NOVEL STRATEGIES FOR HETEROCYCLIC CONSTRUCTIONS *via* 1,4-DIPOLAR INTERMEDIATES

THESIS SUBMITTED TO
COCHIN UNIVERSITY OF SCIENCE AND TECHNOLOGY
IN PARTIAL FULFILMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN CHEMISTRY UNDER THE FACULTY OF SCIENCE

BY

SREEKANTH A.R.

UNDER THE SUPERVISION OF
Dr. G. VIJAY NAIR

ORGANIC CHEMISTRY DIVISION
REGIONAL RESEARCH LABORATORY (CSIR)
TRIVANDRUM-695 019, KERALA, INDIA

NOVEMBER 2002

REGIONAL RESEARCH LABORATORY (CSIR)
GOVERNMENT OF INDIA
TRIVANDRUM-695 019, INDIA

Sreekanth A. R.
Research Fellow

Telephone: 91-471-515257; Fax: 91-471-491712

DECLARATION

I hearby declare that the matter embodied in the thesis entitled "**NOVEL STRATEGIES FOR HETEROCYCLIC CONSTRUCTIONS *VIA* 1,4-DIPOLAR INTERMEDIATES**" is the result of the investigations carried out by me in the Organic Chemistry Division of Regional Research Laboratory (CSIR), Trivandrum, under the supervision of Dr. Vijay Nair and the same has not been submitted elsewhere for a degree.

Sreekanth A. R.

Trivandrum
November, 2002

email: sree@csrrltrd.ren.nic.in; sree_ar@rediffmail.com

REGIONAL RESEARCH LABORATORY (CSIR)
GOVERNMENT OF INDIA
TRIVANDRUM-695 019, INDIA

Dr. Vijay Nair, F. A. Sc.
Director-Grade Scientist

Telephone: 91-471-490406; Fax: 91-471-491712

CERTIFICATE

This is to certify that the work embodied in the thesis entitled **"NOVEL STATEGIES FOR HETEROCYCLIC CONSTRUCTIONS *VIA* 1,4-DIPLOAR INTERMEDIATES"** has been carried out by Mr. Sreekanth A. R. under my supervision at the Organic Chemistry Division of the Regional Research Laboratory (CSIR), Trivandrum and the same has not been submitted elsewhere for any other degree.

Vijay Nair
(Thesis Supervisor)

Trivandrum
November, 2002

email: gvn@csrrltrd.ren.nic.in; vijaynair_2001@yahoo.com

CONTENTS

Declaration		i
Certificate		ii
Acknowledgements		iii
Preface		vi
Abbreviations		viii
Chapter 1		
A Brief Review of 1,4-Dipolar Cycloaddition Reactions		**1-21**
1.1	Introduction	1
1.2	Theoretical Considerations	2
1.3	1,4-Dipolar Cycloaddition Based on Conventional Dipoles	3
1.4	Heterocyclic Betaines in 1,4-Dipolar Cycloaddition Reactions	7
1.4.1	Bimolecular 1,4-Dipolar Cycloaddition Reactions	7
1.4.2	Intramolecular 1,4-Dipolar Cycloaddition Reactions	9
1.5	Formal 1,4-Dipolar Cycloaddition Reactions	11
1.6	Conclusion and the Present Work	17
1.7	References	18
Chapter 2		
Novel Pyridine Catalysed Reaction of Dimethyl acetylenedicarboxylate with Aldehydes and *N*-Tosylimines		**22-61**
2.1	Introduction	22
2.2	Addition of Phosphorous Compounds	22
2.3	Addition of Tertiary Amines	24
2.4	Addition of Imines	25
2.5	Addition of Enamines	26
2.6	Addition of Sulphur Compounds	27
2.7	Addition of Phosphoranes	27
2.8	Addition of Isocyanides	28
2.9	Addition of Pyridine	29
2.10	Statement of the problem	31
2.11	Results and Discussion	32
2.11.1	Reaction of Pyridine and DMAD with Aldehydes	32
2.11.2	Reaction of Pyridine and DMAD with *N*-Tosylimines	38
2.12	Conclusion	42
2.13	Experimental Details	43

2.14	References	59
Chapter 3		
Three Component condensation Reactions of Isoquinoline and Dimethyl acetylenedicarboxylate with *N*-Tosylimines and Aldehydes		**62-90**
3.1	Introduction	62
3.1.1	Multicomponent Reactions (MCRs)	62
3.1.2	Heterocyclic Synthesis Using Multicomponent Reactions	66
3.2	Background to the Present Work	67
3.3	Results and Discussion	68
3.3.1	Reaction of Isoquinoline and DMAD with *N*-Tosylimines	68
3.3.2	Reaction of Isoquinoline and DMAD with Aldehydes	74
3.4	Conclusion	77
3.5	Experimental Details	77
3.6	References	89
Chapter 4		
The Reaction of Isoquinoline and Dimethyl acetylenedicarboxylate with 1,2- and 1,4-Benzoquinones: A Novel Synthesis of Spiro[1,3] oxazino[2,3-a]isoquinolines		**91-121**
4.1	Introduction	91
4.1.1	Diels-Alder Reactions of 1,2-Benzoquinones	91
4.1.2	Dipolar Cycloaddition Reactions of 1,2-Benzoquinones	92
4.2	Background to the Present Work	94
4.3	Results and Discussion	95
4.3.1	Reaction of Isoquinoline and DMAD with 1,2-Benzoquinones	95
4.3.1.1	Mechanistic Consideration	101
4.3.2	Reaction of Isoquinoline and DMAD with 1,4-Benzoquinones	102
4.3.3	Reaction of Isoquinoline and DMAD with *N*-Substituted Isatins	104
4.4	Conclusion	105
4.5	Experimental Details	105
4.6	References	120
Summary		122
List of Publications		125

PREFACE

Synthesis of a complex organic molecule essentially involves the formation of carbon-carbon and carbon-heteroatom bonds. Various synthetic methods are available for these processes involving ionic, pericyclic and radical reactions. Among the pericyclic reactions, dipolar cycloaddition reactions, introduced by Huisgen, have emerged as a very powerful tool for heterocyclic construction.

Heterocyclic compounds remain an important class of organic molecules due to their natural abundance and remarkable biological activity, thus constituting an intergral part of pharmaceutical industry. In this respect, developing newer synthetic methodology for heterocyclic construction has been an area of immense interest. In recent years, 1,3-dipolar cycloaddition reactions proved to be efficient routes to a wide variety of five membered heterocycles, as attested by their application in the total synthesis of various complex organic molecules. However, the potential application of similar 1,4-dipolar cycloaddition reactions for the construction of six memebered heterocycles remained underexploited. In this context, a systematic investigation of the reactivity of 1,4-dipoles generated from nitrogen heterocycles (pyridine and its analogues) and dimethyl acetylenedicarboxylate (DMAD) towards various dipolarophiles has been carried out and the results are embodied in the thesis entitled "**Novel Strategies for Heterocyclic Constructions *via* 1,4-Dipolar Intermediates**".

The thesis is divided into four chapters. Relevant references are given at the end of each chapter.

A general introduction and a brief review of 1,4-dipolar cycloaddition reactions is presented in Chapter 1. The definition of the present research problem is provided at the end of this chapter.

The second chapter contains the results of our investigations of the reaction of 1,4-dipolar intermediate generated from pyridine and DMAD with various aromatic aldehydes and *N*-tosylimines affording a novel route to 2-

benzoyl fumarates and highly substituted 1-azadienes. General information on the experimental procedure is given in this chapter.

The third chapter deals with the reaction of 1,4-dipolar intermediate from isoquinoline and DMAD with various *N*-tosylimines and aromatic aldehydes resulting in a one-pot synthesis of 2*H*-pyrimido[2,1-a]isoquinolines and [1,3]oxazino[2,3-a]isoquinolines.

The fourth chapter describes the interception of the 1,4-dipolar intermediate generated from isoquinoline and DMAD with various 1,2- and 1,4-benzoquinones yielding spiro[1,3]oxazino[2,3-a]isoquinolines in the process.

It may be mentioned that each chapter of the thesis is presented as an independent unit and therefore the structural formulae, schemes and figures are numbered chapterwise.

A summary of the work is given towards the end of the thesis.

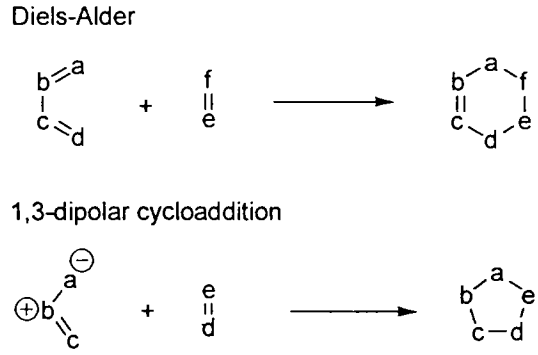
ABBREVIATIONS

d	: doublet
dd	: doublet of doublet
DMAD	: dimethyl acetylenedicarboxylate
DME	: dimethoxy ethane
DMSO	: dimethyl sulfoxide
EI	: electron impact
Et	: ethyl
HRMS	: high-resolution mass spectrum
Hz	: hertz
IR	: infrared
J	: coupling constant
m	: multiplet
Me	: methyl
mg	: milligram
mL	: milliliter
mp	: melting point
NMR	: nuclear magnetic resonance
o	: ortho
p	: para
Ph	: phenyl
PTAD	: 4-phenyl-1,2,4-triazoline-3,5-dione
q	: quartet
RT	: room temperature
s	: singlet
t	: triplet
TMS	: teramethyl silane
Ts	: *p*-toluene sulfonyl
tert	: tertiary
Z	: benzyloxy carbonyl

A Brief Review of 1,4-Dipolar Cycloaddition Reactions

1.1 Introduction

Cycloaddition reactions constitute an important class of carbon-carbon as well as carbon-heteroatom bond forming process in synthetic organic chemistry. Generally cycloaddition reactions are considered to be concerted processes, with the simultaneous formation of two new σ bonds, *via* a cyclic transition state. With the participation of [4+2] π electrons, the Diels-Alder reaction and the 1,3-dipolar cycloaddition (Scheme 1.1) fulfill the Woodward-Hoffmann selection rules for the one-step thermal process.



Scheme 1.1

Both these reactions owe the wide range of their application to the fact that they are stereospecific and proceed through a single transition state which is characteristic of a concerted process. In his pioneering work, Huisgen *et al.* have provided the conceptual framework for a 1,4-dipolar cycloaddition reaction and demonstrated the existence of 1,4-dipoles.[1] Apart from the well known Hetero Diels-Alder reactions,[2] 1,4-dipolar cycloaddition constitutes a

potentially versatile process for the construction of six membered heterocycles. A brief review of the 1,4-dipolar cycloaddition reactions is presented in this chapter.

1.2 Theoretical Considerations

A 1,4-dipole is defined as a system *'a-b-c-d'*, in which *a* has an unfilled electron shell and carries a formal positive charge and *d* is an anionic center with a free electron pair. It is only the internal octet stabilisation with the help of a lone pair on *b* that makes the 1,4-dipole capable of existence (Figure 1.1).

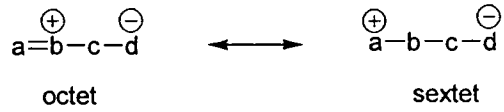
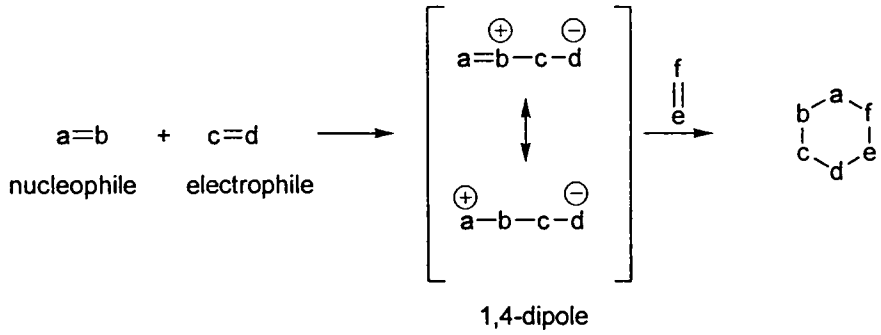


Figure 1.1

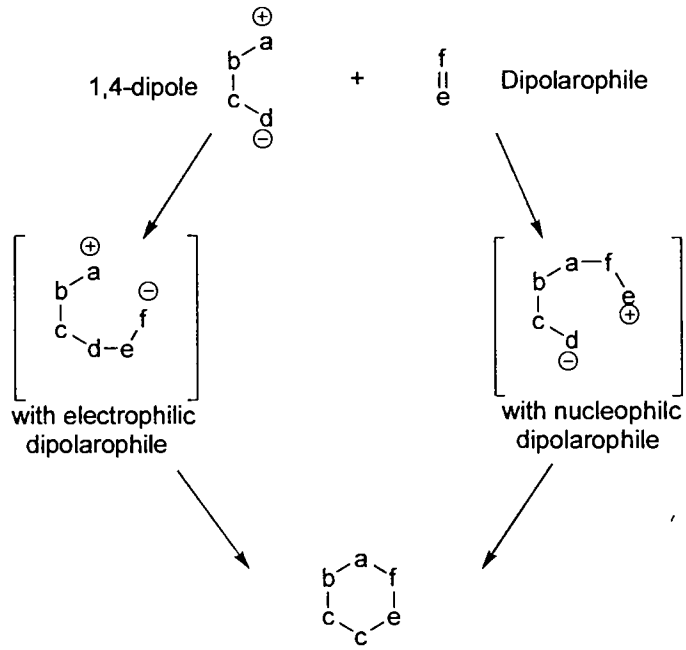
The 1,4-dipole is usually generated *in situ* by the reaction of an electrophile (*c=d*) with a nucleophilic (*a=b*) double bond. The combination of such a 1,4-dipole with a multiple bond system (*e=f*) termed as dipolarophile is referred to as 1,4-dipolar cycloaddition (Scheme 1.2).



Scheme 1.2

The interchangeability of formal charges in mesomeric structures which is so characteristic of 1,3-dipoles is missing in the 1,4-dipole owing to the lack of conjugation. The 1,4-dipolar cycloaddition reaction proceeds *via* a two-step addition mechanism in which the two new σ bonds are formed one after the other. The 1,4-dipole combines only with those dipolarophiles which themselves display pronounced electrophilic or nucleophilic reactivity. It is therefore necessary that the dipolar intermediates indicated must bear a full

negative or positive charge in the portion derived from the former dipolarophile *e*=*f*. This limits severely the range of applicable dipolarophiles (Scheme 1.3).



Scheme 1.3

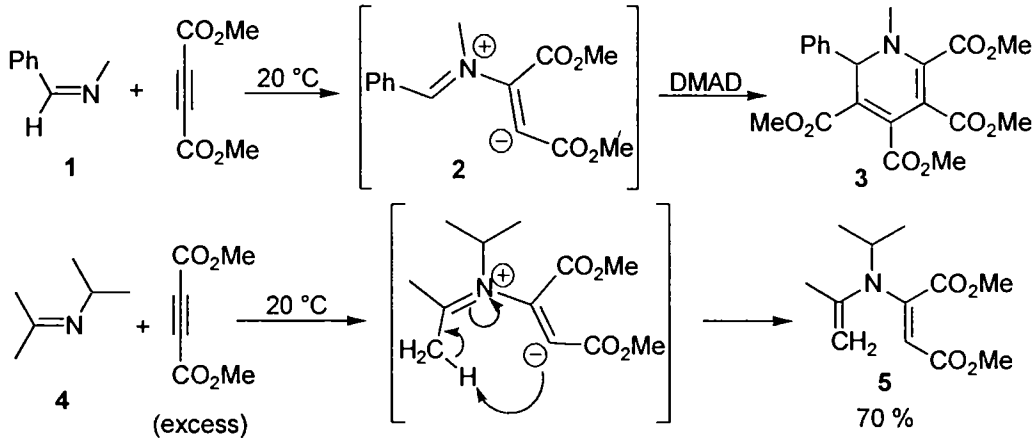
It may be interesting to note that generally 1,4-dipoles have been formulated to arise from *cis* addition, although normally this type of addition seldom occurs. The reason must be that the dipoles are stabilised in this geometry because of the interaction of polar ends. With the limited theoretical work in this area, it is difficult to predict mechanistically their stabilisation by addition of the dipolarophile either through a concerted or stepwise reaction. Whereas these theoretical questions are still open, the practice has bypassed the theory and many reactions are known which can be classified according to this principle of 1,4-dipolar cycloaddition.

1.3 1,4-Dipolar Cycloaddition Based on Conventional Dipoles

The history of 1,4-dipolar cycloaddition dates back to 1932, when Diels and Alder reacted pyridine with dimethyl acetylenedicarboxylate (DMAD) and obtained a 1:2 adduct whose structure was established as a 4*H*-quinolizine much later by the extensive investigations of Acheson and co-workers[3] (details are given in Chapter 2, Section 2.9). Many nitrogen containing heterocyclic

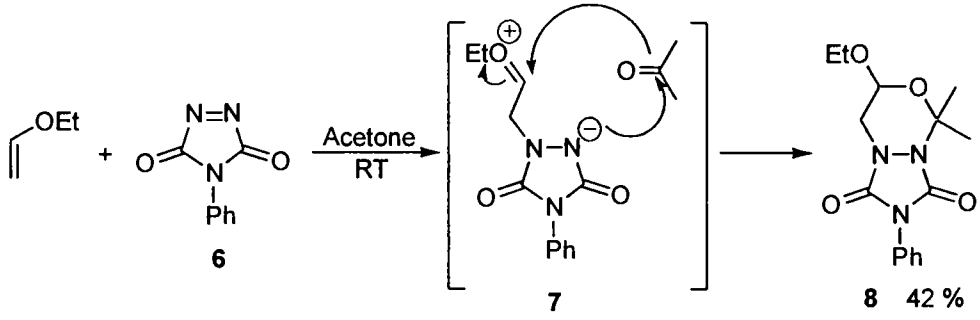
compounds undergo analogous reactions with DMAD; these can be designated as 1,4-dipolar cycloaddition reactions.[4]

One of the earlier reports from Huisgen has shown that the 1,4-dipole **2**, generated from aldimine **1** and DMAD undergoes 1,4-dipolar cycloaddition with second molecule of DMAD to form the cycloadduct **3**. A similar reaction of ketimine **4** with DMAD resulted in an intramolecular proton abstraction to form the product **5** (Scheme 1.4).[5]



Scheme 1.4

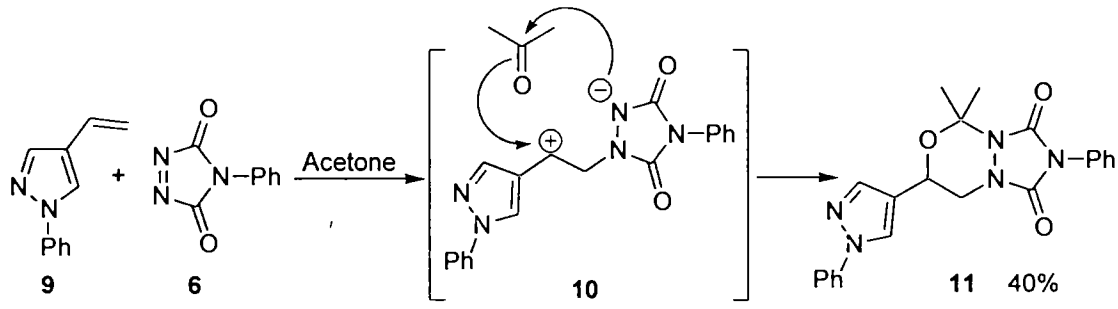
The existence and the reactivity of the 1,4-dipolar species generated from enol ethers and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) **6** was studied by Butler and co-workers.[6] It has been shown that a stabilised 1,4-dipole such as **7** can add to even the weakly dipolarophilic carbonyl group of acetone to form the tetrahydro-oxadiazine **8** (Scheme 1.5).[7]



Scheme 1.5

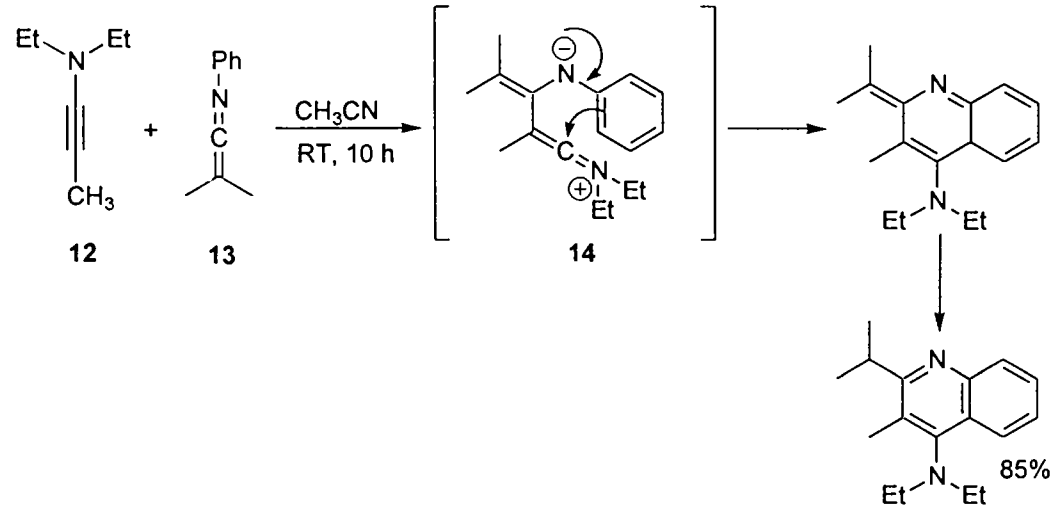
The reactivity of the 1,4-dipole **7** is quite sensitive to stabilisation of its positive center; high yields of oxadiazines were obtained when the carbocation is stabilised by substituents such as alkoxy groups.

The evidence for a similar 1,4-dipolar intermediate **10** in the reaction of PTAD with 1-phenyl-4-vinylpyrazole **9** was provided by its trapping with acetone, affording tetrahydro-oxadiazine **11** (Scheme 1.6).[8]



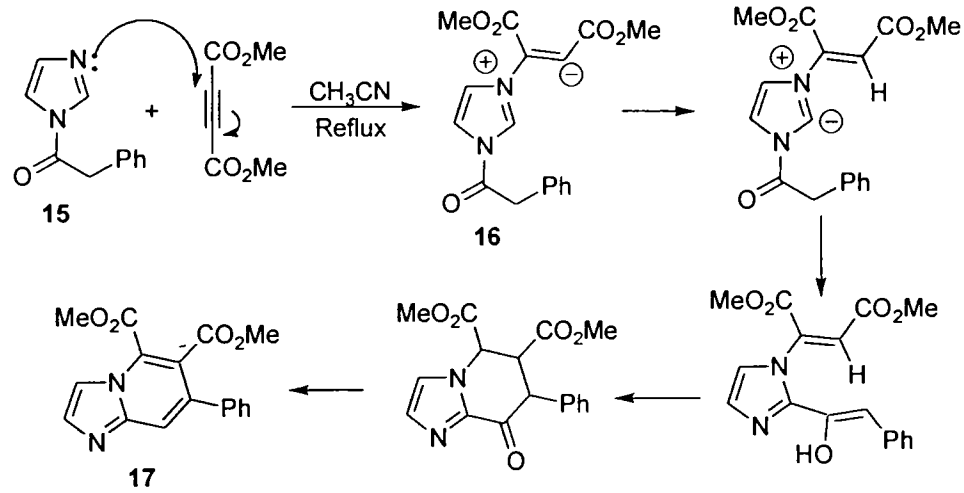
Scheme 1.6

Ghosez *et al.* reported an interesting intramolecular cyclisation of the 1,4-dipole **14** derived from ynamine **12** and *N*-phenylketenimine **13** resulting in a one-pot synthesis of 4-aminoquinoline derivatives in good yields (Scheme 1.7).[9]



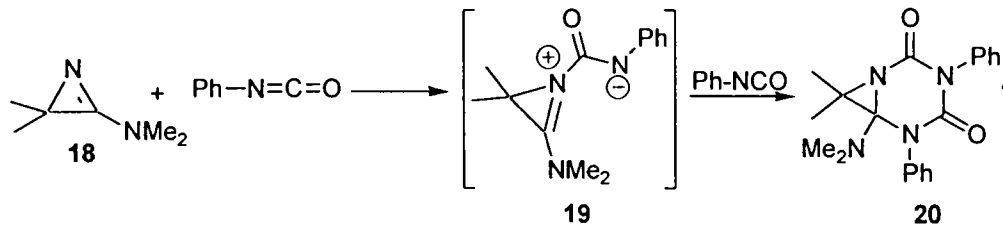
Scheme 1.7

An unusual intramolecular cyclisation of 1,4-dipole **16** derived from *N*-acylimidazole **15** and DMAD resulting in the formation of imidazo[1,2-a]pyridine ring system **17** was observed by Knölker (Scheme 1.8).[10]



Scheme 1.8

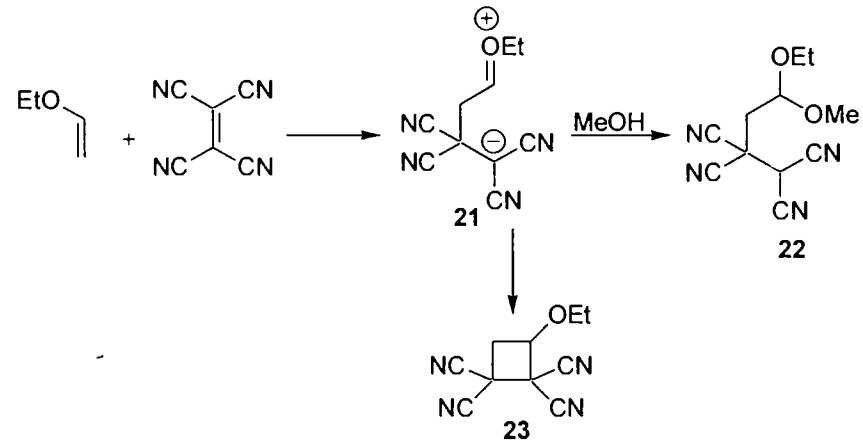
The thermal cycloaddition reactions of highly reactive azirines with heterocumulenes generally proceed through a 1,4-dipolar intermediate, further reaction of which depends on the stability of the dipole thus formed.[11] Schaumann *et al.* have shown that the 1,4-dipole **19** derived from the reaction of 2,2-dialkylaminoazirine **18** with phenyl isocyanate, adds to another molecule of phenyl isocyanate to afford the cycloadduct hexahydro-*s*-triazine **20** (Scheme 1.9).[12]



Scheme 1.9

The [2+2] cycloaddition reactions of enol ethers with tetracyanoethylene, leading to cyclobutanes have been extensively studied by Huisgen and co-workers.[13] This reaction essentially proceeds through a 1,4-dipolar species **21**,

which in aprotic media undergoes ring closure to cyclobutane **23**, while in protic solvent it affords a 1:1:1 adduct **22** (Scheme 1.10).[14]



Scheme 1.10

1.4 Heterocyclic Betaines in 1,4-Dipolar Cycloaddition Reactions

1.4.1 Bimolecular 1,4-Dipolar Cycloaddition Reactions

In spite of the conceptual introduction of 1,4-dipolar cycloaddition by Huisgen in 1967, the synthetic utility of the classical 1,4-dipoles in the construction of six membered heterocycles remained underexploited. This is mainly due to the difficulty encountered in the generation, stabilisation and the reactivity of these dipoles. The introduction of mesoionic compounds with a "masked" 1,4-dipole proved to be an important development in 1,4-dipolar cycloaddition. Mesoionic compounds are generally prepared by the cyclocondensation of an appropriately substituted monotropic amidine or thioamide with a 1,3-bielectrophile derived from malonic acid.[15] These heterocyclic betaines (**24a** ↔ **24b** ↔ **24c**) are capable of undergoing cycloaddition with π-bonds (Figure 1.2).

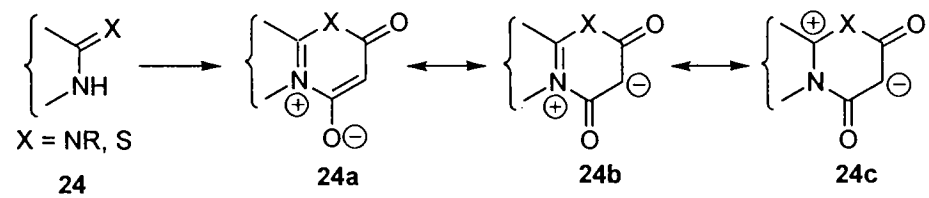
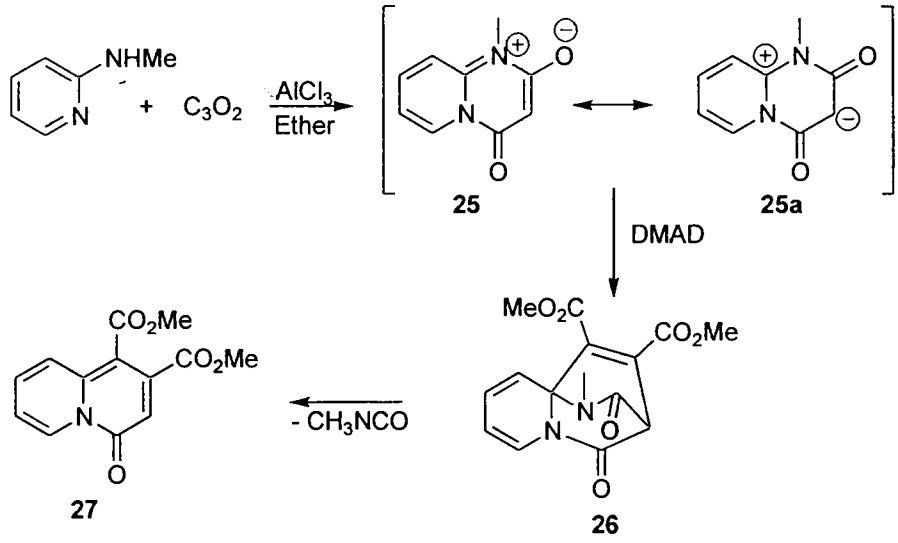


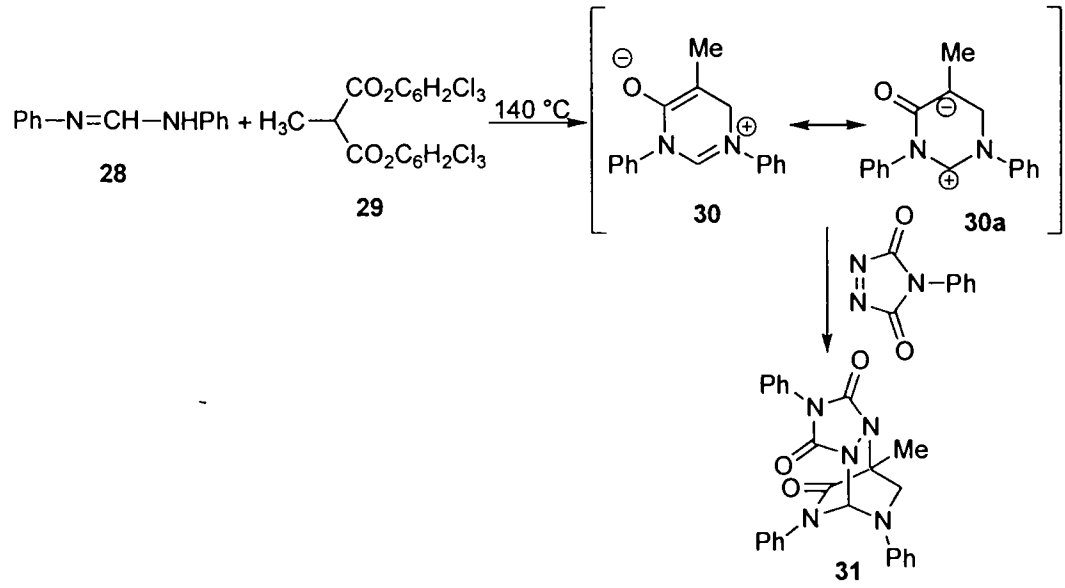
Figure 1.2

One of the earlier reports from Potts and co-workers has shown that the heterocyclic betaine **25** derived from 2-*N*-methylaminopyridine and carbonsuboxide as a crystalline solid, undergoes a bimolecular 1,4-dipolar cycloaddition with DMAD to afford 4*H*-quinolizinone **27** *via* the [4+2] cycloadduct **26** followed by the elimination of methylisocyanate (Scheme 1.11).[16]



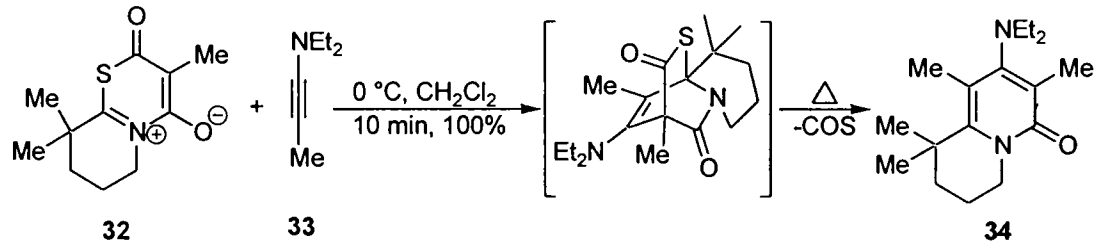
Scheme 1.11

The utility of pyrimidinium-4-olates as 1,4-dipoles in the bimolecular as well as intramolecular 1,4-dipolar cycloaddition reactions was extensively investigated by Gotthardt and co-workers.[17] It has been shown that the pyrimidinium-4-olate **30** prepared from amidine **28** and malonate **29**, adds to 1,2,4-triazoline-3,5-dione at room temperature to afford the [4+2] cycloadduct **31** in high yields (Scheme 1.12).[18]



Scheme 1.12

An easy access to highly substituted bicyclic α-pyridones were developed by Padwa and co-workers utilizing the bimolecular 1,4-dipolar cycloaddition strategy. The reaction of bicyclic anhydro-2-oxo-4-hydroxy-1,3-thiazinium hydroxide **32** with electron rich π-systems such as ynamine **33** afforded the [4+2] cycloadduct, which on heating extruded carbonyl sulfide producing substituted α-pyridone **34** (Scheme 1.13).[19]

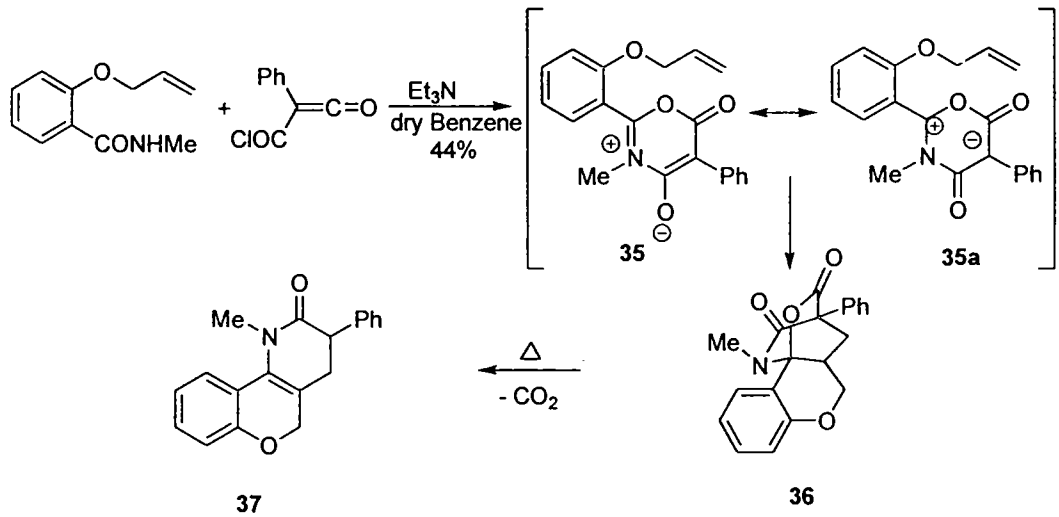


Scheme 1.13

1.4.2 Intramolecular 1,4-Dipolar Cycloaddition Reactions

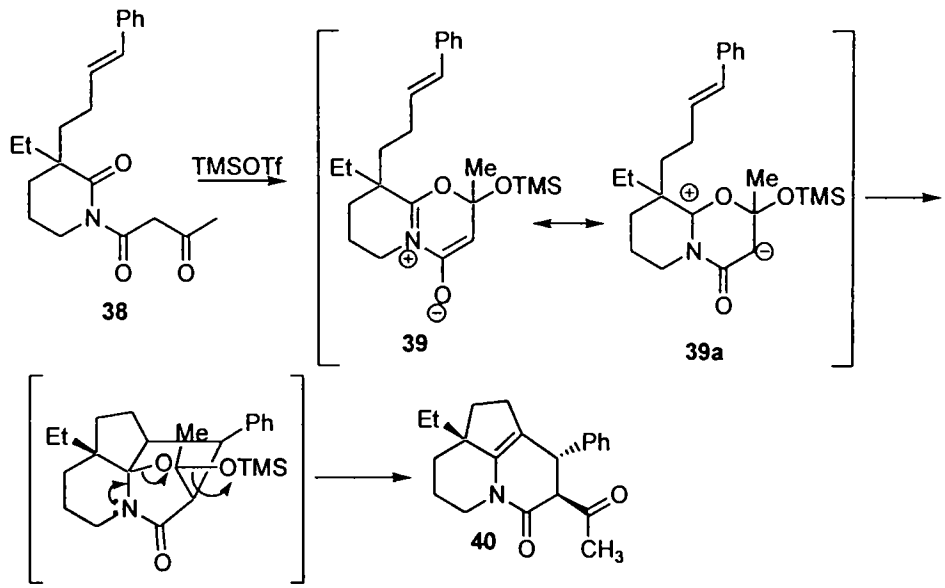
Unlike the well known intramolecular 1,3-dipolar cycloadditions, intramolecular 1,4-dipolar cycloadditions have received less attention. Potts *et al.* have shown that the *in situ* generated anhydro-1,3-oxazinium hydroxide **35** with an *o*-alkenyl tether, undergoes intramolecular 1,4-dipolar cycloaddition to

give the cycloadduct **36**, which on heating eliminates CO_2 to afford chromeno[4,3-b]pyridin-2-one **37** (Scheme 1.14).[20]



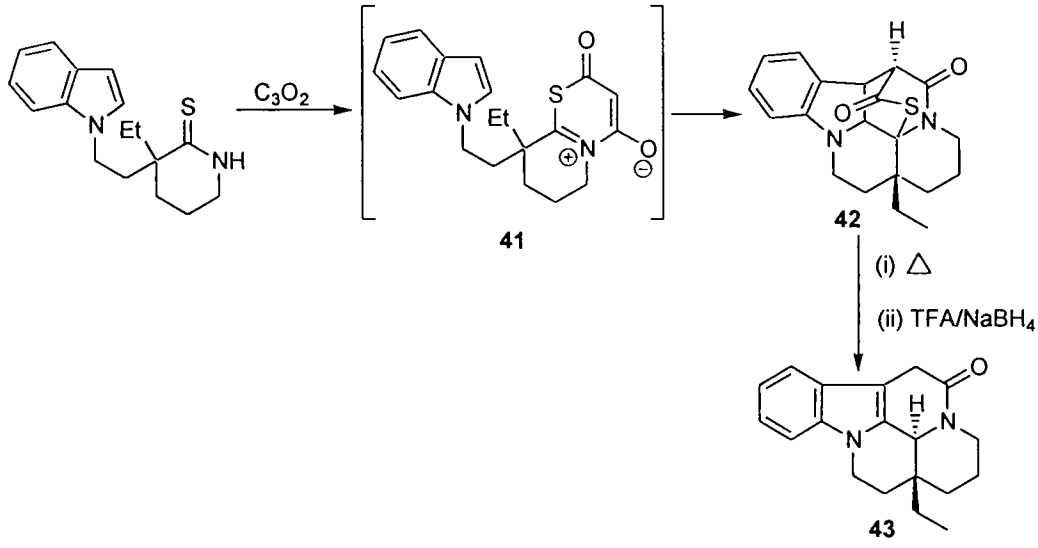
Scheme 1.14

The [4+2] annulation strategy for the synthesis of polycyclic framework was effectively utilized by Padwa in the reaction of TMSOTf promoted intramolecular 1,4-dipolar cycloaddition of *N*-acetoacetylated alkenyl amide **38**. The reaction proceeds through a cross-conjugated heteroaromatic betaine intermediate **39**, which undergoes intramolecular addition across the C=C bond, resulting in the stereoselective formation of the cycloadduct **40** (Scheme 1.15).[21]



Scheme 1.15

The intramolecular 1,4-dipolar cycloaddition reaction was elegantly employed by Padwa *et al.* in the synthesis of *epi*-Eburnamenine alkaloids. The cycloaddition of *in situ* generated anhydro-4-hydroxy-2-oxo-1,3-thiazinium hydroxide **41** across a tethered indole π-bond, afforded the [4+2] cycloadduct **42**, which was easily converted to *epi*-16, 17-dihydroeburnamenine **43** (Scheme 1.16).[22]

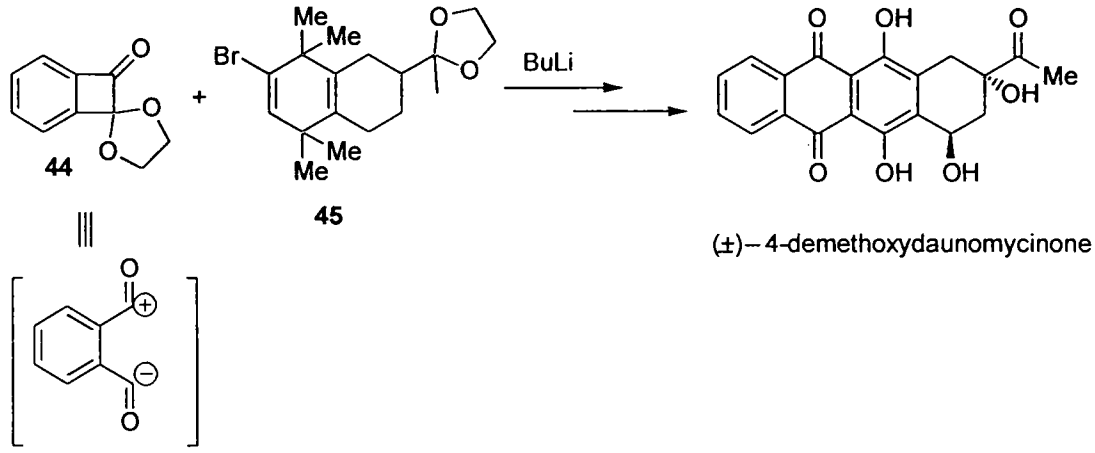


Scheme 1.16

1.5 Formal 1,4-Dipolar Cycloaddition Reactions

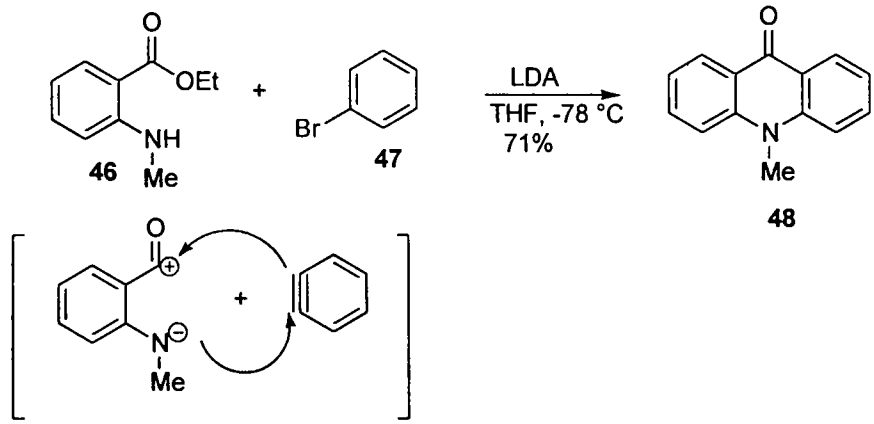
Synthetic routes based on formal 1,4-dipolar cycloaddition have attracted much attention since they have resulted in convergent approaches for the construction of polycyclic systems under mild conditions. A number of reagents such as ortho phenyl substituted diesters,[23] phthalide sulfones,[24] phthalides,[25] cyanophthalides,[26] and ortho tolyl carboxylates[27] have been used as 1,4-dipole synthons.

