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Towards the Synthesis of Magnesidin

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Towards the Synthesis of Magnesidin

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TABLE OF CONTENTS

List of Tables

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

List of schemes

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

List of Figures

Chapter 1

Chapter 2

Chapter 3

Chapter 5

Abstract:

Magnesidin is a magnesium chelate of the 3-hexanoyl and 3-octanoyl tetramic acid derivatives isolated from *Psuedomonas magensiorubra*. Its activity against gram-positive bacteria was found to be a specific target for Gingivitis, a dental plaque. Although the synthesis of magnesidin has been reported earlier, it was not reproducible. The highly polar nature and it's ability to exhibit tautomerization makes their chemical behavior complex and difficult to predict its structure. A variety of reactions and an in depth understanding of the chemical structure is necessary to attain the synthesis of these compounds.

This dissertation focuses on addressing the attempts towards the synthesis of Magnesidin by identifying the important intermediates necessary for the synthesis as β-keto esters, α,β-unsaturated amino esters. The focus of the work has been addressed by developing a TAG molecule approach, which is similar to the concept of solid phase synthesis except for the fact that the TAG molecule can be identified under UV and also can be detected using various spectroscopic techniques. Microwave synthesis has been explored and applied in to the synthesis of benzyl mono and di bromination, 1,3-benzodioxoles have been established. The benzyl mono bromination is applied to synthesize the TAG molecule, which is then applied in developing a method of synthesis for β-keto esters. The azide approach was used to synthesize the α,β-unsaturated amides, which are another essential class of compounds in the synthesis of magnesidin.

Key Words: Magnesidin, tetramic acids, gingivitis, β-keto acids, α,β-unsaturated amino esters, 1,3-benzodioxoles, tautomerization, microwave synthesis and bromination.

Chapter I

Introduction

1.1 Tetramic Acids:

The tetramic acids has were known ever since its simple derivatives were prepared in the early 1940's, but its key importance was realized only in 1960's when they were identified as important structural unit in many natural products. The biological activity of tetramic acids extends from potent antibiotic, antiviral and anti-ulcerative properties, cytotoxicity and mycotoxicity, the inhibition of tumors (in mice and humans) as well as fungicidal action while some Tetramic acids are responsible for pigmentation of certain molds and sponges[1-7]. This attracted the interest of not only natural products chemists, but also of chemical ecologists, medicinal and synthetic chemists. The most common tetramic acids exist as a 3-acyl derivative, and a very few exists as a 4-*O*-alkyl ether derivative. This makes the synthesis of these compounds very challenging and would be a great contribution to synthetic and medicinal chemistry. These target compounds have a very complex chemical behavior and the architectural framework includes not only stereo centers but also many other synthetically challenging substrates[8,9]. For these reasons, there are either no or only few synthetic methodologies available for many classes of these compounds. Some of the synthetic equivalents of tetramic acids were also subjected to clinical investigations and are in the process of drug development [10].

Although the basic structural unit of the tetramic acid does not look very complex, the various reactive sites on the tetramic acid make it more complex to be synthesized. The primary reactions of the tetramic acid ring can be summarized as follows:

- Attack by electrophiles like aldehydes, bromine, nitrating agents on C-3.
- Attack by nucleophilic species like hydrazine on C-2 and C-4.
- Acylation on position N-1, C-3 and O-4.
- With organometallic bases or metallation at C-3.
- Substitution at C-5.

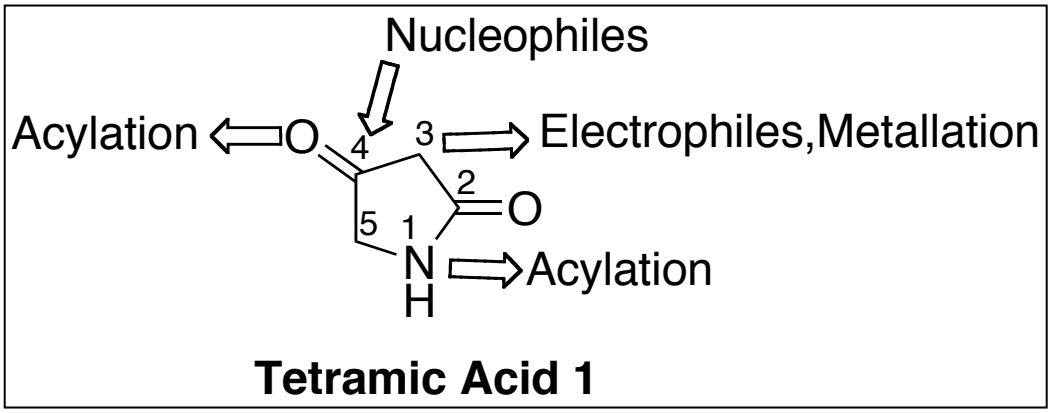


Figure 1.1. The reactive skeleton of tetramic acid 1.

1.1.1 Structure and acidity of tetramic acid:

Tetronic acid, which is very close in structure to tetramic acid, is more explored in comparison to tetramic acids. It is known much earlier and was first prepared[11] in 1896 and its pKa is about 3.76, making it a strong acid in aqueous solution[12]. The solid state IR spectrum proves that it exists in enolic form **2** which showed absorptions at 1690 cm^{-l} for the carbonyl and 1635 cm^{-l} for the alkenyl (C=C) stretching[13]. It was further supported by UV absorptions with λ_{max} at 223 and 248 nm in aqueous ethanol. Whether it exists in the enol **2** or enolate **3** forms in fig 2 is dependent on the pH of the solution[14].

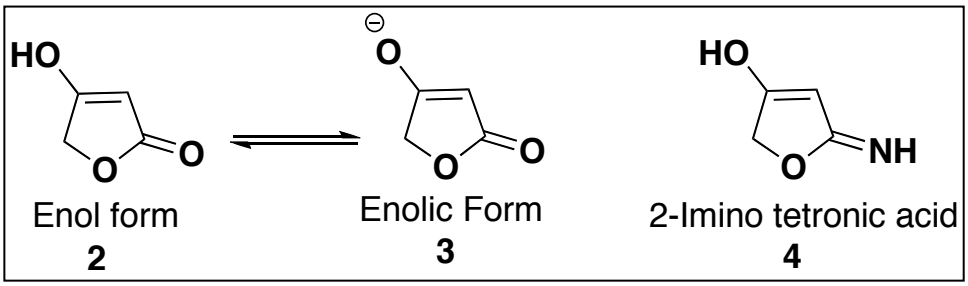


Figure 1.2. Enol and enolic forms of tetronic acid and 2-imino tetronic acid.

As tetramic acid is a nitrogen analogue of tetronic acid, and was assumed to exist in the enol form **5**, however exits in keto form **1** and was first synthesized[15] in 1972. There were few publications that reported tetramic acid prior to then[16,17] but it was later proven that the synthesized compound was 2-iminotetronic acid[18,19] **4** and not tetramic acid **1**. The tetramic acid **1** is much weaker acid[15] with pK_a 6.4 in aqueous solution as compared to its oxygen analogue **2.** The solid state infrared spectrum of **1** shows absorptions at 3230 cm^{-1} (N-H stretch), 1696 cm^{-1} (C=O), 1670 cm^{-1} (N-H bend) and 1782 cm^{-1} (C=O) from the second carbonyl at C-4 unlike **2** or **3**, which is further supported by the negative ferric chloride test with **1.** With the fact that a solid-state existence involves in H bonding, the spectrum was also recorded on a solution phase and C4 band was still observed. The UV spectrum however shows a single absorption (λ_{max} 260 nm) due to the corresponding enolate species **6** with the intensity being strongly dependent on the pH of the solution. To conclude, in aqueous solution, the ionic form **6** exists predominantly in equilibrium with the 2,4-diketo form **5** while the enol form **4** is absent.

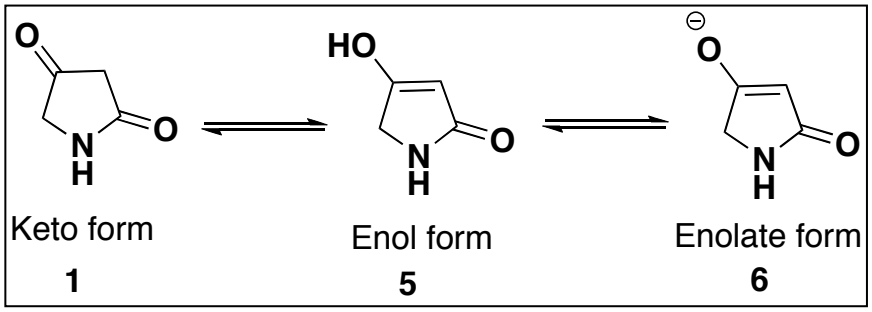


Figure 1.3. Keto, enol and enolate forms of tetramic acid:

The acidity of tetramic acids with a substituent on the 3rd position is comparable to tetronic acids. For example, the pKa of the tetramic acid with acyl substituent **7** on 3rd position is in the range of 3.0-3.5[20,21] and that of the tetramic acid with alkoxy substituent **8** is about 2.3-2.5[12].

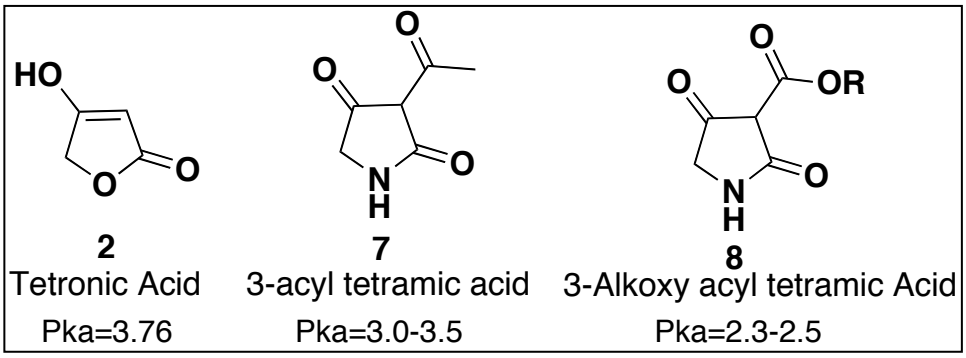


Figure 1.4. Pka comparison of tetronic and tetramic acids substituted at 3.

1.1.2 Tautomerization in Tetramic Acid:

The enolization of the tetramic acid was observed in Proton NMR, however the spectra is complicated due to the presence of other tautomeric forms. The UV absorption spectra for 3-acyltetramic acids and analogues[20] shows an absorption of red light indicating the conversion of enol forms with λ_{max} 220 and 277 nm to enolate forms with

λ_{max} 240 and 279 nm. The 3-acyl tetramic acids **7** exist in two sets of rapidly interchanging internal tautomers **9,10** and **11,12**. The tautomers **9** and **10** just like **11** and **12** are obtained by mutual proton transfer and the two sets **9,10** and **11,12** are inter-converted quite fast amongst themselves. However the tautomerization between sets of **9,10** and **11,12** is slow and detectable on NMR time scale.

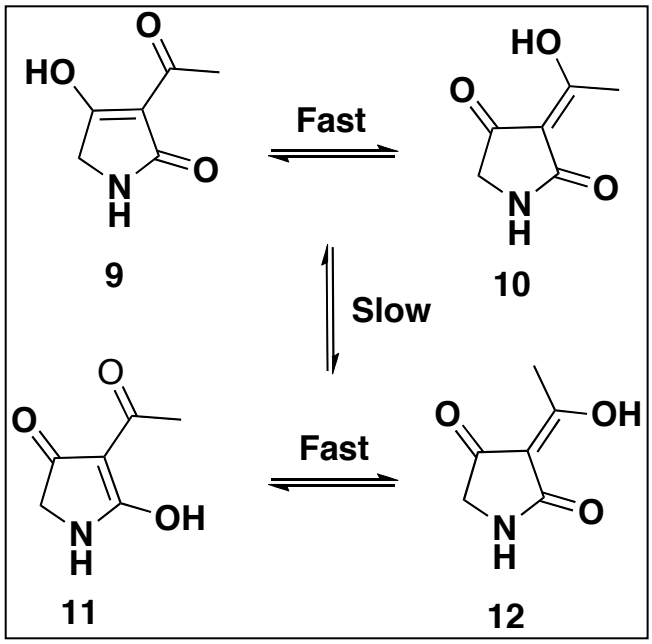


Figure. 1.5. Tautomeric forms of acyl tetramic acid.

The ratios of these tautomers for some specific 3-acyltetramic acids like **13, 14,** and **15** were reported by Steyn and Wessels [22,23]. The ratio of tautomers **9:10:11:12** proposed for these tetramic acids was 5:15:0:80. They were however in contradiction to Yamaguchi's calculations which were based on electron density values[24]. Steyn's calculations were based on the observed chemical shifts and NMR (proton and carbon). The study of ratio of tautomers concluded that the 3-acyl tetramic acid exists predominantly in *exo-enolic* form analogous to **12**. Semi empirical methods like SCF-

MO, ΔH_f calculations, also predict *exo-enolic* form as major tautomer. The results have become more obvious with the X-ray crystallographic structural determination of the tetramic acid **13**, which existed in the *exo*-enolic form[23].

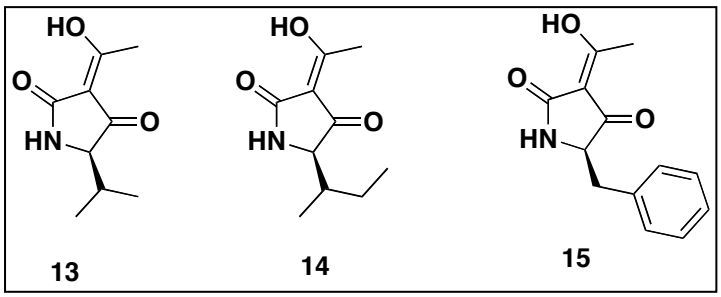


Figure. 1.6. 3-Acyl tetramic acids tested for tautomer ratio.

The idea that the *exo*-enolic form is the principal tautomer was confirmed from the conclusions of X-ray crystal structures[25,26] of the antibiotic Triandamycin A **16** and that of α-Cyclopiazonic acid **17.** The above-mentioned ratios are good only for simple 3-acyltetramic acids, with further more substitution; the ratio and existence of tautomers would differ. In case of N-Acyl tetramic acids[27], tautomer analogous to **9** would be major one, as the possibility of H-bonding with the C-4 carbonyl increases, with the lone pair on nitrogen being no longer able to increase the proton acceptor ability of C-2 carbonyl.

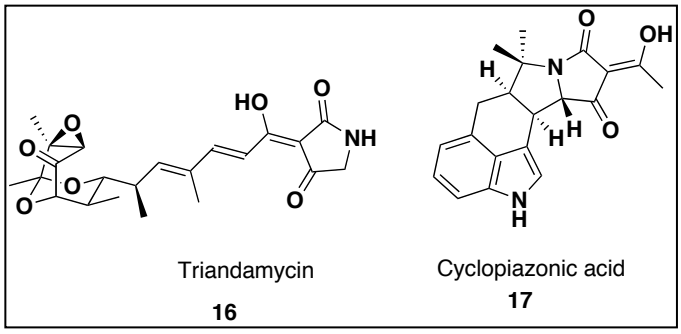


Figure 1.7. Structures of triandamycin A **16** and α-cyclopiazonic acid **17.**

1.2 Naturally Occurring Tetramic Acids:

The tetramic acids that exist in nature can be classified on the basis of their structure. The structural differences are commonly attributed to the substituents on the ring. The discussion in this part focuses on variation of tetramic acids based on their substitution at various centers on the ring. The substitution at C-3 is a key aspect for the biological activity of a tetramic acid and the variation at this position is greatly exhibited by these natural products. Positions 2 and 4 are carbonyls and there are very rare and few compounds with an ethereal linkage at 4 position and hence this classification is ignored for this part of the discussion. The classification of the tetramic acids can be listed as follows:

- 3-Acyl teramic acids.
- Dienoyl tetramic acids.
- Polyenoyl tetramic acids.
- Decalinoyl tetramic acids
- Macrocyclic tetramic acids
- N-Acyl tetramic acids.

1.2.1. 3-Acyl Tetramic Acids:

Tetramic acids with an acyl substitution on the third position (C-3) are most commonly found tetramic acids in nature. Tenuazonic acid **18** is one of the simplest 3-acyltetramic acids with a chiral center at C-5. It was originally isolated from the culture filtrate of *Alternaria tenuis* auct[28]. A great interest has been attributed to this compound because of its extreme biological activity[29-31]. It doesn't exhibit great deal of antibacterial activity

[32] but has an inhibitory effect[33] on several viruses when induced at a high dosage including poliovirus MEF-I, ECHO-9, parainfluenza-3, vaccinia, and herpes simplex (HF). It also involves in the inhibition of amino acid incorporation into microsomal protein of humans, there by inhibiting the growth of human adenocarcinoma in the embryonated egg. Although it does exhibit a wide range of biological activity, its value has been limited due to its extreme toxicity**.** When the microbes have been fed with L-valine, leucine[34] or L-norvaline[28,] they produce isopropyl **19,** isobutyl **20,** or n-propyl **21** tenuazonic acid analogues. These were found to have biological activity similar to, though less potent than, **18** itself.

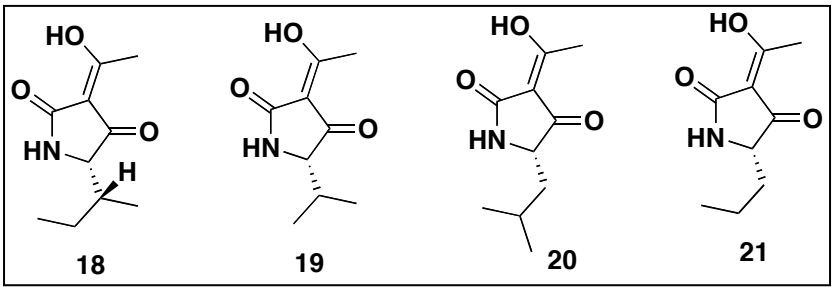


Figure. 1.8 Structures of tenuazonic acid and its variation at C-5 substitution.

Reutericyclin is another tetramic acid that is acylated at C-3 and at position 1(on N) and is isolated[35,36] from *Lactobacillus rueteri*. It is active towards many gram positive bacteria like sourdough lactic acid bacteria, *Staphylococcus aureus, Listerica innocua,* and some pathogens like *Enterococcus faecium* the gram-negative bacteria are resistant to Reutericyclin. It not only exhibits various biological functions but is also used as a preservative in food industry. Pachydermin is an unusual oxalylated tetramic acid that was isolated[37] from the New Zealand basidiomycete *Chamonixia pachydermis.* It exhibits mild antibiotic conditions but is believed to show the activity after it undergoes

degradation in acidic conditions. α-Cyclopiazonic acid, a mycotoxic tetramic acid was isolated by Holzapafel and workers from the fungus *Penicillium cyclopium* Westling[38]. They studied the acid's structure and relative stereochemistry with the help of proton NMR spectroscopy of **17** and its degradation products. Investigation of the biosynthetic route[39-42] of **17** gave an idea of the building blocks, which are L-tryptophan, mavalonic acid and acetate. However the assembly of these intermediates produced β-cyclopiazonic acid **22**, which upon further undergoes ring closure by *syn* addition[43] to give α- cyclopiazonic acid **17**. The imino derivative of the acid **23** has also been obtained by following a similar culture. However, the source of ammonia is not clear, if it is from fungus or by natural chemical reaction, aminolysis of **17.** α-Cyclopiazonic acid acts as an antioxidant and is a potent inhibitor of calcium uptake[44-46] and Ca^{2+}ATP-ase activity in sarco and endoplamic reticulum.

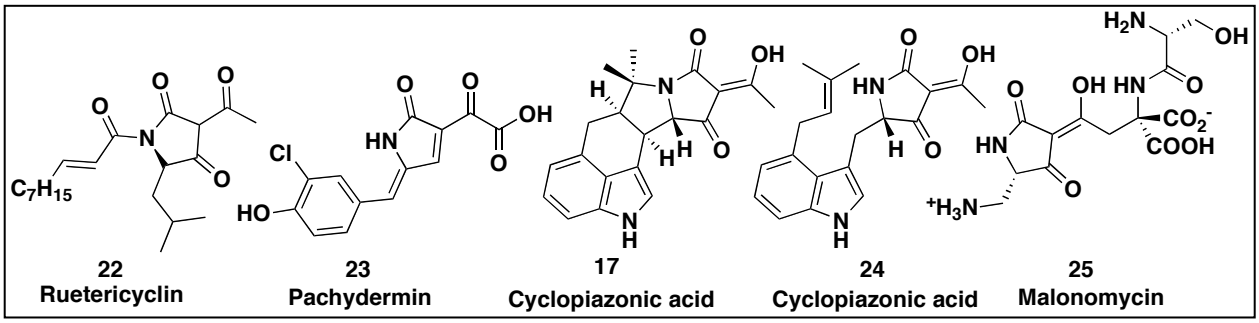


Figure 1.9. Structures of ruetericyclin, pachydermin, α,β-cyclopiazonic acid and malonomycin.

Malonomycin **26** is also a tetramic acid that belongs to similar family and is isolated from *Streptomyces rimosus* var. paromomycinus, which is antiprotozoal and is specifically potent against typanosomes[47]. The unique structure of Malonomycin has

been deduced by van der Baan and coworkers[48, 49]. Aminomalonic acid is the key component responsible for biological activity, because Mono-decarboxylation of this functional group by refluxing in water, led to complete loss of biological activity[49].

1.2.2 Dienoyltetramic acids:

Dienoyltetramic acids are tetramic acids with 1-oxo-pentadienyl substituent at C-3 position in the ring. The first one of its kind streptolydigin **27** was isolated in 1956 from the *Streptomyces lydicus*[50]. It is responsible for inhibition of terminal DNA tranferase and RNA polymerase enzymes and is also effective towards gram-positive bacteria. The structure activity relation studies concluded that the 3-dienoyl substituent is crucial[51]. Oxidative degradation[52,53] of streptolydigin gives streptolic acid **28** and ydiginic acid **29** which were characterized by NMR, mass and UV spectroscopy.

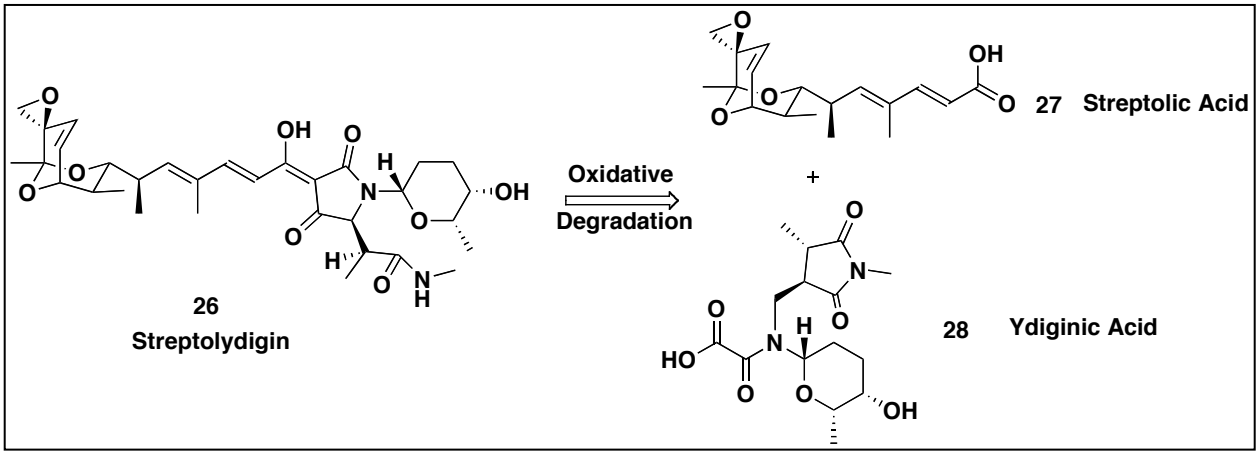


Figure. 1.10. Oxidative degradation of streptolydigin.

Another tetarmic acid that fallsin this class and is very close in structure and behavior to **27** is Tirandamycin A **16**, isolated[54] form the culture of *Streptomyces tirandis*. Its

biological activity is also quite comparable[55,56] to Streptolydigin **27** except that its inbition of DNA transferase is that prominent[51]. Tirandamycin B **30** isolated[57] from also behaves as *Streptomyces flaveolus* is analogous to **16** in structure but also in biological properties. A structural hybrid of **16** and **30** was isolated[58] from the fermented beers of *Streptomyces* sp.AB-1006A-9 and was called Tirandalydigin, showed an antimicrobial spectrum not very different form these other compounds[59].

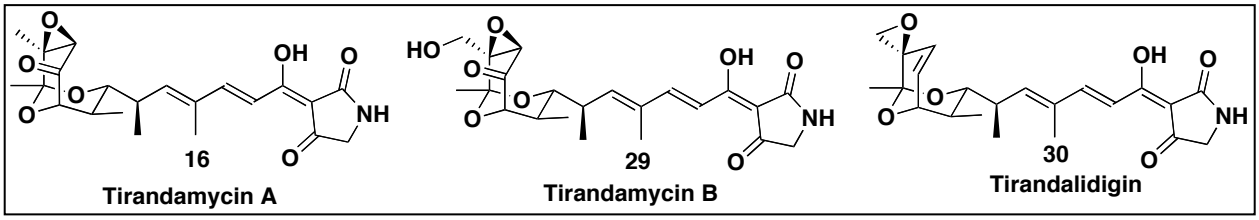


Figure. 1.11. Structural analogues of streptolydigin **27**.

Another class of compounds that act as metabolites and have similar structure is Nocamycin derivatives. Bu-2313A **32** and Bu-2313B **33** (known as Nocamycin I) were isolated[60,61] from an unidentified oligospotic actionomycete strain. These two compounds have a great range of biological activity and are good for both gram positive and negative bacteria. Moreover they were effective against aerobic and anaerobic bacteria like *Streptococci,* with **33** being twice as effective as **32.** Later in 1977, another tetramic acid Nocamycin II **34** has been added to this family. However the biological activity[62] of 34 is surprisingly not the same as **32** and **33,** although a common biosynthetic path way has been postulated for all these compounds.

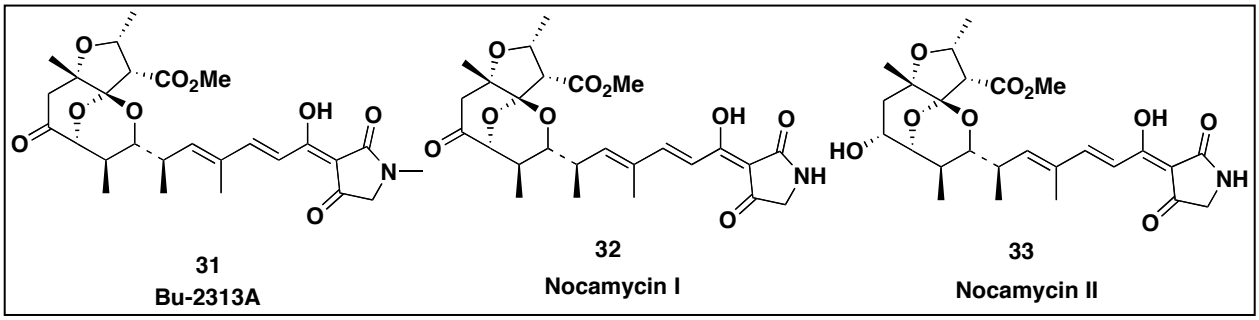


Figure. 1.12. Structures of nocamycin related tetramic acids.

1.2.3 Decalinoyl Tetramic Acids:

This is a special class of tetramic acids because the total synthesis of many of these compounds is still not reported. Equisetin is the first tetramic acid of this kind to be isolated[63] from *Fusarium equiseti* in 1974. It has varied biological activity and exhibits antibiotic function, HIV inhibition, cytotoxicity and even DNA binding in Mammals[64-66]. Trichosetin is the nearest tetramic acid in structure to equisetin and was isolated[67] from dual culture of *Trichloro derma harzianum* and *Bacillus subtillis*. Trichosetin is a *N*-desmethyl homologue of equisetin and coniosetin[68], altersetin[69] and paeciloestin[70] are structurally close to equisetin. Trichosetin was found to be phytotoxic and it was observed in seeding growth assays. It also was found to show damaging effect on the mitochondria. Considering these factors, although Trichosetin is active biologically, its extreme biological toxicity has minimized its importance. Coinsetin, altersetin and paeciloestin are all active against gram-positive but are inactive towards gram-negative bacteria. However these compounds also exhibited an extent of toxicity with coinsetin being twice as toxic as the other two.

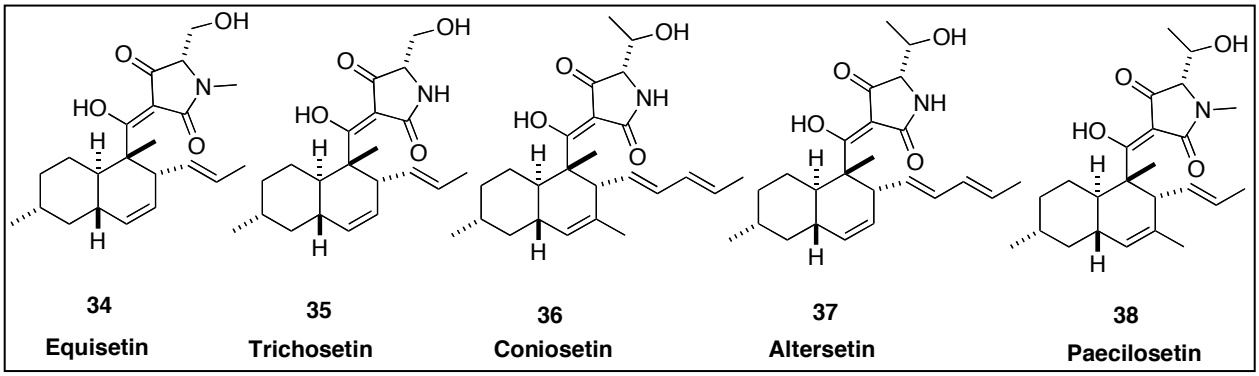


Figure. 1.13. Structures of decalinoyl tetramic acids.

1.2.4 Polyenoyl tetramic acids:

As the name suggests polyenoyl tetramic acids are the tetramic acids with polyenoyl substitution on the tetramic acid at position 3. Erythroskyrine **35** was one of the first tetramic acids identified as the important pigment of *penicillium islandicum* Sopp. It has a strong antibiotic action against *Staphylococcus* species[71]. Fuligorubin A **36,** another tetramic acid of this class has been isolated form *Fuligo Septica* which led to a series of compounds **40-42** derived from tyrosine, isolated[72] from *Leocarpus Fragilis*. However the importance of these compounds as biologically active compounds is not very clear and is limited to use as chelating agents and colorants. The polyenoyl tetramic acid with antibiotic activity has not been identified before the isolation[73] of Oleficin **40** from a strain of *streptomyces parvulus*. A little later α-Lipomycin **41** and β-Lipomycin **42** were isolated[74], which differ from **40** only in the chain length of the olefin connected on the C-3 of the tetramic acid. Both **41** and **42** are highly active against gram-positive bacteria but are in effective towards fungi. Oleficin **40** also plays an important role as ionophore especially for Mg2+ and Ca2+ ions in isolated rat liver mitochondria[75].

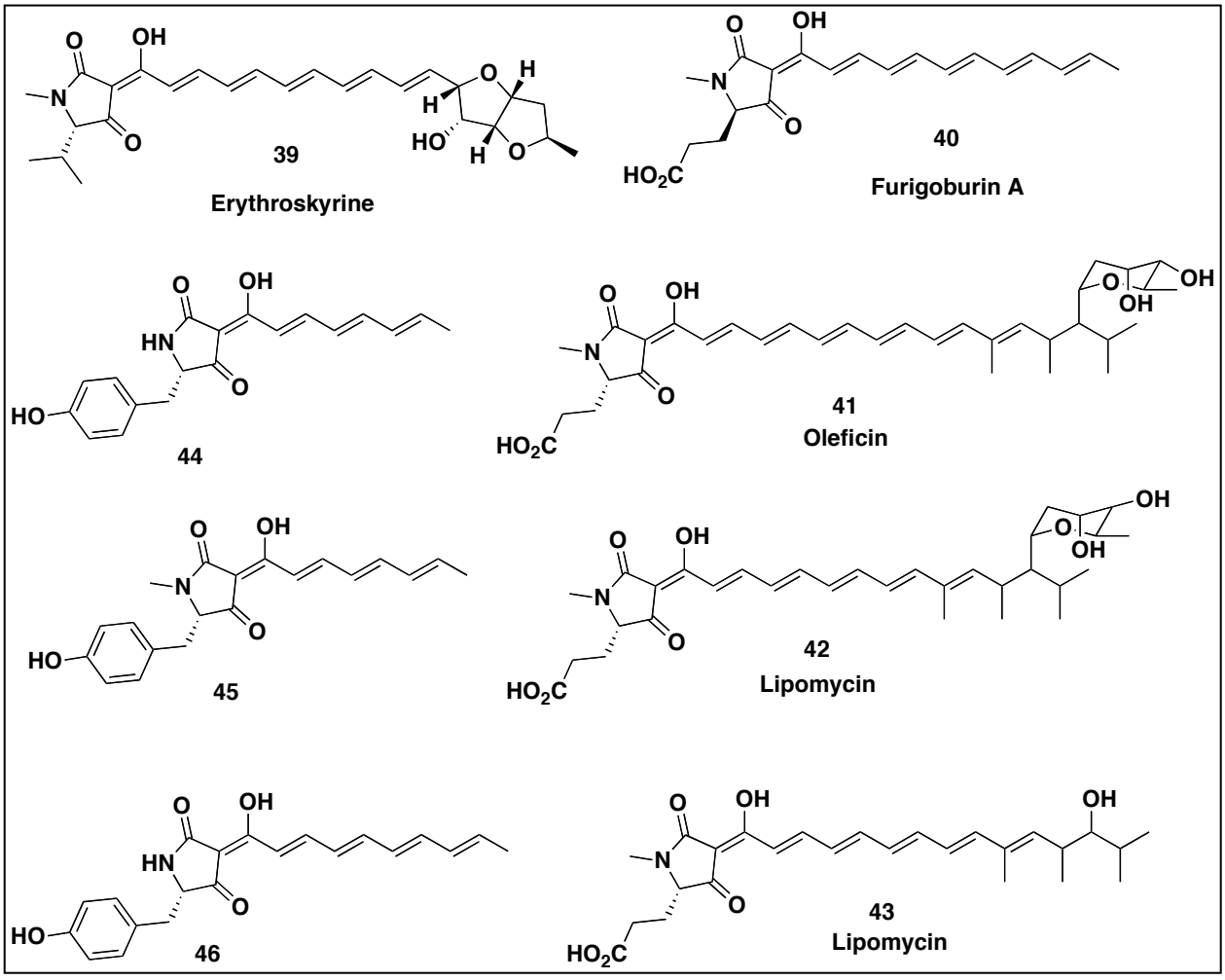


Figure. 1.14. Structures of polyenoyl tetramic acids.

1.2.5 Macrocyclic tetramic acids:

Ikarugamycin is a macro cyclic acid, isolated[76] from the culture broth of *Streptomyces phaeochromogenes* var. ikaruganensis Sakai. Other than antibiotic activity it showed *in vitro* antiamoebic, antiulcer[77] activity and a strong specific antiprotozoal behavior. Ikarugamycin is a 16-membered macro cyclic lactam and the *trans, anti, cis*-decahydro-*as*-indacene skeleton. Another antifungal compound isolated[78,79] from a *Streptomyces* strain is capsimycin **25** also called as antibiotic N-461**.** Heat-stable antifungal factor

(HSAF) is a secondary metabolite produced[80] by the bacterium *Lysobacter enzymogenes.* It is highly active against a variety of fungi. Discodermide is another macro cyclic tetramic acid close in structure to the above compounds and is isolated[81] from a deep-sea sponge of Caribbean called *Discoderma dissoluta.* A macrocyclic tetramic acid with cytotoxic activity against melanoma cells is Cylidramide, isolated[82] from marine sponge *Haliochondria cylindrata* Tanita. Macrocidin A and B are a unique set of macrocyclic tetramic acids, isolated[83] from *Phoma macrostoma* and act as weak plant pathogens.

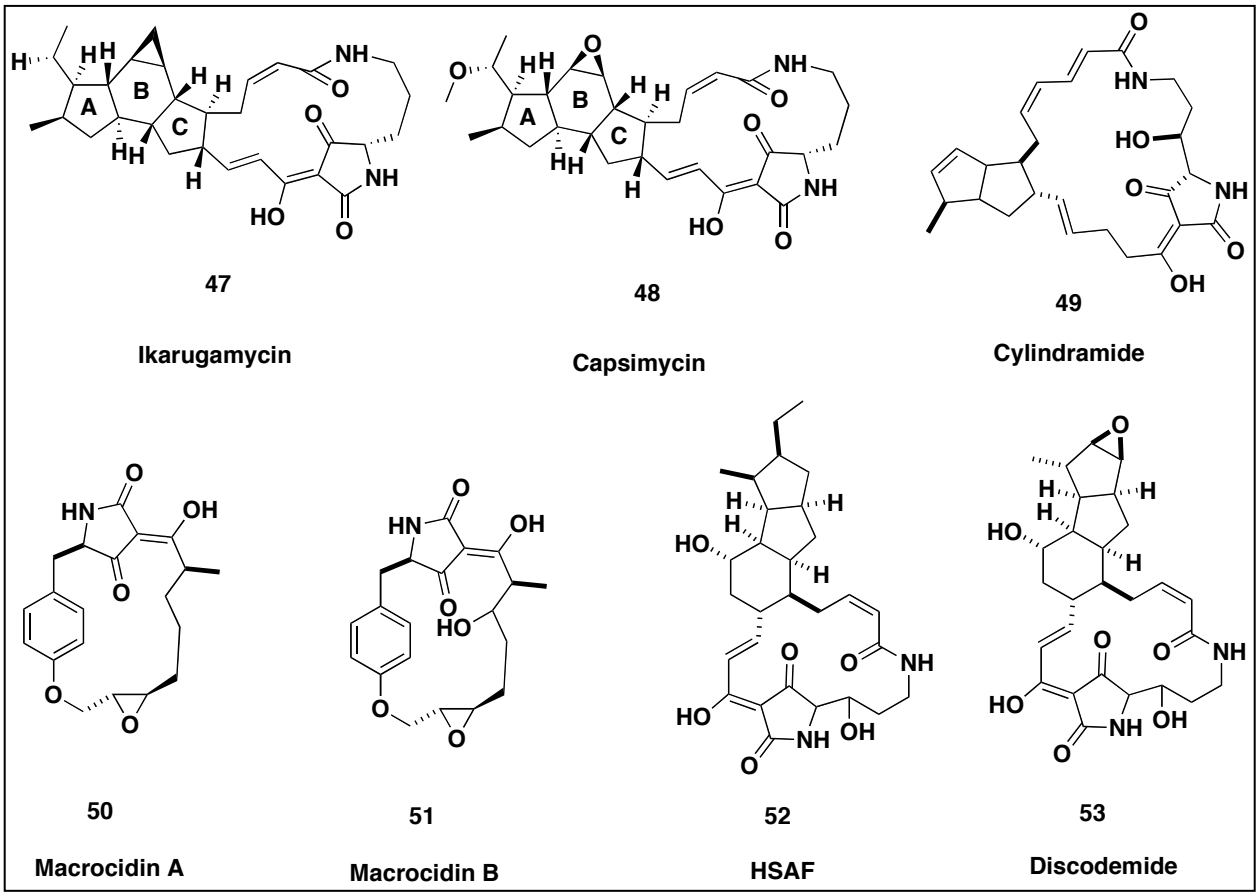


Figure. 1.15. Structures of macrocyclic tetramic acids.

1.2.6 N-Acyl tetramic acids

N-acyl tetramic acids are tetramic acids substituted by acyl derivatives at N-1 of the ring. Dysidin **43** was the first N-acyl tetramic acid to be isolated[84] from the indo Pacific sponge *Dysidea hebacea*. It was also the first chlorine containing tetramic acid and exists with ethereal linkage on C-4. Malingamide A **44,** is a little more complex chlorine containing compound, but is not biologically active[85] like **43** and was isolated from the marine *cyanophyte Lyngbya majuscula*. Magnesidin, another N-acyl tetramic acid with a spectrum of biological activity was isolated[86] as a magnesium salt from *Psuedomonas magnesiorubra*.

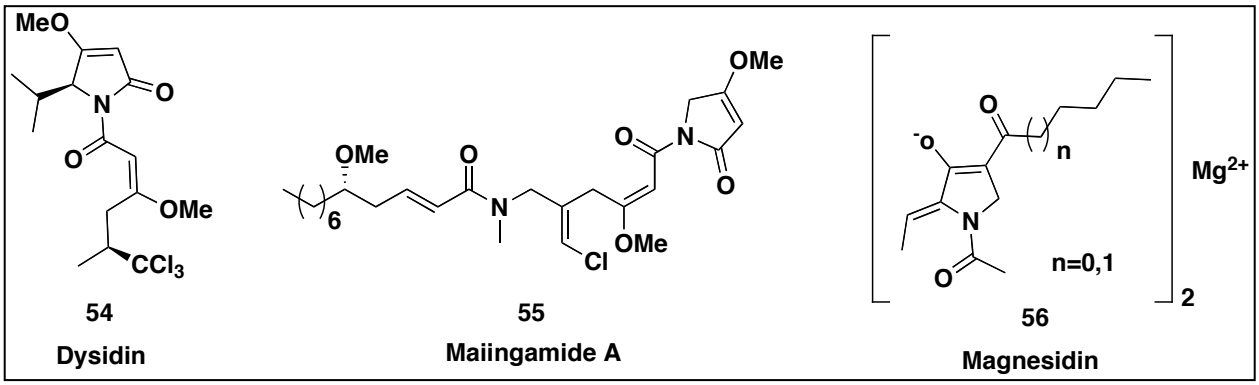


Figure. 1.16. Structures of dysidin, malingamide A and magnesidin.

The blue green algae from which Malingalide A was isolated also contained many other tetramic acids but lacked the long chain fatty acid and the chlorine substitution on it. A series of seven compounds were isolated[87,88] and named Pukeleimide A-G (**44-50**). The X-ray structure has determined that the structure is planar with the hydroxy and hydroxy methyl groups being out of plane.

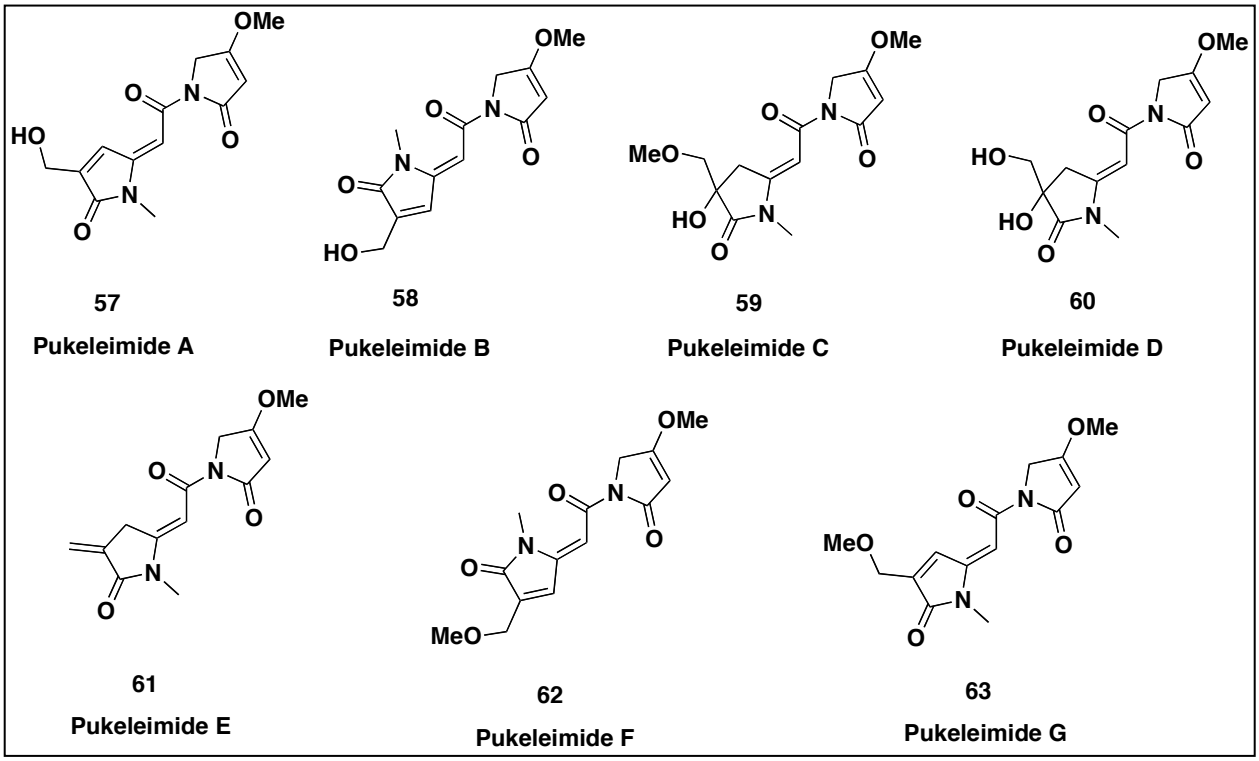


Figure. 1.17. Structures of pukeleimides (A-G).

Althiomycin **51** is another compound of this class, isolated[89] from *Streptomyces althioticus* and exhibited antibacterial activity. However it has become a very important compound due to its extremely low toxicity and activity against both gram positive and negative micro organisms[90]. Dolastain is another N-acyl tetramic acid that was isolated[91] from shell-less Western Indian Ocean mollusk *Dolabella auricularia*. It was observed to be a potent cytostatic agent against leukemia cells.

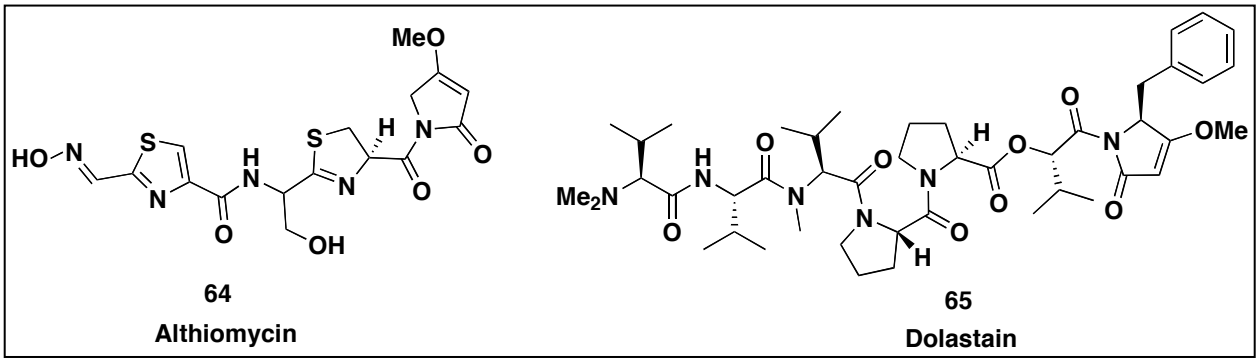


Fig. 1.18. Structures of althiomycin and dolastain.

1.3 Magnesidin:

Of all these tetramic acids, Magnesidin **56** is of a special interest of the dissertation and is the target molecule of the research. Magnesidin is an inseparable 1:1 mixture of the magnesium chelates of the 3-hexanoyl and 3-octanoyl tetramic acid derivatives[86,92,93]. It is a unique magnesium-containing compound and was the first reported example of a naturally occurring tetramic acid as a magnesium salt. It was isolated from a new *Pseudomonas* species called *Psuedomonas. magnesiorubra*, obtained from the surface washings of the marine green alga *Caulerpa peltata.*

1.3.1 Extraction and physical properties of magnesidin: Magnesidin **56** was extracted[93] from *Psuedomonas. Magnesiorubra by* following a step of procedures. Fermentations were carried out under immersed culture conditions for 30 hrs at 28^0 c, in a medium containing 2% glucose, 1.5% peptone, 0.5% yeast extract, 0.5% soluble starch, 3% NaCl, and 0.1% $MgSO_4.{}_7H_2O$ with the p^H being 7.4[94]. At the end of the fermentation, the cells that would contain the antibiotic were centrifuged and extracted

repeatedly with hot acetone until it becomes colorless. The orange extract was decolorized with activated charcoal and the filtrate was evaporated. The powdered Magnesidin thus obtained was purified and crystallized from methanol as colorless needles. It is soluble in ether, ethyl acetate, chloroform, acetic acid, methanol, ethanol, butanol and pyridine but insoluble in water. It is stable up to 121^0 c and over a range of pH between 2 and 8.

1.3.2 Tautomers of magnesidin:

Magnesidin exhibits all the four tautomers and they were studied using 2D NMR. The NOSEY spectrum revealed the cross peaks in this compound and the tautomers exist as shown in the fig. The ratio of external tautomers based on the NMR calculations was found to be 89:11[93,94] while the internal tautomers were inter-converted so fast that they are not recordable on an NMR time scale. The major tautomer mixture was found to be a and b while the minor was c and d.

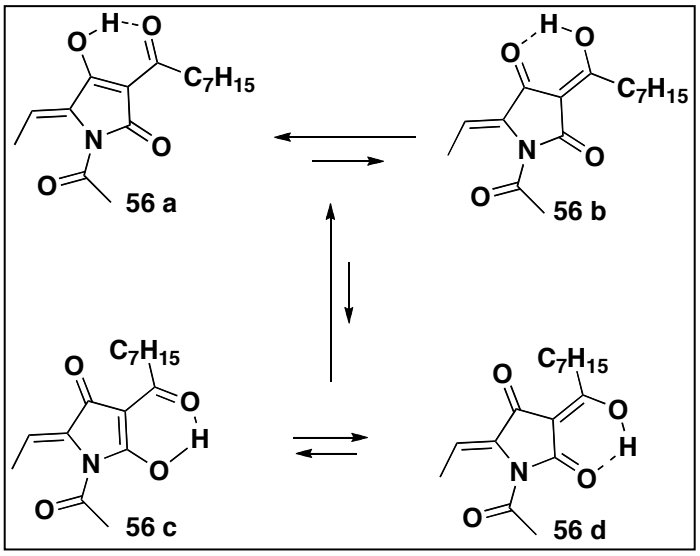


Figure. 1.19. Tautomers of magnesidin.

