NOVEL REACTIONS OF INDIUM REAGENTS WITH 1, 2-DIONES AND DIELS-ALDER CYCLOADDITIONS OF HETEROCYCLIC *o*-QUINONE METHIDES

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

C. N. JAYAN

UNDER THE SUPERVISION OF

Dr. G. VIJAY NAIR

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

JUNE, 2000

DECLARATION

I hereby declare that the matter embodied in the thesis entitled *"NOVEL REACTIONS OF INDIUM REAGENTS WITH 1,2-DIONES AND DIELS-ALDER CYCLOADDITIONS OF HETEROCYCLIC o-QUINONE METHIDES"* is the results of investigations carried out by me in the **Organic Chemistry Division of Regional Research Laboratory [CSIR], Trivandrum** under the supervision of **Dr. G. Vijay Nair** and the same has not been submitted elsewhere for a degree.

Trivandrum

June 2000

C. N. JAYAN

COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH [CSIR]
क्षेत्रीय अनुसंधान प्रयोगशाला, तिरुवनन्तपुरम - 695 019
REGIONAL RESEARCH LABORATORY
TRIVANDRUM - 695 019, INDIA.
Phone : 91 - 471 - 490324 (O), 341707 (R)
Fax : 91 - 471 - 491712, email : gvn@csrrltrd. ren.nic.in

डॉ.जी.विजय नायर
निदेशक
Dr. G. Vijay Nair, F . A . Sc
Director

12 June 2000

CERTIFICATE

This is to certify that the work contained in the thesis entitled ***"NOVEL REACTIONS OF INDIUM REAGENTS WITH 1,2-DIONES AND DIELS-ALDER CYCLOADDITIONS OF HETEROCYCLIC o-QUINONE METHIDES"*** has been carried out by **C. N. Jayan** under my supervision at the **Organic Chemistry Division of Regional Research Laboratory [CSIR], Trivandrum** and the same has not been submitted elsewhere for any other degree.

G. Vijay Nair

G. VIJAY NAIR
THESIS SUPERVISOR

ACKNOWLEDGEMENTS

It gives me immense pleasure to express my deep sense of gratitude to my teacher and guide ***Dr. G. Vijay Nair*** *for suggesting a series of fascinating research problems, and for the encouragement, inspiration and timely criticism during the course of my work.*

I would like to express my gratitude to Director, RRL, Trivandrum for permitting me to utilize all the facilities during my stay at RRL, Trivandrum.

I take this opportunity to express my gratitude to Prof. M. V. George for attracting me to the field of research.

It is my pleasure to thank Dr. Anilkumar G. Nair and Dr. Radhakrishnan K. V. for fruitful discussions.

I am thankful to Prof. Nigam P. Rath for single crystal X-ray data, Dr. Anilkumar G. for the elemental analyses of some of the compounds reported in this thesis and Dr. P. Shanmugam and Ms. Soumini Mathew for providing many ^{1}H *and* ^{13}C *NMR spectra. My sincere thanks are due to Dr. N. Manoj for useful suggestions regarding the theoretical calculations reported in this thesis.*

It is indeed a pleasure to thank all the present and former colleagues and friends in the Organic Chemistry Division and Photochemistry Research Unit for their help and co-operation during the course of my work. I would like to thank senior scientists, Dr. Mangalam S. Nair and Dr. Luxmi Varma, of Organic Chemistry Division for their help.

Words fail me when I try to express my gratitude to my family members for their staunch support, without which it would not have been possible to achieve the goal.

Financial assistance from CSIR, New Delhi, in the form of fellowship, and American Cyanamid Company, U. S. A. is gratefully acknowledged.

Trivandrum
June, 2000

C. N. JAYAN

CONTENTS

PREFACE

Organometallic reactions play a vital role in organic synthesis. Nowadays, it is difficult to perform an efficient and selective multistep synthesis without the use of organometallics. However, the results of organometallic reactions are sometimes disappointing due to the lack of proper procedure and handling of the organometallics used in such procedure. Generally, special precautions are necessary to carry out organometallic reactions such as Barbier and Grignard reactions. However, indium mediated Barbier reactions are exceptional because of the inertness of indium towards aqueous and basic conditions. Thus, it was of interest to undertake an investigation of the reactions of organoindium reagents with 1,2-diones and the author's work in this area constitutes the first phase of the thesis entitled ***"NOVEL REACTIONS OF INDIUM REAGENTS WITH 1,2-DIONES AND DIELS-ALDER CYCLOADDITIONS OF HETEROCYCLIC o-QUINONE METHIDES"***. The second phase of the work is concerned with inverse electron demand hetero Diels-Alder reactions of heterocyclic quinone methides.

The thesis comprises of three chapters. A general introduction to the theme of the thesis is presented in the first chapter. The first chapter has two parts. Part I deals with the introduction to organometallic reactions with special emphasis on reactions of organoindium reagents and carbonyl compounds. Part II briefly describes the cycloaddition reactions of *o*-quinone methides.

The second chapter describes the Barbier reactions of organoindium reagents with 1,2-diones. These reactions are facile and

exceptionally useful in the synthesis of α-hydroxy carbonyl compounds. The aldol and Reformatsky reactions of organoindium reagents with 1,2-diones are also presented in this chapter. General information on experimental procedure is also given.

The last chapter deals with the hetero Diels-Alder reactions of various heterocyclic quinone methides with fulvenes and tetracyclone. The heterocyclic quinone methides selected for this study are coumarin quinone methide, pyrone quinone methide and quinolone quinone methide.

It may be noted that each chapter of the thesis is presented as a separate unit and therefore figures, schemes and structures are numbered accordingly. IUPAC names of the compounds are given in the experimental section. However, for the sake of convenience, occasionally trivial names are also used.

A summary of the work is given towards the end of the thesis. Relevant references are given at the end of each chapter.

ABBREVIATIONS

AM1	:	Austin method 1
Anisyl/PMP	:	4-Methoxy phenyl
BBN	:	9-Borabicyclo[3.3.1]nonane
brs	:	Broad singlet
^{t}Bu	:	*tert*-Butyl
d	:	Doublet
dd	:	Double doublet
DDQ	:	Dichloro dicyano quinone
DMF	:	Dimethyl formamide
E	:	Entgegen (*trans*)
equiv	:	Equivalent
Et	:	Ethyl
EtOAc	:	Ethyl acetate
eV	:	Electron volt
h	:	Hour(s)
J	:	Coupling constant
m	:	Multiplet
Me	:	Methyl
min	:	Minute(s)
mL	:	Milliliter
mp	:	Melting point
m/z	:	Mass charge ratio
N	:	Normality
nm	:	Nanometer
Ph	:	Phenyl
Py	:	Pyridine
q	:	Quartet
r. t.	:	Room temperature
s	:	Singlet
t	:	Triplet
THF	:	Tetrahydrofuran
TLC	:	Thin layer chromatography
U. S.	:	Ultrasonication
Z	:	Zusammen (*cis*)

CHAPTER 1

INTRODUCTION

This chapter is divided into two parts. In the first part, a brief account of the reactions mediated by organometallic reagents followed by an overview of the indium mediated Barbier reactions is presented. Second part briefly describes cycloaddition reactions with special emphasis on Diels-Alder reactions involving quinone methides.

PART I

1.1 THE REACTIONS OF ORGANOINDIUM REAGENTS WITH CARBONYL COMPOUNDS: AN OVERVIEW

1.1.1 INTRODUCTION

An organometallic compound is one that contains a bond between a carbon atom and a metal atom. Many such compounds are known and organometallic chemistry is now a very vast and important area, juxtaposed between organic and inorganic chemistry. The structure of the organic moiety of the molecule determines whether a carbon-metal bond is ionic or polar-covalent. Ionic bonds become more likely as the negative charge on the metal bearing carbon is delocalized by resonance.

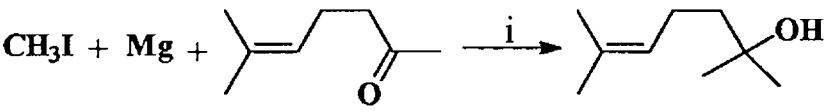
The history of organometallic compounds dates back to 1849 when Frankland established the constitution of diethylzinc **3** which was prepared by the reaction of ethyl iodide and zinc (Scheme 1).[1] Thus, diethylzinc is considered to be the first known organometallic compound.

$$\underset{\mathbf{1}}{2\ C_2H_5I} + \underset{\mathbf{2}}{2\ Zn} \longrightarrow \underset{\mathbf{3}}{(C_2H_5)_2Zn} + \underset{\mathbf{4}}{ZnI_2}$$

Scheme 1

The zinc alkyls played an important part in synthesis until the end of 19th century. In 1899, Barbier introduced magnesium metal to synthetic

organic chemistry.[2] He developed a single step procedure for the conversion of carbonyl compounds to alcohols (Scheme 2). From a synthetic point of view this reaction opened a new vista.

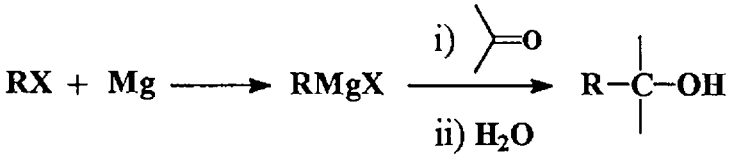


5 6 7

i) Et_2O, 0 °C, 12 h, 30%

Scheme 2

In 1900, Grignard modified Barbier's single step method into a two stage synthetic procedure (Scheme 3).[3] Grignard's method requires, as the first step, the preparation of an organomagnesium compound, a so-called Grignard reagent, followed by the second step in which either the substrate is added to the Grignard reagent or *vice versa* to afford the alcohol.



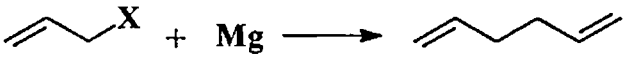
8 9 10

Scheme 3

Although the two step procedure has been widely accepted, the Barbier reaction still finds interesting and useful applications. A general

application of the Barbier reaction as a synthetic tool involves the use of allylic halides. In many cases, this one-step procedure is preferable to the Grignard procedure.

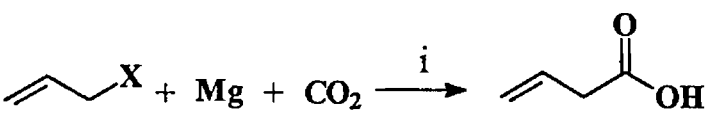
One of the limitations of Grignard procedure is the dimerisation of allyl halide during the preparation of allylic organomagnesium compounds. The main product obtained when allyl halide is reacted with magnesium under rather uncontrolled conditions is the dimer, 1,5-hexadiene, thus, causing unsatisfactory yields of the desired product (Scheme 4).



11 **12**

Scheme 4

However, Houben overcame this difficulty by applying Barbier's single-step procedure in the preparation of 3-butenoic acid (Scheme 5).[4]

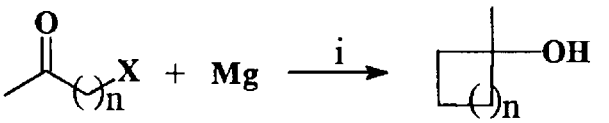


11 **13** **14**

i) a. Et_2O b. H_2O, 11%

Scheme 5

The importance of Barbier reaction can be attested by its application to the synthesis of cyclobutanols and cyclopentanols from the corresponding haloketones and magnesium in THF (Scheme 6).[5]



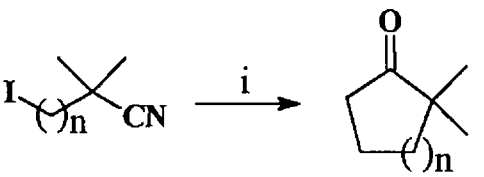
n = 3,4 n = 1,2

15 **16**

i) a. THF b. H_2O, 60-65%

Scheme 6

Barbier reactions of 4-cyano-1-iodo and 5-cyano-1-iodo alkanes with magnesium in diethyl ether have been shown to afford cyclic ketones efficiently (Scheme 7).[6]



n = 3, 4 n = 1, 2

17 **18**

i) Mg, Et_2O, 79%

Scheme 7

A number of metals such as Li, Zn, Mn, Sn, Sb, Ce, Pb and Bi have been successfully used in the allylation reaction of carbonyl compounds.[7-14]

Thus, it is clear that there is increasing interest in performing a wide variety of synthetic transformations by direct reaction of metals with an organic partner. This one step procedure has become popular, although, in many cases a prior activation or depassivation of metal surface is usually required.[15]

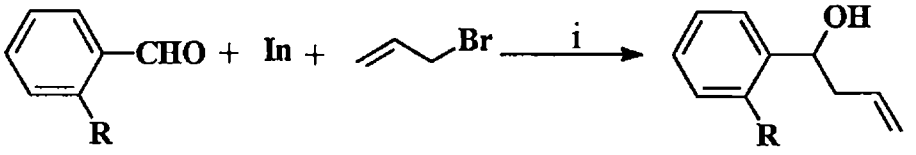
Recently, the synthetic potential of indium mediated reactions has been recognized to offer a powerful tool in organic chemistry.[16] Indium metal has some striking properties. This metal is unaffected by air or oxygen at ordinary temperature, but on heating forms the stable indium(III) oxide. It is practically unaffected by water and very resistant to alkaline conditions, although it dissolves in mineral acids. Since the ionization potential of indium (5.8 eV) is much lower than that of zinc, tin and magnesium, it will be a suitable candidate in single electron transfer (SET) processes. Indium exhibits low heterophilicity in organic reactions which makes indium reagents suitable in C-C bond forming reactions. Thus, oxygen and nitrogen containing functional groups are usually tolerated within the molecule.

1.1.2 BARBIER REACTIONS MEDIATED BY INDIUM

The reactions of metallic indium with allyl halides, either bromides or iodides, in highly polar solvents such as THF or DMF afford corresponding sesquihalide $R_3In_2X_3$. Under these conditions, the insertion of indium takes place regioselectively at the α-carbon of allyl halide.[17] Moreover the allylic indium sesquihalides do not react further with the starting allyl halides, thus avoiding the undesirable Wurtz-type

by-products which are usually formed in the preparation of allyl lithium or Grignard reagents.

A wide variety of aldehydes and ketones can be allylated using indium metal to afford homoallylic alcohols in good yields (Scheme 8).[17,18] It is noteworthy that the allylindium intermediate is stable even towards the phenol functionality under the reaction conditions.

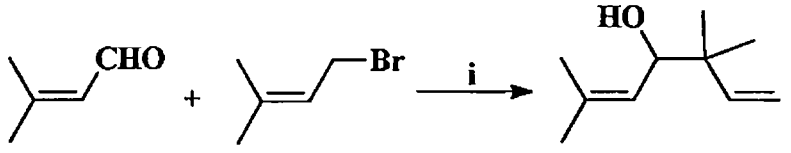


19 **20** **21**

i) DMF, r. t., 1 h, 87-98% **R = H, OH**

Scheme 8

In indium mediated reactions, α,β-unsaturated carbonyl compounds exclusively afford 1,2-addition products and allyl halides react at the γ-position (Scheme 9).[18]

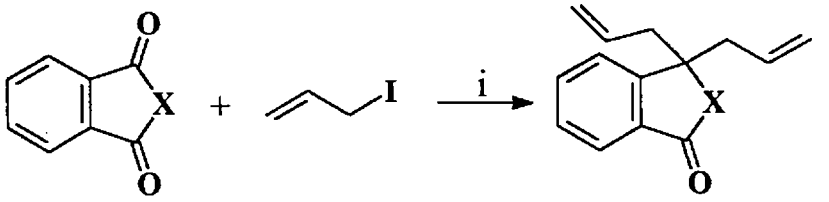


22 **23** **24**

i) In, DMF, r. t., 75%

Scheme 9

Allyl indium reagents react with numerous organic compounds. Indium does not mediate allylation of esters and amides. However, cyclic acid anhydrides[19] and cyclic imides[20] undergo facile allylation (Scheme 10).

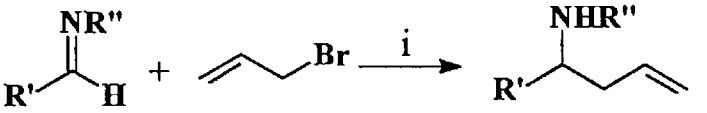


25 **26**

i) In, DMF, r. t., 1 h, 81% **X = O, NH**

Scheme 10

It was reported that aldimines and their derivatives could be allylated in a simple Barbier reaction (Scheme 11).[21]

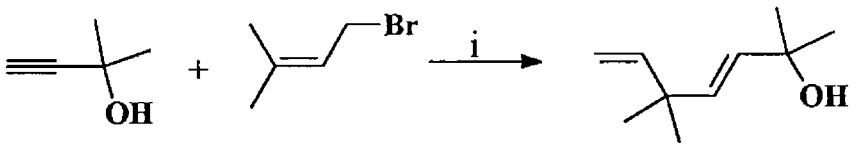


27 **20** **28**

i) In, DMF, r. t. **R', R'' = Ph, Py**

Scheme 11

Araki *et al.* have shown that alkynols underwent allylation in DMF at high temperature.[22] Thus, Yomogi alcohol **31**, a monoterpenic alcohol, was easily prepared using the aforementioned protocol (Scheme 12).

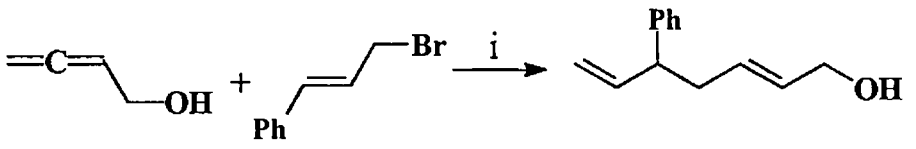


29 **30** **31**

i) In, DMF, 110 °C, 4 h

Scheme 12

It was reported by Araki *et al.* that allenols also can undergo facile allylation in DMF at high temperature in the presence of indium (Scheme 13).[23]

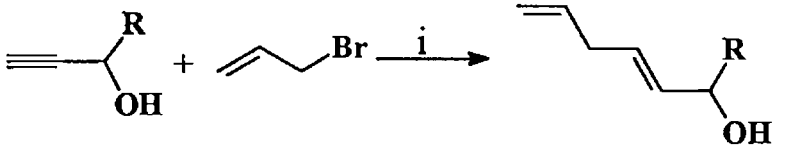


32 **33** **34**

i) In, DMF, 140 °C, 4 h, 97%

Scheme 13

Recently Ranu *et al.* showed that indium can facilitate the allylation of alkynols at room temperature in THF (Scheme 14).[24]

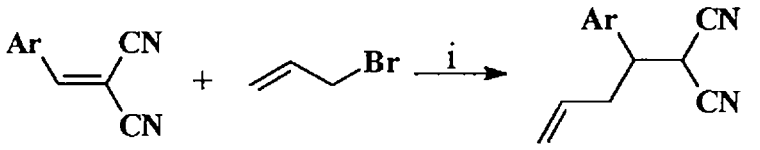


35 **20** **36**

i) In, THF, r. t. **R = H, Ph**

Scheme 14

Activated alkenes such as dicyano styrenes and cyclopropenes have also been allylated by indium metal. Allylation of 1,1-dicyano-2-aryl ethenes[25] afforded Michael adducts in good yields (Scheme 15).

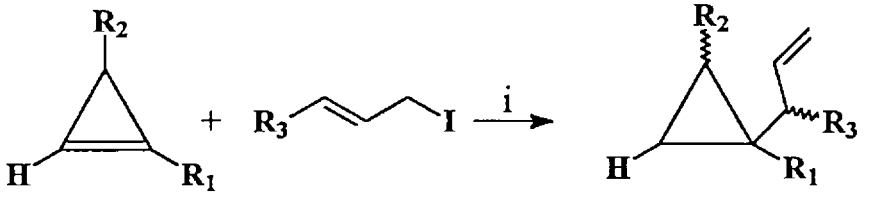


37 **20** **38**

i) In, THF-H_2O, 4 h, 75-85%

Scheme 15

Cyclopropene derivatives have been efficiently allylated by the use of indium to afford novel cyclopropane derivatives (Scheme 16).[26]

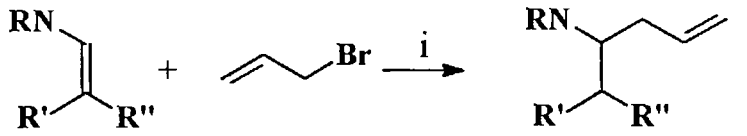


39 **40** **41**

i) In, THF, r. t., 95% R_1 = n-C_6H_{13}, R_2 = CH_2OH, R_3 = H, Me

Scheme 16

Enamines are also reactive towards allyl indium reagents in THF yielding homoallylamines in excellent yields (Scheme 17).[27]

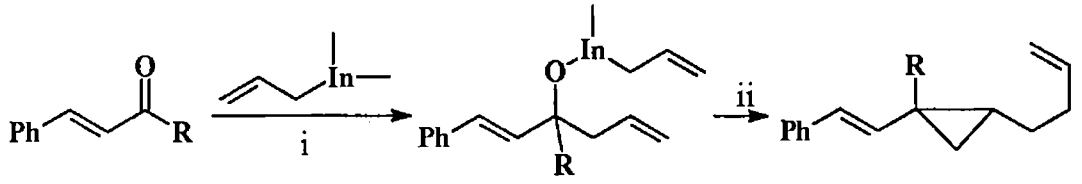


42 **20** **43**

i) In, THF, 22 h, 100% **R = -$(CH_2)_4$-, R' = H, R'' = Et**

Scheme 17

α,β-Unsaturated aldehydes and ketones on treatment with allyl indium reagents in the presence of lithium salt afforded cyclopropane derivatives in good yields (Scheme 18).[28]



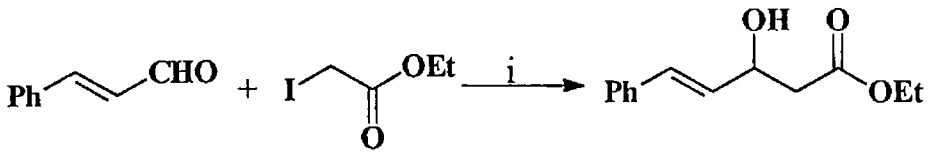
44 **45** **46**

i) THF, r. t. ii) LiBr, Et_2O

Scheme 18

1.1.3 REFORMATSKY REACTIONS

Originally, zinc was used to promote the addition of α-bromo alkanoates to carbonyl compounds and the process is known as Reformatsky reaction. Later, various metals were effectively used in place of zinc. Recently, it has been shown that metallic indium can also promote Reformatsky reaction to furnish β-hydroxy esters (Scheme 19).[29]

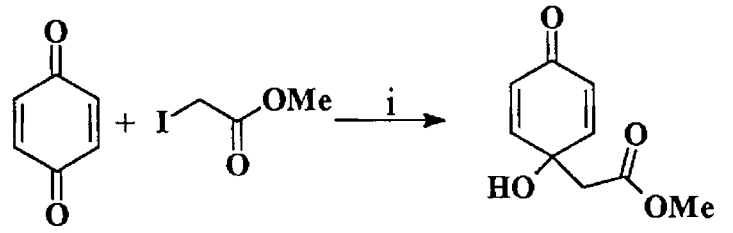


47 **48** **49**

i) In, THF, r. t., 1.5 h, 89%

Scheme 19

This method has been utilized in the synthesis of naturally occuring antitumour compound jacaranone **51** (Scheme 20).[30]



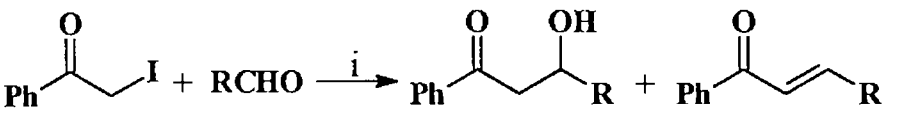
50 **51**

i) In, DMF, 24 h, 51%

Scheme 20

1.1.4 ALDOL REACTIONS

The synthetically important aldol reactions can be promoted by indium reagents. Indium metal has been reported to mediate aldol condensation between α-halo ketones and aldehydes. For example, phenacyl iodide on reaction with aldehyde in the presence of indium led to aldol condensation (Scheme 21).[31]



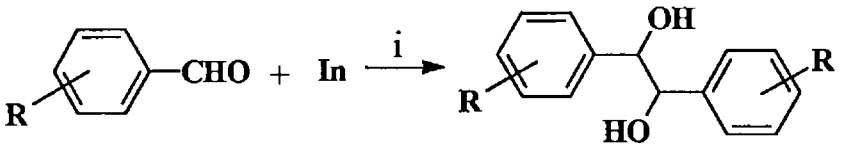
52 **53** **54** **55**

i) In, DMF

Scheme 21

1.1.5 MISCELLANEOUS REACTIONS MEDIATED BY INDIUM

It has been reported that indium can mediate pinacol coupling of aromatic aldehydes (Scheme 22).[32]

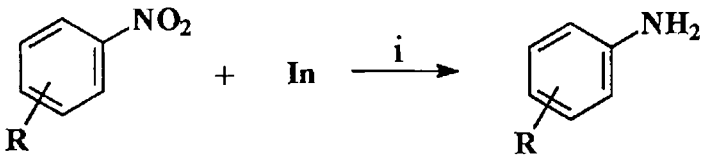


56 **57**

i) In, U. S., H_2O, 70-79% **R = H, CH_3, Br**

Scheme 22

Moody and co-workers reported that indium was very effective in the reduction of nitro group and quinoline cores. Aromatic nitro compounds on treatment with indium powder in aqueous ethanolic ammonium chloride resulted in selective reduction of nitro group while ester, nitrile, amide and halide substituents remain unaffected (Scheme 23).[33]



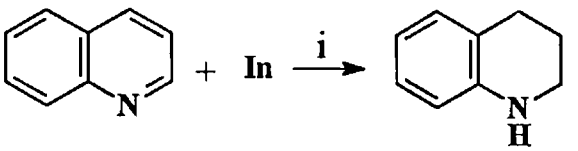
58 **59**

i) NH_4Cl, aq. EtOH, reflux, 92-95%

R = Cl, CN, CO_2Et, AcNH

Scheme 23

Heterocyclic ring in quinolines, isoquinolines and quinoxalines are selectively reduced using indium metal in aqueous ethanol (Scheme 24).[34]

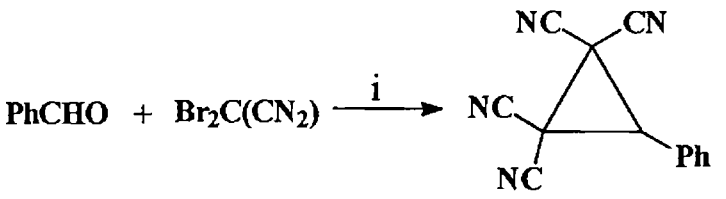


60 **61**

i) NH_4Cl, aq. EtOH, reflux

Scheme 24

Indium mediated Wideqvist-type cyclopropanation reaction has also been reported (Scheme 25).[35]



62 **63** **64**

i) In, LiI, DMF, 0 °C, 1 h, 94%

Scheme 25

1.1.6 DEFINITION OF THE PROBLEM

The reactivity of organoindium halides towards various carbonyl compounds has been studied in detail. However, their reactivity towards 1,2-diones has received only scant attention and there is no systematic study on the reactivity of the organoindium halides towards 1,2-diones. In view of this, it was of interest to undertake an indepth investigation of the reaction of organoindium reagents with various 1,2-diones. This includes the aldol and Reformatsky type reactions of 1,2-diones mediated by indium metal.

The details of this study are presented in Chapter 2.

PART II

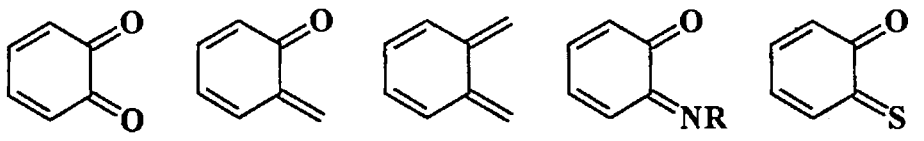
1.2 CYCLOADDITION REACTIONS OF *o*-QUINONE METHIDES: AN INTRODUCTION

1.2.1 INTRODUCTION

Cycloaddition reaction,[36] by definition, results in the formation of a new ring from two reacting molecules. Such reactions have long played an important role in synthetic organic chemistry. The best example of the cycloaddition reaction is the well-known Diels-Alder reaction. The most attractive feature of cycloaddition reactions is the fact that two new bonds are formed in a single step. This can enhance the efficiency of a synthetic process. Cycloaddition reactions usually proceed through cyclic transition state. A concerted mechanism requires a single cyclic transition state; no intermediate lies on the reaction path between reactants and adduct. This concerted mechanism was generally accepted and the regioselectivity and stereospecificity of the reaction was firmly established before the importance of orbital symmetry was recognized. The value of the Diels-Alder reaction in synthesis is due in large measure to its high regio- and stereoselectivity.

1.2.2 CYCLOADDITION REACTIONS OF *o*-QUINONOID COMPOUNDS

Ortho quinonoid compounds can be divided into five major groups. These are represented by *o*-benzoquinone **65**, *o*-quinone methide **66**, *o*-quinodimethane **67**, *o*-quinone imine **68** and *o*-thioquinone **69** (Figure 1).



65 **66** **67** **68** **69**

Figure 1

o-Benzoquinone is an isolable crystalline solid at low temperature, but it dimerises readily. *o*-Quinone methide is stable at -50 °C but trimerises at -20 °C. *o*-Quinodimethane is a reactive intermediate that dimerises at -150 °C. *o*-Quinone imines are more stable than *o*-quinodimethanes.[37] *o*-Thioquinone, generated at 70 °C by the action of base on 2-hydroxy benzothiophthalimide,[38] dimerises in the absence of dienophiles.