The utility of benzocyclobutenedione monoketal as a 1,4-dipole equivalent was elegantly employed by Swenton *et al.* in the synthesis of (±)-4-demethoxydaunomycinone. The key step in the synthesis involves the base induced [4+2] annulation of bromo derivative **45** with the 1,4-dipole equivalent **44** (Scheme 1.17).[28]



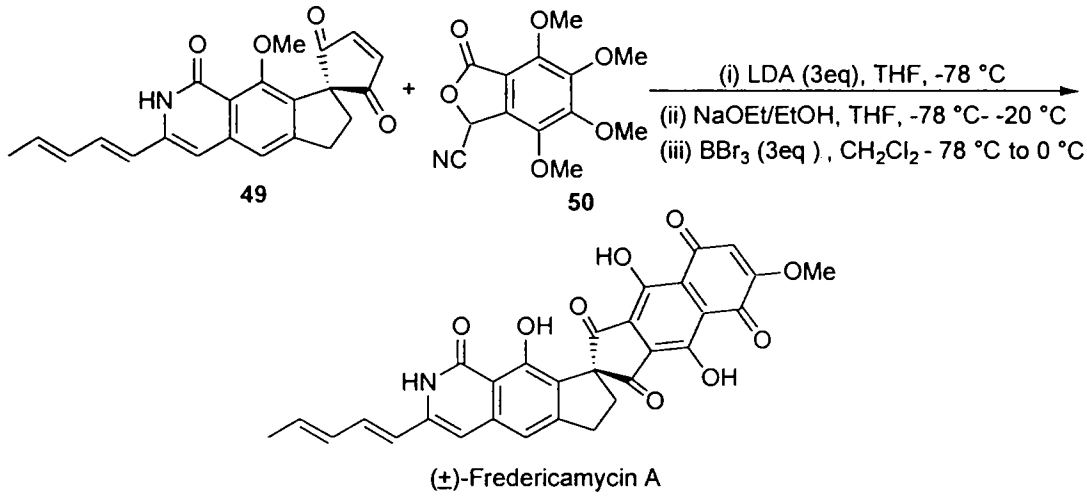
Scheme 1.17

An efficient synthesis of substituted acridones was developed by Biehl and co-workers based on the formal 1,4-dipolar cycloaddition strategy. The reaction of *N*-lithiated ethylanthranilate **46**, as 1,4-dipole equivalent, with benzyne precusor **47** afforded the [4+2] cycloadduct **48** in good yields (Scheme 1.18).[29]



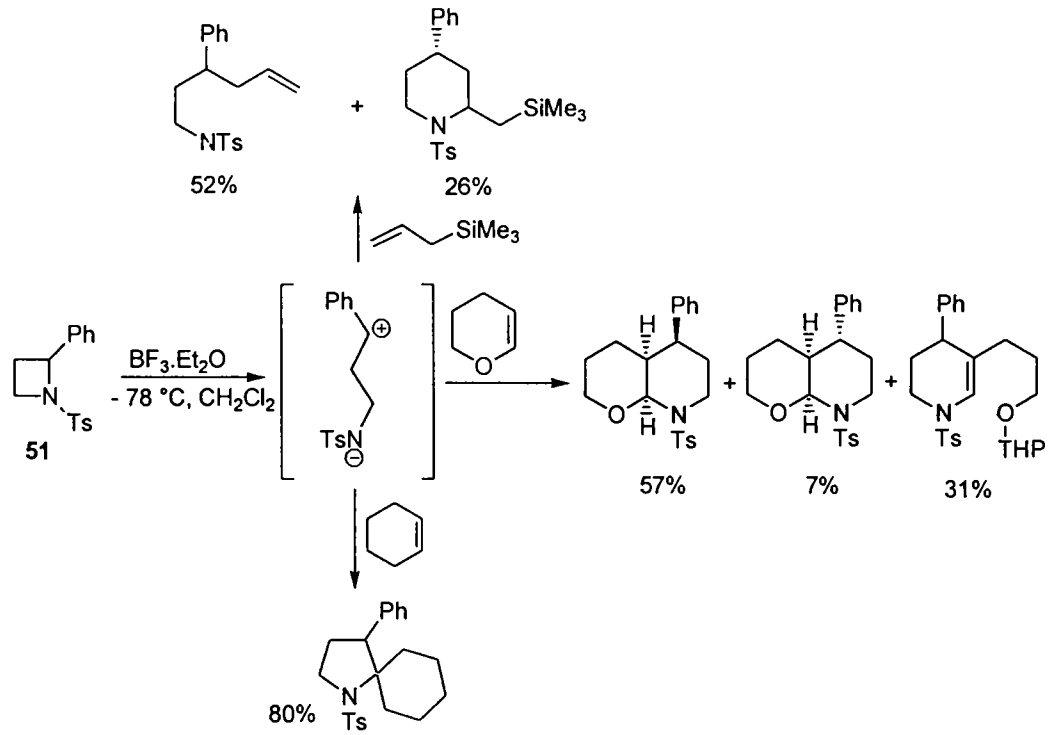
Scheme 1.18

A two step 1,4-dipolar cycloaddition has been utilised as the key step in the total synthesis of antitumor antibiotic (±) Fredericamycin A by Bach and co-workers. The coupling of the fragment **49** with the lithio anion of the lactone **50**, followed by cyclisation of the Michael adduct and demethylation afforded (±)-Fredericamycin A (Scheme 1.19).[30]



Scheme 1.19

Recently Mann *et al.* have observed that *N*-tosyl-2-phenylazetidine **51**, in presence of $BF_3.Et_2O$, reacts as a formal 1,4-dipole with various activated and non-activated alkenes. Thus the reaction of **51** with dihydropyran afforded the [4+2] adduct as the major product, whereas with cyclohexene **51** gave a [4+1] adduct; with allylsilane as the trapping agent **51** afforded the allylated product as the major one along with minor amounts of the [4+2] adduct (Scheme 1.20).[31]



Scheme 1.20

Vinyl isocyanates are readily available, reactive functionalities that can serve as useful 1,4-dipole equivalents in a wide range of cyclisation processes. In combination with various electron rich 1,2-dipoles, they can deliver structurally elaborate six-membered nitrogen heterocycles suitable for conversion into a number of alkaloid targets including benzophenanthridines, phenanthridines as well as pyridone-derived systems. (Figure 1.3).

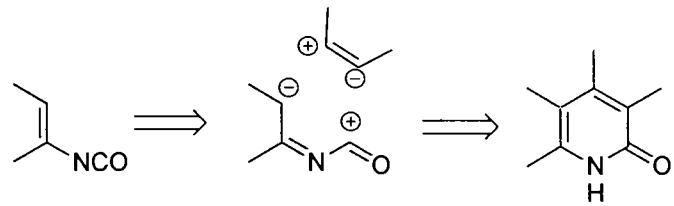
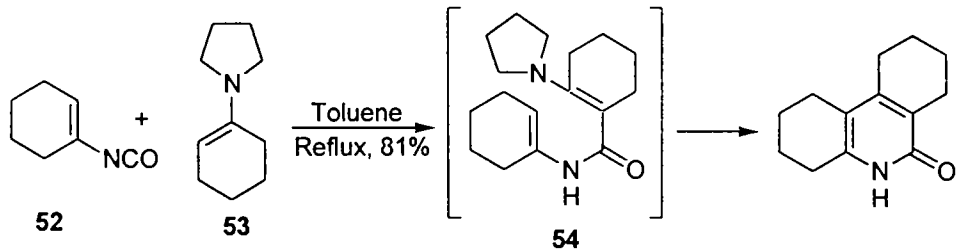


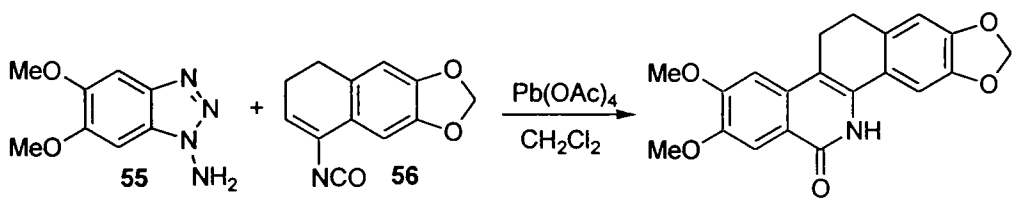
Figure 1.3

Extensive investigations by Rigby and co-workers in this area have unraveled some interesting observations.[32] In one of their earlier reports it was shown that the reaction of vinylisocyanate **52** with enamine **53** provided a facile entry into pyridone heterocycles *via* the intermediate **54** (Scheme 1.21).[33]



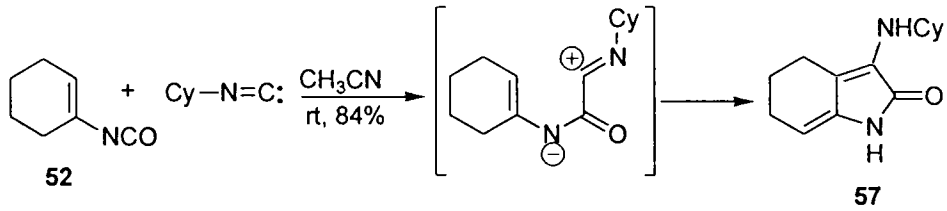
Scheme 1.21

The [4+2] annulation strategy using vinylisocyanate was sucessfully employed in the synthesis of benzophenanthridine alkaloid *N*-nornitidine. The key step involves the cycloaddition of vinylisocyanate **56** with benzyne generated *in situ* by oxidative decomposition of *N*-aminobenzotriazole **55** (Scheme 1.22).[34]



Scheme 1.22

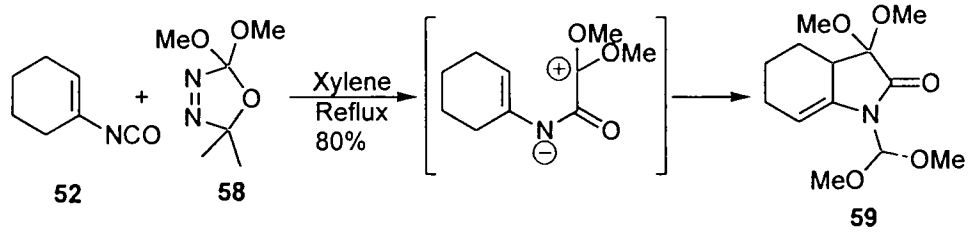
A powerful strategy for the construction of five membered heterocycles was also developed by Rigby utilising a [4+1] annulation reaction of vinylisocyanates with 1,1-dipole equivalents. Thus, a reaction of vinylisocyanate **52** with cyclohexylisocyanide at room temperature afforded the corresponding hydroindolone **57** in excellent yield, which was isolated by simple filtration from the reaction mixture (Scheme 1.23).[35]



52 **57**

Scheme 1.23

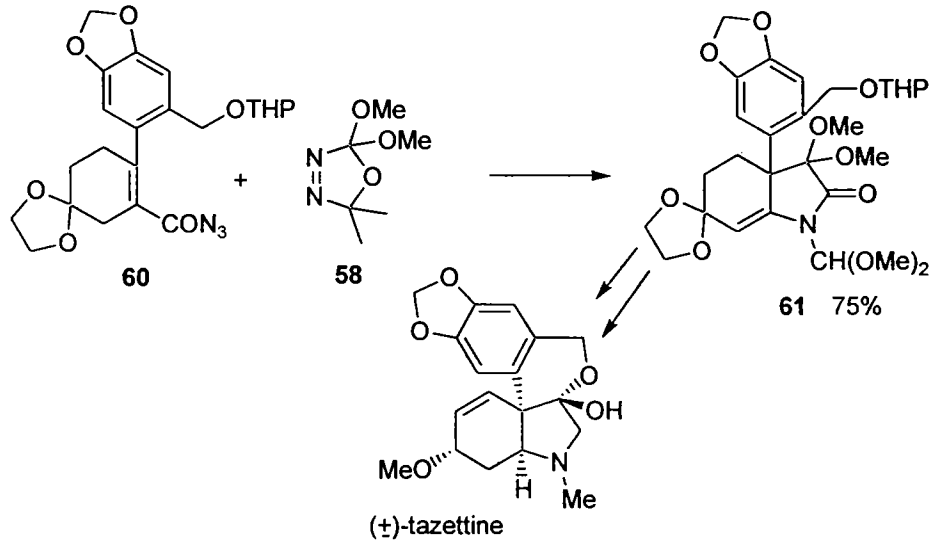
The sucessful introduction of nucleophilic carbenes as a 1,1-dipole equivalent in these [4+1] annulation reactions was also made by Rigby who demonstrated that the reaction of vinylisocyanate **52** with dimethoxy carbene generated by the thermolysis of excess of 2,2-dimethoxy-Δ^3-1,3,4-oxadiazoline **58**, afforded a good yield of the desired hydroindolone **59** (Scheme 1.24).[36]



52 **58** **59**

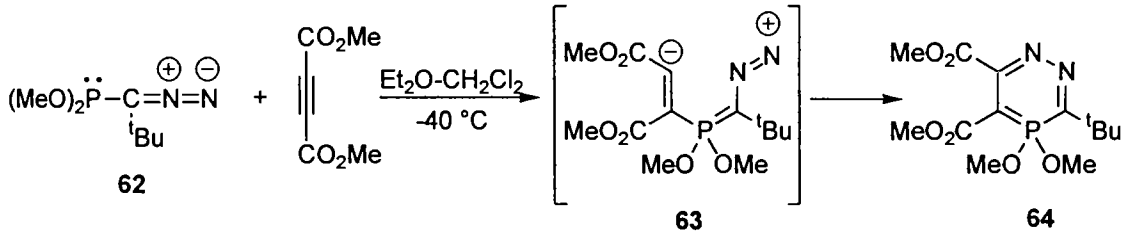
Scheme 1.24

Various nucleophilc carbenes that possess heteroatoms other than oxygen were also sucessfully employed in these cycloaddition reactions.[37] This strategy was then utilised for the total synthesis of the alkaloid (±)-tazettine, which exhibits a bridgehead aryl substituent as a prominent structural feature. Treating the acyl azide **60** in presence of oxadiazoline **58** led in quite good yield to the highly substituted hydroindolone **61**. Relatively straightforward conversion of this advanced intermediate into (±)-tazettine itself was achieved in 16 steps and in 11% overall yield (Scheme 1.25).[38]



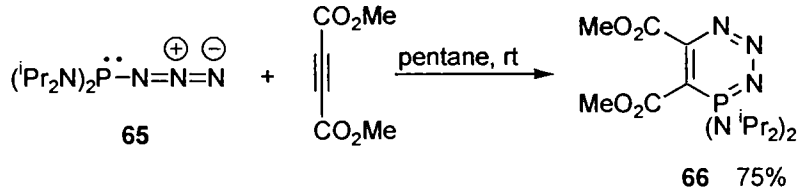
Scheme 1.25

Aliphatic diazo compounds are known to be powerful 1,3-dipoles from their reaction with various dipolarophiles leading to a variety of heterocycles.[39] An interesting reaction was observed by Regitz and co-workers; phosphinodiazoalkane **62** when treated with electron deficient alkynes such as DMAD, underwent a [4+2] cycloaddition resulting in the formation of novel 1,2,4-λ^5-diazaphosphinines **64**. The reaction proceeds by the initial nucleophilic attack of phosphine to electron deficient carbon of DMAD to form a dipolar intermediate **63**, which then cyclised to give the adduct (Scheme 1.26).[40]



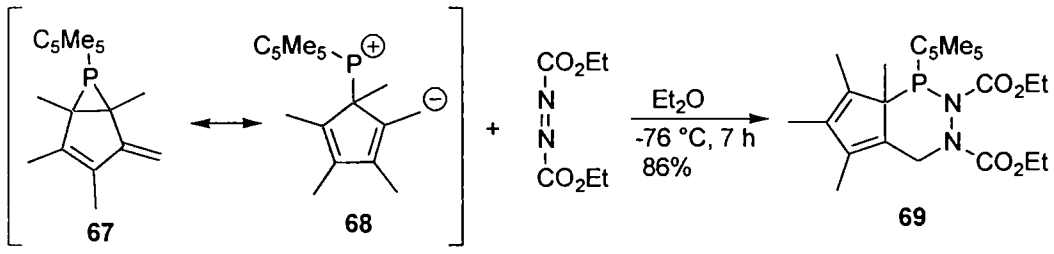
Scheme 1.26

Investigations by Bertrand and co-workers have also shown that bis(diisopropylamino)phosphanylazide **65** can similarly act as a formal 1,4-dipole in its reaction with DMAD, affording the [4+2] cycloadduct **66** in good yield (Scheme 1.27).[41]



Scheme 1.27

Recently Niecke and co-workers have found that 4-methylene-6-phosphabicyclo[1.1.0]hex-2-ene **67** can act as a formal 1,4-dipole in its reaction with diethylazodicarboxylate, affording the [4+2] cycloadduct **69** in excellent yield. The bicyclic phosphorous compound can be represented by a dipolar species **68** with a carbon nucleophilic center (Scheme 1.28).[42]



Scheme 1.28

1.6 Conclusion and the Present Work

It is clear from the literature survey presented above that 1,4-dipolar cycloaddition provides a unique and facile method for the construction of various six membered heterocycles. When compared to the well exploited 1,3-dipolar cycloaddition, the synthetic utility of 1,4-dipolar cycloaddition remained underexploited. It is especially noteworthy that eventhough the incorporation of a 1,4-dipole in heterocyclic betaines and formal 1,4-dipolar cycloadditions have received considerable attention, the potential applications of bimolecular 1,4-dipolar cycloaddition involving classical 1,4-dipoles have not been explored in depth. Against this background, we have undertaken a series of investigations in this area and the results form the subject matter of the present thesis.

The first phase of our investigations deals with the reactivity of 1,4-dipole generated from pyridine and dimethyl acetylenedicarboxylate (DMAD)

towards various dipolarophiles; the results form the subject matter of the second chapter.

The second phase of our study is concerned with the trapping of 1,4-dipole from isoquinoline and DMAD with *N*-tosylimines and aldehydes, thus constituting a novel multicomponent reaction. The details of this work are presented in the third chapter.

The final phase of our work explores the possiblity of intercepting the 1,4-dipolar intermediate from isoquinoline and DMAD with 1,2- and 1,4-quinones. The results of these studies constitute the fourth chapter.

1.7 References

1. (a) Huisgen, R. in *Topics in Heterocyclic Chemistry*; Castle, R., Ed ; John Wiley & Sons : New York, 1969, chapter 8, 223. (b) Huisgen, R., *Ger. Z. Chem.* **1968**, 8(8), 290.
2. *Hetero Diels-Alder Methodology in Organic Synthesis.*; Boger, D. L.; Weinreb, S. M., Eds.; Academic Press: San Diego, 1987.
3. Acheson, R. M. *Adv. Heterocycl. Chem.* **1963**, *1*, 125.
4. Acheson, R. M.; Elmore, N. F. *Adv. Heterocycl. Chem.* **1978**, 23, 263.
5. Huisgen, R. *Liebigs Ann. Chem.* **1965**, *688*, 98.
6. (a) Butler, G. B.; Turner, S. R.; Wagener, K. B. *J. Org. Chem.* **1972**, *37*, 1454. (b) Butler, G. B.; Wagener, K. B. *J. Org. Chem.* **1973**, *38*, 3070.
7. Butler, G. B.; Turner, S. R.; Guilbault, L. J. *J. Org. Chem.* **1971**, *36*, 2838.
8. Sepulveda-Arques, J.; Simon,M. M. *Tetrahedron Lett.* **1985**, *26*, 6357.
9. Ghosez, L.; de Perez, C. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 184.
10. Knölker, H. J.; Boese, R. *J. Chem. Soc. Chem. Commun.* **1988**, 1151.
11. (a) Hassner, A.; Miller, A. S.; Haddadin, M. J. *Tetrahedron Lett.* **1972**, 1353. (b) Woerner, F. P.; Reimlinger, H.; Merenyi, R. *Chem. Ber.* **1971**, *104*, 2786. (c) Ghosez, L.; Rens, M. *Chem. Ber.* **1970**, *103*, 3765.

12. Schaumann, E.; Kausch, E.; Walter, W. *Chem. Ber.* **1974**, *107*, 3574.
13. (a) Huisgen, R.; Steiner, G. *J. Am. Chem. Soc.* **1973**, *95*, 5054. (b) Huisgen, R.; Steiner, G. *J. Am. Chem. Soc.* **1973**, *95*, 5055. (c) Huisgen, R.; Steiner, G. *J. Am. Chem. Soc.* **1973**, *95*, 5056.
14. (a) Huisgen, R.; Steiner, G.; Schug, R. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 80. (b) Huisgen, R.; Steiner, G.; Schug, R. *Angew. Chem., Int. Ed. Engl.* **1974**, *13*, 81.
15. (a) Potts, K. T.; Sorm, M. *J. Org. Chem.* **1972**, *37*, 1422. (b) Potts, K. T.; Ehlinger, R.; Nichols, W. M. *J. Org. Chem.* **1975**, *40*, 2596.
16. Potts, K. T.; Sorm, M. *J. Org. Chem.* **1971**, *36*, 8.
17. Gotthardt, H.; Riegels, M. *Chem. Ber.* **1988**, *121*, 1143. (b) Gotthardt, H.; Riegels, M. *Chem. Ber.* **1987**, *120*, 445. (c) Gotthardt, H.; Riegels, M. *Chem. Ber.* **1986**, *119*, 1315.
18. Gotthardt, H.; Schenk. K. H. *Chem. Ber.* **1985**, *118*, 4567.
19. Padwa, A.; Coats, S. J.; Semones, M. A. *Tetrahedron Lett.* **1993**, *34*, 5405.
20. Potts, K. T.; Dery, M. O.; Kullnig, R. K. *J. Chem. Soc.; Chem. Commun.* **1987**, 840.
21. Padwa, A.; Harring, S. R.; Semones, M. A. *J. Org. Chem.* **1995**, *60*, 2952.
22. Padwa, A.; Semones, M. A. *Tetrahedron Lett.* **1996**, *37*, 335.
23. (a) Eisenhuth, W.; Renfroe, H. B.; Schmid, H. *Helv. Chim. Acta.* **1965**, *48*, 375. (b) Kozikowski, A. P.; Schmiesing, R. *Synth. Commun.* **1978**, *8*, 363.
24. Hauser, F. M.; Prasanna, S.; Combs, D. W. *J. Org. Chem.* **1983**, *48*, 1328.
25. Broom, N. J.; Sammes, P. G. *J. Chem. Soc.; Chem. Commun.* **1978**, 162.

26. (a) Kraus, G. A.; Sugimoto, H. *Tetrahedron Lett.* **1978**, *19*, 2263. (b) Li, T.; Wu, Y. *J. Am. Chem. Soc.* **1981**, *103*, 7007. (c) Morrow, G. W.; Swenton, J. S.; Filipi, J. A.; Wolgemuth, R. L. *J. Org. Chem.* **1987**, *52*, 713.

27. Dodd, J. H.; Weinreb, S. M. *Tetrahedron Lett.* **1979**, *20*, 3593.

28. Swenton, J. S.; Jackson, D. K.; Narasimhan, L. *J. Am. Chem. Soc.* **1979**, *101*, 3989.

29. Biehl, E. R.; Khanapure, S. P.; Bhawal, B. M. *Tetrahedron Lett.* **1990**, *31*, 2869.

30. Bach, R. D.; Wendt, J. A.; Gauvreau, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 9921.

31. Mann, A.; Ungureanu, I.; Klotz, P.; Schoenfelder, A. *Chem. Commun.* **2001**, 958.

32. Rigby, J. H. *Synlett*, **2000**, 1.

33. Rigby, J. H.; Balasubramanian, N. *J. Org. Chem.* **1984**, *49*, 4569.

34. Rigby, J. H.; Holsworth, D. D. *Tetrahedron Lett.* **1991**, *32*, 5757.

35. Rigby, J. H.; Qabar, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 8975.

36. Rigby, J. H.; Cavezza, A.; Ahmed, G. *J. Am. Chem. Soc.* **1996**, *118*, 12848.

37. (a) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *Tetrahedron Lett.* **1999**, *40*, 2473. (b) Rigby, J. H.; Laurent, S. *J. Org. Chem.* **1999**, *64*, 1766.

38. Rigby, J. H.; Cavezza, A.; Heeg, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 3664.

39. Heydt, H.; Regitz, M. in *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A. Ed. Vol I, Wiley, New York 1984; pp 393.

40. Facklam, T.; Wagner, O.; Heydt, H, Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 314.

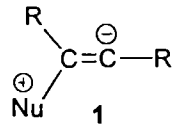
41. Bertrand, G.; Tejeda, J.; Réau, R.; Dahan, F. *J. Am. Chem. Soc.* **1993**, *115*, 7880.

42. Niecke, E.; Nieger, M.; Dombrowski, A. *Chem. Commun.* **1996**, 1705.

Novel Pyridine Catalysed Reaction of Dimethyl acetylenedicarboxylate with Aldehydes and *N*-Tosylimines

2.1 Introduction

The pronounced reactivity of activated carbon-carbon triple bond towards nucleophilic reagents has great significance in organic synthesis. The initial event in the addition of nucleophiles that contain no active hydrogen is the formation of a dipolar intermediate **1** (Figure 2.1), which subsequently undergoes rearrangement, cyclisation or addition reaction resulting in a stabilized product.[1]



1

R = CO_2R; CN; CF_3; SO_2R

Nu = Nucleophile

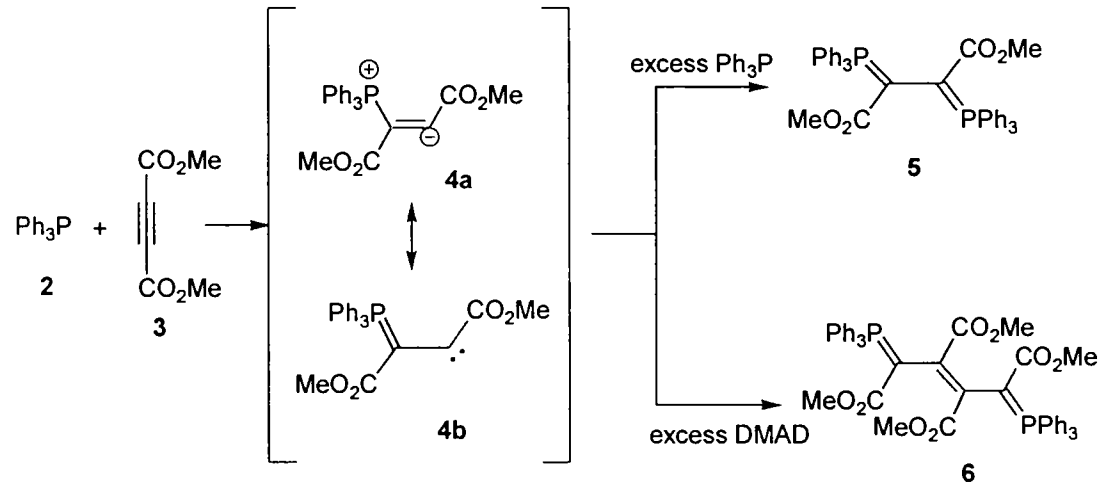
Figure 2.1

A variety of nucleophiles such as triphenyl phosphine, amines, enamines, dimethylsulfoxide, phosphoranes, isocyanides, pyridine *etc.* can invoke the dipolar intermediate formation. A brief account of these reactions is given in the following sections.

2.2 Addition of Phosphorous Compounds

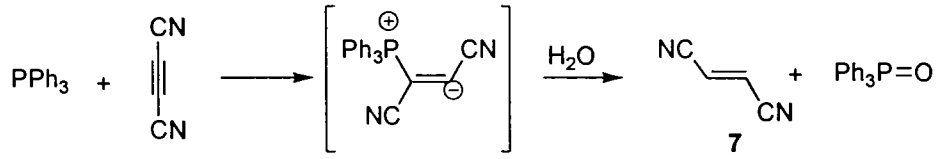
The reactivity of triphenylphosphine towards various activated acetylenes was studied in detail by Tebby and co-workers. It was shown that triphenyl phosphine adds to dimethyl acetylenedicarboxylate (DMAD) to form a

2:1 adduct, a dialkylidene diphosphorane **5** in quantitative yield. In the absence of excess of phophine, **6** was isolated (Scheme 2.1).[2]



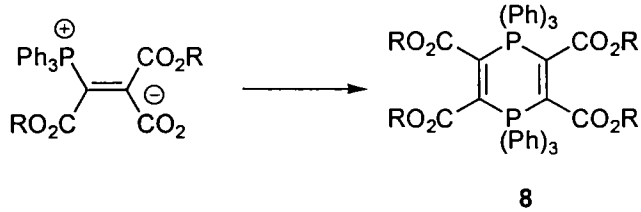
Scheme 2.1

If the reaction is carried out in a protic solvent such as water, the solvent gets added to the zwitterionic species. This is illustrated by the following reaction leading to fumaronitrile **7** and triphenylphosphine oxide (Scheme 2.2).[3]



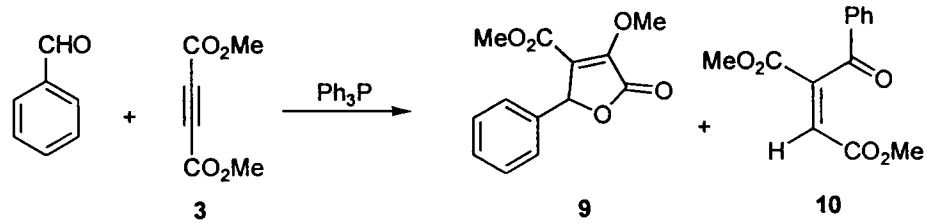
Scheme 2.2

Attempts have been made to trap the zwitterionic intermediate **4** with CO_2 in which case, a betaine is formed. Subsequent dimerization and decarboxylation gives the product **8** as illustrated in Scheme 2.3.[4]



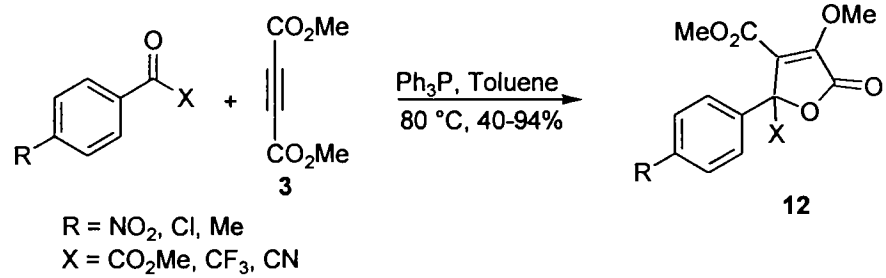
Scheme 2.3

Winterfeldt has made the interesting observation that the 1:1 intermediate derived from triphenylphosphine and DMAD can be trapped with benzaldehyde, resulting in products **9** and **10** albeit in low yields (Scheme 2.4).[5]



Scheme 2.4

Recently Nozaki has modified this reaction with activated carbonyl compounds such as α-ketoesters, α-ketonitriles *etc* as dipolarophiles. The use of catalytic amount of triphenylphosphine afforded unsaturated lactone **12** in moderate to high yields (Scheme 2.5).[6]

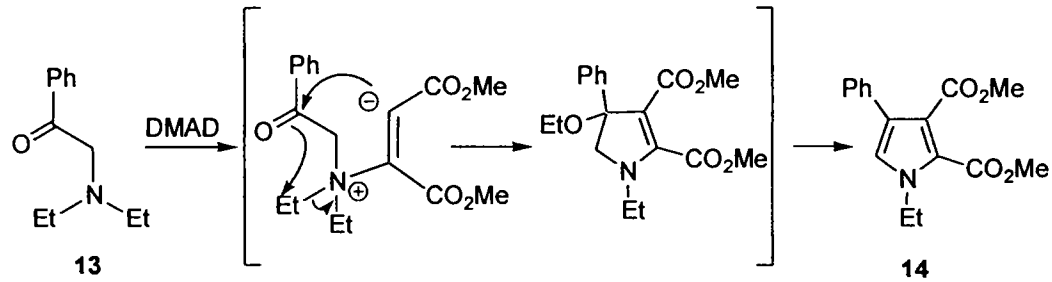


Scheme 2.5

Work in our laboratory has shown that the zwitterionic intermediate, generated from triphenylphosphine and DMAD, undergoes facile addition to 1,2- and 1,4-benzoquinones to afford highly functionalized novel unsaturated γ-spirolactones in good yields (details are given in Chapter 4, Section 4.2).

