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

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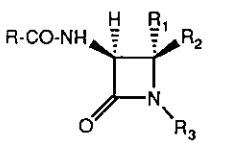
Abstract- Cyclization of amino acid hydrazide afforded a new class of heteroatom activated ß-lactams. These compounds are potent parent nuclei which possess significant biological activity.

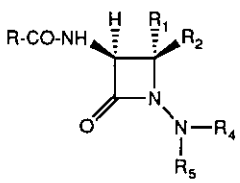
Naturally occurring monobactams **1** [1](sulfazecin)[2] and related monosulfactams **2** [3] are known to have unusually active ß-lactam carbonyl grouping by the presence of electronegative heteroatom on the ring nitrogen. Based on this heteroatom induced activation[4] (S)-3-acylamino-1-amino-2-azetidinones **3** are expected to provide another candidate of activated ß-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.



1 $R_3 = SO_3M$

2 $R_3 = OSO_3M$

R_1, R_2 = H or Me



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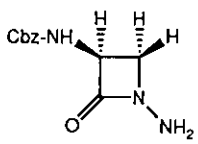
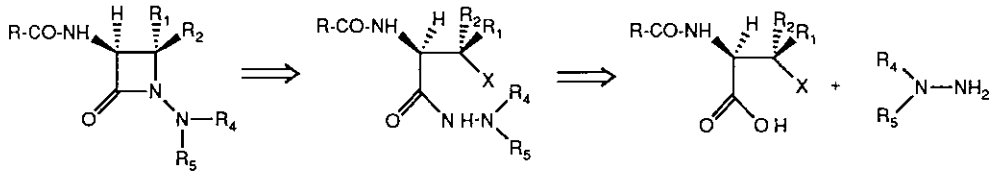
R_4, R_5 = protecive groups for an amino group



4

The key step in the preparation of **4** is the cyclization of N-protected α–amino acid hydrazides **5** to ß-lactams (eq. 1). We have found that N-protected α–amino acid hydrazides **5** could cyclize to ß-lactams under the same conditions as the hydroxamate-mediated synthesis of ß-lactams reported by Miller et al.[5] Due to the lability of ß-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_5NNH- should be a good nucleophile for the later cyclization. Therefore we have chosen N-aminophthalimide as a nitrogen component.

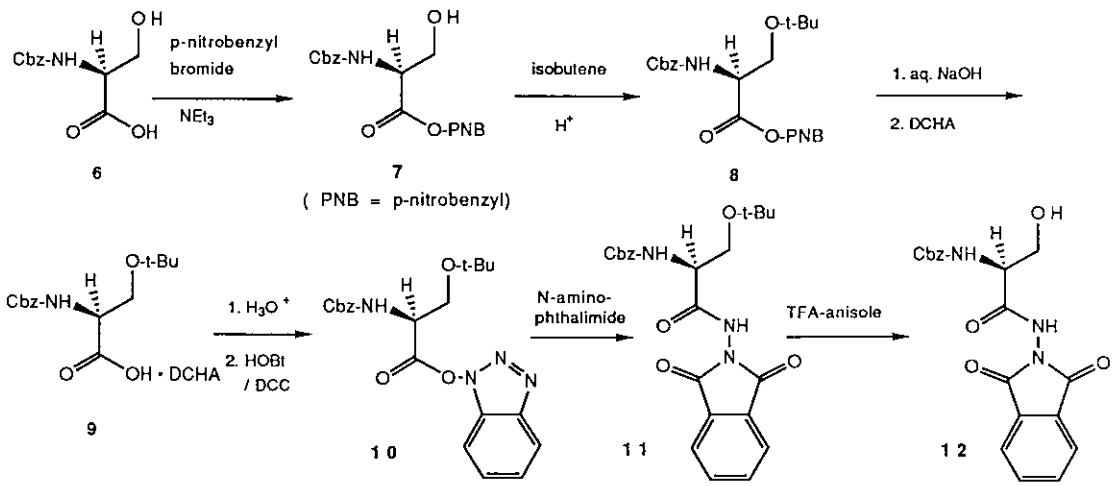


eq. 1

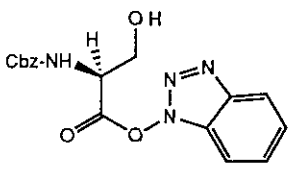
3 5

X = a leaving group

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-aminophthlimide. 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



