DEVELOPMENT OF SYNTHETIC ROUTES FOR CARBON-CARBON AND CARBON-HETEROATOM BOND FORMATION UNDER SOLVENT- AND CATALYST-FREE CONDITIONS

Thesis

Submitted in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

by

SUBRAHMANYA ISHWAR BHAT

DEPARTMENT OF CHEMISTRY

NATIONAL INSTITUTE OF TECHNOLOGY KARNATAKA,

SURATHKAL, MANGALORE - 575 025

JULY, 2013

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DECLARATION

I hereby *declare* that the Research Thesis entitled "DEVELOPMENT OF SYNTHETIC ROUTES FOR CARBON-CARBON AND CARBON-HETEROATOM BOND FORMATION UNDER SOLVENT- AND CATALYST-FREE CONDITIONS" Which is being submitted to the **National Institute of Technology Karnataka, Surathkal** in partial fulfillment of the requirements for the award of the Degree of **Doctor of Philosophy** in Chemistry is a *bonafide report of the research work carried out by me*. The material contained in this Research Thesis has not been submitted to any University or Institution for the award of any degree.

Subrahmanya Ishwar Bhat
Register Number: 092021CY09F06,

Department of Chemistry

Place: NITK, Surathkal

Date:

CERTIFICATE

This is to *certify* that the Research Thesis entitled "DEVELOPMENT OF SYNTHETIC ROUTES FOR CARBON-CARBON AND CARBON-HETEROATOM BOND FORMATION UNDER SOLVENT- AND CATALYST-FREE CONDITIONS" submitted by Subrahmanya Ishwar Bhat (Register Number: 092021CY09F06) as the record of the research work carried out by him, is *accepted as the Research Thesis submission* in partial fulfillment of the requirements for the award of degree of **Doctor of Philosophy.**

Dr. Darshak R. Trivedi
Research Guide

Chairman- DRPC

DEDICATED TO

MY BELOVED PARENTS

FAMILY MEMBERS

&

ALL OF MY FRIENDS

ACKNOWLEDGEMENTS

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Mr. Subrahmanya Ishwar Bhat

ABSTRACT

The toxicity and volatile nature of organic solvents that are widely used in huge amounts for chemical transformations have posed a serious threat to the environment. With the growing awareness in industry and academia for the sustainable development, the development of solvent-free reaction has received tremendous attention in recent years under the title “Green Chemistry”.

Five different chemical transformations viz., aza-Michael addition of amines to α,β-unsaturated acids, Knoevenagel condensation of salicylaldehydes and *o*-aminobenzaldehydes with malononitrile, cascade Knoevenagel-Michael reaction of 4-hydroxy-1-methylquinolin-2(1*H*)-one, aldehydes and several active methylene compounds, one-pot, three-component reactions for the synthesis of quinazolines and densely functionalized pyrroles have been studied under solvent- and catalyst-free conditions during the present investigation.

All the newly synthesized compounds have been characterized using FTIR, ^{1}H NMR, ^{13}C NMR, mass spectral and elemental analyses. Also, structures of a few target molecules have been confirmed by X-ray crystallographic analysis.

From the results, it has been observed that, the organic transformations proceed faster and to a high degree of completion when the reaction occurred via homogeneous melt formation. However, the success of the reaction depends on the reactivity of the starting materials. The greener advantages of solvent- and catalyst-free reactions over conventional protocols are: easy reaction of poor soluble reactants, short reaction time, high product yield, avoidance of (i) distillation of solvents for reaction, (ii) hazardous solvents in reaction, (iii) solvent evaporation from the reaction mixture, (iv) tedious synthesis of catalysts, (v) solvent usage for catalyst separation.

Key-Words: Green Chemistry; Solvent-free; Catalyst-free; Michael addition; Knoevenagel condensation; One-pot; Multicomponent reaction; Cascade reaction; Mechanical activation; Thermal activation.

CONTENTS

NOMENCLATURE

ABBREVIATIONS

AFM	Atomic Force Microscope
AOCHQ	3-((2-amino-6-oxo-cyclohex-1-enyl)methyl)-4-hydroxy1-methylquinolin-2(1*H*)-one
ATR	Attenuated Total Reflectance
$CDCl_3$	Deuterated Chloroform
DMSO	Dimethyl sulfoxide
EAA	Ethyl acetoacetate
ESI	Electrospray Ionization
EWG	Electron Withdrawing Group
EtOAc	Ethyl acetate
EtOH	Ethanol
Fig.	Figure
FTIR	Fourier Transform Infra-Red
MCR	Multicomponnent Reaction
MDBHQ	3,3′-methanediylbis(4-hydroxy-1-methylquinolin-2(1*H*)-one
MeOH	Methanol
mp	Melting point
NMR	Nuclear Magnetic Resonance
ORTEP	Oak ridge thermal ellipsoid plot program
PE	Petroleum Ether (bp 60-80 ˚C used throughout the work)
RB	Round Bottom
RT	Room Temperature

SCXRD	Single Crystal X-Ray Diffraction
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane

SYMBOLS & UNIT

α	Alpha
Å	angstrom
β	Beta
cm	Centi meter
°	Degree
°C	Degree Celsius
γ	Gamma
g	Gram
Hz	hertz
h	Hour
$^{-1}$	Inverse
λ	Lamda
<	Less than
L	Liter
m	Milli
M	Mega
min	Minute
μ	Mu
mol	Mole

ppm	Parts per million
%	Percent
θ	Theta
~	Tilde

CHAPTER 1

GENERAL INTRODUCTION, LITERATURE REVIEW, SCOPE AND OBJECTIVES

This chapter includes brief Introduction to Green Chemistry and its principles. It also covers a brief account on solvent-free synthesis and activation methods involved in solvent-free reactions. Further, literature survey on solvent- and catalyst- free transformations, scope of the present research work and objectives are explained.

1.1 INTRODUCTION

Green chemistry is a multi-disciplinary concept that has emerged over the past two decades, initiated in academia and research & development, which has subsequently attracted chemical industry to a great extent. The rapid growth in this area highlights the drive towards less harmful and more energy efficient processes. In particular green chemistry refers to the use of sustainable resources, development of cleaner, non-toxic substances, and reformation of existing industrial processes within a green framework. The increase of interest in green chemistry has been driven in particular by the increasing desire for sustainable developments. This has led to increasing interest in environmentally friendly technologies and the adoption of green chemistry approaches in both academia and industry. Green chemistry was defined by Anastas and Warner (1998) as "the utilisation of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products."

1.2 HISTORY

With the aim to develop more environmentally acceptable processes in chemical industry, the concept of green or sustainable chemistry was born around 1990. The US Pollution Prevention Act was initiated awareness of the need for innovative chemical technologies that accomplished pollution prevention in a scientifically sound manner. In1991, Paul Anastas coined the term and defined the field of ''Green Chemistry''. In the same year the first Green chemistry research programme, the ''Alternative Synthetic Pathways'' was launched. From the theoretical point of view, B. M. Trost proposed the concept of "atom economy" and R. Sheldon introduced "E-factor". These concepts initiated a new way of thinking about chemistry and quantitative support to compare the ''greenness'' of alternative products and processes. From a practical viewpoint, several endeavours aimed to promote green

chemistry activities got initiated. In 1997, P. T. Anastas and co-workers founded the Green Chemistry Institute, which worked closely with industries and universities on environmental issues, and expanded its international network to association of 27 nations. With the environmental consciousness, the field of green chemistry and its principles spread rapidly throughout the world. Less than two decades after its introduction, green chemistry issues are providing an enormous number of challenges and are the central concern of those who practice chemistry in industry, education and research.

1.3 TWELVE PRINCIPLES OF GREEN CHEMISTRY

1.3.1 Prevention

It is better to prevent waste than to treat or clean up waste after it has been created.

1.3.2 Atom Economy

Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product. Trost (1991) introduced the term atom economy for the first time.

$$\text{Atom Economy} = \frac{\text{Mass of desired product}}{\text{Total mass of all reagents}}$$

1.3.3 Less Hazardous Chemical Synthesis

Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to people or the environment.

1.3.4 Designing Safer Chemicals

Chemical products should be designed to preserve the efficiency of function while minimizing their toxicity.

1.3.5 Safer Solvents and Auxiliaries

The use of auxiliary substances *(e.g.,* solvents or separation agents) should be made unnecessary whenever possible and innocuous when used.

1.3.6 Design for Energy Efficiency

Energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.

1.3.7 Use of Renewable Feedstock's

A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.

1.3.8 Reduce Derivatives

Unnecessary derivatization (use of blocking groups, protection/de-protection, and temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.

1.3.9 Catalysis

Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

1.3.10 Design for Degradation

Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.

1.3.11 Real-Time Analysis for Pollution Prevention

Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.

1.3.12 Inherently Safer Chemistry for Accident Prevention

Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

The field of Green Chemistry has been emerging at a fast pace over the past two decades. This development may be attributed to the increased awareness regarding the effects of industry on the environment, increasing costs for waste disposal and increased environmental legislation. As a consequence, a drive towards sustainable chemistry is inevitable.

1.4 AN ALTERNATE APPROACH TO SOLVENT CHEMISTRY

Removal of organic solvents in chemical synthesis is important in the drive towards benign chemical technologies. Organic solvents are known to be highly toxic or otherwise eco-damaging compounds because of the large volumes used in industry and difficulties in containing volatile compounds. Replacement of reaction media includes ionic liquids, liquid and supercritical CO_2, water, and polyethylene and polypropyleneglycol. The most advantageous alternative is not to use a reaction medium, which is known as solventless reactions. From the clarity point of view, The Scott group (Cave et al. 2001; Rothenberg et al. 2001) distinguished between the concept of solvent-free synthesis as : (i) *solid-phase reaction*: the reaction of molecules from a fluid phase with a solid substrate, e.g., polymer-supported peptide syntheses; (ii) *solvent-free reaction*: any system in which neat reagents react together, in the absence of a solvent; and (iii) *solid-state reaction* or *solid-solid reactions*: in which two macroscopic solids interact directly and form a third, solid product without intervention of a liquid or vapour phase. A cartoon of these three processes is shown in Fig. 1.1.

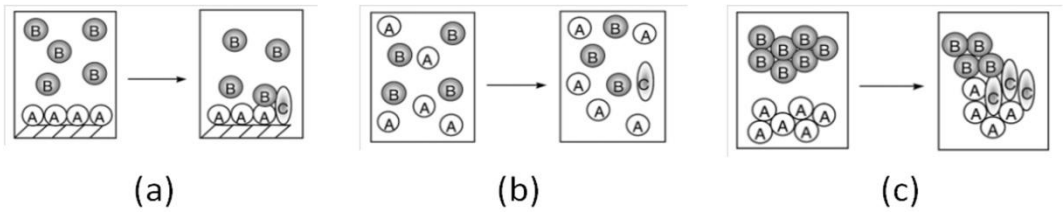


Fig. 1.1: Cartoon representation of (a) Solid phase reaction; (b) Solvent-free reaction; and (c) solid state reaction [Source: Cave et al. (2001); Rothenberg et al. 2001].

The choice of solvent-free reaction medium will depend on several issues, including selectivity, stereochemistry, yield, waste, ease of recycling, energy usage, ease of isolation of product and other competing reactions. Advantages of solvent-free reactions, in comparison to reactions in molecular solvents are: (i) reaction of poor soluble reactants can be easily achievable, (ii) avoidance of distillation of solvents for reaction and hazardous solvents usage in reaction, (iii) there is often no need for specialized equipment; (iv) avoidance of solvent evaporation from the reaction mixture, (v) considerable reduction in the reaction time and increase the product yield

are possible due to the increased reactant concentration (vi) energy usage may be significantly lower, (vii) considerable batch-size reduction and processing-cost savings are achievable, these advantages making solvent-free protocols not only more environmentally benign but also more economically feasible. This is one of the original considerations in order to bring Green Chemistry to the fore (Cave et al. 2001).

1.4.1 Mechanistic Considerations in Solvent-Free Reactions

One of the requirements for solvent-free conditions is the molecular movement of reactants. If one of the reactants is in the liquid phase at the reaction temperature and is miscible with the other reactant(s), the molecular movement and the contact between reactants are same as that of solution reactions. Reactions in which all or one of the reactants are solid at the temperature of reaction, the mechanism of molecular movement is more complex, however, evidence of this movement has been demonstrated and is considered to be the minimal requirement for the solid-solid reaction to proceed (Toda and Tanaka 2000). Under appropriate conditions of stirring (mechanochemistry, microwave, ultrasound, and magnetic stirring), molecules move from crystal to crystal. For a reaction in solution, one would expect the concentration of substrates to be lower than that of the pure compounds, and even when two molecules collide, the reaction may not take place (depending on reactive cross section and orientation). However, in the case of two solid particles, although substrate "concentration" may be high, the actual number of active substrate molecules would be low because only those molecules on the particle surface would be able to react. This limitation is due to the orientation of the molecules, which is fixed in the solid state, making for a lower cross section, and therefore, considerable energy is often required to disrupt the crystal lattice, enabling the individual molecules to react (Martins et al. 2009). The activation mechanisms involved in solvent-free reactions are: (i) microwave irradiation (MW); (ii) ultrasound irradiation (US); (iii) mechanochemistry (mechanical activation); and (iv) conventional thermal heating.

1.4.2 Microwave Irradiation

Microwaves act as high frequency electric fields and will generally heat any material containing mobile electric charges, such as polar molecules in a solvent or conducting ions in a solid (Loupy, 2006). The application of microwave irradiation reduces the reaction time, increases the product yield and sometimes results in a different product distribution compared to conventional thermal heating methods. The rate of acceleration observed in microwave irradiation is due to material-wave interactions leading to thermal and non thermal effects. In addition to the environmental interest of this method in terms of use, separation, economy, safe and clean procedures, absorption of microwave irradiation now be limited only to microwave active species (Martins et al. 2009).

1.4.3 Ultrasound Irradiation

The activation in ultrasound reaction is caused by cavitation, which involves the creation, growth, and collapse of micrometer-sized bubbles that are formed when an acoustic pressure wave propagates through a liquid (Cravotto et al. 2013). The reaction rates are often comparable to those of non-irradiated systems, and the only role of ultrasound is to mix the phases of a heterogeneous system. Thus, the increased yields and reaction rates are due to mechanical effects associated with the sound waves. Chemical effects of ultrasound (true sonochemistry) can only be expected if high-energy species that are released after cavitational collapse act as reaction intermediates. In these cases, changes in product distribution, switching of reaction mechanisms, or changes in regio- or diastereoselectivity may occur (Cravotto and Cintas, 2006).

1.4.4 Mechanochemistry

Mechanochemistry can be grinding two reactants in a pestle and mortar in simple form or more complex, as with the use of ball mills (Stolle et al. 2011). Ball mills have the advantages of requiring no physical effort, supplying greater power, being programmable and allowing more systematic studies of the process. They are readily available commercially, and two types that are appropriate for laboratory scale syntheses are the shaker and planetary mills. With shaker mills, a rapid (e.g., 10-50 Hz) side-to-side motion of the reaction vessel causes a ball within to impact against

the sides of the vessel and its contents (Fig. 1.2a). With planetary mills, the reaction vessel follows a circular pathwhile simultaneously spinning in the reverse direction (Fig. 1.2b).

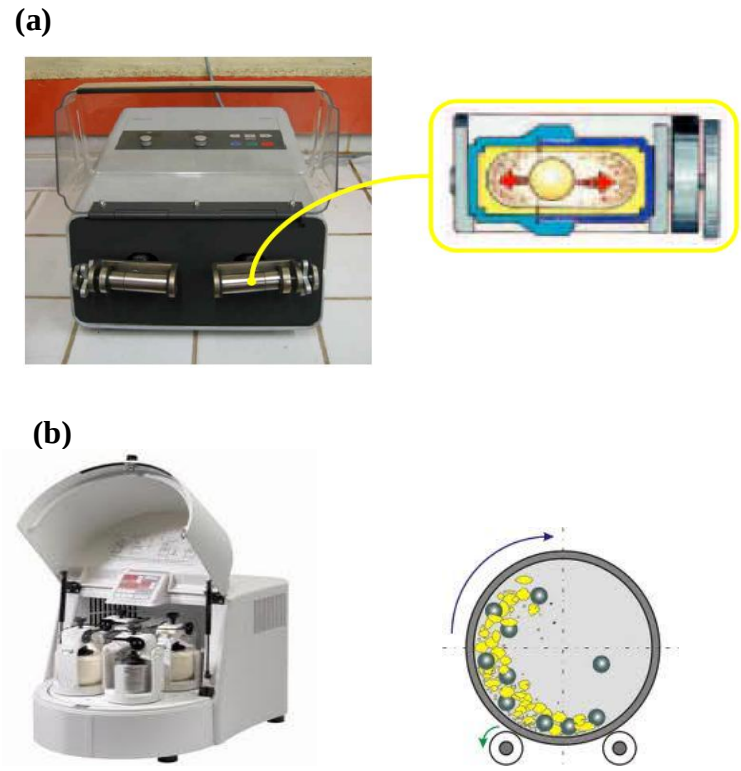


Fig. 1.2: Types of ball mills: (a) Shaker mill; (b) Planetary mill

The kinetic energy supplied during grinding can have several effects on a crystalline solid, including heating, reduction of particle size (with concomitant increase in surface area and the generation of fresh surfaces) and formation of defects and dislocations in crystal lattices, local melting and even phase changes to alternative polymorphs. In chemical synthesis, ball milling modifies the reaction conditions and enhances the reactivity of the reactants (mechanical activation). The latter is generally due to mechanical-induced breaking of molecular bonds (mechanochemistry), but a result of the more efficient mixing and the large increase of reactant surfaces is close contact between the starting materials on a molecular scale. In addition, other factors such as an increased temperature and an enhanced pressure can be responsible for the reactivity changes observed. In most cases, solvent-free reactions between solid

reactants actually proceed through bulk liquid phases (Rothenberg et al. 2001). Such liquid phases are possible due to the formation of eutectics between the reactants and product(s) and any evolution of heat. The solid-solid reactions occurring between two discrete crystalline solids without intervention of a mobile phase and which allows a large number of productive molecular collisions, would be expected to exhibit diffusion-controlled kinetics (slow reaction) (Rothenberg et al. 2001). Thus, the rapid rates exhibited by most of the reactions studied do not support the theory of two solids reacting together without intervention of a new (liquid) phase that would enable higher substrate mobility. Some heat is released upon stirring of the two components, which leads to the complete melting of the mixture. Such heat may be generated by the occurrence of hot spots during initial contact of the solids.

The general mechanism for solvent-free mechanical activation involves three stages [Kaupp et al. 2001]:

- *Phase rebuilding:* Molecules move and directional long-range migrations of molecules of one reactant into cleavage planes or channels in other crystalline reactant occurs. This is driven by the internal pressure that comes from the formation of product at the interface between the reactants. This distorts the original crystal structures and results in a mixed phase.
- *Phase transformation:* Product crystals are formed, and this is the step in which crystals of product grow from the distorted mixed phase. During this step, the growing product crystals remain spatially discontinuous on the reactant particles.
- *Crystal disintegration or detachment:* A new surface is created, and chemical and geometrical mismatch between the starting phases and the product phase causes disintegration of the particles. This in turn reveals new surfaces of the reactants, and continued agitation then serves to bring these new surfaces into contact for further reaction. If the reaction temperature is above the eutectic temperature of the reactants, product formation begins either by grain-boundary diffusion or surface migration and a liquid phase may again intervene due to the formation of eutectic mixture. Thus, a reaction that begins as a solid-solid reaction may proceed much more rapidly by intervention of a liquid phase arising due to the existence of a lower-melting eutectic formed by the product and the reactants. Solvent-free reactions profit from higher

reactivity because the reactants are not solvated. Thus, it is more common to work at room temperature (RT) or to cool down below eutectic temperatures than to heat up. However, some transformations require minimal energy in order to overcome activation barriers, in these cases, alternative energies can be successfully employed under solvent-free conditions.

1.4.5 Conventional Thermal Heating

In conventional thermal heating, the activation involves magnetic stirring and supply of heat energy by using oil-bath or heating mantle. The thermal solid-state reactions involve standing mixture of powdered reactant and reagents at RT or elevated temperature. It has been reported that, for most reactions that form products in good yields by mechanochemistry, MW, or sonochemistry, the product is either not formed or is isolated in low yields in conventional thermal heating (Martins et al. 2009). The Major drawbacks of thermal activation method include inefficient contact between solid reactants during stirring and the kind of energy (direct heat) furnished to reaction media. It seems that, conventional thermal heating is more adequate for reactions in solution or solvent-free reactions of one or all liquid reactants. However, several solid-solid reactions are known to proceed under thermal conditions and quantitative conversion can also be achievable under heating conditions (Kaupp et al. 2001, 2003).

1.4.6 Work-up of Solvent-Free Reactions

For the environmentally-acceptable preparation of an organic product, the transformations must both be relatively efficient and offer easy workup and purification steps. Although, several quantitative transformations do not require extraction of product or purification (Tanaka and Toda 2000; Kaupp et al. 2001, 2002, 2003), one cannot avoid the use of solvents for extraction or purification, when the formed product contaminated with small amount of unconsumed starting materials and in catalytic transformations. However, the avoidance of distillation and use of hazardous solvents in reaction, increase in synthetic efficiency due to high concentration of reactants are the greener advantages in these solvent-free reactions.

1.5 MULTICOMPONENT REACTIONS

A multicomponent reaction (MCR) is generally defined as any process in which three or more reactants combine in one pot to form a product that incorporates structural features of each reagent (Ganem 2008). Therefore, they lead to the association of three or more starting materials in a single synthetic operation with high atom economy and bond-forming efficiency, thereby increasing molecular diversity and complexity in a fast and often experimentally simple fashion. For this reason, MCR's are particularly well suited for diversity-oriented synthesis and the exploratory power arising from their conciseness makes them also very powerful for library synthesis aimed at carrying out structure-activity relationship studies of bioactive compounds, which are an essential part of the research performed in pharmaceutical and agrochemical companies. For all these reasons, the development of new MCR's is rapidly becoming one of the frontiers of organic synthesis. While a large part of the work developed in this field is focused on reactions using isonitriles as one of the starting materials and leading to peptide-like structures, a steady growth in the development of MCR's that lead directly to heterocycles have observed in recent years, the most important single class of compounds in the development of bioactive substances (Estevez et al. 2010). If such reactions with near quantitative yield could be carried out under solvent- and catalyst-free conditions from readily available starting materials, they would comply with most of the green chemistry principles and closely approach the concept of ideal synthesis. (Kumar and Sharma, 2011).

1.6 LITERATURE REVIEW

Since 2000, the groups of Toda (Toda 1995; Tanaka and Toda 2000; Tanaka 2003, Toda 2005), Scott (Roothenberg et al. 2001; Cave et al. 2001) and Kaupp (Kaupp et al. 2001; Kaupp 2005) have reported comprehensive work on the stoichiometric conversion of organic compounds in solvent-free reactions. The advantages of solventless synthesis have thereby been persuasively described. Inspired by their work enormous efforts have been made in last decades and reports on solvent- and catalyst-free reactions have become increasingly frequent in recent years. Since the current research work mainly focused on the solvent- and catalyst-free organic synthesis

under simple mechanochemical and/or thermal conditions, only those organic transformations carried out under solvent- and catalyst-free conditions have been discussed.

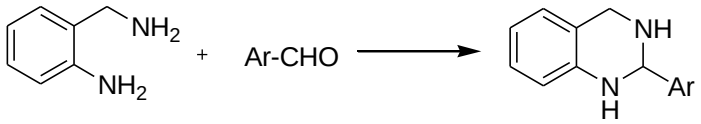
Tanaka and Toda (2000) reviewed several solid-state organic reactions including the reactions that start with a solid, at least one solid reactant or solid catalyst, the reactions in the inclusion crystals and organic solvent-free reactions and clearly demonstrated that organic reactions can occur by mixing powdered reactant and reagent in the absence of solvent and those reaction products can be obtained efficiently. It was found that, in some cases, organic synthesis is accomplished without using any solvent throughout the processes of reaction and isolation of product. Further, solvent-free thermal organic synthesis reported to be a highly useful technique, especially for industry. According to them, all organic synthesis cannot be carried out in the absence of solvent; some organic reactions proceed explosively in the solid state. In such cases, solvent is useful in order to mediate the reaction rate. Further it was concluded that, for reactions that proceed moderately in the absence of solvent or in a water suspension, solid-state reaction would be the better choice. For reactions that proceed vigorously in the solid state, then solution reaction in a nontoxic solvent would be better.

Cave et al. (2001) reviewed solventless organic synthesis and emphasise that, solventless reactions can lead to improved outcomes, and more benign synthetic procedures. Several transformations such as aldol condensation reactions, sequential aldol and Michael addition reactions route to Kröhnke type pyridines, reactions leading to 3-carboxycoumarins, benzylidenes, 4-aryl-1,4-dihydropyridines and 2-aryl-1,2,3,4-tetrahydroquinazolines, and oligomerization reactions for the synthesis of cavitands were discussed and concluded that, kinetic considerations for the reaction of two solids can only be explained if an eutectic melt is formed during the reaction.

Rothenberg et al. (2001) investigated the concept of an organic reaction between two macroscopic solid particles. Several organic reactions were revisited and clearly showed that, in most cases, grinding the two solid reactants together results in the formation of a liquid phase. This liquefaction implies the existence of a eutectic

mixture with the fusion below ambient temperature. Further, it was shown that, in cases where heating is required, a phase change (from solid to liquid) occurs. On the basis of 19 experimental examples, the possibility of solid-phase organic reactions and the implications of these findings to the reaction between two solid reagents were discussed. A general description of such reactive systems was proposed, based on a consideration of the potential for eutectic (or peritectic) formation between the constituents of the liquid phases that arise during the process of mechanical mixing of the solid reagents and products. It was concluded that, few covalent bond forming bimolecular organic transformations that proceed rapidly and to a high degree of completion between two solid reactants actually not occur in the solid state. Instead, a liquid or melt phase, which imbues the individual molecules with the required mobility for productive (or reactive) collision, intervenes, allowing rapid reaction between the two solid reagents.

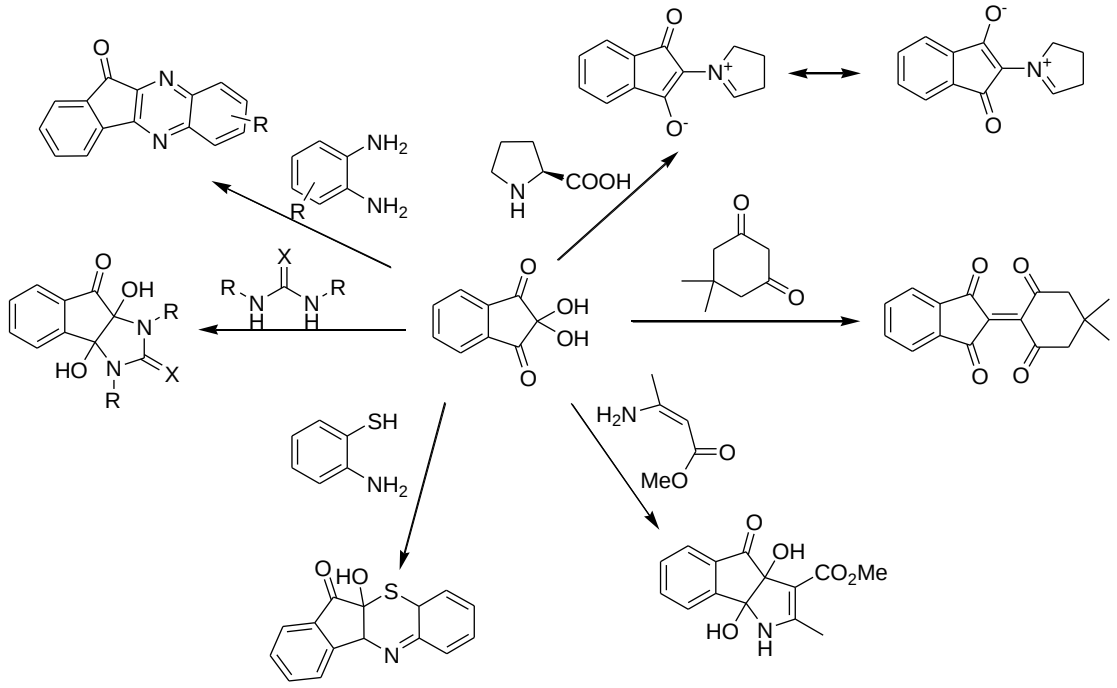
Correa et al. (2002) synthesised 2-Aryl-1,2,3,4-tetrahydroquinazolines by direct reaction of 2-aminobenzylamine and benzaldehyde derivatives by mixing of the reagents either neat, or as an aqueous slurry (Scheme 1.1). Excellent conversion of starting materials was achieved without catalysts, derivatisation or auxiliary reagents. Further, it was observed that, where reaction is sluggish or extent of conversion is poor, application of gentle heating produces a melt phase, which results in rapid and clean conversion to the desired tetrahydroquinazoline product.



Scheme 1.1

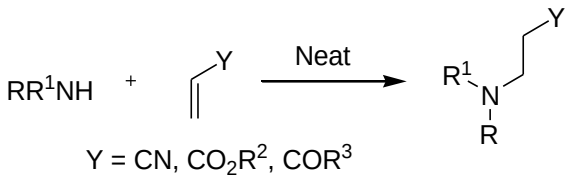
Kaupp et al. (2002) reported the waste-free solid-state cascade reactions of crystalline ninhydrin with dimedone, -proline, o-phenylenediamines, o-mercaptoaniline, ureas, thioureas, and methyl 3-aminocrotonate (Scheme 1.2). All the products were obtained quantitatively without any workup and just by milling stoichiometric mixtures of the crystalline reagents. The structures of the products were established/confirmed by spectroscopic data and density functional calculations using the B3LYP/6-31G* programme. The reaction process was mechanistically

investigated with atomic force microscopy (AFM) techniques on six different faces of crystalline ninhydrin when o-phenylenediamine was the reagent and interpreted on the basis of known crystal structure data. Strict correlations to the crystal packings were observed.



Scheme 1.2

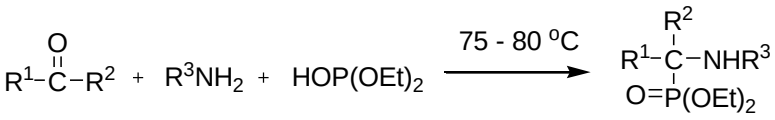
Ranu et al. (2002) carried out Michael-type addition of variety of amines to α,β-unsaturated nitriles, carboxylic ester and ketones in a neat mixture without using any solvent and catalyst to produce the corresponding *β*-amino derivatives (Scheme 1.3). The efficiency, cost-effectiveness and green methodology of this protocol made this protocol very simple and practical alternative to the previous procedures.



Scheme 1.3

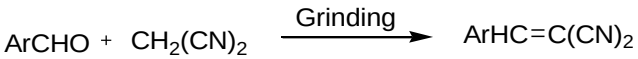
Ranu and Hajra (2002) developed a simple, general, efficient and greener method for the synthesis of *α*-aminophosphonates through a solvent-free and catalyst-free one-pot three-component condensation of carbonyl compound, amine and diethyl

phosphate (Scheme 1.4). Interestingly, when the reaction was carried out in a solvent like Tetrahydrofuran (THF) under similar reaction conditions the condensation proceeds to a marginal extent (10–15%) for aldehydes and does not occur at all for ketones. Further, scale up of the reaction has been achieved up to the extent of a batch of 10g without any difficulty and use of any organic solvent in any step.



Scheme 1.4

Ren et al. (2002) reported Knoevenagel condensation reaction of aldehydes and malononitrile by grinding at RT in the absence of solvents and catalysts (Scheme 1.5). This process is simple, efficient, economical, and environmentally benign. It was found that, compared to Knoevenagel condensation carried out by microwave irradiation, this procedure is completely free from organic solvents during both the reaction and separation of the product.

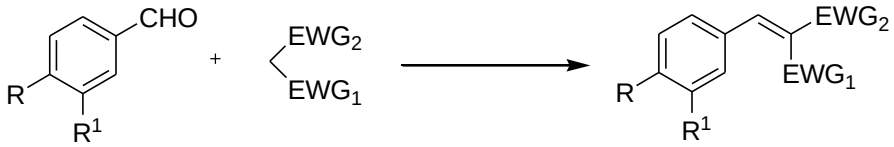


Scheme 1.5

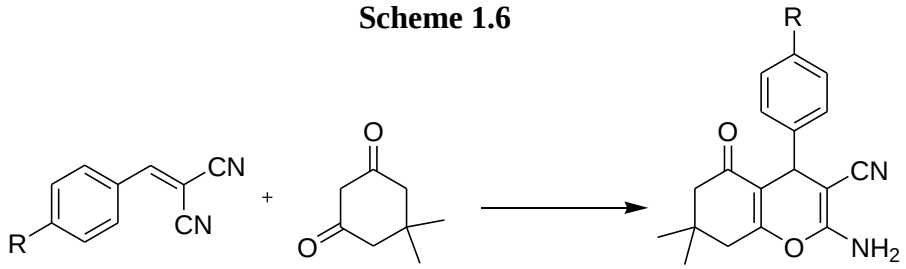
Kaupp (2003) highlighted that, molecular crystals including salts undergo gas–solid, solid–solid, thermal, photochemical and catalyzed reactions if the crystal lattice allows for long-range anisotropic molecular migrations, if the product phase can form fast enough and if crystal disintegration provides fresh surface. This three-step solid-state mechanism was derived from AFM studies. Very detailed solid-state effects that go down to the molecular level emerge from AFM investigations with single crystals on their different faces were discussed. Further, the advantages of these waste-free syntheses are fast, require simple equipment, save resources and are environmentally benign. The reactions were scaled up for industrial application and successfully prepared at the kg level. Numerous selected examples of preparative interest out of more than 1000 transformations were presented in this report.

Kaupp et al. (2003) performed numerous Knoevenagel condensations of solid or liquid aromatic aldehydes with barbituric acids, Meldrum's acid, dimedone,

cyanoacetamide, malodinitrile and methyl cyanoacetate in stoichiometric mixtures of the solids or of stoichiometric melts (Scheme 1.6). The product yields were found quantitative in 23 cases and the products do not require purification or workup. These transformations were found to be highly superior to less productive 'solvent-free' techniques using solid supports and microwave irradiation that require solvents for removal of the support or reagents or side products. Also, quantitative Michael addition reaction by stoichiometric melts in the absence of any auxiliaries or microwave irradiation was demonstrated (Scheme 1.7). It was concluded that, the quantitative yields are most easily obtained if the products are formed in the solid-state or if they crystallize directly from the melt at the reaction temperature.

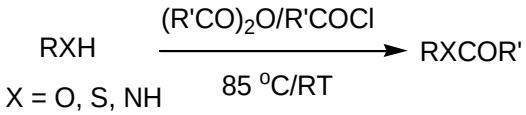


Scheme 1.6



Scheme 1.7

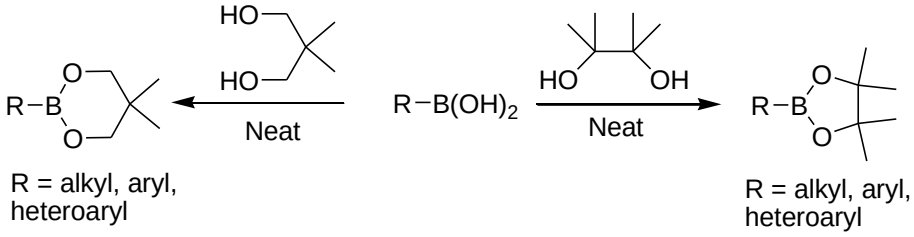
Ranu et al. (2003) reported a general, simple, efficient, cost-effective and green procedure for acylation of alcohols, amines and thiols by treatment with acid anhydride or acid chloride at 80–85 °C under solvent and catalyst-free conditions (Scheme 1.8). This method is endowed with several unique merits namely, simplicity in operation, mild reaction conditions tolerable to acid sensitive functionalities, wide applicability and cost-efficiency.



Scheme 1.8

Kaupp (2006) performed the scale up of numerous organic and some inorganic quantitative solid state reactions of various types without solvent in the kg- scale. Technical solutions with strongly exothermic and with close to thermoneutral procedures were demonstrated for various circumstances. Further, it was found that, melt reactions also profit from high concentration, but the reaction temperatures are considerably higher in the absence of the favorable crystal effects and they often bear the risk of side reactions. From the results it was concluded that, the single products obtained do not require purifying workup when starting with pure crystalline compounds and their prior dissolution in solvents for waste producing liquid-state reactions should be avoided whenever possible.

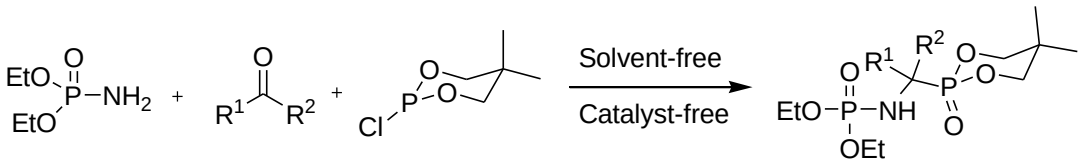
Schnurch et al. (2007) developed a facile and high-yielding mechanochemical protocol for the preparation of boronic acid esters (Scheme 1.9). All different types of boronic acids investigated (aryl, heteroaryl, alkyl) were reacted smoothly under present conditions and gave products in excellent yields and purities. The advantages of this protocol include short reaction times (maximum 1 h) and simple work-up conditions (filtration, evaporation and eventually Kugelrohr distillation). From the experimental results it was emphasize that, Mechanochemistry is a powerful alternative to the classical esterification reaction of boronic acids and complements nicely to other methods starting from alternative substrates (e.g. Pd-catalyzed methods starting from halides). Additionally, the current protocol found to be an environmentally benign, atom efficient, and waste free process, since the reaction is carried out under solvent-free conditions with equimolar amounts of reagents.



Scheme 1.9

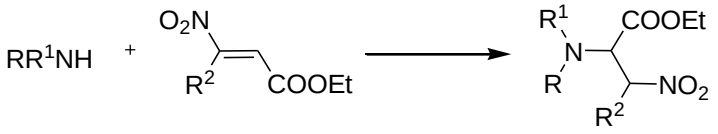
Zhang et al. (2007) developed a convenient and rapid method for the synthesis of various N-phosphoramino α-aminoalkylphosphonates under catalyst-free and solvent-free conditions (Scheme 1.10). All types of aromatic aldehydes produced the

corresponding target compounds with excellent yields. Further, advantages of the current protocol are: rapid reaction, clean, atom economical and environmentally benign. The pure products were obtained by flash chromatography on silica gel.



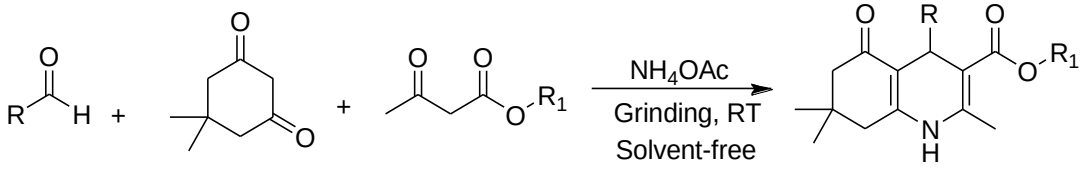
Scheme 1.10

Ballini et al. (2008) demonstrated that, variety of primary and secondary amines give the conjugate reaction with *β*-nitroacrylates via an anti-Michael addition without any catalyst and/or solvent (Scheme 1.11). This protocol has several advantages such as very mild conditions, short reaction times, good yields, atom economy (100%), minimal production of waste, limited energy consumption, and environmentally benign.



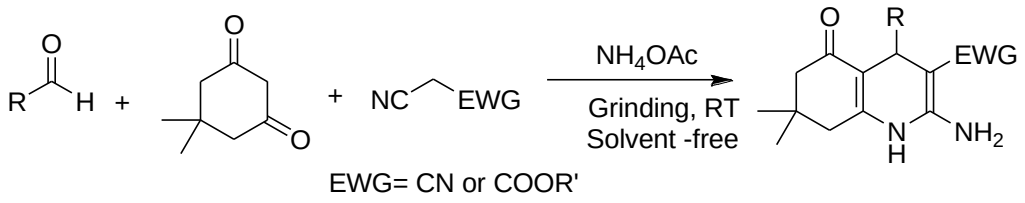
Scheme 1.11

Kumar et al. (2008) reported an efficient synthesis of polyhydroquinolines via a four-component reaction of aldehydes, dimedone, active methylene compounds, and ammonium acetate in one-pot under solvent-free conditions at RT on grinding (Scheme 1.12 and 1.13). This method does not involve any hazardous organic solvent or catalyst. The key advantages of this protocol are the short reaction time, high yields, simple workup, and purification of products by non-chromatographic methods, i.e., by simple recrystallization from ethanol (EtOH).



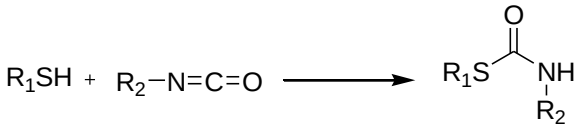
R= aryl, R'= Me, Ethyl

Scheme 1.12



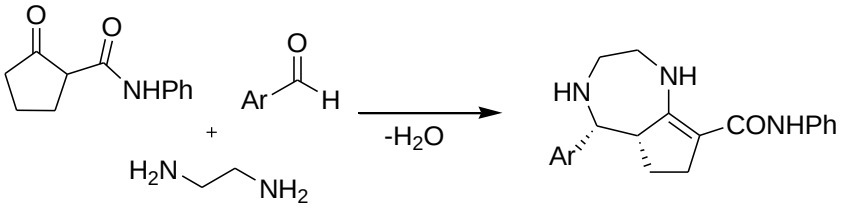
Scheme 1.13

Movassagh and Beigi (2008) developed a simple and efficient procedure for the synthesis of S-alkyl (aryl) thiocarbamates under solvent- free conditions without the use of a catalyst (Scheme 1.14). The significant features of this protocol are operational simplicity, mild reaction conditions, short reaction times, solventfree conditions, and high product yields. It was concluded that, the catalyst- and solvent-free procedure provides a powerful and versatile method for the preparation of S-aryl (alkyl) thiocarbamates.

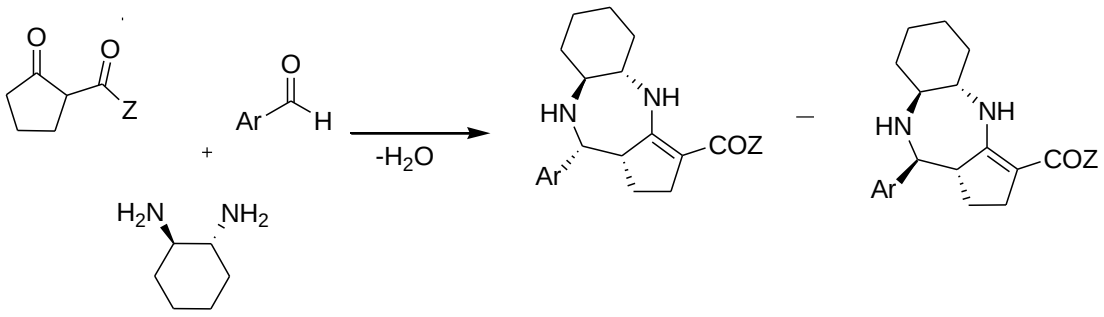


Scheme 1.14

Sotoca et al. (2008) reported the stereoselective one-pot synthesis of polysubstituted 1,4-diazepine derivatives via a new solvent- and catalyst-free multicomponent domino reaction from *β*-ketoamides (Scheme 1.15 and 1.16). The reaction sequence were conducted from easily accessible achiral starting materials, and resulted in a high increase in molecular complexity and diversity. Based on its tolerance to various *β*-ketoamides, acyclic and cyclic 1,2-diamines, and diverse aromatic aldehydes, it was concluded that, this environmentally friendly procedure constitutes a good substrate directed alternative to other previously known methodologies for the synthesis of these heterocycles.

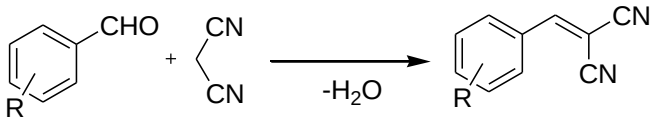


Scheme 1.15



Scheme 1.16

Trotzki et al. (2008a) reported the studies on mechanochemical reaction of malononitrile with various aldehydes to achieve quantitative stoichiometric conversion of the reactants to their corresponding benzylidene-malononitriles in the absence of any solvents and catalysts (Scheme 1.17). In addition to earlier known reactions in the solid state, reactions with liquid aldehydes were also studied. It was concluded that, successful quantitative conversion depends strongly on the choice of the aldehyde, precluding a generalization of the reaction scheme.

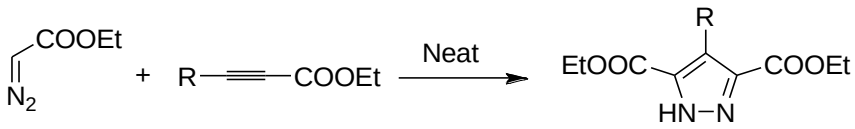


Scheme 1.17

Trotzki et al. (2008b) studied the Knoevenagel condensation of malononitrile with various arylaldehydes as an uncatalyzed reaction at ambient temperature (Scheme 1.17). It was found that, a mixture (solid/solid or solid/liquid) of reactants converts in some cases quantitatively to the target product in the absence of any solvent at RT. The increased product yields observed when the mixture of reactants is seeded with the target product.

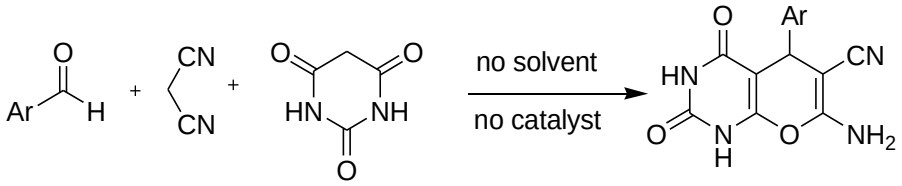
Vuluga et al. (2009) developed synthesis of pyrazoles *via* 1,3-dipolar cycloaddition of diazo compounds to alkynes by heating (Scheme 1.18). Various diazo compounds and alkynes (even without an electron-withdrawing group) were reacted through a 1,3-dipolar cycloaddition without any promoter or special medium. The reaction afforded pyrazoles in excellent yields and purity, without any other work up than distilling the small excess of the lightest reagent. Also, this protocol was found to be

efficient on a multigram scale, and hence reported as promising for industrial applications.



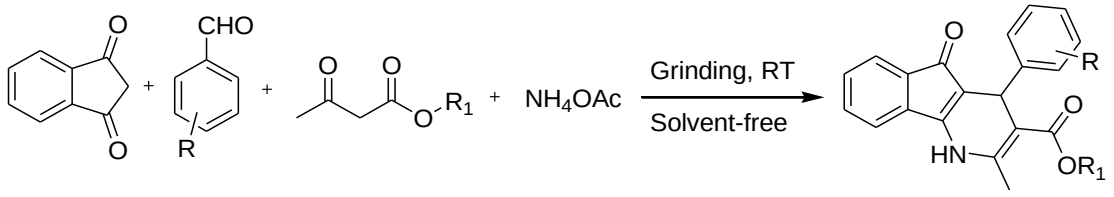
Scheme 1.18

Mashkouri and Naimi-Jamal (2009) reported quantitative synthesis of various pyrano[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-diones from stoichiometric mixtures of pure reactants in a simple mechanochemical method without use of solvents, addition or removal of catalysts, or solvent-consuming work-ups (Scheme 1.19). The pure products were obtained in some cases by recrystallization from dimethylformamide (DMF)- EtOH mixture.



Scheme 1.19

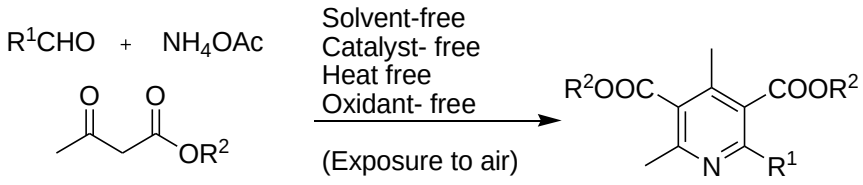
Samai et al. (2009) developed a simple and efficient method for the synthesis of 4-aryl-4,5-dihydro-1*H*-indeno[1,2-*b*]pyridine derivatives via a four-component cyclocondensation of 1,3-indanedione, aromatic aldehydes, *β*-ketoesters and ammonium acetate in one-pot and in the absence of catalyst and solvent at RT on grinding (Scheme 1.20). The shorter reaction times, higher yields, low cost, simple work-up and easy purification procedure are the notable advantages of this green protocol.