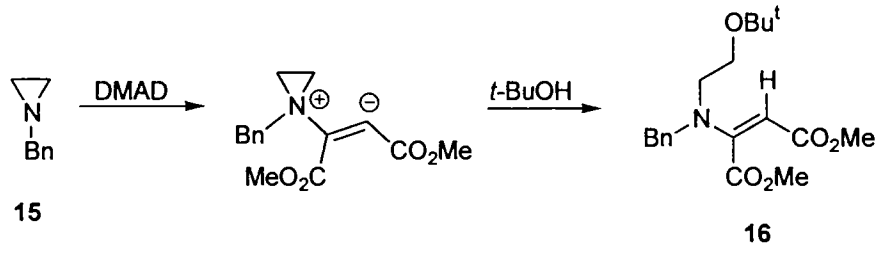
2.3 Addition of Tertiary Amines

Teritary amines are known to add to activated acetylenes. For example, ω-diethylaminoacetophenone **13**, reacts with DMAD in dimethylsulfoxide to give the pyrrole **14** (Scheme 2.6).[7]



Scheme 2.6

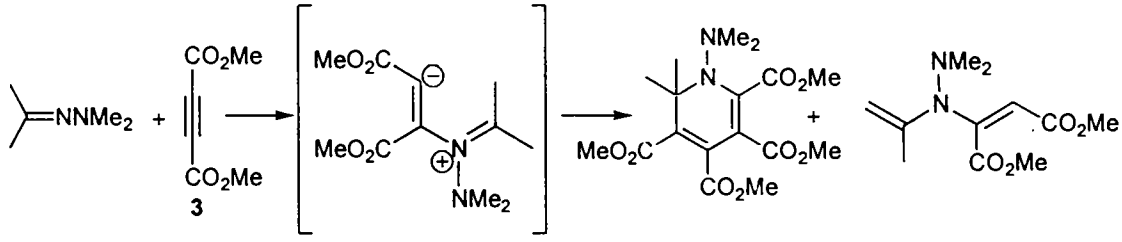
Aziridines react with acetylenic esters to give products which arise *via* either a C-N or C-C bond cleavage. N-Benzyl aziridine **15** reacts with DMAD in t-BuOH to afford the ether derivative **16** by a C-N bond cleavage (Scheme 2.7).[5]



Scheme 2.7

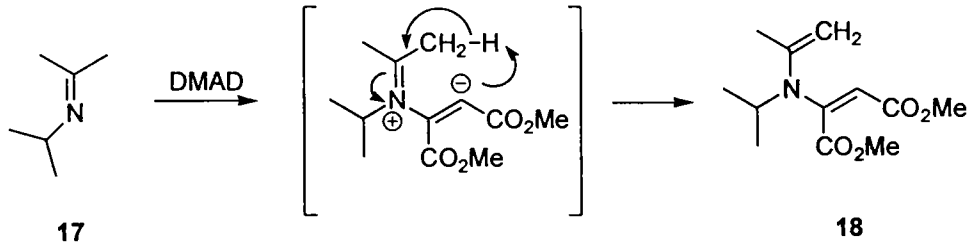
2.4 Addition of Imines

The reaction of Schiff bases and activated acetylenes has received considerable attention. The 1,4-dipole thus generated can undergo internal or external attacks and these are implicit in several synthesis of heterocycles. A typical example is given in Scheme 2.8.[8]



Scheme 2.8

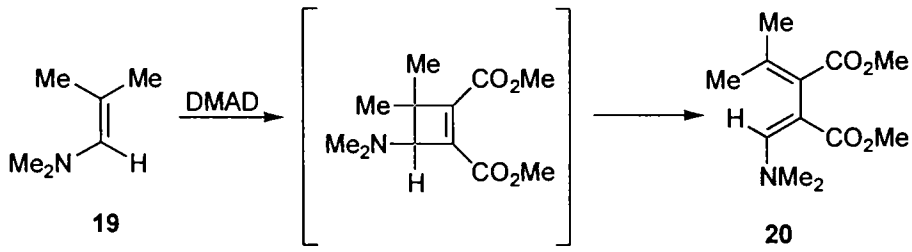
In the case of ketimine **17**, the 1,4-dipolar species generated by the addition to DMAD undergoes internal proton abstraction to give the product **18** (Scheme 2.9).[9]



Scheme 2.9

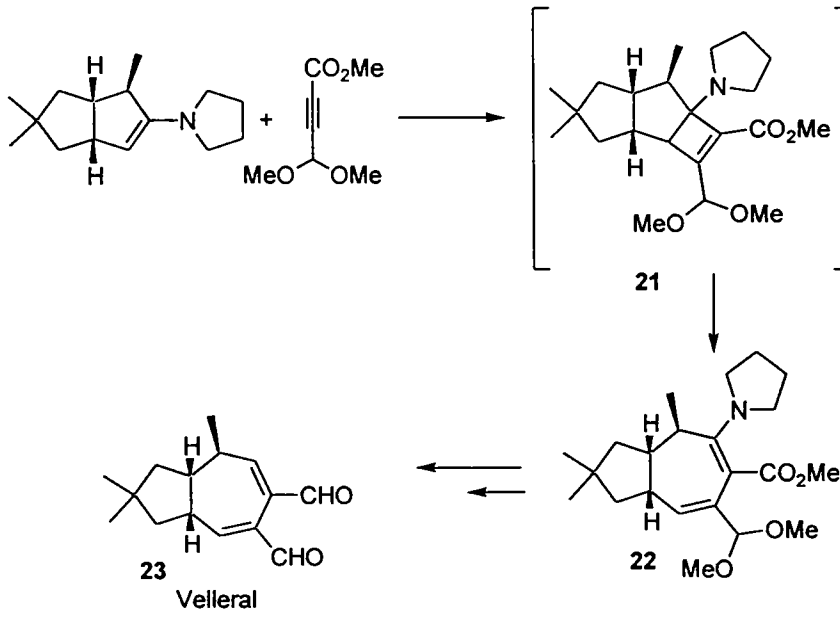
2.5 Addition of Enamines

The reaction of enamines with acetylenic esters has been investigated in detail by a number of groups.[10] In general, the 1,4-dipole generated by the addition of enamines to activated alkynes undergo [2+2] mode of addition leading to cyclobutene intermediates, which undergo ring opening, yielding dienamines. A representative example is given by the reaction of *N,N*-dimethylisobutenylamine **19** with DMAD, to form the dienamine **20** (Scheme 2.10).[11]



Scheme 2.10

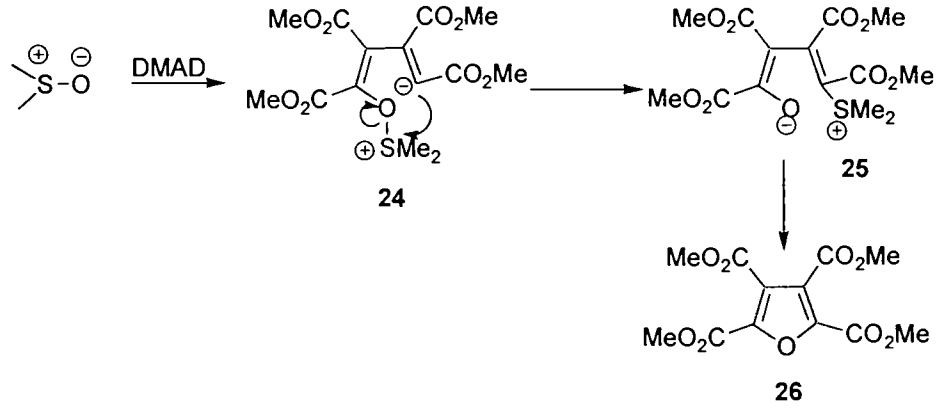
The reaction of cyclic enamines, on the other hand, gives rise to ring-enlarged, cyclic dienamines. This methodology was applied to the synthesis of the sesquiterpene fungal metabolite Velleral **23** *via* the cyclobutene intermediate **21** (Scheme 2.11).[12]



Scheme 2.11

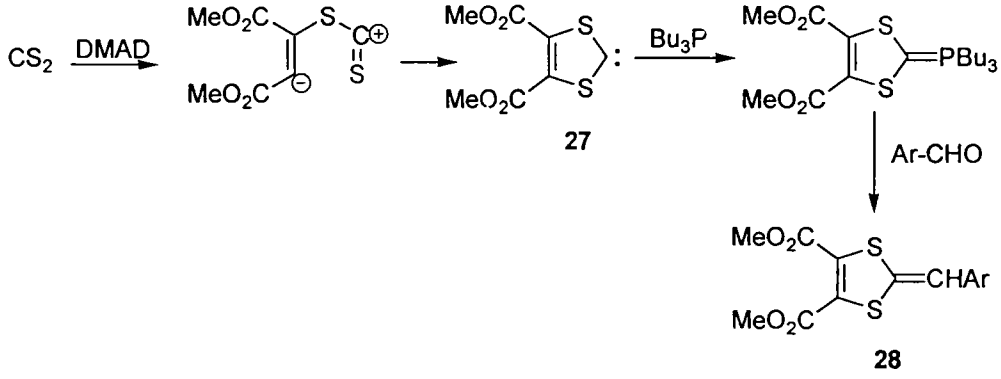
2.6 Addition of Sulphur Compounds

Winterfeldt has shown that the reaction of dimethyl sulfoxide with DMAD gives tetramethyl furan tetracarboxylate **26**, and it was suggested that this reaction may proceed through the intermediates **24** and **25** (Scheme 2.12).[13]



Scheme 2.12

The reaction of carbon disulfide with acetylenic esters gives a number of products, depending on the conditions. Thus DMAD and CS_2, in presence of aromatic aldehydes and tributylphosphine yield 2-benzylidene-1,3-dithioles **28**, presumably through a dithiocarbene intermediate **27** (Scheme 2.13).[14]

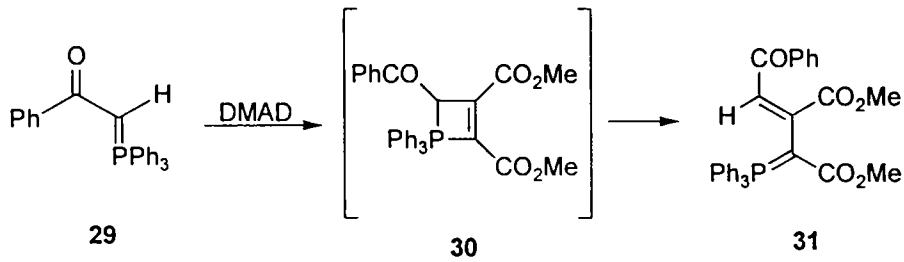


Scheme 2.13

2.7 Addition of Phosphoranes

Alkylidenephosphoranes are known to react with acetylenic esters and the products formed in these reactions are, to a large extent, determined by the nature of the solvent employed. The reaction of alkylidenetriphenylphosporane

29 with DMAD in aprotic solvents gives the ylide **31,** presumably *via* the cyclic phosphorane **30** (Scheme 2.14). [15]

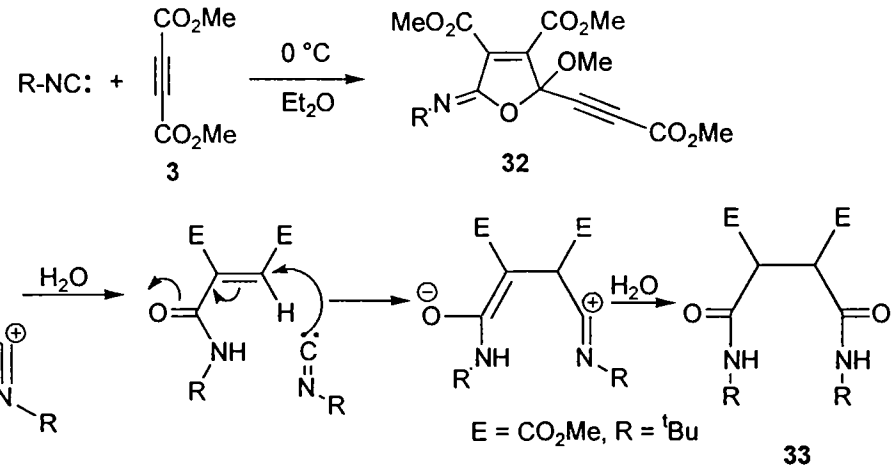


29 30 31

Scheme 2.14

2.8 Addition of Isocyanides

The reaction of nucleophilic carbenes such as isocyanide to activated acetylenes has been investigated in detail. Winterfeldt has shown that the reaction of *t*-butylisocyanide with DMAD at 0 °C in ether gave the 1:2 adduct **32**, whereas in presence of protic solvents such as water, the symmetrical product **33** was obtained (Scheme 2.15).[16]

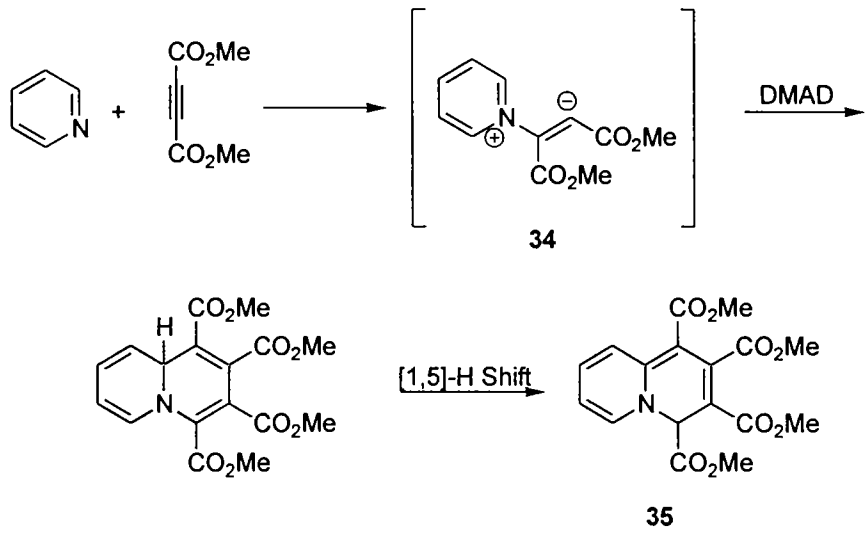


Scheme 2.15

Investigations in our laboratory have shown that the 1,3-dipolar species generated from isocyanide and DMAD can be trapped with dipolarophiles such as aldehydes and N-tosylimines resulting in the facile synthesis of aminofurans and aminopyrroles respectively (details are given in Chapter 3, Section 3.3). Application of this multicomponent reaction with 1,2- and 1,4-diones afforded highly functionalized iminolatones (details are given in Chapter 4, Section 4.2).

2.9 Addition of Pyridine

As early as 1932, Diels and Alder reacted pyridine with DMAD and obtained a 1:2 adduct,[17] whose structure was established later by the detailed investigations of Acheson and co-workers.[18] The formation of 1:2 adduct **35** was explained by a stepwise addition of pyridine to DMAD resulting in the 1,4-dipole **34** and its reaction with a second molecule of DMAD (Scheme 2.16).



Scheme 2.16

The existence of 1,4-dipole **34** was established by its interception with CO_2 to give the isomeric betaine (Figure 2.2).[19]

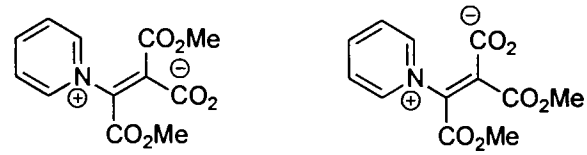
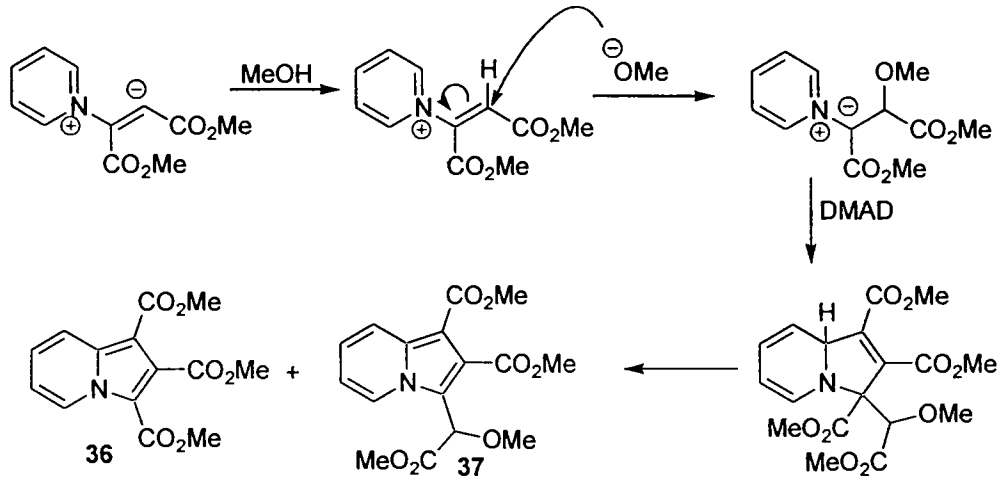


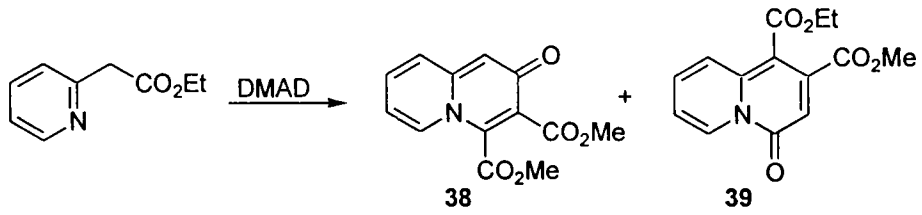
Figure 2.2

The reaction of pyridine and DMAD in methanol, afforded the products **36** and **37** presumably by the protonation of 1,4-dipole, followed by the addition of methoxide ion (Scheme 2.17).[20]



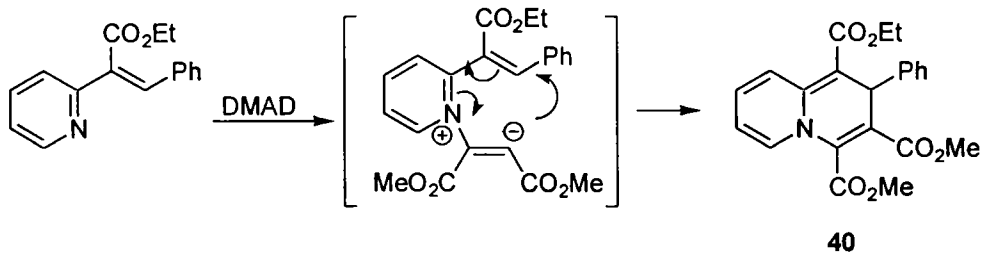
Scheme 2.17

Winterfeldt has shown that intramolecular cyclisation of the 1,4-dipole **34** to a carbonyl group can be achieved in the case of ethylpyridylacetate to give 2*H*-quinolizone **38** as the major product in polar solvents; the 4*H*-quinolizone **39** predominates in non-polar solvents (Scheme 2.18).[21]



Scheme 2.18

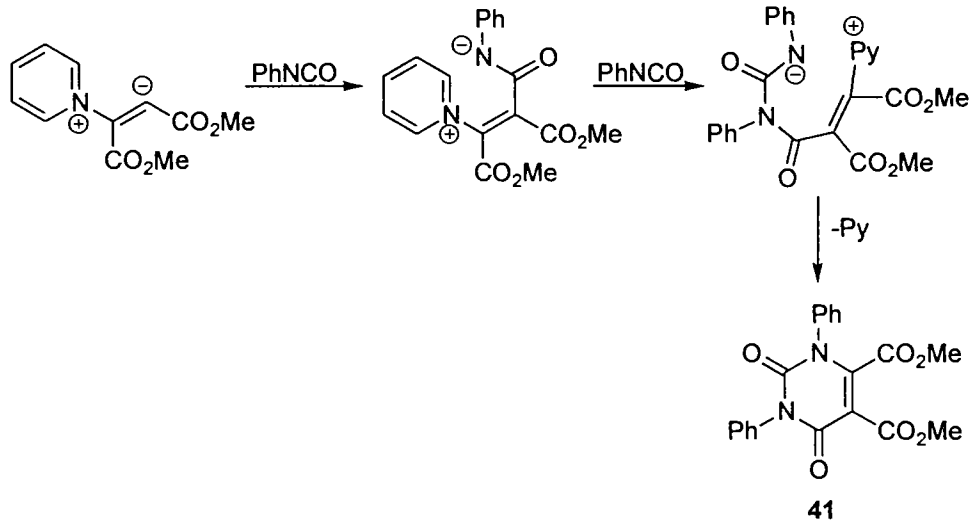
Intramolecular cyclisation to an olefinic bond resulted in the direct synthesis of 2*H*-quinolizines **40** (Scheme 2.19).[22]



Scheme 2.19

Interestingly, the reaction of pyridine and DMAD with excess of phenyisocyanate afforded pyrimidindione **41** albeit only in 25% yield. The reaction proceeds through an initial 1,5-dipole which adds another molecule of

phenyisocyanate to form a 1,7-dipole, which undergoes ring closure to a pyrimidindione **41** with elimination of pyridine (Scheme 2.20).[23]



Scheme 2.20

2.10 Statement of the problem

Against the literature background given above and in the context of our general interest in heterocyclic construction *via* dipolar cycloaddition,[24] we were intrigued by the possibilty of trapping the 1,4-dipolar species generated from pyridine and DMAD with a third component. Eventhough intramolecular addition of this 1,4-dipole to dipolarophiles are known, no sucessful intermolecular trapping with dipolarophiles has been reported. We reasoned that a reaction of pyridine and DMAD with dipolarophiles such as aldehydes and activated imines would lead to novel heterocyclic systems, following the lines of a multicomponent reaction.

On the basis of the above assumption, we have carried out a thorough investgation on the reaction of pyridine and DMAD with different dipolarophiles such as aldehydes and *N*-tosylimines. Surprisingly we observed an unusual reactivity of the 1,4-dipole from pyridine and DMAD towards dipolarophiles; the intermediate from this reaction eliminates pyridine to give substituted fumarate derivatives. The results of our investigations, highlighting the usefulness of the process are presented here.

2.11 Results and Discussion

2.11.1 Reaction of Pyridine and DMAD with Aldehydes

The aldehydes selected for the studies are given below (Figure 2.3)

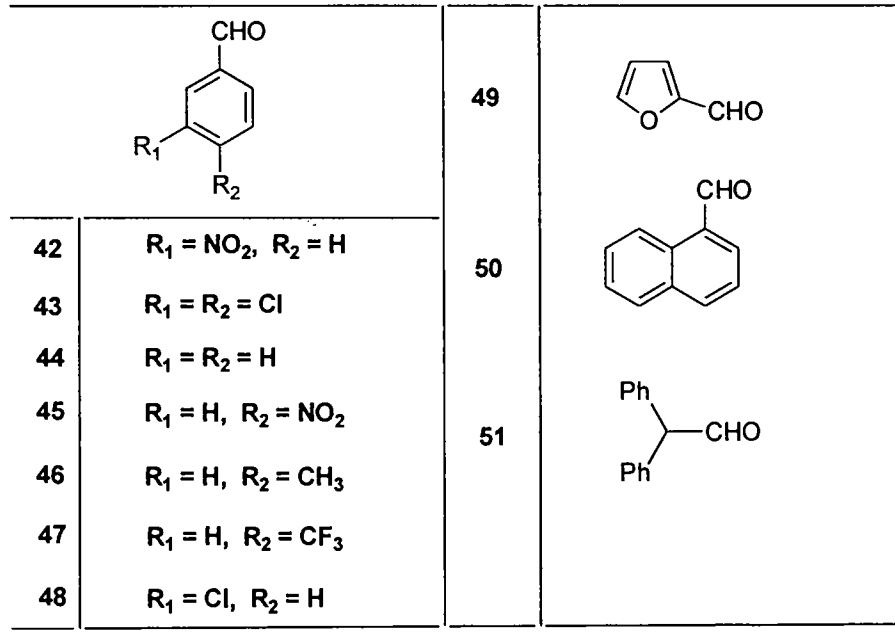
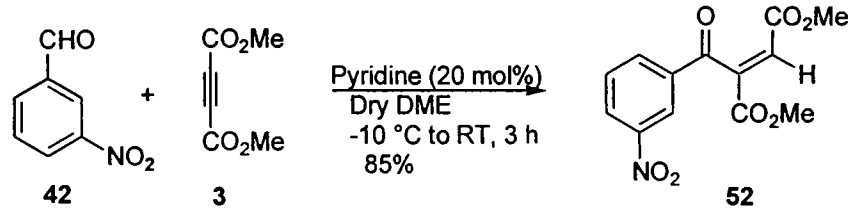


Figure 2.3

In an initial experiment, the reaction of 3-nitrobenzaldehyde with DMAD in presence of catalytic amount of pyridine (20 mol%) in dry DME at -10 °C followed by warming to RT, afforded a product which was characterised as 2-benzoylfumarate **52** in 85% yield (Scheme 2.21).[25]



Scheme 2.21

The structure of the product **52** was elucidated by spectroscopic techniques. In the IR spectrum, a sharp band at 1739 cm^{-1} was assigned to the ester carbonyl, while the absorption at 1686 cm^{-1} was attributed to the benzoyl carbonyl. The ^1H NMR spectrum displayed two methoxy groups as singlets at δ 3.68 and 3.81 and the olefinic proton was observed as a singlet at δ 7.14. In

the ^{13}C NMR spectrum, the two ester carbonyls were observed at δ 162.83 and 164.04, while the benzoyl carbonyl was discernible at δ 189.95. The two methoxy carbons were observed at δ 52.60 and 53.32. Finally the structure and the stereochemistry of the product was unambiguously established by single crystal X-ray analysis (Figure 2.4).

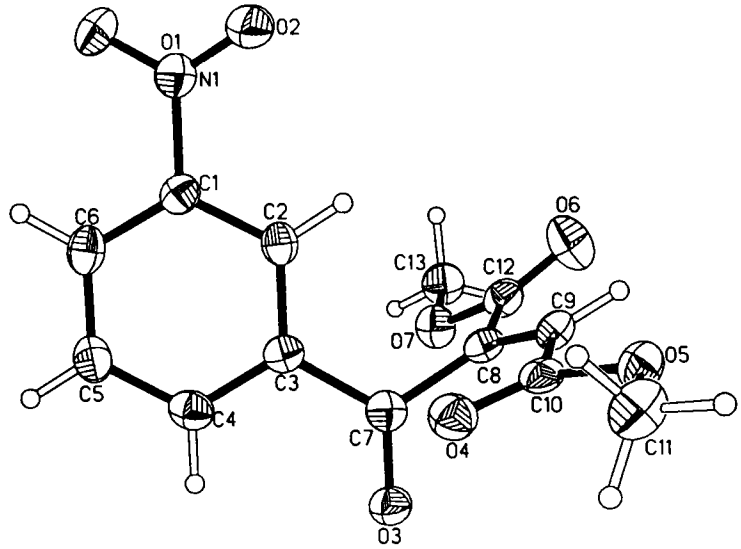


Figure 2.4 X-ray crystal structure of 52

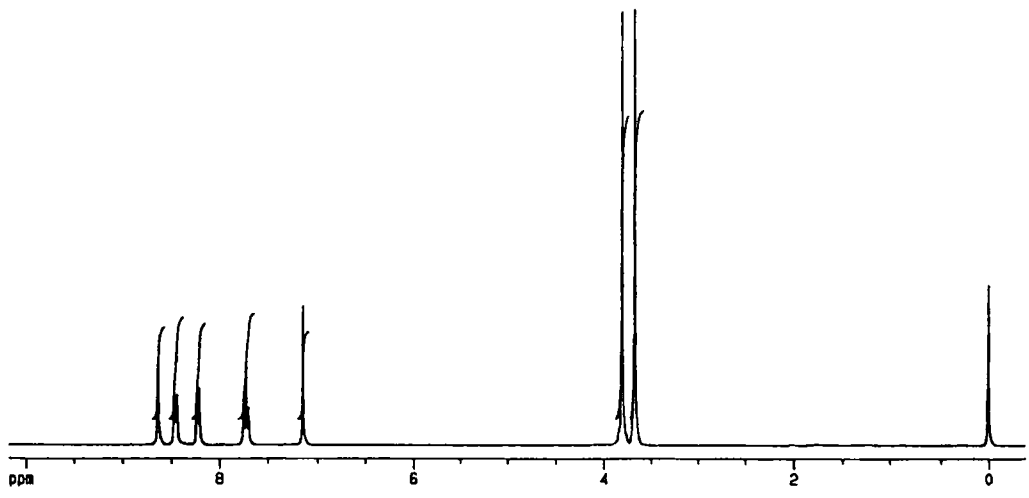


Figure 2.5 ^{1}H NMR of 52

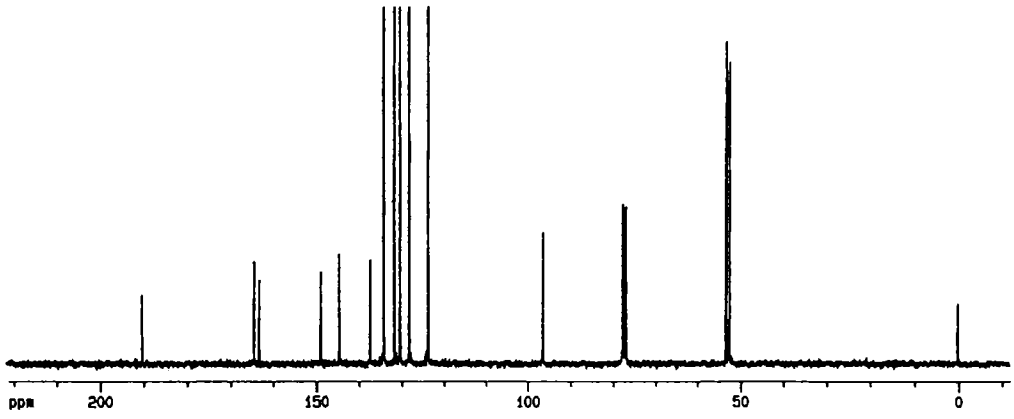
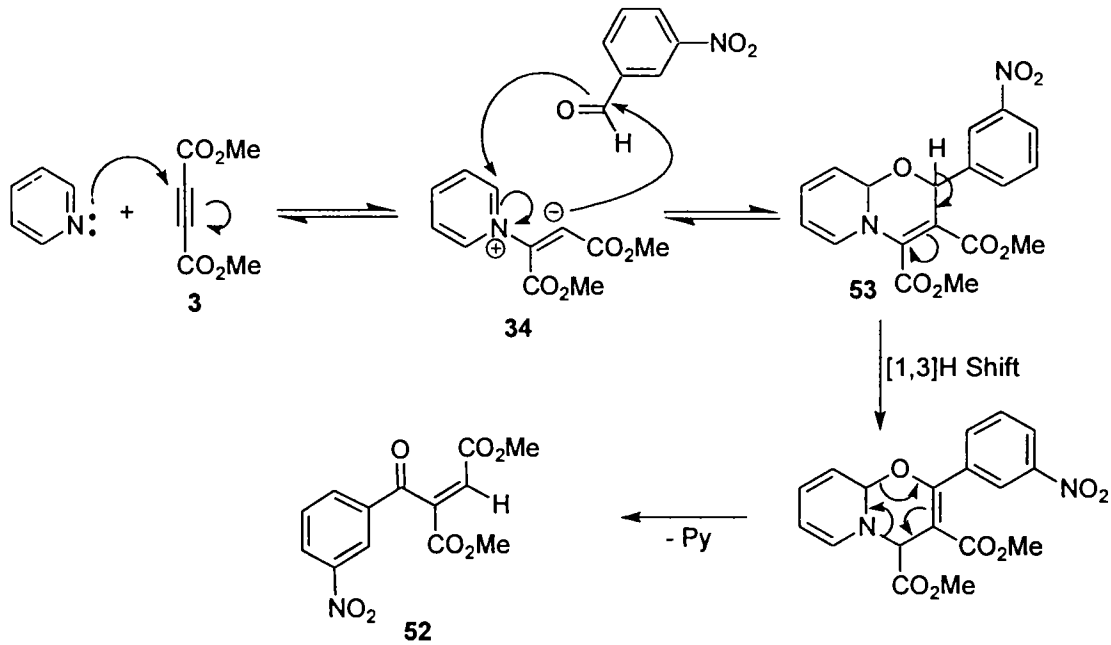


Figure 2.6 ^{13}C NMR of 52

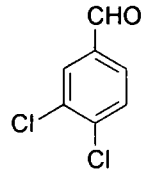
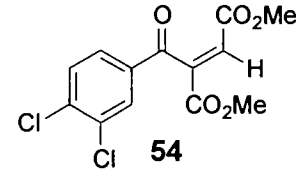
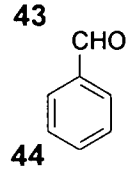
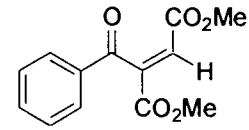
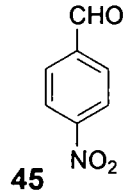
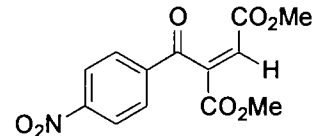
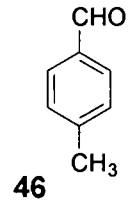
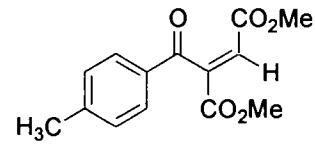
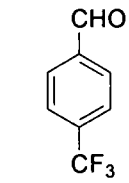
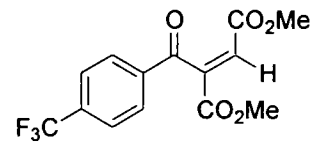
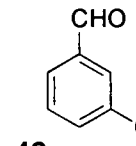
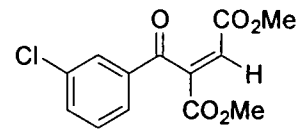
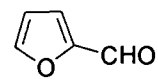
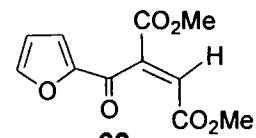
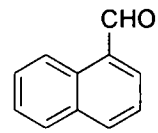
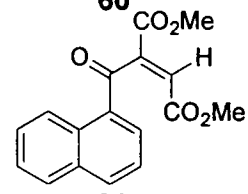
Mechanistically, the reaction may be rationalised to involve the initial addition of pyridine to DMAD to form the 1,4-dipole **34**, and the addition of the latter to the aldehyde carbonyl, yielding the [4+2] cycloadduct **53**. The latter then undergoes a [1,3] H shift followed by the elimination of pyridine, resulting in the formation of 2-benzoyl fumarate **52** (Scheme 2.22).



Scheme 2.22

The reaction was found to be generally applicable to aromatic aldehydes containing both electron withdrawing and electron donating groups, affording benzoylfumarates in moderate to excellent yields (Table 2.1).

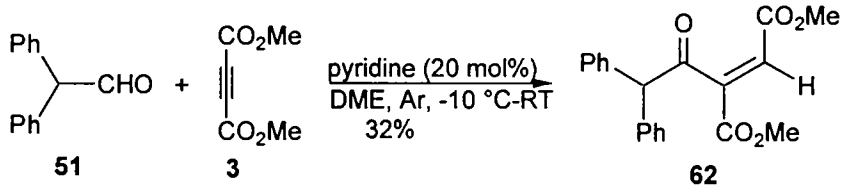
Table 2.1

Entry	Aldehyde	Product	Yield (%) *
1	 **43**	 **54**	84
2	 **44**	 **55**	44
3	 **45**	 **56**	72
4	 **46**	 **57**	43
5	 **47**	 **58**	84
6	 **48**	 **59**	66
7	 **49**	 **60**	61
8	 **50**	 **61**	46

Reaction conditions: pyridine (20 mol%), DME, Argon, -10 °C - RT, 3 h. * = isolated yield

In all cases the compounds were completely characterised and their structure established by spectroscopic methods. The benzoylfumarates **54-61**, showed characteristic carbomethoxy carbonyls both in the IR and ^{13}C NMR spectra. All other spectroscopic data were also in good agreement with the assigned structure.

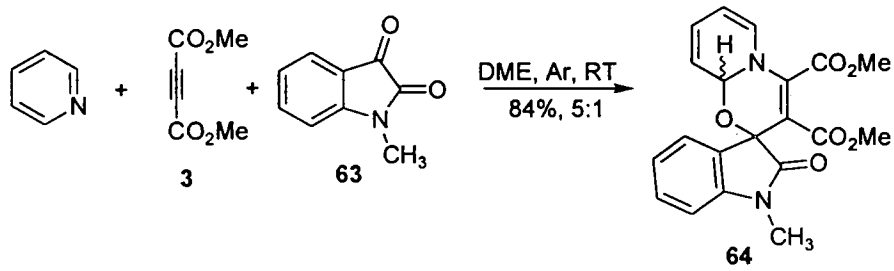
Diphenylacetaldehyde **51**, on reaction with dimethyl acetylenedicarboxylate in presence of catalytic amount of pyridine in DME at -10 °C and then warming to RT afforded the fumarate **62** in 32% yield (Scheme 2.23).



Scheme 2.23

The IR spectrum of **62** showed ester carbonyls at 1738 cm^{-1} and the acetyl carbonyl at 1632 cm^{-1}. In ^{1}H NMR spectrum, the carbomethoxy groups resonated as singlets at δ 3.71 and 3.84; the olefinic and the benzylic protons were observed as singlets at δ 6.63 and 6.36 respectively. In ^{13}C NMR spectrum, the ester carbonyls were observed at δ 162.33 and 163.75 and the acetyl carbonyl was discernible at δ 191.37. All other signals were in good agreement with the assigned structure.

With a view to establish the intermediacy of six membered cycloadduct in these reactions we explored the possibility of the three component reaction of pyridine and dimethyl acetylenedicarboxylate with *N*-substiuted isatins. In our initial experiment, the reaction of pyridine and DMAD with *N*-methyl isatin **63** in DME at room temperature for 6 h afforded the spiro pyrido[2,1-b][1,3]oxazino derivative **64** as an inseparable diastereomeric mixture (5:1) in 84 % yield (Scheme 2.24).

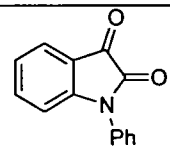
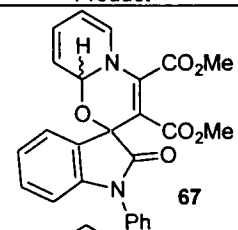
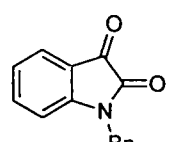
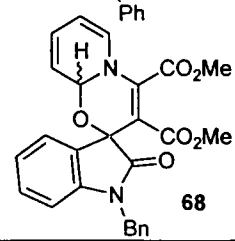


Scheme 2.24

The product was characterised by spectroscopic methods. The diastereomeric ratio (5:1) of the mixture was determined from ^{1}H NMR. In the IR spectrum, the ester carbonyls were observed at 1742 and 1721 cm^{-1} while the amide carbonyl was seen at 1613 cm^{-1}. In ^{1}H NMR spectrum, the carbomethoxy groups displayed singlets at δ 3.43 and 3.92 and the *N*-methyl group was discernible at δ3.19 as a singlet. The ring junction proton resonated as a doublet at δ6.36. In ^{13}C NMR spectrum, ester carbonyls were observed at δ 162.96 and 163.29 and the amide carbonyl at δ 173.63. The characteristic signal due to spiro carbon was discernible at δ 78.54 and the *N*-methyl carbon was seen at δ 25.93.

The reaction was found to be applicable to other substituted isatins such as **65** and **66**, resulting in spiro pyrido[2,1-b][1,3]oxazino derivatives **67** and **68** respectively as inseparable diastereomeric mixtures in excellent yields (Table 2.2).

Table 2.2

Entry	Isatin	Product	Ratio	Yield (%)
1.	 **65**	 **67**	7:1	90
2.	 **66**	 **68**	5:1	88

Reaction conditions: DME, Ar, RT, 6 h. * = isolated yield

The compounds were characterised and the structure established by spectroscopic techniques. The adducts **67** and **68** showed characteristic peaks for ester carbonyl in both IR and ^{13}C NMR and the signal for spiro carbon in ^{13}C NMR.

2.11.2 Reaction of Pyridine and DMAD with *N*-tosylimines

Prompted by the success in developing a synthesis of benzoylfumarate derivatives by the reaction of aldehydes and the 1,4-dipoles generated from pyridine and DMAD (*vide supra*), we reasoned that a similar reaction would occur with *N*-tosylimines to afford highly substituted 1-azadienes.

The *N*-tosylimines selected for our study are shown in Figure 2.7

Ar—CH=N—Ts

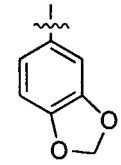
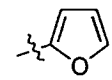
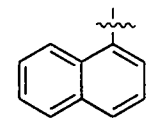
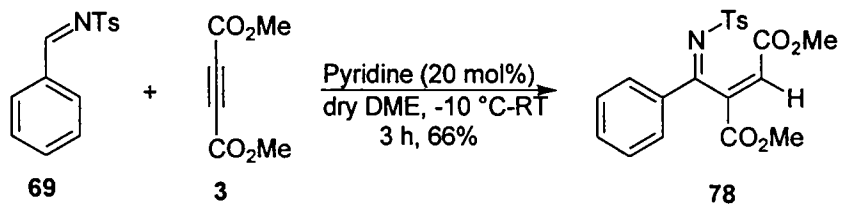
69	Ar = C_6H_5		
70	Ar = 4-ClC_6H_4	**75**	Ar = 
71	Ar = 4-MeC_6H_4		
72	Ar = 4-$OMeC_6H_4$	**76**	Ar = 
73	Ar = 4-$CF_3C_6H_4$		
74	Ar = 2,4-$(OMe)_2C_6H_3$	**77**	Ar = 

Figure 2.7

In a pilot experiment, reaction of *N*-tosylimine **69** with DMAD in presence of catalytic amount of pyridine (20 mol%) in dry DME at -10 °C and then warming to RT, led to the facile synthesis of highly substituted 1-azadiene **78** (Scheme 2.25).



69 **3** **78**

Scheme 2.25

The structure of the product **78** was elucidated by spectroscopic analysis. In the IR spectrum, strong absorption at 1748 and 1719 cm^{-1} were attributed to

ester carbonyls, while absorption at 1580 cm^{-1} was assigned to imino group. In the ^1H NMR spectrum, the two methoxy groups were observed as singlets at δ 3.59 and 3.84. The olefinic proton appeared as a singlet at δ 7.18 and the methyl protons of *p*-toluenesulfonyl group displayed a singlet at δ 2.44. In the ^{13}C NMR spectrum, signals due to the ester carbonyls were observed at δ 162.69 and 163.67, while the imino carbon signal was seen at δ 172.55. The methoxy carbons were discernible at δ 52.29 and 53.25. All other signals were in good agreement with the assigned structure. Finally the stereochemistry of the product was unambiguously established by single crystal X-ray analysis (Figure 2.8).

