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Synthesis of β-Functionalized α,β-Dehydroamino Acid Derivatives[1]

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Summary: β-Functionalized α,β-unsaturated amino acids were synthesized by an addition-elimination pathway. Reaction of methyl β-bromo-α-formylaminoacrylates (3a-e), which were prepared by the condensation of methyl isocyanoacetate (1) with aldehydes followed by bromination, with thiols gave β-alkylthio-α,β-unsaturated amino acid derivatives (6a-f). The reaction of (3a) with sodium azide resulted in the formation of a 2-oxoimidazoline derivative (4). On the other hand, β-benzyloxy- and β-benzylamino-α,β-unsaturated amino acids (9 and 12) were synthesized by the reaction of methyl β-bromo-α-isocyanocinnamates (7a and 7d), prepared from (3a and 3d), with benzyl alcohol and benzylamine followed by acidic hydration, respectively.

Various kinds of α,β-dehydroamino acids occur as components of naturally occurring peptides which often possess potent antimicrobial and phytotoxic activities.[2]

Many synthetic methods have been reported for α,β-dehydroamino acids to date,[3] but there are only a few effective routes for the synthesis of β-functionalized α,β-dehydroamino acid derivatives, which are analogs of serine, phenylserine, cysteine, α,β-diaminopropionic acid etc.. Shin *et al.* reported a synthesis of α,β-dehydrodiaminopropionic acid by azidation of N-bromo-α-acylaminoacrylic acid esters followed by 1,3-azide rearrangement.[4] Olsen *et al.* synthesized β-mercaptodehydroalanine derivatives using a radical reaction of β-chlorodehydroalanine esters with several thiols.[5]

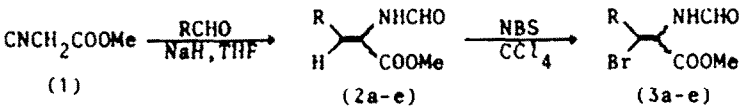
These methods, however, lack versatility for the synthesis of many types of β-functionalized α,β-dehydroamino acids.

In our synthetic studies[6] on amino acids and related compounds using isocyano compounds we have observed that α-isocyanoacrylic acids and α-formylaminoacrylic acids, which are easily derived from isocyanoacetic acid derivatives, are useful intermediates for the syntheses of biologically interesting α,β- and β,γ-unsaturated amino acids[7-9] and heterocyclic compounds.[10]

Recently, we have focused on β-bromo-α-formylaminoacrylic acid and β-bromo-α-isocyanoacrylic acid derivatives and now report the syntheses of β-substituted α,β-unsaturated cysteine, serine, and α,β-diaminopropionic acid derivatives using these versatile synthons.

Results and Discussion.

First, in order to examine the reactivity of β-bromo-α-formylamino-acrylic acid esters (3), several derivatives as shown in Table 1 were synthesized. Condensation of methyl isocyanoacetate (1) with appropriate



(1) (2a-e) (3a-e)

a:R=Ph, b:R=4-Me-Ph, c:R=4-MeO-Ph, d:R=4-Cl-Ph, e:R=Et_2CH-

Scheme 1

aldehydes[9] followed by bromination using N-bromosuccinimide (NBS)[11] afforded (3) as a mixture of E- and Z-isomers. These isomers were separated by column chromatography on silica gel and the stereochemistry of the aromatic derivatives (3a-d) was elucidated by comparison of the methyl proton signal of the ester group and the formyl proton signal in the ^1H n.m.r. spectra.[12] The methyl proton signal of the Z-isomer appears at higher field than that of the corresponding E-isomer because of the anisotropic effect of the adjacent benzene ring. The chemical shift of the formyl proton of the E-isomer is observed at higher field than that of the Z-isomer. The structures of the isomers of the aliphatic compound (3e) were assigned by comparison of the β-alkyl proton signals in their ^1H n.m.r.

spectra.[13] In the bromination of either (Z)- or (E)-methyl α-formylaminoacrylate (2), β-bromo derivatives (3) having Z-geometry were predominantly obtained as shown in Table 1.

