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Asymmetric synthesis of 2,4,5- substituted prolines through 1,3-dipolar addition reaction of N-arylidene menthyl esters of α-aminoacid with methyl acrylate

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Proline and its derivatives constitute the important organic entities as organocatalyst, ACE inhibitors, bioactive molecules/intermediates to bioactive molecules as well as components of various natural products *e.g.* Kainic acid, (-)-domoic acid, *etc*. Due to its wide range of utility extensive studies have been made for the synthesis of 2, 3, 4 or 5 substituted prolines. One pot synthesis of 2,4,5-substituted prolines through 1,3-dipolar addition of various amino acids with homochiral acrylate has also been carried out successfully. Herein we wish to report the 1,3-dipolar addition of Schiff bases, where chiral auxiliary has been introduced in the Schiff bases and 1,3dipolar addition with methyl acrylate leading to the synthesis of 2(S),4(S),5(R)-substituted prolines has been achieved successfully.

Keywords: Asymmetric synthesis, α-amino acid, Schiff base, 1,3-dipolar addition, 2,4,5-substituted prolines

Proline and its derivatives have been recognized as important organic entities as organocatalyst[1], ACE inhibitors[2-4], bioactive molecules/intermediates to bioactive molecules[5-8] as well as components of various natural products *e.g.* Kainic acid[9-11], (−)-domoic acid[12], *etc*. Due to its wide range of utility extensive studies have been made for the synthesis of 2, 3,4 or 5 substituted prolines[13-19]. One pot syynthesis of 2,4,5-substituted prolines through 1,3-dipolar addition of various aminoacids with homochiral acrylate has also been carried out successfully[20-25]. 1,3-Dipolar additions have a long held reputation of being one of the most efficient transformations in organic synthesis[26,27]. These reactions provide functionally and stereochemical complex carbo and heterocyclic structures present as the key intermediates in many of the biologically active molecules. Transition metals specially Cu(I) and Ag(I) catalyzed 1,3-dipolar addition reaction of imines with various dipolarophiles have given a very effective outcome. Likewise use of lithium bromide and tetramethylenediamine using THF as the solvent in 1,3-dipolar addition reactions leading to the synthesis of substituted prolines has been quite successful[20-25]. Cycloaddition of a range of imines of α-aminoacid esters to homochiral menthylacrylate has been reported to proceed with complete asymmetric induction at room temperature in the presence of Ag(I) or Li(I) salt giving substituted prolines in one step.

We were interested in the synthesis of substituted prolines in relation to our ongoing research programme on the development of ACE inhibitors and since the 1,3-dipolar addition reactions have already provided effective outcome, we wished to attempt the same approach for the synthesis of 2,4,5-substituted prolines.

Results and Discussion

Earlier reports for the synthesis of 2,4,5-substituted prolines involved 1,3-dipolar addition of homochiral menthyl acrylate with Schiff bases obtained from various amino acid esters where 2(S),4(S),5(R)-substituted prolines were obtained in one step selectively[20-22], however there is no report in the literature till date where chiral auxilliary has been introduced in the Schiff bases and the reaction was attempted in similar manner with acrylate and therfore it was of particular interest for us to study the reaction pattern and the sterechemical out come by introducing menthyl chiral auxilliary in the amino acid itself prior to conversion to Schiff bases and then to look for the outcome of the product when 1,3-dipolar addition reaction is attempted with acrylate.

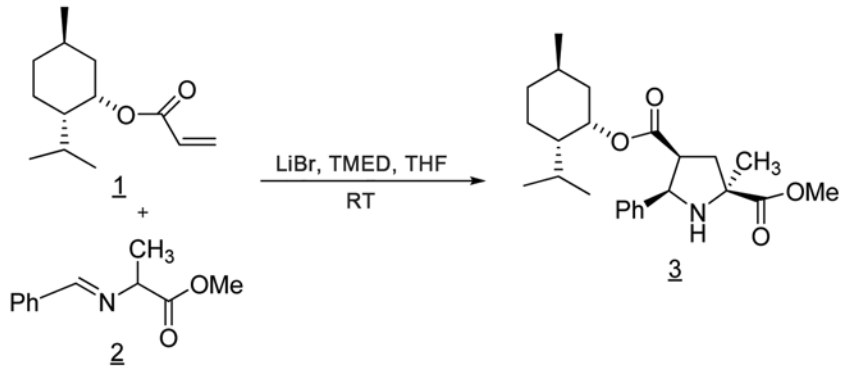
Just to check the feasibility of literature reported methodology reaction of homochiral menthyl acrylate with Schiff bases of α-aminoacid ester as shown in Scheme I, was attempted where 2(S),4(S),5(R)-substituted prolines were obtained in one step. The data were compared and found to be identical with the reported values.