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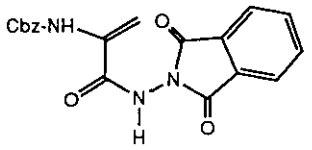

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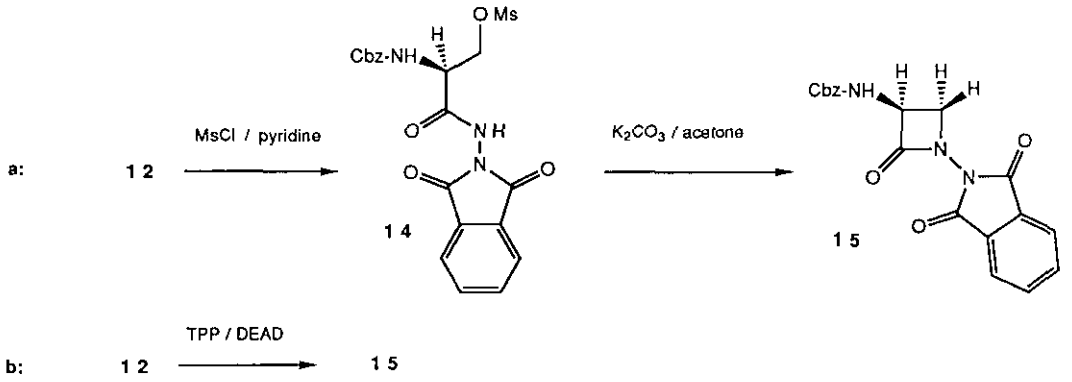
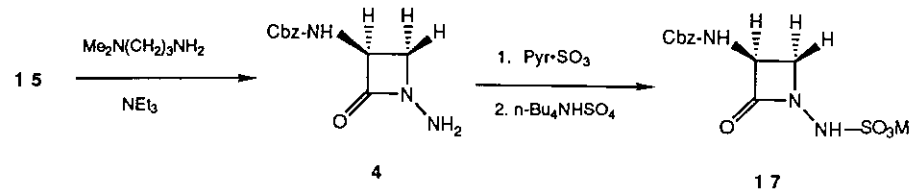
Our first approach toward the cyclization of **12** to ß-lactam **15** utilized the intramolecular substitution reaction (Scheme IIa)of mesylate **14** which was obtained by treatment of **12** with methanesulfonyl chloride in pyridine (81%). The mesylate **14** was added portionwise to boiling acetone 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 cyclizaton under Mitunobu 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 ß-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[7] afforded the sulfonate **17** in 36% yield.

Syntheses of appropriate analogues starting from **15** are in progress.



Scheme II



Scheme III

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[10] before use. Melting points were determined using a Büchi 510 apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-nmr) spectra were obtained on a Varian EM-390 (90MHz) spectrometer; chemical shifts are expressed in ppm downfield from internal tetramethylsilane. ^{1}H-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 F_{254} 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.[6] Yield 86%; ^{1}H-nmr ($CDCl_3$) δ2.27 (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.[6] Yield 90% ;^{1}H-nmr($CDCl_3$) δ1.12(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.[6] Yield 94%; mp 145-146°C (lit.[6] 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 Et_2O and 100 ml of H_2O. The pH was adjusted to 2.5 with 0.5M citric acid. The Et_2O layer was washed (H_2O and then brine), dried ($MgSO_4$) and concentrated in vacuo to give O-t-butyl-N-carbobenzoxy-L-serine as a colorless amorphous powder: yield 2.84 g (100%); ^{1}H-nmr ($CDCl_3$) δ1.16 (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%); ^{1}H-nmr($CDCl_3$) δ1.28(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 , 1708cm^{-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-aminophthlimide (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%); ^{1}H-nmr ($CDCl_3$) δ1.27(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, 1700,1680cm^{-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 Et_2O and was stirred for 1 h at room temperature. After filtration, the obtained powder was washed with Et_2O and recrystallized from ethyl acetate-ethanol to give **12** as a white powder: yield 1.33 g (87%); ^{1}H-nmr(DMSO-d^6) δ3.7-3.9(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-Carbobenzoxyamino-1-phthalyl-2-azetidinone (15).

