DEVELOPMENT OF NEW STRATEGIES FOR STEREOSELECTIVE AND GREEN SYNTHESIS OF SOME BIOLOGICALLY RELEVANT MOLECULAR SCAFFOLDS

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Chapter 1

Stereoselective carbon-carbon bond forming reactions - an overview

Asymmetric version of C-C bond forming reactions has witnessed an exponential growth over the last decade as it provides access to the chiral molecular architechture. Owing to the importance and requirement of chiral molecules, scientists have developed new approaches viz. (i) chiral pool synthesis, (ii) kinetic resolution and (iii) asymmetric synthesis; for its preparation over the last century.

Organocatalytic stereoselective carbon-carbon bond forming reactions: Asymmetric organocatalysts are remarkable for its structural simplicity and their mode of interaction with the substrate. In general, organocatalysts are non-toxic and environment friendly. Multiple advantages associated with this catalytic domain have forced the rapid growth and acceptance of organocatalysis.

Biocatalytic stereoselective carbon-carbon bond formation: Enzymatic catalysis constitutes a complementary method used for stereoselective C-C bond formation. Because of their high chemo- and stereoselectivity, enzymatic catalysis is highly useful for the synthesis of complex natural products.

Stereoselective carbon-carbon bond formation by metal catalyst: Despite the remarkable success of organocatalytic direct aldol processes, heterobimetallic-catalyzed direct aldol reactions work under milder conditions than enamine-based organocatalysts employing nucleophilic amines.

Chapter 2

Stereoselective Henry reaction employing Cu(II) complex of D-Fructose derived amines

Among the various C-C bond forming reactions, the nitroaldol reaction developed by L. Henry in the year 1895 has been subject of extensive research. In the Henry reaction, C-C coupling between nucleophilic nitroalkane with an electrophilic aldehyde or ketone takes place to produce a synthetically useful β-nitroalcohol. The fact that Henry reaction forms two new stereo-centers along with the formation of a C-C bond, its stereoselective synthesis becomes very important as the β-nitroalcohol is a versatile building block which can be manipulated to achieve diverse products such as 2-
hydroxyketones, 2-hydroxycarboxylic acids, 2-nitroketones, 2-aminoalcohols, and nitroalkenes having important applications in natural products and drug development. Although controlling the absolute stereochemistry in the final Henry adducts can be achieved various catalytic pathways such as organocatalysis and enzymatic catalysis, catalysis by metal complex is proven to be most effective in controlling stereoselectivity. In this perspective, we planned to employ the said amines and their Schiff bases to study their effectiveness against Henry reaction for synthesis of β-nitroalcohols.

Chapter 3
C-C bond formation in aqueous medium at neutral pH: Stereoselective synthesis of 1,3-dinitroalkane

Water is cheap, highly abundant, nonflammable, environment benign natural liquid, which made it as the best possible alternative reaction medium in designing environment friendly organic transformations. The Michael addition of nitroalkane to nitroolefin provides an atom-economic access to 1, 3-dinitroalkanes. However, the sensitivity of nitroalkanes towards acid and base make the Michael addition nitroalkane to nitroolefin a difficult reaction to deal with. Further, this reaction suffered from serious drawback of low reaction yield due to the formation of byproducts including oligomeric
byproducts. Considering the complicacies attached to the base catalyzed synthesis of 1,3-dinitroalkanes and its perceived importance as versatile building blocks along with growing environmental concerns regarding organic solvents, development of a synthetic methodology devoid of traditional base catalysts and organic solvent is highly desirable. In this context, we envisaged that the use of neutral phosphate buffer in aqueous medium will eliminate the formation of oligomeric byproducts due to poor solubility of more hydrophobic 1,3-dinitroalkane in aqueous medium.

![Chemical reaction diagram]

Chapter 4

Knoevenagel condensation in aqueous medium at neutral pH

The Knoevenagel condensation is one of the most powerful strategies for the construction of carbon–carbon double bonds in organic chemistry. The condensation products were found to be useful intermediates for the synthesis of fine chemical, as well as carbocyclic and heterocyclic compounds of biological significance. This reaction is generally carried out in organic solvents in the presence of bases, but use of these homogeneous base catalysts often leads to the complicated work-up procedure and undesired side-reactions such as oligomerizations. Current interest in the Knoevenagel condensation is shifted towards the development of environmentally as well as economically benign reaction conditions such as employment of heterogeneous catalysts or ionic liquids. Given the fact that phosphate buffer at neutral pH to be an excellent catalyst for Henry and Michael addition reaction, we proposed to employ phosphate buffer at neutral pH Knoevenagel condensation of aldehyde and active methylene compounds (Scheme 4.5). We assumed that the absence of acid and base catalysts will help in reducing the formation of possible byproducts.

![Chemical reaction diagram]
Chapter 5

I₂-DMSO: An efficient reagent for the synthesis of unsymmetrical urea from isocyanide

Urea is one of the most abundant moiety in biologically active molecules and natural products. Apart from their presence in pharmaceuticals, compounds containing unsymmetrical urea moiety have also been identified as potent HIV protease inhibitors, CCK-B receptor antagonists, MCH1R antagonist endothelin antagonists, CCR8 ligands, and kinase inhibitors, human sEH inhibitor, CYP1B1 inhibitors, anti-malaria compounds, hepatitis C protease inhibitors, antinociceptive, antiglycation, antidiabetics, anticonvulsants, anti tuberculosis and anticancer agents. Classical synthesis of urea involves the use of phosgene, but due to the various toxicological and environmental issues associated with the production, storage, use and transportation of phosgene, recent approaches were directed towards development of alteranative routes devoid of phosgene, for the synthesis of ureas. Moreover, most synthesis of urea derivatives are dependent on the nature of amines, i.e. many methods employed for electron rich amines are not good for relatively electron deficient amines and vice versa. Therefore, the development of simple and metal free isocyanide insertion into amines is necessary. In this chapter we proposed to develop a simple and efficient synthesis of urea derivatives catalysed by iodine in DMSO.

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\text{RNC} + \text{R}^1\text{NH}_2 \xrightarrow{\text{I}_2, \text{DMSO}} \xrightarrow{100 \, \text{°C}} \text{R}_2\text{NH}_2\text{O} \quad \text{R, R}^1 = \text{alkyl, aryl} \quad 55-96\%
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