Electrochemical Synthesis and Reactivity of α-Alkoxy α-Amino Acid Derivatives[1,2]

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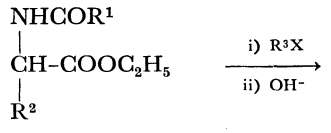
α-Alkoxy α-amino acid derivatives were synthesized in good yields by anodic oxidation of acylaminomalonic acid monoesters in alcohols. Transformation of ethyl *N*-acetyl-α-methoxyalaninate into ethyl *N*-acetyl-α,β-dehydroalaninate was achieved in an excellent yield by thermal treatment of the former amino acid with a catalytic amount of ammonium bromide. Substitution of the α-alkoxy group of the α-alkoxy amino acids with nucleophiles was effected by tin tetrachloride to afford the α-substituted α-amino acids.

α-Functionalized α-amino acids such as α-methoxy or α-acetoxy α-amino acids[3a,b] have been found to be useful for the preparation of physiologically important amino acids. Some remarkable examples have been shown by Ben-Ishai *et al.*;[4] α-methoxyglycine derivatives undergo the reaction with a variety of nucleophiles to afford a novel class of α-substituted α-amino acids. However, the synthetic versatility of the α-methoxy α-amino acids other than the α-methoxyglycines in amino acid chemistry has not yet been explored.

Several α-methoxy α-amino acids were prepared by the addition reaction to α,β-dehydro amino acids,[5a,b] oxidation of *N*-acylamino acid derivatives with *t*-BuOCl,[6a-d] or oxidation of α-methylthio *N*-acylamino acids.[7] However, difficulty is still encountered in these reactions in which the starting materials and/or the reagents are not readily available, and the experimental procedures are often tedious. In the course of our synthetic studies by electrochemical method, Kolbe type oxidation has been found to be a suitable method for a selective replacement of carboxylic acid group with acetoxyl[3a] or olefinic functional group.[8] In the present paper, we wish to report a convenient synthesis of various types of α-alkoxy α-amino acid derivatives by anodic oxidation of substituted and nonsubstituted acylaminomalonic acid monoesters. Transformation of the α-alkoxy amino acids into α,β-dehydroalaninate and α-substituted α-amino acids is also described, the synthetic potentiality of the α-alkoxy amino acids in amino acid chemistry, being taken into account.

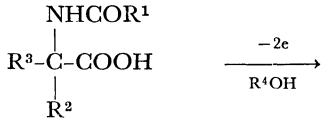
Results and Discussion

Electrochemical Synthesis. Synthesis of α-alkoxy amino acid derivatives **3** was carried out according to the reaction Scheme 1. Substituted acylaminomalonic acid monoesters **2b—f** were synthesized in good yields by the reaction of acylaminomalonates **1a**, **b** with alkyl halides in ethanol–sodium ethoxide, followed by the saponification of the coupling products with potassium hydroxide in ethanol. α-Acetamido-α-cyano-β-phenylpropionic acid (**2g**) was similarly prepared from **1c** in 68% overall yield. Anodic oxidation was carried out at 10—15 °C with use of a graphite anode-graphite cathode in a non-divided cell. On electrolysis of **2a** in methanol containing 1/20 molar equivalent of sodium methoxide to that of **2a**, ethyl *N*-acetyl-α-methoxyglycinate (**3a**) was obtained in 89% yield. The monoesters **2b—f** were also oxidized under the same conditions as above to afford the corresponding α-methoxy α-amino acid derivatives **3b—f** in 80—97% yield. The presence of the cyano group in electrolysis of **2g** did not obstruct methoxylation. In these reactions, the starting materials were consumed completely by passing a theoretical amount of current which is calculated as a two-electron



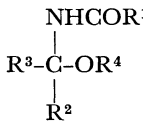
1a—c

a, $R^1=CH_3$; $R^2=COOC_2H_5$
b, $R^1=OCH_2Ph$; $R^2=COOC_2H_5$
c, $R^1=CH_3$; $R^2=CN$



2a—g

a, $R^1=CH_3$; $R^2=COOC_2H_5$; $R^3=H$
b, $R^1=CH_3$; $R^2=COOC_2H_5$; $R^3=CH_3$
c, $R^1=CH_3$; $R^2=COOC_2H_5$; $R^3=C_2H_5$
d, $R^1=CH_3$; $R^2=COOC_2H_5$; $R^3=CH_2Ph$
e, $R^1=CH_3$; $R^2=COOC_2H_5$; $R^3=CH_2CH=CH_2$
f, $R^1=OCH_2Ph$; $R^2=COOC_2H_5$; $R^3=H$
g, $R^1=CH_3$; $R^2=CN$; $R^3=CH_2Ph$



