Abstract

Due to growing number of bacterial strains acquiring resistance to the current arsenal of chemotherapeutic drugs, the search for novel mechanism based anti bacterial agents continue to be a major area of research on many fronts.

During the last decade, various groups have directed their efforts to synthesize non β-lactam mimics of several β-lactam antibiotics and this has enriched the γ-lactam chemistry with the development of many γ-lactam compounds with and without significant bioactivity. Modification of lactam ring has been playing a vital role in determining the biological activities of these derivatives and so exploration of a novel methodology in a simple way is a pivotal focal point of research activity in bioorganic chemistry. Progress in the art of organic synthesis in the last decades has been achieved by marked advances in chemo-, regio- and stereoselective functional group transformations by using classical and newly developed reagents.

The dissertation entitled "**Studies on *N*-aryl-γ-lactams: Selective Functional Group Transformations and Development of Synthetic Routes to *N*-aryl-formylpyrroles and Pyrroloquinoline Derivatives**" is an embodiment of research aimed at developing simple methodologies for selective functional group transformations of *N*-aryl-γ-lactam derivatives and an effort towards the development of new synthetic strategies for conversion of *N*-aryl-γ-lactams to substituted pyrrole and pyrroloquinoline derivatives. The deliberation has been organized in four major chapters.

CHAPTER 1: Chemoselective Reduction of *gem*-Diesters and Lactam carbonyls

This chapter has been subdivided into 2 parts.

Chapter 1A: $NaBH_4$-$InCl_3$ Mediated One-Pot Chemo- and Stereoselective Decarboxylative Reduction of α-Aza *gem*-Dicarboxylates to *trans*-Monoalcohols

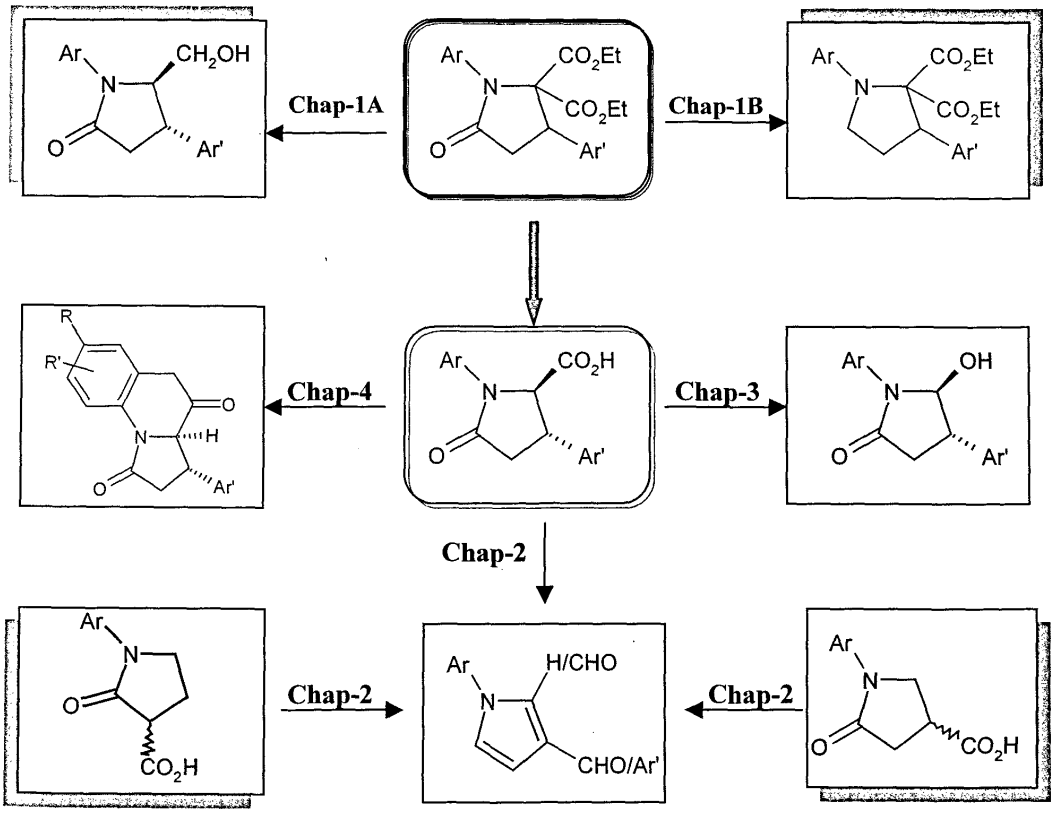
Chapter 1B: $NaBH_4$-I_2 Mediated Chemoselective Reduction of Lactam Carbonyls of *N*-aryl-γ-lactam *gem*-Dicarboxylates

