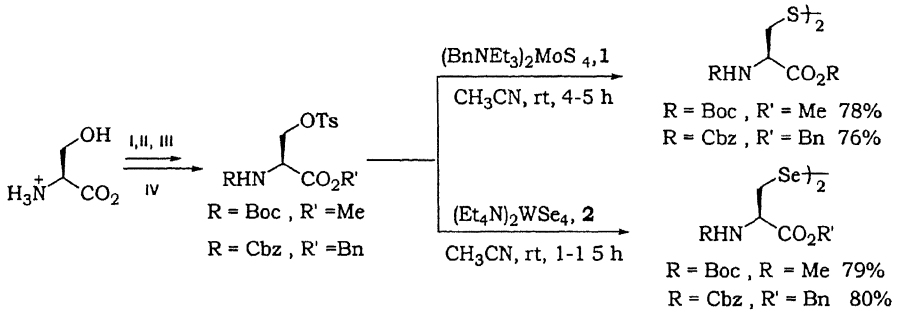
Synopsis

The thesis entitled ***'Development of Novel Methods for the Synthesis of Amines, Amino Acids and Peptides'*** comprises of four chapters.

Chapter 1

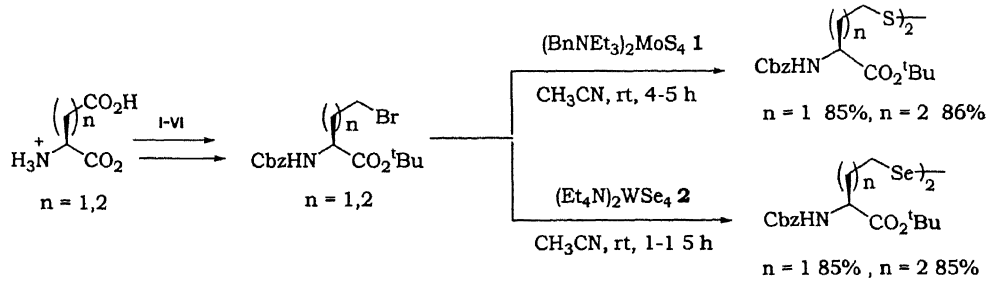
Development of synthetic methodologies for the preparation of protected proteinogenic and non-proteinogenic amino acids, viz, cystine, selenocystine, homocystine, selenohomocystine, and higher homologues are described in the first chapter Benzyltriethylammonium tetrathiomolybdate $(BnNEt_3)_2MoS_4$ **1** and tetraethylammonium tetraselenotungstate $(Et_4N)_2WSe_4$, **2** were used as sulfur and selenium transferring reagents respectively Cystine and selenocystine derivatives have been synthesised in good yields (76-80%) starting from optically active L-serine (Scheme 1)



i) Boc_2O, 1,4-dioxane, 1N NaOH 98% ii) Cbz-Cl, 1N aq $NaHCO_3$, 79% iii) MeI, K_2CO_3, DMF, 85% iv) BnBr, DBU, Benzene 95%

Scheme 1

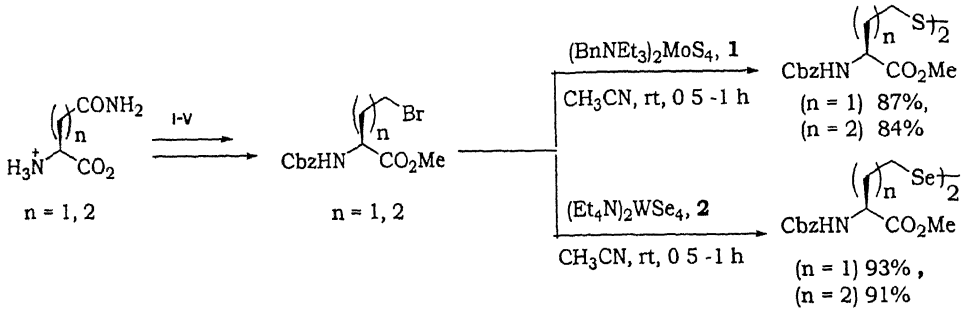
Homocystine, selenohomocystine and their higher homologues have been synthesised in very good yields (85-86%) from aspartic acid and glutamic acid using tetrathiomolybdate and tetraselenotungstate as key reagents (Scheme 2)



i) $SOCl_2$, MeOH, 0 °C 92% ii) Cbz-Cl, 1N aq $NaHCO_3$, 81% iii) Boc_2O, ^tBuOH, DMAP, 85% iv) NaOH, MeOH, v) ClO_2CEt, $NaBH_4$ vi) Ph_3P, CBr_4

Scheme 2

Homocystine, selenohomocystine and their higher homologues have also been synthesised using an alternative route starting from aparagine and glutamine in using **1** and **2** for transferring sulfur and selenium respectively (Scheme 3)



