Concise Synthesis and Antimicrobial Activities of New Substituted 5-Isoxazolpenicillins

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The synthesis of a series of new 5-isoxazolpenicillins is described, which were obtained by coupling substituted isoxazoles with 6-APA. Concise large-scale synthesis of 3,5-disubstituted isoxazoles by 1,3-dipolar cycloaddition using copper(I) as catalyst was also investigated. Representative compounds were assayed for antimicrobial activities, showing satisfactory antimicrobial activities against Gram-negative bacteria.

Keywords: Penicillin; Isoxazole; Synthesis; Antimicrobial activity.

INTRODUCTION

Emergence of penicillinase-producing bacterial strains led to the development of the first generation of semi-synthetic penicillinase-resistant penicillin, which achieve their effectiveness by attaching a bulky substituted isoxazole fragment to the penicillin molecule, preventing penicillinase from entering the penicillin molecule and cleaving the β-lactam ring.[1] The present study in this field focuses on the structural modification and the improvement of antimicrobial activity of 4-isoxazolpenicillins (Fig. 1, A), which contain the 3,5-disubstituted-4-isoxazolyl group. However, little attention has been paid to substituted 5-isoxazolpenicillins (Fig. 1, B), except for a few examples, such as 6-[(3-arylisoxazol-5-yl)acetamido]penicillins (Fig. 1, C) with low yields and a hard work-up procedure.[2]

Furthermore, considerable progress had been made recently in the synthesis of isoxazole compounds, since isoxazole derivatives are often encountered in the molecules of medicinal interest and used as important intermediates in organic synthesis.[3-5] Sharpless found that copper(I) was an effective catalyst for the cycloaddition reactions of nitrile oxides with alkynes to produce isoxazoles,[6] and Fokin synthesized a number of 3,5-disubstituted isoxazoles in good yields in a analogous manner.[7] Given the bacterial resistance to antibiotics and the frequent generation of drug-fast bacteria, the development of new antibiotic drugs has become urgent.[8-10] We therefore undertook a concise synthetic program in order to improve the synthesis of 5-isoxazolpenicillins and develop new antimicrobial agents.

RESULTS AND DISCUSSION

3,5-Disubstituted isoxazoles are important intermediates for the synthesis of isoxazolpenicillins, and using an experimentally convenient method, we obtained the re-

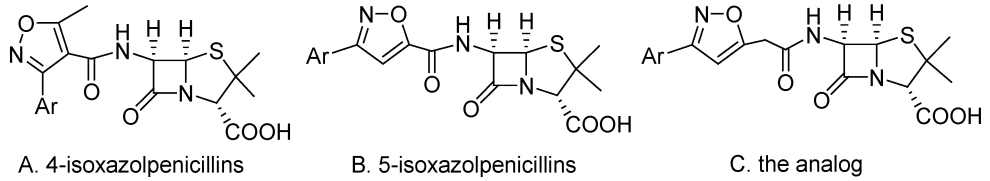

Fig. 1. Structures of two kinds of isoxazolpenicillins and an analog.

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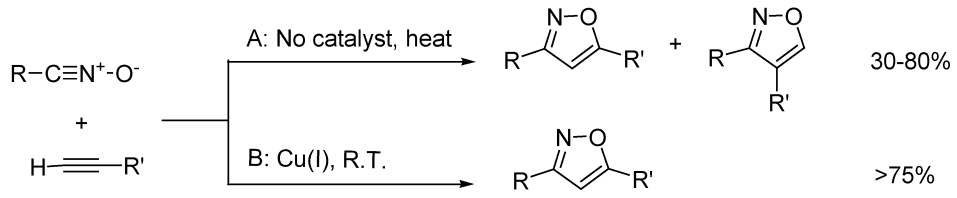
gioselective 3,5-disubstituted isoxazoles on a large-scale through 1,3-dipolar cycloaddition of nitrile oxides to acetylenes. Although 1,3-dipolar cycloaddition has been known for a long time,[11] its application to the synthesis of isoxazole is scarce. In the reported process (Scheme I, A), the reaction conditions are variable from several hours at 60-70 °C to several days at ambient temperature and while both isoxazole regioisomers are usually obtained, the yields of isoxazole products are often quite low, and side reactions result in impurities which complicate the isolation and purification.[6]

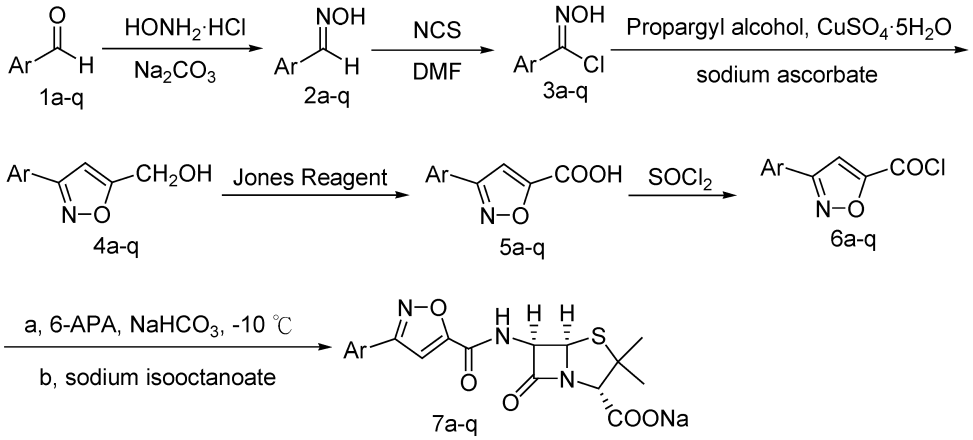
Recently several new catalysts for the 1,3-dipolar cycloaddition reaction of nitrile oxides and alkynes, especially the copper(I) catalysts, have been found to form isoxazole concisely and efficiently. In the presence of a catalytic amount of copper(I), the *in situ* generated nitrile oxide undergoes a stepwise addition to a copper(I) acetylenide under mild reaction conditions (Scheme I, B). By this concise method, 3,5-disubstituted isoxazole compounds were prepared on a large-scale with high yields, and only one regioisomer was obtained and without tedious chromatographic purification.

