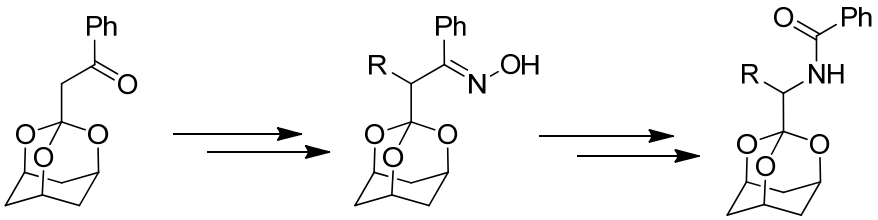
SYNOPSIS

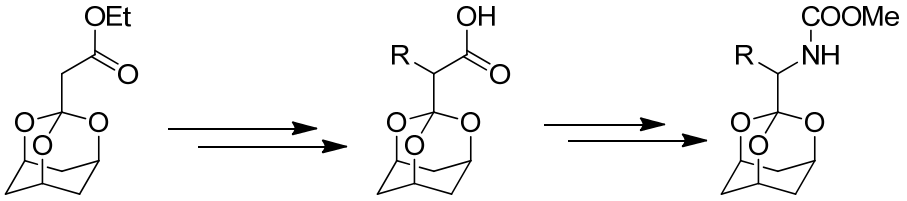
The thesis entitled "***Novel Approaches for the Synthesis of Amino Acids and Piperidines, including Asymmetric Strategies"*** is divided into four chapters.

Chapter I deals with novel approaches for α-amino acids. This chapter has been divided into three sections. **Section A** describes the synthesis of *α*-amino acids *via* the Beckmann rearrangement of carboxyl-protected *β*-keto acid oximes. The synthesis of *α*-amino acids using the Beckmann rearrangement involves the preparation of the *Z*-oxime and efficient protection of the carboxyl group. Various 2-substituted benzoylacetic acids were synthesized, in which the carboxyl function was masked as a 2,4,10-trioxaadamantane unit (an orthoacetate), and were converted to their oximes (Scheme 1).[1] The oximes were converted to the their mesylates, which underwent the Beckmann rearrangement with basic Al_2O_3 in refluxing $CHCl_3$. The corresponding 2-substituted-*N*-benzoyl-*α*-amino orthoacetates were obtained in excellent overall yields.



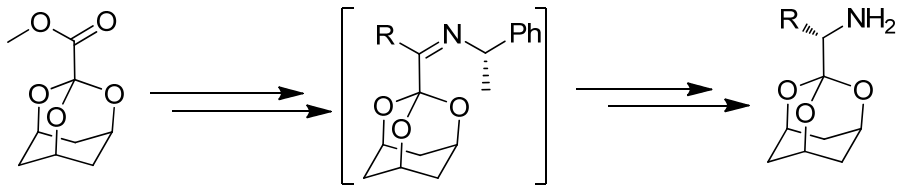
Scheme 1. Synthesis of *α*-amino acids *via* the Beckmann rearrangement.

In **Section B**, the synthesis of *α*-amino acids *via* the Hofmann rearrangement of carboxyl-protected malonamic acids is described. The Hofmann rearrangement involves the migration of the alkyl moiety of the amide onto the *N*-centre. Various 2-substituted malonamic acids (malonic acid mono amides) were synthesized with the carboxyl group masked as a 2,4,10-trioxaadamantane unit (an orthoacetate). These underwent the Hofmann rearrangement with phenyliodoso acetate and KOH/MeOH (Scheme 2). The resulting (*N*-methoxycarbonyl)-trioxaadmantylmethylamines (carbamates) were formed in yields > 90%, and are *α*-amino acids with both carboxyl and amino protection.[2]



Scheme 2. Synthesis of *α*-amino acids *via* the Hofmann rearrangement.

