A Conventional Route for the Synthesis of New Oxazolidin-2-one Derivatives with β-Aminoalanines

Fumiko FUJISAKI, Nobuhiro ABE, and Kunihiro SUMOTO*

Faculty of Pharmaceutical Sciences, Fukuoka University; Nanakuma, Jonan-ku, Fukuoka 814–0180, Japan.
Received March 10, 2004; accepted July 12, 2004

A conventional new route to the novel oxazolidin-2-one derivatives (3a—f) having two substituents on *N*-3 and C-4 in the oxazolidin-2-one ring was established with racemic β-aminoalanine derivatives (1) as the key starting materials.

Key words oxazolidin-2-one; oxazolidinone; β-aminoalanine; cyclization; benzoylation; dehydration

The derivatives of oxazolidin-2-one have recently attracted much attention for showing an interesting new class of synthetic antibacterial activity.[1)] Many of the target compounds for investigations of new drug candidates have two substituents at the *N*-3 and C-5 positions of the oxazolidin-2-one ring.

We have recently developed a new synthetic method for synthesizing the racemic β-aminoalanine derivatives (**1**).[2)] One of the applications of this unique amino acid for the synthesis of *N*-[2-(1-piperidinyl)ethyl]benzamides (**2**) has been reported recently.[3)] These β-aminoalanine derivatives (**1**) are also expected to be applicable for the ring formation of novel oxazolidin-2-one derivatives such as (**3**), which has two substituents on *N*-3 and C-4 of the oxazolidin-2-one ring and this mimics the fundamental structural framework of Linezolid (**4**).[4,5)] These derivatives (**3**) are selected as the target heterocycles for one of the synthetic applications of the above unique amino acid β-aminoalanine derivatives (**1**) (Fig. 1). The molecular modification (**4**→**3**) is one of the well-known procedures in the search for biologically active compounds, the so-called disjunctive approach in medicinal chemistry.[6)] In this paper, we report a new conventional route to the synthesis of the above novel oxazolidin-2-one derivatives.

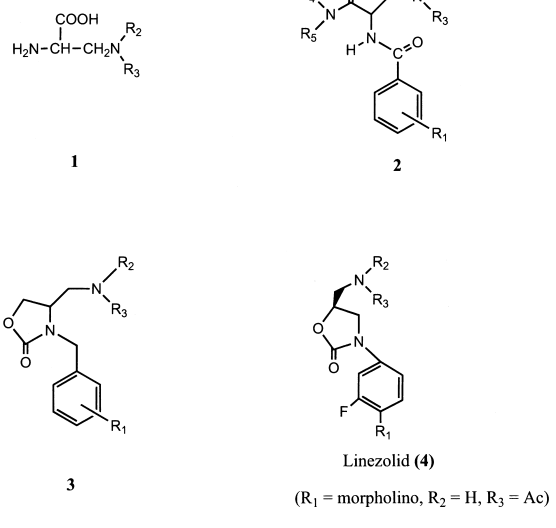


Fig. 1

Results and Discussion

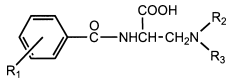
The starting compounds (**1**) and the *N*-benzoyl derivatives (**5a**—**f**) were prepared according to the procedure described previously.[3)] Benzoylation of these amino acids (**1**) with substituted benzoyl chlorides under Schotten–Baumann reaction conditions easily proceeded and gave the desired **5a**—**f** in good to excellent yields. The physical data of the compounds (**5a**—**f**) are summarized in Table 1, and spectroscopic data are given in the Experimental section. From these data, the structures of **5a**—**f** were easily elucidated. Thus the introduced substituted benzoyl group and a *tert*-amino group ($-NR_2R_3$) were confirmed in both ^{1}H- and ^{13}C-NMR spectra. Full assignments of these data for the structures of **5a**—**f** (represented in Chart 1) are recorded in the Experimental section. These assignments and correlations of ^{1}H- and ^{13}C-NMR signals were supported by two-dimensional (2D) spectroscopic analysis. Interestingly, IR spectra (KBr) showed two typical strong absorption bands at 1647—1662 and 1570—1584 cm^{-1} attributable to the amide C=O and carboxylate (COO^-) groups, respectively. This apparently indicates these compounds require the well-known twitterion structure between the carboxy (COOH) and basic *tert*-amino groups in the solid state (see Table 1). The reductions of both these two carbonyl groups (*N*-benzoyl amide and COOH) in the derivatives (**5a**—**f**) were successfully achieved by treatment with $NaAlH_2(OCH_2CH_2OCH_3)_2$ in anhydrous benzene to afford the corresponding amino alcohols **6a**—**f**. These compounds (**6a**—**f**) were relatively sensitive to exposure to air and included trace amounts of unknown contaminants upon TLC analysis. The purification of the products to remove these unknown contaminants resulted in a great loss of the target compounds (**6a**—**f**). Therefore we used the above obtained material for the next cyclization process without further purification (see Experimental).

