DEVELOPMENT OF GREEN METHODOLOGIES FOR SELECTED ORGANIC REACTIONS USING SOLVENTLESS TECHNIQUES OR AQUEOUS MEDIUM AS GREEN SOLVENT

A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

By

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NOVEMBER 2010

To My Parents and Teachers...

ABSTRACT

(Submitted as partial requirement for Ph.D. on June 16, 2010)

The motivation of this research work was to develop new protocols for some established chemical processes in accordance with the guidelines of green chemistry. The key control parameters were (i) elimination of toxic organic solvent usage by solventless techniques or (ii) use of water as reaction medium. Firstly, the concept of MORE and grindstone chemistry have been widely utilized in the process development with solventless techniques. Secondly, the catalytic efficacies of some existing chemicals have been studied in detail in coordination with our first strategy. Throughout our work, the regularity of the key principles of green chemistry was envisaged, such as: simplicity of procedure, enhanced reaction rates, yield and selectivity of products, energy efficiency and reusability of catalysts along with the improvements over classical methods. Three important organic transformations namely Henry reaction, Biginelli or Biginelli like reaction and ester enolate-imine condensation reaction were studied in detail. The other parameters of interest were solvent effect, electronic effect of substituent on product conversion, reactivity and action of catalysts, and reusability of catalyst *via* proper modeling of support. Novel protocols were established for Biginelli or Biginelli like reaction and Henry reaction under solventless grinding method and also in preparing some new β-lactam and β-amino ester compounds using easily available esters and simple Schiff base under simplified and mild conditions using ester enolate-imine condensation reaction.

Chapter 1: Introduction

Section 1A: *Green Chemistry and methods*

The chapter starts with motivation of the present work and provides a brief introduction of green chemistry and green techniques, primarily applied in our work. Green chemistry is the science which helps in addressing the issues of

environment protection from hazards of chemicals and processes at the design stage, and at the most fundamental level rather than treatment and abetment of pollution after their formation. It has further led to explore certain technologies which gained tremendous research interest. In this respect use of water as reaction medium, application of microwave energy and mechanical energy such as grinding under solventless conditions are fascinating. Along with dearth of information on various aspects of these methods, attention has been drawn towards advantages of their application in organic synthesis in terms of incorporation of maximum number of green matrices via this chapter.

Section 1B: *Background on Henry reaction, Biginelli or Biginelli like reaction & ester enolate - imine condensation*

The chapter comprises a thorough literature review on Biginelli or Biginelli like reaction, Henry reaction, and ester enolate-imine condensation reaction with prime emphasis on their classical and non-classical methods of synthesis, pharmacological and synthetic utility of these reactions and their products. With their versatility in providing a wide range of pharmacological and synthetic applications, realization of significances of their types as fundamental C-C bond forming reaction, multicomponent reaction (MCR) and single one pot route for assessing C(4) alkyl substituted β-lactams respectively have been emphasized. A brief account on the studies of mechanistic pathways and stereochemistry are also included. The loopholes associated with classical methods in terms of efficiency and environmental safety factors have been clearly pointed out throughout this chapter and their feasible greener solutions. A large numbers of improved protocols are reported in literature; they either involve slight modifications of the classical method or designing of new non-classical methods. This chapter has exclusively described these methods under different sections with their advantages over classical ones. The motivation of our work lies in the large scope and demand of more number of newer methodologies for Henry reaction, Biginelli type reactions and ester-enolate imine cyclocondensation because of their pharmacological importance. This towards the end will not only rectify the drawbacks of conventional methods but also lead to synthesis of newer compounds for development of compound

library of derivatives under the arena of incorporation of green matrices. Based on these insights through literature we found various possibilities of developing greener methods for above mentioned reactions which remained the goal in achieving the objectives. The scope and objectives of work are clearly defined here.

Chapter 2: Materials and methods

Details about the protocols used and the techniques for characterization of the products constitute this chapter along with instrumentation. These include: elemental analysis, chromatographic reaction monitoring and purification, recrystallisation, distillation methods, spectroscopy for structural assessment and instrumental details of microwave oven, melting point apparatus, spectrometer instruments etc. The general methods of synthesis of nitroaldol products, 5-substituted (or unsubstituted) 3, 4-dihydropyrimidin-2(1*H*)-ones, 3, 4-dihydropyrimidin-2(1*H*)-thiones, β-lactams and β-amino esters under different greener strategies have been described in detail. In addition, the reported methods used for the preparation of Schiff bases and supported catalysts have been mentioned with references.

Chapter 3: Development of synthetic strategies for nitro-aldol condensation using aqueous and solventless reaction medium

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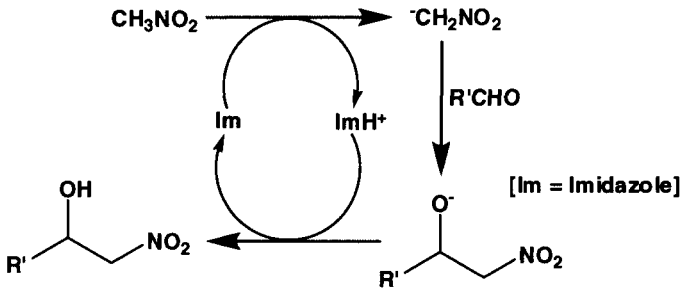
Section 3A: *Imidazole catalyzed Henry reaction in aqueous medium*

The Henry reaction involves base-catalyzed addition of nitroalkanes to a carbonyl compound to form nitroaldol. Reported catalysts such as alkali metal hydroxides, alkaline earth metal oxides, carbonates, bicarbonates, alkoxides etc. catalyze the reaction to great extent but concomitantly lead to the formation of unwanted side products because of competing side reactions such as Aldol condensation, Cannizzaro reaction, Tishchenko reaction and Nef-type reaction. Moreover, high content of bases used can lead to the formation of nitroolefins which polymerize easily. In an attempt to minimize the side product and maximize the yield, the conventional Henry reaction was

modified in presence of catalytic amount of base imidazole in eco-friendly solvent water at room temperature (*Scheme 3A*). To our observations, mild Lewis basicity of imidazole along with mild condition provided by aqueous medium have been able to suppress different competitive reactions associated with Henry reaction (product yield >90% in all cases) and hence eliminate the use as well as generation of toxic wastes.



Scheme 3A: Plausible reaction mechanism of Henry reaction catalyzed by recyclable imidazole in water

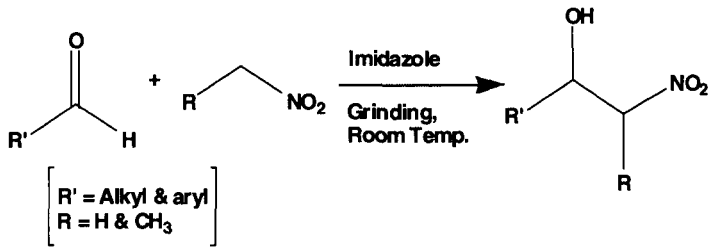
A general molar ratio of aldehyde: nitroalkane: imidazole at 1:3:0.25 in 1 mmol scale was used for all the reactions. The *recyclability* of imidazole was tested and the catalyst showed consistent activity and product selectivity for at least three cycles. *Solvent effect* has been studied using non-polar and polar (aprotic and protic) organic solvents and their 1:1 mixture with water. The results show that the reaction proceeds with much faster rate in polar (protic or aprotic) solvents because of homogeneity of reaction mixture and catalyst imidazole. To our surprise, the use of 50% water as a reaction medium does not alter the reaction rate and yield whereas use of water only gives the highest yield. This justifies the possible use of water as a greener solvent over conventional organic solvents. *Effect of substituents* on the reaction rate was investigated with a series of electron donating and withdrawing groups on the aldehyde keeping the nitroalkane constant. Electron withdrawing groups favor the reaction to a greater extent than electron donating groups irrespective of the side chain in nitroalkane. Also, aryl aldehydes show faster rates and higher yield (typically >90% yield) than aliphatic aldehydes (typically <60% yield).

Section 3B: *A new and simple approach toward synthesis of β-nitroaldols using solventless grinding method*

The catalytic activity of imidazole in synthesizing nitroaldol derivatives using solventless manual grinding in the context of Henry reaction was reported for

the first time as shown in *Scheme 3B*. The grinding technique presented here leads to an extension of the work presented in *section 2A*.

Scheme 3B: Henry reaction using grinding in presence of catalytic amount of imidazole



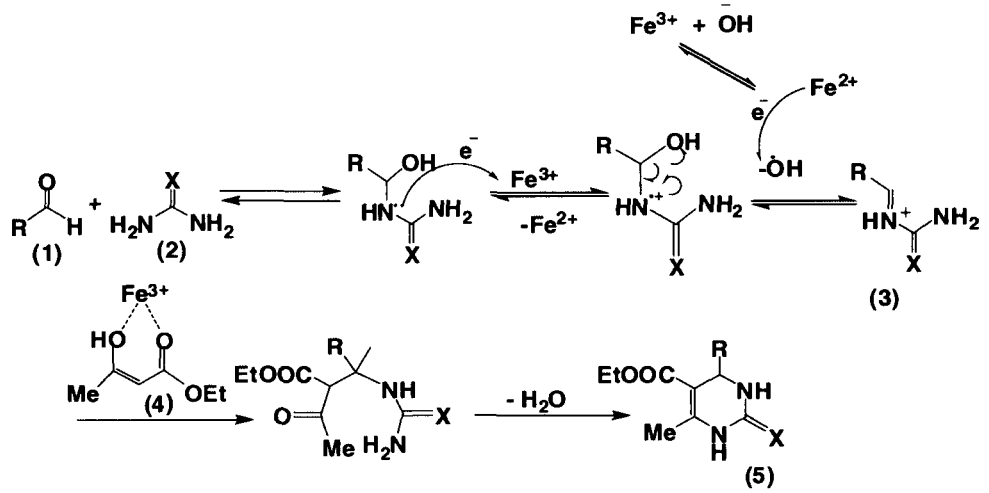
Drastic improvements in yield of isolated products and reaction rate over classical method have been observed in this protocol. The catalytic amounts of imidazole and nitroalkane play crucial roles in the overall conversion. Determination of effective amount of nitroalkane and the exact molar ratio of imidazole with respect to substrate has been established after several test experiments. We found that the reaction shows the best result with molar ratios of 1:5:0.35 in 1 mmol scale of benzaldehyde, nitromethane, and imidazole. With 0.25 mmol of imidazole, it yielded only 60% of 2-nitroalkanol within 5 minutes as monitored by TLC. Interestingly, 0.25 mmol of imidazole was however found to be sufficient to complete most of the reaction of the aromatic aldehyde within a short period of time in the aqueous phase as reported in *section 2A*. This implies, in solid state this amount of catalyst is not sufficient to catalyze the Henry reaction. Utilizing the optimized molar ratio, large variety of aldehydes ranging from aliphatic to aromatic to heterocyclic aldehydes was used in a series of reactions. The various electron withdrawing and donating substituents on aldehydes affected the reaction rate and yield which follows the same trend as observed in *section 2A*. The chapter also provides interesting results obtained regarding reaction rate enhancement, mainly those involving liquid-liquid and solid-liquid substrate pairs through charging friction enhancing material sand.

Chapter 4: Development of synthetic strategies for Biginelli (or like) reaction using solventless techniques

***Section 4A**: A new protocol for Biginelli (or Biginelli like) reaction under solvent-free grinding method using Fe $(NO_3)_3.9H_2O$ as catalyst*

Under the utilization of green chemistry, solid state (solventless) grinding reactions have gained importance because they are more eco-friendly, involve low costs, produce higher yields and simplicity in process and handling make them suitable for industrial process development. Also, multi component reactions (MCR) have gained wide importance because of their possible exploitation to generate a compound library of biologically active compounds. One such MCR is the classical *Biginelli (three components) reaction, which involves acid catalyzed one pot condensation of an aldehyde, a β-ketoester and urea in ethanol for the synthesis of 3, 4-dihydropyrimidinone derivatives* (DHPM). A novel protocol for Biginelli (or Biginelli like) reaction under solvent-free grinding method using catalytic amount of hydrated ferric nitrate or clay impregnated ferric nitrate (clayfen) has been described in this chapter. Manual grinding using mortar and pestle and utilization of strong oxidizing agent and its supported form using clay (for example) for the synthesis of 3,4-dihydropyrimidinones (DHPMs), specifically 5-unsubstituted derivatives using solventless grinding technique for the first time form the basis of the chapter. A large number of DHPM derivatives have been synthesized with an optimized molar ratio of carbonyl compound: aldehyde: urea (or thiourea): catalyst as 1:1:1.5:0.1 in 1 mmol scale using various catalysts and aldehydes. It was observed that except $Fe(NO_3)_3.9H_2O$ and clayfen, all others catalysts were inactive for this reaction. The hydrated ferric nitrate took less reaction time (typically 1.5hr, yield >90%) as compared to supported catalyst (clayfen, typically 3hr, yield ~80%). Furthermore, the catalyst $Fe(NO_3)_3.9H_2O$ retained its activity in organic solvents as reaction medium. A plausible mechanism (based on the original route proposed by *Kappe*) of the three component reaction in presence of the catalyst $Fe(NO_3)_3.9H_2O$ is shown in *Scheme 4A*. The good performance of hydrated iron (III) nitrate as catalyst may be ascribed to its easy electron accepting property as a strong oxidant which catalyzes the formation of imnium intermediate in the slowest step as well as activating β-ketoester. Problem encountered in regeneration and recycling of $Fe(NO_3)_3.9H_2O$ was overcome by clayfen as catalyst (prepared using a reported method). The separation of the catalyst was achieved by simple

filtration via post washing several times with hot ethanol and dried in a vacuum desiccator for reuse. Reactions were monitored with TLC and FT-IR.

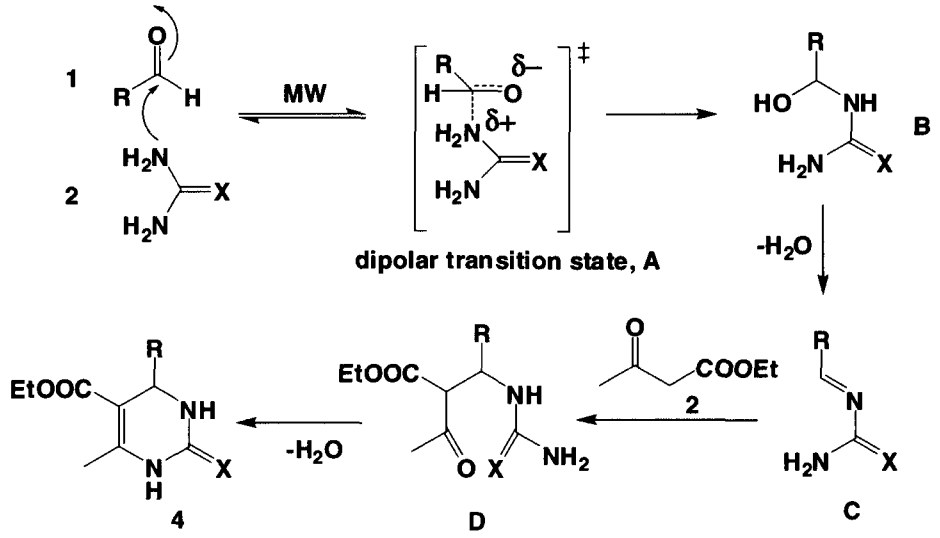


Scheme 4A: Plausible mechanism for 3-component Biginelli (or Biginelli like) reaction

Section 4B: *Investigation of Biginelli reaction under solvent less microwave irradiation in absence of catalyst*

This chapter accounts for studies related to the development of protocols based on solvent less MORE techniques for Biginelli reaction and ester enolate-imine cyclocondensation reaction. Biginelli reaction under solvent less and catalyst free condition has been performed by taking a homogeneous mixture of the aromatic aldehyde: β-ketoester: urea or thiourea in 1 mmol scale with a molar ratio of 1:1:1.5 in a 100ml beaker and irradiated inside the cavity of a domestic MW oven (*Samsung C103FL*) in neat at specified power level (180-900W). Most of the reactions completed at applied power level of 600 W. Lower power levels (~180W) were not sufficient to bring the complete conversion. The isolated yields of crude products are > 90% almost in all cases. Effect of MWI will be more prominent in case of polar pathways (Loupy *et al.*). As far as mechanism (*Scheme 4B*) of the reaction is concerned, we believe the reaction proceeds with an increase of polarity via the formation of dipolar transition state. Consequently in solvent-free condition, favorable outcomes are expected. The efficacy of using MWI as an energy efficient method can be realized by the significant decrease in reaction time due to rapid heating in MORE as compared to that reported under solvent less and

catalyst free Biginelli reaction at 100-105°C for an hour (Ranu *et al.*) and also to that reported in classical method.



Scheme 4B: Biginelli reaction pathways involving a dipolar transition state

Chapter 5: Development of synthetic strategies for ester enolate-imine condensation reaction

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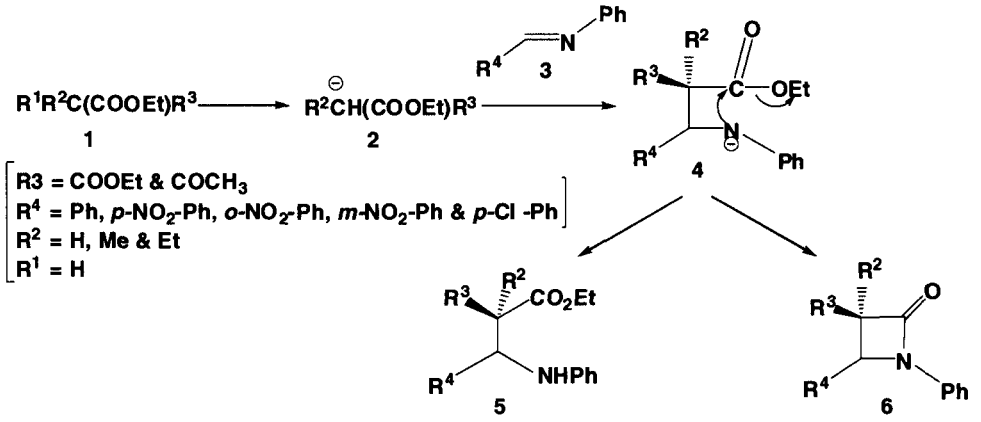
***Section 5A**: Investigation of solvent effect on ester enolate-imine condensation in basic condition*

Experiments have been carried out in designing a three component one pot pathway for ester enolate-imine cyclocondensation using benzaldehyde, aniline and diethylmalonate using base K_2CO_3 in methanol. However, it involves Knoevenagel condensation as the competing reaction under this condition which suppresses the formation of β- lactam or β- amino ester. Thus reaction protocols were designed following the traditional route of employing prepared Schiff bases for condensation with enolate. Traditional method of ester enolate-imine cyclocondensation for the synthesis of β- lactams or β-amino esters or both involves critical reaction conditions along with the use of large amount of toxic organic solvents. There is lack of simple and eco-friendly protocols. Emphasis is mainly on an aqueous method. Feasibility of ester enolate-imine cyclocondensation is checked by creating aqueous basic medium with bases like K_2CO_3, KF, Al_2O_3, imidazole, Dowex-60, K_2CO_3/Cetrimide, Na_2CO_3/TBAB, polyvinyl pyridine and KF/Al_2O_3 at room

temperature. All of these conditions failed to show reaction feasibility except Na_2CO_3/TBAB which facilitates only 30% reaction conversion in water after 48 hours. To examine any increase in the reactivity of Na_2CO_3/TBAB, a biphasic system of H_2O/THF was utilized. Though a slight increase in reaction conversion was observed within 12 hours of reaction progress, the conversion was not smooth with large number of byproduct formation which further rose on increasing the reaction time to 24 hours. Reactivity of these bases in other organic solvents such as MeOH and DCM is also nil. However, KF/Al_2O_3 in acetone under reflux condition at 56^{O}C shows higher conversion (greater than 90%). Extension of this reaction condition to different substrates leads to the synthesis of novel β- lactam and β- amino ester compounds (*Scheme 5A*).



Scheme 5A: Synthesis routes for novel β- lactam and β- amino ester

In all the reactions the common product is the β-amino ester (**5**) which is accompanied by β-lactam compound (**6**) especially in reactions with bezaldimine and Cl-substituted bezaldimine. This common trend suggests that the base KF/Al_2O_3 is capable of generating enolate *in situ* which react with aldimines to form β-amino ester, passes through a transition state, followed by gradual cyclization to afford β-lactam in some cases. Product selectivity indicates that fate of transition state is controlled by the electronic effects of the substituents on the aldehyde and also by the α-substituents of diethylmalonate derivatives. Importance of this new strategy is that it is a simplified and convenient version of one pot ester enolate-imine cyclocondensation utilizing easily available esters and simple nonenolizable N-aryl aldimines.

***Section 5B**: Formation of β-amino-ester/β-lactam using ester enolate-imine condensation reaction under microwave irradiation method*

Microwave specific effects mainly in case of solventless systems leading to rapid heating can also be realized in case of ester enolate-imine cyclocondensation on using basic alumina. Recent work (Li *et al.)* showed that various active methylene compounds such as diethyl malonate, nitromethane, cyclohexanone, ethyl acetoacetate and acetylacetone as donors in Michael addition are catalyzed by KF/basic alumina; this leads to our present investigation on ester enolate-imine cyclocondensation catalyzed by KF/Al_2O_3. A set of test experiments with diethylmalonate (1 mmol), and N-phenylbenzaldimine (1 mmol) under microwave irradiation were carried out using KF/Al_2O_3, different amounts of alumina and also with KF separately. It was observed that KF (3 mmol) alone cannot facilitate the reaction, while supported catalyst of KF with alumina (500 g; 3 mmol KF) showed reactivity to some extent with a very low yield (~42%) of only the β-amino ester product. Moreover, prolonged irradiation and increased MW power level leads to charring of the reaction mixture. When only basic Al_2O_3 (1g) is used under MW irradiation with power 600 watt, only 40% yield of amino ester is attained. On increasing the power level to 1250 W, enhancement of yield up to 67% is observed. The same trend in product selectivity is observed here as found in chapter 5 which is an indication that reaction passes through a transition state (*Scheme 5A*), whose fate is controlled by the electronic effects of the substituents on the aldehyde and also by the α-substituents of diethylmalonate derivatives.

Chapter 6: Summary and future scopes of the present work

The chapter gives the summary of the above mentioned work with an insight into the significances of the protocols developed for Henry reaction, Biginelli or Biginelli like reaction, and ester enolate-imine condensation reaction under different conditions in terms of green chemistry. Future scopes and prospects of the present work have also been mentioned in this part of the thesis.

DECLARATION

I agree that my PhD thesis entitled "*Development of green methodologies for selected organic reactions using solventless techniques or aqueous medium as green solvent*" will be lodged in the University Library, and made available (if applicable after the expiry of any period of approved restricted access) to any person(s) entitled to use the Library and may be photocopied or microfilmed by or on behalf of the Librarian for use for research or private study pursuant to the provisions of the Copyright Act 1968.

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CERTIFICATE

This is to certify that the thesis entitled ***"Development of Green Methodologies for Selected Organic Reactions using Solventless Techniques or Aqueous Medium as Green Solvent"*** submitted by Ms Mridula Phukan, Research Scholar, Department of Chemical Sciences, Tezpur University, is a record of research work carried out under my supervision since July, 2006 for the degree of Doctor of Philosophy . She has been duly registered (Registration No. 012 dated 17-06-2010) and has fulfilled all the requirements under the rules and regulations for the award of Doctor of Philosophy of the Tezpur University.

It is certified that the thesis is the result of her own investigations on the subject. No part of this thesis has been submitted elsewhere for award of any other degree or diploma.

(Signature of the thesis supervisor)

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This is to certify that the thesis entitled ***"Development of green methodologies for selected organic reactions using solventless techniques or aqueous medium as green solvent"*** submitted to the Tezpur University in the Department of Chemical Sciences under the School of Science and Technology, in partial fulfillment for the award of the Degree of Doctor of Philosophy in Science, has been examined by us on .....and found to be satisfactory.

The committee recommends for the award of the Degree of Doctor of Philosophy.

Principal Supervisor

External Examiner

Date:

Date:

ACKNOWLEDGEMENTS

I would like to express my heartfelt gratitude to many supportive people at Tezpur University, without whom this thesis would not have been possible.

Firstly I wish to thank my thesis supervisor, Dr. Ruli Borah, whose endless patience, enthusiasm, support and suggestions were my constant source of energy and confidence. I feel myself lucky for not only being a member of her research group but also as her first Ph. D. student. My thanks also go to Head of department of Chemical Sciences and my departmental research committee members, Prof. N. S. Islam and Dr. A. J. Thakur for their enormous suggestions, encouraging words and helpful advice. In the early part of the work, my sincere thanks go to the co-supervisor Dr. R. C. Deka in the UGC sponsored project, for his insight into the theoretical aspects of work. I will always remain grateful to all the other faculty members of the department for their help and encouraging words that I received time to time.

I am gratified to Vice Chancellor of Tezpur University for providing me institutional fellowship and also to UGC, New Delhi for financial support.

I am grateful to the administrative and technical staff of the Department of Chemical Sciences, Dr. B. Saikia, Dr. B. Gohain, R. Borah, N. Dutta, S. Phukan and R. K. Borah for their help and support in analytical tools such as FT-IR, ^{1}H-NMR, CHN and GC-MS. Labmates Diganta -da, Kalyan-da, Siva Prasad, Jeena and Papiya remain thankful forever who were always ready to help; they are the people who nourished the research environment within the laboratory. Discussions, suggestions and fun that I shared with them will always remain as a sweet memory. I would also like to specially thank my undergraduate chemistry teachers from Darrang College: Dr. Pankaj Hazarika, Dr. Paritosh Mondal and Dr. Palash Moni Saikia who inspired me to pursue a research career at Tezpur University. My heartfelt thanks also go to all the research scholars and friends of the department for the beautiful moments they shared with me and also for academic helps. I am also grateful to previous research scholars Dr. S. Dutta and Dr. S. S.Mahapatra for

valuable help and suggestions. Here I would be happy to mention people/my friends from different institutes whose unconditional support and help enabled me to cross all hurdles that came along the journey; they are Ranjit, Sanjeev, Mousumi, Laksheswar, Bipul, Jayanta Madhab, Rupam, Rana-da and Dr. S. Bharadwaj. I am very fortunate to have a friend like Dhrubajyoti who always stood strong beside me to support and encourage at stressful and tough times.

I gratefully acknowledge Department of Chemical Sciences, Sophisticated Equipment Facilities and Central library at Tezpur University for technical and resource related facilities. My acknowledgement also goes to Central Instrumentation Facility (CIF) and Department of Chemistry, IIT Guwahati and NEIST, Jorhat.

Finally, I would like to give special and sincere thanks to my beloved parents and my lone sister Dr. Monjula for their unwavering encouragement. In particular I would like to thank my mother for her extra effort in taking care of my health in these hectic days and helping me in keeping endurance at tough times.

I will probably forget what I have been through; however, I will keep all the courage and confidence and effort through my entire life.

Mridula Phukan

Tezpur University

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ABBREVIATIONS / SYMBOLS USED

^{13}C	Carbon -13 isotope
AFM	Atomic Force Microscopy
$CDCl_3$	Deuterated chloroform (used as NMR solvent)
CHN	Carbon Hydrogen Nitrogen
CTACl	Cetyltrimethylammonium chloride
Cy	Cyclohexyl
DCM	Dichloromethane
DFT	Density Functional Theory
DHPM	Dihydropyrimidinone
DME	Dimethoxyethane
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
DMSO-d_6	DMSO-hexadeuterated (used as NMR solvent)
EHS	Environmental, Health and Safety
EPA	Environment Protection Act
Eq.	Equation
Et	Ethyl
Et_2O	Diethyl ether
EtOH	Ethanol
FGI	Functional Group Interconversion
FT-IR	Fourier Transform - Infra Red
GCMS	Gas Chromatography Mass Spectroscopy
HIU	High-Intensity Ultrasound
HIV	Human immunodeficiency virus
HMPA	Hexamethylphosphoramide
HT	Hydrotalcites
Hz	Hertz
^{i}Pr	Isopropyl
IUPAC	International Union for Pure and Applied Chemistry
LCA	Life-Cycle Assessment
LDA	Lithium diisopropylamide
Ltd.	Limited
m	Meta
MCP	Mechano Chemical Process
MCRs	Multicomponent Reactions
Me	Methyl
Me_2O	Dimethyl ether
MeOH	Methanol
MORE	Microwave Enhanced Organic Reaction
MTBD	Methyl -TBD
MW	Microwave
MWI	Microwave Irradiation
NBS	N-Bromosuccinimide
NMR	Nuclear Magnetic Resonance
o	Ortho
p	Para

Ph	Phenyl
PhH	Benzene
ppm	Parts per million
PsTBAC	Polystyrene-Supported Tributylammonium Chloride
P-TBD	polymer supported TBD
p-TsOH	Para-Toluenesulfonic acid
RADAR	RAdio Detection And Ranging
tan δ	Dielectric Loss tangent
TBAB	Tetra Butyl Ammonium Bromide
TBD	1, 5, 7-triazabicyclo [4.4.0] dec-1-ene
^{t}Bu	Tertiary butyl
^{t}BuOK	Potassium tertiary butoxide
TFA	Trifluoroacetic acid
T_{fusion}	Eutectic Temperature
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMEDA	N,N,N′,N′-tetramethylethylenediamine
TMG	Tetramethylguanidine
TMSCl	Trimethylsilyl chloride
TMSI	Trimethylsilyl iodide
UV	Ultra Violet
W	Watt
A	Arrhenius constant
E	Entgegen/ trans
R	Gas constant (8.314 $JK^{-1}mol^{-1}$)
R	Rectus
S	Sinister
Z	Zusammen/ cis
$\Delta G^{\ddagger}$	Change in Gibbs free energy of activation
brs	Broad singlet (in NMR)
c.e.d	Cohesive Energy Densities
C_2	2- fold axis of rotation
cal	Calorie
d	Doublet (in NMR)
h	Hour
k	Rate constant
m	Multiplet (in NMR)
M	Mega
mg	Milligram
Mins	Minutes
mL	Milliliter
mm	Millimeter
mmol	Millimole
^oC	Degree Celsius
Pa	Pascal
P^H	-log (Hydrogen ion concentration)
pK_a	Acid dissociation constant
q	Quartet (in NMR)
r.t	Room Temperature

S_N1	Nucleophilic substitution unimolecular
T	Temperature (in Kelvin)
t	Triplet (in NMR)
δ	Chemical shift (in NMR)
ε	Dielectric constant
ε'	Relative permittivity
ε''	Dielectric loss
π	Internal pressure

Chapter 1

Introduction

Section 1A

Green Chemistry and Methods

1A.1 Motivation

The work in this thesis to develop green methodologies for Henry reaction, Biginelli or Biginelli- like reaction and enolate- imine condensation reactions is motivated by recent advancement in organic synthesis revolutionized by Green Chemistry in view of protecting ecological factors from chemical hazards. Such processes have not only added advantages to a reaction by eliminating toxic solvents, reducing number of reaction steps, simplifying work up stage, reuse of reagent or catalyst but also facilitate reactions which are not even possible under conventional methods. The significances of above mentioned reactions and their products are diverse; however, they are futile if achieved at the cost of environment and health hazards. It is thus interesting to design improved protocols for them in order to overcome the drawbacks associated with their classical methods and also exploring newer strategies so as to accelerate the pursuit of scientific unknowns within the field of Green Chemistry.

1A.2 Green chemistry

Green chemistry is that ideal science both in theory and practice which has emerged out of the growing concern to prevent growing environmental pollution out of chemical processes and manufacture [1]. The rising health and environment hazards because of chemical manufacturing and utilization prompted legislation to form laws which will regulate and control manufacture, use and disposal of chemicals. Thus Environment Protection Act (EPA) was established in 1970, which passed over 100 environmental laws with 12 considered as major ones. These laws however mainly deal with treatment and abetment of pollution after their formation. It is in 1990[2] when

EPA gave focus on pollution prevention rather than typical treatment and remediation and in 1991 'Green Chemistry' has gained formal consideration. Green chemistry is defined[3] by IUPAC as: *"The invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances"*. The twelve tenants of green chemistry given by Anastas and Warner are as follows [4]:

1. Prevent waste
2. Design safer chemicals and products
3. Design less hazardous chemical syntheses
4. Use renewable feed stocks
5. Use catalysts, not stoichiometric reagents
6. Avoid chemical derivatives
7. Maximize atom economy
8. Use safer solvents and reaction conditions
9. Increase energy efficiency
10. Design chemicals and products to degrade after use
11. Analyze in real time to prevent pollution
12. Minimize the potential for accidents

Thus, any greener synthesis involves pulling together tools, techniques and technologies to design and develop more eco- friendly and efficient products and processes along with financial benefits. Green chemistry has made it possible to explore certain technologies which gained tremendous research interest. Some significant trends have been approached by our works which are discussed in next sections.

1A.3 Aqueous reaction medium

The discoveries of Breslow[5] and Grieco[6] in the early 1980s showing the efficiency of water in enhancing rates and selectivity of Diels-Alder reactions are often recognized as the "Big Bang" in aqueous synthesis that started new route for organic synthesis. Water as reaction medium remained neglected for a long time because of the insolubility of organic compounds and incompatibility of the intermediates in water. Besides the Diels-Alder reaction, new additions are continuously being made to the list of organic

transformations which include[7-8] Claisen-rearrangements, Aldol reaction, allylation reactions and oxidations and hydrogenations of alkenes, to mention a few. There are many advantages of using water as reaction medium[9] which are as follows:

- Water is naturally available and safe to handle.
- Water provides mild conditions, leading to improvements in yields and product selectivity.
- Tedious protection and deprotection steps can be avoided, particularly in carbohydrate, nucleoside or peptide chemistry.
- Water can facilitate ligand exchange in transition metal catalyzed reactions.
- Water insoluble catalysts can be reused by filtration and decantation.
- Water soluble catalyst can be reused in homogeneous condition.

Synthetic organic reactions in aqueous media at ambient or slightly elevated temperatures have become interesting because of unique reactivity and selectivity[9a]. Water directs the selectivity of synthetic organic reactions through the interaction of nonpolar or hydrophobic regions of the reactants. These forces are normally too weak to compete with any steric and electronic effects in organic solvents whereas in water, hydrophobic interaction is strong as a result of the tendency of water to exclude nonpolar species and thus minimize the Gibbs energy of solvation, a phenomenon known as the *hydrophobic effect*[10]. There is another effect known as *hydrophobic hydration* which decreases the rate of aqueous phase organic reactions and it occurs on transfer of non-polar solutes to water which is thermodynamically an unfavorable process. Temperature and pressure also bring changes to physicochemical properties[11] of liquid water. e.g. when temperature is raised from 25°C to 300°C, density of water decreases from 0.997 to 0.713 (g cm^{-3}), its dielectric constant decreases from 78.85 to 19.66, its cohesive density decreases from 550 cal cm^{-3} to 210 cal cm^{-3}, and its pK_a decreases from 14 to 11.30 (and thus water can behave as an acid- base biocatalyst). This shows the

applicability of water in recycle, regeneration, disposal and detoxification of chemicals. Reactivity in water is also influenced by the solute-solvent interaction and reorganization of solvent around the solute[11]. For example, in S_N1 solvolysis reactions where it passes through a more polar transition state, solvent like water with high dielectric constant $\varepsilon = 78$, would accelerate the reaction by rendering strong interaction between carbocation and solvent in the transition state. Whereas in non-polar reactions such as Diels-Alder cycloaddition; the reaction rate is enhanced by hydrophobic effect of water, attributed to high cohesive energy density. When two hydrophobic molecules susceptible to reaction, are put together in water, apart from hydrophobic interaction another effect comes to play which is called *enforced hydrophobic interaction.* To take advantage of this effect, the reactants must be at least partially dissolved which can also be achieved by implanting the hydrophobic moiety onto a hydrophilic residue[11]. Thus, the efficacy of water as a solvent is widely believed to be due to the unique physicochemical properties of water. They are: (a) smaller size of molecule, (b) high cohesive force (Table 1A.1), (c) large heat capacity, (d) large surface tension, (e) low compressibility, (f) decrease of viscosity with pressure, (g) Maximum density at 4°C, (h) hydrophobic effects arising in water solution of non polar solutes.

