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Primary Aminomethylation at the α-Position of Carboxylic Acids and Esters. Trimethylsilyl Triflate-Catalyzed Reaction of Ketene Silyl Acetals with *N,N*-Bis(trimethylsilyl)methoxymethylamine

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A new, general method for the synthesis of β-aminocarboxylic esters (**9**) and acids (**10**) was developed. The introduction of a primary aminomethyl unit at the α-position of carboxylic esters (**2**) and acids (**3**) was achieved in high yields by the silyl trifluoromethanesulfonate (**6**)-catalyzed reaction of ketene silyl acetals (**4**) and ketene bissilyl acetals (**5**) with *N,N*-bis(trimethylsilyl)-methoxymethylamine (**1**). A possible mechanism for the reaction is proposed.

Keywords——aminomethylation; Mannich reaction; β-amino acid; ketene silyl acetal; silyl trifluoromethanesulfonate; catalysis; desilylation; silanamine; iminium salt; β-lactam

The aminomethylation of electron-rich carbon is an important subject in synthetic organic chemistry. For *N,N*-dialkylaminomethylation, the Mannich reaction[1] of ketones and aromatic compounds is the most popular method and other modified reactions recently reported are the reactions of sily enol ethers with iminium salts[2] or oxonium salts.[3] Concerning *N*-monoalkylaminomethylation, only the reactions of ketones with primary amine oxalates[4a,b] or hydrochlorides[4b,c] and of ketene silyl acetals with 1,3,5-trialkylhexahydro-1,3,5-triazines[5] have been reported. Very few methods are known for the selective introduction of the primary aminomethyl group H_2NCH_2 at carbon,[4b,c,6] in spite of its broad usefulness in organic synthesis.

In our recent communications, *N,N*-bis(trimethylsilyl)methoxymethylamine (**1**) has

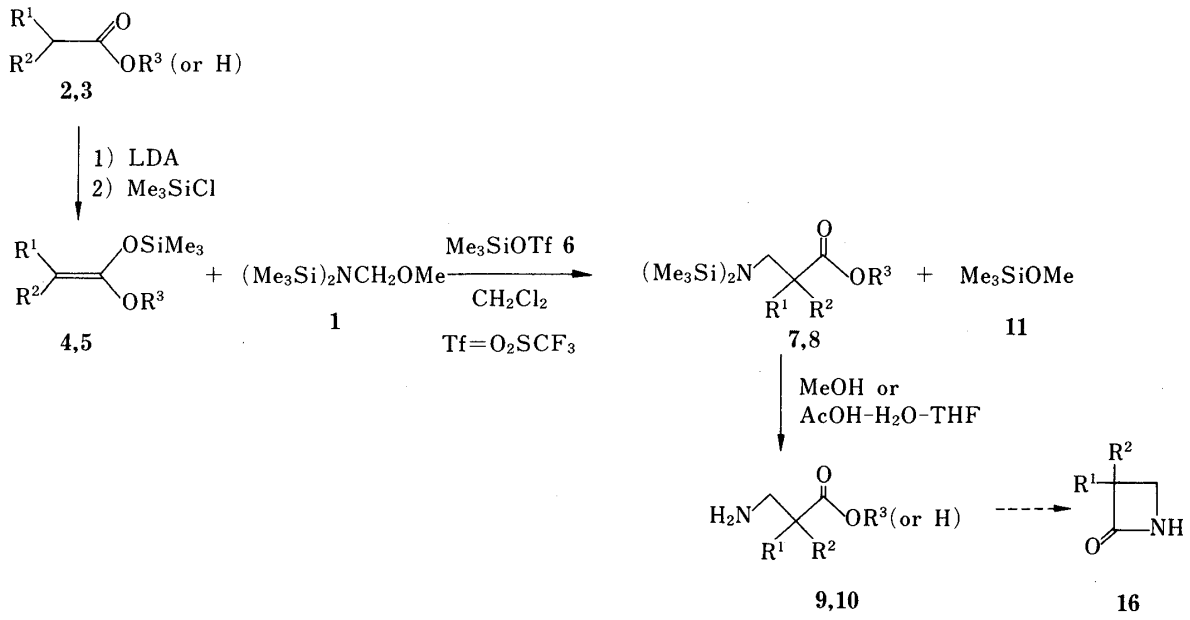


Chart 1

been reported to be a convenient synthon for $^{+}CH_2NH_2$, as exemplified by primary aminomethylation of organometallics,[7] ketene silyl acetals,[8] silyl sulfides, and silyl phosphites.[9]

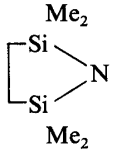
In the present paper, we wish to report in detail the primary aminomethylation of carboxylic esters (**2**) and also of carboxylic acids (**3**), through *N*,*N*-bis(trimethylsilyl)-aminomethylation of ketene silyl acetals (**4**, **5**) with **1** followed by desilylation, as illustrated in Chart 1.