Thus, starting from the inexpensive and readily obtainable aryldehydes **1**, the corresponding aldoximes **2** were synthesized via the reaction with hydroxylamine (Scheme II).[12] As for chlorination of the aldoximes, previously reported preparations of imidoyl chlorides required either the use of chlorine, nitrosyl chloride, *t*-butyl hypochlorite and a complex experimental procedure utilizing N-chlorosuccinimide (NCS) in DMF or the hydrogen chloride/DMF/Oxone.[13,14] In this paper, the aldoximes **2** were readily transformed to the corresponding imidoyl chlorides **3** using NCS/DMF which is suitable for aromatic aldoximes. The base-induced dehydrohalogenation of imidoyl chlorides **3** produced nitrile oxides that are important intermediates in 1,3-dipolar cycloaddition reactions to form isoxazoles. As nitrile oxides are unstable and dimerize readily,[5] NCS was added in small portions while maintaining a low

Scheme I 1,3-Dipolar cycloaddition of nitrile oxides to acetylenes



Scheme II The synthetic strategy to the title compounds



Ar = C_6H_5 (**7a**), 4-FC_6H_4 (**7b**), 2-ClC_6H_4 (**7c**), 4-ClC_6H_4 (**7d**), 2-BrC_6H_4 (**7e**), 2-$CH_3OC_6H_4$ (**7f**), 4-$CH_3OC_6H_4$ (**7g**), 2-$NO_2C_6H_4$ (**7h**), 4-$NO_2C_6H_4$ (**7i**), 3-$CF_3C_6H_4$ (**7j**), 4-$CF_3C_6H_4$ (**7k**), 2,4-$Cl_2C_6H_3$ (**7l**), 3,4-$Cl_2C_6H_3$ (**7m**), 2,4,5-$Cl_3C_6H_2$ (**7n**), 3,4,5-$Cl_3C_6H_2$ (**7o**), pyridin-2-yl (**7p**), pyridin-4-yl (**7q**).

temperature, and nitrile oxides were used without purification immediately after they were prepared. The freshly generated nitrile oxides reacted with propargyl alcohol via 1,3-dipolar cycloaddition in the presence of a catalytic amount of copper(I), obtained from reduction of copper(II) sulfate with sodium ascorbate. The 3,5-disubstituted isoxazole products **4** were obtained in moderate to good overall yields (55-75%) after a simple filtration or extraction.

Utilizing a copper(I)-catalyzed regioselective cycloaddition reaction, 3,5-disubstituted isoxazoles **4** were obtained in good yields by a convenient three-step procedure between *in situ* generated nitrile oxides and terminal acetylenes, and the oxidation of isoxazoles **4** gave the isoxazol-5-yl carbonic acid compounds **5**. So far, there have been several reagents to achieve the oxidation reaction, such as $KMnO_4$, $K_2Cr_2O_7$, and so forth. However, we found that Jone's Reagent was the most effective reagent for this reaction with a yield of up to 95% and the work-up procedure was very simple. The carbonic acids reacted with refluxing $SOCl_2$ or $POCl_3$ to produce isoxazol-5-yl carbonyl chlorides **6**, which coupled with 6-amino-penicillanic acid (6-APA), the main precursor for the production of penicillin, to yield the title compounds **7** in moderate yields. The work-up procedure would be very difficult if the starting material, especially the compounds **5**, had a small amount of impurities, and therefore the purification of isoxazoles **4** through chromatography on silica gel were necessary in certain cases. In addition, to obtain more pure title compounds, the transformation of penicillanic acids to sodium salts was often necessary.

Biological Activity

Compounds **7b-7e**, **7g**, **7i**, **7j** were selected and screened *in vitro* for their antibacterial activity against Gram positive bacteria (*Staphylococcus aureus* and *Bacillus pumilus*) and Gram negative bacteria (*Pseudomonass aureginosa* and *Klebsiella pneumoniae*) employing the cup-plate method at the concentration of 50 mg/mL in nutrient agar media.[15] Azithromycin (AZ) and Gentamycin Sulfate (GS) were used as standard antibacterial agents. The results which are presented in Table 1 show that most of the compounds were active against Gram positive bacteria, especially compounds **7b**, **7c** and **7i** showed better inhibitory effect to *Staphylococcus aureus* than AZ; however, the activities against Gram negative bacteria were weak. And the investigation on the structure-activity relationship shows that halogen atoms can enhance the antibacterial action of the title compounds. Further investigation on the biological activity of other compounds is still in progress.

EXPERIMENTAL

All melting points were determined with an XT-4 microscopic melting apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance DPX400 spectrometer with TMS as internal standard. IR spectra were

Table 1. The antibacterial activity of the tested products (**7b-7e**, **7g**, **7i**, **7j**)

NO.	*Staphylococcus aureus*	*Bacillus pumilus*	*Pseudomonass aureginosa*	*Klebsiella pneumoniae*
7b	0.99	6.16	> 100	92.59
7c	0.91	5.51	90.21	73.53
7d	0.62	4.07	> 100	> 100
7e	1.53	8.45	> 100	84.75
7g	0.69	4.47	> 100	58.14
7i	0.93	6.88	> 100	> 100
7j	1.61	5.61	96.30	69.32
AZ[a]	1	1		
GS[b]			1	1

[a] Azithromycin (AZ) was used as a standard antibacterial agent against Gram positive bacteria. The concentration is set to 1 ug/mL.

[b] Gentamycin Sulfate (GS) was used as a standard antibacterial agent against Gram negative bacteria. The concentration is set to 1 ug/mL.

The activity is presented as the relative value of the concentration with the same activity of the standard antibacterial agent (1ug/mL).

obtained from a Nicolet 5700 FT-IR spectrophotometer as KBr pellets. Elemental analyses were performed with an Elementar EL Vario III analyzer. The mass spectra were obtained on an API2000 LC-mass spectrometer, utilizing electrospray ionization technique (ESI). TLC (Thin Layer Chromatography) analysis was utilized to ascertain the purities of the products.

1. General Procedure for Preparation of Aromatic Aldoximes (2a-2q)

To a suspension of aldehydes (100 mmol) in a 1:2 mixture of H_2O/MeOH (80 mL) was added hydroxylamine hydrochloride (100 mmol), followed by adding Na_2CO_3 (55 mmol). After being stirred at room temperature for 3 h, was added to the solution 100 mL of water and then extracted with diethyl ether. The aqueous phase was acidified to pH 6 by concentrated hydrogen chloride while keeping the temperature below 30 °C and extracting with ether. The organic phase was dried over $MgSO_4$, and the solvent was evaporated to give the oximes in 85-95% yield, which were used directly in the next step.

