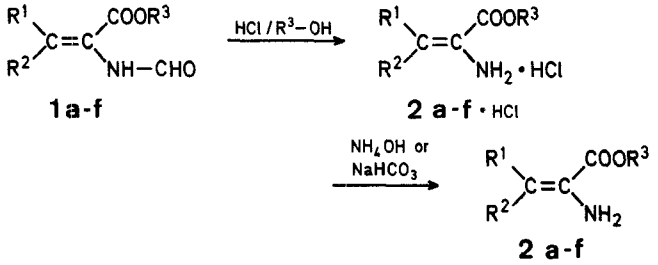
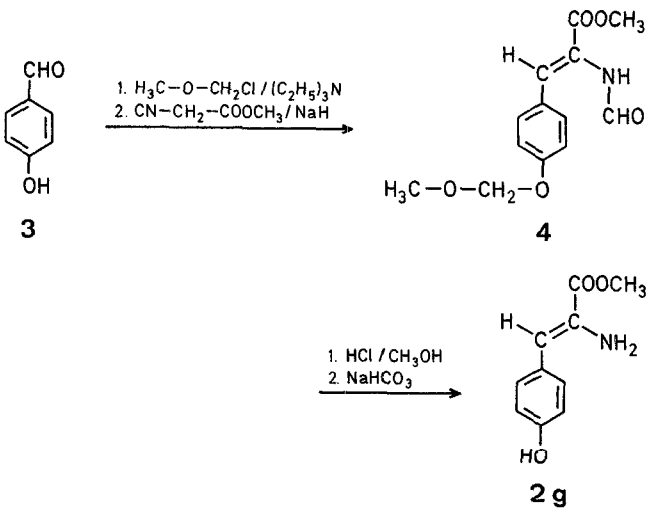
kenoates[5] are of interest. Nevertheless, a more useful method is still desired, since the above synthetic methods are not always satisfactory as a general method.

In this paper, we report a facile preparation of the 2-amino-2-alkenoates **2** by selective acidolysis of 2-formylamino-2-alkenoates **1**. The starting materials **1a–f** are easily prepared by conventional condensation of isocyanoacetates with carbonyl compounds[1,6,7,8]. Generally, usual hydrolysis of **1** with dilute hydrochloric acid, hydrogen peroxide, or hydrogen bromide in acetic acid at low temperature led to the formation of the corresponding 2-oxo acids and other by-products. To overcome these disadvantages, we attempted the selective deformylation of **1** by acidolysis in non-aqueous solution. The deformylation of **1** was carried out with hydrogen chloride in an organic solvent containing alcohol as a co-solvent at room temperature as shown in the Table. Without the alcohol co-solvent, the deformylation did not proceed. The product **2a** was easily obtained as a crystalline hydrochloride in quantitative yield. Since the hydrochlorides of **2b–f** were not crystalline, they were converted into the free bases **2** in the usual way and then purified by distillation.



The reactions were monitored by T.L.C. (silica gel; eluent: chloroform/ethyl acetate/ethanol, 8 : 2 : 1). As a typical example, the behaviour of the relatively labile **2f** on T.L.C. was observed as follows. The R_f value of **2f** was higher than that of the corresponding formamide **1f** and the spot was positive to ultraviolet light and ninhydrin test but negative to 2,4-dinitrophenylhydrazine test. After 1 h, however, the intensity of ultraviolet absorption of the spot decreased and the test with ninhydrin was negative but the test with 2,4-dinitrophenylhydrazine was positive. The enamine on the silica gel plate changed to the corresponding α-oxo acid on standing. The resulting **2f** was converted to the stable *N*-benzoyl derivative by Schotten-Baumann reaction.

For the synthesis of α,β-dehydrotyrosin methyl ester [**2g**; methyl (*Z*)-2-amino-(4-hydroxyphenyl)-acrylate], methyl (*Z*)-



Acidolysis of 2-Formylamino-2-alkenoic Esters to 2,3-Dehydro Amino Acid Esters[1]

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Since a number of 2,3-dehydro amino acids have recently been found in natural products having antimicrobial activities[2], attention has been given to their synthesis. Especially, the synthesis of *N*-deblocked 2,3-dehydro amino acids or 2-amino-2-alkenoates is important for the preparation of physiologically active peptides containing dehydro amino acids. With regard to the synthesis, several methods have been reported[3,4,5]: of these, halogenation followed by dehydrohalogenation of the 2-amino acids[4] and reduction of 2-azido-2-al-

