Practical Preparation of (*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetic Acid: A Side-Chain of the Fourth Generation of Cephem Antibiotics

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A *Z*-isomer (**4**) of 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetic acid, which is the common acyl moiety of clinically useful cephem antibiotics, has been prepared from the aminoisoxazoles through the skeletal rearrangement in several routes. Reaction of 3-amino-5-methoxyisoxazole (**7**) with alkoxycarbonyl isothiocyanates gave methyl 2-(5-alkoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetates (**8**), which were converted into the target compound **4** through the reaction of the corresponding keto ester with *O*-methylhydroxylamime. Compound **4** was prepared similarly from 3-aminoisoxazole (**10**). Also, *O*-methylation of 2-hydroxyimino-2-(5-methoxycarbonylamino-1,2,4-thiazol-3-yl)acetate (**15**) with methyl iodide or dimethyl sulfate in the presence of barium oxide and barium hydroxide octahydrate was found to afford exclusively the desired *Z*-isomer (**14a**) of methyl 2-(5-methoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetate, which was led to **4**.

The molecular architecture associated with the β-lactam antibiotics has posed some of the greatest challenges for synthetic chemistry, and this family has provided the stimulus for the development of methodology of the construction of their skeletons and side chains.[1] Especially, in cephem antibiotics, the fourth generation has been already developed.[2] Recently, (*Z*)-7β-[2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(alkoxyimino)acetamido]cephalosporins such as SCE2787 (**1**),[3] E1040 (**2**),[4] and E1077 (**3**)[5] have been reported as clinically useful antibiotics having excellent antimicrobial activities (Fig. 1). Their common acyl moiety at the C-7 position is corresponding to the *Z*-isomer (for example, **4**) of 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(alkoxyimino)acetic acid. The *E*-isomer is known to be not valuable for useful β-lactam antibiotics, so far. Consequently, it was our intention to successfully develop a general method of entry into the *Z*-isomer by our own strategy, although several methods have been reported for the production of **4**.[6,7]

Herein we provide full details of a novel and concise preparation[8] directed toward the mass production of the (*Z*)-methoxyimino compound: (*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetic acid (**4**) based on the skeletal rearrangement of the aminoisoxazoles **7** or **10**, and the stereoselective *O*-methylation of the hydroxyimino compound **15**.

Results and Discussion

The starting 3-amino-5-methoxyisoxazole (**7**) was prepared from malononitrile (**5**) through 3,3-dimethoxyacrylonitrile (**6**).[9] Thus, malononitrile (**5**) was treated with HCl gas and MeOH to give methyl cyanoacetimidate, which was further submitted to methanolysis followed by thermolysis to **6** (Scheme 1). Conversion of **6** into **7** was carried out according to the patent of Morita and Saraie.[9] Compound **7** was subjected to the skeletal rearrangement in question. A suspension of methyl chloroformate and KSCN in acetonitrile was stirred at 70 °C for 30 min to give methoxycarbonyl isothiocyanate in situ, which in turn reacted with **7** to afford methyl 2-(5-methoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetate (**8a**) in 86% yield by the skeletal rearrangement of the intermediary thiourea derivative **9**. This reaction mechanism was reasonably supported by the isolation of the similar intermediate **11** as described below.[10] The use of ethyl chloroformate, phenyl chloroformate, and benzyl chloroformate for this reaction instead of methyl chloroformate led to the corresponding alkoxycarbonylamino derivatives **8b**, **8c**, and **8d** in moderate yields.

Alternatively, the key compounds **8a**, **8b**, and **8c** were prepared from 3-aminoisoxazole (**10**) (Scheme 2). Reaction of **10** with the aforesaid methoxycarbonyl isothiocyanate gave the intermediary 1-(3-isoxazolyl)-3-(methoxycarbonyl)thiourea (**11a**) in 60% yield, which was warmed in MeOH at 35 °C for 1 h to give quantitatively 2-(5-methoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetaldehyde (**12a**) through the similar rearrangement as described above. Oxidation of **12a** with peracetic acid followed by esterification provided the methyl ester **8a** in 80% yield. Similarly, **8b** and **8c** were obtained from **10** through **12b** and **12c**.

Compounds **8a**—**d** were converted into methyl 2-(5-alkoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2-oxoacetates (**13a**—**d**) by oxidation with DMSO and I_2 in the presence of catalytic amounts of H_2SO_4 in 83—58% yields (Scheme 3). Their moderate yields were ascribed to the difficult purification due to their polar nature. Without isolation of **13a**, the methyl ester **8a** was *quantitatively* converted into the desired methyl (*Z*)-2-(5-methoxycarbonylamino-1,2,4-thiadiazol-3-