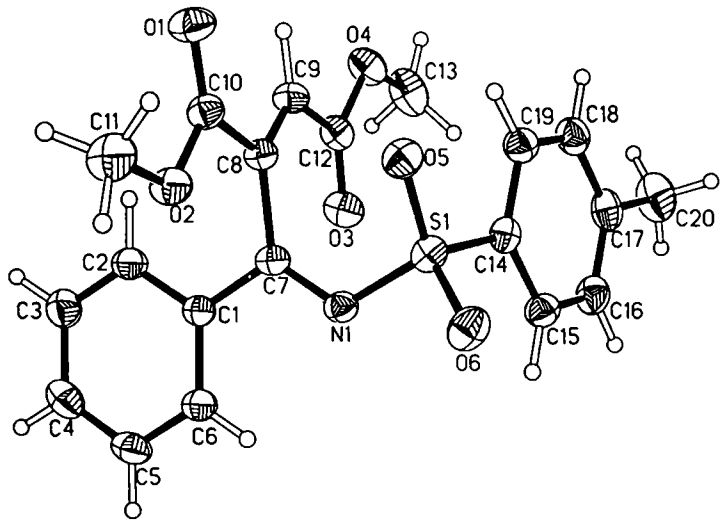


Figure 2.8 X-ray crystal structure of 78

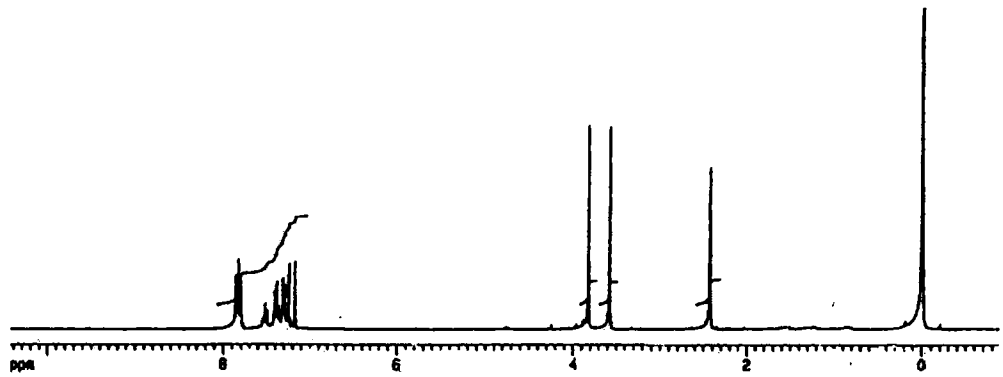


Figure 2.9 ^1H NMR of 78

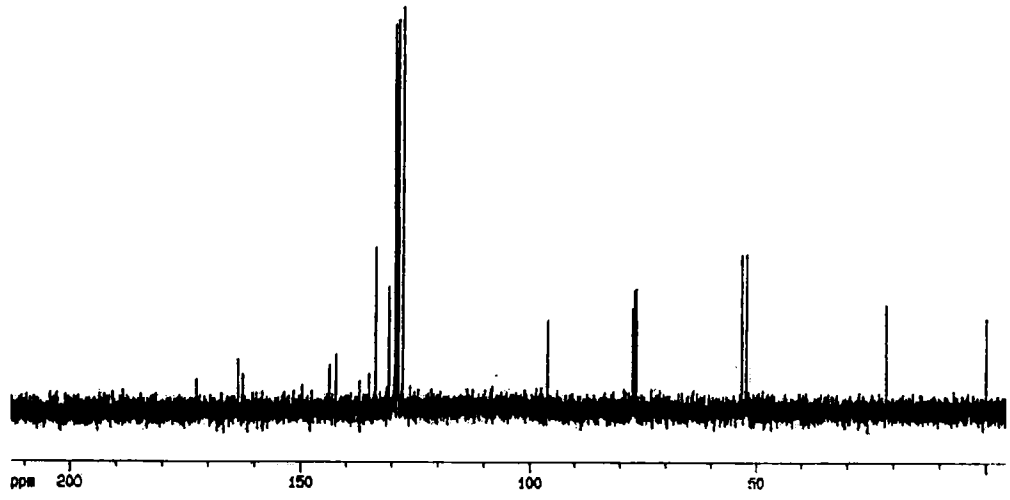
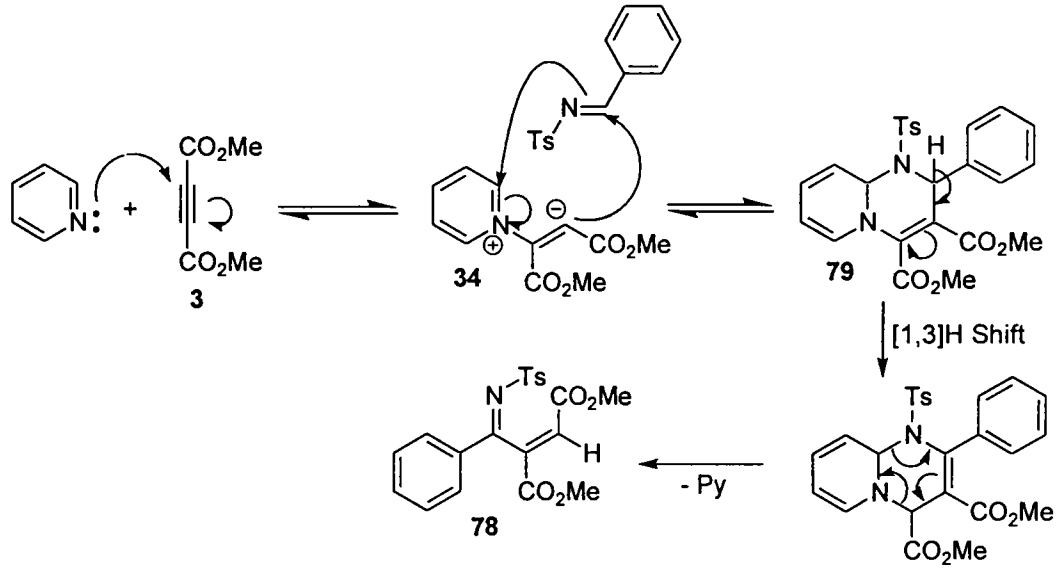


Figure 2.10 ^{13}C NMR of 78

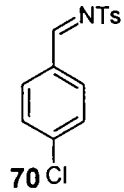
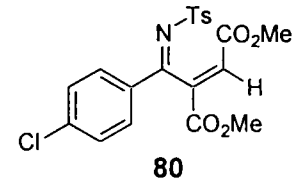
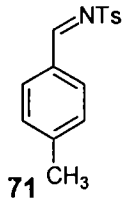
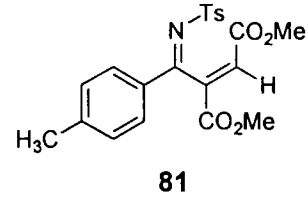
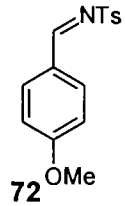
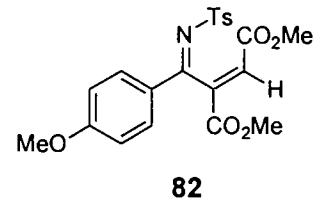
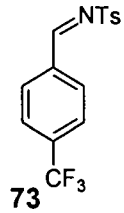
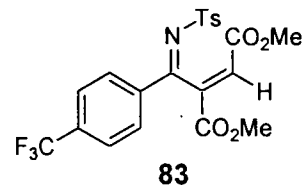
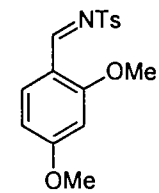
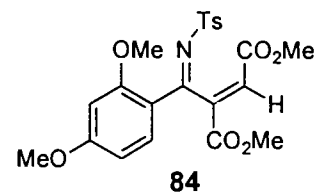
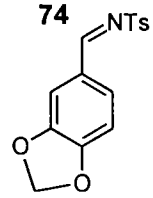
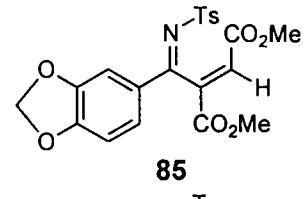
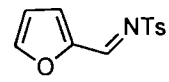
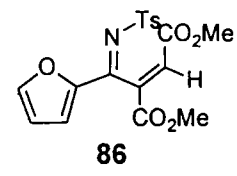
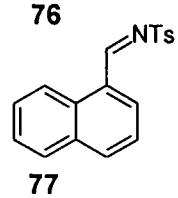
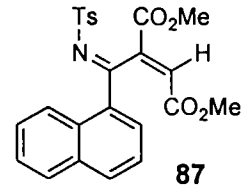
Mechanistically, the reaction can be considered to proceed through a six membered cycloadduct **79**, analogous to **53** invoked in the reaction of aldehydes with the 1,4-dipole derived fom pyridine and DMAD. This can undergo a [1,3] H shift followed by the elimination of pyridine to give the product (Scheme 2.26).



Scheme 2.26

The reaction is applicable to aromatic *N*-tosylimines containing either electron withdrawing or electron donating groups, affording 1-azadienes in moderate to excellent yields (Table 2.3).

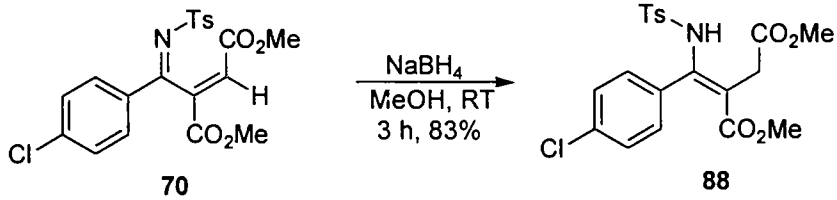
Table 2.3

Entry	N-tosylimines	Product	Yield (%) *
1	 **70**	 **80**	86
2	 **71**	 **81**	65
3	 **72**	 **82**	70
4	 **73**	 **83**	76
5	 **74**	 **84**	52
6	 **75**	 **85**	78
7	 **76**	 **86**	50
8	 **77**	 **87**	77

Reaction conditions: pyridine (20 mol%), DME, -10 °C - RT, 3 h. * = isolated yield

In all cases, the compounds were completely characterised and their structure established by spectroscopic methods. The azadienes **80-87**, showed characteristic carbomethoxy carbonyls both in the IR and ^{13}C NMR spectra. All other spectroscopic data were also in good agreement with the assigned structure.

Interestingly, it was found that $NaBH_4$ reduction of 1-azadiene **70** in dry MeOH at room temperature afforded the novel enaminodiester **88** (Scheme 2.27). It may be noted that enaminoesters are synthetic precursors of saturated amino acids.[26]



70 **88**

Scheme 2.27

The product **88** was characterised by spectroscopic techniques. In the IR spectrum, strong absorption at 3117 cm^{-1}, was due to amine functionality, while the absorption at 1742 cm^{-1} was attributable to ester carbonyls. In ^1H NMR, the NH proton was observed as a singlet at δ 11.52 (exchangable with D_2O). The methoxy groups displayed singlets at δ 3.52 and 3.77 and the methylene protons displayed a singlet at δ 2.89. In ^{13}C NMR spectrum, the ester carbonyls were observed at δ 169.13 and 171.47, while the methylene carbon was discernible at δ 33.59. All other signals were also in good agreement with the assigned structure.

2.12 Conclusion

In conclusion, we have uncovered a novel reaction of the 1,4-dipole derived from pyridine and DMAD with aldehydes, resulting in a facile synthesis of 2-benzoylfumarates; with N-tosylimines as dipolarophiles, the reaction afforded highly functionalised 1-azadienes. Interestingly, the reaction of this 1,4-dipole with isatins resulted in the synthesis of novel spiro pyrido[2,1-

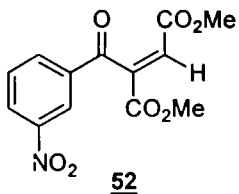
b][1,3]oxazino dervatives *via* 1,4-dipolar cycloaddition. It is noteworthy that pyrido[2,1-b][1,3]oxazino derivatives manifest a number of important and therapeutically useful biological activities.[27]

2.13 Experimental Details

General: Melting points were recorded on a Buchi melting point apparatus and are uncorrected. NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz respectively on a Bruker DPX-300 MHz NMR spectrometer. Chemical shifts are reported (δ) relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constant (J) is reported in Hertz (Hz). Mass spectra were recorded under EI/HRMS (at 5000 resolution) using Auto Spec. M mass spectrometer. IR spectra were recorded on a Nicolet Impact 400D FT-IR spectrophotometer. Elemental analyses were performed on a Perkin Elmer-2400 Elemetal Analyzer. Dimethyl acetylenedicarboxylate (DMAD) was purchased from Aldrich Chemical Co. and was used without further purification. N-tosylimines **69-77** were prepared according to a reported procedure.[28] Commercial grade solvents were distilled prior to use. Analytical thin layer chromatography was performed on glass plates coated with silica gel containing calcium sulfate binder. Gravity column was performed using 100-200 mesh silica gel and mixtures of hexane-ethylacetate were used for elution.

Dimethyl 2-(3-nitrobenzoyl)-2-butenedioate 52

A solution of 3-nitrobenzaldehyde **42** (75 mg, 0.53 mmol) and DMAD (80 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at room temperature. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **52** as a colourless crystalline solid (133 mg, 85%).



52

Mp: 97-99 °C.

IR (KBr) ν_{max}: 2959, 1719 (C=O), 1686 (C=O), 1533, 1440, 1261, 1202, 1016 cm^{-1}.

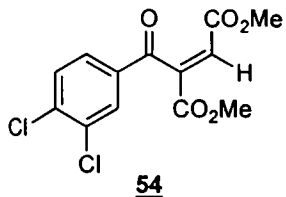
^{1}H NMR: δ 8.63 (s, 1H), 8.45 (d, J = 8.10 Hz, 1H), 8.21 (d, J = 7.74 Hz, 1H), 7.72 (t, J = 7.92 Hz, 1H), 7.14 (s, 1H), 3.81 (s, 3H), 3.68 (s, 3H).

^{13}C NMR: δ 189.95, 164.04, 162.83, 148.59, 144.22, 136.97, 133.82, 131.32, 130.00, 127.82, 123.33, 53.33, 52.60.

Anal. Calcd. for $C_{13}H_{11}NO_7$: C, 53.25; H, 3.78; N, 4.78. Found: C, 53.40; H, 3.79; N, 4.91.

Dimethyl 2-(3,4-dichlorobenzoyl)-2-butenedioate 54

A solution of 3,4-dichlorobenzaldehyde **43** (185 mg, 1.05 mmol) and DMAD (150 mg, 1.05 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **54** as a colourless crystalline solid (260 mg, 84%).



54

Mp: 68-70 °C.

IR (KBr) ν_{max}: 2955, 1721, 1681, 1438, 1249, 1196 cm^{-1}.

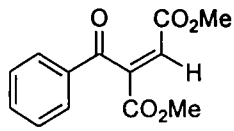
^{1}H NMR: δ 7.93 (s, 1H), 7.66 (d, J = 8.10 Hz, 1H), 7.56 (d, J =8.28 Hz, 1H), 7.09 (s, 1H), 3.80 (s, 3H), 3.68 (s, 3H).

^{13}C NMR: δ 189.78, 164.01, 163.01, 144.46, 138.52, 135.26, 133.72, 131.06, 131.00, 130.39, 127.56, 53.34, 52.62.

Anal. Calcd. for $C_{13}H_{10}Cl_2O_5$: C, 49.24; H, 3.18; Found C, 49.49, H, 3.36.

Dimethyl 2-(benzoyl)-2-butenedioate 55

A solution of benzaldehyde **44** (56 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **55** as a colourless crystalline solid (55 mg, 44%).



55

Mp: 80-82 °C.

IR (KBr) ν_{max}: 2957, 1726, 1685, 1590, 1420, 1255 cm^{-1}.

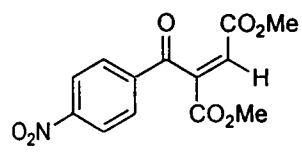
^{1}H NMR: δ 7.86 (d, J = 7.77 Hz, 2H), 7.61-7.45 (m, 3H), 7.08 (s, 1H), 3.78 (s, 3H), 3.63 (s, 3H).

^{13}C NMR: δ 191.74, 164.00, 163.46, 145.26, 135.63, 133.73, 130.36, 129.61, 128.71, 128.66, 104.78, 53.05, 52.33.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87; Found C, 63.22; H, 4.88.

Dimethyl 2-(4-nitrobenzoyl)-2-butenedioate 56

A solution of 4-nitrobenzaldehyde **45** (80 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **56** as a colourless crystalline solid (110 mg, 72%).



56

Mp: 115-117 °C.

IR (KBr) ν_{max}: 2959, 1732, 1686, 1520, 1348, 1275, 1202 cm^{-1}.

^{1}H NMR: δ 8.32 (d, J = 8.38 Hz, 2H), 8.02 (d, J = 8.41 Hz, 2H), 7.12 (s, 1H), 3.81 (s, 3H), 3.67 (s, 3H).

^{13}C NMR: δ 190.43, 164.06, 162.88, 150.70, 144.53, 139.92, 131.29, 129.56, 124.07, 119.83, 104.82, 53.39, 52.69.

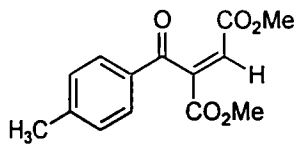
Anal. Calcd. for $C_{13}H_{11}NO_7$: C, 53.25; H, 3.78; N, 4.78; Found C, 53.46; H, 4.13; N 4.98.

Dimethyl 2-(4-methylbenzoyl)-2-butenedioate 57

A solution of 4-methylbenzaldehyde **46** (80 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL)under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave 57 as a colourless crystalline solid (60 mg, 43%).

Mp: 85-87 °C.

IR (KBr) ν_{max}: 2955, 1728, 1670, 1600, 1431, 1344, 1263 cm^{-1}.



57

^{1}H NMR: δ 7.75 (d, J = 8.10 Hz, 2H), 7.26 (d, J = 7.92 Hz, 2H), 7.05 (s, 1H), 3.76 (s, 3H), 3.62 (s, 3H), 2.41 (s, 3H).

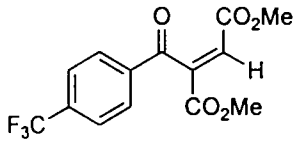
^{13}C NMR: δ 191.31, 163.98, 163.51, 145.31, 144.61, 133.24, 130.07, 129.45, 128.75, 104.25, 53.03, 52.24, 21.75.

HRMS (EI) for $C_{14}H_{14}O_5$, Calcd. 262.0841; Found 262.0831.

Dimethyl 2-(4-trifluromethylbenzoyl)-2-butenedioate 58

A solution of 4-trifluoromethylbenzaldehyde **47** (92 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using

hexane-ethylacetate (80:20) gave **58** as a colourless crystalline solid (140 mg, 84%).



58

Mp: 52-54 °C.

IR (KBr) ν_{max}: 2956, 1725, 1682, 1502, 1437, 1408 1298 cm^{-1}.

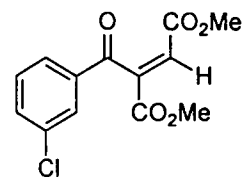
^{1}H NMR: δ 7.98 (d, J = 7.92 Hz, 2H), 7.74 (d, J = 7.94 Hz, 2H), 7.11 (s, 1H), 3.79 (s, 3H), 3.66 (s, 3H).

^{13}C NMR: δ 190.92, 164.01, 163.05, 144.74, 138.19, 134.70, 130.95, 129.45, 128.89, 125.87, 125.84, 121.67, 53.25, 52.52.

Anal. Calcd. for $C_{14}H_{11}F_3O_5$: C, 53.17; H, 3.51; Found C, 53.32; H, 3.71.

Dimethyl 2-(3-chlorobenzoyl)-2-butenedioate 59

A solution of 3-chlorobenzaldehyde **48** (74 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **59** as a colourless crystalline solid (98 mg, 66%).



59

Mp: 75-77 °C.

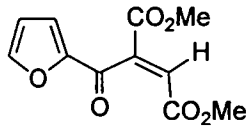
IR (KBr) ν_{max}: 2955, 1730, 1675, 1540, 1420, 1255 cm^{-1}.

^{1}H NMR: δ 7.84 (s, 1H), 7.71 (d, J = 7.48 Hz, 1H), 7.55 (d, J = 7.56 Hz, 1H), 7.41 (t, J = 7.73 Hz, 1H), 7.08 (s, 1H), 3.79 (s, 3H), 3.65 (s, 3H).

^{13}C NMR: δ 190.51, 163.87, 163.03, 144.60, 137.07, 135.07, 133.58, 130.69, 130.69, 130.02, 128.34, 126.69, 53.13, 52.38.

Dimethyl 2-(furyl)-2-butenedioate 60

A solution of furfural **49** (51 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **60** as a colourless crystalline solid (76 mg, 61%).



60

Mp: 98-100 °C.

IR (KBr) ν_{max}: 2952, 1725, 1653, 1467, 1394, 1275, 1215, 1192 cm^{-1}.

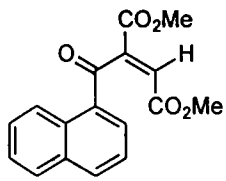
^{1}H NMR: δ 7.59 (s, 1H), 7.20 (d, J = 3.12 Hz, 1H), 7.04 (s, 1H), 6.57 (d, J = 1.66 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H).

^{13}C NMR: δ 179.27, 163.98, 163.23, 152.08, 147.06, 143.51, 131.05, 118.23, 112.68, 53.17, 52.46.

Anal. Calcd. for $C_{11}H_{10}O_6$: C, 55.47; H, 4.23; Found C, 55.80; H, 4.45.

Dimethyl 2-(napthoyl)-2-butenedioate 61

A solution of 1-napthaldehyde **50** (82 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **61** as a colourless crystalline solid (73 mg, 46%).



61

Mp: 134-136 °C.

IR (KBr) ν_{max}: 2948, 1728, 1667, 1506, 1580, 1438, 1276, 1095 cm^{-1}.

^{1}H NMR: δ 9.19 (d, J = 8.63 Hz, 1H), 8.01 (d, J = 8.15 Hz, 1H), 7.85 (d, J = 8.02 Hz, 1H), 7.77 (d, J = 6.79 Hz, 1H), 7.67 (t, J = 7.43 Hz, 1H), 7.52 (t, J = 7.00 Hz, 1H), 7.43 (t,

J = 7.70 Hz, 1H), 7.04 (s, 1H), 3.76 (s, 1H), 3.52 (s, 3H).

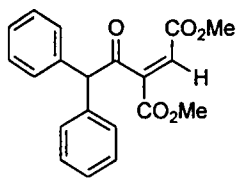
^{13}C NMR: δ 193.14, 164.19, 163.94, 146.35, 134.68, 134.01, 131.86, 131.03, 130.77, 129.51, 128.88, 128.40, 126.77, 126.33, 124.14, 53.17, 52.36.

HRMS (EI) for $C_{17}H_{14}O_5$, Calcd. 298.0841; Found 298.0830.

Dimethyl 2-(diphenylacetyl)-2-butenedioate 62

A solution of diphenylacetaldehyde **51** (104 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **62** as a yellow viscous oil (56 mg, 32%).

IR (KBr) ν_{max}: 2956, 1738, 1632, 1445, 1270, 1183, 1033, 958 cm^{-1}.



62

^{1}H NMR: δ 7.47 (d, J = 8.24 Hz, 2H), 7.35-7.24 (m, 8H), 6.63 (s, 1H), 6.36 (s, 1H), 3.84 (s, 3H), 3.71 (s, 3H).

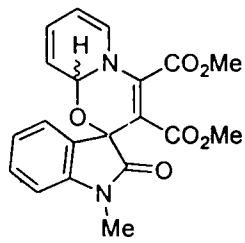
^{13}C NMR: δ 191.37, 163.75, 162.33, 151.22, 140.75, 139.31, 136.38, 130.22, 128.47, 128.41, 128.31, 128.05, 127.90, 127.24, 127.19, 124.56, 111.09, 53.05, 51.86, 29.72.

HRMS (EI) for $C_{20}H_{18}O_5$, Calcd. 338.1154; Found 338.1150.

Dimethyl-1,2-dihydro-1-methyl-2-oxospiro[3H-indole-3,2'-[2*H*,6*H*]pyrido[2,1-b][1,3]oxazine]- 3', 4'-dicarboxylate 64

To a solution of *N*-methyl isatin **63** (85 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (15 mL) under an argon atmosphere, pyridine (0.04 mL, 0.53 mmol) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate

(80:20) gave **64** as a mixture of diastereomers in the ratio 5:1 yellow crystalline solid (170 mg, 84%). The spectral data for the major diastereomer is given below.



64

IR (KBr) ν_{max}: 2955, 1742, 1721, 1613, 1566, 1472, 1351, 1270, 1229, 1034 cm^{-1}.

^{1}H NMR: δ 7.27 (t, J = 6.68 Hz, 1H), 7.15 (d, J = 6.98 Hz, 1H), 6.97 (t, J = 7.69 Hz, 1H), 6.81 (d, J = 7.06 Hz, 1H), 6.62-6.61 (m, 1H), 6.36 (d, J = 7.54 Hz, 1H), 6.22 (q, J = 3.81 Hz, 1H), 5.58 (dd, J = 3.27, 6.66 Hz, 1H), 5.31 (t, J = 7.05 Hz, 1H), 3.92 (s, 3H), 3.43 (s, 3H), 3.19 (s, 3H).

^{13}C NMR: δ 173.63, 163.29, 162.96, 145.17, 144.90, 129.89, 128.16, 125.21, 124.92, 124.37, 122.78, 122.62, 116.23, 108.08, 106.19, 101.47, 78.54, 53.03, 51.46, 25.93.

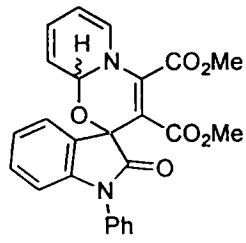
HRMS (EI) for $C_{20}H_{18}N_2O_6$, Calcd. 382.1164 Found 382.1168.

Dimethyl-1,2-dihydro-1-phenyl-2-oxospiro[3H-indole-3,2'-[2*H*, 6*H*]pyrido[2,1-b][1,3]oxazine]-3', 4'-dicarboxylate 67

To a solution of *N*-phenyl isatin **65** (78 mg, 0.35 mmol) and DMAD (50 mg, 0.35 mmol) in dry DME (15 mL) under an argon atmosphere, pyridine (0.028 mL, 0.35 mmol) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **67** as a mixture of diastereomers in the ratio 7:1; yellow crystalline solid (140 mg, 90%).The spectral data for the major diastereomer is given below.

IR (KBr) ν_{max}: 2948, 1748, 1708, 1607, 1573, 1499, 1330, 1270, 1243, 1155 cm^{-1}.

^{1}H NMR: δ 7.55-7.37 (m, 5H), 7.25-7.17 (m, 2H), 7.01



67

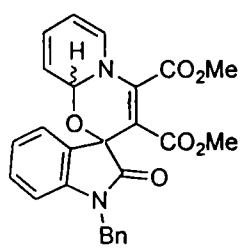
(t, J = 7.51 Hz, 1H), 6.77 (d, J = 7.79 Hz, 1H), 6.66 (s, 1H), 6.39 (d, J = 7.50 Hz, 1H), 6.26 (q, J = 6.09 Hz, 1H), 5.65 (dd, J = 3.21, 9.92 Hz, 1H), 5.34 (t, J = 6.63 Hz, 1H), 3.96 (s, 3H), 3.53 (s, 3H).

^{13}C NMR: δ 173.34, 163.32, 163.25, 145.49, 134.36, 129.99, 129.59, 129.54, 128.09, 126.61, 126.47, 125.64, 125.18, 124.58, 123.56, 123.35, 116.58, 109.62, 106.53, 101.79, 78.93, 53.32, 51.82

HRMS (EI) for $C_{25}H_{20}N_2O_6$, Calcd. 444.1321 Found 444.1330.

Dimethyl-1,2-dihydro-1-benzyl-2-oxospiro[3H-indole-3,2'-[2*H*, 6*H*]pyrido[2,1-b][1,3]oxazine]-3', 4'-dicarboxylate 68

To a solution of *N*-benzyl isatin **66** (125 mg, mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (15 mL) under an argon atmosphere, pyridine (0.043 mL, 0.53 mmol) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **68** as a mixture of diastereomers in the ratio 5:1; yellow crystalline solid (213 mg, 88%). The spectral data for the major diastereomer is given below.



68

IR (KBr) ν_{max}: 2948, 1748, 1715, 1607, 1566, 1438, 1351, 1270, 1229, 1155, 1007 cm^{-1}.

^{1}H NMR: δ 7.40-7.25 (m, 3H), 7.18 (d, J = 8.25 Hz, 2H), 6.94 (t, J = 7.59 Hz, 1H), 6.69 (d, J = 7.10 Hz, 2H), 6.37 (d, J = 7.53 Hz, 1H), 6.25 (q, J = 7.99 Hz, 1H), 5.63 (dd, J = 3.19, 9.93 Hz, 1H), 5.32 (t, J = 6.74 Hz, 1H), 5.07 (d, J = 15.59 Hz, 1H), 4.72 (d, J = 15.63 Hz, 1H), 3.96 (s, 3H), 3.29 (s, 3H), 2.84 (s, 2H).

^{13}C NMR: δ 174.03, 163.40, 163.32, 145.53, 144.53,

135.79, 130.15, 130.02, 129.03, 128.77, 128.51, 127.69, 125.61, 125.49, 125.18, 124.63, 123.24, 122.99, 122.55, 116.60, 109.29, 101.70, 78.83, 53.32, 51.63, 44.00.

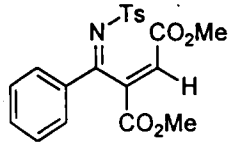
HRMS (EI) for $C_{26}H_{22}N_2O_6$, Calcd. 458.1477 found 458.1491.

Dimethyl-2-[(phenyl)[[(4-methylphenyl)sulfonyl]imino]methyl]-2-butenedioate 78

A solution of *N*-tosyl benzaldimine **69** (137 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **78** as a colourless crystalline solid (140 mg, 66%).

Mp: 128-130 °C.

IR (KBr) ν_{max}: 2955, 1748, 1719, 1553, 1317, 1243, 1162, 1088 cm^{-1}.



78

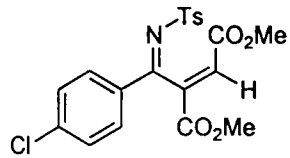
^{1}H NMR: δ 7.84 (t, J = 8.97 Hz, 3H), 7.53 (t, J = 7.32 Hz, 1H), 7.39 (t, J = 7.66 Hz, 2H), 7.31 (d, J = 8.07 Hz, 2H), 7.25 (s, 1H), 7.18 (s, 1H), 3.84 (s, 3H), 3.59 (s, 3H), 2.44 (s, 3H).

^{13}C NMR: δ 172.55, 163.67, 162.69, 149.73, 143.82, 142.40, 137.18, 135.09, 133.61, 131.19, 130.66, 129.58, 129.43, 128.88, 128.72, 127.70, 126.12, 53.25, 52.29, 21.71.

Anal. Calcd. for $C_{20}H_{19}NO_6S$: C, 59.84; H, 4.77; N, 3.49; S, 7.99; Found C, 59.54; H, 5.15; N, 3.71; S, 8.25.

Dimethyl-2-[(4-chlorophenyl)[(4-methylphenyl)sulfonyl]imino] methyl]-2-butenedioate 80

A solution of *N*-tosyl 4-chlorobenzaldimine **70** (155 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **80** as a colourless crystalline solid (197 mg, 86%).



80

Mp: 165-167°C.

IR (KBr) ν_{max}: 2948, 1728, 1580, 1553, 1438, 1270, 1162, 1088, 1013 cm^{-1}.

^{1}H NMR: δ 7.80 (dd, J = 8.08, 24.36 Hz, 4H), 7.38-7.30 (m, 4H), 7.17 (s, 1H), 3.84 (s, 3H), 3.62 (s, 3H), 2.42 (s, 3H).

^{13}C NMR: δ 171.45, 163.69, 162.54, 142.07, 140.22, 133.62, 130.90, 130.12, 129.50, 129.12, 127.75, 83.69, 53.36, 52.45, 21.67.

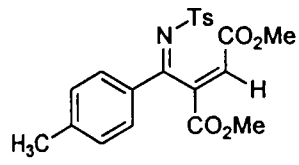
Anal. Calcd. for $C_{20}H_{18}ClNO_6S$; C; 55.11, H; 4.16, N; 3.21; S; 7.36; Found C, 55.31; H, 4.39; N, 3.48; S, 7.70.

Dimethyl-2-[(4-methylphenyl)[(4-methylphenyl)sulfonyl]imino] methyl]-2-butenedioate 81

A solution of *N*-tosyl 4-methylbenzaldimine **71** (144 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **81** as a colourless crystalline solid (143 mg, 65%).

Mp: 117-119 °C.

IR (KBr) ν_{max}: 2955, 1735, 1580, 1553, 1317, 1256, 1122, 1088 cm^{-1}.



81

^{1}H NMR: δ 7.84 (d, J = 8.25 Hz, 2H), 7.72 (d, J = 8.26 Hz, 2H), 7.30 (d, J = 8.10 Hz, 2H), 7.18 (d, J = 9.42 Hz, 3H), 3.83 (s, 3H), 3.61 (s, 3H), 2.43 (s, 3H), 2.35 (s, 3H).

^{13}C NMR: δ 172.39, 163.69, 162.78, 144.76, 143.67, 142.51, 137.40, 132.52, 130.50, 129.62, 129.54, 129.40, 129.02, 127.69, 53.25, 52.29, 21.78, 21.64.

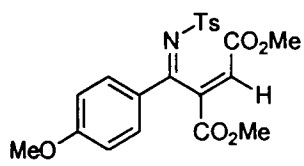
Anal. Calcd. for $C_{21}H_{21}NO_6S$: C, 60.71; H, 5.09; N, 3.37; S, 7.72; Found C, 60.64; H, 5.03; N, 3.71; S, 7.73.

Dimethyl-2-[(4-methoxyphenyl)[(4-methylphenyl)sulfonyl]imino] methyl] -2-butenedioate 82

A solution of *N*-tosyl 4-methoxybenzaldimine **72** (153 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **82** as a colourless crystalline solid (160 mg, 70%).

Mp: 132-134 °C.

IR (KBr) ν_{max}: 2955, 1742, 1521, 1438, 1344, 1270, 1169 cm^{-1}.



82

^{1}H NMR: δ 7.81 (t, J = 9.25 Hz, 4H), 7.28 (d, J = 8.13 Hz, 2H), 7.14 (s, 1H), 6.86 (d, J = 8.98 Hz, 2H), 3.81 (s, 6H), 3.56 (s, 3H), 2.39 (s, 3H).

^{13}C NMR: δ 171.54, 169.42, 160.54, 153.04, 143.47,

142.41, 137.48, 131.15, 130.23, 129.27, 127.59, 127.48, 114.12, 55.38, 53.12, 53.13, 21.49.

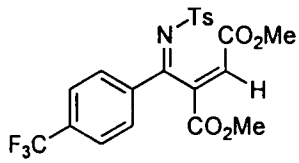
Anal. Calcd. for $C_{21}H_{21}NO_7S$; C, 58.46; H, 4.91; N, 3.25; Found C, 58.68; H, 5.08; N, 3.35; S, 7.74.

Dimethyl-2-[(4trifluoromethylphenyl)[(4methylphenyl)sulfonyl] imino]methyl]-2-butenedioate 83

A solution of *N*-tosyl 4-trifluoromethylbenzaldimine **73** (173 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **83** as a colourless crystalline solid (188 mg, 76%).

Mp: 175-177 °C.

IR (KBr) ν_{max}: 2954, 1723, 1598, 1570, 1329, 1267, 1164, 1129, 1020 cm^{-1}.



83

^{1}H NMR: δ 7.88 (dd, J = 8.26, 23.60 Hz, 4H), 7.64 (d, J = 8.37 Hz, 2H), 7.33 (d, J = 8.15 Hz, 2H), 7.19 (s, 1H), 3.85 (s, 3H), 3.63 (s, 3H), 2.43 (s, 3H).

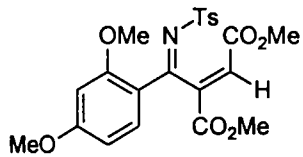
^{13}C NMR: δ 171.38, 163.70, 162.40, 144.25, 141.93, 138.29, 136.70, 134.86, 134.43, 131.12, 129.55, 129.30, 129.07, 128.50, 127.78, 126.44, 125.66, 125.26, 53.38, 52.48, 21.61.

Anal. Calcd. for $C_{21}H_{18}F_3NO_6S$; C, 53.73, H, 3.86, N, 2.98, S, 6.83; Found C, 54.02; H, 3.99; N, 3.21; S, 7.10.

Dimethyl-2-[(2,4-dimethoxyphenyl)[(4-methylphenyl)sulfonyl] imino]methyl] -2-butenedioate 84

A solution of *N*-tosyl-2,4-dimethoxybenzaldimine **74** (168 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon

atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **84** as a colourless crystalline solid (127 mg, 52 %).



84

Mp: 140-142 °C.

IR (KBr) ν_{max}: 2955, 1722, 1607, 1533, 1352, 1263, 1088, 1020 cm^{-1}.

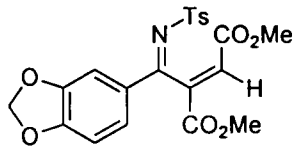
^{1}H NMR: δ 8.02 (d, J = 8.95 Hz, 1H), 7.81 (d, J = 8.21 Hz, 2H), 7.27 (d, J = 8.10 Hz, 2H), 6.82 (s, 1H), 6.51 (dd, J = 2.21, 8.97 Hz, 1H), 6.33 (d, J = 2.14 Hz, 1H), 3.82 (s, 6H), 3.68 (s, 3H), 3.54 (s, 3H), 2.40 (s, 3H).

^{13}C NMR: δ 170.87, 165.68, 164.13, 163.01, 161.45, 145.74, 143.15, 137.99, 132.91, 129.15, 127.37, 125.14, 118.27, 106.88, 98.43, 55.44, 52.58, 51.77, 21.42.

Anal. Calcd. for $C_{22}H_{23}NO_8S$: C, 57.26; H, 5.02: N, 3.04; S, 6.95; Found C, 57.18; H, 4.98; N, 3.30; S, 6.94.

Dimethyl-2-[(pipernoyl)[[(4-methylphenyl)sulfonyl]imino]methyl]-2-butenedioate 85

A solution of *N*-tosyl-3-[1,3]dioxolobenzaldimine **75** (160 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **85** as a colourless crystalline solid (181 mg, 78%).



85

Mp: 187-189 °C.

IR (KBr) ν_{max}: 2955, 1728, 1553, 1492, 1445, 1270, 1148, 1034 cm^{-1}.

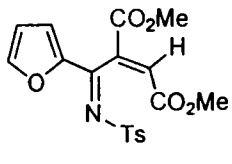
^{1}H NMR: δ 7.82 (d, J = 8.15 Hz, 2H), 7.42 (s, 1H), 7.29 (d, J = 8.09 Hz, 3H), 7.14 (s, 1H), 6.76 (d, J = 8.25 Hz, 1H), 6.01 (s, 2H), 3.83 (s, 3H), 3.60 (s, 3H), 2.42 (s, 3H).

^{13}C NMR: δ 171.18, 163.65, 162.72, 152.75, 148.52, 143.59, 142.36, 137.52, 130.54, 129.68, 129.36, 127.60, 126.00, 108.14, 108.06, 102.08, 96.16, 53.23, 53.28, 21.60.

Anal. Calcd. for $C_{21}H_{19}NO_8S$: C,56.62; H, 4.30; N, 3.14; S, 7.20; Found C, 56.78; H, 4.32; N, 3.34; S, 7.33.

Dimethyl-2-[(furyl)[[(4-methylphenyl)sulfonyl]imino]methyl]-2-butenedioate 86

A solution of *N*-tosyl furfuraldimine **76** (132 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **86** as a colourless crystalline solid (108 mg, 50%).



86

Mp: 174-176 °C.

IR (KBr) ν_{max}: 2955, 1728, 1573, 1256, 1088 cm^{-1}.

^{1}H NMR: δ7.82 (d, J= 8.23 Hz, 2H), 7.61 (s, 1H), 7.28 (t, J = 6.90 Hz, 2H), 7.15 (d, J= 3.52 Hz, 1H), 7.11 (s, 1H), 6.55-6.54 (m, 1H), 3.85 (s, 3H), 3.61 (s, 3H), 2.42 (s, 3H).

^{13}C NMR: δ172.25, 163.66, 162.49, 160.60, 156.42, 150.62,

148.32, 143.80, 140.83, 137.09, 130.78, 129.40, 127.78, 119.81, 113.30, 53.25, 52.34, 21.63.

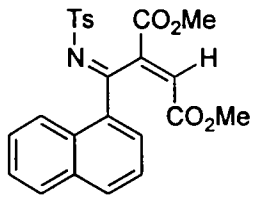
Anal. Calcd. for $C_{18}H_{17}NO_7S$: C, 55.24; H, 4.38; N, 3.58; S, 8.19; Found C, 55.34; H, 4.31; N, 3.75; S, 8.52.