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Table. Synthesis of 2,3-Dehydro Amino Acid Esters **2a–g**

Product No.	R^1	R^2	R^3	Solvent	Hydrochloric acid concentration [%]	Yield[a] [%]	m.p. [°C] or b.p. [°C]/torr found	m.p. [°C] or b.p. [°C]/torr reported
2a	H	4-H_3CO—C_6H_4	CH_3	dioxan/methanol (5/2)	20	100	129–131° (HCl salt)[b]	—[c]
2b	H	C_6H_5	CH_3	ether/methanol (4/1)	5	80	47–48.5°; 95°/1	—[c]
2c	H	C_6H_5	C_2H_5	ether/ethanol (4/1)	5	61	110°/1	90–95°/0.5[5]
2d	H	CH_3	CH_3	ether/methanol (5/1)	5	50	65°/5	—[c]
2e	CH_3	CH_3	CH_3	ether/methanol (5/1)	5	60	75°/10	76°/11[9]
2f	—$(CH_2)_5$—		CH_3	ether/methanol (2/1)	10	71	65°/2	—[c]
2g	H	4-HO—C_6H_4	CH_3	ether/methanol (2/1)	7	90	90–91.5°	—[c]

[a] Yield of isolated, pure product.
[b] Decomposition.
[c] See experimental for spectral and analytical data.

2-formylamino-3-(4-methoxymethoxyphenyl)-acrylate **(4)**, prepared from 4-methoxymethoxybenzaldehyde (from **3** and chloromethyl methyl ether) and methyl α-isocyanoacetate, was used as a starting material. Deformylation of **4** by the acidolysis was carried out as above. Simultaneous cleavage of *O*-methoxymethyl group occurred and the desired product **2g** was obtained in quantitative yield.

This newer method seems to be superior to the conventional methods in technical procedure and yields.

Methyl (*Z*)-2-Amino-3-(4-methoxyphenyl)-acrylate Hydrochloride (2a·HCl):
Methyl (*Z*)-2-formylamino-3-(4-methoxyphenyl)-acrylate (**1a**; 10.0 g, 0.042 mol) is dissolved in dioxan (50 ml) and methanol (20 ml) containing 20% hydrogen chloride at 0°C and then stirred for 30 min at 20°C. The reaction mixture is evaporated in vacuo and the residue is triturated with acetone (20 ml) to afford **2a**·HCl as colorless, fine crystals: yield 10.4 g (quantitative); m.p. 129–131°C (dec).

$C_{11}H_{14}ClNO_3$	calc.	C 54.22	H 5.79	N 5.74	Cl 14.55
(243.7)	found	54.15	5.63	5.83	14.81

I.R. (Nujol): ν = 1730, 1650, 1600, 1515 cm^{-1}.
^{1}H-N.M.R. (DMSO-d_6): δ = 3.80 (s, 6H, $2CH_3$); 6.15 (s, 3H, D_2O-exchangeable, $\overset{\oplus}{N}H_3$); 6.75 (s, 1H, olefinic H, D_2O-exchangeable); 6.95, 7.67 ppm ($A_2'B_2'$, 2H each, aromatic H).
M.S.: *m/e* = 207 ($M^{\oplus}$ − HCl).

Methyl 2-Amino-2-cyclohexylideneacetate (2f); Typical Procedure:
Methyl 2-formylamino-2-cyclohexylideneacetate (**1f**; 9.86 g, 0.05 mol) is dissolved in ether (500 ml) and methanol (250 ml) containing 10% hydrogen chloride at 0°C and the mixture is then stirred for 6 h at 20°C. The reaction mixture is concentrated under reduced pressure. To the residue is added chloroform (500 ml) and the mixture is shaken with chilled 15% aqueous ammonia solution (150 ml). The organic layer is dried with magnesium sulfate, concentrated, and then distilled to afford colorless oil of **2f**; yield: 5.97 g (71%); b.p. 65°C/2 torr.

$C_9H_{15}NO_2$	calc.	C 63.88	H 8.93	N 8.28
(169.2)	found	63.65	8.98	7.89

I.R. (Film): ν = 3430, 3360, 1730, 1640 cm^{-1}.
^{1}H-N.M.R. ($CDCl_3$): δ = 1.0–3.5 [m, 12H, among them 2H were D_2O-exchangeable, —$(CH_2)_5$— and NH_2]; 4.95 ppm (s, 3H, CH_3).
M.S.: *m/e* = 170 ($M^{\oplus}$ + 1).