Scheme 1.20

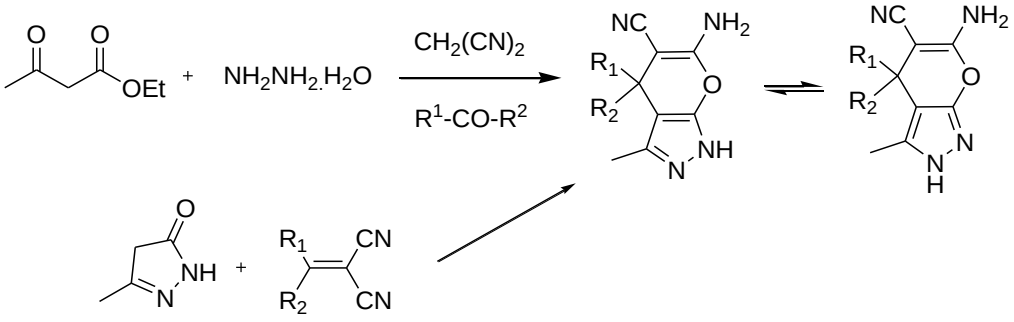
Shen et al. (2009) developed a novel, efficient and environmentally friendly one-pot three-component method for the synthesis of the 2-arylpyridines in air at RT

(Scheme 1.21). This protocol does not require the use of any organic solvent, catalyst and additional oxidant, thus eminently meeting green chemistry objectives. According to them, these efforts do not mean that everything is known, and there is still a lot to learn about this fascinating and useful reaction.



Scheme 1.21

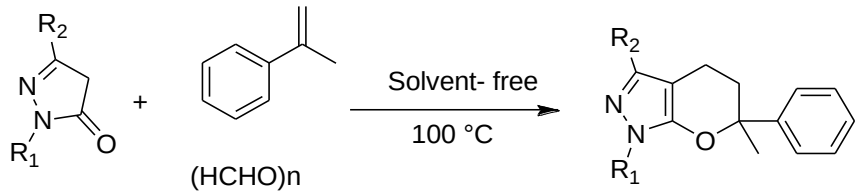
Matar et al. (2010) synthesized pyrano[2,3-*c*]pyrazoles via mixing ethyl acetoacetate (EAA), hydrazine hydrate, aldehydes or ketones and malononitrile in the absence of solvent (Scheme 1.22). The same products were also obtained by reacting arylidenemalononitriles with 3-methyl-2-pyrazolin-5-ones. A novel 4-oxo-4*H*-pyrano[2,3-*c*]pyrazole was achieved via reacting 3-methyl-2-pyrazolin-5-one with a mixture of cyanoacetic acid and acetic anhydride. Similarly 3-aminopyrazole with the benzylidene-malononitrile produced the pyrazolo[2,3-*a*]pyrimidines. From the experimental results it was found that, the yields in multi-component synthetic approaches are almost the same as those utilizing original synthetic approach but the protocols are greener, avoiding use of solvent, separation and purification steps.



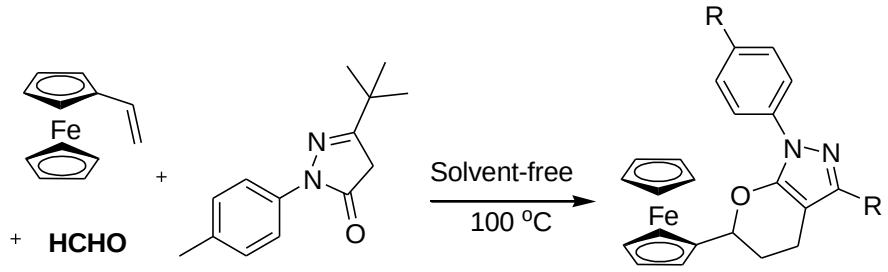
Scheme 1.22

Tan et al. (2010) developed MCR's of 1,3-disubstituted 5-pyrazolones, formaldehyde and Styrenes (Scheme 1.23) or vinylferrocene (Scheme 1.24) to afford a variety of complex skeletons in moderate to excellent yields under catalyst-free heating conditions. It was found that, these sequential MCR's not only open a

straightforward way to synthesize the target compounds, but also maximize the synthetic efficiency significantly. Because these MCR's were conducted either under solvent-free conditions or in green media, including glycerol and ionic liquid, the reaction systems possess many properties of green chemistry, such as simple work-up procedure, recyclable solvent and minimization of waste.

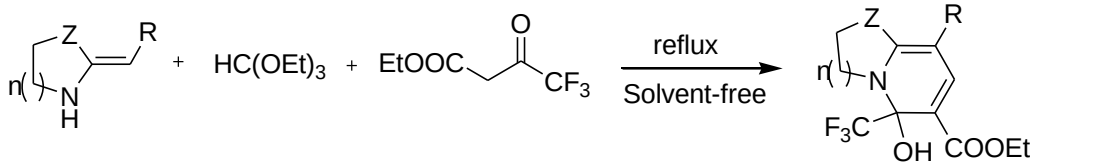


Scheme 1.23



Scheme 1.24

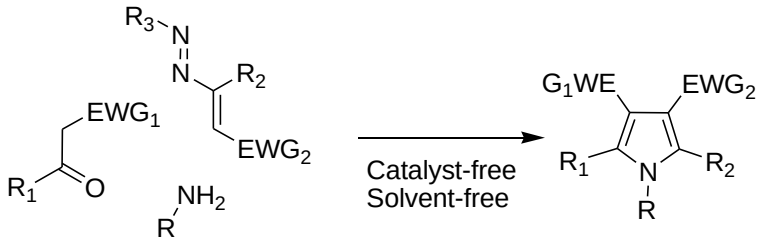
Yan et al. (2010) described an efficient one-pot, three-component synthesis of highly substituted bicyclic pyridines containing ring-junction nitrogen, starting from simple and readily available materials (Scheme 1.25). Bicyclic pyridines were synthesized by the cyclocondensation of heterocyclic ketene aminals, triethoxymethane, and active methylene compounds by refluxing under solvent- and catalyst-free conditions. The crude reaction mixture was flash column chromatographed to get pure products in excellent yields.



n= 1, 2, 3; Z = NH, O, S
R = COOEt, NO_2, MeCO, ArCO

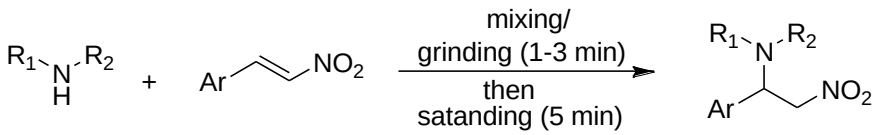
Scheme 1.25

Attanasi et al. (2011) reported a new and efficient synthesis of polysubstituted pyrroles by a sequential one-pot, three-component reaction between primary aliphatic amines, active methylene compounds, and 1,2-diaza-1,3-dienes (Scheme 1.26). The reactions were performed without catalyst and under solvent-free conditions. The ready availability of the starting materials and the high level of practicability of the reaction and work up are the notable advantages of this protocol. Further, this method circumvents some of the problems and limitations associated with frequently used procedures. The pure products were obtained in high yield by column chromatography.

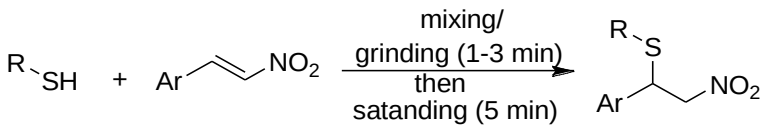


Scheme 1.26

Choudhary and Peddinti (2011) demonstrated the synthesis of nitroamines (Scheme 1.27) and nitrosulfides (Scheme 1.28) by the Michael addition of amines and thiols to nitroolefins by simple mixing or grinding the reactants. This catalyst-free and solvent-free green approach provided the addition products in quantitative yield within min at RT. This procedure does not require any water quenching, solvent separations and purification steps such as recrystallization and column chromatography, also incorporates the reactants into the final product to a maximum possible extent without side products in short reaction time.

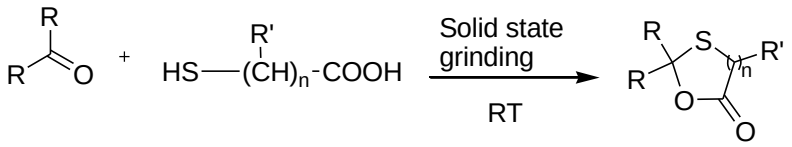


Scheme 1.27



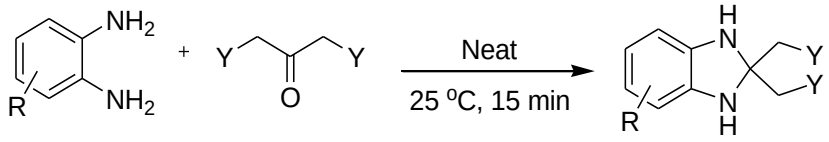
Scheme 1.28

Dandia et al. (2011) developed a solvent- and catalyst-free method for the synthesis of spiro 1,3-oxathiolan/oxathianes in the solid state reaction at RT (Scheme 1.29). Quantitative yields of products were obtained in a simple and inexpensive way. Further, different thia heterocycles were synthesized to evaluate the scope of this green methodology.



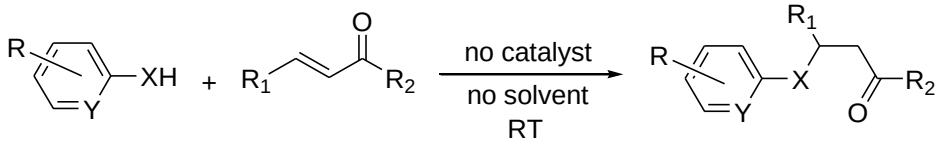
Scheme 1.29

Li et al. (2011) carried out reactions of acyclic ketones and *o*-phenylenediamines under solvent- and catalyst-free conditions for the preparation of dihydrobenzimidazoles (Scheme 1.30). Further it was found that, this method can be used for the synthesis of other heterocyclic compounds such as dihydrobenzothiazoles and perimidines.



Scheme 1.30

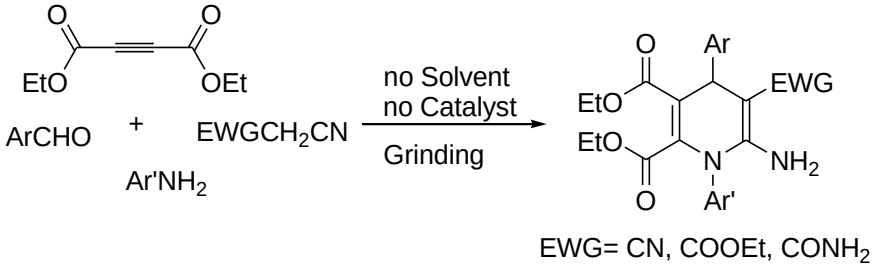
Jiang et al. (2011) reported catalyst- and solvent-free mono-addition of aromatic amines to *α,β*-unsaturated ketones with high selectivity, effectively at RT in good to excellent yields (Scheme 1.31). Part of adducts obtained almost in quantitative yield without column chromatography. This procedure offered a green, efficient, and practical approach for the synthesis of *β*-amino ketones. No decrease in yield observed when the reaction was carried out in gram scales; hence this green protocol can be applied in industrial processes.



X= NH, S; Y=C, N; R= H, Me, I, Cl, Br, CN, Ac etc; R_1, R_2=Alkyl, H.

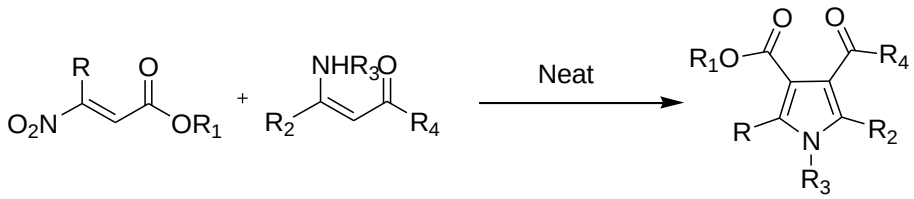
Scheme 1.31

Kumar and Sharma (2011) developed a grinding-induced catalyst- and solvent-free domino MCR for the synthesis of 1, 4- dihydropyridines using aldehydes, amines, diethyl acetylenedicarboxylate, and malononitrile/ethyl cyanoacetate (Scheme 1.32). The reaction was carried out successfully in a porcelain mortar and pestle without using any catalyst. Interestingly, almost quantitative conversion observed on grinding for 15 min, but no reaction was observed in EtOH (in the absence of catalyst). The purity of the product was enough for spectroscopic analysis without any further purification.



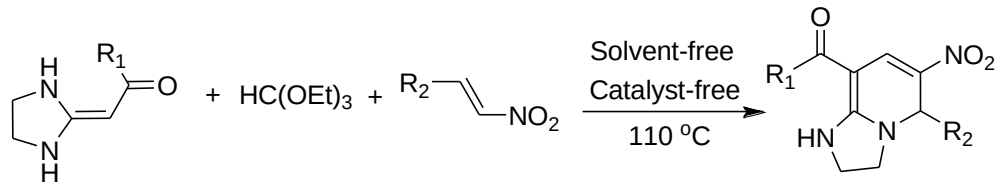
Scheme 1.32

Palmieri et al. (2011) reported a highly improved procedure for the synthesis of polyfunctionalized pyrroles under environmentally benign manner showing acceptable to good E-factor (Scheme 1.33). The advantages of this method are general applicability, it affords good to excellent yields of the products, tolerates the presence of a variety of functionalities and is performed under solvent- and promoter-free conditions, avoiding the need of high temperature and of any excess of the reagents.



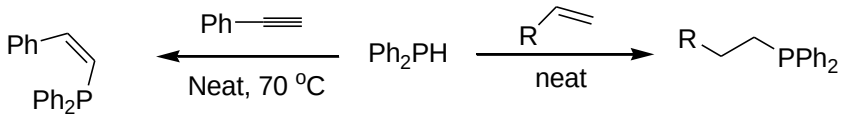
Scheme 1.33

Yu et al. (2011) developed one pot synthesis of substituted tetrahydroimidazo[1,2-*a*]pyridines by three component reactions of heterocyclic ketene aminals, triethoxymethane and nitroalkenes in the absence of catalyst and solvent (Scheme 1.34). High yields, short reaction time and convenient operation are notable advantages of this protocol.



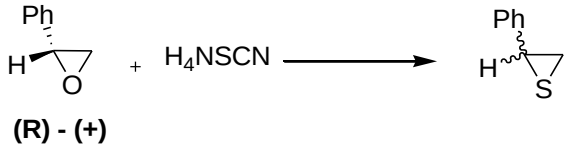
Scheme 1.34

Alonso et al. (2012) demonstrated the feasibility of the uncatalysed direct addition of phosphanes to alkenes in the absence of a solvent (Scheme 1.35). The process found to be highly regioselective, producing all tertiary phosphanes in an anti-Markovnikov fashion. These results emphasize how important it is to perform control experiments in the absence of a catalyst and the crucial role that the concentration effect can play in solvent-free reactions.



Scheme 1.35

Akhlaghinia et al. (2012) reported a simple and efficient method for the conversion of oxiranes to thiiranes using ammonium thiocyanate (NH_4SCN) under solvent- and catalyst-free conditions (Scheme 1.36). These reaction conditions enabled clean and fast conversion of oxiranes to the corresponding thiirane. The advantages of this method are simple procedure, short reaction time, easy workup, and high product yield.



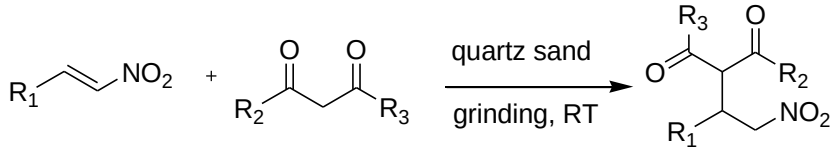
(R) - (+)

Scheme 1.36

Singh and Chowdhury (2012) overviewed the open literature on the development of more sustainable methodologies for the synthesis of acyclic, carbocyclic, and heterocyclic compounds under solvent-free conditions. Further, the developments in multicomponent approaches from 2000 to 2010 on the preparation of compounds with the emphasis on the rationale behind each synthetic procedure and the dependence of the results on a proper selection of reaction conditions have been discussed. Further,

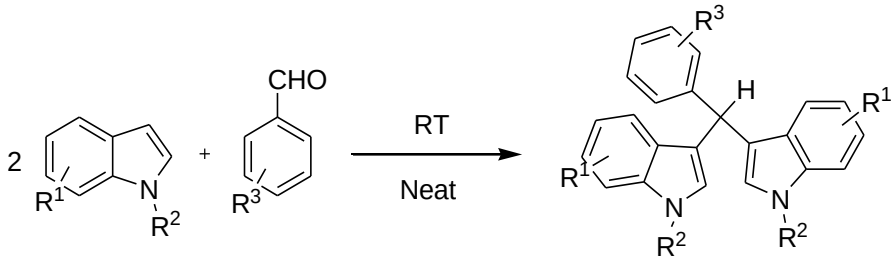
the distinct advantages of solvent-free multicomponent approaches in organic synthesis are discussed. Also, the unique selectivities, which are not contrivable in solution synthesis are highlighted.

Xie et al. (2012) reported an environmentally benign, fast and convenient protocol for the Michael addition of 1,3-dicarbonyl compounds to *β*-nitroalkenes in good to excellent yields by a grinding method under catalyst- and solvent-free conditions (Scheme 1.37). The reactions were performed smoothly between solid–solid or solid–liquid materials at RT with a wide range of reactants. To get pure product, the reaction mixture was filtered through a sand core funnel containing a thin layer of silica instead of column chromatography.



Scheme 1.37

Reddy and Leelavathi (2013) developed one-pot reactions of indole derivatives and aromatic aldehydes under solvent- and catalyst- free conditions for the synthesis of corresponding bis(indolyl)methanes in moderate to high yields (Scheme 1.38). The key features of these reactions are the simple procedure, absence of organic solvent or acid catalyst and easy product separation. The reaction mixture was treated with water and extracted with ethyl acetate (EtOAc) and the organic layer was dried over sodium sulphate and evaporated to get pure products.



Scheme 1.38

1.7 SCOPE AND OBJECTIVES OF THE PRESENT WORK

Development of new methods and the strategic deployment of known methods for the synthesis of complex organic compounds are the major objectives of synthetic organic chemistry. Along with developing new chemicals and improved ways of synthesizing existing chemicals, the greener alternatives are gaining increasing importance in synthetic chemistry to make it environmental friendly. As a result, the significant objectives in modern organic chemistry incorporate the improvement of reaction efficiency, the avoidance of toxic reagents, the reduction of waste and the conscious utilization of resources.

MCR's have been much utilized for the synthesis of diverse highly functionalized molecules via the formation of carbon–carbon and carbon– heteroatom bonds in one pot. The development of several methods for the generation of libraries of structurally complex and diverse small molecules has provided new applications for the "chemical genetic" approach, as well as playing an important part in drug discovery, namely the rapid identification and optimization of biologically active lead compounds.

Based on the above facts and the detailed literature survey, in the present research study, it has been planned to develop solvent- and catalyst-free synthetic routes for the novel heterocycles and already known heterocycles synthesized under conventional routes. The expected synthetic routes would be synthetically efficient, circumvent the limitations of earlier protocols and incorporate most of the green chemistry principles. Also, it has been thought of investigating their mechanistic pathways by reaction monitoring by FTIR or the isolation of stable intermediates. The newly synthesized intermediates in the proposed schemes may be explored for their applications in other research areas.

The main objectives of the present research work are as follows:

- To develop newer, environmental friendly, waste minimizing routes in organic synthesis keeping Green Chemistry principles in mind.

- To carry out the well known reactions like Michael addition, Knoevenagel condensation etc. for the carbon-carbon and carbon-heteroatom bond formation under greener conditions.
- To develop facile and efficient routes for the synthesis of complex heterocyclic compounds via multicomponent approach using readily available starting materials and under environmentally acceptable conditions.
- To study the organic transformations under solvent- and catalyst-free reaction conditions via mechanical activation and/or thermal heating.
- To explore the mechanism of reactions whenever possible through characterization of stable reaction intermediates.
- Characterization of newly synthesized compounds using spectral methods like FTIR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy followed by elemental analysis.
- Single Crystal X-Ray diffraction (SCXRD) studies of selected compounds for elucidation of final three-dimensional structure.

Conclusively, the present research investigation has been aimed at the development of synthetic routes for the formation of carbon-carbon and carbon-heteroatom bond formation in organic and complex heterocyclic compounds with reduced waste generation and improved efficiency. Hence in the present work, five series of transformations have been studied under solvent- and catalyst-free reaction conditions. The **Chapter 2** deals with the solvent- and catalyst-free method for the synthesis of N-substituted *β*-aminobutyric acids by aza-Michael addition of various amines to crotonic acid (series 1). The **Chapter 3** describes the condensation of malononitrile with salicylaldehydes and *o*-aminobenzaldehydes under solvent- and catalyst-free conditions to yield 4*H*-chromenes and quinolines (series 2). Development of green protocol for the synthesis of 3,3'-methanediylbis(4-hydroxy-1-methylquinolin-2(1*H*)-one) (MDBHQ) derivatives and 3-((2-amino-6-oxocyclohex-1-enyl)methyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one derivatives via cascade Knoevenagel-Michael reaction has been described in the **Chapter 4** (Series 3). The **Chapter 5** deals with the one-pot synthesis of variously substituted quinazolines by three-component reactions of 2-aminoaryl ketones, orthoesters and ammonium acetate

under solvent- and catalyst-free reaction conditions (series 4). The **Chapter 6** describes the green and regioselective synthesis of polysubstituted pyrroles under solvent- and catalyst-free condition using 1,3-dicarbonyls, benzoin derivatives and ammonium acetate as building blocks in one-pot (Series 5). Towards the end, **Chapter 7** summarizes the conclusion and outcome of the research work.

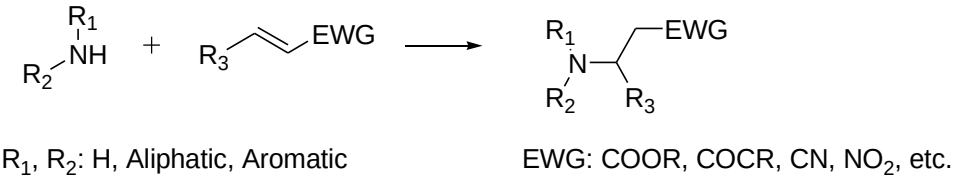
CHAPTER 2

A FACILE, SOLVENT- AND CATALYST-FREE SYNTHESIS OF N-SUBSTITUTED *β*-AMINOBUTYRIC ACIDS BY AZA-MICHAEL ADDITION

This chapter describes an efficient, eco-friendly synthetic route for N-substituted derivatives of β-aminobutyric acid by the aza-Michael addition of various amines to crotonic acid under solvent- and catalyst-free conditions. Further, evaluation of the scope of the protocol with other α,β–unsaturated acids and gram scale synthesis of 3-[(4-methylphenyl)amino]butanoic acid have been discussed.

2.1 INTRODUCTION

Synthesis of *β*-amino acid derivatives has become a field of increasing interest in organic synthesis; due to their interesting pharmacological properties in free form and the functionalized *β*-amino acids are the key components of a variety of bioactive molecules (Azizi and Saidi 2004; Ege and Wanner 2004). N-substituted *β*-Alanines are versatile starting materials for the synthesis of a variety of heterocyclic systems which are biologically important and are also useful in pharmaceuticals (Mickevicius et al. 2004; Vaickelioniene et al. 2005).

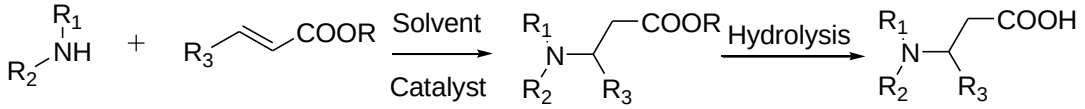


Scheme 2.1: Aza-Michael addition

The conjugate addition of nitrogen nucleophiles to electron deficient *α,β*-unsaturated compounds is known as aza Michael reaction (Scheme 2.1) (Cardillo and Tomasini 1996). Being an atom economical reaction it has been widely used for carbon–nitrogen bond formation (Bartoli et al. 2005).

A number of procedures have been developed for aza- Michael addition using different catalysts in organic solvents (Reboule et al. 2005; Wabnitz and Spencer 2003; Verma et al. 2011; Dhake et al. 2010), water (Surendra et al. 2006; Chaudhuri et al. 2005; Ranu and Banerjee 2007), solvent-free conditions (Das and Chowdhury 2007; Reddy et al. 2008; Saidi et al. 2009), microwave conditions (Escalante et al. 2008; Polshettiwar and Varma 2010), using ionic liquids (Xu et al. 2004; Yang et al. 2006), and under catalyst-free, solvent-free conditions (Choudhary and Peddinti 2011;

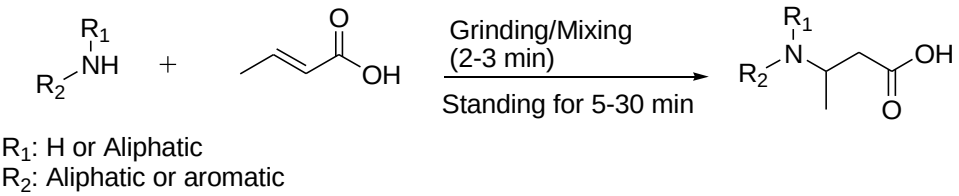
Ranu et al. 2002; Jiang et al. 2011). Michael addition of amines to *α,β*-unsaturated nitriles, esters, amides, ketones and nitro compounds have been extensively studied. However, there are only few reports on Michael addition of amines to *α,β*-unsaturated acids to yield N-substituted derivatives of *β*-Amino acids in the literature (Vaickelioniene et al. 2005; Zilkha and Rivlin 1957; Beresnevicius et al. 2000; Mickevicius and Patupaite 2000). Unfortunately, the reported methods have many disadvantages such as long reaction time, drastic conditions, use of hazardous solvents (pyridine, benzene, toluene), use of catalyst and tedious work-up operations. These aspects are in disagreement with the green chemistry point of view (Sanderson 2011). Also, the usage of amines in reported literature has been restricted to aliphatic and aromatic primary amines. The traditional synthesis of N-substituted *β*–amino acids follows a two step mechanism in which, the first step involves the aza- Michael addition to esters followed by the catalytic hydrolysis to yield the desired product (Scheme 2.2). Hence, with the increase of environmental consciousness in chemical research, the development of greener, more efficient method for the synthesis of *β*–amino acids using wide range of amines including secondary amines as Michael donors in single step is highly desirable and challenging.



R_1, R_2: H, Aliphatic, Aromatic

Scheme 2.2: Traditional two step synthesis of N-substituted *β*–amino acids

Against the background, a very simple and greener procedure has been developed for the synthesis of N-substituted derivatives of *β*–aminobutyric acid by aza-Michael addition of various amines to crotonic acid, an *α,β*–unsaturated acid (Scheme 2.3). The reactions occur in a short time by simple mixing or grinding of stoichiometric amounts of the reactants under solvent-free and catalyst-free conditions. Most of the product obtained in quantitative yield, only few products were purified by column chromatography to remove unconsumed starting materials.



R_1: H or Aliphatic
R_2: Aliphatic or aromatic

Scheme 2.3: Synthesis of N-substituted *β*–aminobutyric acid

2.2 EXPERIMENTAL

2.2.1 General

All chemicals were purchased from commercial suppliers and used without further purification. Melting points were determined with Stuart SMP3 melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo scientific Nicolet Avatar 330 Fourier transform infrared (FTIR) spectrometer by Attenuated Total Reflectance (ATR) method. Nuclear magnetic resonance (NMR) spectra were recorded as a solution in deuterated Dimethyl sulfoxide (DMSO-d_6) or deuterated Methanol (CD_3OD), at 500 MHz (^1H) and 400 MHz (^{13}C) instrument. Chemical shifts (δ) are reported in parts per million (ppm) with tetramethylsilane (TMS) as internal standard. *J*-values are given in Hz. NMR raw data was analysed with the program MestReNova 7.0.0-8331. Mass spectra were performed on Waters Micromass Q-Tof Micro spectrometer with an Electrospray ionization (ESI) source. Elemental analysis was performed using Perkin Elmer, Series II, 2400 analyzer. The X-ray single-crystal diffraction (SCXRD) was performed on the Bruker AXS APEX II system. All experiments were monitored by Thin layer chromatography (TLC), performed on pre-coated silica gel 60 F_{254} plates (Merck). Column chromatography was performed on silica gel (60-120 mesh, Merck) using EtOAc-petroleum ether (boiling range 60-80 ˚C) (PE) as eluent.

2.2.2 Typical procedure for the reaction between amines and *α,β*-unsaturated acids

2.2.2.1 Solid-solid reactions: In an Agate mortar, an amine (2 mmol) and *α,β*-unsaturated acid (2 mmol) were subjected to mechanical grinding for two min at RT. The reaction mixture was then left for standing at RT for completion of the reaction. The reaction was monitored by TLC. Most of the products were obtained with

sufficient purity for spectral analysis. In case of **$S_1$1e,** the reaction was carried out by five min of grinding and 30 min standing at RT to get adduct. The pure solid product **$S_1$3e** was obtained by column chromatography. The column chromatography was performed over Merck Aluminium oxide active (neutral activity I-II) as stationary phase.

2.2.2.2 Solid-liquid reactions: *α,β*-unsaturated acid (2 mmol) and an aniline derivative (2 mmol) were mixed together thoroughly with a spatula for two min in a petri dish to form homogeneous liquid and then the mixture was allowed to stand for five min. The Michael adducts were attained with high purity. The reaction of **$S_1$1f** and crotonic acid was carried out by two min of mixing and 30 min standing at RT, and the pure Michael adduct **$S_1$3f** was obtained by column chromatography.

The reaction between aliphatic amines (2 mmol) and crotonic acid(2 mmol) was carried out by mixing together in a petri dish to form white solid immediately, which liquefied in short time and then the mixture was allowed to stand for five min to get the adduct. Compounds **$S_1$3i,j,k** were scratched with spatula with 0.5 mL of EtOAc to obtain light brownish solid. The wet solid was filtered and washed with EtOAc (2 mL) and then dried under reduced pressure. Compound **$S_1$3k** was low melting and liquid at RT.

All the newly synthesized compounds were characterized by spectral analysis and the spectral data of the final compounds are given below.

3-(phenylamino)butanoic acid ($S_1$3a)

Blood red coloured liquid; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.15 (d, 3H, J = 6.5Hz, Me), 2.21-2.26 (dd, 1H, J_1=7.5Hz, J_2 = 15.5Hz, CHCH_2CO), 2.49-2.54 (dd, 1H, J_1 = 5.5Hz, J_2 = 15Hz, CHCH_2CO), 3.74-3.80 (m, 1H, CH), 5.38 (br s, 1H, NH), 6.50-6.56 (m, 3H, ArH), 7.05-7.08 (t, 2H, J = 8Hz, ArH), 12.16 (br s, 1H, COOH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 20.2, 41.0, 44.9, 112.5, 115.7, 128.9, 147.6, 172.9; IR (Neat, cm^{-1}): 3372 (NH), 3046 (CH $_{arom.}$), 2969 ($CH_{aliph.}$), 2910 ($CH_{aliph.}$), 2666br (OH), 1704 (C=O), 1497 (C=C), 1250 (C-O), 1189 (C-N); Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.24; H, 7.48; N, 7.89; ESI MS (m/z) = 202.1 $(M+Na)^+$, 180.1$(M+H)^+$, 120.1$(M-CH_2COOH)^+$.

3-[(4-methylphenyl)amino]butanoic acid ($S_1$3b)

Blood red coloured liquid; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.12 (d, 3H, J = 6Hz, Me), 2.14 (s, 3H, ArCH_3), 2.17-2.22 (dd, 1H, J_1=8Hz, J_2=15Hz, CHCH_2CO), 2.47-2.52 (m, 1H, CHCH_2CO), 3.69-3.75 (m, 1H, CH), 5.28 (br s, 1H, NH), 6.46 (d, 2H, J = 8.5Hz, ArH), 6.88 (d, 2H, J = 8Hz, ArH), 12.05 (br s, 1H, COOH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 20.5, 20.6, 41.5, 45.8, 113.3, 124.7, 129.9, 145.8, 173.5; IR (Neat, cm^{-1}): 3365 (NH), 2970 ($CH_{aliph.}$), 2921 ($CH_{aliph.}$), 2869 ($CH_{aliph.}$), 2664br (OH), 1706 (C=O), 1513 (C=C), 1246 (C-O), 1191 (C-N) ; Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.53; H, 7.97; N, 7.31; ESI MS (m/z) = 216.1 $(M+Na)^+$, 194.1$(M+H)^+$, 134.1$(M-CH_2COOH)^+$.

3-{[4-(propan-2-yl)phenyl]amino}butanoic acid ($S_1$3c)

Blood red coloured liquid; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.12 (d, 9H, J = 7Hz, Me), 2.18-2.23 (dd, 1H, J_1 = 7.5Hz, J_2 = 15Hz, CHCH_2CO), 2.47-2.52 (dd, 1H, J_1 = 6Hz, J_2 = 15Hz CHCH_2CO), 2.69-2.74 (m, 1H, ArCHMe$_2$) 3.69-3.76 (m, 1H, CH), 5.17 (br s, 1H, NH), 6.48 (d, 2H, J = 8.5Hz, ArH), 6.94 (d, 2H, J = 8.5Hz, ArH), 12.11 (br s, 1H, COOH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 20.2, 24.2, 32.5, 41.1, 45.3, 112.7, 126.6, 135.7, 145.6, 173.0; IR (Neat, cm^{-1}): 3365 (NH), 2961 ($CH_{aliph.}$), 2925 ($CH_{aliph.}$), 2851 ($CH_{aliph.}$), 2671br (OH), 1696 (C=O), 1515 (C=C), 1282 (C-O), 1193 (C-N); ESI MS (m/z) = 266.1 (M+HCOOH), 244.1 $(M+Na)^+$, 222.1$(M+H)^+$, 162.1$(M-CH_2COOH)^+$; Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.73; H, 8.81; N, 6.42.

3-[(4-methoxyphenyl)amino]butanoic acid ($S_1$3d)

White Solid, mp 102 ˚C; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.11 (d, 3H, J = 6.5Hz, Me), 2.16-2.21 (dd, 1H, J_1 = 7.5Hz, J_2 = 15Hz, CHCH_2CO), 2.46-2.50 (dd, 1H, J_1 = 6Hz, $J2$=15Hz, CHCH_2CO), 3.63 (s, 3H, OCH_3), 3.65-3.71 (m, 1H, CH), 5.14 (br s, 1H, NH), 6.52 (d, 2H, J = 9Hz, ArH), 6.71 (d, 2H, J = 9Hz, ArH), 12.04 (br s, 1H, COOH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 20.2, 41.1, 45.9, 55.3, 114.0, 114.7, 141.7, 150.8, 173.0; IR (Neat, cm^{-1}): 3216 (NH), 2993 ($CH_{aliph.}$), 2960 ($CH_{aliph.}$), 2904 ($CH_{aliph.}$), 1684 (C=O), 1504 (C=C), 1244 (C-O), 1169 (C-N); ESI MS (m/z) = 232.1

$(M+Na)^+$, 210.1$(M+H)^+$, 150.1$(M-CH_2COOH)^+$; Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.18; H, 7.18; N, 6.62.

3-[(4-chlorophenyl)amino]butanoic acid ($S_1$3e)

Bownish Solid, mp 62 ˚C; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.14 (d, 3H, J = 6.5Hz, Me), 2.23-2.27 (dd, 1H, J_1 = 7.5Hz, J_2 = 15Hz, CHCH_2CO), 2.47-2.50 (dd, 1H, J_1 = 6Hz, J_2 = 15Hz, CHCH_2CO), 3.73-3.74 (m, 1H, CH), 5.66 (br s, 1H, NH), 6.54-6.58 (m, 2H, ArH), 7.05-7.08 (m, 2H, ArH), 12.19 (br s, 1H, COOH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 20.1, 40.9, 45.1, 113.8, 118.8, 128.6, 148.5, 172.7; IR (Neat, cm^{-1}): 3371 (NH), 3028 ($CH_{arom.}$), 2971 ($CH_{aliph.}$), 2925 ($CH_{aliph.}$), 2666br (OH), 1702 (C=O), 1497 (C=C), 1248 (C-O), 1186 (C-N), 1085 (C-Cl); ESI MS (m/z) = 214.1$(M+H)^+$, 154.0$(M-CH_2COOH)^+$; Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.33; H, 5.72; N, 6.63.

3-[methyl(phenyl)amino]butanoic acid ($S_1$3f)

Blood red coloured liquid; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.09 (d, 3H, J = 6.5Hz, Me), 2.40-2.44 (dd, 1H, J_1 = 7Hz, J_2 = 15Hz, CHCH_2CO), 2.47-2.52 (dd, 1H, J_1 = 7.5Hz, J_2 = 15Hz, CHCH_2CO), 2.65 (s, 3H, NCH_3), 4.28-4.35 (m, 1H, CH), 6.63 (t, 1H, J = 7.5Hz, ArH), 6.79 (d, 2H, J = 8Hz, ArH), 7.15-7.18 (dd, 2H, J_1 = 7.5Hz, J_2 = 8.5Hz, ArH) 12.12 (br s, 1H, COOH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 21.8, 35.3, 44.1, 56.2, 118.7, 121.8, 134.1, 155.1, 178.10; IR (Neat, cm^{-1}): 3039 ($CH_{arom.}$), 2969 ($CH_{aliph.}$), 2928 ($CH_{aliph.}$), 2814 ($CH_{aliph.}$), 2667br (OH), 1701 (C=O), 1497 (C=C), 1283 (C-O), 1205 (C-N); Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.58; H, 7.99; N, 7.34.

3-(pyridin-3-ylamino)butanoic acid ($S_1$3g)

Blood red coloured liquid; ^{1}H NMR (500 MHz, MeOD) δ: 1.64 (d, 3H, J = 7Hz, Me), 2.81-2.87 (m, 2H, CHCH_2CO), 4.94-4.99 (m, 1H, CH), 7.54-7.56 (dd, 1H, J_1 = 2.5Hz, J_2 = 8Hz, ArH), 7.58-7.61 (dd, 1H, J_1 = 5.5Hz, J_2 = 8.5Hz, ArH), 8.086 (d,1H, J = 5.5Hz, ArH), 8.51 (t, 1H, J = 2Hz, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 21.4, 44.8, 66.7, 126.7, 127.1, 127.5, 129.0, 148.6, 171.4;` IR (Neat, cm^{-1}): 3328br,vs (NH), 1630 (C=O), 1568 (C=N), 1508 (C=C), 1384 (C-O), 1152 (C-N); ESI MS (m/z) =

361.2 $(2M+H)^+$, 181.1$(M+H)^+$; Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 59.92; H, 6.76; N, 15.64.

3-(pyridin-4-ylamino)butanoic acid ($S_1$3h)

White crystals, mp 221˚C; ^{1}H NMR (500 MHz, MeOD) δ: 1.53 (d, 3H, *J* = 7Hz, Me), 2.63-2.71 (m, 2H, CH*CH*$_2$CO), 4.65-4.72 (m, 1H, CH), 6.77-6.79 (dt, 2H, J_1 = 3Hz, J_2 = 7.5Hz, ArH), 8.11-8.14 (dt, 2H, J_1 = 3Hz, J_2 = 7.5Hz, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 21.1, 45.7, 64.4, 110.7, 142.6, 160.9, 176.6; IR (Neat, cm^{-1}): 3472 (NH), 3060br, vs (OH), 1648 (C=O), 1571 (C=N), 1520 (C=C), 1389 (C-O), 1167 (C-N); ESI MS (m/z) = 203.1 $(M+Na)^+$, 181.1$(M+H)^+$; Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.04; H, 6.79; N, 15.67.

3-(benzylamino)butanoic acid ($S_1$3i)

White Solid, mp 169 ˚C (lit. 186-187 ˚C)[1]; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.13 (d, 3H, *J* = 6.5Hz, Me), 2.12-2.17 (dd, 1H, J_1 = 8Hz, J_2 = 16Hz, CH*CH*$_2$CO), 2.24-2.29 (dd, 1H, J_1 = 5Hz, J_2 = 16Hz, CH*CH*$_2$CO), 3.06-3.09 (m, 1H, CH) 3.48 (br s, 2H, NH), 3.83, 3.93 (2d, 2H, *J* = 13Hz, Ar*CH*$_2$NH), 7.30-7.42 (m, 5H, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 18.3, 48.0, 49.8, 127.5, 128.4, 128.5, 137.0, 173.2; IR (Neat, cm^{-1}): 3053 ($CH_{arom.}$), 2973 ($CH_{aliph.}$), 2930 ($CH_{aliph.}$), 2814 ($CH_{aliph.}$), 2794br, 2365 (NH), 1554 (COO^-_{asym}), 1367 (COO^-_{sym}), 1067 (C-N); ESI MS (m/z) = 216.1 $(M+Na)^+$, 194.1$(M+H)^+$, 134.1$(M-CH_2COOH)^+$; Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.29; H, 7.68; N, 7.43.

3-(cyclopropylamino)butanoic acid ($S_1$3j)

Light brownish solid, mp 104 ˚C; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.34-0.36 (m, 2H, CH_2), 0.46-0.51 (m, 2H, CH_2), 1.09 (d, 3H, *J* = 6.5Hz, Me), 2.13-2.27 (m, 3H, CH*CH*$_2$CO and NH*CH*(C_2H_4)), 2.24-2.29 (dd, 1H, J_1 = 5Hz, J_2 = 16Hz, CH*CH*$_2$CO), 3.05-3.11 (m, 1H, CH), 5.18 (br s, 2H, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 4.6, 5.4, 19.0, 27.2, 40.1, 50.9, 173.4; IR (Neat, cm^{-1}): 3369br, 2737br (NH), 2973 ($CH_{aliph.}$), 2978 ($CH_{aliph.}$), 1542 (COO^-_{asym}), 1377 (COO^-_{sym}), 1037 (C-N); ESI MS (m/z) = 166.1 $(M+Na)^+$, 144.1$(M+H)^+$; Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.86; H, 9.28; N, 10.04.

3-{[2-(morpholin-4-yl)ethyl]amino}butanoic acid ($S_1$3k)

Orange liquid; ^{1}H NMR (500 MHz, MeOD) δ: 1.32 (d, 3H, *J* = 7Hz, Me), 2.33-2.39 (dd, 1H, J_1 = 9Hz, J_2 = 17Hz, CH*C*H_2CO), 2.46-2.67 (m 7H), 3.09-3.13, 3.14-3.20 (2m, 2H), 3.39-3.46 (m, 1H, CH), 3.69-3.76 (m, 4H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 17.4, 50.8, 52.9, 53.1, 54.9, 66.0, 66.1, 173.3; IR (Neat, cm^{-1}): 3383br, 2358br, (NH), 2963 ($CH_{aliph.}$), 2867 ($CH_{aliph.}$), 2819 ($CH_{aliph.}$), 1575 (COO^-_{asym}), 1389 (COO^-_{sym}), 1246 (C-O-C $_{asym.}$), 1110 (C-N), 1023 (C-O-C $_{sym.}$); ESI MS (m/z) = 239.1 $(M+Na)^+$, 217.1$(M+H)^+$, 157.1$(M-CH_2COOH)^+$, 114.1 $(M-CH_2NHCH(CH_3)CH_2COOH)^+$; Anal. Calcd for $C_{10}H_{20}N_2O_3$: C, 55.53; H, 9.32; N, 12.95. Found: C, 55.70; H, 9.46; N, 13.23.

3-(morpholin-4-yl)butanoic acid ($S_1$3l)

Orange liquid; ^{1}H NMR (500 MHz, DMSO-d_6, D_2Oexch) δ: 1.17 (d, 3H, *J* = 6.5Hz, Me), 2.25-2.29 (dd, 1H, J_1 = 6Hz, J_2 = 16.5Hz, CH*C*H_2CO), 2.39-2.45 (dd, 1H, J_1 = 8.5Hz, J_2 = 16.5Hz, CH*C*H_2CO), 2.98-2.99 (br, d 2H), 30.9-3.12 (m, 2H), 3.36-3.40 (m, 1H, CH), 3.78-3.86 (m, 4H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 14.1, 37.3, 47.8, 56.0, 66.2, 66.3, 173.4; IR (Neat, cm^{-1}): 3373br, vs (NH), 1542 (COO^-_{asym}), 1382 (COO^-_{sym}),1293 (C-O-C $_{asym.}$), 1103 (C-N), 1068 (C-O-C $_{sym.}$); ESI MS (m/z) = 196.1 $(M+Na)^+$, 174.1$(M+H)^+$, 114.1$(M-CH_2COOH)^+$; Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.34; H, 8.80; N, 8.23.

3-(piperidin-1-yl)butanoic acid ($S_1$3m)

Orange liquid; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 0.99 (d, 3H, *J* = 6.5Hz, Me), 1.45-1.49 (m, 2H), 1.53-1.64 (m, 3H), 2.05-2.09 (dd, 1H, J_1 = 5Hz, J_2 = 16.5Hz, CH*C*H_2CO), 2.31-2.37 (dd, 1H, J_1 = 10.5Hz, J_2 = 16.5Hz, CH*C*H_2CO), 2.55-2.59 (m, 2H), 2.78-2.83 (m, 2H), 3.07-3.14 (m, 1H, CH), 3.51 (br s, 1H NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 13.1, 22.9, 24.7, 36.3, 47.3, 57.3, 173.5; IR (Neat, cm^{-1}): 3379br, vs (NH), 2949 ($CH_{aliph.}$), 2864 ($CH_{aliph.}$), 1579 (COO^-_{asym}), 1378 (COO^-_{sym}), 1020 (C-N); ESI MS (m/z) = 194.1 $(M+Na)^+$, 172.1$(M+H)^+$, 112.1$(M-CH_2COOH)^+$; Anal. Calcd for $C_9H_{17}NO_2$: C, 63.13; H, 10.01; N, 8.18. Found: C, 62.96; H, 9.89; N, 8.27.

Table 2.1: Crystal data and measurement details of compound **$S_1$3j**

Crystal data [CCDC No. 938804]	
Empirical formula	C_7 H_{15} N O_3
Formula weight	161.2
Crystal size (mm)	0.4 x 0.3 x 0.2
Crystal system	Monoclinic
Space group	P21/n
a (Å); b (Å); c (Å)	9.6886 (5); 8.1903 (4); 10.9598 (6)
α (˚); β (˚); γ (˚)	90.00; 99.022 (3); 90.00
Volume (Å^3)	858.93 (8)
Z	4
Crystal density, g/cm^3	1.246
F(000)	312
Absorption coefficient	0.096
Temperature (T)	296 (2)
Radiation wavelength	0.71073
Radiation type	MoKα
Radiation source	Fine-focus sealed tube
Radiation monochromator	Graphite
h_{min}; k_{min}; l_{min}	-12; -10; -13
h_{max}; k_{max}; l_{max}	12; 10; 13
R-Factor (%)	3.44

The ^{1}H NMR, ^{13}C NMR, ESI MS spectra of representative compound **$S_1$3h** are shown below.