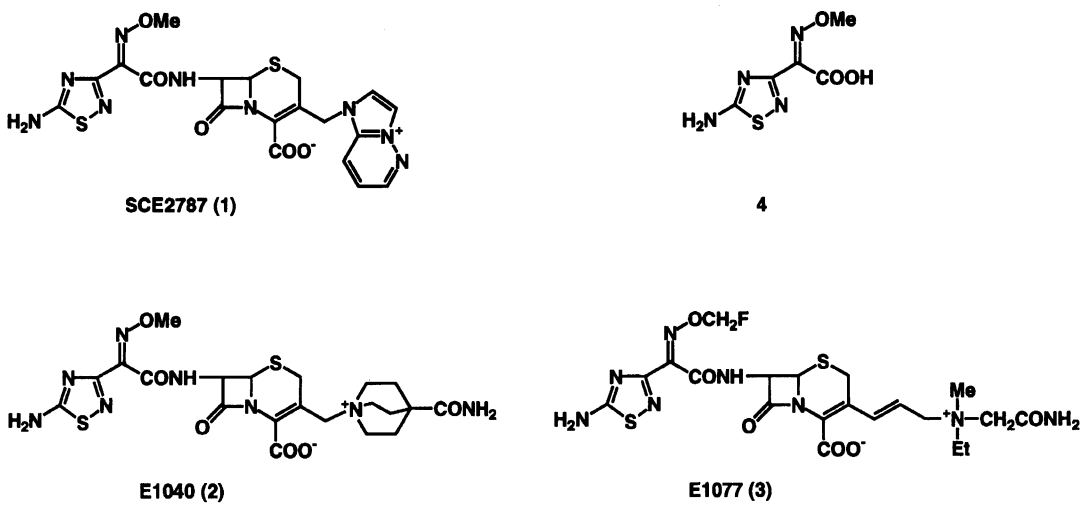
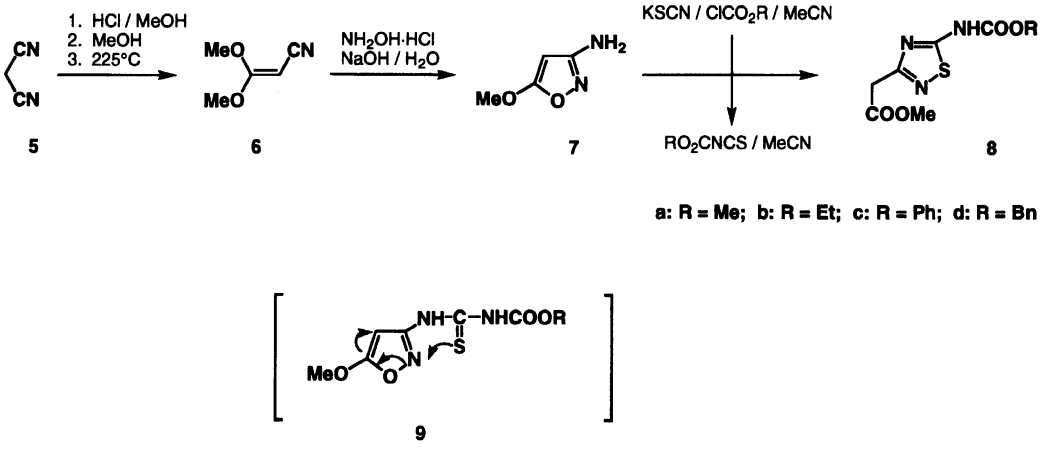
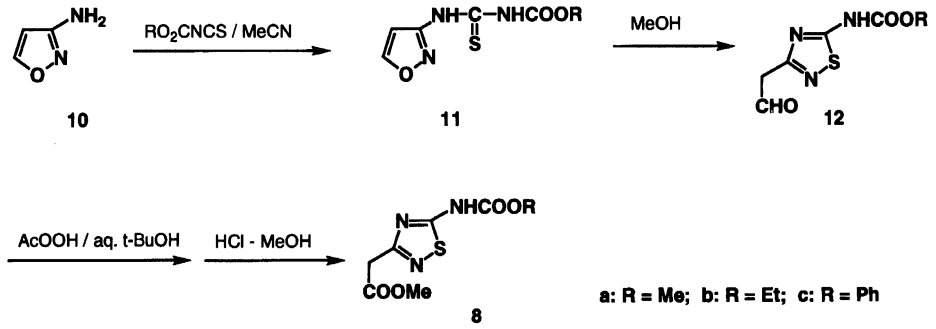


Fig. 1.

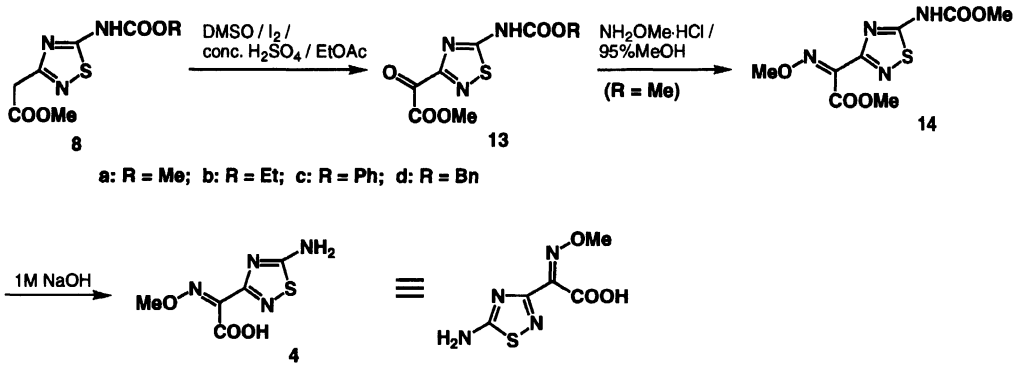


Scheme 1.