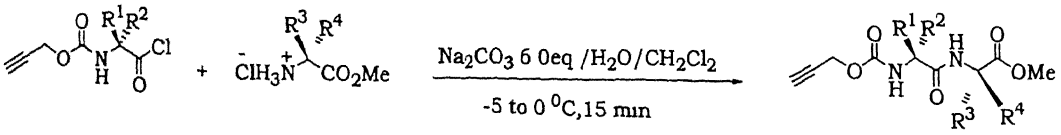
i) $SOCl_2$, MeOH, 0 °C 94 % ii) Cbz-Cl, 1 N aq $NaHCO_3$, 83 % iii) ^tBuONO, CH_3CN, 85% iv) ClO_2CEt, $NaBH_4$ v) Ph_3P, CBr_4

Scheme 3

Rapid and efficient direct synthesis of sulfur and selenium containing amino acids has been explored All the amino acid derivatives were obtained in good to excellent yields and were optically pure

Chapter 2

This chapter deals with the development of new coupling agent propargyloxycarbonyl amino acid chloride (Poc-AA-Cl), in peptide synthesis without using any additives, or trapping agents Facile, and efficient deprotection of propargyloxycarbonyl group was achieved with benzyltriethylammonium tetrathiomolybdate or resin bound tetrathiomolybdate under stirring/sonochemical conditions Efficacy of this methodology has been demonstrated in the synthesis of a number of short-segmented peptides, sterically hindered peptides, and *N*-methylated peptides (Scheme 4-6) without any racemisation

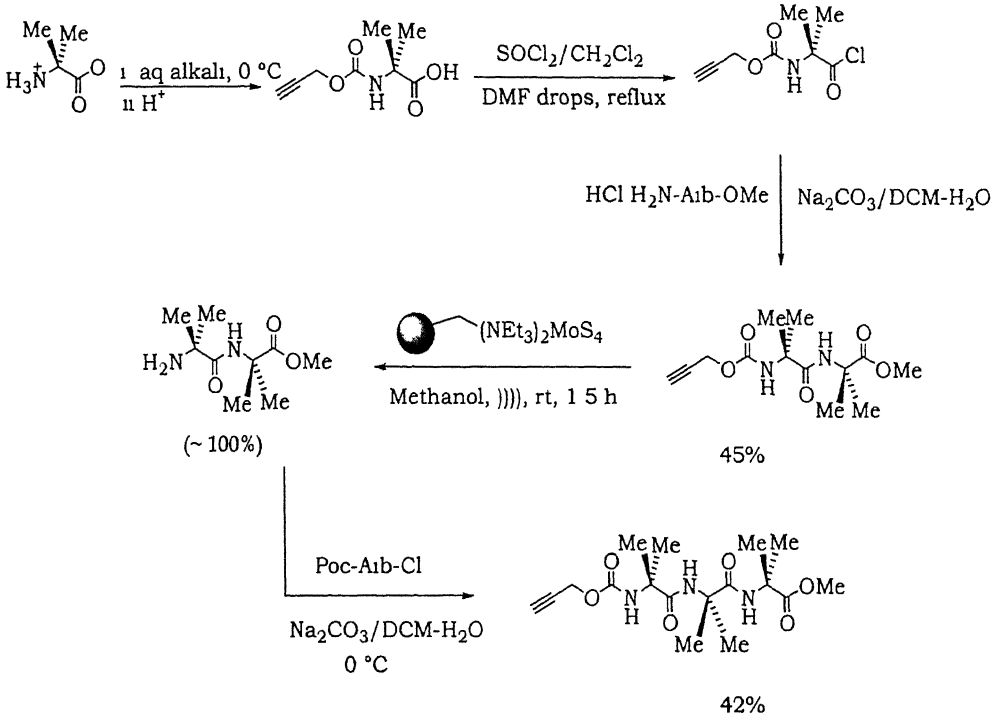


$R^1 = CH_3$, $R^2 = H$ $R^3 = CH_3$, $R^4 = H$
$R^1 = CH_2Ph$, $R^2 = H$ $R^3 = CH_2Ph$, $R^4 = H$
$R^1 = CH_2Ph$, $R^2 = H$ $R^3 = CH_3$, $R^4 = H$

Poc-Ala-Ala-OMe 83%
Poc-Phe-Phe-OMe 86%
Poc-Phe-Ala-OMe 83%

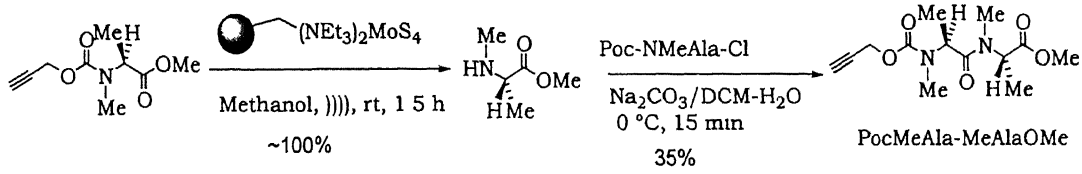
Scheme 4

Sterically hindered aminoisobutyric (Aib) containing di- and tri-peptides have been synthesised in satisfactory yields (43-45%)