The reactivity profiles of *o*-quinones in cycloaddition have received wide attention. *o*-Benzoquinones can function as carbodienes, heterodienes, dienophiles and dipolarophiles in cycloaddition reactions. Investigations in our own laboratory have highlighted the influence of electronic and steric factors on the cycloaddition reactions of *o*-benzoquinones.[39] The participation of *o*-benzoquinone in cycloaddition

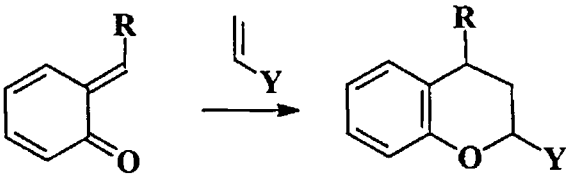
as carbodiene,[40] heterodiene,[41] dienophile,[42] heterodienophile[43] and dipolarophile[44] has been thoroughly investigated.

1.2.3 CYCLOADDITION REACTIONS OF *o*-QUINONE METHIDES

o-Quinone methides[45] constitute a class of reactive intermediates involved in many chemical and biochemical processes. It is known that the mode of action of potent anticancer drug mitomycin C involves an *o*-quinone methide intermediate, which efficiently modifies DNA to result in a crosslinking of DNA.[46]

Because of their synthetic utility and biological importance, various methods for generating *o*-quinone methide, eg. thermal and Lewis acid catalyzed dehydration of *o*-hydroxybenzyl alcohol and photoinduced cheletropic extrusion of carbon monoxide, carbon dioxide and sulfur dioxide have been reported.[45]

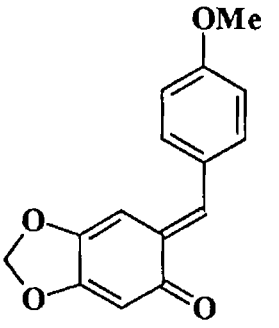
o-Quinone methides can function as the heterodiene components in Diels-Alder reactions resulting in the formation of chromans. The role of-quinone methides in cycloaddition chemistry has invoked considerable attention. *o*-Quinone methides are generally very unstable, but these can be trapped by electron rich alkenes.



70 **71**

Scheme 26

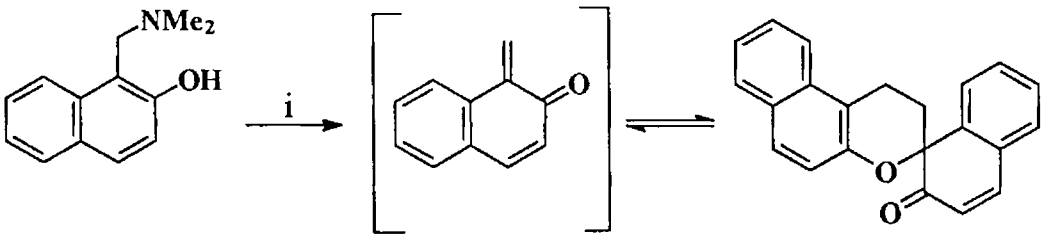
In the literature it is known that electron rich *o*-quinone methide, 6-(*p*-methoxybenzylidene)-3,4-methylenedioxy-2,4-cyclohexadiene-1-one **72**, is stable and can be isolated.[47]



72

Figure 2

It has been reported that many natural products can be generated *via* the intermolecular cycloaddition of *o*-quinone methides and alkenes.[48] The higher reactivity of *o*-quinone methides *vis a vis* α,β-unsaturated carbonyl compounds may be attributed at least in part to the regeneration of aromaticity as a consequence of the cycloaddition process. This behaviour is apparent from the ease with which *o*-quinone methides dimerise, especially in the absence of an external diene or dienophile, to yield a spiroannulated chroman **75** (Scheme 27).[49]

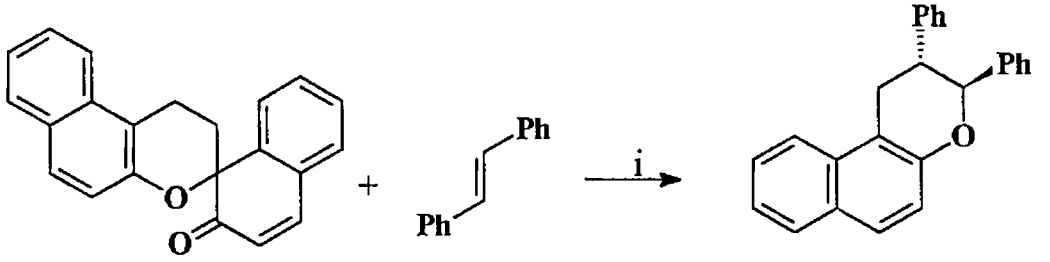


73 74 75

i) Xylene, reflux

Scheme 27

The thermal dissociation of the spiro annulated chroman **75** provides an excellent route to the quinone methide. For example naphthoquinone methide was trapped with stilbene to give chroman derivative in good yield (Scheme 28).[50]



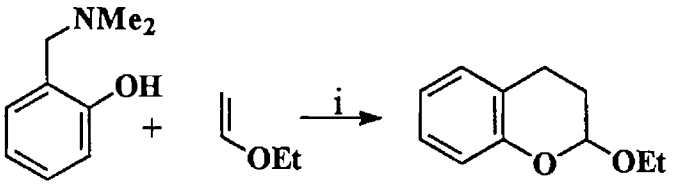
75 76 77

i) Xylene, reflux

Scheme 28

The general method for the synthesis of *o*-quinone methide involves a photochemical elimination from *ortho* substituted phenols. Commonly eliminated molecules are H_2O, MeOH or Me_2NH. However, these methods are not entirely suitable because the eliminated molecules may promote side reactions. It has been reported that *o*-quinone methide

can be efficiently generated by low energy UV irradiation (>300 nm) of Mannich bases of phenol derivatives in aqueous solvents (Scheme 29).[51]

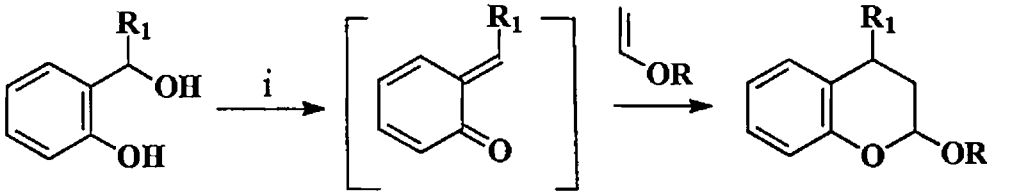


78 **79** **80**

i) UV (>300 nm), CH_3CN

Scheme 29

The photochemical dehydration of *o*-hydroxy benzyl alcohol is also utilized for the generation of *o*-quinone methide which on trapping with vinyl ether afforded chroman derivatives (Scheme 30).[52]



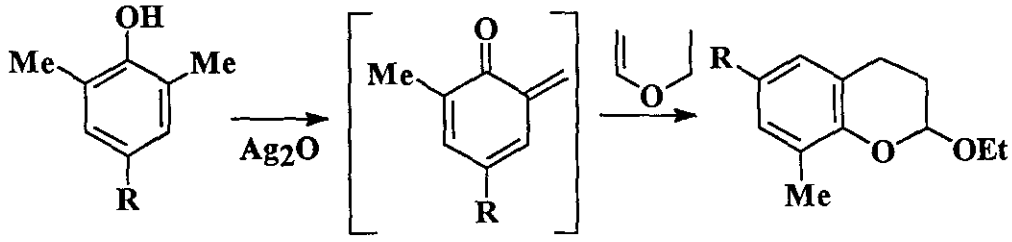
81 **82** **83**

i) hν, CH_3CN R_1 = H, Ph R = Et

Scheme 30

Another method that has proved to be of value for the formation of substituted quinone methides is exemplified by the reaction of silver oxide on 2,6-dimethyl-4-*tert*-butyl phenol; the intermediate quinone

methide is trapped with ethylvinylether to afford 2-ethoxy chroman derivative in quantitative yield (Scheme 31).[53]

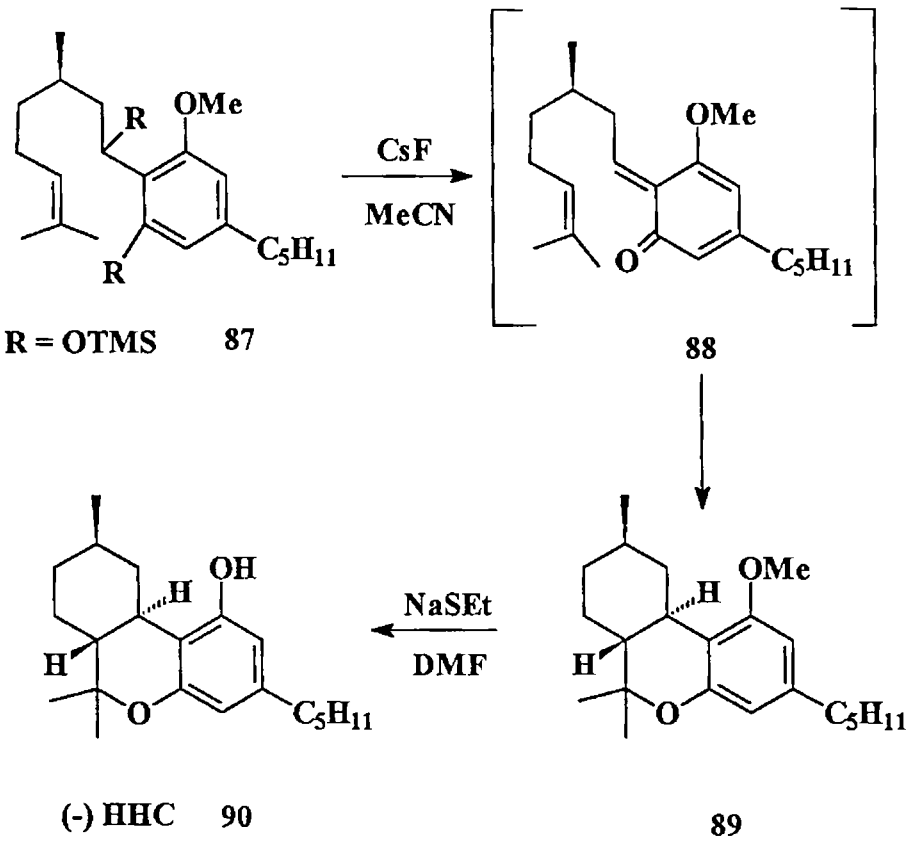


84 **85** **86**

R = *tert*-butyl

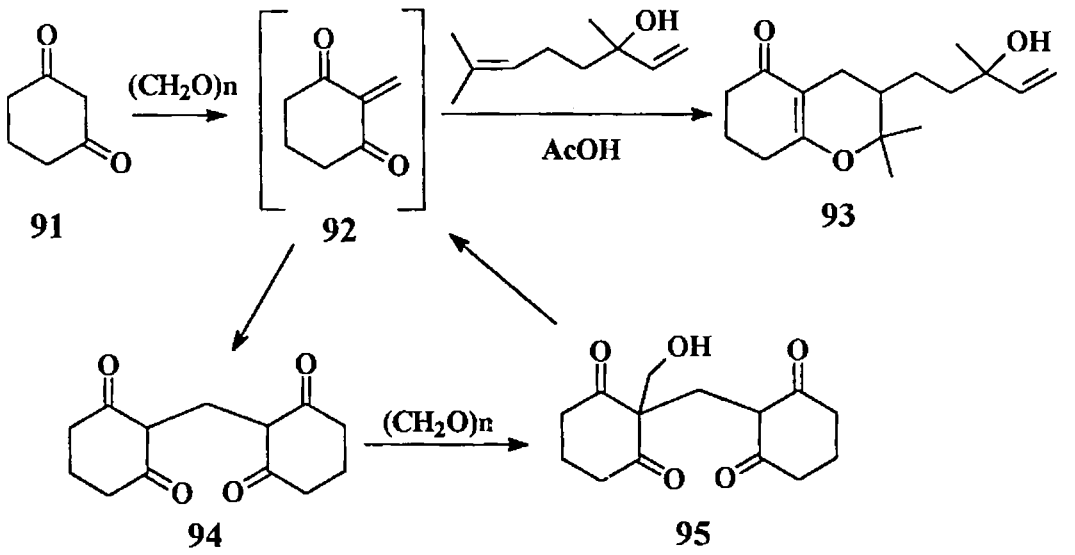
Scheme 31

The widespread occurrence of phenolic compounds and their potential use as precursors to polycyclic aromatic natural products has stimulated efforts directed toward the synthetic exploitation of *o*-quinone methides. The bis-silylated *o*-hydroxy benzyl alcohol derivative undergoes regiospecific 1,4-desilylation-elimination to incipient *o*-quinone methide that is trapped in an intramolecular Diels-Alder reaction to yield (+)- or (-)-hexahydrocannabinols (HHC) (Scheme 32).[54]



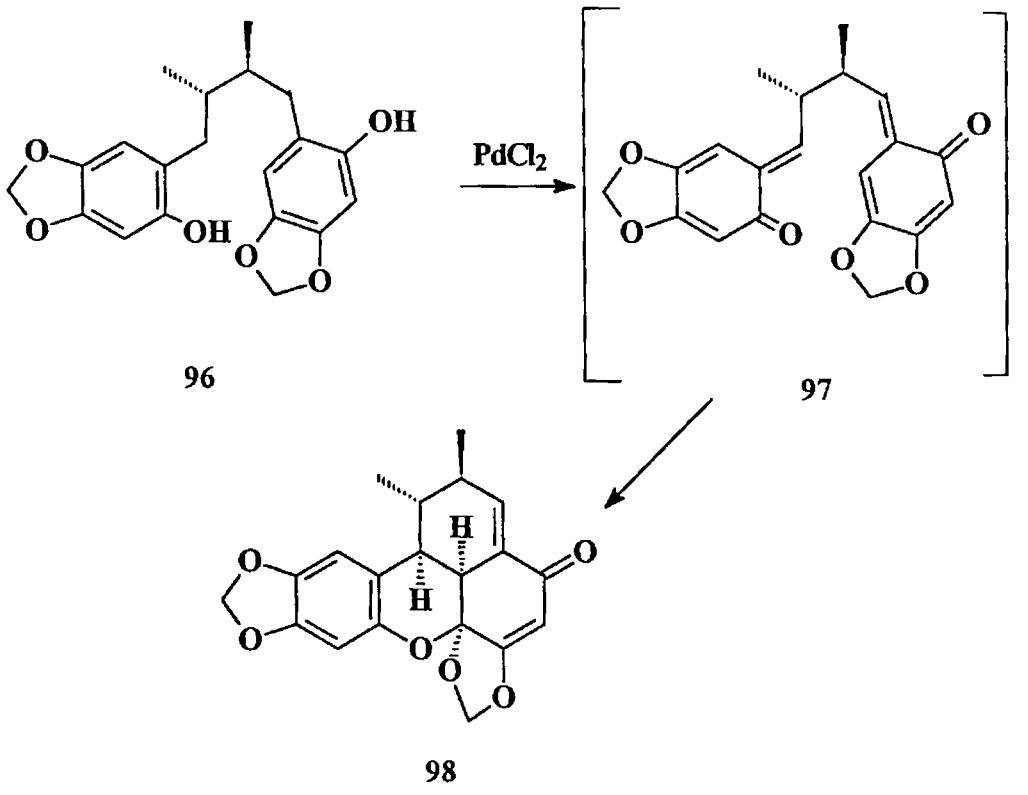
Scheme 32

The highly reactive methylene diketone **92**, derived from cyclohexan-1,3-dione **91** and paraformaldehyde, can be trapped readily as the Michael adduct **94**. The adduct **94** can be conveniently reconverted to the quinone methide and the latter has been trapped by a variety of monoterpenes (Scheme 33).[55]



Scheme 33

The intramolecuclar [4+2] cycloaddition reactions of *o*-quinone methides, generated by the oxidation of substituted *o*-allyl phenols, have been utilized in the development of a biomimetic synthesis of carpanone (Scheme 34).[56]



96 97 98

Scheme 34

Interestingly, *o*-quinone methides play a major role in the biomimetic total synthesis of citrans[57] and (+/-)-deoxybruceol.[58]

1.2.4 DEFINITION OF THE PROBLEM

The Diels-Alder chemistry of *o*-quinone methides has received considerable attention. However, heterocyclic quinone methides are an under-investigated group of compounds. The main interest in heterocyclic quinone methides as synthetic intermediates is due to their potential role as precursors of complex heterocycle compounds.

Details of these studies are presented in Chapter 3.

1.3 REFERENCES

1. Frankland, E. *Ann.* **1849**, *71*, 213.
2. Barbier, P. *C. R. Acad. Sci. Paris* **1899**, *110*, 128.
3. Grignard, V. *C. R. Acad. Sci. Paris* **1900**, *130*, 1322.
4. Houben, J. *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2897.
5. Leroux, Y. *Bull. Soc. Chim. Fr.* **1968**, 359.
6. Larcheveque, M.; Debal, A.; Cuvigny, T. *J. Organomet. Chem.* **1975**, *87*, 25.
7. Katzenellenbogen, J. A.; Lenox, R. S. *J. Org. Chem.* **1973**, *38*, 326.
8. (a) Ruppert, J. F.; White, J. D. *J. Org. Chem.* **1976**, *41*, 550. (b) Petrier, C.; Luche, J. -L. *J. Org. Chem.* **1985**, *50*, 910.
9. Hiyama, T.; Sawahara, M.; Obayashi, M. *Chem. Lett.* **1983**, 1237.
10. Mukaiyama, T.; Harada, T. *Chem. Lett.* **1981**, 1527.
11. Butsugan, Y.; Ito, H.; Araki, S. *Tetrahedron Lett.* **1987**, *28*, 3707.
12. Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.
13. Tanaka, H.; Yamashita, S.; Hamatani, T.; Ikemoto, Y.; Torii, S. *Chem. Lett.* **1986**, 1611.
14. Wada, M.; Akiba, K. -Y. *Tetrahedron Lett.* **1985**, *26*, 4211.
15. Cintas, P. *Activated Metals in Organic Synthesis;* CRC Press: Boca Raton, FL, 1993.
16. (a) Miller, J. A. *Chemistry of Aluminium, Gallium, Indium and Thallium;* Down, A. J., Ed.; Blackie Academic: Glasgow, 1993; p 403. (b) Leman, J. T.; Barron, A. R. *Encyclopedia of Inorganic*

Chemistry; King, R. B. Ed.; Wiley: New York, 1994; Vol. 3, p 1531.

17. Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831.
18. Cintas, P. *Synlett* **1995**, 1087.
19. Araki, S.; Katsumura, N.; Ito, H.; Butsugan, Y. *Tetrahedron Lett.* **1989**, *30*, 1581.
20. Araki, S.; Shimizu, T.; Johar, P. S.; Jin, S. -J.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2538.
21. (a) Beuchet, P.; Marrec, N. L; Mosset, P. *Tetrahedron Lett.* **1992**, *33*, 5959. (b) Jin, S. -J.; Araki, S.; Butsugan Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1528. (c) Loh, T. P.; Ho, D. S. -C.; Xu, K. -C.; Sim, K. -Y. *Tetrahedron Lett.* **1997**, *38*, 865. (d) Chan, T. H.; Lu, W. *Tetrahedron Lett.* **1998**, *39*, 8605.
22. Araki, S.; Imai, A.; Shimizu, K.; Butsugan, Y. *Tetrahedron Lett.* **1992**, *33*, 2581.
23. Araki, S.; Usui, H.; Kato, M.; Butsugan, Y. *J. Am. Chem. Soc.* **1996**, *118*, 4699.
24. (a) Ranu, B. C.; Majee, A. *J. Chem. Soc., Chem. Commun.* **1997**, 1225. (b) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 2318.
25. Wang, L.; Sun, X.; Zhang, Y. *Synth. Commun.* **1998**, *28*, 3263.
26. Araki, S.; Nakano, H.; Subburaj, K.; Hirashita, T.; Shibutani, K.; Yamamura, H.; Kawai, M.; Butsugan, Y. *Tetrahedron Lett.* **1998**, *39*, 6327.
27. Bossard, F.; Dambrin, V.; Lintanf, V.; Beuchet, P.; Mosset, P. *Tetrahedron Lett.* **1995**, *36*, 6055.

28. (a) Capps, S. M.; Lloyd-Jones, G. C.; Murray, M.; Peakman, T. M.; Walsh, K. E. *Tetrahedron Lett.* **1998**, *39*, 2853. (b) Höppe, H. A.; Lloyd-Jones, G. C.; Murray, M.; Peakman, T. M.; Walsh, K. E. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1545.

29. Araki, S.; Ito, H.; Butsugan, Y. *Synth. Commun.* **1988**, *18*, 453.

30. Araki, S.; Katsumura, N.; Kawasaki, K. -I.; Butsugan, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 499.

31. Araki, S.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 727.

32. Lim, H. J.; Keum, G.; Kang, S. B.; Chung, B. Y.; Kim, Y. *Tetrahedron Lett.* **1998**, *39*, 4367.

33. Moody, C. J.; Pitts, M. R. *Synlett* **1998**, 1028.

34. Moody, C. J.; Pitts, M. R. *Synlett* **1998**, 1029.

35. Araki, S.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 1286.

36. Carruthers, W. *Some Modern Methods of Organic Synthesis;* Cambridge University Press: London, 1978; p 161.

37. Patai, S.; Rappoport, Z. *The Chemistry of Quinonoid Compounds;* John Wiley & Sons: New York, 1988; Vol. 2.

38. (a) Capozzi, G.; Falciani, C.; Menichetti, S.; Nativi, C. *J. Org. Chem.* **1997**, *62*, 2611. (b) Nair, V.; Mathew, B.; Radhakrishnan, K. V.; Rath, N. P. *Synlett* **2000**, 61.

39. (a) Nair, V.; Kumar, S. *Synlett* **1996**, 1143. (b) Nair, V.; Kumar, S. *Tetrahedron* **1996**, *52*, 4029. (c) Thomas, A.; Anilkumar, G.; Nair, V. *Tetrahedron* **1996**, *52*, 2481.

40. (a) Ansell, M. F.; Gosden, A. F.; Leslie, V. J.; Murray, R. A. *J. Chem. Soc., (C)* **1971**, 1401. (b) Nair, V.; Anilkumar, G.;

Eigendorf, G. K.; Williard, P. G. *Tetrahedron Lett.* **1996**, *37*, 8271. (c) Verboom, W.; Bos, H. J. T. *Recl. J. R. Neth. Chem. Soc.* **1981**, *100*, 207. (d) Friedrichsen, W.; Schroer, W.D.; Smidt, R. *Justus Liebigs Ann. Chem.* **1976**, 793.

41. (a) Nair, V.; Kumar, S. *Synth. Commun.* **1996**, *26*, 697. (b) Omote, Y.; Tomotake, A.; Kashima, C. *J. Chem. Soc., Perkin Trans. 1* **1988**, 151. (c) Pitea, D.; Gastaldi, M.; Orsini, F.; Pelizzoni, F.; Mungoli, A.; Abbondanti, E. *J. Org. Chem.* **1985**, *50*, 1853.

42. Al-Hamdany, R.; Ali, B. *J. Chem. Soc., Chem. Commun.* **1978**, 397.

43. (a) Ansell, M. F.; Leslie, V. J. *J. Chem. Soc., (C)* **1971**, 1423. (b) Nair, V.; Kumar, S. *J. Chem. Soc., Chem. Commun.* **1994**, 1341. (c) Nair, V.; Kumar, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 443.

44. (a) 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. (Eng. Transl.). **1981**, 2360. (b) Nair, V.; Radhakrishnan, K. V.; Nair, A. G.; Bhadbhade, M. M. *Tetrahedron Lett.* **1996**, *37*, 5623.

45. (a) Wagner, H. -U.; Gompper, R. *The Chemistry of Quinonoid Compounds*; Patai, S. Wiley: New York, 1974; Vol. 2, p 1145. (b) Boger, D. L.; Weinreb, S. N. *Hetero Diels-Alder Methodology in Organic Synthesis;* Academic Press: New York, NY, San Diego, 1987; p 167.

46. Tomasz, M. *Advances in DNA sequence specific agents;* Hurley, L. H. Ed.; JAI Press: Greenwich, CT, 1992; Vol. 1, p 247.

47. (a) Jurd, L. *Tetrahedron* **1977**, *33*, 163. (b) Inoue, T.; Inoue, S.; Sato, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1647.

48. (a) Weenen, H.; Nleunya, M. H. H. *J. Org. Chem.* **1990**, *55*, 5107. (b) Parmar, V. S.; Tyagi, O. D.; Malhotra, A.; Singh, S. K.; Bisht, K. S.; Jain, R. *Nat. Prod. Rep.* **1994**, 219.

49. (a) Chauncey, M. A.; Grundon, M. F. *Synthesis* **1990**, 1005. (b) Chauhan, M. S.; McKinnon, D. M. *Can. J. Chem.* **1981**, *59*, 2223.

50. Brugidou, J.; Christol, H. *Compt. Rend.* **1963**, *256*, 3149.

51. Nakatani, K.; Higashide, N.; Saito, I. *Tetrahedron Lett.* **1997**, *38*, 5005.

52. Diago, L.; Yang, C.; Wan, P. *J. Am. Chem. Soc.* **1995**, *117*, 5369.

53. Bolon, D. A. *J. Org. Chem.* **1970**, *35*, 3666.

54. Marino, J. P.; Dax, S. L. *J. Org. Chem.* **1984**, *49*, 3671.

55. (a) Koser, S.; Hoffmann, H. M. R.; Williams, D. J. *J. Org. Chem.* **1993**, *58*, 6163. (b) Koser, S.; Hoffmann, H. M. R. *Heterocycles* **1994**, *37*, 661.

56. (a) Chapman, O. L.; Engel, M. R.; Spoinger, J. P.; Clardy, J. C. *J. Am. Chem. Soc.* **1971**, *93*, 6696. (b) Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1981**, *22*, 4437.

57. Bandaranayake, W. M.; Crombie, L.; Whiting, D. A. *J. Chem. Soc., (C)* **1971**, 804.

58. (a) Bengley, M. J.; Crombie, L.; Slack, D. A.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1976**, 140. (b) Bengley, M. J.;

Crombie, L.; Slack, D. A.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2402.

CHAPTER 2

NOVEL REACTIONS OF INDIUM REAGENTS WITH 1,2-DIONES

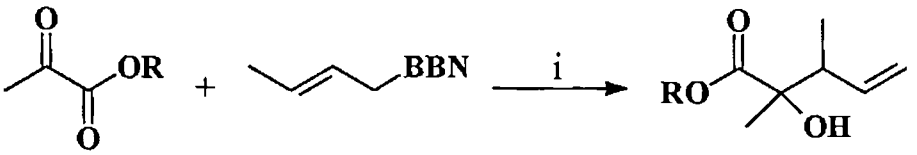
2.1 INTRODUCTION

The reaction of allylic metal reagents with carbonyl compounds leading to homoallylic alcohols is one of the most important and well studied reactions in organic synthesis. A number of metals have been effectively utilized in such transformations. The metal mediated organic reactions of carbonyl compounds such as aldehydes and ketones are well studied, while those of 1,2-diones have received only limited attention.

Generally with one equivalent of organometallic reagent, 1,2-diones afford α-hydroxy carbonyl compounds. α-Hydroxy carbonyl compounds, acyloins, are valuable intermediates in organic synthesis[1] and they are often found as structural subunits of a variety of natural products. Consequently several methods have been devised for their preparation.[2,3]

The practical and simplest route to α-hydroxy carbonyl compounds involves the direct enolate oxidation which has been explored in detail with two reagents, molecular oxygen (O_2)[4] and Vedejs's reagent[5] [molybdenum peroxide-pyridine-hexamethyl phosphoramide (MoOPH)]. However, these reagents often lead to by-products.

Yamamoto and co-workers[6,7] reported that pyruvate underwent facile crotylation using crotyl-BBN (Scheme 1).