The reagent, *N*,*N*-bis(trimethylsilyl)methoxymethylamine (**1**) was prepared in 86% yield by treating chloromethyl methyl ether with lithium bis(trimethylsilyl)amide in tetrahydrofuran (THF)–hexane at 0 °C. The reagent (**1**) is quite stable in neutral and basic media but is susceptible to acids and Lewis acids. In a similar manner, *N*,*N*-bis(trimethylsilyl)ethoxymethylamine (**1'**) was also prepared in 74% yield.

Ketene silyl acetals (**4**) and ketene bissilyl acetals (**5**), easily derived from carboxylic esters (**2**) and acids (**3**), respectively, are efficient nucleophilic synthons.[10] The reaction of ketene silyl acetals (**4**, **5**) with **1** was effectively catalyzed by trimethylsilyl trifluoromethanesulfonate (TMS triflate) (**6**).[11] Thus, the *N*,*N*-bis(trimethylsilyl)aminomethyl group was introduced into carboxylic esters (**2**) and acids (**3**) at the α position and successive desilylation gave the corresponding β-aminocarboxylic esters (**9**) and acids (**10**).

In the presence of 0.01 mol eq of **6** the reaction of ketene silyl acetals (**4**, **5**) and **1** proceeded smoothly at 25—30 °C in dichloromethane. After removal of the catalyst (**6**) by treatment with magnesium oxide, the products (**7**, **8**) were obtained in high yields by vacuum distillation. As summarized in Table I, a variety of β-aminocarboxylic esters (**7a—g**, **8a—e**) were obtained from the corresponding ketene silyl acetals (**4a—g**, **5a—e**). Runs 7 and 12 demonstrate the high-yield preparation of α,β-diaminoacid derivatives (**7g**, **8e**). The structures

Table I. Reaction[a] of Ketene Silyl Acetals (**4**, **5**) with *N*,*N*-Bis(trimethylsilyl)methoxymethylamine (**1**)

Run No.	Ketene silyl acetal				Product	Yield[b] (%)
	No.	R^1	R^2	R^3	No.	
1	**4a**	Me	Me	Me	**7a**	84
2	**4b**	Me	H	Me	**7b**	85
3	**4c**	H	H	CH_2Ph	**7c**	88
4	**4d**	$-(CH_2)_4-$		Me	**7d**	78
5	**4e**	$-(CH_2)_5-$		Me	**7e**	85
6	**4f**	Ph	H	Me	**7f**	95
7	**4g**		H	Me	**7g**	93
8	**5a**	Me	Me	$SiMe_3$	**8a**	87
9	**5b**	Me	H	$SiMe_3$	**8b**	81
10	**5c**	$-(CH_2)_5-$		$SiMe_3$	**8c**	92
11	**5d**	Ph	H	$SiMe_3$	**8d**	98
12	**5e**		H	$SiMe_3$	**8e**	94

a) Molar ratio, ketene silyl acetal (**4**, **5**) : **1** : silyl triflate (**6**) = 1 : 1—1.2 : 0.01; solvent, CH_2Cl_2; reaction temp., 25—30 °C; reaction time, 1 h (20 h in run 10). *b*) Isolated yield based on **4** or **5**.

