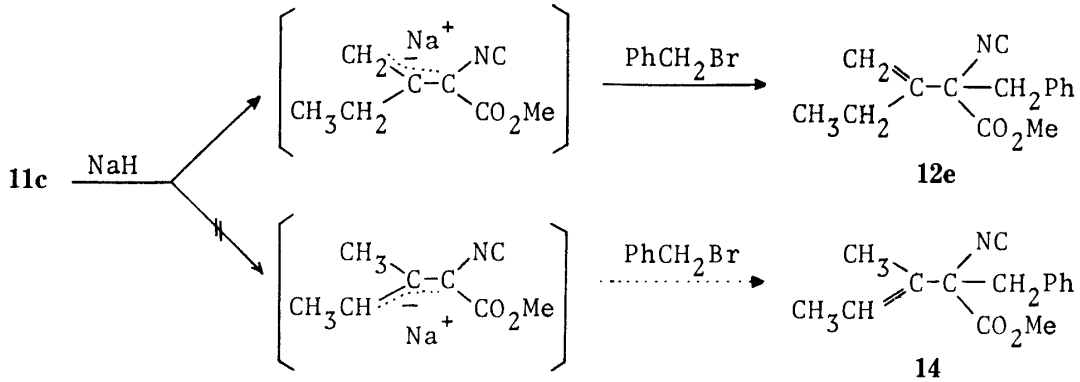
Chart 4



85% from (*E*)-**11a**
82% from (*Z*)-**11a**

(*E*), (*Z*)-**11a**

12a

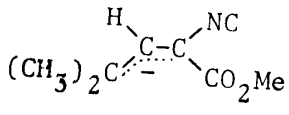


12e

14

Chart 5

group was obtained predominantly in 71% yield, while formation of **14** derived by double bond migration into the ethyl group was scarcely observed (Chart 5). Similarly, methyl 2-isocyano-3,4-dimethyl-2-pentenoate (**11d**) gave only the vinyl compound (**12g**) in 67% yield. Using 3,4-methylenedioxybenzyl bromide as the electrophile, a similar result was observed, and **12f** and **12h** were obtained. The regioselectivity can be attributed both to the different acidities of the alkyl groups (kinetic acidity) and to the stability of the anion formed on proton abstraction (thermodynamic acidity); it is generally accepted that the order of the above acidity or stability is methyl>ethyl>isopropyl.[13]



15

Fig. 1

Furthermore, a similar alkylation using methyl 2-isocyano-4-methyl-2-pentenoate (**11e**) was tried, but in this case polymerization occurred, resulting in tarry products, while the desired β,γ-unsaturated isocyano compound (**12i**) was obtained in onyl poor yield. This result suggests that the intermediate ambident anion (**15**) is very unstable under the conditions used (Fig. 1). These results are summarized in Tables V and VI.

Table V. Yields and Physical Properties of **12**

Compd.	Yield (%)	IR ν_{max}^{film} cm^{-1}	NMR ($CDCl_3$) δ OMe	NMR ($CDCl_3$) δ Other
12a	85[a] 82[b]	2140, 1753	3.80	1.85 (3H, s), 5.41 (1H, s), 5.71 (1H, s), 7.10—7.50 (5H, m)
12b	82	2140, 1750	3.78	1.05 (3H, t), 1.90—2.30 (2H, m), 5.39 (1H, s), 5.70 (1H, s), 7.00—7.50 (5H, m)
12c	75	2125, 1745	3.75	1.90 (3H, d), 3.10, 3.50 (2H, ABq), 5.16 (1H, d), 5.32 (1H, s), 7.30 (5H, s)
12d	83	2140, 1743	3.77	1.88 (3H, d), 2.99, 3.44 (2H, ABq), 5.14 (1H, d), 5.30 (1H, s), 5.92 (2H, s), 6.60—6.90 (3H, br s)
12e	71	2140, 1745	3.74	1.10 (3H, t), 1.90—2.40 (2H, m), 3.10, 3.51 (2H, ABq), 5.18 (1H, d), 5.39 (1H, s), 7.27 (5H, s)
12f	82	2140, 1745	3.76	1.10 (3H, t,), 2.16 (2H, o), 3.00, 3.43 (2H, ABq), 5.17 (1H, t), 5.38 (1H, s), 5.92 (2H, s), 6.60—6.90 (3H, br s)
12g	67[c]	2140, 1750[d]	3.71	1.07 (3H, d), 1.09 (3H, d). 2.20—2.80 (1H, m), 3.04, 3.53 (2H, ABq), 5.25 (1H, s), 5.42 (1H, s), 7.26 (5H, s)
12h	77	2140, 1743	3.75	1.12 (6H, d), 2.20—2.80 (1H, m), 2.96, 3.46, (2H, ABq), 5.26 (1H, s), 5.41 (1H, s), 5.91 (2H, s), 6.60—6.80 (br s, 3H)
12i	25	2120, 1742	3.71	1.79 (6H, d), 3.10, 3.39 (2H, ABq), 5.25—5.45 (1H, m), 7.30 (5H, s)

