Development of New Synthetic Methodologies Leading to β-Amino Carbonyl Compounds: Some Aspects of Multicomponent Reactions

A Thesis Submitted

in Partial Fulfillment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

By

Tasneem Parvin

Roll No 06612213

to the

Department of Chemistry

Indian Institute of Technology Guwahati

Guwahati-781 039

March 13, 2009

Dedicated to my

Parents & husband

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI
DEPARTMENT OF CHEMISTRY
INDIA

CERTIFICATE-I

This is to certify that Tasneem Parvin has satisfactorily completed all the courses required for the Ph. D degree programme.

These courses include:

CH 621	New Reagents for Organic Synthesis
NT 701	Quantum Mechanics and Spectroscopy
CH 611	Bioinorganic Chemistry
CH 630	Art in Organic Syntheses

Tasneem Parvin successfully completed her Ph. D. qualifying examination on August 02, 2007.

Professor Abu T. Khan
Head
Department of Chemistry
IIT Guwahati
Guwahati-781 039

Dr. T. Punniyamurthy
Secretary, DPPC
Department of Chemistry
IIT Guwahati
Guwahati-781 039

Indian Institute of Technology Guwahati
Guwahati-781 039, India

Tel. No.: 0091-361-26902305
Fax No.: 0091-361-2582349
E. mail: atk@iitg.ernet.in

Dr. Abu T. Khan
Professor & Head, Department of Chemistry

CERTIFICATE – II

Date: 13th March, 2009

This is to certify that Mrs.Tasneem Parvin has been working in my research group since July 28, 2006 as a regular registered Ph. D. student. I am forwarding her thesis entitled "Development of new synthetic methodologies leading to β-amino carbonyl compounds: Some aspects of multicomponent reactions" being submitted for the Ph. D. (Science) Degree of this Institute. I certify that she has fulfilled all the requirements according to the rules of this Institute regarding the investigations embodied in her thesis and this work has not been submitted elsewhere for a degree.

(Dr. A. T. Khan)

STATEMENT

I do hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, India under the supervision of Professor Abu T. Khan.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators.

Guwahati

13th March 2009 Tasneem Parvin

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Ph.D. GRADE CARD

ROLL NO: 06612213 **DEPT:** Chemistry

NAME: Tasneem Parvin

Semester I (July –November) 2006

Course	Course Name	Credit	Grade
CH 621	New Reagents for Organic Synthesis	6	AA
NT 701	Quantum Mechanics and Spectroscopy	6	AB

Semester Performance Index (S.P.I.) : 9.50
Cumulative Performance Index (C.P.I.): 9.50

Semester II (January–May) 2007

Course	Course Name	Credit	Grade
CH 611	Bioinorganic Chemistry	6	AB
CH 625	Art in Organic Syntheses	8	AA

Semester Performance Index (S.P.I.) : 9.57
Cumulative Performance Index (C.P.I.) : 9.54

Date: 13th March 2009

Deputy Registrar
(Academic)

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Tasneem Parvin

SUMMARY

This dissertation describes the successful efforts on the development of some new methodologies by multicomponent reactions for the synthesis of various β-amino carbonyl compounds using Lewis acid and bromodimethylsulfonium bromide as catalyst.

The thesis contains mainly four chapters namely Chapter I, II, III and IV. Among them, the Chapter II and III are divided into two parts namely Section A and Section B.

Chapter I describes the general introduction on multicomponent reaction and β-amino carbonyls. A brief literature survey on the recent advances in multicomponent reactions and importance of β-amino carbonyl compounds are highlighted in this chapter precisely.

In **Chapter II**, we have described two new methodologies using very cheap and readily available Lewis acid catalysts for the four component one-pot synthesis of β-acetamido carbonyl compounds. **Section A** demonstrates a simple, efficient and greener protocol for the preparation of β-acetamido carbonyl compounds using $CeCl_3 \cdot 7H_2O$ as a catalyst. The salient features of this protocol include operational simplicity, high yields of the products, avoidance of column chromatography, ready availability, low toxicity, moisture compatibility and reusability of the catalyst. **Section B** describes another new synthetic methodology using $FeCl_3 \cdot 6H_2O$, a cheap, readily available, and efficient catalyst for the one-pot synthesis of β-acetamido carbonyl compounds. The simplicity of the present protocol, high yields, and efficiency of the catalyst are the key features of this methodology. Due to the low cost and ready availability of the reagent $FeCl_3 \cdot 6H_2O$, we prefer this protocol than our earlier reported method. Mechanistic investigations as well as variability of all the components in this transformation are addressed in this section. Both enolizable ketones and β-keto esters are suitable for the preparation of corresponding β-acetamido carbonyl compounds under mild reaction conditions by these developed methods.

Chapter III contains two new methodologies namely Aza-Michael and Mannich-type reaction using a versatile reagent bromodimethylsulfonium bromide as catalyst. A wide range of β-amino carbonyl compounds were synthesized by our developed methods.

Section A demonstrates a simple and efficient methodology for the conjugate addition of amines to electron deficient alkenes using bromodimethylsulfonium bromide as an inexpensive and efficient catalyst. This method is highly effective for the 1,4-addition of primary and secondary aliphatic amines to electron deficient alkenes. However, in case of aromatic amines the present protocol is not suitable. The significant features of this method are: simplicity of the procedure, no need of column purification process to get the pure product, high yields and very short reaction time. Thus the present method demonstrates the potential of BDMS as an efficient promoter in organic synthesis.

Section B describes the catalytic activity of BDMS for three component direct Mannich-type reaction for the synthesis of β-amino carbonyl compounds by the reaction of aromatic aldehydes, aromatic amines and enolizable ketones or diethyl malonates in presence of BDMS as a catalyst. Simplicity of the procedure, avoidance of column chromatography as well as high yields and good diastereo selectivities are the salient features of this protocol.

In **Chapter IV** of this thesis, a very interesting multicomponent reaction is presented from the combination of aldehyde, amine and 1,3-dicarbonyl comounds leading to different products depending upon the effect of substituent in β-position of 1,3-dicarbonyl compounds. This protocol demonstrate an efficient path for the facile access of highly functionalized piperidines. This strategy is interesting as both the α and γ positions of β-keto esters are involved in C-C bond formation under the mild conditions. The resultant heterocyclic systems have both secondary amine and enamino esters, which enable further modifications leading to molecular diversity.

In conclusion, the thesis describes some new and effective synthetic methodologies for the synthesis of variety of β-amino carbonyl compounds. Due to the advantages of these methodologies, it is expected that these methodologies will be applicable in target-oriented synthesis as well as valuable additions in the arsenal of synthetic organic chemistry literature.

CONTENTS

GENERAL REMARKS

The present investigations were carried out in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati -781 039, Assam, from July 28, 2006 to March 13, 2009 as a research scholar under the supervision of Prof. Abu T. Khan.

The analytical samples were routinely dried *in vacuo* at 50 ^{o}C for 8 hours. Column chromatography was carried out with silica gel (60-120 mesh, Merck, SRL or Qualigen), for purifications of reaction mixture. After purification, the solvent was usually removed in rotavapor using Buchi R-114V instrument. In TLC experiments, silica gel G (SRL) or silica gel GF 254 (SRL) were employed as adsorbent and spots were detected by staining with iodine vapour or under UV light. ^{1}H-Nuclear Magnetic Resonance spectra and ^{13}C-Nuclear Magnetic Resonance spectra were recorded on Varian (400 MHz) instruments using tetramethylsilane (TMS) as an internal standard and $CDCl_3$ as solvent. The chemical shift values were expressed in ppm and their multiplications were described using the following symbols: s-singlet, d-doublet, t-triplet, q-quartet, quin-quintet, m-multiplet, brs-broad singlet.

The infrared spectra were recorded in KBr pellets or in liquid film on a Perkin Elmer 1330. Melting points were determined at Buechi B-545 instrument and were uncorrected. Elemetal analysis has been done by Perkin Elmer CHNS/O-2400 instrument. All the solvents and reagents employed were purified using recommended procedures in literature.

X-ray diffraction data were collected with a Bruker Apex II smart diffractometer with CCD area detectors using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å).

Abbreviations

Ac_2O	Acetic anhydride
BDMS	Bromodimethylsulfonium bromide
Bu	Butyl
Bn	Benzyl
CAN	Cericammonium nitrate
DIBALH	Diisobutylaluminium hydride
DCM	Dichloromethane
DHP	3,4-Dihydro-*2H*-pyran
DMSO	Dimethyl sulfoxide
DMF	N, N-dimethylformamide
EtOAc	Ethyl acetate
DMAP	4-(Dimethylamino) pyridine
IR	Infrared
NBS	N-bromosuccinimide
NMR	Nuclear magnetic resonance
MW	Microwave
Mp	Melting point
MS	Molecular sieves
py	Pyridine
rt	Room temperature
TBS	*tert*-butyldimethylsilyl
TMSCl	Trimethylchlorosilane
PTSA	*p*-Toluenesulfonic acid
THP	Tetrahydropyranyl
Ts	*p*-Toluenesulfonyl
TMS	Trimethylsilyl
MCR	Multicomponent reaction
Ph	Phenyl
ppm	Parts per million
TLC	Thin layer chromatography

CHAPTER I

General Introduction

1. Introduction:

The development of new synthetic methodologies is one of the most important areas of research in modern organic chemistry because of the increasing demand for selective, efficient and environmentally friendly chemical processes in academics as well as in industry. The efficacy of a target synthesis directly depends on the effectiveness of all the involved methodologies. In traditional organic synthesis individual bonds are usually formed in a stepwise manner. This often involves isolation and purification of intermediates and alteration of reaction conditions for the next synthetic step. However, in case of 'ideal synthesis', a target molecule can be accomplished from readily available starting materials in a simple, safe, environmentally friendly and resource-efficient operation that proceeds quickly and in quantitative yield (Figure 1).[1] In the past decade, many research groups have aimed for the realization of this concept of ideal synthesis by the development of multi-step, single operation processes for the construction of complex molecules in which several bonds are formed in a chain of events and without the necessity of isolating the intermediates. A particular reactions that meet these criteria, commonly known as tandem reactions,[2] allow the economically and environmentally favorable synthesis of a wide range of organic molecules. A special class of tandem sequential reactions constitutes the multicomponent reactions (MCRs).

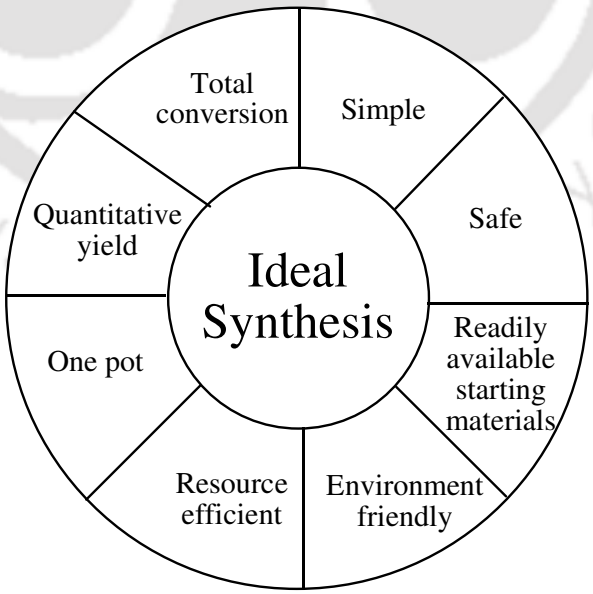


Figure 1. General aspects of the Ideal Synthesis

Green chemistry is one of the most important concerns in the mind of chemist.[3] The various reaction types most commonly used in synthesis can have different degrees of impact on human health and environment. For example, addition reactions completely incorporate the starting materials into the final products, and therefore do not produce any byproduct that needs to be treated, disposed of or otherwise dealt with. On the other hand, substitution reaction invariably generates stoichiometric amount of byproducts and waste. Similarly, elimination reactions do not require input of materials but they generate stoichiometric amount of substances that are not part of the final target molecule. As a result elimination reactions are the least atom economical transformations. For any synthetic transformations, it is important to evaluate the hazardous properties of all starting materials and reagents that are added in a synthetic transformation as well as all substances necessarily being generated from the transformations.

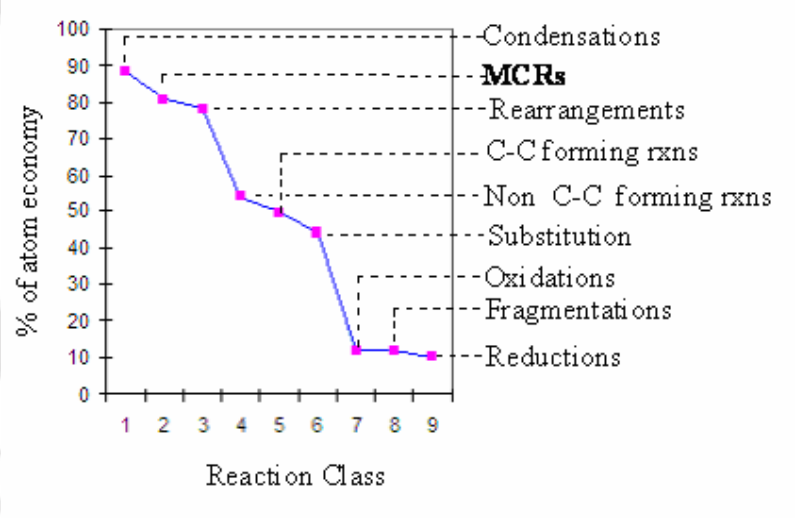


Figure 2.

The atom-economy of various types of reactions can be graphically represented by Figure 2. Among them, the most atom-economy suited reactions are condensation reaction, multicomponent reactions and rearrangements. As I have chosen my research topics on the synthesis of β-aminocarbonyl compounds mainly by multicomponent approach, I would like to highlight the important aspects of it.

1.1 Multicomponent reactions

A multicomponent reaction (MCR) is a process in which three or more easily accessible components are combined together in a single reaction vessel to produce a

final product displaying features of all inputs and thus offers greater possibilities for molecular diversity per step with a minimum of synthetic time and effort. Thus MCR is a domino process, a sequence of elementary steps according to a program in which subsequent transformations are determined by the functionalities produced in the previous step. Therefore, one can call MCRs as convergent reactions, in analogy to a convergent synthesis.

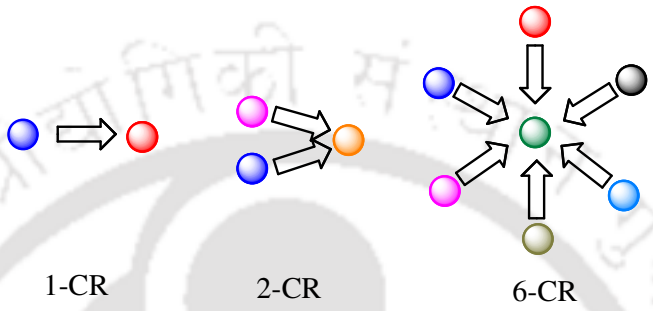


Figure 3

The increasing demand for rapid syntheses of functional and biologically active molecules has encouraged synthetic chemists to explore and develop intelligent strategies that inevitably address the very fundamental principles of efficiency and efficacy. Besides the crucial issues of chemo-, regio- and stereoselectivity in a synthetic method, the importance of economical and ecological aspects of 'Green Chemistry' is also very important. In this regard MCRs are more environmentally benign and atom economic as they avoid time consuming and costly purification processes, as well as protection-deprotection steps. In addition, they are easier to carry out as compared to multistep synthesis since they are conventionally one-pot reactions (Figure 4).

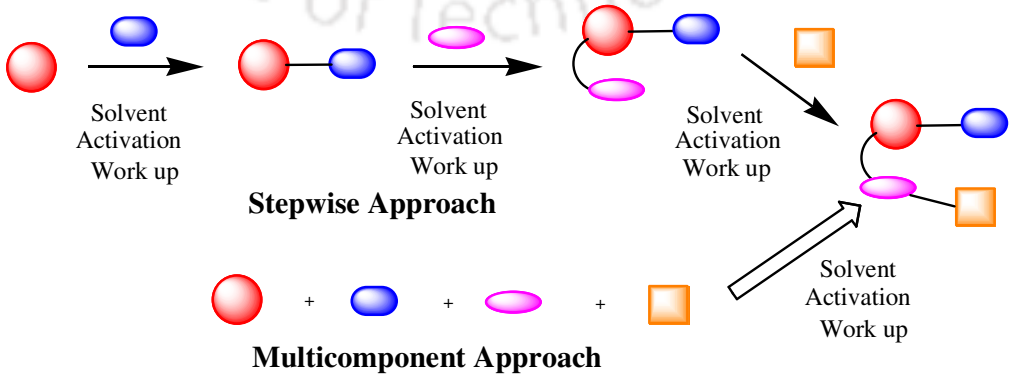
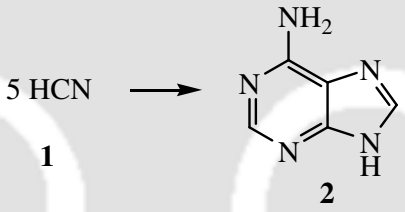


Figure 4. Stepwise vs. Multicomponent Approach

The story of multicomponent reaction began as far back as 1850 by the publication of the Strecker reaction,[4] arriving nowadays at its apogee. Multicomponent reaction has emerged as a powerful synthetic tool only after the discovery of Ugi reaction[5] even though the history of MCRs was started in the second half of 19th century with the reactions of Strecker,[4] Hantzsch[6] and Biginelli.[7] In recent time, it has become a promising tool for the efficient synthesis of natural products and screening compounds for the discovery of biological probes and drugs.[8a]

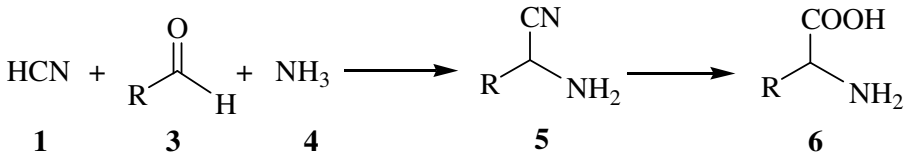
1.1.1 Brief History of Multicomponent Chemistry

The concept of MCRs is not unknown in nature, it is important especially in evolution. It seems that adenine (**2**), one of the major constituents of DNA and RNA, was prebiotically formed by the condensation of five molecules of HCN in a reaction catalyzed by NH_3 (Scheme 1).[8b] The other nucleic bases have been generated in similar reactions involving HCN and H_2O.



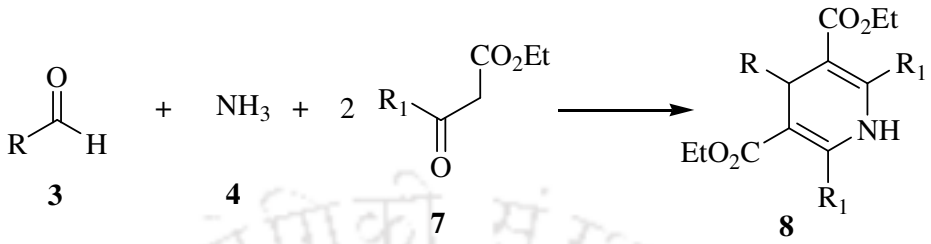
Scheme 1 Prebiotic synthesis of adenine

The first modern contribution to the development of multicomponent chemistry was made by Strecker[4] in 1850. The crucial step in the well-known Strecker synthesis of α-amino acids is the formation of α-amino nitriles from aldehydes, HCN and NH_3 in one-pot. Subsequent hydrolysis of these synthetically valuable intermediates **5** results the amino acid **6**.



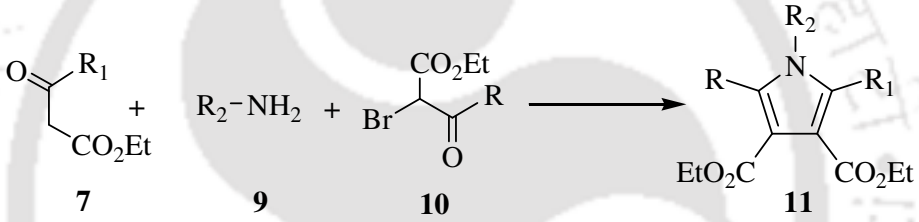
Scheme 2 Strecker synthesis of α-amino acids

Further progress of multicomponent chemistry can be attributed to the work of Hantzsch in 1882. He synthesized symmetrically substituted dihydropyridines **8** from NH_3, aldehydes and two equivalents of β-ketoesters (Scheme 3).[5]



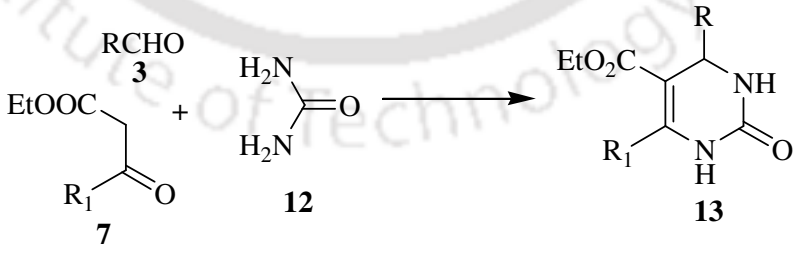
Scheme 3 Hantzsch synthesis of dihydropyridines

Another contribution made by Hantzsch to MCRs was the synthesis of pyrroles by reacting primary amines, β-ketoesters and α-halogenated β-ketoesters.[9]



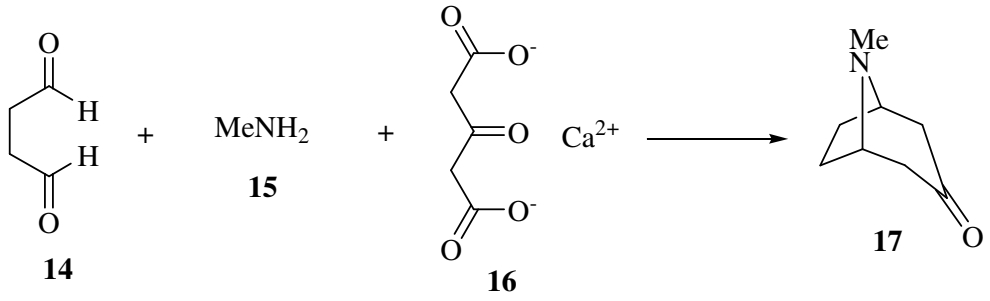
Scheme 4 Hantzsch synthesis of pyrroles

The Biginelli reaction first described in 1893 represents multicomponent synthesis of substituted dihydropyrimidines by acid-catalyzed cyclocondensation of β-ketoesters, aromatic aldehydes and urea.[6]



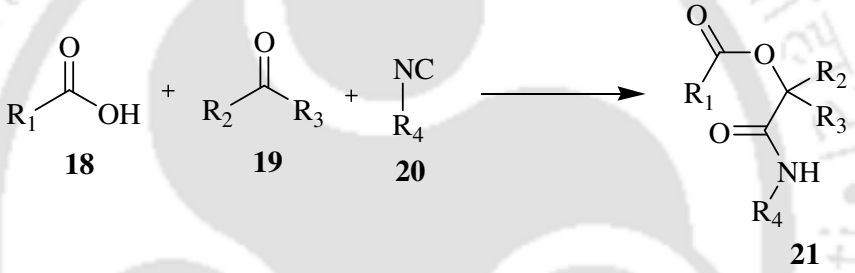
Scheme 5 Biginelli synthesis of dihydropyrimidines

The first important application of MCRs in natural product synthesis was the Robinson synthesis of the alkaloid tropinone (**17**) from succinic dialdehyde, methylamine and calcium salt of acetonedicarboxylic acid, carried out in 1917.[10]



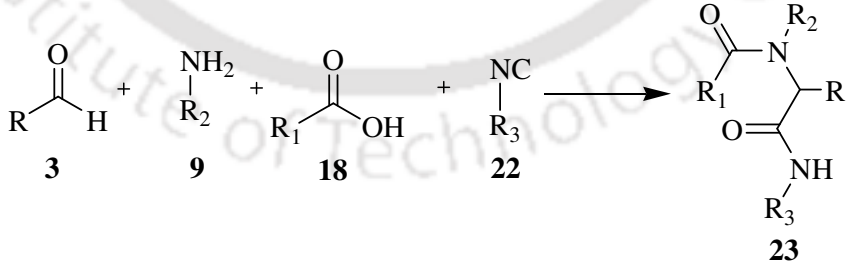
Scheme 6 Robinson synthesis of tropinone

Subsequently, in 1921 Passerini developed the first isocyanide based MCR involving carboxylic acids, carbonyl compounds and isocyanides to afford the corresponding α-acyloxy carboxamides.[11]



Scheme 7 Passerini 3-component reaction

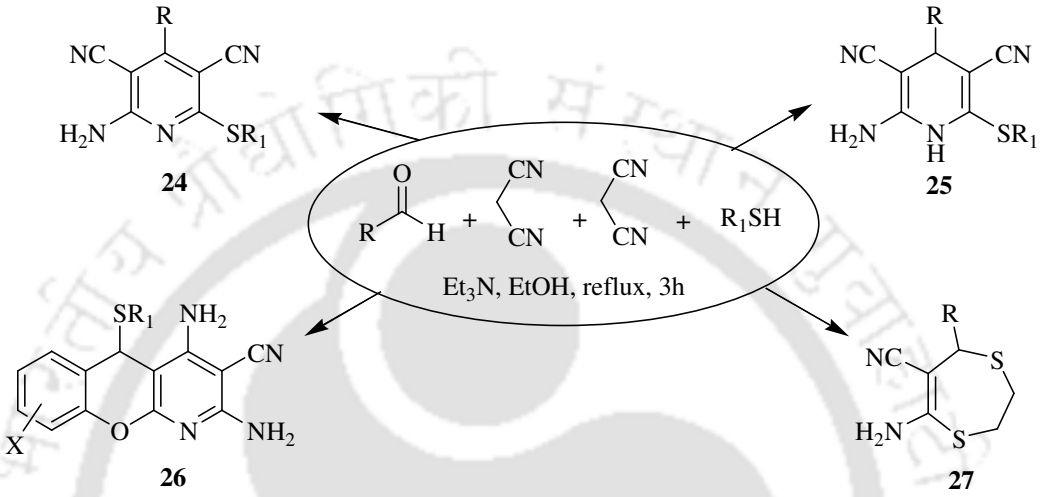
One of the most utilized multicomponent reactions was discovered[12] in 1959 by Ugi et al. for the synthesis of α-acylamino amides **23** by reacting aldehydes, primary amines, carboxylic acids and isocyanides as shown in scheme 8.



Scheme 8 Ugi-four component reaction

After Ugi's discovery a plethora of isocyanide based MCRs have been reported in the literature.[13] At the same time a wide range of new miscellaneous multicomponent reactions are also found in the literature. Some of the recently reported interesting MCRs are discussed below.

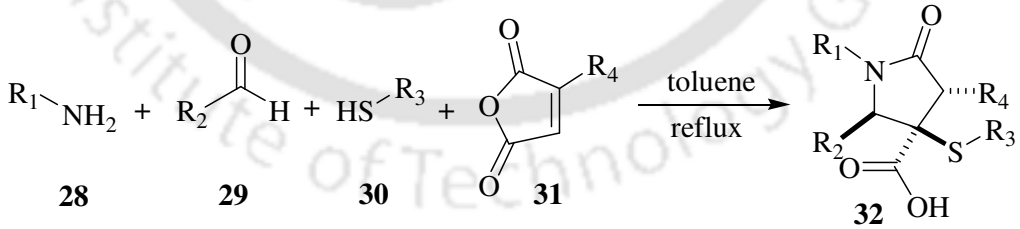
Magedov et al have demonstrated a new multicomponent reaction for the generation of medicinal scaffolds involving pyridine, 1,4-dihydropyridine, chromeno[2,3-*b*]-pyridine, and dihydro-1,4-dithiepine frameworks via a single-step multicomponent reaction of structurally diverse aldehydes with various thiols and malononitrile as shown in Scheme 9.[14]



24 **25** **26** **27**

Scheme 9

Shaw et al reported a one-pot methodology for the diastereoselective synthesis of γ-lactams from the reaction of amines, maleic anhydrides, aldehydes, and thiols, as shown in Scheme 10. Interestingly this reaction creates new three stereogenic center in a single step.[15]

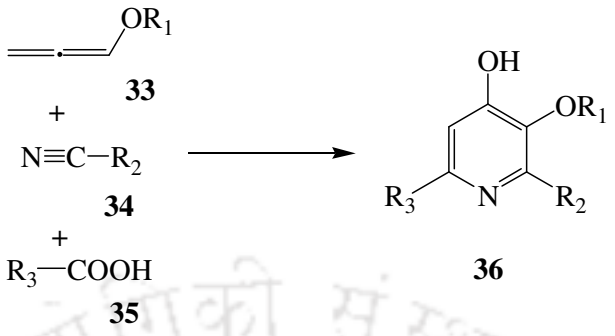


28 **29** **30** **31** **32**

Scheme 10

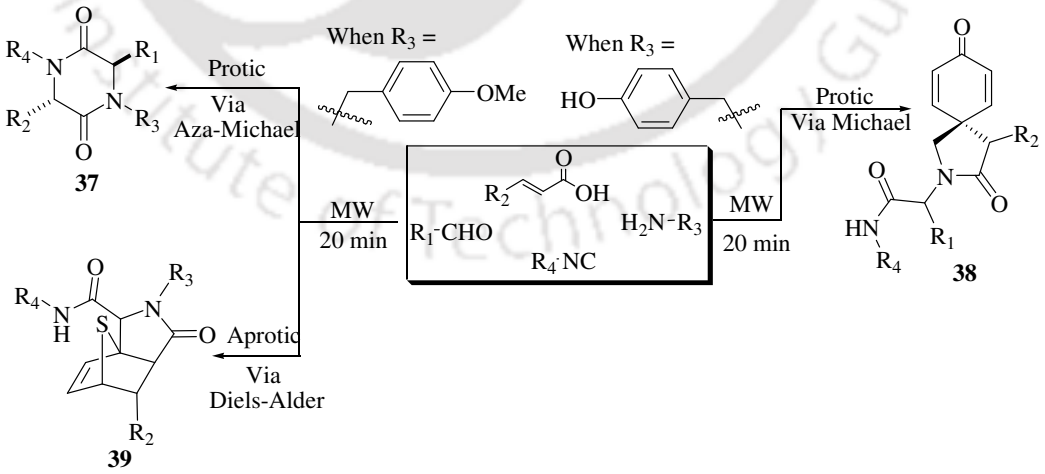
Reissig et al demonstrated[16] a novel three-component reaction for the synthesis of highly functionalized pyridines **36** as shown in Scheme 11. This strategy is not restricted to methoxyallene and trifluoroacetic acid as precursors. However, a variety of carboxylic acids or other alkoxyallene derivatives can be employed in this

methodology. In addition, the use of dinitriles established an extremely simple route to highly conjugated dipyridyl systems.



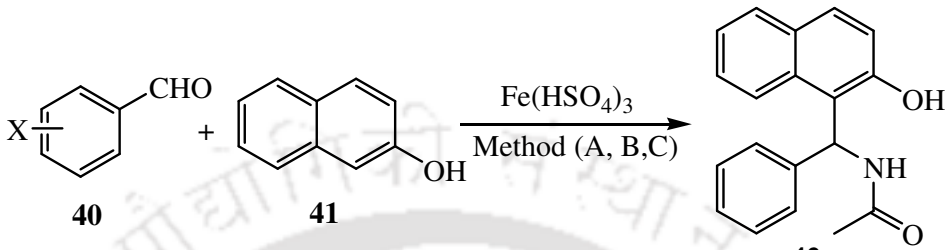
Scheme 11

Andreana et al have revealed a one-pot, additive-free method for constructing molecular diversity from a multicomponent coupling reaction based on solvent effects and microwave irradiation.[17] Bifunctional substrates provide diverse small molecules from the Ugi reaction with complete control of pathway selectivity (Scheme 12). Using water as the solvent gives rise to 2,5-diketopiperazines (**37**) from an aza-Michael reaction and 2-azaspiro[4.5]deca-6,9-diene-3,8-diones (**38**) from a 5-*exo* Michael cyclization. An intramolecular thiophene Diels-Alder reaction was observed to afford **39** in the presence of methylene chloride and microwave irradiation, arguing against hydrophobic effects for rate acceleration in this intramolecular [4π + 2π] transformation.



Scheme 12

Shaterian et al have described an efficient and direct protocol for the preparation of amidoalkyl naphthols (**42**) employing a multi-component, one-pot condensation reaction of β-naphthol, aromatic aldehydes and acetamide in the presence of ferric hydrogensulfate under solvent-free and microwave conditions.[18]

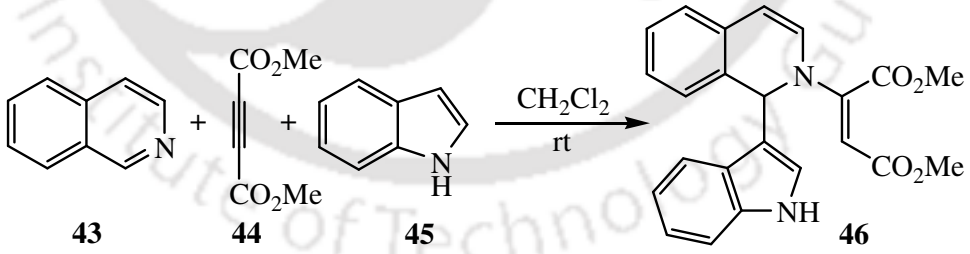


40 **41** **42**

Method A: CH_3CN (Ritter type reaction)
Method B: CH_3CONH_2 (Thermal solvent free conditions)
Method C: CH_3CONH_2 (Microwave solvent free conditions)

Scheme 13

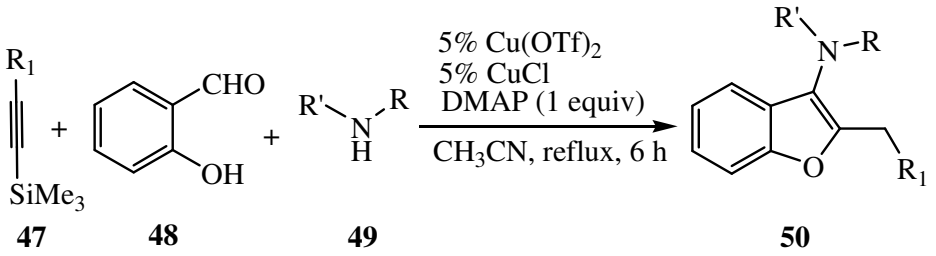
Recently, Yadav et al have demonstrated a novel three-component coupling of isoquinolines, dimethyl acetylenedicarboxylate (DMAD) and indoles to produce dimethyl (E)-2-[1-(1H-3-indolyl)-1,2-dihydro-2-isoquinolinyl]-2-butenedioates (**46**) in excellent yields with high selectivity (Scheme 14).[19] This method is useful and attractive process for the synthesis of indolyl quinoline and isoquinolines in a single step operation.



43 **44** **45** **46**

Scheme 14

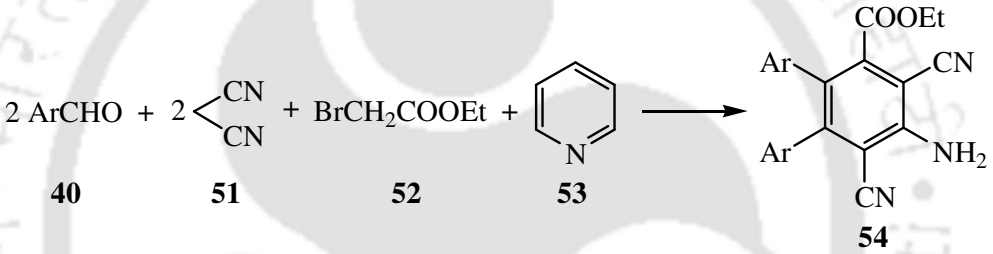
Sakai et al have reported a three-component coupling reaction involving alkynylsilane, *o*-hydroxybenzaldehyde derivative and a secondary amine catalyzed by the combination of 5-mol % $Cu(OTf)_2$ and CuCl in the presence of DMAP.[20] A wide range of poly functionalized benzofurans can be easily accessed by this methodology (Scheme 15).



47 **48** **49** **50**

Scheme 15

Polysubstituted benzene derivatives (**54**) with an unprecedented substitution pattern can be achieved from the novel one-pot multi-component cyclization reaction from pyridine, ethyl α-bromoacetate, malononitrile and aromatic aldehyde in refluxing acetonitrile (Scheme 16).[21]



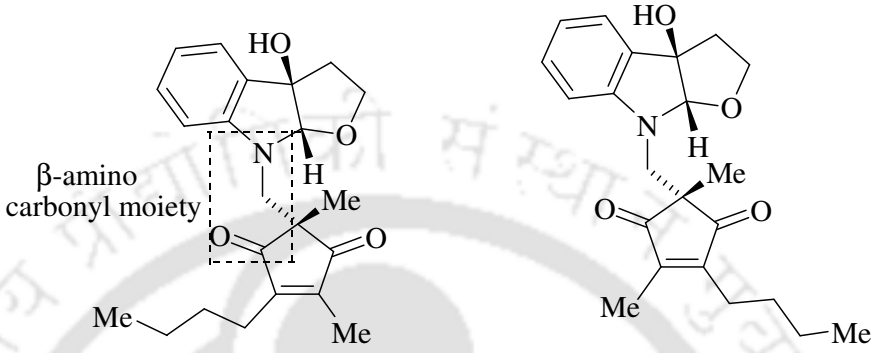
40 **51** **52** **53** **54**

Scheme 16

From this survey it is apparent that development of novel multicomponent reactions is a challenging area in synthetic chemistry to articulate as well as to implement. MCRs are of particular interest for three reasons: efficiency, diversity and their large unexplored chemical space. The number of steps needed for generating a particular chemical structure or chemical diversity is a measure of the efficiency of chemical synthesis. MCRs have been shown to enable the most efficient approach to a variety of chemical synthetic problems, especially for the synthesis of natural-product-like molecules. Thus we were motivated to work on this promising field of chemistry. As the theme of my research work was to synthesize β-amino carbonyl compounds, I would like to mention their importance and some of their recently developed methods as described below.

1.2 β-Amino carbonyl compounds & their importance

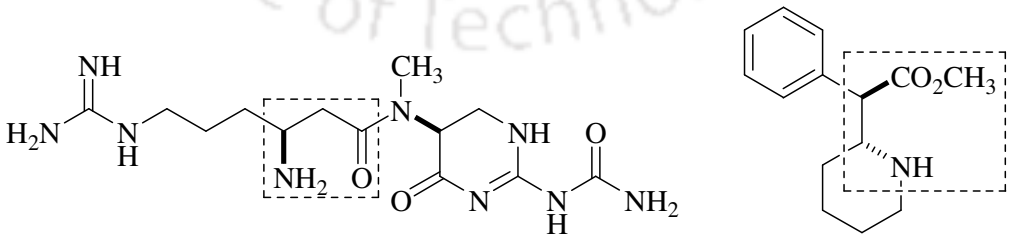
β-amino carbonyl compounds are the integral components in many biologically potent molecules. For example, the indole alkaloids, (+)-madindolines A (**55**) and B (**56**), which are used as selective inhibitors of interleukin-6 (IL-6),[22] have β-amino carbonyl moiety (Figure 5).



(+)-Madindoline A **55** (+)-Madindoline B **56**

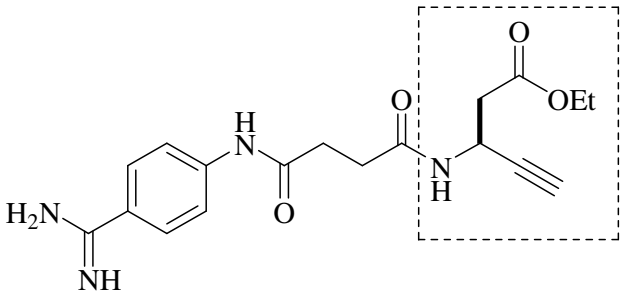
Figure 5. Structure of (+)-Madindolines A and B.

In addition, β-amino carbonyl compounds are valuable building blocks for a number of biologically and pharmaceutically important compounds, examples being for the preparation of β-peptides,[23] 1,3-amino alcohols,[24] antibiotic nikkomycins or neopolyoxines[25] etc. Some of the potent molecule used as drugs containing β-amino carbonyl moieties are shown below (Figure 6). For examples, TAN-1057 A (**57**) is an antibiotic;[26] methylphenidate (**58**) is used for the treatment of hyperactive children with attention-deficit disorder,[27] Xemilofiban (**59**) or (+)-NSL-95301[28] (**60**) are used as antithrombotic agent.[29]



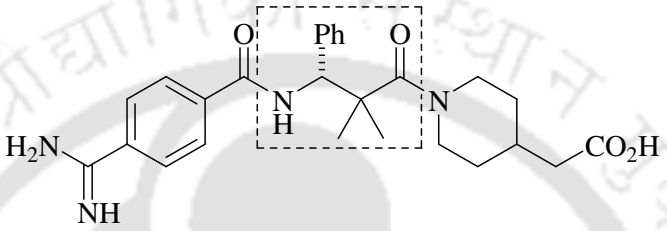
TAN-1057 A
57

Methylphenidate
58



Xemilofiban

59



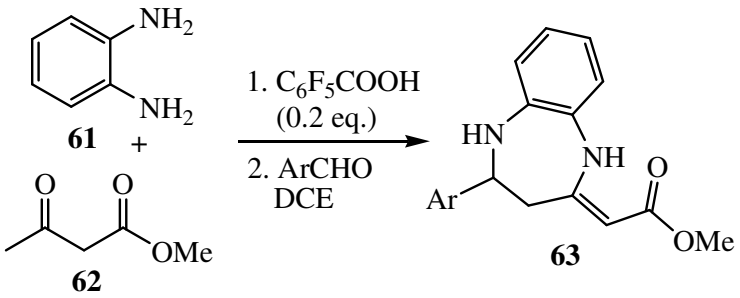
(+)-NSL-95301

60

Figure 6

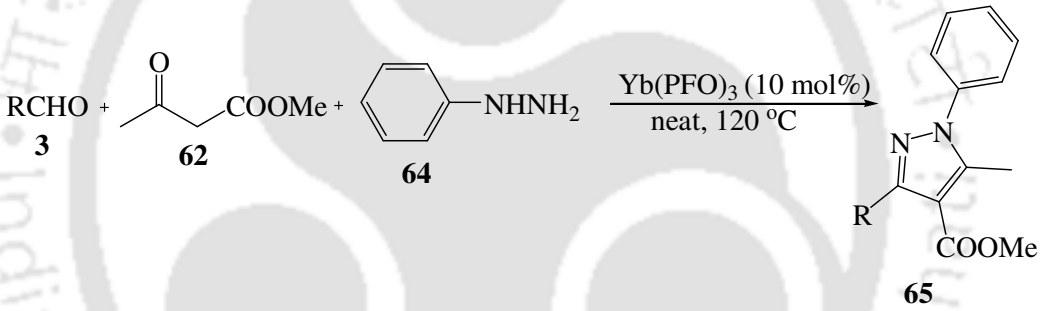
The conventional methods for preparing β-amino carbonyl compounds are aza-Michael addition and Mannich reaction. Aza-Michael addition is a two component reaction of amine with electron deficient alkenes, whereas Mannich reaction is a three component reaction of aldehyde, amine and enolozable ketone. Another approach to achieve these compounds is by multicomponent reactions. A plethora of new methodologies leading to the preparation of β-amino carbonyl compounds are emerging in current literature. Some recently developed multicomponent reactions for the synthesis of various β-amino carbonyl compounds are discussed below.

Fujioka et al developed a novel one-pot three-component reaction of aromatic aldehydes, 1,2-phenylenediamine, and β-ketoesters in the presence of a catalytic acid producing 1,5-benzodiazepine derivatives (**63**) having β-amino carbonyl moiety (Scheme 17).[30] This reaction involves the γ-selective C–C bond formation of methylacetoacetate. From the biological point of view, 1,5-benzodiazepines having β-amino carbonyl moiety are one of the important heterocyclic compounds.



Scheme 17

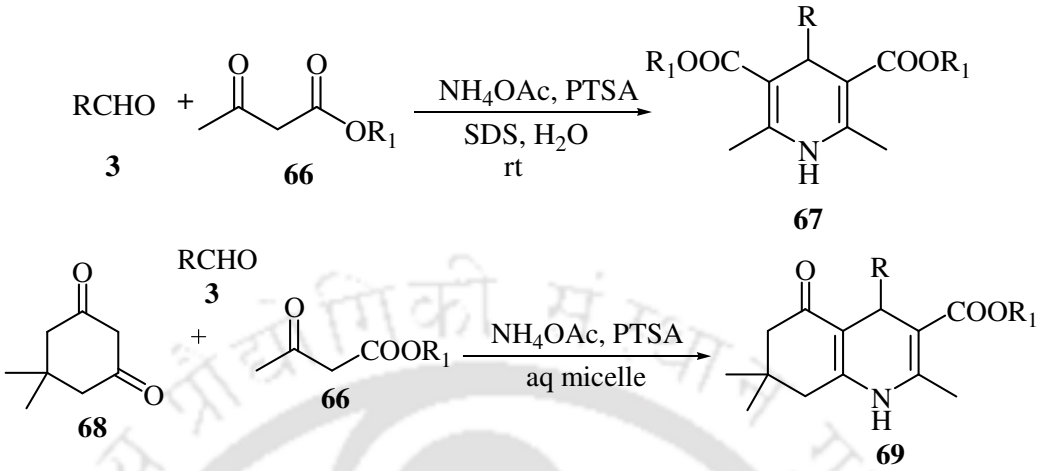
Fully substituted pyrazole and their derivatives have received much attention because they also exhibit useful pharmacological properties. Quian et al reported a convenient synthesis of fully substituted pyrazole **65** via three component condensation of phenyl hydrazine, aldehyde and methylacetoacetate using [$Yb(PFO)_3$] as catalyst (Scheme 18).[31]



Scheme 18

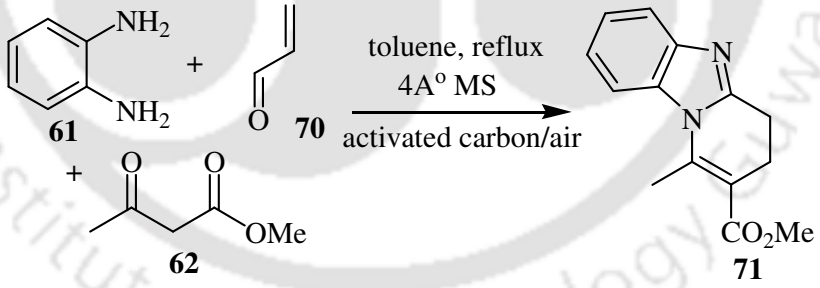
Hantzsch 1,4-dihydropyridines (1,4-DHP) and their derivatives are an important class of bioactive molecules in the pharmaceutical field.[32] These compounds are well known as calcium channel modulators and have emerged as one of the most important classes of drugs for the treatment of hypertension.[33] 1,4-Dihydropyridine derivatives possess a variety of biological activities such as vasodilator, branchodilator, antitumor, hepatoprotactive, and geroprotactive activity.[34] The classical method for the synthesis of 1,4-dihydropyridines is the one-pot condensation of aldehydes with ethyl acetoacetate and ammonia either in acetic acid or by refluxing in alcohol.[4] The classical method, however, has several drawbacks such as harsh reaction conditions, long reaction times, and generally low yields of products. Thus, improved synthetic procedures for the synthesis of Hantzsch esters and polyhydroquinoline derivatives are in constant demand. Recently, Kumar et.al[35] accomplised Hantzsch 1,4-dihydropyridine and polyhydroquinoline derivatives in excellent yields in aqueous

micelles (Scheme 19). The reaction is catalyzed by PTSA and strongly accelerated by ultrasonic irradiation.



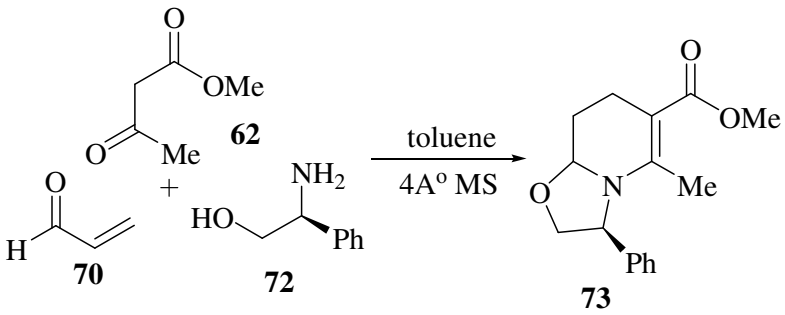
Scheme 19

Rodriguez et al reported first one-pot synthesis of polycyclic benzimidazoles via a molecular-sieves promoted three-component domino reaction and *in situ* aerobic oxidation sequence from 1,3-dicarbonyls, aromatic *o*-diamines and unsaturated aldehydes.[36] This environmentally friendly sequence does not require any harmful reagents, and liberates water as the only by-product.



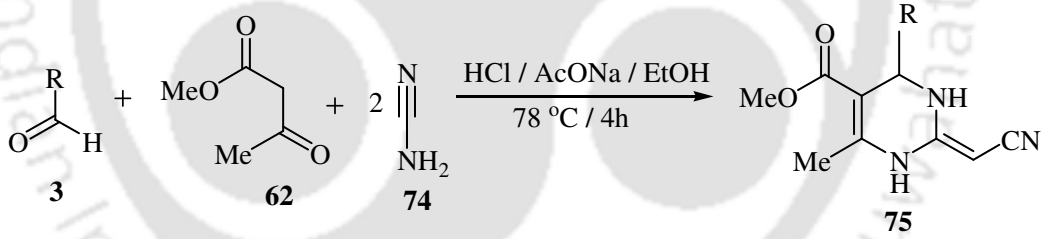
Scheme 20

The multicomponent condensation of methyl acetoacetate, acrolein and (*S*)-2-phenylglycinol was found to provide a one-pot access to chiral 6-carbonyl-3-phenyl-2,3,8,8*a*-tetrahydro-7*H*-[1,3]oxazolo[3,2-*a*]pyridines (Scheme 21)[37] which are proved to be useful intermediates for the preparation of various natural products such as matrine, cytosine and tashiromine.



Scheme 21

Recently, Hulme et al explored the construction of 4-aryl-2-cyanoimino-3,4-dihydro-1H-pyrimidine (aryl-CIDHPM)[38] compounds containing the N-cyanoguanidinyl moiety in their structure which is found in other biologically active molecules such as the potentially antimycotic agent N-cyanoiminopyrimidine, pinacidil, a KATP channel activator. Methyl acetoacetate has played vital role in this reaction. They have explored multicomponent reaction of arene or heteroarenecarbaldehyde, methyl acetoacetate, and cyanamide under acidic conditions for the preparation of these compounds (Scheme 22).



Scheme 22

From the literature it is evident that β-amino carbonyl moiety plays an important role in various bioactive molecules and development of new methodologies leading to these compounds is a challenging task. Thus the objective of my thesis work was to develop new synthetic methodologies for the preparation of β-amino carbonyl compounds. In an endeavor to achieve our target we have developed a few new methodologies using Lewis acid catalysis and bromodimethylsulfonium bromide. In the subsequent chapters we have described a few multicomponent reactions and one methodology on aza-Michael addition.

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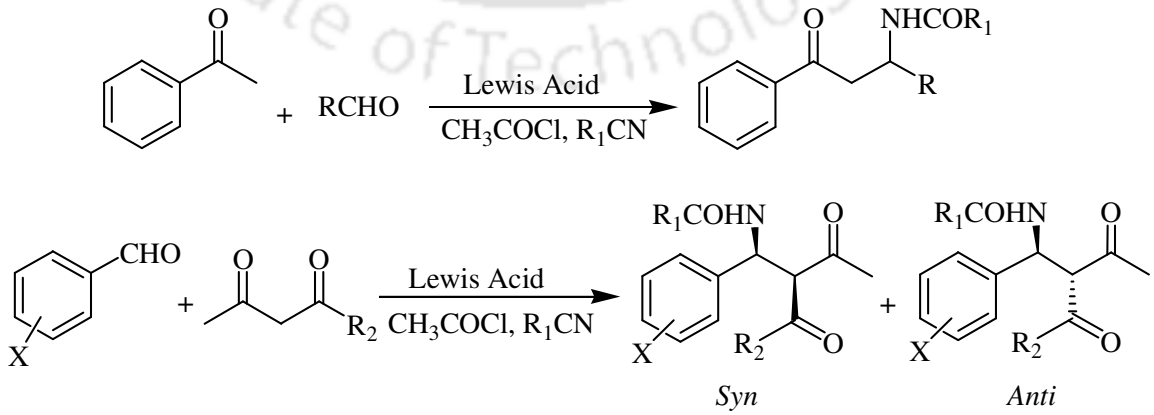
CHAPTER II

Synthesis of β-acetamido carbonyl compounds by multi-component reactions using Lewis acid catalysts.

2.1 Introduction

In the previous chapter we have discussed about the importance of β-amino carbonyl compounds and a brief literature survey on new methodologies for the preparation of these compounds. β-Acetamido carbonyl compounds are synthetically important β-amino carbonyl compounds. Interestingly, they have been found to be an effective inhibitor of α-glucosidase.[1] Inhibition of α-glucosidase, an enzyme abundant in brush border of the small intestine, has been found to delay carbohydrate digestion, absorption, and thereby diminish postprandial hyperglycemia (PPHG) level.[2-4] It has also proved to be a promising therapeutics strategy for reducing increased risk for diabetes, hypertension, dyslipidemia, obesity and cardiovascular diseases in patients with metabolic syndrome.[5] Recent studies have shown that β-acetamido carbonyl compounds display antihyperglycemic activity equivalent to the standard drug acarbose. In addition, β-acetamido carbonyl compounds are valuable building blocks for preparation of 1,3 amino alcohols,[6] β-amino acids[7] as well as for synthesis of various antibiotics.[8] Therefore, synthesis of β-acetamido carbonyl compounds have gained considerable attention in organic synthesis.

Conventionally, these class of compounds are prepared by Dakin-West reaction,[9] using the condensation of α-amino acid with acetic anhydride in the presence of a base to provide the α-acetamido ketones through an azalactone intermediate.[10] However, for the preparation of β-acetamido carbonyl compounds, Iqbal et al developed a multicomponent approach using aromatic aldehydes, enolizable ketones or β-keto esters and acetonitrile in



Scheme 1

the presence of acetyl chloride and catalytic amount of Lewis acid (Scheme 1) such as $CoCl_2$[11] or Montmorilonite K-10 clay.[12] Although these methods are useful, still they suffer from some drawbacks such as requirement of either longer reaction time or harsh reaction conditions or the reaction has to be carried out under inert atmospheric conditions. Recently, a few more methods have also been reported for the same transformation by involving $Cu(OTf)_2$/$Sc(OTf)_3$,[13] silica sulfuric acid,[14] BiOCl[15] and $ZrOCl_2 \cdot 8H_2O$.[16] However, most of these methods employ either expensive catalysts or longer reaction time or harsh reaction conditions.

In continuation of our efforts towards the development of newer and greener synthetic methodologies,[17] we were in quest of a simple and improved protocol for the facile preparation of β-acetamido carbonyl compounds using a friendly Lewis acid catalyst.
A 'friendly' Lewis acid catalyst should possess the following properties: low cost, easy availability, low toxicity and high stability towards water, oxygen, and air moisture. In addition, reusability without loss of efficiency and the ability to work in solvent free as well as hydrous conditions are also worthwhile features. In this context, hydrated Ce (III) chloride stand for an ideal 'friendly' Lewis acid. From the literature survey we have found that $CeCl_3 \cdot 7H_2O$ is an effective catalyst in organic synthesis.[18] Thus encouraged by the literature background, we sought to explore this reagent for the preparation of β-acetamido carbonyl compounds by multicomponent approach. Interestingly, $CeCl_3 \cdot 7H_2O$ was found to be an efficient catalyst for this transformations.[19] The successful results of our observation are described in Section A of this Chapter.

After successful exploration of $CeCl_3 \cdot 7H_2O$ for the synthesis of β-acetamido carbonyl compounds, we were looking for an alternative method employing relatively cheaper and more abundant transition metal Lewis acid. Among transition metal Lewis acids, iron salts have attracted much attention of synthetic organic chemists[20] since iron is one of the most abundant metals on earth as well as one of the most inexpensive and environmentally friendly ones.[23] Many iron salts and complexes are commercially available. Among them $FeCl_3 \cdot 6H_2O$ has emerged as a potentially useful Lewis acid and has been extensively used in various organic transformations. Due to its unique catalytic properties, it has been used for a plethora of organic transformations such as for the

construction of 10*H*-indeno[1,2-*b*]triphenylene skeletons by oxidative cyclization,[24] cleavage of silyl protecting groups,[25] amino halogenation of arylmethylenecyclopropanes and arylvinylidenecyclopropanes,[26] hydroarylation of styrenes,[27] one-pot synthesis of 1,2-dihydro-2-oxo-3-pyridinecarboxylate derivatives,[28] Friedlander synthesis of quinolines,[29] one-pot synthesis of homoallyl benzyl ethers from aldehydes,[30] and synthesis of nicotinic acid derivatives [31] etc. From this brief literature survey we realized that iron (III) chloride can be explored further as a versatile catalyst for the synthesis of β-acetamido carbonyl compounds by four component reactions. The results and discussions using this catalyst are described in section B of this chapter.

SECTION A

Synthesis of β-acetamido carbonyl compounds using $CeCl_3 \cdot 7H_2O$ as catalyst

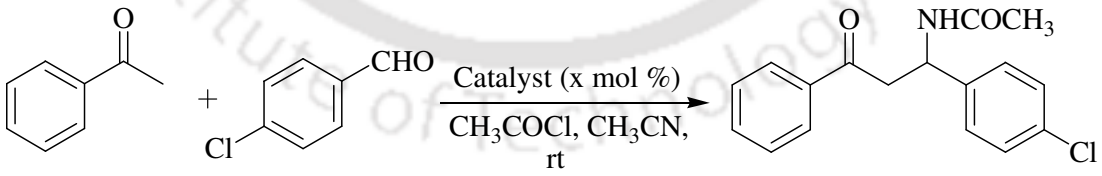
RESULTS AND DISCUSSION

2.2.1 Results and Discussion:

The reactivity as well as the virtue of $CeCl_3 \cdot 7H_2O$ in organic synthesis is well known in the literature.[18] In an endeavor to develop a convenient multicomponent reaction for the facile access of β-acetamido carbonyl compounds using effective Lewis acid catalyst, we perceived that $CeCl_3 \cdot 7H_2O$ might be useful. Initially, the reaction 4-chlorobenzaldehyde (2 mmol), acetophenone (2 mmol), acetyl chloride (3 mmol) and acetonitrile (5 mL) was stirred in presence of 5 mol% $CeCl_3 \cdot 7H_2O$ at room temperature. After 15h of stirring the corresponding β-acetamido ketone (**2**) was isolated in 87% yield. The product **2** was characterized by recording IR, ^1H and ^{13}C NMR spectra. The presence of IR absorption band at 3291, 1687, 1647 cm^{-1} indicates the presence of NH and carbonyl functionalities. In ^1H NMR the appearance of signals in the region 2.01 (3H, s, -COC*H*$_3$), 3.41 (1H, dd, *J* = 6.0 Hz, *J* = 16.8 Hz, -COC*H*$_2$CH-), 3.73 (1H, dd, *J* = 5.2 Hz, *J* = 17.2 Hz, -COC*H*$_2$CH-), 5.50 -5.55 (1H, m, -C*H*-NHCO-), 6.74 (1H, d, *J* = 7.2 Hz, -N*H*CO-) and in ^{13}C NMR the presence of signals at 165.0, 198.7 ppm clearly indicate the formation of the product.

After this initial success, we wanted to optimize the reaction conditions as well as to see the scope and generality of this methodology. For optimization, the same combination, i.e. a mixture of 4-chlorobenzaldehyde (2 mmol), acetophenone (2 mmol), acetyl chloride (3 mmol) and acetonitrile (5 mL) was stirred under a number of different reaction conditions (Table 1).

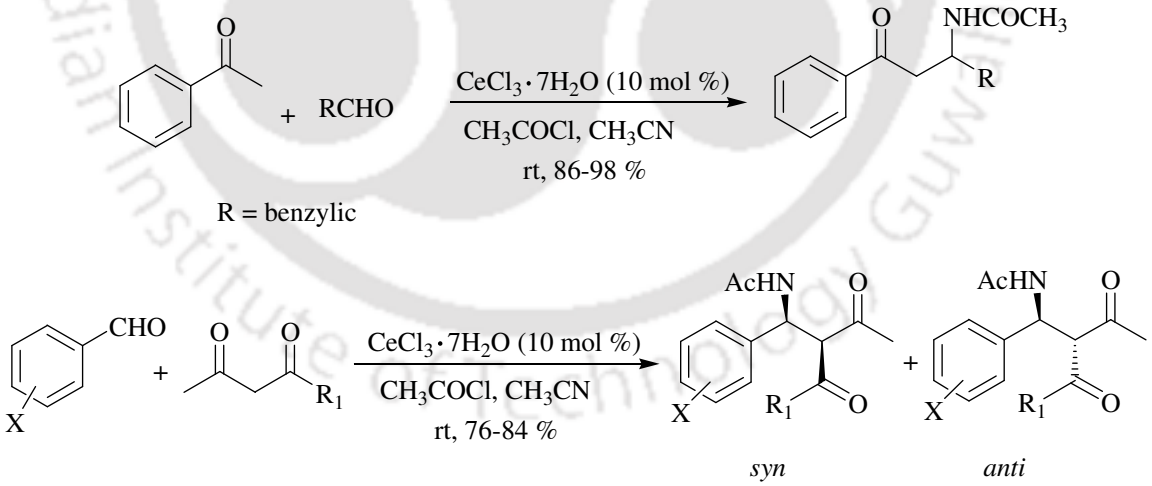
Table 1. Optimization of $CeCl_3 \cdot 7H_2O$ catalyzed multicomponent reaction



Entry	Catalyst $CeCl_3 \cdot 7H_2O$ mol%	Time /h	% Yield
1	0	24	15
2	5	15	87
3	10	6	98
4	10	24	0 [a]

[a]Reaction was carried out in absence of acetyl chloride

In absence of the catalyst, the product β-acetamido ketone was obtained with a very poor yield 15% only even after 24 h of stirring. Interestingly, in presence of 10 mol% catalyst we obtained very good yield (98 %) within shorter reaction time (6h) (Table 1, entry 3). Next, the same set of reaction was stirred without adding acetyl chloride and the reaction was unsuccessful. Therefore the reaction condition of entry 3, Table 1, was considered as the optimized reaction condition. It is worthwhile to mention here that for the same transformation, the existing method using $CoCl_2$ afforded lower yields taking longer time (12-14 h) even under the heating condition (70-80 ^oC) and at room temperature it took 5 days with the same amount of catalyst loading. As a result, we were impressed with the catalytic activity of $CeCl_3{\cdot}7H_2O$. Moreover, it is relatively cheap, water, air tolerant and absolutely non-toxic reagent. Due to the hardness of the cerium cation, it is able to activate the carbonyl functionalities for the nucleophilic attack and acts as a good Lewis acid for several transformations in organic synthesis. In this section, we will report a mild and efficient protocol for the preparation of β-acetamido carbonyl compounds by four-component reaction of aromatic aldehyde, acetonitrile, enolizable ketone or β-keto ester and acetyl chloride catalyzed by $CeCl_3{\cdot}7H_2O$ at room temperature (Scheme 2).

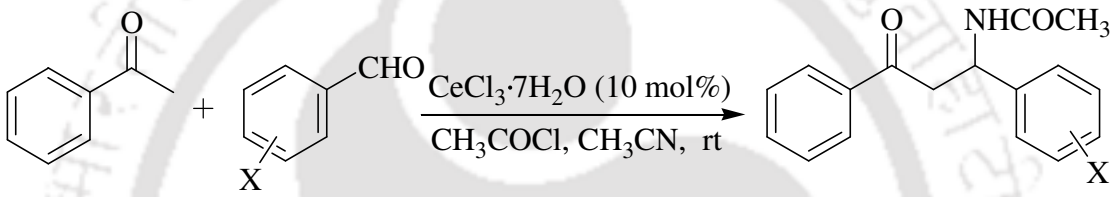


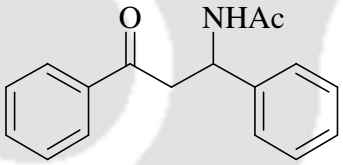
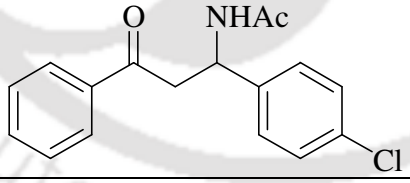
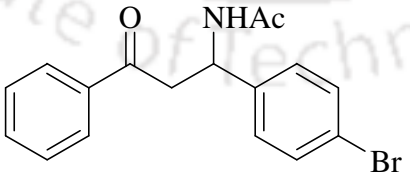
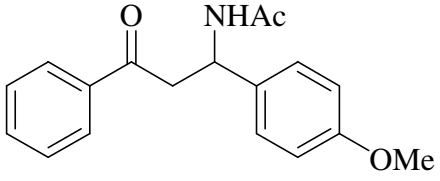
Scheme 2

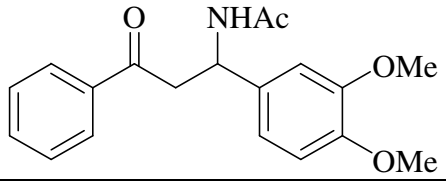
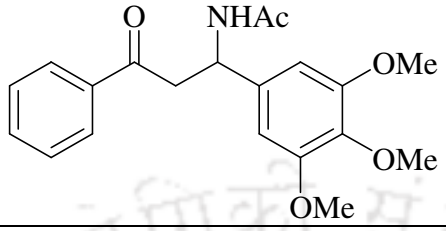
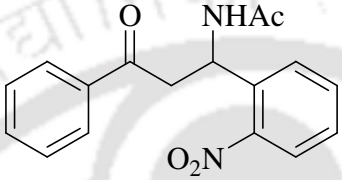
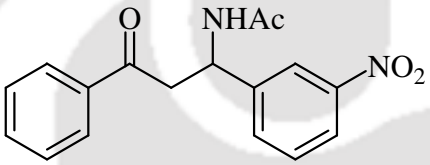
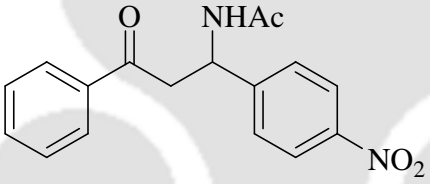
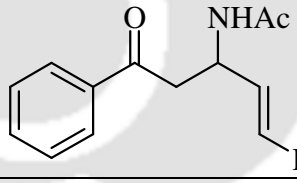
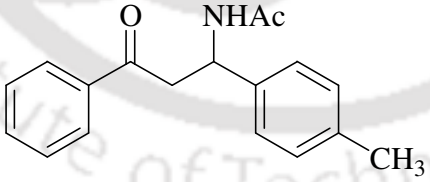
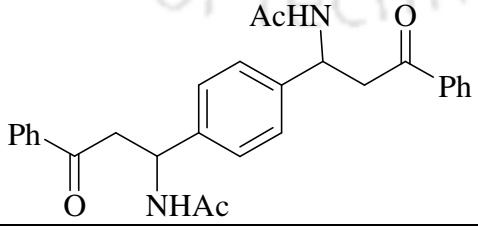
Next, a wide variety of other aromatic aldehydes having electron-donating as well as electron-withdrawing substituents were treated under the same experimental conditions to afford the corresponding desired products (**3-9** and **11**) in good yields without any difficulty. The results are summarized in Table 2. All the products were fully

characterized by spectroscopic methods and compared with the authentic spectra. We have noted that an aromatic aldehyde containing a nitro substituent at the ring took longer time to afford corresponding products **7-9** as compared to the other aldehydes as shown in Table 2. Similarly, α,β-unsaturated aldehyde such as cinnamaldehyde also reacted under the same experimental conditions and provided the corresponding β-acetamido ketone **10** in excellent yield. Likewise, terephthalaldehyde on treatment with two equivalents of acetophenone and other ingredients provided the corresponding β-acetamido ketone **12** in good yields, where both the aldehydic groups reacted.

Table 2. $CeCl_3 \cdot 7H_2O$ catalyzed multi-component reaction for the preparation of β-acetamido ketone



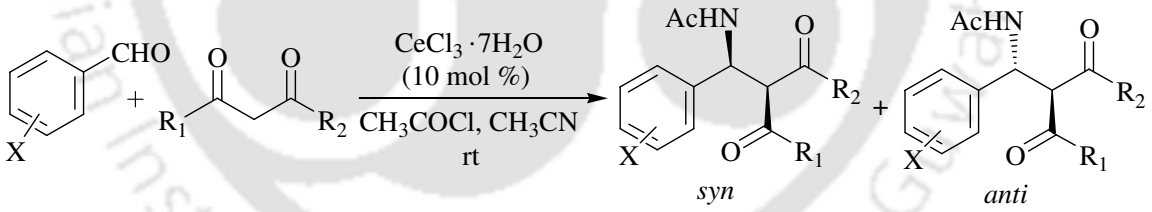
Product No.	β-acetamido ketones[a]	Time /h	Yield[b] (%)
1		7	96
2		6	98[c]
3		6	95
4		6	89

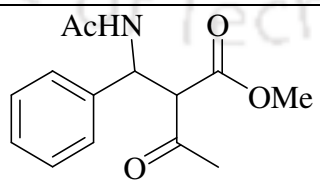
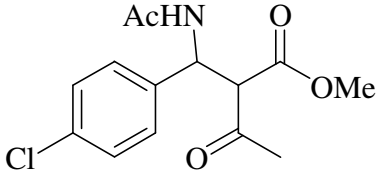
5		6	96
6		5	93
7		11	86
8		10	90
9		12	96
10		6	94
11		7	92
12		8	76

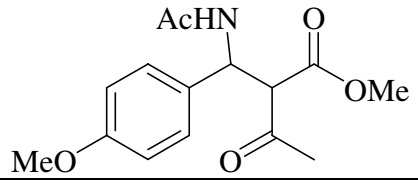
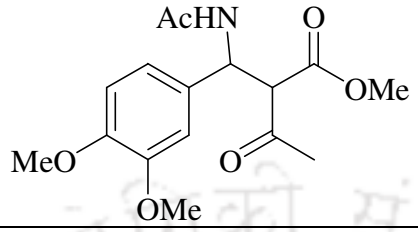
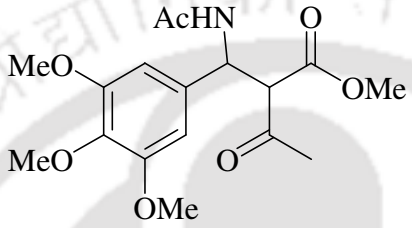
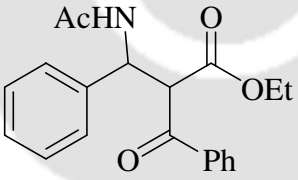
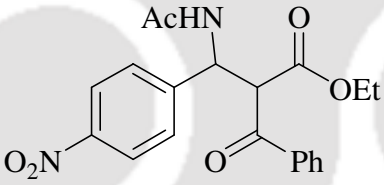
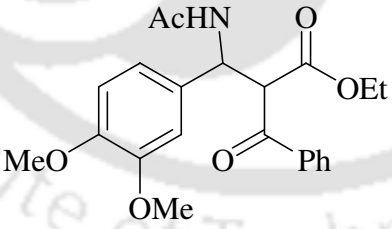
[a]All the products were characterized by recording IR and ^{1}H NMR and ^{13}C NMR spectra as well as by elemental analysis. [b]Yields obtained after work-up. [c]The catalyst was recovered and reused in subsequent reactions three times without losing any significant activity with 91, 88, and 85% yield respectively.

To explore the further applicability of Ce (III) catalyzed multicomponent reactions, a variety of aromatic aldehydes were treated with methylacetoacetate and acetyl chloride in presence of 10 mol% catalyst at room temperature and the corresponding β-acetamido ketoesters (**13-17**) were obtained in good yields from moderate to good diastereoselectivity. The *syn / anti* ratio was determined from the crude ^{1}H NMR spectra. The active methylene proton of these β-acetamido keto esters appears as doublet in ^{1}H NMR. However, the *syn* and the *anti* diastereomer can be distinguished from each other from their different coupling constants. For *syn* the *J* value is around 4.0 Hz, whereas for *anti* it is around 6.0 Hz. Next, ethyl benzoylacetate was treated with different aldehydes such as benzaldehyde, 4-nitro benzaldehyde and 3,4-dimethoxybenzaldehyde under similar experimental conditions to afford the corresponding multicomponent products (**18-20**) in excellent yields with good diastereoselectivity. Interestingly, the product obtained from the reaction of methyl acetoacetate (**13-17**) provided a*nti* as a major isomer whereas ethyl benzoylacetate afforded s*yn* as the major one (**18-20**).

Table 3. $CeCl_3 \cdot 7H_2O$ catalyzed multicomponent reaction for the preparation of β-acetamido ketoester



Product No.	Product	% Yield[a]	*Syn: anti*[b]
13		76	25: 75
14		84	24: 76

15		78	5: 95
16		83	7: 93
17		81	10: 90
18		81	90: 10
19		84	72: 28
20		83	70: 30

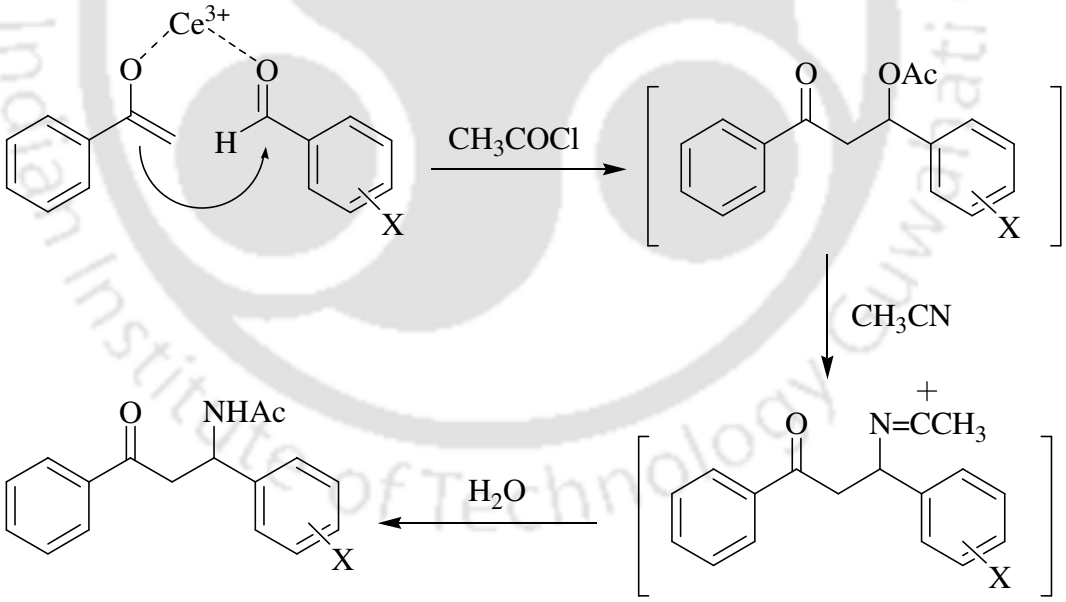
[a]Yields obtained after work-up. [b]The ratio of *syn*:*anti* was determined from ^{1}H NMR of the crude reaction mixture.

The generality and superiority of the present protocol over the other existing methods can be visualized at a glance by comparing our results with those of some recently reported procedures as shown in Table 4. The reaction of benzaldehyde with acetophenone for the preparation of N-(3-Oxo-1,3-diphenyl-propyl)acetamide (**1**) has been chosen as a model reaction and the comparison is done in terms of mol% of the catalysts used, reaction time and reaction condition as well as percentage of yield obtained.

Table 4. Comparison of results for the preparation of β-acetamido ketone (**1**) using multi-component reactions with other catalysts

Catalyst	Mol-%	Reaction time	Reaction temp	Yield/%
Silica sulfuric acid	78	65 min	80 °C	91[14]
$ZrOCl_2 \cdot 8H_2O$	20	5 h	rt	90[16]
$Sc(OTf)_3$	10	30 h	rt	82[13]
BiOCl	20	7 h	rt	92[15]
$CeCl_3 \cdot 7H_2O$	10	7 h	rt	96

The plausible mechanistic aspect can be rationalized as follows: As we have noticed that the reaction proceeds with only 15% yield even after 24 hour of stirring in absence of catalyst, we believe here cerium (III) chloride activates the aldehyde group for nucleophilic attack as well as to facilitate enolization and as a whole it makes the process convenient (Scheme 3).



Scheme 3 Plausible mechanism

Next, we were interested to investigate the mechanism, whether it goes through chalcone intermediate (by aldol condensation) or not. To verify this, we took a mixture of chalcone

(2 mmol), acetyl chloride (3 mmol) and acetonitrile (5 mL) at room temperature; we did not observe any desired β-acetamido ketone formation even after 6 h of stirring.

In conclusion, we have revealed a simple, efficient and greener protocol for the facile preparation of β-acetamido carbonyl compounds using a $CeCl_3 \cdot 7H_2O$ as a reusable catalyst. The salient features of this protocol include operational simplicity, high yields of the products, avoidance of column chromatographic separation, ready availability, low toxicity, moisture compatibility, and reusability of the catalyst that render this procedure as an attractive methodology for the facile preparation of β-acetamido carbonyl compounds.