CHAPTER 2: Synthetic Route towards *N*-aryl-formylpyrroles from γ-Lactam Carboxylic Acids

CHAPTER 3: Ceric Ammonium Nitrate Mediated Steroselective Decarboxylative Hydroxylation/Alkoxylation of *N*-aryl-γ-lactam Carboxylic Acids at Room Temperature

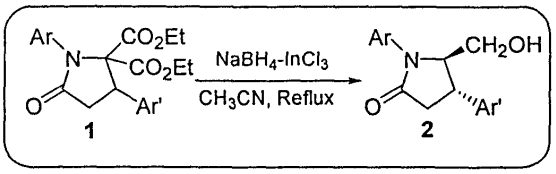
CHAPTER 4: Highly Regioselective Rhodium(II)-Catalyzed Carbenoid Insertion Reaction into sp^2 C-H bond: A General Method for the Synthesis of 3,3a-Dihydro-2*H*,5*H*-pyrrolo[1,2-*a*]quinoline-1,4-dione Ring System

All the chapters have been schematically represented in the following diagram.



Chapter 1A: $NaBH_4$-$InCl_3$ Mediated One-Pot Chemo- and Stereoselective Decarboxylative Reduction of α-Aza *gem*-Dicarboxylates to *trans*-Monoalcohols

In this part we have explored an exclusively novel and efficient method for the chemo- and stereoselective reduction of *gem*-diesters of *N*-aryl-γ-lactam-5,5-dicarboxylic esters to *trans*-monoalcohols by using the $NaBH_4$-$InCl_3$ reagent system. The starting materials for this study, 1,4-diarylpyrrolidin-2-one-5,5-dicarboxylic esters (**1**), were synthesized following the general method developed in our laboratory. Chemoselective and *in situ* stereoselective decarboxylative reduction of these dicarboxylic esters with sodium borohydride and catalytic indium trichloride in dry acetonitrile at reflux temperature for 8-11 h, furnished exclusively *trans*-1,4-diaryl-5-hydroxymethyl-pyrrolidin-2-ones (**2**) in high yields.



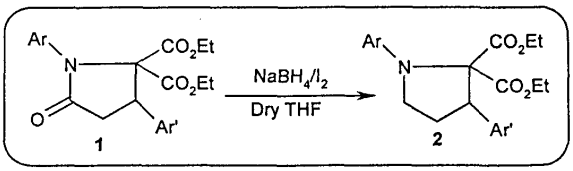
Though the mechanism of the reaction is still uncertain, we speculated that the decarboxylative reduction to alcohols proceeds via an initial stereoselective radical decarboxylation mediated by $HInCl_2$ (generated *in situ* from sodium borohydride and catalytic indium trichloride) followed by chemoselective reduction of the ester functionality.

We extended this protocol successfully in case of amine derivatives like diethyl 1-(4-fluorophenyl)-4-phenylpyrrolidine-2,2-dicarboxylate and diethyl 2-(4-fluorophenyl-amino)malonate.