a) From (*Z*)-**11**. *b*) From (*E*)-**11**. *c*) mp 70—72°C (colorless prisms from Et_2O-hexane). *d*) Taken in Nujol.

Table VI. Yields, Physical Properties, and Analytical Data of **13**

Compd.	Yield (%)	mp (°C, dec.)	IR ν_{max}^{KBr} cm^{-1}	NMR (CF_3CO_2D) δ	Analysis (%) Calcd (Found) C	H	N
13a	65	213—214	3430, 1600	2.14 (3H, s), 5.72 (1H, s), 5.96 (1H, s), 7.00—7.60 (5H, m)	69.09 (68.88	6.85 6.91	7.33 7.17)
13b	59	222—224	3440, 1620, 1595	1.23 (3H, t), 2.30—2.80 (2H, m), 5.71 (1H, s), 5.94 (1H, s), 7.10—7.60 (5H, m)	70.22 (70.10	7.37 7.39	6.82 6.59)
13c	61	245—247	3430, 1625	2.15 (3H, s), 3.45, 3.90 (2H ABq), 5.50 (1H, br s), 5.57 (1H, br s), 7.40 (5H, br s)	70.22 (70.03	7.37 7.50	6.82 6.80)
13d	82	256—258	3260, 1640	2.12 (3H, s), 3.40, 3.82 (2H, ABq), 5.40—5.65 (2H, m), 5.99 (2H, s), 6.85 (3H, s)	62.64 (62.51	6.07 6.15	5.62 5.52)
13e	76	203—205	3420, 1630	1.26 (3H, t), 2.10—2.60 (2H, m), 3.47, 3.87 (2H, ABq), 5.60 (2H,s), 7.00—7.60 (5H, m)	71.20 (71.13	7.81 7.83	6.39 6.30)
13f	89	249—251	3260, 1640	1.26 (3H, t), 2.30 (2H, q), 3.42, 3.84 (2H, ABq), 5.60 (2H, br s), 5.99 (2H, s), 6.82 (3H, s)	63.86 (63.80	6.51 6.70	5.32 5.21)
13g	87	242—243	3420, 1630	1.26 (3H, d), 1.30 (3H, d), 2.30—2.90 (1H, m), 3.45, 3.94 (2H, ABq), 5.70 (2H, s), 7.00—7.60 (5H, m)	72.07 (72.01	8.21 8.27	6.00 6.10)
13h	90	250—252	3260, 1638	1.27 (3H, d), 1.30 (3H, d), 2.30—2.90 (1H, m), 3.45, 3.89 (2H, ABq), 5.70 (2H, broad s), 5.99 (2H, s), 6.86 (3H, s)	64.97 (64.88	6.91 6.95	5.05 5.01)
13i	53	226—227	3410, 1615	1.86 (3H, s), 1.96 (3H, s), 3.38, 3.78 (2H, ABq), 5.52 (1H, br s), 7.38 (5H, br s)	71.20 (70.97	7.81 7.73	6.39 6.11)

Direct Synthesis of Methyl α-Isocyanocycloalkylideneacetate

Since a new and versatile synthetic method for the preparation of α-alkylated β,γ-unsaturated α-amino acids has been found, a more convenient synthesis of methyl α-isocyanoalkylideneacetates, which are the starting materials, is required. Accordingly, using cyclic ketones and methyl isocyanoacetate, we attempted to develop a direct synthesis of methyl α-isocyano-

cycloalkylideneacetates under various basic conditions.

