Synthesis of α-[(Aminomethylene)amino]acrylic Acid Esters[1]

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The reaction of methyl isocyanoacetate with aldehydes and secondary amines was carried out to synthesize methyl α-[(aminomethylene)amino]acrylates; the *E* isomer was the predominant product. The reaction is postulated to proceed by a Michael type addition of the amine to the methyl α-isocyanoacrylate, followed by a synchronous elimination–insertion of the amine into the isocyano group.

Recently a number of synthetic studies using α-isocyanoacetic acid compound, which is one of the α-amino acid analogues, have figured prominently and many useful synthetic methods of biologically active compounds have been developed.[2] In particular, the reactions of the isocyanoacetate with aldehydes have been frequently investigated. Schöllkopf et al. reported that the reaction in the presence of sodium hydride[3] and sodium cyanide[4] afforded α-*N*-formylaminoacrylates and oxazoline carboxylates, respectively, as main products. Saegusa et al. described the formation of the oxazoline compound by the reaction in the presence of copper catalyst.[5] We also stated that α-isocyano-β-hydroxybutyrates and α-isocyanoacrylates[6] and pyrrole dicarboxylates[7] were obtained in the 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 obtained in the reaction of α-isocyanoacetate with aldehydes depend upon the variety of the reaction conditions.

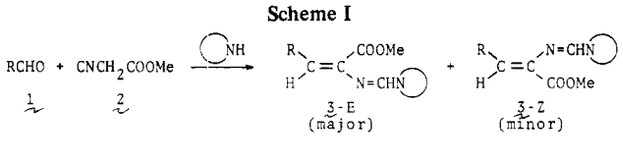
In the course of our studies on the syntheses of α-amino acids and heterocyclic compounds using isocyano compounds, we have found that the reaction of methyl isocyanoacetate (**2**) with aldehydes (**1**) in the presence of secondary amines such as pyrrolidine and piperidine gives directly methyl α-[(aminomethylene)amino]acrylates (**3**) in good yields.

When an equimolar mixture of *p*-chlorobenzaldehyde, methyl isocyanoacetate (**2**), and pyrrolidine was stirred in methanol at room temperature, a product sensitive to the Dragendorff reagent was isolated as the hydrochloride having mp 163–164 °C dec. The IR spectrum (Nujol) showed an ester C=O band at 1730 cm^{-1}, a C=N band at 1690 cm^{-1}, and a C=C band at 1635 cm^{-1}, and the ^1H NMR spectrum (DMSO-d_6) indicated the presence of two methyl ester groups (δ 3.77 and 3.86), which suggests a mixture of *Z* and *E* isomers, an iminomethylene proton (δ 8.47 and 8.70), aromatic group, and pyrrolidinyl group. These data and the elemental analyses suggest this compound is methyl α-[(pyrrolidinylmethylene)amino]-*p*-chlorocinnamate (**3a**).

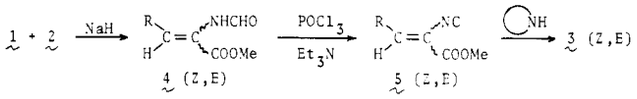
Using the same method, various methyl α-[(aminomethylene)aminoacrylate derivatives (**3b–e**) were prepared as a mixture of *Z* and *E* isomers, except **3e**, as summarized in Table I.

With regard to the formation of an amidine compound, Saegusa et al. reported[8] that a reaction of aliphatic isocyanide with amine took place using a catalyst such as group 1B and 2 metal compounds. On the other hand, we found that methyl isocyanoacetate was easily converted into the isocyanoacetamides[9] by the reaction with amines. Moreover, we reported that a reaction of the isocyanoacetate with aldehydes in the presence of tertiary amines afforded the oxazoline carboxylate

Scheme I



Scheme II



and α-isocyanoacrylate.[6] In contrast to these results, the reaction of the isocyanoacetate with aldehydes and secondary amines proceeded smoothly to yield the amidines (**3**) without the metallic catalysts; furthermore, only small amounts of the amide compounds were formed.