Dimethyl-2-[(napthyl)[[(4-methylphenyl)sulfonyl]imino]methyl]-2-butenedioate 87

A solution of *N*-tosyl napthaldimine 77 (155 mg, 0.5 mmol) and DMAD (71 mg, 0.5 mmol) in dry DME (10 mL) under an argon atmosphere was cooled to -10 °C. To this, pyridine (20 mol%) was added, and the reaction mixture was stirred for 3 h at RT. The solvent was then removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **87** as a colourless crystalline solid (175 mg, 77%).

Mp: 144-146 °C.

IR (KBr) ν_{max}: 2955, 1724, 1582, 1328, 1249, 1162, 1094, 937 cm^{-1}.



87

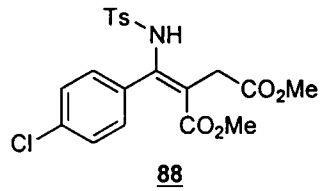
^{1}H NMR: δ 8.86 (d, J = 9.50 Hz, 1H), 7.95-7.89 (m, 3H), 7.81 (t, J = 4.73 Hz, 1H), 7.60 (d, J = 7.32 Hz, 1H), 7.53-7.49 (m, 2H), 7.40 (t, J = 7.70 Hz, 1H), 7.32 (d, J = 8.11 Hz, 2H), 7.17 (s, 1H), 3,86 (s, 3H), 3.45 (s, 3H), 2.43 (s, 3H).

^{13}C NMR: δ 172.38, 163.92, 163.19, 144.40, 143.91, 137.34, 136.55, 134.15, 134.05, 132.87, 132.61, 131.15, 131.00, 130.34, 129.52, 128.48, 128.22, 127.75, 126.50, 126.35, 124.11, 53.33, 52.49, 21.67.

Anal. Calcd. for $C_{24}H_{21}NO_6S$: C, 63.85; H, 4.69; N, 3.10; S, 7.10; Found C, 64.17; H, 4.68; N, 3.32; S, 7.28.

2-[4-chlorophenyl-(toluene-4-sulfonylamino)-methylene]-succinic acid dimethyl ester 88

To a solution of 1-azadiene **70** (75 mg, 0.17 mmol) in dry MeOH at room temperature was added $NaBH_4$ (10 mg, 0.2 mmol). The reaction mixture was stirred for 5 h, solvent was removed under vacuum, and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **88** as a colourless crystalline solid (62 mg, 83%).



88

Mp: 156-158 °C.

IR (KBr) ν_{max}: 3117, 2955, 1742, 1674, 1613, 1492, 1344, 1276, 1169, 1088, 1007 cm^{-1}.

^{1}H NMR: δ 11.52 (s, 1H), 7.31 (d, J = 8.16 Hz, 2H), 7.19-7.15 (m, 4H), 6.91 (d, J = 8.27 Hz, 2H), 3.77 (s, 3H), 3.52 (s, 3H), 2.89 (s, 2H), 2.41 (s, 3H).

^{13}C NMR: δ 171.47, 169.13, 151.70, 143.86, 137.15, 135.89, 130.87, 129.86, 129.28, 128.10, 127.46, 103.89, 52.24, 51.84, 33.59, 21.59.

Anal. Calcd. for $C_{20}H_{21}NO_6S$: C, 59.54, H; 5.25; N, 3.47; S, 7.95; Found C, 59.75; H, 5.38; N, 3.77; S, 8.02.

2.14 References:

1. (a) Winterfeldt, E. *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 423. (b) Winterfeldt, E. in "Newer Methods of Preparative Organic Chemistry" Forest, W. Ed. AP: New York. 1970, Vol. VI, 243.
2. (a) Johnson, A. W.; Tebby, J. C. *J. Chem. Soc.* **1961**, 2126. (b) Tebby, J. C.; Wilson, I. F.; Griffiths, D. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2133.
3. Butterfield, P. J.; Tebby, J. C.; Griffiths, D. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1189.

4. Shaw, M. A.; Tebby, J. C.; Ward, R. S.; Williams, D. H. *J. Chem. Soc.(C)* **1968**, 2795.
5. Winterfeldt, E.; Dillinger, H. J. *Chem. Ber.* **1966**, *99*, 1558.
6. Nozaki, K.; Sato, N.; Ikeda, K.; Takaya, H. *J. Org. Chem.* **1996**, *61*, 4516.
7. Winterfeldt, E. *Chem. Ber.* **1964**, *97*, 1952.
8. Nelson, S. F. *J. Org. Chem.* **1969**, *34*, 2248.
9. Huisgen, R.; Herbig, K. *Liebigs Ann. Chem.* **1965**, 98.
10. (a) Bertholdt, G. A.; Uhlig, F. *J. Org. Chem.* **1964**, *29*, 1459. (b) Huebner, C. F.; Dorfman, L.; Robison, M. M.; Donoghue, E.; Pierson, W. G.; Strachan, P. *ibid*, **1963**, *28*, 3134. (c) Bose, A. K.; Mina, G.; Manhas, M. S.; Rzucidlo, E. *Tetrahedron Lett.* **1963**, 1467.
11. Brannock, K. C.; Burpitt, G. R. D.; Goodlet, V. W.; Thweatt, J. G. *J. Org. Chem.* **1964**, *29*, 1464.
12. Froborg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728.
13. Winterfeldt, E. *Chem. Ber.* **1965**, *98*, 1581.
14. Hartzler, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 4961.
15. Hendrickson, C.; Hall, C.; Rees, R.; Templeton, J. F. *J. Org. Chem.* **1965**, *30*, 3312.
16. (a) Winterfeldt, E.; Schumann, D.; Dillinger, H. J. *Chem. Ber.* **1969**, *102*, 1656. (b) Dillinger, H. J.; Fengler, G.; Schumann, D.; Winterfeldt, E. *Tetrahedron* **1974**, *30*, 2553. (c) Dillinger, H. J.; Fengler, G.; Schumann, D.; Winterfeldt, E. *ibid*, **1974**, *30*, 2561.
17. Diels, O.; Alder, K. *Liebigs Ann. Chem.* **1932**, *16*, 498.
18. (a) Acheson, R. M.; Plunkett, A. O. *J. Chem. Soc., Perkin Trans. 1* **1975**, 438. (b) Acheson, R. M.; Taylor, G. A. *Proc. Chem. Soc.* **1959**, 186. (c) Acheson, R. M.; Taylor, G. A. *J. Chem. Soc.* **1960**, 1691. (d) Acheson, R. M.; Gagan, J. M. F.; Taylor, G. A. *J. Chem. Soc.* **1963**, 1903.

19. (a) Crabtree, A.; Johnson, A. W.; Tebby, J. C. *J. Chem. Soc.* **1961**, 3497. (b) Acheson, R. M.; Plunkett, A. O. *J. Chem. Soc.* **1964**, 2676.

20. (a) Diels, O.; Meyer, R.; *Liebigs Ann. Chem.* **1934**, *513*, 129. (b) Acheson, R. M. *Adv. Heterocycl. Chem.* **1963**, *1*, 125.

21. Winterfeldt, E.; Naumann, A. *Chem. Ber.* **1965**, *98*, 3537.

22. Acheson, R. M.; Hodgson, S. J.; Wright, R. G. M. *J. Chem. Soc. Perkin Trans. 1* **1976**, 1911.

23. Huisgen, R.; Morikawa, M.; Herbig, K.; Brunn, E. *Chem Ber.* **1967**, *100*, 1094.

24. (a) Nair, V.; Nair, J. S.; Vinod, A. U. *Synthesis*, **2000**, 1713. (b) Nair, V.; Vinod, A. U. *Chem. Commun.* **2000,** 1019. (c) Nair, V.; Vinod, A. U.; Nair, J. S.; Sreekanth, A. R.; Rath, N. P. *Tetrahedron Lett.* **2000**, *41*, 6675. (d) Nair, V.; Vinod, A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66,* 4427. (e) Nair, V.; Bindu, S.; Balagopal, L. *Tetrahedron. Lett.* **2001**, *42*, 2043.

25. Nair, V.; Sreekanth, A. R.; Vinod, A. U. *Org. Lett.* **2001**, *3*, 3495.

26. (a) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1988**, 159. (b) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595.

27. Hermecz, Istvan. *Adv. Heterocycl. Chem.* **1998**, *72*, 225.

28. Proctor, G. R.; McKay, W. R. *J. Chem. Soc. Perkin Trans. 1* **1981**, 2435.

Three Component Condensation Reactions of Isoquinoline and Dimethyl acetylenedicarboxylate with *N*-Tosylimines and Aldehydes

3.1 Introduction

Organic synthesis has reached a high degree of sophistication, thus allowing the synthesis of complex molecules, natural and unnatural, divergently rather than convergently or sequentially in many steps according to their complexity. An "ideal synthesis" should lead to the desired product in as few steps as possible, in good overall yield and by using environmentally compatible reagents.[1] In this respect, multicomponent reactions provide a powerful tool for the one-pot synthesis of diverse and complex organic molecules on the one hand, and small and 'drug like' heterocycles on the other hand. In the following section a brief introduction to multicomponent reactions is provided.

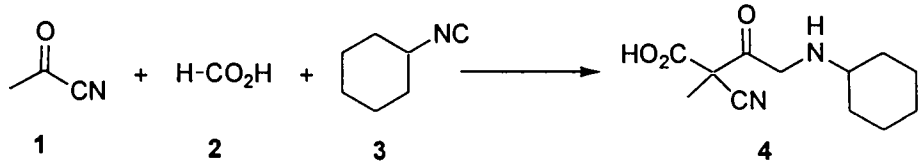
3.1.1 Multicomponent Reactions (MCRs)

Reactions in which more than two starting materials react to form a product, in such a way that most of the atoms of the starting materials are retained in the product are called multicomponent reactions (MCRs). These are efficient reactions where atom economy is maintained. These reactions by virtue of their convergence, productivity, facile execution and generally high yields of products, are especially attractive from the vantage point of combinatorial chemistry.

In contrast to the conventional two component reactions, MCRs are variable. Many of the classical MCRs are name reactions; Strecker synthesis,[2] Mannich reaction,[3] Biginelli reaction[4] and Hantzsch pyridine synthesis[5] are examples of well-known MCRs that have been known for nearly a centuary. A large and important class of MCRs are the isocyanide based multicomponent reactions (IMCRs).[6] The following sections will give a brief account of IMCRs. Passerini reaction (P-3CR) and Ugi reaction (U-4CR) are the two major IMCRs.

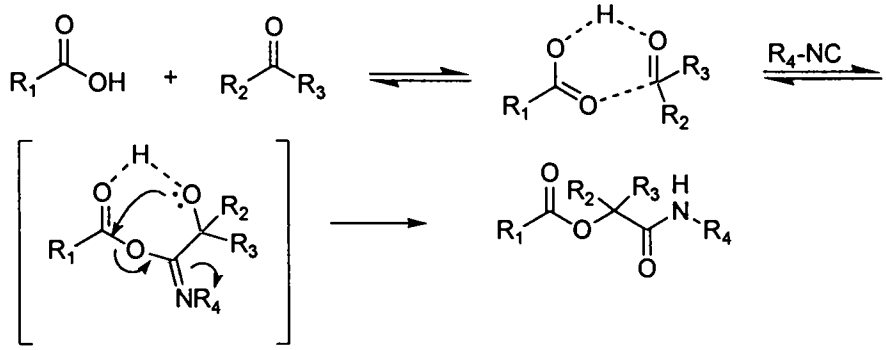
Passerini Reaction (P-3CR)

The classical reaction between carboxylic acids, oxo compounds and C-isocyanides, described by Passerini in 1921, provided an efficent and direct access to α-acyloxy carboxamides in one step.[7] A typical example of Passerini reaction is given below (Scheme 3.1).



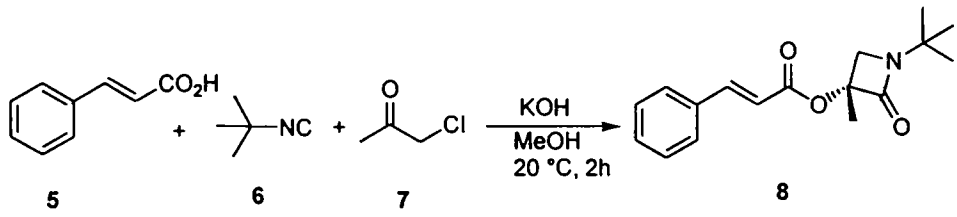
Scheme 3.1

The Passerini reaction is accelerated in aprotic solvents, indicating a non-ionic mechanism. A plausible mechanistic rationale for the reaction is given in Scheme 3.2.



Scheme 3.2

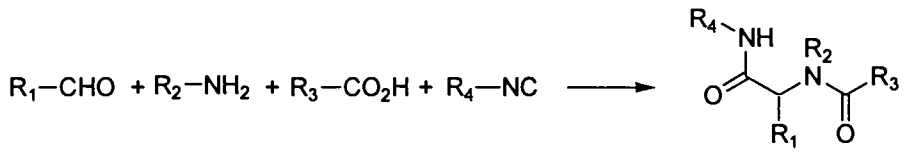
An interesting variation of Passerini reaction with α-chloroketone **5**, isocyanide **6** and carboxylic acid **7**, resulted in the synthesis of 3-acyloxy-2-azetidinones (Scheme 3.3).[8]



Scheme 3.3

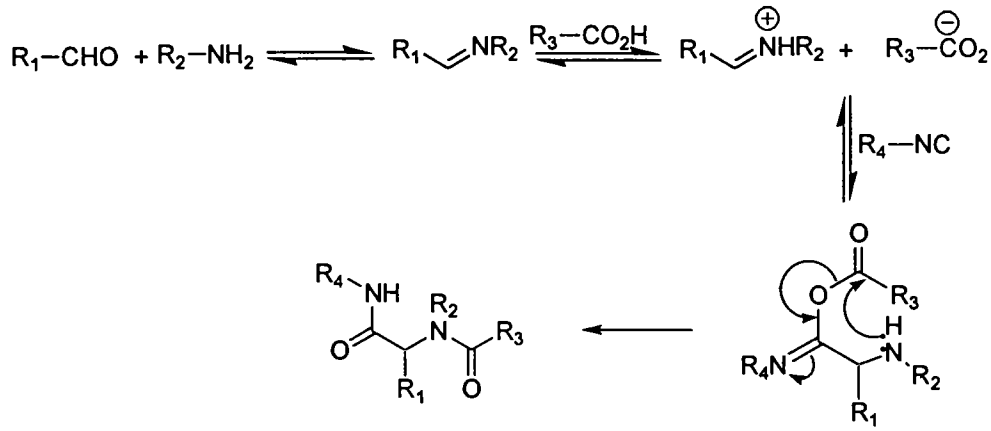
Ugi Reaction (U-4CR)

In 1959, Ugi *et al.* described an important four-component condensation, the U-4CRs.[9] The characteristic feature of the Ugi reaction is the α-addition of an iminium ion and the anion of a suitable acid to an isocyanide, followed by a spontaneous rearrangement of the α-adduct into a stable α-amino carboxamide derivative (Scheme 3.4).



Scheme 3.4

The mechanism for the formation of stable α-amino carboxamide derivatives can be outlined as folows (Scheme 3.5).

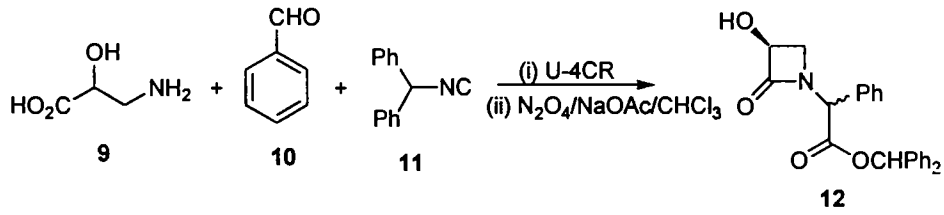


Scheme 3.5

This reaction was found to be general and applicable to the synthesis of a variety of organic compounds depending on the selection of each component. Any known type of C-isocyanide can be used as the isocyanide component and the only restriction for the acid component is that it must be able to rearrange

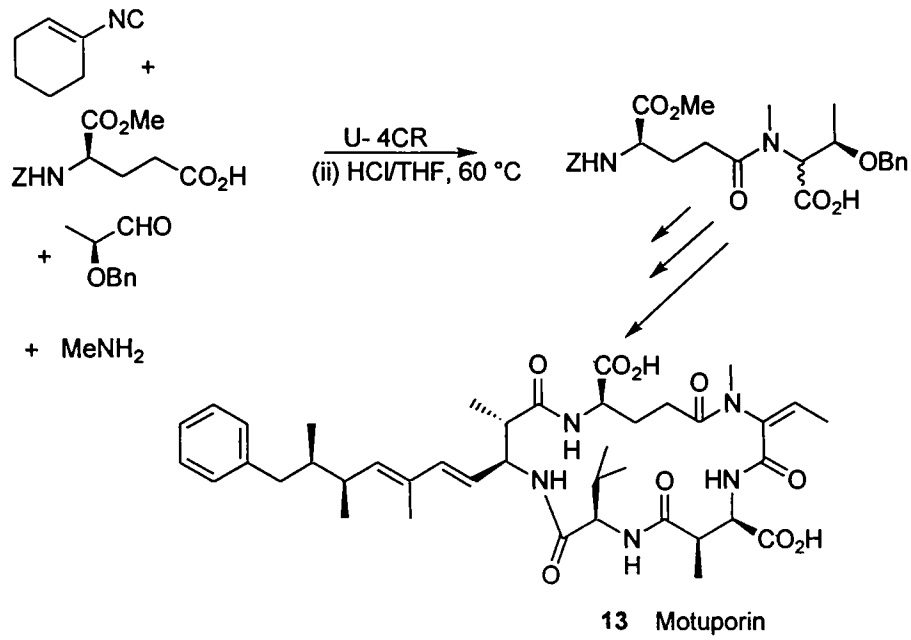
irreversibly from the intermediate α-adduct of the isocyanide to deliver a stable product. Except for sterically hindered diaryl ketones, most aldehydes and ketones can generally be used as carbonyl components. Ammonia, primary amines and secondary amines as well as hydrazine derivatives can be used as amine component. The U-4CR and related reactions can produce more different classes of chemical products than any other type of known reaction and are highly useful for the synthesis of peptide and β-lactam derivatives.[10]

An interesting application of U-4CR is the one step formation of the β-lactam **12** from β-aminoacid **9**, oxo compound **10** and isocyanide **11** (Scheme 3.6).[11]



Scheme 3.6

MCRs with isocyanides are often used in the total synthesis of natural products. A typical example of this application is furnished in the total synthesis of protein phosphatase (PP) inhibitor Motuporin **13** (Scheme 3.7).[12]

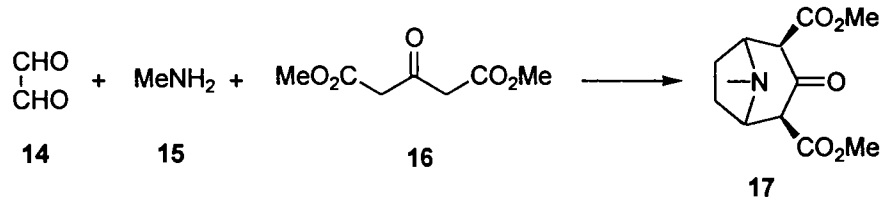


13 Motuporin

Scheme 3.7

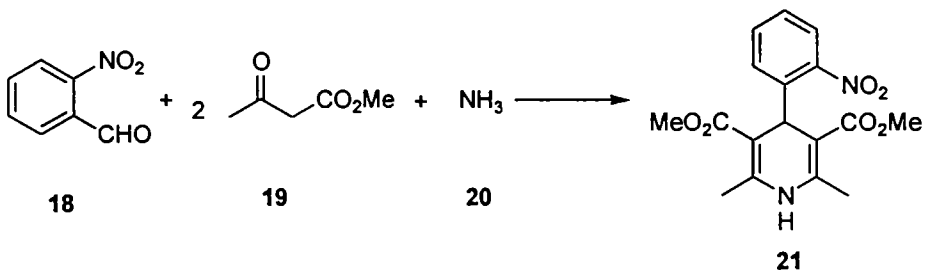
3.1.2 Heterocyclic Synthesis Using Multicomponent Reactions

The first important application of MCRs in natural product synthesis dates back to 1917, when Robinson synthesised the alkaloid tropinone **17** from succinic aldehyde **14**, methylamine **15** and dimethyl acetonedicarboxylate **16** (Scheme 3.8).[13]



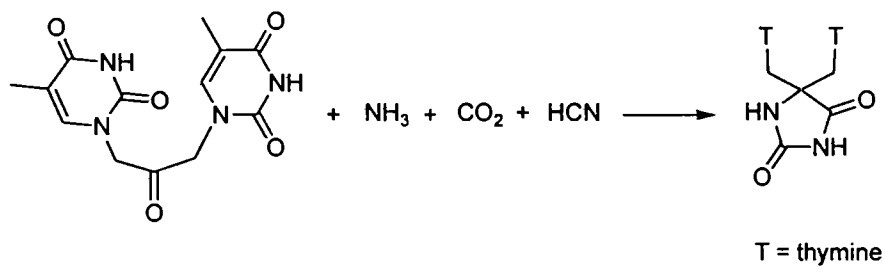
Scheme 3.8

1,4-Dihydropyridines such as **21** were first synthesized more than a hundred years ago in a four component reaction by Hantzsch *et al.* from ammonia **20**, aldehyde **18** and acetoacetic ester **19** (Scheme 3.9).[4] Recently this dihydropyridine synthesis has been applied to the synthesis of Nifedipin®, a very important calcium channel blocker for cardiovascular therapy.[14]



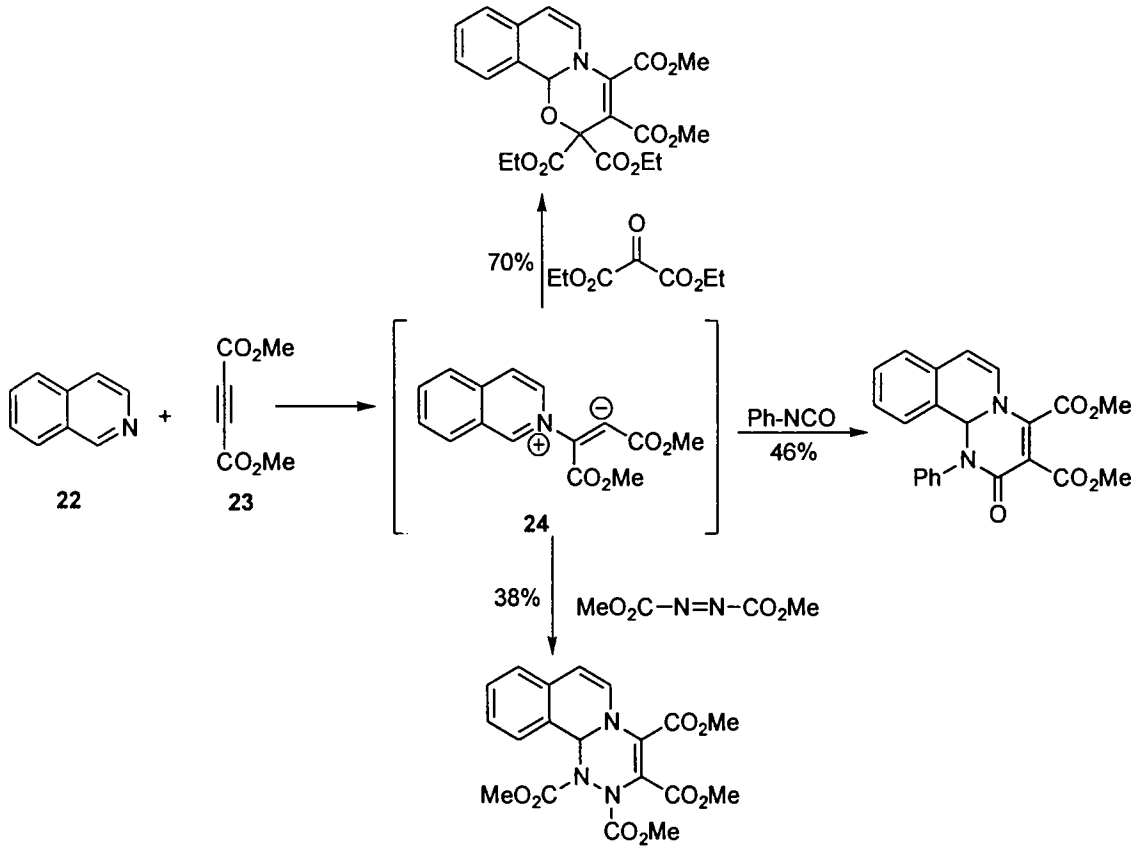
Scheme 3.9

Another important MCR is the Bucherer-Bergs hydantoin synthesis, an extension of Strecker's α-aminoacid synthesis, by the introduction of CO_2 as the fourth component (Scheme 3.10).[15]



Scheme 3.10

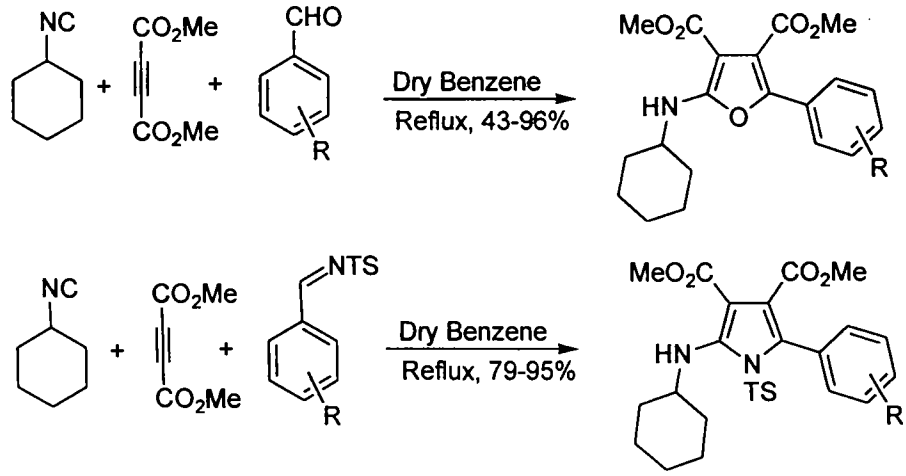
In 1967 Huisgen *et al.* described an efficient three component condensation based on 1,4-dipolar cycloaddition reaction. They have shown that the reaction of isoquinoline, DMAD and various dipolarophiles leads to the synthesis of condensed isoquinoline derivatives (Scheme 3.11).[16]



Scheme 3.11

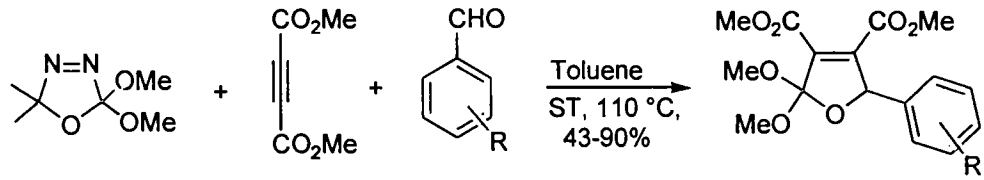
3.2 Background to the Present Work

In the context of the general interest in heterocyclic constructions *via* dipolar cycloaddition reactions, investigations carried out in our laboratory have shown that the 1,3-dipolar species generated by the reaction of cyclohexyl isocyanide and DMAD can be trapped with dipolarophiles such as aldehydes and *N*-tosylimines, resulting in the facile synthesis of aminofurans and aminopyrroles respectively (Scheme 3.12).[17]



Scheme 3.12

Related investigations in our laboratory have also shown that dipolar species generated by the addition of dimethoxy carbene to DMAD can be trapped with aldehydes, leading to the formation of dihydrofurans in high yields (Scheme 3.13).[18]



Scheme 3.13

Impressed by the reactivity of the 1,4-dipole generated from pyridine and DMAD towards dipolarophiles (see Chapter 2), it was considered worthwhile to explore the reactivity of 1,4-dipole generated from isoquinoline and DMAD towards various dipolarophiles. The results of our investigations constitute the subject matter of this chapter.

3.3 Results and Discussion

3.3.1 Reaction of Isoquinoline and DMAD with N-tosylimines

The *N*-tosylimines selected for our study are shown in Figure 3.1

Ar—CH=N—Ts

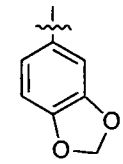
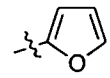
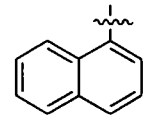
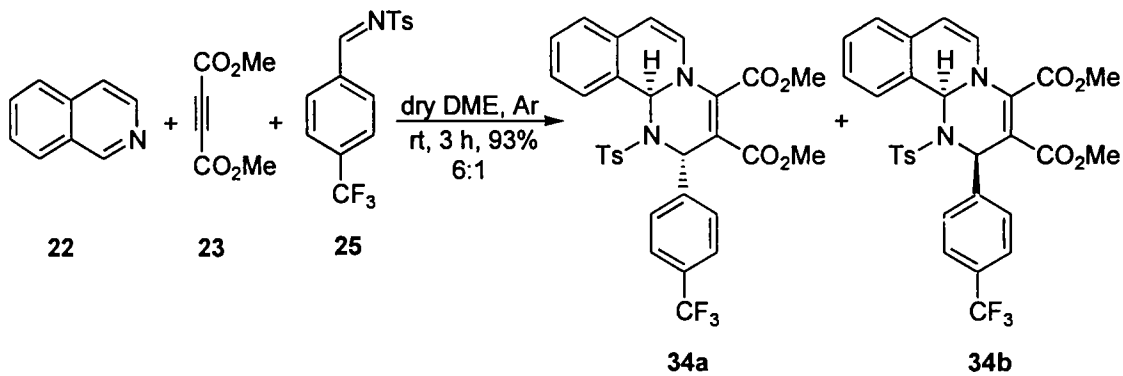
25	Ar = 4-$CF_3C_6H_4$		
26	Ar = 2-ClC_6H_4	**31**	Ar = 
27	Ar = 3-$NO_2C_6H_4$		
28	Ar = 3,4-$(Cl)_2C_6H_3$	**32**	Ar = 
29	Ar = C_6H_5		
30	Ar = 4-MeC_6H_4	**33**	Ar = 

Figure 3.1

Our studies were set to motion by dissolving isoquinoline, DMAD and *N*-tosylimine **25**, in dry DME and stirring the solution at room temperature for 3 h under argon atmosphere. An exceedingly facile reaction occurred with stereoselective formation of novel 2*H*-pyrimido[2,1-a]isoquinoline derivatives **34a** and **34b** in 93% yield in the ratio 6:1 (Scheme 3.14).[19]



22 **23** **25** **34a** **34b**

Scheme 3.14

The structure of the products **34a** and **34b** were elucidated by spectroscopic methods. The diastereomeric ratio was determined from ^{1}H NMR and the major diastereomer **34a** was separated by crystallisation. In the IR spectrum, the sharp bands at 1748 and 1703 cm $^{-1}$ were assigned to the two ester carbonyls. In the ^{1}H NMR spectrum, the signals due to methoxy groups were observed at δ 3.63 and 3.85 as two singlets, while the ring junction proton was observed as a singlet at δ 6.13. The other benzylic proton was observed as a

singlet at δ 5.90, while the two olefinic protons were discernible as doublets at δ 5.89 and 5.64 respectively. In the ^{13}C NMR spectrum, the two ester carbonyl signals were observed at δ 164.99 and 162.91, while the two methoxy carbons were seen resonating at δ 52.98 and 51.88. Finally, the structure and stereochemistry of the major diastereomer **34a** was established unambiguously by single crystal X-ray analysis (Figure 3.2).

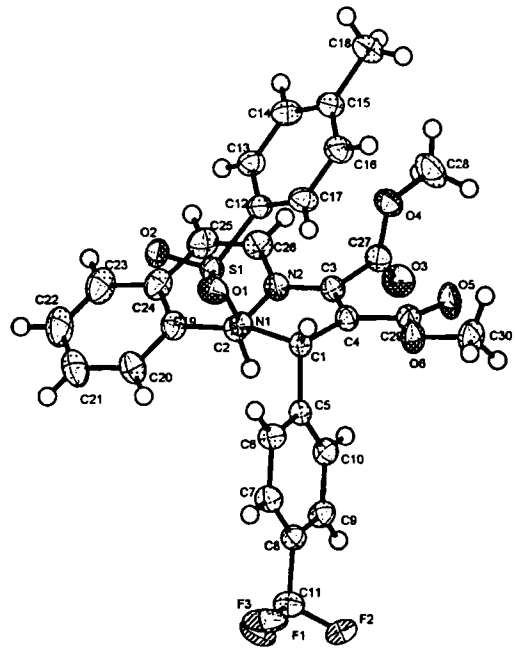


Figure 3.2 X-ray Crystal structure of 34a

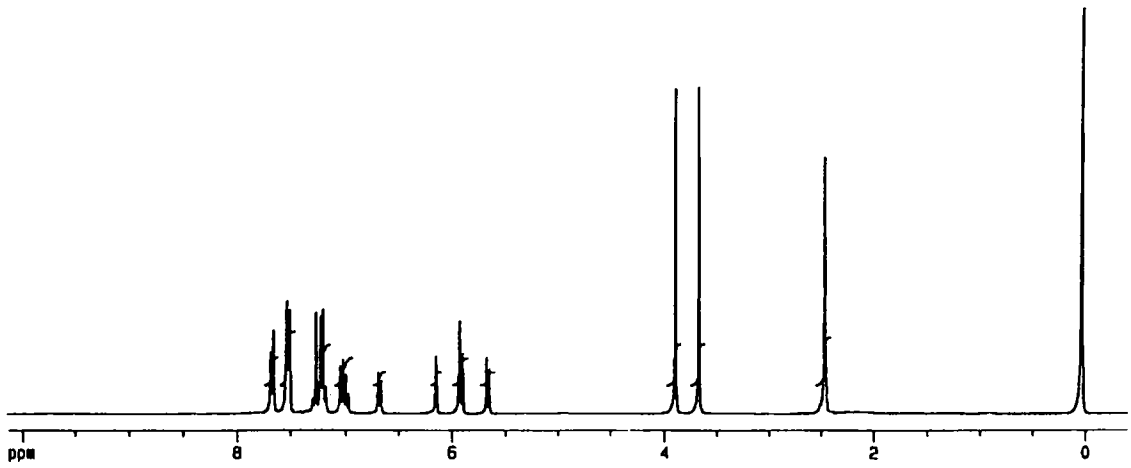


Figure 3.3 ^{1}H NMR of 34a

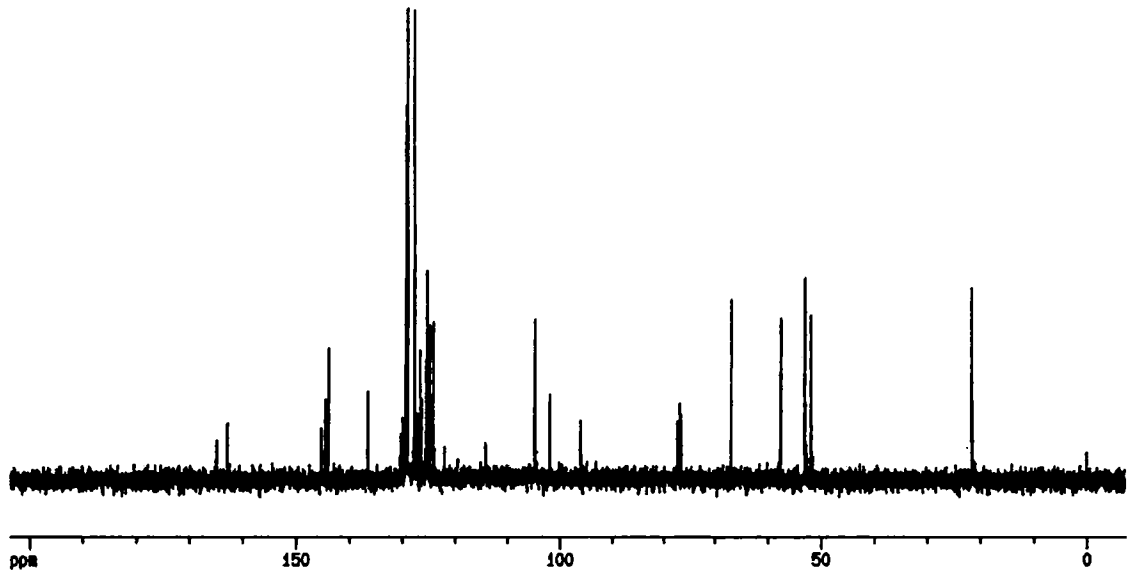
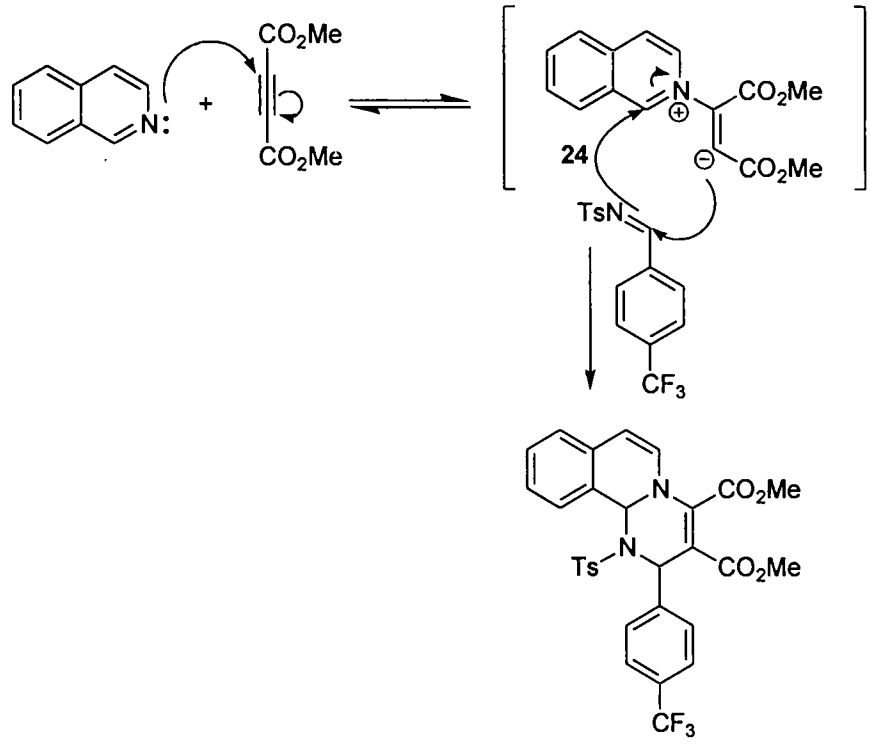


Figure 3.4 ^{13}C NMR of 34a

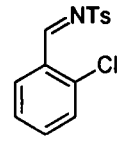
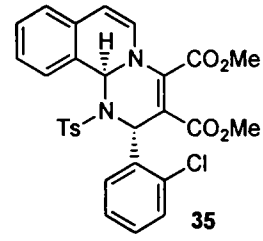
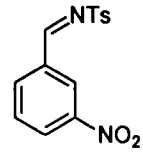
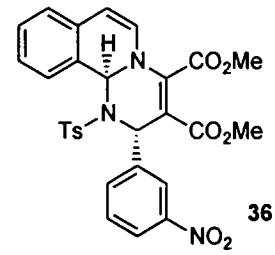
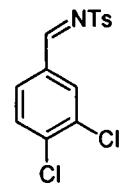
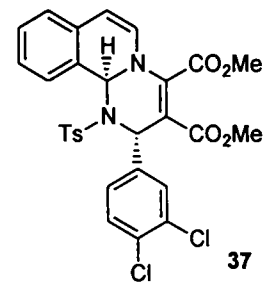
Mechanistically the reaction may be rationalized to involve the initial addition of isoquinoline to DMAD to form the 1,4-dipole **24**, which adds to carbon-nitrogen double bond of the *N*-tosylimine, resulting in the [4+2] adduct (Scheme 3.15).