The procedure for the cyclization step with the treatment of **6a**—**f** with diethyl carbonate in the presence of sodium methoxide in anhydrous benzene was effective, and resulted in the formation of **3a**—**f** in good yields (58—81%) (Chart 1), which were comparable with the results reported by Homeyer.[7)] The physical data on the compounds (**3a**—**f**) are summarized in Table 2, and ^{1}H- and ^{13}C-NMR spectroscopic data are reported in the Experimental section.

The structures of the target oxazolidin-2-ones (**3a**—**f**) were easily confirmed from the above elemental and spectroscopic analysis. Thus IR spectra of **3a**—**f** showed a typical

* To whom correspondence should be addressed. e-mail: kunihiro@cis.fukuoka-u.ac.jp

Table 1. Physical Data on Compounds **5a**—**f**



Compound no.	R_1	$-N(R_2)(R_3)$	Yield (%)	mp (°C) (recryst. solvent)	Formula	FAB-MS $(M+H)^+$	IR (KBr) cm^{-1} Amide C=O	IR (KBr) cm^{-1} (COO^-)	Analysis (%) Calcd (found) C	H	N
5a	H		67	139—141 (dec.) (H_2O)	$C_{15}H_{20}N_2O_3 \cdot H_2O$	277	1647 (1570)		61.21 (61.08	7.53 7.53	9.52 9.51)
5b	3-OCH_3		53	100—106 (dec.)[a]	$C_{15}H_{20}N_2O_4S$	325	1651 (1578)		325.1222[b] (325.1220)		
5c	H		64	97—101[a]	$C_{14}H_{18}N_2O_3S$	295	1662 (1578)		295.1116[b] (295.1115)		
5d	H		60	162—164 (dec.) (H_2O)	$C_{19}H_{22}N_2O_3$	327	1655 (1578)		69.92 (70.06	6.79 6.80	8.58 8.61)
5e	3-OCH_3		81	122—132 (dec.) (AcOEt)	$C_{20}H_{24}N_2O_4$	357	1647 (1584)		67.4 (67.12	6.79 6.80	7.86 7.91)
5f	H		62	173—175 (dec.) (EtOH)	$C_{14}H_{18}N_2O_3 \cdot 0.4H_2O$	263	1651 (1578)		62.39 (62.37	7.03 6.98	10.39 10.56)

a) Melting point of the material purified by silica gel column chromatography with EtOH/NH_3 (25/1) as the solvent. *b*) Since the compound was hygroscopic, analysis was carried out using HR-MS spectrometry. The correct $(M+H)^+$ ion peaks, $C_{15}H_{21}N_2O_4S$ and $C_{14}H_{19}N_2O_3S$, were observed for compounds **5b** and **5c**, respectively.