The reactions of the isocyanoacetate with carbonyl compounds have been frequently investigated, and various reaction products have been reported. Schöllkopf *et al.* reported that the reaction in the presence of sodium hydride[11] and sodium cyanide[14] afforded α-formylaminoacrylates and oxazoline carboxylates, respectively, as the main products. Saegusa *et al.* described the formation of the oxazoline by this reaction in the presence of a copper catalyst.[15] β-Hydroxy-α-isocyanobutyrates[16] and pyrrole dicarboxylates[17] were obtained by us in this reaction using organic bases such as triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Thus, these results show that various interesting products can be obtained in the reaction of methyl isocyanoacetate with carbonyl compounds, depending upon the reaction conditions. However, no direct synthetic method for methyl isocyanoacrylates by a Knoevenagel-type reaction is known.[16]

On the basis of the above information, we chose to use a secondary amine as a base for the Knoevenagel-type reaction. For example, using cyclopentanone as the carbonyl compound, the reaction proceeded smoothly in the presence of pyrrolidine in DMF to afford directly the desired methyl α-isocyanocyclopentylideneacetate (**4a**) in 67% yield. Similarly, the corresponding isocyano compounds, (**4b**) and (**4d**), were also obtained from cyclohexanone and cycloheptanone in 41% and 58% yields, respectively. These reactions also proceeded when piperidine or *N*-methylpiperazine was used as the catalyst (Table VII). On the other hand, when this synthetic method was extended to acyclic ketones, such as acetone or diethyl ketone, the expected reaction did not proceed and only isocyanoacetic acid amides were obtained (Chart 6).

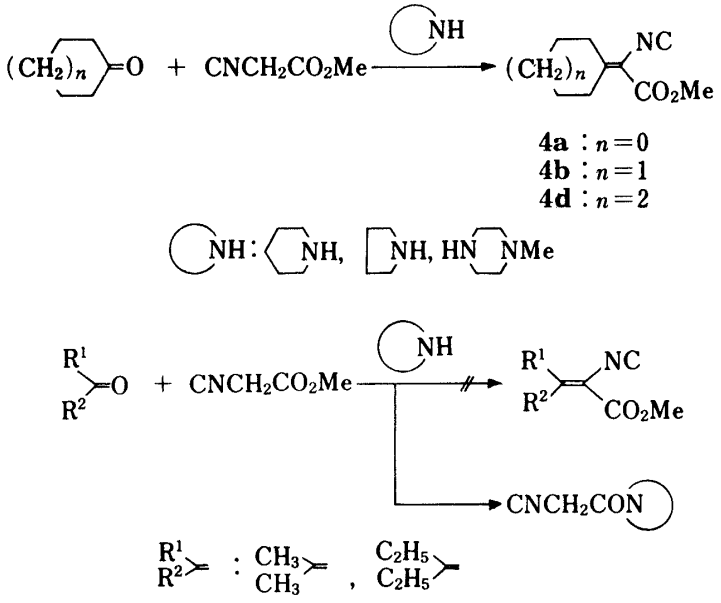


Chart 6

TABLE VII. Formation of **4a**, **4b**, and **4d**

Compd.	Base	Solvent	Yield (%)
4a	Piperidine	CH_2Cl_2	31
4a	Piperidine	MeOH	42
4a	Piperidine	DMF	67
4a	Pyrrolidine	DMF	58
4a	*N*-Methylpiperazine	DMF	63
4b	Piperidine	DMF	41
4d	Piperidine	DMF	58

Experimental

Melting points (which were measured by the use of a Yamato melting point apparatus) and boiling points are uncorrected. The IR spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer. The ^{1}H-NMR spectra were obtained using a Hitachi Perkin-Elmer R-20A high resolution NMR spectrometer with tetramethylsilane as an internal standard. Column chromatography was carried out on silica gel (Kieselgel, 0.063—0.200 mm, E. Merck).