TABLE II. Physical Properties

Compound No.	bp (°C/mmHg)	IR (neat) ν_{max} cm^{-1} (C=O)	^{1}H-NMR ($CDCl_3$) δ (J=Hz)		
			$[(CH_3)_3Si]_2$ (18H, s)	NCH_2 (2H)	Others
7a	114—115/19	1731	0.11	3.15 (s)	1.13 (6H, s, $(CH_3)_2C$), 3.64 (3H, s, OCH_3)
7b	102—103/15	1740	0.12	2.89 (dd, J=14.9, 6.6) 3.21 (dd, J=14.9, 7.2)	1.08 (3H, d, J=6.8, CH_3), 2.52 (1H, ddq, J=6.6, 7.2, 6.8, CH), 3.66 (3H, s, OCH_3)
7c	110—112/0.03	1736	0.11	2.95—3.28 (m)	2.22—2.53 (2H, m, CH_2CO), 5.09 (2H, s, $C\underline{H}_2Ph$), 7.33 (5H, s, Ph)
7d	93—94/0.4	1730	0.13	3.20 (s)	1.35—2.19 (8H, m, $(CH_2)_4$), 3.65 (3H, s, OCH_3)
7e	88—91/0.15	1728	0.13	3.01 (s)	0.80—2.28 (10H, m, $(CH_2)_5$), 3.66 (3H, s, OCH_3)
7f	106—107/0.2	1737	0.09	3.61 (d, J=8.8)	3.12 (1H, t, J=8.8, CH), 3.63 (3H, s, OCH_3), 7.20—7.37 (5H, m, Ph)
7g	100—101/0.03	1745	0.13	2.82 (dd, J=13.2, 4.8) 3.30 (dd, J=13.2, 11.3)	0.10 (6H, s, $Si(CH_3)_2$), 0.15 (6H, s, $Si(CH_3)_2$), 0.66 (4H, s, $Si(CH_2)_2Si$), 3.71 (1H, dd, J=11.3, 4.8, CH), 3.64 (3H, s, OCH_3)
8a	150/0.4[a]	1712	0.13	3.16 (s)	0.27 (9H, s, $OSi(CH_3)_3$), 1.11 (6H, s, $C(CH_3)_2$)
8b	130/0.7[a]	1719	0.13	2.78 (dd, J=13.6, 8.0) 3.24 (dd, J=13.6, 6.2)	0.28 (9H, s, $OSi(CH_3)_3$), 1.08 (3H, d, J=6.8, CH_3), 2.48 (1H, ddq, J=6.2, 8.0, 6.8, CH)
8c	170/0.4[a]	1711	0.16	3.04 (s)	0.29 (9H, s, $OSi(CH_3)_3$), 0.98—2.19 (10H, m, $(CH_2)_5$)
8d	160/0.07[a]	1717	0.08	3.36—3.74 (m)	0.22 (9H, s, $OSi(CH_3)_3$), 2.90—3.22 (1H, m, CH), 7.05—7.40 (5H, m, Ph)
8e	170/0.2[a]	1723	0.15	2.77 (dd, J=12.9, 4.6) 3.18 (dd, J=12.9, 11.5)	0.05 (6H, s, $Si(CH_3)_2$), 0.12 (6H, s, $Si(CH_3)_2$), 0.29 (9H, s, $OSi(CH_3)_3$), 0.66 (4H, s, $Si(CH_2)_2Si$), 3.69 (1H, dd, J=11.5, 4.6, CH)

a) Boiling point refers to the bath temperature in a "Kugelrohr" short-path apparatus.

of all theses new compounds (**7a—g**, **8a—e**) were supported by the infrared (IR) and nuclear magnetic resonance (NMR) spectra and elemental analyses. The physical properties and analytical data of **7** and **8** are listed in Table II.

A probable reaction scheme is shown in Chart 2. The mechanism of the triflate (**6**)-catalyzed reaction may be essentially similar to that of the silyl iodide- or triflate-catalyzed *N*,*N*-dialkylaminomethylation reported previously.[3] It was observed that the addition of a catalytic amount of **6** to a solution of **1** in dichloromethane caused rapid and considerable release of methoxytrimethylsilane (**11**) which was detected by proton nuclear magnetic resonance (^{1}H-NMR). Chart 3 shows a probable path of this decomposition. The rapid release of **11** suggests that the actual electrophile is not the oxonium salt (**12**)[12] but the iminium salt (**13**). However, in the presence of only a catalytic amount of the triflate (**6**), **1** is