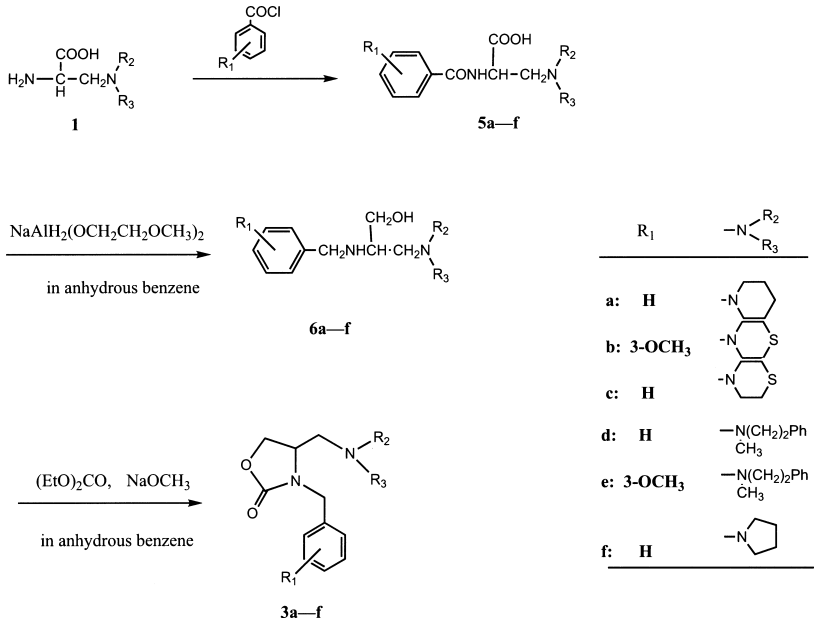


Chart 1

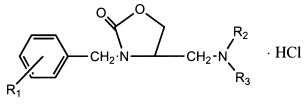
absorption band at 1738—1757 cm^{-1} attributable to the oxazolidin-2-one ring C=O group (see Table 2). In all ^{1}H-NMR spectra, a ring proton (C-4) was observed at δ 4.06—4.39 ppm as a multiplet, and two methylene protons on C-5 ring carbon at δ 4.34—4.68 ppm were observed. Some of the C-5 ring protons overlapped with other protons. The ^{13}C-NMR spectra are also in good agreement with the represented structures of oxazolidin-2-ones (**3a**—**f**). Regarding the oxazolidin-2-one ring in **3a**—**f**, two ^{13}C signals were observed at δ 49.9—53.3 and δ 66.6—70.0 ppm, ascribable to the C-4 and C-5 of oxazolidin-2-one ring, respectively. The NMR data are given in the Experimental section. These assignments and correlations of ^{1}H- and ^{13}C-NMR signals were supported by 2D spectroscopic methods.

To the best of our knowledge, no previous report has dealt with this class of oxazolidin-2-one derivatives (**3**). We emphasize that these easily obtainable β-aminoalanine derivatives (**1**) can be used in the synthesis of novel *N*-3 and C-4 disubstituted oxazolidin-2-ones (**3**) as efficient starting materials. Further synthetic application of this method for related derivatives[8,9] is in progress.

Experimental

Melting points are uncorrected. IR spectra were measured with a Shimadzu FTIR-8100 spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained with a JEOL JNM A-500 at 35 °C unless otherwise noted. Chemical shifts are expressed as δ ppm downfield from an internal tetramethylsilane (TMS) or sodium salt of 3-(trimethylsilyl)propionic-2,2,3,3-d_4 acid (TSP) signal (0 ppm) (in D_2O) for ^{1}H-NMR, and the carbon signal of the corresponding

Table 2. Physical Data on 3,4-Disubstituted Oxazolidine-2-one Hydrochlorides **3a**—**f**



Compound no.	R_1		Yield (%)	mp (°C) (recryst. solvent)	Formula	FAB-MS $(M+H)^+$	IR (KBr) cm^{-1}	Analysis (%) Calcd (found)		
								C	H	N
3a	H		67	207 (dec.) (CH_3CN)	$C_{16}H_{22}N_2O_2 \cdot HCl$	275	1752	61.83 (61.93	7.46 7.49	9.01 9.09)
3b	3-OCH_3		71	185—189 (CH_3CN)	$C_{16}H_{22}N_2O_3S \cdot HCl$	323	1757	53.55 (53.83	6.46 6.49	7.81 7.83)
3c	H		81	198—203 (dec.) (CH_3CN)	$C_{15}H_{20}N_2O_2S \cdot HCl$	293	1755	54.78 (54.71	6.44 6.32	8.52 8.56)
3d	H		61	142—144 (Acetone)	$C_{20}H_{24}N_2O_2 \cdot HCl$	325	1736	66.57 (66.50	6.70 6.98	7.76 7.80)
3e	3-OCH_3		58	128—130 (Acetone/Et_2O)	$C_{21}H_{26}N_2O_3 \cdot HCl$	355	1738	64.52 (64.38	6.96 7.06	7.17 7.14)
3f	H		74	182—184 (dec.) (EtOH/acetone)	$C_{15}H_{20}N_2O_2 \cdot HCl$	261	1740	60.7 (60.87	7.13 7.37	9.44 9.53)

solvent [$CDCl_3$ (77.0 ppm), DMSO-d_6 (39.5 ppm), CD_3OD (49.8 ppm)], and TSP (0 ppm) (in D_2O) for ^{13}C-NMR, respectively. The signal assignments were confirmed with ^1H–^1H correlation spectroscopy (COSY). ^1H–^{13}C heteronuclear multiple-quantum coherence (HMQC), or ^1H–^{13}C heteronuclear multiple-bond connectivity (HMBC) spectra. FAB-MS were obtained with a JEOL JMS-HX110 mass spectrometer. The preparation of racemic β-aminoalnines (**1**) as starting materials has already been described in our previous paper.[2] The following abbreviation was used for the oxazolidin-2-one ring (Oxzln) in NMR spectroscopic data.

Preparation of 3-(*N*,*N*-Disubstituted amino)-2-benzoylaminopropionic Acids (5a—f) 3-(*N*,*N*-Disubstituted amino)-2-benzoylaminopropionic acids (**5a**—**f**) were prepared by the same method as described previously.[3] Yields and physical data (MS and analysis) for compounds **5a**—**f** are summarized in Table 1. Other spectroscopic data are reported below.