3a—i

a, $R^1=CH_3$; $R^2=COOC_2H_5$; $R^3=H$; $R^4=CH_3$
b, $R^1=CH_3$; $R^2=COOC_2H_5$; $R^3=R^4=CH_3$
c, $R^1=CH_3$; $R^2=COOC_2H_5$; $R^3=C_2H_5$; $R^4=CH_3$
d, $R^1=CH_3$; $R^2=COOC_2H_5$; $R^3=CH_2Ph$; $R^4=CH_3$
e, $R^1=CH_3$; $R^2=COOC_2H_5$; $R^3=CH_2CH=CH_2$; $R^4=CH_3$
f, $R^1=OCH_2Ph$; $R^2=COOC_2H_5$; $R_3=H$; $R^4=CH_3$
g, $R^1=CH_3$; $R^2=COOC_2H_5$; $R^3=C_2H_5$; $R^4=C_2H_5$
h, $R^1=CH_3$; $R^2=COOC_2H_5$; $R^3=CH_3$; $R^4=CH(CH_3)_2$
i, $R^1=CH_3$; $R^2=CN$; $R^3=CH_2Ph$; $R^4=CH_3$

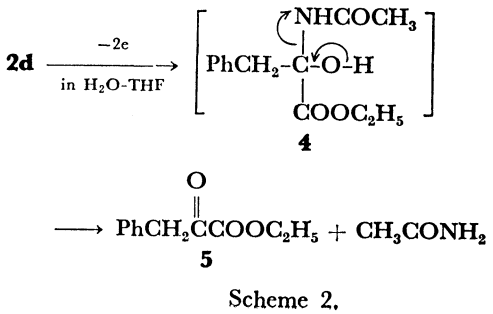
Scheme 1.

Table 1. Yields and characterization of electrolysis products

Compd	Yield (%)	Mp [Bp] (°C)	IR (cm^{-1})	NMR (δ, in $CDCl_3$)	Formula	Analysis (%)[a]		
						C	H	N
3a	89	[85—6/0.3 mmHg]	3300, 1750, 1670, 1520	1.33 (t, 3H), 2.12 (s, 3H), 3.49 (s, 3H), 4.29 (q, 2H), 5.56 (d, 1H), 7.12 (broad d, 1H)	$C_7H_{13}NO_4$	47.99 47.63	7.48 7.21	8.00 8.10
3b	97	40—42	3270, 1750, 1665, 1550	1.35 (t, 3H), 1.77 (s, 3H), 2.09 (s, 3H), 3.32 (s, 3H), 4.32 (q, 2H), 6.97 (broad s, 1H)	$C_8H_{15}NO_4$	50.78 50.55	7.99 7.94	7.40 7.51
3c	91	80—81	3270, 1755, 1650, 1545	0.83 (t, 3H), 1.36 (t, 3H), 2.10 (s, 3H), 1.6—2.9 (m, 2H), 3.28 (s, 3H), 4.32 (q, 2H), 6.68 (broad s, 1H)	$C_9H_{17}NO_4$	53.19 52.91	8.43 8.21	6.89 6.78
3d	96	97—98	3300, 1743, 1685, 1527	1.33 (t, 3H), 2.04 (s, 3H), 3.29 (s, 3H), 3.22 and 3.87 (AB q, 2H, J=13 Hz), 4.26 (q, 2H), 6.58 (broad s, 1H), 7.23 (s, 5H)	$C_{14}H_{19}NO_4$	63.38 63.11	7.22 6.99	5.28 5.28
3e	83	63—65	3300, 1740, 1670, 1530	1.33 (t, 3H), 2.09 (s, 3H), 2.4—3.3 (m, 2H), 3.30 (s, 3H), 4.26 (q, 2H), 4.9—6.0 (m, 3H), 6.9 (broad s, 1H)	$C_{10}H_{17}NO_4$	55.80 55.65	7.96 8.01	6.51 6.77
3f	93	[138—9/0.5 mmHg]	3300, 1725, 1520	1.30 (t, 3H), 3.44 (s, 3H), 4.24 (q, 2H), 5.17 (s, 2H), 5.31 (d, 1H), 6.00 (broad d, 1H), 7.30 (s, 5H)	$C_{13}H_{17}NO_5$	58.42 58.12	6.41 6.51	5.24 5.29
3g	79	102—104	3330, 1740, 1680, 1550	0.32 (t, 3H), 1.21 (t, 3H) 1.32 (t, 3H), 1.7—2.8 (m, 2H), 2.08 (s, 3H), 3.47 (q, 2H), 4.28 (q, 2H), 6.83 (broad s, 1H)	$C_{10}H_{19}NO_4$	55.28 55.31	8.82 8.80	6.45 6.35
3h	80	71—73	3330, 1738, 1685, 1536	1.15 (d, 6H), 1.32 (t, 3H), 1.78 (s, 3H), 2.03 (s, 3H), 3.83 (m, 1H), 4.26 (q, 2H), 6.73 (broad s, 1H)	$C_{10}H_{19}NO_4$	55.28 55.39	8.82 8.62	6.45 6.51
3i	80	68—70	3200, 1660, 1540	1.96 (s, 3H), 3.39 (s, 2H), 3.50 (s, 3H), 7.03 (broad s, 1H), 7.31 (s, 5H)	$C_{12}H_{14}N_2O_2$	66.03 65.85	6.47 6.67	12.84 12.53