Scheme 5

Optically pure *N*-methylated peptide, Poc(Me)Ala-(Me)Ala-OMe has been synthesised in satisfactory yield using this strategy without the use of any additives

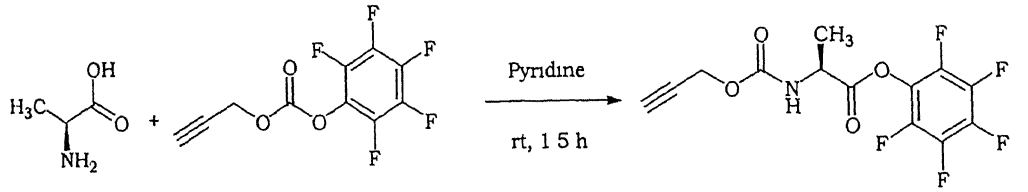


Scheme 6

Peptides were obtained in excellent yields All the peptides obtained were diastereomerically pure Shift reagent NMR and chiral HPLC analyses confirmed the optical purity of the peptides Propargyloxycarbonyl group was efficiently deprotected by resin bound tetrathiomolybdate in almost quantitative yields Free amine obtained was essentially pure and it was ready for coupling without further purification

Chapter 3

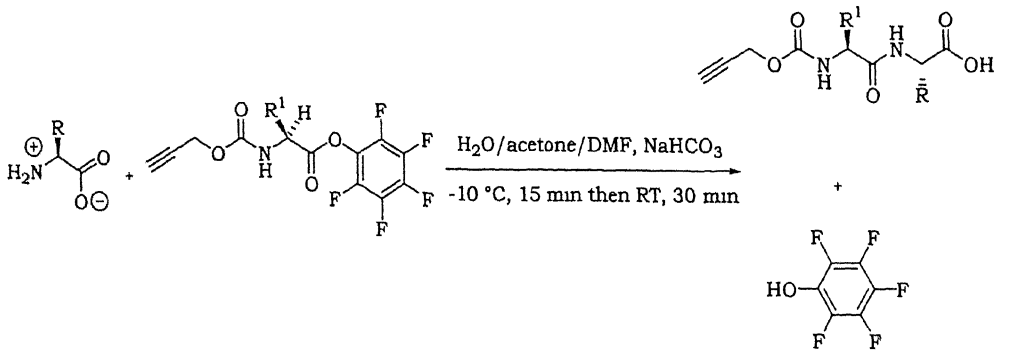
This chapter describes the development of novel reagent propargyl pentafluorophenyl carbonate (PocOPfp) for simultaneous protection of amino group and activation of carboxyl group, which could be utilised further in peptide synthesis (Scheme 7) Utility of the reagent was demonstrated in the synthesis of *N*-Poc amino acids, N-Poc-amino acid pentafluoropentafluoro esters, and *N*-Poc peptides



PocOPfp

Scheme 7

Several *N*-Poc amino acids have been synthesised in excellent yields The corresponding *N*-Poc amino acid pentafluorophenyl esters were treated with natural amino acids to furnish *N*-Poc peptides in excellent yields (Scheme 8)



Scheme 8

We have observed an interesting C-H F interaction in the crystal structure of propargyl pentafluorophenyl carbonate (PocOPfp) (**2**), which has over shadowed the very likely C-H O interaction, which was anticipated between acidic acetylenic hydrogen and oxygen of carbonyl group (Fig 1). This is one of the unusual favourable C-H F interaction observed in the literature

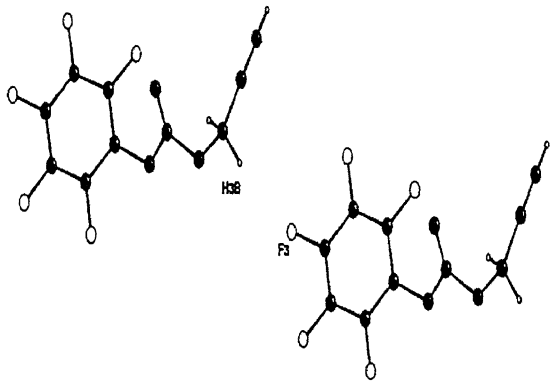
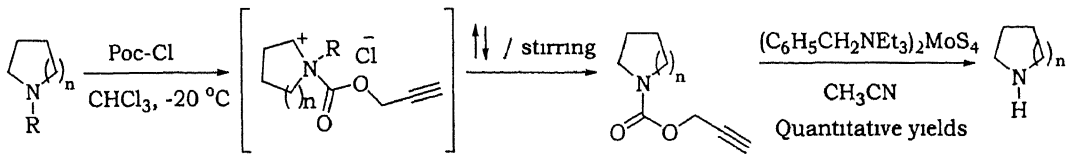