and Analytical Data of **7** and **8**

^{13}C-NMR ($CDCl_3$) δ					Formula	Analysis (%) Calcd (Found)		
$[(\underline{C}H_3)_3Si]_2$ (q)	NCH_2 (t)	$\geqslant\underline{C}$–CO	C=O (s)	Others		C	H	N
2.9	53.6	44.6 (s)	178.4	24.5 (q, $(\underline{C}H_3)_2C$), 51.4 (q, OCH_3)	$C_{12}H_{29}NO_2Si_2$	52.31 (52.18	10.61 10.62	5.08 5.12)
2.4	49.0	43.7 (d)	176.1	14.9 (q, CH_3), 51.2 (q, OCH_3)	$C_{11}H_{27}NO_2Si_2$	50.52 (50.62	10.41 10.40	5.36 5.38)
2.0	41.3	40.0 (t)	171.6	66.0 (t, $\underline{C}H_2Ph$), 128.1, 128.5, 136.5 (d, d, s, Ph)	$C_{16}H_{29}NO_2Si_2$	59.39 (59.76	9.03 9.00	4.33 4.23)
2.9	51.5	58.0 (s)	177.9	24.4 (t, CH_2), 34.4 (t, CH_2), 51.5 (q, OCH_3)	$C_{14}H_{31}NO_2Si_2$	55.76 (55.47	10.36 10.33	4.64 4.69)
3.2	55.7	50.6 (s)	176.6	23.9 (t, CH_2), 25.8 (t, CH_2), 33.5 (t, CH_2), 51.1 (q, OCH_3)	$C_{15}H_{33}NO_2Si_2$	57.09 (57.17	10.54 10.53	4.44 4.70)
2.4	50.3	56.4 (d)	173.8	51.6 (q, OCH_3), 127.4, 128.4, 128.6, 138.0 (d, d, d, s, Ph)	$C_{16}H_{29}NO_2Si_2$	59.39 (59.88	9.03 9.13	4.33 4.38)
2.7	50.6	59.7 (d)	174.7	0.7 (q, $Si(CH_3)_3$), 1.4 (q, $Si(CH_3)_3$), 8.6 (t, $Si(CH_2)_2Si$), 51.0 (q, OCH_3)	$C_{16}H_{40}N_2O_2Si_4$	47.47 (46.81	9.96 10.01	6.92 6.88)
3.0	52.9	45.3 (s)	179.0	−0.2 (q, $OSi(CH_3)_3$), 24.5 (q, $(\underline{C}H_3)_2C$)				
2.5	48.8	45.1 (d)	176.0	−0.2 (q, $OSi(CH_3)_3$), 14.8 (q, CH_3)				
3.4	55.3	51.1 (s)	177.1	0.0 (q, $OSi(CH_3)_3$), 24.0 (t, CH_2), 25.9 (t, CH_2), 33.3 (t, CH_2)				
2.7	50.3	58.3 (d)	173.7	0.3 (q, $OSi(CH_3)_3$), 127.4, 128.7, 138.6 (d, d, s, Ph)				
2.8	50.4	60.8 (d)	174.2	0.0 (q, $OSi(CH_3)_3$), 0.6 (q, $Si(CH_3)_3$), 1.7 (q, $Si(CH_3)_3$), 8.6 (t, $Si(CH_2)_2Si$)				

transformed into another product, presumably the less reactive *N*-silylmethylenimine (**14**) or its trimer (**15**) to a large extent, nearly corresponding to the release of **11**. In fact, an attempt to carry out the reaction of **4a** with this altered solution of **1** resulted in a very slow reaction to give the product, **7a**, in somewhat lower yield (70%) as compared with the direct use of **1**. This result implies that the reverse shift to the iminium salt (**13**) from **14** or **15** in the equilibrium is much slower than the formation of **13** from **1**. Furthermore, the triflate (**6**)-catalyzed reaction of **5c** with **1** (run 10) proceeded very slowly, requiring 20 h for completion. Presumably, the considerable shift of **1** to the less active **14** or **15** through **13** occurs because of the lower reactivity of **5c**.