a) Upper lines show calculated values and lower lines found values.

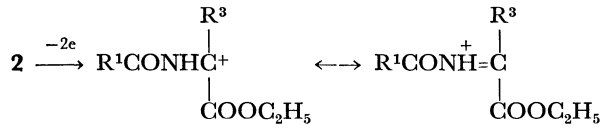
transfer. Furthermore, the use of ethanol or 2-propanol as an electrolysis solvent resulted in the formation of the corresponding alkoxylated products **3g,h** in excellent yields despite rather poor current efficiency (60—70%). No Kolbe dimer was observed throughout the alkoxylation. Furthermore, no elimination and rearrangement products were detected. Meanwhile, in the hope of preparing ethyl *N*-acetyl-α-hydroxyphenylalaninate (**4**), the electrolysis of **2d** was carried out in aqueous tetrahydrofuran. However, **4** was extremely unstable under the reaction conditions, and carbon–nitrogen bond cleavage ocurred to give ethyl phenylpyruvate (**5**) and acetamide[9] (Scheme 2).



Scheme 2.

The structural elucidation was carried out based on the spectral data and elemental analyses. The results are summarized in Table 1.

The electrode reaction in the alkoxylation is thought to be a typical abnormal Kolbe reaction in which the carbonium ion is generated *via* a two-electron transfer[3a,8,10a-c] (Scheme 3). The delocalization



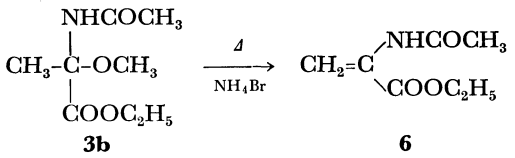
Scheme 3.

of the carbonium ion character onto the neighboring nitrogen atom would make the lifetime longer enough to be susceptible of nucleophilic attack of the solvent, though the inductive effect of both the *N*-acyl and the ethoxycarbonyl groups destabilizes the carbonium ion. Participation of the neighboring acylamino group in the anodic replacement of carboxylic acid group by methoxyl or acetoxyl group has been described by us[3a] and other workers.[11a,b]

The α-methoxy amino acid derivative **3d** was saponified with potassium hydroxide in methanol to afford *N*-acetyl-α-methoxyphenylalanine in 51% yield.