2. General Procedure for Preparation of Arylhydroximoyl Chloride (3a-3q)

To a solution of oximes (50 mmol) in DMF (20 mL) was added NCS (10 mmol) in one portion. The beginning of the reaction caused a slight increase of the reaction temperature. (If the reaction does not start, a small amount of aqueous HCl in DMF can be added. With the electron-deficient oximes, the reaction mixture is heated to 45 °C). The remaining 40 mmol of NCS was added in small portions while keeping the temperature below 35 °C. The mixture was stirred at room temperature for 1 h, poured into water, and extracted with diethyl ether. The organic phase was washed with brine and dried over Na_2SO_4, and the solvent was removed to give the imidoyl chlorides in 70-90% yields. They were used directly without further purification in the next step.

3. General Procedure for Copper(I)-Catalyzed Synthesis of 3,5-Disubstituted Isoxazoles (4a-4q)

Arylhydroximoyl chloride (20 mmol) and propargyl alcohol (22 mmol) were dissolved in 50 mL of a 1:1 *tert*-BuOH/H_2O mixture. While the mixture was being stirred, sodium ascorbate (2 mmol in 3 mL of water) was added, followed by copper(II) sulfate pentahydrate (0.6 mmol in 2 mL of water). The reaction mixture was then treated with $KHCO_3$ (60 mmol) and left to be stirred for 1.5 h at ambient temperature. The reaction mixture was diluted with water, and the solid off-white isoxazole product was filtered off (82-92% yields).

3-Phenyl-5-hydroxymethylisoxazole 4a

Yield: 2.98 g, 85%. m.p. 52-53.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.25 (bs, 1H), 4.75 (s, 2H), 6.40 (s, 1H), 7.32 (m, 3H), 7.73 (m, 2H). Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00%. Found: C, 68.70; H, 5.12; N, 7.99%.

3-(4-Fluorophenyl)-5-hydroxymethylisoxazole 4b

Yield: 3.13 g, 81%. m.p. 97-98 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.24 (bs, 1H), 4.84 (s, 2H), 6.51 (s, 1H), 7.12 (m, 2H), 7.51 (m, 2H). Anal. Calcd. for $C_{10}H_8FNO_2$: C, 62.18; H, 4.17; N, 7.25%. Found: C, 62.10; H, 4.12; N, 7.29%.

3-(2-Chlorophenyl)-5-hydroxymethylisoxazole 4c

Yield: 3.35 g, 80%. m.p. 73.5-74 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.16 (bs, 1H), 4.82 (s, 2H), 6.72 (s, 1H), 7.37 (m, 2H), 7.49 (m, 1H), 7.72 (m, 1H). Anal. Calcd. for $C_{10}H_8ClNO_2$: C, 57.30; H, 3.85; N, 6.68%. Found: C, 57.26; H, 3.88; N, 6.63%.

3-(4-Chlorophenyl)-5-hydroxymethylisoxazole 4d

Yield: 3.44 g, 82%. m.p. 99.5-100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.74 (bs, 1H), 4.79 (s, 2H), 6.51 (s, 1H), 7.41 (m, 2H), 7.79 (m, 2H). Anal. Calcd. for $C_{10}H_8ClNO_2$: C, 57.30; H, 3.85; N, 6.68%. Found: C, 57.21; H, 3.84 N, 6.65%.

3-(2-Bromophenyl)-5-hydroxymethylisoxazole 4e

Yield: 3.05 g, 75%. m.p. 82-83 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.16 (bs, 1H), 4.73 (s, 2H), 6.58 (s, 1H), 7.24-7.31 (m, 3H), 7.64 (m, 1H). Anal. Calcd. for $C_{10}H_8BrNO_2$: C, 47.27; H, 3.17; N, 5.51%. Found: C, 47.19; H, 3.25; N, 5.60%.

3-(2-Methoxyphenyl)-5-hydroxymethylisoxazole 4f

Yield: 3.12 g, 76%. m.p. 74-75 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.25 (bs, 1H), 3.83 (s, 3H), 4.76 (s, 2H), 6.71 (s, 1H), 6.93-7.01 (m, 3H), 7.40 (m, 1H). Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83%. Found: C, 64.33;

H, 5.36 N, 6.85%.

3-(4-Methoxyphenyl)-5-hydroxymethylisoxazole 4g

Yield: 3.03 g, 74%. m.p. 89-90.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.88 (bs, 1H), 3.85 (s, 3H), 4.81 (s, 2H), 6.51 (s, 1H), 7.02 (m, 2H), 7.39 (m, 2H). Anal. Calcd. for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83%. Found: C, 64.43; H, 5.42 N, 6.86%.

3-(3-Nitrophenyl)-5-hydroxymethylisoxazole 4h

Yield: 3.09 g, 70%. m.p. 134-134.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.96 (bs, 1H), 4.81 (s, 2H), 6.77 (s, 1H), 7.56 (m, 1H), 7.95 (m, 2H), 8.39 (m, 1H). Anal. Calcd. for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72%. Found: C, 54.48; H, 3.61 N, 12.70%.

3-(4-Nitrophenyl)-5-hydroxymethylisoxazole 4i

Yield: 3.21 g, 73%. m.p. 145-146 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.29 (bs, 1H), 4.87 (s, 2H), 6.58 (s, 1H), 7.98 (m, 2H), 8.35 (m, 2H). Anal. Calcd. for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72%. Found: C, 54.53; H, 3.60 N, 12.76%.

3-3-(Trifluoromethyl)phenyl-5-hydroxymethylisoxazole 4j

Yield: 3.41 g, 70%. m.p. 86-87 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.16 (bs, 1H), 4.85 (s, 2H), 6.59 (s, 1H), 7.49 (m, 2H), 7.98 (m, 2H). Anal. Calcd. for $C_{11}H_8F_3NO_2$: C, 54.33; H, 3.32; N, 5.76%. Found: C, 54.41; H, 3.40; N, 5.71%.