SECTION A

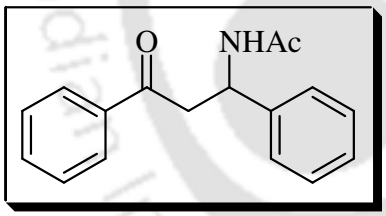
Synthesis of β-acetamido carbonyl compounds using $CeCl_3 \cdot 7H_2O$ as catalyst

EXPERIMENTAL

2.2.2 General procedure for the preparation of β-acetamido/benzamido ketones or keto esters:

A mixture of aromatic aldehyde (2 mmol), acetophenone or β-keto ester (2 mmol), acetyl chloride (3 mmol) and $CeCl_3 \cdot 7H_2O$ (75 mg, 10 mol %) in acetonitrile (5 mL) was stirred at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was poured into 50 mL of ice water. On solidification, it was filtered, washed with ice water and recrystallized from ethyl acetate/hexane to give the pure β-acetamido ketone. For all the β-acetamido ketoesters in Table 3, the reactions were stirred for 12 h, and then 50 mL of water was added. The mixture was extracted with ethyl acetate (3 x 20 mL), the extracts were washed with water (3 x 20 mL), dried over Na_2SO_4 and the solvent was removed using a rotary evaporator. The crude mixture was recrystallized from ethyl acetate/hexane and the solid product (mixture of diastereomers) was isolated. For the recovery of the catalyst, the aqueous layer was evaporated under reduced pressure, and the residue was reused in subsequent reactions without losing any significant activity.

N-(3-Oxo-1,3-diphenyl-propyl)acetamide (1)



Nature: White solid

Yield: 96% (0.514 g)

M.p. 103-105 °C (lit.[12] M.p. 104-105 °C)

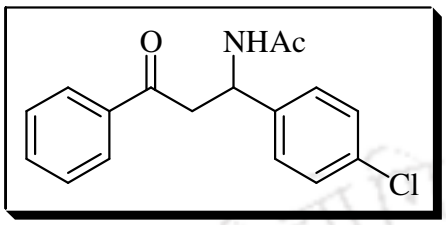
IR(KBr): 3278, 3099, 2925, 1682, 1646, 1556, 1447, 1372, 1195, 990, 750 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.01 (3H, s), 3.43 (1H, dd, *J* = 6.4 Hz, *J* = 16.8 Hz), 3.75 (1H, dd, *J* = 5.2 Hz, *J* = 16.8 Hz), 5.53-5.57 (1H, m), 6.68 (1H, d, *J* = 7.6 Hz), 7.19-7.23 (2H, m), 7.26-7.30 (3H, m), 7.43 (2H, t, *J* = 8.0 Hz), 7.55 (1H, t, *J* = 6.4 Hz), 7.88 (2H, d, *J* = 8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.6, 43.2, 49.9, 126.6, 127.7, 128.3, 128.9, 133.7, 136.4, 140.7, 169.3, 198.3 ppm.

Elemental Analysis: $C_{17}H_{17}NO_2$ (267.32): Found C, 76.49; H, 6.39; N, 5.19. Calculated C, 76.38; H, 6.41; N, 5.24 %

N-[1-(4-Chlorophenyl)-3-oxo-3-phenyl-propyl]acetamide (2)



Nature: White solid

Yield: 98% (0.591 g)

M.p. 145-147 °C (lit.[14] M.p. 146-148 °C)

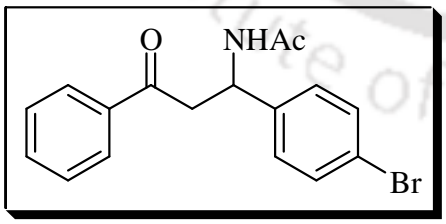
IR (KBr): 3291, 2329, 1687, 1647, 1547, 1445, 1349, 1229, 1009, 754 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.01 (3H, s), 3.41 (1H, dd, *J* = 6.0 Hz, *J* = 16.8 Hz), 3.73 (1H, dd, *J* = 5.2 Hz, *J* = 17.2 Hz), 5.50-5.55 (1H, m), 6.74 (1H, d, *J* = 7.2 Hz), 7.25 (4H, d, *J* = 4.4 Hz), 7.44 (2H, t, *J* = 8.0 Hz), 7.56 (1H, t, *J* = 7.6 Hz), 7.87 (2H, d, *J* = 8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.0, 43.2, 49.4, 128.1, 128.3, 128.9, 133.6, 133.9, 140.0, 142.0, 148.0, 165.0, 198.7 ppm.

Elemental Analysis: $C_{17}H_{16}ClNO_2$ (301.77): Found C, 67.53; H, 5.28; N, 4.72. Calculated C, 67.66; H, 5.34; N, 4.64 %

N-[1-(4-Bromophenyl)-3-oxo-3-phenyl-propyl]acetamide (3)



Nature: White solid

Yield: 95% (0.658 g)

M.p. 148-150 °C

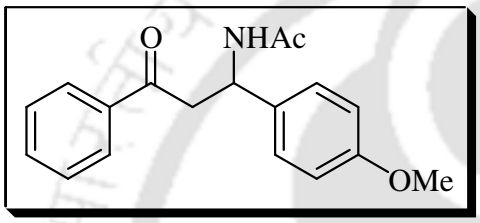
IR (KBr): 3285, 2923, 1684, 1651, 1550, 1374, 1292, 1006, 757 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.02 (3H, s), 3.40 (1H, dd, *J* = 6.0 Hz, *J* = 17.2 Hz), 3.72 (1H, dd, *J* = 5.2 Hz, *J* = 16.8 Hz), 5.49-5.51 (1H, m), 6.73 (1H, d, *J* = 6.8 Hz), 7.19 (2H, d, *J* = 8.4 Hz), 7.40 (2H, d, *J* = 8.4 Hz), 7.44 (2H, d, *J* = 8.0 Hz), 7.55 (1H, t, *J* = 7.2 Hz), 7.87 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.7, 42.9, 49.4, 128.3, 128.4, 129.0, 131.9, 134.0, 136.2, 140.2, 166.5, 196.5 ppm.

Elemental Analysis: $C_{17}H_{16}BrNO_2$ (346.22): Found C, 58.85; H, 4.70; N, 4.12. Calculated C, 58.98; H, 4.66; N, 4.05 %

N-[1-(4-Methoxyphenyl)-3-oxo-3-phenyl-propyl]acetamide (4)



Nature: White solid

Yield: 89% (0.530 g)

M.p. 110-111 °C (lit.[16] M.p. 110-112 °C)

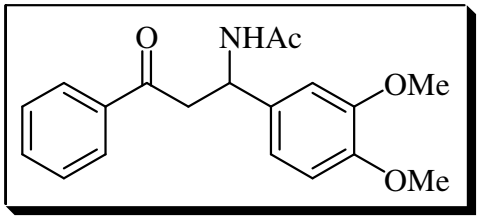
IR (KBr): 3301, 2928, 1688, 1648, 1545, 1372, 1238, 1033, 754 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.01 (3H, s), 3.39 (1H, dd, *J* = 6.4 Hz, *J* = 16.8 Hz), 3.72 (1H, dd, *J* = 5.2 Hz, *J* = 17.2 Hz), 3.74 (3H, s), 5.46-5.51 (1H, m), 6.57 (1H, d, *J* = 8.0 Hz), 6.81 (2H, d, *J* = 8.4 Hz), 7.23 (2H, d, *J* = 8.0 Hz), 7.42 (2H, t, *J* = 7.6 Hz), 7.54 (1H, t, *J* = 7.2 Hz), 7.89 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.6, 43.5, 49.7, 55.4, 114.2, 127.9, 128.3, 128.9, 133.1, 133.7, 136.7, 158.9, 169.7, 198.8 ppm.

Elemental Analysis: $C_{18}H_{19}NO_3$ (297.35): Found C, 72.59; H, 6.49; N, 4.79. Calculated C, 72.71; H, 6.44; N, 4.71 %

N-[1-(3,4-Dimethoxyphenyl)-3-oxo-3-phenyl-propyl]acetamide (5)



Nature: Brownish solid

Yield: 96% (0.629 g)

M.p. 118-119 °C

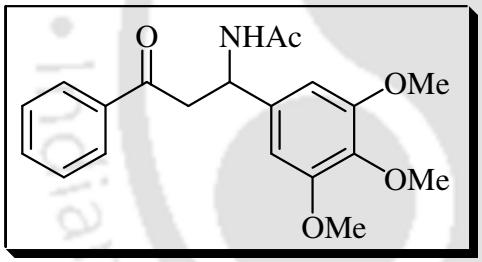
IR (KBr): 3247, 3076, 2917, 2846, 1681, 1637, 1519, 1462, 1253, 1026, 751 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.01 (3H, s), 3.39 (1H, dd, *J* = 6.4 Hz, *J* = 16.8 Hz), 3.72 (1H, dd, *J* = 5.2 Hz, *J* = 16.4 Hz), 3.81 (3H, s), 3.82 (3H, s), 5.45-5.50 (1H, m), 6.58 (1H, d, *J* = 8.0 Hz), 6.76 (1H, d , *J* = 8.0 Hz), 6.83 (2H,s + d, *J* = 8.0 Hz), 7.43 (2H, t, *J* = 7.6 Hz), 7.55 (1H, t, *J* = 7.6 Hz), 7.89 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.7, 43.4, 50.1, 56.1, 110.5, 111.3, 118.3, 128.3, 128.9, 133.6, 133.7, 149.2, 169.6, 199.0 ppm.

Elemental Analysis: $C_{19}H_{21}NO_4$ (327.37): Found C, 69.58; H, 6.40; N, 4.37. Calculated C, 69.71; H, 6.47; N, 4.28 %

N-[1-(3,4,5-Trimethoxyphenyl)-3-oxo-3-phenyl-propyl]acetamide (6)



Nature: White solid

Yield: 93% (0.665 g)

M.p. 158-160 °C

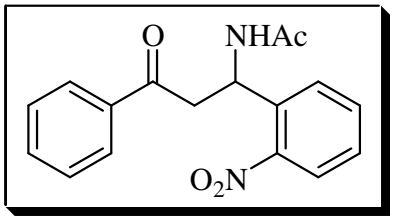
IR (KBr): 3277, 1687, 1647, 1592, 1560, 1126, 1002 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.03 (3H, s), 3.38 (1H, dd, *J* = 5.2 Hz, *J* = 16.4 Hz), 3.70 (1H, dd, *J* = 5.2, *J* = 16.8 Hz), 3.77 (3H, s), 3.79 (6H, s), 5.45 (1H, m), 6.52 (2H, s), 6.67 (1H, d, *J* = 6.8 Hz), 7.43 (2H, t, *J* = 7.2 Hz), 7.55 (1H, t, *J* = 6.4 Hz), 7.88 (2H, d, *J* = 7.6 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.6, 43.3, 50.6, 56.2, 60.8, 103.8, 103.9, 128.0, 128.6, 133.4, 136.6, 153.1, 169.2, 198.5 ppm.

Elemental Analysis: $C_{20}H_{23}O_5N$ (357.40): Found C, 67.29; H, 6.42; N 3.82. Calculated C, 67.21; H, 6.49; N, 3.92 %

N-[1-(2-Nitrophenyl)-3-oxo-3-phenyl-propyl]acetamide (7)



Nature: White solid

Yield: 86% (0.537 g)

M.p. 190-191°C (lit[12] M.p. 186-188 °C)

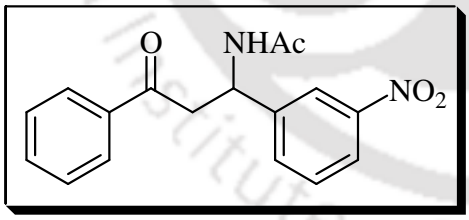
IR (KBr): 3326, 2379, 1686, 1651, 1544, 1517, 1357, 1337, 1059, 682 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.00 (3H, s), 3.63 (1H, dd, *J* = 5.6, *J* = 16.8 Hz), 3.71 (1H, dd, *J* = 6.4 Hz, *J* = 17.2 Hz), 5.93-5.97 (1H, m) , 7.07 (1H, d, *J* = 5.6 Hz), 7.39 (1H, t, *J* = 8.0 Hz), 7.46 (2H, t, *J* = 8.0 Hz), 7.57 (2H, t, *J* = 7.6 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.92 (2H, d, *J* = 7.2 Hz), 7.94 (1H, d, *J* = 6.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.5, 42.4, 47.7, 125.3, 128.5, 128.6, 129.0, 130.1, 133.7, 134.1, 136.5, 137.1, 148.7, 169.5, 198.5 ppm.

Elemental Analysis: $C_{17}H_{16}N_2O_4$ (312.32): Found C, 65.49; H, 5.23; N, 8.88. Calculated C, 65.38 ; H, 5.16; N, 8.97 %

N-[1-(3-Nitrophenyl)-3-oxo-3-phenyl-propyl]acetamide (8)



Nature: White solid

Yield: 90% (0.562 g)

M.p. 139-140 °C (lit.[16] M.p. 139-140 °C)

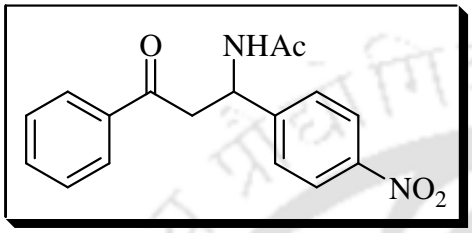
IR (KBr): 3306, 1693, 1644, 1545, 1522, 1347, 983, 684 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.08 (3H, s), 3.51 (1H, dd, *J* = 5.6 Hz, *J* = 17.6 Hz), 3.79 (1H, dd, *J* = 5.2 Hz, *J* = 17.6 Hz), 5.62-5.67 (1H, m), 6.91 (1H, d, *J* = 7.6 Hz), 7.42-7.49 (3H, m), 7.57 (1H, t, *J* = 7.6 Hz), 7.68 (1H, d, *J* = 7.6 Hz), 7.87 (2H, d, *J* = 7.6 Hz), 8.06 (1H, d, *J* = 6.8 Hz), 8.19 (1H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.6, 42.9, 49.3, 121.5, 122.6, 128.3, 129.1, 129.8, 130.8, 133.1, 134.2, 136.4, 143.7, 169.9, 198.3 ppm.

Elemental Analysis: $C_{17}H_{16}N_2O_4$ (312.32): Found C, 65.29; H, 5.22; N, 8.88. Calculated C, 65.38; H, 5.16; N, 8.97 %

N-[1-(4-Nitrophenyl)-3-oxo-3-phenyl-propyl]acetamide (9)



Nature: Yellow crystalline solid

Yield: 96% (0.600 g)

M.p. 152-154 °C (lit.[16] M.p. 154 °C)

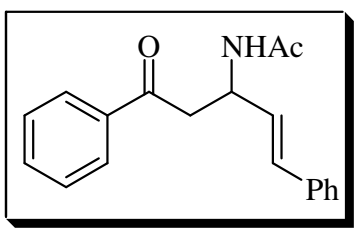
IR (KBr): 3306, 1696, 1646, 1595, 1537, 1350, 988, 755 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.10 (3H, s), 3.51 (1H, dd, *J* = 5.6, *J* = 17.6 Hz), 3.81 (1H, dd, *J* = 5.2 Hz, *J* = 17.6 Hz), 5.65-5.67 (1H, m), 6.96 (1H, d, *J* = 8.0 Hz), 7.47 (2H, t, *J* = 8.0 Hz), 7.51 (2H, d, *J* = 8.8 Hz), 7.60 (1H, t, *J* = 7.2 Hz), 7.89 (2H, d, *J* = 7.2 Hz), 8.17 (2H, d, *J* = 8.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.5, 42.6, 49.2, 123.7, 127.2, 127.9, 128.7, 131.0, 133.9, 136.0, 138.4, 169.5, 197.8 ppm.

Elemental Analysis: $C_{17}H_{16}N_2O_4$ (312.32): Found C, 65.29; H, 5.23; N, 8.99. Calculated C, 65.38; H, 5.16; N, 8.97 %

N-[1-(4-Styryl)-3-oxo-3-phenyl-propyl]acetamide (10)



Nature: Light yellow solid

Yield: 94% (0.552 g)

M.p. 120-121 °C

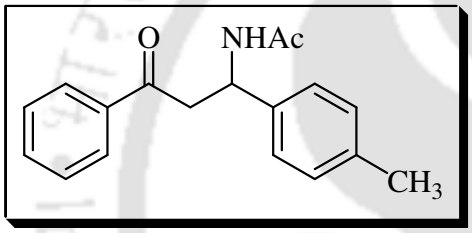
IR (KBr): 3291, 3065, 2928, 1687, 1648, 1635, 1547, 1445, 1366, 1083, 751 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.04 (3H, s), 3.35 (1H, dd, *J* = 5.6 Hz, *J* = 17.6 Hz), 3.53 (1H, dd, *J* = 4.4 Hz, *J* = 17.6 Hz), 5.09-5.13 (1H, m) , 6.33 (1H, dd, *J* = 6.8 Hz, *J* = 16.0 Hz), 6.54 (1H, d, *J* = 15.6 Hz), 7.20 (1H, d, *J* = 6.8 Hz), 7.25 (2H, t, *J* = 6.8 Hz), 7.29 (3H, d, *J* = 7.2 Hz), 7.46 (2H, t, *J* = 7.6 Hz), 7.57 (1H, t, *J* = 7.6 Hz), 7.93 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.8, 42.8, 48.3, 126.7, 127.9, 128.3, 128.6, 128.7, 128.9, 1301.7, 133.9, 169.5, 199.7 ppm.

Elemental Analysis: $C_{19}H_{19}NO_2$ (293.36): Found C, 77.68; H, 6.45; N, 4.83. Calculated C, 77.79; H, 6.53; N, 4.77 %

N-[1-(4-methylphenyl)-3-oxo-3-phenyl-propyl]acetamide (11)



Nature: White solid

Yield: 92% (0.518 g)

M.p. 112-113 °C

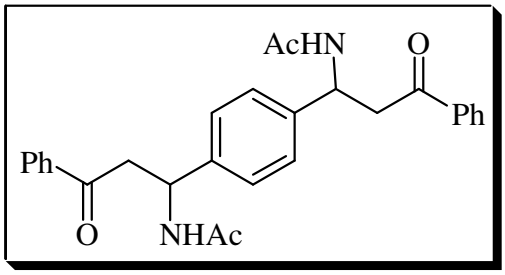
IR: (KBr): 3296, 1681, 1650, 1550, 1350, 1200, 811, 756 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.85 (3H, s), 2.97 (1H, dd, *J* = 6.0 Hz, *J* = 16.8 Hz), 3.29 (1H, dd, *J* = 5.2 Hz, *J* = 17.2 Hz), 5.06 (1H, m), 6.13 (1H, d, *J* = 6.8 Hz), 6.65 (2H, d, *J* = 7.6 Hz), 6.75 (2H, d, *J* = 8.0 Hz), 6.98 (2H, t, *J* = 7.6 Hz), 7.10 (1H, t, *J* = 7.2 Hz), 7.44 (2H, t, *J* = 7.6 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 21.1, 23.6, 43.3, 49.8, 126.3, 128.0, 128.5, 129.2, 133.3, 136.5, 137.0, 137.7, 167.4, 198.3 ppm.

Elemental Analysis: $C_{18}H_{19}NO_2$ (281.35): Found C, 76.73; H, 6.86; N, 5.08. Calculated C, 76.84; H, 6.81; N, 4.98 %

***Bis*- N-(3-oxo-1, 3-diphenyl-propyl)acetamide (12)**



Nature: White solid

Yield: 76 % (0.694 g)

M.p. 215-217 °C

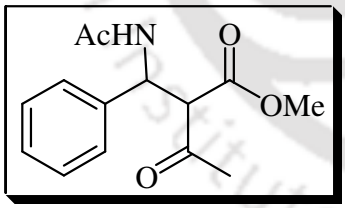
IR (KBr): 3365, 2928, 1690, 1648, 1297, 1199, 815 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.01 (6H, s), 3.43 (2H, dd, *J* = 6.0 Hz, *J* = 17.2 Hz), 3.72 (2H, dd, *J* = 4.8 Hz, *J* = 16.8 Hz), 5.52 (2H, m), 6.63 (2H, d, *J* = 8.8 Hz), 7.27 (4H, d, *J* = 6.0 Hz), 7.44 (4H, t, *J* = 8.0 Hz), 7.56 (2H, t, *J* = 8.0 Hz), 7.89 (4H, d, *J* = 8.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.7, 43.2, 49.8, 125.4, 127.1, 128.3, 128.9, 133.8, 140.4, 169.6, 212.8 ppm.

Elemental Analysis: $C_{28}H_{28}N_2O_4$ (456.53): Found C, 73.75; H, 6.09; N, 6.27. Calculated C, 73.66; H, 6.18; N, 6.14 %

Methyl 2-acetyl-3-acetamido-3-phenylpropionate (13)



Nature: White solid

Yield: 76% (0.400 g)

M.p. 128-130 °C (lit.[13] M.p. 129-131 °C)

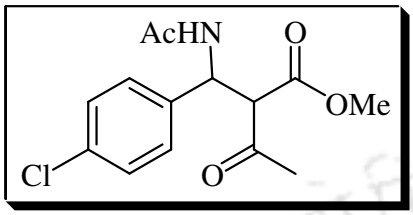
IR (KBr): 3329, 3049, 2961, 1747, 1717, 1643, 1528, 1451, 1371, 1037, 754 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.99 (3H, s), 2.10 (3H, s), 3.69 (3H, s), 4.07 (1H, d, *J* = 5.6 Hz), 5.73 (1H, dd, *J* = 6.0 Hz, *J* = 9.2 Hz), 6.91 (1H, d, *J* = 8.4 Hz), 7.23-7.31 (5H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.5, 31.1, 52.5, 53.0, 62.5, 126.6, 128.0, 128.9, 139.3, 166.1, 169.9, 203.8 ppm.

Elemental Analysis: $C_{14}H_{17}NO_4$ (263.29): Found C, 63.74; H, 6.45; N, 5.43. Calculated C, 63.87; H, 6.51; N, 5.32 %.

Methyl 2-acetyl-3-acetamido-3-(p-chlorophenyl)propionate (14)



Nature: White solid

Yield: 84% (0.500 g)

M.p. 131-133 °C (lit.[11] M.p. 130-132 °C)

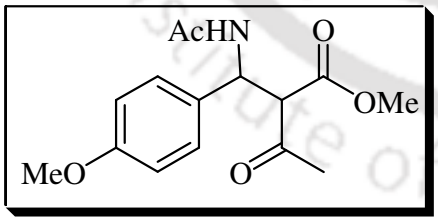
IR (KBr): 3324, 1744, 1714, 1646, 1541, 1486, 1371, 1091, 724 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.99 (3H, s), 2.13 (3H, s), 3.70 (3H, s), 4.04 (1H, d, *J* = 5.6 Hz), 5.68 (1H, dd, *J* = 5.6 Hz, *J* = 9.2 Hz), 6.94 (1H, d, *J* = 8.4 Hz), 7.20 (2H, d, *J* = 8.8 Hz), 7.25 (2H, d, *J* = 8.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.5, 31.0, 52.0, 53.1, 62.4, 128.2, 129.1, 133.9, 138.0, 167.8, 169.9, 203.8 ppm.

Elemental Analysis: $C_{14}H_{16}ClNO_4$ (297.73): Found C, 56.60; H, 5.36; N, 4.82. Calculated C, 56.49; H, 5.42; N, 4.71 %

Methyl 2-acetyl-3-acetamido-3-(p-methoxyphenyl)propionate (15)



Nature: Light yellow solid

Yield: 78% (0.458 g)

M.p. 140-143 °C (lit.[11] M.p. 142-144 °C)

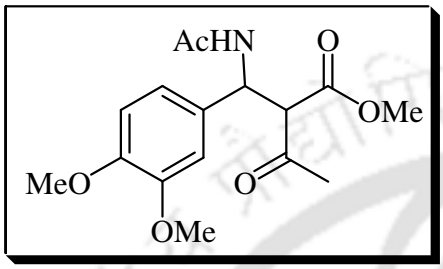
IR (KBr): 3335, 2967, 1739, 1714, 1648, 1602, 1517, 1434, 1369, 1028, 587 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.97 (3H, s), 2.14 (3H, s), 3.68 (3H, s), 3.76 (3H, s), 3.86 (1H, d, *J* = 6.0 Hz), 5.61 (1H, dd, *J* = 6.0 Hz, *J* = 9.2 Hz), 6.81 (2H, d, *J* = 8.0 Hz), 6.98 (1H, d, *J* = 8.4 Hz), 7.18 (2 H, d, *J* = 8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.3, 30.7, 52.8, 55.2, 55.4, 62.7, 127.7, 131.2, 131.7, 131.9, 160.3, 169.5, 187.8 ppm.

Elemental Analysis: $C_{15}H_{19}NO_5$ (293.32): Found C, 61.53; H, 6.48; N, 4.86. Calculated C, 61.42; H, 6.53; N, 4.77 %

Methyl 2-acetyl-3-acetamido-3-(dimethoxyphenyl)propionate (16)



Nature: White solid

Yield: 83% (0.537 g)

M.p. 125-127 °C

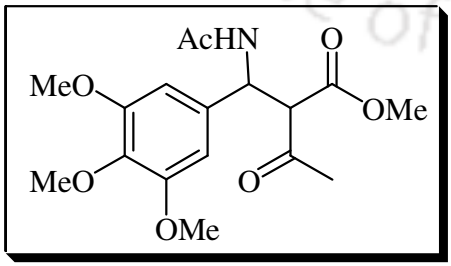
IR (KBr): 3331, 2928, 1745, 1718, 1648, 1542, 1458, 1372, 1023, 546 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.98 (3H, s), 2.15 (3H, s), 3.68 (3H, s), 3.83 (3H, s), 3.85 (3H, s), 4.03 (1H, d, *J* = 6.0 Hz), 5.66 (1H, dd, *J* = 6.4 Hz, *J* = 9.2 Hz), 6.78 (1H, s), 6.79 (2H, d, *J* = 7.6 Hz), 6.84 (1H, d, *J* = 9.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.6, 30.9, 52.4, 53.0, 56.1, 63.0, 110.3, 111.3, 118.8, 131.9, 149.0, 149.2,167.9, 169.7, 204.2 ppm.

Elemental Analysis: $C_{16}H_{21}NO_6$ (323.34): Found C, 59.55; H, 6.49; N, 4.42. Calculated C, 59.43; H, 6.55; N, 4.33 %

Methyl 2-acetyl-3-acetamido-3-(trimethoxyphenyl)propionate (17)



Nature: Brown solid

Yield: 81% (0.573 g)

M.p. 130-133 °C

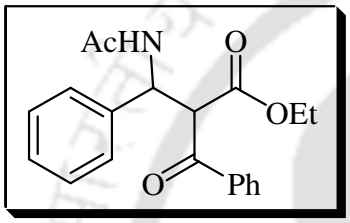
IR (KBr): 3326, 2928, 1747, 1718, 1683, 1651, 1592, 1458, 1339, 1003, 670 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.00 (3H, s), 2.16 (3H, s), 3.69 (3H, s), 3.78 (3H, s), 3.82 (6H, s), 4.01 (1H, d, *J* = 6.0 Hz), 5.64 (1H, dd, *J* = 5.6 Hz, *J* = 8.8 Hz), 6.47 (2H, s), 6.90 (1H, d, *J* = 8.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.5, 31.1, 31.2, 52.9, 53.0, 56.3, 60.9, 62.8, 103.9, 135.1, 153.5, 153.6, 167.9, 169.8, 200.0 ppm.

Elemental Analysis: $C_{17}H_{23}NO_7$ (353.37): Found C, 57.89; H, 6.50; N, 4.09. Calculated C, 57.78; H, 6.56; N, 3.96 %

Ethyl 2-benzoyl-3-acetamido-3-phenylpropionate (18)



Nature: White solid

Yield: 78% (0.530 g)

M.p. 133-134 °C

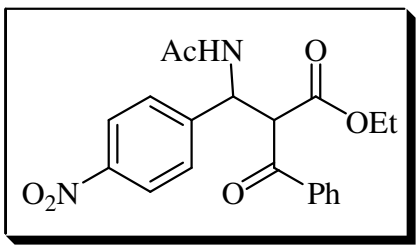
IR (KBr): 3311, 1724, 1691, 1651, 1597, 1352, 1097, 695, 543 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.20 (3H, t, *J* = 7.2 Hz), 2.08 (3H, s), 4.18 (2H, q, *J* = 7.2 Hz), 4.98 (1H, d, *J* = 4.0 Hz), 5.91 (1H, dd, *J* = 4.0 Hz, *J* = 9.2 Hz), 7.15 (1H, t, *J* = 7.2 Hz), 7.22 (3H, m), 7.30 (2H, d, *J* = 7.6 Hz), 7.40 (1H, t, *J* = 7.6 Hz), 7.47 (1H, d, *J* = 9.2 Hz), 7.54 (1H, t, *J* = 8.4 Hz), 7.79 (2H, d, *J* = 8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 31.8, 41.8, 53.0, 53.3, 62.2, 126.6, 127.3, 128.0, 128.8, 129.0, 131.9, 134.2, 139.3, 169.1, 169.9, 196.0 ppm.

Elemental Analysis: $C_{20}H_{21}NO_4$ (339.39): Found C, 70.89; H, 6.29; N, 4.03. Calculated C, 70.78; H, 6.24; N, 4.13 %

Ethyl 2-benzoyl-3-acetamido-3-[4-nitrophenyl]propionate (19)



Nature: Yellow solid

Yield: 84% (0.646 g)

M.p. 159-160 °C

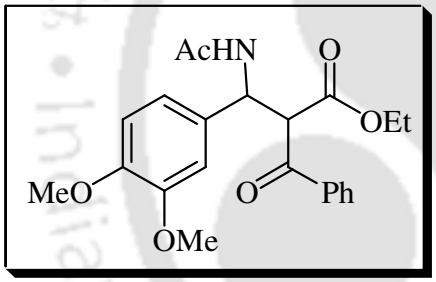
IR (KBr): 3303, 1724, 1688, 1649, 1540, 1521, 1348, 1298, 1173 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.22 (3H, t, *J* = 6.8 Hz), 2.09 (3H, s), 4.18 (2H, q, *J* = 6.8 Hz), 4.98 (1H, d, *J* = 4.4 Hz), 5.97 (1H, dd, *J* = 4.4 Hz, *J* = 9.2 Hz), 7.42 (2H, t, *J* = 7.6 Hz), 7.50 (3H, d, *J* = 8.8 Hz), 7.57 (1H, t, *J* = 7.2 Hz), 7.79 (2H, d, *J* = 7.2 Hz), 8.10 (2H, d, *J* = 8.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 23.5, 52.6, 56.3, 62.7, 124.0, 127.9, 128.5, 129.2, 134.7, 136.2, 147.0, 147.4, 167.3, 170.0, 195.2 ppm.

Elemental Analysis: $C_{20}H_{20}N_2O_6$ (384.39): Found C, 62.38; H, 5.18; N, 7.36. Calculated C, 62.50; H, 5.24; N, 7.29 %

Ethyl 2-benzoyl-3-acetamido-3-[3,4-dimethoxyphenyl]propionate (20)



Nature: White solid

Yield: 83% (0.663 g)

M.p. 127-128 °C

IR (KBr): 3305, 2932, 1730, 1685, 1649, 1592, 1544, 1456, 1256, 1130 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$):1.85 (3H, t, *J* = 7.2 Hz), 2.04 (3H, s), 3.77 (3H, s), 3.78 (3H, s), 4.15 (2H, q, *J* = 7.2 Hz), 4.95 (1H, d, *J* = 4.0 Hz), 5.80 (1H, dd, *J* = 4.0 Hz, *J* = 9.2 Hz), 6.71 (1H, d, *J* = 7.6 Hz), 6.82 (2H, d, *J* = 7.2 Hz), 7.39-7.44 (3H, m), 7.55 (1H, t, *J* = 7.2 Hz), 7.80 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$):14.0, 23.5, 52.8, 55.9, 56.8, 62.1, 110.3, 111.1, 119.0, 128.4, 128.9, 132.0, 134.7, 136.7, 148.4, 148.8, 167.6, 169.7, 195.8 ppm.

Elemental Analysis: $C_{22}H_{25}NO_6$ (399.44): Found C, 66.26; H, 6.26; N, 3.57. Calculated C, 66.15; H, 6.31; N, 3.51 %

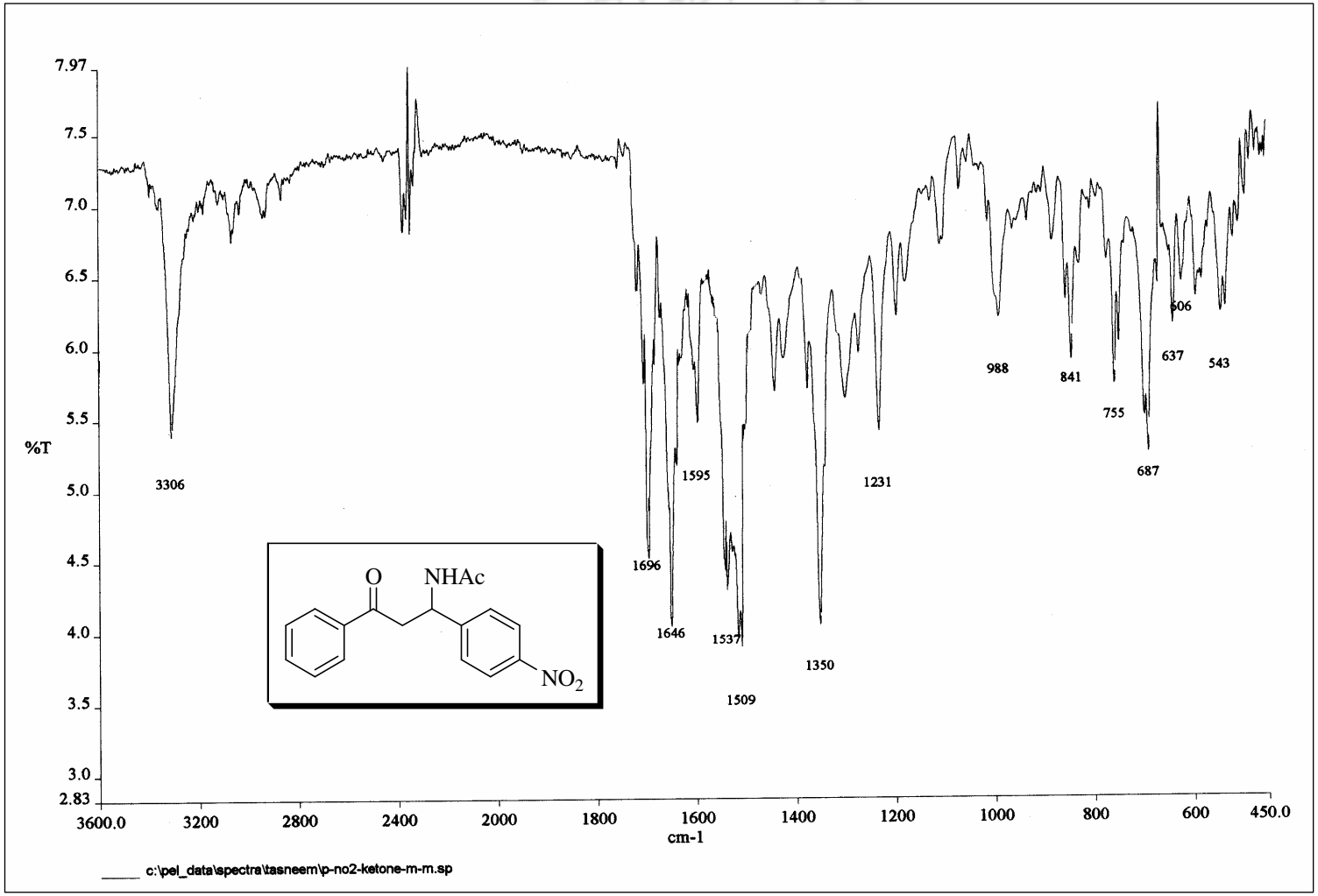


Figure 1: IR spectrum of N-[1-(4-Nitrophenyl)-3-oxo-3-phenyl-propyl]acetamide (9)

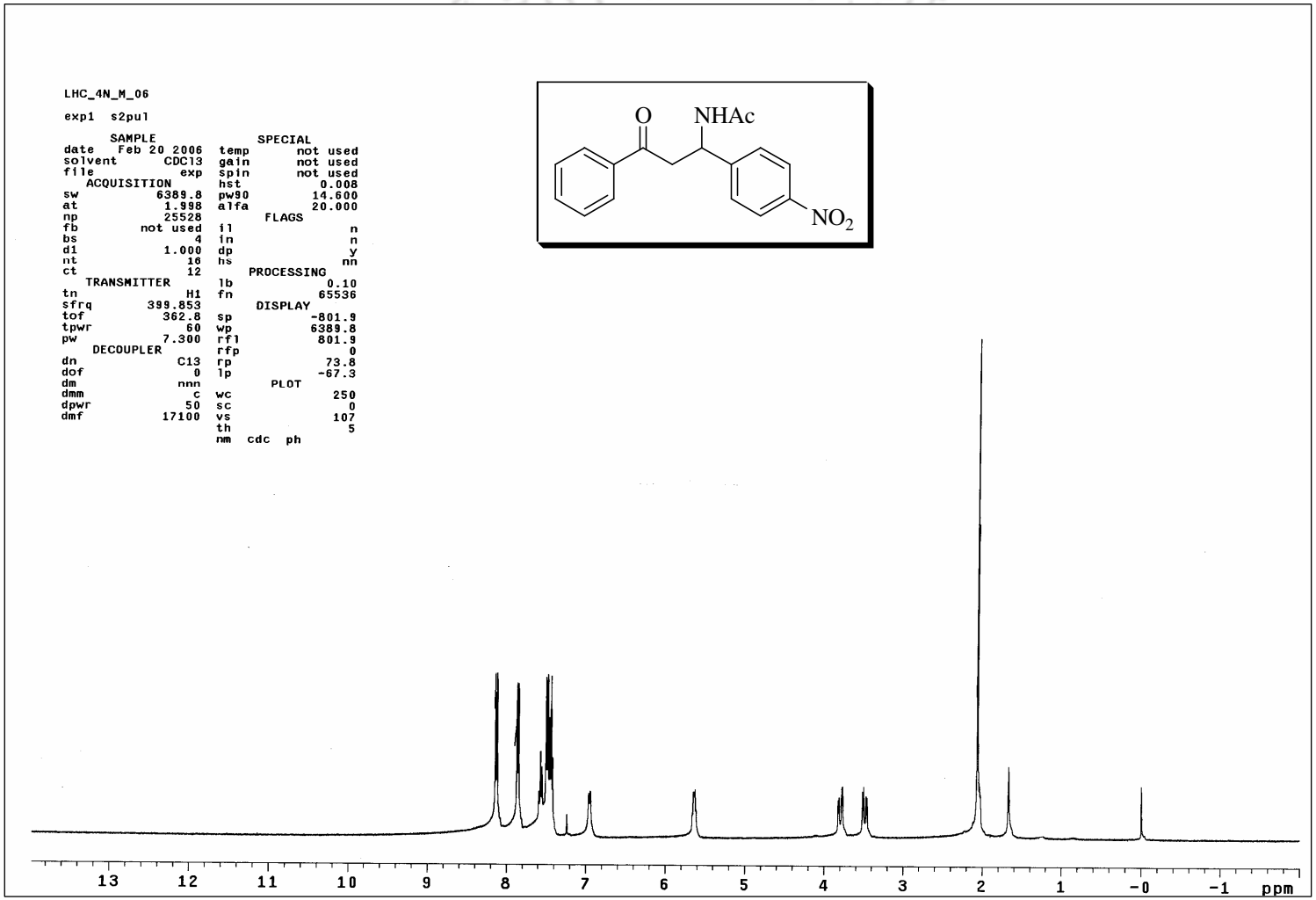


Figure 2: ^{1}H NMR spectrum of N-[1-(4-Nitrophenyl)-3-oxo-3-phenyl-propyl]acetamide (9)

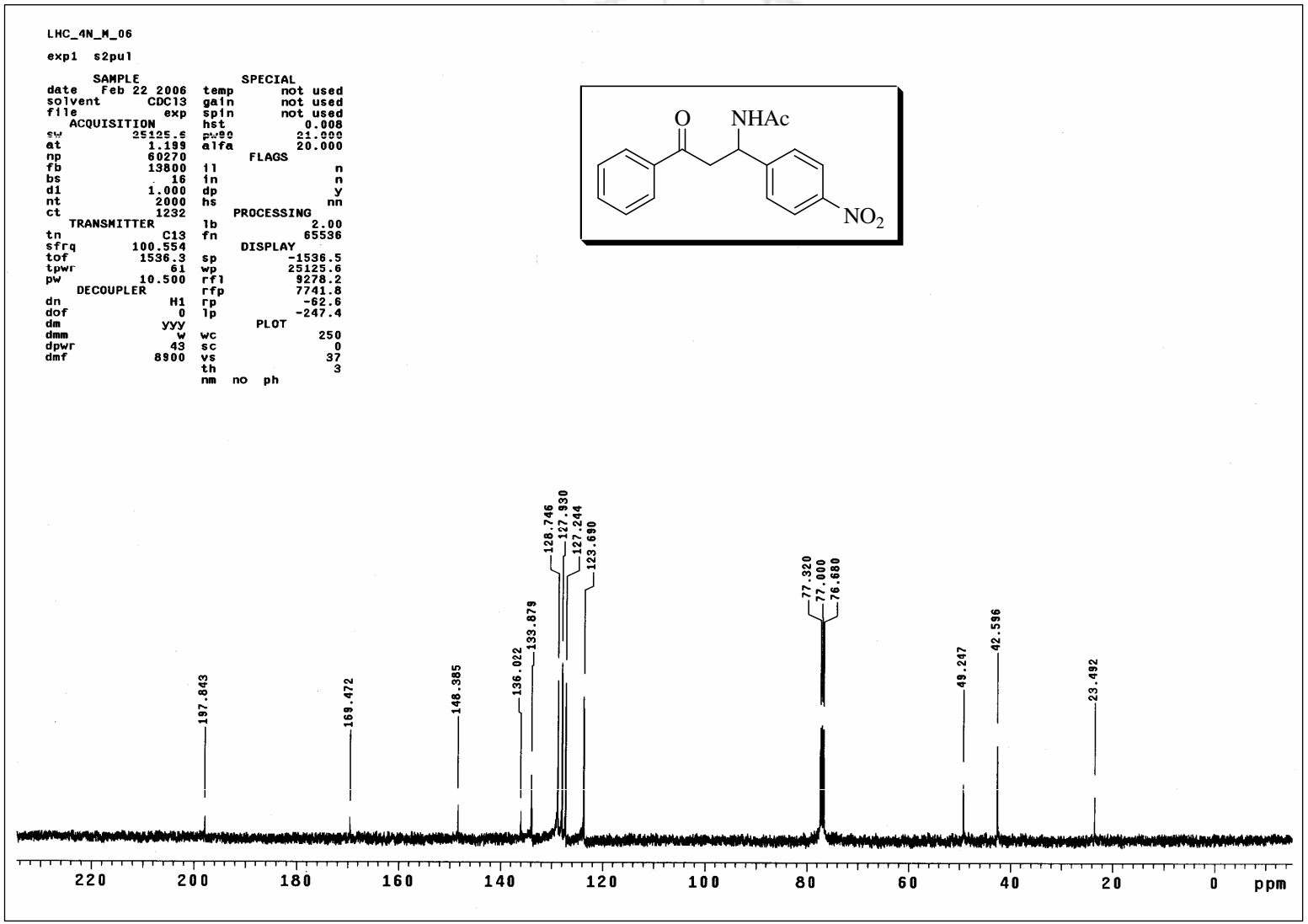


Figure 3: ^{13}C NMR spectrum of N-[1-(4-Nitrophenyl)-3-oxo-3-phenyl-propyl]acetamide (9)

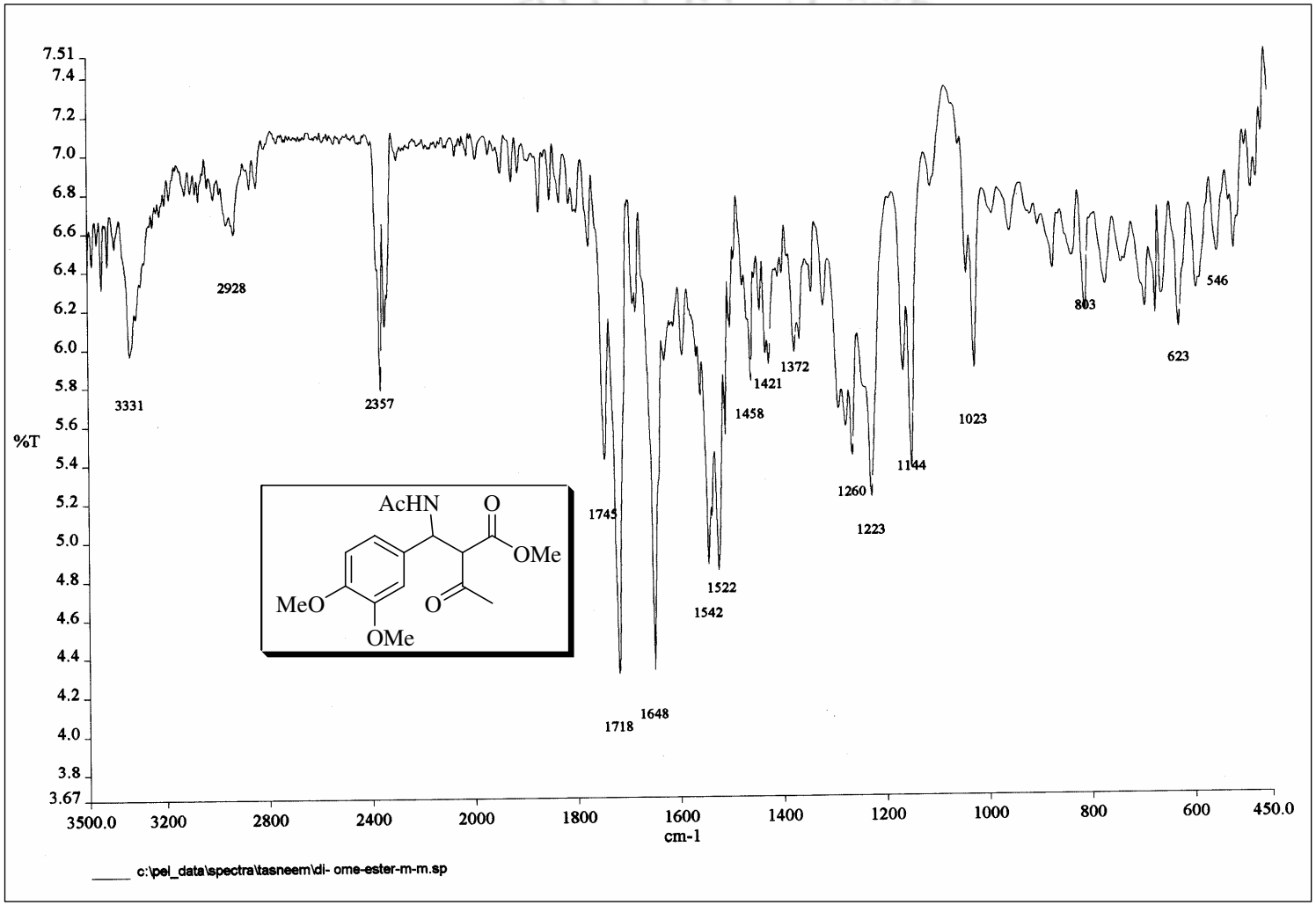


Figure 4: IR spectrum of Methyl 2-acetyl-3-acetamido-3-(dimethoxyphenyl)propionate (16)

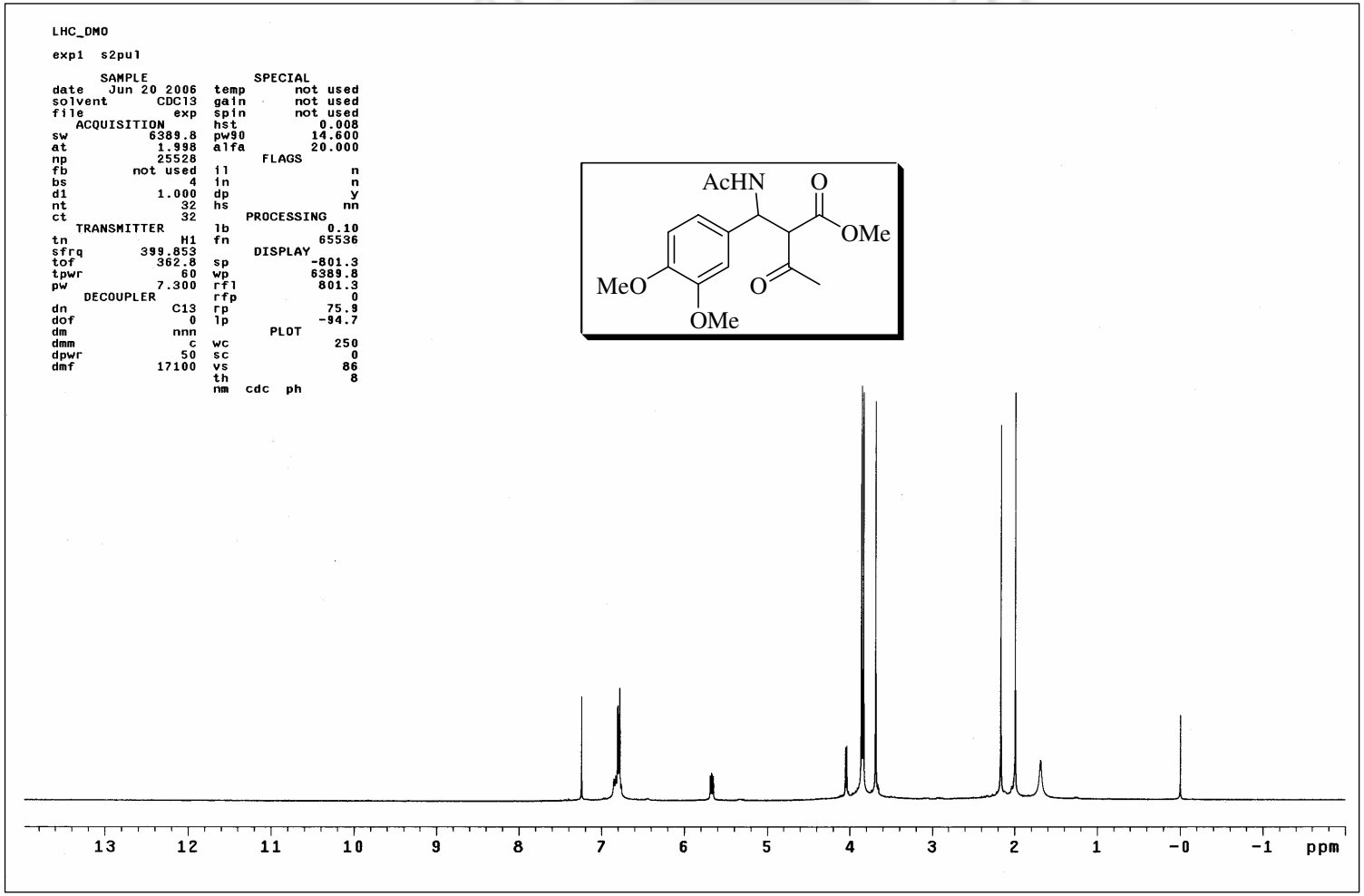


Figure 5: ^{1}H NMR spectrum of Methyl 2-acetyl-3-acetamido-3-(dimethoxyphenyl)propionate (16)

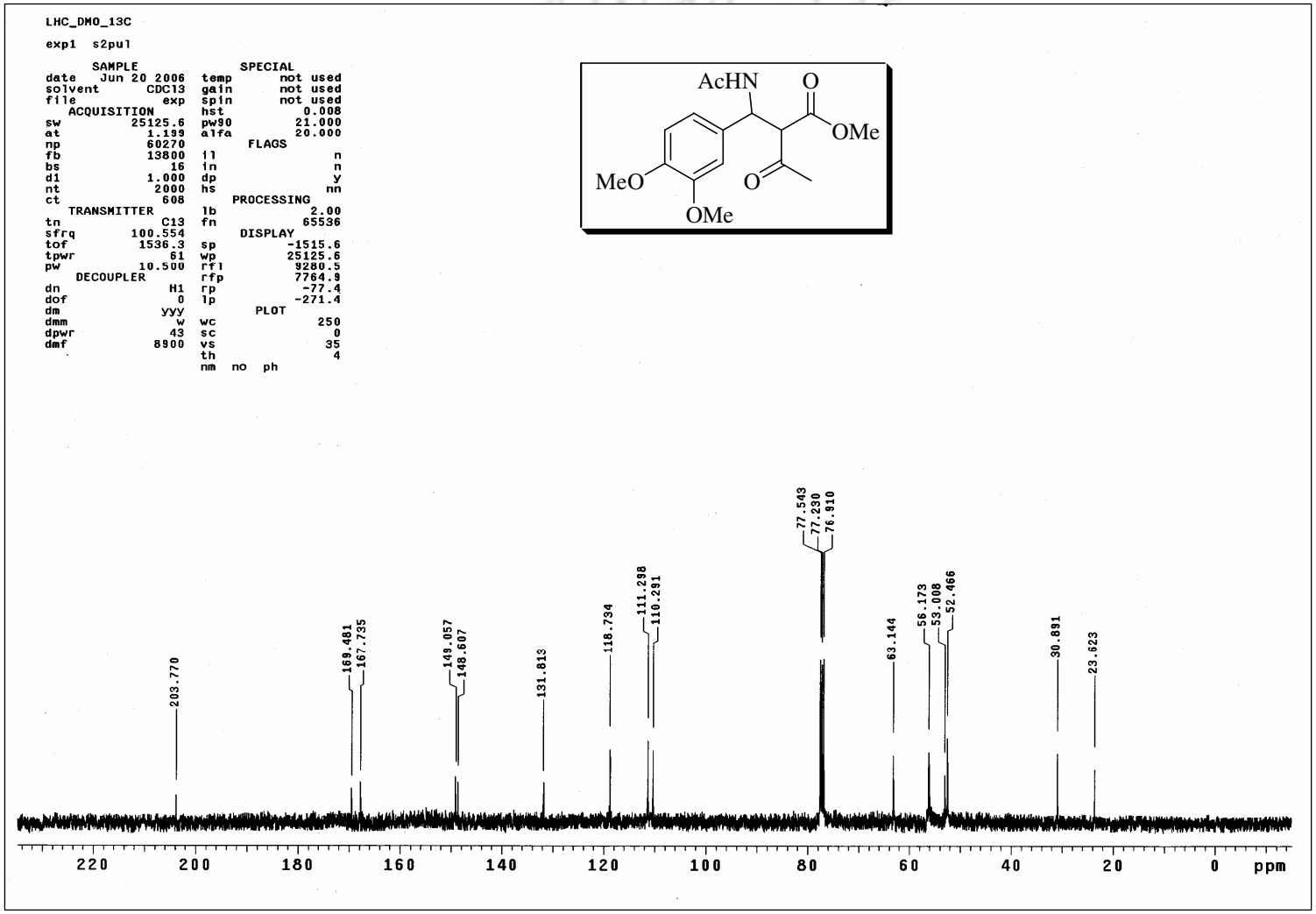


Figure 6: ^{13}C NMR spectrum of Methyl 2-acetyl-3-acetamido-3-(dimethoxyphenyl)propionate (16)

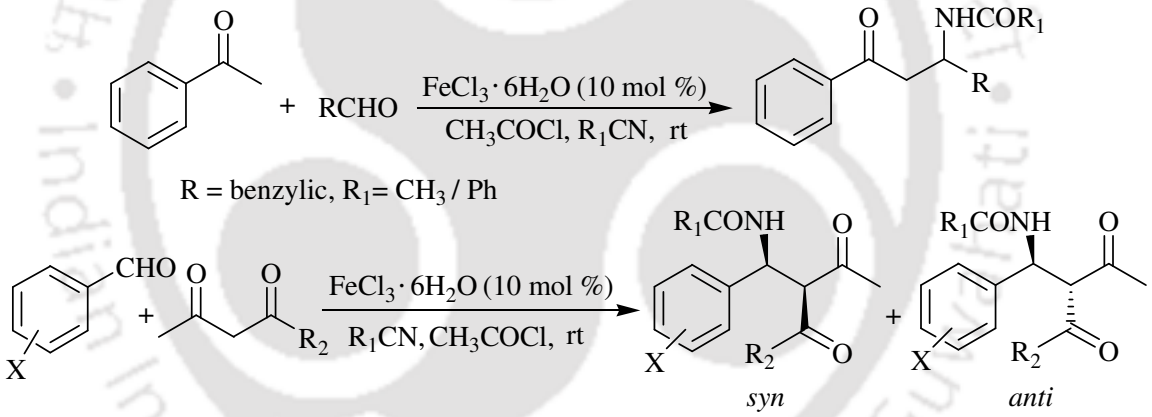
SECTION B

Synthesis of β-acetamido carbonyl compounds using $FeCl_3 \cdot 6H_2O$ as catalyst

RESULTS AND DISCUSSION

2.3.1 Results and discussion:

We have successfully demonstrated that $CeCl_3 \cdot 7H_2O$ is an effective catalyst for facile preparation of β-acetamido carbonyl compounds in the previous section of this chapter. After that we were looking for an alternative method using a cheaper and readily available transition metal catalyst for similar transformation. In addition, we were interested to study the mechanism of this reaction. We found from the literature that $FeCl_3 \cdot 6H_2O$ is an effective catalyst in organic synthesis. Therefore, we wanted to explore the catalytic activity of this Fe (III) salt for the preparation of β-acetamido carbonyl compounds using four-component reaction. In this section, we will discuss a mild and efficient protocol for the preparation of β-acetamido carbonyl compounds by four-component reaction of aromatic aldehyde, acetonitrile, enolizable ketone or β-keto ester and acetyl chloride catalyzed by $FeCl_3 \cdot 6H_2O$ at room temperature (Scheme 4).

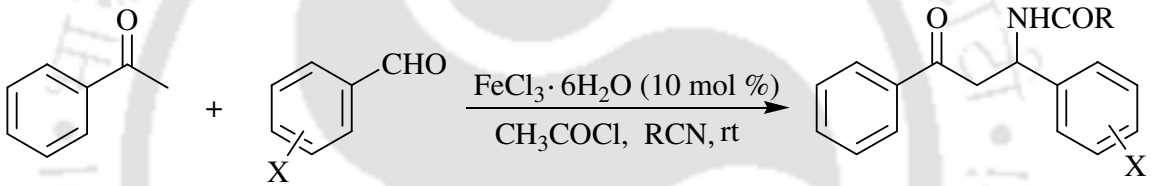


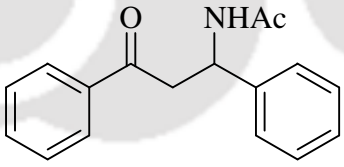
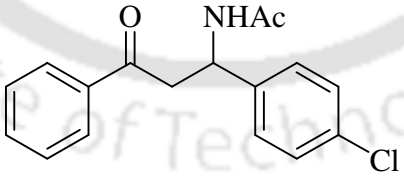
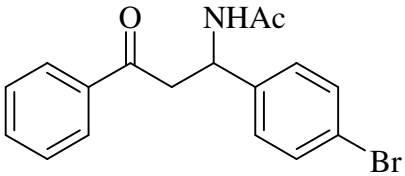
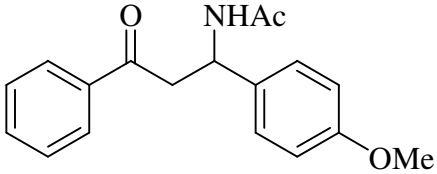
Scheme 4

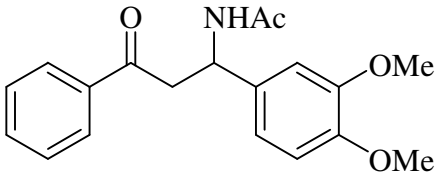
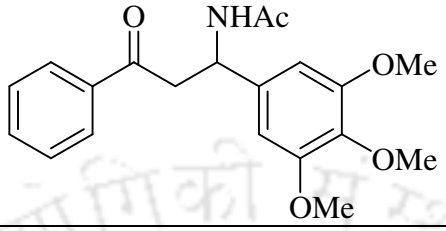
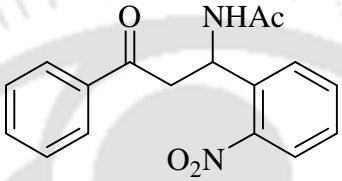
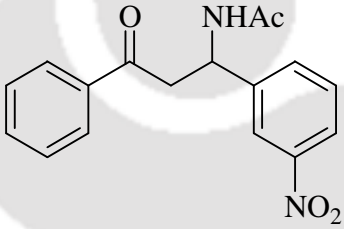
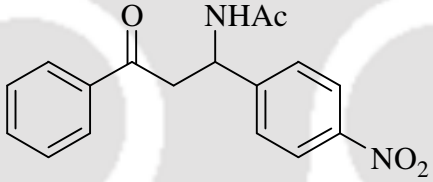
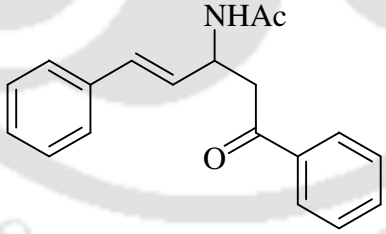
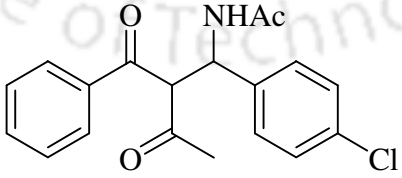
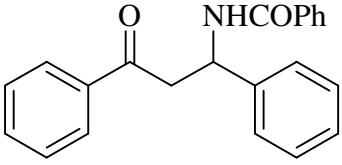
For the preliminary study, 4-chlorobenzaldehyde (2 mmol) and acetophenone (2 mmol) in acetonitrile (5 mL) was stirred in the presence of a catalytic amount of $FeCl_3 \cdot 6H_2O$ (10 mol%) and acetyl chloride (3 mmol) at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, it was poured into a beaker containing crushed ice to solidify the product. On solidification of the product, it was filtered off and dried to obtain the corresponding β-acetamido ketone. The solid product was recrystallized from ethyl acetate and hexane, and fully characterized by recording IR, ^1H NMR, ^{13}C NMR and elemental analysis. Encouraged by this result, a wide variety of aromatic aldehydes, containing both electron withdrawing and donating substituents, were treated under the same experimental conditions and afforded the corresponding β-

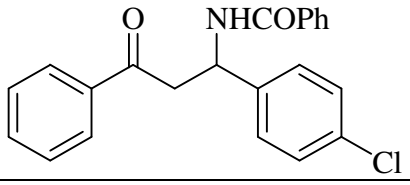
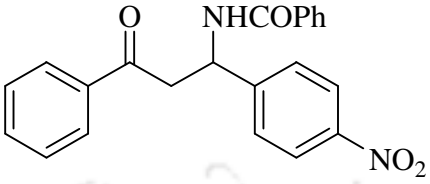
acetamido ketones (**2-9**) in good to excellent yields. Similarly, α,β-unsaturated aldehydes such as cinnamaldehyde also reacts under the same experimental conditions and provided the desired product (**10**) without any difficulty. A 1,3-diketone, namely benzoylacetone, was treated under the same experimental conditions to provide β-acetamido diketones (**21**) with poor diastereoselectivity. Next, we wanted to study whether the reaction will be successful if the source of nitrogen can be replaced, i.e. actonitrile by other nitrile such as benzonitrile. Interestingly, a variety of aldehydes were transformed to their corresponding β-benzamido ketones (**22-24**) in excellent yields under the similar experimental conditions. This clearly demonstrates that in this reaction, the alkyl/aryl nitrile acts as a nucleophile.

Table 5. $FeCl_3 \cdot 6H_2O$ catalyzed multicomponent reaction for the preparation of β-acetamido/ benzamido Ketones



Product No.	β-acetamido ketones[a]	Time/h	Yield[b] (%)
1		8	88
2		5	99
3		5	98
4		7	94

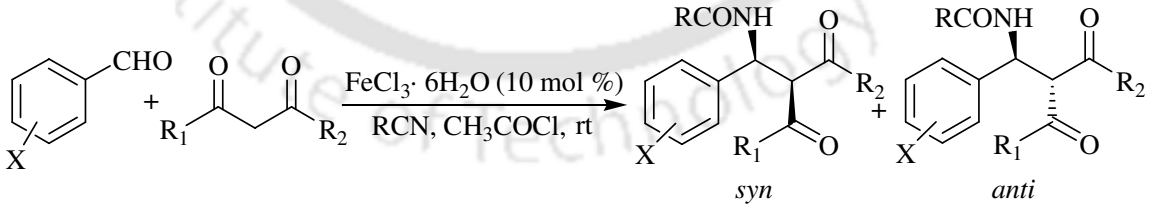
5		5	98
6		6	96
7		12	90
8		10	96
9		11	95
10		6	85
21		12	83
22		9	97

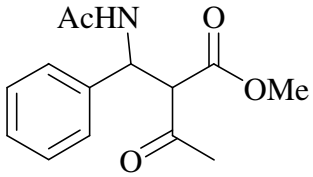
23		8	96
24		12	92

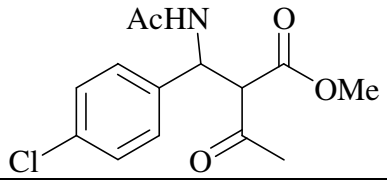
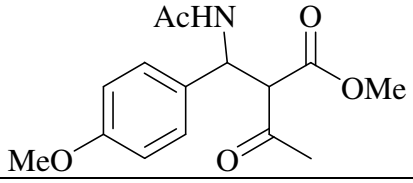
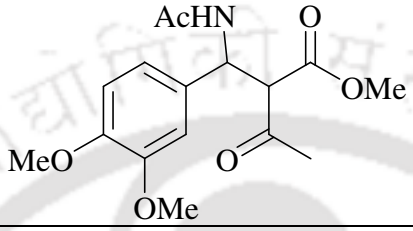
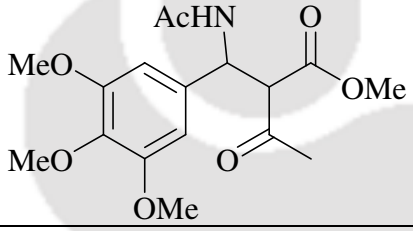
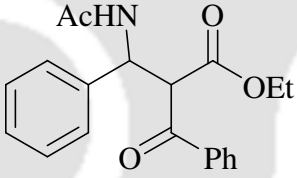
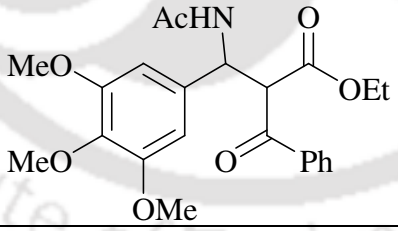
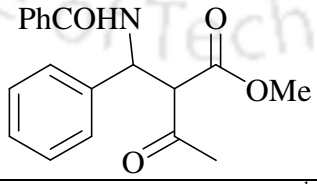
[a]All the products were fully characterized by usual spectroscopic techniques. [b]Yields were calculated just after aq. work-up.

To extend the preparative utility and generality of this multicomponent reaction, a variety of aromatic aldehydes were treated with methyl acetoacetate or ethyl benzoylacetate under the same experimental conditions, and the corresponding β-acetamido keto esters (**13-18** and **25**) were obtained in good yields with moderate to good diastereoselectivities. These β-acetamido keto esters are useful precursor for the synthesis of β-aryl homoisothreonine derivatives, which can be used for the preparation of dipeptide isoesters by incorporation with an amino acid residue. Next, metylacetoacetate, benzaldehyde and acetyl chloride were treated with benzonitrile under the similar reaction condition to afford the corresponding β-benzamido keto ester (**26**). The ratio of *syn*:*anti* diastereomers were determined from the ^{1}H NMR spectrum of the crude reaction mixture. The ratio of diastereomers differed with substitution on the aromatic ring.

Table 6. $FeCl_3 \cdot 6H_2O$ catalyzed multicomponent reaction for the preparation of β-acetamido keto esters.



Product No	Product	% Yield[a]	*Syn: anti*[b]
13		81	26:74

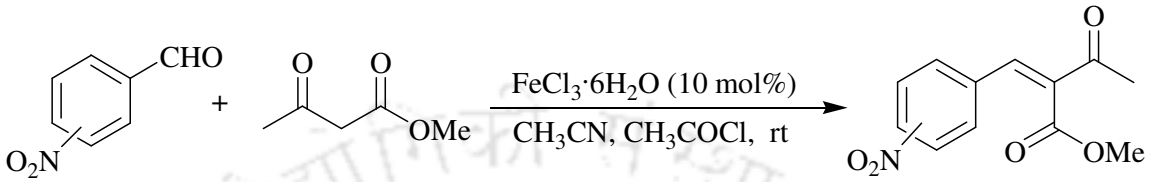
14		80	27:73
15		82	46:54
16		86	5:95
17		84	25:75
18		78	98:2
25		80	95:5
26		85	71: 29

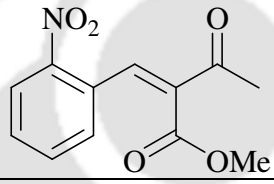
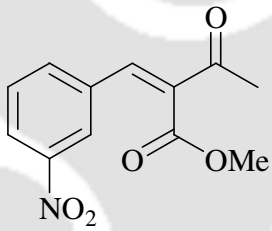
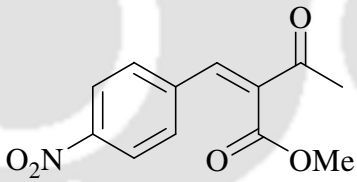
[a]Yields were calculated without further purification. [b]The *syn : anti* ratio was determined from ^{1}H NMR spectrum of crude reaction mixture.

Interestingly, during the course of our study we have observed that when the aldehyde contains a nitro group either at the ortho, meta or para positions, and is treated with a β-keto ester under similar experimental conditions, it gives only the Knoevenagel

condensation product (**27-29**) instead of our expected β-acetamido keto ester. All these products were fully characterized by recording IR, ^{1}H NMR, ^{13}C NMR and elemental analysis.

Table 7. $FeCl_3 \cdot 6H_2O$ catalyzed Knoevenagel products for nitro benzaldehydes along with trace multicomponent products.



Product No.	Product[a]	%Yield[b]
27		81
28		80
29		82

[a] All the products were characterized by usual spectroscopic analysis. [b]Isolated yield.

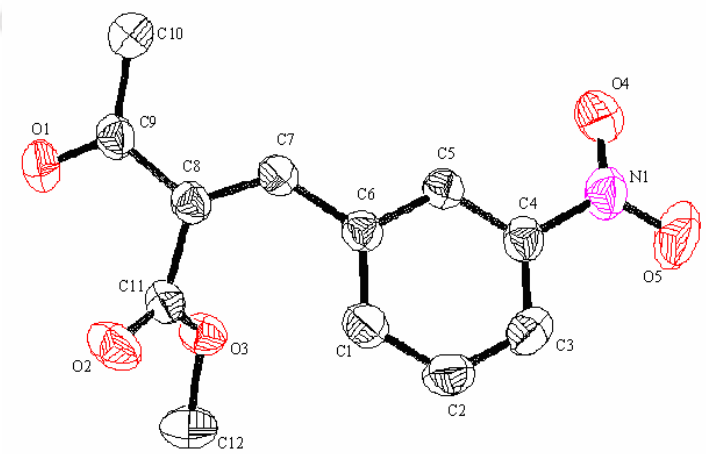
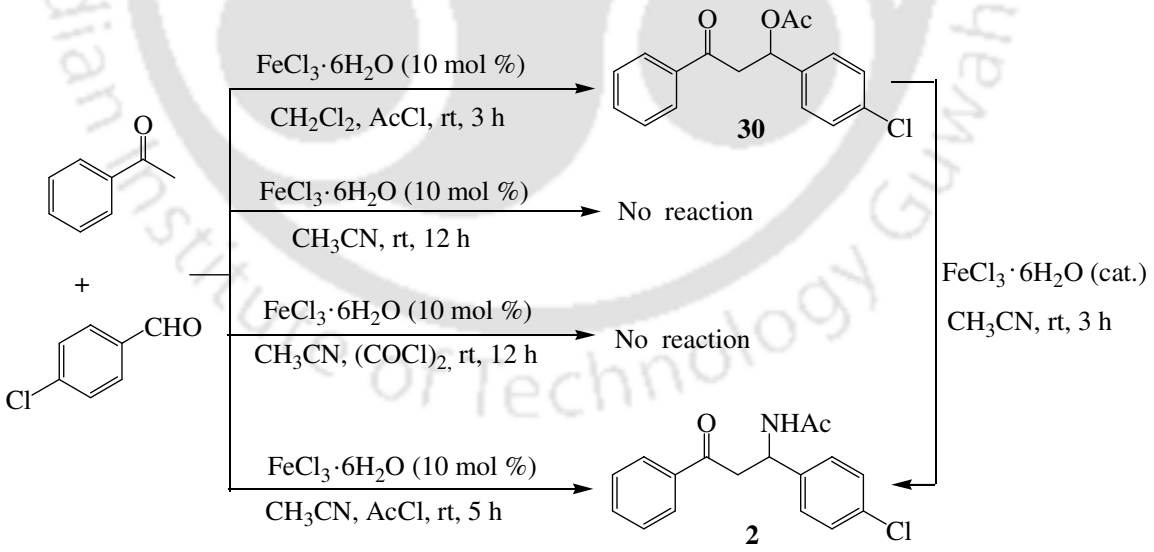


Figure 7: X-ray structure of compound **28**

To further confirm the formation of these alkenes and to know the geometry of the substiuents on the double bond, the product **28** was recrystallized from ethyl acetate/hexane and a single crystal XRD was recorded. It shows the (*Z*)-configuration of the alkene as depicted in Figure 7.

Although the exact explanation of this anomaly is yet to be determined, we assumed that due to electronic effects i.e. electron withdrawing nature of the nitro group, it provides the Knoevenagel condensation alkenes.

Next, we turned our attention to study the mechanistic aspect of this multicomponent reaction. Thus, the reaction of 4-chlorobenzaldehyde with acetophenone was chosen as a model reaction for this study. In the absence of acetyl chloride, the reaction failed to provide the desired product, which clearly indicates that it plays a vital role in this reaction, although not directly involved in the final product. Then the same reaction was tried using oxalyl chloride, instead of acetyl chloride, and the reaction was also unsuccessful. From this observation, it is clear that the chloride ion does not have any role in the above transformation. Similarly, the same reaction was carried out in absence of acetonitrile using dichloromethane as a solvent, and the corresponding β-acetoxy ketone (**30**) was obtained in 60% yields after 3h of stirring at room temperature.

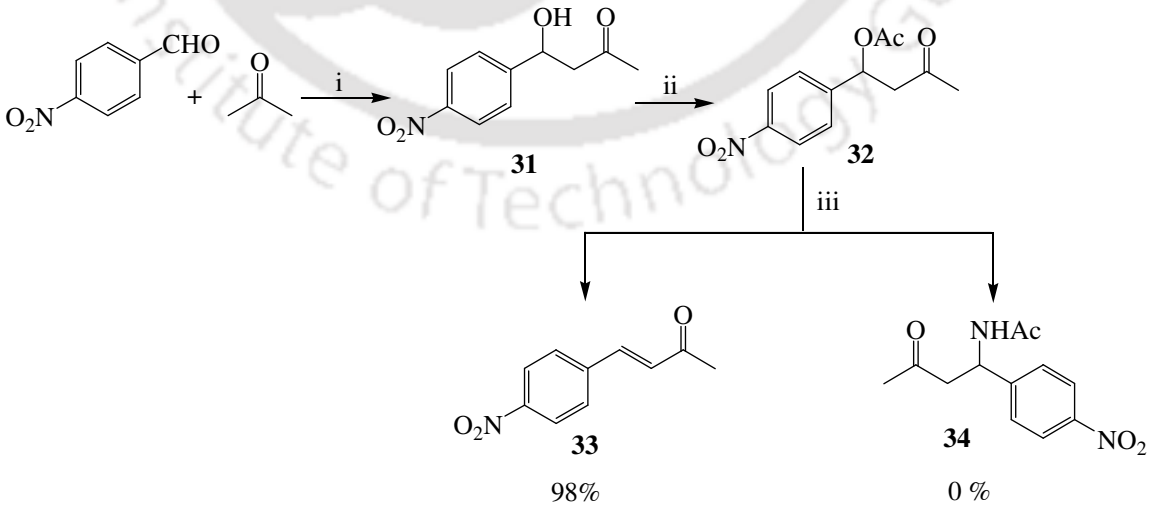


Scheme 5

Consequently, this β-acetoxy ketone as shown in Scheme 5 was once again treated with 10 mol% of the catalyst in acetonitrile as solvent, and the corresponding β-acetamido ketone (**2**) was obtained in 80% yield under the same experimental conditions. This clearly demonstrates the working hypothesis that the reaction goes *via* an aldol reaction

followed by acetylation and subsequent nucleophilic displacement by the alkyl/aryl nitrile to get the desired product as shown in Scheme 7.