Methyl (Z)-2-Amino-3-phenylacrylate **(2b)**; yield: 80%; b.p. 95°C/1 torr; m.p. 47–48.5°C.

$C_{10}H_{11}NO_2$	calc.	C 67.78	H 6.26	N 7.90
(177.2)	found	67.45	6.47	7.71

I.R. (Nujol): ν = 3490, 3380, 1705, 1625, 1590 cm^{-1}.
^{1}H-N.M.R. ($CDCl_3$): δ = 3.93 (s, 3H, CH_3); 4.3 (br, 2H, D_2O-exchangeable, NH_2); 6.60 (s, 1H, olefinic H); 7.2–7.7 ppm (m, 5H, aromatic H).
M.S.: *m/e* = 177 ($M^{\oplus}$).

Methyl (Z)-2-Aminocrotonate **(2d)**; yield: 50%; b.p. 65°C/5 torr.

$C_5H_9NO_2$	calc.	C 52.16	H 7.88	N 12.17
(115.1)	found	52.49	8.05	11.82

I.R. (Film): ν = 3450, 3330, 1720, 1650, cm^{-1}.
^{1}H-N.M.R. (CCl_4): δ = 1.63 (d, *J* = 7 Hz, 3H, CH_3); 3.17 (br s, 2H, D_2O-exchangeable, NH_2); 3.75 (s, 3H, OCH_3); 5.46 ppm (q, *J* = 7 Hz, 1H, olefinic H).
M.S.: *m/e* = 116 ($M^{\oplus}$ + 1).

Methyl 2-Benzamido-2-cyclohexylideneacetate:
Benzoyl chloride (2.24 g, 0.016 mol) and a chilled chloroform (50 ml) solution of **2f** (2.0 g, 0.012 mol) are added at once to saturated aqueous sodium hydrogen carbonate solution (50 ml) at 0–5°C with vigorously stirring. After 1 h, the organic layer is dried, concentrated, and then chromatographed on a silica gel column using chloroform/ethyl acetate (10:1) as eluent to afford the title compound as colorless prisms; yield: 1.31 g (40%); m.p. 149–150°C.

$C_{16}H_{19}NO_3$	calc.	C 70.31	H 7.01	N 5.12
(273.34)	found	70.21	7.25	5.01

I.R. (Nujol): ν = 3220, 1740, 1725, 1640, 1520 cm^{-1}.
^{1}H-N.M.R. ($CDCl_3$): δ = 1.4–2.0 [m, 6H, —$(CH_2)_3$—]; 2.2–2.5, 2.6–3.0 (m, each 2H, CH_2—C<); 3.85 (s, 3H, CH_3); 7.3–8.2 ppm (m, 5H, aromatic H).
M.S.: *m/e* = 273 (M^+).

Methyl (*Z*)-2-Formylamino-3-(4-methoxymethoxyphenyl)-acrylate (4):
To a mixture of 4-hydroxybenzaldehyde (**3**; 12.2 g, 0.1 mol) and triethylamine (28 ml, 0.2 mol) in tetrahydrofuran (100 ml) is added a solution of chloromethyl methyl ether (9.7 g, 0.12 mol) in tetrahydrofuran (50 ml) at 0°C and then the mixture is stirred at room temperature for 2 h. After removal of the resulting triethylamine hydrochloride by suction filtration, the mixture is concentrated to dryness under reduced pressure. A mixture of the resultant 4-methoxymethoxybenzaldehyde, obtained quantitatively, and methyl α-isocyanoacetate (9.9 g, 0.1 mol) in tetrahydrofuran (100 mol) is added to a suspension of sodium hydride (4.8 g, 0.2 mol; prepared by washing a commercial dispersion in paraffin with *n*-hexane) in tetrahydrofuran (200 ml) at 35–40°C within 30 min. After stirring for 2 h at the same temperature, to the reaction mixture diluted with ethyl acetate (500 ml) is added acetic acid (12 ml, 0.2 mol) for neutralization. The mixture is washed with water (3 × 500 ml), dried with magnesium sulfate, concentrated, and then triturated with diethyl ether (100 ml) to afford **4** as yellow prisms; yield: 9.2 g (35%); m.p. 106–107°C (from methanol/water).