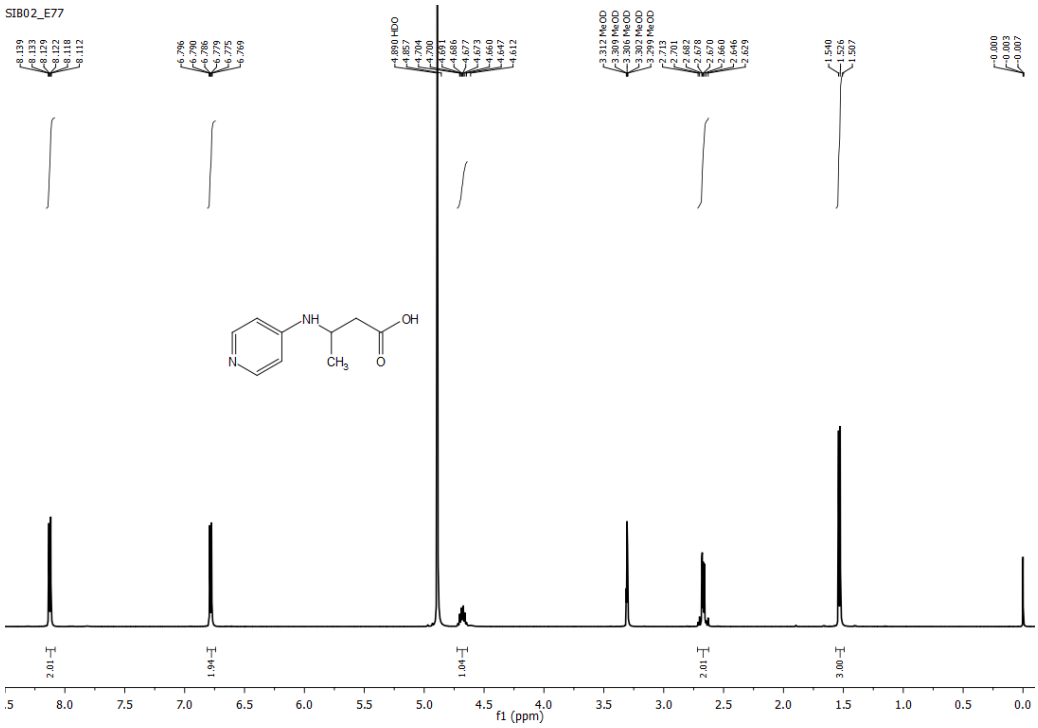


Fig. 2.1: ^{1}H NMR spectrum of **$S_1$3h**

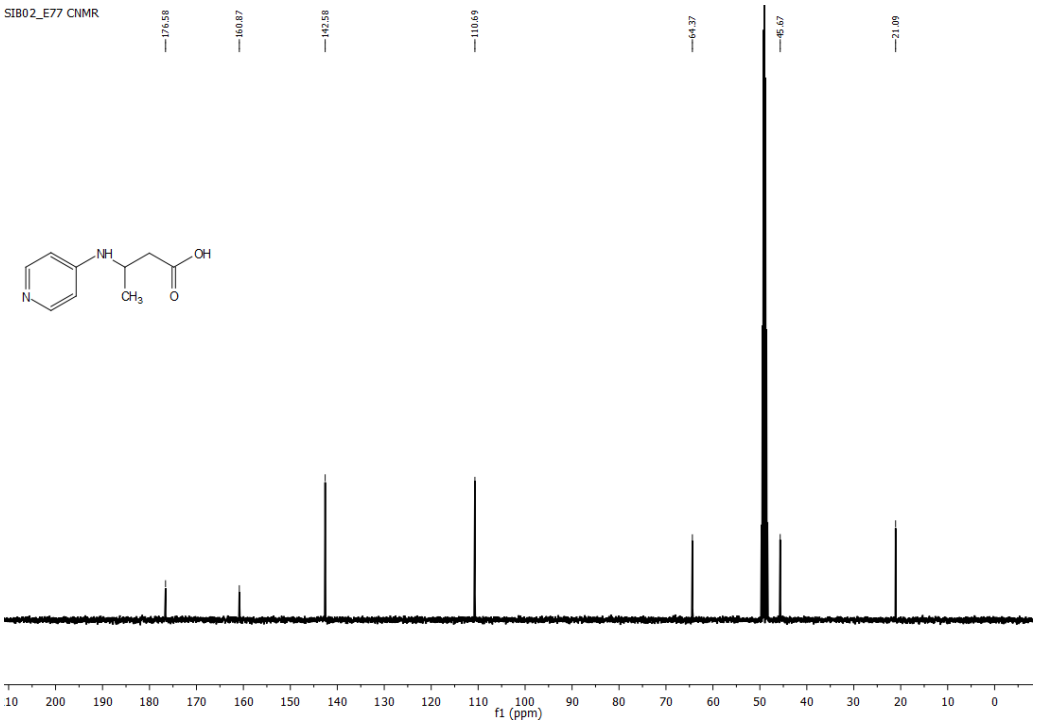


Fig. 2.2: ^{13}C NMR spectrum of **$S_1$3h**

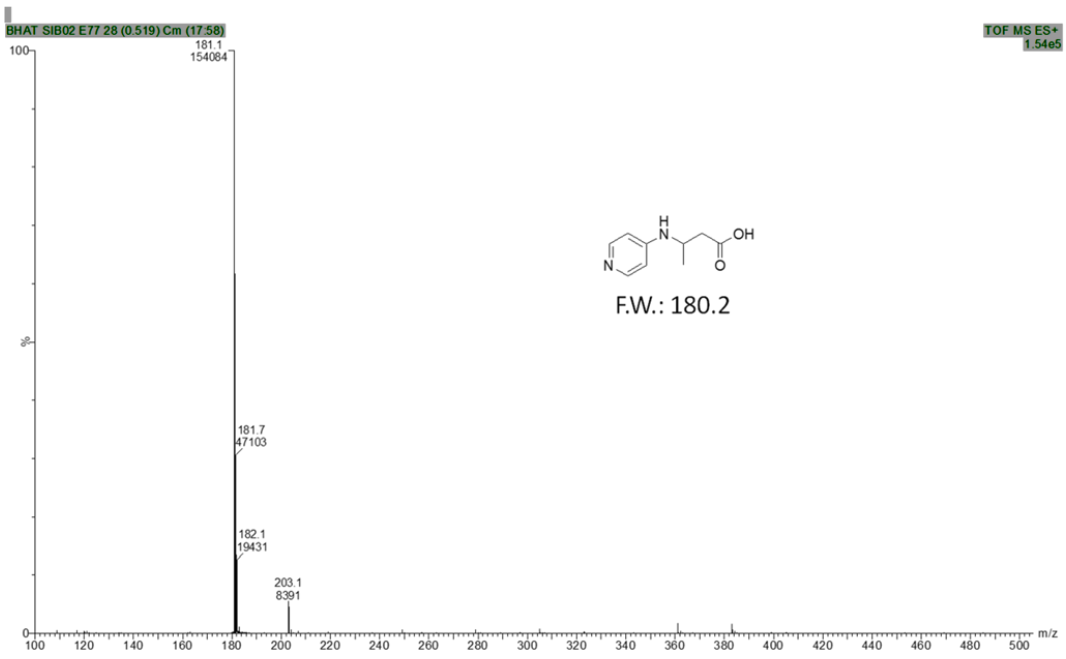


Fig. 2.3: ESI MS spectrum of **$S_1$3h**

2.3 RESULTS AND DISCUSSION

Since the preliminary experiments aimed to obtain *β*–aminobutyric acid via aza-Michael addition of amines to crotonic acid by mechanical activation, the reaction between solid-solid and solid-liquid reactants were carried out. In solid-solid reactants, equimolar amounts of amines and crotonic acid were taken in an Agate mortar and ground for two min at RT. The starting materials resulted in formation of a liquid melt completely during grinding. The homogeneous liquid thus formed was allowed to stand for another 5-30 min for completion of the reaction. In case of liquid-solid interactions, the reactants were taken in pre-weighed petri dish and mixed with spatula for two min at RT and then mixture was allowed to stand for 5-30 min. The reaction completion was monitored by TLC. The purity of the product obtained was good enough for spectroscopic analysis in most of the cases. In few cases small amount of starting materials were remained unreacted along with the product, even after prolonged standing time. Only for those reactions the products were purified by column chromatography. The product formation was confirmed by FTIR, ^{1}H and ^{13}C NMR analysis and further, **$S_1$3j** was selected as representative compound and the structure was unequivocally confirmed by the SCXRD studies (Fig. 2.4).

In order to delineate the scope of the current green protocol, a series of N-substituted *β*–aminobutyric acid were synthesized by reacting crotonic acid with wide variety of amines. The reaction with aromatic, aliphatic substituted primary as well as secondary amines and pyridyl amines has been carried out to study the affect of amine nucleophilicity. The results are summarized in Table 2.2.

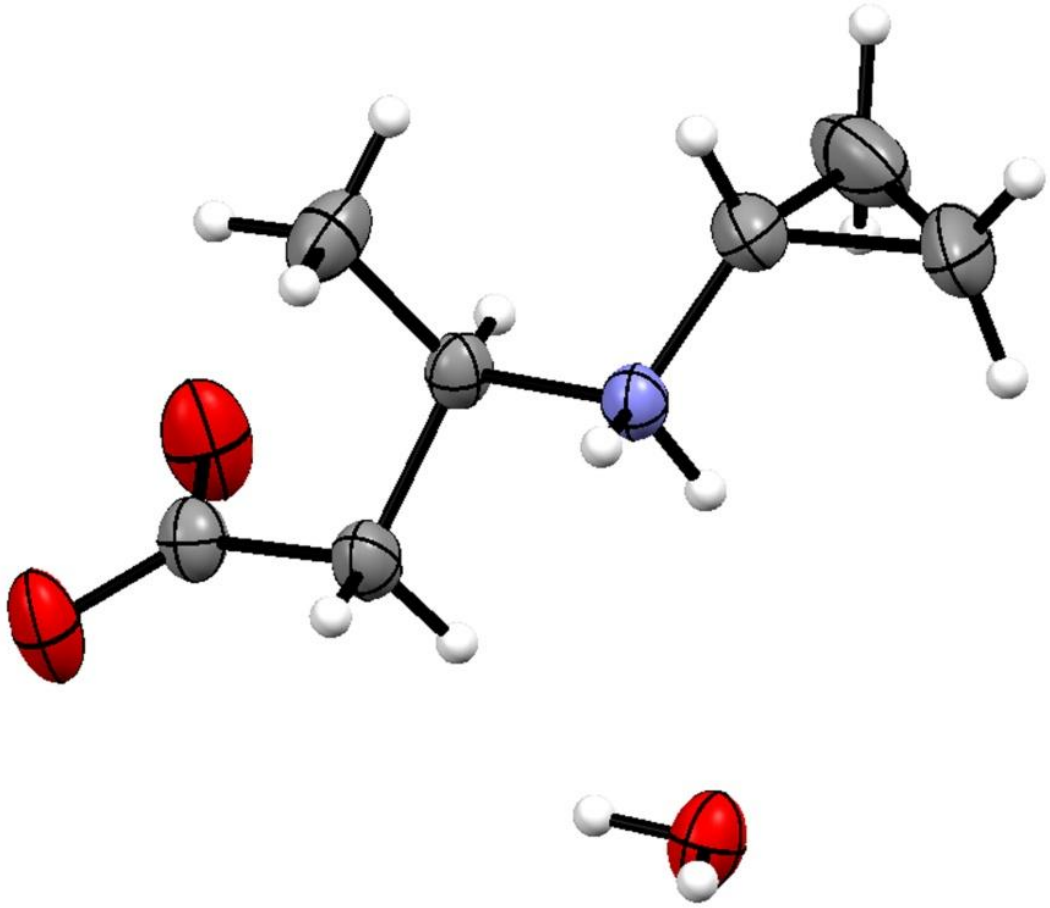
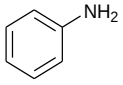
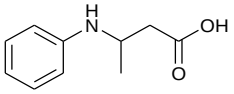
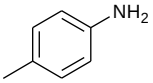
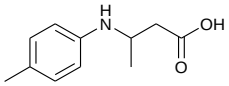
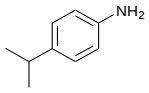
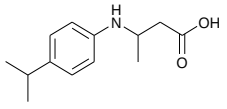
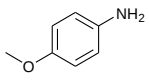
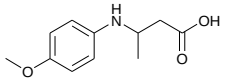
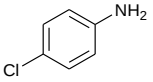
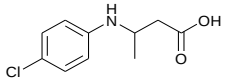


Fig. 2.4: ORTEP (50% probability) diagram of the crystal structure of **$S_1$3j** obtained as hydrate

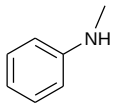
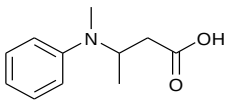
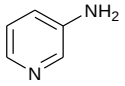
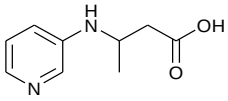
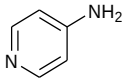
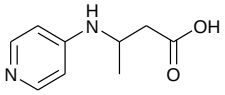
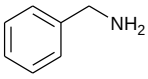
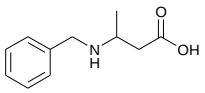
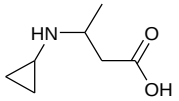
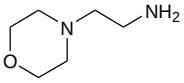
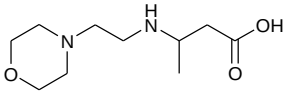
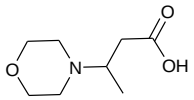
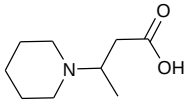
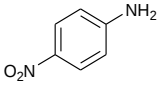
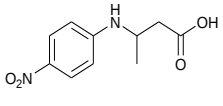
Initial study was carried out by the reaction of crotonic acid with aniline (Table 2.2 entry **1**), which yielded the Michael adduct quantitatively without using any auxiliary substances. It was found that the nature of the substitution on the anilines had great influence on the reaction. As expected, the reaction proceeded faster with electron rich anilines. Weak electron donating alkyl substitution at *p*-position (Table 2.2 entry

2, 3) didn't make much difference in the reaction progress as compared to aniline. However, the Michael adduct obtained quantitatively within two min when crotonic acid was reacted with *p*-anisidine (Table 2.2, entry **4**). The reaction with 4-chloroaniline (Table 2.2, entry **5**), resulted in comparatively low yield and small amount of starting materials were remain unreacted even after prolonged reaction time. On the other hand, only unreacted starting materials were observed when 4-nitroaniline (Table 2.2 entry 14) was used as Michael donor. This may be attributed to the poorer nucleophilicity of aniline due to the presence of strong electron withdrawing group (Jiang et al. 2011). The reaction of crotonic acid with N-methyl aniline (Table 2.2, entry **6**), a secondary aromatic amine was slower and incomplete. This low reactivity of secondary amine as compared to primary amine may be due to the steric hindrance in the later case. Surprisingly, aminopyridines (Table 2.2, entry **7, 8**), which generally protonate on the ring due to the existence of amino tautomeric form (Joule and Mills, 2007) could also able to yield Michael adduct efficiently by present green protocol.

Table 2.2: Synthesis of N-substituted derivatives of *β*-aminobutyric acid

Entry	Amines	Method[a]/Time (min)	*β*-aminobutyric acid	%Yield [b]
1	**$S_1$1a** 	Method B/2+10	**$S_1$3a** 	Quantitative
2	**$S_1$1b** 	Method A/2+10	**$S_1$3b** 	Quantitative
3	**$S_1$1c** 	Method B/2+10	**$S_1$3c** 	Quantitative
4	**$S_1$1d** 	Method B/2+0	**$S_1$3d** 	Quantitative
5	**$S_1$1e** 	Method A/5+30	**$S_1$3e** 	88%[c]

Contd.

6	**$S_1$1f** 	Method B/2+30	**$S_1$3f** 	82%[c]
7	**$S_1$1g** 	Method A/2+5	**$S_1$3g** 	Quantitative
8	**$S_1$1h** 	Method A/2+0	**$S_1$3h** 	Quantitative
9	**$S_1$1i** 	Method B/2+5	**$S_1$3i** 	97%
10	**$S_1$1j** 	Method B/2+0	**$S_1$3j** 	99%
11	**$S_1$1k** 	Method B/2+5	**$S_1$3k** 	94%
12	**$S_1$1l** 	Method B/2+10	**$S_1$3l** 	Quantitative
13	**$S_1$1m** 	Method B/2+10	**$S_1$3m** 	Quantitative
14	**$S_1$1n** 	Method A/10+60	**S13n** 	00

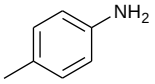
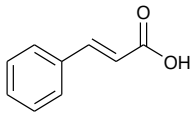
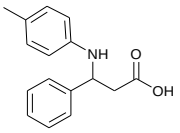
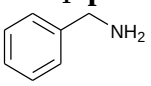
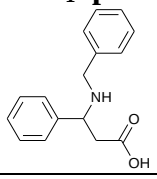
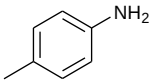
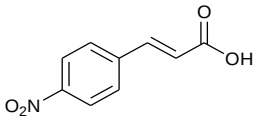
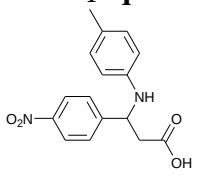
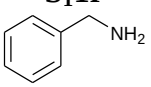
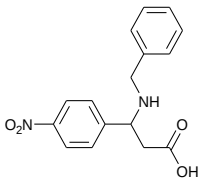
[a]Method A: grinding of reactants with mortar and pestle followed by allowing the mixture for standing; Method B: mixing the reactants with spatula in a petri dish followed by allowing the mixture for standing. [b]Yield of pure product. [c]Pure product obtained by column chromatography.

Inspired by the successful attempt with aromatic amines, the current green protocol was further extended to the reaction of crotonic acid with more basic aliphatic

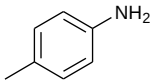
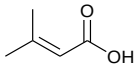
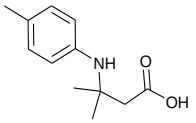
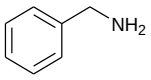
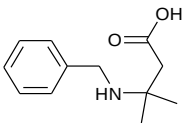
primary and secondary amines. An exothermic reaction started immediately after mixing equimolar ratio of the reactants and formed white solid which further liquefied at RT. Primary aliphatic amines (Table 2.2 entry **9, 10, 11**) solidified after scratching the viscous liquid with few drops of EtOAc in ice cold condition. The solid product was then filtered and washed with minimum quantity of EtOAc to get pure Michael adduct in excellent yield. However the reaction with secondary aliphatic amines (Table 2.2, entry **12, 13**) resulted in quantitative yield without any purification.

In order to evaluate the applicability of the present methodology to other *α,β*-unsaturated acids, Michael addition of *p*-toluidine and benzylamine (chosen as representatives for aromatic and aliphatic amines) was carried out with various other *α,β*-unsaturated acids (Table 2.3).

Table 2.3: List of reactions that were failed to get product under present protocol

Entry	Amines	*α,β*-unsaturated acid	*β*-amino acid	%Yield
1	**$S_1$1o** 		**$S_1$3o** 	00[a]
2	**$S_1$1p** 		**$S_1$3p** 	00[b]
3	**$S_1$1q** 		**$S_1$3q** 	00 [a]
4	**$S_1$1r** 		**$S_1$3r** 	00 [b]

Contd.

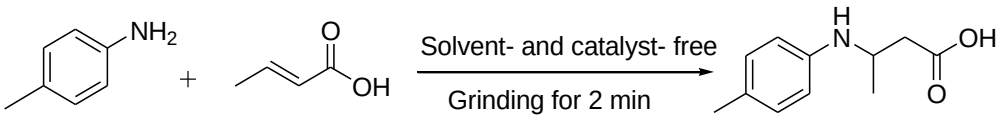
5	**$S_1$1s** 		**$S_1$3s** 	00 [a]
6	**$S_1$1t** 		**$S_1$3t** 	00 [b]

[a]Method A: grinding of reactants with mortar and pestle followed by allowing the mixture for standing; [b]Method B: mixing the reactants with spatula in a petri dish followed by allowing the mixture for standing.

The mechanochemical grinding of *p*-toluidine with cinnamic acid (Table 2.3, entry **1**) resulted in instantaneous melt formation. However, the Michael adduct was not formed even after 48 h of standing. Similar observation was found when benzylamine was reacted with cinnamic acid (Table 2.3, entry **2**). Further, the present solvent- and catalyst-free protocol was examined with more electron deficient *trans*-4-nitrocinnamic acid. The presence of electron withdrawing nitro-group increases the reactivity of *α*,*β*-unsaturated carbonyls towards Michael addition. However, the present method fails to yield the Michael adduct when the reaction of *p*-toluidine and benzylamine was carried out with *trans*-4-nitrocinnamic acid (Table 2.3, entries **3** and **4**). This limitation of the present grinding protocol towards *α*,*β*-unsaturated acids containing aromatic substitution at *β*-carbon may be attributed to the poorer reactivity of *α*,*β*-unsaturated acids induced by the steric factor and resonance stability due to the presence of phenyl group at the *β*-carbon of acid. Further, the reaction of *p*-toluidine and benzylamine with 3,3-dimethylacrylic acid (Table 2.3, entries **5** and **6**) fails to yield corresponding Michael adducts. The steric hindrance caused by the dimethyl group present on *β*-carbon may restrict further addition to 3,3-dimethylacrylic acid.

To further explore the potential of this protocol for industrial application, a gram scale synthesis of 3-[(4-methylphenyl)amino]butanoic acid (**$S_1$3b**) was carried out in an Agate mortar and pestle (Scheme 2.4). Stoichiometric amounts of **$S_1$1b** (20 mmol)

and crotonic acid (20 mmol) were ground for 2 min and allowed to stand for 15 min. The desired product was obtained quantitatively without using any auxiliaries.



2.14 g 1.72 g 15 min standing, quantitative yield

Scheme 2.4: Gram scale synthesis of 3-[(4-methylphenyl)amino]butanoic acid (**$S_1$3b**)

2.4 CONCLUSION

In conclusion, a simple, atom economical, highly efficient, environmentally benign procedure for the synthesis of N-substituted *β*-aminobutyric acids has been developed using grinding induced solvent- and catalyst-free conditions. The developed methodology is applicable for wide variety of amines to obtain the desired products in excellent yield. Nevertheless, the present grinding protocol fails to yield Michael adduct with *α,β*-unsaturated acids with aromatic substitution at *β*-position and sterically hindered *α,β*-unsaturated acids. The reaction proceeded efficiently even in gram scale without any decrease in product yield. Auxiliary free conditions, short reaction time, less energy requirement, operational simplicity, high atom economy, and quantitative yield are the main features of the present procedure.

CHAPTER 3

CONDENSATION OF MALONONITRILE WITH SALICYLALDEHYDES AND *O*-AMINOBENZALDEHYDES: SOLVENT- AND CATALYST-FREE SYNTHESIS OF 4*H*-CHROMENES AND QUINOLINES

In this chapter, the solvent- and catalyst-free reaction of malononitrile with salicylaldehydes and o-aminobenzaldehydes has been described. Further, the reaction pathway, versatility of the current green protocol has been discussed.

3.1 INTRODUCTION

Knoevenagel condensation of aldehyde with active methylene compound is one of the classical methods for olefin synthesis. Although the Knoevenagel condensation is well known since 1898 (Knoevenagel 1898), several advantages like reaction simplicity, mild condition, application in synthesizing biologically privileged compounds made it incessant field of research among organic chemists. Owing to the importance of this reaction, several green approaches have been developed under solvent-free conditions (Ren et al. 2002), on solid support (Wada and Suzuki 2003), promoted by infrared (Delgado et al. 1995; Obrador et al. 1998), ultrasonic (Shindalkar et al. 2005), microwave (Sabitha et al. 1998; Mitra et al. 1999; Bandgar et al. 1999; Biradar and Sasidhar 2011) electrochemical (Feroci et al. 2007) and thermal heating (Rao and Venkataratnam 1991) conditions. Kaupp et al. (2003) conducted quantitative Knoevenagel condensation reactions of aldehydes with various active methylene components in the solid state and melt condition. Inspired by their work, Trotzki et al. (2008a; 2008b) studied Knoevenagel condensation by reacting series of aldehydes with malononitrile under solvent and waste free conditions and at ambient temperature. The resulting product by reacting malononitrile with salicylaldehyde was reported as benzofuran-2-carbonitrile through intramolecular cyclization followed by elimination of hydrocyanic acid. However, the structure of the product was assigned with inadequate spectroscopic data. The detailed literature survey reveals that, it could be plausible to synthesize various chromene derivatives (Fig. 3.1) (Yadav et al. 2007; Vaghei et al. 2011; Sakurai et al. 1972; Fringuelli et al. 2003; Elinson et al. 2006; O'Callaghan et al. 1995; Costa et al. 2008) by delicate control of the experimental conditions in conventional reaction of salicylaldehyde with malononitrile.

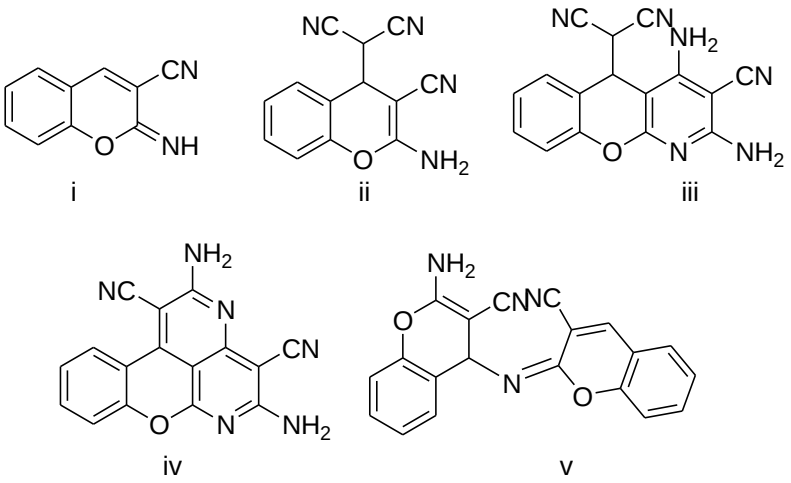


Fig. 3.1: Various products observed in the reaction of salicylaldehyde and malononitrile under conventional methods

With the aim to elucidate the exact structure of the product and to determine reaction pathway, the solvent- and catalyst-free reaction of salicylaldehyde and malononitrile was reinvestigated under mechanochemical mixing, thermal heating and direct crystallization process. The structure of the product was fully characterized by spectroscopic measurements (FTIR, ^{1}H and ^{13}C NMR, MS) and it was further confirmed with reported literature (Yadav et al. 2007; Vaghei et al. 2011; Sakurai et al. 1972; Fringuelli et al. 2003; Elinson et al. 2006; O'Callaghan et al. 1995; Costa et al. 2008). Further, in order to expand the scope of the developed methodology eleven derivatives of *o*-hydroxybenzaldehyde and three *o*-aminobenzaldehydes were reacted with malononitrile to obtain 4*H*-chromene derivatives and quinoline derivatives respectively.

3.2 EXPERIMENTAL

3.2.1 General

All chemicals were purchased from commercial suppliers and used without further purification. Melting points were determined with Stuart SMP3 melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo scientific Nicolet Avatar 330 FTIR spectrometer by ATR method. NMR spectra were recorded as a solution in DMSO-d_6 at 500 MHz (^{1}H) and 400 MHz (^{13}C) instrument. Chemical shifts (δ) are reported in ppm with TMS as internal standard. *J*-values are given in Hz.

NMR raw data was analysed with the program MestReNova 7.0.0-8331. Mass spectra were performed on Waters Micromass Q-Tof Micro spectrometer with an ESI source. Elemental analysis was performed using Perkin Elmer, Series II, 2400 analyzer. The SCXRD analysis was performed on the Bruker AXS APEX II system. X-ray powder diffraction patterns were recorded on an XPERT Philips (Cu Kα radiation) diffractometer. All experiments were monitored by TLC, performed on pre-coated silica gel 60 F_{254} plates (Merck).

3.2.2 General Procedure for the preparation of $S_2$3

Mechanochemical grinding: In an Agate mortar, an aldehyde (2 mmol) and malononitrile (4 mmol) were subjected to mechanical grinding/mixing (in case of liquid aldehydes) for five min at RT. The homogeneous liquid reaction mixture was then allowed to stand at RT for the times given in Table 3.3. Solidification of the final products took place during this period. The crude solid was then washed with EtOH, filtered and dried under vacuum to obtain pure solid product.

3.2.3 General Procedure for the preparation of $S_2$4

Melt reaction: 1:1.2 molar ratios of aldehyde (2 mmol) and malononitrile (2.4 mmol) were taken in a 10 mL round bottom (RB) flask and subjected to melt using conventional oil bath at 150 ˚C and stirred for 1 h. The reaction mixture was cooled to RT and recrystallized with 60% EtOAc in PE, filtered and dried under vacuum to obtain pure solid products in good yield (as shown in Table 3.4).

All the newly synthesized compounds were characterized by spectral analysis and the spectral data of the final compounds are given below.

(2-amino-3-cyano-4*H*-chromen-4-yl)malononitrile ($S_2$3a)

White solid; mp: 151~153 ˚C (lit. 150-153˚C) ^{1}H NMR (500MHz, DMSO-d_6) δ: 4.59 (d, 1H, *J* = 4Hz, CH), 5.07 (d, 1H, *J* = 4Hz, CN*CH*CN), 7.14 (dd, 1H, J_1 = 8.5Hz, J_2 = 0.9Hz, ArH), 7.27 (dt, 1H, J_1 = 7.5Hz, J_2 = 0.9Hz, ArH), 7.43-7.45 (m, 1H, ArH), 7.47-7.49 (m, 1H, ArH), 7.53 (s, 2H, NH); ; IR (Neat, cm^{-1}): 3448 (NH_{asym}), 3326 (NH_{sym}), 2929 (CH), 2239 (CN_{aliph}), 2188 (CN_{conj}), 1635 (C=C), 1223 (C-N); ESI MS (m/z) = 235.2 $(M-H)^-$.

(2-amino-3-cyano-8-methoxy-4*H*-chromen-4-yl)malononitrile ($S_2$3b)

White solid; mp: 160~162 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 3.84 (s, 3H, O*CH*$_3$), 4.57 (d, 1H, *J* = 3Hz, CH), 5.05 (d, 1H, 3Hz, CN*CH*CN), 7.00 (d, 1H, *J* = 7.5Hz, ArH), 7.12 (d, 1H, *J* = 8Hz, ArH), 7.19-7.22 (m, 1H, ArH), 7.54 (s, 2H, NH); IR (Neat, cm^{-1}): 3459 (NH_{asym}), 3352 (NH_{sym}), 2915 (CH), 2242 (CN_{aliph}), 2190 (CN_{conj}), 1641 (C=C), 1275 (C-N), 1216 (C-O), 1083.

(2-amino-3-cyano-7-methoxy-4*H*-chromen-4-yl)malononitrile ($S_2$3c)

White solid; mp: 149~151 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 3.79 (s, 3H, OCH_3), 4.50 (d, 1H, *J* = 4Hz, CH), 5.01 (d, 1H, *J* = 4Hz, CN*CH*CN), 6.65 (d, 1H, *J* = 2.5Hz, ArH), 6.87 (dd, 1H, J_1 = 8.5Hz, J_2 = 3Hz, ArH), 7.38 (d, 1H, *J* = 8.5Hz, ArH), 7.49 (s, 2H, NH); ^{13}C NMR (125.75 MHz, DMSO-d_6) δ: 34.4, 38.7, 57.4, 103.2, 111.6, 113.5, 114.9, 115.1, 121.3, 131.5, 152.5, 162.2, 165.2; IR (Neat, cm^{-1}): 3409 (NH_{asym}), 3332 (NH_{sym}), 2956 (CH), 2242 (CN_{aliph}), 2186 (CN_{conj}), 1645 (C=C), 1293 (C-N); ESI MS (m/z) = 267.2 $(M+H)^+$; Anal. Calcd for $C_{14}H_{10}N_4O_2$: C, 63.15; H, 3.79; N, 21.04, Found: C, 63.26; H, 3.88; N, 21.22.

(2-amino-3-cyano-6-methoxy-4*H*-chromen-4-yl)malononitrile ($S_2$3d)

White solid; mp: 144~146 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 3.76 (s, 3H, O*CH*$_3$), 4.54 (d, 1H, *J* = 4Hz, CH), 5.10 (d, 1H, *J* = 3.5Hz, CN*CH*CN), 6.98 (dd, 1H, J_1 = 3Hz, J_2 = 9Hz, ArH), 7.06-7.08 (m, 2H, ArH), 7.45 (s, 2H, NH); IR (Neat, cm^{-1}): 3395 (NH_{asym}), 3335 (NH_{sym}), 2260 (CN_{aliph}), 2182 (CN_{conj}), 1654 (C=C), 1211 (C-N).

(2-amino-3-cyano-8-ethoxy-4*H*-chromen-4-yl)malononitrile ($S_2$3e)

White solid; mp: 141~143 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 1.36 (t, 3H, *J* = 7Hz, OCH_2CH_3), 4.09-4.16 (m, 2H, CH_3CH_2Ar), 4.56 (d, 1H, *J* = 4Hz, CH), 5.04 (d, 1H, 4Hz, CN*CH*CN), 7.00 (dd, 1H, J_1 = 8Hz, J_2 = 1Hz, ArH), 7.10-7.12 (m, 1H, ArH), 7.18 (t, 1H, *J* = 8Hz, ArH), 7.5 (s, 2H, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 15.0, 32.8, 37.8, 49.4, 64.9, 113.4, 113.6, 114.5, 119.4, 119.8, 120.2, 125.4, 139.9, 146.8, 163.8; IR (Neat, cm^{-1}): 3469 (NH_{asym}), 3348 (NH_{sym}), 2989 (CH), 2945, 2895, 2254 (CN_{aliph}), 2190 (CN_{conj}), 1640 (C=C), 1275 (C-N); ESI MS (m/z) = 281.2 $(M+H)^+$; Anal. Calcd for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.32; N, 19.99, Found: C, 64.37; H, 4.37; N, 20.06.

(2-amino-6-chloro-3-cyano-4*H*-chromen-4-yl)malononitrile ($S_2$3f)

White solid; mp: 152~154 ˚C (lit. 151-154˚C) ; ^{1}H NMR (500MHz, DMSO-d_6) δ: 4.62 (d, 1H, *J* = 3.5Hz, CH), 5.15 (d, 1H, *J* = 3.5Hz, CN*CH*CN), 7.18 (d, 1H, *J* = 8.5Hz, ArH), 7.48 (dd, 1H, J_1 = 8.5Hz, J_2 = 2.5Hz, ArH), 7.58 (d, 1H, 2.5Hz, ArH), 7.61 (s, 2H, NH); IR (Neat, cm^{-1}): 3438 (NH_{asym}), 3327 (NH_{sym}), 2882 (CH), 2239 (CN_{aliph}), 2189 (CN_{conj}), 1636 (C=C), 1227 (C-N).

(2-amino-3-cyano-6-nitro-4*H*-chromen-4-yl)malononitrile ($S_2$3g)

White solid; mp: 179~181 ˚C (lit. 180-181˚C) ; ^{1}H NMR (500MHz, DMSO-d_6) δ: 4.81 (d, 1H, *J* = 4Hz, CH), 5.23 (d, 1H, *J* = 4Hz, CN*CH*CN), 7.40 (d, 1H, *J* = 9Hz, ArH), 7.81 (s, 2H, NH), 8.30 (dd, 1H, J_1 = 9Hz, J_2 = 2.5Hz, ArH), 8.53 (d, 1H, *J* = 2.5Hz, ArH); IR (Neat, cm^{-1}): 3403 (NH_{asym}), 3316 (NH_{sym}), 2901 (CH), 2256 (CN_{aliph}), 2195 (CN_{conj}), 1654 (C=C), 1251 (C-N).

(2-amino-3-cyano-8-methoxy-6-nitro-4*H*-chromen-4-yl)malononitrile ($S_2$3h)

White solid; mp: 189~191 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 4.00 (s, 3H), 4.77 (d, 1H, *J* = 3.5Hz, CH), 5.21 (d, 1H, *J* = 3.5Hz, CN*CH*CN), 7.82 (s, 2H, NH), 7.91 (d, 1H, *J* = 2.5Hz, ArH), 8.10 (d, 1H, *J* = 3Hz, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 32.8, 37.4, 49.1, 57.2, 108.1, 113.1, 113.2, 116.5, 119.2, 119.8, 144.1, 144.4, 148.2, 163.1; IR (Neat, cm^{-1}): 3442 (NH_{asym}), 3339 (NH_{sym}), 2871 (CH), 2254 (CN_{aliph}), 2191 (CN_{conj}), 1638 (C=C), 1230 (C-N); ESI MS (m/z) = 312.2 $(M+H)^+$; Anal. Calcd for $C_{14}H_9N_5O_4$: C, 54.02; H, 2.91; N, 22.50, Found: C, 53.96; H, 2.97; N, 22.63.

(2-amino-3-cyano-6,8-dinitro-4*H*-chromen-4-yl)malononitrile ($S_2$3i)

Light brown solid; mp: 188~190 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 4.92 (d, 1H, *J* = 4Hz, CH), 5.29 (d, 1H, *J* = 4Hz, CN*CH*CN), 8.02 (s, 2H, NH), 8.78 (d, 1H, *J* = 3Hz, ArH), 8.89 (d, 1H, *J* = 3Hz, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ:32.6, 37.2, 49.3, 112.8, 113.0, 118.6, 121.9, 122.5, 129.2, 138.4, 142.9, 146.9, 162.3; IR (Neat, cm^{-1}): 3406 (NH_{asym}), 3321 (NH_{sym}), 2900 (CH), 2257 (CN_{aliph}), 2199 (CN_{conj}), 1645 (C=C), 1216 (C-N); ESI MS (m/z) = 327$(M+H)^+$; Anal. Calcd for $C_{13}H_6N_6O_5$: C, 47.86; H, 1.85; N, 25.76, Found: C, 48.04; H, 1.89; N, 25.89.

(2-amino-8-bromo-6-chloro-3-cyano-4*H*-chromene-4-yl)malononitrile ($S_2$3j)

White solid; mp: 173~175 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 4.67 (d, 1H, *J* = 4Hz, CH), 5.17 (d, 1H, *J* = 4.5Hz, CN*CH*CN), 7.60 (d, 1H, *J* = 2Hz, ArH), 7.75 (s, 2H, NH), 7.90 (d, 1H, *J* = 2.5Hz, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 32.7, 37.7, 49.3, 111.1, 113.1, 113.2, 119.2, 121.8, 128.6, 129.4, 133.3, 146.3, 163.4; IR (Neat, cm^{-1}): 3435 (NH_{asym}), 3334 (NH_{sym}), 2891 (CH), 2256 (CN_{aliph}), 2189 (CN_{conj}), 1649 (C=C), 1245 (C-N); ESI MS (m/z) = 350.1 $(M+H)^+$; Anal. Calcd for $C_{13}H_6BrClN_4O$: C, 44.67; H, 1.73; N, 16.03, Found: C, 44.72; H, 1.79; N, 16.19.

(2-amino-3-cyano-6,8-diiodo-4*H*-chromen-4-yl)malononitrile ($S_2$3k)

White solid; mp: 197~199 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 4.59 (d, 1H, *J* = 4Hz, CH), 5.13 (d, 1H, *J* = 4Hz, CN*CH*CN), 7.69 (s, 2H, NH), 7.82 (s, 1H, ArH), 8.2 (s, 1H, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 32.8, 37.4, 49.5, 87.3, 90.2, 113.1, 113.3, 119.2, 121.5, 137.8, 146.9, 149.9; IR (Neat, cm^{-1}): 3410 (NH_{asym}), 3322 (NH_{sym}), 2888 (CH), 2255 (CN_{aliph}), 2195 (CN_{conj}), 1648 (C=C), 1245 (C-N); ESI MS (m/z) = 489$(M+H)^+$; Anal. Calcd for $C_{13}H_6I_2N_4O$: C, 31.99; H, 1.24; N, 11.48, Found: C, 32.08; H, 1.32; N, 11.57.

2-amino-6-chloro-3-quinolinecarbonitrile ($S_2$4a)

Pale yellow solid; mp: 311~313 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 6.71 (s, 2H, NH), 6.79 (d, 1H, *J* = 9Hz, ArH), 7.32 (dd, 1H, J_1 = 9Hz, J_2 = 2Hz, ArH), 7.77 (d, 1H, *J* = 2.5Hz, ArH), 8.31 (s, 1H, ArH); ^{13}C NMR (125.75 MHz, DMSO-d_6) δ: 97.5, 118.1, 123.4, 128.4, 128.8, 129.4, 134.8, 146.5, 149.6, 157.9; IR (Neat, cm^{-1}): 3432 (NH_{asym}), 3364 (NH_{sym}), 2221 (CN), 1653 (NH_{bend}); ESI MS (m/z) = 204.1$(M+H)^+$; Anal. Calcd for $C_{10}H_6ClN_3$: C, 58.98; H, 2.97; N, 20.64, Found: C, 59.12; H, 3.08; N, 20.77.

2-amino-6,8-dibromo-3-quinolinecarbonitrile ($S_2$4b)

Pale yellow solid; mp: 314~316 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 7.42 (s, 2H, NH), 8.03 (d, 1H, *J* = 1.5Hz, ArH), 8.17 (d, 1H, *J* = 2Hz, ArH), 8.69 (s, 1H, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 114.1, 116.2, 121.7, 123.2, 130.7, 138.1, 145.4, 145.9, 156.8; IR (Neat, cm^{-1}): 3476 (NH_{asym}), 3308 (NH_{sym}), 2219 (CN), 1645

(NH_{bend}); ESI MS (m/z) = 328 $(M+H)^+$; Anal. Calcd for $C_{10}H_5Br_2N_3$: C, 36.73; H, 1.54; N, 12.85, Found: C, 36.77; H, 1.52; N, 12.92.

2-amino-1,8-naphthyridine-3-carbonitrile ($S_2$4c)

Pale yellow solid; mp: 279~280 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 7.30 (dd, 1H, J_1 = 8Hz, J_2 = 4Hz, ArH), 7.39 (s, 2H, NH), 8.18 (dd, 1H, J_1 = 8Hz, J_2 = 2Hz, ArH), 8.76(s, 1H, ArH), 8.86 (dd, 1H, J_1 = 4Hz, J_2 = 2Hz, ArH); ^{13}C NMR (125.75 MHz, DMSO-d_6) δ: 97.4, 117.2, 117.9, 120.7, 139.6, 148.7, 157.8, 158.8, 159.9; IR (Neat, cm^{-1}): 3385 (NH_{asym}), 3332 (NH_{sym}), 2205 (CN), 1657 (NH_{bend}); Anal. Calcd for $C_9H_6N_4$: C, 63.52; H, 3.55; N, 32.92, Found: C, 63.58; H, 3.63; N, 33.02.

Table 3.1: Crystal data and measurement details of compound **$S_2$3a**

Crystal data [CCDC No. 870509]	
Empirical formula	C_{13} H_8 N_4 O
Formula weight	236.23
Crystal size (mm)	0.20 x 0.18 x 0.1
Crystal system	Triclinic
Space group	P-1
a (Å); b (Å); c (Å)	5.6073(8); 8.1748(11); 12.5000(17)
α (˚); β (˚); γ (˚)	103.057(7); 90.883(8); 96.555(8)
Volume ($Å^3$)	1759.02 (10)
Z	2
Crystal density, g/cm^3	1.416
F(000)	244
Absorption coefficient	0.096
Temperature (T)	296 (2)
Radiation wavelength	0.71073
Radiation type	MoKα
Radiation source	Fine-focus sealed tube
Radiation monochromator	Graphite
h_{min}; k_{min}; l_{min}	-6; -9; -14
h_{max}; k_{max}; l_{max}	6; 9; 14
R-Factor (%)	5.4

The ^{1}H NMR, and ESI MS spectra of **$S_2$3a** and ^{1}H NMR, ^{13}C NMR and ESI MS **$S_2$4b** are shown below