Generally, it has been suggested that the compound **3** seems to be formed by the simple α addition of the amine to the isocyano group of methyl α-isocyanoacrylate (**5**),[8] which would be a reactive species obtained by the Knoevenagel type reaction of **1** with **2**.[7] In order to confirm the mechanism and the stereochemistry of the resulting compound (**3**), the reaction of **5** with the secondary amines was investigated.

The methyl α-formylaminoacrylates (**4a–e**) were synthesized to give a mixture of *E* and *Z* isomers according to a similar method as described by Schöllkopf et al.[3] as shown in Scheme II. This mixture was easily separated by either recrystallization or silica gel chromatography. The geometric structure of the resulting compound (**4**) was readily determined by a comparison of the methyl proton signal of the ester group and the formyl proton signal in the ^1H NMR spectra. The chemical shift of the methyl proton of the *E* configuration appeared at higher field than that of the *Z* configuration because of the anisotropic effect of the adjacent benzene ring,[3] while the chemical shift of the formyl group of the *Z* configuration was observed at higher field. In the case of **4e** having thiophene ring, the assignment of a geometric structure could not be made from the ^1H NMR spectrum. These results are summarized in Table II.

The resulting (*Z*)- or (*E*)-α-formylaminoacrylate compounds (**4**) were readily converted to methyl α-isocyanoacrylates (**5**) using phosphoryl chloride in the presence of triethylamine[10] in high yields as shown in Table III.

To clarify the reaction mechanism of the formation of the amidines, (*Z*)- or (*E*)-methyl α-isocyano-*p*-chlorocinnamate (**5a**) was allowed to react with pyrrolidine in a typical reaction. Surprisingly, both ^1H NMR signals of the products (**3a**) derived from (*Z*)- and (*E*)-**5a** showed a similar pattern. Moreover, these spectra were nearly in accord with that of **3a** obtained by the one-step reaction. The ratio of *E* and *Z* isomers was determined as 5:1 from the ^1H NMR spectrum.

In a similar way, the reactions using other isocyano compounds (**5b–e**) were carried out to obtain the corresponding amidine compounds (**3b–e**) in good yields as shown in Table I.

In this reaction, the *E* form amidine (**3**), which is the thermodynamically stable isomer, was predominantly obtained, although the reaction resulting in the formation of the *Z* and *E* isomers of **3** would proceed through the same reaction pathway. From these results, it appears that the direct α addition of the isocyano group of the methyl α-isocyanoacrylate

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Table I. Formation of Methyl α-[(Aminomethylene)amino]acrylate (3) Hydrochlorides[a]

			method by Scheme I			method by Scheme II		
compd	R	HN◯	yield, %	mp, °C dec	isomer ratio[b] E/Z	yield, %	mp, °C dec	isomer ratio[b] E/Z
3a	4-chlorophenyl	HN⬠	47	163–164	5/1	62 (from (Z)-**5a**) 48 (from (E)-**5a**)	162–164 163–164	5/1 5/1
3b	3,4-methylenedioxyphenyl	HN⬠	42	151–153	20/1	70 (from (Z)-**5b**) 58 (from (E)-**5b**)	151–152 153–154	20/1 9/1
3c	*p*-tolyl	HN⬠	36	162–164	4/1	74 (from (Z)-**5c**)	159–162	10/1
3d	4-(dimethylamino)phenyl	HN⬡	45	175–177	10/1	52 (from (Z)-**5d**)	174–176	only *E*
3e	2-thienyl	HN⬠	53	170–172	single isomer[c]	58 (from **5e**)	170–172	single isomer[c]

[a] **3a–c** and **3e** were monohydrochloride and **3d** was dihydrochloride. [b] Isomer ratio based on ^{1}H NMR analyses; the differences of the ratio are due to the fractionation during the recrystallization. [c] The geometric structure could not be apparently determined in the ^{1}H NMR spectrum.