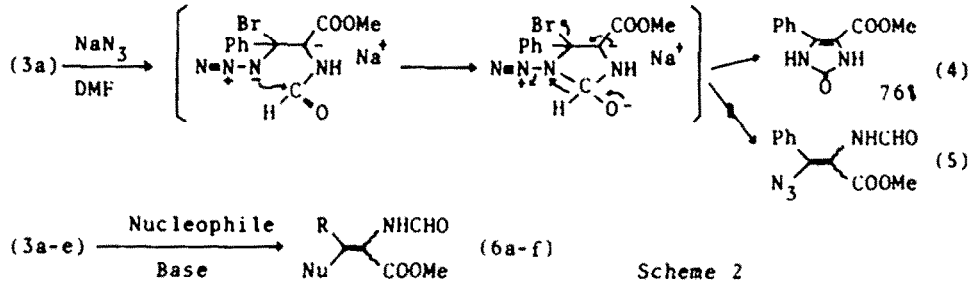
Table 1 Yields and physical data of (3)

Compound	R	Yield[a] (%)	M.p.(°C)	ν_{max}(Nujol) cm^{-1}	^{1}H n.m.r.[b] OMe[c]	CHO[d]	NH[e]
Z-(3a)	Ph	56	136-138	3210,1740,1690,1665	3.51	8.25	9.18[f]
E-(3a)	Ph	4	109-110	3270,1740,1685,1665	3.88	7.89	7.86[f]
Z-(3b)	4-Me-Ph	62	147-150	3210,1735,1665	3.42	8.15	10.03
E-(3b)	4-Me-Ph	8	101-103	3210,1735,1690,1665	3.74	7.87	9.76
Z-(3c)	4-MeO-Ph	34	156-158	3220,1735,1660	3.48	8.20	10.01
E-(3c)	4-MeO-Ph	5	131-133	3150,1745,1655	3.79	7.92	9.85
Z-(3d)	4-Cl-Ph	67 62[g]	164-166	3240,1730,1660	3.50	8.23	10.20
E-(3d)	4-Cl-Ph	3 3[g]	112-114	3220,1725,1655	3.76	7.90	9.94
Z-(3e)	Et_2CH-	54	91-92	3210,1730,1695,1670	3.75	8.06	7.55[f]
E-(3e)	Et_2CH-	4	62-63	3340,1725,1700,1690	3.76	8.01	7.55[f]

[a]Isolation yield. Z-(2) was used as a starting material. [b]δ Values. $(CD_3)_2SO$ as solvent. [c]Singlet. [d]Doublet J 2Hz. [e]Broad singlet. [f]$CDCl_3$ as solvent. [g]E-(2d) was used as a starting material.

Shin *et al.* have reported that α-acetylamino-β-bromoacrylic acid esters are inert to sodium azide (NaN_3). We carried out the same reaction using (Z)-methyl β-bromo-α-formylaminocinnamate (3a) and NaN_3 in N,N-dimethylformamide (DMF) at room temperature. The product obtained did not show an amide band in its i.r. spectrum, and other spectral data and elemental analysis suggested that the product was not β-azido-α-formylaminocinnamate (5) as expected, but 4-methoxycarbonyl-2-oxo-5-phenylimidazoline (4). Compound (4) would be produced *via* β-azidation by the route as shown in Scheme 2.

Next, the reaction of Z-(3a) with ethanethiol was carried out in the presence of sodium hydride (NaH) in hexamethylphosphoramide (HMPA). The product was a mixture of E- and Z-isomers of methyl β-ethylthio-α-formylaminocinnamate (6a) and the isomer ratio was determined by ^{1}H n.m.r. spectroscopy as described above.[13] The same reaction with E-isomers [E-(3c)



Scheme 2

and E-(3d)] proceeded without any change of the products' geometric ratio. This result was suggestive of an addition-elimination process. Other β-alkylthio-α,β-dehydroamino acids (6a-f) were similarly prepared from the corresponding β-bromo-α-formylamino compounds (3a-e) as shown in Table 2.