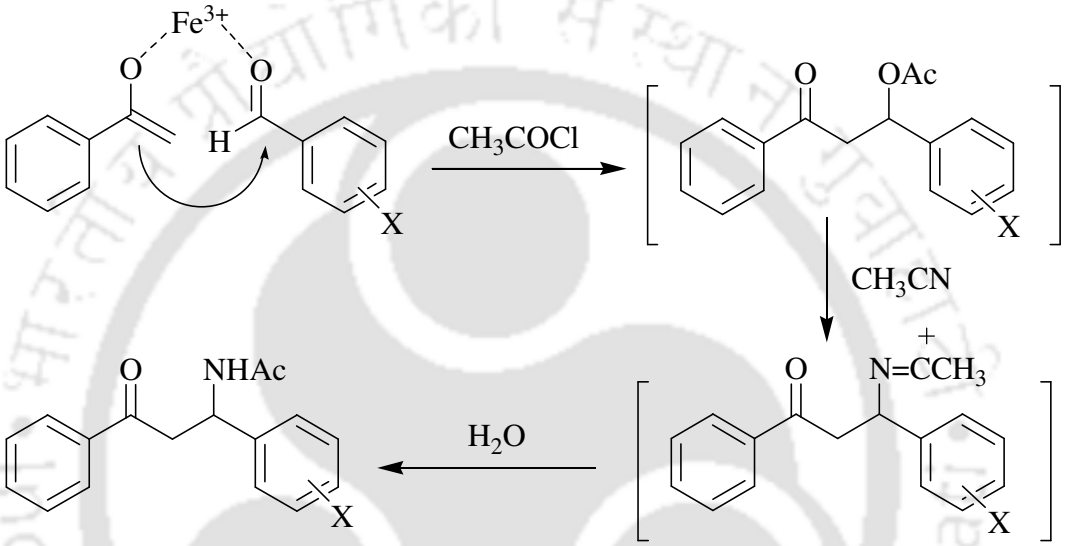
Next, the aldol product **31** was prepared following a literature procedure using proline as an organo catalyst,[30] and acetylated by our self developed BDMS method[31] to get the product **32.** Subsequently, the compound **32** was treated separately with acetonitrile under the same experimental conditions using 10 mol% $FeCl_3 \cdot 6H_2O$ as catalyst. Interestingly, after 12 h of stirring, α, β-unsaturated ketone **33** was isolated in 98% yield instead of the desired β-acetamido ketone **34** as shown in Scheme 6. Similarly, in Table 7 we have noted that nitro substituted aldehydes react with methylacetoacetate and provide the Knoevenagel condensation products under the experimental conditions. These studies lead us to the conclusion that when aliphatic ketones or keto esters react with nitro substituted aldehydes, the intermediate acetylated aldol products (e.g. **32)** prefer α-H elimination to provide α,β-unsaturated ketones to the formation of desired acetamido ketone by nucleophilic substitution by alkyl or aryl nitrile. This may be attributed to the electronic effect i.e. the electron withdrawing nature of the substituent as well as, the stability of the elimination products. Later, the Knovenagel product **28** was treated further with acetonitrile and acetyl chloride in the presence of 10 mol % catalyst and kept stirring. No detectable amount of the desired β-acetamido keto ester was found, even after stirring for 12 h. Thus it is clear that these unsaturated ketones are more stable compared to the corresponding β-acetamido ketones.



Reagents: (i) proline (20 mol%), H_2O, (ii) BDMS (5 mol%), Ac_2O (iii) $FeCl_3.6H_2O$ (10 mol%), CH_3CN, CH_3COCl.

Scheme 6

Next, to exemplify that acetyl chloride is not incorporated in the final product and acetonitrile itself is the N-donor and nucleophile (i.e. it follows the Ritter reaction pathway), we tried the reaction of 4-chlorobenzaldeyde under similar experimental conditions using benzonitrile (1.5 equivalent) instead of acetonitrile. The formation of the benzamide (**98**) clearly indicates that in this reaction nitrile acts not only as solvent but also as a nitrogen donor. Therefore, the most probable mechanism for this reaction is illustrated in Scheme 7.



Scheme 7: Probable mechanism of Fe (III) chloride catalyzed multicomponent reactions for the preparation of β-acetamido carbonyl compounds.

In summary, we have devised a new synthetic methodology using $FeCl_3 \cdot 6H_2O$, a cheap, readily available and efficient catalyst for the one pot synthesis of β-acetamido carbonyl compounds. In the case of nitro aldehydes, the reaction with methyl acetoacetate provides α,β-unsaturated ketones instead of the expected β-acetamido carbonyl compounds. The simplicity of the present protocol, high yields and efficiency of the catalyst are the key features of this present protocol. Due to the low cost and ready availability of the reagent $FeCl_3.6H_2O$, we prefer this protocol than our earlier reported method. In addition, we have presented a thorough study on the mechanistic aspect of this multi-component reaction in this discussion. Thus the present method will be useful for the facile preparation of β-acetamido ketones and keto esters.

SECTION B

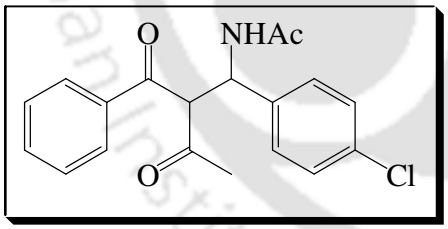
Synthesis of β-acetamido carbonyl compounds using $FeCl_3 \cdot 6H_2O$ as catalyst

EXPERIMENTAL

2.3.2 General procedure for the preparation of β-acetamido/benzamido ketones or keto esters:

To a stirred solution of aldehyde (2 mmol) and acetophenone /methyl acetoacetate (2 mmol) in acetonitrile (3 mL) or benzonitrile (3 mmol) was added acetyl chloride (3 mmol) and $FeCl_3 \cdot 6H_2O$ (0.2 mmol) and the reaction stirred at room temperature. The progress of the reaction was monitored by TLC, and after completion of the reaction, crushed (50 ml) ice was added to the reaction mixture and stirred thoroughly. On solidification, the products were filtered off and dried to get the corresponding β-acetamido ketones. For all the substrates of Table 6, the reactions were stirred for 12 h, then 50 mL of water was added. The mixture was extracted with ethyl acetate (3 x 20 mL), washed with water (3 x 20 mL), dried over Na_2SO_4 and the solvent was removed using a rotary evaporator. The crude mixture was recrystallized from ethyl acetate/hexane and solid product (mixture of diastereomers) was isolated. The solid products were recrystalized from the mixture of solvents (hexane/ ethylacetate) and fully characterized by recording IR, NMR and elemental analysis. The spectral details of the compounds **1-20** have already mentioned in the previous experimental section.

N-[1-(4-Chlorophenyl)-2-acetyl-3-oxo-3-phenyl-propyl]acetamide (21)



Nature: White solid

Yield: 83% (0.571 g)

M.p. 172-174 °C

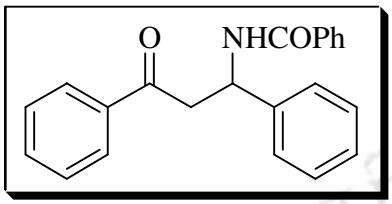
IR (KBr): 3301, 1704, 1688, 1648, 1527, 1370, 1087 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.95 (3H, s), 2.13 (3H, s), 5.05 (1H, d, *J* = 7.6 Hz), 5.85 (1H, t, *J* = 8.4Hz), 6.57 (1H, d, *J* = 8.4 Hz), 7.23 (4H, d, *J* = 6.4 Hz), 7.47 (2H, t, *J* = 7.2 Hz), 7.59 (1H, t, *J* = 8.8 Hz), 7.73 (1H, d, *J* = 8.0 Hz), 7.90 (1H, d, *J* = 8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.5, 29.2, 52.4, 66.7, 128.5, 128.8, 129.2, 129.3, 133.9, 134.5, 135.9, 138.5, 169.8, 193.8, 204.0 ppm.

Elemental Analysis: $C_{19}H_{18}NClO_3$ (343.80): Found C, 66.49; H, 5.21; N, 4.18. Calculated C, 66.38; H, 5.28; N, 4.07 %

N-(3-Oxo-1,3-diphenyl-propyl)benzamide (22)



Nature: Yellowish solid

Yield: 97% (0.639 g)

M.p. 153-154 °C

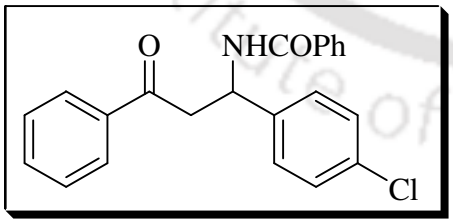
IR (KBr): 3306, 3062, 1681, 1634, 1599, 1488, 1357, 981, 754 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 3.52 (1H, dd, *J* = 6.0 Hz, *J* = 16.4 Hz), 3.87 (1H, dd, *J* = 4.8 Hz, *J* = 16.8 Hz), 5.73-5.78 (1H, m), 7.22 (1H, t, *J* = 7.2 Hz), 7.30 (2H, t, *J* = 7.6 Hz) 7.37 - 7.45 (5H, m), 7.49 (2H, t, *J* = 7.2 Hz), 7.55 (1H, t, *J* = 7.2 Hz), 7.60 (1H, d, *J* = 8.0 Hz), 7.82 (2H, d, *J* = 8.0 Hz), 7.90 (2H, d, *J* = 8.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 43.1, 50.4, 126.6, 127.2, 127.6, 128.3, 128.7, 128.8, 128.9, 131.8, 133.8, 134.4, 136.7, 141.1, 166.9,199.3 ppm.

Elemental Analysis: $C_{22}H_{19}NO_2$ (329.39): Found C, 80.33; H, 5.76; N, 4.31.Calculated C, 80.22; H, 5.81; N, 4.25 %

N-[1-(4-Chlorophenyl)-3-oxo-3-phenyl-propyl]benzamide (23)



Nature: Yellow solid

Yield: 96% (0.699 g)

M.p. 180-182 °C

IR (KBr): 3276, 2928, 2372, 1683, 1641, 1542, 1490, 1362, 1087, 689 cm^{-1}

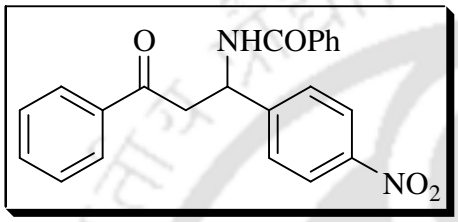
^{1}H NMR (400 MHz, $CDCl_3$): 3.52 (1H, dd, *J* = 5.6, *J* = 17.2 Hz), 3.86 (1H, dd, *J* = 4.8 Hz, *J* = 17.6 Hz), 5.71-5.75 (1H, m), 7.28 (2H, d, *J* = 8.4 Hz), 7.35 (2H, d, *J* = 8.4 Hz)

7.44-7.49 (5H, m), 7.59 (1H, t, *J* = 7.2 Hz), 7.69 (1H, d, *J* = 8.0 Hz) 7.84 (2H, d, *J* = 7.6 Hz), 7.91 (2H, d, *J* = 8.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 42.6, 49.6, 127.0, 127.9, 128.1, 128.6, 128.8, 131.7, 133.1, 133.8. 136.4, 139.5, 166.7, 198.9 ppm.

Elemental Analysis: $C_{22}H_{18}ClNO_2$ (363.84): Found C, 72.74; H, 4.93; N, 3.93 Calculated C, 72.63; H, 4.99; N, 3.85 %

N-[1-(4-Nitrophenyl)-3-oxo-3-phenyl-propyl]benzamide (24)



Nature: Yellow solid

Yield: 92% (0.689 g)

M.p. 142-144 °C

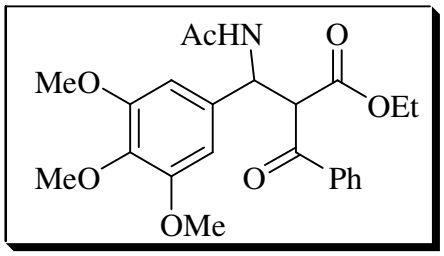
IR (KBr): 3313, 3060, 2934, 1684, 1626, 1517, 1399, 1111, 688 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 3.57 (1H, dd, *J* = 4.4 Hz, *J* = 18.0 Hz), 3.90 (1H, dd, *J* = 4.4 Hz, *J* = 16.8 Hz), 5.82-5.86 (1H, m), 7.46 (4H, t, *J* = 7.6 Hz), 7.52 (1H, d, *J* = 6.8 Hz), 7.58 (4H, t, *J* = 8.4 Hz), 7.84 (2H, d, *J* = 7.6 Hz), 7.89 (2H, d, *J* = 7.6 Hz), 8.16 (2H, d, *J* = 8.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 42.7, 49.9, 124.1, 127.3, 127.7, 128.4, 128.9, 129.1, 132.2, 133.8,134.3, 136.4, 147.2, 148.8, 167.0, 198.0 ppm.

Elemental Analysis: $C_{22}H_{18}N_2O_4$ (374.39): Found C, 70.69; H, 4.80; N, 7.39. Calculated C, 70.58; H, 4.85; N, 7.48 %

Ethyl 2-benzoyl-3-acetamido-3-(trimethoxyphenyl)propionate (25)



Nature: white solid

Yield: 80% (0.687 g)

M.p. 150-152 °C

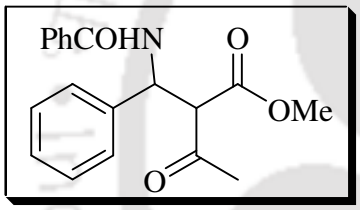
IR (KBr): 3306, 2931, 1729, 1686, 1648, 1592, 1456, 1370, 1001, 733 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.21 (3H, t, *J* = 7.2 Hz), 2.07 (3H, s), 3.74 (3H, s), 3.75 (6H, s), 4.17 (2H, q, *J* = 7.2 Hz), 4.93 (1H, d, *J* = 4.0 Hz), 5.80 (1H, dd, *J* = 4.0 Hz, *J* = 8.8 Hz), 6.49 (2H, s), 7.41 (2H, t, *J* = 8.0 Hz), 7.50 (1H, d, *J* = 8.8 Hz), 7.55 (1H, t, *J* = 7.2 Hz), 7.77 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 23.6, 53.5, 56.3, 56.6, 60.9, 62.4, 104.3, 128.5, 129.1, 134.3, 135.4, 153.4, 167.0, 168.1, 199.5 ppm.

Elemental Analysis: $C_{23}H_{27}NO_7$ (429.46): Found C, 64.21; H, 6.39; N, 3.15. Calculated C, 64.32; H, 6.34; N, 3.26 %

Methyl 2-acetyl-3-benzamido-3-phenylpropionate (26)



Nature: Light yellow solid

Yield: 85% (0.553 g)

M.p. 151-153 °C

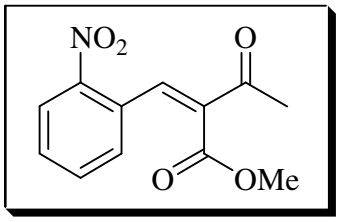
IR (KBr): 3346, 2941, 1744, 1719, 1633, 1527, 1458, 1360, 1031, 700 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.15 (3H, s), 3.71 (3H, s), 4.21 (1H, d, *J* = 4.4 Hz), 5.91 (1H, dd, *J* = 4.4 Hz, *J* = 9.6 Hz), 7.30-7.32 (4H, m), 7.43 (2H, t, *J* = 7.6 Hz), 7.49 (2H, d, *J* = 7.6 Hz), 7.80 (2H, d, *J* = 7.2 Hz), 7.88 (1H, d, *J* = 9.6 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 30.1, 53.0, 53.3, 62.2, 126.6, 127.3, 128.0, 128.8, 129.0, 131.9, 134.2, 139.0, 166.9, 167.9, 204.5 ppm.

Elemental Analysis: $C_{19}H_{19}NO_4$ (325.36): Found C, 70.25; H, 5.84; N, 4.39. Calculated C, 70.14; H, 5.89; N, 4.30 %

Methyl 2-(o-nitrobenzylidene)acetoacetate (27)



Nature: Crystalline white solid

Yield: 81% (0.404 g)

M.p. 90-93 °C

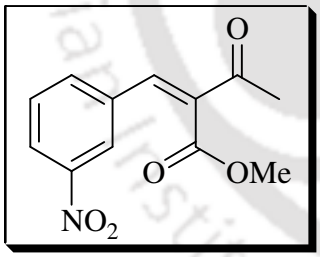
IR (KBr): 3062, 2953, 1733, 1683, 1599, 1448, 1362, 1053, 736, 605 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.49 (3H, s), 3.61 (3H, s), 7.43 (1H, t, *J* = 7.6 Hz), 7.59 (1H, d, *J* = 7.6 Hz), 7.69 (1H, t, *J* = 7.6 Hz), 8.08 (1H, s), 8.24 (1H, d, *J* = 7.6 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 26.3, 51.5, 124.3, 129.0, 129.6, 129.8, 132.0, 133.3, 135.4, 139.8, 166.9, 193.8 ppm.

Elemental Analysis: $C_{12}H_{11}NO_5$ (249.22): Found C, 57.71; H, 4.39; N, 5.74. Calculated C, 57.83; H, 4.45; N, 5.62 %

Methyl 2-(m-nitrobenzylidene)acetoacetate (28)



Nature: Yellow crystalline solid

Yield: 80% (0.399 g)

M.p. 151-152 °C

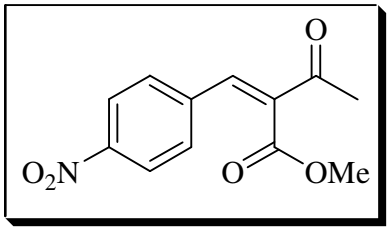
IR (KBr): 3065, 1732, 1651, 1618, 1525, 1443, 1390, 1091, 735, 688 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.43 (3H, s), 3.87 (3H, s), 7.58 (1H, s), 7.59 (1H, t, *J* = 6.4 Hz), 7.72 (1H, d, *J* = 7.6 Hz), 8.25 (1H, d, *J* = 8.4 Hz), 8.29 (1H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 27.0, 53.1, 123.9, 125.2, 130.2, 134.8, 135.2, 136.7, 137.9, 138.6, 168.0, 194.0 ppm.

Elemental Analysis: $C_{12}H_{11}NO_5$ (249.22): Found C, 57.72; H, 4.39; N, 5.71. Calculated C, 57.83; H, 4.45; N, 5.62 %

Methyl 2-(p-nitrobenzylidene)acetoacetate (29)



Nature: Yellow crystalline solid

Yield: 82% (0.408 g)

M.p. 110-114 °C

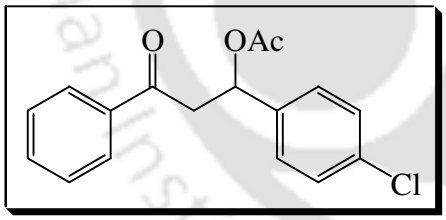
IR (KBr): 1736, 1659, 1624, 1599, 1440, 1349, 1042, 817, 537 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.43 (3H, s), 3.82 (3H, s), 7.56 (2H, d, *J* = 8.8 Hz), 7.59 (1H, s), 8.23 (2H, d, *J* = 8.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 27.1, 53.1, 109.9, 124.2, 130.1, 138.7, 139.6, 148.1, 167.0, 194.1 ppm.

Elemental Analysis: $C_{12}H_{11}NO_5$ (249.22): Found C, 57.74; H, 4.40; N, 5.54. Calculated C, 57.83; H, 4.45; N, 5.62 %

1-(4-chlorophenyl)-3-oxo-3-phenylpropylacetate (30)



Nature: Viscous liquid

Yield: 60% (0.363 g)

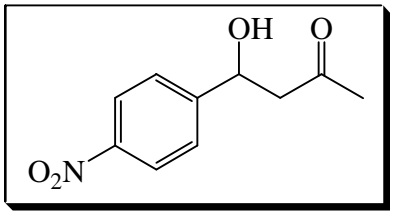
IR (neat): 2932, 1736, 1687, 1445, 1349, 1229, 1009, 754 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.01 (3H, s), 3.05 (1H, dd, *J* = 6.0 Hz, *J* = 16.8 Hz), 3.34 (1H, dd, *J* = 5.2 Hz, *J* = 17.2 Hz), 5.60-5.64 (1H, m), 7.25 (4H, d, *J* = 4.4 Hz), 7.44 (2H, t, *J* = 8.0 Hz), 7.56 (1H, t, *J* = 7.6 Hz), 7.87 (2H, d, *J* = 8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 22.0, 44.2, 69.4, 128.2, 128.4, 128.9, 133.7, 133.9, 140.0, 142.0, 149.0, 169.0, 199.7 ppm.

Elemental Analysis: $C_{17}H_{15}ClO_3$ (302.75): Found C, 67.56; H, 5.04. Calculated C, 67.44; H, 4.99 %

4-hydroxy-4-(4-nitrophenyl)butan-2-one (31)



Nature: White powder

Yield: 85% (0.356 g)

M.p. 59–61 °C

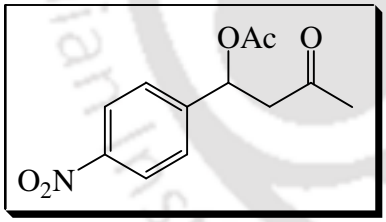
IR (KBr): 3350, 2932, 1715**,** 1614, 1521, 1475, 1352, 1042, 820 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.22 (3H, s), 2.84-2.87 (2H, m), 3.57 (1H, d, *J* = 3.2 Hz), 5.25-5.29 (1H, m), 7.54 (2H, d, *J* = 8.4 Hz), 8.21 (2H, d, *J* = 8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 21.9, 31.2, 51.9, 69.2, 123.9, 124.5, 126.7, 129.1, 147.4, 150.2, 208.6 ppm.

Elemental Analysis: $C_{10}H_{11}NO_4$ (209.20): Found C, 57.52; H, 5.36; N, 6.55. Calculated C, 57.41; H, 5.30; N, 6.70 %

1-(4-nitrophenyl)-3-oxobutylacetate (32)



Nature: Viscous liquid

Yield: 90% (0.452 g)

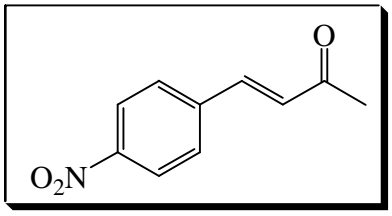
IR (neat): 2934, 1738, 1715**,** 1616, 1525, 1478, 1356, 1049, 720 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.01 (3H, s), 2.19 (3H, s), 2.77-2.80 (2H, m), 5.20-5.24 (1H, m), 7.50 (2H, d, *J* = 8.4 Hz), 8.23 (2H, d, *J* = 8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 22.1, 31.0, 50.4, 69.0, 122.9, 123.5, 127.7, 129.1, 147.4, 150.2, 170.1, 207.6 ppm.

Elemental Analysis: $C_{12}H_{13}NO_5$ (251.24): Found C, 57.50, H, 5.27; N, 5.42. Calculated C, 57.37; H, 5.22; N, 5.58 %

4-(4-nitrophenyl)but-3-en-2-one (33)



Nature: Yellow solid

Yield: 98% (0.375 g)

M.p. 104-106 °C

IR (KBr): 1675, 1523, 1347, 735 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.42 (3H, s), 6.81 (1H, d, *J* = 16.4 Hz), 7.52 (1H, d, *J* = 16.4 Hz), 7.70 (2H, m), 8.26 (2H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 28.0, 124.2, 128.8, 130.4, 140.0, 140.7, 148.6, 197.4 ppm.

Elemental Analysis: $C_{10}H_9NO_3$ (191.18): Found C, 62.95; H, 4.80; N, 7.19. Calculated C, 62.82; H, 4.74; N, 7.33 %

Crystal data and structure refinement for Methyl 2-(m-nitro benzylidene) acetoacetate (28)

Empirical formula	$C_{12}\ H_{11}\ N\ O_5$	
Formula weight	249.22	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 8.1700(2) Å	α= 90°.
	b = 12.7153(4) Å	β= 91.581(2)°.
	c = 11.2206(3) Å	γ = 90°.
Volume	1165.20(6) $Å^3$	
Z	4	
Density (calculated)	1.421 Mg/m^3	
Absorption coefficient	0.112 mm^{-1}	
F(000)	520	
Crystal size	0.40 x 0.26 x 0.18 mm^3	
Theta range for data collection	2.42 to 28.26°.	
Index ranges	-10<=h<=9, -14<=k<=16, -14<=l<=14	
Reflections collected	14939	
Independent reflections	2879 [R(int) = 0.0214]	
Completeness to theta = 28.26°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2879 / 0 / 166	
Goodness-of-fit on F^2	1.038	
Final R indices [I>2sigma(I)]	R1 = 0.0401, wR2 = 0.1043	
R indices (all data)	R1 = 0.0548, wR2 = 0.1136	
Extinction coefficient	0.004(2)	
Largest diff. peak and hole	0.216 and -0.129 $e.Å^{-3}$	

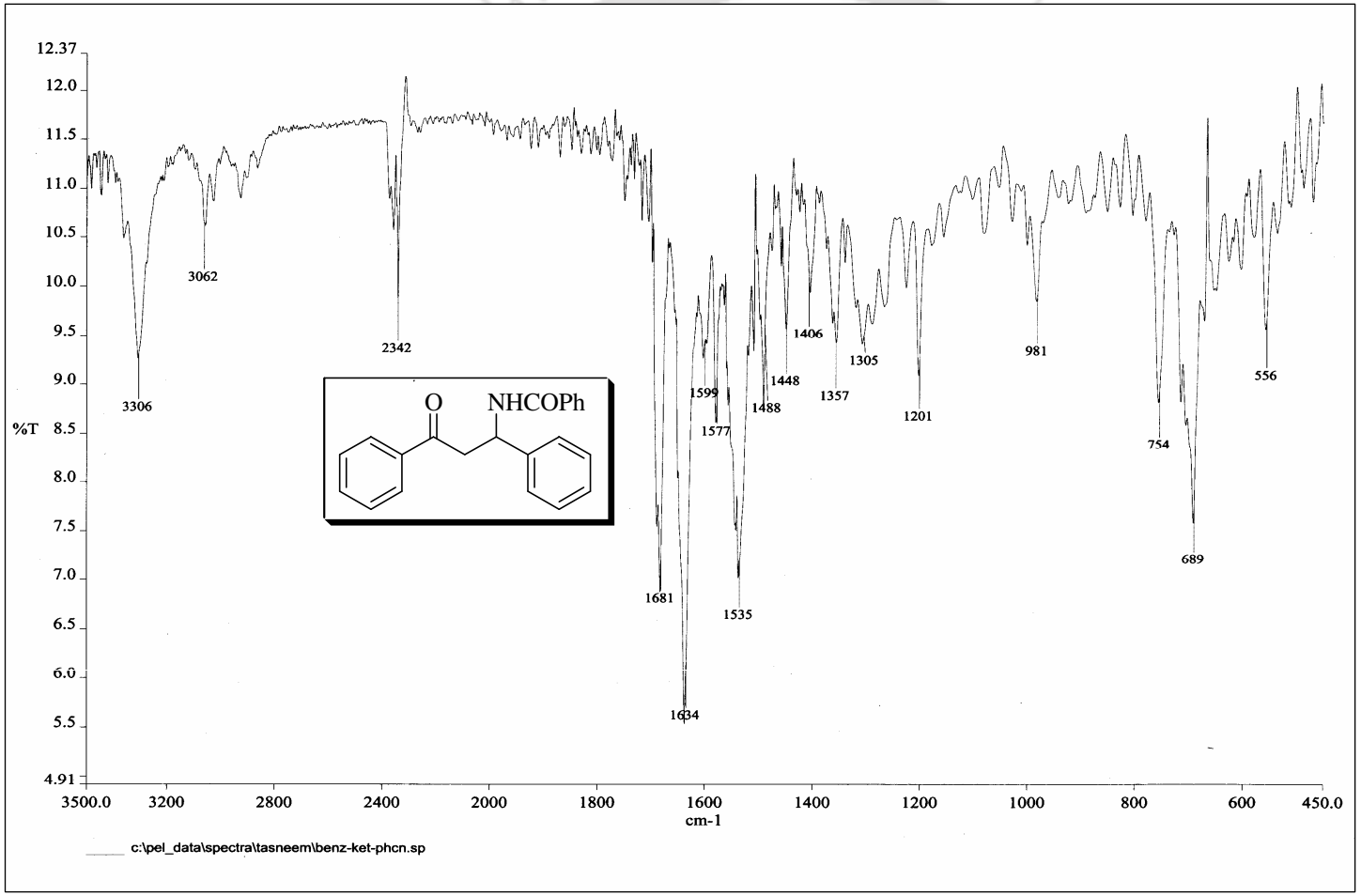


Figure 8: IR Spectrum of N-(3-Oxo-1, 3-diphenyl-propyl)benzamide (22)

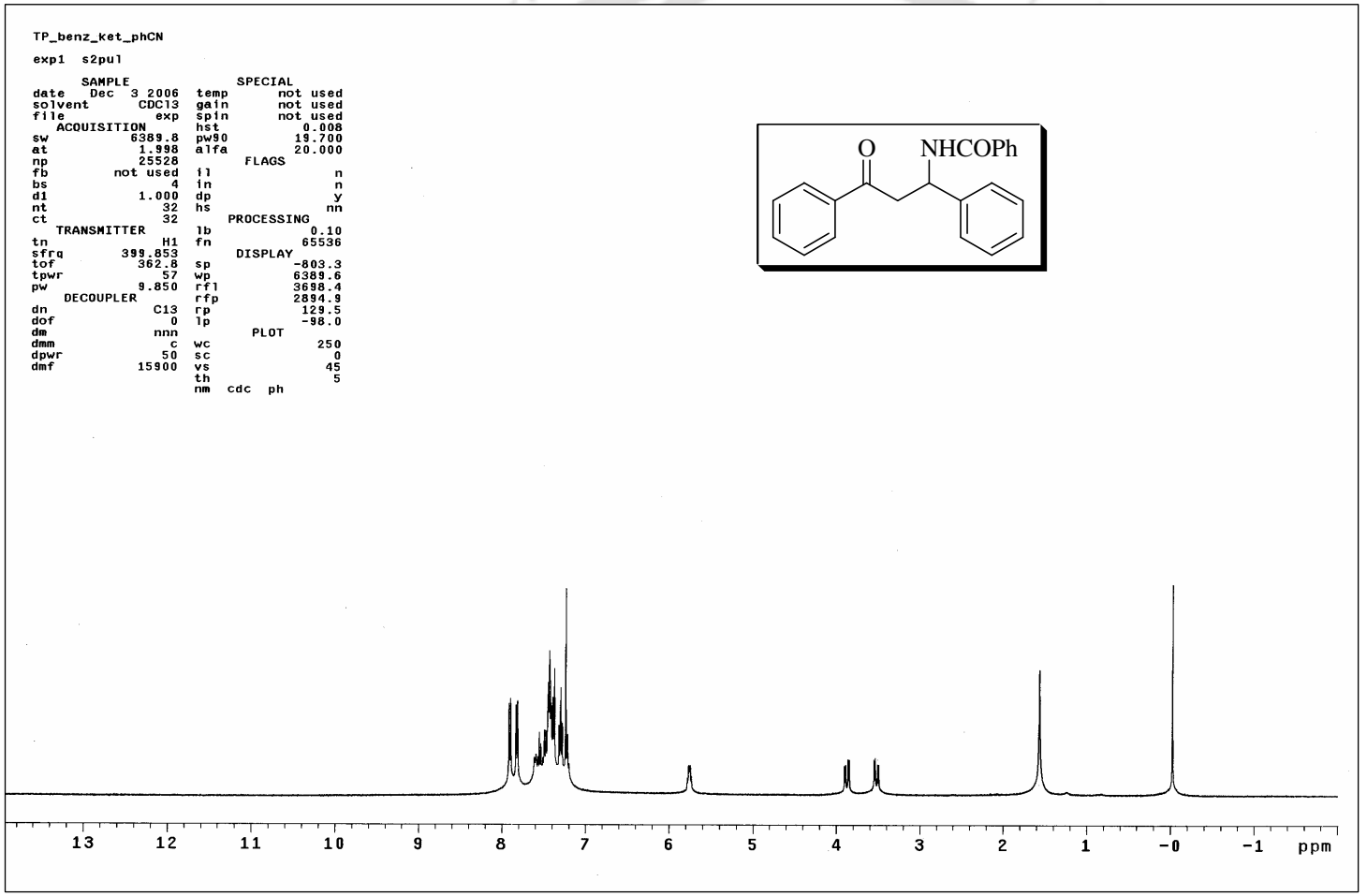


Figure 9: ^{1}H NMR Spectrum of N-(3-Oxo-1, 3-diphenyl-propyl)benzamide (22)

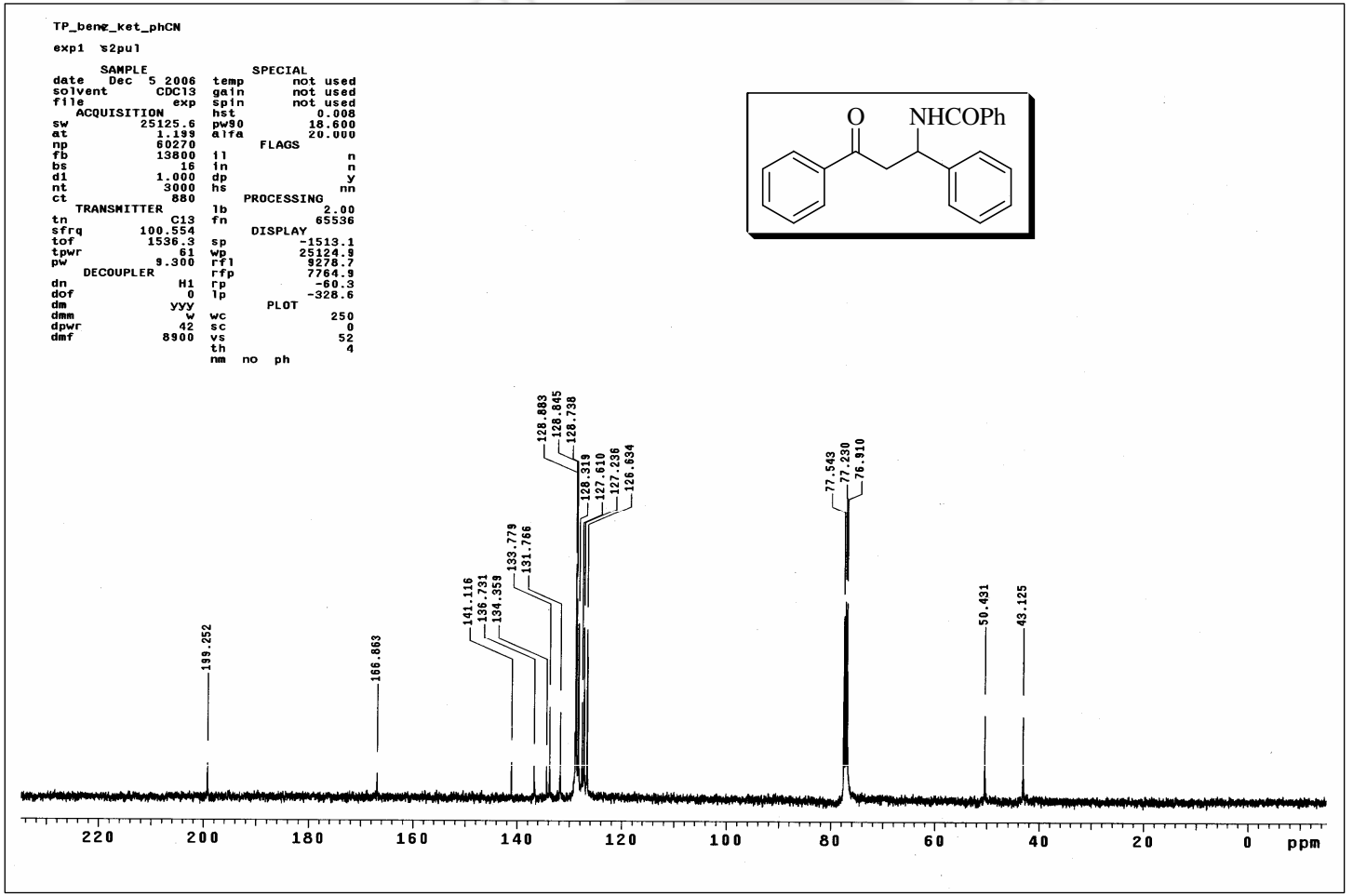


Figure 10: ^{13}C NMR Spectrum of N-(3-Oxo-1, 3-diphenyl-propyl)benzamide (22)

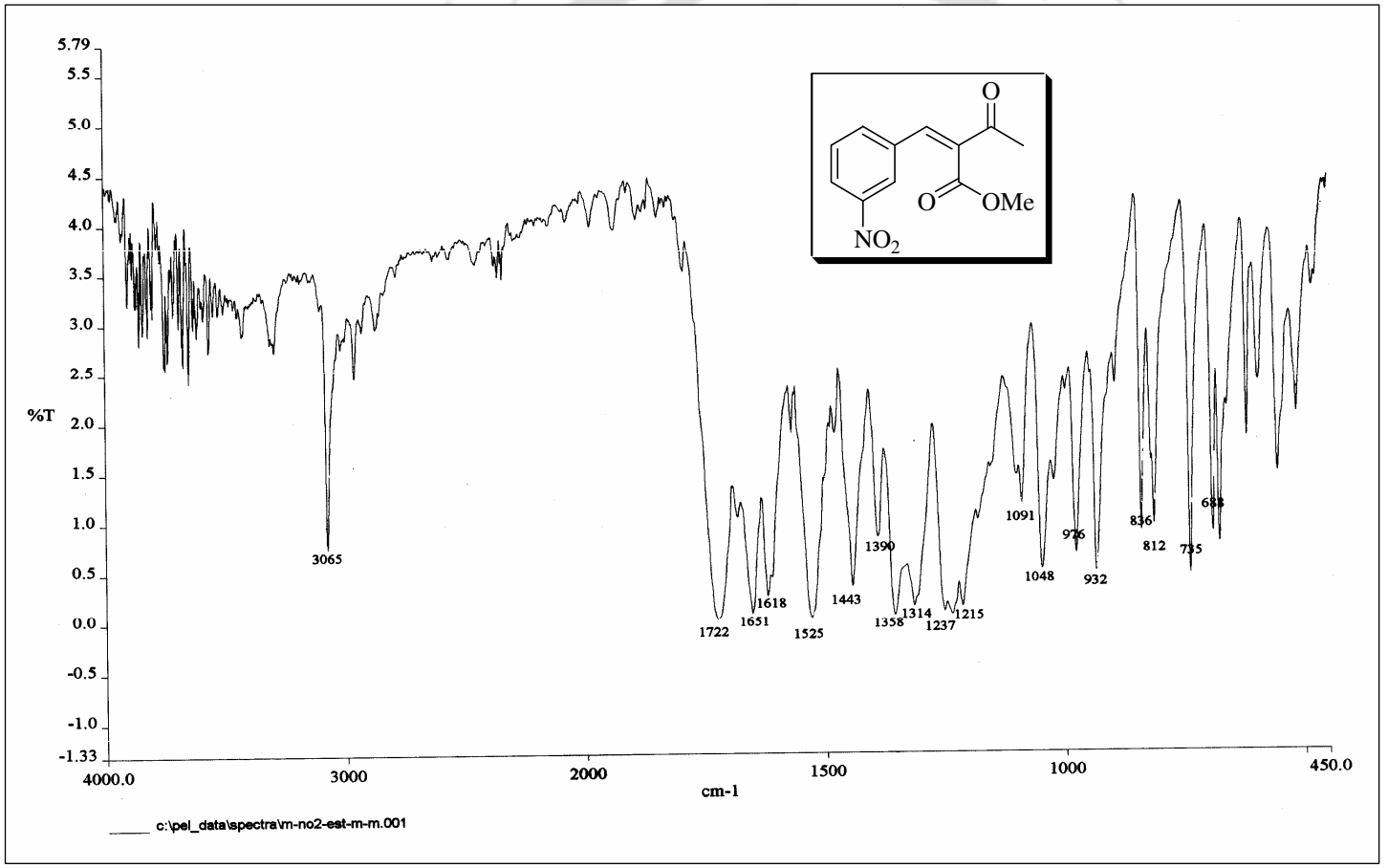


Figure 11: IR Spectrum of Methyl 2-(m-nitrobenzylidene)acetoacetate (28)

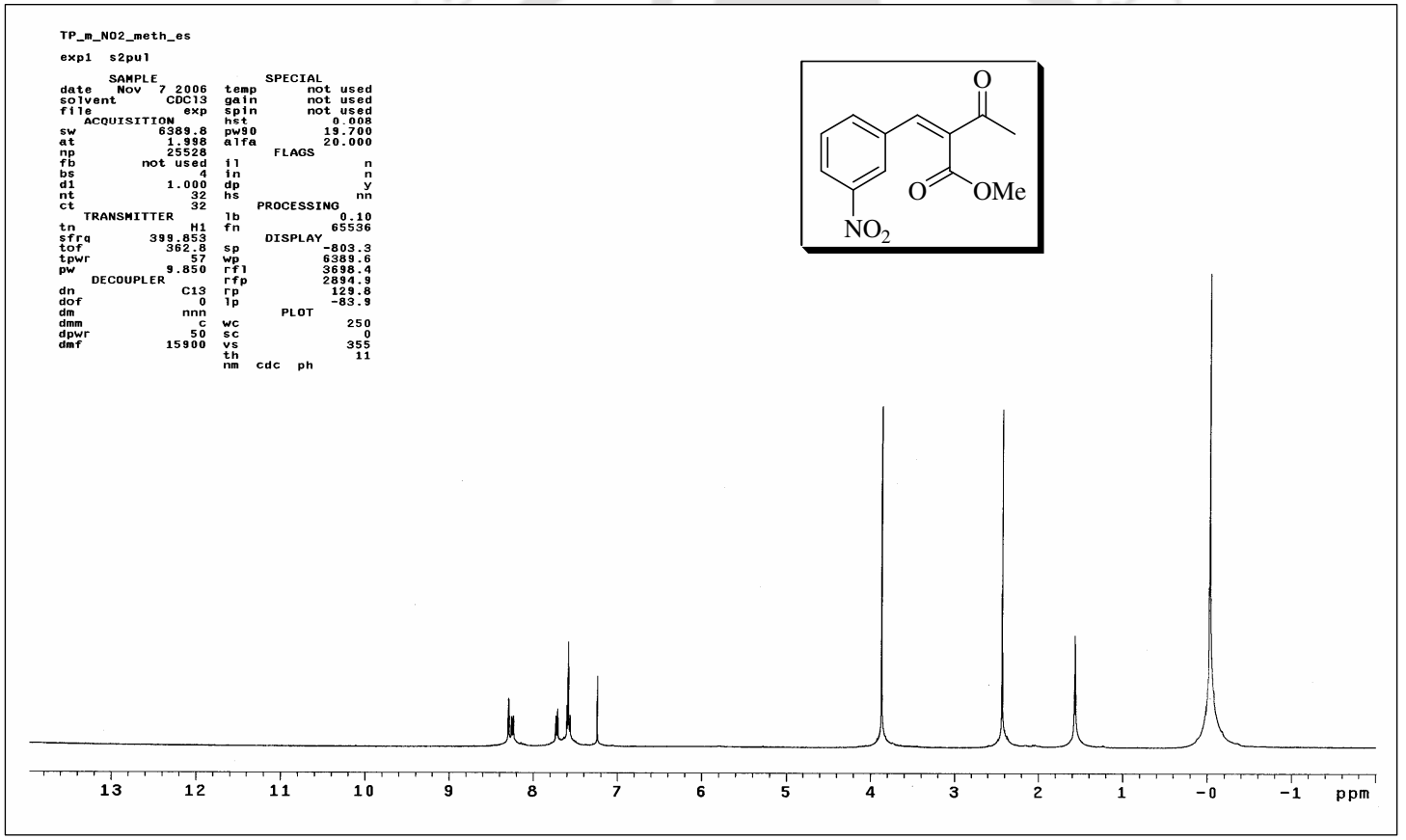


Figure 12: ^{1}H NMR Spectrum of Methyl 2-(m-nitrobenzylidene)acetoacetate (28)

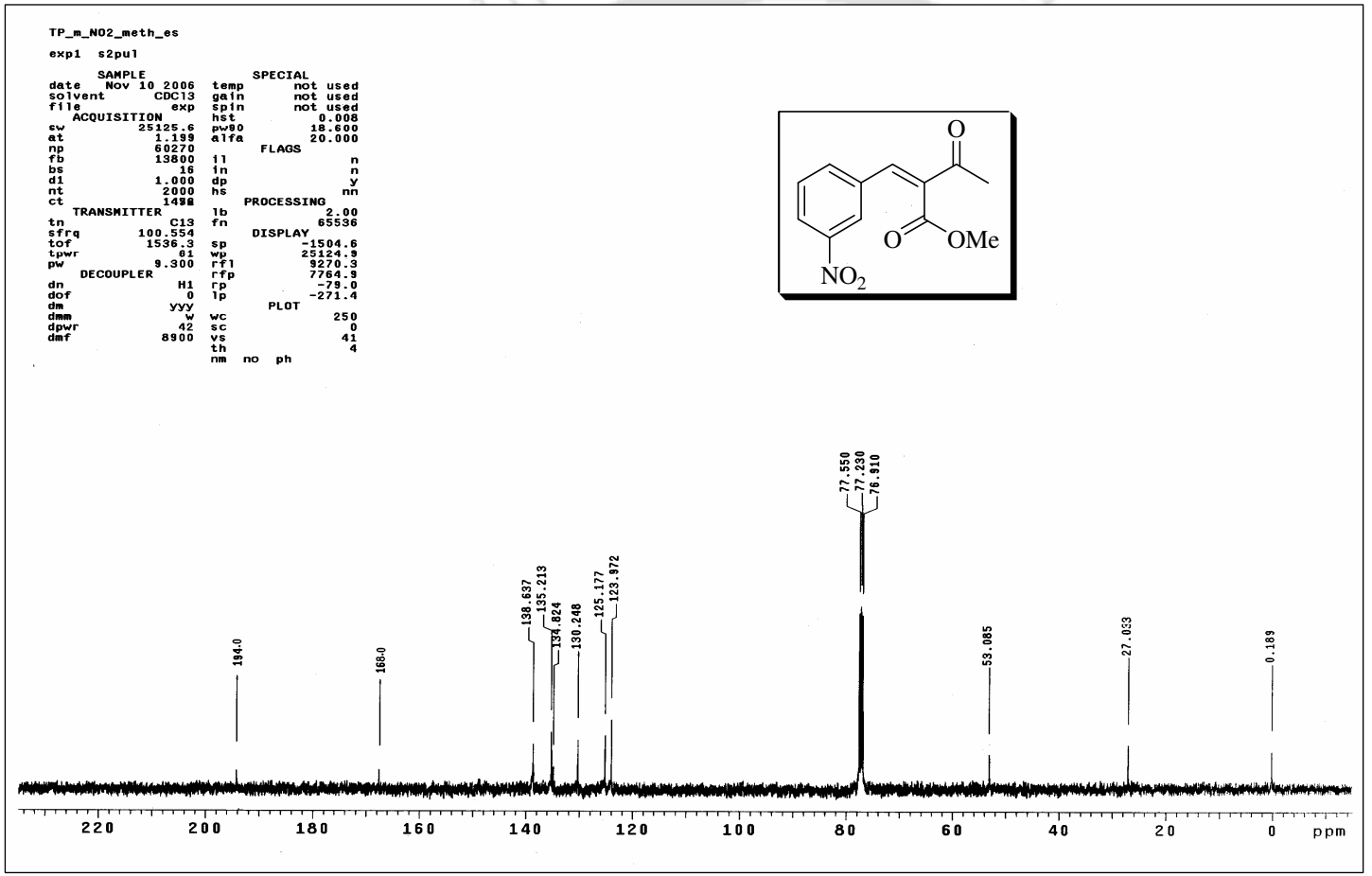


Figure 13: ^{13}C NMR Spectrum of Methyl 2-(m-nitrobenzylidene)acetoacetate (28)

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CHAPTER III

Synthesis of β-amino carbonyl compounds using bromodimethyl-sulfonium bromide (BDMS) as catalyst

3.1 Introduction

From the literature survey of Chapter I, it is evident that β-amino carbonyl moiety is an integral component in various bioactive molecules and development of new methodologies leading to these compounds is of common interest of synthetic organic chemists. Conventionally these compounds can be achieved either by aza-Michael addition reaction or by Mannich reaction.

In this chapter we will describe the two newly developed synthetic methodologies on aza-Michael reaction and direct Mannich type reaction using a versatile reagent bromodimethylsulfonium bromide as catalyst.

3.1.1 Bromodimethylsulfonium bromide a versatile reagent in organic synthesis:

Bromodimethylsulfonium bromide (BDMS) is a light orange solid, which can be easily prepared from molecular bromine and dimethylsulfide.[1] Interestingly, it can also be generated *in situ* by treating aqueous HBr with dimethylsulfoxide.[2] The reagent BDMS can be considered as a convenient storage of bromine molecule or source of bromonium ion by analogy with hypobromite,[3] N-bromosuccinimide[4] or bromoazide.[5] It is safer and easier to handle as compared to hazardous molecular bromine. Meerwein[6] discovered bromodimethylsulfonium bromide in 1965 and subsequently Corey et al disclosed[7] chlorodimethylsulfonium chloride. Olah et al and Chow et al have extensively used this reagent in various organic transformations. However, the potentiality of this reagent was not explored completely. In continuation of our endeavor to develop new synthetic methodologies, our group disclosed for the first time that BDMS exhibit very efficient catalytic activity in acid catalyzed organic transformations.[8a] After this disclosure, this reagent has achieved a new dimension in current organic synthesis.

Presently our group is engaged in exploration of the virtue of this reagent in various organic transformations. A plethora of organic transformations mediated by this reagent have been reported by several other groups in current literature.[8b-d] We believe that the dawn of BDMS has just started and it will be emerging as a versatile reagent in organic synthesis. Very recently we have published a review article on recent advances in the application of this reagent in organic synthesis.[8e] In continuation of our efforts towards the exploration of BDMS, herein we are presenting two methodologies in Section A and Section B of this chapter for accessing β-amino carbonyl compounds.

3.1.2 Aza-Michael addition a convenient way to prepare β-amino carbonyl compounds

The Michael reaction and its modified form such as aza-Michael and thia-Michael reaction is one of the most exploited reactions in organic chemistry.[9] The β-amino esters/ketones/nitriles are useful synthons for the preparation of several nitrogen containing bioactive natural products,[10] antibiotics[11] and chiral auxiliaries.[12] Besides these, a large number of biologically active compounds containing β-amino-ketone or ester moiety exist in literature.[13]

The development of novel synthetic methodologies for the preparation of these compounds is an attractive area of research in synthetic organic chemistry. In general, the aza-Michael reaction requires a basic condition or some special reaction condition.[14] However, this reaction can also be mediated by acid catalysis.[15] Both protic and Lewis acid can enhance the rate of the reaction by making the Michael acceptor more electrophilic. To avoid the typical disadvantages resulting from the presence of such catalysts, a number of alternative procedure have been developed in the past few years.[16] Among these methods, most of them are employing various Lewis acids. However, the fact that stoichiometric amounts of Lewis acids such as $AlCl_3$, $TiCl_4$, or $SnCl_4$ are required[17] constitutes a serious draw back since this oxophilic promoters have a significant cost factor and cause environmental problems due to strongly acidic waste streams. To overcome these limitations over the years, numerous methods have been developed using a variety of reagents such as $ZrOCl_2 \cdot 8H_2O$ on montmorillonite K10,[18] CAN,[19] β-cyclodextrine,[20] NaN_3,[21] *p*-TsOH·H_2O,[22] $SnCl_4/FeCl_3$,[23] $InCl_3$,[24] $CeCl_3 \cdot 7H_2O$-NaI,[25] $Yb(OTf)_3$,[26] $Cu(OTf)_2$,[27] $Bi(NO_3)_3$,[28] $Bi(OTf)_3$,[29] $LiClO_4$,[30] KF/alumina,[31] SmI_2,[32] $Cu(acac)_2$/ionicliquid,[33] ionic liquid/quaternary ammonium salt in water,[34] boric acid in water,[35] borax[36] etc. Although these methods are quite useful, many of them suffer from limitations such as the requirement for a large excess of reagents, long reaction times, drastic reaction conditions and also involvement of toxic solvents such as acetonitrile or 1,2-dichloroethane. Hence, there is a further scope to develop a convenient, environmentally friendly method for conjugate addition of amines to electron deficient alkenes. In section A of this chapter we will discuss our work done on aza-Michael addition using BDMS under solvent free conditions.

3.1.3 Three component Mannich-type reaction an alternative way to synthesize β-amino carbonyl compounds

The Mannich reaction is an important carbon-carbon-bond forming reaction[37] that is commonly employed in the synthesis of naturally occurring alkaloids and is involved in a number of biosynthetic pathways. The reaction uses three components: an amine, a non-enolizable aldehyde or ketone, and a compound containing an enolizable carbonyl moiety. The final product of the reaction is β-amino-carbonyl compound. The major problem of the classical Mannich reaction is that the reaction is very sluggish and requires heating/reflux conditions and some times the reagents (and desired product) start polymerising.

Mannich-type reactions can be classified into two types- a) Indirect Mannich type and b) Direct Mannich type reactions. Indirect Mannich type reactions involve imines and preformed enolate equivalents such as silyl enol ethers, which are more reactive than their parent carbonyl compounds. Because of their reliance on the use of preformed key intermediates rather than their generation *in situ*, there is an important advancement in synthetic utility of Mannich reactions. However, they suffer from the drawback of the necessity of the isolation and purification of enol equivalents. As for the construction of β-amino carboxylic acid derivatives, catalytic direct Mannich type reactions are the most convenient method that proceed via C–C bond formation with a proton transfer pathway. This protocol is superior in terms of atom economy as compared to conventional methods that require stoichiometric amounts of bases and/or silicon sources.

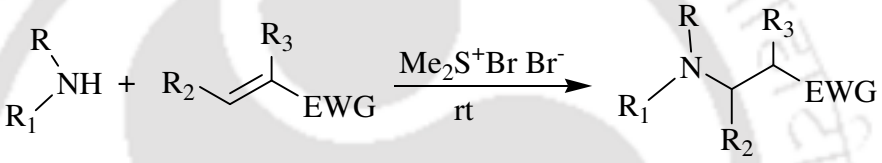
Over the years several methods both indirect and direct types have been developed using various catalysts such as $InCl_3$,[38] $Bi(OTf)_3{\cdot}4H_2O$,[39] AgOAc in presence of chiral ligand,[40] chiral cyclic secondary amines,[41] silica sulfuric acid,[42] $ZrOCl_2{\cdot}8H_2O$,[43] CAN/PEG,[44] $NbCl_5$,[45] $Zn(OTf)_2$,[46] I_2,[47] $Yb(OPf)_3$,[48] $[NaBAr_4^F]$,[49] $H_3PW_{12}O_{40}$,[50] and (L)-Serine[51] etc. Although these methodologies are quite useful still some of the methods encounter some limitations such as either employ expensive catalysts or longer reaction time. It is thus evident that there remains a lot of scope for the development of clean and efficient methodologies for the preparation of β-amino carbonyl compounds using a convenient, environmentally friendly method. In section B of this chapter we will demonstrate another new methodology of direct Mannich-type reaction using bromodimethyl sulfonium bromide as a catalyst.

SECTION A

Bromodimethylsulfonium bromide mediated Michael addition of amines to electron deficient alkenes

3.2.1 Results and Discussion:

In continuation of our endeavour to explore versatility of new reagents in organic synthesis, we sought to test the catalytic activity of BDMS for the development of new methodologies leading to β-amino carbonyl compounds. The Michael addition of amines to electron deficient alkenes i.e., aza-Michael addition is one of the most widely used technique to achieve β-amino carbonyl compounds. Thus we wanted to see whether BDMS can be used as a catalyst in aza-Michael reaction. In this section we will discuss the results of our study on catalytic activity of bromodimethylsulfonium bromide (BDMS) in aza-Michael reaction (Scheme 1). For our study the reagent bromodimethylsulfonium bromide was prepared from dimthylsulfide and molecular bromine in 1:1 ratio using reported literature procedure.[1]



R= H/ alkyl; R_1= alkyl/ benzyl; R_2= H; R_3= H/ Me;

EWG = CN, COMe, COEt, $CONH_2$

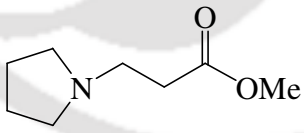
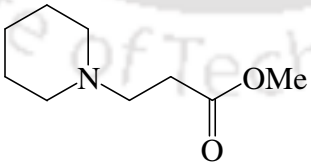
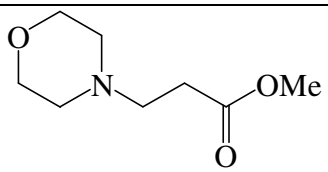
Scheme 1

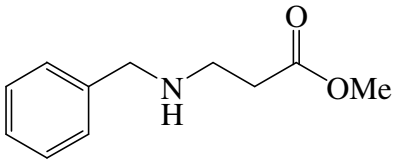
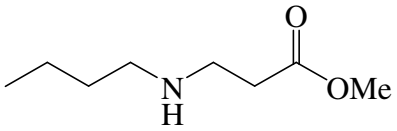
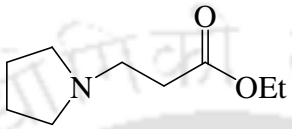
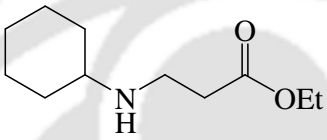
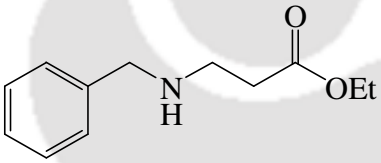
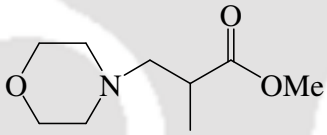
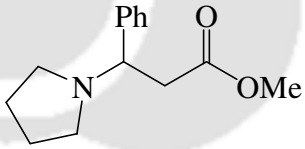
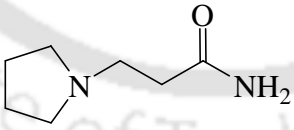
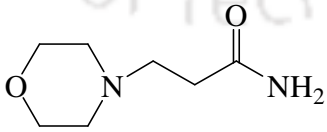
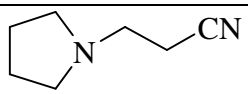
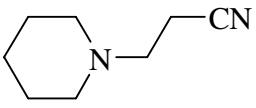
In a preliminary experiment pyrolidine (5 mmol) was treated with electron deficient alkene, methyl acrylate (5 mmol) in the presence of bromodimethylsulfonium bromide (0.25 mmol) under solvent-free conditions at room temperature. Interestingly, within five minutes the reaction was completed as indicated by TLC. The reaction mixture was extracted with ethyl acetate (2 x 20 mL) and washed with water. Then the combined extract was dried over Na_2SO_4 and evaporated to leave the crude product. Interestingly, the crude product obtained after aqueous work-up was found to be pure as there was no detectable amount of impurities or starting material in the ^{1}H NMR. The Michael adduct **1** was characterized by IR, ^{1}H and ^{13}C NMR spectroscopy as well as by comparison with reported data. ^{1}H NMR spectrum gave the signals at 1.77-1.80 (4H, m), 2.50-2.57 (6H, m), 2.78 (2H, t, *J* = 7.6 Hz), 3.69 (3H, s) ppm. The disappearence of signals in the alkene region and appearance of a signal at 2.78 ppm as triplet clearly indicates the formation of the 1,4-addition product. In ^{13}C NMR spectrum, it showed peaks at 23.6, 34.1, 51.6, 51.7, 51.8, 54.2, 173.2 ppm which clearly support the formation of product.

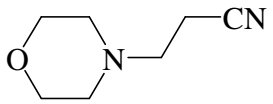
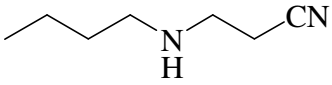
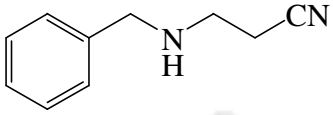
Encouraged by this, other secondary amines such as piperidine and morpholine were treated with the same Michael acceptor under the same experimental conditions and the corresponding Michael adducts (**2-3**) were isolated in excellent yields within a short time. Similarly, the primary amines benzylamine and *n*-butylamine underwent Michael addition smoothly providing the corresponding adducts (**4-5**) in good yields. It is worthwhile to mention here that these primary amines provided selectively the mono addition product under the given experimental procedure. The present protocol represents an improvement over some of the recently reported methods in terms of reaction time as well as % yields obtained.

To asses the efficiency of BDMS, we have applied our methodology to synthesize substituted β-amino carbonyl compounds. Thus, the α,β-unsaturated ester (ethyl acrylate) was treated with a wide variety of amines under the same conditions to afford very good yields of the corresponding Michael adducts (**6-8**). Methyl methacrylate and methyl *trans*-cinnamate also underwent Michael addition with morpholine and pyrrolidine, respectively, without any difficulty (**9-10**).

Table 1. Bromodimethylsulfonium bromide mediated Michael addition of amines to conjugated alkenes under solvent-free conditions.

Product No	Product[a]	Time/ min	% Yield[b]
1		5	97
2		5	96
3		5	97

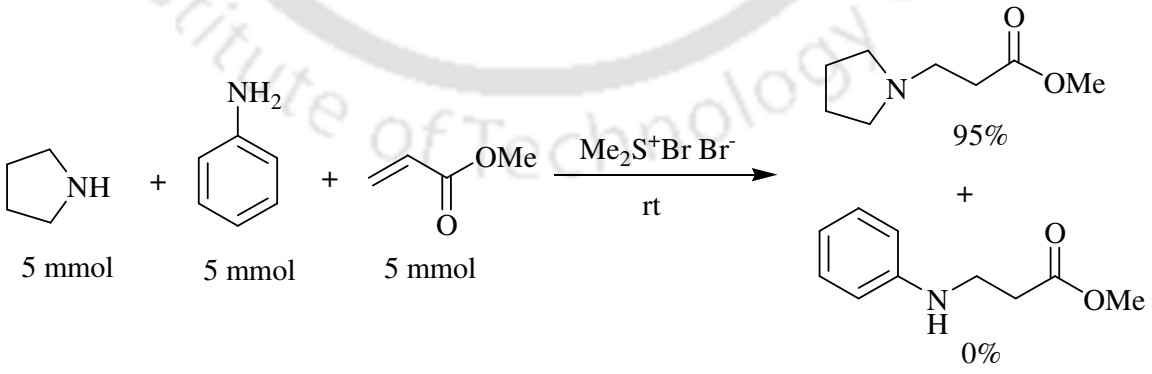
4		15	84
5		15	85
6		5	94
7		10	85
8		20	89
9		20	88
10		15	83
11		5	91
12		15	89
13		5	98
14		5	99

15		5	93
16		10	92
17		15	91

[a] All the products were fully characterized by recording IR, ^{1}H, ^{13}C NMR and elemental analysis. [b] Isolated yields.

Likewise, acrylamide underwent Michael addition with pyrrolidine and morpholine under the given experimental procedure to provide the corresponding adducts (**11**-**12**) in very good yields. Encouraged by these results next acrylonitrile was treated with a wide variety of amines to provide the corresponding addition products (**13**-**17**) in relatively good yields. These compounds can be converted to the β-amino carbonyl compounds by hydrolysis followed by esterification.

Next, to exemplify the chemoselectivity of this present protocol a competitive study was carried out using a mixture of 5 mmol of pyrrolidine, 5 mmol of aniline and 5 mmol of methyl acrylate as shown in Scheme 2. The Michael adduct of pyrrolidine was obtained exclusively. This clearly reflects the chemoselectivity of aliphatic amines versus aromatic amines.

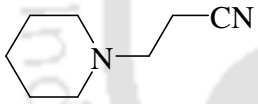
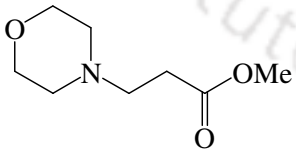


Scheme 2 Chemoselective conjugate addition of aliphatic amines in the presence of aromatic amines

However, the same protocol was unsuccessful while it was treated with an aromatic amine, and yielded only starting material even after 2 h of stirring.

The catalytic activity of bromodimethylsulfonium bromide was ascertained by the fact that in the absence of the catalyst the reaction of pyrrolidine with acrylonitrile afforded only a 20% yield of adduct even after 6 h of stirring at room temperature. The efficacy and generality of the present protocol can be realized by comparing some of the results presented here with recently reported methods as shown in Table 2; which compares reaction time, % yields and reaction conditions.

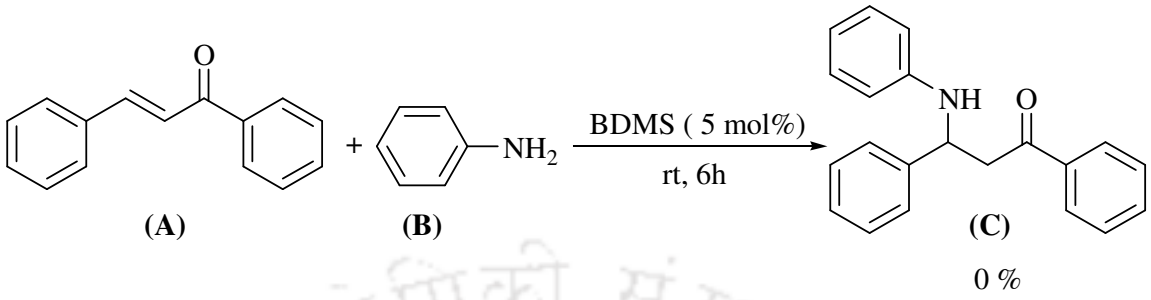
Table 2. Comparison of the present protocol with reported methods

Product	Catalyst (mol%)[a]	Reaction conditions/solvent	Time min/[h]	% Yield[b]
	$LiClO_4$ (100)[30]	rt /solvent-free	[1]	80
	$ZrOCl_2.8H_2O$/ montmorillonite (0.075 g/mmol)[18]	rt /solvent-free	15	94
	CAN (10)[19]	Ultrasonication/ THF	20	96
	H_3BO_3 (10)[35]	rt/H_2O	[1.5]	95
	Borax (10)[36]	rt/ H_2O	[2]	90
	β-Cyclodextrin (100)[20]	rt/ H_2O	[6]	84
	BDMS (5)	rt /solvent-free	5	99
	$ZrOCl_2.8H_2O$/ montmorillonite (0.075 g/mmol)[18]	rt/ solvent-free	35	76
	H_3BO_3 (10)[35]	rt/H_2O	[3]	85
	Borax (10)[36]	rt/ H_2O	[3]	92
	BDMS (5)	Solvent-free	5	97

[a]Corresponding reference. [b]Isolated yield.

Next, we wanted to see whether the same catalyst will be useful for Michael addition of aromatic amines to the α,β-unsaturated ketones. Then, the chalcone (**A**) was treated with one equivalent of aniline in presence of 10 mol % BDMS and stirred upto 6 hour at room

temperature. Unfortunately, we were unsuccessful to achieve the desired Michael adduct(**C**) and the starting materials were recovered from the reaction mixture (Scheme 3).



Scheme 3

Mechanistically, we believe bromodimethylsulfonium bromide here acts as a pre catalyst to generate *in situ* dry HBr which acts basically to promote the reaction. In addition, the sulfonium moiety which is a positively charged species may also work like a Lewis acid catalyst to activate the electrophile.

In summary we have developed a simple and efficient methodology for the conjugate addition of amines to electron deficient alkenes using bromodimethylsulfonium bromide as an inexpensive and efficient catalyst. This method is highly effective for the 1,4-addition of primary and secondary aliphatic amines to electron deficient alkenes. However, in case of aromatic amines the present protocol is not suitable. In addition, the reactions of chalcones with amines are also not encouraging under the given experimental conditions.

The significant features of this method are: (1) The procedure is very simple and no need of column purification process to get the pure product. (2) BDMS is a very cheap reagent and easy to handle. (3) The reactions are high yielding and take very short reaction time. Thus the present method demonstrates the potential of BDMS as an efficient promoter in organic synthesis.

SECTION A

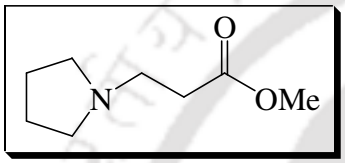
Bromodimethylsulfonium bromide mediated Michael addition of amines to electron deficient alkenes

EXPERIMENTAL

3.2.2 General experimental procedure for the Michael reaction:

To a mixture of methyl acrylate (430 mg, 5 mmol) and pyrrolidine (355 mg, 5 mmol), bromodimethylsulfonium bromide (56 mg, 0.5mmol) was added and the reaction mixture was stirred at room temperature.The reaction was completed within 5 minutes as indicated by TLC. After that the reaction mixture was extracted with ethyl acetate (2 x 20 mL) and water. The combined organic extract was dried over Na_2SO_4 and evaporated to leave a crude product which was sufficiently pure as ascertained by ^{1}H NMR of the crude product.

Methyl 3-(pyrrolidin-1-yl)propanoate (1)



Nature: Yellow liquid

Yield: 97% (0.762 g)

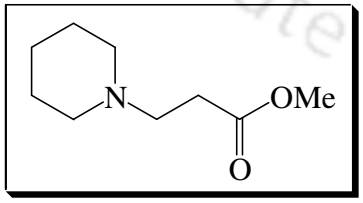
IR (neat): 2956, 2785, 1739, 1434, 1349, 1262, 1204, 1048 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.77-1.80 (4H, m), 2.50-2.57 (6H, m), 2.78 (2H, t, *J* = 7.6 Hz), 3.69 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.6, 34.1, 51.6, 51.7, 51.8, 54.2, 173.2 ppm.

Elemental Analysis: $C_8H_{15}NO_2$ (157.21): Found C, 61.24; H, 9.56; N, 9.03. Calculated C, 61.12; H, 9.62; N, 8.91 %

Methyl 3-(piperidin-1-yl)propanoate (2)



Nature: Yellow liquid

Yield: 96% (0.822 g)

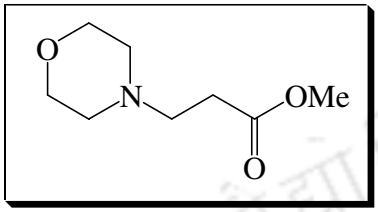
IR (neat): 2934, 2846, 1742, 1432, 1349, 1171, 1116, 1006 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.41-1.45 (2H, m), 1.55-1.60 (4H, m), 2.32-2.41 (4H, brs), 2.52 (2H, t, *J* = 6.8 Hz), 2.67 (2H, t, *J* = 6.8 Hz), 3.70 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 24.4, 26.1, 32.1, 51.8, 54.4, 173.4 ppm.

Elemental Analysis: $C_9H_{17}NO_2$ (171.24): Found C, 63.27; H, 10.05; N, 8.01. Calculated C, 63.13; H, 10.01; N, 8.18 %.

Methyl 3-morpholinopropanoate (3)



Nature: Yellow liquid

Yield: 97% (0.840 g)

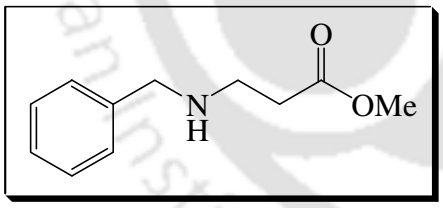
IR (neat): 2946, 2826, 1738, 1456, 1115, 1026 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 2.40-2.43 (4H, m), 2.48 (2H, t, *J* = 7.6 Hz), 2.65 (2H, t, *J* = 7.6 Hz), 3.65 (3H, s), 3.66-3.67 (4H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 31.7, 51.4, 53.2, 53.8, 66.7, 172.6 ppm.

Elemental Analysis: $C_8H_{15}NO_3$ (173.21): Found C, 55.60; H, 8.78; N, 7.93. Calculated C, 55.47; H, 8.73; N, 8.09 %

Methyl 3-(benzylamino)propanoate (4)



Nature: Yellow liquid

Yield: 84% (0.812 g)

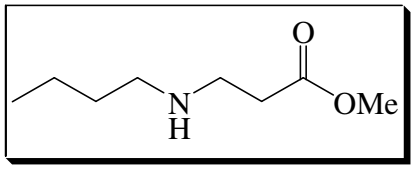
IR (neat): 3330, 2980, 2845, 1732, 1453, 1370, 1180, 1024 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.47 (2H, t, *J* = 7.2 Hz), 2.80 (2H, t, *J* = 7.2 Hz), 3.59 (2H, s), 3.65 (3H, s), 7.26-7.28 (5H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 32.6, 49.2, 51.6, 58.4, 127.1, 128.3, 128.8, 139.0, 173.0 ppm.

Elemental Analysis: $C_{11}H_{15}NO_2$ (193.24): Found C, 68.50; H, 7.86; N, 7.10. Calculated C, 68.37; H, 7.82; N, 7.25 %

Methyl 3-(butylamino)propanoate (5)



Nature: Yellow liquid

Yield: 85% (0.677 g)

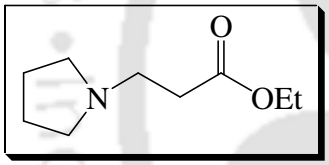
IR (neat): 3456, 2950, 2862, 1736, 1440, 1253, 1198, 1039 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 0.90 (3H, t, *J* = 7.2 Hz), 1.29 (2H, sex, *J* = 7.2 Hz), 1.40 (2H, quint, *J* = 7.2 Hz), 2.38-2.47 (4H, m), 2.77 (2H, t, *J* = 7.2 Hz), 3.67 (3H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 20.6, 29.4, 32.7, 49.4, 51.7, 53.6, 173.3 ppm.

Elemental Analysis: $C_8H_{17}NO_2$ (159.23): Found C, 60.22; H, 10.72; N 8.96. Calculated C, 60.35; H, 10.76; N, 8.80 %.

Ethyl 3-(pyrrolidin-1-yl)propanoate (6)



Nature: Yellow liquid

Yield: 94% (0.805 g)

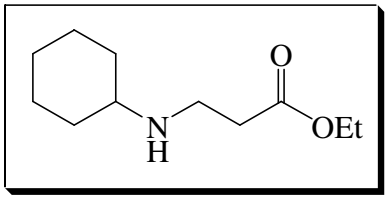
IR (neat): 2937, 2789, 1737, 1183, 1147 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.27 (3H, t, *J* = 7.2 Hz), 1.75-1.83 (4H, m), 2.51-2.56 (6H, m), 2.78 (2H, t, *J* = 7.2 Hz), 4.15 (2H, q, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 23.5, 34.2, 51.4, 54.0, 60.3, 172.5 ppm.

Elemental Analysis: $C_9H_{17}NO_2$ (171.24): Found C, 63.25; H, 10.05; N, 8.12. Calculated C, 63.13; H, 10.01; N, 8.18 %

Ethyl 3-(cyclohexylamino)propanoate (7)



Nature: Yellow liquid

Yield: 85% (0.847 g)

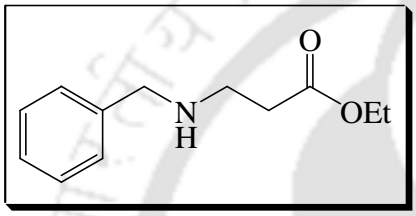
IR (neat): 3445, 2928, 2851, 1733, 1179, 1045 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.17-1.20 (2H, m), 1.24 (3H, t, *J* = 7.2 Hz), 1.58-1.70 (8H, m), 2.41 (2H, t, *J* = 7.2 Hz), 2.49-2.51 (1H, m), 2.78 (2H, t, *J* = 7.2 Hz), 4.12 (2H, q, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 14.5, 26.3, 26.5, 29.3, 35.1, 46.4, 60.3, 60.5, 173.0 ppm.

Elemental Analysis: $C_{11}H_{21}NO_2$ (199.29): Found C, 66.41; H, 10.67; N, 6.91. Calculated C, 66.29; H, 10.62; N, 7.03 %

Ethyl 3-(benzylamino)propanoate (8)



Nature: Yellow liquid

Yield: 89% (0.922 g)

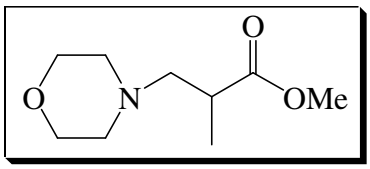
IR (neat): 3329, 2983, 2846, 1731, 1454, 1369, 1179, 1023 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.25 (3H, t, *J* = 7.2 Hz), 2.54 (2H, t, *J* = 6.4 Hz), 2.90 (2H, t, *J* = 6.4 Hz), 3.81 (2H, s), 4.14 (2H, q, *J* = 7.2 Hz), 7.31-7.33 (5H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 14.4, 34.8, 44.6, 53.9, 60.7, 127.2, 128.3, 128.6, 138.8, 172.0 ppm.

Elemental Analysis: $C_{12}H_{17}NO_2$ (207.27): Found C, 69.66, H, 8.32; N, 6.60. Calculated C, 69.54; H, 8.27; N, 6.76 %

Methyl 2-(morpholinomethyl)propanoate (9)



Nature: Yellow liquid

Yield: 88% (0.824 g)

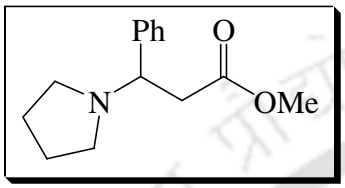
IR (neat): 2947, 1825, 1738, 1432, 1347, 1118, 1040 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.20 (3H, d, *J* = 5.6 Hz), 2.27-2.32 (1H, m), 2.35-2.42 (2H, m), 2.46-2.51 (2H, m), 2.63-2.70 (2H, m), 3.65 (3H, s), 3.66-3.74 (4H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 15.8, 37.4, 51.8, 53.6, 61.9, 66.8, 176.4 ppm.

Elemental Analysis: $C_9H_{17}NO_3$ (187.24): Found C, 57.85; H, 9.20; N, 7.32. Calculated C, 57.73; H, 9.15; N, 7.48 %

Methyl 3-phenyl-3-(pyrrolidin-1-yl)propanoate (10)



Nature: Yellow liquid

Yield: 83% (0.968 g)

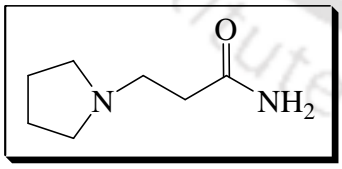
IR (neat): 2954, 2781, 1738, 1436, 1348, 1265, 1203 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.73-1.76 (4H, m), 2.39-2.42 (2H, m), 2.54-2.56 (2H, m), 2.74 (1H, dd, *J* = 8.8 Hz, 14.8 Hz), 3.02 (1H, dd, *J* = 5.6 Hz, *J* = 14.8 Hz), 3.51 (3H, s), 3.73 (1H, dd, *J* = 5.6 Hz, 8.8 Hz), 7.26-7.34 (5H,m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.5, 41.4, 51.7, 52.4, 66.6, 127.7, 128.2, 128.5, 141.5, 172.1 ppm.

