SYNTHESIS OF (S)-3-CARBOBENZOXYAMINO-1-AMINO-2-AZETIDINONES

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Abstract: Cyclization of amino acid hydrazide afforded a new class of heteroatom activated β-lactams. These compounds are potent parent nuclei which possess significant biological activity.

Naturally occurring monobactams 1 (sulfazecin) 2 and related monosulfactams 2 3 are known to have unusually active β-lactam carbonyl grouping by the presence of electronegative heteroatom on the ring nitrogen. Based on this heteroatom induced activation 4 (S)-3-acyl-amino-1-amino-2-azetidinones 3 are expected to provide another candidate of activated β-lactams. Herein we describe the preparation of (S)-3-carbobenzoxyamino-1-amino-2-azetidinone 4, a synthetic intermediate of 3. Our interest is to prepare a new parent nucleus which may possess significant biological activities.

The key step in the preparation of 4 is the cyclization of N-protected α-amino acid hydrazides 5 to β-lactams (eq. 1). We have found that N-protected α-amino acid hydrazides 5 could cyclize to β-lactams under the same conditions as the hydroxamate-mediated synthesis of β-lactams reported by Miller et al. 5 Due to the lability of β-lactam ring, the choice of the appropriate protecting group was important in designing a synthetic route. Especially neither R 4 nor R 5 should be a hydrogen atom in order to prevent the formation of five-membered ring in the cyclization step. Furthermore, the nitrogen component R 4 R 5 NNH- should be a good nucleophile for the later cyclization. Therefore we have chosen N-aminophthalimide as a nitrogen component.
As shown in Scheme I, N-carbobenzyo-L-serine 6 was treated with p-nitrobenzyl bromide and triethylamine in ethyl acetate to provide p-nitrobenzyl ester 7 (86%). A crystalline compound 8 was obtained by O-alkylation followed by a chromatographic separation on silica gel (90%). Removal of the p-nitrobenzyl group with 2N NaOH in aq. dioxane followed by the treatment with dicyclohexylamine(DCHA) gave dicyclohexylammonium salt 9 (94%). The free acid obtained by acidification was esterified to 10 with DCC / 1-hydroxybenztriazole (96%). Coupling of 10 with N-aminophthalimide gave 11 which was separated by chromatography on silica gel and was recrystallized from ethyl acetate-n-hexane (71% from 9). Removal of the t-butyl group with anisole and trifluoroacetic acid followed by recrystallization gave 12 (87%). Our initial attempt to prepare 12 was a coupling of 13, prepared from L-serine and 1-hydroxybenztriazole, with N-aminophthalimide. However no desired product 12 was obtainable by the low solubility of N-aminophthalimide below room temperature. Attempts at higher temperature (e.g. reflux in THF) gave predominantly self-condensation products of 13 with a trace amount of 12.
Our first approach toward the cyclization of 12 to β-lactam 15 utilized the intramolecular substitution reaction (Scheme IIa) of mesylate 14 which was obtained by treatment of 12 with methanesulfonyl chloride in pyridine (81%). The mesylate 14 was added portionwise to boiling acetone in the presence of potassium carbonate. However, the desired product 15 was obtained only in a low yield (14% from 14 after chromatography on silica gel by eluting with toluene-ethyl acetate). Unfortunately, the dehydro amino acid amide 16 was isolated as a main product. We therefore turned our attention to the cyclization under Mitunobu condition (Scheme IIb). The desired reaction proceeded smoothly. Thus, the reaction of 12 with triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) followed by repeated chromatographic separation on silica gel by eluting with toluene-ethyl acetate (5:1) gave 15 as a colorless crystal (75%). Removal of the phthaloyl group by the method of Kamiya et al. and chromatography (silica gel, ethyl acetate) afforded 4 in 61% yield (Scheme III). All of the spectroscopic data were in accord with the desired structure 4. To make sure the availability of 4, N-sulfonation was conducted on N-amino β-lactam 4. Thus, the treatment of 4 with pyridine-sulfur trioxide complex (3 equiv.) in pyridine for 2 h at room temperature followed by an ion-pair workup afforded the sulfonate 17 in 36% yield.