Scheme 3.15

Similar reactivity was observed with other aromatic *N*-tosylimines with electron withdrawing groups such as *N*-tosyl-2-chlorobenzaldimine **26**, *N*-tosyl-3-nitrobenzaldimine **27**, *N*-tosyl-3,4-dichlorobenzaldimine **28**, which underwent facile reaction with isoquinoline and DMAD yielding the corresponding 2*H*-pyrimido[2,1-a]isoquinoline derivatives as mixture of diastereomers with good selectivity and in high yields (Table 3.1).

Table 3.1

Entry	*N*-tosylimine	Product [a]	Ratio [b]	Yield(%)*
1.	 **26**	 **35**	10:1	92
2.	 **27**	 **36**	10:1	73
3.	 **28**	 **37**	5:1	60

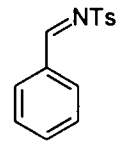
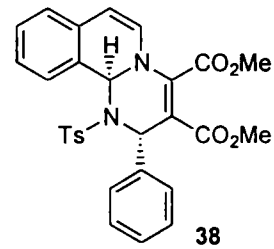
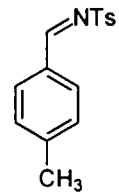
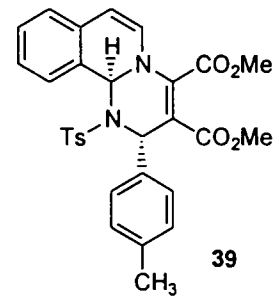
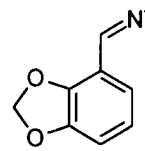
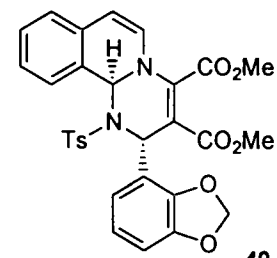
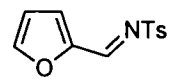
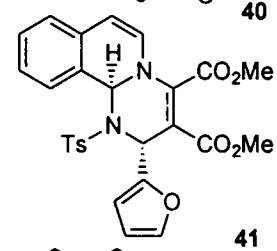
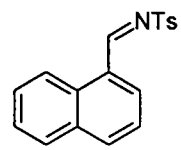
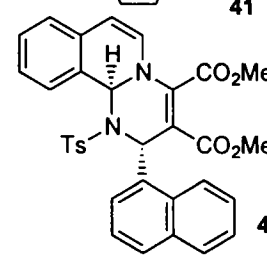
Reaction conditions: dry DME, Ar, rt, 3 h, a = structure of major isomer shown, b = ratio determined by ^{1}H NMR, * = isolated yield

In all the cases, the compounds were completely characterised and their structure established by spectroscopic methods. The pyrimido-isoquinolines **35-37**, showed characteristic carbomethoxy carbonyls both in the IR and ^{13}C NMR spectra. All the other spectroscopic data were also in good agreement with the assigned structure.

Analogous reaction was observed with other *N*-tosylimines **29-33** derived from electron donating aldehydes, furnishing the pyrimido-isoquinoline adducts

38-42 in moderate yields with good diastereoselectivity (Table 3.2).

Table 3.2

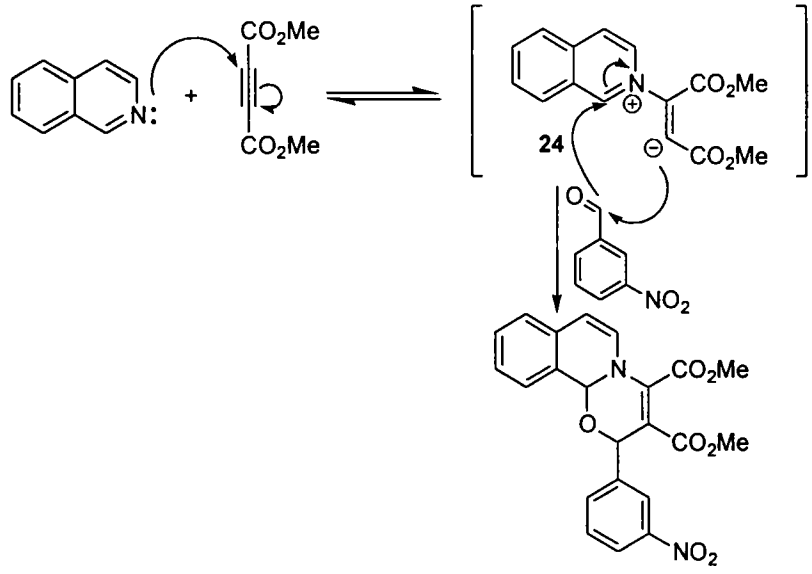
Entry	N-tosylimine	Product [a]	Ratio [b]	Yield(%)*
1.	 **29**	 **38**	6:1	43
2.	 **30**	 **39**	6:1	35
3.	 **31**	 **40**	5:1	56
4.	 **32**	 **41**	5:1	45
5.	 **33**	 **42**	5:1	50

Reaction conditions: dry DME, Ar, RT, 3 h, a = major isomer was shown,
b = determined by ^{1}H NMR, * = isolated yield

In all cases, the compounds were completely characterised and their structure established by spectroscopic methods. The ^{1}H and ^{13}C NMR spectra of compounds are similar to those of **34a**, which exihibited characteristic signals with expected chemical shifts.

The structure of the product **48** was elucidated using spectroscopic techniques. The diastereomeric ratio was determined by ^{1}H NMR. The major diastereomer of **48** showed the following characteristic spectral data. In the IR spectrum, the sharp bands at 1748 and 1708 cm^{-1} were assigned to the two ester carbonyls. In the ^{1}H NMR spectrum, the signals due to methoxy groups were observed at δ 4.02 and 3.63 as two singlets, while the ring junction proton was observed as a singlet at δ 5.85. The other benzylic proton was observed as a singlet at δ 5.78, while the two olefinic protons were discernible as doublets at δ 6.27 and 5.70. In the ^{13}C NMR spectrum, the two ester carbonyls were observed at δ 164.63 and 163.44.

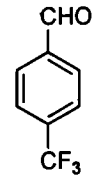
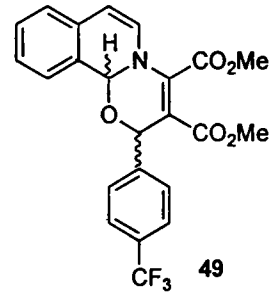
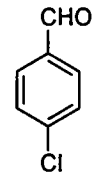
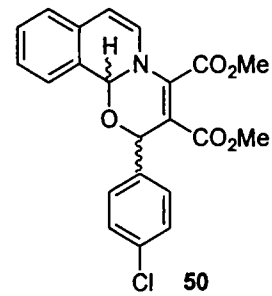
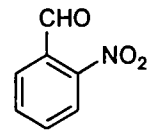
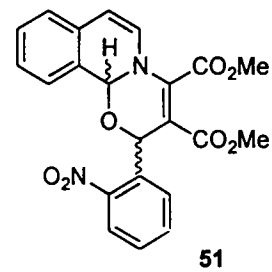
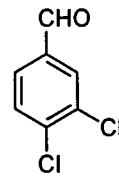
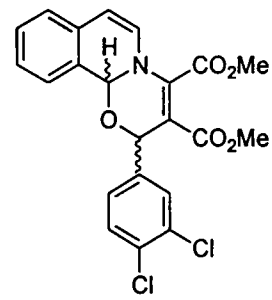
A mechanistic rationale similar to that involved in the reaction of *N*-tosylimines may be invoked in this case also. Thus the initial formation of 1,4-dipole **24** followed by its addition to carbonyl group of aldehyde can deliver the cycloadduct (Scheme 3.17).



Scheme 3.17

Analogous reaction was observed with other aromatic aldehydes with electron withdrawing groups such as 4-trifluoromethylbenzaldehyde **44**, 4-chloro benzaldehyde **45**, 2-nitrobenzaldehyde **46** and 3,4-dichlorobenzaldehyde **47**, affording an inseparable diastereomeric mixture of [1,3]oxazino[2,3-a] isoquinoline derivatives in good yields (Table 3.3).

Table 3.3

Entry	Aldehyde	Product	Ratio [b]	Yield(%)*
1.	 **45**	 **49**	6:1	75
2.	 **46**	 **50**	6:1	42
3.	 **47**	 **51**	1.7:1	76
4.	 **48**	 **52**	5.5:1	72

Reaction conditions: dry DME, Ar, RT, 3 h, b = determined by ^{1}H NMR, * = isolated yield

In all the cases, the compounds were characterised and their structure established by spectroscopic methods. The [1,3]oxazino[2,3-a]isoquinoline derivatives **49-52**, showed characteristic carbomethoxy carbonyls both in the IR and ^{13}C NMR spectra. All the other spectroscopic data were also in good agreement with the assigned structure.

3.4 Conclusion

In conclusion, we have found that the one pot reaction of isoquinoline and DMAD with *N*-tosylimines leads to an efficient diastereoselective synthesis of 2*H*-pyrimido[2,1-a]isoquinoline derivatives. Similarly aldehydes, as dipolarophiles, afforded novel [1,3]oxazino[2,3-a]isoquinoline derivatives. It may be mentioned that both 2*H*-pyrimido[2,1-a]isoquinoline and [1,3]oxazino[2,3-a]isoquinoline derivatives manifest a number of important and therapeutically useful biological activities.[20] It is conceivable that the novel three component reaction described herein will be applicable to the synthesis of a variety of heterocycles.

3.5 Experimental Details

General information about the experiments is given in Section 2.13 (Chapter 2).

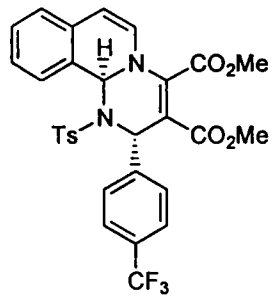
Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-[(4-trifluoromethylphenyl)]-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 34a

To a mixture of *N*-tosyl-4-trifluoromethylbenzaldimine **25** (173 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of **34a** and **34b** (232 mg, 93%). The major diastereomer **34a** was separated by crystallisation from CH_2Cl_2-hexane mixture as a pale yellow crystalline solid.

Mp: 150-152 °C.

IR (KBr) ν_{max}: 2955, 1748, 1703, 1600, 1573, 1420, 1330, 1230, 1162, 1128, 1080 cm^{-1}.

^{1}H NMR: δ 7.66 (d, J = 8.17 Hz, 2H), 7.51 (d, J = 9.32



34a

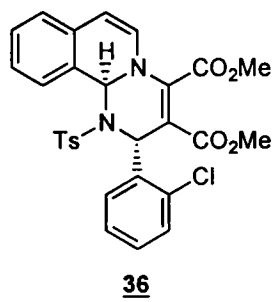
Hz, 4H), 7.29-7.16 (m, 3H), 7.03-6.95 (m, 2H), 6.66 (d, J = 7.68 Hz, 1H), 6.13 (s, 1H), 5.90 (s, 1H), 5.89 (d, J = 8.10 Hz, 1H), 5.64 (d, J = 7.84 Hz, 1H), 3.85 (s, 3H), 3.63 (s, 3H), 2.39 (s, 3 H).

^{13}C NMR: δ 164.99, 162.91, 145.61, 144.65, 143.89, 136.95, 129.76, 129.64, 129.57, 129.33, 129.05, 127.90, 127.87, 127.40, 126.77, 126.54, 125.66, 125.61, 125.41, 125.04, 124.30, 104.84, 102.46, 67.18, 57.84, 52.98, 51.88, 21.52.

Anal. Calcd. for $C_{30}H_{25}F_3N_2O_6S$: C, 60.19; H, 4.21; N, 4.68; S, 5.36; Found C, 59.90; H, 4.07; N, 4.91; S, 5.40.

Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-[(2-chloro phenyl)]-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 36

To a mixture of *N*-tosyl-2-chorobenzaldimine **26** (155 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (274 mg, 92%). The major diastereomer **36** was separated by crystallisation from CH_2Cl_2-hexane mixture as a pale yellow crystalline solid.



36

Mp: 122-124 °C.

IR (KBr) ν_{max}: 2948, 2362, 1742, 1708, 1593, 1566, 1425, 1337, 1276, 1236, 1108 cm^{-1}.

^{1}H NMR: δ 7.47, (d, J = 7.89 Hz, 1H), 7.38-7.25 (m, 5H), 7.07-6.93 (m, 4H), 6.64-6.57 (m, 2H), 6.30 (d, J = 7.71 Hz, 1H), 6.22 (s, 1H), 6.13 (d, J = 7.86 Hz, 1H), 5.61 (d, J = 7.88 Hz, 1H), 3.96 (s,

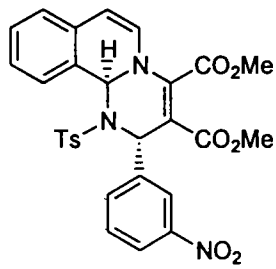
3H), 3.59 (s, 3H), 2.34 (s, 3H).

^{13}C NMR: δ 164.82, 163.81, 144.45, 143.10, 139.02, 137.98, 133.67, 132.27, 130.67, 130.59, 129.57, 128.84, 128.78, 128.29, 128.08, 127.76, 126.62, 126.17, 125.22, 125.13, 124.30, 104.24, 102.96, 66.38, 55.71, 53.31, 51.96, 21.53.

Anal.Calcd. for $C_{29}H_{25}ClN_2O_6S$: C, 61.64; H, 4.46; N, 4.96; S, 5.68; Found C, 61.32; H, 4.56; N, 4.75; S, 5.64.

Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-[(3-nitrophenyl)]-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 37

To a mixture of *N*-tosyl-3-nitrobenzaldimine **27** (160 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (220 mg, 73 %). The major diastereomer **37** was separated by crystallisation from CH_2Cl_2-hexane mixture as a pale yellow crystalline solid.



37

Mp: 160-162 °C.

IR (KBr) ν_{max}: 2955, 1748, 1708, 1593, 1573, 1533, 1430, 1351, 1236, 1162 cm^{-1}.

^{1}H NMR: δ 8.18 (d, J = 8.12 Hz, 1H), 8.11 (s, 1H), 7.77 (d, J = 6.18 Hz, 2H), 7.60 (t, J = 7.92 Hz, 1H), 7.51 (d, J = 8.24 Hz, 2H), 7.26-7.16 (m, 2H), 7.03 (d, J = 7.44 Hz, 1H), 6.95 (t, J = 7.55 Hz, 1H), 6.60 (d, J = 7.71 Hz, 1H),6.12 (s, 1H), 5.95 (d, J = 7.82 Hz, 1H), 5.87 (s, 1H), 5.68 (d, J = 7.86 Hz, 1H), 3.87 (s, 3H), 3.63 (s, 3H), 2.43

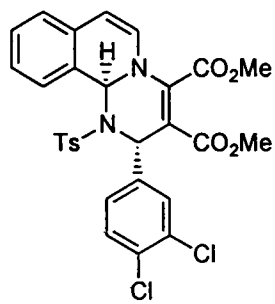
(s, 3H).

^{13}C NMR: δ 164.80, 162.87, 148.49, 144.22, 143.84, 136.50, 134.58, 129.64, 129.52, 129.48, 129.10, 127.79, 127.71, 127.48, 127.31, 126.78, 126.37, 125.51, 124.77, 124.11, 123.25, 122.97, 105.10, 101.46, 67.15, 57.45, 53.19, 52.07, 21.51.

Anal. Calcd. for $C_{29}H_{25}N_3O_8S$: C, 60.51; H, 4.38; N, 7.30; S, 5.57; Found C, 60.23; H, 4.05; N, 7.25; S, 5.41.

Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-[(3,4-dichlorophenyl)]-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 38

To a mixture of *N*-tosyl-3,4-dichorobenzaldimine **28** (173 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (190 mg, 60%). The major diastereomer **38** was separated by crystallisation from CH_2Cl_2-hexane mixture as a pale yellow crystalline solid.



38

Mp: 159-161 °C.

IR (KBr) ν_{max}: 2955, 1748, 1708, 1593, 1573, 1465, 1425, 1360, 1236, 1169 cm^{-1}.

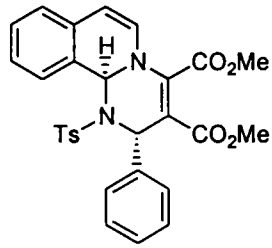
^{1}H NMR: δ7.51-7.42 (m, 4H), 7.34-7.10 (m, 4H), 7.02 (d, J = 8.01 Hz, 2H), 6.71 (d, J = 7.62 Hz, 1H), 6.01 (s, 1H), 5.91 (s, 1H), 5.87 (d, J = 7.82 Hz, 1H), 5.65 (d, J = 7.84 Hz, 1H), 3.84 (s, 3H), 3.63 (s, 3H), 2.44 (s, 3H).

^{13}C NMR: δ 164.92, 162.93, 144.76, 144.05, 141.94, 136.57, 132.52, 130.64, 130.59, 129.46, 129.38, 129.12, 127.88, 127.82, 126.87, 125.48, 124.93, 124.17, 104.99, 101.69, 67.00, 57.25, 53.16, 52.09, 21.64.

Anal.Calcd. for $C_{29}H_{24}Cl_2N_2O_6S$: C, 58.10; H, 4.04; N, 4.67; S, 5.35; Found C, 58.22; H, 3.86; N, 4.88; S, 5.67

Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-phenyl-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 39

To a mixture of *N*-tosyl-benzaldimine **29** (137 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (121 mg, 43%). The major diastereomer **39** was separated by crystallisation from CH_2Cl_2-hexane mixture as a pale yellow crystalline solid.



39

Mp: 150-152 °C.

IR (KBr) ν_{max}: 2955, 1742, 1694, 1600, 1499, 1357, 1236, 1007 cm^{-1}.

^{1}H NMR δ 7.52 (d, J = 8.26 Hz, 2H), 7.39-7.25 (m, 5H), 7.20-7.14 (m, 3H), 7.01-6.92 (m, 2H), 6.67 (d, J = 7.69 Hz, 1H), 6.10 (s, 1H), 5.99 (s, 1H), 5.88 (d, J = 7.83 Hz, 1H), 5.61 (d, J = 7.84 Hz, 1H), 3.84 (s, 3H), 3.57 (s, 3H), 2.42 (s, 3H).

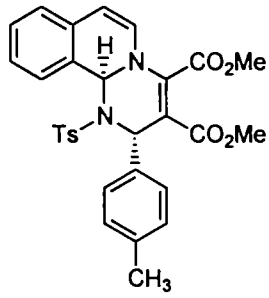
^{13}C NMR: δ 165.26, 163.16, 144.02, 143.58, 141.60, 129.53, 129.15, 128.78, 128.59, 128.54, 128.17, 127.87, 127.77, 127.36, 126.51, 125.22,

125.16, 124.38, 105.75, 103.11, 66.66, 58.12, 52.98, 51.86, 21.53.

Anal. Calcd. for $C_{29}H_{26}N_2O_6S$: C, 65.65; H, 4.94; N, 5.28; S, 6.04; Found C, 65.52; H, 5.13; N, 5.46; S, 6.17.

Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-[(4-methylphenyl)]-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 40

To a mixture of *N*-tosyl-4-methylbenzaldimine **30** (144 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (105 mg, 35%). The major diastereomer **40** was separated by crystallisation from CH_2Cl_2-hexane mixture as a pale yellow crystalline solid.



40

Mp: 175-177 °C.

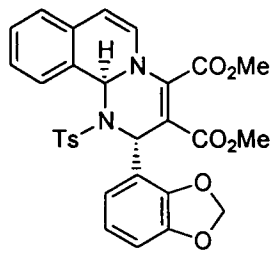
IR (KBr) ν_{max}: 2948, 2362, 1742, 1701, 1593, 1431, 1337, 1280, 1229, 1162, 1000 cm^{-1}.

^{1}H NMR δ 7.52 (d, J = 8.22 Hz, 2H), 7.25-7.13 (m, 7H), 7.01-6.92 (m, 2H), 6.68 (d, J = 7.69 Hz, 1H), 6.06 (s, 1H), 5.99 (s, 1H), 5.88 (d, J = 7.81 Hz, 1H), 5.61 (d, J = 7.83 Hz, 1H), 3.84 (s, 3H), 3.61 (s, 3H), 2.42 (s, 3H), 2.35 (s, 3H).

^{13}C NMR: δ 165.42, 163.30, 143.91, 138.76, 137.63, 137.23, 136.96, 129.66, 129.38, 129.23, 128.84, 128.62, 127.98, 127.93, 126.58, 125.47, 125.23, 124.59, 120.05, 104.33, 66.70, 58.12, 52.99, 51.89, 21.61, 21.16.

Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-pipernyl-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 41

To a mixture of *N*-tosyl-3-[1,3]dioxolobenzaldimine **31** (160 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (170 mg, 56%). The major diastereomer **41** was separated by crystallisation from CH_2Cl_2-hexane mixture as a pale yellow crystalline solid.



41

Mp: 170-172 °C.

IR (KBr) ν_{max}: 2955, 1748, 1705, 1600, 1573, 1485, 1445, 1351, 1236, 1169, 1040 cm^{-1}.

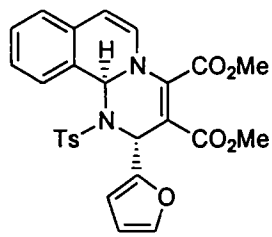
^{1}H NMR δ 7.51 (d, J = 8.25 Hz, 2H), 7.19-7.15 (m, 3H), 7.00 (dd, J = 2.35, 7.68 Hz, 2H), 6.93 (s, 1H), 6.79-6.72 (m, 3H), 6.03-5.98 (m, 4H), 5.86 (d, J = 7.81 Hz, 1H), 5.62 (d, J = 7.84 Hz, 1H), 3.83 (s, 3H), 3.62 (s, 3H),2.41 (s, 3H).

^{13}C NMR: δ 165.31, 163.21, 148.16, 147.52, 143.91, 143.71, 136.85, 135.81, 129.65, 129.58, 128.89, 127.95, 127.84, 126.65, 126.53, 125.36, 125.29, 124.45, 122.70, 108.86, 107.98, 104.50, 103.20, 101.32, 66.47, 57.96, 53.07, 52.00, 21.64.

Anal. Cald. for $C_{30}H_{26}N_2O_8S$: C, 62.71; H, 4.56; N, 4.88; S, 5.58; Found C, 62.53; H, 4.58; N, 4.67; S, 5.61.

Dimethyl-1,11b-dihydro-1-[(4-methylphenyl)sulfonyl]-2-furyl-2H-pyrimido[2,1-a]isoquinoline-3,4-dicarboxylate 42

To a mixture of *N*-tosyl-1-furfuraldimine **32** (132 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (125 mg, 45%). The major diastereomer **42** was separated by crystallisation from CH_2Cl_2-hexane mixture as a pale yellow crystalline solid. .



42

Mp: 147-149 °C.

IR (KBr) ν_{max}: 2955, 1748, 1708, 1593, 1573, 1357, 1263, 1236, 1162, 1020. cm^{-1}.

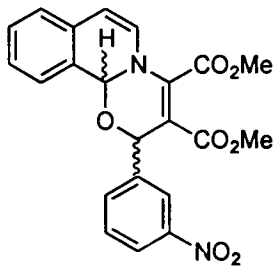
^{1}H NMR δ 7.80 (d, J = 8.27 Hz, 2H), 7.46 (s, 1H), 7.40 (d, J = 8.26 Hz, 2H), 7.29 (d, J = 8.10 Hz, 1H), 7.13 (t, J = 8.12 Hz, 1H), 7.01 (d, J = 7.30 Hz, 1H), 6.77 (t, J = 7.51 Hz, 2H), 6.55 (d, J = 7.68 Hz, 1H), 6.34 (s, 1H), 6.24-6.18 (m, 1H), 6.04 (d, J = 7.80 Hz, 1H), 5.67 (d, J = 7.83 Hz, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 2.41(s, 3H).

^{13}C NMR: δ 165.00, 163.31, 153.95, 143.79, 143.03, 137.99, 131.34, 130.28, 129.96, 129.52, 128.77, 127.87, 127.47, 126.41, 125.36, 124.52, 124.17, 110.50, 110.23, 104.59, 102.91, 68.40, 66.89, 53.16, 51.91, 21.51.

Anal.Calcd. for $C_{27}H_{24}N_2O_7S$: C, 62.30; H, 4.65; N, 5.38; S, 6.16; Found C, 62.15; H, 4.42; N, 5.17; S, 5.96.

Dimethyl-2-(3-nitrophenyl)-2H,11bH-[1,3]oxazino[2,3-a]isoquinoline-3,4-dicarboxylate 49

To a mixture of 3-nitro benzaldehyde **43** (80 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (215 mg, 96%, 2:1). The spectral data for the major diastereomer is given below.



49

IR (KBr) ν_{max}: 2955, 1748, 1708, 1600, 1573, 1539, 1357, 1236 cm^{-1}.

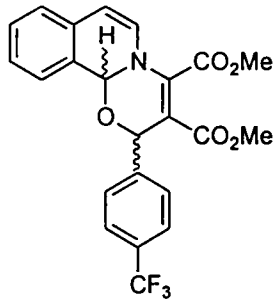
^{1}H NMR: δ 8.34 (s, 1H), 8.23 (d, J = 8.15 Hz, 1H), 7.77 (d, J = 7.69 Hz, 1H), 7.61 (t, J = 7.90 Hz, 1H), 7.23 (d, J = 7.60 Hz, 1H), 7.15 (t, J = 7.55 Hz, 1H), 7.03-6.95 (m, 2H), 6.27 (d, J = 7.78 Hz, 1H), 5.85 (s, 1H), 5.78 (s, 1H), 5.70 (d, J = 7.80 Hz, 1H), 4.02 (s, 3H), 3.63 (s, 3H).

^{13}C NMR: δ 164.63, 163.44, 148.52, 143.21, 141.95, 134.89, 133.91, 129.65, 129.44, 127.16, 126.70, 126.20, 125.03, 123.68, 123.22, 108.69, 105.03, 102.48, 82.97, 72.60, 53.34, 51.80.

Dimethyl-2-(4-trifluoromethylphenyl)-2H,11bH-[1,3]oxazino[2,3-a]isoquinoline-3,4-dicarboxylate 50

To a mixture of 4-trifluoromethyl benzaldehyde **44** (92 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an

inseparable mixture of diastereomers (175 mg, 75%, 6:1). The spectral data for the major diastereomer is given below.



50

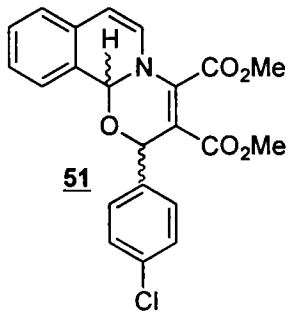
IR (KBr) ν_{max}: 2955, 1743, 1703, 1600, 1431, 1330, 1243, 1128 cm^{-1}.

^{1}H NMR: δ 7.69 (d, J = 8.16 Hz, 2H), 7.57 (d, J = 8.13 Hz, 2H), 7.23 (t, J = 6.67 Hz, 1H), 7.13 (t, J = 6.92 Hz, 1H), 7.02-6.95 (m, 2H), 6.26 (d, J = 7.77 Hz, 1H), 5.84 (s, 1H), 5.75 (s, 1H), 5.68 (d, J = 7.79 Hz, 1H), 4.01 (s, 3H), 3.62 (s, 3H).

^{13}C NMR: δ 164.96, 163.73, 143.73, 141.80, 129.81, 129.62, 129.45, 128.60, 127.79, 127.15, 126.91, 126.49, 125.60, 125.04, 123.68, 109.64, 104.89, 103.31, 83.03, 73.00, 53.41, 51.84.

Dimethyl-2-(4-chlorophenyl)-2H,11bH-[1,3]oxazino[2,3-a]isoquinoline-3,4-dicarboxylate 51

To a mixture of 4-chlorobenzaldehyde **45** (74 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (92 mg, 42%). The spectral data for the major diastereomer is given below.



51

IR (KBr) ν_{max}: 2955, 1742, 1708, 1600, 1438, 1249, 1101 cm^{-1}.

^{1}H NMR: δ 7.40-7.35 (m, 3H), 7.25-7.18 (m, 2H), 7.11 (t, J = 7.47 Hz, 1H), 6.97 (t, J = 7.30 Hz, 2H), 6.25 (d, J = 7.77 Hz, 1H), 5.84 (s, 1H), 5.67-5.64 (m, 2H), 3.99 (s, 3H), 3.60 (s, 3H).

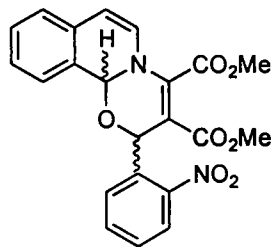
^{13}C NMR: δ 164.98, 163.73, 143.43, 139.66, 134.36, 130.39, 129.78, 129.51, 129.29, 128.73, 127.73, 127.00, 126.90, 126.57, 124.91, 123.70, 104.63, 103.78, 82.96, 72.92, 53.30, 51.72.

Dimethyl-2-(2-nitrophenyl)-2H,11bH-[1,3]oxazino[2,3-a]isoquinoline-3,4-dicarboxylate 51

To a mixture of 2-nitro benzaldehyde **46** (80 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (170 mg, 76%, 1.7:1). The spectral data for the major diastereomer is given below.

IR (KBr) ν_{max}: 2955, 1748, 1715, 1607, 1526, 1438, 1357, 1236 cm^{-1}.

^{1}H NMR: δ 7.91 (d, J = 7.84 Hz, 1H), 7.68-7.45 (m, 3H), 7.29-7.13 (m, 2H), 6.91 (dd, J = 7.42, 17.18 Hz, 1H), 6.57 (s, 1H), 6.26-6.21 (m, 2H), 5.72 (s, 1H), 5.59 (d, J = 7.80 Hz, 1H), 4.00 (s, 3H), 3.65 (s, 3H).



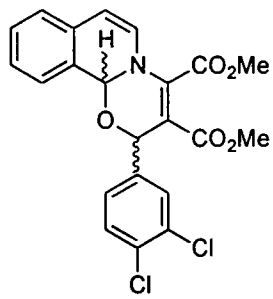
52

^{13}C NMR: δ 164.46, 163.28, 148.64, 143.90, 142.37, 133.98, 131.63, 129.39, 129.14, 128.48, 127.65, 127.17, 126.53, 124.94, 123.68, 123.08, 105.00, 101.26, 82.99, 71.87, 53.17, 51.62.

Dimethyl-2-(3,4-dichlorophenyl)-2H,11bH-[1,3]oxazino[2,3-a]isoquinoline-3,4-dicarboxylate 53

To a mixture of 3,4-dichloro benzaldehyde **47** (92 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 3 h.

The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave an inseparable mixture of diastereomers (170 mg, 72%, 5.5:1). The spectral data for the major diastereomer is given below.



52

IR (KBr) ν_{max}: 2955, 1735, 1701, 1593, 1465, 1236, 1142 cm^{-1}.

^{1}H NMR: δ 7.53-7.48 (m, 2H), 7.29-7.20 (m, 2H), 7.14 (t, J = 7.45 Hz, 1H), 6.99 (t, J = 6.48 Hz, 2H), 6.25 (d, J = 7.77 Hz, 1H), 5.85 (s, 1H), 5.69-5.64 (m, 2H), 4.00 (s, 3H), 3.62 (s, 3H).

^{13}C NMR: δ 164.80, 163.60, 143.82, 141.43, 133.07, 132.85, 130.57, 129.46, 128.30, 127.44, 126.97, 126.51, 125.06, 123.65, 121.91, 108.83, 104.99, 103.01, 78.08, 72.56, 53.38, 51.85.

3.6 References

1. "Towards the ideal synthesis": Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind.*, **1997**, 765.
2. Strecker, A. *Liebigs Ann. Chem.* **1850**, *75*, 27.
3. Mannich, C.; Krösche, W. *Arch. Pharm.* **1912**, *250*, 647.
4. Biginelli, P. *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 1317.
5. Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, *215*, 1.
6. (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 3168. (b) Ugi, I.; Dömling, A.; Hörl, W. *Endeavour* **1994**, *18*, 430. (c) Armstrong, R. W.; Combs A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123.
7. Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126.
8. Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Tetrahedron Lett.* **1997**, *38*, 2519.

9. Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386.

10. (a) Ugi, I.; Lohberger, S.; Karl, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 1083.

11. Isenring, H. P.; Hofheinz, W. *Synthesis* **1981**, 385.

12. Bauer, S. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1999**, *121*, 6355.

13. Robinson, R. *J. Chem. Soc* **1917**, *111*, 876.

14. Bossert, F.; Meyer, H.; Wehinger, R. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 762.

15. (a) Bergs, H. German Patent DE-B 566,094, **1929**. (b) Bucherer, T.; Barsch, H. J. Prakt. Chem. **1934**, *140*, 151.

16. Huisgen, R.; Morikawa, M.; Herbig, K.; Brunn, E. *Chem. Ber.* **1967**, *100*, 1094.

17. (a) Nair, V.; Vinod, A. U.; *Chem. Comm.* **2000**, 1019. (b) Nair, V.; Vinod A. U.; Rajesh, C. *J. Org. Chem.* **2001**, *66*, 4427.

18. Nair, V.; Bindu, S.; Balagopal, L. *Tetrahedron Lett.* **2001**, *42*, 2043.

19. Nair, V.; Sreekanth A. R.; Abhilash, N.; Bhadbhadhe, M. M.; Gonnade, R. C. *Org. Lett.* **2002**, *4*, 3575.

20. (a) Houlihan, W. J.; Cheon, S. H.; Parrino.; V. A.; Handley, D.A.; Larson, D. A. *J. Med. Chem*, **1993**, 36, 3098. (b) Scholz, D.; Schmidt, H.; Prieschl, E. E.; Csonga, R.; Scheirer, W.; Weber, V.; Lembachner.; A; Seidl, G.; Werner, G.; Mayer, P.; Baumruker, T. *J. Med. Chem.* **1998**, *41*, 1050. (c) Campagna, F.; Carotti, A.; Casini, G.; Otto, A. M. *Farmaco*, **1995**, *50*, 137. (d) Bernath, G.; Fulop, F.; Kobor, J. *Acta Pharm. Hung.* **1993**, *63*, 129.

The Reaction of Isoquinoline and Dimethyl acetylenedicarboxylate with 1,2- and 1,4-Benzoquinones: A Novel Synthesis of Spiro[1,3]oxazino[2,3-a]isoquinolines

4.1 Introduction

The chemistry of quinonoid compounds has been employed elegantly for the construction of a variety of natural as well as unnatural molecules.[1] Of all the quinonoids, the benzoquinones have been the subject of most of these studies.[2, 3] The reactivity of 1,2-benzoquinones in cycloaddition reactions depends on the electronic and steric nature of substituents.[4] The different types of reactivity shown by 1,2-benzoquinones in cycloaddition reactions is briefly discussed in the following sections.

4.1.1 Diels-Alder Reactions of 1,2-Benzoquinones

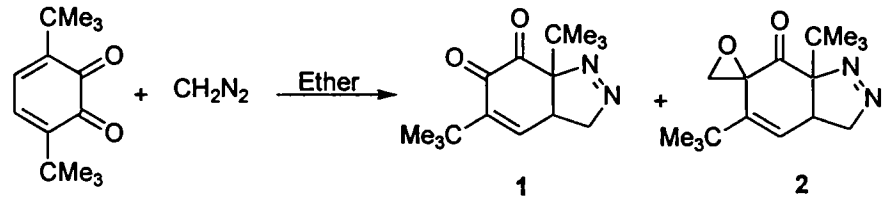
1,2-Benzoquinones can participate as 4π or 2π components in cycloaddition reactions. They afford benzodioxin derivatives with heterocyclic dienes such as furans[5] and pyrroles,[6] with the latter participating as dienophiles and the quinones as heterodienes. The highly electron deficient carbodiene moiety of *o*-benzoquinones undergoes facile Diels-Alder reactions with carbocyclic dienes, pentafulvenes, acetylenes *etc* leading to bicyclo[2.2.2]systems.[7] It is noteworthy that the resulting bicyclo[2.2.2]octenediones undergo a number of interesting and useful transformations.[8] It has been shown that 1,2-benzoquinone acts as an electron deficient dienophile in its reaction with 2,3-dimethylbutadiene, 1-acetoxy

butadiene *etc via* an inverse electron demand Diels-Alder pathway.[9] 1,2-Benzoquinone can also act as a heterodienophile due to the presence of two activated carbonyl groups, which was evident from its reaction with 1,4-diacetoxybutadiene, affording a benzodioxin derivative *via* a [3,3] sigmatropic rearrangement of the primary spiroadduct at higher temperature.[9, 10]

4.1.2 Dipolar Cycloaddition Reactions of 1,2-Benzoquinones

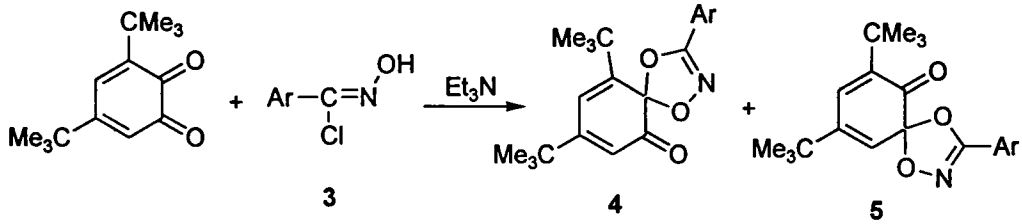
In contrast to the large amount of work carried out on the Diels-Alder cycloadditions of 1,2-quinones, very little is known about their dipolar cycloadditions. The available information is summarised below.