Table II. Formation of Methyl α-(Formylamino)acrylates (4)

			yield,		^{1}H NMR ($CDCl_3$) δ	
compd[c]	R	registry no.	%	mp, °C	CHO	COOMe
4a	(Z)-4-chlorophenyl	68001-79-6	58	109–110	8.26	3.86
	(E)-4-chlorophenyl	68001-80-9	29[a]	(syrup)	8.31	3.66
4b	(Z)-3,4-methylenedioxyphenyl	68001-81-0	48	136–138	8.20	3.84
	(E)-3,4-methylenedioxyphenyl	68001-82-1	25[a]	(syrup)	8.25	3.70
4c	(Z)-*p*-tolyl	68001-83-2	44	116–117	8.27	3.86
4d	(Z)-4-(dimethylamino)phenyl	68001-84-3	42	122–124	8.18	3.82
4e	2-thienyl	68001-85-4	39[b]	135–137	8.32	3.73

[a] Contaminated by a small amount of the *Z* isomer. [b] A single isomer. [c] Satisfactory analytical data (±0.4% for C,H,N) were submitted for review.

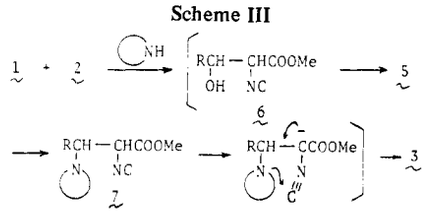
Table III. Formation of Methyl α-Isocyanoacrylates (5)

			yield,		IR ν_{max} (Nujol), cm^{-1}		^{1}H NMR, δ ($CDCl_3$)
compd[b]	R	registry no.	%	mp, °C	NC	COOMe	COOMe
5a	(Z)-4-chlorophenyl	68001-86-5	95	88–89	2120	1730	3.90
	(E)-4-chlorophenyl	68185-82-0	89[a]	59–61	2120	1735	3.82
5b	(Z)-3,4-methylenedioxyphenyl	68001-87-6	90	119–121	2120	1730	3.89
	(E)-3,4-methylenedioxyphenyl	68001-88-7	92[a]	79–84	2120	1730	3.85
5c	(Z)-*p*-tolyl	68001-89-8	82	79–80	2100	1715	3.90
5d	(Z)-4-(dimethylamino)phenyl	68001-90-1	95	106–108	2120	1715	3.88
5e	2-thienyl	62879-42-9	95	77–78	2120	1720	3.91

[a] Contaminated by a small amount of the *Z* isomer. [b] Satisfactory analytical data (±0.4% for C,H,N) were submitted for review.

(**5**) to amine does not occur. Instead, it is likely that nucleophilic addition of the secondary amine to the double bond of the α-isocyanoacrylate (**5**) occurs resulting in the formation of β-amino isocyanide (**7**), which is a Michael-type adduct. The formation of **7** is also supported by the synthesis of imidazoline compound reported by Schöllkopf et al.[11] and by our pyrrole synthesis.[7] Finally, the addition of the amino group to the isocyano group may proceed synchronously with the cleavage of the C–N bond to form the α-[(aminomethylene)-amino]acrylate (**3**) by an intramolecular rearrangement as shown in Scheme III.

Scheme III



Experimental Section[12]

Typical Procedure for Preparation of Amidines (3a). One-Step Reaction. To a mixture of pyrrolidine (1.42 g, 0.02 mol) and methanol (10 mL) was added a mixture of *p*-chlorobenzaldehyde (2.81 g, 0.02 mol) and methyl isocyanoacetate (**2**, 1.08 g, 0.02 mol) in methanol (10 mL) at 30–35 °C for a period of 15 min with stirring. After stirring was continued for 3 h at room temperature, the reaction mixture was evaporated in vacuo and the resulting residue was extracted with ethyl acetate. After the extract was washed with water, 10% hydrochloric acid (30 mL) was added to the extract and the mixture was vigorously stirred. Subsequently, the separated acidic layer was neutralized with sodium bicarbonate and the oily products which appeared were extracted with ethyl acetate. The organic extract was washed with water, dried over sodium sulfate, and then evaporated in vacuo to obtain the crude oily product (**3a**). The product was treated with 20% hydrochloric acid in dioxane (5 mL). Recrystallization of the crude salt from a mixture of methanol and ether gave methyl α-[(pyrrolidinylmethylene)amino]-*p*-chlorocinnamate (a mixture of (*Z*)- and (*E*)-**3a**; the ratio is ca. 1:5) hydrochloride as colorless leaflets: yield 3.1 g (47%); IR (Nujol) 1730 (COOMe), 1690 (N=C), and 1635 cm^{-1} (C=C); ^{1}H NMR (Me_2SO-d_6) δ 11.85 (br, 1, HCl), 8.70 and 8.47 (broad s, 1, N=CH), 7.20–7.60 (m, 5, CH=C and