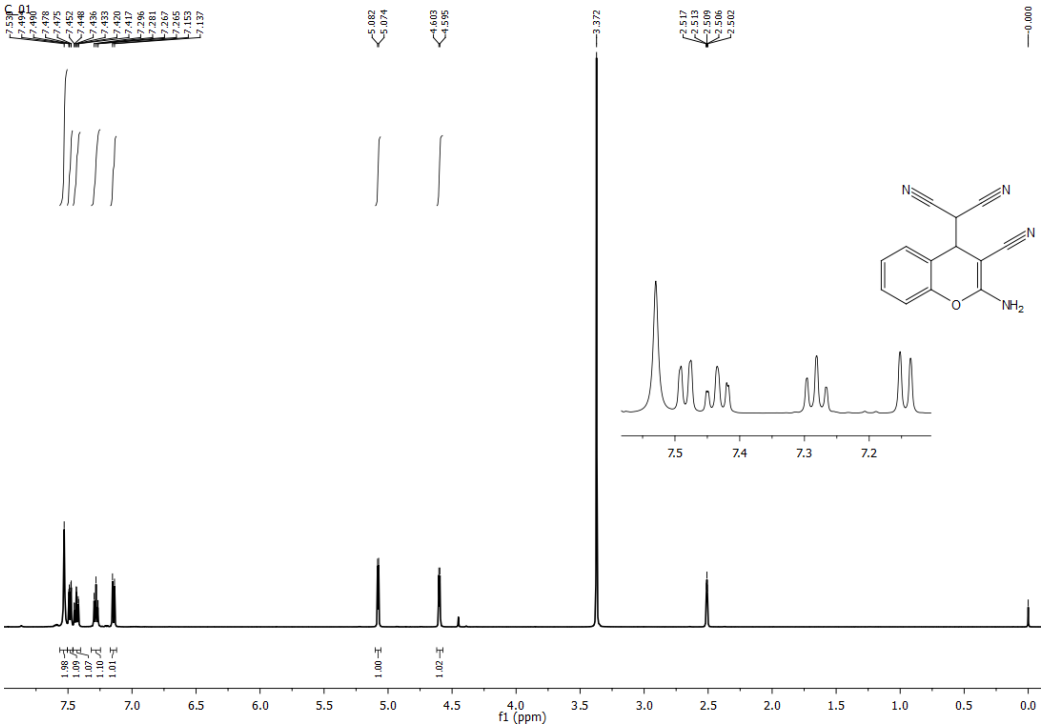


Fig. 3.2: ^{1}H NMR spectrum of **$S_2$3a**

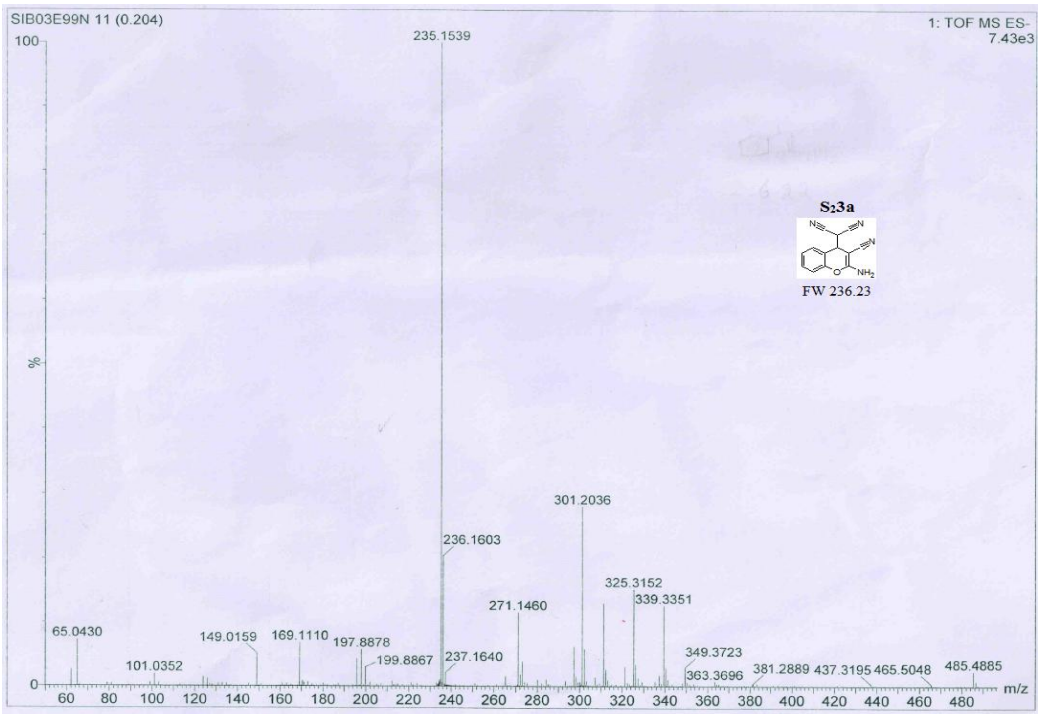


Fig. 3.3: ESI MS spectrum of **$S_2$3a**

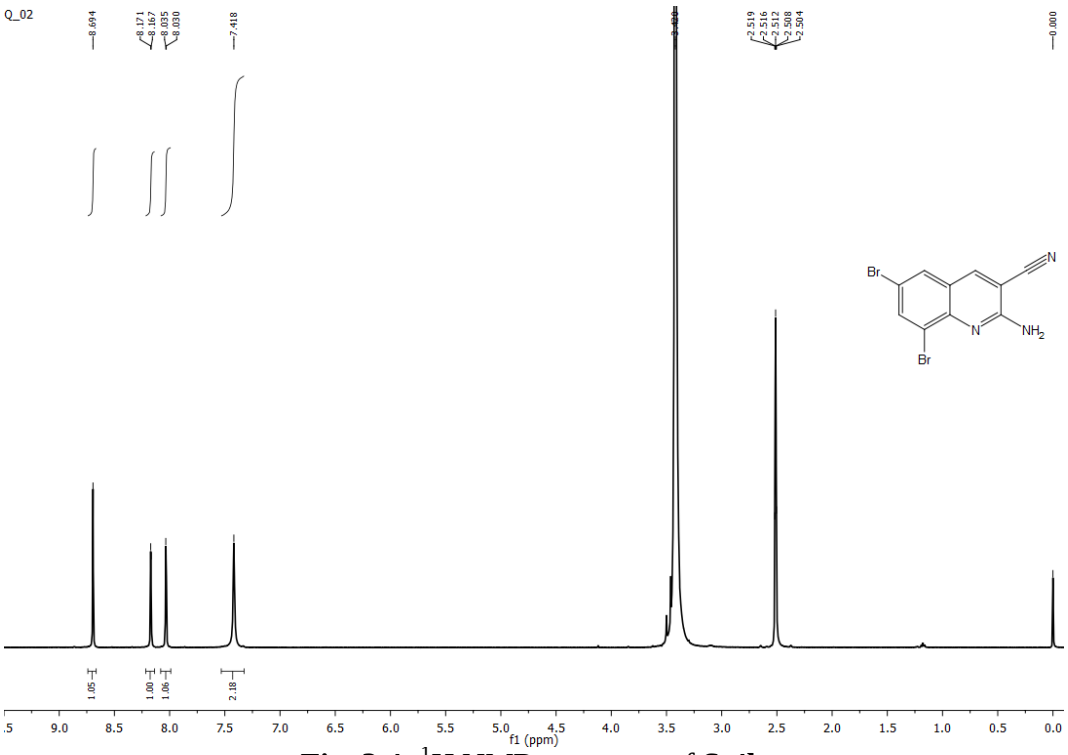


Fig. 3.4: ^{1}H NMR spectrum of **$S_2$4b**

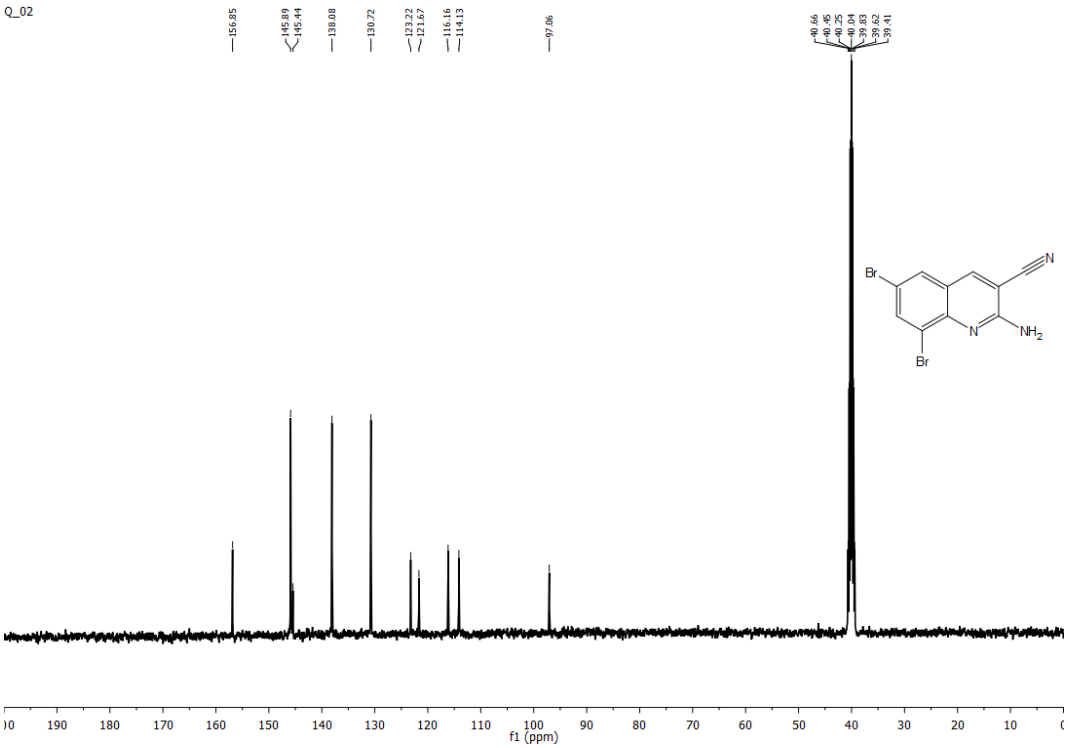


Fig. 3.5: ^{13}C NMR spectrum of **$S_2$4b**

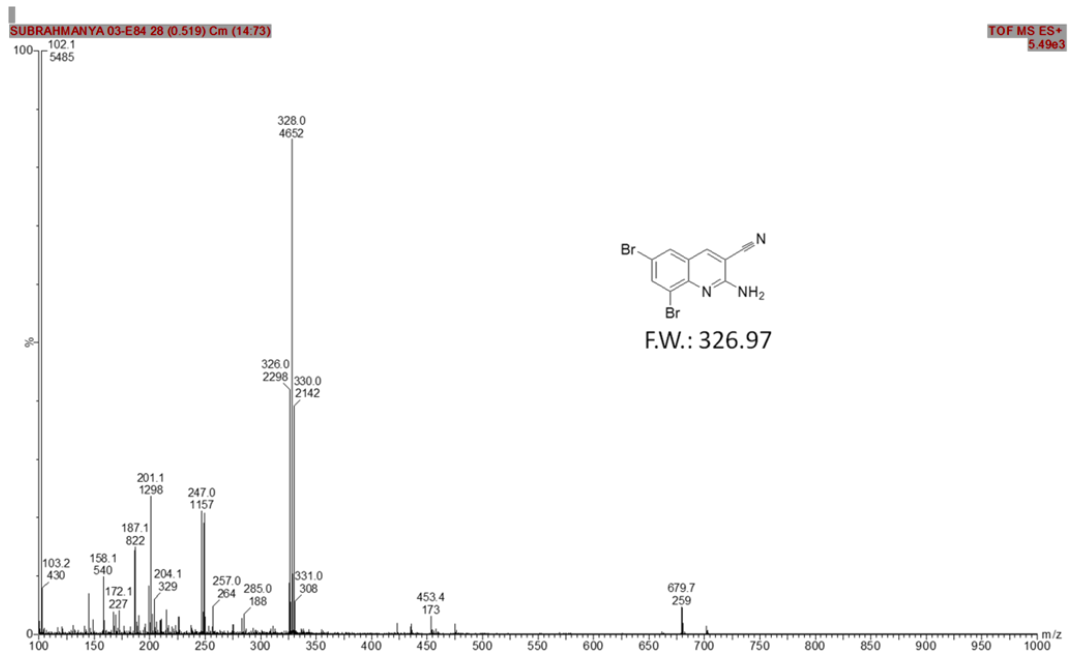


Fig. 3.6: ESI MS spectrum of **$S_2$4b**

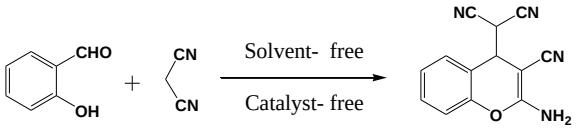
3.3 RESULTS AND DISCUSSION

Initially the reaction of salicylaldehyde with malononitrile was performed by mechanochemical activation, using mortar and pestle. Equimolar amounts of reactants were taken in a pre-weighed Agate mortar and mixed thoroughly with pestle. The reaction mixture slowly converted to viscous liquid after 5 min of mixing, and then it was allowed to stand for 3 h at RT (Table 3.2, entry **1**). During this period the reaction mixture slowly converted into white wet solid. The white solid thus obtained was partially soluble in EtOAc and completely got dissolved when 1 drop of DMSO was added. The TLC analysis (30% EtOAc in PE) showed incomplete conversion of salicylaldehyde. The extended standing time did not reach the complete conversion of salicylaldehyde. Then, the wet solid was washed with EtOH to obtain pure white solid and characterized by mp (151~153 ˚C), FTIR (neat) and ^{1}H NMR (in DMSO-d_6 solvent). The structure assignment of the product was done based on the spectral analysis and confirmed with reported literature (O'Callaghan et al. 1995; Costa et al. 2008). Surprisingly, the obtained product was neither benzylidene-malononitrile nor benzofuran-2-carbonitrile, as reported earlier (Trotzki et al. 2008a, 2008b), but it was found to be (2-amino-3-cyano-4*H*-chromene-4-yl)malononitrile as shown in Fig. 3.1

(Product **ii**). The resultant product formed as a condensation reaction of malononitrile with aldehyde in 2:1 molar ratio. Further, no formation of any by-product or 1:1 condensation product 2-imino-2*H*-chromene-3-carbonitrile (Fig. 3.1, product **i**) was observed. This may be attributed to the relatively unstable nature of 2-imino-2*H*-chromene-3-carbonitrile (Fig. 3.1, product **i**) (O'Callaghan et al. 1995).

Inspired by the interesting condensation product achieved by mechanical activation, the stoichiometric reaction of malononitrile with salicylaldehyde was further carried out under thermal condition, using a conventional pre-heated oil bath at 150 ˚C. A vigorous reaction was observed as reported (Trotzki et al. 2008a). The reaction mixture was cooled to RT after 10 min to obtain brown coloured solid. The pure product yielded after washing with EtOH was found to be identical with the chromene that obtained from mechanochemical activation. The parallel reaction with elongated heating resulted in complete decomposition of the product. Further, by the optimization of reaction temperature, it was found that, the reaction carried out at 60 ˚C resulted in desired product after 30 min without decomposition (Table 3.2, entry **2**).

Table 3.2: Reaction of salicylaldehyde with malononitrile under various condiitions



S_2**1a** S_2**3a**

Entry	Reaction Condition	Reactant ratio used	Reaction time (h)[a]	% Yield[c]
1	Mechanochemical grinding	1:1	3	49
2	Thermal heating[b]	1:1	0.5	42
3	Direct crystallization	1:1	3.5	48
4	Mechanochemical grinding	1:2	3	98

[a] Reactions were monitored by TLC; [b] Reaction carried out at 60 ˚C; [c] Yield of pure product.

Furthermore, direct crystallization process (Kaupp, 2006) for the reaction of salicylaldehyde with malononitrile has been performed at ambient temperature. Equimolar amounts of reactants were mixed by brief swirling of the reactants in 10 mL RB flask and kept as such at RT under nitrogen atmosphere. White crystalline solid contaminated with light yellowish liquid observed after 3.5 h (Table 3.2, entry **3**). The crystals were filtered and washed with small amount of EtOH. The structure of the resultant product was assigned by FTIR and ^{1}H NMR spectral analysis, and confirmed unequivocally by SCXRD analysis (Fig. 3.7). Further, X-ray powder diffraction data of the solids obtained by mechanochemical grinding, thermal heating and the bulk solid obtained by direct crystallization process were compared as shown in Fig. 3.8. The virtually superimposible patterns indicate that, the crystal phase of the solid obtained by all methods and that of the single crystal are identical.

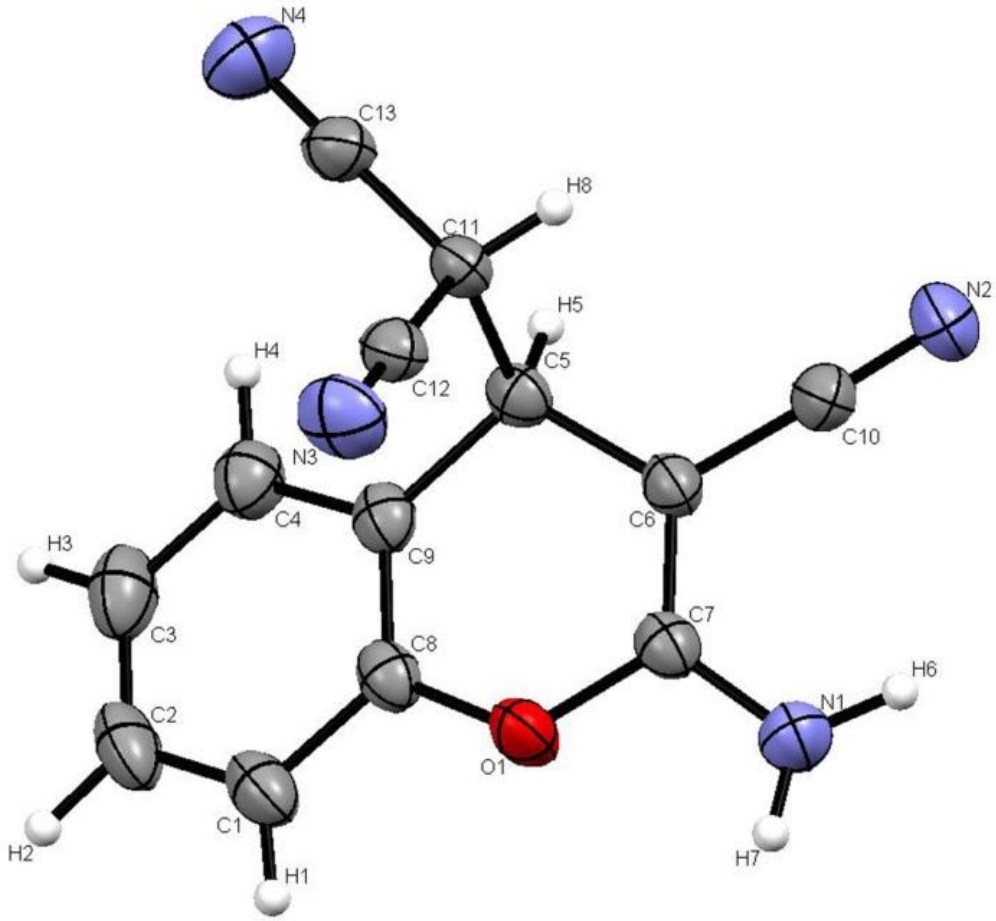


Fig. 3.7: ORTEP (50% probability) diagram of the crystal structure of **$S_2$3a** obtained from direct crystallization process

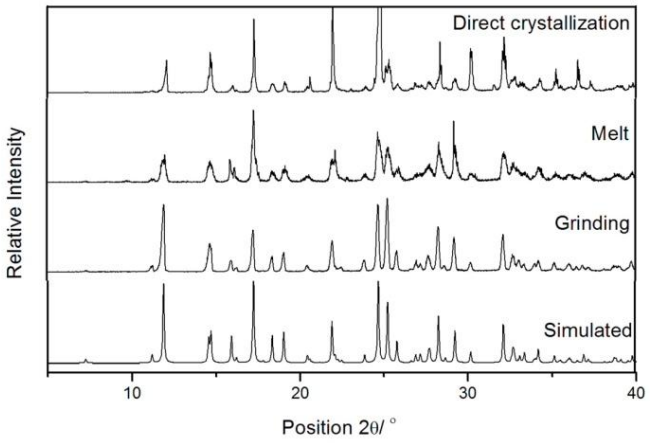


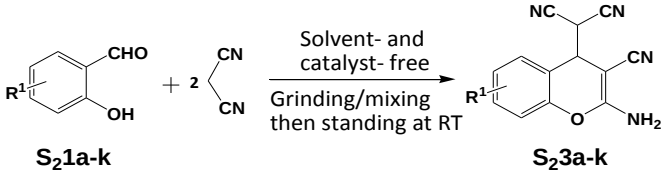
Fig. 3.8: Powder X-ray diffraction pattern of **$S_2$3a** obtained by the reaction of 1:1 molar ratio of salicylaldehyde and malononitrile under various conditions followed by EtOH wash

The structural elucidation based on spectral analysis revealed that, the product obtained from mechanical activation, thermal condition and by direct crystallyzation process was identical. These results are dissimilar to earlier reports (Trotzki et al. 2008a, 2008b), in which, no product was observed by direct crystallization process in the absence of solvent and at ambient temperature.

To achieve maximum conversion of starting materials in to the final product, the reaction was then performed with 1:2 molar equivalents of salicylaldehyde and malononitrile. Complete conversion of reactants to product **$S_2$3a** took place when the reaction mixture was mixed thoroughly for 5 min and then allowed to stand for 3 h at RT in presence of atmospheric air (Table 3.2, entry **4**). The white solid product thus formed was characterized without further purification and the structure was confirmed by comparing the data with that obtained in earlier methods. Thus, the present protocol is an example for liquid state reaction in which the product crystallizes during the reaction (Kaupp 2001) to obtain near quantitative yield.

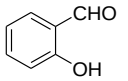
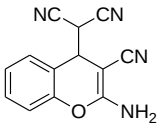
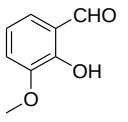
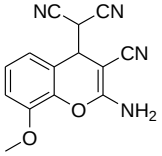
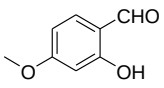
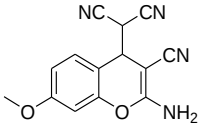
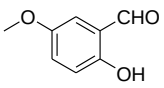
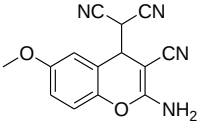
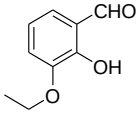
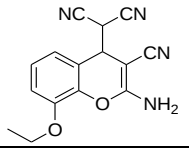
The conventional methods used for the synthesis of (2-amino-3-cyano-4*H*-chromene-4-yl)malononitrile derivatives suffer from many disadvantages such as long reaction time, usage of solvent and catalyst etc. Also, the vast biological importance of 2-aminochromenes (Das et al. 2011; Kumar et al. 2011b; Reddy et al. 2011; Erichsen et al. 2010) inspired us to extend the scope of the present protocol. Hence, to

evaluate the generality of the present protocol and to confirm similar chromene formation, twelve salicylaldehyde derivatives were reacted with malononitrile at RT as shown in Scheme 3.1 and listed in Table 3.3. All the reactions proceeded with the liquification of the reaction mixture during grinding or thorough mixing of the reactants in an Agate mortar with pestle followed by solidification of the final product, as explained by the group of Scott (Rothenberg et al. 2001). Purity of the final products obtained was good enough for spectroscopic analysis, however all the compounds were further washed with EtOH.

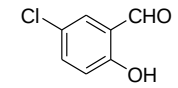
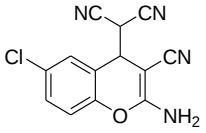
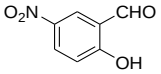
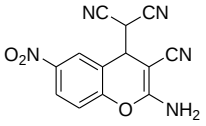
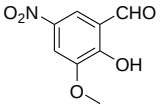
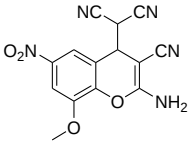
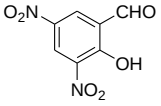
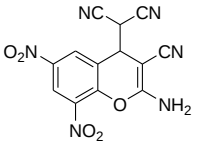
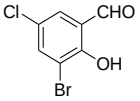
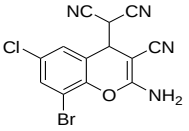
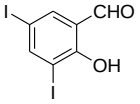
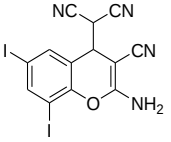
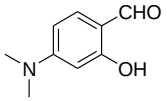
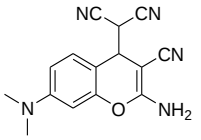


Scheme 3.1: Reaction of salicylaldehydes with malononitrile under solvent- and catalyst-free conditions

Table 3.3: Substituents of the aldehydes used, reaction time and yield of the products

Entry		Aldehyde	Reaction Time (h) [a,b]		Chromene derivative	Yield%[c]
1	**$S_2$1a**		3	**$S_2$3a**		98
2	**$S_2$1b**		4.5	**$S_2$3b**		97
3	**$S_2$1c**		6	**$S_2$3c**		89
4	**$S_2$1d**		5.5	**$S_2$3d**		95
5	**$S_2$1e**		4	**$S_2$3e**		98

Contd.

6	**$S_2$1f**		3	**$S_2$3f**		97
7	**$S_2$1g**		0.5	**$S_2$3g**		97
8	**$S_2$1h**		0.5	**$S_2$3h**		98
9	**$S_2$1i**		0.5	**$S_2$3i**		96
10	**$S_2$1j**		1	**$S_2$3j**		96
11	**$S_2$1k**		2	**$S_2$3k**		94
12	**$S_2$1l**		24	**$S_2$3l**		00

[a] All the reactions were carried out by grinding/mixing 1:2 molar ratio of reactants with Agate mortar and pestle for 5 min followed by allowing the mixture for standing; [b] Reactions were monitored by checking TLC for every half an hour after mixing; [c] Yield of pure product.

In order to elucidate the reaction pathway, neat reaction of salicylaldehyde (**$S_2$1a**) and malononitrile in 1:2 molar ratios was monitored by IR spectral measurements. IR spectra were recorded until the completion of the reaction for every 3 min intervals. The absorption peaks were assigned by comparing with the literature references (Silverstein 2007; Stuart 2004). IR spectrum obtained just after mixing both reactants appeared as a superimposed spectrum of both the starting materials (Fig. 3.9). At the beginning of the measurement, two absorption peaks appeared at 2960 cm^{-1} and 2927 cm^{-1} which have been assigned to asymmetrical and symmetrical methylene C-H

stretching of malononitrile (Binev et al. 2003). These peaks were merged towards the completion of the reaction and appeared as a single peak at 2932 cm^{-1} corresponding to methine C-H stretching absorption of the product. Also the absorption bands of aldehyde group (C=O stretching at 1654 cm^{-1}, C-H stretching Fermi doublet at 2857 cm^{-1} and 2758 cm^{-1}) disappeared gradually as the condensation reaction proceeds and concomitantly, a new absorption band corresponding to vinyl nitrile C=C stretching appeared at 1636 cm^{-1} (Makarem et al. 2008). After 6 min of reaction, a new absorption peak appeared at ν_{max} = 2195 cm^{-1} and as the reaction proceeds the peak intensity enhanced rapidly with small shift towards lower frequency. This has been assigned to the conjugated C≡N stretching absorption (Sridevi et al. 2012). After 15 min, new asymmetrical and symmetrical νNH absorptions and νC-N absorption of product **$S_2$3a** appeared at 3450 cm^{-1}, 3329 cm^{-1} and 1223 cm^{-1} respectively (Fig. 3.9).

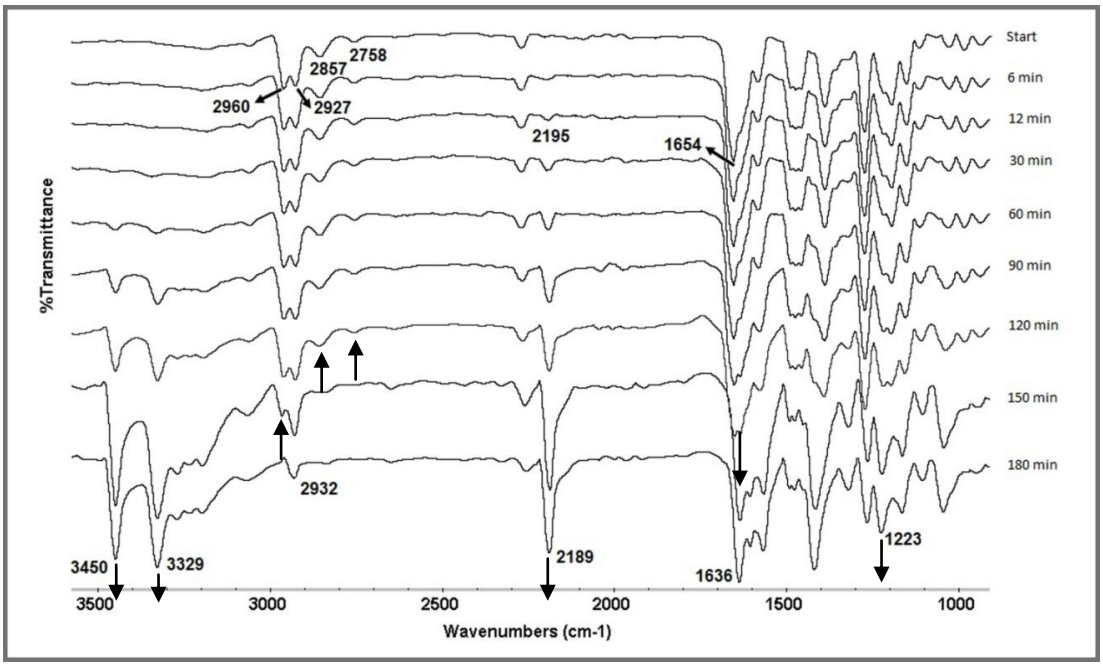
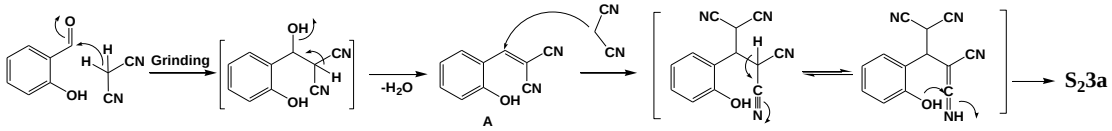


Fig. 3.9: IR Monitoring by the ATR method at RT of the solvent- and catalyst-free reaction between salicylaldehyde and malononitrile under grinding condition (Product **$S_2$3a**)

Taking into consideration above facts and the final product characterization data, a possible mechanistic pathway is proposed in Scheme 3.2, using **$S_2$1a** as an example. Initially, condensation of the salicylaldehyde and malononitrile with the elimination

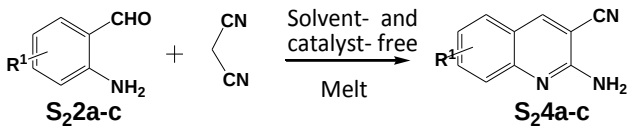
of water molecule for the formation of salicylidene-malononitrile (A) occur (known to take place under catalyst-free grinding conditions (Ren et al. 2002; Kumar and Sharma, 2011). Since, malononitrile is the most reactive methylene component and the intervention of liquid phase allows a large number of productive molecular collisions (Rothenberg et al. 2001), the proper mixing and energy generated by the friction of the mortar and pestle may drive the reaction to occur. The Knoevenagel adduct thus formed undergoes simultaneous Michael addition with malononitrile and intramolecular cyclization to obtain stable product **$S_2$3a**. This was further supported in IR, by the appearance of absorption peak corresponding to conjugated cyano group (2193 cm^{-1}) well before the appearance of absorption bands corresponding to amine group present in the bicyclic product.



Scheme 3.2: Proposed mechanism for the reaction between salicylaldehyde and malononitrile to obtain chromene derivative **$S_2$3a**

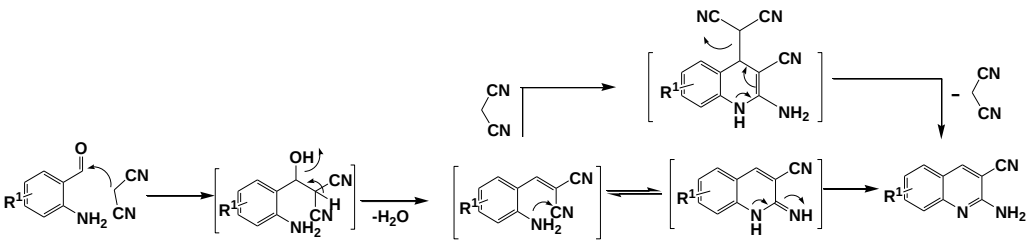
It was also found that the nature of the substitution on the aromatic ring of salicylaldehyde had great influence on the reaction. The presence of electron withdrawing groups on the aromatic ring leads the reaction very fast and in contrast, electron donating groups lead the reaction slower. For instance, the reaction with 5-nitrosalicylaldehyde (Table 3.3, entry **7**) completed very fast, however the reaction fails to give product with 4-N,N-dimethylaminosalicylaldehyde even after 24 h standing time (Table 3.3, entry **12**).

Some of the solvent-free reactions suffer from the possibility of runaway reactions at larger scale (Martins et al. 2009). Thus to explore the present protocol at gram scale, the reaction of salicylaldehyde (**$S_2$1a**, 20 mmol) with malononitrile (40 mmol) was carried out under neat condition. The reactants were mixed thoroughly using pre-weighed mortar and pestle and the homogeneous liquid thus formed was left standing at RT. Complete conversion of reactants to product **$S_2$3a** took place after 5 h standing. Also, the reaction was not highly exothermic and hence there was no thermal runaway during the course of the reaction.



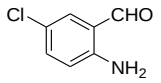
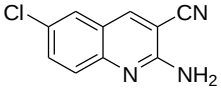
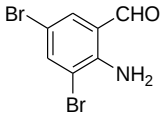
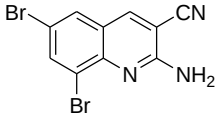
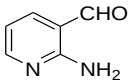
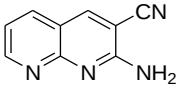
Scheme 3.3: Reaction of *o*-aminobenzaldehydes with malononitrile under solvent- and catalyst-free conditions

The next series of experiments concern Knoevenagel product by the reaction of malononitrile with aldehydes containing amine group in *ortho*-position under neat conditions. The reaction with 5-chloro-2-aminobenzaldehyde resulted in very poor conversion under solvent- and catalyst-free grinding conditions at RT. The main reason for the decreased conversion, one can assume the poorer reactivity of aldehyde due to the presence of more nucleophilic amine group in *ortho*-position. The reaction was then attempted under melt condition. The neat reactants (1:2 ratio) were taken in 10 mL RB and then heated to 150 ˚C using a conventional preheated-oil bath. The solid thus obtained was recrystallized with 60% EtOAc in PE and then characterized. As expected, the bicyclic product thus obtained was 2-amino-3-cyano-quinoline derivative (Scheme 3.3). The stability caused by aromaticity (Hepworth, 2002) may be the reason for avoiding Michael addition product as in the case of *o*-hydroxybenzaldehydes. Similar product was reported by solution synthesis using base catalyst under reflux conditions (Kiran and Mahadevan 2006). Further, different ratios of reactants were tested to derive the optimized conditions. The ratio 1:1.2 of aldehydes and malononitrile found to be the more suitable system to obtain the product with good yield. Under similar conditions, the reaction of malononitrile with 3,5-dibromo-2-aminobenzaldehyde resulted in corresponding quinoline derivative (Table 3.4, entry **2**). Further, the reaction proceeded successfully with heteroaromatic 2-amino-pyridine-3-carboxaldehyde to obtain corresponding quinolines derivative (Table 3.4, entry **3**). Two possible mechanisms for the product formation are shown in Scheme 3.4. The pure products were obtained in good yield by recrystallization from 60% EtOAc in PE (Table 3.4).



Scheme 3.4: Possible mechanism for the reaction between *o*-aminobenzaldehyde and malononitrile

Table 3.4: Substituents of the 2-aminobenzaldehydes used, reaction time, Product and yield

Entry		Aldehyde	Reaction Time (h)[a]		Quinoline derivative	%Yield[b]
1	**$S_2$2a**		1	**$S_2$4a**		79
2	**$S_2$2b**		1	**$S_2$4b**		83
3	**$S_2$2c**		1	**$S_2$4c**		82

[a] All the reactions were carried out by heating 1:1.2 molar ratio of aldehydes and malononitrile at 150 °C; [b] yield of pure product.

3.4 CONCLUSION

In conclusion, the solvent- and catalyst-free reaction of salicylaldehyde with malononitrile leads to the formation of (2-amino-3-cyano-4*H*-chromene-4-yl)malononitrile, instead of benzofuran-2-carbonitrile as reported earlier. The reaction monitored by IR spectral measurements show that, the Knoevenagel adduct undergoes simultaneous Michael addition with malononitrile and intramolecular cyclization to yield bicyclic chromene derivative. Further, eleven salicylaldehyde derivatives were successfully reacted with malononitrile to generate corresponding chromene derivatives. The products were characterized by spectroscopic techniques and were further confirmed by SCXRD (**$S_2$3a)**. Neat conditions, short reaction time, high product yield without tedious work up procedures and applicability to gram scale

synthesis are the green relevance and notable advantages of the present methodology over conventional synthesis.

Additionally it was observed that, the reaction of 2-aminobenzaldehydes with malononitrile yield 2-amino-3-cyanoquinolines under melt conditions. The Knoevenagel adduct undergoes simultaneous cyclization and aromatization to obtain the products in good yield.

Overall findings of these studies show that, the Knoevenagel condensation of benzaldehydes containing hydroxyl or amine group in *ortho*-position leads to the bicyclic heterocycles via six membered cyclization.

CHAPTER 4

A HIGHLY EFFICIENT AND GREEN CASCADE SYNTHESIS OF 3-METHYL-SUBSTITUTED-4-HYDROXY-1-METHYL-QUINOLIN-2(1*H*)-ONES UNDER SOLVENT- AND CATALYST-FREE CONDITIONS

The present chapter deals with an expeditious and green protocol for the synthesis of 3,3'-methanediylbis(4-hydroxy-1-methylquinolin-2(1H)-one) (MDBHQ) derivatives and 3-((2-amino-6-oxocyclohex-1-enyl)methyl)-4-hydroxy-1-methylquinolin-2(1H)-one (AOCHQ) derivatives via cascade Knoevenagel-Michael reaction. The functional tolerance and reaction mechanism of this environmentally benign protocol is discussed.

4.1 INTRODUCTION

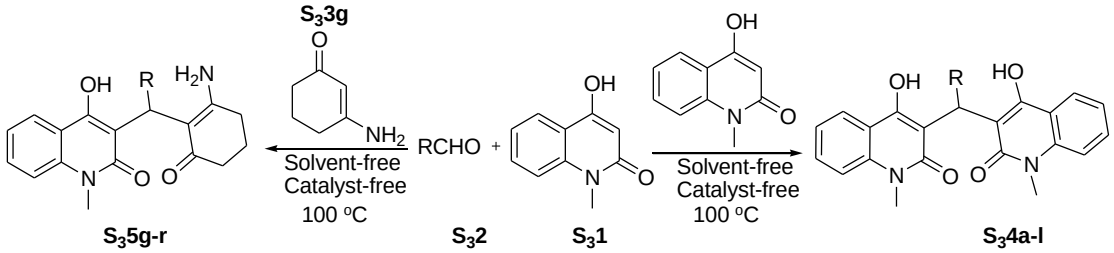
Cascade reactions constitute an attractive branch of organic chemistry and the area of intense research in recent years. The cascade reactions involve two or more bond-forming transformations in one synthetic operation (Nicolaou et al. 2006; Nicolaou and Chen 2009). Cascade reactions have gained wide acceptance because they provide molecular complexity and diversity from simple precursors (Lu et al. 2012) and incorporate green chemistry values such as atom economy as well as economies of time, labour, resource management and waste generation (Nicolaou and Chen 2009). Also, these reactions can facilitate ecologically and economically favourable syntheses such as in vitro biological reactions (Ramachari et al. 2007).

Knoevenagel condensation and Michael addition are the classical reactions for the carbon-carbon bond forming strategies in organic synthesis (Csaky et al. 2010; Jones, 1967; Rodriguez et al. 2007; Tietze and Beifuss 1991). Owing to their importance, various conventional protocols have been developed and several near absolute green protocols under solvent- and catalyst-free conditions have also been developed in recent years (Kaupp et al. 2003; Jiang et al. 2011; Trotzki et al. 2008a & 2008b; Xie et al. 2012). Further, development of their combination in to cascade reaction gained recent attention in organic synthesis due to their flexibility to generate complex molecular systems from simple precursors under environmentally acceptable conditions (Chen et al. 2010; Hong et al. 2012; Verma et al. 2012; Zhang et al. 2011).

Functionalized 4-hydroxyquinolin-2(1*H*)-ones are attractive targets in organic synthesis because of their highly prominent biological activities and found as useful intermediates for many medicinal products (Buckle et al. 1975; Hewawasam et al. 2003; Angibaud et al. 2004; Cappelli et al. 2004; Mohamed et al. 1995; Stadlbauer et

al. 2001). In recent years, a number of different synthetic pathways have been developed to access functionalized 4-hydroxyquinolin-2(1*H*)-ones (Glasnov et al. 2005; Abass et al. 2011; Jampilek et al. 2009; Abe et al. 2006; Xie et al. 2007; Grigg et al. 2009). However, the construction of functionalized 4-hydroxyquinolin-2(1*H*)-ones under solvent- and catalyst-free conditions has not been reported and is very significant in the context of green chemistry.

The heterocyclic dimeric compounds such as dicoumarols (Karmakar et al. 2012), bisindolylmethanes (Talukdar and Thakur 2013; Mulla et al. 2012), bisquinolines (Karle et al. 2002; Barr et al. 1995; Kamperdick et al. 1999; Raynes 1999), methylenebistetronic acids (Zhang et al. 2011) were found in natural products and broad range of pharmaceuticals. Several efforts have been made and large numbers of reports are available in the literature for the synthesis of such privileged compounds. However, only two reports are available on the synthesis of MDBHQ derivatives (Grigg et al. 2009; Gunasekaran et al. 2013), which obtained as side product. Hence, the development of efficient and green protocol for the synthesis of MDBHQ derivatives is of great importance, which could lead to study their applications in various fields of chemistry.



Scheme 4.1: Cascade reaction for the synthesis of MDBHQ's and AOCHQ's

Against the background, herein the synthesis of MDBHQ derivatives and AOCHQ derivatives via cascade Knoevenagel-Michael reaction has been reported (Scheme 4.1). The solvent- and catalyst-free reaction conditions, applicability to wide range of aldehydes, avoidance of tedious work-up procedure, and high product yield are notable advantages of the current protocol.

4.2 EXPERIMENTAL

4.2.1 General

All chemicals were purchased from commercial suppliers and used without further purification. Melting points were determined with Stuart SMP3 melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO 4200 FTIR spectrometer by ATR method. NMR spectra were recorded as a solution in DMSO-d_6/$CDCl_3$/MeOD at 400 MHz (^1H & ^{13}C) instrument. Chemical shifts (δ) are reported ppm with TMS as internal standard. *J*-values are given in Hz. NMR raw data was analysed with the program MestReNova 7.0.0-8331. Mass spectra were performed on Waters Micromass Q-Tof Micro spectrometer with an ESI source. Elemental analysis was performed using Perkin Elmer, Series II, 2400 analyzer. The SCXRD analysis was performed on the Bruker AXS APEX II system. All experiments were monitored by TLC, performed on pre-coated silica gel 60 F_{254} plates (Merck).

4.2.1 General Procedure for the synthesis of MDBHQ derivatives ($S_3$4)

4-hydroxy-1-methylquinolin-2(1*H*)-one **$S_3$1** (2 mmol) and aldehydes **$S_3$2** (1 mmol) were charged into a 10 mL round-bottom flask and the mixture was heated to 100 ˚C using conventional oil bath till completion of the reaction (Reaction times given in Table 4.2). The reaction mixture was turned to liquid melt and then became progressively more viscous often hardening to a solid mass. The solid thus obtained was washed with EtOH (2 mL) and dried under vacuum to obtain pure solid product **$S_3$4**.

4.2.2 General Procedure for the synthesis of 3-((2-amino-6-oxocyclohex-1-enyl)methyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one derivatives ($S_3$5)

Equimolar quantities of 4-hydroxy-1-methylquinolin-2(1*H*)-one **$S_3$1** (1 mmol), aldehydes **$S_3$2** (1 mmol) and 3-aminocyclohex-2-enone **$S_3$3g** (1 mmol) were charged into a 10 mL round-bottom flask and then the mixture was heated to 100 ˚C using conventional oil bath till the completion of the reaction (times given in Table 4.3). The reaction mixture was turned to liquid melt and then became progressively more viscous often hardening to a solid mass. The solid was washed with EtOH (2 mL) and dried under vacuum to obtain pure solid product **$S_3$5g-q**.

All the newly synthesized compounds were characterized by spectral analysis and the spectral data of the final compounds are given below.

3-((4-chlorophenyl)(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one ($S_3$4a)

White solid; mp: 175~176 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 3.64 (s, 3H, N*CH*$_3$), 3.75 (s, 3H, N*CH*$_3$), 6.30 (s, 1H, CH), 7.03 (dt, 2H, J_1 = 1.6Hz, J_2 = 6.4Hz, ArH), 7.13 (dd, 2H, J_1 = 2Hz, J_2 = 6.4Hz, ArH), 7.24-7.27 (m, 2H, ArH), 7.33 (d, 2H, J = 8.4Hz, ArH), 7.52-7.57 (m, 2H, ArH), 8.11 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8Hz, ArH), 8.17 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8Hz, ArH), 12.41 (s, 1H, OH), 12.77 (s, 1H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 29.0, 29.5, 35.8, 108.4, 110.0, 113.1, 113.2, 116.7, 117.0, 121.6, 123.8, 123.9, 126.9, 127.2, 130.3, 130.4, 135.4, 137.4, 137.5, 160.1, 161.3, 163.8, 165.6; IR (Neat, cm^{-1}): 2568br (OH), 1627 (C=O), 1556 (C=C), 1490 (C=C); Anal. Calcd for $C_{27}H_{21}ClN_2O_4$: C, 68.57; H, 4.48; N, 5.92, Found: C, 68.48; H, 4.54; N, 5.83; MS (ESI MS): 474.1$(M+H)^+$.

4-hydroxy-3-((4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)(phenyl)methyl)-1-methylquinolin-2(1*H*)-one ($S_3$4b)

White solid; mp: 289~291 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 3.73 (s, 3H, N*CH*$_3$), 3.84 (s, 3H, N*CH*$_3$), 6.45 (s, 1H, CH), 7.18-7.22 (m, 3H, ArH), 7.25-7.35 (m, 4H, ArH), 7.41-7.44 (m, 2H, ArH), 7.60-7.65 (m, 2H, ArH), 8.20 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.4 Hz, ArH), 8.26 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8.4 Hz, ArH), 12.47 (s, 1H, OH), 12.86 (s, 1H, OH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 30.2, 36.6, 115.4, 116.9, 122.8, 123.6, 125.7, 126.2, 128.1, 131.7, 137.6, 138.1, 160.1, 163.2; IR (Neat, cm^{-1}): 2569br (OH), 1627 (C=O), 1551 (C=C), 1496 (C=C); Anal. Calcd for $C_{27}H_{22}N_2O_4$: C, 73.96; H, 5.06; N, 6.39, Found: C, 74.02; H, 4.97; N, 6.31; MS (ESI MS): 439.1$(M+H)^+$.

4-hydroxy-3-((4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)(4-nitrophenyl)methyl)-1-methylquinolin-2(1*H*)-one ($S_3$4c)

White solid; mp: 292~294 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 3.73 (s, 3H, N*CH*$_3$), 3.85 (s, 3H, N*CH*$_3$), 6.46 (s, 1H, CH), 7.34-7.38 (m, 4H, ArH), 7.45 (d, 2H, J = 8.4 Hz, ArH), 7.64-7.69 (m, 2H, ArH), 8.11-8.15 (m, 2H, ArH), 8.19 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8 Hz, ArH), 8.26 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8 Hz, ArH), 12.51 (s, 1H, OH), 12.82

(s, 1H, OH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 30.2, 37.2, 94.4, 109.6, 115.4, 116.8, 122.9, 123.2, 123.7, 127.8, 131.9, 138.2, 145.7, 146.7, 156.4, 160.8; IR (Neat, cm^{-1}): 2567br (OH), 1626 (C=O), 1560 (NO), 1545 (C=C), 1498 (C=C), 1344 (NO); Anal. Calcd for $C_{27}H_{21}N_3O_6$: C, 67.07; H, 4.38; N, 8.69, Found: C, 67.18; H, 4.29; N, 8.56; MS (ESI MS): 484.2$(M+H)^+$.

4-(bis(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)benzonitrile ($S_3$4d)

White solid; mp: 290~292 ˚C; ^{1}H NMR (400MHz, MeOD+DMSO-d_6) δ: 3.76 (s, 6H, NCH_3), 6.36 (s, 1H, CH), 7.29-7.31 (m, 2H, ArH), 7.39 (t, 2H, *J* = 7.2 Hz, ArH), 7.65-7.68 (m, 4H, ArH), 7.11-7.75 (m, 2H, ArH), 8.10 (d, 2H, *J* = 8 Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$+DMSO-d_6) δ: 28.2, 29.6, 108.6, 114.9, 116.7, 118.6, 121.2, 122.5, 123.5, 127.3, 131.5, 131.6, 132.7, 138.2, 143.9, 146.3, 154.4, 164.8; IR (Neat, cm^{-1}): 2564br (OH), 2224 (C≡N), 1630 (C=O), 1603(C=C), 1542(C=C), 1498 (C=C); Anal. Calcd for $C_{28}H_{21}N_3O_4$: C, 72.56; H, 4.57; N, 9.07, Found: C, 72.61; H, 4.54; N, 9.13.

4-hydroxy-3-((4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)(4-hydroxyphenyl)methyl)-1-methylquinolin-2(1*H*)-one ($S_3$4e)

White solid; mp: 208~210 ˚C; ^{1}H NMR (400MHz, DMSO-d_6) δ: 3.73 (s, 6H, NCH_3), 6.20 (s, 1H, CH), 6.65-6.67 (m, 2H, ArH), 6.86 (d, 2H, *J* = 8.4 Hz, ArH), 7.34 (t, 2H, *J* = 7.6 Hz, ArH), 7.67-7.74 (m, 4H, ArH), 8.08 (s, 2H, ArH), 9.22 (s, 1H, OH), 12.49 (s, 1H, OH), 12.88 (s, 1H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 30.1, 30.3, 35.9, 107.7, 110.1, 110.8, 114.9, 115.3, 116.8, 122.7, 123.6, 127.2, 127.3, 131.5, 138.1, 142.3, 155.3, 162.3, 165.8; IR (Neat, cm^{-1}): 2570br (OH), 1636 (C=O), 1546(C=C), 1491 (C=C); Anal. Calcd for $C_{27}H_{22}N_2O_5$: C, 71.35; H, 4.88; N, 6.16, Found: C, 71.28; H, 4.93; N, 6.28.

4-hydroxy-3-((4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)(4-methoxyphenyl)methyl)-1-methylquinolin-2(1*H*)-one ($S_3$4f)

White solid; mp: 236~237 ˚C; ^{1}H NMR (400MHz, DMSO-d_6) δ: 3.70 (s, 9H, NCH_3 & -OCH_3), 6.23 (s, 1H, CH), 6.79-6.82 (m, 2H, ArH), 6.97 (d, 2H, *J* = 8.4 Hz, ArH),

7.40 (t, 2H, *J* = 7.6 Hz, ArH), 7.67-7.76 (m, 4H, ArH), 8.07 (s, 2H, ArH), 12.78 (brs, 2H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 30.0, 30.3, 35.9, 38.8, 54.9, 113.4, 115.4, 116.9, 122.8, 123.6, 127.3, 129.2, 131.6, 138.1, 142.9, 162.4, 162.5; IR (Neat, cm^{-1}): 2566br (OH), 1631 (C=O), 1545(C=C), 1493 (C=C); Anal. Calcd for $C_{28}H_{24}N_2O_5$: C, 71.78; H, 5.16; N, 5.98, Found: C, 71.66; H, 5.23; N, 5.87; ESI MS: 469.9$(M+H)^+$.

4-hydroxy-3-((4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)(pyridin-2-yl)methyl)-1-methylquinolin-2(1*H*)-one ($S_3$4g)

White solid; mp: 267~268 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 3.74 (s, 6H, NCH_3), 6.49 (s, 1H, CH), 7.10-7.13 (m, 1H, ArH), 7.25 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8 Hz, ArH), 7.30 (tt, 2H, J_1 = 0.8 Hz, J_2 = 8 Hz, ArH), 7.40 (d, 2H, *J* = 8.4 Hz, ArH), 7.57-7.62 (m, 3H, ArH), 8.21 (dd, 2H, 1.6 Hz, J_2 = 8 Hz, ArH), 8.51-8.52 (m, 1H, ArH), 12.71 (brs, 2H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 30.3, 40.3, 110.6, 114.2, 118.1, 121.1, 121.4, 122.5, 124.9, 131.1, 136.2, 138.6, 149.0, 158.1, 161.5, 165.9; IR (Neat, cm^{-1}): 2563br (OH), 1629 (C=O), 1550 (C=C), 1487 (C=C); Anal. Calcd for $C_{26}H_{21}N_3O_4$: C, 71.06; H, 4.82; N, 9.56, Found: C, 71.15; H, 4.77; N, 9.42; ESI MS: 440.8$(M+H)^+$.

3-(furan-2-yl(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one ($S_3$4h)

White solid; mp: 240~241 ˚C; ^{1}H NMR (400MHz, DMSO-d_6) δ: 3.73 (s, 6H, NCH_3), 6.08-6.09 (m, 1H, ArH), 6.20 (s, 1H, CH), 6.38-6.39 (m, 1H, ArH), 7.40 (t, 2H, *J* = 7.6 Hz, ArH), 7.49 (s, 1H, ArH), 7.63-7.75 (m, 4H, ArH), 8.07 (dd, 2H, J_1 = 1.6 Hz, J_2 = 8 Hz, ArH), 12.49 (s, 1H, OH), 12.85 (s, 1H, OH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 30.06, 30.08, 32.7, 106.3, 110.3, 115.4, 116.8, 122.8, 123.6, 131.7, 138.1, 141.4, 150.9, 156.2, 160.2; IR (Neat, cm^{-1}): 2566br (OH), 1633 (C=O), 1532 (C=C), 1499 (C=C); Anal. Calcd for $C_{25}H_{20}N_2O_5$: C, 70.08; H, 4.71; N, 6.54, Found: C, 69.96; H, 4.63; N, 6.43; ESI MS: 429.9$(M+H)^+$.

4-hydroxy-3-((4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)(thiophen-2-yl)methyl)-1-methylquinolin-2(1*H*)-one ($S_3$4i)

White solid; mp: 263~264 ˚C; ^{1}H NMR (400MHz, DMSO-d_6+ MeOD) δ: 3.77 (s, 6H, NCH_3), 6.43 (s, 1H, CH), 6.73-6.74 (m, 1H, ArH), 6.91-6.93 (m, 1H, ArH), 7.25-7.27 (m, 1H, ArH), 7.41 (t, 2H, *J* = 7.6 Hz, ArH), 7.66 (d, 2H, *J* = 8.4 Hz, ArH), 7.72-

7.76 (m, 2H, ArH), 8.14 (d, 2H, *J* = 7.6 Hz, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 29.3, 30.07, 33.3, 103.6, 105.9, 114.7, 121.6, 122.4, 125.4, 126.0, 131.2, 138.1, 142.7, 147.7, 148.3, 156.1, 164.2; IR (Neat, cm^{-1}): 2567br (OH), 1634 (C=O), 1533 (C=C), 1498 (C=C); Anal. Calcd for $C_{25}H_{20}N_2O_4S$: C, 67.55; H, 4.54; N, 6.30, Found: C, 67.46; H, 4.49; N, 6.39.

