Efficient Preparation of (*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-[(fluoromethoxy)imino]acetic Acid

Takeo KANAI, Yasunobu KAI,†† Nobuaki SATO,† Toshihiko NAITO,† Takashi KAMIYA,† Takaharu NAKAMURA,† and Katsuyuki OGURA*

Graduate School of Science and Technology, Chiba University, 1-33 Yayoicho, Inageku, Chiba 263
† Eisai Chemical Co., Ltd., 22 Sunayama, Hazaki-cho, Kashima-gun, Ibaraki 314-02
†† Tsukuba Research Laboratories, Eisai Co., Ltd., Tsukuba, Ibaraki 300-26

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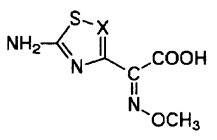
(*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-[(fluoromethoxy)imino]acetic acid (**2**), a useful chemical modifier of cephalosporin antibiotics, was efficiently synthesized from 2-[(fluoromethoxy)imino]-1,3-propanedinitrile. The stereochemical structure of **2** was unambiguously determined by X-ray crystallography.

Hitherto, much attention has been paid to (*Z*)-2-(2-aminothiazol-4-yl)-2-(methoxyimino)acetic acid (**1a**) and 2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)-acetic acid (**1b**) because they are utilized as chemical modifiers for the 7-amino group of cephalosporin antibiotics (Chart 1).[1,2] Recently, (*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(fluoromethoxy)imino]acetic acid (**2**) was also found to be a useful chemical modifier: Cephalosporin E-1077 (**3**) shows a wide range of antibacterial activities, including strong activity against *pseudomonas aeruginosa*.[3] However, no report has been published regarding the synthesis of **2**. The methods reported for the synthesis of **1b** cannot be applied in a straightforward way to the preparation of **2**, since the inductive effect of the fluorine atom causes an easy *E*–*Z* isomerization of the imino double bond. Here, we report on an efficient synthesis of **2**, as summarized in Scheme 1.

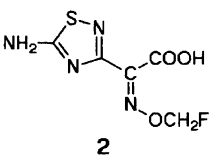
Results and Discussion

We employed 2-[(fluoromethoxy)imino]-1,3-propanedinitrile (**7**) as a key intermediate, since it is easily prepared from commercially available 2-cyanoacetamide (**4**). When 2-cyano-2-(hydroxyimino)acetamide (**5**), obtainable from **4** and nitrous acid, was treated with bromofluoromethane and triethylamine in DMF (0 °C/3 h), 2-cyano-2-[(fluoromethoxy)imino]acetamide (**6**) was produced in 75% yield. The dehydration of **6** leading to **7** was achieved with $POCl_3$ in acetonitrile (reflux/4 h). This reaction occurred smoothly in the presence of a large amount of sodium chloride, though the role of the sodium chloride is not clear at the present time. A simple treatment of **7** with ammonia and ammonium chloride in water at −5 °C gave an amidine (**8**) in 84% yield. Furthermore, 1,2,4-thiadiazol ring formation was performed according to a modified Goerdeler's general procedure.[4] Successive treatments of **8** with bromine and potassium thiocyanate gave (*E*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(fluoromethoxy)imino]acetonitrile (**9**) in 88% yield. For the conversion of **9** to **2**, the route via the corresponding methyl ester (**11**) was chosen, since the direct hydrolysis of **9** with 2 mol dm^{-3} aqueous NaOH (50 °C/2 h) was accompanied by isomerization of the N=C bond. At first, **9** was led to **11** by a sodium methoxide-catalyzed addition of methanol, followed by acid hydrolysis. Upon the treatment of **11** with 2.1 mol dm^{-1} aqueous NaOH in methanol or methanol–THF, a dimerization product (**14**) was formed as the main product, which made it difficult to isolate **2** in its pure form (Chart 2). Hence, we once converted **11** to an *N*-formyl derivative (**12**). Upon the hydrolysis of **12** with 1 mol dm^{-3} aqueous NaOH, the corresponding acid (**13**) appeared at an initial stage; subsequently, the desired (*Z*)-**2** was formed. The isolation yield of (*Z*)-**2** was 84%.