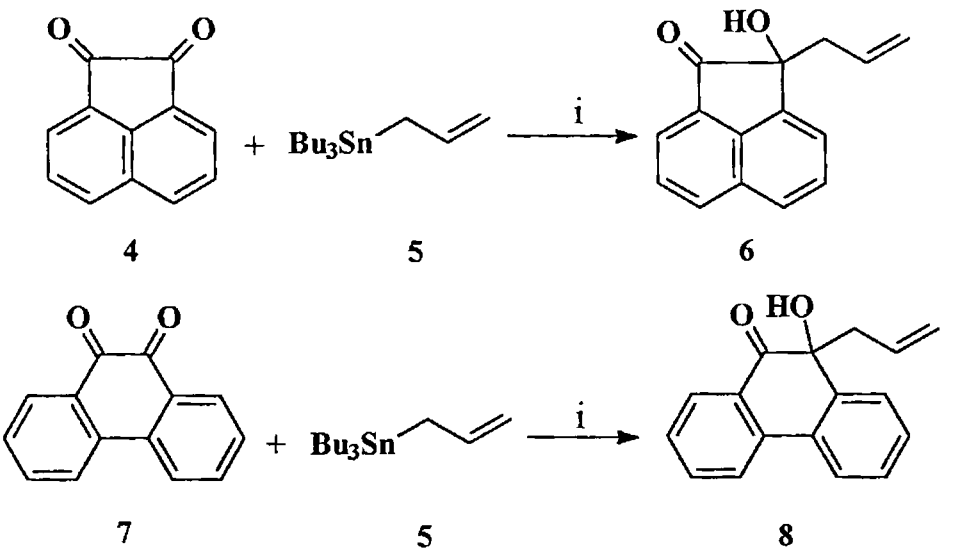


1 **2** **3**

i) Et_2O, -78 °C, 90-96% **R = Me, Ph**

Scheme 1

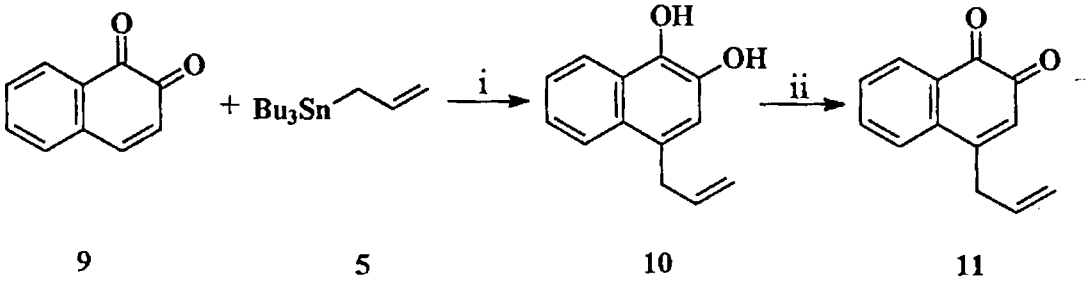
Recently, allyltin compounds have received considerable attention because of their marked reactivity towards electrophiles. Naruta has reported that acenaphthenequinone and phenanthrenequinone underwent facile allylation by allyltributyltin in the presence of BF_3-OEt_2 (Scheme 2).[8]



i) (a) BF_3-OEt_2, CH_2Cl_2, N_2 (b) H_2O

Scheme 2

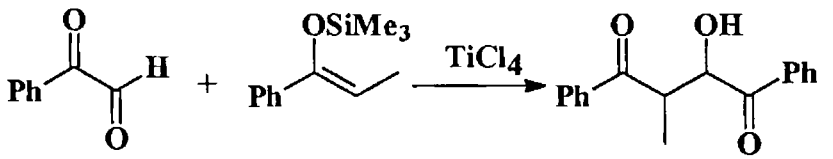
The reaction of **5** with 1,2-naphthoquinone afforded 4-allyl-1,2-naphthalenediol which is a precursor for allyl naphthoquinone (Scheme 3).[9]



i) (a) BF_3-OEt_2, CH_2Cl_2, N_2 (b) H_2O ii) Ag_2O

Scheme 3

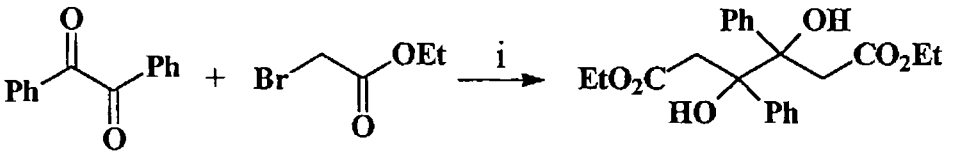
Mukaiyama *et al.* reported the aldol-type reactions of 1,2-diones in the presence of a Lewis acid (Scheme 4).[10,11]



12 **13** **14**

Scheme 4

The Reformatsky reaction of alkyl α-bromoalkanoates and zinc with benzil afforded the multifunctional compounds in good yields (Scheme 5).[12]

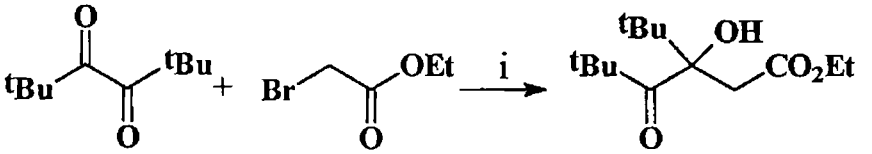


15 **16** **17**

i) 2 equiv. Zn, PhH, reflux, 71%

Scheme 5

Similarly, the Reformatsky reaction of other 1,2-diones has also been reported (Scheme 6).[13]

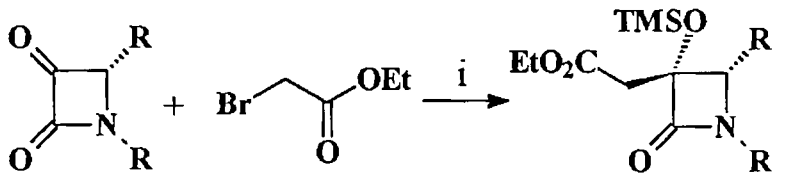


18 **16** **19**

i) Zn, Et_2O, PhH, reflux, 2 h, 39%

Scheme 6

It has been reported that the azetidin-2,3-dione derivative **20** undergoes the Reformatsky reaction smoothly (Scheme 7).[14]



20 **16** **21**

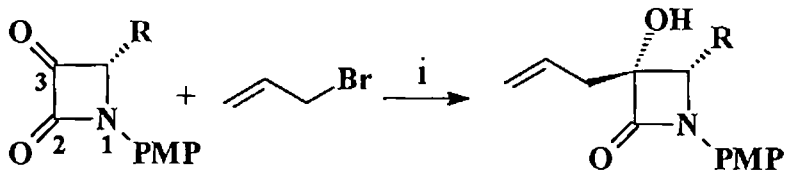
i) TMSCl, Zn, THF, r. t., 90% **R = *p*-Anisyl**

Scheme 7

2.2 INDIUM MEDIATED REACTIONS OF ACTIVATED ALKYL HALIDES WITH 1,2-DIONES

Although carbon-carbon bond forming reactions mediated by indium reagents have invoked considerable interest recently, very little is known about such reactions involving 1,2-diones.

Bose *et al.* reported that indium can promote allylation of azetidin-2,3-diones. As expected, the reaction occurs exclusively with the 3-keto group (Scheme 8).[15]



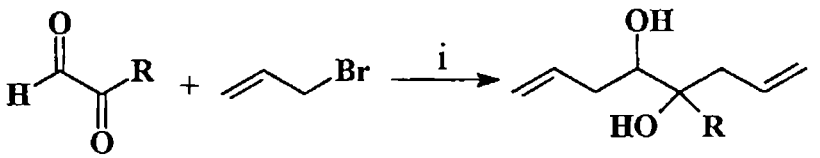
22 **23** **24**

i) In, H_2O/THF, r. t., 5-16 h, 77-99% **R = Ph**

Scheme 8

Later, Paquette and co-workers extensively studied the stereochemical course of the reactions of N-benzyl azetidin-2,3-dione with a variety of functionalized allylic bromides promoted by indium metal in aqueous tetrahydrofuran system.[16,17]

Very recently, while our work was in progress, a report on the indium mediated diallylation of glyoxal and methyl glyoxal in aqueous medium appeared (Scheme 9).[18]



25 **23** **26**

i) 2 equiv. In, H_2O, r. t., 3 h, 94% **R = H, CH_3**

Scheme 9

2.3 PRESENT WORK

It is evident from the literature survey presented above that except for isolated reports there has been no information available on the

reactions of indium reagents with 1,2-diones. In view of the synthetic potential offered by indium reagents, it was of interest to undertake a detailed investigation in this area.

2.4 RESULTS AND DISCUSSION

The 1,2-diones and various bromides selected for our investigations are shown in Figures **1** and **2** respectively.

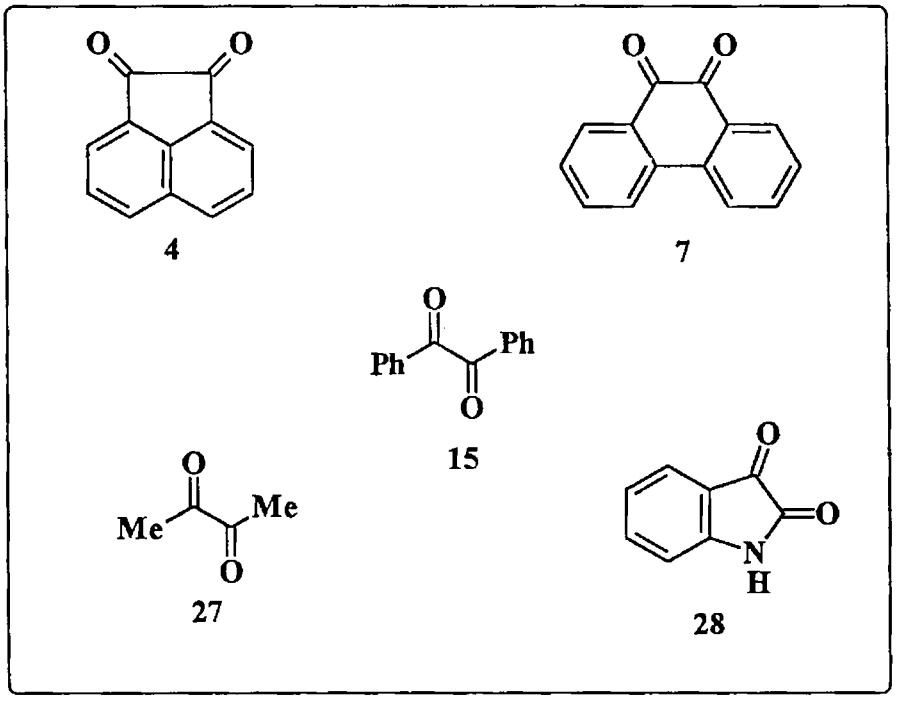


Figure 1

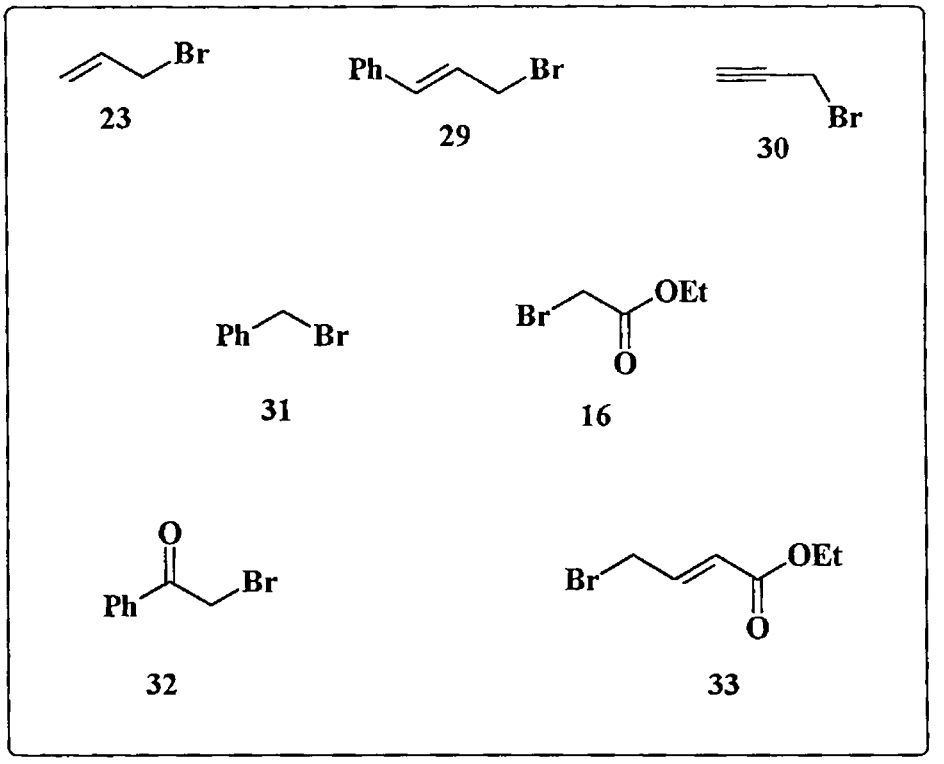
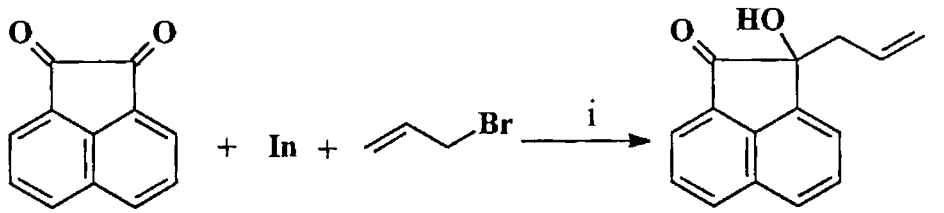


Figure 2

2.4.1 ALLYLATION OF 1,2-DIONES

Our studies were initiated with the reaction of allyl bromide and acenaphthenequinone **4** mediated by indium in the presence of sodium iodide in dimethyl formamide. The reaction proceeded smoothly to afford the α-hydroxy ketone **6** (Scheme 10). In the absence of sodium iodide the reaction was very slow.



4 **23** **6**

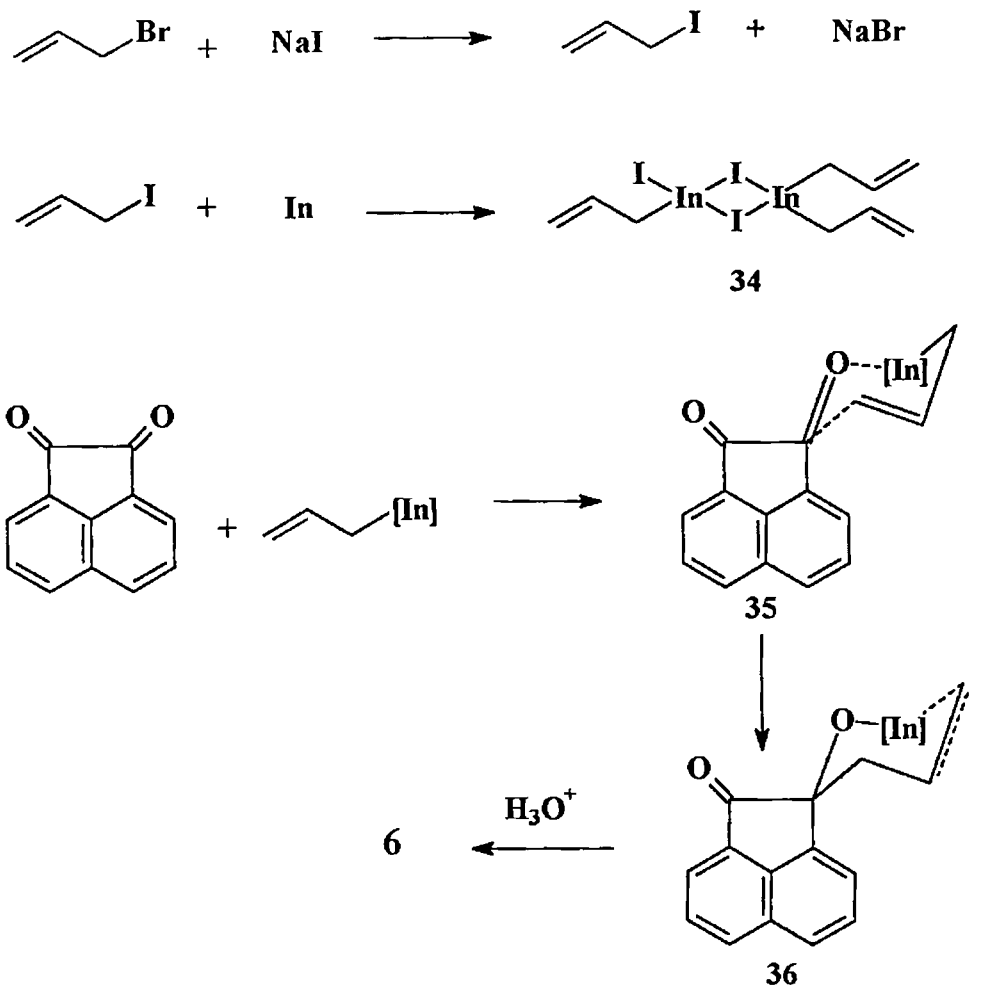
i) NaI, DMF, r. t., 4 min, 94%

Scheme 10

The structure of the product was assigned on the basis of spectral data. The IR spectrum of **6** showed strong absorptions at 3380 and 1715 cm^{-1} indicating the presence of hydroxyl and carbonyl groups respectively. In the ^{1}H NMR spectrum, the aromatic protons appeared as a multiplet between δ 7.63-8.11. The terminal olefinic protons appeared as a multiplet centered at δ 5.05. The other olefinic proton showed a multiplet centered at δ 5.65. The ^{13}C NMR spectrum was in good agreement with the proposed structure.

All the spectral data of the product were in good agreement with those reported for an authentic sample.[8]

Regarding the mechanism of the formation of **6,** a rationalization as outlined in Scheme 11 may be invoked.

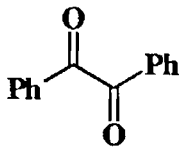
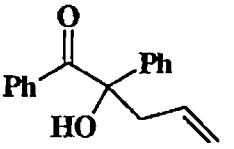
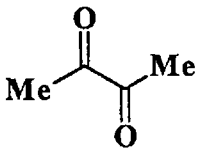
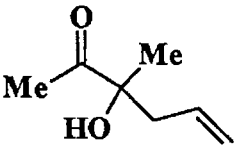
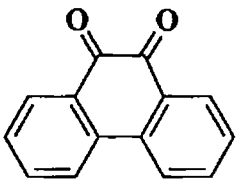
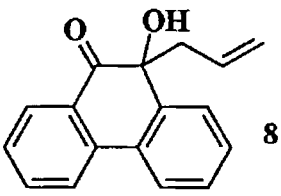
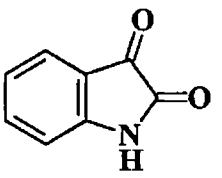
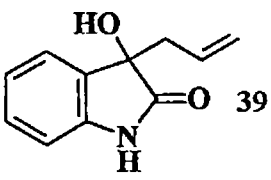


[In] = InL_n

Scheme 11

The allylation reactions of other 1,2-diones also proceeded in a similar fashion yielding only the mono allylated product in excellent yields. The results are summarized in Table 1. In all cases, the products were characterized on the basis of spectral data. In the case of known compounds, the spectral data, melting points, *etc.* have been compared with those reported in the literature.

Table 1: Allylation of 1,2-diones

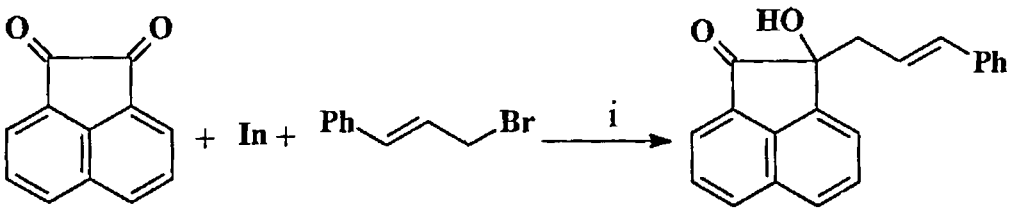
Entry	Diones	Reaction conditions[a]	Product		Yield[b]
1		5 min		37	97%
2		10 min		38	95%
3		2 min		8	95%
4		4 min		39	96%

[a] NaI, DMF, r. t. [b] isolated yield.

2.4.2 CINNAMYLATION OF 1,2-DIONES

Subsequent to the above investigations, we turned our attention to the indium mediated cinnamylation of 1,2-diones, with a view to gain some insight into the regioselectivity of these reactions.

In a prototype experiment, acenaphthenequinone **4** on reaction with cinnamyl bromide and indium metal in DMF in the presence of sodium iodide afforded exclusively the *E* isomer of the α-cinnamylated product in high yield (Scheme 12). The experimental simplicity and high yield of the product are especially noteworthy.



4 **29** **40**

i) NaI, DMF, r. t., 4 min, 92%

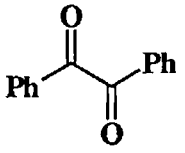
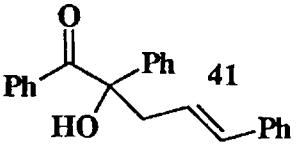
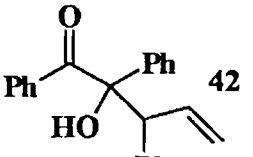
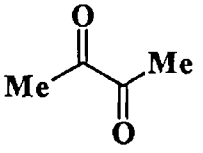
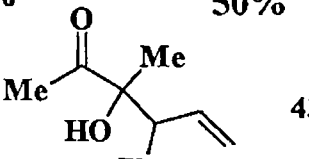
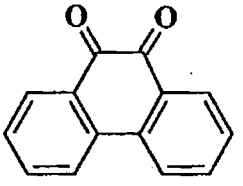
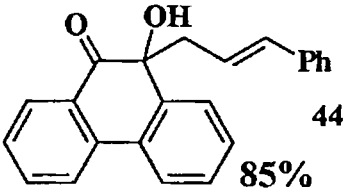
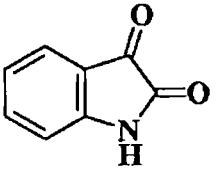
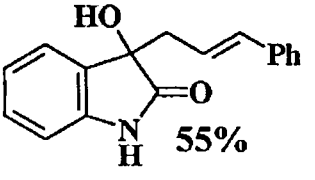
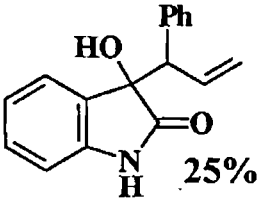
Scheme 12

The product **40** was characterized as usual. The IR spectrum showed a strong absorption at 1695 cm^{-1} due to the carbonyl group. The absorption at 3474 cm^{-1} can be attributed to the hydroxyl group. In the ^1H NMR spectrum, one of the methylene protons appeared as a multiplet centered at δ 2.72. The other proton gave a signal centered at δ 2.94 as a multiplet. The hydroxyl proton resonated at δ 3.40 as a broad peak (exchangeable by D_2O). The olefinic proton α to the methylene group gave a multiplet signal centered at δ 6.13. The other olefinic proton appeared as a doublet (J = 15.8 Hz) at δ 6.35. This large coupling constant for olefinic proton indicates a *trans* geometry for the alkene. In the ^{13}C NMR spectrum, the methylene carbon resonated at δ 42.03. The carbon bearing hydroxyl group was discernible at δ 79.79. The carbonyl

carbon gave a signal at δ 205.17. All other signals were in agreement with the assigned structure.

Similarly, the reaction of cinnamyl bromide and indium with various 1,2-diones in the presence of sodium iodide afforded corresponding mono cinnamylated products in good yields. The results are summarized in Table **2**.

Table 2: Cinnamylation of 1,2-diones

Entry	Diones	Reaction conditions[a]	Product(s), Yield(s)
1		25 min	 41 25%  42 50%
2		10 min	 43 88%
3		U. S.,* 7 min	 44 85%
4		U. S.,* 25min	 45 55%  46 25%

[a] NaI, DMF, r. t. * Ultrasonication

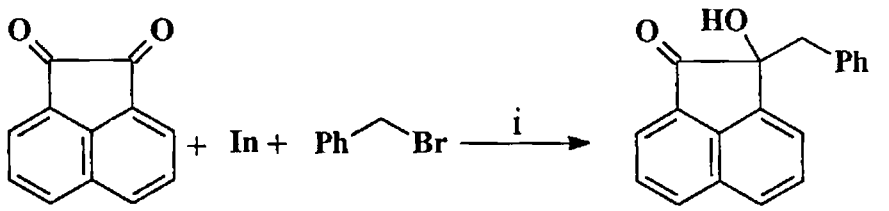
As usual, the products were completely characterized by spectral analysis. In some cases, cinnamylation afforded regioisomeric mixture of products which are separable. It is noteworthy that cinnamylation leading to both α and γ isomers in certain cases is in keeping with the characteristic behavior of other substituted allyl organometallics.[19] However, it has been suggested by Araki *et al.* that in the case of indium mediated Barbier reactions, the steric environment of the carbonyl group may be responsible for the formation of the α-cinnamylated product.[20]

In the cinnamylation of phenanthrenequinone and isatin under the above conditions, the reaction was found to be very slow and low yielding. However, under ultrasonication conditions the reaction was found to be facile.

2.4.3 BENZYLATION OF 1,2-DIONES

It has already been seen that activated halides such as allyl bromide and cinnamyl bromide react with metallic indium to form organoindium complexes and these reagents have been shown to be useful in transforming 1,2-diones to α-hydroxy ketones. In order to extend the synthetic utility of this method, we have studied the indium mediated reaction of benzyl bromide with selected 1,2-diones.

Acenaphthenequinone underwent facile reaction with benzyl bromide mediated by indium in the presence of sodium iodide in DMF under ultrasonication conditions to afford the product **47** in 90% yield (Scheme 13).



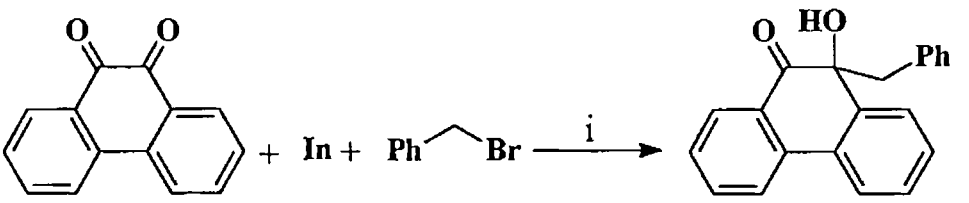
4 **31** **47**

i) NaI, DMF, U. S., r. t., 3 min, 90%

Scheme 13

The product was characterized by usual spectral methods. The IR spectrum of **47** showed strong carbonyl absorption at 1721 cm^{-1}. A strong absorption at 3454 cm^{-1} was due to the hydroxyl group. In the ^1H NMR spectrum, the hydroxyl proton displayed a singlet signal at δ 2.96. The benzylic protons appeared as two mutually coupled doublets (J = 13.3 Hz) at δ 3.10 and 3.35 respectively. The aromatic protons were visible between δ 6.98-8.06 as a multiplet. In the ^{13}C NMR spectrum, the benzylic carbon resonated at δ 44.45. The carbon bearing hydroxyl group appeared at δ 80.32. The carbonyl carbon showed a signal at δ 204.84. All other signals also supported the proposed structure.

Phenanthrenequinone on benzylation under similar conditions afforded the product **48** in 90% yield (Scheme 14).



7 **31** **48**

i) NaI, DMF, U. S., r. t., 15 min, 90%

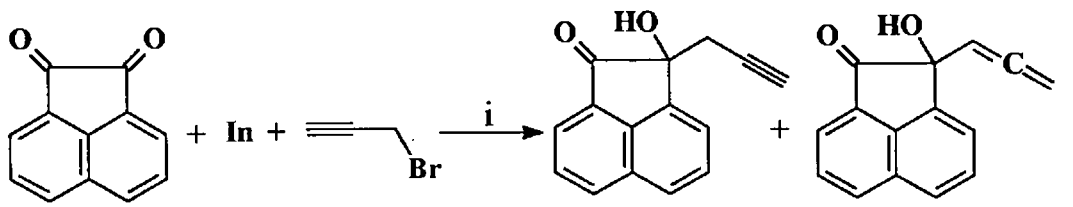
Scheme 14

As usual, the product was characterized by spectral data. The IR spectrum showed two strong absorptions at 3480 and 1670 cm^{-1} due to the hydroxyl and carbonyl group respectively. In the ^1H NMR spectrum, the two benzylic protons appeared as two separate doublets (J = 13.3 Hz) at δ 2.94 and 3.01. The hydroxyl proton showed a singlet signal (exchangeable with D_2O) at δ 3.97. The ^{13}C NMR spectrum was in complete agreement with the assigned structure.

2.4.4 PROPARGYLATION OF 1,2-DIONES

Subsequently, we decided to explore the reactivity of propargylindium complex with various 1,2-diones in the presence of sodium iodide.

Acenaphthenequinone on reaction with propargyl bromide, mediated by indium, afforded an inseparable mixture of corresponding alkyne and allene derivatives in the ratio 5:2 in 90% total yield (Scheme 15).



4 **30** **49** **50**

i) NaI, DMF, r. t., 5 min, 90%

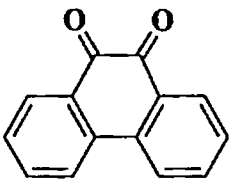
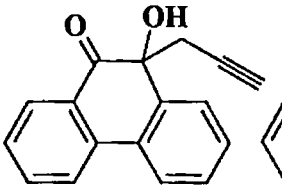
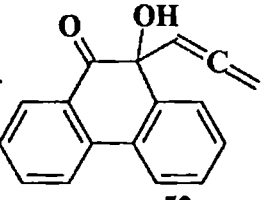
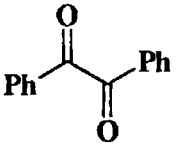
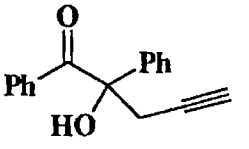
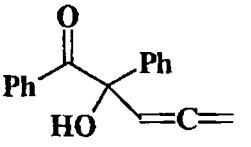
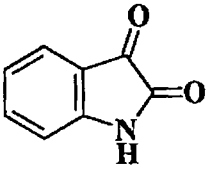
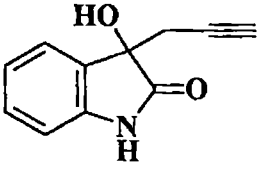
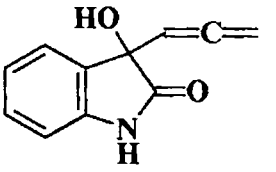
Scheme 15

The IR spectrum of the isomeric mixture showed strong carbonyl absorption at 1707 cm^{-1} and the hydroxyl group absorption was seen at 3430 cm^{-1}. An absorption at 3293 cm^{-1} was due to the presence of acetylenic functionality and the absorption at 1944 cm^{-1} was due to the allene in the isomeric mixture. In the ^1H NMR spectrum, the singlet signal at δ 1.93 was ascribed to the acetylenic proton. The methylene protons appeared as two mutually coupled double doublets (J = 16.6 Hz, 2.4 Hz) at δ 2.74 and 2.96 respectively. The methylene protons of the allene **50** resonated as a multiplet between δ 4.86-4.98. The other olefinic proton of the allene appeared as a multiplet between δ 5.50-5.55. The aromatic protons resonated as a mutiplet between δ 7.67-8.16. The ^{13}C NMR spectrum was also in accordance with the assigned structures.