Table 1A.1: Internal Pressures, Dielectric constant (ε) and Cohesive Energy Densities (c. e. d) for some common solvents (25°C)

Solvent	c. e. d (cal/cm^3)	Internal Pressure/π (MPa)	Dielectric constant (ε)
Water	550.2	41.0	78
Formamide	376.4	131.0	109
Methanol	208.8	70.9	32.7
Dimethyl sulfoxide	168.6	123.7	47
Dimethylformamide	139.2	114	37
Acetone	94.3	79.5	21
THF	87	-	7.6
Hexane	52.4	57.1	1.9
Diethyl ether	59.9	63.0	4.3

In case of reactants, sparingly soluble in water, co-solvent is used with water and the effects of water are attained in that biphasic reaction medium.

Alternatively, use of miscible co-solvents as well as surfactants or hydrophilic phase transfer agents such as carbohydrates, sulfonates, or carboxylate groups on hydrophilic reactants or ligands can enhance the solubility. Further reaction rate can be enhanced in pure water by adding some additives which acts as salting-in or salting-out agents[11]. Depending upon the solubility of reacting species and products in water, reaction mixtures can be both homogeneous and heterogeneous. The amount of water can also range widely, from sub stoichiometric quantities to a large volume in which the reactants are suspended or dissolved. Several terms have been used in the literature to describe reactions in aqueous medium. *In water*, *in the presence of water*, and *on water* are commonly found in the recent publications and are often used[12].

1A.4 Solventless techniques

The use of solvent in organic synthesis has earlier been considered indispensible until the emergence of solvent less method[13a]. Removing organic solvents in chemical synthesis is important as organic solvents are high on the list of toxic or otherwise damaging compounds because of the large volumes used in industry, and difficulties in containing volatile compounds. The solvent-free syntheses are found to be superior over those carried out in solvent[13b] in the following points.

- There is no reaction medium to collect, purify and recycle.
- The compounds formed are often sufficiently pure to circumvent extensive purification using chromatography, and indeed in some cases the need for recrystallization.
- Sequential solvent less reaction is possible leading to high yield.
- The reactions can be rapid, often reaching substantial completion in several minutes compared to hours in organic solvents.
- There is often no need for specialized equipment for reaction set up.
- Energy usage can be much lower.

- The need for pre-formed salts and metal–metalloid complexes may often be dispensed with.
- Functional group protection-deprotection can be avoided.
- Lower capital outlay for equipment in setting up industrial processes.
- Considerable batch size reduction and processing cost savings are achievable such that such solvent-free protocols are not only more environmentally benign but are also more economically feasible.

In the literature these reaction conditions are often described as 'solvent less', in addition to the term 'solvent free'. However, F. M. Kerton suggested the word 'neat' to be a better description to explain the highly concentrated nature of the reagents which lack additional solvent in order to remove confusion in many instances[14]. Some of the solid phase reactions have been reported to be solvent free but they clearly involve the formation of a liquid phase, e.g. Aldol condensations and oligomerisation of benzylic compounds to form cavitands, proceed *via* a liquid phase. Many non-catalytic reactions including Baeyer–Villiger oxidations, oxidative coupling of naphthols using iron chloride, condensation of amines and aldehydes to form azomethines, homo-etherification of benzylic alcohols using *p*- toluene-sulfonic acid, and nuclear aromatic bromination with NBS[13b]. This liquefaction implies the presence of a eutectic mixture with T_{fusion} below ambient temperature. Thus intervention of a liquid phase resulting from the occurrence of a eutectic (or peritectic) melt phase led Rothenberg et al to distinguish these so called solvent free reactions are from solid-phase synthesis and solid-solid reactions or solid-state synthesis[15]. Accordingly,

- *Solid-phase synthesis* is the reaction of molecules from a fluid phase with a solid substrate, e.g. solid phase peptide syntheses.
- *Solvent-free synthesis* involves any system in which neat reagents react together, in the absence of a solvent.
- *Solid-state synthesis* or solid-solid reactions, in which two macroscopic solids interact directly and form a third, solid,

product without intervention of a liquid or vapor phase[15]. (*Figure 1A.1*)

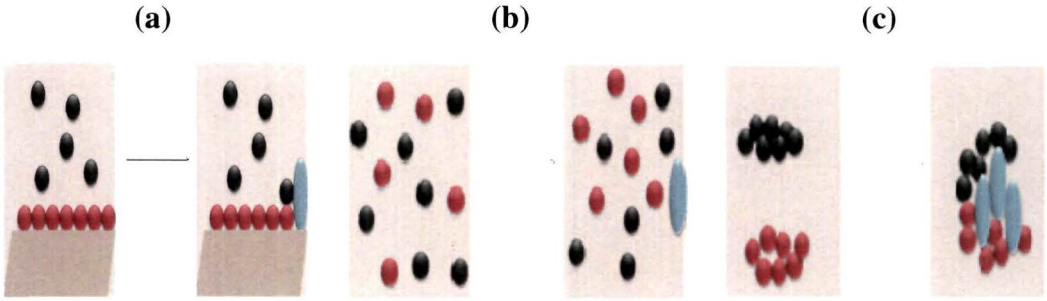


Figure 1A.1: Cartoon of solid phase reaction (a), solvent-free reaction (b), and solid-state reaction (c) [adapted from Ref.15].

Solvent free organic synthesis covers a wide range of synthetic methodologies and more new methods are continuously growing. Consequently, apart from thermal and photochemical solvent free reactions, nowadays alternative energy sources like microwave energy and mechanochemical energy are associated with these solvent free reactions for better results in terms of greener synthesis which further need developments in engineering reactor technology. Thus, solvent free microwave irradiation and grinding have emerged as the newest trends of green methodologies.

1A.4.1 Microwave Organic Reaction Enhancement (MORE)

The direct use of microwave energy to heat chemical reactions and its advantages was described for the first time by Gedye and his co-workers in 1986[16]. The exploitation of MORE is not only confined to organic synthesis[17] but gradually covering areas like medicinal chemistry/drug discovery[18], polymer synthesis[19], material sciences[20], and nanotechnology[21], and biochemical processes[22]. In many instances, controlled microwave heating under sealed vessel conditions dramatically reduce reaction times, increase product yields, and enhance product purities by reducing unwanted side reactions compared to conventional synthetic methods. Microwave region is in between infrared radiation and radio waves in electromagnetic spectrum having wavelengths between 0.01m and 1m and a frequency range between

0.3GHz and 300GHz. In order to avoid interference with Microwave RADAR equipment which operates at the lower wavelengths (0.01-0.25 m), the wavelengths at which industrial and domestic microwave apparatus operate worldwide is regulated at 2.450 (+/- 0.050) GHz. In Microwave chemistry the reaction mixture absorbs microwave energy, using "microwave dielectric heating" phenomena such as dipolar polarization or ionic conduction mechanisms[23]. In dipolar mechanism, a molecule with a dipole moment when trying to reorient itself with respect to an alternative electric field of microwave radiation loses energy in the form of heat through molecular friction. The heat generated depends on the nature of the dipole and the frequency of the applied radiation[24]. Similarly, in conduction mechanism, under the influence of an electric field a solution containing ions will move through the solution, resulting in expenditures of energy due to an increased collision rate converting the kinetic energy to heat. Thus, in both these mechanisms energy dissipation at the core of the materials allows internal heating in molecules and more regular distribution of temperature compared to classical heating where heating is a conduction process. Moreover, internal heat transfer results in minimized wall effects (due to collision) which results in diminished catalyst deactivation. The ability of a material to convert electromagnetic energy to heat (dielectric loss tangent, tan δ) at a given frequency and temperature is calculated using the following equation:

tan $\delta = \varepsilon'' / \varepsilon'$, where, ε' (relative permittivity) = measure of the ability of a molecule to be polarized by an applied electric field. ε'' (dielectric loss) = ability of medium to convert dielectric energy into heat.

Table 1A.2: Loss Tangents (tan δ) of different solvents (2.45GHz, 20°C)[25]

Solvent	tan δ	Solvent	tan δ
Ethylene glycol	1.350	Water	0.123
Ethanol	0.941	Chloroform	0.091
DMSO	0.825	Acetonitrile	0.062
MeOH	0.659	Acetone	0.054
1,2-dichlorobenzene	0.280	THF	0.047
Acetic Acid	0.174	Dichloromethane	0.042
DMF	0.161	Toluene	0.040
1, 2-dichloroethane	0.127	Hexane	0.020

A high value for tanδ indicates a high susceptibility to microwave energy. Polar solvents have high tanδ value and therefore, preferably absorb microwave (*Table 1A.2*) compared to non-polar solvents with lower dielectric constants[26]. Non-polar solvents with lower dielectric constants are not heated under microwave irradiation. However, use of non-polar solvents under microwave condition is possible on addition of small amounts of alcohols or water to these solvents or addition of salts. Apart from polarity, another property that needs consideration before applying microwave energy is the boiling point of solvent. This is due to the superheating of solvents which increases the boiling points of solvents up to 26°C, above their conventional values on using microwave irradiation[26]. Thus, the solvent to be used must have a dipole moment and a boiling points at least 20-30°C higher than the desired reaction temperature. In microwave assisted synthesis homogeneous mixture is preferred over heterogeneous mixture[24].

For carrying out chemical reactions microwave reactors are preferred over domestic microwave ovens because they have the facility of monitoring and controlling the reaction temperature and thus reduce the risk of flammability and explosion. All of today's commercially available dedicated microwave reactors have built-in magnetic stirrers with IR sensors, and software that enables on-line temperature/ pressure control by regulation of microwave power output[26]. Presently, there are two types of microwave reactor used in organic synthesis: (a) multi-mode oven and (b) mono-mode oven[27]. The reaction vessels employed are typically made out of (nearly) microwave transparent materials such as borosilicate glass, quartz, or Teflon.

Reviewing the present literature it appears that today most scientists agree that in the majority of cases the reason for the observed rate enhancements is the result of a thermal/kinetic effect[28]. Interesting study on rapid heating leading to rate enhancement was reported by Loupy et.al. While heating under microwave is described by microwave effect; speeding up (shorter reaction time) of chemical reactions is related to specific microwave effects. The origin of specific microwave effect involves a thermal effect responsible for the intervention of hot spots and non- thermal (other than simple dielectric heating). Non- thermal effect is associated with increase in

pre-exponential factor A and decrease in activational energy, results in increase of k (rate constant) [28] (based on Arrhenius law, $k = Ae^{\frac{-\Delta G^{\#}}{RT}}$). Though polar solvents are good microwave absorbers, they may mask the specific microwave effects on reactants and reaction rate remains nearly same as conventional heating. Thus, the most useful situation to achieve rapid heating is solvent free conditions in presence or absence of inert solid supports such as various clays, aluminium oxides and silica[23], since microwave effects are not masked by solvent absorption. However, when polarity is increased from ground state to transition state the specific microwave effects are expected which accelerates the rate.

Recently, Kappe and Razzaq[29] addressed the question whether "greenness" of microwave heating in chemical processing can be considered as energy efficiency. Kappe and Razzaq showed that in case of open-vessel reflux processing, microwave dielectric heating required significantly more energy than conventional techniques using oil baths or heating mantles. This is a consequence of the comparably low energy efficiency of the magnetron (present in the microwave oven) in converting electrical to microwave energy and energy savings can be achieved only with sealed- vessel microwave processing at high temperature. This indicates that energy saving is connected to reduced time and is not an inherent feature of microwave heating[29]. Therefore it can be interpreted that it is rapid microwave heating and not microwave heating itself which makes the process energy efficient. Avoiding organic solvents during the reactions in organic synthesis generate a clean, efficient, and economical technology along with various advantages such as safety to handle, simple isolation procedure and decrease of cost. One limitation of using solvent free technique is the difficulty to obtain good temperature control at the surface of the solids which leads to problem regarding reproducibility of experimental results.

1A.4.2 Solvent less grinding

More and more green techniques are emerging in a quest to develop eco-friendly and efficient conditions as alternatives to the hazardous and complex

conventional chemical processes. Of these non-conventional techniques, solventless grinding is gaining popularity as the simplest and the newest green method[30]. In recent years the dramatic increases in the investigation of the solvent-free reactions under grinding have been seen[30-32], such as the Grignard reaction, Knoevenagel condensation, Aldol condensation, Dieckmann condensation, Reformatsky reaction, reduction, and other reactions.

Solventless grinding is a form of mechanochemical processes. Mechanochemical processes (MCP) use mechanical energy to activate substances by developing structural changes. The establishment of mechanochemistry as a separate branch of chemistry is usually attributed to Mattew Carey Lea at the end of the 19th century[30], who demonstrated that halides of gold, silver, platinum and mercury decomposed to halogen and metal during fine grinding in a mortar but melt or sublime undecomposed when heated. Mechanochemical process has been used mostly and only for inorganic solids until recently when the pioneering work of Toda and coworkers revealed application of this method to purely organic reactions. Mechanochemical mixing or process includes simply grinding reactants manually, using mortar and pestle as well as the more effort-free use of ball mills[33]. These techniques have many advantages: reduced pollution, low costs, simplicity in process and handling and more importantly eliminating excessive and wasteful heating. While ball milling can be easily scaled up and thus providing increased use in the paint industry, material science, pharmaceutical industry, and also for environmental remediation, simple grinding with mortar and pestle is still to be accepted industrially[34]. The groundbreaking work of Toda *et al.*[13a] shows that manual grinding is limited to interactions between solids only and earlier it is believed that when two solid organic compounds capable of a chemical reaction are ground in the absence of a solvent (therefore, "solvent-free"), a chemical reaction occurs in the solid phase , which is simply classified as solid-solid reaction. Recently, Rothenberg *et al.* reviewed these reactions and found that such reactive systems involve intervention of a liquid phase resulting from the occurrence of a eutectic (or peritectic) melt phase[15]. The existence of a liquid phase is a prerequisite for reaction in these systems and it is oversimplified to term these reactions solid-

49649

state or solid-solid reactions. Moreover, this limitation is now busted by the modified approach towards the manual grinding process given by Bose *et al.* as "Grindstone Chemistry". Grindstone chemistry includes grinding of all types of reagent pairs that may be solid/solid, solid/liquid, or even liquid/liquid at room temperature[35]. Because of this flexibility in choice of reagent pairs grindstone chemistry is more appropriately recognized as solvent less syntheses rather than confining into solid state or solid phase syntheses. Significantly, use of a hand held electric food mixer with stainless steel rotors for grinding together the reagents in a large glass or porcelain bowl makes the method suitable for the large-scale preparation of pharmaceuticals and their intermediates[35]. According to them, during grinding, energy is transferred through friction which initiates the reaction. Thus, exothermic reactions are suitable for this method. Heating under reflux for several hours is only logical for endothermic reactions. It is seen that in case of liquid/liquid reagent pairs, the rate of reaction is slow and can be accelerated by the use of friction enhancing components such as sand and $MgSO_4.7H_2O$. However, it should be noted that kinetic energy is supplied during the grinding of solid reagents and this can have several effects including heating, decrease in particle size (with concomitant increase in surface area and the generation of fresh surfaces), and formation of surface defects[36]. Grinding also provides mass transfer i.e. it is a sort of 'stirring' and can prevent exothermic reactions forming hot spots, which would lead to decomposition. From Atomic Force Microscopy (AFM) data, mechanisms have been proposed by Gerd Kaupp, regarding solid-solid reactions of this kind. Initially, reagent molecules (A) migrate into cleavage planes or channels present within the structure of the other reagent (B). The product (C) starts to form at the interface which further distorts the crystalline structures, and a mixed A–B–C phase forms. Next, as the concentration of the product (C) increases, crystals of C begin to form within the A–B–C phase. In turn, growing amounts of C cause the mixed A–B–C phase to disintegrate and form new particles, which reveal fresh surfaces for further reaction[37].

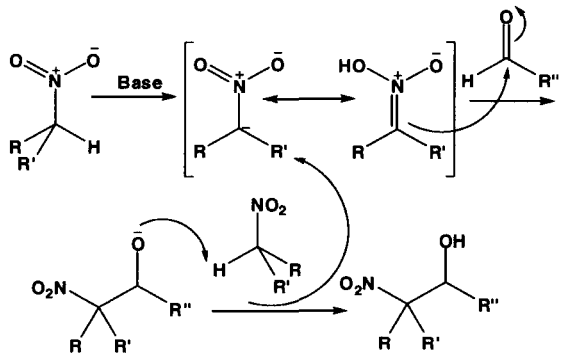
LBI

Section 1B

Background on Henry reaction, Biginelli or Biginelli-like reaction & Ester enolate-imine condensation

1B.1 Henry reaction

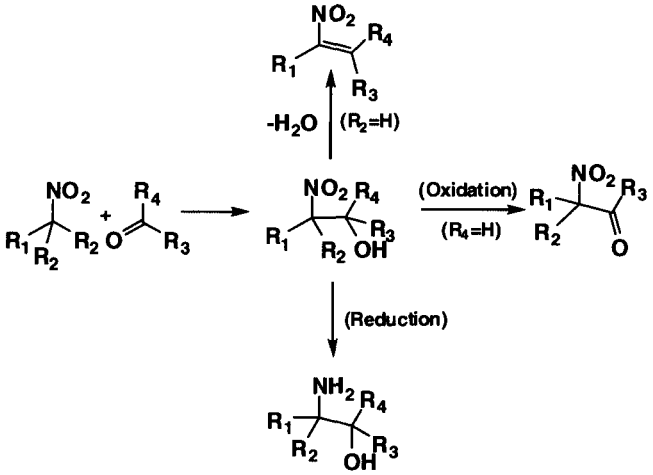
Henry reaction or nitroaldol reaction is one of the most recognizable atom economical C-C bonds forming reaction which involves coupling between a carbonyl compound and an alkylnitro compound bearing α-hydrogen in presence of a base[38] with the concomitant generation of a new difunctional compounds, namely β-nitroalcohol. The reaction was first described by a Belgian chemist, Louis Henry, in 1895. The mechanism of Henry reaction *(Scheme 1B.1)* involves base initiated deprotonation of the active methylene of the nitroalkane to give carbanion which is in tautomerism with nitronate. Nitronate eventually reacts with carbonyl compound followed by proton abstraction to form nitroaldol.



Scheme 1B.1: Mechanism of Henry reaction

The classical nitroaldol reaction is usually carried out in presence of a base in an organic solvent. When aldehydes are used as a source of carbonyl compounds, it is very essential to adopt experimental conditions which

suppress the various competitive side reactions like Aldol condensation, Cannizzaro reaction and Tishchenko reaction [39]. To obtain better results, a careful control of the basicity of the reaction medium is necessary and long reaction times are required. Furthermore, the formed β–nitroalcohol may undergo base-catalyzed water elimination to nitroalkenes that readily polymerize [40]. This elimination is difficult to avoid when aryl aldehydes are employed. As a result, attaining selectivity of product in Henry reaction is a critical job and needs proper strategies with control in parameters like basicity, mildness in reaction condition, temperature control etc.



Scheme 1B.2: Conversion of nitroaldol to other compounds

1B.1.1 Synthetic and pharmacological significances

The Henry reaction involves joining of two molecular fragments , under milder conditions, with the formation of two asymmetric centers at the new C-C juncture , in more complex synthetic routes. Furthermore, transformations of β -nitroalcohol will give different versatile intermediates such as nitroalkenes, 2-amino alcohols and α–nitro ketones through dehydration, reduction and oxidation reactions (*Scheme 1B.2*). The utility of nitroalkenes in organic synthesis is largely due to their ease of conversions into a variety of functionalities. In Diels-Alder reactions nitroalkene is used as strong dienophiles and readily undergo addition reaction with various nucleophiles. The Henry reaction has high demand in syntheses where nitroaldol products bearing labile protecting and sensitive functionality involves reduction or removal of the nitro group. Additionally,

retroaldolization and/or epimerization may accompany any of the conversion of the β –nitroalkanol group. The exploration and development of newer types of chiral catalysts [41] for Henry reaction have fulfilled the requirement for stereochemically pure amino alcohols in pharmaceutical and natural product synthesis. As a result, the scope of the Henry reaction has expanded its utilization in syntheses from nitroalkanol [42] functional group interconversions (FGI) to groups such as nitroalkenes, nitroketones and ketones, to employment as a highly efficient and reliable asymmetric transform.

β-Nitroalkanols are also important because of their properties as fungicides[43] and their utility as intermediates in the synthesis of amino sugars[44a], antibiotics such as ezomycins[44a] and tunicamycin[44b], natural products such as the sex pheromone of the Douglas Fir Tussock moth or cyclopeptide alkaloids[45]. While β-amino alcohols are used in the synthesis of biologically important compounds such as epinephrine[46] and anthracycline antibiotics[47], and some derivatives of β-amino alcohols are pharmacologically important such as chloramphenicol **(1)**, ephedrine **(2)** and quinine **(3)**. Similarly, nitroalkenes possess significant biological activities such as insecticidal, fungicidal, rodent-repellent, bactericidal and antitumor agents[40c,48]. α-Nitroketones are valuable intermediates in the synthesis of several natural products[49]. Presently, the availability of newer types of chiral catalysts for Henry reaction has enabled this classical organic reaction to widen its applicability in synthetic chemistry.

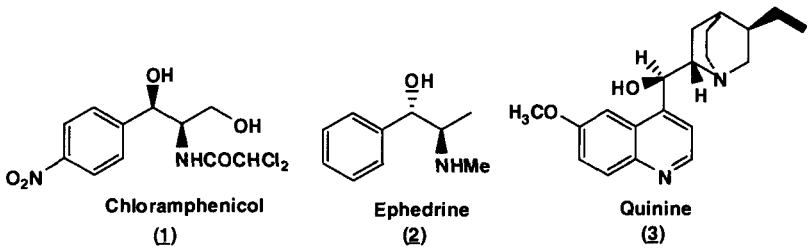


Figure 1B.1: Some pharmacologically important β-amino alcohols

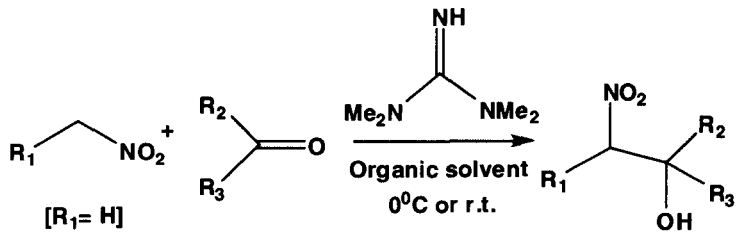
1B.1.2 Classical methods

Classical methods for preparing β-nitroalkanols include the condensation of the carbonyl substrates and a nitroalkane in the presence of an ionic base such as alkali metal hydroxides, alkaline earth oxides, carbonates, bicarbonates,

alkoxides, alkaline earth hydroxides, or magnesium and aluminum alkoxides[50]. Though this approach is quite simple and inexpensive, it has limitations such as occurrence of base-catalyzed elimination of water to form nitroolefins which unfortunately polymerize readily. Moreover, removal of the base before workup is not easy because acidification of the reaction mixture may lead to the Nef reaction[51] unless done with extreme care. The use of primary amines and triethylamine as condensing agents has also been reported[50]. Although this methodology leads to high yields of the β-nitroalkanol, the production of unsaturated nitro compounds through base-catalyzed elimination of water has been observed as well as formation of 1, 3-dinitro compounds. The latter substances are also the predominant products when diethylamine is used as a base[50].

Several variations of the nitroaldol reaction have recently been developed which include the use of tetramethylguanidine[52], dendritic catalysts[53], Amberlyst A-21[54], and a sodium hydroxide-catalyzed process in the presence of cetyltrimethylammonium chloride (CTACl)[55]. Although these methods afford high yields of the nitroaldol with aldehydes, they suffer from their inability to produce high product yields with alicylic or aliphatic ketones when such reactions are even observed. Self-condensation[52] of aliphatic ketones has been cited as a possible reason for the inability of this class of compounds to form the nitroaldol product in appreciable amounts.

The uses of strong bases like alkoxide or hydroxide were normally used to promote reactions between relatively simple substrate bearing limited functionality in alcoholic solvent[56].



(1)

Attempts to perform the reaction in organic solvent using 1,1,3,3-tetramethylguanidine (TMG) in the presence of one equivalent of nitromethane (***Eq. 1***) , resulted in the formation of 1,3-dinitro derivative as major product[52] for aromatic and aliphatic aldehydes.

Verkade had developed a series of proazaphosphatranes[57] (**4**, **5**, **6**) which efficiently promote nitroaldol reactions with ketones as well as aldehydes.

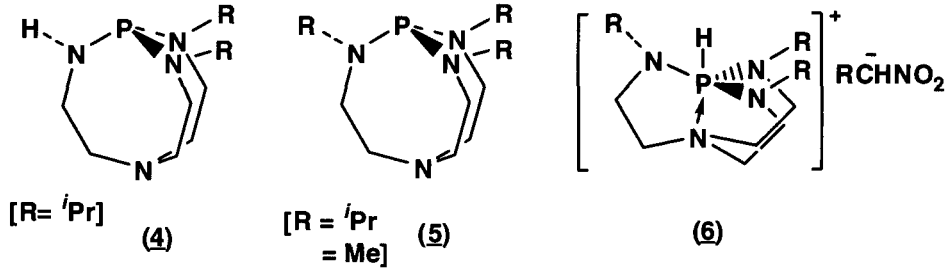
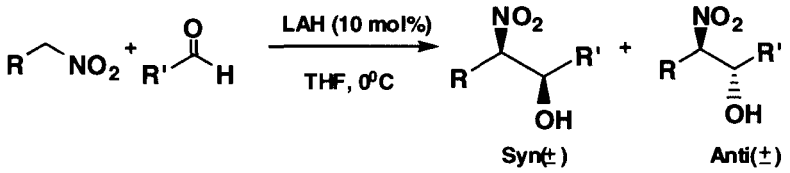


Figure 1B.2: Proazaphosphatranes developed by Verkade

Kim *et al.* reported that $LiAlH_4$ (10 mol %) in THF efficiently catalyze the nitroaldol reaction (***Eq. 2***) between a variety of aromatic and aliphatic aldehydes and simple nitroalkanes such as nitromethane, nitroethane or nitropropane[58a]. The reaction times vary from 2-8 h while the isolated yields range from 71% to quantitative.



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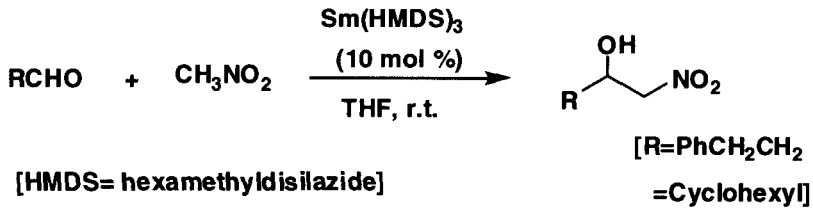

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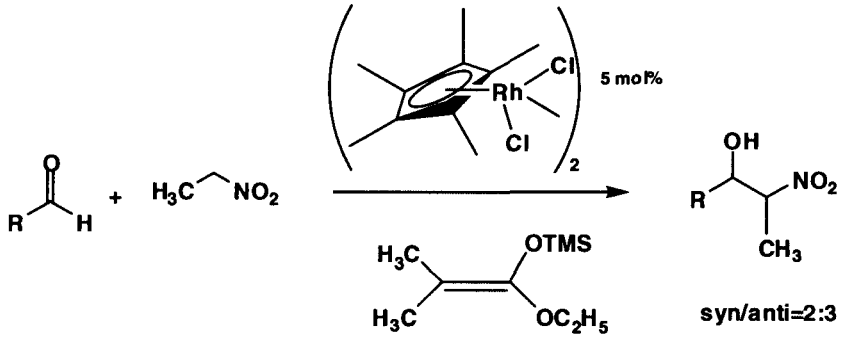


(4)

The use of the rare earth nitroaldol catalyst Sm $(HMDS)_3$ was reported by Shibasaki *et al.* [58b] in THF as solvent at room temperature during 3-25 hrs reaction periods (***Eq. 3***).

The reaction of nitroethane and a series of aldehydes gave only the corresponding nitroaldol products when promoted by the rhodium catalyst [{Rh (C_5Me_5) Cl}$_2$(μ-Cl)$_2$] (***Eq. 4***) and the silylketene acetal [59] in nitroethane as solvent. The reaction was inhibited in presence of dichloromethane and THF as solvents, presumably due to coordination with rhodium.

Chisholm *et al.* observed that trialkyl phosphines (7) and electron rich triaryl phosphines (8) are excellent catalysts for the Henry reaction in methanol .The reaction needed 24 hours stirring at room temperature [60a].

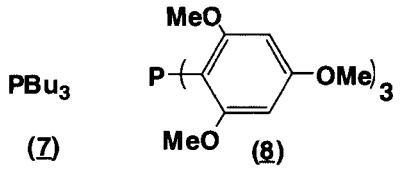
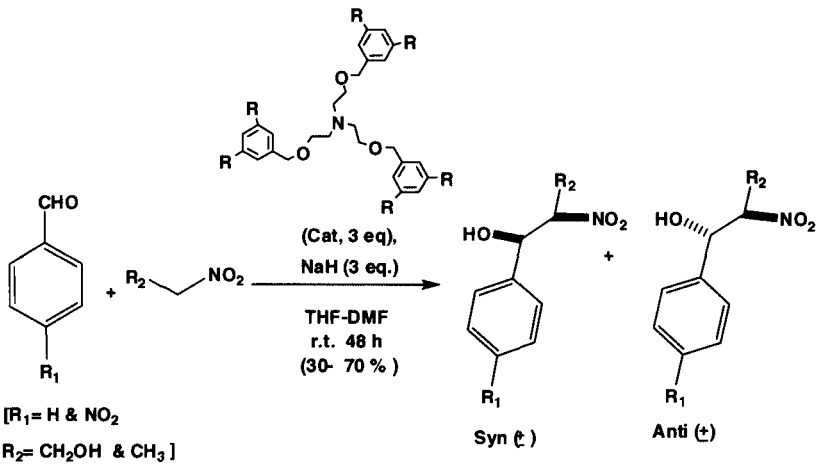


Figure 1B.3: Trialkyl phosphines (7) and electron rich triaryl phosphines (8)

Desai [60b] developed potassium phosphate as an efficient catalyst for the condensation of nitroalkanes with various aliphatic and aromatic aldehydes in acetonitrile medium at room temperature.

In 1997, Morao and Cossio [53] developed a series of dendritically encapsulated amine capable of catalyzing Henry reaction using nitroalkane as

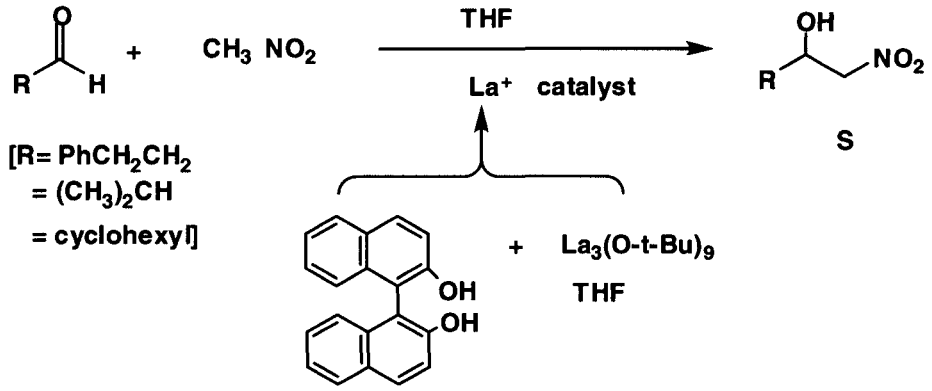


(5)

solvent. These catalysts were slower than triethylamine as a consequence of the steric hindrance caused by the branching; as the dendritic generation increased, the rate of reaction decreased (***Eq. 5***).

The first asymmetric version of the Henry reaction was reported by Shibasaki in 1992[61] who utilized (S)-(-)-binaphthol in conjunction with a

lanthanide alkoxide (***Eq. 6***). Enantiomeric excesses of 79-91% were obtained with the chiral binaphthol/rare earth protocol.



(6)

Since then various reports have been continuously appearing in the literature [41] on development of various metal and nonmetal based catalysts for the asymmetric Henry reaction. In 1994 Chinchilla *et al.* [62] reported the first organocatalytic asymmetric Henry reaction using enantiomerically pure guanidines with or without C_2- symmetry (**9, 10, 11, 12**).

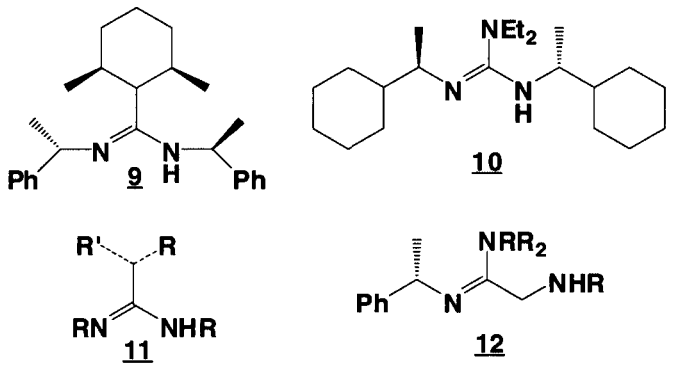


Figure 1B.4: Catalysts developed by Chinchilla

Bulbule *et al.* in 1999 [63a] described the use of activated Mg-Al hydrotalcites (HT) (*Fig. 1B.5*) in THF as efficient heterogeneous catalyst for the condensation of nitroalkanes producing *threo* -nitroalkanols in high yields and high diastereoselectivity under reflux in nitrogen atmosphere for 6-8 hours.

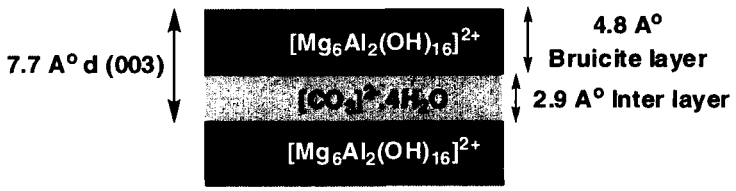
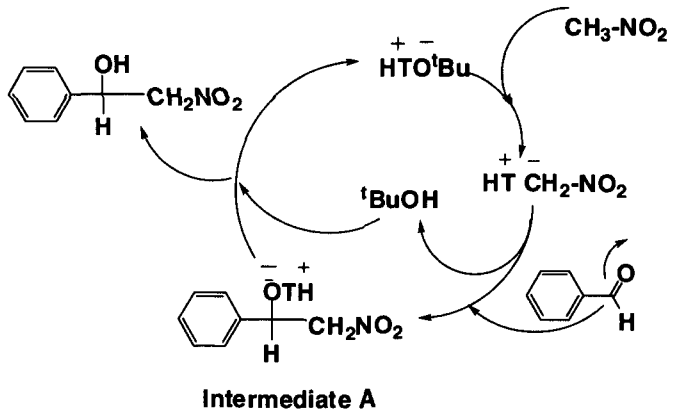


Figure 1B.5: Schematic presentation of Mg-Al hydrotalcite



Scheme 1B.3: Recycling of activated Mg–Al hydrotalcite in Henry reaction

Choudary *et al.* performed [63b] nitroaldol reaction with activated Mg–Al-O-t-Bu hydrotalcite (*Scheme 1B.3*) catalyst in quantitative yields in heterogeneous medium at a faster rate under mild condition in absence of nitrogen atmosphere.