The desilylation of silanamines by treatment with an acid[13] or an alcohol without[14] or in the presence of potassium fluoride[15] is known. Typically, **7a** was heated in methanol for 24 h

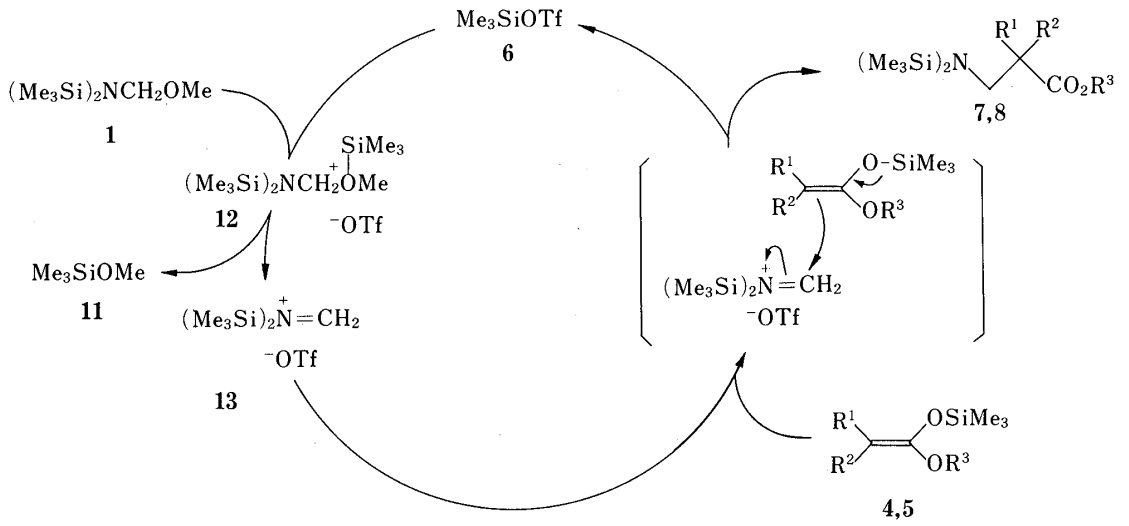


Chart 2

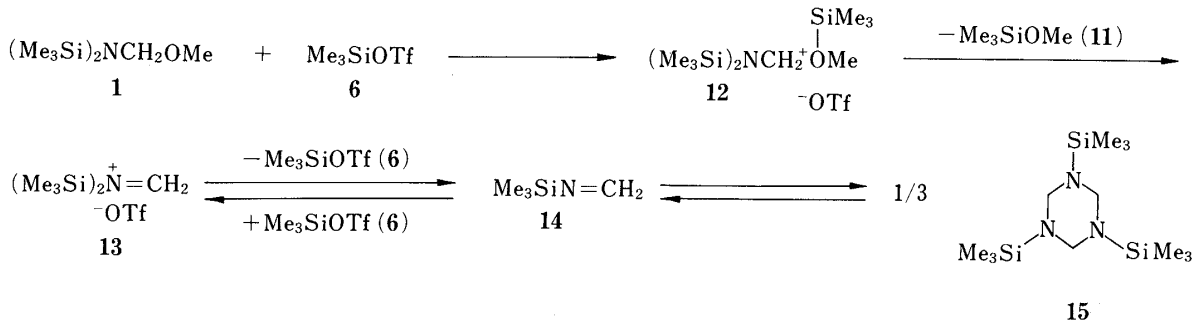


Chart 3

to afford β-aminocarboxylic ester (**9a**) in 80% yield. In the case of silyl esters, desilylation has been performed by treatment with acetic acid–aqueous THF,[16] tetrabutylammonium fluoride in dimethylformamide,[16] or potassium carbonate in aqueous methanol.[17] In a typical example, **8a** was desilylated by treatment with acetic acid–aqueous THF at room temperature to give the β-aminocarboxylic acid (**10a**) quantitatively.

β-Aminocarboxylic esters (**9**) and β-aminocarboxylic acids (**10**) are known to be converted to β-lactams (**16**) by treatment with Grignard reagents[18] and triphenylphosphine–2,2′-dipyridyl disulfide[19] or 2-chloro-1-methylpyridinium iodide–triethylamine,[20] respectively. β-Aminocarboxylic esters (**7a—g**, **8a—e**) obtained in the present work should be useful intermediates for synthesizing *N*-unsubstituted β-lactams (**16**); in particular, **7g** and **8e** may be useful as precursors of monobactams.[21]

Finally, it should be noted that the utilization of the reagent, *N*,*N*-bis(trimethylsilyl)-methoxymethylamine (**1**), as a convenient synthetic equivalent for $^{+}CH_2NH_2$ permits the ready introduction of a primary aminomethyl unit into carboxylic acids (**3**) and esters (**2**) at the α-position. Thus, the present work serves to illustrate the potential applicability of the reagent (**1**) for the preparation of β-amino acids (**10**) and esters (**9**) from carboxylic acids (**3**) and esters (**2**) in high yields by simple procedures.