Scheme 2.

yl)-2-(methoxyimino)acetate (**14**) in one pot. Namely, **8a** was oxidized by the aforesaid conditions followed by treatment with *O*-methylhydroxylamine to give **14** in quantitative yield. The *Z* or *syn* configuration was confirmed by conversion into **4**.[6] Compound **8a** was also oxidized to the keto ester **13a** by SeO_2 in dioxane at 95 °C for 3 h in 80% yield,[11] but this reagent might be not adapted in the industrial scale production because of its toxicity. Saponification of **14** with 1 M NaOH (1 M=1 mol dm^{-3}) provided the target product, (*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetic acid (**4**) in quantitative yield. The ^{1}H NMR spectrum of **4** was identical with the reported data,[6] confirming the *Z*-configuration. Although this route gave the desired *Z*-isomer **4** of the methoxyimino derivative in fairly good total yield through the aforesaid reaction of **13a** with *O*-methylhydroxylamine, this procedure was restricted to the preparation of the methoxyimino derivative. Consequently, the general procedure was developed for the preparation of other alkoxyimino derivatives.



Scheme 3.

Compound **14** was also found to be obtained from **8a** through methyl 2-hydroxyimino-2-(5-methoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetate (**15**), although the stereochemistry of **15** could not be determined (Scheme 4). Namely, **8a** was converted into **15** in 92% yield by treatment with methyl nitrite gas. And also, **15** was derived from 3-amino-5-methoxyisoxazole (**7**) without isolation of **8a** (See Experimental). Consequently, the conditions of *O*-methylation of **15** were assayed with a large number of variables including methylating reagent, base, solvent and temperature as shown, in part, in Table 1. Most of conditions gave only the *E*-isomer **16** having R_f 0.41 (1:1 hexane–EtOAc). Remarkably, the use of combined reagents barium oxide and barium hydroxide octahydrate with methyl iodide or dimethyl sulfate gave exclusively the desired *Z*-isomer **14** having R_f 0.29 (1:1 hexane–EtOAc) in 84 and 80% yields, respectively. The yields were little dependent on methylating reagents MeI or Me_2SO_4. Also, methylation of **15** with MeI and Ag_2O afforded the *Z*-isomer **14** in 80% yield. These conditions provided significantly the high possibility of the industrial production of a variety of useful (*Z*)-alkoxyimino analogs by using appropriate alkylating reagents.

Experimental

The melting points were determined on a micro hot-stage Yanaco MP-S3 and were uncorrected. IR spectra were recorded on either a BIO RAD DIGILAB FTS-65 or a JASCO FT/IR-5M spectrometer with KBr, Mass spectra were on JOEL JMS-DX303, and ^{1}H NMR spectra were on a JEOL GSX270 spectrometer in $CDCl_3$ using TMS as internal standard unless otherwise noted. Silica-gel TLC and column chromatography were performed on a Merck TLC 60F-254 and a Merck Kieselgel 60 or a Fuji–Davison BW-820MH, respectively. In general, the organic solvents were purified and dried by appropriate procedures, and evaporation and concentration were carried out under reduced pressure below 30 °C, unless otherwise noted.

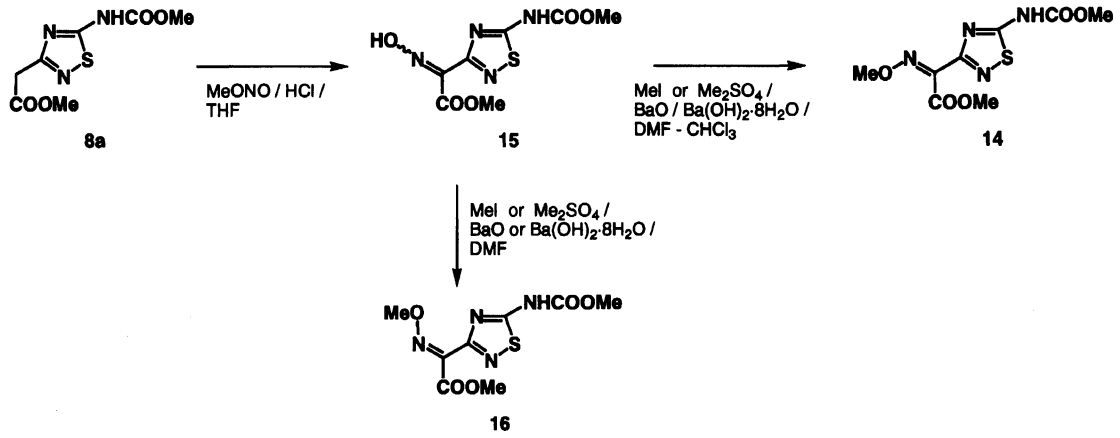
(*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetic Acid (4). A solution of **14** (137 mg, 0.5 mmol) in 1 M NaOH (2.0 ml, 2.0 mmol) was stirred at 100 °C for 4 h. After cooling, the mixture was acidified with 6 M HCl to pH 1, and extracted with EtOAc (2 ml×5). The extracs were combined, dried, and evaporated to give **4** as colorless crystals (97 mg, 97%): R_f=0.43 (4:4:2:3 *n*-BuOH–EtOH–$CHCl_3$–H_2O); mp 179—181 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=3.90 (3H, s, Me) and 8.20 (2H, br s, NH_2) [lit,[6] mp 182 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=3.90 (3H, s, Me) and 8.10 (2H, br s, NH_2)]. Found: C, 29.31; H, 3.22; N, 27.42%. Calcd for $C_5H_6N_4O_3S$: C, 29.70; H, 2.99; N, 27.71%.