While in the report of Cwik *et al.*[63c], the commercially available non-activated 2:1 Mg: Al hydrotalcite is shown as reusable heterogeneous catalyst for the nitroaldol reaction between a variety of aromatic and aliphatic aldehydes with simple nitroalkanes such as nitromethane and nitroethane. In this method nitromethane apart from being a substrate, serves as a solvent in different temperature. By increasing the temperature to 100 °C, 1, 3-dinitro compounds were obtained. On the other hand, the reaction of nitroethane used THF as solvent at 60°C with various aldehydes. The threo/erythro diastereoselectivity of the nitroethane adduct was found to range from 50:50 to 70:30.

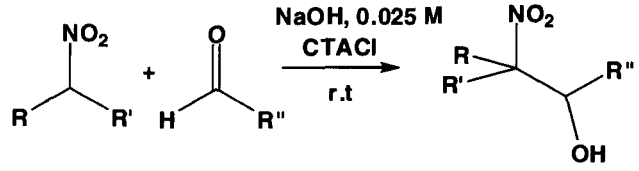
Recently Baruah *et al.* reviewed[41] the development of catalytic asymmetric Henry reaction using various types of metal based chiral catalysts containing metal such as Zn, Co, Cu, Mg, Cr and organocatalysts such as guanidine based derivatives, cinchona alkaloid derived organocatalysts etc.

Study of all the above mentioned reports based on classical method revealed that though they are able to prevent side reactions unlike initial classical method and thus providing improved product yields; there are still some drawbacks like excessive use of organic solvents, longer reaction time,

and laborious procedure. In some cases it is noticed that nitroalkane is used in large amount for reaction to occur which at the same time act as solvent.

1B.1.3 Aqueous medium assisted methods

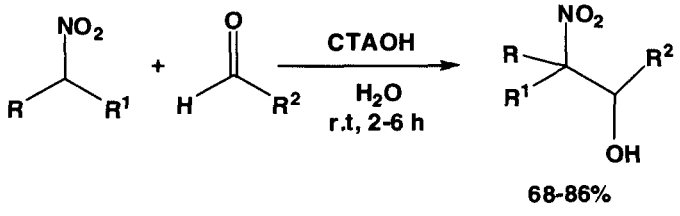
The aqueous medium with respect to organic solvent is less expensive, less dangerous, and environment-friendly, while it allows the control of the pH and the use of micro aggregates such as surfactants [64]. Increasing recognition of water as an attractive medium for many organic reactions have also initiated research interest in investigating Henry reaction in this medium. First time in 1997, Ballini and Bosica[55] reported very mild reaction conditions using 0.025 M NaOH, in the presence of cetyltrimethylammonium chloride (CTACl) as cationic surfactant (***Eq. 7***).



(7)

The method has been able to achieve tremendous improvements over conventional methods. The approach is independent from the ratio catalyst/substrates and does not need long reaction times, tedious preparation of the catalyst, large excess of the nitroalkane, or severe reaction conditions that are too cumbersome, especially for large-scale preparations. Typical side reactions such as retro-aldol reaction or dehydration of the 2-nitro alcohols into nitroalkenes (especially associated with aromatic aldehydes) and self condensation (associated with ketones) can be prevented. Most of the reactions completed within 2- 6 hours.

Again in 2004, Ballini and his coworkers[65] showed the use of catalytic amount of cetyltrimethylammonium hydroxide (CTAOH) (10 mol % water solution), at room temperature for Henry reaction which successfully furnish nitroaldol



68-86%

(8)

products with high chemo-selectivity in very short reaction times (***Eq. 8***). However, these reactions took more reaction time (2-6 hours) to produce good yield (68-86%) of nitro aldol product.

In a report Wang *et al.*[66a] illustrates that chemo selective addition of aldehydes in aqueous medium can be obtained under mild condition choosing triethylamine as a base for Henry reaction. In this method also, both aliphatic and aromatic aldehydes showed good product yields after 3 to 12 hours of reaction time. Aryl and aliphatic ketones appeared to be inert compared to aldehydes under the same reaction conditions.

McNulty *et al.*[66b] performed Henry reaction in water using trihexyl(tetradecyl)phoshonium decanoate which rather working as a base or phase transfer-mediated route involving proton transfer from the nitroalkane, involves in Lewis acid activation of the carbonyl group proceeding through a trigonal-bipyramidal intermediate. Recently, Wang *et al.*[66c] synthesized a series of 1-aryl-2-nitroalkan-1-ols with good yield, presenting the efficiency of catalytic system consisting immobilized phase-transfer catalyst polystyrene-supported tributylammonium chloride (PsTBAC) and KOH either in H_2O containing 10% of THF (biphasic system) or in neat H_2O at room temperature. The catalyst can be effectively re-used several times, basically without loss in activity.

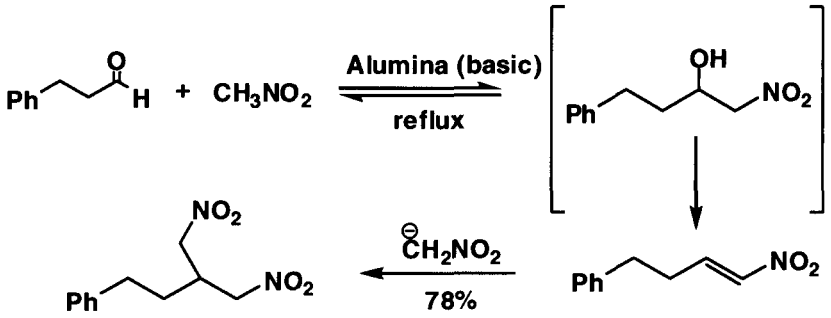
It is observed that most of the methods involving water as reaction medium utilized surfactants and phase transfer catalysts. Recycling of catalysts was not possible with most of the reported aqueous mediated reactions. Moreover, some of them suffer from their inability to produce high product yields with alicylic or aliphatic ketones. Therefore, in this respect use of organocatalysts is promising area and seems to have lots of scopes towards the development of Henry reaction in aqueous medium.

1B.1.4 Solvent-free methods

Among the benefits of solvent-free processes are cost savings, decreased energy consumption, reduced reaction times, and a large reduction in reactor size and capital investment[67]. Nitroaldol synthesis has also been carried out under solventless conditions. The use of soventless condition in combination

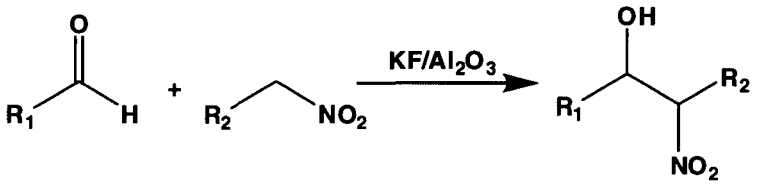
with heterogeneous catalysts represents one of the more powerful green chemical technology procedures with one pot conversion.

Rosini [68a] synthesized 2- nitroalkanol on alumina surface without solvent. Here, alumina works well in gram scale. Ballini *et al.* investigated[68b] the reactions of aldehydes with an excess of nitromethane in the presence of basic alumina as solid catalysts, allows the one pot preparation of 1, 3-dinitroalkanes (***Eq. 9***).



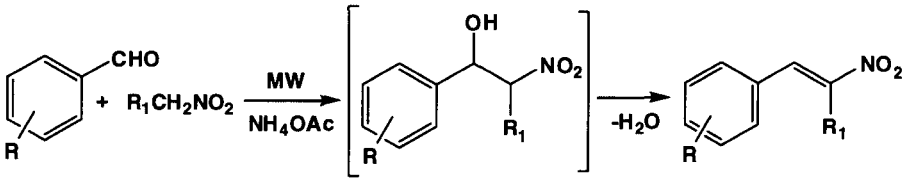
(9)

Later on Melot *et al.*[68c] developed alumina supported potassium fluoride, more efficient catalyst than alumina itself in terms of shorter reaction time, for the preparation of 2-nitro alkanols by condensation of aldehydes with nitroalkanes (***Eq. 10***).



(10)

Costantino *et al.* investigated [68d] layered Zr $(KOPO_3)_2$ as efficient catalyst for Henry reaction under mild condition without any solvent. Amberlyst A-21[54] was found to be superior heterogeneous catalyst to furnish 2- nitorladol compounds both with and without solvent. This catalyst did not affect labile functional groups and obtained high yields with a large variety of derivatives, under mild conditions. But the limitation of this method was the longer reaction time (3-20 hrs) with different types of substrates.

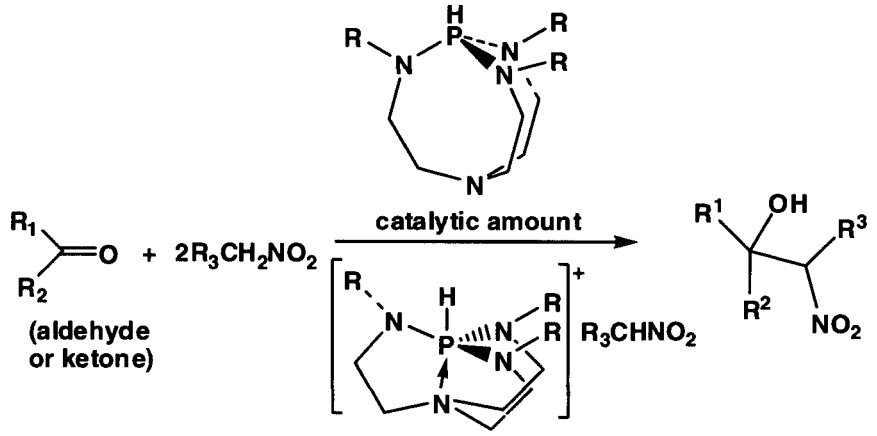


(11)

Solvent less organic reaction can also be further associated with microwave irradiation and mechanochemical processes such as grinding.

Varma *et al.*[69a] had made an attempt of employing microwave irradiation under solvent less condition using catalytic amount of ammonium acetate (***Eq. 11***) to produce β-nitoalkanols from aromatic aldehydes. However, the reaction conditions predominantly form nitroalkene by facile dehydration of β-nitoalkanols.

Microwave irradiated SiO_2 surface[69b] developed a quick heterogeneous method for the effective synthesis of 2-nitroalkanols from primary nitroalkanes and a variety of aromatic aldehydes under solvent-free condition. The catalyst recovered during the work-up, could be effectively reused after activation. Ballini performed another[70a] solvent-free nitro-aldol reaction in presence of stoichiometric amount of powered potassium hydroxide within short reaction time. The N, N-diethylpropylamine supported on amorphous silica (KG-60-NEt_2) reported to be an efficient and reusable solid catalyst for the Henry reaction under solventless condition[70b]. The method afforded a diastereomeric mixture of nitroalkanols within reaction time of 5-24 hours.



(12)

Proazaphosphatranes showed[57] to be strong nonionic bases which (***Eq. 12***) can promote the Henry reaction under solvent less condition at room temperature in the presence of 2.2 equiv of magnesium sulfate. The high yields observed in the nitroaldol reaction of ketones promoted by such nonionic bases are due to the virtual lack of free base present at the concentrations used in these reactions. However, the procedure seems to be tedious and it requires nitrogen atmosphere.

Simoni *et al.*[52] reported the synthesis of 2-nitroalkanol by tetramethylguanidine (TMG) catalyzed addition of primary nitroalkanes to aldehydes and alicyclic ketones at 0°C using excess amount of nitroalkanes as

reaction medium. The very mild conditions employed, together with the short reaction times, make the procedure tolerant of a range of functionalities and highly versatile for the synthesis of a variety of 2- nitroalkanols. In another report, Simoni[71a] used 1, 5, 7-triazabicyclo [4.4.0] dec-1-ene (TBD) (**13**), 7-methyl-TBD (MTBD) (**14**) and the polymer supported TBD (P-TBD) (**15**) as catalysts for nitroaldol reaction in neat condition at 0°C within few minutes. The catalysts were found to be very effective in many cases to the parent tetramethylguanidine (TMG) in terms of yield. However the reaction was not generally applicable, as aliphatic ketones and acetophenone did not react in the presence of bicyclic guanidine bases.

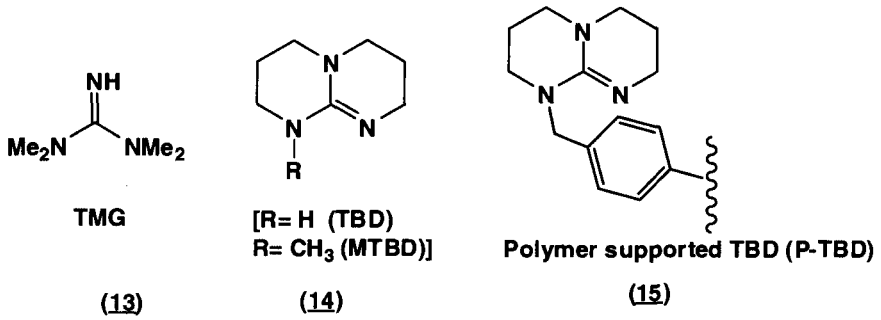
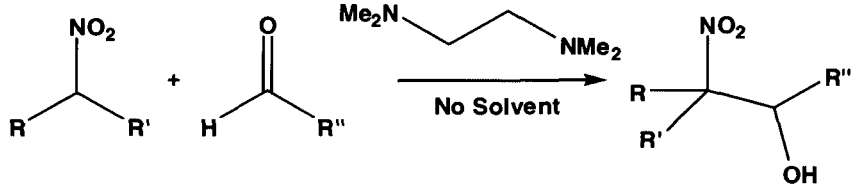


Figure 1B.6: Catalysts developed by Simoni

N,N,N',N'-tetramethylethylenediamine (TMEDA) can be classified as an organic base like amines and amidines, and regarded as a strong base due to the resonance stability of their conjugate acid. Kim *et al.*[71b] utilized this property to afford β-nitro alkanols in considerably excellent yield. Structurally diverse aldehydes react with nitromethane in presence of 0.3 equiv of TMEDA under metal and solvent-free condition at room temperature (***Eq. 13***).



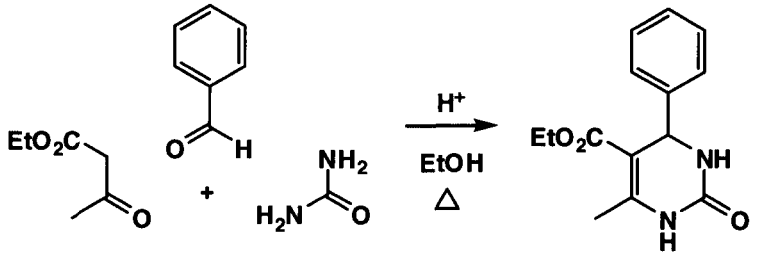
(13)

From these literatures it has been observed that most of the solvent-free methods suffer from different types of drawbacks such as more reaction time, use of toxic reagents or catalyst and formation of side products. Again, it has come to notice that no significant reports of using mechanochemical energy for Henry reaction are available. Therefore, investigation of this reaction under

solvent less grinding method in presence of organocatalysts is so far an overlooked area of research.

1B.2 Biginelli (or like) reaction

Biginelli reaction is one of the most significant multicomponent reactions (MCRs), reported for the first time by an Italian chemist Pietro Biginelli in 1893[72]; using aromatic aldehyde, urea, and ethyl acetoacetate as starting components under acidic condition in ethanol. The reaction leads to the synthesis of 5- substituted-3, 4-dihydropyrimidin-2 (1*H*)-ones (***Eq. 14***).

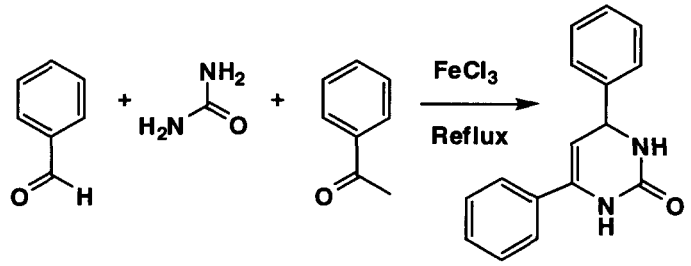


(14)

Various improvements on this reaction led to employment of different aldehydes ranging from aromatic aldehydes, aliphatic and heterocyclic aldehydes, but aldehydes like carbohydrates, isophthalaldehyde, and terephthalaldehyde are also present[73]. Apart from β-ketoester component of common alkyl acetoacetate type, other acetoacetic acid esters such as benzyl acetoacetate, (-)-menthyl acetoacetate, o-chloroethyl acetoacetate, 2-furanylmethyl acetoacetate, and ethylthio-aceto acetates have been used successfully in the Biginelli reaction [74]. Reports on the use of benzoylacetic acid esters, ethyl 4-bromoacetoacetate, ethyl trifluoromethylacetoacetate and primary, secondary, and tertiary acetoacetamides are also available [75]. Urea has been replaced by substituted ureas and thioureas[76].

Wang *et al.* in 2004 reported [77a] the utility of ketones in Biginelli reactions other than activated β-dicarbonyl compounds (acetoacetate) for the synthesis of interesting 5-unsubstituted 3, 4-dihydropyrimidin-2-(1H)-ones (***Eq. 15***). At present, there are few articles describing the synthesis of certain 5-unsubstituted 3, 4- dihydropyrimidin-2(1H)-ones using one pot three component protocol of Biginelli reaction and they have been specifically categorized as *Biginelli- like reactions*[77]. Very recently, for novel Biginelli-like scaffold syntheses, the use of common open-chain β-dicarbonyl

compounds has been extended to cyclic β-diketones, β -ketolactones, cyclic β -diesters or β -diamides, benzocyclic ketones and α-ketoacids[77].



(15)

1B.2.1 Synthetic and pharmacological significances

Many interesting pharmacological properties are associated with this dihydropyrimidine scaffold. These heterocyclic compounds exhibit excellent pharmacological and therapeutic properties such as antibacterial, antitumour, antiviral, antiinflammatory and antihypertensive activity as well as behaving as calcium channel blockers, α-1a-antagonists, neuropeptides Y (NPY) antagonists and more recently found as potent HIV gp-120-CD4 inhibitors in some alkaloids (batzelladine alkaloids A and B) of marine resources and are probable new leads for AIDS therapy[78]. A very recent highlight that has surfaced is the identification of the structurally simple DHPM monastrol (**16**) (*Figure 1B.7*) which specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a lead for the development of anticancer drugs[79a]. Interestingly, the closely related DHPMs (**17**) did not affect mitotic kinesin in mitosis.

In vitro calcium antagonist activity on isolated rat ileum and lamb carotid artery of few 5-unsubstituted 3, 4-dihydropyrimidin-2-(1H)-ones such as 4-aryl- 7, 7-dimethy and 1, 7, 7-trimethyl- 1, 2, 3, 4, 5, 6, 7, 8 - octahydroquinazoline - 2, 5- diones, have been studied by M. Yarım et al. they found that some of these compounds have calcium antagonist activity as high as that of nicardipine[79b].

Many structural and functional modifications on DHPMs were carried out after the recognition of cardiovascular activity of DHPMs by Khanina *et al.* in 1978, for obtaining improved pharmacological activity [80] on β-

aminoethyl esters of type (**18**) that exhibit moderate hypotensive activity and coronary dilatory properties.

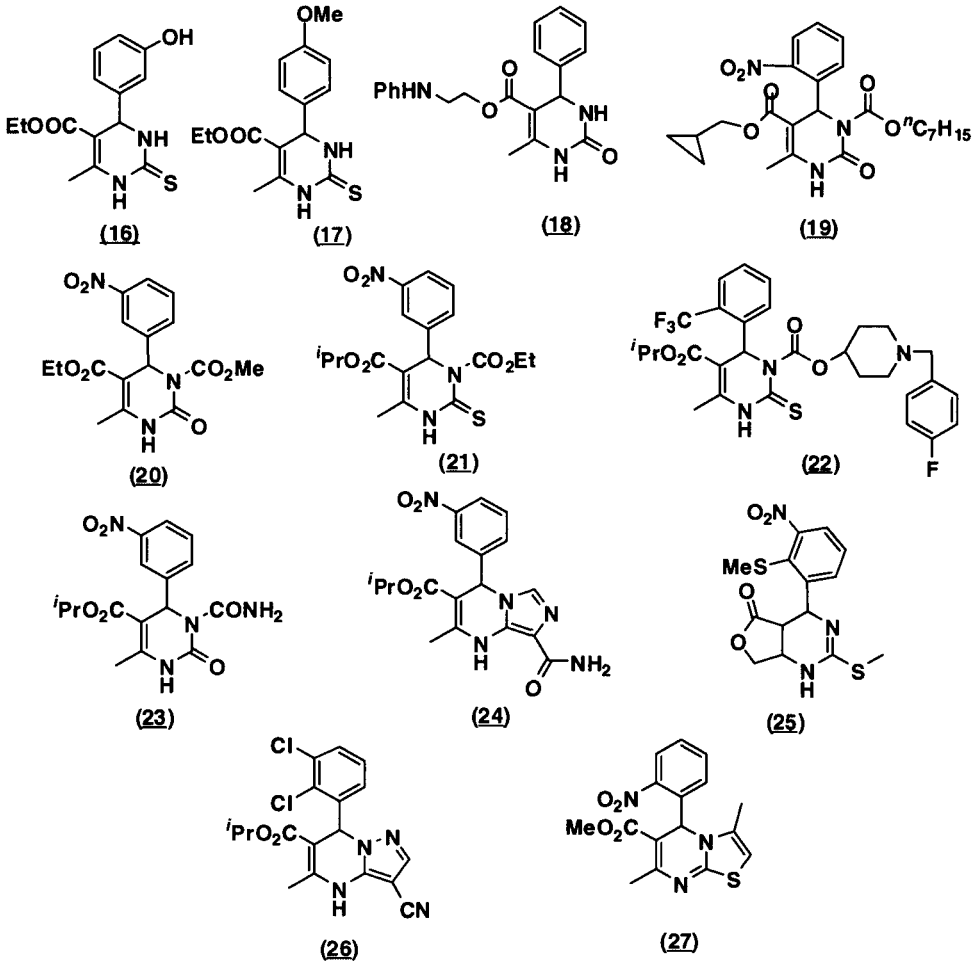


Figure 1B.7: Structures of DHPM calcium channel modulators

For example:

- DHPMs bearing an ester group at N-3 (**19**-**21**) which resembles nifedipine-type dihydropyridines displayed hypotensive activity with slow onset, more potent and longer lasting vasodilative action compared to DHPMs [81].
- Orally active long-lasting antihypertensive agents, such as DHPMs (**22**-**23**) [82] were obtained by modification of the substituent at N-3. They have also antiichemic properties in animal models [83].
- DHPM derivatives with fused analogs involving hetero- or carbocyclic rings attached to either the C5/C6 or the C2/N3

positions of the dihydropyrimidine nucleus possess calcium channel blocking activity (**24-27**) [84].

Later on detailed pharmacological studies of DHPMs calcium channel blockers by Rovnyak *et al.*[82, 85] presented a general structure–activity relationship for N-3-functionalized[80] DHPMs (*Figure 1B.8*).

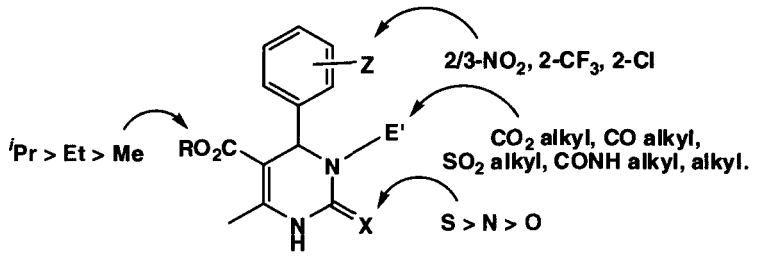


Figure 1B.8: General structure–activity relationship of DHPM calcium channel blockers.

Accordingly,

- *Ortho* or *meta* aromatic substituents essential for optimal activity *in vivo*.
- The C-5 ester alkyl group was found to be a major determinant of potency.
- A substituent on N-3 of the dihydropyrimidine ring is a strict requirement for activity.
- The order of potency for the 2-hetero atom was S/O/N (*Figure 1B.8*).The absolute configuration at C-4 determines whether the analogue has antagonist or agonist activity.

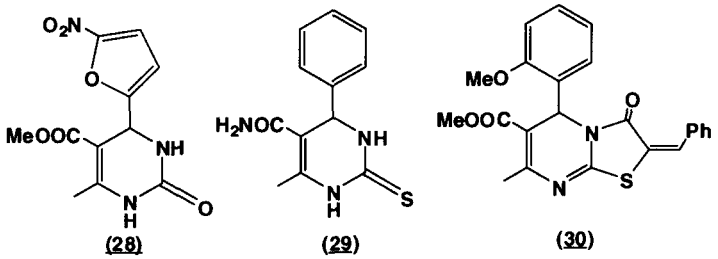


Figure 1B.9: DHPMs with antibacterial, anticarcinogenic and anti-inflammatory activity.

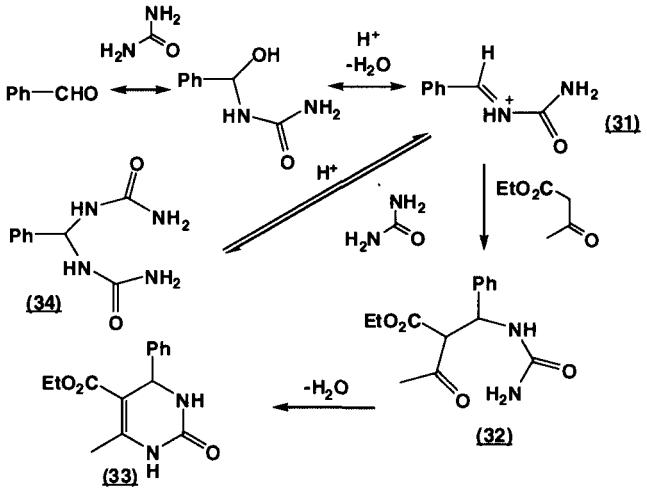
The nitrofuryl-substituted analog nitracin (**28**) displayed good activity against the viruses of the trachoma group, in addition to showing modest antibacterial

activity. Pyrimidine-5-carboxamides of type (**29**) shown to have anticarcinogenic activity while other derivatives reported to have blood platelet aggregation inhibitor activity. Similarly fused DHPMs, such as thiazolo [3, 2, a]-pyrimidine (**30**) was reported to have anti-inflammatory activity.

1B.2.2 Mechanistic studies

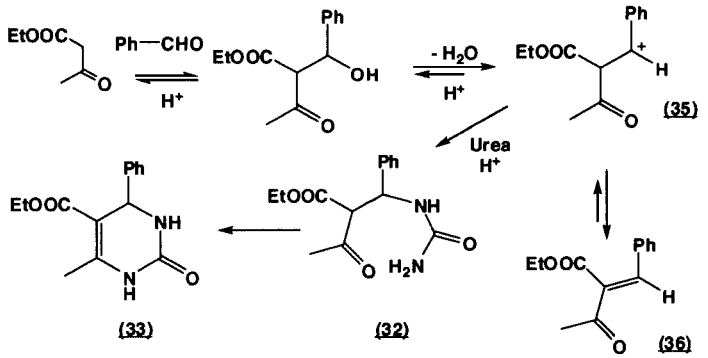
Different opinions on the mechanism of the reaction have been proposed. They are:

1. *Folkers and Johnson[86a] suggestion:* The primary bimolecular condensation product bisureide (**34**) of benzaldehyde and urea is the first intermediate in this reaction *(Scheme 1B.4).*



*Scheme 1B.4: N-acyliminium ion intermediate (**31**) mechanisms for Biginelli Reaction*

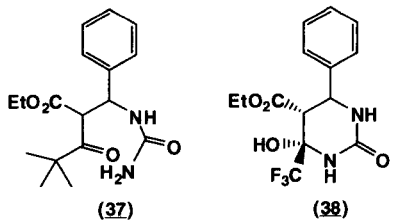
2. *Sweet and Fissekis[86b] suggestion:*



*Scheme 1B.5: Carbenium ion (**35**) mechanism for Biginelli reaction*

The first and limiting step of the Biginelli condensation is generation of carbenium ion (**35**), produced by an acid-catalyzed aldol reaction of benzaldehyde with ethyl acetoacetate to form compound (**33**) (*Scheme 1B.5*). Interception of cation (**35**) by urea then produces ureide (**32**), which ultimately cyclizes to the Biginelli products.

3. *Kappe and co-worker's*[86c] *suggestion:* In their study the formation of carbenium ion intermediate (**35**) in Biginelli reaction is cancelled because in an acid catalyzed aldol reaction, the reaction products are in most cases the β-unsaturated carbonyl compounds and not the β –hydroxy carbonyl (aldol) products. Monitoring the reaction of benzaldehyde and ethylacetoacetate in CD_3OH/HCl by ^1H and ^{13}C NMR spectroscopy, no evidence for an aldol reaction or any other reaction between the two components at room temperature could be obtained. Thus, the two components do not react under such conditions whereas the Biginelli condensation itself proceeds smoothly without formation of carbenium ion intermediate. In addition, the original mechanistic proposal made by Folkers and Johnson was again reinvestigated in a different manner. When benzaldehyde and urea were treated under Biginelli conditions (CH_3OH/HCl) at room temperature, bisureide (**34**) started to precipitate within 15-20 min. From these experimental observations , it was proposed that *N*-acyliminium ion intermediate (**31**) formed from aldehyde and urea precursors by acid- catalysis is the key step which intercepted by ethyl acetoacetate through its enol tautomer and forms an open chain ureide (**32**) *(Scheme 1B.4)* which then cyclizes to the final DHPM after elimination of water molecule. However, evidence to support this mechanism was provided by two trapped species: (**37**)[87a] and (**38**)[87b] *(Figure 1B.10).*



(**37**) (**38**)

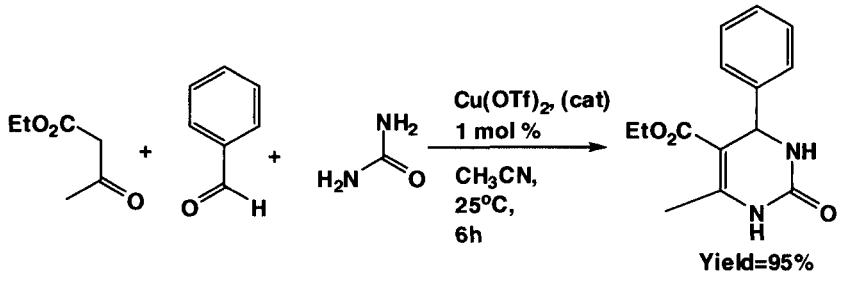
Figure 1B.10: Observed intermediates to support the Kappe mechanism

Moreover, Jenner studied the effect of high pressure on Biginelli reactions, catalyzed by ZnI_2[87c]. With increasing steric congestion associated with bulky aldehydes, the sensitivity of the reaction to pressure is enhanced compared to the unhindered aldehydes. The results further support a multistep mechanism where the first step consisting of the nucleophilic addition of aldehyde to urea would be rate determining.

Various reaction conditions were designed based on the mechanism proposed by Kappe and coworkers which helped in improving yield and experimentation with different types of variants.

1B.2.3 Classical methods for Biginelli reaction

The original Biginelli protocol for the preparation 5-substituted DHPMs consisted of heating a mixture of three components (β- keto ester, aldehyde and urea) in ethanol under reflux containing a catalytic amount of HCl. This classical method involves strong acidic conditions, high temperature reaction, long reaction times, low to moderate yields of products particularly for substituted aromatic and aliphatic aldehydes and use of large quantity of solvent[72]. A number of synthetic procedures based on the modification of the classical Biginelli's approach have been developed during past few decades using different Lewis acid ***(Eq. 16)*** and protic acid catalysts[88] such as BF_3, $FeCl_3$, $ZnCl_2$, $InCl_3$, $LiClO_4$, $Cu(OTf)_2$, $Mn(OAc)_3$, CAN, H_2SO_4, *p*-TsOH etc. in a solvent such as acetonitrile, toluene, dichloromethane or THF. Some reagents required Bronsted acids combination for reactivity, such as hydrochloric acid and acetic acid, as additives. Moreover, reactivity of most of the catalysts is limited to simple acetoacetate esters, either methyl or ethyl acetoacetate, and, mainly, meta- and para-substituted aromatic aldehydes with no significant steric demands.

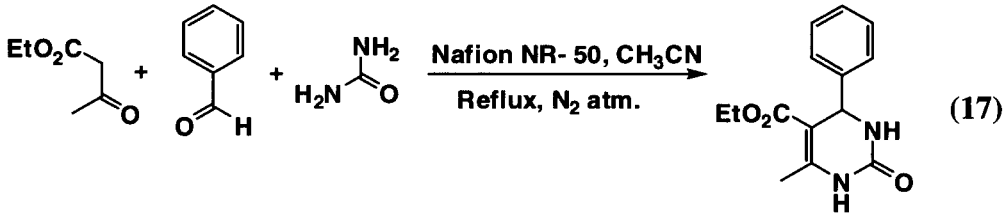


(16)

Many of these catalysts and solvents are not acceptable in the context of green synthesis especially most of these catalysts fail to meet the criterion of reusability of catalyst.

The problem with regeneration of the catalyst is to some extent resolved by the use of heterogeneous catalysts in place of Lewis acids or protic acids by many groups. Keggin-type heteropoly acids with the molecular formula $H_{8-x}[XM_{12}O_{40}]$, where X is the heteroatom (e.g., P^{5+} or Si^{4+}), x is its oxidation state and M is the addenda atom (usually Mo^{6+} or W^{6+})[89] provide an efficient route for Biginelli condensation with the advantage of reusability of catalyst in acetonitrile, acetic acid or THF as solvent.

Silica supported sodium hydrogensulfate[90a] and silica-sulphuric acid[90b] are efficient reusable heterogeneous catalysts in furnishing Biginelli products with good to excellent yield. Also, natural HEU-type zeolites, HY- zeolite, Nafion NR-50 [91] (Eq. 17) have been employed as heterogeneous catalysts for the synthesis of DHPMs.

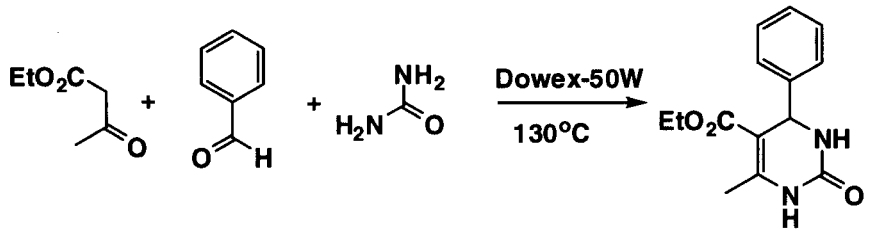


(17)

In all the above mentioned methods we noticed that acetonitrile is the highly used solvent among THF, EtOH, toluene and glacial acetic acid which is not recommendable solvent from an environmental point of view based on the results of the EHS (environmental, health and safety) method and the LCA (life-cycle assessment) method[92].