3-4-(Trifluoromethyl)phenyl-5-hydroxymethylisoxazole 4k

Yield: 3.45 g, 71%. m.p. 96-97.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.25 (bs, 1H), 4.83 (s, 2H), 6.53 (s, 1H), 7.57 (m, 2H), 7.92 (m, 2H). Anal. Calcd. for $C_{11}H_8F_3NO_2$: C, 54.33; H, 3.32; N, 5.76%. Found: C, 54.26; H, 3.35; N, 5.74%.

3-(2,4-Dichlorophenyl)-5-hydroxymethylisoxazole 4l

Yield: 3.85 g, 79%. m.p. 115-116 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.47 (bs, 1H), 4.82 (s, 2H), 6.69 (s, 1H), 7.42-7.75 (m, 3H). Anal. Calcd. for $C_{10}H_7Cl_2NO_2$: C, 49.21; H, 2.89; N, 5.74%. Found: C, 49.25; H, 2.94; N, 5.71%.

3-(3,4-Dichlorophenyl)-5-hydroxymethylisoxazole 4m

Yield: 3.81 g, 78%. m.p. 106-107 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.45 (bs, 1H), 4.81 (s, 2H), 6.51 (s, 1H), 7.38-7.66 (m, 3H). Anal. Calcd. for $C_{10}H_7Cl_2NO_2$: C, 49.21; H, 2.89; N, 5.74%. Found: C, 49.24; H, 2.96; N, 5.70%.

(2,4,5-Trichlorophenyl)-5-hydroxymethylisoxazole 4n

Yield: 4.23 g, 76%. m.p. 121-122 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.16 (bs, 1H), 4.85 (s, 2H), 6.57 (s, 1H), 7.68 (s, 1H), 7.79 (s, 1H). Anal. Calcd. for $C_{10}H_6Cl_3NO_2$: C, 43.12; H, 2.17; N, 5.03%. Found: C, 43.11; H, 2.20; N, 5.12%.

(3,4,5-Trichlorophenyl)-5-hydroxymethylisoxazole 4o

Yield: 4.12 g, 74%. m.p. 135-136 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.27 (bs, 1H), 4.84 (s, 2H), 6.58 (s, 1H), 7.78 (d, J = 1.9, 2H). Anal. Calcd. for $C_{10}H_6Cl_3NO_2$: C, 43.12; H, 2.17; N, 5.03%. Found: C, 43.19; H, 2.11; N, 5.08%.

3-(Pyridin-2-yl)-5-hydroxymethylisoxazole 4p[16]

Yield: 2.53 g, 72%. m.p. 100-100.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.77 (bs, 1H), 4.82 (s, 2H), 6.91 (s, 1H), 7.57-8.65 (m, 4H). Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90%. Found: C, 61.39; H, 4.61; N, 15.88%.

3-(Pyridin-4-yl)-5-hydroxymethylisoxazole 4q

Yield: 2.48 g, 71%. m.p. 105-106 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.59 (bs, 1H), 4.84 (s, 2H), 6.90 (s, 1H), 8.01-8.63 (m, 4H). Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90%. Found: C, 61.31; H, 4.64; N, 15.93%.

4. General Procedure for Synthesis of Isoxazol-5-yl Carbonic Acid (5a-5q)

To a solution of 3,5-disubstituted isoxazoles (20 mmol) in acetone (25 mL) at 0 °C was added the Jones reagent (40 mmol) dropwise. After stirring at the same temperature for 0.5 h, the reaction mixture was allowed to stand at 35 °C for another 3 h. This mixture was diluted with water and extracted with ether. The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated to give the desired carbonic acid compound **5** (95-98% yields).

3-Phenyl-5-isoxazolylcarboxylic acid 5a

Yield: 3.70, 97%. m.p. 176-177 °C. ^{1}H NMR (DMSO, 400 MHz): δ 7.58-7.98 (m, 5H), 7.64 (s, 1H), 14.10 (bs, 1H). IR (KBr): υ 3425 (OH, acid), 1750 (C=O, acid), 1432 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{10}H_7NO_3$: C,

63.49; H, 3.73; N, 7.40%. Found: C, 63.56; H, 3.71; N, 7.44%.

3-(4-Fluorophenyl)-5-isoxazolylcarboxylic acid 5b

Yield: 3.93, 95%. m.p. 197-197.5 °C. ^{1}H NMR (DMSO, 400 MHz): δ 7.39 (m, 2H), 7.81 (s, 1H), 8.04 (m, 2H), 14.30 (bs, 1H). IR (KBr): υ 3435 (OH, acid), 1754 (C=O, acid), 1433 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{10}H_6FNO_3$: C, 57.98; H, 2.92; N, 6.76%. Found: C, 57.94; H, 3.01; N, 6.74%.

3-(2-Chlorophenyl)-5-isoxazolylcarboxylic acid 5c

Yield: 4.23, 95%. m.p. 176-177 °C. ^{1}H NMR (DMSO, 400 MHz): δ 7.68-8.06 (m, 4H), 7.71 (s, 1H), 14.34 (bs, 1H). IR (KBr): υ 3436 (OH, acid), 1753 (C=O, acid), 1436 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{10}H_6ClNO_3$: C, 53.71; H, 2.70; N, 6.26%. Found: C, 53.74; H, 2.76; N, 6.29%.

3-(4-Chlorophenyl)-5-isoxazolylcarboxylic acid 5d

Yield: 4.25, 95%. m.p. 185-186 °C. ^{1}H NMR (DMSO, 400 MHz): δ 7.64 (m, 2H), 7.75 (s, 1H), 8.05 (m, 2H), 14.60 (bs, 1H). IR (KBr): υ 3437 (OH, acid), 1753 (C=O, acid), 1430 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{10}H_6ClNO_3$: C, 53.71; H, 2.70; N, 6.26%. Found: C, 53.65; H, 2.73; N, 6.31%.

3-(2-Bromophenyl)-5-isoxazolylcarboxylic acid 5e

Yield: 5.12, 96%. m.p. 172-172.5 °C. ^{1}H NMR (DMSO, 400 MHz): δ 7.48-7.98 (m, 4H), 7.88 (s, 1H), 14.54 (bs, 1H). IR (KBr): υ 3436 (OH, acid), 1751 (C=O, acid), 1434 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{10}H_6BrNO_3$: C, 44.81; H, 2.26; N, 5.23%. Found: C, 44.90; H, 2.31; N, 5.28%.