After standardizing the reported procedure, α-aminoacids (glycine, alanine) were converted to their respective menthyl esters by reaction with menthol in presence of catalytic amount of sulphuric acid and the resultant menthyl esters were converted to Schiff bases according to procedures described in the literature[20-22] and these Schiff bases were subsequently used in the1,3-dipolar addition with methyl acrylate with an objective to look for the out come of these reactions.

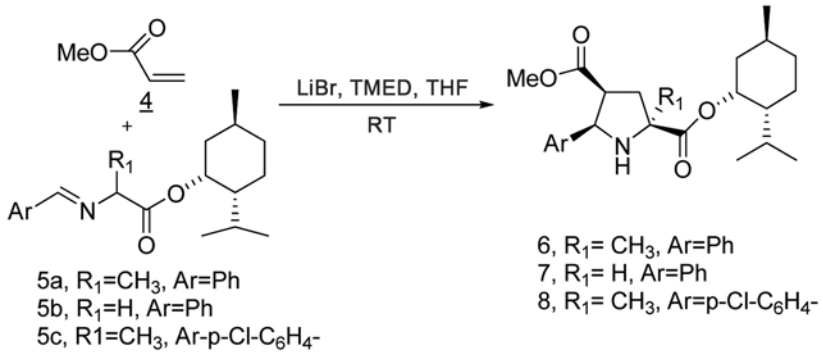
Initially the 1,3-dipolar addition reaction of the Schiff base **5a**, obtained from alanine menthyl ester and benzaldehyde with methyl acrylate in presence of lithium bromide and tetramethylenediamine using THF as solvent (Scheme II) was carried out, where the compound **6** was obtained which was purified by column chromatography. The structural asignments of compound **6** were made on the basis of ^{1}H NMR, which apart from the usual peaks of menthyl showed a singlet at δ 1.49 for 3 protons for CH_3 at C-2, one proton for H-3 at δ 2.04, for H-3' at δ 2.65 and a doublet centred at δ 3.40 for H-5, a singlet for OCH_3 at δ 3.73 along with α-Hydrogen of menthyl group at δ 4.64. IR spectrum for this compound showed a band at 1740cm^{-1} corresponding to the ester group of the molecule. MS spectra for this compound was also in agreement with the assigned structure showing molecular ion peak (M+1) at m/z 402 corresponding to the molecular weight of this compound. Stereochemical assignments were made based on 1H NMR decoupling and NOE experiments, which were in agreement to the assigned structure.

To standardize our approach further, reactions of other Schiff bases (imines) of glycine, alanine menthyl ester with acrylic acid methyl ester were attempted under similar conditions as described for **6** where compounds **7** and **8** were obtained respectively.

The structural assignments were made on the basis of ^{1}H NMR, where one proton for H-3 was observed at δ 2.0-2.20 as a multiplet. H-3' was observed at δ 2.35-2.65. H-4 was observed at 3.2-3.4 and H-5 was obserced as a doublet at δ 3.20-3.30. O-CH of menthyl group was observed at δ 4.40-4.70. IR spectrum for this compound showed a band at 1732 cm^{-1} corresponding to the ester group of the



Scheme I



Scheme II

molecule Ms spectra for this compound was also in agreement with the assigned structure showing molecular ion peak corresponding to the molecular weight of the molecule.

Experimental Section

Melting points are uncorrected, spectral data were recorded as follows: Beckmann Acculab 1 (IR); Jeol JMS D 300 (MS); Bruker WM-400 (^{1}H and ^{13}C), Perkin-Elmer-241 polarimeter (optical rotation). THF and Et_2O were distilled.

Synthesis of Schiff bases (2 and 5), homochiral menthyl acrylate, 1 and methyl acrylate, 4

Compound **1**, **2**, **4** and **5** were prepared according to the literature reported methodologies[20-22,27-29] and used as such for further 1,3-dipolar addition reactions.

General procedure for the synthesis of 2(S), 4(S)-menthyloxycarbonyl-5-(R)-substituted proline methyl ester

It was prepared by the 1,3-dipolar addition of corresponding Schiff base with acrylic acid menthyl ester where N-arylidine amino acid methyl ester (1 eq) was taken in THF (20 mL) and tetramethyl ethylenediamine (TMED) (1.1 eq) added to it, along with LiBr (1.1 eq) and acrylic acid menthyl ester (1.1 eq). The mixture was stirred at RT for 6 h. Progress of the reaction was monitored by TLC. At the completion of the reaction, the solvent was evaporated under vacuum, poured into water and extracted twice with ethyl acetate. The combined ethyl acetate layer was washed with saturated NaCl solution, dried over anhyd. Na_2SO_4, concentrated and purified by column chromatography using 20% EtOAc-hexane as eluent to afford the pure compound.