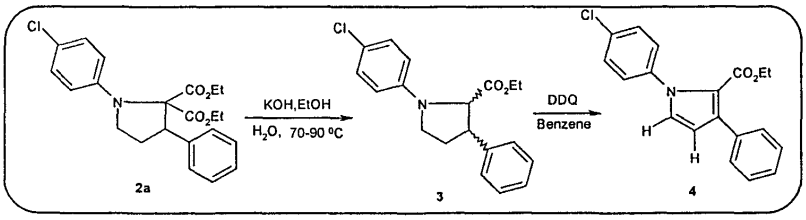
Chapter 1B: $NaBH_4$-I_2 Mediated Chemoselective Reduction of Lactam Carbonyls

Presented in this part a chemoselective method for the reduction of the lactam-carbonyl in the presence of *gem*-dicarboxylicesters preserving the integrity of stereogenic centers in the substrate.

1,4-Diarylpyrrolidin-2-one-5,5-dicarboxylic esters (**1**) on treatment with the sodium borohydride and iodine in dry THF under inert atmosphere, furnished substituted pyrrolidines (**2**) in high yields.

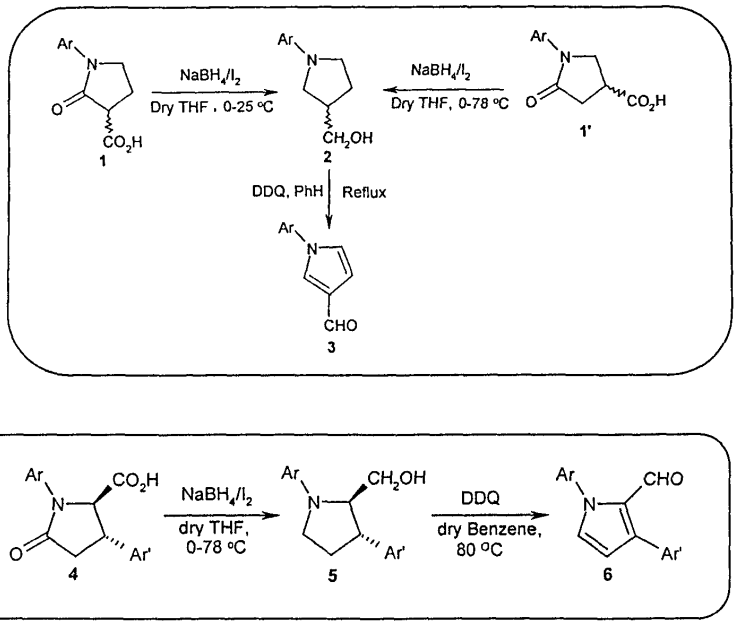


By hydrolysis with 1.2 equivalent KOH in H_2O-EtOH, followed by *in situ* decarboxylation of the pyrrolidine derivative **2a** we synthesized the substituted pyrrolidine monoester **3**, which was converted to the substituted pyrrole derivative **4** by dehydrogenation using DDQ in refluxing benzene.



Chapter 2: Synthetic Route towards *N*-aryl-formylpyrroles from γ-Lactam Carboxylic Acids

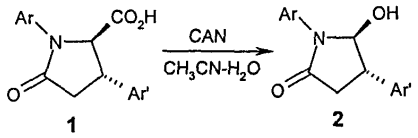
In this part we have described a new synthetic route for the synthesis of *N*-aryl-formylpyrroles (**3** & **6**) via $NaBH_4$-I_2 mediated reduction of *N*-aryl-γ-lactam carboxylic acids (**1**, **1'**& **4**), followed by one-pot oxidative aromatisation of *N*-aryl pyrrolidinylmethanols (**2** & **5**). We also demonstrated a comparative study of the effect of $NaBH_4$-I_2 system on the reduction of three different types of γ-lactam carboxylic acids.