1B.2.4 Solvent-free methods for Biginelli reaction

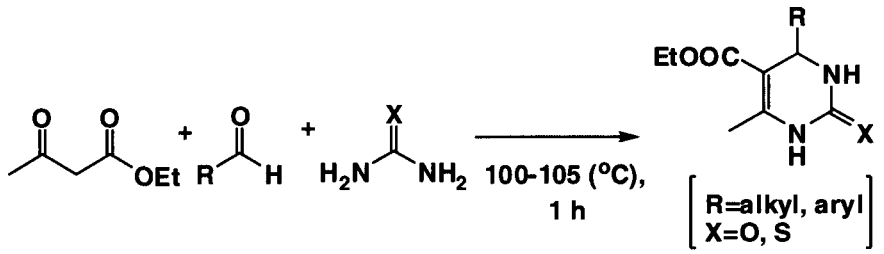
Various solventless methods for the synthesis 5-substituted DHPMs have been reported to get improved results over classical methods. One such solvent-free treatment of three components mixture reported in neat condition under thermal energy using different types of catalysts such as $Yb(OTf)_3$, $Sr(OTf)_3$, $Fe(OTf)_3$,$Y(NO_3)_3{\cdot}6H_2O$ $Ce(NO_3)_3.6H_2O$, $Ca(NO_3)_2.4H_2O$, HBF_4, NH_4Cl dowex- 50W (***Eq. 18***), montmorillonite-KSF, $TMSCl$[93] etc.



(18)

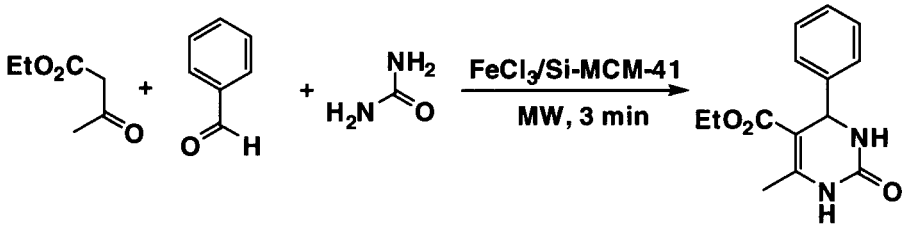
Among them Fe (OTf) $_3$, Sr (OTf) $_3$ and Y $(NO_3)_3 \cdot 6H_2O$ can be recycled [94]. Although, these methods have many greener components such as avoid of organic solvent, good yield and short reaction time however, very high temperature is required in most of the reactions.

The efficiency of solventless thermal heating is best realized by the report of Ranu *et al.*[95] on Biginelli reaction carried out under this condition without using catalyst for 1 hour (***Eq. 19***).



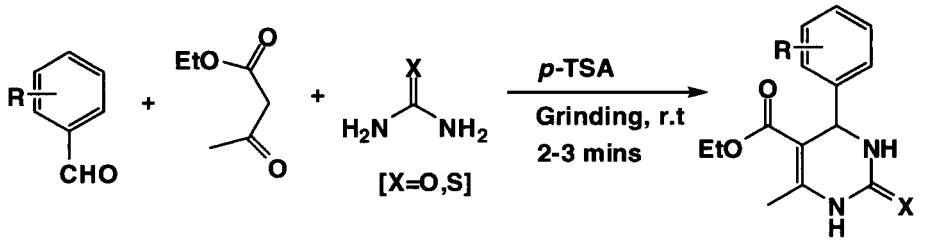
(19)

Reports on the use of microwave irradiation in combination with solventless conditions are also present. Acetic acid, formic acid, $FeCl_3$/Si-MCM-41 (***Eq. 20***), amberlyst- 15, $CuSO_4.5H_2O$ etc. are some of the catalysts which have been reported to furnish DHPMs using solventless microwave irradiation technique [96].



(20)

Peng *et al.*[97] developed a solvent-free method for Biginelli reaction using ionic liquid as catalyst. Another method that can be employed in solventless condition is the grinding. The first significant and only report [35] on Biginelli reaction using this condition came from A. K. Bose *et al.* (***Eq. 21***).



(21)

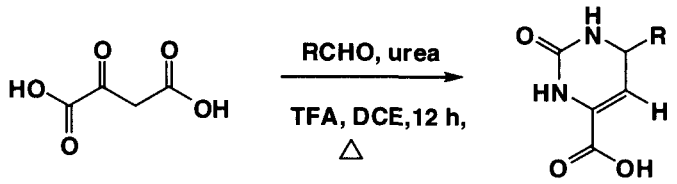
They devised this technique for reagent pairs that are solid/solid, solid/liquid, or even liquid/liquid and thus, described this modified approach as *Grindstone Chemistry*. This remarkable work explored grinding using mortar and pestle to be the simplest and at the same time efficient greener method of synthesis.

From these reported methods it is observed that microwave irradiation reduces the reaction time from hours to minutes in case of solvent-free Biginelli reaction. Similarly, the use of grinding technique is also efficient to increase the rate of reaction under solventless medium as compared to thermal treatment in presence of organic solvent. Thus, solvent-less reaction will be more advantageous in terms of energy savings on combining the method with other techniques like rapid microwave heating and grinding.

1B.2.5 Biginelli- like reaction protocols

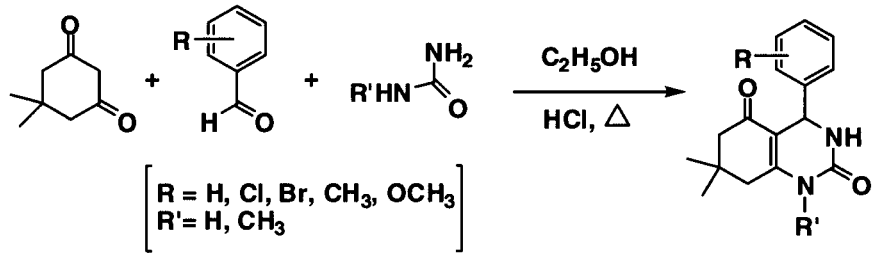
Biginelli -like reaction is the extended form of Biginelli reaction which emerged on replacing the β-ketoester component with various types of carbonyl derivatives such as enolizable ketone, cyclic β-diketones, β-ketolactones, cyclic β-diesters or β -diamides, benzocyclic ketones and α-ketoacids[77]. All these protocols suffer from various limitations such as low yields, very long reaction times, harsh reaction conditions and unrecoverable strong acids. Moreover, at present there are few articles describing the synthesis of certain 5-unsubstituted 3, 4-dihydropyrimidin-2(1*H*)-ones. Earlier the synthesis of 5-unsubstituted dihydropyrimidones were performed in a multistep fashion via the saponification of the C (5) ester on the preassembled pyrimidone followed by thermal decarboxylation[98]. These harsh and inefficient methods have resulted in low yielding transformations and multiple side-products. These problems have been significantly eradicated by one pot Biginelli-like reaction.

Jacqueline C. Bussolari and Patricia A. McDonnell described[77c] oxalacetic acid as an unprecedented substrate for the preparation of 5-unsubstituted 3, 4-dihydropyrimidin-2-(1*H*)-ones in high yield employing a unique set of conditions (i.e. TFA in refluxing dichloroethane) (***Eq. 22***).



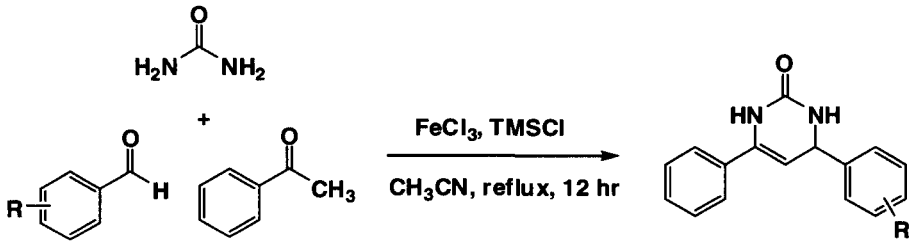
(22)

M. Yarım *et al.* prepared [79b] a series of 4-aryl-7,7-dimethyl and 1,7,7-trimethyl-1,2,3,4,5,6,7,8-octahydroquinazoline-2,5-diones (Biginelli-like compounds) by condensing urea or N-methyl urea with 5,5-dimethyl-1,3-cyclohexanedione and aromatic aldehydes under reflux condition (***Eq. 23***).



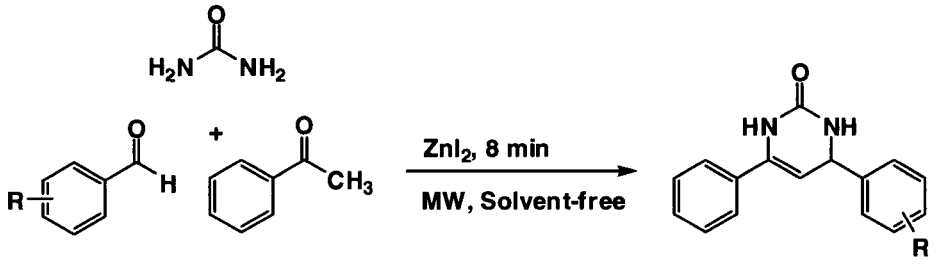
(23)

Wang *et al.* [77a] performed Biginelli-like reactions efficiently in acetonitrile using catalyst $FeCl_3.6H_2O$ and TMSCl to afford the corresponding 5-unsubstituted 3,4-dihydropyrimidin-2-(1H)-ones in high yields. However, the protocol required long reaction time (12 h), highly toxic organic solvent (CH_3CN) and stoichiometric TMSCl. The protocol extended the utility of ketones in Biginelli reactions (***Eq. 24***).



(24)

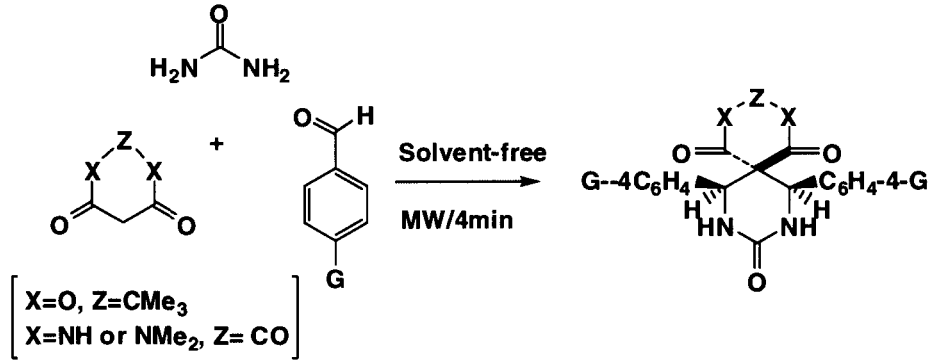
Liang *et al.* [99] introduced another three-component Biginelli-like reaction of aldehyde, acetophenone and urea to prepare 5-unsubstituted DHPMs using inexpensive ZnI_2 as catalyst under solvent-free Microwave (MW) irradiation (***Eq. 25***).



(25)

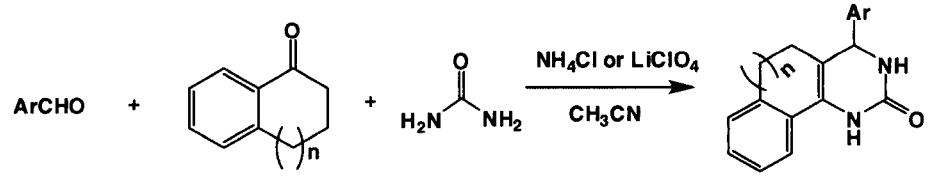
Saini *et al.* reported [100] the synthesis of 5-unsubstituted DHPMs via Biginelli-like reaction of acetophenone, aldehyde and urea under reflux condition using aluminium (III) halide as catalysts within time range of 6-7 hours. Sabitha *et al.* described an iodotrimethylsilane (TMSI) catalyzed Biginelli-like one pot condensation of ketones with aldehydes and urea to afford 5-unsubstituted DHPMs in acetonitrile at room temperature [101].

In the recent years, development of Biginelli- like scaffolds leads to synthesis of two families of fused heterobicyclic and spiro-fused heterobicyclic compounds. Shabbani *et al.* synthesized [102] a series of spiro-fused heterocyclic compounds through Biginelli-like reactions of p-substituted aldehydes, urea, barituric acid or Meldrum's acid derivatives using acetic acid catalyst under solvent-free microwave irradiation (***Eq. 26***).



(26)

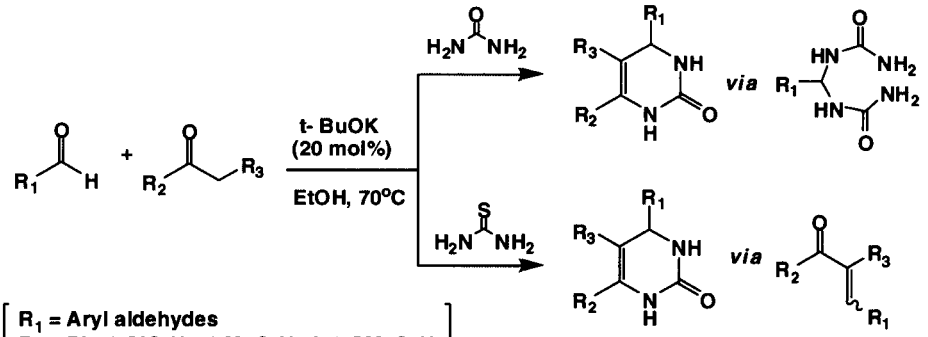
Aghayan *et al.* developed [103] a practical, simple, and inexpensive procedure for the synthesis of dihydropyrimidinone derivatives from aldehydes, cyclic ketones or acyclic ketones, and urea using a catalytic amount



(27)

of $CuCl_2$ (10 mol %) /TMSCl (2 mmol) or ammonium chloride or lithium perchlorate, refluxing in CH_3CN (***Eq. 27***).

Shen *et al.* [104] reported another Biginelli-like reaction for the synthesis 4, 5, 6-triaryl-3, 4-dihydropyrimidin-2(1H)-ones via a three-component condensation of aldehyde, 2-phenylacetophenone, and urea/thiourea in the presence of a catalytic amount of Bronsted Base ^tBuOK (20 mol %). Further mechanistic studies showed that urea and thiourea proceeds through two totally different pathways. The condition is able to afford the desired products in moderate to good yields (***Eq. 28***).



(28)

The exploration of interesting and diverse biological activity of dihydropyrimidinones have attracted many organic chemists for the development of the three component Biginelli (or like) reaction with the addition of new catalysts and non-conventional methods using different types of carbonyl derivatives. We also found that solventless grinding technique has great potential in creating further new protocols for both Biginelli and Biginelli like reaction. As there is lack of protocols for Biginelli like reaction compared to Biginelli reaction, designing of improved protocols and creating compound library out of this reaction will be a significant addition towards greener synthesis.

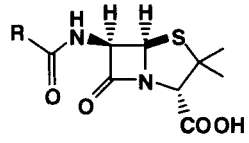
1B.3 Ester enolate- imine condensation reaction

Gillman and Speeter were the first to report the preparation of β-lactam by the condensation of Reformatsky reagents (i.e. zinc ester enolates) derived from ethyl α-bromoacetate with simple N-phenylbenzaldimine [105] in 1943. The application of ester-imine condensation route to β-lactams remained

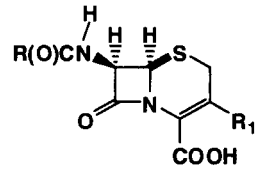
unexplored for many years in spite of extensive interest in the area of β-lactam synthesis after the structure elucidation of Penicillin and cephalosporin (*Fig - 10*). However in 1970 the isolation of new potent β -lactam antibiotics (**41**, **42**) (*Figure 1B.11*) from fermentation broths revealed that C (4) sulfur substituents were unnecessary for activity [106]. The realization that β-lactams carrying C(4) alkyl substituents instead of C(4) sulfur substituents of the β-lactam nucleus which are accessible via ester-imine condensations, were pharmacologically interesting are responsible for accelerating the research activity surrounding ester-imine condensations during the past decade.

1B.3.1 Synthetic and pharmacological significances

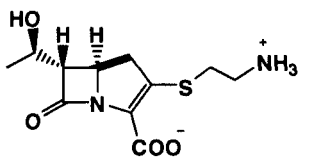
The synthesis of chiral and achiral 2-azetidinone (β -lactam) skeletons is ever mounting in connection with the structure-activity relationship study and the development of new derivatives of the β –lactam antibiotics and inhibitors of β -lactamase. Due to the increased bacterial resistance, there has been effort expended to prepare new structural types having the 2-azetidinone as common feature. Discovery of new active β-lactam compounds [107] such as cholesterol acyl transferase inhibitors, thrombin inhibitors, human leucocyte elastase, cysteine protease and apoptosis inductors has renewed interest in the field.



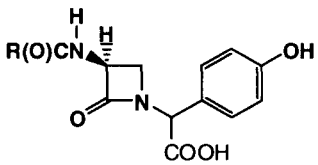
(39) Penicillin (natural, 1929)



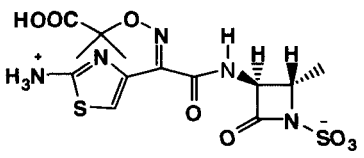
(40) Nocardicin (natural, 1976)



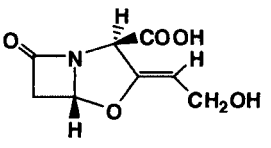
(41) Thenamycin (natural, 1976)



(42) Cephalosporin (natural, 1945)



(43) Aztreonam (synthetic, 1981)



(44) Clavulanic acid (natural, 1974)

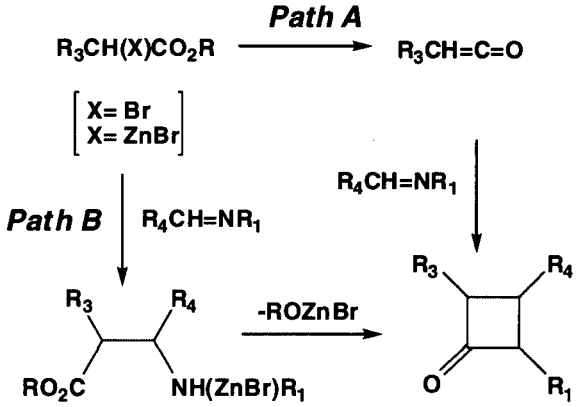
Figure 1B.11: Important β-lactam antibiotics

Apart from their antibacterial activities, the β-lactams are also increasingly being used as synthons for the synthesis of variety of natural products. The strain energy present in the four-membered azetidin-2-one ring is responsible for their applications as synthon for various stereoselective syntheses. Attempts have been made in exploring such new aspects of β–lactam chemistry using enantiomerically pure β-lactam as versatile intermediates for the synthesis of aromatic β-amino acids and their derivatives[108a], oligopeptides[108b] which are further converted to polyamines, polyamino alcohols, amino sugars and polyamino ethers. The development of such methodologies based on β-lactam nucleus is known as *β-lactam synthon method*[109]. Depending on reaction conditions, this enolate-imines condensation can generate β -amino ester as major products which are also useful building blocks for molecules with applications in pharmaceutical and material science[110].

1B.3.2 Mechanistic studies

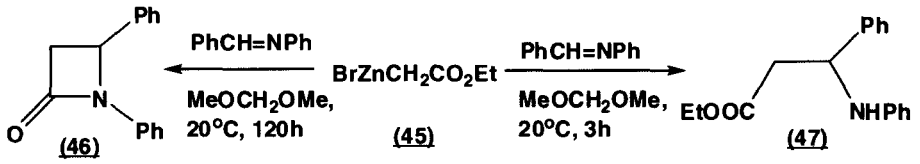
Several mechanistic studies revealed the existence of two types of reaction path (*Scheme 1B.6*) for enolate-imine condensation reaction. The path ***A*** follows the ketene-imines route which was originally[111] proposed for the Staudinger β-lactam synthesis which involves with the fragmentation of initially formed Reformatsky reagent to a ketene. Subsequently, cycloaddition between ketene and imines affords the β-lactam.

In the path ***B***, the Reformatsky reagent could add to the imine to afford a β-amido ester followed by cyclization to form the corresponding β-lactam.



Scheme 1B.6: Mechanistic paths of ester enolate-imine condensation reaction.

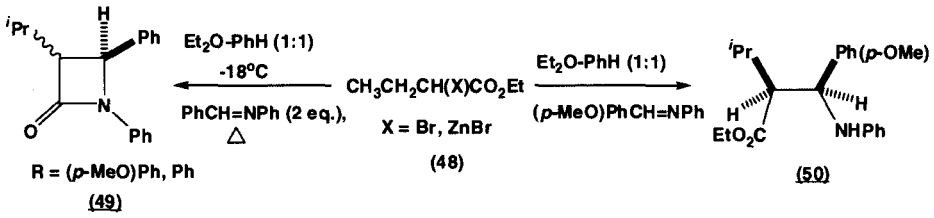
In a series of experiments by Gaudemar it is showed [112] that "preformed" Reformatsky reagents reacted with N-arylaldimines to afford either β-amino esters or β-lactams or both depending on the reaction conditions.



(29)

For example, treatment of Reformatsky reagent (**45**) with N-arylaldimines at 20°C for 3 h gave only β-amino ester (**47**) (63%). When the reaction was allowed to proceed for 120 h, β-lactam (**46**) was obtained (***Eq. 29***) in 77%. These results were interpreted as evidence for a condensation-cyclization mechanism ***B*** *(Scheme 1B.6)*, in which the cyclization was rate determining.

Kagan and Luche [112,113] observed that treatment of the "preformed" Reformatsky reagent (**48**) with imines at -18°C in ether-benzene (1:1) gave an 85 % yield of β-amino ester (**50**) *(eq. 30)*. When N- arylbenzaldimine was added to the cold reaction mixture and then reflux, it yielded a mixture of four β –lactam (**49**) ***(Eq. 30)***.



(30)

All these results established the existence of β-lactam against its stability to the reaction condition and showed the reversible nature of enolate-imines condensation along with isomerization process. However, these results did not rule out the possibility for the production of β-lactam compounds via the ketene mechanism.

1B.3.3 Stereochemical studies

Kagan and Luche [113] first investigated the stereochemical course of reactions between various Reformatsky reagent of α–substituted acetates and N-aryl aldimines using THF and toluene as solvents under reflux conditions. It was found that the stereochemistry of various products as a function of the solvent, α-substituent and alkyl portion of the ester. The following general trends

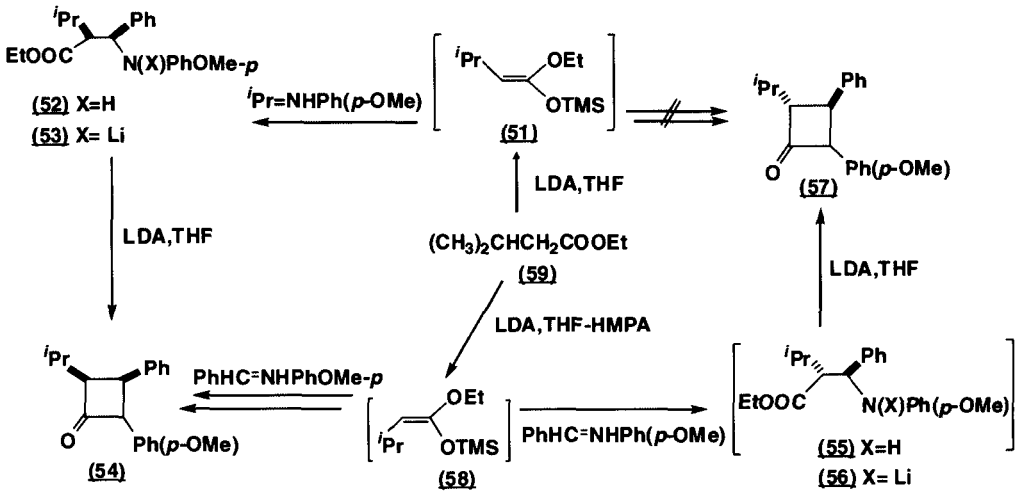
observed with various Reformatsky reagents under different reaction conditions [114,115].

With the α-substituted alkyl group (R_3 = Me, Et, ^{i}Pr, Cy, ^{t}Bu), the major product was *cis* geometry.

- With the branched α-substituent (R_3 = ^{i}Pr, Cy, ^{t}Bu), the only product was the *cis* isomer using THF as solvent.
- In toluene, the secondary ester generated trans geometrical isomer as major product.
- While using phenyl acetates, trans isomer is favored regardless of solvent.

Like Reformatsky reagent, several mechanistic studies have been reported for the enolate-imine condensation reaction of lithium, aluminium, zinc and other enolates.

I. The stereochemical studies[116a] on lithium enolate for β–lactam synthesis showed that azomethine addition is the rate determining step for many lithium enolate -imine condensation in THF as solvent. Thus, treatment of β-amino esters **(52)** and **(55)** with LDA in THF gave **(54)** and **(57)**, respectively with no crossover in stereochemistry at -70^{0}C. Further it was shown that enolate **(51)** did not react with azomethine at -70^{0}C in THF.



Scheme 1B.7: Schematic presentation of azomethine addition as the rate determining step

These experiments demonstrate the kinetic competence of β–amido esters (**53**) and (**56**) to serve as intermediate in reactions affording β–lactam (*Scheme 1B.7*).

II. Ha *et al.*[116a] investigated the effect of enolate geometry on the stereochemical course of reaction using aliphatic ester enolates and non- enolizable imine for β–lactam synthesis. He reported that (***E***) - enolates afford β -lactams with high diastereoselectivity while (***Z***) enolates show little stereoselectivity. Since addition of an (***E***)-enolate to an (***E***)-imine via a chair-like transition state should afford a cis - lactam as observed while there is a lack of selectivity with (***Z***)-enolates which is because of an additional steric interaction in hypothetical transition state , presented in the transition state model for ester-imine condensations discussed by Evans [116b].(*Figure 1B.12)*

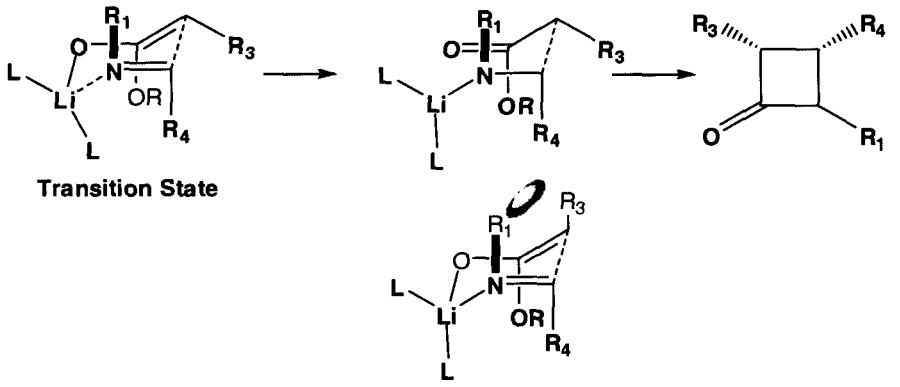
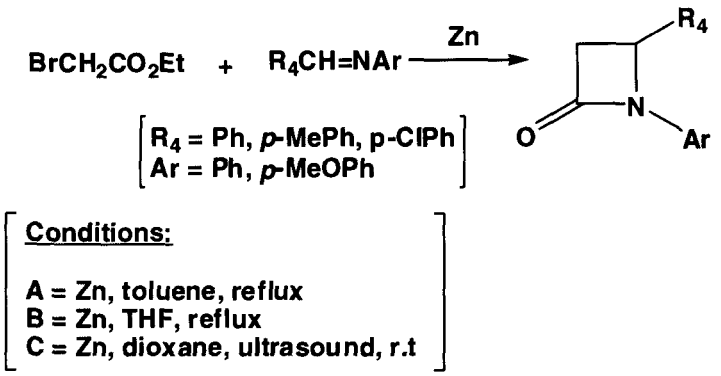


Figure 1B.12: Transition-state models for ester-imine condensations

III. Ha *et al.* also observed that isomerization of β-lactams under the basic reaction conditions using lithium enolate is a function of the nitrogen and C (3) substituents and the reaction medium. N-aryl β-lactams isomerizes more easily than N-protio or N-trialkylsilyl β-lactams. Substituents at C (3) that enhance acidity render β-lactams more susceptible to isomerization. The smaller the C (3) substituent, the faster the rate of isomerization. The more polar the solvent, the faster the rate of isomerization.

1B.3.4 Classical methods

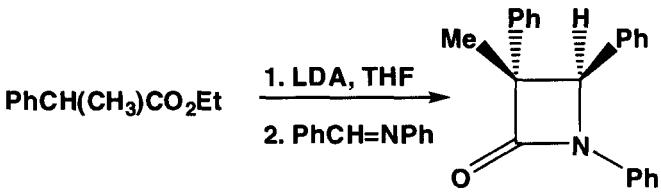
Under the name of Gilman-Speeter reaction, several kinds of conditions are described [112] using zinc, lithium, aluminium, tin, boron, zirconium, and titanium enolates, although most of these approaches end up producing the β-aminoesters.



(31)

For example, Bose *et al.* reported [117] that the use of ultrasound appears to increase the yields of β-lactam to 70-95 % relative to those obtained (28-52% yields) under standard Reformatsky condition (***Eq. 31***).

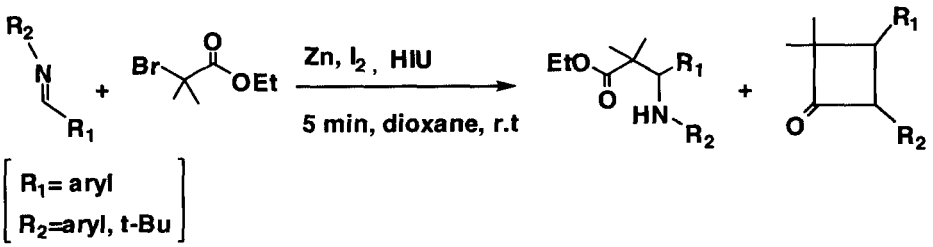
Bergbreiter and Newcomb[118a] (***Eq. 32***) disclosed the reaction between enolates derived from treatment of a variety of α, α-disubstituted acetates with lithium diisopropylamide (LDA) with nonenolizable N-arylaldimines to afford β-lactams in good yields and with excellent diastereoselectivity.



(32)

This report initiated more efficient route than the Reformatsky route because esters are more readily available than α-bromo esters. The above method failed to afford β- lactam without C (3)-substituted azetidinones.

Although, the use of zinc enolates was the first to be described, still several recent examples of this reaction are known. The use of high intensity ultrasounds[118b, 118c] afforded in good yield mixtures of β-amino ester and β-lactam (***Eq. 33***), with different ratio depending on the structural characteristics of the imine and the α–bromoester.

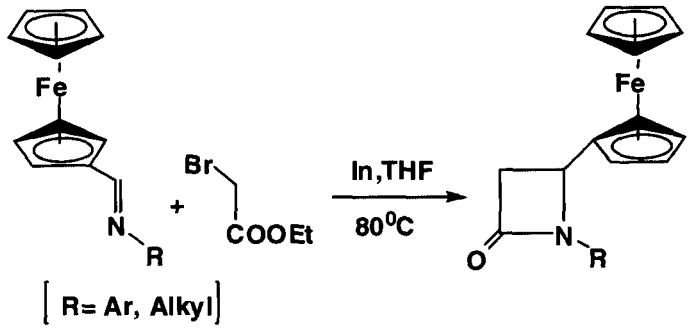


(33)

Ding *et al.*[119a] presented the use of Zn/Cp_2TiCl_2 catalyzed Reformatsky reaction of α-bromoalkanoates and 4-bromocrotonates with N-aryl aldimines at room temperature in THF to form the corresponding β-lactams and 3-vinyl-β-lactam, respectively.

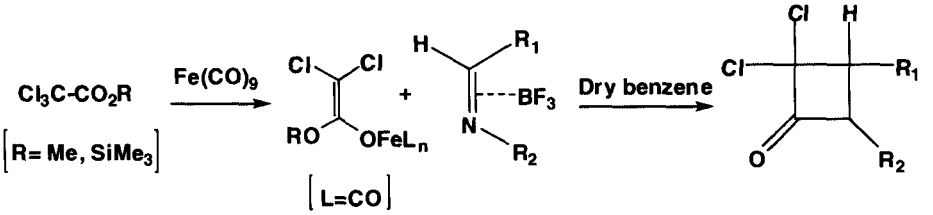
Kanai *et al.*[119b] reported the use of Wilkinson catalyst in Reformatsky reaction for the selective formation of β-aminoester or β-lactam with the change of solvent and reaction temperature.

Analogously, titanium complexes can also act as catalyst in the presence of a stoichiometric amount of Zinc[119c]. A series of ferrocenylimines reacted with ethylbromoacetate in the presence of Indium instead of Zinc (***Eq. 34***).



(34)

Khajavi *et al.*[120] reported that diiron nonacarbonyl promoted the reaction of methyl or trimethylsilyl trichloroacetate with N-arylaldimines in dry benzene for the synthesis of 3,3-dichloro-β-lactams through the formation of iron enolate in presence of small amount of boron trifluoride etherate (***Eq. 35***).



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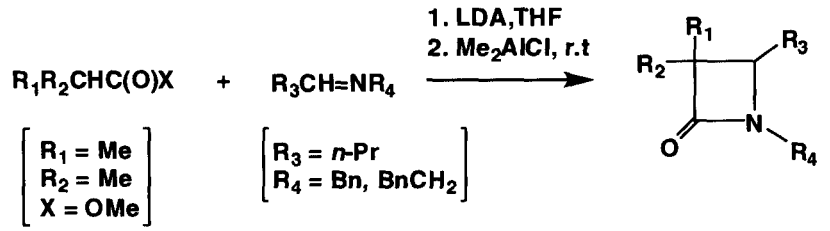
The reaction of aluminium enolate[121] derived from lithium enolate with enolizable N-alkylimines afforded good yields of β–lactam at room

temperature, but this enolizable imines do not generally give good yields in reaction with lithium enolates (*Eq. 36*).



(36)

Apart from variety in the enolate components; there has been significant advancement of the title reaction with other variants of the azomethine components such as N-arylaldimines, N-alkylimines, N-(trialkylsilyl)imines, oxime ethers, sulfenimines and azacumulenes[117] derived from enolizable and non enolizable aldehydes Some enolate-imine condensations which do not directly afford β-lactams, require another step to convert β-aminoester to β-lactams.

Most of these methods of ester- imine condensation involve the use of volatile organic solvents like THF, toluene, benzene, dioxane, diethyl ether, dichloromethane. We have categorized different protocols for ester enolate-imine condensation with respect to the types of ester enolate and aldimines utilized [121,122,123,112] and observed the types of solvent used in these reactions (*Table 1B.1*).