Experimental

All boiling and melting points are uncorrected. IR spectra were measured on Hitachi EPI-G2 and JASCO A-202 spectrometers. ^{1}H- and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra were taken with Hitachi R-24B

(60 MHz) and JEOL FX-90Q (90 MHz, 22.5 MHz) spectrometers using tetramethylsilane as an internal standard.

Ketene Silyl Acetals (4a—g, 5a—e)——The starting ketene trimethylsilyl acetals (**4a—g**) and ketene bis-(trimethylsilyl) acetals (**5a—e**) were prepared from the corresponding carboxylic esters (**2a—g**) and acids (**3a—e**) by the previously reported method.[22,23] The structures of new compounds (**4g, 5e**) were confirmed by ^{1}H-NMR spectral measurement in $CDCl_3$. **4g**: bp 79—86 °C (1 mmHg), ^{1}H-NMR δ: 0.07 (18H, s, $2\times SiMe_3$), 0.21 (9H, s, $OSiMe_3$), 0.71 (4H, s, $(CH_2)_2$), 3.44 (3H, s, OCH_3), 4.59 (1H, s, =CH–). **5e**: bp 98 °C (0.2 mmHg), ^{1}H-NMR δ: 0.05 (18H, s, $2\times SiMe_3$), 0.19 (9H, s, $OSiMe_3$), 0.22 (9H, s, $OSiMe_3$), 0.71 (4H, s, $(CH_2)_2$), 4.43 (1H, s, =CH–).

***N,N*-Bis(trimethylsilyl)methoxymethylamine (1) and *N,N*-Bis(trimethylsilyl)ethoxymethylamine (1′)**——A solution of *n*-butyllithium (67.7 ml of 1.55 M in hexane, 0.105 mol) was added dropwise at 0 °C to a stirred solution of hexamethyldisilazane (16.1 g, 0.1 mol) in THF (100 ml) under a nitrogen atmosphere and the mixture was stirred for 0.5 h. Chloromethyl methyl ether (8.1 g, 0.1 mol) was added dropwise to the cooled and stirred mixture, and stirring was continued for 2 h at 0 °C. The solvent was removed by evaporation and the resulting residue was filtered to remove solid lithium chloride, which was rinced with hexane. After removal of the solvent, distillation of the liquid residue gave pure **1** (17.7 g, 86% yield), bp 91—92 °C (86 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.14 (18H, s, $2\times(CH_3)_3Si$), 3.17 (3H, s, OCH_3), 4.28 (2H, s, CH_2). ^{13}C-NMR ($CDCl_3$) δ: 1.9 (q, $(CH_3)_3Si$), 53.4 (q, OCH_3), 80.9 (t, CH_2). *Anal.* Calcd for $C_8H_{23}NOSi_2$: C, 46.77; H, 11.28; N, 6.82. Found: C, 47.20; H, 11.36; N, 6.79. Compound **1′** was also prepared by the use of chloromethyl ethyl ether in a similar manner in 74% yield, bp 84—85 °C (35 mmHg). ^{1}H-NMR ($CDCl_3$) δ: 0.13 (18H, s, 2 $(CH_3)_3Si$), 1.16 (3H, t, J=7.1 Hz, CH_3), 3.36 (2H, q, J=7.1 Hz, CH_2), 4.35 (2H, s, CH_2). ^{13}C-NMR ($CDCl_3$) δ: 2.0 (q, $(CH_3)_3Si$), 15.3 (q, CH_3), 61.2 (t, CH_2), 79.1 (t, CH_2). *Anal.* Calcd for $C_9H_{25}NOSi_2$: C, 49.25; H, 11.48; N, 6.38. Found: C, 49.03; H, 11.67; N, 6.28.