3,3-Dimethoxyacrylonitrile (6). To a stirred solution of malononitrile (**5**, 12.0 g, 182 mmol) and methanol (7.35 ml, 182 mmol) in dry ether (240 ml) was bubbled hydrogen chloride gas (8.5 g, 230 mmol) during 1 h at −5 °C. After stirring at the same temperature for 1 h and at room temperature for 6 h, the formed crystals were filtered off, washed with ether and dried in vacuo to give methyl cyanoacetimidate hydrochloride (23.8 g, 98%).

A suspension of methyl cyanoacetimidate hydrochloride (23.8 g, 177 mmol) in methanol (177 ml) was stirred at room temperature for 12 h and the reaction mixture was concentrated to a resiude, which was dissolved in EtOAc. The solution was washed with saturated aqueous Na_2CO_3 and saturated aqueous NaCl, dried, and concentrated. The crude syrup obtained was purified by distillation under reduced pressure to give 3,3,3-trimethoxypropionitrile (22.1 g, 86%) as a syrup: Bp 110—112 °C/2533 Pa; ^{1}H NMR δ=2.87 (2H, s, CH_2) and 3.36 (9H, s, 3×Me).

A syrup of 3,3,3-trimethoxypropionitrile (22.1 g, 153 mmol) was stirred at 222—225 °C for 7 min. The reactant was distilled under reduced pressure to give **6** as a syrup (14.2 g, 70% from **5**): Bp 112—115 °C/2533 Pa; ^{1}H NMR δ=3.50 (1H, s, H-2), 3.74 (3H, s, OMe), and 3.80 (3H, s, OMe). Found: C, 52.91; H, 6.10; N, 12.04%. Calcd for $C_5H_7NO_2$: C, 53.09; H, 6.24; N, 12.38%.

3-Amino-5-methoxyisoxazole (7).[9] To a stirred solution of hydroxylamine hydrochloride (1.55 g, 22.3 mmol) in water (3.41 ml) was added 8 M NaOH solution (3.35 ml, 26.8 ml) at room temperature. After the solution warmed to 45 °C, a solution of **6** (2.27 g, 20.1 mmol) in methanol (5.50 ml) was added dropwise during 30 min, and the resulting mixture was stirred at the same temperature for 1 h. After the comsumption of **6** was completed, 8 M NaOH solution (1.25 ml, 10.1 mmol) was added at 45 °C, and the reaction mixture was stirred at 60 °C for 6 h and then concentrated until precipitates of inorganic compound separated out. The mixture was extracted with EtOAc and then the extracts were dried and evaporated to a residue. Recrystallization from hexane–EtOAc gave **7** as colorless crystals



Scheme 4.

Table 1. *O*-Methylation of **15** with MeI or Me_2SO_4

Entry	Base	Solvent	Product (Yeild)
1	Ag_2O	DMF	*Z*-Isomer : **14** (80%)
2	BaO–$Ba(OH)_2 \cdot 8H_2O$	DMF–$CHCl_3$	*Z*-Isomer : **14** (84%)
3	BaO	DMF	*E*-Isomer : **16**
4	$Ba(OH)_2 \cdot 8H_2O$	DMF	*E*-Isomer : **16**
5	K_2CO_3	DMSO	*E*-Isomer : **16**
6	CaO	DMF	*E*-Isomer : **16**
7	$Ca(OH)_2$	DMF	*E*-Isomer : **16**
8	TEA	Dioxane	*E*-Isomer : **16**

(1.71 g, 75%): Mp 82—83 °C; IR ($CHCl_3$) 3840, 1628, and 1487 cm^{-1}; ^1H NMR ($CDCl_3+D_2O$) δ=3.93 (3H, s, OMe) and 4.83 (1H, s, H-4). Found: C, 41.74; H, 5.06; N, 24.35%. Calcd for $C_4H_6N_2O_2$: C, 42.11; H, 5.30; N, 24.55%.

Methyl 2-(5-Methoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetate (8a). A) From 7: A suspension of methyl chloroformate (0.927 ml, 12 mmol) and KSCN (1.26 g, 13 mmol) in MeCN (10 ml) was stirred at 70 °C for 30 min and, after ice-cooling, **7** (1.14 g, 10 mmol) was added under stirring. The reaction mixture was further stirred at 5 °C for 10 min and at room temperature for 15 min, and poured into ice-water (18 ml). The formed precipitates were filtered off, washed successively with water and ether, and dired in vacuo. Recrystallization from MeOH gave **8a** as colorless crystals (1.98 g, 86%): Mp 167—169 °C; IR ($CHCl_3$) 3406, 1736, and 1549 cm^{-1}; ^1H NMR δ=3.73 (3H, s, COOMe), 3.95 (3H, s, NCOOMe), 3.97 (2H, s, CH_2), and 10.50 (1H, br s, NH). Found: C, 36.40; H, 3.94; N, 18.11%. Calcd for $C_7H_9N_3O_4S$: C, 36.36; H, 3.92; N, 18.17%.