3-(2-Methoxyphenyl)-5-isoxazolylcarboxylic acid 5f

Yield: 4.29, 98%. m.p. 165-166 °C. ^{1}H NMR (DMSO, 400 MHz): δ 7.39-7.94 (m, 4H), 7.63 (s, 1H), 14.46 (bs, 1H). IR (KBr): υ 3431 (OH, acid), 1755 (C=O, acid), 1431 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39%. Found: C,60.24; H, 4.11; N, 4.19%.

3-(4-Methoxyphenyl)-5-isoxazolylcarboxylic acid 5g

Yield: 4.26, 97%. m.p. 181-182 °C. ^{1}H NMR (DMSO, 400 MHz): δ 7.37 (m, 2H), 7.60 (s, 1H), 7.96 (m, 2H), 14.61 (bs, 1H). IR (KBr): υ 3433 (OH, acid), 1751 (C=O, acid), 1430 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39%. Found: C, 60.23; H, 4.09; N, 6.44%.

3-(3-Nitrophenyl))-5-isoxazolylcarboxylic acid 5h

Yield: 4.53, 96%. m.p. 223-222 °C. ^{1}H NMR (DMSO, 400 MHz): δ 8.03-8.46 (m, 4H), 7.93 (s, 1H), 14.30 (bs, 1H). IR (KBr): υ 3435 (OH, acid), 1759 (C=O, acid), 1437 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{10}H_6N_2O_5$: C, 51.29; H, 2.58; N, 11.96%. Found: C, 51.36; H, 2.49; N, 11.91%.

3-(4-Nitrophenyl)-5-isoxazolylcarboxylic acid 5i

Yield: 4.60, 97%. m.p. 242-243 °C. ^{1}H NMR (DMSO, 400 MHz): δ 7.90 (s, 1H), 8.01 (m, 2H), 8.44 (m, 2H), 14.53 (bs, 1H). IR (KBr): υ 3438 (OH, acid), 1760 (C=O, acid), 1439 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{10}H_6N_2O_5$: C, 51.29; H, 2.58; N, 11.96%. Found: C, 51.35; H, 2.62; N, 11.99%.

3-3-(Trifluoromethyl)phenyl-5-isoxazolylcarboxylic acid 5j

Yield: 4.98, 97%. m.p. 156-157 °C. ^{1}H NMR (DMSO, 400 MHz): δ 7.64 (s, 1H), 7.66-7.97 (m, 4H), 14.54 (bs, 1H). IR (KBr): υ 3430 (OH, acid), 1755 (C=O, acid), 1437 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{11}H_6F_3NO_3$: C, 51.37; H, 2.35; N, 5.45%. Found: C, 51.43; H, 2.39; N, 5.41%.

3-4-(Trifluoromethyl)phenyl-5-isoxazolylcarboxylic acid 5k

Yield: 4.86, 95%. m.p. 176-177 °C. ^{1}H NMR (DMSO, 400 MHz): δ 7.72-8.05 (m, 4H), 7.63 (s, 1H), 14.34 (bs, 1H). IR (KBr): υ 3438 (OH, acid), 1754 (C=O, acid), 1439 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{11}H_6F_3NO_3$: C, 51.37; H, 2.35; N, 5.45%. Found: C, 51.41; H, 2.31; N, 5.42%.

3-(2,4-Dichlorophenyl)-5-isoxazolylcarboxylic acid 5l

Yield: 5.06, 99%. m.p. 168-169 °C. ^{1}H NMR (DMSO, 400 MHz): δ 7.59-8.02 (m, 3H), 7.71 (s, 1H), 14.64 (bs, 1H). IR (KBr): υ 3436 (OH, acid), 1753 (C=O, acid), 1432 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{10}H_5Cl_2NO_3$: C, 46.54; H, 1.95; N, 5.43%. Found: C, 46.58; H, 1.98; N, 5.40%.

3-(3,4-Dichlorophenyl)-5-isoxazolylcarboxylic acid 5m

Yield: 4.99, 98%. m.p. 191-192 °C. ^{1}H NMR (DMSO, 400 MHz): δ 7.54-7.89 (m, 3H), 7.82 (s, 1H), 14.60 (bs, 1H). IR (KBr): υ 3434 (OH, acid), 1753 (C=O, acid), 1436 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{10}H_5Cl_2NO_3$: C, 46.54; H, 1.95; N, 5.43%. Found: C, 46.52; H, 1.99; N, 5.48%.

(2,4,5-Trichlorophenyl)-5-isoxazolylcarboxylic acid 5n

Yield: 5.56, 96%. m.p. 196 °C (dec.). ^{1}H NMR (DMSO, 400 MHz): δ 7.48-7.98 (m, 2H), 7.84 (s, 1H), 14.54 (bs, 1H). IR (KBr): υ 3435 (OH, acid), 1756 (C=O, acid), 1438 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{10}H_4Cl_3NO_3$: C, 41.06; H, 1.38; N, 4.79%. Found: C, 41.01; H, 1.37; N, 4.74%.

(3,4,5-Trichlorophenyl)-5-isoxazolylcarboxylic acid 5o

Yield: 5.64, 98%. m.p. 185-186 °C. ^{1}H NMR (DMSO, 400 MHz): δ 7.86 (d, J = 2.0, 2H), 7.79 (s, 1H), 14.50 (bs, 1H). IR (KBr): υ 3431 (OH, acid), 1757 (C=O, acid), 1436 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_{10}H_4Cl_3NO_3$: C, 41.06; H, 1.38; N, 4.79%. Found: C, 50.41; H, 3.50; N, 9.74%.

3-(Pyridin-2-yl)-5-isoxazolylcarboxylic acid 5p

Yield: 3.61, 95%. m.p. 210 °C (dec.). ^{1}H NMR (DMSO, 400 MHz): δ 7.59-8.65 (m, 4H), 7.87 (s, 1H), 14.90 (bs, 1H). IR (KBr): υ 3429 (OH, acid), 1756 (C=O, acid), 1434 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.85; H, 3.18; N, 14.73%. Found: C, 56.81; H, 3.15; N, 14.76%.