4-hydroxy-3-((4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)(naphthalen-2-yl)methyl)-1-methylquinolin-2(1*H*)-one (S$_3$4j)

White solid; mp: 303~304 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 3.65 (s, 3H, NCH_3), 3.79 (s, 3H, NCH_3), 6.52 (s, 1H, CH), 7.23-7.32 (m, 5H, ArH), 7.36-7.39 (m, 2H, ArH), 7.54-7.71 (m, 6H, ArH), 8.16 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8 Hz, ArH), 8.21 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8 Hz, ArH), 12.45 (s, 1H, OH), 12.81 (s, 1H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 30.1, 30.6, 37.5, 109.7, 111.6, 114.2, 114.3, 117.8, 118.2, 122.6, 122.7, 124.8, 124.9, 125.0, 125.2, 125.3, 125.7, 127.5, 127.7, 127.9, 131.2, 131.3, 132.1, 133.5, 135.4, 138.5, 138.6, 161.3, 162.2, 165.0, 166.8; IR (Neat, cm^{-1}): 2569br (OH), 1631 (C=O), 1539 (C=C), 1472 (C=C); Anal. Calcd for $C_{31}H_{24}N_2O_4$: C, 76.21; H, 4.95; N, 5.73, Found: C, 76.10; H, 4.82; N, 5.66; ESI MS: 489.2 (M+H)$^+$.

4-hydroxy-3-((4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)-1-methylquinolin-2(1*H*)-one (S$_3$4k)

White solid; mp: 293~294 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 3.72 (s, 6H, NCH_3), 3.96 (s, 2H, CH_2), 7.19-7.25 (m, 2H, ArH), 7.31 (d, 2H, *J* = 8.4 Hz, ArH), 7.49-7.54 (m, 2H, ArH), 8.11 (dd, 2H, J_1 = 1.6 Hz, J_2 = 8 Hz, ArH), 12.44 (s, 2H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 20.0, 28.7, 29.1, 108.1, 113.1, 116.6, 121.5, 123.4, 129.9, 137.3, 159.6, 165.2; IR (Neat, cm^{-1}): 2563br (OH), 1630 (C=O), 1537 (C=C), 1483 (C=C); Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73, Found: C, 69.51; H, 5.14; N, 7.68; ESI MS: 363.2 (M+H)$^+$.

3-((2-amino-6-oxocyclohex-1-enyl)(4-chlorophenyl)methyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one (S$_3$5g)

White solid; mp: 266~267 ˚C; ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.85-1.92 (m, 2H), 2.24-2.35 (m, 2H), 2.43-2.46 (m, 2H), 3.69 (s, 3H, NCH_3), 5.72 (s, 1H, CH), 7.04-7.07 (m, 2H, ArH), 7.23-7.32 (m, 3H, ArH), 7.57 (d, 1H, *J* = 8 Hz, ArH), 7.64-7.69

(m, 1H, ArH), 7.93-7.97 (m, 2H, ArH), 8.35 (s, 1H, ArH), 13.7 (s, 1H, OH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 20.3, 29.4, 29.9, 34.7, 35.7, 108.7, 109.2, 114.7, 121.9, 123.7, 127.7, 128.2, 129.6, 131.1, 138.4, 159.9, 164.7, 171.2, 195.5; IR (Neat, cm^{-1}): 3224 (OH), 3069 (CH_{arom}), 1693 (C=O), 1561 (C=C), 1489 (C=C); Anal. Calcd for $C_{23}H_{21}ClN_2O_3$: C, 67.56; H, 5.18; N, 6.85, Found: C, 67.49; H, 5.03; N, 6.78; ESI MS: 409.2 $(M+H)^+$.

3-((2-amino-6-oxocyclohex-1-enyl)(phenyl)methyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one ($S_3$5h)

White solid; mp: 250~251 ˚C; ^{1}H NMR (400MHz, DMSO-d_6+MeOD) δ: 1.91-1.97 (m, 2H), 2.29-2.38 (m, 2H), 2.50-2.67 (m, 2H), 3.74 (s, 3H, N*CH*$_3$), 5.82 (s, 1H, CH), 7.07-7.13 (m, 3H, ArH), 7.19-7.23 (m, 2H, ArH), 7.29-7.32 (m, 1H, ArH), 7.56 (d, 1H, *J* = 8.4 Hz, ArH), 7.64-7.69 (m, 1H, ArH), 8.00-8.04 (m, 1H, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6+MeOD) δ: 20.2, 29.1, 29.3, 35.1, 37.8, 108.6, 109.2, 116.8, 121.6, 123.5, 124.7, 126.0, 127.5, 130.7, 138.2, 139.6, 160.0 164.8, 170.5, 195.6; IR (Neat, cm^{-1}): 3226 (OH), 3066 (CH_{arom}), 1691 (C=O), 1564 (C=C), 1492 (C=C); Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48, Found: C, 73.59; H, 5.86; N, 7.59; ESI MS: 375.2 $(M+H)^+$.

3-((2-amino-6-oxocyclohex-1-enyl)(4-nitrophenyl)methyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one ($S_3$5i)

White solid; mp: 249~250 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.961-1.99 (m, 2H), 2.44-2.47 (m, 2H), 2.48-2.49 (m, 2H), 3.66 (s, 3H, N*CH*$_3$), 5.91 (s, 1H, CH), 7.24-7.39 (m, 4H, ArH), 7.53-7.61 (m, 1H, ArH), 8.01-8.14 (m, 3H, ArH), 8.85 (s, 1H), 12.82 (s, 1H, OH); ^{13}C NMR (100.6 MHz, DMSO-d_6+MeOD) δ: 20.2, 29.4, 35.1, 35.9, 114.7, 116.9, 121.1, 123.1, 123.7, 127.6, 131.3, 138.4, 145.3, 148.8, 160.0 164.5, 171.4, 195.6; IR (Neat, cm^{-1}): 3222 (OH), 3059 (CH_{arom}), 1696 (C=O), 1559 (C=C), 1485 (C=C); Anal. Calcd for $C_{23}H_{21}N_3O_5$: C, 65.86; H, 5.05; N, 10.02, Found: C, 65.98; H, 5.16; N, 9.89; ESI MS: 420.2$(M+H)^+$.

4-((2-amino-6-oxocyclohex-1-enyl)(4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methyl)benzonitrile ($S_3$5j)

White solid; mp: 258~259 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.93-1.99 (m, 2H), 2.23-2.29 (m, 2H), 2.42-2.49 (m, 2H), 3.70 (s, 3H, N*CH*$_3$), 5.88 (s, 1H, CH), 7.19-7.22 (m, 2H, ArH), 7.31 (d, 1H, *J* = 8.4 Hz, ArH), 7.44-7.59 (m, 4H, ArH), 8.08 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8 Hz, ArH), 8.83 (s, 1H), 12.83 (s, 1H, OH); ^{13}C NMR (100.6 MHz, DMSO-d_6+MeOD) δ: 20.1, 29.1, 35.4, 36.1, 107.9, 109.0, 114.1, 118.7, 119.6, 121.7, 123.5, 127.2, 130.9, 131.4, 138.4, 151.7, 155.2, 164.5, 165.3, 195.1; IR (Neat, cm^{-1}): 3226 (OH), 3061 (CH_{arom}), 2224 (C≡N), 1690 (C=O), 1558 (C=C), 1490 (C=C); Anal. Calcd for $C_{24}H_{21}N_3O_3$: C, 72.16; H, 5.30; N, 10.52, Found: C, 72.08; H, 5.21; N, 10.41; ESI MS: 400.1$(M+H)^+$.

3-((2-amino-6-oxocyclohex-1-enyl)(4-methoxyphenyl)methyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one ($S_3$5l)

White solid; mp: 251~252 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.89-1.98 (m, 2H), 2.19-2.27 (m, 2H), 2.41-2.45 (m, 2H), 3.68 (s, 6H, -O*CH*$_3$ & N*CH*$_3$), 5.82 (s, 1H, , CH, ArH), 6.69-6.72 (m, 2H), 7.00 (d, 2H, *J* = 8.4 Hz, ArH), 7.17-7.30 (m, 3H, ArH), 7.48-7.53 (m, 1H, ArH), 8.09-8.11 (m, 1H, ArH), 8.80 (s, 1H), 13.03 (s, 1H, OH); ^{13}C NMR (100.6 MHz, DMSO-d_6+MeOD) δ: 19.8, 29.2, 30.1, 34.4, 35.2, 54.2, 109.1, 110.4, 112.4, 112.6, 116.9, 120.9, 123.9, 126.5, 129.7, 130.1, 137.7, 156.3, 159.9, 164.9, 167.5, 196.2; IR (Neat, cm^{-1}): 3227 (OH), 3062 (CH_{arom}), 1694 (C=O), 1559 (C=C), 1483 (C=C); Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93, Found: C, 71.36; H, 6.09; N, 6.77; ESI MS: 405.0$(M+H)^+$.

3-((2-amino-6-oxocyclohex-1-enyl)(furan-2-yl)methyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one ($S_3$5n)

White solid; mp: 239~241 ˚C; ^{1}H NMR (400MHz, DMSO-d_6+MeOD) δ: 1.87-1.97 (m, 2H), 2.18-2.25 (m, 2H), 2.38-2.41 (m, 2H), 3.67 (s, 3H, N*CH*$_3$), 5.78 (s, 1H, ArH), 5.92 (s, 1H, CH), 6.20 (s, 1H, ArH), 7.17-7.34 (m, 2H, ArH), 7.48-7.55 (m, 1H, ArH), 8.11-8.16 (m, 1H, ArH), 8.64 (s, 1H), 13.06 (s, 1H, OH); ^{13}C NMR (100.6 MHz, DMSO-d_6+MeOD) δ: 19.43, 28.8, 30.9, 34.4, 104.1, 106.4, 106.7, 108.7, 113.1, 116.1, 120.8, 121.4, 122.7, 129.9, 137.4, 139.6, 152.4, 153.2, 159.5, 195.1; IR (Neat,

cm^{-1}): 3226 (OH), 3072 (CH_{arom}), 1681 (C=O), 1625 (C=C), 1598 (C=C); Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69, Found: C, 69.34; H, 5.48; N, 7.57; ESI MS: 365.2$(M+H)^+$.

3-((2-amino-6-oxocyclohex-1-enyl)(thiophen-2-yl)methyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one ($S_3$5o)

White solid; mp: 242~244 ˚C; ^{1}H NMR (400MHz, DMSO-d_6+MeOD) δ: 1.84-1.91 (m, 2H), 2.25-2.29 (m, 2H), 2.37-2.49 (m, 2H), 3.71 (s, 3H, NCH_3), 5.92 (s, 1H, CH), 6.55-6.56 (m, 1H, ArH), 6.82-6.84 (m, 1H, ArH), 7.18-7.20 (m, 1H, ArH), 7.41 (t, 1H, J = 7.6 Hz, ArH) 7.56 (d, 1H, J = 8.4 Hz, ArH) 8.01 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8Hz, ArH), 8.12 (d, 1H, J = 8 Hz, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6+MeOD) δ: 20.1, 26.2, 32.8, 98.1, 100.5, 114.3, 114.9, 121.7, 123.6, 125.9, 130.9, 138.3, 140.9, 146.1, 157.3, 158.9, 164.2, 196.8; IR (Neat, cm^{-1}): 3226 (OH), 3069 (CH_{arom}), 1683 (C=O), 1620 (C=C), 1594 (C=C); Anal. Calcd for $C_{21}H_{20}N_2O_3S$: C, 66.29; H, 5.30; N, 7.36, Found: C, 66.18; H, 5.22; N, 7.27; ESI MS: 381.1 $(M+H)^+$.

3-((2-amino-6-oxocyclohex-1-enyl)(naphthalen-2-yl)methyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one ($S_3$5p)

White solid; mp: 202~204 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.89-2.06 (m, 2H), 2.19-2.28 (m, 2H), 2.42-2.48 (m, 2H), 3.72 (s, 3H, NCH_3), 6.02 (s, 1H, CH), 7.21-7.35 (m, 5H, ArH), 7.47-7.48 (m, 1H, ArH), 7.53-7.71 (m, 4H, ArH), 8.11-8.13 (m, 1H, ArH), 8.77 (s, 1H), 12.97 (s, 1H, OH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 20.9, 30.6, 31.1, 36.4, 37.5, 109.7, 111.3, 114.2, 118.0, 122.6, 124.7, 125.1, 125.5, 125.7, 127.4, 127.6, 127.7, 127.9, 131.3, 131.8, 133.5, 136.9, 138.8, 161.1, 165.9, 168.6, 197.3; IR (Neat, cm^{-1}): 3229 (OH), 3060 (CH_{arom}), 1690 (C=O), 1560 (C=C), 1493 (C=C); Anal. Calcd for $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.70; N, 6.60, Found: C, 76.27; H, 5.66; N, 6.44; ESI MS: 425.9 $(M+H)^+$.

3-((2-amino-6-oxocyclohex-1-enyl)methyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one ($S_3$5q)

White solid; mp: 241~242 ˚C; ^{1}H NMR (400MHz, DMSO-d_6+MeOD) δ: 1.77-1.95 (m, 2H), 2.30 (t, 2H, J = 6.4 Hz) 2.45 (t, 2H, J = 6.4 Hz), 3.67 (s, 3H, NCH_3), 3.51 (s, 2H, CH_2), 7.25-7.29 (m, 1H, ArH), 7.50 (d, 1H, J = 8.8 Hz, ArH) 7.57-7.62 (m, 1H,

ArH), 8.00 (dd, 1H, J_1 = 1.6 Hz, J_2 = 8 Hz, ArH); ^{13}C NMR (100.6 MHz, DMSO-d_6+MeOD) δ: 18.6, 20.5, 28.3, 28.7, 34.1, 37.6, 37.8, 38.2, 101.0, 106.7, 108.9, 113.9, 116.4, 121.4, 123.0, 130.2, 133.9, 137.9, 164.4, 169.1, 196.1; IR (Neat, cm^{-1}): 3226 (OH), 3050 (CH_{arom}), 1685 (C=O), 1570 (C=C), 1479 (C=C); Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39, Found: C, 68.36; H, 5.95; N, 9.44; ESI MS: 298.9 $(M+H)^+$.

Table 4.1: Crystallographic data of compound **$S_3$5h**

Crystal data [CCDC No. 938662]	
Empirical formula	$C_{23}H_{22}N_2O_3$
Formula weight	374.43
Crystal size (mm)	0.3 x 0.2 x 0.1
Crystal system	Monoclinic
Space group	P21/c
a (Å); b (Å); c (Å)	14.0952(13); 10.0541(9); 14.1685(13)
α (˚); β (˚); γ (˚)	90; 111.8180(10); 90
Volume ($Å^3$)	1864.1(3)
Z	4
Crystal density, g/cm^3	1.334
F(000)	792
Absorption coefficient	0.089
Temperature (T)	296 (2)
Radiation wavelength	0.71073
Radiation type	MoKα
Radiation source	Fine-focus sealed tube
Radiation monochromator	Graphite
h_{min}; k_{min}; l_{min}	-17; -12; -17
h_{max}; k_{max}; l_{max}	17; 12; 17
R-Factor (%)	3.82

The representative ^{1}H NMR, ^{13}C NMR and ESI MS spectra of **$S_3$4a** and **$S_3$5g** are given below

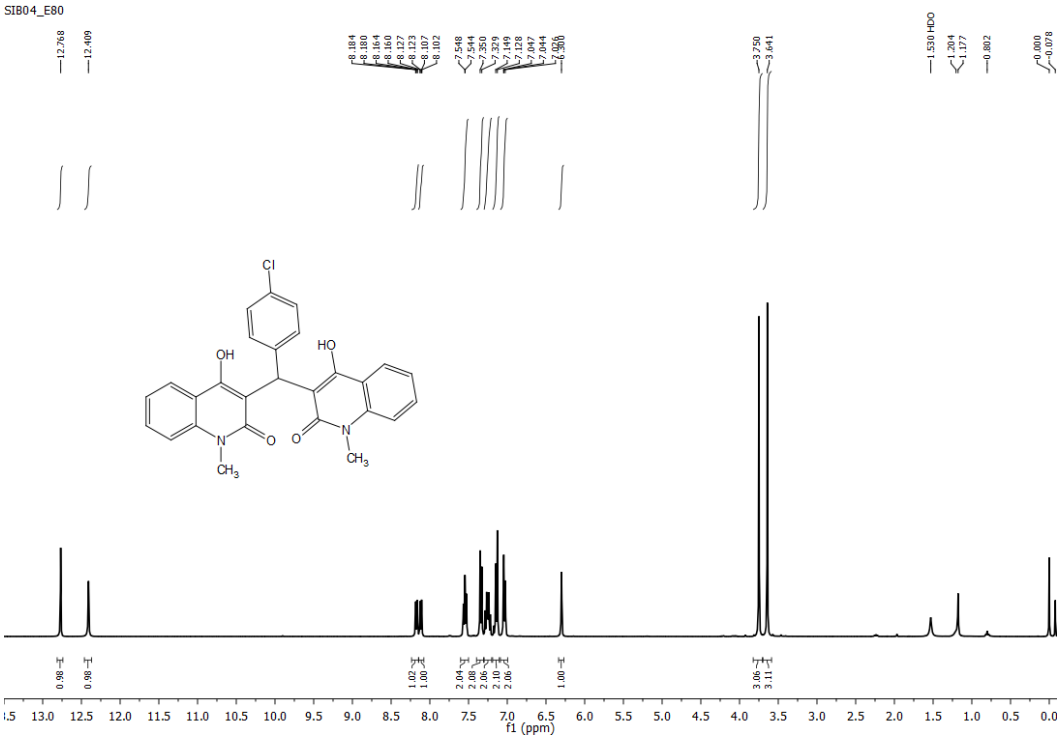


Fig. 4.1: ^{1}H NMR spectrum of **$S_3$4a**

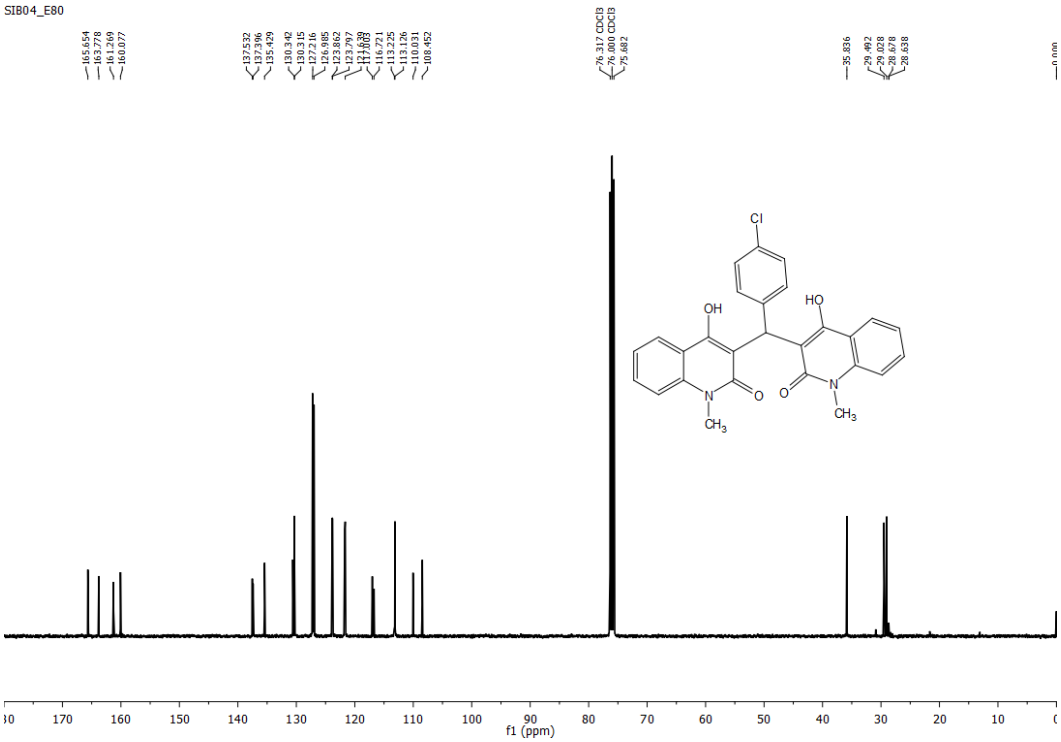


Fig. 4.2: ^{13}C NMR spectrum of **$S_3$4a**

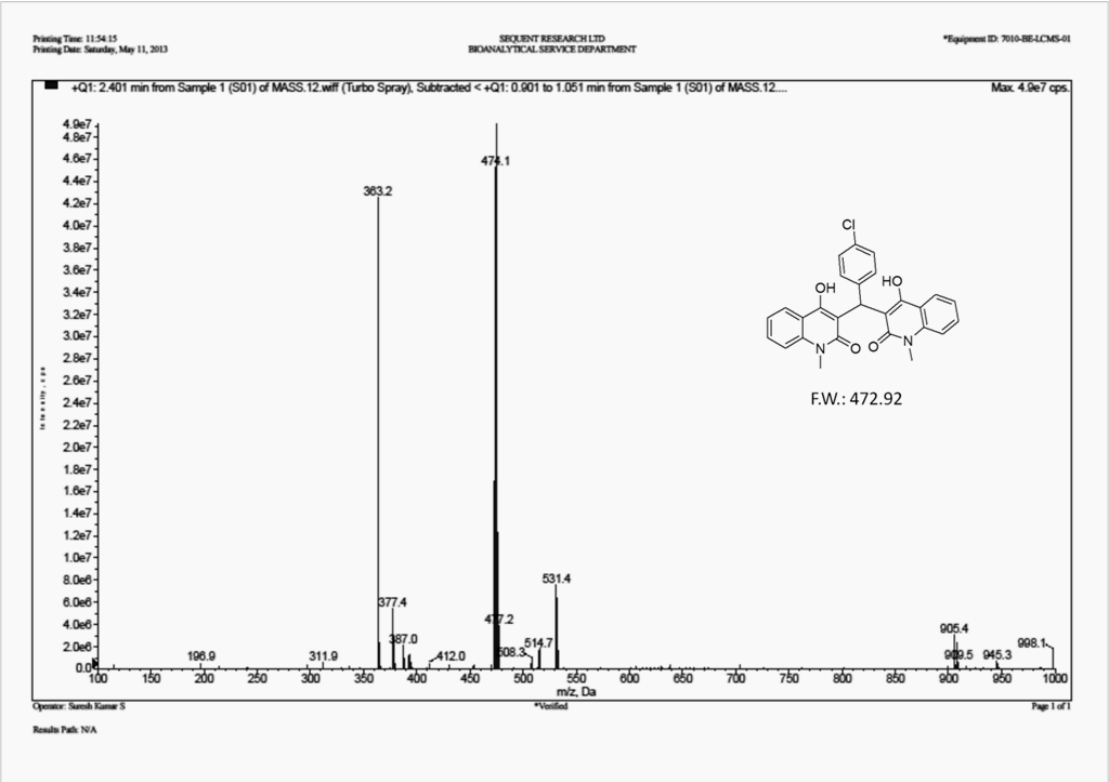


Fig. 4.3: ESI MS spectrum of **$S_3$4a**

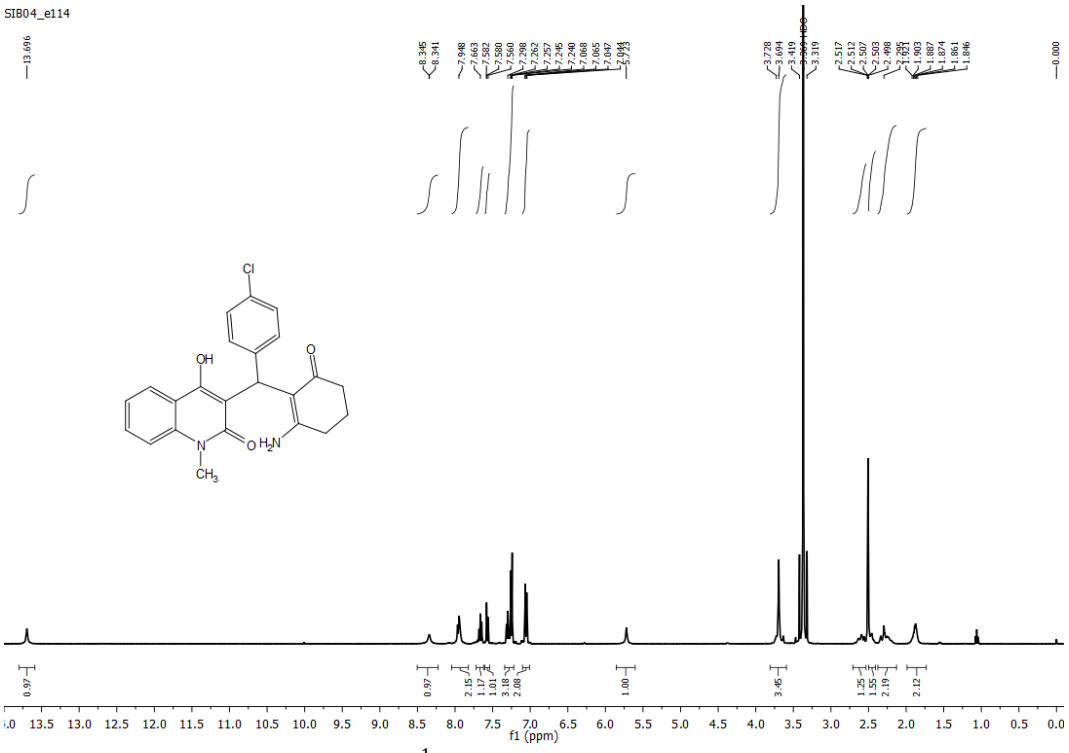


Fig. 4.4: ^{1}H NMR spectrum of **$S_3$5g**

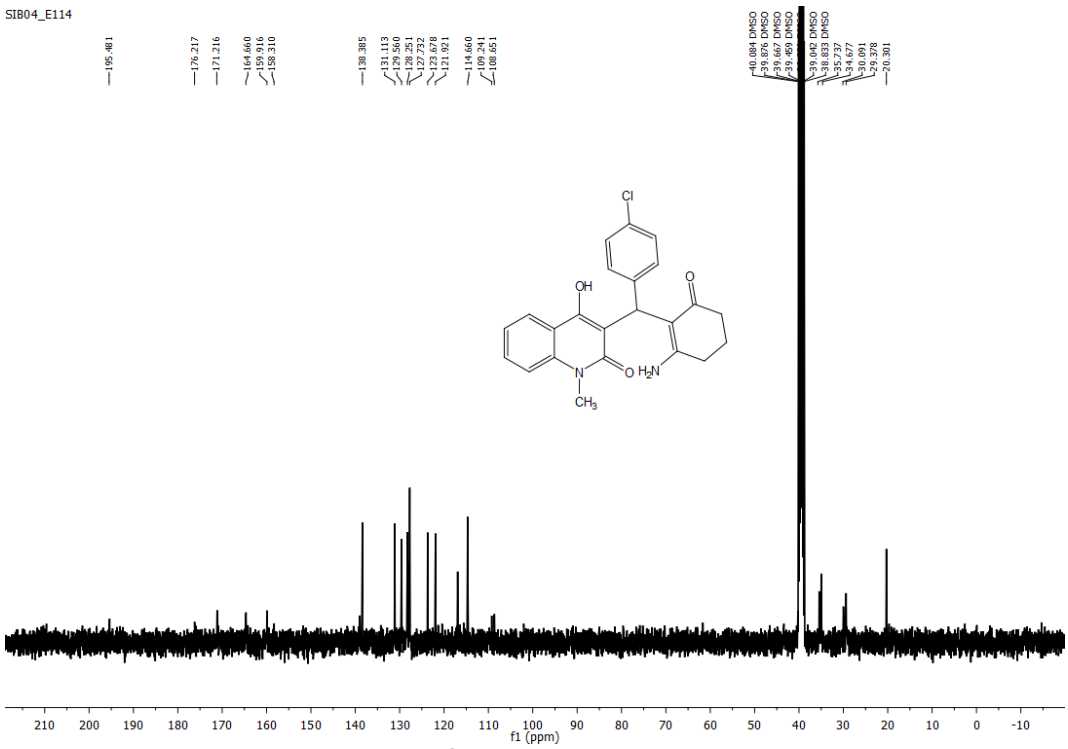


Figure 4.5: ^{13}C NMR spectrum of **$S_3$5g**

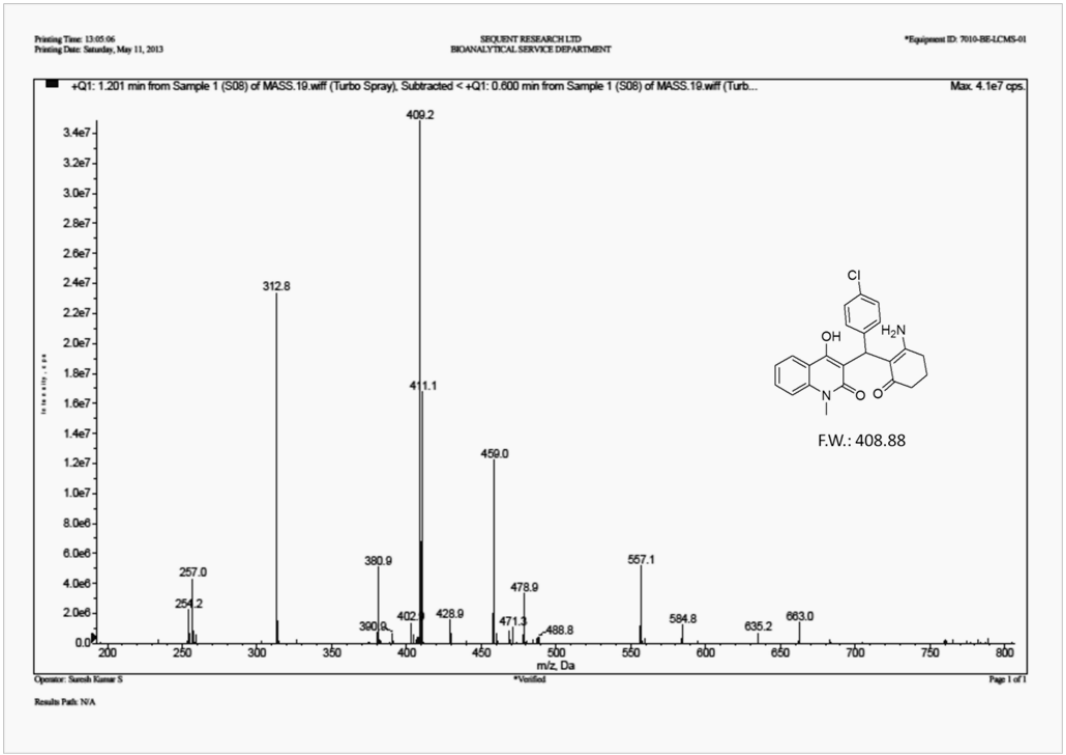
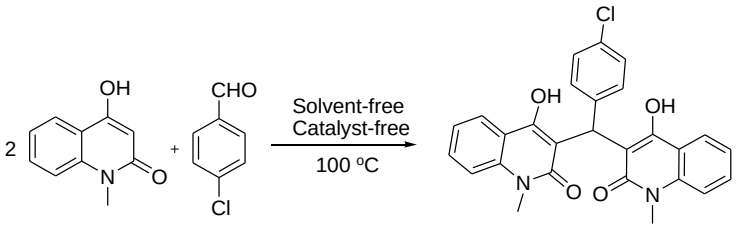


Fig. 4.6: ESI MS spectrum of **$S_3$5g**

4.3 RESULTS AND DISCUSSION

Initially, the 2:1 reaction of 4-hydroxyquinolin-2(1*H*)-one **($S_3$1)** and 4-chlorobenzaldehyde **($S_3$2a**) as a probe reaction under solvent- and catalyst-free reaction conditions at 80 ˚C. The partial melt of the reaction mixture was observed and the reaction was monitored by TLC (6:4 EtOAc: PE). The reaction proceeded via cascade Knoevenagel-Michael reaction to yield corresponding product **$S_3$4a** in 64% within 30 min. However, no further improvement in conversion was observed even after 60 min. The reaction was optimized by varying the temperature to obtain the best possible result. In order to compare the efficiency of the solvent-free reaction with solution reaction, the reaction was carried out under solution state using different solvents (Table 4.2, entry **5-7**). The increased reaction time was observed with poor product yield in solution state. This may be attributed to the decreased reactant concentration due to dilution.

Table 4.2: Optimization of the reaction condition and comparison with solvent assisted reaction [a]

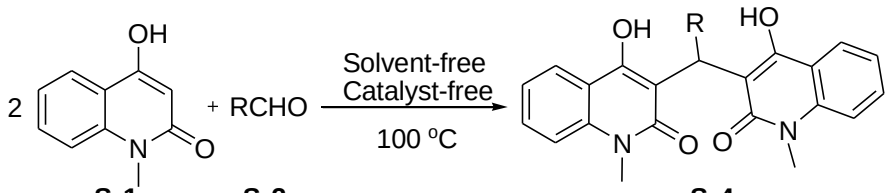


Entry	Solvent	Reaction temperature	Reaction time [b]	Yield [c]
1	None	80	60 min	64
2	None	90	60 min	72
3	**None**	**100**	**30 min**	**93**
4	None	110	30 min	93
4	EtOH	100	180 min	42
5	Acetonitrile	100	180 min	56
5	Water	100	180 min	trace
6	1,4-dioxane	100	180 min	23
7	Toluene	100	180 min	trace

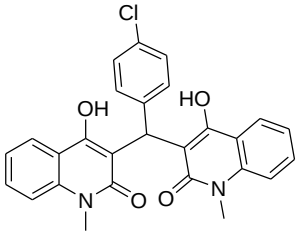
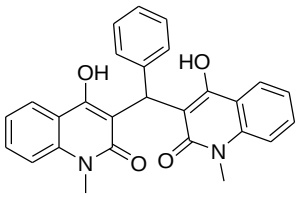
[a]All the reactions were carried out using 4-hydroxyquinolin-2(1*H*)-one (2 mmol) and 4-chlorobenzaldehyde (1 mmol). [b]Reactions were monitored by TLC. [c]Isolated yield.

To evaluate the scope of the present solvent- and catalyst-free heating protocol, 4-hydroxyquinolin-2(1*H*)-one was reacted with various aldehydes with diverse functionality and reactivity. As expected, the reaction proceeded faster with aldehydes with electron withdrawal substituents than electron donating substituents. For instance, the reaction with 4-nitrobenzaldehyde (Table 4.3, entry **3**) was completed faster than with 4-methoxybenzaldehyde (Table 4.3, entry 6). This may be due to the increased reactivity of electron deficient aldehydes towards Knoevenagel condensation as well as Michael addition. Further, the heterocyclic aldehydes (Table 4.3, entry **7-9**) and formaldehyde (Table 4.3, entry **11**) also underwent smooth reaction to yield corresponding products in high yield. However, the reaction with propionaldehyde (Table 4.3, entry **12**), an aliphatic aldehyde failed to yield required product.

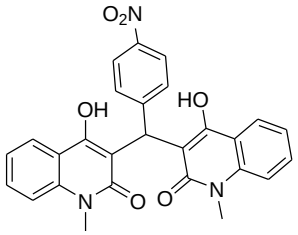
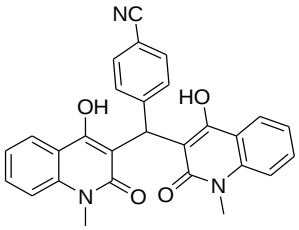
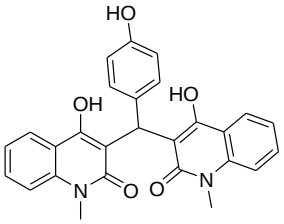
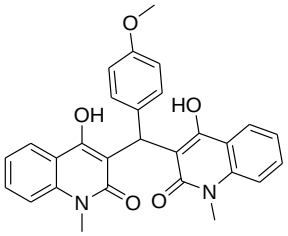
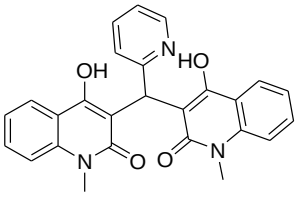
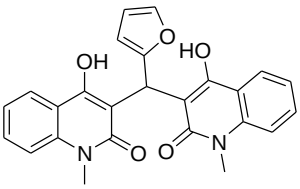
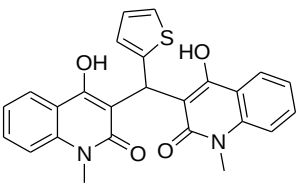
Table 4.3: Evaluation of the scope for the synthesis of **$S_3$4**



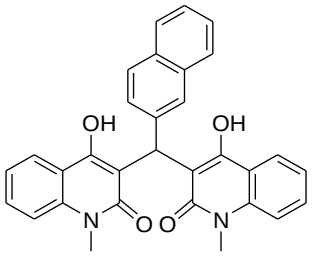
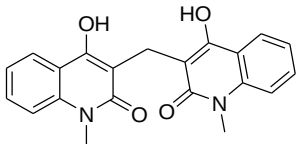
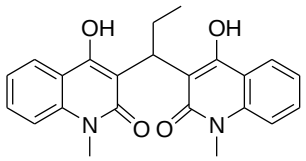
$S_3$1 **$S_3$2** **$S_3$4**

Entry	Aldehydes $S_3$2 (R)	Reaction time (min)[a]	Product $S_3$4		Yield[b]
1	**$S_3$2a:** 4-ClC_6H_4	30	**$S_3$4a**		94
2	**$S_3$2b:** C_6H_4	30	**$S_3$4b**		86

Contd.

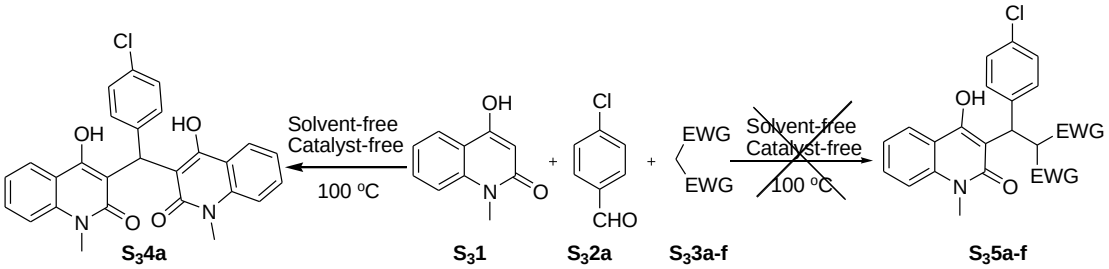
3	**$S_3$2c:** 4-$NO_2C_6H_4$	15	**$S_3$4c**		92
4	**$S_3$2d:** 4-CNC_6H_4	20	**$S_3$4d**		90
5	**$S_3$2e:** 4-OHC_6H_4	45	**$S_3$4e**		81
6	**$S_3$2f:** 4-$OCH_3C_6H_4$	45	**$S_3$4f**		83
7	**$S_3$2g:** 2-pyridyl	20	**$S_3$4g**		89
8	**$S_3$2h:** 2-furyl	20	**$S_3$4h**		91
9	**$S_3$2i:** 2-thienyl	20	**S34i**		83

Contd.

10	**$S_3$2j:** 2-naphthyl	45	**$S_3$4j**		78
11	**$S_3$2k:** formyl	20	**$S_3$4k**		93
12	**$S_3$2l:** CH_3CH_2-	60	**$S_3$4l**		00

[a] All the reactions were monitored by TLC. [b] yield of pure product.

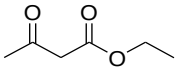
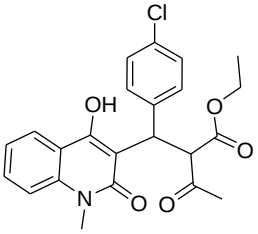
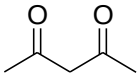
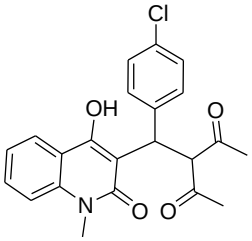
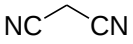
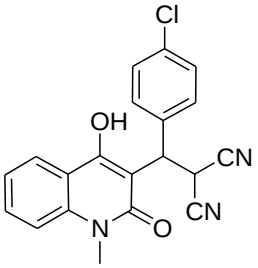
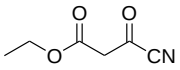
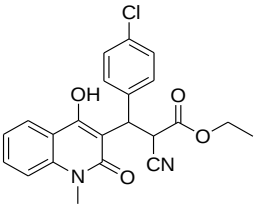
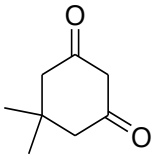
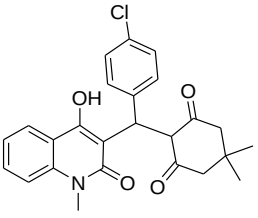
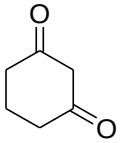
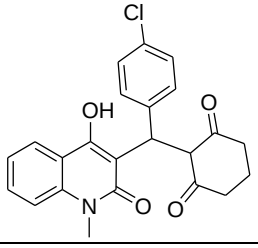
Inspired by the above results, the studies have been extended to solvent- and catalyst-free three component cascade reaction by reacting 4-hydroxyquinolin-2(1*H*)-one and 4-chlorobenzaldehyde with various active methylene compounds (Scheme 4.2). However, initial attempts with EAA (Table 4.4, entry **1**), acetylacetone (Table 4.4, entry **2**), malononitrile (Table 4.4, entry **3**), ehylcyanoacetate (Table 4.4, entry **4**), dimedone (Table 4.4, entry **5**), 1,3-cyclohexanedione (Table 4.4, entry **6**) failed to yield expected three component product and only **$S_3$4a** was obtained as product and active methylene compounds remained unreacted.



$S_3$4a **$S_3$1** **$S_3$2a** **$S_3$3a-f** **$S_3$5a-f**

Scheme 4.2: Three component cascade reaction of **$S_3$1** and **$S_3$2a** attempted with various active methylene compounds

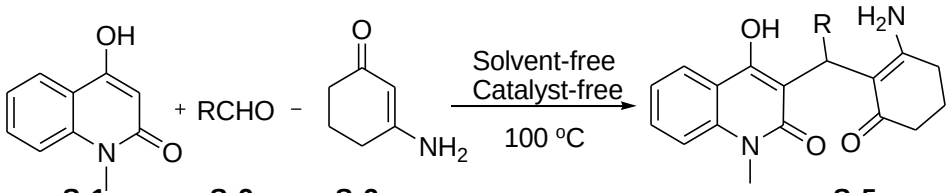
Table 4.4: Three component cascade that were failed to yield expected product under present protocol

Entry	Active methylenes $S_3$3	Reaction time (min) [a]	Product $S_3$5	Yield
1	**$S_3$3a:** 	60	**$S_3$5a** 	00
2	**$S_3$3b:** 	60	**$S_3$5b** 	00
3	**$S_3$3c:** 	60	**$S_3$5c** 	00
4	**$S_3$3d:** 	60	**$S_3$5d** 	00
5	**$S_3$3e:** 	60	**$S_3$5e** 	00
6	**$S_3$3f:** 	60	**$S_3$5f** 	00

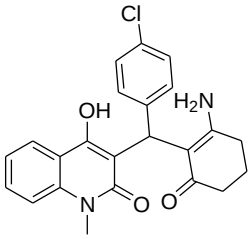
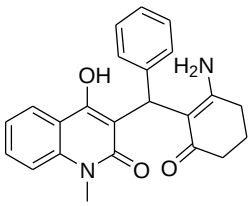
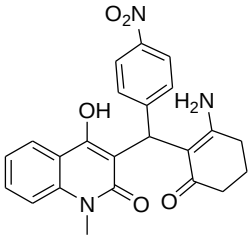
[a] All the reactions were monitored by TLC.

After several unsuccessful attempts with various active methylene compounds, the reaction with 3-aminocyclohex-2-enone **($S_3$3g)** successfully underwent three component cascade Knoevenagel-Michael reaction to yield product **$S_3$5g**. Interestingly, it was found that by the sequential addition of reactants **$S_3$1**, **$S_3$2a** followed by **$S_3$3g** only trace amount of the desired product **$S_3$5g** was obtained with the formation of **$S_3$4a** as a major product and other unidentified impurities. In order to explore reaction generality, various aldehydes were reacted with 4-hydroxyquinolin-2(1*H*)-one and 3-aminocyclohex-2-enone. The reaction proceeded smoothly with aldehydes bearing electron donating and electron withdrawing substituents. However, the reaction with propionaldehyde (Table 4.5, entry **12**) failed without product formation.

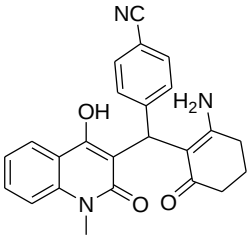
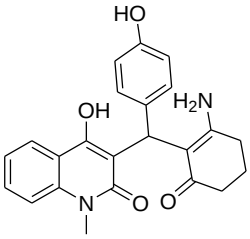
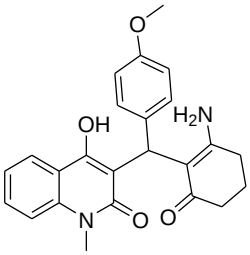
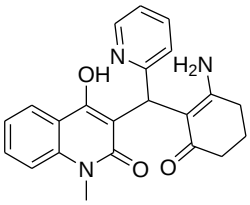
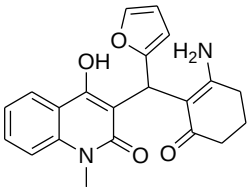
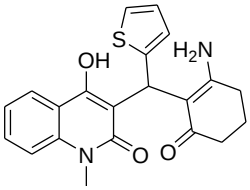
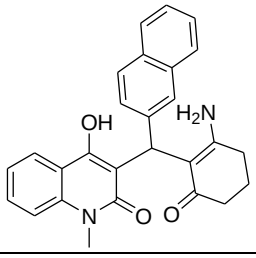
Table 4.5: Evaluation of the scope for the synthesis of **$S_3$5** via three component cascade



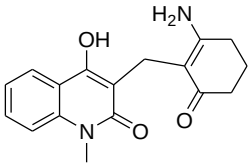
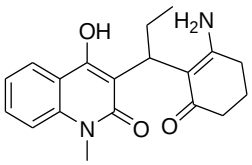
$S_3$1 **$S_3$2** **$S_3$3g** **$S_3$5g-r**

Entry	Aldehyde $S_3$2 (R)	Reaction time (min)[a]	Product $S_3$5		Yield[b]
1	**$S_3$2a:** 4-ClC_6H_4	20	**$S_3$5g**		89
2	**$S_3$2b:** C_6H_4	20	**$S_3$5h**		92
3	**$S_3$2c:** 4-$NO_2C_6H_4$	15	**$S_3$5i**		94

Contd.

4	**$S_3$2d:** 4-CNC_6H_4	15	**$S_3$5j**		88
5	**$S_3$2e:** 4-OHC_6H_4	60	**$S_3$5k**		00
6	**$S_3$2f:** 4-$OCH_3C_6H_4$	30	**$S_3$5l**		92
7	**$S_3$2g:** 2-pyridyl	15	**$S_3$5m**		00
8	**$S_3$2h:** 2-furyl	20	**$S_3$5n**		90
9	**$S_3$2i:** 2-thienyl	20	**S35o**		78
10	**$S_3$2j:** 2-naphthyl	30	**$S_3$5p**		81

Contd.

11	**$S_3$2k:** formyl	10	**$S_3$5q**		94
12	**$S_3$2l:** CH_3CH_2-	60	**$S_3$5r**		00

[a] All the reactions were monitored by TLC. [b] yield of pure product.

The structure of the products was confirmed by spectral data and elemental analysis. Further, in order to confirm the three component cascade product unambiguously, **$S_3$5h** was selected as a representative compound and characterized by SCXRD as shown in Fig. 4.7.