Other 1,2-diones such as phenanthrenequinone, benzil and isatin also underwent facile propargylation under similar conditions. The results are summarized in Table 3. In all cases, the products were

characterized by spectral analysis. The ratio of the isomers was determined from the ^{1}H NMR spectrum.

Table 3: Propargylation of 1,2-diones

Entry	Diones	Reaction conditions[a]	Product(s), Yield(s)
1		3 min	 51  52 99% (13:2)
2		10 min	 53  54 75% (1:1)
3		25 min	 55  56 85% (4:1)

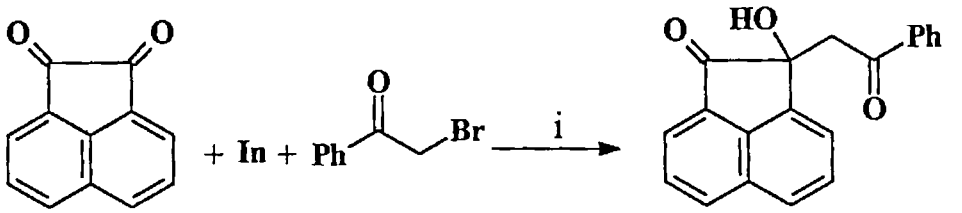
[a] NaI, DMF, r. t.

2.4.5 ALDOL REACTIONS OF 1,2-DIONES

The addition of a metal enolate, formed from an α-bromo ketone, to a carbonyl compound results in a β-hydroxy ketone. Such reactions are classified as metal mediated aldol reactions.

We have already seen that the procedure described in the previous sections is very convenient for the Barbier reactions of 1,2-diones. Consequently, we decided to investigate the aldol and Reformatsky-type reactions of 1,2-diones mediated by indium under similar conditions.

Acenaphthenequinone when treated with phenacyl bromide in the presence of indium and sodium iodide under ultrasonication conditions afforded the corresponding aldol product **57** in 93% yield (Scheme 16).



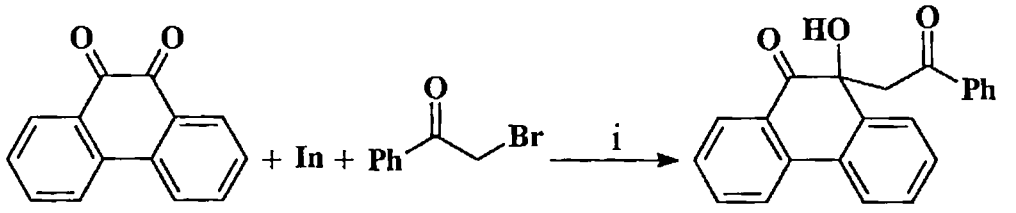
4 **32** **57**

i) NaI, DMF, U. S., r. t., 5 min, 93%

Scheme 16

The IR spectrum of the product showed strong absorption at 3420 cm^{-1} due to the hydroxyl group. The benzoyl carbonyl group appeared at 1688 cm^{-1}. The other carbonyl showed an absorption at 1735 cm^{-1}. In the ^1H NMR spectrum, the methylene protons resonated as two mutually coupled doublets (J = 17.4 Hz) at δ 3.55 and 3.90 respectively. The hydroxyl proton gave a singlet signal at δ 4.61 and was exchangeable by D_2O. In the ^{13}C NMR spectrum, the methylene carbon resonated at δ 44.32. The quaternary carbon bonded to hydroxyl group showed a signal at δ 78.14. All other signals also supported the assigned structure.

Phenanthrenequinone on treatment with phenacyl bromide under similar conditions afforded the aldol product 58 in 95% yield (Scheme 17).



7 32 58

i) NaI, DMF, U. S., r. t., 10 min, 95%

Scheme 17

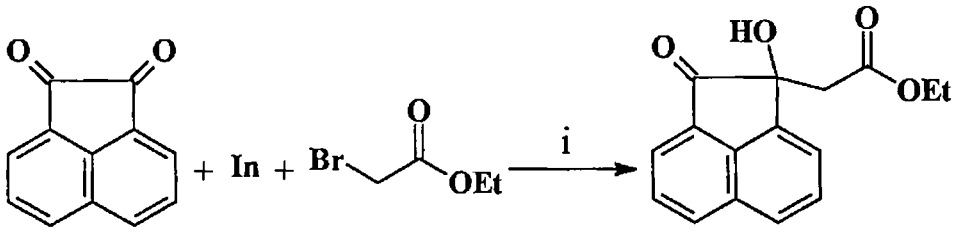
The product was characterized by usual spectroscopic methods. In the IR spectrum, a strong absorption at 3474 cm^{-1} was due to the hydroxyl group. The two carbonyls showed strong absorptions at 1704 and 1676 cm^{-1}. In the ^1H NMR, the methylene protons resonated as two distinct doublets (J = 14.8 Hz) at δ 3.17 and 3.61 respectively. In the ^{13}C NMR, the carbonyl carbons were visible at δ 196.49 and 202.15. All other signals were in complete agreement with the assigned structure.

2.4.6 REFORMATSKY REACTIONS OF 1,2-DIONES

Ethyl bromoacetate is also an activated halide like allyl and phenacyl halides. The reaction of ethyl bromoacetate with carbonyl compounds mediated by metal, especially Zn, affords β-hydroxy esters and is called Reformatsky reaction. Naturally, it was of interest to

investigate the indium mediated Reformatsky reaction of 1,2-diones. The results of our experiments are presented here.

Acenaphthenequinone on reaction with ethyl bromoacetate afforded the product **59** in 60% yield (Scheme 18).



4 **16** **59**

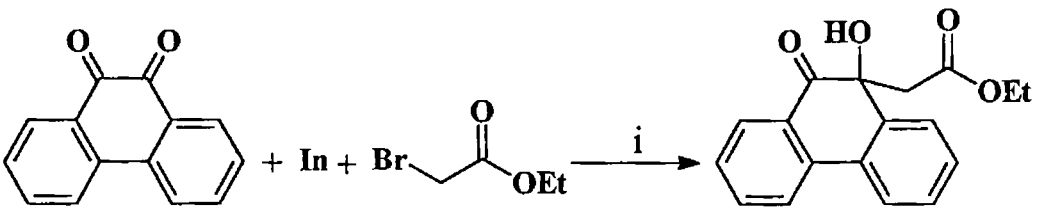
i) NaI, DMF, U. S., r. t., 6 min, 60%

Scheme 18

The IR spectrum of the product **59** showed strong absorption at 3440 cm^{-1} due to the hydroxyl group. The ester carbonyl absorption was observed at 1737 cm^{-1} and the absorption at 1714 cm^{-1} was attributed to the keto group. In the ^1H NMR spectrum, the ester methyl group ($-CO_2CH_2\underline{CH_3}$) resonated as a triplet (J = 7.0 Hz) at δ 1.03. The signal due to the ester methylene group was visible as a quartet (J = 7.0 Hz) at δ 4.02. The methylene protons α to the ester carbonyl group ($-\underline{CH_2}-CO_2Et$) resonated at δ 3.02 as a singlet. The hydroxyl proton was visible at δ 4.51 as a singlet (exchangeable with D_2O). In the ^{13}C NMR spectrum, the ester methyl carbon was discernible at δ 13.88. The methylene carbon of the ester group appeared at δ 61.05. The other methylene carbon showed a signal at δ 41.20. The quaternary carbon

bearing hydroxyl group resonated at δ 76.66. All other signals were in good agreement with the proposed structure.

Phenanthrenequinone under similar conditions afforded the corresponding Reformatsky product **60** in good yield (Scheme 19).



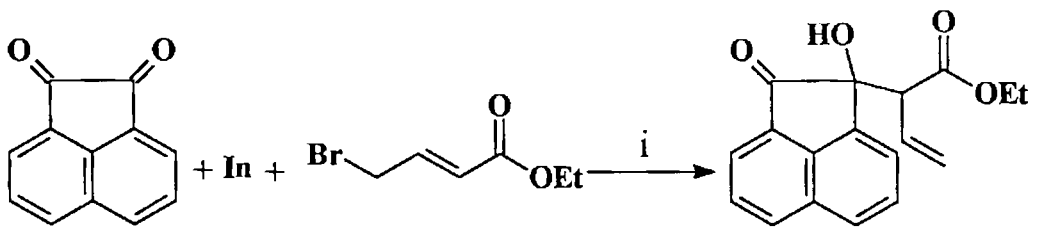
7 **16** **60**

i) NaI, DMF, U. S., 15 min, 60%

Scheme 19

The product showed two strong carbonyl absorptions at 1735 and 1701 cm^{-1} due to ester and keto groups respectively. In the ^1H NMR spectrum, the ester methyl group appeared as a triplet (J = 7.1 Hz) at δ 1.16. The protons of the methylene group, α to the ester carbonyl, were visible as a multiplet centered at δ 2.78. The ^{13}C NMR spectrum also was in complete agreement with the assigned structure.

Acenaphthenequinone, on treatment with ethyl-4-bromocrotonate in the presence of indium and sodium iodide under ultrasonication conditions afforded only the γ-addition product **61** in 87% yield (Scheme 20).



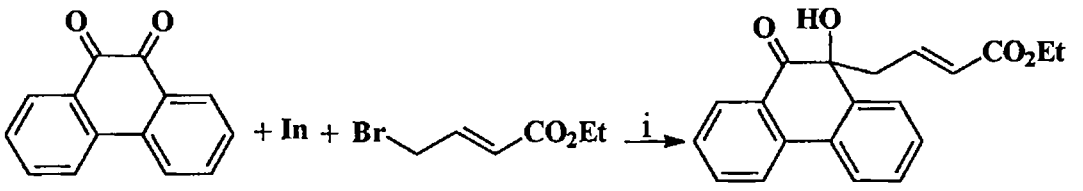
4 **33** **61**

i) NaI, DMF, U. S., 12 min, 87%

Scheme 20

The product was characterized by usual spectroscopic methods. The IR spectrum of the product showed the characteristic absorption due to the hydroxyl group at 3443 cm^{-1}. The ester carbonyl showed a strong absorption at 1732 cm^{-1}. The absorption at 1713 cm^{-1} was due to the keto group. The ^1H NMR spectrum showed that the product is a mixture of isomers, *syn* and *anti*, in the ratio 3:1. The methyl protons ($C\underline{H}_3$-CH_2-O-) of the isomeric mixture appeared as triplets (J = 7.0 Hz) at δ 0.81 and 1.07. The proton α to the ester carbonyl showed signals at δ 3.64 and 3.82. The signals due to the hydroxy protons were visible at δ 4.58 and 4.63. The terminal olefinic protons appeared between δ 5.10-5.23 as a multiplet. In the ^{13}C NMR spectrum, the methyl carbons ($\underline{C}H_3$-CH_2-O-) of the isomeric mixture were discernible at δ 13.42 and 13.78. The quaternary carbons bearing hydroxyl group were visible at δ 79.19 and 79.39. The ester carbonyl carbons resonated at δ 170.62 and 171.34. All other signals also supported the assigned structure.

Similarly, phenanthrenequinone on treatment with ethyl-4-bromocrotonate in the presence of sodium iodide under ultrasonication conditions afforded the product **62** in 68% yield (Scheme 21).



7 **33** **62**

i) NaI, DMF, U. S., 10 min, 68%

Scheme 21

The IR spectrum of the product **62** showed strong absorption at 3475 cm^{-1} due to the hydroxyl group. The ester carbonyl absorption was visible at 1722 cm^{-1} while the ketone absorbed at 1695 cm^{-1}. In the ^{1}H NMR spectrum, the methyl group of the ester resonated as a triplet (J = 7.0 Hz) at δ 1.19. The methylene protons of the ester were visible as a multiplet between δ 2.49-2.67. The olefinic proton, near to the ester carbonyl group, appeared as a doublet (J = 15.6 Hz) at δ 5.54. This large value of coupling constant indicates a *trans* geometry for the alkene. In the ^{13}C NMR spectrum, the ester methyl carbon showed a signal at δ 14.16. The ester carbonyl and keto groups were visible at δ 179.94 and 202.14 respectively. All other signals were also in good agreement with the proposed structure.

2.5 CONCLUSION

The facile reaction of organoindium reagents with 1,2-diones provides a useful synthetic method for the generation of α-hydroxy ketones. The versatility and generality of the reaction are especially noteworthy. α-Hydroxy compounds are important intermediates in organic synthesis.

2.6 EXPERIMENTAL DETAILS

Dimethyl formamide was freshly distilled and kept over 4Å molecular sieves. Other solvents for extraction and chromatography were distilled prior to use. Silica gel used for column chromatography was of 100-200 mesh. All the diones and bromides used were commercially available. Reactions were monitored by thin-layer chromatography on glass plates coated with silica gel. IR spectra were recorded on Nicolet Impact 400D and Bomem MB Series FT-IR spectrophotometers, with solid compounds compressed into KBr pellets and liquid compounds examined as films on KBr discs.

^{1}H (300 MHz) and ^{13}C NMR spectra were recorded on Bruker Avance DPX 300 spectrometer using $CDCl_3$ and the chemical shifts are reported in δ units downfield from tetramethylsilane, used as the internal standard. Electron impact mass spectra (EIMS) of some of the compounds were obtained using GCMS-MD 800 instrument.

1,2-Dihydro-1-hydroxy-1-(2-propenyl)-2-oxacenaphthene [6]

A mixture of acenaphthenequinone (0.182 g, 1 mmol), allyl bromide (0.186 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL dimethyl formamide was stirred at 25 °C until completion of the reaction (4 min). The reaction mixture was quenched with a few drops of 1N HCl and extracted with diethyl ether (3 x 30 mL). The ether layer was washed with water, brine and then dried over anhydrous sodium sulfate. Evaporation of the ether followed by purification of the product by silica gel column chromatography provided 0.211 g (94%) of the pure product as a colorless solid; recrystallized from dichloromethane in hexane solvent system (mp: 148-150 °C, Lit. mp: 147-148 °C).

Spectral data for 6

IR (KBr) ν_{max} : 3380, 1715, 1607, 1256, 1027, 791, 596 cm^{-1}.

^1H NMR : δ 2.62-2.69 (m, 1H), 2.77-2.87 (m, 2H), 5.00-5.10 (m, 2H), 5.59-5.71 (m, 1H), 7.63-8.11 (m, 6H).

^{13}C NMR : δ 42.79, 79.30, 120.07, 120.64, 125.22, 128.18, 128.58, 131.83, 139.26, 141.26, 204.85.

EIMS m/z : 224 (M^+).

9,10-Dihydro-9-hydroxy-9-(2-propenyl)-10-oxophenanthrene [8]

A mixture of phenanthrenequinone (0.208 g, 1 mmol), allyl bromide (0.186 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL dimethyl formamide was

stirred at 25 °C until completion of the reaction (2 min). The usual work up followed by purification of the product by silica gel column chromatography using 10% ethyl acetate in hexane as eluent afforded **8** (0.237 g, 95%) as a colorless solid; recrystallized from a solution of dichloromethane in hexane (mp: 47-48 °C, Lit. mp: 44-46 °C).

Spectral data for 8

IR (KBr) ν_{max} : 3488, 3083, 1708, 1600, 1458, 1290, 1202, 939, 778 cm^{-1}.

^1H NMR : δ 2.38-2.56 (m, 2H), 4.04 (s, 1H), 4.80-5.02 (m, 2H), 5.54-5.66 (m, 1H), 7.35-7.92 (m, 8H).

^{13}C NMR : δ 49.03, 79.53, 119.46, 123.12, 123.96, 126.23, 127.29, 128.11, 128.36, 128.56, 128.99, 129.14, 131.41, 134.93, 137.52, 146.26, 202.75.

EIMS m/z : 250 (M^+).

1,2-Diphenyl-2-hydroxy-4-penten-1-one [37]

A mixture of benzil (0.210 g, 1 mmol), allyl bromide (0.210 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL dimethyl formamide was stirred at 25 °C until completion of the reaction (5 min). The usual work up followed by purification of the product by silica gel column chromatography using 5% ethyl acetate in hexane as eluent afforded **37** (0.244 g, 97%) as a colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 88-90 °C).

Spectral data for 37

IR (KBr) ν_{max} : 3467, 3070, 2955, 1681, 1458, 1229, 1007, 946, 710 cm^{-1}.

^1H NMR : δ 2.90-2.97 (m, 1H), 3.09-3.16 (m, 1H), 4.09 (s, 1H), 4.98-5.13 (m, 2H), 5.66-5.80 (m, 1H), 7.25-7.73 (m, 10H).

^{13}C NMR : δ 44.06, 81.30, 120.28, 125.50, 127.96, 128.76, 130.10, 132.34, 141.77, 200.44.

3-Methyl-3-hydroxy-5-hexen-2-one [38]

A mixture of butan-2,3-dione (0.086 g, 1 mmol), allyl bromide (0.186 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55mmol) in 3 mL dimethyl formamide was stirred at 25 °C until completion of the reaction (10 min). The usual work up followed by purification of the product by silica gel column chromatography using 3% ethyl acetate in hexane as eluent afforded **38** (0.112 g, 95%) as a colorless liquid.

Spectral data for 38

IR (neat) ν_{max} : 3486, 3080, 2980, 1707, 1638, 1426, 1357, 1158, 989, 914 cm^{-1}.

^1H NMR : δ 1.37 (s, 3H), 2.21 (s, 3H), 2.44-2.46 (m, 2H), 3.85 (s, 1H), 5.08-5.13 (m, 2H), 5.65-5.79 (m, 1H).

^{13}C NMR : δ 23.94, 24.90, 43.84, 78.62, 118.65, 132.34, 211.42.

3-Hydroxy-3-(2-propenyl)-2-indolone [39]

A mixture of isatin (0.147 g, 1 mmol), allyl bromide (0.186 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55mmol) in 3 mL dimethyl formamide was stirred at 25 °C until completion of the reaction (4 min). The usual work up followed by purification of the product by silica gel column chromatography using 30% ethyl acetate in hexane as eluent afforded **39** (0.182 g, 96%) as a colorless solid; recrystallized from dichloromethane in hexane solvent system (mp: 150-152 °C).

Spectral data for 39

IR (KBr) ν_{max} : 3334, 1720, 1626, 1474, 1189, 922 cm^{-1}.

^1H NMR (DMSO-d_6) : δ 2.55-2.62 (m, 1H), 2.69-2.76 (m, 1H), 3.43 (s, 1H), 5.07-5.12 (m, 2H), 5.57-5.71 (m, 1H), 6.84-7.35 (m, 4H), 8.43 (s, 1H).

^{13}C NMR (DMSO-d_6) : δ 42.80, 77.20, 104.70, 110.14, 120.39, 122.90, 124.42, 129.50, 130.24, 140.21, 179.89.

EIMS m/z : 189 (M^+).

1,2-Dihydro-1-hydroxy-1-(3-phenyl-2-propenyl)-2-oxacenaphthene [40]

A mixture of acenaphthenequinone (0.182 g, 1 mmol), cinnamyl bromide (0.305 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL dimethyl formamide was

stirred at 25 °C until completion of the reaction (4 min). The usual work up followed by purification of the product by silica gel column using 10% ethyl acetate in hexane as eluent afforded **40** (0.281 g, 92%) as a colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 98-100 °C).

Spectral data for 40

IR (KBr) ν_{max} : 3474, 1695, 1595, 1339, 1195, 970, 746 cm^{-1}.

^1H NMR : δ 2.68-2.76 (m, 1H), 2.90-2.97 (m, 1H), 3.40 (brs, 1H), 6.10-6.16 (m, 1H), 6.35 (d, J = 15.8 Hz, 1H), 7.13-7.18 (m, 5H), 7.61-8.08 (m, 6H).

^{13}C NMR : δ 42.03, 79.79, 120.98, 122.25, 122.69, 125.36, 126.29, 127.42, 128.32, 128.48, 128.74, 130.67, 132.03, 134.99, 137.05, 139.44, 141.32, 205.17.

Anal. Calcd for $C_{21}H_{16}O_2$: C, 83.98; H, 5.37. Found: C, 83.86; H, 5.44.

1,2,5-Triphenyl-2-hydroxy-4-penten-1-one [41] and 1,2,3-Triphenyl-2-hydroxy-4-penten-1-one [42]

A mixture of benzil (0.210 g, 1 mmol), cinnamyl bromide (0.305 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL dimethyl formamide was stirred at 25 °C until completion of the reaction (25 min). The usual work up followed by purification of the product by silica gel column using 5% ethyl acetate in hexane as eluent afforded α adduct **41** (0.082 g, 25%) as colorless solid; recrystallized from dichloromethane/hexane solvent system

(mp: 108-111 °C) and γ adduct **42** (0.164 g, 50%) as colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 112-114 °C). From the ^{1}H NMR spectrum, the product **42** was found to be a mixture of *syn* and *anti* isomers in the ratio 1:1.

Spectral data for 41

IR (KBr) ν_{max} : 3499, 3024, 2912, 1670, 1588, 1445, 1351, 1201, 1126, 1020, 958, 827, 746, 702, 615 cm^{-1}.

^{1}H NMR : δ 3.02-3.09 (m, 1H), 3.24-3.31 (m, 1H), 4.17 (s, 1H), 6.08-6.15 (m, 1H), 6.26 (d, J = 15.9 Hz, 1H), 7.18-7.73 (m, 15H).

^{13}C NMR : δ 43.50, 81.93, 123.68, 125.71, 126.42, 127.67, 128.21, 128.62, 129.04, 130.34, 132.81, 134.84, 135.45, 136.95, 142.04, 200.77.

Spectral data for 42

IR (KBr) ν_{max} : 3494, 3058, 3027, 2921, 1676, 1595, 1489, 1446, 1346, 1203, 960, 830, 749, 699 cm^{-1}.

^{1}H NMR : δ 3.83 (s, 1H), 4.10 (s, 1H), 4.58 (d, J = 7.5 Hz, 1H), 4.65 (d, J = 7.8 Hz, 1H), 4.96-5.17 (m, 4H), 6.11-6.23 (m, 2H), 7.09-7.97 (m, 30H).

^{13}C NMR : δ 54.69, 55.92, 83.61, 84.51, 117.36, 117.92, 125.17, 125.48, 125.72, 125.91, 126.41, 126.80, 126.89, 126.91, 127.09, 127.16, 127.49, 127.89, 128.57,

128.74, 128.82, 128.88, 131.11, 131.14, 133.64, 135.92, 136.10, 199.97, 200.44.

3-Hydroxy-3-methyl-4-phenyl-5-hexen-2-one [43]

A mixture of butan-2,3-dione (0.086 g, 1 mmol), cinnamyl bromide (0.305 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL dimethyl formamide was stirred at 25 °C until completion of the reaction (10 min). The usual work up followed by purification of the product by silica gel column using 3% ethyl acetate in hexane as eluent afforded **43** (0.179 g, 88%) as a pale yellow semi-solid. The product was found to be a mixture of *syn* and *anti* isomers in the ratio 1:1 by ^{1}H NMR.

Spectral data for 43

IR (neat) ν_{max} : 3467, 3062, 3030, 2980, 1701, 1626, 1451, 1351, 1220, 1145, 1089, 995, 914, 739, 689 cm^{-1}.

^{1}H NMR : δ 1.07 (s, 3H), 1.35 (s, 3H), 2.02 (s, 3H), 2.19 (s, 3H), 3.47 (d, J = 9.2 Hz, 2H), 3.92 (brs, 2H), 4.97 (dd, J = 13.1 Hz, 2.6 Hz, 2H), 5.15 (dd, J = 8.3 Hz, 1.9 Hz, 2H), 6.05-6.11 (m, 1H), 6.19-6.25 (m, 1H), 7.12-7.35 (m, 10H).

^{13}C NMR : δ 23.71, 23.94, 24.13, 56.79, 57.12, 80.81, 81.02, 116.69, 117.52, 125.70, 126.74, 126.84, 127.99, 128.04, 128.18, 129.33, 136.52, 136.65, 138.89, 139.46, 210.70, 211.27.

9,10-Dihydro-9-hydroxy-9-(3-phenyl-2-propenyl)-10-oxophenanthrene [44]

A mixture of phenanthrenequinone (0.208 g, 1 mmol), cinnamyl bromide (0.305 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL DMF was ultrasonicated for 7 min. The usual work up followed by purification of the product by silica gel column using 10% ethyl acetate in hexane as eluent afforded **44** (0.276 g, 85%) as a colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 93-95 °C).

Spectral data for 44

IR (KBr) ν_{max} : 3474, 1682, 1595, 1445, 1283, 964, 727 cm^{-1}.

^1H NMR : δ 2.55-2.70 (m, 2H), 4.10 (s, 1H), 5.89-5.99 (m, 1H), 6.10 (d, J = 15.8 Hz, 1H), 7.17-7.93 (m, 13H).

^{13}C NMR : δ 48.63, 80.01, 123.03, 123.30, 124.10, 126.39, 126.44, 127.51, 128.32, 128.53, 128.75, 129.19, 129.36, 134.61, 135.13, 137.13, 137.78, 140.29, 202.88.

EIMS m/z : 326 (M^+).

3-Hydroxy-3-(3-phenyl-2-propenyl)-2-indolone [45] and 3-Hydroxy-3-(1-phenyl-2-propenyl)-2-indolone [46]

A mixture of isatin (0.147 g, 1 mmol), cinnamyl bromide (0.305 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL DMF was ultrasonicated for 25 min. The usual work up followed by purification of the product by silica gel column using 30% ethyl acetate in hexane as eluent afforded **45** (0.145 g, 55%) as colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 163-166 °C) and **46** (0.066 g, 25%) as colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 160-162 °C). The product **46** was found to be a mixture of *syn* and *anti* isomers in the ratio 1:1 as determined by ^{1}H NMR.

Spectral data for 45

IR (KBr) ν_{max} : 3333, 3274, 1726, 1695, 1470, 1208, 752 cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 2.67-2.74 (m, 1H), 2.86-2.92 (m, 1H), 4.76 (s, 1H), 6.00-6.10 (m, 1H), 6.35 (d, J = 15.7 Hz, 1H), 6.85-7.45 (m, 9H), 9.10 (s, 1H).

^{13}C NMR (DMSO-d_6) : δ 41.33, 109.55, 121.50, 122.49, 123.80, 125.59, 126.60, 127.84, 128.53, 130.76, 133.52, 136.75, 140.85, 179.27.

Spectral data for 46

IR (KBr) ν_{max} : 3340, 3267, 1723, 1680, 1475, 1210, 755 cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 3.50 (s, 1H), 3.82 (d, J = 10.1 Hz, 1H), 5.33 (m, 2H), 6.31 (m, 1H), 6.9-7.25 (m, 9H), 8.10 (s, 1H).

^{13}C NMR (DMSO-d_6) : δ 58.20, 109.75, 119.77, 120.58, 122.46, 125.00, 125.33, 127.07, 127.83, 128.78, 129.01, 129.55, 129.70, 133.81, 136.84, 140.53, 179.04.

1,2-Dihydro-1-hydroxy-1-(phenylmethyl)-2-oxacenaphthene [47]

A solution of acenaphthenequinone (0.182 g, 1.0 mmol), benzyl bromide (0.265 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL DMF was ultrasonicated for 3 min. The usual work up followed by purification of the product by silica gel column using 10% ethyl acetate in hexane as eluent afforded **47** (0.247 g, 90%) as a colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 155-157 °C).

Spectral data for 47

IR (KBr) ν_{max} : 3454, 3056, 3029, 2921, 1721, 1613, 1506, 1438, 1344, 1276, 1074, 1013, 784, 703, 542 cm^{-1}.

^{1}H NMR : δ 2.96 (s, 1H), 3.10 (d, J = 13.3 Hz, 1H), 3.35 (d, J = 13.3 Hz, 1H), 6.98-8.06 (m, 11H).

^{13}C NMR : δ 44.45, 80.32, 121.21, 121.93, 125.24, 126.75, 127.71, 128.09, 128.34, 130.43, 130.61, 131.75, 134.57, 138.72, 141.33, 204.84.

9,10-Dihydro-9-hydroxy-9-(phenylmethyl)-10-oxophenanthrene [48]

A solution of phenanthrenequinone (0.208 g, 1.0 mmol), benzyl bromide (0.265 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and

sodium iodide (0.232 g, 1.55 mmol) in 3 mL DMF was ultrasonicated for 15 min. The usual work up followed by purification of the product by silica gel column using 10% ethyl acetate in hexane as eluent afforded **48** (0.270 g, 90%) as a colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 149-151 °C).

Spectral data for 48

IR (KBr) ν_{max} : 3480, 3068, 3030, 2918, 1670, 1595, 1445, 1276, 1220, 1095, 1008, 902, 758, 727, 696 cm^{-1}.

^1H NMR : δ 2.94 (d, J = 13.3 Hz, 1H), 3.01 (d, J = 13.3 Hz, 1H), 3.97 (s, 1H), 6.80-6.81 (m, 2H), 7.12-7.14 (m, 3H), 7.33-7.42 (m, 3H), 7.58-7.80 (m, 2H), 7.86-7.91 (m, 3H).

^{13}C NMR : δ 51.12, 80.13, 123.06, 123.77, 126.40, 126.89, 127.36, 127.63, 128.08, 128.32, 128.71, 129.05, 130.19, 134.55, 134.82, 137.51, 140.05, 202.26.