$C_{13}H_{15}NO_5$	calc.	C 58.86	H 5.70	N 5.28
(265.3)	found	58.95	5.72	5.30

I.R. (Nujol): ν = 3210, 1715, 1660, 1605, 1510, 1180, 1080 cm^{-1}.
^{1}H-N.M.R. ($CDCl_3$): δ = 3.57 (s, 3H, CH_3); 3.97 (s, 3H, CH_3); 5.30 (s, 2H, CH_2); 7.0–7.8 (m, 6H, aromatic, olefinic, and amide protons among them 1H was D_2O-exchangeable); 8.45 ppm (s, 1H, CHO).
M.S.: *m/e* = 265 (M^+), 237 (M^+ − CO), 45 ($H_3COCH_2^+$).

Methyl (*Z*)-2-Amino-3-(4-hydroxyphenyl)acrylate (2 g):
A solution of **4** (5.30 g, 0.02 mol) in ether (100 ml) and methanol (50 ml) containing 7% hydrogen chloride is stirred for 30 min at 20 °C. The reaction mixture is evaporated under reduced pressure and the residue is triturated with acetone (20 ml) to afford **2g** · HCl as pale yellow prisms; yield 4.60 g (quantitative), m.p. 137–140 °C.

I.R. (KBr): $\nu_{max} = 3400, 1700, 1600, 1510, 1440, 1290, 1210, 1180$ cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): $\delta = 3.20$ (s, 3 H, CH_3); 5.0–5.8 (br, 5 H, D_2O-exchangeable, $\overset{\oplus}{N}H_3$, H_2O); 6.78 (s, 1 H, D_2O-exchangeable); 6.82, 7.43 ppm ($A'_2B'_2$, 4 H, aromatic H).

The hydrochloride (2.0 g) is shaken with saturated aqueous sodium hydrogen carbonate solution (30 ml) in chloroform (200 ml). The organic layer is dried, concentrated, and then crystallized from diisopropyl ether (20 ml) and *n*-hexane (50 ml) to afford **2g** as pale yellow prisms; yield: 1.51 g (90%); m.p. 90–91.5 °C.

$C_{10}H_{11}NO_3$	calc.	C 62.17	H 5.74	N 7.25
(193.2)	found	61.98	5.70	6.95

I.R. (Nujol): $\nu = 3450, 3360, 1720, 1700, 1590, 1505, 1260$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): $\delta = 3.90$ (s, 3 H, CH_3); 4.1 (br, 2 H, D_2O-exchangeable, NH_2); 6.50 (s, 1 H, olefinic H); 6.86, 7.37 ppm ($A'_2B'_2$, 2 H each, aromatic H).

M.S.: $m/e = 193$ (M^+).

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[1] Synthesis of Amino Acids and Related Compounds, Part 23. Part 22: K. Matsumoto et al., *Chem. Pharm. Bull.* **28,** 2374 (1980).

[2] T. Takita, T. Tamura, H. Taniyama, *J. Biochem.* **81,** 1759 (1977).
Y. Shimohigashi, N. Izumiya, *Yuki Gosei Kyokaishi* **36,** 1023 (1978); *C. A.* **90,** 98596 (1979); and references are therein.

[3] S. Tatsuoka, M. Murakami, T. Tamura, *J. Pharm. Soc. Jpn.* **70,** 230 (1950).
C. Chin, M. Masaki, M. Ohta, *Bull. Chem. Soc. Jpn.* **43,** 3219 (1970).
E. G. Breitholle, C. H. Stammer, *Tetrahedron Lett.* **1975,** 2381.
H. Poisel, U. Schmidt, *Angew. Chem.* **88,** 295 (1976); *Angew. Chem. Int. Ed. Engl.* **15,** 294 (1976).

[4] U. Schmidt, E. Ohlar, *Angew. Chem.* **89,** 344 (1977); *Angew. Chem. Int. Ed. Engl.* **16,** 327 (1977).

[5] C. Shin, Y. Yonezawa, J. Yoshimura, *Chem. Lett.* **1976,** 1095.

[6] U. Schöllkopf, F. Gerhart, R. Schröder, D. Hoppe, *Justus Liebigs Ann. Chem.* **766,** 116 (1972).

[7] K. Nunami, M. Suzuki, N. Yoneda, *J. Chem. Soc. Perkin Trans. 1* **1979,** 2224.

[8] K. Matsumoto, Y. Ozaki, M. Suzuki, M. Miyoshi, *Agric. Biol. Chem.* **40,** 2045 (1976).

[9] H. Poisel, *Chem. Ber.* **110,** 942 (1977).

0039-7881/81/1132-0917 $ 03.00