2-Benzoylamino-3-piperidinopropionic Acid (5a) ^1H-NMR (D_2O) δ: 1.55—2.10 (6H, br, piperidine ring H-3, H-4, H-5), 2.90—3.82 (4H, br, piperidine ring H-2, H-6), 3.47 [1H, dd, J=13.0, 8.0 Hz, NHCH(COOH)CHH], 3.61 [1H, dd, J=13.0, 6.0 Hz, NHCH(COOH)CHH], 4.84 [1H, dd, J=8.0, 6.0 Hz, NHCH(COOH)CH_2], 7.55—7.58 (2H, m, Ar H-3, H-5), 7.65—7.66 (1H, m, Ar H-4), 7.85—7.87 (2H, m, Ar H-2, H-6). ^{13}C-NMR (D_2O) δ: 23.9 (piperidine ring C-4), 25.6 (piperidine ring C-3, C-5), 52.8 [CH(COOH)CH_2], 56.6 (piperidine ring C-2, C-6), 60.9 [CH(COOH)CH_2], 130.2 (Ar C-2, C-6), 131.7 (Ar C-3, C-5), 135.5 (Ar C-1 or C-4), 135.6 (Ar C-4 or C-1), 173.4 (CONH), 176.8 (COOH).

2-(3-Methoxybenzoylamino)-3-thiomorpholinopropionic Acid (5b) ^1H-NMR ($CDCl_3$) δ: 2.82 (4H, m, thiomorpholine ring H-2, H-6), 3.07 [1H, dd, J=13.0, 8.0 Hz, –CH(COOH)CHHN=], 3.17—3.19 (2H, m, thiomorpholine ring H-3, H-5), 3.29 (2H, m, thiomorpholine ring H-3, H-5), 3.32 [1H, dd, J=13.0, 6.0 Hz, –CH(COOH)CHHN=], 3.81 (3H, s, OCH_3), 4.62 [1H, dd, J=13.0, 6.0 Hz, –CONHCH(COOH)CH_2], 6.7 (1H, br, COOH), 6.99—7.02 (1H, m, Ar H-4), 7.28 (1H, t, J=8.0 Hz, Ar H-5), 7.37—7.41 (2H, m, Ar H-2, H-6), 7.72 (1H, d, J=5.0 Hz, CONH). ^{13}C-NMR ($CDCl_3$) δ: 26.0 (thiomorpholine ring C-2, C-6), 50.1 [NHCH(COOH)CH_2], 54.7 (thiomorpholine ring C-3, C-5), 55.4 (OCH_3), 58.1 [NHCH(COOH)CH_2], 112.6 (Ar C-2), 117.9 (Ar C-4), 119.1 (Ar C-6), 129.6 (Ar C-5), 135.0 (Ar C-1), 159.8 (Ar C-3), 167.3 (CONH), 173.7 (COOH).

2-Benzoylamino-3-thiomorpholinopropionic Acid (5c) ^1H-NMR ($CDCl_3$) δ: 2.82 (4H, m, thiomorpholine ring H-2, H-6), 3.10 [1H, dd, J=13.0, 8.0 Hz, CH(COOH)CHHN=], 3.18—3.20 (2H, m, thiomorpholine ring H-3, H-5), 3.29 (2H, m, thiomorpholine ring H-3, H-5), 3.33 [1H, dd, J=13.0, 6.0 Hz, CH(COOH)CHHN=], 4.63 [1H, dd, J=13.0, 6.0 Hz, CONHCH(COOH)CH_2], 7.38 (2H, t, J=7.5 Hz, Ar H-3, H-5), 7.40 (1H, br, COOH), 7.47 (1H, t, J=6.0 Hz, Ar H-4), 7.75 (1H, d, J=5.0 Hz, CONH), 7.84 (2H, d, J=7.0 Hz, Ar H-2, H-6). ^{13}C-NMR ($CDCl_3$) δ: 22.8 (thiomorpholine ring C-2, C-6), 50.1 [CONHCH(COOH)CH_2], 54.6 (thiomorpholine ring C-3, C-5), 58.0 [CH(COOH)CH_2N=], 127.2 (Ar C-2, C-6), 128.5 (Ar C-3, C-5), 131.8 (Ar C-4), 133.6 (Ar C-1), 167.4 (CONH), 173.7 (COOH).