1,2-Dihydro-1-(2-propynyl)-1-hydroxy-2-oxacenaphthene [49] and 1,2-Dihydro-1-(prop-1,2-dienyl)-1-hydroxy-2-oxacenaphthene [50]

A solution of acenaphthenequinone (0.182 g, 1 mmol), propargyl bromide (0.179 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL dimethyl formamide was stirred at 25 °C until completion (5 min) of the reaction (TLC). The usual work-up followed by purification of the product by silica gel column using 10% ethyl acetate in hexane as eluent afforded a mixture of alkyne

(**49**) and allene (**50**) in the ratio 5:2 (0.200 g, 90%) as pale yellow solid.

Spectral data for 49 and 50

IR (neat) ν_{max} : 3430, 3374, 3293, 2120, 1944, 1707, 1601, 1495, 1345, 1270, 1164, 1058, 1020, 870, 777, 639 cm^{-1}.

^1H NMR : δ 1.93 (s, 1H), 2.74 (dd, J = 16.6 Hz, 2.4 Hz, 1H), 2.96 (dd, J = 16.6 Hz, 2.4 Hz, 1H), 3.18 (s, 1H), 7.67-8.16 (m, 6H).

3.18 (s, 1H), 4.86-4.98 (m, 2H), 5.50-5.55 (m, 1H), 7.67-8.16 (m, 6H).

^{13}C NMR : δ 28.42, 71.73, 77.31, 77.60, 78.07, 79.91, 93.13, 120.82, 121.25, 122.31, 122.50, 125.42, 125.68, 128.26, 128.70, 130.28, 130.53, 131.97, 132.08, 132.35, 138.43, 141.50, 203.11, 212.00.

9,10-Dihydro-9-hydroxy-9-(2-propynyl)-10-oxophenanthrene [51] and 9,10-Dihydro-9-hydroxy-9-(prop-1,2-dienyl)-10-oxophenanthrene [52]

A solution of phenanthrenequinone (0.208 g, 1 mmol), propargyl bromide (0.179 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL dimethyl formamide was stirred at 25 °C until completion (3 min) of the reaction (TLC). The usual work up followed by purification of the product by silica gel column using 10% ethyl acetate in hexane as eluent afforded alkyne **51**

(0.213 g, 86%) as a pale yellow solid; recrystallized from dichloromethane/hexane solvent system (mp: 130-133 °C) and allene **52** (0.032 g, 13%) as a pale yellow solid; recrystallized from dichloromethane/hexane solvent system (mp: 122-125 °C).

Spectral data for 51

IR (KBr) ν_{max} : 3480, 3293, 3068, 2918, 2123, 1695, 1601, 1451, 1283, 1189, 1102, 1026, 933, 783, 764, 747, 626 cm^{-1}.

^1H NMR : δ 2.03 (s, 1H), 2.56 (dd, J = 16.7 Hz, 2.3 Hz, 1H), 2.68 (dd, J = 16.7 Hz, 2.4 Hz, 1H), 4.35 (s, 1H), 7.39-7.42 (m, 3H), 7.68-7.97 (m, 5H).

^{13}C NMR : δ 35.29, 72.69, 79.31, 97.40, 123.06, 127.53, 128.45, 128.55, 129.21, 135.04, 138.86, 200.80.

Spectral data for 52

IR (KBr) ν_{max} : 3474, 3068, 1950, 1695, 1595, 1451, 1283, 1195, 1002, 846, 758, 733 cm^{-1}.

^1H NMR : δ 4.27 (s, 1H), 4.58-4.72 (m, 2H), 5.22-5.26 (m, 1H), 7.38-7.44 (m, 3H), 7.67-7.96 (m, 5H).

^{13}C NMR : δ 79.35, 97.42, 104.71, 123.07, 123.75, 126.40, 127.75, 128.27, 128.35, 129.13, 129.30, 134.92, 137.57, 138.88, 199.91, 206.95.

1,2-Diphenyl-2-hydroxy-4-pentyn-1-one [53] and 1,2-Diphenyl-2-hydroxy-3,4-pentadien-1-one [54]

A mixture of benzil (0.210 g, 1.0 mmol), propargyl bromide (0.179 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL dimethyl formamide was stirred at 25 °C until completion of the reaction (10 min). The usual work up followed by purification of the product by silica gel column using 3% ethyl acetate in hexane as eluent afforded alkyne and allene in the ratio 1:1 in 75% (0.188 g) total yield as a pale yellow solid.

Spectral data for 53 and 54

IR (neat) ν_{max} : 3453, 3299, 3065, 2922, 2128, 1958, 1678, 1593, 1490, 1444, 1353, 1239, 1119, 1068, 862, 760, 697 cm^{-1}.

^1H NMR : δ 2.01 (s, 1H), 2.89 (dd, J = 16.5 Hz, 2.4 Hz, 1H), 3.26 (dd, J = 16.5 Hz, 2.3 Hz, 1H), 4.20 (s, 1H), 4.79-4.96 (m, 3H), 5.94 (t, J = 6.6 Hz, 1H), 7.23-7.77 (m, 20H).

^{13}C NMR : δ 31.44, 72.53, 79.32, 79.88, 80.24, 81.39, 95.27, 125.18, 126.72, 128.08, 128.16, 128.28, 128.39, 128.88, 129.00, 129.92, 130.36, 130.70, 132.74, 133.07, 133.51, 134.38, 134.76, 140.46, 141.67, 198.58, 199.01, 207.76.

3-Hydroxy-3-(2-propynyl)-2-indolone [55] and 3-Hydroxy-3-(prop-1,2-dienyl)-2-indolone [56]

A mixture of isatin (0.147 g, 1 mmol), propargyl bromide (0.178 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL DMF was ultrasonicated for 25 min. The usual work up followed by purification of the product by chromatography on silica gel column using 30% ethyl acetate in hexane as eluent afforded alkyne **55** and allene **56** in the ratio 4:1 in 85% (0.159 g) total yield as pale yellow semi-solid.

Spectral data for 55 and 56

IR (neat) ν_{max} : 3338, 3301, 3195, 2815, 1956, 1695, 1620, 1471, 1359, 1185, 1110, 749, 643 cm^{-1}.

^1H NMR (DMSO-d_6) : δ 1.99 (s, 1H), 2.56 (dd, J = 16.1 Hz, 1.8 Hz, 1H), 2.78 (dd, J = 16.1 Hz, 1.7 Hz, 1H), 3.10 (s, 2H), 4.73-4.82 (m, 2H), 5.47-5.51 (m, 1H), 6.00 (s, 2H), 6.82-7.44 (m, 8H).

^{13}C NMR (DMSO-d_6) : δ 27.09, 69.91, 73.50, 77.74, 92.23, 94.98, 108.83, 120.69, 120.79, 123.20, 123.93, 128.00, 128.21, 129.79, 140.97, 177.50, 206.67.

1,2-Dihydro-1-(phenylcarboxymethyl)-1-hydroxy-2-oxacenaphthene [57]

A mixture of acenaphthenequinone (0.182 g, 1.0 mmol), phenacyl bromide (0.308 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL DMF was ultrasonicated for

5 min. The usual work up followed by purification of the product on silica gel column using 10% ethyl acetate in hexane as eluent afforded **57** (0.281 g, 93%) as a pale yellow semi-solid.

Spectral data for 57

IR (KBr) ν_{max} : 3420, 3060, 2928, 1735, 1688, 1600, 1357, 1222, 1054, 1027, 791 cm^{-1}.

^1H NMR : δ 3.55 (d, J = 17.4 Hz, 1H), 3.90 (d, J = 17.4 Hz, 1H), 4.61 (s, 1H), 7.25-8.14 (m, 11H).

^{13}C NMR : δ 44.32, 78.14, 120.80, 122.50, 125.66, 128.27, 128.40, 128.70, 130.84, 130.91, 131.90, 133.79, 136.43, 139.83, 141.45, 198.84, 202.18.

9,10-Dihydro-9-hydroxy-9-(phenylcarboxymethyl)-10-oxophenanthrene [58]

A mixture of phenanthrenequinone (0.208 g, 1.0 mmol), phenacyl bromide (0.308 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL DMF was ultrasonicated for 10 min. The usual work up followed by purification of the product on silica gel column using 10% ethyl acetate in hexane as eluent afforded **58** (0.311 g, 95%) as a colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 73-75 °C).

Spectral data for 58

IR (KBr) ν_{max} : 3474, 3070, 2935, 1704, 1676, 1600, 1465, 1297, 1209, 1013, 764, 697, 589 cm^{-1}.

^1H NMR : δ 3.17 (d, J = 14.8 Hz, 1H), 3.61 (d, J = 14.8 Hz, 1H), 4.48 (s, 1H), 7.24-7.91 (m, 13H).

^{13}C NMR : δ 51.26, 78.54, 123.02, 124.40, 126.27, 128.01, 128.51, 128.71, 128.78, 129.36, 129.57, 129.60, 133.31, 134.60, 136.77, 137.20, 140.12, 196.49, 202.15.

1,2-Dihydro-1-(methoxycarbonylmethyl)-1-hydroxy-2-oxacenaphthene [59]

A mixture of acenaphthenequinone (0.182 g, 1.0 mmol), ethyl bromoacetate (0.259 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.05 mmol) in 3 mL DMF was ultrasonicated for 6 min. The usual work up followed by purification of the product on silica gel column using 10% ethyl acetate in hexane as eluent afforded **59** (0.162 g, 60%) as a colorless solid; recrystallized from dichloromethane /hexane solvent system (mp: 169-171 °C).

Spectral data for 59

IR (KBr) ν_{max} : 3440, 3056, 2982, 2928, 1737, 1714, 1607, 1202, 1027, 791 cm^{-1}.

^{1}H NMR : δ 1.03 (t, J = 7.0 Hz, 3H), 3.02 (s, 2H), 4.02 (q, J = 7.0 Hz, 2H), 4.51 (s, 1H), 7.62-8.12 (m, 6H).

^{13}C NMR : δ 13.88, 41.20, 61.05, 76.66, 120.63, 122.45, 125.79, 128.41, 128.76, 131.94, 138.98, 141.48, 170.67, 202.56.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.80; H, 5.00.

9,10-Dihydro-9-hydroxy-9-(3-ethoxycarbonylmethyl)-10-oxophenanthrene [60]

A mixture of phenanthrenequinone (0.208 g, 1.0 mmol), ethyl bromoacetate (0.259 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL DMF was ultrasonicated for 15 min. The usual work up followed by purification of the product on silica gel column chromatography using 10% ethyl acetate in hexane as eluent afforded **60** (0.178 g, 60%) as a colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 175-178 °C).

Spectral data for 60

IR (KBr) ν_{max} : 3467, 3070, 2982, 1735, 1701, 1607, 1458, 1372, 1297, 1202, 1135, 1108, 1040, 946, 771 cm^{-1}.

^{1}H NMR : δ 1.16 (t, J = 7.1 Hz, 3H), 2.73-2.84 (m, 2H), 3.98-4.08 (m, 3H), 7.38-7.93 (m, 8H).

^{13}C NMR : δ 14.22, 48.92, 60.97, 77.78, 123.21, 124.34, 126.33, 127.87, 128.80, 129.11, 129.52, 134.93, 137.08, 139.58, 168.75, 201. 97.

Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.96; H, 5.44. Found: C, 73.02; H, 5.48.

1,2-Dihydro-1-(1-ethoxycarbonyl-2-propenyl)-1-hydroxy-2-oxacenaphthene [61]

A mixture of acenaphthenequinone (0.182 g, 1.0 mmol), ethyl-4-bromocrotonate (0.299 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL DMF was sonicated for 12 min. The usual work up followed by purification of the product on silica gel column chromatography using 10% ethyl acetate in hexane as eluent afforded **61** (0.257 g, 87%) as a pale yellow semi-solid. The product was found to be a mixture of *syn* and *anti* isomers in the ratio 1:3 as determined by the ^{1}H NMR.

Spectral data for 61

IR (neat) ν_{max} : 3443, 3055, 2980, 2899, 1732, 1713, 1632, 1489, 1432, 1370, 1314, 1251, 1183, 1014, 933, 833, 777, 671 cm^{-1}.

^{1}H NMR : δ 0.81 (t, J = 7.0 Hz, 3H), 3.64 (d, J = 9.5 Hz, 1H), 4.03-4.10 (m, 2H), 4.58 (s, 1H), 5.10-5.23 (m, 2H), 5.97-6.03 (m, 1H), 7.58-8.05 (m, 6H).

1.07 (t, J = 7.0 Hz, 3H), 3.80-3.84 (m, 3H), 4.63 (s, 1H), 5.10-5.23 (m, 2H), 5.76-5.82 (m, 1H), 7.58-8.05 (m, 6H).

^{13}C NMR : δ 13.42, 13.78, 56.12, 56.64, 60.99, 61.14, 79.19. 79.39, 121.06, 121.49, 121.74, 121.86, 122.24, 125.51, 125.62, 128.04, 128.22, 128.44, 129.82, 130.15, 130.42, 130.75, 131.12, 131.65, 131.74, 132.42, 136.94, 137.81, 141.70, 170.62, 171.34, 202.57.

9,10-Dihydro-9-hydroxy-9-(3-ethoxycarbonyl-2-propenyl)-10-oxophenanthrene [62]

A mixture of phenanthrenequinone (0.208 g, 1.0 mmol), ethyl-4-bromocrotonate (0.299 g, 1.55 mmol), indium powder (0.120 g, 1.05 mmol) and sodium iodide (0.232 g, 1.55 mmol) in 3 mL DMF was sonicated for 10 min. The usual work-up followed by purification of the product by silica gel column chromatography using 5% ethyl acetate in hexane as eluent afforded **62** (0.229 g, 68%) as pale yellow semi-solid.

Spectral data for 62

IR (neat) ν_{max} : 3475, 3071, 2983, 1722, 1695, 1595, 1452, 1365, 1272, 1197, 1041, 761, 730 cm^{-1}.

^{1}H NMR : δ 1.19 (t, J = 7.0 Hz, 3H), 2.49-2.67 (m, 2H), 4.09-4.16 (m, 3H), 5.54 (d, J = 15.6 Hz, 1H), 6.69-6.74 (m, 1H), 7.36-8.12 (m, 8H).

^{13}C NMR : δ 14.16, 46.88, 60.13, 78.99, 123.17, 125.23, 126.27, 127.40, 128.40, 128.51, 129.23, 130.32, 135.19, 135.75, 137.39, 139.37, 141.15, 165.46, 179.94, 202.14.

2.7 REFERENCES

1. (a) Davis, F. A.; Vishwakarma, L. C.; Billmers, J. M.; Finn, J. *J. Org. Chem.* **1984**, *49*, 3241. (b) Kido, F.; Kitahara, H.; Yoshikoshi, A. *J. Org. Chem.* **1986**, *51*, 1478.
2. Krepski, L. R.; Heilmann, S. T.; Rasmussen, J. K. *Tetrahedron Lett.* **1983**, *24*, 4075.
3. Adamczyk, M.; Dolence, E. K.; Watt, D. S.; Christy, M. R.; Reibenspies, J. H.; Anderson, O. P. *J. Org. Chem.* **1984**, *49*, 1378.
4. (a) Gardner, J. N.; Carbon, F. E.; Gnoj, O. *J. Org. Chem.* **1968**, *33*, 3294. (b) Wasserman, H. H.; Lipshutz, B. H. *Tetrahedron Lett.* **1975**, *16*, 1731.
5. (a) Vedejs, E. *J. Am. Chem. Soc.* **1974**, *96*, 5944. (b) Vedejs, E.; Engler, D. A.; Telshow, J. E. *J. Org. Chem.* **1978**, *43*, 188.
6. Yamamoto, Y.; Maeda, N.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1983**, 774.
7. Yamamoto, Y.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Org. Chem.* **1986**, *51*, 886.
8. Naruta, Y. *J. Am. Chem. Soc.* **1980**, *102*, 3774.
9. Takuwa, A.; Naruta, Y.; Soga, O.; Maruyama, K. *J. Org. Chem.* **1984**, *49*, 1857.
10. Banno, K.; Mukaiyama, T. *Chem. Lett.* **1975**, 741.
11. Banno, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2284.
12. Bost, H. W.; Bailey, P. S. *J. Org. Chem.* **1956**, *21*, 803.
13. Newman, M. S.; Kahle, G. R. *J. Org. Chem.* **1958**, *23*, 666.

14. Palomo, C.; Aizpurua, J. M.; Lopez, M. C.; Aurrekoetxea, N.; Oiarbide, M. *Tetrahedron Lett.* **1990**, *31*, 6425.

15. Jayaraman, M.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1997**, *38*, 709.

16. Paquette, L. A.; Isaac, M. B. *Heterocycles* **1998**, *47*, 107.

17. Paquette, L. A.; Rothhaar, R. R.; Isaac, M. B.; Rogers, L. M.; Rogers, R. D. *J. Org. Chem.* **1998**, *63*, 5463.

18. Cere, V.; Pery, F.; Pollicino, S.; Ricci, A. *Synlett* **1999**, 1585.

19. Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

20. Araki, S.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1991**, *415*, 7.

CHAPTER 3

NOVEL CYCLOADDITION REACTIONS OF HETEROCYCLIC QUINONE METHIDES

3.1 INTRODUCTION

Cycloaddition reactions[1] have emerged as the most powerful C-C bond forming processes in organic synthesis during the past few decades. The well-known Diels-Alder reaction involves the combination of a 4π component and a 2π component to afford a six membered ring product.

In the terminology of orbital symmetry classification, Diels-Alder reaction is a $[4\pi + 2\pi]$ cycloaddition, an allowed process. The transition

state for a concerted reaction requires that the diene adopt the *cis* conformation. The diene and dienophile should approach each other in approximately parallel planes. Most Diels-Alder reactions involve an electron rich diene and an electron deficient dienophile. But there is another group of cycloaddition which involves the reaction between an electron deficient diene and an electron rich dienophile. These reactions, inverse electron demand Diels-Alder reactions as they are known, have recently found substantial use in organic synthesis.

The mechanism of Diels-Alder reactions can be clearly explained by Woodward-Hoffman rules.[2] These orbital symmetry rules apply only to concerted reactions and are based on the principle that reaction takes place in such a way as to maintain maximum bonding throughout the course of the reaction.

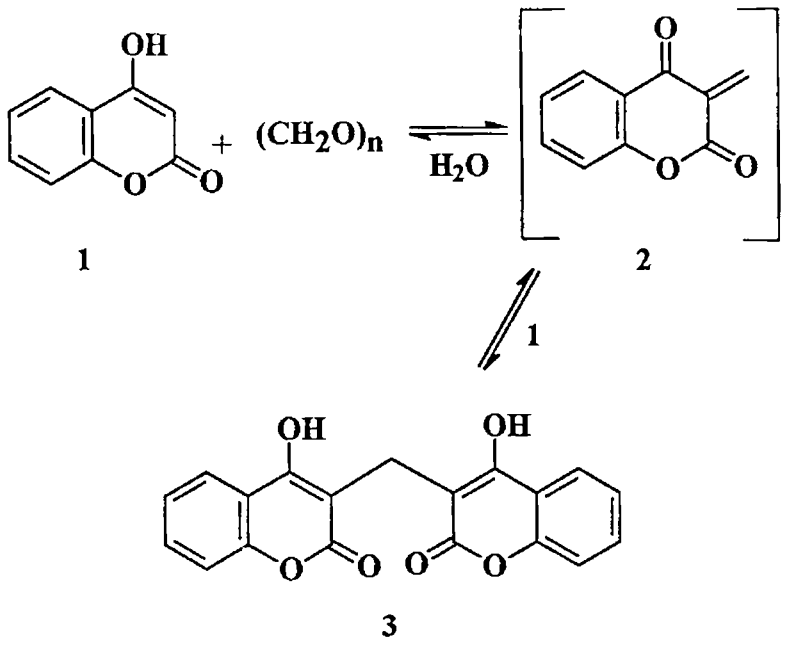
In a normal Diels-Alder reaction, the highest occupied molecular orbital (HOMO) of the electron rich diene interacts with the lowest unoccupied molecular orbital (LUMO) of the dienophile[3] whereas LUMO of the diene interacts with HOMO of the dienophile in the case of inverse electron demand Diels-Alder reaction. Electron donating substituents on the double bond of the dienophile, in an inverse electron demand Diels-Alder reaction, facilitate the reaction by increasing the energy of the HOMO and thus decreasing the energy separation between the LUMO of diene and HOMO of dienophile. Electron withdrawing substituents on the diene accelerate the reaction by decreasing the energy level of the LUMO.

3.2 CYCLOADDITION REACTIONS OF HETEROCYCLIC *o*-QUINONE METHIDES

α-Methylene ketones derived from heterocyclic compounds are termed heterocyclic quinone methides. The cycloaddition reactions of the latter have received only limited attention. There are a few reports on the Diels-Alder trapping of coumarin quinone methide and quinolone quinone methide. However, pyrone quinone methide has not received practically any attention.

3.2.1 CYCLOADDITION REACTIONS OF COUMARIN QUINONE METHIDE

One of the widely studied heterocyclic *o*-quinone methides is the 3-methylene-2,4-chromandione, **2**. This quinone methide[4] can be generated *in situ* from dicoumarol **3** or its monomer **1**, accessible *via* the reaction of **1** and paraformaldehyde (Scheme 1).



Scheme 1

The structural features of coumarin quinone methide predispose it to exhibit multiple cycloaddition profile; it can participate as ambident heterodienes and dienophile as highlighted in Figure 1.

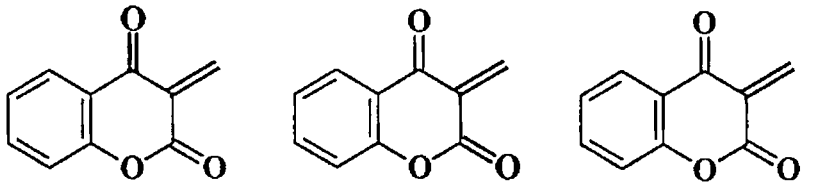
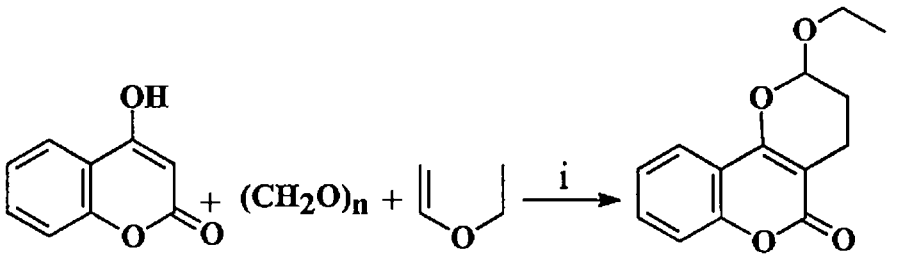


Figure 1

3.2.1a COUMARIN QUINONE METHIDE AS HETERO DIENE

The Diels-Alder reaction of quinone methide **2**, generated from **1**, with ethylvinylether has been reported to afford pyrano coumarin derivative **5** (Scheme 2).[4]

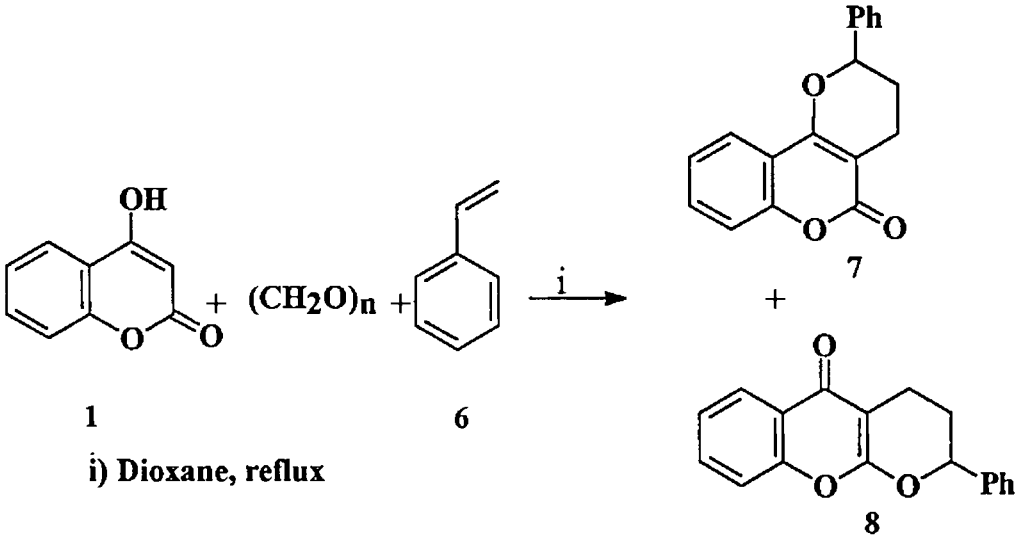


1 **4** **5**

i) Dioxane, reflux

Scheme 2

The reaction of 4-hydroxy coumarin **1** with paraformaldehyde and styrene afforded both angular and linear adducts (Scheme 3).[4]



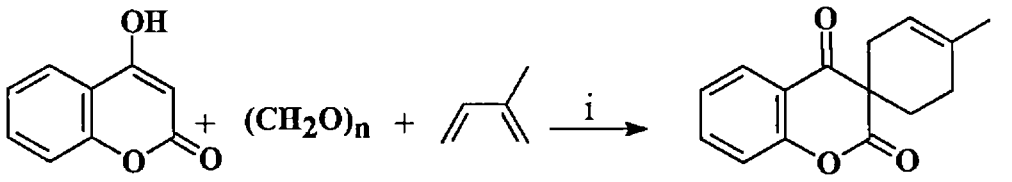
1 **6** **7** + **8**

i) Dioxane, reflux

Scheme 3

3.2.1b COUMARIN QUINONE METHIDE AS DIENOPHILE

In the Diels-Alder reaction of isoprene and quinone methide **2**, the latter acts as a dienophile to afford spiro compound **10** (Scheme 4).[4]

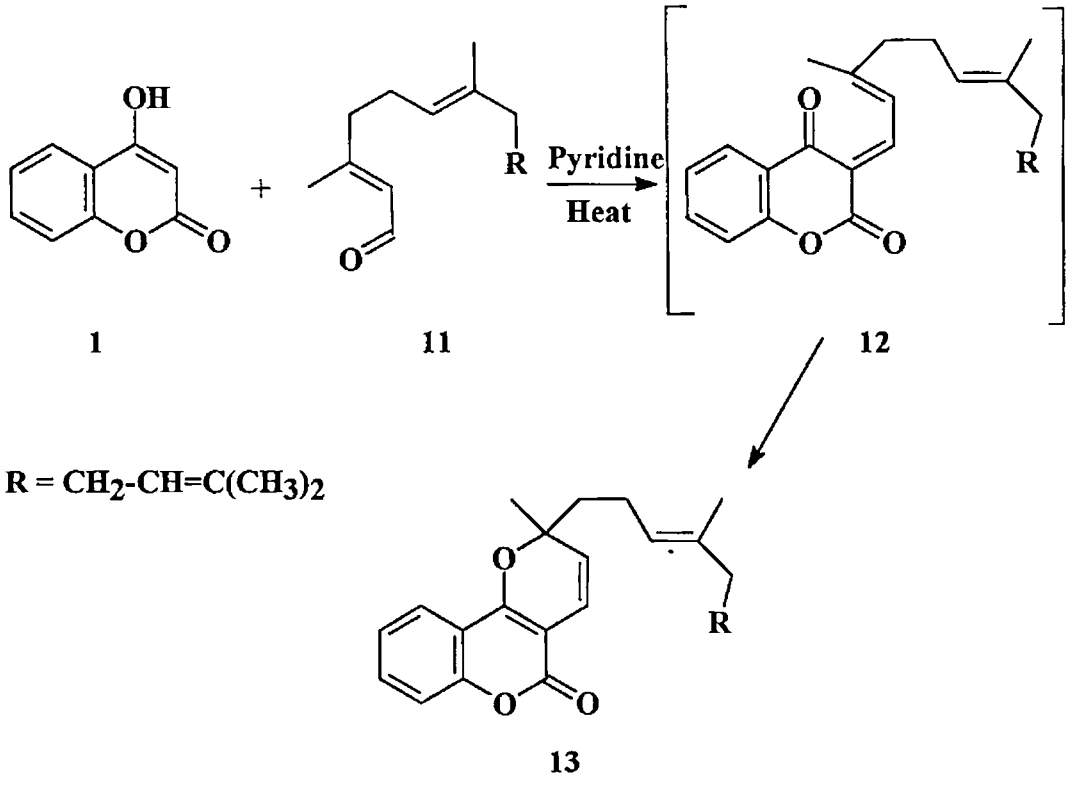


1 **9** **10**

i) Dioxane, reflux

Scheme 4

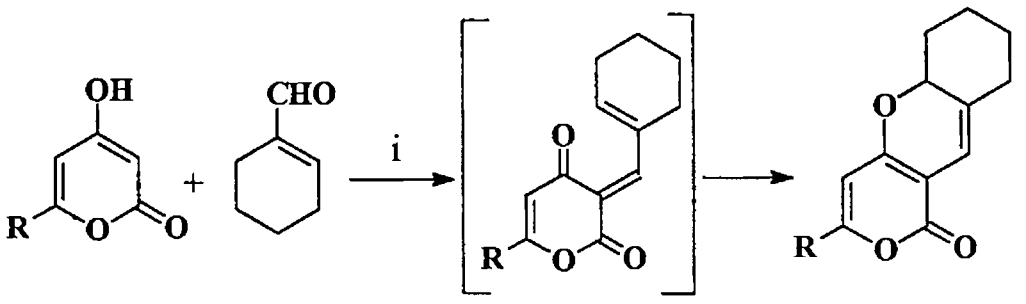
4-Hydroxy coumarin reacts with enals bearing alkyl groups at C(*β*), to afford pyranocoumarin as the only product. Thus the haemorrhagic 2H-pyrano[3,2-c]coumarin ferprenin **13** could be synthesized by a tandem Knoevenagel/hetero-Diels-Alder reaction sequence (Scheme 5).[5]



Scheme 5

3.2.2 CYCLOADDITION REACTIONS OF PYRONE QUINONE METHIDE

Condensation of various 6-substituted-4-hydroxy pyrones **14** with cyclohexene carboxaldehyde **15** in the presence of L-proline in ethyl acetate resulted in high yields of tricyclic pyrone derivatives **17** (Scheme 6).[6]



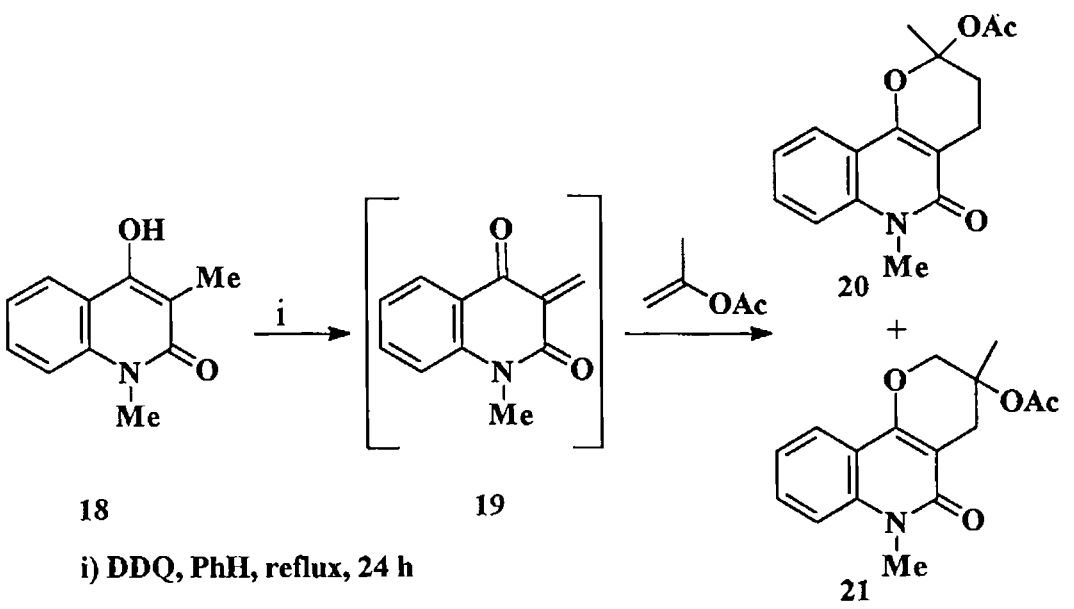
14 **15** **16** **17**

i) L-proline, EtOAc **R = Ph, Py, Me**

Scheme 6

3.2.3 CYCLOADDITION REACTIONS OF QUINOLONE QUINONE METHIDE

The reactivity of the aza analog such as quinolone quinone methide **19**, has received only scant attention.[7] It is reported that **19** can be generated by the DDQ oxidation of 4-hydroxyl-1,3-dimethyl-2(1H)-quinolone **18**; trapping of the heterodiene with isopropenyl acetate led to pyrano quinolone derivatives (Scheme 7).[8]



18 19

i) DDQ, PhH, reflux, 24 h

Scheme 7

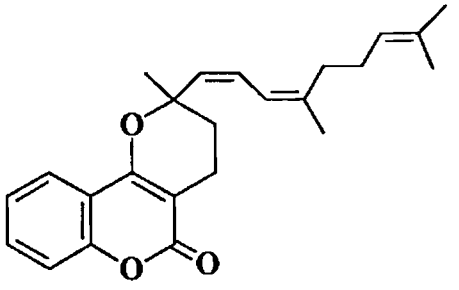
The oxidative procedure for the generation of quinolone quinone methide is not of much synthetic value due to the side reactions and low yields of products.