Conversion into α,β-Dehydroalanine Derivative. α,β-Dehydro amino acids, especially α,β-dehydroalanine derivatives, are used as important intermediates in the synthesis of natural peptides possessing antibacterial activity.[12] α,β-Dehydroalanine derivatives have hitherto been prepared by the methods involving the following: thermal condensation of primary amines with pyruvic acid;[13] base-catalyzed elimination of *N*-acyl-α-methoxyalanines,[5a] *N*-acyl-*N*-chloroalaninates prepared *in situ*,[5a] and *N*-acylserine derivatives.[14] These methods, however, are not suitable for large scale production[15] of α,β-dehydroalanine.

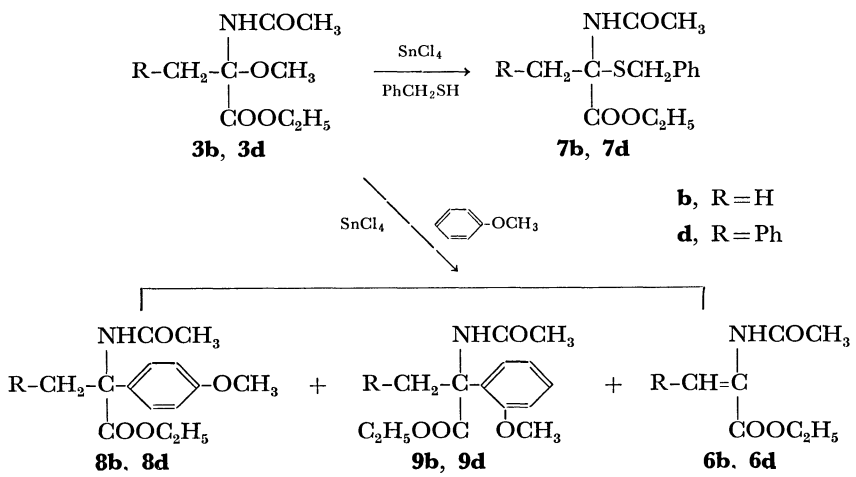
In order to develop a method for a convenient and large scale preparation of the α,β-dehydroalanines, thermal conversion of α-methoxyalaninate into α,β-dehydroalaninate was carried out. Ethyl *N*-acetyl-α-methoxyalaninate (**3b**) was heated at 120 °C for 20 min in the presence of a catalytic amount of ammonium bromide to afford the corresponding α,β-dehydroalaninate **6b** in 76% yield (Scheme 4). Prolonged heating or the use of a greater amount of ammonium bromide than that employed here resulted in a low yield, owing to the thermal polymerization of the product.



Scheme 4.

Reaction with Nucleophiles. *N*-Acyl-α-methoxyglycines have been reported to amidoalkylate olefins,[16a,b] active methylene compounds,[17] and aromatic compounds[18a-c] through *N*-acylimine intermediates in the presence of Lewis acid catalyst. The acylamino group functions to stabilize the carbonium ion generated at the α-carbon, thus providing enhanced reactivity toward nucleophiles. In α-amidoalkylation on tertiary carbon atom of the α-methoxy α-amino acids, however, the substitution as well as competitive elimination reactions should be considered. Thus, the reactions of the methoxy amino acids with typical nucleophiles have been investigated in the presence of Lewis acid, in order to examine the scope and limitation of amidoalkylation using the amino acids.

First of all, the reactions of the α-methoxy amino acid derivatives with thiols were carried out. Ethyl *N*-acetyl-α-methoxyalaninate (**3b**) was subjected to react with phenylmethanethiol in acetonitrile in the presence of $SnCl_4$ to afford ethyl *N*-acetyl-α-benzylthioalaninate (**7b**) in 92% yield. **3d** was similarly treated with phenylmethanethiol to give **7d** in 84% yield (Scheme 5). Careful analysis of the reaction mixture by liquid chromatography indicated no formation of the elimination and rearrangement products. Furthermore, α-amidoalkylation of aromatic compounds was carried out by using anisole as a typical example. Treatment of **3b** with anisole using a molar equivalent of $SnCl_4$ to that of **3b** gave the α-substituted product **8b** (para isomer) in 58% yield along with the ortho isomer **9b** (29%). In this case, α,β-dehydro amino acid **6b** was obtained in 5% yield. Furthermore, **3d** was allowed to react with anisole to afford a mixture



Scheme 5.

of **8d** and **9d** in 70% yield in a 4 : 1 ratio determined by NMR spectrum of the crude products. The α,β-dehydro amino acid derivative **6d** was detected.