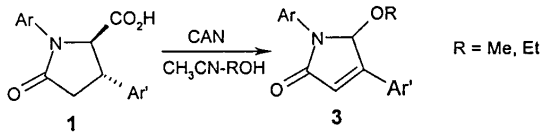
Chapter 3: Ceric Ammonium Nitrate Mediated Steroselective Decarboxylative Hydroxylation/Alkoxylation of *N*-aryl-γ-lactam Carboxylic Acids at Room Temperature

In this part we have presented CAN mediated one-pot protocol for the stereoselective decarboxylative hydroxylation/alkoxylation of 1,4-diaryl-γ-lactam-5-carboxylic acids at room temperature in organo-aqueous solvent.

Decarboxylative hydroxylation of γ-lactam-carboxylic acids **1** with CAN in acetonitrile-water at room temperature furnished exclusively *trans*-5-hydroxy-1,4-diaryl-pyrrolidin-2-ones **2** in high yields.



We extended this method to include other nucleophilic solvents. Now instead of water we performed the same reaction by using alcohol as the other component with acetonitrile. But in this case dehydrogenation occurred with the decarboxylative alkoxylation.



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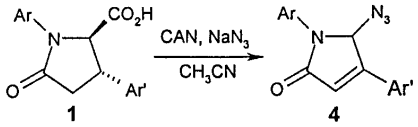
To further test the generality of this reaction we next investigated the reaction of 1,4-diaryl-γ-lactam-5-carboxylic acids at room temperature in acetonitrile solvent using sodium azide as nucleophilic agent. And as usual we got exclusively 5-azido-1,4-diaryl-1,5-dihydro-pyrrol-2-one.



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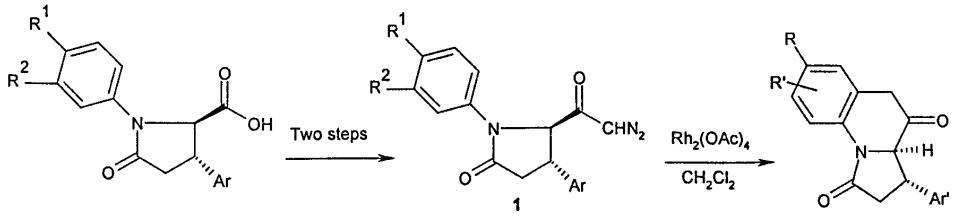
Chapter 4: Highly Regioselective Rhodium(II)-Catalyzed Carbenoid Insertion Reaction into sp^2 C-H bond: A General Method for the Synthesis of 3,3a-Dihydro-2*H*,5*H*-pyrrolo[1,2-*a*]quinoline-1,4-dione Ring System

In this part we have described the synthesis of substituted 3,3a-dihydro-2*H*,5*H*-pyrrolo[1,2-*a*]quinoline-1,4-dione derivatives through an intramolecular Rh(II) catalyzed regioselective sp^2 C-H insertion reaction on suitable diazocarbonyl compounds which were synthesized from the corresponding γ-lactam carboxylic acids.

Thus diazoketones **1** when subjected to the Rh(II) catalyzed regioselective sp^2 C-H insertion reaction furnished the substituted 3,3a-dihydro-2*H*,5*H*-pyrrolo[1,2-*a*]quinoline-1,4-dione derivatives in 67-71% yields as the only isolable products.



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The cyclization was found to be highly regioselective and the insertion reaction took place exclusively in *N*-aryl ring presumably because of a "proximity effect", which was explained by calculating the distance between the "CH" of the diazoketone functionality and the *ortho* protons of *N*-aryl moiety and the aryl moiety of the 4-position of the lactam ring from the energy minimized lock structure of the diazocarbonyl compounds. In addition, for unsymmetrically substituted *N*-aryl groups the regioselectivity is further influenced by the heteroaryl/aryl moiety present at the C-4 of the γ-lactam ring and also by the substituents present in the *N*-aryl moiety.