Elemental Analysis: $C_{14}H_{19}NO_2$ (233.31): Found C, 72.15; H, 8.16; N, 6.18; Calculated C, 72.07; H, 8.21; N, 6.00 %

3-Pyrrolidin-1-yl-propionamide (11)



Nature: Yellow solid

Yield: 91% (0.647 g)

M.p. 54-55 ^oC

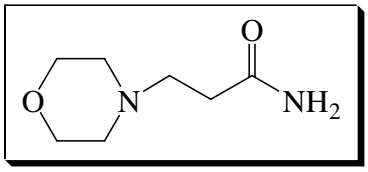
IR (KBr): 3362, 3197, 2961, 2807, 1670, 1410, 1264 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.79-1.82 (4H, m), 2.42 (2H, t, *J* = 6.4 Hz), 2.56-2.59 (4H, m), 2.73-2.76 (2H, t, *J* = 6.4 Hz), 5.41 (2H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.7, 34.3, 51.8, 53.6, 174.5 ppm.

Elemental Analysis: $C_7H_{14}N_2O$ (142.2) : Found: C, 59.23; H, 9.84; N, 19.85; Calculated C, 59.12; H, 9.92; N, 19.70 %

3-Morpholinopropanamide (12)



Nature: Yellow liquid

Yield: 89 % (0.704 g)

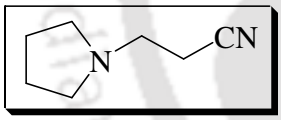
IR (KBr): 3360, 3195, 2960, 2806, 1672, 1412, 1266 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.39 (2H, t, *J* = 6.4 Hz), 2.45-2.52 (4H, m), 2.61 (2H, t, *J* = 6.4 Hz), 3.66-3.71 (4H, m), 5.53 (2H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 36.7, 51.6, 53.0, 66.8, 175.6 ppm.

Elemental Analysis: $C_7H_{14}N_2O_2$ (158.2): Found C, 53.26; H, 8.86; N, 17.86. Calculated C, 53.15; H, 8.92; N, 17.71 %

3-Pyrrolidin-1-yl-propionitrile (13)



Nature: Yellow liquid

Yield: 98% (0.609 g)

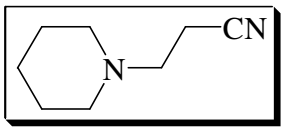
IR (neat): 2956, 2802, 2241, 1456, 1421, 1380, 1349, 1146, 1127 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.79-1.82 (4H, m), 2.52-2.58 (6H, m), 2.79 (2H, t, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 17.8, 23.7, 51.5, 54.0, 119.2 ppm.

Elemental Analysis: $C_7H_{12}N_2$ (124.18): Found C, 67.81; H, 9.79; N, 22.40. Calculated C, 67.70; H, 9.74; N, 22.56 %

3-Piperidin-1-yl-propionitrile (14)



Nature: Yellow liquid

Yield: 99% (0.684 g)

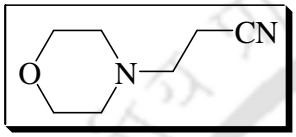
IR (neat): 2928, 2807, 2241, 1470, 1443, 1352, 1116, 1039 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.41-1.47 (2H, m), 1.57-1.62 (4H, m), 2.41-2.45 (4H, m), 2.51 (2H, t, *J* = 7.2 Hz), 2.68 (2H, t, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 15.8, 24.2, 25.9, 54.1, 54.3, 119.2 ppm.

Elemental Analysis: $C_8H_{14}N_2$ (138.21): Found C, 69.64; H, 10.25; N, 20.11. Calculated C, 69.52; H, 10.21; N, 20.27 %

3-Morpholin-4-yl-propionitrile (15)



Nature: Yellow liquid

Yield: 93% (0.652 g)

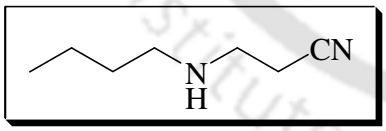
IR (neat): 2945, 2824, 2240, 1650, 1458, 1113, 1030 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.49-2.54 (6H, m), 2.68 (2H, t, *J* = 7.2 Hz), 3.72 (4H, t, *J* = 4.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 15.7, 53.0, 53.6, 66.7, 118.8 ppm.

Elemental Analysis: $C_7H_{12}N_2O$ (140.18): Found C, 59.85; H, 8.69; N, 20.12. Calculated C, 59.98; H, 8.63; N, 19.98 %

3-Butylaminopropionitrile (16)



Nature: Yellow liquid

Yield: 92% (0.580 g)

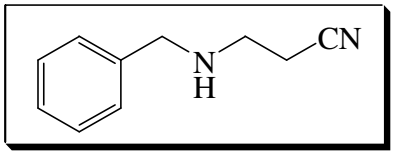
IR (neat): 3313, 2956, 2934, 2868, 2241, 1646, 1462, 1127 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 0.92 (3H, t, *J* = 7.6 Hz), 1.36 (2H, sex, *J* = 7.6 Hz), 1.44-1.51 (2H m), 2.53 (2H, t, *J* = 6.8 Hz), 2.64 (2H, t, *J* = 6.8 Hz), 2.93 (2H, t, *J* = 6.8 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 18.8, 20.4, 32.2, 45.2, 49.0, 118.9 ppm.

Elemental Analysis: $C_7H_{14}N_2$ (126.20): Found C, 66.51; H, 11.13; N, 22.36. Calculated C, 66.62; H, 11.18; N, 22.20 %

3-Benzylaminopropionitrile (17)



Nature: Yellow liquid

Yield: 91% (0.729 g)

IR (neat): 3313, 2923, 2851, 2241, 1643, 1492, 1451, 1023 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.54 (2H, t, *J* = 6.8 Hz), 2.94 (2H, t, *J* = 6.8 Hz), 3.84 (2H, s), 7.33-7.35 (5H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 18.8, 44.4, 53.3, 119.0, 127.6, 128.4, 128.8, 129.4 ppm.

Elemental Analysis: $C_{10}H_{12}N_2$ (160.22): Found C, 74.87; H, 7.50; N 17.63. Calculated C, 74.97; H, 7.55; N, 17.48 %

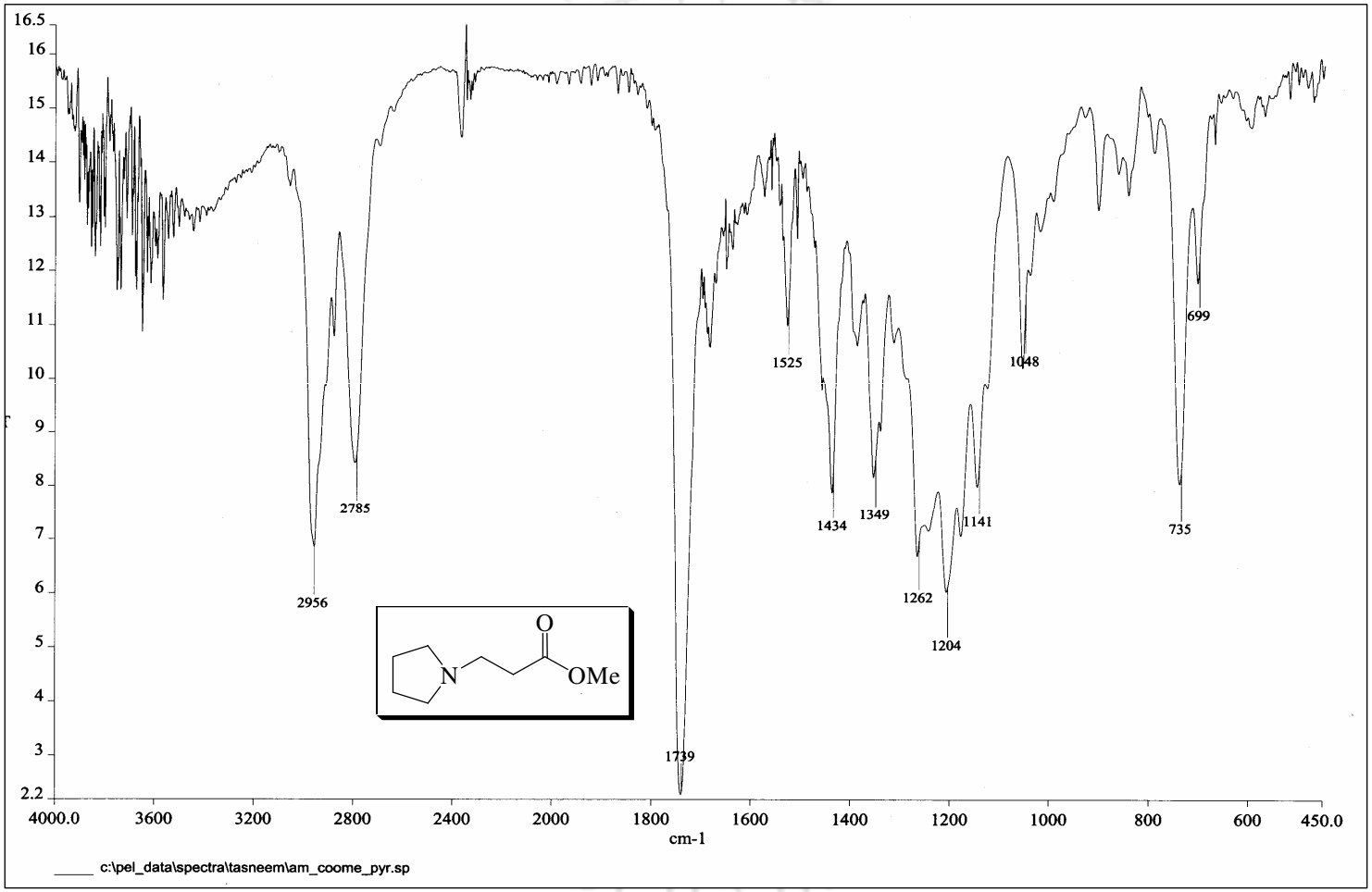


Figure 1: IR Spectrum of Methyl 3-(pyrrolidin-1-yl)propanoate (1)

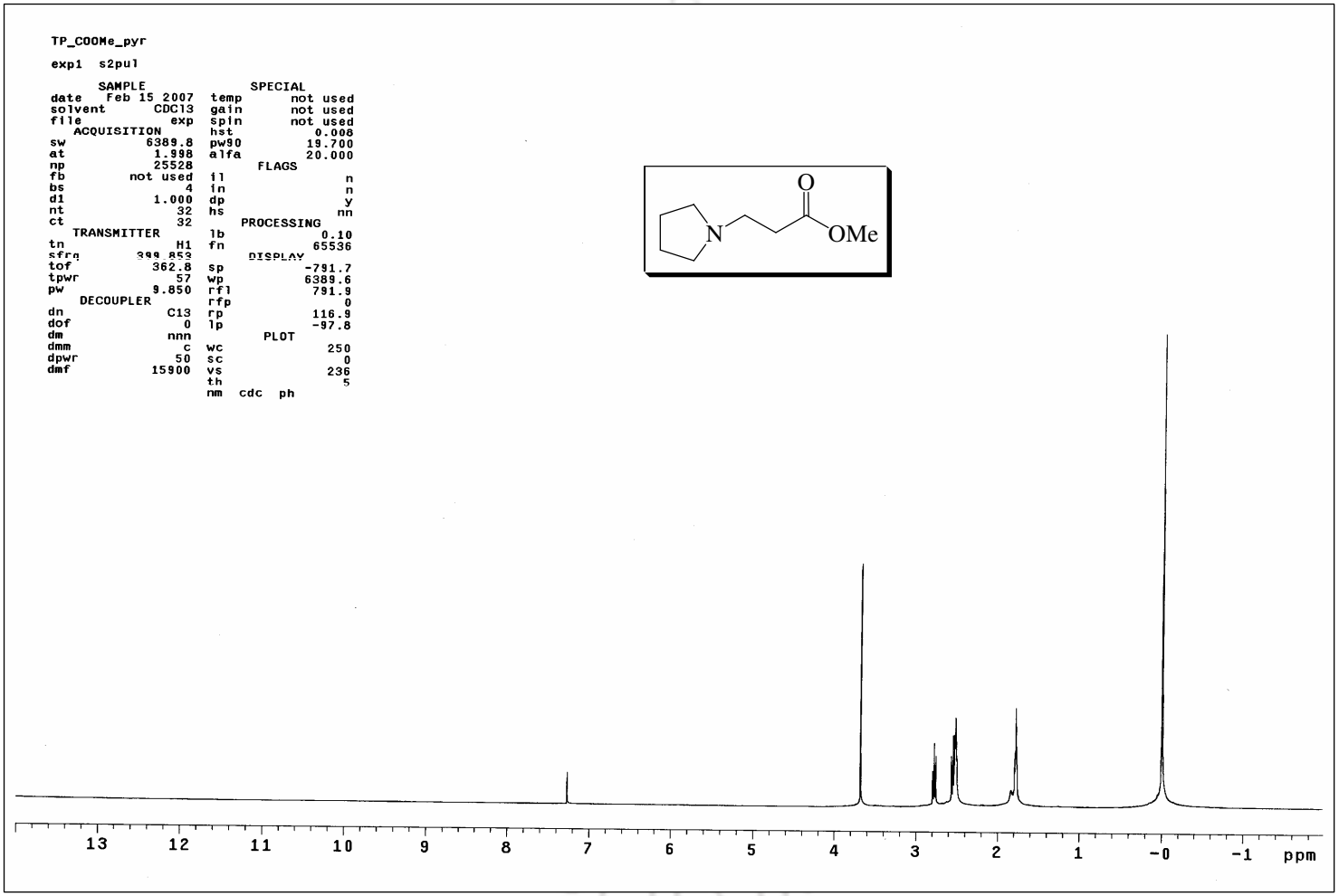


Figure 2: ^{1}H NMR Spectrum of Methyl 3-(pyrrolidin-1-yl)propanoate (1)

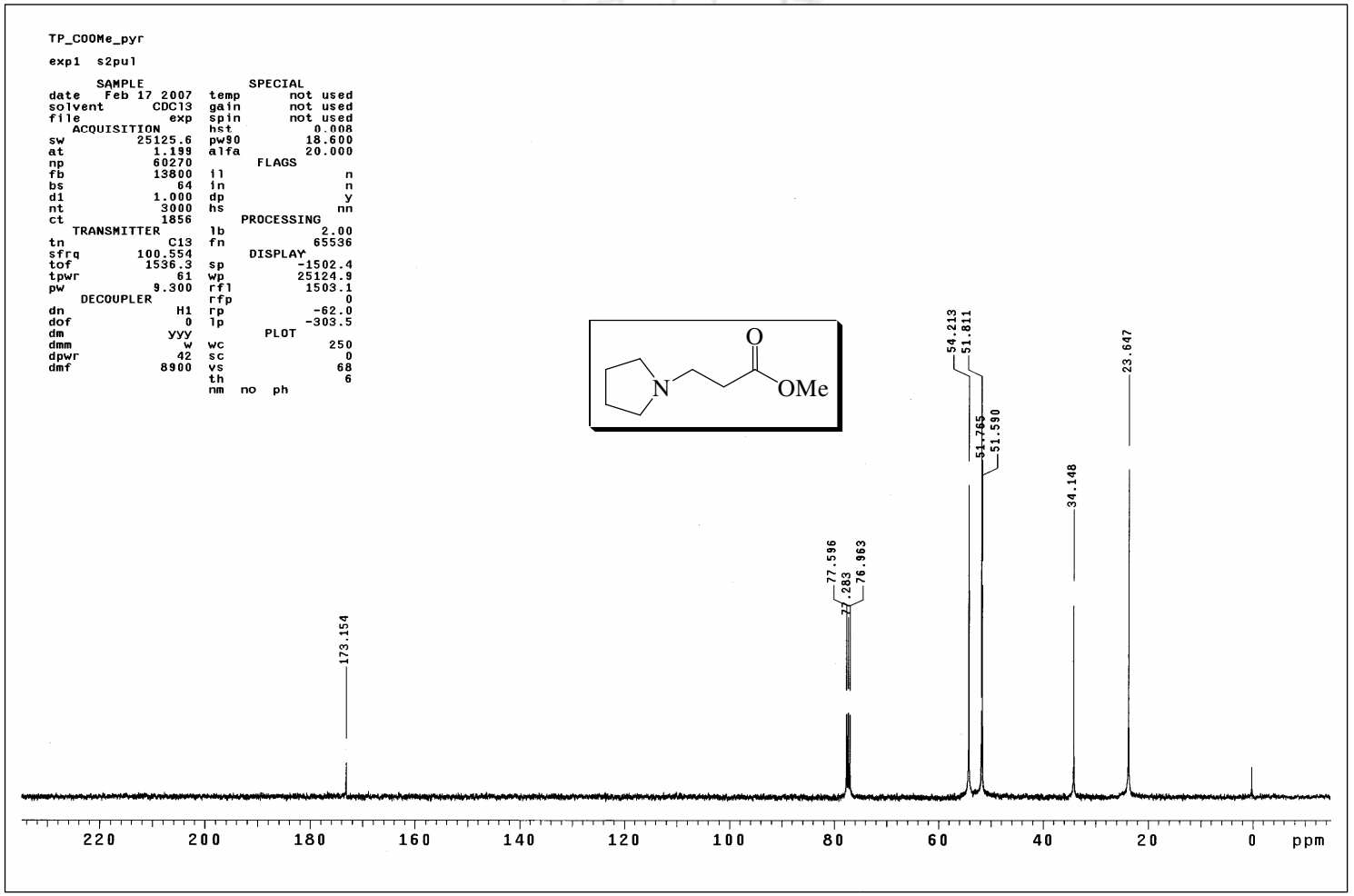


Figure 3: ^{13}C NMR Spectrum of Methyl 3-(pyrrolidin-1-yl)propanoate (1)

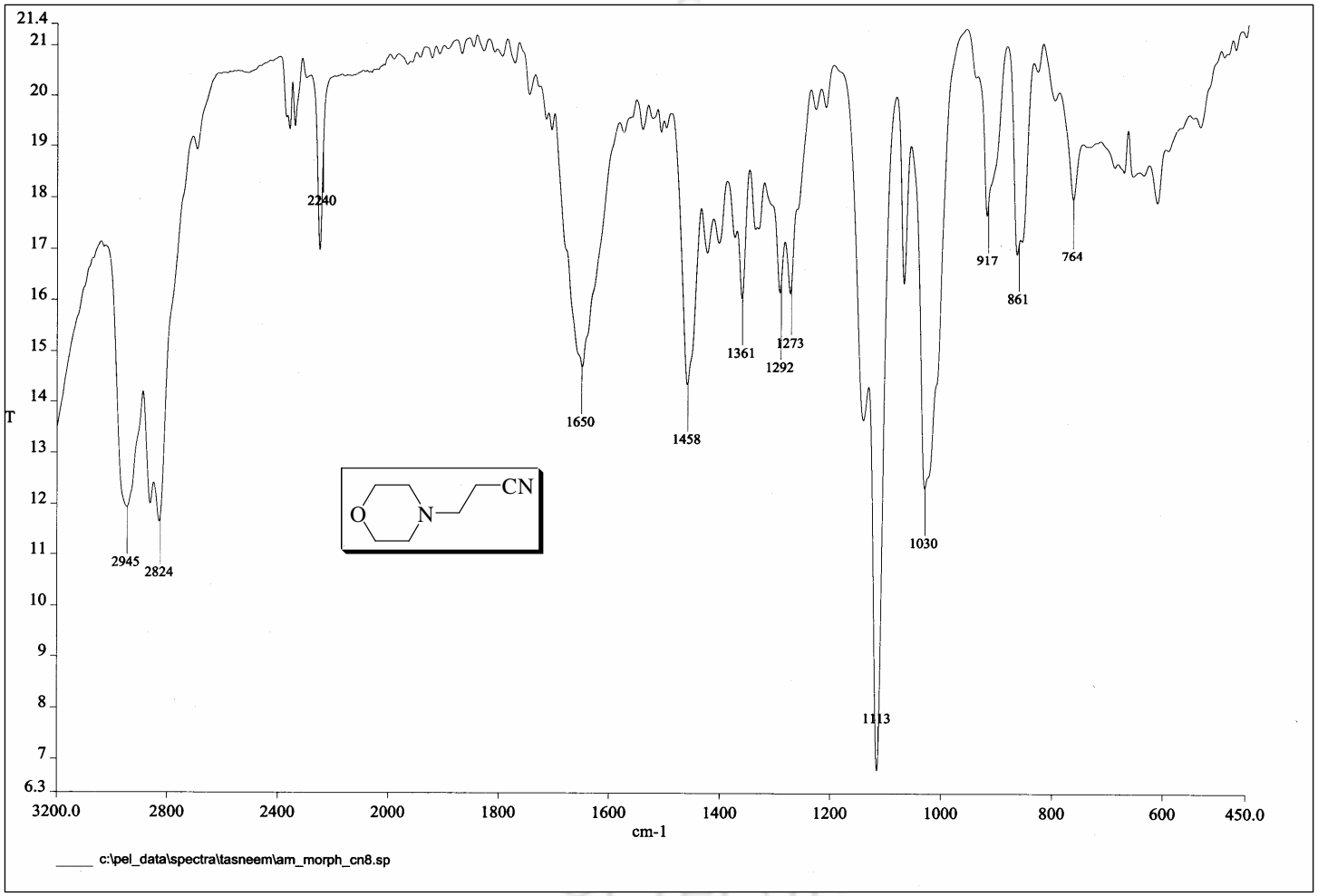


Figure 4: IR Spectrum of 3-Morpholin-4-yl-propionitrile (15)

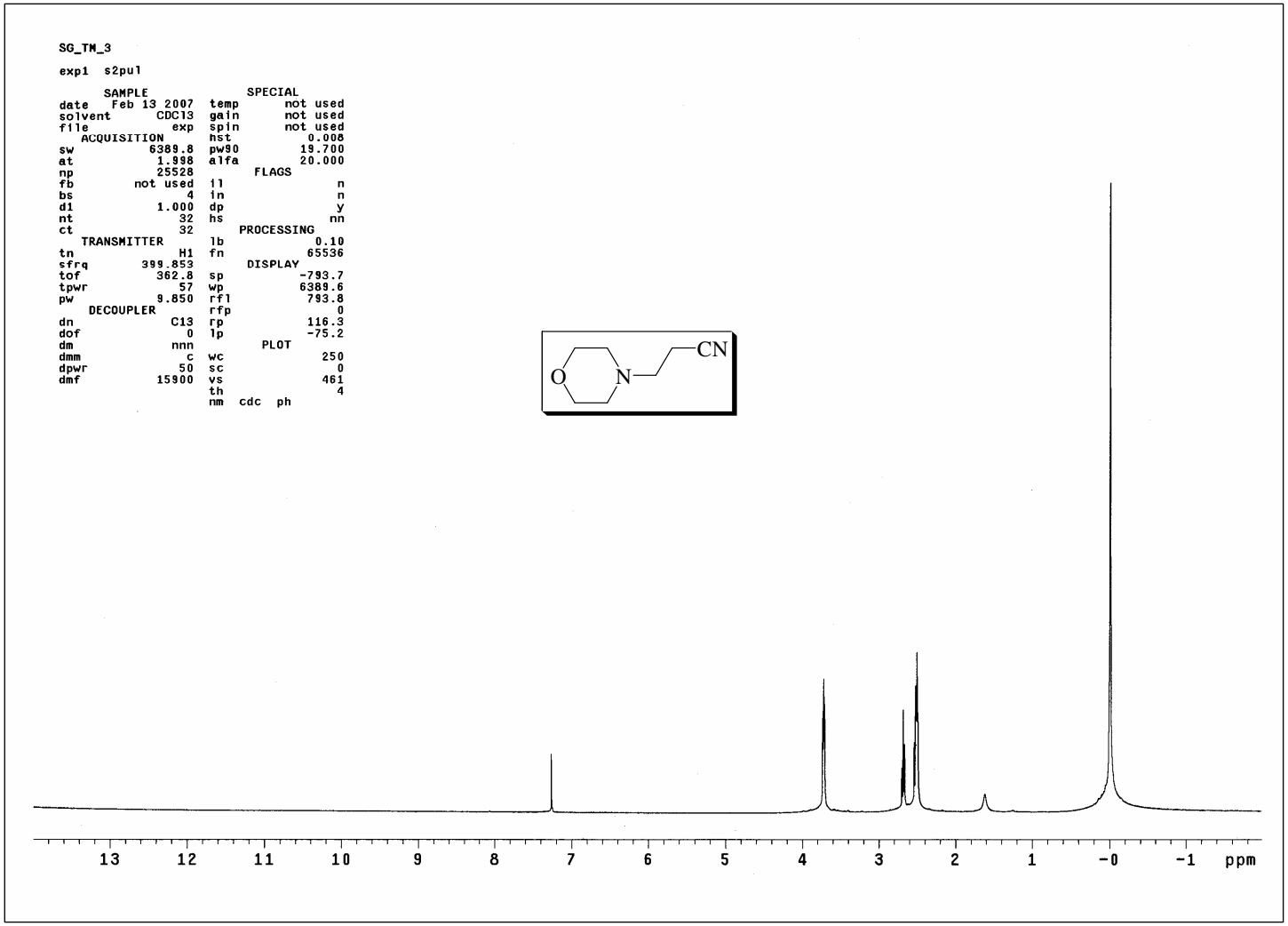


Figure 5: ^{1}H NMR Spectrum of 3-Morpholin-4-yl-propionitrile (15)

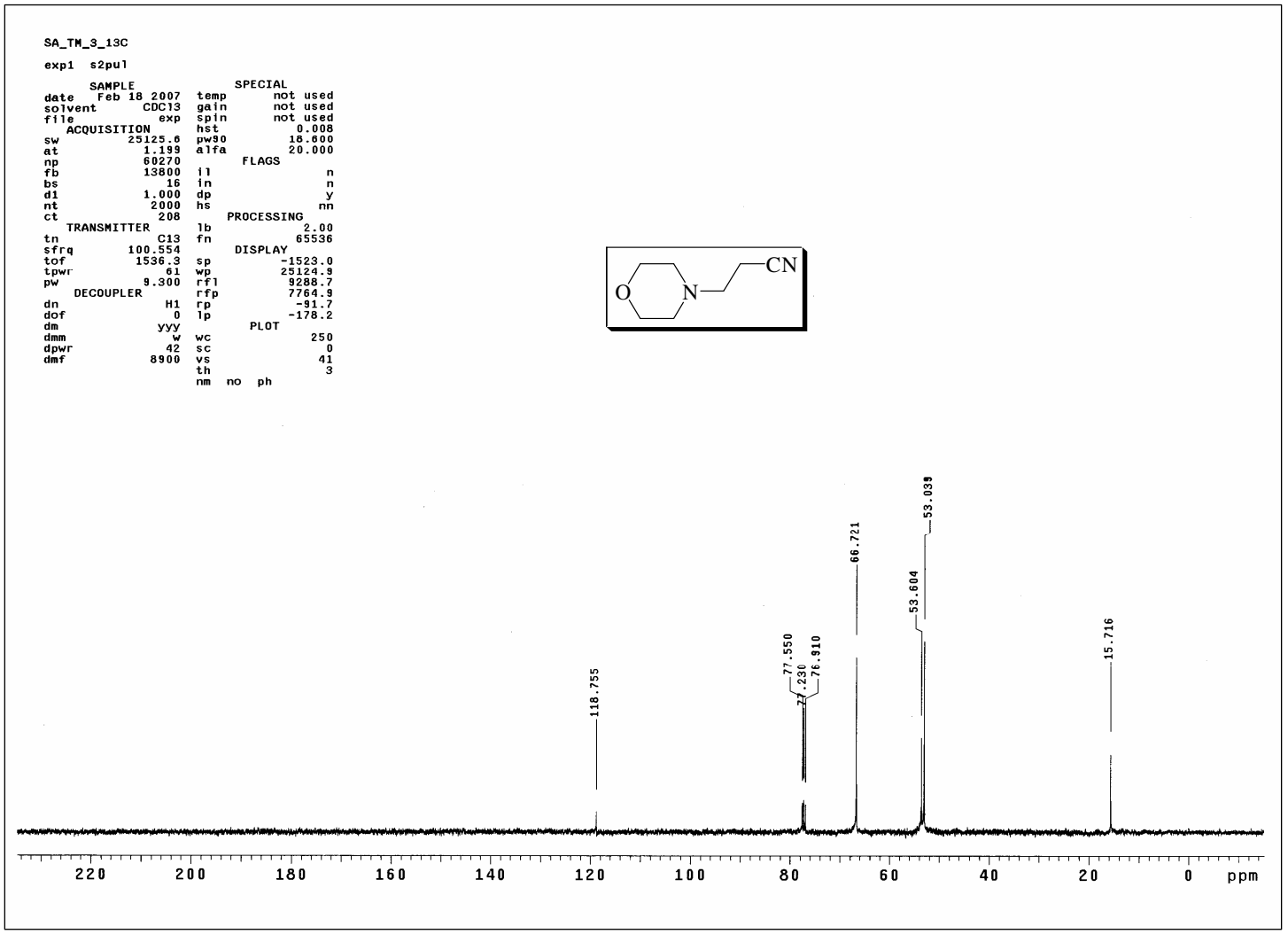


Figure 6: ^{13}C NMR Spectrum of 3-Morpholin-4-yl-propionitrile (15)

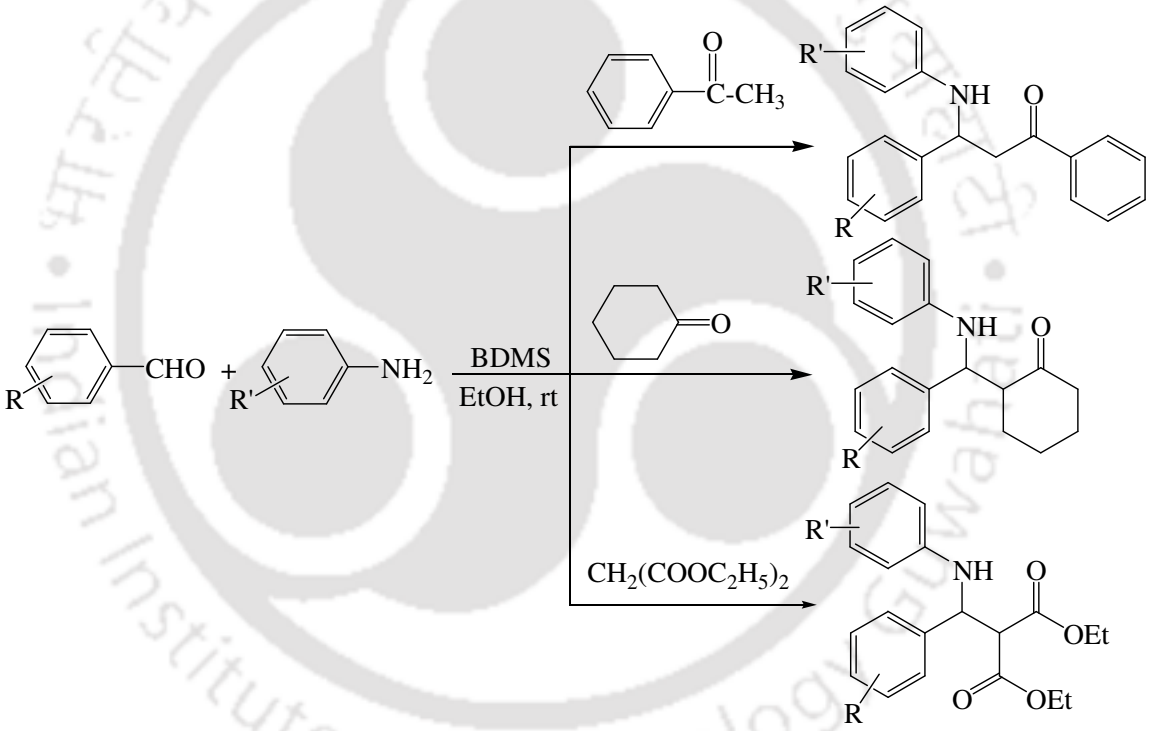
SECTION B

Bromodimethylsulfonium bromide (BDMS) catalyzed three-component Mannich-type reaction

RESULTS AND DISCUSSION

3.3.1 Results and Discussion:

Though we have successfully demonstrated the synthesis of β-amino carbonyl compounds using BDMS by aza-Michael reaction approach, which is elaborated in the previous section, but it was unsuccessful in case of aromatic amine.Therefore, we wanted to synthesize β-amino carbonyl compounds by employing the same catalyst by redesigning the strategy. In this section we will discuss our successful results on the catalytic activity of BDMS for three component direct Mannich-type reaction for the synthesis of β-amino carbonyl compounds. The reactions of aromatic aldehydes, aromatic amines and enolizable ketones or diethyl malonates in presence of BDMS as a catalyst are shown in Scheme 4.



Scheme 4

Initially, the three-component Mannich-type reaction of benzaldehyde (2.0 mmol), aniline (2.0 mmol) and acetophenone (2.0 mmol) was examined using bromodimethylsulfonium bromide as a catalyst. Interestingly, we observed that 10 mol% of bromodimethylsulfonium bromide is sufficient enough to catalyze the three-component one-pot reaction to afford the corresponding β-amino ketone **18** in a very good yield within 30 minutes (Table 3). The product **18** was characterized by usual spectroscopic techniques. Appearance of a broad peak at 3370 and a strong absorption at

1685 cm^{-1} in IR spectrum indicate the presence of NH and carbonyl functionalities respectively. The ^1H NMR signals appeared at 3.42 (1H, dd, *J* = 7.6 Hz, *J* = 16.0 Hz, -C*H*$_2$-), 3.51 (1H, dd, *J* = 5.2 Hz, *J* = 16.4 Hz, -C*H*$_2$-), 4.55 (1H, bs, -NH), 5.00 (1H, dd, *J* = 5.2 Hz, *J* = 7.2 Hz, -C*H*NH-), 6.56 (2H, d, *J* = 7.6 Hz, Ar), 6.66 (1H, t, *J* = 7.6 Hz, Ar), 7.09 (2H, t, *J* = 7.6 Hz, Ar), 7.23 (1H, t, *J* = 7.6 Hz, Ar), 7.32 (2H, t, *J* = 7.6 Hz, Ar), 7.43-7.46 (4H, m, Ar), 7.56 (1H, t, *J* = 7.2 Hz, Ar), 7.91 (2H, d, *J* = 7.6 Hz, Ar) ppm, clearly showed the formation of the product. In addition, ^{13}C NMR signals appeared at 46.3, 54.8, 113.8, 117.8, 126.4, 127.5, 128.2, 128.7, 128.8, 129.1, 133.4, 136.7, 143.0, 147.0, 198.3 ppm, supports the structure of the product **18**.

To see the role of the catalyst, the same set of combination was stirred in absence of BDMS. Interestingly, the reaction failed to provide the desired product even after 48 hour of stirring. The present protocol provides wealth of advantages in contrast to the indirect methods since there is no need of preparation of silyl enol ethers or preformed imines. During the screening of different solvents to find out the most suitable solvent for this transformation, ethanol was found to be superior as compared to the other solvents like THF, toluene, 1,4-dioxane and CH_2Cl_2 in terms of reaction time and yields obtained. Encouraged by this result, we examined the scope of this protocol by using various electron withdrawing aromatic aldehydes and amines. It is interesting to note that pure product of all these reactions can be obtained just by recrystallization of the crude from ethanol avoiding aqueous work up and tedious column chromatographic separation. Next, benzaldehyde was treated individually with a variety of aromatic amines such as 3-chloro-, 2-nitro- or 4-nitroaniline in combination with acetophenone and the corresponding products **19-21** were achieved in very good to excellent yields within 30 minutes to 1h time. It is gratifying to mention that the present method does not encounter any steric effects for the ortho substituted amines e.g., 2-nitro aniline as reported by recent methods.[45] In addition, 4-ethyl aniline provided the desired β-amino ketone **22** in a good yield.

Next, aldehydes tethered with electron withdrawing group such as 3-bromo- and 4-chlorobenzaldehyde were treated separately with a variety of aromatic amines in combination with acetophenone under the same experimental condition and the corresponding desired products (**23-30**) were isolated in very good yields without any

difficulty. It is worth mentioning that nitro aldehydes such as 4-nitrobenzaldehyde and 3-nitro benzaldehyde provided the corresponding chalcone instead of the desired β-amino ketone on treatment with aniline and acetophenone separately under the same experimental conditions. We believe nitro substituted aldehydes prefer the aldol reaction followed by subsequent dehydration rather than the *in situ* aldimine formation and subsequent nucleophilic addition. Next, terephthalaldehyde was treated with 2 equivalents of aniline and acetophenone to afford a *bis* product **31** as shown in Table 3.

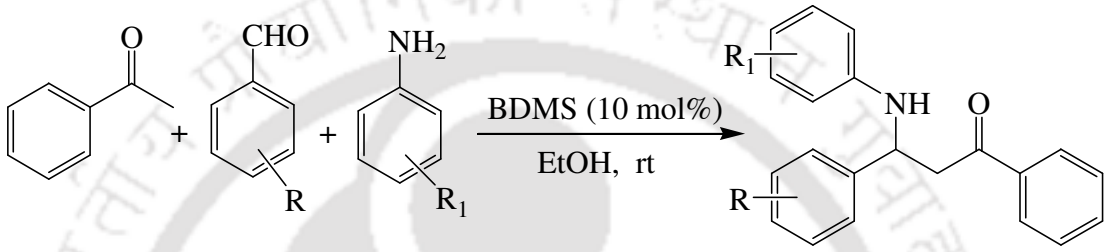
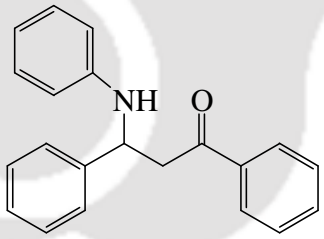
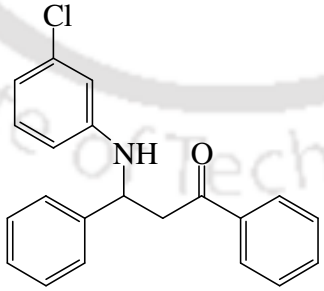
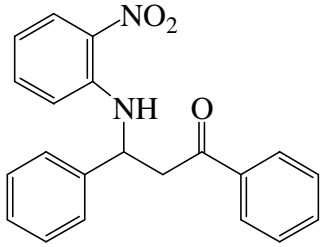
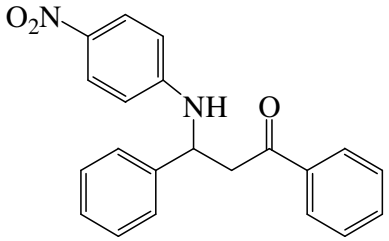
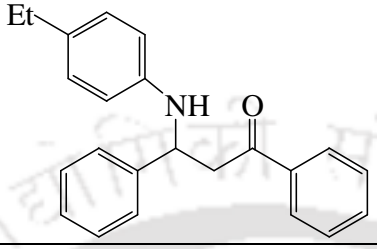
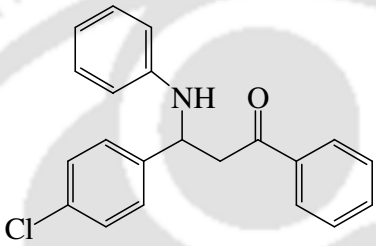
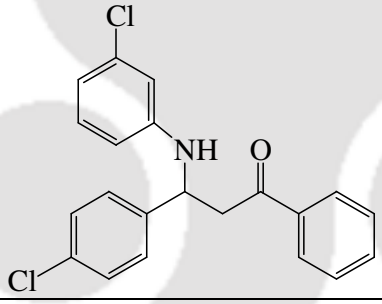
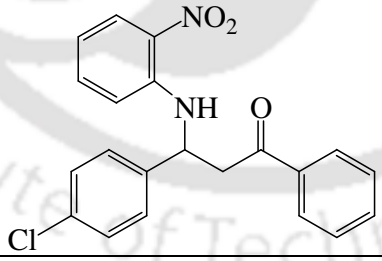
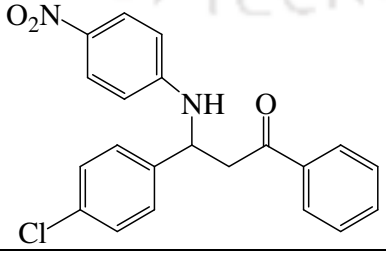
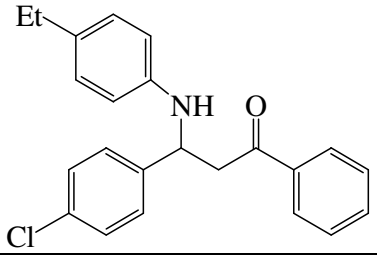
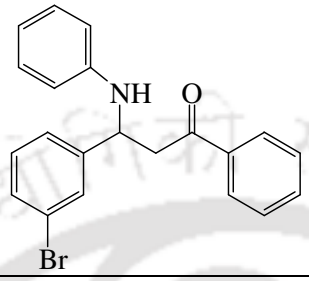
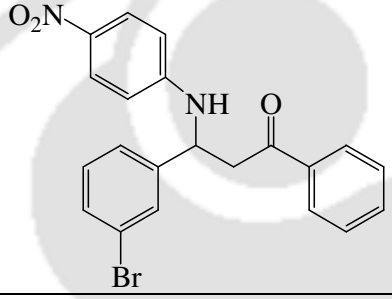
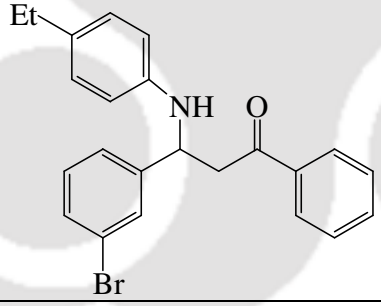
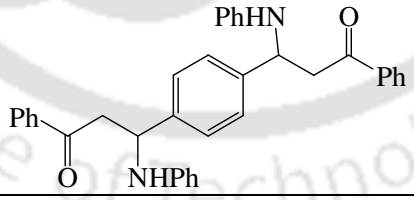


Table 3. Three component bromodimethylsulfonium bromide catalyzed direct Mannich-type reaction of various aromatic aldehydes, amines and ketones.

Product No.	Product[a]	Time min/[h]	Yield (%)[b]
18		30	96[38]
19		30	98
20		[1]	88

21		30	95
22		[1]	97
23		40	97[38]
24		[4]	98
25		[2]	87
26		40	97

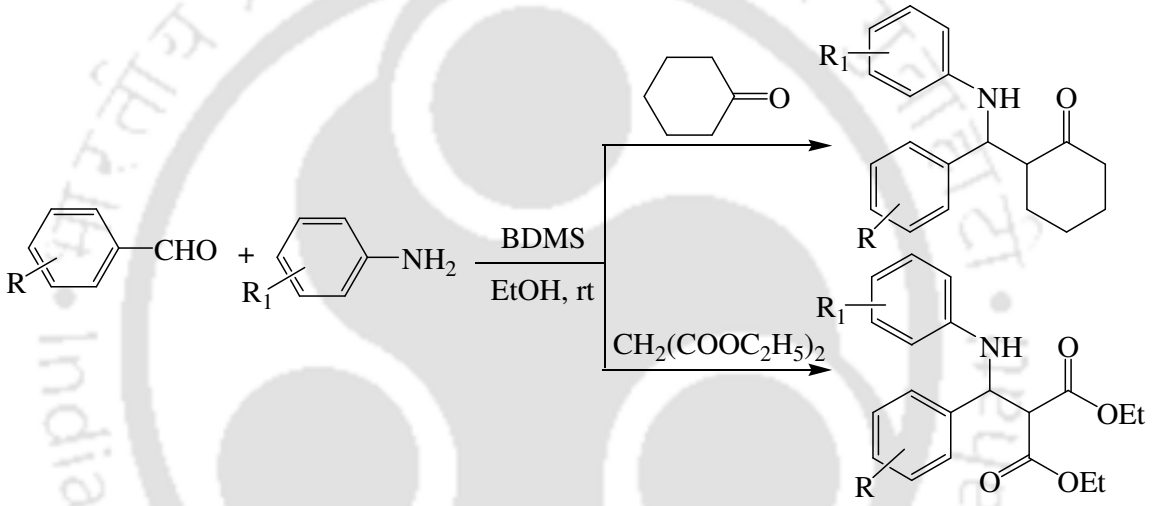
27		[4]	95
28		[3]	90
29		[1]	89
30		[2]	92
31		30	89

[a]All the products were fully characterized by usual spectroscopic techniques. [b]Isolated yield.

To generalize the method, an aliphatic aldehyde such as heptanal was treated with aniline and acetophenone under similar conditions. After 12 h of stirring, we could not get the desired Mannich product. Similarly, the combination of aliphatic amine such as *n*-butylamine with benzaldehyde and acetophenone under the same experimental condition was also unsuccessful even after prolong stirring. Likewise, the reaction of aliphatic ketone such as acetone was also not applicable for Mannich type reaction with

benzaldehyde and aniline under the given experimental condition. In an attempt to check the applicability of benzyl amine, we were unsuccessful to achieve the desired β-amino ketone. From these studies we have revealed that the present method is a selective method for Mannich type reaction of aromatic aldehydes, amine and ketones.

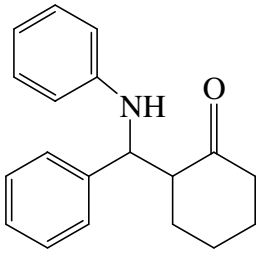
Subsequently, to extend the preparative utility and generality of this multi-component reaction, benzaldehyde and 4-chlorobenzaldehyde were treated individually with aniline and 3-chloroaniline in combination with other enolizable carbonyl compounds such as cyclohexanone or diethyl malonate under the same experimental condition as shown in Scheme 5.

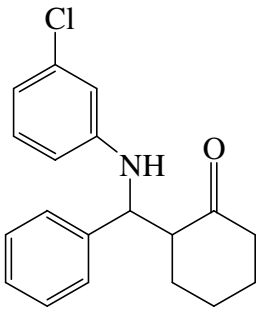
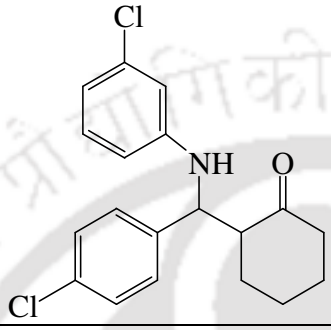
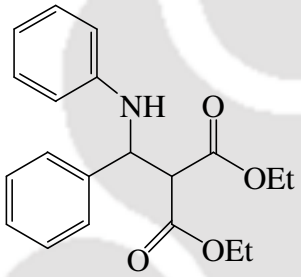
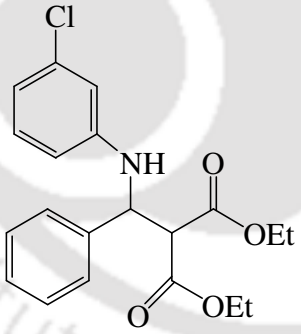


Scheme 5

The results are summarized in Table 4. Interestingly, the reaction of cyclohexanone with benzaldehyde or 4-chlorobenzaldehyde exhibit good diastereoselectivity and provides *anti* as a major isomer (**32-34**). The *anti / syn* ratio was determined from the ^{1}H NMR spectrum.

Table 4. BDMS catalyzed multi-component reaction of aromatic aldehydes, amines and cyclo hexanone or diethyl malonate

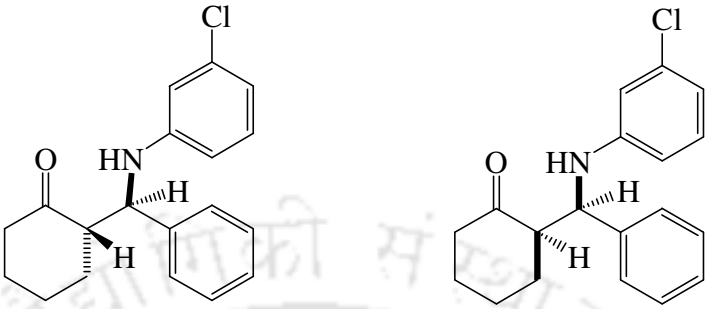
Product No	Product[a]	Time min/[h]	Yield[b] (%)	*anti:syn*[c]
32		15	86	98:2

33		15	92	98:2
34		20	88	99:1
35		[6]	92	-
36		[7]	94	-

[a]All the products were fully characterized by usual spectroscopic techniques**.** [b]Isolated Yields. [c]ratio was determined from the ^{1}H NMR spectra.

To confirm unambiguously the *anti*-configuration of these products, the compound **33** was recrystallized from ethanol and a single crystal XRD was recorded. The ORTEP plot of the product showing *anti*- configuration is depicted in Figure 7. A unit cell consists of four molecules and they exhibit intermolecular hydrogen bonding between the C=O of one molecule with the N-H of the other. Likewise, diethylmalonate also reacted under the

same experimental condition and provided the corresponding ethyl ester of β-amino acid (**35-36**) in good yields.



anti $J = 6.8$ Hz *syn* $J = 4.0$ Hz

Scheme 6 *Syn* and *anti* isomer of product **33**.

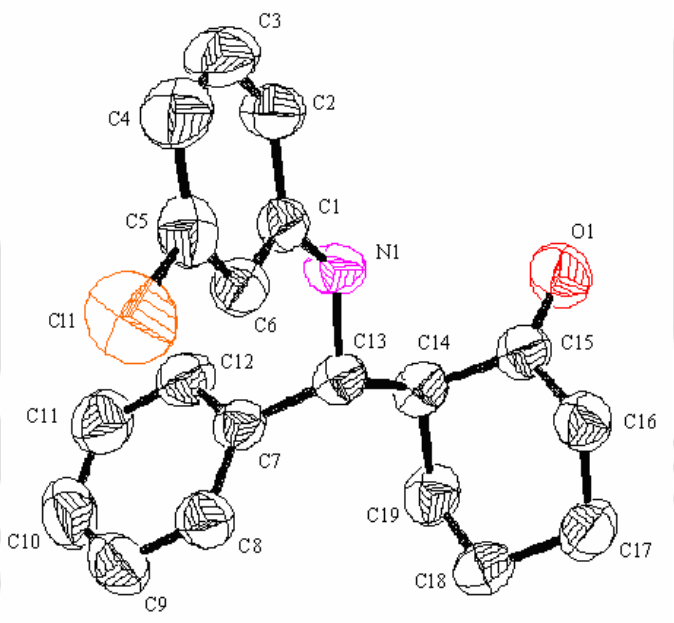


Figure 7: ORTEP plot of **33** showing *anti* configuration

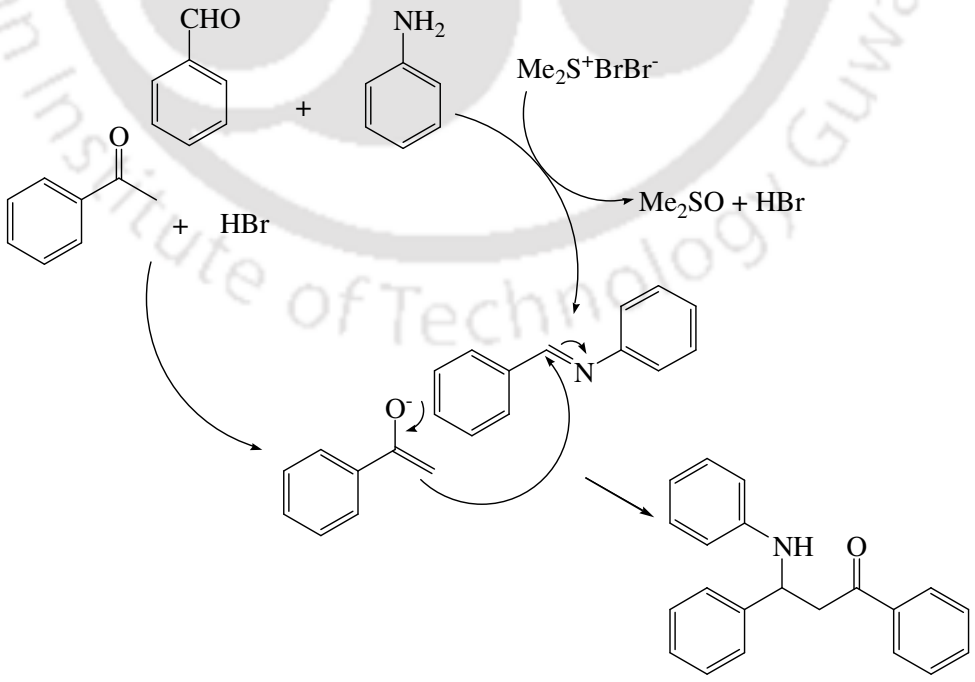
It is noteworthy to mention that the present method is reasonably faster, cost-effective and simpler than the most of the existing methods. The efficacy and generality of the catalyst bromodimethylsulfonium bromide can be ascertained from the comparison depicted in Table 5. For this comparison the reaction of acetophenone, benzaldehyde and aniline was chosen as a model reaction and comparison was carried out on the basis of reaction condition, reaction time and % of yields obtained.

Table 5. Comparison of the catalytic activity of BDMS with different catalysts for the Mannich reaction of benzaldehyde, aniline and acetophenone.

Run	Catalyst	Reaction condition	Reaction Time	Yield (%)[a]
1	No Catalyst	EtOH, rt	48h	NR
2	$FeCl_3$	EtOH, rt	24h	NR[45]
3	$NbCl_5$	EtOH, rt	12 h	95[45]
4	$Yb(OPf)_3$	$PhCH_3/C_6F_5CF_3$	12 h	98[48]
5	Silica sulfuric acid	EtOH, rt	12 h	92[42]
6	$[NaBAr_4^F]$	H_2O, 30 ^oC	48 h	81[49]
7	BDMS	EtOH, rt	30 min	96

[a]Corresponding reference.

The catalyst, bromodimethylsulfonium bromide, is an inexpensive reagent. We believe BDMS catalyzes the present conversion with the rapid formation of imines along with its simultaneous transformation into Me_2SO and HBr.



Scheme 7 Plausible mechanistic illustration of BDMS catalyzed Mannich-type reaction

The nucleophilic addition of enolizable ketone to these imines in the presence of HBr followed by subsequent hydrolysis afforded β-amino carbonyl compounds. The reaction of Me_2SO with HBr regenerated the catalyst bromodimethylsulfonium bromide.

In summary, we have achieved the synthesis of β-amino carbonyl compounds, using bromodimethylsulfonium bromide as a versatile catalyst, by Mannich-type reaction of a variety of *in situ* generated aldimines using aldehydes and anilines, with enolizable ketones or diethyl malonate. The salient features of this protocol are: (a) simplicity of the procedure, (b) ready accessibility of the catalyst and cost effectiveness (c) avoidance of column chromatography as well as (d) high yields and good diastereo selectivities.

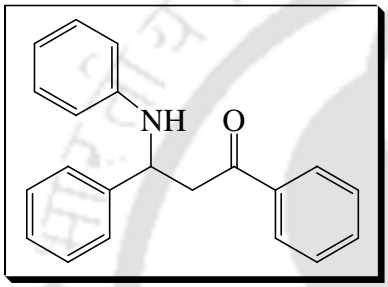
SECTION B

Bromodimethylsulfonium bromide (BDMS) catalyzed three-component Mannich-type reaction

3.3.2 General Reaction Procedure:

To a mixture of benzaldehyde (2 mmol), aniline (2 mmol) and acetophenone (2 mmol), bromodimethylsulfonium bromide (0.2 mmol) was added and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction the crude solid was just filtered off and washed it with a mixture of hexane-ethanol (80:20). Then the solid residue was dissolved in hot ethanol and was recrystallized to get the pure product. The pure product was characterized by usual spectroscopic methods and compared with the reported data.

1,3-diphenyl-3-(phenylamino)propan-1-one (18)



Nature: White solid

Yield: 96% (0.579 g)

M.p. 169-171 ^{o}C

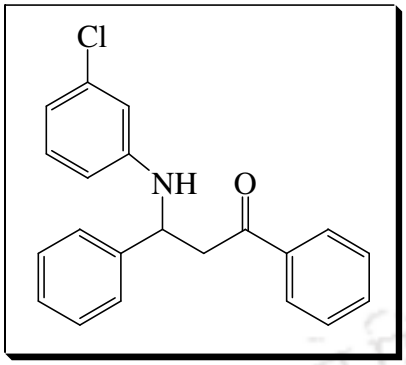
IR (KBr): 3370, 1685 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 3.42 (1H, dd, *J* = 7.6 Hz, *J* = 16.4 Hz), 3.51 (1H, dd, *J* = 5.2 Hz, *J* = 16.4 Hz), 4.55 (1H, bs), 5.00 (1H, dd, *J* = 5.2 Hz, *J* = 7.2 Hz), 6.56 (2H, d, *J* = 7.6 Hz), 6.66 (1H, t, *J* = 7.6 Hz), 7.09 (2H, t, *J* = 7.6 Hz), 7.23 (1H, t, *J* = 7.6 Hz), 7.32 (2H, t, *J* = 7.6 Hz), 7.43-7.46 (4H, m), 7.56 (1H, t, *J* = 7.2 Hz), 7.91 (2H, d, *J* = 7.6 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 46.3, 54.8, 113.8, 117.8, 126.4, 127.5, 128.2, 128.7, 128.8, 129.1, 133.4, 136.7, 143.0, 147.0, 198.3 ppm.

Elemental Analysis: $C_{21}H_{19}NO$ (301.38): Found C, 83.82, H, 6.29, N, 4.81 Calculated C, 83.69; H, 6.35; N, 4.65 %

3-Phenyl-1-phenyl-3-(3-chlorophenylamino)propan-1-one (19)



Nature: White solid

Yield: 98% (0.658 g)

M.p. 140-141 ^{o}C

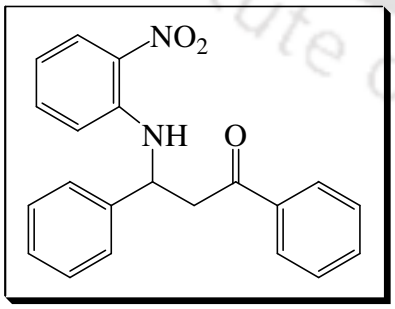
IR (KBr): 3372, 1686 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 3.42 (1H, dd, *J* = 7.2 Hz, *J* = 16.4 Hz), 3.50 (1H, dd, *J* = 4.8 Hz, *J* = 16.0 Hz), 4.71 (1H, bs), 4.97 (1H, t, *J* = 6.0 Hz), 6.42 (1H, d, *J* = 8.0 Hz), 6.54 (1H, s), 6.62 (1H, d, *J* = 7.6 Hz), 6.98 (1H, t, *J* = 8.0 Hz), 7.27 (1H, d, *J* = 7.2 Hz), 7.34 (2H, t, *J* = 7.2 Hz), 7.41-7.47 (4H, m), 7.59 (1H, t, *J* = 7.2 Hz), 7.90 (2H, d, *J* = 8.4 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 45.9, 54.5, 111.8, 113.5, 117.5, 126.1, 127.4, 128.0, 128.6, 128.8, 129.9, 133.4, 134.6, 136.4, 142.1, 148.0, 197.9 ppm.

Elemental Analysis: $C_{21}H_{18}ClNO$ (335.83): Found C, 75.28; H, 5.43; N, 4.07. Calculated C, 75.11; H, 5.40; N, 4.17 %

3-Phenyl-1-phenyl-3-(2-nitrophenylamino)propan-1-one (20)



Nature: Yellow solid

Yield: 88% (0.610 g)

M.p. 100-101 ^{o}C

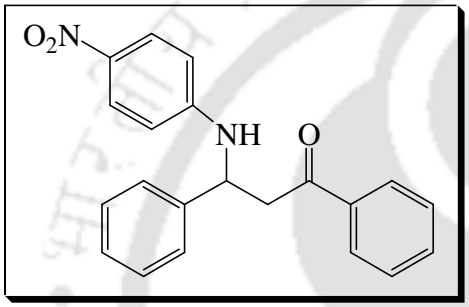
IR (KBr): 3370, 1685, 1592, 1352 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 3.52 (1H, dd, *J* = 5.2 Hz, *J* = 17.2 Hz), 3.66 (1H, dd, *J* = 7.6 Hz, *J* = 17.2 Hz), 5.33-5.39 (1H, m), 6.63 (1H, t, *J* = 7.2 Hz), 6.80 (1H, d, *J* = 8.0 Hz), 7.29-7.37 (4H, m,), 7.43-7.48 (4H, m), 7.58 (1H, t, *J* = 7.2 Hz), 7.92 (2H, d, *J* = 7.2 Hz), 8.16 (1H, d, *J* = 7.2 Hz,), 8.63 (1H, bs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 47.2, 54.0, 115.5, 116.5, 126.8, 127.3, 128.3, 128.7, 129.3, 129.6, 133.0, 134.1, 136.7, 136.9, 142.0, 144.8, 197.2 ppm.

Elemental Analysis: $C_{21}H_{18}N_2O_3$ (346.38): Found C, 72.93; H, 5.20; N, 7.94. Calculated C, 72.82; H, 5.24; N 8.09 %

3-Phenyl-1-phenyl-3-(4-nitrophenylamino)propan-1-one (21)



Nature: Yellow solid

Yield: 95% (0.658 g)

M.p. 177-178 ^oC (Lit[52] M.p. 179-180 ^0C)

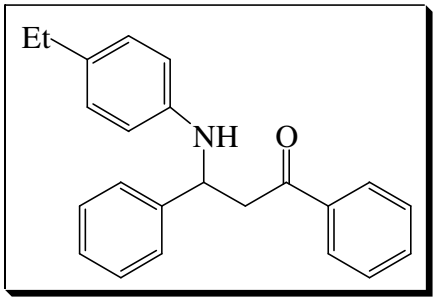
IR (KBr): 3371, 1685, 1590, 1350 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 3.53 (2H, d, *J* = 6.8 Hz), 5.10 (1H, t, *J* = 6.0 Hz), 5.58 (1H, bs), 6.52 (2H, d, *J* = 9.2 Hz), 7.28 (1H, d, *J* = 7.2 Hz), 7.34 (1H, d, *J* = 8.0 Hz), 7.38 (3H, t, *J* = 7.2 Hz), 7.46 (2H, t, *J* = 7.6 Hz), 7.59 (1H, t, *J* = 7.2 Hz), 7.89 (2H, d, *J* = 7.2 Hz), 8.00 (2H, d, *J* = 9.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 46.0, 55.0, 101.9, 112.9, 126.7, 128.5, 128.7, 129.3, 129.7, 134.4, 136.9, 139.1, 141.6, 152.6, 198.4 ppm.

Elemental Analysis: $C_{21}H_{18}N_2O_3$ (346.38): Found C, 72.65; H, 5.16; N, 8.19. Calculated C, 72.82; H, 5.24; N 8.09 %

3-Phenyl-1-phenyl-3-(4-ethylphenylamino)propan-1-one (22)



Nature: White solid

Yield: 97% (0.639 g)

M.p. 126-127 ^{o}C

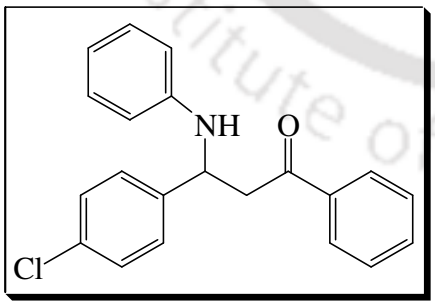
IR (KBr): 3400, 1679 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.13 (3H, t, *J* = 7.6 Hz), 2.48 (2H, q, *J* = 7.6 Hz), 3.42 (1H, dd, *J* = 7.6 Hz, *J* = 16.4 Hz), 3.51 (1H, dd, *J* = 5.2 Hz, *J* = 16.4 Hz), 4.60 (1H, bs), 4.97 (1H, dd, *J* = 5.2 Hz, *J* = 7.6 Hz), 6.51 (2H, d, *J* = 8.4 Hz), 6.93 (2H, d, *J* = 8.4 Hz), 7.23 (1H, t, *J* = 7.2 Hz), 7.32 (2H, t, *J* = 7.2 Hz), 7.42-7.46 (4H, m), 7.56 (1H, t, *J* = 7.2 Hz,), 7.91 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 16.0, 28.0, 46.4, 55.2, 114.2, 126.6, 127.4, 128.3, 128.5, 128.8, 128.9, 133.5, 133.8, 136.7, 143.2, 144.9, 198.4 ppm.

Elemental Analysis: $C_{23}H_{23}NO$ (329.44): Found C, 83.60; H, 7.11; N, 4.38. Calculated C, 83.86; H, 7.04; N, 4.25 %

3-(4-chlorophenyl)-1-phenyl-3-(phenylamino)propan-1-one (23)



Nature: White solid

Yield: 97% (0.652 g)

M.p. 117-118 ^{o}C

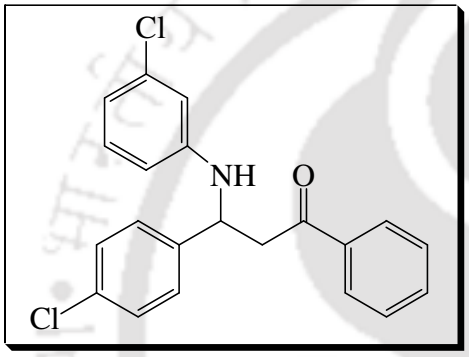
IR (KBr): 3376, 1684 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 3.41 (1H, dd, *J* = 7.2 Hz, *J* = 16.0 Hz), 3.48 (1H, dd, *J* = 5.2 Hz, *J* = 16.0 Hz), 4.55 (1H, bs), 4.97 (1H, t, *J* = 7.2 Hz), 6.53 (2H, d, *J* = 7.6 Hz), 6.68 (1H, t, *J* = 7.6 Hz), 7.10 (2H, t, *J* = 7.2 Hz), 7.28 (2H, t, *J* = 8.8 Hz), 7.38 (2H, t, *J* = 8.8 Hz), 7.45 (2H, t, *J* = 7.6 Hz), 7.57 (1H, t, *J* = 7.6 Hz), 7.89 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 46.3, 54.3, 114.0, 118.2, 128.0, 128.4, 129.0, 129.2, 129.4, 133.1, 133.8, 141.7, 146.9, 151.5, 198.1 ppm.

Elemental Analysis: $C_{21}H_{18}ClNO$ (335.83): Found C, 75.22; H, 5.34; N, 4.32. Calculated C, 75.11; H, 5.40; N, 4.17 %

3-(4-Chlorophenyl)-1-phenyl-3-(3-chlorophenylamino)propan-1-one (24)



Nature: White solid

Yield: 98% (0.726 g)

M.p. 117-118 ^oC

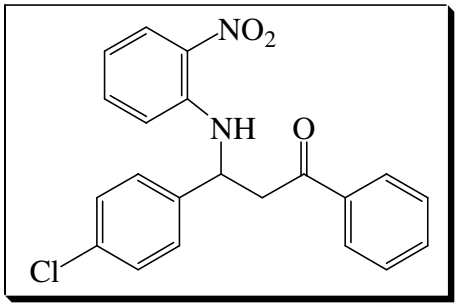
IR (KBr): 3376, 1684 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 3.42-3.46 (2H, m), 4.71 (1H, bs), 4.93-4.96 (1H, m), 6.40 (1H, d, *J* = 8.4 Hz), 6.51 (1H, s), 6.64 (1H, d, *J* = 8.0 Hz), 6.99 (1H, t, *J* = 8.4 Hz), 7.30 (2H, d, *J* = 8.4 Hz), 7.36 (2H, d, *J* = 8.4 Hz), 7.46 (2H, t, *J* = 7.2 Hz), 7.58 (1H, t, *J* = 8.4 Hz), 7.89 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 46.4, 54.4, 112.4, 114.0, 118.4, 128.2, 128.6, 129.3, 129.5, 130.6, 133.6, 134.2, 135.3, 136.9, 141.4, 148.4, 198.2 ppm.

Elemental Analysis: $C_{21}H_{17}Cl_2NO$ (370.28): Found C, 67.90; H, 4.57; N, 3.69. Calculated C, 68.12; H, 4.63; N, 3.78 %.

3-(4-Chlorophenyl)-1-phenyl-3-(2-nitrophenylamino)propan-1-one (25)



Nature: Yellow solid

Yield: 87% (0.663 g)

M.p. 92-93 ^{o}C

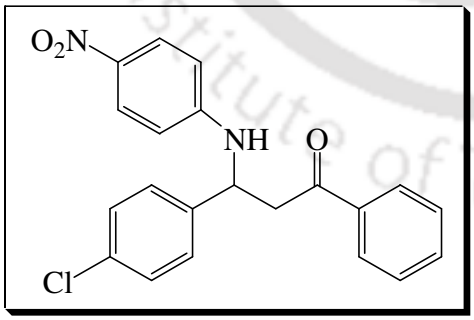
IR (KBr): 3376, 1685, 1591, 1297 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 3.48 (1H, dd, *J* = 4.4 Hz, *J* = 16.8 Hz), 3.62 (1H, dd, *J* = 6.4 Hz, *J* = 16.4 Hz), 5.29-5.33 (1H, m), 6.64 (1H, t, *J* = 8.8 Hz), 6.71 (1H, d, *J* = 8.8 Hz), 7.28-7.32 (3H, m), 7.36 (2H, d, *J* = 7.6 Hz), 7.44 (2H, t, *J* = 8.0 Hz), 7.56 (1H, t, *J* = 7.2 Hz), 7.89 (2H, d, *J* = 7.2 Hz), 8.14 (1H, d, *J* = 8.8 Hz), 8.57 (1H, d, *J* = 5.6 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 46.7, 53.1, 115.0, 116.4, 127.0, 128.0, 128.3, 129.0, 129.4, 132.7, 133.7, 134.0, 136.4, 136.5, 140.3, 144.2, 196.5 ppm.

Elemental Analysis: $C_{21}H_{17}ClN_2O_3$ (380.83): Found C, 66.32; H, 4.42; N, 7.25. Calculated C, 66.23; H, 4.50; N, 7.36 %

3-(4-Chlorophenyl)-1-phenyl-3-(4-nitrophenylamino)propan-1-one (26)



Nature: Yellow solid

Yield: 97% (0.739 g)

M.p. 150-151 ^{o}C (Lit[52] M.p. 149-150 ^{o}C)

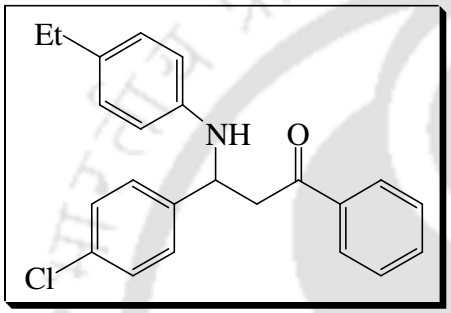
IR (KBr): 3375, 1685, 1593, 1296 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 3.52 (2H, d, *J* = 6.4 Hz), 5.07 (1H, q, *J* = 6.0 Hz), 5.56 (1H, d, *J* = 6.0 Hz), 6.50 (2H d, *J* = 9.2 Hz) , 7.30-7.35 (4H, m), 7.47 (2H, t, *J* = 8.0 Hz), 7.60 (1H, t, *J* = 7.6 Hz), 7.89 (2H, d, *J* = 7.6 Hz), 8.01 (2H, d, *J* = 9.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 45.5, 53.7, 112.4, 126.4, 127.8, 128.3, 129.0, 129.4, 133.7, 134.1, 136.3, 138.6, 139.9, 152.2, 197.7 ppm.

Elemental Analysis: $C_{21}H_{17}ClN_2O_3$ (380.83): Found C, 66.31; H, 4.46; N, 7.27. Calculated C, 66.23; H, 4.50; N, 7.36 %

3-(4-Chlorophenyl)-1-phenyl-3-(4-ethylphenylamino)propan-1-one (27)



Nature: White solid

Yield: 95% (0.691 g)

M.p. 91-92 ^oC

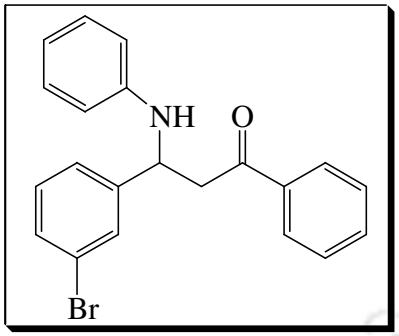
IR (KBr): 3400, 1680 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.12 (3H, t, *J* = 7.6 Hz), 2.47 (2H, q, *J* = 7.6 Hz), 3.47 (2H, d, *J* = 7.2 Hz), 4.71 (1H, bs), 4.92 (1H, t, *J* = 6.8 Hz), 6.51 (2H, d, *J* = 8.4 Hz), 6.92 (2H, d, *J* = 8.4 Hz), 7.26 (2H, d, *J* = 8.4 Hz), 7.38 (2H, d, *J* = 8.4 Hz), 7.43 (2H, t, *J* = 7.6 Hz), 7.55 (1H, t, *J* = 7.6 Hz,), 7.88 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 16.0, 28.1, 46.1, 55.2, 114.8, 128.2, 128.4, 128.7, 128.9, 129.1, 133.2, 133.8, 134.8, 136.6, 141.3, 143.9, 198.0 ppm.

Elemental Analysis: $C_{23}H_{22}ClNO$ (363.89): Found C, 75.81; H, 6.14; N, 3.96. Calculated C, 75.92; H, 6.09; N, 3.85 %.

3-(3-Bromophenyl)-1-phenyl-3-phenylamino-propan-1-one (28)



Nature: Light blue solid

Yield: 90% (0.685 g)

M.p. 95-96 ^{o}C

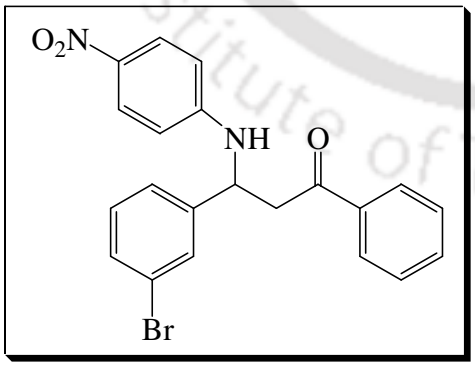
IR (KBr): 3380, 1681 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 3.47-3.50 (2H, m), 4.68 (1H, bs), 4.94-4.97 (1H, m), 6.58 (2H, d, *J* = 7.6 Hz), 6.72 (1H, t, *J* = 7.2 Hz), 7.11 (2H, t, *J* = 7.2 Hz), 7.19 (1H, t, *J* = 7.6 Hz), 7.37 (1H, d, *J* = 7.6 Hz), 7.41 (1H, d, *J* = 7.6 Hz), 7.46 (2H, t, *J* = 7.2 Hz), 7.58 (1H, t, *J* = 7.2 Hz), 7.60 (1H, s), 7.91 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 46.2, 55.0, 114.4, 118.7, 123.2, 125.4, 128.4, 129.0, 129.4, 129.8, 130.6, 130.8, 133.8, 134.9, 145.4, 146.4, 197.9 ppm.

Elemental Analysis: $C_{21}H_{18}BrNO$ (380.28): Found C, 66.42; H, 4.70; N, 3.59. Calculated C, 66.33; H, 4.77; N, 3.68 %

3-(3-Bromophenyl)-1-phenyl-3-(4-nitrophenylamino)propan-1-one (29)



Nature: Light yellow solid

Yield: 89% (0.757 g)

M.p. 159-160 ^{o}C

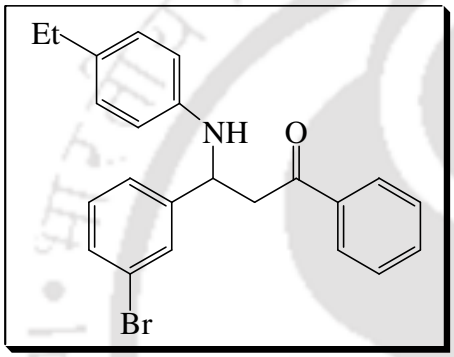
IR (KBr): 3380, 1685, 1598, 1337 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 3.48 (2H, d, *J* = 6.0 Hz), 5.02 (1H, q, *J* = 6.0 Hz), 5.48 (1H, d, *J* = 6.4 Hz), 6.48 (2H, d, *J* = 9.2 Hz), 7.18 (1H, t, *J* = 8.0 Hz), 7.30 (1H, d, *J* = 8.0 Hz), 7.37 (1H, d, *J* = 8.0 Hz), 7.44 (2H, t, *J* = 7.6 Hz), 7.51 (1H, s), 7.57 (1H, t, *J* = 7.2 Hz), 7.87 (2H, d, *J* = 7.2 Hz), 7.99 (2H, d, *J* = 9.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 45.5, 53.8, 112.3, 123.3, 125.0, 126.3, 128.2. 128.9, 129.3, 130.8, 131.2, 134.0, 136.1, 138.7, 143.8, 152.0, 197.4 ppm.

Elemental Analysis: $C_{21}H_{17}BrN_2O_3$ (425.28): Found C, 59.10; H, 4.08; N, 6.50. Calculated C, 59.31; H, 4.03; N, 6.59 %

3-(3-Bromophenyl)-1-phenyl-3-(4-ethylphenylamino)propan-1-one (30)



Nature: White solid

Yield: 92% (0.751 g)

M.p. 119-120 ^oC

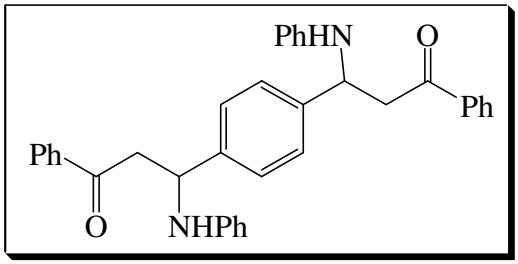
IR (KBr): 3401, 1680 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.11 (3H, t, *J* = 7.6 Hz), 2.46 (2H, q, *J* = 7.6 Hz), 3.35 (1H, dd, *J* = 7.6 Hz, *J* = 16.4 Hz), 3.44 (1H, dd, *J* = 5.2 Hz, *J* = 16.0 Hz), 4.40 (1H, bs), 4.88 (1H, dd, *J* = 5.2 Hz, J = 7.2 Hz), 6.45 (2H, d, *J* = 8.4 Hz), 6.91 (2H, d, *J* = 8. 4 Hz), 7.15 (1H, t, *J* = 7.6 Hz), 7.32-7.36 (2H, m), 7.43 (2H, t, *J* = 7.6 Hz), 7.53 (1H, d, *J* = 7.6 Hz), 7.57 (1H, s), 7.88 (2H, d, *J* = 7.6 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 16.0, 28.0, 46.4, 54.7, 114.1, 123.1, 125.3, 128.3, 128.6, 128.9, 129.6, 130.5, 130.6, 133.7, 134.0, 136.6, 144.8, 146.1, 197.9 ppm.