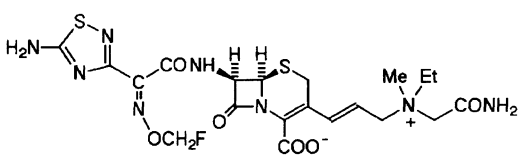
Finally, we describe the geometry of the C=N bond of the thus-obtained **2**. The geometry of **2** originates in that of **8**. Since ammonia can attack favorably the less-hindered cyano group of **7**, the geometry of **8** is deduced to be *E*. This was confirmed by an X-ray crystallography determination of the structure of the intermediate **11**.



1a: X=CH
b: X=N



2



Cephalosporin E1077 (3)

Chart 1.

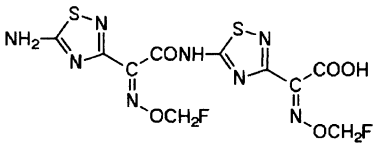


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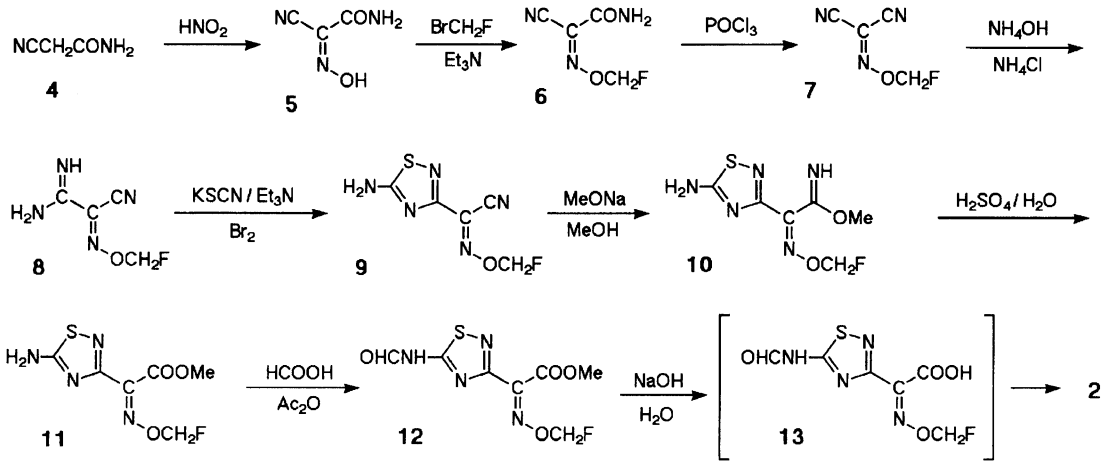
Chart 2.



Scheme 1.

The molecular structure of **11** is shown in Fig. 1, which exhibits a *Z* geometry around its C=N bond. Methanolysis of the corresponding acyl chloride, which was obtained by reaction of **2** with PCl_5,[7] gave **11** again. We thus concluded the geometry of **2** to be *Z*.

Experimental

The melting points were determined on a hot-stage microscope apparatus (Yanagimoto) and are uncorrected. ^{1}H NMR spectra were obtained on a JEOL JNM-A-400 (400 MHz) spectrometer. Infrared spectra were determined with a Perkin–Elmer 1600 FT-IR spectrometer. Mass spectra were measured with a JEOL JMS-HX100 spectrometer.

2-Cyano-2-(hydroxyimino)acetamide (5). To a solution of 2-cyanoacetamide (**4**) (33.0 g, 0.39 mol) and sodium nitrite (33.0 g, 0.47 mol) in water (132 ml), was dropwise added acetic acid (46 ml, 0.80 mol) at 30—38 °C over a period of 2 h. After being stirred for an additional 2 h at the same temperature, the mixture was cooled at 5 °C. The deposited crystalline **5** (36.0 g, 81%) was collected by filtration and washed with 2-propanol (66 ml). Mp 268—270 °C (decomp); ^{1}H NMR (DMSO-d_6) δ=8.0—10.5 (1H, broad), 7.54 (1H, s), and 7.23 (1H, s). Without further purification, these crystals were used in the subsequent alkylation.

