

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

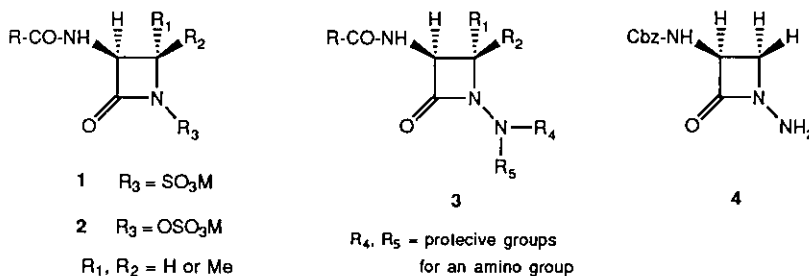
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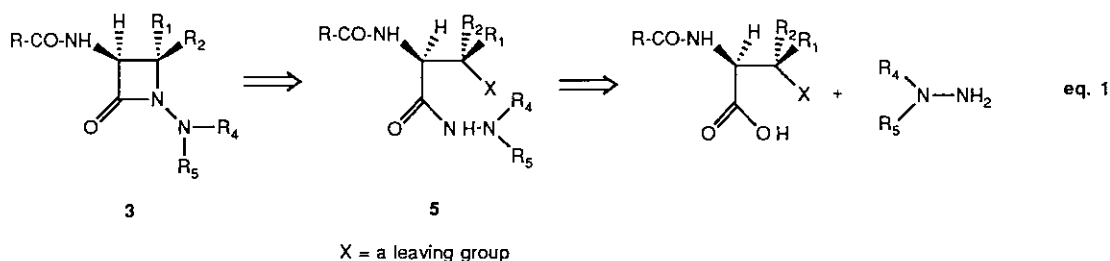
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Abstract- Cyclization of amino acid hydrazide afforded a new class of heteroatom activated β -lactams. These compounds are potent parent nuclei which possess significant biological activity.

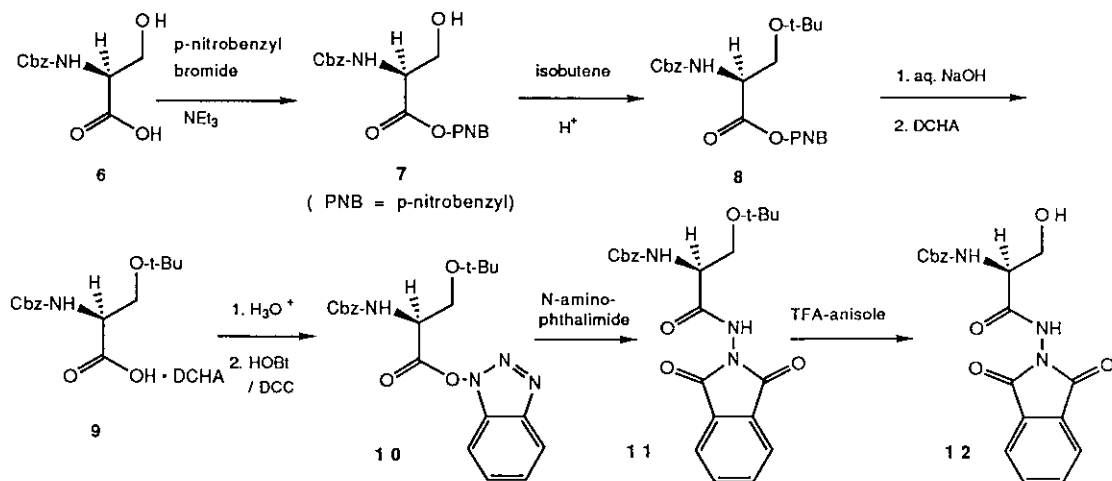
Naturally occurring monobactams **1**¹ (sulfazecin)² and related monosulfactams **2**³ are known to have unusually active β -lactam carbonyl grouping by the presence of electronegative heteroatom on the ring nitrogen. Based on this heteroatom induced activation⁴ (S)-3-acylamino-1-amino-2-azetidinones **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.



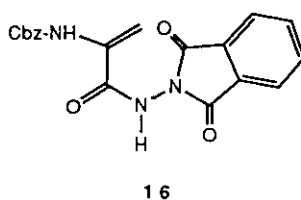
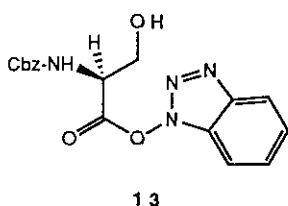
The key step in the preparation of **4** is the cyclization of N-protected α -amino acid hydrazides **5** to β -lactams (eq. 1). We have found that N-protected α -amino acid hydrazides **5** could cyclize to β -lactams under the same conditions as the hydroxamate-mediated synthesis of β -lactams reported 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 $R_4R_5\text{NNH-}$ should be a good nucleophile for the later cyclization. Therefore we have chosen N-aminophthalimide as a nitrogen component.