B) From 12a: To a stirred and ice-cooled solution of **12a** (3.72 g, 18.5 mmol) in a mixture of *t*-butyl alcohol (50 ml) and water (5 ml) was added dropwise peracetic acid (20 ml, 86.8 mmol), and then the reaction mixture was stirred at 20 °C overnight. After completion of the reaction, excess peracetic acid was decomposed with 30% aqueous sodium hydrogensulfite. The formed crystals were filtered off, and the filtrates were concentrated up to 1/3 of the original volume. After coolling, the second crop of crystals were filtered off, combined with the first crop, and dried in vacuo to give the corresponding carboxylic acid (3.3 g): Mp 188—190 °C: IR (KBr) 2959, 1720, 1555, and 1355 cm^{-1}; ^1H NMR (DMSO-d_6) 3.90 (2H, br s, CH_2), 3.92 (3H, s, Me), and 10.50 (1H, br s, NH).

The carboxylic acid (3.3 g) was dissolved in 2% methanolic HCl solution at room temperature. After 5 h, the solution was evaporated to a residue, which was recrystallized from MeOH to give **8a** (3.4 g, 80% from **12a**) identical with the authentic sample obtained from **7** by the route A.

Methyl 2-(5-Ethoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetate (8b). A) From 7: A suspension of ethyl chloroformate (1.15 ml, 12 mmol) and KSCN (1.26 g, 13 mmol) in MeCN (10 ml) was treated with **7** (1.14 g, 10 mmol) in the same manner as described in the preparation of **8a** from **7**. Recrystallization from MeOH gave **8b** as colorless crystals (2.0 g, 83%): Mp 110—112 °C; IR ($CHCl_3$) 3406, 1732, and 1564 cm^{-1}; ^1H NMR δ=1.38 (3H, t, Me), 3.37 (3H, s, COOMe), 3.97 (2H, s, CH_2), 4.39 (2H, q, CH_2 of Et), and 10.45 (1H, br s, NH). Found: C, 39.16; H, 4.40; N, 17.18%. Calcd for $C_8H_{11}N_3O_4S$: C, 39.18; H, 4.52; N, 17.13%.

B) From 12b: A sample of **12b** (4.02 g, 18.7 mmol) was dissolved in EtOAc (70 ml) and treated with peracetic acid in the same manner as described in the preparation of **8a** from **12a**. The crystals were filtered off and dried in vacuo to give the corresponding carboxylic acid (3.42 g): Mp 170—172 °C; IR (KBr) 2962, 1719, 1557, and 1358 cm^{-1}; ^1H NMR (DMSO-d_6) δ=1.24 (3H, t, J=7 Hz, Me of Et), 3.91 (2H, br s, CH_2), 4.24 (2H, q, J=7 Hz, CH_2 of Et), and 10.52 (1H, br s, NH).

A solution of the carboxylic acid (3.42 g) in 2% methanolic HCl solution (35 ml) was stirred at room temperature for 5 h, and evaporated to a residue, which was recrystallized from MeOH to give **8b** (3.57 g, 78% from **12b**) identical with the authentic sample obtained from **7** by the route A.

Methyl 2-(5-Phenoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetate (8c). A) From 7: A suspension of phenyl chloroformate (0.788 ml, 6.25 mmol) and KSCN (637 mg, 6.50 mmol) in MeCN (5 ml) was treated with **7** (570 mg, 5 mmol) in the same manner as described in the preparation of **8a** from **7**. Recrystallization from MeOH gave **8c** as colorless crystals (879 mg, 60%): Mp 162—164 °C; IR ($CHCl_3$) 3432, 1743, and 1576 cm^{-1}; ^1H NMR (270 MHz) δ=3.66 (3H, s, Me), 3.99 (2H, s, CH_2), 7.13—7.48 (5H, m, Ph), and 10.87 (1H, br s, NH). Found: C, 48.81; H, 3.79; N, 14.31%. Calcd for $C_{12}H_{11}N_3O_4S$: C, 49.14; H, 3.78; N, 14.33%.

B) From 12c: A sample of **12c** (1.0 g, 3.8 mmol) was dissolved in 1,2-dichloroethane (30 ml) and treated with peracetic acid in the same manner as described in the preparation of **8a** from **12a**. The formed crystals were filtered off and dried in vacuo to give the corresponding carboxylic acid (820 mg): Mp 174—176 °C; IR (KBr) 3095, 1730, and 1595 cm^{-1}; ^1H NMR (DMSO-d_6) δ=3.92 (2H, bs, CH_2), 7.16—7.54 (5H, m, Ph), and 10.86 (1H, br s, NH).