Table 1B.1: Types of solvent utilized with different combinations of enolate and aldimines

Sr. No.	Enolate	Aldimines	Types of solvent used
1	α-bromoacetates	N-Arylaldimines	THF, toluene, dioxane,
2	α-substituted α-bromoacetates	N-Arylaldimines	toluene, THF, benzene-Et_2O (1:1)
3	α-substituted/ unsubstituted α-bromoacetates	N- Alkyl & Enolizable Aldimines	Me_2O, toluene,
4	Lithium enolates	N-Aryl- & N-Alkylaldimines	THF, HMPA-THF,
5	Lithium & Zinc enolates	N-(Trimethylsilyl) imines	THF,THF-HMPA,Et_2O,PhH

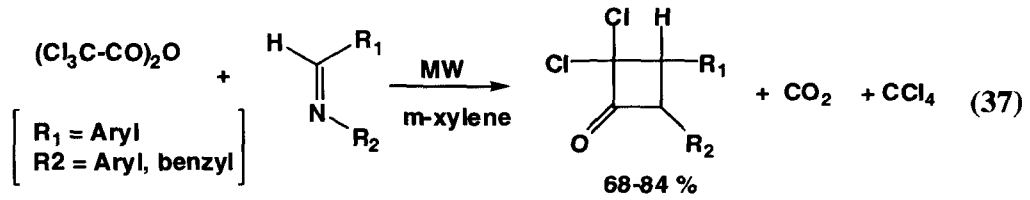
6	Lithium & Zinc enolates	Oxime Ethers & Sulfenimines	THF
7	Zinc &Aluminum enolates	N-Aryl- & N-Alkylaldimines	THF, Et_2O
8	Acyliron & Thioester enolates	N-Aryl- &N-Alkylaldimines	THF, DME, CH_2Cl_2, PhMe, THF-hexane, Et_2O
9	Boron& Tin enolates	N-Aryl- & N-Alkylaldimines	Et_2O, CH_2Cl_2, THF,

All these methods require the use of THF as common solvent along with proper control of reaction temperature (e.g. -78°C) and longer reaction time to obtain the target compound in good yield and stereoselectively. Reaction procedures and work up steps are very tedious. Precaution has to be taken in preventing the compounds from decomposing. Thus, it needs extensive research for elimination or reduction of environmentally hazardous factors associated with traditional methods of enolate-imine condensation reaction.

1B.3.5 Non- classical methods

For ester enolate-imine condensation reactions, various non-classical methods have been reported involving the use of *microwave irradiation* and *solid phase synthesis*.

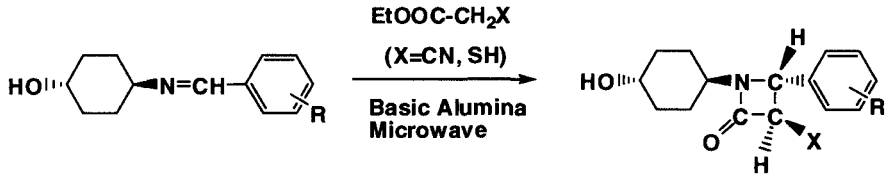
Khajavi *et al.*[120] described the synthesis of 3, 3-dichloro-β-lactams by the reaction of trichloroacetic anhydride and N-arylaldimines or N-benzylaldimines under microwave irradiation in xylene within short reaction time (1-2 min) (***Eq. 37***). Although, this is a rapid method with good yields of products under microwave irradiation but it does not avoid the use of organic solvent as reaction medium.



(37)

Kidwai *et al.* developed another method for the synthesis of N-(4-hydroxycyclohexyl)-3-mercapto/cyano-4-arylazetidine-2-one from N-(4-hydroxycyclohexyl)-arylaldimine by reacting with ethyl a-mercapto/ex-cyanoacetate on basic alumina (***Eq. 38***) [124] under microwave irradiation in

solution or solid phase conditions. In comparison to conventional heating, the reaction time decreased from hours to minutes under microwaves with improved yields.



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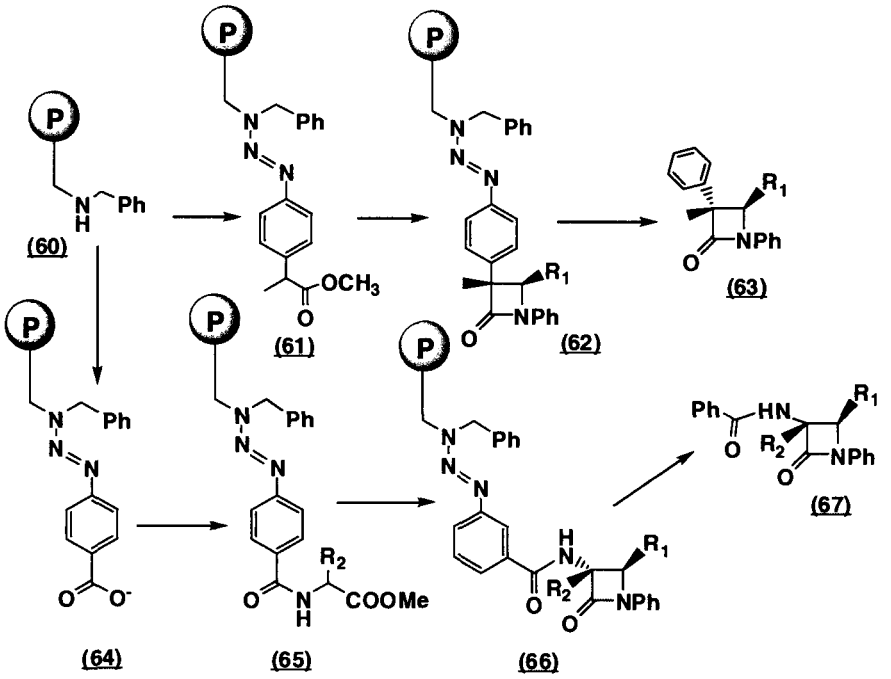
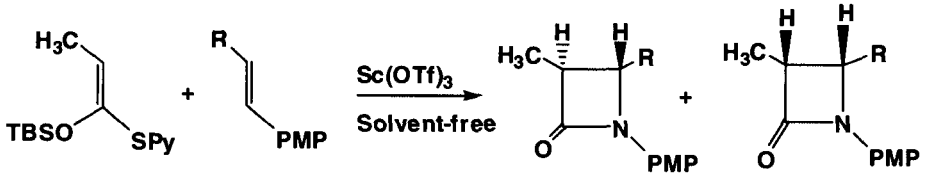
Schunk and Enders [125] presented the solid phase approach to ester enolate- imine by using an immobilized ester enolate. Esters were attached to benzylamine resin (**60**) by a triazene linker employing the respective diazonium salts. Immobilized ester enolates (**61**) and (**64**) were reacted with various imines afforded the corresponding polymer bound β-lactams (**63**) and (**66**). The traceless triazene junction was finally removed (*Scheme 1B.8*).

Functionalized carbosilane dendritic species demonstrated [126a] useful soluble supports for the stereo- and enantioselective synthesis of β –lactam through the reaction of dendritic zinc enolate with various imines. Wang and coworkers [126b] also applied soluble polymer support to the Reformatsky procedure of α–bromoimide with good results.



Scheme 1B.8: Solid phase approach to ester enolate-imine by using an immobilized ester enolate

Recently, silyl ketene thiacetals derived [127] from 2-pyridyl thioesters were used in a Sc (OTf) $_3$ catalyzed reaction with imines to (***Eq. 39***) get β-lactams. The use of Sc (OTf) $_3$ allowed the development of a catalyzed, solvent-free process.



(39)

All the above mentioned routes are capable of increasing yield and reaction rate compared to the classical methods. However there is still lack of simplification of the procedure, elimination of solvent and recycling of catalyst and thus development of improved protocols for this reaction has so far remained overlooked area. Our group realized that there is a need of incorporation of green chemistry matrices as many as possible to the ester enolate- imine condensation reaction to draw maximum benefit out of this significant reaction.

1B.4 Overall objectives

A thorough study of the literatures on Henry reaction, ester enolate-imine condensation reaction and Biginelli reaction or Biginelli-like reaction provides us information on various scopes of developing improved new strategies for them which serve the motif behind our research work i.e. to contribute and accelerate the recent trend of synthesis in a greener way. Based on these possibilities we framed the objectives which are as follows:

1. Development of greener synthetic strategies for *nitro-aldol condensation* using aqueous and solventless reaction medium.
2. Investigation of *Biginelli reaction* under solventless microwave irradiation condition for the synthesis of *5- substituted 3, 4-dihydropyrimidinones.*
3. Design of environmentally benign synthetic routes for *synthesis of 5-unsubstituted 3, 4-dihydropyrimidinones* (Biginelli like reactions).
4. Investigation of *ester enolate-imine condensation reaction* in aqueous medium under basic conditions.

5. Synthesis of novel β–amino ester/β-lactam by ester enolate-imine condensation reaction under solvent-free microwave irradiation method.
6. Study of *Solvent effect and substituent effect* on the conversion rate and feasibility of the above reactions.
7. Examination of *catalyst reusability* and *proper modeling of support* to achieve maximum catalytic efficiency.

Chapter 2

Materials and methods

Chapter 2

Materials and Methods

2.1 Materials

Details of the chemicals used in various reactions mentioned in this thesis along with the general information on apparatus that are used commonly during experimentation are discussed below.

2.1.1 Chemicals

All chemicals were procured from commercial suppliers and used as received except organic solvents such as DCM, ethanol, acetone and ethyl acetate, which were used only after distillation. The chemicals used were all reagent grade and procured from SRL, Sigma-Aldrich, Merck-India, SD fine chemicals, Loba chemie, Acros organics, Alfa Aesar, G. S. Chemicals, Rankem, Qualigen and HiMedia Laboratories, India. Distillation of dichloromethane, acetone, ethylacetate and ethanol are carried out using normal distillation setup and refluxing the solvents using heating mantle.

2.1.2 Reaction assembly

A. *Microwave apparatus:* All MORE synthetic routes were developed using two types of domestic microwave oven. They are:
    - *Samsung C103FL* with power levels as 900/600/450/300/180W
    - *Panasonic NN-SN 667B* with power levels as 125/ 250/ 375/ 500/ 625/ 750/ 875/ 1000/ 1125/ 1250W
B. *Heating mantle:* MSW-431 Heating mantle, *Macro Scientific Works (P) Ltd.*
C. *Mortar and pestle:* Porcelain, (80mm, 60ml)
D. *Rotary evaporator:* Buchi R-210/R-215

2.2 Methods

Details of different general methods for synthesis of 2- nitroalkanols, DHPMs, β-amino esters and β- lactams compounds that are standardized under various conditions are mentioned here. The techniques used for purification and characterization of these compounds are also discussed along with the details of instruments for characterization.

2.2.1 General methods of synthesis

A. General Method for Henry Reaction in Aqueous Medium

A mixture of 2-nitrobenzaldehyde (1 mmol), nitromethane (3 mmol), and imidazole (0.25 mmol) was charged in 2mL of distilled water in a round bottom flask. The heterogeneous reaction mixture was stirred at ambient temperature with magnetic stirring and monitored by thin-layer chromatography (TLC). After completion of the reaction, the product was extracted with 10 mL of diethyl ether. The organic layer was dried over anhydrous Na_2SO_4 and filtered. The organic filtrate was evaporated under reduced pressure (at 40°C) and dried under vacuum to give the crude product, which is reasonably pure (>95% purity from ^1H NMR spectral data) for aromatic aldehydes. However, the residue was further purified by preparative TLC on silica gel to give the desired analytically pure products.

B. General Method for Henry reaction under solvent free grinding at room temperature using mortar and pestle

A mixture of benzaldehyde (1 mmol), nitromethane (5 mmol), and imidazole (0.35 mmol) were ground together in a mortar with a pestle at room temperature for appropriate time. The progress of the reaction was monitored by TLC which indicates the formation of single product along with some amount of unreacted starting compound. The mixture becomes sticky during the course of reaction. Finally it was diluted with distilled water and the organic mixture was extracted with diethyl ether. The organic layer was dried with anhydrous Na_2SO_4 and decanted. The dried organic layer was evaporated under reduced pressure to give the crude reaction mixture. The crude mixture

was further purified by column chromatography by using n-hexane and ethyl acetate as eluent to get the desired analytically pure products.

C. General Method for Henry reaction in presence of sand under solvent free grinding at room temperature using mortar and pestle

In this method the above reaction mixture was ground for appropriate time by adding 80mg of sand. The progress of the reaction was monitored by TLC which indicates the formation of single product along with some amount of unreacted starting material. The sticky reaction mixture was diluted with diethyl ether and then filtered. The filtrate was again washed with distilled water to remove water soluble imidazole. After this the ether layer is dried over anhydrous Na_2SO_4 and decanted. The ether extract was evaporated under reduced pressure to give the crude reaction mixture which was further purified by column chromatography by using n-hexane and ethyl acetate as eluent to get the desired analytically pure products.

D. General method for the synthesis of Biginelli (or like) product under solvent –free grinding technique

A mixture of acetophenone (1 mmol), aldehyde, (1 mmol), urea (1.5 mmol) and hydrated ferric nitrate (or clayfen) (0.1 mmol) was gently ground by hand using mortar and pestle of appropriate size. The progress of the reaction was monitored by TLC which indicates the formation of single product. The mixture becomes a sticky paste during the course of reaction which finally solidifies on completion of reaction. Finally, it was washed with a cold saturated solution of $NaHCO_3$ (5 mL) and then filtered through a sintered funnel under vacuum to afford the crude product which was further purified by recrystallisation from ethanol. With *clayfen* catalyst, the reaction mixture was dissolved in hot ethanol and filtered. The insoluble clayfen residue was washed several times with hot ethanol and dried in a vacuum desiccator for reuse.

E. General method for the synthesis of Biginelli product under solvent –free and catalyst- free MORE technique

Aryl aldehyde 1 (2 mmol), β-ketoester 2 (2 mmol), (thio)urea 3 (3 mmol) were taken in a 100ml beaker and irradiated inside the cavity of a domestic MW oven (*Samsung C103FL*) in neat without any solvent/catalyst at specified power level (900/600/450/300/180W) and reaction period. After completion of the reaction, as indicated by TLC, the resulting reaction mixture was cooled with ice-cold water. The solid product was washed with cold water (20mL) to remove the excess of urea or thiourea and then filtered. The remaining solid material was recrystallized from ethyl acetate/ n-hexane or ethanol mixture to afford the pure products.

F. General Method for Ester enolate- imine condensation under reflux condition

A mixture of diethylmalonate derivate (1 mmol), N-phenylaldimine (1mmol) and KF/Al_2O_3 (37 mol %) in distilled acetone (10 mL) was refluxed at 56°C for required time of completion of reaction (monitored by TLC). On completion, the reaction mixture was filtered through Whattman 40 filter paper to remove KF/Al_2O_3.The organic filtrate was evaporated under reduced pressure and dried under vacuum to give the residue. However, the residue was further purified by preparative TLC on silica gel to give the desired analytically pure products.

G. General Method for Ester enolate- imine condensation under solvent free MORE technique

A mixture of diethylmalonate derivate (1 mmol), N- phenylaldimine (1mmol) and Al_2O_3 (basic, 1 gm), in a 500 ml beaker covered with glass funnel was placed in a domestic microwave oven (Panasonic N,N-SN 667B) at different power levels. The mixture was irradiated for required time of completion of reaction (monitored by TLC). On completion, the reaction mixture was extracted with distilled DCM (3X20mL) and filtered through Whattman 40 filter paper to remove Al_2O_3. The organic filtrate was evaporated under reduced pressure and dried under vacuum to give the residue. However, the

residue was further purified by preparative TLC on silica gel to give the desired analytically pure products.

H. Method of preparation of Schiff bases

Schiff bases were prepared with minor modifications from reported method[128]. Aldehyde (5 mmol) is stirred with basic alumina (0.5g) in 10 mL DCM. A mixture of aniline (5 mmol) dispersed on alumina is added slowly to aldehyde-alumina mixture in DCM. After 15-17 hours of reaction time at room temperature imine is extracted with DCM (2x10 mL) and extract is evaporated under reduced pressure. The imine is recrystallized from ethanol before using it for further reaction.

I. Method of preparation of supported catalyst clayfen

The method of preparation of supported catalyst clayfen is reported with minor changes [129]. $Fe(NO_3)_3.9H_2O$ (500 mg) was added to acetone (8.3 mL) in a 100 mL round bottom flask and stirred vigorously for 5 min, until complete dissolution of the crystals. Monmorillonite K-10 clay (667 mg) was added in small portions and stirred again for 5 min. The solvent was evaporated under reduced pressure on rotary evaporator at 50°C. Yellow color powder of $Fe(NO_3)_3.9H_2O$ supported on K-10 clay (clayfen) was obtained which was further dried under the same condition for 30 mins. Freshly prepared clayfen was used in every reaction.

J. Preparation of KF supported on basic alumina as reagent (KF/Al_2O_3)

The method of preparation of supported catalyst KF/Al_2O_3 is reported with minor changes [130]. Anhydrous potassium fluoride (1 g) was dissolved in distilled water (2 mL) and mixed with neutral alumina (2 g) as solid support. The mixture was stirred at 65-75 °C for 1h. The water was removed under reduced pressure. The resulting free flowing powder was dried at 120 °C for 4 h.

2.2.2 Purification methods

A. Chromatography

Two types of chromatographic techniques were used in purification of compounds. They are TLC (Thin Layer Chromatography) and column chromatography. TLC is also used for reaction monitoring.

TLC

Both analytical and preparative thin- layer chromatography (TLC) was performed with TLC silica gel (*Merck*, 60-120 mesh). Visualization of spots was effected by either UV irradiation or exposure to iodine vapor. Eluent generally used in all the above procedures is the solvent mixture of ethyl acetoacetate and n-hexane/ petroleum ether in different ratios.

Column chromatography

Column chromatography was carried out using column silica gel (60-120 mesh) purchased from *Rankem*, India. Eluent generally used in all the above procedures is the solvent mixture of ethyl acetoacetate and n-hexane in different ratios.

B. Recrystallization

Solid crude products of 5-substituted and unsubstituted 3, 4-dihydropyrimidin-2(1H)-ones and 3, 4-dihydropyrimidin-2(1H)-thiones were recrystallized from ethyl acetate/ n-hexane or ethanol to afford the pure products.

2.2.3 Characterization techniques

A. ^{1}H NMR spectra

^{1}HNMR spectra were recorded on a *Jeol JNM-ECS* 400 MHz FT-NMR spectrometer at the Department of Chemical Sciences, Tezpur University, *Varian 400 MHz* FT-NMR at IIT, Guwahati and *Bruker DPX-300* NMR spectrometer at NIEST, Jorhat using $CDCl_3$ or DMSO-d_6 as solvent and TMS as internal standard. ^{1}H NMR spectral data were reported as chemical shifts in parts per million (ppm); multiplicity (brs = broad singlet, d = doublet, t = triplet, q = quartet & m = multiplet; coupling constant J in Hz.

B. CHN analysis

The compounds were analyzed for carbon, hydrogen and nitrogen on a *Perkin-Elmer 20* Analyzer at the Department of Chemical Sciences, Tezpur University.

C. FT-IR analysis

FT-IR spectra were recorded on *Nicolet instruments* 410-FTIR spectro-photometer at the Department of Chemical Sciences, Tezpur University using either KBr pellets or by applying thin film of compounds on CsBr window (neat) and reported in wavenumbers.

D. Mass Spectra

GC-MS analyses of amino ester and lactams were recorded on a *Clarus 600* instrument at the Department of Chemical Sciences, Tezpur University. Nebulizing gas: Helium, Gas flow rate: 1mL/min, Column: polyethylene glycol (*Elite wax*), Temperature: 220°C

E. Melting point

Melting points were determined on a *Buchi* melting point apparatus, (Model B-540) at the Department of Chemical Sciences, Tezpur University.

Chapter 3

Development of synthetic strategies for nitro-aldol condensation using aqueous and solventless reaction medium

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Published with small modifications from:

Phukan M., Borah K. J., Borah R.; "*Imidazole-catalyzed Henry reaction in aqueous medium*". ***Synthetic Communications,*** Volume 38, Issue 18, 2008, 3068-3073

Phukan M., Borah R.; "*Henry reaction in environmentally benign methods using imidazole as catalyst*". ***Green Chemistry Letters and Reviews***, Volume 2, Issue 4, 2009, 249-253

Section 3A

Imidazole catalyzed Henry reaction in aqueous medium

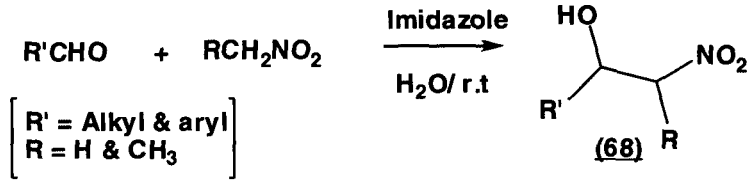
3A.1 Objective

The incentive of our research to design reaction protocols in aqueous medium started with the Henry reaction. Literature study on this reaction as discussed in *section 1B.2.3* revealed lack of protocols exploiting the advantages of using water compatible organocatalysts for performing reactions in aqueous medium. It is also observed that basicity of catalyst for Henry reaction is crucial to achieve selectivity and maximum yield of β-nitroalkanols (**68**). In such cases, longer reaction times are demanded and such standard procedures furnish a enantiomeric mixture of nitroaldols in case of nitromethane and diastereomeric mixture of nitroalkanols in case of nitroethane. Nevertheless these diastereomeric mixtures of nitroaldols are capable of retaining their importance in synthesis as their conversion into β -nitro ketones or conjugated nitroalkenes eventually involves loss of at least one stereogenic center[55]. Thus, taking all these factors under consideration we selected imidazole for examining the progress of Henry reaction in aqueous medium. Imidazole is an organic moiety which at the same time water soluble. Interestingly, it has mild Lewis basicity and is easily available and cost effective. To our delight, we found imidazole a highly active catalyst for synthesis of nitroaldols in water within short reaction time.

3A.2 Results and discussion

Initially we decided to evaluate the effect of solvent on the imidazole catalyzed Henry reaction in different organic solvents as well as in aqueous medium. For this study, the reaction between p-nitrobenzaldehyde and

nitromethane was chosen as a model. Types of organic solvents used for carrying out the reaction at room temperature are dichloromethane, 1, 4-dioxane, chloroform, THF, acetonitrile, and methanol (*Table 3A.1*).



Scheme 3A.1: Imidazole catalyzed Henry reaction in aqueous medium

Table 3A.1: Effect of solvent on the imidazole catalyzed reactions of p-nitrobenzaldehyde with nitromethane.

Entry	Solvent	Time (minute)	Nitroalcohol (68) (%) Yield [a,b]
1	Dichloromethane (DCM)	35	94
2	1,4-Dioxane	25	93
3	Chloroform	30	92
4	Water	30	98
5	Tetrahydrofuran (THF)	5	95
6	Acetonitrile (ACN)	5	95
7	Methanol	5	94
8	Tetrahydrofuran-water (1:1)	5	92
9	Acetonitrile- water (1:1)	5	95
10	Methanol -water (1:1)	5	91
11	Dichloromethane-water (1:1)	35	92
12	Chloroform-water (1:1)	35	90

[a] *Reactions were carried out on a 0.5 mmol scale (2 ml of solvent) in the molar ratio of aldehyde / nitromethane / catalyst = 1:3:0.25;* [b] *Isolated yields of pure products.*

The reaction proceeds smoothly at room temperature in water (*Table 3A.1, entry 4*) with 98% yield of β-nitroalcohol in 30 min. In the case of non-polar solvents such as dichloromethane, 1, 4-dioxane, and chloroform (*Table 3A.1, entries 1–3*) the conversions were quite similar to aqueous medium in terms of reaction time and yield. However, the use of polar aprotic and protic organic solvents such as tetrahydrofuran, acetonitrile, and methanol (*Table 3A.1, entries 5–7*) gave excellent conversion to the nitroaldol product within 5 min. This can be explained in terms of a homogeneous solution of reaction mixture

with the catalyst imidazole in polar organic solvent, which possesses slight amount of miscible water. But in case of non-polar organic solvents, the reactants are in a different phase with the catalyst imidazole. Similarly, for an aqueous medium, the reactants are in different phases with the water-soluble catalyst imidazole. Thus, the aqueous medium reaction took a similar reaction period to less polar organic solvents. Carrying out the same reaction in a 1:1 mixture of various organic solvents and water medium (*Table 3A.1, entries 8–12*) can indirectly prove this explanation. It was observed that the reaction completed within 35 min in a heterogeneous 1:1 mixture of less polar organic and aqueous solvent systems (*Table 3A.1, entries 11 and 12*). Similarly, a homogeneous 1:1 mixture of polar organic and aqueous solvent systems showed comparable results with the polar organic solvent (*Table 3A.1, entries 8–10*).

We next examined the extent and feasibility of the imidazole catalyzed aqueous Henry reaction of nitroalkane with various aldehydes (*Table 3A.2*). For aryl aldehydes bearing electron-withdrawing groups such as ortho-, meta- and para- nitrobenzaldehyde, the reaction took place smoothly to afford the desired nitroaldol products in good to excellent yields (*Table 3A.2, entries 3–7*). However, for arylaldehydes bearing electron-donating groups such as p-tolualdehyde, anisaldehyde (*Table 3A.2, entries 8–12*), and aliphatic aldehyde (*Table 3A.2, entries 13 and 14),* the reactions were slow. Similarly, the reaction of furaldehyde (*Table 3A.2, entry 15*) with nitroethane was slow, resulting in 65% of the corresponding nitroalcohol after 4 h. These differences are clearly visible on plotting histogram, showing types of aldehydes as X-axis vs. time taken by them for reaction completion *(Figure 3A.1).*

Table 3A.2: Henry reaction in aqueous medium with different aldehydes

Entry	R′ (Aldehydes)	R (Nitroalkane)	Time (min)	Nitroaldol (**68**) (%) Yield [a,b]
1	C_6H_5	H	15	90
2	C_6H_5	CH_3	30	88
3	4-O_2N-C_6H_4	H	30	98
4	2-O_2N-C_6H_4	H	15	97
5	3-O_2N-C_6H_4	H	15	90

6	4-O_2N-C_6H_4	CH_3	15	85
7	3-O_2N-C_6H_4	CH_3	15	94
8	4-MeC_6H_4	H	45	96
9	4-$OMeC_6H_4$	CH_3	2 hr	87
10	2-OHC_6H_4	H	90	97
11	4-ClC_6H_4	H	3 hr	95
12	4-MeC_6H_4	CH_3	1 hr	96
13	Pentanal	CH_3	12 hr	60
14	Pentanal	H	12 hr	55
15	Furyl	CH_3	4 hr	65

[a]*All products were characterized by FT-IR, ^{1}H NMR, CHN analysis and also their comparison with authentic sample;* [b] *Isolated yield*

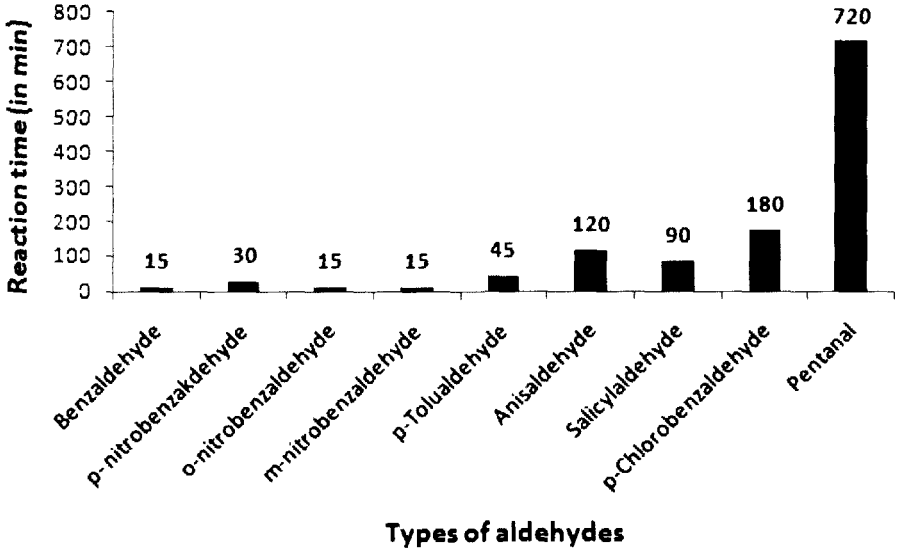
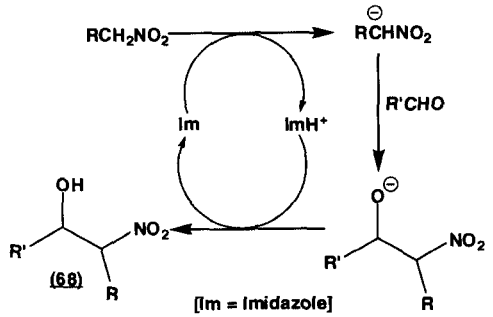


Figure 3A.1: Histogram of the nitroaldol reaction demonstrating electronic effect of aldehydes on reaction rate with nitromethane.

The role of the imidazole catalyst appears to be that of a base that deprotonates the active methylene of the nitroalkane, giving carbanion with



Scheme 3A.2: Plausible reaction mechanism of Henry reaction catalyzed by recyclable imidazole in water.

the release of imidazolium ion. The carbanion further adds to the carbonyl component to give an intermediate, which in turn abstracts proton from imidazolium ion to give the final nitroaldol along with the regeneration of imidazole in the mixture (*Scheme 3A.2*). In addition, the imidazole containing aqueous phase (after extraction of the product) was recycled (*Table 3A.2, entry 4*) three times using a similar amount of 2-nitrobenzaldehyde (1 mmol). (*Table 3A.3*).

Table 3A.3: Recycling of imidazole catalyst in homogeneous solution for Henry reaction

Entry	R′ (Aldehyde)	R (Nitroalkane)	Time (min)	Nitro-aldol (**68**) (%) Yield
1	2-O_2N-C_6H_4	H	15	95
2	2-O_2N-C_6H_4	H	15	93
3	2-O_2N-C_6H_4	H	15	92

In addition to these studies, characterization of all the nitroaldol products synthesized with nitroethane under this method by ^1H NMR reveals presence of stereoisomeric mixtures.

3A.3 Conclusion

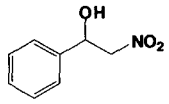
We have developed a new environmentally benign Henry reaction condition in aqueous medium using imidazole as catalyst. The importance of this protocol lies in avoidance of toxic organic solvent, fast reaction rate, high yield and high product selectivity particularly in case of aromatic aldehydes. This seems possible because of the mild conditions provided by both water and catalyst. Mild Lewis basicity of imidazole seems capable of suppressing the competitive side reactions usually associated with Henry reaction. Moreover, imidazole is inexpensive and easily available and is recyclable for several times without appreciable loss of activity.

3A.4 Experimental section

General method of synthesis of 2-nitroaldols in aqueous medium using imidazole as catalyst has been explained in section *2.2.1 (A)*.

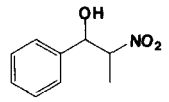
3A.5 Spectral elucidation

1-Phenyl-2-nitroethan-1-ol: (Table 3A.2, entry 1)



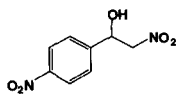
FT-IR (colorless oil, neat, cm^{-1}): 3540, 3034, 1685, 1552, 1492, 1377. **CHN:** Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.38; N, 8.37. Found: C, 57.55; H, 5.32; N, 8.42. **GC-MS:** *(m/z, rel. intensity, %):* 167(M^+), 149, 134,120, 105(100), 77. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.45-7.33 (m, 5H), 5.47-5.40 (m, 1H), 4.56-4.47 (m, 1H), 4.42-4.39 (m 1H), 2.91(brs, 1H).

1-Phenyl-2-nitropropan-l-ol: (Table 3A.2, entry 2)



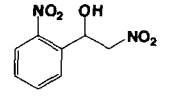
FT-IR (colorless oil, neat, cm^{-1}): 3533, 1552, 1492, 1385. **CHN:** Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.67; H, 6.08; N, 7.73. Found: C, 59.62; H, 6.10; N, 7.76. **GC-MS:** *(m/z, rel. intensity, %):* 181 (M^+), 135, 107 (100), 91, 77, 57. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.5 (s, 5H), 4.9 (dd, *J*=5.8 Hz, each, 1 H), 4.62-4.88 (m, 3H) , 2.72-2.81 (brs, 1H) 1.50 (d, *J*= 7.2 Hz, 3H), 1.32 (d, *J*= 7.2 Hz, 3H).

1-(4-nitrophenyl)-2-nitroethan-1-ol: (Table 3A.2, entry 3)



FT-IR (yellow oil, neat, cm^{-1}): 3537, 2923, 2854, 1555, 1525, 1350. **CHN:** Anal. Calcd. for $C_8H_8N_2O_5$: C, 45.28; H, 3.77; N, 13.20. Found: C, 45.30; H, 3.72; N, 13. 22. **GC-MS:** *(m/z, rel. intensity, %):* 212 (M^+), 194, 148, 151(100), 150, 77. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 8.25 (d, *J*= 8.7Hz, 2H), 7.64-7.62 (d, *J*= 8.7Hz, 2H), 5.62-5.58 (m, 1H), 4.63-4.55 (m, 2H), 3.60 (brs, 1H).

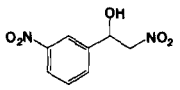
1-(2-nitrophenyl)- 2-nitroethan-1-ol: (Table 3A.2, entry 4)



FT-IR (Viscous liquid, neat, cm^{-1}): 3538, 1548, 1530, 1360. **CHN:** Anal. Calcd. for $C_8H_8N_2O_5$: C, 45.28; H, 3.77; N,

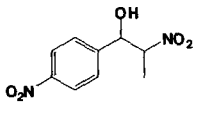
13.20. Found: C, 45.27; H, 3.74; N, 13.30. **GC-MS:** (*m/z, rel. intensity, %):* 212 (M^+), 194, 151(100), 135, 120, 105, 77. **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) 8.12-8.08 (m, 1H), 7.95-7.89 (m, 1H), 7.78-7.74 (m, 1H), 7.60-7.54 (m, 1H), 6.05(m, 1H), 4.87(dd, *J* =13.8, 2.5 Hz, 1H), 4.55 (m, 1H), 3.14 (brs,1H).

1-(3-nitrophenyl)-2-nitroethan-1-ol: (Table 3A.2, entry 5)



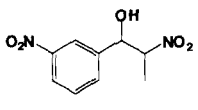
FT-IR (Viscous liquid, neat, cm^{-1}): 3525, 1565, 1525, 1368. **CHN:** Anal. Calcd. for $C_8H_8N_2O_5$: C, 45.28; H, 3.77; N, 13.20. Found: C, 45.35; H, 3.80; N, 13.38. **GC-MS:** (*m/z, rel. intensity, %):* 212 (M^+), 163, 151(100), 135, 120, 105, 77, 51. **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) 8.33 (s, 1H), 8.23 (d, *J* = 9.6 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 8.1 Hz, 1H), 5.60–5.62 (m, 1H), 4.58–4.67 (m, 2H), 3.15 (s, 1H).

1-(4-Nitrophenyl)-2-nitropropan-l-ol: (Table 3A.2, entry 6)



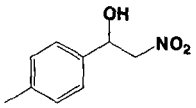
FT-IR (Viscous liquid, neat, cm^{-1}): 3540, 2841, 1560, 1340. **CHN:** Anal. Calcd. for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.38. Found: C, 47.76; H, 4.37; N, 12.49. **GC-MS:** (*m/z, rel. intensity, %):* 226 (M^+), 180 , 151 (100), 150, 134 , 115, 105,77 . **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 8.25 (d, *J*=8.7 Hz, 2H), 7.52 (d, *J*=8.7 Hz, 2H), 5.56-5.30 (m,1H), 4.74- 4.64 (m, lH), 2.95 (brs, 1H) , 1.50 (d, *J*= 6.8 Hz, 3H) , 1.38 (d, *J*= 6.8 Hz, 3H).