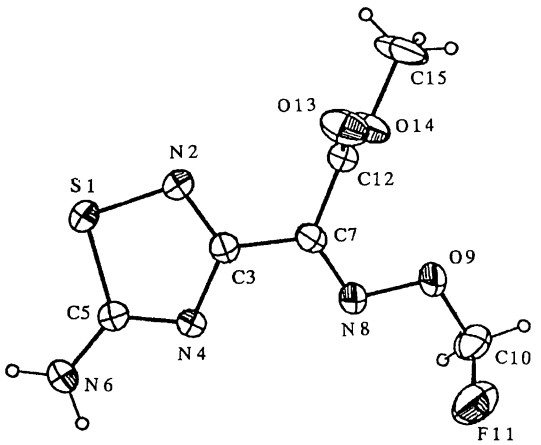


Fig. 1. ORTEP drawing of **11**.

2-Cyano-2-[(fluoromethoxy)imino]acetamide (6). To a stirred solution of **5** (36.0 g, 0.31 mol) in DMF (207 ml), was added triethylamine (50 ml, 0.35 mol) at 20 °C; the resulting mixture was stirred for an additional 20 min. After a solution of bromofluoromethane (37.8 g, 0.33 mol) was added, the mixture was stirred at room temperature for 2 h. The reaction took place exothermally to slightly raise the temperature of the solution. The mixture was poured into ice-water (360 ml) and extracted with ethyl acetate (270 ml×2). The combined extracts were washed with 1.5 mol dm^{-3} HCl (94 ml), a saturated aqueous solution (90 ml) of $NaHCO_3$, and brine (90 ml). After being dried over magnesium sulfate, the solvent was evaporated in vacuo and the crystalline residue was washed with diisopropyl ether (150 ml) to give **6** (34.7 g, 75%) as colorless crystals: Mp 124—125 °C (ethanol); IR (Nujol) 3410, 3290, 3150, 1690, and 1590 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=5.97 (2H, d, J=54 Hz), 8.09 (1H, s), and 8.18 (1H, s). Calcd for $C_4H_4FN_3O_2$: C, 33.11; H, 2.78; N, 28.96%. Found: C, 33.09; H, 2.81; N, 29.26%.

2-[(Fluoromethoxy)imino]-1,3-propanedinitrile (7). A mixture containing **6** (14.0 g, 0.100 mol), $POCl_3$ (14 ml), and sodium chloride (15 g) in acetonitrile (15 ml) was refluxed for 2 h. After the addition of phosphoryl chloride (5.0 ml), the resulting mixture was refluxed for an additional 3 h. The mixture was poured into ice-water (200 ml) and stirred at room temperature for 1 h. After extraction with dichloromethane (50 ml×2), the combined extracts were washed with aqueous solution of $NaHCO_3$ and brine, dried over magnesium sulfate, and evaporated. Distillation of the residue gave **7** (9.1 g, 72% yield): A colorless oil; bp 69—70 °C/3333 Pa; IR (neat) 2990, 2243, and 1546 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ=6.08 (2H, d, J=52 Hz). Calcd for $C_4H_2FN_3O$: C, 37.81; H, 1.59; N, 33.07%. Found: C, 37.91; H, 1.72; N, 33.22%.

2-Cyano-2-[(fluoromethoxy)imino]acetamidine (8). To a solution containing ammonia (1.1 mol) and ammonium chloride (3.5 g, 0.065 mol) in water (37 ml), was added **7** (10.0 g, 0.078 mol) at −15 °C. After the mixture was stirred at −5 °C for 3 h, it was extracted with ethyl acetate (50 ml×2). The combined extracts were washed with brine (16 ml) and dried over magnesium sulfate. The addition of acetic acid (5 g) deposited the acetate of **8** (13.5 g, 84%

yield). The acetate of **8**: Colorless crystals; mp 125—127 °C (from ethanol); IR (Nujol) 2996, 1686, 1570, 1492, and 1414 cm^{-1}; ^1H NMR (DMSO-d_6) δ=5.97 (2H, d, J=54 Hz), 8.10 (1H, s), and 8.19 (1H, s). Calcd for $C_4H_5FN_4O$; C, 35.30; H, 4.40; N, 27.44%. Found: C, 35.23; H, 4.30; N, 27.72%.