Elemental Analysis: $C_{23}H_{22}BrNO$ (408.34): Found C, 67.50; H, 5.39; N, 3.58. Calculated C, 67.65; H, 5.43; N, 3.43 %

***Bis*-1,3-diphenyl-3-(phenylamino)propan-1-one (31)**



Nature: Light green solid

Yield: 89% (0.934 g)

M.p. 128-129 ^{o}C

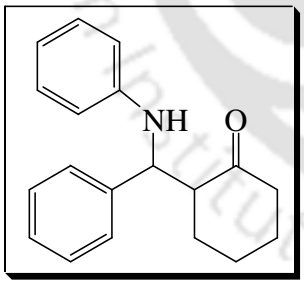
IR (KBr): 3447, 1680 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 3.43 (4H, d, *J* = 6.0 Hz), 4.70 (2H, bs), 4.96 (2H, t, *J* = 5.6 Hz), 6.55 (4H, d, *J* = 6.8 Hz), 6.67 (2H, t, *J* = 6.8 Hz), 7.08 (4H, t, *J* = 6.8 Hz), 7.38 (4H, s), 7.42 (4H, t, *J* = 7.2 Hz), 7.53 (2H, t, *J* = 8.0 Hz), 7.87 (4H, d, *J* = 7.2 Hz) ppm

^{13}C NMR (100 MHz, $CDCl_3$): 46.1, 54.9, 114.2, 118.3, 121.2, 127.2, 128.4, 128.9, 129.3, 133.7, 136.8, 142.1, 143.8, 146.8, 198.6 ppm

Elemental Analysis: $C_{36}H_{32}N_2O_2$ (524.66): Found C, 82.63; H, 6.08; N, 5.23. Calculated C, 82.41; H, 6.15; N, 5.34 %

2-(Phenyl(phenylamino)methyl)cyclohexanone (32)



Nature: White solid

Yield: 86% (0.481 g)

M.p. 115-117 ^{o}C

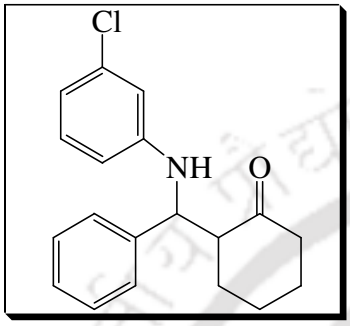
IR (KBr): 3332, 1704 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.61-1.73 (2H, m), 1.81-1.92 (4H, m), 2.30-2.37 (1H, m), 2.40-2.47 (1H, m), 2.73-2.78 (1H, m), 4.62 (1H, d, *J* = 7.2 Hz), 4.71 (1H, bs), 6.53 (2H, d, *J* = 7.6 Hz), 6.62 (1H, t, *J* = 7.2 Hz), 7.06 (2H, t, *J* = 7.6 Hz), 7.21 (1H, t, *J* = 7.6 Hz), 7.32 (2H, t, *J* = 7.6 Hz), 7.37 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.6, 27.9, 31.3, 41.7, 57.3, 57.9, 113.6, 117.5, 127.3, 127.5, 128.4, 129.0, 141.6, 147.2, 213.0 ppm.

Elemental Analysis: $C_{19}H_{21}NO$ (279.38): Found C, 81.80; H, 7.64; N, 4.88. Calculated C, 81.68; H, 7.58; N, 5.01 %

2-((3-chlorophenylamino)(phenyl)methyl)cyclohexanone (33)



Nature: White solid

Yield: 92% (0.577 g)

M.p. 125-127 ^{o}C

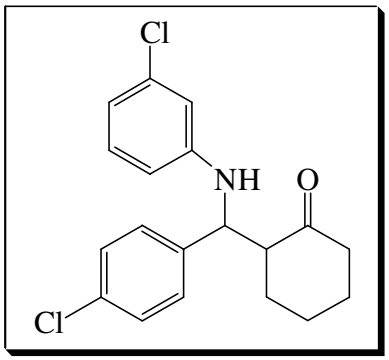
IR (KBr): 3343, 1702 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.67-1.72 (2H, m), 1.75-1.95 (4H, m), 2.31-2.45 (2H, m), 2.76-2.80 (1H, m), 4.55 (1H, d, *J* = 6.8 Hz), 4.99 (1H, bs), 6.42 (1H, d, *J* = 8.0 Hz), 6.53 (1H, s), 6.60 (1H, d, *J* = 8.0 Hz), 6.96 (1H, t, *J* = 8.0 Hz), 7.23 (1H, t, *J* = 7.2 Hz), 7.31 (2H, t, *J* = 7.2 Hz), 7.35 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 23.9, 28.0, 31.7, 42.0, 57.3, 58.1, 111.9, 113.4, 117.5, 127.3, 127.5, 128.6, 130.1, 134.8, 141.1, 148.5, 212.9 ppm.

Elemental Analysis: $C_{19}H_{20}ClNO$ (313.82) Found C, 72.84; H, 6.48; N, 4.32. Calculated C, 72.72; H, 6.42; N, 4.46 %

2-((3-Chlorophenylamino)(4-chlorophenyl)methyl)cyclohexanone (34)



Nature: Light brown solid

Yield: 88% (0.613 g)

M.p. 154-155 ^{o}C

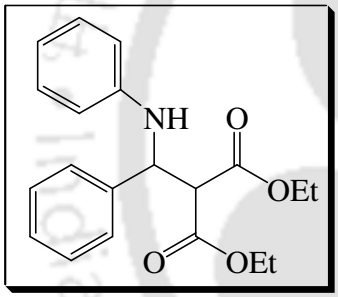
IR (KBr): 3339, 1706 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.69-1.79 (3H, m), 1.90-1.99 (3H, m), 2.31-2.41 (2H, m), 2.72-2.76 (1H, m), 4.52 (1H, d, *J* = 6.0 Hz), 4.90 (1H, bs), 6.38 (1H, d, *J* = 8.4 Hz), 6.48 (1H, s), 6.61 (1H, d, *J* = 7.2Hz), 6.97 (1H, t, *J* = 8.0 Hz), 7.29 (4H, s) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 24.3, 28.0, 32.0, 42.4, 57.3, 57.7, 112.0, 113.5, 117.8, 128.7, 128.9, 130.3, 133.1, 135.0, 140.0, 148.4, 212.5 ppm.

Elemental Analysis: $C_{19}H_{19}Cl_2NO$ (348.27): Found C, 65.34; H, 5.43; N, 3.90. Calculated C, 65.53; H, 5.50; N, 4.02 %

Diethyl 2-(phenyl(phenylamino)methyl)malonate (35)



Nature: White solid

Yield: 92% (0.628 g)

M.p. 92-94 ^{o}C

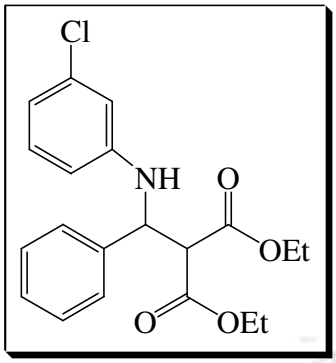
IR (KBr): 3376, 1727 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.13 (3H, t, *J* = 7.2 Hz), 1.15 (3H, t, *J* = 7.2 Hz), 3.90 (1H, d, *J* = 5.6 Hz), 4.09 (2H, q, *J* = 7.2 Hz), 4.13 (2H, q, *J* = 7.2 Hz), 5.22 (1H, d, *J* = 5.6 Hz), 5.30 (1H, bs), 6.60 (1H, d, *J* = 8.0 Hz), 6.66 (1H, t, *J* = 7.2 Hz), 7.09 (2H, t, *J* = 8.0 Hz), 7.21(1H, d, *J* = 7.2 Hz), 7.26-7.31 (3H, m), 7.36 (2H, d, *J* = 7.2 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 57.2, 58.4, 61.8, 62.1, 114.0, 118.0, 127.0, 127.8, 128.8, 129.3, 139.9, 146.8, 167.5, 168.3 ppm.

Elemental Analysis: $C_{20}H_{23}NO_4$ (341.4) Found C, 70.47; H, 6.74; N, 4.26. Calculated C, 70.36; H, 6.79; N, 4.10 %

Diethyl 2-(phenyl(3-chlorophenylamino)methyl)malonate (36)



Nature: White solid

Yield: 94% (0.707 g)

M.p. 111-112 ^{o}C

IR (KBr): 3370, 1730 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.13 (3H, t, *J* = 7.2 Hz), 1.17 (3H, t, *J* = 7.2 Hz), 3.88 (1H, d, *J* = 5.2 Hz), 4.11 (2H, q, *J* = 7.2 Hz), 4.15 (2H, q, *J* = 7.2 Hz), 5.18 (1H, d, *J* = 5.6 Hz), 5.56 (1H, bs), 6.47 (1H, d, *J* = 8.8 Hz), 6.58 (1H, s), 6.62 (1H, d, *J* = 8.8 Hz), 6.99 (1H, t, *J* = 8.8 Hz), 7.26-7.35 (5H, m) ppm

^{13}C NMR (100 MHz, $CDCl_3$): 13.7, 13.9, 56.7, 57.8, 61.5, 61.9, 111.8, 113.3, 117.6, 126.5, 127.7, 128.6, 130.0, 134.9, 139.0, 147.8, 167.0, 168.0 ppm.

Elemental Analysis: $C_{20}H_{22}ClNO_4$ (375.85): Found C, 63.71; H, 5.83; N, 3.61. Calculated C, 63.91; H, 5.90; N, 3.73 %

Crystal data and structure refinement for 2-((3-chlorophenyl amino) (phenyl) methyl)cyclohexanone (33)

Empirical formula	$C_{19}H_{20}NOCl$	
Formula weight	313.81	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 10.8074(2) Å	α= 90°.
	b = 8.6744(5) Å	β= 103.694(3)°.
	c = 18.3806(10) Å	γ = 90°.
Volume	1674.16(16) $Å^3$	
Z	4	
Density (calculated)	1.245 Mg/m^3	
Absorption coefficient	0.230 mm^{-1}	
F(000)	664	
Crystal size	0.42 x 0.26 x 0.18 mm^3	
Theta range for data collection	2.00 to 27.93°.	
Index ranges	-14<=h<=14, -11<=k<=10, -24<=l<=24	
Reflections collected	16738	
Independent reflections	3946 [R(int) = 0.0213]	
Completeness to theta = 28.26°	69.7 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3946 / 0 / 204	
Goodness-of-fit on F^2	1.069	
Final R indices [I>2sigma(I)]	R1 = 0.0750, wR2 = 0.2314	
R indices (all data)	R1 = 0.0979, wR2 = 0.2539	
Extinction coefficient	0.230	

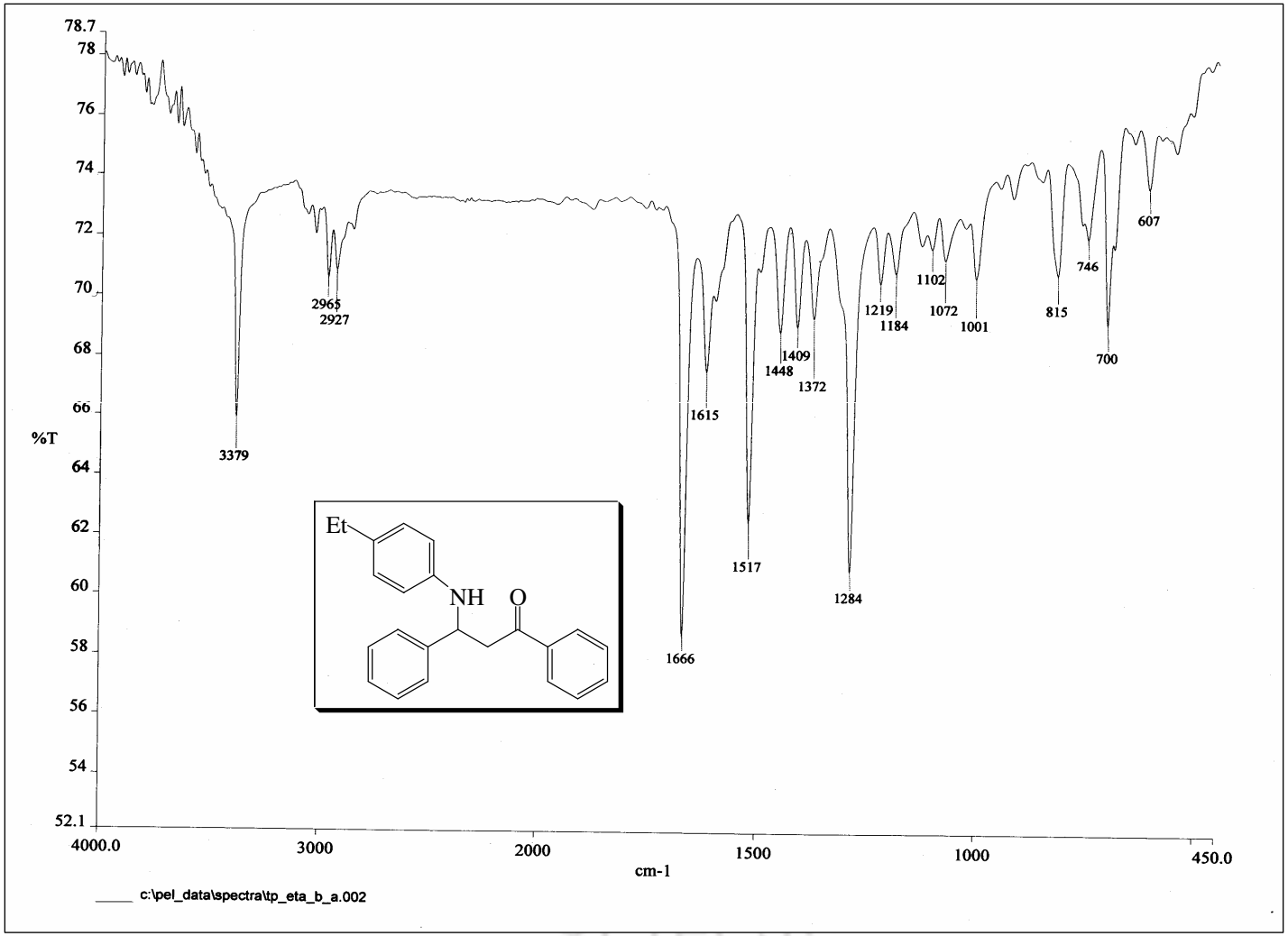


Figure 8: IR spectrum of 3-Phenyl-1-phenyl-3-(4-ethylphenylamino)propan-1-one (22)

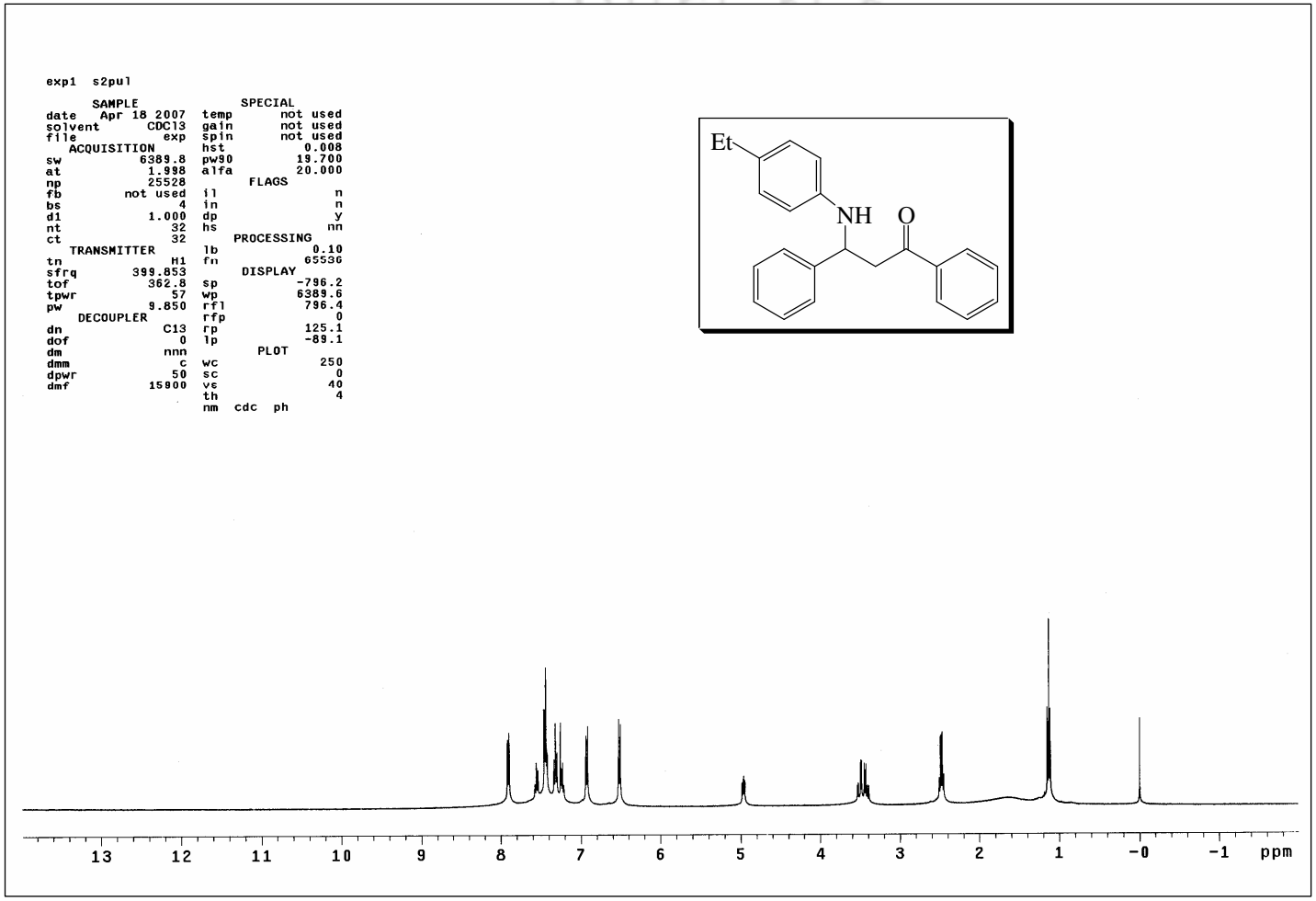


Figure 9: ^{1}H NMR spectrum of 3-Phenyl-1-phenyl-3-(4-ethylphenylamino)propan-1-one (22)

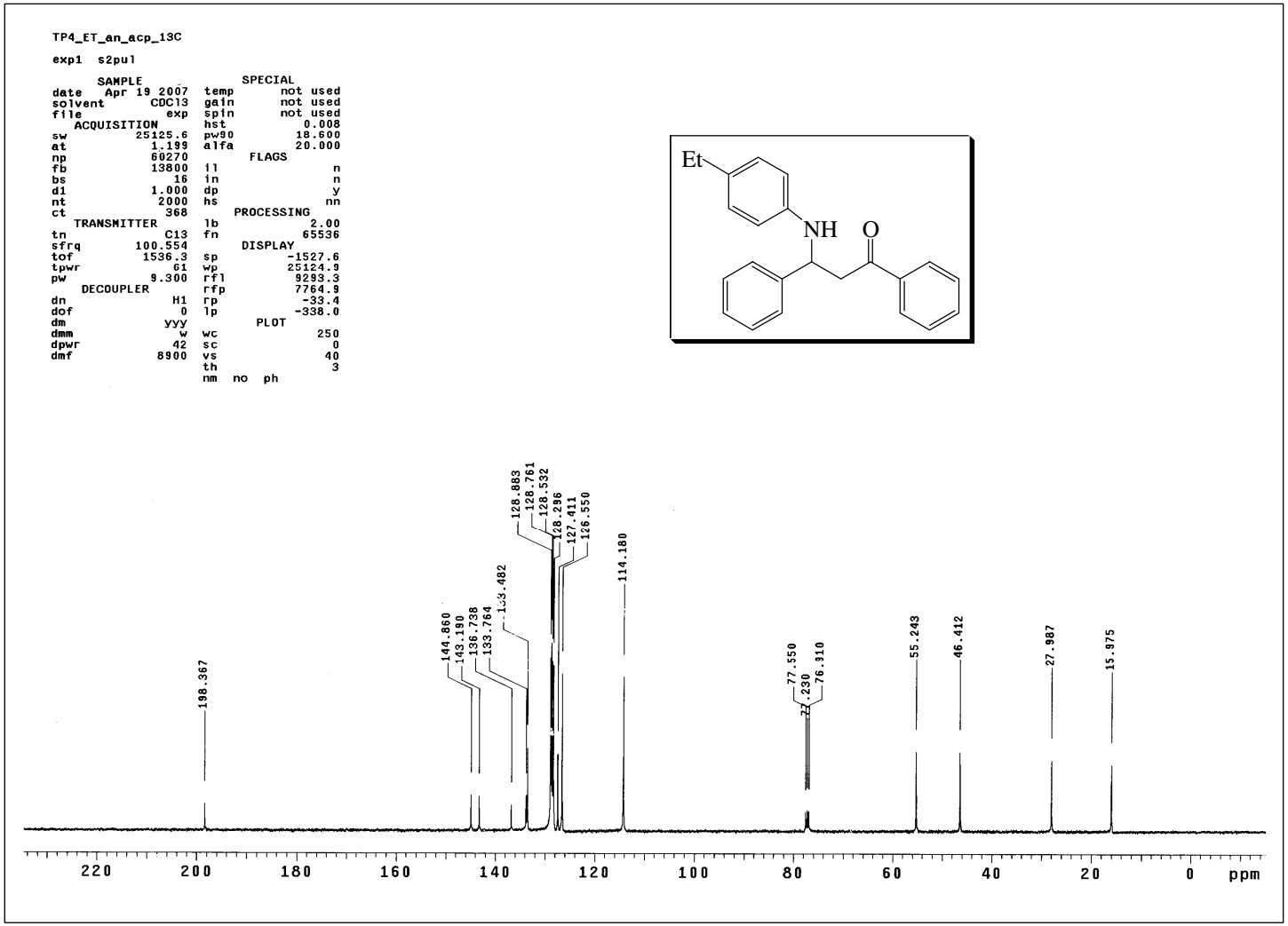


Figure 10: ^{13}C NMR spectrum of 3-Phenyl-1-phenyl-3-(4-ethylphenylamino)propan-1-one (22)

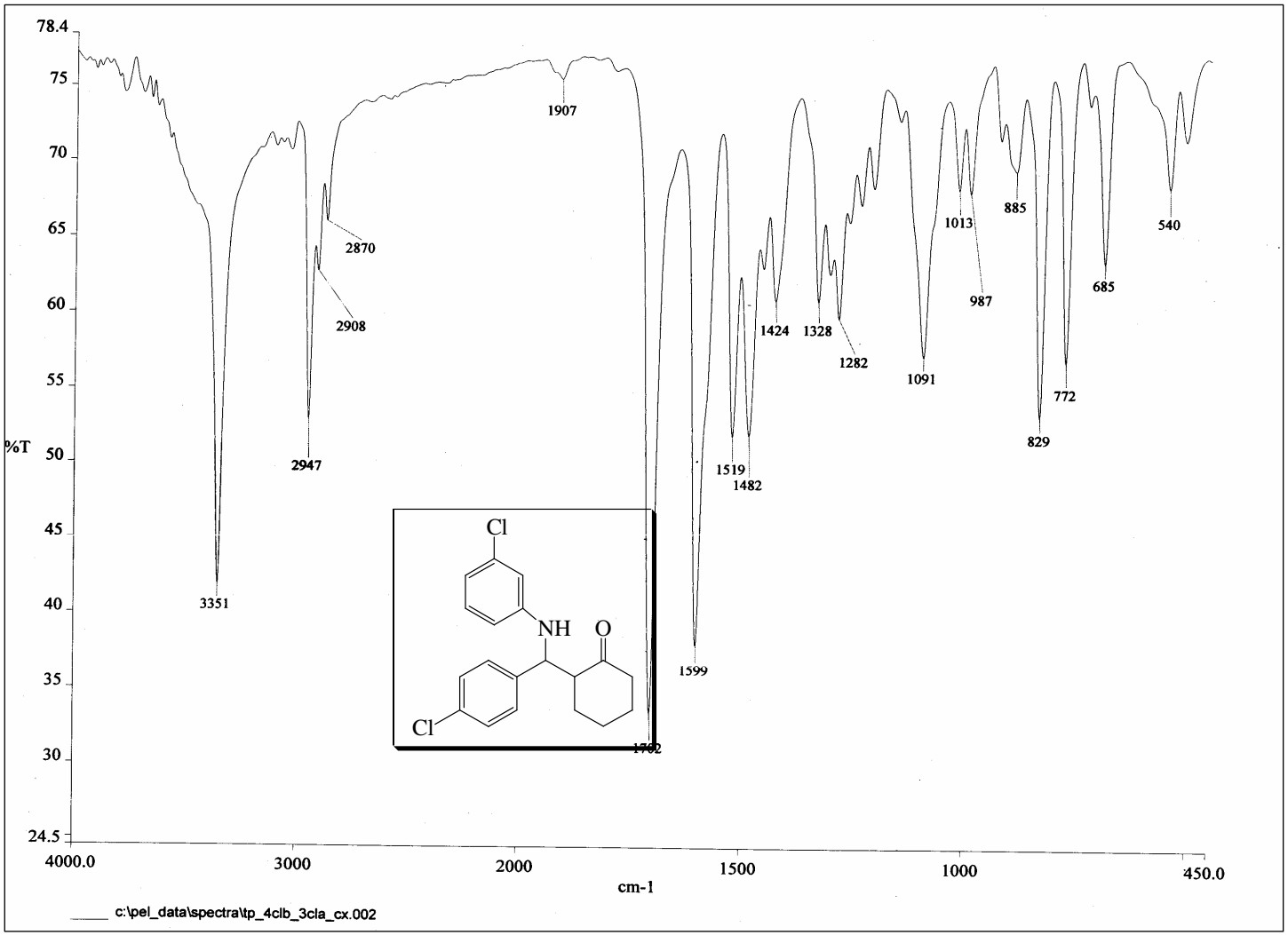


Figure 11: IR spectrum of 2-((3-Chlorophenylamino)(4-chlorophenyl)methyl)cyclohexanone (34)

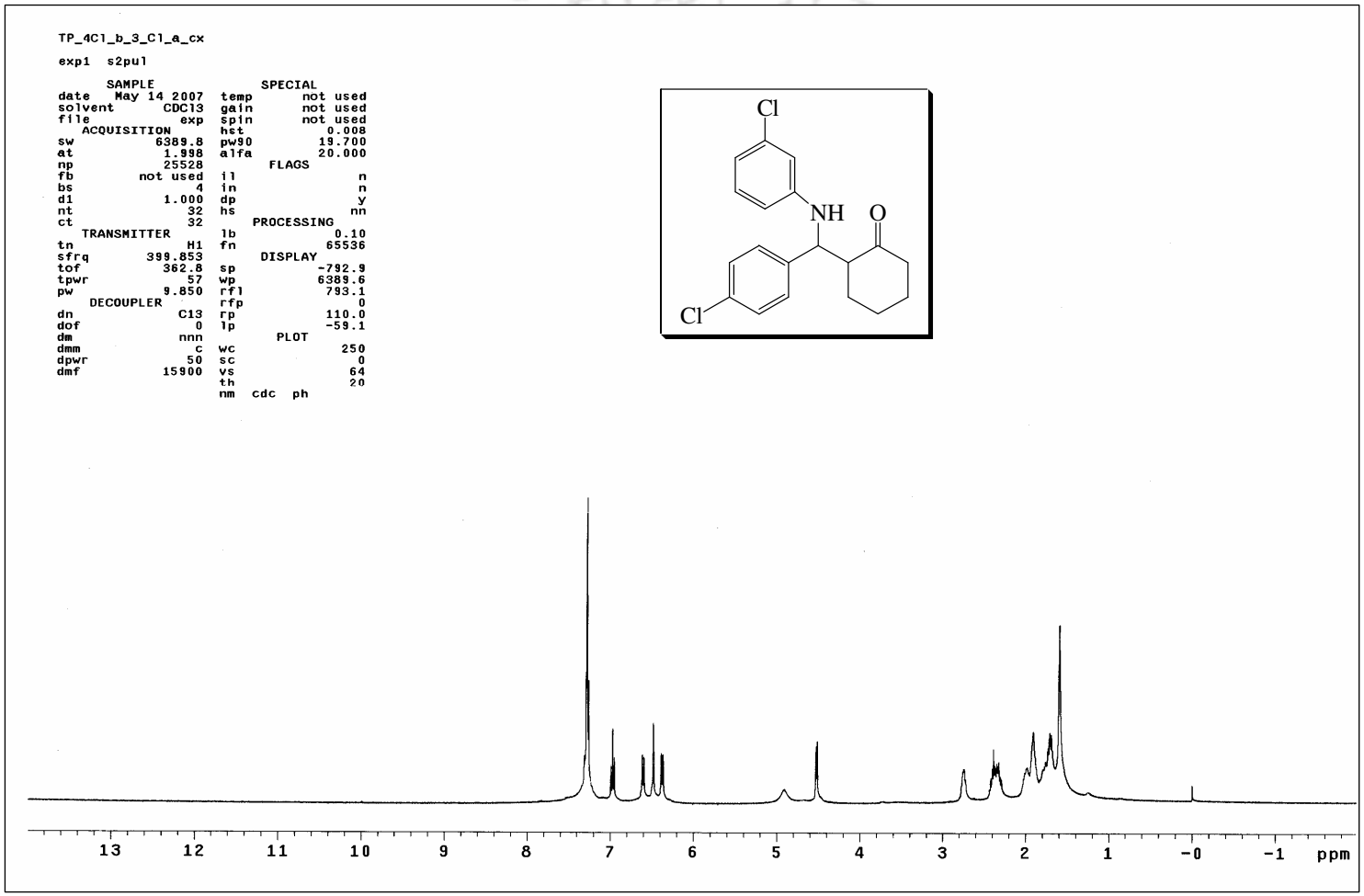


Figure 12: ^{1}H NMR spectrum of 2-((3-Chlorophenylamino)(4-chlorophenyl)methyl)cyclohexanone (34)

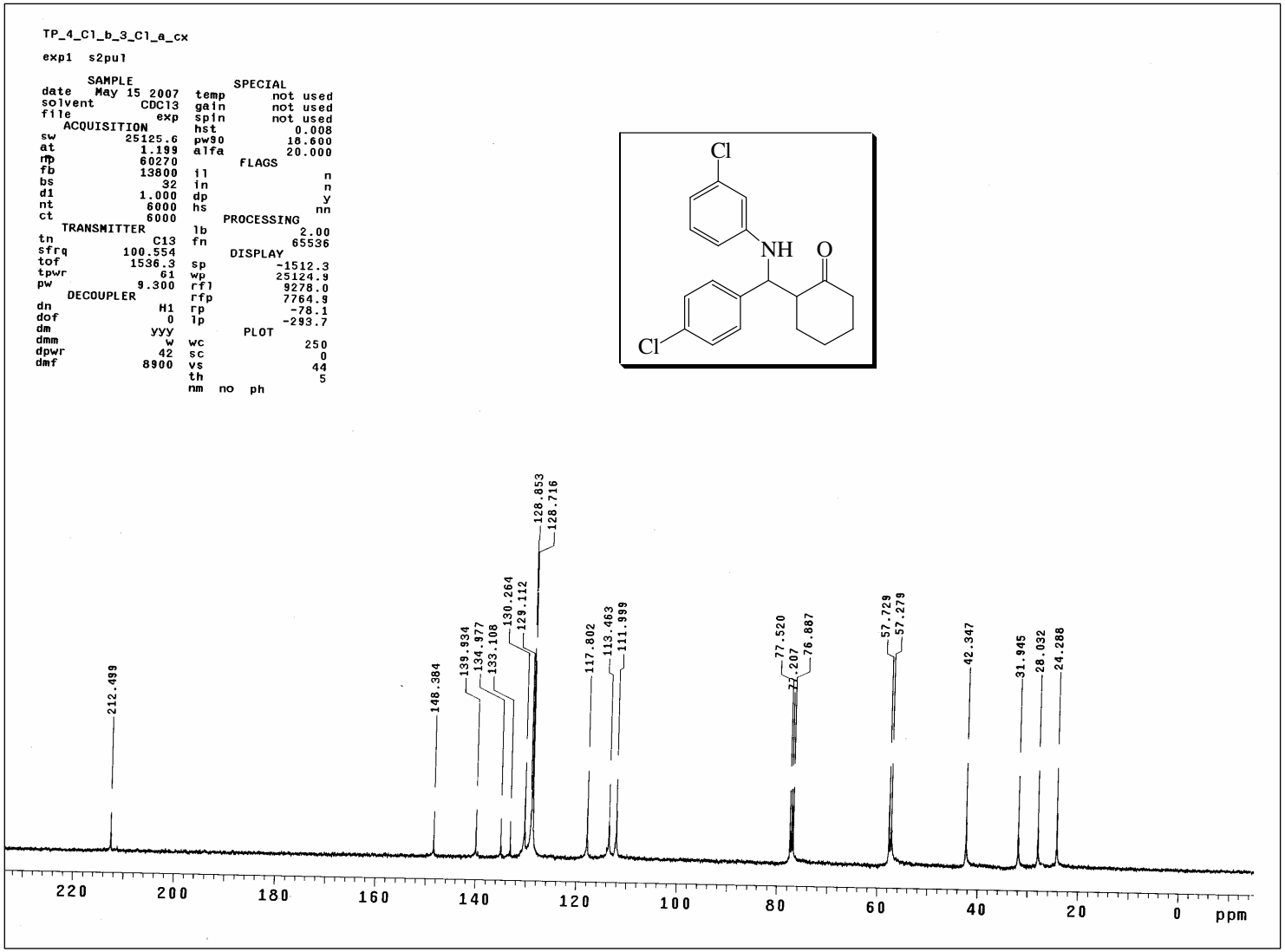


Figure13: ^{13}C NMR spectrum of 2-((3-Chlorophenylamino)(4-chlorophenyl)methyl)cyclohexanone (34)

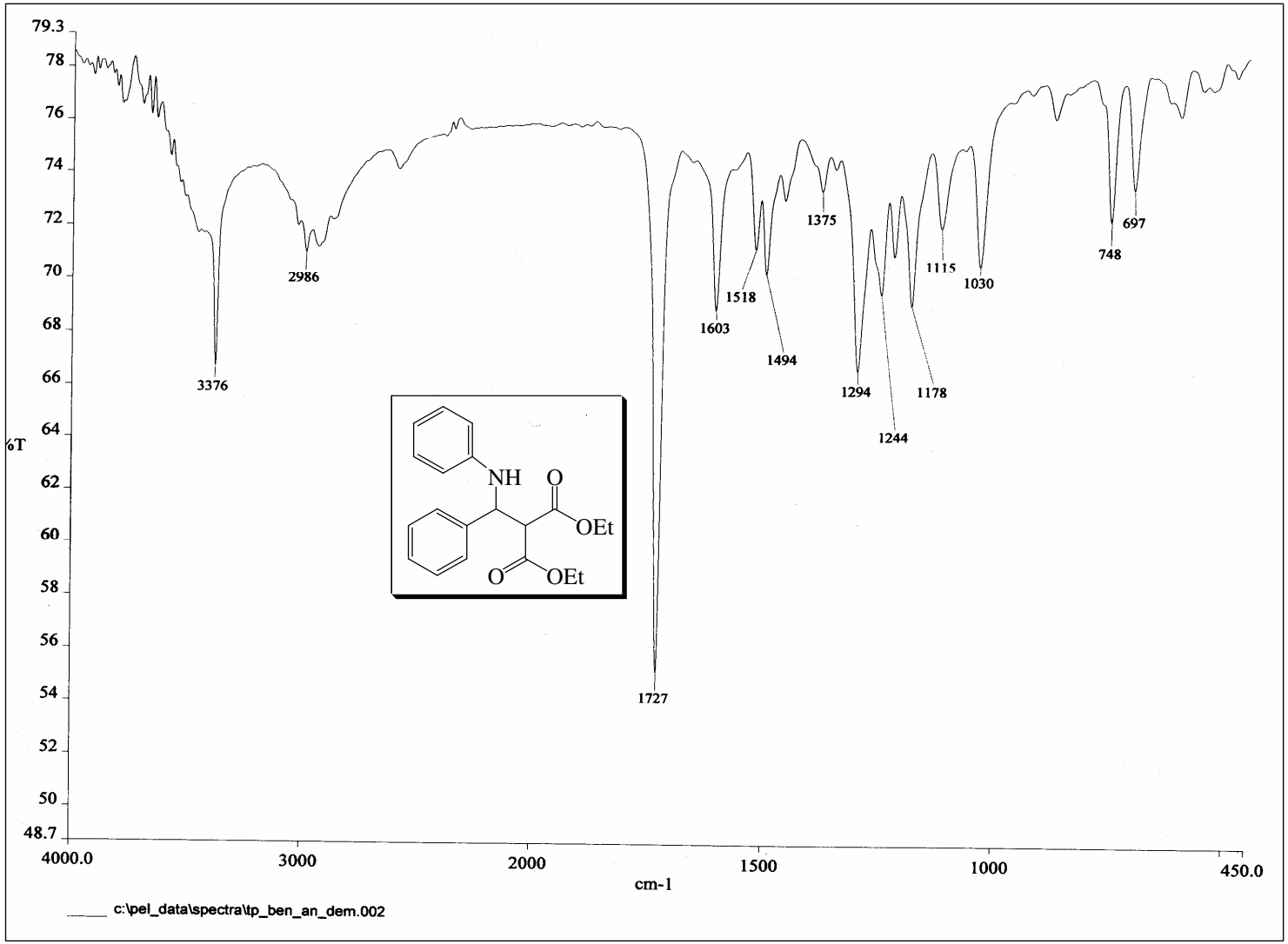


Figure 14: IR spectrum of Diethyl 2-(phenyl(phenylamino)methyl)malonate (36)

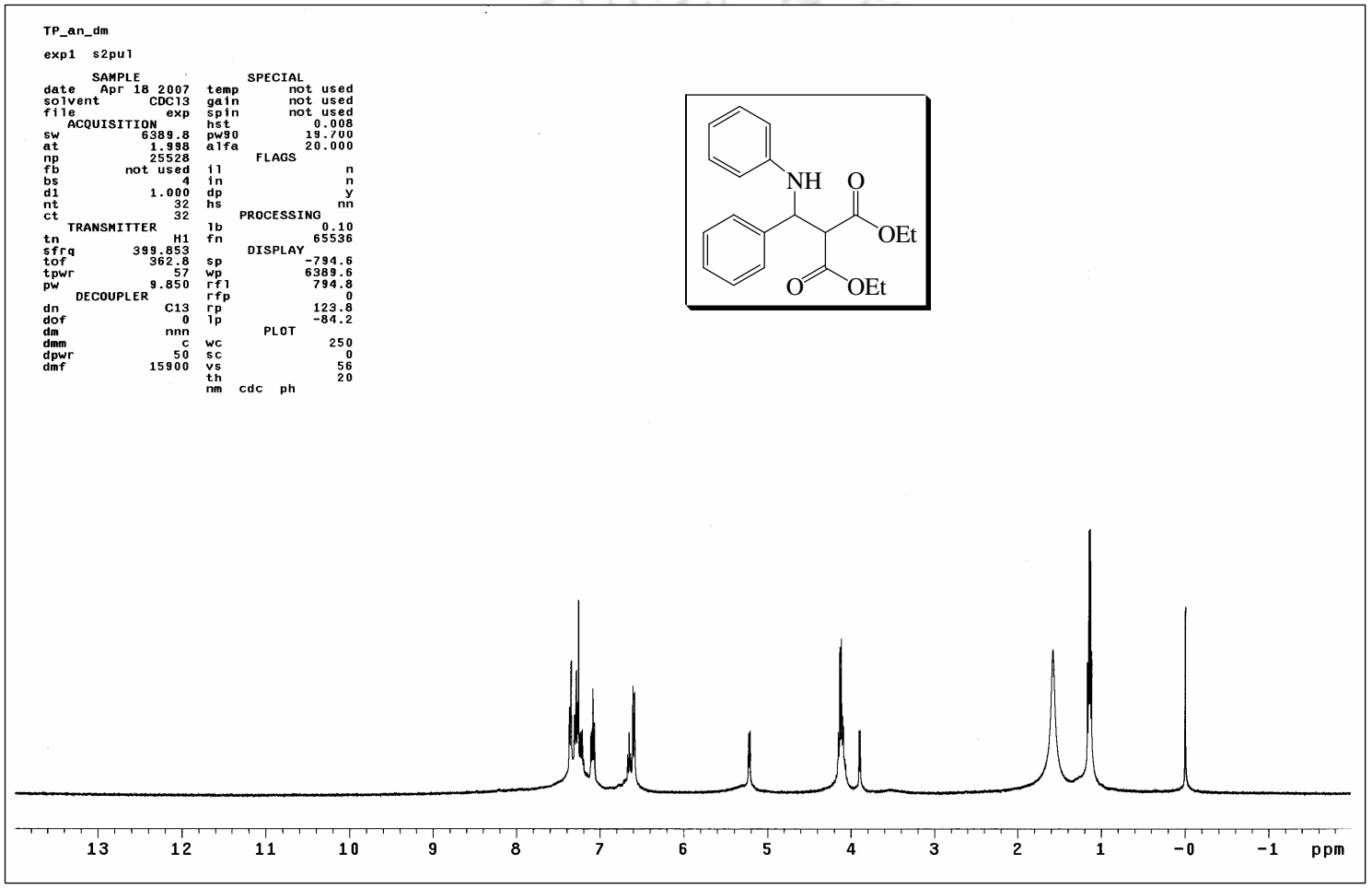


Figure 15: ^{1}H NMR spectrum of Diethyl 2-(phenyl(phenylamino)methyl)malonate (36)

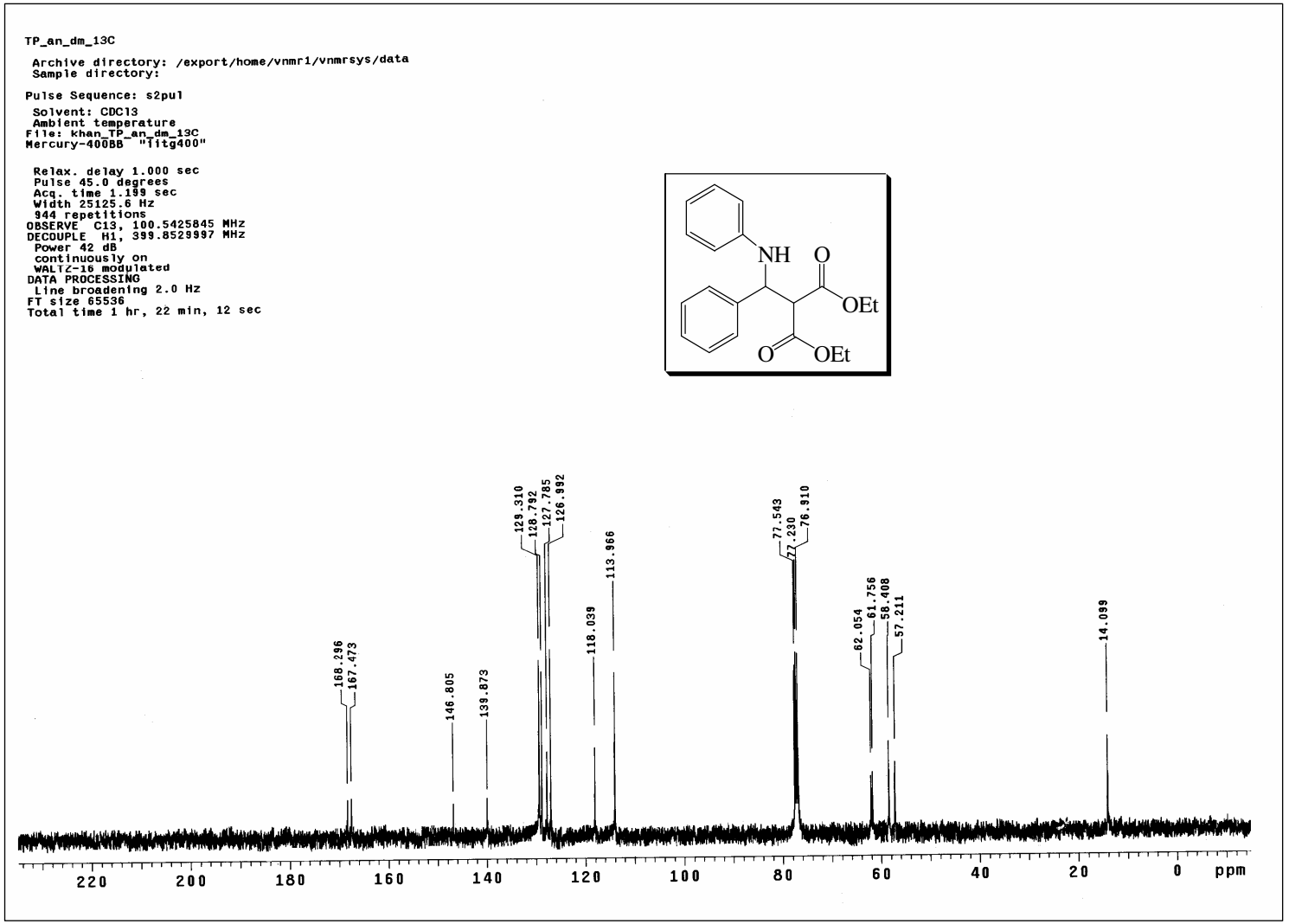


Figure 16: ^{13}C NMR spectrum of Diethyl 2-(phenyl(phenylamino)methyl)malonate (36)

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CHAPTER IV

Effects of substituent in β-position of 1,3-dicarbonyl compounds in bromodimethylsulfonium bromide catalyzed multicomponent reactions: A facile access to functionalized piperidines

4.1 Introduction

In continuation of our work on the development of new synthetic methodologies leading to β-amino carbonyl compounds by multicomponent approach, we revealed that 1,3-dicarbonyl compounds and their derivatives are promising synthetic intermediates in organic synthesis owing to their versatile reactivity.[1a] These compounds are widely used as starting material in various multicomponent reactions for the preparation of diverse heterocycles.[1b] Development of new methodologies for efficient synthesis of heterocycles is an ever enduring challenge.Heterocycles are ubiquitous in natural products, pharmaceuticals, organic materials, and numerous functional molecules. Especially polyfunctionalized heterocyclic compounds play important roles in drug discovery process, and analysis of drugs already existing in the market or in the pipeline shows that 68% of them are heterocycles.[1c] As a consequence, the ongoing interest for developing new versatile and efficient syntheses of heterocycles has always been a thread in the synthetic community.

4.1.1 Substituted piperidine and its importance in organic synthesis

Among heterocycles, six membered nitrogen heterocycles, piperidines are widespread in nature as well as most promising bioactive heterocycles. The piperidine ring is a structural unit of many alkaloids and drug candidates. Several piperidine compounds

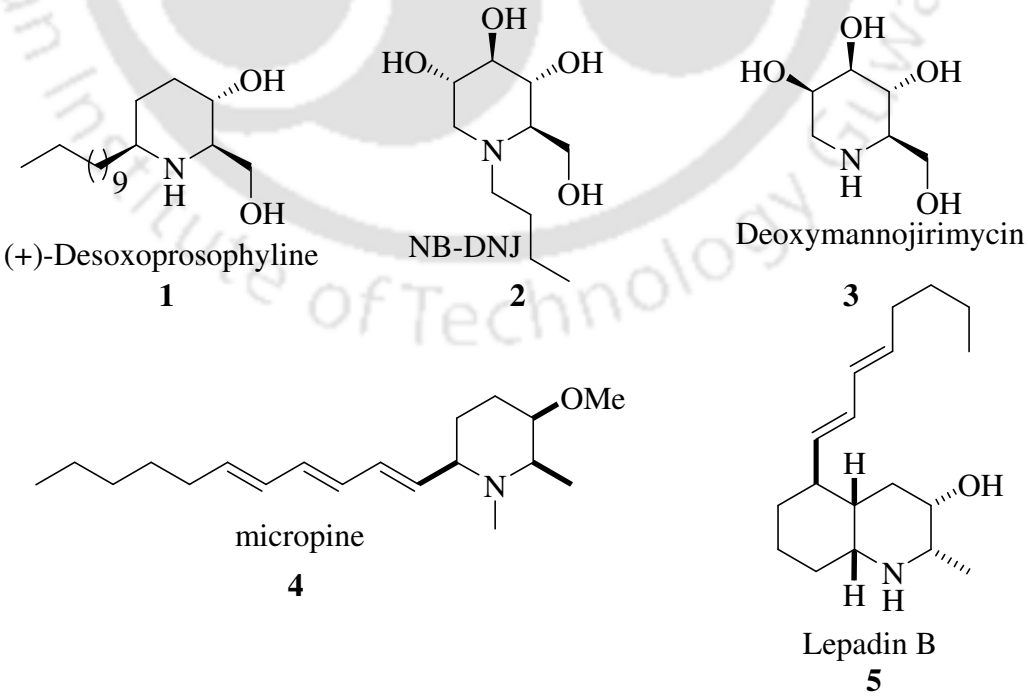
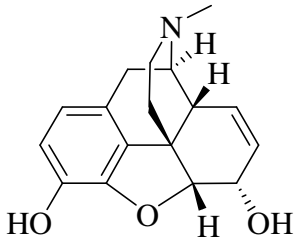


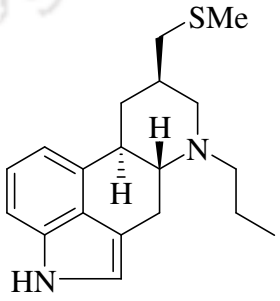
Figure 1

have been mentioned in clinical and preclinical studies.[2a] Piperidine alkaloids comprise a large family of compounds that exhibit a large spectrum of biological activities of medicinal interest. In particular, alkaloid lipids such as (+)-desoxoprosophylline (**1**, Figure 1)[2b-c] display significant anesthetic, analgesic and antibiotic activities,[3-5] while their corresponding iminosugars-exemplified by N-butyl-1-deoxynojirimycin (NB-DNJ, **2**) which was recently approved for the treatment of Gaucher disease[6] constitute promising leads for the development of immunosuppressive,[7] antiviral,[8] antidiabetic[9] and antitumour agents.[10] In addition, deoxymannojirimycin (**3**) have also been shown to inhibit various enzymes that participate in the binding and processing of diverse glycoproteins, underlying their possible therapeutic values.[11] Similarly, Lepadin B (isolated from North Sea flatworms) possess significant cytotoxic activity whilst the insecticidal activity of micropine (**4**) illustrates the wide range of biological activities exhibited by natural products of this class.

Most of the piperidines isolated from nature are substituted, e.g., pergoline (**6**) and morphine (**7**). The chemistry of a group of piperidines which is rapidly growing during the last two decades, due to their diverse biological applications, is the group of the sterically hindered piperidines. Some hindered amines are used as local anaesthetics (eucaine) while others have other pharmacological properties. Some hindered piperidines are also good polymerization inhibitors as well as thermo-and photostabilizers.[12] Several other substituted piperidines display important biological properties like antiviral activity,[13] antidepressant effects,[14] cytotoxic activity[15] and antimalarial activity.[16] Some piperidine derivatives are also used as neuroleptic agents.[17] In addition, the secondary



morphine
7

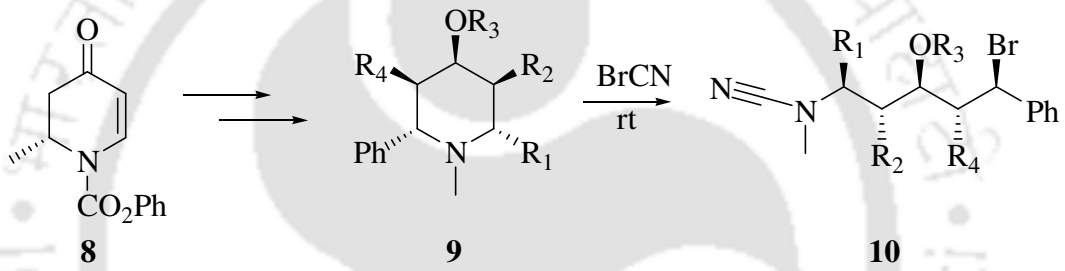


pergoline
6

Figure 2

plant metabolites such as coniine, pinidine, isopelletierine, sedamine, anaferin, etc. play crucial role in biological systems.

Very recently, Comins and his coworkers have revealed that substituted piperidines containing a phenyl group at C-2 can be used as a starting material for the stereoselective synthesis of uniquely substituted alkylamine derivatives containing multiple chiral centers and various functionality.[18] Multisubstituted piperidines containing a phenyl group at C-2 undergo ring opening with cyanogen bromide regio- and stereoselectively (Scheme 1). Diastereomerically pure amino alcohols containing three to five contiguous stereocenters can be achieved using this strategy.



8 **9** **10**

Scheme 1

The preceding facts amply demonstrate the importance of piperidines in modern organic chemistry. As these compounds are useful in medical and clinical applications, efficient and versatile methods amenable to accessing this class of compounds with selectivity are highly desirable.

Over the years, several approaches have been developed for the synthesis of substituted piperidines.[19] It is evident from the literature survey that the development of efficient methodology for the synthesis of substituted piperidines is an emerging field in organic synthesis. In continuation of our work on multicomponent reactions we were motivated to develop a pot atom and step economic (PASE) process for the synthesis of highly substituted piperidines. In the next section i.e. **4.2** we will describe our successful efforts towards these objectives.

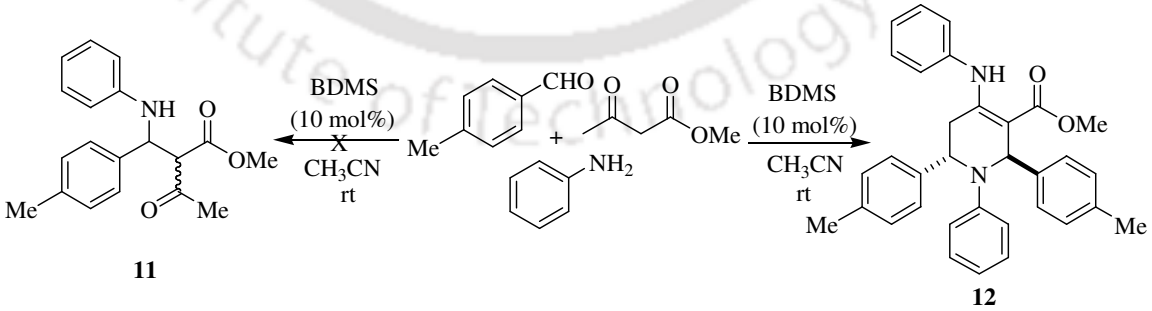
Effects of substituent in β-position of 1,3-dicarbonyl compounds in bromodimethylsulfonium bromide catalyzed multicomponent reactions: A facile access to functionalized piperidines

RESULTS AND DISCUSSION

4.2 Results and Discussion:

In the section B of the previous chapter, we have shown the three component Mannich type reaction of aromatic aldehyde, amine and 1,3-dicarbonyl compound like diethyl malonate, for the preparation of β-amino ester using bromodimethylsulfonium bromide as catalyst. Interestingly, when the same reaction was carried out with other 1,3-dicarbonyl compounds such as methyl acetoacetate, we did not get the expected Mannich type product as indicated in the ^{1}H NMR spectrum. After establishing the structure through ^{1}H NMR as well as XRD, it was revealed that the product is highly functionalized piperidine. From the literature survey, as discussed in the introduction part of this chapter, we realized the importance of piperidines in modern organic chemistry. Synthesis of functionalized piperidine in a concise and effective manner is an important area of research in organic chemistry owing to their bioactivities and medicinal properties. Therefore, we were interested to synthesize these 6-membered nitrogen-containing heterocyclic compounds. Herein we will describe a convenient method for the synthesis of functionalized piperidines from the five component reaction of aromatic aldehyde, amine and β-keto esters.

In our initial study, a mixture of 4-methylbenzaldehyde (2 mmol), aniline (2 mmol) and methyl acetoacetate (2 mmol) in acetonitrile (5 ml) was stirred in the presence of 10 mol% BDMS. At the outset we were expecting a Mannich-type product **11.** Interestingly, instead of that we isolated a highly functionalized piperidine **12** in a moderate yield of 39% (Scheme 2).



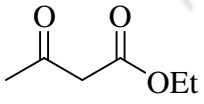
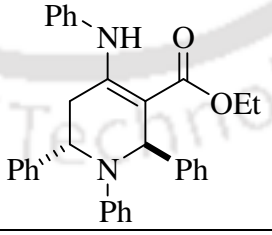
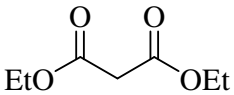
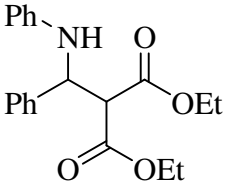
Scheme 2 Preferential formation of functionalized piperidines over the Mannich-type product

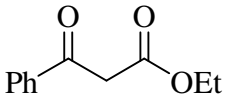
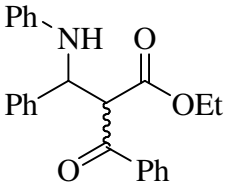
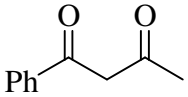
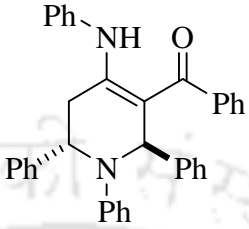
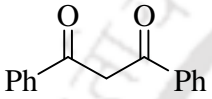
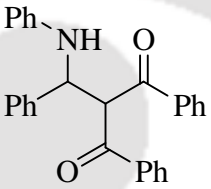
Generally, β-keto esters react with electrophiles at the α-position.[21] Only a few cases of α-alkylated β-keto esters/amides reacting with aldehyde electrophiles at the γ-position

have been reported in the literature.[22] Fujioka and Kita et al have reported a multicomponent reaction employing the γ-position of β-keto esters to form seven membered ring products from the combination of aromatic aldehydes, ethylenediamine and β-keto esters.[23] Interestingly, the formation of **12** is an example in which both the α and γ positions of a β-keto ester are involved in C-C bond formation.

This unexpected result encouraged us to investigate the scope of this multicomponent reaction through a systematic study. A variety of 1, 3-dicarbonyl compounds were treated with benzaldehyde and aniline in the presence of a catalytic amount of bromodimethylsulfonium bromide and the results are summarized in Table 1. Like methyl acetoacetate, ethyl acetoacetate provides the corresponding piperidine derivative (**13**) in moderate yield. This suggests that the alkoxy moiety of these β-keto esters does not have any significant role in determining the course of the reaction. However, in the case of diethyl malonate, the corresponding Mannich-type product **14** was obtained in good yield, as there is no other option due to the lack of an enolizable position. Likewise, ethyl benzoylacetate gave Mannich-type product **15** as a mixture of diastereomers, with the *trans* isomer predominating. However, in the case of benzoyl acetone the corresponding piperidine **16** was obtained in moderate yield.

Table 1. Results for the reaction of benzaldehyde, aniline and different 1,3-dicarbonyl compounds in presence of catalytic amount of BDMS[a]

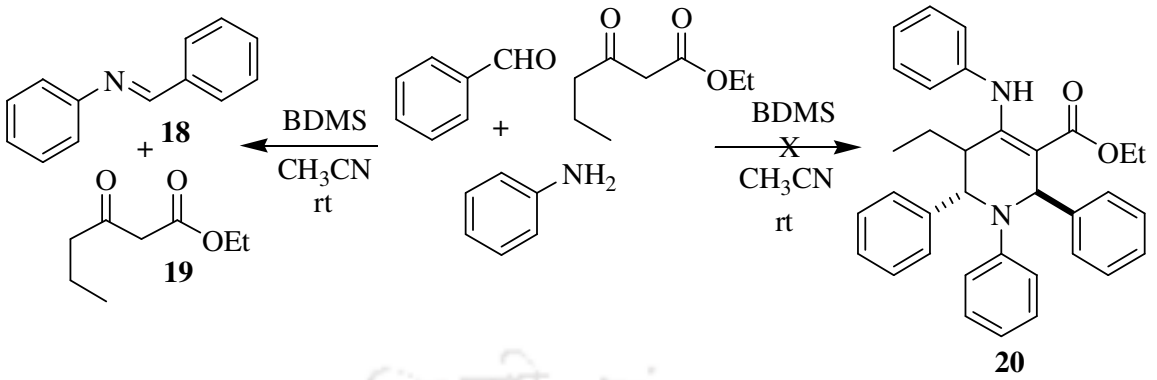
1,3-dicarbonyl compounds	Time /h	Product	Product No.	% Yield[b]
	6		**13**	38[c]
	6		**14**	92

	8		**15**	40
	12		**16**	20[d]
	12		**17**	0[e]

[a]Reactions were performed in a ratio of 1:1:1 (benzaldehyde : aniline : 1,3-dicarbonyl compounds) in presence of 10 mol% BDMS at room temperature. [b]yield of pure product after crystallization. [c]For optimized yield see Table 2. [d]Optimized yield was 35%. [e]Starting material dibenzoyl acetone was recovered along with aldimine.

In the case of dibenzoyl methane only the imine formed between benzaldehyde and aniline was obtained in addition to unreacted dibenzoyl methane. From these results it is clear that diethylmalonate is acting as a better nucleophile in this Mannich-type reaction than the other 1,3-dicarbonyl compounds in presence of bromodimethylsulfonium bromide (Table 1). We believe that the bulkiness of the phenyl group may have an effect on the nucleophilicity of ethyl benzoyl acetate and dibenzoyl methane. From these studies it is apparent that substituents on the 1,3-dicarbonyl component play a vital role in determining the reactivity of substrates and the course of reactions.

A γ-substituted β-keto ester ethyl butyrylacetate was next treated with aniline and benzaldehyde under similar experimental conditions. Piperidine **20** was not observed as was revealed from the crude ^{1}H NMR even after 24 h of reaction (Scheme 3). This suggests that the presence of methyl group in the β-position of β-keto esters is necessary for the successful formation of highly functionalized piperidines using these multicomponent reactions.



Scheme 3 Reaction of ethyl butyrylacetate with aniline and benzaldehyde

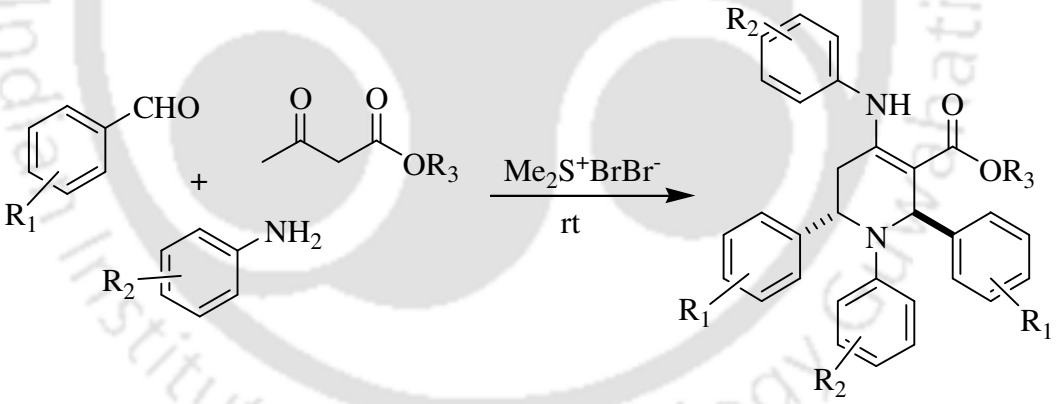
After this initial study we were interested for the optimization of this multicomponent reaction. For this purpose, the influence of the catalyst, solvent and the ratio of the components were investigated using the combination of *p*-methylbenzaldehyde, aniline and methylacetoacetate as a model reaction. The stoichiometric ratio 2:2:1 (aldehyde: aniline: methyl acetoacetate) in the presence of 10 mol% of bromodimethylsulfonium bromide at room temperature were found to be the most suitable conditions for obtaining functionalized piperidines. Under these standard reaction conditions, the product **12** was synthesized in good yield (80%) within a short time (3 hours). A range of solvents were screened to find out the best solvent for this transformation. Among dichloromethane, acetonitrile, ethanol and water, the use of acetonitrile was found to give superior yields. However ethanol can also be used for this transformation. The neat reaction, without any solvent, resulted in a moderate yield (40%) that may be due to the lack of effective interaction of the reactants under solvent-free reaction conditions. In the absence of BDMS, the same combination of reactants failed to provide **12** under identical reaction conditions even after 24 h stirring. This illustrates the efficacy of BDMS as a catalyst. Using a catalytic amount of aqueous 48% HBr instead of BDMS gave lower yields (45%). This result indicates that the generation of the protic acid HBr may not be the only factor responsible for the catalytic activity of BDMS. It is possible that the positive sulfonium moiety also has some role in facilitating the process.

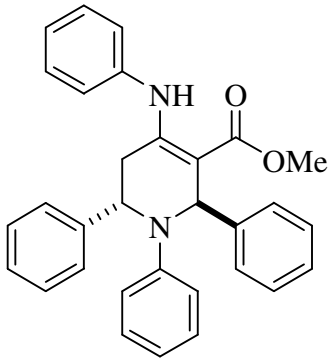
To explore the generality and scope of this multicomponent reaction a variety of aldehydes, β-keto esters, and aniline derivatives were tested and the results are summarized in Table 2. Aromatic aldehydes bearing substituents such as Cl, Me, and OMe as well as NO_2 were treated with aniline and methylacetoacetate under the standard

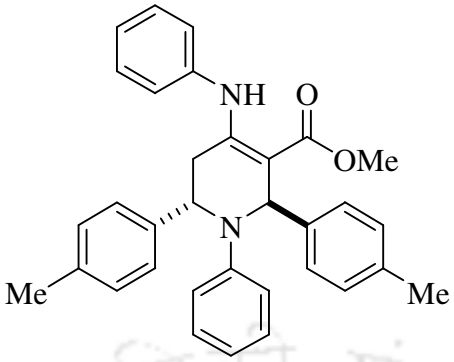
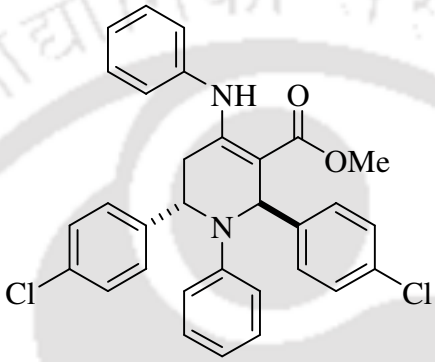
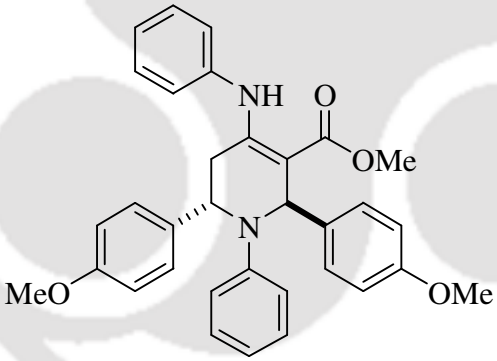
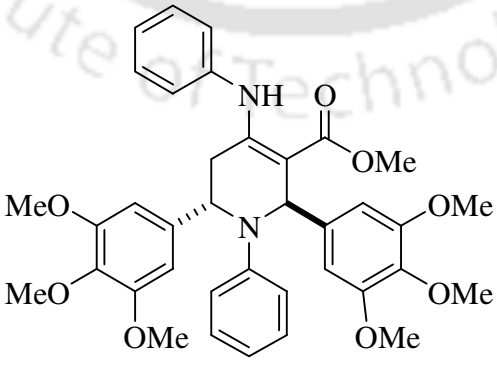
reaction conditions and the corresponding products (**22-27**) were obtained in good to moderate yields. In the case of nitro aldehydes (**25-27**) the yields were low which may be due to steric factors as well as the electron withdrawing effect of the nitro group.

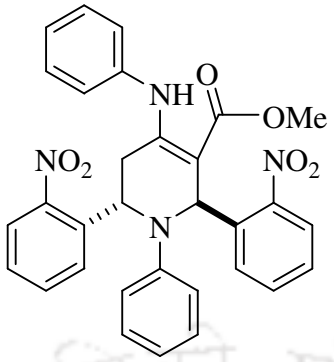
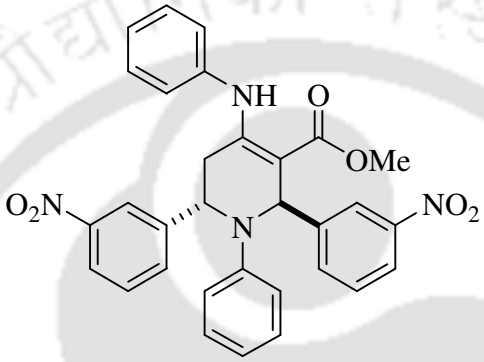
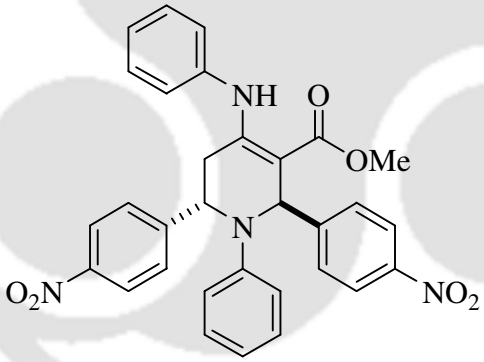
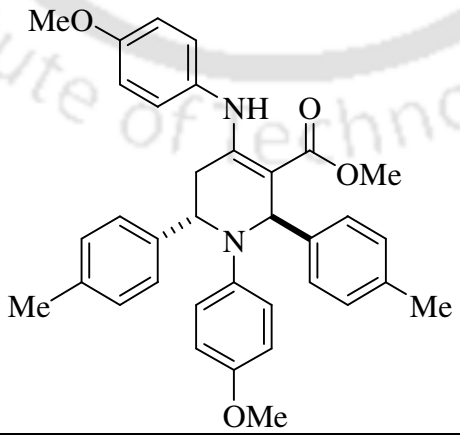
Aniline derivatives such as 4-methoxyaniline and 4-bromoaniline were also tested in the multi component reaction, smoothly providing the corresponding piperidine derivatives (**28-29**) in good yields. To further explore the generality and scope of this MCR, benzyl amine and butyl amine were also treated under the same reaction conditions. The corresponding piperidines (**30-31**) were obtained in low to moderate yields. Other β-keto esters such as ethyl acetoacetate, *tert*-butyl acetoacetate and allyl acetoacetate also took part in this multicomponent reaction to provide the corresponding piperidine derivatives (**32-37**) with good yields under the optimized reaction conditions. Unfortunately, in the case of the aliphatic aldehyde, heptanal, the present method failed to produce the corresponding functionalized piperidines.

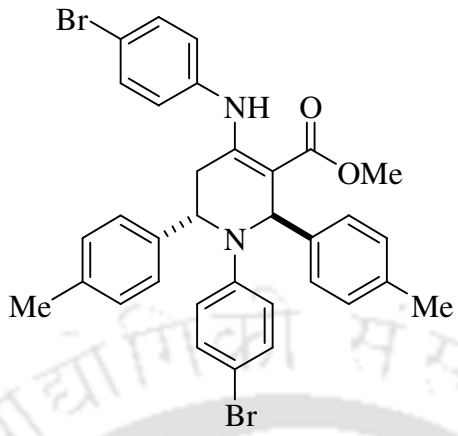
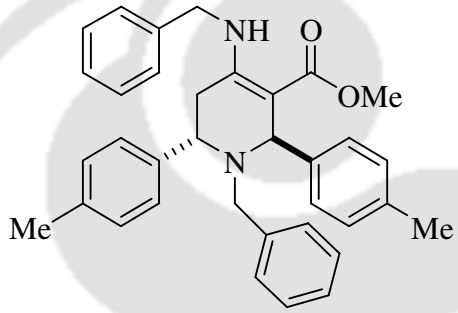
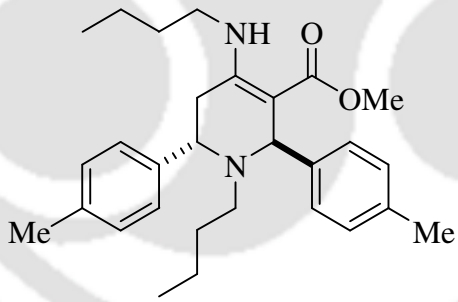
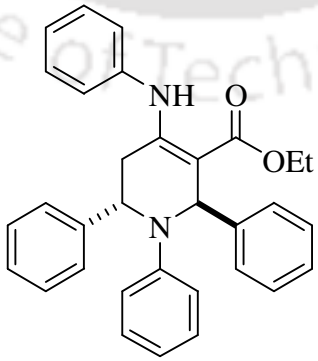
Table 2. Results for the reaction of aldehydes, anilines and β-keto esters in the presence of bromodimethylsulfonium bromide in acetonitrile[a]

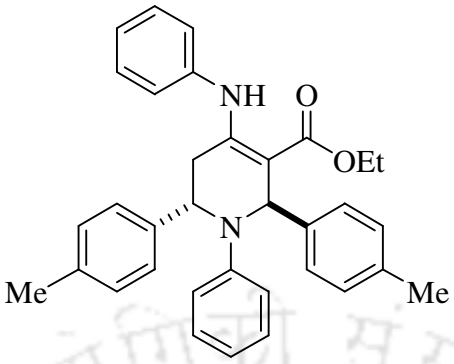
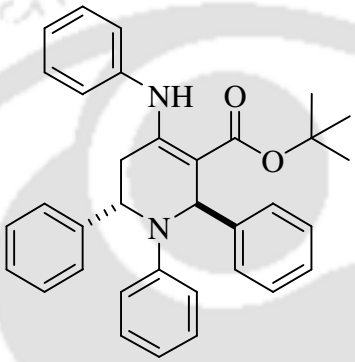
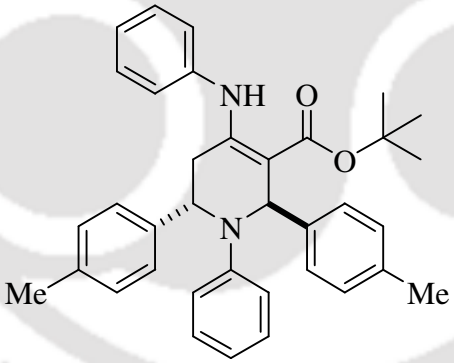
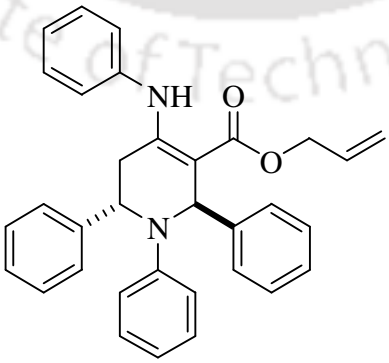


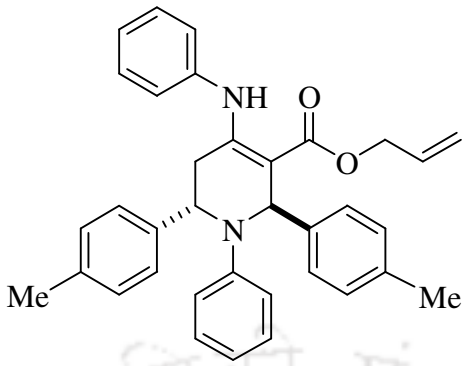
Serial No.	Product	Product No.	% Yield[b]
1		**21**	75

2		**12**	80
3		**22**	76
4		**23**	77
5		**24**	62

6		**25**	50
7		**26**	40
8		**27**	32
9		**28**	77

10		**29**	68
11		**30**	48
12		**31**	63
13		**32**	76

14		**33**	79
15		**34**	60
16		**35**	65
17		**36**	70

18		**37**	77

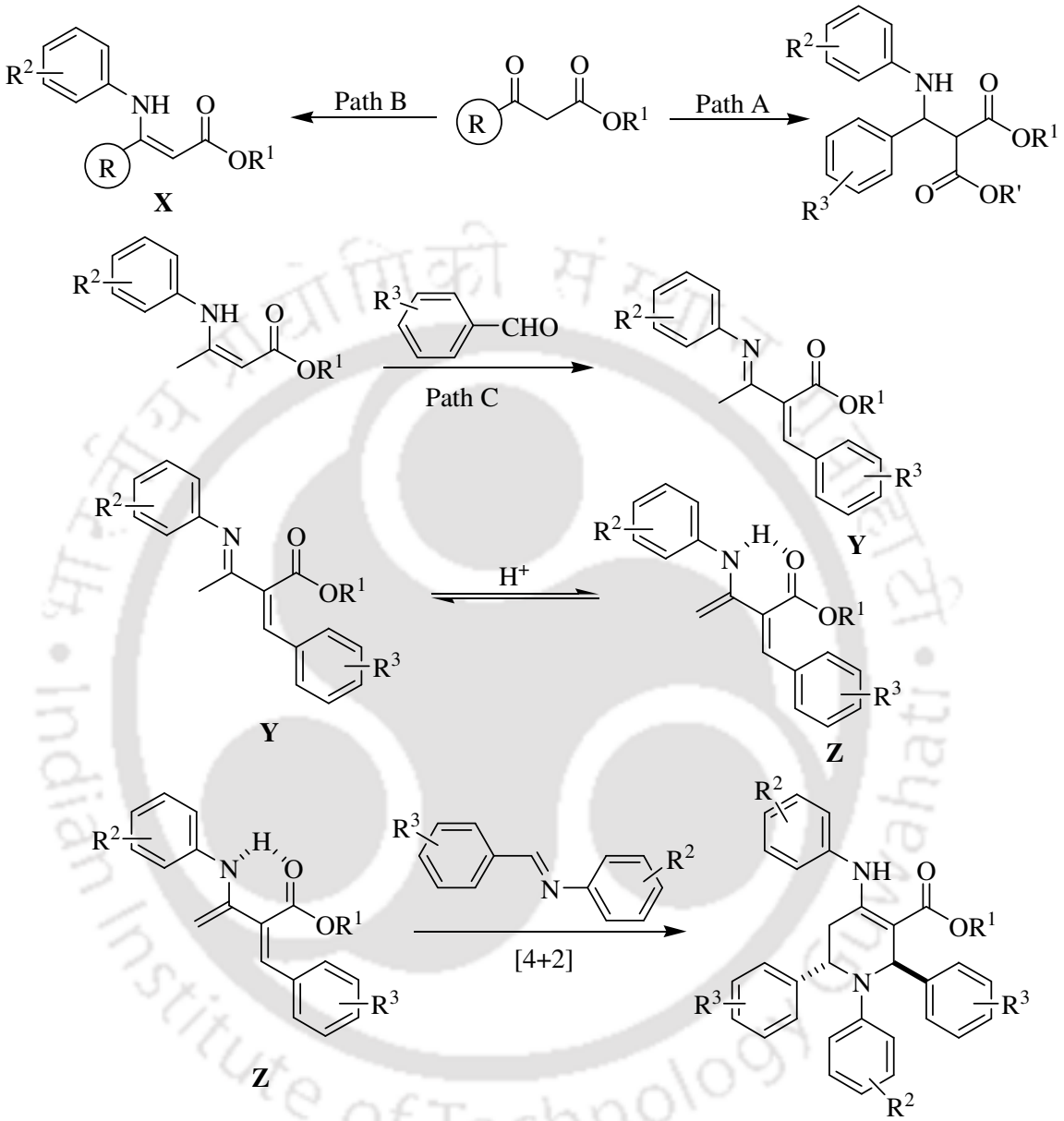
[a] Aldehyde, amine and β-keto esters were taken in (2:2:1) ratio in presence of 10 mol% BDMS.
[b]Yield of pure product after crystallization from the reaction mixture.