Starting Materials——Methyl *N*-formylalkylideneglycinates were prepared by the condensation of methyl isocyanoacetate with ketones or aldehydes using a method similar to that described in the previous paper.[18] Yields, physical, and analytical data of new compounds are as follows.

Methyl *N*-Formyl-(1,3-dithian-5-ylidene)glycinate: Yield 81%, mp 161—163°C (colorless needles from AcOEt). IR ν_{max}^{Nujol} cm^{-1}: 3220, 1722, 1645, and 1618. NMR (in $CDCl_3$+DMSO-d_6) δ: 3.45 (2H, s, S-CH_2-C=), 3.75 (3H, s, OCH_3), 3.84 (2H, s, S-CH_2-C=), 3.95 (2H, s, S-CH_2-S), 8.09 (1H, d, J=1 Hz, CHO), and 9.15—9.50 (1H, m, NH). *Anal.* Calcd for $C_8H_{11}NO_3S_2$: C, 41.18; H, 4.75; N, 6.00; S, 27.49. Found: C, 41.11; H, 4.76; N, 5.95; S, 27.31.

Methyl *N*-Formyl-(tetrahydro-4*H*-pyran-4-ylidene)glycinate: Yield 61%, mp 127—129°C (colorless prisms from AcOEt). IR ν_{max}^{Nujol} cm^{-1}: 3300, 1725, and 1667. NMR (in $CDCl_3$) δ: 2.20—2.65 (2H, m, -CH_2-C=), 2.78—3.20 (2H, m, -CH_2C-), 3.60—4.00 (4H, m, 2×OCH_2-), 3.70 (3H, s, OCH_3), 7.20—7.50 (1H, br, NH), and 8.19 (1H, d, J=1 Hz, CHO). *Anal.* Calcd for $C_9H_{13}NO_4$: C, 54.26; H, 6.53; N, 7.03. Found: C, 54.22; H, 6.51; N, 7.01.

(*E*)-Methyl 2-Formylamino-3-phenyl-2-butenoate: Yield 32%, mp 109—111°C (colorless needles from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3260, 1730, 1678, and 1659. NMR (in $CDCl_3$) δ: 2.14 (3H, s, CH_3), 3.46 (3H, s, OCH_3), 7.00—7.50 (5H, m, arom-H), 7.40—7.70 (1H, m, NH), and 8.25 (1H, d, J=1 Hz, NH). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.69; H, 6.03; N, 6.31.

(*Z*)-Methyl 2-Formylamino-3-phenyl-2-butenoate: Yield 48%, mp 94—96°C (colorless leaflets from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3220, 1730, and 1660. NMR (in $CDCl_3$) δ: 2.30 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 6.60—7.10 (1H, br, NH), 7.00—7.55 (5H, m, arom-H), and 7.89 (1H, d, J=1 Hz, CHO). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.61; H, 6.01; N, 6.30.

Methyl 2-Formylamino-3,4-dimethyl-2-pentenoate: Yield 83%, colorless syrup. IR ν_{max}^{film} cm^{-1}: 3290, 1725, and 1660. NMR (in $CDCl_3$) δ: 1.20, 1.05 [6H, d, d, J=7 Hz, CH($\underline{CH}_3$)$_2$], 2.00, 2.07 (3H, d, d, J=3 Hz, CH_3), 2.70—3.30 [1H, m, $\underline{CH}$(CH_3)$_2$], 3.74, 3.76 (3H, s, s, OCH_3), 7.70—8.10 (1H, br, NH), and 8.17 (1H, d, J=2 Hz, CHO).