The reaction of diazomethane with 3,6-di-*tert*-butyl-1,2-benzoquinone affords indazole **1**. With excess of diazomethane, one of the carbonyl groups is converted to a spirooxirane **2** (Scheme 4.1).[11]



Scheme 4.1

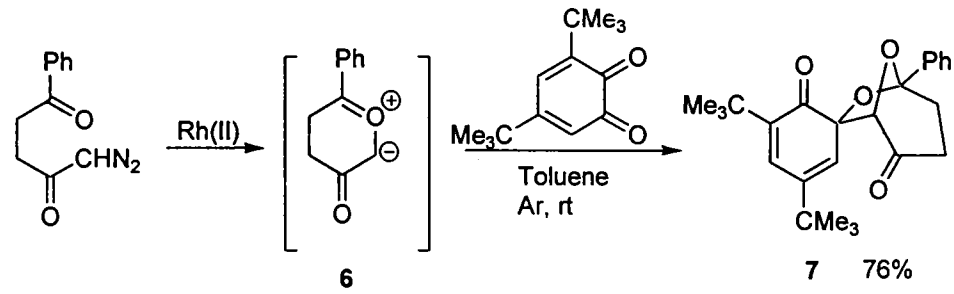
It has been shown that, aryl nitrile oxides undergo facile cycloaddition with 1,2-benzoquinones. For example 3,5-di-*tert*-butyl-1,2-benzoquinone on treatment with 4-methyl benzohydroximoyl chloride and triethylamine in benzene at room temperature afforded a regioisomeric mixture of products **4** and **5** in 3:1 ratio (Scheme 4.2).[12]



Scheme 4.2

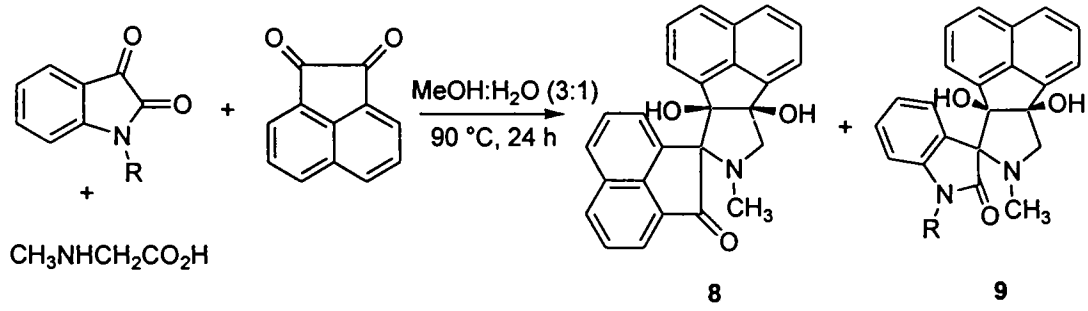
The dipolar cycloaddition reactions of carbonyl ylides with 1,2-diones have been reported from our laboratory. The rhodium(II) acetate catalysed cycloaddition reaction of 1-diazo-5-phenyl-2,5-pentanedione with 3,5-di-*tert*-

butyl-1,2-benzoquinone proceeded smoothly *via* the intermediacy of the carbonyl ylide **6** to afford a yellow crystalline cycloadduct **7** in 76% yield (Scheme 4.3).[13]



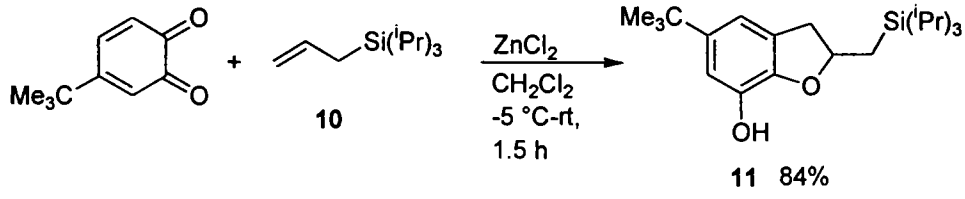
Scheme 4.3

Grigg *et al.* have shown that azomethine ylides resulting from the condensation of 1,2-dicarbonyl compounds with α-aminoacids or amines undergo cycloaddition reaction with maleimides and acyclic esters.[14] Interestingly, it was found that an isatin and acenaphthenequinone on reaction with sarcosine underwent an unusual mode of cycloaddition to yield the products **8** and **9** *via* the azomethine ylides (Scheme 4.4).[15]



Scheme 4.4

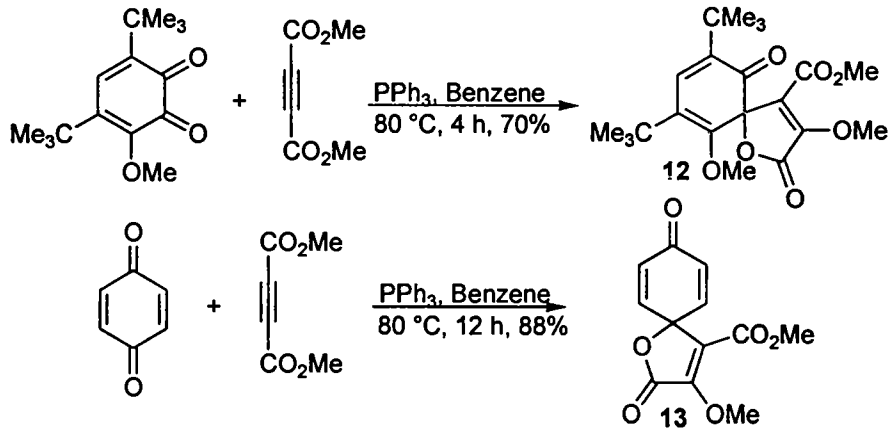
In presence of Lewis acids, allylsilane undergoes a formal [2+3] cycloaddition with 4-*tert*-butyl-1,2-benzoquinone to yield the benzofuran derivative **11** (Scheme 4.5).[16]



Scheme 4.5

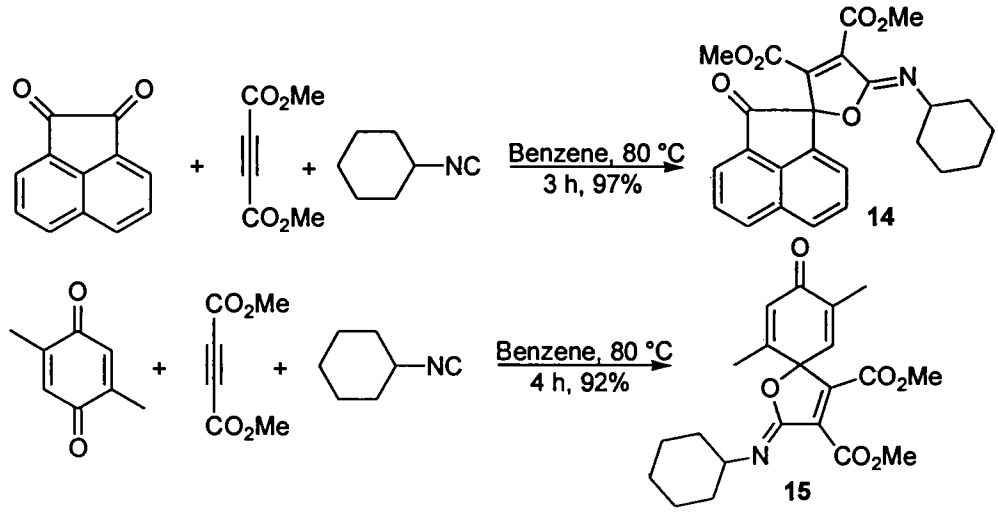
4.2 Background to the Present Work

In the context of the general interest in the cycloaddition reactions of 1,2-benzoquinones (*vide supra*), investigations carried out in our laboratory have shown that the dipolar intermediate generated by the addition of triphenylphosphine and DMAD underwent a facile addition to 1,2- and 1,4-benzoquinones to afford highly functionalised novel γ-spirolactones in high yields (Scheme 4.6).[17]



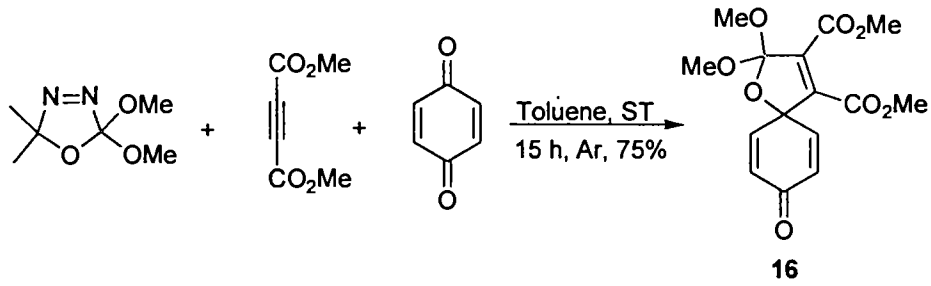
Scheme 4.6

It has been shown that the 1,3-dipolar intermediate generated by the addition of isocyanide to DMAD can be trapped with 1,2- and 1,4-benzoquinones to afford novel spiro iminolactones in high yields (Scheme 4.7).[18]



Scheme 4.7

Related investigations in our laboratory have also shown that the dipolar intermediate generated by the addition of dimethoxy carbene to DMAD can be trapped with the quinone carbonyl to afford novel spiro dihydrofuran derivative **16** (Scheme 4.8).[19]



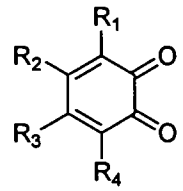
Scheme 4.8

A subject of continuing interest in this area has been the investigation of dipolar intermediates generated from dimethyl acetylenedicarboxylate and other nucleophiles and interception of such species with a third component (dipolarophile). It was surmised that the 1,4-dipolar intermediate derived from isoquinoline and DMAD was likely to undergo cycloaddition to quinones leading to novel heterocycles. The results validating the assumption constitute the subject matter of this chapter.

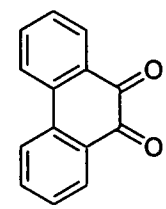
4.3 Results and Discussion

4.3.1 Reaction of Isoquinoline and DMAD with 1,2-Benzoquinones

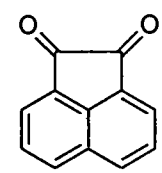
The 1,2-quinones selected for our study are listed in Figure 4.1.



17 (a-d)

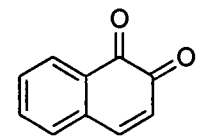


18



19

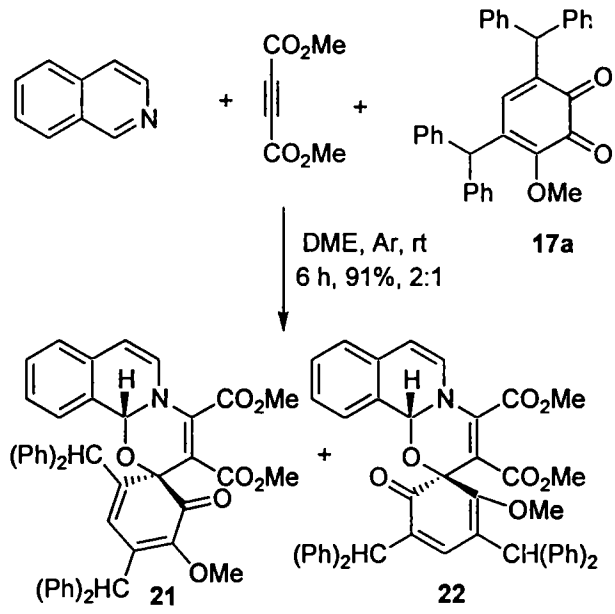
(a) $R_1 = R_3 = CH(Ph)_2$, $R_2 = H$, $R_4 = OMe$
(b) $R_1 = R_3 = CMe_3$, $R_2 = R_4 = H$
(c) $R_1 = R_3 = CMe_3$, $R_2 = H$, $R_4 = OMe$
(d) $R_1 = R_2 = R_4 = H$, $R_3 = CMe_3$



20

Figure 4.1

In a pilot experiment, it was observed that a mixture of 3-methoxy-4,6-bis(1,1-diphenylmethyl)-1,2-benzoquinone **17a** and DMAD at room temperature in anhydrous DME, when treated with isoquinoline afforded the spiro [1,3]oxazino[2,3-a]isoquinoline derivatives **21** and **22** in 91% yield in the ratio 2:1 (Scheme 4.9).



Scheme 4.9

The products **21** and **22** were characterised by spectroscopic techniques. The IR spectrum showed strong absorptions at 1742, 1708 and 1667 cm^{-1} indicating the presence of ester and enone carbonyls. In the ^1H NMR spectrum of **21**, signals due to the three methoxy groups were visible at δ 3.94, 3.54 and 3.40; the corresponding signals for **22** were observed at δ 3.90, 3,64 and 3.47. The ring junction proton of **21** was discernible as a singlet at δ 6.50; the corresponding signal for **22** was seen as singlet at δ 6.68. In ^{13}C NMR spectrum of **21**, the characteristic signal for the spirocarbon was observed at δ 78.22, whereas in the spectrum of **22**, it was discernible at δ 80.92. The signals corresponding to ester and enone carbonyls of **21** were seen at δ 163.48, 163.55 and 194.94 and those for **22** were visible at δ 163.44, 164.23 and 193.17. Finally

the structure and stereochemistry of the product **22** was unambiguously established by single crystal X-ray analysis (Figure 4.2).

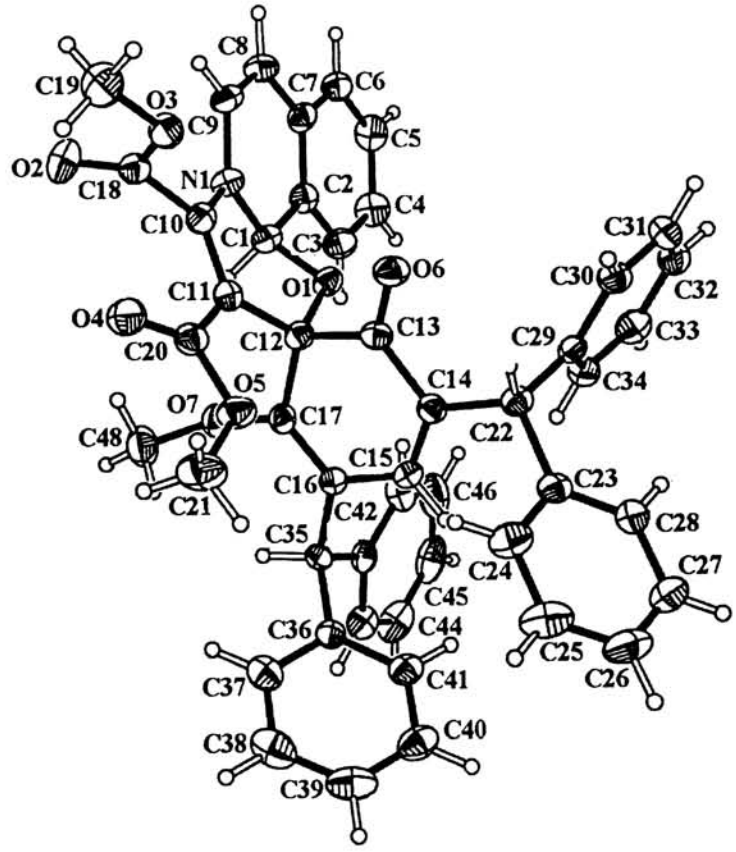


Figure 4.2 X-ray crystal structure of 22

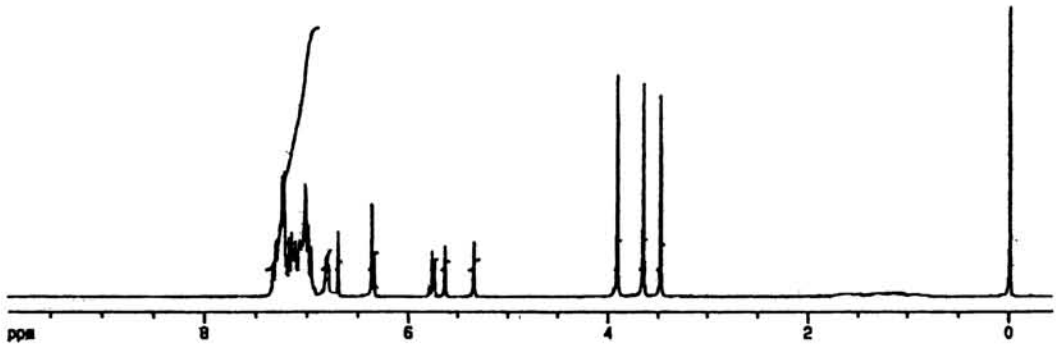


Figure 4.3 ^{1}H NMR of 22

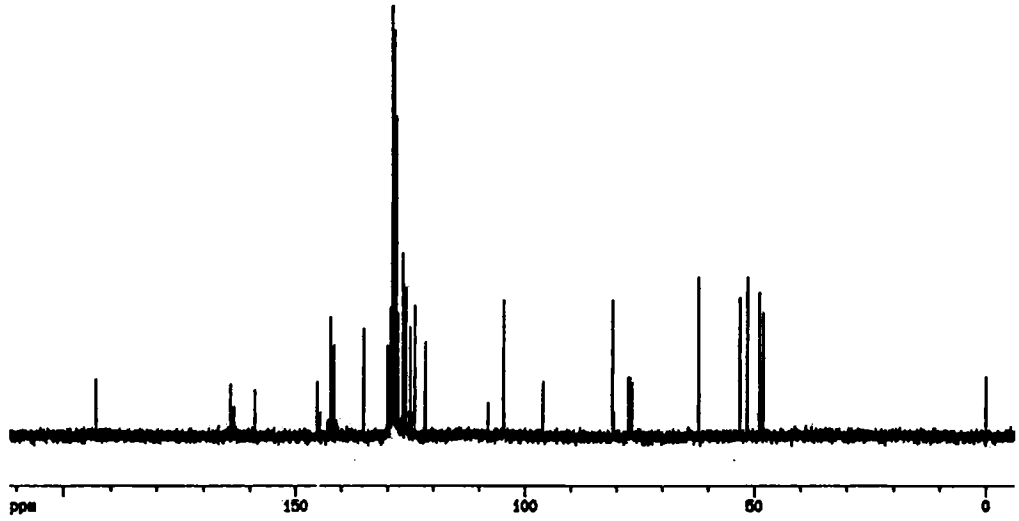
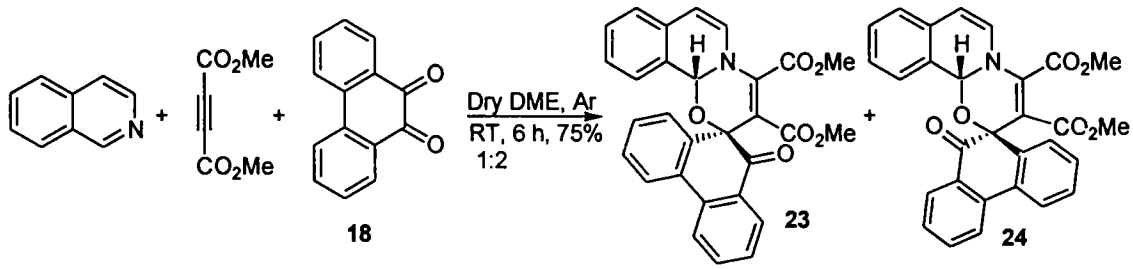


Figure 4.4 ^{13}C NMR of 22

A similar reaction occurred with 9,10-phenanthrenequinone **18**, when it was treated with isoquinoline and DMAD at room temperature to afford the regioisomers **23** and **24** in the ratio 1:2 in 75% yield (Scheme 4.10).

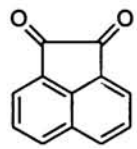
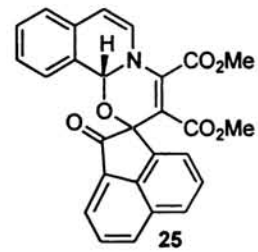
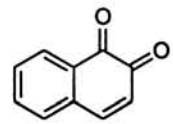
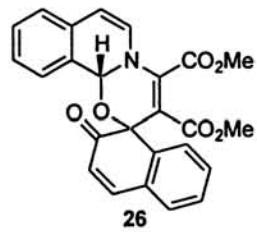
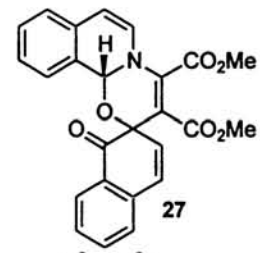
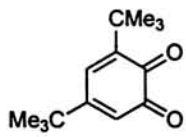
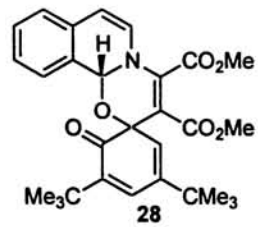
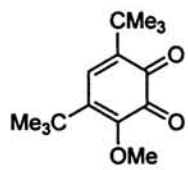
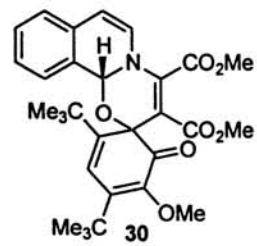
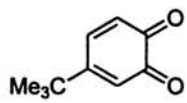
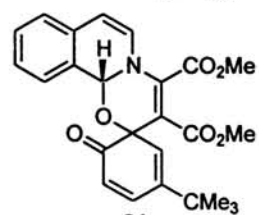
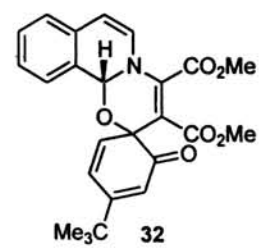


Scheme 4.10

The regioisomers were separated by column chromatography and characterised by spectroscopic techniques. In the IR spectrum, both **23** and **24** showed absorptions at 1748 and 1708 cm^{-1} due to ester carbonyls. In the ^{1}H NMR spectrum, **23** showed singlets at δ 4.03 and 3.45 which are diagnostic for the methoxy groups; the corresponding signal for **24**, were seen at δ 4.00 and 3.35. The ^{13}C signals for the ester and benzoyl carbonyls for **23** were seen at δ 162.93, 163.72 and 193.52, whereas in the spectrum of **24**, these signals were observed at δ 163.63, 163.88 and 194.70. The characteristic spirocarbon signal for **23** and **24** were discernible at δ 79.92 and 79.20 respectively.

Similar reactivity was observed with acenaphthenequinone **19**, 1,2-naphthoquinone **20**, 3,5-di-*tert*-butyl-1,2-benzoquinone **17b**, 3-methoxy-4,6-di-*tert*-butyl-1,2-benzoquinone **17c** and 4-*tert*-butyl-1,2-benzoquinone **17d**, yielding the [1,3]oxazino[2,3-a]isoquinoline derivatives **25-32**. The results obtained are summarised in Table 4.1.

Table 4.1

Entry	Quinone	Products	Ratio [a]	Yield(%) [b]
1.	 **19**	 **25**		53
2.	 **20**	 **26**  **27**	1:1	62
3.	 **17b**	 **28**  **29**	1:2	85
4.	 **17c**	 **30**		89
5.	 **17d**	 **31**  **32**	3.5:1	94

Reaction conditions: DME, Ar, rt, 6 h; a = ratio of regioisomers; b = isolated yield

The reaction of acenaphthenequinone **18** afforded the spiro[1,3]oxazinoisoquinoline **25** in 53% yield. The IR spectrum showed strong absorptions at 1748 and 1728 cm^{-1} due to the ester carbonyls. The sharp band at 1700 cm^{-1} was assigned to the keto carbonyl. In the ^1H NMR spectrum, the two carbomethoxy groups displayed singlets at δ 3.99 and 3.17, while the signals due to olefinic protons were observed as doublets at δ 6.46 and 5.81. In the ^{13}C NMR spectrum of **25**, the characteristic signal for the spirocarbon was discernible at δ 80.00. The signals at δ 163.66 and 163.54 revealed the presence of ester carbonyls and the corresponding methoxy carbon signals were observed at δ 53.30 and 51.33. The keto carbonyl signal was visible at δ 200.79.

Similarly, the reaction of 1,2-naphthoquinone **20** afforded the regioisomers **26** and **27** in the ratio 1:1. The strong absorptions at 1742 and 1708 cm^{-1} in the IR spectrum of **26** and **27** correspond to ester carbonyls, whereas the absorption at 1679 cm^{-1} for **26** and 1667 cm^{-1} for **27**, are due to enone carbonyls. In ^1H NMR, the signal for the ring junction proton in **26** was observed as a singlet at δ 6.92, the corresponding signal for **27**, was seen as a singlet at δ 6.84. The ^{13}C NMR spectrum of **26** showed signals at δ 163.48, 163.95 and 196.22 for the carbomethoxy and enone carbonyls. In the spectrum of **27**, the signals appeared at δ 163.33, 163.51 and 196.70 corresponding to carbomethoxy and enone carbonyls. The characteristic spirocarbon signal for **26** and **27** were seen at δ 79.27 and 78.36 respectively.

Reaction of 3,5-di-*tert*-butyl-1,2-benzoquinone **17b** gave a 2:1 regioisomeric mixture of [1,3]oxazino[2,3-a]isoquinoline derivatives **28** and **29**. The isomers were separated and characterised by spectroscopic analysis. In the IR spectrum, strong absorptions at 1742, 1708 and 1667 cm^{-1} for both **28** and **29** were attributable to the ester and enone carbonyls. In the ^1H NMR spectrum, **28** showed two singlets at δ 1.31 and 1.11 due to the teritary butyl groups, whereas in the spectrum of **29**, the *tert*-butyl groups displayed singlets at δ 1.22 and 1.14.

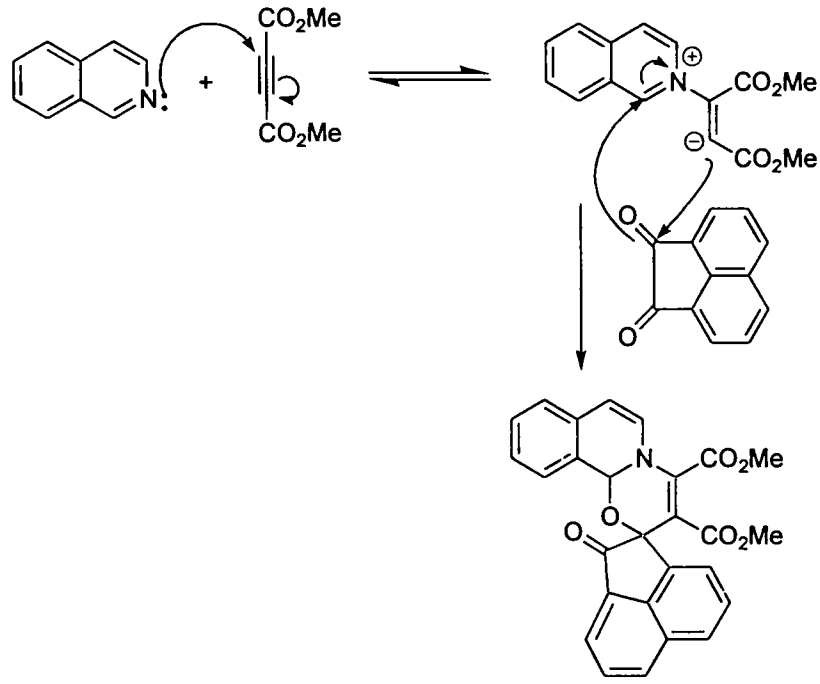
The ring junction proton for **29** was discernible as singlet at δ 6.92. In the ^{13}C NMR spectrum, the characteristic spirocarbon signal for **28** and **29** were seen at δ 78.17 and 78.60 respectively. The signals at δ 163.73, 164.03 and 198.10 in the spectrum of **28** and those at δ 163.76, 164.13 and 200.00 in the spectrum of **29** correspond to the ester and enone carbonyls.

Interestingly, the reaction of 3-methoxy-4,6-di-*tert*-butyl-1,2-benzoquinone **17c** afforded a single product **30**. The IR spectrum of **30** showed characteristic ester carbonyl absorptions at 1748 and 1708 cm^{-1} and enone carbonyl at 1667 cm^{-1}. The ^1H NMR showed three singlets at δ 4.03, 3.58 and 3.54 corresponding to the three methoxy groups. The two *tert*-butyl groups displayed their signals as singlets at δ 1.29 and 1.21. The ring junction proton displayed a singlet at δ 6.62. The ^{13}C NMR spectrum showed the typical signals at δ 78.65 and 195.90 corresponding to the spiro and enone carbonyl carbons respectively. The carbomethoxy signals were visible at δ 163.88 and 163.64. All other signals were also in good agreement with the proposed structure.

4-*tert*-Butyl-1,2-benzoquinone **17d** also afforded regioisomers **31** and **32** in the ratio 3.8:1. In the IR spectrum, absorptions at 1742, 1708 and 1667 cm^{-1} are due to ester and enone carbonyls. In the ^1H NMR, the major isomer **31** showed singlet at δ 1.18 due to *tert*-butyl group whereas the singlets at δ 3.97 and 3.58 were assigned to methoxy protons. The ring junction proton was discernible at δ 6.87. In the ^{13}C NMR spectrum, the characteristic spirocarbon signal was observed at δ 78.79 and the ester carbonyls were discernible at δ 163.44 and 163.03.

4.3.1.1 Mechanistic Consideration

It is reasonable to assume that the reaction involves the initial formation of a 1,4-dipolar intermediate from isoquinoline and DMAD, which adds to the carbonyl moiety of the quinone in a [4+2] fashion to yield the spiro[1,3]oxazino[2,3-a]isoquinolines (Scheme 4.11).

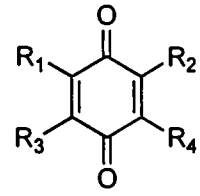


Scheme 4.11

4.3.2 Reaction of Isoquinoline and DMAD with 1,4-Benzoquinones

In view of the interesting results obtained in the addition of the 1,4-dipolar intermediate generated from isoquinoline and DMAD to 1,2-benzoquinones, it was reasonable to explore the reactivity of 1,4-benzoquinones towards the 1,4-dipolar intermediate.

The quinones selected for the study are listed in Figure 4.5.

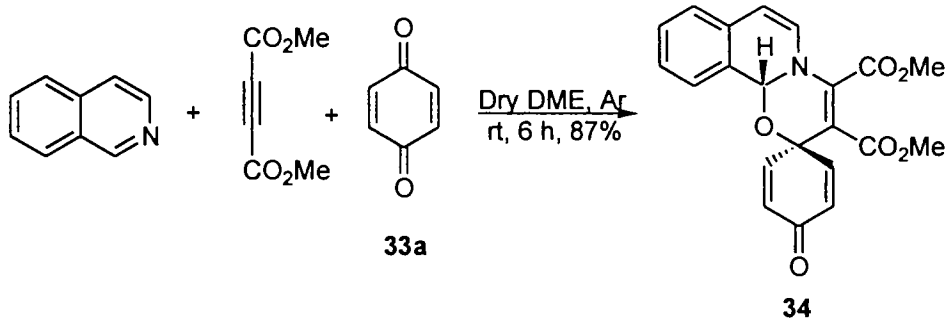


33 (a-d)

(a) $R_1 = R_2 = R_3 = R_4 = H$
(b) $R_1 = R_4 = H$, $R_2 = R_3 = CH_3$
(c) $R_1 = R_3 = R_4 = H$, $R_2 = Ph$
(d) $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$

Figure 4.5

1,4-Benzoquinone **33a** when treated with DMAD and isoquinoline in anhydrous DME at room temperature for 6 h afforded the spiro[1,3]oxazino[2,3-a]isoquinoline derivative **34** in 87% yield (Scheme 4.12).



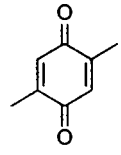
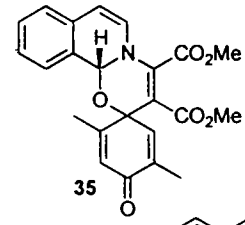
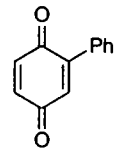
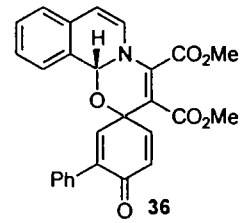
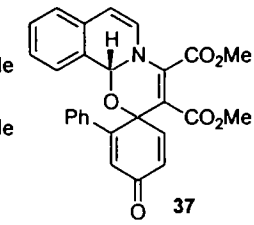
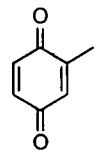
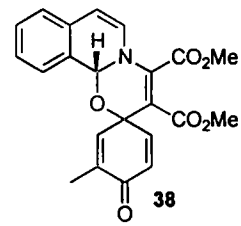
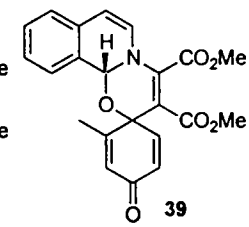
33a **34**

Scheme 4.12

The IR spectrum of **34** showed strong absorptions at 1742 and 1702 cm^{-1} due to ester carbonyls; the enone carbonyl was discernible at 1672 cm^{-1}. In the ^1H NMR spectrum, the carboxy methyl groups resonated as singlets at δ 3.96 and 3.59. The signals due to the protons of the cyclohexadienone ring was observed as a multiplet in the region δ 6.36-6.25. In the ^{13}C NMR spectrum, the ester carbonyls resonated at δ 163.75 and 163.12. The signal at δ 185.46 was assigned to the dienone carbonyl. The characteristic signal due to the spirocarbon was discernible at δ 85.96 and the signal due to the methoxy carbons were seen at δ 53.48 and 51.81. All other signals were in agreement with the assigned structure.

Similar results were obtained with other 1,4-benzoquinones yielding the [1,3]oxazino[2,3-a]isoquinoline derivatives **35-39**; the results are summmarized in Table 4.2.

Table 4.2

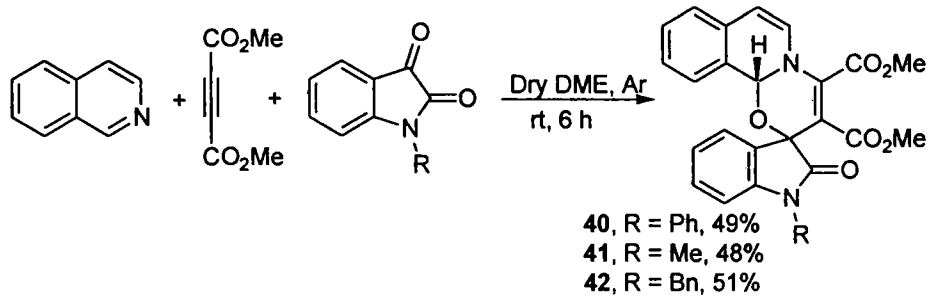
Entry	Quinone	Products	Ratio [a]	Yield(%) [b]
1.	 **33b**	 **35**		76
2.	 **33c**	 **36**  **37**	2:1	90
3.	 **33d**	 **38**  **39**	2.7:1	89

Reaction conditions: DME, Ar, rt, 6 h; a = ratio of regioisomers; b = isolated yield

In all the cases, compounds were characterised by spectroscopic techniques. The spiro[1,3]oxazino[2,3-a]isoquinoline derivatives **35-39** showed characteristic ester carbonyls both in the IR and ^{13}C NMR spectra. All other signals were also in good agreement with the assigned structure.

4.3.3 Reaction of Isoquinoline and DMAD with *N*-substituted Isatins

Subsequently we carried out some experiments using *N*-substituted isatins. Thus the reaction of *N*-substituted isatins with DMAD and isoquinoline afforded the spiro[1,3]oxazino[2,3-a]isoquinoline derivative **40-42** in moderate yields (Scheme 4.13).



Scheme 4.13

The products were purified by chromatography and characterised by spectroscopic analysis. The IR spectrum of **40** showed the characteristic ester carbonyl absorptions at 1741 and 1711 cm^{-1}. The amide carbonyl absorption was seen at 1620 cm^{-1}. In the ^{1}H NMR spectrum, the methoxy groups were observed as singlets at δ 3.98 and 3.53 whereas the olefinic protons were visible as doublets at δ 6.42 (J = 7.73 Hz) and 5.83 (J = 7.74 Hz). In the ^{13}C NMR spectrum, the three resonance signals corresponding to the ester and amide carbonyls were seen at δ 162.89, 163.15 and 173.37. The signal due to the spirocarbon was discernible at δ 79.16. All the other signals were in agreement with the assigned structure.

The products **41** and **42** were also characterised by spectroscopic methods. Both showed characteristic ester carbonyls both in the IR and ^{13}C NMR spectra. All other spectroscopic data were also in good agreement with the assigned structure.

4.4 Conclusion

In conclusion, we have observed a novel three component condensation reaction that offers an easy and one pot entry into spiro[1,3]oxazino[2,3-a]isoquinolines *via* 1,4-dipolar cycloaddition. In this context, it is noteworthy that spiro[1,3]oxazino[2,3-a]isoquinoline derivatives are known to possess interesting biological activities.[20]

4.5 Experimental Details

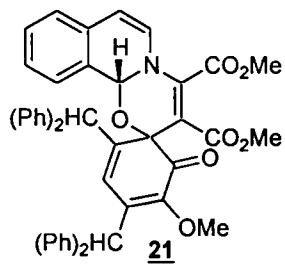
General information about the experiments is given in Section 2.13 (Chapter 2).

[1,3]Oxazino[2,3-a]isoquinolines 21 and 22

To a solution of 3-methoxy-4,6-bis(1,1-diphenylmethyl)-1,2-benzoquinone **17a** (248 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using

hexane-ethylacetate (80:20) gave **21** (222 mg, 57%) and **22** (143 mg, 34%) as yellow crystalline solids.

Dimethyl-2-methoxy-3,5-(dibenzhydryl)-6-oxospiro[cyclohexa-2,4-diene-1,2'-[2H,11bH][1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 21



21

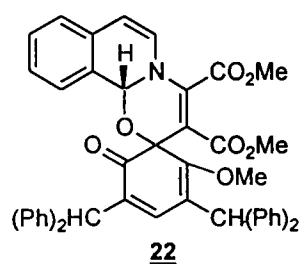
Mp: 208-210 °C.

IR(KBr) ν_{max}: 2948, 1742, 1708, 1667, 1600, 1499, 1431, 1276, 1236, 1148 cm^{-1}.

^{1}H NMR: δ 7.28-6.88 (m, 21H), 6.72 (d, J = 7.66 Hz, 2H), 6.50 (s, 1H), 6.39 (s, 1H), 6.34 (d, J = 7.67 Hz, 1H), 5.84-5.72 (m, 2H), 5.55 (s, 1H), 5.49 (s, 1H), 3.94 (s, 3H), 3.54 (s, 3H), 3.40 (s, 3H).

^{13}C NMR: δ 194.94, 163.55, 163.48, 155.95, 148.02, 143.19, 141.99, 134.63, 129.95, 129.53, 129.32, 129.12, 129.06, 128.96, 128.92, 128.54, 128.46, 128.35, 128.26, 128.14, 126.48, 126.41, 126.37, 123.30, 105.10, 104.66, 78.22, 61.63, 53.30, 51.62, 48.94, 47.89.

Dimethyl-3-methoxy-4,6-(dibenzhydryl)-2-oxospiro[cyclohexa-2,4-diene-1,2'-[2H,11bH][1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 22



22

Mp: 198-200 °C.

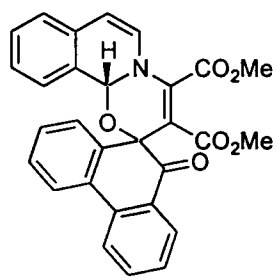
IR(KBr) ν_{max}: 2955, 1742, 1708, 1667, 1600, 1499, 1431, 1229, 1148 cm^{-1}.

^{1}H NMR: δ 7.30-6.95 (m, 22H), 6.80-6.78 (m, 2H), 6.68 (s, 1H), 6.34 (d, J = 7.48 Hz, 2H), 5.74 (d, J = 7.76 Hz, 1H), 5.62 (s, 1H), 5.33 (s, 1H), 3.90 (s, 3H), 3.64 (s, 3H), 3.47 (s, 3H).

^{13}C NMR: δ 193.17, 164.23, 163.44, 158.96, 142.41, 142.39, 135.16, 129.39, 129.00, 128.95, 128.92, 128.83, 128.52, 128.50, 128.09, 128.05, 127.79, 126.69, 126.69, 126.22, 126.18, 126.06, 124.13, 108.10, 104.72, 80.92, 62.11, 53.26, 48.97, 48.10.

Dimethyl-2-oxospiro[phenanthrene-1,2'-[2H,11bH][1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 23 and 24

To a solution of phenanthrenequinone (110 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at room temperature 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) **23** (62 mg, 25%) and **24** (127 mg, 50%) as yellow crystalline solids.



23

Mp: 202-204 °C

IR(KBr) ν_{max}: 2955, 1748, 1708, 1595, 1573, 1431, 1283, 1222, 1162 cm^{-1}

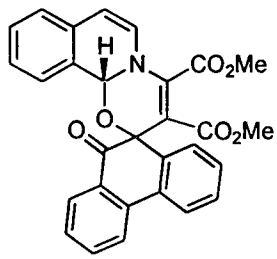
^{1}H NMR: δ8.07 (q, J = 4.56 Hz, 2H), 7.96 (d, J = 7.69 Hz, 1H), 7.70 (t, J = 7.67 Hz, 1H), 7.52 (q, J = 7.05 Hz, 2H), 7.44-7.35 (m, 2H), 7.16 (t, J =7.42 Hz, 1H), 6.98 (d, J = 7.46 Hz, 2H), 6.63 (d, J = 7.57 Hz, 1H), 6.36 (d, J = 7.76 HZ, 1H), 6.23 (s, 1H), 5.72 (d, J = 7.79 Hz, 1H), 4.03 (s, 3H), 3.45 (s, 3H).

^{13}C NMR: δ 193.52, 163.72, 162.93, 145.21, 137.35, 135.94, 134.23, 130.55, 129.26, 129.05, 128.78, 127.99, 127.88, 127.78, 127.47, 126.54, 126.24, 124.89, 124.41, 124.28, 123.12, 122.64, 104.65, 103.84, 79.92, 52.76, 51.03.

Mp: 192-194 °C.

IR(KBr) ν_{max}: 2955, 1748, 1708, 1685, 1600, 1569, 1431, 1276, 1220, 1155 cm^{-1}.

^{1}H NMR: δ 8.22 (d, J = 7.72 Hz, 1H), 7.96 (dd, J = 8.00, 11.78 Hz, 2H), 7.66 (t, J = 7.65 Hz, 1H), 7.48-7.42 (m, 2H), 7.36-7.23 (m, 2H), 7.16 (t, J = 7.39 Hz, 1H), 7.05-6.98 (m, 3H), 6.77 (s, 1H), 6.41 (d, J = 7.74 Hz, 1H), 5.75 (d, J = 7.74 Hz, 1H), 4.00 (s, 3H), 3.35 (s, 3H).



24

^{13}C NMR: δ 194.70, 163.88, 163.63, 145.10, 137.30, 136.96, 134.86, 131.25, 129.83, 129.34, 129.32, 129.23, 128.50, 128.28, 127.72, 127.66, 126.97, 125.86, 125.04, 123.68, 123.42, 123.24, 109.58, 104.80, 79.20, 53.35, 51.59.