To confirm the structure as well as the relative stereochemistry of these highly functionalized piperidines, X-ray crystallographic analysis of **22** and **32** was carried out. In both cases, the relative stereochemistry at the 2 and 6 positions of the piperidines was shown to be *anti* (see experimental section, Figure 3 and 4). In addition, amino groups at the 4-position and carboxyl groups at the 3-position show intramolecular hydrogen bonding.

Next, we turned our attention to gaining mechanistic insights into this transformation. From our study we have revealed that the R group of the β-keto esters play a crucial role in this multicomponent reaction (See Table 1). A possible mechanism is illustrated in Scheme 4.

In the case when R = alkoxy group, e.g. OEt, the combination of an aromatic amine, such as aniline, and an aromatic aldehyde, with the diester, leads to the Mannich type products following the path A via the formation of an imine followed by nucleophilic attack by the 1,3-diesters. As the carbonyl group of ester substrates is less electrophilic than that of the ketone substrates, therefore there is no reaction with the aromatic amines at room temperature, and straightforward formation of β-amino acid derivatives (Mannich type product) is observed. However, when R is an alkyl or aryl group then the scenario becomes different. This can be attributed to the more reactive keto functionality and the emergence of other reaction pathways. In the case of β-keto esters, where R is a methyl group, enamine **X** (path B) is formed by reaction with the amine. This enamine **X** may

then react with the aromatic aldehyde to produce the Knoevenagel-type product **Y** (path C).



Scheme 4 Possible mechanistic illustration showing the role of R group and the formation of functionalized piperidines via intermediates Z.

Next, there will be a spontaneous tendency under acidic conditions for tautomerization to give the intramolecular hydrogen bonded enamine **Z**. Presumably, this hydrogen bonding along with high conjugation is the driving force for the tautomerization. The X-ray structure of compound **22** and **32** shows that the carboxyl and amino groups are on the same face of the products and show intramolecular hydrogen bonding (Figure 3 and 4) thus indirectly support our hypothesis. Another equivalent of amine and aldehyde react in

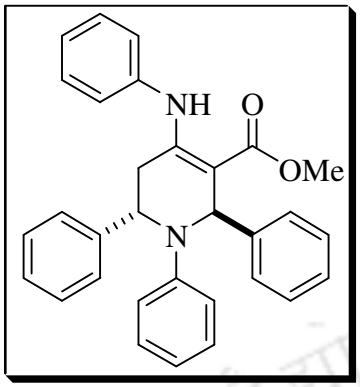
presence of BDMS to provide the corresponding imine. We believe that BDMS facilitates the formation of imine as well as enamine **X** in this multicomponent reaction. This imine and the intermediate **Z** undergo [4+2] aza-Diels-Alder reaction to provide the functionalized piperidine. In an attempt to prove this mechanism, we synthesized the enamine from methyl acetoacetate and aniline and the resultant enamine was treated with another equivalent of 4-methylbenzaldehyde. However we could not isolate the intermediate **Z**, instead we found a trace amount of the corresponding piperidine **12.** It is possible that the intermediate is highly reactive and not possible to trap. However, the exact explanation is not yet clear.

In summary, we have demonstrated that bromodimethylsulfonium bromide mediates a new multicomponent reaction for the synthesis of highly functionalized piperidines. In addition we have shown that substituents on the 1,3-dicarbonyl components determine the course of the reaction. This strategy is interesting as both the α and γ positions of β-keto esters are involved in C-C bond formation under the mild conditions. The resultant heterocyclic systems have both secondary amine and enamino esters, which enable further modifications leading to molecular diversity. Studies towards the further generalization of this approach and the application of this method to access other heterocyclic scaffolds are under way.

Effects of substituent in β-position of 1,3-dicarbonyl compounds in bromodimethylsulfonium bromide catalyzed multicomponent reactions: A facile access to functionalized piperidines

EXPERIMENTAL

Methyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (21)



Nature: Light yellow solid

Yield: 75% (0.345 g)

M.p. 169-171 °C

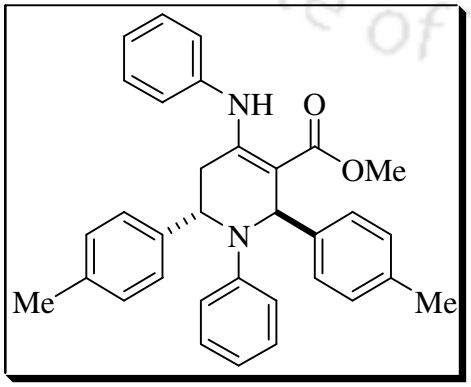
IR (KBr): 3241, 3058, 2948, 1655, 1594, 1500, 1257, 1072 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.75 (1H, dd, *J* = 2.4 Hz, *J* = 15.2 Hz), 2.86 (1H, dd, *J* = 5.6 Hz, *J* = 15.2 Hz), 3.93 (3H, s), 5.13-5.14 (1H, m), 6.26-6.28 (2H, m), 6.44 (1H, s), 6.51 (2H, d, *J* = 8.8 Hz), 6.59 (1H, t, *J* = 7.2 Hz), 7.03-7.10 (5H, m), 7.16 (2H, d, *J* = 8.0 Hz), 7.20-7.22 (1H, m), 7.24-7.32 (7H, m), 10.24 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 33.8, 51.2, 55.2, 58.3, 98.0, 113.0, 116.3, 125.9, 126.0, 126.5, 126.8, 127.3, 128.4, 128.8, 128.9, 129.0, 137.9, 142.9, 144.0, 147.1, 156.4, 168.7 ppm.

Elemental Analysis: $C_{31}H_{28}N_2O_2$ (460.58): Found C, 80.71; H, 6.07; N, 6.19. Calculated C, 80.84; H, 6.13; N, 6.08 %

Methyl 2,6-*bis*(4-methylphenyl)-1-Phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (12)



Nature: White solid

Yield: 80% (0.391 g)

M.p. 212-214 °C

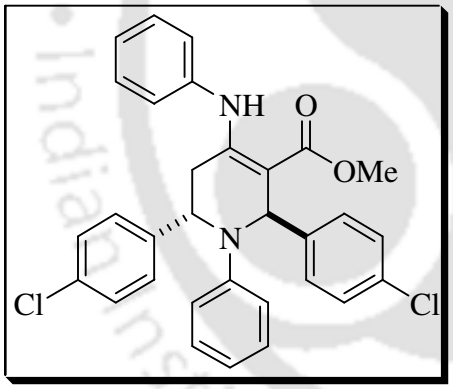
IR (KBr): 3436, 2924, 1658, 1589, 1503, 1252, 1078 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.30 (3H, s), 2.32 (3H, s), 2.74 (1H, dd, *J* = 2.4 Hz, *J* = 15.2 Hz), 2.84 (1H, dd, *J* = 5.6 Hz, *J* = 15.2 Hz), 3.90 (3H, s), 5.08-5.09 (1H, m), 6.26-6.29 (2H, m), 6.37 (1H, s), 6.50 (2H, d, *J* = 8.4 Hz), 6.57 (1H, t, *J* = 7.2 Hz), 7.01-7.10 (11H, m), 7.17 (2H, d, *J* = 8.0 Hz), 10.23 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 21.2, 21.3, 33.8, 51.2, 55.1, 58.1, 98.3, 113.1, 116.2, 125.8, 126.0, 126.5, 126.7, 128.9, 129.0, 129.1, 129.4, 136.0, 136.8, 138.1, 139.8, 141.1, 147.2, 156.5, 168.8 ppm.

Elemental Analysis: $C_{33}H_{32}N_2O_2$ (488.64): Found C, 80.98, H, 6.54, N, 5.85. Calculated C, 81.12; H, 6.60; N, 5.73 %

Methyl 2,6-*bis*(4-chlorophenyl)-1-Phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (22)



Nature: Light yellow solid

Yield: 76% (0.402 g)

M.p. 189-191 °C

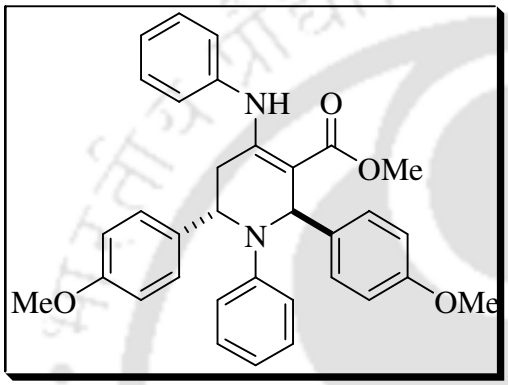
IR (KBr): 3230, 2945, 1659, 1588, 1492, 1251, 1070 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.74 (1H, dd, *J* = 2.4 Hz, *J* = 15.2 Hz), 2.82 (1H, dd, *J* = 5.6 Hz, *J* = 15.2 Hz), 3.92 (3H, s), 5.09-5.10 (1H, m), 6.35 (1H, s), 6.40 (2H, d, *J* = 6.8 Hz), 6.45 (2H, d, *J* = 8.4 Hz), 6.64 (1H, t, *J* = 7.2 Hz), 7.04-7.08 (4H, m), 7.12- 7.18 (2H, m), 7.21-7.26 (7H, m), 10.25 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 33.8, 51.3, 54.8, 57.5, 97.6, 113.1, 116.9, 125.9, 126.2, 127.9, 128.2, 128.6, 128.9, 129.2, 132.3, 133.0, 137.7, 141.0, 142.5, 146.6, 156.2, 168.5 ppm.

Elemental Analysis: $C_{31}H_{26}Cl_2N_2O_2$ (529.47): Found C, 70.19; H, 4.89; N, 5.41. Calculated C, 70.32; H, 4.95; N, 5.29 %

Methyl 2,6-*bis*(4-methoxyphenyl)-1-Phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (23)



Nature: White solid

Yield: 77% (0.401 g)

M.p. 187-188 °C

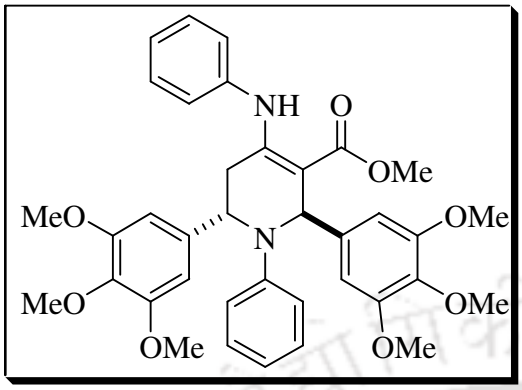
IR (KBr): 3240, 2945, 1653, 1607, 1591, 1501, 1248, 1067 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.73 (1H, dd, *J* = 2.4 Hz, *J* = 15.2 Hz), 2.83 (1H, dd, *J* = 5.6 Hz, *J* = 15.2 Hz), 3.76 (3H, s), 3.77(3H, s), 3.90 (3H, s), 5.06-5.07 (1H, m), 6.32-6.34 (3H, m), 6.50 (2H, d, *J* = 8.4 Hz), 6.58 (1H, t, *J* = 7.2 Hz), 6.79 (4H, d, *J* = 8.0 Hz), 7.03-7.13 (7H, m), 7.19 (2H, d, *J* =8.4 Hz), 10.25 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 33.9, 51.2, 54.7, 55.5, 57.7, 98.3, 113.1, 113.7, 114.1, 116.2, 125.8, 125.9, 127.6, 127.9, 129.0, 134.8, 136.0, 138.1, 147.2, 156.5, 158.2, 158.8, 168.8 ppm.

Elemental Analysis: $C_{33}H_{32}N_2O_4$ (520.63): Found C, 76.01; H, 6.13; N, 5.51. Calculated C, 76.13; H, 6.20; N, 5.38 %

Methyl2,6-*bis*(3,4,5-trimethoxyphenyl)-1-Phenyl-4-(phenylamino)-1,2,5,6-tetrahydro pyridine-3-carboxylate (24)



Nature: Light yellow solid

Yield: 62% (0.397 g)

M.p. 153-156 °C

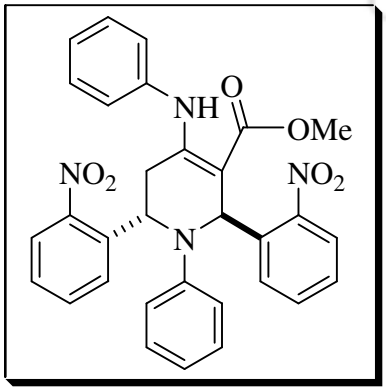
IR (KBr):3241, 2996, 2938, 1656, 1592, 1502, 1461, 1416, 1323, 1256, 1126, 1006 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.74 (1H, dd, *J* = 2.4 Hz, *J* = 14.8 Hz), 2.93 (1H, dd, *J* = 5.6 Hz, *J* = 14.8 Hz), 3.67 (6H, s), 3.71 (6H, s), 3.81 (3H, s), 3.82 (3H, s), 3.88 (3H, s), 5.01-5.02 (1H, m), 6.33 (3H, s), 6.37 (2H, d, *J* = 6.8 Hz), 6.51 (2H, s), 6.55 (2H, d, *J* = 8.4 Hz), 6.62 (1H, t, *J* = 7.2 Hz), 7.06 -7.16 (5H, m), 10.24 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 33.8, 51.0, 55.6, 56.0, 58.3, 60.9, 97.3, 103.2, 103.9, 113.1, 116.6, 126.1, 126.3, 128.9, 137.8, 138.5, 139.7, 146.9, 153.1, 153.4, 157.0, 168.5 ppm.

Elemental Analysis: $C_{37}H_{40}N_2O_8$ (640.74): Found C, 69.21; H, 6.34; N, 4.51. Calculated C, 69.36; H, 6.29; N, 4.37 %

Methyl 2,6-*bis*(2-nitrophenyl)-1-Phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine -3-carboxylate (25)



Nature: Yellow solid

Yield: 50% (0.276 g)

M.p. 217-219 ^{o}C

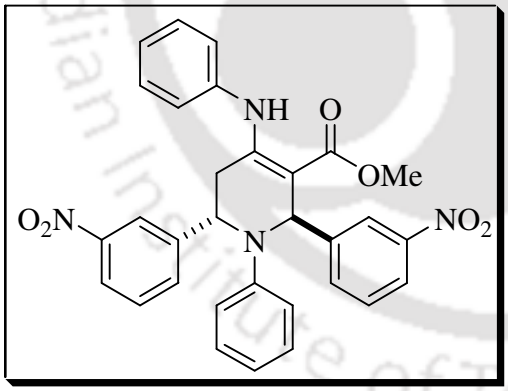
IR (KBr): 3240, 3063, 2950, 1658, 1594, 1502, 1359, 1263, 1068 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.88 (1H, dd, *J* = 3.2 Hz, *J* = 16.8 Hz), 3.00 (1H, dd, *J* = 5.6 Hz, *J* = 16.8 Hz), 3.77 (3H, s), 5.97-5.98 (1H, m), 6.45 (2H, d, *J* = 7.2 Hz), 6.66 (2H, d, *J* = 8.4 Hz), 6.71 (1H, t, *J* = 7.2 Hz), 6.83 (1H, s), 7.08 (2H, t, *J* = 8.0 Hz), 7.13-7.17 (3H, m), 7.30 (1H, d, *J* = 8.0 Hz), 7.32-7.46 (5H, m), 7.65 (1H, d, *J* = 8.0 Hz), 7.92 (1H, d, *J* = 7.6 Hz), 10.44 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 31.5, 51.2, 53.1, 53.8, 95.0, 115.3, 119.0, 124.9, 125.3, 125.8, 126.5, 128.0, 128.4, 128.7, 129.4, 129.6, 131.8, 133.6, 137.4, 137.5, 137.9, 145.9, 148.4, 150.2, 155.8, 168.2 ppm.

Elemental Analysis: $C_{31}H_{26}N_4O_6$ (550.58): Found C, 67.50; H, 4.68; N, 10.31. Calculated C, 67.63; H, 4.76; N, 10.18 %

Methyl 2,6-*bis*(3-nitrophenyl)-1-Phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine -3-carboxylate (26)



Nature: Yellow solid

Yield: 40% (0.220 g)

M.p. 181-182 ^{o}C

IR (KBr): 3246, 3063, 2943, 1659, 1594, 1528, 1349, 1258, 1071 cm^{-1}

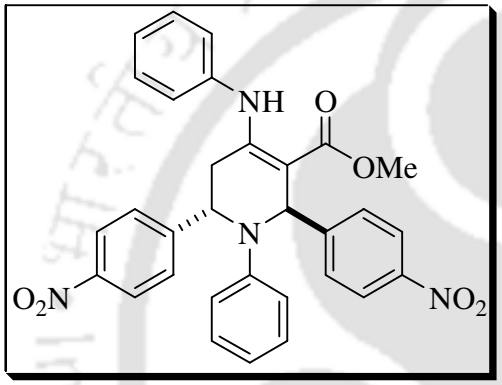
^{1}H NMR (400 MHz, $CDCl_3$): 2.85 (2H, d, *J* = 4.0 Hz), 3.96 (3H, s), 5.29-5.30 (1H, m), 6.36-6.39 (2H, m), 6.42 (2H, d, *J* = 8.4 Hz), 6.46 (1H, s), 6.67 (1H, t, *J* = 7.6 Hz), 7.07

(2H, t, *J* = 7.6 Hz), 7.12-7.14 (3H, m), 7.43-7.48 (3H, m), 7.64 (1H, d, *J* = 7.6 Hz), 7.92 (1H, s), 8.07-8.12 (2H, m), 8.19 (1H, s), 10.27 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 33.9, 51.6, 55.3, 57.2, 96.9, 113.2, 117.8, 121.5, 121.7, 122.0, 122.6, 125.8, 126.7, 129.3, 129.5, 129.8, 132.7, 137.3, 144.6, 145.9, 146.5, 148.7, 148.8, 155.7, 168.2 ppm.

Elemental Analysis: $C_{31}H_{26}N_4O_6$ (550.58): Found C, 67.49; H, 4.71; N, 10.33. Calculated C, 67.63; H, 4.76; N, 10.18 %

Methyl 2,6-*bis*(4-nitrophenyl)-1-Phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine -3-carboxylate (27)



Nature: Light yellow solid

Yield: 32% (0.176)

M.p. 239-241 ^{o}C

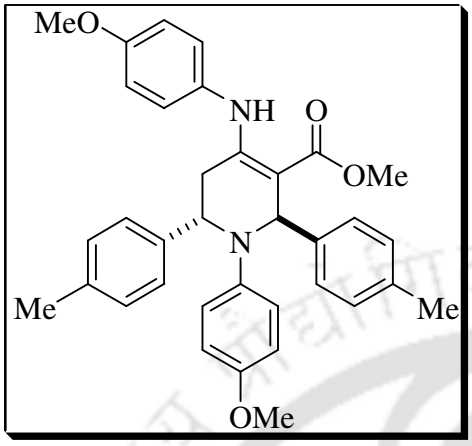
IR (KBr): 3356, 2950, 1660, 1593, 1518, 1499, 1346, 1257, 1072 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.85 (2H, d, *J* = 4.0 Hz), 3.95 (3H, s), 5.24-5.25 (1H, m), 6.37-6.42 (4H, m), 6.46 (1H, s), 6.68 (1H, t, *J* = 7.2 Hz), 7.07 (1H, d, *J* = 7.2 Hz), 7.09 (1H, d, *J* = 7.2 Hz), 7.13-7.17 (3H, m), 7.27 (2H, d, *J* = 8.8 Hz), 7.48 (2H, d, *J* = 8.4 Hz), 8.12 (2H, d, *J* = 8.8 Hz), 8.14 (2H, d, *J* = 8.8 Hz), 10.26 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 33.7, 51.6, 55.4, 57.5, 96.8, 113.1, 117.8, 123.9, 124.1, 125.7, 126.6, 127.5, 127.6, 129.4, 129.5, 137.3, 145.9, 146.9, 147.5, 149.9, 151.8, 155.7, 168.1 ppm.

Elemental Analysis: $C_{31}H_{26}N_4O_6$ (550.58): Found C, 67.51; H, 4.69; N, 10.31. Calculated C, 67.63; H, 4.76; N, 10.18 %

Methyl2,6-*bis*(4-methylphenyl)-1-(4-methoxyphenyl-4-(4-methoxyphenylamino)-1,2, 5,6-tetrahydropyridine -3-carboxylate (28)



Nature: White solid

Yield: 77% (0.423 g)

M.p. 225-226 °C

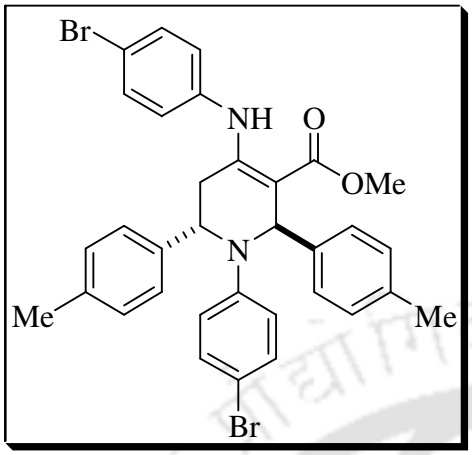
IR (KBr): 3245, 2948, 2835, 1656, 1611, 1510, 1458, 1242, 1037 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.29 (3H, s), 2.32 (3H, s), 2.60 (1H, dd, *J* = 2.8 Hz, *J* = 15.2 Hz), 2.75 (1H, dd, *J* = 5.6 Hz, *J* = 15.2 Hz), 3.63 (3H, s), 3.73 (3H, s), 3.87 (3H, s), 4.98-4.99 (1H, m), 6.19 (2H, d, *J* = 8.8 Hz), 6.25 (1H, s), 6.41 (2H, d, *J* = 9.2 Hz), 6.59 (2H, d, *J* = 8.8 Hz), 6.63 (2H, d, *J* = 9.2 Hz), 7.01-7.08 (6H, m), 7.15 (2H, d , *J* = 8.0 Hz), 10.07 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 21.2, 21.3, 33.8, 51.0, 55.6, 55.7, 55.8, 58.1, 97.3, 114.1, 114.2, 114.6, 126.6, 126.9, 128.0, 129.0, 129.4, 131.0, 135.8, 136.7, 140.4, 141.5, 141.9, 151.0, 157.2, 157.9, 168.8 ppm.

Elemental Analysis: $C_{35}H_{36}N_2O_4$ (548.69): Found C, 76.48; H, 6.56; N, 5.23. Calculated C, 76.62; H, 6.61; N, 5.11 %.

Methyl 2,6-*bis*(4-methylphenyl)-1-(4-bromophenyl-4-(4-bromophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (29)



Nature: White solid

Yield: 68% (0.440 g)

M.p. 229-230 °C.

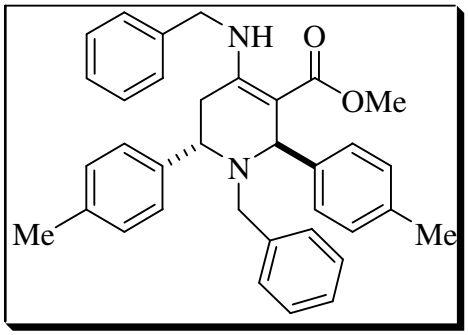
IR (KBr): 3240, 2949, 2917, 1656, 1607, 1587, 1492, 1255, 1071 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.30 (3H, s), 2.32 (3H, s), 2.67 (1H, dd, *J* = 2.4 Hz, *J* = 15.2 Hz), 2.82 (1H, dd, *J* = 5.6 Hz, *J* = 15.2 Hz), 3.91 (3H, s), 5.03-5.04 (1H, m), 6.10 (2H, d, *J* = 8.4 Hz), 6.29 (1H, s), 6.36 (2H, d, *J* = 9.2 Hz), 7.00 (2H, d, *J* = 8.0 Hz), 7.05-7.13 (8H, m), 7.18 (2H, d, *J* = 8.8 Hz), 10.16 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 21.2, 21.3, 33.6, 51.4, 55.2, 58.2, 98.9, 108.5, 114.7, 119.3, 126.4, 126.6, 127.5, 129.3, 129.6, 131.7, 132.1, 136.3, 137.2, 137.3, 139.2, 140.2, 146.1, 155.6, 168.7 ppm.

Elemental Analysis: $C_{33}H_{30}Br_2N_2O_2$ (646.43): Found C, 61.18; H, 4.62; N, 4.47. Calculated C, 61.32; H, 4.68; N, 4.33 %

Methyl 2,6-*bis*(4-methylphenyl)-1-benzyl-4-(benzylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (30)



Nature: Light yellow solid

Yield: 48 % (0.248 g)

M.p. 172-173 °C

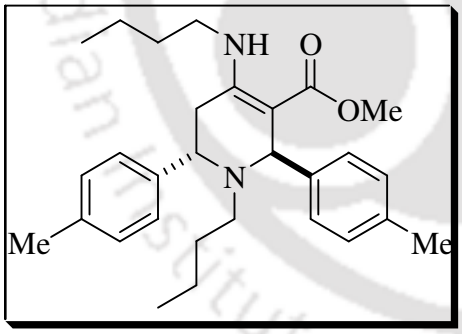
IR (KBr): 3277, 3026, 2945, 1649, 1597, 1452, 1229, 1071 cm^{-1} .

^{1}H NMR (400 MHz, $CDCl_3$): 2.27 (3H, s), 2.29 (3H, s), 2.60 (1H, dd, *J* = 5.2 Hz, *J* = 17.2 Hz), 2.71 (1H, dd, *J* = 11.6 Hz, *J* = 17.2 Hz), 3.30 (1H, d, *J* = 13.6 Hz), 3.35 (1H, d, *J* = 13.6 Hz), 3.44 (3H, s), 4.00 (1H, dd, *J* = 5.2 Hz, 11.6 Hz), 4.55 (1H, dd, *J* = 6.0 Hz, *J* = 15.6 Hz), 4.61 (1H, dd, *J* = 6.0 Hz, *J* = 15.6 Hz), 4.71 (1H, s), 7.06 (4H, t, *J* = 8.4 Hz), 7.18-7.23 (5H, m), 7.30 (3H, t, *J* = 7.2 Hz), 7.34-7.38 (6H, m), 9.65 (1H, t, *J* = 5.6 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 21.3, 25.7, 33.1, 46.4, 49.8, 50.6, 52.3, 58.2, 89.5, 126.9, 127.0, 127.4, 127.6, 128.3, 128.5, 128.8, 129.1, 129.2, 135.8, 136.8, 138.8, 139.2, 140.5, 141.9, 159.0, 171.3 ppm.

Elemental Analysis: $C_{35}H_{36}N_2O_2$ (516.69): Found C, 81.22; H, 7.07; N, 5.57. Calculated C, 81.36; H, 7.02; N, 5.42 %

Methyl 2,6-*bis*(4-methylphenyl)-1-butyl-4-(butylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (31)



Nature: Light yellow solid

Yield: 63% (0.283 g)

M.p. 153-154 °C

IR (KBr): 3263, 2931, 1647, 1595, 1454, 1244, 1124, 1048 cm^{-1}

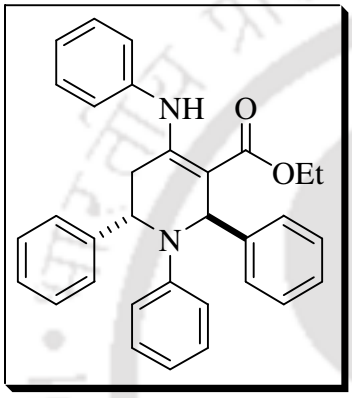
^{1}H NMR (400 MHz, $CDCl_3$): 0.77 (3H, t, *J* = 7.2 Hz), 0.96 (3H, t, *J* = 7.2 Hz), 1.08 - 1.21 (2H, m), 1.24-1.34 (2H, m), 1.41-1.50 (2H, m), 1.58-1.66 (2H, m), 2.06-2.13 (2H, m), 2.28 (3H, s), 2.30 (3H, s), 2.49 (1H, dd, *J* = 5.2 Hz, *J* = 17.2 Hz), 2.58 (1H, dd, *J* = 11.2 Hz, *J* = 17.2 Hz), 3.24-3.34 (m, 2H), 3.52 (3H, s), 3.83 (1H, dd, *J* = 5.2 Hz, *J* = 11.2

Hz), 4.90 (1H, s), 7.05 (2H, d, *J* = 7.6 Hz), 7.07 (2H, d, *J* = 7.6 Hz), 7.15 (2H, d, *J* = 7.6 Hz), 7.29 (2H, d, *J* = 7.6 Hz), 9.19 (1H, m) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 14.3, 20.5, 20.6, 21.3, 25.6, 31.1, 32.6, 42.1, 44.8, 50.6, 52.5, 58.5, 88.0, 127.4, 128.4, 128.8, 128.9, 135.6, 136.4, 139.3, 142.5, 159.7, 171.4 ppm.

Elemental Analysis: $C_{29}H_{40}N_2O_2$ (448.64): Found C, 77.51; H, 8.91; N, 6.37 Calculated C, 77.64; H, 8.99; N, 6.24 %

Ethyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate(32)



Nature: White solid

Yield: 76% (0.361 g)

M.p. 174-175 °C

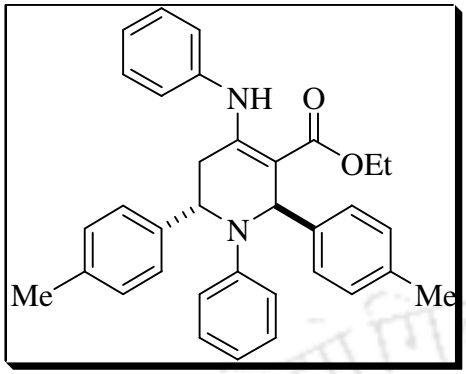
IR (KBr): 3242, 3059, 2979, 1651, 1594, 1500, 1251, 1068 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): 1.47 (3H, t, *J* = 7.2 Hz), 2.77 (1H, dd, *J* = 2.4 Hz, *J* = 15.2 Hz), 2.87 (1H, dd, *J* = 5.6 Hz, *J* = 15.2 Hz), 4.29-4.37 (1H, m), 4.42-4.50 (1H, m), 5.14-5.15 (1H, m), 6.27-6.29 (2H, m), 6.46 (s, 1H), 6.52 (2H, d, *J* = 8.0 Hz), 6.61 (1H, t, *J* = 7.2 Hz), 7.05-7.11 (5H, m), 7.16-7.19 (2H, m), 7.22 (1H, d, *J* = 7.2 Hz), 7.25-7.30 (5H, m), 7.34 (2H, d, *J* = 7.6 Hz), 10.29 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 15.0, 33.8, 55.3, 58.4, 59.9, 98.4, 113.1, 116.3, 125.9, 126.0, 126.5, 126.6, 126.8, 127.3, 128.4, 128.8, 129.0, 129.1, 138.1, 143.0, 144.2, 147.2, 156.3, 168.4 ppm.

Elemental Analysis: $C_{32}H_{30}N_2O_2$ (474.61): Found C, 80.83; H, 6.32; N, 6.04 Calculated C, 80.98; H, 6.37; N, 5.90 %

Ethyl 2,6-*bis*(4-methylphenyl)-1-Phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine -3-carboxylate (33)



Nature: White solid

Yield: 74% (0.386 g)

M.p. 227-230 °C

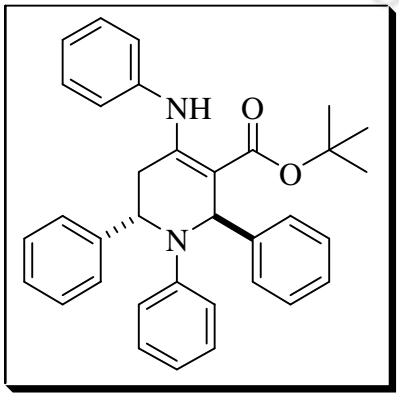
IR (KBr): 3240, 2980, 1651, 1594, 1501, 1248, 1068 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.45 (3H, t, *J* =7.2 Hz), 2.31 (3H, s), 2.32 (3H, s), 2.75 (1H, dd, *J* = 2.4 Hz, *J* = 15.2 Hz), 2.85 (1H, dd, *J* = 5.6 Hz, *J* = 15.2 Hz), 4.26-4.34 (1H, m), 4.40-4.48 (1H, m), 5.09-5.10 (1H, m), 6.27-6.29 (2H, m), 6.39 (1H,s), 6.51 (2H, d, *J* = 8.4 Hz), 6.58 (1H, t, *J* = 7.2 Hz), 7.02-7.08 (11H, m), 7.21 (2H, d, *J* = 8.0Hz), 10.28 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 15.0, 21.2, 21.3, 33.8, 55.0, 58.1, 59.8, 98.6, 113.1, 116.1, 125.7, 125.9, 126.5, 126.7, 128.9, 129.0, 129.1, 129.4, 135.9, 136.7, 138.2, 139.9, 141.2, 147.2, 156.2, 168.4 ppm.

Elemental Analysis: $C_{34}H_{34}N_2O_2$ (502.65): Found C, 81.10; H, 6.86; N, 5.70 Calculated C, 81.24; H, 6.82; N, 5.57 %

Tert-butyl-1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxyla te (34)



Nature: White solid

Yield: 60% (0.302 g)

M.p. 162-163 °C

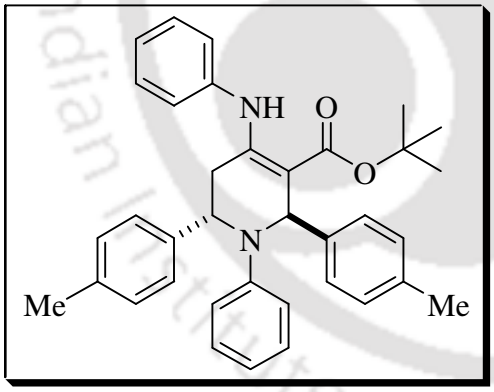
IR (KBr): 3241, 3054, 2974, 1649, 1594, 1500, 1250, 1153, 1065 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.64 (9H, s), 2.74 (1H, dd, *J* = 2.8 Hz, *J* = 15.2 Hz), 2.83 (1H, dd, *J* = 5.6 Hz, *J* = 15.2 Hz), 5.10-5.11 (1H, m), 6.27 (2H, d, *J* = 7.2 Hz), 6.39 (1H, s), 6.49 (2H, d, *J* = 8.0 Hz), 6.59 (1H, t, *J* = 7.2 Hz), 7.03-7.17 (4H, m), 7.16 (2H, d, *J* = 7.6 Hz), 7.20 (1H, d. *J* = 7.2 Hz), 7.23-7.29 (6H, m), 7.34 (2H, d, *J* = 7.6 Hz), 10.24 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 29.0, 33.8, 55.6, 58.4, 80.2, 99.9, 113.2, 116.3, 125.5, 125.7, 126.4, 126.6, 126.8, 127.3, 128.4, 128.7, 128.9, 129.1, 138.3, 143.0, 144.4, 147.2, 155.3, 168.4 ppm.

Elemental Analysis: $C_{34}H_{34}N_2O_2$ (502.65): Found C, 81.11; H, 6.77; N, 5.71. Calculated C, 81.24; H, 6.82; N, 5.57 %

Tert-butyl 2,6-*bis*(4-methylphenyl)-1-Phenyl-4-(phenylamino)-1,2,5,6-tetrahydro pyridine -3-carboxylate (35)



Nature: Light yellow solid

Yield: 65% (0.345 g)

M.p. 97-98 °C

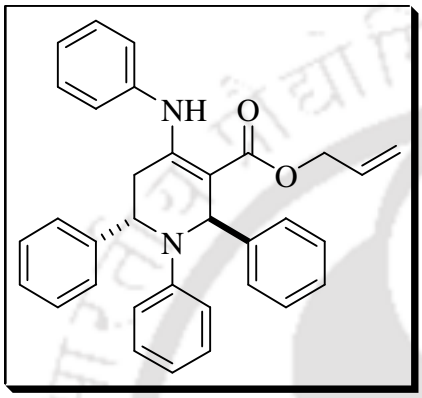
IR (KBr): 3242, 2976, 2924, 1650, 1594, 1502, 1368, 1251, 1155, 1066 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.65 (9H, s), 2.32 (3H, s), 2.33 (3H, s), 2.74 (1H, dd, *J* = 2.8 Hz, *J* = 15.2 Hz), 2.83 (1H, dd, *J* = 5.6 Hz, *J* = 15.2 Hz), 5.08-5.09 (1H, m), 6.30 (2H, d, *J* = 7.2 Hz), 6.36 (1H, s), 6.51 (2H, d, *J* = 8.0 Hz), 6.59 (1H, t, *J* = 7.2 Hz), 7.04-7.10 (11 H, m), 7.23 (2H, d, *J* = 8.0 Hz), 10.26 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 21.2, 21.3, 29.0, 33.8, 55.4, 58.1, 80.1, 100.1, 113.1, 116.0, 125.3, 125.7, 126.5, 126.7, 128.9, 129.0, 129.4, 135.8, 136.7, 138.4, 139.9, 141.4, 147.3, 155.3, 168.4 ppm.

Elemental Analysis: $C_{36}H_{38}N_2O_2$ (530.72): Found C, 81.33; H, 7.28; N, 5.40. Calculated C, 81.48; H, 7.22; N, 5.28 %

Allyl-1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (36)



Nature: Light yellow solid

Yield: 70 % (0.341 g)

M.p. 149-150 °C

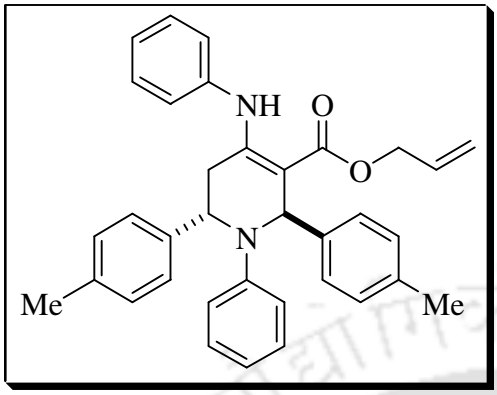
IR (KBr): 3243, 3058, 2936, 1653, 1594, 1498, 1374, 1249, 1177, 1064 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.77 (1H, dd, *J* = 2.4 Hz, *J* = 15.2 Hz), 2.88 (1H, dd, *J* = 5.6 Hz, *J* = 15.2 Hz), 4.81 (1H, ddt, *J* = 1.6 Hz, *J* = 5.2 Hz, *J* = 13.6 Hz), 4.89 (1H, ddt, *J* = 1.6 Hz, *J* = 5.2 Hz, *J* = 13.2 Hz), 5.15-5.16 (1H, m), 5.33 (1H, dq, *J* =1.6 Hz, *J* = 10.4 Hz), 5.47 (1H, dq, *J* = 1.6 Hz, *J* = 17.2 Hz), 6.08-6.17 (1H, m), 6.27-6.29 (2H, m), 6.50 (2H, d, *J* = 6.4 Hz), 6.53 (1H, s), 6.61 (1H, t, *J* = 7.2 Hz), 7.04-7.12 (5H, m), 7.16-7.18 (2H, m), 7.22 (1H, d, *J* = 7.2 Hz), 7.25-7.30 (5H, m), 7.35 (2H, d, *J* = 7.2 Hz), 10.27 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 33.9, 55.3, 58.4, 64.6, 98.0, 113.2, 116.4, 117.9, 126.0, 126.1, 126.5, 126.6, 126.9, 127.4, 128.5, 128.8, 129.0, 129.1, 133.3, 138.0, 142.9, 144.2, 147.2, 156.8, 168.0 ppm.

Elemental Analysis: $C_{33}H_{30}N_2O_2$ (486.62): Found C, 81.31; H, 6.14; N, 5.89. Calculated C, 81.45; H, 6.21; N, 5.76 %

Allyl 2,6-*bis*(4-methylphenyl)-1-Phenyl-4-(phenylamino)-1,2,5,6-tetrahydro pyridine -3-carboxylate (37)



Nature: Light yellow solid

Yield: 77% (0.396 g)

M.p. 172-174 °C

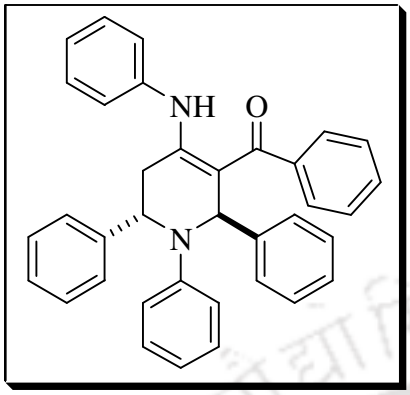
IR (KBr): 3241, 3022, 2922, 1655, 1594, 1501, 1372, 1246, 1063 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.30 (3H, s), 2.31 (3H, s), 2.74 (1H, dd, *J* = 2.4 Hz, *J* = 15.2 Hz), 2.85 (1H, dd, *J* = 5.6 Hz, *J* = 15.2 Hz), 4.78 (1H, ddt, *J* = 1.6 Hz, *J* = 5.6 Hz, *J* = 13.6 Hz), 4.86 (1H, ddt, *J* = 1.6 Hz, *J* = 5.6 Hz, *J* = 13.6 Hz), 5.09-5.10 (1H, m), 5.30 (1H, dq, *J* = 1.6 Hz, *J* = 10.4 Hz), 5.44(1H, dq, *J* = 1.6, *J* = 17.2 Hz), 6.05-6.14 (1H, m), 6.27-6.29 (2H, m), 6.42 (1H, s), 6.50 (2H, d, *J* = 8.0 Hz), 6.57 (1H, t, *J* = 7.2 Hz), 7.01-7.07 (11H, m), 7.20 (2H, d, *J* = 8.0 Hz), 10.25 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 21.2, 21.3, 33.9, 55.0, 58.1, 64.5, 98.1, 113.1, 116.2, 117.8, 125.8, 126.0, 126.5, 126.8, 126.9, 128.9, 129.0, 129.1, 129.4, 133.3, 136.8, 138.1, 139.8, 141.1, 147.2, 156.8, 168.0 ppm.

Elemental Analysis: $C_{35}H_{34}N_2O_2$ (514.67) Found C, 81.54; H, 6.61; N, 5.58. Calculated C, 81.68; H, 6.66; N, 5.44 %

Phenyl-(1,2,6-triphenyl-4-phenylamino-1,2,5,6-tetrahydro-pyridin-3-yl)-methanone (16)



Nature: Yellow solid

Yield: 42% (0.213 g)

M.p. 191-193 °C

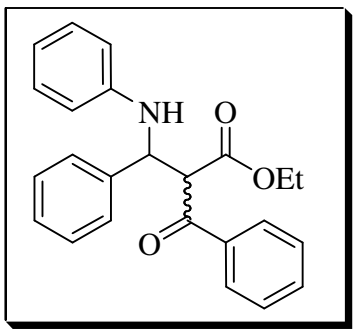
IR (KBr): 3060, 3021, 1591, 1574, 1544, 1497, 1319, 1278, 1026 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 2.81 (2H, d, *J* = 4.0 Hz), 5.14 (1H, t, *J* = 4.0 Hz), 6.27 (2H, dd, *J* = 2.0 Hz, *J* = 7.6 Hz), 6.44 (2H, d, *J* =8.0 Hz), 6.55 (1H, s), 6.62 (1H, t, *J* = 7.2 Hz), 7.03-7.07 (3H, m), 7.08-7.14 (5H, m), 7.14-7.16 (1H, m), 7.18-7.22 (3H, m), 7.33-7.35 (4H, m), 7.46-7.50 (2H, m), 7.73 (2H, dd, *J* = 2.0 Hz, *J* = 7.6 Hz), 12.90 (1H, brs) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 34.2, 57.0, 58.1, 108.9, 112.5, 116.5, 126.3, 126.5, 126.6, 126.9, 127.6, 128.4, 128.7, 128.9, 129.2, 129.4, 130.0, 130.4, 133.8, 137.2, 141.2, 143.0, 143.5, 147.2, 161.2, 192.1 ppm.

Elemental Analysis: $C_{36}H_{30}N_2O$ (506.65): Found C, 85.19; H, 5.91; N, 5.66 Calculated C, 85.34; H, 5.97; N, 5.53 %

Ethyl-2-benzoyl-3-phenyl-3-(phenylamino)propanoate(15)



Nature: White solid

Yield: 40% (0.150 g)

M.p. 101-103 ^{o}C

IR (KBr): 3385, 1735, 1679, 1601, 1516, 1451, 1364, 1286, 1149 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$): 1.12(3H, t, *J* = 7.2 Hz), 4.12 (2H, q, *J* = 7.2 Hz), 4.86 (1H, d, *J* = 7.6 Hz), 4.93 (1H, brs), 5.34 (1H, d, *J* = 7.2 Hz), 6.56 (2H, d, *J* = 8.4 Hz), 6.63 (1H, t, *J* = 7.6 Hz), 7.05 (2H, t, *J* = 7.2 Hz), 7.17 (1H, t, *J* = 8.4 Hz), 7.26 (2H, t, *J* = 7.2 Hz), 7.40 (2H, d, *J* = 8.4 Hz), 7.44 (2H, t, *J* = 7.2 Hz), 7.56 (1H, t, *J* = 7.2 Hz), 7.92 (2H, d, *J* = 8.0 Hz) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): 14.1, 57.4, 61.3, 61.9, 114.2, 118.2, 127.1, 127.7, 128.6, 128.8, 129.0, 129.2, 133.8, 136.1, 140.7, 146.7, 168.3, 193.0 ppm.

Elemental Analysis: $C_{24}H_{23}NO_3$ (373.44): Found C, 77.05; H, 6.26; N, 3.89 Calculated C, 77.19; H, 6.21; N, 3.75 %

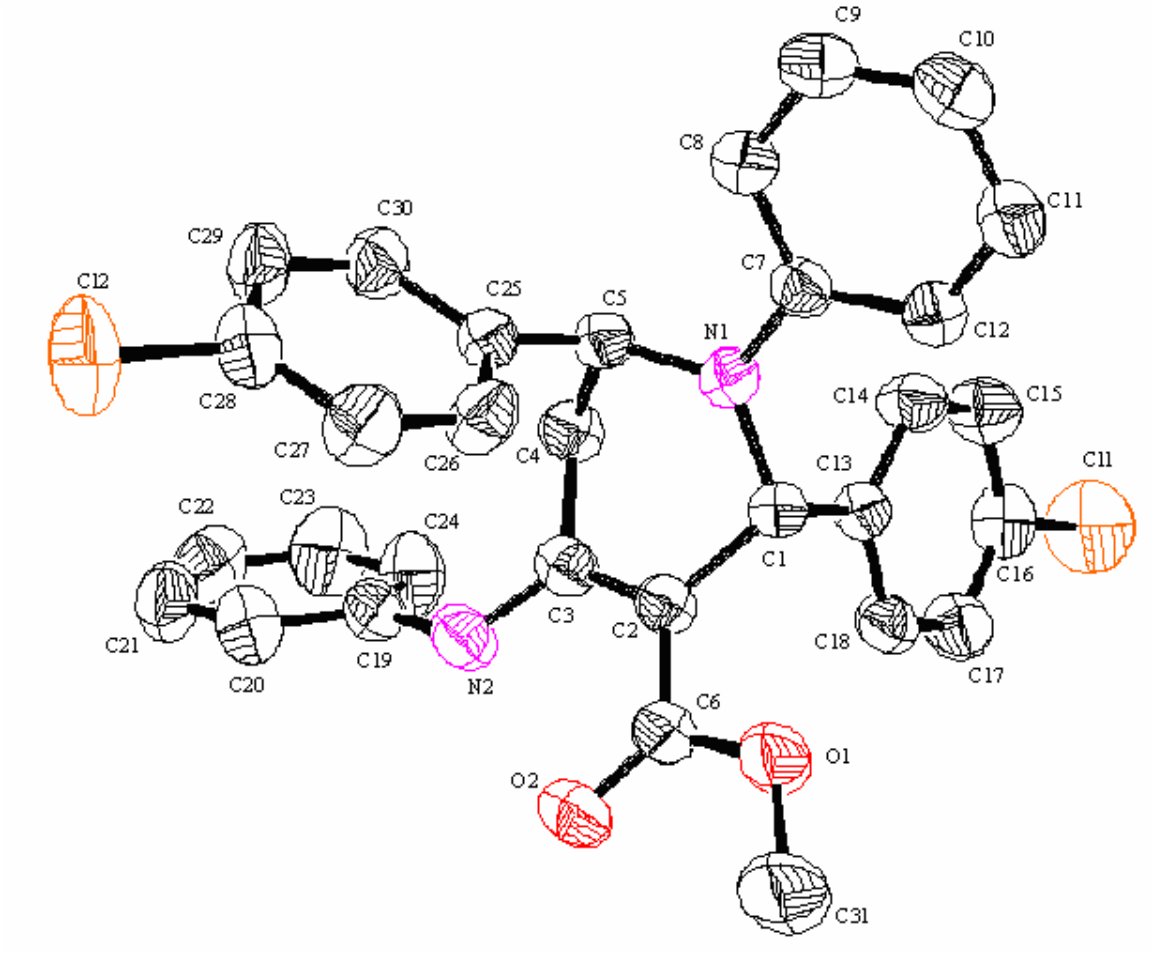


Figure 3. ORTEP plot of Methyl 2,6-*bis*(4-chlorophenyl)-1-Phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (22)

Crystal data and structure refinement for Methyl 2,6-*bis*(4-chlorophenyl)-1-Phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridi ne-3-carboxylate (22)

Identification code	tppip4cl_0m	
Empirical formula	$C_{31}H_{26}Cl_2N_2O_2$	
Formula weight	529.44	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 10.1383(3) Å	α= 103.1880(10)°.
	b = 10.6645(3) Å	β= 105.7350(10)°.
	c = 13.7231(4) Å	γ = 98.5930(10)°.
Volume	1354.67(7) $Å^3$	
Z	2	
Density (calculated)	1.298 Mg/m^3	
Absorption coefficient	0.271 mm^{-1}	
F(000)	552	
Crystal size	0.48 x 0.24 x 0.18 mm^3	
Theta range for data collection	1.61 to 28.37°.	
Index ranges	-13<=h<=13, -14<=k<=14, -18<=l<=18	
Reflections collected	16678	
Independent reflections	6665 [R(int) = 0.0170]	
Completeness to theta = 28.37°	98.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6665 / 0 / 339	
Goodness-of-fit on F^2	1.066	
Final R indices [I>2sigma(I)]	R1 = 0.0459, wR2 = 0.1272	
R indices (all data)	R1 = 0.0650, wR2 = 0.1395	
Largest diff. peak and hole	0.356 and -0.409 $e.Å^{-3}$	

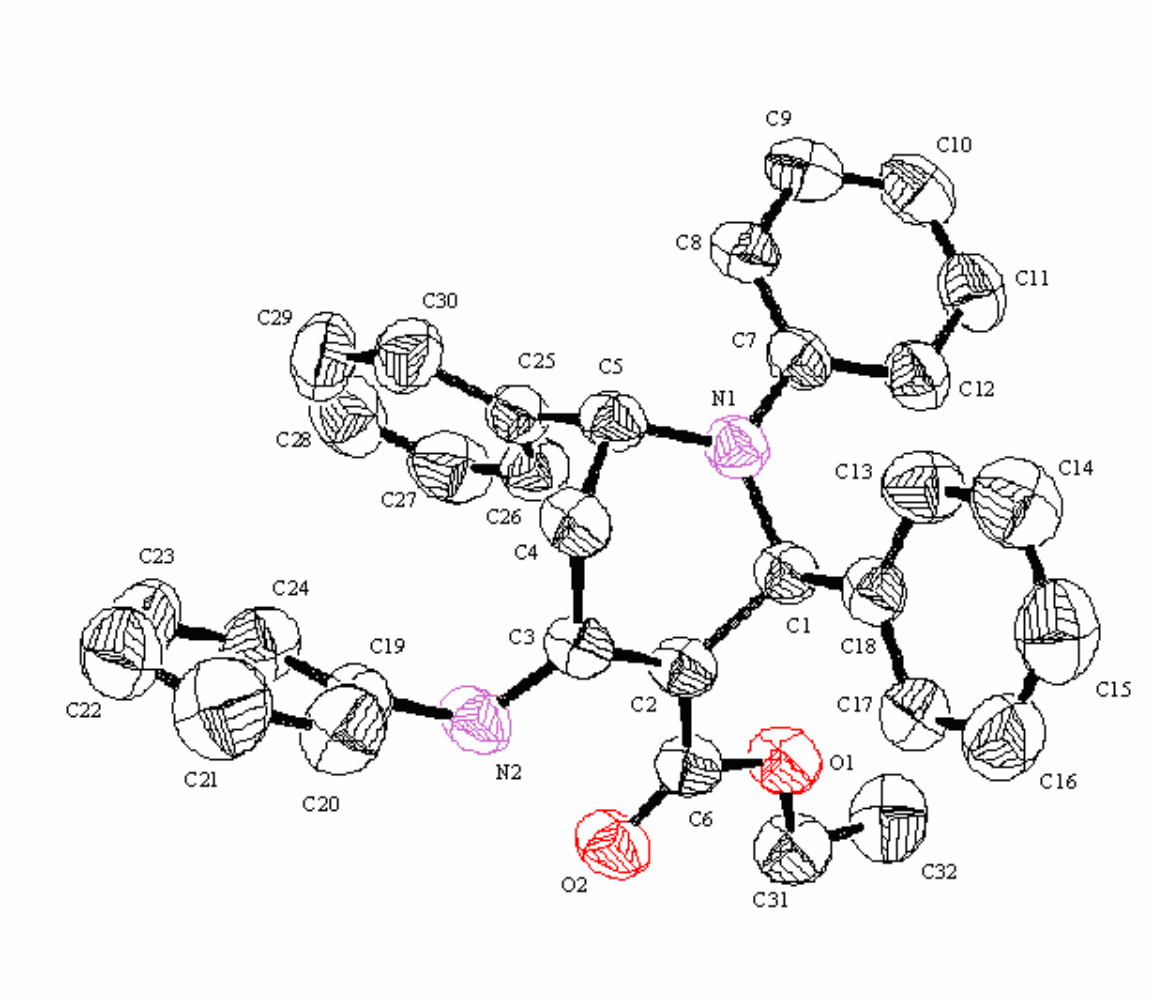


Figure 4. ORTEP plot of Ethyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydro-pyridine-3-carboxylate(32)

Crystal data and structure refinement for Ethyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate(32)

Empirical formula	$C_{32}H_{30}N_2O_2$	
Formula weight	474.58	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.7957(3) Å	α= 106.190(3)°.
	b = 11.0139(4) Å	β= 108.639(3)°.
	c = 13.9330(6) Å	γ = 99.894(2)°.
Volume	1310.44(8) $Å^3$	
Z	2	
Density (calculated)	1.203 Mg/m^3	
Absorption coefficient	0.075 mm^{-1}	
F(000)	504	
Crystal size	0.50 x 0.30 x 0.20 mm^3	
Theta range for data collection	1.65 to 28.39°.	
Index ranges	-12<=h<=13, -11<=k<=14, -18<=l<=18	
Reflections collected	15836	
Independent reflections	5946 [R(int) = 0.0223]	
Completeness to theta = 28.39°	95.7 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5946 / 0 / 330	
Goodness-of-fit on F^2	1.000	
Final R indices [I>2sigma(I)]	R1 = 0.0497, wR2 = 0.1438	
R indices (all data)	R1 = 0.0917, wR2 = 0.1701	
Largest diff. peak and hole	0.197 and -0.161 $e.Å^{-3}$	

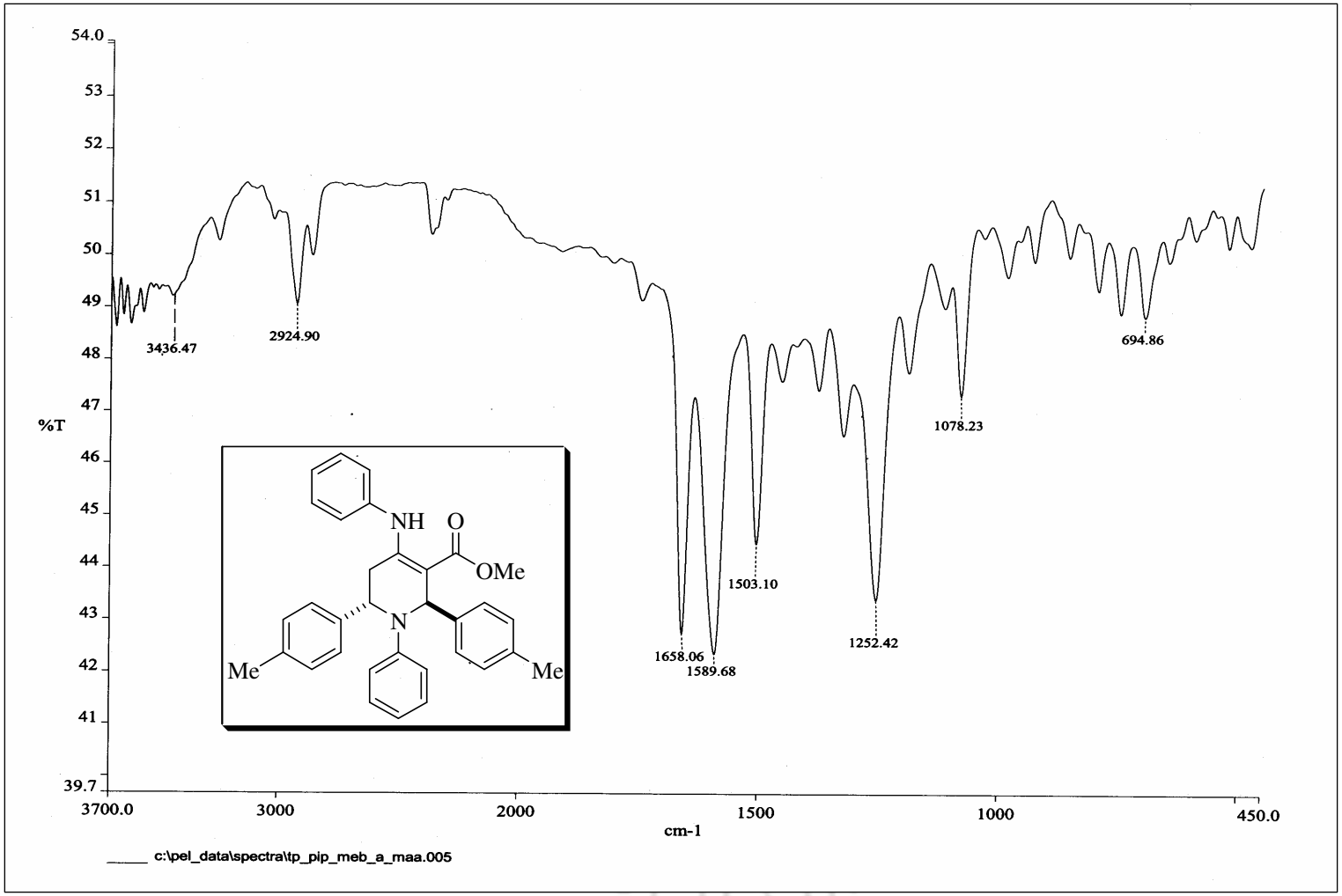


Figure 5: IR Spectrum of Methyl 2,6-*bis*(4-methylphenyl)-1-Phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (12)

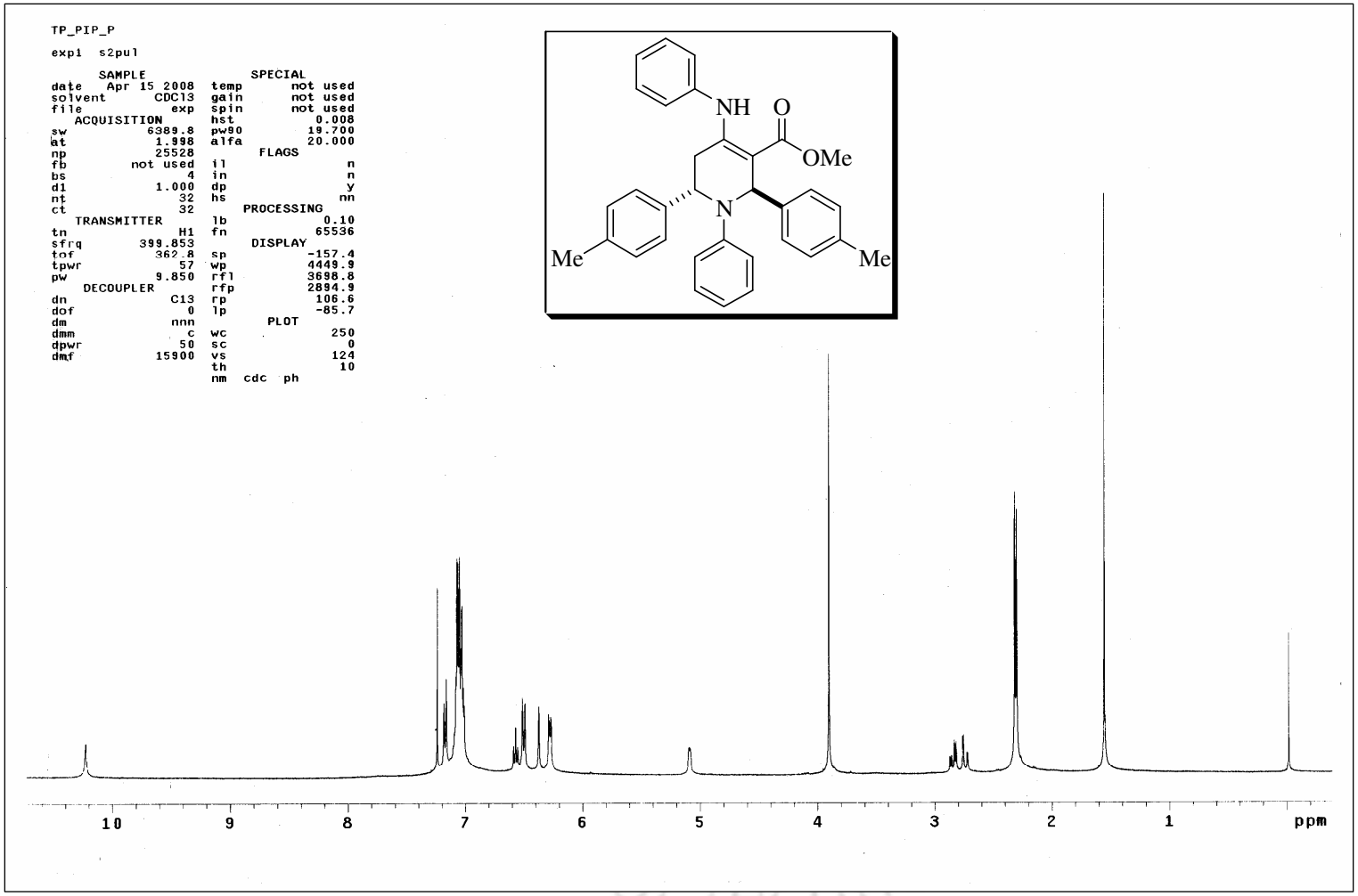


Figure 6: ^{1}H NMR spectrum of Methyl 2,6-*bis*(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (12)

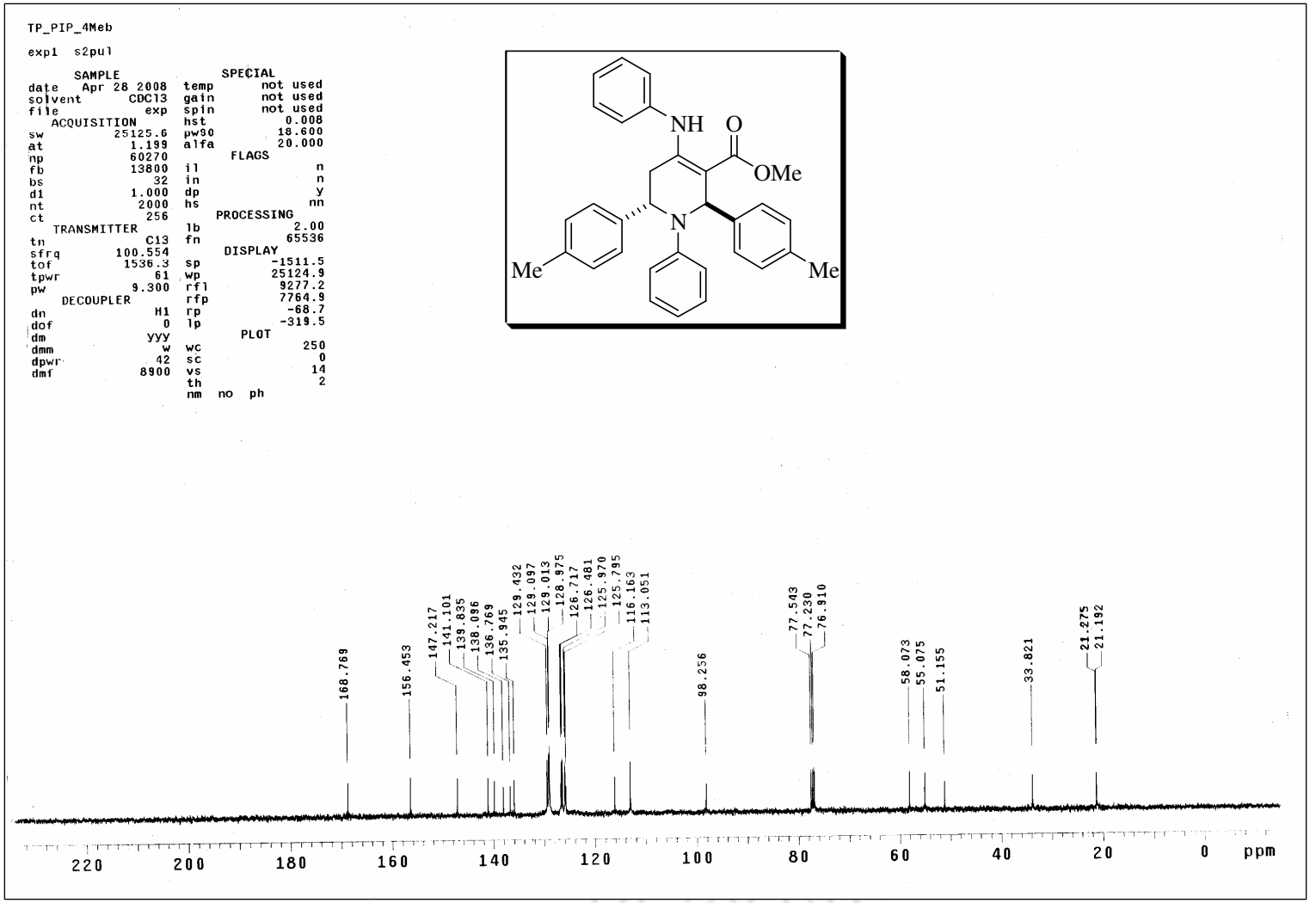


Figure 7: ^{13}C NMR spectrum of of Methyl 2,6-*bis*(4-methylphenyl)-1-phenyl-4-(phenylamino)-1,2,5,6-tetrahydro pyridine -3-carboxylate (12)

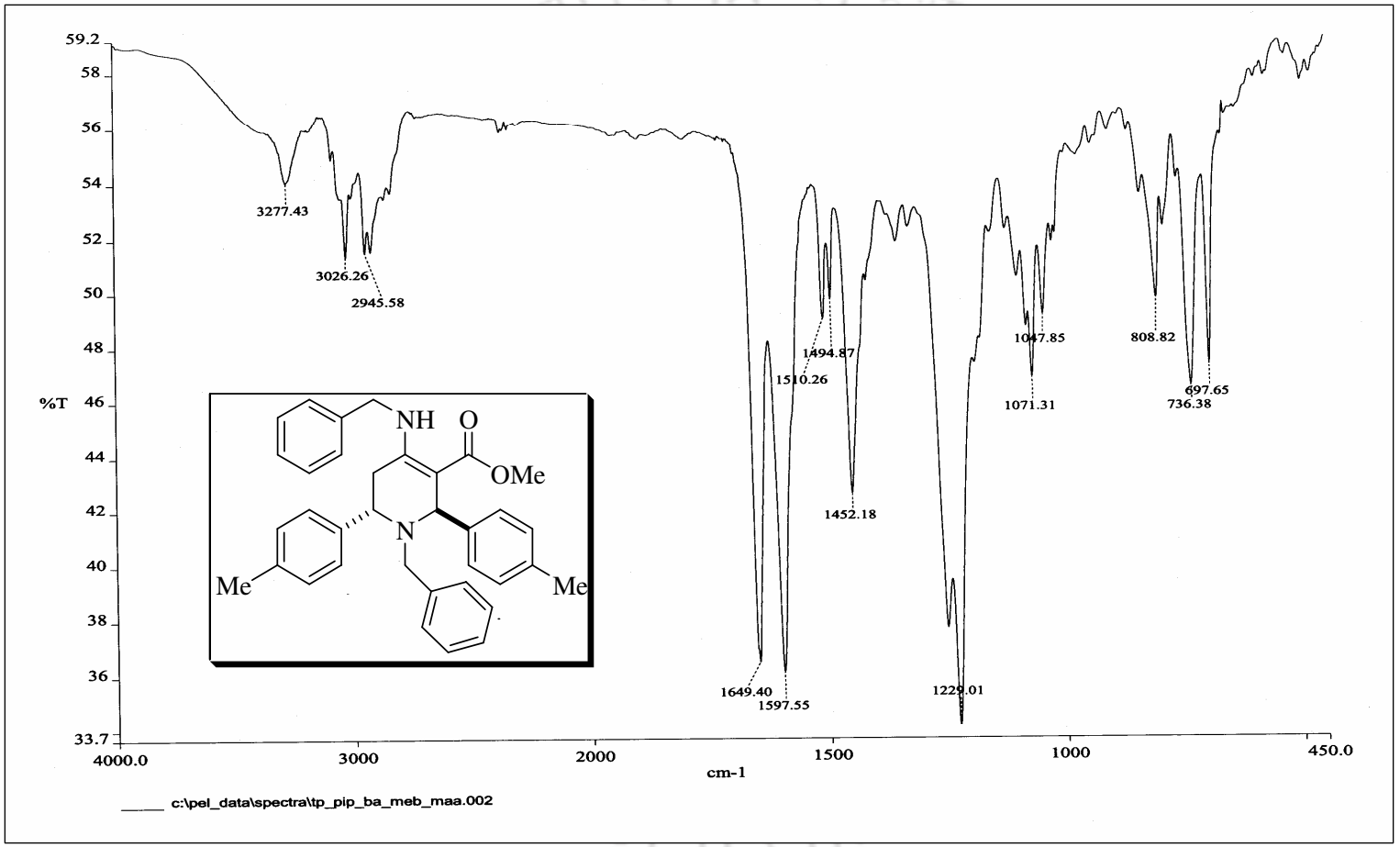


Figure 8: IR spectrum of Methyl 2,6-*bis*(4-methylphenyl)-1-benzyl-4-(benzylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (30)

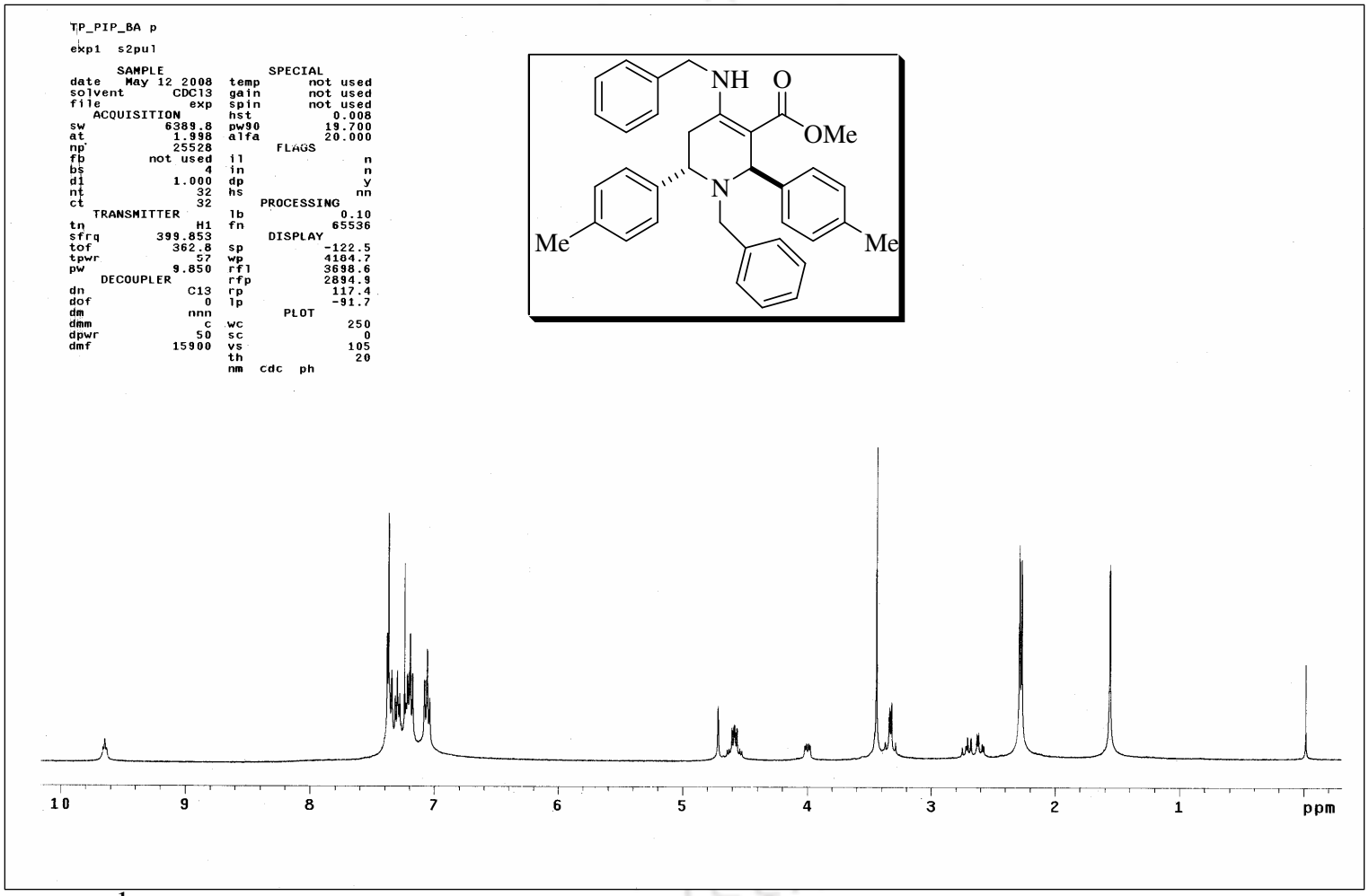


Figure 9: ^{1}H NMR spectrum of Methyl 2,6-*bis*(4-methylphenyl)-1-benzyl-4-(benzylamino)-1,2,5,6-tetrahydro pyridine-3-carboxylate (30)