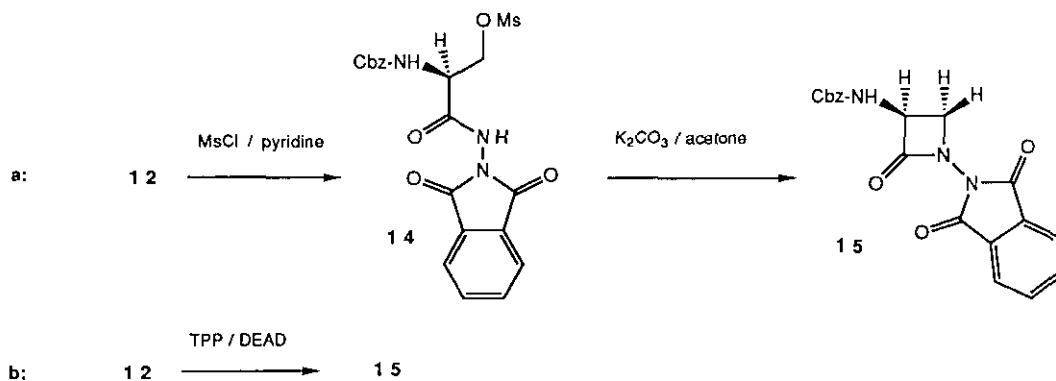
As shown in Scheme I, N-carbobenzoxy-L-serine **6** was treated with p-nitrobenzyl bromide and triethylamine in ethyl acetate to provide p-nitrobenzyl ester **7**⁶ (86%). A crystalline compound **8**⁶ was obtained by O-alkylation followed by a chromatographic separation on silica gel (90%). Removal of the p-nitrobenzyl group with 2N NaOH in aq. dioxane followed by the treatment with dicyclohexylamine(DCHA) gave dicyclohexylammonium salt **9**⁶ (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**.



Scheme I



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.⁷ 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 Mitsunobu condition (Scheme IIb).⁸ 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.⁹ 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 workup⁷ afforded the sulfonate **17** in 36% yield. Syntheses of appropriate analogues starting from **15** are in progress.



Scheme II



— 532 —

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) 1820, 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-aminophthalimide (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,

1H), 5.09 (s, 2H), 6.8-7.0(bd, 1H, J= 7.5 Hz), 7.33(m, 5H), 7.83(m, 4H); ir(KBr) 1790, 1730, 1690, 1675 cm^{-1} (C=O); mass spectrum(FD) m/z 383(M^+); tlc(silica gel, ethyl acetate-n-hexane, 2:1) Rf=0.22.

(3S)-3-Carbobenzoxamino-1-phthalyl-2-azetidinone (15).

Method A(Scheme II a).⁷

O-Mesyl- α -N-carbobenzoxo-N-phthalyl-L-serine carboxamide (14).

To a solution of **12** (0.383 g, 1.0 mmol) in 1 ml of anhydrous pyridine was added methane-sulfonyl chloride (0.086 ml, 1.1 mmol) at 0°C and the mixture was stirred at 0°C for 2.5 h. 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%); ^1H -nmr(CDCl_3) δ 3.03(s,3H), 4.37(dd, 1H, J= 4.8 and 10 Hz), 4.62 (dd, 1H, J= 4.2 and 10 Hz), 4.75-5.0(m, 1H), 5.09(s, 2H), 5.8-6.2(bd, 1H, J= 7.5 Hz), 7.28(s, 5H), 7.6-7.9(m, 4H), 8.92(b, 1H); tlc(silica gel, toluene-ethyl acetate, 2:1) Rf=0.20.

(3S)-3-Carbobenzoxamino-1-phthalyl-2-azetidinone (15). 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.

Chromatographic separation on silica gel (6 g, toluene-ethyl acetate, 5:1) gave **15** as a white powder: yield 38 mg (14%); ^1H -nmr(CDCl_3) δ 3.76(dd, 1H, J=4.8 and 2.6 Hz), 4.07(dd, 1H, J=4.8 and 5.1 Hz), 5.1-5.3(m, 1H), 5.13(s, 2H), 5.5-5.8(bd, 1H, J= 6.6 Hz), 7.34 (s, 5H), 7.7-8.0(m, 4H); ir(KBr) 1802, 1775, 1723, 1680 cm^{-1} (C=O); mass spectrum (FD) m/z 366(M^++1); tlc(silica gel, toluene-ethyl acetate, 5:1) Rf=0.13.

Method B(Scheme II b).⁷

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 diazocarbonate (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-Carbobenzoxamino-1-amino-2-azetidinone (4). To a solution of **15** (0.365 g, 1.0 mmol) in 6 ml of methanol were added NEt_3 (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%); $^1\text{H-nmr}$ (DMSO-d_6 , D_2O) 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^+); $\text{tlc(silica gel, pure ethyl acetate)}$ $\text{Rf}=0.13$.

(3S)-3-Carbobenzoxamino-1-sulphoamino-2-azetidinone tetra-n-butylammonium 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 KH_2PO_4 and the obtained solution was extracted with CH_2Cl_2 (20 ml x 2). The extracts were washed with 0.5 N KH_2PO_4 and the washings were combined with the above aqueous layer. To the combined aqueous layer was added $(\text{n-Bu})_4\text{NHSO}_4$ (33.9 mg, 0.1 mmol). After stirring at room temperature for 5 min, the mixture was extracted with CH_2Cl_2 (10 ml x 4). The extracts were dried (MgSO_4) and was concentrated in vacuo to give **17** as a colorless oil: yield 20.1 mg (36%); $^1\text{H-nmr}(\text{CDCl}_3)$ 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).

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