3-(Pyridin-4-yl)-5-isoxazolylcarboxylic acid 5q

Yield: 3.67, 96%. m.p. 204 °C (dec.). ^{1}H NMR (DMSO, 400 MHz): δ 8.02-8.69 (m, 4H), 7.89 (s, 1H), 14.84 (bs, 1H). IR (KBr): υ 3436 (OH, acid), 1757 (C=O, acid), 1435 (isoxazolyl ring) cm^{-1}. Anal. Calcd. for $C_9H_6N_2O_3$: C, 56.85; H, 3.18; N, 14.73%. Found: C, 56.89; H, 3.11; N, 14.68%.

5. General Procedure for Synthesis of 3,5-Disubstituted Isoxazol-5-yl Carbonyl Chlorides (6a-6q)

A mixture of isoxazol-5-yl carboxylic acid (8 mmol) and $SOCl_2$ (6 mL) was heated under reflux for 7 h. The excess $SOCl_2$ was removed with a water vacuum pump and the residue was distilled *in vacuo* to give carbonyl chlorides (over 85% yield). The product was dissolved in 10 mL of dry acetone, which was used directly in next step.

6. General Procedure for the Synthesis of 5-Isoxazolpenicillins (7a-7q)

A stirred suspension of 6-APA (7 mmol) in water (15 mL) was adjusted to pH 7.0-7.5 with 1 N aqueous sodium hydroxide at 0 °C and with a buffer function of Na_2HPO_4 solution. The resulting solution was treated with the acetone solution of isoxazol-5-yl carbonyl chloride (7 mmol) prepared in the procedure above below -5 °C, and was adjusted to pH 7.5-8.0 with saturated $NaHCO_3$ solution. After stirring vigorously at the same temperature for 1 h, the reaction was allowed to stand at 20 °C for another 3 h. This mixture was diluted with water and acidified to pH 2.5 by adding 10% hydrochloric acid while keeping the temperature below 25 °C and extracting with ethyl acetate. The organic phase was washed with brine, dried over $MgSO_4$ and was concentrated under reduced pressure. Adding petroleum ether to the above concentrated solution, the precipitated solid was filtered off and dissolved in a little ethyl acetate. Sodium isooctanoate was added and stored below -5 °C overnight; pale powder was filtrated and dried to obtain isoxazolpenicillin.

6-(3-Phenylisoxazole-5-carboxamido)-penicillanate sodium 7a

Yield: 2.03 g, 71%. m.p. 133 °C (dec.). IR (KBr): υ 3406 (NH, amide), 1791 (C=O, lactam), 1682 (C=O, amide), 1606 (C=O, carboxylate ion), 1575 (NH, amide), 1560, 1434 (isoxazolyl ring) cm^{-1}. ^{1}H NMR (D_2O, 400 MHz): δ 1.64 (s, 3H), 1.75 (s, 3H), 4.56 (s, 1H), 5.65 (d, J = 4.0 Hz, 1H), 5.88 (d, J = 4 Hz, 1H), 7.30 (s, 1H), 7.51 (m, 2H), 7.81 (m, 2H). ESI-MS: *m/z* 409 (M^+), 411 (M^++2). Anal. Calcd. for $C_{18}H_{16}N_3NaO_5S$: C, 52.81; H, 3.94; N, 10.26%. Found: C, 52.69; H, 4.05; N, 10.30%.

6-3-(4-Fluorophenyl)isoxazole-5-carboxamido-penicillanate sodium 7b

Yield: 2.04 g, 68%. m.p. 112 °C (dec.). IR (KBr): υ 3401 (NH, amide), 1795 (C=O, lactam), 1697 (C=O, amide), 1608 (C=O, carboxylate ion), 1578 (NH, amide), 1558, 1439 (isoxazolyl ring) cm^{-1}. ^{1}H NMR (D_2O, 400 MHz): δ 1.65 (s, 3H), 1.76 (s, 3H), 4.53 (s, 1H), 5.63 (d, J = 4.1 Hz, 1H), 5.86 (d, J = 4.0 Hz, 1H), 7.22 (m, 2H), 7.31 (s, 1H), 7.61 (m, 2H). ESI-MS: *m/z* 427 (M^+). Anal. Calcd. for $C_{18}H_{15}FN_3NaO_5S$: C, 50.59; H, 3.54; N, 9.83%. Found: C, 50.41; H, 3.50; N, 9.74%.

6-3-(2-Chlorophenyl)isoxazole-5-carboxamido-penicillanate sodium 7c

Yield: 2.17 g, 70%. m.p. ~145 °C (dec.). IR (KBr): υ 3411 (NH, amide), 1797 (C=O, lactam), 1692 (C=O, amide), 1607 (C=O, carboxylate ion), 1574 (NH, amide), 1556, 1434 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.64 (s, 3H), 1.75 (s, 3H), 4.56 (s, 1H), 5.66 (d, J = 4.1 Hz, 1H), 5.89 (d, J = 4.2 Hz, 1H), 7.30 (s, 1H), 7.39-7.74 (m, 4H). ESI-MS: *m/z* 443 (M^+), 445 (M^++2). Anal. Calcd. for $C_{18}H_{15}ClN_3NaO_5S$: C, 48.71; H, 3.41; N, 9.47. Found: C, 48.78; H, 3.55; N, 9.55%.

6-3-(4-Chlorophenyl)isoxazole-5-carboxamido-penicillanate sodium 7d

Yield: 2.48 g, 80%. m.p. 155 °C (dec.). IR (KBr): υ 3415 (NH, amide), 1798 (C=O, lactam), 1691 (C=O, amide), 1604 (C=O, carboxylate ion), 1571 (NH, amide), 1555, 1433 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.62 (s, 3H), 1.78 (s, 3H), 4.54 (s, 1H), 5.64 (d, J = 4.2 Hz, 1H), 5.84 (d, J = 4.2 Hz, 1H), 7.32 (s, 1H), 7.44 (m, 2H), 7.75 (m, 2H). ESI-MS: *m/z* 443 (M^+), 445 (M^++2). Anal. Calcd. for $C_{18}H_{15}ClN_3NaO_5S$: C, 48.71; H, 3.41; N, 9.47. Found: C, 48.65; H, 3.31; N, 9.36%.