General Procedure for the Reaction of Ketene Silyl Acetals (4a—g, 5a—e) with 1 in the Presence of Trimethylsilyl Triflate (6)——A mixture of ketene silyl acetal (**4** or **5**) (10 mmol) and **1** (10 mmol for **4** or 12 mmol for **5**) in dichloromethane (20 ml) was stirred and ice-cooled under a nitrogen atmosphere. Then a dichloromethane solution of silyl triflate (**6**) (0.1 ml of 1 M solution, 0.1 mmol) was added with a syringe. The whole was stirred for 1 h (20 h for **5c**) at 25—30 °C, then anhydrous MgO (20 mg) was added. The reaction mixture was stirred for 0.5 h to remove **6**, then filtered and the solvent was removed by evaporation. Vacuum distillation of the oily residue gave pure *N,N*-bis(trimethylsilyl)-*β*-aminocarboxylic ester (**7** or **8**) in high yield as shown in Table I. The physical properties and analytical data of the products (**7a—g, 8a—e**) are summarized in Table II.

Alteration of 1 Catalyzed by 6 and Reaction of the Altered Mixture with 4a——A dichloromethane solution of **6** (0.1 ml of 1 M solution, 0.1 mmol) was added to a cooled and stirred solution of **1** (2.06 g, 10 mmol) in dichloromethane (20 ml) under a nitrogen atmosphere. The reaction mixture was stirred at 25—30 °C for 1 h, then a small sample was taken out and its ^{1}H-NMR spectrum was measured. The signals of **1** had disappeared and those of methoxytrimethylsilane (**11**) were observed at δ 0.11 ($Si(CH_3)_3$) and 3.42 (OCH_3), which were identical with those of an authentic specimen.

Next, **4a** (1.74 g, 10 mmol) was added to the altered mixture and the whole was stirred at 25—30 °C. It took 45 h to complete the reaction. Work-up of the reaction mixture in the usual manner gave **9a** (1.92 g, 70% yield).

Preparation of 2,2-Dimethyl-*β*-alanine Methyl Ester (9a) as a Typical Procedure for Desilylation of *N,N*-Bis(trimethylsilyl)-*β*-aminocarboxylic Esters (7) to *β*-Aminocarboxylic Esters (9)——A solution of 2,2-dimethyl-*N,N*-bis(trimethylsilyl)-*β*-alanine methyl ester (**7a**) (1.35 g, 5 mmol) in MeOH (5 ml) was heated under reflux for 24 h. Removal of the solvent and vacuum distillation gave **9a** (0.525 g, 80% yield), bp 63—64 °C (14 mmHg) [lit.[23] 57 °C (11 mmHg)]. IR (neat) cm^{-1}: 3384 (NH_2), 1727 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.17 (6H, s, $(CH_3)_2C$), 1.45 (2H, s, NH_2), 2.74 (2H, s, CH_2), 3.68 (3H, s, OCH_3). ^{13}C-NMR ($CDCl_3$) δ: 22.9 (q, $(\underline{C}H_3)_2C$), 44.6 (s, $(CH_3)_2\underline{C}$), 51.5 (t, CH_2), 51.6 (q, CH_3), 177.6 (s, C=O). *Anal.* Calcd for $C_6H_{13}NO_2$: C, 54.94; H, 9.99; N, 10.68. Found: C, 54.58; H, 10.15; N, 10.17.

Preparation of 2,2-Dimethyl-*β*-alanine (10a) as a Typical Procedure for Desilylation of *N,N*-Bis(trimethylsilyl)-*β*-aminocarboxylic Acid Trimethylsilyl Esters (8) to *β*-Aminocarboxylic Acids (10)——A solution of 2,2-dimethyl-*N,N*-bis(trimethylsilyl)-*β*-alanine trimethylsilyl ester (**8a**) (5 mmol) in a mixture of AcOH–H_2O–THF (3 : 1 : 1) (3 ml) was stirred for 1 h at room temperature. Removal of the solvent by evaporation gave **10a** quantitatively. Recrystallization from H_2O–MeOH gave an analytical sample, mp 238 °C (dec.) [lit.[25] 239 °C (dec.)]. ^{1}H-NMR (D_2O) [internal standard: 3-(trimethylsilyl)propanesulfonic acid sodium salt] δ: 1.17 (6H, s, $(CH_3)_2C$), 2.98 (2H, s, CH_2). ^{13}C-NMR (D_2O) δ: 25.6 (q, $(\underline{C}H_3)_2C$), 43.1 (s, $(CH_3)_2\underline{C}$), 49.8 (t, CH_2), 185.7 (s, C=O). *Anal.* Calcd for $C_5H_{11}NO_2$: C, 51.26; H, 9.46; N, 11.96. Found: C, 51.05; H, 9.48; N, 11.85.

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