2-Benzoylamino-3-(*N*-methyl-*N*-phenethylamino)propionic Acid (5d) ^1H-NMR (DMSO-d_6) δ: 2.48 (3H, s, NCH_3), 2.78—2.83 [2H, m, $N(CH_3)CH_2CH_2Ph$], 2.84—2.87 [2H, m, $N(CH_3)CH_2CH_2Ph$], 2.99—3.01 [2H, m, NHCH(COOH)CH_2], 4.59 [1H, q, J=7.5 Hz, NHCH(COOH)CH_2N=], 5.0 (1H, br, COOH), 7.16—7.19 [1H, m, Ar H-4 of $PhCH_2$], 7.22—7.27 [4H, m, Ar H-2, H-3, H-5, H-6 of $PhCH_2$], 7.46—7.49 [2H, m, Ar H-3, H-5 of PhCONH], 7.53—7.56 [1H, m, Ar H-4 of PhCONH], 7.84—7.86 [2H, m, Ar H-2, H-6 of PhCONH], 8.39 (1H, d, J=7.5 Hz, CONH). ^{13}C-NMR (DMSO-d_6) δ: 31.8 (CH_2CH_2Ph), 41.0 (NCH_3), 49.9 [CONHCH(COOH)-CH_2], 56.7 [$CH_2N(CH_3)CH_2CH_2$], 57.8 (CH_2CH_2Ph), 126.0 [Ar C-4 of $Ph(CH_2CH_2)$], 127.2 [Ar C-2, C-6 of PH(CONH)], 128.2 [Ar C-2, C-3, C-5, C-6 of $Ph(CH_2CH_2)$], 128.5 [Ar C-3, C-5 of Ph(CONH)], 131.3 [Ar C-4 of Ph(CONH)], 133.9 [Ar C-1 of Ph(CONH)], 139.3 [Ar C-1 of $Ph(CH_2CH_2)$], 166.0 (CONH), 172.4 (COOH).

2-(3-Methoxybenzoylamino)-3-(*N*-methyl-*N*-phenethylamino)propionic Acid (5e) ^1H-NMR (DMSO-d_6) δ: 2.46 (3H, s, NCH_3), 2.78—2.80 (2H, m, NCH_2CH_2Ph), 2.81—2.84 (2H, m, NCH_2CH_2Ph), 2.98 [2H, d, J=7.5 Hz, NHCH(COOH)$CH_2N(CH_3)$], 3.80 (3H, s, OCH_3), 4.58 (1H, q, J=7.5 Hz, NHCH(COOH)$CH_2N(CH_3)$], 7.10—7.12 (1H, m, Ph H-4), 7.17—7.18 (1H, m, *m*-methoxyphenyl H-4), 7.22—7.27 (4H, m, Ph H-2, H-3, H-5, H-6), 7.37—7.43 (3H, m, *m*-methoxyphenyl H-2, H-5, H-6), 8.40 (1H, d, J=7.5 Hz, CONH). ^{13}C-NMR (DMSO-d_6) δ: 31.9 (CH_2CH_2Ph), 41.0 (NCH_3), 49.6 [NHCH(COOH)CH_2], 55.2 (OCH_3), 56.7 [NHCH(COOH)CH_2], 57.8 (CH_2CH_2Ph), 112.5 (*m*-methoxyphenyl group C-2), 117.1 (*m*-methoxyphenyl group C-4), 119.4 (*m*-methoxyphenyl group C-6), 125.9 (Ph group C-4), 128.2 (Ph group C-2, C-6 or C-3, C-5), 128.5 (Ph group C-3, C-5 or C-2, C-6), 129.4 (*m*-methoxyphenyl group C-5), 135.4 (*m*-methoxyphenyl group C-1), 139.4 (Ph group C-1), 159.1 (*m*-methoxyphenyl group C-3), 165.7 (CONH), 172.3 (COOH).

2-Benzoylamino-3-(1-pyrrolidinyl)propionic Acid (5f) ^1H-NMR (D_2O) δ: 2.11 (4H, br, pyrrolidine ring H-3, H-4), 3.48 (4H, br, pyrrolidine ring H-2, H-5), 3.57 [1H, dd, J=13.0, 8.0 Hz, NHCH(COOH)CHHN=], 3.72 [1H, dd, J=13.0, 6.0 Hz, NHCH(COOH)CHHN=], 4.79 [1H, dd, J=8.0, 6.0 Hz, NHCH(COOH)CH_2N=], 7.57 (2H, m, Ar H-3, H-5), 7.66 (1H, m, Ar H-4), 7.87 (2H, m, Ar H-2, H-5). ^{13}C-NMR (D_2O) δ: 25.5 (pyrrolidine ring C-3, C-4), 54.4 [NHCH(COOH)CH_2], 57.7 (pyrrolidine ring C-2, C-5), 59.2 [NHCH(COOH)CH_2], 130.1 (Ar C-2, C-6), 131.7 (Ar C-3, C-5), 135.4 (Ar C-4), 135.6 (Ar C-1), 173.3 (CONH), 176.8 (COOH).