Efforts to amidoalkylate benzene or toluene, a less reactive nucleophile, were made under the Lewis acid-catalyzed conditions. However, though no substitution product was detected, formation of the elimination product was observed. The reaction of **3j** with toluene gave the same result as above. Treatment of **3b** or **3d** with active methylene compounds such as diethyl malonate and ethyl acetoacetate did not lead to the formation of any substitution products. The results are in sharp contrast with those reported by Ben-Ishai *et al.*[16–18] in which α-methoxyglycine derivatives react easily with benzene as well as active methylene compounds to afford the α-substituted α-amino acids derivatives.

It may be concluded that the α-methoxy α-amino acid derivatives can be used as reagents for α-amidoalkylation by which various types of amino acid skeletons are introduced to afford α-substituted amino acids. However, formation of α,β-dehydro amino acids becomes overwhelming when a feeble nucleophile such as toluene is employed.

Experimental

Equipment. Melting points were measured with a Yamato melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-27G infrared spectrophotometer, and NMR spectra on a Hitachi Perkin-Elmer R-20 high resolution NMR spectrometer with tetramethylsilane as an internal standard. High performance liquid chromatography was taken by Waters ALC-GPC-244. The electrolyses were carried out with use of a Hokuto Potentio-Galvanostat HA 104 (1A-55V), PGS 2500 (2.5 A-60V) or PGS 2000 (2A-100V) equipped with a Hokuto HA 108A coulomb meter.

*Preparation of the Starting Materials **2a—g**.* **2a—f** were prepared according to the method reported previously.[3a] **2g**: Sodium hydride (65%) (4.4 g, 0.12 mol) was suspended in 100 ml of tetrahydrofuran. To this was added **1c** (17 g, 0.1 mol) dissolved in 30 ml of tetrahydrofuran at 10—15 °C under vigorous stirring. Stirring was continued for additional 1 h at the same temperature. To the mixture was added dropwise benzyl bromide (17 g, 0.1 mol) at 10—30 °C. After being stirred overnight, the reaction mixture was neutralized with acetic acid and the solvent was evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate, and the solution was washed with water, dried over magnesium sulfate, then evaporated to dryness *in vacuo*. The resulting crystals were recrystallized from ethyl acetate–hexane to afford 22 g (90%) of ethyl α-acetamido-α-cyano-β-phenylpropionate as colorless needles: mp 111—113 °C; IR (Nujol) 3330, 1748, 1670, 1510 cm^{-1}; NMR ($CDCl_3$) δ 1.15 (t, 3H), 2.05 (s, 3H), 3.39 (s, 2H), 4.16 (q, 2H), 7.3 (m, 6H); Found: C, 64.61; H, 6.35; N, 10.48%. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76%.

Ethyl α-acetamido-α-cyano-β-phenylpropionate (10 g, 0.04 mol) obtained above was dissolved in 20 ml of ethanol. To this was added dropwise potassium hydroxide (2.3 g, 0.04 mol) dissolved in 5 ml of water at 5—10 °C under vigorous stirring. The reaction mixture was allowed to stand at room temperature for 3 days, and then concentrated to dryness *in vacuo* below 30 °C. The residue was dissolved in 10 ml of water and the solution was shaken once with ethyl acetate. The aqueous layer was acidified to Congo Red with 12 M hydrochloric acid. The acidified solution was shaken with three 50 ml portions of ethyl acetate, and the combined ethyl acetate layer was washed twice with 10 ml of brine, dried over magnesium sulfate, then evaporated to dryness *in vacuo* below 30 °C. The resulting crystals were recrystallized from ethyl acetate–hexane to afford 6.5 g (75%) of **2g** : mp 140—141 °C; IR (Nujol) 3350, 1730, 1630, 1540 cm^{-1} ; NMR ($CDCl_3$+DMSO-d_6) δ 2.02 (s, 3H), 3.43 (s, 2H), 7.30 (s, 5H), 8.17 (s, 1H); Found: C, 61.81; H, 5.35; N, 12.22%. Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06%.

General Electrolysis Procedure. The general electrolysis procedure is the same as reported previously.[2] In the electrolysis in 2-propanol, a 50 mA of current was passed. For large scale (1 mol) electrolysis, electrodes of an area of 40 cm^2 were used in a non-divided cell.