Recently, the synthesis of pyranoquinolinones has been reported by making use of quinolone quinone methide intermediate generated from the Knoevenagel condensation of 4-hydroxy quinolinone with aliphatic aldehydes. The quinone methide then undergoes cycloaddition with the *in situ* formed enamine leading to the pyran ring compound.[7]

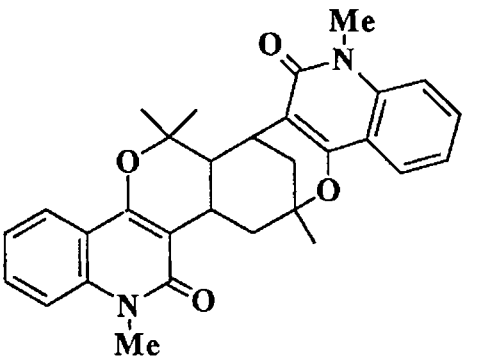
3.3 IMPORTANCE OF POLYCYCLIC PYRAN DERIVATIVES

Coumarin quinone methide, pyrone quinone methide and quinolone quinone methide on cycloaddition with dienophiles afford polycyclic pyran derivatives. It is noteworthy that such structural motifs

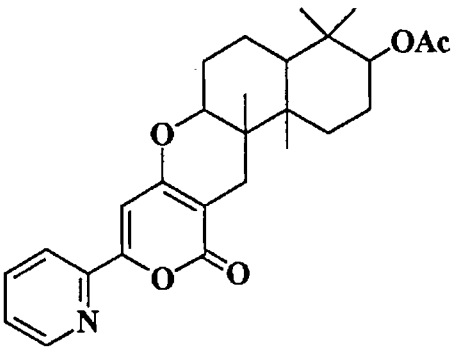
are present in a number of biologically active natural products (Figure 2). Several of the tricyclic pyrones known in literature are powerful inhibitors of acetyl cholinesterase and DNA synthase *in vitro.*



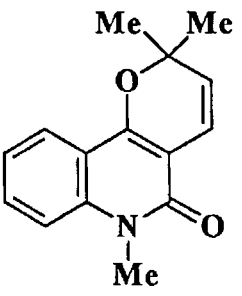
Coumarin isoferprenin



Paraensidimerin



Pyripyropene E4



N-methylflindersine

Figure 2

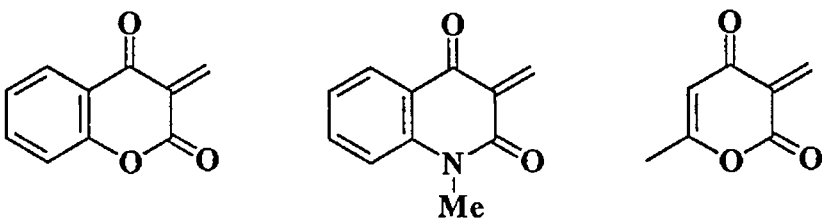
3.4 DEFINITION OF THE PROBLEM

Against the literature background given above and in view of the current interest in hetero Diels-Alder reactions, an investigation was undertaken to explore the reactivity of heterocyclic quinone methides with a variety of fulvenes. The latter is an important class of compounds[9] and their role in organic synthesis has been the subject of extensive

investigation.[10,11] The cycloaddition of quinone methides with tetracyclone was also of interest. The results of these investigations along with a theoretical rationalization using AM1 calculations in PC SPARTAN program are discussed in this chapter.

3.5 RESULTS AND DISCUSSION

The heterocyclic *o*-quinone methides selected for our study are listed below (Figure 3). These were generated *in situ* from the appropriate precursors.



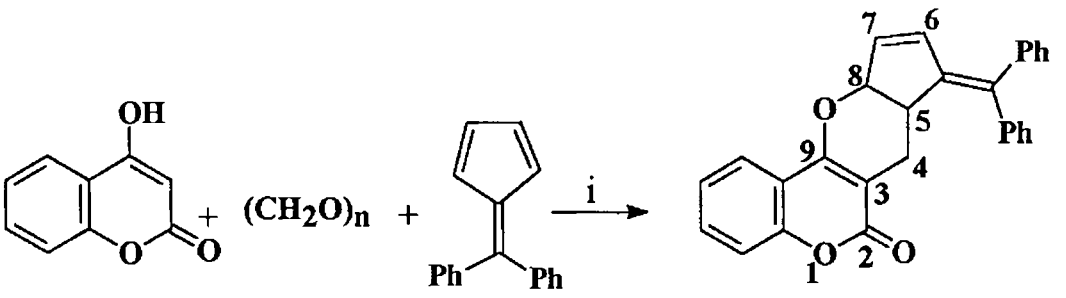
2 **19** **22**

Figure 3

All the fulvenes utilized in our investigations were prepared using the literature procedure involving the condensation of cyclopentadiene with the appropriate carbonyl compound.[9]

3.5.1 CYCLOADDITION REACTIONS OF COUMARIN QUINONE METHIDE

Our investigations were initiated with 4-hydroxy coumarin which on treatment with paraformaldehyde in presence of 6,6-diphenyl fulvene in refluxing dioxane afforded a colorless crystalline product **24** in 85% yield (Scheme 8).



1 **23** **24**

i) Dioxane, reflux, 5 h, 85%

Scheme 8

The structure of the product was established by spectral analysis. The IR spectrum of the product **24** showed a strong peak at 1701 cm^{-1}. This value is typical for coumarin carbonyl group, thus indicating that the product is an angular adduct. In the ^1H NMR spectrum, one of the methylene (C-4) protons of pyran ring appeared as a double doublet (J = 16.5 Hz, 8.1 Hz) at δ 2.18 due to the geminal and vicinal couplings respectively. The other proton appeared as a double doublet (J = 16.5 Hz, 8.4 Hz) at δ 2.64. This large difference in the δ value for these protons can be attributed to the influence of phenyl group of the fulvene moiety. This strongly supported the regiochemistry of the product. The proton at C-5 appeared as a multiplet centered at δ 3.36. The proton at C-8 appeared as a double triplet (J = 6.9 Hz, 2.4 Hz) at δ 5.57. The olefinic proton at C-6 appeared as a double doublet (J = 6.0 Hz, 3.0 Hz) at δ 6.17 and the proton at C-7 resonated as a double doublet (J = 5.1 Hz, 3.0 Hz) at δ 6.53. In the ^{13}C NMR spectrum, the carbonyl carbon resonated at δ 162.30. All other signals were in good agreement with the proposed

structure. Elemental analysis of the compound was also satisfactory. Finally, the structure was confirmed by single crystal X-ray analysis.

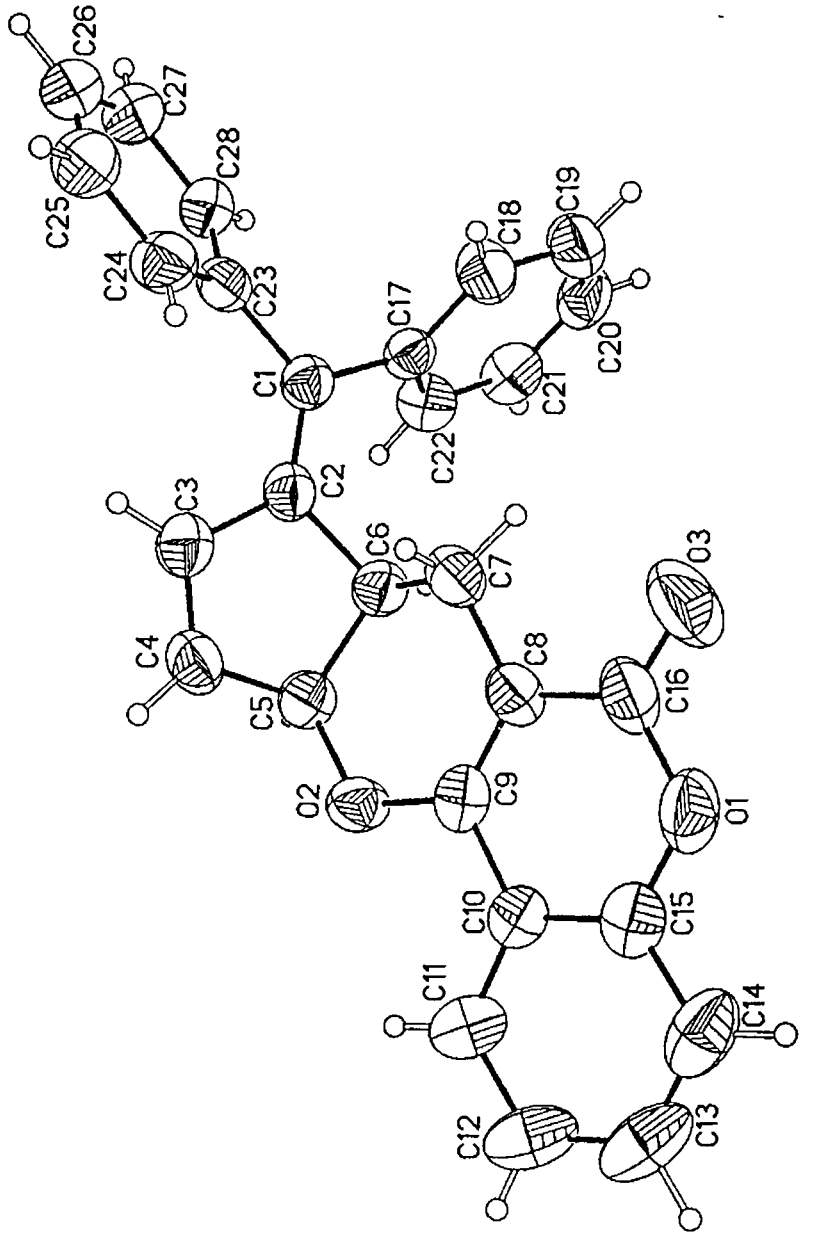
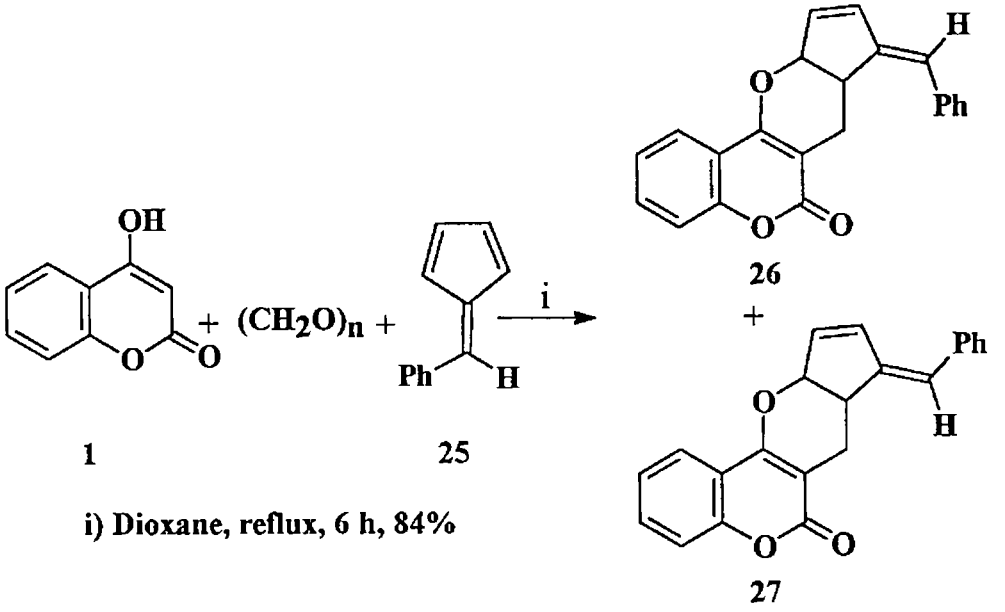


Figure 4. Single Crystal X-Ray Structure of 24

Similarly, the addition of quinone methide **2** to 6-phenyl fulvene **25** afforded a mixture of *Z* and *E* isomers **26** and **27** in the ratio 1:1 (Scheme 9). The isomers were separated by column chromatography.



Scheme 9

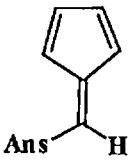
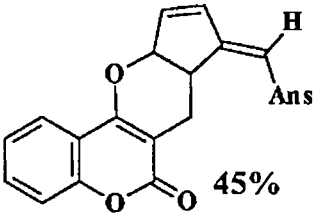
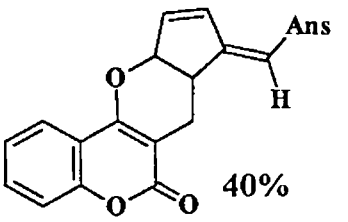
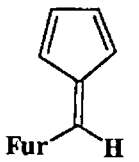
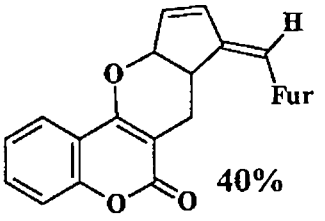
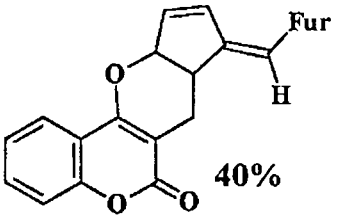
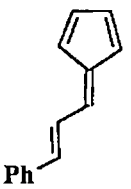
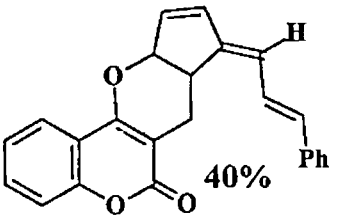
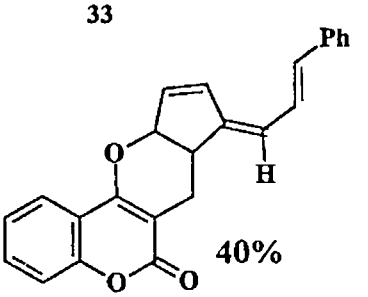
The IR spectrum of **26** showed lactone carbonyl at 1701 cm^{-1}. In the ^1H NMR spectrum, one of the methylene protons of pyran ring appeared as a double doublet (J = 16.5 Hz, 8.4 Hz) at δ 2.21 due to geminal and vicinal couplings respectively. The other proton on the same carbon resonated as a double doublet (J = 16.5 Hz, 7.4 Hz) at δ 3.11. The large difference in the δ values of the two protons on the same

carbon can be due to the orientation of the phenyl group. The proton at C-8 appeared as a doublet (J = 6.3 Hz) at δ 5.68. The ^{13}C NMR spectrum showed the characteristic signal due to the lactone carbonyl at δ 162.50. All other signals were also in agreement with the proposed structure.

The IR spectrum of **27** showed the characteristic lactone carbonyl absorption at 1701 cm^{-1}. The ^{1}H NMR spectrum exhibited signals at δ 2.77 (dd, J = 16.6 Hz, 5.1 Hz) and δ 2.97 (dd, J = 16.7 Hz, 7.4 Hz) due to the two protons of the methylene group. This small difference in the δ value indicated that the orientation of phenyl group is away from the pyran ring. The ^{13}C NMR spectrum showed the characteristic lactone carbonyl at δ 162.64. All other signals were in good agreement with the proposed structure.

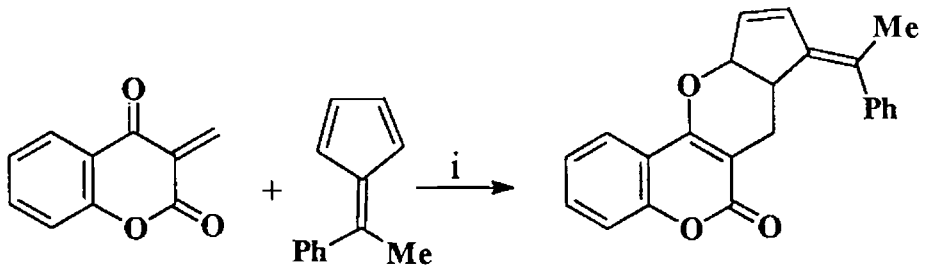
Similarly, the Diels-Alder reaction of other unsymmetrically substituted 6-aryl fulvenes with coumarin quinone methide afforded a separable mixture of *E* and *Z* isomers in good yields. The results are summarized in Table 1.

Table 1

Entry	Fulvene	Reaction conditions[a]	Product(s), Yield(s)
1	 28	5 h	 45% 29  40% 30
2	 31	4 h	 40% 32  40% 33
3	 34	4 h	 40% 35  40% 36

[a] Dioxane, reflux Ans = 4-methoxy phenyl, Fur = 2-furanyl

The reaction of 6-phenyl-6-methyl fulvene with the quinone methide **2** showed a notable difference. This reaction resulted in the formation of a single isomer (*Z*) in 75% yield (Scheme 10).



2 **37** **38**

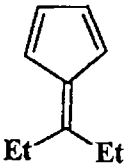
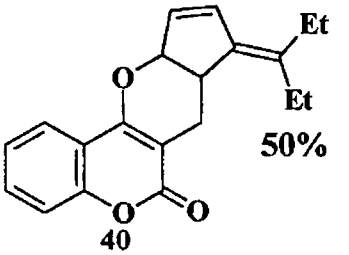
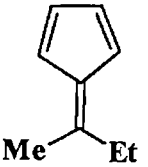
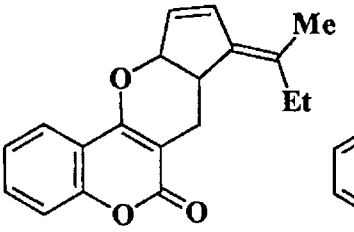
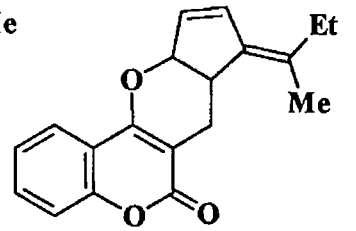
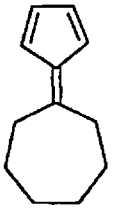
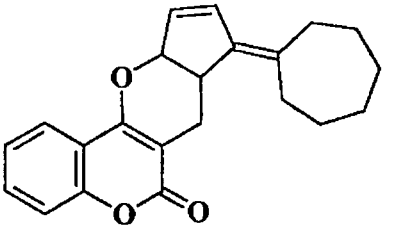
i) Dioxane, reflux, 7 h, 75%

Scheme 10

The structure of the product was assigned on the basis of spectral data. The IR spectrum exhibited a strong peak at 1701 cm^{-1}. In the ^{1}H NMR spectrum, one of the methylene protons of the pyran ring and the methyl group appeared together as a multiplet centered at δ 2.20 whereas the other proton of the methylene group resonated as a double doublet at δ 3.17 (J = 16.1 Hz, 7.3 Hz). In the ^{13}C NMR spectrum, the lactone carbonyl carbon resonated at δ 162.80. All other signals were in good agreement with the assigned structure.

Subsequent to the above investigations, we turned our attention to the reaction of **2** with 6,6-dialkyl and cycloalkyl fulvenes. These cycloaddition reactions afforded pyranocoumarin derivatives in moderate yields. The results are summarized in Table 2.

Table 2

Entry	Fulvene	Reaction conditions [a]	Product(s), Yield(s)
1	 39	4 h	 40 50%
2	 41	3 h	 42  43 70% (1:1)
3	 44	2.5 h	 45 50%

[a] Dioxane, reflux

3.5.2 THEORETICAL CONSIDERATIONS

In order to explain the reactivity and selectivity in the above reactions, we have carried out some AM1 calculations using PC SPARTAN Graphical Interface Package for Molecular Mechanics and Molecular Orbital Models.[12]

As a representative example, the correlation diagram for the reaction of **2** with 6,6-diethyl fulvene is illustrated in Figure 5.

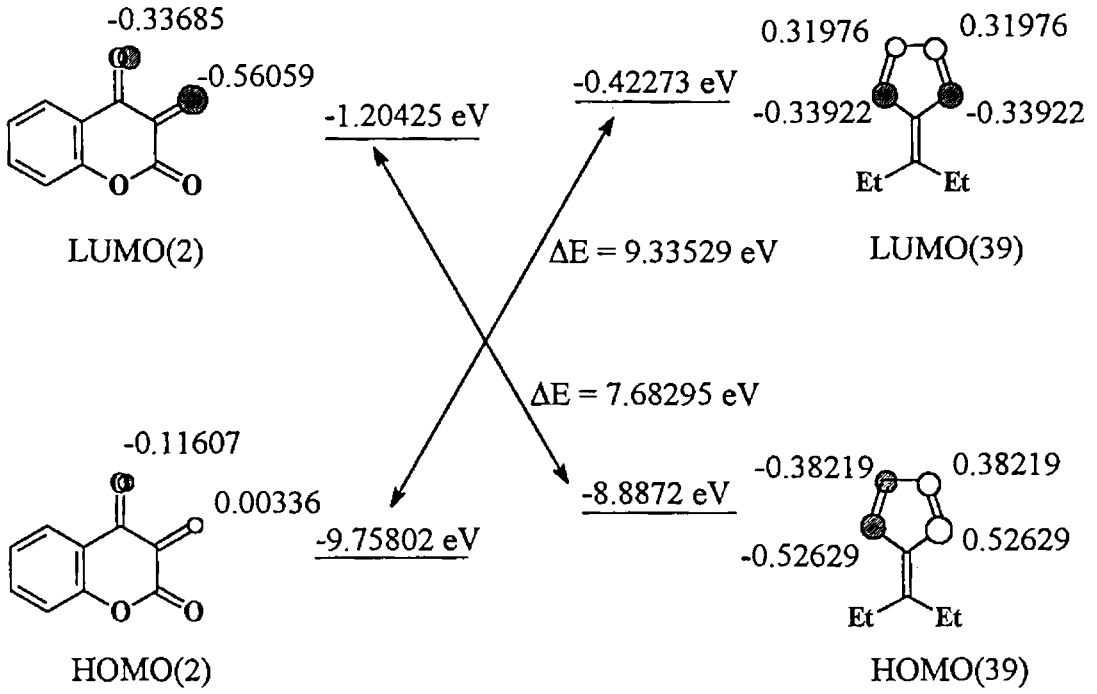


Figure 5

It is evident from the correlation diagram that the LUMO(2)-HOMO(39) interaction is allowed in terms of energetics and symmetry. The observed regiochemistry of the product can be clearly understood on the basis of matching of signs and sizes of the orbital coefficients.

It may be recalled that the Diels-Alder reaction of coumarin quinone methide **2** with 6-phenyl-6-methyl fulvene afforded only the *Z* isomer. This can also be clearly explained on the basis of matching of signs of the orbital coefficients (Figure 6).

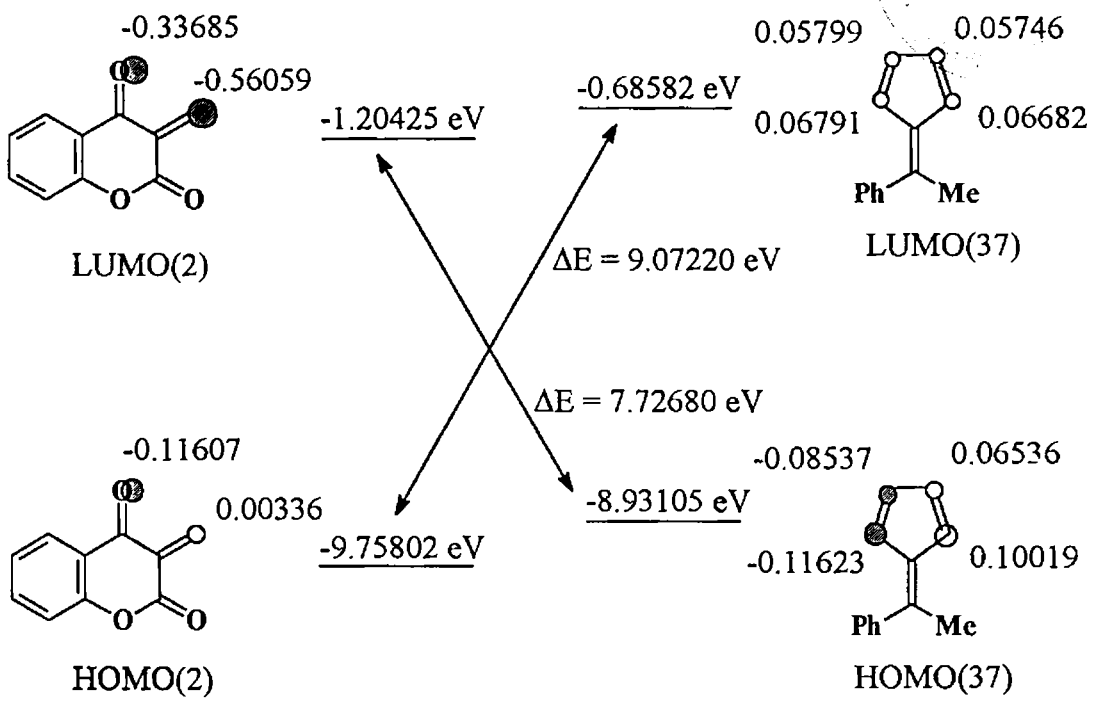
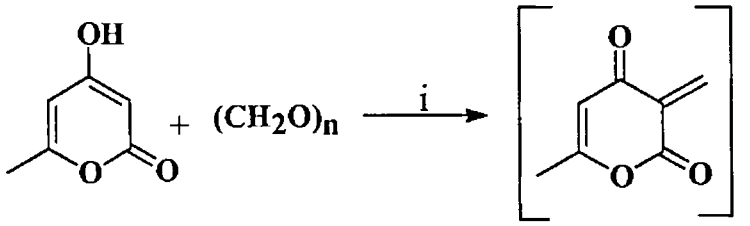


Figure 6

3.5.3 CYCLOADDITION REACTIONS OF PYRONE QUINONE METHIDE

Subsequent to the above studies, we briefly investigated the quinone methide from 4-hydroxy-6-methyl pyrone. The quinone methide **22** was generated *in situ* by refluxing **46** with paraformaldehyde (Scheme 11). The results obtained in the cycloaddition of **22** with fulvenes are discussed in this section.