2(S)-Methyl-4(S)-menthyloxycarbonyl-5-(R)-phenyl proline methyl ester, 3

It was prepared from N-(Benzylidine) alanine methyl ester **2** (1.90 g, 1eq, 0.01 mol) and menthyl acrylate **1** (2.31 g,.011 mol) and was obtained as an oil. Yield 2.0 g (51%). $[\alpha]_{25}^{D}$ −13.70° (c 0.1, $CHCl_3$); IR (KBr): 1706, 1732, 2950 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.57(3H, d, J = 8Hz, CH_3), 0.80(6H, d, J = 8Hz, CH_3), 0.90-1.69 (12H, m, menthyl- H+CH_3), 1.92-2.04(1H, m, H-3), 2.15-2.22(1H, m, H-3'), 3.45(1H, m, H-4), 3.82(3H, s, -OMe), 4.38(1H, m, O-CH), 4.60(1H, d, J = 8Hz, H-5), 6.90(1H, br, s, NH), 7.23-7.42(5H, m, ArH); MS: *m/z* 402 (M+)1, 400 (M-1), 342, 264, 158.

2(S) Methyl-4(S) -methyloxycarbonyl-5(R)-phenyl proline menthyl ester, 6

It was prepared from N-(benzylidine) alanine menthyl ester **5a** (3.15 g, 1eq, 0.01 mol) and methyl acrylate **4** (0.95 g,.011 mol) according to the procedure as described above and was obtained as an oil. Yield 2.0 g (51%). $[\alpha]_{25}^{D}$ –85.970° (c 0.1, $CHCl_3$); IR (KBr): 1706, 1732, 2950 cm^{-1}; 1H NMR ($CDCl_3$): δ 0.80 (3H, d, J = 8Hz, CH_3), 0.92(6H, d, J = 8Hz, CH_3), 0.96- 1.72 (12H, m, menthyl- H+CH_3), 2.05-2.19(1H, m, H-3), 2.63- 2.71(1H, m, H-3'), 3.21-3.23(1H, d, J = 7Hz, H-5), 3.37-3.45(1H, m, H-4), 3.73(3H, s, -OMe), 4.62-4.66(1H, m, O-CH), 6.34(1H, br, s, NH), 7.26-7.36(5H, m, ArH); MS: *m/z* 402 (M+1), 400 (M-1), 342, 264, 158. Anal. Calcd for $C_{24}H_{35}NO_4$: C, 71.82; H, 8.72; N, 3.49. Found: C, 71.45; H, 8.34; N, 3.2%.

2(S), 4(S)-Methyloxycarbonyl-5(R)-phenyl proline menthyl ester, 7

It was prepared from N-(benzylidine) glycine menthyl ester **5b** (3.15 g, 1 eq, 0.01 mol) and methyl acrylate **4** (0.95 g, 1.1 eq,.011 mol) and was obtained as an oil. Yield 1.85 g (48%). IR (KBr): 1701, 1733, 2956 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.80(3H, d, J = 8Hz, CH_3), 0.94(6H, d, J = 8Hz, CH_3), 0.97- 1.76(9H, m, menthyl-H), 2.13-2.23(1H, m, H-3'), 2.45-2.56(1H, m, H-3'), 3.25 (1H, d, J = 8Hz, H-5), 3.37-3.45(1H, m, H-4), 3.89 (3H, s, -OMe), 4.35(1H, m, C-2), 4.64-4.79(1H, m, O-CH), 6.25 (1H, br, s, NH), 7.26-7.36(5H, m, ArH); MS: *m/z* 387 (M+), 342, 264, 158. Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.31; H, 8.52; N, 3.61. Found: C, 70.95; H, 8.14; N, 3.25%.

2(S)-Methyl-4(S)-methyloxycarbonyl-5(R)-(*p*-chlorophenyl) proline menthyl ester, 8

It was prepared from N-(*p*-chlorobenzylidine) alanine menthyl ester **5c** (3.50 g,0.01 mol) and methyl acrylate **4** (0.95 g,.011 mol) and was obtained as an oil. Yield: 2.35 g (53.4%); IR (KBr): 1730, 1750, 2970 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.70(3H, d, J = 8Hz, CH_3), 0.80(6H, d, J = 8Hz, CH_3), 0.96- 1.86(12H, m, menthyl-H+CH_3), 2.08-2.12(1H, m, H-3'), 2.33-2.44(1H, m, H-3'), 3.29-3.37(1H, m, H-4), 3.78-3.81(4H, m, - OMe+H-5), 4.61-4.72(1H, m, O-CH), 6.25(1H, br, s, NH), 6.91- 6.94 (2H, m, ArH(*p*-Cl)), 7.75-7.78 (2H, m, ArH (*p*-Cl)); MS: *m/z* 436 (M+), 342, 264, 158. Anal. Calcd for $C_{24}H_{34}NO_4Cl$: C, 66.20; H, 7.81; N, 3.21. Found: C, 65.95; H, 7.34; N, 2.95%.

Conclusion

Thus we have successfully accomplished the synthesis of 2,4,5-substituted prolines through 1,3 –dipolar addition reaction of the menthyl esters of α-amino acids with methyl acrylate, where chiral auxillary has been introduced in the α-aminoacid itself rather than acrylates providing effective outcome.

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