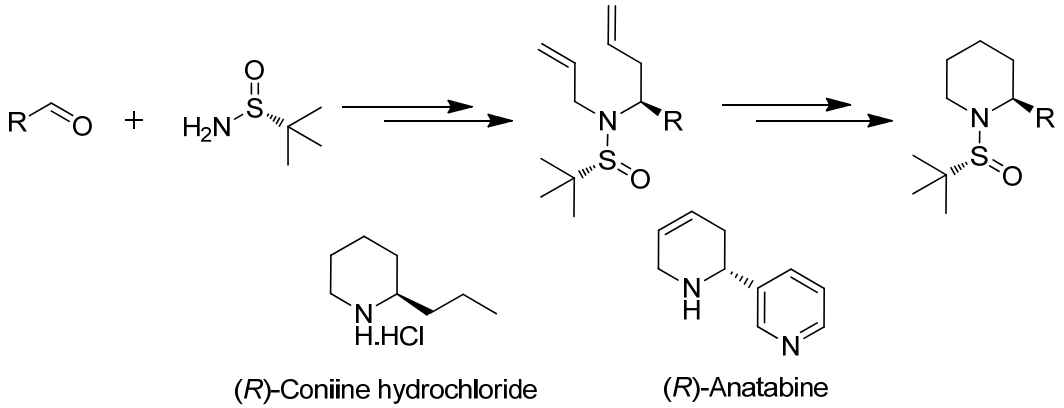
In **Section C**, an approach to chiral amino acids *via* the reductive amination of ketones, involving the hydride reduction of 1-(*S*)-phenethyl amine derived Schiff bases of *C*-protected *α*-keto acids is described. An efficient synthesis of *α*-amino acids has thus been developed in high diastereoselectivity. Various 1-acyl-2,4,10-trioxaadamantanes were prepared from the corresponding 1-methoxycarbonyl derivatives, *via* conversion to the *N*-acylpiperidine derivative followed by reaction with a Grignard reagent in refluxing THF (Scheme 3). These *α*-keto orthoformates were converted to corresponding imines with 1-(*S*)-phenethyl amine ($TiCl_4/Et_3N$/toluene/reflux), the Schiff bases being reduced with $NaBH_4$ (MeOH/0 °C) to the corresponding 1-(*S*)-phenethyl *N*-alkylamines (diastereomeric excess by NMR ~ 90:10).[3] Hydrogenolysis of the phenethyl group (Pd-C/H_2/MeOH) finally led to the (aminoalkyl)trioxaadamantanes, which are chiral *C*-protected *α*-amino acids, in excellent overall yields. Here a mild, inexpensive and efficient hydride reducing agent for the reductive amination of *α*-keto acids has been developed.



Scheme 3. Reductive amination of *C*-protected-*α*-keto acids to *α*-amino acids.

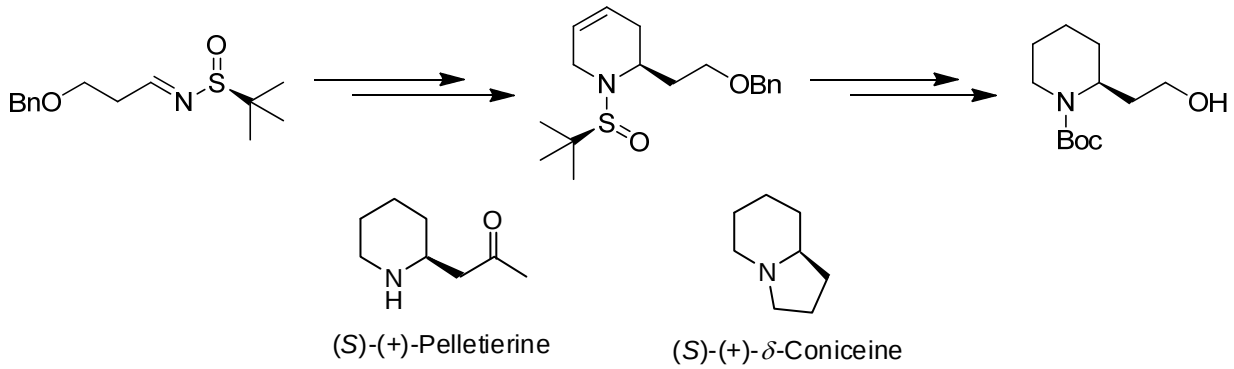
Chapter II deals with the enantioselective synthesis of piperidines and its applications in the synthesis of piperidine alkaloids.[4] This chapter has been divided into two sections. In **Section A**, the enantioselective synthesis of 2-substituted piperidines and its applications in the synthesis of (*R*)-(-)-coniine and (*R*)-(+)-anatabine are described. Various *N*-*tert*-butylsulfinyl imines were synthesized, which upon allyl Grignard addition followed by *N*-allylation gave the diallyl

compound with good diastereoselectivity (Scheme 4). The diallyl compound underwent ring closing metathesis with Grubbs' first generation catalyst and subsequent reduction of the double bond with H_2-Pd/C, furnished *N*-sulfinyl-2-susbstituted piperidines. Using this methodology (*R*)-(-)-coniine hydrochloride and (*R*)-(+)-anatabine were synthesized.