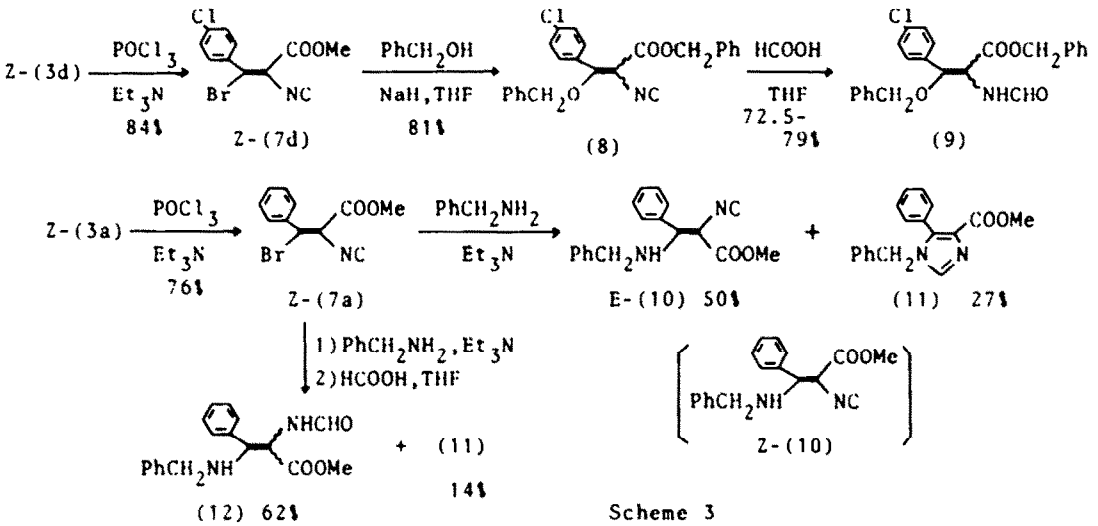
Table 2 Reaction of (3a-e) with nucleophiles

Compound	R	Nucleophile	Base	Solvent	Yield(%)[a]	Isomer ratio[b] (E/Z)
(6a)	Ph	EtSH	NaH	HMPA	72 from Z-(3a)	45/55
(6b)	Ph	$PhCH_2SH$	^tBuOK	THF	73 from Z-(3a)	30/70
(6c)	4-Me-Ph	EtSH	NaH	HMPA	74 from Z-(3b)	22/78
(6d)	4-MeO-Ph	EtSH	NaH	HMPA	68 from Z-(3c)	40/60
					65 from E-(3c)	38/62
(6e)	4-Cl-Ph	EtSH	NaH	HMPA	69 from Z-(3d)	48/52
					66 from E-(3d)	45/55
(6f)	Et_2CH-	EtSH	NaH	HMPA	68 from Z-(3e)	c
(6g)	4-Cl-Ph	$PhCH_2OH$	NaH	HMPA	no reaction	
(6h)	4-Cl-Ph	$PhCH_2NH_2$	Et_3N	HMPA	no reaction	

[a]Isolation yield. [b]Determined by ^1H n.m.r. analysis. [c]The stereochemistry could not be determined in the ^1H n.m.r. spectrum.

The reactions of (3d) with benzyl alcohol and benzylamine were attempted under various conditions but failed to give the desired methyl β-substituted α-formylamino-(4-chloro)cinnamate [(6g) and (6h)]. Only starting materials were recovered. Then, we turned our attention to the isocyano group which has not only strong electron-withdrawing character, but is also easily converted to the formylamino group under mild conditions.

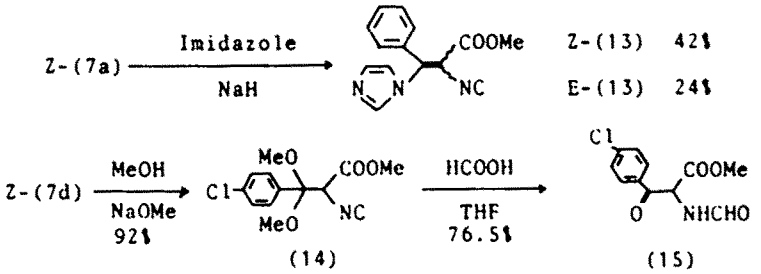
As a typical example, we carried out the reaction of (Z)-methyl β-bromo-α-isocyano-(4-chloro)cinnamate [Z-(7d)] prepared from Z-(3d) by our method[9] with various nucleophiles. When benzyl alcohol was used, the reaction was accompanied by transesterification and benzyl β-benzyloxy-α-isocyano-(4-chloro)cinnamate (8) was obtained in a good yield as a 21:79 mixture of E- and Z-isomers. After separation of each isomer, each of the phenylserine derivatives was converted to the corresponding α-formylamino derivative (9) by treatment with anhydrous 40% V/V HCOOH-THF at room temperature.