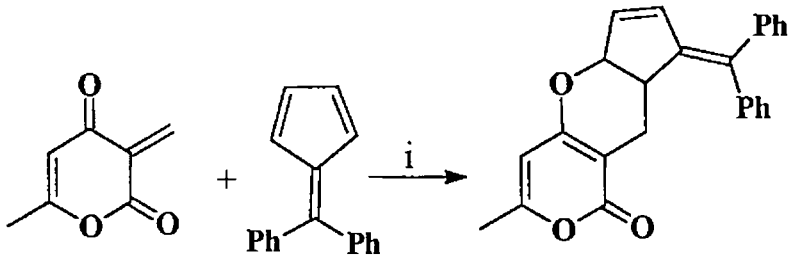


46 **22**

i) Dioxane, reflux

Scheme 11

The cycloaddition reaction of **22**, with 6,6-diphenyl fulvene afforded the product **47** in 65% yield (Scheme 12).



22 **23** **47**

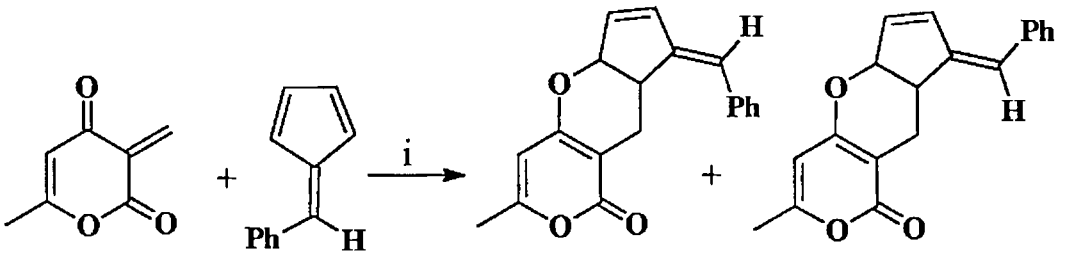
i) Dioxane, reflux, 4 h, 65%

Scheme 12

The IR spectrum of the product **47** exhibited a strong peak at 1701 cm^{-1} due to the lactone carbonyl. The ^1H NMR spectrum of **47** showed a multiplet centered at δ 2.11 (4H) accounting for the methyl protons and one of the protons of pyran methylene group. The other proton of pyran methylene group appeared as a double doublet

(J = 16.4 Hz, 7.5 Hz) at δ 2.53. The signal due to the olefinic proton of the pyrone ring resonated as a singlet at δ 5.73. The ^{13}C NMR spectrum showed a signal at δ 19.64 due to the methyl carbon. The carbonyl carbon exhibited a signal at δ 164.05. All other signals were in complete agreement with the assigned structure.

The reaction of quinone methide **22**, generated from **46**, with 6-phenyl fulvene afforded a mixture of separable geometrical isomers *Z* and *E* in the ratio 7:4 in total yield of 55% (Scheme 13).



22 **25** **48** **49**

i) Dioxane, reflux, 5 h, 55%

Scheme 13

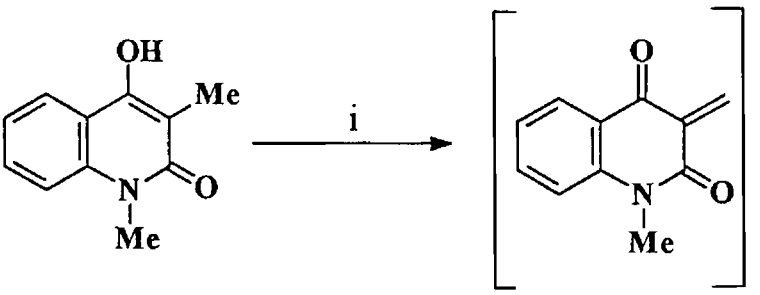
The IR spectrum of the product **48** showed strong absorption at 1707 cm^{-1} due to the lactone carbonyl moiety. In the ^1H NMR spectrum, a multiplet centered at δ 2.10 (4H) was due to the protons of methyl and one of the protons of the pyranoid methylene group. The other proton of the methylene group showed a signal as a double doublet (J = 16.3 Hz, 7.4 Hz) at δ 2.92. In the ^{13}C NMR spectrum, the methyl carbon

appeared at δ 19.70 and the lactone carbonyl appeared at δ 164.35. All other signals were in complete agreement with the assigned structure.

The product **49** showed a strong carbonyl peak at 1701 cm^{-1} in the IR spectrum. The methyl protons in ^{1}H NMR gave signals at δ 2.17. One of the methylene protons appeared as a double doublet (J = 16.5 Hz, 4.9 Hz) at δ 2.60 and the other one as a double doublet (J = 16.5 Hz, 7.3 Hz) at δ 2.81. The ^{13}C NMR spectrum showed characteristic signal of the lactone carbonyl carbon at δ 165.00. All other signals were in agreement with the assigned structure.

3.5.4 CYCLOADDITION REACTIONS OF QUINOLONE QUINONE METHIDE

The cycloaddition reactions of quinone methide, generated from quinolinone, with pentafulvenes appeared interesting from the standpoint of potential synthesis of novel pyranoquinolone compounds. Except for some isolated reports,[7,8] the chemistry of the quinolone quinone methide has not received much attention. 1,3-Dimethyl-quinolin-2,4-dione has been reported to undergo DDQ oxidation to generate the quinone methide (Scheme 14) and the latter has been trapped by alkene to afford pyranoquinolinone in low yield.[8]

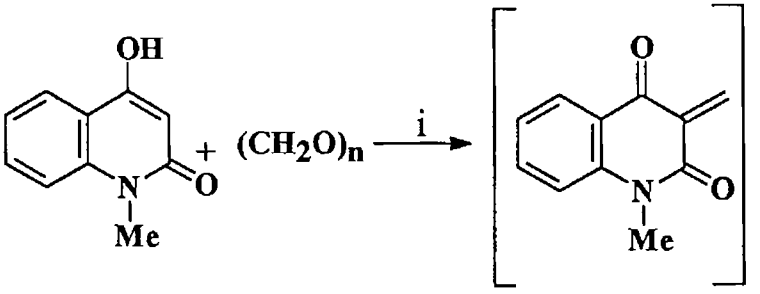


50 **19**

i) DDQ, PhH, reflux, 24 h

Scheme 14

We have found that refluxing the 4-hydroxy-1-methyl quinolinone **51**, with paraformaldehyde in dioxane is a convenient alternative for the generation of this quinone methide (Scheme 15).

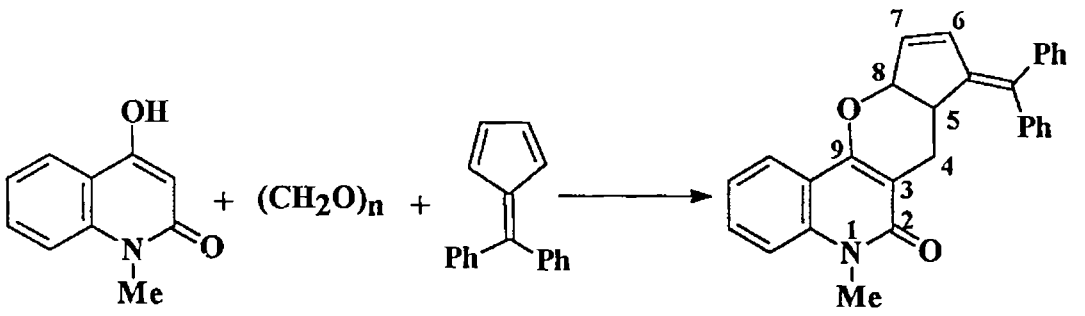


51 **19**

i) Dioxane, reflux

Scheme 15

In our initial experiment involving the quinone methide **19**, generated from **51**, and 6,6-diphenyl fulvene the product **52** was obtained in 98% yield (Scheme 16).



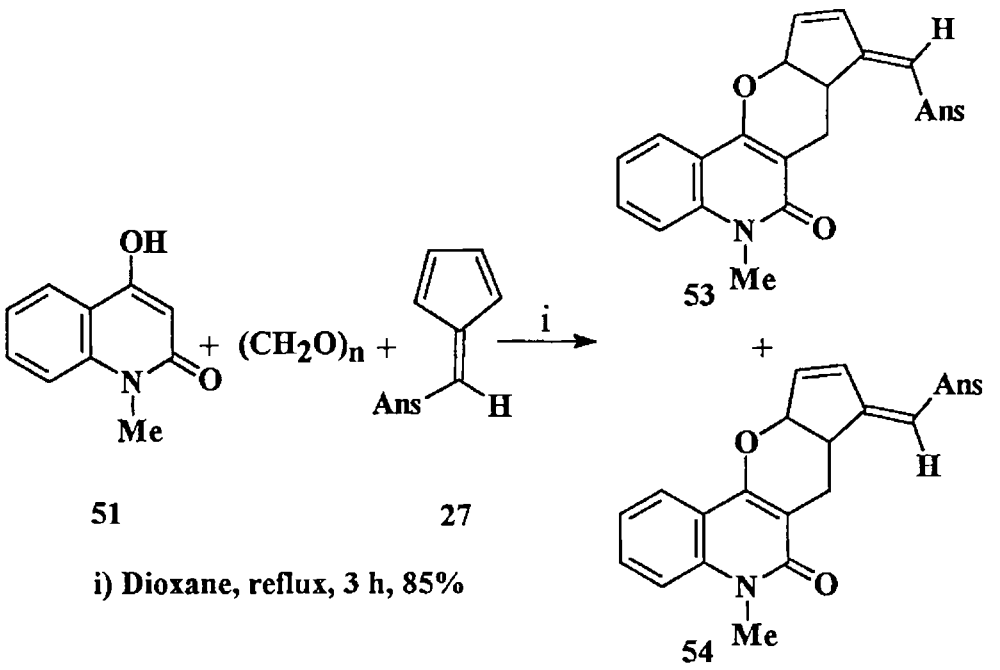
51 **23** **52**

i) Dioxane, reflux, 3.5 h, 98%

Scheme 16

The product **52** was characterized by spectroscopic methods. The IR spectrum showed a strong peak at 1642 cm^{-1} due to the lactam carbonyl group. In the ^1H NMR spectrum, a double doublet (J = 16.4 Hz, 8.1 Hz) appeared at δ 2.24 due to one of the C-4 protons. The other proton on the same carbon also appeared as a double doublet (J = 16.5 Hz, 7.6 Hz) at δ 2.80. The methyl protons resonated as a singlet at δ 3.64. The doublet (J = 6.6 Hz) at δ 5.53 was assigned to the proton at C-8. In the ^{13}C NMR spectrum, the methyl carbon appeared at δ 82.41. The C-4 resonated at δ 22.35. The signal at δ 162.29 was due to lactam carbonyl carbon. All other signals were in agreement with the above structure.

The cycloaddition of quinone methide **19** generated from **51** with 6-(4-methoxy phenyl) fulvene under the conditions described above, afforded two isomers *Z* and *E* in 45% and 40% yields, respectively (Scheme 17).



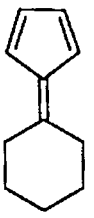
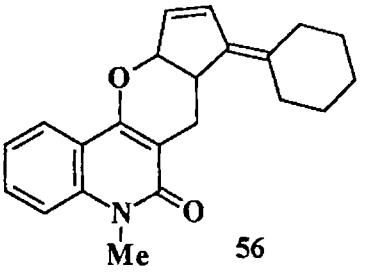
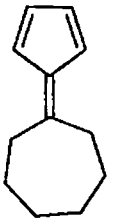
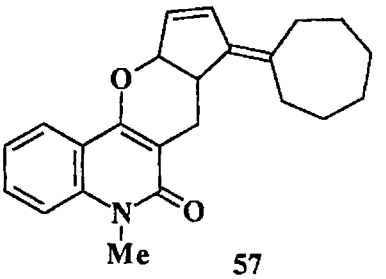
Scheme 17

The products were characterized by spectroscopic methods. The IR spectrum of the *Z* isomer (**53**) exhibited a strong peak at 1645 cm^{-1} due to the lactam carbonyl group. In the ^{1}H NMR spectrum, one of the methylene protons of pyran ring appeared as a double doublet (J = 16.2 Hz, 8.3 Hz) at δ 2.27. The other proton of the same carbon resonated at δ 3.26 as a double doublet (J = 16.1 Hz, 7.3 Hz). The methyl protons gave a singlet signal at δ 3.69. The ^{13}C NMR spectrum also supported the assigned structure.

The IR spectrum of other isomer **54** displayed carbonyl absorption at 1638 cm^{-1}. The methylene protons of pyran ring resonated at δ 2.81 and 3.04 respectively. Each appeared as a double doublet. This small difference in the δ value supported the structure of the product as an *E* isomer.

Similar cycloaddition was observed between **19** and cycloalkyl fulvenes. The results are summarized in Table 3.

Table 3

Entry	Fulvene	Reaction conditions	Product	Yield (%)
1	 55	Dioxane, reflux, 2 h	 56	60
2	 44	Dioxane, reflux, 2 h	 57	50

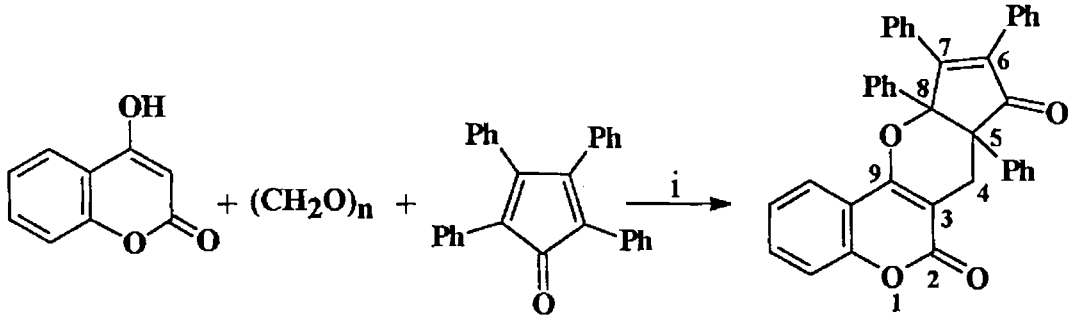
The products were characterized by spectroscopic methods. The adducts showed only one carbonyl absorption around 1640 cm^{-1}. Both the products gave satisfactory ^{1}H and ^{13}C NMR signals.

3.5.5 CYCLOADDITION REACTIONS OF QUINONE METHIDES WITH TETRACYCLONE

It may be noted that tetracyclone has been frequently employed as a reactive diene in Diels-Alder reactions with a large number of vinylic and alkynic dienophiles, especially arynes. Investigations in our

laboratory have shown that tetracyclone can participate as 2π component in its reaction with *o*-quinones.[13] Therefore it was of interest to study its reaction with quinone methides.

4-Hydroxy coumarin **1**, on treatment with paraformaldehyde and tetracyclone **58** in refluxing dioxane afforded the product **59** in 80% yield (Scheme 18).



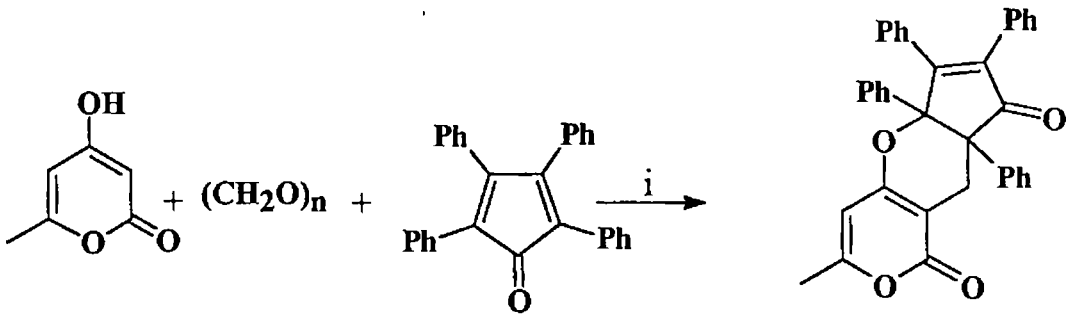
1 **58** **59**

i) Dioxane, reflux, 3 h, 80%.

Scheme 18

The IR spectrum of the product **59** exhibited two strong peaks at 1713 and 1695 cm^{-1} due to the keto carbonyl and the lactone carbonyl respectively. In the ^1H NMR spectrum, the methylene protons of the pyran ring appeared as two distinct doublets (J = 18.6 Hz) at δ 3.29 and 3.49 respectively. All other protons resonated as a multiplet between δ 6.83-7.39. In the ^{13}C NMR, the methylene carbon of the pyran ring showed a signal at δ 30.55. The ring junction carbons C-5 and C-8 resonated at δ 60.11 and 92.07 respectively. The lactone carbonyl carbon gave a signal at δ 162.90 while the other carbonyl carbon was discernible at δ 201.03. All other signals appeared in the olefinic region.

The quinone methide, generated from 4-hydroxy-6-methyl pyrone, on cycloaddition with tetracyclone afforded the product **60** in 40% yield (Scheme 19).



46 **58** **60**

i) Dioxane, reflux, 10 h, 40%

Scheme 19

The product **60** was characterized by spectroscopic methods. The IR spectrum exhibited two strong absorptions at 1719 and 1708 cm^{-1} due to cyclopentenone and lactone carbonyls respectively. In the ^1H NMR spectrum, the methylene protons of the pyran ring appeared as two distinct doublets (J = 18.1 Hz) at δ 3.16 and 3.30 respectively. The methyl carbon gave a signal at δ 19.77 in the ^{13}C NMR spectrum. The signals due to lactone and ketone carbons were visible at δ 163.33 and 201.11 respectively. All other signals were in accordance with the assigned structure.

3.6 CONCLUSION

In conclusion, we have synthesized a variety of polycyclic pyran derivatives such as pyranocoumarins, pyranopyrones and

pyranoquinolinones. Generally, polycyclic pyran derivatives constitute a large group of naturally occurring biologically active compounds. It is also noteworthy that the present procedure for the synthesis of quinolone quinone methide offers a more convenient alternative to the existing method.

3.7 EXPERIMENTAL DETAILS

The melting points were recorded on a Büchi-530 melting point apparatus. The infra red (IR) spectra were recorded on Nicolet (Impact 400D) and Bomem (MB Series) FT-IR spectro-photometers. The NMR spectra were recorded on Bruker-300 MHz NMR spectrometer and were obtained using chloroform-d as solvent. Chemical shifts are given in δ scale with tetramethylsilane as internal standard. Elemental analyses were carried out using Perkin-Elmer elemental analyzer. Solvents used for experiments were distilled and dried according to literature procedures.

Column chromatography was done using 100-200 mesh silica gel and appropriate mixture of petroleum ether (60-80 °C) and ethyl acetate for elution. The solvents were removed using Büchi-EL rotary evaporator.

GENERAL PREPARATION OF FULVENES

To a solution of carbonyl compound (1 mmol) and cyclopentadiene (2.5 mmol) in methanol (10 mL) under argon at ice temperature, pyrrolidine (2.5 mmol) was added dropwise and stirred at

room temperature for 4 h. The reaction mixture was neutralized with acetic acid, washed with water (4 x 25 mL) and extracted with diethyl ether (4 x 50 mL). The organic layer was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. The residue on silica gel column chromatography (60-120 mesh) afforded the corresponding fulvene.

8-[(Diphenyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [24]

4-Hydroxy coumarin (0.162 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6,6-diphenyl fulvene (0.460 g, 2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 5 h. The solvent was removed *in vacuo* and the residue was extracted with chloroform (3 x 20 mL). The organic layer was washed with sodium carbonate solution and brine and dried over anhydrous sodium sulfate. The chloroform was evaporated off and the residue was subjected to chromatography on silica gel using 10% ethyl acetate in hexane as eluent to afford 0.343 g (85%) of product as a colorless crystalline solid; recrystallized from dichloromethane/hexane solvent system (mp: 155-157 °C).

Spectral data for 24

IR (KBr) ν_{max} : 3059, 2913, 1701, 1640, 1612, 1495, 1409, 1361, 1276, 1175, 1114, 1051, 1606, 895 cm^{-1}.

^1H NMR : δ 2.18 (dd, J = 16.5 Hz, 8.1 Hz, 1H), 2.64 (dd, J = 16.5 Hz, 8.4 Hz, 1H), 3.32-3.40 (m, 1H), 5.57 (dt, J =

6.9 Hz, 2.4 Hz, 1H), 6.17 (dd, J = 6.0 Hz, 3.0 Hz, 1H), 6.53 (dd, J = 5.1 Hz, 3.0 Hz, 1H), 7.15-7.44 (m, 13H), 7.73 (d, J = 6.3 Hz, 1H).

^{13}C NMR : δ 21.99, 38.28, 83.07, 101.26, 116.00, 116.71, 122.47, 123.92, 127.37, 127.64, 128.27, 128.67, 129.42, 129.83, 131.51, 135.31, 135.99, 136.27, 141.54, 141.73, 144.17, 159.76, 162.30.

Anal. Calcd for $C_{28}H_{20}O_3$: C, 83.15; H, 4.98. Found: C, 83.23; H, 4.79.

X-ray crystal Data $C_{28}H_{20}O_3$, Fw 404.44, 0.42 x 0.40 x 0.25 mm^3, orthorhombic, space group Pbca, unit cell dimensions: a = 9.9051(1) Å. α = 90°, b = 16.0715(2) Å. β = 90°, c = 25.3875(4) Å, γ = 90°. R indices (all data) R1 = 0.1368, wR2 = 0.2195. Volume = 4041.43(9) Å^3, Z = 8. D calc = 1.329 Mg/m^3. F(000) = 1696. Absorption coefficient 0.086 mm^{-1}, reflections collected 67771. (Sheldrick, G. M., Siemens, Analytical X-ray Division, Madison, WI, 1995).

8-*Z*-[(Phenyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [26] and 8-*E*-[(Phenyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [27]

4-Hydroxy coumarin (0.162 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6-phenyl fulvene (0.308 g, 2 mmol) were

dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 6 h. After usual work up, the residue was subjected to silica gel column chromatography using 10% ethyl acetate in hexane as eluent to afford **26** (0.138 g, 42%) as colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 153-155 °C) and **27** (0.137 g, 42%) as colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 148-151 °C).

Spectral data for 26

IR (KBr) ν_{max} : 3059, 2915, 1701, 1647, 1418, 1189, 764 cm^{-1}.

^1H NMR : δ 2.21 (dd, J = 16.5 Hz, 8.4 Hz, 1H), 3.11 (dd, J = 16.5 Hz, 7.4 Hz, 1H), 3.68-3.75 (m, 1H), 5.68 (d, J = 6.3 Hz, 1H), 6.19 (d, J = 3.4 Hz, 1H), 6.46 (s, 1H), 7.25-7.53 (m, 9H), 7.81 (d, J = 7.9 Hz, 1H).

^{13}C NMR : δ 20.87, 37.43, 84.01, 101.33, 116.62, 122.36, 123.82, 127.32, 128.33, 128.83, 131.46, 136.42, 138.39, 147.11, 152.39, 159.85, 162.50.

Anal. Calcd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91. Found: C, 80.45; H, 4.68.

Spectral data for 27

IR (KBr) ν_{max} : 3020, 2910, 1701, 1647, 1411, 1067, 771 cm^{-1}.

^1H NMR : δ 2.77 (dd, J = 16.6 Hz, 5.1 Hz, 1H), 2.97 (dd, J = 16.7 Hz, 7.4 Hz, 1H), 3.37-3.41 (m, 1H), 5.48 (d, J =

6.4 Hz, 1H), 6.38 (dd, J = 5.3 Hz, 1.9 Hz, 1H), 6.47 (s, 1H), 6.96 (d, J = 5.4 Hz, 1H), 7.18-7.50 (m, 8H), 7.73 (d, J = 7.8 Hz, 1H).

^{13}C NMR : δ 20.85, 40.70, 81.87, 100.65, 116.68, 122.39, 123.70, 128.40, 128.46, 131.36, 134.82, 136.39, 145.36, 152.42, 160.35, 162.64.

Anal. Calcd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91. Found: C, 80.60; H, 4.80.

8-*Z*-[(4-Methoxyphenyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [29] and 8-*E*-[(4-Methoxyphenyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [30]

4-Hydroxy coumarin (0.162 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6-(4-methoxy phenyl) fulvene (0.368 g, 2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 5 h. After usual work up, the residue was subjected to silica gel column chromatography using 10% ethyl acetate in hexane as eluent to afford **29** (0.161 g, 45%) as colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 144-147 °C) and **30** (0.143 g, 40%) as colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 139-143 °C).

Spectral data for 29

IR (KBr) ν_{max} : 3070, 2955, 2935, 2847, 1708, 1647, 1411, 1263, 1182, 1047, 879, 764, 528 cm^{-1}.

^{1}H NMR : δ 2.18 (dd, J = 16.5 Hz, 8.6 Hz, 1H), 3.12 (dd, J = 16.5 Hz, 7.3 Hz, 1H), 3.65-3.67 (m, 1H), 3.82 (s, 3H), 5.67 (d, J = 5.6 Hz, 1H), 6.12 (d, J = 3.8 Hz, 1H), 6.38 (s, 1H), 6.42 (d, J = 4.3 Hz, 1H), 6.87 (d, J = 8.5 Hz, 2H), 7.24-7.52 (m, 5H), 7.79 (d, J = 7.6 Hz, 1H).

^{13}C NMR : δ 20.73, 37.51, 55.29, 84.32, 101.50, 113.96, 114.39, 116.02, 116.69, 122.43, 123.38, 123.82, 129.73, 131.46, 132.82, 138.67, 145.08, 152.47, 158.91, 159.88, 162.39.

Spectral data for 30

IR (KBr) ν_{max} : 3070, 2955, 2935, 2840, 1708, 1640, 1512, 1398, 1256, 1182, 1108, 1034, 838, 764, 542 cm^{-1}.

^{1}H NMR : δ 2.75 (dd, J = 16.7 Hz, 4.9 Hz, 1H), 2.94 (dd, J = 16.7 Hz, 7.3 Hz, 1H), 3.35-3.37 (m, 1H), 3.78 (s, 3 H), 5.44 (dd, J = 6.4 Hz, 1.5 Hz, 1H), 6.34-6.38 (m, 2H), 6.80 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 5.5 Hz, 1H), 7.18-7.49 (m, 5H), 7.72 (d, J = 7.8 Hz, 1H).

^{13}C NMR : δ 20.71, 40.57, 55.19, 81.87, 100.50, 113.90, 116.04, 116.60, 122.13, 122.40, 123.70, 129.58, 129.84, 131.33, 134.86, 135.67, 143.54, 152.33, 158.75, 160.38, 162.70.

8-*Z*-[(2-Furanyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [32] and

8-*E*-[(2-Furanyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [33]

4-Hydroxy coumarin (0.162 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6-(2-furyl) fulvene (0.288 g, 2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 4 h. After usual work up, the residue was subjected to silica gel column chromatography using 10% ethyl acetate in hexane as eluent to afford 0.138 g of **32** (40%) as colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 139-142 °C) and 0.137 g of **33** (40%) as colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 136-138 °C).

Spectral data for 32

IR (KBr) ν_{max} : 3070, 1715, 1634, 1411, 757 cm^{-1}.

^1H NMR : δ 2.13 (dd, J = 16.4 Hz, 7.5 Hz, 1H), 3.29 (dd, J = 16.4 Hz, 7.5 Hz, 1H), 3.75-3.83 (m, 1H), 5.67 (d, J = 6.5 Hz, 1H), 6.18 (d, J = 3.5 Hz, 1H), 6.25 (s, 1H), 6.31 (d, J = 3.0 Hz, 1H), 6.42, (s, 2H), 7.26-7.33 (m, 2H), 7.46-7.53 (m, 2H), 7.82 (d, J = 7.8 Hz, 1H).

^{13}C NMR : δ 21.63, 38.21, 84.00, 101.61, 110.42, 110.58, 111.64, 116.64, 122.35, 123.79, 131.37, 134.72, 136.84, 142.75, 145.00, 152.21, 152.36, 159.89, 162.68.

Anal. Calcd for $C_{20}H_{14}O_4$: C, 75.46; H, 4.43. Found: C, 75.20; H, 4.70.

Spectral data for 33

IR (KBr) ν_{max} : 3050, 1708, 1627, 1404, 764 cm^{-1}.

^1H NMR : δ 2.78 (dd, J = 16.6 Hz, 4.3 Hz, 1H), 2.91 (dd, J = 16.5 Hz, 7.1 Hz, 1H), 3.39 (d, J = 5.7 Hz, 1H), 5.44 (d, J = 4.7 Hz, 1H), 6.13 (s, 1H), 6.24 (d, J = 2.8 Hz, 1H), 6.36 (s, 1H), 7.20-7.98 (m, 6H), 7.71 (d, J = 7.0 Hz, 1H).

^{13}C NMR : δ 20.28, 40.36, 81.65, 100.38, 109.70, 109.96, 111.37, 115.94, 116.49, 122.25, 123.57, 131.23, 135.37, 136.46, 142.17, 152.24, 152.80, 160.37, 162.56.

8-*Z*-[(2-phenylethenyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [35] and 8-*E*-[(2-phenylethenyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [36]

4-Hydroxy coumarin (0.162 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6-(2-phenyl ethenyl) fulvene (0.360 g, 2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 4 h. After usual work up, the residue was subjected to silica gel column chromatography using 10% ethyl acetate in hexane as eluent to afford 0.142 g of **35** (40%) as colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 143-145 °C) and

0.142 g of **36** (40%) as colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 136-139 °C).

Spectral data for 35

IR (KBr) ν_{max} : 3050, 3030, 2950, 1701, 1640, 1418, 1128, 764 cm^{-1}.