1.3.3 Antibacterial activity of magnesidin:

Magnesidin inhibits[95] gram-positive bacteria (MIC 2-7 g/mol), particularly spore bearers, and also prevents the decay of foodstuff caused by spore germinating organisms. Table 1 explains in detail the activity of Magnesidin against various gram-positive bacteria.

Table 1.1: Antibiotic properties of magnesidin.

S.No	Test Oraganism	Minimal Inhibitory Concentration (MIC)
1	*Bacillus subtilis* ATTC 6633	3
2	*Bacillus megatherium*	2
3	*Bacillus anthracis*	2
4	*Staphylococcus aureus* FDA 209P	*3*
5	*Staphylococcus albus*	4
6	*Sarcina lutea*	2
7	*Gaffkya tetagena*	5
8	*Streptococcus faecalis*	7
9	*Escherichia coli*	>100
10	*Salmonella typhimurium*	>100
11	*Proteus vulgaris*	>100

Along with its activity, it has been found mildly toxic, and so cannot be absorbed orally. There are several other tetramic acids that are active against gram-positive bacteria but the specific use of Magnesidin is prevention of gingivitis and reducing dental plaque. Its use as food preservative has also been reported but it has not much been explored.

1.4 Probable application of magnesidin for gingivitis:

Gingivitis is characterized by gingival inflammation and/or bleeding and is caused by plaque at and under the gingival margins. Epidemiological surveys indicate that an average of 50% of the adult population of the United States have gingivitis. Most people brush their teeth however; toothbrushes cannot effectively remove plaque at or under the gum line.

Floss is effective at removing plaque in locations, difficult to reach; however only about 20% of the US population use floss. Inconvenience is a commonly cited reason for not flossing. Since gingivitis is caused by plaque and plaque is composed of various kinds of bacteria, in theory anti-microbial agents should be effective against gingivitis.

There are a number of anti-microbial agents formulated in toothpaste or rinses on the market. The most effective of these agents is chlorhexidine digluconate (CHG). CHG reduced gingivitis by 50-80% in clinical trials. However, CHG is available in the US by prescription only and is generally used on a short-term basis (2-4 weeks only). Patient compliance is generally poor due to the unpleasant side effects associated with the use of CHG, which include staining of the teeth, interference with taste function, and enhanced calculus formation[96]. Two products available on over-the-counter (OTC) market have shown marginal effectiveness in clinical trials, called Total® and Listerine®. Total, a toothpaste containing triclosan, reduced gingivitis by 20-25% in clinical trials. Listerine reduced gingivitis by 20-35% in clinical trials. Neither triclosan nor Listerine are substantive agents, thus the anti-microbial effect is lost quickly[97]. The remaining anti-microbial agents available in OTC products have failed to show effectiveness in clinical trials. Thus, there is currently no truly efficacious anti-gingivitis

product that is both convenient to use and appealing to the consumer. It appears that the only chemicals that have been shown to have potent anti-plaque and anti-cavity activity are fluoride and chlorhexidine, both of which are halogenated[65,98].

Other commonly used compounds including the phenolics are not as effective as plaque and cavity-control agents[99]. Considering the importance of healthy teeth and gums in general human health, and the lack of availability of a proper remedy, it is very important to develop an industrially viable synthetic approach for Magnesidin. In addition the synthetic method should be a method that can be used to produce in an industrial scale and apply it to other tetramic acids of medicinal significance.

1.5 Synthesis and complications in mimicking the biosynthesis:

There are two literature reports outlining preparation of Magnesidin which were reported three decades ago[95], however the reported methods have too many disadvantages, including low reaction yields, difficulty to reproduce and isolate the intermediates. In many literature reported attempts to reproduce this procedure, intermediates were lost during purification. The key steps in these preparations are the acylation of 5-ethylidene pyrrolidine-2,4-dione with an appropriate acid chloride in the presence of boron trifloride-ethereate. Jones and coworkers investigated[5] the viability of this strategy and they reported that the product was being lost during the basic workup required for the lewis acid-mediated acylation. These problems explain why there is no manufacturing procedure for the preparation of such an important antibiotic. It is even more important that there are no reliable synthetic procedures for many other tetramic acid derivatives, considering that tetramic acids show a remarkable diversity in terms of biogenetic

descent as well as structural variations and biological activity. The high polarity of these compounds and the fact that they can exist in various tautomeric forms (2,4-diketo form prevails in solution) renders them difficult to handle and their spectra difficult to interpret. In designing a successful preparation route for Magnesidin, it is wise to explore the way that nature assembles tetramic acid. Biosynthesis of the tetramic acid more often originates from the respective a-amino acid precursors (N1-C5-C4 fragment) [13]. The source of the C2-C3 segment of the tetramic acid, as well as of potential 3-alkanoyl side chains has been found for most cases to be acetate (Scheme 1). In case of Magnesidin the α-amino acid should be substitutes by α-β unsaturated amino acid and the acetate to be substituted by malonate.

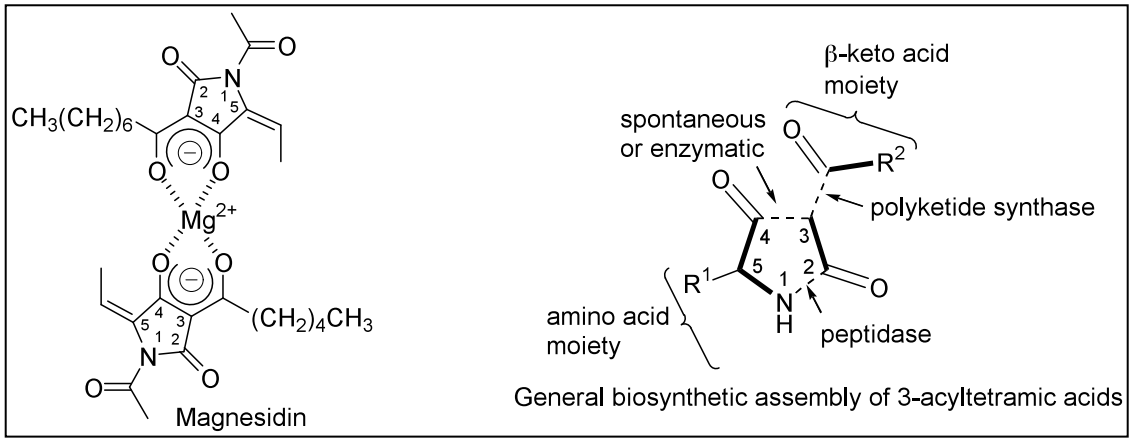
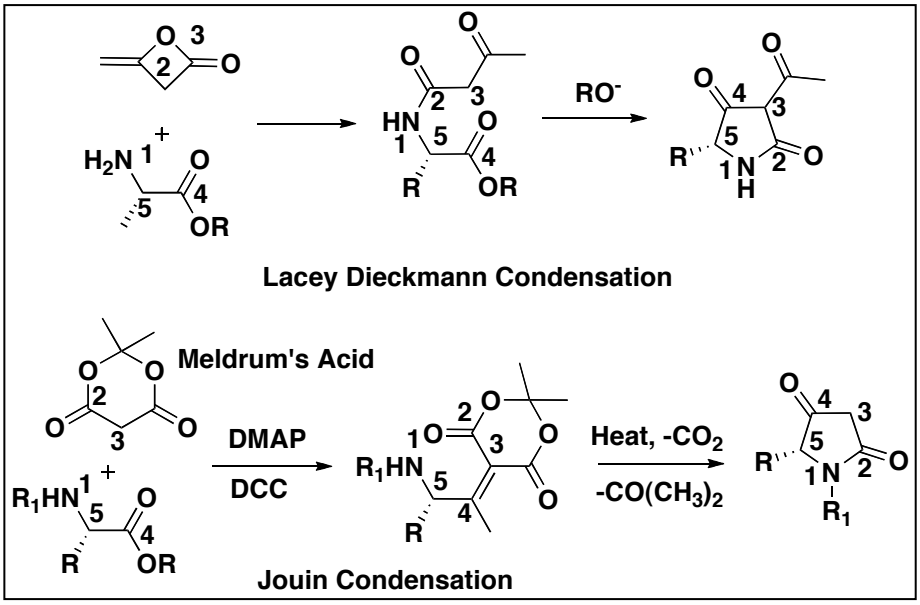


Figure. 1.21. Structure of magnesidin and biosynthetic assembly of the tetramic acid.

However, there are a few relatively old synthetic procedures that have already emulated biosynthesis for tetramic acids in general, although not necessarily with the same order of individual steps, starting from Meldrum's acid and α-amino acids under neutral pH that preserve the C-5 chirality. For instance Lacey's classical sequence[100] starts from α-

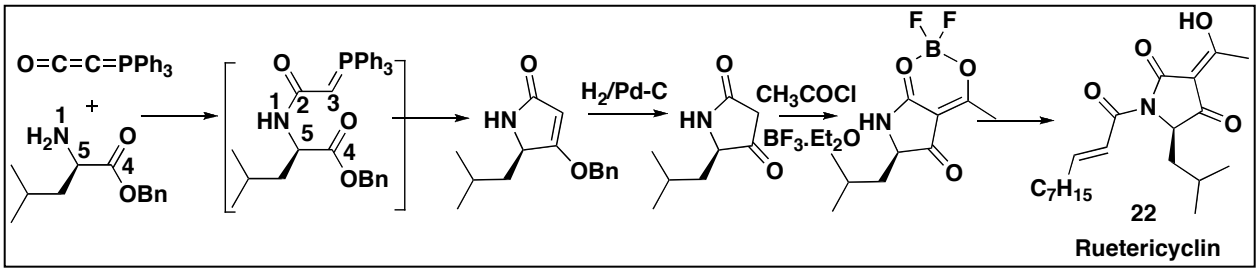
amino ester that condenses with a β-keto acid or with diketene followed by the basic Dieckmann condensation (C3-C4 bond formation) [101]. The mildest and most versatile of all is Jouin's synthesis[102]. The synthesis involves use of meldrums acid in synthesizing the teramic acid and the figure 1.22 explains the reaction sequence. Condensation between the methylene carbon in meldrum's acid and the amino acid is initiated with dicyclohehyl carbodiimide (DCC) and dimethyl aminopyridine (DMAP) as the catalyst and heating the intermediate γ-amino-β-keto ester leads to the corresponding tetramic acid.



Scheme 1.1. The Lacey-Dieckmann and the Jouin tetramic acid ring cyclization.

Perhaps the major contribution toward tetramic acid synthesis comes from introducing ketenylidene-triphenyl phosphorane ($Ph_3P=C=C=O$) as a C2-C3 tetramic acid building block (Scheme 3)[102]. This approach is best demonstrated in preparation of the antibiotic (*R*)-reutericyclin from a D-leucine ester [103]. The preparation starts with a domino addition of Ph_3PCCO to the amino ester followed by boron trifloride catalyzed C3-

acylation and sodium hexamethyl disilazanide catalyzed N1 acylation (Scheme 3). The antibiotic is prepared in four steps without racemization at the C5 position.



Scheme 1.2. Utilization of $Ph_3P=C=O$ as a tetramic acid building block.

Although the presented synthetic procedure substantially shortens the preparation of the antibiotic, these acylation procedures are very difficult to perform, which seems to be a general problem in the preparation of tetramic acid derivatives. The success of the downstream 3-acylation depends on the system being acylated. C5- or N1-unsubstituted tetramic acids are particularly difficult to react. Another problem is the introduction of long-chain acyl residues, and these shortcomings are present in each and every known tetramic acid preparation procedure. For instance, the Jones acylation[104] using acyl halides and a boron trifluoride-ether complex does not work well with 5-usubstituted tetramic acid and is unsuitable for the introduction of Lewis acid sensitive highly unsaturated tetramic acid moieties. Yoshi's protocol[105] initially involved 4-*O*-acylation in the presence of dicyclohexyl carbodiimide and a catalytic amount of 4-dimethylaminopyridine and acyl-migration, which was promoted by adding Et_3N, and this method had low reproducibility mostly in the 4-O to 3C acyl shift. Boeckman's approach via 2-b-phosphonylacetyltetramic acid compromises stereochemistry in C5 position[106]. Given these described synthetic problems, it is easy to see that there is a

need for a general synthetic procedure that would allow the introduction of a diverse number of substituents in any of the tetramic acid positions.

1.6 Aim of dissertation:

From the literature reports, it is understood that in designing a successful synthesis of Magnesidin, reproducibility, product yield and reaction conditions are few of many important considerations. Most importantly, it is acknowledged that new synthetic approaches should substantially differ from currently available ones. The thesis will focus on the following goals and each goal would be addressed further in the following chapters.

- Tag(s) should be introduced in early stage of preparation that will facilitate easier isolation, purification and analysis synthetic intermediates.
- Starting materials should be simple and their synthetic procedures should be available for all the intermediates.
- Overall Synthetic procedure for tetramic acid should be applicable to large-scale tetramic acid manufacturing.
- To develop a general synthetic procedure to prepare any derivative of tetramic acid focusing on the synthesis of Magnesidin.

Each Chapter of the dissertation addresses one of the above set goals for the project.

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Chapter II

Synthesis of TAG Molecule:

2.1 Abstract:

The synthesis of magnesidin involves very complex reactions and complicated purification methods. A tag molecule is assumed to solve the problems associated with the synthesis and the chapter discusses the synthesis of the tag molecule in an environmentally friendly reaction conditions.

2.2 Introduction to TAG molecule:

The syntheses reported earlier for Magnesidin when attempted to reproduce by other researchers indicated that the intermediates would evaporate or decompose either during the reaction or work up[2]. The purification of tetramic acids and their intermediates would be tough due to the physical properties of the compounds (like low volatility), tautomerization, and high polarity. Also in many earlier attempts it was reported that the intermediates were tough to be handled during work up and purification because of their chemical behavior. For example if we consider the case of β–keto acids which are essential intermediates in the synthesis of tetramic acids, there isn't a reliable synthetic procedure[3], which can be applied in general to prepare any type of β–keto acids available due to afore mentioned reasons. The main problem associated with the synthesis of these compounds is that they undergo β–decarboxylation even at slightly elevated temperatures and often involve complicated

purification methods. Preparation and purification of b-keto esters is complicated because the majority of them are oils and so it is hard to monitor the reaction processes. If these oils can be transformed in to solids, it would not only be easy to monitor the reaction but also simple to purify. Simple crystallization techniques can be employed for purification, and hence better yields can be obtained. Considering these facts, a tag molecule, application of which can change the physical properties of the intermediates there by providing easy purification and handling, is necessary for a successful synthesis of magnesidin and the intermediates required for.

2.3 Results and Discussion:

After a careful consideration of various important synthetic facts, structural studies and chemical behavior, a set of phthtalic and naphthalic compounds have been identified to have the potency to serve as tag molecules as shown in figure 2.1.'

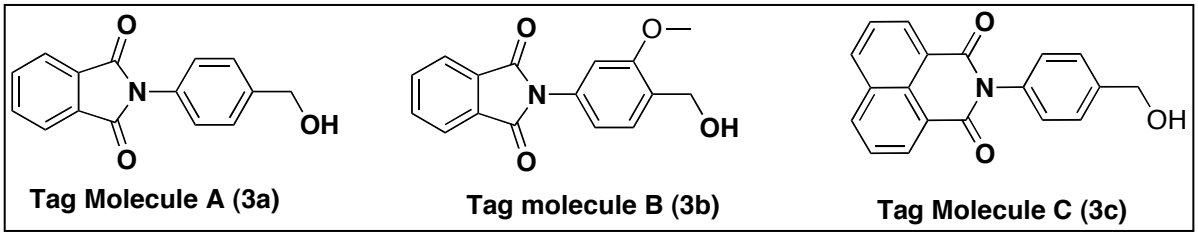
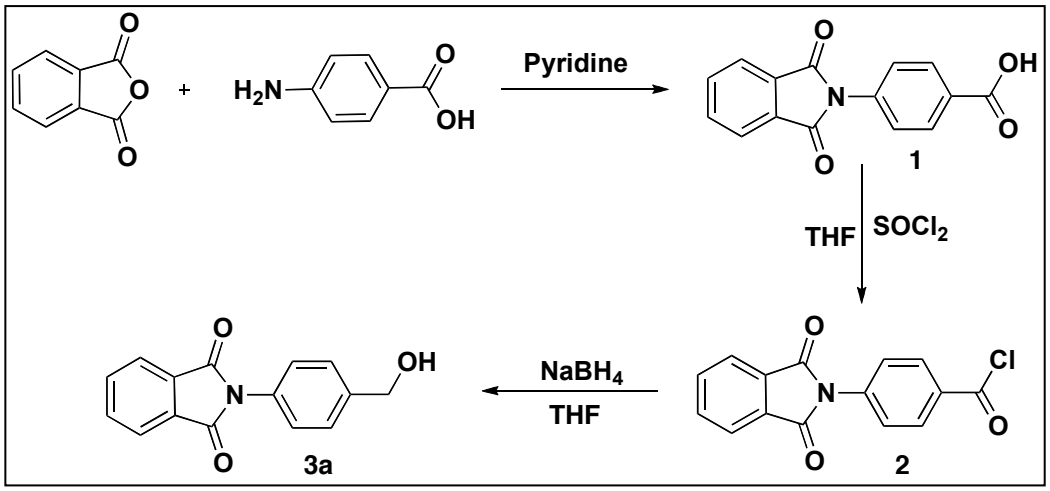


Figure.2.1. The tag molecules designed for synthesis.

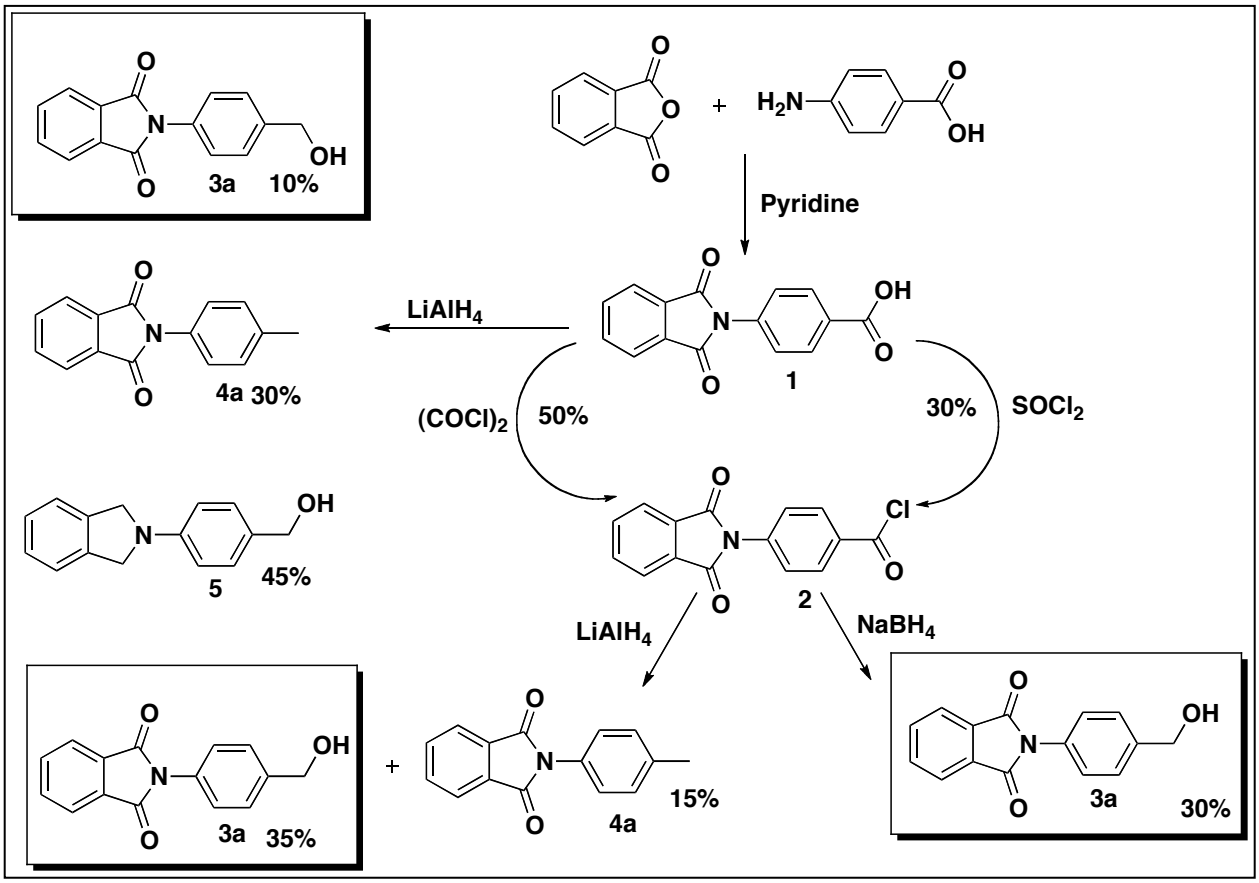
While designing the synthesis of the tag molecule, there are several aspects to be considered. The procedure should be simple, economical and reproducible on industrial scale and should not involve too many steps, keeping in mind the possible low yield at the end. The strategy in scheme 2.1 was the preliminarily designed for synthesizing the

tag molecule A, with an intention to follow up the same procedures for tag molecules B and C.



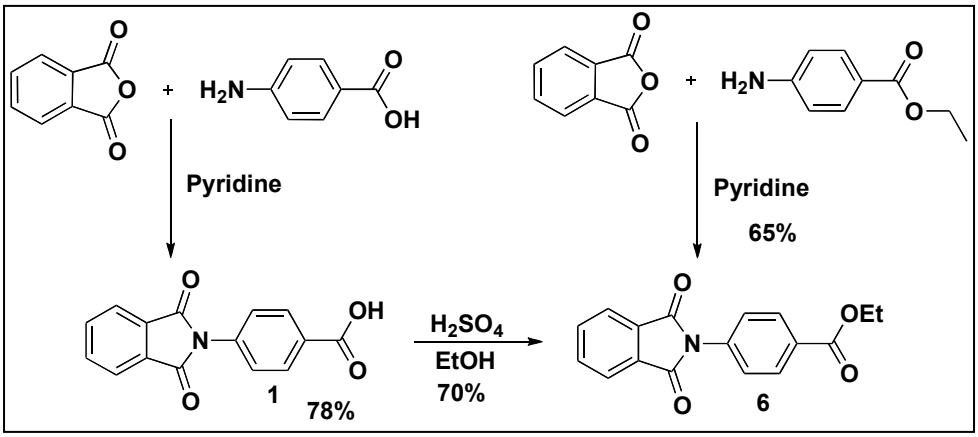
Scheme 2.1. Proposed synthesis of the tag Molecule A.

However in the proposed synthesis the step in which acid **1** has to be converted to acid chloride **2** and acid chloride **2** to alcohol **3a**, the acid and acid chloride were not very well dissolved in spite of trying various solvents and their mixtures. As a result, the yield of the acid chlorides produced are very low and even the small amount of acid chloride produced could not be reduced to the corresponding alcohol **3a**. The reduction could not be accomplished even after trying a range of reducing agents and is summarized in in scheme 2.2. When lithium aluminium hydride ($LiAlH_4$) was used, it led to over reduction on the carbonyl of the acid leading to the product **4** and over reduction of the carbonyl of amide leading to the product **5**. Sodium borohydride on the other hand was not very effective in reducing the acid chloride. It only produced 30% of the desired alcohol **3a** and the main product of this reaction is the corresponding aldehyde.



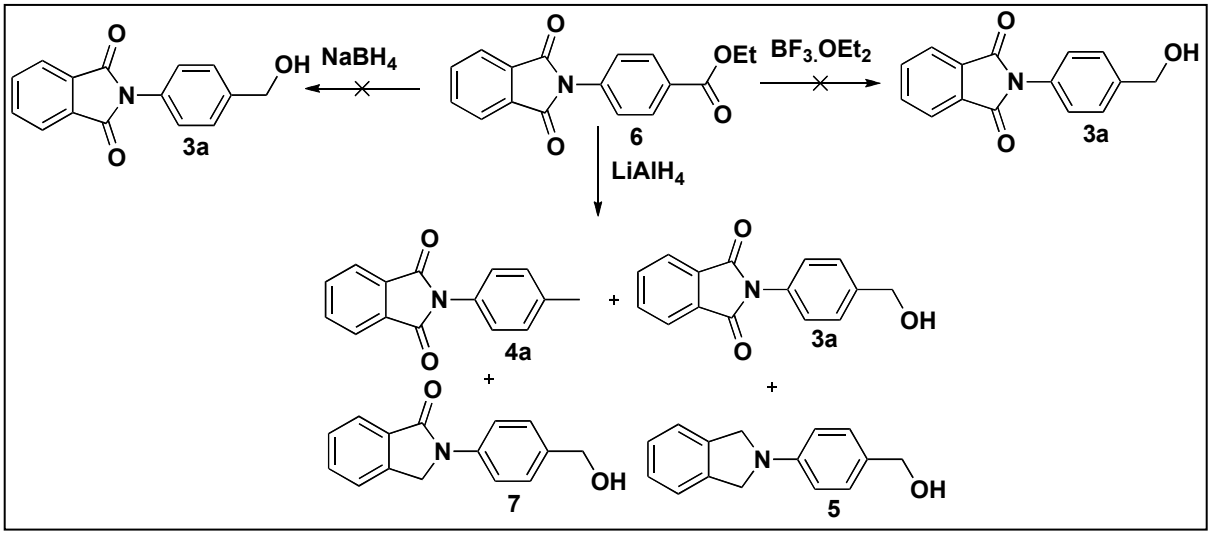
Scheme 2.2. Attempts in synthesizing the tag molecule A.

Since solubility was one of the main problems faced during the reduction of above-mentioned acids, the acid was transformed into the corresponding ethyl ester **6** of the acid **1** to increase the solubility. A strong acid like sulphuric acid was used as catalyst for the esterification reaction to produce 70% of the ester and the reaction results are presented in scheme 2.3.



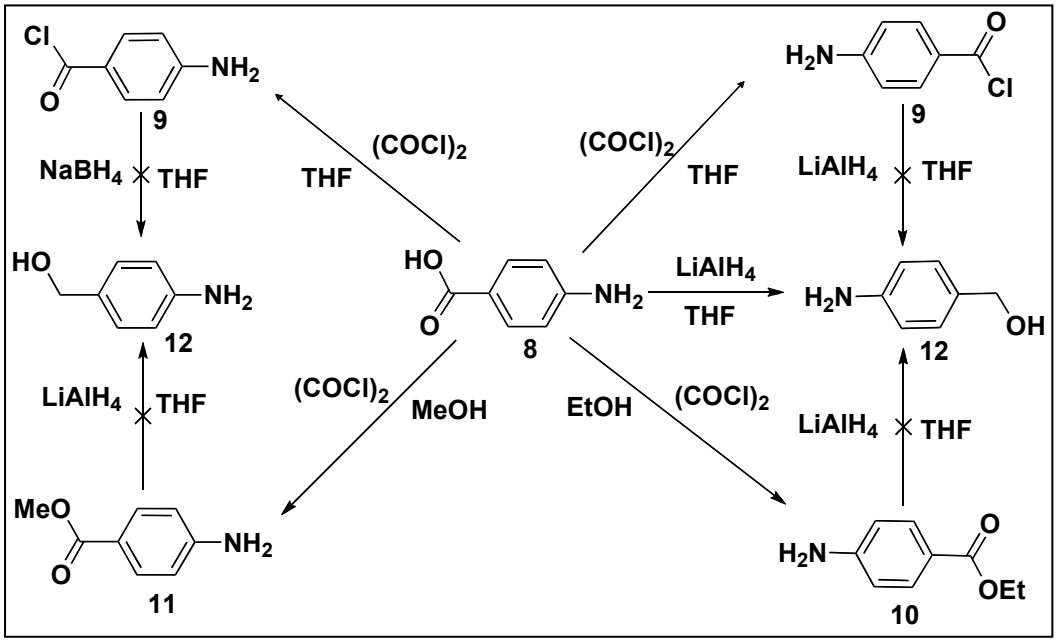
Scheme 2.3 Synthesis of the ester to be reduced.

Once the ester has been synthesized, with an improved solubility it was anticipated that the reduction reaction would be favored to produce the corresponding alcohol but even in this case various attempts to reduce the ester **6** remained unsuccessful. And in case of the ester the over reduction has led to different products **4a, 5**, and **7** other than **3a** as shown in scheme 2.4.



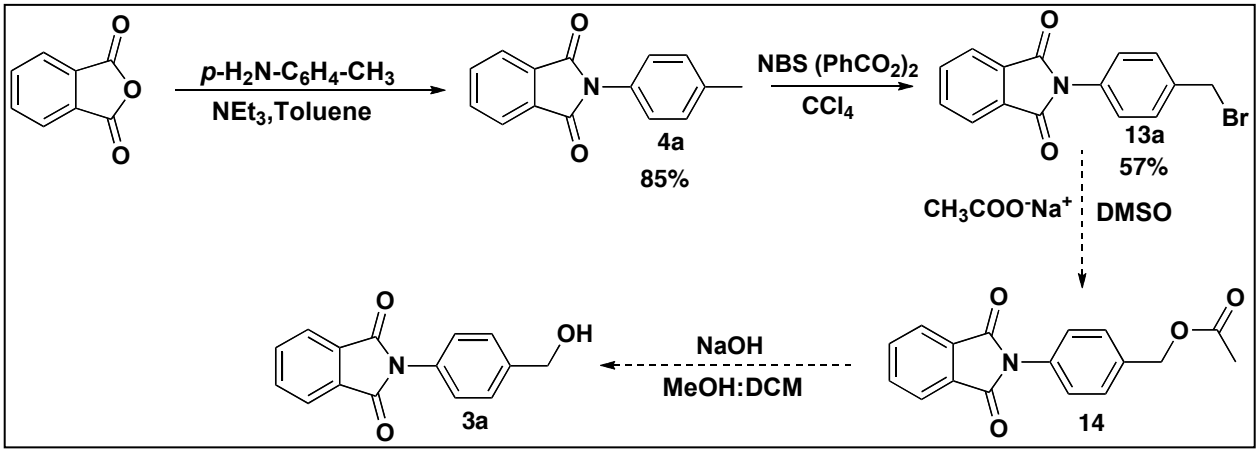
Scheme 2.4 Attempts towards reducing the ester to alcohol.

As there wasn't any success with reducing the acid, acid chloride or ester in to corresponding alcohols, the order of the steps is slightly modified and it was first attempted to synthesize p-amino benzyl alcohol **12** which can further be coupled with phthalic anhydride to obtain the tag molecule **3a**. Not only the acid **8** but the acid chloride **9** and both the methyl and ethyl esters **10** and **11** have been subjected for reduction as shown in scheme 2.5. The results were not very encouraging even for p-amino benzyl alcohol, the molecule being very polar. It was tough to isolate the compound even if some product is formed. $NaBH_4$ and $LiAlH_4$ were both unsuccessful in producing the desired compound in desired yields. That could be one of the reasons why this compound is not commercially available on all catalogues for sale and if available is very expensive.



Scheme 2.5. Attempts to reduce *p*-amino benzoic acid and its esters.

After a series of changes in methodology and unsuccessful attempts, it was understood that the tag molecule itself needs a good method of preparation and the previous scheme would not be successful. A new strategy has been proposed aiming the synthesis of tag molecule compromising on no of steps in the reaction, as shown in scheme 2.6.



Scheme.2.6 Altered procedure to synthesize Tag Molecule A.

The attempts to synthesize the Tag molecule A, following the scheme 2.6 were not very impressive as few of these reaction conditions had to be developed and stabilized. Like the first step of the reaction to produce **4** has a moderately good yield but its completion takes as long as 16 hrs. And upon investigation, it was identified that the general procedures available for the cyclic imides involve long reaction times and also poor yields. The reaction time has to be cut short along with improving the yields. In the step 2 of the scheme, where benzyl bromination occurs to produce **5a,** it was obtained only in a 57% yield with the rest being the di-bromo product **5b**[4]. The mono and di-bromo products are so close in R_f that the separation of these compounds is very tedious, time

taking and also results in reducing the yield. Also it involves use of CCl_4 as solvent, which is very toxic and is banned in some of the countries. Since Microwave is a good media to increase selectivity, reduce reaction times, and also environmentally friendly, a general method of synthesis using the microwave is established for both these classes of compounds-cyclic imides (which need shorter reaction times and better yields) and benzyl mono, di-bromo products (which require selectivity, thereby better yielding and also environmentally friendly).

2.3.1 Microwave Synthesis of phthalimides and naphthalimides:

Phthalimides have been widely used, as amino acid protection groups[5] and also have been widely used in the field of medicinal chemistry[6]. However an efficient high yielding, inexpensive synthetic procedure for these compounds is unavailable. Long reaction time is also another major problem associated with these types of compounds. The use of microwave irradiation to accelerate chemical reactions has become increasingly popular[7]. The most recent observations suggest that the high energy heating is responsible for the acceleration of chemical reactions[8]. In a typical cyclization reaction producing imides, anhydride is condensed with the corresponding amine at elevated temperatures. The reaction involves dehydration too and dehydration reactions are facilitated in a microwave, it was hypothesized that microwave synthesis of phthalimide and naphthalimide derivatives would be ideal. But a common problem associated with microwave synthesis is over heating of the reaction mixture. Solvent-free procedure using $TaCl_5$-silica gel as a catalyst is an example described for the preparation of imides

under microwave irradiation[9]. Sandhu *et al*. advocated the use of a more ecofriendly solvent-free system, involving the reaction of equal amounts of anhydride and amines or amino acids in the absence of solvent in a domestic oven without any catalyst[10]. All these cases being solvent free conditions and the reaction temperatures being not reported[10], decomposition of the products is possible with a slight change in temperature or power.

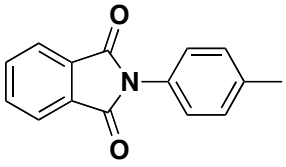
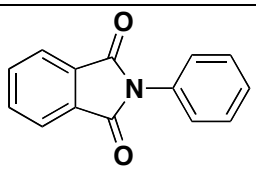
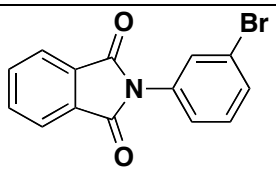
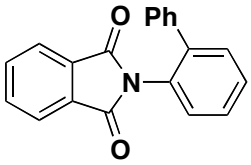
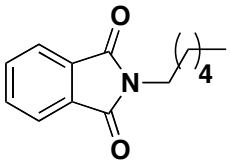
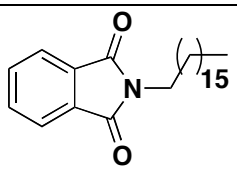
To circumvent this, as well as several other problems associated with the use of a domestic microwave, it has been modified and several reactions were performed to outline the efficiency of the same. The use of our modified microwave reactor offers a number of advantages over traditional household ones[1]. For instance, the temperature inside the reaction vessel can be constantly monitored and the radiation power can be adjusted. Subsequently, a condenser has been fixed, which allows the reaction mixture to the solvent's boiling point without any loss of the solvent. Additionally, the set up allows the use of magnetic stirrer, making the reaction mixture homogenous and minimizing the overheating on a particular side of the reaction vessel. On the whole microwave-assisted reactions can be conducted with or without solvent and also in the environmentally friendly solvents such as ionic liquids[11].

Considering that microwave absorption is stronger for polar molecules, given a reaction mixture, all the components may not be heated equally, refluxing the mixture using a magnetic stirrer allows formation of fewer byproducts. With the mentioned advantages, controlled microwave assisted reactions would be superior to conventional heating in regards to isolated yield. To test these anticipated advantages, microwave-assisted

reactions were employed for the preparation of cyclic imides. The reaction time is however dependent on the size of the ring and conjugation in the cyclic imides from the corresponding cyclic anhydride and amine.

As the precursor of tag molecule A can be prepared from phthalic anhydride or naphthalic anhydride and *p*-toluidene, the first set of reactions were focused on phthalimides and corresponding amines in DMF and then extended to naphthalic derivatives. The reaction mixture was refluxed at a particular magnetron of the microwave, depending on the reaction composition and polarity. Once the reaction is complete, product was isolated by ice-water precipitation from the still hot reaction mixture. The reaction time and yields are presented in Table 1. Preparation of aromatic and aliphatic phthalimides under conventional heating from the corresponding amines usually requires prolonged time in solvents such as toluene, acidic acid, and etc[12]. There are also reports of solvent free microwave assisted synthesis[13]. However, solvent free approach can be successful only if one of the reactants absorbs microwave irradiation and has relatively low melting point. On the other hand, this procedure is applicable to broad range of amines regardless of their physical state or microwave radiation absorption because solvent (DMF) is an excellent microwave reaction media, as it was demonstrated on the examples of aromatic amines (**4a-4d**) and aliphatic amines (**4e** and **4f**, Table 2.1).

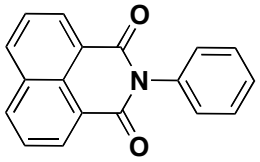
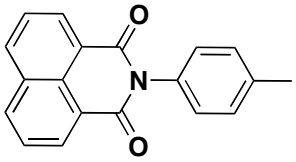
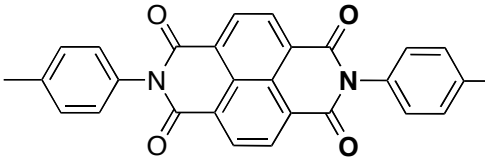
Table 2.1: Preparation of derivatives of phthalimides.

Entry	Product	Microwave		Conventional	
		Time (hr)	Yield (%)	Time (hr)	Yield (%)
4a		1	94[P1]	16	85
4b		1	95 [P1]	16	65
4c		0.5	97 [P1]	12	65
4d		1	85 [P2]	16	60
4e		0.75	95 [P2]	16	60
4f		0.75	90 [P2]	16	63

P1=300 Watts and P2= 450 Watts in microwave.

In general, five-membered cyclic anhydrides are more reactive than six-membered cyclic anhydrides. Therefore, it is not surprising that microwave assisted reaction conditions used for the preparation of cyclic imides with 1,8-naphthalic anhydride were longer than that of phthalic anhydride. The reaction time is more than quadrupled. However replacing the DMF with pyridine as solvent, the isolated yield was higher and the reaction time was shortened (Table 2.2). The isolation of the product requires quenching the reaction mixture with water or with aqueous hydrochloric acid followed by crystallization of the product.

Table 2.2 Preparation of derivatives of 1,8- naphthalimides.

Entry	Product	Microwave		Conventional	
		Time (hr)	Yield (%)	Time (hr)	Yield (%)
4g		2	90[P1]	20	70
4h		2	95 [P1]	24	75
4i		1	93 [P1]	24	50

P1=450 Watts in microwave

As the desired imides **4a** and **4h** are prepared; the next step of the reaction is benzyl bromination. The reported procedures available resulted in very low yields due to possible di bromination and hence complicated purification methods, so a better preparation of benzyl bromination needs to be developed.

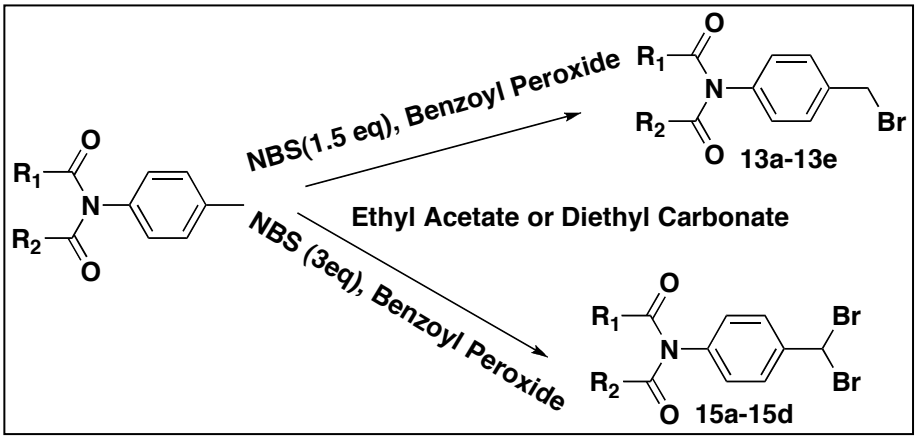
2.3.2 Microwave synthesis of mono and di-bromo benzyl derivatives:

The majority of benzyl radical bromination reactions have been performed using elemental bromine[14-16] or N-bromoimides[17,18] and chlorinated organic solvents, such as the highly toxic carbon tetrachloride (CCl_4) as reaction media. More recently, however, bromine has been mostly replaced by other sources due to its corrosive behavior. CCl_4 is the most effective solvent for performing these reactions but its ozone-depleting capability and increasing restrictions to its use due to environmental impacts necessitates synthetic teams to find a more applicable system for free radical bromination with less impact on the environment. In spite of the above listed restrictions and hazards, use of CCl_4 as a common organic solvent has been reported even as recently as in this decade[19-21]. This is largely due to the fact that even today, as we develop a firm understanding of the impact of performing chemical synthesis using green chemistry[22], the quest for greener solvents has provided chemists with few alternatives for CCl_4. Chloroform and methylene chloride were used as less toxic alternatives to CCl_4, but the real advancement towards the realization of environmentally friendly reactions has been in the possibility to perform radical reactions in non-chlorinated solvents, such as methyl acetate, benzene, and carbon disulfide[23].

More attempts toward replacing chlorinated solvents with environmentally friendly reaction media were recognized when an attempt of benzyl bromination was performed with bromine in water media[24]. Even so, in this process, depending on the nature of the substrate, a substantial amount of the aromatic ring bromination was also observed. Also in the search of safer bromination reagents, a bromine complex of the styrene vinyl pyridine co-polymer[25], bromotrichloroethane[26,27] and copper (II) bromide[28] have been reported to be effective for benzylic bromination as environmentally safe alternatives. However, these bromination reagents are expensive and are not recyclable for multiple uses in reaction mixtures.

Water is an ideal reaction media from the environmental standpoint, and remains the gold standard for solvents for green chemistry. Although water has already been used as a green solvent (HBr/H_2O_2 reaction media)[29-31] and visible-light-promoted solvent-free NBS benzyl bromination[32], these approaches have several drawbacks. The selectivity of the reaction is low and even result in lower isolated yields of benzyl bromides. In addition, the reaction requires longer times (20-30 hrs). These drawbacks stress the need for a more selective, environmentally friendly procedure for preparation of benzyl bromides with good yields. Goswami and coworkers went a step ahead in this aspect and reported microwave-assisted benzyl bromination without solvents and a radical initiation[33]. The reaction was performed in a few minutes with microwave magnetron power of 450W. However, the isolated yields following column chromatography were still low (around 40%), even though the reaction time was substantially reduced (~15 minutes), and therefore a more efficient and environmentally friendly benzyl bromination method was still sought after.

Herein a new benzyl bromination approach that requires short reaction times, has been developed in environmentally friendly solvents, and produces high to excellent isolated yields for both mono- and di- benzyl bromination. Ethyl acetate and diethyl carbonate were the two environmentally friendly solvents chosen[34]. While a few radical bromination reactions in ethyl acetate were explored previously[20], the reported ratio of mono to di bromination is 1:2, and to the best of our knowledge there are no reported radical benzyl bromination reactions using diethyl carbonate as reaction media. Both of these solvents are environmentally friendly, and recyclable. To shorten the reaction time benzyl bromination was performed under microwave-assisted conditions as shown in scheme 2.7. The conditions mentioned apply for both mono and di-bromination of N-protected toluidenes.



Scheme. 2.7 Microwave-assisted radical benzyl bromination of N-protected toluidines.

The reaction conditions were optimized for these compounds using microwave and diethyl carbonate as the solvent. Comparison of the NMR reaction following in (a)

carbon tetrachloride, (b) diethyl carbonate, and (c) diethyl carbonate with microwave heating is presented in Figure 2.2.

As demonstrated numerous times in the literature, carbon tetrachloride is an exceptionally powerful benzyl bromination solvent[35]. In the case of preparation of **13a** (Figure 2.2), the reaction is complete after refluxing for one hour with isolated yield higher than 90%. If carbon tetrachloride is substituted with ethyl acetate as the reaction media, then the reaction progress is much slower. For instance, ~65% benzyl mono-bromination was obtained together with benzyl di-bromination after twenty-four hours of the reaction mixture refluxing. With diethyl carbonate as the solvent, the reaction mixture was refluxed for only six hours before completion (Figure 2.2).

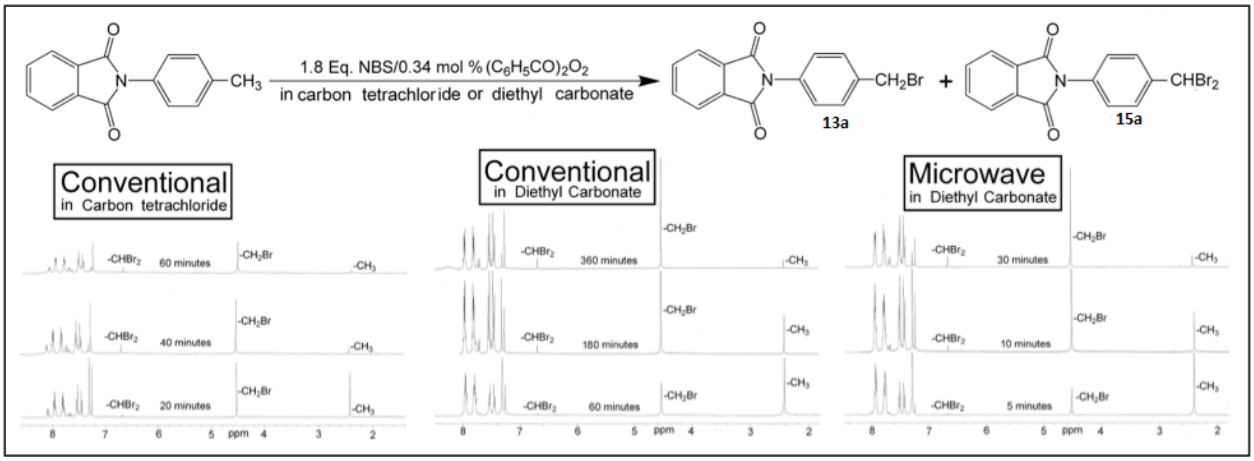


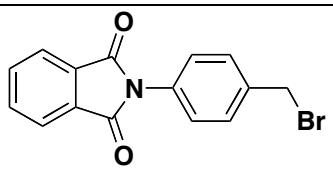
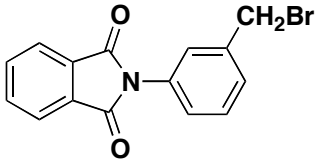
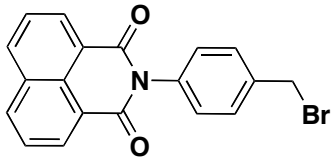
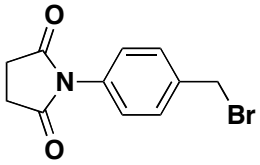
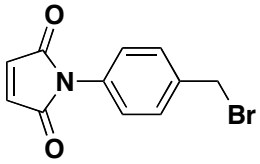
Figure 2.2. Comparison of various reaction conditions for benzyl mono-bromination

As mentioned above, and in one of the previous research reports, microwave heating is superior to conventional heating in radical reactions[36]. This procedure was applied to the reactions described in this report, and found that the required reaction time was

significantly shortened from 360 minutes to 30 minutes (Figure 2.2), when diethyl carbonate was used as the reaction media. The diethyl carbonate microwave benzyl bromination can be considered both environmentally friendly and superior to conventional benzyl bromination in carbon tetrachloride.

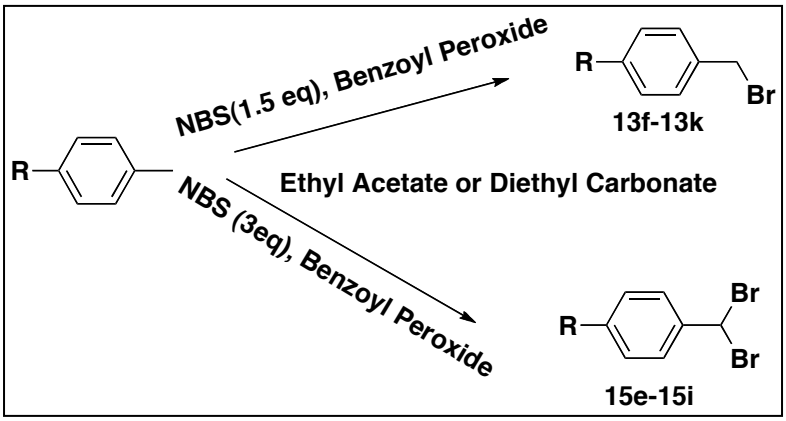
These optimized reaction conditions for microwave-assisted benzyl bromination in both ethyl acetate and diethyl carbonate as reaction media were used for preparation of a number of other compounds (Table 2.3). The isolated yields and reaction conditions are similar to those presented in Table 1. Microwave-assisted reactions are, in general, superior to conventional reactions[37]. In the case of radical bromination, microwave-assisted reactions require shorter reaction times, higher reaction selectivity and ultimately better-isolated yields when compared to conventional bromination reactions[38] and is even more effective for polar molecules such as amides[38]. The time difference between conventional and microwave-assisted bromination of these compounds is quite large. For instance, in the case of **13a** (Table 2.3) in the conventional preparation of this compound, took twenty-four hours for completion with the ratio of mono- to di-bromo product was 3:1, and the isolated yield of mono-bromo product **13a** was only 55%.