The carboxylic acid (820 mg) was stirred in 2% methanolic HCl solution at room temperature for 5 h, and evaporated to a residue, which was recrystallized from MeOH to give **8c** (835 mg, 75%) identical with the authentic sample obtained from **7** by the route A.

Methyl 2-(5-Benzyloxycarbonylamino-1,2,4-thiadiazol-3-yl)acetate (8d). A suspention of benzyl chloroformate (0.86 ml, 6 mmol) and KSCN (610 mg, 6.5 mmol) in MeCN (5 ml) was treated with **7** (570 mg, 5 mmol) in the same manner as described in the preparation of **8a** from **7**. Recrystallization from MeOH gave **8d** as colorless crystals (630 mg, 41%): Mp 121—123 °C; IR ($CHCl_3$) 3404, 1736, and 1564 cm^{-1}; ^1H NMR (270 MHz) δ=3.70 (3H, s, Me), 3.85 (2H, s, CH_2), 5.33 (2H, s, CH_2 of Bn), 7.35—7.45 (5H, m, Ph), and 9.96 (1H, br s, NH). Found: C, 50.85; H, 4.27; N, 13.44%. Calcd for $C_{13}H_{13}N_3O_4S$: C, 50.81; H, 4.26; N, 13.67%.

1-(3-Isoxazolyl)-3-(methoxycarbonyl)thiourea (11a). To a suspension of KSCN (47.5 g, 0.49 mol) in MeCN (300 ml) was added dropwise methyl chloroformate (43.0 g, 0.46 mol), and the mixture was stirred at 70 °C for 30 min. 3-Aminoisoxazole (**10**: 29.4 g, 0.35 mol), which was purchased from Ube Industries, Ltd. Tokyo, was added dropwise under ice-cooling and stirring. The reaction mixture was stirred at 5 °C for 30 min and at room temperature for 15 min, and then poured into ice-water (800 ml). The formed precipitates were filtered off, washed with water, and dried in vacuo. Recrystallization from EtOAc–hexane gave **11a** as colorless crystals (42 g, 60%): Mp 165—167 °C; IR (KBr) 1730, 1596, 1549, 1342, 1245, and 1200 cm^{-1}; ^1H NMR δ=3.85 (3H, s, Me), 7.36 (1H, d, J=2 Hz, H-4), 8.28 (1H, d, J=2 Hz, H-5), 8.50 (1H, br s, NH), and 10.50 (1H, br s, NH). Found: C, 35.96; H, 3.74; N, 20.64%. Calcd for $C_6H_7N_3O_3S$: C, 35.82; H, 3.51; N, 20.88%.

2-(5-Methoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetaldehyde (12a). A sample of **11a** (30 g, 0.15 mol) was warmed in methanol (200 ml) at 30—35 °C for 1 h. After cooling, the formed crystals were filtered off. The mother liquor was concentrated to precipitate more crystals. The second crop of crystals were filtered off, combined with the first crop of crystals and dried in vacuo to give **12a** (28.5 g, 98%): Mp 164—166 °C; IR (KBr) 2955, 1720, 1565, 1295, 1245, and 1110 cm^{-1}; ^1H NMR δ=3.90 (2H, d, J=2 Hz, CH_2), 3.92 (3H, s, Me), 9.87 (1H, t, CHO), and 10.50 (1H, br s, NH). Found: C, 35.97; H, 3.77; N, 20.59%. Calcd for $C_6H_7N_3O_3S$: C, 35.82; H, 3.51; N, 20.88%.

2-(5-Ethoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetaldehyde (12b). A suspension of ethyl chloroformate (6.51 g, 60 mmol) and KSCN (6.31 g, 65 mmol) in MeCN (60 ml) was treated with **10** (4.2 g, 50 mmol) in the same manner as described above in the preparation of **11a**, and the formed precipitates were filtered off, washed with water, and dried in vacuo to give a mixture (5.20 g) of the thiourea **11b** and the aldehyde **12b**.

The mixture (5.16 g) was warmed in MeOH (100 ml) at 40—45 °C for 2 h and treated in the same manner, as described above in the preparation of **12a**, to give **12b** as colorless crystals (4.90 g, 46% from **10**): Mp 152—154 °C; IR (KBr) 2960, 1719, 1580, 1275, and 1245 cm^{-1}; ^1H NMR δ=1.23 (3H, t, J=7 Hz, Me of Et), 3.90 (2H, d, J=2 Hz, CH_2), 4.22 (2H, q, J=7 Hz, CH_2 of Et), 9.87 (1H, t, CHO), 10.50 (1H, br s, NH). Found: C, 39.28; H, 4.46; N, 19.31%. Calcd for $C_7H_9N_3O_3S$: C, 39.06; H, 4.21; N, 19.52%.