6-3-(2-Bromophenyl)isoxazole-5-carboxamido-penicillanate sodium 7e

Yield: 2.45 g, 72%. m.p. 132 °C (dec.). IR (KBr): υ 3424 (NH, amide), 1791 (C=O, lactam), 1686 (C=O, amide), 1606 (C=O, carboxylate ion), 1573 (NH, amide), 1559, 1429 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.64 (s, 3H), 1.75 (s, 3H), 4.55 (s, 1H), 5.65 (d, J = 4.0 Hz, 1H), 5.88 (d, J = 4.0 Hz, 1H), 7.33 (s, 1H), 7.48-7.84 (m, 4H). ESI-MS: *m/z* 487 (M^+), 489 (M^++2). Anal. Calcd. for $C_{18}H_{15}BrN_3NaO_5S$: C, 44.28; H, 3.10; N, 8.61%. Found: C, 44.20; H, 3.02; N, 8.54%.

6-3-(2-Methoxyphenyl)isoxazole-5-carboxamido-penicillanate sodium 7f

Yield: 2.18 g, 71%. m.p. 103 °C (dec.). IR (KBr): υ 3406 (NH, amide), 1786 (C=O, lactam), 1678 (C=O, amide), 1601 (C=O, carboxylate ion), 1577 (NH, amide), 1550, 1421 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.64 (s, 3H), 1.74 (s, 3H), 3.91 (s, 3H), 4.56 (s, 1H), 5.65 (d, J = 4.3 Hz, 1H), 5.88 (d, J = 4.3 Hz, 1H), 7.02 (m, 2H), 7.29 (s, 1H), 7.51 (m, 1H), 7.90 (m, 1H). ESI-MS: *m/z* 439 (M^+), 440 (M^++1). Anal. Calcd. for $C_{19}H_{18}N_3NaO_6S$: C, 51.93; H, 4.13; N, 9.56%. Found: C, 51.86; H, 4.06; N, 9.44%.

6-3-(4-Methoxyphenyl)isoxazole-5-carboxamido-penicillanate sodium 7g

Yield: 2.34 g, 76%. m.p. 124 °C (dec.). IR (KBr): υ 3411 (NH, amide), 1784 (C=O, lactam), 1672 (C=O, amide), 1602 (C=O, carboxylate ion), 1572 (NH, amide), 1551, 1424 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.61 (s, 3H), 1.72 (s, 3H), 3.84 (s, 3H), 4.54 (s, 1H), 5.64 (d, J = 4.2 Hz, 1H), 5.84 (q, J = 4.3 Hz, 1H), 6.97 (m, 2H), 7.32 (s, 1H), 7.74 (m, 2H). ESI-MS: *m/z* 439 (M^+). Anal. Calcd. for $C_{19}H_{18}N_3NaO_6S$: C, 51.93; H, 4.13; N, 9.56%. Found: C, 51.81; H, 4.09; N, 9.39%.

6-3-(3-Nitrophenyl)isoxazole-5-carboxamido-penicillanate sodium 7h

Yield: 2.57 g, 81%. m.p. 160 °C (dec.). IR (KBr): υ 3430 (NH, amide), 1789 (C=O, lactam), 1686 (C=O, amide), 1606 (C=O, carboxylate ion), 1579 (NH, amide), 1557, 1434 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.63 (s, 3H), 1.74 (s, 3H), 4.55 (s, 1H), 5.65 (d, J = 4.4 Hz, 1H), 5.86 (d, J = 4.4 Hz, 1H), 7.30 (s, 1H), 7.69 (m, 1H), 8.06-8.34 (m, 3H). ESI-MS: *m/z* 454 (M^+), 455 (M^++1). Anal. Calcd. for $C_{18}H_{15}N_4NaO_7S$: C, 47.58; H, 3.33; N, 12.33%. Found: C, 47.65; H, 3.36; N, 12.19%.

6-3-(4-Nitrophenyl)isoxazole-5-carboxamido-penicillanate sodium 7i

Yield: 2.60 g, 82%. m.p. 153 °C (dec.). IR (KBr): υ 3427 (NH, amide), 1788 (C=O, lactam), 1691 (C=O, amide), 1607 (C=O, carboxylate ion), 1577 (NH, amide), 1560, 1436 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.63 (s, 3H), 1.73 (s, 3H), 4.55 (s, 1H), 5.64 (d, J = 4.2 Hz, 1H), 5.84 (d, J = 4.2 Hz, 1H), 7.32 (s, 1H), 8.01-8.35 (m, 4H). ESI-MS: *m/z* 454 (M^+), 455 (M^++1). Anal. Calcd. for $C_{18}H_{15}N_4NaO_7S$: C, 47.58; H, 3.33; N, 12.33%. Found: C, 47.39; H, 3.25; N, 12.26%.

6-3-(3-Trifluoromethylphenyl)isoxazole-5-carboxamido-penicillanate sodium 7j

Yield: 2.23 g, 67%. m.p. 89 °C (dec.). IR (KBr): υ 3403 (NH, amide), 1781 (C=O, lactam), 1686 (C=O, amide), 1606 (C=O, carboxylate ion), 1571 (NH, amide), 1561, 1439 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.64 (s, 3H), 1.75 (s, 3H), 4.56 (s, 1H), 5.65 (d, J = 4.4 Hz, 1H), 5.88 (d, J = 4.4 Hz, 1H), 7.30 (s, 1H), 7.48-7.94 (m, 4H). ESI-MS: *m/z* 477 (M^+). Anal. Calcd. for $C_{19}H_{15}F_3N_3NaO_5S$: C, 47.80; H, 3.17; N, 8.80%. Found: C, 47.66; H, 3.08; N, 8.67%.

6-3-(4-Trifluoromethylphenyl)isoxazole-5-carboxamido-penicillanate sodium 7k

Yield: 2.13 g, 64%. m.p. 105 °C (dec.). IR (KBr): υ 3409 (NH, amide), 1780 (C=O, lactam), 1681 (C=O, amide), 1604 (C=O, carboxylate ion), 1576 (NH, amide), 1567, 1436 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.64 (s, 3H), 1.75 (s, 3H), 4.56 (s, 1H), 5.65 (d, *J* = 4.2 Hz, 1H), 5.88 (d, *J* = 4.2 Hz, 1H), 7.31 (s, 1H), 7.41 (m, 2H), 7.94 (m, 2H). ESI-MS: *m/z* 477 (M^+). Anal. Calcd. for $C_{19}H_{15}F_3N_3NaO_5S$: C, 47.80; H, 3.17; N, 8.80%. Found: C, 47.69; H, 3.08; N, 8.75%.