Table 2.3. Time and yields of benzyl monobromination of protected toluidenes

Entry	Product	Time (min) [a]	Yield (%)[a]	Time (min) [b]	Yield (%)[b]
13a		30	90	30	95
13b		60	85	30	90
13c		40	90	30	90
13d		60	95	40	95
13e		40	5	40	85

a: Ethyl Acetate (400 W), b: Diethyl carbonate (450W)

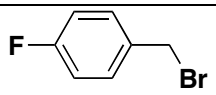
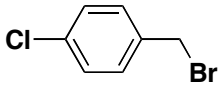
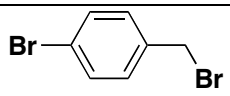
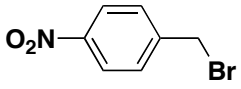
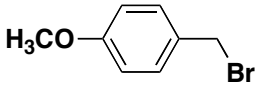
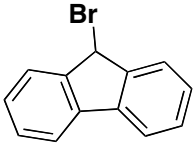
Once successful results were obtained for N-protected *p*-amino toluidenes, the method has been generalized for various other toluidenes and the reaction conditions for microwave-assisted mono benzyl bromination are presented in Scheme 2.8.



Scheme 2.8 Microwave-assisted radical benzyl bromination of substituted toluenes

The reaction conditions remained same even for simple aromatic compounds; and the optimized reaction time and isolated yields for mono benzyl bromination in environmentally friendly solvents are presented in Table 2.4. The reaction times were shortened from a few hours (conventional solvent refluxing) to around 0.5 h under microwave conditions. With ethyl acetate as a solvent, the reaction can be conducted with microwave power of 400 W. The power for diethyl carbonate is slightly higher, 450 W, resulting in shorter (by 5 to 10 minutes) reaction times and marginally better isolated yields (Table 2.4).

Table 2.4. Time and isolated yields of benzyl monobromination of substituted toluenes.

Entry	Product	Time (Min) [a]	Yield (%)[a]	Time (Min) [b]	Yield (%)[b]
13f		30	92	20	95
13g		30	85	20	85
13h		30	90	20	95
13i		40	80	30	80
13j		20	98	15	98
13k		30	90	20	98

Solvent used a: Ethyl acetate, 400W b: Diethyl carbonate, 450W.

2.3.3 Benzyl di bromination of toluidenes:

Considering that the introduction of the second bromine in the benzyl position by radical bromination is much more difficult, the reaction conditions for di bromination have also been explored. Although the di bromination product is almost always present in radical benzyl bromination reactions as it is demonstrated in Figure 2.2, the common problem

associated with these reactions is complete conversion of benzyl bromides into benzal bromides (radical di bromination)[39]. The reaction usually requires aggressive reagents and longer reaction times. In this case, microwave-assisted di bromination is superior to conventional heating procedures for the preparation of these compounds.

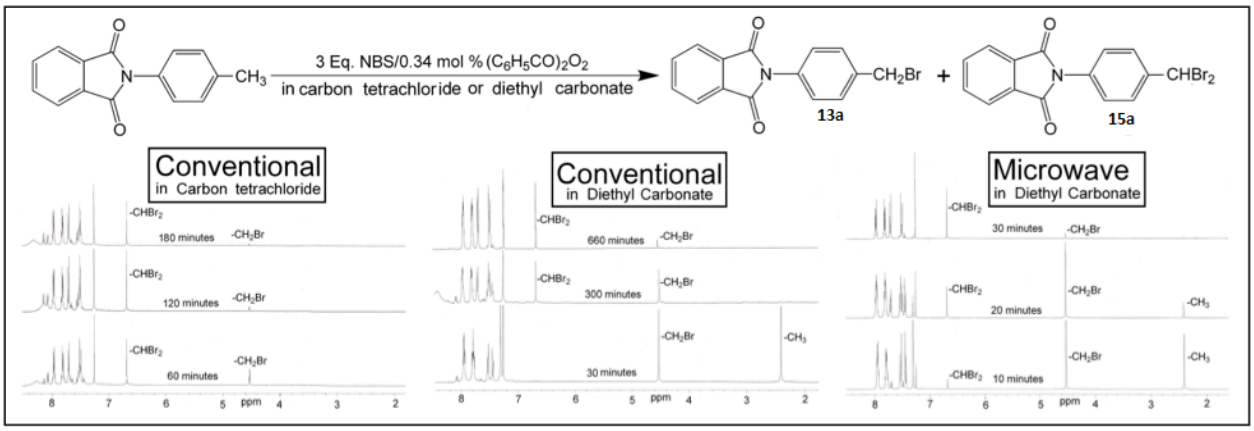
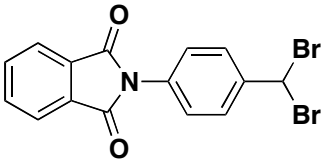
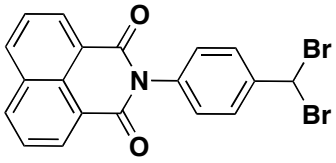
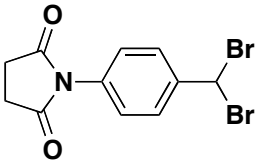
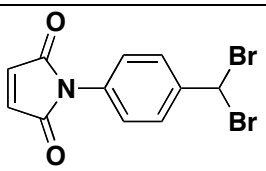


Figure 2.3. NMR reaction following of comparative benzyl di-bromination

To further optimize the reaction conditions on molecules of our interest comparative radical benzyl di-bromination was performed (Figure 2.3). In carbon tetrachloride, the reaction is complete after three hours. In ethyl acetate, the reaction was not completed even after refluxing for twenty-four hours. Diethyl carbonate was a better solvent than ethyl acetate, but still required eleven hours of refluxing for completion (Figure 2.3). With conventional heating, carbon tetrachloride was superior to diethyl carbonate as the benzyl di-bromination solvent. However, diethyl carbonate, as the reaction media in a microwave was superior to conventional heating with carbon tetrachloride as the reaction media. This reaction was complete in half an hour as in comparison to three hours in carbon tetrachloride. There is yet another advantage of using diethyl

carbonate. After cooling the reaction mixture to 15˚C almost all succinimide crystallizes from the reaction mixture and can be recycled into NBS. The solvent was distilled off under reduced pressure and used in new bromination reactions.

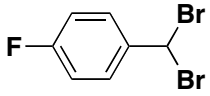
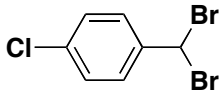
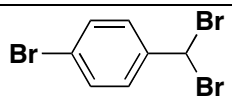
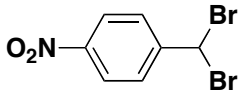
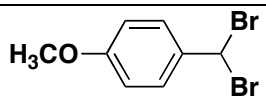
Table 2.5. Time and isolated yields of benzyl dibromination of protected *p*-toluidine

Entry	Product	Time (min)	Yield (%)	Time (min)	Yield (%)
15a		80	70	30	85
15b		100	60	30	80
15c		90	65	30	85
15d		90	75	40	90

These optimized reaction conditions were used to perform benzyl di bromination on several cyclic amides (Table 2.5). These compounds (*p*-amino benzaldehydes and p-amino benzal bromides) are precursors for preparation of tagged monosaccharide used

in preparation of diverse oligosaccharide library published elsewhere[35,40,] Microwave-assisted benzyl di-bromination in both ethyl acetate and diethyl carbonate proceeded smoothly. However diethyl carbonate is the superior solvent regarding both reaction times and isolated yields (Table 2.5). The reactions were completed in less than 40 min with a microwave magnetron power of 600 W.

Table 2.6. Time and isolated yields of benzyl di-bromination of substituted toluene

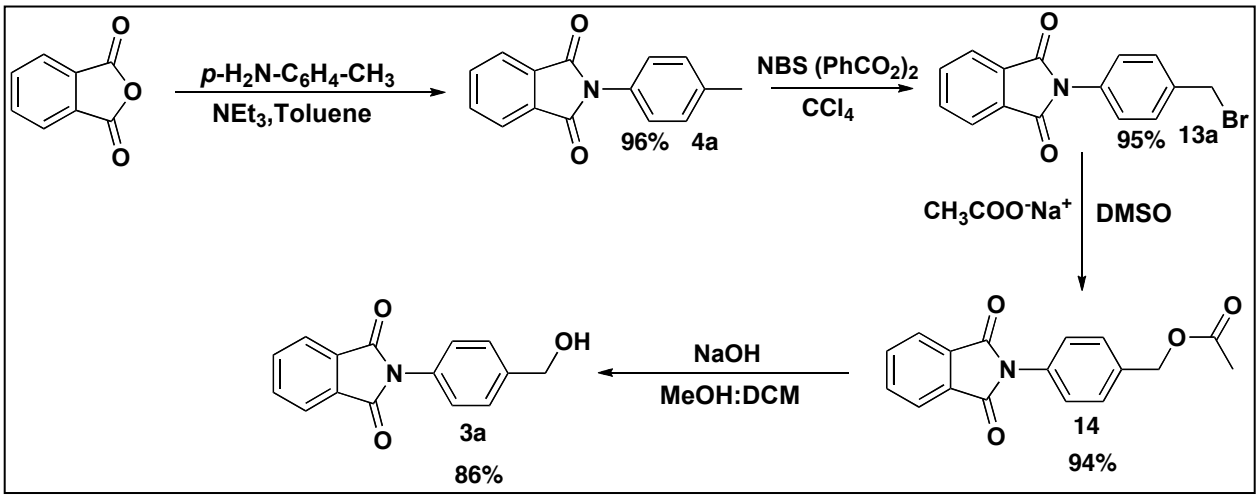
Entry	Product	Time (Min) [a]	Yield (%)[a]	Time (Min) [b]	Yield (%)[b]
15e		90	70	60	85
15f		90	75	75	85
15g		90	70	60	90
15h		120	60	90	85
15i		60	75	40	95

As for imides, simple toluidenes also showed better results using diethyl carbonate instead of ethyl acetate. Switching the solvents, gave selectivity and hence better-

isolated yields with less reaction times for di-bromo products and all the reactions were complete in less than 90 min (Table 2.6).

2.3.4 Synthesis of the tag molecule:

The methodologies developed have been applied to the synthesis of the tag molecule as proposed above. After the bromo derivative was prepared, the corresponding ester was synthesized using sodium acetate which was then hydrolyzed using sodium hydroxide to obtain the desired tag molecule A in 74% overall yield.



Scheme.2.9. The synthesis of the tag Molecule A (**3a**).

2.4 Conclusion:

In conclusion, the effect of microwave irradiation on the preparation of cyclic imides, benzyl and benzal bromides have been explored and reported. With the possibility to control the power of microwave radiation, it was easy to achieve selectivity, better yields and less reaction time. This approach is superior to conventional synthetic approach in both isolated yield of the product and required reaction time for preparation of cyclic imides and bromides. Also benzyl mono- and di-bromination procedure not only gave good results but is also environmentally friendly and superior to same reaction in carbon tetrachloride as a solvent. These reactions are conducted under microwave radiation and in diethyl carbonate as the reaction media with NBS as a source of bromine. Upon completion of the reaction, the formed succinimide was separated by filtration and the solvent distilled off. With an easy, environmentally friendly preparation of NBS from succinimide, both the reagent and the solvent are also recyclable. Diethyl carbonate is our solvent of choice with microwave heating for both benzyl mono- and di-bromination. Isolation of products and recycling the reagents and the solvent is a simple process. Successfully establishing the methods of preparation of afore mentioned compounds, the tag molecule synthesis was made possible.

2.5 Experimental and spectral data:

Phthalimide synthesis in Microwave, General procedure A: To a suspension of phthalic anhydride (1.48 gm, 10 m.mol) in N, N-dimethyl formamide was added the corresponding amine (10m.mol, 1 eq). The reaction mixture was put in the microwave reactor equipped with condenser and magnetic stirrer and stirred under mild solvent refluxing (magnetron power between 300 and 450 W). After reaction was completed reaction mixture was poured onto crushed ice (~200 g). Formed white precipitate was separated by filtration, washed with water and dried under reduced pressure. According to the NMR spectra compounds are more than 96% pure.

Preparation of 2-*p*-tolylisoindoline-1,3-dione (4a): Titled compound was produced following the general procedure A from phthalic anhydride (1.48g, 10m.mol) and *p*-toluidine (1.07g, 10 m.mol). The product was obtained in (2.2g) 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.77 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.31 (s, 4H), 2.41 (s, 3H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.6, 138.4, 134.6, 132, 130.2, 130, 129.9, 129.2, 126.9, 126.7, 126.6, 123.9, 21.4 ppm.

Preparation of 2-*p*-phenylisoindoline-1,3-dione (4b): Titled compound was produced following the general procedure A from phthalic anhydride (1.48g, 10m.mol) and aniline (0.93g, 10m.mol). The product was obtained in (2.1g) 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.50 (t, *J* = 7.3 Hz, 2H), 7.44 (d, *J* = 7.3 Hz, 1H), 7.40 (dt, *J* = 2.7, 1.6 Hz, 1H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.5, 134.6, 131.9, 131.9, 129.3, 128.3, 126.8, 123.9 ppm.

Preparation of 2-(3-bromophenyl) isoindoline-1,3-dione (4c): Titled compound was produced following the general procedure A from phthalic anhydride (1.48g, 10m.mol)

and *m*-bromo aniline (1.07g, 10m.mol). The product was obtained in (2.9g) 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 1H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 1H), 7.62(s, 1H), 7.48(d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.6, 139.4, 134.6, 132.0, 131.7, 129.3, 129.2, 127.5, 124, 123.9, 21.6 ppm.

Preparation of 2-(biphenyl-2-yl) isoindoline-1,3-dione (4d): Titled compound was produced following the general procedure A from phthalic anhydride (1.48g, 10m.mol) and biphenyl-2-amine (1.69g, 10m.mol). The product was obtained in (2.5g) 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 1H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 1H), 7.62(s, 1H), 7.48(d, *J* = 7.8 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.6, 139.4, 134.6, 132, 131.7, 129.3, 129.2, 127.5, 124, 123.9, 21.6 ppm.

Preparation of 2-hexylisoindoline-1,3-dione (4e): Titled compound was produced following the general procedure A from phthalic anhydride (1.48g, 10m.mol) and hexyl amine (1g, 10m.mol). The product was obtained in (2.2g) 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 3.62 (t, *J* = 7.2 Hz, 2H), 1.82 (m, 2H), 1.3(m, 6H), 0.83 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.1, 134.2, 132.2, 123.8, 38, 31.8, 28.5, 26.7, 22.5,13.8 ppm.

Preparation of 2-heptadecylisoindoline-1,3-dione (4f): Titled compound was produced following the general procedure A from phthalic anhydride (1.48g, 10m.mol) and heptadecyl amine (2.6g, 10m.mol). The product was obtained in (3.5g) 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.0 Hz, 2H), 3.62 (t, *J* = 7.2 Hz, 2H), 1.82 (m, 2H), 1.3(m, 28H), 0.83 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.3, 134.2, 132.2, 123.8, 38.6, 30.7, 29.8, 29.8, 29.6, 29.3, 29.2, 27.5, 22.5, 22.5, 14.3 ppm.

Phthalimides by conventional heating, General procedure B: To a suspension of phthalic anhydride (1.48g, 10m.mol) in 20 ml of toluene, was added the corresponding amine (10m.mol, 1 eq) and 1ml of triethyl amine. The suspension was refluxed at 70°c for about 12-24 hrs, until the completion of the reaction as monitored by TLC and the excess solvent was distilled and collected into a collector by increasing the reflux temperature. The pure compound was obtained as colorless needles upon cooling the remaining solution. Compounds 1a-1f were synthesized using the general procedure B.

Naphthalimide synthesis in Microwave, General procedure C: Pyridine (100 ml) solution of 1,8-Naphthyl anhydride (1.98g, 10 m.mol) and corresponding amine (10 m.mol, 1eq) was refluxed at microwave magnetron power of 450W. After cooling to room temperature, reaction mixture was poured onto ice. Formed white solid was separated by filtration, washed with water, and dissolved in dichloromethane (100 ml). Dichloromethane solution was washed with 10% hydrochloric acid (3x50 ml), water (3x50 ml), dried over anhydrous sodium sulfate and evaporation of the solvent under vacuum gave pure product.

2-phenyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (4g[1]): Titled compound was prepared according to the general procedure C described above using naphthyl anhydride(1.98g, 10m.mol), aniline(0.93g, 10m.mol) and 15ml of DMF. The product was obtained in 70% yield (1.91g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 7.3 Hz, 2H), 8.27 (d, *J* = 8.3 Hz, 2H), 7.79 (t, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.6, 135.7, 134.5, 132, 131.8, 129.6, 128.9, 128.8, 128.7, 127.3, 123.1 ppm.

2-phenyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (4g^2): Titled compound was prepared according to the general procedure C described above using naphthyl anhydride(1.98g, 10m.mol), aniline(0.93g, 10m.mol) and 15ml of pyridine. The product was obtained in 90% yield (2.45g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 7.3 Hz, 2H), 8.27 (d, *J* = 8.3 Hz, 2H), 7.79 (t, *J* = 8.0 Hz, 2H), 7.56 (t, *J* = 7.5 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.6, 135.7, 134.5, 131.9, 131.8, 129.6, 128.9, 128.8, 128.7, 127.3, 123.1 ppm.

2-*p*-tolyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (4h^1): Titled compound was prepared according to general method C described above using naphthyl anhydride (1.98g, 10m.mol), *p*-bromo toluene (0.93g, 10m.mol) and 15ml of DMF. The product was obtained in 65% yield (1.98g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 7.3 Hz, 2H), 8.27 (d, *J* = 8.3 Hz, 2H), 7.79 (t, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (400MHz, $CDCl_3$) δ 164.6, 139.6, 135.6, 134.5, 131.9, 131.7, 129.8, 129.5, 129.4, 128.7, 127.3, 125.8, 123.1, 21.7 ppm.

2-*p*-tolyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (4h^2): Titled compound was prepared according to general method C described above using naphthyl anhydride (1.98g, 10m.mol), *p*-bromo toluene (0.93g, 10m.mol) and 15ml of pyridine. The product was obtained in 95% yield (2.89g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 7.3 Hz, 2H), 8.27 (d, *J* = 8.3 Hz, 2H), 7.79 (t, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (400MHz, $CDCl_3$) δ 164.6, 139.6, 135.6, 134.5, 131.9, 131.8, 129.8, 129.5, 129.4, 128.7, 127.3, 125.8, 123.1, 21.7 ppm.

2,7-di*p*-tolylbenzo[*lmn*][3,8]phenanthroline-1,3,6,8(2*H*,7*H*)-tetraone (4i^2):

Titled compound was prepared according to general method C described above using naphthyl anhydride (1.98g, 10m.mol), *p*-bromo toluene (1.86g, 20m.mol) and 20ml of pyridine. The product was obtained in 93% yield (4.14g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 4H), 7.42 (d, *J* = 7.8 Hz, 4H), 7.24 (d, *J* = 7.8 Hz, 4H), 2.45 (s, 6H) ppm. ^{13}C NMR (400MHz, $CDCl_3$) δ 163.6, 139.7, 132.3, 131.9, 130.6, 128.2, 126.9, 21.7 ppm.

Naphthalimides by Conventional Heating, General Procedure D:

A suspension of 1,8-Naphthyl anhydride (1.98g, 10m.mol) and corresponding amine (10m.mol, 1eq) in 20 ml of pyridine was refluxed at 70°c for about 20 hrs and the excess solvent was distilled off by increasing the reflux temperature and setting up a collector to collect the solvent. The compound was obtained upon cooling the solution. Compounds 2a[1,2] , 2b[1,2] and 2c[2] have been prepared using this procedure and were obtained in yields from 50-75%.

Monobromination, General Procedure E (*the product is insoluble in reaction media at room temperature*)**.** To an ethyl acetate (15 ml) or diethyl carbonate (10 ml) solution of substituted toluenes (10 m.mol, 1eq) was added benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) and *N*-bromo succinimide (18 m.mol, 1.8 equivalents). The reaction mixture was refluxed (for respective times as in tables 1 and 2 for ethyl acetate and diethyl carbonate) under microwave heating (magnetron power of 400W for ethyl acetate and 450W diethyl carbonate). Clear reaction mixture was cooled down to room temperature. Formed white crystalline product was separated by filtration, washed with ice-cold solvent and dried at room temperature. The yield is 1.2 g (90%) for ethyl acetate as solvent and 1.26 g (95%) for diethyl carbonate as reaction media. Filtrate was left at 5°C

overnight. Formed white precipitate was separated by filtration and dried to give 925 mg (88%) for ethyl acetate and 967 mg (93%) for diethyl carbonate of succinimide.

2-(4-(bromomethyl)phenyl)isoindoline-1,3-dione (13a):

Titled compound is prepared according to the general procedure E from 2-*p*-tolylisoindoline-1,3-dione (2.37g, 10m.mol), *N*-bromo succinimide(3.2g,1.8m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 25 ml of ethyl acetate or 20 ml of diethyl carbonate. The product was obtained in 90% yield (2.83g) in ethyl acetate and 95% yield (2.99g) in diethyl carbonate. ^{1}H NMR δ 7.94-7.97 (m, 2H), 7.78-7.81 (m, 2H), 7.53 (d, *J* = 8.42 Hz, 2H), 7.45 (d, *J* = 8.42 Hz, 2H), 4.52 (s, 2H) ppm. ^{13}C NMR δ 167.4, 137.7, 134.8, 131.9, 130.7, 126.9, 124.1 and 32.8 ppm.

2-(2-(bromomethyl)phenyl)isoindoline-1,3-dione (13b):

Titled compound is prepared according to the general procedure E from 2-*m*-tolyl isoindoline-1,3-dione (2.37g, 10m.mol), *N*-bromo succinimide(3.2g,1.8m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 25 ml of ethyl acetate or 20 ml of diethyl carbonate. The product was obtained in 75% yield (2.36g) in ethyl acetate and 85% yield (2.68g) in diethyl carbonate. ^{1}H NMR δ 7.94-7.97 (m, 2H), 7.78-7.81 (m, 2H), 7.58 (t, *J* = 8.42 Hz, 1H), 7.44 (d, *J* = 8.42 Hz, 2H), 7.24 (d, *J* = 7.6Hz, 1H), 4.52 (s, 2H) ppm. ^{13}C NMR δ 167.4, 137.7, 134.8, 131.9, 130.1, 126.9, 124.1 and 32.8 ppm.

2-(4-(bromomethyl)phenyl)-1*H*-benzo[*de*] isoquinoline-1,3 (2*H*)-dione (13c):

Titled compound is prepared according to the general procedure E from 2-*p*-tolyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (2.87g, 10m.mol), *N*-bromo succinimide (3.2g, 1.8m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 25 ml of ethyl acetate or 20 ml of diethyl carbonate. The product was obtained in 90% yield (2.39g) in

ethyl acetate and 90% yield (2.39g) in diethyl carbonate. ^{1}H NMR δ 8.65 (d, *J* = 7.2Hz, 2H), 8.28 (d, *J* = 7.2Hz, 2H), 7.80 (t, *J* = 7.8Hz 2H), 7.58 (d, *J*=8.2 Hz 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 4.57 (s, 2H) ppm. ^{13}C NMR δ 167.4, 137.7, 134.8, 131.9, 130.1, 126.9, 124.1, 32.8 ppm.

1-(4-(bromomethyl)phenyl)pyrrolidine-2,5-dione (13d):

Titled compound is prepared according to the general procedure E from 1-*p*-tolylpyrrolidine-2,5-dione (1.89g, 10m.mol), *N*-bromo succinimide(3.2g,1.8m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 25 ml of ethyl acetate or 20 ml of diethyl carbonate. The product was obtained in 85% yield (2.28g) in ethyl acetate and 90% yield (2.41g) in diethyl carbonate. ^{1}H NMR δ 7.68 (d, *J* = 6.42 Hz 2H), 7.34(d, *J* = 6.42 Hz 2H), 4.63(s, 2H), 2.92 (s, 4H) ppm. ^{13}C NMR δ 176.26, 138.4, 132.1, 130.1, 126.9, 126.5, 32.6, and 28.6 ppm.

1-(4-(bromomethyl)phenyl)-1*H*-pyrrole-2,5-dione (13e):

Titled compound is prepared according to the general procedure E from 1-*p*-tolyl-1H-pyrrole-2,5-dione (1.87g, 10m.mol), *N*-bromo succinimide (3.2g,1.8m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 25 ml of ethyl acetate or 20 ml of diethyl carbonate. The product was obtained in 90% yield (2.39g) in ethyl acetate and 90% yield (2.39g) in diethyl carbonate. ^{1}H NMR δ 7.50 (d, *J* = 6.82 Hz, 2H), 7.34 (d, *J* = 6.82 Hz, 2H), 7.04 (s, 2H), 4.51(s, 2H) ppm. ^{13}C NMR δ 164.3, 138.8, 132.2, 130.2, 126.4, 32.5 ppm.

1-(bromomethyl)-4-nitrobenzene (13i): Titled compound is prepared according to the general procedure F from 4-nitro toluene (1.37g, 10m.mol), *N*-bromo succinimide (3.2g, 18m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 25 ml of ethyl acetate

or 20 ml of diethyl carbonate and was obtained in 80% yield (1.73g) in both ethyl acetate and diethyl carbonate. ^{1}H NMR (400MHz, $CDCl_3$) δ 8.16 (d, *J*=7.8 Hz, 2H), 7.54 (d, *J*=7.8 Hz, 2H), 4.51 (s, 2H) ppm. ^{13}C NMR (400MHz, $CDCl_3$) δ 147.9, 145.1, 130.2, 124.2, 37.9 ppm.

Monobromination, General Procedure F: (*For products soluble at room temperature in the reaction media*). To an ethyl acetate (15 ml) or diethyl carbonate (10 ml) solution of substituted toluenes (10 m.mol, 1eq) was added benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) and *N*-bromo succinimide (18 m.mol, 1.8 equivalents). The reaction mixture was refluxed (for respective times as in tables 1 and 2 for ethyl acetate and diethyl carbonate) under microwave heating (magnetron power of 400W for ethyl acetate and 450W diethyl carbonate). Clear reaction mixture was cooled at 5˚C for 4-5 hours. Formed white precipitate was separated by filtration and dried to give 990 mg (94%) for ethyl acetate and 1.0 g (95 %) for diethyl carbonate of succinimide. The filtrate was then evaporated under vacuum, to obtain a powdery material, which was purified by silica gel column chromatography with hexane-ethyl acetate (1:4) as an eluent. The isolated yield of 1-bromo-4-bromomethylbenzene is 1.33 g (90%) for ethyl acetate and 1.40g (95%) for diethyl carbonate as reaction media.

1-(bromomethyl)-4-fluorobenzene (13f): Titled compound is prepared according to the general procedure F from 4-flouro toluene (1.1g, 10m.mol), *N*-bromo succinimide (3.2g, 18m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 25 ml of ethyl acetate or 20 ml of diethyl carbonate and was obtained in 92% yield (1.7g) in ethyl acetate and 95% yield (1.8g) in diethyl carbonate. ^{1}HNMR (400MHz, $CDCl_3$) δ 7.37 (d, *J*

=7.2 Hz, 2H), 7.04 (d, *J* =7.2 Hz, 2H), 4.48 (s, 2H) ppm; ^{13}CNMR (400MHz, $CDCl_3$) δ 164.1, 161.6, 134.1, 131.2, 131.4, 116.1, 115.9, 32.9 ppm.

1-(chloromethyl)-4-fluorobenzene (13g): Titled compound is prepared according to the general procedure F from 4-chloro toluene (1.3g, 10m.mol), *N*-bromo succinimide (3.2g, 1.8m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 25 ml of ethyl acetate or 20 ml of diethyl carbonate. The product was obtained in 85% yield (1.73g) in both ethyl acetate and diethyl carbonate. ^{1}HNMR (400MHz, $CDCl_3$) δ 7.32 (4H, s), 4.45 (2H,s) ppm; ^{13}C NMR (400MHz, $CDCl_3$) δ 164.06, 161.6, 134.1, 131.2, 131.4, 116.1, 32.9 ppm.

1-bromo-4-(bromomethyl)benzene (13h): Titled compound is prepared according to the general procedure F from 4-bromo toluene (1.7g, 10m.mol), *N*-bromo succinimide (3.2g, 18m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 25 ml of ethyl acetate or 20 ml of diethyl carbonate. The product was obtained in 90% yield (2.3g) in ethyl acetate and 95% yield (2.4g) in diethyl carbonate. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 4.44 (s, 2H) ppm; ^{13}C NMR (400MHz, $CDCl_3$) δ 137.1, 132.2, 130.9, 122.7, 32.7 ppm.

1-(bromomethyl)-4-methoxy benzene (13j): Titled compound is prepared according to the general procedure F from 4-methoxy toluene (1.2g, 10m.mol), *N*-bromo succinimide (3.2g, 18m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 25 ml of ethyl acetate or 20 ml of diethyl carbonate. The product was obtained in 98% yield (1.9g) in both ethyl acetate and diethyl carbonate. ^{1}H NMR (400MHz, $CDCl_3$) 7.36 (d, *J*= 6.2 Hz,

2H), 7.94 (d, *J*= 6.2 Hz, 2H), 4.61 (s, 2H), 3.82 (s, 3H) ppm; ^{13}C NMR (400MHz, $CDCl_3$) δ160.05, 130.44, 130.1, 114.5, 55.5, 37.9 ppm.

9-bromo-9*H*-fluorene (13k): Titled compound is prepared according to the general procedure F from fluorene (1.7g, 10m.mol), *N*-bromo succinimide (3.2g, 1.8m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 25 ml of ethyl acetate or 20 ml of diethyl carbonate. The product was obtained in 90% yield (2.2g) in ethyl acetate and 98% yield (2.4g) in diethyl carbonate ^{1} HNMR (400MHz,$CDCl_3$) δ ppm; ^{13}C NMR (400 MHz, $CDCl_3$) δ 144.39, 140.01, 129.44, 128.31, 126.59, 120.49, 46.24 ppm.

Dibromination General Procedure G (*product insoluble in reaction media at room temperature*). Ethyl acetate (15 ml) or diethyl carbonate (10 ml) suspension of substituted toluenes (4.2 mmol, 1 eq), benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %), and *N*-bromo succinimide (12.6 mmol, 3equivalents) was refluxed for 80 minutes (ethyl acetate) or 30 minutes (diethyl carbonate) and under microwave heating (magnetron power of 500W for ethyl acetate and 600W for diethyl carbonate). Clear reaction mixture was cooled down to room temperature. Formed white crystalline product was separated by filtration, washed with ice-cold solvent and dried at room temperature. According to the HPLC the product is ~97% pure. The isolated yield of 3g was 1.2 g (70%) for ethyl acetate and 1.32 g (85%) for diethyl carbonate as reaction media. Filtrate was left at 5˚C overnight. Formed white precipitate was separated by filtration and dried to give 1.5 g (86%) for ethyl acetate and 1.6 g (92%) for diethyl carbonate of succinimide.

2-(4-(dibromomethyl)phenyl)isoindoline-1,3-dione (15a):

Titled compound is prepared according to the general procedure G from 2-*p*-tolylisoindoline-1,3-dione(2.37g, 10m.mol), *N*-bromo succinimide(5.4g, 30m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 50 ml of ethyl acetate or 40 ml of diethyl carbonate. The product was obtained in 85% yield (2.3g) in ethyl acetate and 90% yield (2.4g) in diethyl carbonate. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.96-7.98 (m, 2H), 7.81-7.83 (m, 2H), 7.5-7.7 (d, *J* = 8.42 Hz, 2H), 7.49-7.52 (d, *J* = 8.42 Hz, 2H), 6.68 (s, 1H) ppm. ^{13}C NMR (400MHz, $CDCl_3$) δ 167.2, 141.5, 134.8, 133.1, 131.8, 127.6, 124.2, 40.1 ppm.

1-(4-(dibromomethyl)phenyl)pyrrolidine-2,5-dione (15b):

Titled compound is prepared according to the general procedure G from 1-*p*-tolylpyrrolidine-2,5-dione (1.89g,10m.mol), *N*-bromo succinimide(5.37g,1.8m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 50 ml of ethyl acetate or 40 ml of diethyl carbonate. The product was obtained in 60% yield (2.1g) in ethyl acetate and 80% yield (2.8g) in diethyl carbonate. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.67 (d, *J*=6.8 Hz, 2H), 7.27 (d, *J*=6.8 Hz, 2H), 6.64(s, 1H), 2.92(s, 4H) ppm. ^{13}C NMR (400MHz, $CDCl_3$) δ 176.3, 138.4, 132.1, 130.1, 126.9, 32.6, and 28.6 ppm.

1-(4-(dibromomethyl)phenyl)-1*H*-pyrrole-2,5-dione (15c):

Titled compound is prepared according to the general procedure G from 1-*p*-tolyl-1H-pyrrole-2,5-dione (1.87g,10m.mol), *N*-bromo succinimide(5.37g,1.8m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 50 ml of ethyl acetate or 40 ml of diethyl carbonate. The product was obtained in 65% yield (2.2g) in ethyl acetate and 85% yield (2.9g) in diethyl carbonate. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.68 (d, *J* = 6.42 Hz 2H), 7.34

(d, *J* = 6.42 Hz 2H), 7.03(s, 1H), 6.68 (s, 1H) ppm. ^{13}C NMR (400MHz, $CDCl_3$) δ 164.3, 138.1, 135.3, 134.4, 131.7, 130.1, 129.1, 128.5, 127.1, 122.7, 32.6 ppm.

2-(4-(dibromomethyl)phenyl)-1*H*-benzo[*de*] isoquinoline-1,3 (2*H*)-dione (15d):

Titled compound is prepared according to the general procedure G from 2-*p*-tolyl-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione (2.87 g,10 m.mol), *N*-bromo succinimide (5.37g, 18 m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 50 ml of ethyl acetate or 40 ml of diethyl carbonate. The product was obtained in 75% yield (3.3g) in ethyl acetate and 90% yield (4g) in diethyl carbonate. ^{1}H NMR δ 8.65 (d, *J* = 7.2Hz, 2H), 8.28 (d, *J* = 7.2Hz, 2H), 7.80 (t, *J* = 7.8Hz 2H), 7.58 (d, *J*=8.2 Hz 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 6.89 (s, 1H) ppm. ^{13}C NMR (400MHz, $CDCl_3$) δ 167.4, 137.7, 134.8, 131.9, 130.1, 126.9, 124.1, 40.1 ppm.

1-(dibromomethyl)-4-nitrobenzene (15e):

Titled compound is prepared according to the general procedure G from 4-nitro toluene (1.37g, 10 m.mol), *N*-bromo succinimide (5.37g, 30 m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 50 ml of ethyl acetate or 40 ml of diethyl carbonate and was obtained in 60% yield (1.8 g) in ethyl acetate and 85% yield (2.5 g) in diethyl carbonate. ^{1}HNMR(400MHz, $CDCl_3$) δ 8.16(d, *J*=5.6 Hz, 2H), 7.54(d, *J*=5.6 Hz, 2H), 6.64(s, 1H) ppm. ^{13}C NMR (400MHz, $CDCl_3$) δ 147.9, 145.1, 130.2, 124.2, and 37.9 ppm.

Dibromination, General Procedure H (*product soluble in reaction media*). The ethyl acetate (15 ml) or diethyl carbonate (10 ml) suspension of substituted toluenes (10 m.mol, 1 eq), benzoyl peroxide (5 mg; 0.02 mmol; 0.34 mol %) and *N*-bromo succinimide (30 m.mol, 3 equivalents) was refluxed (30 minutes for ethyl acetate and 20 minutes for diethyl carbonate) under microwave heating (microwave magnetron power

of 500W for ethyl acetate and 600W for diethyl carbonate). Clear reaction mixture was cooled at 5˚C for 4-5 hours. Formed white precipitate was separated by filtration and dried to give 82-96% of succinimide for ethyl acetate and 88-97% for diethyl carbonate. The filtrate was then evaporated under reduced pressure to a powdery material, which was subjected to column chromatography with 25% hexane, ethyl acetate to obtain pure product.

1-(dibromomethyl)-4-fluorobenzene (15e): Titled compound is prepared according to the general procedure H from 4-flouro toluene (1.1g, 10m.mol), *N*-bromo succinimide (5.37g, 30m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 50 ml of ethyl acetate or 40 ml of diethyl carbonate and was obtained in 70% yield (1.9g) in ethyl acetate and 85% yield (2.3g) in diethyl carbonate. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.37 (d, *J* =7.2 Hz, 2H), 7.04 (d, *J* =7.2 Hz, 2H), 6.64 (s, 1H) ppm; ^{13}C NMR (400MHz, $CDCl_3$) δ 164.1, 162.1, 134.2, 131.2, 131.1, 116.1, 115.9, 40.7 ppm

1-(chloromethyl)-4-fluorobenzene (15f): Titled compound is prepared according to the general procedure H from 4-chloro toluene (1.3g, 10 m.mol), *N*-bromo succinimide (5.37g, 18 m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 50 ml of ethyl acetate or 40 ml of diethyl carbonate. The product was obtained in 75% yield (2.1g) in ethyl acetate and 85% yield (2.4g) in diethyl carbonate. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.32 (4H, s), 6.64 (1H, s) ppm; ^{13}C NMR (400MHz, $CDCl_3$) δ 136.6, 134.5, 130.6, 129.3, 40.1 ppm.

1-bromo-4-(bromomethyl)benzene (15g): Titled compound is prepared according to the general procedure H from 4-bromo toluene (1.7g, 10m.mol), *N*-bromo succinimide (5.37g, 1.8m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 50 ml of ethyl

acetate or 40 ml of diethyl carbonate and was obtained in 70% yield (2.3g) in ethyl acetate and 90% yield (3g) in diethyl carbonate. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.47 (2H, d, *J*=8.4 Hz), 7.26 (2H, d, *J*=8.4 Hz), 6.44 (s,1H). ^{13}C NMR (400MHz, $CDCl_3$) δ 137.1, 132.2, 130.9, 122.7, 40.1 ppm.

1-(bromomethyl)-4-methoxybenzene (15i): Titled compound is prepared according to the general procedure H from 4-methoxy toluene (1.2g, 10m.mol), *N*-bromo succinimide (5.37g, 1.8m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 50 ml of ethyl acetate or 40 ml of diethyl carbonate. The product was obtained in 75% yield (2.1g) in ethyl acetate and 95% yield (2.7g) in diethyl carbonate. **^{1}**H NMR (400MHz, $CDCl_3$) δ 7.36 (d, *J*=6.2 Hz, 2H), 7.94 (d, *J*=6.2 Hz, 2H), 6.14 (s, 1H), 3.82 (s, 3H) ppm; ^{13}C NMR (400MHz, $CDCl_3$) δ 160.1,130.4, 130.1, 114.5, 55.5, 40.1 ppm.

2.6 References and notes:

1. **Microwave Specifications**: The laboratory version of our microwave has cavity size 21.6 cm in height, 17.30 cm wide, and 25.4 cm deep with two 2.54 cm whole on the top the microwave for the condenser and thermometer. The magnetron transformer (700W) was wired directly to variable autotransformer for control of the magnetron power. ECM meter (10 Amps) was wired to the magnetron transformer to control the microwave power. The magnetic stirrer was installed beneath the cavity for stirring the reaction mixture. Reaction temperature was measured directly with a thermometer inserted into the reaction mixture through a condenser and/or by infrared reading.
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Chapter III

Synthesis of β-keto acids:

3.1. Abstract: β-Keto acids are one of the important biological components from nature and their synthesis involves complex procedures. The chapter focuses on development of the tag molecule as a protection for acid group, its deprotection and application in the synthesis of β-Keto Acids.

3.2 Introduction

3.2.1 β-Keto acids:

β-Keto acids are very important and are essential starting materials and/or intermediates in many organic syntheses like preparations of ketones[1] and many natural products[2-4]. For example in all the biosyntheses of 3-acyl tetramic acid, it was reported that the β-Keto acids are one of the primary intermediates and also play a key role in synthesis of substituted cyclopenteno phenathrenes[5]. They are very important intermediates in synthesizing biologically active compounds[6,7] like SR141716, phloroglucinols, and 5-dezaminopterin. These acids, also known as 3-oxaoalkanoic acids are used extensively for biochemical investigations, especially for studies of the mechanisms of enzyme-induced decarboxylations[8]. There are many methods reported for synthesis of these compounds but none of these are general and applicable to all compounds of this class and often very low yielding and involve tedious purification

methods. One common way that these compounds are synthesized is from 1,3 dicarbonyl compounds[9-14]. Acylation of the active carbon of these dicarbonyl compounds followed hydrolysis and decarboxylation gives β-Keto acids. However these methods require use of strong bases such as EtONa[15], EtMgBr[16], n-BuLi[17] or powerful metals like Na[18] which are not very suitable if the substrates are very sensitive. Another known method of preparation is conversion aldehydes to β-Keto acids by addition of ethyl diazoacetate in various thermal conditions[19] and also in presence of tin (II) chloride[20]. There are several other reports that used aldehydes for preparing the β-Keto acids but none of these were reliable in terms of yields and purification methods. And another major concern regarding the use of these procedures is that the method is generalized and is applicable to only a specific group of compounds. The reports themselves indicate formation of different intermediates during the reaction of some of the substrates. The article by Gutsche et al. reported formation of dioxolane from n-heptanal but not the corresponding β-Keto acid[21]. So a good method that can be applied in general to prepare any type of a β-Keto acid, good yielding, simple to purify and also applicable to industry is on demand. The chapter describes the efforts towards developing a methodology for β-Keto acids that satisfies all the above-mentioned advantages and reports a successful preparation of the compounds.

3.2.2: Protection groups and their role in synthesis:

If a chemical reaction has to be carried out selectively at one reactive site in a compound with many functional groups, the other reactive sites need to be blocked temporarily. Those compounds that are used to block the reactive sites are called

Protection Groups[22]. It is very difficult to envision the synthesis of some organic compounds and natural products without the use of protection groups and with the increasing complexity in molecules and hence their syntheses, the chemists needed and developed more new protection groups with specific tasks to be performed. However there are some minimum requirements that are looked for in a new protection group.

1. It must react selectively in good yield to give a protective substrate that is stable to projected reactions.
2. Should have minimum additional functionality to avoid further sites of reaction.
3. It should be selectively removed in good yield by readily available, preferably non toxic reagents
4. The protective group should form a crystalline derivative without generating any new stereogenic centers and can be easily separated from side products

Since only a few protection groups can satisfy all these criteria for elaborate substrates, a large number of mutually complementary protective groups are needed and are available too.

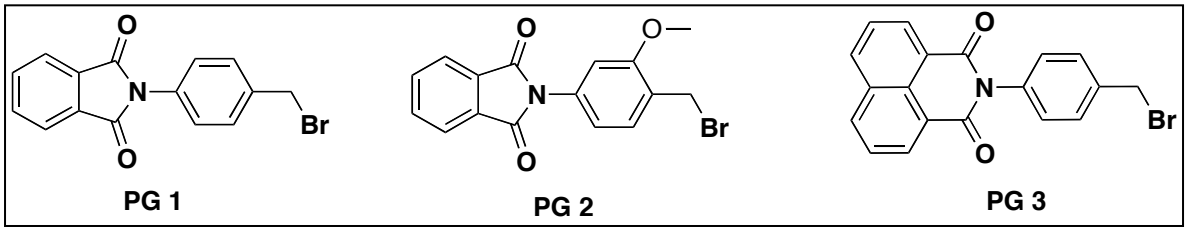


Figure 3.1. The tag molecules to be used for synthesis.

Three tag molecules, PG1, PG2 and PG3 as in fig.1 were designed, which satisfied the first two conditions from the studies done in chapter II but the conditions 3 and 4 ought to be tested out and is done in the following results and discussion. Along with designing the protection groups, the protection and deprotection methods should be established and these conditions also have to come over a set of requirements to be proven as able protection groups.

Phthalic anhydride and its derivatives are known to be used for protection of amines and acids[23-28]. The protection and deprotection of amines and acids with these protection groups is well studied and is performed in a variety of conditions. While there are many protection groups for acids, more are being invented and used because of their specific use in a particular synthesis. In this chapter the tag molecule phthalimido benzyl group, its derivatives and naphthalimido benzyl groups are identified as a protection group for acids and its protection-deprotection chemistry is studied. The assumption that it can be deprotected under variety of conditions was made with the idea that they can be hydrogenated and also hydrolyzed in presence of a base and an acid. And so its orthogonality in deprotection can be taken advantage of, especially in preparation of peptides from amino acids. Depending on the type of protection on amine group, the deprotection of ester can be altered. When benzyloxy carbonyl protected amine is used the ester can be deprotected under acidic conditions for selective acid deprotection and catalytic hydrogenation or simple NaOH hydrolysis can be used for butoxy carbonyl protected amino esters. And in acids other than amino acids, the deprotection can be altered depending on whether the substrate has acid or base labile groups. On the whole the tag molecules as shown in fig.1 as protection groups seemed

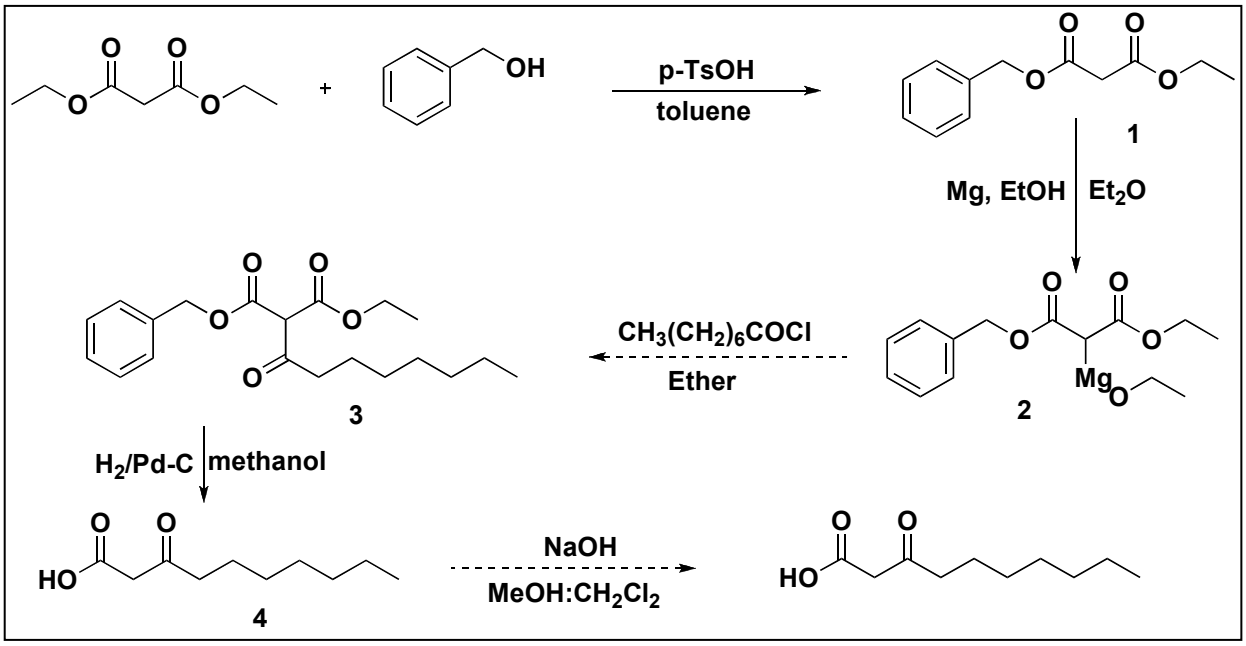
to have promising application in protection deprotection of acids, amines and sulfides. Moreover their broad range of applications as protection groups and tag molecules envisions potency in synthesizing the β-Keto acids.

3.3 Results and Discussion:

3.3.1: The Tag molecule in the synthesis of β-keto acids:

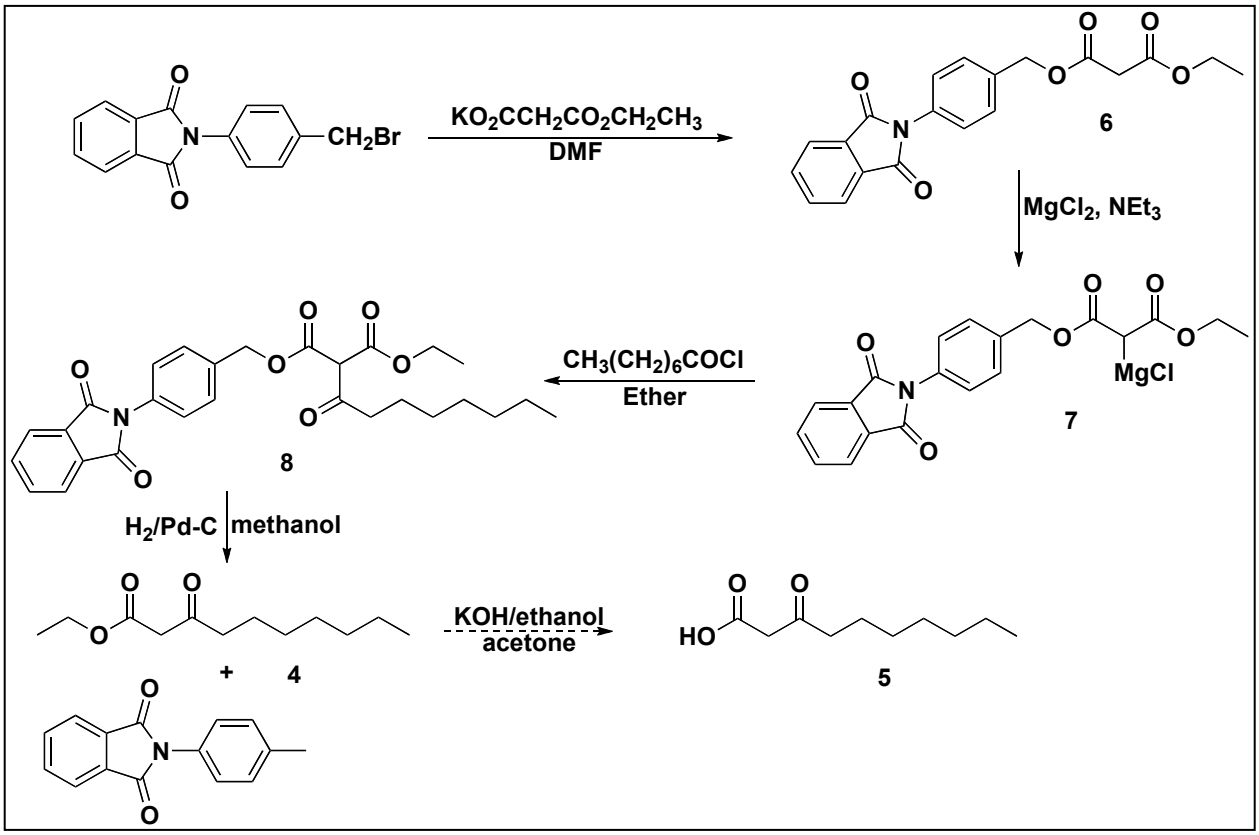
Of all these methods using 1,3 dicarbonyls and especially malonate esters is the commonly used method but still has many disadvantages. Diethyl malonate was the first used of its kind for the synthesis of these acids. But the problem associated with the use of diethyl malonate was that the two ethyl esters compete against each other for hydrolysis in spite of using one equivalent of the base (NaOH, LiOH or KOH), there by reducing the yield of the reaction at this stage greatly. Also the diethyl malonate esters are liquids and remain liquids after c- acylation. The R_f values of these compounds being very close they are tough to be isolated using column chromatography and hence have to be distilled to obtain pure compounds. But being very sensitive to heat (as they undergo decarboxylation at elevated temperature), distilling these liquids often results in loss of some of the product, which decomposes to the corresponding ketone. To over come this problem one of the ethyl esters was replaced by tert-butyl ester and the same synthetic sequence has been studied for preparation of some β-Keto acids[29]. This method has improved the handling of the reaction but the yields were still very low. Later trimethyl silyl esters were used instead of the ethyl esters but the yield and purification methods did not make any substantial improvements even in this method[30].