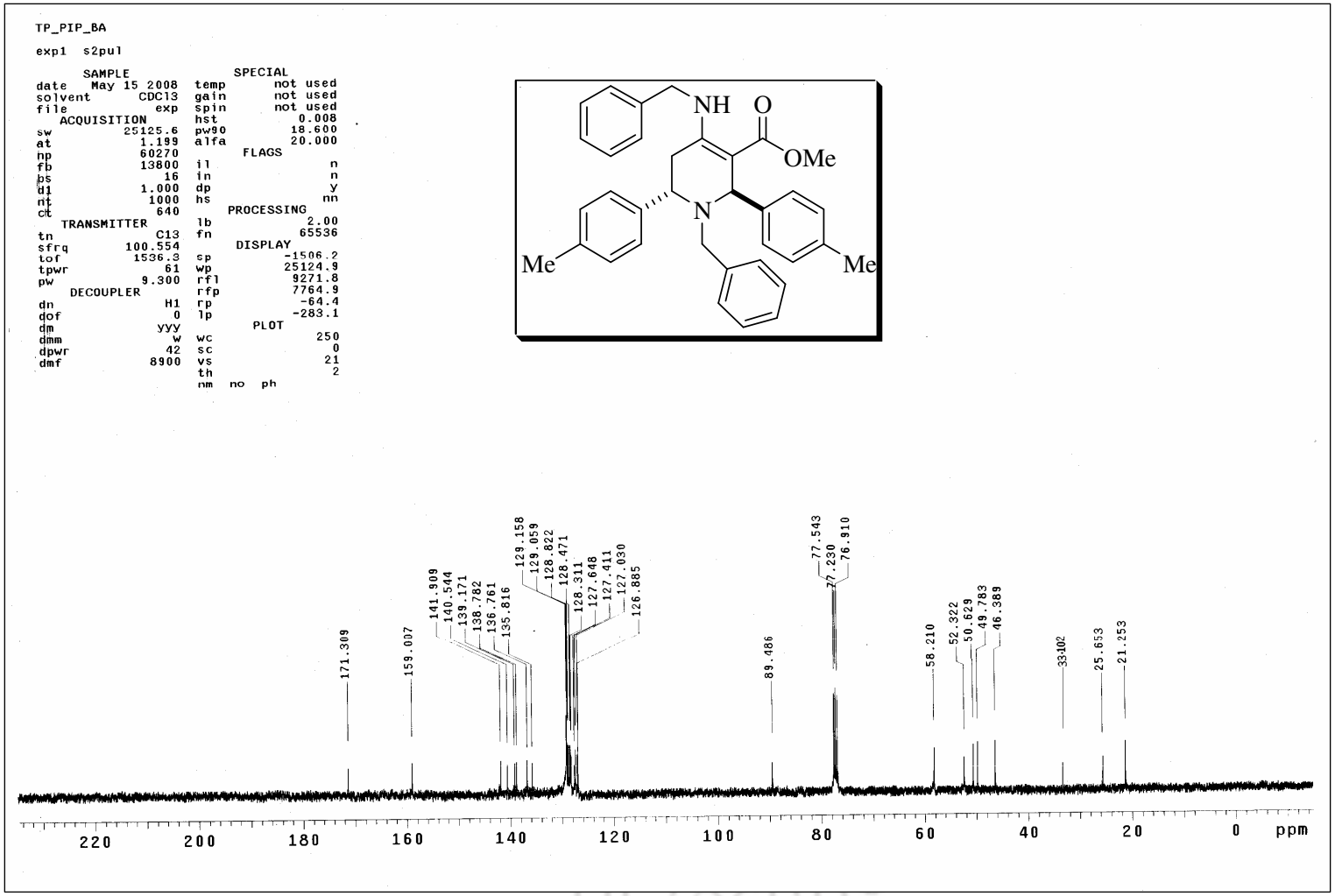


Figure 10: ^{13}C NMR spectrum of Methyl 2,6-*bis*(4-methylphenyl)-1-benzyl-4-(benzylamino)-1,2,5,6-tetrahydro pyridine-3-carboxylate (30)

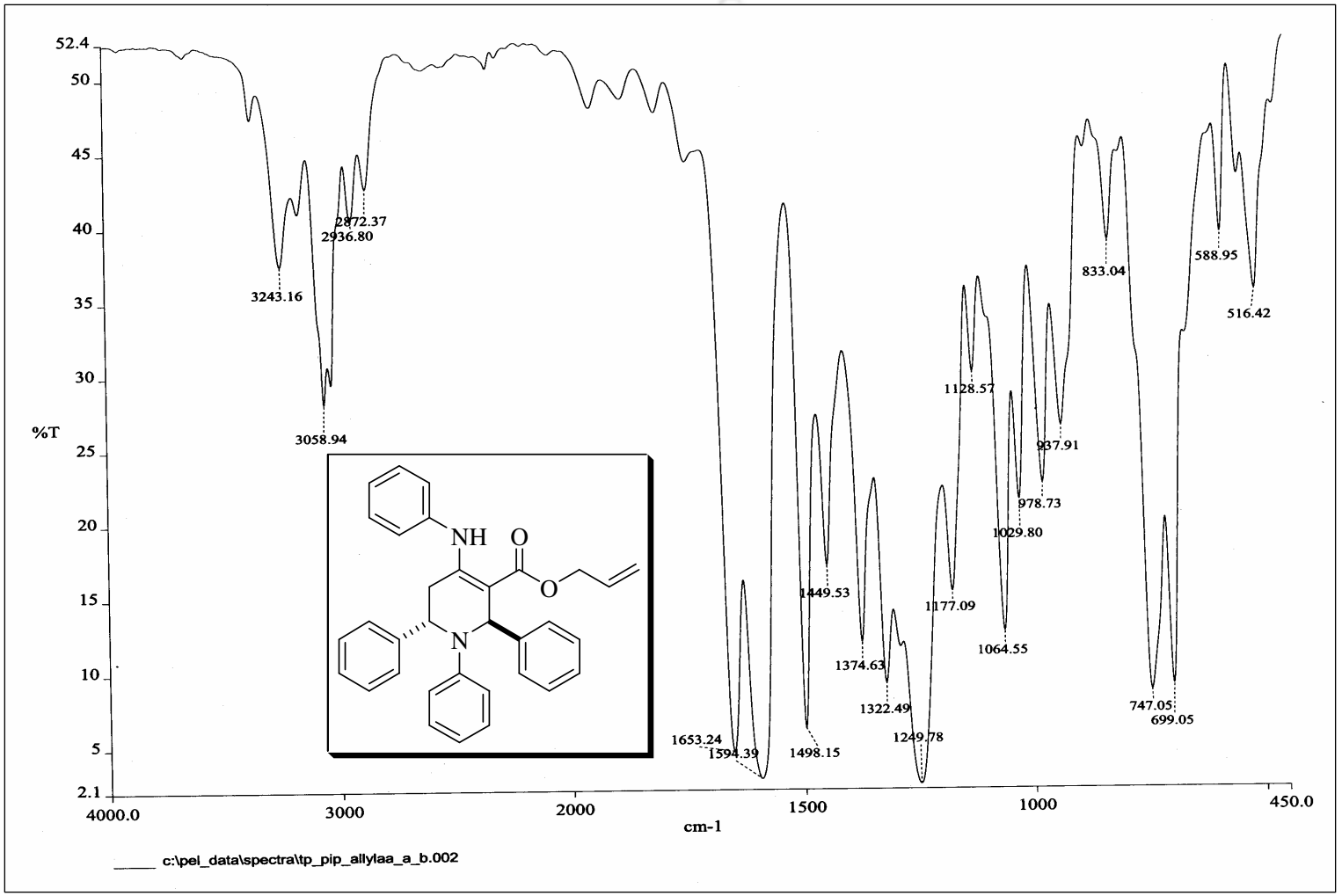


Figure 11: IR spectrum of Allyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (36)

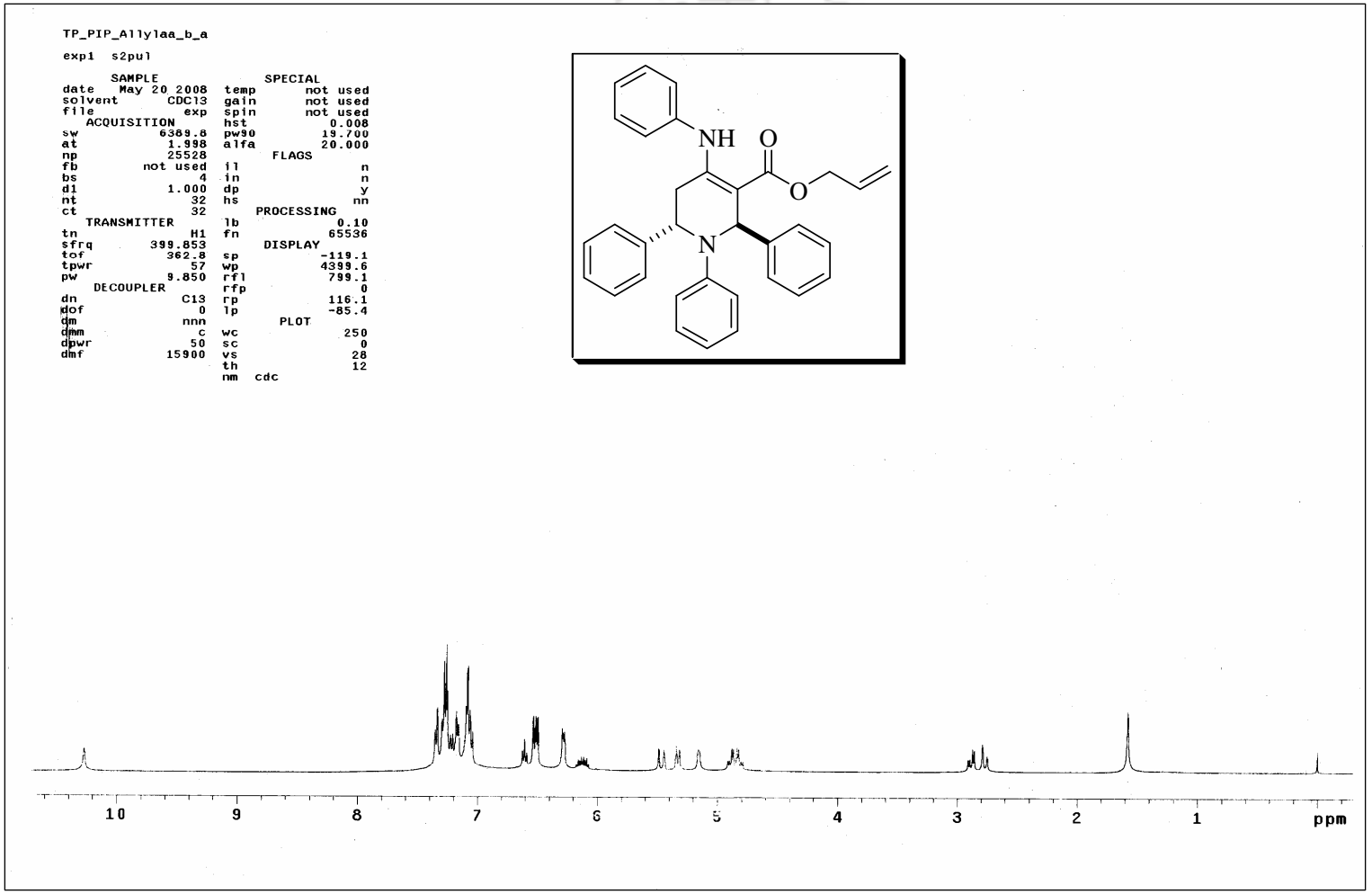


Figure 12: ^{1}H NMR spectrum of Allyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (36)

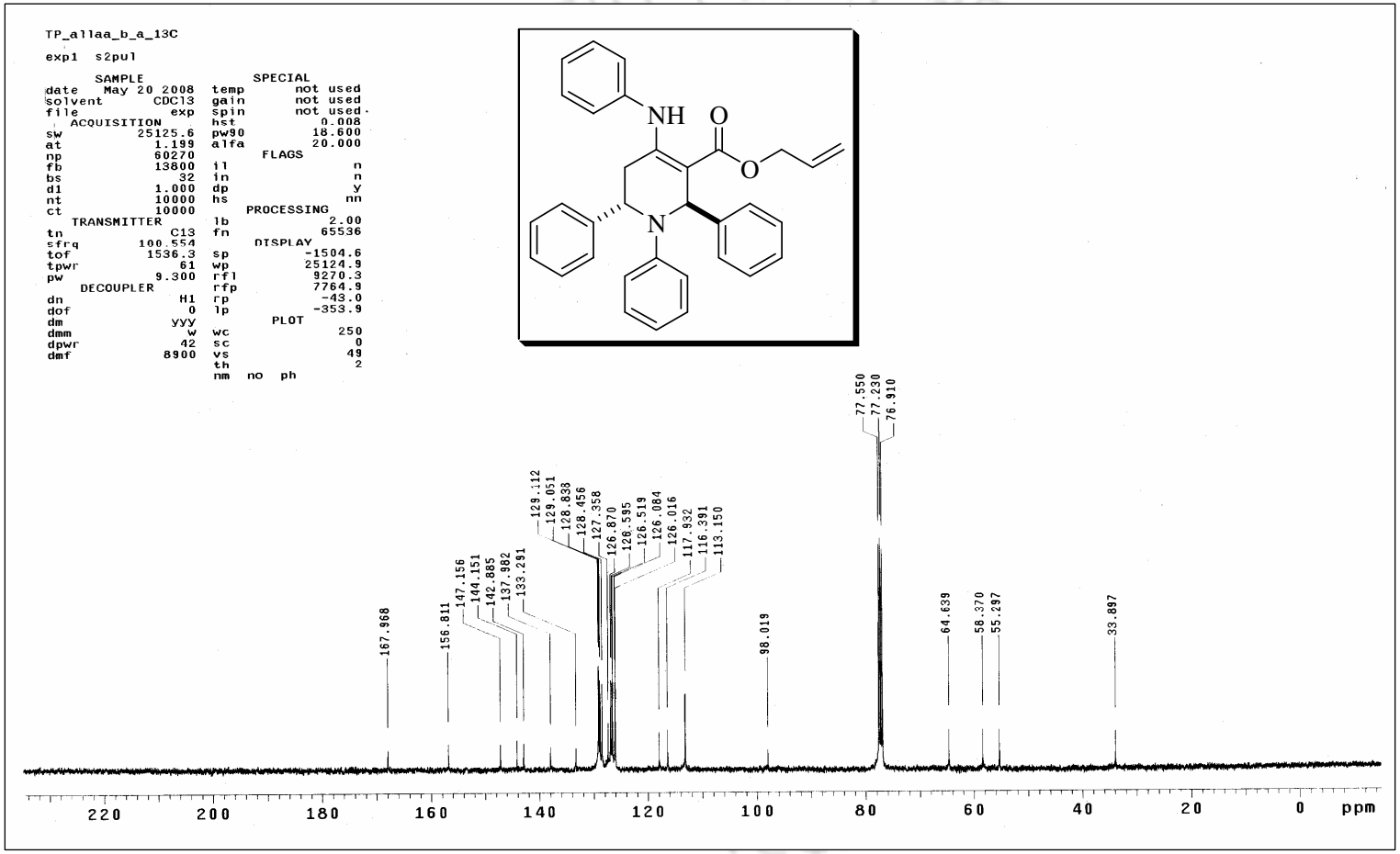


Figure 13: ^{13}C NMR spectrum of Allyl 1,2,6-triphenyl-4-(phenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (36)

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Conclusion and Future perspectives:

In summary the thesis describes some new methodologies on multicomponent reactions for the synthesis of β-amino carbonyl compounds using Lewis acid and bromodimethylsulfonium bromide as catalyst. We have synthesized a wide variety of β-acetamido carbonyl compounds, which can be used as starting material for the preparation of γ-lactum and β-peptides. Recently, it is found that some of the β-acetamido carbonyl compounds act as an effective inhibitor of α-glucosidase and thereby may be useful for diabetes. We believe that these efficient methodologies will be useful to access these class of compounds for further study for biological activities. After that, in continuation of our work for the exploration of bromodimethylsulfonium bromide we have developed two efficient methodologies for the preparation of β-amino carbonyl compounds using aza-Michael and Mannich-type reactions. These compounds may be tested as ligands in complex formation with various metal ions. Subsequently these complexes could be utilized in organic synthesis as catalysts. In addition, we have demonstrated an interesting multicomponent reaction for the preparation of highly functionalized piperidines. It is evident from the literature that functionalized piperidines display important biological properties in medicinal chemistry. Bioactivities of our synthesized highly functionalized piperidines are to be study yet. At the same time, we studied the effects of substituents of 1,3-dicarbonyl compounds to determine the course of the multicomponent reactions. Only a few methods are known involving the reactivity of γ-position of 1,3-dicarbonyl compounds. Thus the reactivity of γ-position in multicomponent reactions for the synthesis of library of heterocyclic molecules are yet to be explore systematically. From synthetic point of view the produced piperidine ring has both secondary amine and enamino esters, which enable further modifications leading to molecular diversity. Further studies are in progress in our laboratory.

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6. Abu T. Khan, **Tasneem Parvin**, and Lokman H. Choudhury, Bromodimethylsulfonium bromide (BDMS) catalyzed three-component Mannich-type reaction.
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Bromodimethylsulfonium Bromide Catalyzed Three-Component Mannich-Type Reactions

Abu T. Khan,*[a] Tasneem Parvin,[a] and Lokman H. Choudhury[b]

Keywords: β-Amino carbonyl compounds / Aldehydes / Amines / Bromodimethylsulfonium bromide

Bromodimethylsulfonium bromide catalyzes Mannich-type reactions of a variety of aldimines, generated in situ from aldehydes and anilines, with enolizable ketones or diethyl malonate in three-component reactions to afford the corresponding β-amino carbonyl compounds. The salient features of this protocol are: shorter reaction times, simplicity of the procedure, good to excellent yields, avoidance of aqueous workup and column-chromatographic separations, and high stereoselectivities.

Introduction

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry, as high degrees of molecular diversity can be introduced in these reactions in a very fast, efficient, and timesaving manner, and without the isolation of any intermediates. As a result, considerable attention has been paid to the development of new and improved one-pot multicomponent reactions in recent years.[1]

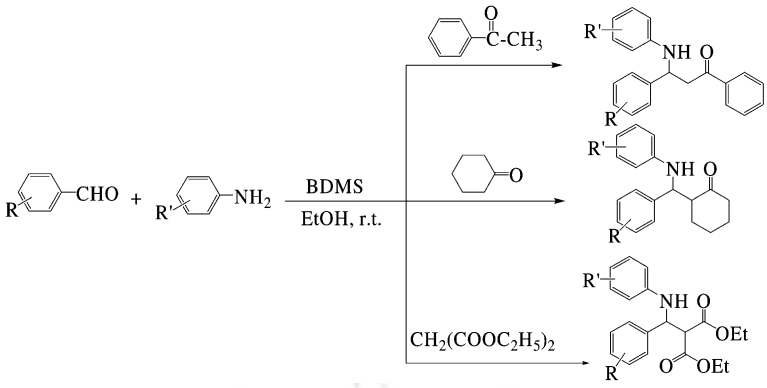
A Mannich-type reaction is a multicomponent reaction of a non-enolizable aldehyde, a primary or secondary amine, and an enolizable carbonyl compound to afford the corresponding β-amino carbonyl compound.[2] These β-amino carbonyl compounds are important synthetic intermediates for various pharmaceuticals and natural products[3] and have found wide application in organic synthesis.

The classical Mannich reaction has some limitations, such as requirements for harsh reaction conditions and long reaction times. In addition, indirect-type[4] Mannich reactions using preformed electrophiles such as imines and stable nucleophiles such as enolates or enol ethers suffer from the drawback of the necessity for the isolation and purification of the preformed intermediates. Therefore, a modified and improved methodology, known as the direct-type Mannich reaction, in the presence of various catalysts and using directly carbonyl compounds as nucleophiles was introduced.

Owing to the importance of β-amino carbonyl compounds, numerous methods for the synthesis of these compounds either by indirect-type or direct-type Mannich reactions have been reported over the years. Recently, direct-type Mannich reactions of aldehydes, enolizable ketones or diethyl malonate, and arylamines in the presence of various catalysts such as $NbCl_5$,[5] $Zn(OTf)_2$,[6] silica sulfuric acid,[7] $Yb(OPf)_3$,[8] $[NaBAr^F{}_4]$,[9] $ZrOCl_2 \cdot 8H_2O$,[10] etc. have been reported. Although these methodologies are useful, most of the methods still encounter some limitations, such as requirements for expensive catalysts or longer reaction times. It is thus evident that there remains a wide scope for the development of clean and efficient methodologies for the preparation of β-amino carbonyl compounds through a convenient and environmentally friendly method.

Bromodimethylsulfonium bromide (BDMS) is a readily accessible, cheap, and highly effective reagent,[11] as well as a catalyst for various organic transformations.[12] Recently, Das et al. reported the efficiency of bromodimethylsulfonium bromide in one-pot multicomponent syntheses of homoallylic amines.[13] In addition, very recently we have demonstrated the virtue of this catalyst for Michael additions of amines to electron-deficient alkenes.[12a] In continuation of our work on the development of new synthetic methodologies,[14] we sought to explore the advantages of this reagent further for other important transformations. Here we report a simple and effective methodology for one-pot, three-component, Mannich-type reactions of aromatic aldehydes, aromatic amines, and enolizable ketones or diethyl malonates in the presence of BDMS as a catalyst as shown in Scheme 1.

[a] Department of Chemistry, Indian Institute of Technology Guwahati,
Guwahati 781039, India
E-mail: atk@iitg.ernet.in
[b] Department of Basic Sciences and Social Sciences, North-Eastern Hill University,
Shillong 793022, India



Scheme 1.

Results and Discussion

Initially, the three-component Mannich-type reaction of benzaldehyde (2.0 mmol), aniline (2.0 mmol), and acetophenone (2.0 mmol) in the presence of bromodimethylsulfonium bromide as a catalyst was examined. Interestingly, we observed that 10 mol-% of bromodimethylsulfonium bromide is sufficient to catalyze the three-component, one-pot reaction in a very good yield within 30 min. In the absence of the catalyst the reaction failed to provide the desired product even after 48 h of stirring. Interestingly, this protocol offers a wealth of advantages over the indirect methods, since there is no need for the preparation of silyl enol ethers or preformed imines. In the screening of different solvents to find the most suitable solvent for this transformation, ethanol was found to be superior to other solvents such as THF, toluene, 1,4-dioxane, and CH_2Cl_2 in terms both of reaction time and of yields obtained. Encouraged by this result, we examined the scope of this protocol by using various electron-withdrawing aromatic aldehydes and amines. It is interesting to note that the pure products of all these reactions can be obtained just by recrystallisation of the crude materials from ethanol, avoiding aqueous workup and tedious column-chromatographic separation.

Next, benzaldehyde was treated individually with a variety of aromatic amines such as 3-chloro-, 2-nitro-, or 4-nitroaniline in combination with acetophenone, which provided very good to excellent yields within 30 min to 1 h (Table 1, Entries 2–4). It is gratifying to mention that this method does not suffer from any steric effects for *ortho*-substituted amines such as 2-nitroaniline as reported for other recent methods.[5] Similarly 4-ethylaniline provided the desired β-amino ketone with good yields (Table 1, Entry 5).

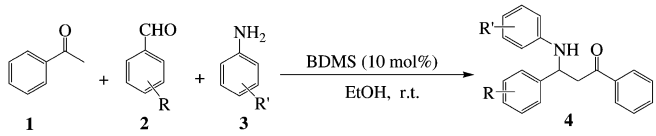
Next, aldehydes substituted with electron-withdrawing groups, such as 3-bromo- and 4-chlorobenzaldehyde, were treated separately with a variety of aromatic amines in combination with acetophenone under the same experimental conditions, and the corresponding desired products were isolated in very good yields without any difficulty (Entries 6–13). It is worth mentioning that nitro aldehydes such as 4-nitrobenzaldehyde and 3-nitrobenzaldehyde provided the corresponding chalcones instead of the desired β-amino ketones on treatment with aniline and acetophenone separately under the same experimental conditions. We believe that the nitro-substituted aldehydes prefer the aldol reaction followed by subsequent dehydration rather than in situ aldimine formation and subsequent nucleophilic addition. Next, terephthalaldehyde was treated with 2 equiv. of aniline and acetophenone to afford a bis product as shown in Table 1 (Entry 14).

Next, to generalize the method, aliphatic aldehydes such as acetaldehyde were treated with aniline and acetophenone under the same experimental conditions. After 12 h of stirring, we were unable to obtain the desired Mannich products. Similarly, the combination of an aliphatic amine such as butylamine with benzaldehyde and acetophenone under the same experimental conditions was not successful even after prolonged stirring. Likewise, the reaction of an aliphatic ketone such as acetone was also not applicable for a Mannich-type reaction with benzaldehyde and aniline under the given experimental conditions. Next, in an attempt to check the applicability of benzylamine, we were unsuccessful in achieving the desired β-amino ketone. From these studies we have established that our new method is a selective procedure for Mannich-type reactions of aromatic aldehydes, amines, and ketones.

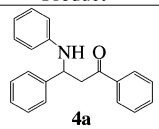
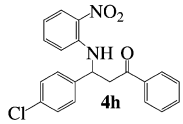
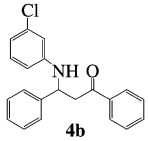
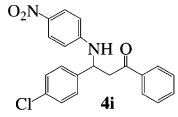
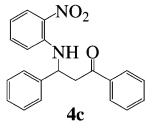
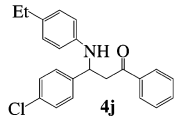
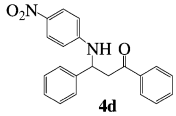
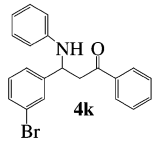
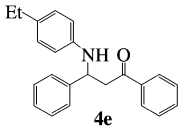
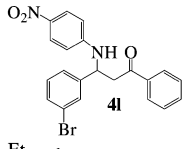
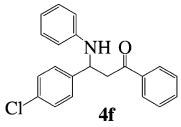
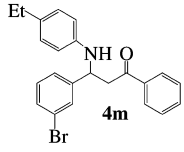
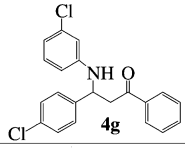
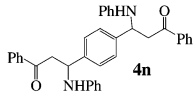
After that, to extend the preparative utility and generality of this multicomponent reaction, benzaldehyde and 4-chlorobenzaldehyde were treated individually with aniline and 3-chloroaniline in combination with other enolizable carbonyl compounds such as cyclohexanone or diethyl malonate under the same experimental conditions, as shown in Scheme 2.

The results are summarized in Table 2. Interestingly, the reactions of cyclohexanone with benzaldehyde or 4-chlorobenzaldehyde exhibit good diastereoselectivity and provide the *anti* isomers as the major products (Table 2, Entries 1–3). A similar diastereoselectivity was also observed by Hashemi and his group.[10] The *anti*/*syn* ratios were determined by ^{1}H NMR spectroscopy. To confirm the *anti* configurations of these products unambiguously, compound **5b** was recrystallised from ethanol and a single-crystal XRD was performed. The ORTEP plot of the product, showing the *anti* configuration, is depicted in Figure 1. The unit cell

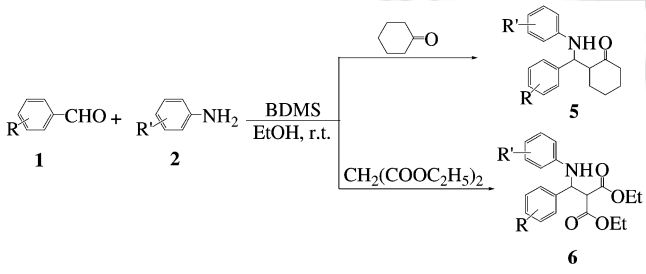
Table 1. Three-component bromodimethylsulfonium bromide catalyzed direct Mannich-type reactions of various aromatic aldehydes, amines, and ketones.



1 2 3 4

Entry	Product[a]	Time	Yield (%)[b]	Entry	Product[a]	Time	Yield (%)[b]
1	 4a	30 min	96[4]	8	 4h	2 h	87
2	 4b	30 min	98	9	 4i	40 min	97
3	 4c	1 h	88	10	 4j	4 h	95
4	 4d	30 min	95	11	 4k	3 h	90
5	 4e	1 h	97	12	 4l	1 h	89
6	 4f	40 min	97[4]	13	 4m	2 h	92
7	 4g	4 h	98	14	 4n	30 min	89

[a] All the products were fully characterized by the usual spectroscopic techniques. [b] Isolated yield.



1 2 5 6

Scheme 2.

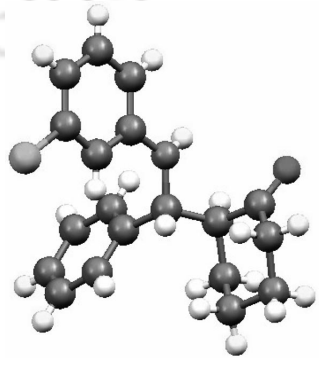


Figure 1. ORTEP plot of **5b** showing *anti* configuration.

consists of four molecules, and they exhibit intermolecular hydrogen bonding between the C=O group of one molecule and the N–H group of another.

Likewise, diethyl malonate also reacted under the same experimental conditions and provided the corresponding ethyl ester of the β-amino acid (Table 2, Entries 4–5) in good yields (Scheme 3).

Table 2. BDMS-catalyzed multicomponent reactions of aromatic aldehydes, amines, and either cyclohexanone or diethyl malonate.

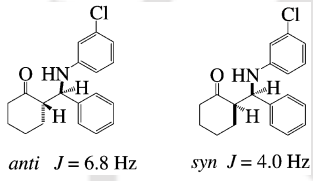
Entry	R	R′	Product[a]	Time	Yield[b] (%)	*anti*/*syn*[c]
1	H	H	**5a**	15 min	86[6]	98:2
2	H	3-Cl	**5b**	15 min	92[7]	98:2
3	4-Cl	3-Cl	**5c**	20 min	88	99:1
4	H	H	**6a**	6 h	92[6]	–
5	H	3-Cl	**6b**	7 h	94	–

[a] All the products were fully characterized by usual spectroscopic techniques. [b] Isolated yields. [c] Ratios were determined by ^{1}H NMR spectroscopy.

Table 3. Comparison of the catalytic activity of BDMS with those of different catalysts for the Mannich reaction of benzaldehyde, aniline, and acetophenone.

Run	Catalyst	Reaction conditions	Reaction time	Yield (%)[a]
1	no catalyst	EtOH, room temp.	48 h	n.r.
2	$FeCl_3$	EtOH, room temp.	24 h	n.r.[6]
3	$NbCl_5$	EtOH, room temp.	12 h	95[6]
4	$Yb(OPf)_3$	$PhCH_3/C_6F_5CF_3$	12 h	98[9]
5	silica sulfuric acid	EtOH, room temp.	12 h	92[8]
6	$[NaBAr^F{}_4]$	H_2O, 30 °C	48 h	81[10]
7	BDMS	EtOH, room temp.	30 min	96

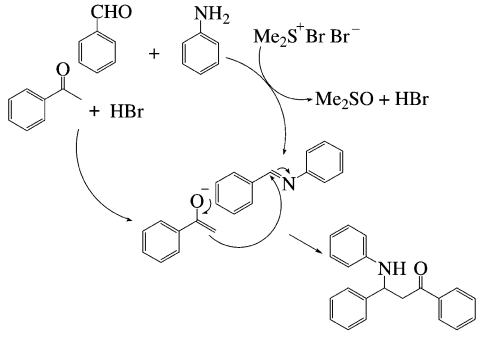
[a] Corresponding reference; n.r. = no reaction.



Scheme 3. *syn* and *anti* isomers of product **5b**.

It is worth mentioning that this method is faster, more cost-effective, and simpler than most of the existing methods. The efficacy and generality of the catalyst bromodimethylsulfonium bromide can be gauged by comparison (Table 3). For this comparison the reaction of acetophenone, benzaldehyde, and aniline was chosen as a model reaction, and comparison was carried out on the basis of reaction conditions, reaction time, and percentage yields obtained.

The catalyst bromodimethylsulfonium bromide is an inexpensive reagent. We believe that BDMS catalyzes these conversions through the rapid formation of imines, along with its simultaneous transformation into Me_2SO and HBr. The nucleophilic additions of enolizable ketones into these imines in the presence of HBr, followed by hydrolysis, afforded β-amino carbonyl compounds. The reaction between Me_2SO and HBr then regenerated the bromodimethylsulfonium bromide catalyst (Scheme 4).



Scheme 4. Plausible mechanistic illustration of BDMS-catalyzed Mannich-type reactions.

Conclusions

We have demonstrated the efficacy and generality of bromodimethylsulfonium bromide as a versatile catalyst for the synthesis of β-amino carbonyl compounds through the Mannich-type reactions of a variety of aldimines, generated in situ from aldehydes and anilines, with enolizable ketones or diethyl malonate. The salient features of this protocol are: (a) the simplicity of the procedure, (b) the ready accessibility of the catalyst and its cost effectiveness, (c) the avoidance of column chromatography, and (d) high yields and good diastereoselectivities.

Experimental Section

General: Melting points were recorded with a Büchi B-545 melting point apparatus. IR spectra were recorded in KBr with a Nicolet Impact 410 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with a Varian 400 MHz spectrometer in $CDCl_3$ with TMS as internal reference. Elemental analyses were carried out with a Perkin–Elmer 2400 automatic C,H,N,S analyzer. The XRD was performed with a Bruker Nonius Smart Apex II single-crystal X-ray diffractometer. CCDC-665099 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Preparation of Bromodimethylsulfonium Bromide (BDMS):[15] Dimethyl sulfide (1.83 mL, 25 mmol) was added to dry dichloromethane (5 mL) in a 150 mL standard joint conical flask. Then, bromine

(1.3 mL, 25 mmol) was dissolved in dry dichloromethane (5 mL) and added slowly to the above solution at ice-bath temperature over a period of 5 min. During the addition, light orange crystals of bromodimethylsulfonium bromide began to separate. After the addition of bromine was complete, the crystals of bromodimethylsulfonium bromide were collected by filtration. The solid material was then washed with dry hexane and dried under vacuum. The crystalline product (4.3 g) was obtained in 77% yield, m.p. 80 °C.

General Reaction Procedure: Bromodimethylsulfonium bromide (0.2 mmol) was added to a mixture of benzaldehyde (2 mmol), aniline (2 mmol), and acetophenone (2 mmol), and the reaction mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the crude solid was just filtered off and washed with a hexane/ethanol (80:20) mixture. The solid residue was then dissolved in hot ethanol and was recrystallized to provide the pure product. The pure product was characterized by conventional spectroscopic methods, and its data were compared with those reported.[4]

3-[(3-Chlorophenyl)amino]-1,3-diphenylpropan-1-one (4b): Yield: 0.658 g, 98%. White solid, m.p. 140–141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.42 (dd, J = 7.2 Hz, J = 16.4 Hz, 1 H), 3.50 (dd, J = 4.8 Hz, J = 16.0 Hz, 1 H), 4.71 (br. s, 1 H), 4.97 (t, J = 6.0 Hz 1 H), 6.42 (d, J = 8.0 Hz, 1 H), 6.54 (s, 1 H), 6.62 (d, J = 7.6 Hz, 1 H), 6.98 (t, J = 8.0 Hz, 1 H), 7.27 (d, J = 7.2 Hz, 1 H), 7.34 (t, J = 7.2 Hz, 2 H), 7.41–7.47 (m, 4 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.90 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.9, 54.5, 111.8, 113.5, 117.5, 126.1, 127.4, 128.0, 128.6, 128.8, 129.9, 133.4, 134.6, 136.4, 142.1, 148.0, 197.9 ppm. IR (KBr): $\tilde{\nu}$ = 3372, 1686 cm^{-1}. $C_{21}H_{18}ClNO$ (335.83): C 75.11, H 5.40, N 4.17; found C 75.28, H 5.43, N 4.07.

1,3-Diphenyl-3-[(2-nitrophenyl)amino]propan-1-one (4c): Yield: 0.610 g, 88%. Yellow solid, m.p. 100–101 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (dd, J = 5.2 Hz, J = 17.2 Hz, 1 H), 3.66 (dd, J = 7.6 Hz, J = 17.2 Hz, 1 H), 5.33–5.39 (m, 1 H), 6.63 (t, J = 7.2 Hz, 1 H), 6.80 (d, J = 8.0 Hz, 1 H), 7.29–7.37 (m, 4 H), 7.43–7.48 (m, 4 H), 7.58 (t, J = 7.2 Hz, 1 H), 7.92 (d, J = 7.2 Hz, 2 H), 8.16 (d, J = 7.2 Hz, 1 H), 8.63 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.2, 54.0, 115.5, 116.5, 126.8, 127.3, 128.3, 128.7, 129.3, 129.6, 133.0, 134.1, 136.7, 136.9, 142.0, 144.8, 197.2 ppm. IR (KBr): $\tilde{\nu}$ = 3370, 1685, 1592, 1352 cm^{-1}. $C_{21}H_{18}N_2O_3$ (346.38): C 72.82, H 5.24, N 8.09; found C 72.93, H 5.20, N 7.94.

1,3-Diphenyl-3-[(4-nitrophenyl)amino]propan-1-one (4d): Yield: 0.658 g, 95%. Yellow solid, m.p. 177–178 °C (ref.[16] m.p. 179–180 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.53 (d, J = 6.8 Hz, 2 H), 5.10 (t, J = 6.0 Hz, 1 H), 5.58 (br. s, 1 H), 6.52 (d, J = 9.2 Hz, 2 H), 7.28 (d, J = 7.2 Hz, 1 H), 7.34 (d, J = 8.0 Hz, 1 H), 7.38 (t, J = 7.2 Hz, 3 H), 7.46 (t, J = 7.6 Hz, 2 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.89 (d, J = 7.2 Hz, 2 H), 8.00 (d, J = 9.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.0, 55.0, 101.9, 112.9, 126.7, 128.5, 128.7, 129.3, 129.7, 134.4, 136.9, 139.1, 141.6, 152.6, 198.4 ppm. IR (KBr): $\tilde{\nu}$ = 3371, 1685, 1590, 1350 cm^{-1}. $C_{21}H_{18}N_2O_3$ (346.38): C 72.82, H 5.24, N 8.09; found C 72.65, H 5.16, N 8.19.

3-[(4-Ethylphenyl)amino]-1,3-diphenylpropan-1-one (4e): Yield: 0.639 g, 97%. White solid, m.p. 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, J = 7.6 Hz, 3 H), 2.48 (q, J = 7.6 Hz, 2 H), 3.42 (dd, J = 7.6 Hz, J = 16.4 Hz, 1 H), 3.51 (dd, J = 5.2 Hz, J = 16.4 Hz, 1 H), 4.60 (br. s,1 H), 4.97 (dd, J = 5.2 Hz, J = 7.6 Hz 1 H), 6.51 (d, J = 8.4 Hz, 2 H), 6.93 (d, J = 8.4 Hz, 2 H), 7.23 (t, J = 7.2 Hz, 1 H), 7.32 (t, J = 7.2 Hz, 2 H), 7.42–7.46 (m, 4 H), 7.56 (t, J = 7.2 Hz, 1 H), 7.91 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 28.0, 46.4, 55.2, 114.2, 126.6, 127.4, 128.3, 128.5, 128.8, 128.9, 133.5, 133.8, 136.7, 143.2, 144.9, 198.4 ppm. IR (KBr): $\tilde{\nu}$ = 3400, 1679 cm^{-1}. $C_{23}H_{23}NO$ (329.44): C 83.86, H 7.04, N 4.25; found C 83.60, H 7.11, N 4.38.

3-(4-Chlorophenyl)-3-[(3-chlorophenyl)amino]-1-phenylpropan-1-one (4g): Yield: 0.726 g, 98%. White solid, m.p. 117–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.42–3.46 (m, 2 H), 4.71 (br. s, 1 H), 4.93–4.96 (m, 1 H), 6.40 (d, J = 8.4 Hz, 1 H), 6.51 (s, 1 H), 6.64 (d, J = 8.0 Hz, 1 H), 6.99 (t, J = 8.4 Hz, 1 H), 7.30 (d, J = 8.4 Hz, 2 H), 7.36 (d, J = 8.4 Hz, 2 H), 7.46 (t, J = 7.2 Hz, 2 H), 7.58 (t, J = 8.4 Hz, 1 H), 7.89 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 46.4, 54.4, 112.4, 114.0, 118.4, 128.2, 128.6, 129.3, 129.5, 130.6, 133.6, 134.2, 135.3, 136.9, 141.4, 148.4, 198.2 ppm. IR (KBr): $\tilde{\nu}$ = 3376, 1684 cm^{-1}. $C_{21}H_{17}Cl_2NO$ (370.28): C 68.12, H 4.63, N 3.78; found C 67.90, H 4.57, N 3.69.

3-(4-Chlorophenyl)-3-[(2-nitrophenyl)amino]-1-phenylpropan-1-one (4h): Yield: 0.663 g, 87%. Yellow solid, m.p. 92–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.48 (dd, J = 4.4 Hz, J = 16.8 Hz, 1 H), 3.62 (dd, J = 6.4 Hz, J = 16.4 Hz, 1 H), 5.29–5.33 (m, 1 H), 6.64 (t, J = 8.8 Hz, 1 H), 6.71 (d, J = 8.8 Hz, 1 H), 7.28–7.32 (m, 3 H), 7.36 (d, J = 7.6 Hz, 2 H), 7.44 (t, J = 8.0 Hz, 2 H), 7.56 (t, J = 7.2 Hz, 1 H), 7.89 (d, J = 7.2 Hz, 2 H), 8.14 (d, J = 8.8 Hz, 1 H), 8.57 (d, J = 5.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.7, 53.1, 115.0, 116.4, 127.0, 128.0, 128.3, 129.0, 129.4, 132.7, 133.7, 134.0, 136.4, 136.5, 140.3, 144.2, 196.5 ppm. IR (KBr): $\tilde{\nu}$ = 3376, 1685, 1591, 1297 cm^{-1}. $C_{21}H_{17}ClN_2O_3$ (380.83): C 66.23, H 4.50, N 7.36; found C 66.32, H 4.42, N 7.25.

3-(4-Chlorophenyl)-3-[(4-nitrophenyl)amino]-1-phenylpropan-1-one (4i): Yield: 0.739 g, 97%. Yellow solid, m.p. 150–151 °C (ref.[16] m.p. 149–150 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.52 (d, J = 6.4 Hz, 2 H), 5.07 (q, J = 6.0 Hz, 1 H), 5.56 (d, J = 6.0 Hz, 1 H), 6.50 (d, J = 9.2 Hz, 2 H), 7.30–7.35 (m, 4 H), 7.47 (t, J = 8.0 Hz, 2 H), 7.60 (t, J = 7.6 Hz, 1 H), 7.89 (d, J = 7.6 Hz, 2 H), 8.01 (d, J = 9.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 45.5, 53.7, 112.4, 126.4, 127.8, 128.3, 129.0, 129.4, 133.7, 134.1, 136.3, 138.6, 139.9, 152.2, 197.7 ppm. IR (KBr): $\tilde{\nu}$ = 3375, 1685, 1593, 1296 cm^{-1}. $C_{21}H_{17}ClN_2O_3$ (380.83): C 66.23, H 4.50, N 7.36; found C 66.31, H 4.46, N 7.27.

3-(4-Chlorophenyl)-3-[(4-ethylphenyl)amino]-1-phenylpropan-1-one (4j): Yield: 0.691 g, 95%. White solid, m.p. 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (t, J = 7.6 Hz, 3 H), 2.47 (q, J = 7.6 Hz, 2 H), 3.47 (d, J = 7.2 Hz, 2 H), 4.71(br. s, 1 H), 4.92 (t, J = 6.8 Hz, 1 H), 6.51 (d, J = 8.4 Hz, 2 H), 6.92 (d, J = 8.4 Hz, 2 H), 7.26 (d, J = 8.4 Hz, 2 H), 7.38 (d, J = 8.4 Hz, 2 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.55 (t, J = 7.6 Hz, 1 H), 7.88 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 28.1, 46.1, 55.2, 114.8, 128.2, 128.4, 128.7, 128.9, 129.1, 133.2, 133.8, 134.8, 136.6, 141.3, 143.9, 198.0 ppm. IR (KBr): $\tilde{\nu}$ = 3400, 1680 cm^{-1}. $C_{23}H_{22}ClNO$ (363.89): C 75.92, H 6.09, N 3.85; found C 75.71, H 6.12, N 3.96.

3-(3-Bromophenyl)-1-phenyl-3-(phenylamino)propan-1-one (4k): Yield: 0.685 g, 90%. Light blue solid, m.p. 95–96 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.47–3.50 (m, 2 H), 4.68 (br. s, 1 H), 4.94–4.97 (m, 1 H), 6.58 (d, J = 7.6 Hz, 2 H), 6.72 (t, J = 7.2 Hz, 1 H), 7.11 (t, J = 7.2 Hz, 2 H), 7.19 (t, J = 7.6 Hz, 1 H), 7.37 (d, J = 7.6 Hz, 1 H), 7.41 (d, J = 7.6 Hz, 1 H), 7.46 (t, J = 7.2 Hz, 2 H), 7.58 (t, J = 7.2 Hz, 1 H), 7.60 (s, 1 H), 7.91 (d, J = 7.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 46.2, 55.0, 114.4, 118.7, 123.2, 125.4, 128.4, 129.0, 129.4, 129.8, 130.6, 130.8, 133.8, 134.9, 145.4, 146.4, 197.9 ppm. IR (KBr): $\tilde{\nu}$ = 3380, 1681 cm^{-1}. $C_{21}H_{18}BrNO$ (380.28): C 66.33, H 4.77, N 3.68; found C 66.42, H 4.70, N 3.59.

3-(3-Bromophenyl)-3-[(4-nitrophenyl)amino]-1-phenylpropan-1-one (4l): Yield: 0.757 g, 89%. Light yellow solid, m.p. 159–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.48 (d, J = 6.0 Hz, 2 H), 5.02 (q, J = 6.0 Hz, 1 H), 5.48 (d, J = 6.4 Hz, 1 H), 6.48 (d, J = 9.2 Hz, 2 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.37 (d, J = 8.0 Hz, 1 H), 7.44 (t, J = 7.6 Hz, 2 H), 7.51 (s, 1 H), 7.57 (t, J = 7.2 Hz, 1 H), 7.87 (d, J = 7.2 Hz, 2 H), 7.99 (d, J = 9.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 45.5, 53.8, 112.3, 123.3, 125.0, 126.3, 128.2. 128.9, 129.3, 130.8, 131.2, 134.0, 136.1, 138.7, 143.8, 152.0, 197.4 ppm. IR (KBr): $\tilde{\nu}$ = 3380, 1685, 1598, 1337 cm^{-1}. $C_{21}H_{17}BrN_2O_3$ (425.28): C 59.31, H 4.03, N 6.59; found C 59.10, H 4.08, N 6.50.

3-(3-Bromophenyl)-3-[(4-ethylphenyl)amino]-1-phenylpropan-1-one (4m): Yield: 0.751 g, 92%. White solid, 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, J = 7.6 Hz, 3 H), 2.46 (q, J = 7.6 Hz, 2 H), 3.35 (dd, J = 7.6 Hz, J = 16.4 Hz, 1 H), 3.44 (dd, J = 5.2 Hz, J = 16.0 Hz, 1 H), 4.40 (br. s, 1 H), 4.88 (dd, J = 5.2, J = 7.2 Hz, 1 H), 6.45 (d, J = 8.4 Hz, 2 H), 6.91 (d, J = 8. 4 Hz, 2 H), 7.15 (t, J = 7.6 Hz, 1 H), 7.32–7.36 (m, 2 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.53 (d, J = 7.6 Hz, 1 H), 7.57 (s, 1 H), 7.88 (d, J = 7.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.0, 28.0, 46.4, 54.7, 114.1, 123.1, 125.3, 128.3, 128.6, 128.9, 129.6, 130.5, 130.6, 133.7, 134.0, 136.6, 144.8, 146.1, 197.9 ppm. IR (KBr): $\tilde{\nu}$ = 3401, 1680 cm^{-1}. $C_{23}H_{22}BrNO$ (408.34): C 67.65, H 5.43, N 3.43; found C 67.50, H 5.39, N 3.58.

1,4-Bis[3-oxo-3-phenyl-1-(phenylamino)propyl]benzene (4n): Yield: 0.934 g, 89%. Light green solid, m.p. 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.43 (d, J = 6.0 Hz, 4 H), 4.70 (br. s, 2 H), 4.96 (t, J = 5.6 Hz, 2 H), 6.55 (d, J = 6.8 Hz, 4 H), 6.67 (t, J = 6.8 Hz, 2 H), 7.08 (t, J = 6.8 Hz, 4 H), 7.38 (s, 4 H), 7.42 (t, J = 7.2 Hz, 4 H), 7.53 (t, J = 8.0 Hz, 2 H), 7.87 (d, J = 7.2 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.1, 54.9, 114.2, 118.3, 121.2, 127.2, 128.4, 128.9, 129.3, 133.7, 136.8, 142.1, 143.8, 146.8, 198.6 ppm. IR (KBr): $\tilde{\nu}$ = 3447, 1680 cm^{-1}. $C_{36}H_{32}N_2O_2$ (524.66): C 82.41, H 6.15, N 5.34; found C 82.63, H 6.08, N 5.23.

2-{(4-Chlorophenyl)[(3-chlorophenyl)amino]methyl}cyclohexanone (5c): Yield: 0.613 g, 88%. Light brown solid, m.p. 154–155 °C. Data for the major isomer (*anti*): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.69–1.79 (m, 3 H), 1.90–1.99 (m, 3 H), 2.31–2.41 (m, 2 H), 2.72–2.76 (m, 1 H), 4.52 (d, J = 6.0 Hz, 1 H), 4.90 (br. s, 1 H), 6.38 (d, J = 8.4 Hz, 1 H), 6.48 (s, 1 H), 6.61 (d, J = 7.2 Hz, 1 H), 6.97 (t, J = 8.0 Hz, 1 H), 7.29 (s, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.3, 28.0, 32.0, 42.4, 57.3, 57.7, 112.0, 113.5, 117.8, 128.7, 128.9, 130.3, 133.1, 135.0, 140.0, 148.4, 212.5 ppm. IR (KBr): $\tilde{\nu}$ = 3339, 1706 cm^{-1}. $C_{19}H_{19}Cl_2NO$ (348.27): C 65.53, H 5.50, N 4.02; found C 65.34, H 5.43, N 3.90.

Diethyl 2-{[(3-Chlorophenyl)amino](phenyl)methyl}malonate (6b): Yield: 0.707 g, 94%. White solid, m.p. 111–112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (t, J = 7.2 Hz, 3 H), 1.17 (t, J = 7.2 Hz, 3 H), 3.88 (d, J = 5.2 Hz, 1 H), 4.11 (q, J = 7.2 Hz, 2 H), 4.15 (q, J = 7.2 Hz, 2 H), 5.18 (d, J = 5.6 Hz, 1 H), 5.56 (br. s, 1 H), 6.47 (d, J = 8.8 Hz, 1 H), 6.58 (s, 1 H), 6.62 (d, J = 8.8 Hz, 1 H), 6.99 (t, J = 8.8 Hz, 1 H), 7.26–7.35 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 13.7, 13.9, 56.7, 57.8, 61.5, 61.9, 111.8, 113.3, 117.6, 126.5, 127.7, 128.6, 130.0, 134.9, 139.0, 147.8, 167.0, 168.0 ppm. IR (KBr): $\tilde{\nu}$ = 3370, 1752 cm^{-1}. $C_{20}H_{22}ClNO_4$ (375.85): C 63.91, H 5.90, N 3.73; found C 63.71, H 5.83, N 3.61.

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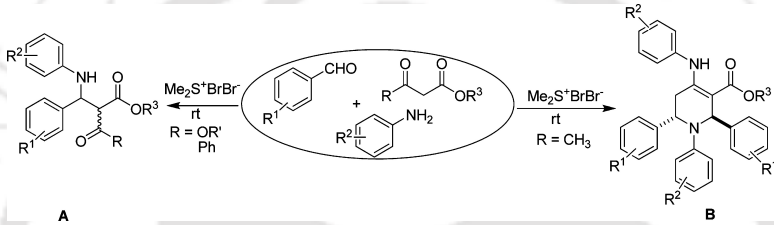

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Effects of Substituents in the β-Position of 1,3-Dicarbonyl Compounds in Bromodimethylsulfonium Bromide-Catalyzed Multicomponent Reactions: A Facile Access to Functionalized Piperidines

Abu T. Khan,*[,†] Tasneem Parvin,[†] and Lokman H. Choudhury[‡]

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781 039, India, and Department of Basic Sciences & Social Sciences, North-Eastern Hill University, Shillong 793 022, India

atk@iitg.ernet.in

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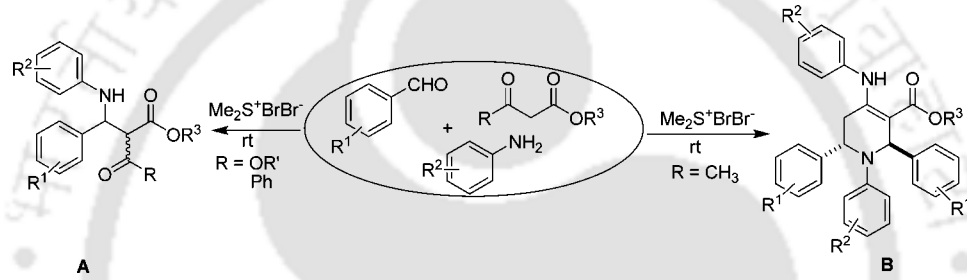

1,3-Dicarbonyl compounds can be converted to Mannich-type products **A** or highly functionalized piperidines **B** in the presence of a catalytic amount of bromodimethylsulfonium bromide (BDMS). The combination of aromatic aldehyde, amine, and 1,3-dicarbonyl compounds in the presence of a catalytic amount of BDMS leads to the formation of Mannich-type product **A** when R is a non-enolizable carbon or an alkoxy group, whereas in cases when R = CH_3, the same combination yielded highly functionalized piperidines **B**. A synthetic study and mechanistic proposal are presented.

Introduction

Multicomponent reactions (MCRs) involving domino processes, with at least three different substrates reacting in a well-defined manner to form a single compound, have emerged as a powerful tool in organic synthesis.[1] In recent years MCRs have received considerable attention from the organic community due to their advantages over conventional multistep synthesis.[2] These reactions constitute an especially attractive synthetic strategy since they provide easy and rapid access to large libraries of organic compounds with diverse substitution patterns. In addition, MCRs are more environmentally benign and atom economic as they avoid time-consuming and costly purification processes, as well as protection−deprotection steps.[3] The synthesis of heterocycles with use of multicomponent reactions often involves classical carbonyl condensation chemistry. Among carbonyl compounds, 1,3-dicarbonyl derivatives constitute important synthetic intermediates, incorporating multiple functionalities that can be involved either as nucleophilic or electrophilic species in a variety of synthetic transformations.[4] The high synthetic potential of these easily accessible reagents has found numerous applications, especially for the synthesis of complex heterocyclic structures.[5]

[†] Indian Institute of Technology Guwahati.
[‡] North-Eastern Hill University.

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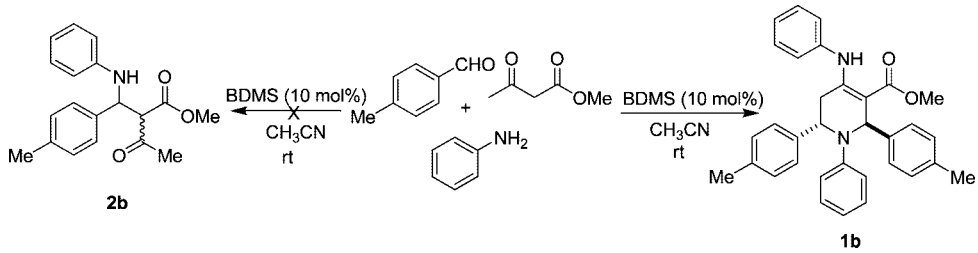
SCHEME 1. Preferential Formation of Functionalized Piperidines 1b over the Mannich-Type Product 2b



Bromodimethylsulfonium bromide (BDMS) has proven to be a very useful reagent in organic synthesis.[6] Due to its versatile activity both as a brominating agent[6b,7] and as a catalyst, it has recently been used in a wide variety of synthetic transformations.[8] As part of our ongoing research program to develop new methodologies, we have been engaged in an exploration of the virtues of BDMS for organic synthesis,[9] and envisaged that BDMS might act as an efficient catalyst for a diverse range of multicomponent reactions. Herein we report interesting MCRs of 1,3-dicarbonyl compounds that lead to different products, depending upon the substituent in the β-position.

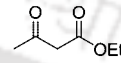
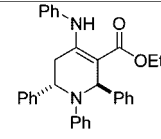
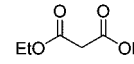
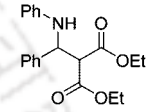
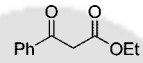
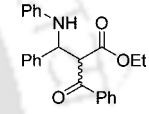
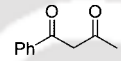
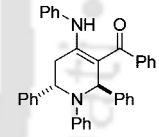
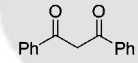
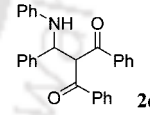
Results and Discussion

Bromodimethylsulfonium bromide was prepared from dimethyl sulfide and molecular bromine by using the reported procedure.[6e] In our initial study to assess the utility of bromodimethylsulfonium bromide in multicomponent reactions, a mixture of 4-methylbenzaldehyde (2 mmol), aniline (2 mmol), and methyl acetoacetate (2 mmol) in acetonitrile (5 mL) was stirred in the presence of 10 mol % of BDMS. At the outset we were expecting a Mannich-type reaction leading to product **2b**. Interestingly, instead we isolated a highly functionalized piperidine **1b** in a moderate yield of 39% (Scheme 1).

It is noteworthy that we have recently reported a three-component reaction involving aromatic aldehyde, aniline, and enolizable carbonyl compounds for the synthesis of corresponding Mannich-type product using bromodimethylsulfonium bromide.[9e] We therefore sought to use the same strategy for the synthesis of β-amino acid derivative **2b**. Generally, β-keto esters react with electrophiles at the α-position.[10] Only a few cases of α-alkylated β-keto esters/amides reacting with aldehyde electrophiles at the γ-position have appeared in the literature.[11] Fujioka and Kita et al. have reported a multicomponent reaction employing the γ-position of β-keto esters to form seven-membered-ring products from the combination of aromatic aldehydes, ethylenediamine, and β-keto esters.[1c] Interestingly, the formation of **1b** is an example in which both the α- and γ-positions of a β-keto ester are involved in C−C bond formation.

This unexpected result encouraged us to investigate the scope of this multicomponent reaction through a systematic study. A variety of 1,3-dicarbonyl compounds were treated with benzaldehyde and aniline in the presence of a catalytic amount of bromodimethylsulfonium bromide and the results are summarized in Table 1. As with methyl acetoacetate, ethyl acetoacetate provides the corresponding piperidine derivative in

TABLE 1. Results for the Reaction of Benzaldehyde, Aniline, and Different 1,3-Dicarbonyl Compounds in the Presence of a Catalytic Amount of BDMS[a]

Entry	1,3-dicarbonyl compounds	Time /h	Product	% Yield[b]
1.		6	 **1m**	38[c]
2.		6	 **2a**	92
3.		8	 **2c**	40
4.		12	 **1s**	20[d]
5.		12	 **2d**	0[e]

[a] Reactions were performed in a ratio of 1:1:1 (benzaldehyde: aniline:1,3-dicarbonyl compounds) in the presence of 10 mol % BDMS at room temperature. [b] Yield of pure product after crystallization. [c] For optimized yield see Table 2. [d] Optimized yield was 35%. [e] Starting material dibenzoyl acetone was recovered along with aldimine.

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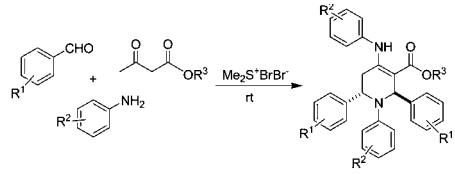
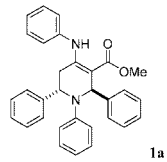
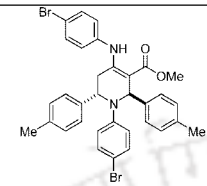
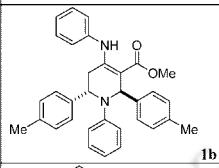
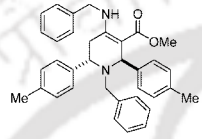
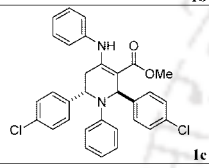
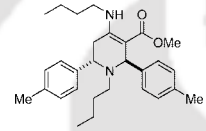
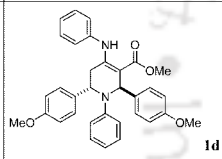
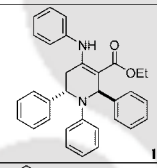
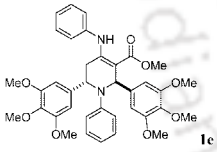
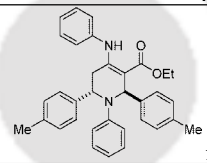
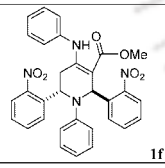
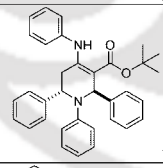
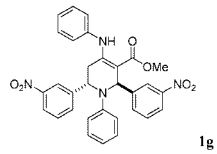
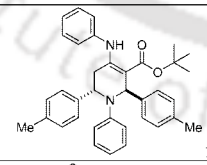
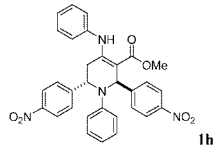
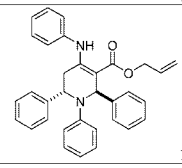
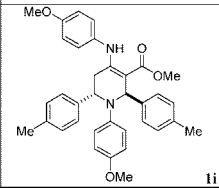
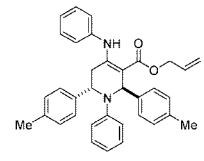
TABLE 2. Results for the Reaction of Aldehydes, Anilines, and β-Keto Esters in the Presence of Bromodimethylsulfonium Bromide in Acetonitrile[a]



Entry	Product	% Yield[b]	Entry	Product	% Yield[b]
1.	 **1a**	75	10.	 **1j**	68
2.	 **1b**	80	11.	 **1k**	48
3.	 **1c**	76	12.	 **1l**	63
4.	 **1d**	77	13.	 **1m**	76
5.	 **1e**	62	14.	 **1n**	79
6.	 **1f**	50	15.	 **1o**	60
7.	 **1g**	40	16.	 **1p**	65
8.	 **1h**	32	17.	 **1q**	70
9.	 **1i**	77	18.	 **1r**	77

[a] Aldehyde, amine, and β-keto esters were taken in (2:2:1) ratio in presence of 10 mol % of BDMS. [b] Yield of pure product after crystallization from the reaction mixture.

moderate yield (Table 1, entry 1). This suggests that the alkoxy moiety of these β-keto esters does not have any significant role in determining the course of the reaction. However, in the case of diethyl malonate (Table 1, entry 2), the corresponding Mannich-type product **2a** was obtained in good yield, as there is no other option due to the lack of an enolizable position. Likewise, ethyl benzoylacetate (Table 1, entry 3) gave Mannich-type product **2c** as a mixture of diastereomers, with the trans isomer predominating. However, in the case of benzoyl acetone (Table 1, entry 4) the corresponding piperidine was obtained in moderate yield.

In the case of dibenzoyl acetone (Table 1, entry 5) only the imine formed between benzaldehyde and aniline was obtained in addition to unreacted dibenzoyl acetone. From these results it is clear that diethyl malonate is acting as a better nucleophile in this Mannich-type reaction than the other 1,3-dicarbonyl compounds in the presence of bromodimethylsulfonium bromide (Table 1). We believe that the bulkiness of the phenyl group may have an effect on the nucleophilicity of ethyl benzoyl acetate and dibenzoyl acetone. From these studies it is apparent that substituents on the 1,3-dicarbonyl component play a vital role in determining the reactivity of substrates and the course of reactions.

A γ-substituted β-keto ester ethyl butyrylacetate was next treated with aniline and benzaldehyde under similar experimental conditions. Piperidine **1t** was not observed in the crude ^{1}H NMR after 24 h (Scheme 2). This suggests that the presence of methyl group in the β-position of β-keto esters is necessary for the successful formation of highly functionalized piperidines using these multicomponent reactions.

Functionalized piperidine rings are present in many natural products[12] and are important building blocks in pharmaceuticals. Recently, considerable attention has been paid to the synthesis of functionalized piperidines,[13,14] while, in general, the development of new synthetic methods for the efficient preparation of nitrogen heterocycles is an interesting challenge.[16] Thus we turned our attention to the optimization of this multicomponent approach to piperidines.

The influences of the catalyst, solvent, and the ratio of the components were investigated by using the combination of *p*-methylbenzaldehyde, aniline, and methylacetoacetate as a model reaction. The stoichiometric ratio 2:2:1 (aldehyde:aniline: methyl acetoacetate) in the presence of 10 mol % of bromodimethylsulfonium bromide at room temperature was found to be the most suitable condition for obtaining functionalized piperidines. Under these standard reaction conditions, the product **1b** was synthesized in good yield (80%) after a short time (3 h). A range of solvents were screened to find out the best solvent for this transformation. Among dichloromethane, acetonitrile,

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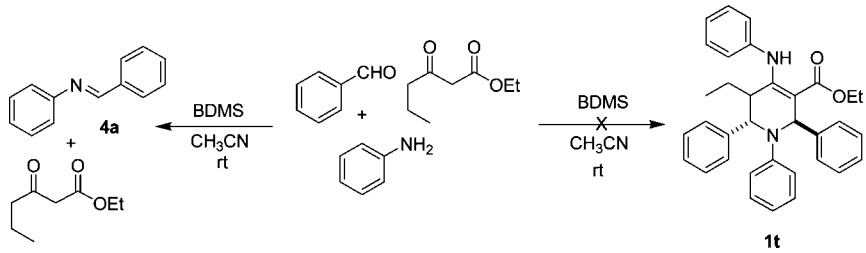
SCHEME 2. Reaction of Ethyl Butyrylacetate with Aniline and Benzaldehyde



ethanol, and water, the use of acetonitrile was found to give superior yields. However, ethanol can also be used for this transformation. The neat reaction, without any solvent, resulted in a moderate yield (40%) that may be due to the lack of effective interaction of the reactants under solvent-free reaction conditions. In the absence of BDMS, the same combination of reactants failed to provide **1b** under identical reaction conditions even after 24 h of stirring. This illustrates the efficacy of BDMS as a catalyst. Using a catalytic amount of aqueous 48% HBr instead of BDMS gave lower yields (45%). This result indicates that the generation of the protic acid HBr may not be the only factor responsible for the catalytic activity of BDMS. It is possible that the positive sulfonium moiety also has some role in facilitating the process.

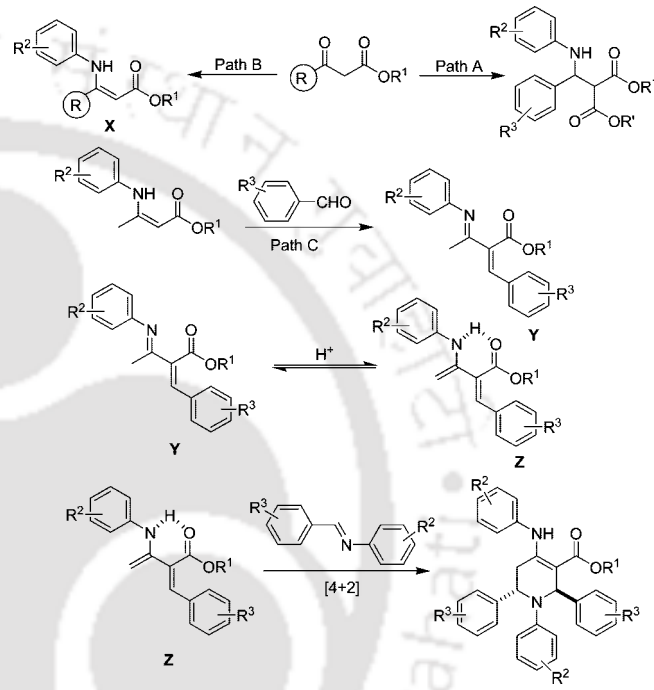
To explore the generality and scope of this multicomponent reaction a variety of aldehydes, β-keto esters, and aniline derivatives were tested and the results are summarized in Table 2. Aromatic aldehydes bearing substituents such as Cl, Me, and OMe as well as NO_2 were treated with aniline and methyl acetoacetate under the standard reaction conditions and the corresponding products (**1a**−**h**) were obtained in good to moderate yields. In the case of nitro aldehydes (Table 2, entries 6−8) the yields were low, which may be due to steric factors as well as the electron-withdrawing effect of the nitro group.

Aniline derivatives such as 4-methoxyaniline and 4-bromoaniline were also tested in the multicomponent reaction, smoothly provding the corresponding piperidine derivatives in good yields (Table 2, entries 9 and 10). To further explore the generality and scope of this MCR, benzylamine and butylamine were also treated under the same reaction conditions. The corresponding piperidines were obtained in low to moderate yields. Other β-keto esters such as ethyl acetoacetate, *tert*-butyl acetoacetate, and allyl acetoacetate also took part in this multicomponent reaction to provide the corresponding piperidine derivatives (Table 2, entries 13−18) with good yields under the optimized conditions. Unfortunately, in the case of the aliphatic aldehyde, heptanal, the present method failed to produce the corresponding functionalized piperidines.

To confirm the structure as well as the relative stereochemistry of these highly functionalized piperidines, X-ray crystallographic analysis of **1c** and **1m** was carried out. In both cases, the relative stereochemistry at the 2- and 6-positions of the piperidines was shown to be *anti* (see the Supporting Information, Figure 1). In addition, amino groups at the 4-position and carboxyl groups at the 3-position show intramolecular hydrogen bonding.

Next, we turned our attention to gaining mechanistic insights into this transformation. From our study we have revealed that the R group of the β-keto esters plays a crucial role in this multicomponent reaction (see Table 1). A possible mechanism is illustrated in Scheme 3.

SCHEME 3. Possible Mechanistic Illustration Showing the Role of the R Group and the Formation of Functionalized Piperidines via Intermediates Z



In the case when R = alkoxy group, e.g., OEt, the combination of an aromatic amine, such as aniline, and an aromatic aldehyde, with the diester, leads to the Mannich-type products following path A via the formation of an imine followed by nucleophilic attack by the 1,3-diesters. As the carbonyl group of ester substrates is less electrophilic than that of the ketone substrates, there is no reaction with the aromatic amines at room temperature, and straightforward formation of β-amino acid derivatives (Mannich-type product) is observed. However, when R is an alkyl or aryl group then the scenario becomes different. This can be attributed to the more reactive keto functionality and the emergence of other reaction pathways. In the case of β-keto esters, where R is a methyl group, enamine **X** (path B) is formed by reaction with the amine. This enamine **X** may then react with the aromatic aldehyde to produce the Knoevenagel-type product **Y** (path C).

Next, there will be a spontaneous tendency under acidic conditions for tautomerization to give the intramolecular hydrogen bonded enamine **Z**. Presumably, this hydrogen bonding along with high conjugation is the driving force for this tautomerism. The X-ray structure of compounds **1c** and **1m** shows that the carboxyl and amino goups are on the same face of the products and show intramolecular hydrogen bonding (Figure 1) thus indirectly supporting our hypothesis. Another equivalent of amine and aldehyde react in the presence of BDMS

to provide the corresponding imine. We believe BDMS facilitates the formation of imine as well as enamine **X** in this multicomponent reaction. This imine and the intermediate **Z** undergo [4+2] aza-Diels−Alder reaction to provide the functionalized piperidine. In an attempt to prove this mechanism, we synthesized the enamine from methyl acetoacetate and aniline and the resulting enamine was treated with another equivalent of 4-methylbenzaldehyde. However, we could not isolate the intermediate **Z**, instead we found a trace amount of the corresponding piperidine **1b**. It is possible that the intermediate is highly reactive and not possible to trap. However, the exact explanation is not yet clear.

Conclusions

In summary, we have demonstrated that bromodimethylsulfonium bromide mediates a new multicomponent reaction for the synthesis of highly functionalized piperidines. In addition, we have shown that substituents on the 1,3-dicarbonyl components determine the course of the reaction. This strategy is interesting as both the α- and γ-positions of β-keto esters are involved in C−C bond formation under the mild conditions. The resultant heterocyclic systems have both secondary amine and enamino esters, which enable further modifications leading to molecular diversity. Studies toward the further generalization of this approach and the application of this method to access other heterocyclic scaffolds are underway.

Experimental Section

General Procedure for Mannich-Type Reaction.[9e] To a solution of benzaldehyde (2 mmol), aniline (2 mmol), and 1, 3-dicarbonyl compound (2 mmol) in 5 mL of acetonitrile was added bromodimethylsulfonium bromide (0.2 mmol) then the solution was stirred at room temperature. After completion of the reaction, the crude solid was just filtered off and washed with a hexane/ethanol (80:20) mixture. The solid residue was then dissolved in hot ethanol and recrystallized to provide the pure product. The pure product was characterized by conventional spectroscopic methods.

General Procedure for the Synthesis of Highly Functionalized Piperidines. To a solution of aniline (2 mmol) and methyl acetoacetate (1 mmol) in 5 mL of acetonitrile was added bromodimethylsulfonium bromide (0.1 mmol). Subsequently 4-methylbenzaldehyde (2 mmol) was added to the mixture. The resulting mixture was stirred at room temperature. After completion of the reaction as checked by TLC, the solvent was evaporated in a rotatory evaporator and the crude product was washed with ethanol and filtered off. The pure product was characterized by conventional spectroscopic methods.

Representative data for compound 1a: light yellow solid (0.345 g, 75%); mp 169−171 °C; IR (KBr) 3241, 3058, 2948, 1655, 1594, 1500, 1257, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.75 (1H, dd, J = 2.4 Hz, J = 15.2 Hz), 2.86 (1H, dd, J = 5.6 Hz, J = 15.2 Hz), 3.93 (3H, s), 5.13−5.14 (1H, m), 6.26−6.28 (2H, m), 6.44 (1H, s), 6.51 (2H, d, J = 8.8 Hz), 6.59 (1H, t, J = 7.2 Hz), 7.03−7.10 (5H, m), 7.16 (2H, d, J = 8.0 Hz), 7.20−7.22 (1H, m), 7.24−7.32 (7H, m), 10.24 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.8, 51.2, 55.2, 58.3, 98.0, 113.0, 116.3, 125.9, 126.0, 126.5, 126.8, 127.3, 128.4, 128.8, 128.9, 129.0, 137.9, 142.9, 144.0, 147.1, 156.4, 168.7. Anal. Calcd for $C_{31}H_{28}N_2O_2$ (460.58): C, 80.84; H, 6.13; N, 6.08. Found: C, 80.71; H, 6.07; N, 6.19.

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Supporting Information Available: The general experimental methods, full characterization data for **1b**−**s**, **2a**, and **2c**, ^1H NMR,^{13}C NMR spectra of new compounds, and X-ray structure, data, and CIFs of **1c** and **1m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Iron(III) chloride-catalyzed convenient one-pot synthesis of β-acetamido carbonyl compounds

Abu T. Khan,* Tasneem Parvin and Lokman H. Choudhury

Indian Institute of Technology Guwahati, Department of Chemistry, Guwahati 781 039, India

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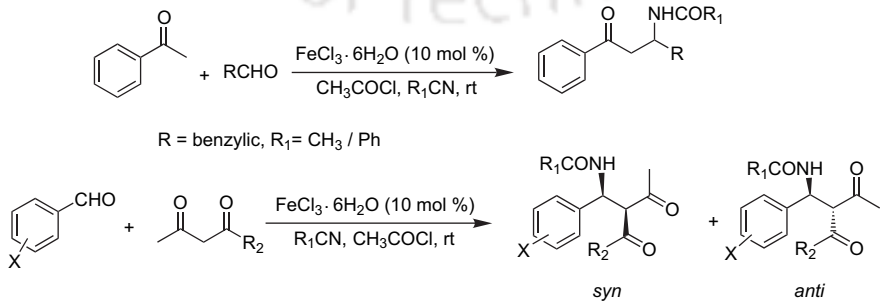
Abstract—A one-pot multi-component reaction of aldehydes, enolizable ketones or 1,3-dicarbonyls, acetonitrile/benzonitrile, and acetyl chloride is described for the preparation of β-acetamido carbonyl compounds using $FeCl_3 \cdot 6H_2O$ as a mild, inexpensive, and highly efficient catalyst. The effect of substrate as well as substituent for multi-component reaction versus Knoevenagel condensation is also illustrated. The key features of this methodology are operational simplicity, mild reaction conditions, and good yields.

1. Introduction

Multi-component reactions (MCRs) are a promising and vital field of chemistry because the synthesis of complicated molecules can be achieved in a very fast, efficient, and time-saving manner without the isolation of any intermediate. As a result, it requires minimum effort, which minimizes the environmental loading and is acceptable from a 'Green Chemistry' point of view. In recent years, the discovery of novel MCRs has become an increasingly active area of research, yielding novel chemical scaffolds for drug discovery. Thus, the development of new multi-component reactions is a popular area of research in current organic chemistry.[1]

The synthesis of β-acetamido carbonyl compounds has gained considerable attention in organic synthesis, owing to their importance as valuable building blocks for the preparation of 1,3-amino alcohols[2a,b] or β-amino acids,[2c] as well as for the synthesis of various bioactive molecules such as antibiotic nikkomycins or neopolyoxines.[3] The conventional way for the preparation of these compounds is the Dankin–West reaction using α-amino acids and acetic anhydride.[4] Later on, Iqbal et al. introduced both $CoCl_2$[5] and Montmorillonite K-10 clay[6] catalyzed multi-component reactions involving an aldehyde, enolizable ketone or keto ester in acetonitrile, and acetyl chloride for the one-pot synthesis of β-acetamido carbonyl compounds. Subsequently, $Cu(OTf)_2$/$Sc(OTf)_3$,[7] silica supported sulfuric acid,[8] BiOCl,[9] $ZrOCl_2 \cdot 8H_2O$,[10] $H_6P_2W_{18}O_{62}$,[11a] $H_3PW_{12}O_{40}$,[11b] I_2,[12] and Amberlyst-15[13] are reported as effective catalysts for the synthesis of β-acetamido carbonyl compounds. Recently, we have introduced $CeCl_3 \cdot 7H_2O$ as an efficient catalyst for the preparation of β-acetamido carbonyl compounds by MCRs.[14] Though the above methodologies are quite useful, most of the methods encounter some limitations, such as requirement of expensive catalysts, longer reaction time, and



Scheme 1.