Scheme 3

When this type of reaction was extended to the condensation of Z-(7a) with benzylamine in the presence of triethylamine, (E)-methyl β-benzylamino-α-isocyanocinnamate (10) and an unexpected compound were isolated in 50% and 27% yield, respectively, while Z-isomer [Z-(10)] was not obtained at all. The physicochemical and analytical data of the by-product suggested it to be 4-methoxycarbonyl-2-oxo-5-phenylimidazoline (11) which would be obtained *via* formation of Z-isomer. Thus, in order to obtain the (Z)-β-benzylamino-α,β-dehydroamino acid derivative, after the starting material [Z-(7a)] disappeared, the reaction mixture was treated with 40% V/V HCOOH-THF for 1hr to prevent from the formation of (11). Consequently, methyl β-benzylamino-α-formylaminocinnamate (12) was obtained in 62% yield

as a mixture of geometric isomers (E/Z=19/5) with a small amount of (11) (14%). In a similar manner, the α,β-unsaturated β-(1-imidazolyl) compound (13) was obtained from the reaction of Z-(7a) with imidazole as shown in Scheme 4. Furthermore, the reaction of Z-(7d) with methanol in the presence of sodium methoxide gave the α-isocyano-β-dimethylketal derivative (14) in 92% yield. This compound was easily coverted to N-formyl-β-ketophenyl-



Scheme 4

alanine ester (15) which is an α,β-dehydrophenylserine analog as well as an interesting intermediate for the synthesis of other amino acids and heterocyclic compounds.

Thus, the aforementioned β-bromo-α-isocyanoacrylic acid derivatives and their precursors are valuable materials for the synthesis of β-functionalized α,β-dehydroamino acids.

Experimental

M.p.s. were measured with a Yamato melting point apparatus and are uncorrected. I.r. spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer and ^{1}H n.m.r. spectra on a HITACHI R-40 high resolution n.m.r. spectrometer using tetramethylsilane as the internal standard. Mass spectra were determined on a HITACHI M-60 spectrometer. Column chromatography was carried out on silica gel (Kieselgel, 0.040-0.063 mm Merck).

Starting Materials (2a-e). — The appropriate aldehydes were condensed with methyl isocyanoacetate (1)[14] in the presence of NaH according to the method described in previous papers.[9,15]

Methyl β-Bromo-α-formylaminoacrylates (3a-e). — *General procedure*.

To a solution of Z-(2) (20 mmol) in carbon tetrachloride (50 ml) was added NBS (3.93g, 22 mmol) under ice cooling. After stirring had been continued overnight at room temperature, the solution was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel using $CHCl_3$-AcOEt (8:1) as eluant. Crystals (3) obtained were recrystallized from AcOEt-hexane to afford Z-(3a), E-(3a), E-(3c), Z-(3d), and E-(3d) as colorless needles, Z-(3b), E-(3b), and Z-(3c) as colorless leaflets, and Z-(3e) and E-(3e) as colorless prisms. The results are summarized in Table 1.

Reaction of (3a) with NaN_3. —— A mixture of (3a) (1.42g, 5 mmol) and NaN_3 (0.98g, 15 mmol) in DMF (10 ml) was stirred for 2 days at room temperature and insoluble materials were filtered off. The filtrate was concentrated *in vacuo* and the syrupy residue was subjected to column chromatography on silica gel using $CHCl_3$-MeOH (15:1) as eluant. The crude product (4) was crystallized as colorless needles from AcOEt-hexane (0.83g, 76%), m.p. 224-226°C (decomp.); ν_{max} (Nujol) 3150, 1700, and 1630cm^{-1} ; δ[$CDCl_3$+$(CD_3)_2SO$] 3.72 (3H, s, OMe), 7.25-7.55 (3H, m, ArH) 7.55-7.85 (2H, m, ArH), and 9.80-11.00 (2H, br, 2NH); m/z 218 (M^+) (Found: C, 60.5; H, 4.7; N, 12.8. $C_{11}H_{10}N_2O_3$ requires C, 60.55; H, 4.6; N, 12.8%).