Methyl 2-Formylamino-4-methyl-2-pentenoate: Yield 85%, colorless syrup. IR ν_{max}^{film} cm^{-1}: 3270, 1725, and 1660. NMR (in $CDCl_3$) δ: 1.06 [6H, d, J=7 Hz, CH($\underline{CH}_3$)$_2$], 2.40—2.90 [1H, m, $\underline{CH}$(CH_3)$_2$], 3.78, 3.82 (3H, s, s, OCH_3), 6.30—6.70 (1H, m, =CH), 7.30—7.80 (1H, br, NH), and 8.24, 8.28 (1H, d, d, J= 2 Hz, CHO).

Methyl α-isocyanoalkylideneacetates (**4**, **8**, and **11**) were obtained by dehydration of methyl *N*-formylalkylideneglycinates with phosphoryl chloride and triethylamine using a method similar to that described in the previous paper.[18,19] These results are summarized in Table VIII.

Reaction of Methyl *N*-Formylcyclopentylideneglycinate (1a) with Methyl Iodide——A mixture of **1a** (3.66 g, 0.02 mol) and methyl iodide (2.82 g, 0.02 mol) in THF (10 ml) was added dropwise to a suspension of NaH (65% in oil) (0.82 g, 0.022 mol) in THF (10 ml) at 30—40°C. Stirring was continued for 3 h at room temperature, then the reaction mixture was neutralized with 10% AcOH and concentrated *in vacuo*. The residue was extracted with AcOEt and the extract was washed with H_2O, dried over $MgSO_4$, and then concentrated to dryness *in vacuo*. The resulting oil was subjected to column chromatography (80 g) using $CHCl_3$–AcOEt (6: 1) as the eluent to give methyl *N*-formyl-*N*-methylcyclopentylideneglycinate (**3**) as a colorless oil (3.19 g, 81%). IR ν_{max}^{film} cm^{-1}: 1715, 1680, and 1635. NMR (in $CDCl_3$) δ: 1.50—2.00 (4H, m, 2×CH_2), 2.20—2.60 (2H, m, CH_2), 2.65—3.90 (2H, m, CH_2), 2.95 (3H, s, NCH_3), 3.73 (3H, OCH_3), and 7.86 (1H, s, CHO).

General Procedure for the Preparation of Methyl α-Alkyl-α-isocyano-α-(alk-1-enyl)acetates (6, 9, and 12)——A mixture of **4**, **8** or **11** (0.03 mol) and alkyl halide (0.03 mol) in THF (20 ml) was added dropwise to a suspension of NaH (65% in oil) (1.23 g, 0.033 mol) in THF (20 ml) at 30—40°C with vigorous stirring. Stirring was continued for 3 h at room temperature, then the reaction mixture was neutralized with 10% AcOH under ice cooling and concentrated *in vacuo*. The residue was extracted with AcOEt and the extract was washed with H_2O, dried over $MgSO_4$, and then concentrated *in vacuo*. The resulting oil was purified by distillation or column chromatography to give **6**, **9** or **12** as a colorless oil. These results are summarized in Tables I, III, and V.

General Procedure for the Preparation of α-Alkyl-α-(alk-1-enyl)glycines (7, 10, and 13)——A solution of **6**, **9** or **12** (0.01 mol) in a mixture of MeOH (15 ml) and conc. HCl (3 ml) was stirred for 4 h at room temperature. The reaction mixture was concentrated to dryness *in vacuo*. The resulting residue was triturated with Et_2O and the crystals obtained were filtered by suction. Subsequently, these crystals were dissolved in 2 N aqueous sodium hydroxide (20 ml), and the solution was stirred for 6 h at room temperature, then

