An efficient and straightforward strategy for the synthesis of enantiomerically pure (S)-1-benzyl-5-(alkyl/aryl amino) methyl-pyrrolidin-2-ones

Sharad Kumar Panday*, Manoher Bhushan Pathak & Jagdish Prasad
Department of Chemistry, Faculty of Engineering & Technology, M.J.P. Rohilkhand University, Bareilly, India
E-mail: skpandey@mjpru.ac.in
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A simple, efficient and straightforward strategy for the synthesis of enantiomerically pure (S)-5-(alkyl/aryl amino) methyl-pyrrolidin-2-ones from N-benzyl-5(S)-pyroglutaminol through Mitsunobu reaction has been described. These pyrrolidin-2-ones have great potential to act as asymmetric precursors for the synthesis of bioactive compounds/natural products requiring suitably substituted aminomethyl group at C-5 of native pyrrolidin-2-ones.

Keywords: Enantiomerically pure, dysibetaine, 4,5-diaminovaleric acid (DAVA), conformationally restricted PNA analogues, (S)-5-((Alkyl/aryl amino) methyl) pyrrolidin-2-ones

Pyroglutamic acid is an inexpensive source of chirality for the synthesis of many of the bioactive natural/synthetic products such as (−)-anatoxin1, (−)-bulgicine2,3, (−)-domoic acid4, salinosporamide5, angiotensin converting enzyme (ACE) inhibitors6,7 and conformationally constrained peptides8,9. Last three decades have witnessed an exceptional outgrowth of publications on the chemistry/biology of unnatural amino acids especially those on pyroglutamates10,11. (S)-5-(Alkyl/arylamino)methyl pyrrolidin-2-ones 4 are not only the essential components of many bioactive natural products such as dysibetaine 1 (Ref 12), but are also the precursors for 4,5-diaminovaleric acid (DAVA) 2 (Ref 13). These also act as novel conformationally restricted peptide nucleic acid (PNA) analogues 3 (Ref 14) (Figure 1).

Even though the chemistry of pyroglutamates has been well explored10,11, the synthesis of (S)-5-(alkyl/arylamino)methylpyrrolidin-2-ones from pyroglutamic acid has received less attention15,16 and this has prompted us to study and standardize a procedure for the synthesis of such an important class of molecules from N-protected-5(S)-pyroglutaminol via the Mitsunobu reaction17. The Mitsunobu reaction is an efficient method for the reaction of alcohols with amines/amides/acids etc. furnishing a variety of products19-23. Even though the chemistry/stereochemistry of Mitsunobu reaction has been well studied, the reaction of pyroglutaminols with amines has been relatively less explored17. This fact prompted us to study the said reaction of N-benzyl-5(S)-pyroglutaminol 6 with various amines in presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (Ph3P) in tetrahydrofuran (THF), where (S)-1-benzyl-5-(alkyl/aryl/aralkylaminomethyl)-pyrrolidin-2-ones 4a-e were obtained in satisfactory yields. The probable mechanism for above stated Mitsunobu reaction of N-protected-5(S)-pyroglutaminol with amines in presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (Ph3P) is proposed in Figure 2.

Results and Discussion

To standardize the above reaction and to check the feasibility of our strategy, initial reaction of N-benzyl-5(S)-pyroglutaminol 6 with aniline 7a, was attempted, where (S)-1-benzyl-5-((phenyl amino)methyl)-pyrrolidin-2-one 4a, was obtained in 71% yield. Structural assignment of compound 4a was made on the basis of 1H NMR, where aromatic protons were observed in the region 6 7.24-7.64 as multiplets (10H). Further support to the assigned structure was obtained by MS spectroscopy, where molecular ion peak corresponding to the molecular weight of the compound was observed. To ensure that no racemization/epimerization had occurred during the reaction, chiral high performance liquid chromatography (HPLC) was performed using column chiral 1C, where only single prominent peak was obtained in better than 90% overall purity. The desired (S)-1-benzyl-5-(alkyl/aryl aminomethyl) pyrrolidin-2-ones 4b-e were obtained similarly in satisfactory yields (Scheme 1).

Experimental Section

Spectral data were recorded using: Perkin Elmer (FTIR); Jeol SX-102(FAB) (MS); Bruker Advance 300 (1H NMR), Rudolf Autopol III polarimeter (optical rotation); Elementar Vario EL III (elemental analysis). Tetrahydrofuran (THF) was distilled over sodium benzophenone ketyl and was used in Mitsunobu reactions. Chiral high performance liquid chromatography (HPLC) was performed on a D-7000 HPLC
Figure 1 — Applications of (S)-5-(alkyl/arylaminomethyl)pyrrolidin-2-ones

Figure 2 — Proposed mechanism for mitsunobu reaction using N-benzyl-5(S)-pyroglutaminol

Reagents and reaction conditions: (i). PhCHO, NaOH, NaBH₄; (ii). H₂O, Δ; (iii). MeOH, H⁺, NaBH₄; (iv). DEAD, Ph₃P, THF, R₁R₂NH (7a-e), rt, 7h

a) R₁=C₆H₅, R₂=H b) R₁=p-NO₂C₆H₄, R₂=H c) R₁=R₂=[CH(CH₃)₂]₂ d) R₁=CH₂C₆H₅, R₂=H e) R₁,N = — — N — — N — —

Scheme I
manager report system using column chiral 1C and using hexane as solvent.