Syntheses of appropriate analogues starting from 15 are in progress.
EXPERIMENTAL SECTION

General. All reactions were carried out under nitrogen atmosphere. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Solvents were generally purified and dried by standard methods before use. Melting points were determined using a Büchi 510 apparatus and are uncorrected. Proton nuclear magnetic resonance (1H-nmr) spectra were obtained on a Varian EM-390 (90MHz) spectrometer; chemical shifts are expressed in ppm downfield from internal tetramethylsilane. 1H-nmr data are tabulated in the order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. Infrared (ir) spectra were obtained on a Shimadzu IR-430 spectrophotometer in the indicated phase. Mass spectra were taken on a JEOL DX-300 mass spectrometer. Analytical thin-layer chromatography (tlc) was performed on Merck silica gel 60 F254 glass-backed plates. Column chromatography was done using Merck silica gel 60 (70-230 mesh).

N-Carbobenzoxy-L-serine p-nitrobenzyl ester (7). This was prepared from N-carbobenzoxy-L-serine by using literature method. Yield 86%; 1H-nmr (CDCl3) δ 2.27 (t, 1H, J = 5.4 Hz), 3.9-4.1(m, 2H), 4.4-4.6(m, 1H), 5.11(s, 2H), 5.26(s, 2H), 5.6-5.9(bd, 1H, J = 6.3 Hz), 7.33(s, 5H), 7.47(d, 2H, J = 7.8 Hz), 8.17(d, 2H, J = 7.8 Hz); ir(KBr)1740, 1687cm⁻¹ (C=O); tlc(silica gel, ethyl acetate-n-hexane, 2:1) Rf=0.46.

O-t-Butyl-N-carbobenzoxy-L-serine p-nitrobenzyl ester (8). This was prepared from 7 by using literature method. Yield 90%; 1H-nmr(CDCl3) δ 1.12(s, 9H), 3.57(dd, 1H, J = 3.0 and 8.4 Hz), 3.84(dd, 1H, J = 2.4 and 8.4 Hz), 4.4-4.6(m, 1H), 5.10(s, 2H), 5.24(s, 2H), 5.45-5.70(bd, 1H, J = 7.5 Hz), 7.32(s, 5H), 7.45(d, 2H, J = 7.5 Hz), 8.15(d, 2H, J = 7.5 Hz); ir(KBr)1743, 1708cm⁻¹ (C=O); tlc(silica gel, ethyl acetate-n-hexane, 1:1) Rf=0.24.

O-t-Butyl-N-carbobenzoxy-L-serine dicyclohexylamine salt (9). This was prepared from 8 by using literature method. Yield 94%; mp 145-146°C (lit. 149-150 °C).
O-t-Butyl-N-carbobenzoxy-L-serine 1-hydroxybenztriazole ester (10). The cyclohexylamine salt 9 (4.76 g, 10 mmol) was suspended in 100 ml of Et₂O and 100 ml of H₂O. The pH was adjusted to 2.5 with 0.5M citric acid. The Et₂O layer was washed (H₂O and then brine), dried (MgSO₄) and concentrated in vacuo to give O-t-butyl-N-carbobenzoxy-L-serine as a colorless amorphous powder: yield 2.84 g (100%); ¹H-nmr (CDCl₃) δ 1.16 (s, 9H), 3.56(dd, 1H, J= 3.6 and 10 Hz), 3.88(dd, 1H, J= 2.4 and 10 Hz), 4.4-4.6(m, 1H), 5.10(s, 2H), 5.5-5.7(bd, 1H, J= 7.5 Hz), 7.33 (s, 5H), 9.71(b, 1H). To a cooled (0°C) solution of O-t-butyl-N-carbobenzoxy-L-serine prepared above and 1-hydroxybenztriazole (1.30 g, 9.63 mmol) in 30 ml of THF was slowly added dicyclohexylcarbodiimide (1.98 g, 9.63 mmol) with stirring. The mixture was stirred at 0°C for 1 h and then at room temperature for another 1 h. After filtration the filtrate was concentrated in vacuo to give an oil, which was suspended in 50 ml of AcOEt, filtered, and concentrated in vacuo to afford 10 as a colorless oil: yield 3.97 g (96%); ¹H-nmr(CDCl₃) δ 1.28(s, 9H), 3.79(dd, 1H, J= 4.2 and 10 Hz), 4.10 (dd, 1H, J= 3.0 and 10 Hz), 4.8-5.1(m, 1H), 5.16(s, 2H), 5.6-5.8(bd, 1H, J= 7.5 Hz), 7.3-8.1(m, 9H); ir(neat)1708 cm⁻¹ (C=O).