aromatic H), 3.86 and 3.77 (s, s, 3, OCH_3), 3.50–4.00 (m, 4, $CH_2 \times 2$), 1.80–2.20 (m, 4, $CH_2 \times 2$).

Anal. Calcd for $C_{15}H_{18}Cl_2N_2O_2$: C, 54.72; H, 5.51: N, 8.51; Cl, 21.54. Found: C, 54.49; H, 5.77; N, 8.22; Cl, 21.78.

In the same manner, other amidine (**3b–e**) hydrochlorides were obtained as a mixture of *Z* and *E* having the ratio shown in Table I. IR and NMR spectra and elemental analyses are shown as follows:

Methyl α-[(Pyrrolidinylmethylene)amino]-p-methylcinnamate (3b) Hydrochloride: IR (Nujol) 1738 (COOMe), 1695 (N=C), 1640 cm^{-1} (C=C); ^1H NMR (Me_2SO-d_6) δ 11.70 (br, 1, HCl), 8.70 and 8.47 (broad s, 1, N=CH), 7.26 (s, 1, CH=C), 7.40–8.10 and 7.21 (m, s, 4, aromatic H), 3.40–4.00 (m, 4, $CH_2 \times 2$), 3.80 and 3.70 (s, s, 3, OCH_3), 2.40 and 2.30 (s, s, 3, CH_3), 1.70–2.20 (m, 4, $CH_2 \times 2$).

Anal. Calcd for $C_{16}H_{21}ClN_2O_2$: C, 62.23; H, 6.85; N, 9.07; Cl, 11.48. Found: C, 62.25; H, 6.74; N, 9.15; Cl, 11.71.

Methyl α-[(Pyrrolidinylmethylene)amino]-3,4-methylenedioxycinnamate (3c) Hydrochloride: IR (Nujol) 1737 (COOMe), 1700 (N=C), 1640 cm^{-1} (C=C); ^1H NMR (Me_2SO-d_6) δ 11.50 (br, 1, HCl), 8.68 and 8.51 (broad s, 1, N=CH), 7.20 (s, 1, CH=C), 6.90 (s, 3, aromatic H), 6.08 (s, 2, OCH_2-O), 3.71 and 3.80 (s, s, 3, OCH_3), 3.10–4.10 (m, 4, $CH_2 \times 2$), 1.60–2.30 (m, 4, $CH_2 \times 2$).

Anal. Calcd for $C_{16}H_{19}ClN_2O_4$: C, 56.72; H, 5.65; N, 8.27; Cl, 10.47. Found: C, 56.48; H, 5.78; N, 8.28; Cl, 10.50.

Methyl α-[(Piperidinomethylene)amino]-p-dimethylaminocinnamate (3d) Dihydrochloride: IR (Nujol) 1730 (COOMe), 1690 (N=C), 1638 cm^{-1} (C=C); ^1H NMR (Me_2SO-d_6) δ 11.80 and 9.00 (broad s, 2, HCl × 2), 8.0–8.70 (m, 1, N=CH), 6.80–7.80 (m, 5, CH=C and aromatic H), 3.70 and 3.78 (s, s, 3, OCH_3), 3.50–4.10 (m, 4, $CH_2 \times 2$), 3.02 and 3.08 (s, s, 6, $NCH_3 \times 2$), 1.60–1.90 (m, 6, $CH_2 \times 3$).

Anal. Calcd for $C_{18}H_{27}Cl_2N_3O_2$: C, 55.67; H, 7.01; N, 10.82; Cl, 18.26. Found: C, 55.52; H, 6.96; N, 10.81; Cl, 18.13.