Methyl β-Ethylthio-α-formylaminoacrylates (6a and 6c-f). —— *General procedure*. To a suspension of NaH (60% suspension in oil; 0.2g, 5 mmol) in HMPA (2.5 ml) was added dropwise a solution of ethanethiol (0.78g, 12.5 mmol) in HMPA (2.5 ml) at 5-10°C. After stirring had been continued for 12hr at room temperature, Z-(3) (2.5 mmol) was added to the solution at 5-10 °C and the solution was stirred for 1hr at room temperature. The reaction mixture was poured into a mixture of 0.5 M aqueous citric acid (30 ml) and AcOEt (30 ml) under ice cooling. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel eluting with AcOEt-hexane (1:2) to give Z-(6a-e) and E-(6b,d,e) as crystals which were recrystallized from AcOEt-iPr_2O. E-(6a,c) were contaminated with Z-(6a,c) and the E- and Z-isomers of (6f) were not separated. These results are summarized in Tables 2 and 3.

Table 3 Physical data of (6a-e)

Compound	M.p. (°C)	ν_{max} (Nujol) cm^{-1}	^1H n.m.r.[a] C-Me[b]	CH_2[c]	OMe[d]	NH[e]	CHO[f]
Z-(6a)	104-106[h]	3300,1720,1685,1660	1.08	2.34	3.48	7.14-7.66	8.26
E-(6a)[g]			1.08	2.22	3.86	7.08-7.52	7.85
Z-(6b)	113-114[h]	3250,1715,1680,1640			3.45	6.92-7.54	8.15
E-(6b)	110-111[h]	3250,1700,1690,1660			3.81	6.94-7.53	7.80
Z-(6c)	90-91[h]	3300,1720,1680	1.08	2.33	3.49	7.34-7.63	8.24
E-(6c)[g]			1.08	2.33	3.85	7.05-7.32	7.86
Z-(6d)	117-118[i]	3280,1720,1680	1.06	2.36	3.51	7.38-7.74	8.24
E-(6d)	138-139[h]	3250,1710,1680,1650	1.08	2.28	3.82	6.72-7.34	7.88
Z-(6e)	128-129[h]	3400,1710,1680	1.08	2.34	3.51	7.45-7.64	8.24
E-(6e)	98-99[h]	3300,1740,1680	1.08	2.24	3.82	6.47-6.88	7.84
E- and Z-(6f)	68-69	3250,1740,1680,1650	1.26	2.71	3.82	7.67-7.95	8.20

[a] δ Values. $CDCl_3$ as solvent. [b] Triplet J 7Hz. [c] Quartet J 7Hz. [d] Singlet. [e] Broad. [f] Singlet. [g] Contaminated with Z-isomer. [h] Colorless needles. [i] Colorless prisms.

Methyl β-*Benzylthio*-α-*formylaminocinnamate* (6b). — To a suspension of potassium *tert*-butoxide (0.56g, 5 mmol) in tetrahydrofuran (THF) (10 ml) was added dropwise a solution of benzylmercaptan (1.6g, 12.5 mmol) in THF (5 ml) at -30°C. After stirring had been continued for 30 min at the same temperature, Z-(3a) (0.7g, 2.5mmol) was added to the reaction mixture and the solution was stirred for 3hr at room temperature. The reaction mixture was treated as described above to give crystalline Z- and E-(6b) (Tables 2 and 3).

Methyl (Z)-β-*Bromo*-α-*isocyanoacrylates* [Z-(7a) *and* Z-(7d)].— These compounds were prepared from Z-(6a) and Z-(6d) by a method similar to that described previously.[9,15] Compound Z-(7a) was a syrup and showed ν_{max} (film) 2110 and 1735 cm^{-1}; δ ($CDCl_3$) 3.65 (3H, s, OMe) and 7.0-7.70 (5H, m, ArH). Compound Z-(7d) (colorless needles from hexane) had m.p. 79-81°C (decomp.); ν_{max} (Nujol) 2100 and 1735 cm^{-1}; δ ($CDCl_3$) 3.69 (3H, s, OMe) and 7.20-7.50 (4H, m, ArH) (Found: C, 44.85; H, 2.4; N, 4.6; Br, 26.5; Cl, 12.0.

$C_{11}H_7NO_2BrCl$ requires C, 44.0; H, 2.35; N, 4.7; Br, 26.6; Cl, 11.8%).