*Electrolysis of **2d** in Aqueous Tetrahydrofuran.* **2d** (2.8 g, 0.01 mol) was electrolyzed in a mixture of 25 ml of water and 6 ml of tetrahydrofuran containing 0.38 ml of 1 M potassium hydroxide. The other electrolysis conditions were the same as those described above. The electrolyzed solution was evaporated to dryness *in vacuo* and the resulting residue was extracted with ethyl acetate, washed once with brine, dried over magnesium sulfate, then evaporated to dryness *in vacuo*. Extraction of the resulting residue with 100 ml of hexane gave 1.8 g (93%) of ethyl phenylpyruvate (**5**). The derivative of the 2,4-dinitrophenylhydrazone showed mp 130—131 °C (lit,[19] mp 132—133 °C).

*Saponification of Compound **3d**.* Compound **3d** (2.65 g, 0.01 mol) was dissolved in 30 ml of methanol. To this was added potassium hydroxide (0.56 g, 0.01 mol) dissolved in 3 ml of water under vigorous stirring at room temperature. The reaction mixture was allowed to stand at room temperature for 24 h, and then concentrated to dryness *in vacuo*. The residue was dissolved in 10 ml of water and the solution was shaken once with ethyl acetate. The aqueous layer was acidified to Congo Red with 6 M hydrochloric acid. The acidified solution was shaken with three 30 ml portions of ethyl acetate, and the combined ethyl acetate layer was washed once with brine, dried over magnesium sulfate, then concentrated to dryness *in vacuo*. The resulting crystals were recrystallized from ethyl acetate–hexane to afford 1.2 g (51%) of *N*-acetyl-α-methoxyphenylalanine: mp 133—135 °C; IR (Nujol) 3290, 1760, 1633, 1564 cm^{-1}; NMR (DMSO-d_6) δ 1.90 (s, 3H), 3.17 (s, 5H), 7.17 (s, 5H), 8.18 (broad s, 1H); Found: C, 60.77; H, 6.36; N, 6.01%. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90%.

*Conversion to **6b**.* Compound **3b** (80 g, 0.42 mol) and ammonium bromide (80 mg) were put into a distillation apparatus. The mixture was heated at 120 °C for 20 min at 70—100 mmHg under nitrogen atmosphere, methanol being distilled off. Subsequent distillation at 5 mmHg afforded 50 g (76%) of **6b**: bp 100—103 °C (5 mmHg). IR and NMR spectra of **6b** were identical with those of an authentic sample.[13]

*Reactions of **3b** and **3d** with Phenylmethanethiol.* Ethyl *N*-acetyl-α-methoxyalaninate (**3b**) (0.95 g, 5 mmol) and phenylmethanethiol (0.62 g, 5 mmol) were dissolved in 5 ml of acetonitrile. To this was added dropwise $SnCl_4$ (0.58 ml, 5 mmol) at 0—5 °C under vigorous stirring . Stirring was continued for 1 h at the same temperature and the reaction was quenched by addition of 5 ml of saturated aqueous sodium hydrogencarbonate solution. The insoluble materials were filtered off and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in ethyl acetate and the solution was washed with brine, dried over

magnesium sulfate, and then evaporated to dryness *in vacuo*. The resulting syrup was treated with silica gel chromatography using bezene–acetone (5 : 1) as eluent to afford 1.29 g (92%) of ethyl *N*-acetyl-α-benzylthioalaninate (**7b**). Recrystallization from ethyl acetate–hexane gave colorless needles: mp 79—80 °C; IR (Nujol) 3230, 1739, 1637, 1528 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (t, 3H), 1.73 (s, 3H), 1.86 (s, 3H), 3.82 (s, 2H), 4.18 (q, 2H), 6.37 (broad s, 1H), 7.27 (s, 5H); Found: C, 59.61; H, 6.79; N, 4.69%. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98%.