Table VIII. Yields and Physical Properties of **4**, **8**, and **11**

Compd.	Yield (%)	bp (°C/mmHg)	IR ν_{max}^{film} cm^{-1}	NMR ($CDCl_3$) δ OMe	Compd.	Yield (%)	bp (°C/mmHg)	IR ν_{max}^{film} cm^{-1}	NMR ($CDCl_3$) δ OMe
4a	90	97/3	2120, 1730, 1630	3.81	**8c**	83	——[a]	2110, 1730, 1616	3.84
4b	97	83/2	2120, 1730, 1630	3.81	**8d**	85	——[a]	2120, 1730, 1600	3.89
4c	84	90/2	2120, 1730, 1610	3.80	**11a**	96	——[a]	2120, 1730, 1600	3.61
4d	85	95/2	2120, 1730, 1600	3.80		90	——[a]	2120, 1730, 1600	3.89
4e	82	100/2	2110, 1730, 1590	3.82	**11b**	82	106/38	2130, 1737, 1626	3.83
4f	87	——[a]	2120, 1735, 1614	3.82	**11c**	87	81—83/7	2110, 1730, 1618	3.82
8a	67	——[a]	2120, 1730, 1612	3.87	**11d**	81	86—88/9	2110, 1730, 1608	3.83
8b	83	——[b]	2105, 1727,[c] 1607	3.90	**11e**	85	73—77/5	2125, 1740, 1640	3.86

a) Purified by column chromatography. *b*) mp 79—81°C (colorless needles from Et_2O–hexane). *c*) Taken in Nujol.

concentrated to dryness *in vacuo*. The resulting residue was dissolved in 20% aqueous alcohol and the solution was neutralized with 10% HCl to give **7**, **10** or **13** as colorless crystals. These results are summarized in Tables II, IV and VI.

Typical Procedure for the Direct Synthesis of Methyl α-Isocyanocycloalkylideneacetate (4a, b, d)—A solution of cyclopentanone (1.68 g, 0.02 mol) and methyl isocyanoacetate (2 g, 0.02 mol) in DMF (10 ml) was added dropwise to a solution of piperidine (1.7 g, 0.02 mol) in DMF (10 ml) at room temperature. After being stirred for 3 h at the same temperature, the solution was neutralized with 10% AcOH under cooling and the solvent was removed *in vacuo*. The residue was extracted with AcOEt and the extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The oily residue was distilled to give **4a** as a colorless oil (2.21 g, 67%).

Acknowledgement We wish to express our thanks to Dr. I. Chibata, Director, and Dr. M. Miyoshi, Vice Director, of this Research Laboratory, for their encouragement of this study. Thanks are also extended to Dr. K. Matsumoto for valuable comments.

References and Notes

1) A part of this study was presented at the 28th Annual Meeting of the Kinki Branch, Pharmaceutical Society of Japan, Nishinomiya, October 1978.
2) J.P. Seannell, D.L. Preuss, J.C. Demney, L.H. Sello, T. Williams, and A. Stempel, *J. Antibiot.*, **25**, 122 (1972); U. Sahm, G. Knoblock, and F. Wagner, *ibid.*, **26**, 389 (1973); D.L. Preuss, J.P. Seannell, M. Kellett, H.A. Ax, J. Janecek, T.H. Williams, A. Stempel, and J. Berger, *ibid.*, **27**, 229 (1974); Y. Kuroda, M. Okuhara, T. Goto, E. Iguchi, M. Kohsaka, H. Aoki, and H. Imanaka, *ibid.*, **33**, 125 (1980); *idem*, *ibid.*, **33**, 132 (1980).
3) R.R. Rando, *Science*, **185**, 320 (1974); J.P. Scannell and D.L. Preuss, *Chem. Biochem. Amino Acids, Pept. Proteins*, **3**, 189 (1974); R.R. Rando, *Acc. Chem. Res.*, **8**, 281 (1975); H.G. Gehring, R.R. Rando, and P. Christen, *Biochemistry*, **16**, 4832 (1977); E.W. Miles, "Enzyme-Activated Irreversible Inhibitors," ed. by N. Seiler, M.J. Jung, and J. Koch-Weser, Elsevier, Amsterdam. 1978, p. 73 and references cited therein.
4) B. Levenberg, *J. Biol. Chem.*, **243**, 6009 (1968); T. Asako, T. Soma, H. Masuya, T. Harukawa, and T. Miki, Ger. Patent 2165990 (1972) [*Chem. Abstr.*, **77**, 127059 (1972)]; H.J. Christopher, Brit. Patent 1315443 (1973) [*Chem. Abstr.*, **79**, 53308 (1973)]; P. Friis, P. Helboe, and P.O. Larsen, *Acta Chem. Scand.*, **B28**, 317 (1974); J.E. Baldwin, S.B. Haber, C. Hoskins, and L.I. Kruse, *J. Org. Chem.*, **42**, 1239 (1977); D. Ben-Ishai, R. Moshenberg, and J. Altmen, *Tetrahedron*, **33**, 1533 (1977); D.D. Keith, J.A. Tortora, and R. Yang, *J. Org. Chem.*, **43**, 3711 (1978); D.D. Keith, R. Yang, J.A. Tortora, and M. Weigele, *ibid.*, **43**, 3713 (1978); R.V.J. Chari and J. Wemple, *Tetrahedron Lett.*, **1979**, 111; P. Dowd and C. Kaufman, *J. Org. Chem.*, **44**, 3956 (1979); A. Afzali-Ardakani and H. Rapoport, *ibid.*, **45**, 4817 (1980); F. Heinzer