2-(5-Phenoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetaldehyde (12c). A suspension of phenyl chloroformate (3.5 g, 22.3 mmol) and KSCN (2.35 g, 24 mmol) in MeCN (24 ml) was treated with **10** (1.68 g, 20 mmol) in the same manner as described above in the preparation of **11a**. The formed crystals were filtered off and dried in vacuo to give **12c** without recognition of the intermediate **11c**. Recrystallization from MeOH gave **12c** as colorless crystals (2.3 g, 40%): Mp 159—162 °C; IR (KBr) 3090, 1729, and 1590 cm^{-1}: ^1H NMR δ=3.92 (2H, d, J=2 Hz, CH_2), 7.15—7.53 (5H, m, Ph), 9.87 (1H, t, CHO), and 10.85 (1H, br s, NH). Found: C, 50.49; H, 3.51; N, 15.74%. Calcd for $C_{11}H_9N_3O_3S$: C, 50.18; H, 3.44; N, 15.96%.

Methyl 2-(5-Methoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2-oxoacetate (13a). A solution of **8a** (580 mg, 2.5 mmol), DMSO (0.89 ml, 12.5 mmol), iodine (60 mg, 0.25 mmol), and concd H_2SO_4 (0.007 ml) in EtOAc (5.9 ml) was refluxed for 3 h. After cooling, the reaction mixture was diluted with EtOAc (13 ml). The solution was washed successively with saturated aqueous Na_2SO_3, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl, dried, and then evaporated to give **13a** as a foam (508 mg, 83%): IR ($CHCl_3$) 3406, 1759, and 1546 cm^{-1}; ^1H NMR δ=3.96 (3H, s, Me), 4.02 (3H, s, Me), and 10.15 (1H, br s, NH). Found: C, 33.91; H, 2.74; N, 16.92%. Calcd for $C_7H_7N_3O_5S$: C, 34.29; H, 2.88; N, 17.54%.

Methyl 2-(5-Ethoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2-oxoacetate (13b). A solution of **8b** (52.8 mg, 0.215 mmol), DMSO (0.076 ml, 1.07 mmol), iodine (5.5 mg, 0.022 mmol), and concd H_2SO_4 (0.0006 ml) in EtOAc (0.53 ml) was treated in the same manner, as described above in the preparation of **13a**, to give **13b** as colorless crystals (43 mg, 78%). Recrystallization from EtOAc–hexane gave an analytically pure sample: Mp 170—174 °C; ^1H NMR δ=1.40 (3H, t, Me of Et), 4.01 (3H, s, COOMe), 4.41 (2H, q, CH_2 of Et), and 9.10 (1H, br s, NH). Found: C, 37.03; H, 3.43; N, 16.21%. Calcd for $C_8H_9N_3O_5S$: C, 37.06; H, 3.50; N, 16.21%.

Methyl 2-(5-Phenoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2-oxoacetate (13c). A solution of **8c** (58.6 mg, 0.20 mmol), DMSO (0.07 ml, 1.00 mmol), iodine (5.0

mg, 0.02 mmol), and concd H_2SO_4 (0.0005 ml) in EtOAc (0.6 ml) was treated in the same manner, as described in the preparation of **13a**, to give **13c** as a foam (36 mg, 58%): ^{1}H NMR δ=4.00 (3H, s, Me), 7.25—7.49 (5H, m, Ph), and 9.45 (1H, br s, NH). Found: C, 46.71; H, 2.91; N, 13.34%. Calcd for $C_{12}H_9N_3O_5S$: C, 46.90; H, 2.95; N,13.67%.

Methyl 2-(5-Benzyloxycarbonylamino-1,2,4-thiadiazol-3-yl)-2-oxoacetate (13d). A solution of **8d** (64.0 mg, 0.208 mmol), DMSO (0.074 ml, 1.04 mmol), iodine (5.3 mg, 0.021 mmol), and concd H_2SO_4 (0.0006 ml) in EtOAc (0.64 ml) was treated in the same manner as described in the preparation of **13a** to give colorless crystals of **13d** (39 mg, 59%). Recrystallization from EtOAc–hexane gave an analytically pure sample: Mp 145–147 °C; ^{1}H NMR δ=4.00 (3H, s, Me), 5.35 (2H, s, CH_2), 7.32—7.49 (5H, m, Ph), and 9.07 (1H, br s, NH). Found: C 48.43; H, 3.49; N, 13.06%. Calcd for $C_{13}H_{11}N_3O_5S$: C, 48.60; H, 3.45; N, 13.08%.

Methyl (*Z*)-2-(5-Methoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetate (14). A) From 8a: A solution of **8a** (1.15 g, 5.0 mmol), DMSO (1.78 ml, 25 mmol), iodine (127 mg, 0.5 mmol), and concd H_2SO_4 (0.014 ml) in EtOAc (11.5 ml) was refluxed for 3 h. After cooling, 95% aqueous MeOH (11.5 ml) and *O*-methylhydroxylamine hydrochloride (496 mg, 5.95 mmol) were added to the reaction mixture under stirring at room temperature. After 30 min, the resulting solution was evaporated to a residue, which was diluted with EtOAc (12 ml). The solution was washed successively with saturated aqueous Na_2SO_3, saturated aqueous Na_2CO_3, and saturated aqueous NaCl, dried, and evaporated to a residue. Recrystallization from EtOAc–hexane gave **14** as colorless crystals (1.33 g, 97%): R_f=0.29 (1:1 hexane–EtOAc); Mp 159—161 °C; ^{1}H NMR δ=3.94 (3H, s, N–OMe), 3.97 (3H, s, COOMe), 4.12 (3H, s, N–COOMe), and 9.58 (1H, br s, NH). Found: C, 34.98; H, 3.52; N, 20.29%. Calcd for $C_8H_{10}N_4O_5S$: C, 35.03; H, 3.67; N, 20.43%.