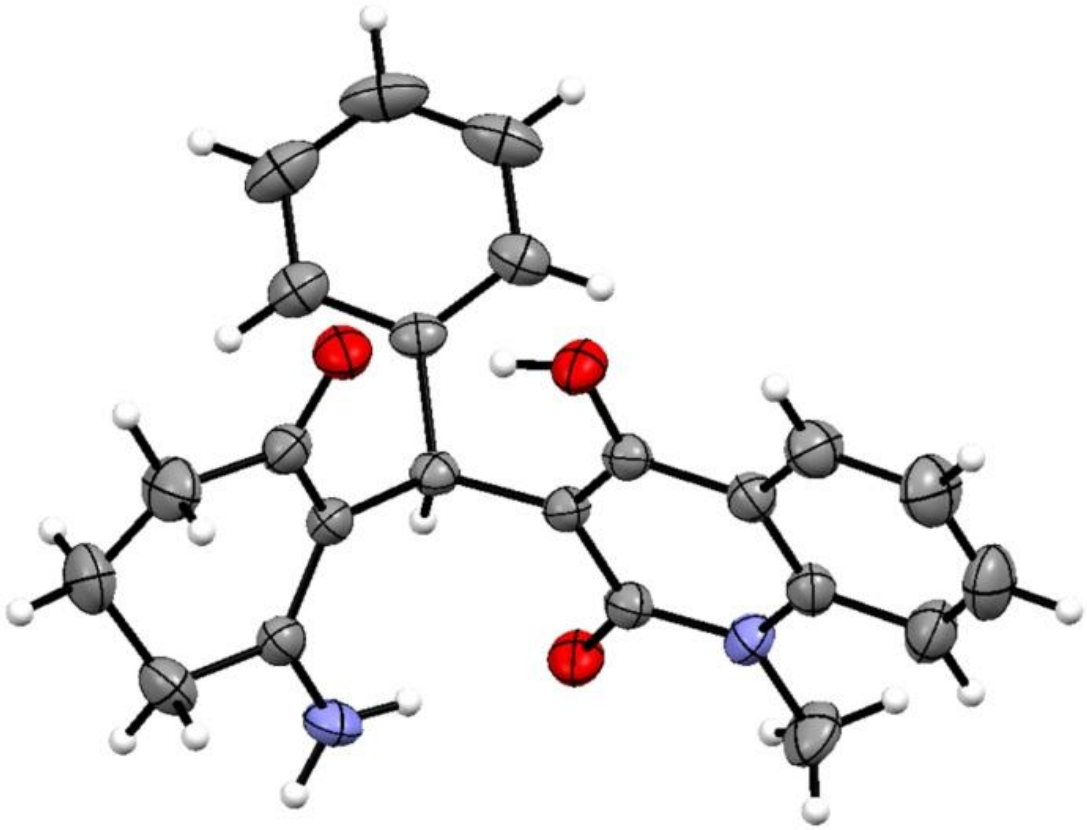
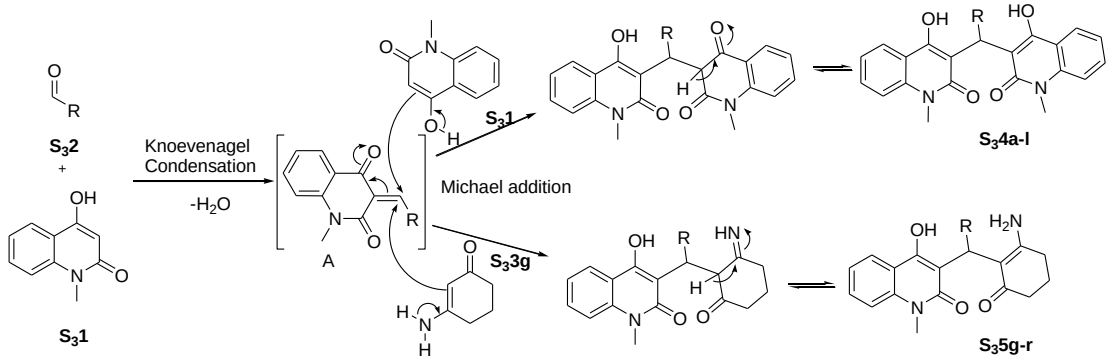


Figure 4.7: ORTEP (50% probability) diagram of the crystal structure of **$S_3$5h**.

Further, in order to isolate the intermediate Knoevenagel condensation product, the reaction was carried out with equimolar ratio of 4-hydroxyquinolin-2(1*H*)-one and 4-chlorobenzaldehyde. However, even with varied reaction time and temperature only product **S$_3$4a** was obtained with unreacted 4-chlorobenzaldehyde. This may be attributed to the high reactivity of electron deficient alkene intermediate which further undergoes simultaneous Michael addition with 4-hydroxyquinolin-2(1*H*)-one.

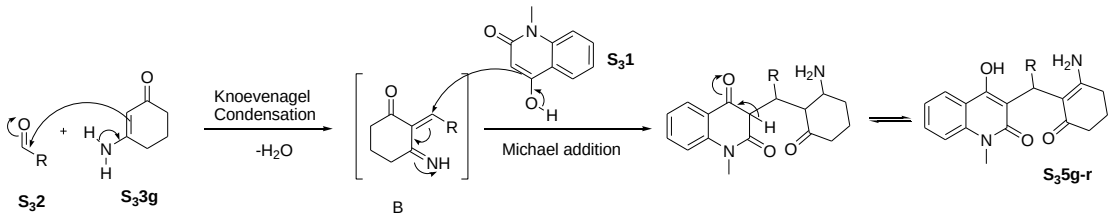
Based on the above results and available literatures, a probable mechanistic rationale portraying sequence of events for this cascade reaction is proposed in Scheme 4.3. The first step is believed to be the Knoevenagel condensation (known to occur under solvent- and catalyst-free conditions) between the aldehydes and 4-hydroxyquinolin-2(1*H*)-one to generate adduct **A,** which acts as strong Michael acceptor. Another molecule of 4-hydroxyquinolin-2(1*H*)-one (in case of two component reaction) or 3-aminocyclohex-2-enone (in case of three component reaction) attacks to electron deficient alkene **A** in a Michael addition fashion to yield corresponding product.



Scheme 4.3: Plausible mechanism for the formation of **S$_3$4** and **S$_3$5**

Based on the results obtained from the sequential addition reaction, the alternative possible mechanistic pathway for the three component cascade reaction is proposed as shown in Scheme 4.4. The Knoevenagel condensation of aldehydes with 3-aminocyclohex-2-enone can form electron poor alkene B, which can undergo Michael addition with 4-hydroxyquinolin-2(1*H*)-one to obtain final AOCHQ product.

-



Scheme 4.4: Plausible alternative mechanism for the formation of **$S_3$5**

Further attempts to synthesise fused ring systems through cyclization of **$S_3$4** and **$S_3$5** under solvent- and catalyst-free conditions have failed even at elevated temperature (up to 150 ˚C). Also, the thermal reaction of **$S_3$4** and **$S_3$5** with ammonium acetate did not yield fused ring compounds. This may be attributed to the resonance stabilized structures of **$S_3$4** and **$S_3$5** resist vinylic –OH to undergo condensive cyclization.

4.4 CONCLUSION

In conclusion, a highly efficient, green synthetic protocol for the synthesis of MDBHQ derivatives and AOCHQ derivatives has been developed under solvent- and catalyst- free conditions for the first time. Further, the three component cascade reactions of 4-hydroxy-1-methylquinolin-2(1*H*)-one, aldehydes and several active methylene compounds have been attempted. However, the desired product obtained successfully only with 3-aminocyclohex-2-enone. The current protocol is tolerable to various aldehydes with wide functionality. The cascade Knoevenagel-Michael reaction occurred in short reaction time in the absence of solvent and catalyst to yield desired products in high yield.

CHAPTER 5

AN EFFICIENT THREE COMPONENT, ONE-POT SYNTHESIS OF QUINAZOLINES UNDER SOLVENT- AND CATALYST-FREE REACTION CONDITION

This chapter describes an efficient and green protocol for the quinazolines synthesis by three-component one-pot reactions of 2-aminoaryl ketones, orthoesters and ammonium acetate in the absence of any solvent and catalyst. The mechanism of the reaction has been established based on the isolated intermediate.

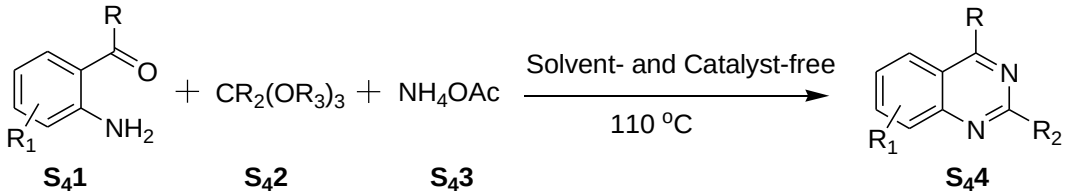
5.1 INTRODUCTION

Quinazoline is one of the most important nitrogen containing fused heterocycles present in wide variety of natural products and synthetic pharmaceutical ingredients (Foster et al. 1999; Gundla et al. 2008). They are known to show diverse biological and therapeutic properties such as antitumor (Noolvi et al. 2011), antibacterial (Tiwari and Chhabra 2010), anti-inflammatory (Balakumar et al. 2010), anti-plasmodial (Kabri et al. 2010), antitubercular (Waisser et al. 2001; Kunes et al. 2000), antiviral (Chien et al. 2004), antioxidant (Kumar et al. 2011a), anti-malarial (Ashton and Hynes, 1973) etc. They find extensive applications as photochemotherapeutic agents (Barraja et al. 2011), T-type calcium channel blockers (Seo et al. 2007), CB2 receptor agonists (Saari et al. 2011), potent tyrosine kinase and cellular phosphorylation inhibitors (Fry et al. 1994). Several drugs have been developed based on quinazoline motif and marketed by various pharmaceutical companies (Selvam and Kumar 2011). In addition, quinazoline scaffolds have also been found importance in other fields such as material science (Mei et al. 2012), agrochemicals (Bhattacharyya et al. 2003), explosives (Millar et al. 2004) etc.

A variety of conventional procedures have been reported for the synthesis of quinazolines (Zhang et al. 2010; Han et al. 2011; Karnakar et al. 2011; Sharma and Prajapati 2011; Ju et al. 2012; Panja et al. 2012; Fang et al. 2013) but most of them suffer from multistep synthesis, lower yield, harsh conditions, use of toxic solvents, expensive catalyst and additives. Quite recently, practical protocols in the absence of solvents (Anand et al. 2012) and catalysts (Zhang et al. 2012) have been reported. However, these methods suffer from drawbacks such as requirement of additives, much effort to recycle the materials etc. Moghadam and Samavi (2006) reported one-pot, three component synthesis of 4-aminoquinazolines under microwave condition; however, it suffers from limitation of substrate generality. Kumar et al. (2005) have reported the synthesis of quinazolines under solvent- and catalyst-free conditions

using conventional microwave oven. However, this method requires tedious synthesis of starting materials. Bandaru et al. (2012) synthesized 2,4-disubstituted quinazolines in aqueous medium using 2-aminocarbonyl compounds, aldehydes and ammonium acetate, however this method has limitations such as low product yield, requirement of excess ammonium acetate (10 equivalents) and failed to yield the required product with aliphatic aldehydes. Owing to their widespread applications, the quest for new, simple and efficient method for the synthesis of quinazolines from readily available precursors under green reaction condition is of continuing interest among the chemists.

Among various green approaches, MCR's (Zhu and Bienayme 2005) have gained significant importance due to their highly flexible, (chemo)selective, convergent and atom efficient nature (Ganem 2009; Domling and Ugi 2000; Domling 2006) and hence become current area of interest in organic, medicinal and combinatorial chemistry research (Climent et al. 2012, Singh and Chowdhury 2012). Being one-pot reactions, MCR's are practically single step conversions and they are easier to carry out than classical multistep approach to synthesize complex organic molecules. If such reactions with near quantitative yield could be carried out under solvent- and catalyst-free conditions from readily available starting materials, they would comply with most of the green chemistry principles and closely approach the concept of ideal synthesis.



S$_4$1 **S$_4$2** **S$_4$3** **S$_4$4**

Scheme 5.1: Synthesis of quinazolines under solvent- and catalyst-free conditions

Considering the above factors herein, a one-pot three component protocol for the synthesis of quinazolines has been developed. This method involves the reaction of 2-aminoarylketones, orthoesters and ammonium acetate under solvent- and catalyst-free conditions in one-pot (Scheme 5.1). The present protocol has several advantages such as it avoids the use of solvent and catalyst, involves the use of readily available

starting materials which are well known in several green transformations, high yield, moderate reaction time and hence can be considered as green or sustainable protocol.

5.2 EXPERIMENTAL

5.2.1 General

Melting points were determined with Stuart SMP3 melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo scientific Nicolet Avatar 330 FTIR spectrometer as neat sample. NMR spectra were recorded as a solution in $CDCl_3$/DMSO-d_6 500 MHz (^1H) and 400 MHz (^{13}C) instrument. Chemical shifts (δ) are reported in ppm with TMS as an internal standard. NMR raw data was analysed with the program MestReNova 7.0.0-8331. Mass spectra were performed on Waters Micromass Q-Tof Micro spectrometer with an ESI source. Elemental analysis was performed using Perkin Elmer, Series II, 2400 analyzer. The SCXRD analysis was performed on the Bruker AXS APEX II system. All experiments were monitored by TLC, performed on pre-coated silica gel 60 F_{254} plates (Merck). Column chromatography was performed on silica gel (60-120 mesh, Merck) using EtOAc-PE as eluent.

5.2.2 General Procedure for the synthesis of quinazoline derivatives

2-aminoaryl ketone **$S_4$1** (1 mmol), orthoester **$S_4$2** (1.5 mmol) and ammonium acetate **$S_4$3** (1.5 mmol) were charged into a 10 mL round-bottom flask and the mixture was heated to 110 ˚C using conventional oil bath. The reaction mixture was stirred to 90-150 min until the starting material 1 was consumed to maximum extent. The mixture was diluted with EtOAc (10 mL×2) and quenched with water (10 mL). The organic layer was separated and directly column chromatographed using 1:9 EtOAc – PE as the eluent to obtain pure quinazoline **$S_4$4**.

All the newly synthesized compounds were characterized by spectral analysis and the spectral data of the final compounds and isolated intermediates are given below.

4-phenylquinazoline ($S_4$4a)

White solid; Yield: 93%; mp: 95~97 ˚C; ^1H NMR (500MHz, DMSO-d_6) δ: 7.62-7.65 (m, 3H, ArH), 7.75-7.81 (m, 3H, ArH), 8.04-8.12 (m, 3H, ArH), 9.37 (s, 1H, ArH);

^{13}C NMR (100.6 MHz, $CDCl_3$) δ:123.2, 127.1, 127.7, 128.7, 128.9, 129.9, 130.1, 133.7, 137.2, 151.2, 154.7, 168.4; IR (Neat, cm^{-1}): 3031 (ArCH), 1607 (ring C=N), 1555 (C=C), 1536 (C=C), 1483 (C=C); Anal. Calcd for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58, Found: C, 81.42; H, 5.06; N, 13.41; ESI MS (m/z) = 207.1 $(M+H)^+$.

2-methyl-4-phenylquinazoline ($S_4$4b)

Blood red liquid; Yield: 89%; ^{1}H NMR (500MHz, DMSO-d_6) δ: 2.82 (s, 3H, CH_3), 7.62-7.68 (m, 4H, ArH), 7.76-7.78 (m, 2H, ArH), 7.97-8.03 (m, 3H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 26.6, 121.1, 126.7, 127.1, 128.2, 128.6, 129.9, 133.7, 137.3, 151.5, 163.9, 168.6; IR (Neat, cm^{-1}): 3058 (ArCH), 2923 (CH), 2854 (CH), 1607 (ring C=N), 1555 (C=C), 1536 (C=C), 1483 (C=C); Anal. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72, Found: C, 81.68; H, 5.67; N, 12.53; ESI MS (m/z) = 221.1 $(M+H)^+$.

2-ethyl-4-phenylquinazoline ($S_4$4c)

White solid; Yield: 90%; mp: 85-88 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 1.40 (t, 3H, J = 7.5Hz, CH_3), 3.10 (q, 2H, J = 7.5Hz, CH_2), 7.60-7.68 (m, 4H, ArH), 7.76-7.80 (m, 2H, ArH), 7.97-8.04 (m, 3H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.1, 33.3, 121.3, 126.7, 127.0, 128.4, 128.6, 129.8, 129.9, 133.5, 137.5, 151.6, 168.1, 168.6; IR (Neat, cm^{-1}): 3057 (ArCH), 2968 (CH), 2923 (CH), 2864 (CH), 1610 (ring C=N), 1547 (C=C), 1483 (C=C); Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96, Found: C, 82.21; H, 5.88; N, 11.73; ESI MS (m/z) = 235.2 $(M+H)^+$.

2-butyl-4-phenylquinazoline ($S_4$4d)

Yellow liquid; Yield: 86%; ^{1}H NMR(500MHz, DMSO-d_6) δ: 0.94 (t, 3H, J = 7.5Hz, CH_3), 1.38-1.43 (sextet, 2H, J = 7.5Hz, $CH_3CH_2CH_2$), 1.83-1.89 (m, 2H, $CH_3CH_2CH_2$), 3.06 (t, 2H, J = 7.5Hz, $ArCH_2CH_2$), 7.61-7.68 (m, 4H, ArH), 7.77-7.79 (m, 2H, ArH), 7.97-8.04 (m, 3H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.1, 22.8, 29.7, 31.2, 39.9, 121.2, 126.6, 127.0, 128.4, 128.6, 129.8, 129.9, 133.5, 137.5, 151.5, 167.3, 168.5; IR (Neat, cm^{-1}): 3060 (ArCH), 2955 (CH), 2925 (CH), 2869 (CH), 2856 (CH), 1614 (ring C=N), 1561 (C=C), 1545 (C=C), 1484 (C=C); Anal. Calcd for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92; N, 10.68, Found: C, 82.58; H, 6.71; N, 10.49; ESI MS (m/z) = 263.2 $(M+H)^+$.

2,4-diphenylquinazoline ($S_4$4e)

White solid; Yield: 90%; mp: 119~121 ˚C (lit 118~120 ˚C); ^{1}H NMR (500MHz, $CDCl_3$) δ: 7.48-7.55 (m, 4H, ArH), 7.59-7.62 (m, 3H, ArH), 7.87-7.90 (m, 3H, ArH), 8.13 (d, 1H, *J* = 8.5Hz, ArH), 8.16 (d, 1H, *J* = 8.5Hz, ArH), 8.7 (dd, 2H, J_1=8Hz, J_2=1.5Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 121.7, 126.9, 128.4, 128.6, 128.7, 129.2, 129.9, 130.2, 130.5, 133.5, 137.7, 138.2, 152.0, 160.3, 168.3; IR (Neat, cm^{-1}): 3056 (ArCH), 1610 (ring C=N), 1562 (C=C), 1535 (C=C), 1482 (C=C); Anal. Calcd for $C_{20}H_{14}N_2$: C, 85.08; H, 5.00; N, 9.92, Found: C, 84.94; H, 5.14; N, 9.82; ESI MS (m/z) = 283.1 $(M+H)^+$.

6-chloro-4-phenylquinazoline ($S_4$4f)

White solid; Yield: 94%; mp: 139~141 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 7.63-7.68 (m, 3H, ArH) 7.80-7.83 (m, 2H, ArH), 8.02 (d, 1H, *J*=2 Hz, ArH), 8.1 (dd, 1H, J_1= 2Hz, J_2= 9Hz, ArH), 8.15 (d, 1H, *J* = 9Hz, ArH), 9.4 (s, 1H, ArH); ^{13}C NMR(100.6 MHz, $CDCl_3$) δ:123.8, 125.8, 128.9, 129.9, 130.4, 130.7, 133.6, 134.7, 136.6, 149.7, 154.9; IR (Neat, cm^{-1}): 3050 (ArCH), 1610 (ring C=N), 1533 (C=C), 1479 (C=C); Anal. Calcd for $C_{14}H_9ClN_2$: C, 69.86; H, 3.77; N, 11.64, Found: C, 69.74; H, 3.86; N, 11.53; ESI MS (m/z) = 241.1 $(M+H)^+$.

6-chloro-2-methyl-4-phenylquinazoline ($S_4$4g)

Pale Yellow solid; Yield: 88%; mp: 107~109 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 2.82 (s, 3H, CH_3), 7.62-7.67 (m, 3H, ArH), 7.76-7.78 (m, 2H, ArH), 7.93 (d, 1H, *J* = 2Hz, ArH), 7.99-8.04 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 26.6, 121.6, 125.8, 128.8, 129.8, 129.9, 130.2, 132.4, 134.6, 136.7, 150.0, 164.2, 167.8; IR (Neat, cm^{-1}): 3053 (ArCH), 2955 (CH), 2919 (CH), 2852 (CH), 1612 (ring C=N), 1543 (C=C), 1475 (C=C); Anal. Calcd for $C_{15}H_{11}ClN_2$: C, 70.73; H, 4.35; N, 11.00, Found: C, 70.60; H, 4.48; N, 10.89; ESI MS (m/z) = 255.1 $(M+H)^+$.

6-chloro-2-ethyl-4-phenylquinazoline ($S_4$4h)

White solid; Yield: 88%; mp: 103~105 ˚C; ^{1}H NMR (500MHz, $CDCl_3$) δ: 1.49 (t, 3H, *J* = 7.5Hz, CH_3), 3.19 (q, 2H, *J* = 7.5Hz, CH_2), 7.580-7.60 (m, 3H, ArH), 7.74-7.76 (m, 2H, ArH), 7.80 (dd, 1H, J_1 = 2.5Hz, J_2 = 9Hz, ArH), 8.00 (d, 1H, *J* = 9Hz, ArH), 8.03 (d, 1H, *J* = 2.5Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 12.9, 33.1, 121.8,

125.7, 128.8, 129.8, 130.0, 130.1, 132.2, 134.4, 136.9, 150.0, 167.7, 168.3; IR (Neat, cm^{-1}): 2978 (CH), 1612 (ring C=N), 1541 (C=C), 1519 (C=C); Anal. Calcd for $C_{16}H_{13}ClN_2$: C, 71.51; H, 4.88; N, 10.42, Found: C, 71.38; H, 4.97; N, 10.31.

6-chloro-2,4-diphenylquinazoline ($S_4$4j)

White solid; Yield: 87%; mp: 196~198 ˚C (lit. 190~192 ˚C); ^{1}H NMR (500MHz, $CDCl_3$) δ: 7.49-7.55 (m, 3H, ArH), 7.60-7.64 (m, 3H, ArH), 7.81 (dd, 1H, J_1 = 2Hz, J_2 = 9Hz, ArH), 7.85-7.88 (m, 2H, ArH), 8.09-8.11 (m, 2H, ArH), 8.66-8.68 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 122.2, 125.8, 128.6, 128.7, 128.8, 130.1, 130.2, 130.8, 130.9, 132.6, 134.5, 137.1, 137.8, 150.5, 160.5, 167.6; IR (Neat, cm^{-1}): 3051 (ArCH), 1556 (C=C), 1530 (C=C), 1473 (C=C); Anal. Calcd for $C_{20}H_{13}ClN_2$: C, 75.83; H, 4.14; N, 8.84, Found: C, 75.67; H, 4.28; N, 8.71; ESI MS (m/z) = 317.1 $(M+H)^+$.

6-chloro-4-(2-fluorophenyl)quinazoline ($S_4$4k)

White solid; Yield: 93%; mp: 125~127 ˚C; ^{1}H NMR(500MHz, $CDCl_3$) δ: 7.31 (td, 1H, J_1 = 1Hz, J_2 = 9Hz, ArH); 7.39 (td, 1H, J_1 = 1Hz, J_2= 7.5Hz, ArH), 7.58-7.62 (m, 2H, ArH), 7.80 (t, 1H, J = 2.5Hz, ArH), 7.87 (dd, 1H, J_1= 2.5Hz, J_2= 9Hz, ArH), 8.08 (d, 1H, J = 9Hz, ArH), 9.42 (t, 1H, J = 4.5Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 116.3, 116.5, 124.9, 125.7, 130.6, 131.5, 132.2, 133.8, 135.1, 149.2, 154.9, 158.5, 161.0, 163.7; IR (Neat, cm^{-1}): 3033 (ArCH), 1611 (ring C=N), 1532 (C=C), 1484 (C=C); Anal. Calcd for $C_{14}H_8ClFN_2$: C, 65.00; H, 3.12; N, 10.83, Found: C, 64.87; H, 3.26; N, 10.68; ESI MS (m/z) = 259.1 $(M+H)^+$.

6-chloro-4-(2-fluorophenyl)-2-methylquinazoline ($S_4$4l)

White solid; Yield: 86%; mp: 139~141 ˚C; ^{1}H NMR (500MHz, $CDCl_3$) δ: 2.95 (s, 3H, CH_3), 7.27-7.31 (m, 1H, ArH), 7.38 (td, 1H, J_1 = 1Hz, J_2 = 7.5Hz, ArH); 7.56-7.59 (m, 2H, ArH), 7.72 (t, 1H, J = 2.5Hz, ArH), 7.81 (dd, 1H, J_1 = 2.5Hz, J_2 = 9Hz, ArH), 7.96 (d, 1H, J = 9Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 26.5, 116.2, 116.4, 124.9, 125.6, 129.9, 131.5, 132.0, 132.1, 132.7, 135.0, 149.5, 161.0, 163.9; IR (Neat, cm^{-1}): 3059 (ArCH), 2913 (CH), 1614 (ring C=N), 1548 (C=C); Anal. Calcd for $C_{15}H_{10}ClFN_2$: C, 66.06; H, 3.70; N, 10.27, Found: C, 65.90; H, 3.81; N, 10.13; ESI MS (m/z) = 273.1 $(M+H)^+$.

6-chloro-4-(2-fluorophenyl)-2-phenylquinazoline ($S_4$4o)

White solid; Yield: 84%; mp: 190~192 ˚C; ^{1}H NMR (500MHz, $CDCl_3$) δ: 7.31 (t, 1H, *J* = 7.6Hz, ArH), 7.40 (t, 1H, *J* = 6Hz, ArH), 7.50-7.62 (m, 4H, ArH), 7.67-7.71 (m, 1H, ArH), 7.77-7.78 (m, 1H, ArH), 7.81-7.83 (m, 1H, ArH), 8.1 (d, 1H, *J* = 7.2Hz, ArH), 8.62-8.65 (m, 2H, ArH); ^{13}C NMR(100.6 MHz, $CDCl_3$) δ: 116.2, 116.4, 123.0, 124.7, 124.8, 124.9, 125.5, 125.6, 128.6, 128.7, 130.7, 130.8, 131.8, 131.9, 132.0, 132.8, 134.8, 137.7, 149.9, 158.6, 160.7, 161.1, 163.8; IR (Neat, cm^{-1}): 3063 (ArCH), 1614 (ring C=N), 1559 (C=C), 1532 (C=C); Anal. Calcd for $C_{20}H_{12}ClFN_2$: C, 71.75; H, 3.61; N, 8.37, Found: C, 71.63; H, 3.75; N, 8.22; ESI MS (m/z) = 335.1 $(M+H)^+$.

6-nitro-4-phenylquinazoline ($S_4$4p)

Pale Yellow solid; Yield: 88%; mp: 121~123 ˚C; ^{1}H NMR(500MHz, DMSO-d_6) δ: 7.69- 7.75 (m, 3H, ArH), 7.89-7.91 (m, 2H, ArH), 8.32 (d, 1H, *J* = 9.5 Hz, ArH), 8.73 (dd, 1H, J_1 = 2.5 Hz, J_2 = 9.5 Hz, ArH), 8.86 (d, 1H, *J* = 2.5 Hz, ArH), 9.56 (s, 1H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 122.1, 124.2, 127.1, 129.2, 130.1, 131.2, 135.8, 153.5, 157.3; IR (Neat, cm^{-1}): 3049 (ArCH), 1613 (ring C=N), 1573 (C=C), 1529 (C=C); Anal. Calcd for $C_{14}H_9N_3O_2$: C, 66.93; H, 3.61; N, 16.73, Found: C, 67.17; H, 3.48; N, 16.58; ESI MS (m/z) = 252.1 $(M+H)^+$.

2-ethyl-6-nitro-4-phenylquinazoline ($S_4$4r)

Pale Yellow solid; Yield: 76%; mp: 127~129 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 1.43 (t, 3H, *J* = 7.5Hz, CH_3), 3.16 (q, 2H, *J* = 7.5Hz, CH_2), 7.68-7.73 (m, 3H, ArH), 7.88 (dt, 2H, J_1 = 2Hz, J_2 = 5.5 Hz, ArH), 8.22 (d, 1H, *J* = 9Hz, ArH), 8.68 (dd, 1H, J_1 = 2 Hz, J_2 = 9Hz, ArH), 8.82 (d, 1H, *J* = 2.5Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 12.1, 32.9, 119.6, 123.7, 126.3, 128.6, 129.5, 129.9, 130.4, 135.6, 144.9, 153.5, 170.0, 170.9; IR (Neat, cm^{-1}): 3090 (ArCH), 2975 (CH), 2917 (CH), 2850 (CH), 1611 (ring C=N), 1578 (C=C), 1542 (C=C); Anal. Calcd for $C_{16}H_{13}N_3O_2$: C, 68.81; H, 4.69; N, 15.05, Found: C, 68.94; H, 4.78; N, 14.91; ESI MS (m/z) = 280.2 $(M+H)^+$.

2-butyl-6-nitro-4-phenylquinazoline ($S_4$4s)

White solid; Yield: 79%; mp: 104~107 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 0.95 (t, 3H, *J* = 7.5Hz, CH_3), 1.39-1.46 (sextet, *J* = 7.5Hz, 2H, $CH_3CH_2CH_2$), 1.86-1.92 (m,

2H, $CH_3CH_2CH_2$), 3.13 (t, 2H, *J* = 7.5Hz, $ArCH_2CH_2$), 7.68-7.73 (m, 3H, ArH), 7.86-7.88 (m, 2H, ArH), 8.21 (d, 1H, *J* = 9.5Hz, ArH), 8.67 (dd, 1H, J_1 = 2.5 Hz, J_2 = 9.5 Hz, ArH), 8.81 (d, 1H, *J* = 2.5Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.9, 22.7, 30.8, 40.0, 120.1, 124.2, 126.9, 129.1, 130.1, 130.4, 130.9, 136.2, 145.4, 153.9, 170.5, 170.8; IR (Neat, cm^{-1}): 3059 (ArCH), 2953 (CH), 2925 (CH), 2860 (CH), 1615 (ring C=N), 1543 (C=C), 1491 (C=C); Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67, Found: C, 70.50; H, 5.41; N, 13.49; ESI MS (m/z) = 308.2 $(M+H)^+$.

4-methylquinazoline ($S_4$4u)

Blood Red coloured viscous liquid; Yield: 88%; ^{1}H NMR (500MHz, DMSO-d_6) δ: 2.94 (s, 3H), 7.73-7.79 (m, 1H, ArH), 7.99-8.03 (m, 2H, ArH), 8.26 (d, 1H, *J* = 8.5 Hz, ArH), 9.15 (s, 1H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 21.8, 124.5, 125.0, 127.6, 129.0, 133.7, 149.6, 154.6, 168.3; IR (Neat, cm^{-1}): 2921, 1647 (ring C=N), 1615, 1566, 1495, 1394, 1355, 1258, 1169; Anal. Calcd for $C_9H_8N_2$: C, 74.98; H, 5.59; N, 19.43, Found: C, 74.79; H, 5.68; N, 19.30; ESI MS (m/z) = 145.1 $(M+H)^+$.

2,4-dimethylquinazoline ($S_4$4v)

Yellow solid; Yield: 79%; mp: 290~292 ˚C; ^{1}H NMR (500MHz, DMSO-d_6) δ: 2.71 (s, 3H, OCH_3), 2.87 (s, 3H, OCH_3), 7.64-7.67 (m, 1H, ArH), 7.87 (d, 1H, *J* = 8Hz, ArH), 7.92-7.95 (m, 1H, ArH), 8.22 (dd, 1H, J_1 = 8Hz, J_2 = 1Hz, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 21.7, 26.4, 122.3, 124.9, 126.6, 128.3, 133.6, 150.0, 163.6, 168.2; IR (Neat, cm^{-1}): 2923 (CH), 2855 (CH), 1618 (ring C=N), 1565 (C=C), 1494 (C=C); Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71, Found: C, 75.78; H, 6.58; N, 17.53; ESI MS (m/z) = 159.1 $(M+H)^+$.

4-methyl-2-phenylquinazoline ($S_4$4w)

White solid; Yield: 81%; mp: 71~74 ˚C (lit 72~76 ˚C); ^{1}H NMR (500MHz, $CDCl_3$) δ: 3.03 (s, 3H), 7.49-7.55 (m, 3H, ArH), 7.57-7.60 (m, 1H, ArH), 7.85-7.88 (m, 1H, ArH), 8.07-8.11 (m, 2H, ArH), 8.61-8.63 (m, 2H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 22.03, 123.05, 125.0, 126.9, 128.6, 129.3, 130.4, 133.5, 138.4, 150.5, 160.2, 168.2; IR (Neat, cm^{-1}): 3058 (ArCH), 3007, 2920, 1611 (ring C=N), 1540, 1489, 1432, 1387, 1335, 1226, 1023; Anal. Calcd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72, Found: C, 81.90; H, 5.33; N, 12.65; ESI MS (m/z) = 221.1 $(M+H)^+$.

6,7-dimethoxy-2,4-dimethylquinazoline ($S_4$4y)

Light brownish solid; Yield: 82%; mp: 87~89 ˚C; ^{1}H NMR (500MHz, $CDCl_3$) δ: 2.8 (s, 3H, $ArCH_3$), 2.85 (s, 3H, $ArCH_3$), 4.04 (s, 6H, OCH_3), 7.18 (s, 1H, ArH), 7.25 (s, 1H, ArH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 21.7, 26.2, 56.2, 56.3, 102.3, 106.7, 155.7, 164.7; IR (Neat, cm^{-1}): 2944 (CH), 2838 (CH), 1614 (ring C=N), 1568 (C=C), 1500 (C=C); Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84, Found: C, 65.93; H, 6.55; N, 12.77; ESI MS (m/z) = 219.1 $(M+H)^+$.

6,7-dimethoxy-4-methyl-2-phenylquinazoline ($S_4$4z)

Light Brownish solid; Yield: 84%; mp: 155~157 ˚C; ^{1}H NMR (500MHz, $CDCl_3$) δ: 2.94 (s, 3H, $ArCH_3$), 4.06 (s, 3H, OCH_3), 4.09 (s, 3H, OCH_3), 7.22 (s, 1H, ArH), 7.39 (s, 1H, ArH), 7.46-7.53 (m, 3H, ArH), 8.54-8.56 (m, 2H, ArH); ^{13}C NMR(100.6 MHz, $CDCl_3$) δ: 22.0, 30.9, 56.2, 56.4, 102.4, 107.6, 118.4, 128.2, 128.5, 129.9, 138.7, 148.3, 149.8, 155.6, 159.3, 164.8; IR (Neat, cm^{-1}): 2952 (CH), 2919 (CH), 2854 (CH), 1613 (ring C=N), 1573 (C=C), 1545 (C=C), 1496 (C=C); Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99, Found: C, 72.72; H, 5.89; N, 9.83; ESI MS (m/z) = 281.2 $(M+H)^+$.

methyl *N*-2-benzoylphenylbenzimidate ($S_4$4ei)

Pale yellow viscous liquid; ^{1}H NMR (500MHz, $CDCl_3$) δ: 3.52 (s, 3H, OCH_3), 6.76 (dd, 1H, J_1= 1.5Hz, J_2 = 8Hz, ArH), 7.05 (td, 1H, J_1 = 1Hz, J_2 = 7.5 Hz, ArH), 7.16-7.23 (m, 4H, ArH), 7.28-7.41 (m, 5H, ArH), 7.50-7.53 (m, 1H, ArH), 7.67-7.69 (m, 2H, ArH); ^{13}C NMR(100.6 MHz, $CDCl_3$) δ: 53.9, 115.5, 117.0, 122.3, 122.5, 128.0, 128.1, 129.1, 129.1, 129.8, 130.1, 131.5, 132.5, 147.3, 159.4, 197.3; IR (Neat, cm^{-1}): 3059 (ArCH), 1648 (ring C=N), 1594 (C=C), 1446 (C=C); Anal. Calcd for $C_{21}H_{17}NO_2$: C, 79.98; H, 5.43; N, 4.44, Found: C, 79.92; H, 5.51; N, 4.38; ESI MS (m/z) = 338.2 $(M+Na)^+$, 316.2 $(M+H)^+$, 284.2$(M-OMe)^+$.

methyl *N*-2-benzoyl-4-chlorophenylbenzimidate ($S_4$4ji)

White solid; mp: 96~98 ˚C; ^{1}H NMR (500MHz, $CDCl_3$) δ: 3.50 (s, 3H, OCH_3), 6.70 (d, 1H, J = 8.5Hz, ArH), 7.2 (d, 2H, J = 4 Hz, ArH), 7.28-7.33 (m, 4H, ArH), 7.40-7.43 (m, 2H, ArH), 7.53-7.56 (m, 1H, ArH), 7.7 (dd, 2H, J_1 = 1Hz, J_2 = 8Hz, ArH); ^{13}C NMR(100.6 MHz, $CDCl_3$) δ: 54.0, 123.9, 127.8, 128.2, 128.3, 129.0, 129.3,

129.8, 130.4, 130.7, 131.3, 132.6, 132.9, 137.3, 145.8, 160.1, 195.8; IR (Neat, cm^{-1}): 3059 (ArCH), 2949 (CH), 1651 (ring C=N), 1590 (C=C); Anal. Calcd for $C_{21}H_{16}ClNO_2$: C, 72.10; H, 4.61; N, 4.00, Found: C, 71.98; H, 4.56; N, 4.11; ESI MS (m/z) = 372.2 $(M+Na)^+$, 350.2 $(M+H)^+$, 318.2$(M-OMe)^+$.

methyl *N*-4-chloro-2-(2-fluorobenzoyl)phenylbenzimidate ($S_4$4oi)

White solid; mp: 93~96 ˚C; ^{1}H NMR (500MHz, $CDCl_3$) δ: 3.43 (s, 3H), 6.60 (d, 1H, *J* = 9Hz, ArH), 7.06-7.10 (m, 1H, ArH), 7.19-7.25 (m, 6H, ArH), 7.31-7.34 (m, 1H, ArH), 7.46-7.50 (m, 3H, ArH); ^{13}C NMR(100.6 MHz, $CDCl_3$) δ: 53.9, 116.1, 116.3, 123.8, 124.2, 128.2, 129.0, 129.5, 130.4, 130.5, 130.9, 132.2, 133.7, 133.8, 146.1, 159.8, 160.0, 162.3, 192.4; IR (Neat, cm^{-1}): 3061 (ArCH), 2933 (CH), 2921 (CH), 1645 (ring C=N), 1597 (C=C), 1477 (C=C); Anal. Calcd for $C_{21}H_{15}ClFNO_2$: C, 68.58; H, 4.11; N, 3.81, Found: C, 68.47; H, 4.18; N, 3.78; ESI MS (m/z) = 390.2 $(M+Na)^+$, 368.2 $(M+H)^+$, 336.2$(M-OMe)^+$.

Table 5.1: Crystallographic data of compound **$S_4$4a**

Crystal data [CCDC No. 912137]	
Empirical formula	C_{14} H_{10} N_2
Formula weight	206.24
Crystal size (mm)	0.20 x 0.20 x 0.1
Crystal system	Orthorhombic
Space group	Pca21
a (Å); b (Å); c (Å)	13.666(3); 11.155(3); 6.9207(17)
α (˚); β (˚); γ (˚)	90; 90; 90
Volume ($Å^3$)	1055.0(4)
Z	4
Crystal density, g/cm^3	1.298
F(000)	432
Absorption coefficient	0.078
Temperature (T)	296 (2)
Radiation wavelength	0.71073
Radiation type	MoKα

Contd.

Radiation source	Fine-focus sealed tube
Radiation monochromator	Graphite
h_{min}; k_{min}; l_{min}	-14; -12; -7
h_{max}; k_{max}; l_{max}	13; 11; 7
R-Factor (%)	5.08

Table 5.2: Crystallographic data of compound **$S_4$4ji**

Crystal data [CCDC No. 912138]	
Empirical formula	$C_{21}H_{16}ClNO_2$
Formula weight	349.80
Crystal size (mm)	1 x 0.26 x 0.24
Crystal system	Monoclinic
Space group	P21/c
a (Å); b (Å); c (Å)	14.4362(4); 7.8528(2); 15.5028(3)
α (˚); β (˚); γ (˚)	90; 93.6940(10); 90
Volume ($Å^3$)	1753.82(7)
Z	4
Crystal density, g/cm^3	1.325
F(000)	728
Absorption coefficient	0.231
Temperature (T)	296 (2)
Radiation wavelength	0.71073
Radiation type	MoKα
Radiation source	Fine-focus sealed tube
Radiation monochromator	Graphite
h_{min}; k_{min}; l_{min}	-15; -10; -20
h_{max}; k_{max}; l_{max}	19; 10; 20
R-Factor (%)	4.85

The ^{1}H NMR, ^{13}C NMR, and ESI MS spectra of **S$_4$4ei** and **S$_4$4e** are shown below.

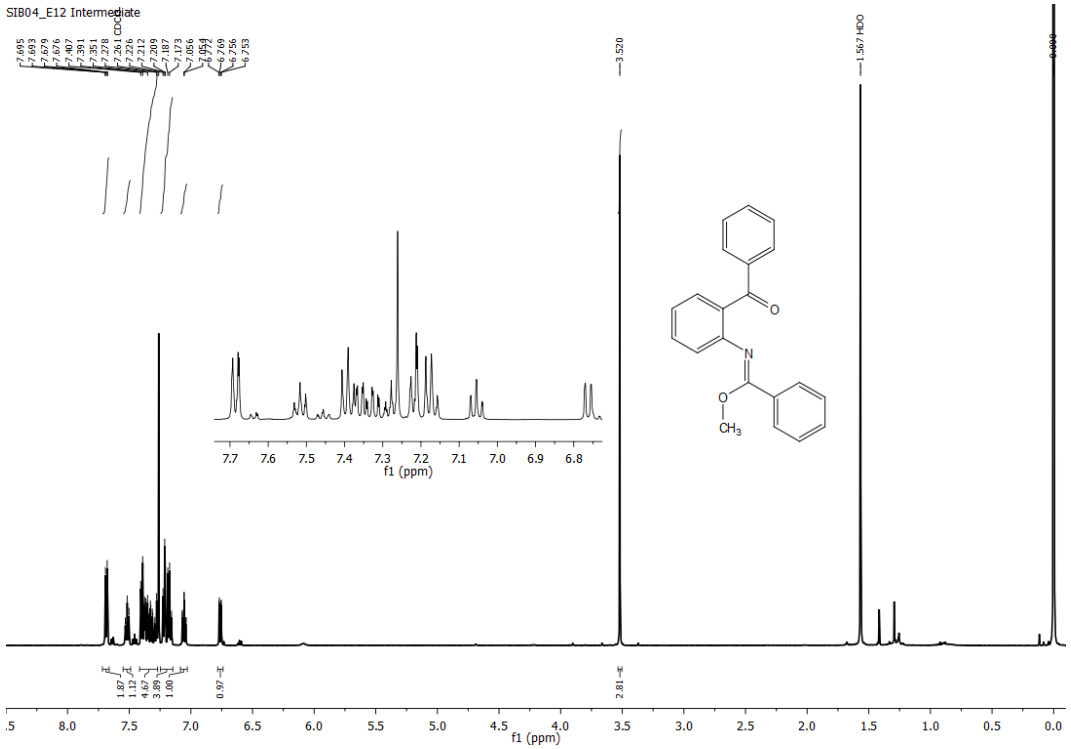


Fig. 5.1: ^{1}H NMR spectrum of **S$_4$4ei**

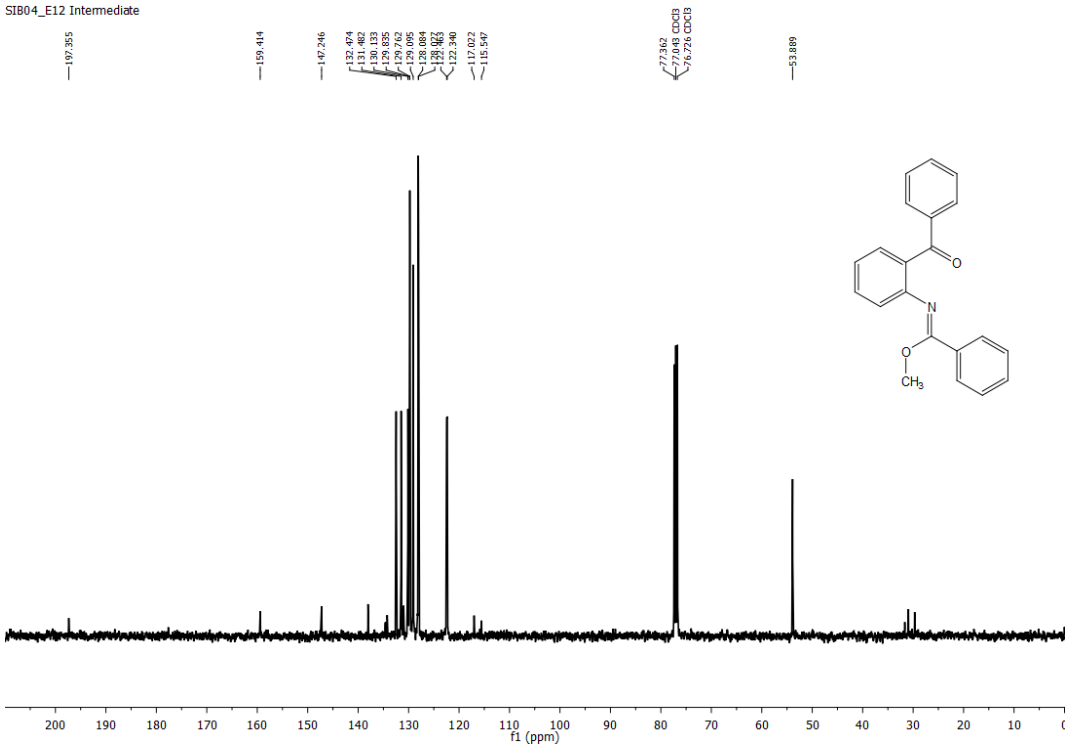


Fig. 5.2: ^{13}C NMR spectrum of **S$_4$4ei**

Fig. 5.3: ESI MS spectrum of **$S_4$4ei**

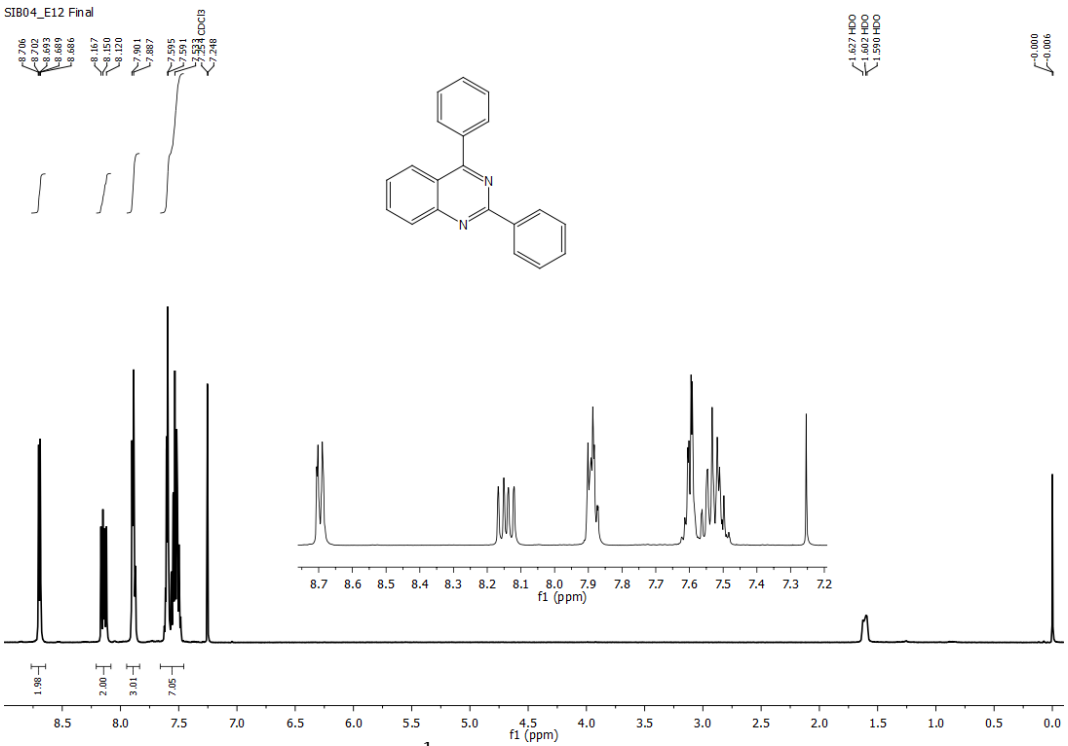


Fig. 5.4: ^{1}H NMR spectrum of **$S_4$4e**

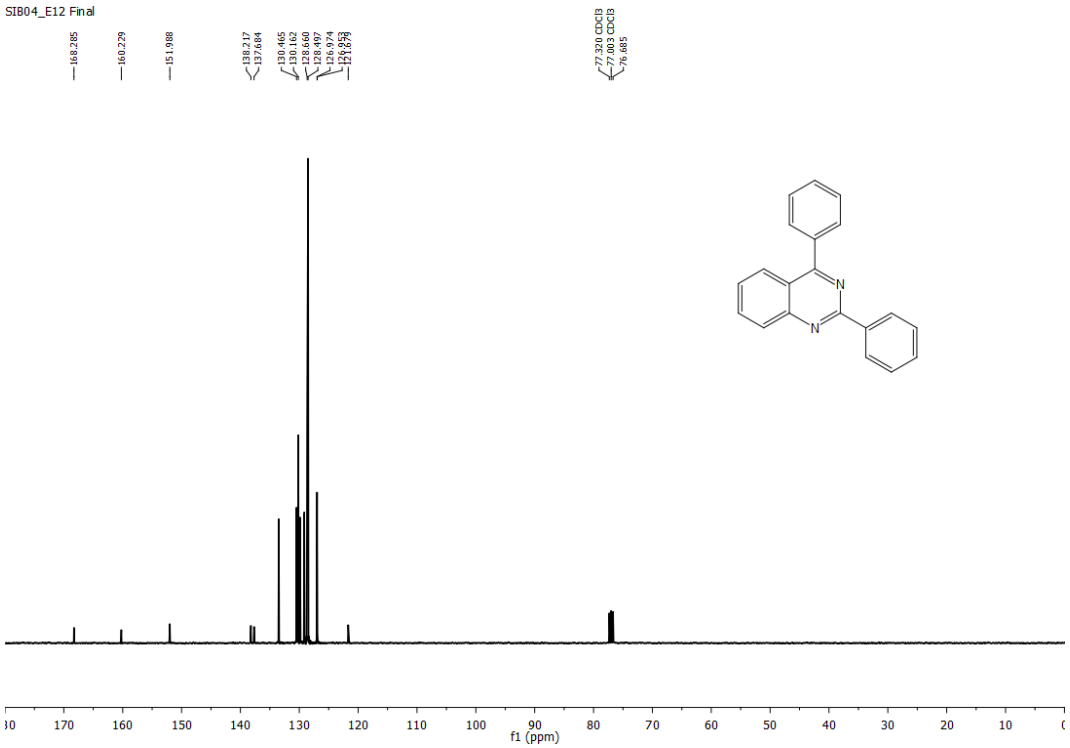


Fig. 5.5: ^{13}C NMR spectrum of **$S_4$4e**

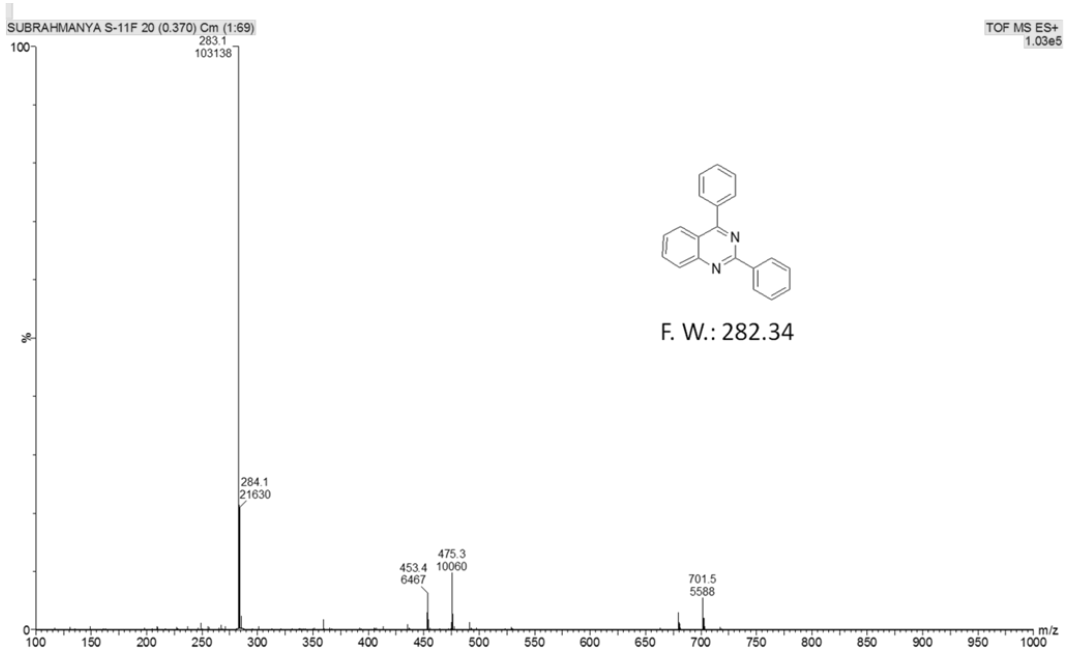
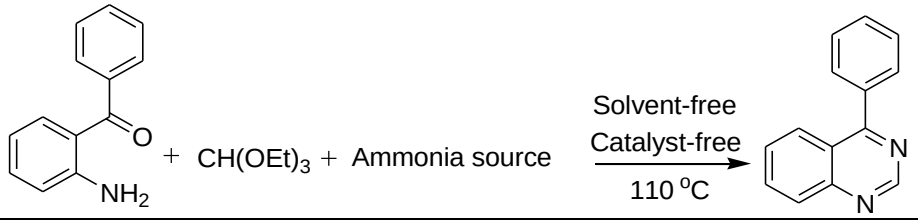


Fig. 5.6: ESI MS spectrum of **$S_4$4e**

5.3 RESULTS AND DISCUSSION

Initially, the three component reaction of 2-aminobenzophenone (**$S_4$1a**) with one equivalent of triethyl orthoformate (**$S_4$2a**) and one equivalent of ammonium acetate were investigated under solvent- and catalyst-free conditions at 110 ˚C. The reaction was monitored with TLC (9:1 PE: EA). Partial conversion was observed after 1 h, but the complete conversion was not observed even after prolonged reaction time (Table 5.3 entry **1**). However, quinazoline (**$S_4$4a**) was isolated in 52% yield and unconsumed starting material **$S_4$1a** was recovered. These results encouraged to optimize the reaction conditions and hence excess amounts of triethyl orthoformate and ammonium acetate have been used in order to improve the product yield (Table 5.3 entries **2-4**). The optimized ratio of $S_4$1a/ $S_4$2a/NH_4OAc = 1/1.5/1.5 was determined to be the more suitable combination for better conversion and to obtain the desired product with good yield, without any impurity formation and in moderate reaction time (Table 5.3 entry **4**). Further, decrease of temperature to 90 ˚C resulted in poor reactant conversion even after prolonged reaction time. Subsequently, series of solvent-free reaction of 2-aminobenzophenone and triethyl orthoformate have been carried out with various other ammonia sources under identical conditions in order to compare the efficiency (Table 5.3 entries **5-12**) of current green protocol. Decreased yields, small amount of unidentified impurities along with unconsumed starting materials were observed when urea, ammonium chloride, ammonium fluoride, ammonium phosphate, ammonium oxalate, ammonium hydroxide and ammonium sulphate were used as ammonia source. Comparative conversion was observed when ammonium carbonate was used as ammonia source, however it requires longer reaction time. Hence ammonium acetate was found to be the most efficient ammonia source for the present three component synthesis and further reactions were carried out using ammonium acetate as a source of ammonia. In order to evaluate the scope and limitations of the present protocol, the reaction was further performed using various substituted 2-aminoaryl ketones and trialkyl orthoesters and the results are summarised in Table 5.4.