6-3-(2,4-Dichlorophenyl)isoxazole-5-carboxamido-penicillanate sodium 7l

Yield: 2.40 g, 72%. m.p. 141 °C (dec.). IR (KBr): υ 3417 (NH, amide), 1796 (C=O, lactam), 1701 (C=O, amide), 1608 (C=O, carboxylate ion), 1581 (NH, amide), 1559, 1439 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.62 (s, 3H), 1.74 (s, 3H), 4.56 (s, 1H), 5.65 (d, *J* = 4.2 Hz, 1H), 5.88 (d, *J* = 4.2 Hz, 1H), 7.31 (s, 1H), 7.49-7.85 (m, 3H). ESI-MS: *m/z* 477 (M^+), 479 (M^++2), 481 (M^++4). Anal. Calcd. for $C_{18}H_{14}Cl_2N_3NaO_5S$: C, 45.20; H, 2.95; N, 8.79%. Found: C, 45.11; H, 2.79; N, 8.66%.

6-3-(3,4-Dichloropheny)isoxazole-5-carboxamido-penicillanate sodium 7m

Yield: 2.44 g, 73%. m.p. 123 °C (dec.). IR (KBr): υ 3431 (NH, amide), 1799 (C=O, lactam), 1701 (C=O, amide), 1608 (C=O, carboxylate ion), 1581 (NH, amide), 1559, 1439 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.64 (s, 3H), 1.75 (s, 3H), 4.56 (s, 1H), 5.65 (d, *J* = 4.2 Hz, 1H), 5.88 (d, *J* = 4.2 Hz, 1H), 7.31 (s, 1H), 7.38-7.66 (m, 3H). ESI-MS: *m/z* 477 (M^+), 479 (M^++2), 481 (M^++4). Anal. Calcd. for $C_{18}H_{14}Cl_2N_3NaO_5S$: C, 45.20; H, 2.95; N, 8.79%. Found: C, 45.15; H, 2.87; N, 8.68%.

6-3-(2,4,5-Trichlorophenyl)isoxazole-5-carboxamido-penicillanate sodium 7n

Yield: 2.42 g, 68%. m.p. 136 °C (dec.). IR (KBr): υ 3423 (NH, amide), 1797 (C=O, lactam), 1706 (C=O, amide), 1609 (C=O, carboxylate ion), 1576 (NH, amide), 1557, 1440 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 Mhz): δ 1.64 (s, 3H), 1.75 (s, 3H), 4.56 (s, 1H), 5.65 (d, *J* = 4.2 Hz, 1H), 5.88 (d, *J* = 4.2 Hz, 1H), 7.33 (s, 1H), 7.78 (s, 1H), 7.85 (s, 1H). ESI-MS: *m/z* 511 (M^+), 513 (M^++2), 515 (M^++4), 517 (M^++6). Anal. Calcd. for $C_{18}H_{13}Cl_3N_3NaO_5S$: C, 42.17; H, 2.56; N, 8.20%. Found: C, 42.09; H, 2.43; N, 8.11%.

6-3-(3,4,5-Trichlorophenyl)isoxazole-5-carboxamido-penicillanate sodium 7o

Yield: 2.39 g, 67%. m.p. 146 °C (dec.). IR (KBr): υ 3426 (NH, amide), 1793 (C=O, lactam), 1703 (C=O, amide), 1606 (C=O, carboxylate ion), 1578 (NH, amide), 1554, 1441 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.64 (s, 3H), 1.75 (s, 3H), 4.56 (s, 1H), 5.65 (d, *J* = 4.4 Hz, 1H), 5.88 (d, *J* = 4.2 Hz, 1H), 7.30 (d, 1H), 7.31 (s, 1H), 7.82 (d, *J* = 1.9, 2H). ESI-MS: *m/z* 511 (M^+), 513 (M^++2), 515 (M^++4), 517 (M^++6). Anal. Calcd. for $C_{18}H_{13}Cl_3N_3NaO_5S$: C, 42.17; H, 2.56; N, 8.20%. Found: C, 42.01; H, 2.47; N, 8.13%.

6-3-(Pyridin-2-yl)isoxazole-5-carboxamido-penicillanate sodium 7p

Yield: 2.01 g, 70%. m.p. 101 °C (dec.). IR (KBr): υ 3423 (NH, amide), 1794 (C=O, lactam), 1713 (C=O, amide), 1605 (C=O, carboxylate ion), 1582 (NH, amide), 1558, 1436 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.64 (s, 3H), 1.76 (s, 3H), 4.56 (s, 1H), 5.65 (d, *J* = 4.4 Hz, 1H), 5.88 (d, *J* = 4.4 Hz, 1H), 7.34 (s, 1H), 7.59-8.68 (m, 4H). ESI-MS: *m/z* 410 (M^+). Anal. Calcd. for $C_{17}H_{15}N_4NaO_5S$: C, 49.75; H, 3.68; N, 13.65%. Found: C, 49.66; H, 3.59; N, 13.61%.

6-3-(Pyridin-4-yl)isoxazole-5-carboxamido-penicillanate sodium 7q

Yield: 2.23 g, 71%. m.p. 89 °C (dec.). IR (KBr): υ 3429 (NH, amide), 1789 (C=O, lactam), 1714 (C=O, amide), 1608 (C=O, carboxylate ion), 1581 (NH, amide), 1551, 1438 (isoxazolyl ring) cm^{-1}. ^1H NMR (D_2O, 400 MHz): δ 1.66 (s, 3H), 1.77 (s, 3H), 4.56 (s, 1H), 5.64 (d, *J* = 4.4 Hz, 1H), 5.89 (d, *J* = 4.4 Hz, 1H), 7.35 (s, 1H), 8.01-8.63 (m, 4H). ESI-MS: *m/z* 410 (M^+). Anal. Calcd. for $C_{17}H_{15}N_4NaO_5S$: C, 49.75; H, 3.68; N, 13.65%. Found: C, 49.69; H, 3.58; N, 13.53%.

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