Method A(Scheme II a).[7]

O-Mesyl-α-N-carbobenzoxy-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 methanesulfonyl 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%); ^{1}H-nmr($CDCl_3$) δ3.03(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-Carbobenzoxyamino-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%); ^{1}H-nmr($CDCl_3$) δ3.76(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, 1680cm^{-1} (C=O); mass spetrum (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 diazocarboxlate (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 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}H-nmr (DMSO-d^6, D_2O)δ3.27(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-Carbobenzoxyamino-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 $(n\text{-}Bu)_4NHSO_4$ (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}H-nmr($CDCl_3$) δ0.8-1.8(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, 1710cm^{-1}(C=O).

REFERENCES AND NOTES

1. R. B. Sykes, C. M. Cimarusti, D. P. Bonner, K. Bush, D. M. Floyd, N. H. Geogopapadakou, W. H. Koster, W. C. Liu, W. L. Parker, P. A. Principe, M. L. Rathnum, W. A. Slusarchyk, W. H. Trejo, and J. S. Wells, Nature, **1981**, 291, 489. D. M. Floyd, A. W. Fritz, and C. M. Cimarusti, J. Org. Chem., **1982**, 47, 176. C. M. Cimarusti, H. E. Applegata, H. W. Chang, D. M. Floyd, A. W. Fritz, W. A. Slusarchyk, and M. G. Young, J. Org. Chem., **1982**, 47, 179.
2. A. Imada, K. Kitano, M. Muroi, and M. Asai, Nature, **1981**, 289, 590.
3. E. M. Gordon, M. A. Ondetti, J. Pluscec, C. M. Cimarusti, D. P. Bonner, and R. B. Sykes, J. Am. Chem. Soc., **1982**, 104, 6053.

4. S. R. Woulfe and M. J. Miller, Tetrahedron Lett., **1984**, 25, 3293. S. R. Woulfe and M. J. Miller, J. Med. Chem., **1985**, 28, 1447. S. R. Woulfe, H. Iwagami, and M. J. Miller, Tetrahedron Lett., **1985**, 26, 3891. H. Iwagami, S. R. Woulfe, and M. J. Miller, Tetrahedron Lett., **1986**, 27, 3095.
5. P. G. Mattingly, J. F., Jr. Kerwin, and M. J. Miller, J. Am. Chem. Soc., **1979**, 101, 3983. M. J. Miller, P. G. Mattingly, M. A. Morrison, and J. F., Jr. Kerwin, J. Am. Chem. Soc., **1980**, 102, 7026.
6. E. Wunsch and J. Jentsch, Chem. Ber., **1964**, 97, 2490.
7. D. M. Floyd, A. W. Fritz, J. Pluscec, E. R. Weaver, and C. M. Cimarusti, J. Org. Chem., **1982**, 47, 5160.
8. O. Mitunobu, Synthesis, **1981**, 1.
9. T. Kamiya, M. Hashimoto, O. Nakaguchi, and T. Oku, Tetrahedron, **1979**, 35, 323.
10. D. D. Perrin, W. F. L. Armarego, and D. R. Perrin, 'Purification of Laboratory Chemicals' Pergamon, Oxford, 1980.

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