and D. Bellus, *Helv. Chim. Acta*, **64**, 2279 (1981).
5) K. Nunami, M. Suzuki, and N. Yoneda, *J. Chem. Soc., Perkin Trans. 1*, 2224 (1979).
6) P. Bey and J.P. Vevert, *J. Org. Chem.*, **45**, 3249 (1980); C. Danzin, P. Casara, N. Claverie, and B.W. Metcalf, *J. Med. Chem.*, **24**, 16 (1981).
7) D. Taub and A.A. Patchett, *Tetrahedron Lett.*, **1977**, 2745; B.W. Metcalf and K. Jund, *ibid.*, **1977**, 3689; W.J. Greenlee, D. Taub, and A.A. Patchett, *ibid.*, **1978**, 3999; B.W. Metcalf and E. Bonilavri, *Chem. Commun.*, **1978**, 914; W. Steglich and H. Wegmann, *Synthesis*, **1980**, 481.
8) K. Nunami, M. Suzuki, and N. Yoneda, *Synthesis*, **1978**, 840.
9) Schöllkopf *et al.* independently reported the synthesis of α-vinyl-α-amino acids by a similar method using α-isocyanoacrylates in *Synthesis*, **1981**, 646.
10) A.C. Cope and E.M. Hancock, *J. Am. Chem. Soc.*, **60**, 2644, 2901 (1938).
11) U. Schöllkopf, F. Gerhart, R. Schröder, and D. Hoppe, *Ann. Chem.*, **766**, 116 (1972).
12) R. Glaser, S. Geresh, U. Schöllkopf, and R. Meyer, *J. Chem. Soc., Perkin Trans. 1*, 1746 (1979).
13) For example: J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure," McGraw-Hill Book Company, New York, 1968, pp. 142—143.
14) D. Hoppe and U. Schöllkopf, *Ann. Chem.*, **763**, 1 (1972).
15) T. Saegusa, Y. Ito, H. Kinoshita and S. Tomita, *J. Org. Chem.*, **36**, 3316 (1971).
16) K. Matsumoto, M. Suzuki, Y. Ozaki, and M. Miyoshi, *Agric. Biol. Chem.*, **40**, 2045 (1976).
17) M. Suzuki, M. Miyoshi, and K. Matsumoto, *J. Org. Chem.*, **39**, 1980 (1974); K. Matsumoto, M. Suzuki, Y. Ozaki, and M. Miyoshi, *Agric. Biol. Chem.*, **40**, 2271 (1976); K. Sakai, M. Suzuki, K. Nunami, N. Yoneda, Y. Onoda, and Y. Iwasawa, *Chem. Pharm. Bull.*, **28**, 2384 (1980).
18) M. Suzuki, K. Nunami, T. Moriya, K. Matsumoto, and N. Yoneda, *J. Org. Chem.*, **43**, 4933 (1978).
19) M. Suzuki, K. Nunami, K. Matsumoto, N. Yoneda, O. Kasuga, H. Yoshida, and T. Yamaguchi, *Chem. Pharm. Bull.*, **28**, 2374 (1980).