* Corresponding author. Tel.: +91 361 2582305; fax: +91 361 2582349; e-mail: atk@iitg.ernet.in

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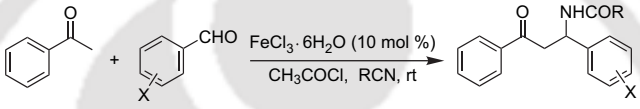
harsh reaction conditions. It is thus evident that there remains a wide scope for the development of clean and efficient methodologies for the preparation of β-acetamido carbonyl compounds using a cheap and readily available catalyst.

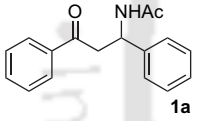
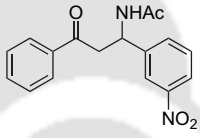
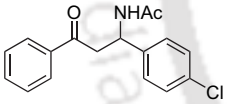
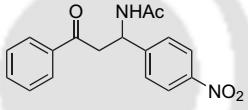
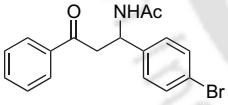
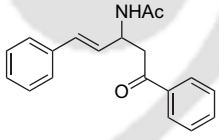
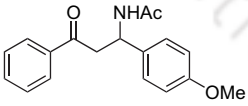
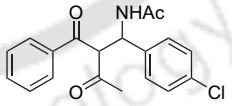
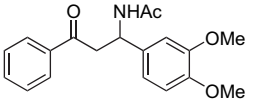
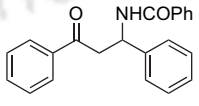
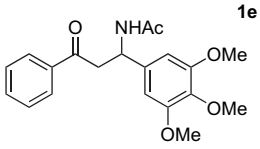
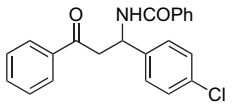
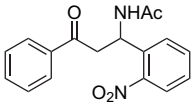
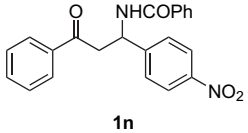
$FeCl_3 \cdot 6H_2O$ has emerged as a potentially useful Lewis acid and has been extensively used in various organic transformations.[15] Due to its unique catalytic properties, it has been used for a plethora of organic transformations such as the construction of 10*H*-indeno[1,2-*b*]triphenylene skeletons by oxidative cyclization,[16] cleavage of silyl protecting groups,[17] amino halogenation of arylmethylenecyclopropanes and arylvinylidenecyclopropanes,[18] hydroarylation of styrenes,[19] one-pot synthesis of 1,2-dihydro-2-oxo-3-pyridinecarboxylate derivatives,[20] Friedlander synthesis of quinolines,[21] one-pot synthesis of homoallyl benzyl ethers from aldehydes,[22] and synthesis of nicotinic acid derivatives,[23] etc (Scheme 1).

2. Results and discussion

For the preliminary study, 4-chlorobenzaldehyde (2 mmol) and acetophenone (2 mmol) in acetonitrile (5 mL) were stirred in the presence of a catalytic amount of $FeCl_3 \cdot 6H_2O$ (10 mol %) and acetyl chloride (3 mmol) at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, it was poured into a beaker containing crushed ice to solidify the product. On solidification of the product, it was filtered off and dried to obtain the corresponding β-acetamido ketone. The solid product was recrystallized from ethyl acetate and hexane, and fully characterized by recording IR, ^1H NMR, and elemental analysis. Encouraged by this result, a wide variety of aromatic aldehydes, containing both electron withdrawing and donating substituents, were treated under the same experimental conditions and afforded the corresponding β-acetamido ketones (Table 1, entries 2–9) in good to excellent yields. Similarly, α,β-unsaturated

Table 1. $FeCl_3 \cdot 6H_2O$ catalyzed multi-component reaction for the preparation of β-acetamido ketones



Entry	β-Acetamido ketones[a]	Time (h)	Yield[b,c] (%)	Entry	β-Acetamido ketones[a]	Time (h)	Yield[b,c] (%)
1	 **1a**	8	88[6]	8	 **1h**	10	96[6]
2	 **1b**	5	99[8]	9	 **1i**	11	95[6]
3	 **1c**	5	98	10	 **1j**	6	85
4	 **1d**	7	94[10]	11	 **1k**	12	83
5	 **1e**	5	98	12	 **1l**	9	97
6	 **1f**	6	96	13	 **1m**	8	96
7	 **1g**	12	90[6]	14	 **1n**	12	92

[a] All the products were fully characterized by usual spectroscopic techniques and their data were compared with authentic data.
[b] Yields were calculated just after aqueous work up.
[c] Corresponding literature reference.

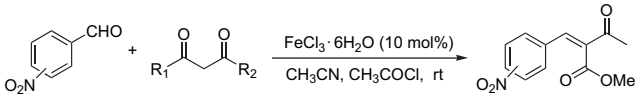
aldehydes such as cinnamaldehyde also reacts under the same experimental conditions and provided the desired product (Table 1, entry 10) without any difficulty. A 1,3-diketone, namely benzoylacetone, was treated under the same experimental conditions to provide β-acetamido diketones with poor diastereoselectivity. Next, by using benzonitrile in place of acetonitrile, a variety of aldehydes were transformed to their corresponding β-benzamido ketones in excellent yields (Table 1, entries 12–14). This clearly demonstrates that in this reaction, the alkyl/aryl nitrile acts as a nucleophile.

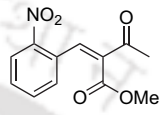
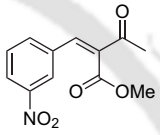
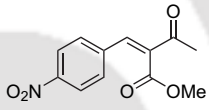
To extend the preparative utility and generality of this multicomponent reaction, a variety of aromatic aldehydes were treated with methyl acetoacetate or ethyl benzoyl acetoacetate under the same experimental conditions, and the corresponding β-acetamido/benzamido keto esters were obtained in good yields with moderate to good diastereoselectivities. These β-acetamido esters are useful precursor for the synthesis of β-aryl homoisothreonine derivatives, which can be used for the preparation of dipeptide isoesters by incorporation with an amino acid residue. The ratio of *syn*:*anti* diastereomers was determined from the ^{1}H NMR spectrum of the crude reaction mixture. The ratio of diastereomers differed with substitution on the aromatic ring (Table 2).

Interestingly, during the course of our study we have noticed that when the aldehyde contains a nitro group either at the ortho, meta or para positions, and is treated with a β-keto ester under the same experimental conditions, it gives only the Knoevenagel condensation product instead of our expected β-acetamido keto ester (Table 3). All these products were fully characterized by recording IR, ^{1}H NMR, and elemental analysis.

To further confirm the formation of these alkenes and to know the geometry of the substituents on the double bond,

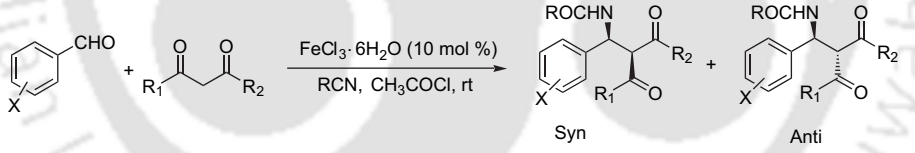
Table 3. $FeCl_3\cdot 6H_2O$ catalyzed Knoevenagel products for nitro benzaldehydes along with trace multi-component products

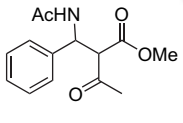
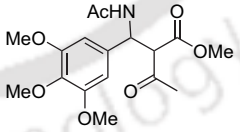
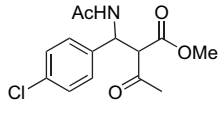
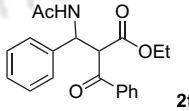
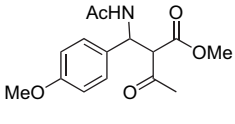
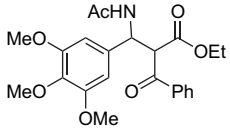
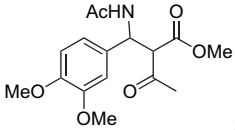
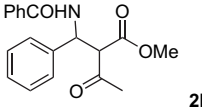


Entry	Product[a]	Yield[b] (%)
1	 **3a**	81
2	 **3b**	80
3	 **3c**	82

[a] All the products were characterized by usual spectroscopic analysis.
[b] Isolated yield.

Table 2. $FeCl_3\cdot 6H_2O$ catalyzed multi-component reaction for the preparation of β-acetamido esters



Entry	Product	Yield[a,c] (%)	*syn*:*anti*[b]	Entry	Product	Yield[a] (%)	*syn*:*anti*[b]
1	 **2a**	81[5]	26:74	5	 **2e**	84	25:75
2	 **2b**	80[5]	27:73	6	 **2f**	78	98:2
3	 **2c**	82[5]	46:54	7	 **2g**	80	95:5
4	 **2d**	86	5:95	8	 **2h**	85	71:29

[a] Yields were calculated without further purification.
[b] The *syn*:*anti* ratio was determined from ^{1}H NMR spectrum of crude reaction mixture.
[c] Corresponding literature reference.

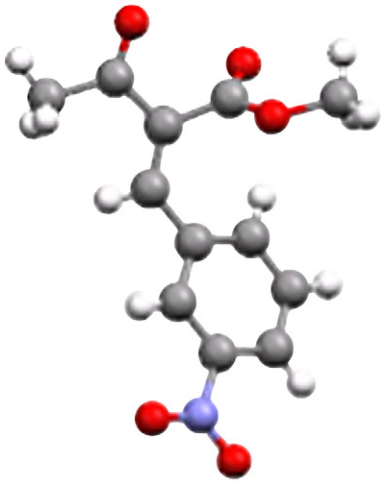


Figure 1. ORTEP plot of compound **3b**.

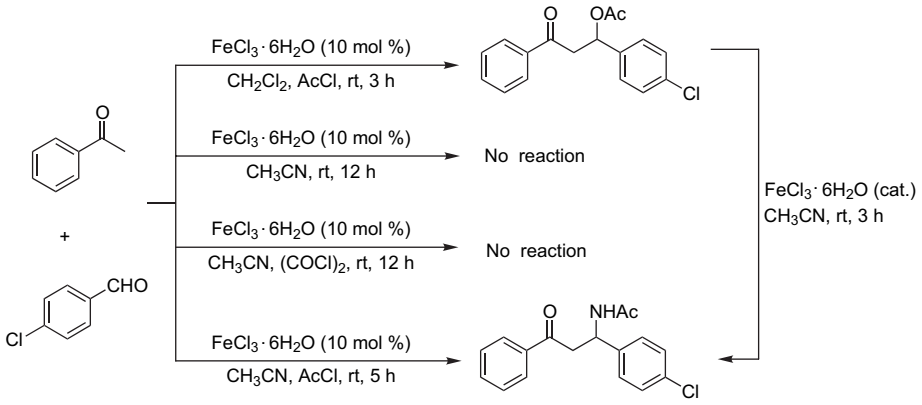
the product **3b** was recrystallized from ethyl acetate–hexane and a single crystal XRD was recorded. It shows the (*Z*)-configuration of the alkene as depicted in Figure 1.

Although the exact explanation of this anomaly is yet to be determined, we assumed that due to electronic effects, i.e., electron withdrawing nature of the nitro group, it provides the Knoevenagel condensation alkenes.

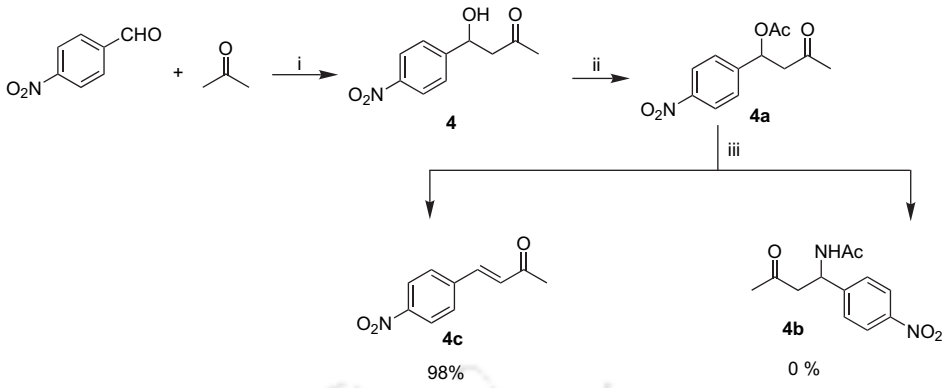
Next we turned our attention to study the mechanistic aspect of this multi-component reaction. Thus, the reaction of 4-chlorobenzaldehyde with acetophenone was chosen as a model reaction for this study. In the absence of acetyl chloride, the reaction failed to provide the desired product, which clearly indicates that it plays a vital role in this reaction, although not directly involved in the final product. Then the same reaction was tried using oxalyl chloride, instead of acetyl chloride, and the reaction was also unsuccessful. From this observation, it is clear that the chloride ion does not have any role in the above transformation. Similarly, the same reaction was carried out in the absence of acetonitrile using dichloromethane as a solvent, and the corresponding β-acetoxy ketone was obtained in 60% yield after 3 h of stirring at room temperature. Consequently, this β-acetoxy ketone as shown in Scheme 2 was once again treated with 10 mol % of the catalyst in acetonitrile as solvent, and the corresponding β-acetamido ketone was obtained in 80% yield under the same experimental conditions. This clearly demonstrates the working hypothesis that the reaction goes via an aldol reaction followed by acetylation and subsequent nucleophilic displacement by the alkyl/aryl nitrile to get the desired product as shown in Scheme 4.

Next, the aldol product **4** was prepared following a literature procedure using proline as an organo catalyst,[24] and acetylated by our self developed BDMS method[25] to get the product **4a**. Subsequently, the compound **4a** was treated separately with acetonitrile under the same experimental conditions using 10 mol % $FeCl_3 \cdot 6H_2O$ as a catalyst. Interestingly, after 12 h of stirring, α,β-unsaturated ketone **4c** was isolated in 98% yield instead of the desired β-acetamido ketone **4b** as shown in Scheme 3. Similarly, in Table 3 we have noted that nitro substituted aldehydes react with methyl acetoacetate and provide the Knoevenagel condensation products under the experimental conditions. These studies lead us to the conclusion that when aliphatic ketones or keto esters react with nitro substituted aldehydes, the intermediate acetylated aldol products (e.g., **4a**) prefer α-H elimination to provide α,β-unsaturated ketones to the formation of desired acetamido ketone by nucleophilic substitution by alkyl or aryl nitrile. This may be attributed to the electronic effect, i.e., the electron withdrawing nature of the substituent as well as, the stability of the elimination products. Later, the Knoevenagel product **3b** was treated further with acetonitrile and acetyl chloride in the presence of 10 mol % catalyst and kept stirring. No detectable amount of the desired β-acetamido keto ester was found, even after stirring for 12 h. Thus it is clear that these unsaturated ketones are more stable compared to the corresponding β-acetamido ketones.

Next to exemplify that acetyl chloride is not incorporated in the final product and acetonitrile itself is the N-donor and nucleophile (i.e., it follows the Ritter reaction pathway), we tried the reaction of 4-chlorobenzaldeyde under similar experimental conditions using benzonitrile (1.5 equiv) instead of acetonitrile (Table 1, entry 13). The formation of benzamide clearly indicates that in this reaction nitrile acts not only as a solvent but also as a nitrogen donor. Therefore,

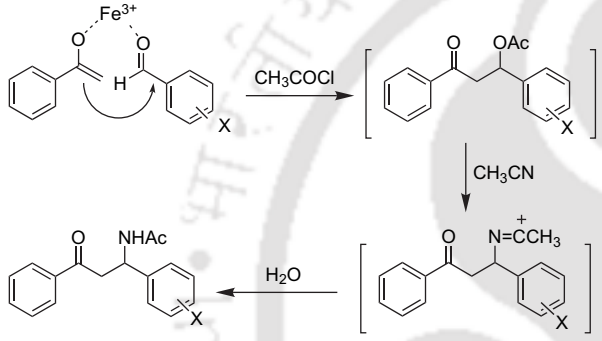


Scheme 2.



Scheme 3. Reagents: (i) proline (20 mol %), H_2O; (ii) BDMS (5 mol %), Ac_2O; (iii) $FeCl_3 \cdot 6H_2O$ (10 mol %), CH_3CN, CH_3COCl.

the most probable mechanism for this reaction is illustrated in Scheme 4.



Scheme 4. Probable mechanism of iron(III) chloride-catalyzed multi-component reactions for the preparation of β-acetamido carbonyl compounds.

3. Conclusion

In summary, we have devised a new synthetic methodology using $FeCl_3 \cdot 6H_2O$, a cheap, readily available, and efficient catalyst for the one-pot synthesis of β-acetamido carbonyl compounds. In the case of nitro aldehydes, the reaction with methyl acetoacetate provides α,β-unsaturated ketones instead of the expected β-acetamido carbonyl compounds. The simplicity of the present protocol, high yields, and efficiency of the catalyst are the key features of this present protocol. Due to the low cost and ready availability of the reagent $FeCl_3 \cdot 6H_2O$, we prefer this protocol than our earlier reported method.[14] In addition we have presented a thorough study on the mechanistic aspect of this multi-component reaction in this article. Thus the present method will be useful for the facile preparation of β-acetamido ketones and keto esters.

4. Experimental

4.1. General

All reagents were of commercial quality and were used as received. Solvents were dried and purified using standard techniques. Melting points were recorded on a Buchi B-545 melting point apparatus and are uncorrected. IR spectra were recorded in KBr on a Nicolet Impact 410 spectrophotometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a Varian 400 MHz spectrometer in $CDCl_3$ or DMSO, d_6 using TMS as an internal reference. Elemental analyses were carried out in a Perkin Elmer 2400 automatic carbon, hydrogen, nitrogen, and sulfur analyzer. Column chromatographic separations were done on SRL silica gel (60–120 mesh).

4.2. General procedure for the preparation of β-acetamido/benzamido ketones or keto esters

To a stirred solution of aldehyde (2 mmol) and acetophenone/methyl acetoacetate (2 mmol) in acetonitrile (3 mL) or benzonitrile (3 mmol) were added acetyl chloride (3 mmol) and $FeCl_3 \cdot 6H_2O$ (0.2 mmol) and the reaction stirred at room temperature. The progress of the reaction was monitored by TLC, and after completion of the reaction, crushed (50 mL) ice was added to the reaction mixture and stirred thoroughly. On solidification, the products were filtered off and dried to get the corresponding β-acetamido ketones. For all the substrates of Table 2, the reactions were stirred for 12 h, then 50 mL of water was added. The mixture was extracted with ethyl acetate (3×20 mL), washed with water (3×20 mL), dried over Na_2SO_4, and the solvent was removed using a rotary evaporator. The crude mixture was recrystallized from ethyl acetate–hexane and the solid product (mixture of diastereomers) was isolated. The solid products were recrystallized from the mixture of solvents (ethyl acetate–hexane) and fully characterized by recording IR, NMR, and elemental analysis.

4.2.1. *N*-(3-Oxo-1,3-diphenyl-propyl) acetamide (1a).[6] Yield 88% (470.0 mg), white crystal (EtOAc–hexane), mp 103–105 °C (lit.[6] mp 102–104 °C) [Found: C, 76.49; H, 6.39; N, 5.19. $C_{17}H_{17}NO_2$ requires C, 76.38; H, 6.41; N, 5.24%]; ν_{max} (KBr): 3278, 3099, 2925, 1682, 1646, 1556, 1447, 1372, 1195, 990, 750 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.01 (3H, s, CO*Me*), 3.43 (1H, dd, *J* 6.0, 16.8 Hz, CH_2), 3.75 (1H, dd, *J* 5.2, 16.8 Hz, CH_2), 5.53–5.57 (1H, m, C*H*), 6.68 (1H, d, *J* 7.6 Hz, N*H*), 7.19–7.30 (5H, m, Ph), 7.43 (2H, t, *J* 8.0 Hz, Ph), 7.55 (1H, t, *J* 7.6 Hz, Ph), 7.88 (2H, d, *J* 8.0 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 23.6, 43.2, 49.9, 126.6, 127.7, 128.3, 128.9, 133.7, 136.4, 140.7, 169.3, 198.3.

4.2.2. *N*-[1-(4-Chlorophenyl)-3-oxo-3-phenyl-propyl] acetamide (1b).[8] Yield 99% (597.0 mg), white crystal

(EtOAc–hexane), mp 146 °C (lit.[8] mp 146–148 °C) [Found: C, 67.53; H, 5.28; N, 4.72. $C_{17}H_{16}ClNO_2$ requires C, 67.66; H, 5.34; N, 4.64%]; ν_{max} (KBr): 3291, 2329, 1687, 1647, 1547, 1445, 1349, 1229, 1009, 754 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.01 (3H, s, CO*Me*), 3.41 (1H, dd, *J* 6.0, 16.8 Hz, CH_2), 3.73 (1H, dd, *J* 5.2, 17.2 Hz, CH_2), 5.50–5.55 (1H, m, C*H*), 6.74 (1H, d, *J* 7.2 Hz, N*H*), 7.25 (4H, d, *J* 4.4 Hz, Ph), 7.44 (2H, t, *J* 8.0 Hz, Ph), 7.56 (1H, t, *J* 7.6 Hz, Ph), 7.87 (2H, d, *J* 8.4 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 23.0, 43.2, 49.4, 128.1, 128.3, 128.9, 133.6, 133.9, 140.0, 142.0, 148.0, 165.0, 198.7.

4.2.3. *N*-[1-(4-Bromophenyl)-3-oxo-3-phenyl-propyl] acetamide (1c). Yield 98% (678.0 mg), white crystal (EtOAc–hexane), mp 148–150 °C [Found: C, 58.85; H, 4.70; N, 4.12. $C_{17}H_{16}BrNO_2$ requires C, 58.98; H, 4.66; N, 4.05%]; ν_{max} (KBr): 3285, 2923, 1684, 1651, 1550, 1374, 1292, 1006, 757 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.02 (3H, s, CO*Me*), 3.40 (1H, dd, *J* 6.0, 17.2 Hz, CH_2), 3.72 (1H, dd, *J* 5.2, 16.8 Hz, CH_2), 5.49–5.51 (1H, m, C*H*), 6.73 (1H, d, *J* 6.8, N*H*), 7.19 (2H, d, *J* 8.4 Hz, Ph), 7.40 (2H, d, *J* 8.4 Hz, Ph), 7.44 (2H, d, *J* 8.0 Hz, Ph), 7.55 (1H, t, *J* 7.2 Hz, Ph), 7.87 (2H, d, *J* 7.2 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 23.7, 42.9, 49.4, 128.3, 128.4, 129.0, 131.9, 134.0, 136.2, 140.2, 166.5, 196.5.

4.2.4. *N*-[1-(4-Methoxyphenyl)-3-oxo-3-phenyl-propyl] acetamide (1d).[10] Yield 94% (560.0 mg), white crystal (EtOAc–hexane), mp 110–111 °C (lit.[10] mp 110–112 °C) [Found: C, 72.59; H, 6.49; N, 4.79. $C_{18}H_{19}NO_3$ requires C, 72.71; H, 6.44; N, 4.71%]; ν_{max} (KBr): 3301, 2928, 1688, 1648, 1545, 1372, 1238, 1033, 754 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.0 (3H, s, CO*Me*), 3.39 (1H, dd, *J* 6.4, 16.8 Hz, CH_2), 3.72 (1H, dd, *J* 5.2, 17.2 Hz, CH_2), 3.74 (3H, s, O*Me*), 5.46–5.51 (1H, m, C*H*), 6.57 (1H, d, *J* 8.0 Hz, N*H*), 6.81 (2H, d, *J* 8.4 Hz, Ph), 7.23 (2H, d, *J* 8.0 Hz, Ph), 7.42 (2H, t, *J* 7.6 Hz, Ph), 7.54 (1H, t, *J* 7.2 Hz, Ph), 7.89 (2H, d, *J* 7.2 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 23.6, 43.5, 49.7, 55.4, 114.2, 127.9, 128.3, 128.9, 133.1, 133.7, 136.7, 158.9, 169.7, 198.8.

4.2.5. *N*-[1-(3,4-Dimethoxyphenyl)-3-oxo-3-phenyl-propyl] acetamide (1e). Yield 98% (640.0 mg), brownish solid, mp 118–119 °C [Found: C, 69.58; H, 6.40; N, 4.37. $C_{19}H_{21}NO_4$ requires C, 69.71; H, 6.47; N, 4.28%]; ν_{max} (KBr): 3247, 3076, 2917, 2846, 1681, 1637, 1519, 1462, 1253, 1026, 751 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.01 (3H, s, CO*Me*), 3.39 (1H, dd, *J* 6.4, 16.8 Hz, CH_2), 3.72 (1H, dd, *J* 5.2, 16.4 Hz, CH_2), 3.81 (3H, s, O*Me*), 3.82 (3H, s, O*Me*), 5.45–5.50 (1H, m, C*H*), 6.58 (1H, d, *J* 8.0 Hz, N*H*), 6.76 (1H, d, *J* 8.0 Hz, Ph), 6.83 (2H, s+d, *J* 8.0 Hz, Ph), 7.43 (2H, t, *J* 7.6 Hz, Ph), 7.55 (1H, t, *J* 7.6 Hz, Ph), 7.89 (2H, d, *J* 7.2 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 23.7, 43.4, 50.1, 56.1, 110.5, 111.3, 118.3, 128.3, 128.9, 133.6, 133.7, 149.2, 169.6, 199.0.

4.2.6. *N*-[1-(3,4,5-Trimethoxyphenyl)-3-oxo-3-phenyl-propyl] acetamide (1f). Yield 96% (685.0 mg), white solid, mp 168–169 °C [Found: C, 67.34; H, 6.42; N, 3.99. $C_{20}H_{23}NO_5$ requires C, 67.21; H, 6.49; N, 3.92%]; ν_{max} (KBr): 3276, 2928, 1688, 1648, 1592, 1458, 1339, 1246, 1001, 754 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.01 (3H, s, CO*Me*), 3.31 (1H, dd, *J* 6.0, 16.8 Hz, CH_2), 3.69 (1H, dd, *J* 5.2, 16.8 Hz, CH_2), 3.76 (3H, s, O*Me*), 3.78 (6H, s, 2×O*Me*), 5.44 (1H, q, *J* 7.6 Hz, C*H*), 6.52 (2H, s, Ph), 6.67 (1H, d, *J* 7.6 Hz, N*H*), 7.43 (2H, t, *J* 7.6 Hz, Ph), 7.55 (1H, t, *J* 7.2 Hz, Ph), 7.88 (2H, d, *J* 8.0 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 23.7, 43.4, 50.7, 56.3, 60.9, 103.9, 128.3, 128.9, 133.8, 136.8, 136.9, 153.5, 156.2, 169.5, 199.4.

4.2.7. *N*-[1-(2-Nitrophenyl)-3-oxo-3-phenyl-propyl] acetamide (1g).[6] Yield 90% (560.0 mg), white solid, mp 190–191 °C (lit.[6] mp 186–188 °C) [Found: C, 65.49; H, 5.23; N, 8.88. $C_{17}H_{16}N_2O_4$ requires C, 65.38; H, 5.16; N, 8.97%]; ν_{max} (KBr): 3326, 2379, 1686, 1651, 1544, 1517, 1357, 1337, 1059, 682 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.00 (3H, s, CO*Me*), 3.63 (1H, dd, *J* 5.6, 16.8 Hz, CH_2), 3.71 (1H, dd, *J* 6.4, 17.2 Hz, CH_2), 5.93–5.97 (1H, m, C*H*), 7.07 (1H, d, *J* 5.6 Hz, N*H*), 7.39 (1H, t, *J* 8.0 Hz, Ph), 7.46 (2H, t, *J* 8.0 Hz, Ph), 7.57 (2H, t, *J* 7.6 Hz, Ph), 7.71 (1H, d, *J* 8.0 Hz, Ph), 7.92 (2H, d, *J* 7.2 Hz), 7.94 (1H, d, *J* 6.8, Ph); δ_C (100 MHz, $CDCl_3$) 23.5, 42.4, 47.7, 125.3, 128.5, 128.6, 129.0, 130.1, 133.7, 134.1, 136.5, 137.1, 148.7, 169.5, 198.5.

4.2.8. *N*-[1-(3-Nitrophenyl)-3-oxo-3-phenyl-propyl] acetamide (1h).[6] Yield 96% (593.0 mg), white solid, mp 139–140 °C (lit.[10] mp 139–140 °C) [Found: C, 65.29; H, 5.22; N, 8.88. $C_{17}H_{16}N_2O_4$ requires C, 65.38; H, 5.16; N, 8.97%]; ν_{max} (KBr): 3306, 1693, 1644, 1545, 1522, 1347, 983, 684 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.08 (3H, s, CO*Me*), 3.51 (1H, dd, *J* 5.6, 17.6 Hz, CH_2), 3.79 (1H, dd, *J* 5.2, 17.6 Hz, CH_2), 5.62–5.67 (1H, m, C*H*), 6.91 (1H, d, *J* 7.6 Hz, N*H*), 7.42–7.49 (3H, m, Ph), 7.57 (1H, t, *J* 7.6 Hz, Ph), 7.68 (1H, d, *J* 7.6 Hz, Ph), 7.87 (2H, d, *J* 7.6 Hz, Ph), 8.06 (1H, d, *J* 6.8 Hz, Ph), 8.19 (1H, s, Ph); δ_C (100 MHz, $CDCl_3$) 23.6, 42.9, 49.3, 121.5, 122.6, 128.3, 129.1, 129.8, 130.8, 133.1, 134.2, 136.4, 143.7, 169.9, 198.3.

4.2.9. *N*-[1-(4-Nitrophenyl)-3-oxo-3-phenyl-propyl] acetamide (1i).[6] Yield 95% (593.0 mg), yellow crystalline solid, mp 153 °C (lit.[10] mp 154 °C) [Found: C, 65.29; H, 5.23; N, 8.99. $C_{17}H_{16}N_2O_4$ requires C, 65.38; H, 5.16; N, 8.97%]; ν_{max} (KBr): 3306, 1696, 1646, 1595, 1537, 1350, 988, 755 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.10 (3H, s, CO*Me*), 3.51 (1H, dd, *J* 5.6, 17.6 Hz, CH_2), 3.81 (1H, dd, *J* 5.2, 17.6 Hz, CH_2), 5.65–5.67 (1H, m, C*H*), 6.96 (1H, d, *J* 8.0 Hz, N*H*), 7.47 (2H, t, *J* 8.0 Hz, Ph), 7.51 (2H, d, *J* 8.8 Hz, 2H, Ph), 7.60 (1H, t, *J* 7.2 Hz, Ph), 7.89 (2H, d, *J* 7.2 Hz, Ph), 8.17 (2H, d, *J* 8.8 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 23.5, 42.6, 49.2, 123.7, 127.2, 127.9, 128.7, 131.0, 133.9, 136.0, 138.4, 169.5, 197.8.

4.2.10. *N*-[1-(4-Styryl)-3-oxo-3-phenyl-propyl] acetamide (1j). Yield 85% (497.0 mg), light yellow solid, mp 120–121 °C [Found: C, 77.68; H, 6.45; N, 4.83. $C_{19}H_{19}NO_2$ requires C, 77.79; H, 6.53; N, 4.77%]; ν_{max} (KBr): 3291, 3065, 2928, 1687, 1648, 1635, 1547, 1445, 1366, 1083, 751 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.04 (3H, s, CO*Me*), 3.35 (1H, dd, *J* 5.6, 17.6 Hz, CH_2), 3.53 (1H, dd, *J* 4.4, 17.6 Hz, CH_2), 5.09–5.13 (1H, m, C*H*), 6.33 (1H, dd, *J* 6.8, 16.0 Hz, C*H*═), 6.54 (1H, d, *J* 15.6 Hz, C*H*═), 7.20 (1H, d, *J* 6.8 Hz, N*H*), 7.25 (2H, t, *J* 6.8 Hz, Ph), 7.29 (3H, d, *J* 7.2 Hz, Ph), 7.46 (2H, t, *J* 7.6 Hz, Ph), 7.57 (1H, t, *J* 7.6 Hz, Ph), 7.93 (2H, d, *J* 7.2 Hz, Ph); δ_C (100 MHz,

$CDCl_3$) 23.8, 42.8, 48.3, 126.7, 127.9, 128.3, 128.6, 128.7, 128.9, 1301.7, 133.9, 169.5, 199.7.

4.2.11. *N*-[1-(4-Chlorophenyl)-2-acetyl-3-oxo-3-phenyl-propyl] acetamide (1k). Yield 83% (571.0 mg), white solid (mixture of diastereomers): (*syn*:*anti*=40:60), mp 172–174 °C [Found: C, 66.49; H, 5.21; N, 4.18. $C_{19}H_{18}NClO_3$ requires C, 66.38; H, 5.28; N, 4.07%]; ν_{max} (KBr): 3301, 1704, 1688, 1648, 1527, 1370, 1087 cm^{-1}; Data for the major isomer (*anti*): δ_H (400 MHz, $CDCl_3$) 1.95 (3H, s, CO*Me*), 2.13 (3H, s, CO*Me*), 5.05 (1H, d, *J* 7.6 Hz, C*H*), 5.85 (1H, t, *J* 8.4 Hz, C*H*), 6.57 (1H, d, *J* 8.4 Hz, N*H*), 7.23 (4H, d, *J* 6.4 Hz, Ph), 7.47 (2H, t, *J* 7.2 Hz, Ph), 7.59 (1H, t, *J* 8.8 Hz, Ph), 7.73 (1H, d, *J* 8.0 Hz, Ph), 7.90 (1H, d, *J* 8.4 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 23.5, 29.2, 52.4, 66.7, 128.5, 128.8, 129.2, 129.3, 133.9, 134.5, 135.9, 138.5, 169.8, 193.8, 204.0.

4.2.12. *N*-(3-Oxo-1,3-diphenyl-propyl) benzamide (1l). Yield 97% (639.0 mg), yellowish solid, mp 153–154 °C [Found: C, 80.33; H, 5.76; N, 4.31. $C_{22}H_{19}NO_2$ requires C, 80.22; H, 5.81; N, 4.25%]; ν_{max} (KBr): 3306, 3062, 1681, 1634, 1599, 1488, 1357, 981, 754 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.52 (1H, dd, *J* 6.0, 16.4 Hz, CH_2), 3.87 (1H, dd, *J* 4.8, 16.8 Hz, CH_2), 5.73–5.78 (1H, m, C*H*), 7.22 (1H, t, *J* 7.2 Hz, Ph), 7.30 (2H, t, *J* 7.6 Hz, Ph), 7.37–7.45 (5H, m, Ph), 7.49 (2H, t, *J* 7.2 Hz, Ph), 7.55 (1H, t, *J* 7.2 Hz, Ph), 7.60 (1H, d, *J* 8.0 Hz, Ph), 7.82 (2H, d, *J* 8.0 Hz, Ph), 7.90 (2H, d, *J* 8.0 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 43.1, 50.4, 126.6, 127.2, 127.6, 128.3, 128.7, 128.8, 128.9, 131.8, 133.8, 134.4, 136.7, 141.1, 166.9, 199.3.

4.2.13. *N*-[1-(4-Chlorophenyl)-3-oxo-3-phenyl-propyl] benzamide (1m). Yield 96% (699.0 mg), yellow solid, mp 180–182 °C [Found: C, 72.74; H, 4.93; N, 3.93. $C_{22}H_{18}ClNO_2$ requires C, 72.63; H, 4.99; N, 3.85%]; ν_{max} (KBr): 3276, 2928, 2372, 1683, 1641, 1542, 1490, 1362, 1087, 689 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.52 (1H, dd, *J* 5.6, 17.2 Hz, CH_2), 3.86 (1H, dd, *J* 4.8, 17.2 Hz, CH_2), 5.71–5.75 (1H, m, C*H*), 7.28 (2H, d, *J* 8.4 Hz, Ph), 7.35 (2H, d, *J* 8.4 Hz, Ph), 7.46 (2H, t, *J* 7.6 Hz, Ph), 7.47 (2H, t, *J* 7.6 Hz, Ph), 7.53 (1H, t, *J* 7.2 Hz, Ph), 7.59 (1H, t, *J* 7.2 Hz, Ph), 7.69 (1H, d, *J* 8.0 Hz, N*H*), 7.84 (2H, d, *J* 7.6 Hz, Ph), 7.91 (2H, d, *J* 8.0 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 42.6, 49.6, 127.0, 127.9, 128.1, 128.6, 128.8, 131.7, 133.1, 133.8, 136.4, 139.5, 166.7, 198.9.

4.2.14. *N*-[1-(4-Nitrophenyl)-3-oxo-3-phenyl-propyl] benzamide (1n). Yield 92% (689.0 mg), solid, mp 142–144 °C [Found: C, 70.69; H, 4.80; N, 7.39. $C_{22}H_{18}N_2O_4$ requires C, 70.58; H, 4.85; N, 7.48%]; ν_{max} (KBr): 3313, 3060, 2934, 1684, 1626, 1517, 1399, 1111, 688 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.57 (1H, dd, *J* 4.4, 18.0 Hz, CH_2), 3.90 (1H, dd, *J* 4.4, 16.8 Hz, CH_2), 5.82–5.86 (1H, m, C*H*), 7.46 (4H, t, *J* 7.6 Hz, Ph), 7.52 (1H, d, *J* 6.8 Hz, N*H*), 7.55–7.59 (4H, m, Ph), 7.84 (2H, d, *J* 7.6 Hz, Ph), 7.89 (2H, d, *J* 7.6 Hz, Ph), 8.16 (2H, d, *J* 8.8 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 42.7, 49.9, 124.1, 127.3, 127.7, 128.4, 128.9, 129.1, 132.2, 133.8, 134.3, 136.4, 147.2, 148.8, 167.0, 198.0.

4.2.15. Methyl 2-acetyl-3-acetamido-3-phenyl propionate (2a). Yield 81% (426.0 mg), white solid, mp 128–130 °C (lit.[5] mp 129–131 °C) [Found: C, 63.74; H, 6.45; N, 5.43. $C_{14}H_{17}NO_4$ requires C, 63.87; H, 6.51; N, 5.32%]; ν_{max} (KBr): 3329, 3049, 2961, 1747, 1717, 1643, 1528, 1451, 1371, 1037, 754 cm^{-1}. Data for the major isomer (*anti*): δ_H (400 MHz, $CDCl_3$) 1.99 (3H, s, CO*Me*), 2.10 (3H, s, CO*Me*), 3.69 (3H, s, O*Me*), 4.07 (1H, d, *J* 5.6 Hz, C*H*), 5.73 (1H, dd, *J* 5.6, 9.2 Hz, C*H*), 6.91 (1H, d, *J* 8.4 Hz, N*H*), 7.23–7.31 (5H, m, Ph); δ_C (100 MHz, $CDCl_3$) 23.5, 31.1, 52.5, 53.0, 62.5, 126.6, 128.0, 128.9, 139.3, 166.1, 169.9, 203.8.

4.2.16. Methyl 2-acetyl-3-acetamido-3-(*p*-chlorophenyl) propionate (2b).[5] Yield 80% (477.0 mg), white solid (mixture of diastereomers), mp 131–133 °C (lit.[5] mp 130–132 °C) [Found: C, 56.60; H, 5.36; N, 4.82. $C_{14}H_{16}ClNO_4$ requires C, 56.49; H, 5.42; N, 4.71%]; ν_{max} (KBr): 3324, 1744, 1714, 1646, 1541, 1486, 1371, 1091, 724 cm^{-1}. Data for the major isomer (*anti*): δ_H (400 MHz, $CDCl_3$) 1.99 (3H, s, CO*Me*), 2.13 (3H, s, CO*Me*), 3.70 (3H, s, O*Me*), 4.04 (1H, d, *J* 5.6 Hz, C*H*), 5.68 (1H, dd, *J* 5.6, 9.2 Hz, C*H*), 6.94 (1H, d, *J* 8.4 Hz, N*H*), 7.20 (2H, d, *J* 8.8 Hz, Ph), 7.25 (2H, d, *J* 8.0 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 23.5, 31.0, 52.0, 53.1, 62.4, 128.2, 129.1, 133.9, 138.0, 167.8, 169.9, 203.8.

4.2.17. Methyl 2-acetyl-3-acetamido-3-(*p*-methoxy-phenyl) propionate (2c).[5] Yield 82% (480.0 mg), light yellow solid (mixture of diastereomers), mp 140–143 °C (lit.[5] mp 142–144 °C) [Found: C, 61.53; H, 6.48; N, 4.86. $C_{15}H_{19}NO_5$ requires C, 61.42; H, 6.53; N, 4.77%]; ν_{max} (KBr): 3335, 2967, 1739, 1714, 1648, 1602, 1517, 1434, 1369, 1028, 587 cm^{-1}. Data for the major isomer (*anti*): δ_H (400 MHz, $CDCl_3$) 1.97 (3H, s, CO*Me*), 2.14 (3H, s, CO*Me*), 3.68 (3H, s, O*Me*), 3.76 (3H, s, O*Me*), 3.86 (1H, d, *J* 6.0 Hz, C*H*), 5.61 (1H, dd, *J* 6.0, 9.2 Hz, C*H*), 6.81 (2H, d, *J* 8.0 Hz, Ph), 6.98 (1H, d, *J* 8.4 Hz, N*H*), 7.18 (2H, d, *J* 8.4 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 23.3, 30.7, 52.8, 55.2, 55.4, 62.7, 127.7, 131.2, 131.7, 131.9, 160.3, 169.5, 187.8.

4.2.18. Methyl 2-acetyl-3-acetamido-3-(dimethoxy-phenyl) propionate (2d). Yield 86% (556.0 mg), white solid (mixture of diastereomers), mp 125–127 °C [Found: C, 59.55; H, 6.49; N, 4.42. $C_{16}H_{21}NO_6$ requires C, 59.43; H, 6.55; N, 4.33%]; ν_{max} (KBr): 3331, 2928, 1745, 1718, 1648, 1542, 1458, 1372, 1023, 546 cm^{-1}. Data for the major isomer (*anti*): δ_H (400 MHz, $CDCl_3$) 1.98 (3H, s, CO*Me*), 2.15 (3H, s, CO*Me*), 3.68 (3H, s, O*Me*), 3.83 (3H, s, O*Me*), 3.85 (3H, s, O*Me*), 4.03 (1H, d, *J* 6.0 Hz, C*H*), 5.66 (1H, dd, *J* 6.4, 9.2 Hz, C*H*), 6.78 (1H, s, Ph), 6.79 (2H, d, *J* 7.6 Hz, Ph), 6.84 (1H, d, *J* 9.2 Hz, N*H*); δ_C (100 MHz, $CDCl_3$) 23.6, 30.9, 52.4, 53.0, 56.1, 63.0, 110.3, 111.3, 118.8, 131.9, 149.0, 149.2, 167.9, 169.7, 204.2.

4.2.19. Methyl 2-acetyl-3-acetamido-3-(trimethoxy-phenyl) propionate (2e). Yield 84% (593.0 mg), brown solid (mixture of diastereomers), mp 130–133 °C [Found: C, 57.89; H, 6.50; N, 4.09. $C_{17}H_{23}NO_7$ requires C, 57.78; H, 6.56; N, 3.96%]; ν_{max} (KBr): 3326, 2928, 1747, 1718, 1683, 1651, 1592, 1458, 1339, 1003, 670 cm^{-1}. Data for the major isomer (*anti*): δ_H (400 MHz, $CDCl_3$) 2.00 (3H, s, CO*Me*), 2.16 (3H, s, CO*Me*), 3.69 (3H, s, O*Me*), 3.78 (3H, s, O*Me*), 3.82 (6H, s, 2×O*Me*), 4.01 (1H, d, *J* 6.0 Hz,

C*H*), 5.64 (1H, dd, *J* 5.6, 8.8 Hz, C*H*), 6.47 (2H, s, Ph), 6.90 (1H, d, *J* 8.8 Hz, N*H*); δ_C (100 MHz, $CDCl_3$) 23.5, 31.1, 31.2, 52.9, 53.0, 56.3, 60.9, 62.8, 103.9, 135.1, 153.5, 153.6, 167.9, 169.8, 200.0.

4.2.20. Ethyl 2-benzoyl-3-acetamido-3-phenyl propionate (2f). Yield 78% (529.0 mg), white solid (mixture of diastereomers), mp 133–134 °C [Found: C, 70.89; H, 6.29; N, 4.03. $C_{20}H_{21}NO_4$ requires C, 70.78; H, 6.24; N, 4.13%]; ν_{max} (KBr): 3311, 1724, 1691, 1651, 1597, 1352, 1097, 695, 543 cm^{-1}. Data for the major isomer (*syn*): δ_H (400 MHz, $CDCl_3$) 1.20 (3H, t, *J* 7.2 Hz, *Me*), 2.08 (3H, s, *Me*), 4.18 (2H, q, *J* 7.2 Hz, OC*H*$_2$), 4.98 (1H, d, *J* 4.0 Hz, C*H*), 5.91 (1H, dd, *J* 4.0, 9.2 Hz, C*H*), 7.15 (1H, t, *J* 7.2 Hz, Ph), 7.22 (3H, m, Ph), 7.30 (2H, d, *J* 7.6 Hz, Ph), 7.40 (1H, t, *J* 7.6 Hz, Ph), 7.47 (1H, d, *J* 9.2 Hz, N*H*), 7.54 (1H, t, *J* 8.4 Hz, Ph), 7.79 (2H, d, *J* 8.4 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 31.8, 41.8, 53.0, 53.3, 62.2, 126.6, 127.3, 128.0, 128.8, 129.0, 131.9, 134.2, 139.3.

4.2.21. Ethyl 2-benzoyl-3-acetamido-3-(trimethoxyphenyl) propionate (2g). Yield 80% (687 mg), white solid (mixture of diastereomers), mp 150–152 °C [Found: C, 64.21; H, 6.39; N, 3.15. $C_{23}H_{27}NO_7$ requires C, 64.32; H, 6.34; N, 3.26%]; ν_{max} (KBr): 3306, 2931, 1729, 1686, 1648, 1592, 1456, 1370, 1001, 733 cm^{-1}. Data for the major isomer (*syn*): δ_H (400 MHz, $CDCl_3$) 1.21 (3H, t, *J* 7.2 Hz, *Me*), 2.07 (3H, s, CO*Me*), 3.74 (3H, s, O*Me*), 3.75 (6H, s, 2×O*Me*), 4.17 (2H, q, *J* 7.2 Hz, OC*H*$_2$), 4.93 (1H, d, *J* 4.0 Hz, C*H*), 5.80 (1H, dd, *J* 4.0, 8.8 Hz, C*H*), 6.49 (2H, s, Ph), 7.41 (2H, t, *J* 8.0 Hz, Ph), 7.50 (1H, d, *J* 8.8 Hz, N*H*), 7.55 (1H, t, *J* 7.2 Hz, Ph), 7.77 (2H, d, *J* 7.2 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 14.2, 23.6, 53.5, 56.3, 56.6, 60.9, 62.4, 104.3, 128.5, 129.1, 134.3, 135.4, 153.4, 167.0, 199.5.

4.2.22. Methyl 2-acetyl-3-benzamido-3-phenyl propionate (2h). Yield 85% (553.0 mg), light yellow solid (mixture of diastereomers), mp 151–153 °C [Found: C, 70.25; H, 5.84; N, 4.39. $C_{19}H_{19}NO_4$ requires C, 70.14; H, 5.89; N, 4.30%]; ν_{max} (KBr): 3346, 2941, 1744, 1719, 1633, 1527, 1458, 1360, 1031, 700 cm^{-1}. Data for the major isomer (*syn*): δ_H (400 MHz, $CDCl_3$) 2.15 (3H, s, CO*Me*), 3.71 (3H, s, O*Me*), 4.21 (1H, d, *J* 4.4 Hz, C*H*), 5.91 (1H, dd, *J* 4.4, 9.6 Hz, C*H*), 7.30–7.32 (4H, m, Ph), 7.43 (2H, t, *J* 7.6 Hz, Ph), 7.49 (2H, d, *J* 7.6 Hz, Ph), 7.80 (2H, d, *J* 7.2 Hz, Ph), 7.88 (1H, d, *J* 9.6 Hz, N*H*); δ_C (100 MHz, $CDCl_3$) 30.1, 53.0, 53.3, 62.2, 126.6, 127.3, 128.0, 128.8, 129.0, 131.9, 134.2, 139.0, 166.9, 167.9, 204.5.

4.2.23. Methyl 2-(*o*-nitrobenzylidene) acetoacetate (3a). Yield 81% (404.0 mg), crystalline white solid (EtOAc–hexane), mp 90–93 °C (lit.[27] mp 102 °C) [Found: C, 57.71; H, 4.39; N, 5.74. $C_{12}H_{11}NO_5$ requires C, 57.83; H, 4.45; N, 5.62%]; ν_{max} (KBr): 3062, 2953, 1733, 1683, 1599, 1448, 1362, 1053, 736, 605 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.49 (3H, s, CO*Me*), 3.61 (3H, s, O*Me*), 7.43 (1H, t, *J* 7.6 Hz, Ph), 7.59 (1H, d, *J* 7.6 Hz, Ph), 7.69 (1H, t, *J* 7.6 Hz, Ph), 8.08 (1H, s, =C*H*), 8.24 (1H, d, *J* 7.6 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 26.3, 51.5, 124.3, 129.6, 129.8, 132.0, 133.3, 135.4, 139.8, 147.1, 166.9, 193.8.

4.2.24. Methyl 2-(*m*-nitrobenzylidene) acetoacetate (3b). Yield 80% (329.0 mg), crystalline solid (EtOAc–hexane), mp 151–152 °C (lit.[26] mp 148 °C) [Found: C, 57.72; H, 4.39; N, 5.71. $C_{12}H_{11}NO_5$ requires C, 57.83; H, 4.45; N, 5.62%]; ν_{max} (KBr): 3065, 1732, 1651, 1618, 1525, 1443, 1390, 1091, 735, 688 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, O*Me*), 3.87 (3H, s, O*Me*), 7.58 (1H, s, Ph), 7.59 (1H, t, *J* 7.6 Hz, Ph), 7.72 (1H, d, *J* 7.6 Hz, Ph), 8.25 (1H, d, *J* 8.4 Hz, Ph), 8.29 (1H, s, =C*H*); δ_C (100 MHz, $CDCl_3$) 27.0, 53.1, 123.9, 125.2, 130.2, 134.8, 135.2, 136.7, 138.6, 147.5, 168.0, 194.0.

4.2.25. Methyl 2-(*p*-nitrobenzylidene) acetoacetate (3c). Yield 82% (408.0 mg), yellow crystalline solid (EtOAc–hexane), mp 110–114 °C [Found: C, 57.74; H, 4.40; N, 5.54. $C_{12}H_{11}NO_5$ requires C, 57.83; H, 4.45; N, 5.62%]; ν_{max} (KBr): 1736, 1659, 1624, 1599, 1440, 1349, 1042, 817, 537 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s, CO*Me*), 3.82 (3H, s, OMe), 7.56 (2H, d, *J* 8.8 Hz, Ph), 7.59 (1H, s, =C*H*), 8.23 (2H, d, *J* 8.8 Hz, Ph); δ_C (100 MHz, $CDCl_3$) 27.1, 53.1, 109.9, 124.2, 130.1, 138.7, 139.6, 148.1, 167.0, 194.1.

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$CeCl_3 \cdot 7H_2O$: an efficient and reusable catalyst for the preparation of β-acetamido carbonyl compounds by multi-component reactions (MCRs)

Abu T. Khan,* Lokman H. Choudhury, Tasneem Parvin and Md. Asif Ali

Indian Institute of Technology Guwahati, Department of Chemistry, Guwahati 781 039, India

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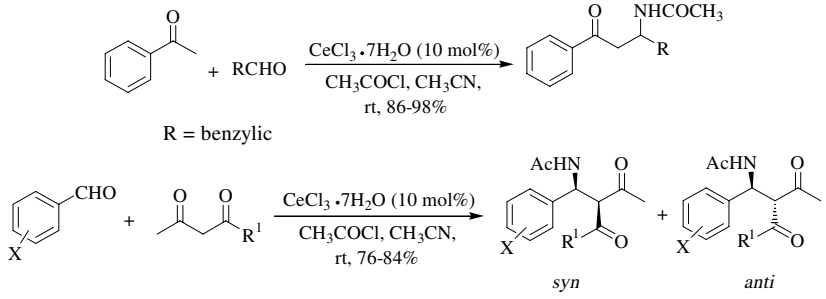
Abstract—A convenient method for the preparation of β-acetamido carbonyl compounds is described by multi-component reactions of aromatic aldehydes, enolizable ketones or β-keto esters and acetonitrile in the presence of acetyl chloride and 10 mol % $CeCl_3 \cdot 7H_2O$ at room temperature.

After the discovery of multi-component reactions (MCRs) in 1850 by Strecker,[1] the concept has stimulated substantial interest in organic chemistry because it provides useful product(s) in a single step by the creation of several new bonds in one pot. In drug discovery as well as 'Green Chemistry', MCRs are the preferred techniques due to high throughput synthesis of compounds in a cost- and time effective manner.

β-Acetamido carbonyl compounds are valuable building blocks for a number of biologically and pharmaceutically[2] important compounds, examples being for the preparation of 1,3-amino alcohols,[3] antibiotic nikkomycins or neopolyoxines.[4] Thus, the synthesis of β-acetamido carbonyl compounds has attracted much attention in organic synthesis. Conventionally, this class of compounds is prepared by the Dakin–West reaction,[5] the condensation of an α-amino acid with acetic anhydride in the presence of a base provides the α-acetamido ketones through an intermediate azalactone.[6] Iqbal et al. developed a route using aromatic aldehydes, enolizable ketones or β-keto esters and acetonitrile in the presence of acetyl chloride and a catalytic amount of a Lewis acid catalyst such as $CoCl_2$[7] or Montmorillonite K-10 clay.[8] Although these methods are valuable some drawbacks remain such as a requirement for either a long reaction time or harsh reaction conditions, or the reaction has to be carried out under an inert



Scheme 1.

* Corresponding author. Tel.: +91 361 2582305; fax: +91 361 2582349; e-mail: atk@iitg.ernet.in

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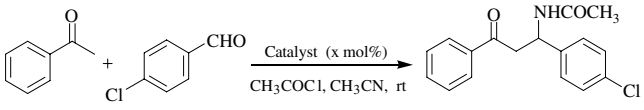
Table 1. Optimization of the $CeCl_3{\cdot}7H_2O$ catalyzed multi-component reaction



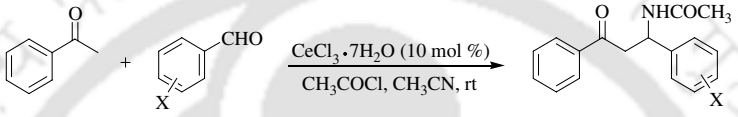
Entry	Catalyst $CeCl_3{\cdot}7H_2O$ mol %	Time (h)	Yield[a] (%)
1	0	24	15
2	5	15	87
3	10	6	98
4	10	24	0[b]

[a] Crude yields.
[b] Reaction was carried out in the absence of acetyl chloride.

atmosphere. Recently, other methods have also been reported involving $Cu(OTf)_2/Sc(OTf)_3$,[9] silica sulfuric acid,[10] BiOCl[11] and $ZrOCl_2{\cdot}8H_2O$.[12] However, most of these methods also employ either expensive catalysts or long reaction times or harsh reaction conditions. In continuation of our effort towards the development of newer and 'greener' synthetic methodologies,[13] we set out to find out a simple and improved protocol for the preparation of β-acetamido carbonyl compounds using a readily available, cheap and non-toxic catalyst.

$CeCl_3{\cdot}7H_2O$ is a relatively cheap, water, air-stable and non-toxic reagent.[14] Due to the hardness of the cerium cation, it is able to activate carbonyl functional-

Table 2. $CeCl_3{\cdot}7H_2O$ catalyzed multi-component reaction for the preparation of β-acetamido ketones



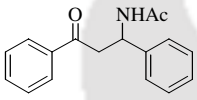
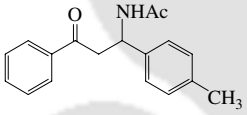
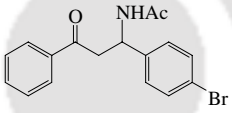
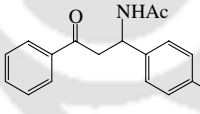
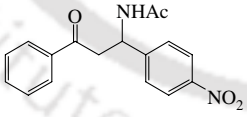
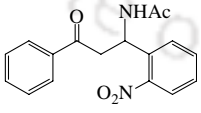
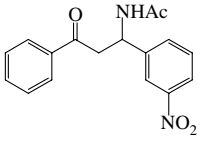
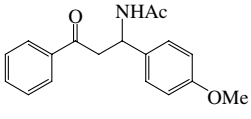
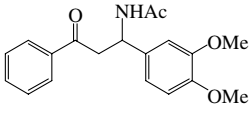
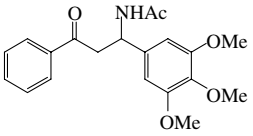
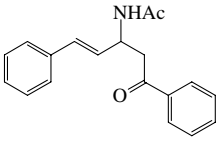
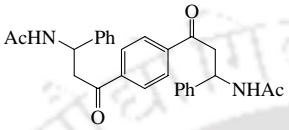
Entry	β-Acetamido ketones[a]	Time (h)	Yield[b] (%)
1		7	96
2		7	92
3		6	95
4		6	98[c]
5		12	96
6		11	86
7		10	90
8		6	89
9		6	96

Table 2 (*continued*)

Entry	β-Acetamido ketones[a]	Time (h)	Yield[b] (%)
10		5	93
11		6	94
12		8	76

[a] All the products were characterized by IR and ^{1}H NMR spectroscopy as well as by elemental analysis.
[b] Yields after work-up.
[c] The catalyst was recovered and reused in subsequent reactions three times without losing any significant activity affording 91%, 88%, and 85% yields, respectively.

ities for nucleophilic attack and has been used as a Lewis acid for several transformations.[15] Herein, we report a mild and efficient protocol for the preparation of β-acetamido carbonyl compounds by four-component reactions of an aromatic aldehyde, acetonitrile, an enolizable ketone or β-keto ester and acetyl chloride, catalyzed by $CeCl_3{\cdot}7H_2O$ at room temperature (Scheme 1).

To find the optimal conditions, a mixture of 4-chlorobenzaldehyde (2 mmol), acetophenone (2 mmol), acetyl chloride (3 mmol) and acetonitrile (5 mL) was stirred under various reaction conditions (Table 1). In the absence of the catalyst, the product β-acetamido ketone was obtained in 15% yield only after 24 h. Even with the inclusion of 5 mol % $CeCl_3{\cdot}7H_2O$, the transformation took a long time, however, using 10 mol % catalyst furnished the β-acetamido carbonyl compound in an excellent yield (Table 1).

After optimization,[16] a variety of other aromatic aldehydes having electron-donating as well as electron-withdrawing substituents were shown to undergo the reaction smoothly giving the desired products in good yields. The results are summarized in Table 2. All the products were fully characterized by spectroscopic methods and compared with the authentic spectra. Aromatic aldehydes containing a nitro substituent took longer reaction times (entries 5–7). The α,β-unsaturated aldehyde, cinnamaldehyde, also reacted under the same experimental conditions (entry 11), as did terephthaldehyde on treatment with 2 equiv of acetophenone and the other reactants (entry 12).

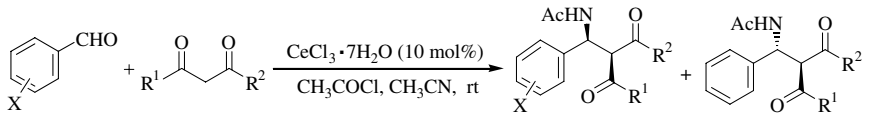
To explore the further applicability of Ce(III)-catalyzed multi-component reactions, a variety of aromatic aldehydes (Table 3, entries 1–5) were treated with methyl acetoacetate and acetyl chloride in the presence of 10 mol % of catalyst at room temperature and the corresponding β-acetamido keto esters were obtained in good yields with moderate to good diastereoselectivities. Similarly, ethyl benzoylacetate afforded the corresponding products (Table 3, entries 6–8) in excellent yields with good diastereoselectivity. Interestingly, the major products obtained using methyl acetoacetate (Table 3, entries 1–5) were the *anti* isomers, whereas ethyl benzoylacetate afforded mainly the *syn* isomers (Table 3, entries 6–8).

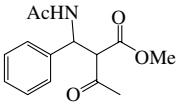
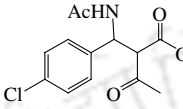
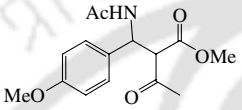
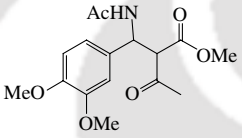
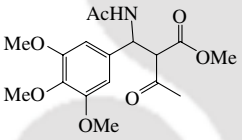
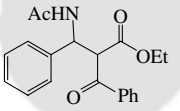
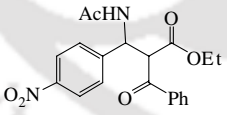
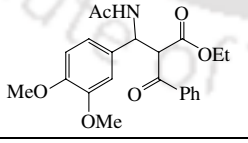
The generality and superiority of the present protocol over existing methods can be seen by comparing our results with those of some recently reported procedures, as shown in Table 4. The reaction of benzaldehyde with acetophenone for the preparation of β-acetamido-β-(phenyl)-propiophenone (Table 2, entry 1) was chosen as a model reaction and the comparison is in terms of mol % of the catalysts used, reaction time, and reaction conditions and percentage yields.

Noting that the reaction proceeds with only 15% yield even after 24 h in the absence of a catalyst, we believe that the cerium chloride activates the aldehyde group for nucleophilic attack as well as facilitating enolization. We were interested to determine whether a chalcone intermediate (by aldol condensation) is involved. Thus, a mixture of chalcone (2 mmol), acetyl chloride (3 mmol) and acetonitrile (5 mL) was stirred at room temperature for 6 h, but no β-acetamido ketone was formed.

In conclusion, we have revealed a simple, efficient and 'greener' protocol for the preparation of β-acetamido carbonyl compounds using $CeCl_3{\cdot}7H_2O$ as a reusable catalyst (Scheme 2). The salient features of this protocol include operational simplicity, high yields of the products, avoidance of column chromatography, ready availability, low toxicity, moisture compatibility and reusability of the catalyst.

Table 3. $CeCl_3 \cdot 7H_2O$ catalyzed multi-component reaction for the preparation of β-acetamido keto esters

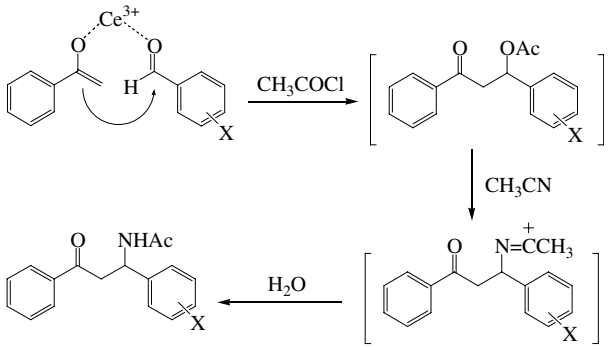


Entry	Product	Yield[a] (%)	*syn*:*anti*[b]
1		76	25:75
2		84	24:76
3		78	5:95
4		83	7:93
5		81	10:90
6		81	90:10
7		84	72:28
8		83	70:30

[a] Yields after work-up.
[b] The *syn*:*anti* ratio was determined from ^1H NMR measurements of the crude reaction mixture.

Table 4. Comparison of the results for the preparation of β-acetamido ketone (Table 2, entry 1) using multi-component reactions with other catalysts

Catalyst	mol %	Reaction time	Reaction temperature (°C)	Yield (%)
Silica sulfuric acid	78	65 min	80	91[10]
$ZrOCl_2 \cdot 8H_2O$	20	5 h	rt	90[12]
$Sc(OTf)_3$	10	30 h	rt	82[9]
BiOCl	20	7 h	rt	92[11]
$CeCl_3 \cdot 7H_2O$	10	7 h	rt	96



Scheme 2. A plausible mechanism for the $CeCl_3{\cdot}7H_2O$ catalyzed multicomponent reaction for the preparation of β-acetamido carbonyl compounds.

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16. Typical procedure: A mixture of aromatic aldehyde (2 mmol), acetophenone or β-keto ester (2 mmol), acetyl chloride (3 mmol) and $CeCl_3{\cdot}7H_2O$ (75 mg, 10 mol %) in acetonitrile (5 mL) was stirred at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was poured into 50 mL of ice water. On solidification, it was filtered, washed with ice water and recrystallized from ethyl acetate/hexane to give the pure β-acetamido ketone. For all the substrates in Table 3, the reactions were stirred for 12 h, then 50 mL of water was added. The mixture was extracted with ethyl acetate (3×20 mL), the extracts were washed with water (3×20 mL), dried over Na_2SO_4 and the solvent was removed using a rotary evaporator. The crude mixture was recrystallized from ethyl acetate/hexane and the solid product (mixture of diastereomers) was isolated. For the recovery of the catalyst, the aqueous layer was evaporated under reduced pressure, and the residue reused in subsequent reactions without losing any significant activity. The spectral data of some representative β-acetamido carbonyl compounds are given below.
β-Acetamido-β-(3,4,5-trimethoxyphenyl)propiophenone (entry 10, Table 2): Solid; mp: 159 °C. IR (KBr): 3277, 1687, 1647, 1592, 1560, 1126, 1002 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.03 (s, 3H), 3.38 (dd, $J = 5.2$ Hz, $J = 16.4$ Hz, 1H), 3.70 (dd, $J = 5.2$, 16.8 Hz, 1H), 3.77 (s, 3H), 3.79 (s, 6H), 5.45 (m, 1H), 6.52 (s, 2H), 6.67 (br, d, $J = 6.8$ Hz, 1H), 7.43 (t, $J = 7.2$ Hz, 2H), 7.55 (t, $J = 6.4$ Hz, 1H), 7.88 (d, $J = 7.6$ Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.59, 43.28, 50.58, 56.18 (2C), 60.78, 103.77, 103.89, 127.97 (3C), 128.59 (3C), 133.43 (2C), 136.56, 153.11, 169.21, 198.51. Anal. Calcd for $C_{20}H_{23}O_5N$ (357.40): C, 67.21; H, 6.49; N, 3.92; found C, 67.29; H, 6.42; N 3.82. *Ethyl 2-benzoyl-3-acetamido-3-(p-nitrophenyl)propionate* (entry 7, Table 3): (mixture of diastereomers) data for the major isomer: IR (KBr): 3303, 1724, 1688, 1649, 1540, 1521, 1348, 1298, 1173 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.22 (t, $J = 6.8$ Hz, 3H), 2.09 (s, 3H), 4.18 (q, $J = 6.8$ Hz, 2H), 4.98 (d, $J = 4.4$ Hz, 1H), 5.97 (dd, $J = 4.4$, 9.2 Hz, 1H), 7.42 (t, $J = 7.6$ Hz, 2H), 7.50 (d, $J = 8.8$ Hz, 3H), 7.57 (t, $J = 7.2$ Hz, 1H), 7.79 (d, $J = 7.2$ Hz, 2H), 8.10 (d, $J = 8.8$ Hz, 2H). Anal. Calcd for $C_{20}H_{20}N_2O_6$ (384.39): C, 62.50; H, 5.24; N, 7.29; found C, 62.38; H, 5.18; N, 7.36.

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Bromodimethylsulfonium bromide mediated Michael addition of amines to electron deficient alkenes

Abu T. Khan,[a,*] Tasneem Parvin,[a] Sarifuddin Gazi[a] and Lokman H. Choudhury[b]

[a]*Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781 039, India*
[b]*Department of Basic Sciences and Social Sciences, North-Eastern Hill University, Shillong 793 022, India*

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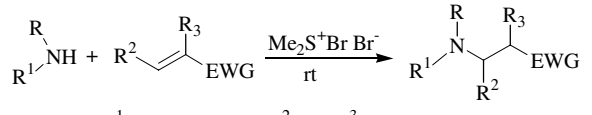
Abstract—Bromodimethylsulfonium bromide has been found to be an efficient catalyst for the Michael addition of a wide variety of amines to electron deficient alkenes at room temperature. The protocol is very simple and chemoselective. Aliphatic and benzylic amines undergo conjugate addition within a very short period under solvent-free conditions and provide excellent yields of products.

The conjugate addition of amines to electron deficient alkenes is an important and widely used transformation in organic synthesis owing to the importance of the resultant β-amino ketones, esters, nitriles or amides. It provides an easy route to β-amino acid derivatives as well as for the synthesis of heterocycles containing a β-amino carbonyl unit.[1] These β-amino carbonyl compounds are versatile synthetic intermediates for the synthesis of a variety of biologically important natural products, antibiotics and are useful in fine chemicals and pharmaceuticals.[2] The conventional method for the preparation of these compounds is via the Mannich reaction;[3] however, it has several shortcomings including long reaction times, low yields and harsh reaction conditions.

An alternative method for preparing these compounds is via Michael addition. Both from an atom economic point of view as well as simplicity of the procedure, the Michael addition is the preferred method for the preparation of β-amino carbonyl compounds. Either acid or base can be used as a promoter for this transformation. Over the years, numerous methods have been developed using a variety of reagents such as $SnCl_4$/$FeCl_3$,[4] $InCl_3$,[5] $CeCl_3{\cdot}7H_2O$–NaI,[6] $Yb(OTf)_3$,[7] $Cu(OTf)_2$,[8] CAN,[9] $Bi(NO_3)_3$,[10] $Bi(OTf)_3$,[11] $LiClO_4$,[12] KF/alumina,[13] SmI_2,[14] etc. Recently, additional methods have been reported, among them $Cu(acac)_2$/ionic liquid,[15] ionic liquid/quaternary ammonium salt in water,[16] boric acid in water,[17] β-cyclodextrin,[18] $ZrOCl_2{\cdot}8H_2O$,[19] borax,[20] etc., are notable. Although these methods are quite useful, many suffer from limitations such as the requirement for a large excess of reagents, long reaction times, harsh reaction conditions and also involvement of toxic solvents such as acetonitrile or 1,2-dichloroethane. Hence, there is a need to develop a convenient, environmentally friendly method for conjugate addition of amines to electron deficient alkenes.

Bromodimethylsulfonium bromide (BDMS) is a readily accessible, cheap and highly effective reagent[21] as well as a catalyst for various organic transformations.[22] In continuation of our work on the development of new synthetic methodologies, we have observed that



R= H/ alkyl; R^1= alkyl/benzyl; R^2= H; R^3= H/Me; EWG = CN, COMe, COEt, $CONH_2$

Scheme 1.

* Corresponding author. Tel.: +91 361 2582305; fax: +91 361 2690762; e-mail: atk@iitg.ernet.in

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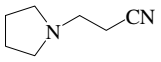
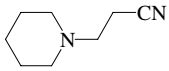
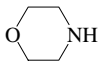
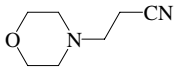
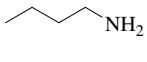
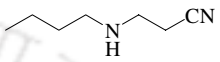
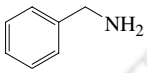
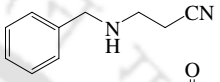
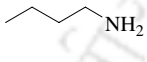
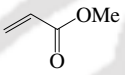
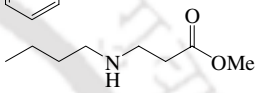
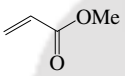
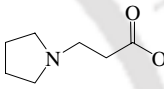
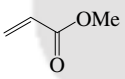
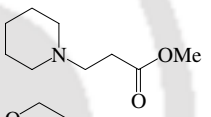
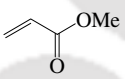
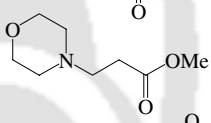
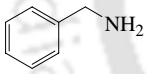
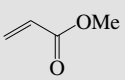
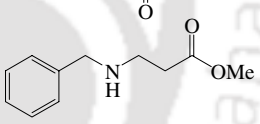
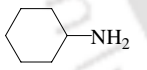
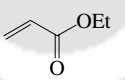
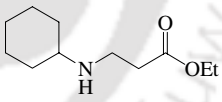
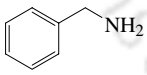
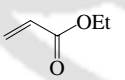
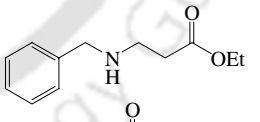
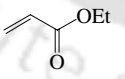
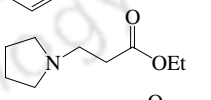
bromodimethylsulfonium bromide efficiently catalyzes the conjugate addition of various amines to electron deficient alkenes at room temperature (Scheme 1).

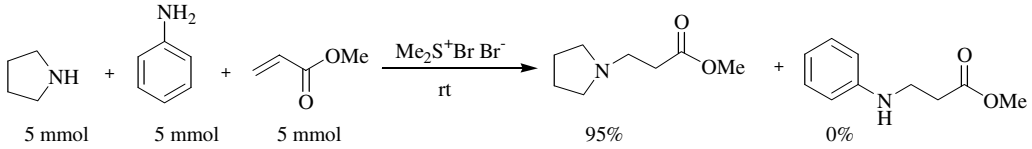
In a preliminary experiment pyrolidine (5 mmol) was treated with acrylonitrile (5 mmol) in the presence of bromodimethylsulfonium bromide (0.25 mmol) under

Table 1. Bromodimethylsulfonium bromide mediated Michael addition of amines to conjugated alkenes under solvent-free conditions

Entry	Amine **a**	Unsaturated alkene **b**	Time (min)	Product[a] **c**	Yield[b] (%)
1			5		98
2			5		99
3			5		93
4			10		92
5			15		91
6			15		85
7			5		97
8			5		96
9			5		97
10			15		84
11			10		85
12			20		89
13			5		94
14			20		88
15			15		83
16			5		91
17			15		89
18			120		0

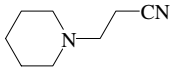
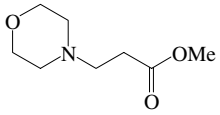
[a] All the products were fully characterized by recording IR, ^{1}H, ^{13}C NMR and elemental analyses.

[b] Isolated Yields.



Scheme 2. Chemoselective conjugate addition of aliphatic amines in the presence of aromatic amines.

Table 2. Comparison of the present protocol with reported methods

Product	Catalyst[a] (mol %)	Reaction conditions/solvent	Time min/[h]	Yield[b] (%)
	$LiClO_4$ (100)[12]	rt/solvent-free	[1]	80
	$ZrClO_4{\cdot}8H_2O$/montmorillonite (0.075 g/mmol)[19]	rt/solvent-free	15	94
	CAN (10)[9]	Ultrasonication/THF	20	96
	H_3BO_3 (10)[17]	rt/H_2O	[1.5]	95
	Borax (10)[20]	rt/H_2O	[2]	90
	β-Cyclodextrin (100)[18]	rt/H_2O	[6]	84
	BDMS (5)	rt/solvent-free	5	99
	$ZrClO_4{\cdot}8H_2O$/montmorillonite (0.075 g/mmol)[19]	rt/solvent-free	35	76
	H_3BO_3 (10)[17]	rt/H_2O	[3]	85
	Borax (10)[20]	rt/H_2O	[3]	92
	BDMS (5)	Solvent-free	5	97

[a] Corresponding reference.
[b] Isolated yield.

solvent-free conditions at room temperature, providing the corresponding Michael adduct, exclusively, within 5 min in 98% yield (Table 1, entry 1). Product **1c** was characterized by ^1H and ^{13}C NMR spectroscopy as well as by comparison with authentic data.[23] Interestingly, the crude product obtained after aqueous work-up was found to be pure as there was no detectable amount of impurities or starting material in the ^1H NMR of the crude product. Encouraged by this, other secondary amines such as piperidine and morpholine (entries 2 and 3) were treated with the same Michael acceptor under the same experimental conditions[24] and the corresponding Michael adducts were isolated in excellent yields within a short time. Similarly, the primary amines *n*-butylamine and benzylamine (entries 4 and 5) underwent Michael addition smoothly providing good yields of the desired adducts. The present protocol represents an improvement over some of the recently reported methods in terms of reaction time as well as % yields obtained. Similarly, the α,β-unsaturated esters methyl acrylate and ethyl acrylate reacted with a wide variety of amines under the same conditions to afford very good yields of the corresponding Michael adducts (entries 6–13). Methyl methacrylate and methyl *trans*-cinnamate also underwent Michael addition with morpholine and pyrrolidine, respectively, without any difficulty (entries 14 and 15).

Likewise acrylamide underwent Michael addition with pyrrolidine and morpholine (entries 16 and 17) in very good yields. However, in an attempt to react an aromatic amine, the same protocol was unsuccessful and yielded only the starting material even after 2 h of stirring (entry 18). Interestingly, the present protocol could be used on a 100 mmol scale using only 2 mol % of catalyst.

Next, to exemplify the chemoselectivity of this present protocol a competitive study was carried out using a mixture of 5 mmol of pyrrolidine, 5 mmol of aniline and 5 mmol of methyl acrylate as shown in Scheme 2. The Michael adduct of pyrrolidine was obtained exclusively and clearly reflects the chemoselectivity of aliphatic amines versus aromatic amines.

The catalytic activity of bromodimethylsulfonium bromide was ascertained by the fact that in the absence of the catalyst, the reaction of pyrrolidine with acrylonitrile afforded only a 20% yield of adduct even after 6 h of stirring at room temperature. The efficacy and generality of the present protocol can be realized by comparing some of the results presented here with recently reported methods as shown in Table 2, which compares reaction time, % yields and reaction conditions.

In summary we have developed a simple and efficient methodology[24] for the conjugate addition of amines to electron deficient alkenes using bromodimethylsulfonium bromide as an inexpensive and efficient catalyst. This method demonstrates the potential of BDMS as an efficient promoter.

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24. *Representative experimental procedure for the Michael reaction* (**1c**): To a mixture of acrylonitrile (265 mg, 5 mmol) and pyrrolidine (355 mg, 5 mmol), bromodimethylsulfonium bromide (56 mg, 0.5 mmol) was added and the reaction mixture stirred at room temperature. The reaction was complete within 5 min as indicated by TLC. The reaction mixture was extracted with ethyl acetate (2×20 mL) and the combined extract was dried over Na_2SO_4 and evaporated to leave a crude product, which was sufficiently pure as ascertained by ^1H NMR of the crude product. The Michael adduct (Table 1, entry 1) was characterized by recording IR, ^1H and ^{13}C NMR spectra as well as by comparison with reported data.[23]