3d was also allowed to react with phenylmethanethiol under the same conditions as above to afford the substitution product **7d** in 84% yield. **7d**: mp 103—104 °C ; IR (Nujol) 3230, 1728, 1640, 1534 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (t, 3H), 1.68 (s, 3H), 3.43 and 3.98 (AB q, 2H, J=13 Hz), 3.75 (s, 2H), 4.25 (q, 2H), 6.20 (broad s, 1H), 7.14 (s, 5H), 7.25 (s, 5H); Found: C, 67.37; H, 6.52; N, 3.90%. Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.49; N, 3.92%.

*Reactions of **3b** and **3d** with Anisole.* To a stirred solution of ethyl *N*-acetyl-α-methoxyalaninate (1.0 g, 5.3 mmol) dissolved in anisole (10 ml) was added dropwise $SnCl_4$ (0.61 ml, 5.3 mmol) at 0—5 °C. The reaction mixture was stirred for 1 h at the same temperature and the reaction was quenched by addition of 10 ml of saturated aqueous sodium hydrogencarbonate solution. The insoluble materials were filtered and washed thoroughly with acetonitrile. The filtrate was evaporated to dryness *in vacuo* and the residue was extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate, and then concentrated to dryness *in vacuo*. The resulting syrup was treated with silica gel chromatography using chloroform as an eluent to afford 0.82 g, (58%) of **8b** (para isomer), 0.41 g (29%) of **9b** (ortho isomer), and 0.04 g (5%) of ethyl *N*-acetyl-α,β-dehydroalaninate **6b**. **8b**: mp 108—109 °C; IR (Nujol) 3240, 1736, 1632, 1560, 1513 cm^{-1}; NMR ($CDCl_3$) 1.17 (t, 3H), 1.96 (s, 3H), 2.01 (s, 3H), 3.77 (s, 3H), 4.14 (q, 2H), 6.75 (broad s, 1H), 6.83 (d, 2H), 7.34 (d, 2H); Found: C, 63.27; H, 7.01; N, 5.33%. Calcd for $C_{14}H_{29}NO_4$: C, 63.38; H, 7.22; N, 5.28%. **9b** : syrup; IR (film) 3410, 1730, 1660, 1600, 1490 cm^{-1}; NMR ($CDCl_3+D_2O$) δ 1.14 (t, 3H), 1.87 (s, 3H), 2.02 (s, 3H), 3.73 (s, 3H), 4.15 (q, 2H), 6.7—7.7 (m, 4H); MS (30 eV), *m/e* (rel intensity), 265 (M^+, 10), 192 (73), 150 (100), 133 (32), 118 (32), 105 (47), 43 (36). The physical constants of **6b** were identical with those of an authentic sample.

3d was also treated with anisole in the presence of $SnCl_4$. The work-up was the same as that described above. TLC of the reaction mixture showed the presence of the substitution products **8d** and **9d** and the elimination product **6d**. The resulting residue was treated with silica gel chromatography using benzene–acetone (5 : 2) as an eluent to afford a mixture of **8d** and **9d** as syrup in 70% yield, the ratio of **8d** to **9d** being 4:1, based on the NMR spectrum. Elemental analysis of the mixture showed a reasonable result. Found: C, 70.12; H, 6.80; N, 4.11%. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10%. We failed in separating each isomer by liquid chromatography under various conditions. As an example, liquid chromatography of the mixture by use of μ Porasil as resin (column: 4 mm × 30 cm; flow rate : 1 ml/min) showed a single peak at retention time of 10.5 min. The mixture was crystallized from ethyl acetate–hexane to afford **8d** as needles: mp 95—96 °C; IR ($CHCl_3$) 3420, 1726, 1675, 1608, 1593 cm^{-1} ; NMR ($CDCl_3$) δ 1.19 (t, 3H), 1.95 (s, 3H), 3.78 (s, 3H), 3.74 and 4.10 (AB q, 2H, J=14 Hz), 4.13 (q, 2H), 6.83 (d, 2H), 6.6—7.4 (m, 6H), 7.33 (d, 2H). **9d** could not be isolated as a pure form. The structure of **9d** was assigned by the NMR spectrum of the mixture of **8d** and **9d**. **9d**: NMR ($CDCl_3$) δ 1.17 (t, 3H), 1.88 (s, 3H), 3.65 (s, 3H), 3.32 and 4.50 (AB q, 2H, J=14 Hz), 4.13 (q, 2H), 6.6—7.4 (m, 10H).

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