N-benzyl-5(S)-pyroglutaminol 6. The compound 6 was synthesized from l-glutamic acid, 5 in three steps according to the procedure reported in literature. The data were compared and found to be identical with the reported values.

General procedure for the synthesis of compounds 4

N-Benzyl-5(S)-pyroglutaminol 6, (1.03 g, 5.0 mmol) was taken in THF (15 mL) and added to diethylzadecarboxylic acid (DEAD) (1.21 g, 1.4 eq) and triphenylphosphine (PPh3) (1.83 g, 1.4 eq), and the reaction mixture was stirred at RT for 30 min, after 30 min a solution of the amine (1.2 eq) in THF (10 mL) was added and the reaction mixture was stirred again at RT for 7 hr. The progress of the reaction was monitored by thin layer chromatography (TLC). At the completion of the reaction, the solvents were evaporated under vacuum to give a liquid which was poured into water (15 mL) and extracted twice with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine solution (15 mL), dried over sodium sulfate, concentrated and purified by column chromatography on silica gel using 20% EtOAc-hexane as eluent to give pure compounds 4a-e in satisfactory yields.

(S)-1-Benzyl-5(phenylaminomethyl) pyrrolidin-2-one 4a. Compound 4a was prepared from 6 (1.03 g, 5.0 mmol) and aniline 7a (0.55 g, 1.2 eq) according to the procedure described above and was obtained as a light yellow oil (1.0 g 71%); [α]D20-11.8 (C 1.0, MeOH); IR (KBr): 1673, 1711, 2365, 2985, 3729 cm⁻¹; 1H NMR (CDCl3): δ 1.93-2.11 (2H, m, H-4), 2.33-2.44 (1H, m, H-3), 2.51-2.62 (1H, m, H-2), 3.34-3.54 (2H, m, H-5 and H-6), 3.70-3.85 (2H, m, NHCH2), 7.45-7.64 (5H, m, ArH); 13C NMR (CDCl3): δ 21.35 (CH2NH), 31.97 (C-4), 45.15 (N-CH2Ph), 58.43 (C-3), 62.67 (C-5), 126.87, 128.72, 128.22 (aromatic carbons), 135.92 (C-2); MS: m/z 280 (M+), 279 (M-1), 206, 89, 75, 61. Anal. Calcd for C17H20N2O: C, 77.14; H, 7.14; N, 9.52. Found: C, 77.12; H, 7.21; N, 9.23%.

(S)-1-Benzyl-5(p-nitrophenylaminomethyl) pyrrolidin-2-one 4b. Compound 4b was prepared from 6 (1.03 g, 5.0 mmol) and p-nitroaniline 7b (0.73 g, 1.2 eq) according to the procedure described above and was obtained as a light yellow oil, (1.2 g 73%); [α]D25-28.5 (C 1.2, MeOH); IR (KBr): 1670, 1815, 3030, 3385 cm⁻¹; 1H NMR (CDCl3): δ 1.98-2.08 (2H, m, H-4), 2.30-2.40 (1H, m, H-3), 2.48-2.6 (1H, m, H-3'), 3.25-3.45 (3H, m, H-5+ CH2NH2), 3.70-3.85 (2H, m, NKCCH2Ph), 4.0-4.1 (1H, d, J = 15.0 Hz), N-CH2Ph), 7.1-7.3 (5H, m, ArH); MS: m/z 294 (M+), 206, 188, 105, 91. Anal. Calcd for C16H22N2O C, 77.55; H, 7.48; N, 9.52. Found: C, 77.12; H, 7.21; N, 9.23%.

(S)-1-Benzyl-5(piperidin-1-ylmethyl) pyrrolidin-2-one 4c. Compound 4c was prepared from 6 (1.03 g, 5.0 mmol) and piperidine 7d (0.64 g, 1.2 eq) according to the procedure described above and was obtained as a light yellow oil, (1.1 g 75%); [α]D25+19.7 (C 1.1, MeOH); IR (KBr): 1667, 1815, 2952, 3016, 3385 cm⁻¹; 1H NMR (CDCl3): δ 1.80-2.30 (8H, m, H-4+ H-3', H-4' and H-5 of piperidine ring), 2.35-2.70 (2H, m, H-3), 3.3-3.8 (7H, m, H-5+ CH2H2-2'and H-6' of piperidine ring), 4.05-4.2 (1H, d, J = 15.5 Hz), N-CH2Ph), 4.85-5.0 (1H, d, J = 15.0 Hz, N-CH2Ph), 7.1-7.4 (10H, m, ArH); MS: m/z 272 (M+), 206, 188, 91, 84. Anal. Calcd for C17H22N2O: C, 75; H, 8.82; N, 10.29. Found: C, 74.65; H, 8.46; N, 9.95%.
Conclusion

A simple, efficient and straightforward strategy for the synthesis of enantiomerically pure (S)-5-((alkyl/aryl amino) methyl)-pyrrolidin-2-ones from N-benzyl-5(S)-pyroglutaminol through Mitsunobu reaction has been developed. These (S)-5-((alkyl/aryl amino) methyl)-pyrrolidin-2-ones could be useful for the synthesis of complex natural products requiring alkyl/aryl amino methyl group at C-5 position of native pyrrolidin-2-one moiety.

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