General Procedure for the Preparation of Amino Alcohols (6) by Reduction of 5 To a solution of sodium bis(2-methoxyethoxy)aluminum hydride (51 mmol) in anhydrous benzene was added **5** (10.2 mmol) with stirring at room temperature. The reaction mixture was allowed to stand for 2 h and then refluxed for 2 h. After decomposition of the reaction mixture with water, the benzene layer was isolated and then the viscous residue was washed with benzene. The combined benzene layer was shaken with 1 N-HCl

(×3). The separated aqueous layer was washed with benzene, and then the aqueous layer was made alkaline with K_2CO_3. The precipitate was extracted with Et_2O. The ethereal solution was dried over K_2CO_3 and concentrated *in vacuo* to give a crude product of **6**.[10] As a typical example, the free base of compound **6d** was obtained in 86% yield. To obtain an analytical sample, this material was converted to dihydrochloride with 20% ethanolic HCl. Recrystallization from ethanol gave **6d** dihydrochloride in 41% yield, mp 172—174 °C. FAB-MS (positive) *m/z*: 299 $(M+H)^+$. ^{1}H-NMR (DMSO-d_6) δ: 2.93 (3H, s, NC$\underline{H}_3$), 3.09—3.13 (2H, m, $CH_2C\underline{H}_2$Ph), 3.41—3.63 [4H, m, $C\underline{H}_2N(CH_3)C\underline{H}_2CH_2$], 3.80—3.95 [4H, m, NHC$\underline{H}$($C\underline{H}_2O\underline{H}$)$CH_2$], 4.26—4.29 and 4.39—4.41 (2H, m, PhC$\underline{H}_2$), 7.24—7.44 (8H, m, Ar-H), 7.67—7.69 (2H, m, Ar-H), 9.80—9.92 (2H, m, N$\underline{H}_2^+$), 11.1 (1H, br s, N$\underline{H}^+$). ^{13}C-NMR (DMSO-d_6, 69 °C) δ: 29.5 ($CH_2\underline{C}H_2$Ph), 40.6 (N$\underline{C}H_3$), 48.4 (Ph-$\underline{C}H_2$NH), 54.2 [NH$\underline{C}$H(CH_2OH)CH_2], 54.4 [NHCH(CH_2OH)$\underline{C}H_2$], 57.3 ($\underline{C}H_2CH_2$Ph), 57.8 ($\underline{C}H_2$OH), 127.0, 128.7, 128.8, 129.2, 130.1, 131.5, 136.6 (Ar). *Anal.* Calcd for $C_{19}H_{26}N_2O\cdot 2HCl$: C, 61.45; H, 7.60; N, 7.54. Found: C, 61.55, H, 7.52; N, 7.55.

General Procedure for the Preparation of 3-Phenylmethyl-4-(*N*,*N*-disubstituted aminomethyl)oxazolidin-2-one Hydrochloride (3a—f) A mixture of **6** (9.19 mmol) and diethyl carbonate (46 mmol) in anhydrous benzene (100 ml) was subjected to azeotropic distillation. Sodium methoxide (0.1 g) was added to the residue and then the resulting mixture was heated at 130 °C for 1 h. The excess diethyl carbonate was distilled off by raising the bath temperature to 160 °C to give a viscous residue. After the addition of Et_2O, the resulting mixture was extracted with 1 N-HCl (×3). The acidic aqueous layer was washed with Et_2O, neutralized with K_2CO_3, and then re-extracted with Et_2O. The ethereal extract was dried over anhydrous $MgSO_4$ and then evaporation of the solvent under reduced pressure afforded a solid material. This was treated with 10% methanolic HCl and concentrated under reduced pressure to give the crude product of **3**. Recrystallization from an appropriate solvent gave pure hydrochloride of **3a**—**f**. Yields and physical data are listed in Table 2. Other specroscopic data are reported below.

3-Phenylmethyl-4-piperidinomethyloxazolidin-2-one Hydrochloride (3a) ^{1}H-NMR (DMSO-d_6) δ: 1.32—1.35 (1H, m, piperidine ring H-4), 1.65—1.74 (3H, m, piperidine ring H-3, H-4, H-5), 1.77—1.88 (2H, m, piperidine ring H-3, H-5), 2.80—2.91 (2H, m, piperidine ring H-2, H-6), 3.27—3.47 (4H, m, piperidine ring H-2, H-6 and =CH–C$\underline{H}_2$–N=), 4.20—4.25 (1H, m, Oxzln H-4), 4.34 (1H, d, J=16 Hz, CHHPh), 4.40—4.44 and 4.51—4.54 (2H, m, Oxzln H-5), 4.55 (1H, d, J=16.0 Hz, CHHPh), 7.37 (5H, m, Ar-H), 11.21 (1H, br s, NH^+). ^{13}C-NMR (DMSO-d_6) δ: 21.0 (piperidine ring C-4), 21.9 (piperidine ring C-3), 22.0 (piperidine ring C-5), 45.1 (Ph–$\underline{C}H_2$), 50.2 (Oxzln C-4), 51.9, 52.9 (piperidine ring C-2, C-6), 56.0 (=CH–$\underline{C}H_2$–N=), 67.4 (Oxzln C-5), 127.5, 127.8, 128.5 (Ar C-2—C-6), 136.5 (Ar C-1), 157.1 (C=O).