Benzyl β-Benzyloxy-α-isocyano-(4-chloro)cinnamate (8). — To benzyl alcohol was added NaH (60% suspension in oil; 0.8g, 20 mmol) under vigorous stirring and the solution was diluted with THF (30 ml). To the solution was added dropwise Z-(7d) (3g, 10 mmol) in THF (50 ml) under ice cooling. After stirring had been continued for 1hr at the same temperature, the solution was poured into a mixture of 0.5 M aqueous citric acid (100 ml) and AcOEt (100 ml) under ice cooling. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel eluting with toluene-AcOEt (49:1) to give Z-(8) and E-(8) as colorless oils. The Z-isomer (2.6g, 64%) showed ν_{max} (film) 2150 and 1750 cm^{-1}; δ ($CDCl_3$) 4.5-4.75 (2H, m, C-O-CH_2), 5.00-5.25 (2H, m, $COOCH_2$), and 7.05-7.55 (14H, m, ArH). The E-isomer (0.7g, 17%) showed ν_{max}(film) 2150 and 1750 cm^{-1}; δ ($CDCl_3$) 4.45-4.75 (2H, m, C-O-CH_2), 4.97-5.25 (2H, m, $COOCH_2$), and 7.00-7.50 (14H, m, ArH).

Benzyl β-Benzyloxy-α-formylamino-(4-chloro)cinnamate (9). — 40% V/V HCOOH in THF (30 ml) was added to Z-(8) or E-(8) (2g, 5 mmol) and the reaction mixture was stirred for 2hr at 0°C. The solution was concentrated *in vacuo* and the residue was dissolved in AcOEt, washed with saturated aqueous $NaHCO_3$, and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel eluting with $CHCl_3$-AcOEt (39:1) to give Z-(9) or E-(9) as colorless syrups. Z-(9) (1.67g, 79%) showed ν_{max} (film) 3350, 1740, and 1690 cm^{-1}; δ ($CDCl_3$) 4.50-4.58 (2H, m, OCH_2), 4.95-5.26 (2H, m, $COOCH_2$), 5.80-6.10 (1H, br, NH), 7.10-7.50 (14H, m, ArH), and 8.11 (1H, d *J* 1Hz, CHO). E-(9) (1.53g, 72.5%) showed ν_{max} (film) 3350, 1740, and 1690 cm^{-1}; δ ($CDCl_3$) 4.28-4.70 (2H, m, OCH_2), 5.00-5.15 (2H, m, $COOCH_2$), 5.85 (1H, br d *J* 9Hz, NH), 7.00-7.50 (14H, m, ArH), and (1H, d *J* 1Hz, CHO).

Reaction of Z-(7a) with Benzylamine. — To a mixture of Z-(7a) (1.33g, 5 mmol) and triethylamine (0.55g, 5.5 mmol) in HMPA (5 ml) was added dropwise benzylamine (0.53g, 5 mmol) at 10°C. After stirring had been continued for 1hr at the same temperature, the reaction mixture was concentrated *in vacuo* and the residue was subjected to column chromatography on silica gel eluting with AcOEt-hexane (1:2) to give E-10 as a syrup (0.78g, 50%) and 11 as colorless needles (0.39g, 27%). E-10 showed ν_{max}

(film) 3230, 2100, and 1680 cm^{-1}; δ ($CDCl_3$) 3.81 (3H, s, OMe), 4.18 (1H, d *J* 7Hz, CH_2), 6.99-7.58 (10H, m, ArH), and 9.30-9.67 (1H, br, NH). 11 had m.p. 112-3°C; ν_{max} (Nujol) 1700 cm^{-1}; δ ($CDCl_3$) 3.76 (3H, s, OMe), 4.96 (2H, s, CH_2), 6.84-7.52 (10H, m, ArH), and 7.56 (1H, s, N=CH) (Found: C, 74.1; H, 5.4; N, 9.5, $C_{18}H_{16}N_2O_2$ requires C, 74.0; H, 5.5; N, 9.6%).