(*E*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-[(fluoromethoxy)imino]acetonitrile (9). To a solution of potassium thiocyanate (13.0 g, 0.13 mol) and **8** (23.9 g, 0.11 mol) in methanol (220 ml), was added triethylamine (39.0 ml, 0.28 mol) at 0 °C. Bromine (19.2 g, 0.12 mol) was dropwise added at −15 °C. After being stirred for 30 min, water (520 ml) was added to deposit **9** as colorless crystals, which were collected by filtration and washed with methanol (120 ml). The yield of **9** was 20.6 g (88% yield). **9**: Colorless crystals; mp 236—238 °C (from acetone); IR (Nujol) 3450, 3250, 3075, 1610, and 1520 cm^{-1}; ^1H NMR (DMSO-d_6) δ=6.02 (2H, d, J=54 Hz) and 8.38 (2H, br.). Calcd for $C_5H_4FN_4OS$: C, 29.85; H, 2.00; N, 34.81%. Found: C, 29.85; H, 1.83; N, 35.01%.

Methyl (*Z*)-2-(5-Amino-1,2,4-thiadiazol-3-yl)-2-[(fluoromethoxy)imino]acetimidate (10). To a solution of **9** (20.6 g, 0.10 mol) in methanol (406 ml), was added a 28% methanolic solution of sodium methoxide (4.9 ml, 0.025 mol) at 20 °C; the resulting solution was stirred at the same temperature for 24 h. The deposited **10** was collected by filtration and washed with methanol (70 ml) and diisopropyl ether (42 ml). The amount of **10** was 22.0 g (92% yield). **10**: Colorless crystals; mp 173—174 °C; IR (Nujol) 3270, 3100, 1645, 1110, and 1050 cm^{-1}; ^1H NMR (DMSO-d_6) δ=3.68 (3H, s), 5.74 (2H, d, J=54 Hz), 8.16 (2H, br), and 8.90 (1H, s). Calcd for $C_6H_7FN_5O_2S$: C, 30.90; H, 3.46; N, 30.03%. Found: C, 30.61; H, 3.12; N, 29.87%.

Methyl (*Z*)-(5-Amino-1,2,4-thiadiazol-3-yl)[(fluoromethoxy)imino]acetate (11). To a solution of **10** (20.2 g, 0.094 mol) in acetone (260 ml), was added 4 mol dm^{-3} sulfuric acid (260 ml); the resulting solution was stirred at 20 °C for 2 h. After concentration in vacuo and the addition of ice-water (225 ml), the deposited **11** was collected by filtration. The amount of **11** was 18.6 g (84% yield). **11**: Colorless crystals; mp 173—175 °C; IR (Nujol) 3279, 3131, 1659, 1616, 1539, 1443, and 1393 cm^{-1}; ^1H NMR (DMSO-d_6) δ=3.83 (3H, s), 5.78 (2H, d, J=54 Hz), and 8.24 (2H, br). Calcd for $C_6H_7FN_4O_3S$: C, 30.77; H, 3.01; N, 23.92%. Found: C, 30.57; H, 2.71; N, 24.01%.

X-Ray Crystallography of 11. Crystal data are as follows: $C_6H_7FN_4O_4S$, F.W.=234.21, triclinic, space group $P\bar{1}$, a=9.472(2), b=11.003(6), c=9.375(3) Å; α=93.26(3)°, β=95.48(2)°, γ=96.80(3)°; V=963.4 $Å^3$; D_x=1.61 g cm^{-3}; Z=4. A computer program (SDP/VAX) run on a VAX-11/750 computer was employed for the analysis. The intensity data were collected in the region $4°<2\theta<130°$; 3130 independent reflections with $I_0>3\sigma(I_0)$ were used for a structure analysis. The final refined R value was 0.052. The atomic positional and thermal parameters, bond distances, bond angles, and torsional angles are summarized in Tables 1, 2, 3, and 4.