Methyl α-[(Pyrrolidinylmethylene)amino]-β-2-thienylacrylate (3e) Hydrochloride: IR (Nujol) 1710 (COOMe), 1680 (N=C), 1617 cm^{-1} (C=C); ^1H NMR (Me_2SO-d_6) δ 11.50 (broad s, 1, HCl), 8.69 (broad s, 1, N=CH), 7.40–7.90 (m, 2, CH=C and thiophene 5-H), 7.40–7.60 (m, 1, thiophene 3 H), 7.00–7.20 (m, 1, thiophene 4 H), 3.82 (s, 3, OCH_3), 3.20–4.00 (m, 4, $CH_2 \times 2$), 1.70–2.20 (m, 4, $CH_2 \times 2$).

Anal. Calcd for $C_{13}H_{17}ClN_2O_2S$: C, 51.91; H, 5.70; N, 9.31; Cl, 11.79; S, 10.66. Found: C, 51.88; H, 5.79; N, 9.18; Cl, 11.91; S, 10.57.

Typical Procedure for Preparation of the Amidine Compound (3a) from Isocyanides (5a). After a mixture of (*Z*)-methyl α-isocyano-*p*-chlorocinnamate ((*Z*)-**5a,** 662 mg, 3 mmol) and pyrrolidine (497 mg, 7 mmol) in methanol (15 mL) was stirred for 5 h at room temperature, the same treatment as described in the one-step reaction was carried out to afford **3a.**

In a similar way, other amidine (**3b–e**) hydrochlorides were prepared in good yields as shown in Table I. The IR and ^1H NMR spectra were in accord with those of **3** hydrochlorides obtained by the one-step reaction.

Acknowledgment. We wish to express our thanks to Dr. Ichiro Chibata, Director and Dr. Muneji Miyoshi, Vice Director of this Research Laboratory for their encouragement in this study.

Registry No.—**2,** 39687-95-1; (*Z*)-**3a,** 68001-91-2; (*E*)-**3a,** 68001-92-3; (*Z*)-**3b,** 68001-93-4; (*E*)-**3b,** 68001-94-5; (*Z*)-**3c,** 68024-33-9; (*E*)-**3c,** 68024-32-8; (*E*)-**3d,** 68001-95-6; **3e,** 68001-96-7; pyrrolidine, 123-75-1; p-chlorobenzaldehyde, 104-88-1; 3,4-methylenedioxybenzaldehyde, 120-57-0; *p*-methylbenzaldehyde, 104-87-0; 4-dimethylaminobenzaldehyde, 100-10-7; 2-thiophenecarboxaldehyde, 98-03-3; piperidine, 110-89-4.

References and Notes

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

One-Proton Catalysis in the Intermolecular Imidazole-Catalyzed Hydrolysis of Esters and Amides[1]

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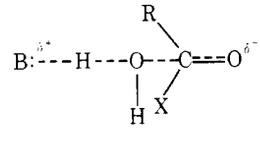
The linear proton inventories observed for the imidazole-catalyzed hydrolysis of both 1-acetylimidazole and ethyl trifluorothiolacetate are interpreted in terms of transition-state structures. The observed solvent isotope effects arise from a single transition-state proton (i.e., one-proton catalysis).

Intermolecular general base catalysis is known to occur in a variety of hydrolytic reactions.[3] A number of bases such as imidazole, acetate, or even water can function as general base catalysts in such reactions. It has been presumed that a typical transition state for such a reaction could be represented as in eq 1.



(1)

Evidence for such transition states comes mainly from Brønsted plots. For example, the logarithms of the second-order rate constants for the hydrolysis of ethyl dichloroacetate catalyzed by oxygen bases bear a linear relationship to the pK_a of the bases. The Brønsted β value is 0.47.[4] Interestingly, the rate constant for the "water" reaction also falls on the Brønsted line suggesting that water also functions as a general base in this reaction. In fact, considerable evidence has accumulated which indicates that the neutral,water-catalyzed hydrolysis of esters, amides, and carbonates involves transition states such as those shown in eq 2. Most of the support

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