However all these esters, diethyl, mono ethyl tert-butyl and di silyl esters of malonate are all liquids and hence purification of these compounds would still remain complicated with them being liquids. It will ultimately result in low yields and tedious purification procedures. This was the starting point of the current synthesis towards β-Keto acids where the benzyl esters substituted the above-mentioned esters. Initial attempts were towards the making of dibenzyl malonate with an assumption that the di benzyl ester would be a solid and so can be easily handled. The proposed synthesis of β-Keto acids is as shown in fig.2 and the proposal was based on the idea that benzyl ester would be a solid as compared to ethyl ester and so purification methods would be easier as compared to the other esters previously reported. But during the synthesis of mono benzyl ethyl malonate it was realized that it is a liquids too and the purification and handling of this compound is as tough and tedious as handling the ethyl ad silyl esters. In process of obtaining the product **3** there was decomposition of **2** observed due to the vigorous reactivity of Mg in ether. The scheme was later altered by switching mono benzyl ethyl malonate to di benzyl malonate and was not successful in spite of the change.



Scheme 3.1. Proposed synthesis of β-Keto acids using mono benzyl ester.

So a more stable ester than mono benzyl ethyl malonate, dibenzyl malonate was necessary to obtain a successful synthesis and in this context the proposed tag molecules from previous chapters were introduced in to the synthesis. The idea behind using these tag molecules is that they are of a much higher molecular weight as compared to benzyl esters and so the physical properties of these compounds would be much different and better than them. The tag molecule PG 1 was chosen for its simplicity, to start with amongst the three and based on the above assumption the synthesis of β-Keto acids was proposed is as shown in scheme 3.2.



Scheme 3.2 Synthesis of β-Keto acids using the tag molecule.

The scheme was successful in preparation of compound **6a** and the idea of transforming them into solids was successful and **6a** was also recrystallized from dichloromethane. However the attempts to synthesize **7** remained unsuccessful as the tag molecule would hydrolyze in the process. The Grignard conditions which were proposed earlier as were too harsh for these types of compounds, the alternatives to this method were explored and the $MgCl_2$, NEt_3 conditions suited best. **8** was successfully synthesized using $MgCl_2$ conditions. But the next step which involves the removal of tag molecule by hydrogenation gave only a satisfactory yield. In order to improve the yield of this reaction and to explore the alternatives it was felt that the tag

molecule should be investigated for protection-deprotection sequences. Since the protection in the above sequence is acid protection as an ester, it was first explored for ester protection and deprotection.

3.3.2 Tag molecule as protection group for acids:

The tag molecules were prepared using microwave synthesis as reported in chapter II and since the high molecular weight of the protection group can change the physical properties of some liquids and oily substances with a low molecular weight, by making them solids and hence making purification easier by recrystallization or a simple wash with non polar solvents. The advantages of the using the tag molecules as protection groups PG 1, PG 2 or PG 3 are as follows:

- They are prepared from inexpensive starting materials in few steps
- The protection groups can be easily deprotected and recycled in most cases.
- The protection groups are organic equivalents of resin, due to high molecular weight and hence simple solvent wash can purify the products.
- The imidic bond in the molecules give crystalline properties to the products there by making purification easier by recrystallization.
- Their UV activity solves the characterization problems usually associated with resins.
- Dry conditions are not required to monitor the reactions.

As the protection group has been designed and synthesized in a good yield, it has been applied to the protection of the acid and the protection group can be incorporated on to the acids in three different ways as shown in fig.3.2.

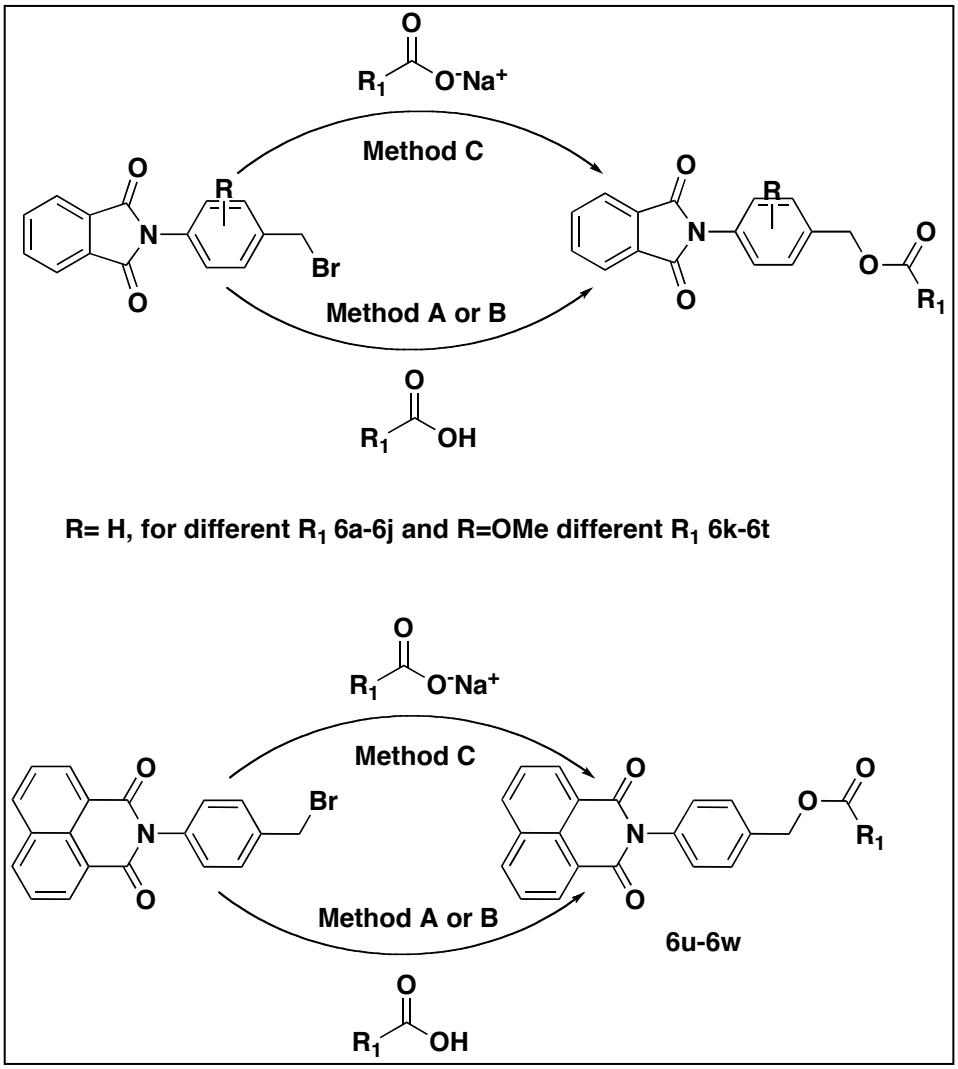


Figure 3.2 Protection of Acids with PG1, PG2 and PG3.

The protection group can be incorporate onto the acid by reacting it with the acid in three ways.

1) The salt of corresponding acid.
2) The acid in presence of cyclohexyl amine.
3) The acid in presence of $NaHCO_3$.

All the protection groups PG 1, PG 2 and PG 3 were studied for protection deprotection sequences. In the first method the salt of an acid is used and the tag molecule is mixed with the salt of an acid in solvents like DMF or DMSO and sonicated for few hours to obtain the esters. Three acid salts, sodium acetate, sodium benzoate and potassium salt of mono ethyl malonate have been transformed into their corresponding esters using this method. However it would not be practically possible to produce the salt of every acid. As alternatives, the other two methods involve use of acids directly with the protection groups in presence of two bases $NaHCO_3$ and cyclohexyl amine. When DMSO was used as solvent, the benzyl bromides would react with cyclohexyl amine to produce about 5% of the corresponding secondary amine. However switching the solvent from DMSO to DMF has solved the problem and hence increased the yield of the desired product. All three methods involve very simple reaction conditions. The mixture is sonicated for few hours and precipitation of product would occur with ice. The first two protection groups PG1 and PG 2 were successful in synthesizing the esters (**6a-6t**) using all the three methods. All methods yielded good to excellent yields as shown in table 3.1. The structures of the acids are shown in figure 3.3.

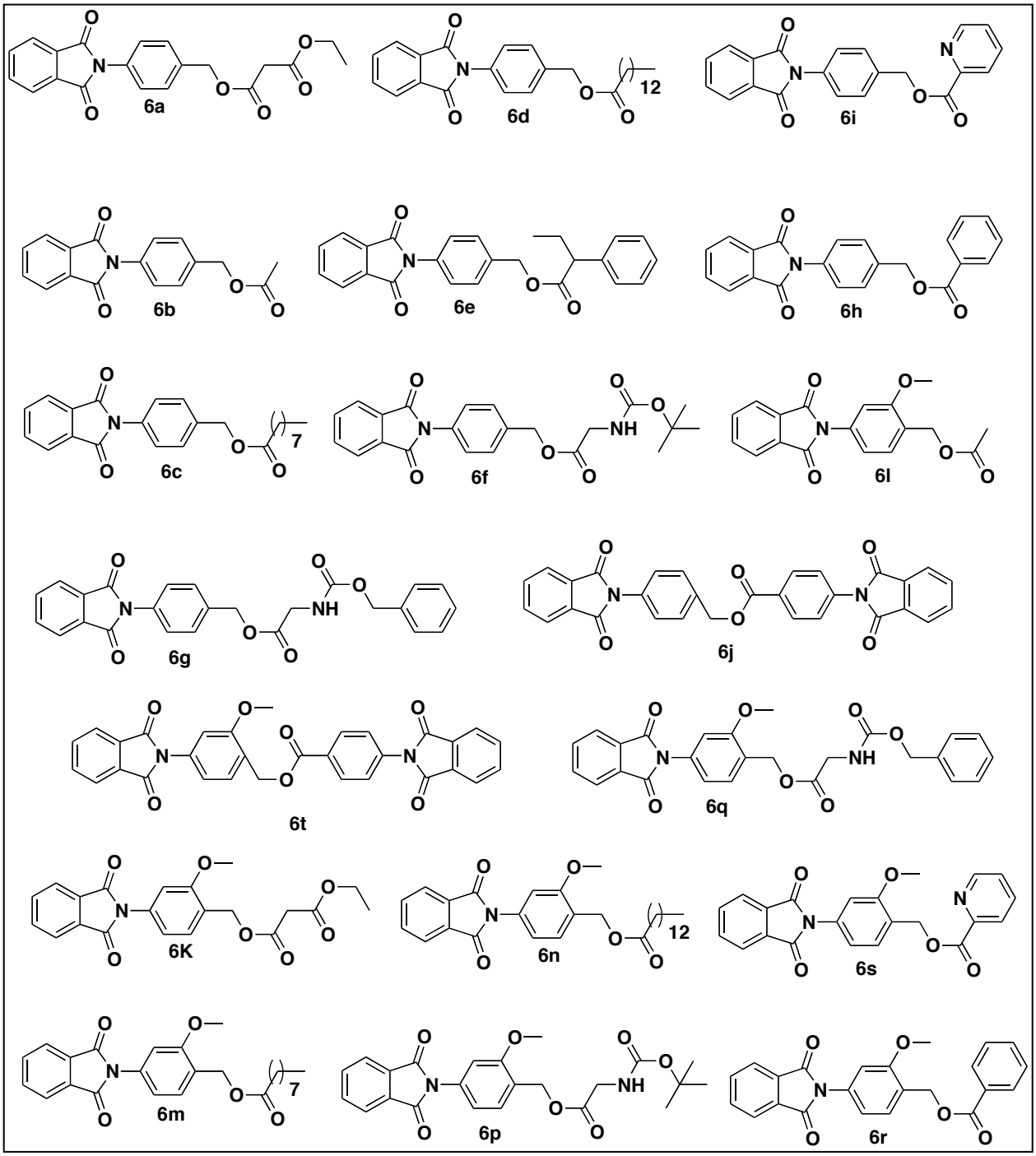


Figure 3.3 Structures of protected esters using protection groups with PG1 and PG2.

Table 3.1. Protection of acids as corresponding esters with PG1 and PG2.

Esters	Isolated Yield (%)		
	Method A	Method B	Method C
6a	NA	NA	90
6b	76	79	93
6c	89	92	NA
6d	87	91	NA
6e	84	95	96
6f	87	90	NA
6g	84	91	NA
6h	88	94	NA
6i	78	81	NA
6j	91	94	NA
6k	NA	NA	93
6l	75	77	91
6m	86	90	NA
6n	87	93	NA
6o	86	93	NA
6p	81	91	NA
6q	79	87	NA
6r	88	95	96
6s	84	88	NA
6t	93	96	NA

NA- Not Applicable, NP - No Product

However, the third protection group PG 3 was not successful except for the salt of acids method. In presence of the bases, the protection group PG 3 was hydrolyzed and hence did not produce desired esters. The products (**6u-6w**) are shown in figure 3.4 and their yields using the protection group PG 3 are reported in table 3.2.

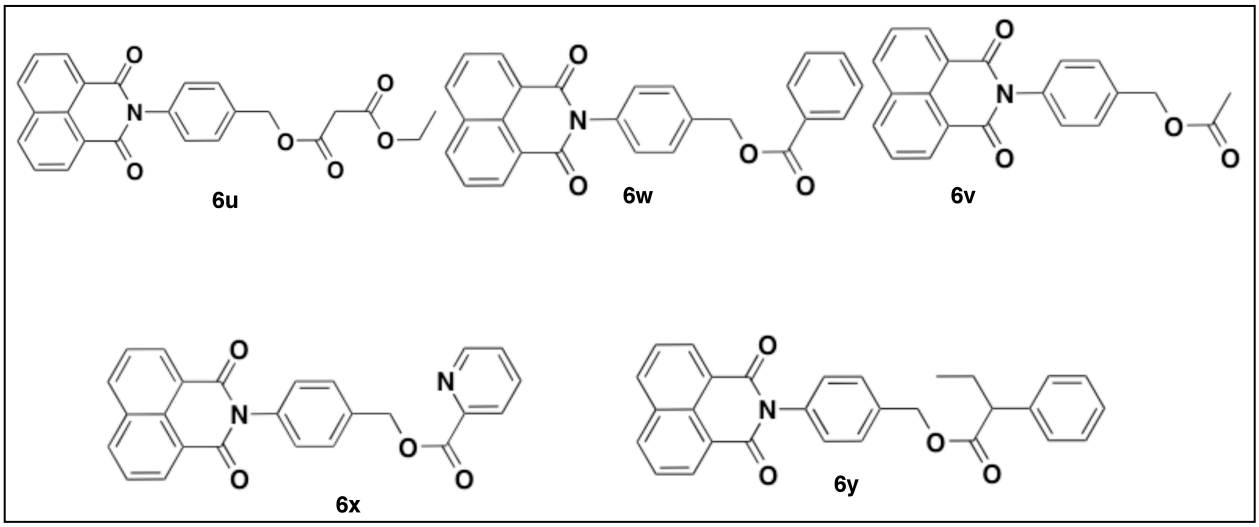


Fig 3.4 Esters produced using the protection group PG 3.

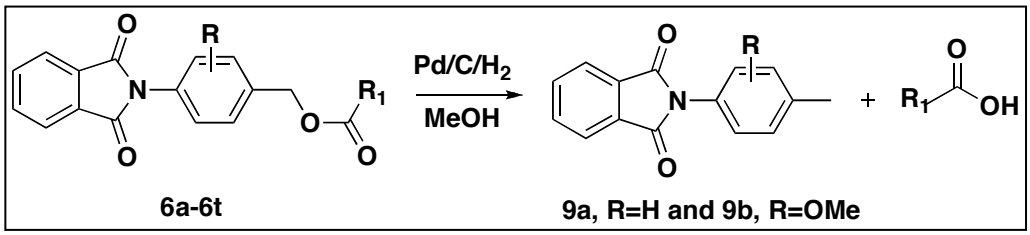
Table 3.2. Protection of acids as corresponding esters with PG 3.

Ester	Isolated Yield (%)		
	Method A	Method B	Method C
6u	NA	NA	79
6v	NA	NA	84
6w	NA	NA	92
6x	NP	NP	NP
6y	NP	NP	NP

NA - Not Applicable, NP - No Product (Hydrolysis of PG3)

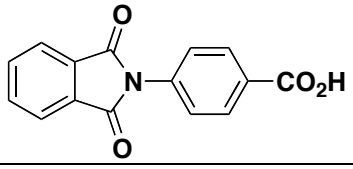
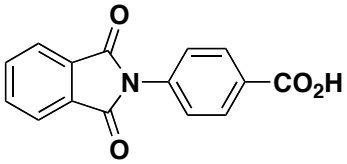
3.3.3. Deprotection with Palladium (neutral conditions):

While exploring the deprotection methods for the esters various factors were considered. The deprotection conditions should mild and simple and should not affect any of the substrates in the process. They should also be good yielding as the yield loss in this step greatly affects the yield of overall other reactions in the sequence. The idea behind designing the protection group was to make its applicability vast and general for most of the substrates. The orthogonality of deprotection is one of the main factors that decides the applicability of the protection groups and hence having different deprotection methods that not only vary in their behavior but also can be altered as per the substrate requirements is desired. All the esters **6a-6t** were deprotected with this method and yielded about 78-96% yield. For those substrates, which are sensitive to hydrogenation, it was observed that the product underwent complete hydrogenation. In those reactions where a parallel deprotection needs to be employed, with these protection groups, both deprotections can be obtained in single step. For example in case of **6g** and **6q** Cbz-protected glycine ester produced glycine as end product deprotecting both PG 1/PG 2 and Cbz at the same time. As an added advantage the precursor of the protection group corresponding toluene was obtained as by product in deprotection, which can further be brominated in the benzyl position to obtain the desired protection group. So this method also helps recycle the protection group and re use of the same was tested out form one of the deprotection. The recycle and re-use was successful not just on small scale but was acceptable up to a scale of 10g produced in our lab. The scheme and results for deprotecion[9] using $Pd/C/H_2$/MeOH are as shown in fig.5 and table 4:

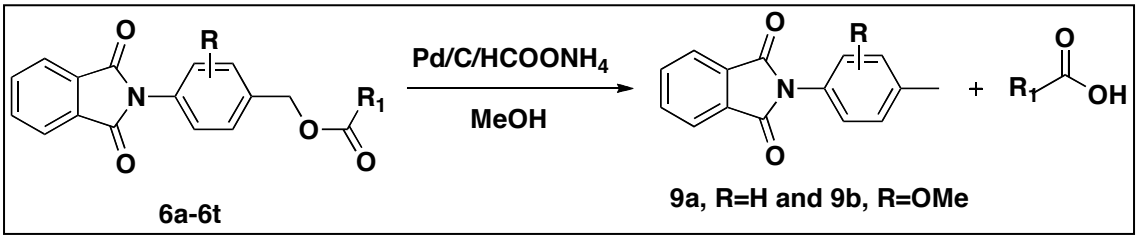


Scheme 3.3. Deprotection of PG1 and PG 2 with $Pd/C/H_2$

Table 3.3: Deprotection using $Pd/C/H_2$ in MeOH.

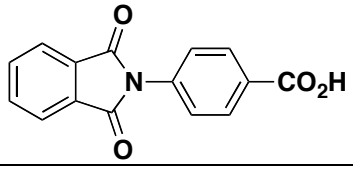
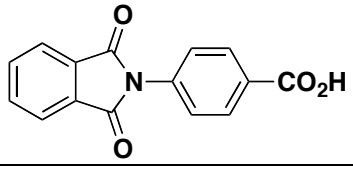
Ester	Isolated Acid	Yield (%)	9a/9b(%)
6a	Monoethlyl malonate	87	86
6b	Acetic acid	82	85
6c	Octanoic acid	84	81
6d	Dodecanoic acid	82	84
6e	2-Phenyl butanoic acid	93	88
6f	Boc-Glycine	84	87
6g	Glycine	79	81
6h	Benzoic acid	96	89
6i	Picolinic acid	84	87
6j		92	86
6k	Mono ethyl malonate	86	85
6l	Acetic acid	79	89
6m	Octanoic acid	83	88
6n	Dodecanoic acid	87	83
6o	2-Phenyl butanoic acid	91	88
6p	Boc-Glycine	83	84
6q	Glycine	81	79
6r	Benzoic acid	94	91
6s	Picolinic acid	85	88
6t		92	90

Although hydrogenation using Pd/C is one of the most common methods, it might not be practically possible to use in all scales and is not convenient to use a balloon of hydrogen or par shaker at all times. And since palladium has been extensively studied and various other sources of H_2 have been reported, $Pd/C/HCOONH_4$ was tried as second method of deprotection for the esters. The method is comparable to the results from previous method to most of the esters. It was most effective for aromatic esters and in case of aliphatic esters; the yields of the obtained acids were a little lower than aromatic esters. Even in this method, the protection group ca be reproduced from a recycled compound upon benzyl bromination. Table 5 explains the isolated yields of the acids and the precursor of the protection group produced in the reaction. In both cases the results were in comparison to the previous method and so the choice of method would depend on convenience and availability of raw materials and the equipment in the lab. In case of malonic ester **6a** and **6k** however this method was not very successful because it involves heating the reaction mixture and malonic esters being sensitive to heat, decomposed during the reaction.



Scheme 3.4. Deprotection using $Pd/C/HCOONH_4/MeOH$[10].

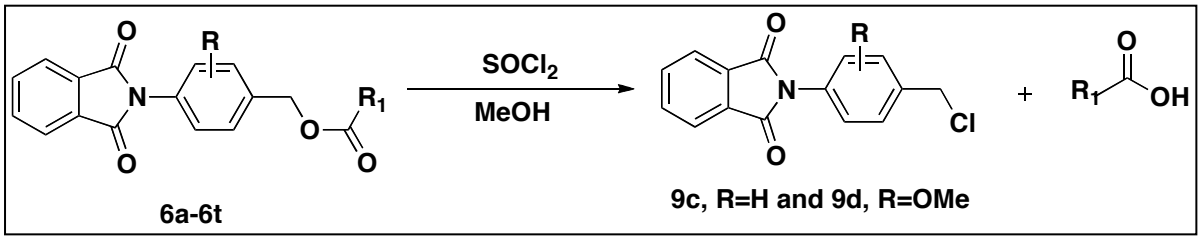
Table 3.4: Deprotection using Pd/C/$HCOONH_4$/MeOH

Ester	Isolated Acid	Yield (%)	9a/9b(%)
6a	No reaction	NA	86
6b	Acetic acid	82	85
6c	Octanoic acid	84	81
6d	Dodecanoic acid	82	84
6e	2-Phenyl butanoic acid	93	88
6f	Boc-Glycine	84	87
6g	Glycine	79	81
6h	Benzoic acid	96	89
6i	Picolinic acid	84	87
6j		92	86
6k	No reaction	NA	85
6l	Acetic acid	79	89
6m	Octanoic acid	83	88
6n	Dodecanoic acid	87	83
6o	2-Phenyl butanoic acid	91	88
6p	Boc-Glycine	83	84
6q	Glycine	81	79
6r	Benzoic acid	94	91
6s	Picolinic acid	85	88
6t		92	90

3.3.4 Deprotection in acidic conditions.

If there would any palladium labile groups on the substrate the hydrogenation conditions would not suit and so an alternative deprotection is desirable. The ester deprotection in general can be done in both acidic and basic conditions. The acidic conditions were first explored and various acids were tested out for deprotection. One of the first acids to try

was, trifloro acetic acid, however this acid was not strong enough to hydrolyze the ester. All the esters **6a-6j** were resistant to TFA. It was initially postulated that the methoxy group on esters **6k-6t** would make the ester more labile than that of esters **6a-6j** but the results obtained proved that an acid stronger than TFA is required to hydrolyze the esters. HCl, SO_2Cl_2 and $(COCl)_2$ were then used as sources of acid. Using HCl as acid with methanol as solvent at zero degrees, most of the esters were hydrolyzed[10] and in those esters with acid labile groups or other acid labile protection groups like BOC both the protection groups were deprotected. In esters **6f** and **6p** glycine esters protected with BOC are completely hydrolyzed and glycine was the end product obtained. Oxalyl chloride was more reactive than thionyl chloride under same conditions towards same esters.

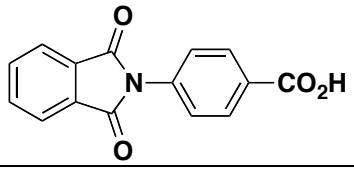
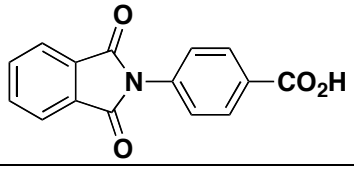


Scheme 3.5. Deprotection using $SOCl_2$/MeOH.

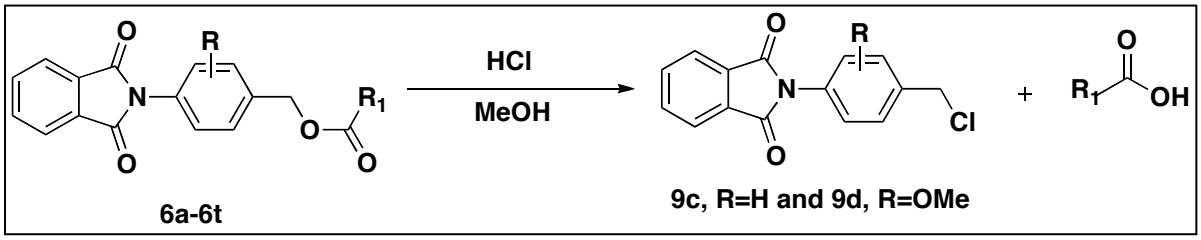
Some of the esters were decomposed also under these conditions and since these conditions were too harsh, oxalyl chloride was eliminated as one of the deprotectants. The ester of mono ethyl malonate was not stable under either conditions of thionyl or oxalyl chloride. The overall yields for all the acids obtained through this deprotection was a little lower than the hydrogenation conditions with the low yield being accounted

to the loss of products during work up. The scheme in fig and the table below explain the reaction conditions and results of the deprotection of various esters.

Table 3.5: Deprotection under acidic conditions using $SOCl_2$.

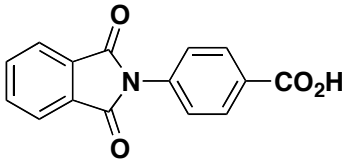
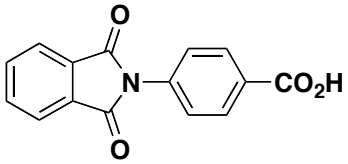
Ester	Isolated Acid	Yield (%)	9a/9b(%)
6a	No reaction	NA	86
6b	Acetic acid	82	85
6c	Octanoic acid	84	81
6d	Dodecanoic acid	82	84
6e	2-Phenyl butanoic acid	93	88
6f	Glycine	84	87
6g	Cbz-Glycine	79	81
6h	Benzoic acid	96	89
6i	Picolinic acid	84	87
6j		92	86
6k	No reaction	NA	85
6l	Acetic acid	79	89
6m	Octanoic acid	83	88
6n	Dodecanoic acid	87	83
6o	2-Phenyl butanoic acid	91	88
6p	Boc-Glycine	83	84
6q	Cbz-Glycine	81	79
6r	Benzoic acid	94	91
6s	Picolinic acid	85	88
6t		92	90

As thionyl chloride conditions resulted too low yields, another method of acidic deprotection, which is a little stronger than thionyl chloride is tried and was successful, is to use HCl. The results were comparable to the thionyl chloride method with improved



Scheme 3.6. Deprotection using HCl/MeOH.

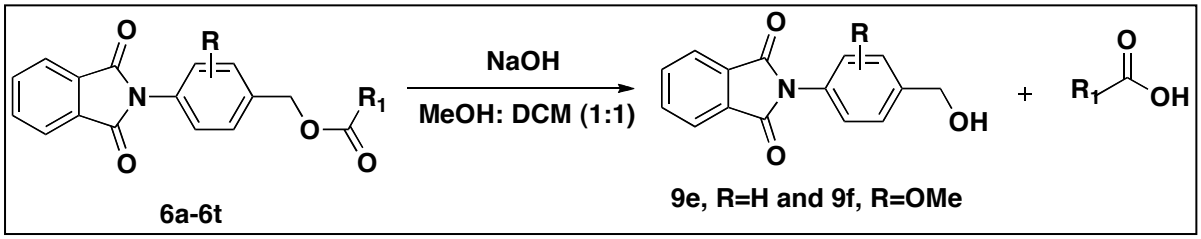
Table 3.6. Deprotection of esters using HCl/MeOH:

Ester	Isolated Acid	Yield (%)	9a/9b(%)
6a	Monoethlyl malonate	87	86
6b	Acetic acid	82	85
6c	Octanoic acid	84	81
6d	Dodecanoic acid	82	84
6e	2-Phenyl butanoic acid	93	88
6f	Glycine	84	87
6g	Cbz-Glycine	79	81
6h	Benzoic acid	96	89
6i	Picolinic acid	84	87
6j		92	86
6k	Mono ethyl malonate	86	85
6l	Acetic acid	79	89
6m	Octanoic acid	83	88
6n	Dodecanoic acid	87	83
6o	2-Phenyl butanoic acid	91	88
6p	Glycine	83	84
6q	Cbz-Glycine	81	79
6r	Benzoic acid	94	91
6s	Picolinic acid	85	88
6t		92	90

yields in comparison. The figure 8 below explains the reaction conditions with the table 7 showing the acids obtained. In both these methods, using thionyl chloride or HCl, the byproducts 9c and 9d are produced in good yields which themselves can be used as protection groups or undergo exchange of bromides to produce the tag molecule.

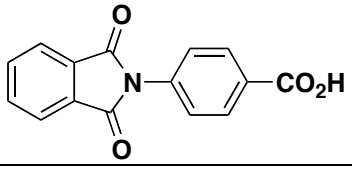
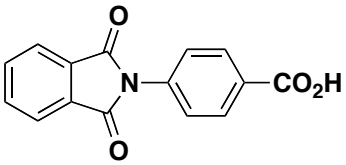
3.3.5 Deprotection in basic conditions.

As the acidic conditions showed good results the conditions were then extended to basic conditions and the hydrolysis with NaOH was one of the common base hydrolyses used in general, so the same conditions were first explored. The hydrolysis of esters in presence of NaOH was successful for almost all of the esters and also was a reliable synthetic procedure. The yields of the acids were good and it also produced a by products **9e** and **9f** which is the protection group with hydroxy substituent instead of the bromo derivative. The by products **9e** and **9f** can directly be used as protection groups for esters directly as alcohols and so recycling of the tag molecule is still a possibility in this deprotection method also. The isolation of **9e** and **9f** was not difficult too because it precipitates, as the reaction proceeds to completion and hence can be filtered off to obtain in 100% purity. The only exceptions in this case are esters 6a and 6k, both of these esters have two centers of hydrolysis, an ethyl ester and benzyl ester, both hydrolysable under these conditions. The hydrolysis was not selective even with 1 equivalent of NaOH or by using milder conditions like LiOH. All the acids were produced in excellent yields as shown in table 8 and the byproduct was easily isolated from the reaction mixture for a reuse. The figure 9 explains the reaction condition for deprotecting with NaOH.

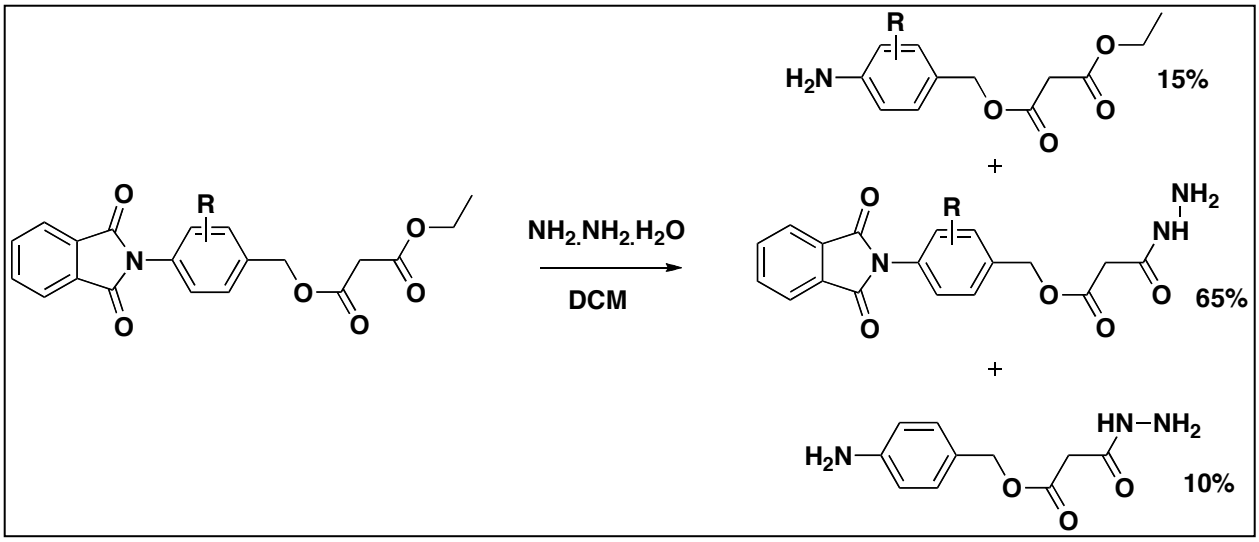


Scheme 3.7. Deprotection using NaOH/DCM: MeOH (1:1).

Table 3.8. Deprotection using NaOH/DCM: MeOH (1:1).

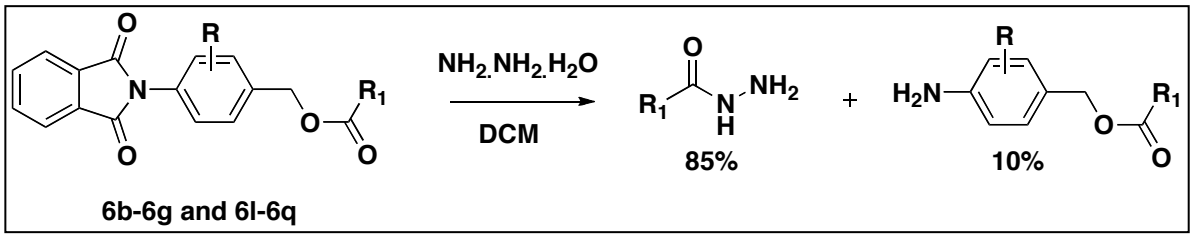
Ester	Isolated Acid	Yield (%)	9e/9f(%)
6a	Monoethlyl malonate	87	86
6b	Acetic acid	82	85
6c	Octanoic acid	84	81
6d	Dodecanoic acid	82	84
6e	2-Phenyl butanoic acid	93	88
6f	Boc-Glycine	84	87
6g	Cbz-Glycine	79	81
6h	Benzoic acid	96	89
6i	Picolinic acid	84	87
6j		92	86
6k	Mono ethyl malonate	86	85
6l	Acetic acid	79	89
6m	Octanoic acid	83	88
6n	Dodecanoic acid	87	83
6o	2-Phenyl butanoic acid	91	88
6p	Boc-Glycine	83	84
6q	Cbz-Glycine	81	79
6r	Benzoic acid	94	91
6s	Picolinic acid	85	88
6t		92	90

Use of hydrazine hydrate as deprotecting reagent for phthalimide protection has been reported before several years and since the protection groups PG1 and PG2 are structurally related to phthalimide, hydrazine was tested out for these protection groups too. However the deprotection of esters under these conditions were different for different types of ester. The aliphatic esters had different results form the aromatic ones. For example, protected malonate ester **6a** lead to a group of strange byproducts in different yield % as shown in fig 3.8.



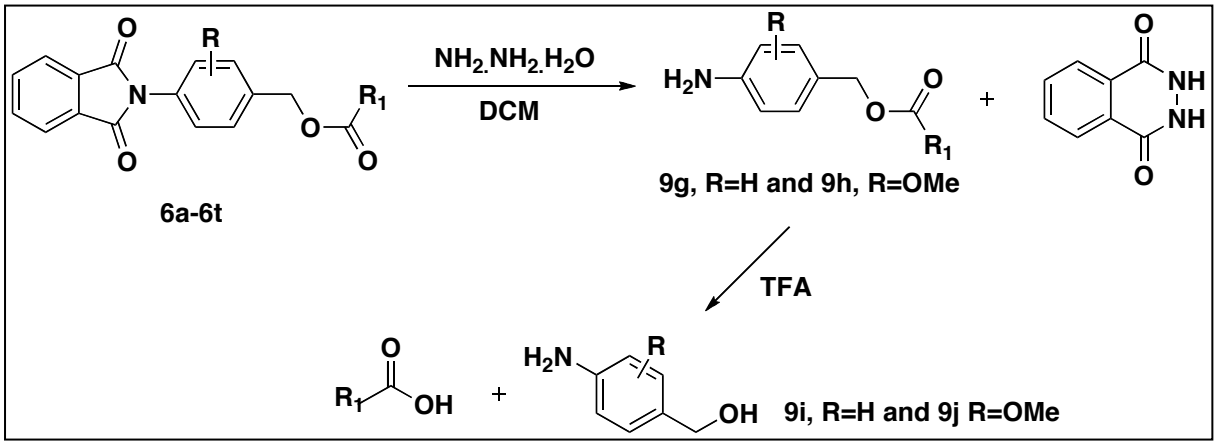
Scheme 3.8. Deprotection of protected mono ethyl malonate in Hydrazine.

And in case of the other aliphatic esters **6b** - **6g** and **6l** - **6q** there would be only two products unlike **6a** due to the fact that the centers of hydrolysis is less in those esters as in comparison with **6a**. But even in this case the deprotection was not successful, as desired reactions did not occur. The figure 12 explains the products obtained in the deprotection of these aliphatic esters. The site of aliphatic ester was more reactive to hydrazine than on the phthalimide.



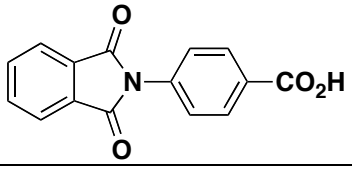
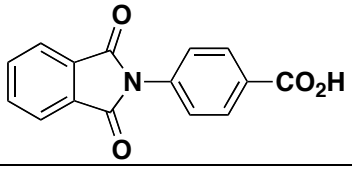
Scheme 3.9 Deprotection of protected aliphatic esters in Hydrazine.

In case of aromatic esters however the deprotection was successful but had to be done in two steps. The aromatic esters when reacted with hydrazine, another protected ester **9g** or **9h** was produced but did not completely deprotect it. However **9g** or **9h** upon further treatment with TFA hydrolyzed the ester completely to give the unprotected acid. The scheme in fig 13 explains the two-step deprotection procedure for aromatic esters using hydrazine hydrate followed by trifloro acetic acid. Although the ester deprotection is done in two steps, the purification is easy and not complicated because the hydrazide of phallic acid precipitates in DCM and filtering the precipitate leaves the ester solution of **9g** or **9h** in DCM when treated with TFA and a HCl wash gives the desired acid. All the aromatic esters were produced in good yields and the table below summarizes the byproducts formed with various substrates.



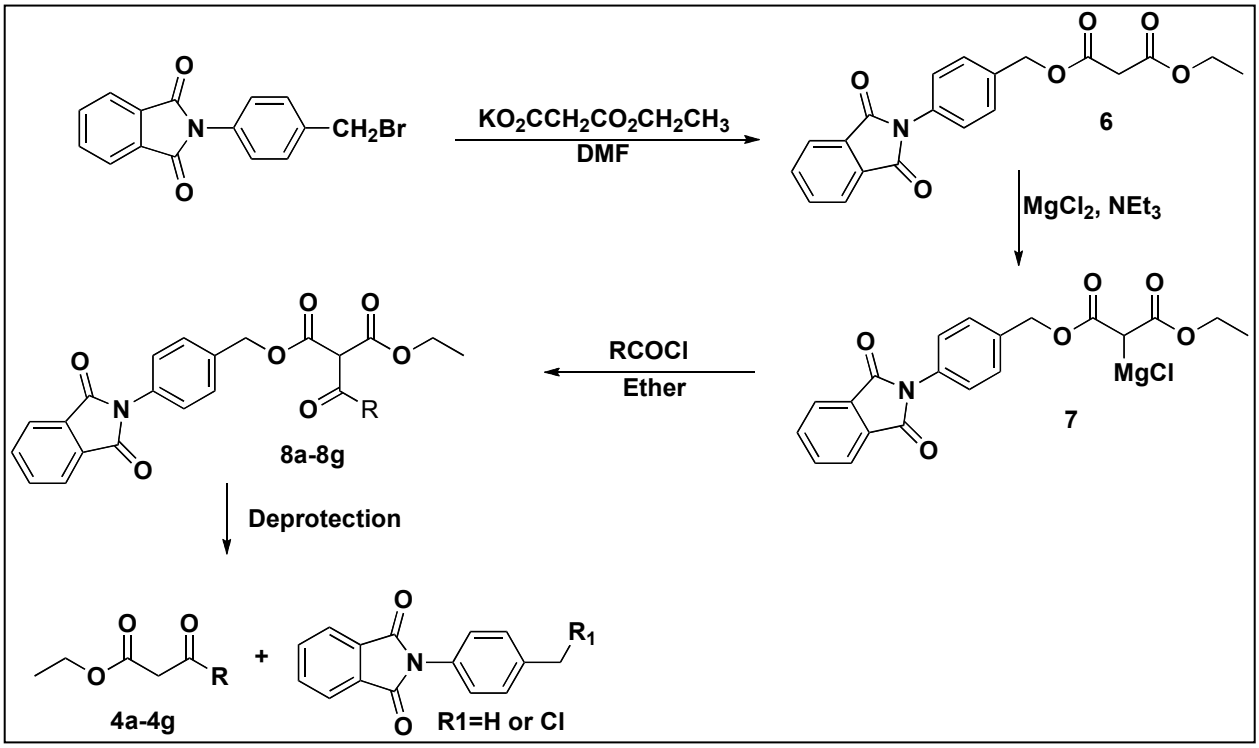
Scheme 3.10 Deprotection of protected aromatic esters in Hydrazine.

Table 3.9: Deprotection using $NH_2NH_2.H_2O$/MeOH and TFA/DCM

Ester	Isolated Acid	Yield (%)
6h	Benzoic acid	96
6i	Picolinic acid	84
6j		92
6r	Benzoic acid	94
6s	Picolinic acid	85
6t		92

3.4 Application of the protection group in synthesizing β-keto esters:

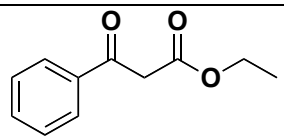
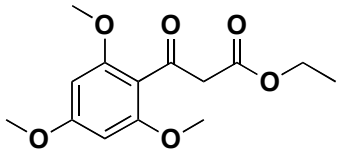
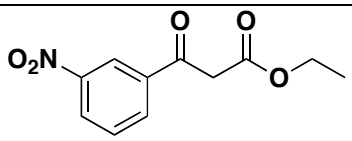
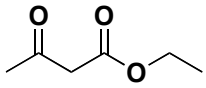
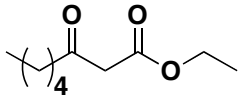
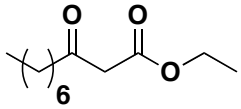
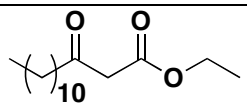
After various deprotection methods are explored for the various esters, they were incorporated into the synthesis of β-keto esters. The base hydrolysis with NaOH was not a good method for hydrolysis to β-keto esters as discussed earlier and the hydrazine hydrate hydrolysis was good only for aromatic esters and the β-keto esters are aliphatic and so base hydrolysis can be eliminated from deprotection methods. The acid hydrolysis is however useful in deprotection to obtain the β-keto esters. The ethyl ester was stable to the acid hydrolysis and the protection group was successfully deprotected during the synthesis of β-keto esters. The hydrogenation conditions were successful with palladium, carbon but the palladium; ammonium formate conditions were not suitable as the reaction conditions involve heating the mixture and the β-keto esters were not stable at these temperatures. The β-keto esters would decompose in these reaction conditions. Effectively, not all conditions were successful but the acidic hydrolysis and hydrogenation conditions were suitable in producing the β-keto esters and the scheme explains the synthesis of β-keto esters.



Scheme.3.11 Synthesis of β-keto esters.

Using the above mentioned deprotection methods the β-keto esters shown in the table 13 were produced in good to excellent yields. The substituent R on the esters was substituted by various aliphatic and substituted aromatic esters to explore the possibility of synthesis with various substrates. All the reactions in the scheme resulted in good yields there by enhancing the overall yield of the final product.

Table 3.9. The β-keto esters produced using the protection group.

S.No	β-Keto ester	Deprotection Method	Yield (%)
4a		$Pd/C/H_2$	96
4b		$Pd/C/H_2$	94
4c		$Pd/C/H_2$	93
4d		$Pd/C/H_2$	87
4e		$Pd/C/H_2$	84
4f		$Pd/C/H_2$	86
4g		$Pd/C/H_2$	88

3.5 Conclusion:

The protection group was tested for protecting the acids and various deprotection methods were developed. The protection of acids to esters has been done in three different ways and the deprotection groups were classified as acidic, basic and neutral conditions. They can be employed depending on the substrates, substrates with acidic labile moieties can use basic conditions and those with base labile moieties use acidic conditions. And so different deprotection conditions can be used, especially in those cases where parallel deprotections necessary. All the protection and deprotection methods yielded good to excellent results. And also in most cases the protection groups were recycled and can be re used. And these results were then applied to the synthesis of the β-keto esters**.** Although all deprotection conditions were used in synthesizing the β-keto esters, only acidic conditions and the palladium with carbon conditions were successful in application of their synthesis. Using these deprotection methods, a variety of β-keto esters were produced in very good yields. This method of synthesis was proven to be better than the existing ones and hence is a good contribution to synthetic chemistry. To conclude the protection group was not only successful in acid protection and deprotection but also was successful in synthesizing the β-keto esters in excellent yields.

3.6 Experimental and spectral data:

General Method of Preparation of Esters:

Method A: To a suspension PG 1, PG 2 or PG 3 (10 m.mol, 1 eq) and corresponding acid (10 m.mol, 1 eq) in 10ml of dimethylsulfoxide, was added 1 ml of dicyclohexyl amine*. The clear solution thus obtained was sonicated for about 4 hrs and the solution was poured on to ice to form a white precipitate. The precipitate was then filtered and washed with water 2-3 times. The product is crystallized from the precipitate in methanol, alternatively can be subjected to column chromatography and is isolated in 3% Methanol, Chloroform.

Method B: To A suspension of PG 1, PG 2 or PG 3 (10 m.mol, 1 eq) and corresponding acid (10 m.mol, 1 eq) in 10ml of dimethylsulfoxide, was added $NaHCO_3$ (12 m.mol, 1.2 eq). The reaction mixture was then sonicated for 4-5 hrs. The hot clear solution thus obtained, indicating the completion of reaction was poured on to ice to form a white precipitate. The precipitate was then filtered and washed with water 2-3 times. The product is crystallized from the precipitate in methanol, alternatively can be subjected to column chromatography and is isolated in 3% Methanol, Chloroform.

Method C: A suspension of PG 1, PG 2 or PG 3 (10 m.mol, 1 eq) and corresponding salt of the acid (10 m.mol, 1 eq) in 10ml of dimethylsulfoxide or dimethyl formamide was sonicated for about 4 hrs and the solution was poured on to ice to form a white precipitate. The precipitate was then filtered and washed with water 2-3 times. The product was crystallized from the precipitate in methanol, alternatively can be purified by column chromatography and is isolated in 3% Methanol, Chloroform.