Direct Hydrolysis of 11. To a solution of **11** (2.3 g, 0.010 mol) in methanol (10 ml), was added 2.1 mol dm^{-3} aqueous NaOH (23 ml); the resulting solution was stirred at room temperature for 1 h. After removing of the methanol in vacuo, the remaining aqueous layer was neutralized with 1 mol dm^{-3} hydrochloric acid. The deposited solid was

Table 1. Atomic Positional and Thermal Parameters for **11**

Atom	x	y	z	B/Å^2
S1	0.1576(1)	0.9810(1)	0.9088(1)	2.90(2)
N2	0.0246(4)	0.9336(3)	0.7814(4)	2.61(7)
C3	−0.0290(4)	1.0309(4)	0.7386(4)	2.21(8)
N4	0.0243(4)	1.1458(3)	0.7987(4)	2.26(7)
C5	0.1303(4)	0.0341(4)	0.7863(5)	2.40(8)
N6	0.2090(4)	1.2274(3)	0.9750(4)	3.44(8)
C7	−0.1482(4)	0.0162(4)	0.6261(4)	2.27(8)
N8	−0.1809(4)	1.1113(3)	0.5654(4)	2.63(7)
O9	−0.3025(3)	1.0819(3)	0.4642(3)	3.29(6)
C10	−0.3200(6)	1.1847(4)	0.3766(5)	4.0(1)
F11	−0.3701(4)	1.2700(3)	0.4761(4)	6.64(9)
C12	−0.2290(5)	0.8886(4)	0.5920(5)	2.49(8)
O13	−0.3059(4)	0.8406(3)	0.6714(4)	3.74(7)
O14	−0.1990(4)	0.8437(3)	0.4661(3)	3.53(7)
C15	−0.2709(7)	0.7212(4)	0.4167(6)	4.8(1)

Table 2. Bond Distances of **11**

Atom 1	Atom 2	Distance/Å
S1	N2	1.665(3)
S1	C5	1.744(4)
N2	C3	1.306(5)
C3	N4	1.372(5)
C3	C7	1.457(5)
N4	C5	1.315(5)
C5	N6	1.335(5)
C7	N8	1.275(5)
C7	C12	1.519(5)
N8	O9	1.414(4)
O9	C10	1.397(6)
O14	C12	1.323(5)
C10	F11	1.380(6)
C12	O13	1.191(6)
O14	C15	1.465(6)

Table 3. Bond Angles of **11**

Atom 1–Atom 2–Atom 3	Angle/°
N2–S1–C5	92.2(2)
C3–C7–C12	117.7(4)
F11–C10–O9	107.4(4)
S1–N2–C3	107.3(3)
O13–C12–O14	127.8(4)
O14–C12–C7	109.6(3)
N2–C3–N4	121.1(3)
N4–C3–C7	119.9(4)
S1–C5–N6	123.9(3)
N8–C7–C3	118.3(3)
N8–C7–C12	124.0(4)
N8–O9–C10	108.1(4)
C12–O14–C15	116.2(4)
C3–N4–C5	108.1(3)
O13–C12–C7	122.6(4)
O9–N8–C7	111.0(4)
N2–C3–C7	119.0(3)
S1–C5–N4	111.6(3)
N4–C5–N6	24.6(4)