Table 5.3: Optimization of the one pot three component synthesis of quinazolines



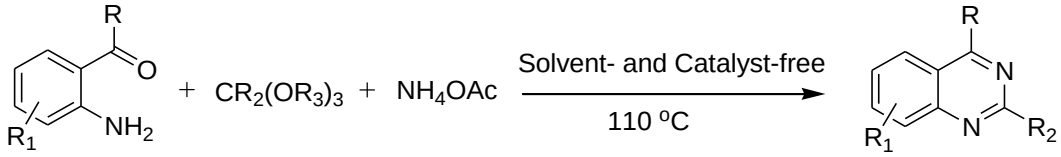
Entry	Ammonia Source	2-Aminobenzophenone/Triethyl orthoformate/Ammonia source	Time[a] (min)	Yield[b] (%)
1	Ammonium acetate	1:1:1	240	52
2		1:1.2:1.2	240	66
3		1:1.2:1.5	240	70
4		**1: 1.5:1.5**	**120**	**93**
5	Urea	1: 1.5:1.5	180	32
6	Ammonium sulphate	1: 1.5:1.5	180	46
7	Ammonium chloride	1: 1.5:1.5	180	trace
8	Ammonium fluoride	1: 1.5:1.5	180	trace
9	Ammonium phosphate	1: 1.5:1.5	180	67
10	Ammonium oxalate	1: 1.5:1.5	180	43
11	Ammonium hydroxide	1: 1.5:1.5	180	52
12	Ammonium carbonate	1: 1.5:1.5	180	81

[a] The reactions were monitored by TLC. [b] Isolated Yield

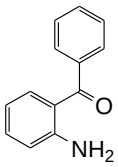
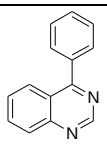
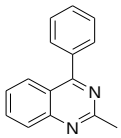
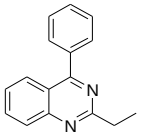
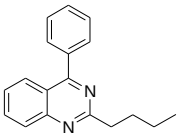
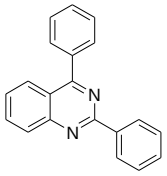
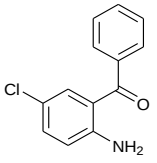
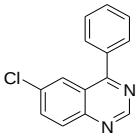
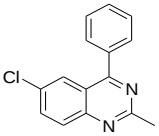
In order to evaluate the generality of the reaction, the reaction was performed with both 2-aminobenzophenones and 2′-aminoacetophenones. The reaction with 2′-aminoacetophenones proceeds faster than 2-aminobenzophenones to yield corresponding quinazolines. This may be attributed to the steric factor and extended conjugation induced by the aryl substitution which reduces the reactivity of carbonyl group. The reaction worked well with both electron withdrawing and donating substituents on the aniline ring of 2-aminobenzophenones. However, poor conversion was observed with strong electron donating group on the aniline ring of 2′-aminoacetophenone and unexpectedly only trace amount of product was observed

when 2-amino-4′,5′-dimethoxyacetophenone reacted with triethyl orthoformate, even after prolonged reaction time as shown in Table 5.4 entry **24**.

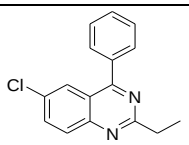
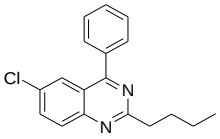
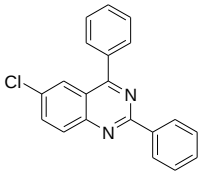
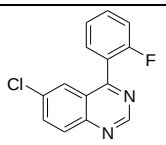
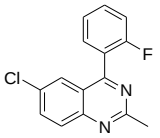
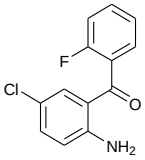
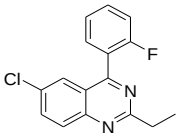
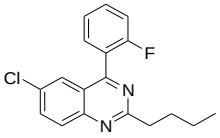
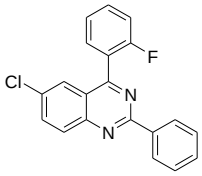
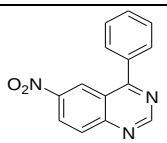
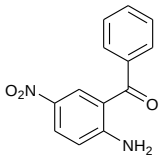
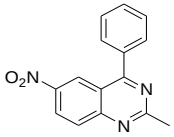
Table 5.4: Three component synthesis of quinazolines under solvent- and catalyst-free conditions



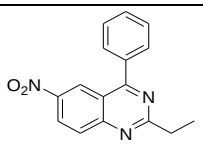
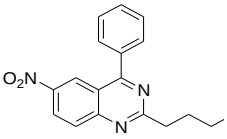
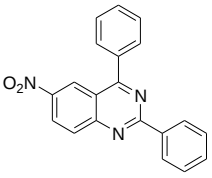
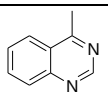
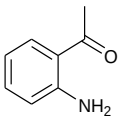
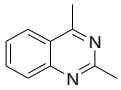
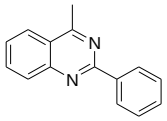
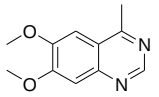
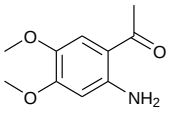
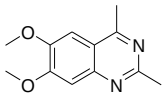
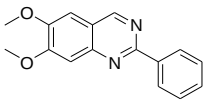
$S_4$1 **$S_4$2** **$S_4$3** **$S_4$4**

Entry	2-aminoarylketone	Trialkylothroester	Time (min)	Product[a]		% Yield[b]
1		H-C(OC_2H_5)$_3$	120	**$S_4$4a**		93
2		H_3C-C(OC_2H_5)$_3$	120	**$S_4$4b**		89
3		H_5C_2-C(OC_2H_5)$_3$	120	**$S_4$4c**		90
4		H_9C_4-C(OCH_3)$_3$	120	**$S_4$4d**		86
5		H_5C_6-C(OCH_3)$_3$	150	**$S_4$4e**		90
6		H-C(OC_2H_5)$_3$	120	**$S_4$4f**		94
7		H_3C-C(OC_2H_5)$_3$	120	**$S_4$4g**		88

Contd.

8		H_5C_2-$C(OC_2H_5)_3$	120	**$S_4$4h**	 88
9		H_9C_4-$C(OCH_3)_3$	120	**$S_4$4i**	 00
10		H_5C_6-$C(OCH_3)_3$	150	**$S_4$4j**	 87
11		H-$C(OC_2H_5)_3$	120	**$S_4$4k**	 93
12		H_3C-$C(OC_2H_5)_3$	120	**$S_4$4l**	 86
13		H_5C_2-$C(OC_2H_5)_3$	120	**$S_4$4 m**	 00
14		H_9C_4-$C(OCH_3)_3$	120	**$S_4$4n**	 00
15		H_5C_6-$C(OCH_3)_3$	150	**$S_4$4o**	 84
16		H-$C(OC_2H_5)_3$	120	**$S_4$4p**	 88
17		H_3C-$C(OC_2H_5)_3$	120	**$S_4$4q**	 00

Contd.

18		H_5C_2-$C(OC_2H_5)_3$	120	**$S_4$4r**		76
19		H_9C_4-$C(OCH_3)_3$	120	**$S_4$4s**		79
20		H_5C_6-$C(OCH_3)_3$	150	**$S_4$4t**		trace
21		H-$C(OC_2H_5)_3$	90	**$S_4$4u**		88
22		H_3C-$C(OC_2H_5)_3$	120	**$S_4$4v**		79
23		H_5C_6-$C(OCH_3)_3$	120	**$S_4$4w**		81
24		H-$C(OC_2H_5)_3$	90	**$S_4$4x**		trace
25		H_3C-$C(OC_2H_5)_3$	120	**$S_4$4y**		82
26		H_5C_6-$C(OCH_3)_3$	120	**$S_4$4z**		84

[a] Reaction conditions: 2-aminoaryl ketone (1mmol), Trialkyl orthoester (1.5 mmol), Ammonium acetate (1.5 mmol) at 110 ˚C. [b] Isolated Yield.

Furthermore, the reaction feasibility was also examined with different substituted trialkyl orthoesters. The reactivity of aliphatic orthoesters was found to be better than orthobenzoate and their order of reactivity is orthoformate > orthoalkylate (orthoacetate ≈ orthopropionate ≈ orthovalerate) > orthobenzoate. This may be attributed to the steric effect induced by the substituent on the orthoester functionality. It was found that, there was no remarkable effect of chain length of orthoalkylates on the present reaction. For instance, the reaction of 2-aminobenzophenone with orthoacetate, orthopropionate and orthovalerate underwent smoothly to obtain

corresponding quinazolines in good yields. The reactions of 2-aminobenzophenones with trimethyl orthobenzoate found to be very slow and took longer time to complete. This may be attributed to the formation of stabilized imidate intermediate (**I,** Scheme 5.2) due to the presence of phenyl group at 2-position and this phenomenon helps to isolate the intermediate in order to predict the mechanistic pathway.

The structures of the products were unequivocally confirmed by spectral data and elemental analysis. Further, quinazoline **$S_4$4a** was selected as a representative compound and characterized by SCXRD analysis as shown in Fig. 5.7.

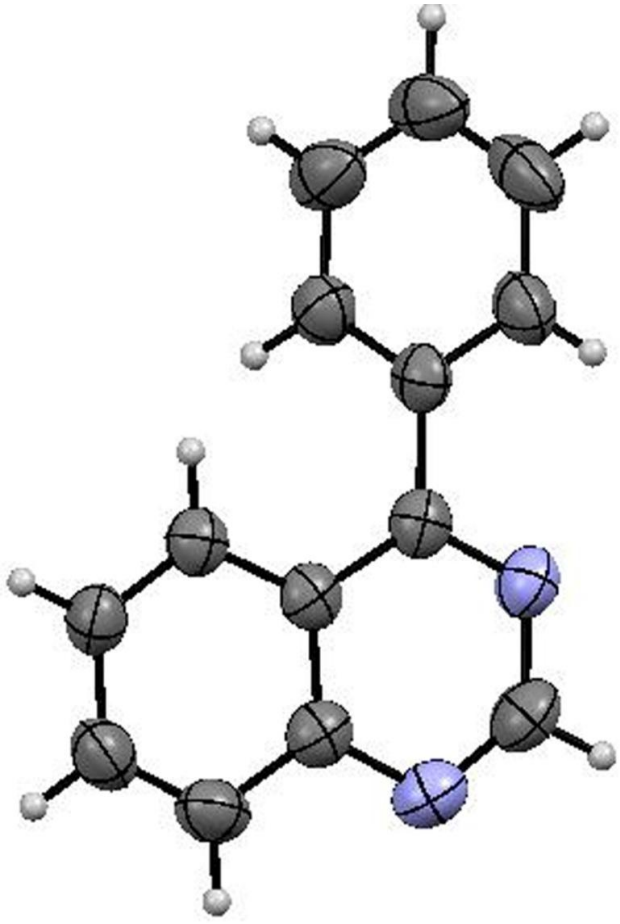
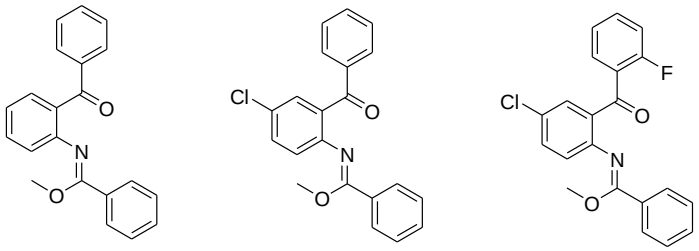


Fig. 5.7: ORTEP (50% probability) diagram of the crystal structure of 4-phenylquinazoline (**$S_4$4a**)

To elucidate the reaction mechanism, the reaction of 2-aminobenzophenone with ammonium acetate and trimethylorthobenzoate was quenched after 60 min. It was found that, the reaction was incomplete and methyl N-2-benzoylphenylbenzimidate was formed as a major product with trace amount of aromatized quinazoline **$S_4$4e**.

Further, similar observation was found when the three component reaction was performed using (2-amino-5-chlorophenyl)(phenyl)methanone, and (2-amino-5-chlorophenyl)(2-fluorophenyl)methanone. The isolated intermediates **$S_4$4ei, $S_4$4oi** and **$S_4$4ji** (Fig. 5.8) were confirmed by spectral analysis and in addition N-2-benzoyl-4-chlorophenylbenzimidate (**$S_4$4ji**) was confirmed by SCXRD analysis (Fig. 5.9).



S_4ei **S_4ji** **S_4oi**

Fig. 5.8: Isolated benzimidate intermediates

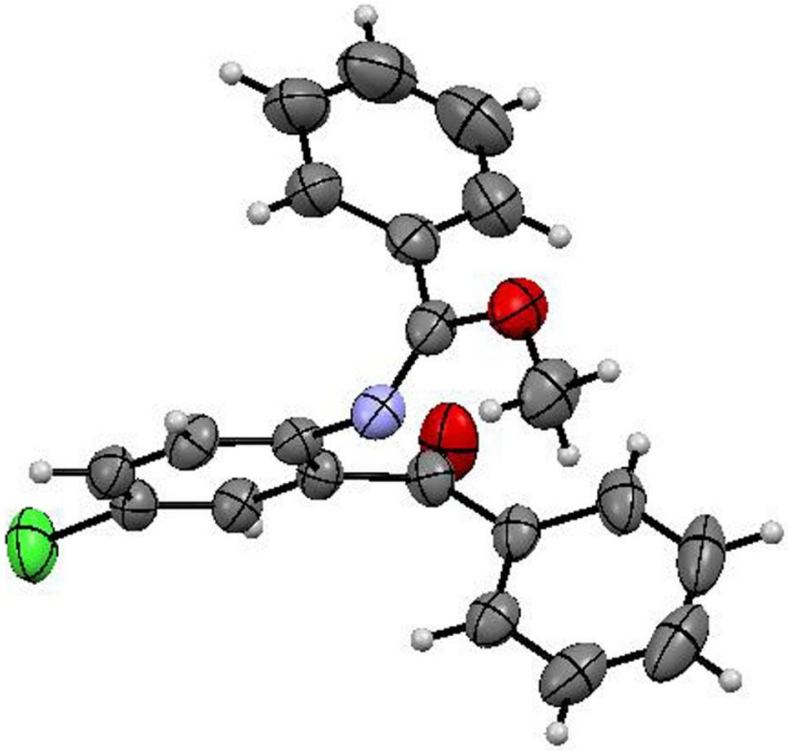
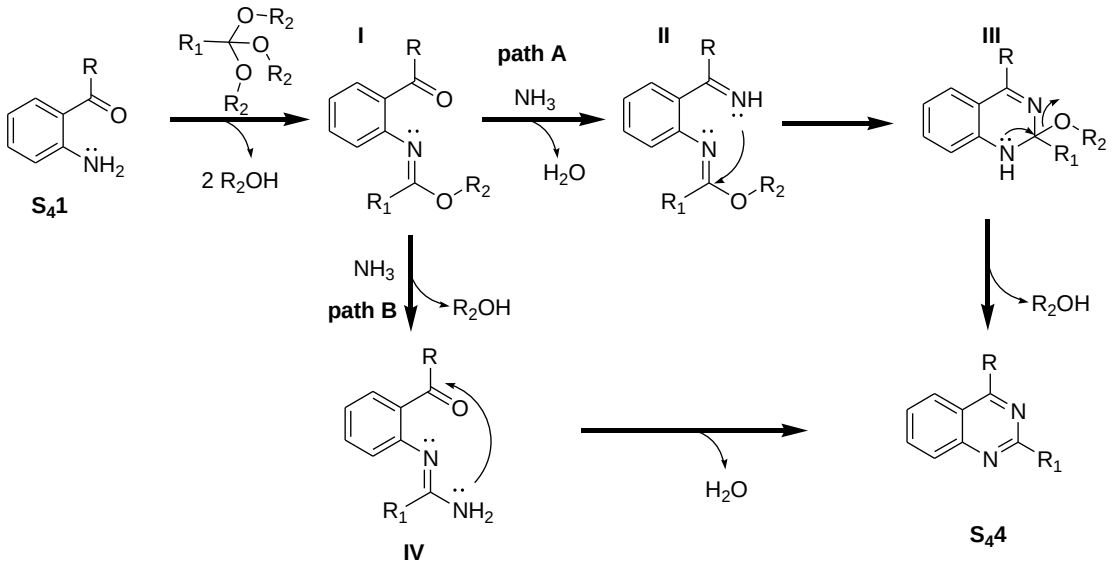


Fig. 5.9: ORTEP diagram of the crystal structure of N-2-benzoyl-4-chlorophenylbenzimidate (**$S_4$4ji**) with 50% probability.

Based on the above results and literature references, two plausible mechanistic pathways are proposed as shown in Scheme 5.2. It was unambiguously confirmed that, the initial reaction of 2-aminoketone and orthoester leads to the formation of

imidate intermediate [**I]** with the elimination of alcohol. The imidate intermediate [**I]** can undergo two different pathways to obtain the final quinazoline **($S_4$4)**. According to Panja et al. (2012) the ketone group can form an ketimine [**II**] by condensation with the ammonia generated, which on simultaneous intramolecular cyclization and aromatization with the elimination of alcohol yields quinazoline **($S_4$4**). Alternatively, the imidate can react with ammonia, to form vinylamidine intermediate [**IV**] (Sasada et al. 2009), which can lead to formation of the final quinazoline **($S_4$4**) product through intramolecular cyclization with the elimination of water.



Scheme 5.2: Proposed mechanism for the formation of quinazolines **$S_4$4** in current protocol

5.4 CONCLUSION

In conclusion, a novel three component, one pot synthesis of quinazolines has been developed using 2-aminoaryl ketones, orthoesters and ammonium acetate as building blocks under solvent- and catalyst-free conditions. The mechanism has been investigated scientifically with the confirmation of the intermediate using spectral and SCXRD analysis. It was clearly found that, the first step of the reaction involves the formation of imidate intermediate. The current protocol offers easier method to synthesize both aliphatic and aromatic substitutions at 2- and 4- position of quinazolines.

CHAPTER 6

A GREEN AND ONE-POT PROTOCOL FOR THE REGIOSELECTIVE SYNTHESIS OF POLYFUNCTIONALIZED PYRROLES

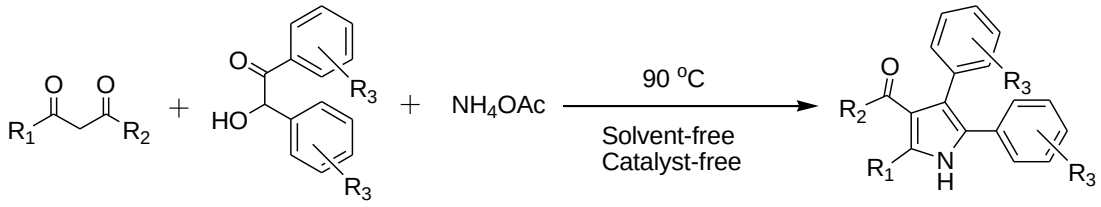
This Chapter describes a facile and green method for the regioselective synthesis of tetrasubstituted pyrroles, from readily accessible 1,3-dicarbonyls, benzoin derivatives and ammonium acetate under solvent- and catalyst-free conditions. The scope of the reaction, advantages over existing protocols and possible mechanism of the current protocol have been discussed.

6.1 INTRODUCTION

Pyrroles represent an important class of nitrogen containing heterocycles, which can be found in broad range of natural products (Fujita et al. 2003; Furstner, 2003), pharmaceuticals (Walsh et al. 2006; Zeng et al. 2006), material science (Groenendaal et al. 1997; Lee et al. 2000) and widely employed as versatile building blocks in synthetic organic chemistry (Bellina and Rossi 2006; Trofimov et al. 2004). Further, substituted pyrroles found importance in molecular sensors (Sessler et al. 2006). Within diversified derivatives of pyrroles, tetrasubstituted pyrroles are of great importance due to their tremendous application in bioactive molecules (Almerico et al. 1997; Lehuede et al. 1999). Owing to their widespread applications, in addition to the classical approaches (Manley et al. 2003; Shiner and Lash 2005; Minetto et al. 2005), continuous interest has been directed to the development of new and efficient synthetic protocols for the synthesis of pyrrole nucleus under traditional and green conditions (Balme 2004; Estevez et al. 2010; Liu et al. 2010; Estevez et al. 2013; Suresh et al. 2013). However, only few reports are available in the literature for the synthesis of functionalised pyrroles under solvent- and catalyst- free conditions (Attanasi et al. 2011; Palmieri et al. 2011), which are not only beneficiary in terms of cost and efficiency but make the organic transformations environmentally benign. Hence, the development of efficient synthetic approach for the construction of polysubstituted pyrroles under solvent- and catalyst-free condition is still an attractive goal for synthetic chemists aiming for green and sustainable development.

Meanwhile, 1,3-dicarbonyl compounds have drawn much attention in the synthesis of many important heterocycles, particularly in one-pot multicomponent approach (Simon et al. 2004; Wan et al. 2012; Singh and Chowdhury 2012). Their advantages such as easy availability, unique reactivity and simple handling procedure make them privileged starting materials for structurally diversified heterocycles. On the other hand, benzoins/α-hydroxy ketones have found potential value as building blocks in

the construction of various heterocycles (Sithambaram et al. 2008; Bhattacharya et al. 2012; Xue et al. 2012). Procopiou et al. (1993) developed three component synthesis of tetrasubstituted pyrroles using benzoin derivatives, ethyl isobutyrylacetate, and ammonium acetate. However, this method requires the reaction under acetic acid reflux condition followed by solvent evoparation and tedious work-up procedure. Recently, solvent-free catalytic synthesis of tetrasubstituted pyrroles using 1,3-dicarbonyls, benzoin derivatives and ammonium acetate have been reported (Tamaddon and Farahi 2012; Tamaddon et al. 2012). Despite the satisfactory product yield, these methods require much effort in the preparation and reuse of solid acid catalyst and in the extraction of product. The repeated reuse of catalyst resulted in the decreased product yield. Further, cyclic diketones and poor reactive benzoins such as anisoin failed to yield corresponding product using these protocols. Although, the organic transformations are well known under solvent/catalytic process, their improvement in terms of reaction efficiency, substrate modification, avoidance of toxic reagents, reduction of waste have significant values in modern organic chemistry.



S51 **S5**2 **S5**3 **S5**4

Scheme 6.1: One-pot three-component synthesis of tetrasubstituted pyrroles

Considering the above factors, herein one pot, three component synthesis of tetrasubstituted pyrroles has been developed using 1,3-dicarbonyl compounds, benzoin derivatives and ammonium acetate as an efficient ammonia source under solvent-free condition in the absence of any additional catalyst (Scheme 6.1). High product yields were obtained in moderate reaction time and after simple recrystallization with mixture of water and EtOH which are well known as ecofriendly solvents.

6.2 EXPERIMENTAL

6.2.1 General

Melting points were determined with Stuart SMP3 melting point apparatus and are uncorrected. NMR spectra were recorded as a solution in $CDCl_3$/DMSO-d_6 400 MHz instrument. IR spectra were recorded on a Thermo scientific Nicolet Avatar 330 Fourier transform infrared (FTIR) spectrometer by Attenuated Total Reflectance (ATR) method. Chemical shifts (δ) are reported in ppm with TMS as an internal standard. NMR raw data was analysed with the program MestReNova 7.0.0-8331. Elemental analysis was performed using Perkin Elmer, Series II, 2400 analyzer. The SCXRD analysis was performed on the Bruker AXS APEX II duo system. All experiments were monitored by TLC, performed on pre-coated silica gel 60 F_{254} plates (Merck). Column chromatography was performed on silica gel (60-120 mesh, Merck) using EtOAc-PE as eluent.

6.2.2 General Procedure for the synthesis of tetrasubstituted pyrroles ($S_5$4)

1,3-dicarbonyl **$S_5$1** (1.1 mmol), benzoin derivative/ phenyl glyoxal **$S_5$2** (1.0 mmol) and ammonium acetate **$S_5$3** (1.5 mmol) were charged into a 10 mL round-bottom flask and the mixture was heated to 90 ˚C/50 ˚C using conventional oil bath. The reaction mixture was stirred to 120 min until the starting material **$S_5$2** was consumed to maximum extent. The reaction mixture was then cooled and recrystallized with EtOH water 80:20 mixture to obtain pure product **$S_5$4**. (The reaction mixture was dissolved in EtOAc (2 mL) and washed with water (2×2 mL) and the organic layer was separated and adsorbed to silica gel (60-120 mesh size) and column chromatographed using EtOAc and PE as elutants to obtain pure polyfunctionalized indoles **$S_5$4m** and **$S_5$4n)**.

All the newly synthesized compounds were characterized by spectral analysis and the spectral data of the final compounds are given below.

ethyl 2-methyl-4,5-diphenyl-1*H*-pyrrole-3-carboxylate ($S_5$4a)

White solid; mp: 204~205 ˚C (lit. 205-206 ˚C); ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.02 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 2.60 (S, 3H, Pyrrole (Py)-CH_3), 4.06 (q, 2H, *J* = 7.2 Hz,

CH_2), 7.09-7.33 (m, 10H, ArH), 8.34 (s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.8, 13.9, 59.2, 112.7, 123.4, 126.3, 126.5, 126.7, 127.3, 127.6, 128.2, 128.5, 129.9, 130.8, 132.2, 135.4, 136.1, 165.6; IR (Neat, cm^{-1}): 3305 (NH), 3055 (CH_{arom}), 2983 (CH_{aliph}), 2927 (CH_{aliph}), 2927 (CH_{aliph}), 1675 (C=O), 1600 (C=C), 1484 (C=C), 1477 (C=C); Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59, Found: C, 78.53; H, 6.21; N, 4.63; MS (ESI APCI) for $C_{20}H_{19}NO_2$: 306.1$(M+H)^+$.

ethyl 4,5-bis(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-carboxylate ($S_5$4b)

White solid; mp: 141~142 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.09 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 2.58 (s, 3H, Py-CH_3), 3.75 (s, 3H, -OCH_3), 3.81 (s, 3H, -OCH_3), 4.10 (q, 2H, *J* = 7.2 Hz, CH_3CH_2), 6.73-6.76 (m, 2H, ArH), 6.80-6.84 (m, 2H, ArH), 7.02-7.06 (m, 2H, ArH), 7.13-7.17 (m, 2H, ArH), 8.21 (s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.9, 14.1, 55.1, 55.2, 59.2, 112.4, 113.1, 113.7, 113.9, 122.1, 125.0, 127.3, 128.1, 128.4, 131.1, 131.9, 134.8, 158.2, 158.3, 165.7; IR (Neat, cm^{-1}): 3286 (NH), 3059 ($ArCH_{arom}$), 2981 (CH_{aliph}), 2928 (CH_{aliph}), 2923 (CH_{aliph}), 1668 (C=O), 1600 (C=C), 1484 (C=C), 1477 (C=C); Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83, Found: C, 72.26; H, 6.39; N, 3.75; MS (ESI APCI) for $C_{22}H_{23}NO_4$: 366.1$(M+H)^+$.

ethyl 4,5-di(furan-3-yl)-2-methyl-1*H*-pyrrole-3-carboxylate ($S_5$4c)

White solid; mp: 118~119 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.16 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 2.57 (s, 3H, Py-CH_3), 4.15 (q, 2H, *J* = 7.2 Hz, CH_2CH_3), 6.04 (dd, 1H, J_1 = 0.8 Hz, J_2 = 3.6 Hz, ArH), 6.32-6.33 (m, 1H, ArH), 6.40 (d, 1H, *J* = 0.8 Hz, ArH), 6.47 (d, 1H, *J* = 1.6 Hz, ArH), 7.30-7.31 (m, 1H, ArH), 7.50-7.51 (m, 1H, ArH), 8.75 (s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 13.6, 14.1, 59.4, 105.1, 109.5, 110.7, 111.0, 111.8, 113.1, 122.1, 135.7, 140.6, 141.4, 145.9, 147.7, 164.9; IR (Neat, cm^{-1}): 3211 (NH), 1659 (C=O), 1565 (C=C), 1521 (C=C), 1476 (C=C); Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91, Found: C, 67.43; H, 5.22; N, 4.83; MS (ESI APCI) for $C_{16}H_{15}NO_4$: 286.0 $(M+H)^+$.

tert-butyl 2-methyl-4,5-diphenyl-1*H*-pyrrole-3-carboxylate ($S_5$4d)

White solid; ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.19 (s, 9H, -CCH_3), 2.50 (s, 3H, Py-CH_3), 7.11-7.39 (m, 10H, ArH), 11.48 (s, 1H, NH); ^{13}C NMR (100.6 MHz, DMSO-

d$_6$) δ: 13.0, 27.7, 77.9, 112.9, 122.4, 125.8, 125.9, 126.4, 126.5, 127.5, 128.1, 128.2, 128.7, 129.5, 130.5, 132.3, 135.2, 137.1, 164.2; IR (Neat, cm^{-1}): 3285 (NH), 3055 (CH_{arom}), 2983 (CH_{aliph}), 2924 (CH_{aliph}), 2918 (CH_{aliph}), 1666 (C=O), 1596 (C=C), 1490 (C=C), 1480 (C=C); Anal. Calcd for $C_{22}H_{23}NO_2$: C, 79.25; H, 6.95; N, 4.20, Found: C, 79.15; H, 6.99; N, 4.11.

tert-butyl 4,5-di(furan-3-yl)-2-methyl-1*H*-pyrrole-3-carboxylate ($S_5$4f)

White solid; ^{1}H NMR (400MHz, DMSO-*d*$_6$) δ: 1.32 (s, 9H, -C*CH*$_3$), 2.45 (s, 3H, Py-CH3), 6.06 (d, 1H, *J* = 2.8Hz, ArH), 6.32 (d, 1H, *J* = 0.8Hz, ArH) 6.47-6.48 (m, 1H, ArH), 6.50-6.51 (m, 1H, ArH), 7.64-7.66 (m, 2H, ArH), 11.82 (s, 1H, NH); ^{13}C NMR(100.6 MHz, DMSO-*d*$_6$) δ: 12.7, 27.9, 78.3, 105.2, 108.8, 110.6, 110.7, 111.5, 113.3, 121.1, 135.8, 141.5, 146.1, 147.9, 163.6; IR (Neat, cm^{-1}): 3216 (NH), 1654 (C=O), 1558 (C=C), 1518 (C=C), 1482 (C=C); Anal. Calcd for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47, Found: C, 68.90; H, 6.19; N, 4.39.

1-(2-methyl-4,5-diphenyl-1*H*-pyrrol-3-yl)ethanone ($S_5$4g)

White solid; mp: 172~173 ˚C (lit. 170-171 ˚C); ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.93 (s, 3H, Py-CH_3), 2.65 (s, 3H, -(CO)*CH*$_3$), 7.15-7.43 (m, 10H, ArH) 8.69 (s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 14.4, 30.9, 122.8, 123.0, 126.6, 126.7, 127.0, 127.1, 128.2, 128.4, 128.5, 129.9, 130.9, 132.1, 135.1, 136.6, 197.2; IR (Neat, cm^{-1}): 3304 (NH), 3046 (CH_{arom}), 1632 (C=O), 1604 (C=C), 1523 (C=C).

1-(4,5-bis(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl)ethanone ($S_5$4h)

White solid; mp: 182~183 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 1.89 (s, 3H, Py-CH_3), 2.57 (s, 3H, -(CO)*CH*$_3$), 3.74 (s, 3H, -OCH_3), 3.83 (s, 3H, -OCH_3), 6.73 (d, 2H, *J* = 8.8 Hz, ArH), 6.87-6.90 (m, 2H, ArH), 7.03-7.07 (m, 2H, ArH), 7.16-7.18 (m, 2H, ArH), 8.56 (s, 1H, NH); ^{13}C NMR(100.6 MHz, $CDCl_3$) δ: 14.4, 30.8, 55.2, 113.9, 121.5, 122.8, 124.9, 127.0, 127.9, 128.8, 131.9, 134.6, 158.3, 158.7, 197.2; IR (Neat, cm^{-1}): 3346 (NH), 3055 (CH_{arom}), 1634 (C=O), 1596 (C=C), 1516 (C=C); Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18, Found: C, 75.12; H, 6.26; N, 4.11; MS (ESI-APCI) for $C_{21}H_{21}NO_3$: 336.1 $(M+H)^+$.

1-(4,5-di(furan-3-yl)-2-methyl-1*H*-pyrrol-3-yl)ethanone ($S_5$4i)

White solid; mp: 151~152˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 2.01 (s, 3H, Py-CH_3), 2.58 (s, 3H, -(CO)CH_3), 5.96 (dd, 1H, J_1 = 0.8 Hz, J_2 = 3.6 Hz, ArH), 6.32 (d, 1H, J = 1.6 Hz, ArH), 6.42 (dd, 1H, J_1 = 0.8 Hz, J_2 = 3.2 Hz, ArH), 6.52 (d, 1H, J = 2 Hz, ArH), 7.30 (d, 1H, J = 2 Hz, ArH), 7.56 (dd, 1H, J_1 = 0.8 Hz, J_2 = 2 Hz, ArH), 9.08 (s, 1H, NH), ^{13}C NMR(100.6 MHz, $CDCl_3$) δ:14.2, 29.2, 104.9, 110.2, 110.6, 111.2, 111.8, 122.3, 122.5, 135.8, 140.8, 142.3, 145.8, 147.5, 196.2; IR (Neat, cm^{-1}): 3209 (NH), 1624 (C=O), 1554 (C=C), 1501 (C=C); Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49, Found: C, 70.52; H, 5.21; N, 5.38; MS (ESI APCI) for $C_{15}H_{13}NO_3$: 256.0 $(M+H)^+$.

(2-methyl-4,5-diphenyl-1*H*-pyrrol-3-yl)(phenyl)methanone ($S_5$4j)

White solid; mp: 221~222 ˚C (lit. 221-223 ˚C)[1]; ^{1}H NMR (400MHz, $CDCl_3$) δ: 2.42 (s, 3H, Py-CH_3), 6.90-7.26 (m, 13H, ArH), 7.59-7.62 (m, 2H, ArH), 8.47 (s, 1H, NH); ^{13}C NMR(100.6 MHz, $CDCl_3$) δ: 13.2, 121.9, 122.9, 125.9, 126.8, 127.1, 127.3, 127.6, 127.7, 128.6, 129.6, 130.5, 131.5, 132.3, 133.9, 135.0, 139.6, 194.3; IR (Neat, cm^{-1}): 3283 (NH), 3054 (CH_{arom}), 1609 (C=O), 1597 (C=C), 1576 (C=C); Anal. Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15, Found: C, 85.38; H, 5.76; N, 4.10; MS (ESI APCI) for $C_{24}H_{19}NO$: 338.1 $(M+H)^+$.

(4,5-bis(4-methoxyphenyl)-2-methyl-1*H*-pyrrol-3-yl)(phenyl)methanone ($S_5$4k)

White solid; mp: 232~236 ˚C; ^{1}H NMR (400MHz, $CDCl_3$) δ: 2.39 (s, 3H, Py-CH_3), 3.67 (s, 3H, -OCH_3), 3.77 (s, 3H, -OCH_3), 6.55-6.58 (m, 2H, ArH), 6.77-6.80 (m, 2H, ArH), 6.92-6.94 (m, 2H, ArH), 7.15-7.18 (m, 4H, ArH), 7.26-7.30 (m, 1H, ArH), 7.60-7.62 (m, 2H, ArH), 8.32 (s, 1H, NH); ^{13}C NMR(100.6 MHz, $CDCl_3$) δ: 13.2, 55.1, 55.2, 113.3, 113.7, 114.1, 125.0, 126.8, 127.6, 128.5, 129.6, 131.1, 131.4, 131.5, 133.3, 139.7, 157.8, 158.5, 194.3; IR (Neat, cm^{-1}): 3281 (NH), 3048 (CH_{arom}), 1606 (C=O), 1592 (C=C), 1566 (C=C); Anal. Calcd for $C_{26}H_{23}NO_3$: C, 78.57; H, 5.83; N, 3.52, Found: C, 78.63; H, 5.88; N, 3.44; MS (ESI APCI) for $C_{26}H_{23}NO_3$: 398.1 $(M+H)^+$.

(4,5-di(furan-3-yl)-2-methyl-1*H*-pyrrol-3-yl)(phenyl)methanone ($S_5$4l)

Blood red coloured liquid; ^{1}H NMR (400MHz, $CDCl_3$) δ: 2.42 (s, 3H, Py-CH_3), 6.11 (d, 1H, *J* = 0.8 Hz, ArH), 6.14-6.15 (m, 1H, ArH), 6.32 (d, 1H, *J* = 0.8 Hz, ArH), 6.38 (dd, 1H, J_1 = 2 Hz, J_2 = 3.6 Hz, ArH), 7.2 (s, 1H, ArH), 7.24-7.26 (m, 2H, ArH), 7.34-7.35 (m, 2H, ArH), 7.64-7.67 (m, 2H, ArH), 8.90 (s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 12.9, 105.5, 109.7, 110.9, 111.3, 111.8, 120.7, 121.4, 127.7, 129.1, 131.6, 134.2, 139.6, 140.9, 141.0, 146.1, 147.2, 193.5; IR (Neat, cm^{-1}): 3283 (NH), 3054 (CH_{arom}), 1609 (C=O), 1597 (C=C), 1576 (C=C); Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41, Found: C, 75.62; H, 4.79; N, 4.37; MS (ESI APCI) for $C_{20}H_{15}NO_3$: 318.0 $(M+H)^+$.

2,3-diphenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one ($S_5$4p)

White solid; mp: 304 ˚C (decomposed); ^{1}H NMR (400MHz, DMSO-d_6) δ: 2.05-2.11 (m, 2H, -CH_2*CH_2*CH_2-), 2.32-2.35 (m, 2H, Py-*CH_2*CH_2-), 2.86-2.89 (m, 2H, -CH_2*CH_2*CO-), 7.15-7.27 (m, 10H, ArH), 11.7 (s, 1H, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 22.5, 23.3, 118.0, 119.3, 126.0, 126.5, 127.2, 127.4, 128.2, 128.7, 130.5, 132.1, 135.3, 144.2, 192.5; IR (Neat, cm^{-1}): 3297 (NH), 3052 (CH_{arom}), 2986 (CH_{aliph}), 2932 (CH_{alph}), 1615 (C=O), 1594 (C=C), 1512 (C=C); Anal. Calcd for $C_{20}H_{17}NO$: C, 83.59; H, 5.96; N, 4.87, Found: C, 83.52; H, 5.88; N, 4.81.

6,6-dimethyl-2,3-diphenyl-6,7-dihydro-1*H*-indol-4(5*H*)-one ($S_5$4q)

White solid; mp: 303~306 ˚C; ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.10 (s, 6H), 2.25 (s, 2H), 2.76 (s, 2H), 7.16-7.27 (m, 10H), 11.62 (s, 1H); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 28.2, 34.8, 36.2, 52.9, 116.8, 119.1, 126.0, 126.5, 127.2, 127.4, 128.2, 130.5, 132.1, 135.1, 143.0, 191.9; IR (Neat, cm^{-1}): 3292 (NH), 3046 (CH_{arom}), 2974 (CH_{aliph}), 2921 (CH_{aliph}), 2886 (CH_{aliph}), 1619 (C=O), 1589 (C=C), 1510 (C=C); Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44, Found: C, 83.73; H, 6.65; N, 4.37; MS (ESI APCI) for $C_{22}H_{21}NO$: 316.1 $(M+H)^+$.

ethyl 4-hydroxy-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate ($S_5$4r)

White solid; mp: 231~233 ˚C (lit. 232 ˚C); ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.09 (t, 3H, *J* =7.2 Hz, -CH_2*CH_3*), 2.35 (s, 3H, Py-CH_3), 3.86-3.96 (m, 2H, -*CH_2*CH_3), 7.28-7.31 (m, 3H, ArH), 7.77-7.79 (m, 2H, ArH), 10.56 (s, 1H, NH); ^{13}C NMR (100.6

MHz, DMSO-d_6) δ: 14.2, 16.2, 17.2, 58.0, 110.9 112.0, 122.8, 124.1, 127.1, 128.2, 132.4, 148.8, 162.7, 180.9; IR (Neat, cm^{-1}): 3230 (NH), 3068 (CH_{arom}), 2981 (CH_{aliph}), 1690 (C=O), 1518 (C=C), 1443 (C=C).

tert-butyl 4-hydroxy-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate ($S_5$4s)

White solid; mp: 238~239 ˚C (lit. 237 ˚C); ^{1}H NMR (400MHz, DMSO-d_6) δ: 1.30 (s, 9H, -CCH_3), 2.33 (s, 3H, Py-CH_3), 7.27-7.28(m, 3H, ArH), 7.77-7.78 (m, 2H, ArH), 10.43 (s, 1H, NH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 14.3, 27.7, 79.8, 110.9, 112.0, 123.8, 124.8, 128.9, 132.4, 133.0, 145.7, 169.6, 180.9; IR (Neat, cm^{-1}): 3241 (NH), 3065 (CH_{arom}), 2981 (CH_{aliph}), 2931 (CH_{aliph}), 1687 (C=O).

1-(4-hydroxy-2-methyl-5-phenyl-1*H*-pyrrol-3-yl)ethanone ($S_5$4t)

White solid; mp: 233~234 ˚C (lit. 233 ˚C); ^{1}H NMR (400MHz, DMSO-d_6) δ: 2.42 (s, 3H), 2.52 (s, 3H, Py-CH_3), 7.07-7.11 (m, 1H, ArH), 7.33-7.37 (m, 2H, ArH), 7.69-7.72 (m, 2H, ArH), 9.99 (s, 1H, NH), 11.27 (s, 1H, OH); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ: 14.3, 28.8, 109.8, 111.1, 122.7, 124.1, 128.4, 131.6, 132.9, 144.5, 197.4; 3250, 3130, 3050. 1638, 1562, 1476

Table 6.1: Crystallographic data of compound **$S_5$4c**

Crystal data [CCDC No. 929558]	
Empirical formula	$C_{16}H_{15}NO_4$
Formula weight	285.29
Crystal size (mm)	0.3 x 0.2 x 0.2
Crystal system	Monoclinic
Space group	P21/c
a (Å); b (Å); c (Å)	10.1036(9); 12.6989(11); 11.9912(10)
α (˚); β (˚); γ (˚)	90.00; 106.5920(10); 90.00
Volume ($Å^3$)	1474.5(2)
Z	4
Crystal density, g/cm^3	1.285
F(000)	600
Absorption coefficient	0.093

Contd.