3-(3-Methoxyphenylmethyl)-4-thiomorpholinomethyloxazolidin-2-one Hydrochloride (3b) ^{1}H-NMR (DMSO-d_6+D_2O) δ: 2.89 (4H, t, J=5.0 Hz, thiomorpholine ring H-2, H-6), 3.33—3.37 (6H, m, thiomorpholine ring H-3, H-5 and =CH–C$\underline{H}_2$–N=), 3.82 (3H, s, OC$\underline{H}_3$), 4.24—4.25 (1H, m, Oxzln H-4), 4.34—4.40 (2H, m, CHHPh and Oxzln H-5), 4.58—4.63 (2H, m, CHHPh and Oxzln H-5), 6.93—7.42 (4H, m, Ar-H). ^{13}C-NMR (DMSO-d_6+D_2O) δ: 26.7 (thiomorpholine ring C-2, C-6), 48.3 (Ph–$\underline{C}H_2$–N=), 53.3 (Oxzln C-4), 56.9 (thiomorpholine ring C-3, C-5), 57.8 (O$\underline{C}H_3$), 60.0 (=CH–$\underline{C}H_2$–N=), 70.0 (Oxzln C-5), 115.8 (Ar C-4), 116.1 (Ar C-2), 122.6 (Ar C-6), 132.9 (Ar C-5), 139.5 (Ar C-1), 161.4 (C=O), 161.8 (Ar C-3).

3-Phenylmethyl-4-thiomorpholinomethyloxazolidin-2-one Hydrochloride (3c) ^{1}H-NMR (DMSO-d_6) δ: 2.76 (2H, br, thiomorpholine ring H-2, H-6), 3.08—3.15 (2H, m, thiomorpholine ring H-3, H-5), 3.35—3.45 (4H, m, thiomorpholine ring H-2, H-6 and =CH–C$\underline{H}_2$–N=), 3.61 (2H, br, thiomorpholine ring H-3, H-5), 4.22—4.23 (1H, m, Oxzln H-4), 4.31 (1H, d, J=16.0 Hz, CHHPh), 4.49—4.50 (2H, m, Oxzln H-5), 4.55 (1H, d, J=16.0 Hz, CHHPh), 7.29—7.38 (5H, m, Ar-H), 11.76 (1H, br s, NH^+). ^{13}C-NMR (DMSO-d_6) δ: 23.5 (thiomorpholine ring C-2, C-6), 45.1 ($\underline{C}H_2$Ph), 49.9 (Oxzln C-4), 52.8, 53.7 (thiomorpholine ring C-3, C-5), 56.5 (=CH–$\underline{C}H_2$–N=), 67.3 (Oxzln C-5), 127.5, 127.8, 128.6 (Ar C-2—C-6), 136.4 (Ar C-1), 157.1 (C=O).

3-Phenylmethyl-4-(*N*-methyl-*N*-phenethylamino)methyloxazolidin-2-one Hydrochloride (3d) ^{1}H-NMR ($CDCl_3$) δ: 2.60 (3H, br s, NC$\underline{H}_3$), 2.99—3.36 (6H, m, $C\underline{H}_2N(CH_3)C\underline{H}_2C\underline{H}_2$Ph), 4.31—4.39 (2H, m, a benzylic proton of *N*-3 substituent and H-4 on Oxzln), 4.61—4.64 (2H, m, Oxzln H-5), 4.66—4.72 (1H, m, a benzylic proton of *N*-3 substituent on Oxzln), 7.01—7.35 (10H, m, Ar-H), 12.49 (1H, br s, NH^+). ^{13}C-NMR ($CDCl_3$, as free base) δ: 33.6 ($CH_2\underline{C}H_2$Ph), 42.6 (N$\underline{C}H_3$), 46.7 (Ph–$\underline{C}H_2$N=), 52.2 (Oxzln C-4), 60.0 ($\underline{C}H_2$–N(CH_3)–$\underline{C}H_2CH_2$), 66.8 (Oxzln C-5), 126.1, 127.8, 128.2, 128.4, 128.7 (two Ar C-2—C-6), 136.3 (Ar C-1 of $PhCH_2N$=), 140.0 (Ar C-1 of $PhCH_2CH_2N$=), 158.6 (C=O).