1-(3-Nitrophenyl)-2-nitropropan-l-o1: (Table 3A.2, entry 7)



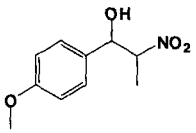
FT-IR (Viscous liquid, neat, cm^{-1}): 3515, 1610, 1525, 1350, 1210. **CHN:** Anal. Calcd. for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.38. Found: C, 47.65; H, 4.49; N, 12.45. **GC-MS:** (*m/z, rel. intensity, %):* 226 (M^+), 179, 151, 150, 149(100), 105, 77. **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) 8.23-8.18 (m.2H), 7.76-7.54 (m,2H), 5.23 (dd, *J*= 5.2 Hz, each 1H), 4.88-4.72 (m,1H),3.30 (d, *J*= 10.5 Hz, lH), 1.55 (d, *J*= 6.2 Hz, 3H), 1.37 (d, *J*= 6.3 Hz, 3H).

1-(4-methylphenyl) - 2-nitroethan-1-ol: (Table 3A.2, entry 8)



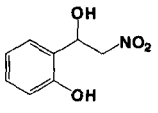
FT-IR (Viscous liquid, neat, cm^{-1}): 3437, 2925, 1553. **CHN:** Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.66; H, 6.07; N, 7.73 found: C, 59.3; H, 6.1; N, 7.5. **GC-MS:** *(m/z, rel. intensity, %):* 181 (M^+), 163, 135, 121 (100), 104, 77. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.34 (d, *J*= 8.0 Hz, 2H), 7.25 (d, *J*= 8.0Hz, 2H), 5.45-5.39 (m, 1H), 4.62-4.56 (m, 1H), 4.46-4.51 (m, 1H) , 2.90-2.62 (brs, 1H), 2.38(s, 3H).

1-(4-Methoxyphenyl)-2-nitropropan-l-ol: (Table 3A.2, entry 9)



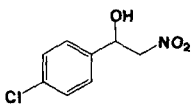
FT-IR (Viscous liquid, neat, cm^{-1}): 3481, 2920, 1668, 1551, 1452, 1365. **CHN:** Anal. Calcd. for $C_{10}H_{13}NO_4$: C, 56.87; H, 6.16; N, 6.63 , Found C, 56.85; H, 6.35; N, 6.25. **GC-MS:** *(m/z, rel. intensity, %):* 211 (M^+), 193, 137(100), 135, 109, 94,77. **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) 7.35-7.33 (d, *J*= 8 Hz, 2H) ,6.75 (d, *J*= 7.7 Hz, 2H), 5.33 (d, *J*= 5.2 Hz, lH), 4.85 (m lH), 4.81-4.65 (m, lH),3.87 (s, 3H), 1.52 (d, *J*= 6.7 Hz, 3H), 1.39 (d, *J*= 6.5 Hz, 3H).

1-(2-Hydroxyphenyl)-2-nitroethan-1-ol: (Table 3A.2, entry 10)



FT-IR (Yellow oil, neat, cm^{-1}): 3537, 1382, 1552. **CHN:** Anal. Calcd. for $C_8H_9NO_4$: C 52.46, H 7.65, N 4.92. Found C 52.65, H 7.82, N 5.01. **GC-MS:** *(m/z, rel. intensity, %):* 183 (M^+), 165, 136, 123 (100), 93.77. **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) 11.0 (s,1H) 7.55–7.49 (m,2H), 7.02–6.95 (m ,2H), 5.62 (d, *J*=8.8Hz, 1H), 4.75 (m,1H), 4.58 (dd, *J*=3.2, 10.5Hz, 1H), 4.35 (brs, 1H).

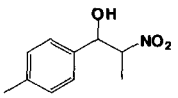
1-(4-chlorophenyl) - 2-nitroethan-1-ol: (Table 3A.2, entry 11)



FT-IR (Yellow oil, neat, cm^{-1}): 3510, 2924, 1604, 1560, 1488, 1380. **CHN:** Anal. Calcd. for $C_8H_8NO_3Cl$: C 47.76, H 3.98, N 6.97. Found C 47.80, H 4.00, N 7.01. **GC-MS:** *(m/z, rel. intensity, %):* 203(M^++2), 201(M^+), 157, 155, 141(100), 143, 124, 113, 111, 77. **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm) 7.36 (d, *J*=8.5Hz, 2H), 7.32 (d, *J*=8.5Hz, 2H), 5.46-5.36 (m, 1H), 4.57-4.49 (m, 1H), 4.46-4.42 (m,1H), 3.16

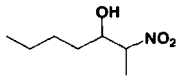
(brs, 1H).

1-(4-methylphenyl) - 2-nitropropan-1-ol: (Table 3A.2, entry 12)



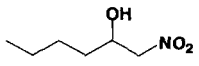
FT-IR (Pale yellow oil, neat, cm^{-1}): 3460, 2915, 1682, 1552, 1459, 1376. **CHN:** Anal. Calcd. for $C_{10}H_{13}NO_3$: C, 61.53; H, 6.71; N, 7.18 Found: C, 61.47; H, 6.63; N, 7.15. **GC-MS:** *(m/z, rel. intensity, %):* 195 (M^+), 177, 120, 119 (100), 91, 76. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm)*:* 7.29 -7.18 (m, 4H), 5.32-5.0 (m, 1H), 4.80-4.72 (m, 1H), 2.78 (brs, 1H) , 2.38 (s, 3H), 1.49 (d, *J*= 6.8Hz, 3H), 1.35 (d, *J*= 6.8Hz, 3H).

2-Nitro-heptane-3-ol: (Table 3A.2, entry 13)



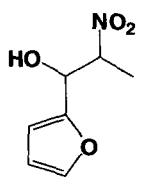
FT-IR (Viscous Liquid, neat, cm^{-1}): 3455, 2945, 1537, 1458. **CHN:** Anal. Calcd. for $C_7H_{15}NO_3$: C, 52.18; H, 9.3; N, 8.69 found: C, 52; H, 9.5; N, 8.72. **GC-MS:** *(m/z, rel. intensity, %):* 161(M^+), 104, 97, 57, 55 (100). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm): 4.82-4.60 (m, 1H), 4.0-3.87 (m, 1H), 1.62 (m, 7H), 1.06-0.98 (m, 6H).

1-Nitrohexan-2-ol: (Table 3A.2, entry 14)



FT-IR (Viscous Liquid, neat, cm^{-1}): 3417, 2949, 2860, 1553, 1470, 1422, 1381. **CHN:** Anal. Calcd. for $C_6H_{13}NO_3$: C, 48.9; H, 8.84; N, 9.52 Found: C, 48.87; H, 8.52; N, 9.45. **GC-MS:** *(m/z, rel. intensity, %):* 147(M^+), 129, 90, 83, 57, 55(100). **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm): 4.44 (dd, 1H, *J* = 13.2, 2.9 Hz), 4.37 (dd, 1H, *J* = 13.2, 8.6 Hz), 4.34-4.25 (m, 1H), 2.78 (brs, 1H), 1.59-1.28 (m, 6H), 0.88 (t, *J* = 6.4 Hz , 3H).

1-(2-Furyl)-2-nitropropan-l-ol: (Table 3A.2, entry 15)



FT-IR (Viscous Liquid, neat, cm^{-1}): 3512, 1535, 1345, 1201, 1011. **CHN:** Anal. Calcd. for $C_7H_9NO_4$: C, 49.12; H, 5.26; N, 8.19 Found: C, 49.15; H, 5.30; N, 8.21. **GC-MS:** *(m/z, rel. intensity, %):* 171 (M^+), 153, 124, 108, 97 (100), 83. **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm): 7.46-7.43 (m,1H), 6.44 (m, 2H), 5.2-4.8 (m, 2H), 2.8 (m, 1H), 1.67 (d, *J*= 6.7Hz,

3H), 1.42 (d, J= 6.8 Hz, 3H)

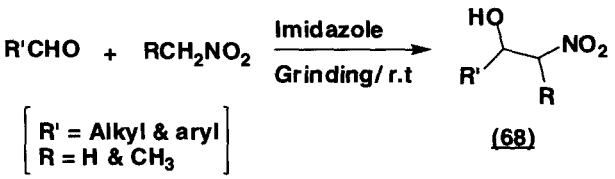
Section 3B

A new and simple approach toward synthesis of β- nitroaldols using solventless grinding method

3B.1 Objective

High catalytic activity of imidazole found in case of using aqueous reaction medium prompts us to investigate its efficacy for Henry reaction in solventless grinding method. As no report on synthesizing nitroaldol product employing this technique is available in literature, our focus was drawn mainly towards this area.

3B.2 Results and discussion



Scheme 3B.1: Imidazole catalyzed Henry reaction under solventless grinding condition

In order to generalize the reaction procedure, two test experiments (*Table 3B.1, entry 1-2*) were conducted by grinding together different molar ratios of (1: 5: 0.25 and 1:5: 0.35 respectively) benzaldehyde, nitromethane and imidazole as mild Lewis base catalyst. We found that the reaction shows the best result (*Table 3B.1, entry 2*) with molar ratio 1:5: 0.35 of benzaldehyde, nitromethane and imidazole. With 0.25 mmol of imidazole, it yielded only 60% of 2-nitroalkanol within 5 min (*Table 3B.1, entry 1*) as monitored by TLC. Interestingly, unlike Henry reaction in aqueous medium, 0.25mmol of imidazole failed to complete most of the reaction of aromatic aldehyde within short period. Most probably, in solid state this amount of

catalyst is not sufficient to catalyze the Henry reaction. Similarly, on reducing the amount of nitromethane to 3 mmol with 0.35 mmol of catalyst, it resulted in incompleteness of reaction (*Table 3B.1, entry 3*).

After exploring the effective amount of catalyst and nitroalkane, the extent and feasibility of the imidazole catalyzed Henry reaction of nitroalkane with various aldehydes (*Table 3B.1*) in solventless grinding with molar ratio 1:5:0.35 of aldehyde, nitroalkane and imidazole was carried out. Under this novel condition, the reaction time was significantly shortened from hours of the classical method to minutes (*Table 3B.1, entry 2*) with improved yields (94%). Further investigations on the electronic effects of the substituted groups on the benzene ring of the aromatic aldehydes were done. For aryl aldehydes bearing electron-withdrawing groups, the reaction took place smoothly to afford the desired nitroaldol products in good to excellent yields within short interval of time (*Table 3B.1, entries 5-11*). However, for aryl aldehyde bearing electron-donating groups such as p-tolualdehyde, anisaldehyde (*Table 3B.1, entries 12-19*) the reactions were slow *(Figure 3B.1).* Change in reaction rate is also influenced by the chain length of nitroalkane. With increasing chain length of nitroalkane, the reaction showed longer reaction time (*Table 3B.1, entries 4, 7,9,11, 17, and 19*). For aliphatic aldehyde *(Table 3B.1, entry 22)* the results are satisfactory on increasing the amount of catalyst from 0.35 mmol to 0.5 mmol of imidazole. In a similar way, anisaldehyde showed 40-45 % conversion with 0.5mmol of catalyst (*Table 3B.1, entries 16, 17)* as compared to 15% (*Table 3B.1, entry 15*) conversion with 0.35 mmol of catalyst in 3 hours.

Table 3B.1: Henry reaction under solvent free grinding at room temperature using mortar and pestle

Entry	R'	Nitroalkane	Time (minute)	Nitroaldol (**68**) Yield (%)[a]
1	C_6H_5	CH_3NO_2	5	60[b]
2	C_6H_5	CH_3NO_2	5	94
3	C_6H_5	CH_3NO_2	5	50[c]
4	C_6H_5	$CH_3CH_2NO_2$	20	95
5	4-$NO_2C_6H_4$	CH_3NO_2	70	75
6	4-$NO_2C_6H_4$	CH_3NO_2	15	95[d]

7	4-$NO_2C_6H_4$	$CH_3CH_2NO_2$	90	70
8	2-$NO_2C_6H_4$	CH_3NO_2	10	90
9	2-$NO_2C_6H_4$	$CH_3CH_2NO_2$	20	95
10	3-$NO_2C_6H_4$	CH_3NO_2	10	84
11	3-$NO_2C_6H_4$	$CH_3CH_2NO_2$	25	85
12	4-MeC_6H_4	CH_3NO_2	60	95
13	2-OHC_6H_4	CH_3NO_2	60	87
14	2-OHC_6H_4	$CH_3CH_2NO_2$	120	60
15	4-$OMeC_6H_4$	CH_3NO_2	180	15
16	4-$OMeC_6H_4$	CH_3NO_2	180	45[d]
17	4-$OMeC_6H_4$	$CH_3CH_2NO_2$	210	40[d]
18	4-ClC_6H_4	CH_3NO_2	36	97
19	4-ClC_6H_4	$CH_3CH_2NO_2$	180	98
20	Furyl	CH_3NO_2	20	55
21	Furyl	$CH_3CH_2NO_2$	60	45
22	Pentanal	CH_3NO_2	90	90[d]
23	Pentanal	CH_3NO_2	45	60
24	Pentanal	$CH_3CH_2NO_2$	90	92[d]

[a]*Isolated yields. All products were characterized by FT-IR, CHN analyzer, ^1H NMR and also their comparison with authentic sample.* [b]*Molar ratio 1:5:0.25 of aldehyde/nitroalkane/catalyst.* [c]*Molar ratio 1:3:0.35 of aldehyde/nitroalkane/catalyst.* [d] *Molar ratio 1:5:0.5 of aldehyde/nitroalkane/catalyst.*

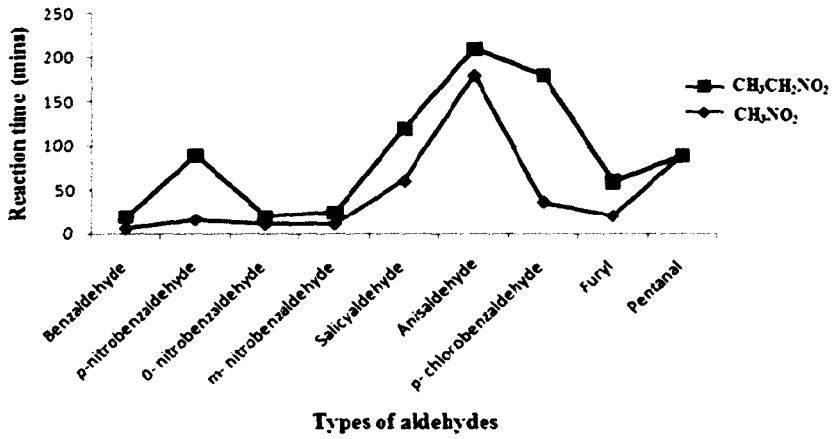
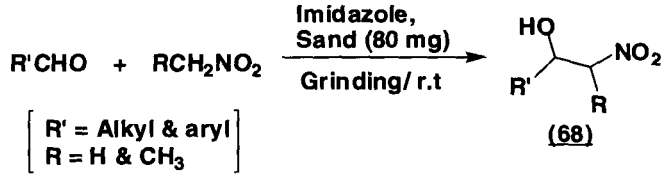


Figure 3B.1: Graphical representation of electronic effect of aldehydes and nitroalkanes on reaction rate for Henry reaction



Scheme 3B.2: Imidazole catalyzed Henry reaction under solventless grinding condition in presence of sand

In grinding method, friction is the driving force for the reaction. Thus, we next observed the change in rate of conversion on enhancing friction in the reaction mixture by adding non reacting frictional material sand *(Scheme 3B.2).*

Table 3B.2: Henry reaction in presence of sand under solvent free grinding at room temperature using mortar and pestle.

Entry	R'	Nitroalkane	Time (mins)	Nitroaldol (**68**) Yield (%) [a]
1	C_6H_5	$CH_3CH_2NO_2$	15	95
2	4-$NO_2C_6H_4$	$CH_3CH_2NO_2$	25	90
3	2-$NO_2C_6H_4$	$CH_3CH_2NO_2$	12	95
4	3-$NO_2C_6H_4$	$CH_3CH_2NO_2$	20	85
5	2-OHC_6H_4	$CH_3CH_2NO_2$	35	65
6	4-$OMeC_6H_4$	$CH_3CH_2NO_2$	120	42
7	Furyl	$CH_3CH_2NO_2$	45	62
8	Pentanal	$CH_3CH_2NO_2$	75	94
9	4-Me C_6H_4	CH_3NO_2	15	95
0	2-OHC_6H_4	CH_3NO_2	25	88
11	4-$OMeC_6H_4$	CH_3NO_2	90	60
12	Furyl	CH_3NO_2	13	50
13	Pentanal	CH_3NO_2	45	95

[a]*The reactions were carried out in 1mmol scale with molar ratio 1:5:0.35 of aldehyde/ nitroalkane/ catalyst in presence of 80 mg of sand.*

Addition of sand as a friction-enhancing solid has accelerated the rate of Henry reaction tremendously (*Table 3B.2*) for solid/liquid and liquid/liquid reagent pairs with 0.35 mmol of imidazole as catalyst. It was found that for pentanal, in presence of sand the yield of 2-nitroalkanol increases from 60% *(Table 3B.1, entry 23)* to 95% (*Table 3B.2, entry 13*) within 45 min using 0.35 mmol of catalyst. Similarly, the reaction of furaldehyde (*Table 3B.2, entry 12*) with nitromethane was also fast resulting in 50% of the corresponding nitroalcohol after 13 min. The role of the imidazole catalyst in this protocol also appears to be that of a base which deprotonates the nitromethane, facilitating the nitroaldol reaction. In both the reaction conditions discussed above, stereoisomeric mixtures of nitroaldols are formed which is evident from their ^{1}H NMR data.

3B.3 Conclusion

In this work we have developed the first solventless grinding method for the Henry reaction without formation of any side product using imidazole as a catalyst. The protocol is efficient not only in terms of product yield, selectivity and reaction time but also in terms of energy consumption.

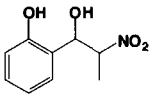
3B.4 Experimental section

General methods of synthesis of 2- nitroaldols under solventless grinding method using imidazole as catalyst both in absence and in presence of sand have been explained in section 2.2.1(B) and 2.2.1(C) respectively.

3B.5 Spectral elucidation

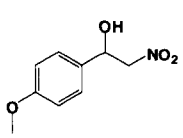
Spectral data of all compounds are similar to those mentioned in section 3A.5 except the following compounds:

1-(2-Hydroxyphenyl)-2-nitropropan-1-ol: (Table 3B.1, entry 14)



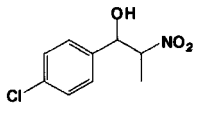
FT-IR (Viscous Liquid, neat, cm^{-1}): 3659, 3328, 1668, 1552, 1456, 1388. **CHN:** Anal. Calcd. For $C_9H_{11}N0_4$ (MW 197.19): C, 54.82; H, 5.61; N, 7.1 Found C, 54.66 H; 5.5; N, 7.0. **GC-MS:** *(m/z, rel. intensity, %):* 197 (M^+), 179, 133, 132, 123, 121(100), 105, 93, 77. **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm): 9.65 (s, 1H), 7.52-6.85 (m, 4H), 5.20-4.88 (m, 1H), 4.50-4.45 (m, 1H), 3.88 (brs, 1H), 1.37 (d, *J*= 7.2Hz, 3H).

1-(4-Methoxyphenyl)-2-nitroethanol: (Table 3B.1, entry 16)



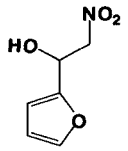
FT-IR (Viscous Liquid, neat, cm^{-1}): 3436, 2920, 1552, 1383. **CHN:** Anal. Calcd. for $C_9H_{11}NO_4$ (MW 197.19): C, 54.82; H, 5.58; N, 7.11 Found: C, 54.77; H, 5.51; N, 7.13. **GC-MS:** *(m/z, rel. intensity, %):* 197(M+), 193, 150, 137(100), 110. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm): 7.35-7.18 (m, 2H), 6.88-6.96 (m, 2H), 5.55 (m, 1H), 4.73 (dd, *J* = 13.5Hz, 3.2 Hz, 1H), 4.54 (dd, *J* = 13.3 Hz, 8.0 Hz, 1H), 4.90 (brs, 1H), 3.88 (s, 3H).

1-(4-chlorophenyl)-2- nitropropan-1-ol: (Table 3B.1, entry 19)



FT-IR (Viscous Liquid, neat, cm^{-1}): 3518, 2998, 2921, 1554, 1385, 1095. **CHN:** Anal. Calcd. for $C_9H_{10}NO_3Cl$ (MW 215.63): C, 50.12; H, 4.67; N, 6.50 Found C, 50.05 H; 4.60; N, 6.45. **GC-MS:** *(m/z, rel. intensity, %):* 217, 215 (M^+), 140, 139 (100), 111, 76. **^{1}H NMR** (300 MHz, $CDCl_3$): δ (ppm): 7.32-7.25 (m, 4H), 5.32-4.95 (m, 1H), 4.65-4.60 (m, 1H), 2.98 (brs, 1H), 1.45 (d, *J*= 6.7Hz, 3H), 1.25 (d, *J*= 6.8Hz, 3H).

1-(Furan-2-yl)-2-nitroethan-1-ol: (Table 3B.1, entry 20)



FT-IR (Viscous Liquid, neat, cm^{-1}): *):* 3460, 1556, 1503. **CHN:** Anal. Calcd. for $C_6H_7NO_4$ (MW 157.12): C, 45.86; H, 4.46; N, 8.92 Found C, 45.83; H; 4.40; N, 8.88. **GC-MS:** *(m/z, rel. intensity, %):* 157(M^+), 139, 153, 110, 97(100), 83, 81. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm): 7.47-7.42 (m, 1H), 6.55-6.37 (m, 2H), 5.48-5.42 (m, 1H), 4.85- 4.74 (m, 1H), 4.72- 4.64 (m, 1H), 2.83 (brs, 1H).

Chapter 4

Development of synthetic strategies for Biginelli (or like) reaction using solventless techniques

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Published with small modifications from:

Phukan M., Chaliha P., Borah K.; Thakur A. J., Borah R.; "*Microwave accelerated green synthesis of dihydropyrimidinones*". ***Organic Chemistry, An Indian Journal*** (India), Volume 4, Issue1, 2008, 50-43. Publisher: (Trade Science Inc.)

Phukan M., Kalita M. K., Borah R.; "*A new protocol for Biginelli (or like) reaction under solvent-free grinding method using Fe $(NO_3)_3.9H_2O$ as catalyst*". ***Green Chemistry Letters and Reviews*** (In Press, 2010)

Section 4A

A new protocol for Biginelli (or like) reaction under solvent-free grinding method using $Fe(NO_3)_3.9H_2O$ as catalyst

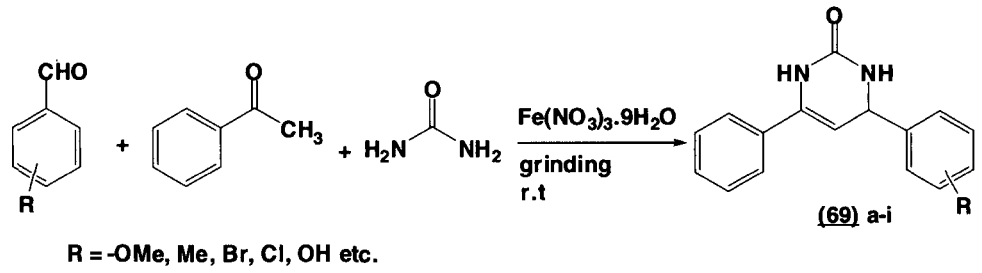
4A.1 Objective

While Biginelli reaction is a versatile multicomponent reaction (MCR) which leads to the formation of 5- substituted dihydropyrimidinone, its extensive form is Biginelli like reaction involve in synthesis of 5- unsubstituted dihydropyrimidininones (DHPMs). Due to significant pharmacological activity of DHPMs and being a multicomponent reaction, Biginelli reaction is still considered as a growing interest of research even after 117 years of its discovery. However, Biginelli like reaction is in nascent stage and more research impetus is waiting. Of the various catalysts explored so far for Biginelli reaction, our attention was drawn to oxidizing agents. Oxidizing agents like Lewis acids are electron acceptor. The basic difference between them is that oxidant involves complete transfer of one or several electron facilitating redox reactions while Lewis acid involves partial transfer of a pair of electron leading to formation of covalent bond via Lewis acid-base reaction. Thus, oxidizing agents provide high probability of fulfilling the requirement of acid catalyst for Biginelli reaction. We found ferric nitrate nonahydrate to successfully serve our purpose. Moreover, growing importance of grindstone chemistry as a new greener technology prompt us to design synthetic routes for Biginelli (or like) reactions with this technique.

4A.2 Results and discussion

We first started to investigate the reaction (*Scheme 4A.1*) of anisaldehyde (1 mmol), acetophenone (1 mmol), and urea (1.5 mmol) in presence of different

catalysts (0.1 mmol) (*Table 4A.1*) under solvent-free grinding method and in presence of various solvents.



R = -OMe, Me, Br, Cl, OH etc.

*Scheme 4A.1: Synthesis of 5-unsubstituted 3,4-dihydropyrimidinones (**69**) using 0.1 mmol of $Fe(NO_3)_3.9H_2O$ under solventless grinding condition at room temperature*

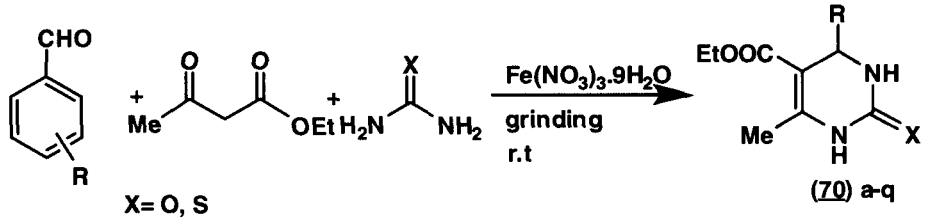
*Table 4A.1: Synthesis of 5-unsubstituted 3,4-dihydropyrimidinones (**69**) using 0.1 mmol of different catalysts*

Entry	Catalyst	Solvent	Time (hour)	Product (**69**) Yield [a] (%)
1	Borax	Nil	2	5
2	$BF_3.(OEt)_2$	"	1.5	10
3	H_3BO_3	"	2	NR
4	Sulfamic acid	"	1.5	10
5	Oxalic acid	"	1.5	8
6	NH_4Cl	"	1	NR
7	CAN	"	1	NR
8	$FeNO_3.9H_2O$	"	1.5	92
9	clayfen	"	3	80
10	$Mn(OAc)_2.4H_2O$	"	1.5	NR
11	P-TsOH	"	1.5	NR
12	Monmorillonite -KSF	"	1.5	NR
13	I_2	"	1.5	NR
14	$FeNO_3.9H_2O$	MeOH	12	90
15	"	Acetone	12	75
16	"	CH_2Cl_2	12	NR
17	"	$CHCl_3$	12	NR
18	"	H_2O	12	NR

[a] *All solvent-free reactions were carried out under grinding method;* NR*: No Reaction*

From these results, it was observed that except hydrated ferric nitrate and clayfen, all others catalysts were found to be inactive for this reaction. The hydrated ferric nitrate took less reaction time (*Table 4A.1, entry 8*) as

compared (*Table 4A.1, entry 9*) to supported catalyst (clayfen). Furthermore, the catalyst ferric nitrate retained its activity in methanol and acetone as reaction medium (*Table 4A.1, entries 14, 15*). The above optimized condition of Biginelli-like reaction of acetophenone under solvent-free method, extended to other aromatic aldehydes with different substituents and the results are summarized in (*Table 4A.2, entries 1-9*). All aromatic aldehydes containing different substituent reacted efficiently to form the corresponding 5-unsubstituted 3,4-dihydropyrimidinones (**69**) derivatives. Finally, we applied this method for the synthesis of 5-substituted 3, 4-dihydropyrimidone derivatives (**70**) using acetoacetic ester (*Scheme 4A.2*) as carbonyl compound (*Table 4A.2*) with different aldehydes and urea (or thiourea).



Scheme 4A.2: Synthesis of 5-substituted 3, 4- dihydropyrimidinones (70) using 0.1 mmol of Fe $(NO_3)_3.9H_2O$ under solventless grinding condition at room temperature

In our overall study on the different types of experimentations to come up with a simple and environmentally benign reaction system, we explored efficacy of ferric nitrate in synthesizing more importantly 5-unsubstituted 3,4-dihydropyrimidinones (**69**) employing green method.

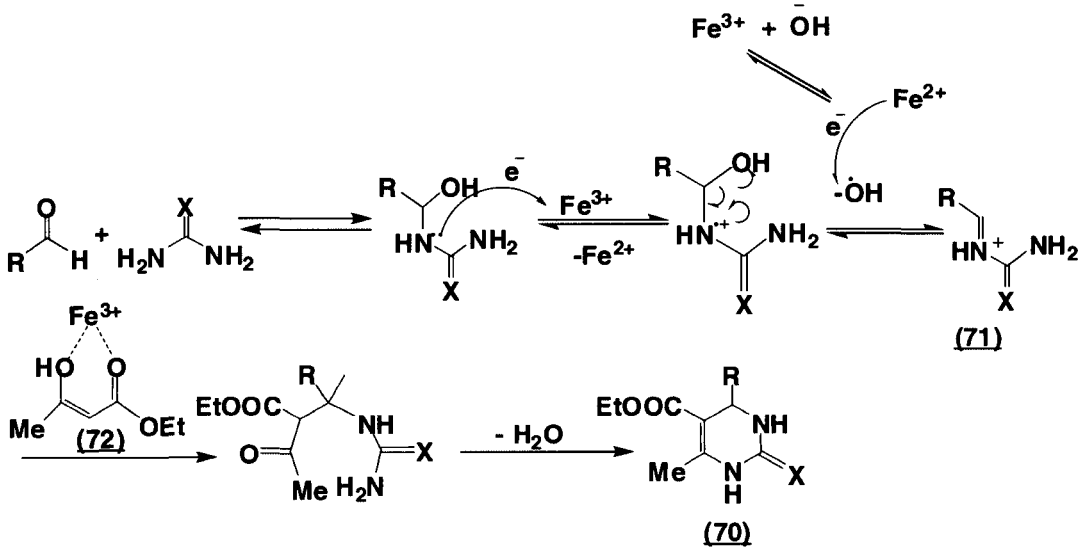
*Table 4A.2: Synthesis of 5-unsubstituted 3, 4- dihydropyrimidinones (**69a-i**) and 5-substituted 3, 4-dihydropyrimidinone derivatives (**70a-q**)*

Entry	R	Product code[a]	X	Yield[b] (%)	Time (min)	M.P (°C)	
						Found	Reported[c]
1	C_6H_5	(**69a**)	O	90	35	244	245-246
2	4-ClC_6H_4	(**69b**)	O	95	75	266	267-269
3	4-$MeOC_6H_4$	(**69c**)	O	92	1.5 h	258	259-261
4	2-ClC_6H_4	(**69d**)	O	85	25	261-62	260-263
5	3- Br C_6H_4	(**69e**)	O	80	40	257-58	256-58
6	4-OHC_6H_4	(**69f**)	O	90	25	256	255–257
7	3-$MeOC_6H_4$	(**69g**)	O	92	55	256	257–258
8	4-MeC_6H_4	(**69h**)	O	88	45	249	248-250

9	3,4-$(OMe)_2$ C_6H_3	**(69i)**	O	93	60	244	243-245
10	C_6H_5	**(70a)**	O	95	1h	202-203	202-204
11	4-$NO_2C_6H_4$	**(70b)**	O	89	2h	206-208	208-209
12	2-$NO_2C_6H_4$	**(70c)**	O	90	1.5 h	220	218-220
13	3-$NO_2C_6H_4$	**(70d)**	O	93	75	226-227	226-227
14	4-ClC_6H_4	**(70e)**	O	83	45	211-212	213-215
15	4-$MeOC_6H_4$	**(70f)**	O	98	55	201-202	201-203
16	4-MeC_6H_4	**(70g)**	O	90	1h	169-170	168-170
17	C_6H_5 CH=CH	**(70h)**	O	94	75	242-243	241-242
18	$CH_3(CH_2)_3$	**(70i)**	O	65	1h	156-157	157-158
19	$CH_3(CH_2)_2$	**(70j)**	O	70	2h	153-155	152-154
20	Furyl	**(70k)**	O	75	45	202-203	204.5-205
21	C_6H_5	**(70l)**	S	87	30	200-205	205-206
22	4-$MeOC_6H_4$	**(70m)**	S	83	45	150	152-154
23	3-$NO_2C_6H_4$	**(70n)**	S	80	80	204-206	206-207
24	4-$NO_2C_6H_4$	**(70o)**	S	85	2	108-110	109-111
25	4-ClC_6H_4	**(70p)**	S	81	75	191-192	192-193
[a] 26	3,4,5-$(OMe)_3C_6H_4$	**(70q)**	S	80	1.5	203-205	202-204

[A]*ll products were characterized by FT-IR, ^{1}HNMR, CHN analyzer and also their melting points with that of previous literature; [b]Isolated yield; [c] Matches with reported data. Ref. 77a, 99, 100, 104, 78d, 89b, 90-93.*

The good performance of hydrated iron (III) nitrate as catalyst may be ascribed to its easy electron accepting property as a strong oxidant which catalyzes the formation of iminium intermediate **(71)** in the slowest step as well as activating β ketoester **(72)** in the process of Biginelli reaction based on the proposed mechanism by Kappe[86c] shown in *Scheme 4A.3*.



Scheme 4A.3: *Plausible mechanism for 3-component Biginelli (or Biginelli like) reaction*

However, problem regarding the regeneration of the catalyst is a hindrance in assigning it as green catalyst. This problem can also be solved by using clay supported ferric nitrate (clayfen) as catalyst. Although, the catalytic activity of clayfen is less than ferric nitrate, it can be easily regenerated by altering the aqueous work up with hot ethanol solvent. The insoluble clayfen residue washed several times with hot ethanol and dried in a vacuum desiccator. The regenerated clayfen can be reused three times without appreciable loss of catalytic activity (*Table 4A.3*). The progress of these solid state reactions was further monitored by recording IR spectrum of the reaction mixture (*Scheme 4A.1*) of acetophenone, anisaldehyde and urea at various time intervals (*Figure 4A.1*) using clayfen as catalyst where gradual change of N-H and C=O stretching frequencies represents the completion of reaction into Biginelli product. The IR spectra of regenerated clayfen shows similar absorptions peak with clayfen catalyst (*Figure 4A.2*).