4-(1, 3-dioxoisoindolin-2-yl) benzyl ethyl malonate (6a):

The titled compound was prepared according to the general method C from 2-(4-(bromomethyl)phenyl)isoindoline-1,3-dione **PG1** (3.16 g, 10 m.mol) and potassium mono ethyl malonate (1.7 g, 10 m.mol) to yield 2.86 g (90%). ^{1}H NMR (400 MHz, CDCl3); δ 7.95-7.98 (m, 2H), 7.78-7.82 (m, 2H), 7.48-7.51 (d, *J*=8.42, 2H), 7.43-7.47 (d, *J*=8.42, 2H), 5.22(s, 2H), 4.15-4.24 (q, *J*=6.9, 2H), 3.42(s, 2H), 1.20-1.28(t, *J* =6.9, 3H).^{13}C NMR (400 MHz, $CDCl_3$); δ 12.1, 39.6, 59.7, 64.5, 121.8, 124.7, 127.1, 129.7, 129.8, 132.6, 133.2, 164.4, 165.2.

4-(1, 3-dioxoisoindolin-2-yl) benzyl acetate (6b):

The titled compound was prepared according to the general method C from 2-(4-(bromomethyl)phenyl)isoindoline-1,3-dione **PG1** (3.16 g, 10 m.mol) and sodium acetate (0.8 g, 10 m.mol) to yield 2.24 g (86%). ^{1}H NMR (400 MHz, CDCl3); δ 7.95-7.98 (m, 2H), 7.78-7.81 (m, 2H), 7.48-7.51(d, *J*=8.42, 2H), 7.43-7.47(d, *J*=8.42, 2H), 5.16 (s, 2H), 2.11(s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$); δ 21.2, 65.8, 124.1, 126.8, 129.2, 131.8, 131.9, 134.7, 136.1, 167.4, 171.1.

4-(1,3-dioxoisoindolin-2-yl)benzyl Octanoate (6c):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl)phenyl)isoindoline-1,3-dione **PG1** (3.16 g, 10 m.mol) and octanoic acid (1.44 g, 10 m.mol) to yield 3.4 g (89%) and 3.6 g (92%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ 7.95-7.98 (m, 2H), 7.78-7.81 (m, 2H), 7.48-7.512 (d, *J*=8.42, 2H), 7.43-7.47(d, *J*=8.42, 2H), 5.16(s, 2H), 2.35-2.4(t, *J*=7.61, 2H), 1.6-1.7(m, 2H), 1.2-139(m, 8H), 0.9-1.1(t, *J*=6.59, 3H). ^{13}C NMR (400 MHz, $CDCl_3$); δ 14.3, 22.8, 25.1, 29.1, 29.3, 31.9, 34.5, 65.6, 124.1, 126.8, 129.1, 131.7, 131.9, 134.7, 136.3, 167.4, 173.8 ppm.

4-(1,3-dioxoisoindolin-2-yl)benzyl tetradecanoate (6d):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl)phenyl)isoindoline-1,3-dione **PG1** (3.16 g, 10 m.mol) and decanoic acid (1.72 g, 10 m.mol) to yield 4 g (87%) and 4.2 g (91%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ 7.95-7.98 (m, 2H), 7.78-7.81 (m, 2H), 7.48-7.51 (d, *J*=8.42, 2H), 7.43-7.47 (d, *J*=8.42, 2H), 5.16 (s, 2H), 2.35-2.4(t, *J*=7.62, 2H), 1.6-1.7(m, 2H), 1.2-1.3 (m, 20H), 0.8-0.9(t, *J*=7.69, 3H). ^{13}C NMR (400 MHz, $CDCl_3$); δ 14.4, 22.9, 25.2, 29.4, 29.5, 29.6, 29.7, 29.8, 29.8, 29.9, 32.2, 34.5, 65.6, 124.1, 126.8, 129.1, 131.6, 131.9, 134.7, 136.3, 167.4, 173.8 ppm

4-(1,3-dioxoisoindolin-2-yl) benzyl 2-phenylbutanoate (6e):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl)phenyl)isoindoline-1,3-dione **PG1** (3.16 g, 10 m.mol) and 2-phenyl butanoic acid (1.64 g, 10 m.mol) to yield 3.35 g (84%) and 3.79 g (88%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ 7.95-7.98 (m, 2H), 7.78-7.82 (m, 2H), 7.48-7.51 (d, *J*=8.42, 2H), 7.43-7.47 (d, *J*=8.42, 2H), 7.24-7.35(m, 5H),5.1-5.22(q, *J*=12.8, 2H), 3.48-3.59(t, *J*=7.69,1H), 2.06-2.2(m,1H), 1.79-1.89(m,1H), 0.87-0.98(t, *J* = 7.33,3H).^{13}C NMR (400 MHz, $CDCl_3$); δ 12.4, 26.8, 53.7, 65.9, 124.1, 126.7, 127.5, 128.3, 128.8, 128.8, 131.6, 131.9, 134.7, 136.2, 139.1, 167.4, 174.1 ppm.

4-(1,3-dioxoisoindolin-2-yl)benzyl 2-(tert-butoxycarbonylamino)acetate (6f):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl)phenyl)isoindoline-1,3-dione **PG1** (3.16 g, 10 m.mol) and BOC-Glycine (1.75 g, 10 m.mol) to yield 3.56 g (87%) and 3.69 g (90%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ 7.95-7.98 (m, 2H), 7.78-7.82 (m, 2H), 7.48-7.51 (d, *J*=8.42, 2H), 7.43-

7.47 (d, *J*=8.42, 2H), 5.21(s, 2H), 5.1(s, br, 1H), 4.02-4.06 (d, *J*=5.4, 2H), 1.3-1.5(d, *J*=, 9H). ^{13}C NMR (400 MHz, $CDCl_3$); δ 28.54(3C), 42.7, 66.6, 80.3, 124.1, 126.8, 129.3, 131.8, 131.9, 134.8, 135.4, 155.9, 167.4, 170.5.

4-(1,3-dioxoisoindolin-2-yl)benzyl 2-(benzyloxycarbonylamino)acetate(6g):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl)phenyl)isoindoline-1,3-dione **PG1** (3.16 g, 10 m.mol) and Z-glycine (2.1 g, 10 m.mol) to yield 3.72 g (84%) and 4.04 g (91%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ 7.95-7.98 (m, 2H), 7.78-7.82 (m, 2H), 7.48-7.51 (d, *J*=8.42, 2H), 7.43-7.47 (d, *J*=8.42, 2H), 7.3-7.38(m, 5H), 5.25 (s,br,1H), 5.22(s,2H), 5.14 (s,2H), 4.02-4.06 (d, *J*=5.4, 2H).^{13}C NMR (400 MHz, $CDCl_3$); δ 43.1, 66.6, 67.4, 124.1, 126.9, 128.4, 128.5, 128.8, 129.4, 131.9, 132.1, 134.8, 135.3, 136.5, 156.5, 167.3, 170.1 ppm.

4-(1,3-dioxoisoindolin-2-yl)benzyl benzoate (6h):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl)phenyl)isoindoline-1,3-dione **PG1** (3.16 g, 10 m.mol) and sodium benzoate (1.44 g, 10 m.mol) to yield 3.14 g (88%) and 3.35 g (94%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ 8.08-8.14(dd, J_1=8.4, J_2=1.46, 2H), 7.95-7.98 (m, 2H), 7.78-7.81 (m, 2H), 7.58-7.65(d,*J*=8.4,2H), 7.55-7.58 (td, J_1=7.42 J_2=1.46, 1H), 7.47-7.51(d,J=8.4,2H), 7.43-7.47 (dd, J_1=7.42, J_2=1.12, 2H), 5.41 (s,2H). ^{13}C NMR (400 MHz, $CDCl_3$); δ 65.9, 123.7, 126.5, 128.3, 128.8, 129.6, 129.8, 131.5, 131.6, 133.1, 134.4, 135.8, 166.3, 167.1 ppm.

4-(1, 3-dioxoisoindolin-2-yl) benzyl picolinate (6i):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl)phenyl)isoindoline-1,3-dione **PG1** (3.16 g, 10 m.mol) and picolinic acid

(1.23 g, 10 m.mol) to yield 2.79 g (78%) and 2.89 g (84%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ 8.75-8.78 (d, *J*=4.61, 1H), 8.11-8.19 (d,*J*=7.69,1H), 7.95-7.98 (m, 2H), 7.82-7.86(t, *J*=8.4, 1H), 7.78-7.81 (m, 2H), 7.60-7.65(d, *J*=, 2H), 7.44-7.50 (m,3H), 5.49 (s,2H).^{13}C NMR (400 MHz, $CDCl_3$); δ 67.11, 124.1, 125.6, 126.9, 127.3, 129.6, 131.9, 131.9, 134.7, 135.7, 137.3, 148.1, 150.2, 165.2, 167.4 ppm.

4-(1,3-dioxoisoindolin-2-yl)benzyl 4-(1,3-dioxoisoindolin-2-yl)benzoate (6j):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl)phenyl)isoindoline-1,3-dione **PG1** (3.16 g, 10 m.mol) and 4-(1,3-dioxoisoindolin-2-yl)benzoic acid (2.67 g, 10 m.mol) to yield 4.56 g (91%) and 4.71 g (94%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ 8.22-8.26(d, *J*=8.4, 2H), 7.94-8.0(m, 4H), 7.78-7.86(m, 4H), 7.62-7.64(d, *J*=4.8, 2H), 7.58-7.61 (d, *J*=4.8, 2H), 7.48-7.52 (d, *J* =0.84, 2H), 5.44 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$); δ 66.5, 124.1, 124.2, 126.21(2C), 126.9, 129.1, 129.3, 130.8, 131.7, 131.8, 131.9, 134.7, 134.92(2C), 136.01, 136.3, 165.8, 167.1, 167.4 ppm.

4-(1,3-dioxoisoindolin-2-yl)-3-methoxybenzyl ethyl malonate (6k):

The titled compound was prepared according to the general method C from 2-(4-(bromomethyl)3-methoxyphenyl)isoindoline-1,3-dione **PG2** (3.46 g, 10 m.mol) and potassium mono ethyl malonate (1.7 g, 10 m.mol) to yield 3.13 g (91%). ^{1}H NMR (400 MHz, CDCl3); δ 7.85-7.89 (m, 2H), 7.68-7.71 (m, 2H), 7.58 (d, *J*=7.2, 2H), 7.23(s, 1H), 6.98 (d, *J*=7.2, 2H), 5.22(s, 2H), 4.15-4.24 (q, *J*=6.9, 2H), 3.42(s, 2H), 1.20-1.28(t, *J* =6.9, 3H).^{13}C NMR (400 MHz, $CDCl_3$); δ 12.1, 39.6, 59.6, 64.5, 121.8, 124.6, 127.1, 129.7, 129.8, 132.5, 133.2, 164.4, 165.2 ppm.

4-(1, 3-dioxoisoindolin-2-yl)-3-methoxybenzyl acetate (6l):

The titled compound was prepared according to the general methods B and C from 2-(4-(bromomethyl)3-methoxyphenyl)isoindoline-1,3-dione **PG2** (3.46 g, 10 m.mol) and sodium acetate (0.8 g, 10 m.mol) to yield 2.95 g (88%). ^{1}H NMR (400 MHz, CDCl3); δ 7.85-7.89 (m, 2H), 7.68-7.71 (m, 2H), 7.58 (d, *J*=7.2, 2H), 7.23(s, 1H), 6.98 (d, *J*=7.2, 2H), 5.22(s, 2H), 2.11(s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$); δ 21.2, 65.8, 124.1, 126.8, 129.2, 131.8, 131.9, 134.7, 136.1, 167.4, 171.1 ppm.

4-(1,3-dioxoisoindolin-2-yl)-3-methoxybenzyl Octanoate (6m):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl) 3-methoxy phenyl)isoindoline-1,3-dione **PG2** (3.46 g, 10 m.mol) and octanoic acid (1.44 g, 10 m.mol) to yield 3.63 g (86%) and 3.8 g (90%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ δ 7.85-7.89 (m, 2H), 7.68-7.71 (m, 2H), 7.58 (d, *J*=7.2, 2H), 7.23(s, 1H), 6.98 (d, *J*=7.2, 2H), 5.16(s, 2H), 2.35-2.4(t, *J*=7.61, 2H), 1.6-1.7(m, 2H), 1.2-139(m, 8H), 0.9-1.1(t, *J*=6.59, 3H). ^{13}C NMR (400 MHz, $CDCl_3$); δ 14.3, 22.8, 25.1, 29.1, 29.3, 31.8, 34.5, 65.6, 124.1, 126.8, 129.1, 131.7, 131.9, 134.7, 136.3, 167.4, 173.8 ppm.

4-(1,3-dioxoisoindolin-2-yl)-3-methoxybenzyl tetradecanoate (6n):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl) 3-methoxy phenyl)isoindoline-1,3-dione **PG2** (3.46 g, 10 m.mol) and decanoic acid (1.72 g, 10 m.mol) to yield 4.28 g (87%) and 4.58 g (93%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ δ 7.85-7.89 (m, 2H), 7.68-7.71 (m, 2H), 7.58 (d, *J*=7.2, 2H), 7.23(s, 1H), 6.98 (d, *J*=7.2, 2H), 5.16 (s, 2H), 2.35-2.4(t, *J*=7.62, 2H), 1.6-1.7(m, 2H), 1.2-1.3 (m, 20H), 0.8-0.9(t, *J*=7.69, 3H). ^{13}C NMR (400 MHz, $CDCl_3$); δ 14.4, 22.9,

25.2, 29.4, 29.5, 29.6, 29.6, 29.8, 29.8, 29.9, 32.2, 34.5, 65.6, 124.1, 126.8, 129.1, 131.6, 131.9, 134.7, 136.3, 167.4, 173.8 ppm.

4-(1,3-dioxoisoindolin-2-yl)-3-methoxybenzyl 2-phenylbutanoate (6o):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl) 3-methoxy phenyl)isoindoline-1,3-dione **PG2** (3.46 g, 10 m.mol) and 2-phenyl butanoic acid (1.64 g, 10 m.mol) to yield 3.68 g (81%) and 3.98 g (91%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ δ 7.85-7.89 (m, 2H), 7.68-7.71 (m, 2H), 7.58 (d, *J*=7.2, 2H), 7.23(s, 1H), 6.98 (d, *J*=7.2, 2H), 7.24-7.35(m, 5H), 5.1-5.22(q, *J*=12.8, 2H), 3.48-3.59(t, *J*=7.69,1H), 2.06-2.2(m, 1H), 1.79-1.89(m,1H), 0.87-0.98(t, *J* = 7.33,3H).^{13}C NMR (400 MHz, $CDCl_3$); δ 12.38, 26.76, 53.7, 65.9, 124.1, 126.7, 127.5, 128.2, 128.7, 128.8, 131.6, 131.9, 134.7, 136.2, 139.1, 167.4, 174.1 ppm.

4-(1,3-dioxoisoindolin-2-yl)-3-methoxybenzyl2-(tert-butoxycarbonylamino)acetate (6p):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl) 3-methoxy phenyl)isoindoline-1,3-dione **PG2** (3.46 g, 10 m.mol) and BOC-Glycine (1.75 g, 10 m.mol) to yield 3.56 g (79%) and 4.01 g (87%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ 7.85-7.89 (m, 2H), 7.68-7.71 (m, 2H), 7.58 (d, *J*=7.2, 2H), 7.23(s, 1H), 6.98 (d, *J*=7.2, 2H), 5.21(s, 2H), 5.1(s, br, 1H), 4.02-4.06 (d, *J*=5.4, 2H), 1.3-1.5(d, *J*=, 9H). ^{13}C NMR (400 MHz, $CDCl_3$); δ 28.5, 42.7, 66.6, 80.3, 124.1, 126.9, 129.3, 131.9, 131.9, 134.8, 135.4, 155.9, 167.4, 170.5 ppm.

4-(1,3-dioxoisoindolin-2-yl)-3-methoxybenzyl2-(benzyloxycarbonylamino)acetate (6q):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl) 3-methoxy phenyl)isoindoline-1,3-dione **PG2** (3.46 g, 10 m.mol) and Z-glycine (2.1 g, 10 m.mol) to yield 3.74 g (88%) and 4.12 g (95%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ δ 7.85-7.89 (m, 2H), 7.68-7.71 (m, 2H), 7.58 (d, *J*=7.2, 2H), 7.23(s, 1H), 6.98 (d, *J*=7.2, 2H), 7.3-7.38(m, 5H), 5.25 (s,br,1H), 5.22(s,2H), 5.14 (s,2H), 4.02-4.06 (d, *J*=5.4, 2H).^{13}C NMR (400 MHz, $CDCl_3$); δ 43.1, 66.7, 67.4, 124.1, 126.9, 128.4, 128.5, 128.8, 129.4, 131.9, 132.1, 134.8, 135.3, 136.5, 156.6, 167.4, 170.1 ppm.

4-(1,3-dioxoisoindolin-2-yl)-3-methoxybenzyl benzoate (6r):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl)3-methoxyphenyl)isoindoline-1,3-dione **PG2** (3.46 g, 10 m.mol) and sodium benzoate (1.44 g, 10 m.mol) to yield 3.41 g (84%) and 3.68 g (88%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ 8δ 7.85-7.89 (m, 2H), 7.68-7.71 (m, 2H), 7.58 (d, *J*=7.2, 2H), 7.23(s, 1H), 7.55-7.58 (td, J_1=7.42 J_2=1.46, 1H), 7.43-7.47 (dd, J_1=7.42, J_2=1.12, 2H), 6.98 (d, *J*=7.2, 2H), 5.41 (s,2H). ^{13}C NMR (400 MHz, $CDCl_3$); δ 65.9, 123.7, 126.6, 128.3, 128.8, 129.6, 129.9, 131.5, 131.6, 133.1, 134.4, 135.9, 166.3, 167.1 ppm.

4-(1, 3-dioxoisoindolin-2-yl)-3-methoxybenzyl picolinate (6s):

The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl) 3-methoxy phenyl)isoindoline-1,3-dione **PG2** (3.46 g, 10 m.mol) and picolinic acid (1.23 g, 10 m.mol) to yield 3.25 g (83%) and 3.42 g (86%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ 8.75-8.78 (d, *J*=4.61, 1H), 8.11-8.19 (d,*J*=7.69,1H), 6.98 (d, *J*=7.2, 2H), 7.44-7.50 (m,3H), 5.49 (s,2H).^{13}C NMR (400 MHz, $CDCl_3$); δ 67.1, 124.1,

125.6, 126.9, 127.3, 129.6, 131.9, 131.9, 134.7, 135.7, 137.3, 148.1, 150.2, 165.2, 167.4 ppm.

4-(1,3-dioxoisoindolin-2-yl)-3-methoxybenzyl 4-(1,3-dioxoisoindolin-2-yl) benzoate (6t): The titled compound was prepared according to the general methods A and B from 2-(4-(bromomethyl) 3-methoxy phenyl)isoindoline-1,3-dione **PG2** (3.46 g, 10 m.mol) and 4-(1,3-dioxoisoindolin-2-yl)benzoic acid (2.67 g, 10 m.mol) to yield 4.94 g (93%) and 5.10 g (96%) respectively. ^{1}H NMR (400 MHz, CDCl3); δ 8.22-8.26(d, *J*=8.4, 2H), 7.94-8.0(m, 4H), 7.78-7.86(m, 4H), 7.62-7.64(d, *J*=4.8, 2H), 7.58-7.61 (d, *J*=4.8, 2H), 7.48-7.52 (d, *J* =8.4, 2H), 5.44 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$); δ 66.5, 124.1, 124.2, 126.2, 126.9, 129.1, 129.3, 130.8, 131.7, 131.8, 131.9, 134.7, 134.9, 136, 136.3, 165.8, 167, 167.4 ppm.

4-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)benzyl 3-oxobutanoate (6u):

The titled compound was prepared according to the general method C from 2-(4-(bromomethyl)phenyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione **PG3** (3.65 g, 10 m.mol) and potassium mono ethyl malonate (1.7 g, 10 m.mol) to yield 3.13 g (91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 7.3 Hz, 2H), 8.27 (d, *J* = 8.3 Hz, 2H), 7.79 (t, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.22(s, 2H), 4.15-4.24 (q, *J*=6.9, 2H), 3.42(s, 2H), 1.20-1.28(t, *J* =6.9, 3H). ^{13}C NMR (400MHz, $CDCl_3$) δ 164.6, 139.6, 135.6, 134.5, 131.9, 131.7, 129.8, 129.5, 129.4, 128.7, 127.3, 125.8, 123.1, 77.8, 64.5, 59.7, 39.6, 12.1 ppm.

4-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)benzyl acetate (6v):

The titled compound was prepared according to the general method C from 2-(4-(bromomethyl)phenyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione **PG3** (3.65 g, 10 m.mol)

and sodium acetate (0.8 g, 10 m.mol) to yield 2.95 g (88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 7.3 Hz, 2H), 8.27 (d, *J* = 8.3 Hz, 2H), 7.79 (t, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.26(s, 2H), 2.25 (s, 3H). ^{13}C NMR (400MHz, $CDCl_3$) δ 164.6, 139.6, 135.6, 134.5, 131.9, 131.7, 129.8, 129.5, 129.4, 128.7, 127.3, 125.8, 123.1, 77.8, 21.6 ppm.

4-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)benzyl benzoate (6w):

The titled compound was prepared according to the general method C from 2-(4-(bromomethyl)phenyl)-1*H*-benzo[*de*]isoquinoline-1,3(2*H*)-dione **PG3** (3.65 g, 10 m.mol) and sodium benzoate (1.44 g, 10 m.mol) to yield 3.41 g (84%) and 3.68 g (88%) respectively.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 7.3 Hz, 2H), 8.27 (d, *J* = 8.3 Hz, 2H), 7.79 (t, *J* = 7.8 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.16(m, 5H), 7.21 (d, *J* = 8.1 Hz, 2H), 5.26(s, 2H), 2.25 (s, 3H). ^{13}C NMR (400MHz, $CDCl_3$) δ 164.6, 139.6, 135.6, 134.5, 131.9, 131.7, 130.8, 129.8, 129.5, 129.4, 127.3, 124.3, 128.7, 126.5, 127.3, 125.8, 123.1, 77.8 ppm.

General Methods of Deprotection:

Method D-1: To a suspension of 1 gm of ester in 15 ml of Methanol was added 400mg of 10% Pd/C and the solution was kept in the par shaker at a pressure of 65 atm for 5-6 hrs until completion of the reduction. The solvent was then evaporated and the residue was taken in sodium bicarbonate solution. This solution was washed with dichloromethane to collect the byproducts and acidified using 10% HCl to yield the acid as a crystalline compound or oil that is obtained upon extraction with ethyl acetate.

Method D-2: To a suspension of 1 gm of ester in 15 ml of Methanol were added 177 mg of $HCOONH_4$ and 300mg of 10% Pd/C. The suspension was then heated at 50 deg

c for 2-3 hrs until completion of the reduction. The solvent was then evaporated and the residue was taken in sodium bicarbonate solution. This solution was washed with dichloromethane to collect the byproducts and acidified using 10% HCl to yield the acid as a crystalline compound or oil that is obtained upon extraction with ethyl acetate.

Method D-3: A solution of 1 gm of ester in 15 ml of ethyl acetate was purged with excess of HCl (using MeOH and $SOCl_2$). 2-3 hours after passing HCl the solvent was evaporated and the residue was taken in sodium bicarbonate solution. This solution was washed with dichloromethane to collect the byproducts and acidified to yield the acid as a crystalline compound or oil that is obtained upon extraction with ethyl acetate.

Method D-4: To a suspension of 1 gm of ester in 15 ml of 1:1 MeOH, Dichloromethane was added powdered NaOH (112mg, 2.8m.mol) at 0 deg C and the reaction mixture was stirred for about 2 hrs and the methanol was evaporated. The residue was taken into Sodium bicarbonate solution, washed with DCM to collect the byproducts and acidified to yield the acid as a crystalline compound or oil that can be obtained upon extraction using ethyl acetate.

Method D-5: To a suspension of 1 gm ester in 10 ml of MeOH was added 2-3 eqs of Hydrazine hydrate. As the reaction proceeds a gradual increase in precipitation of pthalhydrazide is observed. After completion of reaction in about 5-6 hrs, the pthalhydrazide was separated by filtering it out and the filtrate was evaporated under vacuum. The residue thus obtained upon concentration is diluted in 5 ml of DCM; 1 equivalent of TFA was added and allowed the mixture to stir for 15 minutes. The mixture was further diluted with 15 ml of DCM and washed with 10% HCl solution followed by water, dried with Na_2SO_4 and concentrated to give the acid.

General method of preparation of the β- keto esters (E):

To a solution of the esters **6a**-**6w** (10 m.mol, 1 eq) in 25 ml of dry acetonitrile or DCM was added $MgCl_2$ (0.9g, 10 m.mol, 1eq), triethyl amine (2g, 20 m.mol, 2eq) and the mixture was stirred under nitrogen. After 2 hrs of stirring, the acid chloride (10 m.mol, 1eq) was added drop wise at 0°C. The mixture was stirred for additional 2 hrs. After the completion of reaction was confirmed by TLC, solvent was evaporated under vacuum and the products **8a**-**8g** can be crystallized in a mixture of hexane and DCM

1-(4-(1,3-dioxoisoindolin-2-yl)benzyl) 3-ethyl 2-benzoylmalonate (8a):

The title compound is prepared by general procedure E from **6a** (3.67g, 10 m.mol) and benzoyl chloride (1.4g, 10 m.mol) in 82% yield (3.8 g). 1H NMR 13.39 (s), 7.98-7.95 (m, 2H), 7.78-7.81 (m, 2H), 7.48-7.51(d, *J*=8.42, 2H), 7.43-7.47(d, *J*=8.42 Hz, 2H), 7.49 – 7.42 (m, 5H), 5.28 (br, s), 5.16 (s, 2H), 4.23 (q, *J*=7.13, 2H), 1.23 (t, *J*=7.13, 3H); 13C NMR (CDCl3) 189.4, 165.3, 165.2, 164.4, 135.8, 134.4, 133.2, 132.6, 129.1, 128.7, 127.1, 124.7,121.8, 64.5, 62.7, 61.9, 14.4, 14.1 ppm.

1-(4-(1,3-dioxoisoindolin-2-yl)benzyl) 3-ethyl 2-(2,4,6-trimethoxybenzoyl)malonate (8b): The title compound is prepared by general procedure E from **6a** (3.67g, 10 m.mol) and trimethoxy benzoyl chloride (2.3 g, 10 m.mol) in 85% yield (4.78 g). 1H NMR 13.39 (s), 7.98-7.95(m, 2H), 7.78-7.81 (m, 2H), 7.48-7.51(d, *J*=8.42, 2H), 7.43-7.47(d, *J*=8.42 Hz, 2H), 7.44 (s, 2H), 5.28 (br, s), 5.16 (s, 2H), 4.62(s, 9H), 4.23 (q, *J*=7.13, 2H), 1.23 (t, *J*=7.13, 3H); 13C NMR (CDCl3) 189.4, 165.3,164.4, 135.8, 134.4, 133.2,132.6, 128.8, 127.1, 124.6,121.8, 64.5, 62.7, 61.9, 14.4, 14.1 ppm.

1-(4-(1,3-dioxoisoindolin-2-yl)benzyl) 3-ethyl 2-(3-nitrobenzoyl)malonate (8c):

The title compound is prepared by general procedure E from **6a** (3.67g, 10 m.mol) and

3-nitro benzoyl chloride (1.85 g, 10 m.mol) in 69% yield (3.56 g). 1H NMR 13.28 (s), 7.98-7.95(m, 2H), 7.78-7.81 (m, 2H), 7.48-7.51(d, *J*=8.42, 2H), 7.43-7.47(d, *J*=8.42 Hz, 2H), 7.63–8.92 (m, 4H), 5.28 (br, s), 5.16 (s, 2H), 4.23 (q, *J*=7.13, 2H), 1.23 (t, *J*=7.13, 3H); 13C NMR (CDCl3) 189.4, 165.3, 165.2, 164.4, 135.8, 134.4, 133.2, 132.6, 129.1, 128.7, 127.1, 124.6,121.8, 64.5, 63.7, 51.2, 61.9, 14.4, 14.1 ppm.

1-(4-(1,3-dioxoisoindolin-2-yl)benzyl) 3-ethyl 2-acetylmalonate (8d):

The title compound is prepared by general procedure E from **6a** (3.67g, 10 m.mol) and acetyl chloride (0.8 g, 10 m.mol) in 74% yield (3.02 g). 1H NMR 13.45, 7.98-7.95(m, 2H), 7.78-7.81 (m, 2H), 7.48-7.51(d, *J*=8.42, 2H), 7.43-7.47(d, *J*=8.42 Hz, 2H), 5.18 (s, 2H), 4.38 (br, s), 4.23 (q, *J*=7.13 Hz, 2H), 2.27 & 2.13 (s, s, total 3H), 1.23 (t, *J*=7.13 Hz, 3H); 13CNMR (CDCl3) 197.1, 165.3, 165.2, 164.4, 133.2, 132.6, 128.7, 127.1, 124.7, 100.2, 64.5, 62.2, 61.4, 21.1, 14.4, 14.3 ppm.

1-(4-(1,3-dioxoisoindolin-2-yl)benzyl) 3-ethyl 2-hexanoylmalonate (8e):

The title compound is prepared by general procedure E from **6a** (3.67g, 10 m.mol) and hexanoyl chloride (1.34 g, 10 m.mol) in 67% yield (3.11 g). 1H NMR 13.31, 4.37 (br s, br s, total 1H), 7.98-7.95(m, 2H), 7.78-7.81 (m, 2H), 7.48-7.51(d, *J*=8.42 Hz, 2H), 7.43-7.47(d, *J*=8.42 Hz, 2H), 5.16 (s, 2H), 4.26 (q, *J*=6.87 Hz, 2H), 2.59 (t, *J*=7.29 Hz, 1H), 2.41 (t, *J*=7.29, 1H), 1.64–1.57 (m, 2H), 1.21–1.15 (m, 8H), 1.08 (t, *J*=7.13,1.5H), 0.98 (t, J.7.13, 1.5 H); 13CNMR (CDCl3) 199.8, 171.5, 164.9, 164.4, 165.1, 134.4, 133.2, 132.6, 99.5, 64.2, 62.5, 61.3, 27.6, 14.3, 14.2, 7.8 ppm.

1-(4-(1,3-dioxoisoindolin-2-yl)benzyl) 3-ethyl 2-octanoylmalonate (8f):

The title compound is prepared by general procedure E from **6a** (3.67g, 10 m.mol) and octanoyl chloride (1.58 g, 10 m.mol) in 64% yield (3.15 g). 1H NMR 13.36, 4.43 (br s, br

s, total 1H), 7.98-7.95(m, 2H), 7.78-7.81 (m, 2H), 7.48-7.51(d, *J*=8.42 Hz, 2H), 7.43-7.47(d, *J*=8.42 Hz, 2H), 5.16 (s, 2H), 4.26 (q, *J*=6.87 Hz, 2H), 2.59 (t, *J*=7.29 Hz, 1H), 1.64–1.57 (m, 2H), 1.31–1.21 (m, 10H), 0.86 (t, *J*=6.87 Hz, 3H); 13C NMR 199.4, 171.6, 165.3, 165.1, 134.4, 133.2, 132.6, 129.1, 128.7, 100.1, 64.1, 62.6, 61.5, 34.2, 32.2, 29.8, 29.6, 27.2, 25.4, 23.8, 23.1, 14.6, 14.5, 14.4 ppm.

1-(4-(1,3-dioxoisoindolin-2-yl)benzyl) 3-ethyl 2-dodecanoylmalonate (8g):

The title compound is prepared by general procedure E from **6a** (3.67g, 10 m.mol) and dodecanoyl chloride (1.86 g, 10 m.mol) in 68% yield (3.54 g). 1H NMR 13.39, 4.48 (br s, br s, total 1H), 7.98-7.95(m, 2H), 7.78-7.81 (m, 2H), 7.48-7.51(d, *J*=8.42 Hz, 2H), 7.43-7.47 (d, *J*=8.42 Hz, 2H), 5.16 (s, 2H), 4.26 (q, *J*=6.87 Hz, 2H), 2.59 (t, *J*=7.29 Hz, 1H), 2.41 (t, *J*=7.29, 1H), 1.64–1.57 (m, 2H), 1.31–1.21 (m, 10H), 0.86 (t, *J*=6.87 Hz, 3H); 13C NMR 199.39, 171.58, 165.26, 165.17, 164.42, 165.05, 134.41, 133.21, 132.56, 129.07, 128.69, 100.08, 62.61, 61.5, 34.2, 32.2, 29.8, 29.6, 27.2, 25.4, 23.8, 23, 14.6, 14.4, 14.3 ppm.

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Chapter IV

Synthesis of α-β unsaturated amino acids

4.1 Introduction:

α-β Unsaturated amino acids also known as α-dehydroaminoacids (DHA's) are very important intermediates in biological epimerization[1] of L-α-amino acid into the enatiomer by the process of dehydrogenation-hydrogenation[1]. Also there are many peptide antibiotics[2-5], which are prepared from these compounds. Some of these compounds with antibiotic activity also exhibited phytotoxic activity[6-8]. Dehhydro peptides, another important class of biological compounds can be derived only from DHAs making them even more powerful class of compounds. A vast number of reports wee found on correlating the structure and biological activity of dehydro oligopeptides containing one or more DHA moieities[9-11]. For example, Berninamycin A, an antibiotic is a cyclodehydropeptide with two DHP sequences and about seven DHA residues and has been isolated from a culture of *Streptomyces bernensis*[5]. The syntheses of DHPs are well established and have been known for quite sometime. Elimination of peptides with a leaving group[12-15], by direct coupling of DHAs with amino acids[16,17], ring cleavage of unsaturated azalactones[18-21], are few of the most common methods used to synthesize these compounds. Although there are many methods of synthesis available for DHPs, DHAs one of the main components for preparation of DHPs are not very well established in synthesis and only few methods are reported for these compounds[22]. One of the methods involves reduction of 2-azido alkenoates in to corresponding 2-amino alkenoates in presence of Al-Hg[23] and the other reports preparation of methyl 2-

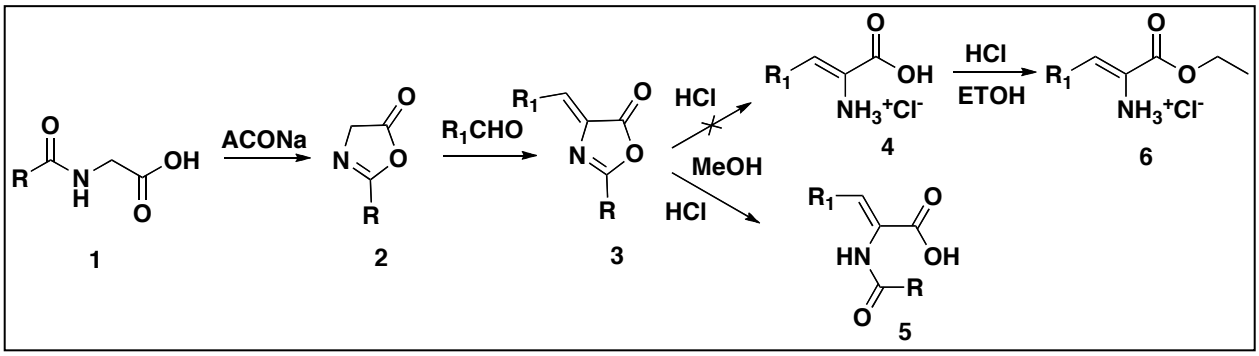
α-amino-2-α-alkenoates by elimination[24] of methanol from corresponding methoxy-amino acids. But both these methods report a very low yield, involve complex purification methods and also were found hard to reproduce. Dehydrochlorination of α-chloro amino acids[25] is one another method reported, however the procedures to make α- chloro amino acids only are not well established and using these as starting materials would not be a wise proposal. Therefore, a good method of synthesis for DHAs is on demand and also the method to be developed should applied in general to any type of compounds along with good yield and easy purification methods.

4.3 Results and Discussion:

The synthesis of α-β unsaturated amino acids is not very well established and there are only a few methods available for synthesis of these compounds and hence a great deal of interest is put into these compounds. Our research started off with oxazolones as starting materials for these compounds, later extended to attempts with a tag molecule and azide approach, which will further be discussed in the rest of the chapter.

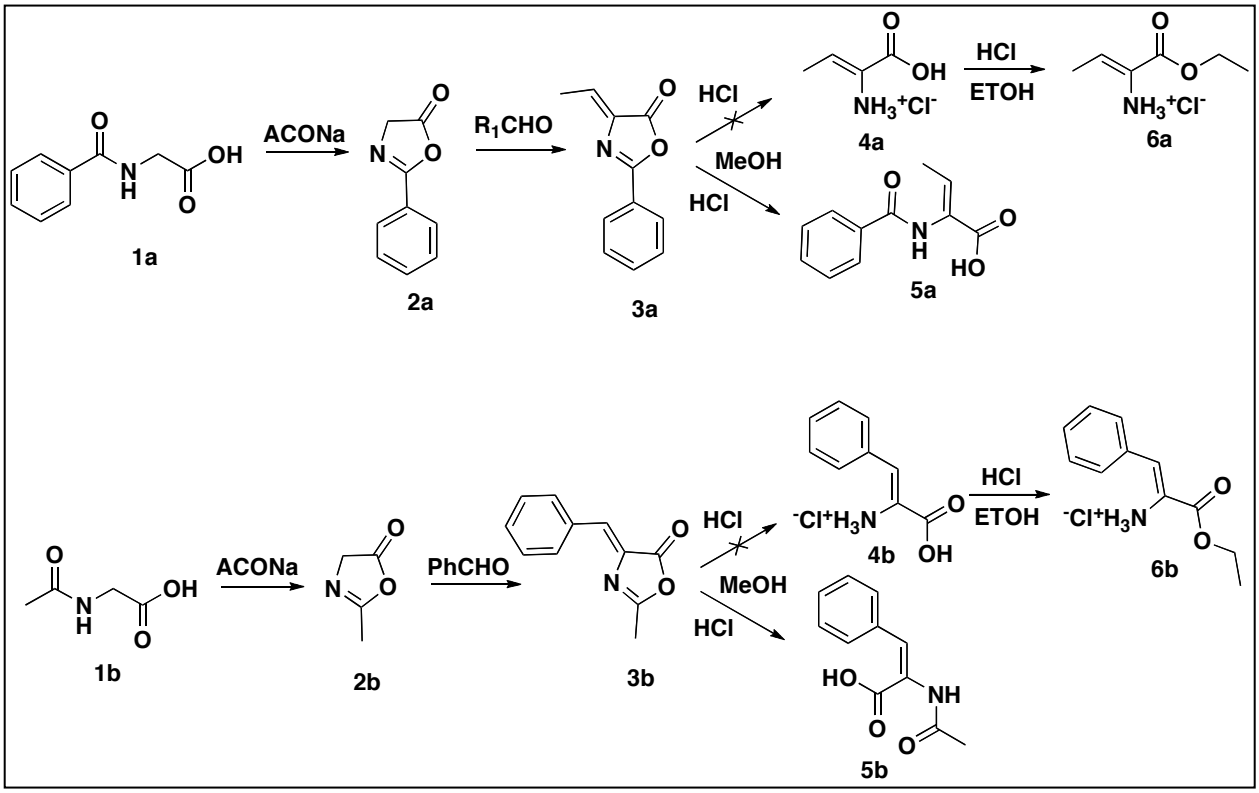
4.3.1. The oxazolone approach:

In one of the previous attempts as part of synthesizing a class of oxazolones[26], a method has been stabilized in our research group where in oxazolone with common structure as shown in scheme 1 is produced. These oxazolones were used as starting materials in synthesis of α-β unsaturated amino acids. Since the oxazolone ring can be opened up in acidic conditions, it was expected that the acidic hydrolysis could both open up the ring and also yield α-β unsaturated amino acids which can further be transformed into the corresponding esters.



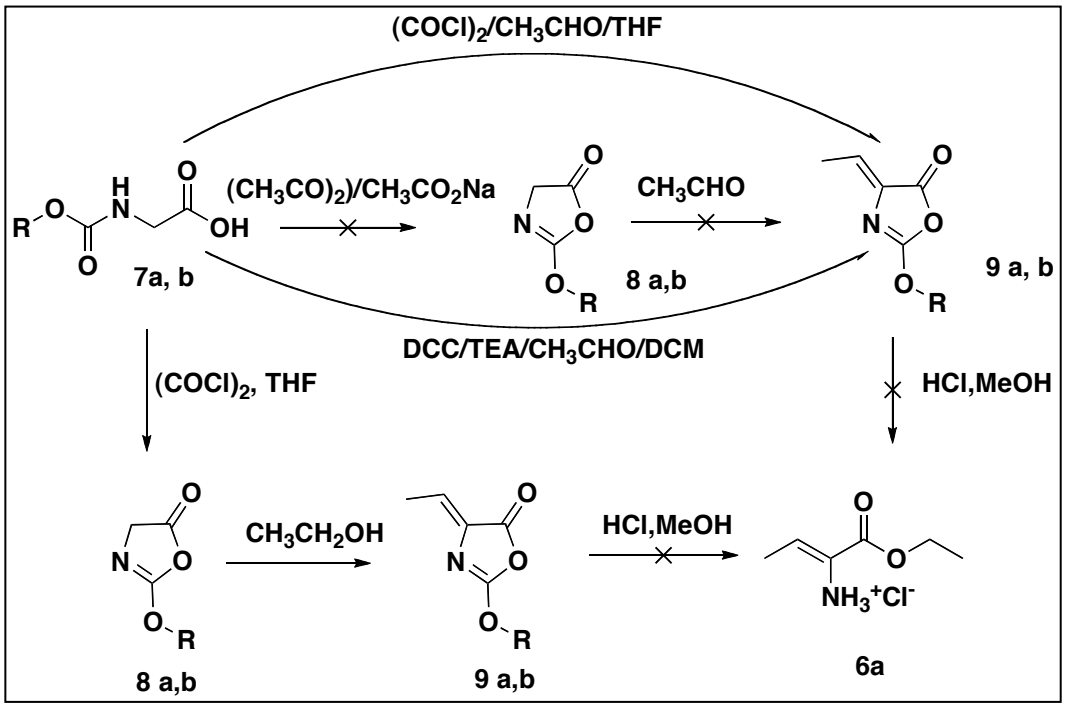
Scheme 4.1: Synthesis of N-acyl α-β unsaturated amino acids.

When the proposed synthesis was attempted, it was realized that the opening of the oxazolone ring was possible but the further hydrolysis to obtain an α-β unsaturated amino acid was unsuccessful. With milder conditions of acidic hydrolysis since the oxazolone produced N-acyl α-β unsaturated amino ester and conditions harsher than that decomposed the products, various acidic conditions were explored based on their reactivity. These reactions were applied two sets of compounds **1a** with acetyl protection of N-glycine and **1b** with benzoyl protection of N-glycine to obtain the oxazolones **3a** and **3b** and upon hydrolysis produced **5a** and **5b** but not **4a** and **4b** as shown in scheme 4.2.



Scheme. 4.2: Synthesis of α-β unsaturated amino acids using acetyl and benzoyl protection on *N*-Glycine.

The results remained unaltered even after trying various acidic conditions for hydrolysis and so it was proposed that changing the acyl substitution on the compound from an amidic linkage to a carbamate linkage would make it more labile to acidic hydrolysis. In scheme 4.2 the oxazolones were made from N-acyl glycines and to make the protection on N more labile, acyl protection has been altered to ethoxy carbonyl and carboxy benzyl protections as in scheme 4.3.

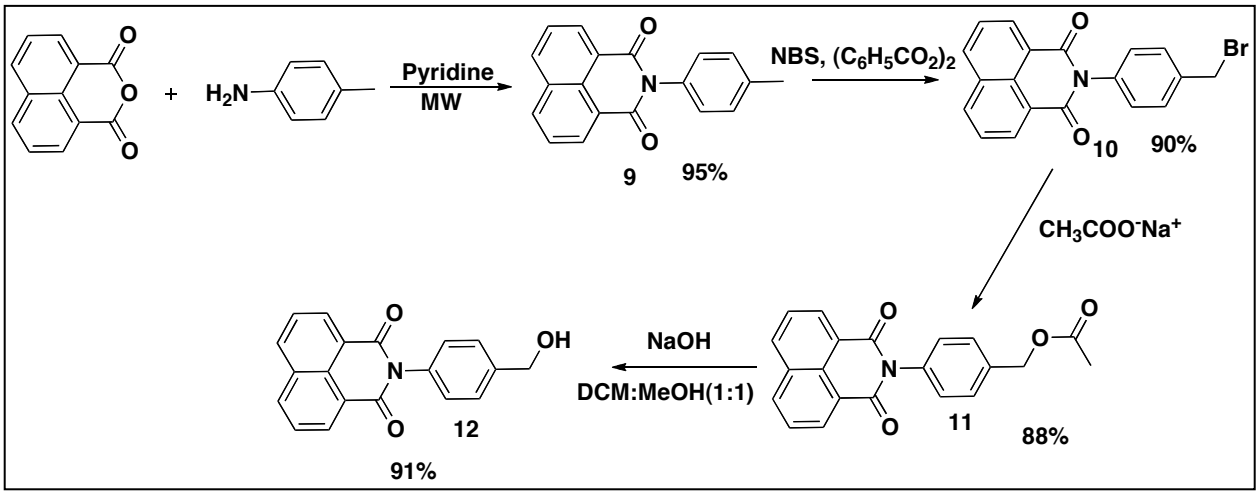


Scheme 4.3 Synthesis of ethoxy and benzoxy oxazolones.

4.3.2 The TAG molecule approach:

By changing the N- protection on glycine, the reactivity of glycines as N-acyl glycines was different from these and so the oxazolones and the following condensation reaction did not occur in the same conditions using Sodium acetate and had to be altered to oxalyl chloride in DCM after trying other reagents like DCC. Although the oxazolones were prepared the synthesis of α-β unsaturated amino esters was not successful even after. The hydrolysis would have been easier in this case as compared to the previous case but the stability and existence of these oxazolones was by itself a problem, the ethoxy oxazolone was completely lost during the evaporation of solvent under nitrogen and the benzoxy oxazolone was lost during work up, probably due to their very low volatility. So since the loss of compound during work up is greatly dependent on the

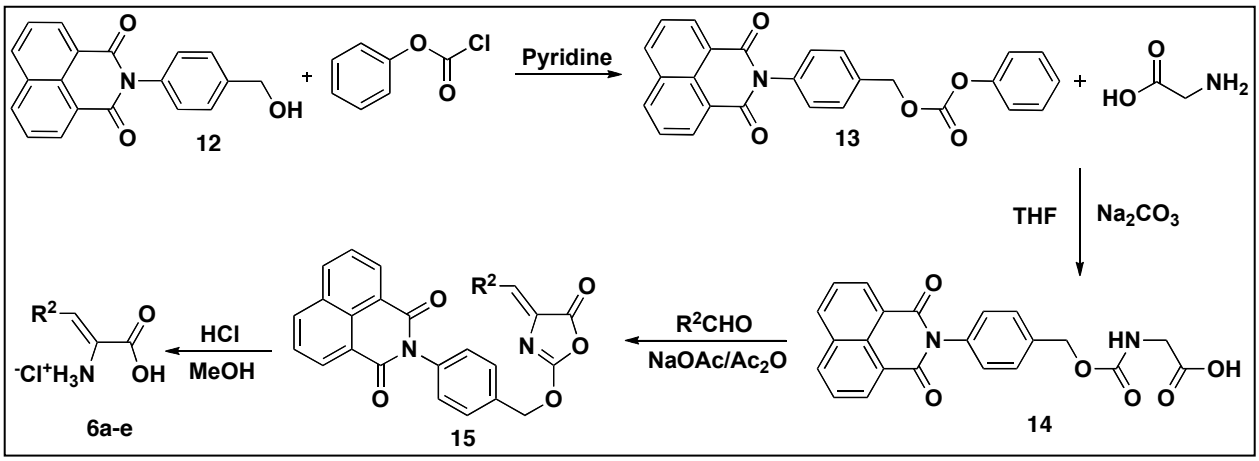
physical nature of the compound rather than its chemical behavior, the tag molecule was introduced as it is done in case of α-β keto esters. However in case of β keto esters, the pthalimide based tag molecule was used as a bromo derivative but the naphthalimide based tag molecule is used as a hydroxy derivative in this case[27]. The tag molecule has been prepared in few steps starting from naphthalimide and is obtained as its hydroxy derivative in a very good yield. The reason for changing the tag molecule from phthalyl to naphthyl is that the naphthyl based protection group is of higher molecular weight as compared to the phthalyl and also hydroxy derivative was necessary for reactivity with the substrates in this sequence. The scheme 4.4 below explains the step-by-step procedure for preparing the naphthalimide based tag molecule.



Scheme. 4.4 Synthesis of the tag molecule.