Fig 1 Crystal structure of PocOPfp

Chapter 4

The utility of propargyl chloroformate and benzyltriethylammonium tetrathiomolybdate in the dealkylation of tertiary amines to secondary amines is described in this chapter Tertiary amines were treated with propargyloxycarbonyl chloride (1 2 equiv) in chloroform, and the corresponding intermediate salts were either refluxed or stirred depending on the nature of substrates, for 0 5 – 2 h All the tertiary amines resulted in the formation of the corresponding carbamates in excellent yields (52-90%)(Scheme 9) The dealkylation followed the order as Bn > Allyl > ^{i}Pr > Me and is in line with the electrophilicity of the alkyl chain



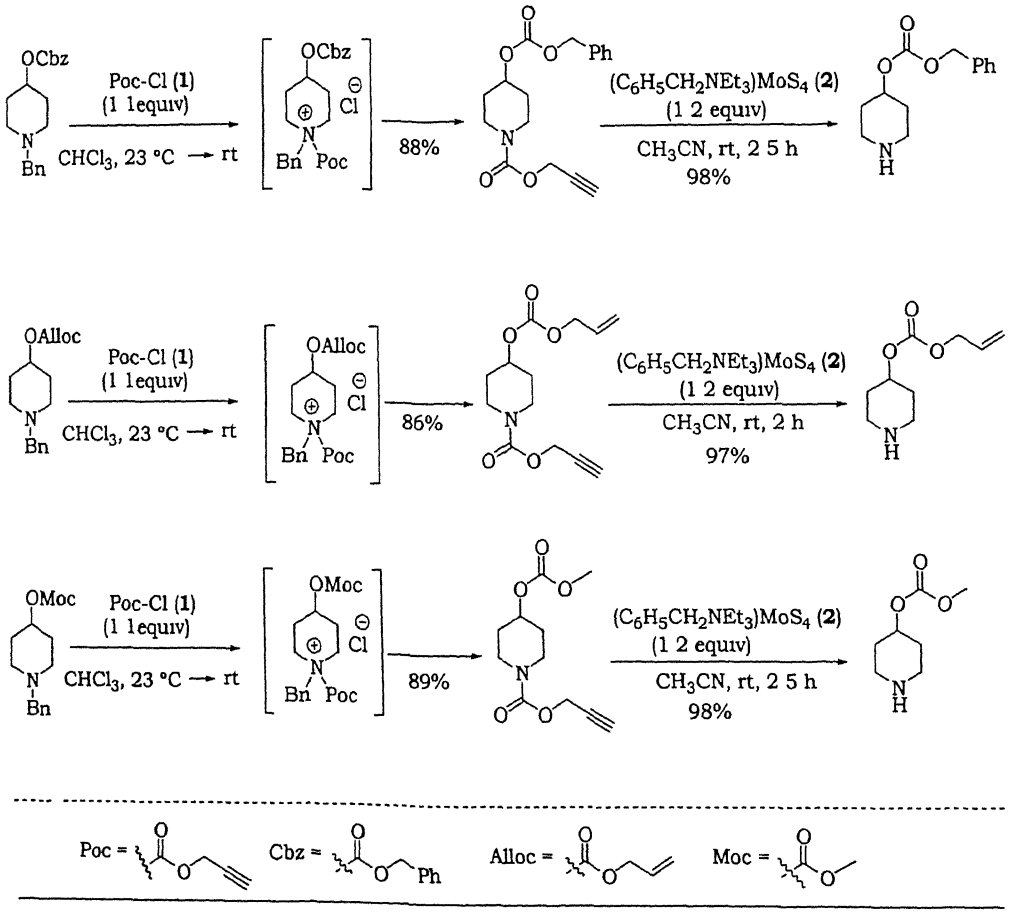
n = 1, 2

R = Me, ^{i}Pr, Allyl, $CH_2C_6H_5$

Scheme 9

The propargyloxycarbonyl (Poc) group was readily cleaved on treatment with benzyltriethylammonium tetrathiomolybdate under neutral and mild conditions in 3-4 hours to give secondary amines in almost quantitative yields

Orthogonality of the Poc group has been shown during *N*-dealkylation Propargyl group was swiftly deprotected leaving carbonates untouched (Scheme 10)



Scheme 10

The methodology is very general and many other tertiary amines have been converted into secondary amines efficiently in excellent yields