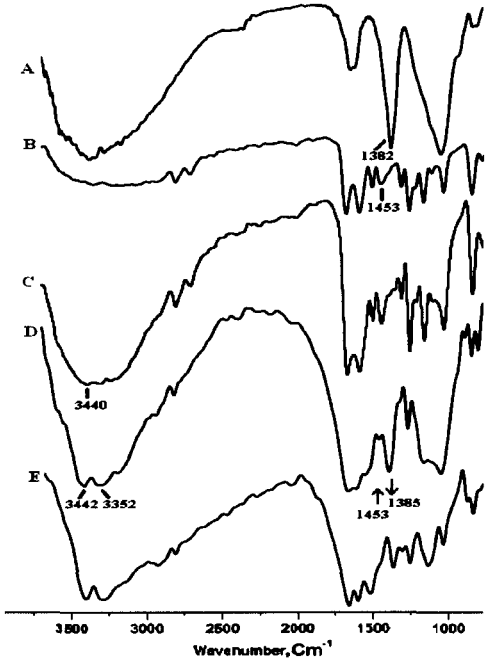


Figure 4A.1: FT-IR spectra of clayfen (A), reaction mixture after 60 min (B)120 min (C), 3 hr (D)& pure product (E)

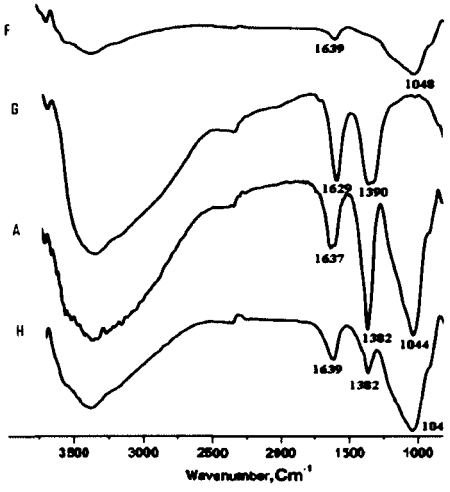


Figure 4A.2: FT-IR spectra of Monmorillonite K -10 (F), Fe $(NO_3)_3.9H_2O$ (G), clayfen (A)& regenerated clayfen (H)

Table 4A.3: Recycling of clayfen catalyst for Biginelli like reaction of acetophenone, anisaldehyde and urea under solvent-free grinding method

Entry	R	X	Yield[a] (%)	Time (hour)
1	4-$MeOC_6H_4$	O	80	3
2	4-$MeOC_6H_4$	O	76	3
3	4-$MeOC_6H_4$	O	75	3

[a] *Isolated yield*

Moreover, as the reaction progresses, the reaction mixture transform into liquid phase melt (viscous paste) which eventually solidifies on reaction completion. This change in the phase of the reaction mixture is clearly visible in the photographs of the reaction mixture (Figure 4A.3), taken in different interval of reaction progress. For this purpose we selected the model reaction of *p*-nitrobenzaldehyde (1mmol), ethylacetoacetate (1mmol), and urea (1.5 mmol) in presence of catalyst $FeNO_3.9H_2O$ (0.1 mmol).

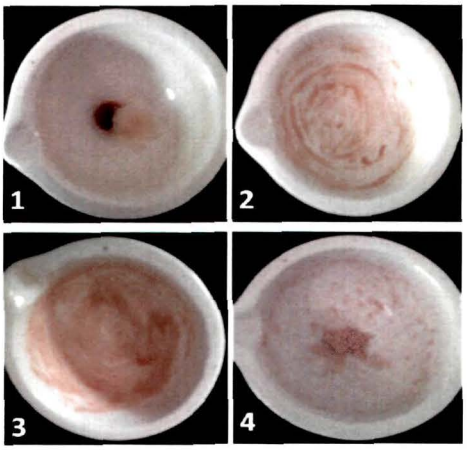


Figure 4A.3: Photographs showing the change in phase of reaction mixture at different interval of time; (1) taken at the initiation of reaction, (2) after 1 hr of grinding, (3) after 1.5 hr of grinding and (4) on reaction completion.

4A.3 Conclusion

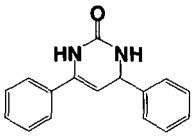
We have developed a general and efficient greener path for the synthesis of 5-unsubstituted 3,4-dihydropyrimidinones (**69**) and 5-substituted-3,4-dihydropyrimidinones (**70**) under solvent-free grinding condition using hydrated ferric nitrate/clayfen as catalyst. The advantage of this novel protocol lies in the avoidance of organic solvent, high yield, energy efficiency, variation of substrates and cheaper catalyst. Moreover hydrated ferric nitrate is used in very small amount and is made reusable on transforming into supported catalyst clayfen.

4A.4 Experimental section

General method for the synthesis of 5-unsubstituted 3, 4-dihydropyrimidinones (**69**) and 5-substituted- 3, 4- dihydropyrimidinones (**70**) under solvent-free grinding condition using hydrated ferric nitrate/clayfen as catalyst have been described in section 2.2.1 (D) of chapter 2. The method for the preparation of supported catalyst clayfen has also been mentioned in the same section (I).

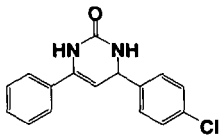
4A.5 Spectral elucidation

3,4-Dihydro-4,6-diphenylpyrimidin-2(1H)-one: *(Table 4A.2, entry 1)*



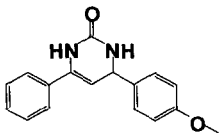
M.P: 244 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3220, 2915, 1671, 1600, 1456. **CHN:** Anal. Calcd. for $C_{16}H_{14}N_2O$: C 76.78, H 5.64, N 11.19; found C 76.50, H 5.58, N 11.14. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 8.55 (s, 1H), 7.53–7.26 (m, 10H), 5.20 (d, *J*=3.6 Hz, 1H), 5.10 (d, *J*=3.6 Hz, 1H), 3.40 (brs, 1H).

4-(4-Chlorophenyl)-3,4-dihydro-6-phenylpyrimidin-2(1H)-one: *(Table 4A.2, entry 2)*



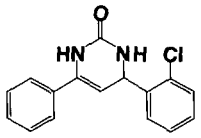
M.P: 266 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3230, 2934, 1682, 1575, 1467. **CHN:** Anal. Calcd. for $C_{16}H_{13}ClN_2O$: C 67.48, H 4. 56, N, 9.84; found C 66.75, H 4.55, N 10.00. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 8.67(s, 1H), 8.10 (s, 1H), 7.52-7.30 (m, 9H), 5.46 (d, *J*= 2.8 Hz, 1H), 5.16 (d, *J*= 2.8Hz, 1H).

3,4-Dihydro-4-(4-methoxyphenyl)-6-phenylpyrimidin-2(1H)-one: *(Table 4A.2, entry 3)*



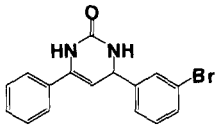
M.P: 258 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3384, 2935, 1615, 1520, 1410. **CHN:** Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C 72.85, H 5.71, N, 10.00 ; found C 72.60, H 5.73, N 10.10. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 12.00 (s, 1H), 9.30(s, 1H), 8.35-7.28 (m, 9H), 6.94 (d, *J*= 8.7 Hz, 1H), 5.42 (d, *J*= 8.7Hz, 1H), 3.76 (s, 3H).

4-(2-Chlorophenyl)-3,4-dihydro-6-phenylpyrimidin-2(1H)-one: *(Table 4A.2, entry 4)*



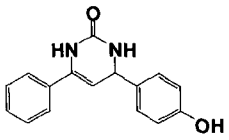
M.P: 261-262 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3287, 2940, 1652, 1587, 1418. **CHN:** Anal. Calcd. for $C_{16}H_{12}ClN_2O$: C 60.21, H 3.79, N 8.78; found C 60.28, H 3.75, N 9.00. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 8.60 (s, 1H), 8.15 (s, 1H), 7.42–7.15 (m, 9H), 5.45 (d, *J*=4.4 Hz, 1H), 5.12 (d, *J*=2.8 Hz, 1H).

4-(3-Bromophenyl)-3,4-dihydro-6-phenylpyrimidin-2(1H)-one: *(Table 4A.2, entry 5)*



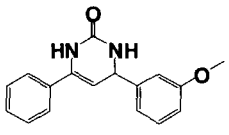
M.P: 257-258 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3130, 2929, 1683, 1575, 1400. **CHN:** Anal. Calcd. for $C_{16}H_{13}BrN_2O$: C 58.38, H 3.98, N 8.51; found C 58.30, H 4.00, N 8.47. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.18 (s, 1H), 8.30–7.29 (m, 9H), 7.11 (s, 1H), 5.54 (d, *J*=5.5 Hz, 1H), 5.15 (d, *J*=5.5 Hz, 1H).

3,4-Dihydro-4-(4-hydroxyphenyl)-6-phenylpyrimidin-2(1H)-one: *(Table 4A.2, entry 6)*



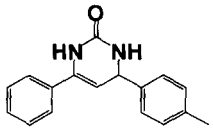
M.P: 256 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3387, 2920, 1628, 1517, 1448. **CHN:** Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C 72.17, H 5.26, N, 10.50; found C 72.30, H 5.33, N 10.40. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.22 (s, 1H), 8.16-7.54 (m, 9H), 7.36-7.32 (s, 1H), 7.25 (d, *J*= 8.8 Hz, 1H), 5.52 (s, 1H) 5.12 (d, *J*= 8.8Hz, 1H).

3,4-Dihydro-4-(3-methoxyphenyl)-6-phenylpyrimidin-2(1H)-one: *(Table 4A.2, entry 7)*



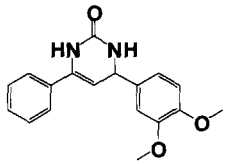
M.P: 256 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3202, 2929, 1677, 1599, 1406. **CHN:** Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C 72.84, H 5.75, N 9.99; found C 72.15, H 5.71, N 10.00. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 8.53 (s, 1H), 7.56–6.84 (m, 9H), 5.16 (d, *J*=4.3 Hz, 1H), 5.08 (d, *J*=4.3 Hz, 1H), 3.44 (brs, 1H).

3,4-Dihydro- 4-(4-methylphenyl)-6-phenylpyrimidin-2(1H)-one: *(Table 4A.2, entry 8)*



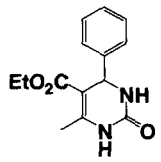
M.P: 249 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3233, 2917, 1645, 1579, 1400. **CHN:** Anal. Calcd. for $C_{17}H_{16}N_2O$: C 77.25, H 6.10, N 10.60; found C 77.28, H 6.01, and N 10.64. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.22 (s, 1H), 8.45 (s, 1H), 7.82– 5.58 (m, 9H), 5.54 (d, *J*=6.7 Hz, 1H), 5.30 (d, *J*=6.8 Hz, 1H), 2.40 (s, 3H).

3,4-Dihydro-4-(3,4-dimethoxyphenyl)-6-phenylpyrimidin-2(1H)-one: *(Table 4A.2, entry 9)*



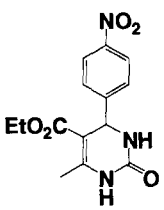
M.P: 244 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3277, 2930, 1617, 1515, 1462. **CHN:** Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C 69.67, H 5.85, N, 9.03 ; found C 69.60, H 5.78, N 9.00 %. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 11.92 (s, 1H), 8.55 (s, 1H), 8.52-7.50 (m, 8H), 7.45 (d, *J*= 8.3 Hz, 1H), 7.08 (d, *J*= 8.3Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H).

5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one: *(Table 4A.2, entry 10)*



M.P: 202-203 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3226, 3099, 2971, 2931, 1718, 1700, 1657, 1601. **CHN:** Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.61; H, 6.15; N, 10.76; found: C, 64.56; H, 6.20; N, 10.72. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.20 (s, 1H), 7.73 (d, *J* =2.5 Hz, 1H), 7.31 (m, 5H), 5.13 (d, *J* =3.2 Hz, 1H), 3.97 (q, *J* = 7.2 Hz, 2H), 2.22(s, 3H), 1.07 (t, *J* =7.2 Hz, 3H).

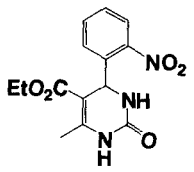
5-Ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one: *(Table 4A.2, entry 11)*



M.P: 206-208 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3398, 3101, 2973, 1700, 1649, 1588, 1520, 1380. **CHN:** Anal. Calcd. for $C_{14}H_{15}O_5N_3$: C, 55.08, H4.91, N, 13.77; found: C, 55.03; H, 4.94; N, 13.80. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.33 (s, 1H), 8.21 (d, *J* =8.7 Hz, 2H), 7.87 (d, *J* =2.46 Hz, 1H), 7.45 (d, *J* =8.7 Hz, 2H), 5.24 (s, 1H),

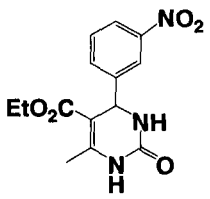
3.95 (q, *J* =7.2 Hz, 2H), 2.23 (s, 3H), 1.6 (t, *J* = 7.1 Hz, 3H).

5-Ethoxycarbonyl-6-methyl-4-(2-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one: *(Table 4A.2, entry 12)*



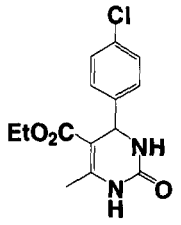
M.P: 220 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3380, 3100, 1710, 1648, 1556, 1517. **CHN:** Anal. Calcd. for $C_{14}H_{15}O_5N_3$: C, 55.08, H4.91, N, 13.77; found: C, 55.10; H, 4.94; N, 13.75. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.39 (s, 1H), 7.98– 7.49 (m, 5H), 5.81 (d, *J* = 3.0 Hz, 1H), 3.88 (q, *J* = 7.3 Hz, 2H), 2.30 (s, 3H), 0.94 (t, *J* = 7.3 Hz, 3H).

5-Ethoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one: *(Table 4A.2, entry 13)*



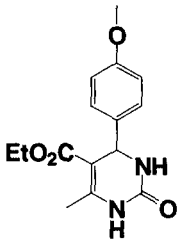
M.P: 226-227 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3402, 1728, 1610, 1518, 1345. **CHN:** Anal. Calcd. for $C_{14}H_{15}O_5N_3$: C, 55.08, H4.91, N, 13.77; found: C, 55.07; H, 4.96; N, 13.74. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.35 (s, 1H), 7.88 (s, 1H), 8.09-7.61 (m, 4H), 5.31 (s, 1H), 3.88 (q, *J*=6.9 Hz, 2H), 2.24 (s, 3H), 1.06 (t, *J*= 6.9Hz, 3H).

4-(4-Chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-one: *(Table 4A.2, entry 14)*



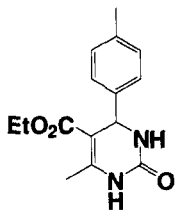
M.P: 211-212 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3331, 3087, 2970, 2931, 1700, 1641. **CHN:** Anal. Calcd. for $C_{14}H_{15}O_3N_2Cl$: C, 57.05, H 5.09, N 9.51; found: C, 57.01; H, 4.99; N, 9.47. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.22 (s, 1H), 7.76 (s, 1H), 7.36 (d, *J* =8.2 Hz, 2H), 7.22 (d, *J*= 8.2 Hz, 2H), 5.11 (s, 1H), 3.92 (q, *J* = 6.8 Hz, 2H), 2.23 (s, 3H), 1.10 (t, *J* =6.8 Hz, 3H).

5-Ethoxycarbonyl-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one: *(Table 4A.2, entry 15)*



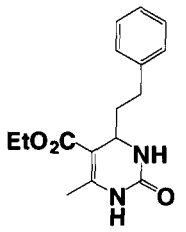
M.P: 201-202 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3349, 2918, 2829, 1705, 1734, 1611. **CHN:** Anal. Calcd. for $C_{15}H_{18}O_4N_2$: C 62.07, H 6.21, N 9.66; found: C, 62.00; H, 6.19; N, 9.64 %. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.11 (s, 1H), 7.64 (s, 1H), 7.12 (d, *J* =8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.07 (d, *J* =3.1 Hz, 1H), 3.95 (q, *J* =7.2 Hz, 2H), 3.70 (s, 3H), 2.21 (s, 3H), 1.09 (t, *J*= 7.2 Hz, 3H).

5-Ethoxycarbonyl-6-methyl-4-(4-methylphenyl)-3,4-dihydropyrimidin-2(1H)-one: *(Table 4A.2, entry 16)*



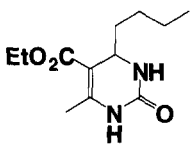
M.P: 169-170 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3162, 2920, 2830, 1686, 1631. **CHN:** Anal. Calcd. for $C_{15}H_{18}O_3N_2$: C, 65.69; H, 6.56; N, 10.21; found: C, 65.70; H, 6.58; N, 10.25. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.13 (s, 1H), 7.78 (s, 1H), 7.08 (s, 4H), 5.07 (s, 1H), 3.94 (q, *J*= 7.3Hz, 2H), 2.24(s, 3H), 2.22 (s, 3H), 1.08 (t, *J*= 7.3 Hz, 3H).

5-(Ethoxycarbonyl)-6-methyl-4-styryl-3,4-dihydropyrimidin-2(1H)-one: *(Table 4A.2, entry 17)*



M.P: 242-243 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3241, 1700, 1648. **CHN:** Anal. Calcd. for $C_{16}H_{18}O_3N_2$: C, 67.13; H, 6.29; N, 9.79; found: C, 67.18; H, 6.33; N, 9.77. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.12 (s, 1H), 7.51 (s, 1H), 7.44–7.22 (m, 5H), 6.35 (d, *J*= 15.7,1H), 6.22 (m, 1H), 4.72 (d, *J*= 5.7 Hz, 1H), 4.02 (q, *J*= 7.0 Hz, 2H), 2.18 (s, 3H), 1.16 (t, *J*= 7.0 Hz, 3H).

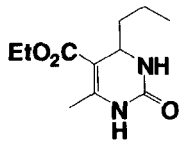
4-n-Butyl-5-(ethoxycarbonyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one: *(Table 4A.2, entry 18)*



M.P: 156-157 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3247, 1723, 1650. **CHN:** Anal. Calcd. for $C_{12}H_{20}O_3N_2$: C, 60; H, 8.33; N, 11.67; found: C, 59.97; H, 8.30; N, 11.62. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 8.90 (s, 1H), 7.28 (s, 1H), 4.64 (m, 1H), 4.03 (q, *J*= 6.5 Hz, 2H), 2.13 (s, 3H), 1.42–

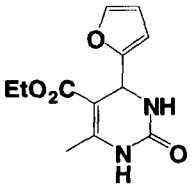
1.16 (m, 9H), 0.84 (t, *J*=7.2 Hz, 3H).

5-(Ethoxycarbonyl)-6-methyl-4-(n-propyl)-3,4-dihydropyrimidin-2(1H)-one: *(Table 4A.2, entry 19)*



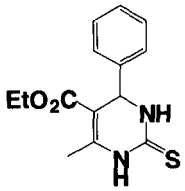
M.P: 153-155 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3246, 3116, 1723, 1650. **CHN:** Anal. Calcd. for $C_{11}H_{18}O_3N_2$: C, 58.41; H, 7.96; N, 12.39; found: C, 58.36; H, 7.92; N, 12.43. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 8.90 (s, 1H), 7.31 (s, 1H), 4.82 (m, 1H), 3.85 (q, *J*= 6.7, 2H), 2.26 (s, 3H), 1.50–1.39 (m, 4H), 1.25 (t, *J*= 6.7 Hz, 3H), 0.88 (t, *J*= 7.2 Hz, 3H).

5-Ethoxycarbonyl-4-(2-furyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-one: *(Table 4A.2, entry 20)*



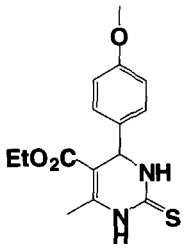
M.P: 202-203 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3317, 3223, 1692, 1635. **CHN:** Anal. Calcd. for $C_{12}H_{14}O_4N_2$: C, 57.60; H, 5.60; N, 11.20; found: C, 57.58; H, 5.62; N, 11.17. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.21 (s, 1H), 7.72 (s, 1H), 7.53 (s, 1H), 6.32 (s, 1H), 6.06 (s, 1H), 5.16 (s, 1H), 4.00 (q, *J*= 6.8Hz, 2H), 2.20 (s, 3H), 1.10 (t, *J*= 6.8 Hz, 3H).

5-(Ethoxycarbonyl)-6-methyl-4–phenyl-3,4-dihydropyrimidin-2(1H)-thione: *(Table 4A.2, entry 21)*



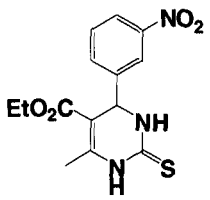
M.P: 200-205 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3409, 3225, 1705, 1631. **CHN:** Anal. Calcd. for $C_{14}H_{16}O_2N_2S$: C, 60.80; H, 5.79; N, 10.14; found: C, 60.84; H, 5.84; N, 10.17. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 10. 27 (s, 1H), 9.62 (s, 1H), 7.38-7.16 (m, 5H), 5.14 (d, *J*= 3.3 Hz, 1H), 3.96 (q, *J*= 6.8Hz, 2H), 2.26 (s, 3H), 1.12 (t, *J*= 6.8 Hz, 3H).

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: *(Table 4A.2, entry 22)*



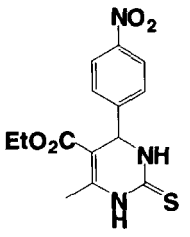
M.P: 150 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3252, 1655, 1600, 1557. **CHN:** Anal. Calcd. for $C_{15}H_{18}O_3N_2S$: C, 58.82; H, 5.9; N, 9.15; found: C, 58.77; H, 6.01; N, 9.11 %. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 10.25 (s, 1 H), 9.56 (s, 1 H), 7.15 (d, *J* =8.2 Hz, 2 H), 6.67 (d, *J* =8.2 Hz, 2 H), 5.15 (s, 1 H), 4.03 (q, *J* =6.9 Hz, 2 H), 3.72 (s, 3H) ,2.23 (s, 3 H), 1.15 (t, *J* = 6.9 Hz, 3 H).

5-(Ethoxycarbonyl)-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-thione: *(Table 4A.2, entry 23)*



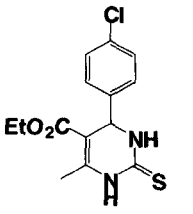
M.P: 204-206 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3245, 1725, 1632, 1575, 1545. **CHN:** Anal. Calcd. for $C_{14}H_{15}O_4N_3S$: C, 52.33; H, 4.67; N, 13.08; found: C, 52.38; H, 4.65; N, 13. 10. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 10.34 (s, 1H), 9.28 (s, 1H), 7.75-7.48 (m, 4H), 5.77 (d, *J* = 2.06, 1H), 4.00 (q, *J* = 7.0 Hz, 2H), 2.17 (s, 3H), 1.11 (t, *J* = 7.0 Hz, 3H).

5-(Ethoxycarbonyl)-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-thione: *(Table 4A.2, entry 24)*



M.P: 108-110 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3246, 1730, 1628, 1565, 1540. **CHN:** Anal. Calcd. for $C_{14}H_{15}O_4N_3S$: C, 52.33; H, 4.67; N, 13.08; found: C, 52.30; H, 4.62; N, 13. 14. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 10.36 (s, 1H), 9.56 (s, 1H), 8.22 (d, *J* =8.6 Hz, 2H), 7.40 (d, *J* =8.6 Hz, 2H), 5.21 (s, 1H,), 3.97 (q, *J* =7.0 Hz, 2H), 2.27 (s, 3H), 1.07 (t, *J* =7.0 Hz, 3H).

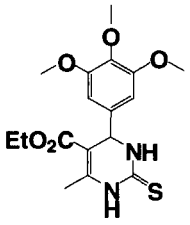
4-(4-chlorophenyl)-5-ethoxycarbonyl-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: *(Table 4A.2, entry 25)*



M.P: 191-192 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3257, 1660, 1558. **CHN:** Anal. Calcd. for $C_{14}H_{15}O_2N_2SCl$: C, 54.10; H, 4.83; N, 9.01; found: C, 54.15; H, 4.86; N, 9.00. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 10.32 (s, 1 H), 9.62 (s, 1H), 7.42 (d, *J* =8.1 Hz, 2H), 7.17 (d, *J*= 8.1 Hz, 2H), 5.14 (s, 1H), 4.02 (q, *J* =6.7 Hz, 2H), 2.35 (s, 3H), 1.06 (t,

J=6. 7 Hz, 3H).

5 - Ethoxycarbony - 6 - methyl - 4 - (3, 4, 5- trimethoxyphenyl)- 3, 4-dihydropyrimidin - 2(1H)-thione: *(Table 4A.2, entry 26)*



M.P: 203-205 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3288, 3155, 2921, 2845, 1659, 1580, 1565, 1419, 1327. **CHN:** Anal. Calcd. for $C_{17}H_{22}N_2O_5S$: C, 55.72; H, 6.05; N, 7.64; S, 8.75; found: C, 55.59; H, 5.95; N, 7.61; S, 8.70. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 10.18 (s, 1H), 9.36 (s, 1H), 7.27 (m, 2H), 5.01 (s, 1H), 6.35 (s, 2H), 3.88 (q, *J* = 6.68 Hz, 2H), 3.50–3.58 (s, 9H), 2.07 (s, 3H), 1.01 (t, *J* = 6.9 Hz, 3H).

Section 4B

Investigation of Biginelli reaction under solvent less microwave irradiation in absence of catalyst

4B.1 Objective

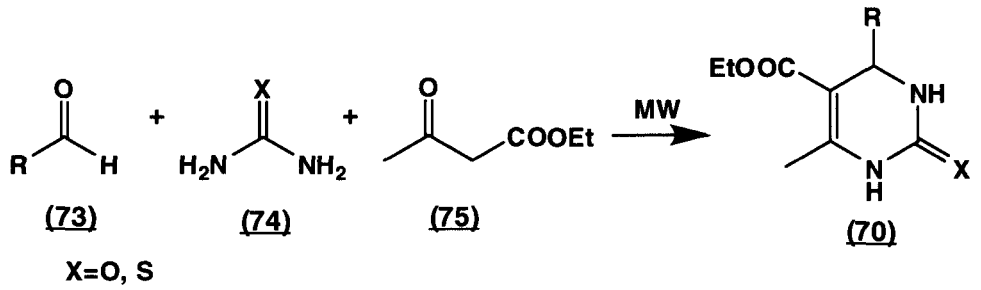
The use of microwave irradiation (MWI) in organic synthesis as non-conventional energy has gained more importance in terms of shorter reaction time, higher yields, and cleaner reaction. In addition, MWI increases the selectivity of some organic reaction under solventless condition. Sometimes microwave irradiation can lead to less by-products and/or decomposition products with homogeneous reaction mixture because of uniform heating throughout the sample as compared to traditional heating systems. Kappe *et al.*[131] investigated a series of acid catalyst Biginelli reactions in polar solvent (ethanol) using MWI at atmospheric pressure and showed neither a rate increase nor an increase in yields when the temperature was identical with conventional thermal heating. But superheating of reaction mixture by MWI increases the rate or yield of reaction at atmospheric pressure in ethanol that is due to rapid evaporation of solvent ethanol from the reaction mixture in open system.

For better understanding of the microwave specific heating for rapid synthesis in solventless condition we performed Biginelli reaction under solventless microwave irradiation in absence of catalyst. Results of experiments are discussed below.

4B.2 Results and discussion

In a typical procedure, a mixture of the aromatic aldehyde **(73)** (2 mmol), urea or thiourea **(74)** (3 mmol) and β-ketoester **(75)** (2 mmol), was taken in a 100ml beaker and irradiated inside the cavity of a domestic MW oven in neat without

any solvent or catalyst at specified power level (900/600/450/300/180W) (*Scheme 4B.1*) to form the corresponding 5- substituted DHPMs (**70**). In case of benzaldehyde, this new method yielded 98% product at 600W power within 5 minutes of irradiation. Kappe *et al.*[131] observed that MWI of benzaldehyde in ethanol solution using HCl acid as catalyst yielded only 89% product during 5minutes at power 400W. In order to generalize our findings, this novel method for the synthesis of DHPMs was applied to a number of substituted aromatic aldehyde compounds. The experimental results are summarized in *Table 4B.1.*



Scheme 4B.1: Solventless and catalyst free microwave assisted synthesis of 5-substituted dihydropyrimidinones (70)

Aromatic aldehydes (containing either electron-withdrawing or electron donating substituents) afforded high yields of products in high purity *(Entry 3-10).*Acid sensitive aldehyde such as cinnamaldehyde and furaldehyde also worked well without any side product, which is normally observed in the presence of protic acids or Lewis acid due to their polymerization under acidic conditions *(Entry 11 and 12).* In addition, this method efficiently worked in presence of thiourea to provide the corresponding 3, 4- dihydropyrimidin-2(1H)-thiones, (**70**) *(Entry 13- 22)* which are also of interest with regard to their biological activities. 4-Methoxy benzaldehyde *(Entry 16)* and furaldehyde *(Entry18)* did not participate in the reaction under 180W power of MW; instead we get the starting compounds back. The driving energy by microwave irradiation results from material wave interactions leading to thermal and specific effects. Loupy *et al.*[28d] already reviewed the effect of microwave irradiation on polarity of reaction systems. Effect of MWI will be more in case of polar mechanism. As far as mechanism of the reaction is

concerned, we believe the reaction proceeds with an increase of polarity via the formation of dipolar transition state (**76**) (*Scheme 4B.2*). This further reacts with the ethyl acetoacetate (**75**) to give the cyclized product with the elimination of water.

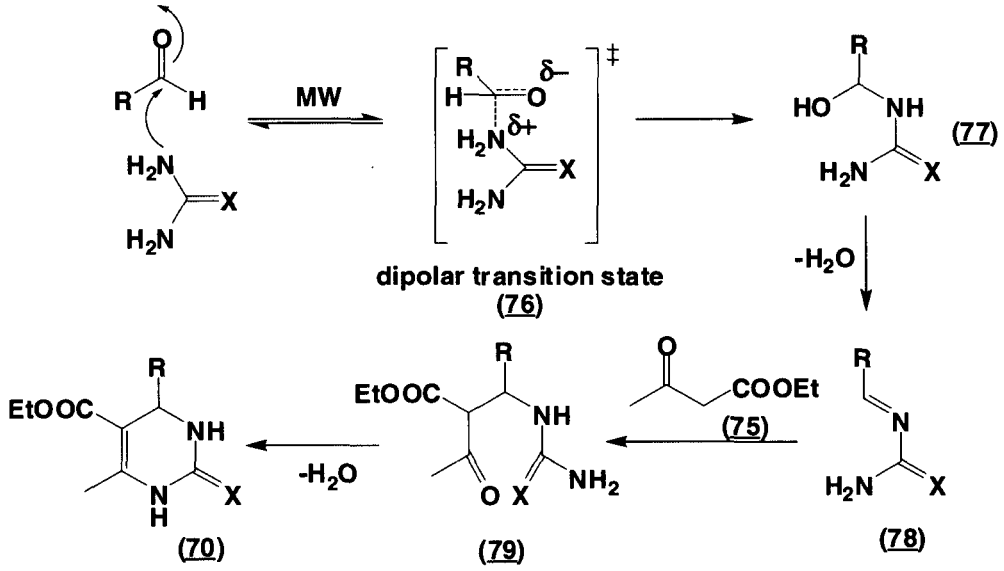
Table 4B.1: Microwave synthesis of 5-substituted dihydropyrimidinones [a] (**70**)

Entry	R	X	Power (W)	Product (**70**) Yield[b] (%)	Time (min)	M.P. (°C)	
						Found	Reported[c]
1	C_6H_5	O	300	42	6	203	202-204
2	C_6H_5	O	600	98	5	203	202-204
3	4-$NO_2C_6H_4$	O	600	94	6	209-210	208-209
4	4-ClC_6H_4	O	600	93	5	210-213	213-215
5	4-$MeOC_6H_4$	O	600	90	5	204-206	201-203
6	2-$NO_2C_6H_4$	O	600	85	5	220	218-220
7	3,4,5-$(OMe)_3C_6H_2$	O	600	86	13	217-218	216-218
8	3-$NO_2C_6H_4$	O	600	97	6	227-228	226-227
9	2-OHC_6H_4	O	900	85	6	202-203	201–203
10	4-MeC_6H_4	O	600	98	10	169-171	168–170
11	Cinnamyl	O	600	96	7	242-243	241-242
12	Furyl	O	600	80	7	203-204	204-205
13	C_6H_5	S	450	98	2	205-207	205-206
14	4-$NO_2C_6H_4$	S	450	97	12	108-110	109-111
15	4-ClC_6H_4	S	450	87	10	193-195	192-194
16	4-$MeOC_6H_4$	S	180	-	10	-	-
17	4-$MeOC_6H_4$	S	450	85	5	151-153	152-154
18	Furyl	S	180	-	6	-	-
19	Furyl	S	300	90	10	216-217	215-216
20	3-$NO_2C_6H_4$	S	600	93	5	205-206	206-207
21	4-MeC_6H_4	S	900	95	7	193-194	192-194
22	3,4,5-$(OMe)_3C_6H_2$	S	900	96	7	203-205	202-204

[a]All products were characterized by FT-IR, ^{1}HNMR, CHN analyzer and also their melting points were compared with those from literature; [b]Isolated yield;[c] Matches with reported data. Ref.89a, 90-93'-': No product

Formation of dipolar transition state increases the specific microwave effect which in turn results in enhancement of reactivity by decrease in the activation energy. Consequently in solvent-free condition, favorable outcomes

are expected. The efficacy of using MWI as an energy efficient method can be realized by the significant decrease in reaction time (from hours to minutes) due to rapid heating in MORE as compared to that reported by Ranu *et al.*[93] under solvent-less and catalyst free Biginelli reaction at 100-105°C for an hour and also to that reported in classical method.



Scheme 4B.2: Plausible mechanism Biginelli reaction under microwave irradiation in absence of catalyst and solvent

4B.3 Conclusion

In this work, 5- substituted 3, 4-Dihydropyrimidin-2(1H)-ones (DHPMs) are synthesized under MWI without any solvent as well as catalyst. The main advantages of this methodology are (a) simple work up procedure using water as the solvent (b) shorter reaction time (c) higher yields (d) solventless and catalyst-free condition. In summary, the present procedure provides an efficient and improved modification of the Biginelli reaction in green synthesis and at the same time brings to light the importance of microwave heating.

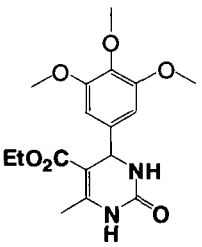
4B.4 Experimental section

General method for the synthesis of 3, 4- dihydropyrimidinones and thiones under solventless microwave irradiation in absence of catalyst has been described in section *2.2.1(E)*.

4B.5 Spectral elucidation

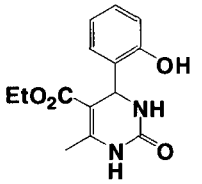
Characterization of all the products was performed by FT-IR, ^{1}HNMR and CHN analysis which are similar to those described in section *4A.5* except for the following compounds (*Table 4B.1*, entries 7, 9, 10, 18).

5-Ethoxycarbonyl-6-methyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin- 2(1H)- one: *(Table 4B.1, entry 7)*



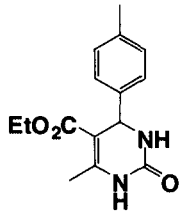
M.P: 217-218 °C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3240, 1717, 1680. **CHN:** Anal. Calcd. for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.28; N, 8.00; found: C, 58.30; H, 6.31; N, 8.07. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.13 (s, 1H), 7.66 (s, 1H), 6.87-6.74 (m, 2H), 5.15(d, *J*=3.3Hz, 1H), 3.96 (q, *J* = 6.7 Hz, 2H), 3.64 (s, 9H), 2.33 (s, 3H), 1.15(t, *J* = 6.7 Hz, 3H).