Methyl β-Benzylamino-α-formylaminocinnamate (12). —— To a mixture of Z-(7a) (1.33g, 5 mmol) and triethylamine (0.55g, 5.5 mmol) in HMPA (5 ml) was added dropwise benzylamine (0.53g, 5 mmol) at 10°C. After stirring was continued for 1hr at room temperature, 40% V/V HCOOH in THF (70 ml) was added to the mixture at -20°C. The reaction mixture was stirred for 1hr at 0°C and concentrated *in vacuo*. The residue was dissolved in AcOEt, washed with 15% aqueous K_2CO_3 and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel eluting with AcOEt-hexane (1:1) to give a mixture of Z-(12) and E-(12) as crystals and (11) as crystals (0.21g, 14%). A mixture of Z-(12) and E-(12) (0.96g, 62%) showed ν_{max} (Nujol) 3250, 1690, and 1660 cm^{-1}; δ($CDCl_3$) 3.68, 3.70 (3H, s, s, COOMe), 4.06, 4.10 (2H, d, d, *J* 6 Hz, CH_2), 5.81-6.18 (1H, br, NH) 6.97-7.48 (10H, m, ArH), 7.61, 7.74 (1H, s, s, CHO), and 9.24-9.57 (1H, br, NH).

Methyl β-(1-Imidazolyl)-α-isocyanocinnamate (13). —— To a mixture of imidazole (0.75g, 11 mmol) in HMPA (5 ml) and THF (20 ml) was added NaH (60% suspension in oil; 0.44g, 11 mmol) at room temperature and the reaction mixture was stirred for 20 min. To the solution was added dropwise Z-(7a) (2.66g, 10 mmol) in THF (10 ml) under ice cooling. After stirring had continued for 3hr at room temperature, the reaction mixture was neutralized with 0.5 M aqueous citric acid and extracted with AcOEt. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel using $CHCl_3$-AcOEt (4:1) as eluant. The sepatrated isomers were crystallized as colorless needles from iPr_2O. The (Z)-isomer (1.06g, 42%) had m.p. 87-89°C (decomp.); ν_{max} (Nujol) 2110, 1735, and 1605 cm^{-1}; δ ($CDCl_3$) 3.68 (3H, s, OMe), 7.13-7.70 (8H, m, ArH) (Found: C, 66.4; H, 4.45; N, 16.5. $C_{14}H_{11}N_3O_2$ requires C, 66.4; H, 4.4; N, 16.6%). The (E)-isomer (0.61g, 24%) had m.p. 99-101°C (decomp.); ν_{max} (Nujol) 2110, 1730, and 1600 cm^{-1}; δ ($CDCl_3$) 3.76 (3H, s, OMe), 6.77-6.86 (1H, m, CH=N),

and 7.10-7.70 (7H, m, ArH) (Found: C, 66.3; H, 4.4; N, 16.6. $C_{14}H_{11}N_3O_2$ requires C, 66.4; H, 4.4; N, 16.6%).

Methyl 3-(4-Chlorophenyl)-2-isocyano-3,3-dimethoxypropionate (14). —— To a mixture of NaOMe (0.65g, 12 mmol) in MeOH (20 ml) was added Z-(7d) (3g, 10 mmol) under ice cooling. The reaction mixture was stirred for 30 min at the same temperature and poured into a mixture of 0.5 M aqueous citric acid (150ml) and Et_2O (50 ml). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel eluting with toluene-AcOEt (39:1) to give (14) as a colorless oil (2.32g, 92%), ν_{max} (film) 2160 and 1750 cm^{-1}; δ ($CDCl_3$) 3.32 (3H, s, C-OMe), 3.38 (3H, s, C-OMe), 3.62 (3H, s, COOMe), 4.76 (1H, s, CH), and 7.26-7.55 (4H, m, ArH).

Methyl 3-(4-Chlorophenyl)-2-formylamino-3-oxopropionate (15). —— Compound (14) (1.7g, 6 mmol) was dissolved in 40% V/V HCOOH in THF (40 ml) and treated in a similar way as described in the synthesis of (9). The crude oil was subjected to column chromatography on silica gel using $CHCl_3$-AcOEt (19:1) as eluant. The crude product was crystallized from AcOEt-iPr_2O to give (15) as colorless needles (1.17g, 76.5%); m.p. 116-118° C; ν_{max} (Nujol) 3350, 1750, 1700, and 1670cm^{-1}; δ ($CDCl_3$) 3.75 (3H, s, OMe), 6.23 (1H, s, CH), 7.02-7.34 (1H, br, NH), 7.45 (2H, d *J* 9Hz, ArH), 8.04 (2H, d *J* 9Hz, ArH), and 8.28 (1H, s, CHO) (Found: C, 51.5; H, 4.0; N, 5.5; Cl, 13.8. $C_{11}H_{10}NO_4Cl$ requires C, 51.7; H, 3.9; N, 5.5; Cl, 13.9%).

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