O-t-Butyl-α-N-carbobenzoxy-N-phthalyl-L-serine carboxamide (11). To a solution of 10 (3.97 g, 9.63 mmol) in 50 ml of THF was added N-aminophthalamide (1.56 g, 9.63 mmol) and the mixture was stirred at reflux for 2 h. The solvent was removed in vacuo to give an oil, which was subjected to chromatographic separation (silica gel 200 g, toluene-ethyl acetate, 3:1) followed by recrystallization from ethyl acetate-hexane to afford 11 as a colorless powder: yield 2.98 g (71%); ¹H-nmr(CDCl₃) δ 1.27(s,9H), 3.50 (dd, 1H, J=8.5 and 8.5 Hz), 3.85(dd, 1H, J=8.5 and 4.3 Hz), 4.4-4.6(m, 1H), 5.11(s, 2H), 5.55-5.75 (bd, 1H, J= 6.0 Hz), 7.33 (s, 5H), 7.6-7.95(m, 4H), 8.75(b, 1H); ir(KBr)1792, 1730, 1700,1680 cm⁻¹ (C=O); mass spectrum(FD) m/z 439(M⁺); tlc(silica gel, ethyl acetate-hexane, 1:1) Rf=0.68.

α-N-Carbobenzoxy-N-phthalyl-L-serine carboxamide (12). The amide 11 (1.76 g, 4.0 mmol) was dissolved in a mixture of anisole (2.0 ml) and trifluoroacetic acid (10 ml). The mixture was stirred at room temperature for 3 h. Trifluoroacetic acid was removed in vacuo below 30°C to give a brownish oil, which was suspended in 100 ml of Et₂O and was stirred for 1 h at room temperature. After filtration, the obtained powder was washed with Et₂O and recrystallized from ethyl acetate-ethanol to give 12 as a white powder: yield 1.33 g (87%); ¹H-nmr(DMSO-d⁶) δ 3.7-3.9(m, 1H), 4.35-4.6(m, 1H), 4.65-4.85(m,
\( \text{H}, 5.09 \text{ (s, 2H)}, 6.8-7.0 \text{(bd, 1H, J= 7.5 Hz)}, 7.33 \text{(m, 5H)}, 7.83 \text{(m, 4H)}; \text{ir(KBr)} \\
1790, 1730, 1690, 1675 \text{cm}^{-1} \text{(C=O)}; \text{mass spectrum(FD) m/z 383(M^+)}; \text{tlc(silica gel, ethyl acetate-n-hexane, 2:1) Rf=0.22.} \\
\text{(3S)-3-Carbobenzoxyamino-1-phthalyl-2-azetidinone (15).} \\
\text{Method A (Scheme II a).}^{7} \\
\text{O-Mesy1-}\alpha\text{-N-carbobenzoxy-1-phthalyl-L-serine carboxamid e (14).} \\
\text{To a solution of 12 (0.383 g, 1.0 mmol) in 1 ml of anhydrous pyridine was added methanesulfonyl chloride (0.086 ml, 1.1 mmol) at 0°C and the mixture was stirred at 0°C for 2.5 h.} \\
\text{To the reaction mixture was added 10 ml of 1N HCl cooled to 0°C and all were extracted with ethyl acetate (20 ml x2). The combined extracts were washed (1N HCl cooled to 0°C, satd. aq. NaHCO}_3, H_2O and finally brine), dried (MgSO}_4, and concentrated in vacuo to give 14 as a colorless oil: yield 0.371 g (81%); \text{H-nmr(CDC}_3) \delta 3.03 \text{ (s, 3H)}, 4.37 \text{(dd, 1H, J= 4.8 and 10 Hz)}, 4.62 \text{(dd, 1H, J= 4.2 and 10 Hz)}, 4.75-5.0 \text{(m, 1H)}, 5.09 \text{(s, 2H)}, 5.8-6.2 \text{(bd, 1H, J= 7.5 Hz)}, 7.28 \text{(s, 5H)}, 7.6-7.9 \text{(m, 4H)}, 8.92 \text{(b, 1H)}; \text{tlc(silica gel, toluene-ethyl acetate, 2:1) Rf=0.20.} \\
\text{(3S)-3-Carbobenzoxyamino-1-phthalyl-2-azetidinone (15).} \\
\text{To a boiling suspension of potassium carbonate (0.320 g, 2.32 mmol) in 45 ml of acetone was added a solution of 14 (0.356 g, 0.77 mmol) in 5 ml of acetone. After the addition, the mixture was stirred at reflux for 1 h. After filtration, the filtrate was washed (1N HCl, satd. aq. NaHCO}_3, H_2O and brine in order), dried (MgSO}_4, and concentrated in vacuo to afford an oil.} \\
\text{Chromatographic separation on silica gel (6 g, toluene-ethyl acetate, 5:1) gave 15 as a white powder: yield 38 mg (14%); \text{H-nmr(CDC}_3) \delta 3.76 \text{(dd, 1H, J= 4.8 and 2.6 Hz)}, 4.07 \text{(dd, 1H, J= 4.8 and 5.1 Hz)}, 5.1-5.3 \text{(m, 1H)}, 5.13 \text{(s, 2H)}, 5.5-5.8 \text{(bd, 1H, J= 6.6 Hz)}, 7.34 \text{(s, 5H)}, 7.7-8.0 \text{(m, 4H)}; \text{ir(KBr)} 1802, 1775, 1723, 1680 \text{cm}^{-1} \text{(C=O)}; \text{mass spectrum (FD) m/z 366(M^+1)}; \text{tlc(silica gel, toluene-ethyl acetate, 5:1) Rf=0.13.} \\
\text{Method B (Scheme II b).}^{7} \\
\text{To a solution of 12 (1.00 g, 2.61 mmol) in 50 ml of THF was added triphenylphosphine (0.821 g, 3.13 mmol). To the obtained mixture was added a solution of diethyl diazocarboxylate (0.545 g, 3.13 mmol) in 20 ml of THF over 30 min at 0°C. After the addition, the reaction was stirred at room temperature for 3 h. The solvent was removed in vacuo to give a powder, which was subjected to chromatographic separation (silica gel 60 g, toluene-ethyl acetate, 5:1) to afford 15 as a white powder: yield 0.711 g (75%). The spectral data were identical with those of 15 prepared above.}
(3S)-3-Carbobenzoxyamino-1-amino-2-azetidinone (4). To a solution of 15 (0.365 g, 1.0 mmol) in 6 ml of methanol were added NEt₃ (0.28 ml, 2.0 mmol) at 0°C and 3-dimethylamino-n-propylamine (0.26 ml, 2.2 mmol). The mixture was stirred at room temperature for 7 h. The solvent was removed in vacuo to give an oil. Chromatographic separation on silica gel (10 g, pure ethyl acetate) gave 4 as a white powder: yield 0.144 g (61%); ¹H-nmr (DMSO-d₆, D₂O) δ 3.27 (dd, 1H, J=5.0 and 2.4 Hz), 3.56 (dd, 1H, J=5.0 and 5.0 Hz), 4.48 (dd, 1H, J=5.0 and 2.4 Hz), 5.02 (s, 2H), 7.34 (s, 5H); ir(KBr) 1773, 1683 cm⁻¹ (C=O); mass spectrum (FD) m/z 235 (M⁺); tlc (silica gel, pure ethyl acetate) Rf=0.13.