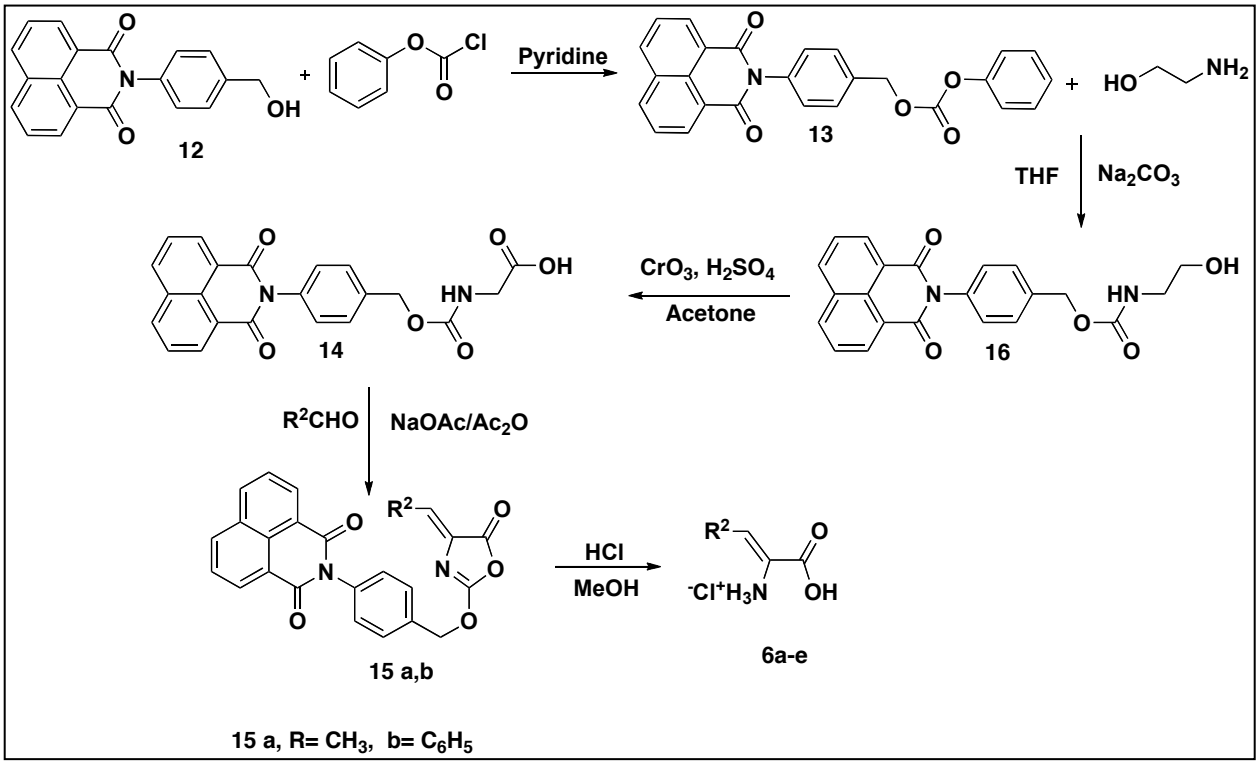
The tag molecule thus synthesized was incorporated into the synthesis of α-β unsaturated amino acids and the scheme 4.5 explains the proposed synthesis using the naphthalimide based protection group. The reaction of the protection group with phenyl

chloroformate yields the corresponding carbonate in a good yield with pyridine as solvent. Pyridine itself acts as a base also in this reaction.



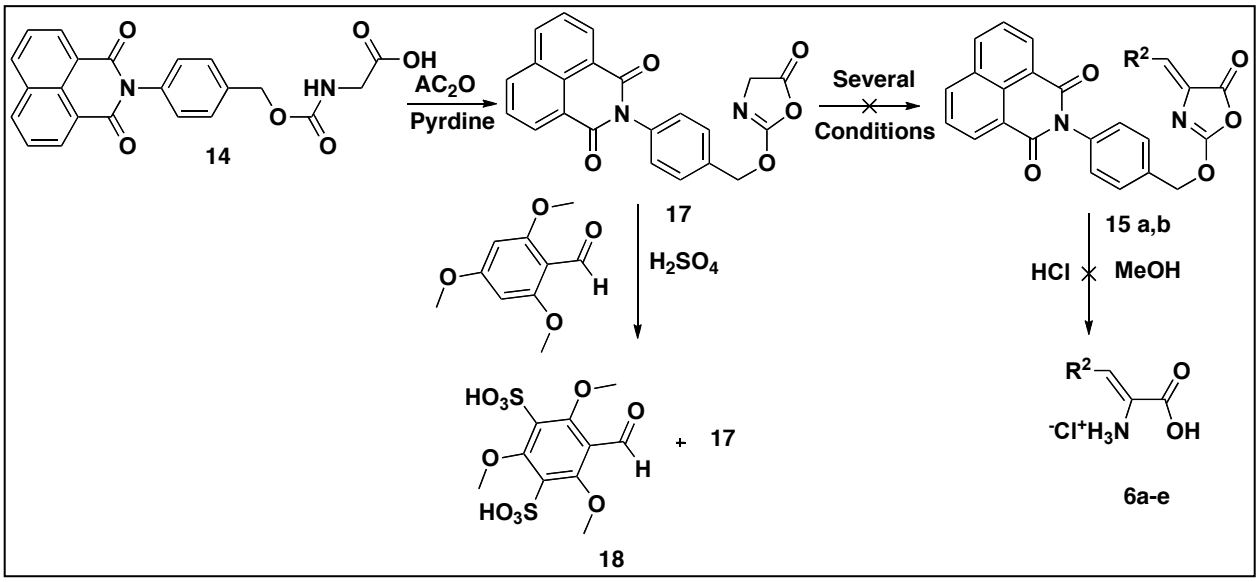
Scheme 4.4 Proposed synthesis of α,β-unsaturated amino acid with protection group.

However, the reaction with glycine was not successful because of the solubility issues associated with glycine. With this reaction not proceeding further, glycine was replaced with ethanolamine to react with the carbonate followed by an oxidation reaction and this yielded the desired product as shown in scheme 4.5. The oxidation was performed in Jones oxidation conditions in chromic acid and was produced in a very good yield[28]. But the following reaction, which involves formation of oxazolone and condensation with aldehyde in sodium acetate and acetic anhydride, was not successful under these conditions, like it was possible with the simple alkyl substituted oxazolones. The glycine protected with naphthalimide-based protection group was resistant to these conditions and so this reaction needs to be explored further.



Scheme 4.5 Synthesis of α,β-unsaturated amino acid with ethanolamine

Initially, it was felt that the reaction did not proceed due to the solubility issues associated with naphthalimide-protected glycine and so the solvent conditions had to be explored. After trying several solvents, DMF, DMSO and pyridine were the best solvents for any of these reactions. DBU, DCC, TFA, pyridine, H_2SO_4 and $NaHCO_3$ are few of the coupling reagents[29-35] tried as shown in scheme 4.6 and table 1. DBU, TFA, pyridine and acetic anhydride in DMSO or DMF did not yield the product, H_2SO_4 resulted in sulfonification on the ring of the aromatic aldehyde and no reaction with aliphatic aldehydes, but acetic anhydride in pyridine and $NaHCO_3$ in pyridine conditions resulted in oxazolone formation but the following condensation reaction was not successful.



Scheme. 4.6 Intermediates and byproducts in oxazolone synthesis with tag molecule.

Table 4.1. Various coupling reagents used for oxazolone synthesis:

Entry	Reagent	Solvent	Product
1	NaOAc	Acetic anhydride	NR
2	Lead Acetate	Acetic anhydride	NR
3	Triphosgene	Ethyl Acetate	NR
4	DCC	DCM, DMF, DMSO, Pyridine	NR
5	$(COCl)_2$, AgCN	DCM,	NR
6	DBU	Pyridine	17
7	Acetic Anhydride	Pyridine	17
8	H_2SO_4	H_2SO_4	18
9	TFA	DCM	NR

NR- No Reaction

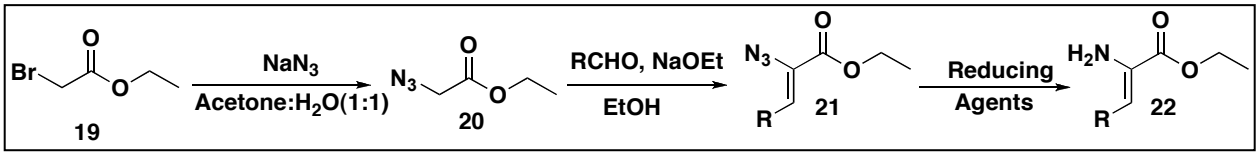
So the oxazolone was isolated from the reaction mixture by precipitating it in 10% HCl and was further investigated for reaction with aldehyde. The oxazolone formed with the protection group attached is resistant to condensation reaction even when tried with various bases. The table below shows all the bases tried and the results obtained in the process. With increase in basicity, instead of the condensation reaction, the protection group was completely hydrolyzed, leaving glycine as the product. After a series of trials it was realized that the protection group is very labile to basic conditions and hence could not sustain the reaction conditions. Although the protection group solved the problem associated with low volatility, it was not successful in synthesizing α-β unsaturated amino acids. Hence alternative methods of synthesis were desirable and needed to be explored.

Table. 4.2 Various bases tried in condensation of aldehydes with oxazolones.

Entry	Reagent	Solvent	Result
1	$NaOAc/Ac_2O$	Various Solvents	No Reaction
2	Acetic Anhydride	DCM, DMF	No Reaction
3	TFA	DCM	No Reaction
4	$KHCO_3$	Acetic Anhydride	No product
5	H_2SO_4	Acetic Anhydride	No product
6	LDA	THF	Mixed Products
7	n-BuLi	THF	Hydrolysis
8	Li(trimethylsilyl) amide	Ether	No Product
9	HMDS	Ether	Hydrolysis

4.3.3. The azide approach:

As the oxazolone approach and the tag molecule approach failed in synthesizing the α-β unsaturated amino acids, the azide approach was used to synthesize α-β unsaturated amino esters. The reaction sequence is as shown in the scheme 4.7 below and is started from ethyl bromo acetate, a commercially available compound which is transformed into the corresponding azide. The azide is than condensed with the aldehyde and the azide is reduced to the corresponding amino group to obtain the desired product.



Scheme 4.7 Proposed scheme of synthesis of α-β unsaturated amino esters.

The first step of the reaction in which a bromide is transformed into the azide, the reaction was successful and the product was obtained in a 100% yield. The second step where the aldehyde condensation takes place, it was not successful with all the aldehydes especially with small chain aldehydes. For aromatic and long chain aldehydes it gave a moderate yield and is good for this type of condensation reactions. The table 3 explains the results obtained based on various aldehydes tried out.

The final step where azide has to be reduced into an amine, the reduction reaction was not successful even after trying out several conditions as shown in table 4. Shin *et. al* earlier reported the reduction of these types of azides, but reproduction of the same procedure did not result in any reaction[36]. And as the azide was resistant to the various

other reducing agents like phosphine, boron trifloride ethereate Zn and Fe[37-42], the method was not very useful and applicable in this case and so an alternative has to be looked for.

Table 4.3. Various condensed aldehydes produced and their yields.

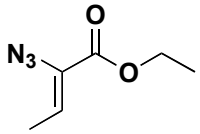
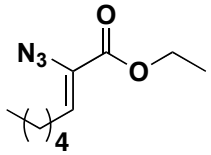
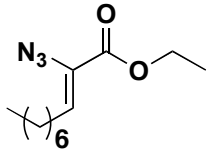
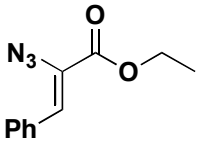
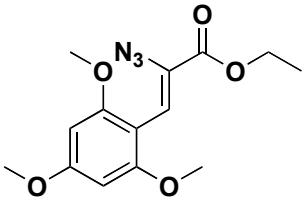
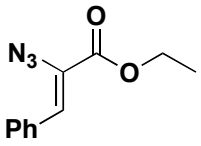
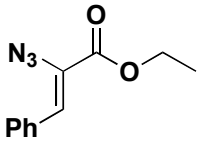
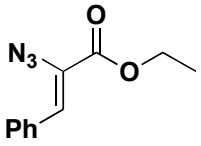
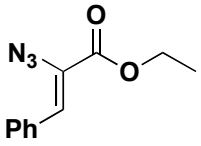
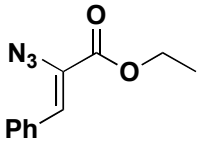
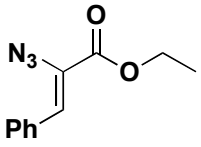
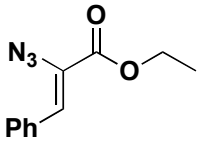
Entry	Aldehyde	Product	Yield(%)
21a	Acetaldehyde		6
21b	Hexanal		54
21c	Octanal		52
21d	Benzaldehyde		82
21e	TrimethoxyBenzaldehyde		78

Table 4.4. Various reduction methods tried for reducing azides:

Entry	Substrate	Reducing agent	Result
1		Al-Hg	Mixed Products
2		PPh_3, THF:H_2O(1:1)	Imino Phosphorane
3		PPh_3, Toluene-HCl, (5%)	Imino Phosphorane
4		$BF_3(OEt)_2$	Decomposed
5		$NaBH_4$	No Reduction
6		Zn/NH_4Cl	Mixed products
7		Fe/NH_4Cl	No Reduction

4.4 Conclusion:

α-β Unsaturated amino esters and acids are very important intermediates for synthesizing Magnesidin and many other biologically active compounds, their structural behavior and existence makes them tough to synthesize. Although many attempts have been made to synthesize these compounds due to their complexity, they were not synthesized. The oxazolone approach had problems with condensation reaction and in those cases where the condensation was successful; the intermediates were lost during the work up or evaporation of solvents. Changing the protection on N of glycine from acyl to ethoxy carbonyl or benzoxy carbonyl did not improve the results of the reaction. The tag molecule was then introduced as a protection on the N, but this however did not improve the results of synthesis. The oxazolone formation was achieved and was isolated as pure product but the condensation reaction to be done further was not accomplished. So the introduction of the tag molecule did not contribute to the synthesis of unsaturated amino acids. So the concentration was diverted from making unsaturated amino acids to unsaturated amino esters. The azide approach was used for this class of compounds and this method not successful either as the condensation reaction was a problem in the sequence. Only aromatic and long chain aliphatic aldehyde condensations were possible in low to moderate yields but the next step of reduction was unsuccessful even after attempting with various reducing agents. Since DHAs were not synthesized, DHPs the analogues of DHAs were used as part of synthesis of magnesidin and these compounds are discussed in the next chapter.

4.5 Experimental and spectral data:

4-ethylidene-2-phenyloxazol-5(4*H*)-one (3a):

A suspension of *N*-benzoyl glycine (1.8 g, 10 m.mol), sodium acetate (540 mg, 10 m.mol), and acetic anhydride (10 ml) was stirred at 0°C for 30 minutes. Into the white suspension, acetaldehyde (0.6 g; 15 m.mol) was added. The resulting suspension was stirred at room temperature for 1 h and then at 60°C for 5 h. The reaction mixture became a brown solution that upon cooling to room temperature again became a suspension. This suspension was mixed with water (300 ml) and stirred at room temperature for a half an hour. The insoluble material was separated by filtration, washed with water (3 x 20 ml), and recrystallized from methanol (50 ml). Product obtained as yellow needles in 95% yield. MP: 148-150°C; 1H NMR ($CDCl_3$, 300 MHz) δ 7.32-8.20 (5H, m), 7.16 (1H, s), 2.45 (3H, s); ^{13}C NMR ($CDCl_3$, 100MHz) δ 166.1, 137.3,135.1,133.3,129.0,128.2, 125.8, 14.8 ppm.

4-Benzylidene-2-methyl-4H-oxazol-5-one (3b):

A suspension of *N*-acetylglycine (1.6 g, 10 m.mol), sodium acetate (540 mg, 10 m.mol), and acetic anhydride (10 ml) was stirred at room temperature for 30 minutes. Into the white suspension, benzaldehyde (1.1 g; 10 m.mol) was added. The resulting suspension was stirred at room temperature for 1 h and then at 60°C for 5 h. The reaction mixture became a brown solution that upon cooling to room temperature again became a suspension. This suspension was mixed with water (300 ml) and stirred at room temperature for a half an hour. The insoluble material was separated by filtration, washed with water (3 x 20 mL) and recrystallized from methanol (50 mL). 90% product was obtained as off white amorphous solid. MP: 148-150°C. ^1H NMR (400 MHz,

$CDCl_3$) δ 7.32-8.20(5H, m), 7.16(1H, s), 2.45 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3, 132.4, 131.7, 131.3, 129.1, 55.9, 15.8 ppm.

2-benzamidobut-2-enoic acid (5a):

A 30% aqueous HCl solution was added a methanol solution of 4-ethylidene-2-phenyl-4H-oxazol-5-one (1.8 g; 10 m.mol). The reaction mixture was stirred at room temperature for 30 minutes, followed by methanol evaporation at reduced pressure. The remaining clear water solution was basified with $NaHCO_3$ solution to pH 3 and left at room temperature overnight. The formed crystalline product was separated by filtration, washed with cold water (3 x 50 mL) and dried at 110°C for 30 min to afford pure product. It was isolated in 91% yield, white amorphous solid. MP: 135.5-137.5°C; ^1H NMR (400 MHz, DMSO-d6) δ 9.54(1H, s), 8.21(2H, d, *J* =8.4 Hz), 7.98-7.44 (3H, m), 6.68(1H, q, *J* =6.8 Hz), 1.72(3H, d, *J* =6.8 Hz). ^{13}C NMR (100 MHz, DMSO-d6) δ 171.9, 165.7, 133.9, 133.8, 133.0, 131.6, 131.5, 128.3, 127.7, 127.6, 13.6 ppm.

2-acetamido-3-phenylacrylic acid (5b):

A 30% aqueous HCl solution was added a methanol solution of 4-benzylidene-2-methyl-4H-oxazol-5-one (18.7g; 0.1 mol). The reaction mixture was stirred at room temperature for 30 minutes, followed by methanol evaporation at reduced pressure. The remaining clear water solution was basified with $NaHCO_3$ solution to pH 3 and left at room temperature overnight. The formed crystalline product was separated by filtration, washed with cold water (3 x 50 mL) and dried at 110°C for 30 min to afford pure product. It was obtained in 93% yield and product was obtained as white amorphous solid. MP: 190°C. ^1H NMR (DMSO-d6, 300MHz) d 9.5 (1H, s, NH), 7.62 (2H, d, *J* = 7.2 Hz), 7.41 (2H, t, *J* = 6.0 Hz), 7.35 (1H, t, *J* = 7.2 Hz). 7.24 (1H, s), and 1.91 (3H, s); ^{13}C

NMR (DMSO-d6, 100 MHz) d 169.4, 166.5, 133.8, 131.2, 129.8, 129.2,128.6, 127.5, and 22.6 ppm. Anal. calcd. for $C_{11}H_{11}NO_3$ (MW 205.21): C, 64.38; H, 5.40; N, 6.83. Found: C, 64.26; H, 5.49; N, 6.89.

Ethoxycarbonylamino-acetic acid (7a)

To a stirred solution of glycine (0.75 g, 10 m.mol) in 2 M NaOH (1.0 equiv.) at 0°C were added simultaneously ethyl chloroformate (1.08 g, 10 m.mol) and 2 M NaOH (1.0 equiv.) drop wise. The mixture was stirred at 0°C for 3 h then washed with ether (3x 20ml). The aqueous phase was acidified with 2 M HCl and extracted with ethyl acetate (3 × 30 ml). The combined organic phase was dried and the solvent evaporated to obtain the product as colorless solid in 70% yield. M.P. 67-69°C. ^{1}H-NMR (400 MHz, DMSO-d6) 7.34(1H, t, *J* =6 Hz), 4.05-3.97(2H, m), 3.62(2H, d, *J* =6.4 Hz), 1.15(3H, t, *J* =6.8 Hz); ^{13}C-NMR (100 MHz, DMSO-d6) d 174.4, 173.7, 157.2, 43.2, 42.6, 62.4, 61.8, 14.6 ppm.

Ethoxycarbonylamino-acetic acid (7a)

To a stirred solution of glycine (0.75 g, 10 m.mol) in 2 M NaOH (1.0 equiv.) at 0°C were added simultaneously benzyl chloroformate (1.95 g, 10 m.mol) and 2 M NaOH (1.0 equiv.) drop wise. The mixture was stirred at 0°C for 3 h then washed with ether (3x 20ml). The aqueous phase was acidified with 2 M HCl and extracted with ethyl acetate (3 × 30 ml). The combined organic phase was dried and the solvent evaporated to obtain the product as colorless solid in 70% yield. M.P. 67-69°C. ^{1}H NMR (400 MHz, DMSO-d6) 7.53(m, 5H), 7.34(1H, t, *J* =6 Hz), 4.05-3.97(2H, m), ^{13}C NMR (100 MHz, DMSO-d6) d 174.4, 173.7, 157.2, 43.2, 42.6, 62.4, 61.8, 14.6 ppm.

2-p-tolyl-1H-benzo[de]isoquinoline-1,3(2H)-dione (9):

A suspension of benzo[*de*]isochromene-1,3-dione (1.98 g, 10 mmol) and *p*-amino toluene (1.07 g, 10 m.mol) in 25 ml of pyridine was heated at 70°C for about 20 hours. Increasing the temperature to reflux and setting up a collector to collect the solvent distilled off the excess solvent, the solvent was collected until enough solvent remained for recrystallization. The compound was obtained as white needles upon bringing the reaction mixture to room temperature in 80% yield. MP: 311°C. ^{1}H NMR (400 MHz, $CDCl_3$) d 8.64 (2H, dd, *J*=1.2, 1.2 Hz), 8.26 (2H, dd, *J*=1.2, 1.2 Hz), 7.79 (2H, dd, *J*=7.80, 7.80 Hz), 7.36 (2H, d, *J*=8 Hz), 7.20 (2H, d, *J*=8 Hz), 2.44 (3H, s); ^{13}C NMR (400 MHz, $CDCl_3$) d 164.7, 138.8, 134.5, 132.9, 131.9, 131.8, 130.4, 128.8, 128.5, 127.2, 123.1, 55.9, 21.6 ppm.

2-(4-(bromomethyl)phenyl)-1H-benzo[de]isoquinoline-1,3 (2H) -dione (10):

To a solution of 2-*p*-Tolyl-benzo[de]isoquinoline-1,3-dione (2.8g, 10m.mol) **9** in 75ml of chloroform was added *N*-bromo-succinimide (3.63g, 20 m.mol) and catalytic amount of benzoyl peroxide (15mg) at 0°C. The solution was stirred under a flashlight for the reaction to occur. TLC monitored the reaction for completion. After completion of the reaction the solvent was removed under vacuum and the residue was subjected to column chromatography. The compound was isolated in 65% dichloromethane and 35% hexane mixture. Alternatively the product can be recrystallized from dichloromethane. Yield of the obtained product was observed to be 85%. MP: Starts decomposing before melting at 249.1°C. ^{1}H NMR (400 MHz, $CDCl_3$) d 8.66 (2H, dd, *J*=1.2, 1.2 Hz), 8.29 (2H, dd, *J*=0.8, 0.8 Hz), 7.81 (4H, t, *J*=7.6 Hz), 7.59 (2H, d, *J*= 8.4 Hz), 3.31(2H, d,

J = 8.4 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) d 164.5, 138.3, 135.6, 134.6, 131.9, 130.3, 129.3, 127.3, 122.9, 32.8 ppm.

4-(1,3-dioxoisoindolin-2-yl) benzyl acetate (11):

A suspension of 2-(4-Bromomethyl-phenyl)-benzo[de]isoquinoline-1,3-dione **10** (3.5 g, 10 mmol) and sodium acetate (1g, 12mmol) in 10 ml of dimethyl sulfoxide was sonicated for 4 hours. The reaction mixture was poured on to ice and left for 1 hour. The product precipitated out as a white solid. The solid was washed with a 100 mL water (x 3) to give the crude product. The product was recrystallized from methanol to give pure product in 95% yield. MP: Does not melt till 400°C. ^1H NMR(400 MHz, $CDCl_3$) d 8.65(2H, d, *J* = 6.4 Hz), 8.27(2H, d, *J* =7.6 Hz), 7.79(4H, t, *J*=8 Hz), 7.54(2H, d, *J* =8 Hz), 7.32(2H, d, 8 Hz), 5.19(2H, s), 2.16(3H, s). ^{13}C NMR (400 MHz, $CDCl_3$) d 163.3, 142.6, 134.5, 131.5, 130.8, 128.8, 127.9, 127.3, 126.9, 122.7, 75.2, 62.7, 55.3, 21.6 ppm.

2-(4-(hydroxymethyl) phenyl)-1H-benzo[de] isoquinoline-1,3(2H)-dione (12):

To a solution of acetic acid 4-(1,3-dioxo-1H,3H-benzo[de]isoquinolin-2-yl)-benzyl ester (3.5g, 10 m.mol) **11** in a 15 ml of 1:1 methanol and dichloromethane was added powdered NaOH (400 mg, 10 m.mol) at 0°C and the reaction mixture was stirred for 2 hours and the methanol was evaporated. The residue was taken into 1N sodium bicarbonate solution and the product was extracted into dichloromethane, which is dried under $MgSO_4$. The solvent is evaporated under vacuum to yield a yellowish solid. MP: 282°C. ^1H NMR (400 MHz, $CDCl_3$) d 8.66 (2H, dd, *J*=0.8, 0.8 Hz), 8.29 (2H, dd, *J*=1.2, 1.2 Hz), 7.81 (4H, dd, *J*=7.6 Hz), 7.57(2H, d, *J*=8.4 Hz), 7.33(2H, d, *J*=8.4 Hz), 4.81(2H,

d, *J*=6 Hz); ^{13}C NMR (400 MHz, $CDCl_3$) 163.3, 142.6, 134.5, 131.5, 130.8, 128.8, 127.9, 127.3, 126.9, 122.7, 75.2, 62.7, 55.3, 48.6 ppm.

4-(1,3-dioxoisoindolin-2-yl) benzyl phenyl carbonate (13):

To a solution of 2-(4-(hydroxymethyl)phenyl)-1H-benzo[de] isoquinoline-1,3 (2H)-dione (3.03 g, 10 m.mol) **12** in pyridine was added phenyl chloroformate (1.56 g, 10 m.mol) drop wise. As the addition is complete a solid appears on the solution and when the reaction is left to stir longer the precipitate slowly disappears back into the solution. The solution was then stirred for an additional 1 hr and was poured in to 100ml of 10% HCl. The solid obtained was then filtered to obtain the product and was directly used in the next step. ^{1}H NMR (400 MHz, CDCl3); 8.66 (2H, dd, *J*=1.2, 1.2 Hz), 8.29 (2H, dd, *J*=0.8, 0.8 Hz), 7.81 (4H, t, *J*=7.6 Hz), 7.59 (2H, d, *J*= 8.4 Hz), 7.34-7.39 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$) d 164.5, 138.3, 135.6, 134.6, 132.1, 131.2, 131.9, 130.3, 128.6, 129.3, 127.3, 122.9, 32.8 ppm.

2-((4-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)benzyloxy)carbonylamino)acetic acid (14):

To a solution of 4-(1,3-dioxo-1H-benzo[de]isoquinolin-2 (3H)-yl)benzyl-2-hydroxy ethyl carbamate **16** (3.9 g, 10 m.mol) in acetone was added 2ml of sulphuric acid and 2ml of chromic acid. The reaction mixture was stirred at room temperature for 3 hrs and acetone was evaporated under vacuum and quenched with $NaHCO_3$ to obtain the product as white solid in 84% yield. ^{1}H NMR (400 MHz, CDCl3); 8.48-8.5(m, 2H), 7.89 (t, 2H), 7.49(t, 1H), 7.37(t, 2H), 7.47 (d, 2H), 5.09 (s, 2H), 3.68 (d, 2H). 13C NMR 163.3, 142.6, 134.5, 131.5, 130.8, 128.7, 127.9, 127.3, 126.9, 122.7, 75.2, 62.6, 55.3, 28.6 ppm.

4-(1,3-dioxo-1H-benzo [de] isoquinolin-2(3H)-yl) benzyl 2-hydroxy ethyl carbamate (16): To a solution of 4-(1,3-dioxoisoindolin-2-yl) benzyl phenyl carbonate (3.7g, 10 m.mol) **13** in DCM was added ethanol amine (0.6 g, 10 m.mol) drop wise. The solution is left to stir for about 3-4 hrs and the reaction completion was monitored by TLC. After the completion of reaction, DCM was evaporated under vacuum to obtain the pure product and was directly used in the next step.

2-(4-((5-oxo-4,5-dihydrooxazol-2-yloxy)methyl) phenyl)-1H-benzo[de] isoquinoline-1,3(2H)-dione (17): To a solution of 2-((4-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl)benzyloxy) carbonyl amino) acetic acid (4g, 10 m.mol) **14** in 40 ml of pyridine and acetic anhydride (1 ml) was added to the solution. The reaction mixture was refluxed for 3-4 hrs and was poured on to 10% HCl Solution. The white precipitate thus formed is the product, which was filtered and dried and used for next step directly. ^{1}H NMR (400 MHz, CDCl3); 8.6 (d, 2H), 8.28(d, 2H), 7.8(t, 2H), 7.42(t, 2H), 7.28(d, 2H), 5.38 (s, 2H), 4.48 (s, 2H). 13C NMR 163.3, 142.6, 134.5, 131.5, 130.8, 128.8, 127.9, 127.3, 126.9, 122.7, 75.2, 62.7, 55.3, 38.2 ppm.

Ethyl 2-azidoacetate (20):

To a stirred solution of ethyl bromo acetate (1.65 g, 10 m.mol) **19** in 15 ml water and acetone mixture (1:4) was added NaN_3 (0.65 g, 8.9mmol). The resulting suspension was stirred at room temperature for 2 hours. DCM was added to the mixture and the organic layer was separated. The aqueous layer was extracted with 2 x 10 ml DCM and the combined organic layers were dried over Na_2SO_4. Solvent was removed under reduced pressure, and the azide was directly used without purification. ^{1}H NMR (400

MHz, CDCl3); δ 4.13 (q, *J*=6.2 Hz, 2H), 3.82 (s, 2H), 1.18 (t, *J*= 6.2 Hz, 3H).) 13C NMR (400, $CDCl_3$) 162.6, 46.5, 38.2, 13.4 ppm.

Ethyl 2-azidobut-2-enoate (21a):

To a well stirred solution containing potassium methoxide (0.7 g, 10 mmol) in dry methanol (20 ml), a solution of ethyl azidoacetate **20** (1.29 g, 10 mmol) and acetaldehyde (0.4 g, 10 mmol) in dry methanol (20 ml) was added drop wise at -10°C under nitrogen. The reaction mixture was stirred at this temperature for 4h and it was poured into aqueous 30% ammonium chloride (100ml). The aqueous layer is then extracted with ethyl acetate (3x20 ml), the organic layer is dried with sodium sulfate, and the solvent was evaporated under vacuum to give the corresponding vinyl azide **21a**, yield 93 mg (6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (q, 1H), 4.22 (q, *J*=6.2 Hz, 2H), 2.05(t, 3H), 1.29 (t, *J*=6.2 Hz, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 167.9, 141.5, 136.5, 61.2, 14.2, 9.5 ppm.

Ethyl 2-azidooct-2-enoate (21b):

To a well stirred solution containing potassium methoxide (0.7 g, 10 mmol) in dry methanol (20 ml), a solution of ethyl azidoacetate **20** (1.29 g, 10 mmol) and hexanaldehyde (1 g, 10 mmol) in dry methanol (20 ml) was added drop wise at -10°C under nitrogen. The reaction mixture was stirred at -10°C for 4h and it was poured into aqueous 30% ammonium chloride (100ml). The aqueous layer is then extracted with ethyl acetate (3x20 ml), the organic layer is dried with sodium sulfate, and the solvent was evaporated under vacuum to give the corresponding vinyl azide **21b**, yield 1.13g (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (q, 1H), 4.14 (q, *J*=6.2 Hz, 2H), 2.16 (q, 2H), 1.29 (m, 2H) 1.24 (t, *J*=6.2 Hz, 3H), 0.9 (t, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 167.8,

149.4, 135, 132.9, 61.9, 31.9, 29.7, 29.6, 29.3, 24.2, 22.7, 14.8, 14.2 ppm.

Ethyl 2-azidodec-2-enoate (21c):

To a well stirred solution containing potassium methoxide (0.7 g, 10 mmol) in dry methanol (20 ml), a solution of ethyl azidoacetate **20** (1.29 g, 10 mmol) and octanaldehyde (1.28 g, 10 mmol) in dry methanol (20 ml) was added drop wise at -10°C under nitrogen. The reaction mixture was stirred at -10°C for 4h and it was poured into aqueous 30% ammonium chloride (100ml). The aqueous layer is then extracted with ethyl acetate (3x20 ml), the organic layer is dried with sodium sulfate, and the solvent was evaporated under vacuum to give the corresponding vinyl azide **21c**, yield 1.29g (54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (q, 1H), 4.18 (q, *J*=6.2 Hz, 2H), 2.18(q, 2H), 1.31 (m, 14H) 1.24 (t, *J*=6.2 Hz, 3H), 0.88(t, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 167.8, 149.4, 135, 132.9, 61.9, 31.9, 29.7, 29.6, 29.3, 24.2, 22.7, 14.8, 14.2 ppm.

Ethyl 2-azido-3-phenylacrylate (21d):

To a well stirred solution containing sodium (0.23 g, 10 mmol) in dry ethanol (30 ml), a solution of ethyl azidoacetate **20** (1.29 g, 10 mmol) and benzaldehyde (0.53 g, 5 mmol) in dry ethanol (10 ml) was added drop wise at -10°C under nitrogen. The reaction mixture was stirred at 0°C for 4 h and it was poured into aqueous 30% ammonium chloride (100ml) and the formed solid was separated by filtration, washed with water (30 ml) and dried to give vinyl azide **21d**, yield 1.8 g (82%). ^{1}H NMR (400 MHz, CDCl3); δ 7.91 (s, 1H), 7.60 (d, 2H), 7.4(d, 2H), 7.33(t, 1H), 4.24 (q, *J*=6.2 Hz, 2H), 1.24 (t, *J*=6.2 Hz, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 167.1, 135.2, 128.6, 128.5, 127.9, 132.9, 118.8, 61.8, 14.8 ppm.

Ethyl 2-azido-3-(2,4,6-trimethoxyphenyl)acrylate (21e):

To a well-stirred solution containing sodium (0.23 g, 10 mmol) in dry ethanol (30 ml), a solution of ethyl azidoacetate **20** (1.29 g, 10 mmol) and trimethoxy benzaldehyde (0.98 g, 5 mmol) in dry ethanol (30 ml) was added drop wise at -10°C under nitrogen. The reaction mixture was stirred at 0°C for 4 h and it was poured into aqueous 30% ammonium chloride (100ml) and the formed solid was separated by filtration, washed with water (30 ml) and dried to give vinyl azide **21e**, yield 2.39 g (78%). ^{1}H NMR (400 MHz, CDCl3); δ 8.19 (s, 1H), 6.09 (s, 2H), 4.2 (q, *J*=6.2 Hz, 2H), 3.83 (s, 9H), 1.29 (t, *J*=6.2 Hz, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 167.4, 160.6, 159.6, 132.9, 118.8, 101.7, 90.9, 61.4, 56.2, 55.8, 14.2 ppm.

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Chapter V

Synthetic approaches towards Magnesidin:

5.1 Abstract:

Magnesidin is a tetramic acid isolated from nature, responsible for the formation of dental plaque. In spite of its biological activity, the complexity of its structure makes its synthesis complex. The intermediates like β- keto acids synthesized in previous chapters and few other intermediates like 1,3-benzodioxoles, α-β unsaturated amides synthesized in this chapter would be used towards synthesizing magnesidin.

5.2 Introduction:

5.2.1 Magnesidin:

Magnesidin, a magnesium salt of tetramic acid isolated from *pseudomonas magnesiorubra* demonstrates strong antibiotic activity against bacteria (mainly streptococcus and anaerobes) responsible for the formation of dental plaque. There are only two literature reports outlining the synthetic preparation of magnesidin, these reported procedures are very difficult to reproduce and apply to the large-scale preparation[1]. The viability of this strategy was investigated by Jones and coworkers[2]. Therefore, for the commercialization of magnesidin and/or its analogs a new reliable and large-scale applicable synthetic procedure must be developed. In many literature reported attempts to reproduce this procedure, intermediates were lost during purification. These problems explain why there is no manufacturing procedure for the preparation of such an important antibiotic. It is even more important that there are no reliable synthetic procedures for many other tetramic acid derivatives, considering that

they show a remarkable diversity in terms of biogenetic descent as well as structural variations. The high polarity of these compounds and the fact that they can exist in various tautomeric forms (2,4-diketo form prevails in solution) renders them difficult to handle and their spectra difficult to interpret tetramic acid. In designing a successful synthesis of tetramic acid, it was felt that it would be wise to explore the way in which nature assembles the tetramic acid. The retro synthetic analysis and synthesis is discussed in results and discussion section.

5.2.2 .1,3-benzoxodioles:

In many instances, protection groups that are commonly used in synthetic organic chemistry are also present in nature for completely different purposes[3]. This is certainly the case with 1,3-benzodioxoles[4-7]. Probably the most commonly known and widely used natural products with 1,3-benzodioxole moieties are safrole[8], myristicin,[9,10] and piperin[11]. Derivatives of these natural products are used as inhibitors of mono-oxygenase enzymes,[12] pesticides or pesticide intermediates,[13] herbicides,[14] antioxidants,[15] antimicrobials,[16] and medicines.[17-19] And in the similar way 1,3-benzodioxoles are also important intermediates in synthesizing magnesidin derivatives. β- keto esters an important intermediate in derivative in synthesis of magnesidin needs to be protected during he reaction process and protection of these compounds with catechol would result in 1,3-benzodioxole derivatives. And as there is such an importance for these compounds it should not be a surprise that there is a substantial demand for simple and very effective method for preparation of wide variety of the 1,3-benzodioxole derivatives.

5.2.3 α-β Unsaturated amides:

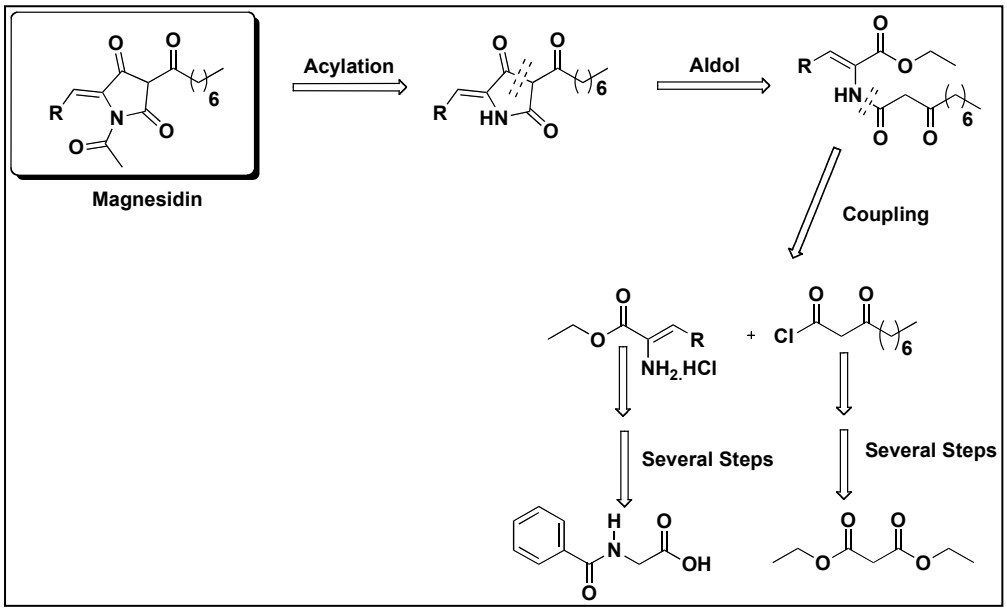
α-β unsaturated amides also known as α-dehydropeptides (DHPs) are also another type of intermediates necessary for synthesizing magnesidin. Dehydro amino acids (DHAs) were actually necessary intermediates for the synthesis but since their synthesis was complicated and unaccomplishable; dehhydro peptides were targeted for synthesis. Going beyond magnesidin, DHPs are also an important class of biological compounds can be derived only from DHAs making them even more powerful class of compounds. A vast number of reports wee found on correlating the structure and biological activity of dehydro oligopeptides containing one or more DHA moieities[20-22]. For example, Berninamycin A, an antibiotic is a cyclodehydropeptide with two DHP sequences and about seven DHA residues and has been isolated from a culture of *Streptomyces bernensis*[23]. The syntheses of DHPs are well established and have been known for quite sometime. Elimination of peptides with a leaving group[24-27], by direct coupling of DHAs with amino acids[28,29], ring cleavage of unsaturated azalactones[30-33], are few of the most common methods used to synthesize these compounds. Although there are many methods of synthesis available for DHPs, DHAs one of the main components for preparation of DHPs are not very well established in synthesis and only few methods are reported for these compounds[34,35].

5.3 Results and discussion:

5.3.1 Retro synthesis based on biosynthesis of magnesidin:

In synthesizing magnesidin, the structure of synthetic equivalent of magnesidin has been studied and it can be classified into the following important synthetic fragments.

The retro analysis of magnesidin is shown in scheme 5.1. The retro synthetic pathway involves synthesizing magnesidin from fragments like β-keto acids and α-β unsaturated amino acids, both these further prepared from smaller molecules as starting materials. Of these fragments β-keto acids have been synthesized successfully and their synthesis has been described in chapter III. But synthesis of α-β unsaturated amino acids was not very successful and hence this failure has to be addressed in designing the total synthesis of magnesidin. The synthesis has been addressed with various approaches and each of these approaches is described in detail in the following section as the oxazolone approach, the tag molecule approach and the azide approach.

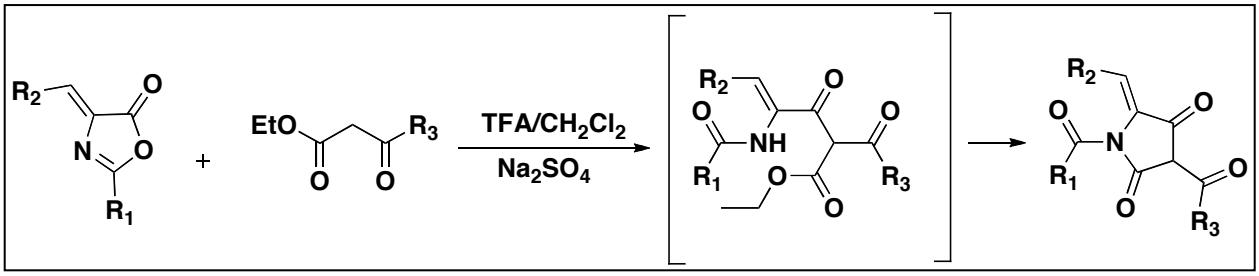


Scheme 5.1 Retro synthetic analysis of Magnesidin.

5.3.2 The oxazolone approach:

This was one of the first approaches towards the synthesis of magnesidin wherein a methodology has been developed to synthesize various oxazolones, which were initially proposed to be used for the synthesis of α-β unsaturated amino acids. As the

oxazolones were unsuccessful to be used as starting materials for α-β unsaturated amino acids, they were directly applied in the synthesis of magnesidin as shown in scheme 5.2. Few oxazolones were picked, all starting from N-protected aryl glycines and aromatic aldehydes and are coupled with aryl β-keto esters i.e. all R_1, R_2 and R_3 are aromatic. The aryl-substituted oxazolone is treated with aryl β-keto esters in presence of TFA and sodium sulphate to produce tetramic acids. Aromatic analogues are chosen because aromatic compounds would be easier to follow on NMR.



Scheme 5.2 Direct oxazolone condensation with β-keto esters.

A particular oxazolone was used which was synthesized using N-benzoyl glycine and trimethoxy benzaldehyde in presence of sodium acetate and acetic anhydride. This oxazolone **1** was reacted with benzoyl ethyl acetate **2** to obtain the tetramic acid **3**. The tetramic acid differs form magnesidin with its substituents in the ring. The 1H NMR in the figure 5.1 also clearly shows the formation of the tetramic acid obtained in this reaction.

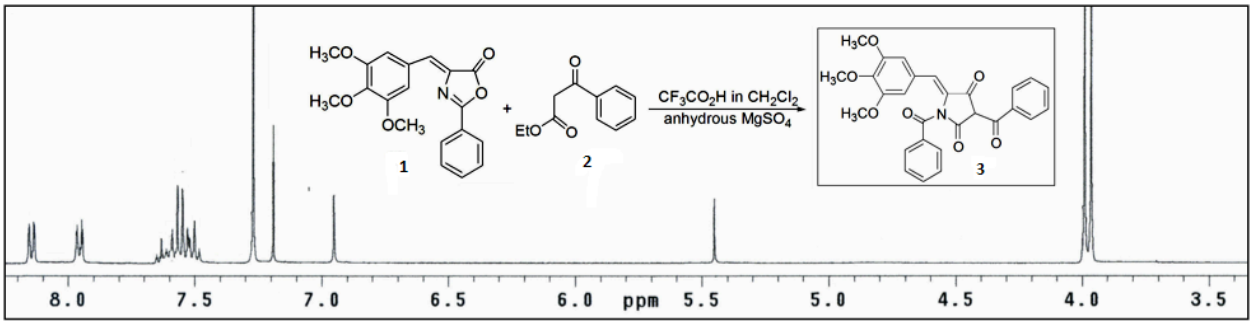


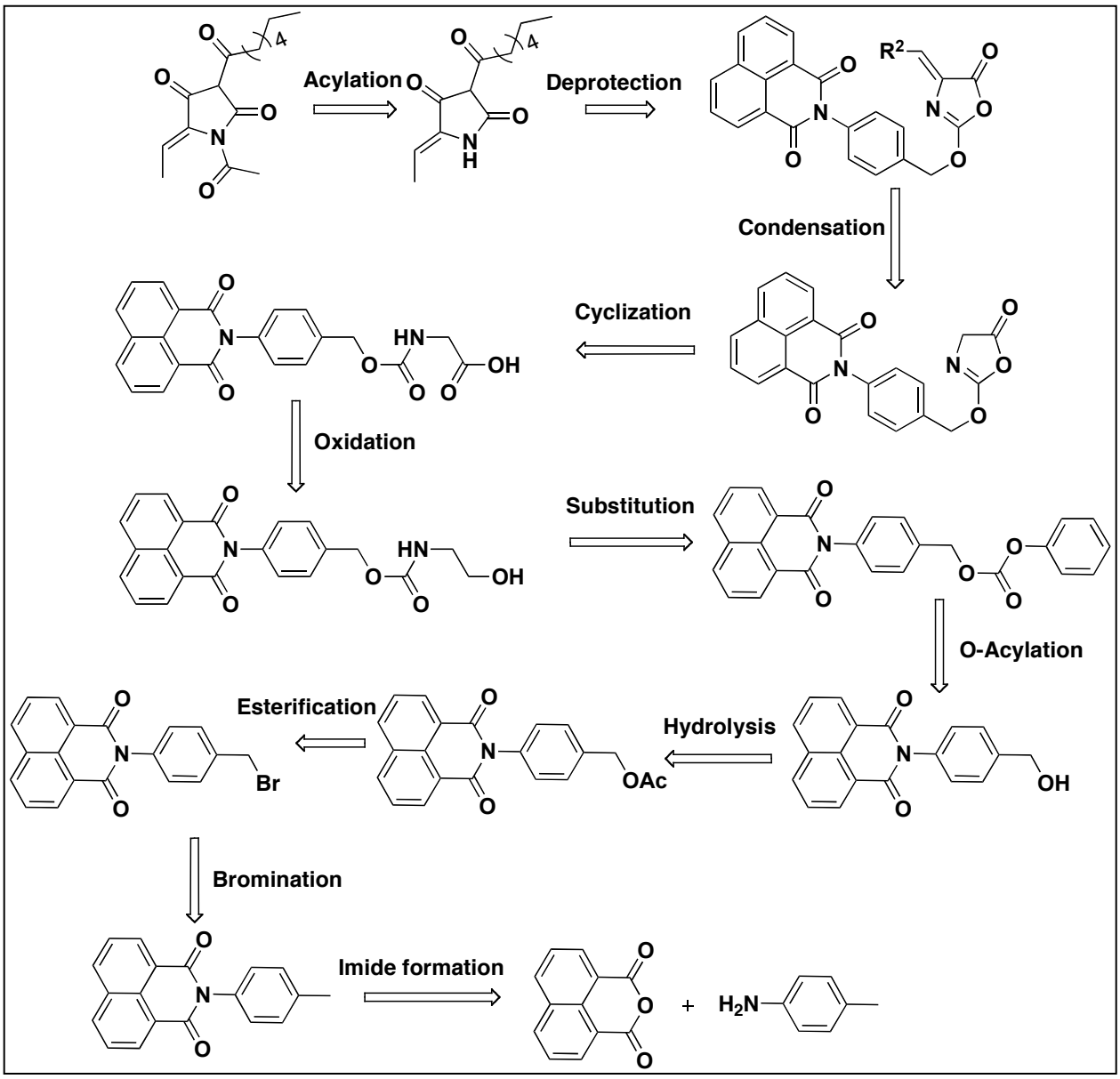
Fig. 5.1 1H-NMR of tetramic acid prepared from oxazolone and β-keto esters.

Based on the preliminary results it was hypothesized that the synthesis of magnesidin would be possible when appropriate oxazolones are made and treated with β-keto esters. However the oxazolone required to synthesize magnesidin would need an oxazolone with a low molecular weight and synthesizing and isolating low molecular weight oxazolones was a synthetic challenge as reported in earlier chapter. So the tag molecule used in previous cases is considered to be used even in these syntheses.