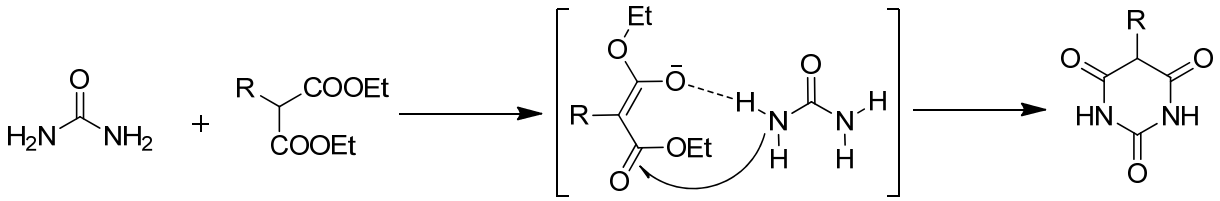
Scheme 4. Enantioselective synthesis of 2-substituted piperidines.

In **Section B**, the enantioselective synthesis of (*S*)-*tert*-butyl 2-(2-hydroxyethyl)piperidine-1-carboxylate and its elaboration to the synthesis of (*S*)-(+)-*δ*-coniceine and (*S*)-(+)-pelletierine are described. The (*S*)-*tert*-butyl 2-(2-hydroxyethyl)piperidine-1-carboxylate is a synthon used for the synthesis of various 2-substituted piperidine natural products. Using the above methodology (*S*)-*tert*-butyl 2-(2-hydroxyethyl)piperidine-1-carboxylate was synthesized starting from (*S*)-(+)-2-methyl-2-propanesulfinamide and 3-(benzyloxy)propanal (Scheme 5). This alcohol was further elaborated to furnish two piperidine alkaloids (*S*)-(+)-pelletierine and (*S*)-(+)-*δ*-coniceine.



Scheme 5. Enantioselective synthesis of (*S*)-*tert*-butyl 2-(2-hydroxyethyl)piperidine-1-carboxylate, (*S*)-(+)-pelletierine and (*S*)-(+)-*δ*-coniceine.

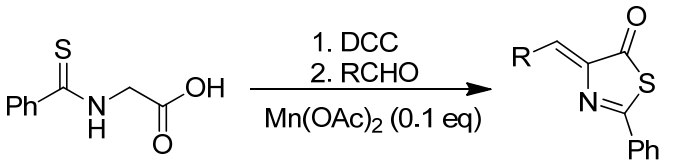
Chapter III deals with the formation of barbituric acid in an aprotic medium and related mechanistic studies. The generally accepted mechanism for the formation of barbituric acid involves the nucleophilic attack of urea anion on diethyl malonate.[5] This is debatable for at least two reasons: (1) the normally employed base, sodium ethoxide, is too weak to deprotonate urea and (2) diethyl malonate is more acidic than urea, so the initial deprotonation by base has to be from diethyl malonate. When diethyl malonate (DEM) enolate was treated with urea in DMF, barbituric acid was formed in 61% yield. The reaction was also extended to several 2-substituted DEM derivatives, the corresponding substituted barbituric acids being formed in reasonable yields. The reaction between diethyl 2-(ethoxycarbonyl)malonate and urea, with potassium carbonate in refluxing ethanol, led to the formation of barbituric acid. This is apparently facilitated by hydrogen bonding involving the enolate oxygen atom, which renders one of the carbonyl groups relatively electrophilic (Scheme 6). Meldrum's acid failed to react with urea, despite its greater acidity, indicating that the reaction requires the formation of the *E* from of the *s*-trans enolate ion, in which the hydrogen bonding interaction and nucleophilic attack can occur in concert.



Scheme 6. Proposed transition state for formation of Barbituric acid.

Chapter IV deals with an improved Erlenmeyer synthesis with 5-thiazolone and catalytic manganese (II) acetate for aliphatic and aromatic aldehydes. A serious limitation to the classical Erlenmeyer reaction is that it generally fails in the case of aliphatic aldehydes. This chapter describes a convenient approach to this problem that extends the scope of the Erlenmeyer synthesis. The present study was aimed at developing milder conditions for the synthesis of 4-arylidene and alkylidenethioazlactones. Thus, *N*-(thiobenzoyl)glycine was treated with DCC in DCM at room temperature for 10 min., according to a reported procedure, to form the thioazlactone.[6] The same reaction mixture was treated with catalytic Mn(II) acetate and an equivalent of an aromatic aldehyde, to furnish the corresponding 4-arylidenethioazlactones in

good yields. The scope of the reaction was extended to alphatic aldehydes also under similar reaction conditions, to obtain the 4-alkylidene thioazlactones in good to moderate yields (Scheme 7).



Scheme 7. The Erlenmeyer synthesis with 5-thiazolone and manganese acetate.

References

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2. Chandrasekhar, S.; Rao, V. M.; *Beilstein J. Org. Chem.* **2012**, *8*, 1393-1399.
3. Chandrasekhar, S.; Rao, V. M.; *Tetrahedron: Asymmetry* **2012**, *23*, 1005-1009.
4. Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701-1729.
5. Smith, M. B.; March, J. (2007). March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure, 6th ed.; John Wiley: Hoboken; p. 1439.
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