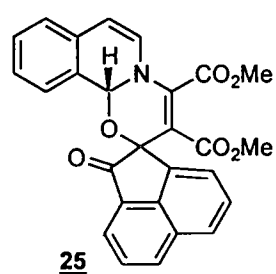
Dimethyl-2-oxospiro[acenaphthylene-1,2'-[2H,11bH][1,3]oxazino [2,3-a]isoquinoline]-3',4'-dicarboxylate 25

To a solution of acenaphthenequinone (96 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **25** as an yellow crystalline solid (127 mg, 53%).

Mp: 155-157 °C.

IR(KBr) ν_{max}: 2955, 1748, 1728, 1700, 1593, 1573, 1431, 1290, 1222, 1148 cm^{-1}.

^{1}H NMR: δ 8.05 (q, J = 7.53 Hz, 2H), 7.82 (d, J = 8.16 Hz, 1H), 7.74 (t, J = 7.59 Hz, 1H), 7.57-7.48 (m, 2H), 7.26-7.03 (m, 5H), 6.46 (d, J = 7.75 Hz,



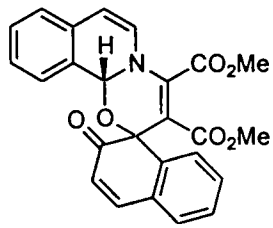
25

1H), 5.81 (d, J = 7.76 Hz, 1H), 3.99 (s, 3H), 3.17 (s, 3H).

^{13}C NMR: δ 200.79, 163.66, 163.54, 145.13, 143.07, 138.42, 131.44, 130.97, 130.56, 129.71, 129.39, 128.57, 128.14, 127.94, 127.03, 126.20, 125.68, 125.13, 123.22, 122.03, 119.85, 106.11, 105.05, 80.00, 53.30, 51.33.

Dimethyl-2-oxo-spiro[naphthylene-1,2'-[2H,11bH][1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 26 and 27

To a solution of 1,2-naphthoquinone (83 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **26** (75 mg, 33%) and **27** (65 mg, 29%) as yellow crystalline solids.



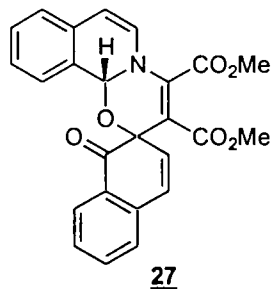
26

Mp: 165-167 °C.

IR(KBr) ν_{max}: 2955, 1739, 1708, 1679, 1594, 1565, 1431, 1277, 1236, 1148 cm^{-1}.

^{1}H NMR: δ 8.12 (d, J = 7.60 Hz, 1H), 7.56 (t, J = 7.48 Hz, 1H), 7.39 (t, J = 7.52 Hz, 1H), 7.25-7.06 (m, 5H), 6.92 (s, 1H), 6.71 (d, J = 9.77 Hz, 1H), 6.36 (d, J = 7.73 Hz, 1H), 5.81-5.76 (m, 2H), 3.97 (s, 3H), 3.44 (s, 3H).

^{13}C NMR: δ 196.22, 163.95, 163.48, 144.30, 136.90, 134.63, 132.96, 130.39, 129.70, 129.43, 129.35, 128.95, 128.36, 128.09, 127.78, 127.69, 127.39, 127.10, 126.19, 125.17, 123.13, 108.32, 104.97, 79.27, 53.30, 51.53.



27

Mp: 170-172 °C.

IR(KBr) ν_{max}: 2955, 1742, 1708, 1667, 1598, 1570, 1430, 1320, 1277, 1149 cm^{-1}.

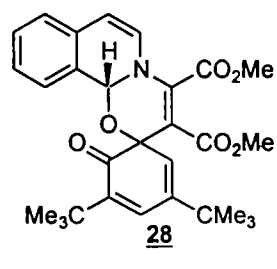
^{1}H NMR: δ 7.44-7.03 (m, 9H), 6.84 (s, 1H), 6.41 (d, J = 7.72 Hz, 1H), 6.24 (d, J = 9.93 Hz, 1H), 5.79 (d, J = 7.74 Hz, 1H), 3.99 (s, 3H), 3.46 (s, 3H).

^{13}C NMR: δ 196.70, 163.51, 163.33, 144.92, 144.70, 140.36, 130.61, 130.36, 129.67, 129.52, 129.23, 128.74, 127.66, 127.07, 126.89, 125.77, 124.95, 123.48, 123.15, 109.36, 104.80, 78.36, 53.19, 51.46.

[1,3]oxazino[2,3-a]isoquinolines 28 and 29

To a solution of 3,5-di-*tert*-butyl-1,2-benzoquinone (116 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 053 mmol) and the mixture was stirred at RT for 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **28** (152 mg, 58%) and **29** (70 mg, 27%) as yellow semi-solids.

Dimethyl-3,5-(t-butyl)-6-oxospiro[cyclohexa-2,4-diene-1,2'-[2H,11bH][1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 28



28

IR(film) ν_{max}: 2955, 1742, 1708, 1667, 1593, 1566, 1430, 1276, 1229, 1148 cm^{-1}.

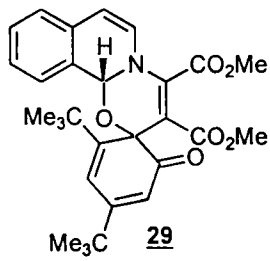
^{1}H NMR: δ 7.25-7.20 (m, 3H), 7.06 (d, J = 7.37 Hz, 1H), 6.89-6.84 (m, 2H), 6.35 (d, J = 7.71 Hz, 1H), 5.76 (d, J = 7.72 Hz, 1H), 5.52 (d, J = 2.22 Hz, 1H), 3.96 (s, 3H), 3.55 (s, 3H), 1.31 (s, 9H), 1.11 (s, 9H).

^{13}C NMR: δ 198.10, 164.03, 163.73, 145.17, 143.91, 142.69, 135.12, 130.02, 129.27, 128.29, 127.99, 126.99, 126.37, 125.14, 123.43, 109.30, 104.38, 78.17, 53.26, 51.11, 34.64, 31.21, 29.39, 28.54.

Dimethyl-4,6-(t-butyl)-2-oxospiro[cyclohexa-2,4-diene-1,2'-[2H,11bH][1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 29

IR(film) ν_{max}: 2955, 1742, 1708, 1667, 1592, 1566, 1430, 1276, 1230, 1150 cm^{-1}.

^{1}H NMR: δ 7.25-7.13 (m, 3H), 7.04 (d, J = 7.49 Hz, 1H), 6.92 (s, 1H), 6.54 (d, J = 1.29 Hz, 1H), 6.31 (d, J = 7.75 Hz, 1H), 5.95 (d, J = 1.31 Hz, 1H), 5.73 (d, J = 7.74 Hz, 1H), 3.97 (s, 3H), 3.55 (s, 3H), 1.22 (s, 9H), 1.14 (s, 9H).

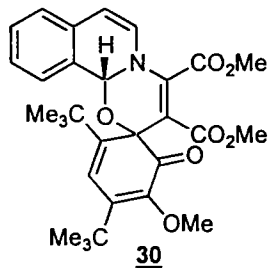


29

^{13}C NMR: δ 200.00, 164.13, 163.76, 144.34, 142.50, 136.26, 130.41, 129.94, 129.11, 127.85, 126.92, 126.36, 124.90, 123.75, 123.15, 115.85, 104.59, 78.60, 53.23, 51.33, 37.98, 35.77, 31.44, 28.36.

Dimethyl-2-methoxy-3,5-di(t-butyl)-2-oxospiro[cyclohexa-2,4-diene-1,2'-[2H,11bH][1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 30

To a solution of 3-methoxy-4,6-di-*tert*-butyl-1,2-benzoquinone (132 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL. 0.53 mmol) and the mixture was stirred at RT for 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave 30 (220 mg, 89%) as an yellow viscous liquid.



30

IR(film) ν_{max}: 2955, 1748, 1708, 1667, 1600, 1566, 1431, 1270, 1148 cm^{-1}.

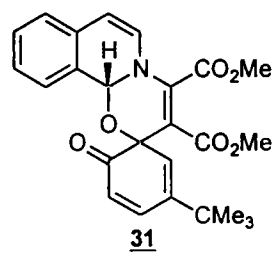
^{1}H NMR: δ 7.28-7.12 (m, 3H), 7.04 (d, J = 8.70 Hz, 2H), 6.62 (s, 1H), 6.33 (d, J = 7.71 Hz, 1H), 5.72 (d, J = 7.72 Hz, 1H), 4.03 (s, 3H), 3.58 (s, 3H), 3.54 (s, 3H), 1.29 (s, 9H), 1.21 (s, 9H).

^{13}C NMR: δ 195.90, 163.88, 163.64, 154.61, 144.90, 141.32, 138.79, 138.42, 130.21, 129.30, 128.61, 127.73, 126.98, 126.07, 124.99, 123.61, 109.51, 104.26, 78.65, 59.53, 53.18, 51.24, 34.61, 34.58, 30.08, 29.86.

[1,3]oxazino[2,3-a]isoquinolines 31 and 32

To a solution of 4-*tert*-butyl-1,2-benzoquinone (87 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **31** (169 mg, 73 %) as yellow solid and **32** (49 mg, 21%) as yellow viscous oil.

Dimethyl-3-(t-butyl)-6-oxospiro[cyclohexa-2,4-diene-1,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 31



31

Mp: 96-98 °C.

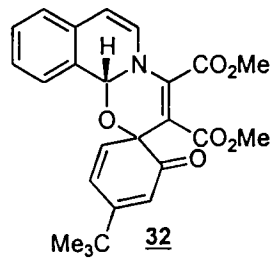
IR(KBr) ν_{max}: 2962, 1741, 1708, 1667, 1593, 1566, 1430, 1276, 1236, 1148 cm^{-1}.

^{1}H NMR: δ 7.31-7.17 (m, 3H), 7.08 (d, J = 7.38 Hz, 1H), 6.87 (s, 1H), 6.46 (d, J = 9.89 Hz, 1H), 6.35 (d, J = 7.71 Hz, 1H), 6.01 (s, 1H), 5.89 (d, J = 9.87 Hz, 1H), 5.79 (d, J = 7.73 Hz, 1H), 3.97 (s, 3H), 3.58 (s, 3H), 1.18 (s, 9H).

^{13}C NMR: δ 198.95, 163.44, 163.03, 144.41, 141.53, 138.70, 130.65, 129.92, 129.35, 128.22, 127.13, 126.34, 125.70, 124.80, 123.29, 118.48, 108.36, 104.95, 78.79, 53.19, 51.37, 35.40, 28.19.

Dimethyl-4-(t-butyl)-6-oxospiro[cyclohexa-2,4-diene-1,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 49

IR (film) ν_{max}: 2955, 1743, 1712, 1672, 1597, 1565, 1434, 1287 cm^{-1}.



32

^{1}H NMR: δ 7.29-7.16 (m, 3H), 7.06 (d, J = 7.50 Hz, 1H), 6.65 (d, J = 10.08 Hz, 1H), 6.43 (d, J = 10.04 Hz, 1H), 6.34 (d, J = 7.73 Hz, 1H), 6.25 (d, J = 9.56 Hz, 1H), 5.98 (s, 1H), 5.75 (d, J = 7.75 Hz, 1H), 3.94 (s, 3H), 3.56 (s, 3H), 1.21 (s, 9H).

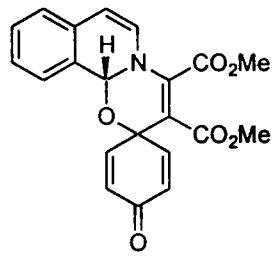
^{13}C NMR: δ 195.79, 164.06, 163.47, 144.95, 138.66, 135.38, 130.13, 129.57, 128.23, 127.14, 126.88, 125.99, 125.39, 124.10, 123.81, 119.23, 118.45, 104.63, 79.78, 53.25, 51.52, 35.30, 28.19.

Dimethyl-4-oxospiro[cyclohexa-2,4-diene-1,2'-[2H,11bH][1,3]oxazino [2,3-a]isoquinoline]-3',4'-dicarboxylate 34

To a solution of 1,4-benzoquinone (57 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **34** (175 mg, 87%) as an yellow crystalline solid.

Mp: 167-169 °C.

IR(KBr) ν_{max}: 2956, 1742, 1702, 1672, 1587, 1562, 1427, 1273, 1233 cm^{-1}.



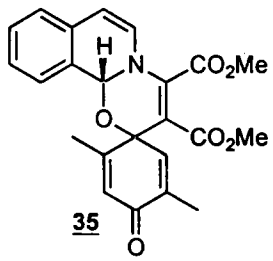
34

^{1}H NMR: δ7.37-7.25 (m, 3H), 7.14-7.06 (m, 2H), 6.51 (dd, J = 2.94, 9.92 Hz, 1H), 6.36-6.25 (m, 4H), 5.82 (d, J = 7.74 Hz, 1H), 3.96 (s, 3H), 3.59 (s, 3H).

^{13}C NMR: δ 185.46, 163.75, 163.12, 147.64, 145.35, 143.15, 130.34, 129.90, 129.65, 128.42, 127.73, 127.45, 125.87, 125.52, 123.29, 113.73, 111.86, 105.24, 85.96, 53.48, 51.81.

Dimethyl-2,5-dimethyl-4-oxospiro[cyclohexa-2,4-diene-1,2'-[2H, 11bH][1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 35

To a solution of 2,5-dimethyl-1,4-benzoquinone (72 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **35** (164 mg, 76%) as an yellow crystalline solid.



35

Mp: 168-170 °C.

IR(KBr) ν_{max}: 2955, 1742, 1721, 1681, 1647, 1593, 1566, 1438, 1283, 1236, 1148 cm^{-1}.

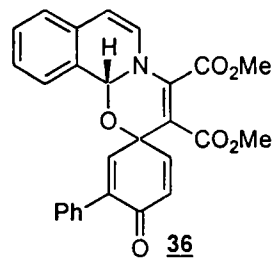
^{1}H NMR: δ7.33-7.24 (m, 3H), 7.13 (t, J = 8.10 Hz, 1H), 6.89 (s, 1H), 6.39 (dd, J = 7.68, 14.15 Hz, 1H), 6.25-6.19 (m, 1H), 6.06 (s, 1H), 5.83 (q, J = 7.74 Hz, 1H), 3.94 (s, 3H), 3.61 (s, 3H), 1.96 (s, 3H), 1.83 (s, 3H).

^{13}C NMR: δ 186.11, 163.94, 163.27, 156.36, 153.70, 143.59, 138.66, 134.65, 129.71, 129.05, 127.51, 127.18, 125.99, 125.30, 123.60, 109.93, 104.89, 104.66, 79.34, 53.33, 52.03, 17.45, 15.67.

[1,3]oxazino[2,3-a]isoquinolines 36 and 37

To a solution of 2-phenyl-1,4-benzoquinone (97 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave 36 (139 mg, 58%) and 37 (70 mg, 29%) as yellow solids.

Dimethyl-3-phenyl-4-oxospiro[cyclohexa-2,4-diene-1,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 36



36

Mp: 175-177 °C.

IR (KBr) ν_{max}: 2955, 1742, 1708, 1670, 1600, 1566, 1431, 1270, 1235, 1148 cm^{-1}.

^{1}H NMR: δ 7.45-7.20 (m, 5H), 7.13 (t, J = 8.10 Hz, 2H), 7.01 (d, J = 7.47 Hz, 1H), 6.94 (d, J = 7.58 Hz, 1H), 6.40-6.28 (m, 3H), 6.17 (d, J = 1.64 Hz, 1H), 5.73 (d, J = 7.73 Hz, 1H), 5.48 (s, 1H), 3.96 (s, 3H), 3.71 (s, 3H).

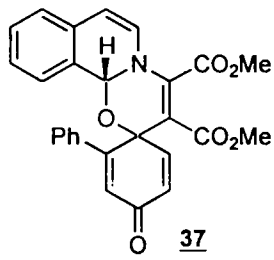
^{13}C NMR: δ 186.07, 163.28, 163.14, 156.43, 149.18, 144.96, 142.03, 138.05, 129.50, 129.08, 128.95, 128.67, 128.52, 128.16, 127.97, 127.74, 127.30, 127.12, 125.40, 123.15, 105.05, 79.68, 53.42, 52.07.

Dimethyl-2-phenyl-4-oxospiro[cyclohexa-2,4-diene-1,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 37

Mp: 162-164 °C.

IR(KBr) ν_{max}: 2955, 1742, 1708, 1667, 1593, 1566, 1431, 1276, 1236, 1148 cm^{-1}.

^{1}H NMR: δ 7.40-7.14 (m, 10H), 6.37 (d, J = 1.77



37

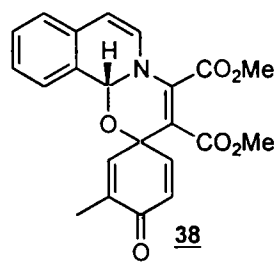
Hz, 1H), 6.31 (dd, J = 1.75, 10.02 Hz, 1H), 6.19 (s, 1H), 6.05 (d, J = 7.71 Hz, 1H), 5.80 (d, J = 7.73 Hz, 1H), 3.72 (s, 3H), 3.60 (s, 3H).

^{13}C NMR: δ 185.95, 163.69, 162.77, 157.80, 145.08, 143.37, 136.99, 130.09, 129.87, 129.73, 128.77, 128.25, 128.13, 127.78, 127.37, 127.27, 125.66, 125.44, 123.70, 110.36, 104.75, 79.60, 53.09, 51.77.

[1,3]oxazino[2,3-a]isoquinolines 38 and 39

To a solution of 2-methyl-1,4-benzoquinone (65 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave 38 (135 mg, 65%) and 39 (49 mg, 24%) as yellow crystalline solids.

Dimethyl-3-phenyl-4-oxospiro[cyclohexa-2,4-diene-1,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 38



38

Mp: 195-197 °C.

IR (KBr) ν_{max}: 2955, 1742, 1708, 1670, 1647, 1593, 1566, 1431, 1276, 1236, 1155 cm^{-1}.

^{1}H NMR: δ7.32-7.21 (m, 3H), 7.16-7.09 (m, 2H), 6.36 (d, J= 7.71 Hz, 1H), 6.29-6.20 (m, 3H), 5.82 (d, J = 7.74 Hz, 1H), 3.95 (s, 3H), 3.58 (s, 3H), 1.85 (s, 3H).

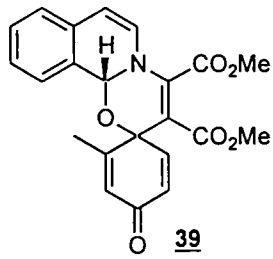
^{13}C NMR: δ 185.45, 163.75, 163.16, 156.67, 148.44, 145.48, 143.30, 129.77, 129.61, 129.15, 128.57, 127.89, 127.79, 127.53, 127.47, 127.26, 125.81, 125.54, 125.36, 123.66, 123.40, 109.03,

105.07, 79.42, 53.37, 51.76, 17.73.

Dimethyl-2-phenyl-4-oxospiro[cyclohexa-2,4-diene-1,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 39

Mp: 184-186 °C.

IR(KBr) ν_{max}: 2955, 1742, 1715, 1670, 1647, 1593, 1566, 1431, 1236 cm^{-1}.



39

^{1}H NMR: δ 7.38-7.22 (m, 3H), 7.11 (d, J = 7.56 Hz, 1H), 6.87 (s, 1H), 6.47 (dd, J = 3.03, 9.82 Hz, 1H), 6.34 (d, J = 7.96 Hz, 1H), 6.28 (d, J = 6.26 Hz, 1H), 6.23 (d, J = 4.38 Hz, 1H), 5.80 (d, J = 7.75 Hz, 1H), 3.95 (s, 3H), 3.58 (s, 3H), 1.93 (s, 3H).

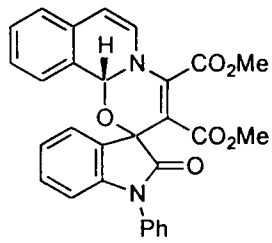
^{13}C NMR: δ 186.13, 163.86, 163.40, 147.38, 144.85, 142.77, 138.49, 137.16, 135.07, 130.18, 129.75, 129.64, 128.33, 127.73, 127.31, 127.25, 125.97, 125.40, 123.38, 107.45, 104.95, 79.35, 53.36, 51.75, 15.99.

Dimethyl-1,2-dihydro-2-oxo-1-phenylspiro[3H-indole-3,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 40

To a solution of *N*-phenyl isatin (78 mg, 0.35 mmol) and DMAD (50 mg, 0.35 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.042 mL, 0.35 mmol) and the mixture was stirred at RT for 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **40** (84 mg, 49%) as an yellow crystalline solid.

Mp: 240-242 °C.

IR(KBr) ν_{max}: 2955, 1741, 1711, 1620, 1580, 1501, 1426, 1276, 1145 cm^{-1}.



40

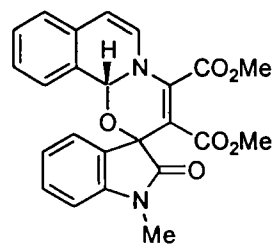
^{1}H NMR: δ 7.57-7.48 (m, 4H), 7.44-7.38 (m, 2H), 7.26-7.14 (m, 5H), 7.08 (d, J = 7.54 Hz, 1H), 6.99 (t, J = 7.18 Hz, 1H), 6.79 (d, J = 7.80 Hz, 1H), 6.42 (d, J = 7.73 Hz, 1H), 5.83 (d, J = 7.74 Hz, 1H), 3.98 (s, 3H), 3.53 (s, 3H).

^{13}C NMR: δ 173.37, 163.15, 162.89, 144.76, 144.71, 133.88, 129.49, 129.18, 129.10, 128.98, 127.76, 127.60, 127.57, 126.65, 125.93, 125.58, 124.68, 123.27, 122.84, 122.59, 109.03, 105.17, 104.77, 79.16, 52.82, 51.24.

Anal. Calcd. for $C_{29}H_{22}N_2O_6$: C, 70.44; H, 4.48; N, 5.67; Found C, 70.80; H, 4.62; N, 5.51.

Dimethyl-1,2-dihydro-2-oxo-1-methylspiro[3H-indole-3,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 41

To a solution of *N*-methyl isatin (85 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **41** (110 mg, 48%) as an yellow crystalline solid.



41

Mp: 210-212 °C.

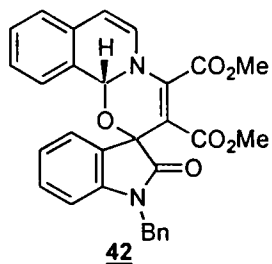
IR(KBr) ν_{max}: 2955, 1742, 1721, 1647, 1593, 1566, 1431, 1276, 1155 cm^{-1}.

^{1}H NMR: δ 7.36 (d, J = 7.48 Hz, 1H), 7.29-7.16 (m, 4H), 7.08 (t, J = 7.57 Hz, 2H), 6.96 (t, J = 7.47 Hz, 1H), 6.80 (d, J = 7.74 Hz, 1H), 6.39 (d, J = 7.73 Hz, 1H), 5.81 (d, J = 7.74 Hz, 1H), 3.97 (s, 3H), 3.46 (s, 3H), 3.28 (s, 3H).

^{13}C NMR: δ 174.52, 163.47, 163.42, 145.32, 145.19, 130.17, 129.79, 129.48, 128.32, 127.15, 126.24, 125.19, 123.43, 123.22, 122.97, 120.47, 108.21, 105.71, 105.24, 79.65, 53.30, 51.69, 26.32.

Dimethyl-1,2-dihydro-2-oxo-1-benzylspiro[3H-indole-3,2'-[2H,11bH] [1,3]oxazino[2,3-a]isoquinoline]-3',4'-dicarboxylate 42

To a solution of *N*-benzyl isatin (125 mg, 0.53 mmol) and DMAD (75 mg, 0.53 mmol) in anhydrous DME (15 mL) was added isoquinoline (0.062 mL, 0.53 mmol) and the mixture was stirred at RT for 6 h. The solvent was removed under vacuum and the residue on chromatographic separation on silica gel column using hexane-ethylacetate (80:20) gave **42** (mg, 51%) as an yellow solid.



42

Mp: 235-237 °C.

IR(KBr) ν_{max}: 2955, 1742, 1715, 1600, 1565, 1431, 1351, 1222, 1148, 1000 cm^{-1}.

^{1}H NMR: δ 7.43-7.06 (m, 9H), 6.92 (t, J = 7.47 Hz, 1H), 6.71 (d, J = 7.74 Hz, 1H), 6.40 (d, J = 7.72 Hz, 1H), 5.81 (d, J = 7.74 Hz, 1H), 5.28 (s, 1H), 5.09 (d, J = 15.58 Hz, 1H), 4. 83 (d, J = 15.59 Hz, 1H), 3.98 (s, 3H), 3.30 (s, 3H), 2.81 (s, 2H).

^{13}C NMR: δ 174.59, 164.87, 163.51, 145.49, 144.35, 135.88, 130.04, 129.86, 129.49, 128.80, 128.66, 128.20, 127.73, 127.66, 127.17, 126.30, 125.21, 123.50, 123.22, 123.00, 109.21, 105.23, 104.95, 79.52, 53.32, 51.56, 43.97.

4.6 References

1. *The Chemistry of Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; John Wiley and Sons, New York, 1988; Vol. 2, Parts I & II.
2. Thomson, R. H. in *Naturally Occurring Quinones; Recent Advances*, Chapman and Hall, New York, 1987.
3. Bruce, J. M. in *Rodd's Chemistry of Carbon Compounds*, 2nd ed.; Coffey, S., Ed.; Elsevier, Amsterdam, 1974, Vol. III, Part B, Chapter 8.
4. Nair, V.; Kumar, S. *Synlett* **1996**, 1143 and the references cited therein.
5. Horspool, W. M.; Tedder, J. M.; Din, Z. U. *J. Chem. Soc. (C)* **1969**, 1962.
6. Nair, V.; Kumar, S. *Synth. Commun.* **1996**, *26*, 697.
7. Ansell, M. F.; Gosden, A. F.; Leslie, V. J.; Murray, R. A. *J. Chem. Soc. (C)* **1971**, 1401.
8. (a) Nair, V.; Anilkumar, G.; Eigendorf, G. K.; Willard, P. G. *Tetrahedron Lett.* **1996**, *37*, 8271. (b) Verboom, W.; Bos, H. T. J. *Recl. Trav. Chim. Pays Bas.* **1981**, *100*, 207. (c) Nair, V.; Sethumadhavan, D.; Nair, S. M. *J. Org. Chem.* **2002**, *67*, 7533.
9. Nair, V.; Kumar, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 443.
10. Nair, V.; Kumar, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1341.
11. Komissarova, N. L.; Belostotskaya, I. S.; Vol'eva, V. B.; Dzhurayan, E. V.; Novikova, I. A.; Ershov, V. V. *Izv. Akad. Nauk. SSSR, Ser. Khim.* (Engl. Transl.) **1981**, 2360.
12. a) Nair, V.; Radhakrishnan, K. V.; Nair, A. G.; Bhadbhade, M. M. *Tetrahedron Lett.* **1996**, *37*, 5623. (b) Nair, V.; Radhakrishnan, K. V.; Sheela, K. C.; Rath, N. P. *Tetrahedron* **1999**, *55*, 14199.
13. Nair, V.; Sheela, K. C.; Radhakrishnan, K. V.; Rath, N. P. *Tetrahedron Lett.* **1998**, *39*, 5627.
14. (a) Grigg, R.; Thianpatanagul, S. *J. Chem. Soc., Chem. Commun.* **1984**, 180. (b) Grigg, R.; Aly, M. F.; Sridharan, V.; Thianpatanagul, S. *J.*

Chem. Soc., Chem. Commun. **1984**, 182. (c) Coulter, T.; Grigg, R.; Malone, J. F.; Sridharan, V. *Tetrahedron Lett.* **1991**, *32*, 5417.

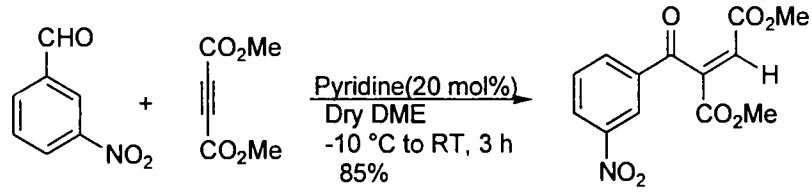
15. Nair, V.; Sheela, K. C.; Rath, N. P.; Eigendorf, G. *Tetrahedron Lett.* **2000**, *41*, 6217.
16. Nair, V.; Rajesh, C.; Dhanya, R.; Rath, N. P. *Tetrahedron Lett.* **2002**, *43*, 5349.
17. (a) Nair, V.; Nair, J. S.; Vinod, A. U.; Rath, N. P. *J. Chem. Soc., Perkin Trans 1* **1997**, 3129. (b) Nair, V.; Nair, J. S.; Vinod, A. U. *Synthesis* **2000**, 1713.
18. Nair, V.; Vinod, A. U.; Nair, J. S.; Sreekanth, A. R.; Rath, N. P. *Tetrahedron Lett.* **2000**, *41*, 6675.
19. Nair, V.; Bindu, S.; Balagopal, L. *Tetrahedron Lett.* **2001**, *42*, 2043.
20. Campagna, F.; Carotti, A.; Casini, G.; Otto, A. M. *Farmaco*, **1995**, *50*, 137. (b) Campagna, F.; Altomore, C.; Carotti, A.; Casini, G.; Ferappi, M. *Steroids* **1986**, *47*, 307. (c) Böhme, T. M.; Augelli-Szafran, C. E.; Hallak, H.; Pugsley, T.; Serpa, K.; Schwarz, R. D. *J. Med. Chem.* **2002**, *45*, 3094.

SUMMARY

The thesis entitled "**Novel Strategies for Heterocyclic Constructions *via* 1,4-Dipolar Intermediates**" embodies the results of extensive investigations carried out to gain some insight into the reactivity of 1,4-dipolar intermediates generated from nitrogen heterocycles (pyridine and its benzoanalogues) and dimethyl acetylenedicarboxylate (DMAD) with various dipoarophiles such as aldehydes, N-tosylimines and benzoquinones.

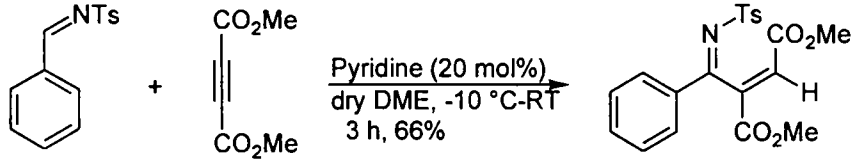
A general introduction and a brief survey of 1,4-dipolar cycloaddition reactions is presented in chapter 1. A definition of the present work is also incorporated in this chapter.

The second chapter describes the unusual reactivity of 1,4-dipolar intermediate generated from pyridine and DMAD with aromatic aldehydes, resulting in the facile synthesis of benzoyl fumarates *via* the elimination of pyridine. A typical example is given in scheme 1.



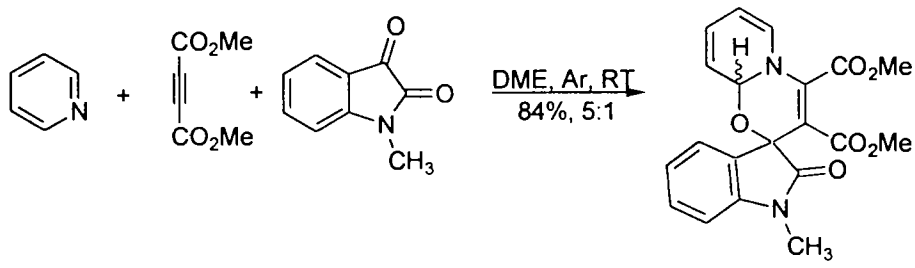
Scheme 1

A similar reaction of the 1,4-dipolar intermediate with N-tosylimines, provided a facile entry into highly substituted 1-azadienes, in good yields (Scheme 2).



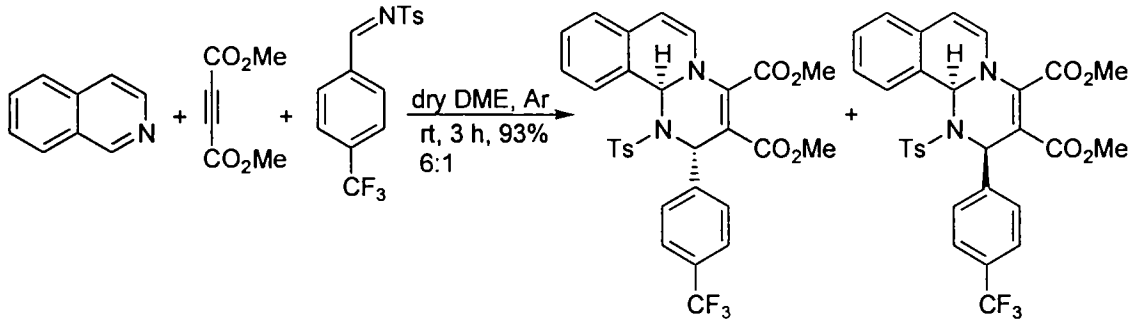
Scheme 2

The introduction of 1,2-dicarbonyl compounds such as N-substituted isatins as dipolarophiles in this reaction resulted in a novel three component condensation, yielding spiro pyrido[2,1-b][1,3]oxazino derivatives as mixture of diastereomers *via* 1,4-dipolar cycloaddition pathway (Scheme 3).



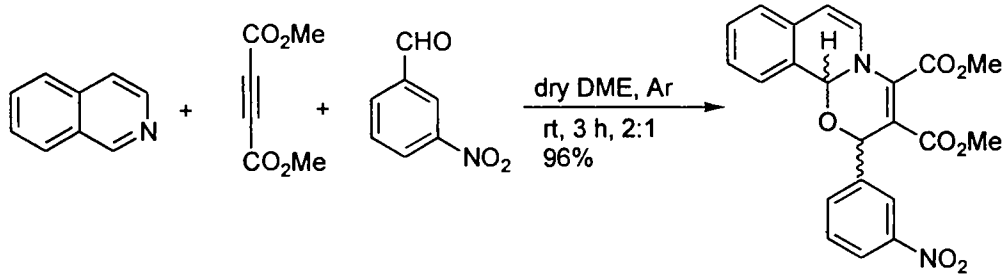
Scheme 3

The third chapter describes the interception of 1,4-dipolar intermediate from isoquinoline and DMAD with N-tosylimines, resulting in the diastereoselctive synthesis of 2*H*-pyrimido[2,1-a]isoquinoline derivatives in high yields, thus constituting a novel multicomponent reaction (Scheme 4).



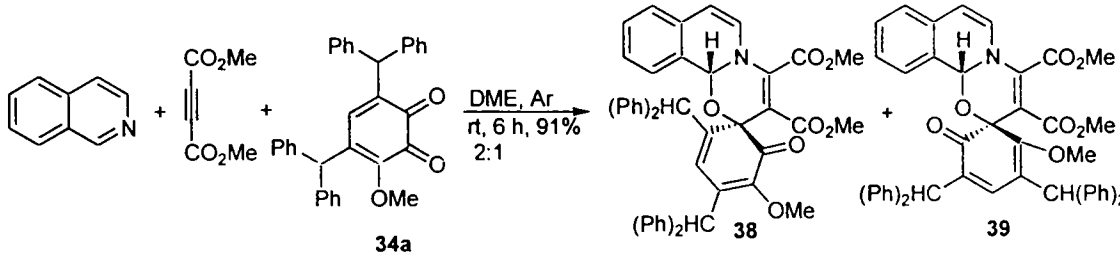
Scheme 4

A similar multicomponent reaction of isoquinoline, DMAD and aromatic aldehydes resulted an inseparable diastereomeric mixture of [1,3]oxazino[2,3-a]isoquinoline derivatives (Scheme 5).



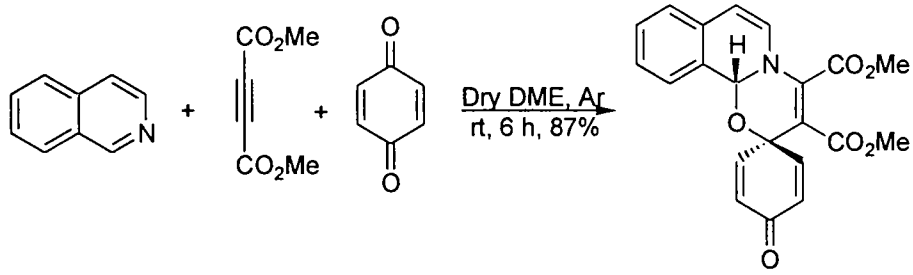
Scheme 5

The fourth chapter deals with the trapping of 1,4-dipolar intermediate from isoquinoline and DMAD by 1,2-benzoquinones affording novel spiro[1,3]oxazino[2,3-a]isoquinoline derivatives in high yields (Scheme 6).



Scheme 6

A logical extension of this reaction to 1,4-benzoquinones as dipolarophiles also afforded the expected spiro[1,3]oxazino[2,3-a]isoquinoline derivatives (Scheme 7).



Scheme 7

In conclusion, we have unraveled some novel and interesting reactivity of 1,4-dipoles derived from pyridine and its analogues towards dipolarophiles such as aldehydes and N-tosylimines. A general method for the synthesis of benzoyl fumarates under mild conditions was developed along with a novel synthesis of highly substituted 1-azadienes, which are important precursors of saturated amino acids. A diastereoselctive synthesis of 2*H*-pyrimido[2,1-a]isoquinolines and [1,3]oxazino[2,3-a]isoquinolines was also developed; such compounds are known to possess therapeutically important biological activities. It is conceivable that the novel synthetic strategies described herein will be applicable to the synthesis of a variety of interesting heterocycles.

LIST OF PUBLICATIONS

1. The Reaction of Cyclohexyl Isocyanide and Dimethyl acetylenedicarboxylate with *o*- and *p*-Quinones: A Novel Synthesis of Iminolactones. Nair, V.; Vinod, A. U.; Nair, J. S.; **Sreekanth, A. R.** and Rath, N. P. *Tetrahedron Lett.*, **2000**, *41*, 6675.
2. Novel Pyridine Catalysed Reaction of Dimethyl Acetylenedicarboxylate with Aldehydes: Formal [2+2] Cycloaddition Leading to 2-Oxo-3-benzylidenesuccinates. Nair, V.; **Sreekanth**, **A. R.**; Vinod, A. U. *Org. Lett.*, **2001**, *3*, 3495.
3. A Novel Three Component Reaction for the Diastereoselective Synthesis of 2*H*-Pyrimido[2,1-a]isoquinolines *via* 1,4-Dipolar Cycloaddition. Nair, V.; **Sreekanth**, **A. R.**; Abhilash N., Bhadbhade, M. M. and Gonnade, R. *Org. Lett.* **2002**, *4*, 3575.
4. The Reaction of Isoquinoline and Dimethyl acetylenedicarboxylate with 1,2- and 1,4-diones: A Novel Synthesis of Spiro[1,3]oxazino[2,3-a]isoquinolines Nair, V.; **Sreekanth**, **A. R.**; Biju, A. T. and Rath, N. P. *Tetrahedron Lett.* (accepted).
5. Novel Pyridine Catalysed Reaction of Dimethyl Acetylenedicarboxylate with Carbonyl Compounds and N-Tosylimines: Efficient Synthesis of 2-Benzoyl fumarates and 1-Azadienes Nair, V.; **Sreekanth, A. R.**; Abhilash, N.; Biju, A. T.; Rath, N. P. and Sreenivas, R. (communicated to *Synthesis*).
6. Multicomponent Reaction *via* 1,4-Dipolar Cycloaddition: A Facile Route to Condensed Isoquinoline Heterocycles Nair, V.; **Sreekanth, A. R.** (to be communicated to *J. Org. Chem.*).
7. Strategies for Heterocyclic Construction *via* Novel Multicomponent Reactions based on Isocyanides and Nucleophilic Carbenes Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; **Sreekanth, A. R.**; Mathen, J. S. and Balagopal, L. (communicated to *Acc. Chem. Res.*)

Posters Presented at Symposia

1. Nair, V.; **Sreekanth, A. R.**; Abhilash, N. "Novel pyridine catalysed reaction of dimethyl acetylenedicarboxylate with aldehydes" presented at the Fourth National Symposium in Chemistry held at Pune, February 1-3, 2002, P-184.