(3S)-3-Carbobenzyoxamino-1-sulphoamino-2-azetidinone tetra-n-butyl-ammonium salt (17). To a solution of 15 (23.5 mg, 0.1 mmol) in 1 ml of pyridine was added pyridine-sulfur trioxide complex (47.7 mg, 0.3 mmol). The mixture was stirred at room temperature for 2 h. To the reaction mixture were added 20 ml of 0.5N KH₂PO₄ and the obtained solution was extracted with CH₂Cl₂ (20 ml x 2). The extracts were washed with 0.5N KH₂PO₄ and the washings were combined with the above aqueous layer. To the combined aqueous layer was added (n-Bu)₄NHSO₄ (33.9 mg, 0.1 mmol). After stirring at room temperature for 5 min, the mixture was extracted with CH₂Cl₂ (10 ml x 4). The extracts were dried (MgSO₄) and was concentrated in vacuo to give 17 as a colorless oil: yield 20.1 mg (36%); ¹H-nmr (CDCl₃) δ 0.8-1.8 (m, 28H), 3.0-3.4 (m, 8H), 3.69 (dd, 1H, J= 4.8 and 2.4 Hz), 4.02 (dd, 1H, J= 4.8 and 4.8 Hz), 4.6-4.9 (m, 1H), 5.05 (s, 2H), 5.78 (bs, 1H), 5.91 (bd, 1H, J= 7.5 Hz), 7.30 (s, 5H); ir(neat) 1770, 1710 cm⁻¹ (C=O).

REFERENCES AND NOTES


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