B) From 15: Entry 1 in Table 1: A suspension of **15** (260 mg, 1.0 mmol), MeI (0.19 ml, 3.0 mmol), and Ag_2O (700 mg, 3.0 mmol) in dry DMF (2.5 ml) was stirred at room temperature. After 1 h, the mixture was filtered through Celite, and the filter cake was washed with EtOAc. The filtrates and washings were combined, and evaporated. The residue was chromatographed on silica gel (7.5 g) with 1:1 hexane–EtOAc to give **14** as colorless crystals (219 mg, 80%), identical with the authentic sample obtained from **8a** by the route A.

C) From 15: Entry 2 in Table 1: To a stirred suspension of **15** (260 mg, 1.0 mmol), barium oxide (767 mg, 4.99 mmol), and barium hydroxide octahydrate (158 mg, 0.50 mmol) in a mixture of DMF (5.2 ml) and $CHCl_3$ (1.85 ml) was added dimethyl sulfate (0.10 ml, 1.1 mmol), and the resulting mixture was stirred at room temperature for 30 min. After dilution with EtOAc (7 ml), a small piece of Dry Ice® was added, and the insoluble mass was filtered through Celite and washed with EtOAc. The filtrates and washings were combined, washed with saturated aqueous NaCl, dried, and evaporated to a residue. Recrystallization from EtOAc–hexane gave **14** as colorless crystals (230 mg, 84%), identical with the authentic sample obtained from **8a** by the route A.

Methyl 2-Hydroxyimino-2-(5-methoxycarbonylamino-1,2,4-thiadiazol-3-yl)acetate (15). A) From 8a: Into a solution of **8a** (230 mg, 0.996 mmol) and concd HCl (0.0124 ml, 0.149 mmol) in THF (2.3 ml) was bubbled at room temperature for 10 min methyl nitrite gas, which was produced by adding dropwise 12 M H_2SO_4 (0.5 ml, 6 mmol) to a suspension of $NaNO_2$ (137 mg, 1.99 mmol) in 50% MeOH (0.242 ml). The reaction mixture was stirred at room temperature for 1 h, and then evaporated to a residue, which was stirred with ether (5 ml). The formed crystals were filtered off, washed with ether, and dried in vacuo. Recrystallization from $CHCl_3$ gave **15** as colorless crystals (239 mg, 92%): Mp 188—190 °C; ^{1}H NMR δ=3.96 (3H, s, COOMe), 4.02 (3H, s, NCOOMe), and 9.45 and 9.92 (each 1H, br s, NH and N–OH). Found: C, 32.17; H, 2.99; N, 21.42%. Calcd for $C_7H_8N_4O_5S$: C, 32.31; H, 3.10; N, 21.53%.

B) From 7: A solution of methyl chloroformate (0.0533 ml, 0.69 mmol) and KSCN (72.6 mg, 0.747 mmol) in dry THF (0.575 ml) was stirred at 70 °C for 1 h, and then, under ice-cooling and stirring, **7** (65.6 mg, 0.575 mmol) was added. After the reaction mixture was stirred at 5 °C for 30 min and at room temperature for 12 h, water (0.0726 ml) was added to the mixture to decompose residual KSCN. Further, the mixture was stirred for 3 h to give **8a**. To the resulting mixture was added concd HCl (0.010 ml) and was bubbled methyl nitrite gas, which was produced from $NaNO_2$ (120 mg) and 12 M H_2SO_4 (0.5 ml) in 50% MeOH (0.14 ml). The reaction mixture was stirred at room temperature for 1 h, and evaporated to a residue, which was dissolved in EtOAc (0.5 ml). The solution was washed with saturated aqueous NaCl, dried, and evaporated to give crude yellow crystals of **15**. Recrystallization from $CHCl_3$ afforded **15** as colorless crystals (125 mg, 83%), identical with the authentic sample obtained from **8a** by the route A.

Methyl (*E*)-2-(5-Methoxycarbonylamino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetate(16). Entry 3 in Table 1. To a stirred suspension of **15** (130 mg, 0.5 mmol) and barium oxide (382 mg, 2.5 mmol) in DMF (2.6 ml) was added dimethyl sulfate (0.05 ml, 0.55 mmol), and the mixture was stirred at room temperature for 1 h. After dilution with EtOAc, a small piece of Dry Ice® was added, and the insoluble mass was filtered through Celite and washed with EtOAc. The filtrates and washings were combined and evaporated to a residue, which was chromatographed on silica gel (10 g) with 1:1 hexane–EtOAc to give s solid of **16** (94 mg, 69%): R_f=0.41 (1:1 hexane–EtOAc); ^{1}H NMR δ=3.63 (3H, s, Me), 4.00 (6H, s, 2×Me), and 9.11 (1H, br s, NH). Found: C, 34.67; H, 3.43; N, 20.19%. Calcd for $C_8H_{10}N_4O_5S$: C, 35.03; H, 3.67; N, 20.43%.

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