^1H NMR : δ 2.23 (dd, J = 16.3 Hz, 9.1 Hz, 1H), 3.20 (dd, J = 16.3 Hz, 7.6 Hz, 1H), 3.46-3.51 (m, 1H), 5.64 (d, J = 6.5 Hz, 1H), 6.19 (d, J = 5.1 Hz, 1H), 6.26 (d, J = 11.4 Hz, 1H), 6.41 (d, J = 5.5 Hz, 1H), 6.59 (d, J = 15.2 Hz, 1H), 6.93-6.97 (m, 1H), 7.24-7.55 (m, 8H), 7.82 (d, J = 7.7 Hz, 1H).

^{13}C NMR : δ 22.48, 37.26, 83.64, 101.25, 115.94, 116.66, 123.86, 124.80, 126.59, 127.84, 128.69, 134.82, 136.71, 148.01, 152.41, 160.32, 162.64.

Anal. Calcd for $C_{24}H_{18}O_3$: C, 81.33; H, 5.12. Found: C, 80.99; H, 5.37.

Spectral data for 36

IR (KBr) ν_{max} : 3063, 2950, 1701, 1640, 1418, 778 cm^{-1}.

^1H NMR : δ 2.71-2.97 (m, 2H), 3.35-3.37 (m, 1H), 5.43-5.45 (m, 1H), 6.21-6.58 (m, 3H), 6.92-7.70 (m, 11H).

^{13}C NMR : δ 20.06, 39.89, 81.98, 101.30, 115.92, 116.50, 122.24, 122.37, 123.58, 124.62, 126.32, 127.55, 127.76, 128.52, 131.24, 132.94, 134.36, 137.13, 145.63, 152.22, 160.31, 162.57.

8-*Z*-[(1-Methyl-1-phenyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [38]

4-Hydroxy coumarin (0.162 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6-phenyl-6-methyl fulvene (0.336 g, 2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 7 h. After usual work up, the residue was subjected to silica gel column chromatography using 10% ethyl acetate in hexane as eluent to afford 0.256 g (75%) of **38** as a colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 148-150 °C).

Spectral data for 38

IR (KBr) ν_{max} : 3070, 2955, 2935, 1701, 1647, 1492, 1398, 1128, 1047, 764 cm^{-1}.

^1H NMR : δ 2.16-2.25 (m, 4H), 3.17 (dd, J = 16.1 Hz, 7.3 Hz, 1H), 3.29-3.35 (m, 1H), 5.68 (d, J = 6.3 Hz, 1H), 6.07 (d, J = 4.8 Hz, 1H), 6.38 (dd, J = 5.5 Hz, 1.5 Hz, 1H), 7.20-7.36 (m, 7H), 7.48-7.54 (m, 1H), 7.83 (d, J = 7.8 Hz, 1H)

^{13}C NMR : δ 21.38, 30.90, 38.52, 83.74, 101.06, 116.64, 122.39, 123.83, 126.97, 128.09, 128.20, 134.12, 142.61, 152.38, 160.15, 162.80.

Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.68; H, 5.30. Found: C, 80.62; H, 4.99.

8-[(Diethyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [40]

4-Hydroxy coumarin (0.162 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6,6-diethyl fulvene (0.402 g, 2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 4 h. After usual work up, the crude product when subjected to silica gel column chromatography afforded 0.154 g (50%) of **40** as a pale yellow semi-solid.

Spectral data for 40

IR (neat) ν_{max} : 3353, 3030, 2969, 1708, 1640, 1418, 1061, 771 cm^{-1}.

^1H NMR : δ 0.77-1.01 (m, 6H), 1.89-1.98 (m, 1H), 2.04-2.11 (m, 4H), 2.85 (dd, J = 16.1 Hz, 7.0 Hz, 1H), 3.00-3.05 (m, 1H), 5.45 (d, J = 6.3 Hz, 1H), 5.94 (d, J = 4.0 Hz, 1H), 6.43 (d, J = 3.8 Hz, 1H), 7.12-7.21 (m, 2H), 7.35-7.40 (m, 1H), 7.67 (d, J = 7.6 Hz, 1H).

^{13}C NMR : δ 13.20, 13.63, 21.81, 23.79, 25.24, 36.90, 83.51, 100.72, 115.69, 122.16, 123.60, 131.14, 132.28, 132.38, 132.49, 137.39, 138.79, 151.98, 159.97, 162.66.

8-*Z*-[(1-Ethyl-1-methyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [42] and 8-*E*-[(1-Ethyl-1-methyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [43]

4-Hydroxy coumarin (0.162 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6-ethyl-6-methyl fulvene (0.360 g, 2 mmol) were

dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 3 h. After usual work up, the crude product when subjected to silica gel column chromatography afforded an inseparable mixture of **42** and **43** (0.167 g, 70%) as a pale yellow semi-solid.

Spectral data for 42 and 43

IR (neat) ν_{max} : 3050, 2968, 1698, 1495, 1401, 1176, 1108, 1039, 746 cm^{-1}.

^1H NMR : δ 0.99-1.04 (t, J = 7.5 Hz, 3H), 1.08-1.18 (t, J = 7.5 Hz, 3H), 1.78 (s, 3H), 1.85 (s, 3H), 2.01-2.08 (m, 2H), 2.12-2.21 (m, 4H), 3.00-3.17 (m, 4H), 5.55 (s, 2H), 6.00-6.04 (m, 2H), 6.53 (s, 2H), 7.21-7.28 (m, 4H), 7.44-7.49 (m, 2H), 7.76-7.79 (m, 2H).

^{13}C NMR : δ 12.97, 13.18, 17.55, 18.50, 21.36, 21.92, 27.75, 28.19, 29.63, 37.38, 37.68, 88.69, 101.17, 116.92, 116.45, 122.25, 131.13, 131.43, 132.22, 132.40, 132.56, 132.90, 139.16, 139.43, 152.27, 159.90, 162.31, 162.38.

8-[(cycloheptyl)methylene]-7,7a,8,10a-tetrahydro-6H-*cis*-cyclopenta[5,6]pyrano[3,2-c][1]benzopyran-6-one [45]

4-Hydroxy coumarin (0.162 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6,6-hexamethylene fulvene (0.480 g, 2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 2.5 h. After usual work up, the crude product when

subjected to silica gel column chromatography afforded 0.167 g of pure product **45** (50%) as a pale yellow semi-solid.

Spectral data for 45

IR (neat) ν_{max} : 3058, 2921, 2854, 1708, 1640, 1452 cm^{-1}.

^1H NMR : δ 1.55-1.69 (m, 8H), 2.02 (dd, J = 15.8 Hz, 9.1 Hz, 1H), 2.37-2.43 (m, 4H), 3.01-3.16 (m, 2H), 5.55 (d, J = 5.9 Hz, 1H), 6.02 (d, J = 4.5 Hz, 1H), 6.54 (d, J = 3.9 Hz, 1H) 7.23-7.51 (m, 3H), 7.79 (d, J = 7.7 Hz, 1H).

^{13}C NMR : δ 21.53, 27.78, 28.21, 28.95, 29.78, 32.06, 32.94, 37.61, 83.81, 101.23, 115.99, 116.56, 122.33, 123.64, 131.22, 132.29, 132.70, 135.57, 139.58, 152.33, 159.99, 162.51.

Pyranopyrone [47]

4-Hydroxy-6-methyl pyrone (0.126 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6,6-diphenyl fulvene (0.460 g, 2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 4 h. After usual work up, the residue was subjected to silica gel column chromatography using 10% ethyl acetate in hexane as eluent to afford 0.240 g (65%) of the product **47** as a pale yellow semi-solid.

Spectral data for 47

IR (neat) ν_{max} : 3045, 2970, 1701, 1488, 1400, 1180, 750 cm^{-1}.

^{1}H NMR : δ 2.05-2.18 (m, 4H), 2.53 (dd, J = 16.4 Hz, 7.5 Hz, 1H), 3.23-3.26 (m, 1H), 5.40 (d, J = 6.3 Hz, 1H), 5.73 (s, 1H), 6.11 (d, J = 4.1 Hz, 1H), 6.52 (d, J = 5.3 Hz, 1H), 7.12-7.33 (m, 10H).

^{13}C NMR : δ 19.64, 21.13, 38.04, 82.21, 97.90, 100.09, 127.97, 128.36, 129.12, 129.55, 135.81, 141.30, 144.01, 159.56, 164.05.

Pyranopyrones [48] and [49]

4-Hydroxy-6-methyl pyrone (0.126 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6-phenyl fulvene (0.480 g, 2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 5 h. After usual work up, the crude product when subjected to silica gel column chromatography afforded 0.102 g of the product **48** (35%) and 0.058 g of the product **49** (20%) as pale yellow semi-solids.

Spectral data for 48

IR (neat) ν_{max} : 3058, 3027, 2927, 2853, 1707, 1583, 1446, 1408, 1209, 1141, 1029, 792, 749, 687 cm^{-1}.

^{1}H NMR : δ 2.04-2.16 (m, 4H), 2.92 (dd, J = 16.3 Hz, 7.4 Hz, 1H), 3.50-3.55 (m, 1H), 5.42 (d, J = 5.7 Hz, 1H), 5.75 (s, 1H), 6.05 (d, J = 4.1 Hz, 1H), 6.37 (s, 2H), 7.18-7.32 (m, 5H).

^{13}C NMR : δ 19.70, 20.90, 37.17, 83.25, 98.02, 100.21, 123.41, 127.16, 128.18, 128.69, 134.02, 136.30, 137.90, 147.04, 159.84, 164.04, 164.35.

Spectral data for 49

IR (neat) ν_{max} : 3058, 2965, 2927, 2853, 1701, 1651, 1589, 1446, 1408, 1216, 1141, 1029, 998, 755, 699 cm^{-1}.

^{1}H NMR : δ 2.17 (s, 3H), 2.60 (dd, J = 16.5 Hz, 4.9 Hz, 1H), 2.81 (dd, J = 16.5 Hz, 7.3 Hz, 1H), 3.27-3.29 (m, 1H), 5.26 (dd, J = 6.3 Hz, 1.6 Hz, 1H), 5.72 (s, 1H), 6.27 (dd, J = 3.6 Hz, 1.8 Hz, 1H), 6.41 (s, 1H), 6.93-6.95 (m, 1H), 7.20-7.33 (m, 5H).

^{13}C NMR : δ 19.68, 19.79, 40.45, 81.11, 97.26, 100.39, 122.25, 126.90, 128.25, 128.31, 134.42, 136.42, 137.14, 145.26, 159.68, 164.40, 165.00.

3-[(Diphenyl)methylene]-3,3a,4,11a-tetrahydro-5H-*cis*-cyclopenta[5,6]pyrano[3,2-c]quinolin-5-one [52]

4-Hydroxy-1-methyl-2(H)-quinolinone (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6,6-diphenyl fulvene (0.460 g, 2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 3.5 h. The solvent was removed *in vacuo* and the residue was extracted with chloroform (3 x 20 mL). The organic layer was washed with sodium carbonate solution, brine and dried over anhydrous sodium sulfate. The chloroform was evaporated off

and the residue was subjected to silica gel column chromatography to afford 0.412 g (98%) of the product **52** as a colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 159-162 °C).

Spectral data for 52

IR (KBr) ν_{max} : 3024, 2940, 2840, 1642, 1460, 1505, 1165, 750 cm^{-1}.

^1H NMR : δ 2.24 (dd, J = 16.4 Hz, 8.1 Hz, 1H), 2.80 (dd, J = 16.5 Hz, 7.6 Hz, 1H), 3.37-3.42 (m, 1H), 3.64 (s, 3H), 5.53 (d, J = 6.6 Hz, 1H), 6.19 (dd, J = 5.5 Hz, 1.7 Hz, 1H), 6.56 (dd, J = 5.4 Hz, 1.3 Hz, 1H), 7.14-7.51 (m, 13H), 7.92 (d, J = 7.8 Hz, 1H).

^{13}C NMR : δ 22.35, 29.19, 39.08, 82.41, 107.80, 113.61, 116.28, 121.32, 122.54, 126.92, 127.24, 127.93, 128.33, 129.27, 129.66, 129.98, 135.17, 136.18, 138.41, 141.52, 141.79, 144.84, 156.06, 162.29.

3-*Z*-[(4-Methoxyphenyl)methylene]-3,3a,4,11a-tetrahydro-5H-*cis*-cyclopenta[5,6]pyrano[3,2-c]quinolin-5-one [53] and 3-*E*-[(4-Methoxyphenyl)methylene]-3,3a,4,11a-tetrahydro-5H-*cis*-cyclopenta[5,6]pyrano[3,2-c]quinolin-5-one [54]

4-Hydroxy-1-methyl-2(H)-quinolinone (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6-(4-methoxy phenyl) fulvene (0.368 g, 2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 3 h. After usual work up, the crude

product was subjected to silica gel column chromatography to afford **53** (0.122 g, 45%) as colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 152-155 °C) and **54** (0.122 g, 40%) as colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 148-151 °C).

Spectral data for 53

IR (KBr) ν_{max} : 3030, 2956, 2837, 1645, 1507, 1463, 1407, 1245, 1170, 1114, 1033, 752 cm^{-1}.

^1H NMR : δ 2.27 (dd, J = 16.2 Hz, 8.3 Hz, 1H), 3.26 (dd, J = 16.1 Hz, 7.3 Hz, 1H), 3.69 (s, 3H), 3.82 (s, 3H), 5.62 (d, J = 6.8 Hz, 1H), 6.11 (d, J = 3.8 Hz, 1H), 6.36 (s, 1H), 6.40 (d, J = 5.0 Hz, 1H), 6.87 (d, J = 8.5 Hz, 1H), 7.10-7.58 (m, 7H), 7.97 (d, J = 7.7 Hz, 1H).

^{13}C NMR : δ 20.93, 29.30, 38.58, 55.07, 83.92, 108.12, 113.71, 114.12, 116.37, 121.45, 122.59, 122.65, 129.59, 130.12, 133.13, 138.44, 138.70, 145.74, 156.56, 158.53, 162.40.

Spectral data for 54

IR (KBr) ν_{max} : 3043, 2949, 2899, 2837, 1638, 1595, 1507, 1395, 1245, 1158, 1114, 1026, 821, 752 cm^{-1}.

^1H NMR : δ 2.81 (dd, J = 16.4 Hz, 5.3 Hz, 1H), 3.04 (dd, J = 16.4 Hz, 7.3 Hz, 1H), 3.36-3.39 (m, 1H), 3.69 (s, 3H),

3.78 (s, 3H), 5.42 (d, J = 5.6 Hz, 1H), 6.33 (d, J = 5.4 Hz, 1H), 6.39 (s, 1H), 6.80 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 5.5 Hz, 1H), 7.17-7.52 (m, 5H), 7.91 (d, J = 7.0 Hz, 1H).

^{13}C NMR : δ 21.58, 29.31, 41.39, 55.07, 81.50, 107.46, 113.72, 116.53, 121.38, 121.52, 122.62, 129.43, 130.05, 130.16, 134.38, 136.29, 138.47, 144.67, 156.98, 158.46, 162.64.

3-[(Cyclohexyl)methylene]-3,3a,4,11a-tetrahydro-5H-*cis*-cyclopenta[5,6]pyrano[3,2-c]quinolin-5-one [56]

4-Hydroxy-1-methyl-2(H)-quinolinone (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6,6-pentamethylene fulvene (0.438 g, 2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 2 h. After usual work up, the residue was subjected to silica gel column chromatography using 10% ethyl acetate in hexane as eluent to afford 0.200 g (60%) of the product **56** as a pale yellow solid; recrystallized from dichloromethane/hexane solvent system (mp: 114-116 °C).

Spectral data for 56

IR (KBr) ν_{max} : 3030, 2934, 2853, 1639, 1589, 1502, 1465, 1396, 1166, 1110, 1041, 998, 755 cm^{-1}.

^{1}H NMR : δ 1.54-1.60 (m, 6H), 2.13-2.33 (m, 5H), 3.09-3.19 (m, 2H), 3.68 (s, 3H), 5.50 (d, J = 5.2 Hz, 1H), 6.00 (d,

J = 4.0 Hz, 1H), 6.54 (dd, J = 4.6 Hz, 1.6 Hz, 1H), 7.17-7.52 (m, 3H), 7.94 (dd, J = 7.8 Hz, 1.0 Hz, 1H).

^{13}C NMR : δ 22.49, 26.61, 28.06, 31.37, 31.88, 38.29, 83.34, 96.21, 108.14, 113.67, 116.48, 121.37, 122.59, 129.98, 132.37, 132.69, 133.49, 137.45, 156.88, 162.51.

3-[(Cycloheptyl)methylene]-3,3a,4,11a-tetrahydro-5H-*cis*-cyclopenta[5,6]pyrano[3,2-c]quinolin-5-one [57]

4-Hydroxy-1-methyl-2(H)-quinolinone (0.175 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and 6,6-hexamethylene fulvene (0.480 g, 2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 2 h. After usual work up, the crude product when subjected to silica gel column chromatography afforded 0.173 g of the product **57** (50%) as a pale yellow solid; recrystallized from dichloromethane/hexane solvent system (mp: 119-122 °C).

Spectral data for 57

IR (KBr) ν_{max} : 3064, 2921, 2859, 1645, 1502, 1465, 1396, 1284, 1159, 1116, 1004, 749 cm^{-1}.

^{1}H NMR : δ 1.52-1.70 (m, 8H), 2.07-2.15 (m, 1H), 2.36-2.48 (m, 4H), 3.12-3.21 (m, 2H), 3.69 (s, 3H), 5.49 (d, J = 5.6 Hz, 1H), 6.01 (d, J = 4.4 Hz, 1H), 6.52 (d, J = 4.2 Hz, 1H), 7.18-7.52 (m, 3H), 7.95 (d, J = 7.7 Hz, 1H).

^{13}C NMR : δ 22.03, 27.82, 28.22, 28.95, 29.32, 29.96, 32.09, 32.87, 38.83, 83.46, 108.11, 113.73, 121.42, 122.66, 130.04, 132.68, 132.80, 134.86, 138.46, 140.19, 156.84, 162.59.

Pyranocoumarin [59]

4-Hydroxy coumarin (0.162 g, 1 mmol), paraformaldehyde (0.240 g, 8 mmol) and tetracyclone (0.460 g, 1.2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 3 h. After usual work up, the residue was subjected to silica gel column chromatography using 10% ethyl acetate in hexane as eluent to afford 0.446 g (80%) of the product **59** as a colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 218-220 °C).

Spectral data for 59

IR (KBr) ν_{max} : 3058, 3024, 1713, 1695, 1645, 1489, 1395, 1064, 746, 689 cm^{-1}.

^{1}H NMR : δ 3.29 (d, J = 18.6 Hz, 1H), 3.49 (d, J = 18.6 Hz, 1H), 6.83-7.39 (m, 24H).

^{13}C NMR : δ 30.55, 60.11, 92.07, 101.18, 115.02, 116.80, 122.14, 124.00, 126.63, 126.91, 127.80, 128.22, 128.40, 128.47, 128.76, 129.19, 129.84, 129.92, 130.15, 131.32, 131.88, 138.46, 139.75, 140.03, 152.41, 158.41, 161.76, 162.90, 201.03.

Pyranopyrone [60]

4-Hydroxy-6-methyl pyrone (0.126 g, 1 mmol), paraformaldehyde (0.240 g, 8mmol) and tetracyclone (0.460 g, 1.2 mmol) were dissolved in dry dioxane (4 mL) and refluxed (100 °C) under argon atmosphere for 10 h. After usual work up, the crude product when subjected to silica gel column chromatography afforded 0.209 g of pure product **60** (40%) as a colorless solid; recrystallized from dichloromethane/hexane solvent system (mp: 155-157 °C).

Spectral data for 60

IR (KBr) ν_{max} : 3055, 3030, 2924, 2850, 1719, 1708, 1651, 1595, 1489, 1445, 1401, 1339, 1220, 1145, 1033, 989, 752, 689 cm^{-1}.

^1H NMR : δ 2.12 (s, 3H), 3.16 (d, J = 18.1 Hz, 1H), 3.30 (d, J = 18.1 Hz, 1H), 5.68 (s, 1H), 6.80-7.36 (m, 20H).

^{13}C NMR : δ 19.77, 26.92, 29.51, 59.99, 98.08, 99.59, 126.51, 126.72, 127.61, 127.97, 128.15, 128.24, 128.59, 128.97, 129.67, 129.81, 130.04, 130.19, 131.44, 138.54, 139.53, 139.99, 160.72, 162.90, 163.01, 163.33, 201.11.

3.8 REFERENCES

1. (a) Butz, L. W. A.; Rytina, W. *Org. React.* **1949**, *5*, 136. (b) Kloetzel, M. C. *Org. React.* **1948**, *1*, 4. (c) Wasserman, A. *Diels-Alder reactions;* Elsevier: New York, 1965.
2. Sauer, J.; Sustmann, R. *Angew. Chem., Int. Edn. Engl.* **1980**, *19*, 779.
3. Fleming, I. *Frontier Orbitals and Organic Chemical Reactions;* John Wiley: New York, 1976.
4. (a) Appendino, G.; Cravotto, G.; Tagliapietra, S.; Ferraro, S.; Nano, G. M.; Palmisano, G. *Helv. Chim. Acta.* **1991**, *74*, 1451. (b) Appendino, G.; Cravotto, G.; Toma, L.; Annunziata, R.; Palmisano, G. *J. Org. Chem.* **1994**, *59*, 5556.
5. Appendino, G.; Cravotto, G.; Tagliapietra, S.; Nano, G. M. *Helv. Chim. Acta.* **1990**, *73*, 1865.
6. Hua, D. H.; Chen, Y.; Sin, H. -S.; Maroto, M. J.; Robinson, P. D.; Newell, S. W.; Perchellet, E. M.; Ladesich, J. B.; Freeman, J. A.; Perchellet, J. P.; Chiang, P. K. *J. Org. Chem.* **1997**, *62*, 6888.
7. Ye, J. -H.; Ling, K. Q.; Zhang, Y.; Li, N.; Xu, J. -H. *J. Chem. Soc., Perkin Trans. 1* **1999**, *14*, 2017.
8. (a) Grundon, M. F.; Ramachandran, V. N.; Sloan, B. M. *Tetrahedron Lett.* **1981**, *22*, 3105. (b) Chauncey, M. A.; Grundon, M. F. *Synthesis* **1990**, 1005.
9. (a) Yates, P. *Advances in Alicyclic Chemistry;* Academic Press: New York, 1968; Vol. 2 and the references cited there in. (b) Erickson, M. S.; Cronan, J. M.; Garcia, J. G.; McLaughlin, M. L.

J. Org. Chem. **1992**, *57*, 2504. (c) Neuenschwander, M. *Fulvenes;* Patai, S., Ed.; John Wiley: New York, 1989; p 1131.

10. Houk, K. N. *Tetrahedron* **1974**, *30*, 523.
11. Rigby, J. H. *Comprehensive Org. Synth.* Trost, B. M.; Fleming, I., Ed.; Pergamon Press: New York, 1991; Vol. 5, p 617.
12. AM1 Calculations using PC SPARTAN Graphical Interface Package for Molecular Orbital Models by wavefunction Inc. 18401. Von Karman, Suite 370, Irvine, California, 92612 USA.
13. Nair, V.; Mathew, B.; Radhakrishnan, K. V.; Rath, N. P. *Tetrahedron* **1999**, *55*, 11017.

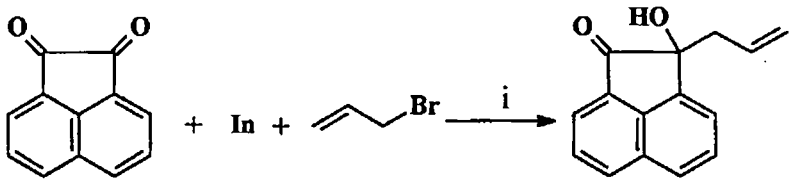
SUMMARY

The thesis entitled *"NOVEL REACTIONS OF INDIUM REAGENTS WITH 1,2-DIONES AND DIELS-ALDER CYCLOADDITIONS OF HETEROCYCLIC o-QUINONE METHIDES"* has been divided into three chapters.

Chapter 1 is divided into two parts. Part I consists of a general introduction to organometallic reactions with special emphasis on Barbier and Grignard reactions followed by an overview of the reactions of organoindium reagents with carbonyl compounds. The second part deals with the introduction to the generation and cycloaddition reactions of *o*-quinone methides derived from heterocycles.

The second chapter is concerned with the reactions of organoindium reagents with various 1,2-diones. An exhaustive literature survey of the reactions of organoindium reagents is followed by the results of the studies involving a variety of 1,2-diones and organoindium reagents generated *in situ*. We have observed that in the presence of sodium iodide in dimethyl formamide, the reaction of various organoindium reagents with 1,2-diones was facile. The reaction of allylindium reagent with acenaphthenequinone afforded monoallylated α-hydroxy ketone in excellent yield (Scheme 1). Other 1,2-diones showed similar reactivity pattern. The cinnamylation of 1,2-diones also occurred smoothly under the above conditions. It was observed that the regiochemical outcome of the cinnamylation reactions depends on the nature of 1,2-diones. In the case of acenaphthenequinone and phenanthrenequinone, only α-isomers were formed while butan-2,3-dione afforded only the γ-isomer. However, benzil and isatin, on

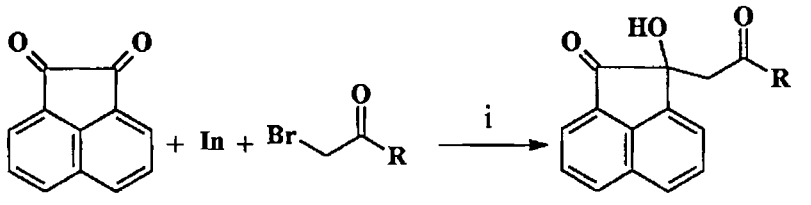
cinnamylation, afforded regioisomeric mixture of products which are separable. It is noteworthy that cinnamylation leading to both α and γ isomers is in keeping with the characteristic behavior of substituted allyl organometallics. Propargylation and benzylation of 1,2-diones afforded the corresponding α-hydroxy ketones in good yields.



i) NaI, DMF, r. t., 4 min, 94%

Scheme 1

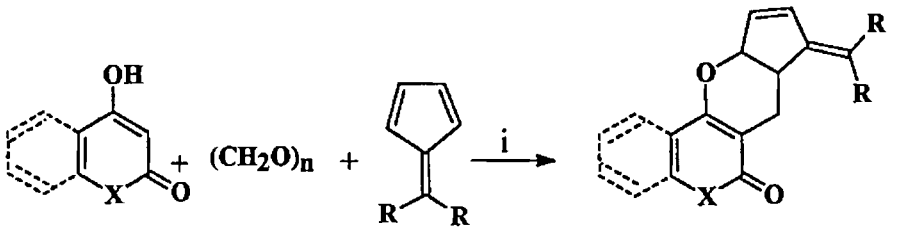
Indium mediated aldol and Reformatsky reactions of 1,2-diones have also been reported in the second chapter. The reaction of phenacyl bromide with 1,2-diones such as acenaphthenequinone and phenanthrenequinone afforded β-hydroxy ketones (aldol) in excellent yields. Similarly, the reaction of ethyl bromoacetate and ethyl-4-bromocrotonate with 1,2-diones led to multifunctional compounds in good yields (Scheme 2).



i) NaI, DMF, U. S. **R = Ph, OEt**

Scheme 2

The third and final chapter deals with the Diels-Alder reactions of heterocyclic quinone methides with pentafulvenes and tetracyclone. The reaction of coumarin quinone methide, generated from 4-hydroxy coumarin and paraformaldehyde, with 6-aryl fulvenes afforded novel pyranocoumarin derivatives in high yields (Scheme 3). Unsymmetrically substituted fulvenes afforded the *Z* and *E* stereoisomers. The reaction is general. Under similar conditions, the generation of pyrone and quinolone quinone methides was found to be facile and their trapping with fulvenes led to polycyclic pyran derivatives which may be of pharmacological interest.



i) Dioxane, reflux **X = O, NMe**

Scheme 3

In conclusion, we have uncovered a novel and fascinating transformation of 1,2-diones to α-hydroxy ketones; the latter are important in synthesis, and the method appears to be of general application. The Diels-Alder reactions of heterocyclic quinone methides have been shown to offer an attractive and efficient route to complex heterocycles.

LIST OF PUBLICATIONS

ARTICLES IN JOURNAL

1. V. Nair, G. Anilkumar, **C. N. Jayan** and N. P. Rath. "A Novel Photochemical Rearrangement of 1,3-Diaryl-1,2-dihydropentalenes to the 1,5-Isomers and their Domino Diels-Alder reactions", *Tetrahedron Lett.*, **1998**, *39*, 2437.
2. V. Nair and **C. N. Jayan.** "Indium mediated Barbier reactions of 1,2-diones: a facile synthesis of α-hydroxy ketones", *Tetrahedron Lett.*, **2000**, *41*, 1091.
3. V. Nair and **C. N. Jayan.** "A Facile Synthesis of α-Hydroxy Ketones from 1,2-Diones Mediated by Indium" (to be communicated to *Tetrahedron*).
4. V. Nair, **C. N. Jayan** and Sindu Ros. "Indium Mediated Aldol and Reformatsky Reactions of 1,2-Diones: Novel Synthesis of Multifunctional Compounds" (to be communicated to *Tetrahedron Lett.*).

POSTERS AT SYMPOSIA

1. A. G. Nair, **C. N. Jayan** and V. Nair. "Photoinduced Rearrangement of Diaryl-1,2-dihydropentalenes to 1,5-Dihydropentalenes and Domino Diels-Alder reactions with Dienophiles", National Symposium On Emerging Trends in Organic Chemistry held at Trivandrum, November 18-19, 1996, Abstract, P 1907/06/1999.
2. **Jayan, C. N.** and V. Nair. "Indium Mediated Barbier Reactions of 1,2-Diones: A Facile Synthesis of α-Hydroxy Ketones", Second National Symposium in Chemistry held at IICT, Hyderabad, January 27-29, 2000, Abstract, p 121.