5.3.3. The TAG molecule approach:

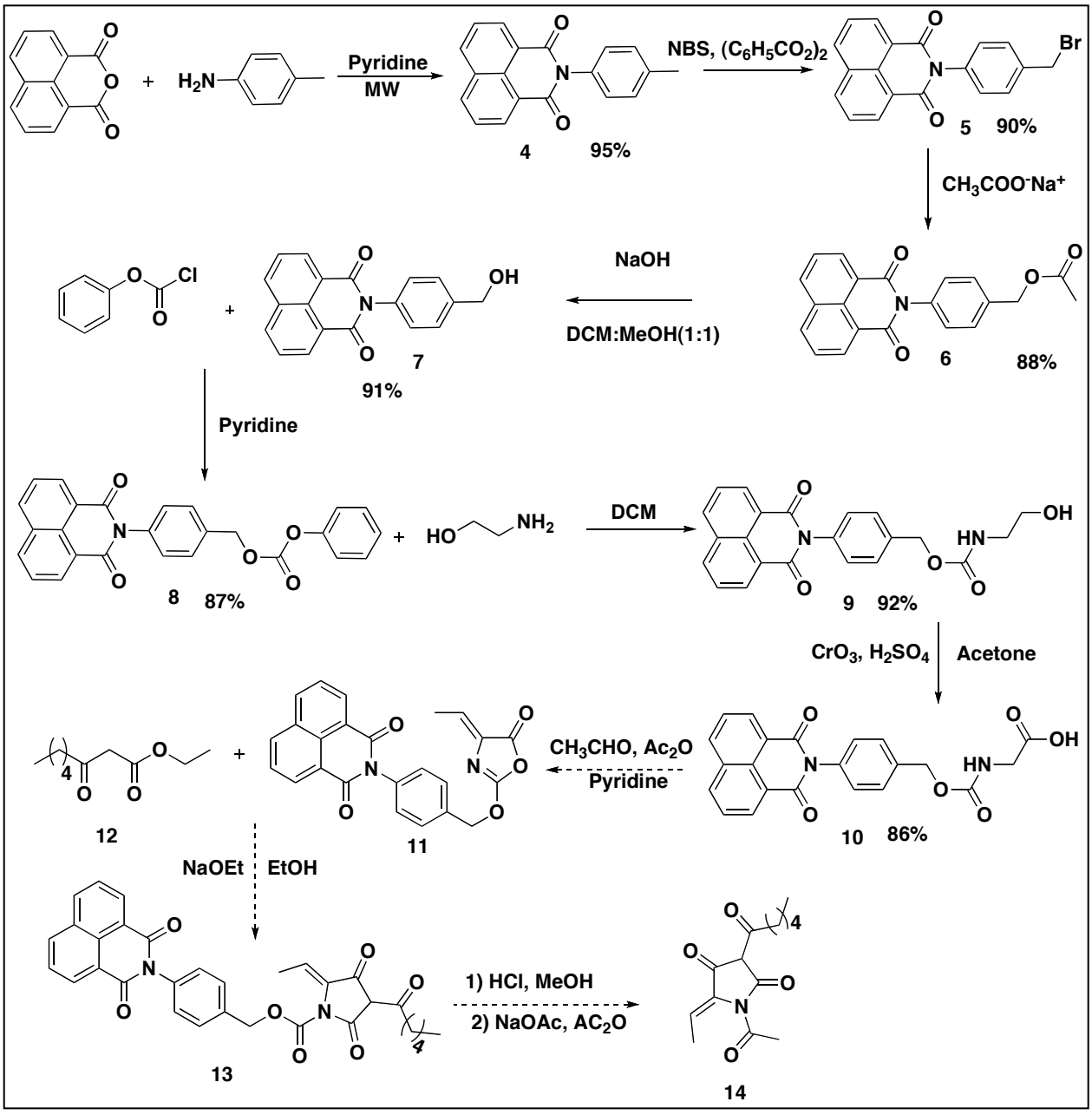
The tag molecule can PG 3 was used in analyzing the retro synthetic pathway for magnesidin, the tag molecule can be prepared in few steps starting from 1,8- naphthalic anhydride and *p*-toluidene. The tag molecule would react with phenyl chloroformate to produce the corresponding carbamate, which further can be reacted with glycine. The obtained product is transformed into the corresponding oxazolone, which would further be condensed with acetaldehyde. Opening the oxazolone ring with the active carbon of β - keto acids followed by a ring closure yields the tetramic acid, protected on N-1 by the tag molecule. Hydrolysis cleaves the protection group and an acylation reaction that follows would produce the desired tetramic acid Magnesidin and the retro synthetic

analysis to produce magnesidin with the use of tag molecule would be as shown in scheme 5.3.



Scheme 5.3 Retro synthetic analysis of Magnesidin using the tag molecule PG 3.

After identifying the retro synthetic analogues a design for the synthesis is necessary and using the retro analysis the synthesis of magnesidin is proposed as shown in scheme 5.4.

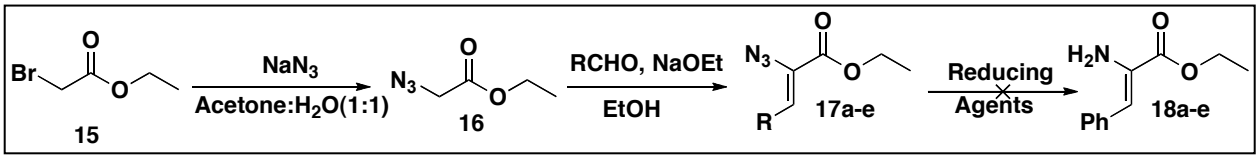


Scheme 5.4 Attempt for synthesis of magnesidin using the tag molecule.

However, the total synthesis was not accomplished and could not produce magnesidin. The method could not be generalized and it was not possible to produce tetramic acids other than **3** in fig 5.1. From the step, which produces **11** in the above reaction scheme 5.4, the reactions did not work out well. The product was obtained in very few cases, especially when trimethoxy benzaldehyde has been replaced with acetaldehyde and other aliphatic aldehydes. Even in case of aromatic aldehydes it was not possible to synthesize with simple unsubstituted aldehydes like benzaldehyde. So the oxazolone approach favored the formation of few selected tetramic acids where the aromatic aldehydes were condensed. However it was not successful in producing the desired tetramic acid magnesidin, which requires condensation with acetaldehyde.

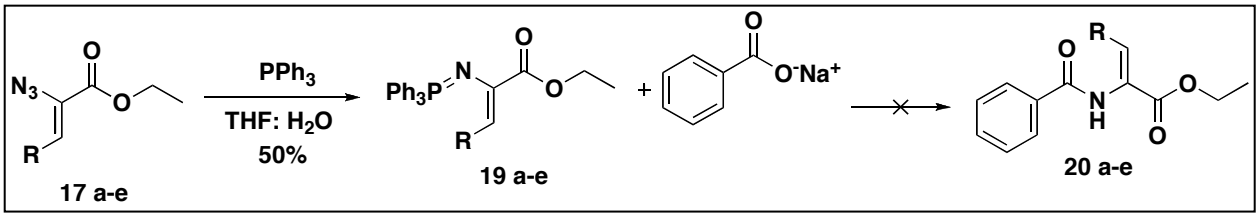
5.3.4. The azide approach:

The azide approach is another approach that was attempted to be used in synthesizing α-β unsaturated amino acids and was unsuccessful in synthesizing these compounds. The idea behind synthesizing α-β unsaturated amino acids is to couple the N-terminal with the β-keto acids to obtain the corresponding α-β unsaturated peptides. There are few methods of synthesis available for these compounds but the methods of synthesis are not very effective in terms of yield and feasibility with synthesis. So a method of synthesis is on demand for these compounds.



Scheme 5.5 Proposed synthesis of α-β unsaturated amino acids

While synthesizing α-β unsaturated amino acids, the scheme involved synthesis of azides of α-β unsaturated esters **16** condensed with aldehydes to produce compounds like **17**, which further had to be reduced to α-β unsaturated amino acids **18** as shown in scheme 5.5. Various reducing agents are tried for reduction and triphenyl phosphine is one of them. Triphenyl phosphine in presence of THF and water reduces azide to amine in general cases but the azides **17 a-m** that have been tried did not undergo reduction but formed the corresponding iminophosphoranes **19 a-m** in 50% yield. Changing the solvent system from THF-Water to DCM has increased the yield of iminophosphoranes from 50% to 94%. Since the iminophosphoranes did not undergo any further reduction, they were explored at this stage to react directly with the corresponding acids or acid chloride to obtain the corresponding dehydro amides as shown in scheme 5.6. The reaction between the salt of an acid and the iminophosphorane was not successful as anticipated so the salt of an acid was replaced with acid chloride to obtain the desired products **20a-e**.

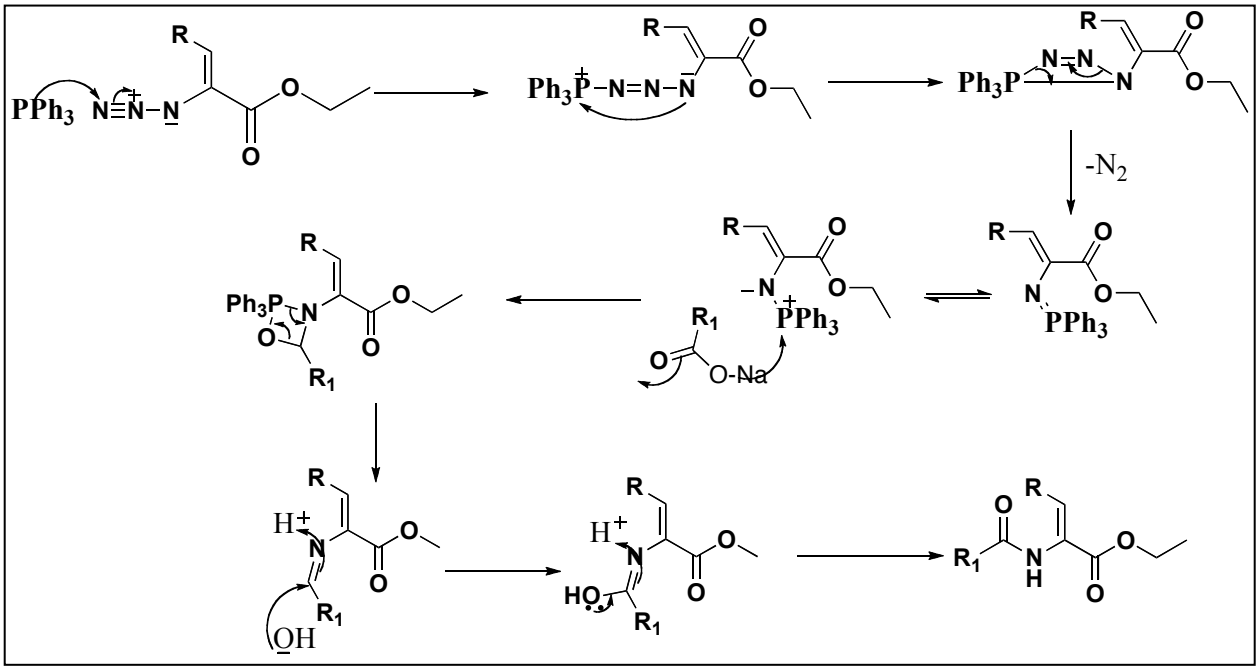


Scheme 5.6 Proposed synthesis of α-β unsaturated amides.

5.3.5 Synthesis of α-β unsaturated amides:

The affinity between oxygen and phosphorous has been known for quite some time a lot of chemistry has been developed based on their affinity[36-43]. Wittig reaction is one of the famous and most used reaction amongst these. Based on the mechanism of Wittig reaction, a mechanism has been proposed as shown in scheme 5.7. Although the mechanism has been proposed and several type of acid salts have been used for synthesis, the reaction did not proceed under these conditions. To further extend the studies on these reactions the salt of the acid has been replaced by an acid chloride.

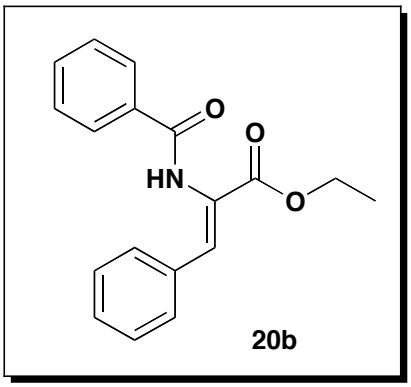
When the iminophsophorane reacted with the acid chloride the acid chloride and the iminophsophorane were both consumed but there wasn't any trace of the product on 1H NMR when the crude was analyzed. But later when the reaction mixture was worked up using, $NaHCO_3$ or NaOH solution there was some product observed however the yield were a little low. To solve this problem various other reagents were tried to substitute the use of base and silica was found to be very useful. After the reaction is complete stirring the reaction mixture

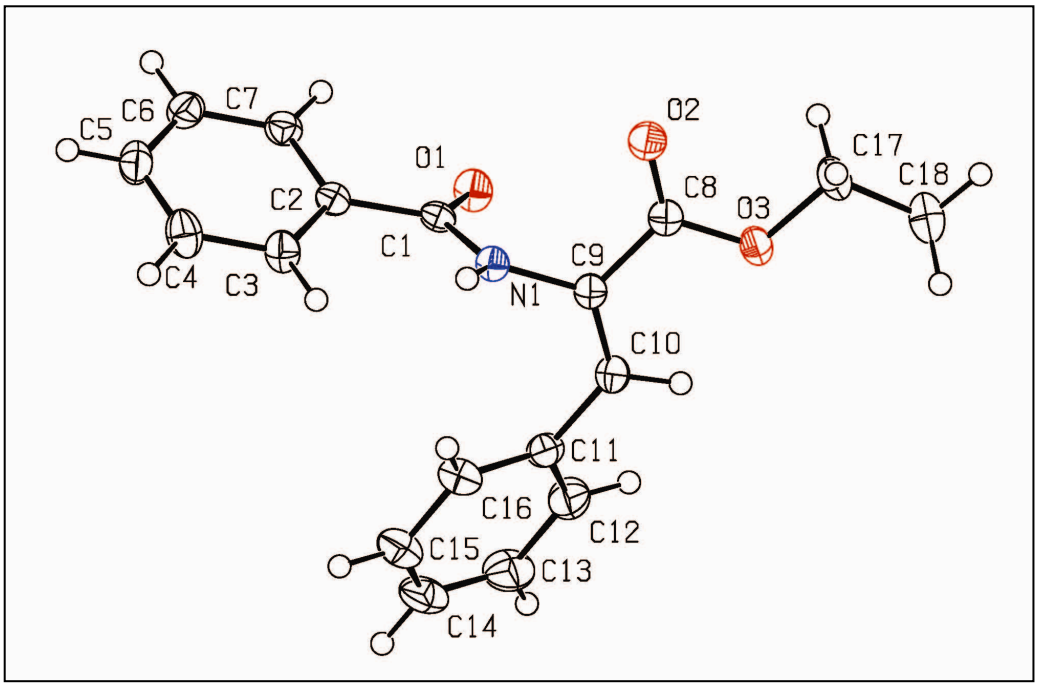


Scheme 5.7 Proposed mechanism of reaction between salt of an acid and iminophosphoranes.

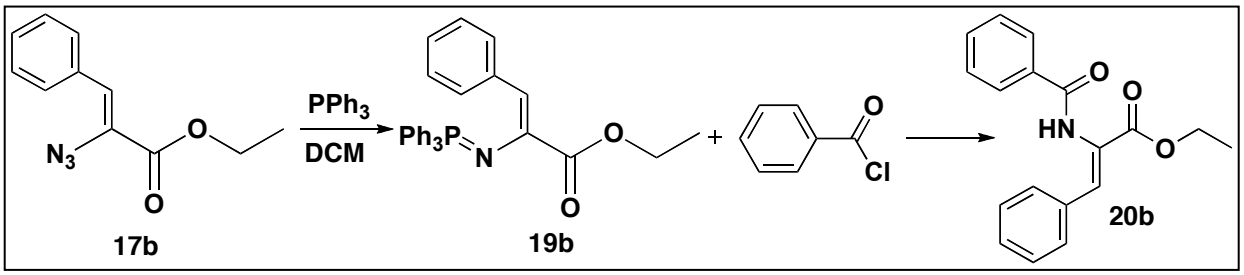
in silica gave a better yield of the product than it did in $NaHCO_3$. Although the product was confirmed on 1H NMR and 13C NMR, since the product was not formed obviously, the product **20b** obtained from the reaction between benzoyl chloride and the corresponding iminophsophorane (scheme 5.8) was analyzed using crystallography as shown in figure 5.2. The x-ray crystallographic structure obtained confirms the product and also shows that the double bond exists in *z*- configuration or the trans configuration as desired because the structure elucidation of magnesidin[1] shows that the methyl (in this case phenyl) group exists trans to the carbonyl on the ring (in this case, the carbonyl of ethyl ester.

Figure 5.2 X-ray Crystallographic structure of the product.



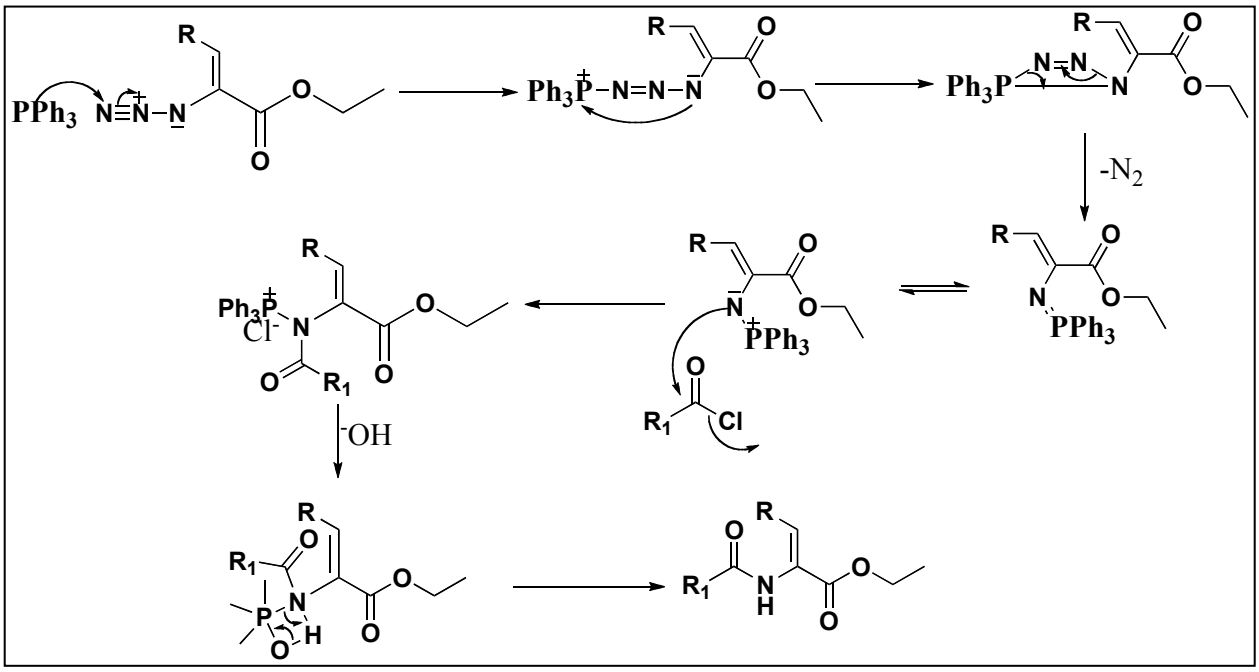


Provided courtesy of Prof. Edwin D. Stevens



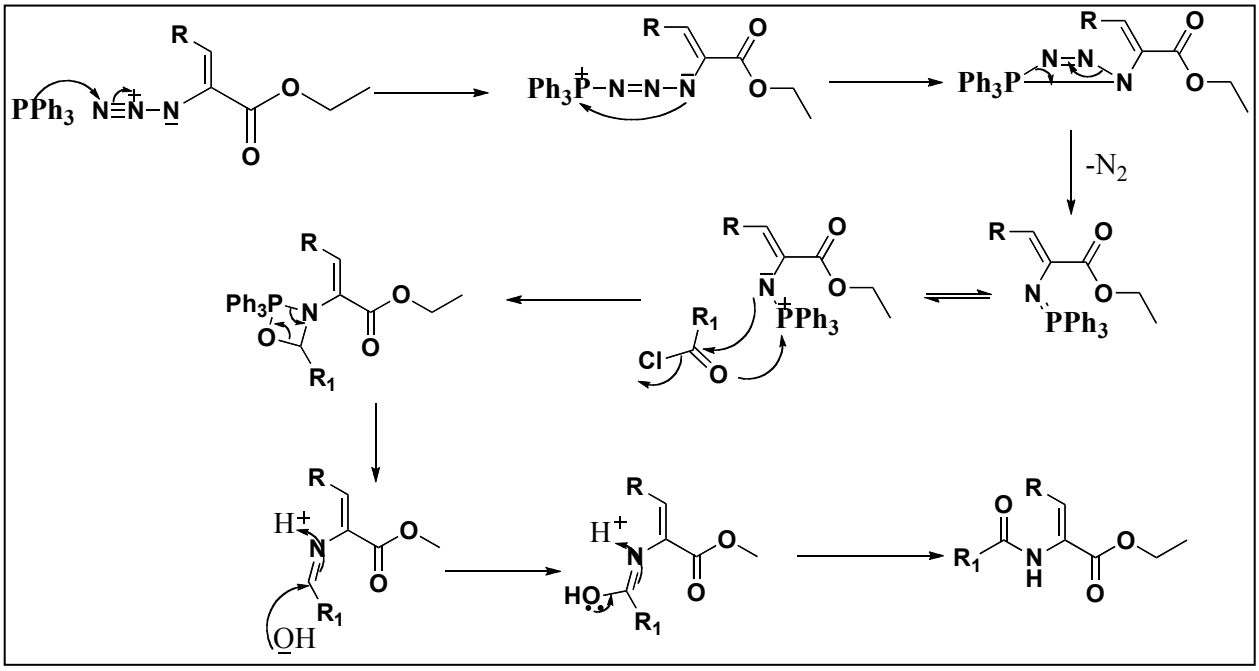
Scheme 5.8 Synthesis of the product 20b.

While investigating the mechanism of the reaction between acid chloride and the iminophosphorane, various phosphorane reactions like Wittig and Wittig related reactions which are very close to the current reaction are studied and the mechanism can be proposed to happen in two ways; the N attack as shown in scheme 5.8 and the O attack as shown in scheme 5.9. In both these mechanisms the release of phosphine oxide has been predicted and was also observed to form during the reactions. The need a base or a nucleophile in order to yield the product was a necessary condition, otherwise the product would not be observed either on TLC or NMR. In scheme 5.9 where the N- attack was proposed, after the nitrogen ylide is formed nucleophilic N attacks the carbonyl of the acid and the chlorine group leaves forming the counter anion for the adduct thus formed. The adduct then forms a 4-membered ring like in any other Wittig reaction and elimination of phosphine oxide produces the desired candidate.



Scheme 5.9 Mechanism proposed to occur by N-attack.

In scheme 5.10 where the attack was proposed to be an O- attack, the oxygen in the carbonyl of the acid is the active species and the phosphorous in phosphine is prone to attack by the oxygen, followed by 4-membered ring formation and release of phosphine oxide to yield the product.



Scheme 5.10 Mechanism proposed to occur by O-attack.

As this method of preparation of α-β unsaturated amides from the azides is not well explored, and also because the analogues of these compounds are essential intermediates for not only synthesizing the derivatives of tetramic acids but also many other natural products, the method has been applied to prepare a various other α-β unsaturated amides with different substituents. Three aldehydes benzaldehyde, trimethoxy benzaldehyde, hexanal and octanal are used for condensation and acetyl chloride, benzoyl, hexanoyl and octanoyl chlorides have been tried as other acid sources. The results were not very impressive with acetaldehyde. Derivatives prepared are shown in the figure 5.3.

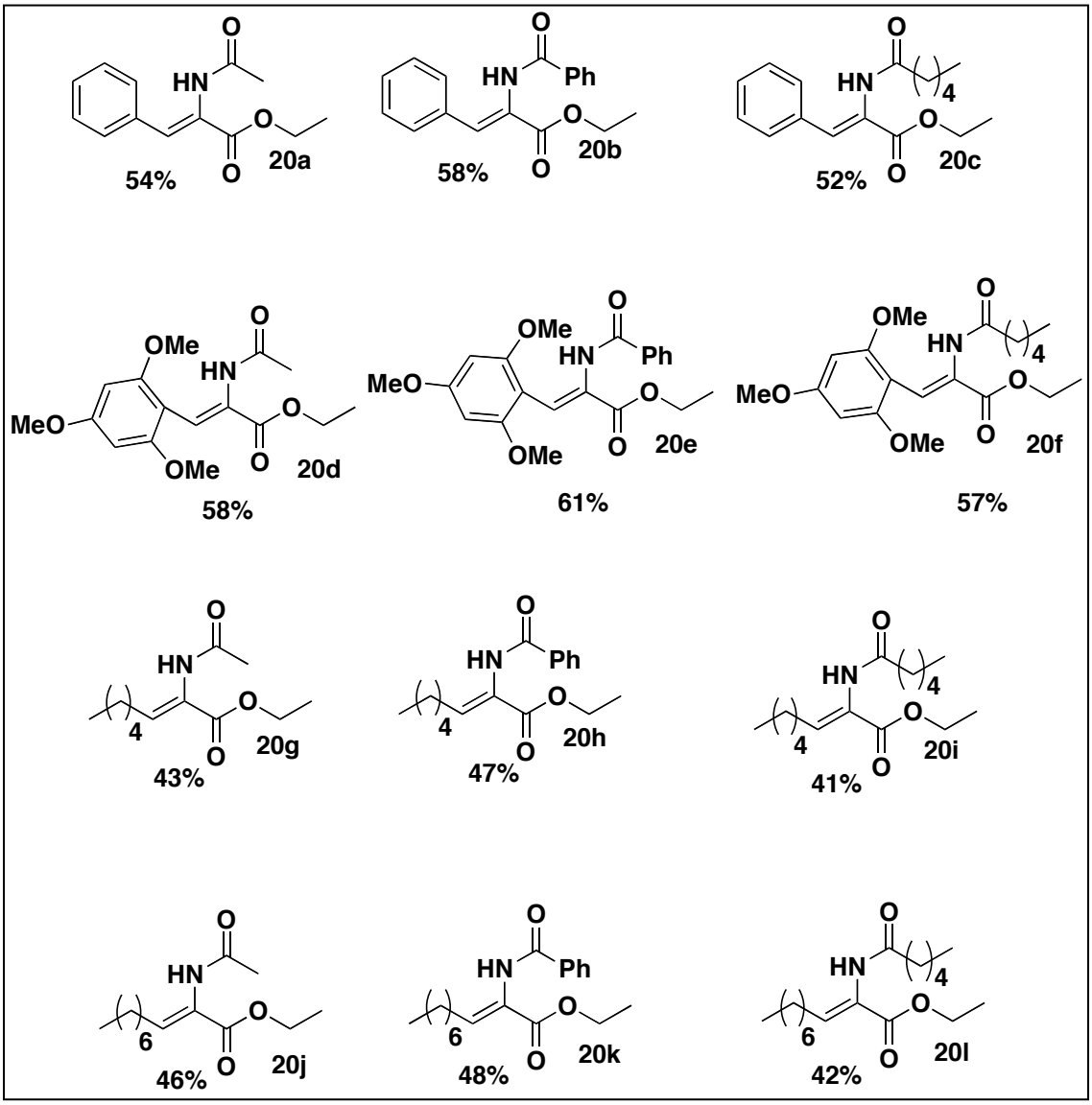
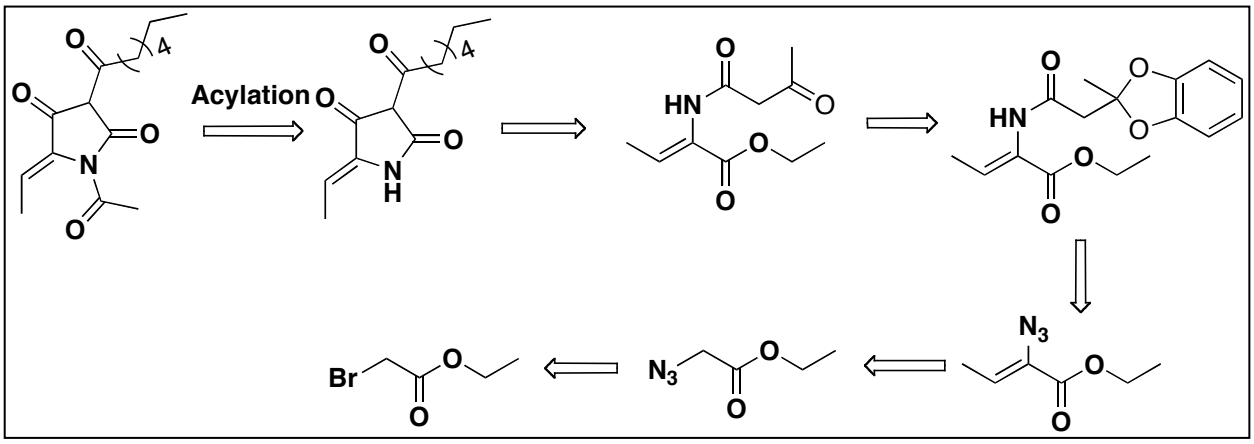


Figure 5.3: Various α-β unsaturated amides synthesized:

Since the method was successful in synthesizing the α-β unsaturated amides the synthesis is applied in the synthesis of magnesidin. With the application of the above-developed methodology, the retro synthetic analysis for Magnesidin has been proposed as shown in scheme 5.11.



Scheme 5.11 Retro synthetic analysis of magnesidin using α-β unsaturated amides

In the proposed retro synthetic analysis, one of the step involves protection of β-keto ester and after a couple of protections are analyzed it was concluded that protection with catechol would be the best one, considering the fact that the protection group must survive the following reaction conditions in the scheme. There are few methods of synthesis reported, which involve protection of these compounds and keto group protected with catechol produce compounds called benzodioxoles.

5.3.6 Synthesis of 1,3 benzodioxoles:

There are several synthetic approaches for preparation of these important compounds. One of the most common approaches is through condensation of carbonyl compounds with catechol in the presence of an acid catalyst.[44] The applicability of this synthetic approach strongly depends on the efficiency of the acidic catalyst.[45] In particular 1,3-benzodioxoles have been prepared from corresponding carbonyl compounds and catechol with catalysts such as *p*-toluenesulfunic acid,[46] copper *p*-toluenesulfonate,[47] pyridinium p-toluene sulfonate,[48] and KSF or K-10[49] to name a few. There are also

methods that utilize aggressive Lewis acid catalysts, such as phosphorus pentoxide[50] or phosphorus trichloride.[51] clearly there is a demand for simple and highly efficient synthetic procedures for the preparation of these valuable compounds.

Recently, we designed a microwave organic synthetic reactor[52] that allows the synthetic organic chemist to carry out organic reactions together with magnetic stirring, stable microwave power control, temperature control, and solvent refluxing.[53] This reactor design adds an advantage in performing a number of very efficient reactions over conventional synthetic methods.[54-56] Microwave assisted reactions are particularly effective when small polar molecules are part of the reaction transformation.[57-59] One can also speculate that microwave heating should be especially effective for chemical transformations in which water is one of the reaction products. In conventional approaches, to drive the reaction to completion, the addition of water-consuming and aggressive reagents, such as phosphorus pentoxide and phosphorus trichloride, are used. We believe that the combination of simple and safe catalysts, such as acidic polymers (dowex), acidic clay (K10), and *p*-toluenesulphonic acid, in microwave will be a prevailing alternative approach for 1,3-benzodioxole derivatives.

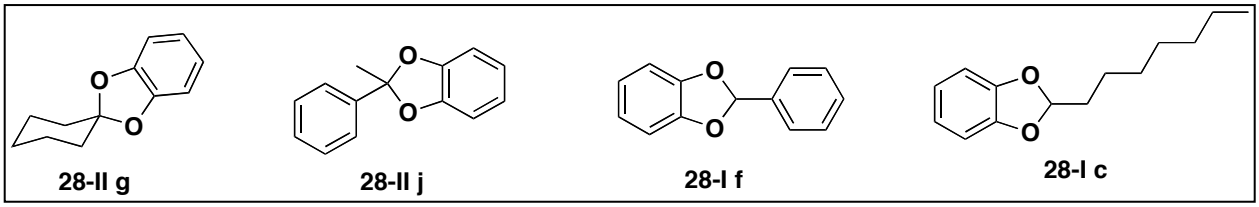


Figure 5. 4. Structures of 1,3- benzodioxoles used for optimizing reaction conditions

To test the validity of this assumption, we subsequently selected four different carbonyl compounds (both aliphatic and aromatic ketones and aldehydes) that have the

capability of producing four different derivatives of 1,3-benzodioxoles presented in figure 5.2. Three acid catalysts (amberlite, clay K-10, and p-toluenesulfonic acid) and three solvents (benzene, toluene, and xylene) were selected for a comparison of the differences in conventional and microwave-assisted preparation of the 1,3-benzodioxoles. Overall, 72 reactions were performed and the isolated yields of the corresponding 1,3-benzodioxoles are presented in Table 5.1. Microwave magnetron power was adjusted to generate vigorous solvent refluxing (400W for benzene, 500W for toluene, and 560W for xylene). There are substantial differences regarding the nature of substrate, solvent, acid catalyst, and above all conventional vs. microwave assisted reactions. There is a clear improvement in using microwave over conventional heating in all of the substrates. The reaction time for microwave-assisted reactions is up to twenty times shorter than for comparable reactions under conventional heating. When the reaction time was shortened, thermal decomposition was also minimized, resulting in higher isolated yields and more simplified product purification. The choice of the acid catalyst was also important. *p*-Toluenesulfonic acid (PTSA) continuously gave the best results in comparison to amberlite and clay K-10 (Table 5.1). In many instances, the solvent of choice was benzene, although xylene as a solvent somewhat shortened reaction times, the amount of thermal decomposition byproducts increased. Isolated yields were good to excellent for the aromatic and aliphatic ketones as well as aromatic aldehydes. Isolated yields seem to be slightly lower for aliphatic aldehydes. Under both conventional and microwave heating, a considerable amount (10-30%) of the aldol condensation product was formed. However, separation of the aldol byproduct from the corresponding 1,3-benzodioxole was simple and involved filtration through a

short column of silica gel. Nevertheless, the microwave-assisted preparation of 1,3-benzodioxole from aliphatic aldehydes can be optimized to about 80-85% conversion with more than 75% isolated yield.

Now that the advantage of the microwave versus conventional heating was demonstrated (Table 5.1), we would also like to show the NMR reaction following the preparation of (**1f**) from benzaldehyde and catechol in benzene with PTSA as an acid catalyst (Figure 5.5).[60] This reaction is a perfect demonstration of the efficiency and selectivity of the microwave assisted preparation of 1,3-benzodioxoles. There is no formation of byproducts and according to ^{1}H-NMR, the conversion is almost quantitative. The isolated yield reflects loss during isolation and purification. If xylene is used instead of benzene as reaction media, the reaction time has shortened to 90 minutes (benzaldenhyde is consumed) and a small amount of decomposition byproduct is formed, reflecting slightly lower isolated yield (Table 5.1).

The efficiency of the microwave-assisted preparation of 1,3-benzodioxole from both aliphatic and aromatic aldehydes was demonstrated in Table 5.2. All reactions were performed in benzene as a reaction media, *p*-tolunebenzoic acid (PTSA) as the acid catalyst, and the microwave heating with magnetron power of 400W. For aromatic aldehydes, the reactions are very clean but for aliphatic aldehydes the reaction should be carefully monitored because the aldol byproducts are formed.

Table 5.1.Comparison of microwave and conventional carbonyl protection with catechol.

Product	Solvent	Catalyst	Conventional		Microwave	
			Time (min.)	Yield (%)	Time (min.)	Yield (%)
28-IIg	S1	A	300	71	120	78
		B	1440	68	120	96
		C	162	93	105	84
	S2	A	270	77	105	72
		B	1440[1]	87	105	89
		C	160	85	90	78
	S3	A	220	58	90	66
		B	1200	72	90	74
		C	150	74	90	62
28-IIj	S1	A	3600	68	240	63
		B	7440	58	240	59
		C	2400	69	210	66
	S2	A	3240	72	120	71
		B	7440	71	120	91
		C	1440	73	120	82
	S3	A	3000	63	90	73
		B	7200	76	90	79
		C	1200	69	90	84
28-IIf	S1	A	1080	48	120	62
		B	4200	58	120	87
		C	900	58	120	69
	S2	A	900	54	120	62
		B	2880	80	120	84
		C	510	65	120	74
	S3	A	720	53	90	59
		B	2400	68	90	72
		C	450	61	90	71
28-IIc	S1	A	900	34	90	28
		B	1200	42	90	53
		C	900	29	90	39
	S2	A	780	31	90	33
		B	1080	60	90	72
		C	840	26	90	41
	S3	A	690	22	75	25
		B	900	38	75	49
		C	600	18	75	33

S1 = Benzene, S2 = toluene, S3 = Xylene, A = Dowex, B = PTSA, C = Clay K-10, a-conventional, b-microwave.

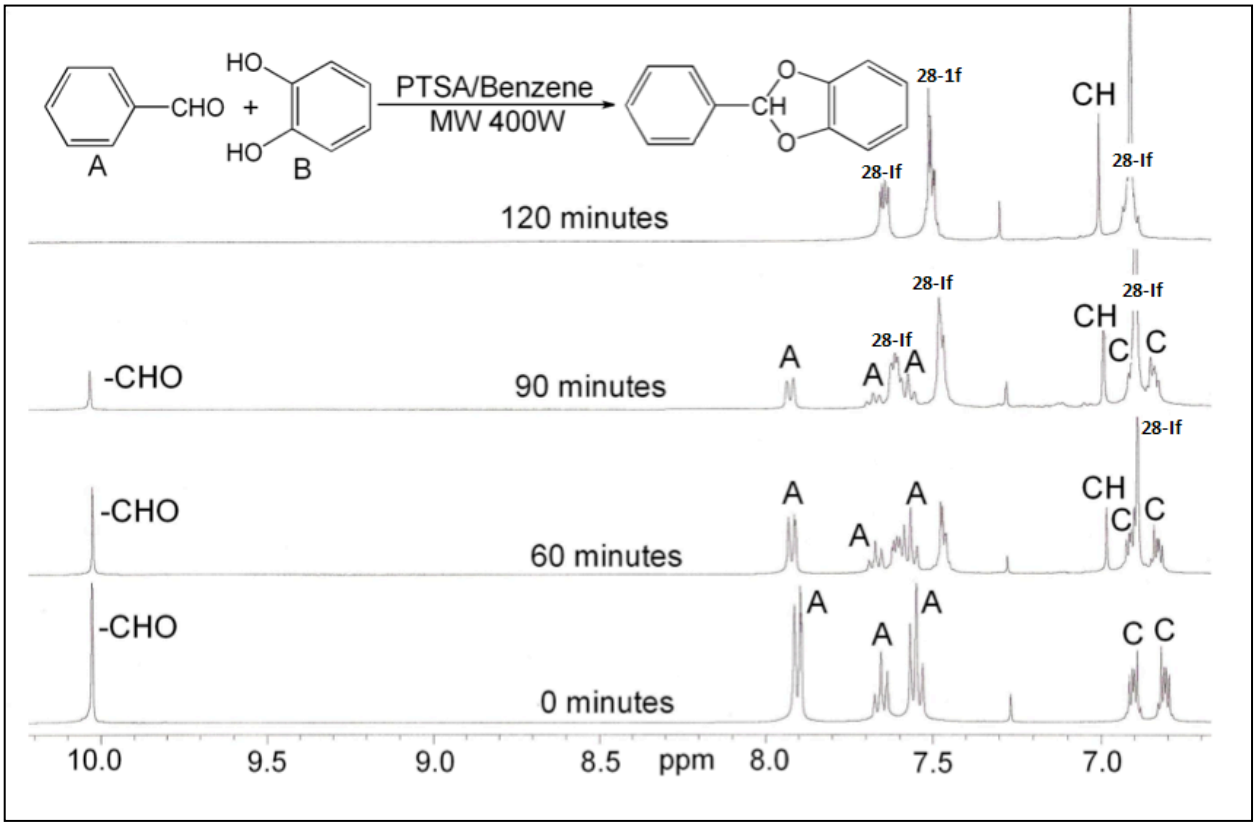
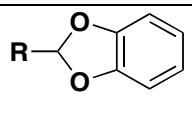


Figure 5.5. The ^{1}H NMR microwave assisted reaction following for preparation of **28-If**

Considering these problems, benzene is better solvent choice when using aliphatic aldehydes because benzene as a solvent presents lower amounts of the aldol product formation when compared to xylene. For aliphatic aldehydes, the optimal reaction time seems to be between 90-120 minutes. The formation of the aldol product with aliphatic aldehydes appears to not be a problem for 1,3-benzodioxole purification (filtration through short silica gel column) resulting that their isolated yields of in general ~10% lower than for aromatic aldehydes (Table 5.2). However, aliphatic 1,3- benzodioxoles can be prepared with this method in 70-80% making it a method of choice for the preparation of these valuable compounds.

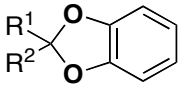
Table 5.2. Microwave assisted preparation of 1,3-benzodioxole from aldehydes

 **28-I**	Time (Minutes)	Yield (%)
28-I a: R = *n*-C_3H_7	120	79
28-I b: R = *n*-C_4H_9	120	73
28-I c: R = *n*-C_7H_{15}	90	72
28-I d: R = *n*-C_9H_{19}	90	72
28-I e: R = *n*-$C_{11}H_{23}$	90	70
28-I f: R = C_6H_5	120	87
28-I g: 2-$CH_3OC_6H_4$	90	91
28-I h: 3-$CH_3OC_6H_5$	90	89
28-I i: 3-$NO_2C_6H_4$	150	79

Ketones are ideal starting materials for the preparation of 1,3- benzodioxoles. They are more reactive and therefore the required microwave heating is shorter than in comparison with aldehydes. Contrary to the problem with aldol condensation products forming as a byproduct in reaction with aliphatic aldehydes, with aromatic aldehydes the condensation is not present at all or the formed amount is negligible (1-2% at the most). The reaction with both aliphatic and aromatic ketones with one aliphatic group is practically quantitative. The lower isolated yields result from the loss of product during isolation and the acid catalyst removal (Table 5.3). However, we were not able to prepare 2,2-diphenyl-1,3-benzodioxole from benzophenone and catechol. This was the case with several other diaromatic ketones. Aromatic substituents such as nitro, methoxy, hydroxyl, dimethylamino, and amino do not interfere with the reaction;

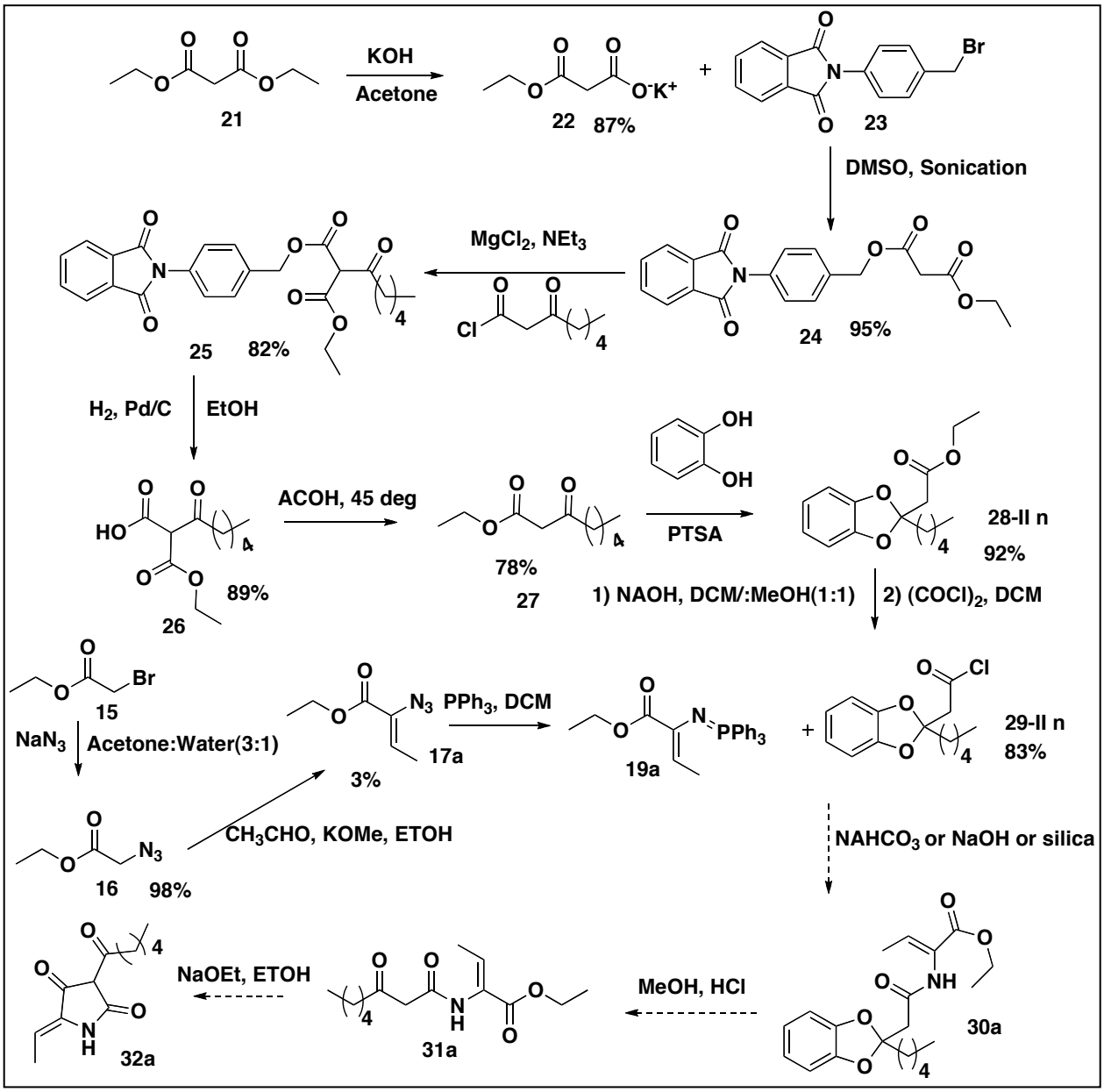
however, they can either facilitate (electron donating group) or retard (electron withdrawinggroup) the reaction. This reaction is very simple and is applicable to large-scale preparation of 1,3- benzodioxoles. Hundred gram quantities of these compounds can be prepared in research laboratories in a matter of hours. For instance, 104 g of 2-methyl-2-phenyl-1,3-benzodioxole was prepared from acetophenone and catechol in less than three hours.

Table 5.3. Microwave assisted preparation of 1,3-benzodioxole from ketones

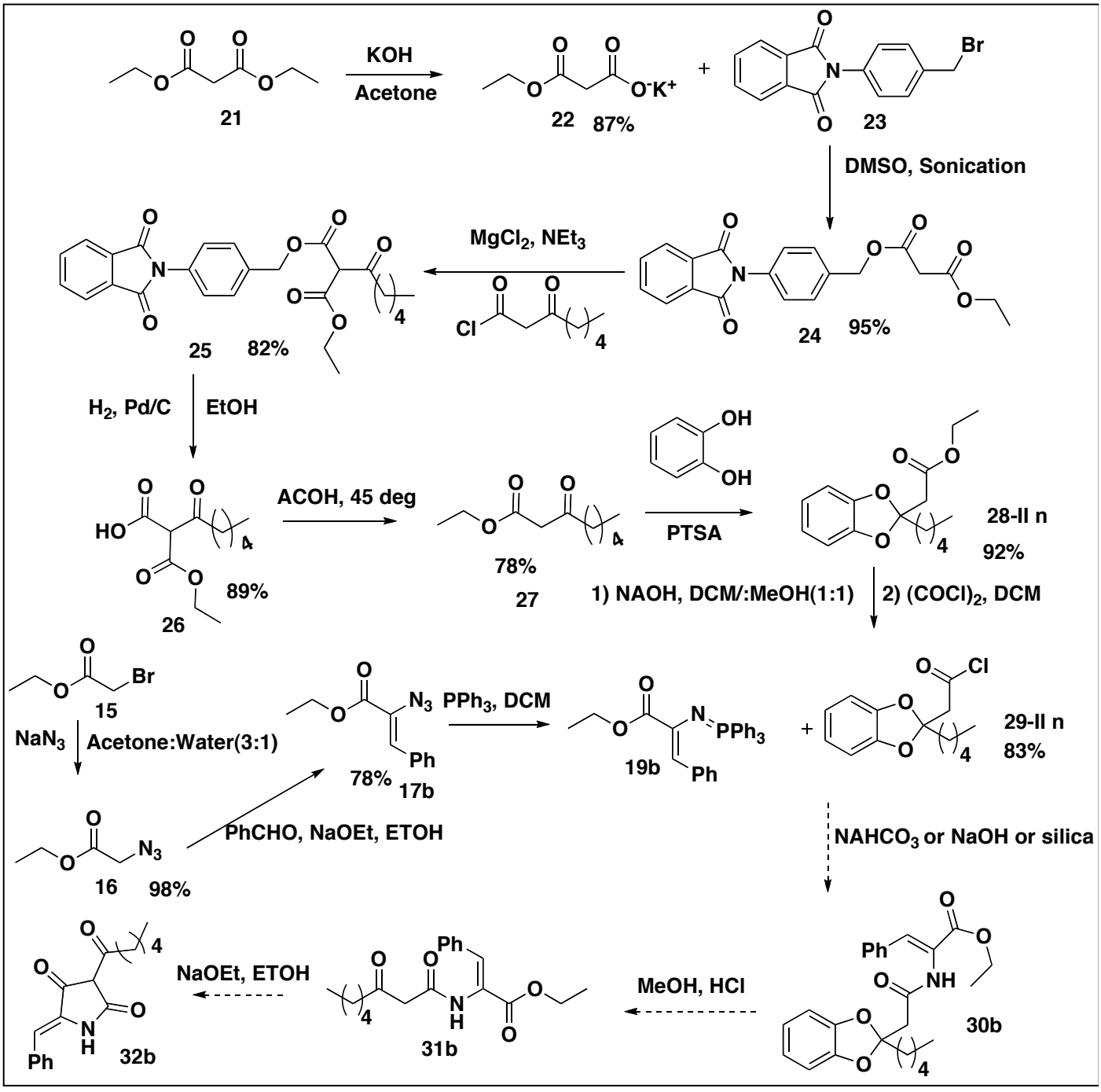
 **28-II**	Time (Minutes)	Yield (%)
28-II a: $R^1 = R^2 = CH_3$	120	82
28-II b: $R^1 = CH_3$; $R^2 = C(CH_3)_3$	60	98
28-II c: $R^1 = CH_3$, $R^2 = CH_2CH_3$	120	96
28-II d: $R^1 = R^2 = CH_2CH_3$	90	93
28-II e: $R^1 = CH_3$; $R^2 = n\text{-}C_6H_{13}$	60	92
28 II f: $R^1\text{-}R^2 = \text{-}(CH_2)_4\text{-}$	60	91
28 II g: $R^1\text{-}R^2 = \text{-}(CH_2)_5\text{-}$	120	96
28-II h: $R^1 = CH_3$; $R^2 = CH_2COCH_3$	75	86
28-II i: $R^1 = CH_3$; $R^2 = CH_2CH_2COCH_3$	75	89
28-II j: $R^1 = CH_3$; $R^2 = C_6H_5$	120	96
28-II k: $R^1 = CH_3$; $R^2 = 4\text{-}ClC_6H_4$	120	87
28-II l: $R^1 = CH_3$; $R^2 = 3,5\text{-}(CH_3)_2C_6H_4$	120	97
28-II m: $R^1 = CH_3$; $R^2 = CH_2CO_2C_2H_5$	120	89

5.3.7 Attempts towards total synthesis of magnesidin:

Once a stable and efficient method has been developed for preparation of benzodioxoles, it was incorporated back into the synthesis of magnesidin and the total synthesis of Magnesidin goes as shown in scheme 5.12. In the scheme 5.12 where acetaldehyde has to be condensed with the corresponding azide **16**, to produce **17a** the yield is very low and isolation of that compound would not be possible. This is accounted towards the low volatility of this compound and also to the fact that acetaldehyde readily undergoes polymerization, there by making the reaction complicated. Even to obtain a 3% product in this reaction various bases were tried for condensation. Usually in a typical condensation like this, NaOEt or NaOMe are ideal bases to be used but they both did not yield good results with acetaldehyde. After trying several bases it was observed a small amount of product formation was possible with KOMe, MeOH conditions. Since reaction has too many complications along with the negligible amount of product formed, the possibility of the entire scheme, acetaldehyde has been replaced with benzaldehyde and the same reactions applied to prepare the corresponding phenyl derivative of tetramic acid and the synthesis of this compound can be performed in several steps as shown in scheme 5.13. In this sequence however the reactions proceeded a little farther than in scheme 5.12. With benzaldehyde it was possible to do the condensation reaction in NaOEt, EtOH and the product **17b** was isolated in 78% yield, which was further reacted with catechol protected acid **28-In** chloride to give the corresponding amide **30b**. 1H and 13C NMR spectra confirmed the product formation and hence was taken forth in the reaction scheme.