Table 4. Torsion Angles of **11**

Atom 1–Atom 2–Atom 3–Atom 4	Angle/°
C5–S1–N2–C3	0.4(0.3)
C3–C7–C12–O14	−108.2(0.4)
C3–C7–C12–O13	71.4(0.6)
N8–C7–C12–O14	73.9(0.5)
N2–C3–C7–N8	−166.2(0.4)
N2–C3–C7–C12	15.8(0.6)
N4–C3–C7–N8	14.4(0.6)
N4–C3–C7–C12	−163.6(0.4)
N8–C7–C12–O13	−106.5(0.4)
N2–S1–C5–N4	−0.1(0.4)
N2–S1–C5–N6	−179.2(0.4)
C10–O9–N8–C7	−171.3(0.4)
N8–O9–C10–F11	−73.2(0.5)
C15–O14–C12–O13	1.3(0.7)
C15–O14–C12–C7	−179.1(0.4)
S1–N2–C3–N4	−0.7(0.5)
S1–N2–C3–C7	179.9(0.3)
C5–N4–C3–N2	0.7(0.5)
C5–N4–C3–C7	−179.9(0.4)
C3–N4–C5–S1	0.3(0.4)
C3–N4–C5–N6	178.9(0.4)
O9–N8–C7–C3	−177.2(0.3)
O9–N8–C7–C12	0.7(0.6)

subjected to column chromatography on ODS using methanol–water as an eluent to give **2** (0.72 g; 38% yield) and **14** (1.38 g; 60.5% yield). **14**: Colorless crystals; mp>260°C (from AcOEt); IR (KBr) 3421, 1727, 1705, 1624, 1560, 1405, 1124, 1070, and 1010 cm^{-1}; ^1H NMR (DMSO-d_6) δ=5.71 (2H, d, J=56 Hz) and 5.76 (2H, d, J=57 Hz); MS m/z=423 (M^++H). Calcd for $C_{10}H_8F_2N_8O_5S_2$: C, 28.44; H, 1.91; N, 26.53%. Found: C, 28.31; H, 1.81; N, 26.19%.

Methyl (*Z*)-(5-Formylamino-1,2,4-thiadiazol-3-yl)-[(fluoromethoxy)imino]acetate (12). Acetic anhydride (37.0 ml; 0.36 mol) and **11** (18.6 g, 0.080 mol) were successively added to 98% formic acid (46.5 ml, 1.37 mol) at 8 °C. The resulting mixture was stirred at 25 °C for 12 h. The addition of diisopropyl ether (93 ml) deposited **12** (17.4 g, 84% yield). **12**: Colorless crystals; mp 221—223 °C (decomp); IR (Nujol) 3471, 3144, 1732, 1617, 1535, 1440, and 1408 cm^{-1}; ^1H NMR (DMSO-d_6) δ=3.93 (3H, s), 5.89 (2H, d, J=55 Hz), and 8.86 (1H, s). Calcd for $C_7H_7FN_4O_4S$: C, 32.06; H, 2.68; N, 21.36%. Found: C, 32.14; H, 2.39; N, 21.41%.

(*Z*)-(5-Amino-1,2,4-thiadiazol-3-yl)[(fluoromethoxy)imino]acetic Acid (2). To an aqueous solution (1 mol dm^{-3}/60 ml) of sodium hydroxide was added **12** (5.0 g, 0.019 mol) at 22 °C; the resulting mixture was stirred at the same temperature for 6 h. The reaction mixture was acidified (pH 1.0) with 1 mol dm^{-3} hydrochloric acid and extracted with ethyl acetate (55 ml and 30 ml). The combined extracts were dried ($MgSO_4$) and concentrated to about 15 ml. The deposited **2** (3.5 g, 84% yield) was isolated by filtration. **2**: Colorless crystals; mp 210 °C (decomp) (from water); IR (Nujol) 3379, 3111, 1624, 1535, and 1415 cm^{-1}; ^1H NMR (DMSO-d_6) δ=5.75 (2H, d, J=55 Hz) and 8.24 (2H, br.). Calcd for $C_5H_5FN_4O_3S$: C, 23.79; H, 3.43; N, 22.19%. Found: C, 23.48; H, 3.36; N, 22.31%.

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5) In sharp contrast to (*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-(methoxyimino)acetamide, alkaline hydrolysis of (*Z*)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-[(fluoromethoxy)imino]-acetamide, which was obtained by treating **9** with H_2O_2 and NaOH in water, was accompanied by formation of a geometric isomer of **2** (*E*/*Z*=2/1).

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