3-(3-Methoxyphenylmethyl)-4-(*N*-methyl-*N*-phenethylamino)methyloxazolidin-2-one Hydrochloride (3e) ^{1}H-NMR (CD_3OD) δ: 2.87—2.92 (5H, m, N($C\underline{H}_3$)$CH_2C\underline{H}_2$Ph), 3.30—3.74 (4H, m, $C\underline{H}_2N(CH_3)C\underline{H}_2CH_2$Ph), 3.75 (3H, s, OC$\underline{H}_3$), 4.19—4.23 (1H, m, Oxzln H-4), 4.34 (1H, d, J=16.0 Hz, Ph–CHH–N=), 4.43 (1H, dd, J=8.0, 5.0 Hz, Oxzln H-5), 4.60—4.68 (1H, m, Oxzln H-5), 4.70 (1H, d, J=16.0 Hz, Ph–CHH–N=), 6.87—6.89 (1H, m, Ar-H), 6.94—6.95 (2H, m, Ar-H), 7.24—7.34 (6H, m, Ar-H). ^{13}C-NMR (CD_3OD) δ: 31.0 ($CH_2\underline{C}H_2$Ph), 41.9 (N$\underline{C}H_3$), 47.3 (Ph$\underline{C}H_2$–N=), 51.9 (Oxzln C-4), 55.8 (O$\underline{C}H_3$), 57.6, 59.8 ($\underline{C}H_2$–N(CH_3)–$\underline{C}H_2$), 68.7 (Oxzln C-5), 114.8 (*m*-methoxyphenyl group C-2, C-4), 121.2 (*m*-methoxyphenyl group C-6), 128.4 (Ph group C-4), 129.9 (Ph group C-3, C-5), 130.0 (Ph group C-2, C-6), 131.4 (*m*-methoxyphenyl group C-5), 137.1 (Ph group C-1), 138.5 (*m*-methoxyphenyl group C-1), 159.9 (C=O), 161.8 (*m*-methoxyphenyl group C-3).

3-Phenylmethyl-4-(1-pyrrolidinylmethyl)oxazolidin-2-one Hydrochloride (3f) ^{1}H-NMR (DMSO-d_6) δ: 1.88—1.97 (4H, m, pyrrolidine ring H-3, H-4), 2.90—2.96 (2H, m, =CH–C$\underline{H}_2$–N=), 3.42—3.49 (4H, m, pyrrolidine ring H-2, H-5), 4.06—4.08 (1H, m, Oxzln H-4), 4.32 (1H, d, J=15.5 Hz, CHHPh), 4.46—4.50 (1H, m, Oxzln H-5), 4.54—4.58 (1H, m, Oxzln H-5), 4.56 (1H, d, J=15.5 Hz, CHHPh), 7.31—7.42 (5H, m, Ar-H), 11.76 (1H, br s, NH^+). ^{13}C-NMR (DMSO-d_6) δ: 22.4 (pyrrolidine ring C-3), 22.5 (pyrrolidine ring C-4), 45.1 (Ph–$\underline{C}H_2$–N=), 51.3 (Oxzln C-4), 52.8, 53.6, 54.0 (pyrrolidine ring C-2, C-5 and =CH–$\underline{C}H_2$–N=), 66.6 (Oxzln C-5), 127.6, 127.7, 128.5 (Ar C-2—C-6), 136.3 (Ar C-1), 157.2 (C=O).

References and Notes

1) Bronson J. J., Barrett J. F., *Annu. Rep. Med. Chem.*, **36**, 89—98 (2001).
2) Abe N., Fujisaki F., Sumoto K., *Chem. Pharm. Bull.*, **46**, 142—144 (1998), and related references cited therein.
3) Fujisaki F., Abe N., Sumoto K., *Chem. Pharm. Bull.*, **50**, 129—132 (2002).
4) Park C.-H., Brittelli D. R., Wang C.-L. J., Marsh F. D., Gregory W. A., Wuonola M. A., McRipley R. J., Eberly V. S., Slee A. M., Forbes M., *J. Med. Chem.*, **35**, 1156—1165 (1992).
5) Brickner S. J., Hutchinson D. K., Barbachyn M. R., Manninen P. R., Ulanowicz D. A., Garmon S. A., Grega K. C., Hendges S. K., Toops D. S., Ford C. W., Zurenko G. E., *J. Med. Chem.*, **39**, 673—679 (1996).
6) Camille G. W., "The Practice of Medicinal Chemistry," 2nd ed., Academic Press, San Diego, 2003.
7) Homeyer A. H., U.S. Patent 2399118 (1946) [*Chem. Abst.*, **40**, 404084 (1946)].
8) Further modifications of two substituents on the oxazolidin-2-one ring are under investigation to develop a lead compound for new antibacterial agents.
9) The compound having –NHAc functionality as a part of the $-NR_1R_2$ group in the target molecule (**3**) can be obtained with a similar cyclization procedure with diethyl carbonate. However, the procedure for this class of compounds consists of multistage reactions. We will describe the synthesis of these analogues elsewhere.
10) Other amino alcohols (**6**) were obtained in good to moderate yields (51—83%) using this procedure. However, these compounds contained trace amounts of unknown contaminants. As mentioned in the Discussion, the purifications of these amino alcohols (**6**) were attributed to a loss of materials, and therefore we used the materials for the next stage without further purification.