Scheme 5.12 Partially accomplished total synthesis of magnesidin.



Scheme 5.13 Partially accomplished total synthesis of phenyl derivative of Magnesidin.

However, the deprotection of catechol in acidic conditions to produce **31b** were unsuccessful even after trying several conditions and so the last step of acidic proton

abstraction to obtain **32b** was performed prior to the deprotection of catechol to check the possibility of the reaction and even after trying one of the mildest and strongest bases, the reaction did not proceed. The highest concentration of HCl used for deprotection of catechol was 12M solution. Any concentration beyond this would lead to a complicated spectrum of the mixture, indicating a decomposition of the tetramic acid. Same was the case when tried to abstract the base, when a slightly stronger base is tried it would decompose. And this can be explained from the fact that the tetramic acid is pH sensitive. It is stable only at a certain pH in the actual form and attaining that pH would be difficult to attain artificially.

5.4. Conclusion:

To summarize, the synthesis of Magnesidin was not achieved in the course of research but good progress has been made towards its synthesis. Various intermediates were synthesized using the tag molecule approach. The tag molecule itself was not well explored in terms of reaction yield and conditions. Using the microwave provided a stable, efficient, less time consuming, very selective and environmentally safe procedure for mono and di bromination of toluidenes. The microwave conditions that assisted in preparation of 1,3-benzodioxole derivatives from aldehydes and ketones is superior to currently existing preparation methods. The isolated yields are generally higher and the required reaction time is significantly (up to 20 times) shorter in comparison with conventional heating. Aromatic aldehydes, aromatic-aliphatic ketones, and aliphatic ketones are excellent starting materials; however reaction with aliphatic aldehydes must be carefully monitored to maximize the isolated yield of the product due to formation aldol byproduct. Even in this case isolated yield of corresponding 1,3-benzodioxole is higher than 70%. Due to its simplicity the method is applicable to large-scale preparation of benzodioxoles. The microwave prepared tag molecule was used in synthesizing another essential class of compounds called β-keto acids. All β-keto acids were produced in good to excellent yields. The tag molecule was not successful in synthesizing the α-β unsaturated amino acids, but the oxazolones that were intended to be used for their synthesis were made using the tag molecules. These oxazolones were not otherwise produced due to their very weak structures and their readiness to undergo side reactions. The change in the approach and the idea to use azide has made it possible to synthesize the α-β unsaturated amides which are precursors of α-β

unsaturated amino acids. In this case, all of the aldehydes were condensed with the corresponding esters of the azide except for acetaldehyde. It underwent polymerization which prevented it from reacting in the desired or expected ways. After all the intermediates were synthesized and incorporated to form magnesidin, the synthesis was still not successful. This can be attributed to the complex structure and improper chemical behavior of the compound. In the azide approach, the synthesis was almost accomplished when the aldehyde used was a benzaldehyde. The product formation was observed in this case but isolation was a problem. The product decomposed during the deprotection of catechol or proton abstraction. Since the desired product was observed, future synthetic attempts should focus on the isolation of the product as a metal salt instead of attempting conventional purification such as column chromatography. As the synthesis has almost been accomplished through this thesis, all that remains to be found is a stable and simple isolation method for magnesidin production.

5.5. Experimental and spectral data:

2-p-tolyl-1H-benzo[de]isoquinoline-1,3(2H)-dione (3):

A suspension of benzo[*de*]isochromene-1,3-dione (1.98 g, 10 mmol) and *p*-amino toluene (1.07 g, 10 m.mol) in 25 ml of pyridine was heated at 70°C for about 20 hours. Increasing the temperature to reflux and setting up a collector to collect the solvent distilled off the excess solvent, the solvent was collected until enough solvent remained for recrystallization. The compound was obtained as white needles upon bringing the reaction mixture to room temperature in 80% yield. MP: 311°C. ^{1}H NMR (400 MHz, $CDCl_3$) d 8.64 (2H, dd, *J*=1.2, 1.2 Hz), 8.26 (2H, dd, *J*=1.2, 1.2 Hz), 7.79 (2H, dd, *J*=7.80, 7.80 Hz), 7.36 (2H, d, *J*=8 Hz), 7.20 (2H, d, *J*=8 Hz), 2.44 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) d 164.72, 138.85, 134.47, 132.94, 131.96, 131.83, 130.39, 128.76, 128.49, 127.24, 123.09, 55.91, 21.57.

2-(4-(bromomethyl)phenyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione (4): To a solution of 2-*p*-Tolyl-benzo[de]isoquinoline-1,3-dione (2.8g, 10m.mol) **9** in 75ml of chloroform was added *N*-bromo-succinimide (3.63g, 20 m.mol) and catalytic amount of benzoyl peroxide (15mg) at 0°C. The solution was stirred under a flashlight for the reaction to occur. TLC monitored the reaction for completion. After completion of the reaction the solvent was removed under vacuum and the residue was subjected to column chromatography. The compound was isolated in 65% dichloromethane and 35% hexane mixture. Alternatively the product can be recrystallized from dichloromethane. Yield of the obtained product was observed to be 85%. MP: Starts decomposing before melting at 249.1°C. ^{1}H NMR (400 MHz, $CDCl_3$) d 8.66 (2H, dd, *J*=1.2, 1.2 Hz), 8.29 (2H, dd, *J*=0.8, 0.8 Hz), 7.81 (4H, t, *J*=7.6 Hz), 7.59 (2H, d, *J*= 8.4 Hz), 3.31(2H, d, *J* = 8.4

Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 164.5, 138.3, 135.6, 134.6, 131.9, 130.3, 129.3, 127.3, 122.9, 32.8 ppm.

4-(1,3-dioxoisoindolin-2-yl) benzyl acetate (5):

A suspension of 2-(4-Bromomethyl-phenyl)-benzo[de]isoquinoline-1,3-dione **10** (3.5 g, 10 mmol) and sodium acetate (1g, 12mmol) in 10 ml of dimethyl sulfoxide was sonicated for 4 hours. The reaction mixture was poured on to ice and left for 1 hour. The product precipitated out as a white solid. The solid was washed with a 100 ml water (x 3) to give the crude product. The product was recrystallized from methanol to give pure product in 95% yield. MP: Does not melt till 400°C. ^1H-NMR(400 MHz, $CDCl_3$) d 8.65(2H, d, *J* = 6.4 Hz), 8.27(2H, d, *J* =7.6 Hz), 7.79(4H, t, *J*=8 Hz), 7.54(2H, d, *J* =8 Hz), 7.32(2H, d, 8 Hz), 5.19(2H, s), 2.16(3H, s).

2-(4-(hydroxymethyl)phenyl)-1H-benzo[de]isoquinoline-1,3(2H)-dione(6):

To a solution of acetic acid 4-(1,3-dioxo-1H,3H-benzo[de]isoquinolin-2-yl)-benzyl ester (3.5g, 10 m.mol) **11** in a 15 ml of 1:1 methanol and dichloromethane was added powdered NaOH (400 mg, 10 m.mol) at 0°C and the reaction mixture was stirred for 2 hours and the methanol was evaporated. The residue was taken into 1N sodium bicarbonate solution and the product was extracted into dichloromethane, which is dried under $MgSO_4$. The solvent is evaporated under vacuum to yield a yellowish solid. MP: 282°C. ^1H NMR (400 MHz, $CDCl_3$) d 8.66 (2H, dd, *J*=0.8, 0.8 Hz), 8.29 (2H, dd, *J*=1.2, 1.2 Hz), 7.81 (4H, dd, *J*=7.6, 7.6 Hz), 7.57(2H, d, *J*=8.4 Hz), 7.33(2H, d, *J*=8.4 Hz), 4.81(2H, d, *J*=6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) d 163.3, 142.6, 134.5, 131.5, 130.8, 128.8, 127.9, 127.3, 126.9, 122.7, 75.2, 62.7, 55.3, 48.6 ppm.

4-(1,3-dioxoisoindolin-2-yl)benzylphenyl carbonate (7):

To a solution of 2-(4-(hydroxymethyl)phenyl)-1H-benzo[de] isoquinoline-1,3 (2H)-dione (3.03 g, 10 m.mol) **12** in pyridine was added phenyl chloroformate (1.56 g, 10 m.mol) drop wise. As the addition is complete a solid appears on the solution and when the reaction is left to stir longer the precipitate slowly disappears back into the solution. The solution was then stirred for an additional 1 hr and was poured in to 100ml of 10% HCl. The solid obtained was then filtered to obtain the product and was directly used in the next step. ^{1}H NMR (400 MHz, CDCl3); δ 8.66 (2H, dd, *J*=1.2, 1.2 Hz), 8.29 (2H, dd, *J*=0.8, 0.8 Hz), 7.81 (4H, t, *J*=7.6 Hz), 7.59 (2H, d, *J*= 8.4 Hz), 7.34-7.39 (m, 5H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 164.5, 138.3, 135.6, 134.6, 132.1, 131.1, 131.9, 130.3, 128.6, 129.3, 127.3, 122.9, 32.8 ppm.

4-(1,3-dioxo-1H-benzo[de] isoquinolin-2 (3H)-yl) benzyl 2-hydroxy ethyl carbamate (8): To a solution of 4-(1,3-dioxoisoindolin-2-yl) benzyl phenyl carbonate (3.7g, 10 m.mol) **13** in DCM was added ethanolamine (0.6 g, 10 m.mol) drop wise. The solution is left to stir for about 3-4 hrs and the reaction completion was monitored by TLC. After the completion of reaction, DCM was evaporated under vacuum to obtain the pure product and was directly used in the next step.

2-((4-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)yl)benzyloxy)carbonylamino) acetic acid (9): To a solution of 4-(1,3-dioxo-1H-benzo[de]isoquinolin-2 (3H)-yl)benzyl-2-hydroxy ethyl carbamate **16**(3.9 g, 10 m.mol) in acetone was added 2ml of sulphuric acid and 2ml of chromic acid. The reaction mixture was stirred at room temperature for 3 hrs and acetone was evaporated under vacuum and quenched with $NaHCO_3$ to obtain the product as white solid in 84% yield. ^{1}H NMR (400 MHz, CDCl3); 8.48-8.5(m, 2H),

7.89 (t, 2H), 7.49(t, 1H), 7.37(t, 2H), 7.47 (d, 2H), 5.09 (s, 2H), 3.68 (d, 2H). 13C NMR 163.3, 142.6, 134.5, 131.5, 130.8, 128.8, 127.9, 127.3, 126.9, 122.7, 75.2, 62.7, 55.3, 28.6 ppm.

2-(4-((5-oxo-4,5-dihydrooxazol-2-yloxy)methyl) phenyl)-1H-benzo[de] isoquinoline-1,3(2H)-dione (10):

2-((4-(1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2-3*H*yl)benzyloxy)carbonylamino) acetic acid (4g, 10 m.mol) **14** was dissolved in 40 ml of pyridine and acetic anhydride (1 ml) was added to the solution. The reaction mixture was refluxed for 3-4 hrs and was poured on to 10% HCl Solution. The white precipitate thus formed is the product, which was filtered and dried and used for next step directly. ^{1}H NMR (400 MHz, CDCl3); 8.6 (d, 2H), 8.28(d, 2H), 7.8(t, 2H), 7.42(t, 2H), 7.28(d, 2H), 5.38 (s, 2H), 4.48 (s, 2H). 13C NMR 163.25, 142.63, 134.49, 131.52, 130.81, 128.76, 127.90, 127.31, 126.90, 122.68, 75.15, 62.65, 55.25, 38.24.

Ethyl 2-azidoacetate (16):

To a stirred solution of ethyl bromo acetate (1.65 g, 10 m.mol) **19** in 15 ml water and acetone mixture (1:4) was added NaN_3 (0.65 g, 8.9mmol). The resulting suspension was stirred at room temperature for 2 hours. DCM was added to the mixture and the organic layer was separated. The aqueous layer was extracted with 2 x 10 ml aliquots of DCM and the combined organic layers were dried over Na_2SO_4. Solvent was removed under reduced pressure, and the azide was good for use without further purification. 1H NMR (400, $CDCl_3$) δ 4.13 (q, *J*=6.2 Hz, 2H), 3.82 (s, 2H), 1.18 (t, *J*= 6.2 Hz, 3H).) 13C NMR (400, $CDCl_3$) δ 162.5, 46.5, 38.2, 13.4 ppm.

***(Z)*-Ethyl 2-azidobut-2-enoate (17a):**

To a well stirred solution containing potassium methoxide (0.7 g, 10 mmol) in dry methanol (20 ml), a solution of ethyl azidoacetate **16** (1.29 g, 10 mmol) and acetaldehyde (0.4 g, 10 mmol) in dry methanol (20 ml) was added drop wise at -10°C under nitrogen. The reaction mixture was stirred at -10°C for 4h and it was poured into aqueous 30% ammonium chloride (100ml). The aqueous layer is then extracted with ethyl acetate (3x20 ml), the organic layer is dried with sodium sulfate, and the solvent was evaporated under vacuum to give the corresponding vinyl azide **21a**, yield 93 mg (6%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (q, 1H), 4.22 (q, *J*=6.2 Hz, 2H), 2.05(t, 3H), 1.29 (t, *J*=6.2 Hz, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 167.9, 141.5, 136.5, 61.2, 14.2, 9.5 ppm.

***(Z)*-Ethyl 2-azidooct-2-enoate (17b):**

To a well stirred solution containing potassium methoxide (0.7 g, 10 mmol) in dry methanol (20 ml), a solution of ethyl azidoacetate **16** (1.29 g, 10 mmol) and hexanaldehyde (1 g, 10 mmol) in dry methanol (20 ml) was added drop wise at -10°C under nitrogen. The reaction mixture was stirred at -10°C for 4h and it was poured into aqueous 30% ammonium chloride (100ml). The aqueous layer is then extracted with ethyl acetate (3x20 ml), the organic layer is dried with sodium sulfate, and the solvent was evaporated under vacuum to give the corresponding vinyl azide **21b**, yield 1.13g (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (q, 1H), 4.14 (q, *J*=6.2 Hz, 2H), 2.16 (q, 2H), 1.29 (m, 2H) 1.24 (t, *J*=6.2 Hz, 3H), 0.9 (t, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 167.8, 149.4, 135, 132.9, 61.9, 31.9, 29.7, 29.6, 29.3, 24.2, 22.7, 14.8, 14.2 ppm.

***(Z)*-Ethyl 2-azidodec-2-enoate (17c):**

To a well stirred solution containing potassium methoxide (0.7 g, 10 mmol) in dry

methanol (20 ml), a solution of ethyl azidoacetate **16** (1.29 g, 10 mmol) and octanaldehyde (1.28 g, 10 mmol) in dry methanol (20 ml) was added drop wise at -10°C under nitrogen. The reaction mixture was stirred at -10°C for 4h and it was poured into aqueous 30% ammonium chloride (100ml). The aqueous layer is then extracted with ethyl acetate (3x20 ml), the organic layer is dried with sodium sulfate, and the solvent was evaporated under vacuum to give the corresponding vinyl azide **21c**, yield 1.29g (54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (q, 1H), 4.18 (q, *J*=6.2 Hz, 2H), 2.18(q, 2H), 1.31 (m, 14H) 1.24 (t, *J*=6.2 Hz, 3H), 0.88(t, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 167.8, 149.4, 135, 132.9, 61.9, 31.9, 29.7, 29.6, 29.3, 24.2, 22.7, 14.8, 14.2 ppm.

***(Z)*-Ethyl 2-azido-3-phenylacrylate (17d):**

To a well stirred solution containing sodium (0.23 g, 10 mmol) in dry ethanol (30 ml), a solution of ethyl azidoacetate **16** (1.29 g, 10 mmol) and benzaldehyde (0.53 g, 5 mmol) in dry ethanol (10 ml) was added drop wise at -10°C under nitrogen. The reaction mixture was stirred at 0°C for 4 h and it was poured into aqueous 30% ammonium chloride (100ml) and the formed solid was separated by filtration, washed with water (30 ml) and dried to give vinyl azide **21d**, yield 1.8 g (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.60 (d, 2H), 7.4(d, 2H), 7.33(t, 1H), 4.24 (q, *J*=6.2 Hz, 2H), 1.24 (t, *J*=6.2 Hz, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 167.1, 135.2, 128.6, 128.5, 127.9, 132.9, 118.8, 61.8, 14.8 ppm.

***(Z)*-Ethyl 2-azido-3-(2,4,6-trimethoxyphenyl)acrylate (17e):**

To a well-stirred solution containing sodium (0.23 g, 10 mmol) in dry ethanol (30 ml), a

solution of ethyl azidoacetate **16** (1.29 g, 10 mmol) and trimethoxy benzaldehyde (0.98 g, 5 mmol) in dry ethanol (30 ml) was added drop wise at -10°C under nitrogen. The reaction mixture was stirred at 0°C for 4 h and it was poured into aqueous 30% ammonium chloride (100ml) and the formed solid was separated by filtration, washed with water (30 ml) and dried to give vinyl azide **21e**, yield 2.39 g (78%). ^{1}H NMR (400 MHz, CDCl3); δ 8.19 (s, 1H), 6.09 (s, 2H), 4.2 (q, *J*=6.2 Hz, 2H), 3.83 (s, 9H), 1.29 (t, *J*=6.2 Hz, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 167.4, 160.6, 159.6, 132.9, 118.8, 101.7, 90.9, 61.4, 56.2, 55.8, 14.2 ppm.

(*Z*)-ethyl 2-acetamido-3-phenylacrylate (20a)

To a solution of (*Z*)-ethyl 2-azido-3-phenylacrylate **17d** (2.17 g, 10 m.mol) in DCM was added triphenyl phosphine (2.62 g, 10 m.mol) and the mixture was stirred at room temperature. After it was stirred for 2 hrs, triethyl amine (2.01 g, 20 m.mol) was added to it at 0°C. To this cooled solution was added a solution of acetyl chloride (0.78g, 10 m.mol) in DCM at 0°C, drop wise. After reaction mixture was stirred for 6 hrs, 100 mg of silica was added into the solution and stirred for another 30 minutes. After evaporating the solvent under vacuum, the desired product is obtained and for further purification it was subject to column chromatography. The pure product was obtained in 54% yield (1.27 g). ^{1}H NMR (400 MHz, CDCl3); δ 8.0 (s, br, 1H), 7.60 (d, 2H), 7.40 (d, 2H), 7.33 (t, 1H), 6.55 (s, 1H), 4.24 (q, 2H), 1.86 (s, 3H), 1.29 (t, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 170.4, 161.7, 134.2, 128.6, 128.5, 127.9, 123.6, 61.4, 23.4, 14.2 ppm.

(*Z*)-ethyl 2-benzamido-3-phenylacrylate (20b)

To a solution of (*Z*)-ethyl 2-azido-3-phenylacrylate **17d** (2.17 g, 10 m.mol) in DCM was added triphenyl phosphine (2.62 g, 10 m.mol) and the mixture was stirred at room temperature. After it was stirred for 2 hrs, triethyl amine (2.01 g, 2 m.mol) was added to it at 0°c. To this cooled solution was added a solution of benzoyl chloride (1.48g, 10 m.mol) in DCM at 0°C, drop wise. After reaction mixture was stirred for 6 hrs, 100 mg of silica was added into the solution and stirred for another 30 minutes. After evaporating the solvent under vacuum, the desired product is obtained and for further purification it was subject to column chromatography. The pure product was obtained in 58% yield (1.71 g). ^{1}H NMR (400 MHz, CDCl3); δ 8.4 (s, br, 1H), 8.03(d, 1H), 7.62-7.78 (m, 5H), 7.31-7.48 (m, 3H), 4.28 (q, 2H), 1.22 (t, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 166.2, 161.4, 134.6, 133.2, 132.1, 128.8, 128.6, 128.5, 127.9, 123.6, 121.7, 14.2 ppm.

(*Z*)-ethyl 2-hexanamido-3-phenylacrylate (20c)

To a solution of (*Z*)-ethyl 2-azido-3-phenylacrylate **17d** (2.17 g, 10 m.mol) in DCM was added triphenyl phosphine (2.62 g, 10 m.mol) and the mixture was stirred at room temperature. After it was stirred for 2 hrs, triethyl amine (2.01 g, 2 m.mol) was added to it at 0°c. To this cooled solution was added a solution of hexanoyl chloride (1.34 g, 10 m.mol) in DCM at 0°C, drop wise. After reaction mixture was stirred for 6 hrs, 100 mg of silica was added into the solution and stirred for another 30 minutes. After evaporating the solvent under vacuum, the desired product is obtained and for further purification it was subject to column chromatography. The pure product was obtained in 52% yield (1.28 g). ^{1}H NMR (400 MHz, CDCl3); δ 8.4 (s, br, 1H), 8.03(d, 1H), 7.62-7.78 (m, 5H), 7.31-7.48 (m, 3H), 4.28 (q, 2H), 1.22 (t, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 166.2, 161.4, 134.6, 133.2, 132.1, 128.8, 128.6, 128.5, 127.9, 123.6, 121.7, 14.2 ppm.

(*Z*)-ethyl 2-acetamido-3-(2,4,6-trimethoxyphenyl)acrylate (20d)

To a solution of *(Z*)-Ethyl 2-azido-3-(2,4,6-trimethoxyphenyl)acrylate **17e** (3.07 g, 10 m.mol) in DCM was added triphenyl phosphine (2.62 g, 10 m.mol) and the mixture was stirred at room temperature. After it was stirred for 2 hrs, triethyl amine (2.01 g, 2 m.mol) was added to it at 0°c. To this cooled solution was added a solution of acetyl chloride (0.78g, 10 m.mol) in DCM at 0°C, drop wise. After reaction mixture was stirred for 6 hrs, 100 mg of silica was added into the solution and stirred for another 30 minutes. After evaporating the solvent under vacuum, the desired product is obtained and for further purification it was subject to column chromatography. The pure product was obtained in 58% yield (1.87 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, br, 1H), 7.52(d, 2H), 7.49-7.36 (m, 3H), 4.28 (q, 2H), 2.28(q, 2H), 1.8(m, 6H), 1.21 (t, 3H), 1.02(t, 2H). 13C NMR (400 MHz, $CDCl_3$) δ 170.5, 161.9, 134.2, 128.8, 128.6, 128.5, 127.9, 123.8, 121.4,14.6, 10.1 ppm.

(*Z*)-ethyl 2-benzamido-3-(2,4,6-trimethoxyphenyl)acrylate (20e)

To a solution of *(Z*)-Ethyl 2-azido-3-(2,4,6-trimethoxyphenyl)acrylate **17e** (3.07 g, 10 m.mol) in DCM was added triphenyl phosphine (2.62 g, 10 m.mol) and the mixture was stirred at room temperature. After it was stirred for 2 hrs, triethyl amine (2.01 g, 2 m.mol) was added to it at 0°c. To this cooled solution was added a solution of benzoyl chloride (1.48g, 10 m.mol) in DCM at 0°C, drop wise. After reaction mixture was stirred for 6 hrs, 100 mg of silica was added into the solution and stirred for another 30 minutes. After evaporating the solvent under vacuum, the desired product is obtained and for further purification it was subject to column chromatography. The pure product was obtained in

61% yield (2.35 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, br, 1H), 8.03 (d, 2H), 7.52(d, 2H), 7.49-7.36 (m, 3H), 4.28 (q, 2H), 3.58(s, 9H), 2.28(q, 2H), 1.8(m, 6H), 1.21 (t, 3H), 1.02(t, 2H). 13C NMR (400 MHz, $CDCl_3$) δ 166.2, 161.7, 160.6, 159.6, 133.2, 132.1, 128.8, 128.6, 128.5, 127.9, 123.8, 121.4, 101.7, 90.9, 61.4, 56.2, 55.8, 14.6 ppm.

(*Z*)-ethyl 2-hexanamido-3-(2,4,6-trimethoxyphenyl)acrylate (20f)

To a solution of *(Z*)-Ethyl 2-azido-3-(2,4,6-trimethoxyphenyl)acrylate **17e** (3.07 g, 10 m.mol) in DCM was added triphenyl phosphine (2.62 g, 10 m.mol) and the mixture was stirred at room temperature. After it was stirred for 2 hrs, triethyl amine (2.01 g, 2 m.mol) was added to it at 0°c. To this cooled solution was added a solution of hexanoyl chloride (1.34 g, 10 m.mol) in DCM at 0°C, drop wise. After reaction mixture was stirred for 6 hrs, 100 mg of silica was added into the solution and stirred for another 30 minutes. After evaporating the solvent under vacuum, the desired product is obtained and for further purification it was subject to column chromatography. The pure product was obtained in 57% yield (1.92 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, br, 1H), 6.55 (q, 1H), 4.28 (q, 2H), 2.28(q, 2H), 1.86(s, 3H), 1.81(m, 6H), 1.21 (t, 3H), 1.02 (t, 2H). 13C NMR (400 MHz, $CDCl_3$) δ 170.4, 170.1,127.9, 115.7, 101.7, 61.4, 23.4, 21.2, 20.8, 16.8, 14.6, 14.1,10.2 ppm.

(*Z*)-ethyl 2-acetamidonon-2-enoate (20g)

To a solution of (*Z*)-ethyl 2-hexanamido-3-phenylacrylate **20c** (2.11 g, 10 m.mol) in DCM was added triphenyl phosphine (2.62 g, 10 m.mol) and the mixture was stirred at room temperature. After it was stirred for 2 hrs, triethyl amine (2.01 g, 2 m.mol) was added to it at 0°C. To this cooled solution was added a solution of acetyl chloride (0.78g, 10 m.mol) in DCM at 0°C, drop wise. After reaction mixture was stirred for 6 hrs,

100 mg of silica was added into the solution and stirred for another 30 minutes. After evaporating the solvent under vacuum, the desired product is obtained and for further purification it was subject to column chromatography. The pure product was obtained in 43% yield (0.8 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, br, 1H), 6.55 (q, 1H), 4.28 (q, 2H), 2.28(q, 2H), 1.86(s, 3H), 1.81(m, 6H), 1.21 (t, 3H), 1.02 (t, 2H). 13C NMR (400 MHz, $CDCl_3$) δ 170.4, 170.1,127.9, 115.7, 101.7, 61.4, 23.4, 21.2, 20.8, 16.8, 14.6, 14.1, 10.2 ppm.

(*Z*)-ethyl 2-benzamidooct-2-enoate (20h)

To a solution of (*Z*)-ethyl 2-hexanamido-3-phenylacrylate **17c** (2.11 g, 10 m.mol) in DCM was added triphenyl phosphine (2.62 g, 10 m.mol) and the mixture was stirred at room temperature. After it was stirred for 2 hrs, triethyl amine (2.01 g, 2 m.mol) was added to it at 0°c. To this cooled solution was added a solution of benzoyl chloride (1.48 g, 10 m.mol) in DCM at 0°C, drop wise. After reaction mixture was stirred for 6 hrs, 100 mg of silica was added into the solution and stirred for another 30 minutes. After evaporating the solvent under vacuum, the desired product is obtained and for further purification it was subject to column chromatography. The pure product was obtained in 47% yield (1.16 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, br, 1H), 6.55 (q, 1H), 4.28 (q, 2H), 2.28(q, 2H), 1.86(s, 3H), 1.81(m, 6H), 1.21 (t, 3H), 1.02 (t, 2H). 13C NMR (400 MHz, $CDCl_3$) δ 170.4, 170.1,127.9, 115.7, 101.7, 61.4, 23.4, 21.2, 20.8, 16.8, 14.6, 14.1, 10.2 ppm.

(*Z*)-ethyl 2-hexanamidooct-2-enoate (20i)

To a solution of (*Z*)-ethyl 2-hexanamido-3-phenylacrylate **17c** (2.11 g, 10 m.mol) in DCM was added triphenyl phosphine (2.62 g, 10 m.mol) and the mixture was stirred at

room temperature. After it was stirred for 2 hrs, triethyl amine (2.01 g, 2 m.mol) was added to it at 0°c. To this cooled solution was added a solution of hexanoyl chloride (1.34 g, 10 m.mol) in DCM at 0°C, drop wise. After reaction mixture was stirred for 6 hrs, 100 mg of silica was added into the solution and stirred for another 30 minutes. After evaporating the solvent under vacuum, the desired product is obtained and for further purification it was subject to column chromatography. The pure product was obtained in 41% yield (0.82 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, br, 1H), 6.55 (q, 1H), 4.28 (q, 2H), 2.28(q, 2H), 1.86(s, 3H), 1.81(m, 6H), 1.21 (t, 3H), 1.02 (t, 2H). 13C NMR (400 MHz, $CDCl_3$) δ 170.4, 170.1,127.9, 115.7, 101.7, 61.4, 23.4, 21.2, 20.8, 16.8, 14.6, 14.1, 10.2 ppm.

(*Z*)-ethyl 2-acetamidoundec-2-enoate (20j)

To a solution of *(Z)*-Ethyl 2-azidooct-2-enoate **17b** (2.39 g, 10 m.mol) in DCM was added triphenyl phosphine (2.62 g, 10 m.mol) and the mixture was stirred at room temperature. After it was stirred for 2 hrs, triethyl amine (2.01 g, 2 m.mol) was added to it at 0°c. To this cooled solution was added a solution of acetyl chloride (0.78g, 10 m.mol) in DCM at 0°C, drop wise. After reaction mixture was stirred for 6 hrs, 100 mg of silica was added into the solution and stirred for another 30 minutes. After evaporating the solvent under vacuum, the desired product is obtained and for further purification it was subject to column chromatography. The pure product was obtained in 46% yield (0.85 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, br, 1H), 6.55 (q, 1H), 4.28 (q, 2H), 2.28(q, 2H), 1.86(s, 3H), 1.81(m, 6H), 1.21 (t, 3H), 1.02 (t, 2H). 13C NMR (400 MHz, $CDCl_3$) δ 170.4, 170.1,127.9, 115.7, 101.7, 61.4, 23.4, 21.2, 20.8, 16.8, 14.6, 14.1, 10.2 ppm.

(*Z*)-ethyl 2-benzamidodec-2-enoate (20k)

To a solution of *(Z)*-Ethyl 2-azidooct-2-enoate 17b (2.39 g, 10 m.mol) in DCM was added triphenyl phosphine (2.62 g, 10 m.mol) and the mixture was stirred at room temperature. After it was stirred for 2 hrs, triethyl amine (2.01 g, 2 m.mol) was added to it at 0°c. To this cooled solution was added a solution of benzoyl chloride (1.48 g, 10 m.mol) in DCM at 0°C, drop wise. After reaction mixture was stirred for 6 hrs, 100 mg of silica was added into the solution and stirred for another 30 minutes. After evaporating the solvent under vacuum, the desired product is obtained and for further purification it was subject to column chromatography. The pure product was obtained in 48% yield (1.19 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, br, 1H), 6.55 (q, 1H), 4.28 (q, 2H), 2.28(q, 2H), 1.86(s, 3H), 1.81(m, 6H), 1.21 (t, 3H), 1.02 (t, 2H). 13C NMR (400 MHz, $CDCl_3$) δ 170.4, 170.1,127.9, 115.7, 101.7, 61.4, 23.4, 21.2, 20.8, 16.8, 14.6, 14.1, 10.2 ppm.

(*Z*)-ethyl 2-hexanamidodec-2-enoate (20l)

To a solution of *(Z)*-Ethyl 2-azidooct-2-enoate 17b (2.39 g, 10 m.mol) in DCM was added triphenyl phosphine (2.62 g, 10 m.mol) and the mixture was stirred at room temperature. After it was stirred for 2 hrs, triethyl amine (2.01 g, 2 m.mol) was added to it at 0°c. To this cooled solution was added a solution of hexanoyl chloride (1.34g, 10 m.mol) in DCM at 0°C, drop wise. After reaction mixture was stirred for 6 hrs, 100 mg of silica was added into the solution and stirred for another 30 minutes. After evaporating the solvent under vacuum, the desired product is obtained and for further purification it was subject to column chromatography. The pure product was obtained in 42% yield (0.83 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, br, 1H), 6.16 (q, 1H), 4.28 (q, 2H), 2.28(q,

2H), 1.86 (3, 8H), 1.81(m, 6H), 1.21 (t, 3H), 1.02 (t, 2H). 13C NMR (400 MHz, $CDCl_3$) δ 170.4, 170.1,127.9, 115.7, 101.7, 61.4, 23.4, 21.2, 20.8, 16.8, 14.6, 14.1,10.2 ppm.

Potassium 3-ethoxy-3-oxopropanoate (22)

To a solution of diethyl malonate (1.75 g, 10 m.mol) in acetone, add potassium hydroxide (0.56g, 10 m.mol) in portions and a precipitation occurs as the reaction proceeds. After stirring the suspension for 12 hrs, it was filtered to obtain the pure product as white amorphous solid with 90% yield (1.55 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, 2H), 3.19(s, 2H), 1.29(t, 3H). 1H NMR (400 MHz, $CDCl_3$) δ 175.4, 166.8, 61.12, 43.28, 14.12 ppm.

2-(4-(bromomethyl)phenyl)isoindoline-1,3-dione (23): Titled compound is prepared according to the general procedure E from 2-*p*-tolylisoindoline-1,3-dione (2.37g, 10m.mol), *N*-bromo succinimide(3.2g,1.8m.mol) and benzoyl peroxide (5 mg; 0.02 mmol, 0.34 mol %) in 25 ml of ethyl acetate or 20 ml of diethyl carbonate. The product was obtained in 90% yield (2.83g) in ethyl acetate and 95% yield (2.99g) in diethyl carbonate. ^{1}H NMR (400 MHz, CDCl3); δ 7.94-7.97 (m, 2H), 7.78-7.81 (m, 2H), 7.53 (d, *J* = 8.42 Hz, 2H), 7.45 (d, *J* = 8.42 Hz, 2H), 4.52 (s, 2H) ppm. ^{13}C NMR δ 167.35, 137.72, 134.78, 131.89, 130.07, 126.92, 124.09 and 32.82 ppm.

4-(1,3-dioxoisoindolin-2-yl) benzyl ethyl malonate (24):

A suspension of potassium 3-ethoxy-3-oxopropanoate **22** (1.7 g, 10 m.mol) and 2-(4-(bromomethyl)phenyl)isoindoline-1,3-dione **23** (3.1 g, 10 m.mol) in 25 ml of DMSO was sonicated for 4 hrs to obtain a clear solution. Once the reaction completion is confirmed by TLC, the solution is poured onto cool ice to get a white amorphous solid (3.55 g, 96%) which is dried and used for next step directly. ^{1}H NMR (400 MHz, CDCl3); δ 7.95-7.98

(m, 2H), 7.78-7.82 (m, 2H), 7.48-7.51 (d, *J*=8.42, 2H), 7.43-7.47 (d, *J*=8.42, 2H), 5.22(s, 2H), 4.15-4.24 (q, *J*=6.9, 2H), 3.42(s, 2H), 1.20-1.28(t, *J* =6.9, 3H). ^{13}C NMR (400 MHz, $CDCl_3$); δ 12.1, 39.6, 59.7, 64.5, 121.9, 124.7, 127.1, 129.7, 129.8, 132.6, 133.2, 164.4, 165.2 ppm.

General Method of preparation of benzodioxoles (28-l): Benzene (10 ml) suspension of carbonyl compound (10 mmol), catechol (1.1 g; 1mmol), and *p*-toluenesulfonic acid (5 mg) were refluxed with Dean Stark trap and microwave power of 400W for time indicated in Tables 2 and 3. Solvent was evaporated at reduced pressure. The solid residue was dissolved in hot dichloromethane-hexane (1:9; 3 ml) place on short (2x2 inches) silica gel column. Silica gel was washed with dichloromethane-hexane (1:9; 3x20 ml). The filtrates were combined and the solvent was evaporated to yield pure product.

2-propylbenzo[*d*][1,3]dioxole (28-la):

The titled compound has been prepared in 120 minutes using the above general method from buteraldehyde (0.72 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 79% yield (1.29g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66(d, 2H), 7.49(m, 3H), 6.96 (s, 1H), 6.94(m, 4H). 13C NMR (400 MHz, $CDCl_3$) δ 145.7,127.6, 124.56,120.9, 118.12, 115.12, 65.8 ppm.

2-butylbenzo[*d*][1,3]dioxole (28-lb):

The titled compound has been prepared in 120 minutes using the above general method from pentanal (0.86 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 73% yield (1.29g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66(d, 2H), 7.49(m, 3H), 6.96 (s, 1H), 6.94(m,

4H). 13C NMR (400 MHz, $CDCl_3$) δ 145.7,127.6, 124.56,120.9, 118.12, 115.12, 65.8 ppm.

2-heptylbenzo[*d*][1,3]dioxole (28-lc):

The titled compound has been prepared in 90 minutes using the above general method from octanal (1.28 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 72% yield (1.58 g). ^1H NMR (400 MHz, $CDCl_3$) δ 7.66(d, 2H), 7.49(m, 3H), 6.96 (s, 1H), 6.94(m, 4H). 13C NMR (400 MHz, $CDCl_3$) δ 145.7,127.6, 124.56,120.9, 118.12, 115.12, 65.8 ppm.

2-nonylbenzo[*d*][1,3]dioxole (28-ld):

The titled compound has been prepared in 90 minutes using the above general method from decanal (1.56 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 72% yield (1.78 g). ^1H NMR (400 MHz, $CDCl_3$) δ 7.66(d, 2H), 7.49(m, 3H), 6.96 (s, 1H), 6.94(m, 4H). 13C NMR (400 MHz, $CDCl_3$) δ 145.7,127.6, 124.56,120.9, 118.12, 115.12, 65.8.

2-undecylbenzo[*d*][1,3]dioxole (28-le):

The titled compound has been prepared in 90 minutes using the above general method from dodecanal (1.84 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 70% yield (1.73 g). ^1H NMR (400 MHz, $CDCl_3$) δ 7.66(d, 2H), 7.49(m, 3H), 6.96 (s, 1H), 6.94(m, 4H). 13C NMR (400 MHz, $CDCl_3$) δ 145.7,127.6, 124.56,120.9, 118.12, 115.12, 65.8.

2-phenylbenzo[*d*][1,3]dioxole (28-lf):

The titled compound has been prepared in 120 minutes using the above general method from benzaldehyde (1.06 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 87% yield (1.72 g). ^1H NMR (400 MHz, $CDCl_3$) δ 7.66(d, 2H), 7.49(m, 3H), 6.96 (s, 1H), 6.94(m, 4H). 13C NMR (400 MHz, $CDCl_3$) δ 145.7,127.6, 123.4, 124.56,120.9, 118.12, 115.54.56, 65.8.

2-(2-methoxyphenyl)benzo[*d*][1,3]dioxole (28-lg):

The titled compound has been prepared in 90 minutes using the above general method from 2-methoxy benzaldehyde (1.36 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 91% yield (2.07 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66(d, 2H), 7.49(m, 3H), 6.96 (s, 1H), 6.94(m, 4H). 13C NMR (400 MHz, $CDCl_3$) δ 145.7,127.6, 124.56,120.9, 118.12, 115.12, 67.74, 58.67.

2-(3-methoxyphenyl)benzo[*d*][1,3]dioxole (28-lh):

The titled compound has been prepared in 90 minutes using the above general method from 3-methoxy benzaldehyde (1.51 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 89% yield (2.02 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66(d, 2H), 7.49(m, 3H), 6.96 (s, 1H), 6.94(m, 4H). 13C NMR (400 MHz, $CDCl_3$) δ 145.7,127.6, 124.6,120.9, 118.1, 115.1, 56.8 ppm

2-(3-nitrophenyl)benzo[*d*][1,3]dioxole (28-li):

The titled compound has been prepared in 150 minutes using the above general method from 3-nitro benzaldehyde (0.72 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 79% yield (1.91g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66(d, 2H), 7.49(m, 3H), 6.96 (s, 1H), 6.94(m, 4H). 13C NMR (400 MHz, $CDCl_3$) δ 145.7,127.6, 124.6,120.9, 118.1, 115.1 ppm.

2,2-dimethylbenzo[*d*][1,3]dioxole (28-lla):

The titled compound has been prepared in 120 minutes using the above general method from acetone (1.04 g, 20 m.mol) and catechol (1.1 g, 10 m.mol) in 82% (1.23 g).

yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88(m, 4H), 1.71(s, 6H). 13C NMR (400 MHz, $CDCl_3$) δ 145.7,127.6, 120.9, 115.1, 25.8 ppm.

2-*tert*-butyl-2-methylbenzo[*d*][1,3]dioxole (28-IIb):

The titled compound has been prepared in 60 minutes using the above general method from pinacolone (1 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 98% yield (1.88 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88(m, 4H), 1.76(s, 3H), 0.94(s, 9H). 13C NMR (400 MHz, $CDCl_3$) δ 145.6,126.4, 120.9, 115.2, 44.7, 24.9, 20.8 ppm.

2-ethyl-2-methylbenzo[*d*][1,3]dioxole (28-IIc):

The titled compound has been prepared in 120 minutes using the above general method from 2-butanone (0.72 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 96% yield (1.57 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88(m, 4H), 2.02(t, 2H), 0.90 (s, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 145.6,126.4, 120.9, 115.2, 44.7, 24.9, 20.8 ppm.

2,2-diethylbenzo[*d*][1,3]dioxole (28-IId):

The titled compound has been prepared in 90 minutes using the above general method from 3-pentanone (0.86 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 93% yield (2.04 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82(s, 4H), 2.02(q, 2H), 1.09 (t, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 148.59,121.06, 108.12, 30.60, 7.32 ppm.

2-hexyl-2-methylbenzo[*d*][1,3]dioxole (28-IIe):

The titled compound has been prepared in 60 minutes using the above general method from octanone (1.28 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 92% yield (2.02 g).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77(s, 4H), 1.92(q, 2H), 1.62(t, 2H), 1.58(s, 3H), 1.32 (m, 8H), 0.89 (t, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 147.9, 121.2, 119.3, 108.5, 39.5, 31.9, 29.6, 24.5, 23.4, 22.8, 14.3 ppm.

spiro[benzo[*d*][1,3]dioxole-2,1'-cyclopentane] (28-IIf):

The titled compound has been prepared in 120 minutes using the above general method from cyclopentanone (0.84 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 91% yield (1.60 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81(m, 4H), 2.14(t, 4H), 1.87 (t, 4H). 13C NMR (400 MHz, $CDCl_3$) δ 147.6,121.1, 118.4, 108.7, 35.4, 24.8, 23.4 ppm.

spiro[benzo[*d*][1,3]dioxole-2,1'-cyclohexane] (28-IIg):

The titled compound has been prepared in 120 minutes using the above general method from cyclohexanone (0.98 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 96% yield (1.82 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81(m, 4H), 2.14(t, 4H), 1.92(t, 2H), 1.87 (t, 4H). 13C NMR (400 MHz, $CDCl_3$) δ 147.6, 121.1, 118.4, 108.7, 35.4, 25.6, 24.8, 23.4 ppm.

1-(2-methylbenzo[*d*][1,3]dioxol-2-yl)propan-2-one (28-IIh):

The titled compound has been prepared in 75 minutes using the above general method from 2,4-petanedione (1 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 86% yield (1.65 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79(m, 4H), 3.05 (s, 2H), 2.21(s, 2H), 1.75 (s, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 204.27, 147.01,129.97, 121.78, 121.54, 116.05, 109.06, 51.98, 46.52, 31.78, 24.56 ppm.

4-(2-methylbenzo[*d*][1,3]dioxol-2-yl)butan-2-one (28-IIi):

The titled compound has been prepared in 75 minutes using the above general method from 2,5-hexanedione (1.14 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 89% yield (1.83 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72(m, 4H), 2.57 (t, 2H), 2.21(t, 2H), 2.06 (s, 3H), 1.57 (s, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 207.3, 147.6,121.4, 121.3, 118.2, 108.6, 37.1, 33.1, 32.9, 30.1, 24.8 ppm.

2-methyl-2-phenylbenzo[*d*][1,3]dioxole (28-llj):

The titled compound has been prepared in 120 minutes using the above general method from acetophenone (1.2 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 96% yield (2.03 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69(m, 2H), 7.42(m, 3H), 6.88(m, 4H), 2.06 (s, 3H), 1.57 (s, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 147.8, 141.8, 129.4, 128.8, 125.5, 121.9, 117.1, 109.2, 22.5 ppm.

2-(4-chlorophenyl)-2-methylbenzo[*d*][1,3]dioxole (28-llk):

The titled compound has been prepared in 120 minutes using the above general method from 4-chloro acetophenone (1.54 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 87% yield (2.14 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69(m, 2H), 7.42(m, 3H), 6.88(m, 4H), 2.06 (s, 3H), 1.57 (s, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 147.8, 141.8, 129.4, 128.8, 125.5, 121.9, 117.1, 109.2, 22.5 ppm.

2-(3,5-dimethylphenyl)-2-methylbenzo[*d*][1,3]dioxole (28-lll):

The titled compound has been prepared in 120 minutes using the above general method from 3,5-dimethyl acetophenone (1.48 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 97% yield (1.32 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27(s, 3H), 6.88(m, 4H), 2.18(s, 6H), 2.06 (s, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 147.8, 141.8, 129.4, 128.9, 125.5, 121.9, 117.1, 109.2, 22.5 ppm.

ethyl 2-(2-methylbenzo[*d*][1,3]dioxol-2-yl)acetate (28-IIm):

The titled compound has been prepared in 120 minutes using the above general method from ethyl acetoacetate (1.3 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 89% yield (1.98 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72(m, 4H), 4.13(q, 2H), 2.94(s, 2H), 1,81(s, 2H), 1.19(t, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 147.8, 141.8, 129.4, 128.9, 125.5, 121.9, 117.1, 109.2, 22.5 ppm.

2-(2-methylbenzo[*d*][1,3]dioxol-2-yl)acetic acid (28-IIn):

The titled compound has been prepared in 120 minutes using the above general method from ethyl 3-oxooctanoate (1.3 g, 10 m.mol) and catechol (1.1 g, 10 m.mol) in 89% yield (1.98 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72(m, 4H), 4.13(q, 2H), 2.94(s, 2H), 1,81(s, 2H), 1.19(t, 3H). 13C NMR (400 MHz, $CDCl_3$) δ 147.8, 141.8, 129.4, 128.9, 125.5, 121.9, 117.1, 109.2, 22.5 ppm.

2-(2-methylbenzo[*d*][1,3]dioxol-2-yl)acetyl chloride (29):

To a solution of ethyl 2-(2-methylbenzo[*d*][1,3]dioxol-2-yl)acetate **28-IIm** (2.2g, 10 m.mol) in 20 ml of 1:1 water and methanol, was added NaOH (0.4g, 10 m.mol) in portions at 0°C. The solution was stirred at 0°C for 30 minutes and then brought to room temperature. After TLC confirms the reaction completion, methanol is evaporated under vacuum, and the aqueous layer is extracted by dichloromethane. The aqueous layer is then acidified with 10% HCl to obtain the desired product as precipitate from the solution. The precipitate thus obtained is dissolved in DCM to which oxalyl chloride (10 m.mol, 1 eq) and a drop of DMF are added at 0°c and the desired product is obtained after 30 min of stirring from 0°C to room temperature and is used directly in the next step.

(*Z*)-ethyl 2-(2-(2-butylbenzo[*d*][1,3]dioxol-2-yl)acetamido)-3- phenyl acrylate (30b):

To a solution of (*Z*)-ethyl 2-azido-3-phenylacrylate (0.217 g, 1 m.mol) in DCM was added triphenyl phosphine (0.262 g, 1 m.mol) and the mixture was stirred at room temperature. After it was stirred for 2 hrs, triethyl amine (0.2g, 2 m.mol) was added to it at 0°c. To this cooled solution was added a solution of 2-(2-methylbenzo [*d*][1,3] dioxol-2-yl) acetyl chloride **29** in DCM at 0°c, drop wise. After reaction mixture was stirred for 6 hrs, 100 mgs of silica was added into the solution and stirred for another 30 minutes. After evaporating the solvent under vacuum, the desired product is obtained and for further purification it was subject to column chromatography. The pure product was obtained in 78% yield.

5.6. References and notes:

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Vita

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