5-Ethoxycarbonyl-6-methyl-4-(2-hydroxyphenyl)-3,4-dihydropyrimidin-2(1H)- one: *(Table 4B.1, entry 9)*



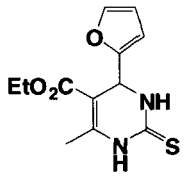
M.P: 202-203°C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3345, 1680, 1600. **CHN:** Anal. Calcd. for $C_{14}H_{16}O_4N_2$: C, 60.86; H, 5.85; N, 10.14; found: C, 60.95; H, 5.81; N, 10.09. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.29 (s, 1H), 8.18 (s, 1H), 7.85 (s, 1H), 7.40–6.93 (m, 4H), 5.21 (s, 1H), 3.86 (q, *J* = 7.2 Hz, 2H), 2.20 (s, 3H,), 1.05 (t, *J* = 7.2 Hz, 3H).

5-Ethoxycarbonyl-6-methyl-4-(4-tolyl-3,4-dihydropyrimidin-2(1H)-one: *(Table 4B.1, entry 10)*



M.P: 169-171°C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3160, 1680, 1627. **CHN:** Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.66; H, 6.62; N, 10.22; found: C, 54.69; H, 6.77; N, 10.18 %. **^{1}H NMR** (400 MHz, DMSO-d_6): δ (ppm) 9.18 (s, 1H), 7.89 (s, 1H), 7.14 (d, *J*=8.1Hz, 2H), 7.11 (d, *J*=8.1 Hz, 2H), 5.11 (s, 1H), 3.99 (q, *J* = 7.1 Hz, 2H), 2.20 (s, 3H), 2.26 (s, 3H), 1.10 (t, 3H, *J* = 7.1 Hz, 3H).

5-Ethoxycarbonyl-4-(furan-2-yl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thione: *(Table 4B.1, entry 19)*



M.P: 216-217°C. **FT-IR** (Solid, *KBr*, cm^{-1}): 3245, 1726, 1689. **CHN:** Analysis Calcd. for $C_{12}H_{14}N_2O_3S$: C, 54.14; H, 5.26; N, 10.53; found: C, 54.21; H, 5.20; N, 10.48. **^{1}H-NMR** (400 MHz, DMSO- d_6) : δ(ppm) 10.36 (s, 1H, 1H), 9.59 (s, 1H, 1H), 7.54 (m, 1H,), 6.36 (m, 1H), 6.10 (m, 1H,), 5.18 (m, 1H), 4.01 (m, 2H), 2.24 (s, 3H), 1.10 (t, *J* = 7.3 Hz, 3H).

Chapter 5

Development of synthetic strategies for ester enolate-imine condensation reaction

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Published with small modifications from:

Phukan, M.; Borah, R.: ''Synthesis of – amino esters/- lactams via ester enolate-imine condensation using basic alumina/ KF supported on alumina''. ***Bulletin of Catalysis Society of India*** *(Accepted, 2010)*

Section 5A

Investigation of solvent effect on ester enolate-imine condensation in basic condition

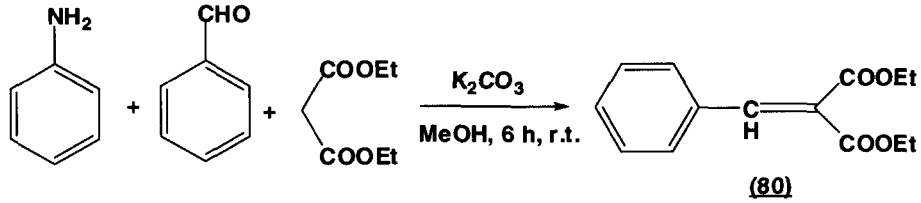
5A.1 Objective

Following the initial report of Gilman and Speeter[105]on ester enolate-imine condensation using Reformatsky reagents (i.e. zinc ester enolates) with simple imines (N-phenylbenzaldimine), studies exploring generality, mechanism, solvent effect and stereochemical course of the reaction, have been done mainly reacting N-aryl nonenolizable aldimines with Reformatsky reagent available from α-substituted-α-bromoacetate [113, 116b, 132]. Later on, the use of Li, Al, Sn, Zn, B enolates derived from esters[114, 117, 121, 133] have been found to be more efficient because of their easy availability than Reformatsky reagents. Though there has been tremendous improvement on the yield and stereoselectivity over the years along with increasing number of variants of the reacting components, almost all procedures are carried out using organic solvents like THF, DMF, dioxane, toluene etc with tedious work up steps. While some required reflux condition others need low temperature control (e.g. -78^{0}C) to afford β-lactam product or β -amino ester product. In such cases, intermediate β-amino esters may be isolated and then converted to β-lactams in a second step. Thus, simplification of experimental procedure and elimination of organic solvent associated with ester enolate-imine condensation is a challenging task showing a lot of scopes to develop newer and greener methodologies. Here we disclose results obtained on experimenting feasibility of the reaction in water and biphasic systems using different bases. Solvent effect of some organic solvents on rendering this conversion is also checked. The efficient use of non-toxic and more selective solid base reagents[134] in heterogeneous medium have a lot of useful properties, for examples, high versatility, easy treatment, and work-up, mild reaction

conditions, high yields and selectivity. From these studies, we developed one pot condensation of simple N-arylaldimines with readily available active methylene compounds using KF/Al_2O_3 under heterogeneous phases in acetone under reflux condition.

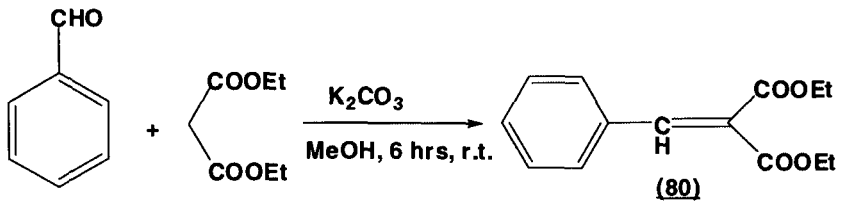
5A.2 Results and discussion

Unlike traditional pathway of ester enolate-imine condensation using prepared azomethinine component for condensation with ester, experiment is done in developing a three component one pot pathway for ester enolate-imine condensation using aldehyde, aniline and ester, with an assumption of in situ generation of both imine and enolate in the reaction mixture. The model reaction is carried out with benzaldehyde, aniline, and diethylmalonate using K_2CO_3 in MeOH *(Scheme 5A.1).*



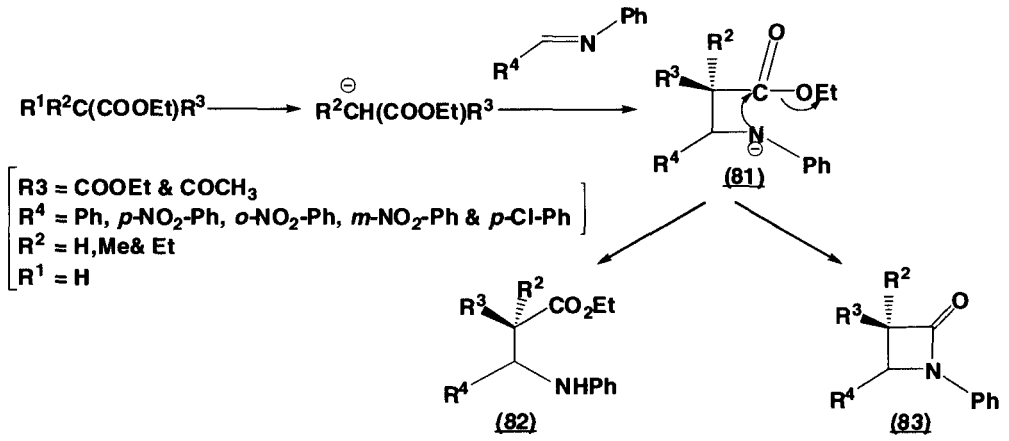
Scheme 5A.1: A three component one pot reaction of aniline, aldehyde and diethylmalonate using K_2CO_3 in MeOH

After six hours of reaction progress, product (**80**) formation observed in 50 % yield from the above reaction mixture while aniline remain unreacted. For further establishment of the observed reaction selectivity, another reaction is carried out using benzaldehyde and diethylmalonate under the same reaction condition *(Scheme 5A.2).* The reaction yielded the same product (**80**) during six hours reaction period which is evident of the selective reactivity of benzaldehyde and diethylmalonate.



Scheme 5A.2: Reaction of benzaldehyde and diethylmalonate using K_2CO_3 in MeOH

The product is isolated and purified using preparative thin layer chromatography and characterized using ^1H NMR and FT-IR, which matched with the reported data of Knoevenagel condensation[135] product. Thus, it is evident that our approach of carrying out the ester enolate-imine cyclocondensation in a three component one pot pathway involves Knoevenagel condensation as the competitive reaction which suppresses the formation of β- lactam or β- amino ester.



Scheme 5A.3: Ester enolate-imine cyclocondensation reaction using N-arylaldimines and active methylene compounds

Thus discarding the above reaction pathway, we chose the traditional route of employing prepared Schiff bases (*Scheme 5A.3).* All the Schiff bases were prepared reacting arylaldehydes and aniline using reported method[128]. Apart from diethylmalonate, its other monoalkylderivatives are also employed. Feasibility of this condensation reaction is checked using different bases like K_2CO_3, KF, basic Al_2O_3, imidazole, Dowex-60, Na_2CO_3/TBAB and KF/Al_2O_3 in water, organic solvents and biphasic systems. For this purpose, some test experiments of diethylmalonate (1 mmol) and N-phenylbenzaldimine (1 mmol) were carried out with bases in various solvents.

Results demonstrated in the *Table 5A.1* illustrates that all the bases employed to test the feasibility of the condensation fails to show reactivity in almost all organic solvents and mainly in water at room temperature except Na_2CO_3/TBAB which facilitates only 30% reaction conversion in water after 48 hours. To examine any increase in the reactivity of Na_2CO_3/TBAB a biphasic system of H_2O/THF is utilized. Though a slight increase in reaction

conversion is observed within 12 hours of reaction progress, the conversion is unclean with large number of by - product formation. In the overall study of the reactivity of various bases, KF/Al_2O_3 (37 mol %) in acetone under reflux condition shows higher conversion (65%) for the formation of β -amino ester during 12h reaction time.

Table 5A.1: Reaction of diethyl malonate (1 mmol) and diphenyl imine (1 mmol) using different bases in various solvent systems

Entry	Bases	Solvent	Temp. (°C)	Amount of Base (mmol)	Time (h)	Product Yield (%)		Reaction conversion[a] (%)
						(82)	**(83)**	
1	K_2CO_3	H_2O	r.t	1	24	-	-	NR
2		MeOH	r.t	1	"	-	-	NR
3		DCM	40	1	"	-	-	NR
4	KF	H_2O	r.t	1	"	-	-	NR
5		MeOH	r.t.	1	"	-	-	NR
6	Al_2O_3	H_2O	r.t	0.5 g	"	-	-	NR
7	(basic)	MeOH	r.t	0.5 g	"	-	-	NR
8		DCM	40	"	"	-	-	NR
9		Acetone	56	"	10	30	10	40
10	Imidazole	H_2O	r.t	1	"	-	-	NR
11		MeOH	r.t	1	"	-	-	NR
12	Dowex-60	H_2O	r.t	20%(w)	"	-	-	NR
13		MeOH	r.t	20%(w)	"	-	-	NR
14	Na_2CO_3/	H_2O	r.t	1 : 0.1	48	20	10	30[c]
15	TBAB	H_2O/THF	r.t	1 : 0.1	12	35	10	45[c]
16	KF/Al_2O_3[b]	Acetone	56	37mol%	12	65	30	> 90
17		Acetone	r.t	"	10	20	10	30
18		DCM	40	"	"	-	-	NR
19		H_2O	r.t	"	"	-	-	NR

NR- *No reaction;* [a]*Total % yield of various products;* [b]*KF/Al_2O_3 is prepared using reported method [Section 2.2.1.(J)];* [c] *Reaction shows large number of side products*

Finally, the reaction condition developed with KF/Al_2O_3 in acetone is further extended to other reactions with different Schiff bases and diethylmalonate derivatives and also ethylacetoacetate *(Scheme 5A.3).* Results obtained are tabulated in *Table 5A.2.* The data show that β-amino ester is formed predominantly in case of reactions with aldimines derived from NO_2 substituted aldehydes *(entries 2-4).* While in case of benzaldimine and *p*-chloro-substituted benzaldimine *(entries 1, 5),* both β-lactam and β-amino ester are formed. However, the major product is β-lactam **(83)** for aldimine with Cl- substituted benzaldehyde *(entry 5)* and in case of aldimine derived

from benzaldehyde, β-amino ester **(82)** is the major product *(entry 1)*. The presence of electron withdrawing nitro group decreases the nucleophilic character of nitrogen atom of β-amino ester **(81)** for cyclization to β-lactam based on the similar mechanism originally proposed by Gaudemar unlike ketene imine cyclocondensation mechanism as in Staudinger β-lactam synthesis[111a] (*Scheme 5A.1*).

Table 5A.2: Ester enolate-imine cyclocondensation reaction using KF/Al_2O_3 in acetone at 56°C

Entry	Code	R^4	R^1	R^2	R^3	Time (h)	Reaction conversion (%)	Product Yield (%)[a,b] (82)	(83)
1	a	C_6H_5	H	H	COOEt	12	95	65[c,d]	30
2	b	4- NO_2 C_6H_4	H	H	COOEt	18	72	72	0
3	c	2- NO_2 C_6H_4	H	H	COOEt	18	75	75	0
4	d	3- NO_2 C_6H_4	H	H	COOEt	18	70	70	0
5	e	4- Cl C_6H_4	H	H	COOEt	24	94	25[d]	69
6	f	C_6H_5	H	Me	COOEt	12	NR	-	-
7	g	C_6H_5	H	Et	COOEt	12	NR	-	-
8	h	C_6H_5	H	H	$COCH_3$	12	NR	-	-

[a]*Isolated yields of products ;* [b]*Reaction condition : 1:1 mmol ratio of ester with Schiff base;* [c] cis β- lactam; [d]*Matches with reported data. Ref.16; NR- No Reaction*

Moreover, it is also observed that other derivatives of diethylmalonate and ethylacetoacetate *(entries 6-8)* failed to show reactivity. Thus, base KF/ Al_2O_3 are capable of generating enolate *in situ* which react with aldimines to form β-amino ester, followed by gradual cyclization to afford β-lactam in some cases. It seems that the feasibility of reactions is also dependent on the electronic effects of the substituents of the aldehyde and the α-substituents of diethylmalonate derivatives. One interesting feature of the reactions generating β-lactam *(entries 1, 5)* is the *cis* stereoselectivity.

5A.3 Conclusion

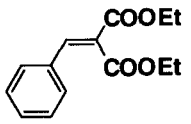
In summary we have developed a simplified strategy for one pot ester enolate-imine condensation for the synthesis of novel β- amino esters and β- lactams compounds utilizing easily available esters and simple nonenolizable N-aryl aldimines under basic conditions in moderate to good yield.

5A.4 Experimental section

General method for the synthesis of β-lactam and β-amino ester compounds via ester enolate imine condensation using KF/Al_2O_3 in presence of solvent. The method for preparation of heterogeneous catalyst KF/Al_2O_3 has also been described in section *2.2.1 (F).*

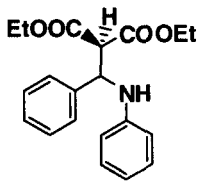
5A.5 Spectral elucidation

Diethyl 2-benzylidenemalonate (80)



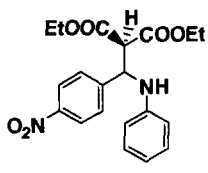
Colorless liquid. **FT-IR** (KBr, cm^{-1}): 1725, 1280, 1112. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.7(s, 1H), 7.4–7.2 (m, 5H), 4.2 (q, *J* = 7.0 Hz, 2H), 4.00 (q, *J* = 7.0 Hz, 2H), 1.3 (t, *J* = 7.0 Hz, 3H), 1.00 (t, *J*= 7.0 Hz, 3H).

Diethyl 2-(phenyl(phenylamino)methyl)malonate (82a) *(Table 5A.2, entry 1)*



Viscous Liquid. **FT-IR** (*KBr*, cm^{-1}): 3375, 1756, 1730, 1600, 1495, 1291. **CHN:** Anal. Calcd. for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10; found: C, 70.22; H, 6.65; N, 4.18. **GC-MS:** (*m/z, rel. intensity, %):* 341 (M^+),264, 191 (100), 171, 182, 109, 91, 76, 73, 58, 57. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.36-7.28 (m, 4H), 7.23– 7.18 (m, 1H), 7.09–7.01 (m, 2H), 6.65–6.62 (m, 1H), 6.57–6.53 (m, 2H), 6.17 (t, *J* =10.8 Hz, 1H), 4.93 (d, *J* = 11.0 Hz, 1H), 4.68 (d, *J* = 10.7 Hz, 1H), 4.25 (q, *J* = 7.2 Hz, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.03 (t, *J* = 7.2 Hz, 3H).

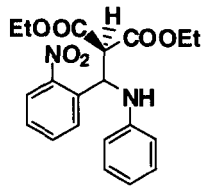
Diethyl 2-(4-nitrophenyl(phenylamino)methyl)malonate (82b) *(Table 5A.2, entry 2)*



Viscous Liquid. **FT-IR** (*KBr*, cm^{-1}): 3396, 2924, 2856, 1737, 1597, 1520, 1347, 1258. **CHN:** Anal. Calcd. for $C_{20}H_{22}N_2O_6$: C 62.18; H 5.69; N 7.25; found: C 62.16; H 5.20; N 7.16. **GC-MS:** (*m/z, rel. intensity, %):* 386 (M^+), 343, 311, 298, 235, 223, 224, 167, 150, 149(100), 132, 121, 93, 76,73, 58, 57. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 8.19 (d, *J* = 8.7Hz, 2H), 8.12 (d, *J* = 8.6Hz, 2H),

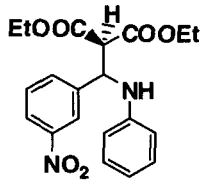
7.69-7.70 (m, 2H), 7.50-7.51 (m, 1H), 6.29 (d, *J* = 8.7Hz, 2H), 4.10-4.23 (m, 4H), 3.99 (q, *J* = 7.3Hz, 2H), 2.84 (m,1H), 1.19 (t, *J* = 6.8Hz, 3H), 1.04 (t, *J* = 7.3Hz, 3H).

Diethyl 2-(2-nitrophenyl(phenylamino)methyl)malonate (82c) *(Table 5A.2, entry 3)*



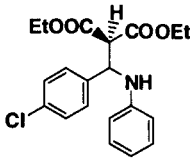
Viscous Liquid. **FT-IR** (*KBr*, cm^{-1}): 3396, 2927, 2859, 1726, 1637, 1604, 1524, 1345. **CHN:** Anal. Calcd. for $C_{20}H_{22}N_2O_6$: C 62.18; H 5.69; N 7.25; found: C 62.17; H 5.40; N 7.5 %. **GC-MS:** (*m/z, rel. intensity, %):* 386 (M^+), 294, 241, 219, 203, 191, 176, 177, 151, 150, 149(100), 133, 122, 121, 115, 93, 77, 73, 58, 57. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 8.19 (d, *J*= 8.8Hz, 1H), 7.52-7.59 (m, 3H), 7.35 (d, *J* = 8.8Hz, 2H), 7.09-7.13 (m,1H), 6.27 (d, *J* =8.8 Hz, 2H), 4.85 (m,1H), 4.11-4.16 (m, 3H), 3.99 (q, *J* =7.2Hz, 2H), 2.84 (m,1H), 1.26 (t, *J* = 6.8Hz, 3H), 1.08 (t, *J* =7.2Hz, 3H).

Diethyl 2-(3-nitrophenyl)phenylamino) methyl) malonate (82d) *(Table 5A.2, entry 4)*



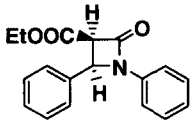
Viscous Liquid. **FT-IR** (*KBr*, cm^{-1}): 3396, 2928, 2862, 1726, 1634, 1604, 1592, 1530, 1352. **CHN:** Anal. Calcd. for $C_{20}H_{22}N_2O_6$: C 62.18; H 5.69: N 7.25; found: C 62.25; H 5.53; N 7.36. **GC-MS:** (*m/z, rel. intensity, %):* 386 (M^+), 294, 280, 279, 206, 192, 191, 167, 162, 150, 149(100), 132, 122, 113, 93, 76, 74, 58, 57. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 8.32 (s, 1H), 8.22-8.25 (m, 2H), 7.73-7.75 (m,1H), 7.69-7.70 (d, *J* = 8.7Hz, 2H), 7.55-7.59 (t, *J* = 8.2Hz, 1H), 6.30 (d, *J* = 8.7Hz, 2H), 4.85 (m, 1H), 4.31-4.41 (m, 3H), 4.09 (q, *J* = 7.3Hz, 2H), 2.85 (m,1H), 1.37 (t, *J* =7.3Hz, 3H), 1.19 (t, *J* = 7.3Hz, 3H).

Diethyl 2-(4-chlorophenyl(phenylamino)methyl)malonate (82e) *(Table 5A.2, entry 5)*



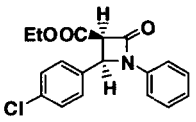
Viscous Liquid. **FT-IR** (*KBr*, cm^{-1}): 3392, 2925, 2860, 1726, 1590, 1493, 1269. **CHN:** Anal. Calcd. for $C_{20}H_{22}NO_4Cl$: C 64; H; 5.87; N 3.73; found: C 64.50; H, 5.86; N, 3.75. **GC-MS:** (*m/z, rel. intensity, %):* 377 (M^++2), 375(M^+), 264, 207, 206, 192, 191(100), 175, 161, 163, 133, 115, 113, 109, 98, 91, 77, 74, 73, 58, 57. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.63-7.64 (m, 2H), 7.46-7.47 (m, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 7.27 (m, 1H), 6.29 (d, *J* = 7.8Hz, 2H), 4.69-4.73 (m, 1H), 4.20- 4.23 (m, 3H), 4.09 (q, *J* = 7.3Hz, 2H),2.75- 2.77 (m, 1H),1.30 (t, *J* = 6.8Hz, 3H), 1.17 (t, *J* = 7.3Hz, 3 H).

Ethyl 2-oxo-1,4-diphenylazetidine-3-carboxylate (83a) *(Table 5A.2, entry 1)*



Viscous Liquid. **FT-IR** (*KBr*, cm^{-1}): 2923, 2855, 1738, 1596, 1493, 1261. **CHN:** Anal. Calcd. for $C_{18}H_{17}NO_3$): C, 73.22; H, 5.76; N, 4.75; found: C, 73.20; H, 5.75; N, 4.74. **GC-MS:** (*m/z, rel. intensity, %):* 221, 219, 180, 176, 145, 143, 128, 119 (100), 115, 103, 91, 89, 77. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.24-7.30 (s, 5 H), 7.12-7.16 (m, 5H), 5.19 (d, *J* = 5.2 Hz, 1H), 4.80 (d, *J* = 5.2 Hz, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.27 (t, *J* = 7.2 Hz, 3H).

Ethyl 2-(4-chlorophenyl)-4-oxo-1-phenylazetidine-3-carboxylate (83e) *(Table 5A.2, entry 5)*



Viscous Liquid. **FT-IR** (*KBr*, cm^{-1}): 2926, 2860, 1727, 1593, 1459, 1273. **CHN:** Anal. Calcd. for $C_{18}H_{16}NO_3Cl$: C, 65.65; H, 4.86; N, 4.26; found: C, 65.72; H, 4.88; N, 4.35. **GC-MS:** (*m/z, rel. intensity, %):* 329 (M+), 237, 219, 180, 179, 167, 165 (100), 145, 137, 125, 113, 111, 97, 77, 73, 69, 58, 57. **^{1}H NMR** (400 MHz, $CDCl_3$): δ (ppm) 7.62-7.65 (m, 2H), 7.45-7.47 (m, 2H), 7.20 (s, 5H), 4.59 (d, *J* = 5.3 Hz, 1H), 4.23 (d, *J* = 5.3 Hz, 1H), 3.8 (q, *J* =7.7 Hz, 2H), 0.90 (t, *J* =7.8 Hz, 3H).

Section 5B

Formation of β–amino-ester/ β-lactam using ester enolate-imine condensation reaction under microwave irradiation method

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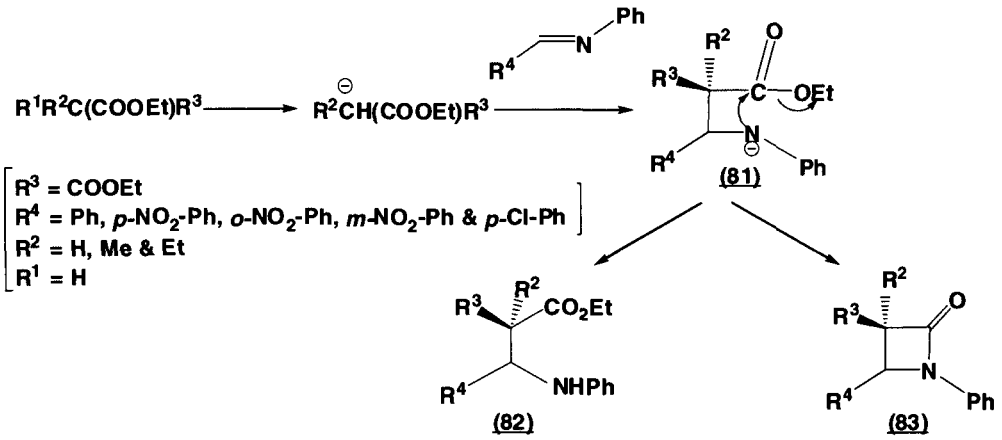
5B.1 Objective

The previous work on ester enolate-imine condensation using heterogeneous phase in presence of solvent acetone involves successful synthesis of novel compounds of amino ester and lactam in a simple way compared to conventional method. However, our search for environmentally benign synthetic strategies for this reaction led us to the development of solventless microwave irradiation technique for this reaction. Additionally, the effect of MWI on ester enolate-imine condensation has been studied only by few groups. Thus our attention has been draw towards these areas relating exploitation of MWI to develop strategies.

5B.2 Results and discussion

At the very beginning the reaction of diethylmalonate (1 mmol) with N-phenylbenzaldimine (1 mmol) was investigated under microwave energy in absence of solvent at different power levels (600W, 900W, 1250W) with various bases such as KF, basic alumina and KF/Al_2O_3 *(Scheme 5B.1).* Detail observations are illustrated in *Table 5B.1.* It is observed that KF (3 mmol) alone cannot facilitate the reaction (*Table 5B.1, entry 1*) at 900W , while KF supported on basic alumina shows reactivity to some extent with different amount of bases (*entry 2*) at 600W microwave power. Moreover prolonged irradiation and increased MW power level leads to charring of the reaction mixture (*entry 2*). It was found that 0.5g of basic alumina isn't sufficient to complete the reaction (*entry 3*) with 600W power while the same

reaction yielded only 35% of β-amino ester using 1 g (*entry 4*) of alumina. On increasing the power level to 1250 watt (*entry 5*), enhancement of overall yield to 75% observed during 20 min.



Scheme 5B.1: Condensation of diethylmalonate derivatives with Schiff base under solvent-free microwave method using basic Al_2O_3

This reaction condition in presence of basic alumina is extended with other aldimines and diethylmalonate derivatives. It was found that the selectivity of products of the reactions follows the same pattern as in the case of enolate-imine condensation reaction in acetone using KF/alumina (*entries 6-13*).

Table 5B.1: Condensation of diethylmalonate derivatives with Schiff base under solvent-free microwave method

Entry	R^3	R^2	Base	Amount of base (g)	Power [b] (Watt)	Time (min)	Reaction conversion (%)	Product yield (%)[a]	
								(82)	(83)
1	C_6H_5	H	KF	3	900	20	NR	-	-
2	C_6H_5	H	KF/Al_2O_3	47 mol %	600	25[c]	42	42	-
			"	37 mol %	900	15[c]	-	-	-
			"	"	600	20	55	35	20
3	C_6H_5	H	Al_2O_3	0.5	600	20	30	25	5
4	C_6H_5	H	Al_2O_3	1	600	20	45	35	10
5	C_6H_5	H	Al_2O_3	1	1250	20	75	50	25
6	4-NO_2-C_6H_4	H	KF/Al_2O_3	37 mol %	600	25	42	42	-

7	4-NO_2 -C_6H_4	H	Al_2O_3	1	600	20	40	40	-
8	4-NO_2 -C_6H_4	H	"	"	1250	25	67	67	-
9	2-NO_2 C_6H_4	H	"	"	"	20	70	70	-
10	3-NO_2 -C_6H_4	H	"	"	"	20	68	68	-
11	4-Cl - C_6H_4	H	"	"	"	30	80	30	50
12	C_6H_5	Me	"	"	"	30	NR	-	-
13	C_6H_5	Et	"	"	"	30	NR	-	-

[a] Isolated yields of products; [b] Reaction condition with varying microwave power : 1:1 mmol ratio of diethyl malonate derivatives with Schiff bas; [c] Decomposed product; NR:No Reaction

Stereochemistry of the β-lactams generated in the reactions too follows similar cis stereoselectivity as observed in enolate-imine condensation reaction in acetone using KF/alumina. More importantly, comparison of yield of the products of both the methods ascertains reflux condition is superior over the MW irradiation method. However reactions take longer time in case of reflux condition.

5B.3 Conclusion

In summary microwave irradiation is effective in furnishing β-amino-ester/ β-lactam using ester enolate -imine condensation reaction under solventless condition using basic alumina. Apart from elimination of toxic organic solvent, the protocol provides simplicity of procedure.

5B.4 Experimental section

General method of condensation of diethylmalonate derivatives with Schiff base under solvent-free microwave method using basic alumina has been described in section *2.2.1(G)*. The method of preparation of Schiff bases are adapted from reported data with minor modifications and described under the section *2.2.1(H)*.

5B.5 Spectral elucidation

Characterization of all the compounds was performed by FT-IR, ^{1}HNMR, MS and CHN analysis and the results obtained match with the spectral data given in section *5A.5*.

Chapter 6

Summary and future scopes of the present work

Summary

In this thesis studies and work related to development of new environmentally benign synthetic methodologies have been described. Green techniques like solventless microwave enhanced organic synthesis, solventless grinding and use of water as reaction medium have been mainly employed for such process development. Apart from exploiting the advantages of these methodologies systematic planning has been done in terms of acquiring the effective reaction condition, selecting catalysts, substrates and in enhancing the reaction rate, product yield and selectivity which was helpful in incorporating maximum green chemistry principles. In our overall work we designed efficient and convenient protocols for reactions such as Henry reaction, Biginelli or Biginelli-like reaction and ester enolate-imine condensation. Synthesis of nitroaldol compounds using aqueous reaction medium is successful attempt in overcoming the drawbacks associated with the classical method of their formation. Introduction of solventless grinding method for the Henry reaction for the first time also shows remarkable results. In both the protocols imidazole emerged as a green catalyst due to its high catalytic activity, efficacy in suppressing various side reactions of Henry reaction and reusability.

Synthesis of 3, 4-dihydropyrimidinones (DHPMs), specifically 5-unsubstituted derivatives using solventless grinding technique for the first time using oxidizing agent Fe $(NO_3)_3.9H_2O$ is significant addition to the number of environmentally benign routes of synthesis for these reactions. The work has been able to exploit the advantage of multicomponent reactions by enduring variations in all the starting components. Moreover, the work also revealed the

importance of supported catalysts in bringing the reusability property to Fe $(NO_3)_3.9H_2O$ by transforming it to catalyst clayfen.

In addition to the above mentioned method for Biginelli reaction, the protocol developed using MW irradiation reveals its effectiveness in furnishing 3, 4-dihydropyrimidinones and thiones even in absence of any catalyst and solvent at a very faster rate.

The advantage of MW irradiation is also employed in ester enolate-imine condensation using basic alumina as reagent. Moreover the same reaction is carried out under reflux condition in acetone using KF/Al_2O_3. These protocols lead to formation of novel β- lactam or β- amino ester compounds using simple esters and aldimines in a simplified manner.

Along with developing these protocols, interesting studies on electronic effect of substituents on reaction rate, solvent effect and mechanistic studies of reaction under the influence of employed catalysts have been carried out which revealed interesting facts of mechanism and catalysts. All these results and observations lead us to develop future scope of the present work.

Future scope of the work

- The observed substituent effect on the reactivity for all the three types of reactions can be better understood with theoretical calculations using DFT and related software packages.
- High catalytic activity of catalyst imidazole that has been explored in our work with Henry reaction opens up vistas in designing protocols for other organic reactions involving generation of nitronates.
- Synthesis of novel 5-unsubstituted 3,4-dihydropyrimidinone compounds can be carried out using other oxidizing agent under solventless grinding method.

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Appendix:

Publications

1. **Phukan M.**, Chaliha P., Borah K.; Thakur A. J., Borah R.; "Microwave accelerated green synthesis of dihydropyrimidinones". ***Organic Chemistry-An Indian Journal***, 4, (1), 2008, 50-53
2. **Phukan M.**, Borah K. J., Borah R.; "Imidazole-catalyzed Henry reaction in aqueous medium". ***Synthetic Communications,*** Volume 38, Issue 18, 2008, 3068-3073
3. Borah K. J., **Phukan M.**, Borah R.; "Synthesis of 1, 3-Dioxanes catalyzed by TsOH-SiO_2 under Solvent-free condition". ***Synthetic Communications,*** Volume 38, Issue 18, 2008, 3082-3087
4. **Phukan M.**, Borah R.; "Henry reaction in environmentally benign methods using imidazole as catalyst". ***Green Chemistry Letters and Reviews***, Volume 2, Issue 4, 2009, 249-253
5. **Phukan M.**, Kalita M. K., Borah R.; "A new protocol for Biginelli (or like) reaction under solvent-free grinding method using Fe $(NO_3)_3.9H_2O$ as catalyst". ***Green Chemistry Letters and Reviews*** (In Press, 2010)
6. Borah K. J., **Phukan M.**, Borah R.; "Aza-Michael addition of amine to α, β- unsaturated compounds using molecular iodine as catalyst". ***Synthetic Communication,*** Volume 40, Issue 19, 2010, 2830-2836.
7. **Phukan, M.**; Borah, R.: ''Synthesis of – amino esters/- lactams via ester enolate-imine condensation using basic alumina/ KF supported on alumina''. ***Bulletin of Catalysis Society of India*** (Accepted, 2010)

Conferences/seminars

1. Borah K. J., **Phukan M.**, Borah R. *"Investigation of Prins reaction of paraformaldehyde with substituted styrene":* 10th CRSI National Symposium at Indian Institute of Science, Bangalore, India, Jan 2008 **(poster)**

2. **Phukan M.**, Borah K. J., Borah R. *"Lewis base catalyzed Henry reactions in aqueous medium":* National Seminar on Green Chemistry and Natural Products Department of Chemistry, University of Delhi, New Delhi, India, Nov 2007 **(poster)**
3. **Phukan M.**, Borah R. *"Investigation of beta lactam synthesis using ester enolate imine cyclocondensation reaction under green chemistry perspective":* National Seminar on Recent Advances in Chemical Sciences, Department of Chemistry, Dibrugarh University, Assam, India, March 2009 **(poster)**
4. **Phukan M**, Borah R. "Imidazole catalyzed Henry reaction in aqueous medium and solvent-free grinding methods".: National Seminar on Catalysis, Tezpur University, Assam, India, Dec 2009 **(poster)**
5. Borah K. J., **Phukan M.**, Dutta, P., ''Borah R.Solvent free organic reactions: An alternative approach of sustainable development.'' National Seminar on Climate Change and Sustainable Development, Tezpur University, Assam, India, Dec 2010 **(Oral Presentation)**