Temperature (T)	296 (2)
Radiation wavelength	0.71073
Radiation type	MoKα
Radiation source	Fine-focus sealed tube
Radiation monochromator	Graphite
h_{min}; k_{min}; l_{min}	-12; -15; -14
h_{max}; k_{max}; l_{max}	12; 15; 14
R-Factor (%)	3.93

The ^{1}H NMR ^{13}C NMR and ESI APCI MS spectra of **$S_5$4a** and **$S_5$4q** are shown below.

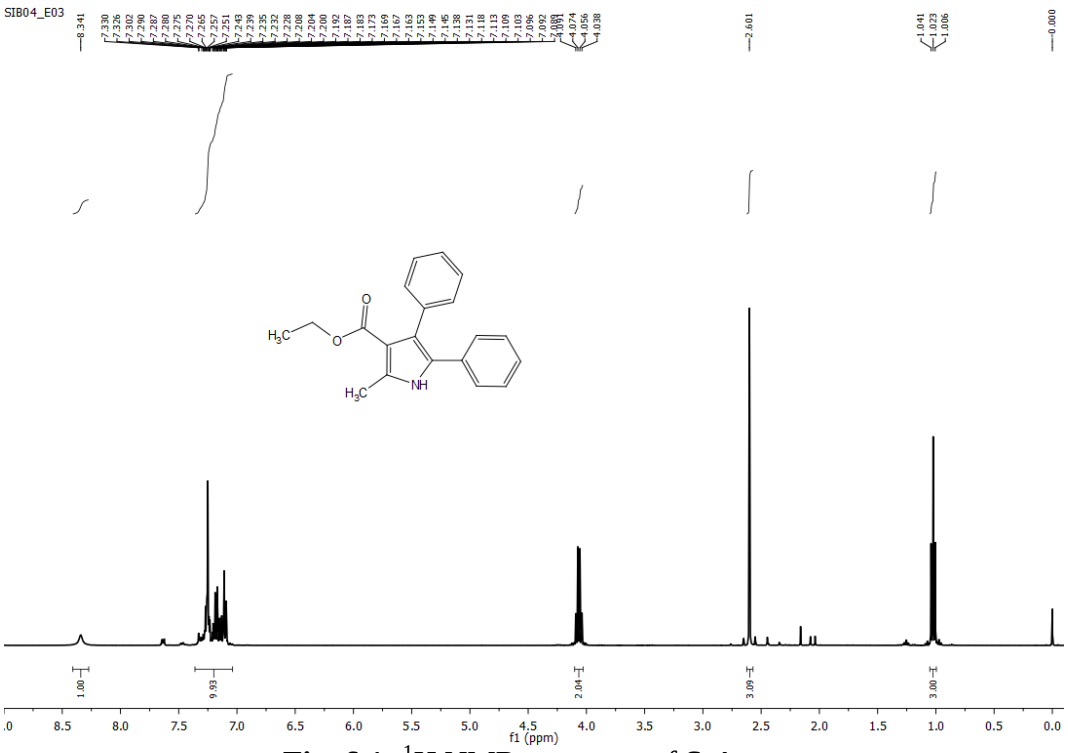


Fig. 6.1: ^{1}H NMR spectrum of **$S_5$4a**

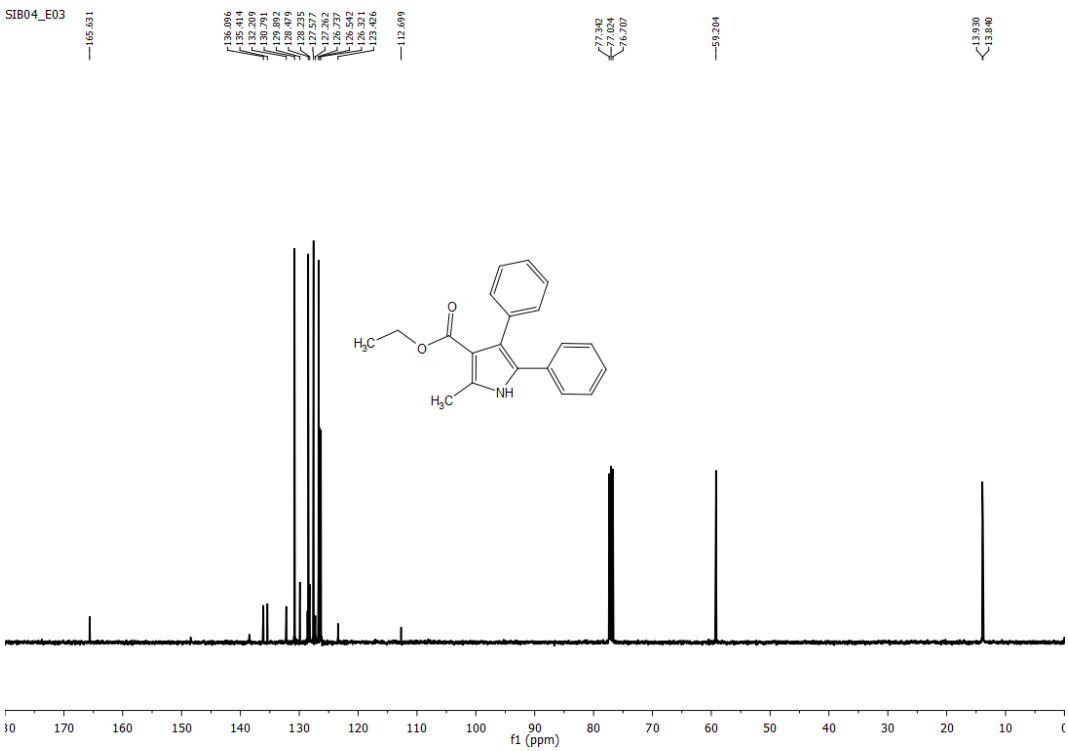


Fig. 6.2: ^{13}C NMR spectrum of **$S_5$4a**

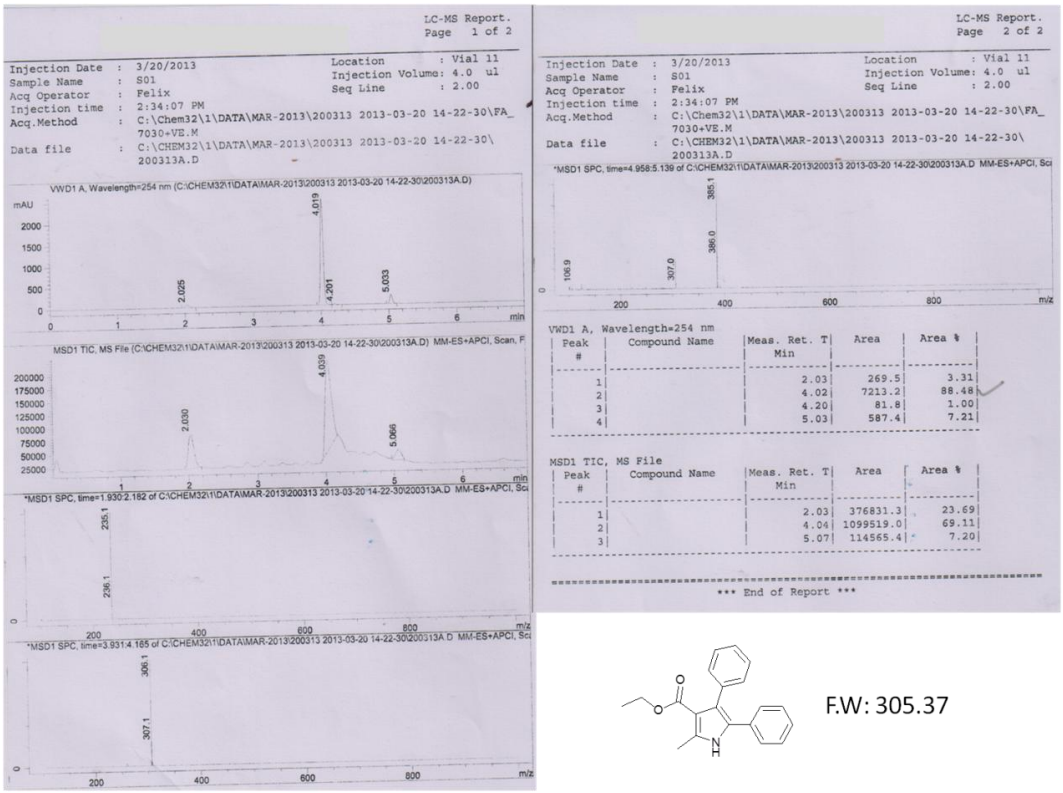


Fig. 6.3: ESI APCI MS spectrum of **$S_5$4a**

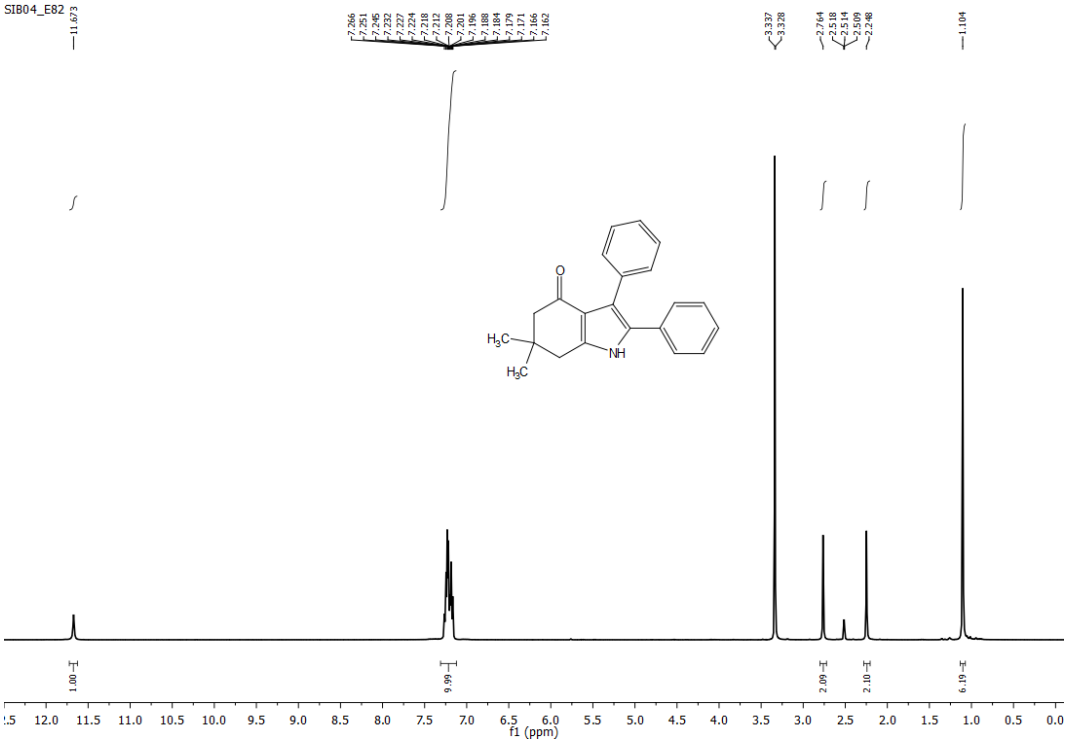


Fig. 6.4: ^{1}H NMR spectrum of **$S_5$4q**

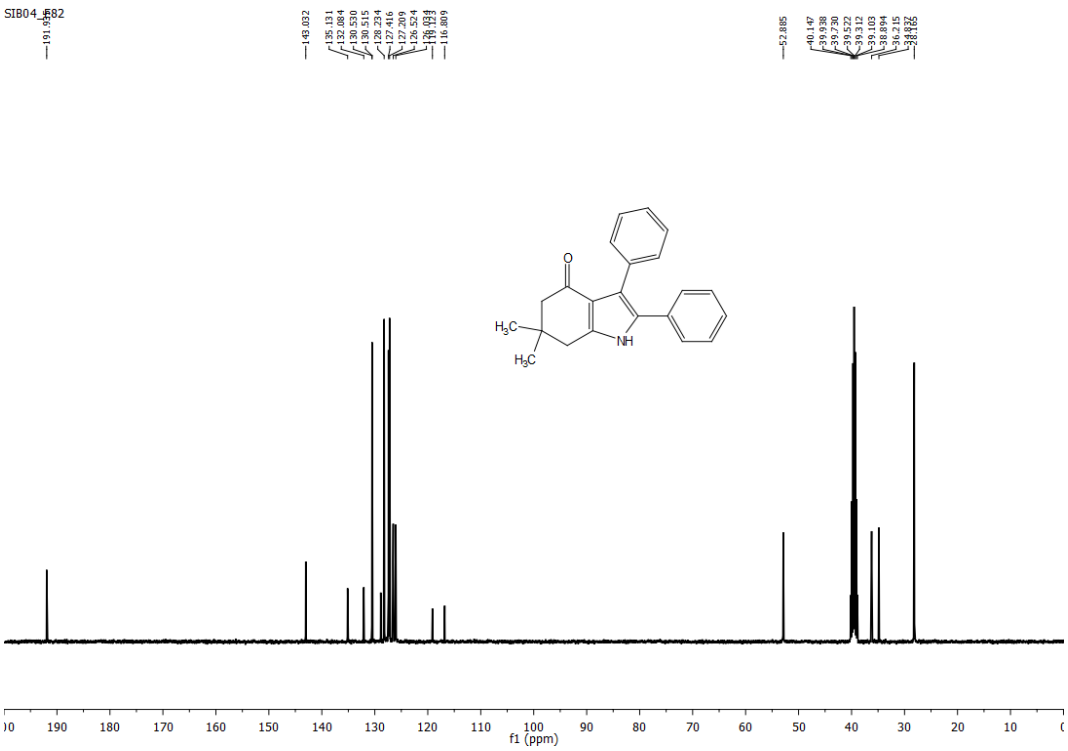


Fig. 6.5: ^{13}C NMR spectrum of **$S_5$4q**

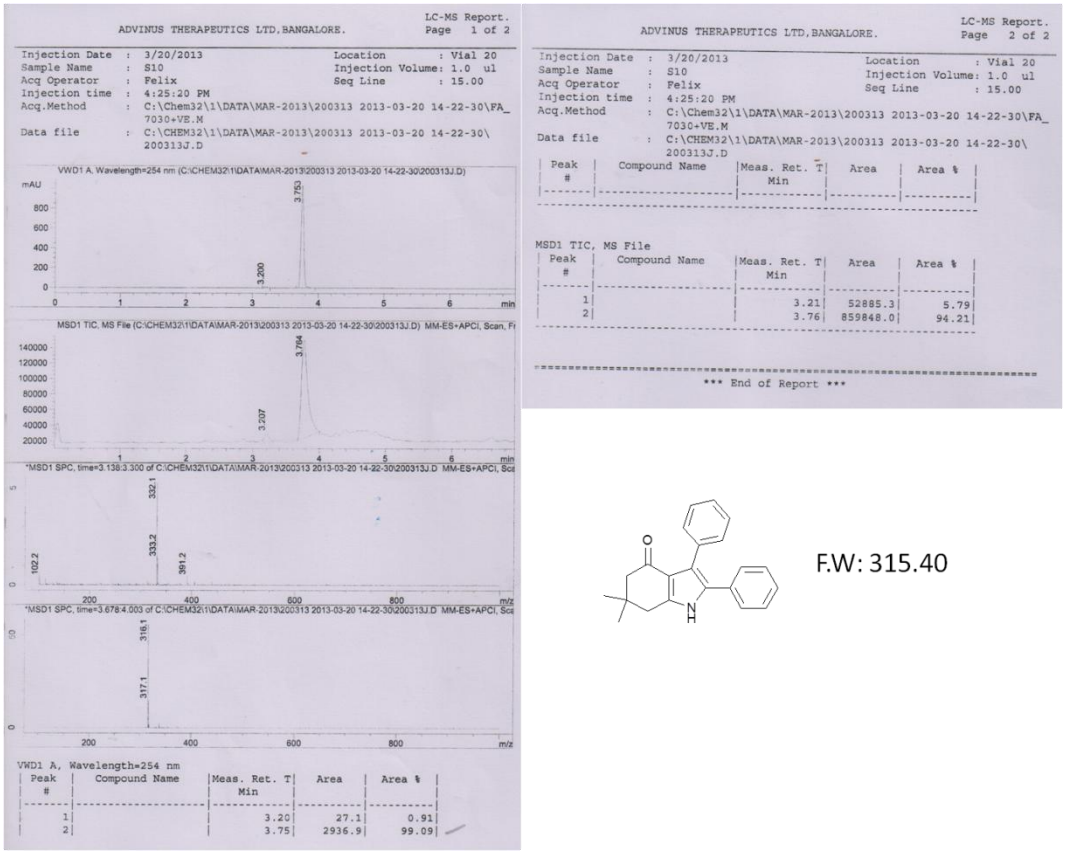
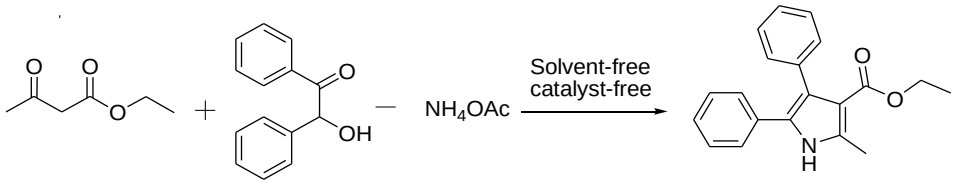


Fig. 6.6: ESI APCI MS spectrum of **$S_5$4q**

6.3 RESULTS AND DISCUSSION

Initially, the one pot, three-component reaction was carried out using equimolar amounts of EAA (**$S_5$1a**), benzoin (**$S_5$2a**) and ammonium acetate (**$S_5$3**) in 10 mL RB flask and heated to 80 ˚C under solvent-free condition. The reaction mass slowly converted to suspension and partial conversion was observed after 60 min (the reaction was monitored by TLC). The continuation of the reaction yielded 42% of the product after 180 min. The reaction was then optimized by varying the molar ratio of starting materials and temperature of the reaction (Table 6.2). The molar ratio 1.1:1:1.5 of EAA (**$S_5$1a**), benzoin (**$S_5$2a**) and ammonium acetate at 90 ˚C was found to be the more suitable condition for better conversion. The reaction mass converted to homogeneous liquid in this condition and the desired product was obtained in high yield in moderate reaction time. Further, increased temperature to 100 ˚C resulted in decreased yield due to the formation of unknown impurities. The pure solid product was obtained after recrystallization with EtOH-water (80:20) mixture.

Table 6.2: Optimization of the reaction



$S_5$1a **$S_5$2a** **$S_5$3** **$S_5$4a**

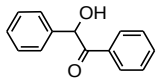
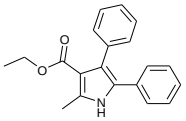
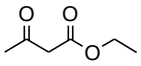
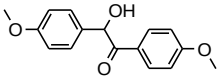
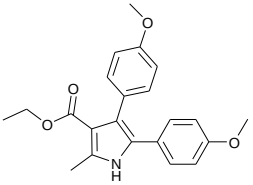
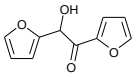
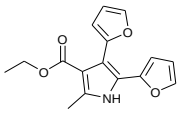
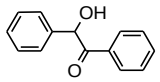
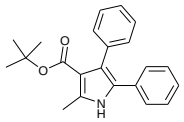
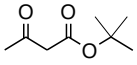
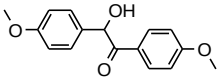
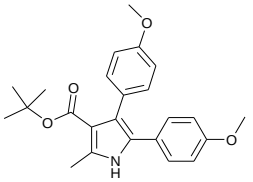
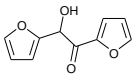
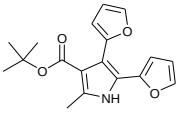
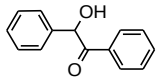
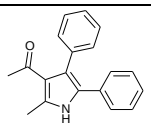
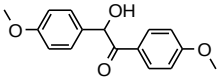
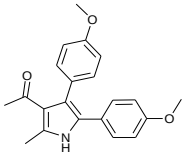
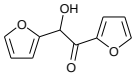
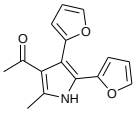
Entry	Molar ratio of **$S_5$1a**: **$S_5$2a**: **$S_5$3**	Reaction Temperature / Time	Yield of **$S_5$4a** (%)
1	1:1:1	80 ˚C/ 180 min	42
2	1:1:1.2	80 ˚C/ 180 min	48
3	1:1:1.2	90 ˚C/ 120 min	74
4	1:1:1.5	90 ˚C/ 120 min	83
5	**1.1:1:1.5**	**90 ˚C/ 120 min**	**93**
6	1.1:1:1.2	90 ˚C/ 120 min	80
7	1.1:1:1.5	100 ˚C/ 120 min	84

In order to explore the synthetic utility of the current protocol, series of reactions were carried out using various 1,3-dicarbonyls (**$S_5$1**), benzoin derivatives (**$S_5$2**) and ammonium acetate (**$S_5$3**) under optimized conditions. The reaction proceeded smoothly with various 1,3-dicarbonyls. However, the reaction with dibenzoylmethane (**$S_5$1e:** Table 6.3 entry **13, 14, 15**) failed to yield pyrrole products through condensation with benzoin derivatives even at elevated temperature. This may be attributed to the poor reactivity of carbonyl groups due to the presence of adjacent bulky phenyl groups. Also, increased reaction temperature (>130 ˚C) resulted in the decomposition of starting materials. Unlike the reaction with symmetrical 1,3-dicarbonyls, in case of unsymmetrical 1,3-dicarbonyl compounds, mixtures of regioisomeric products are possible. However, with all unsymmetrical 1,3-dicarbonyls (**$S_5$1a, $S_5$1b, $S_5$1d**) used, only one regioisomer has been obtained in high yield under present reaction conditions. This may be attributed to the difference in reactivity of carbonyl groups influenced by the nature of substitution on it. The resonance stabilized effect in the ester group (Table 6.3, entry **1-6**) and steric effect in the benzoyl group (Table 6.3 entry **10-12**) reduces the reactivity of carbonyl group and hence remained as side chain in the corresponding pyrroles. The structural evidence

was followed by ^{13}C NMR analysis of the pyrroles. The carbonyl signal of pyrroles **$S_5$4a- $S_5$4f** appeared ~165 ppm corresponding to ester carbonyl group and carbonyl signal of pyrroles **$S_5$4j- $S_5$4l** appeared ~ 194 ppm corresponding to benzoyl carbonyl group while carbonyl signal of pyrroles **$S_5$4g- $S_5$4i** appeared ~197 ppm corresponding to acetyl carbonyl group. In addition, from the SCXRD analysis of **$S_5$4c** (Fig. 6.7), it was clearly found that the ester group was unreacted and remained as side chain in pyrrole **$S_5$4c**. Thus, the difference in reactivity of carbonyl groups of 1,3-dicarbonyls leads to the formation of single regioisomer and hence the present protocol can be considered as regeoselective.

In order to evaluate the scope of the present protocol, the solvent- and catalyst- free reaction was extended to poor reactive anisoin and heteroaromatic 2,2′-furoin. Interestingly, the poor reactive anisoin underwent smooth reaction under present heating condition to obtain corresponding pyrrole derivatives in good yield (Table 6.3 entry **2, 8, 11**). As a main reason for this conversion, it is assumed that, the increased temperature (90 ˚C) and little excess of 1,3-dicarbonyls (1.1 equivalence), induced homogeneous reaction mixture and hence increases the productive collision between the reactant molecules and the elimination rate of water molecules during the reaction progress. This was supported by the initial experiments, when equimolar ratios of EAA and benzoin were reacted at 80 ˚C; the reaction mixture was observed as suspension and resulted in poor product yield (42%). The three-component reaction proceeded smoothly and good product yields were obtained with heteroaromatic 2,2′-furoin (Table 6.3 entry **3,6,9,12**).

Table 6.3: Three-component synthesis of tetrasubstituted pyrroles under solvent- and catalyst-free conditions

Entry	1,3-dicarbonyls	Benzoin derivatives	Product [a]		Yield (%)[b]
1			**$S_5$4a**		93[c]
2			**$S_5$4b**		89 [c]
3			**$S_5$4c**		84 [c]
4			**$S_5$4d**		85 [c]
5			**$S_5$4e**		Trace
6			**$S_5$4f**		92 [c]
7			**$S_5$4g**		90 [c]
8			**$S_5$4h**		86 [c]
9			**$S_5$4i**		83 [c]

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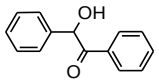
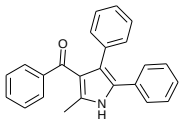
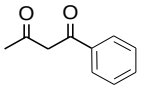
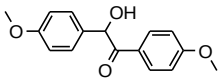
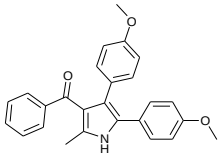
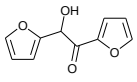
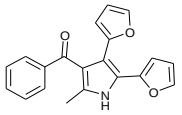
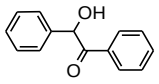
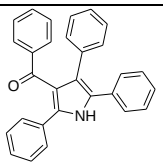
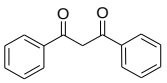
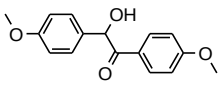
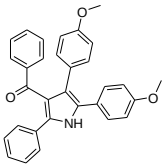
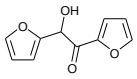
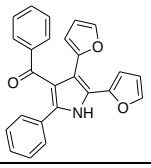
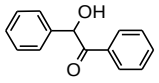
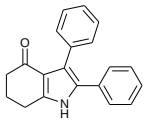
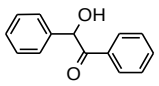
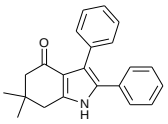
10			**$S_5$4j**		86 [c]
11			**$S_5$4k**		82 [c]
12			**$S_5$4l**		85 [c]
13			**$S_5$4m**		00
14			**$S_5$4n**		00
15			**$S_5$4o**		00
16			**$S_5$4p**		82 [d]
17			**$S_5$4q**		76 [d]

[a] Reaction conditions: 1,3-dicarbonyls (1.1 mmol), Benzoin derivatives (1 mmol), Ammonium acetate (1.5 mmol) at 90 ˚C, 120 min. [b] Yield of pure product. [c] Purified by recrystallization using 80:20 EtOH water mixture. [d] Purified by coulumn chromatography.

The structure of the products was confirmed by spectral data and elemental analysis. The ^{1}H NMR and ^{13}C NMR of known compounds are in agreement with the earlier reports. Further, to confirm the structure of tetrasubstituted pyrroles unambiguously, **$S_5$4c** was selected as a representative compound and characterized by SCXRD analysis as shown in Fig. 6.7.

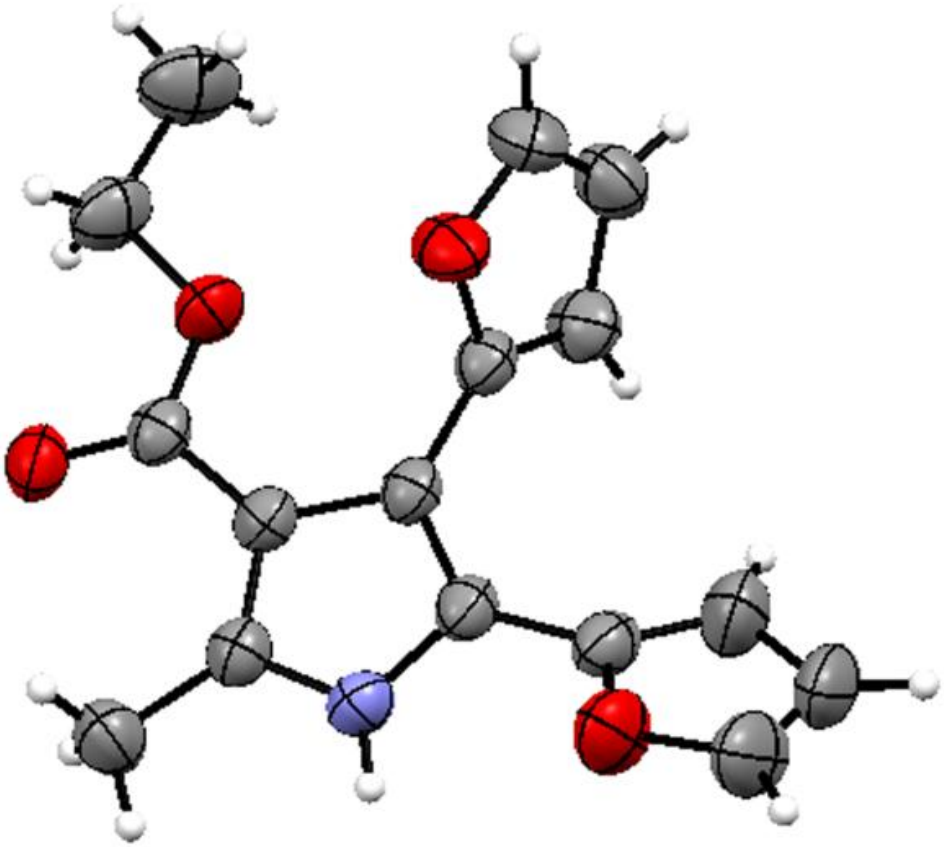
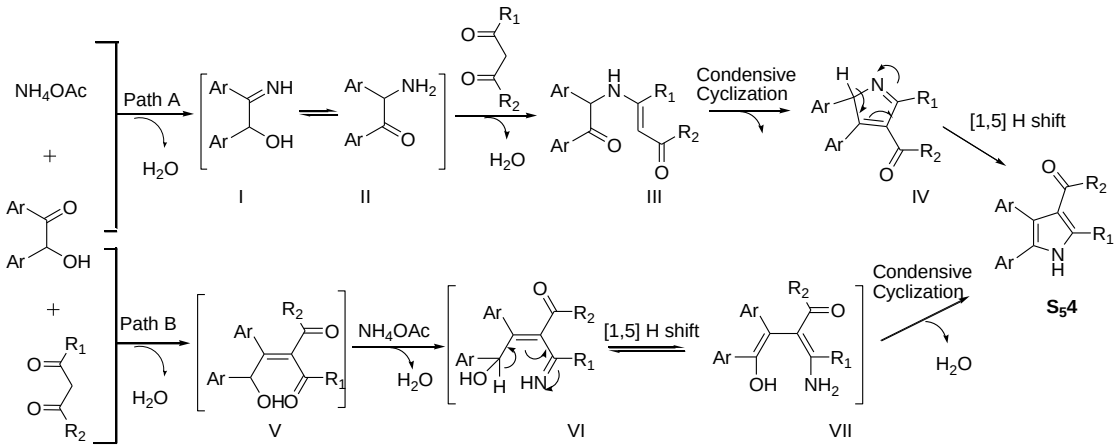


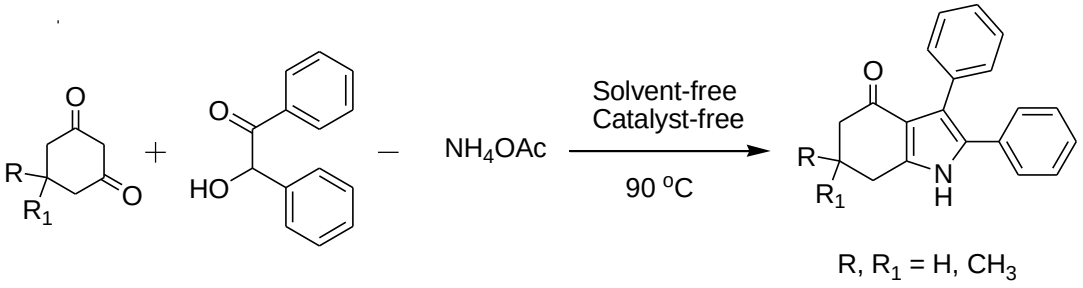
Fig. 6.7: ORTEP (50% probability) diagram of the crystal structure of **$S_5$4c**

On the basis of electronic effects and regioselectivity of the reaction, two plausible pathways for the present three-component protocol are illustrated in Scheme 6.2. The reaction of benzoin carbonyl group with ammonium acetate can form α-hydroxy imine **I**, which can undergo isomerisation under heating condition (Paquette and Hofferberth 2004) to form intermediate **II**. The reaction of amine group in intermediate **II** with more reactive carbonyl group of 1,3-dicarbonyls can form enaminone intermediate **III** under solvent and catalyst-free heating condition (Attanasi et al. 2011). The condensive cyclization of intermediate **III** followed by [1,5] proton shift, leads to the formation of pyrrole **$S_5$4** (Path **A,** Scheme 6.2). Alternatively, Condensation of 1,3-dicarbonyls with carbonyl group of benzoin can form intermediate **V** at present heating temperature. Further, condensation of ammonium acetate with more reactive carbonyl of intermediate **V** can form intermediate **VI**, which on rearrangement and simultaneous condensive cyclization yield the product **$S_5$4** (Path **B,** Scheme 6.2).



Scheme 6.2: Possible mechanistic pathways for the formation of tetrasubstituted pyrroles

The current solvent- and catalyst- free protocol was further extended to cyclic 1,3-diketones. When, dihydroresorcinol and dimedone were reacted with benzoin in the presence of ammonium acetate (Scheme 6.3), polyfunctionalized indoles were obtained in high yield after 120 min of heating at 90 ˚C (Table 6.3 entry **16** & **17**).

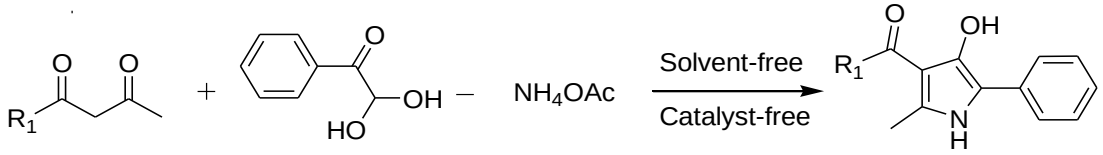


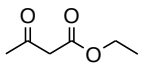
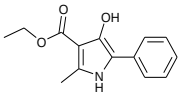
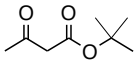
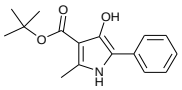
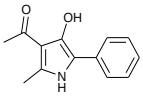
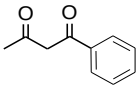
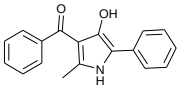
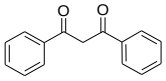
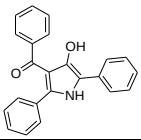
Scheme 6.3: One-pot three-component synthesis of polysubstituted indoles

In order to expand the scope of the solvent and catalyst-free, one pot protocol for the synthesis of tetrasubstituted pyrroles, 1,3-dicarbonyls were reacted with phenylglyoxal to yield corresponding products (Table 6.4). The pure pyrrole products were obtained in high yield after recrystallization with 70:30 EtOH water mixture. It was found that, the requirement of ammonium acetate to yield the pyrrole product reduced significantly compared to the earlier water mediated protocol (Khalili et al. 2008). This may be attributed to the improved molecular interaction between ammonium acetate and other water insoluble starting materials under solvent-free

conditions compared to aqueous media. Further, only one regioisomer was obtained with unsymmetrical 1,3-dicarbonyls.

Table 6.4: Three-component synthesis of tetrasubstituted pyrroles under solvent- and catalyst-free conditions



Entry	1,3-dicarbonyls	Product[a]	Yield (%)[b, c]
1		**$S_5$4r** 	92
2		**$S_5$4s** 	83
3		**$S_5$4t** 	91
4		**$S_5$4u** 	00
5		**$S_5$4v** 	00

a Reaction conditions: 1,3-dicarbonyls (1.1 mmol), Phenyl glyoxal (1 mmol), Ammonium acetate (1.5 mmol) at 50 ˚C, 120 min. bYield of pure product. cPurified by recrystallization using 70:30 EtOH water mixture.

6.4 CONCLUSION

In summary, an improved and greener one-pot protocol for the synthesis of tetrasubstituted pyrroles has been developed through a three-component reaction of 1,3-dicarbonyls, benzoin derivatives and ammonium acetate. Notably, this solvent- and catalyst-free approach leads to the formation of regioselective products from readily accessible starting materials and circumvents several limitations associated with earlier reported catalytic protocols. Further, the present environmental friendly protocol found application in the synthesis of polyfunctionalized indoles and substituted 4-hydroxy pyrroles with improved reaction efficiency and reduced waste.

CHAPTER 7

SUMMARY AND CONCLUSIONS

This Chapter describes the brief summary and conclusion of the present research work. Further the scope for future work is discussed.

7.1 SUMMARY

The concept of Green chemistry and its principles, spread worldwide with the aim to develop environmental consciousness in chemical synthesis. Even though, the organic transformations are well known under solvent/catalytic process, their improvement in terms of substrate modification, reaction efficiency, avoidance of toxic reagents, reduction of waste have significant values in modern organic synthesis influenced by the Green Chemistry principles.

Based on the literature review, it has been aimed to develop synthetic routes for the formation of carbon-carbon and carbon-heteroatom bond formation towards diverse organic molecules under solvent- and catalyst-free reaction conditions. The summary of the current research work are listed below.

- Five different transformations have been studied under solvent- and catalyst-free conditions towards biologically privileged structures.
- Aza-Michael addition of variety of amines to crotonic acid was carried out under solvent- and catalyst-free grinding conditions.
- Wide variety of amines and α,β-unsaturated acids were reacted to evaluate the scope and generality of the reaction.
- To explore the potential for industrial application, gram scale reaction of *p*-toluidine with crotonic acid has been carried out.
- The condensation of salicylaldehyde with malononitrile revisited under solvent- and catalyst-free mechanical activation, thermal activation and direct crystallization conditions.
- The mechanism of the reaction was explored by IR spectral measurements of the reaction mixture for every 3 min time interval.

- The reaction feasibility and functional group tolerance was evaluated with variously substituted salicylaldehydes under grinding condition.
- The solvent- and catalyst- free reaction of 2-aminobenzaldehydes with malononitrile was carried out under thermal activation.
- The reaction of 4-hydroxyquinolin-2(1*H*)-ones with aldehydes were carried out under solvent- and catalyst-free melt condition to synthesize 3-functionalized 4-hydroxyquinolin-2(1*H*)-ones.
- The reaction was carried out under solution conditions using various solvents to evaluate the efficiency of the solvent- and catalyst-free protocol.
- The three component cascade reaction was attempted by reacting 4-hydroxyquinolin-2(1*H*)-one and *p*-chlorobenzaldehyde with various active methylene compounds under thermal activation.
- The three component cascade reactions of 4-hydroxyquinolin-2(1*H*)-one, 3-aminocyclohex-2-enone and various aldehydes were carried out under neat heating conditions.
- Varieties of aldehydes were reacted to explore the functional group tolerance towards product formation under solvent- and catalyst-free conditions.
- A solvent- and catalyst-free three-component reaction of 2-aminoaryl ketones, trialkyl orthoesters and ammonium acetate was carried out in one-pot for the synthesis of 2,4-disubstituted quinolines.
- The optimization of the reaction was carried out by varying reactants ratio and ammonia source to get best results.
- Various 2-aminoaryl ketones and trialkyl orthoesters were reacted to evaluate the scope of the reaction.
- To explore the mechanism, the reaction was quenched after 1 h and intermediate was isolated and characterized for structural confirmation.

- One-pot, three-component reaction of 1,3-dicarbonyls, benzoin derivatives and ammonium acetate was carried out under solvent- and catalyst-free conditions.
- The reaction was optimized by varying the molar ratio of starting materials and temperature of the reaction.
- The feasibility of the three-component reaction with various 1,3-dicarbonyl compounds and benzoin derivatives was explored.
- All the Newly synthesised compounds have been adequately characterized for structural confirmation and selected compounds have been unambiguously confirmed by SCXRD analysis.

7.2 CONCLUSIONS

Based on the experimental results, following important conclusions have been drawn.

- Green synthesis of *β*-aminobutyric acids has been developed by aza-Michael addition of amines to crotonic acid under neat grinding/mixing of equimolar reactants.
- Both aliphatic and aromatic, primary as well as secondary amines can be used as Michael donors to yield corresponding *β*-aminobutyric acids.
- The aza Michael addition of amines to aromatic and sterically hindered *α,β*-unsaturated acids failed to produce corresponding Michael adducts under neat grinding.
- The solvent- and catalyst-free Knoevenagel condensation of benzaldehydes containing hydroxyl or amine group in ortho-position leads to the bicyclic heterocycles via six membered cyclization.
- The electron donating groups on aromatic ring of salicylaldehydes increase the reaction time with decreased product yield and vise versa.

- The melt reaction of 2-aminobenzaldehydes with malononitrile yield 2-amino-3-cyanoquinolines under neat conditions.

- The solvent- and catalyst-free reaction of 4-hydroxyquinolin-2(1*H*)-one with aldehydes undergoes cascade Knoevenagel/Michael reaction to form corresponding MDBHQ derivatives.

- The solvent assisted catalyst-free reaction results either in decreased or no product formation.

- The one-pot reaction of 4-hydroxyquinolin-2(1*H*)-one and aldehydes with 3-aminocyclohex-2-enone undergoes three component cascade to form corresponding 3-((2-amino-6-oxocyclohex-1-enyl)methyl)-4-hydroxy-1-methylquinolin-2(1*H*)-one derivatives.

- The reaction is feasible with variety of functionalized aldehydes.

- An efficient and green protocol for the synthesis of 2,4-substituted quinazolines has been developed under solvent- and catalyst-free reaction condition.

- The building blocks 2-aminoarylketones, trialkylorthoesters and ammonium acetate in the ratio 1:1.5:1.5 at 110 ˚C is the optimized reaction condition to obtain the quinazolines in high yield.

- The three component reaction for the construction of quinazolines follows intermediate imidate formation.

- The solvent- and catalyst-free one-pot reaction of 1,3-dicarbonyls, benzoin derivative and ammonium acetate leads to the regioselective formation of polyfunctionalised pyrroles in high yield.

- The molar ratio 1.1:1:1.5 of starting materials at 90 ˚C is found to be the best possible reaction condition to obtain the polyfunctionalised pyrroles.

- This protocol circumvents several limitations associated with earlier reported protocols such as tedious catalyst preparation, substate limitation, requirement of too excessive reagents etc.

- The carbon-carbon and carbon-heteroatom bond formations via condensation reactions, addition to electron deficient substrates, cyclization reactions involving condensation and intramolecular reactions can be easily achievable under solvent- and catalyst-free reaction conditions.

7.3 SCOPE FOR FUTURE WORK

The avoidance of auxiliary substances is one of the major objectives of Green chemistry and development of solvent- and catalyst-free protocols is of great importance to accomplish this objective. The developed green protocols in the current research work have several advantages over conventional protocols. It is conceivable that the present study offers a facile and expedient way to synthesize privileged organic compounds that can be used in various field of chemistry. Further, in order to avoid auxiliary substances, it is believed that, the future synthetic chemistry research on synthesis new chemical entities and method development of known chemicals begins with solvent- and catalyst-free conditions.

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LIST OF PUBLICATIONS

Papers communicated/ accepted in international journals.

1. Bhat, S.I. and Trivedi, D.R. "A Facile, Solvent and Catalyst-Free Synthesis of N-Substituted β-Aminobutyric Acids By Aza-Michael Addition." *Environ. Chem. Lett.,* 11, 91-97.
2. Bhat, S.I., Choudhury, A.R. and Trivedi, D.R. (2012). "Condensation of malononitrile with salicylaldehydes and *o*-aminobenzaldehydes revisited: Solvent- and catalyst-free synthesis of 4*H*-chromenes and quinolines." *RSC Advances,* 2, 10556-10563.
3. Bhat, S.I., Das, U.K. and Trivedi, D.R. "An efficient three component, one-pot synthesis of quinazolines under solvent-free and catalyst-free condition."
   - Manuscript under review.
4. Bhat, S.I. and Trivedi, D.R. (2013) "A catalyst- and solvent-free three-component reaction for the regioselective one-pot access to polyfunctionalized pyrroles." *Tetrahedron Lett.,* 54, 5577-5582.
5. Bhat, S.I and Trivedi, D.R. "A highly efficient and green cascade synthesis of 3-methyl-substituted-4-hydroxy-1-methyl-quinolin-2(1*H*)-ones under solvent- and catalyst-free conditions."
   -Manuscript under revision.

Paper presented in national and international conferences

Bhat, S.I. and Trivedi, D.R. (2011). "Microwave Assisted Knoevenagel Condensation Under Solvent- and Catalyst-Free Conditions." Paper presented in "International Conference on Futuristic Science and Technology in Frontier Areas & 2nd Annual Conference of Indian JSPS Alumni Association." August 05-06, (Organised by JSPS Alumni Association & SCTIMST), Tiruvantapuram.

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Education

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06/2003-12/2005	**B. Sc.** (Physics Chemistry, Mathematics: 73.4%) Dr. A. V. Baliga College of A & Sc. Kumta (Affiliated to Karnataka University, Dharwad, Karnataka, India)

Research Experience

01/2010-present	**Research Scholar** Department of Chemistry National Institute of Technology Karnataka, India Research Area: Green Synthesis of Biologically Important Organic Molecules
06/2007-01/2010	**Scientist** Syngene International Ltd. (Synthetic Chemistry department) Biocon, India. (http://www.syngeneintl.com) Research Area: Synthesis, Purification and Characterization of New Chemical Entities.

Skills

- **Synthetic Skills**
  - Good knowledge of handling and work-up procedures of *poisonous reagents* like cyanide (up to 200 G)
  - Handled *Hazardous/flammable reagents* like Borane dimethyl sulphide, DIBAL-H, BBr_3, BuLi, sodium triacetoxy borohydride etc.
  - Hydrogenation using Pd/C, Adams catalyst
  - Performed various reactions like Suzuki, Grignard, Vilsmeier-Haack, Mitsunobu, Knoevenagel, Michael etc.
  - Developed solvent free methods in one-pot multicomponent synthesis of some biologically important heterocycles

- **Purification Techniques handled**
  - Column chromatography (from 5 mg – 300 G scale)
  - Biotage (Parallel column purifier and Isolera)
  - Single and multichannel combiflash

- **Analytical Techniques handled**
  - Single crystal X-ray diffractometer (Bruker Apex duo)
  - IR (Thermo scientific, Nicolet AVATAR)
  - UV-VIS spectrometer (Analytikjena Specord)
  - Spectrofluorometer (JASCO)

- **Other Sophisticated Instruments handled**
  - Biotage microwave reactor
  - Buchi Rotavapor (Container size 8 ml to 20 L)
  - Gene Vac Multivapor (EZ- 2 AND HT- 4X)
  - Radley's Parallel synthesizer (heating and cooling unit)
  - Mettler Toledo auto vial weighing system
  - Retsch vibratory shaker
- **Computer knowledge**
  - MS OFFICE
  - MestReNova (NMR processing software)
  - APEX2; Mercury (SCXRD softwares)
  - Chemistry software packages like Chemdraw, ISIS draw, Chemsketch

Research Publications

Papers published/ communicated in international journals.

1. Bhat, S.I. and Trivedi, D.R. (2013). "A Facile, Solvent and Catalyst-Free Synthesis of N-Substituted β-Aminobutyric Acids By Aza-Michael Addition." *Environ. Chem. Lett.* 11, 91-97.
2. Bhat, S.I., Choudhury, A.R. and Trivedi, D.R. (2012). "Condensation of malononitrile with salicylaldehydes and *o*-aminobenzaldehydes revisited: Solvent and catalyst free synthesis of 4*H*-chromenes and quinolines." *RSC Advances,* 2, 10556-10563.
3. Bhat, S.I., Das, U.K. and Trivedi, D.R. "An efficient three component, one-pot synthesis of quinazolines under solvent-free and catalyst-free condition."
   - Manuscript under review (J. Heterocycl. Chem.).
4. Bhat, S.I. and Trivedi, D.R. (2013) "A catalyst- and solvent-free three-component reaction for the regioselective one-pot access to polyfunctionalized pyrroles." *Tetrahedron Lett.,* 54, 5577-5582.
5. Bhat, S.I. and Trivedi, D.R."A highly efficient and green cascade synthesis of 3-methyl-substituted-4-hydroxy-1-methyl-quinolin-2(1*H*)-ones under solvent- and catalyst-free conditions."
   - Manuscript under revision (RSC Advances).

Paper presented in international conference

1. Bhat, S.I. and Trivedi, D.R. (2011). "Microwave Assisted Knoevenagel Condensation Under Solvent and Catalyst Free Conditions." Paper presented in "International Conference on Futuristic Science and Technology in Frontier Areas." August 05-06, (Organised by JSPS Alumni Association & SCTIMST), Tiruvantapuram.

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